ORIGINAL ARTICLE

Early Surgery versus Conventional Treatment for Infective Endocarditis

Duk-Hyun Kang, M.D., Ph.D., Yong-Jin Kim, M.D., Ph.D., Sung-Han Kim, M.D., Ph.D., Byung Joo Sun, M.D., Dae-Hee Kim M.D., Ph.D., Sung-Cheol Yun, Ph.D., Jong-Min Song, M.D., Ph.D., Suk Jung Choo, M.D., Ph.D., Cheol-Hyun Chung, M.D., Ph.D., Jae-Kwan Song, M.D., Ph.D., Jae-Won Lee, M.D., Ph.D., and Dae-Won Sohn, M.D., Ph.D.

ABSTRACT

BACKGROUND

The timing and indications for surgical intervention to prevent systemic embolism in infective endocarditis remain controversial. We conducted a trial to compare clinical outcomes of early surgery and conventional treatment in patients with infective endocarditis.

METHODS

We randomly assigned patients with left-sided infective endocarditis, severe valve disease, and large vegetations to early surgery (37 patients) or conventional treatment (39). The primary end point was a composite of in-hospital death and embolic events that occurred within 6 weeks after randomization.

RESULTS

All the patients assigned to the early-surgery group underwent valve surgery within 48 hours after randomization, whereas 30 patients (77%) in the conventional-treatment group underwent surgery during the initial hospitalization (27 patients) or during follow-up (3). The primary end point occurred in 1 patient (3%) in the early-surgery group as compared with 9 (23%) in the conventional-treatment group (hazard ratio, 0.10; 95% confidence interval [CI], 0.01 to 0.82; P=0.03). There was no significant difference in all-cause mortality at 6 months in the early-surgery and conventional-treatment groups (3% and 5%, respectively; hazard ratio, 0.51; 95% CI, 0.05 to 5.66; P=0.59). The rate of the composite end point of death from any cause, embolic events, or recurrence of infective endocarditis at 6 months was 3% in the early-surgery group and 28% in the conventional-treatment group (hazard ratio, 0.08; 95% CI, 0.01 to 0.65; P=0.02).

CONCLUSIONS

As compared with conventional treatment, early surgery in patients with infective endocarditis and large vegetations significantly reduced the composite end point of death from any cause and embolic events by effectively decreasing the risk of systemic embolism. (EASE ClinicalTrials.gov number, NCT00750373.)

From the Divisions of Cardiology (D.-H. Kang, B.J.S., D.-H. Kim, J.-M.S., J.-K.S.), Cardiac Surgery (S.J.C., C.-H.C., J.-W.L.), Infectious Disease (S.-H.K.), and Biostatistics (S.-C.Y.), Asan Medical Center, University of Ulsan; and the Cardiovascular Center, Seoul National University Hospital, Seoul National University College of Medicine (Y.-J.K., D.-W.S.) — all in Seoul, South Korea. Address reprint requests to Dr. D.H. Kang at the Division of Cardiology, Asan Medical Center, College of Medicine, University of Ulsan 388-1, Poongnap-dong, Songpa-ku, Seoul, South Korea, or at dhkang@amc.seoul.kr.

N Engl J Med 2012;366:2466-73.

Despite advances in medical and surgical treatment, infective endocarditis remains a serious disease that carries a considerable risk of death and morbidity.[1,2] The role of surgery in the treatment of infective endocarditis has been expanding, and current guidelines advocate surgical management for complicated left-sided infective endocarditis.[2,3] Early surgery is strongly indicated for patients with infective endocarditis and congestive heart failure,[1,4] but the indications for surgical intervention to prevent systemic embolism remain to be defined.[5] Early identification of patients with large vegetations and a high risk of embolism,[6] increased experience with complete excision of infected tissue and valve repair, and low operative mortality have been cited as favoring early surgery,[4,7] but there has been concern that such surgery may be more difficult to perform in the presence of active infection and inflammation.[8]

The two sets of consensus guidelines for the performance of early surgery on the basis of vegetation are different, reflecting controversy. The 2006 American College of Cardiology–American Heart Association (ACC–AHA) guidelines[9] recommend early surgery as a class IIa indication only in patients with recurrent emboli and persistent vegetation, whereas the revised 2009 European Society of Cardiology guidelines[3] recommend early surgery as a class IIb indication in patients with isolated, very large vegetations (>15 mm in diameter). Because of ethical, logistical, and financial constraints, no randomized trial has been conducted to clarify the indications for surgery and the timing of it that would associated with favorable outcomes.[4] The Early Surgery versus Conventional Treatment in Infective Endocarditis (EASE) trial was designed to compare the clinical outcomes of early surgery with those of a conventional-treatment strategy that is based on current guidelines for patients with left-sided infective endocarditis and a high risk of embolism. The major hypothesis of this trial was that early surgery would decrease the rate of death or embolic events, as compared with conventional treatment.

METHODS

STUDY DESIGN

We conducted this prospective, randomized trial involving patients with infective endocarditis who were candidates for both early surgery and conventional treatment at two medical centers in Korea. The study protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at each participating center. We designed the protocol and conducted the trial in accordance with the principles of the Declaration of Helsinki. The authors vouch for the fidelity of this report to the protocol and for the accuracy and completeness of the data and the analyses.

PATIENT SELECTION

We enrolled consecutive patients, 18 years of age or older, with left-sided, native-valve infective endocarditis and a high risk of embolism. For all patients with suspected infective endocarditis, blood cultures were obtained and transthoracic echocardiography was performed within 24 hours after hospitalization. Patients were eligible for enrollment if they had received a diagnosis of definite infective endocarditis according to the modified Duke criteria[10] and had severe mitral valve or aortic valve disease and vegetation with a diameter greater than 10 mm. To minimize the number of unnecessary surgeries and the risk of prosthesis-related morbidity, we only enrolled patients with infective endocarditis accompanied by severe valve disease. All patients provided written informed consent.

In accordance with the 2006 ACC–AHA guidelines on surgical indications for infective endocarditis,[9] patients were excluded if they had moderate-to-severe congestive heart failure, infective endocarditis complicated by heart block, annular or aortic abscess, destructive penetrating lesions requiring urgent surgery, or fungal endocarditis. Other exclusion criteria were an age of more than 80 years, coexisting major embolic stroke with a risk of hemorrhagic transformation at the time of diagnosis, and a serious coexisting condition (e.g., cancer) (Fig. 1). Patients were also excluded if they had infective endocarditis involving a prosthetic valve, right-sided vegetations, or small vegetations (diameter, ≤10 mm) or had been referred from another hospital more than 7 days after the diagnosis of infective endocarditis.

STUDY PROCEDURES

Evaluation at baseline included the collection of data on demographic characteristics, predisposing heart disease, manifestations of infective en-

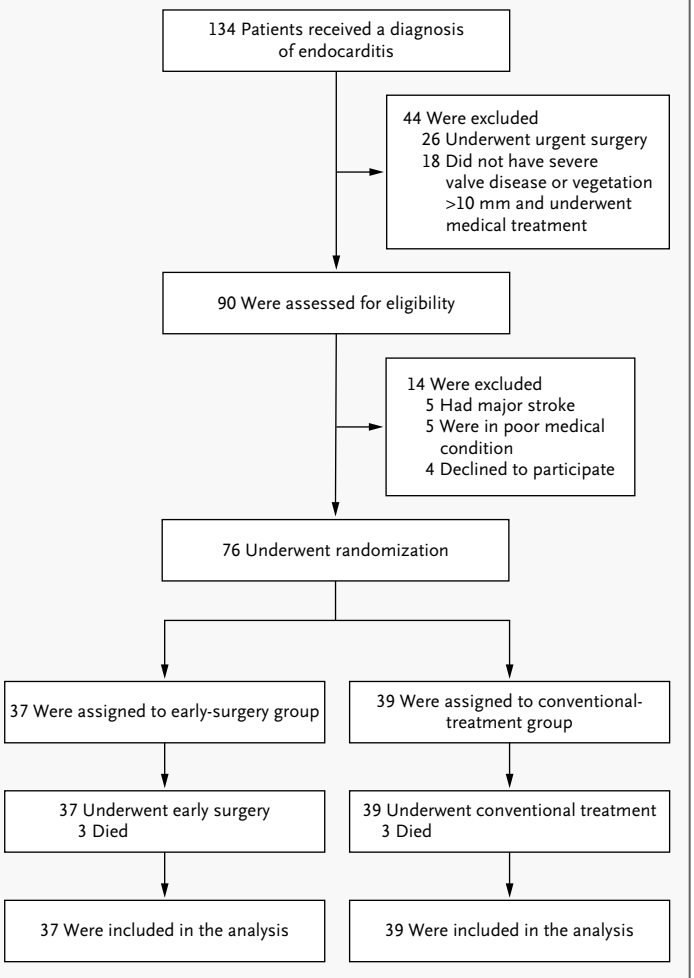

Figure 1. Study Enrollment.

Of the 134 patients who received a definite diagnosis of infective endocarditis, 26 required urgent surgery and 18 did not have large vegetations or severe valve disease; 90 patients were assessed for eligibility, 14 of whom were excluded. Of the 76 patients who underwent randomization, 37 were assigned to the early-surgery group and 39 to the conventional-treatment group; all these patients were included in the intention-to-treat analysis.

docarditis, results of blood cultures, use of antibiotic therapy, results of echocardiography, results of radiologic imaging studies, and operative risk. At baseline, all patients underwent transesophageal echocardiography and computed tomography of the brain and abdomen with the administration of a contrast agent in order to detect any silent embolism. Patients were randomly assigned in a 1:1 ratio to the early-surgery group or the conventional-treatment group with the use of a Web-based interactive response system. The treatment assignments were computer-generated and stratified according to the involved valve and participating center by means of a permuted-block sequence with variable block size. The protocol specified that patients who were assigned to the early-surgery group should undergo surgery within 48 hours after randomization. Patients assigned to the conventional-treatment group were treated according to the AHA guidelines,[2] and surgery was performed only if complications requiring urgent surgery developed during medical treatment or if symptoms persisted after the completion of antibiotic therapy. Details of the study procedures are provided in the Supplementary Appendix, available at NEJM.org.

All patients were followed during hospitalization; at 4 weeks, 6 weeks, 3 months, 6 months, and 1 year; and at 6-month intervals thereafter until September 2011.

STUDY END POINTS

The primary end point was a composite of in-hospital death or clinical embolic events that occurred within 6 weeks after randomization. An embolic event was defined as a systemic embolism fulfilling both prespecified criteria: the acute onset of clinical symptoms or signs of embolism and the occurrence of new lesions, as confirmed by follow-up imaging studies. Cutaneous manifestations or metastatic abscesses were not considered to be embolic events. A specific diagnosis of cerebral embolism was confirmed by an experienced neurologist on the basis of additional magnetic resonance imaging of the brain. We did not perform follow-up imaging studies systematically to detect subclinical embolic events. Prespecified secondary end points, at 6 months of follow-up, included death from any cause, embolic events, recurrence of infective endocarditis, and repeat hospitalization due to the development of congestive heart failure.

STATISTICAL ANALYSIS

We estimated that a sample of 74 patients would provide 80% power to detect a significant difference with respect to the primary end point at a two-sided significance level of 0.05, assuming that the in-hospital event rate would be 23% in the conventional-treatment group and 3% in the early-surgery group. These rates were based on outcome data in the early prospective trial[11] and our previous study.[12]

Analyses were performed on an intention-to-

treat basis. Differences between the treatment groups were evaluated with the use of the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Because randomization was stratified according to involved valve, we performed stratified Cox proportional-hazards regression analyses for the outcomes. A likelihood ratio test for homogeneity was performed, indicating that the assumption of homogeneity was not violated (P=0.99 for both outcomes). Estimates of cumulative event rates were calculated by means of the Kaplan–Meier method and were compared with the use of the log-rank test. For the Kaplan–Meier analysis, we analyzed all clinical events according to the time to the first event. Hazard ratios with 95% confidence intervals were derived with the use of the stratified Cox proportional-hazards model. All reported P values are two-sided; a P value of 0.05 was considered to indicate statistical significance. SAS software, version 9.1 (SAS Institute), was used for statistical analyses.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From September 2006 through March 2011, a total of 76 patients with infective endocarditis who were candidates for early preemptive surgery were enrolled at the Asan Medical Center (71 patients) and Seoul National University Hospital (5) in Korea. We randomly assigned these patients to early surgery (37 patients) or conventional treatment (39). The enrollment profile is shown in Figure 1.

The treatment groups were generally well balanced with regard to baseline clinical characteristics (Table 1). The mean age of the patients was 47 years, and 67% were men. The mitral valve was involved in 45 patients, the aortic valve in 22, and both valves in 9. Severe mitral regurgitation was observed in 45 patients, severe aortic regurgitation in 23, severe aortic stenosis in 3, severe mitral regurgitation and stenosis in 1, and both severe mitral regurgitation and aortic regurgitation in 4. The median diameter of vegetation was 12 mm (interquartile range, 11 to 17). All patients met the Duke criteria for definite endocarditis; the most common pathogens in both groups were viridans streptococci (in 30% of all patients), other streptococci (in 30%), and *Staphylococcus aureus* (in 11%). The adequacy of antibiotic therapy was compared between treat-

Table 1. Clinical and Echocardiographic Characteristics of the Patients at Baseline, According to Treatment Group.*

Characteristic	Conventional Treatment (N=39)	Early Surgery (N=37)
Age — yr	47.8±17.5	45.5±14.9
Male sex — no. (%)	27 (69)	24 (65)
Diabetes — no. (%)	4 (10)	8 (22)
Hypertension — no. (%)	7 (18)	11 (30)
Coronary artery disease — no. (%)	1 (3)	3 (8)
Immunocompromised state — no. (%)†	1 (3)	2 (5)
Underlying valve disease — no. (%)	39 (100)	35 (95)
Serum creatinine — mg/dl	0.90±0.67	1.28±1.85
EuroSCORE value‡	6.7±1.7	6.4±1.6
Embolism on admission — no. (%)	17 (44)	19 (51)
Cerebral	11 (28)	11 (30)
Renal	7 (18)	6 (16)
Splenic	9 (23)	14 (38)
Left ventricular ejection fraction — %	60.7±7.2	61.7±5.1
Valve involved — no. (%)		
Mitral	23 (59)	22 (59)
Aortic	11 (28)	11 (30)
Aortic and mitral	5 (13)	4 (11)
Vegetation diameter	14.1±3.5	13.5±3.2
>10–15 mm — no. (%)	26 (67)	26 (70)
>15 mm — no. (%)	13 (33)	11 (30)
Valvular disease — no. (%)		
Severe stenosis	3 (8)	1 (3)
Severe regurgitation	36 (92)	36 (97)
Blood microorganism — no. (%)		
Viridans streptococci	13 (33)	10 (27)
Other streptococci	12 (31)	11 (30)
Staphylococcus aureus	5 (13)	3 (8)
Enterococcus	1 (3)	2 (5)
Other§	1 (3)	1 (3)
Negative culture¶	7 (18)	10 (27)

* Plus–minus values are means ±SD. There were no significant differences between the groups.
† Patients with an immunocompromised state were those with a solid-organ transplant or a diagnosis of end-stage renal disease.
‡ Scores on the European System for Cardiac Operative Risk Evaluation (euroSCORE), a clinical model for assessing operative risk, range from 0 to 39, with higher scores indicating greater risk.
§ *Lactobacillus acidophilus* was present in 1 patient with end-stage renal disease in the conventional-treatment group, and *Haemophilus parainfluenzae* was present in 1 patient in the early-surgery group.
¶ Of the 17 patients with negative cultures, 5 of 7 patients (71%) in the conventional-treatment group and 8 of 10 (80%) in the early-surgery group had a history of antibiotic use.

Table 2. Characteristics of Antibiotic Therapy, According to Treatment Group.

Characteristic	Conventional Treatment (N=39)	Early Surgery (N=37)	P Value
Control of the underlying infection			
Defeverescence — days			
Median	2	2	0.21
Interquartile range	1–6	1–3	
Persistence of bacteremia — no. (%)*	1 (3)	0	1.00
Antibiotic regimen			
Beta-lactam–based therapy — no. (%)	39 (100)	37 (100)	1.00
Beta-lactam antibiotic alone	26 (67)	27 (73)	0.62
Beta-lactam antibiotic with aminoglycoside†	13 (33)	10 (27)	0.62
Duration — days			
Median	35	35	0.93
Interquartile range	28–42	28–42	

* Persistence of bacteremia was defined as positive blood cultures 1 week after antibiotic therapy was initiated.
† An aminoglycoside was administered for 2 or more weeks.

Table 3. Clinical End Points.

Outcome	Conventional Treatment (N=39)	Early Surgery (N=37)	P Value
Primary end point — no. (%)			
In-hospital death or embolic event at 6 wk	9 (23)	1 (3)	0.01
In-hospital death	1 (3)	1 (3)	1.00
Embolic event at 6 wk			
Any	8 (21)	0	0.005
Cerebral	5 (13)	0	
Coronary	1 (3)	0	
Popliteal	1 (3)	0	
Splenic	1 (3)	0	
Secondary end points at 6 mo — no. (%)			
Any	11 (28)	1 (3)	0.003
Death	2 (5)	1 (3)	1.00
Embolic event	8 (21)	0	0.005
Recurrence of infective endocarditis	1 (3)	0	1.00

ment groups (Table 2). There were no significant between-group differences in terms of control of the underlying infection, the antibiotic regimen used, or the duration of antibiotic therapy.

SURGICAL PROCEDURES

All patients in the early-surgery group underwent valve surgery within 48 hours after randomization; the median time between randomization and surgery was 24 hours (interquartile range, 7 to 45). Of the 22 patients with involvement of the mitral valve, 8 patients underwent mitral-valve repair and 14 underwent mitral-valve replacement with a mechanical valve. Of the 15 patients with involvement of the aortic valve or both the mitral and aortic valves, 14 underwent mechanical-valve replacement and 1 underwent valve replacement with a biologic prosthesis. Concomitant coronary-artery bypass grafting at the time of valve surgery was performed in 2 patients (5%).

Of the 39 patients assigned to the conventional-treatment group, 30 (77%) underwent surgery during the initial hospitalization (27 patients) or during follow-up (3). The surgical procedures included 11 mitral-valve repairs, 6 mitral-valve replacements (with 5 patients receiving a mechanical valve and 1 a biologic prosthesis), 11 aortic-valve replacements (with 9 patients receiving a mechanical valve and 2 a biologic prosthesis), and 2 combined aortic-valve replacements (with 1 patient receiving a mechanical valve and 1 a biologic prosthesis) and mitral-valve repairs. In 8 patients (21%), indications for urgent surgery developed during hospitalization (median time to surgery after randomization, 6.5 days [interquartile range, 6 to 10]). Elective surgery was performed in an additional 22 patients owing to symptoms or left ventricular dysfunction more than 2 weeks after randomization. Surgical results are shown in the Supplementary Appendix.

PRIMARY END POINT

The primary end point of in-hospital death or embolic events within the first 6 weeks after randomization occurred in one patient (3%) in the early-surgery group, as compared with nine (23%) in the conventional-treatment group (hazard ratio, 0.10; 95% confidence interval [CI], 0.01 to 0.82; P=0.03). In the early-surgery group, one patient died in the hospital and no patients had embolic events; in the conventional-treatment group, one patient died in the hospital and eight patients had embolic events (Table 3). All the primary end points in the conventional-treatment group occurred before valve surgery. No patients died within 30 days after surgery in either group. At 6 weeks after randomization, the rate of embolism was 0% in

the early-surgery group, as compared with 21% in the conventional-treatment group (P=0.005). Details of the deaths and embolic events are summarized in Tables S1 and S2 in the Supplementary Appendix.

SECONDARY END POINTS DURING FOLLOW-UP

The median follow-up time was 749 days (interquartile range, 425 to 1242), and all patients underwent complete follow-up, which began at randomization and ended in September 2011. During follow-up, there were two deaths from noncardiac causes and no deaths from cardiac causes in the early-surgery group; in the conventional-treatment group, there was one death from noncardiac causes and one from cardiac causes (Table S1 in the Supplementary Appendix). Anticoagulation was effectively maintained during the entire follow-up period in patients with mechanical-valve replacement and for 3 months in those who received a biologic prosthesis and had no risk factors. No patient in either group had an embolic event or was hospitalized for congestive heart failure during follow-up. Recurrence of infective endocarditis within 6 months after discharge was not observed in any patient in the early-surgery group but was reported in 1 patient in the conventional-treatment group. Among the 11 patients (28%) in the conventional-treatment group who were treated medically and discharged without undergoing surgery, 1 (3%) died suddenly, 7 (18%) had symptoms related to severe valve disease or recurrence of infective endocarditis (3 of whom underwent surgery during follow-up), and 3 (8%) had no symptoms or embolic events (Table S3 in the Supplementary Appendix).

There was no significant difference between the early-surgery and conventional-treatment groups in all-cause mortality at 6 months (3% and 5%, respectively; hazard ratio, 0.51; 95% CI, 0.05 to 5.66; P=0.59) (Fig. 2A). At 6 months, the rate of the composite of death from any cause, embolic events, recurrence of infective endocarditis, or repeat hospitalization due to the development of congestive heart failure was 3% in the early-surgery group, as compared with 28% in the conventional-treatment group (hazard ratio, 0.08; 95% CI, 0.01 to 0.65; P=0.02). The estimated actuarial rate of end points was significantly lower in the early-surgery group than in the conventional-treatment group (P=0.009 by the log-rank test) (Fig. 2B).

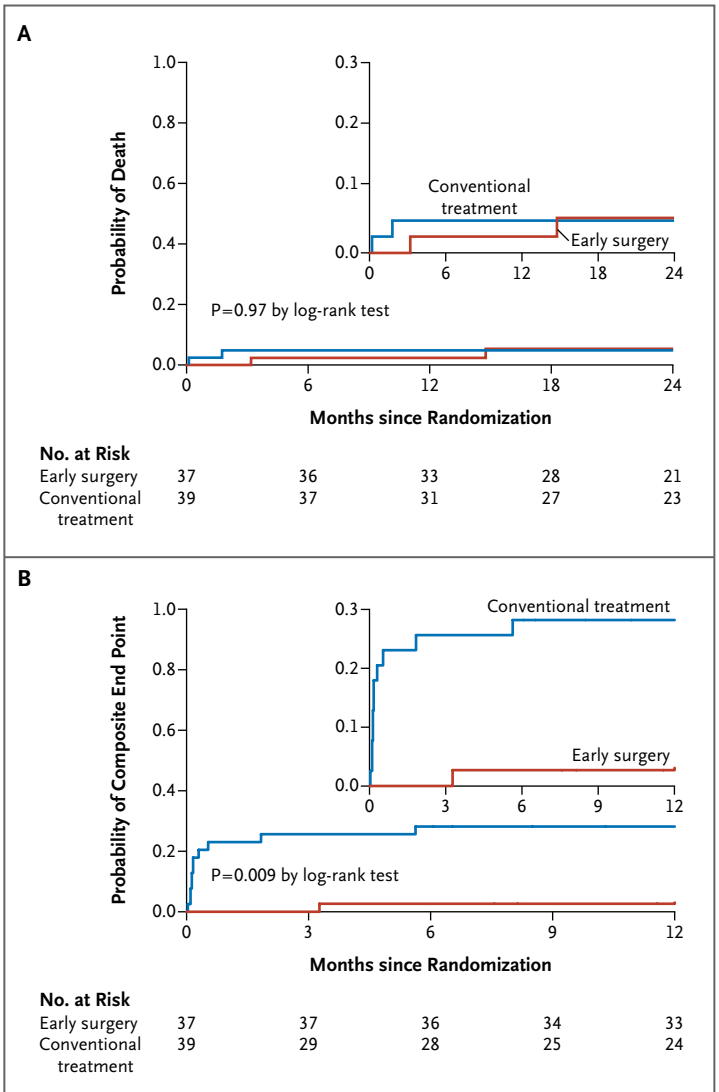

Figure 2. Kaplan–Meier Curves for the Cumulative Probabilities of Death and of the Composite End Point at 6 Months, According to Treatment Group.

There was no significant between-group difference in all-cause mortality at 6 months (Panel A). The rate of the composite end point of death from any cause, embolic events, recurrence of infective endocarditis, or repeat hospitalization due to the development of congestive heart failure was 3% in the early-surgery group versus 28% in the conventional-treatment group (hazard ratio, 0.08; 95% CI, 0.01 to 0.65; P=0.02) (Panel B).

DISCUSSION

Our randomized trial comparing early valve surgery with conventional treatment in patients with infective endocarditis showed that early surgery performed within 48 hours after diagnosis reduced the composite primary end point of death

from any cause or embolic events by effectively reducing the risk of systemic embolism. Moreover, these improvements in clinical outcomes were achieved without an increase in operative mortality or recurrence of infective endocarditis.

Systemic embolism, which occurs in approximately one third of patients with infective endocarditis and involves the central nervous system in up to 65%, is the second most common cause of death, after congestive heart failure, in this patient population.[1,2,13] Several studies using propensity-scoring models have shown conflicting results with respect to the benefits of surgery,[12,14-16] and the choice between surgery and medical therapy has not been clear-cut. Previous observational studies comparing the outcomes of surgery with those of medical therapy have been subject to the limitations imposed by baseline differences between the treatment groups and treatment-selection and survivor biases[12,14-18]; prospective, randomized trials may reduce these limitations.

In this randomized trial, we hypothesized that the benefits of surgical treatment would be maximized by performing surgery within 48 hours after randomization, because the risk of embolism has been reported to be particularly high during the first week after diagnosis.[4,6,19] The rate of embolism in the conventional-treatment group was similar to that reported in other studies,[6,11,12] and the rate of embolism in the early-surgery group was markedly reduced, as compared with conventional treatment, as expected from our previous observational study.[12] Therefore, we suggest that early surgery is a valuable therapeutic option to prevent embolism.

We found that the in-hospital and 6-month mortality in both groups was substantially lower than that reported previously. There may be several explanations for the lower mortality in our study. First, the proportion of patients with poor prognostic factors, such as moderate-to-severe congestive heart failure, altered mental status, and staphylococcal infection, was lower than in previous studies.[15,16,20] Second, the rate of death within 30 days after surgery in this study was very low, and more than 80% of our patients underwent valve surgery during the initial hospitalization. Our aggressive surgical approach may be related to the low mortality, but our study was not designed to address this issue. Third, blood cultures were obtained and echocardiography was performed within 24 hours after hospitalization in all patients with suspected infective endocarditis. Because the diagnosis of infective endocarditis must be made as soon as possible in order to initiate therapy, and a delay in diagnosis causes severe complications,[2] rapid diagnosis might be related to the favorable outcome observed in our study.

Our study has several limitations. The trial was limited in scope, in that it included patients with severe valvular disease and large vegetations and excluded those with major stroke, infective endocarditis involving a prosthetic valve, or aortic abscess. Our exclusion criteria also affected the relative frequencies of causative microorganisms, and the incidence of infective endocarditis due to *S. aureus* was lower than that in previous studies.[1,21] The risk–benefit ratio of early surgery over conventional treatment may differ according to the type of high-risk situation and the causative organism. The rate of death within 30 days after surgery was very low in our study, and our study patients had low operative risk. The results of our study may not be applicable to low-volume medical centers or to patients with high operative risk. Although randomization was stratified according to participating center, an analysis of outcomes according to center was not performed because of the large differences in the number of enrolled patients among the sites.

In conclusion, early surgery, as compared with conventional treatment, significantly reduced the composite end point of death from any cause or embolic events by effectively reducing the risk of systemic embolism among patients with infective endocarditis and large vegetations.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Mylonakis E, Calderwood SB. Infective endocarditis in adults. N Engl J Med 2001;345:1318-30.
2. 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(23):e394-e434. [Errata, Circulation 2005;112:2373, 2007;115(15):e408, 2007;116(21):e547, 2008;118(12):e497.]

3. 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.
4. Prendergast BD, Tornos P. Surgery for infective endocarditis: who and when? Circulation 2010;121:1141-52.
5. Moreillon P, Que YA. Infective endocarditis. Lancet 2004;363:139-49.
6. Thuny F, Di Salvo G, Belliard O, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. Circulation 2005;112:69-75.
7. Tornos P, Iung B, Permanyer-Miralda G, et al. Infective endocarditis in Europe: lessons from the Euro heart survey. Heart 2005;91:571-5.
8. Delahaye F. Is early surgery beneficial in infective endocarditis? A systematic review. Arch Cardiovasc Dis 2011;104:35-44.
9. Bonow RO, Carabello B, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease). Circulation 2006;114(5):e84-e231. [Errata, Circulation 2007;115(15):e409, 2010;121(23) e443.]
10. 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.
11. Chan KL, Dumesnil JG, Cujec BC, et al. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. J Am Coll Cardiol 2003;42:775-80.
12. Kim DH, Kang DH, Lee MZ, et al. Impact of early surgery on embolic events in patients with infective endocarditis. Circulation 2010;122:Suppl:S17-S22.
13. Habib G. Management of infective endocarditis. Heart 2006;92:124-30.
14. 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.
15. Tleyjeh IM, Ghomrawi HM, Steckelberg JM, et al. The impact of valve surgery on 6-month mortality in left-sided infective endocarditis. Circulation 2007;115: 1721-8.
16. Lalani T, Cabell CH, Benjamin DK, et al. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. Circulation 2010;121:1005-13.
17. Tleyjeh IM, Steckelberg JM, Georgescu G, et al. The association between the timing of valve surgery and 6-month mortality in left-sided infective endocarditis. Heart 2008;94:892-6. [Erratum, Heart 2008;94:1496.]
18. Thuny F, Beurtheret S, Mancini J, et al. The timing of surgery influences mortality and morbidity in adults with severe complicated infective endocarditis: a propensity analysis. Eur Heart J 2011;32:2027-33.
19. Steckelberg JM, Murphy JG, Ballard D, et al. Emboli in infective endocarditis: the prognostic value of echocardiography. Ann Intern Med 1991;114:635-40.
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. Miro JM, Anguera I, Cabell CH, et al. Staphylococcus aureus native valve infective endocarditis: report of 566 episodes from the International Collaboration on Endocarditis Merged Database. Clin Infect Dis 2005;41:507-14. [Erratum, Clin Infect Dis 2005;41:1075-7.]