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## USE OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY TO GUIDE CARDIOVERSION IN PATIENTS WITH ATRIAL FIBRILLATION

ALLAN L. KLEIN, M.D., RICHARD A. GRIMM, D.O., R. DANIEL MURRAY, PH.D., CAROLYN APPERSON-HANSEN, M.STAT.,  
RICHARD W. ASINGER, M.D., IAN W. BLACK, M.D., RAVIN DAVIDOFF, M.B., B.CH., RAIMUND ERBEL, M.D.,  
JONATHAN L. HALPERIN, M.D., DAVID A. ORSINELLI, M.D., THOMAS R. PORTER, M.D., AND MARCUS F. STODDARD, M.D.,  
FOR THE ASSESSMENT OF CARDIOVERSION USING TRANSESOPHAGEAL ECHOCARDIOGRAPHY INVESTIGATORS\*

### ABSTRACT

**Background** The conventional treatment strategy for patients with atrial fibrillation who are to undergo electrical cardioversion is to prescribe warfarin for anticoagulation for three weeks before cardioversion. It has been proposed that if transesophageal echocardiography reveals no atrial thrombus, cardioversion may be performed safely after only a short period of anticoagulant therapy.

**Methods** In a multicenter, randomized, prospective clinical trial, we enrolled 1222 patients with atrial fibrillation of more than two days' duration and assigned them to either treatment guided by the findings on transesophageal echocardiography or conventional treatment. The composite primary end point was cerebrovascular accident, transient ischemic attack, and peripheral embolism within eight weeks. Secondary end points were functional status, successful restoration and maintenance of sinus rhythm, hemorrhage, and death.

**Results** There was no significant difference between the two treatment groups in the rate of embolic events (five embolic events among 619 patients in the transesophageal-echocardiography group [0.8 percent] vs. three among 603 patients in the conventional-treatment group [0.5 percent],  $P=0.50$ ). However, the rate of hemorrhagic events was significantly lower in the transesophageal-echocardiography group (18 events [2.9 percent] vs. 33 events [5.5 percent],  $P=0.03$ ). Patients in the transesophageal-echocardiography group also had a shorter time to cardioversion (mean [ $\pm$ SD],  $3.0\pm 5.6$  vs.  $30.6\pm 10.6$  days;  $P<0.001$ ) and a greater rate of successful restoration of sinus rhythm (440 patients [71.1 percent] vs. 393 patients [65.2 percent],  $P=0.03$ ). At eight weeks, there were no significant differences between the two groups in the rates of death or maintenance of sinus rhythm or in functional status.

**Conclusions** The use of transesophageal echocardiography to guide the management of atrial fibrillation may be considered a clinically effective alternative strategy to conventional therapy for patients in whom elective cardioversion is planned. (N Engl J Med 2001;344:1411-20.)

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**A**TRIAL fibrillation is the most common sustained arrhythmia encountered in clinical practice, with an overall prevalence of 0.4 percent in the general population<sup>1-4</sup>; it affects 2.2 million people in the United States.<sup>3,5</sup> Electrical cardioversion is often used to restore sinus rhythm in patients with atrial fibrillation, but the procedure is associated with an increased risk of stroke, which may result if left atrial thrombi are dislodged when sinus rhythm is restored.<sup>6-9</sup> The conventional strategy for anticoagulation in patients with atrial fibrillation of prolonged duration (longer than two days) calls for three weeks of empirical anticoagulant treatment before cardioversion, followed by four weeks of warfarin therapy after cardioversion.<sup>10</sup> Although anticoagulation before cardioversion has been shown to lower the risk of embolism, the conventional strategy for anticoagulation has never been properly evaluated in a large clinical trial.<sup>9</sup> On the other hand, transesophageal echocardiography allows thrombi in the left atrial appendage to be detected with a high degree of accuracy<sup>11-13</sup> and has been proposed as a safe means of expediting cardioversion with short-term anticoagulant therapy.<sup>9,14-18</sup> There remains controversy concerning which strategy should be used,<sup>16,19</sup> but there have been no randomized clinical trials to determine relative efficacy. Therefore, the objective of the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) Multicenter Study was to compare a conventional anticoagulation strategy with

From the Cleveland Clinic Foundation, Cleveland (A.L.K., R.A.G., R.D.M., C.A.-H.); Hennepin County Medical Center, Minneapolis (R.W.A.); Manly Hospital, Manly, N.S.W., Australia (I.W.B.); Boston Medical Center, Boston (R.D.); Universitätsklinikum—Essen, Essen, Germany (R.E.); Mount Sinai School of Medicine, New York (J.L.H.); Ohio State University, Columbus (D.A.O.); the University of Nebraska, Omaha (T.R.P.); and the University of Louisville, Louisville, Ky. (M.E.S.). Address reprint requests to Dr. Klein at the Cleveland Clinic Foundation, 9500 Euclid Ave., Department of Cardiology — Desk F15, Cleveland, OH 44195, or at klein@ccf.org.

\*The study investigators are listed in the Appendix.

the strategy of using transesophageal echocardiography to guide short-term anticoagulant therapy in patients with atrial fibrillation of more than two days' duration for whom electrical cardioversion is prescribed.

**METHODS**

**Study Design**

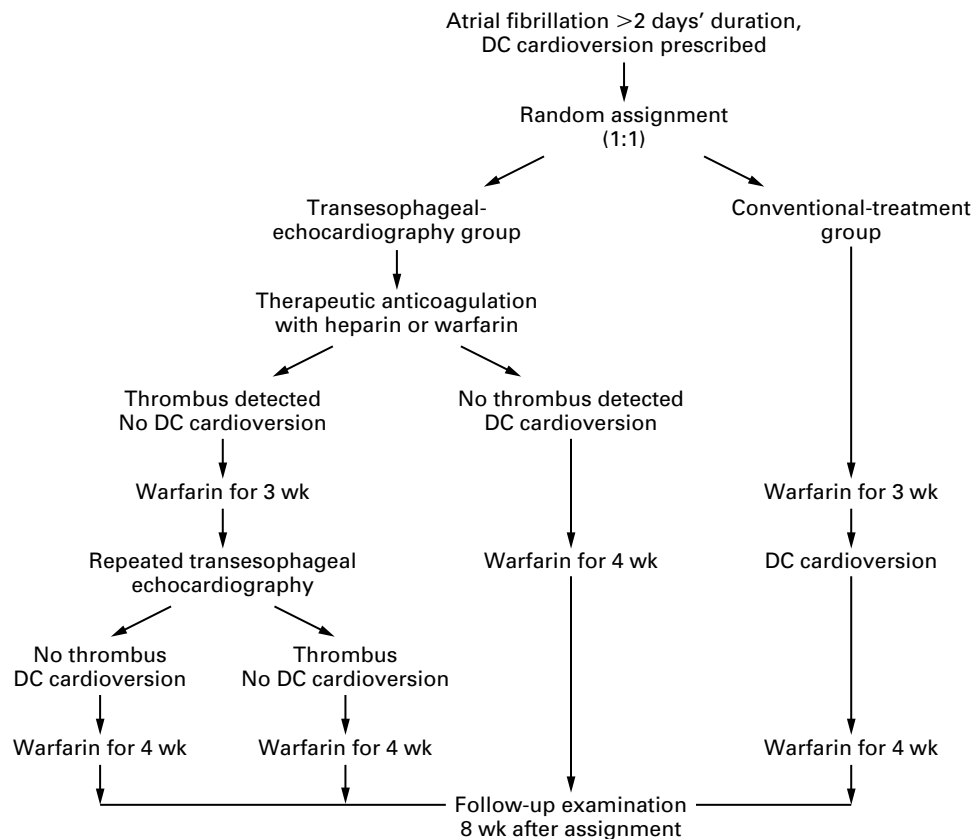
We conducted a controlled, investigator-initiated, prospective, randomized, multicenter trial that compared the clinical outcomes of two distinct treatment strategies in patients with atrial fibrillation for whom electrical cardioversion was prescribed. The study design has been described previously,<sup>20</sup> and the protocol is diagrammed in Figure 1.

Patients were enrolled and randomly assigned to either a strategy of treatment guided by the findings on transesophageal echocardiography, with brief anticoagulant therapy, or a conventional treatment strategy following current guidelines.<sup>10</sup> Patients assigned to the transesophageal-echocardiography group were given anticoagulant therapy at their initial visit with the intention that they would receive therapeutic anticoagulation at the time of cardioversion and for four weeks thereafter. Inpatients were typically treated with intravenous unfractionated heparin (target activated partial-

thromboplastin time, 1.5 to 2.5 times the control value), and the transesophageal echocardiography and subsequent cardioversion were scheduled within 24 hours. Outpatients received warfarin (target international normalized ratio, 2.0 to 3.0), and transesophageal echocardiography and subsequent cardioversion were scheduled for five days later. The anticoagulation status of all patients undergoing cardioversion was checked immediately before cardioversion.<sup>20</sup> With the use of transesophageal echocardiography, the patients were stratified according to the presence or absence of thrombus. Patients assigned to the conventional-treatment group were given warfarin at their initial visit and for three weeks thereafter for therapeutic anticoagulation before cardioversion, followed by a four-week period of warfarin therapy after cardioversion. For both groups, the eight-week study period began at the time of enrollment and lasted until day 56. The study was approved by the institutional review board at each site, and written informed consent was obtained from all patients.

**Patients**

Patients who were candidates for electrical cardioversion were eligible for enrollment in the study if they were at least 18 years old and had atrial fibrillation of more than two days' duration. Patients with atrial flutter who had a documented history of atrial fibrillation were also eligible. Patients with atrial flutter and no history



**Figure 1.** The Study Protocol.

Patients were randomly assigned to either the transesophageal-echocardiography group or the conventional-treatment group. Patients in the transesophageal-echocardiography group were stratified according to the presence or absence of a thrombus in the left atrial appendage as revealed by transesophageal echocardiography. Patients assigned to the conventional-treatment group received warfarin therapy for three weeks before electrical cardioversion was attempted. Both groups received warfarin for four weeks after cardioversion. DC denotes direct current.

of atrial fibrillation and patients with hemodynamic instability were excluded from the study. Also excluded were patients receiving long-term warfarin therapy (of more than seven days' duration), patients with contraindications to warfarin or transesophageal echocardiography, women of childbearing potential, and patients who might need procedures requiring the discontinuation of anticoagulation. Patients who were taking antiarrhythmic medication were not excluded from the study, but the commencement of antiarrhythmic therapy was permitted only after a therapeutic level of anticoagulation was achieved.

### Outcomes

The primary outcome was a composite of cerebrovascular accident, transient ischemic attack, and peripheral embolism. Secondary clinical outcomes were major and minor hemorrhagic events, death from any cause and from cardiac causes, successful return to and maintenance of sinus rhythm, and functional status as assessed by the Duke Activity Status Index.<sup>21,22</sup> Serious adverse events (embolism, hemorrhage, and death) were adjudicated by a central and independent events-review committee, the members of which were blinded to the treatment-strategy assignment. A hemorrhagic complication was considered major if it was fatal, necessitated transfusion, or could not be terminated without a surgical procedure. A central echocardiography laboratory was used to ensure the quality of the echocardiographic data and adherence to the protocol. Protocol violations were recorded and categorized as major or minor on the basis of predefined criteria. A secondary outcome was the relative costs of the two treatment strategies over the eight-week follow-up period.<sup>20,23</sup>

### Statistical Analysis

On the basis of previously reported rates of embolism,<sup>20</sup> we used an estimated sample size of 3000 patients to achieve a statistical power of 92 percent with an alpha level of 0.05 for the analysis of the primary end point of all embolic events. The estimate of sample size was based on anticipated rates of embolism of 1.2 percent in the transesophageal-echocardiography group and 2.9 percent in the conventional-treatment group over the eight-week period. The study was designed to include two interim analyses and a final analysis.<sup>20</sup>

Chi-square tests were conducted for the comparison of categorical variables in the treatment groups. An analysis of variance was used for the comparison of continuous variables. Data are expressed as means  $\pm$  SD, as medians with interquartile ranges, or as frequencies and percentages with 95 percent confidence intervals. All analyses were based on the intention-to-treat principle. All statistical testing was conducted at a significance level of 0.05 with a two-tailed alternative hypothesis.

The first patient was enrolled on August 6, 1994. A scheduled interim analysis of the first 1000 patients by the data safety and monitoring board was performed on June 15, 1999, and indicated that the rates of both recruitment and events were too low to achieve sufficient statistical power to detect differences between groups in the primary end point. Enrollment was terminated on August 18, 1999, with a total of 1222 patients. After collection and entry of the follow-up data, the study was completed on February 18, 2000.

## RESULTS

### Base-Line Characteristics

A total of 1222 patients from 70 clinical sites were randomly assigned to either treatment guided by the findings on transesophageal echocardiography (619 patients) or conventional treatment (603 patients). There were no significant differences between the two groups in the base-line clinical and echocardiographic characteristics (Table 1). Most of the patients in both groups had atrial fibrillation rather than atrial flutter,

and the median estimated duration of the arrhythmia was 13 days in both groups.

### Outcomes after Treatment Assignment

The anticoagulation and antiarrhythmic status of the patients in the two treatment groups is shown in Table 1. There were significantly more patients in the transesophageal-echocardiography group who were treated as inpatients with intravenous heparin, but patients in the conventional-treatment group were more likely to receive a bolus of heparin before cardioversion and to have shorter durations of heparin therapy to augment subtherapeutic levels of anticoagulation that had been achieved at the time of cardioversion.

Figure 2 shows the treatment outcomes. Of the 619 patients assigned to the transesophageal-echocardiography group, 425 (68.7 percent) had early electrical cardioversion at a mean of  $3.0 \pm 5.6$  days, and in 344 of these (80.9 percent) the cardioversion was successful. Among the 124 patients who had transesophageal echocardiography but no early electrical cardioversion (20.0 percent), cardioversion was postponed in 76 (61.3 percent) because of thrombi. Of the 603 patients in the conventional-treatment group, 333 (55.2 percent) underwent electrical cardioversion at a mean of  $30.6 \pm 10.6$  days, and in 266 of these (79.9 percent) the cardioversion was immediately successful. Of the 270 who did not undergo electrical cardioversion (44.8 percent), 127 (47.0 percent) had a spontaneous or chemical conversion. The remaining 143 (53.0 percent) did not undergo cardioversion for various reasons. Thirty-two patients in the conventional-treatment group underwent transesophageal echocardiography during the study period.

An important difference in outcome between treatments was the time to cardioversion, which was much shorter with the approach guided by transesophageal echocardiography ( $3.0 \pm 5.6$  days, vs.  $30.6 \pm 10.6$  days with conventional treatment;  $P < 0.001$ ). The ability to attempt cardioversion earlier with the use of transesophageal echocardiography also resulted in the use of direct-current cardioversion in a higher proportion of patients than did the conventional strategy (461 of 619 patients [74.5 percent] vs. 333 of 603 patients [55.2 percent],  $P < 0.001$ ).

### Embolic Events

Table 2 shows the clinical outcomes, including the composite primary end point of cerebrovascular accidents, transient ischemic attacks, or peripheral embolism, for both groups. In this study, the total number of embolic events was low, and there was no statistically significant difference between the two treatment groups in the rate of such events (five events in the transesophageal-echocardiography group [0.8 percent; 95 percent confidence interval, 0 to 1.5 percent] vs. three events in the conventional-treatment group [0.5 percent; 95 percent confidence interval,

**TABLE 1. CLINICAL AND ECHOCARDIOGRAPHIC CHARACTERISTICS AT ENROLLMENT AND USE OF ANTICOAGULANT AND ANTIARRHYTHMIC AGENTS AT THE TIME OF DIRECT-CURRENT CARADIOVERSION IN PATIENTS IN THE TRANSESOPHAGEAL-ECHOCARDIOGRAPHY AND CONVENTIONAL-TREATMENT GROUPS.\***

VARIABLE	TRANSESOPHAGEAL-ECHOCARDIOGRAPHY GROUP (N=619)	CONVENTIONAL-TREATMENT GROUP (N=603)	P VALUE
<b>At time of enrollment</b>			
Age — yr	64.8±13.2	64.1±15.6	0.99
Male sex — no. of patients (%)	412 (66.6)	403 (66.8)	0.75
Inpatient status — no. of patients (%)	427 (69.0)	375 (62.2)	0.01
Functional status — DASI score†	28.2±17.4	27.9±17.8	0.58
Hypertension — no. of patients (%)	316 (51.1)	332 (55.1)	0.44
Congestive heart failure — no. of patients (%)	164 (26.5)	174 (28.9)	0.54
NYHA class III or IV — no. of patients (%)	98 (15.8)	86 (14.3)	0.70
Left ventricular ejection fraction — %‡	50.7±15.9	49.8±15.2	0.38
Size of left atrium — cm²‡	25.8±9.7	25.5±8.6	0.72
Previous cardioversion — no. of patients (%)	69 (11.1)	73 (12.1)	0.72
Previous embolic event — no. of patients (%)	49 (7.9)	55 (9.1)	0.56
Rhythm at enrollment — no. of patients			0.89
Atrial fibrillation	590	574	
Atrial flutter	29	29	
Estimated duration of atrial fibrillation — days			0.27
Median	13	13	
Interquartile range	4–48	5–53	
<b>At time of cardioversion</b>			
Cardioversion attempted — no.	461	333	
Warfarin therapy — no. of patients (%)	153 (33.2)	274 (82.3)	<0.001
Intravenous heparin therapy — no. of patients (%)	87 (18.9)	6 (1.8)	<0.001
Intravenous heparin and warfarin therapy — no. of patients (%)	221 (47.9)	52 (15.6)	<0.001
Heparin bolus immediately before cardioversion — no. of patients (%)§	50/308 (16.2)	29/58 (50.0)	<0.001
Duration of precardioversion warfarin therapy in outpatients — days	4.3±39.8	31.1±10.8	<0.001
International normalized ratio for outpatients	2.8±1.2	2.8±1.1	0.39
Duration of heparin therapy in inpatients — days	2.3±2.5	1.5±3.1	0.02
Activated partial-thromboplastin time for inpatients — sec	76.2±36.1	82.3±48.9	0.38
Antiarrhythmic therapy — no. of patients (%)	379 (82.2)	309 (92.8)	<0.001

\*Plus-minus values are means ±SD. DASI denotes Duke Activity Status Index, and NYHA New York Heart Association.

†Scores on the Duke Activity Status Index range from 0 to 58.2, with higher scores indicating better function.

‡Transthoracic echocardiography was used for these measurements.

§Denominators equal the number of patients who received heparin before cardioversion.

0 to 1.1 percent], P=0.50). A summary of the embolic events in the patients is provided in Table 3. The mean age of patients with embolic events was 67±7 years, and seven of the eight patients with such events (87.5 percent) had risk factors for stroke at enrollment.

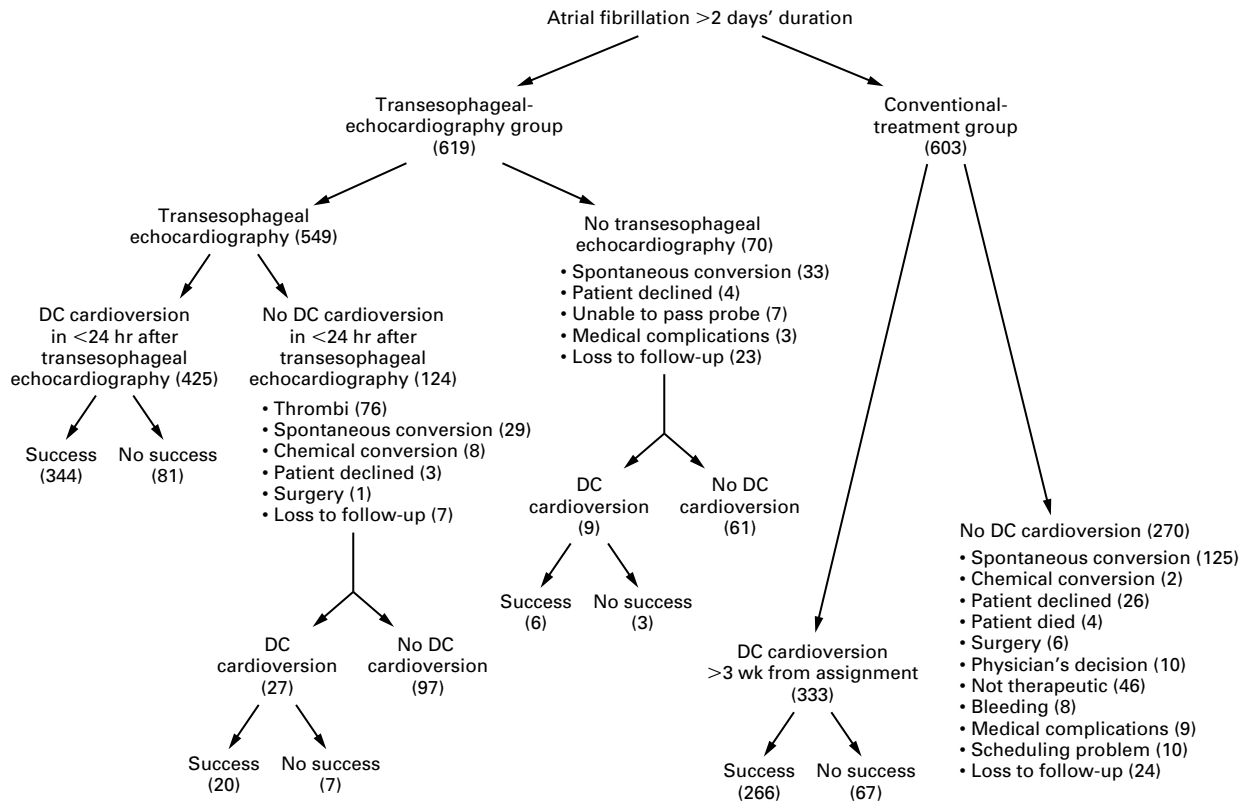
**Thrombus Revealed by Transesophageal Echocardiography**

A total of 76 patients (13.8 percent) with right or left heart thrombi were identified among the 549 patients who underwent a transesophageal echocardiographic examination. Of these 76 patients with thrombi, 67 (88.2 percent) had a thrombus in the left atrial appendage. None of the patients with thrombi had an embolic event during the eight-week study, although four of these patients died from various

causes and two others had major hemorrhagic complications. In subgroup analyses, there were no significant differences between the patients with a thrombus and those without a thrombus in the rates of embolism, hemorrhage, or death.

**Hemorrhagic Events**

The rates of major and minor hemorrhagic events are shown in Table 2. In the transesophageal-echocardiography group, there were 5 major and 14 minor hemorrhagic complications in a total of 18 patients. In contrast, in the conventional-treatment group there were 9 major and 24 minor hemorrhagic complications in 33 patients. The combined rate of major and minor hemorrhagic events was significantly lower in the transesophageal-echocardiography group than in



**Figure 2.** Treatment Outcomes.

Of a total of 1222 patients enrolled in the study, 619 were randomly assigned to a treatment strategy guided by transesophageal echocardiography with brief anticoagulation, and a total of 603 were assigned to the conventional treatment strategy with anticoagulation for three weeks before cardioversion. The extended period of anticoagulation before cardioversion in the conventional-treatment group resulted in a larger number of spontaneous conversions, greater difficulty in maintaining therapeutic anticoagulation levels, more refusals of electrical cardioversion by patients, and more scheduling difficulties. DC denotes direct current, and TEE transesophageal echocardiography. The numbers of patients are given in parentheses.

the conventional-treatment group (2.9 percent [95 percent confidence interval, 1.6 to 4.2 percent] vs. 5.5 percent [95 percent confidence interval, 3.7 to 7.3 percent],  $P=0.03$ ). A summary of the major hemorrhagic events in these patients is provided in Table 4. The mean age of patients with a major hemorrhage was  $73 \pm 8$  years. The most common site of major hemorrhage was the gastrointestinal tract.

**Deaths**

Table 2 includes the secondary end points of death from all causes, deaths from cardiac causes, and deaths from noncardiac causes in the two treatment groups. There was no statistically significant difference between the two groups in the rate of death from cardiac causes and the rate of death from noncardiac causes, but there was a trend toward a higher rate of death from all causes in the transesophageal-echocardiography group (15 deaths [2.4 percent; 95 percent confidence interval, 1.2 to 3.6 percent] vs. 6 deaths [1.0 percent; 95 percent confidence interval, 0.2 to 1.8

percent],  $P=0.06$ ). A summary of deaths of patients (adjudicated events) is provided in Table 4. Twenty of the 21 patients who died (95 percent) had coexisting conditions. Only one death (5 percent) resulted from an embolic event.

**Sinus Rhythm**

The frequency of restoration and maintenance of sinus rhythm at eight weeks in the two treatment groups is shown in Table 2. There was no significant difference between the two groups in the immediate success of electrical cardioversion (370 of 461 attempted cardioversions [80.3 percent; 95 percent confidence interval, 76.6 to 83.9 percent] in the transesophageal-echocardiography group vs. 266 of 333 attempted cardioversions [79.9 percent; 95 percent confidence interval, 75.6 to 84.2 percent] in the conventional-treatment group,  $P=0.90$ ). However, initial success in restoring sinus rhythm (through electrical, spontaneous, or chemical conversion) was achieved in a significantly higher proportion of patients in the

**TABLE 2.** CLINICAL OUTCOMES AT EIGHT WEEKS AMONG PATIENTS WITH ATRIAL FIBRILLATION OF MORE THAN TWO DAYS' DURATION IN THE TRANSESOPHAGEAL-ECHOCARDIOGRAPHY GROUP AND THE CONVENTIONAL-TREATMENT GROUP.\*

VARIABLE	TRANSESOPHAGEAL-ECHOCARDIOGRAPHY GROUP (N=619)	CONVENTIONAL-TREATMENT GROUP (N=603)	RELATIVE RISK (95% CI)	P VALUE
All embolic events — no. (%)	5 (0.8)	3 (0.5)	1.62 (0.39–6.76)	0.50
Cerebrovascular accident	4 (0.6)	2 (0.3)	1.95 (0.36–10.60)	0.43
Transient ischemic attack	1 (0.2)	1 (0.2)	0.97 (0.06–15.54)	0.99
Peripheral embolism	0	0	—	—
Hemorrhagic events — no. (%)	18 (2.9)†	33 (5.5)	0.53 (0.30–0.93)	0.03
Major	5 (0.8)	9 (1.5)	0.54 (0.18–1.61)	0.26
Minor	14 (2.3)	24 (4.0)	0.57 (0.30–1.09)	0.08
Death from all causes — no. (%)	15 (2.4)	6 (1.0)	2.44 (0.95–6.24)	0.06
Cardiac-related	8 (1.3)	4 (0.7)	1.95 (0.59–6.44)	0.27
Noncardiac-related	5 (0.8)	2 (0.3)	2.44 (0.47–12.50)	0.27
Unknown cause	2 (0.3)	0	4.87 (0.23–101.25)	0.16
Sinus rhythm — no. (%)				
Restored immediately after DC cardioversion	370/461 (80.3)	266/333 (79.9)	1.01 (0.94–1.08)	0.90
Restored within 8 wk	440 (71.1)	393 (65.2)	1.09 (1.01–1.18)	0.03
Maintained at 8-wk follow-up	326 (52.7)	304 (50.4)	1.05 (0.95–1.16)	0.43
Functional status at 8 wk — DASI score‡	27.4±18.3	26.7±18.6	—	0.50

\*CI denotes confidence interval, and DC direct current.

†One patient had both a major and a minor hemorrhagic event but was counted only once in the total.

‡The Duke Activity Status Index (DASI) is given as a mean (±SD) score.

**TABLE 3.** SUMMARY OF ADJUDICATED EMBOLIC EVENTS DURING THE EIGHT-WEEK STUDY PERIOD IN THE TRANSESOPHAGEAL-ECHOCARDIOGRAPHY GROUP AND THE CONVENTIONAL-TREATMENT GROUP.\*

TREATMENT	AGE (YR)/SEX	COEXISTING CONDITIONS AND RISK FACTORS FOR EMBOLISM	ADJUDICATED EVENT	DAYS AFTER ENROLLMENT	DC CARDIOVERSION	SPONTANEOUS CARDIOVERSION	DAYS AFTER CARDIOVERSION	RECURRENCE OF ATRIAL FIBRILLATION AFTER DC CARDIOVERSION	DEATH	ANTICOAGULATION AT TIME OF EVENT	
										WARFARIN (INR)	HEPARIN (PTT)
TEE	70/M	HTN, DM, SEC	CVA	2	Yes	No	1	Yes	No	Yes (1.9)	Yes (58)
TEE	77/F	SEC	CVA	5	Yes	No	5	Yes	No	Yes (1.7)	No
TEE	73/M	HTN, cancer, SEC	CVA	28	Yes	No	26	Yes	No	No	No
TEE	58/M	HTN, complex AP	CVA	55	Yes	No	52	No	No	No	No
TEE	65/M	HTN, LVEF <40%, complex AP, SEC	TIA	16	No	Yes	16	NA	No	Yes (2.5)	No
Conventional	65/F	None	CVA	12	Yes	No	6	No	No	Yes (2.4)	No
Conventional	68/F	HTN, DM, LVEF <40%	CVA	20	No	No	NA	NA	Yes	Yes (2.7)	No
Conventional	57/M	HTN, DCM, LVEF <40%	TIA	7	No	No	NA	NA	No	Yes (2.7)	No

\*TEE denotes transesophageal echocardiography, DC direct current, INR international normalized ratio, PTT partial-thromboplastin time (in seconds), HTN hypertension, DM diabetes mellitus, SEC smoke-like echoes on transesophageal echocardiography, CVA cerebrovascular accident, AP aortic plaque, LVEF left ventricular ejection fraction, TIA transient ischemic attack, NA not applicable, and DCM dilated cardiomyopathy.

transesophageal-echocardiography group during the eight-week study period (440 patients [71.1 percent; 95 percent confidence interval, 67.5 to 74.7 percent] vs. 393 patients [65.2 percent; 95 percent confidence interval, 61.4 to 68.9 percent],  $P=0.03$ ). At eight weeks there was no significant difference between the two groups in the proportion of patients in whom normal sinus rhythm had been maintained (52.7 percent [95 percent confidence interval, 46.4 to 54.4 percent] in the transesophageal-echocardiography group vs. 50.4 percent [95 percent confidence interval, 48.7 to 56.6 percent] in the conventional-treatment group,  $P=0.43$ ) (Table 2). There was, however, greater use of antiarrhythmic medication in the conventional-treatment group at the time of cardioversion (92.8 percent [95 percent confidence interval, 90.0 to 95.5 percent] vs. 82.2 percent [95 percent confidence interval, 78.7 to 85.7 percent],  $P<0.001$ ) (Table 1).

#### Atrial Flutter versus Atrial Fibrillation

There were no significant differences between the base-line characteristics or the embolic or hemorrhagic outcomes of patients with atrial flutter and a history of atrial fibrillation and those of patients with atrial fibrillation. There were also no significant differences between the two treatment groups in the proportion of patients with atrial flutter. However, as a subgroup, the 58 patients with atrial flutter (4.7 percent of the total study cohort) had a significantly higher rate of initial success of cardioversion than did the patients with atrial fibrillation (39 of 41 attempted cardioversions [95.1 percent] vs. 593 of 753 attempted cardioversions [78.8 percent],  $P=0.01$ ), as well as a higher rate of maintenance of sinus rhythm at eight weeks (41 of 53 patients with complete follow-up data [77.4 percent] vs. 584 of 1054 [55.4 percent],  $P=0.002$ ).

#### Functional Capacity

Table 1 shows the base-line functional status as assessed by the Duke Activity Status Index: mean ( $\pm$ SD) scores of  $28.2\pm 17.4$  for the patients in the transesophageal-echocardiography group and  $27.9\pm 17.8$  for those in the conventional-treatment group. At eight weeks, the mean Duke Activity Status Index Score was  $27.4\pm 18.3$  in the transesophageal-echocardiography group and  $26.7\pm 18.6$  in the conventional-treatment group (Table 2). These data indicate that there was no significant difference in either treatment group between the functional status of the patients at base line and that at eight weeks, and there was no significant difference between the two groups in functional status at eight weeks.

### DISCUSSION

We found that during the eight weeks of the study, there was no significant difference between the two treatment groups in the rate of embolic events. However, the strategy of treatment guided by transesoph-

ageal echocardiography did allow for early, safe electrical cardioversion and resulted in fewer total hemorrhagic events than the conventional treatment strategy.

The three-week period of therapeutic anticoagulation required before cardioversion is a drawback of the conventional treatment strategy.<sup>16,24</sup> The interval between enrollment and electrical cardioversion was much shorter in the transesophageal-echocardiography group than in the conventional-treatment group (3 days vs. 31 days). The longer duration of anticoagulant therapy before cardioversion with the conventional treatment strategy resulted in a larger number of spontaneous conversions but also in greater difficulty in maintaining anticoagulation at therapeutic levels and more scheduling difficulties and refusals by patients to undergo electrical cardioversion (Fig. 2).

The rate of embolism in the trial was much lower in both treatment groups than had been anticipated<sup>20</sup> (0.7 percent overall), and there was no significant difference between the groups in the rate of cerebrovascular events. This study demonstrates that both treatment strategies are successful in maintaining low rates of embolism when guidelines are followed carefully. In particular, it demonstrates the importance of maintaining therapeutic anticoagulation in the period after cardioversion even if there is no evidence of thrombus on transesophageal echocardiography.<sup>25,26</sup>

The conventional strategy for anticoagulation, as outlined by the American College of Chest Physicians,<sup>10</sup> has not been carefully studied in clinical trials. Furthermore, in clinical practice, conventional guidelines for anticoagulation are not routinely followed in as many as 40 percent of the patients undergoing cardioversion, particularly elderly patients.<sup>27,28</sup> In the transesophageal-echocardiography group, prolonged anticoagulant therapy was limited to the 76 patients with thrombi, which were detected most often in the left atrial appendage. The rate of detection of thrombus in our study, 13.8 percent, is consistent with the rates of 9 to 15 percent reported previously.<sup>14,16,18</sup>

The aggregate rate of hemorrhage among patients in both treatment groups in this trial was 4.2 percent, which was higher than had been anticipated.<sup>20</sup> There were nearly twice as many major and minor hemorrhagic events in the conventional-treatment group as in the transesophageal-echocardiography group over the eight-week period. The fact that the hemorrhagic events in our study were predominantly minor is in accordance with the results of other studies.<sup>16,24,29</sup> The difference between the treatment groups in the rates of hemorrhagic events is not surprising, since the duration of anticoagulant therapy required by the conventional strategy is almost double that with the other approach and thus allows more opportunity for bleeding.<sup>10,16,29,30</sup>

There was a trend toward a higher rate of death from any cause in the transesophageal-echocardiography group. However, there was no significant dif-

**TABLE 4. SUMMARY OF MAJOR BLEEDING EVENTS AND DEATHS AS SECONDARY END POINTS DURING THE EIGHT-WEEK STUDY PERIOD IN THE TRANSSESOPHAGEAL-ECHOCARDIOGRAPHY AND CONVENTIONAL-TREATMENT GROUPS.\***

TREATMENT GROUP	ADJUDICATED EVENT (TYPE)	AGE (YR)/SEX	NYHA CLASS III OR IV	DAYS AFTER ENROLLMENT	THROMBUS ON ECHOCARDIOGRAPHY	DC CARDIOVERSION PERFORMED	COEXISTING CONDITIONS	MEDICATIONS AT TIME OF EVENT	
								WARFARIN (INR)	HEPARIN (PTT)
TEE	Major hemorrhage (pulmonary)	78/M	No	1	No	No	CHF, TB, COPD	Yes (1.3)	Yes (53.7)
TEE	Major hemorrhage (gastrointestinal)	73/M	No	4	No	Yes	Cancer	Yes (3.9)	No
TEE	Major hemorrhage (gastrointestinal)	77/F	No	9	No	No	Diabetes, COPD, orthopedic surgery	Yes (2.4)	Yes (25.3)
TEE	Major hemorrhage (gastrointestinal)	85/M	No	22	Yes	No	HTN, pneumonia	Yes (3.8)	No
TEE	Major hemorrhage (vascular)	72/M	No	30	Yes	No	CAD, CHF, cardiac surgery	No	Yes (48.0)
Conventional	Major hemorrhage (gastrointestinal)	75/M	No	8	—	No	CAD, peptic ulcer	Yes (5.2)	No
Conventional	Major hemorrhage (gastrointestinal)	71/F	Yes	12	—	No	Diabetes, DCM	Yes (4.6)	No
Conventional	Major hemorrhage (gastrointestinal)	61/M	No	13	—	No	None	Yes (5.2)	No
Conventional	Major hemorrhage (gastrointestinal)	60/F	No	16	—	No	Diabetes, peptic ulcer	Yes (3.0)	No
Conventional	Major hemorrhage (gastrointestinal)	69/M	No	21	—	No	None	Yes (12.0)	No
Conventional	Major hemorrhage (gastrointestinal)	86/M	Yes	30	—	No	CHF, previous CVA, renal failure	Yes (1.0)	No
Conventional	Major hemorrhage (gastrointestinal)	67/M	Yes	37	—	Yes	CHF, hyperthyroidism	No	No
Conventional	Major hemorrhage (pleural)	83/M	No	40	—	Yes	None	Yes (4.3)	No
Conventional	Major hemorrhage (pericardium)	70/M	Yes	50	—	Yes	Cardiac surgery	Yes (3.8)	No
ANTIARRHYTHMIC AGENTS (CLASS)									
TEE	Death from cardiac causes (sudden)	33/M	Yes	4	Yes	No	Acute CHF, DCM	No	No
TEE	Death from cardiac causes (sudden)	72/M	Yes	8	No	Yes	CAD	No	Yes
TEE	Death from cardiac causes (sudden)	68/M	Yes	11	Yes	No	CAD, DCM	No	No
TEE	Death from cardiac causes (sudden)	74/M	No	25	No	Yes	Diabetes, acute renal failure	No	No
TEE	Death from cardiac causes (CHF)	80/F	Yes	30	No	Yes	DCM, CHF	Yes (III)	Yes
TEE	Death from cardiac causes (CHF)	85/F	Yes	36	No	Yes	SSS, CHF	Yes (II, IV)	Yes
TEE	Death from cardiac causes (sudden)	63/F	Yes	36	No	Yes	DCM	No	No
TEE	Death from cardiac causes (sudden)	89/F	Yes	37	Yes	No	CAD	Yes (IV)	Yes
TEE	Death from noncardiac causes (CNS)	77/F	No	13	No	No	Diabetes, COPD, meningitis, orthopedic surgery	No	No
TEE	Death from noncardiac causes (respiratory)	78/M	No	15	No	Spontaneous	ARDS, acute renal failure	No	No
TEE	Death from noncardiac causes (sepsis)	33/M	No	33	No	Yes	MOF, pneumonia, cardiac surgery	Yes (III)	Yes
TEE	Death from noncardiac causes (sepsis)	83/M	No	41	No	Yes	Pneumonia, acute peritonitis	Yes (I)	No
TEE	Death from noncardiac causes (respiratory)	69/M	No	47	No	Yes	Cancer, ARDS	Yes (IV)	Yes
TEE	Death (unknown cause)	76/F	No	3	No	Yes	CAD	Yes (II)	No
TEE	Death (unknown cause)	60/F	Yes	6	Yes	No	Previous CVA	No	Yes

TABLE 4. CONTINUED.

TREATMENT GROUP	ADJUDICATED EVENT (TYPE)	AGE (YR)/SEX	NYHA CLASS III OR IV	DAYS AFTER ENROLLMENT	THROMBUS ON ECHOCARDIOGRAPHY	DC CARDOVERSION PERFORMED	COEXISTING CONDITIONS	WARFARIN (INR)	HEPARIN (PTT)
Conventional	Death from cardiac causes (CHF)	73/M	Yes	26	—	Yes	SSS, CHF	Yes (III)	No
Conventional	Death from cardiac causes (sudden)	70/M	No	38	—	No	None	Yes (I)	No
Conventional	Death from cardiac causes (CHF)	53/F	Yes	48	—	No	RCM, CHF	No	No
Conventional	Death from cardiac causes (sudden)	75/M	Yes	52	—	Yes	Acute CHF	Yes (II)	Yes
Conventional	Death from noncardiac causes (CVA, herniation)	68/F	Yes	23	—	No	Diabetes, acute CHF	Yes (II)	Yes
Conventional	Death from noncardiac causes (renal)	82/M	Yes	34	—	No	Pneumonia, cancer	No	No

\*TEE denotes transesophageal echocardiography, NYHA New York Heart Association, DC direct current, INR international normalized ratio, PTT partial-thromboplastin time (in seconds), CHF congestive heart failure, TB tuberculosis, COPD chronic obstructive pulmonary disease, HTN hypertension, CAD coronary artery disease, DCM dilated cardiomyopathy, CVA cerebrovascular accident, SSS sick sinus syndrome, ARDS acute respiratory distress syndrome, MOF multiorgan failure, and RCM restrictive cardiomyopathy.

ference between the groups in the rate of death from cardiac causes. Ninety-five percent of the patients in both groups who died had serious coexisting conditions. On the basis of experimental studies of atrial fibrillation,<sup>31,32</sup> some investigators have postulated that the strategy of treatment guided by transesophageal echocardiography may improve the ability to restore and maintain sinus rhythm with earlier cardioversion and after a shorter duration of atrial fibrillation.<sup>20,33</sup> There was a greater overall rate of success in achieving sinus rhythm in the transesophageal-echocardiography group, but at eight weeks there was no significant difference between the groups in the maintenance of sinus rhythm. It is not known whether the greater use of antiarrhythmic medication in the conventional-treatment group had an effect on the relative rates of maintenance of sinus rhythm.

Several studies in the 1990s suggested that the strategy of using transesophageal echocardiography to guide anticoagulant therapy for atrial fibrillation might be both feasible and safe. In more than 1300 patients previously studied by North American and European investigators, there was only 1 documented embolic event in cases involving treatment guided by transesophageal echocardiography with short-term anticoagulant therapy.<sup>14-16,18,34,35</sup>

Both treatment strategies in our study resulted in low rates of embolism. The strategy of treatment guided by transesophageal echocardiography was associated with an overall reduction in the time to cardioversion and in the total rate of hemorrhagic complications, as compared with the conventional treatment strategy. Thus, the strategy of using transesophageal echocardiography to guide treatment may be considered a safe and clinically effective alternative to the conventional treatment strategy.

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APPENDIX

The following centers and investigators participated in the trial (the number of patients enrolled at each center is given in parentheses): University of Louisville (110) — M. Stoddard; Cleveland Clinic Foundation (104) — A. Klein; Centro Medico de Caracas (53) — H. Acquatella; Winthrop-University Hospital (51) — R. Smith; University of Nebraska (50) — T. Porter; Escorts Heart Institute and Research Centre (50) — N. Trehan; Lancaster Heart Foundation (44) — R. Small; Paulista School of Medicine (44) — W. Mathias, Jr.; Universitätsklinikum-Essen (37) — R. Erbel; University of Pittsburgh Medical Center (29) — W. Katz; Vera Cruz and Socor Hospitals (28) — M. Barbosa; St. Elizabeth Hospital Tilburg (25) — P. Melman, H. Pasteuning; El-Azhar University (25) — M. Madkour; University of Massachusetts (24) — L. Pape; Instituto Cardiovascular de Rosario (24) — E. Tuero; Ospedale Civile (21) — D. Mele; University of California, San Diego, Medical Center (19) — D. Blanchard; University of Rochester-Strong Memorial Hospital (18) — J. Eichelberger; Riverside Methodist Hospital (18) — T. Obarski; University of California, San Francisco, Medical Center (17) — R. Redberg; Queen Elizabeth Hospital (17)

— S. Li; Heart Group (16) — P. Fattal; New England Medical Center (15) — S. Schwartz; University of Cincinnati (14) — B. Hoit; North Shore University Hospital (14) — S. Rosen; St. Luke's-Roosevelt Hospital (14) — N. Krasnow; Central Minnesota Heart Center (14) — R. Jolkovsky; White River Junction Veterans Affairs Medical Center (14) — M. Garcia; Bronx Veterans Affairs Medical Center (13) — L. Baruch; Medical College of Virginia (13) — J. Arrowood; University of Texas Southwestern Medical Center (13) — P. Grayburn; Harbor-UCLA Medical Center (13) — S. Shapiro; Hospital dos Servidores do Estado (13) — J. Filho, M. Carneiro; MacNeal Center for Clinical Research (13) — J. Briller; St. John's Mercy Medical Center (12) — L. Mezei; University of Chicago Medical Center (11) — R. Lang; Manly Hospital (11) — I. Black; St. Nicholas Hospital (10) — L. Coulis; Loma Linda Veterans Affairs Medical Center (10) — R. Pai; Easton Hospital (10) — K. Khalighi; Green Lane Hospital (10) — S. Greaves; Prince Henry Hospital (10) — W. Walsh; Baylor College of Medicine (9) — M. Quinones; North Central Heart Foundation (9) — D. Nagelhout; Ospedale Generale Valduce (9) — G. Corrado; Texas Heart Institute (8) — S. Wilansky; Royal Victoria Hospital (7) — R. Haichin; Columbia Cardiovascular Clinic (7) — B. Feldman; Austin Heart (7) — G. Rodgers; University of New Mexico (7) — B. Shively; Ohio State University (6) — D. Orsinelli; Medical College of Wisconsin (6) — K. Sagar; Sentara Norfolk General Hospital (6) — G. Nye; Southern New Hampshire Regional Medical Center (6) — S. Schwartz; Ochsner Medical Institutions (6) — F. Abi-Samra; Blodgett Memorial Medical Center (6) — D. Langholz; Clearwater Cardiovascular Consultants (6) — P. Phillips; Hungarian Institute of Cardiology (5) — M. Lengyel; Hartford Hospital (5) — L. Gillam; Allegheny University-Hahnemann Hospital (5) — P. Pollack; Beth Israel Hospital (4) — W. Manning; Boston Medical Center (4) — R. Davidoff; Graduate Hospital (4) — R. Schlesinger; East Carolina University (4) — V. Sorrell; Michigan Capital Medical Center (4) — M. Markarian; Albany Medical College (4) — S. Fein; University of Texas Medical Branch at Galveston (3) — R. Sheahan; Maine Medical Center (2) — M. Cohen; University of Kansas Medical Center (1) — D. Wilson; Northwest Ohio Cardiology (1) — B. DeVries.

**Clinical Coordinating Center** — A. Klein (principal investigator), R. Grimm, R.D. Murray, D. Leung, M. Garcia, M. Chung. **Study Monitoring** — S. Jasper, A. Goodman. **Data Management** — K. Arheart, D. Miller, C. Apperson-Hansen, E. Lieber. **Data and Safety Monitoring Board** — S. Ellis (chair), P. Elson, J. Olin. **Adverse Events Adjudication Committee** — A. Furlan, M. Lauer. **Economic Analysis Center** — Emory University; E. Becker, S. Culler, P. Mauldin. **Steering and Publications Committee** — A. Klein (chair), C. Apperson-Hansen, R. Asinger, I. Black, R. Davidoff, R. Erbel, R. Grimm, J. Halperin, R.D. Murray, D. Orsinelli, T. Porter, M. Stoddard.

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