Role of Transesophageal Echocardiography-Guided Cardioversion of Patients With Atrial Fibrillation

Allan L. Klein, MD, FACC, R. Daniel Murray, PhD, Richard A. Grimm, DO, FACC

Cleveland, Ohio

Electrical cardioversion of patients with atrial fibrillation (AF) is frequently performed to relieve symptoms and improve cardiac performance. Patients undergoing cardioversion are treated conventionally with therapeutic anticoagulation for three weeks before and four weeks after cardioversion to decrease the risk of thromboembolism. A transesophageal echocardiography (TEE)-guided strategy has been proposed as an alternative that may lower stroke and bleeding events. Patients without atrial cavity thrombus or atrial appendage thrombus by TEE are cardioverted on achievement of therapeutic anticoagulation, whereas cardioversion is delayed in higher risk patients with thrombus. The aim of this review is to discuss the issues and controversies associated with the management of patients with AF undergoing cardioversion. We provide an overview of the TEE-guided and conventional anticoagulation strategies in light of the recently completed Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) clinical trial. The two management strategies comparably lower the patient's embolic risk when the guidelines are properly followed. The TEE-guided strategy with shorter term anticoagulation may lower the incidence of bleeding complications and safely expedite early cardioversion. The inherent advantages and disadvantages of both strategies are presented. The TEE-guided approach with short-term anticoagulation is considered to be a safe and clinically effective alternative to the conventional approach, and it is advocated in patients in whom earlier cardioversion would be clinically beneficial. (J Am Coll Cardiol 2001;37:691–704) © 2001 by the American College of Cardiology

Electrical cardioversion of patients with atrial fibrillation (AF) to normal sinus rhythm is frequently performed to relieve symptoms, improve cardiac performance and possibly decrease cardioembolic risk. However, the electrical cardioversion procedure itself has an inherent risk of stroke due to possible embolization of pre-existing thrombus in the left atrial appendage (1). Patients undergoing electrical cardioversion are conventionally treated with therapeutic anticoagulation for seven weeks. Transesophageal echocardiography (TEE) has been proposed as an alternative to guide anticoagulation management for patients with AF undergoing electrical cardioversion (3,4). The lack of sound clinical trial data on stroke rates, bleeding risk and healthcare economics in randomized studies has fueled the confusion and controversy on the relative merits of the two strategies.

Since the early 1990s, the TEE-guided approach with short-term anticoagulation was suggested to have several potential advantages over the conventional management of seven weeks of anticoagulation. First, TEE should be able to detect left atrial appendage thrombi that are presumably responsible for embolic stroke after electrical cardioversion. Thus, sparing patients with thrombi from cardioversion may reduce the incidence of embolic events. Second, in the majority of patients without left atrial appendage thrombi, earlier cardioversion may shorten the period of anticoagulation and lower the corresponding risk of bleeding complications. The cost savings from lowered embolic and bleeding rates with earlier cardioversion for patients without thrombi may offset the cost of the TEE-guided strategy. Finally, it was postulated that earlier cardioversion may increase the likelihood of a successful return to and maintenance of sinus rhythm.

In contrast, some investigators have pointed to the potential disadvantages of the TEE-guided strategy (5–8). They maintain that the clinical efficacy of TEE-guided management has not been clearly demonstrated and the cost is not justified in the absence of efficacy data. Defenders of conventional management further argue that small thrombi can be missed by TEE, the TEE examination is labor intensive and the expertise needed to detect thrombi may not be suitable for community hospitals.

The two competing management strategies have prompted written debate on the relative merits of the approaches (6,9). Likewise, recent national cardiology meetings have featured oral debates addressing the controversy (10–12).
Atrial fibrillation and stroke. Approaches, as well as the preliminary results of the recently patients with AF. We present the advantages and disadvantages associated with the anticoagulation management of patients with AF undergoing cardioversion. We discuss the basic mechanisms of stroke after electrical cardioversion for patients with AF. We present the advantages and disadvantages of the conventional and TEE-guided anticoagulation approaches, as well as the preliminary results of the recently completed ACUTE trial. General recommendations based on the prevailing data are presented to guide the clinician in the management of these patients.

Atrial fibrillation and stroke. Atrial fibrillation is the most common sustained arrhythmia encountered in clinical practice, with an overall prevalence of 0.4% in the general population (13,17–19), affecting 2.2 million Americans (18,20). The prevalence of AF increases markedly with advancing age, affecting 0.2% of the population 25 to 34 years old, 2% to 5% of those 60 years and 10% of those 80 years (18,19,21–23). The percentage of the population that is elderly is expected to rise over the next few decades, thus causing an increased burden of diseases related to AF (24,25).

One of the most important sequelae of AF is its association with thromboembolic disease and stroke. A four- to sixfold increase (15-fold with a history of rheumatic heart disease) makes AF one of the most potent risk factors for stroke in the elderly and the most common cause of embolic stroke (19,26–29). The Framingham Heart Study and AF trials showed an annual stroke rate of 4.2% and 4.5% per year, respectively (29–31). The risk of stroke in nonvalvular AF varies with age, beginning at a rate of 1.5% in the sixth decade and increasing two- to threefold with each increasing decade, reaching 24% in the ninth decade (30). Most strokes associated with AF are presumed to be from thrombi formed in the fibrillating left atrial appendage (32,33). Atrial fibrillation has also been associated with a twofold increase in both total and cardiovascular mortality (19). In addition, the morbidity of AF appears to be substantial (34,35). The consequences of AF include a decreased functional capacity as a result of palpitations, fatigue, dyspnea or signs of myocardial ischemia; congestive heart failure; pulmonary edema; or hypotension. Functional capacity decreases in those patients in whom normal sinus rhythm cannot be restored (34,35). The rapid ventricular rates of AF may also impair ventricular function (36,37). Furthermore, continued AF causes mechanical and electrical remodeling. This remodeling may result in an increased propensity for continuing or recurring AF (38).

Nonvalvular AF is responsible for >75,000 strokes annually in the U.S. (28,39). Patients with AF spent an estimated average of five days in the hospital, at a cost of $4,800, which represents a total annual cost of $1 billion (40). Therefore, AF has an enormous impact in the U.S. by increasing not only the incidence of stroke and mortality, but also medical costs, including acute hospital payments and total-care payments (24).

Cardioversion and stroke. Since 1962, direct current (DC) cardioversion has been used to restore sinus rhythm in patients with AF (41). Unfortunately, electrical cardioversion has a risk of clinical thromboembolism that ranges from 0% to 5.6% (without anticoagulation), usually in the first week after the procedure (42–67). Table 1 lists the major studies of embolic events (since the 1960s) grouped by either electrical or chemical cardioversion. A summary of these studies suggests that there is little difference in the embolic risk between electrical and chemical cardioversions (1.4 ± 1.3% vs. 1.2 ± 1.0%).

A period of empiric anticoagulation before DC cardioversion may lower the risk of embolism, as shown in 1969 (60), but because there are few prospective studies (4), the exact rate of embolism is unknown. Notably, the 5.6% risk of stroke in the week after cardioversion in nonanticoagulated patients is similar to the yearly incidence for patients with chronic nonvalvular AF. Thus, cardioversion increases or concentrates the embolic risk of AF by perhaps 50-fold during the week after the procedure.

Conventional anticoagulant strategy. Over the past decade, the ACCP recommended guidelines for managing anticoagulation around the time of cardioversion for AF (2,26,68). These guidelines constitute current conventional therapy and strongly recommend that all patients with AF for more than two days be treated with warfarin for three weeks before and continued until sinus rhythm has been maintained for four weeks after cardioversion. Since 1992, there has been little change in the guidelines, except that the TEE-guided approach may be used in selected circumstances (2).

The rationale for conventional management is based on
nonrandomized studies showing the efficacy of empiric anticoagulation in patients undergoing electrical cardioversion. The rationale for the three weeks of anticoagulation before electrical cardioversion is based on a study suggesting that at least 14 days are needed for fibroblastic infiltration and stabilization of a thrombus in the left atrial appendage (43). The four weeks of anticoagulation after cardioversion is supported by a Doppler echocardiographic study showing that the transmitral atrial (A) wave does not return to normal until three to four weeks after electrical cardioversion (69) and for the recurrence of AF (13).

Table 2 outlines the advantages and disadvantages of the conventional anticoagulation approach. The major advantage for the conventional strategy is that it is relatively easy to administer and especially suitable for community hospitals (13). The clinician is not dependent on the availability of multiplane TEE probes and level III personnel well trained in performing TEE (11). Finally, when done cor-

### Table 1. Reported Incidences of Embolic Events After Electrical and Chemical Cardioversion From Atrial Fibrillation

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference Number</th>
<th>n</th>
<th>AC Rx</th>
<th>Percent Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrical cardioversion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lown (1963)</td>
<td>44</td>
<td>50</td>
<td>Some</td>
<td>1.7</td>
</tr>
<tr>
<td>Killip (1963)</td>
<td>45</td>
<td>62</td>
<td>In</td>
<td>0.0</td>
</tr>
<tr>
<td>Morris (1964)</td>
<td>48</td>
<td>70</td>
<td>In</td>
<td>0.0</td>
</tr>
<tr>
<td>Oram (1964)</td>
<td>49</td>
<td>100</td>
<td>Some</td>
<td>1.9</td>
</tr>
<tr>
<td>Hurst (1964)</td>
<td>50</td>
<td>121</td>
<td>No</td>
<td>1.3</td>
</tr>
<tr>
<td>Morris (1966)</td>
<td>51</td>
<td>108</td>
<td>Some</td>
<td>2.5</td>
</tr>
<tr>
<td>Korsgren (1965)</td>
<td>52</td>
<td>138</td>
<td>Yes</td>
<td>0.0</td>
</tr>
<tr>
<td>Halmoes (1966)</td>
<td>53</td>
<td>175</td>
<td>No</td>
<td>0.4</td>
</tr>
<tr>
<td>Selzer (1966)</td>
<td>54</td>
<td>189</td>
<td>No</td>
<td>2.1</td>
</tr>
<tr>
<td>Lown (1967)</td>
<td>55</td>
<td>350</td>
<td>In</td>
<td>0.9</td>
</tr>
<tr>
<td>Resnekev (1967)</td>
<td>56</td>
<td>204</td>
<td>Some</td>
<td>0.6</td>
</tr>
<tr>
<td>Hall (1968)</td>
<td>57</td>
<td>142</td>
<td>In</td>
<td>0.8</td>
</tr>
<tr>
<td>Radford (1968)</td>
<td>58</td>
<td>156</td>
<td>In</td>
<td>0.0</td>
</tr>
<tr>
<td>Aberg (1968)</td>
<td>59</td>
<td>207</td>
<td>Most</td>
<td>0.7</td>
</tr>
<tr>
<td>Bjerkelund (1969)</td>
<td>60</td>
<td>437</td>
<td>Yes</td>
<td>1.1</td>
</tr>
<tr>
<td>McCarthy (1969)</td>
<td>61</td>
<td>149</td>
<td>Some</td>
<td>1.6</td>
</tr>
<tr>
<td>Henry (1976)</td>
<td>62</td>
<td>37</td>
<td>Some</td>
<td>5.6</td>
</tr>
<tr>
<td>Roy (1986)</td>
<td>63</td>
<td>152</td>
<td>In</td>
<td>1.3</td>
</tr>
<tr>
<td>Arnold (1992)</td>
<td>64</td>
<td>454</td>
<td>Most</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*Mean value ± SD.
AC = anticoagulation; Rx = treatment.

### Table 2. Advantages and Disadvantages of the Conventional Approach to Cardioversion of Patients With Atrial Fibrillation

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of warfarin for 3 to 4 weeks before cardioversion may lower the stroke rate from 5.6% to a very low stroke rate of &lt; 2% (5,60,64,70).</td>
<td>Delaying cardioversion to normal sinus rhythm for 3 to 4 weeks potentially decreases functional capacity (34,35).</td>
</tr>
<tr>
<td>Relatively easy to administer with regular monitoring of INRs (7,13).</td>
<td>Prolonging treatment for 7 to 8 weeks increases the risk of bleeding complications (16,26,30,70–72).</td>
</tr>
<tr>
<td>Suitable for community hospitals (7,13).</td>
<td>Not followed by routine clinical practice, especially in the elderly (65,73).</td>
</tr>
<tr>
<td>The conventional approach has withstood the “test of time” since the 1960s.</td>
<td>Patients who are at the highest risk for developing systemic embolization who should receive more prolonged or intensive anticoagulation are not routinely identified (1,74).</td>
</tr>
</tbody>
</table>

INR = international normalized ratio.
rectly (target international normalized ratio [INR] 2 to 3), conventional management has "stood the test of time," with low stroke rates since the 1960s.

Unfortunately, the conventional strategy also has limitations (Table 2). There have never been any controlled studies showing its efficacy (13,14,26,40,60,64). Furthermore, anticoagulation guidelines are poorly followed in routine clinical practice, especially in the elderly (64,65,70).

Delaying cardioversion to normal sinus rhythm for three to four weeks may have a number of important sequelae. Time may decrease the likelihood of successful cardioversion and maintenance of normal sinus rhythm. Owing to an ongoing atrial remodeling process, the return of atrial function is inversely related to the duration of the atrial arrhythmia, or "atrial fibrillation begets atrial fibrillation" (38). In one study, patients with AF for less than two weeks before cardioversion had a return of atrial function within 24 h, as compared with patients with AF for more than six weeks, who had a delay in the return of atrial function up to three weeks. An intermediate group with AF of two to six weeks needed one week for atrial function to return (71,72).

Thus, the conventional management of anticoagulation necessitates a delay in the return of atrial function and increases the risk of postcardioversion thrombus formation.

Prolonging warfarin treatment for a total of seven to eight weeks increases the risk of major and minor bleeding complications (4,16,26,30,73–77). The period of anticoagulation in conventional management almost doubles the total duration of systemic anticoagulation, thus exposing the patient to potentially greater bleeding complications. In fact, cardioversion patients may be at an increased risk, particularly during the second month of anticoagulation (73). The major nemesis of the conventional strategy is the need for three weeks of therapeutic anticoagulation before cardioversion and the need to "reset the three-week time clock" because of sub-therapeutic anticoagulation or when a bleeding complication occurs. In fact, more than 20% of conventional patients may never make it to electrical cardioversion while waiting the three weeks (4,16).

Major bleeding complications related to cardioversion have been reported in 1% to 2% of patients, whereas minor bleeding has been reported in 6% to 18% of patients (4,16,72,73). These complications result in the physician reducing the level of therapeutic anticoagulation (INR 2 to 3), thus resetting the time clock of three weeks before cardioversion or even stopping anticoagulation. A recent study noted that the anticoagulation ACCP guidelines are not followed, especially in elderly patients (>65 years old) with AF undergoing cardioversion, because of the perceived fear of the increased risk of bleeding complications (65). Thus, elderly patients may especially benefit from a TEE-guided approach to cardioversion with brief anticoagulation.

Furthermore, those patients who are at high risk (i.e., those with left atrial cavity thrombi or left atrial appendage thrombi) who should receive more prolonged or intensive anticoagulation are not routinely identified before undergoing the procedure (1,78).

Role of TEE in detection of thrombus. Transesophageal echocardiography is considered the procedure of choice for detecting left atrial appendage and left atrial cavity thrombi (79–81) (Fig. 1). Therefore, TEE-guided cardioversion was initially proposed as an earlier and safer alternative approach to the conventional therapy of seven weeks of anticoagulation (1,78,82).

Transesophageal echocardiography using monoplane, biplane or multiplane imaging can detect thrombi in both the left atrium and left atrial appendage, with a high degree of sensitivity and a specificity varying from 93% to 100% (72,81,83–88). In contrast, the less invasive transthoracic echocardiography has not been shown to be effective in identifying left atrial cavity or left atrial appendage thrombi (73,89). In addition, TEE is uniquely suited to observe spontaneous echocardiographic contrast, which is considered to be a substrate for thrombus formation (90–92) and systemic embolization (93–95). The safety profile of TEE has been well documented: major complication rates are <0.02% (96,97). Therefore, many investigators have suggested that patients with AF who require cardioversion can be screened effectively for thrombus before undergoing cardioversion. This technique may also be used to serially monitor the resolution of thrombus in the 10% to 15% of patients who had left atrial thrombus on the initial TEE (81). Recently, TEE has been used to evaluate the embolic risk potential in high and low risk patients with AF (98–102).
Use of TEE does not obviate the use of anticoagulation in cardioversion. The initial studies that used TEE in patients undergoing electrical cardioversion attempted to demonstrate that if thrombi could be excluded, anticoagulation before and after the procedure would not be necessary (33,103). The rationale for this earlier TEE strategy was based on the notion that the only potential source of thromboembolism was a pre-existing cardiac thrombus that may embolize after successful cardioversion (43).

In subsequent investigations, TEE was used to assess the events surrounding cardioversion (the presumed precipitating event for thromboembolism) by performing TEE both immediately before and after the procedure (104,105). Interestingly, left atrial appendage function declined and spontaneous echocardiographic contrast increased (it developed or intensified in 35% of patients) from before to after cardioversion (104) (Fig. 2). In fact, Stoddard et al. (106) demonstrated in one patient that thrombi can indeed form in the postcardioversion period. This deterioration of function may be independent of the mode of cardioversion employed, and postconversion dysfunction may occur with spontaneous (107), pharmacologic (108) or internal cardioversion (109). A recent study suggested that thrombogenic potential may be influenced by the duration of AF, with brief-duration AF showing only minimal atrial stunning (110). These findings suggested that a thrombogenic milieu is created as a result of the cardioversion from AF (to a lesser degree in atrial flutter [111]) to sinus rhythm and implied that thromboembolic events can occur in the absence of an existing or precardioversion thrombus.

Black et al. (112) compiled a series of 17 cases of thromboembolic events occurring after a negative TEE study for thrombus. All 17 of these patients had events relatively soon after cardioversion, and all were subtherapeutically anticoagulated. At the time of the embolic event, three patients had AF for less than seven days. This series dispelled many beliefs, including: 1) TEE can preclude the need for anticoagulation; 2) events occur primarily in patients with long-duration AF; and 3) all events occur secondary to existing thrombi. The study gave credence to the alternative mechanism for thrombogenesis and embolism after cardioversion and cast doubt on the ability of TEE to obviate the need for anticoagulation after cardioversion. A recent review of pooled studies from the published data showed that embolic events were more common using TEE without anticoagulation as compared with anticoagulation (5). These data suggest the need to anticoagulate all patients with AF of more than two days duration, including patients with a negative TEE for thrombus. From these important seminal studies, it can be concluded that the role of TEE is to enable early cardioversion without prolonged precardioversion anticoagulation in low risk patients and to identify high risk patients with thrombi in whom cardioversion should be postponed.

TEE-guided cardioversion with short-term anticoagulation. Given the current understanding of the mechanisms involved in thrombogenesis and embolism after cardioversion of AF, many investigators have argued that using both TEE and short-term anticoagulation could be the most clinically rational, convenient and possibly cost-effective strategy (1,78,101). The theoretic basis for this strategy addresses both potential thromboembolic mechanisms, including the existing thrombus in the left atrium or atrial appendage, and the second mechanism, which involves an increased potential for thrombogenesis secondary to diminished left atrial appendage function (104,105). The TEE-guided strategy includes screening for existing thrombus and therapeutic anticoagulation at the time of TEE, as well as continued antithrombotic therapy to reduce the postcardioversion thromboembolic mechanism. Patients identified with left atrial cavity thrombi or left atrial appendage thrombi by TEE may have the cardioversion procedure postponed to allow at least three weeks of anticoagulation in order to stabilize the thrombus. In addition, antithrombotic therapy at the time of TEE and for four weeks after cardioversion reduces the risk of thrombus soon after cardioversion.

Clinical data to support the TEE-guided strategy have emerged over the last decade in nearly 2,000 patients from both nonrandomized and randomized studies. Table 3 shows that in the analysis of multiple randomized and nonrandomized studies on TEE-guided cardioversion, the
cardioversion–related embolic event rate is very low (0.35% [7 of 1,996 patients]) (4,16,103,113–116).

Nonrandomized studies. An important nonrandomized study (3) showed that early cardioversion after TEE could be performed when atrial thrombi were excluded. These investigators studied 230 patients with TEE before cardioversion of AF and detected atrial thrombi in 34 patients (15%). No clinically apparent embolic events were detected after cardioversion in 186 (95%) of 196 patients in whom no atrial thrombi were detected and who were spared long-term anticoagulation. The study compared a TEE-guided strategy with conventional anticoagulation strategy (15) (Fig. 3).

The ACUTE multicenter trial. The ACUTE multicenter study was a randomized clinical trial involving patients undergoing electrical cardioversion of AF lasting longer than two days. The study compared a TEE-guided strategy with short-term anticoagulation with a conventional anticoagulation strategy (15) (Fig. 3).

The study was an investigator-initiated trial lacking principal sponsorship. The termination before enrolling the target 3,000 patients was determined by the Data Safety and

### Table 3. Summary of Studies of Transesophageal Echocardiography (TEE)-Guided Approach to Cardioversion of Atrial Fibrillation, Including the Incidence of Thrombus by TEE and Recorded Embolic Events

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference Number</th>
<th>n</th>
<th>Atrial Thrombi</th>
<th>Embolic Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orsinelli (1993)</td>
<td>103</td>
<td>39</td>
<td>9 (23%)</td>
<td>1 (2.56%)</td>
</tr>
<tr>
<td>Stoddard (1995)</td>
<td>113</td>
<td>206</td>
<td>37 (18%)</td>
<td>0</td>
</tr>
<tr>
<td>Klein (1997)</td>
<td>4</td>
<td>126</td>
<td>7 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Weigner (1998)</td>
<td>114</td>
<td>466</td>
<td>64 (13.9%)</td>
<td>1 (0.21%)</td>
</tr>
<tr>
<td>Grimm (1998)</td>
<td>115</td>
<td>417</td>
<td>28 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Corrado (1999)</td>
<td>116</td>
<td>123</td>
<td>11 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>ACUTE (2000)</td>
<td>16</td>
<td>619</td>
<td>79 (13.6%)</td>
<td>5 (0.81%)</td>
</tr>
<tr>
<td>Total</td>
<td>1,996</td>
<td>235</td>
<td>79 (13.6%)</td>
<td>5 (0.81%)</td>
</tr>
</tbody>
</table>

### Table 4. Feasibility and Safety Outcome Summary for the ACUTE Pilot Study by Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>TEE-Guided Approach</th>
<th>Conventional Approach</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrical cardioversion</td>
<td>76% (47/62)</td>
<td>58% (37/64)</td>
<td>0.03</td>
</tr>
<tr>
<td>Scheduled electrical cardioversion</td>
<td>94% (44/47)</td>
<td>70% (26/37)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time from enrollment to cardioversion (weeks)</td>
<td>0.6 (CI 0.3–0.9)</td>
<td>4.8 (CI 3.8–5.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time from enrollment to normal sinus rhythm (weeks)</td>
<td>1.0 (CI 0.5–1.6)</td>
<td>4.3 (CI 3.0–5.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Safety outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embolic event</td>
<td>0%</td>
<td>2% (1/64)</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>Cardioversion related death</td>
<td>0%</td>
<td>0% (0/64)</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>Hemodynamic instability and bleeding</td>
<td>2%</td>
<td>8% (5/64)</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>Other outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with TEE-detected RA or LA thrombi</td>
<td>13% (CI 5–24%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Patients without thrombus by TEE and converted to normal sinus rhythm</td>
<td>75% (CI 62–86%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Normal sinus rhythm after DCC</td>
<td>85% (CI 51–76%)</td>
<td>76% (28/37)</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>Normal sinus rhythm at 8 weeks</td>
<td>55% (CI 42–68%)</td>
<td>56% (37/64)</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>Time from enrollment to follow-up (weeks)</td>
<td>5.7 (CI 5.1–63)</td>
<td>7.7 (CI 7.1–8.2)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are presented as percentage (n) (95% confidence interval [CI]) or mean value (95% CI).

DCC = direct current cardioversion; LA = left atrial; RA = right atrial; TEE = transesophageal echocardiography.

Reprinted with permission from the American College of Physicians, 1997.
Monitoring Board and the ACUTE Steering Committee, which reported low event rates and slow recruitment. A total of 1,222 patients were randomized from 70 clinical international sites over a five-year period. The eight-week study outcomes of the ACUTE study were presented recently as a late-breaking trial at the ACC’s 2000 Scientific Sessions (16,117).

Of the 1,222 randomized patients, 619 were assigned to the TEE-guided arm, whereas 603 were assigned to the conventional arm. Left or right atrial cavity and atrial appendage thrombi were detected by TEE in 76 patients (14%), resulting in postponement of the cardioversion. The TEE-guided strategy allowed early (mean three days) successful cardioversion in 81% of the patients without thrombi. There were two patients with embolic events occurring within the first week after cardioversion, which were associated with AF recurrence and subtherapeutic INRs (16,117).

Of the 603 patients assigned to the conventional arm, only 333 (55%) had electrical cardioversion (mean 31 days) and 80% were successful. There was one patient who had an embolic stroke occurring within the first week after cardioversion. Of the 270 patients who never underwent electrical cardioversion, the main reason in 127 patients (47%) was spontaneous or chemical conversion. In contrast, 143 patients never had cardioversion, for other reasons, including major or minor bleeding, medical reasons and lost to follow-up. There were also 32 patients (5%) who crossed over to the TEE arm because of hemodynamic instability (hypotension or congestive heart failure) (16).

In the ACUTE study, using intention-to-treat analysis there was no difference in the composite end point of stroke, transient ischemic attack and peripheral embolism between the TEE-guided arm and the conventional arms (0.81% vs. 0.50%; p = 0.50). However, there was a significant difference in the composite end point of major and minor bleeding between the TEE-guided arm and the conventional arms (2.9% vs. 5.5%; p = 0.02) (16).

An important unexpected outcome of the ACUTE multicenter study was that it showed that the aggregate embolic event rate for both arms of the study was much lower than expected (0.7%), and the aggregate composite hemorrhagic complication rate was higher than expected (4.2%). Compared with the conventional strategy, the TEE-guided arm with short-term anticoagulation decreased the composite rate for major and minor bleeding complications. However, there was no significant difference in 8-week maintenance of normal sinus rhythm, cardiac deaths or cardioversion-related deaths between the two arms. The results of this randomized study suggested that the TEE-guided approach with short-term anticoagulation may be considered as a clinically effective alternative to the conventional anticoagulation strategy in the management of patients undergoing cardioversion (16,117).

Registry of patients undergoing TEE-guided cardioversion. The ACUTE registry is a nonrandomized cohort of patients with AF from the Cleveland Clinic who underwent TEE-guided cardioversion and were followed for evidence of stroke. In a recent review of the registry (115), atrial thrombi were detected and cardioversion was postponed in
28 (7%) of the 417 patients. In contrast, cardioversion was performed in 388 patients (93%), 363 (94%) of whom were successfully converted to normal sinus rhythm without embolic stroke (115). These results, using the TEE-guided (ACUTE) approach, have now been extended to over 600 consecutive patients.

Cost-effectiveness. In the absence of published studies showing the relative clinical effectiveness of the two strategies, cost-effectiveness may affect patterns of use. Using a decision analytic model, Seto et al. (118) assessed the cost-effectiveness of the TEE-guided strategy in hospitalized patients with AF. The cost per quality-adjusted life year was compared for three different management strategies: 1) the conventional strategy with initial screening by transthoracic echocardiography (TTE); 2) initial TTE, followed by TEE and early cardioversion if an atrial thrombus is excluded by TEE; and 3) initial TEE, followed by early cardioversion if no atrial thrombus is detected. The TEE-guided early cardioversion without TTE was the least costly. Recently, they have extended their model and showed that it was less costly to perform follow-up TEE to document thrombus resolution for patients with thrombi on their initial TEE (119).

Atrial thrombus resolution after prolonged cardioversion. Table 5 shows a number studies using serial TEE evaluation to document the resolution of thrombi after the initial TEE (4,106,116,120–122) for these high risk patients. The mechanism for reduction of embolic risk using anticoagulant agents was thought to be organization and adherence of the thrombus to the left atrial appendage wall, but these TEE studies support atrial thrombus resolution and prevention of new thrombus (4,116,120). The percentage of thrombi resolved after three to four weeks of anticoagulant therapy has varied widely, from 89% resolution in one study (120) to 50% in the ACUTE pilot study (4) to 5% in another study (106). In a recent follow-up TEE study of 164 patients with left atrial thrombi, thrombus resolution occurred in 80% of the patients at a mean of 6.7 weeks, with little further resolution on subsequent TEE studies (122). These discrepant findings among different studies may relate to several factors, including different patient characteristics, duration of AF and diagnostic criteria for thrombus detection. In addition, the finding of thrombus portends a poor outcome, with a risk of stroke or embolic events of 10.4% per year or a death risk of 15.8% (123). Thus, there are many unresolved issues with regard to management of residual thrombus detected by TEE.

Discrepancy of thrombus detection and thromboembolism. There remains an inconsistency between the finding of thrombus by TEE in 10% to 15% of the patients with AF undergoing cardioversion and stroke rates <1% after cardioversion (1,4,76). There are several explanations for this discrepancy: 1) most thrombi do not embolize and may be related to the characteristics and location of the thrombus in the left atrial appendage; 2) not all thromboembolic events are clinically apparent; and 3) some appendage thrombi detected by TEE represent false positive findings. More investigation is needed to determine the relationship between thrombi by TEE and cardioversion-related embolic events.

Prediction of success of conversion to normal sinus rhythm. Initially, there was a lot of enthusiasm about the use of left atrial appendage areas and flow velocities by pulsed wave Doppler echocardiography to predict the immediate and long-term success of cardioversion (1). However, the results have been variable to date (124–128). In one study (124), the left atrial appendage flow velocities (mean emptying velocity >19 cm/s), maximal left atrial appendage area and duration of AF were useful in predicting the initial recovery of sinus rhythm. However, another study showed that the left atrial appendage flow velocities (mean peak left atrial appendage emptying velocity >35 cm/s) were not predictive of either the success of cardioversion or the maintenance of sinus rhythm at one-year follow-up (126). Thus, the overall data suggest that a reduced peak left atrial appendage velocity (generally <20 cm/s) may play some role in predicting the decreased success of cardioversion and maintenance of normal sinus rhythm, but its unique contribution remains unknown.

Disadvantages of the TEE-guided strategy. In the context of the findings of the ACUTE multicenter study and nonrandomized studies in nearly 2,000 patients, as discussed earlier, the TEE-guided approach with short-term anticoagulation appears to be as feasible and safe as the conventional arm. However, there remain some important disadvantages of using the TEE-guided approach (Table 6). The ability of the TEE-guided strategy, as compared with the conventional approach, to lower the stroke rate has not
been shown (5–7,9,16,129). It has been largely assumed that detecting a left atrial appendage thrombus and not cardioverting the patient would avoid an embolic event. Because the embolic stroke rate was low (0.7%) (16), a subsequent clinical trial would require >10,000 patients for adequate statistical power (15). Using this line of reasoning, one may argue that stroke after cardioversion is so rare; therefore, why bother to spend the resources to detect thrombi (6,7,11)? Another argument is that the bleeding risk reduction with the TEE-guided arm has been exaggerated. Although TEE-guided management cuts the time of anticoagulation in half, Landefeld (130) has shown that the highest risk for major bleeding is in the first three to four weeks of outpatient warfarin therapy, which is common to both strategies. Furthermore, often patients will need anticoagulation beyond the seven- to eight-week cardioversion period, because they may have some of the important risk factors for stroke (7) or they may have recurrent AF in the first three to six months after cardioversion (131–134).

Also, some investigators have argued that the additional cost of the TEE procedure is not justified in the absence of strong efficacy data. It is estimated from industry sources that between $50 and $100 million is spent on TEE for patients with AF, without guidelines or criteria for these patients (135). Despite models showing potential cost-effectiveness (118), the preliminary ACUTE cost data on the TEE-guided arm do not appear to be statistically different from the data on the conventional arm. The TEE-guided strategy may potentially be more costly than the conventional approach because of the increased costs associated with repeating TEE after four weeks of anticoagulation (119).

Despite the sensitivity of multiplane TEE being >95%, TEE may miss thrombi <2 mm, which may have the potential to embolize, especially in the setting of the complex morphology of multilobed appendage (136). In contrast, TEE may render false positive results by erroneously identifying spontaneous echocardiographic contrast, “sludge,” multilobed appendages or pectinate muscles as thrombus.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transesophageal echocardiography should be able to detect left atrial appendage thrombi, which increase the risk of embolic stroke after electrical cardioversion. Thus, sparing patients with thrombi from cardioversion may reduce the incidence of embolic events.</td>
<td>Transesophageal echocardiography is performed without any definite guidelines about who should receive the procedure (high risk vs. low risk) (12).</td>
</tr>
<tr>
<td>In the majority of patients with left atrial appendage thrombi, earlier cardioversion may shorten the period of anticoagulation and lower the corresponding risk of bleeding complications (16,117).</td>
<td>Residual thrombus on repeat TEE may diminish the cost-effectiveness of the TEE-guided approach (119).</td>
</tr>
<tr>
<td>A TEE-guided approach may prove more cost-effective owing to the reduction in laboratory monitoring costs and the reduction in bleeding complications.</td>
<td>Transesophageal echocardiography requires a level III-trained physician and availability of expensive echocardiographic machines.</td>
</tr>
<tr>
<td>Earlier cardioversion is believed to increase the likelihood of a successful return to and maintenance of sinus rhythm (4).</td>
<td>Transesophageal echocardiography may miss thrombi that may embolize after cardioversion (6). In contrast, TEE may render false positive results by erroneously identifying spontaneous echocardiographic contrast, “sludge,” multilobed appendages or pectinate muscles as thrombus.</td>
</tr>
</tbody>
</table>

National use of TEE-guided strategy. There is a growing perception that the use of the TEE-guided approach is increasing nationally. We lack actual Medicare data, and therefore national health statistics are not yet known. Murray et al. (140) performed a survey of 197 clinical practices in the U.S. to evaluate national use of this strategy. The survey revealed that the frequency of the TEE-guided strategy varies within institutions from 0% to 80%, with the highest concentration in tertiary-care institutions and university hospitals. Overall, the TEE-guided procedure was being used at least occasionally in 75% of the institutions surveyed and may account for ~12% of all electrical cardioversions for AF (140). At our own institution, the TEE-guided approach has remained relatively stable, accounting for 14.7% of the 3,329 electrical cardioversions from 1991 to 1997 (140). More recently, TEE-guided cardioversions...
have increased dramatically at our institution and now exceed 29% of all electrical cardioversions performed.

Status of TEE-guided strategy in 2001. The current data suggest that the TEE-guided strategy with short-term anticoagulation is a strong alternative to the conventional strategy (16,141). Clearly, with stroke rates <1.0%, the clinician can utilize either management strategy in their daily practices, depending on the individual patient or physician requirements. For example, the clinician at the community hospital may not have the resources or TEE skills (level III) to perform the TEE-guided approach and may elect to follow the conventional guidelines. In contrast, the hospital-based clinician may tend to perform the TEE-guided strategy more often, because skilled personnel and the infrastructure are readily available.

From the available evidence, there are certain patient subgroups that may benefit from the TEE-guided strategy. First, the inpatient with new-onset AF (<4 weeks duration), regardless of risk profile, may benefit from early cardioversion using the TEE-guided strategy. This may be particularly important for high risk patients (such as those with congestive heart failure, previous embolism or hemodynamic instability) in whom the prompt return of normal sinus rhythm would be beneficial (142). Second, the high-risk patient may benefit from further risk stratification by TEE to identify left atrial appendage thrombus, severe spontaneous echocardiographic contrast or complex atheroma (143,144). The identification of a thrombus before cardioversion would lead to cancellation of the cardioversion and more prolonged (and perhaps intense) anticoagulant therapy. A repeat TEE would be necessary to show thrombus resolution before cardioversion. Third, even for patients in whom the likelihood of thrombus is low (100), eliminating the need for prolonged anticoagulation pre-cardioversion would allow early cardioversion and avoid the delay for return to sinus rhythm. We await further data for the intermediate risk patient in whom the detection rate of thrombus is not well described. Fourth, the inpatient would be better suited to have the TEE-guided approach with intravenous heparin, as com-

Figure 4. Pitfalls in TEE screening for thrombi using the TEE-guided approach to cardioversion, including pectinate muscles (arrows) in the left atrial appendage (A), multilobed appendage (arrows) (B) and viscous spontaneous echocardiographic contrast, or “sludge” (C). Pectinate muscle tissue, multilobed appendage or sludge can be mistaken for thrombi, rendering a false positive TEE screening result. TEE = transesophageal echocardiography.
pared with the outpatient. The outpatient setting has some limitations, because these patients would need three to five days of warfarin before the TEE-guided DC cardioversion, and thus the time benefit of early cardioversion is diminished (4,7,31). Outpatient management may be improved with the use of low molecular weight heparin, which can be used as bridge therapy to warfarin (see later discussion) (145). Finally, the benefit of the TEE-guided strategy seems to be limited in the chronically anticoagulated patient with persistent AF undergoing cardioversion.

**New developments.** A major limitation of the TEE-guided approach with intravenous heparin (for inpatients) is the extended length of the hospital stay to allow for overlap between the heparin and warfarin (four to five days). Recently, a newer TEE-guided strategy has been advocated with the use of low molecular weight heparin therapy to be used as bridge therapy for anticoagulation. This therapy has the potential to lower costs by treating patients as outpatients instead of inpatients (146), provide greater patient convenience and increase quality of life, as compared with intravenous heparin. A randomized clinical pilot study (ACUTE II) is under way to compare TEE-guided cardioversion using low molecular weight heparin with the standard intravenous unfractionated heparin in patients with AF (145). Recently, a TEE-stratified study was able to identify 162 low risk patients with AF and atrial flutter lasting longer than two days and safely perform immediate cardioversion with the use of low molecular weight heparin (dalteparin) to bridge warfarin therapy (147). The low risk patients receiving immediate cardioversion maintained sinus rhythm better after one month, as compared with the patients with prolonged precardioversion warfarin therapy.

In addition, there is work in progress involving direct thrombin inhibitors and glycoprotein IIa/IIIb antiplatelet therapy for thrombotic prophylaxis of patients with AF. There is also growing interest in the use of chemical cardioversion with ibutilide or dofetilide and TEE-guided cardioversion of AF (148,149).

**CONCLUSIONS**

There remains an ongoing controversy about the management of patients with AF undergoing cardioversion. The standard of care is still conventional management, which is performed by most cardiologists worldwide. Based on the findings of both nonrandomized and randomized studies, the TEE-guided approach with short-term anticoagulation can be considered a safe and clinically effective alternative to conventional management, especially for patients who may benefit from early cardioversion.

**Acknowledgments**

The authors wish to thank Susan E. Jasper, BSN, Ariel Goodman-Bizon, BA, and Marie D. Campbell for their assistance in the preparation of this manuscript.

---

**REFERENCES**


lation in patients undergoing electrical cardioversion of atrial fibrillation: results from the ACUTE Registry (abstr). J Am Coll Cardiol 1998;31 Suppl:335A.


