The use of enoxaparin compared with unfractionated heparin for short-term antithrombotic therapy in atrial fibrillation patients undergoing transeosophageal echocardiography-guided cardioversion: Assessment of Cardioversion Using Transoesophageal Echocardiography (ACUTE) II randomized multicentre study†

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Introduction

Atrial fibrillation (AF) is the most commonly sustained arrhythmia encountered in clinical practice with an overall prevalence of 0.4% in the general population.1 Electrical cardioversion (CV) is used to restore sinus rhythm, but the procedure itself may be associated with an increased risk of stroke in patients with AF >2 days' duration.2 Transeosophageal echocardiography (TEE) with short-term anticoagulation has been proposed as an alternative to the conventional strategy of 7–8 weeks of anticoagulation in this group of patients.3 The Assessment of Cardioversion Using Transeosophageal Echocardiography (ACUTE) I trial was a randomized study that compared the TEE-guided group with short-term anticoagulation to the conventional anticoagulant approach. There was no difference in composite embolic events between groups; however, the composite bleeding rate was significantly lower in the TEE-guided group.4 In this trial, i.v. unfractionated heparin (UFH) was the anticoagulant of choice with in-hospital treatment
often necessary with frequent laboratory monitoring during UFH-bridging therapy to overlap with warfarin. The expense of hospitalization and prolonged length of stay (LOS) tends to deter the use of i.v. UFH and TEE-guided approach to CV. Clearly, there is a need for alternative anticoagulation therapies.

Short-term low molecular-weight-heparin (enoxaparin sodium, sanofi-aventis, Paris, France) therapy combined with a TEE evaluation for thrombus has been proposed as an alternative for the anticoagulation management of patients with AF undergoing immediate CV. Since enoxaparin is self-administered subcutaneously and its anticoagulant response is predictable, prolonged in-hospital therapy and monitoring of activated partial-thromboplastin time are not required. Furthermore, by using enoxaparin as a ‘bridge’ antithrombotic therapy, TEE screening and CV can be scheduled after 24 h of the initiation of enoxaparin.

We hypothesized that early TEE-guided CV of AF can be safely performed using a short-term anticoagulation strategy of enoxaparin compared with UFH. The use of enoxaparin with TEE may result in a safe, cost-effective, and potentially efficacious approach to CV of AF. Thus, the aim of this study was to test the safety and efficacy of using enoxaparin in lieu of UFH as an antithrombotic therapy for patients in AF undergoing TEE-guided CV to sinus rhythm.

**Methods**

**Study design**

The ACUTE II pilot study was a controlled, investigator-initiated, prospective, and randomized multicentre trial that determined the general safety and efficacy of a TEE-guided enoxaparin strategy to CV of AF compared with a TEE-guided i.v. UFH strategy. The study design for the ACUTE II study has been published previously.8 Figure 1 summarizes the overall design of the study for both treatment groups. Patients were randomly assigned to treatment groups immediately after study enrolment. Each site was supplied with sealed, numbered randomization envelopes containing the random assignment for each patient. The Data Coordinating Centre generated the random assignments that were stratified by site. Assignment was balanced within each site in randomly chosen blocks of size of two and four. After assignment, the patients in the enoxaparin arm were therapeutically anticoagulated before CV with enoxaparin 1 mg/kg of body weight, subcutaneously every 12 h and warfarin was initiated. Using TEE, the patients were then stratified based on the presence or absence of thrombus. TEE-guided CV occurred after the third or fourth dose of enoxaparin (steady-state). Enoxaparin was continued after initiation of warfarin therapy until the international normalized ratio (INR) was in the therapeutic range of 2.0–3.0. After completion of CV, patients in the enoxaparin group were discharged from the hospital as soon as possible. The INRs were checked frequently and their anticoagulation was managed as outpatients.

After assignment, the patients in the UFH arm were therapeutically anticoagulated before CV with UFH and warfarin was initiated. Patients received an initial i.v. weight-based heparin bolus followed by a continuous infusion using a weight-based heparin algorithm in order to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times control.9 The activated partial-thromboplastin time was measured at 6 and 12 h after the start of the infusion and daily thereafter. TEE-guided CV occurred after 24 h of UFH if there was no evidence of thrombus. Heparin i.v. was continued after initiation of oral warfarin until the INR was in the therapeutic range (INR 2.0–3.0). Patients in the UFH group were discharged from the hospital as soon as possible and once their warfarin was therapeutic.

The 5-week study period included patient data from date of enrolment to 35 days after enrolment. Patients with left atrial or left appendage thrombus on initial TEE were followed for an additional 3 weeks (8 weeks total). Patients were seen in the outpatient clinic for follow-up evaluations. The Institutional Review Board approved the study at each participating site and informed consent was obtained from all patients.

**Patients**

Patients with persistent or paroxysmal AF > 2 days' duration with the option of early electrical or chemical CV were recruited for the study. Patients with atrial flutter having a documented history of AF were also eligible. Patients excluded from the study were those who received warfarin during the previous 14 days or patients having > 24 h of UFH before the time of study enrolment. Also excluded were patients with contraindications to warfarin,

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/27/23/2858/2887603/223_085828176033677.pdf)
heparin, or TEE. Patients with a history of thrombocytopenia, bleeding, stroke <3 months, renal insufficiency (creatinine >2 mg/dL), malignancy, uncontrolled hypertension (SBP >160), haemodynamic instability, weight <40 or >125 kg, life expectancy <6 months, history of drug or alcohol abuse within 2 years, or need for concomitant therapy known to affect platelet function or anticoagulation were also excluded. Patients who were on antiarrhythmic medication at enrolment were not excluded from the study, but commencement of antiarrhythmic therapy was permitted only following therapeutic anticoagulation and transoesophageal echocardiographic exclusion of thrombus.

Outcomes

The safety outcomes were cerebrovascular accident, transient ischaemic attack, peripheral embolism, major or minor bleeding, and death. Efficacy outcomes were LOS and return to normal sinus rhythm (NSR). Efficacy outcomes of cost-effectiveness and patient quality of life, as well as antifactor Xa and tissue factor pathway inhibitor levels\(^6\) will be published separately.

Serious adverse events (embolism, bleeding, and mortality) were adjudicated by a central and independent Events Review Committee. A haemorrhagic complication was considered major if it was fatal, required transfusion, or required a surgical procedure to terminate. A central echocardiographic lab was used to ensure quality of the echocardiographic data, adherence to the protocol as well as to review all thrombi on TEE.

Statistical analyses

Embolic event and major bleeding rates for TEE-guided CV were estimated to be 1.1 and 0.2% respectively for the 5-week period.\(^8,10\) There was no evidence to suggest that embolic or major bleeding rates would differ between the two study groups. A pilot study with a goal of 200 patients was used since there was little or no data regarding actual event rates using enoxaparin with TEE-guided CV. Therefore, the goal of the primary analysis in this pilot study was to report estimates of relative differences in event rates and their 95% confidence interval (CI). The study was designed to ensure that 95% CI widths would range from 0.04 to 0.15 for proportions between 0 and 0.15.

The study was designed with an interim analysis, of the first 100 patients, and a final analysis. \(\chi^2\) tests for treatment group comparisons of categorical variables were conducted. Analysis of variance methods were used to compare treatment groups for continuous variables. Data are expressed as means ± standard deviations, medians (third quartile – first quartile), or as frequencies and percentages (95% CI). All analyses were based on the intention to treat. All statistical testing were conducted at a significance level of 0.05 with a two-tailed alternative hypothesis.

This study was an investigator-initiated trial, supported by a grant-in-aid from sanofi-aventis. The Food and Drug Administration granted an Investigational New Drug Application to the Principal Investigator to conduct the ACUTE II trial. The first patient was enrolled on 29 December 1999. The Data Safety and Monitoring Board determined that it would be appropriate to end the trial after 155 patients were enrolled due to low event rates and rate of enrolment. The database was locked on 24 May 2005.

Results

Baseline characteristics

Figure 2 shows the flow of study subjects through the trial. The baseline characteristics of the patients are shown in Table 1. A total of 155 patients from 17 clinical sites were randomly assigned to either the enoxaparin group (n = 76) or the UFH group (n = 79). No differences were found in the baseline clinical and echocardiographic variables including ejection fraction and left atrial area for the two groups (Table 1). Of note, 85% of the patients were randomized, when they were inpatients, however, only one patient in each group was post-operative. The rhythm was primarily AF. The number of patients using antiarrhythmic therapy in the enoxaparin compared with the UFH group at the time of enrolment (82 vs. 85%; \(P = 0.5904\)) as well as at the time of CV (92 vs. 91%; \(P = 0.8914\)), was similar. Table 2 shows the use of antiarrhythmics for the two arms at the different time points of the study (Table 2).

Treatment outcomes after assignment

In both groups, enoxaparin and UFH were bridged to warfarin with a target INR between 2 and 3. In the enoxaparin

![Figure 2](https://academic.oup.com/eurheartj/article-abstract/27/23/2858/2887603/flowchart.png)
group, the mean enoxaparin dose was 88.7 mg and was administered over an average of a 6-day period. Patients receiving enoxaparin were discharged with a mean INR at hospital discharge of 1.74 ± 0.69. In the UFH group, UFH was given as a continuous infusion using a weight-based heparin algorithm in order to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times control. Patients received UFH for an average of 5.36 days and were discharged with a mean INR at hospital discharge of 2.48 ± 0.87.

Figure 3 presents a branch-tree diagram showing the treatment outcomes. Of the 76 patients assigned to the low molecular weight heparin (LMWH) group, 72 (94.7%) had a transoesophageal echocardiogram; 63 (82.9%) had early electrical CV within 24 h of enrolment; and 59 (93.7%) of these patients had a successful early electrical CV. Of the nine patients having TEE but no CV, there were five (55.6%) patients who had a CV postponed due to thrombi. The central echocardiographic laboratory independently adjudicated all thrombi, and there was 100% agreement. Three of these patients received a second transoesophageal echocardiogram, per protocol, and thrombus resolved in two of the three. One had a CV and the other did not. Two of the five patients did not receive a second transoesophageal echocardiogram; one spontaneously converted to sinus rhythm prior to the second transoesophageal echocardiogram and one had a CV without a second transoesophageal echocardiogram, due to medical decision. There were a total of seven (9.2%) patients who did not have a CV due to spontaneous CV. Three (3.9%) patients had a repeat CV during the 5-week study period. Four patients in the LMWH group were lost to follow-up. One patient withdrew participation in the study, one patient left the hospital

| Table 1 Baseline characteristics for patients in the enoxaparin group and UFH group of the ACUTE II trial |
|---------------------------------------------------|-----------------|-----------------|-----------------|
| Enoxaparin (n = 76) | UFH (n = 79) | **P-value** |
| Mean age (years) | 64.3 ± 13.3 | 64.3 ± 15.5 | 0.5614 |
| Male sex, n (%) | 58 (76) | 57 (72) | 0.9132 |
| Inpatients, n (%) | 64 (84) | 67 (85) | 0.4612 |
| Hypertension, n (%) | 20 (26) | 29 (37) | 0.2433 |
| CHF, n (%) | 16 (21) | 19 (24) | 0.6603 |
| NYHA, III or IV, n (%) | 4 (5) | 4 (5) | 0.9488 |
| LV ejection fraction (%) | 47 ± 15 | 47 ± 16 | 0.8312 |
| Left atrial area (cm²) | 24.8 ± 6.5 | 26 ± 8.8 | 0.0412 |
| History of embolism, n (%) | 5 (7) | 7 (9) | 0.5123 |
| Rhythm (AF/AFL), n (%) | 72/4 (5) | 74/5 (6) | 0.8612 |
| First episode of AF, n (%) | 42 (55) | 48 (61) | 0.3512 |
| AF duration (median days) | 5 (3–18) | 10 (4–19) | 0.2312 |
| Antiarrhythmic therapy, n (%) | 64 (84.2) | 66 (83.5) | 0.6012 |

AFL, atrial flutter; CHF, congestive heart failure; NYHA, New York Heart Association.

| Table 2 Antiarrhythmic drug use for patients in the enoxaparin group and UFH group of the ACUTE II trial |
|---------------------------------------------------|-----------------|-----------------|-----------------|
| Enoxaparin (n = 76) | UFH (n = 79) | **P-value** |
| At enrolment |
| Class 1, n (%) | 3 (4) | 3 (4) | 0.9614 |
| Class 2, n (%) | 39 (51) | 50 (63) | 0.1317 |
| Class 3, n (%) | 9 (12) | 11 (14) | 0.6991 |
| Class 4, n (%) | 19 (25) | 21 (27) | 0.8219 |
| Miscellaneous, n (%) | 16 (21) | 23 (29) | 0.2476 |
| At CV |
| Class 1, n (%) | 5 (8) | 4 (7) | 0.8276 |
| Class 2, n (%) | 39 (62) | 33 (57) | 0.5750 |
| Class 3, n (%) | 20 (32) | 30 (52) | 0.0258 |
| Class 4, n (%) | 10 (16) | 12 (21) | 0.4925 |
| Miscellaneous, n (%) | 17 (27) | 17 (29) | 0.7761 |
| At 5-week follow-up |
| Class 1, n (%) | 3 (4) | 5 (6) | 0.5535 |
| Class 2, n (%) | 46 (64) | 45 (57) | 0.3850 |
| Class 3, n (%) | 29 (40) | 33 (42) | 0.8521 |
| Class 4, n (%) | 9 (12) | 14 (18) | 0.3725 |
| Miscellaneous, n (%) | 15 (21) | 16 (20) | 0.9298 |

Class 1, sodium channel blockade; Class 2, beta-adrenergic blockade; Class 3, prolong repolarization; Class 4, calcium channel blockade; Miscellaneous action (Vaughan Williams classification of antiarrhythmic drugs). Some patients were on more than one class of antiarrhythmic drug.

Some patients were on more than one class of antiarrhythmic drug.
against medical advice, and two patients were unable to be contacted after their baseline procedures.

Of the 79 UFH patients, 66 (83.5%) had a transoesophageal echocardiogram; 58 (73.4%) had early electrical CV within 24 h of enrolment; and 54 (98.2%) of these had a successful early chemical (n = 3) or electrical (n = 51) CV. Of the eight patients having TEE but no CV, there were four (50%) who had CV postponed due to thrombi. All four of these patients received a second transoesophageal echocardiogram, per protocol, and thrombus had resolved in three of the four. Two of the three had a CV and one spontaneously converted to sinus rhythm prior to the second transoesophageal echocardiogram. Of note, there were 13 (16.5%) who did not have a CV primarily due to spontaneous conversion. Six (7.6%) patients had a repeat CV during the 5-week study period. There were no patients who crossed over to the other group during the study.

Safety outcomes

Table 3 shows the safety outcomes, including cerebrovascular accidents, transient ischaemic attacks, and peripheral embolism, major or minor bleeding, and mortality for both groups. In this study, there were no strokes, major bleeds or deaths over the 5-week period. However, there were three minor bleeds in each arm. A patient summary of bleeding outcomes is provided in Table 4. Mean age of patients with minor bleeding was 67 ± 18 years and all six patients had significant risk factors for bleeding. The most commonly reported minor bleeding event was ecchymosis.

Efficacy outcomes

Table 3 also shows the efficacy outcomes in the two groups. There was no difference in thrombi detected in the enoxaparin group compared with the UFH group (five vs. four patients; P = 0.83). There was more NSR in the enoxaparin group vs. UFH group at 5 weeks [55/72 (76%) vs. 44/77 (57%); P = 0.0129], despite fewer repeat CVs in the enoxaparin group though this was not statistically significant [3/76 (3.9%) vs. 6/79 (7.6%); P = 0.495]. The use of antiarrhythmic therapy was similar in both groups at 5 weeks (94% in the enoxaparin vs. 92% in the UFH group; P = 0.6147). The type of antiarrhythmic therapy in the two arms was also similar (Table 2). There was more NSR in the enoxaparin group that had successful TEE-guided CV [45/56 (80%) vs. 30/53 (57%); P = 0.0075]. However, there was a trend for more spontaneous conversion in the UFH group but this was not statistically significant [13/79 (16.5%) vs. 7/76 (9.2%); P = 0.1786]. There was a shorter LOS in the enoxaparin group with a shorter median time from hospital admission to hospital discharge or from enrolment to discharge [4 (3–5) vs. 5 (4–7); P = 0.003] and [3 (2–4) vs. 4 (3–5); P < 0.0001] (Figure 4).

Discussion

LMWH therapy combined with a TEE evaluation for thrombus has been proposed as an alternative for the anticoagulation management of patients with AF undergoing immediate CV.8 The ACUTE II study compared enoxaparin and UFH TEE-guided approaches and found that over a follow-up period of 5 weeks, there was no difference for the safety outcomes of embolic events, major bleeding, or death between the enoxaparin and UFH groups. There was a similar number of minor bleeds between the arms. However, the enoxaparin strategy did demonstrate better efficacy outcomes, including earlier hospital discharge, as well as more patients in NSR at 5 weeks than the UFH arm. There was more NSR in patients in the enoxaparin group that had successful TEE-guided CV.

In the ACUTE I multicentre study, TEE-guided therapy with short-term anticoagulation was shown to be a good clinical alternative to conventional anticoagulation for those patients that need early CV.4 However, this approach was limited by the need to give i.v. UFH in the hospital with overlap to warfarin.8 In the ACUTE II study, we demonstrated in a randomized fashion that enoxaparin was a safe and efficacious approach and that patients could be discharged earlier (median 1 day less with mean INR 1.7) than patients on UFH and be treated as outpatients until the INR became therapeutic. Economic analysis evaluating resource use and costs suggests that the lowered LOS translated to lower total costs for the enoxaparin group ($5976 vs. $8283) with a cost savings of $2307 (95% CI, $1048 to $4309) compared with the UFH group.12

This study showed very few adverse events with only minor bleeding similarly detected in both arms, usually ecchymosis. Interestingly, there were no strokes, major bleeds, or deaths using the TEE-guided approach in 155 patients. This compares with the 0.8% stroke rate in the TEE-guided arm of the ACUTE I multicentre study in 1222 patients4. This finding confirms further refinement of the TEE-guided strategy with therapeutic anticoagulation especially in the post-CV period when atrial stunning occurs.13

The anticoagulation protocol for the enoxaparin arm (three or four doses of enoxaparin prior to TEE) was easily followed with patients undergoing TEE-guided CV 24 h after enrolment compared with the UFH arm with the

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### Table 3 Safety and efficacy outcomes at 5-week follow-up for patients in the enoxaparin group and UFH group of the ACUTE II trial

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin (n = 76)</th>
<th>UFH (n = 79)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolic events</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Minor bleeding, n (%)</td>
<td>3 (4)</td>
<td>3 (4)</td>
<td>0.9614†</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Thrombi</td>
<td>5</td>
<td>4</td>
<td>0.8336</td>
</tr>
<tr>
<td>Repeat CV, n (%)</td>
<td>3 (3.9)</td>
<td>6 (7.6)</td>
<td>0.495</td>
</tr>
<tr>
<td>Sinus Rhythm, n (%)</td>
<td>55/72 (76)</td>
<td>44/77 (57)</td>
<td>0.0129‡</td>
</tr>
<tr>
<td>Hospital admission to hospital discharge in median days</td>
<td>4 (3–5)</td>
<td>5 (4–7)</td>
<td>0.0032‡</td>
</tr>
<tr>
<td>Enrolment to hospital discharge in median days</td>
<td>3 (2–4)</td>
<td>4 (3–5)</td>
<td>&lt;0.0001‡</td>
</tr>
<tr>
<td>Time from enrolment to NSR in median days</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>0.9658‡</td>
</tr>
</tbody>
</table>

†OR and 95% CI for minor bleeding = 0.9605 (0.8889, 0.9918) and sinus rhythm = 0.2361 (0.1440, 0.3509).

‡Wilcoxon.
need for frequent PTT checks. Consequently, in the enoxaparin
arm, there were more patients undergoing TEE (95 vs. 84%;
P = 0.0258) and a trend for more CVs (83 vs. 73%;
P = 0.1541) than in the UFH arm. Other factors that could
explain more frequent TEE in the enoxaparin arm include
more spontaneous conversions as well as technical issues
in passing the transoesophageal echocardiographic probe
in the UFH arm. This could explain the finding of more NSR
in the LMWH group at 5 weeks since more patients received
the intended TEE-guided CV strategy. Of note, there was no
difference in antiarrhythmic use in the two arms at 5-week
follow-up (Table 2) and a trend for fewer repeat CVs in the
enoxaparin group. Another reason for more NSR in the LMWH
group could be a trend for shorter duration of AF in the
enoxaparin group, however, this was not significantly differ-
ent [5 days (3–18) vs. 10 days (4–19); P = 0.11]. In a small
sample size, this trend could be clinically important.
Finally, enoxaparin has been shown to have other effects
aside from anticoagulation including anti-inflammatory
effects
in vitro.14 Recently, increased inflammatory
markers C-reactive protein (CRP) have been shown to be
associated with transoesophageal echocardiographic throm-
boembolic risk factors15 and higher short-term recurrence of
AF or atrial flutter after successful electrical CV.16
The Anticoagulation in Cardioversion using Enoxaparin
(ACE) trial was a randomized, multicentre trial17 that com-
pared enoxaparin with UFH and warfarin in 496 patients
scheduled for CV of AF. Patients were stratified to either
TEE-guided CV (n = 431) or to CV with no TEE (n = 65).
The authors showed that enoxaparin treatment was non-
inferior to UFH and a warfarin equivalent using a combined
endpoint of stroke, death, or major bleeding in a per protocol
analysis (7/216 vs. 12/212; P-value for non-inferiority was
0.016). There are several key differences between the ACE
and ACUTE II studies. Clearly, the ACE trial was a larger
study and was powered for non-inferiority for the primary
combined endpoint. Our study was a pilot study and was
underpowered for the primary single endpoint of stroke. In
the ACE trial, patients were stratified by TEE-guidance
according to centre preference. In our study, all patients
were randomized to a treatment arm and all patients were
scheduled to have early TEE-guided CV. In the ACE trial, enox-
aparin was administered to patients for 4 weeks after CV. In
the ACUTE II study, enoxaparin was only used for bridging
to therapeutic oral anticoagulation. In the ACE trial, there

<table>
<thead>
<tr>
<th>Event</th>
<th>Age/sex</th>
<th>Risk factors</th>
<th>Days from enrolment</th>
<th>INR</th>
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</thead>
<tbody>
<tr>
<td>Hematoma @ injection site</td>
<td>48/M</td>
<td>CAD, bronchitis</td>
<td>2</td>
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<tr>
<td>Skin—back of torso, DCC pad</td>
<td>61/F</td>
<td>CHF</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Hematoma @ injection site</td>
<td>72/F</td>
<td>HTN, mitral regurgitation, asthma</td>
<td>6</td>
<td>2.31</td>
</tr>
<tr>
<td>UFH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>45/F</td>
<td>CHF, MV and AV disorder</td>
<td>29</td>
<td>1.68</td>
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<tr>
<td>Ecchymosis—abdomen</td>
<td>83/F</td>
<td>HTN, DJD</td>
<td>11</td>
<td>4.4</td>
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<tr>
<td>Ecchymosis—arm</td>
<td>89/F</td>
<td>CHF, HTN, DM, CVA</td>
<td>28</td>
<td>2.2</td>
</tr>
</tbody>
</table>

AV, aortic valve; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebral vascular accident; DCC, direct current CV; DJD, degenerative joint disease; DM, diabetes mellitus; HTN, hypertension; MV, mitral valve.
was no difference in NSR in follow-up; whereas in our study, the enoxaparin group had greater NSR at 5-week follow-up.

A recent study18 evaluated the safety and efficacy of discontinuing anticoagulation after 7 days of CV using LMWH (enoxaparin) in patients that had a repeat transoesophageal echocardiogram to exclude thrombi and atrial stunning. The authors found that this approach could be useful to define patients without atrial stunning and a low-risk population in whom low-molecular-weight-heparin could be given only for 1 week as an alternative to long-term anticoagulation.

There is increasing interest in the role of oral thrombin inhibitors in AF and CV because of their prompt onset and offset of anticoagulant action, wider therapeutic window, lower potential for food and drug interactions, and no need for dosage adjustments or anticoagulant monitoring compared with warfarin. The Stroke Prevention using an Oral Thrombin Inhibitor in AF (SPORTIF) III and V trials randomized more than 7000 patients with non-valvular AF to adjusted-dose warfarin (INR 2–3) or fixed-dose ximelagatran. These trials concluded that ximelagatran was not inferior to warfarin for the prevention of stroke and systemic embolic events with an absolute risk reduction of 0.7% (95% CI=0.1–1.4, \( P = 0.13 \)). Rates of major bleeding were similar between the two groups, but minor bleeding was lower in the ximelagatran group.19 However, the drug was not approved by the FDA due to an increase in the liver enzymes which occurred in 6% of patients. A number of other oral thrombin inhibitors are currently in clinical development.20

Study limitations

The study was a pilot study and thus was underpowered for the primary outcomes. There was a relatively slow enrollment in this pilot study over a 5-year period and the Data Safety and Monitoring Board closed the study early at 155 patients. Also, the study mainly enrolled inpatients with co-morbidities rather than outpatients. If outpatients were enrolled, this could have had a more dramatic effect on LOS in the LMWH arm. Since the onset of the trial, there has been a gradual acceptance of bridging therapy with LMWH.21

Clinical implications

The use of LMWH with TEE-guided strategy may be considered feasible and safe. Our trial, together with the ACE trial, demonstrates the potential clinical utility of this approach; however, a larger trial would be necessary for confirmation.

Conclusions

The ACUTE II study showed that there were no differences in embolic or bleeding rates between the enoxaparin and UFH TEE-guided strategies. However, the enoxaparin group had shorter LOS. Thus, the TEE-guided management strategy with enoxaparin may be considered a safe and effective alternative strategy for patients in AF undergoing elective CV. The shorter LOS may translate to lower costs using the enoxaparin TEE-guided approach.

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Conflict of interest: none declared.

Appendix

Author contributions: A.L.K. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.


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Enoxaparin and unfractionated heparin


