Safety and Efficacy of Enoxaparin Compared With Unfractionated Heparin and Oral Anticoagulants for Prevention of Thromboembolic Complications in Cardioversion of Nonvalvular Atrial Fibrillation

The Anticoagulation in Cardioversion using Enoxaparin (ACE) Trial

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Background—Anticoagulation in cardioversion of atrial fibrillation is currently performed with unfractionated heparin (UFH) and oral anticoagulants, with or without guidance by transesophageal echocardiography (TEE). Low-molecular-weight heparins may reduce the risk of bleeding, may obviate the need for intravenous access, and do not require frequent anticoagulation monitoring.

Methods and Results—In a randomized, prospective multicenter trial, we compared the safety and efficacy of enoxaparin administered subcutaneously with intravenous UFH followed by the oral anticoagulant phenprocoumon in 496 patients scheduled for cardioversion of atrial fibrillation of >48 hours’ and ≤1 year’s duration. Patients were stratified to cardioversion with (n=431) and without (n=65) guidance by TEE. The study aimed to demonstrate noninferiority of enoxaparin compared with UFH+phenprocoumon with regard to the incidence of embolic events, all-cause death, and major bleeding complications. Secondary end points included successful cardioversion, maintenance of sinus rhythm until study end, and minor bleeding complications. Of 496 randomized patients, 428 were analyzed per protocol. Enoxaparin was noninferior to UFH+phenprocoumon with regard to the incidence of the composite primary end point in a per-protocol analysis (7 of 216 patients versus 12 of 212 patients, respectively; P=0.016) and in an intention-to-treat analysis (7 of 248 patients versus 12 of 248 patients, respectively; P=0.013). There was no significant difference between the 2 groups in the number of patients reverted to sinus rhythm.

Conclusions—Enoxaparin is noninferior to UFH+phenprocoumon for prevention of ischemic and embolic events, bleeding complications, and death in TEE-guided cardioversion of atrial fibrillation. Its easier application and more stable anticoagulation may make it the preferred drug for initiation of anticoagulation in this setting. (Circulation. 2004;109:997-1003.)

Key Words: heparin ▪ fibrillation ▪ cardioversion ▪ anticoagulants ▪ echocardiography

Atrial fibrillation is the most common arrhythmia in adults, affecting ~0.5% to 1% of the total population and > 8% of patients older than 80 years.1-4 One major therapeutic goal is restoration of sinus rhythm by pharmacological or electrical cardioversion. However, in the absence of adequate anticoagulation, cardioversion is associated with a 5% to 7% risk of thromboembolic complications caused by dislodgement of left atrial thrombi.5-7 These are usually located in the left atrial appendage and may be present before cardioversion or even develop after restoration of sinus rhythm from mechanical atrial dysfunction after cardioversion, the so-called “atrial stunning.”8 For atrial fibrillation of >48 hours’ duration, current guidelines advocate the use of anticoagulation for at least 3 to 4 weeks before and after cardioversion.1 Alternatively, cardioversion may be performed under guidance of transesophageal echocardiography (TEE), allowing early restoration of sinus rhythm.
after exclusion of left atrial thrombi using an intravenous infusion of unfractionated heparin (UFH) followed by 4 weeks of oral anticoagulation. The safety of this approach has been shown to be similar to that of the “conventional” approach and may be associated with a higher cardioversion success rate because of earlier restoration of sinus rhythm. Anticoagulation in atrial fibrillation is frequently underused because of the fear of bleeding complications. Enoxaparin, a low-molecular-weight heparin (LMWH), may be an attractive alternative to UFH because its subcutaneous application allows ambulatory therapy initiation and provides rapid and stable anticoagulation without the need for routine anticoagulation checks. It has been shown to be superior to UFH in patients with unstable angina and myocardial infarction. Moreover, the use of LMWH in patients with atrial fibrillation has been reported to be safe in patients with contraindications to oral anticoagulants and effective in nonrandomized studies of atrial fibrillation cardioversion. The aim of the present study was to compare the efficacy and safety of subcutaneous enoxaparin with conventional anticoagulation using intravenous UFH followed by the oral anticoagulant phenprocoumon in the setting of cardioversion of nonvalvular atrial fibrillation.

Methods

Study Design
Details of the study design have been described previously; an overview is provided in Figure 1. It was a controlled, prospective, randomized, open-label multicenter trial comparing the safety and efficacy of subcutaneous enoxaparin with intravenous UFH followed by oral phenprocoumon in patients scheduled for DC cardioversion of atrial fibrillation. In 9 participating centers, cardioversion was performed without guidance by TEE (stratum A) and in 47 centers with TEE guidance (stratum B), according to center-specific preference. Patients were randomly assigned to receive either enoxaparin or UFH + phenprocoumon. In stratum A, patients assigned to enoxaparin received the drug subcutaneously at an initial dose of 1 mg/kg body wt twice daily for 3 to 8 days, followed by a fixed dose of 40 mg twice daily in patients with a body weight <65 kg and 60 mg twice daily in patients with a body weight ≥65 kg for the rest of the study period. Before hospital discharge, patients or relatives were trained to self-inject the drug for the ambulatory phase of the study. In the UFH + phenprocoumon limb, anticoagulation was started with an intravenous bolus of UFH (80 IU/kg or according to a site-specific nomogram), followed by a continuous intravenous infusion adjusted to activated partial thromboplastin times (initially 18 IU · kg⁻¹ · h⁻¹ or according to a site-specific nomogram) for a minimum of 72 hours. Overlapping treatment with phenprocoumon was started within 72 hours after randomization and was adjusted to an international normalized ratio of 2.0 to 3.0 before discontinuation of UFH for the remaining study period (ie, until 4 weeks after cardioversion). Dosage adjustment of UFH was preferably performed according to the Raschke schedule. Cardioversion was performed 3 weeks after treatment initiation using DC under short-term general anesthesia. In stratum B, study medication was started immediately after randomization before verification or exclusion of a thrombus by TEE. In patients without thrombi, cardioversion was performed 1 to 3 days after TEE when full anticoagulation was achieved. The assigned treatment was then administered for 4 weeks after cardioversion. In case of a left atrial thrombus, cardioversion was deferred for 3 weeks. If a repeat TEE no longer revealed a thrombus, patients were cardioverted, and the randomized treatment was continued for 4 weeks. If thrombus was still present, the patient was excluded from the trial. The ethics committee of each participating center approved the study. All patients gave written informed consent to participate in the trial.

Patients
Patients were eligible if they were at least 18 years old and weighed at least 45 kg. Atrial fibrillation had to be documented on the initial ECG and associated with clinical symptoms (palpitations, dizziness, tachycardia) for at least 48 hours before study inclusion, or persistent atrial fibrillation had to be documented during the previous 3 months on resting or long-term ECG if the patient presented without clinical symptoms. Patients were excluded if they presented with acute neurological deficits, acute clinical signs of systemic thromboembolic events or thrombosis, known left ventricular or aortic thrombus, blood coagulation disorders or (suspected) internal bleeding, a platelet count <100 × 10⁹/L, a history of heparin-associated thrombocytopenia (type II), severe chronic hepatic or renal disease, cerebral or gastrointestinal bleeding during the previous 6 months, or severe arterial hypertension resistant to treatment. Other exclusion criteria were absence of documented sinus rhythm on ECG for >1 year, necessity for permanent oral anticoagulation, presence of disease that may have caused neurological deficits (eg, paralysis agitans, multiple sclerosis), concomitant treatment with other anticoagulants, aspirin at a dose ≥325 mg/d, or other antiplatelet drugs.

Study End Points
The aim of the study was to demonstrate noninferiority of enoxaparin compared with UFH + phenprocoumon with regard to the primary
study end point, which was a composite of cerebral-ischemic neurological events (including transitory ischemic attacks and cerebral infarction); systemic thromboembolism; death from any cause; and major bleeding complications, defined by a decrease in serum hemoglobin by ≥2 g/dL, bleeding events requiring transfusion, retroperitoneal or intracranial bleeding, or macrohematuria. Because the aim of the study was to demonstrate noninferiority, analysis of the primary end point was based on the per-protocol population. Secondary end points included successful cardioversion, sinus rhythm at the end of the study period, other bleeding complications (except major bleedings), injection hematoma ≥5 cm in diameter, and other adverse events. All end points were evaluated within the planned therapy phase, ie, up to day 49±2 for “conventional” patients and patients with thrombi in the initial TEE, and up to day 28±2 for patients without thrombi in the initial TEE. Serious adverse events were evaluated until 14 days after study completion. The conduct of the trial was supervised by a Steering Committee consisting of 4 physicians participating in the study and 1 statistician. All serious adverse events were periodically evaluated and adjudicated by an independent Critical Event Committee consisting of 3 independent physicians not participating in the trial, who were blinded to the treatment. Protocol violations were categorized as minor or major on the basis of predefined criteria by the same committee, which consequently served as the End Point Review Committee.

Statistical Analysis
On the basis of previously published data,9 it was assumed that the event rate of combined safety and efficacy variables (primary study end point) would be ≤4% in the UFH+phenprocoumon arm and that the event rate could be reduced by ~50% with enoxaparin treatment. The statistically required sample size to demonstrate noninferiority with a margin of 2% was n = 250 patients per group at a type I error of α = 0.025 (1-sided) and a power of 1−β = 0.7. Thus, it was necessary to include a total of 500 patients in the trial. Data on the incidence of the composite primary end point were compared between the enoxaparin group and the UFH+phenprocoumon group using a Farrington-Manning test on noninferiority (primary analysis for the per-protocol population, additional analysis for the intention-to-treat population). Confidence intervals (CIs) for the incidences in the individual groups were calculated according to Clopper-Pearson. The first patient was enrolled on November 11, 1999, and the last patient on October 10, 2001. The last patient follow-up was performed on November 26, 2001. After collection of the follow-up data and entry into the database, the study was completed in July 2002.

Results

Baseline Characteristics
A total of 503 patients from 56 centers were enrolled in the study. Seven patients did not receive study medication and were excluded from analysis: 3 patients withdrew consent, 2 were in sinus rhythm before first administration of the study drug, and 2 were found to meet exclusion criteria after randomization (1 hyperthyroidism, 1 endocarditis). Thus, 496 patients were randomly assigned to receive either enoxaparin (248 patients) or UFH+phenprocoumon (248 patients) on an intention-to-treat basis. Of these, 65 (13.1%) (35 in the enoxaparin group, 30 in the UFH+phenprocoumon group) underwent cardioversion without and 431 (86.9%) (213 in the enoxaparin group, 218 in the UFH+phenprocoumon group) with TEE guidance. There were no statistically significant differences between treatment groups with regard to baseline clinical and echocardiographic parameters, except for a higher incidence of heart failure in the enoxaparin group (Table 1).

Incidence of Primary End Point After Treatment Assignment
Of the 496 randomized patients, 428 were analyzed per protocol, 216 in the enoxaparin group and 212 in the UFH+phenprocoumon group. The remaining 68 patients were excluded from the per-protocol analysis by the Critical Event Committee because of major protocol deviations: 28 patients because the study drug was administered for <21 days, 24 because of concomitant intake of other anticoagulant or antiplatelet drugs, 3 because cardioversion was performed <1 hour after first study drug administration, and 13 because of the presence of other exclusion criteria at study entry. A primary end point event occurred in 7 of 216 patients (3.2%; 95% CI, 1.3% to 6.6%) in the enoxaparin group and 12 of 212 (5.7%; 95% CI, 3.0% to 9.7%) in the UFH+phenprocoumon group (probability value for noninferiority = 0.016; 95% CI for difference in incidence rates, −6.9% to 1.8%). In the intention-to-treat analysis, the incidence of the primary end point was 7 of 248 in the enoxaparin group (2.8%; 95% CI, 1.1% to 5.7%) compared with 12 of 248 in the UFH+phenprocoumon group (4.8%; 95% CI, 2.5% to 8.3%; probability value for noninferiority = 0.013; 95% CI for difference in incidence rates, −5.8% to 1.6%). The incidences of the primary end point observed for both treatment arms are illustrated in Figure 2.

In stratum A, a primary end point event occurred in 4 of 65 patients (6.2%): 2 of 35 patients in the enoxaparin group (5.7%; 95% CI, 0.7% to 19.2%) and 2 of 30 patients in the UFH+phenprocoumon group (6.7%; 95% CI, 0.8% to 22.1%). In stratum B, a primary-end-point event occurred in 15 of 431 patients (3.5%): 5 in the enoxaparin group (2.3%; 95% CI, 0.8% to 5.4%) and 10 in the UFH+phenprocoumon group (4.6%; 95% CI, 2.2% to 8.3%, per protocol: probability value for noninferiority = 0.016; 95% CI for difference in incidence, −7.3% to 1.6%; intention-to-treat: probability value for noninferiority = 0.013; 95% CI for difference in incidence, −6.2 to 1.5%).

Deaths and Ischemic, Embolic, and Hemorrhagic Events
The incidence of death and ischemic, embolic, and hemorrhagic events and patient deaths for both treatment groups are summarized in Table 2. There were 8 deaths in the study (1.6%), 5 of which were classified as cardiac. The incidence of ischemic and embolic events was low; there were 2 cerebral embolic infarctions (0.4%), 2 transitory ischemic attacks (0.4%), and 2 systemic thromboembolisms (0.4%). In the enoxaparin group, 1 stroke occurred 45 days after cardioversion, and 1 transient ischemic attack occurred in a patient before planned cardioversion. In the UFH+phenprocoumon group, 3 embolic events occurred within the first week after cardioversion (2 systemic emboli, 1 stroke). In these 3 patients, anticoagulation levels at the time of the event were adequate, as verified by anticoagulation monitoring. One patient who suffered from a transient ischemic attack after cardioversion had been deferred because of a thrombus detected by TEE. Major bleeding events occurred in 8 patients (1.6%) and minor bleeding events in 42 (8.5%). Injection hematomas ≥5 cm in diameter occurred in 49
patients (9.9%) in the enoxaparin group. There was no significant difference for any of the individual events (death, embolism, or bleeding) between treatment arms or between strata A and B.

**Cardioversion Success**

The success rate of DC cardioversion is outlined in Figure 3. In stratum B, a left atrial thrombus was detected in 46 patients (10.7%), and left atrial spontaneous echo contrast was documented in 190 patients (44.1%). Spontaneous rhythm conversion before cardioversion occurred in 21 of 65 patients (32.3%) of stratum A and in 53 of 431 patients (12.3%) of stratum B (P<0.001). In the enoxaparin group, spontaneous reversion to sinus rhythm was observed in 44 of 248 patients (17.7%) compared with 30 patients (12.1%) in the UFH/phenprocoumon group (P=0.10). Cardioversion was not performed as a result of persisting thrombus detected by repeat TEE in 17 patients or for other reasons in 5 patients. Cardioversion success was not reported in 16 patients and was unclear in 1 patient. Thus, cardioversion success could not be analyzed in a total of 39 patients (22 in the enoxaparin group, 17 in the UFH/phenprocoumon group). Cardioversion was successful in 330 of the remaining 383 patients in whom it was attempted (86.2%), 151 of 180 (83.0%) in the enoxaparin group and 179 of 201 (89.1%) in the UFH/phenprocoumon group (P=0.10). In stratum A, cardioversion was successful in 32 of 38 patients (84.2%) and in stratum B, in 298 of 345 patients (86.4%; P=NS). The overall rate of sinus rhythm restoration (successful cardioversions and spontaneous rhythm conversion) was not different between treatment arms: 195 of 248 patients (78.6%) for enoxaparin compared with 209 of 248 (84.3%) for UFH/phenprocoumon (P=0.13).

**Table 1. Baseline Characteristics of Intention-to-Treat Population (n=496)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Enoxaparin (n=248)</th>
<th>UFH+Phenprocoumon (n=248)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age,* y</td>
<td>66±11</td>
<td>65±11</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex</td>
<td>152 (61.3)</td>
<td>151 (60.9)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI,* kg/m²</td>
<td>28.2±4.9</td>
<td>28.5±4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure,* mm Hg</td>
<td>132±19</td>
<td>132±20</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure,* mm Hg</td>
<td>80±11</td>
<td>79±11</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate,* bpm</td>
<td>88±22</td>
<td>89±22</td>
<td>NS</td>
</tr>
<tr>
<td>TEE guidance</td>
<td>213 (85.9)</td>
<td>218 (87.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Underlying heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>82 (31.0)</td>
<td>72 (29.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>182 (73.4)</td>
<td>180 (72.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart failure</td>
<td>82 (33.1)</td>
<td>60 (24.2)</td>
<td>0.037</td>
</tr>
<tr>
<td>Left atrial diameter,* mm</td>
<td>44±6</td>
<td>44±6</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>88 (36.8)</td>
<td>101 (42.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Estimated duration of atrial fibrillation,* d</td>
<td>15±37</td>
<td>11±19</td>
<td>NS</td>
</tr>
<tr>
<td>Symptomatic AF</td>
<td>222 (89.5)</td>
<td>224 (90.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Antiarrhythmic therapy†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>29 (11.7)</td>
<td>17 (6.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Class II (β-blocker except sotalol)</td>
<td>101 (40.7)</td>
<td>123 (49.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Sotalol</td>
<td>55 (22.2)</td>
<td>51 (20.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>36 (14.5)</td>
<td>42 (16.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Digitalis</td>
<td>74 (29.8)</td>
<td>74 (29.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

All data given as n (%) unless otherwise indicated. BMI indicates body mass index; AF, atrial fibrillation.

*Data given as mean±SD.
†Combination therapy possible.
The mean duration of study therapy in stratum A was $47 \pm 12$ days ($45 \pm 12$ days in the enoxaparin group, $49 \pm 11$ days in the UFH+phenprocoumon group, $P=NS$). In stratum B, mean therapy duration was $28 \pm 7$ days ($28 \pm 6$ days in the enoxaparin group versus $28 \pm 7$ days in the UFH+phenprocoumon group, $P=NS$) in the patients with excluded thrombus by TEE. Of the patients with a thrombus detected by the initial TEE, 16 eventually underwent cardioversion after exclusion of a thrombus by repeat TEE. The mean therapy duration in these patients was $45 \pm 16$ days ($44 \pm 12$ in the enoxaparin group, $45 \pm 18$ days in the UFH+phenprocoumon group, $P=NS$). At the end of the study, sinus rhythm was present in 310 of 462 patients who had an ECG at the last follow-up (67.1%): 151 of 229 (65.9%) of the enoxaparin group and 159 of 233 (68.3%) of the UFH+phenprocoumon group ($P=NS$). In the remaining 34 patients, no ECG was recorded at the last follow-up because of premature study termination.

![Figure 3. Results of cardioversion. PPC indicates phenprocoumon; CV, cardioversion; and SR, sinus rhythm.](image-url)
Discussion
This study demonstrates for the first time in a prospective, randomized trial that enoxaparin is noninferior to conventional anticoagulation with UFH, followed by oral anticoagulants in the setting of cardioversion of nonvalvular atrial fibrillation, either with or without guidance by TEE. The fact that conventional anticoagulation is currently used in $\approx 60\%$ of patients undergoing cardioversion highlights the reluctance of many physicians to administer adequate oral anticoagulation in this situation, especially in elderly patients, because of the fear of hemorrhagic complications.\(^{10}\) LMWHs have the advantage of being easy to administer subcutaneously and immediately establishing adequate levels of anticoagulation. In contrast, with oral anticoagulants, full anticoagulation is established only after several days. Thus, treatment with enoxaparin could close a time gap of insufficient anticoagulation until the full effect of phenprocoumon is reached. Moreover, whereas frequent anticoagulation monitoring is necessary for treatment with oral anticoagulants, especially in the initial dose titration phase, this is unnecessary for LMWHs, at least in the absence of significant impairment of renal function.\(^{18}\) A potential disadvantage of using LMWH is the need for repeated subcutaneous injections leading to increased patient discomfort and injection hematoma. However, self-injection has been shown to be generally well-accepted and safe in previous studies.\(^{19}\) In addition, initiating therapy with UFH requires intravenous access and thus hospitalization, so using enoxaparin could reduce the duration of hospitalization. The anticipated reduction in hospitalization duration and anticoagulation monitoring may make treatment with enoxaparin cost-effective in this setting despite the higher cost of the drug compared with UFH and oral anticoagulants.\(^{20}\) Moreover, the risk of heparin-induced thrombocytopenia has been shown to be lower with LMWH than with UFH.\(^{21}\)

The comparison of a drug administered by subcutaneous injection with an oral compound necessitated an open study design, which is a limitation of this trial. Moreover, it is not clear whether the data obtained with enoxaparin in this study hold true for other LMWHs. In one nonrandomized trial using dalteparin, the rate of embolic events in cardioversion of atrial fibrillation was also low.\(^{15}\) However, the effectiveness for the reduction of thromboembolic events in the arterial bed has not been shown consistently for all LMWHs.\(^{22}\)

In this study, phenprocoumon, commonly prescribed in Germany, was used as the oral anticoagulant instead of warfarin, which is the most widely used oral anticoagulant worldwide. The main difference between the compounds concerns the elimination half-life (144 hours for phenprocoumon\(^{23}\) versus 40 hours for warfarin\(^{24}\)). In one study comparing the safety of both drugs, the incidence of hemorrhagic complications was similar.\(^{25}\) However, there are no prospective randomized studies comparing the safety and efficacy of the 2 drugs. Therefore, caution must be taken in extrapolating the results of this study to warfarin.

Most patients in the study were cardioverted under TEE guidance. Because the approach to cardioversion was based on center-specific preference, this may reflect the approach to cardioversion currently favored. The low number of patients who were cardioverted without TEE may limit the interpretation of our results with enoxaparin to patients undergoing TEE guidance. Of note, although patients were not randomly assigned to cardioversion with or without TEE guidance, there was a trend for a lower incidence of the primary study end point for patients in whom TEE was used, which is in agreement with data from the ACUTE-I trial, which found fewer hemorrhagic complications using this approach.\(^{9}\) This finding may be because of the prolonged pretreatment with oral anticoagulation necessary if the conventional approach is used. As a result of the unbalanced, nonrandomized stratification, we could not demonstrate an increased cardioversion success rate in patients undergoing TEE-guided cardioversion in our study.

The concept of cardioversion of atrial fibrillation has been challenged by recent trials\(^{26–28}\) because of the high recurrence rate after cardioversion despite antiarrhythmic prophylaxis, which was also observed in this trial. One of these studies\(^{27}\) found a trend toward increased mortality in high-risk patients with atrial fibrillation in whom rhythm control was attempted compared with patients in whom rate control was the primary therapeutic target. However, in that study, chronic anticoagulation was not administered to all patients in the rhythm-control arm, which may have influenced the rates of embolic events and mortality. Moreover, more patients in the rhythm-control arm received class I antiarrhythmic drugs, which may cause proarrhythmia in patients with atrial fibrillation, especially with underlying cardiac disease.\(^{29}\) Thus, we believe that cardioversion remains an important therapeutic option for many patients with atrial fibrillation, especially if they are asymptomatic, as was the case in 90% of our study population.

In conclusion, enoxaparin is noninferior to UFH plus phenprocoumon in the setting of cardioversion of atrial fibrillation with regard to the occurrence of embolic events, bleeding complications, and death, especially when TEE guidance is used. Because of the greater ease of administration, the reduced need for anticoagulation monitoring, and the potential to reduce hospitalization costs and adverse events, it may be the preferred drug for this purpose in the future.

Appendix
List of participating centers (in alphabetical order of city name): Medizinische Fakultät der RWTH Aachen (T. Schimpf, C. Stellbrink); Erzgebirgsklinikum Annaberg-Buchholz (H. Volkmann); Marienhospital Arnsgberg GmbH (F.J. Altenwerth); Kreiskrankenhaus Am Plattenwald Bad Friedrichshall (A. Wirtch); Kerckhoff-Klinik Bad Nauheim (V. Miltvic, M. Weber); Klinikum Bayreuth (W. Mäurer); Oskar-Ziehen-Krankenhaus Berlin (O. Göing, C. Zemmrich); Städtisches Krankenhaus Neukölln, Berlin (W. Fabrig); DRK-Kliniken Köpenick, Berlin (H.F. Föhringer); Universitätsklinikum Charité, Berlin (G. Baumann); Städtische Kliniken Bielefeld-Mitte (H. Kuhn); St Josef Hospital Bochum (A. Mügge, J. Grote); Universitätsklinikum Bonn (H. Omran, H. Schmidt); Städtisches Klinikum Brandenburg (M. Oeff, M. Diezmann); Landeskrankenhaus Coburg (J. Brachmann); Kreiskrankenhaus Cralshaim (H. Bechtold, H. Sawitzki); Ambulantes Herzzentrum Dresden (S.G. Spitzer); Malteser Krankenhaus St Anna, Duisburg (G. Vollbeck); Friedrich-Alexander-Universität Erlangen (U. Nixdorf, D. Ropers); Alfred Krupp Krankenhaus Essen (T. Budde, A. Lehner); Universitätsklinikum Göttingen (G. Hasenfuß, E. Höcht); Allgemeines Krankenhaus Hagen (J. Rox, K. Zeppenfeld); Universitätskrankenhaus Eppendorf, Hamburg (T. Hofmann); Städtisches Klinikum Hanau (E.P. Kroemer); Städtisches Krankenhaus Heilbronn (J. Cyran, T. Schmidt); Evangelisches Krankenhaus Herne (W. Sehnert); Universitätsklinik...
Marienhospital, Herne (H.J. Trappe); Marienhospital Letmathe, Isel- 
lohn (D. Helmer); Universitätsklinikum Jena (H.H. Figulla); Uni-
iversitätsklinik Kiel (R. Simon); Evangelisches Krankenhaus Kalk, Köln 
(P. Wacker); Kreiskrankenhaus Leer (E. Stammwitz); St Remigius 
Krankenhaus Leverkusen (M. Walthier); Universitätsklinikum Augsburg 
(C. Göller, H.U. Klein); Universitätsklinikum Mainz (S. Mohr-Kahaly); Kreiskrankenhaus 
Mechernich (Claudia Lach, Peter Wirtz); St Franziskus-Hospital Münster 
(P. Kleine-Kathöfer); Universitätsklinikum Münster (T. Wichter); Pius-Hospital Oldenburg (S. Kossian); St Vincenz-Krankenhaus Paderborn (A. Schürl); Klinik 
Dorothea-Chr.-Erxleben, Quedlinburg (S. Peters); Elisabeth 
Krankenhaus Recklinghausen (R. Sack); Matthias-Spital Rheine (H.J. Odenthal); Klinik am See Rüdersdorf (H. Völler); Klinikum Saar- 
brücken Gmbh (G. Gorge); Kreiskrankenhaus Schopfheim (M. Standop); Johanniter-Krankenhaus der Altmark, Stendal (U. Nel- 
lessen); Robert-Bosch-Krankenhaus, Stuttgart (U. Sechtem); Kranken- 
haus der Barnherzigen Brüder Trier (K.E. Hauptmann); St Marien-Hospital Vecchia (R. Kloge); Klinikum der Stadt Villingen- 
Schwenningen (W. Jung); Josephs-Hospital Warendorf (T. Dorsel); 
Marien-Hospital GmBH Wesel (K. Haerten); St Elisabeth Kranken- 
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