Apixaban compared with parenteral heparin and/or vitamin K antagonist in patients with nonvalvular atrial fibrillation undergoing cardioversion: Rationale and design of the EMANATE trial

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Background Stroke prevention in anticoagulation-naïve patients with atrial fibrillation undergoing cardioversion has not been systematically studied.

Objective To determine outcomes in anticoagulation-naïve patients (defined as those receiving an anticoagulant for <48 hours during the index episode of atrial fibrillation) scheduled for cardioversion.

Methods This is a randomized, prospective, open-label, real-world study comparing apixaban to heparin plus warfarin. Early image-guided cardioversion is encouraged. For apixaban, the usual dose is 5 mg BID with a dose reduction to 2.5 mg BID if 2 of the following are present: age ≥80 years, weight <60 kg, or serum creatinine ≥1.5 mg/dL. If cardioversion is immediate, a single starting dose of 10 mg (or 5 mg if the dose is down-titrated) of apixaban is administered. Cardioversion may be attempted up to 90 days after randomization. Patients are followed up for 30 days after cardioversion or 90 days postrandomization if cardioversion is not performed within that timeframe. Outcomes are stroke, systemic embolization, major bleeds, clinically relevant nonmajor bleeding, and death, all adjudication-blinded.

Statistics The warfarin-naive cohort from the ARISTOTLE study was considered the closest data set to the patients being recruited into this study. The predicted incidence of stroke, systemic embolism, and major bleeding within 30 days after randomization was approximately 0.75%. To adequately power for a noninferiority trial, approximately 48,000 participants would be needed, a number in excess of feasibility. The figure of 1,500 patients was considered clinically meaningful and achievable.

Clinical context This first prospective cardioversion study of a novel anticoagulant in anticoagulation-naïve patients should influence clinical practice. [Am Heart J 2016;179:59-68.]
anticoagulants (NOACs) may be a reasonable alternative to heparin and warfarin for patients with NVAF undergoing cardioversion and that event rates are very low (Table I). The major limitation of these post hoc analyses, however, is the prolonged period of anticoagulation preceding the cardioversion. The need for more immediate cardioversion frequently arises in patients presenting with newly identified AF. The X-VeRT trial was the first prospective trial of a NOAC in the setting of cardioversion and found rivaroxaban, an oral factor Xa inhibitor, comparable to VKA in patients with NVAF undergoing cardioversion within 5 days or after 3 weeks and up to a maximum of 8 weeks of anticoagulation, once again with very low event rates (0.5% and 0.6% for efficacy and safety for rivaroxaban and 1.0% and 0.8% for usual therapy, both not significantly different). No studies have specifically evaluated a NOAC in a population of patients who are anticoagulation naïve and who are undergoing cardioversion. EMANATE will uniquely address cardioversion in this population.

Apixaban
Apixaban is an orally active, reversible, direct inhibitor of human coagulation factor Xa developed jointly by Bristol-Myers Squibb (BMS) and Pfizer as an antithrombotic agent, now licensed globally for the prevention of stroke and systemic embolization in patients with NVAF and for treatment and prevention of venous and thromboembolic disease.

Objectives
The goal of this study is to assess clinical outcomes in patients randomized to apixaban against conventional anticoagulant care (parenteral heparin and/or a VKA) in patients with recently detected AF considered for cardioversion. The protocol encourages an image-guided approach (transesophageal echocardiography [TEE] or computed tomography [CT]) or anticoagulation for a minimum of 3 weeks before cardioversion. To avoid confounding by prior treatment, the study focuses on patients who are anticoagulation naïve, excluding patients receiving any anticoagulant for >48 hours during the index episode of AF. Another aim of the study is to define predictors of a successful outcome at 30 days after cardioversion.

Design
This is a randomized, active-controlled, open-label study of approximately 1,500 patients randomized 1:1 to apixaban or usual care (parenteral heparin and/or oral anticoagulation with VKAs [goal international normalized ratio [INR] 2.0-3.0, excluding other NOACs; Figure 1). Anticoagulation is administered from randomization until 30 days after cardioversion. If cardioversion is not performed, anticoagulation will be administered for a maximum of 90 days. Clinical data including cardioversion details, efficacy and safety outcomes, length of in-hospital stay, and information regarding image guidance are collected. The apixaban dose is 5 mg BID, with a dose reduction to 2.5 mg BID if at least 2 of the following exist: age >80 years, weight <60 kg, or serum creatinine >1.5 mg/dL. Five doses of apixaban will be administered before cardioversion to achieve steady-state blood levels. If an immediate cardioversion is planned, a single 10 mg dose (or 5 mg if the dose is down-titrated) is administered at least 2 hours before cardioversion to more rapidly bring exposure up to steady state. Investigators will use their local label for dose adjustment guidance for participants with renal impairment. (See Fig. 2).

Participants randomized to apixaban will transition from their preexisting anticoagulant (oral and/or parenteral) of <48 hours as follows. For participants receiving a VKA, apixaban is started when the INR is below 2.0. For all NOACs, discontinue the drug and begin apixaban at the next scheduled dose but no earlier than 12 hours after the previous oral anticoagulant administration. For low-molecular-weight heparin, apixaban should be started at the time of the next scheduled dose and no earlier than 12 hours after the previous parenteral anticoagulation administration. For intravenous (IV) infusion of unfractionated heparin (UFH), apixaban may be started between 0 and 2 hours after IV UFH has been stopped.

For participants randomized to usual therapy, stop NOAC and start warfarin immediately, and start heparin at

<table>
<thead>
<tr>
<th>Event</th>
<th>RE-LY dabigatran 150 mg</th>
<th>RE-LY dabigatran 110 mg</th>
<th>RE-LY warfarin</th>
<th>ARISTOTLE apixaban</th>
<th>ARISTOTLE warfarin</th>
<th>ROCKET-AF rivaroxaban</th>
<th>ROCKET-AF warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke† or systemic embolism</td>
<td>0.30</td>
<td>0.77</td>
<td>0.60</td>
<td>0</td>
<td>0</td>
<td>1.88</td>
<td>1.86</td>
</tr>
<tr>
<td>Major bleeding ‡</td>
<td>0.60</td>
<td>1.70</td>
<td>0.60</td>
<td>0.30</td>
<td>0.20</td>
<td>18.75</td>
<td>13.04</td>
</tr>
<tr>
<td>Death§</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>0.6</td>
<td>0.5</td>
<td>1.88</td>
<td>3.73</td>
</tr>
</tbody>
</table>

n/a, Not applicable.
† ROCKET-AF combined event rates for cardioversion and ablation procedure.
‡ Both ischemic and hemorrhagic strokes.
⁎ ROCKET-AF combined major and nonmajor clinically relevant bleeding.
§ RE-LY did not report death rates within 30 days of cardioversion.
Figure 1

EMANATE study design.

Figure 2

Participant flow.
the time of the next dose of the novel agent and continue until the INR is above 2. In general, patients will be managed according to the local clinician’s usual practice and in a manner consistent with the design of the study.

Statistical considerations

There was no precedent for evaluating anticoagulation-naïve patients in the setting of cardioversion. The warfarin-naïve cohort from the ARISTOTLE study was considered the closest data set to the patients being recruited into this study. The incidence of stroke and systemic embolism within 30 days after randomization was 0.3% (1 stroke or systemic embolism on apixaban and 3 events on usual care). The incidence of major bleeding was 0.45% (2 events on apixaban and 5 events on usual care). To adequately power for noninferiority, 480 end points would be needed (similar to ARISTOTLE). In this study, follow-up is limited to 30 days after cardioversion or 90 days postrandomization. An estimated event rate of approximately 1% would require 48,000 participants, a number far in excess of practicality. The figure of 1,500 patients was considered clinically meaningful and achievable. Kaplan-Meier curves of the time to first adjudicated stroke or systemic embolism, first major bleeding event, and composite of first major bleed and clinically relevant nonmajor bleed as well as all-cause death will be generated.

Executive Committee

The Executive Committee (EC) comprises 5 academic experts, 4 sponsor representatives (nonvoting), and a biostatistician. The EC takes sole responsibility for the study design, trial management, data analysis, and writing of the manuscript. The EC reviews recommendations from the Data Monitoring Committee (DMC) and oversees the presentation and publication of the results. The EC is aided by a clinical research organization and by designated national leaders in both cardiology and emergency medicine in the participating countries. This trial is sponsored by BMS and Pfizer. The authors acknowledge the editorial assistance of Ms. Paulette Trent.

Data Monitoring Committee

An independent DMC is responsible for monitoring the safety of participants in the study and recommending alterations of the study to the EC and the sponsor. The sponsor forwards decisions, which may include aggregate analyses of end point events and safety data that are not end points, to regulatory authorities as appropriate.

Study procedures

Screening

The investigator or designee at each participating clinical site obtains written informed consent from each participant, as well as contact and demographic information, relevant medical history, and CHA₂DS₂-VASc score, and evaluates clinical laboratory results (Figure 2). The patient must meet inclusion and exclusion criteria, including electrocardiographic confirmation of heart rhythm (Tables II and III). These tables additionally compare the inclusion and exclusion criteria from the first completed trial of rivaroxaban (X-VeRT) and a second ongoing trial of edoxaban (ENSURE-AF) that, like EMANATE, prospectively evaluate novel anticoagulants in the setting of cardioversion.

Randomization

Randomization uses a centralized interactive voice-response system. Study medication is dispensed in accordance with local policies and procedures, with accounting recorded on case report forms. Patients can be randomized and cardioverted on the same day, combining visits 1 and 2.

Cardioversion

The following details are recorded for each cardioversion attempted: time and date attempted; whether pharmacological, electrical, both pharmacological and electrical, or spontaneous; local investigator interpretation of image guidance; type of image guidance; number, date, and time of cardioversion attempts; rhythm status after cardioversion; and adverse events (AEs).

Compliance

Compliance with apixaban is based on pill counts at the time of cardioversion and at the end of the study. For patients randomized to usual care, compliance is assessed by INR monitoring.

Image guidance

In the event TEE or CT imaging identifies atrial thrombus, cardioversion is deferred for at least 3 weeks. Assigned anticoagulation continues, and imaging is repeated to confirm resolution of thrombus before cardioversion. We encourage investigators to continue assigned medication in patients identified with thrombus and repeat imaging studies after 3 weeks.

Management of bleeding

Anticoagulation is interrupted in the event of clinically significant bleeding and managed according to local practice, which may include such measures as surgical hemostasis, volume repletion, transfusion of blood products, and for patients in the conventional therapy arm, administration of protamine and supplemental vitamin K fresh-frozen plasma, as deemed appropriate by the treating physician. An antidote to apixaban is in development but is not yet approved.

Treatment transitions

At the end of the study or upon early withdrawal from the study, the patient’s subsequent management and treatment are conducted by the treating physician.
according to usual practice. When an alternative anticoagulation strategy is necessary, the protocol recommends the transition procedures contained in the apixaban package insert.\footnote{Ezekowitz et al \ac{63}}

**Participant withdrawal**

Participants may withdraw from the study at any time upon request, at the discretion of the investigator or sponsor for safety or behavioral reasons, or because of the inability of the participant to comply with the required schedule of visits or procedures. Participants withdrawn from the study are subsequently managed according to conventional practice. Every effort will be made to ensure follow-up for outcomes relevant to the trial objectives.

**Assessment**

**Clinical outcomes**

Clinical outcomes are assessed by local investigators to determine whether a protocol-specified outcome had occurred. Events are recorded and reviewed by independent adjudicators blinded to treatment allocation. The clinical outcomes are the occurrence of acute stroke, systemic embolism, all-cause death, major bleeding, and clinically relevant nonmajor bleeding.

**Acute stroke**

_Stroke_ is defined as a focal neurological deficit of sudden onset, lasting at least 24 hours, not due to a readily identifiable nonvascular cause. Strokes are classified as primary ischemic, hemorrhagic, infarction with hemorrhagic conversion, or of unknown type if no imaging is available in accordance with definitions established by the American College of Cardiology.\footnote{American Heart Journal Volume 179} A diagnosis of primary hemorrhagic stroke requires documentation by imaging of hemorrhage in the cerebral parenchyma or in the subdural or subarachnoid space or evidence of hemorrhage obtained by lumbar puncture neurosurgery or identified at autopsy. Nonhemorrhagic stroke is a focal neurological deficit resulting from thrombosis or embolism evident at 24 hours. Infarction with hemorrhagic conversion requires absence of hemorrhage on initial scan but evidence of hemorrhage on subsequent scan. Stroke of unknown type is designated when brain imaging is not available.

\begin{table}[h]
\centering
\caption{Inclusion criteria for EMANATE, X-VeRT, and ENSURE-AF}
\begin{tabular}{|p{20cm}|p{8cm}|p{8cm}|}
\hline
\textbf{EMANATE} & \textbf{X-VeRT} & \textbf{ENSURE-AF} \\
\hline
Participants with NVAF (as documented by ECG at visit 1) indicated for cardioversion and initiation of anticoagulation in accordance with the approved local label. Participants presenting with atrial flutter with no evidence of AF are not eligible for enrollment. & Hemodynamically stable NVAF $>48$ h or of unknown duration & Ongoing NVAF lasting for at least 48 h but $\leq 12$ m \\
Age $\geq 18$ y (age $\geq 19$ y for Korea only and age $\geq 20$ y for Japan only) & Men or women aged $>18$ y & Male or female participants older than the minimum legal adult age (country specific) \\
Written informed consent & Written informed consent & Signed informed consent form \\
The participant is willing to provide contact details for at least 1 alternate person for study staff to contact regarding their whereabouts, should the participant be lost to follow-up over the course of the study. (subject to IRB/IEC approval) & Scheduled for cardioversion (electrical or pharmacological) of NVAF & Ongoing NVAF at the time of randomization should be confirmed by any electrical tracing (eg, routine 12-lead ECG, Holter monitor rhythm strip, intracardiac electrogram, or pacemaker) before randomization. \\
Female participants of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 28 d after the last dose of assigned treatment. & Women of childbearing potential and men must agree to use adequate contraception when sexually active. & Duration and proof of AF during the previous 12 m can be confirmed by any electrical tracing or a recording in the participant’s medical records (eg, medical chart, hospital discharge summary). Symptomatic participants with no known history of AF and no prior electrical tracing or recording of/ about the cardiac rhythm available for the past 12 m may be randomized into the study if there is reasonable belief that the current episode of AF lasts for at least 48 h and no longer than 12 m. Participant is planned for electrical cardioversion. Participants with AF after a cardiac surgical procedure (including catheter ablation) will be allowed into the study, providing that they meet all the other inclusion criteria and the time from the surgery to randomization is $\leq 30$ d. The investigator will be responsible for assessment of risks relevant to the cardioversion procedure in such participants. \\
Participants who are willing and able to comply with scheduled visits, treatment plan, and other study procedures & & \\
\hline
\end{tabular}
\end{table}
Table III. Exclusion criteria for EMANATE, X-VeRT, and ENSURE-AF

<table>
<thead>
<tr>
<th>EMANATE</th>
<th>X-VeRT</th>
<th>ENSURE-AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Having taken &gt;48 h of an anticoagulant (oral/or parenteral) immediately before randomization</td>
<td>Severe, disabling stroke (modified Rankin score of 4-5, inclusive) within 3 m or any stroke within 14 d before the randomization visit</td>
<td>AF considered to be of a transient or reversible nature (such as in myocarditis, postsurgery) regardless of when the event has occurred</td>
</tr>
<tr>
<td>Contraindications to apixaban or usual care (eg, VKA) in accordance with the approved local label</td>
<td>Transient ischemic attack within 3 d before randomization</td>
<td>Participants with a history of LAA closure (either by surgery or by a procedure)</td>
</tr>
<tr>
<td>Severe hemodynamically compromised participants requiring emergent cardioversion</td>
<td>Acute thromboembolic events or thrombosis (venous/arterial) within the last 14 d before randomization</td>
<td>Participants with acute MI, stroke, acute coronary syndrome, or percutaneous coronary intervention within the previous 30 d or receiving DAPT regardless of when the event has occurred</td>
</tr>
<tr>
<td>Hemodynamically significant mitral stenosis, mechanical or biological prosthetic valve, or valve repair</td>
<td>Acute MI within the last 14 d before randomization</td>
<td>Participants with moderate or severe mitral stenosis, mitral valve rheumatic disease, unresected atrial myxoma, or a mechanical heart valve (participants with bioprosthetic heart valves and/or valve repair can be included) and/or other conditions, such as pulmonary embolism, considered to be a formal indication for conventional anticoagulation. However, patients with AF and valvular heart diseases such as mitral valve prolapse, mitral valve regurgitation, and aortic valve disease are allowed in the study.</td>
</tr>
<tr>
<td>Conditions other than AF that require chronic anticoagulation (eg, a prosthetic heart valve)</td>
<td>Cardiac-related criteria (known presence of left atrial/LAA thrombus before study inclusion, known presence of atrial myxoma, known left ventricular or aortic thrombus, valvular heart disease (either hemodynamically significant mitral valve stenosis or prosthetic heart valve))</td>
<td>Signs of bleeding or conditions associated with high risk of bleeding including major surgeries or biopsies in the last 10 d</td>
</tr>
<tr>
<td>Simultaneous treatment with both aspirin and a thienopyridine (eg, clopidogrel, ticlopidine, prasugrel) or simultaneous treatment with both aspirin and ticagrelor</td>
<td>Active bleeding or high risk of bleeding contraindicating anticoagulant therapy</td>
<td>Participants with any contraindication to anticoagulant agents</td>
</tr>
<tr>
<td>Pregnant females; breastfeeding females; females of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 d after last dose of investigational product</td>
<td>Concomitant drug therapies: -Indications for anticoagulant therapy for a condition other than AF (eg, VTE) -Chronic ASA therapy &gt;100 mg daily or DAPT -Concomitant use of strong inhibitors of both CYP3A4 and P-gp (ie, all HIV protease inhibitors and the following azole antimycotic agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically)</td>
<td>Participants with any contraindication to anticoagulant agents</td>
</tr>
<tr>
<td>Participation in other studies involving investigational drug(s) (phases 1-4) within 30 d before the current study begins and/or during study participation. Note: participants cannot be randomized into this study more than once.</td>
<td>Concomitant conditions: -Chillbearing potential without proper contraceptive measures, pregnancy, or breastfeeding -Hypersensitivity to investigational treatment or comparator treatment -Calculated CrCl &lt;30 mL/min -Hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk -Severe conditions leading to life expectancy of &lt;6 m -Planned invasive procedure with potential for uncontrolled bleeding (including major surgery or cardiac catheterization) -Inability to take oral medication -Ongoing drug addiction or drug abuse</td>
<td>Participants with conditions associated with high risk of bleeding such as a past history of intracranial (spontaneous or traumatic), spontaneous intraocular, spinal, retroperitoneal, or intraarticular bleeding; overt gastrointestinal bleeding or active ulcer within the previous year; recent severe trauma, major surgery, or deep organ biopsy within the previous 10 d; active infective endocarditis; uncontrolled hypertension (BP above 170/100 mm Hg); or hemorrhagic disorder including known or suspected hereditary or acquired bleeding or coagulation disorder</td>
</tr>
<tr>
<td>Severe acute or chronic medical or surgical disorder including known or suspected hereditary or acquired bleeding or coagulation disorder</td>
<td>Any other contraindication listed in the local label</td>
<td>Participants receiving DAPT</td>
</tr>
<tr>
<td>Table III (continued)</td>
<td>EMANATE</td>
<td>X-VeRT</td>
</tr>
<tr>
<td>------------------------</td>
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<tr>
<td>psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study</td>
<td>labeling for the comparator treatment or experimental treatment</td>
<td>(eg, aspirin plus thienopyridine such as clopidogrel, prasugrel, or ticagrelor) or anticipated to receive such therapy</td>
</tr>
<tr>
<td>Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or participants who are BMS/Pfizer employees directly involved in the conduct of the trial</td>
<td>Participation in a study with an investigational drug or medical device within 30 d before randomization</td>
<td>Participants receiving prohibited concomitant medications (fibrinolytics, nonstudy anticoagulants other than those used as a bridge to/from study drug), chronic oral or parenteral NSAID use for ≥4 d/wk</td>
</tr>
<tr>
<td>Previous randomization in this study</td>
<td>Inability to comply with the study procedures</td>
<td>Participants receiving chronic cyclosporine therapy</td>
</tr>
<tr>
<td>Inability to comply with the study procedures</td>
<td></td>
<td>Participants with active cancer undergoing chemotherapy, radiation, or major surgery within the next 3 m; Significant active concurrent medical illness or infection; life expectancy &gt; 6 m; Participants who are unlikely to comply with the protocol (eg, uncooperative attitude, inability to</td>
</tr>
</tbody>
</table>
Extracranial systemic embolism

Systemic embolism is defined by a clinical presentation consistent with acute loss of blood supply to an anatomical site supplied by a single artery, supported by evidence from angiography, surgical specimens, autopsy, or other objective testing.

Major bleeding

Clinically overt bleeding is defined as visible bleeding, or signs or symptoms suggestive of bleeding with confirmatory imaging that detects the presence of blood (eg, ultrasound, CT, or magnetic resonance). The definition of major bleeding adapted from the International Society on Thrombosis and Hemostasis requires clinically overt bleeding accompanied by 1 or more of the following: a decrease in hemoglobin of >2 g/dL; transfusion of >2 units of packed red blood cells; bleeding that occurs in at least 1 of the following critical sites: intracranial, intraspinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed), pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal; or bleeding that is fatal.

Clinically relevant nonmajor bleeding

The definition of clinically overt bleeding in the EMANATE protocol is adapted from the International Society on Thrombosis and Hemostasis guidelines. Clinically relevant nonmajor bleeding is an overt bleed that compromises hemodynamics, leads to hospitalization, produces subcutaneous hematoma >25 cm², or 100 cm² if traumatic, intramuscular hematoma documented by ultrasonography, and epistaxis lasting >5 minutes or repetitive (ie, 2 or more episodes of bleeding within 24 hours), or leads to intervention (eg, packing or electrocoagulation); gingival bleeding occurring spontaneously (ie, unrelated to eating or tooth brushing) or lasting >5 minutes; spontaneous macroscopic hematuria lasting >24 hours after instrumentation (eg, catheter placement or surgery); macroscopic gastrointestinal hemorrhage, including at >1 episode of melena or hematemesis, if clinically apparent, and hemoptysis outside the context of pulmonary embolism; or any other bleeding considered to have clinical consequences such as medical intervention, unscheduled contact (visit or telephone call) with a physician, temporary interruption of study drug, or associated with pain or impaired activities of daily life.

Length of hospital stay

The date and time of each hospital admission and discharge will be recorded.

Adverse events

An AE is defined as any untoward medical occurrence or worsening of a preexisting medical condition in a participant administered an anticoagulant during the course of the study.

Serious adverse events. Serious adverse events are untoward medical occurrence that are life threatening or fatal, require inpatient hospitalization or prolong an existing hospitalization, result in persistent or significant disability or incapacity, congenital anomaly or birth defect, require intervention to prevent permanent impairment or damage, or based on medical judgment, are important medical events that place a participant in jeopardy and require medical or surgical intervention to prevent 1 of the aforementioned outcomes.

Discussion

The novelty of this trial is the exclusive enrollment of anticoagulant-naïve patients with recently detected AF with a focus on enrolling those patients amenable to early cardioversion. Also unique, if an immediate cardioversion is planned, is the administration of a loading dose of 10 mg (or 5 mg if the dose is down-titrated) of apixaban at least 2 hours before cardioversion. This is done to more rapidly achieve a steady state of anticoagulation. For this reason, potential participants are being actively identified in hospital emergency departments. Image-guided cardioversion with TEEs or CT scans is of special interest. Thus, the
Assessment of Cardioversion Use in Transesophageal Echocardiography study, a multicenter, randomized trial comparing a TEE-guided strategy of abbreviated therapeutic anticoagulation with IV UFH started 24 hours before cardioversion against conventional warfarin (INR 2.0-3.0) for at least 3 weeks before cardioversion, provided important background information. The investigators enrolled 1,222 patients with AF of >2 days duration and found no significant difference between the 2 strategies in the rate of thromboembolic events for an 8-week period. The rate of hemorrhagic events was lower in the TEE-guided group (18 events [2.9%] vs 33 events [5.5%], P = .03). The TEE group had a shorter time to cardioversion (mean ± SD, 3.0 ± 5.6 vs 30.6 ± 10.6 days). The authors concluded that the strategy of TEE-guided treatment was a safe and effective alternative to the conventional treatment strategy. 6

Additional data relevant to cardioversion derive from a post hoc subgroup analysis of the ARISTOTLE trial, in which 540 participants underwent 743 cardioversions and were followed up for 30 days after cardioversion. No stroke or systemic embolic events occurred in patients randomized to apixaban or warfarin. One major bleeding event and 2 deaths were observed in each group.10 All participants undergoing cardioversion in that trial had been chronically anticoagulated before cardioversion, so there was no information on the safety of apixaban in participants newly presenting with AF or in those patients naïve to anticoagulation in whom early cardioversion is indicated. The EMANATE trial is designed to fill this important information gap.

The first and largest post hoc analysis of cardioversion was in the RE-LY trial, which found similarly low event rates in groups treated with warfarin or either of 2 doses of dabigatran, 150 mg BID or 110 mg BID.7 The analysis provided grounds for optimism regarding the potential use of a NOAC in this setting (Table I). Subsequently, secondary analysis of the ROCKET-AF trial described a similar experience with rivaroxaban in a smaller number of patients insofar as event rates were low (Table I).11 The ENGAGE-AF trial of edoxaban also included patients undergoing cardioversion, but the data are not currently available.

The only prospective trial to specifically address cardioversion was the X-VeRT trial, which tested rivaroxaban against usual therapy.12 Site investigators decided whether to randomize participants to early (1-5 days after randomization) or delayed cardioversion (between 21 and 56 days after randomization). Event rates were low in both arms, with a nonsignificant trend favoring rivaroxaban. Another ongoing prospective trial, ENSURE-AF, is evaluating edoxaban against usual care in patients with AF undergoing cardioversion.17

**Limitations**

EMANATE is an ongoing open-label trial. There is precedent for conducting open-label anticoagulation trials with blinded adjudication.12,17,22-24 The outcomes of these completed trials are very similar to those of completed double-blind trials,10,11,24,25 thus, confirming the validity of this type of trial design.

We also describe the difficulty of conducting a statistically valid noninferiority trial in the setting of cardioversion due to the very large sample size required because of low event rates reported in all the recent cardioversion trials evaluating novel agents. This limitation was recognized in the design of the comparable X-VeRT and ENSURE-AF trials. We did consider a cohort study using apixaban alone with comparison to historic controls; however, the unique feature of EMANATE is the anticoagulation-naïve population for which a historical control group would not be available. There is evidence that apixaban is being used in the setting of cardioversion in certain sites without direct evidence to support this approach. We do believe that this study fills an important data gap and that the results of this study should bear importantly upon future clinical practice.

**References**


