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A prospective evaluation of edoxaban compared to warfarin in subjects undergoing cardioversion of atrial fibrillation:

The Edoxaban vs. warfarin in subjects Undergoing cardioversion of Atrial Fibrillation (ENSURE-AF STUDY)

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Abstract

We designed a prospective, randomized, open-label, blinded endpoint evaluation (PROBE) parallel group Phase 3b clinical trial comparing edoxaban (a new oral factor Xa inhibitor) with enoxaparin/warfarin followed by warfarin alone in subjects undergoing planned electrical cardioversion of non-valvular AF. The primary efficacy endpoint is the composite endpoints of stroke, systemic embolic event (SEE), myocardial infarction (MI) and cardiovascular (CV) mortality, from randomization until the end of follow-up (Day 56 post cardioversion). The primary safety endpoint is the composite of major and clinically-relevant non-major (CRNM) bleeding, from the first administration of study drug to end of treatment (Day 28 post cardioversion) + 3 days. The primary efficacy analysis will be conducted on the intention-to-treat population whereas the primary safety analysis – on the safety population (refer to definitions in the main text).

The study includes stratification on the following levels: (i) approach to cardioversion (transoesophagel echocardiography (TEE) or non-TEE) as determined by the Investigator; (ii) subject’s experience in taking anticoagulants at the time of randomization (anticoagulant-experienced or anticoagulant-naïve); and (iii) assigned edoxaban dose (full 60 mg QD or reduced 30 mg dose QD). A subject with one or more factors (CrCl ≥ 15mL/min and ≤ 50 mL/min, low body weight [≤ 60 kg], and concomitant use of p-pg inhibitors (excluding amiodarone) will receive a reduced dose (30 mg) of edoxaban if the subject is randomized to the edoxaban group.

ENSURE-AF will be the largest prospective randomised trial of anticoagulation for cardioversion, also involving a NOAC, edoxaban.

Key words: edoxaban, cardioversion, atrial fibrillation, warfarin
Introduction

For over 50 years warfarin-based anticoagulation has been the pharmacologic approach to reducing thromboembolic risk in this setting. Randomized controlled studies have shown that warfarin, the most commonly used vitamin K antagonist (VKA), reduces the risk of ischemic stroke in patients with AF by two-thirds. The VKAs have various limitations and based on these challenges, only two-thirds of patients eligible for warfarin therapy actually receive treatment. Furthermore, among patients who receive warfarin in preparation for cardioversion, major hemorrhagic complications (defined as complications requiring hospitalization, blood transfusion, or urgent surgery) are reported in 1% to 2% of patients during the first month of therapy. Also, the use of warfarin as an anticoagulation strategy for cardioversion can result in procedure cancellations due to subtherapeutic INRs.

The landscape for stroke prevention in atrial fibrillation (AF) has changed with the availability of the Non-VKA Oral Anticoagulants (NOACs), which offer relative efficacy, safety and convenience compared to the VKAs. In a recent meta-analysis by Ruff et al, the NOACs significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0.81, 95% CI 0.73–0.91; p<0.0001), mainly driven by a reduction in hemorrhagic stroke (0.49, 0.38–0.64; p<0.0001). NOACs also significantly reduced all-cause mortality (0.90, 0.85–0.95; p=0.0003) and intracranial hemorrhage (0.48, 0.39–0.59; p<0.0001), but increased gastrointestinal bleeding (1.25, 1.01–1.55; p=0.04).

Cardioversion and thromboembolism

Cardioversion (both electrical and pharmacological) in patients with AF is associated with an increased risk of thromboembolic events. The risk is higher (5% to 7%) if anticoagulation is inadequate or absent. With adequate anticoagulation, the risk of thromboembolic events in the periprocedural period is in the range of 0.7% to 0.8%.
Rates of thromboembolism from observational studies and post-hoc subgroup analyses from clinical trials are summarised in Table 1\textsuperscript{11-14}. The use and duration of anticoagulation in the setting of cardioversion has undergone limited evaluation in randomized prospective trials. Based on the observational data current recommendations for patients with AF of > 48 hours duration is therapeutic anticoagulation for at least 3 weeks before and 4 weeks after cardioversion regardless of stroke risk. Following cardioversion for AF of any duration, the decision regarding long-term anticoagulation therapy should ultimately be based on the thromboembolic risk profile, rather than the presence of sinus rhythm.

\textit{TEE-guided Cardioversion}

The Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) study including 1222 subjects demonstrated comparable risk of thromboembolic events with both the conventional strategy of 3 weeks of warfarin before cardioversion and the TEE-guided strategy of short-term anticoagulation with intravenous (IV) unfractionated heparin or warfarin just prior to cardioversion (0.5% and 0.8%, respectively; \( p = 0.50 \))\textsuperscript{3}. The TEE-guided group in the ACUTE study had a significantly lower risk of bleeding in the pericardioversion period compared with the conventional group (2.9% versus 5.5%; \( p = 0.03 \)) which was probably related to the longer total duration of anticoagulation in the conventional group. The absence of left atrial thrombus on TEE does not preclude the need for anticoagulation just before and during cardioversion as well as continuation for at least 4 weeks after the procedure\textsuperscript{16}. Finally, it should be acknowledged that the ACUTE study was discontinued prematurely due to problems with recruitment and statistically it was substantially underpowered for non-equivalence. Despite this important limitation, its results were incorporated in current guideline recommendations.

\textit{Use of Non-VKA Oral Anticoagulants (NOACs)}

Major drawbacks of VKAs such as warfarin in the setting of cardioversion are its delayed onset of action. In addition, fluctuations of INR during the pre-cardioversion period or
on the day of cardioversion may lead to cancellation of the procedure with inconvenience and additional costs for both the patient and the health care system.

The availability of new rapid onset anticoagulants such as dabigatran (a direct thrombin inhibitor), apixaban and rivaroxaban (FXa inhibitors) may potentially avoid the therapeutic delay observed with warfarin.

A post-hoc analysis of subjects undergoing cardioversion in the Randomized Evaluation in Long-Term Anticoagulation Study (RE-LY) study demonstrated comparability of dabigatran etexilate to warfarin in the incidence of stroke or major bleeding within 30 days of cardioversion\(^1\). In the rivaroxaban versus warfarin in patients with nonvalvular AF who were at moderate to high risk for stroke (ROCKET AF) study, there was no significant difference between those treated with rivaroxaban or warfarin in stroke or systemic embolism in subjects undergoing rhythm control (including electrical or pharmacological cardioversion)\(^1\). One small (743 cardioversions performed in 540 patients) post-hoc analysis of patients undergoing cardioversion in the ARISTOTLE trial has been published\(^1\). In this analysis, no stroke or systemic emboli occurred in the 30-day follow-up period, whilst major bleeding occurred in 1 patient (0.2%) receiving warfarin and 1 patient receiving apixaban (0.3%).

Only one prospective randomized trial of a NOAC in the cardioversion setting is has been published. The X-VERT trial\(^1\) studied 1504 AF patients undergoing cardioversion who were randomized 2:1 (rivaroxaban:VKA) using 2 cardioversion strategies: (i) the first approach is ‘early cardioversion’ with the pre-cardioversion anticoagulation goal of 1 to 5 days using rivaroxaban or usual therapy (heparin + VKA), and (ii) the alternative approach of ‘delayed cardioversion’, with either rivaroxaban or VKA being administered for 21 to 56 days before cardioversion. The primary efficacy outcome occurred in 0.51% in the rivaroxaban group and 1.02% in the VKA group [risk ratio 0.50; 95% confidence interval (CI) 0.15–1.73]. Major bleeding occurred in 0.6% patients in the rivaroxaban group and 0.8% in the VKA group (risk ratio 0.76; 95% CI 0.21–2.67). The present cardioversion study with edoxaban (ENSURE-AF) is the largest cardioversion trial to be conducted to date, which addresses the gap in knowledge of management of patients
with AF who are at low risk of thromboembolic complications and are candidates for rhythm control.

**Edoxaban**

Edoxaban is an orally active, selective, direct and reversible inhibitor of Factor Xa (FXa). Peak plasma concentrations of edoxaban occur at 1 to 2 hours after dosing with steady-state achieved after three days of QD dosing (study U-151); hence, it could offer a safer, more effective, and easily managed oral anticoagulant agent for use in the pericardioversion setting.

Edoxaban has been investigated for the following indications: (i) the prevention of venous thromboembolic event (VTE) in subjects undergoing total knee replacement, total hip replacement, and hip fracture surgery; (ii) the reduction of the risk of stroke and systemic embolic event (SEE) in subjects with atrial fibrillation (ENGAGE AF-TIMI 48 study); and (iii) the treatment of acute VTE and prevention of recurrence in subjects with acute symptomatic deep vein thrombosis and/or pulmonary embolism (PE) (Hokusai-VTE).

**ENSURE-AF Study design [ClinicalTrials.gov Identifier: NCT02072434]**

We designed a prospective, randomized, open-label, blinded endpoint evaluation (PROBE) parallel group study in subjects with confirmed ongoing AF of no longer than 12 months and in whom electrical cardioversion is planned.

This study is designed to compare the incidence of the composite endpoints of stroke, SEE, myocardial infarction (MI) and CV death and to compare the incidence of major and clinically relevant non-major (CRNM) bleedings after TEE or non-TEE-guided electrical cardioversion in the edoxaban arm versus the enoxaparin/warfarin arm. Composite endpoints of the key efficacy and safety parameters will also be tested.
This study will be conducted in compliance with the protocol, the ethical principles as outlined in the Declaration of Helsinki, the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s).

**Study Population**

This study will enroll subjects with documented AF for at least 48 hours but ≤ 12 months and who are planned for electrical cardioversion and anticoagulation therapy. Subjects who are receiving or have received prior anticoagulant and/or antiplatelet therapies are eligible, as well as subjects who are naive to anticoagulant and/or antiplatelet therapy. Inclusion and Exclusion criteria are shown in webonly **Table w1**.

**Efficacy and safety endpoints**

Trial endpoints are summarized in Table 2.

The *primary efficacy objective* of this study is to compare the incidences of the composite endpoints of stroke, SEE, MI and CV mortality between the edoxaban group and the enoxaparin/warfarin group from randomization to end of follow up (FU).

The *primary safety objective* of this study is to compare the incidence of the composite endpoints of major and CRNM bleeding between the edoxaban group and the enoxaparin/warfarin group from the first administration of study drug to end of treatment + 3 days.

The *secondary objective* of this study is to compare the incidences of the composite endpoints of stroke, SEE, MI, CV mortality and major bleedings between the edoxaban group and the enoxaparin/warfarin group from randomization to end of follow up.

**Exploratory objectives** of this study are shown in webonly **Table w2**.
Stratification

The stratification in the study will be performed on the following levels:

- approach to cardioversion (TEE or non-TEE) as determined by the Investigator;
- subject’s prior experience in taking anticoagulants at the time of randomization (i.e. anticoagulant-experienced or anticoagulant-naïve);
- selected edoxaban dose (full 60 mg or reduced 30 mg dose). A subject with one or more factors (CrCL ≥ 15mL/min and ≤ 50 mL/min, low body weight [≤ 60 kg], and concomitant use of P-gp inhibitors (excluding amiodarone) will receive the reduced dose (30 mg) of edoxaban if the subject is randomized to the edoxaban group. During the course of the study treatment period, if the subject’s CrCl falls between ≤ 50 mL/min and ≥ 15 mL/min (confirmed by repeat measurement at least one week apart) and the CrCl change is > 20% of the subject’s baseline CrCl, the edoxaban dosage will be reduced to 30 mg permanently until the end of the study treatment period, even if the subject subsequently experiences improved CrCl to > 50 mL/min.

Similarly, during the course of the study, if the subject’s body weight drops to ≤ 60 kg (confirmed by repeat measurement at least one week apart) and the body weight change is > 10% of the subject’s baseline body weight, the edoxaban dosage regimen will be reduced to 30 mg permanently, even if the subject subsequently regains weight to > 60 kg.

Subjects on concomitant P-gp inhibitors (with the exception of amiodarone) with the study drug at the time of randomization will be dose reduced to 30 mg. Post randomization, the edoxaban dosage will be reduced by half (60 mg QD to 30 mg QD) at any time that the subject is concomitantly taking one or more of the P-gp inhibitors (again, excluding amiodarone). Conversely, the edoxaban dosage will be returned to the regular dosage of 60 mg QD any time the subject is not taking the concomitant medication.
Subjects will be randomized in a 1:1 ratio to two treatment groups within each stratum based on a computer-generated randomization schedule generated prior to study start. Enrollment will be managed to achieve the balance of treatment assignment within each stratum. Recruitment will continue until at least 1000 subjects in each arm have undergone cardioversion (spontaneous or electric).

Insert Figure 1

1. TEE-guided Stratum

Warfarin arm:

On the day of randomization (Day -3), subjects assigned to this arm will either be:

a) Naive to anticoagulation or have been taking VKA but have a sub-therapeutic INR (<2.0) or have been taking anticoagulants other than VKA (e.g. NOAC or parenteral anticoagulants);

b) Have been taking anticoagulants and have an INR ≥2 at the time of randomization.

Subjects in category a) will start treatment with a minimum of 1 dose each of enoxaparin and warfarin on the day of randomization and these drugs will be continued until INR ≥2 has been obtained. After a therapeutic range (TR) is achieved, subjects will discontinue enoxaparin and continue warfarin until end of treatment (Day 28 following the procedure).

Subjects in category b) will not require enoxaparin and will start treatment with warfarin alone. If INR is >3 at randomisation, the dose of warfarin in the study will be adjusted to achieve and maintain the therapeutic INR level of 2.0-3.0.
In both categories within the first several days from the start of warfarin treatment, INR measurements will be conducted with a frequency of once every 2-3 days until the value reaches the TR; thereafter subjects will attend the planned study visits but may have ad hoc INR checks as deemed necessary by the Investigator.

Both TEE and cardioversion may be performed on the same day of randomization providing that the subject has either received at least 1 dose of enoxaparin or for those patients not requiring enoxaparin at randomization, that the patients INR is in TR (2.0-3.0). In any case, the cardioversion procedure has to be performed within a maximum of 3 days from randomization.

If no thrombi are identified in the atria by TEE, electrical cardioversion will be conducted and subjects will continue on enoxaparin (if started from randomization) and warfarin until their INR reaches the TR. In both categories it will be important to achieve the TR of warfarin within 8 days after randomization and to maintain the TR during the study treatment period. Enoxaparin given beyond 14 days of treatment will trigger automatic notification of the Sponsor.

**Edoxaban arm:**

On the day of randomization, subjects will start treatment with edoxaban and continue treatment until day of TEE/cardioversion (Day 0). If the subject transitions from a prior anticoagulant to edoxaban, this will be done in accordance with the transition algorithm provided in webonly Table 3 (that is, either discontinue VKA and start edoxaban when INR is ≤2.5 or for NOACs or parenteral anticoagulants (e.g. low molecular weight heparins) start edoxaban when the next dose of the NOAC/parenteral anticoagulants is due (note that for unfractionated heparin (UFH) start edoxaban 4 hours after the last dose of UFH). Both TEE and cardioversion may be performed on the same day but cardioversion has to be performed within a maximum of 3 days from randomization.

The next dose of edoxaban will be taken the day after cardioversion and then continued on a 24-hour cycle.
If no thrombi are identified in the atria by TEE, electrical cardioversion will be conducted and the subject will continue with edoxaban until Day 28 following the procedure.

*Follow-up*

All subjects will be followed for safety for 30 days (Day 58) after completing treatment with warfarin or edoxaban in the respective arms. If thrombi are identified during the TEE procedure, the subject will not be eligible for subsequent cardioversion and may be discontinued from treatment (but the subject will continue to participate in the study including the follow-up period). The Investigators will be encouraged to continue treatment with the drug to which the subject was randomized and repeat the TEE on Day 28 to assess progress of the thrombus. This information will be collected in details from the sites and will be further analyzed. A repeat TEE is not mandatory for continuation in the study.

Subjects with unsuccessful cardioversion or relapse of AF may be cardioverted again at the Investigator’s discretion; however, duration of treatment in the study will be calculated based on the initial cardioversion date. These subjects will be encouraged to remain in the study and continue the study treatment as per the protocol.

### 2. Non-TEE-guided Stratum

**Warfarin arm:** Subjects assigned to this arm will either:

a) Have taken VKA prior to randomization and have an INR ≥2 on the day of randomization;

b) Have sub-therapeutic INR at randomization (<2), have taken an anticoagulant other than VKA (e.g. NOAC or parenteral anticoagulants) or are anticoagulant-naïve.

The following algorithms will be implemented:
Subjects in category a) will not require enoxaparin and will start 21 days of warfarin anticoagulation from the day of randomization (Day -21). If INR in the subject is >3 at randomization, the dose of warfarin in the study will be adjusted to achieve and maintain the therapeutic INR level of 2.0-3.0.

Subjects in category b) will receive enoxaparin and daily warfarin until the INR is ≥2.0. At this time, enoxaparin will be discontinued and warfarin continued for a total of 21 days.

In both categories within the first several days from the start of warfarin treatment, INR measurements will be conducted with a frequency of once every 2-3 days until the value reaches the TR; thereafter subjects will attend the planned study visits but may have ad hoc INR checks as deemed necessary by the investigator.

For all subjects, cardioversion will be performed on Day 0, which will occur at a minimum of 21 days following the start of treatment with the study drug or within 3 days thereafter.

Webonly Table w3 summarizes the guidance of patient management in accordance with the INR value before and on the day of cardioversion. In subjects who do not have a TR INR (2.0-3.0) on the day of randomization, it will be important to achieve a TR of warfarin within 8 days after randomization and to maintain the TR during the study treatment period.

**Edoxaban arm:**

After randomization into this stratum, subjects will receive edoxaban for 21 days before cardioversion followed by cardioversion on Day 0 (or within 3 days thereafter) and an additional 28 days of edoxaban treatment starting from the day of cardioversion.

If the subject transitions from a prior anticoagulant to edoxaban, this will be completed in accordance with the transition algorithm provided in webonly Table w4 (that is, for VKA discontinue the drug and start edoxaban when INR is ≤2.5; for NOAC users, start
edoxaban when the next dose of the NOAC is due or for parenteral anticoagulants start edoxaban when the next dose of the anticoagulant is due with the exception of UFH where the first dose of edoxaban will be 4 hours after the last dose of UFH). The count of 21 days will start from the day of the first dose of edoxaban.

**Both arms:**

All subjects will be followed for safety for 30 days (Day 58) after completing treatment with warfarin or edoxaban in both arms.

Subjects with unsuccessful cardioversion or relapse of AF may be cardioverted again at the Investigator’s discretion; however, duration of treatment in the study will be calculated based on the initial cardioversion date. These subjects will be encouraged to remain in the study and continue the study treatment as per the protocol.

All subjects with a CHA$_2$DS$_2$-VASc (or CHADS$_2$) score ≥2 and subjects with CHA$_2$DS$_2$-VASc score =1 (when the use of oral anticoagulants is preferred over aspirin) will require to be transitioned at the end of the study treatment to a standard-of-care anticoagulant in accordance with the current European and US guidelines on the anticoagulant treatment of patients with AF. These subjects will be transitioned to the treatment chosen by the Investigator and strictly in accordance with the transition algorithms provided in webonly Table w3.

Subjects with spontaneous cardioversion in the pre-procedural period (confirmed by a recording of sinus rhythm) will still need to complete 28 days of treatment from the day that spontaneous cardioversion was noted and 30 days of follow-up (58 days in total).

**Trial conduct**

The estimated duration of the trial is 18 months, and approximately 284 study sites in 20 countries in Europe and North America will be used.
Planned sample size

2200 subjects are planned to be randomized into the study (1100 per treatment arm) to achieve at least 2000 electrical or spontaneous cardioversions. Based on the post hoc analyses of the Cardioversion population in the RE-LY study the event rate in the warfarin group is 0.8% of stroke/SEE and 1.7% of major bleeding during the 30 days post cardioversion. Event rates in other cardioversion studies are even lower. Therefore a formal sample size determination based on non-inferiority or superiority of edoxaban versus warfarin is not feasible with the anticipated low event rate and an adequately powered study would require a sample size of over ten thousand patients. The study will be sized with an appropriate number of subjects that will provide an estimate of incidence of primary efficacy or primary safety endpoints. Assuming an incidence rate of the combined efficacy endpoint of 0.6% in both groups, 1000 electrically or spontaneously cardioverted subjects in each treatment group will provide a 95% confidence interval (CI) around the point estimate of the difference of -0.68% to 0.68%.

Study Organization

An Independent Data Monitoring Committee (IDMC) will be created to further protect the rights, safety, and well-being of subjects who will be participating in this study by monitoring their progress and results. The IDMC will comprise of qualified scientists, who are not Investigators in the study and not otherwise directly associated with the Sponsor. The IDMC will monitor data during the study, and can recommend study or treatment regimen/group termination to the Study Oversight Committee.

An independent study specific Clinical Events Committee (CEC) will review and adjudicate key endpoint events (all deaths, suspected strokes/TIAs, suspected SEEs, suspected MIs, and overt bleeding events that require medical attention, liver enzyme abnormalities requiring study drug discontinuation) without unblinding (including all suspected clinical endpoint events from subjects who permanently discontinued study
drug). The CEC will comprise qualified judges, who are not Investigators in the study and not otherwise directly associated with the Sponsor. The CEC judges will remain blinded to treatment throughout the adjudication process and the study. The CEC-adjudicated data will be used in the final efficacy and safety analyses.

The Study Executive Committee will be responsible for the overall design, conduct, and supervision of the study, including the development of any protocol amendments. It will adjudicate policy among the various constituencies of the study, and will be responsible for reviewing the progress of the study at regular intervals to ensure subject safety and study integrity. The Study Executive Committee has the authority to terminate the study or treatment regimen/group based on recommendations from the IDMC.

An ENSURE-AF Study Steering Committee will be created to provide clinical guidance on study implementation and conduct of the study, and interpretation of results. It will consist of national lead investigators from the countries participating in the study as well as designated Sponsor and CRO members.

The study is funded by Daiichi Sankyo Development Ltd. and Daiichi Sankyo Pharma Development. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Conclusion

In summary, ENSURE-AF is a prospective, randomized, open-label, blinded endpoint evaluation (PROBE) parallel group Phase 3b clinical trial comparing edoxaban with enoxaparin/warfarin followed by warfarin alone in subjects undergoing planned electrical cardioversion of non-valvular AF, and will be the largest prospective randomized trial comparing a NOAC (edoxaban) against warfarin for efficacy and safety in the peri-cardioversion period.
Competing interests

Please see webonly Appendix
Table 1. Rates of thromboembolism from observational studies, post-hoc subgroup analyses from clinical trials and a prospective study

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¹Analysis included patients both with ablation and cardioversion
Table 2.

Study Endpoints:

**Efficacy endpoints**
- Stroke, SEE, MI and CV mortality;
- All-cause mortality.

**Safety endpoints**
- Major and CRNM bleedings
- All bleedings.

**Net clinical outcomes**
- Stroke, SEE, MI, all-cause mortality and life-threatening bleed;
- Stroke, SEE, MI and Major bleed;
- Stroke, SEE, MI, Major bleed, and all-cause mortality;
- Disabling or fatal stroke, Fatal SEE, Fatal MI and Life-threatening or fatal bleed;
- Disabling or fatal stroke, Fatal SEE, Fatal MI, Life-threatening or fatal bleed, and CV mortality;
- Disabling or fatal stroke, Fatal SEE, Fatal MI, Life-threatening or fatal bleed, and all-cause mortality;

**Other endpoints**
- Proportion of successful cardioversion and sinus rhythm maintenance
- Incidence and time to first AF recurrence
- Satisfaction with anticoagulation therapy as assessed by the PACT-Q2 questionnaire and EHRA score assessment
- Number of hospital admissions, reason for hospitalization, length of stay and ward type (e.g., intensive care unit, general ward, etc.) for all causes
- Number of subject visits to the investigational site throughout the study
- Number of hospital re-admissions for all causes
- Number of days from randomization to electrical cardioversion in the non-TEE-guided stratum
- Number of subjects out of therapeutic INR range during pre- and post-cardioversion period in the warfarin arm
Figure 1

(a) Study Flow Diagram for TEE-Guided Stratum

DU176b-F-E308: A randomized, open-label parallel group study comparing edoxaban or enoxaparin followed by warfarin in subjects undergoing planned electrical cardioversion of non-valvular atrial fibrillation

CVN=Cardioversion; TEE= Transesophageal Echocardiography

(b) Study Flow Diagram for Non-TEE-Guided Stratum

DU176b-F-E308: A randomized, open-label parallel group study comparing edoxaban or enoxaparin followed by warfarin in subjects undergoing planned electrical cardioversion of non-valvular atrial fibrillation

CVN=Cardioversion
REFERENCES


