Diagnostic accuracy of the ATE score for the exclusion of intra-atrial thrombi before catheter ablation of atrial fibrillation: a confirmatory study

EXTRALUCID-d CS

2017/P02/211

INTERVENTIONAL STUDIES WITH MINIMAL RISK OR BURDEN

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Protocol revision history

Version	Date	Description
1	27/11/2017	Original document
2	26/01/2018	Revised document according to ethical committee comments
3	09/03/2018	Additional information and amendments
4	26/10/2018	Revised document according common practices in care services and amendments
5	27/01/2020	Revised document to increase the duration of the inclusion period

PROTOCOL SIGNATURE PAGE

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PROTOCOL SUMMARY

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TITLE	**EXTRALUCID-d CS** **Diagnostic accuracy of the ATE score for the exclusion of intra-atrial thrombi before catheter ablation of atrial fibrillation: a confirmatory study**
STUDY PRODUCT	STA – Liatest D-Di Plus
BACKGROUND	Atrial fibrillation is the most frequent heart rhythm disorder. Its symptomatic forms, resistant to drug therapy, require invasive management (catheter ablation), which exposes to potentially serious complications including thromboembolic complications. Despite anticoagulant treatment, intra-atrial thrombus, which is a contraindication to catheter ablation, is detected in nearly 2 % of cases. Its diagnosis requires prior transoesophageal echocardiography, an unpleasant examination. The previous EXTRALUCID-d study showed that a zero ATE score, defined by no heart failure, no hypertension, no history of stroke, d-dimer < 270 ng/mL, has a negative predictive value of 100 % for the exclusion of intra-atrial thrombus.
PRIMARY OBJECTIVE	The objective of the study is to confirm the negative predictive value, sensitivity and specificity of the ATE score for the exclusion of intra-atrial thrombus.
SECONDARY OBJECTIVE(S)	• To determine the prevalence of atrial thrombi in the study population, • To determine the negative predictive value of the CHADS2VASC score of cardiac thrombus risk in the study population, • To determine the negative predictive value of the CHADS2 score of cardiac thrombus risk in the study population, • To collect a biobank of plasma samples to further confirm the study performances with other D-dimer assays.
OUTCOME(S)	The primary outcome is the number of patients with intra-atrial thrombus diagnosed by pre-procedural transoesophageal echocardiography.

STUDY TYPE	Prospective, multicentre diagnostic accuracy study in a standard of care setting.
MAIN INCLUSION CRITERIA	• Adult patients • Patients hospitalized for ablation of atrial fibrillation or symptomatic left atrial tachycardia • Affiliated person or beneficiary of a social security system • who have signed or orally given an informed consent
MAIN EXCLUSION CRITERIA	• Contraindication to transoesophageal echocardiography • Transoesophageal echocardiography made in another centre than the centre of ablation • Vulnerable persons • Refusal to participate in the study
INTERVENTION	Patient management (preoperative assessment, intervention, surveillance, and follow-up) is carried out according to centre standard procedures. An additional blood sample (7.2 ml) is collected for the d-dimer assay and the constitution of a biocollection.
TOTAL NUMBER OF SUBJECTS	3,000 patients
DURATION OF THE STUDY	Duration of inclusion: 30 months Duration by subject: at most 48 hours (from enrolment to transoesophageal echocardiography result) Total expected duration of the study: 30 months
STATISTICAL ANALYSIS	Sensitivity, specificity, positive predictive value, negative predictive value, and 95 % confidence intervals will be calculated. The ATE score will be considered clinically relevant if a negative predictive value of 100 % is obtained for a zero score.
EXPECTED RESULTS	This study is expected to confirm the negative predictive value of the ATE score. This score could be proposed for the diagnosis of exclusion of intra-atrial thrombus in patients hospitalized for atrial fibrillation ablation or left atrial tachycardia. A zero score would avoid the systematic transoesophageal echocardiography.

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1. Definitions and abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
ATE	Atrial Thrombus Exclusion
e-CRF	Electronic Case Report Form
INR	International Normalized Ratio
IRB/EC	Institutional review board/ethics committee
LMWH	Low molecular weight heparin
MRI	Magnetic resonance imaging
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TEE	Transoesophageal echocardiography
VKA	Vitamin K antagonists

2. Contacts

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3. Scientific justification and general description

3.1. Background

3.1.1. Pathology

Atrial fibrillation is the most common heart rhythm disorder, and is associated with increased mortality and morbidity, including through its thromboembolic complications. The invasive treatment of atrial fibrillation by catheter ablation is indicated in symptomatic and recurrent forms. Catheter ablation of atrial fibrillation is one of the most complex procedures in electrophysiology. Thromboembolic events are part of the complications and are responsible for cerebral (stroke or transient ischemic attack), coronary and peripheral arterial ischemia. Emboli may be due to thrombus or air, and their incidence varies between 0.28 and 2.8 % (1–5).

Cruoric embolisms are the most alarming on clinical level, and the most difficult to prevent. Several mechanisms are involved:

- Thrombus may result from blood coagulation cascades secondary to the introduction and handling of catheters (6). Ren *et al* reported an incidence of 10 % of left intra-auricular thrombus detected on transept sheaths or circular catheters (LASSO) introduced during ablation despite an effective anticoagulation (activated clotting time > 250 s). These thrombi have been detected with cardiac echocardiography (7). An important anticoagulation, activated clotting time > 300 s and infusion of the transseptal sheaths with a high flow rate (> 180 ml/h), significantly reduces the formation of thrombus and the occurrence of thromboembolic events (8).
- Endothelial lesions secondary to radiofrequency applications are also responsible for blood coagulation. The incidence of thromboembolic events is important when asymptomatic ischemic brain lesions are investigated by magnetic resonance imaging (MRI) after the ablation procedures. The type of energy used to create the ablation lesion affects this incidence. A study examined the effect of atrial fibrillation ablation technique on thromboembolic events. The number of recent asymptomatic ischemic lesions seen in MRI was greater in patients with atrial fibrillation ablation by non-irrigated multi-electrode radio-frequency compared to those who had cryotherapy ablation or conventional radiofrequency catheter ablation (9). These strokes were more often found in the vertebrobasilar territory, which is strongly suggestive of a cardioembolic origin.

- The thromboembolic mechanism may also correspond to the detachment of a pre-existing thrombus localized in the left atrium. The incidence of these thrombi is close to 2 % in the pre-procedural period, with values ranging from 1.2 % to 3.6 % (10–15).

The embolic risk is limited by performing imaging tests in order to eliminate the presence of a left atrial thrombus. The reference examination is the transoesophageal echocardiography which is an unpleasant examination.

3.1.2. Description of the ATE score to be validated

A preliminary study, EXTRALUCID-d (NCT02199080), included 2,494 patients hospitalized for an atrial fibrillation ablation. It studied a combined clinical-biological score, the Atrial Thrombus Exclusion (ATE), associating thromboembolic risk factors (hypertension, cardiac insufficiency, history of stoke) and d-dimer level for the prediction of intra-atrial thrombus.

The primary outcome was the number of intra-atrial thrombus diagnosed by transoesophageal echocardiography. A zero ATE score, defined by no cardiac insufficiency, no hypertension, no history of stroke, and D-dimer < 270 ng/mL, had a negative predictive value of 100% for the diagnosis of intra-atrial thrombus.

3.1.3. Description of the reference method

Transoesophageal echocardiography is performed routinely in more than 72 % of centres that perform atrial fibrillation ablation (16). It has a low morbidity. Most studies reporting transoesophageal echocardiography complications concerned examinations performed at cardiovascular operating room (17). Insertion and manipulation of the probe can damage the oropharynx, oesophagus or stomach. Two mechanisms of oesophageal lesions have been described, the first being a direct trauma occurring after insertion or manipulation of the endoscope. The second comes from the probe thermal energy. A multicentre study in cardiology described 10,419 transoesophageal echocardiographies where 88.7 % of patients were conscious and most of them did not receive sedation. In 1.9 % of cases, the probe could not be inserted because of a lack of patient cooperation (98.5 %) or due to anatomical reasons (1.5 %). In 0.88 % of the cases, when the endoscope was introduced, the examination had to be interrupted due to poor tolerance of the endoscope, pulmonary or cardiac complications or haemorrhage. Pre-transoesophageal echocardiography sedation complications have been described: hypoxia and transient hypotension (18). Transoesophageal echocardiography is recommended prior to any left atrium ablation in patients with persistent atrial fibrillation or with paroxysmal atrial fibrillation lasting longer than

48 hours when anticoagulation has not been satisfactory for more than three weeks. **The most recent recommendations on atrial fibrillation ablation** (19) **state that it was not possible to find a consensus on the indication of transoesophageal echocardiography in patients under well-conducted anticoagulant therapy.**

3.2. Study hypothesis and expected results

This study is lead in an independent population from the previous EXTRALUCID-d study in order to confirm the accuracy of the ATE score.

3.3. Overall risk/benefit assessment

We believe that the benefit / risk balance is very favourable, given that the risk of the study is negligible. The confirmation of an excellent negative predictive value of the ATE score would prevent one transoesophageal echocardiography out of three during the period of preoperative endocardial ablation of atrial fibrillation.

3.4. Justification of low interventional level

In addition to current practice, this study involves blood sampling. The collected volume complies with the conditions described by law for low interventional level (« Arrêté du 2 décembre 2016 fixant la liste des recherches mentionnées au 2° de l'article L.1121-1 du code de la santé publique » for French law).

4. Validation study objectives

4.1. Primary objective

The objective is to confirm the negative predictive value, sensitivity and specificity of the ATE score for the exclusion of cardiac thrombus.

4.2. Secondary objectives

- To determine the prevalence of atrial thrombi in the study population,
- To determine the negative predictive value of the CHADS2VASC score of cardiac thrombus risk in the study population,
- To determine the negative predictive value of the CHADS2 score of cardiac thrombus risk in the study population,

To collect a biobank of plasma samples to further confirm the study performances with other D-dimer assays in the future.

5. Outcomes

5.1. Primary outcome

The primary outcome is the number of patients with atrial thrombus diagnosed by pre-procedural transoesophageal echocardiography.

Detection of spontaneous echocardiographic contrast will not be considered for the primary outcome. In case of cardiac thrombus, data will be recorded and transmitted to the sponsor after de-identification. The maximum time between transoesophageal echocardiography and ablation will be 48 hours. It may also be performed at the beginning of the procedure. The detection of a thrombus prohibits the realization of catheter ablation. In other words, if there is any doubt about the existence of a thrombus (equivocal image) the primary outcome is the contraindication to the intervention. If necessary, this definition may be reviewed according to the evolution of ultrasound images and the diagnosis (persistence of the initial image under increased anticoagulant treatment, decision of the medical team to practice intervention). This revision of the diagnosis will be decided by the medical team in charge of the patient.

5.2. Secondary outcome

- Number of atrial thrombi in the study population
- Number of patients with atrial thrombus among patients with a zero CHADS2VASC score (no congestive heart failure, hypertension, diabetes mellitus, vascular disease [previous myocardial infarction, peripheral arterial disease or aortic plaque], history of stroke or transient ischemic attack, age under 75, and male)
- Number of patients with atrial thrombus among patients with a zero CHADS2 score (no congestive heart failure, hypertension, diabetes mellitus, history of stroke or transient ischemic attack, and age under 75)

6. Study design

This is a European multicentre prospective diagnostic accuracy study.

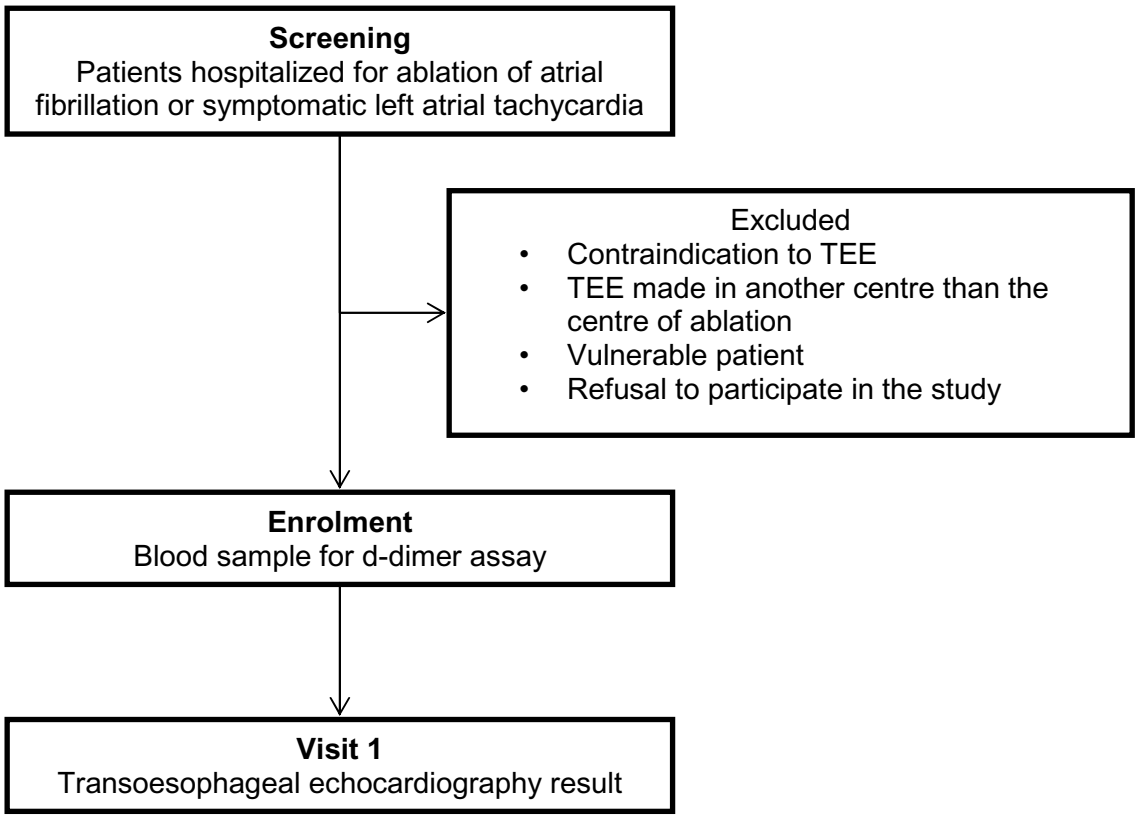


Figure 1 : Study design. TEE: transoesophageal echocardiography

7. Study population

7.1. Inclusion / Exclusion criteria for intended population

Inclusion criteria

- Adult patients
- Patients hospitalized for ablation of atrial fibrillation or symptomatic left atrial tachycardia.
- Affiliated person or beneficiary of a social security system
- Who have signed or orally given an informed consent according to local regulation,

Exclusion criteria

- Contraindication to transoesophageal echocardiography,
- Transoesophageal echocardiography made in another centre than the centre of ablation,
- Pregnant women, parturient mothers and nursing mothers,
- Lives in an institution on court or authority order,
- Severely altered psychological health,
- Persons leaving in health or social establishment,
- Minors,
- Under guardianship,
- Persons unable to give their consent,
- Refusal to participate in the study.

7.2. Feasibility and recruitment modalities

The investigating centres have the following characteristics:

- The number of ablation of atrial fibrillation is greater than 50 per year,
- Transoesophageal echocardiography is performed routinely before any ablation of atrial fibrillation.

Investigating centres compliance with those characteristics will be documented upon selection.

In each centre, patient eligible for atrial fibrillation or left flutter ablation will be screened. In agreement with the physician performing the procedure, the study will be explained and proposed to the eligible patients by an investigator at the admission or at the pre-ablation consultation. It is strongly recommended to include patients consecutively in order to limit

selection bias. We plan to open circa 25 centres in France and Europe, with an average of 120 patients per centre. The provisional duration of enrolment is 30 months.

8. Material and Methods

8.1. Transoesophageal echocardiography

Transoesophageal echocardiography is performed according to the guidelines of the European Association of Cardiovascular Imaging (20).

It is performed at most within 48 hours before intervention.

Images must be stored locally for the duration of the study.

8.2. D-dimer assay

8.2.1. Material

STA - Liatest D-Di Plus will be used following the recommendations in its package insert on STAGO instruments. The STAGO instrument type used in each investigating centre will be documented (type and version) along with the name and lot of reagents (STA – Liatest D-Di Plus and its associated quality control plasmas).

8.2.2. Method

Blood sample (maximum 7.2 ml) will be collected for the determination of d-dimer level and for storage. It will be collected at the same time as standard biological intake and no more than 48 hours before surgery.

8.2.3. D-dimer assay

As STA-Liatest D-Di Plus assay reagents are pre-calibrated, the pre-calibration parameters will be used in each investigating centre. These will be entered on the analyzer through barcode scanning of the Assay Value insert, as described on the STA-Liatest D-Di Plus package insert.

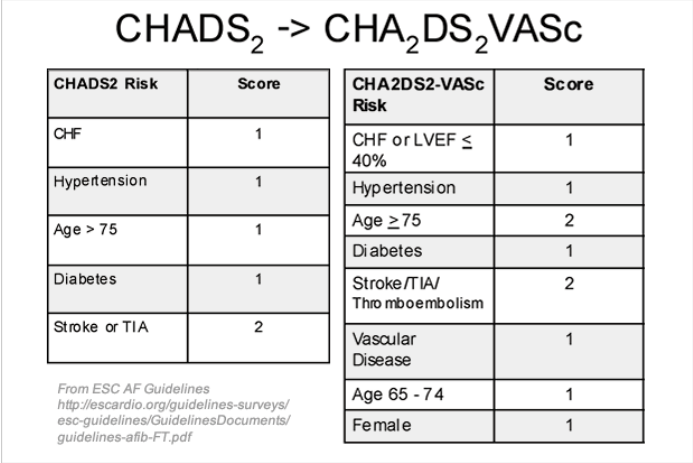
As requested in by the Standard Operating Procedure, quality control (QC) samples will be run to ensure accuracy and reproducibility of the device each time a patient sample will have to be tested. Results of these QC have to fall within their acceptance ranges prior to testing any patient sample and will be collected along with patient's results.

8.3. ATE Score

Condition	Score
Hypertension	1
Heart failure	1
History of stroke	1
High plasma d-dimer level (> 270 ng/ml)	1

A zero ATE score is expected to exclude intra-atrial thrombi.

8.4. $CHADS_2$ and CHA_2DS_2VASC scores



$CHADS_2$ and CHA_2DS_2VASc scores are stroke risk stratification schemes based on a risk factor approach (21–23).

9. Clinical data collection and procedure description

9.1. Study calendar

Duration of inclusion: 30 months

Duration by subject: 48 hours at most (from enrolment to transoesophageal echocardiography result)

Total expected duration of the study: 30 months

9.2. Data collection requirements

	Screening (0 to 3 months)	Inclusion	Visit 1 (0 to 48 hours)
Inclusion/exclusion criteria	✓ (T)		
Informed consent		✓ (T)	
Medical history and demographics		✓ (S)	
Blood sample for D-dimer level assay		✓ (T)	
Transoesophageal echocardiography			✓ (S)

(T) Related to the clinical trial

(S) Standard care

Quality control samples results for D-dimer assay will also be documented.

9.3. Screening

Atrial fibrillation diagnosis may be based on a 12 lead electrocardiogram (ECG) characterized by absence of discrete P waves and an irregularly irregular ventricular rate. In most patients, a single ECG is sufficient to secure the diagnosis, assuming the patient is in AF at the time of the ECG. In some patients it may also be diagnosed using a heart rhythm recording such as a telemetry strip, Holter monitor, or an event monitor.

Women of childbearing age must have a negative beta-hCG blood test.

Patients with a programmed hospitalization for ablation of atrial fibrillation or symptomatic left atrial tachycardia are eligible to the study. The investigator verifies the eligibility criteria.

9.4. Enrolment

During the inclusion visit, the investigator informs the participant and answers all questions about the objectives, nature of constraints, foreseeable risks and expected benefits of the

research. He also specifies the rights of the participant and verifies the eligibility criteria. Oral consent of the patient will be recorded in the medical file.

Medical history, clinical data and demographics are collected (hypertension, diabetes, congestive heart failure, age, history of stroke, peripheral arterial disease and diagnosis).

Peripheral blood sample is collected for d-dimer assay.

9.5. Visit 1

The transoesophageal echocardiography is performed no more than 48 hours before ablation or during the ablation procedure. The vacuity of the left atrial appendage or the presence of a thrombus is specified on the transoesophageal echocardiography report. A spontaneous contrast and emptying velocity may be mentioned but these data are optional. Pictures of the left atrial appendage are recorded on CD if a thrombus is diagnosed.

9.6. Patient exit

Patients may be exited from the study under the following circumstances:

- Included in the trial in violation of the inclusion and/or exclusion criteria
- Patient chooses to withdraw
- Patient death before transoesophageal echocardiography

9.7. Constraints related to the research

The person can participate in another interventional study if the related intervention starts after the transoesophageal echocardiography. There is no exclusion period during which the participant cannot participate in another study after completing this one.

9.8. Blood sample collection

Peripheral blood sample is collected for d-dimer assay at the inclusion.

The following requirements will be followed for the collection:

- Blood samples will be collected in 0.109M (i.e., 3.2%) trisodium citrate anticoagulant, 1 volume of citrate for 9 volumes of blood, in accordance with CLSI Guideline H21-A5 Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Coagulation Assays and Molecular Haemostasis Assays (Vol.28; No.5)(24). Two will be collected to allow sufficient plasma volume for the study.

- Blood samples will be centrifuged within 4 hours after blood draw at 2,000-2,500g for 15 minutes at a temperature close to 18°C, and then plasma samples will be divided in at least 4 aliquots of 0.6 ml each.
- Each aliquot will be de-identified (i.e., only an anonymous number will be available in the data collection form in order to ensure patient anonymity).
- One aliquot will be tested fresh (within 6 hours after blood collection).
- The remaining plasma samples will be frozen and stored at -70°C or colder (as soon as possible and no more than 2 hours after plasma collection).

Frozen samples will be used to constitute a plasma bank. It will be used to confirm results with the STA-Liatest DDi Plus and to assess other d-dimer assays with kits currently under development. Samples will be kept for 10 years. After which, the samples will be destroyed by incineration. Under no circumstances will these samples be used in other studies.

10. Study follow-up

10.1. Protocol deviations

A deviation is defined as an event where the exact instructions written in this protocol, the clinical trial agreement or the applicable regulations have not been followed. Deviations are classified by occurrence, i.e., sporadic vs. repeated and seriousness, i.e., major vs. minor.

Major deviations may impact subject safety, alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study. Minor deviations do not impact subject safety, compromise the integrity of the study data, or affect subjects' willingness to participate in the study.

Investigators are required to obtain prior approval from the sponsor before initiating deviations from the protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval will be documented in writing and maintained in study files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the investigator's control; however, the event is still considered a deviation and must be recorded in the subject Case Report Form.

Protocol deviations will be reported to the sponsor using suitable forms, regardless of whether medically justifiable, pre-approved by the sponsor or taken to protect the subject in an emergency.

Investigators must also adhere to procedures for reporting study deviations to IRB/EC in accordance with their specific IRB/EC reporting policies and procedures.

The monitor will discuss deviations with relevant site personnel, and will document them on monitoring visit reports. If needed, a Note to File will be issued and filed in the relevant file and a copy sent to the sponsor.

The sponsor will review records of deviations and will consider the need for corrective and preventive action and further external reporting to regulatory authorities. A summary report classifying and summarizing the deviations per type will be issued and reviewed by the sponsor personnel.

Deviations will be summarized and included in the study report. Assessment and discussion of their potential impact / lack of impact on study results will be addressed.

10.2. Adverse event reporting

10.2.1. Definition

Adverse Device Effect (ADE): adverse event related to the use of a medical device.

Note 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use or the deployment, implantation, installation, or operation, or any malfunction of the medical device.
Note 2: This definition includes any event resulting from user error or from intentional misuse of the medical device

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other person, whether or not related to the medical device
Note 1: This definition includes events related to the medical device or the comparator
Note 2: This definition includes events related to the procedure involved
Note 3: For users or other persons, this definition is restricted to the medical device.

Serious Adverse Event (SAE): An Adverse Event that:
a) Led to death,
b) Led to serious deterioration in health of the subject, that either resulted in
- life-threatening illness or injury
- permanent physical impairment
- in-patient hospitalization or prolongation of existing hospitalization
- medical or surgical intervention to prevent permanent physical impairment

c) Led to foetal distress, foetal death or congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition without serious deterioration in health is not considered as a serious event.

Serious Adverse Device Effect (SADE) (ISO14155-2011): Adverse device effect that has resulted in any of the consequences of a serious adverse event.

Procedure-Related Adverse Event: An event that occurs due to the procedure and cannot be directly attributed to a particular device or implant tool.

Unanticipated Serious Adverse Device Effect: serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

10.2.2. Description of expected SAE

SAE related to atrial rhythm disorder:

- Congestive Heart Failure
- Cardiogenic shock
- Intra-atrial thrombus
- Cardioembolic stroke
- Myocardial infarction and unstable angina for patients with ischemic disease

SAE related to medical treatment:

- Hemorrhage
- Ventricular rhythm disorder
- Bleeding or pain at the femoral puncture point
- Bradycardia
- Anticoagulant overdose

10.2.3. Event review and reporting

10.2.3.1. Event review

Upon the signature of the consent, the investigator is responsible for the collection of all adverse events. He reports all serious and non-serious adverse events (biological and clinical) that occur between the signature of the consent and the end of patient participation.

10.2.3.2. Reporting

Adverse reactions/adverse reactions/incidents should be reported in accordance with local requirements.

10.2.4. Information for data collection

All information required by the protocol must be recorded on the case report forms and an explanation must be provided for each missing data. The data must be collected as it is obtained and transcribed in these case report forms clearly and legibly.
Data will be collected through electronic case report forms.

10.2.5. Quality control

A clinical researcher mandated by the sponsor visits each research centre on a regular basis, when the research is set up, once or several times during the course of research,

according to the rhythm of the inclusions and at the end of the research. During these visits and in accordance with the risk-based monitoring plan (participant, logistics, impact, resources), the following elements will be reviewed:

- informed consent,
- compliance with the research protocol and the procedures defined therein,
- quality of the data collected in the CRF: accuracy, missing data, consistency of data with source documents (medical records, appointment books, originals of laboratory results, etc.)

A monitoring report will be written after each visit.

Visits will be on-site or through teleconferences or webconferences.

10.2.1. Audit and inspection

The centre can be audited at any time by persons appointed by the sponsor and independent of the persons conducting the research. Its objective is to verify the safety of the participants and the respect of their rights, the respect of the applicable regulations and the reliability of the data.

An inspection may also be carried out by a competent authority (ANSM for France or EMA in the context of a European trial).

The audit, as well as the inspection, can happen at all research stages, from the development of the protocol to the publication of the results and the classification of the data used or produced during the research.

The investigators agree to comply with the sponsor requirements for an audit and the competent authority for a research inspection.

11. Study conclusion and statistical consideration

11.1. Sample size rationale

Given the low rate of atrial thrombi (about 2 % of patients eligible to atrial fibrillation ablation), this study requires a high number of participants in order to allow reliable estimation of diagnostic performance.
To detect a 0.5 % deviation between two negative predictive values (binomial test), 2,000 patients are required for a power of 70 %; 2,400 patients for a power of 80 %; and 3,000 patients for a power of 90%.
Due to the high enrolment capacities of this multicentre study and its simplicity for the centres involved, it was chosen to focus on the power of the study and to retain a sample size of 3,000 patients.

11.2. Statistical analysis plan

The analysis will be performed at the end of the trial. There is no interim analysis planned.

The index test is the ATE score. A zero score is a negative result, while a score above zero is a positive result.
The reference test is the transoesophageal echocardiography. The negative condition is the absence of thrombus, and the positive condition is the presence of thrombus.

Demographics, medical history, clinical characteristics and diagnosis will be presented in tables with descriptive statistics for each sub-population (positive and negative condition) and for the entire analysed population, as follows:

- For quantitative variables: mean and standard deviation,
- For qualitative variables: count, percentage (excluding missing denominator data) and 95% confidence intervals.

ATE score sensitivity, specificity, positive predictive value, negative predictive value, and 95% confidence intervals will be calculated.
Primary objective will be met, if these parameters are similar with the ones obtained during the first study.
The ATE score will be considered clinically relevant if a negative predictive value of 100 % is obtained for a zero score.

12. Ethical and legal aspects

12.1. Access right to files and source data

12.1.1. Data access

Acceptance of participation in the protocol implies that the investigators will make available the individual documents and data strictly necessary for monitoring, quality control and audit to those who have access to these documents in accordance with the laws and regulations in force.

12.1.2. Source data

Source data are all information in original documents or in authenticated copies of these documents relating to clinical examinations, observations or other research activities necessary for the evaluation of the research. The documents in which the source data are stored are called the source documents.

12.1.3. Data confidentiality

In accordance with current legislation, those with direct access to the source data will take all necessary precautions to ensure the confidentiality of information about experimental data, and participating patients and, in particular, their identity and the results obtained. These persons, in the same way as the investigators themselves, are subject to professional secrecy.

During and after the research, the data collected from the patients and forwarded to the sponsor by the investigators (or other specialists) will be made anonymous. They must in no case show clearly the names of the concerned persons or their address.

The sponsor will ensure that each participating patient to the research has given his consent for access to his individual data.

12.2. Ethical conduct of the study

The sponsor and the investigators ensure that this research is carried out in accordance with Law No. 2012-300 of March 5th 2012 on research involving the human person and in agreement with good clinical practice (ICH version 4 of November 9th 2016 and Decision of November 24th 2006) and the Helsinki Declaration (which can be found in its full version at http://www.wma.net).

The research shall be conducted in accordance with this Protocol. Except in emergency situations requiring specific therapeutic procedures, the investigators undertake to comply with the protocol in all respects.

This research has been approved by a French Committee for the Protection of persons and other local ethics committees for sites selected out of France.

The data recorded are subject to a computerized treatment in compliance with the law n°78-17 of January 6th 1978 relating to data processing, files and freedoms as amended by Law 2004-801 of August 6th 2004.

This research falls within the framework of the "Reference Methodology" (MR-001) in application of the article 54 paragraph 5 of the amended law of January 6th 1978 relating to information, files and freedoms. This change was approved by decision of January 5th 2006, updated on July 21st 2016. The Groupe Hospitalier de la Rochelle Ré Aunis has signed a commitment to conform to this "Reference Methodology".

12.3. Study funding and insurance

The Groupe Hospitalier de la Rochelle Ré Aunis, sponsor of this research, has contracted civil liability insurance n°156.549 with sham, Société Hospitalière d'Assurances Mutuelles, 18 rue Edouard Rochet – 69372 Lyon cedex 8, in accordance with the French Public Health Code.

12.4. Publication Policy

Please refer to study agreement

12.5. Confidentiality

Please refer to study agreement

12.6. Data archiving

The investigator should arrange for the archiving of the study documentation file and the raw data from their hospital for at least 15 years after the Close-out visit if not specified in the study agreement.

Patient hospital files and other source data should be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years.

13. References

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14. Appendices

- Protocol summary: English version
- Protocol summary: French version
- Consent form: French version
- Case Report form
- Investigators list
- STA-Liatest DDI Plus package insert (English version, September 2017)