EHRA
European Heart
Rhythm Association

European Snap Shot Survey on Leadless Pacemaker Implantation (ESSS-LLPM)

Study Protocol

Coordinating centre:

Scientific Initiatives Committee (SIC) of the European Heart Rhythm Association (EHRA),

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CONTENT

1. COMMITTEES and BOARDS

The European Snap Shot Survey on Leadless Pacemaker Implantation (ESSS-LLPM) will be conducted under the responsibility of the Scientific Initiatives Committee (SIC) of the European Heart Rhythm Association (EHRA). The writing group will constitute the scientific leadership for the conduct of the ESSS-LLPM.
Authors will be the members of SIC that are actively involved in the creation and undertaking of the survey and co-authors, the investigators from the best contributing centers.

1.1. Country participation

All European countries will be invited to participate in the ESSS-LLPM, with particular focus on the 17 countries in which more than 8000 pacemakers (PM) were implanted in 2014 or 2015 (i.e.: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Portugal, Russian Federation, Spain, Sweden, Switzerland, and UK) [1].

Other centres in other countries brought forward by members of the SIC and in their respective networks will also be included if relevant – based on their clinical activity.

2. BACKGROUND and RATIONALE

Implantable cardiac pacing has been used for more than fifty years for the management of bradycardias [2, 3]. Whereas the efficacy and overall safety of pacing devices are high, complications often related to the use of endovascular leads, including fracture, insulation breakdown and infections may occur [4, 5]. In the FOLLOWPACE study, the reported incidence of perforations, pericardial effusions, pocket complications, and pulse generator-related technical issues was 12.4% at 2 months and additional 9.2% at 5.9 years [6]. In addition, the extraction of the endovascular leads may be challenging and particularly risky. Furthermore, transvenous pacing may sometimes be very difficult or impossible because of venous thrombosis or occlusions [4, 5, 7].

Since a long time, these considerations have motivated the research for developing pacing systems free of endovascular leads. Currently, two devices are routinely used in many European centres: the Nanostim™ (St. Jude Medical, Inc., St. Paul, MN, USA) [8] and the Micra™ (Medtronic, Inc., Minneapolis, MN, USA) [9] which are both totally freestanding, intracardiac, single-chamber ventricular-only (VVIR) pacing devices, implanted in the right ventricular endocardium. The third system (WISE CRT™; EBR Systems, Inc., Sunnyvale, CA, USA) [10] offers leadless cardiac resynchronization therapy (CRT) additionally to a traditional transvenous pacemaker. This device uses a

subcutaneous ultrasound pulse generator with a battery and leadless electrode implanted into the left ventricular endocardium via the retrograde aortic or transseptal approach. All these devices are introduced via the femoral approach, using large (18 to 25 Fr) vascular sheaths, and they are screwed or anchored in the endocardium. The currently available pacemakers are only single-chamber devices, pacing in VVIR mode [11]. Several manufacturers are also working currently on the development of dual-chamber devices, which two "modules" implanted independently, are able to communicate and interact with each other. These dual-chamber devices will include a right ventricular pacemaker, probably very similar to those already available, and a pacemaker implanted in the right atrium. Leadless pacing is just at the beginning of the path, new systems are being developed, and the choice of devices will likely broaden in the near future. This technological break will indisputably impact the future of the patients and the implanters [12]. The aim of this European Heart Rhythm Association (EHRA) survey is to provide better insight into leadless pacemakers (LLPM) utilization across a broad range of European centres, and to anticipate what direction future trends will follow.

3. STUDY DESIGN and METHODS

The ESSS-LLPM is a prospective, observational, multicentre snap shot survey of consecutive patients undergoing PM implantation. The indications for PM, as well as implantation technique, equipment used, or peri-procedural treatment will all be left entirely to the discretion of the responsible physicians, and should be conducted according to the current standards of good clinical practice and clinical routine. Consequently, no specific protocol or recommendation in this survey regulates above mentioned issues.

3.1. Duration of the study

The total study inclusion period is planned to last 8 weeks, and each participating centre will be asked to enrol all consecutive patients undergoing PM or LLPM implantation over 40 consecutive working days. In case of insufficient patient inclusion rate (i.e., less than 10 PM patients per centre), the EHRA-SIC may decide to prolong the inclusion period for additional 5 to 10 working days in all participating centres. There will be no follow-up of enrolled patients.

3.2. Primary and secondary objectives

The primary objective of the ESSS-LLPM is to assess what proportion of all PM candidates are implanted with LLPM and to identify factors that promote LLPM implantation (as opposed to transvenous PM).

The main secondary objectives of the ESSS-LLPM are to analyse:

- LLPM implantation procedural techniques, equipment, peri-procedural treatment and safety measures,

- LLPM implantation-related in-hospital complications,

- The relationships between patient characteristics and LLPM implantation procedural aspects,

- Potential regional differences in PM and LLPM implantation routines in the various parts of Europe,

- The adherence to the ESC guidelines.

3.3. Potential value of the ESSS-LLPM

By means of recognizing dominant routines used for PM and LLPM implantation in daily clinical practice in Europe, this survey is expected to identify the gaps existing between contemporary clinical practice in European countries and current recommendation of cardiac societies. Consequently, the results obtained will allow identifying the main areas of uncertainty and suggesting the directions of further research.

3.4. Population enrolled

3.4.1. Participating Centres

The invitation to participate in the ESSS-LLPM will be sent to partners of the EHRA EP Scientific Research Network, with special emphasis on the larger countries, to ensure large number of included patients. In addition, the chairpersons of the national working groups on cardiac arrhythmias, pacing and electrophysiology will be approached by a letter from the Chair of the SIC, informing them about the purpose of the survey and asking them to propose the participating centres in their country, based on the centre's clinical activity.

Participating centres will be stratified according to the centre's volume (i.e., the annual number of PM implantations performed in that centre), as well as according to the proportion of enrolled patients relative to the centre's volume.

3.4.2. Inclusion criteria

All consecutive patients undergoing PM or LLPM implantation during the survey inclusion period will be included. All patients are required to sign an informed

consent form approved by the local ethical committee (if required by the national rules). **Each participating centre is responsible for obtaining ethics committee approval if this is required by national or local rules.**
The EHRA SIC will only assist in providing, upon request from the investigator, the necessary supporting documents.

3.4.3. Time of inclusion

Patients will be included into the survey on the day of PM or LLPM implantation, but not later than the day of hospital discharge (last day of hospitalization due to index PM or LLPM implantation).

3.4.4. Exclusion criteria

Patients unwilling to participate or unable to give informed consent (when needed) will be excluded from the survey.

3.4.5. Data collection

Data on the PM or LLPM implantation procedural routines will be collected via the online questionnaire, prepared by the EHRA-SIC and posted on the Survey Monkey platform by the EHRA staff. The questionnaire contains 3 general questions on the centre's type and volume and 21 specific questions about individual patient demographics, left ventricular ejection fraction, functional class, underlying heart disease, co-morbidities, ECG, indications for PM implantation, procedural details, outcomes and duration of hospital stay. Data will be entered anonymously making patient identification impossible.

Each participating centre will enter the individual patient-related data via the online platform used by the ESC, by populating the ESSS-LLPM questionnaire. Only the EHRA Staff will have access to the data during data collection. Upon the completion of the survey, the collected data will be exported by the EHRA staff into an Excel file which will be communicated to the executive writing group of this survey and the Chair of the EHRA SIC. The file will be used for further statistical analysis only for the purpose of the survey described in this protocol.

4. STATISTICAL CONSIDERATIONS

All patients will be included in the analysis. Continuous variables will be presented as mean ± standard deviation (SD), or as median with inter-quartile range (IQR, 25th to 75th quartile) if non-normally distributed. Categorical variables will be reported as counts with percentages. The Student t-test will be used for comparison of continuous variables with normal distribution, and Mann-Whitney test for those with non-

normal distribution. Differences in categorical variables will be tested by Chi-square test. Relationships between patient characteristics and procedural aspects, or outcomes will be analysed using the linear regression or multiple logistic regression methods, as appropriate.

A value of P <0.05 will be considered statistically significant in all analyses.

5. STUDY MONITORING and AUDITING

Monitoring of centres will not be performed.

5.1. Source data verification

The national coordinator (SIC member) will be the primary contact person for all questions pertinent to the ESSS-LLPM protocol, the survey requirements and the site responsibilities.

5.2. Heart House Staff

The Heart House administration will operationally coordinate the project, provide support to the EHRA SIC, and participating centres and guard the methodological concepts of the survey. The Heart House is in charge of the ESSS-LLPM database management and statistical analyses.

Specifically, the Heart House and the SIC members involved in the ESSS-LLPM Executive Committee (Writing Group) have to assure the constant quality control and continuity necessary to ensure that the project is completed on time.

The database, to which all data are entered from the internet based data programme (Survey Monkey) will be set up at the European Heart House in Sophia-Antipolis, France, according to the requirements defined by the appointed Executive Committee (Writing group).

6. ETHICAL ISSUES

Each participating centre is responsible for obtaining ethics committee approval if this is required by national or local and institutional rules. The material prepared by the SIC will assist centres in applying for ethics committee approval if this is required. All patients will be approached by the local centre investigator and will be asked for their written informed consent to participate in the

study (if necessary, i.e. based on local standards). A template of the patient information form as well as of the form for the ethical committee application will be provided by EHRA staff o behalf of the SIC, upon request from the participating centres.

6.1. Protection of Human Subject

This study does not dictate the manner in which patients are evaluated or treated with application of specific procedures. Management of patients will be strictly done according to clinical practice and independently of the ESSS-LLPM. Patient unidentifiable data will be stored on a central database. Patient data collected will be strictly anonymous in order to maintain strict security. There will be no storage of clinical data outside the data collection instrument, which will be a secure, web-based form. The main database will be secured according to current standards to ensure both ethical and integrity requirements of the data.

7. PUBLICATION POLICY

Data will be published under the responsibility of the EHRA-SIC and the Writing Committee of the ESSS-LLPM. Authorship will be determined by the SIC. Inclusion investigators as co-authors will be assessed depending on the proportion of enrolled patients, general engagement during the ESSS-LLPM, and contribution to data analysis and manuscript preparation. Manuscript preparation and review will be considered when determining the order of authorship. Participating centres and respective investigators will be listed in an appendix provided that the investigators have given their consent.

8. TIME PLAN

- Preparation of the electronic CRF in a Survey Monkey compatible format: March-April 2018
- Finalization of the protocol, including detailed description of the survey scope, of the CRF questions, of logistics and responsibilities: June 2018
- Final corrections to the protocol after review by EHRA SIC chair and SIC members: July 2018
- Testing of the electronic CRF by the SIC members and adjustments: September-October 2018
- Identification and selection of potential participating centres: September 2018

- Information letters sent by EHRA SIC Chair to the chairpersons of the national working groups in concerned countries, informing them about the survey and asking them to propose centres active in LLPM implantation: September 2018
- Preparation of Ethics committee application template translated by SIC members: September 2018
- Application for ethical committee approval by the individual centres (if needed): October 2018
- Start of patient inclusion: Early November 2018
- End of patient recruitment: Early January 2019
- Analysis of data and review of survey results by SIC: February-March 2019
- Preparation of manuscript and submission to EP Europace Journal: April-May 2019

9. REFERENCES

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