ELECTRA

(INTERNATIONAL ELECTRICAL STORM REGISTRY)

MULTICENTER REGISTRY ON PATIENTS AFFECTED BY

ELECTRICAL STORM

RESPONSIBLE: DR. FEDERICO GUERRA

CLINIC OF CARDIOLOGY AND ARRHYTHMOLOGY

MARCHE POLYTECHNIC UNIVERSITY

(DIRECTOR: PROF. ALESSANDRO CAPUCCI)

1. BACKGROUND

Organized ventricular arrhythmias (ventricular tachycardia (VT), torsades de pointes (TdP) and ventricular fibrillation (VF)) represent a major event in the clinical history of a patient and they can lead to hemodynamic instability and sudden cardiac death (SCD).

Organized ventricular arrhythmias may be associated with structural heart disease (either with ischemic or non-ischemic etiology), genetic arrhythmic syndromes (Brugada syndrome, familial long QT syndrome, right ventricular arrhythmogenic cardiomyopathy) or metabolic disorders. Nonetheless, the etiology of ventricular arrhythmias may remain unknown even after extensive diagnostic workup.

In patients at high risk for ventricular arrhythmias, the guidelines of European Society of Cardiology[1] suggest the implant of an internal defibrillator (ICD), a subcutaneous device that can quickly recognize and treat arrhythmias using fast ventricular pacing (ATP) or internal shock.

Patients that have already had an organized ventricular arrhythmia with hemodynamic instability are considered at high risk for SCD and ICD implant is therefore suggested (secondary prevention). Patients with structural heart disease and severe impairment of contractile function are considered as well at high risk for SCD and an ICD implant is suggested (primary prevention).

Recurrences of ventricular arrhythmias and electrical instability have exponentially increased in the last decades and a new clinical entity called “electrical storm” (ES) has emerged as major morbidity and mortality factor. The ES is defined as a cluster of 3 or more sustained ventricular arrhythmias within 24 hours, or a sustained ventricular tachycardia lasting 12 hours or more and that does not respond to treatments[2].

Most of the patients presenting ES are already implanted with an ICD. This is due to 3 factors: first, patients with ICD implant are at higher risk to develop ventricular arrhythmias for the cardiac disease that led to the ICD implant. Second, the device records and treats also asymptomatic or poor symptomatic arrhythmic episodes that otherwise would not be detected. Third, and more important, the device gives the possibility to survive to an arrhythmic episode, making it possible for the patient to experience an ES.

The incidence of ES is debated in different studies and ranges from 10 to 60% in patients with ICD for secondary prevention and from 4 to 7% in patients with ICD for primary prevention[3].

Despite the wealth of data on ES, there are still gray areas regarding predictors, treatment and prognostic implications of such condition, as a consequence of the small samples of the

[1] Priori G, Blomström-Lundqvist C, Mazzanti A,et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death European Heart Journal 2015 , doi/10.1093/eurheartj/ehv316

[2] Credner SC, Klingenheben T, Mauss O, et al. Electrical storm in patients with transvenous implantable cardioverter-defibrillators: incidence, management and prognostic implications. J Am Coll Cardiol. 1998 Dec;32(7):1909-15.

[3] Guerra F, Shkoza M, Scappini L, et al. Role of electrical storm as a mortality and morbidity risk factor and its clinical predictors. A meta-analysis. Europace 2014; 16:347.353.

studies available so far.[4] Nonetheless, almost all authors agree in considering ES a predictor of poor outcome[5].

Finally, in these last years, a great interest has raised on optimal ICD programming to reduce unnecessary interventions for ventricular arrhythmias. In this context, some multicentric trials, such as MADIT-RIT[6], have showed that restricting ICD intervention to longer or faster arrhythmias is safe and may reduce patient morbidity and mortality.

[4] Stuber T[1], Eigenmann C, Delacrétaz E. Seasonal variations of ventricular arrhythmia clusters in defibrillator recipients. Pacing Clin Electrophysiol. 2006 Aug;29(8):816-20.[4]

[5] Guerra F, Flori M, Bonelli P, et al. Electrical storm and heart failure worsening in implantable cardiac defibrillator patients. Europace. 2015 Feb;17(2):247-54.

[6] Moss Aj, Shuger C, Beck CA, et al. Reduction in Inappropriate Therapy and Mortality through ICD Programming N Engl J Med 2012; 367:2275-2283. 2012DOI: 10.1056/NEJMoa1211107

2. AIM OF THE STUDY

The aim of the ELECTRA registry is twofold:

a) To create an international registry on clinical features, optimal therapy, ablation strategy, prognosis and the effect of ICD programming on patients with ES.
b) To use the data derived from the registry for a prospective, observational study on mortality and rehospitalization rate in patients with ES.

3. REGISTRY DESIGN

The creation of the present registry is aimed at gathering information on a wide cohort of patients affected by ES. All patients will be enrolled for a minimum of three years from the protocol approval. There is no pre-specified date for the end of enrollment, which will be decided by the study responsible according to the enrollment rate.

A minimum of 500 patients will be included in the present registry. The exploratory nature intrinsic to the registry characteristics does not allow a sample size calculation by statistical means. However, the sample presented is based on the estimated enrolment rates of the participating centers during a 3-year enrolment period. Moreover, the sample size is large enough to postulate specific subgroup analyses.

REGISTRY INCLUSION CRITERIA:

- Diagnosis of ES (documentation of 3 or more episodes of sustained ventricular arrhythmia within 24h or documentation of sustained ventricular tachycardia lasted at least 12h).In order to fulfill this criterion, a patient with a previous episode of ES could also be enrolled during routine screening.
- Age ≥18
- Written informed consent

REGISTRY EXCLUSION CRITERIA:

- patient without ICD
- Confirmed or suspected use of drugs or narcotics with known direct pro-arrhythmic effect
- Inability to express an informed consent for the study

At enrollment, each patient will be informed on the aim and the design of the study, and the investigations needed. All patients that meet the inclusion criteria will be included in the study (attachment #1). All recruited patients will receive the informative form (attachment #1) and the informative letter to their general practictioner (attachment #2).

3.1 EVALUATION OF ELIGIBILITY

All patients admitted to the participating centers will be evaluated consecutively by the referent investigators. All patients that meet the above-described criteria will be included in the registry.

3.2 DATA COLLECTION

No additional procedures are required to the participating centers. Data usually collected in the center and necessary for the analysis will be collected by the referent investigator. Considering that ICDs record the principal events of the whole life of the device, patients with an ES previous to the creation of this registry will be included retrospectively providing that:

1) clinical data from the participating center are complete and accurate and allow to check inclusion and exclusion criteria
2) follow-up is available
3) ICD has not been replaced, leading to the loss of original data
4) ECG and echocardiography done in routine practice are available in case of necessity
5) subject agrees to subscribe the informed consent during the next routine visit in the recruiting center

All data will be used with scientific research purposes only. Data will be saved on a dedicated website[7] in agreement with current regulations on the treatment of personal data. Electronic cards of data collection transmitted to the study responsible will be identified by an alphanumeric code. The list of matches between subjects' data and these codes will be created and kept by local investigators or delegates. The data manager is the study responsible.

For the type of data requested, see Case Report Form (attachment #3)

3.3 DATA REPORT

Collected data will be processed, analysed and reported according the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative international guidelines.[8] A descriptive analysis will be perfomed yearly and at the end of enrolment. This will include:

- The prevalence of cardiovascular risk factors (arterial hypertension, diabetes mellitus, prior stroke or TIA, atrial fibrillation, peripheral vascular disease) in the studied population.
- The acute and chronic management of ES, regarding pharmacological and non-pharmacological treatment.
- Centrality and dispersion measures regarding laboratory, echocolorDoppler and electrophysiological parameters.
- Centrality and dispersion measures regarding ES inherent variables, such as total number of arrhythmias, cycle length and ICD programming.

[7] http://clincardio.univpm.it/eulogin.php

[8] on Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. PLoS Med 2007. 4(10): e296.

4. OBSERVATIONAL STUDY DESIGN

Multicente, observational, prospective clinical study. Data from the first 500 patients enrolled in the registry will be used for the present analysis. Please see point #3 of the present protocol for information regarding registry enrollment criteria and data collection.

4.1 PRIMARY ENDPOINT

- All-cause mortality 3 years after the ES

4.2 SECONDARY ENDPOINT

- Hospitalization for all causes 3 years after the ES

4.3 ANALYSIS OF RELAPSES AND MORTALITY

Each center will be asked to report every new hospital admission of patients enrolled in the study and the cause of hospitalization. Moreover, data about subjects' vital status will be asked to be updated every 6 months.

4.4 STATISTICAL ANALYSIS

The primary endpoint will be estimated annually and it will be expressed as absolute and relative numbers. Survival curves free from study endpoint, eventually divided into subgroups according to variables of interest such as gender, age, underlying heart disease, comorbidity and programming mode, will be drawn with Kaplan-Meier method and compared by Log-rank test. Basal and follow-up parameters (clinical, electrocardiographic and echocardiographic) will be compared by χ^2 test or by Fisher test if they are discrete; by T-student test or signed rank test if they are continuous. Every test will be two-tailed and a value of $p>0.05$ will be considered significant.

According to the number of centers involved we expect to recruit at least 500 patients. Considering an annual incidence of the primary endpoint (death from all causes) of 11% according to our experience (Guerra et al. Europace 2015), we expect about 55 events at the first statistical analysis after one year from the start and we expect about 165 events at the end of the follow-up of three years. The statistical analysis will be conducted using the SPSS 21.0 for Windows software (SPSS Inc. Chicago, IL, USA).

5. INDICATIONS OF EXPECTED RISKS AND BENEFITS FOR SUBJECTS IN THE STUDY

As no procedures or therapies are required there are no expected risks for patients participating to the registry. Despite no short-term benefits will be granted to any of participating patients, increasing knowledge of ES will bring to future benefits to the community, especially concerning the capacity to prevent recurrent shocks in ICD bearers.

Each subject will be informed both orally and by an appropriate document concerning procedures and purposes of the study. It will be clearly explained that participating (or not

participating) to the study will not change the frequency and type of clinical evaluations expected for the subject's disease. Patients can consult people they trust and they will have enough time to identify and ask any criticism and to gather further information; finally, patients will be asked to sign the informed consent if they agree to participate to the present registry. It will be stated that patient's participation to the registry is voluntary, free and that the consent can be withdrawn at any time and for any reason.

6. COSTS AND CONFLICT OF INTERESTS

The registry is cost-free as it does not require any further procedure or examination. The present protocol is promoted by the Marche Polytechnic University and it is not financed nor influenced by subjects with commercial interests in health. Participation in the trial by individual centers is free and voluntary and it will not interfere with clinical care activities.

Attachment #1 - Informed consent

ELECTRA registry: Informative Form and Declaration of Consent

INFORMATIVE FORM

Mr./Ms.,

In this hospital

_____ , we are conducting a medical-scientific research named “ELECTRA” (international electrical storm registry).

WHAT IS THE AIM OF THE STUDY

The present registry aims to collect data on patients with an implantable defibrillator that develop recurrent ventricular arrhythmias, a clinical condition named electrical storm. The increase of knowledge on electrical storm will bring to future benefits to the community, in particular about the capacity to prevent recurrent electrical shocks and treat hemodynamically unstable patients.

WHAT DOES YOUR PARTICIPATION IN THE STUDY IMPLY

In case you decide to take part to the registry, as an observational study, you will not be subjected to any different treatment than those provided by your physician for your disease. The acceptance of this informed consent allows the collection, protection and sharing of your clinical data in an anonymous fashion.

EXAMINATION YOU COULD BE SUBJECTED TO DURING THE STUDY

The registry does not require any additional therapies or procedures. You could be contacted by the referring physician of this center and be asked about your health state.

RISKS AND BENEFITS YOU COULD RECEIVE TAKING PART IN THE STUDY

Participating in the registry will not expose you to any risk as no additional procedures, compared to those performed routinely, will be required. Even if it is hard to predict that participating in the trial will bring to short-term benefits for any patient, increasing knowledge on electrical storm will bring future benefits to the community, especially regarding the capacity to prevent recurrent shocks and to manage hemodynamically unstable patients.

WHAT HAPPENS IF YOU DECIDE NOT TO PARTICIPATE IN THE STUDY

You are free to decline your participation to the registry. In that case, you will receive all standard therapies usually provided for your disease and physicians will continue to follow you with due attention care. There will be no changes in the frequency and type of clinical evaluation expected for your disease

INTERRUPTION OF THE STUDY:

Your consent to this research program is entirely voluntary and you can withdraw from the study whenever you want and for any reason.

PRIVACY OF PERSONAL DATA:

The use of your personal data will be marked by principles of fairness, lawfulness and transparency, defending your privacy and your rights. Your personal data will be collected and electronically stored and they will be used for scientific and research purposes only. Data access will be protected by the study manager and data will be kept anonymous. The results of the study you will participate can be object of scientific publication but your identity will always remain anonymous.

DECLARATION OF CONSENT

I, the undersigned _____

subscribe to have received by Dr. _____

detailed information about the request to participate to the “ELECTRA” registry, as reported in the information schedule attached above and handed me previously.

I declare to have been allowed to discuss this information, to have been able to question all I thought was necessary to know and to have received satisfactory answers. I also have had the possibility to talk about the details of the study with a trusted person.

I freely agree to take part in the study, being aware of the meaning of the request and of the risks and benefits involved.

_____ _____

Date Patient signature

_____ _____

Date Investigator signature

Attachment #2 - Letter for the General Practitioner

Studio ELECTRA: Informative Form for the General Practitioner

Dear Colleague,

Your patient has been invited to participate to a clinical registry called: "*ELECTRA International electrical storm registry"*, whose principal investigator for the present Centre is Dr. _____, phone_____, e-mail_____

The present registry aims to collect data on patients with an implantable defibrillator that develop recurrent ventricular arrhythmias, a clinical condition named electrical storm. The increase of knowledge on electrical storm will bring to future benefits to the community, in particular about the capacity to prevent recurrent electrical shocks and treat hemodynamically unstable patients.

The participation to the registry implies that your patient will not be subjected to any different treatment than those provided for his/her disease. The principal investigator will contact you by phone or e-mail only if it will be necessary to know the current vital status of your patient. The registry does not require any additional therapies or procedures. Participating in the registry will not expose your patient to any risk as no additional procedures, compared to those performed routinely, will be required. Even if it is hard to predict that participating in the trial will bring to short-term benefits for any patient, increasing knowledge on electrical storm will bring future benefits to the community, especially regarding the capacity to prevent recurrent shocks and to manage hemodynamically unstable patients.

The use of you and your patient's personal data will be marked by principles of fairness, lawfulness and transparency, defending your privacy and your rights. The patient's personal data will be collected and electronically stored and they will be used for scientific and research purposes only. Data access will be protected by the study manager and data will be kept anonymous. The results of the study you will participate can be object of scientific publication but your identity will always remain anonymous.

Thank you for your collaboration, Best Regards,

_____ _____

Date Investigator signature

Attachment #3- Case report form

Università Politecnica delle Marche - Clinica di Cardiologia
Case Report Forms
ELECTRA

Fill in following fields and "Enter"

0.1 - General Data

Last name - First name - Sex Select - Birth date
Height (m) - Weight (kg) - NYHA Select

0.2 - Risk factors and comorbidities

Hypertension Select - Diabetes mellitus Select - Previous Stroke or TIA Select - Atrial Fibrillation Select
Previous episode of documented myocardial ischemia Select - Peripheral artery disease Select

0.3 - Chronic medical therapy (pre-storm)

Amiodarone Select - Beta-blockers Select - Ranolazine Select
Antiarrhythmic drugs class 1A Select - Antiarrhythmic drugs class 1B Select - Antiarrhythmic drugs class 1C Select - Sotalol Select - Digoxin Select

0.4 - Laboratory exam

Haemoglobin (g/dl) - Hematocrit (%) - Creatinine (mg/dl) - BNP (mg/dl) - Kaliemia (mEq/l) - Magnesemia (mEq/l)

0.5 - Echocardiography (acute phase)

Ejection fraction (%) - End-diastole interventricular septum (mm) - End-sistole interventricular septum (mm)
Left ventricular diastolic diameter - Left ventricular systolic diameter - End-diastole posterior wall (mm) - End-sistole posterior wall (mm)

1.1 - ICD data

ICD type Select - Implantation date - Prevention Select - Cardiomyopathy Select
ICD Brand Select - ICD Model

1.2 - Detection windows

VT detection rate - VT if >24beats/12s Select - ATP on VT Select - Shock on VT Select
VT-1 detection rate (if present) - VT-1 if >24beats/12s Select - ATP on VT-1 Select - Shock on VT-1 Select
VF detection rate - VF if >24beats/12s Select - ATP during charge Select

2.1 - Electrical Storm

Electrical Storm geographical location
Electrical Storm start date - Electrical Storm end date - Electrical Storm beginning hour
Acute Coronary Sindrome as triggering ES event Select - Acute Coronary Sindrome therapy Select - ES triggering arrhytmia Select
Triggering arrythmias cycle length - Number of ATP delivered - Number of shocks delivered - Hospitalization length (days)

2.2 - Previous arrhytmic events

Previous ES Select - Previous VT/VF Select - Previous VT ablation Select - Previous inappropriate ICD therapies Select

2.3 - ES medical management

Amiodarone Select - Lidocaine Select - Beta-blockers Select - Sotalol Select - Procainamide Select
Magnesium Solfate Select - Sedation Select - Ablation Select - CRT upgrade Select - Pacing Overdrive Select - Heart Transplant Select

3.0 - ES ablation

Ablation date - Ablation success Select - Ablation number of attempts - Ablation type Select - Ventricular mapping Select
Endocardial approach Select - Epicardial approach Select - Electroanatomical mapping Select - Non contact mapping Select - Irrigated tip catheters Select -
Fluoroscopy time (min) - Total procedure time (min)

4.0 - Follow Up

Last follow-up date - Vital status at last follow-up Select - Number of total ES recurrences - First ES recurrence date
Number of total VT/VF recurrences - First VT/VF recurrence date - Number of total HF rehospitalizations - First HF rehospitalization date

Enter Exit

Attachment #4 – Follow-up requested data for the observational study

- Last follow-up date
- Vital status (alive, sudden cardiac death, non-sudden cardiac death, non-cardiac death, dead for unknown reasons)
- Total number of electrical storm recurrences
- First electrical storm recurrence date
- Total number of unclustered ventricular arrhythmia recurrences
- First unclustered ventricular arrhythmia recurrence date
- Total number of rehospitalization for heart failure
- First rehospitalization for heart failure