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IntErnationaL eLeCTRicAl storm registry (ELECTRA): Background, rationale, study design, and expected results

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ABSTRACT

Electrical storm (ES) is defined as three or more episodes of ventricular fibrillation (VF) or ventricular tachycardia (VT) within 24 h and is associated with an increased cardiac and all-cause mortality. ES is a full arrhythmic emergency, its prevalence steadily increasing along with the number of implantable cardioverter-defibrillator implanted every year in developed countries. Nowadays, little evidence exists regarding clinical predictors of ES and their potential association on mortality and heart failure (HF), nor optimal pharmacological and non-pharmacological treatment has ever been codified. The intErnationaL eLeCTRicAl storm registry (ELECTRA) is a multicentre, observational, prospective clinical study with two major aims. First, to create an international database on ES encompassing clinical features, pharmacological management, and interventional treatment strategies. Second, to describe mortality and rehospitalization rates in patients with ES over a long follow-up. The primary endpoint is all-cause mortality 3 years after the ES index event. The main secondary endpoint is hospitalization for all causes 3 years after the ES index event. Other secondary endpoints includes ES recurrences, unclustered VTs/VFs recurrences, and hospitalizations for HF worsening. A minimum of 500 patients will be included in the registry, and all patients will be followed-up for a minimum of three years. The present paper describes the background and current rationale of the ELECTRA study and details the study design, from enrolment strategy to data collection methods to planned data analysis. A brief overview of the expected results and their potential clinical and research implications will also be presented (NCT02882139).

1. Introduction

Ventricular arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF) represent a major event in the clinical history of a patient and usually lead to hemodynamic instability and sudden cardiac death (SCD). Organized ventricular arrhythmias may be associated with structural heart disease, genetic arrhythmic syndromes or metabolic disorders [1]. In patients at high risk for ventricular arrhythmias, the guidelines of the European Society of Cardiology suggests the use of an implantable cardioverter-defibrillator (ICD), a subcutaneous device that can quickly recognize and treat ventricular arrhythmias using fast ventricular pacing (ATP) or direct-current shock [2].

Recurrences of ventricular arrhythmias and electrical instability have exponentially increased in the last decades and a new clinical entity called electrical storm (ES) has risen as a major morbidity and mortality factor [3]. ES is usually defined as the occurrence of three or more episodes of VTs/VFs within 24 h requiring either anti-tachycardia pacing (ATP) or cardioversion/defibrillation [4]. Most of the patients presenting with ES are in fact already implanted with an ICD. This is due to three factors. First, as reported before, patients with an ICD have a higher risk to develop ventricular arrhythmias [5]. Second, the ICD is

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able to treat brief and asymptomatic arrhythmic episodes that would not be detected by the patient. Third, and more important, the ICD enables the patient to survive the first arrhythmic episode, making it possible for the patient to experience further VTs/VFs.

The incidence of ES is debated in different studies and ranges from 4 to 7% in primary prevention and from 10 to 60% in secondary prevention [5]. Despite the wealth of data currently available, there are still grey areas regarding predictors and optimal treatment, mostly due to the small samples of the studies available so far [6]. Nonetheless, almost all authors agree in considering ES an independent predictor of poor outcome [7]. More recently, the interest has also shifted towards non patient-related variables as potential predictors of ES. In this context, the MADIT-RIT trial has showed that restricting ICD intervention to longer or faster arrhythmias is safe and may reduce patient morbidity and mortality [8], and a multicentre, patient-level meta-analysis has recently demonstrated that ES presents a higher incidence during daytime hours and working days, and is associated with an increase in monthly temperature variation [9].

The aim of the intErnationaL eLeCTRicAl storm registry (ELECTRA) registry is twofold. First, we want to create an international registry on ES encompassing clinical features, pharmacological management, and interventional treatment strategies. Second, we plan to use the data derived from the registry to describe mortality and rehospitalization rates in patients with ES over a long follow-up.

2. Methods

2.1. Study design

The ELECTRA is a multicentre, observational, prospective clinical study aimed at gathering information on a wide cohort of patients affected by ES. Enrolment started on August 1st, 2016 and will continue for a minimum of three years. There is no pre-specified date for the end of enrolment, which will continue according to the enrolment rate. A minimum of 500 patients will be included in the present registry, and each patient will be followed-up for a minimum of three years. The exploratory nature intrinsic to the registry characteristics does not allow a sample size calculation (see *Statistical analysis* below). However, the sample size was selected on the estimated enrolment rates of the participating centres during a 3-year enrolment period. Moreover, the sample size will be large enough to postulate specific subgroup analyses.

The inclusion criteria are:

- •Diagnosis of ES, defined as three or more episodes of VTs/VFs within 24-hour and separated by at least 5 min or documentation of sustained VT lasted at least 12 h
- age ≥18 years old
- written informed consent

The exclusion criteria are few, and aimed to gather a representative sample of the “real-world” population:

- No ICD implantation
- confirmed or suspected use of drugs or narcotics with known direct pro-arrhythmic effect
- inability to express an informed consent for the study

All patients admitted to the participating centres will be evaluated consecutively by the referent investigators. All patients that meet the above-described criteria will be included in the registry. The study complies with the Declaration of Helsinki; it was approved by the ethic committee of each participating center, and was registered into www.clinicaltrials.gov (NCT02882139). At enrolment, each patient will be informed on the aim and the design of the study. It will be stated to each patient that his participation to the registry is voluntary, free and that the consent can be withdrawn at any time and for any reason. All patients will be informed to the results of the study through their enrolling centres.

2.2. Data collection

All data requested will be collected by the referent investigators at enrolment and during each follow-up visit. Considering that the ICD records all the major arrhythmic events since implantation, patients experiencing an ES previous to the enrolment start can be included retrospectively if they meet the following additional inclusion criteria:

- Availability of complete and accurate clinical data
- No ICD replacement after the index event, leading to the loss of original data
- Availability of ECG and echocardiography done for routine clinical purposes
- Agreement to subscribe the informed consent during the next routine visit

Data are saved on a dedicated website in agreement with the Italian regulations on the treatment of personal data. Electronic cards of data collection transmitted to the study responsible are identified by an alphanumeric code. The list of matches between subjects' data and these codes will be created and kept by local investigators only. The complete list of all collected variables is shown in Supplementary Table 1. Each centre will be asked to report every death and hospital admission of all patients and their causes. Moreover, data about subjects' vital status will be updated every 6 months, either by telephone call or by ambulatory visit.

Collected data will be processed, analysed and reported according the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative international guidelines [10].

2.3. 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 adjusted according to variables of interest such as gender, age, underlying heart disease, comorbidities and programming mode will be calculated according to the Kaplan-Meier method and compared by Log-rank test for primary and secondary endpoints. Primary endpoint subgroup analyses for each of the aforementioned variables will be performed too. According to the number of centres 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 [7], we expect about 55 deaths at 1-year follow-up and about 165 deaths at the end of the 3-year follow-up. The statistical analysis will be conducted using the SPSS 21.0 for Windows software (SPSS Inc. Chicago, IL, USA). Every test will be two-tailed and a value of $p > 0.05$ will be considered significant. Multiplicity between the different endpoints will be controlled by the stepwise Holm procedure.

2.4. Expected results

The primary endpoint of the ELECTRA registry will be all-cause mortality 3 years after the ES index event. The main secondary endpoint will be hospitalization for all causes 3 years after the ES index event. Survival and new hospitalizations will be documented through ICD remote monitoring, internal database checking, and direct phone interview. Deaths will be classified according to a modified Hinkle-Thaler classification [11] and categorized into three predefined groups: sudden death, non-sudden death for cardiovascular causes, and death for other causes. Non-sudden death for cardiovascular causes will be divided into HF-related death, coronary death, and death for other