A prospective multicenter study assessing the clinical significance of connectivity in patients with cardiac implantable electronic devices (CONNECTION Study): Rationale, methods and study design.

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Background

Cardiac Implantable Electronic Devices (CIEDs) are broadly used with expanding indications in clinical practice [1]. To improve device control and patient follow-up, modern CIEDs are provided with remote monitoring (RM) systems, allowing technicians to receive data at specified time intervals without the need for patients' access to Clinics. Moreover, an alert is sent to clinic team in the case of cardiac urgencies, device disconnection, or malfunctioning. Data transmission from RM CIEDs is automatic (wireless RM, w-RM) and does not require direct patient intervention.

RM has been demonstrated to reduce hospitalizations and mortality, by enabling early detection of modifiable cardiac events [2-6]. RM clinical benefit is possible only if its adherence is guaranteed [1,6]. A fundamental requirement of RM is continuous connectivity between the patient's implanted device and the CIED manufacturer's central server, through the correct functioning of the transmitter. Failure in either of these steps prevents an efficient healthcare response to technical or clinical issues.

Despite its importance, RM adherence is supported by limited evidence from outdated trials, and connectivity has not been universally defined [2-4].

This study aims at describing the rationale, methods, and design of the CONNECTION Study. Its protocol has been submitted to the ethics committee. It was conceived and developed by the authors as a project work during the Regional Course "Methodologies and Tools for Clinical Research" promoted by the Emilia-Romagna region.

Objective

The primary objective of the CONNECTION Study is to identify the 2-year incidence of serious cardiovascular adverse events (MACE) in a population of patients with CIEDs, followed by a dedicated healthcare team and monitored via w-RM in a real-world setting.

Secondary objectives include evaluating whether RM connectivity is associated with MACEs and all-cause mortality in a real-world setting; determining the optimal percentage of connectivity that effectively discriminates patients experiencing MACE and/or all-cause mortality.

Patients and methods

The CONNECTION study is a prospective non-randomized, multisite, single-arm, open-label, post-market observational data collection per standard of care. The Connection Study will collect data for various types of commercially available CIEDs (pacemakers, implantable cardioverter defibrillators, and cardiac resynchronization therapy devices), capable of w-RM through one of the following monitoring systems, MERLIN.NET, CARELINK, BIOTRONIK HOME MONITORING, and LATITUDE. Patient data, transferred to a central database, are accessible through a secure website and can be utilized as part of the clinical assessment of the patient. This process is facilitated by a communicator (Merlin@home, CardioMessenger®

Smart, LATITUDE NXT Communicator and MyCareLink Patient Monitor), which is the focus of the study, enabling continuous connectivity between the patient's device and the hospital. The transmitters and the remote monitoring systems are all CE marked and are routinely used in clinical practice across all participating Italian centers.

Eligible patients are subjects scheduled to be or already implanted with a w-RM CIED, which is approved for commercial use in Italy. The selected sites are four specialized Italian centers (AOU di Ferrara; Ospedale di Fidenza; Ospedale S. Maria Nuova, Reggio Emilia; Ospedale Guglielmo da Saliceto, Piacenza) where approved devices are utilized and monitored through one of the previous described RM systems.

Sites will collect all data (clinical data, demographics, medical history/indications, device information, procedure information, connectivity status, and patient status), based solely on their local standard of care. Subjects will be followed up through scheduled and unscheduled clinical visits according to the local standard of care at the participating sites. No study-related visits are planned during follow-up. The occurrence of MACE, together with the patient status, will be collected from the sites by analyzing administrative data related to Italian hospital discharge records (SDO) during the follow-up periods (at 6, 12, and 24 months). To ensure uniformity within the study population, connectivity alerts will be configured for a 14-day period across all device manufacturers. Medical staff at each site will check for the presence of connectivity alerts every 14 days and report them in the electronic case report form (eCRF, REDCap).

Assuming a 2-year incidence of MACE of 15% [7,8] in a mixed population of patients with pacemaker and ICD, a 10% dropout rate, a 1.4% absolute precision and a 95% confidence interval, a total number of 3,400 patients will be enrolled.

Given the longitudinal nature of data, a graphical inspection of Kaplan-Meier curves will be conducted.

To explore the relationship between RM connectivity—defined as the percentage of 14-day intervals without an alert of RM disconnection—and the primary endpoint, we will employ a Cox proportional-hazard model with an adjustment for demographic and clinic covariates (as the model device) other than a site-stratification. For all statistical tests, the significance level is set at p-value = 0.05.

Conclusions

The CONNECTION study will investigate the magnitude of benefits of w-RM among CIED patients in a real-world setting, with a focus on the importance of uninterrupted connectivity to improve patient outcomes. If the study confirms the impact of connectivity on the outcomes, the importance of dedicating and allocating resources will be brought to the attention of organizations and health management structures able to properly monitor the adherence to treatment, in order to guarantee all patients an effective health intervention.

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