STUDY PROTOCOL SUMMARY

TITLE

Descriptive: Role of endomyocardial biopsy and aetiology-based treatment in patients with inflammatory heart disease in arrhythmic and non-arhythmic clinical presentations: an integrated approach for the optimal diagnostic and therapeutic management.

Code: MYOCAR

Final protocol date: 20/02/2020 (V03 - Multicenter)

HEAD CENTER

Department of Electrophysiology and Arrhythmology, San Raffaele Hospital, Milan, Italy.

INVESTIGATORS

Principal Investigators: Giovanni Peretto, MD – Simone Sala, MD
Promoter: Paolo Della Bella, MD, Head Department of Electrophysiology and Arrhythmology, San Raffaele Hospital, Milan, Italy

BACKGROUND

Myocarditis is a complex inflammatory disease, usually occurring secondary to viral infections, autoimmune processes or toxic agents [1]. Clinical presentations are multiple, including chest-pain, heart failure and a broad spectrum of arrhythmias [1]. In turn, outcome is largely unpredictable, ranging from mild self-limiting disease, to chronic stage and progressive evolution towards dilated cardiomyopathy, to rapid adverse outcome in fulminant forms [1,2]. Subsequently, myocarditis is often underdiagnosed and undertreated [3], and optimal diagnostic and therapeutic strategies are still to be defined.

RATIONALE

Our study aims at answering multiple questions about myocarditis, with special attention
to its arrhythmic manifestations.

1. Optimal diagnostic workflow is still to be defined. In fact, although endomyocardial biopsy (EMB) is still the diagnostic gold standard, especially for aetiology identification [1], it is an invasive technique. Furthermore, it may lack sensitivity because of sampling errors. By converse, modern imaging techniques – cardiac magnetic resonance (CMR) in particular – have been proposed as alternative or complementary diagnostic tool in inflammatory heart disease [4,5,6]. Other noninvasive diagnostic techniques, like delayed-enhanced CT (DECT) scan or position emission tomography (PET) scan, are under investigation.

2. Biomarkers to identify myocarditis aetiology, predisposition, prognosis and response to treatment are still to be defined [1,3,5].

3. Arrhythmic myocarditis is largely underdiagnosed and uninvestigated. Importantly, myocarditis presenting with arrhythmias requires specific diagnostic, prognostic and therapeutic considerations [2]. At our hospital, which is an international referral center for ventricular arrhythmias management and ablation, a relevant number of patients with unexplained arrhythmias had myocarditis as underlying aetiology. Our experience may considerably improve knowledge and management of arrhythmic myocarditis.

4. The role of CMR, as well as alternative noninvasive imaging techniques, in defining myocarditis healing is a relevant issue. In particular, optimal timing for follow-up diagnostic reassessment is still to be defined, in patients with myocarditis at different inflammatory stages, either with or without aetiology-dependent treatment [4,7].

5. Uniformly-designed studies are lacking, to compare myocarditis among different patient subgroups, differing by variables like: clinical presentations, myocarditis stage, associated cardiac or extra-cardiac diseases, aetiology-based treatment, associated arrhythmic manifestations, diagnostic workup, and devices or ablation treatment [8,9,10].

AIMS

Our study has multiple aims (full detail in Table 1).

1. To compare EMB with noninvasive diagnostic techniques (CMR, DECT, PET scan, either alone or in association).

2. To assess the role of blood biomarkers for identification of aetiology, predisposition, prognosis, response to treatment, inflammatory activity, clinical presentation.

3. To describe myocarditis presenting with arrhythmias, with special focus on ventricular arrhythmias at different myocarditis stages and in different clinical contexts. To validate and generalize our model for optimal diagnostic and therapeutic management of arrhythmias in myocarditis patients (given the role of our hospital as an international referral center for arrhythmias ablation and management).
4. To evaluate the timing needed for myocarditis healing in different patients subgroups, as assessed by noninvasive imaging techniques (CMR, DECT, PET scan), either alone or in association.

5. To compare patients subgroups of myocarditis, in terms of epidemiology, aetiology, prognosis, and diagnostic-therapeutical strategies. Among the others, the main study subgroups will be:
   A. Arrhythmic vs. non-arrhythmic myocarditis.
   B. Arrhythmic myocarditis subgroups.
   C. Non-arrhythmic myocarditis subgroups (i.e.: fulminant, acute coronary syndrome-like, pericarditis-like, heart failure, nonischaemic dilated /hypokynetic cardiomyopathies of unknown aetiology...).
   D. Infectious vs. autoimmune vs. toxic myocarditis.
   E. Myocarditis treated by aetiology-based treatment vs. isolated cardiac medical treatment.
   F. Myocarditis at different disease stages: acute, hyperacute, fulminant, chronic active, post-inflammatory, or active vs. previous vs. non-myocarditis.
   G. Myocarditis presenting as organ-specific diseases vs. in the context of a genetic disorder or systemic disease.
   H. Myocarditis vs. peri-myocarditis/myo-pericarditis.
   I. Other analyses.

__________________________________________________________

STUDY DESIGN

Our study, previously designed as a single-center experience, is multicenter, observational and both retrospective and prospective. Retrospective phase includes all clinical data occurring before the index event (hospitalization or clinically suspected myocarditis) and myocarditis diagnosis. Prospective phase includes all data following index event and myocarditis diagnosis.

Any adult patient with clinically suspected myocarditis, of any clinical presentation and any degree of severity, will be considered as suitable for study enrollment. Patients will undergo diagnostic and therapeutical strategies considered as clinically indicated in a patient-tailored manner, as suggested by international guidelines recommendations and best local clinical practice. Patients will be free of either accepting or refusing any diagnostic or therapeutical proposal. Whenever accepted, data will be simply collected and analyzed.

Based on clinical presentation, patients will be divided into two groups, arrhythmic (group A) and non-arrhythmic (group NA, including any other clinical presentation).
Independently of A/NA groups, all patients will undergo optimal diagnostic and therapeutic strategies, as summarized in panel A. In parallel, special diagnostic and therapeutical strategies will be performed in patients with arrhythmic presentation or evidence of arrhythmias, as shown in panel B. Proposed flowcharts (panels A and B) represent only an approximate algorithm. Exceptions can be made in single cases, based on clinical indications.

**Panel A – Diagnostic and therapeutical workup in all patients.**
Independently of groups (A/NA), all patients will undergo optimal diagnostic and therapeutical workup, guided by updated scientific evidence merged with the clinical experience of the center.
Baseline diagnostic workup will include: complete blood exams, 12-leads ECG, continuous telemetric monitoring, transthoracic doppler echocardiogram, coronary artery imaging (coronary angiography or CT scan). Any other clinically relevant diagnostic test will be collected.
In life-threatening presentations (cardiogenic shock or malignant arrhythmias), support treatment by optimal medical therapy, inotropic or mechanical circulatory support, and acute-phase arrhythmia management (including cardioversion, defibrillation, or temporary pacing) will be performed, as indicated, before completing diagnostic workup.
Final diagnosis of myocarditis will include, whenever applicable:

A. For stable patients: 1) a second-level imaging technique (CMR as first choice; and/or DECT, PET, or multiple/fusion imaging techniques, based on clinical indications); followed by: 2) EMB, whenever clinically indicated. Blood exams for aetiology screening will be personalized upon clinical indications.

B. For unstable patients: EMB only, as recommended. Blood exams for aetiology screening will be personalized upon clinical indications.

Diagnostic criteria for myocarditis, as assessed by any diagnostic technique, will be defined based on international scientific evidence and will be constantly updated. Similar considerations apply to myocarditis staging and aetiology definition. Whenever not available at local institutions, diagnostic exams can be performed and analyzed at external centers.
All patients with myocarditis (or any alternative final diagnosis), will undergo standard cardiological optimal medical treatment (COMT), as indicated. By converse, aetiology-dependent treatment will be performed only in patients with a final diagnosis of any *active* (acute, fulminant, chronic active) myocarditis of defined aetiology (EMB-proved).
Multidisciplinary assessment, including infective disease specialists (in viral/infective myocarditis), immunologists (in non-infective/autoimmune myocarditis) or any other specialist as needed, will be used to identify indications to treatment, drug choice (either approved or with a justified off-label indication), treatment duration and safety profile, aiming at the best patients’ interest. Toxic myocarditis will be treated accordingly, by evaluating the opportunity of withdrawing pathogenic noxa.
This protocol will not interfere with local best clinical practice.
Patients with non-active myocarditis (previous or healed) or with non-myocarditis, will undergo “standard FU” (see below). Patients with active myocarditis will undergo “intensive FU” (see below).

Independently of FU modalities, diagnostic reassessment will be considered in the presence of at least one of the following instability criteria: a) new unexplained cardiac symptoms (dyspnoea, chest pain, syncope, palpitation); b) new unexplained increase in troponin or natriuretic peptides; c) new imaging abnormal signs; d) new unexplained clinically relevant arrhythmias. Diagnostic reassessment will include second-level imaging and/or EMB, as shown above. Subsequent therapeutical workup will be in line with the above explanations. In stable patients or undergone myocarditis healing, exercise stress test will be obtained, whenever possible.

Panel B – Diagnostic and therapeutical workup of patients with arrhythmias
In parallel with (and independently of) Panel A content, patients with arrhythmias (group A) will undergo specific diagnostic and therapeutical management for arrhythmias, as a result of the integration between international guidelines recommendations and the experience of a third-level center international referral center (San Raffaele Hospital, Milan) for arrhythmia management and ablation.

To oversimplify, 4 groups of patients will be considered.

1. Group 1: major ventricular arrhythmias (haemodynamically unstable VT, hu-VT; ventricular fibrillation, VF).
   After electrical stabilization and support treatment (panel A), indication to secondary prevention ICD implant will be multiparametric and patient-tailored. In patients with active myocarditis, subcutaneous ICD (S-ICD) or wearable CD (WCD) will be considered. Antiarrhythmic drugs will be considered in all Group 1 patients. In addition, all Group 1 patients will undergo COMT and aetiology-dependent treatment whenever applicable (panel A). Ablation of ventricular arrhythmias will be considered in patients with severe arrhythmic presentation, or symptomatic, or refractory to optimal medical treatment. Electrophysiological study (EPS) may be used in selected cases. A CRT-D will replace ICD whenever indicated.

2. Group 2: other ventricular arrhythmias (high-burden premature ventricular complexes = hb-PVC; nonsustained VT = NSVT; haemodynamically stable VT = hs-VT).
   Whenever clinically indicated, Group 2 patients will undergo invasive EPS (or in alternative noninvasive programmed ventricular stimulation in ICD carriers) to stratify arrhythmic risk. Patients with positive EPS will undergo ICD (or S-ICD/WCD) as in Group 1. Patients with negative EPS, as well as Group 2 cases not undergoing EPS, will undergo watchful waiting strategy (always with an intensive FU) with or without loop recorder implant: in these cases, ICD (or S-ICD/WCD) will be implanted only following documentation of relevant VA in FU. In addition, all Group 2 patients will undergo antiarrhythmic treatment, COMT and aetiology-dependent treatment whenever applicable (panel A). In symptomatic or drug-refractory cases, ablation of ventricular arrhythmias will be considered. A CRT-D will replace ICD whenever indicated.
3. Group 3: bradyarrhythmias (2nd type II or 3rd degree atrioventricular block = advanced AVB; critical sinus pauses = SND).
After electrical stabilization and support treatment (panel A), including the use of temporary pacemaker as a bridge-to-decision, patients will undergo watchful waiting strategy or definitive device implant. Instead of a pacemaker (PM), ICD will be considered in the presence of high-risk criteria for ventricular tachyarrhythmias, including: a) overlap with Group 1 presentation; b) overlap with Group 2 presentation, especially in the presence of positive EPS; c) other indications for primary prevention ICD implant (severe systolic dysfunction); d) signs of increased tachyarrhythmic risk (scar signs); e) patients with special aetiologies leading to an increased tachyarrhythmic risk (es: cardiac sarcoid, giant cell myocarditis, Chagas disease, overlapping genetic syndromes). In addition, all Group 3 patients will undergo COMT and aetiology-dependent treatment whenever applicable (panel A). A CRT-D or a CRT-P will replace ICD or PM, respectively, whenever indicated.

4. Group 4: supraventricular arrhythmias (atrial fibrillation = AF; atrial flutter = AFlu; atrial tachycardia = AT).
Following acute-phase rate control (RaC), stable rhythm control (RyC) strategy will be considered as the therapeutical target, together with appropriate anticoagulation, as needed. Normal sinus rhythm will be obtained through either electrical or pharmacological cardioversion. In patients with unsuccessful attempts of sinus rhythm conversion, optimal treatment of active myocarditis will be considered as a primary target. Following myocarditis healing, in the presence of persistent arrhythmias, patients will be considered for RyC via electrical or pharmacological cardioversion. Transcatheter ablation will be an option for patients with drug-symptomatic, recurrent or refractory arrhythmias. Permanent RaC strategy will be considered only in non responders. Widespread use of implantable loop recorders will apply, as clinically indicated. In addition, all Group 4 patients will undergo COMT and aetiology-dependent treatment whenever applicable (panel A).

STUDY POPULATION
We will enroll adult patients (age ≥ 18 y), of any gender or ethnic group, evaluated for clinically suspected myocarditis. Patients can be enrolled from any medical environment or department, including inpatients, outpatients, and patients transferred from other hospitals. The same inclusion criteria will apply to the multicenter study (see below).

INCLUSION CRITERIA
- Written informed consent.
- Age ≥ 18 years.
• Clinically suspected myocarditis [1].
• Enrollment performed by one of the participating Centers.

EXCLUSION CRITERIA

• Absence of written informed consent.
• Age < 18 years (paediatric population).

VARIABLES AND ENDPOINTS

The main study variables are reported in Table 1 and in CRF. Endpoints will include:

- Major endpoints: death; cardiac death; malignant ventricular arrhythmias (VT, VF, appropriate ICD therapy); heart transplantation; end-stage heart failure.
- Minor endpoints: minor arrhythmias (NSVT, supraventricular arrhythmias; bradyarrhythmias); structural or functional myocardial abnormalities (any chamber dilation, systolic or diastolic dysfunction, including strain analysis, pericardial, vascular or valvular involvement, any other detectable abnormalities); abnormalities detectable by advanced imaging techniques (Lake Louise criteria and T-mapping techniques at CMR; any qualitative or quantitative imaging abnormality detectable by CMR, DECT or PET scan, or other imaging techniques, alone or in association); clinical variables (signs and symptoms related to cardiac or multisystemic disease; identification of associated diseases); blood exams abnormalities (inflammatory indexes; cardiac injury, inflammation or stress biomarkers; cardiac and extracardiac autoantibodies; genetic tests; tissue/organ damage indexes; markers of treatment toxicity; others); anatomical or functional abnormalities of coronary macro or microvascular structures (coronary angiography; CT scan; histology; provocative stress tests, nuclear medicine techniques); necessity of invasive electrophysiological techniques (electrophysiological study; arrhythmia ablation; device implant) and related findings; indications and timing for primary and secondary prevention device implant, in relation with different therapeutic strategies; myocarditis recurrences; response to general and specific treatment; multiparametric modeling of prognostic risk stratification and response to treatment prediction; elaboration of multidisciplinary workup models.

The main primary and secondary variables are reported in detail in Table 1.

Tabella 1

<table>
<thead>
<tr>
<th>N patients</th>
<th>Primary Variables</th>
<th>Secondary variables</th>
</tr>
</thead>
</table>

7
| 1 | Comparison between EMB and second level imaging findings | 1000 | • Diagnostic concordance | • Inflammatory activity (presence, type, quantification)  
• Fibrosis (presence, type, quantification)  
• Coronary microvascular disease  
• Comparison between EMB sampling site and abnormal substrate localization at imaging (including substrate-guided EMB or alternative biopsy techniques)  
• Role of EMB guided by electroanatomical map  
• Diagnostic performance of DECT and/or PET, especially when CMR is contraindicated  
• Comparison between CMR/DECT findings and PET scan (including fusion imaging) or advanced imaging techniques including strain analysis at echocardiogram  
• Comparison between substrate abnormalities localizations (as assessed by second level imaging techniques) and arrhythmias (type, characteristics and origin site)  
• Comparison among different diagnostic techniques (EMB, CMR/DECT, PET) in terms of safety and diagnostic accuracy  
• Evaluation of differential diagnosis with other cardiac diseases, and particular with arrhythmogenic cardiomyopathy of any localization (left, right, biventricular, to identify updated diagnostic criteria)  
• Comparison between information provided by all the techniques above, and data from electroanatomical mapping (EAM)  
• Other analyses |
|---|---|---|---|---|
| 2 | Evaluation of blood exams and biomarkers | 1000 | • Identification of diagnostic biomarkers  
• Identification of aetiology biomarkers  
• Cardiac and inflammatory biomarkers evaluation in different myocarditis subtypes  
• Identification of biomarkers of inflammatory stage (acute vs. chronic; active vs. previous)  
• Comparison between local and systemic/peripheral inflammation  
• Correlations with EMB and second-level imaging (CMR, DECT, PET...) findings  
• Identification of genetic factors with any role in predisposition, prognosis, response to treatment, or any other correlation, either in the presence or in the absence of underlying cardiomyopathy or autoimmune/inflammatory disease  
• Identification of prognostic biomarkers  
• Identification of biomarkers associated with treatment response  
• Evaluation of any tissue/organ damage or associated comorbidities  
• Study of cardiac autoantibodies  
• Study of any cell, tissue, genetic or circulating biomarker  
• Correlations with clinical presentations  
• Other analyses |
| 3 | Validation of optimal management of arrhythmic myocarditis | 1000 | • Evaluation of effects on major endpoints  
• Evaluation of effects on minor endpoints  
• Role of electrophysiological study in risk stratification |
### Evaluation of healing timing in myocarditis

| 500 | Any degree of recovery by 3, 6, 9, 12 and > 12 months |

- Comparison of healing times in treated vs. untreated patients
- Correlations between healing times and clinical presentation types
- Correlations between healing times and any biomarker
- Correlations between healing times and any outcomes
- Validation of exercise stress test role after myocarditis healing
- Evaluation of PET scan or other diagnostic techniques as alternatives to CMR in special populations
- Other analyses

### Subgroup analyses

| 500 (hugely variable in each subanalysis) | Differences in major outcomes |

- Differences in minor outcomes
- Differences in any biomarker
- Differences in any diagnostic exam
- Differences in aetiology
- Differences in predisposition
- Differences in inflammatory activity
- Differences in pericardial involvement
- Differences in systemic involvement
- Differences in arrhythmias types and features
- Differences in clinical presentation
- Differences in treatment response, including novel treatments
- Validation of local aetiology/pathophysiology-dependent treatments (group E)
FOLLOW-UP VARIABLES

Any quantitative and qualitative parameters detectable by medical history, objective examination, biomarkers, 12-leads ECG, signal averaged ECG, continuous telemonitoring (during new hospitalization or in device carriers), Holter ECG (at least 24-hours, possibly 12-leads), color Doppler transthoracic echocardiogram, coronary angiography or CT scan, stress tests, CMR, DECT, PET scan (alone or in association/fusion), genetic tests, tilting test, electrophysiological study (either invasive or noninvasive), electroanatomical map, any other imaging or laboratory exam identified as clinically-relevant.

FOLLOW-UP TIMELINE

A clinical time zero (t0) will be considered as the start point for FU. t0 indicates the timing of myocarditis diagnosis, as assessed by EMB (first choice) or by imaging techniques (second choice).

FU calendar will be variable based on clinical indications. As a general line, intensive FU will be planned for the first two years (month 3, month 6, month 9, month 12, month 18, month 24). For patients needing a strict control for relevant clinical issues, minimal FU reassessment is set at 2 weeks timespan. In the absence of clinical issues, from month 24 FU will be performed every 6-12 months up to the end of the study.

FOLLOW-UP EXAMS

- Standard FU: cardiological (or multidisciplinary) assessment 1-2/y with blood exams (at least troponin, natriuretic peptides, and inflammatory indexes), 12-leads ECG, Holter ECG monitoring, device interrogation (in device carriers), and color Doppler transthoracic echocardiogram. Second-level imaging techniques (CMR, DECT, PET scan) or other exams will be performed based on clinical indications.
- Intensive FU: cardiological (or multidisciplinary) assessment 1-2/y with blood exams (at least troponin, natriuretic peptides, and inflammatory indexes), 12-leads ECG, Holter
ECG monitoring, device interrogation (in device carriers), and color Doppler transthoracic echocardiogram. Minimal reassessment timespan is 2 weeks. At least one second-level imaging techniques (CMR, DECT, PET scan) will be performed by 12 months (approximately at 3, 6, 9, or 12 months based on clinical indications). Exercise stress test will be performed whenever clinically indicated, usually not before proved myocarditis healing. Other exams will be performed based on clinical indications.

STUDY DURATION

Estimated study duration is 23 years (from January 2013 to December 2035). In detail:

- Retrospective enrollment: from January 2013 to local institute review board approval.
- Prospective enrollment: from local institute review board approval to December 2025 (estimated enrollment end).
- FU duration per patient: 10 years.
- Estimated last FU for last enrolled patient: December 2035.

CONFOUNDING FACTORS

Not applicable.

EPIDEMIOLOGIC DATA

Because of multiple clinical presentations and heterogeneous diagnostic techniques, myocarditis incidence is widely variable [1]. At our institution, the mean rate of clinically suspected myocarditis is not inferior to 4 new cases/month. Epidemiology may be different at other centers. Target numbers reported in Table 1 are reasonable.

DATA COLLECTION AND STATISTICAL ANALYSIS

Two enrollment modalities are accepted for this study: 1) prospective enrollment: at myocarditis diagnosis (following local institute review board approval); 2) retrospective enrollment: during FU of myocarditis patients (diagnosed before local institute review board approval).
Considering incidence rate, local and general epidemiology, enrollment of 1000 myocarditis cases by December 2020 is expected, including retrospective and prospective enrollment. For aim 1, 95% confidence intervals of 81-89% and of 75-85% are estimated for EMB and CMR, with 85% and 80% sensitivity, respectively. These data are consistent with updated knowledge. EMB will be considered as the diagnostic gold standard, as indicated [1].

Both baseline and FU data will be collected for each enrolled patient. CRF form reports the main study variables, in the form of an Excel document.

Statistical analyses will be performed by certified programs (i.e. SPSS).

Data will be presented as mean/median and standard deviation/interquartile range, or as contingency tables, depending on variables type and distribution. Parametric and non-parametric tests will be used accordingly. Confidence intervals will be set at 95%. Statistical significance threshold will be set at p < 0.05. Regression models will be used for univariable and multivariable risk stratification and survival analyses. Either in all patients or in subgroups, appropriate statistical tests will be used for general and specific analyses, as needed to address each study aim (Table 1).

---

**ETHICAL ISSUES**

Our study will be performed in accordance with Helsinki Declaration and current laws regarding observational prospective and retrospective studies. Diagnostic and therapeutical workup will not differ from daily clinical practice a tour hospital, as the result of updated international scientific evidence, integrated by the experience of a referral center for myocarditis and arrhythmias management, aiming at the best patients’ interest. Follow-up timeline and diagnostic exams will be required as clinically needed. No randomization procedures will be performed. Patient grouping will be “spontaneous”, based on clinical features and personalized overall workup. This study will respect the autonomy principle for any patient. At any time, patients will be free to accept or refuse any diagnostic or therapeutical proposal. As in daily clinical practice, critical or exceptional diagnostic and therapeutical options will be discussed in a multisiciplinary team and shared with patients, as needed. Per protocol, data will be simply collected and analyzed, without interfering with the best clinical practice. Thus, for any diagnostic exam or treatment, no special adverse reactions are expected, as compared to what observed in daily clinical practice.

Written informed consent will be obtained for any enrolled patient. No physical or psychosocial risks are expected regarding study procedures, informed consent, or authorization to use personal data. Institutional review board evaluation is necessary to approve the present study protocol.
All data will be made anonymous. Analyses results will be published in international medical journals with impact factors.

REFERENCES


Principal Investigators: Giovanni Peretto, MD - Simone Sala, MD

Appendix – Abbreviation List

A = arrhythmic  
AAD = anti-arrhythmic drugs  
AF = atrial fibrillation  
AFlu = atrial flutter  
AT = atrial tachycardia  
AVB = atrioventricular block  
BE = blood exams  
BtD = bridge to decision  
CMR = cardiac magnetic resonance  
COMT = cardiologic optimal medical therapy  
CRT = cardiac resynchronization therapy (with ICD function=CRT-D; or without=CRT-P)  
DECT = delayed-enhanced computed tomography
EMB = endomyocardial biopsy
EPS = electrophysiological study
EST = exercise stress test
FU = follow-up
hb-PVC = high-burden premature ventricular complexes
hs-VT = haemodynamically stable ventricular tachycardia
hu-VT = haemodynamically unstable ventricular tachycardia
ICD = implantable cardioverter defibrillator
IST = immunosuppressive therapy
LTC = life-threatening condition
MCS = mechanical circulatory support
NA = non-arrhythmic
NR = non responder
OMT = optimal medical therapy
PM = pacemaker
RaC = rate control strategy
RyC = rhythm control strategy
S-ICD = subcutaneous implantable cardioverter defibrillator
SMT = special medical therapy
SND = sinus node disease
TCA = transcatheter ablation
TTDE = transthoracic doppler echocardiogram
VF = ventricular fibrillation
VT = ventricular tachycardia
WCD = life vest (wearable cardioverter defibrillator)
ww = sorverglianza attiva (watchful waiting)