Arrhythmia-induced cardiomyopathy (AIC) is a diagnosis ex juvantibus: study design and diagnostic criteria of a prospective, observational, multi-center study

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Study protocol

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Abstract

Background: Arrhythmias and heart failure in form of left ventricular systolic dysfunction (LVSD) frequently coexist. Arrhythmia-induced cardiomyopathy (AIC) by definition is a state of reversible LVSD caused by supraventricular or ventricular arrhythmia. Diagnosis of AIC only can be made retrospectively *ex juvantibus*, and thus deserves consideration. Our aim is to determine prevalence and time course of AIC in patients presenting with tachycardia and newly diagnosed, unexplained LVSD.

Methods: In this prospective, observational, investigator-initiated, multi-center trial, we screen for patients with LVSD (left ventricular ejection fraction (LVEF) <50%) and tachyarrhythmia (HR > 100/min). After effective rhythm restoration, they are followed-up at 2, 4 and 6 months to evaluate clinical characteristics, biomarkers and cardiac imaging. Left ventricular morphology and function are assessed with transthoracic echocardiography, and left ventricular scar is quantified with cardia magnetic resonance imaging. Additionally, quality of life is measured with a questionnaire (Minnesota Living with Heart Failure). Unconventionally, the group assignment was done after the last follow-up visit (*diagnosis ex juvantibus*). Patients, whose LVEF recovered from LVSD, i.e. increases by ≥15% vs. baseline or increases to ≥50% with an absolute increase of ≥10% were assigned to the AIC group (arm 1). All other patients serve as comparator (arm 2, non-AIC group). Next, prevalence (equals the number of patients in arm 1 divided by the total number of patients) and time to recovery from AIC (time of follow-up visit, in which the LVEF recovered) were calculated and initial morphologic and functional parameters analyzed for predictive power of an AIC.

Discussion: We investigate the prevalence of and the time to recovery from AIC in a clinically relevant cohort of patients with newly diagnosed and otherwise unexplainable LVSD and coexisting tachyarrhythmia. Results will help to establish correct diagnoses, describe the frequency of this disease, and possibly identify predictors for AIC.

Background

Atrial fibrillation (AFib) is the most frequent rhythm disorder and often coexists with heart failure (HF). These two conditions not only share common risk factors [1] but also interact with each other. [2] Proceeding HF frequently leads to AFib, whereas AFib, especially tachycardic AFib, may lead to HF and thus to arrhythmia-induced cardiomyopathy (AIC). Up to one in four patients with AFib develops tachycardia. [3]

AIC is a condition in which tachyarrhythmia or frequent ectopy results in left ventricular systolic dysfunction (LVSD) and HF. The hallmark of this condition is partial or complete reversibility once rhythm control is achieved. Therefore, correct diagnosis is essential for successful treatment. Because LVSD may also induce rhythm disorders as complications, AIC may be a hidden cause of HF, particularly in case of ‘idiopathic cardiomyopathy’ with concomitant arrhythmia. Although daily clinical practice suggests a high disease frequency, the incidence and prevalence of AIC remain unclear. [4–6] In general, about 30%

of patients with AFib have LVSD. [7] The few small and mainly uncontrolled studies available suggest that a high number (56–88%) of these patients have a relevant component of AIC, depending on the inclusion criteria. [5, 8, 9] However, arrhythmia is frequently considered to be secondary and hence not treated effectively when, in fact, immediate rhythm control may be necessary for full recovery of LV function. [4, 6] Full recovery of LV function has been reported to take weeks to several months. [6] Inter-sectional barriers (e.g. inpatient vs. outpatient care) may lead to physicians losing track of the development of LV function after the initiation of a causal rhythm control therapy.

Two recent trials suggesting a high incidence of AIC have underlined the effectiveness of ablation therapy in patients with HF and concomitant AFib. In the CAMERA-MRI trial, restoration of sinus rhythm through catheter ablation significantly improved LV function in patients with AFib and unclear LVSD. [5] In the CASTLE-AF trial, catheter ablation for AFib in patients with LVSD was associated with a significant reduction in death from any cause and hospitalization for HF. [10] However, there was no direct relation to AIC and no comparison with non-AIC patients. Further, there was no endpoint regarding the time course of recovery. Both trials clearly suggest the need for specific studies investigating the impact of AIC on LV function and clinical outcome. In contrast to AFib ablation, anti-arrhythmic strategies have failed to show an impact on mortality in the AF-CHF and DIAMOND-CHF trials. [10, 11] So far, no sufficient predictors or specific diagnostics have been established in prospective trials targeting this issue. Yet, early recognition of AIC seems to be critical, and aggressive treatment aimed at controlling or eliminating inciting arrhythmia results in symptom resolution and recovery of LV function. [6] There is a clear clinical need for a better identification of patients who may or may not respond to rhythm therapy.

Therefore, the primary aim of this trial is to elucidate the prevalence of AIC in patients with newly diagnosed idiopathic cardiomyopathy and to investigate the time to recovery from LVSD. For this purpose, patients with newly diagnosed systolic HF and concomitant tachyarrhythmia are eligible to participate in this trial.

Methods

Study design

This trial is a prospective, observational, investigator-initiated, multi-center study to investigate the prevalence of and the time to recovery from AIC. A further aim is to identify potential predictors of AIC in patients with newly diagnosed and otherwise unexplained LVSD defined as left ventricular ejection fraction (LVEF) of < 50% and coexisting persistent tachyarrhythmia (AFib or AFlut with a HR > 100/min). The hallmark of AIC is reversibility of LVSD over time after rhythm restoration. Thus, the diagnosis ‘AIC’ is made *ex juvantibus*, so that patient groups are generated at the end of follow-up (6 months after rhythm control). If patients have recovered from LVSD, they are assigned to the AIC group; if not, they are assigned to the non-AIC group as comparator. Recovery is defined as an increase in LVEF of either ≥ 15% or ≥ 10% with an absolute EF of ≥ 50%. The flow diagram is presented in Fig. 1, and the SPIRIT Checklist is provided in Supplemental file 1.

Study objectives and endpoints

Primary endpoints (dual endpoint): The primary endpoint is a combination of a) the prevalence of AIC, i.e. the percentage of patients recovering from LVSD after rhythm restoration (from AFib or AFlut to sinus rhythm) and b) the time required to recover from LVSD.

Secondary endpoints: Prespecified secondary endpoints to identify possible predictive factors are geometric (LV end-diastolic diameter, LV end-systolic diameter and LA area) and functional parameters (grade of mitral regurgitation [MR]), biomarkers (Nterminal-pro hormone brain natriuretic peptide [NT-proBNP] and high-sensitive troponin T [hs-cTnT]), left ventricular late gadolinium enhancement (LGE), quality of life (QoL) and NYHA class. Geometric and functional parameters are measured by means of transthoracic echocardiography, biomarkers are measured in peripheral blood samples and LGE is quantified in a semi-automated analysis of cardiac magnetic resonance images (cMRI). A detailed methodological description of echocardiography and cMRI is provided in Supplemental file 2.

For calculation of the primary endpoint, LVEF at the initial stay and during the follow-up visits is measured via transthoracic echocardiography in the apical four and two chamber view. Group assignment is conducted as described above; the mean time to recovery either is given as the prevalence of AIC at the time of the follow-up visits 2, 4 and 6 months after rhythm restoration or is calculated for each patient from the time point of rhythm restoration to recovery by analyzing the successive echocardiographic studies within the follow-up.

Eligibility Criteria

Patients presenting with persistent tachycardic AFib or AFlut with a HR > 100/min and newly diagnosed and otherwise unexplained LVSD defined as left ventricular ejection fraction (LVEF) of < 50% are enrolled in this study. The patients need to be able and willing to follow the treatment according to current guidelines. [7, 12–15]

The inclusion criteria are as follows: (1) newly diagnosed LVEF < 50%, (2) persistent AFib or AFlut, (3) heart rate > 100 beats/min, (4) age ≥ 18 years and (5) signed, written consent.

The exclusion criteria are as follows: (1) valvular heart disease, (2) permanent AFib, (3) suspicion of accumulative disease or myocarditis, (4) inability to receive coronary angiography, (5) relevant coronary stenosis in the current coronary angiography, (6) percutaneous coronary intervention (PCI) or any other revascularization procedure in the past 3 months, (7) inability to participate in the follow-up visits, (8) life expectancy < 1 year, (9) recurrent arrhythmia during follow-up and (10) development of other diseases during follow-up that could potentially worsen left ventricular function.

Recruitment and screening

Patients with LVSD and tachyarrhythmia are screened in the emergency room and the cardiologic clinics at the University Hospital Regensburg, the Caritas Hospital St. Josef Regensburg and the University Hospital Leipzig (Germany). The presence of tachycardic AFib or AFlut is verified with 12-channel electrocardiography, and LVSD is determined with transthoracic echocardiography after initial rate control. Patient history is evaluated and screened for prior LVSD, which is an exclusion criterion if not explainable by prior arrhythmia. The history of PCI/revascularization and underlying arrhythmia is documented, and corresponding documents are requested, if needed. Rhythm restoration follows local clinical pathways. The patient receives coronary angiography and revascularization, if indicated [16]. Only patients without current or prior (3 months) PCI/revascularization are eligible. Inclusion and exclusion criteria are checked (except the last 2 exclusion criterions (no. 9, 10), which cannot be checked before the end of follow-up). The patient is informed about the study and consent is obtained, if applicable. See Supplemental files 3 and 4 for the forms given to the patients. Because of the observational design of the study, no randomization is needed.

Who Takes Informed Consent?

Signed, written informed consent is taken after a trained physician has explained the study's background, aims and process (including follow-up visits) and has addressed any questions.

Study Treatment

In this observational study, patient treatment follows current guidelines for AFib and HF. [7, 12–15] Groups are assigned after the follow-up period. The procedure for rhythm restoration is the responsibility of the respective local cardiologic center. Treatment options are electrical cardioversion (ECV), pharmacological cardioversion or electrophysiological ablation therapy. In addition, therapeutic strategies can be combined and long-term antiarrhythmic therapy is an option. A detailed description of these procedures is given in Supplemental file 5. Of interest is the medical therapy for HF, which is individually optimized in respect of contraindications until reaching the maximum dose or the onset of side effects as recommended in current guidelines. [13]

Strategies for improving adherence to interventions

Rhythm control strategies may last a few minutes, in the case of ECV, or several hours, in the case of pulmonary vein isolation. Medication for HF is optimized during the initial hospital stay and adapted during follow-up. Attention is paid to potential side effects that may negatively affect adherence. The total trial duration is set at 6 months so that participation in the trial will not be too stressful for the patients. All patients are instructed to consult the study team if any problems occur that may be related to or interfere with the cardiovascular system and, in particular, if any heart rhythm disorders are suspected.

Relevant concomitant care permitted or prohibited during the trial

In case of recurrent arrhythmia or any other disease that may potentially worsen left ventricular function, the patient needs to be excluded from analysis.

Data Collection And Management

Data collection

The following data are collected during the initial hospital stay and the follow-up visits: LVEF, left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD); left atrial (LA) size and the grade of MR are obtained by means of echocardiography. hs-TnT and NT-proBNP are measured in peripheral blood samples, the NYHA class is estimated by means of anamnesis and QoL is assessed with a questionnaire (Minnesota Living with HF Questionnaire). LGE is quantified once. Table 1 lists the timing of the diagnostic procedures. Echocardiographic images are collected and interpreted by an experienced cardiologist, and all cMRI/LGE image data are sent to the core lab and analysed by two experienced radiologists.

Table 1
Assessment schedule

	Initial stay	Visit 1 (2 months after RC)	Visit 2 (4 months after RC)	Visit 3 (6 months after RC)
ECG (heart rate and rhythm)	X	X	X	X
Echocardiography (LVEF, LVESD, LVEDD, MR, LA size)	X	X	X	X
Lab values (NT-proBNP, hs-TnT)	X	X	X	X
NYHA class (grade)	X	X	X	X
QoL questionnaire*	X	X	X	X
cMRI (LGE)	X**			

ECG, echocardiography; cMRI, cardiac magnetic resonance imaging; hs-TnT, high-sensitive Troponin T; LVEF, left ventricular ejection fraction; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; NT-proBNP, N-terminal-pro hormone natriuretic peptide; LGE, late gadolinium enhancement; MR, mitral regurgitation; NYHA, New York Heart Association; QoL, quality of life; RC, rhythm control. * provided in Supplemental file 6. ** If cMRI cannot be scheduled within the hospital stay, a timely appointment is made after discharge.

Data management and confidentiality

Data are documented using Microsoft Excel spreadsheets and merged by C.S., T.K. and B.H. at the University of Regensburg. Personal patient data are stored in a password-protected file (master file) on a

password-protected personal computer (PC) in a locked room at the University Hospital Regensburg. Personal information of participants including the name, residency and contact information is only collected after signed consent. Each patient is assigned a sequential study number (pseudonymous ID). This number is used as an identifier in a second file (working file), in which the above data are collected. The file is stored on a separate PC. For data exchange, a version of the second file is transmitted safely via UKR-Box (https://ukrbox.ukr.de/) or personally with a USB drive. The master file will be archived for 25 years according to the Clinical Trials Regulation. Because of the observational design of the study, no data monitoring committee is required.

Statistical Considerations

The study is designed and powered to allow estimation of the prevalence of AIC and to calculate the time to recovery from LVSD. For sample size calculation we considered a mean difference in LVEF of > 15% at 6 month of follow-up and a AFib/AFlut recurrence rate of 35% after rhythm control based on previous data. [17–19] Taking into account the estimated recurrence rate and applying an additional dropout rate of 5%, a total sample size of at least 64 patients was required for inclusion. The prevalence of AIC is calculated by dividing the number of patients with AIC by the total number of analysed patients. The time to recovery is assessed by calculating the prevalence for each visit; additionally, a mathematical model (curve-fit) will be employed to calculate recovery using the data collected during the visits. Secondary endpoints are calculated by ANOVA (or mixed model) analysis as well as univariate and multivariate logistic regression modelling.

Handling of missing data

Missing data of key parameters (endpoints) at baseline and at the end of follow-up (study visit at month 6) are not acceptable and lead to the exclusion of the participant from analysis. For the visits 2 and 4 months after rhythm restoration, missing data of < 5% of the participants are acceptable.

Standard protocol items: recommendations for interventional trials (SPIRIT)

This protocol was developed according to the SPIRIT guidelines. The SPIRIT checklist is available in Supplemental file 1.

Dissemination policy and plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethics committees)

Any intended modification to the protocol will be submitted to the responsible Ethics Committee. If approved, modifications will be communicated to the participants.

Discussion

This is the first prospective study designed to quantify the prevalence of AIC and the time to recovery from LVSD. Early identification of patients with the potentially curable disease AIC will help to initiate effective and appropriate therapy, thereby giving patients confidence in the good prognosis of their condition. In this prospective, observational, investigator-initiated, multi-center study, we will be able to evaluate the prevalence of AIC in a clinically important patient population with new and otherwise unexplained LVSD and coexisting tachyarrhythmia. Since AIC remains poorly understood and the incidence unclear, our results will raise awareness of the disease and set scientific priorities. Primary endpoints are the prevalence of AIC and the time to recovery from AIC. Secondary endpoints consist of parameters describing left ventricular morphology and function, the grade of MR, left atrial size and the markers for cardiac stress (hs-TnT and NT-proBNP) over time to identify potential predictors of AIC. The design of this study with sequential analysis of recovery from LVSD, the comparison with non-AIC patients and the unconventional diagnosis *ex juvantibus* makes this trial unique in this field.

Choice of endpoints

Despite the availability of few and mostly retrospective trials on AIC, the prevalence of the disease is still uncertain, and the time to recovery from AIC has been reported to widely range from a few weeks to several months. [6, 8, 20, 21] The primary endpoints of this study will add information to the fundamental data on this disease, i.e. the prevalence and time to recovery, thereby helping clinicians to identify affected patients and to establish the therapeutic approach. Especially the time to recovery will be of interest to affected patients and will help to plan follow-up dates in daily clinical practice. So far, there is no trial focusing on the outcomes of this relevant patient cohort. Hsu et al. recognized that patients with uncontrolled HR without coexisting heart disease benefit most from rhythm control via ablation. [8] The follow-up in that study lasted several months up to 12 months after rhythm control. Only minor changes in LVEF were observed 3 months after rhythm control without any significant changes in LVEF between month 6 and 12. However, there was no comparison to a non-responder group as it will be the case in our trial. A study by Mueller-Edenborn et al. showed that some patients may respond earlier to rhythm control; the authors reported an increase in LVEF already after 3 days to 40 days. [20] Because of this uncertainty in the time course of recovery, we decided to conduct the follow-up visits 2, 4 and 6 months after the initial hospital stay, which enables us a) to calculate the time to recovery with high accuracy and b) to also include patients with delayed recovery. The diagnosis of AIC is established *ex juvantibus* after the last follow-up visit if any other reason of LVSD except arrhythmia has been excluded (Fig. 1); thereby we apply a summary of diagnostic criteria used in previous AIC trials. [5, 9, 22–24]

The secondary endpoints consist of parameters that help to estimate cardiac function and thereby recovery over time; these parameters may thus represent indicators for the early recognition of AIC. In particular, LVESD and LVEDD have previously been shown to decrease over time after rhythm control [8, 18] but have not been evaluated prospectively in adults yet. LVEDD may predict recovery from LVSD in pediatric patients with AIC. [25] The Camera-MRI study suggests that left ventricular fibrosis influences recovery from LVSD and may thus be an indicator of non-AIC. [5] However, this has not yet been validated in a prospective study.

Limitations

We expect a positive effect on LVEF in both groups (AIC and non-AIC) because most patients are likely to have their medical therapy optimized and due to termination of AFib. To evaluate the effect of rhythm control on LVSD over time, one would need to leave other therapies for HF unchanged, which is ethically incorrect and thus not an option. In addition, controlling heart rhythm and rate has the potential to also reduce LVSD. Thus, we set a limit for the minimum gain in LVEF of 10% absolute (or 15%, if LVEF does not recover above 50%), which is above the recovery values observed in the CHAMP-HF study (median LVEF increase of 4% in 16 months) and the PROVE-HF study (LVEF improvement of 7% in 6 months). [26, 27] Although this limit is likely to provide sufficient discriminatory power, we cannot guarantee that all patients will be allocated correctly. Although patients are encouraged to see a physician if they experience palpitations or poor performance, we cannot exclude the possibility of silent arrhythmia episodes between the study visits.

Abbreviations

AIC, arrhythmia-induced cardiomyopathy; ECG, echocardiography; cMRI, cardiac magnetic resonance imaging; hs-TnT, high-sensitive Troponin T; ID, identification number; LVEF, left ventricular ejection fraction; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; NT-proBNP, N-terminal-pro hormone natriuretic peptide; LGE, late gadolinium enhancement; MR, mitral regurgitation; NYHA, New York Heart Association; RC, rhythm control

Declarations

Ethics approval

The Ethics Committees of University of Regensburg (19-1261-101) and University of Leipzig (467/19-lk) approved the trial. The version is 2.0, 30 September 2019.

Consent for publication

Results of this study are planned to be communicated to health care professionals through publication in a cardiological journal. The use of professional writers is not intended.

Competing interests

This in an investigator-initiated trial; there are not conflicts of interest.

Availability of data and materials

The final data set generated and analysed during the current study is available from the corresponding author on reasonable request. The final results will be shared with other researchers through publications and presentations at international conferences.

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Authors' contributions

C.S., R.W. and S.S. designed the study. C.S., B.H. and S.S. initiated the study design, T.K., D.L. and L.M. gave intellectual input, S.S. and C.S. are grant holders. M.K and F.Z. provided statistical expertise in the clinical trial design, and F.Z. is the primary statistical supervisor. All authors contributed to refinement of the study protocol. All authors have read and approved the final manuscript.

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Figures

Figure 1

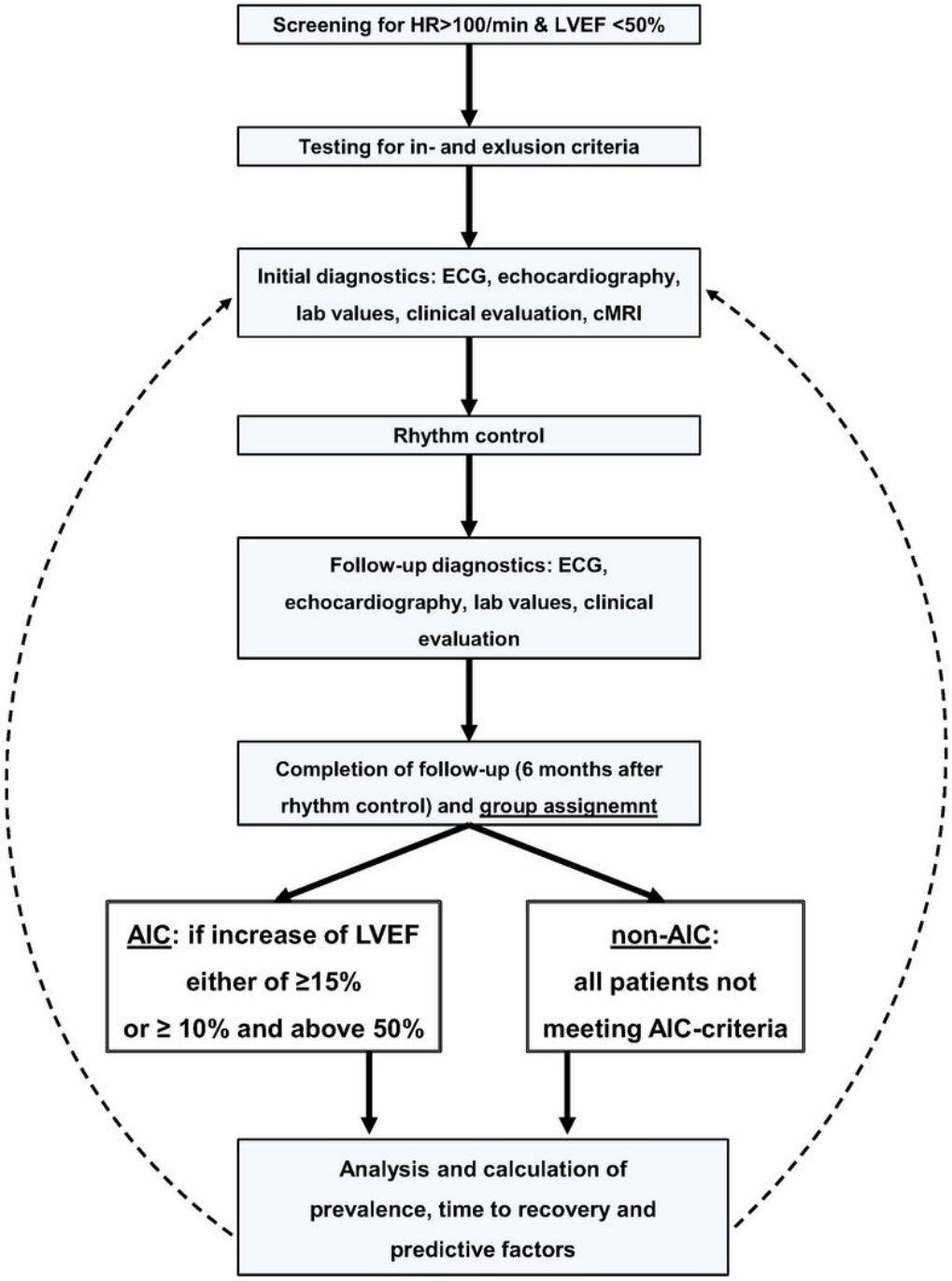

Figure 1

Study flow chart

Follow-up is completed with the last visit 6 months after rhythm restoration. Then, patients are divided into 2 groups according to their recovery from LVSD and diagnosed “AIC” (or “non-AIC”) *ex juvantibus*. Next, the initial diagnostic results are analysed according to the assigned group to determine primary and

secondary endpoints (dashed lines). For calculation of the time to recovery, analysis will include initial and follow-up diagnostics. AIC, arrhythmia-induced cardiomyopathy; cMRI, cardiac magnetic resonance imaging; ECG, electrocardiography; HR, heart rate; LVEF, left ventricular ejection fraction. * Testing for recurrent arrhythmia is done during follow-up.

Supplementary Files

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- supplementalfile.zip