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CARDIAC IMAGING FOR THE PREDICTION OF MAJOR ADVERSE EVENTS

IN PATIENTS WITH HEART FAILURE

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ABSTRACT

Background

Despite proven efficacy of implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT) for primary prevention of sudden cardiac death (SCD) in heart failure (HF) patients, potential risks and selection criteria are currently debated, making patient selection challenging. Since advances in cardiac imaging allow increased diagnostic accuracy, this study aimed to identify novel predictors of adverse events in HF patients.

Methods

This prospective study enrolled patients undergoing ICD/CRT implantation following echocardiography and cardiac magnetic resonance assessment. Primary composite endpoint included appropriate device intervention, cardiac death, left ventricular assist device implantation or heart transplant. Non-appropriate device intervention was secondary endpoint.

Results

The study included 101 patients receiving ICD(63%) or CRT(37%), age 66 ± 14 years, 77% male, 54% with HF of ischemic etiology, left ventricular ejection fraction $26\pm 5\%$, 70% with late gadolinium enhancement. During 17-month (IQR, 11-28) follow-up, primary endpoint occurred in 20% patients with higher heart rate (83 ± 15 vs. 73 ± 17 , HR 1.06, 95%CI 1.01-1.13), estimated right atrial pressure (9 ± 4 vs. 7 ± 4 , HR 1.32, 95%CI 1.01-1.71), early to late diastolic strain rate ratio, SRR (2.61 ± 1.88 vs. 0.99 ± 0.75 , HR 2.14, 95%CI 1.17-3.92) and lower global longitudinal strain (-5.6 ± 2.1 vs. -6.9 ± 2.5 , HR 1.82, 95%CI 1.04-3.18). Non-appropriate device intervention occurred in 8% patients with new-onset atrial fibrillation (HR 17, 95%CI 1.63-196) or device complications (HR 44, 95%CI 4.16-459).

Conclusions

Heart rate, estimated right atrial pressure and left ventricular global longitudinal strain predict SCD in HF patients. SRR is an innovative and powerful SCD predictor, providing increased accuracy in risk stratification and possibly allowing improved selection of patients undergoing ICD/CRT implantation.

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CHAPTER 1 - Multimodality imaging in patients with heart failure

1.1 INTRODUCTION

Arrhythmic sudden cardiac death (SCD) due to ventricular fibrillation or sustained ventricular tachycardia accounts for approximately half cardiovascular deaths, representing a major public health issue¹. SCD occurs more frequently in patients with heart failure (HF), especially those with more extensive myocardial fibrosis and adverse remodeling². In addition to guideline-directed medical treatments for HF, implantable cardioverter defibrillator (ICD) is recommended to prevent SCD in patients with HF and a reduced ejection fraction³⁻⁵. However, many ICD recipients do not receive any appropriate intervention for decades, while exposed to potential complications or a non-negligible risk of inappropriate interventions⁶⁻⁸. Furthermore, despite the well-known benefit of ICD among HF patients with ischemic heart disease (IHD), its role among patients with non-ischemic heart disease (NIHD) is still debated⁷. In patients with HF, left ventricular ejection fraction (LVEF) assessment is crucial since a cut-off of 35% or lower is currently required before considering ICD for primary prevention of SCD. However, the value of LVEF has been widely questioned as a single reliable predictor of ventricular arrhythmias (VA) causing SCD, while in the last few years newer imaging techniques have been developed with increased prognostic significance^{9,10}.

This review will discuss the role of multimodality imaging techniques for the prediction of SCD in patients with HF.

1.2 ECHOCARDIOGRAPHY

Myocardial injury may result in tissue fibrosis, represented by a focal scar, which is often the case after an acute myocardial infarction, or diffuse interstitial, as commonly observed in NIHD. Myocardial fibrosis is a major substrate for ventricular arrhythmias (VA), as it causes electrical dispersion, laying ground for the initiation and maintenance of re-entrant VA¹¹.

Ejection fraction

In 1980s, lacking technologies able to measure scar size and characteristics, systolic function estimated with 2D-echocardiography (i.e., LVEF) emerged as an indirect marker of scar

burden. The most recent European Society of Cardiology guidelines provide a Class I recommendation for ICD implantation for primary prevention of SCD in patients with IHD and a $LVEF \leq 35\%$ and a Class II recommendation in patients with NIHD and a $LVEF \leq 35\%$ ¹². The LVEF cut-off of 35% was chosen based on the inclusion criteria of the major randomized trials demonstrating the efficacy of ICD in the reduction of all-cause mortality and cardiac death^{13–15}. However, this criterion has been later questioned from several Authors, not only because of the poor reproducibility of echocardiography-assessed LVEF but also for its limited sensitivity and specificity^{16,17}. For instance, in 2013 Narayanan et al. assessed a cohort of 2093 patients with SCD, showing that 68% of them had an $LVEF > 35\%$ and would have been considered ineligible for ICD implantation^{7,18}.

Global longitudinal strain

Speckle tracking echocardiography is a modern technique which can accurately quantify the extent and timing of systolic deformation^{19,20}. Left ventricular global longitudinal strain (GLS) not only is more accurate and reproducible than LVEF in quantifying LV systolic function, but its impairment indirectly reflects myocardial fibrosis²¹. GLS proved to be an independent predictor of VA in both patients with previous myocardial infarction and patients with NIHD and its value was confirmed also in patients with $LVEF > 35\%$ ¹⁰. Haugaa et al. found in a prospective study on 94 patients with NIHD and $LVEF < 50\%$ that GLS was a significant predictor of arrhythmic events, with greater accuracy as compared with LVEF (respectively with an AUC of 0.82, 95% CI 0.70-0.95 vs. 0.72, 95% CI 0.57-0.87)²². A study by Kalra et al. on patients with HF reported a 58% increase in the risk of SCD for every unit increase in GLS (hazard ratio 1.58, 95%CI: 1.12 to 2.22). A more recent application of speckle tracking echocardiography includes layer specific GLS assessment. In a recent study of 45 subjects with borderline diagnosis of arrhythmogenic cardiomyopathy, epicardial GLS was superior to traditional, endocardial GLS in the identification of patients with arrhythmias²³.

Mechanical dispersion

Beyond GLS, speckle tracking echocardiography allows the quantification of electromechanical heterogeneity of left ventricular contraction. Mechanical dispersion (MD) is calculated as the standard deviation of the time to peak longitudinal strain in the 16-segments of the

left ventricle²⁴. MD represents the extent of electrical dispersion due to strands of myocardial scar and proved to be an independent predictor of arrhythmic events in both NIHD^{10,21,25} and IHD²⁶ cohorts. Recently, a large retrospective observational multicenter study was performed to assess the long-term prognostic value of MD in patients with moderate or severe LVEF impairment²⁷. This study enrolled 939 consecutive patients with a LVEF $\leq$ 45%. MD $\geq$ 75 ms was a significant predictor of VA events, defined as symptomatic VA or ICD appropriate intervention or death (hazard ratio 9.45, 95% CI 4.75-18.81), while both LVEF, age and etiology were not. Interestingly, among patients with MD <75 ms, there was no difference in VA events between patients with severely reduced LVEF $\leq$ 35% and those with moderately impaired LVEF (36% to 45%), further supporting the potential of MD for risk-stratification.

Diastolic dysfunction and left atrial strain

The assessment of diastolic dysfunction as a predictor of SCD emerged only recently, despite a strong rationale and previous findings from experimental studies^{28,29}. In a recent cohort study, Pezawas et al showed that, among 210 patients (120 with IHD, 60 with NIHD and 30 with normal LVEF), those with grade-III diastolic dysfunction had the highest risk of arrhythmic death or resuscitated cardiac arrest (hazard ratio 3.52, 95% CI 2.00 – 6.22). This was found for both patients with LVEF $\leq$ 35% ($p<0.001$) and patients with LVEF >35% ($p=0.014$)³⁰.

Left atrial strain is a modern technique to assess diastolic dysfunction with increased accuracy across different clinical situations³¹. In a recent study by Carluccio et al.³², including 405 patients with LVEF $\leq$ 40%, an impaired LA reservoir function defined as a reduced peak atrial longitudinal strain, not only was associated with worse left ventricular systolic and diastolic function, but also with increased risk of the all-cause death or HF hospitalization (hazard ratio 1.38 per 1-unit decrease, 95% CI 1.05-1.84). In another study of 357 patients with HF with preserved ejection fraction, peak atrial longitudinal strain was a predictor of the composite endpoint of SCD, cardiac death or HF hospitalization (hazard ratio 0.96 per 1-unit increase, 95% CI 1.05-1.84)³³.

1.3 CARDIAC MAGNETIC RESONANCE

Late gadolinium enhancement

Late gadolinium enhancement (LGE) assessed with cardiac magnetic resonance (CMR) is an accurate technique for the characterization of myocardial tissue and the detection areas of focal myocardial fibrosis, appearing hyperintense on delayed CMR imaging^{34,35}. Most patients with a prior myocardial infarction show myocardial LGE on CMR imaging³⁶. In fact, in the setting of IHD, both LGE presence and extent have been associated with death or appropriate ICD therapy for sustained VAs^{37,38}. In addition, LGE-CMR allows the characterization of the ischemic scar, constituted by a central infarct core zone and a peri-infarct grey zone. The grey zone is the region where the viable myocardium is intertwined with tissue fibrosis, creating an ideal substrate for VA^{39,40}. In a study of 91 patients with IHD referred for ICD implantation, the extent of the gray-zone was the only significant predictor of appropriate ICD therapies (hazard ratio 1.49/10 g, 95% CI 1.01-2.20), while total infarct size, LVEF and LV volumes were not⁴¹. A significant association between the occurrence of VA and the extent of gray zone was also reported in another study of 162 patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention, during a 1-year follow-up⁴². However other studies reported contradictory results and therefore the role of gray zone is still debated⁴³. These contrasting data might be due to lack of consensus on the methodology of scar and gray zone quantification and the use of different study methodologies⁴⁴. LGE was reported as a strong independent predictor of VAs, SCD and ICD appropriate interventions, even when adjusted for other clinical or functional parameters, in prospective and retrospective studies⁴⁵⁻⁴⁹ and meta-analyses^{50,51}.

At variance with IHD, in the setting of NIHD LGE is not a constant feature, being identified in 45-77% of affected patients according to different studies^{37,52}. However, a meta-analysis by Becker et al.⁵¹ including 34 studies on a total of 4554 patients with NIHD, showed that LGE-positive patients had an increased risk of VAs, SCD and ICD appropriate interventions (hazard ratio 4.52, 95% CI 3.41 – 5.99). In the NICM-SCAR study⁴⁴ published in 2021, including 1020 patients with NIHD and a LVEF <50%, only myocardial scar assessed with LGE-CMR provided strong independent and incremental prognostic value for risk stratification for SCD and arrhythmic events ($p=0.001$) as opposed to LVEF $\leq 35\%$ ($p=0.57$). Furthermore, in NIHD, LGE-CMR can be helpful in the differential diagnosis of the underlying myocardial disease, according to the type of enhancement pattern. The

most common pattern in NIHD is linear midwall, subepicardial or patchy without coronary artery territory distribution⁵³. Midwall fibrosis has been well recognized as a negative prognostic marker in NIHD patients, implying a higher risk of SCD^{54,55}. In the recent DERIVATE registry, midwall fibrosis in > 3 segments was the strongest predictor of arrhythmic events in NIHD patients⁵⁶. LGE-CMR imaging could then represent a promising technique to identify the subgroup of NIHD patients who might benefit more from ICD implantation.

An important and still unclear question is whether there is a quantitative relationship between scar extent and cardiac events and whether an optimal threshold of scar extent exists. Some studies reported that scar extent is associated with arrhythmic events in both IHD and NIHD^{55,57,58}. In a recent meta-analysis of 19 studies, Disertori et al. reported a significant association between LGE extent and arrhythmic endpoints. Among 2850 patients included in the meta-analysis, 423 experienced arrhythmic events. This occurred in 23.9% of patients with LGE positive CMR versus 4.9% of patients with negative LGE imaging. Ten of the studies included in the meta-analysis also reported a statistically significant increase of the arrhythmic risk with increasing LGE extension, with no significant differences between IHD and NIHD⁵⁹.

In the last few years there has been a growing interest in a peculiar distribution pattern of LGE: the so-called ring-like left ventricular scar, defined by the presence of at least three contiguous sub-segments with LGE at the subepicardial or mid-wall layer in the same slice. This pattern has been reported to be a common feature of left dominant arrhythmogenic cardiomyopathy⁶⁰, partially overlapping with the arrhythmogenic subtypes of dilatative cardiomyopathy (DCM). A recently published retrospective study⁵² of 157 patients with NIHD investigated the relationship between ring-like LGE and VA. Among all patients, 77% showed LGE, among which 21% showed a ring-like LGE pattern. After a median of 13 ± 7 months of follow-up, arrhythmic events defined as a composite of sustained VT, VF, SCD and appropriate ICD intervention were more common in patients with ring-like (hazard ratio 11.75, 95% CI 2.66-51.92) and multifocal LGE (hazard ratio 5.55, 95% CI 1.21-25.44). A limitation of LGE imaging is that it allows the detection of focal fibrosis but not interstitial diffuse fibrosis.

Parametric mapping

Further advances in CMR imaging techniques allowed the detection of diffuse myocardial fibrosis, by means of myocardial T1-mapping and extracellular volume fraction assessment. Indeed, diffuse myocardial fibrosis results in longer T1 native relaxation times compared with normal myocardium⁶¹, and in shortened T1 relaxation times after contrast-media injection⁶². In a prospective longitudinal study of 130 IHD and NIHD patients⁶³, myocardial native T1 time was an independent predictor of the primary composite endpoint of VA or ICD appropriate intervention (hazard ratio 1.10, 95% CI 1.04 -1.16). In another prospective study, Claridge et al.⁶⁴ performed CMR-based T1-mapping in patients undergoing ICD implantation. In this study on 130 patients, the T1 native value was the only independent predictor of appropriate ICD therapy in the NIHD cohort (hazard ratio 1.09, 95% CI 1.04 – 1.14). In IHD patients, on the contrary, the strongest predictor of arrhythmic events was the presence of a gray-zone. In NIHD, ECV was shown to predict cardiovascular death, hospitalization for HF and sustained symptomatic VA⁶⁵.

1.4 COMPUTED TOMOGRAPHY

Myocardial delayed enhancement (MDE) with computed tomographic (CT) imaging has been demonstrated to accurately display scar tissue as compared with pathological specimens and LGE-CMR^{66,67}. Otha Y. et al.⁶⁸ in a retrospective cohort including 44 patients with HF, demonstrated that MDE-CT enables accurate detection and localization of scar in patients with HF when compared with LGE-CMR, the reference standard. However, as compared to CMR, because of the lower accuracy and increased radiation exposure, MDE-CT imaging has not been widely adopted in clinical routine. Recent refinements in CT scanner technology, as wide-volume scanners, have shown promise in reducing imaging radiation, and could play a role in the future for the risk stratification of patients with absolute contraindications to CMR⁶⁹.

1.5 NUCLEAR IMAGING

Nuclear perfusion imaging using Single Photon Emission Computed Tomography (SPECT) with technetium 99m or positron emission tomography (PET) with rubidium-82, 15O-labeled water or 13N-ammonia are useful techniques to assess the presence of reversible or non-

reversible (i.e., scar) myocardial perfusion defects. Residual myocardial ischemia and viable dysfunctional myocardium may create a vulnerable substrate predisposing to VA. In relation to residual myocardial ischemia, in a retrospective analysis of SPECT imaging in a large cohort of patients with IHD, summed stress score was significantly associated with increased risk of SCD⁷⁰. In a recent retrospective analysis of 170 with IHD⁷¹, myocardial flow reserve assessed by PET imaging was the only significant predictor of a composite primary endpoint including SCD.

In addition to myocardial ischemia, hibernating myocardium was shown to be vulnerable to VA⁷². The PAREPET (prediction of arrhythmic events with positron emission tomography) study showed no significant association between the amount of hibernating myocardium and SCD, however this result could be affected by a very low prevalence of hibernating myocardium, due to the broad use of revascularization in the contemporary era⁷³.

The pivotal role of sympathetic imbalance for the development of VA is well-known, especially in the setting of myocardial ischemia⁷⁴. Indeed the inhomogeneity of myocardial innervation assessed both with SPECT imaging using 123 meta-iodo-benzyl guanidine (123I-mIBG) and with PET imaging using 11C-meta-hydroxyephedrine (11C-HED) was shown to be a strong predictor of SCD^{75–77}. In the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study⁷⁸, in a population of 961 patients with IHD and NIHD with LVEF $\leq$ 35%, a reduced HMR (heart-to-mediastinum ratio) of 123I-mIBG was the strongest predictor of the primary composite endpoint of cardiac death, arrhythmic events and hospitalization for chronic HF. Arrhythmic events were significantly more common in patients with HMR <1.6 . Data were also confirmed in the PARAPET study⁷³ showing that each 1% of the volume of denervated myocardium results in an 6% increase of SCD.

1.6 ARTIFICIAL INTELLIGENCE APPLICATIONS

Artificial intelligence (AI) employs algorithms to make data-driven predictions through both linear and non-linear models. AI algorithms have been recently applied to cardiac imaging for the prediction of SCD. In a study on 10,030 patients undergoing coronary computed tomographic angiography, machine learning was superior to clinical and technical parameters in the prediction of

all-cause mortality at 5-years follow-up.⁷⁹ In the study by Shade et al. including patients with cardiac sarcoidosis, AI was superior to current clinical risk metrics in predicting arrhythmic events⁸⁰. As to application of AI algorithms in HF patients, Meng et al. is conducting a retrospective, multicenter, observational registry including patients with LVEF $\leq 35\%$ aimed to assess the predictors of SCD with machine learning algorithm⁸¹.

1.7 CONCLUSIONS

Recent advances in cardiac imaging techniques led to the identification of a great number of imaging parameters associated with increased risk of SCD in patients with HF. It appears time to overcome the limitations posed by echocardiography-based LVEF assessment, and to implement a multimodal-imaging approach to best predict patients at increased risk of SCD.

CHAPTER 2 – Advanced cardiac imaging for the prediction of sudden cardiac death in patients with heart failure and a reduced ejection fraction

2.1 INTRODUCTION

Sudden cardiac death (SCD) due to electrical instability or mechanical failure is a major cause of death in patients with heart failure (HF) and a reduced left ventricular ejection fraction (LVEF)². Effective medical treatments for HF are constantly being developed, aimed to reduce hospitalizations and mortality^{12,82,83}. Among non-pharmacological treatments for HF, implantable cardioverter defibrillators (ICD) and Cardiac Resynchronization Therapy Defibrillators (CRT) are devices of proven efficacy in the prevention of SCD due to electrical instability (i.e., threatening arrhythmias such as ventricular fibrillation, VF or ventricular tachycardia, VT)^{3,4,7}. CRT, used in selected patients with HF and electrical dyssynchrony, is additionally effective in the prevention of SCD due to mechanical failure, favoring left ventricular reverse remodeling (LVRR)^{84–86}.

According to current guidelines, the use of ICD/CRT for primary prevention of SCD in optimally treated HF patients is generally limited to patients with LVEF below 35%^{12,87,88}. However, studies reported that most SCD events occur in patients with EF>30%, questioning the validity of LVEF as an appropriate selection criteria^{18,89,90}. In addition, it should be considered that among ICD/CRT recipients more than 3 out of 4 will never receive any device intervention, up to 15% will receive inappropriate interventions (including electric shocks) and up to 10% will experience peri-procedural complications (mostly hematomas, infections or reinterventions)^{6,91–93}. Moreover, CRT are associated with even higher rates of complications (up to 18%), risk of unsuccessful implantation (5%) and lack of LVRR (more than 30% patients)^{6,94,95}.

All these data, along with the significant decline of SCD incidence in the last few years due to the adoption of newer anti-remodeling drugs independent of device use, represent a strong call for the identification of novel predictors of SCD, allowing an improved selection of HF patients who should receive an ICD or CRT for the primary prevention of SCD. This study was aimed to assess predictors of SCD in a cohort of HF patients undergoing ICD or CRT implantation for primary prevention of sudden death, using advanced cardiac imaging techniques.

2.2 METHODS

Study design

This single-center prospective cohort study included consecutive adult patients admitted to our institution between 2019 and 2021 with diagnosis of heart failure and reduced ejection fraction, undergoing ICD or CRT implantation for primary prevention of SCD according to current European Society of Cardiology guidelines¹². Patients with history of previous SCD, history of sustained ventricular arrhythmia, ICD or CRT or pacemaker carriers, other comorbidities with estimated prognosis ≤ 1 year, were excluded. The study complied with the Declaration of Helsinki and subsequent modifications. Study protocol was approved by local Ethical Committee (protocol no. 00253). All patients provided oral and written informed consent.

End-points

The primary endpoint, assessed as a surrogate of SCD, was defined as: ICD or CRT appropriate intervention (electric shock or Anti-tachycardia Pacing Therapy, ATP) for ventricular fibrillation or sustained ventricular tachycardia (lasting $>30''$), cardiac death, urgent left ventricular assist device (LVAD) implantation or cardiac transplantation. Non-appropriate device intervention (electric shock or ATP) was the secondary endpoint.

Study protocol

Clinical, laboratory testing and electrocardiographic assessment were performed in all patients at the time of enrollment, according to local practice and following international guidelines. Enrolled patients underwent multimodal cardiac imaging assessment prior to cardiac device implantation, including echocardiography and cardiac magnetic resonance, unless contraindicated. Events occurrence was assessed through outpatient visits according to local practice, direct contact with the patient, device interrogation or medical records review.

Echocardiography protocol and analysis

Echocardiography was performed using Philips (Andover, MA, United States) Epiq CVx with phased-array at frequency of 1.9-3.8 MHz. Standard parasternal, apical, subxiphoid views were acquired. Philips QLAB was used for speckle tracking analysis in patients with an adequate acoustic

window; volumes and LVEF were measured with the biplane Simpson's method. Echocardiograms were performed and examined according to the standards of European Association of Cardiovascular Imaging guidelines⁹⁶. In patients in sinus rhythm, early to late diastolic strain rate ratio was computed as the ratio of the peak average global longitudinal strain rate during the early rapid filling phase of diastole to peak average global longitudinal strain rate during the late filling phase of diastole. Speckle tracking analysis, including early to late diastolic strain rate ratio assessment was blinded to the patients' history. Patients undergoing CRT implantation were reassessed at 12 months with echocardiography and LVRR was defined as end systolic volume reduction of >15%⁹⁷. All images were acquired and off-line anonymously analyzed by a single cardiologist with broad experience in cardiovascular imaging. Reproducibility of echo-doppler and Tissue Doppler measurements in our laboratory was previously reported^{98,99}.

Cardiac magnetic resonance protocol and analysis

Cardiac magnetic resonance (CMR) evaluations were performed on a 1.5-T magnetic resonance imaging scanner (multivendor scanners were included). Imaging was performed using commercially available software, electrographic triggering, and dedicated phased-array receiver coils. CMR acquisition was performed in agreement with the standardized CMR protocols¹⁰⁰. For functional analysis cine steady-state free precession (cine-SSFP) CMR images were acquired in four-, two- and three-chamber and short-axis (repetition time [TR] = 3.4 ms; echo time [TE] = 1.7 ms; flip angle = 80°; slice thickness = 8 mm without interslice gap and 30 cardiac phases per heartbeat). Late gadolinium enhancement (LGE) images were acquired 10 minutes after intravenous administration of 0.15 mmol/kg of gadobutrol (Gadovist, Bayer Healthcare, Berlin, Germany) using segmented inversion recovery gradient echo sequences (IR-GRE) on long- and on short-axis chamber covering the entire LV (TR = 6.1 ms; TE = 3 ms; flip angle = 25°; TI determined by using a Look Locker based TI scout; slice thickness = 10 mm without interslice gap).

Cardiac resynchronization therapy optimization

At 1 month following CRT implantation, patients underwent device optimization through dedicated programming of multipolar left ventricle lead based on speckle tracking echocardiography assessment of dyssynchrony.

Statistical analysis

Continuous variables, presented as means and standard deviations, were compared by non-parametric tests: Mann-Whitney's test was used for independent data. Categorical variables, presented as counts and percentages, were compared using the chi-square test with Fisher's exact test as appropriate. Cox regression analysis was performed to examine the effects of covariates on the endpoint of interest and for hazard ratio (HR) estimation, along with 95% confidence intervals (CIs). Variables with $P < 0.05$ on Univariable Cox proportional analysis were included in a Multivariable Cox regression model, after exclusion of collinear predictors.

The survival probability and the freedom from events were evaluated with the Kaplan-Meier curves, compared by the Log-rank test. The discriminant ability of a test was evaluated by ROC curve analysis, a plot of true positive rates (sensitivity) versus false positive rates (1-specificity). The Area Under the Curve (AUC) measured the quality of discrimination, from 0.5 (poor) to 1 (excellent). The cut-off value to determine the presence/absence of a disease was obtained through the simultaneous maximization of sensitivity and specificity via their harmonic mean. All analyses were performed using STATA version 17 (StataCorp, College Station, Texas, US) and a two-sided significance level of <0.05 was considered as statistically significant.

2.3 RESULTS

This prospective study included 101 patients who underwent ICD (63%) or CRT (37%) implantation for primary prevention of SCD. Patients had a mean age of 66 ± 14 years, 77% of male gender, 54% with heart failure of ischemic etiology. Mean LVEF was $26 \pm 5\%$, QRS interval 138 ± 30 ms, plasma NT-proBNP 7111 ± 7301 ng/L and New York Heart Association Class equal to I in 21% patients, II in 40%, III in 21% and IV in 17% patients. Baseline clinical characteristics are described in Table 1. Cardiac magnetic resonance was performed in 42% patients, while echocardiography was performed in all patients included in the study (83% of which with optimal image quality).

Following device implantation, complications were observed in 16% patients (12% with ICD and 22% with CRT): 5% lead dislodgement requiring reintervention, 5% lead noise, 4% pneumothorax or subcutaneous emphysema, 3% surgical wound infection (in one case requiring

device extraction), 2% surgical pocket hematoma requiring invasive treatment. Unsuccessful CRT implantation was observed in 9% patients, who ultimately received an ICD.

During a median follow-up of 17 months (IQR, 11-28), 13 (12.9%) patients died (46% for cardiovascular causes). A total of 13 patients (12.9%, incidence rate 0.9 per 10 patients-year) received appropriate ICD or CRT intervention because of arrhythmic event: in 6 patients with VT, the arrhythmia was recognized and interrupted by ATP; in other 6 patients with VT, one or more (1.23 ± 1.83) electric shocks were delivered by the device, with arrhythmia resolution; 1 patient with VF received effective electric shock.

Clinical and imaging predictors of sudden cardiac death

A primary endpoint composite event, mostly ICD or CRT appropriate intervention, was observed in 20 (19.8%) patients after a median time of 4.5 months (IQR, 1-12), incidence rate of 1.4 events per 10 patients-year, as shown in Table 2. Patients with events were younger (60 ± 17 vs. 68 ± 13 , $p=0.034$), mostly males (95% vs. 73%, $p=0.038$) with prior history of non-sustained ventricular tachycardia (50% vs. 23%, $p=0.019$) and higher baseline heart rate (83 ± 15 vs. 73 ± 17 , $p=0.024$). In addition, they had a higher prevalence of grade II-III diastolic dysfunction (95% vs. 51%, $p<0.001$) and higher values of E/E' ratio (16 ± 5 vs. 13 ± 6 , $p=0.014$), estimated right atrial pressure (9 ± 4 vs. 7 ± 4 , $p=0.005$) and early to late diastolic strain rate ratio (2.61 ± 1.88 vs. 0.99 ± 0.75 , $p<0.001$). Significantly lower values of tricuspid annular plane systolic excursion, TAPSE (15 ± 4 vs. 18 ± 5 , $p=0.039$), left ventricular global longitudinal strain, GLS (-5.6 ± 2.1 vs. -6.9 ± 2.5 , $p=0.045$), late diastolic strain rate (-0.44 ± 0.32 vs. 0.81 ± 0.39 , $p<0.001$), left atrial reservoir strain (10.2 ± 6.1 vs. 17.3 ± 8.7 , $p=0.045$) and left atrial emptying fraction (32 ± 15 vs. 49 ± 16 , $p<0.001$) were also observed in patients with primary event during the follow-up. In patients with primary endpoint event, cardiac magnetic resonance showed higher number of left ventricular segments with LGE (6.4 ± 4.2 vs. 3.1 ± 3.1 , $p=0.028$) and higher prevalence of mid-wall septal LGE pattern (58% vs. 16%, $p=0.008$).

Cox regression model for the primary endpoint (Table 3) showed that early to late diastolic strain rate ratio (HR 2.14 per 1 unit increase, 95% CI 1.17-3.92), left ventricular GLS (HR 1.82 per 1 unit increase, 95% CI 1.04-3.18), estimated right atrial pressure, RAP (HR 1.32 per 1 unit

increase, 95% CI 1.01-1.71) and heart rate (HR 1.06 per 1 unit increase, 95% CI 1.01-1.13) were independent predictors of SCD.

A comparison between diastolic function-associated predictors of the primary endpoint (Table 4 and Figure 1) showed that early to late diastolic strain rate ratio had the highest prognostic accuracy (AUC 0.88, 95% CI 0.72-0.99) for the prediction of SCD. Moreover, a cut-off of 1.40 yielded good diagnostic value for the prediction of the primary endpoint, with 89% (95% CI 81-97) specificity and 91% negative predictive value, 71% (95% CI 60-83) sensitivity and 67% positive predictive value. Patients with early to late diastolic strain rate ratio > 1.4 before ICD/CRT implantation had lower 24-month freedom from SCD during the follow-up (22% vs. 91%, $p<0.001$), as shown by Kaplan Meier curves (Figure 2) and a markedly higher incidence rate of SCD (7.7 vs. 0.6 events per 10 patients-year, incidence rate ratio 12.9, 95% CI 3.7-56.6, $p<0.001$).

Non appropriate device intervention

Secondary endpoint event was observed in 8 (7.9%) patients after a median time of 2.8 months (IQR, 0.75-11). The incidence rate was 0.6 events per 10 patients-year. Among these 8 patients, 5 received device intervention because of atrial fibrillation with rapid ventricular response, while other 3 because of lead-related noise. In the first case patients were successfully treated with optimization of medical therapy and device settings, with no recurrence. In the second case, 2 out of 3 patients required reintervention for lead replacement. Multivariable cox regression analysis of the secondary endpoint (Table 5) showed that new-onset atrial fibrillation (HR 17, 95% CI 1.63-196) and device complication (HR 44, 95% CI 4.16-459) were independent predictors of non-appropriate intervention.

Left ventricular reverse remodeling in patients receiving CRT

Within the subgroup of 37 patients receiving CRT, significant improvements in left ventricular end diastolic diameter ($p=0.003$), end diastolic volume ($p=0.003$), end systolic volume ($p<0.001$), LVEF ($p<0.001$) and left ventricular GLS ($p=0.001$) were observed at 12 months following implantation. An LVEF improvement was observed in 76% patients while LVRR (i.e. end systolic

volume reduction of >15% at 12 months following implantation) was observed in 58%. LVEF increase was associated with a lower risk of the primary endpoint (HR 0.86 per 1-unit increase, 95% CI 0.75-0.99, $p=0.042$). Patients with occurrence of the primary end-point did not had significant improvements of cardiac structure and function at 12 months, as shown in Table 6.

2.4 DISCUSSION

This prospective cohort study aimed to assess SCD predictors with advanced cardiac imaging techniques in a cohort of patients with HF and reduced LVEF. In these patients, adverse ventricular remodeling is started following acute cardiac injury (mostly ischemia) triggering progressive maladaptive healing processes, boosted by neuro-hormonal activation in predisposed individuals^{101,102}. The subsequent increased differentiation of fibroblasts into myofibroblasts, collagen fibers deposition and extracellular matrix remodeling leading to progressive myocardial fibrosis, produces a highly vulnerable substrate amenable to electrical instability or mechanical failure, causing SCD^{103,104}. Effective medical treatments for HF are constantly being developed, aimed to reduce hospitalizations and mortality. A contemporary medical approach to HF cannot miss four foundational drugs with a true prognosis-modifying role, as demonstrated by recent groundbreaking clinical trials: Angiotensin Receptor-Neprilysin Inhibitors, beta-blockers, Mineralocorticoid Receptor Antagonists and Sodium-glucose co-transporter-2 inhibitors^{12,82,83}. These anti-remodeling drugs reduce the risk of SCD and may favor a variable degree of recovery of left ventricular size and systolic function¹⁰⁵⁻¹⁰⁷. ICD and CRT are cardiac devices effective in the prevention of SCD caused by electrical instability (VT or VF) or mechanical failure, although burdened by non-negligible risks, such as device complications and non-appropriate interventions. In this study, complications occurred in 12% patients receiving ICD and 22% receiving CRT. Non appropriate interventions were observed in 7.9% patients. These data, along with CRT response rate, are in keeping with previous reports^{6,94,95}.

The poor predictive ability of LVEF in the selection of the ideal candidates for ICD/CRT treatment, along with the development of newer imaging techniques prompted us to design and conduct the present study, in an effort to find novel predictors of SCD.

The main findings of the present research are that heart rate, estimated right atrial pressure, left ventricular GLS and early to late diastolic strain rate ratio are independent predictors of SCD.

Heart rate is a well-known risk factor for mortality in patients with heart failure, regardless of beta blocker treatment^{108–110}. Our study confirms this important matter (HR 1.06 per 1-unit increase, 95% CI 1.01-1.13). Indeed, heart rate may be considered as surrogate of sympathetic activity¹¹¹. Increased sympathetic activity not only boosts ventricular adverse remodeling but also an increased risk of lethal arrhythmias due to the intensification of temporal dispersion of repolarization, mainly secondary to autonomic nervous system-mediated norepinephrine release^{112,113}.

The key prognostic role of estimated RAP (HR 1.32 per 1 unit increase, 95% CI 1.01-1.71) in HF was previously reported by our group in 2016, in a cohort of patients with advanced chronic HF^{114–116}. It is a very informative echocardiography – derived measure, reflecting on one hand ventricular function impairment, on the other venous congestion, both contributing to neuro-hormonal activation and reduced renal perfusion leading to sodium retention and worsening HF. Moreover, depending on intracardiac filling pressures, increased RAP might reflect a certain degree of ventricular distention, favoring stretch-induced arrhythmias^{117–120}.

Left ventricular GLS was a strong predictor of SCD (HR 1.82 per 1 unit increase, 95% CI 1.04-3.18), in keeping with previous findings¹⁰. It is more accurate and reproducible than LVEF for the quantification of systolic function, and its impairment indirectly reflect myocardial fibrosis, causing a reduction of left ventricular systolic deformation^{19,20,121}.

Despite a strong rationale and previous findings underlining its importance in the prediction of SCD, the prominent prognostic role of diastolic dysfunction in this context has emerged only recently^{122,123}. Two years ago, a study by Pezawas et al. showed that grade III diastolic dysfunction was associated with a 3.5-fold increased risk of arrhythmic death or resuscitated cardiac arrest in a cohort of patients with ischemic cardiomyopathy or dilated cardiomyopathy or normal LVEF. This finding was confirmed irrespective of LVEF $\leq 35\%$ or $>35\%$ ³⁰. In patients with heart failure, the extent of myocardial fibrosis, correlated with increasing degree of myocardial stiffness, not only is associated with a more rapid progression of adverse remodeling (leading to mechanical SCD), but

also creates a major substrate for ventricular arrhythmias due to the increased degree of spatial dispersion of repolarization (predisposing to electrical SCD)^{124,125}. While all patients with HF and a reduced LVEF have an impairment of systolic function, grading diastolic function may offer additional accuracy in risk stratification for SCD³⁰. Moreover, it is interesting to observe that previous studies in the setting of idiopathic long QT syndrome, reported wall motion abnormalities suggesting an abnormal increase in the intracellular calcium concentration, possibly linked to early afterdepolarizations¹²⁶. We hypothesize that in the current cohort of HF patients, abnormal intracellular calcium handling and overload leading to major arrhythmias and SCD might be reflected by relaxation impairment.

This study reports for the first time the usefulness of early to late diastolic strain rate ratio, a speckle tracking imaging diastolic parameter with higher prognostic accuracy in SCD prediction compared to conventional (traditional and tissue doppler imaging-derived) diastolic (Table 4) and systolic (Table 3) parameters. We hypothesize that its strength may be explained with a more accurate quantification of left ventricular stiffness compared to traditional diastolic parameters, since based on the diastolic deformation rate averaged from all segments during diastole, rather than based on transmitral flow or mitral annular velocity, known to be affected by loading conditions and angle-dependent measurement errors¹²⁷. In addition, the higher reproducibility of speckle tracking vs. traditional echocardiography parameters is a further advantage¹²⁸. A major weight of late (rather than early) diastolic strain rate was observed in this cohort, in the assessment of early to late diastolic strain rate ratio. Its significant reduction in patients with occurrence of primary endpoint event may be explained with a higher left ventricular end diastolic pressure or impaired left atrial active systolic function, as hypothesized in the cohort by Caselli et al.¹²⁹.

We identified a cut-off of 1.4 for early to late diastolic strain rate ratio, with a good prognostic ability in the stratification of patients based on SCD risk (7.7 vs. 0.6 events per 10 patients-year, incidence rate ratio 12.9 - 95% CI 3.7-56.6). Its high specificity (89%) and negative predictive value (91%) could help clinicians through the decision of the timing for ICD/CRT implantation: indeed, in patients with early to late diastolic strain rate ratio ≤ 1.4 and other clinical characteristics

indicative of limited benefit from device implantation, a further attempt of medical therapy optimization might be considered.

The assessment of the secondary end-point showed that new-onset atrial fibrillation and device complications were independent predictors of non-appropriate device interventions, as previously reported¹³⁰. This should prompt clinicians to a closer follow-up and optimized medical treatment in patients at risk for atrial fibrillation or those with device complication following implantation.

Limitations

This observational study was conducted at a single center, with a consequently limited sample size. It would be useful to conduct larger multicenter studies to assess the validity of these findings in patients with LVEF>35%. Unfortunately, cardiac magnetic resonance could be performed only in a minor (42%) proportion of patients, because of contraindications (mostly claustrophobia or severe chronic kidney disease) or operative issues (limited local availability of cardiac magnetic resonance), hampering their assessment with Cox regression model. Moreover, despite its usefulness, early to late diastolic strain rate ratio could not be computed in patients with atrial fibrillation.

2.5 CONCLUSIONS

Heart rate, estimated right atrial pressure and left ventricular global longitudinal strain are independent predictors of sudden cardiac death in patients with heart failure and a reduced ejection fraction. Early to late diastolic strain rate ratio is a novel diastolic parameter, assessed with speckle tracking imaging echocardiography, providing increased accuracy in SCD risk stratification and possibly allowing an improved selection of patients candidate to ICD or CRT implantation.

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Figures

FIGURE 1. Comparison of diastolic function - associated predictors of sudden cardiac death (ROC graph)

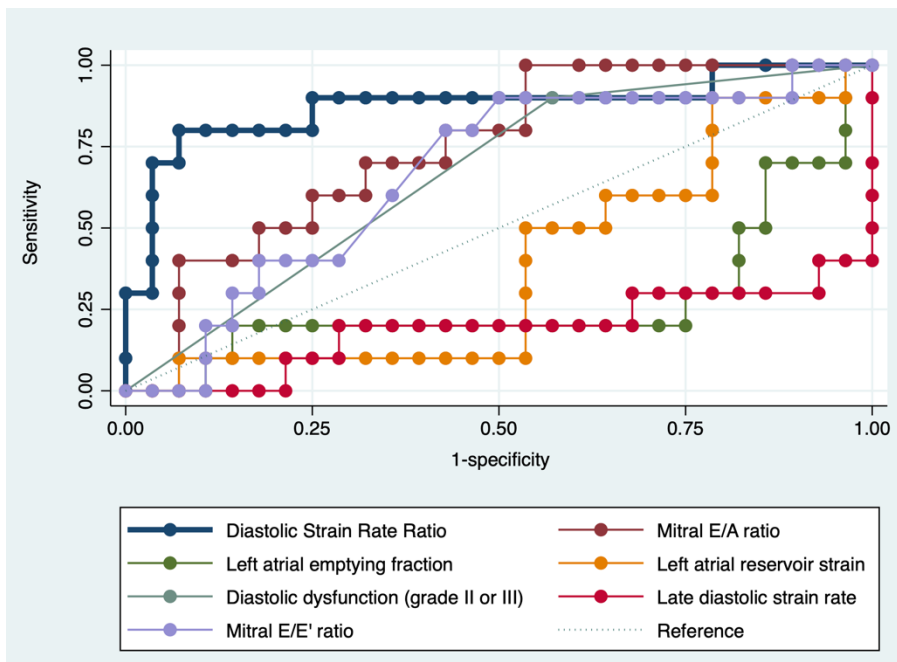
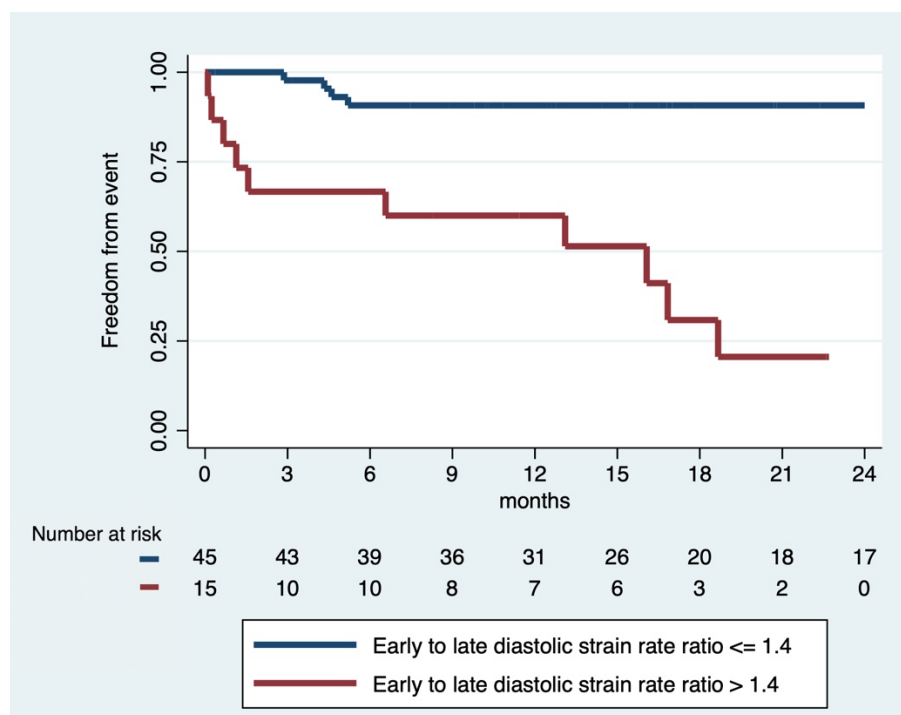


FIGURE 2. Kaplan-Meier curves for sudden cardiac death according to diastolic strain rate ratio



Tables

Table 1. Baseline clinical characteristics

	All patients	Primary endpoint (+)	Primary endpoint (-)	p-value	Secondary endpoint (+)	Secondary endpoint (-)	p-value
Demographics and clinical features							
Age, years	66±14	60±17	68±13	0.034	71±13	66±14	0.229
Male gender	78 (77%)	19 (95%)	59 (73%)	0.038	6 (75%)	72 (78%)	0.999
Hypertension	56 (55%)	12 (60%)	44 (54%)	0.803	4 (50%)	52 (56%)	0.999
Diabetes	30 (30%)	7 (35%)	23 (28%)	0.591	2 (25%)	28 (30%)	0.999
Dyslipidemia	48 (48%)	11 (55%)	37 (46%)	0.455	1 (12%)	47 (50%)	0.062
Chronic Kidney Disease	44 (47%)	10 (53%)	34 (46%)	0.603	2 (29%)	42 (49%)	0.440
Prior myocardial infarction	35 (35%)	8 (40%)	27 (33%)	0.606	4 (50%)	31 (33%)	0.443
Prior non-sustained ventricular tachycardia (lasting <30")	29 (29%)	10 (50%)	19 (23%)	0.019	3 (37%)	26 (28%)	0.686

Prior atrial fibrillation	31 (30%)	9 (45%)	32 (26%)	0.108	4 (50%)	11 (12%)	0.430
<i>Heart failure etiology</i>							
Ischemic Cardiomyopathy	54 (54%)	12 (60%)	42 (52%)	0.619	7 (87%)	47 (51%)	0.065
Non ischemic Cardiomyopathy	47 (47%)	8 (40%)	39 (48%)	0.649	1 (12%)	46 (49%)	0.065
Idiopathic dilated cardiomyopathy	27 (27%)	8 (40%)	19 (23%)	0.162	-	27 (29%)	0.105
Valvular heart disease	3 (3%)	-	3 (4%)		-	3 (3%)	
Myocarditis	7 (7%)	-	7 (9%)		1 (12%)	6 (6%)	
Systemic sclerosis	1 (1%)	-	1 (1%)		-	1 (1%)	
Drug-induced	4 (4%)	-	4 (5%)		-	4 (4%)	
Alcohol	2 (2%)	-	2 (2%)		-	2 (2%)	
Left ventricular non compaction	2 (2%)	-	2 (2%)		-	2 (2%)	
MELAS cardiomyopathy	1 (1%)	-	1 (1%)		-	1 (1%)	
<i>Clinical assessment on enrolment</i>							
New York Heart Association Class III or IV	36 (38%)	10 (50%)	26 (35%)	0.300	1 (12%)	35 (40%)	0.244
Systolic blood pressure, mmHg	115±17	116±19	115±17	0.649	119±17	115±17	0.416
Diastolic blood pressure, mmHg	71±12	72±12	70±11	0.270	76±13	70±12	0.127
Increased C-reactive protein, mg/L	30 (35%)	9 (53%)	21 (31%)	0.099	1 (14%)	31 (33%)	0.413
Creatinine, mg/dl	1.37±0.67	1.42±0.50	1.36±0.71	0.310	1.14±0.21	1.39±0.69	0.421
Troponin T, ng/L	192±454	136±260	214±516	0.979	30±6	211±478	0.822
NT-proBNP, ng/L	7111±7301	9790±8541	6150±6663	0.183	4076±5264	7294±7405	0.363
<i>ECG on enrolment</i>							
Atrial fibrillation	17 (17%)	6 (30%)	11 (14%)	0.098	1 (12%)	16 (17%)	0.999
Heart Rate	75±17	83±15	73±17	0.024	70±12	76±17	0.369
QRS interval, ms	138±30	128±30	139±30	0.296	134±42	138±29	0.836
Left bundle branch block	39 (54%)	4 (40%)	35 (56%)	0.496	3 (50%)	36 (54%)	0.999
<i>Device implanted</i>							
ICD	64 (63%)	16 (80%)	48 (59%)	0.120	5 (62%)	59 (63%)	0.999
CRT	37 (37%)	4 (20%)	33 (41%)	-	3 (38%)	34 (37%)	0.999
<i>Treatment (at the time of discharge)</i>							
Beta blockers	90 (98%)	18 (95%)	72 (99%)	0.372	7 (100%)	83 (98%)	0.999
Mineralocorticoid receptor antagonists	70 (79%)	17 (90%)	53 (76%)	0.343	6 (86%)	64 (78%)	0.999
Sodium-glucose cotransporter-2 inhibitors	5 (5%)	1 (5%)	4 (5%)	0.999	-	5 (6%)	0.999
ARNI/ACE/ARBs	72 (81%)	14 (74%)	58 (83%)	0.510	6 (100%)	66 (79%)	0.591
ARNI	18 (20%)	2 (10%)	16 (23%)	0.340	3 (50%)	15 (18%)	0.094
ACE	44 (49%)	10 (53%)	34 (48%)	0.800	2 (33%)	42 (51%)	0.677
ARBs	10 (11%)	2 (10%)	8 (11%)	0.999	1 (16%)	9 (11%)	0.522
Amiodarone	21 (23%)	2 (11%)	19 (26%)	0.223	1 (14%)	20 (24%)	0.999
Mexiletine	1 (1%)	-	1 (12%)	0.999	-	1 (1%)	0.999
Diuretics	80 (89%)	18 (95%)	62 (87%)	0.682	6 (86%)	74 (89%)	0.575
New-onset atrial fibrillation^	15 (15%)	2 (10%)	13 (16%)	0.729	4 (50%)	12 (13%)	0.016

Device complication	16 (16%)	1 (5%)	15 (18%)	0.184	5 (62%)	11 (12%)	0.002
Echocardiography							
Left ventricular end diastolic diameter, mm	63±6	65±5	62±6	0.072	64±7	62±6	0.815
Left ventricular end diastolic volume, ml	196±57	202±49	193±59	0.556	208±75	195±56	0.850
Left ventricular end systolic volume, ml	147±50	155±40	145±52	0.459	158±72	146±48	0.929
Left ventricular mass index, g/sqm	136±32	133±26	136±34	0.678	137±44	136±32	0.809
Left ventricular stroke volume, ml	49±13	48±14	49±13	0.787	50±9	49±14	0.661
Left ventricular ejection fraction, %	26±5	24±4	26±5	0.065	26±7	26±5	0.724
Septal S' pulsed-wave TDI velocity, cm/s	4.1±0.8	4.1±0.7	4.1±0.9	0.970	3.6±0.3	4.2±0.9	0.365
Left atrial volume index, ml/sqm	59±41	65±19	57±44	0.555	51±13	59±43	0.601
Mitral E/E' ratio	14±5.7	16.4±4.9	13.1±5.7	0.014	12.7±6.7	14.1±5.6	0.392
Lateral E' pulsed-wave TDI velocity, cm/s	7.6±3.9	7.5±2.8	7.6±4.4	0.639	6.7±3.2	7.6±4	0.671
Diastolic dysfunction							
Grade II	34 (37%)	10 (50%)	24 (34%)	0.201	2 (29%)	32 (38%)	0.708
Grade III	21 (23%)	9 (45%)	12 (17%)	0.015	1 (14%)	20 (23%)	0.999
Grade II or III	55 (60%)	19 (95%)	36 (51%)	<0.001	3 (43%)	52 (62%)	0.428
Moderate or severe mitral regurgitation	41 (44%)	12 (63%)	29 (39%)	0.076	3 (43%)	38 (45%)	0.999
Effective regurgitant orifice, sqcm	0.23±0.09	0.27±0.09	0.22±0.09	0.097	0.19±0.05	0.24±0.09	0.455
Right ventricular basal diameter, mm	39±6	41±5	39±6	0.263	35±8	40±6	0.089
TAPSE, mm	17±5	15±4	18±5	0.039	20±6	17±5	0.121
Right ventricle S' pulsed-wave TDI velocity, cm/s	9.1±2.2	8.4±2.1	9.4±2.2	0.239	10.3±1.5	9±2.2	0.195
Tricuspid regurgitation velocity, m/s	2.8±0.5	3±0.4	2.8±0.5	0.123	2.6±0.6	2.8±0.5	0.098
Estimated right atrial pressure, mmHg	7±4	9±4	7±4	0.005	6±2	7±4	0.417
Left ventricular global longitudinal strain, %	-6.6±2.4	-5.6±2.1	-6.9±2.5	0.045	-6.3±1.1	-6.6±2.5	0.854
Left atrial reservoir strain, %	15.9±8.7	10.2±6.1	17.3±8.7	0.003	13.8±4.8	15.7±8.9	0.875
Left atrial emptying fraction, %	45±17	32±15	49±16	<0.001	40±12	46±18	0.489
Early diastolic strain rate, 1/s	0.69±0.35	0.70±0.32	0.69±0.36	0.597	0.71±0.34	0.69±0.35	0.859
Late diastolic strain rate, 1/s	0.72±0.41	0.44±0.32	0.81±0.39	<0.001	0.90±0.57	0.71±0.40	0.533
Early to late diastolic strain rate ratio	1.37±1.30	2.61±1.88	0.99±0.75	<0.001	1.05±0.32	1.39±1.35	0.828
Early to late diastolic strain rate ratio >1.4	15 (25%)	10 (71%)	5 (11%)	<0.001	-	15 (27%)	0.564
Cardiac Magnetic Resonance							
Left ventricular volume index, ml/sqm	171±60	161±16	173±66	0.650	178±74	170±58	0.810
Left ventricular ejection fraction, %	22±7	21±2	22±8	0.708	18±8	23±7	0.269
Right ventricular volume index, ml/sqm	96±35	106±20	94±38	0.528	80±28	99±36	0.334
Right ventricular ejection fraction, %	40±14	33±7	41±15	0.244	43±22	39±13	0.663
Late Gadolinium Enhancement (LGE)	30 (70%)	7 (100%)	23 (64%)	0.082	5 (83%)	25 (68%)	0.649
Subepicardial LGE	7 (16%)	-	7 (19%)	0.577	1 (16%)	6 (16%)	0.999

Intramyocardial LGE	9 (21%)	4 (58%)	8 (22%)	0.081	2 (33%)	10 (27%)	0.999
Subendocardial LGE	9 (21%)	2 (29%)	7 (19%)	0.624	2 (33%)	6 (16%)	0.589
Number of myocardial segments with LGE	3.6±3.4	6.4±4.2	3.1±3.1	0.028	5±3.3	3.4±3.5	0.276
Midwall septal enhancement	7 (16%)	4 (58%)	7 (16%)	0.008	1 (16%)	6 (16%)	0.999

ARNI= Angiotensin receptor neprilysin inhibitors; ACE= Angiotensin receptor neprilysin inhibitors; ARBs= angiotensin receptor blockers;

NT-proBNP= N-Terminal pro-B-Type Natriuretic Peptide; ICD= implantable cardiac defibrillator; CRT= cardiac resynchronization

therapy; TDI=Tissue Doppler imaging; LGE= late gadolinium enhancement; TAPSE=Tricuspid annular plane systolic excursion;

^following discharge.

Table 2. Adverse events during follow-up

	Number of events	Event rate (per 10 patients-year)
<i>Primary endpoint (sudden cardiac death)</i>	20	1.4
ICD or CRT appropriate intervention	13	0.9
- electric shock	7	0.5
- ATP	6	0.4
Cardiac death	6	0.4
LVAD implantation	1	0.07
Heart transplantation	5	0.3
<i>Secondary endpoint (non-appropriate intervention)</i>	8	0.6
Non appropriate electric shock	7	0.5
Non appropriate ATP	1	0.4
All-cause death	13	0.9
Hospitalization for HF	19	1.4
New-onset atrial fibrillation	15	1.3
Non-sustained ventricular tachycardia	30	2.5

ICD= implantable cardiac defibrillator; CRT= cardiac resynchronization therapy; HF=Heart failure; ATP= Anti-tachycardia Pacing

Therapy

Table 3. Uni- and Multivariable Cox regression model for primary endpoint

	Univariable		Multivariable	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Demographics and clinical features				
Age, years *	0.97 (0.94-0.99)	0.016	0.99 (0.94-1.04)	0.579

Male gender	5.65 (0.76-42.24)	0.092		
Hypertension	1.09 (0.45-2.67)	0.847		
Diabetes	1.20 (0.48-2.99)	0.702		
Dyslipidemia	1.43 (0.59-3.46)	0.428		
Chronic Kidney Disease	1.23 (0.49-3.03)	0.653		
Prior myocardial infarction	1.23 (0.49-2.94)	0.688		
Prior non-sustained ventricular tachycardia (lasting <30")	2.59 (1.08-6.25)	0.033	2.53 (0.58-11.12)	0.218
Prior atrial fibrillation	2.19 (0.90-5.31)	0.082		
<i>Heart failure etiology</i>				
Ischemic Cardiomyopathy	1.23 (0.50-3.01)	0.652		
Non ischemic Cardiomyopathy	0.81 (0.33-1.99)	0.652		
Idiopathic dilated cardiomyopathy	2.19 (0.89-5.39)	0.089		
Valvular heart disease				
Myocarditis				
Systemic sclerosis				
Drug-induced				
Alcohol				
Left ventricular non compaction				
MELAS cardiomyopathy				
<i>Clinical assessment on enrolment</i>				
New York Heart Association Class III or IV *	1.90 (0.79-4.58)	0.153		
Systolic blood pressure, mmHg *	0.99 (0.97-1.03)	0.987		
Diastolic blood pressure, mmHg *	1 (0.96-1.05)	0.745		
Increased C-reactive protein	2.25 (0.87-5.84)	0.096		
Creatinine, mg/dl *	1.08 (0.58-2.01)	0.807		
Troponin T, ng/L *	1 (0.99-1.00)	0.902		
NT-proBNP, ng/L *	1 (0.99-1.00)	0.253		
<i>ECG on enrolment</i>				
Atrial fibrillation	2.18 (0.84-5.68)	0.110		
Heart Rate *	1.03 (1.01-1.05)	0.025	1.06 (1.01-1.13)	0.038
QRS interval, ms *	0.99 (0.97-1.01)	0.297		
Left bundle branch block	0.55 (0.16-1.97)	0.361		
<i>Device implanted</i>				
ICD	2.53 (0.85-7.58)	0.097		
CRT	-	-		
<i>Treatment (at the time of discharge)</i>				
Beta blockers	0.25 (0.03-1.87)	0.177		
Mineralocorticoid receptor antagonists	2.64 (0.61-11.42)	0.195		
Sodium-glucose cotransporter-2 inhibitors	1.02 (0.14-7.67)	0.982		
ARNI/ACE/ARBs	0.62 (0.23-1.74)	0.372		
ARNI	0.47 (0.11-2.04)	0.315		

ACE	1.15 (0.47-2.84)	0.760		
ARBs	0.82 (0.19-3.53)	0.785		
Amiodarone	0.41 (0.09-1.78)	0.233		
Mexiletine	-	0.999		
Diuretics	2.42 (0.32-18.24)	0.390		
New-onset atrial fibrillation [^]	0.54 (0.12-2.32)	0.404		
Device complication [^]	0.24 (0.03-1.78)	0.163		
Echocardiography				
Left ventricular end diastolic diameter, mm	1.01 (0.99-1.15)	0.079		
Left ventricular end diastolic volume, ml	1.00 (0.99-1.01)	0.519		
Left ventricular end systolic volume, ml	1.00 (0.99-1.01)	0.433		
Left ventricular mass index, g/sqm	0.99 (0.98-1.01)	0.772		
Left ventricular stroke volume, ml	0.99 (0.96-1.03)	0.888		
Left ventricular ejection fraction, %	0.94 (0.86-1.02)	0.109		
Septal S' pulsed-wave TDI velocity, cm/s *	1.03 (0.59-1.81)	0.912		
Left atrial volume index, ml/sqm *	1.001 (0.99-1.01)	0.371		
Mitral E/E' ratio *	1.07 (1.001-1.15)	0.050	-	-
Lateral E' pulsed-wave TDI velocity, cm/s *	0.99 (0.88-1.12)	0.924		
Diastolic dysfunction				
Grade II	1.76 (0.73-4.24)	0.205		
Grade III	2.88 (1.19-6.94)	0.019	-	-
Grade II or III	13.57 (1.82-101)	0.011	2.39 (0.24-23.5)	0.456
Moderate or severe mitral regurgitation	2.37 (0.93-6.03)	0.070		
Effective regurgitant orifice, sqcm *	33.9 (0.09-1191)	0.239		
Right ventricular basal diameter, mm *	1.04 (0.97-1.11)	0.263		
TAPSE, mm *	0.88 (0.78-0.98)	0.020	1.01 (0.73-1.39)	0.952
Right ventricle S' pulsed-wave TDI velocity, cm/s *	0.84 (0.63-1.12)	0.239		
Tricuspid regurgitation velocity, m/s *	1.83 (0.85-3.93)	0.123		
Estimated right atrial pressure, mmHg *	1.12 (1.02-1.22)	0.015	1.32 (1.01-1.71)	0.042
Left ventricular global longitudinal strain, % *	1.24 (1.01-1.52)	0.045	1.82 (1.04-3.18)	0.037
Left atrial reservoir strain, % *	0.90 (0.83-0.97)	0.008	1.01 (0.89-1.13)	0.915
Left atrial emptying fraction, % *	0.003 (0.001-0.106)	0.001	-	-
Early diastolic strain rate, 1/s *	1.20 (0.35-4.11)	0.766		
Late diastolic strain rate, 1/s *	0.06 (0.07-0.49)	0.009	-	-
Early to late diastolic strain rate ratio *	1.73 (1.32-2.26)	<0.001	2.14 (1.17-3.92)	0.013
Early to late diastolic strain rate ratio >1.4	10.34 (3.23-33.15)	<0.001	-	-
Cardiac Magnetic Resonance				
Left ventricular volume index, ml/sqm *	0.99 (0.98-1.01)	0.675		
Left ventricular ejection fraction, % *	0.98 (0.87-1.01)	0.664		
Right ventricular volume index, ml/sqm *	1.01 (0.98-1.03)	0.524		

Right ventricular ejection fraction, % *	0.96 (0.89-1.03)	0.231		
Late Gadolinium Enhancement (LGE)	-	0.999		
Subepicardial LGE	-	0.999		
Intramyocardial LGE	4.45 (0.99-20.05)	0.052		
Subendocardial LGE	1.37 (0.27-7.07)	0.706		
Number of myocardial segments with LGE *	1.29 (1.03-1.62)	0.023	-	-
Midwall septal enhancement	10.19 (2.22-46.84)	0.003	-	-

ARNI= Angiotensin receptor neprilysin inhibitors; ACE= Angiotensin receptor neprilysin inhibitors; ARBs= angiotensin receptor blockers;

NT-proBNP= N-Terminal pro-B-Type Natriuretic Peptide; ICD= implantable cardiac defibrillator; CRT= cardiac resynchronization

therapy; TDI=Tissue Doppler imaging; LGE= late gadolinium enhancement; TAPSE=Tricuspid annular plane systolic excursion;

^following discharge; *Hazard ratio per 1-unit increase

Table 4. Comparison of diastolic function - associated predictors of the primary endpoint (ROC sensitivity analysis)

	ROC area (95% CI)	p-value
Early to late diastolic strain rate ratio	0.88 (0.72-0.99)	0.001
Late diastolic strain rate	0.81 (0.61-0.99)	0.004
Mitral E/A ratio	0.75 (0.58-0.91)	0.022
Left atrial emptying fraction, %	0.72 (0.51-0.94)	0.037
Mitral E/E' ratio	0.67 (0.47-0.86)	0.159
Diastolic dysfunction (grade II or III)	0.66 (0.53-0.80)	0.127
Left atrial reservoir strain, %	0.62 (0.42-0.82)	0.063

Table 5. Uni- and Multivariable Cox regression model for secondary endpoint

	Univariable		Multivariable	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Demographics and clinical features				
Age, years *	1.02 (0.96-1.09)	0.411		
Male gender	0.82 (0.17-4.01)	0.811		
Hypertension	0.66 (0.16-2.65)	0.556		
Diabetes	0.72 (0.15-3.58)	0.690		
Dyslipidemia	0.14 (0.02-1.16)	0.069		
Chronic Kidney Disease	0.44 (0.08-2.28)	0.330		
Prior myocardial infarction	1.87 (0.47-7.49)	0.375		
Prior non-sustained ventricular tachycardia (lasting <30")	1.56 (0.37-6.54)	0.541		
Prior atrial fibrillation	0.34 (0.04-2.78)	0.315		
<i>Heart failure etiology</i>				
Ischemic Cardiomyopathy	5.89 (0.72-47.99)	0.097		
Non ischemic Cardiomyopathy	0.17 (0.02-1.38)	0.097		
Idiopathic dilated cardiomyopathy	-	0.999		
Valvular heart disease				
Myocarditis				
Systemic sclerosis				
Drug-induced				
Alcohol				
Left ventricular non compaction				
MELAS cardiomyopathy				
<i>Clinical assessment on enrolment</i>				
New York Heart Association Class III or IV *	0.31 (0.04-2.58)	0.279		
Systolic blood pressure, mmHg *	1.01 (0.97-1.05)	0.670		
Diastolic blood pressure, mmHg *	1.03 (0.97-1.10)	0.278		
Increased C-reactive protein	0.35 (0.04-2.91)	0.331		
Creatinine, mg/dl *	0.43 (0.08-2.42)	0.338		
Troponin T, ng/L *	0.99 (0.93-1.05)	0.643		
NT-proBNP, ng/L *	0.99 (0.99-1.00)	0.486		
<i>ECG on enrolment</i>				
Atrial fibrillation	0.69 (0.08-5.65)	0.734		
Heart Rate *	0.98 (0.93-1.04)	0.537		
QRS interval, ms *	0.99 (0.97-1.02)	0.787		
Left bundle branch block	0.85 (0.17-4.21)	0.843		
Device implanted				

ICD	1.02 (0.24-4.27)	0.979		
CRT	-	-		
Treatment (at the time of discharge)				
Beta blockers	-	0.999		
Mineralocorticoid receptor antagonists	1.80 (0.22-14.95)	0.587		
Sodium-glucose cotransporter-2 inhibitors	-	0.999		
ARNI/ACE/ARBs	-	0.999		
ARNI	4.48 (0.90-22.25)	0.066		
ACE	0.52 (0.09-2.83)	0.449		
ARBs	1.34 (0.16-11.54)	0.788		
Amiodarone	0.56 (0.07-4.69)	0.596		
Mexiletine	-	0.999		
Diuretics	0.82 (0.09-6.85)	0.852		
New-onset atrial fibrillation [^]	5.67 (1.40-22.86)	0.015	17 (1.63-196)	0.018
Device complication [^]	9.77 (2.32-41)	<0.001	44 (4.16-459)	0.002
Echocardiography				
Left ventricular end diastolic diameter, mm	1.06 (0.94-1.19)	0.358		
Left ventricular end diastolic volume, ml	1.00 (0.99-1.02)	0.461		
Left ventricular end systolic volume, ml	1.00 (0.99-1.02)	0.440		
Left ventricular mass index, g/sqm	1.00 (0.98-1.02)	0.912		
Left ventricular stroke volume, ml	1.01 (0.96-1.07)	0.738		
Left ventricular ejection fraction, %	1.01 (0.87-1.17)	0.917		
Septal S' pulsed-wave TDI velocity, cm/s *	0.37 (0.05-2.58)	0.318		
Left atrial volume index, ml/sqm *	0.99 (0.94-1.04)	0.635		
Mitral E/E' ratio *	0.95 (0.82-1.10)	0.505		
Lateral E' pulsed-wave TDI velocity, cm/s *	0.93 (0.69-1.24)	0.618		
Diastolic dysfunction				
Grade II	0.66 (0.13-3.39)	0.618		
Grade III	0.52 (0.06-4.33)	0.545		
Grade II or III	0.46 (0.10-2.05)	0.308		
Moderate or severe mitral regurgitation	1.08 (0.24-4.87)	0.919		
Effective regurgitant orifice, sqcm *	0.01 (0.001-9547)	0.436		
Right ventricular basal diameter, mm *	0.85 (0.74-0.99)	0.036	0.87 (0.74-1.02)	0.086
TAPSE, mm *	1.11 (0.97-1.28)	0.129		
Right ventricle S' pulsed-wave TDI velocity, cm/s *	1.30 (0.84-2.03)	0.238		
Tricuspid regurgitation velocity, m/s *	0.37 (0.06-2.33)	0.291		
Estimated right atrial pressure, mmHg *	0.84 (0.59-1.20)	0.345		
Left ventricular global longitudinal strain, % *	1.05 (0.74-1.48)	0.780		
Left atrial reservoir strain, % *	0.97 (0.87-1.08)	0.568		
Left atrial emptying fraction, % *	0.10 (0.001-20.37)	0.396		

Early diastolic strain rate, 1/s *	1.34 (0.12-14.36)	0.808		
Late diastolic strain rate, 1/s *	2.87 (0.33-24.86)	0.338		
Early to late diastolic strain rate ratio *	0.77 (0.26-2.31)	0.646		
Early to late diastolic strain rate ratio >1.4	-	0.999		
Cardiac Magnetic Resonance				
Left ventricular volume index, ml/sqm *	1.01 (0.98-1.02)	0.740		
Left ventricular ejection fraction, % *	0.90 (0.78-1.05)	0.175		
Right ventricular volume index, ml/sqm *	0.98 (0.94-1.02)	0.337		
Right ventricular ejection fraction, % *	1.02 (0.96-1.07)	0.608		
Late Gadolinium Enhancement (LGE)	2.85 (0.33-24.58)	0.340		
Subepicardial LGE	0.82 (0.09-7.10)	0.856		
Intramyocardial LGE	1.79 (0.32-10.2)	0.507		
Subendocardial LGE	1.72 (0.31-9.44)	0.532		
Number of myocardial segments with LGE *	1.19 (0.94-1.51)	0.155		
Midwall septal enhancement	1.77 (0.18-17.2)	0.621		

ARNI= Angiotensin receptor neprilysin inhibitors; ACE= Angiotensin receptor neprilysin inhibitors; ARBs= angiotensin receptor blockers;

NT-proBNP= N-Terminal pro-B-Type Natriuretic Peptide; ICD= implantable cardiac defibrillator; CRT= cardiac resynchronization

therapy; TDI=Tissue Doppler imaging; LGE= late gadolinium enhancement; TAPSE=Tricuspid annular plane systolic excursion;

^following discharge; *Hazard ratio per 1-unit increase

Table 6. Left ventricular reverse remodeling in patients receiving Cardiac Resynchronization Therapy

	All patients		Primary endpoint +		Primary endpoint -	
	%Variation at 12 months	p-value	%Variation at 12 months	p-value	%Variation at 12 months	p-value
Left ventricular end diastolic diameter, mm	-7±10	0.003	-1.4±6	0.854	-8±9	0.004
Left ventricular end diastolic volume, ml	-18±25	0.003	+0.7±10	0.317	-21±24	0.001
Left ventricular end systolic volume, ml	-37±43	<0.001	+0.4±8	0.654	-41±43	<0.001
Left ventricular ejection fraction, %	+18±31	<0.001	-28±62	0.999	+24±20	<0.001
Left ventricular global longitudinal strain, %	+24±18	0.001	+12±0	0.179	25±18	<0.001

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