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From Ejection Fraction to Fibrosis Phenotyping: Rethinking ICD Selection in Non-Ischemic Cardiomyopathy

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Take Home Messages

- Risk stratification for sudden cardiac death in non-ischemic cardiomyopathy remains challenging as left ventricular ejection fraction alone is an inadequate predictor of arrhythmic risk.
- The fibrosis entropy study utilised cardiovascular magnetic resonance to assess myocardial fibrosis and introduced fibrosis entropy, a novel metric quantifying the heterogeneity of scar tissue.
- Higher fibrosis entropy was independently associated with life-threatening ventricular arrhythmias and provided incremental prognostic value beyond conventional risk markers such as ejection fraction and overall scar burden.
- These findings suggest that scar heterogeneity may be an important determinant of arrhythmogenic risk and highlight the role of advanced CMR phenotyping to guide decision-making of device implantation in heart failure.

Background

Prevention of sudden cardiac death (SCD) remains one of the central challenges in contemporary heart failure management (1). In patients with non-ischemic cardiomyopathy (NICM), SCD accounts for up to one-third of all deaths after presentation (2). Current recommendations for primary prevention implantable cardioverter-defibrillator (ICD) implantation have traditionally been guided primarily by left ventricular ejection fraction (LVEF), which is an imperfect surrogate for predicting SCD risk in NICM (3). Many patients with severe systolic dysfunction will never experience malignant ventricular arrhythmias (VA), while others with only modest reductions in LVEF may succumb to SCD (4).

The DANISH trial sough to address this uncertainty and despite its limitation, it demonstrated that ICD implantation in NICM significantly reduced SCD but failed to improve overall mortality in those receiving contemporary medical therapy (5). This emphasized the need for better arrhythmic risk stratification beyond LVEF alone (4).

Fibrosis as the Arrhythmic Substrate

Over the past decade, cardiovascular magnetic resonance (CMR) has emerged as a powerful modality for phenotyping cardiomyopathy and characterising myocardial fibrosis (2,6,7). Late gadolinium enhancement (LGE) imaging by CMR allows direct visualisation of replacement fibrosis (8) and acts as a powerful predictor of VA in both ischemic and NICM (7). Multiple studies have demonstrated that the presence of mid-wall fibrosis in dilated cardiomyopathy (DCM) is strongly associated with VA and SCD independent of LVEF (9,10). A study by Halliday et al. identified a group of DCM patients with mid-wall LGE which showed markedly higher rates of SCD even when left ventricular systolic dysfunction is only mild to moderate (LVEF ≥40%) (11), further highlighting that replacement fibrosis, rather than LVEF alone, serves as a fundamental arrhythmogenic substrate Beyond the imaging markers, electrocardiographic markers such as T-wave alternans and reduced heart rate variability are also recognised to be associated with increased arrhythmic risk in heart failure, particularly in NICM, but their predictive value is greatest with multimodal risk-stratification approach (12,13,14).

The Fibrosis Entropy Study

In this context, Hammersley et al recently introduced the fibrosis entropy study (15) (Table 1), an important refinement in arrhythmic risk assessment by investigating whether the structural complexity of myocardial fibrosis may influence arrhythmogenic potential.

Table 1: Study Design, Outcomes, and Key Findings of Fibrosis Entropy Analysis in Non-Ischemic Cardiomyopathy

Study Design	Prospective observational cohort study of patients undergoing CMR (2009–2017)
Study Population	291 patients with LGE-positive NICM compared with 574 NICM patients without LGE
Baseline Characteristics	Median age 57 years; 75% male; median LVEF 39%
Imaging Biomarker	Fibrosis entropy, derived from CMR image-texture analysis, quantifies the spatial heterogeneity of myocardial scar Higher entropy indicating more heterogeneous fibrosis architecture.
Primary Outcome	Life-threatening VA, aborted SCD or appropriate ICD therapy
Follow-up	Median - 6.3 years

Event Rate	38 patients (13.1%) in the LGE-positive cohort experienced life-threatening VA
Multivariable Analysis (adjusted for LVEF ≤35% and NYHA class >1)	Core fibrosis entropy HR 1.77 (95% CI 1.25–2.52); Gray-zone entropy HR 1.97 (95% CI 1.20–2.54); Combined entropy HR 1.98 (95% CI 1.30–3.02)
Key findings	Higher entropy of both core and gray-zone fibrosis was significantly associated with arrhythmic events LVEF ≤35% was not associated with arrhythmic events
Clinical Implication	Combining fibrosis presence with fibrosis entropy allows risk stratification into low-, intermediate-, and high-risk groups for arrhythmic events
(Abbreviations) CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement; NICM, non-ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; VA, ventricular arrhythmia; SCD, sudden cardiac death; ICD, implantable cardioverter-defibrillator; HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association.	

These findings highlight the limited discriminatory value of LVEF alone in NICM and support an emerging paradigm in which arrhythmic risk in NICM is determined by the myocardial fibrosis phenotype such as scar heterogeneity rather than a binary presence or absence of scar (Figure 1). Validation in larger prospective cohorts may enable more personalized risk stratification strategies, particularly in a subgroup of patients with relatively preserved LVEF but highly heterogeneous fibrosis who could benefit from ICD therapy.

Conclusions

This study provided compelling evidence that the structural complexity of myocardial fibrosis may influence arrhythmic risk in NICM, highlighting the limitations of current LVEF-based ICD selection strategies. Ongoing trials such as the CMR-GUIDE HF study, randomizing patients with LVEF 36–50% and myocardial fibrosis on CMR to ICD implantation or rhythm monitoring (16,17), as well the BRITISH Study which aims to evaluate whether ICD implantation in NICM patients with myocardial scar reduces all-cause mortality (18), will be critical in determining whether imaging-derived markers can translate into improved patient selection for device therapy. Ultimately, integrating advanced imaging phenotyping may move the field toward a more precise and personalised approach to SCD prevention in NICM.

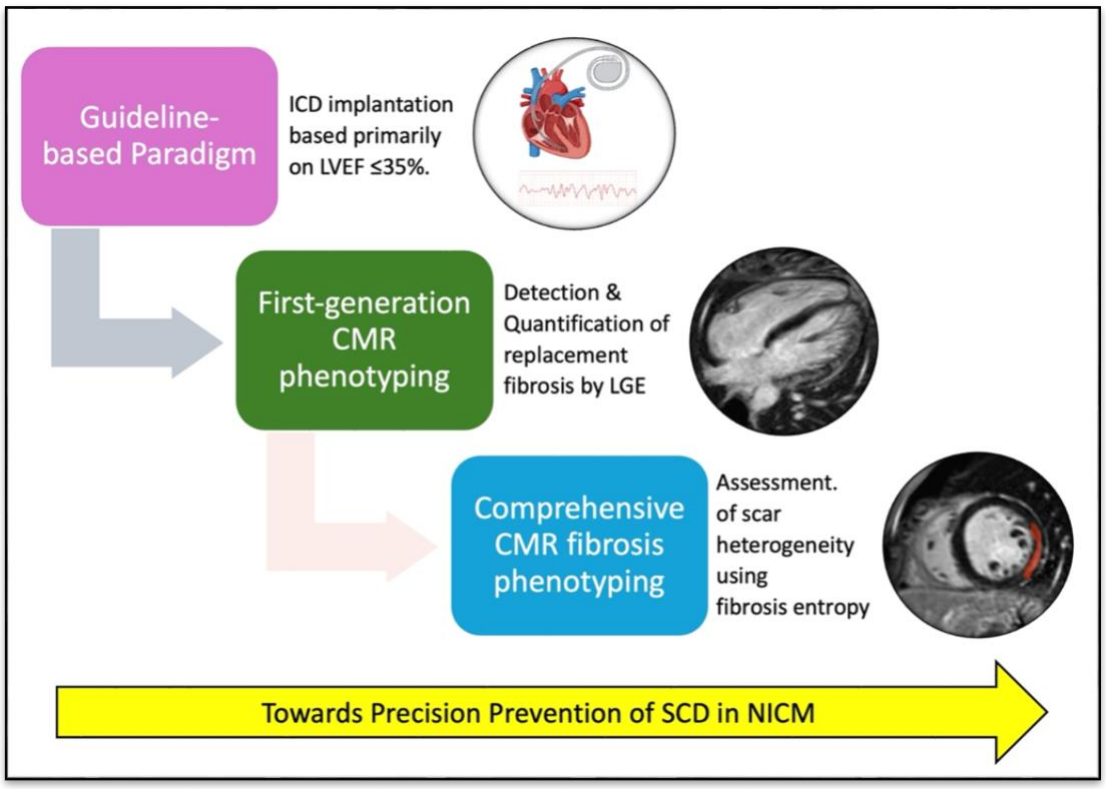

Figure 1. Evolving Paradigm of Arrhythmic Risk Stratification in Non-Ischemic Cardiomyopathy. This is a figure created with images created on Biorender.com and images adapted from case courtesy of Tamara Razon Cuenza, Radiopaedia.org, rID: 77023. (ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement ; NICM, non-ischaemic cardiomyopathy.)

Disclosures

None to declare.

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