

# Primary prevention implantable cardioverter–defibrillator therapy: a matter not yet adequately explored waiting for guidelines update

Implantable cardioverter defibrillator (ICD) therapy is adopted with the aim of preventing cardiac death consequent to arrhythmic events in patients with heart failure and reduced left ventricular ejection fraction (LVEF). To date, the patients considered worthy of primary prevention ICD implantation are all those with non-ischaemic dilated cardiomyopathy (DCM) or ischaemic heart disease at least 40 days post-MI with LVEF of 35% or less and New York Heart Association (NYHA) Class II or III symptoms on chronic guideline-directed medical therapy, and those with ischaemic heart disease with LVEF of 30% or less and NYHA Class I, who have a reasonable expectation of meaningful survival for more than 1 year.<sup>1,2</sup> In parallel, the opportunity to study the anatomic substrate of the myocardium through non-invasive imaging techniques such as cardiac magnetic resonance (CMR) thanks to its ability to well depict irreversible myocardial injury and interstitial fibrosis by late gadolinium enhancement (LGE) imaging has opened a new scenario regarding the potential contribution of tissue characterization in the evaluation of patients undergoing ICD implantation. It is known that the fibrous tissue, result of the healing process after myocardial infarction or of the inflammatory process, induces slow and heterogeneous conduction pathway favouring intramyocardial reentry phenomena.<sup>3,4</sup>

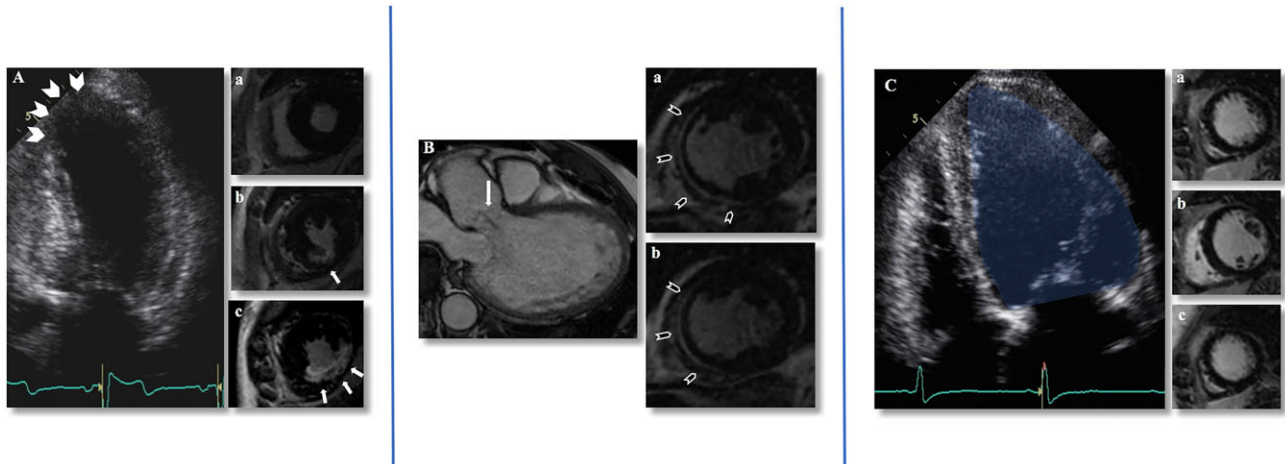
The recent published DANISH (Danish study to assess the efficacy of ICDs in patients with non-ischaemic systolic heart failure on mortality) trial<sup>5</sup> enrolled 1116 patients with symptomatic DCM with LVEF  $\leq$ 35% and randomized to ICD vs. non-ICD arms followed up for a median of 67.6 months. In conclusion, the study shows that ICD therapy does not result in a significant reduction in death of any cause compared with usual clinical care. This underlines the message of not to run the risk of implanting in patients who will not benefit from an ICD. In a recent meta-analysis<sup>6</sup> including 29 observational studies, 2948 patients with DCM were evaluated for the association between LGE-based myocardial scar and the risk of sustained ventricular arrhythmias, appropriate ICD intervention or sudden cardiac

death (SCD) and followed for an average of 36 months. In the subgroup of studies that included patients for primary prevention ICD implantation, the arrhythmic endpoint occurred in 21% of LGE-positive vs. 4.7% of LGE-negative patients with annual event rates of 6.9% and 1.6%, respectively. The investigators concluded that LGE was a strong independent predictor of arrhythmic events and could improve risk stratification for SCD and appropriateness of ICD therapy.

Therefore, because most of the patients with DCM and eligibility criteria for ICD implantation will not have expected benefit from the devices based on LVEF cut-off,<sup>7</sup> the consequent syllogism is that the scar would help identify the patients who will really benefit from this prophylactic therapy.

On the other hand, it is well known that the majority of out-of-hospital cardiac arrests occur in patients with LVEF  $>$ 35%. Stecker *et al.*<sup>8</sup> extrapolated all cases of SCD from the Oregon Sudden Unexpected Death Study and retrospectively assessed LVEF among subjects who underwent cardiac functional evaluation before SCD. Overall, two-thirds of these patients would not meet the criteria for ICD implantation. When we consider the accuracy of CMR-LGE for SCD risk stratification in a mixed setting of patients,<sup>9</sup> ischaemic cardiomyopathy (ICM) and DCM, a 2013 meta-analysis included 1105 patients followed-up for 8.5/41 months and shown that a greater extent of scarring had a markedly increased overall relative risk (RR, 4.33; 95% CI, 2.98–6.29) compared with those with a lower extent. Afterwards, Perazzolo Marra *et al.*<sup>10</sup> evaluated the impact of the presence and amount of myocardial fibrosis on arrhythmogenic risk prediction in DCM. Kaplan–Meier analysis revealed a significant correlation between the LV-LGE presence and malignant arrhythmic events. On this topic, we have recently concluded a study on 409 consecutive ICM and DCM patients with chronic HF referred for evaluation of primary prevention ICD implantation as driven by echocardiography assessment (TTE) and contextually examined by CMR.<sup>11</sup>

**Figure 1** Patient 1: Ischaemic cardiomyopathy (ICM) with three-vessel coronary disease and cardiac magnetic resonance—left ventricle ejection fraction (CMR-LVEF) of 42%. The patient incurred sudden cardiac death (SCD) during the follow up period. (A) Apical two-chamber view echocardiographic image of left ventricle in systolic phase; the arrowheads show the apical and middle segment akinesia of the inferior wall. (a,b,c) Short axis views of the left ventricle at cardiac magnetic resonance late gadolinium enhancement sequences (CMR-LGE); the arrows show the myocardial necrotic area. Patient 2: Non-ischaemic cardiomyopathy (DCM) with CMR-LVEF of 26% and elevated volumes of 166 mL/mq. The patient incurred sustained ventricular arrhythmia during the follow-up period. (B) Three-chamber view CMR image of left ventricle in diastolic phase (the arrow indicates the mild aortic regurgitation) shows the enlarged and globose-shaped left ventricle. (a,b,c) Short axis views of the left ventricle at CMR-LGE; the arrows show the middle wall LGE non-ischaemic pattern. Patient 3: DCM with echocardiography LVEF of 30% and elevated volumes of 108 mL/mq. The patient had no events during the follow-up period. (C) Apical four-chamber view echocardiographic image of left ventricle in diastolic phase. (a,b,c) Short axis views of the left ventricle at CMR-LGE do not show fibrotic signs.



During a median follow-up of 545 days/1.5 years, 103 patients (25%) incurred in an arrhythmic endpoint defined as long runs of non-sustained ventricular tachycardia or sustained ventricular tachycardia, aborted SCD, or SCD. Whereas the lowest risk occurred in patients with LVEF >35% and no LGE, those with LGE had a high rate of events of ≈20%. It is worthy to note that, among those patients with TTE-LVEF in the 'gray zone' (30–40%), the addition of presence of LGE to the model including clinical data, TTE-LVEF and CMR-LVEF, provided a significant refinement in the outcome prediction with a net reclassification improvement of 0.42. In conclusion, CMR imaging demonstrated to effectively identify a subgroup of patients LGE-positive in which ICD implantation was still indicated despite LVEF higher than 35% (Figure 1).

Given considering indicated new data, risk-stratification on the basis of LVEF cut-off values does not seem adequate to identify patient who will benefit from ICD therapy for primary prevention. Further evidences to determine the prognostic benefit of LGE assessment in ICM patients referred for ICD primary prevention therapy and LVEF >35% are warranted. On the opposite side, a comparative evaluation should include DCM patients candidate for prophylactic ICD implantation according to the current guidelines. In these cases, the combination of LGE and LVEF ≤35% would select the subset of patients with higher

probability of SCD and therefore likely better-selected recipients of ICD therapy. This would avoid the generalized approach of implanting all patients showing just severe LV dysfunction. Despite the methodology and interpretation of LGE deserving further standardization, the information collected with such tailored trials would be pivotal for the initial definition of a multi-parametric approach for decision making in SCD.

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