Selecting patients with non-ischemic dilated cardiomyopathy for implantable cardioverter defibrillators – myocardial function, fibrosis and what's attached?

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The benefit of implantable cardioverter defibrillators (ICDs) in patients with non-ischemic dilated cardiomyopathy (NIDCM) and heart failure with reduced left ventricular ejection fraction (LVEF) (HF-REF) has been questioned following the DANISH (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) trial (1). This landmark study of well-treated patients with NIDCM and symptomatic HF-REF found no difference in all-cause mortality between patients who were randomised to receive an ICD compared to those who were not. Notably, as well as high prescription rates of neuro-hormonal pharmacological therapy, 93% of patients with left bundle branch block and QRS duration of 150ms or greater received a cardiac resynchronisation (CRT) device (1). CRT pacemakers (CRT-P) reduce sudden cardiac death (SCD) which may because CRT improves cardiac function, reduces neurohormonal activation and prevents bradycardia-induced fatal arrhythmias (2). A frequently asked question, especially considering the high-rate of super-response to CRT in patients with NIDCM, is whether CRT defibrillators (CRT-D) provide incremental benefit to CRT-P in this setting.

Observational studies have failed to demonstrate an additional benefit with CRT-D over CRT-P in NIDCM (3,4). In a propensity score analysis of over 5000 patients, Barra and colleagues found no difference in mortality when comparing NIDCM patients with CRT-D and those with CRT-P (hazard ratio: 0.92; 95% CI 0.73:1.16; p=0.49)(4). In the same analysis patients with ischemic cardiomyopathy had better survival with CRT-D compared to CRT-P (HR 0.76; 95% CI: 0.62:0.92; p=0.005). However, in a sub-group analysis of the COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) trial patients with NIDCM randomised to CRT-D had a nominally significant reduction in mortality compared to optimal pharmacological therapy (HR 0.50; 95% CI 0.29-0.88; p=0.015) while those randomised to CRT-P did not (HR 0.91; 95% CI 0.55-1.49;p=0.70) (5),

although there were fewer than 130 patients with NIDCM in the control group of this study. Compared to optimal pharmacological therapy, the benefits of CRT-D (HR 0.73; CI 0.52 to 1.04; P=0.082) and CRT-P (HR 0.72; CI 0.51 to 1.01; P=0.058) were similar.

In this issue of the *Journal*, Leyva and colleagues provide further clarification on the issue by stratifying patients on the basis of the presence or absence of mid-wall late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR) prior to CRT implantation (6). Mid-wall LGE occurs in around 1/3 of patients with NIDCM and represents areas of replacement fibrosis, which are thought to act as substrate for re-entrant ventricular tachycardia (7). In keeping with this, mid-wall LGE predicts a 5-9 fold increased risk of SCD and malignant ventricular arrhythmias in patients with NIDCM over the following 5 years (7,8). LGE-CMR therefore offers the potential to identify patients at high risk of malignant ventricular arrhythmias who may gain benefit from ICD therapy in addition to CRT-P (9).

Leyva and colleagues studied 252 patients with NIDCM and HF-REF who underwent LGE-CMR prior to CRT between 2002 and 2017 (6). Multivariable proportional hazard modelling was used to compare all-cause mortality for patients with CRT-D or CRT-P, stratified by the presence or absence of mid-wall fibrosis. The baseline characteristics of the study population were similar to previous CRT trials (2,5). The average age of patients was 66 years, 61% were men and the majority reported moderate-to-severe heart failure symptoms (83% with New York Heart Association Class III-IV symptoms) at baseline. Importantly, however, only 65% were prescribed beta-blockers and 47% mineralocorticoid receptor antagonists at baseline; subsequent pharmacological treatment was not reported. Consistent with the baseline characteristics, which suggested a population with advanced disease, the mortality rate during follow-up was high: patients with mid-wall fibrosis had an annual mortality rate of 12.8% compared to 6.9% in those without fibrosis. As expected, on multivariable analysis, the presence of mid-wall fibrosis predicted higher mortality (HR 2.31; 95% CI: 1.45:3.68;

p<0.001). Following adjustment for the presence of fibrosis, age, NYHA class, hypertension and atrial fibrillation, CRT-D was associated with lower all-cause mortality compared to CRT-P (HR: 0.33; 95% CI: 0.14-0.77; p=0.01). However, when the population was divided based on the presence or absence of mid-wall fibrosis, only those patients with mid-wall fibrosis appeared to gain mortality benefit with CRT-D (HR: 0.23; 95% CI 0.07-0.75).

The findings should be interpreted within the context of an observational study where it is impossible to control for all factors influencing the choice of device at baseline. The reported prescription of pharmacological agents proven to reduce the risk of SCD (10) was also sub-optimal. Nevertheless, the study supports a novel solution to a major challenge encountered within daily practice, highlighting the potential utility of LGE-CMR in identifying patients most likely to benefit ICD therapy in addition to CRT-P. Whether the benefit of ICD therapy is influenced by the proximity of the LGE to the left ventricular lead is also an interesting area for future research. Pacing close to areas of replacement fibrosis could be pro-arrhythmic (11).

The DANISH study has reinforced the urgent need to move beyond left ventricular ejection fraction (LVEF) for the selection of patients with NIDCM for ICD therapy (1). It does not come as a surprise that a single measurement of LVEF does not adequately identify those patients with NIDCM who will benefit from ICDs. NIDCM is a heterogeneous disease affecting a diverse range of patients with a wide range of response to pharmacological therapies. The underlying aetiology is varied with multiple different triggers and a large number of gene-variants encoding a wide range of proteins labelled as pathogenic (12). Reduced ventricular function is only one of the many contributing factors involved in the generation of potentially fatal ventricular arrhythmias. It appears likely that ventricular arrhythmia is the result of many different processes interacting to form a ‘perfect storm’. Structural substrate such as replacement fibrosis, autonomic dysfunction, electrical instability

and genetic susceptibility all confer adverse risk. Other methods of identifying increased arrhythmic risk include microvolt T wave alternans and QRS fragmentation as measures of electrical instability and the detection of high-risk genetic variants such as Lamin A/C in the risk stratification of patients with NIDCM (13).

As LVEF falls and heart failure progresses, the risk of non-sudden death rises even more rapidly than the risk of SCD, resulting in the selection of many patients for ICD therapy based on current guidelines who succumb to non-sudden causes of death rather than sudden causes (*Figure 1*) (14). One, perhaps surprising aspect of the data from Leyva and colleagues is the apparent benefit of ICD therapy in a sub-group of patients with relatively advanced HF and an average age of 66 years. Sub-group analysis of the DANISH study, shows no benefit from ICD therapy in patients aged >59 years or in those with a NT-pro-BNP>1177pg/ml (1). This highlights the need for a model which accurately balances the risk of death from non-sudden causes against the risk of SCD to select those patients most likely to benefit from successful ICD therapies (*Figure 1).* It is likely that the incorporation of multiple variables in addition to LVEF will be required to accomplish such a goal.

One further concept that must be kept in mind is time! Landmark studies of ICDs suggest that they reduce mortality, in absolute terms, by about 1-2% annually. Patients with a higher overall risk obtain less benefit from an ICD either because they die from causes other than an arrhythmia or because the arrhythmia they die from heralds advanced disease from which they are soon to die. Patients must be exposed to a long period of risk in order to justify the implantation of an ICD, both in clinical and economic terms. Younger patients with few co-morbid conditions may be at a low annual risk of events but, if they avoid SCD, they might survive another 30 years. Their cumulative risk will be high. Of course, the duration of risk might not just be dictated by factors that shorten life-expectancy but also by treatments that correct the underlying problem and reduce the arrhythmic risk (15). Currently, the evidence

of a substantial benefit from ICDs is strong only for younger patients with no co-morbidities and 'mild' heart failure but a very low left ventricular ejection fraction, a rather select group.

In conclusion, these new data reinforce the potential utility of LGE-CMR in the selection of patients with NIDCM who may benefit from ICD therapy. In order to change current guidelines, randomised trials are needed to confirm the benefit of interventions, including ICD therapy, in patients on optimal pharmacological therapy with mid-wall fibrosis and/or additional features which confer a high-risk of SCD. CMR-Guide (NCT01918215) is currently underway with the aim of adding much-needed randomised evidence to the observational data currently available. Important additional questions for future research include whether it is possible to prevent the development of arrhythmic substrate, such as replacement fibrosis, through early disease detection and treatment and whether it is potentially reversible with the use of novel therapies such as anti-fibrotic agents.

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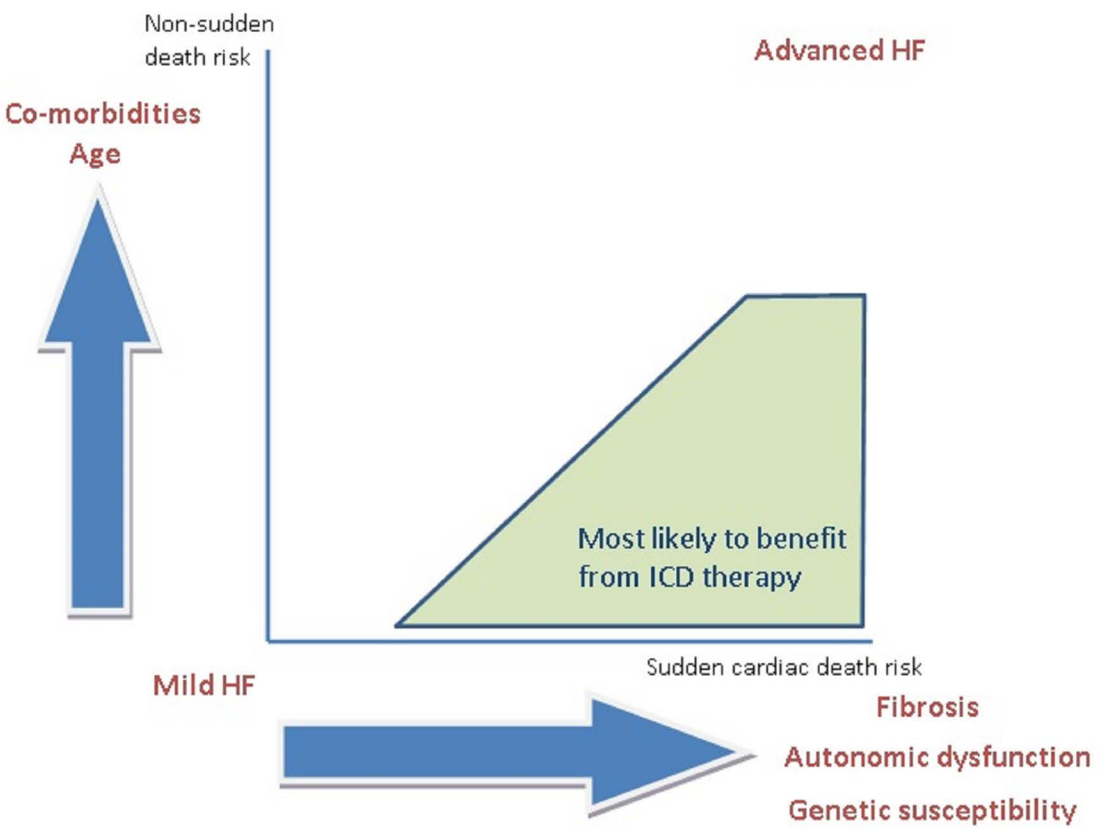
Figure 1. Selecting patients for implantable cardioverter defibrillators

Factors to consider during the selection of patients with non-ischemic cardiomyopathy for implantable cardioverter defibrillators for the primary prevention of sudden cardiac death.



Overall Risk = risk rate x time at risk

Younger patients **and** with mild heart failure **and** no serious co-morbidity:

- low SCD event rate but long exposure & low competing risks of non-sudden death; device longevity important

Older patient **or** severe heart failure **or** serious co-morbidity:

- high SCD event rate but short exposure & high competing risks of non-sudden death