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Arrhythmic risk stratification in non-ischemic dilated cardiomyopathy: Where do we stand after DANISH?

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A B S T R A C T

Publication of the DANISH randomized trial led to considerable debate, given that it demonstrated no survival benefit stemming from current implantable cardioverter-defibrillator (ICD) allocation criteria in patients with non-ischemic dilated cardiomyopathy (NIDCM). Consequently, a thorough reconsideration of our approach to sudden cardiac death (SCD)-risk stratification appears to be in order. NIDCM encompasses a wide spectrum of disease entities, often with differing arrhythmogenicity; however, in its kernel, is still defined by the fundamentals of electrophysiology that dictate that abnormal tissue, exhibiting altered electrophysiological properties is necessary for arrhythmogenesis, but not enough, given that formation of functional circuits is required. In this review article, we will attempt a presentation of the current status in SCD-risk stratification in NIDCM and introduce the concept of multifactorial tiered approach, bringing together non-invasive indices of arrhythmic potential and programmed ventricular stimulation, as an alternative approach, in order to finally delineate a potential basis for the design and realization of trials necessary to achieve a paradigm shift and improvement in NIDCM SCD-risk stratification.

Key words: Non-ischemic dilated cardiomyopathy, Sudden cardiac death risk stratification, Multifactorial approach, Programmed ventricular stimulation, Multitiered approach.

Introduction: Current status

Non-ischemic dilated cardiomyopathy (NIDCM) is currently defined as left ventricular (LV) dilatation and reduced contractility not attributable to loading conditions or coronary perfusion defects. Usually, echocardiography (or, alternatively, magnetic resonance imaging) will suffice to make the diagnosis, by detecting both reduced contractility (LV ejection fraction—EF $< 45\%$) and increased internal diameter (greater than two standard deviations higher than the average predicted value [1]). Alternatively, a limit of LV diameter $>117\%$ of the predicted value (Henry formula) has been used in the literature [2]. It is an either familial—in 10–35% of cases [3,4]—or sporadic form of progressive, and usually irreversible, cardiomyopathy with a prevalence and annual incidence estimated at 0.04% and 0.007%, respectively, that nevertheless accounts for most cases of cardiac transplantation, due to the younger age of patients. A multitude of heterogeneous genetic and non-genetic causes have been identified, often acting in tandem [1], including, but not limited to, sarcomeric and non-sarcomeric protein gene mutations, drugs and toxins (including ethanol abuse), infectious agents and inflammatory disorders, as well as endocrine and physiological (peripartum cardiomyopathy) alterations.

Sudden cardiac death [5] is the most feared complication of NIDCM and introduction of implantable cardioverter-defibrillators

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has significantly reduced its occurrence. Current guidelines [6] are focusing on LVEF and functional status to determine which patients, reasonably expected to survive for at least 1 year, should receive an ICD for the primary prevention of sudden death. In short, those at New York Heart Association (NYHA) functional class II–III and with an EF $\leq$ 35%, on optimal medical therapy for at least 3 months [6], or at NYHA class I and with an EF $\leq$ 30%, have a class I recommendation for an ICD insertion.

Guideline-shaping trials

None of the four landmark trials [7–10] (Table 1) established an ICD benefit over optimal medical therapy regarding survival/all-cause mortality. The NIDCM subgroup in the Sudden Cardiac Death in Heart Failure Trial—SCD-HeFT—receiving an ICD had a beneficial effect on survival of borderline statistical significance compared to those control groups receiving either placebo or amiodarone [8]. Although a favorable effect on *arrhythmic* mortality was noted in the DEFINITE (defibrillators in non-ischemic cardiomyopathy treatment evaluation) study (hazard ratio of ICD versus medical therapy 0.2, $p = 0.006$), there was no survival benefit ($p = 0.08$) [9]. To put the latter into perspective, the (much smaller) AMIOVIRT (amiodarone versus implantable cardioverter-defibrillator randomized trial) reported a trend toward reduced arrhythmic mortality with amiodarone versus ICD ($p = 0.1$) [10]. On the contrary, in the comparison of medical therapy, pacing, and defibrillation in heart failure (COMPANION) trial [11], where cardiac resynchronization therapy (CRT) devices were inserted, a statistically significant reduction in all-cause mortality, compared with pharmacologic therapy, was noted in NIDCM with the use of a defibrillation-capable device (CRT-D—hazard ratio 0.5, $p = 0.015$). There was no direct CRT-P/D group comparison, however, a post hoc analysis yielded a statistically significant difference regarding all-cause mortality [12]. Thus, current recommendations are based on a meta-analysis of the aforementioned trials [13], suggesting a survival benefit for the ICD group in the 31% range ($p = 0.002$).

The DANISH effect

Køber et al. critically reappraised established guidelines [6,14], more than a decade after the initial trials were published, by randomizing 1116 ESC-guidelines ICD-eligible NIDCM patients to receive either an ICD or usual, evidence based, care [15]. Strikingly, all-cause mortality was similar in both groups, although sudden cardiac death was halved (hazard ratio for ICD = 0.5, $p = 0.005$), implying a high competing (non-arrhythmic) mortality negating any ICD benefit (similar to how non-arrhythmic mortality offset ICD benefit in the DINAMIT and IRIS trials [16,17]). Accordingly, the only NIDCM subgroup demonstrating a benefit from guideline-guided ICD implantation was that of patients <59 years of age, with less comorbidities burden being a plausible interpretation. CRT-D did not demonstrate a benefit over CRT-P. Furthermore, incidence of sudden cardiac death (SCD) was only 1.46% per annum in the non-ICD receiving group, showing a further marked decrease as compared with previously reported rates [8].

A recent meta-analysis [12] pooled together data from DANISH with all previous randomized trials and reached the conclusion that an EF < 35% is associated with a survival benefit following ICD insertion but the effect did not persist in the case of CRT recipients, lending credibility to the notion of antiarrhythmic effects of resynchronization. Although providing some assurance for the continuing use of EF as SCD-risk stratifier, this meta-analysis pooled together data from studies whose cohorts were almost 20 years apart, with widely differing event rates [8,15] and even design.

Consequently, the aforementioned findings from a contemporary trial, incorporating all currently available pharmacological and device-based tools for treating NIDCM, cast doubt on currently accepted arrhythmic risk stratification and ICD implantation algorithms, raising the need for careful reconsideration and improvement of our approach.

Principles of arrhythmogenesis in NIDCM

The prevalent (~90%) underlying mechanism of arrhythmogenesis in NIDCM is, as in its ischemic counterpart, re-entry, triggered by the presence of patchy/diffuse fibrosis [18,19]. Cardiomyocyte bundle separation leads to non-uniform anisotropy regarding conduction velocity and induces a micro-ischemic condition, leading to action potential duration prolongation and reductions in conduction velocity. Furthermore, fibrotic tissue per se, initially thought of as electrically quiescent, has the potential to aggravate electrophysiological disarray by exhibiting electrical connectivity, impulse stimulation, and may act as sources or sinks of current [20,21]. With advancing remodeling and more pronounced dyssynchrony, alterations in the expression of junctophilin [22] and other structural proteins, lead to couplon [23] disintegration and consequently requirement for greater sarcolemmal calcium spikes in order to induce calcium-induced calcium release from the sarcoplasmic reticulum, generating the potential for early afterdepolarizations and triggered activity [24]. Stretch-activated channels may also come into play [25], aggravating the triggering effects of dyssynchrony.

Given that the ejection fraction usually is a surrogate for the extent of myocardial lesion, and that prerequisites for re-entry/triggered activity may be fulfilled in any diseased area, regardless of its size, it follows that the relationship between ejection fraction and arrhythmogenesis is probabilistic, rather than determinate [26]. Finally, formation or dissolution of functional circuits/arrhythmic foci is a *dynamic* process, in tandem with disease progression and tissue involvement, leading to differing arrhythmogenetic potential along the disease course. A relatively increased regional stability/low-voltage entropy is associated with functional circuit presence in ischemic cardiomyopathy [27] and the same principle is applicable to NIDCM.

The host of causative factors ultimately causing NIDCM inadvertently lead to different arrhythmogenesis mechanisms dominating each case as well as to divergent disease