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EDITORIAL

Preventing Sudden Death in Idiopathic Dilated Cardiomyopathy: A Difficult to Settle Issue

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Abstract

Risk stratification for sudden cardiac death in non-ischemic dilated cardiomyopathy remains a difficult and controversial issue. This is currently guided by left ventricular ejection fraction, severity of heart failure symptoms according to New York Heart Association classification, and the morphology and duration of the QRS complex. The results of a recent study stirred some initial controversy with regards to the utility of the implantable cardioverter defibrillator in these patients, however, a subsequent meta-analysis confirmed prior findings of the survival-prolonging benefit of device therapy. These issues are herein briefly reviewed. *Rhythmios* 2017;12(1):1-6.

Key Words: sudden cardiac death; dilated cardiomyopathy; implantable cardioverter defibrillator; ventricular tachyarrhythmias; heart failure; cardiac resynchronization therapy

Abbreviations: CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement; LV = left ventric-le(-ular); LVEF = LV ejection fraction; NYHA = New York Heart Association; QUALY = quality-adjusted

life-year; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia

Introduction

Risk stratification for sudden cardiac death (SCD) in non-ischemic dilated cardiomyopathy (DCM) remains a hard task for clinicians.¹ According to a meta-analysis to estimate the performance of 12 commonly reported risk stratification tests as predictors of arrhythmic events in patients with nonischemic DCM, comprising 45 studies enrolling 6,088 patients with a mean left ventricular ejection fraction (LVEF) of 30.6±11.4%, none of the autonomic tests (heart rate variability, heart rate turbulence, baroreflex sensitivity) were significant predictors of arrhythmic outcomes.¹ The best predictors of adverse outcomes included T-wave alternans, left ventricular end-diastolic diameter, electrophysiology study (EPS), signal-averaged ECG, LVEF, QRS duration, and non-sustained ventricular tachycardia (VT).

Current guidelines for implantable cardioverter defibrillator (ICD) implantation in patients with non-ischemic DCM rely solely on the imprecise parameters of depressed LVEF and NYHA functional class, criteria that are neither specific nor sensitive enough to adequately capture the highest risk patients.²⁻⁶ Cardiac resynchronization therapy (CRT) is further relied upon the morphology and duration of the QRS complex.⁷ Nevertheless, survival in patients with idiopathic DCM has

improved substantially over the last decades; DCM patients have a better outcome than previously reported when treated according to current guidelines, including optimal medical therapy and ICD implantation.⁸

Prior ICD Trials (Table 1)

The Cardiomyopathy Trial (*CAT*) (2002), comprising 104 patients with recent onset of DCM (≤ 9 months) and an LVEF $\leq 30\%$, randomly assigned to the implantation of an implantable cardioverter-defibrillator (ICD) (n=50) or control (n=54), did not provide evidence in favor of prophylactic ICD implantation in patients with DCM of recent onset and impaired LVEF.⁹

Also, according to the *AMIOVIRT* trial (2003), comprising 103 patients with DCM, LVEF $\leq 35\%$ and asymptomatic non-sustained VT, randomized to ICD (n=51) vs amiodarone (n=52), mortality and quality of life in patients with non-ischemic DCM and non-sustained VT treated with amiodarone or an ICD were not statistically different.¹⁰ There was a trend towards a more beneficial cost profile and improved arrhythmia-free survival with amiodarone therapy.

According to the Marburg Cardiomyopathy Study (MACAS), comprising 343 patients with idiopathic DCM, reduced LVEF and lack of beta-blocker use were important arrhythmia risk predictors in DCM, whereas signal-averaged ECG, baroreflex sensitivity, heart rate variability, and T-wave alternans were not helpful for arrhythmia risk stratification.¹¹

The *DEFINITE* trial enrolled 458 patients with non-ischemic DCM, a LVEF of $\leq 35\%$ (mean 21%), and premature ventricular complexes or nonsustained VT, randomized to standard therapy (n=229) or standard therapy plus ICD (n=229).¹² Over 29 ± 14 months, there was a nonsignificant reduction in total death rate with 28 deaths in the ICD group and 40 in the control group (hazard ratio, 0.65; $P=0.08$), with 2-year mortality rate of 14.1% in the standard-therapy group (annual mortality rate, 7 percent) and 7.9% in the ICD group. However, the risk of sudden death was significantly reduced, with 3 sudden deaths in the ICD group, as compared with 14 in the standard-therapy group (hazard ratio, 0.20; $P=0.006$).

Although the role of EPS in DCM patients has been limited and controversial,¹³⁻¹⁵ the *DEFINITE* trial and other investigators have indicated that inducibility of either VT or ventricular fibrillation (VF) may be associated with an increased likelihood of subsequent ICD therapy for VT or VF.^{16, 17} Specifically, according to the *DEFINITE* trial, at follow-up, 34.5% of the inducible group (10 of 29) experienced ICD therapy for VT or VF or arrhythmic death versus 12% (21 of 175) noninducible patients (hazard ratio = 2.60, $P = 0.014$).¹⁶

Based on all the above trials, considered underpowered to detect differences in survival, it was not clear whether ICD implantation was of real benefit to DCM patients with regards to a reduction of total mortality. This was only shown by a subsequent study, the *SCD-HeFT* trial, which randomized 2521 patients with NYHA class II (70%) or III (30%) CHF and a LVEF of $\leq 35\%$ to conventional heart failure therapy plus placebo (847 patients), conventional therapy plus amiodarone (845 patients), or conventional therapy plus an ICD (829 patients).¹⁸ However, this study was not a pure DCM trial, as it included both ischemic (52%) and non-ischemic (48%) heart failure patients with a median LVEF of 25%. Over a median follow-up of 45.5 months, there were 244 deaths (29%) in the placebo group, 240 (28%) in the amiodarone group, and 182 (22%) in the ICD group. As compared with placebo, amiodarone was associated with a similar risk of death (hazard ratio, 1.06; $P=0.53$) and ICD therapy was associated with a decreased risk of death of 23 percent (0.77; $P=0.007$) and an absolute decrease in mortality of 7.2% points after 5 years in the overall population. Results did not vary according to either ischemic or nonischemic causes of CHF, but they did vary according to the NYHA class, thus the conclusion was that in ischemic or non-ischemic patients with NYHA class II or III heart failure symptoms and LVEF of $\leq 35\%$, amiodarone has no favorable effect on survival, whereas ICD therapy reduces overall mortality by 23%.

Hence, based on the results of the *SCD-HeFT* trial, subsequent and recent guidelines have adopted the recommendation for ICD implantation for primary prevention of SCD in DCM patients with a LVEF $< 35\%$ and NYHA class II-III, despite ≥ 3 months of treatment with optimal pharmacological therapy who are expected to survive for > 1 year with good functional status.^{3, 5, 6}

A CRT trial (*COMPANION*) also evaluated ischemic and non-ischemic (41-46%) patients (total N=1520) with advanced heart failure (NYHA class III or IV) and a QRS interval of ≥ 120 ms, randomly assigned (1:2:2 ratio) to optimal pharmacologic therapy alone or in combination with CRT with either a pacemaker or an ICD.¹⁹ As compared with optimal therapy alone, CRT with a pacemaker decreased the risk of the primary end point (time to death from or hospitalization for any cause) by 34% (hazard ratio-HR, 0.81; $P=0.014$), as did CRT with an ICD by 40% (HR, 0.80; $P=0.01$). However, total mortality was reduced non-significantly by the pacemaker (24%; $P=0.059$), and significantly by the ICD (36%; $P=0.003$).

There was also a CRT trial employing only a CRT pacemaker without an ICD (*CARE-HF*) which included 813 (43-48% DCM) heart failure patients with NYHA class III or IV, LVEF $\leq 35\%$ and cardiac dyssynchrony, who were randomized to medical therapy alone or with

CRT.²⁰ Over a mean of 29.4 months, the primary end point (time to death from any cause or an unplanned hospitalization) was reached in 39% in the CRT group vs 55% in the medical-therapy group (HR, 0.63; $P < 0.001$). Mortality was 20% in the CRT group compared with 30% in the medical group (hazard ratio 0.64; $P < 0.002$).

Recent guidelines were also based on a pooled analysis of 5 primary prevention trials (1854 patients with non-ischemic DCM) demonstrating a statistically significant 31% reduction in all-cause mortality for ICD relative to medical therapy (RR 0.69, $P = 0.002$).²¹ Mortality reduction remained significant even after elimination of the CRT-D trial (RR 0.74, $P = 0.02$). Indications for ICD and CRT device implantation in patients with DCM are summarized in Table 2.

Current Data

Doubt on the efficacy of ICD in prolonging total survival in DCM patients was recently cast by the **DANISH** trial, which randomized 1116 patients with symptomatic systolic heart failure (LVEF $\leq 35\%$) to an ICD ($n=556$) or usual clinical care ($n=560$; control group). In both groups, 58% of the patients received CRT.²² Over a median follow-up period of 67.6 months, total mortality rate was 21.6% in the ICD group and 23.4% in the control group (hazard ratio, 0.87; $P = 0.28$). Nevertheless, the SCD rate was 4.3% in the ICD group and 8.2% in the control group (hazard ratio, 0.50; $P = 0.005$). As the accompanying editorial of this trial indicates,²³ the finding of no significant benefit in overall mortality in the DANISH trial was a result of the low risk of SCD among the patients included in the trial. This low risk reflects the fact that DCM patients have lower rates of SCD and total mortality compared to ischemic patients, and also the effect of optimal medical therapy that these patients were receiving, including a large percentage of patients (58%) also fitted with a CRT device.

Most recently, the DANISH trial was included in a new meta-analysis, which showed that the benefit of ICD implantation in DCM patients still remains solid.²⁴ Specifically, this meta-analysis comprised 6 randomized controlled trials, enrolling 2,970 patients with DCM, that studied the efficacy of ICD for primary prevention. Pooled analysis of these 6 trials (including those with CRT-D) demonstrated a statistically significant 23% risk reduction in all-cause mortality in favor of ICD therapy (HR 0.77). In addition, a separate analysis of trials that assessed ICD plus optimal therapy vs optimal therapy alone (after exclusion of trials that involved patients with CRT-D), a statistically significant 24% reduction was found in all-cause mortality with ICD (HR 0.76).

As a considerable percentage of patients diagnosed with DCM, estimated at ~30%, may show partial or full

recovery of the LV function with medical therapy, with consequent favorable prognosis, a minimal 3-month period of medical therapy has been suggested to precede formal evaluation and recommendation for ICD implantation.²⁵ Furthermore, LV functional recovery may continue well beyond this 3-month period, obviating the need for device implantation. LGE cardiac magnetic resonance imaging (CMR) has been suggested as a tool to evaluate for the presence or absence of myocardial fibrosis and the likelihood of reverse remodeling, and also follow DCM patients for longer periods of time under medical treatment before a decision is made for ICD implantation.²⁶ One should also be conservative for DCM patients with a potentially reversible etiology, such as alcohol-related DCM, peripartum cardiomyopathy, or possible myocarditis. A major drawback of this ICD deferring approach is the unknown risk of SCD lurking during this waiting period.

Indeed, during the early period of ICD approval for primary prevention in DCM patients, a 9-month time restriction was applied by regulatory authorities based on earlier studies.²⁷ However, this did not pan out in subsequent studies,²⁷ and this time qualifier is not reflected in the current American guidelines, which state that “ICD therapy should be considered in such patients provided that a reversible cause of transient LV function has been excluded and their response to optimal medical therapy has been assessed. The optimal time required for this assessment is uncertain...use of a time qualifier relative to the time since diagnosis of a nonischemic DCM may not reliably discriminate patients at high risk for SCD in this selected population”.^{2,3}

However, according to current ESC guidelines, implantation of an ICD for primary prevention is not recommended within the first 3 months after initial diagnosis of non-ischemic CM.⁶ Specifically, the 2016 ESC heart failure guidelines state that “an ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic heart failure (NYHA Class II–III), and an LVEF $\leq 35\%$ despite ≥ 3 months of optimal medical therapy, provided they are expected to survive substantially longer than 1 year with good functional status”.⁶ The expectation is that recovery of left ventricular function may occur during this period. If not, implantation of an ICD for primary prevention can be useful following this 3-month waiting period after initial diagnosis of non-ischemic CM. To circumvent such restrictions, an HRS/ACC/AHA Expert Consensus document recommends ICD implantation in the following situations:²⁸ patients < 9 months from the initial diagnosis of DCM who require nonelective permanent pacing, who would meet primary prevention criteria for implantation of

an ICD, and recovery of LV function is uncertain or not expected; patients <9 months from the initial diagnosis of non-ischemic CM with syncope that is thought to be due to a ventricular tachyarrhythmia (by clinical history or documented non-sustained VT); and patients <9 months from the initial diagnosis of non-ischemic CM who have been listed for heart transplant or implanted with a left ventricular assist device. Of course, ICD implantation for secondary prevention is recommended for all patients with DCM who present with sustained (or hemodynamically significant) ventricular tachyarrhythmia, regardless of the time of diagnosis of the disease.

Opposing the strategy of the waiting period and deferring ICD implantation comes from studies indicating that patients with DCM present a significant risk of major arrhythmic events in the first phase of the disease.²⁹ Among 952 patients with DCM included in the Heart Muscle Disease Registry of Trieste, 20 patients (2.1%) experienced SCD/malignant ventricular arrhythmias within the first 6 months after enrollment.²⁹ At baseline, these patients showed a worse functional class (NYHA class III-IV 42% vs 22%, $p = 0.038$), a longer QRS complex duration (127 ± 41 ms vs 108 ± 33 ms; $p = 0.013$) and a larger indexed LV end-systolic volume (82 ± 49 ml/m² vs 67 ± 34 ml/m²; $p = 0.049$). Beta-blockers were less tolerated (59% vs. 83%; $p = 0.008$), mostly due to hemodynamic intolerance. At multivariate analysis, LV end-diastolic volume index (odds ratio -OR: 1.012; $p = 0.043$) and QRS complex duration (OR: 1.017; $p = 0.015$) were independently associated with early occurrence of arrhythmias, whereas beta-blockers demonstrated a protective effect (OR: 0.169; $p = 0.006$). Another study indicated that patients with nonischemic DCM experienced equivalent occurrences of treated and potentially lethal arrhythmias irrespective of diagnosis duration.²⁷ Others suggest ICD implantation early after the initial diagnosis of DCM only in patients with positive LGE or patients with non-sustained VT.³⁰ In the remainder, the wearable cardioverter defibrillator may play a role as a bridge to ICD decision.

According to an American Appropriate Use Criteria report,³¹ a most appropriate indication for ICD implantation for primary prevention of SCD in non-ischemic DCM patients includes patients with LVEF $\leq 35\%$, NYHA class I-III who have been on optimal therapy for at least 3 months. A “may be appropriate” indication comprises patients with a newly diagnosed ischemic DCM with narrow QRS, an LVEF $\leq 30\%$ and class II-III symptoms. Also, appropriate indications for ICD implantation comprise patients with LVEF $\leq 35\%$ and specific types of cardiomyopathies, such as sarcoid heart disease, myotonic dystrophy or Chagas disease, or

peripartum cardiomyopathy that persists >3 months post-partum, or giant cell myocarditis of any LVEF. For CRT-D implantation, appropriate patients would be considered those with non-ischemic DCM, sinus rhythm, LVEF $\leq 35\%$, QRS ≥ 150 ms, LBBB and NYHA II/III/ ambulatory IV; or non-LBBB, NYHA III / ambulatory IV; or QRS 120-149 ms, LBBB and NYHA class II, III/ambulatory IV.

With regards to cost-effectiveness, a recent analysis documented the cost-efficacy of implantable cardiac devices in patients with systolic heart failure, with CRT-D remaining the most cost-effective choice in a much wider group.³² Specifically, according to data from 13 randomized trials, at a threshold of £30,000 per QALY gained, CRT-D was cost-effective in 10 of the 24 subgroups including all LBBB morphology patients with NYHA class I-III. ICD was cost-effective for all non-NYHA IV patients with QRS duration <120 ms and for NYHA I-II non-LBBB morphology patients with QRS duration 120-149 ms. CRT-P was also cost-effective in all NYHA III-IV patients with QRS duration >120 ms. Device therapy is cost-effective in most patient groups with LBBB at a threshold of £20,000 per QALY gained.

According to a systematic review of clinical trials of non-ischemic DCM and the use of ICDs and cardiac magnetic resonance imaging with late gadolinium enhancement (LGE) for risk stratification, LGE can identify patients with non-ischemic DCM who are at high risk for SCD and may enable optimized patient selection for ICD placement.²⁶ On the other hand, the absence of LGE may reduce the need for ICD implantation in patients with NIDM who are at low risk for future VF/VT or SCD.

Similar findings were recently confirmed by a new systematic review and meta-analysis of 29 studies comprising 2,948 patients with DCM and LVEF 20-43%, stratified by the presence or absence of LGE.³³ LGE was significantly associated with the arrhythmic endpoint (ventricular arrhythmias or SCD) both in the overall population (odds ratio: 4.3; $p < 0.001$) and when including only those studies that performed multivariate analysis (hazard ratio: 6.7; $p < 0.001$). The association between LGE and the arrhythmic endpoint remained significant among studies with mean LVEF >35% (odds ratio-OR: 5.2; $p < 0.001$) and was maximal in studies that included only patients with primary prevention ICDs (OR: 7.8; $p = 0.008$). The authors concluded that LGE could be a powerful tool to improve risk stratification for SCD in patients with DCM, while 2 major questions need to be addressed in future studies: whether patients with LGE could benefit from primary prevention ICDs irrespective of their LVEF, while patients without LGE might not need preventive ICDs despite having severe LV dysfunction.

Table 1. Randomized Controlled Trials of Primary Prevention ICD Therapy in Patients with DCM

Study/year	Pts	Inclusion Criteria	Results
CAT / 2002 ⁹	104	DCM ≤9 mos LVEF ≤30% Randomized to ICD or no ICD	No difference in mortality between groups at up to 4 y of follow-up
AMIOVIRT/2003 ¹⁰	103	DCM Asymptomatic NSVT LVEF ≤35% Randomized to either amiodarone or ICD	No difference between groups in overall mortality or quality of life. Trend to improved arrhythmia-free survival & lower cost in amio gp
DEFINITE/ 2004 ¹²	458	LVEF ≤35% PVCs or NSVT Randomized to ICD + medical therapy or medical therapy alone	Significant ↓ in sudden death in the ICD group (hazard ratio 0.2) & trend to ↓ in all-cause mortality
COMPANION / 2004 ¹⁹	1520	NYHA III-IV Ischemic or nonischemic QRS ≥ 120 ms Randomized to optimal pharmacological therapy alone, or in combination with CRT-P or CRT-D (1:2:2 ratio)	c/t optimal drug therapy alone, CRT-D (& CRT-P) ↓time to death or hospitalization for any cause. CRT-D (but not CRT-P) also ↓ overall mortality
SCD-HeFT/ 2005 ¹⁸	2521	NYHA II-III LVEF ≤35% 52% ischemic, 48% nonischemic cause of LV impairment Randomized to (i) conventional therapy + placebo, (ii) conventional therapy + amiodarone or (iii) conservative therapy + ICD	ICD therapy was a/w 23% ↓ in risk of death and an absolute mortality decrease of 7.2% after 5 years (results did not vary according to cause of CM). No difference between amiodarone and placebo for risk of death.
DANISH / 2016 ²²	1116	NYHA class II - IV LVEF ≤35% NT-proBNP >200 pg/ml ICD (n=556) vs usual clinical care (n=560)	At 67.6 mos: 120 deaths (21.6%) in ICD gp & 131 (23.4%) in control gp (HR, 0.87; P = NS). SCD in 24 pts (4.3%) in ICD gp & in 46 pts (8.2%) in control gp (HR, 0.50; P=0.005)

a/w = associated with; CM = cardiomyopathy; CRT = cardiac resynchronization therapy; c/t = compared to; DCM = dilated cardiomyopathy; gp = group; HR = hazard ratio; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; mos = months; NSVT = non-sustained ventricular tachycardia; NYHA = New York Heart Association; pts = patients; PVCs = premature ventricular contractions; SCD = sudden cardiac death

Table 2. Current Guidelines for ICD/CRT Implantation in Patients with DCM

Guidelines	Indication	Class / LOE	Device	Comments
ACC/AHA/HRS 2008/2012 ^{2,3}	DCM, LVEF ≤35%, NYHA II-III	I / B	ICD	
	DCM, LVEF ≤35%, SUO	Ila / C	ICD	
	DCM, LVEF ≤35%, NYHA I	Iib / C	ICD	
	LVEF ≤35%, LBBB, NYHA II-IV, QRS ≥ 150 ms	<ul style="list-style-type: none"> I/A (SR) (NYHA III-IV) I/B (SR) (NYHA II) Ila / B (AF) Ila / A (non-LBBB / SR) Iib/B (non-LBBB, NYHA II) Ila/B (non-LBBB / NYHA III-IV / AF) 	CRT-P / CRT-D	
	LVEF ≤35%, LBBB, NYHA II-IV, QRS 120-149 ms	Ila / B (SR) Iib / B (non-LBBB, NYHA III-IV)	CRT-P / CRT-D	
ESC 2013/2015/2016 ^{4,6}	LVEF ≤35% NYHA II-III ≥3 mos OMT	I / B	ICD	
	LVEF ≤35%, SR, LBBB, QRS ≥150 ms	I / A I/B (QRS 130-149 ms)	CRT	
NICE 2014 [*]	LVEF ≤35%, NYHA I-III, QRS < 120 ms		ICD	NYHA IV: ICD & CRT not indicated
	NYHA I-III, QRS 120-149, non-LBBB • NYHA I, LBBB		ICD	NYHA IV: CRT-P
	NYHA II-III, QRS 120-149 ms, LBBB		CRT-D	NYHA I: ICD NYHA IV: CRT-P
	NYHA I-III, QRS ≥150 ms		CRT-D	NYHA IV: CRT-P

* <file:///D:/SCD/CM/NICE%20guidelines%202014.pdf>

AF = atrial fibrillation; CRT = cardiac resynchronization therapy; CRT-D = CRT-defibrillator; CRT-P = CRT-pacemaker; DCM = dilated cardiomyopathy; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LOE = level of evidence; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OMT = optimal medical therapy; SR = sinus rhythm; SUO = syncope of unknown origin

Conclusion

Risk stratification for SCD in non-ischemic DCM remains a difficult task. Device (ICD or CRT) implantation that effectively prevents SCD in this population is currently guided by left ventricular ejection fraction, severity of heart failure symptoms according to NYHA classification, and the morphology and duration of the QRS complex. The results of a recent study stirred some initial controversy with regards to the utility of the ICD in these patients, however, a subsequent meta-analysis confirmed prior findings of the survival-prolonging benefit

conferred by device therapy. Newer findings with use of LGE CMR detecting myocardial fibrosis are encouraging in risk stratifying patients in an attempt to circumvent the limitations of relying mainly on a LVEF $\leq 35\%$ which is currently considered the gold-standard approach.

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