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Defibrillator and non-ischaemic dilated cardiomyopathy: a never ending story

Francesco Notaristefano[1] and Giuseppe Ambrosio[2]

[1]*Cardiology Unit, Azienda Ospedaliera Universitaria di Perugia, Italy; and*
[2]*Department of Cardiology and Cardiovascular Pathophysiology, Azienda Ospedaliera Universitaria di Perugia, Italy*

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Dilated cardiomyopathy (DCM) carries an increased risk of ventricular arrhythmias and sudden cardiac death (SCD), although lower than ischaemic heart disease (IHD). The understanding of the impact of IHD on SCD derives from post-mortem studies, in which 50–80% of the cases had significant coronary artery disease. Besides *channelopathies* and other arrhythmogenic syndromes, DCM is the cause of SCD in 10–20% of the cases, thus being responsible for a considerable portion of the fatalities.[1] In the DEFINITE (Defibrillators in Non-Ischaemic Cardiomyopathy Treatment Evaluation) study, implantable cardioverter defibrillator (ICD) implant reduced significantly the risk of SCD over conventional medical therapy. In this study more than 80% of the patients were on treatment with ACE (*Angiotensin-Converting Enzyme*) inhibitors and beta-blockers, and this regimen could have contributed to decreasing mortality also in the control group, thus mitigating the perceived benefit of ICD on overall mortality. More recently the DANISH[2] (*Danish* ICD *Study* in Patients with Dilated Cardiomyopathy) study, specifically evaluated the efficacy of ICD vs. optimal medical therapy in primary prevention of 1116 patients with DCM (76% idiopathic), the implant of ICD did not affect a reduction of all-cause mortality (21.6% vs. 23.4%, P = not significant), but decreased the incidence of SCD by 50% (4.3% vs. 8.2%, $P = 0.005$). The results of the study should be interpreted considering that more than 90% of the patients were treated with ACE inhibitors and beta-blockers, that more than 50% of the patients received mineralocorticoid receptor antagonists, and that more than half of them received cardiac resynchronization therapy (CRT). It is well established that both pharmacologic treatment and CRT decrease arrhythmic and cardiovascular deaths, thus limiting ICD impact on all-cause mortality.[3] The lack of all-cause mortality reduction reported by the DANISH study emphasized the scarce diagnostic accuracy of left ventricular ejection fraction (LVEF) in predicting the risk of SCD in heart failure patients. The progressive improvement of the therapeutic regimens increased the proportion of non-cardiovascular related deaths in patients with heart failure, as attested by a dramatic reduction of the rate of appropriate shocks in randomized clinical trials (from 6% per year reported by the DEFINITE trial, to 2.1% per year of the DANISH study[2,4]). Furthermore, the incidence of inappropriate shocks is not negligible, despite the technological improvements of the devices, (10% DEFINITE; 10% SCD-HeFT, 5.9% DANISH), so that the choice as to whether to recommend a device implant is ever more subtle.

The limited sensibility of the LVEF in identifying patients at risk for SCD, is evident also from the analysis of the data of the sudden death registries (Oregon e Maastricht Registries), in which 80% of the victims of sudden death had LVEF $>35\%$, thus not candidate for ICD implant.[5,6] The integration of the clinical characteristics with the stage of the cardiac condition could identify patients at higher risk for non-arrhythmic deaths; nonetheless further refinements, even in this selected group of patients are required for a rational selection of patients at high risk for arrhythmias.

Several electrophysiologic parameters have been considered over the years without reaching definitive conclusions. The presence of fibrosis in DCM appears to be a reliable factor for selecting patients at higher risk for ventricular arrhythmias.

Cardiac magnetic resonance reveals the presence of fibrosis in 30–50% of patients with DCM, late gadolinium enhancement (LGE) identifies replacement fibrosis, which is a dense and circumscribed scar replacing necrotic myocytes. Interstitial fibrosis can be missed by LGE but is detected by advanced T1 mapping techniques before and after gadolinium infusion. By adding the presence of

Table 1 Randomized trials evaluating the role of implantable defibrillator in primary prevention of patients with non-ischaemic dilated cardiomyopathy

Trials	Inclusion criteria	Groups	Follow-up (months)	All-causes mortality	Sudden cardiac death
CAT[a] ($N = 104$)	EF $\leq$30% NYHA II–III	ICD vs. OMT	66	Non-significant reduction	NA
AMIOVIRT[a] ($N = 103$)	EF $\leq$35% NYHA I–III NSVT	ICD vs. Amiodarone	24	Non-significant reduction	NA
DEFINITE ($N = 458$)	EF $<$36% NYHA I–III PVCs/NSVT	ICD vs. OMT	29	Non-significant reduction	80% Reduction
SCD-HeFT ($N = 1211$) (solo DCM)	EF $\leq$35% NYHA II–III	ICD vs. OMT vs. Amiodarone	46	Non-significant reduction	NA
DANISH ($N = 1116$)	EF $\leq$35% NYHA I–III; IV (CRT) NT proBNP $>$200 pg/mL	ICD vs. OMT (including CRT)	68	Non-significant reduction	50% Reduction

CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; EF, ejection fraction; ICD, implantable cardioverter defibrillator; NA, not applicable; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; OMT, optimal medical therapy; PVC, premature ventricular contraction.

[a]Studies terminated ahead of time.

fibrosis to the LVEF allowed to correctly reclassify 29% of the patients for the risk of SCD/aborted SCD.[7] During the last few years significant progress has been made in the genetic characterization of DCM. Unfortunately genetic characterization can be utilized for stratification of the risk of SCD in a limited number of cases.

It is well established that ICD decreases mortality in patients with reduced LVEF after myocardial infarction. This benefit is less evident in patients with DCM (*Table 1*). The lack of reduction of all-cause mortality in patients with severe left ventricular systolic dysfunction could be explained by the decreased incidence of SCD brought by the modern therapy for heart failure. The LVEF, by itself, is, then, not accurate enough in stratifying the arrhythmic risk.

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