**Use of implantable cardioverter defibrillator in nonischaemic cardiomyopathy: a U-turn?**

# Use of Implantable Cardioverter Defibrillator in Nonischaemic Cardiomyopathy: A U-Turn?

Fiorenzo Gaita, Davide Castagno, Matteo Anselmino

Division of Cardiology, "Città della Salute e della Scienza" Hospital, Turin, Italy
Department of Medical Sciences, University of Turin, Turin, Italy

Keywords: Implantable Cardioverter Defibrillator, Nonischaemic Cardiomyopathy, Heart Failure, Sudden Cardiac Death, Primary Prevention

**Abstract**

Use of implantable cardioverter defibrillator (ICD) in primary prevention has been shown to reduce the risk of death among patients with severe left ventricular systolic dysfunction (LVSD) due to ischaemic cardiomyopathy. However, among patients with heart failure (HF) and severe LVSD who do not have coronary artery disease, the evidence of ICD benefit is less robust. As a matter of fact data supporting the use of ICD in such patients are limited to few randomized controlled clinical trials that included a small number of patients, subgroup analysis of larger trials or meta-analysis. Recently, in the *Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality (DANISH)* trial, which included 1116 patients with symptomatic nonischaemic HF and severe LVSD, ICD therapy did not show a significant reduction of the overall mortality primary endpoint raising doubts about its use in this category of patients. Low mortality rates and use of a better background HF treatment as compared with prior trials may partly explain the results of the DANISH Study. Anyway, these findings underline the importance of careful selection of candidates receiving an ICD for sudden cardiac death primary prevention.

**Text.**

According to the World Health Organization sudden cardiac death (SCD) is defined as a natural, non-traumatic, unexpected death characterized by a sudden loss of consciousness and subsequent decease within one hour of symptoms onset [1]. This temporal limit is conventionally extended to 24 hours when death occurs unwitnessed [1]. It has been estimated that 30 to 50% of SCDs occur in patients with known severe LVSD independently from underlying aetiology (ischaemic vs. nonischaemic) [2,3]. Among patients with HF and severe LVSD, the percentage of deaths attributable to SCD is higher in subjects with less severe degree of symptoms (64% in NYHA functional class II patients enrolled in the MERIT-HF trial) and decreases with the worsening of HF (33% in NYHA functional class IV patients enrolled in the MERIT-HF trial) [4]. Ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) degenerating in VF are the commonest malignant arrhythmias causing SCD in patients with HF or dilated cardiomyopathy and severe LVSD. However, the occurrence of pathological bradiarrhythmias and of pulseless electrical activity can determine SCD in a significant proportion of patients with advanced HF [5]. From a pathophysiological standpoint, the occurrence of SCD in patients with HF and severe LVSD can be explained by the three determinants of arrhythmogenesis proposed by Philippe Coumel at the end of the last century [6]. The presence of remodelled, often hypertrophied myocardial tissue, mixed with fibrotic area of varying extension may act as substrate for the onset of arrhythmic events under the effect of pro-arrhythmic triggers such as premature ventricular contractions (isolated or repetitive), electrolyte abnormalities and haemodynamic and/or ischaemic disorders which are extremely frequent in this category of patients. Moreover, the imbalance between the sympathetic and parasympathetic nervous systems (with the hyperactivation of the first and the suppression of the latter) may negatively modulate these interactions further facilitating the onset of malignant and life-threatening arrhythmic events (Figure 1).

The use of antiarrhythmic drugs for SCD prevention in patients with HF and severe LVSD is of limited utility. Several studies have demonstrated that class I antiarrhythmic drugs can increase mortality whereas class III antiarrhythmic drugs, although safe, are no effective in reducing the risk of death. Therefore, the implantable cardioverter defibrillator (ICD), which was developed in the seventies by Mirowski and Mower

and tested in human for the first time in February 1980, has progressively become established for SCD prevention among patients with HF and LVSD. The small size of modern ICDs makes the subcutaneous, subclavicular implant of such devices, including one or more transvenous leads, feasible and relatively safe. Besides antibradycardia pacing, the ICD can detect and treat malignant tachyarrhythmias by means of overdrive pacing, electrical cardioversion and defibrillation. Initially, the impact of ICD on mortality has been shown in randomized controlled clinical trials enrolling SCD survivors (secondary prevention trials) and comparing the clinical efficacy of ICD with antiarrhythmic drugs (e.g. *Antiarrhythmics Versus Implantable Defibrillators [AVID]*, *Cardiac Arrest Survivor Hamburg [CASH]* and the *Canadian Implantable Defibrillator Study [CIDS]*)[7]. The vast majority of patients enrolled in these studies had an underlying ischaemic cardiomyopathy. More recently, randomized controlled clinical trials enrolled patients without prior ventricular arrhythmias deemed at risk for SCD because of severe LVSD and symptoms of HF (primary prevention trials). Several studies like the *Multicenter Automatic Defibrillator Implantation Trial (MADIT-I)*, the *Multicenter Unsustained Tachycardia Trial (MUSTT)* and the *Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II)* have shown the efficacy of ICD in reducing all-cause mortality among patients with previous myocardial infarction and severe LVSD demonstrating a relative risk reduction ranging from 28% to 59% [8]. Although patients with nonischaemic cardiomyopathy carry an annual SCD risk of 4% [9], the efficacy of ICD for SCD primary prevention seems inferior in these patients as compared with those with an underlying ischaemic cardiomyopathy [10].

Five prospective randomized controlled clinical trials have tested the use of ICD in primary prevention of SCD among patients with nonischaemic cardiomyopathy so far (main features of these studies are summarized in Table 1). The first studies which included approximately 200 patients with nonischaemic cardiomyopathy (i.e. the *Cardiomyopathy Trial [CAT]* and the *Amiodarone Versus Implantable Cardioverter Defibrillator Trial [AMIOVIRT]*) did not show significant benefit for ICD therapy on the primary endpoint of all-cause mortality [11,12]. Until 2016, the larger prospective randomized study exclusively enrolling patients with nonischaemic cardiomyopathy was the *Defibrillator in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Trial* which randomized 458 patients with severe LVSD (i.e. left ventricular ejection

fraction ≤35%) and prior nonsustained ventricular tachycardia to ICD implantation and medical therapy vs. optimized medical therapy (approximately 85% of patients were taking an ACE-inhibitor and a beta-blocker) [13]. Over a mean follow-up of 2.5 years there was a trend toward reduction in the primary endpoint of all-cause mortality in patients treated with ICD (two years all-cause mortality 8% *vs.* 14% in ICD recipients and patients treated with optimal medical therapy respectively, p=0.08).

Other data in support of the use of ICD for primary prevention of SCD among patients with nonischaemic cardiomyopathy derive from the *Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)* which enrolled patients with both ischaemic (52%) and nonischaemic (48%) cardiomyopathy and severe LVSD [14]. The design feature of this trial envisaged three-arms randomization: placebo group *vs.* amiodarone group *vs.* ICD group. During a median follow-up of 45.5 months, amiodarone therapy showed no survival benefit over placebo (HR = 1.06, 97.5% CI 0.86-1.30, p = 0.53) whereas a significant reduction was observed in patients receiving an ICD (HR = 0.77, 97.5% CI 0.62-0.96, p = 0.007) with a significant absolute risk reduction of 7.2% as compared with control. As a pre-specified subgroup analysis the benefit of ICD was tested in patients with nonischaemic cardiomyopathy separately: all-cause mortality reduction was similar to that observed in the overall study although not reaching statistical significance (HR = 0.73, 97.5% CI 0.50 – 1.07, p =0.06).

On the basis of these data the recent guidelines on diagnosis and treatment of patients with HF issued by the European Society of Cardiology suggest ICD therapy for primary prevention of SCD in symptomatic (functional class NYHA II-III) patients with nonischaemic cardiomyopathy, severe LVSD (i.e. left ventricular ejection fraction ≤35%) despite ≥ three months of optimal medical therapy with a Class I recommendation, level of evidence B (whereas for patients with ischaemic cardiomyopathy the level of evidence is A) [15].

However, these recommendations should be revisited in the light of the new findings from the *Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality (DANISH)* which were presented at the Congress of the European Society of Cardiology in August 2016 [16]. This study enrolled 1116 patients with symptomatic HF and severe LVSD (i.e. left ventricular ejection fraction ≤35%) not caused by ischaemic heart disease (which was ruled out in the vast majority of patients

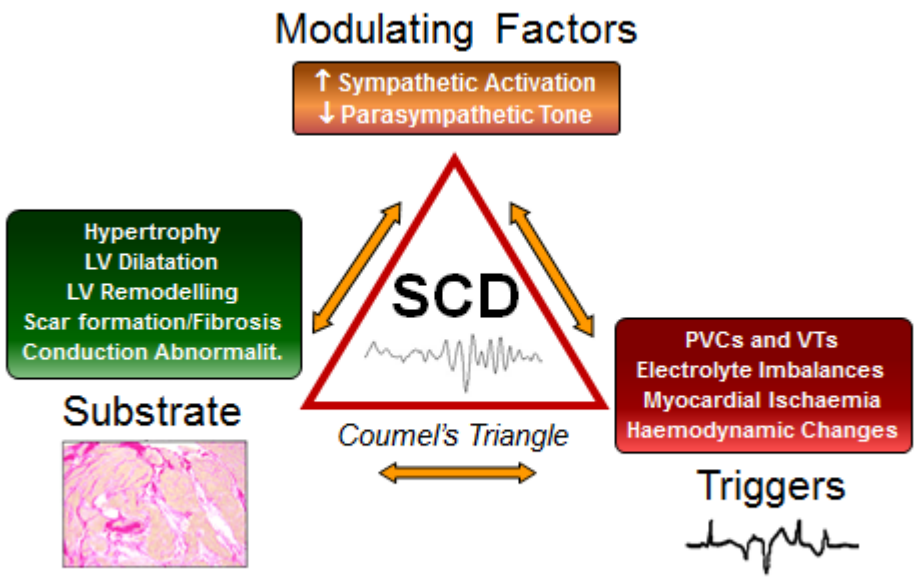
by means of coronary angiography, coronary CT or single-photon emission CT). Demonstration of ventricular premature contractions at the time of enrolment or history of nonsustained ventricular tachycardia, which have an uncertain and inconstant prognostic impact (see Figure 2), were not amongst the inclusion criteria in contrast to prior studies (i.e. AMIOVIRT and DEFINITE). Patients were randomized 1:1 to ICD with guideline-directed optimal medical therapy or medical therapy alone. There were no significant differences between the two study arms at the time of randomization and both groups were optimally treated from a pharmacological (97% of patients were on an ACE-inhibitor or an ARB, 92% on a beta-blocker and 58% on a mineralcorticoid receptor antagonist) and non-pharmacological (58% of patients had a cardiac resynchronization therapy device) standpoint. Over a median follow-up of 5.6 years, there were no significant differences in the primary endpoint of all-cause mortality between ICD recipients and the control group (120 deaths [21.6%] vs. 131 deaths [23.4%] in the ICD and in the control group respectively, HR = 0.87, 95% CI 0.68 – 1.12, p = 0.28, 1.8% absolute risk reduction). Similarly, taking into account the secondary endpoint of cardiovascular mortality, there were no significant differences between the two arms (77 deaths [13.8%] vs. 95 deaths [17.0%], HR 0.77, 95% CI 0.57 – 1.05, p = 0.10, 3.2% absolute risk reduction) whereas a significant reduction in SCD occurrence was observed among ICD recipients as compared with control group (24 SCDs [4.3%] vs. 46 SCDs [8.2%], HR 0.50, 95% CI 0.31-0.82, p = 0.005, 3.9% absolute risk reduction). Subgroup analysis did not show significant differences in the primary outcome across pre-specified subgroups with the exception of age. More in detail, among patients aged 68 years or less receiving an ICD, a significant reduction in all-cause mortality was observed as compared with the control group (HR = 0.64, 95% CI 0.45-0.90). When interpreting the findings from the DANISH study a few remarks must be made: 1) compared with prior primary prevention ICD trials, observed mortality rates were significantly lower, possibly reflecting the improvements in HF medical therapy and the extensive use of cardiac resynchronization therapy which was not available when older primary prevention trials were conducted; in addition, the results from DANISH study suggest that patients with HF due to nonischaemic causes receiving optimized therapy have a much better prognosis than commonly perceived;

2) considering that the event rates was lower than expected, it is likely that the DANISH sample size was insufficient to demonstrate an ICD benefit on overall mortality; however, patients enrolled in clinical trials are usually younger and have less comorbidities as compared with patients encountered in everyday clinical practice: therefore the risk of death for cardiovascular vs. noncardiovascular causes (on which the ICD has no effect) is greater in the context of a clinical trial possibly favouring an overestimation of ICD efficacy; 3) whenever an ICD is indicated for primary prevention, the existence of competing causes of death should always be considered, especially among the elderly; in other words, both frailty and the high number of comorbidities typical of such group of patients might increase the risk of death for noncardiovascular causes hampering ICD efficacy.

The findings of the DANISH trial have been recently included in a meta-analysis that grouped all the studies testing ICD efficacy in SCD primary prevention among patients with HF and nonischaemic aetiology [17]. Overall, among the 2970 patients included, ICD was associated with a significant all-cause mortality relative risk reduction as compared with medical therapy (HR = 0.76, 95% CI 0.62-0.94). The authors of the same study, by combining the results of the DANISH trial and of the *Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Study*[18], speculated on the hypothesis that ICD may be effective in reducing mortality among candidates to cardiac resynchronization therapy.

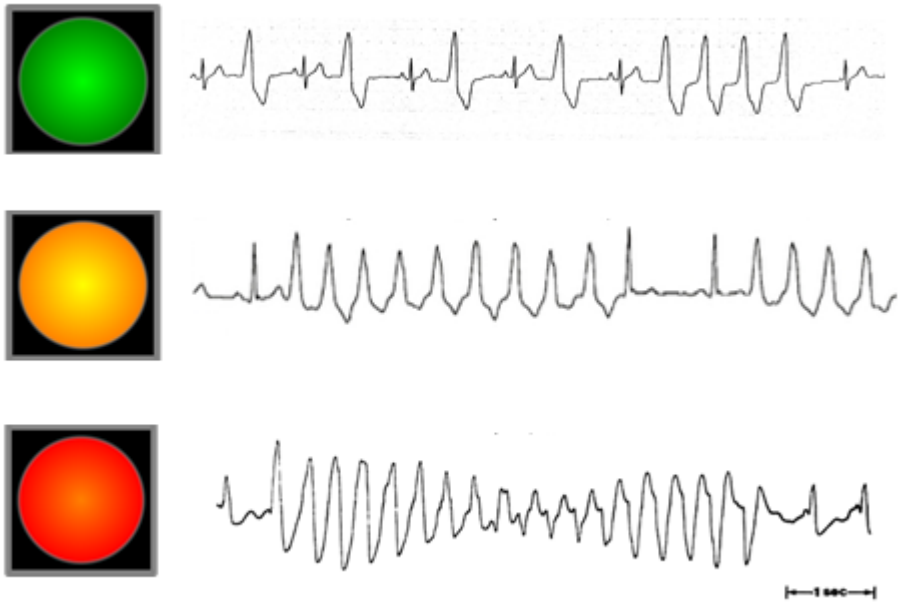
In conclusion, the recent findings from the DANISH trial underline the importance of accurate selection of ICD candidates in the setting of SCD primary prevention and question current knowledge and beliefs. Selection of patients for ICD therapy should be based on careful weighting of expected advantages and potential risks bearing in mind that, in primary prevention of SCD, elderly and nonischaemic patients may benefit less than other patients. Guidelines recommendations should be revised in the light of these new pivotal observations.

**Figure 1**




The arrhythmogenesis triangle proposed by Coumel is useful to describe the main pathophysiological mechanisms involved in sudden cardiac death among patients with heart failure. SCD = sudden cardiac death, LV = left ventricle, PVC = premature ventricular contraction, VT = ventricular tachycardia.

**Figure 2**



Nonsustained ventricular arrhythmias can have a different prognostic impact among patients with heart failure. Premature ventricular contractions, especially if isolated and monomorphic, together with slow nonsustained ventricular tachycardia of short duration are usually benign (green light); short coupling nonsustained ventricular tachycardia of longer duration and with shorter cycle length may be potentially dangerous (yellow light); rapid, polymorphic nonsustained ventricular tachycardia are always malignant (red light).

**Table 1. Randomized controlled clinical trials testing ICD therapy for SCD primary prevention among patients with nonischaemic cardiomyopathy.**

| | CAT | AMIOVIRT | DEFINITE | SCD-HeFT | DANISH |
|---|---|---|---|---|---|
| **Publication year** | 2002 | 2003 | 2004 | 2005 | 2016 |
| **Number of patients enrolled** | 104 | 103 | 458 | 2521 | 1116 |
| **% pts with nonischaemic CMP** | 100% | 100% | 100% | 48% | 100% |
| **Mean age (±SD)/median (IQR)** | 52 (11) | 59 (11) | 58 (20 – 84)* | 60 (51 – 68) | 64 (56 – 72) |
| **Mean EF (±SD)/median (IQR)** | 24 (7) | 23 (9) | 21 (7 – 35)* | 25 (20 – 30) | 25 (20 – 30) |
| **Comorbidities**<br>- **Hypertension**<br>- **Diabetes** | <br>-<br>- | <br>65 (63%)<br>35 (34%) | <br>-<br>105 (23%) | <br>1400 (55%)<br>767 (30%) | <br>348 (31%)<br>211 (19%) |
| **All-cause mortality**<br>**Control vs. ICD**<br>**HR (95% CI)** | <br>2 (4%) vs. 4 (8%)°<br>- | <br>7 (14%) vs. 6 (12%)<br>- | <br>40 (14%) vs. 28 (8%)<br>HR 0.65 (0.40 – 1.06) | <br>244 (29%) vs. 182 (22%)<br>HR 0.77 (0.62 – 0.96) | <br>131 (23%) vs. 120 (22%)<br>HR 0.87 (0.68 – 1.12) |
| **Cardiovascular mortality**<br>**Control vs. ICD**<br>**HR (95% CI)** | <br>1 (2%) vs 4 (8%)°<br>- | <br>5 (10%) vs. 4 (8%)<br>- | <br>26 (11%) vs. 12 (5%)<br>- | <br>167 (20%) vs. 122 (15%)<br>HR 0.76 (0.60 – 0.95) | <br>95 (17%) vs. 77 (14%)<br>HR 0.77 (0.57 – 1.05) |
| **Mortality due to SCD**<br>**Control vs. ICD**<br>**HR (95% CI)** | <br>0 vs. 0°<br>- | <br>2 (4%) vs. 1 (2%)<br>- | <br>14 (6%) vs. 3 (1%)<br>HR 0.20 (0.06 – 0.71) | <br>37 (5%) vs. 95 (11%)<br>HR 0.40 (0.27 – 0.59) | <br>46 (8%) vs. 24 (4%)<br>HR 0.50 (0.31 – 0.82) |

Legend: CMP = cardiomyopathy, EF = ejection fraction, HR = hazard ratio, CI = confidence interval, SD = standard deviation, IQR = interquartile range, ° = 1 year Follow-up,

* = Range min - max

**References**


1 Chugh SS, Jui J, Gunson K, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. J Am Coll Cardiol. 2004; 44(6):1268-75.

2 Chugh SS, Reinier K, Teodorescu C, et al. Epidemiology of sudden cardiac death: clinical and research implications. Prog Cardiovasc Dis. 2008; 51(3):213-28.

3 Stecker EC, Vickers C, Waltz J, et al. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study. J Am Coll Cardiol. 2006; 47(6):1161-6.

4 Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999; 353(9169):2001-7.

5 Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. Circulation. 1989; 80(6):1675-80.

6 Coumel P. Cardiac arrhythmias and the autonomic nervous system. J Cardiovasc Electrophysiol 1993; 4:338-355.

7 Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest StudyHamburg . Canadian Implantable Defibrillator Study. Eur Heart J 2000; 21(24):2071-8.

8 Hohnloser SH, Israel CW. Current evidence base for use of the Implantable Cardioverter-Defibrillator. Circulation 2013;128:172-183.

9 Grimm W1, Christ M, Bach J, Müller HH, Maisch B. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: results of the Marburg Cardiomyopathy Study. Circulation. 2003 Dec 9;108(23):2883-91.

10 Theuns DA, Smith T, Hunink MG, Bardy GH, Jordaens L. Effectiveness of prophylactic implantation of cardioverter-defibrillators without cardiac resynchronization therapy in patients with ischaemic or non-ischaemic heart disease: a systematic review and meta-analysis. Europace. 2010 Nov;12(11):1564-70.

11 Bansch D, Antz m, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). Circulation 2002; 105: 1453-1458.

12 Strickberger SA, Hummel JD, Bartlett TG, et al. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia – AMIOVIRT. J Am Coll Cardiol 2003; 41: 1707-1712.

13 Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004; 350: 2151-2158.

14 Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005; 352; 225-237.

15 Ponikowski P, Voors AA, Anker SD, et al. The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016; 37: 2129–2200.

16 Kober L, Thune JJ, Nielsen JC, et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med 2016; 375:1221-1230.

17 Golwala H, Bajaj NS, Arora G, Arora P. Implantable Cardioverter-Defibrillator for Non Ischemic Cardiomyopathy: An Updated Meta-Analysis. Circulation 2016 [Epub ahead of print].

18 Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350; 2140-2150.