Implantable Cardioverter Defibrillator Therapy for Primary Prevention in Non-Ischaemic Cardiomyopathy

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Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMIOVIRT (5)</td>
<td>Amiodarone versus implantable cardioverter-defibrillator: Randomised trial</td>
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<td>CAT (4)</td>
<td>The Cardiomyopathy Trial</td>
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<td>COMPANION (9)</td>
<td>Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial</td>
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<td>CRTD</td>
<td>Chronic resynchronisation therapy with defibrillator</td>
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<td>CRTP</td>
<td>Chronic resynchronisation therapy</td>
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<td>DEFINITE (6)</td>
<td>Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation trial</td>
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<td>ICD</td>
<td>Implantable cardioverter defibrillator</td>
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<td>ICM</td>
<td>Ischaemic cardiomyopathy</td>
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<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
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<td>NICM</td>
<td>Non-ischaemic cardiomyopathy</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<td>OMT</td>
<td>Optimal medical therapy</td>
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<td>SCD-HeFT (7)</td>
<td>Sudden Cardiac Death in Heart Failure Trial</td>
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Introduction

The mortality in non-ischaemic dilated cardiomyopathy (NICM) is significant, being estimated at 20 % at five years. One third to half of these deaths can be attributed to sudden cardiac death due mainly to ventricular arrhythmias (1), and could thus potentially be prevented by an implantable cardioverter defibrillator (ICD). The benefit of ICD therapy in patients who have previously suffered a ventricular arrhythmia, and for primary prevention in ischaemic cardiomyopathy (ICM) is clearly established (2, 3). However, the evidence for the use of ICD in primary prevention in NICM is less clear.
Aims of this Editorial
This editorial aims to address the following issues concerning ICD therapy for primary prevention in NICM:
1. Review of the evidence for ICD therapy for primary prevention
2. Outline of current guidelines
3. Current practice in the UK
4. Risk stratification strategy

Randomised Controlled Trials of Primary Prevention in NICM
There have been 4 prospective randomised controlled trials evaluating the role of primary prevention ICD-only therapy in NICM (Table 1) (4, 5, 6, 7). As can be seen in Table 1, there was significant heterogeneity between the trials, including their inclusion criteria, trial design and intervention groups, cohort size, length of follow-up, and power for detecting a significant difference in mortality between different intervention arms.

Briefly, these trials involved patients with significant left ventricular impairment who were mostly in New York Heart Association (NYHA) class II and III, and compared ICD plus optimal medical therapy (OMT) versus OMT (4, 6); or ICD plus OMT versus amiodarone plus OMT (5, 7). In DEFINITE (6) and AMIOVIRT (5), patients also needed to have evidence of non-sustained ventricular arrhythmias. The CAT, AMIOVIRT and DEFINITE (4, 5, 6) trials only enrolled patients with NICM and had 2 intervention arms. The SCD-HeFT trial (7), on the other hand, had 3 intervention arms and enrolled both patients with NICM and ICM.

Individually, CAT, AMIOVIRT and DEFINITE did not demonstrate significant mortality benefit for ICD therapy versus OMT. CAT and AMIOVIRT were underpowered to show mortality benefit due to their cohort size. In DEFINITE, all-cause mortality was no different for ICD versus OMT groups [hazard ratio (HR) 0.65, 95 % confidence interval (CI) 0.40-1.06, p=0.08], although arrhythmic death was significantly reduced in the ICD group (HR 0.20, p=0.006). SCD-HeFT demonstrated a 23 % reduction of overall mortality for the whole cohort of patients with ICM and NICM, however the mortality benefit in NICM patients (HR 0.73, 95 % CI 0.50-1.07, p=0.06) was not significant.

Thus, data showing benefit from prophylactic ICD therapy in NICM seems to come mainly from meta-analyses of the above four studies. With strong influence from the
NICM population from SCD-HeFT, one meta-analysis showed a statistically significant effect in favour of ICD with no statistical heterogeneity found for all-cause mortality (RR 0.74, 95% CI 0.58 to 0.93, p=0.009) (8). The COMPANION study (9) was one of the largest heart failure trials where NYHA class III and IV patients with severe ICM and NICM were randomised to receive chronic resynchronisation therapy with a defibrillator (CRTD) versus chronic resynchronisation therapy without a defibrillator (CRTP) versus OMT in a ratio of 2:2:1. The primary end point of combined all-cause mortality or hospitalisation was significantly lower in the two device groups compared to OMT, although there was no significant difference between CRTD and CRTP. Desai et al. performed a meta-analysis of all 4 of the above ICD-only therapy studies combined with the NICM cohort from the COMPANION study, including in total 1854 patients (10). This revealed a 31% reduction in all-cause mortality with ICD relative to OMT (RR 0.69, 95% CI 0.58-0.96, p=0.02). However, in COMPANION, it is uncertain how much of this mortality benefit is due to CRT and how much is due to ICD therapy, and these results should be interpreted with caution. Furthermore, meta-analyses are always vulnerable to publication bias, especially when the number of studies included is limited.

**Current Guidelines for the Use of ICD therapy for Primary Prevention in NICM**

Based on the above evidence, the use of ICDs for primary prevention in NICM is endorsed by international guidelines. The European Society of Cardiology 2012 guidelines on acute and chronic heart failure (3) recommend ICD therapy in symptomatic NICM patients (NYHA class II and III) with left ventricular ejection fraction (LVEF) ≤35% despite ≥3 months on OMT with expected survival of >1 year (Class I, level of evidence B). Similarly, the 2013 American College of Cardiology/American Heart Association (2) recommend ICD therapy in symptomatic NICM patients (NYHA class II and III) with LVEF < 40% despite at least 3 months of guideline-directed medical therapy (Class I). However, the NICE guidelines on ICDs for arrhythmias issued in 2006 do not cover the use of ICDs for NICM (11). Only data from the CAT study (4) was included in the development of these guidelines. DEFINITE and AMIVOIRT (6, 5) were excluded due to their population, and data analysis from SCD-HeFT (7) was still in progress at the time of publication of the 2006 NICE guidelines.

This exclusion from the NICE guidelines of prophylactic ICD use in NICM can not only lead to a clinical conundrum in the routine management of NICM patients due to issues with financial re-imbursement from the National Health Service, but also to the
misinterpretation by clinicians to mean that patients with NICM do not benefit from an ICD. These guidelines are currently under review, with publication of new guidelines due to combine recommendations for the use of ICDs and CRT devices awaited imminently (12). The evidence and cost-effectiveness for ICD use for primary prevention in NICM is an integral part of this on-going review.

**Current Practice in the UK**

A glimpse of current practice in the UK with regards to primary prevention ICD therapy in NICM can be obtained from the most recent Cardiac Rhythm Management National Clinical Audit Report (13). Current guidelines are clearly reflected in data showing that from 2006 to 2011, 35.6 % of CRTD devices were implanted in NICM compared to 64 % for ICM, whereas 66.9 % of CRTP devices were implanted in NICM compared to 33.1% for ICM. Although the exact proportion of CRTD devices implanted for primary prevention in NICM was not reported, there was wide variation between different cardiac networks in the ratio of implantation of CRTP versus CRTD in general.

**Risk Stratification of NICM Patients**

Based on the most optimistic results of mortality benefit from ICD therapy for primary prevention in NICM (10), the number of NICM patients needed to treat to prevent 1 death at 2 years was 25 versus 18 in ICM. The SCD-HeFT study showed that at 5 years, the number of patients needed to prevent 1 death was 15.4 compared to 13.7 in ICM (7). Thus, NICM may represent a low death risk subgroup among all cardiomyopathy patients. As such, ICD implantation in this subgroup will be most cost-effective when used for patients at high risk of arrhythmic death and low risk for non-arrhythmic causes of death.

No risk-stratification test specifically predicts the occurrence of sudden cardiac death. In a prospective study by Grimm et al., LVEF was the only significant predictor of sudden cardiac death, with a relative risk of 2.3 per 10 % decrease in LVEF in patients in sinus rhythm (14). In patients with atrial fibrillation, reduced LVEF appears to have more prognostic power, with the relative risk of a major arrhythmic event rising to 4.5 % per 10 % reduction in LVEF. Lack of beta-blockers and non-sustained ventricular arrhythmias had borderline significance as predictors. However, the presence of the latter, in combination with LVEF, was associated with an 8-fold risk of subsequent major arrhythmic events. Furthermore, on subgroup analysis, the length of duration of non-sustained ventricular tachycardia was shown to have
incremental prognostic value, with the annual incidence rate of a major arrhythmic event rising from 2% in patients with no non-sustained ventricular tachycardia to 10% in patients with ≥10 beats of non-sustained ventricular tachycardia (15).

Thus, in general, NICM patients with more advanced disease, poorer LVEF, and with long runs of non-sustained ventricular arrhythmias in whom the use of beta-blockers is limited appear to potentially benefit most from a primary prevention ICD. However, by virtue of their advanced disease, these patients are also at increased risk of pump failure, such that they may in fact be less likely to benefit from an ICD in the long term.

The importance of OMT in NICM needs to be emphasised. Typically OMT should be instituted for a period of at least 3-6 months from the point of diagnosis, before further assessment of risk factors and the decision to implant an ICD. Significant improvements of LVEF have been observed in about one third of patients after the initial diagnosis with NICM (16). Factors contributing to this include spontaneous recovery in myocarditis, benefits of OMT, and removal of aetiological factors such as alcohol intake.

Another factor to consider when offering ICD therapy to NICM patients is the risk of adverse events from the ICD versus the potential benefits on mortality risk. The complication rates from ICD implantation are not insignificant, ranging from 4-9% in the NICM trials (4, 5, 6, 7, 9). This can increase the cost of ICD therapy even further and impacts on patients’ morbidity and even mortality in rare cases. Similarly, inappropriate shocks from the ICD, affecting 18% of patients receiving a prophylactic ICD at 4 years (17), have significant effects on patients’ quality of life, and are linked to poorer prognosis (18).

**Conclusion**

In summary, prophylactic ICD therapy in NICM appears to reduce mortality based on the results of meta-analyses, although seemingly not to the same extent as in ICM. Although NICM may represent a lower risk subgroup for arrhythmic death, this may also be accounted for by the smaller total population studied (1854 patients in the meta-analysis by Desai et al. compared to over 3500 patients in the ICM subgroup (12)). For prophylactic ICD use to be most cost effective in NICM, it needs to be used in patients who are at highest risk of sudden cardiac death and low risk of non-arrhythmic death. While the updated NICE guidelines on ICD and CRT are awaited,
the benefits and risks of prophylactic ICD therapy in NICM need to be carefully balanced, and decisions need to be made on a case-by-case basis. The lack of power of each of the individual trials of primary prevention ICDs in NICM and the inherent bias of meta-analyses calls for more longitudinal prospective studies of this issue.

References


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