New Zealand primary implantable cardioverter defibrillator implantation and biventricular pacing guidelines

Warren Smith on behalf of the New Zealand Pacing and Electrophysiology Group

Abstract

Primary implantation of an implantable Cardioverter Defibrillator (ICD) is recommended for patients with ischaemic or non-ischaemic cardiomyopathy present for at least 3 months, with ejection fraction (EF) $\leq 30\%$ measured $\geq 3$ months after optimal heart failure treatment. Patients should be on maximal heart failure treatment as tolerated for $\geq 3$ and preferably 6 months, and in New York Heart Association (NYHA) Class II or III. They should be $\geq 3$ months remote from any revascularisation procedure or have no clinical symptoms or findings that would make them a candidate for revascularisation. There should be no associated disease reducing survival $<18$ months.

Biventricular pacing is recommended for patients with an EF $\leq 35\%$ after $\geq 6$ weeks of optimal heart failure treatment, whose QRS duration is $>149$ ms or is 120–149 ms with two additional criteria for dyssynchrony (aortic pre-ejection delay $>140$ ms, interventricular mechanical delay $>40$ ms or delayed activation of the posterolateral left ventricular wall). They should be NYHA Class III, have had no major cardiovascular event in the prior 6 weeks and be in sinus rhythm. There should be no major comorbidity reducing survival $<18$ months or seriously impairing quality of life.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
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<tr>
<td>ACE</td>
<td>Angiotensin-Converting Enzyme</td>
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<td>AF</td>
<td>Atrial fibrillation</td>
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<td>AHA</td>
<td>American Heart Association</td>
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<tr>
<td>AMIOVIRT</td>
<td>Amiodarone Versus Implantable Cardioverter-Defibrillator: Randomised Trial in Patients With Nonischemic Dilated Cardiomyopathy and Nonsustained Ventricular Tachycardia</td>
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<tr>
<td>CARE</td>
<td>Cardiac Resynchronization in Heart failure</td>
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<td>CAT</td>
<td>The cardiomyopathy trial</td>
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<td>COMPANION</td>
<td>Comparison of medical therapy, pacing and defibrillation in heart failure</td>
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<td>CRT</td>
<td>Cardiac resynchronisation therapy</td>
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<td>DEFINITE</td>
<td>Defibrillators in nonischaemic cardiomyopathy treatment evaluation</td>
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<td>DINAMIT</td>
<td>Defibrillation in acute myocardial infarction trial</td>
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<td>ICD</td>
<td>Implantable cardiac defibrillator</td>
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<td>IDM</td>
<td>Ischaemic dilated cardiomyopathy</td>
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<td>LBBB</td>
<td>Left bundle branch block</td>
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<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
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<td>MADIT II</td>
<td>Multicenter automatic defibrillator implantation trial II</td>
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<td>MUSTIC</td>
<td>Multisite stimulation in cardiomyopathy</td>
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<td>MIRACLE</td>
<td>Multicenter InSync™ randomised clinical evaluation</td>
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<tr>
<td>NIDCM</td>
<td>Non-ischaemic dilated cardiomyopathy</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
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Recently a number of randomised trials have established a survival benefit for defined patients with heart failure treated with a prophylactic implantable cardiac defibrillator and/or biventricular pacing. The implementation of these treatments in all patients meeting trial criteria has major economic implications.

This document was originally prepared on behalf of the New Zealand Pacing and Electrophysiology Group (NZPEG) and subsequently made available to the New Zealand National Heart Foundation to assist with device based therapy decisions for the revision of the New Zealand Heart Failure Guidelines. Mindful of the costs involved, the author suggested a set of criteria based on the available evidence and modified from the guidelines approved in the United States by the Centers for Medicare and Medicaid Services.¹

These criteria were submitted in successive drafts to the NZPEG members until a consensus document was achieved. Publication of these guidelines is intended to guide Cardiologists, General Physicians and General Practitioners as to which patients should presently be referred for prophylactic device therapy. These guidelines do not address ICD implantation for familial cardiac conditions with a high risk of sudden death such as the long QT and Brugada syndromes, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and congenital heart disease.

**Current indications for primary ICD implantation**

**The United States of America**

The US Centers for Medicare Services have approved as of February 2005 the following indications for Primary ICD implantation.

- Ischaemic dilated cardiomyopathy (IDM), documented prior myocardial infarction (MI), NYHA Class II and III heart failure and measured (angiography, radionuclide scanning, echocardiography) LVEF ≤35%.
- Non-ischaemic dilated cardiomyopathy (NIDCM) >3 months, NYHA Class II and Class III heart failure and measured LVEF ≤35%.

These groups must also meet the additional criteria of not having:

- Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm.
- Had a coronary artery bypass graft or percutaneous coronary intervention within the past 3 months.
• Clinical symptoms or findings that would make them a candidate for coronary revascularisation.
• Irreversible brain damage from pre-existing cerebral disease.
• Any disease other than cardiac disease associated with a likelihood of survival less than one year.

Furthermore the recipient must be enrolled in either an approved clinical trial or a qualifying data collection system.

The American Heart Association and the American College of Cardiology (AHA/ACC) have summarised current Class I indications for primary ICD implantation on their website (www.acc.org) as:

• Patients with LVEF less than or equal to 35% due to prior MI who are at least 40 days post-MI and are in NYHA functional class II or III (Level of evidence A)
• Patients with nonischaemic dilated cardiomyopathy who have an ejection fraction less than or equal to 35% and who are in NYHA functional Class II or III (level of evidence B)
• Patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than or equal to 30% and are in NYHA functional class I. (level of evidence A)
• Patients with nonsustained ventricular tachycardia (NSVT) due to prior MI, LVEF less than or equal to 40%, and inducible VF or sustained VT at electrophysiological study. (level of evidence B).

Europe

The most recent review update from the National Institute for health and Clinical Excellence (NICE)2, July 2007, by comparison with the AHA/ACC guideline is conservative. It approves primary ICD implantation in patients with a history of previous (more than 4 weeks) myocardial infarction and either left ventricular dysfunction with an LVEF of less than 35%, no worse than class III NYHA and NSVT on Holter monitoring and inducible VT on electrophysiological testing or left ventricular dysfunction with an LVEF of less than 30%, no worse than class III NYHA and a QRS duration of >120ms.

Primary ICD implantation is not approved for any patients with non-ischaemic cardiomyopathy. The Committee was not persuaded that extending the use of ICDs for primary prevention to populations in whom EP testing for arrhythmia had not been carried out was a cost-effective use of NHS resources. It should be noted that no cardiologist was a committee member.

New Zealand perspective

While the CMS1 criteria provide evidence based best practice guidelines, they are not directly referable to New Zealand given the large number of potential candidates (possibly 14,000) and the practical constraints of limited implanting specialist resource and funding. Cardiologists cannot and should not unilaterally decide which
patients merit primary ICD treatment and/or biventricular pacing in the absence of agreed guidelines.

The following consensus guidelines represent a conservative but pragmatic prioritisation from the available trial evidence according to the magnitude of proven benefit. Ultimately their implementation is a political/economic decision which needs to take into account competing health needs.

**Cost effectiveness**

The cost-effectiveness of a prophylactic ICD in this setting is subject to a range of estimates. In the article by Gillian Sanders, Mark Hlaty and Douglas Owens published in 2005, the cost effectiveness of the ICD as compared with control therapy in six populations where the device was implanted prophylactically ranged from US$34,000 to US$70,000 per QALY gained.

Sensitivity analyses showed this cost-effectiveness ratio would remain below US$100,000 per QALY as long as the ICD reduced mortality for 7 or more years. They calculated that the implantation of an ICD added between 2-12 and 6.21 undiscounted years of life and commented “This increment in life expectancy is substantial as compared with that provided by many other medical interventions, and the incremental cost-effectiveness of the ICD, in appropriately selected patients, is similar to that of other interventions often accepted as cost-effective”.

In the cost-effectiveness analysis of the SCD-HeFT trial the estimate was US$38,000 per life-year saved. Interventions costing <US$60,000 annually are generally regarded as good value for money. There is no cost-effective study published in New Zealand.

**Recommendations for primary ICD implantation in New Zealand (see Appendix 1 at end of article)**

Individual recommendations are marked with an asterisk to indicate where they have been modified from an AHA/ACC Class I recommendation and represent local expert consensus opinion. Other requirements not listed in the AHA/ACC recommendations derive from Medicare criteria and are denoted by **.

- Patients with ischaemic cardiomyopathy at least 1 month after acute myocardial infarction or a non- ischaemic cardiomyopathy present for at least 3 months.
- EF ≤30% measured ≥3 months after optimal heart failure treatment.
- NYHA class II or III
- On maximal heart failure medications, including ACE inhibitors or angiotensin receptor blockers, beta-blockers and spironolactone as tolerated for at least 3 and preferably 6 months*.
- No clinical symptoms or findings that would make them a candidate for a revascularisation procedure**.
- At least 3 months remote from any revascularisation procedure**.
- No associated disease with a likelihood of survival <18 months*. 
Additionally it is recommended on pragmatic grounds

- Age \( \leq 75 \) years*

**Justification of the criteria**

- The evidence for a survival benefit is unequivocal for patients with an ischaemic cardiomyopathy and impaired LV function (MADIT-II\(^5\) and SCD-HeFT\(^6\)). Pooled data support a similar survival benefit for non-ischaemic cardiomyopathy but no single study reaches significance. The DEFINITE\(^7\) study, which enrolled only patients with non-ischaemic cardiomyopathy, additionally required the presence of non-sustained VT.

  Bardy, in discussing this study comments that 22% of patients were NYHA class I and the backup pacing rate was higher (40 vs. 34 beats/min in SCD-HeFT), which may have influenced the result.\(^6\) The higher death rate at 2 years in SCD-HeFT non-ischaemic patients (14% vs 10% DEFINITE) also suggests differences in the study populations. The CAT study enrolled patients earlier than 9 months and while underpowered showed unexpectedly low mortality rates.

- The mean LVEF is well below 35% in all trials. Relatively few patients with EF 30-35% have been randomised and they did not seem to show a survival benefit from the ICD (HR = 0.76,95% CI 0.51-1.13).\(^8\) Although such an analysis may lack sufficient statistical power to show such an improvement, it seems reasonable however to place such a group at lower priority.

- The discrepant results according to NYHA Class II or III subgroups between SCD-HeFT and other studies are unexplained, but meta-analysis supports a benefit for class III patients.\(^8\) Class IV patients were excluded from MADIT-II, DEFINITE and SCD-HeFT and comprised only 14% and 6% of COMPANION\(^9\) and CARE\(^10\) making it uncertain if they derive a survival benefit from ICD treatment.

- Symptomatic heart failure was required to be present for at least 3 months in SCD-HeFT. Myocardial function will improve with ACE inhibition and beta-blockade and adequate time should be allowed for equilibration. Similar comments pertain for revascularisation.

- The benefit of primary ICD therapy is delayed for one year in SCD-HeFT and approximately 9 months in MADIT-II. It seems reasonable to allow 18 months as a minimum estimate to allow benefit.

- Very few patients over the age of 75 years have been enrolled in trials. Combining SCD-HeFT and MADIT-II with 3753 patients only 375 patients (10%) were >75 years. CMS\(^1\) advise implantation not be routinely recommended in such patients. In New Zealand it is suggested therefore that primary implantation be limited to patients \( \leq 75 \) years.

**Observations**

- The majority of patients implanted with a primary ICD never received therapy from their device. In SCD-HeFT, with the longest follow-up of 45 months,
21% of patients received an appropriate shock and 19% of patients in MADIT-II with a shorter follow-up of 20 months. Recent post hoc analysis\textsuperscript{11} suggests use of simple criteria may substantially improve patient selection. However this has not been prospectively validated.

- Inappropriate shocks are frequent, occurring in approximately a third of patients in MADIT-II and SCD-HeFT.
- Although post-hoc analyses of trial data have not shown a significant mortality benefit for women, far fewer women than males have been enrolled and there is no plausible biological reason why they should not derive similar benefit to men.

**Biventricular pacing for heart Failure**

At present this is an actively developing field and controversy exists to both the exact mechanism of benefit and the importance of demonstrating left ventricular dyssynchrony on echocardiography. The proposed criteria for patient selection therefore remain trial based:

**Previous studies**

Prior to COMPANION and CARE, there have been at least 7 smaller trials of cardiac resynchronisation therapy (CRT) (MUSTIC,\textsuperscript{13} PATH-CHF1,\textsuperscript{14} PATH-CHFII,\textsuperscript{15} MIRACLE,\textsuperscript{16} InSynch ICD,\textsuperscript{17} MIRACLE ICD,\textsuperscript{18} CONTAK ICD.\textsuperscript{19} In the overview by Al-Khatib et al.\textsuperscript{8} the comment is made that these studies are small, follow-up brief and, as blinding was not possible, outcome assessment unavoidably biased. Two meta-analyses of CRT trials have been published, one showing a reduction in heart failure hospitalisation by 29% but no reduction in all cause mortality,\textsuperscript{20} while the second\textsuperscript{21} did show a significant improvement in all cause mortality (RR 0.79, 95% CI 0.66-0.96). This latter analysis however included benefit from combined therapy with an ICD. These data have been strengthened by the two major randomised trials, COMPANION and CARE.

Comparing these two latter studies, the mean age of patients was very similar (66–67 years), the great majority were in class III NYHA and the mean QRS durations was 160 ms in both. The ejection fraction was slightly higher in the CARE patients (25% cf 22%). At least 90% of patients were receiving ACE inhibition or an angiotensin receptor blocker and approximately two thirds were on beta-blockers.

As per the comments in the primary ICD section, it should be recognised that few patients older than age 75 are represented in the trials and resynchronisation therapy in the ninth decade would be exceptional. The comments in the ACC/AHA Practice Guidelines\textsuperscript{22} with regard to primary ICD implantation are also relevant in this context; “co-morbidities common in the elderly population, such as prior stroke, chronic pulmonary disease and crippling arthritic conditions, as well as nursing home residence should be factored into discussions”.

**Recommendations for biventricular pacing**

The AHA/ACC Recommendations for Cardiac Resynchronisation Therapy (biventricular pacing) in Patients with Severe Systolic Heart Failure include:
• **Class I**—For patients with an LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and sinus rhythm, CRT with or without an ICD is indicated for the treatment of NYHA functional Class III or ambulatory class IV heart failure symptoms with optimal recommended medical therapy. (Level of evidence :A).

• **Class IIa**—For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and AF, CRT with or without an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy. (Level of evidence: B)

**Any qualification of the above in the following guideline reflects local consensus expert agreement**

- Class III NYHA and ambulatory class IV NYHA
- Ejection fraction ≤35% after at least 6 weeks of optimal heart failure treatment with ACE inhibitors or angiotensin receptor blockers, beta-blockers and spironolactone as appropriate.
- QRS duration >149 ms or 120-149 ms with two additional criteria for dyssynchrony (aortic pre-ejection delay >140 ms, interventricular mechanical delay >40 ms or delayed activation of the posterolateral left ventricular wall).
- Sinus rhythm
- No major cardiovascular event in the prior 6 weeks.
- Absence of major comorbidity likely to seriously and persistently impair quality of life
- Any disease other than cardiac disease associated with a likelihood of survival <18 months.

**Observations**—At present there are no randomised trials for patients with AF. One small study of 20 patients noted an improvement in NYHA class and quality of life score after upgrade to biventricular pacing after AV nodal ablation and RV pacing. A sub-study of the MUSTIC trial of 37 patients who required ventricular pacing because of slow heart rates with a QRS width of least 200 ms improved their 6 minute walk distance and decreased hospitalisation for heart failure. A third study of 37 patients of whom 15 were in AF noted symptomatic improvement irrespective of the presence or absence of sinus rhythm. Provided the heart rate is well controlled to allow predominantly ventricular capture with pacing, selected patients with AF could be considered for biventricular pacing.

Although LBBB is not made a specific inclusion criterion, most trials have only small numbers of patients with RBBB. Whether these patients derive similar benefit to LBBB is presently unknown. Until further evidence is presented RBBB should be a relative contraindication.
Addition of an ICD to cardiac resynchronisation therapy

The additional benefit of an ICD additional to cardiac resynchronisation therapy (biventricular pacing) alone has not been proven. In the COMPANION study, pacing alone reduced all cause mortality by 24%, p=0.059 and in the CARE study by 31%, p<0.002. Combination therapy (ICD + resynchronisation) in the former study was associated with a larger mortality risk reduction of 36%, p=0.003. The Companion authors concluded that “the decision of which of these two therapeutic options is appropriate for a particular setting is best determined on an individual basis by patients and their physicians”. The authors of the CARE study noted that 7% of the cardiac–resynchronisation group died suddenly and estimated a future study would require 2600 patients with a 2.5 year follow-up to detect an absolute reduction in the risk of all cause mortality of 5% with the addition of an ICD (combination therapy). At the present time therefore, until the results of ongoing (e.g. RAFT) studies of the role of the ICD in conjunction with biventricular pacing are available to further guide cardiologists, patients should be managed on a case by case basis.

Competing interests: None known.

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9. Bristow MR, Saxon LA, Bohemer J, et al. Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization...


Appendix 1. The evidential base

There are potentially 11 randomised trials of primary prevention of sudden death using ICD therapy and/or biventricular pacing. Three of these, the Coronary Artery Bypass Graft Patch Trial26 (1997), the Multicentre Unsustained Tachycardia Trial27 (1999) and the Multicentre Automatic Defibrillator Implantation trial28 (1996) have been excluded as inappropriate to current decision-making. The remainder comprise 6 trials of primary ICD implantation (nos. 1-3 non-ischaemic cardiomyopathy, nos. 4-5 ischaemic cardiomyopathy, no 6 both) and 2 trials (nos. 7-8) of biventricular pacing with or without an ICD:

CAT29 randomised 104 patients NYHA class II-III with recent onset (≤9 months) non-ischaemic cardiomyopathy and EF ≤30% to ICD or control with no survival benefit for the ICD after 5 years (13 deaths ICD group vs. 17 control, p=0.554). The authors noted “even if 1348 patients had been included as originally planned, the trial would have been underpowered”.

Amiovirt30 randomised 103 patients NYHA class I-III with chronic non-ischaemic cardiomyopathy and EF ≤35% to ICD or amiodarone with no survival benefit for the ICD after 2 years (6 deaths in the ICD group vs 7 in the amiodarone group, p=0.8). The study was stopped because the prospective stopping rule for futility was reached.

Definite7 randomised 458 patients NYHA class II-III with non-ischaemic cardiomyopathy and EF ≤35% to ICD or control with a non-significant trend to survival benefit for the ICD after 2.4 years (28 deaths ICD group vs 40 in control, p=0.08). Patients were required to have NSVT (3-15 beats) or ≥10 PVC’s per hour. Eighteen percent of patients received an appropriate and 21% an inappropriate shock.
**Dinamit**\(^\text{31}\) randomised 674 patients NYHA class II-III to ICD or control 6-40 days post acute MI and EF \(\leq 35\%\) with no survival benefit for the ICD after 2.5 years (62 deaths ICD group vs 58 control., \(p=0.66\)). Patients were required to show depressed heart rate variability or an elevated 24 hour heart rate. Although ICD therapy reduced arrhythmic deaths, that was offset by an increase in non-arrhythmic deaths.

**Madit-II**\(^\text{5}\) randomised 1232 patients NYHA class I-IV with prior myocardial infarction \(\geq\) one month prior, and EF \(\leq 30\%\) in a 3:2 ratio to ICD or control with an absolute survival benefit for the ICD of 5.2% at 20 months (105 deaths ICD group vs 97 deaths control, \(p=0.016\)).

**SCD-HeFT**\(^\text{6}\) randomised 2521 patients NYHA class II-III with ischaemic or non-ischaemic cardiomyopathy and EF \(\leq 35\%\) to placebo, amiodarone or ICD with an absolute survival benefit of 7.2% after 5 years for the ICD (182 deaths ICD vs 244 placebo, \(p=0.0007\)). Prespecified subgroups showed no apparent reduction in the risk of death with ICD therapy in NYHA class III patients and a marginally significant trend for survival in non-ischaemic CHF (\(p=0.06\)).

**Companion**\(^\text{9}\) randomised 1520 patients NYHA class III-IV with ischaemic or non-ischaemic cardiomyopathy and EF \(\leq 35\%\) to control, biventricular pacing alone or combined with an ICD with a survival benefit for the combined therapy group only at 16 months (36% reduction in risk of death, \(p=0.004\)). Biventricular pacing alone was associated with a marginally significant reduction in the risk of death from any cause, adjusted \(p=0.06\).

**Care**\(^\text{10}\) randomised 813 patients with ischaemic and non-ischaemic cardiomyopathy and EF \(\leq 35\%\) to biventricular pacing or control with an absolute survival benefit of 7.1% for pacing at 2 years. Calculations suggested that for every nine devices implanted one death and 3 hospitalisations for major cardiovascular events were prevented.