

Implantable Cardioverter Defibrillators. Prophylactic Use

An Evidence-Based Analysis

September 2005



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The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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Table of Contents

Table of Contents.....	4
Executive Summary	7
Objective	7
Clinical Need.....	7
The Technology	7
Review Strategy.....	7
Summary of Findings	8
GRADE Quality of the Evidence	9
Conclusions.....	11
Abbreviations	14
Objective.....	15
Background.....	15
Clinical Need: Target Population and Condition	15
Indicators of Increased Risk of Sudden Cardiac Death from Arrhythmia	17
Existing Treatments Other than Technology Being Reviewed.....	25
New Technology Being Reviewed	25
Regulatory Status.....	26
Literature Review on Effectiveness	28
Objective	28
Methods.....	28
Inclusion criteria	28
Exclusion criteria	28
Databases searched	28

Outcomes of Interest.....	28
GRADE Quality of Evidence and Strength of Recommendations	28
Results of Literature Search	29
Blue Cross Blue Shield Association Technology Evaluation Center, March 2005.....	30
Centers for Medicare and Medicaid Services, January 2005	33
Technology Assessment Report Commissioned by the HTA Programme on Behalf of the National Institute for Clinical Excellence, January 2004.....	39
Summary of Updated Medical Advisory Secretariat Review: Studies Other Than Health Technology Assessments.....	42
Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)	42
Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation Trial (DEFINITE)	43
Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)	44
Studies of Implantable Cardioverter Defibrillators in Progress	45
GRADE Quality of Evidence	46
Economic Analysis	48
Literature Review: Update.....	48
Blue Cross Blue Shield Technology Evaluation Centre, April 2004	51
Ontario-Based Budget Impact Analysis.....	52
Existing Guidelines for Use of Technology.....	56
AHA/ACC/NASPE 2005 Guideline Update.....	56
National Institute for Clinical Excellence Appraisal Committee’s Recommendations (United Kingdom, 2006)	56
European Society of Cardiology Guidelines for the Diagnosis and Treatment of Chronic Heart Failure 2005	57
Canadian Cardiovascular Society/Canadian Heart Rhythm Society Position Paper on ICD Use in Canada (2005).....	58
Canadian Cardiovascular Society Consensus Conference Recommendations on Heart Failure 2006	59
Aetna, United States, March 2005	60

Centers for Medicare and Medicaid Services..... 61

Appraisal 63

Health Systems Implications..... 63

Glossary 67

References 69

Executive Summary

Objective

The use of implantable cardiac defibrillators (ICDs) to prevent sudden cardiac death (SCD) in patients resuscitated from cardiac arrest or documented dangerous ventricular arrhythmias (secondary prevention of SCD) is an insured service. In 2003 (before the establishment of the Ontario Health Technology Advisory Committee), the Medical Advisory Secretariat conducted a health technology policy assessment on the prophylactic use (primary prevention of SCD) of ICDs for patients at high risk of SCD. The Medical Advisory Secretariat concluded that ICDs are effective for the primary prevention of SCD. Moreover, it found that a more clearly defined target population at risk for SCD that would be likely to benefit from ICDs is needed, given that the number needed to treat (NNT) from recent studies is 13 to 18, and given that the per-unit cost of ICDs is \$32,000, which means that the projected cost to Ontario is \$770 million (Cdn).

Accordingly, as part of an annual review and publication of more recent articles, the Medical Advisory Secretariat updated its health technology policy assessment of ICDs.

Clinical Need

Sudden cardiac death is caused by the sudden onset of fatal arrhythmias, or abnormal heart rhythms: ventricular tachycardia (VT), a rhythm abnormality in which the ventricles cause the heart to beat too fast, and ventricular fibrillation (VF), an abnormal, rapid and erratic heart rhythm. About 80% of fatal arrhythmias are associated with ischemic heart disease, which is caused by insufficient blood flow to the heart.

Management of VT and VF with antiarrhythmic drugs is not very effective; for this reason, nonpharmacological treatments have been explored. One such treatment is the ICD.

The Technology

An ICD is a battery-powered device that, once implanted, monitors heart rhythm and can deliver an electric shock to restore normal rhythm when potentially fatal arrhythmias are detected. The use of ICDs to prevent SCD in patients resuscitated from cardiac arrest or documented dangerous ventricular arrhythmias (secondary prevention) is an insured service in Ontario.

Primary prevention of SCD involves identification of and preventive therapy for patients who are at high risk for SCD. Most of the studies in the literature that have examined the prevention of fatal ventricular arrhythmias have focused on patients with ischemic heart disease, in particular, those with heart failure (HF), which has been shown to increase the risk of SCD. The risk of HF is determined by left ventricular ejection fraction (LVEF); most studies have focused on patients with an LVEF under 0.35 or 0.30. While most studies have found ICDs to reduce significantly the risk for SCD in patients with an LVEF less than 0.35, a more recent study (Sudden Cardiac Death in Heart Failure Trial [SCD-HeFT]) reported that patients with HF with nonischemic heart disease could also benefit from this technology. Based on the generalization of the SCD-HeFT study, the Centers for Medicare and Medicaid in the United States recently announced that it would allocate \$10 billion (US) annually toward the primary prevention of SCD for patients with ischemic and nonischemic heart disease and an LVEF under 0.35.

Review Strategy

The aim of this literature review was to assess the effectiveness, safety, and cost effectiveness of ICDs for the primary prevention of SCD.

The standard search strategy used by the Medical Advisory Secretariat was used. This included a search of all international health technology assessments as well as a search of the medical literature from January 2003–May 2005.

A modification of the GRADE approach (1) was used to make judgments about the quality of evidence and strength of recommendations systematically and explicitly. GRADE provides a framework for structured reflection and can help to ensure that appropriate judgments are made. GRADE takes into account a study's design, quality, consistency, and directness in judging the quality of evidence for each outcome. The balance between benefits and harms, quality of evidence, applicability, and the certainty of the baseline risks are considered in judgments about the strength of recommendations.

Summary of Findings

Overall, ICDs are effective for the primary prevention of SCD. Three studies – the Multicentre Automatic Defibrillator Implantation Trial I (MADIT I), the Multicentre Automatic Defibrillator Implantation Trial II (MADIT II), and SCD-HeFT – showed there was a statistically significant decrease in total mortality for patients who prophylactically received an ICD compared with those who received conventional therapy (Table 1).

Table 1: Results of Key Studies on the Use of Implantable Cardioverter Defibrillators for the Primary Prevention of Sudden Cardiac Death – All-Cause Mortality

Study,* Year	Population	N	Follow-up, Months	Mortality, ICD† Group, %	Mortality, Control Group, %	Hazard Ratio (95% CI)	P	NNT†
MADIT, 1996 (2)	Ischemic Prior myocardial infarction Ejection fraction ≤ 0.35 NSVT† EP† +	196	27	15.8	38.6	0.46 (0.26–0.82) 54% relative reduction	.009	4
MADIT II, 2002 (3)	Ischemic Prior myocardial infarction Ejection fraction ≤ 0.30	1232	20	14.2	19.8	0.69 (0.51–0.93) 31% relative reduction	.016	18
SCD-HeFT, 2005 (4)	Ischemic & Nonischemic Ejection fraction ≤ 0.35	2521	60	22	29	0.77 (0.62–0.96) 23% relative reduction	.007	13

*MADIT I: Multicentre Automatic Defibrillator Implantation Trial I; MADIT II: Multicentre Automatic Defibrillator Implantation Trial II; SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial.

†EP indicates electrophysiology; ICD, implantable cardioverter defibrillator; NNT, number needed to treat; NSVT, nonsustained ventricular tachycardia. The NNT will appear higher if follow-up is short. For ICDs, the absolute benefit increases over time for at least a 5-year period; the NNT declines, often substantially, in studies with a longer follow-up.

When the NNT are equalized for a similar period as the SCD-HeFT duration (5 years), the NNT for MADIT-I is 2.2; for MADIT-II, it is 6.3.

GRADE Quality of the Evidence

Using the GRADE Working Group criteria, the quality of these 3 trials was examined (Table 2).

Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.

Consistency refers to the similarity of estimates of effect across studies. If there is important unexplained inconsistency in the results, our confidence in the estimate of effect for that outcome decreases.

Differences in the direction of effect, the size of the differences in effect, and the significance of the differences guide the decision about whether important inconsistency exists.

Directness refers to the extent to which the people interventions and outcome measures are similar to those of interest. For example, there may be uncertainty about the directness of the evidence if the people of interest are older, sicker or have more comorbidity than those in the studies.

As stated by the GRADE Working Group, the following definitions were used to grade the quality of the evidence:

- High: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low: Any estimate of effect is very uncertain.

Table 2: Quality of Evidence – MADIT I, MADIT II, and SCD-HeFT*

Trial	Design	Quality	Consistency	Directness†	Quality Grade
MADIT I	RCT	<p>Imbalance in β-blocker usage between study arms.</p> <p>The overall number of patients from which the study was drawn was not reported.</p> <p>Selection bias may have occurred since patients were selected for randomization if they did not respond to procainamide, thereby introducing a potential bias into the medication arm.</p> <p>Specific details regarding allocation concealment and blinding procedures were not provided.</p>	<p>Single-chamber ICD used in study.</p> <p>Trial started with transthoracic implants, and then switched to nontransthoracic implants.</p> <p>Ischemic cardiomyopathy only.</p> <p>5-year NNT = 2.</p>	<p>The overall number of patients from which the study was drawn was not reported.</p> <p>Selection bias may have occurred since patients were selected for randomization if they did not respond to procainamide, thereby introducing a potential bias into the medication arm.</p>	Moderate
MADIT II	RCT	<p>~ 90% of patients were recruited \geq 6 months post-MI; 20% of control group died after mean 20-month follow-up.</p> <p>How and where patients recruited?</p> <p>Specific details regarding allocation concealment/blinding procedures not provided.</p> <p>Subset had MADIT I criteria; post hoc analysis of incomplete data suggested “weak-moderate evidence that ICD effect greater in inducible than noninducible patients in MADIT II.” (5;6)</p>	<p>First study to assess both single- and dual-chamber ICD devices for primary prevention.</p> <p>Programming of device and medications left to the discretion of the patients’ physician.</p> <p>Higher rate of hospitalization for new or worsened heart failure in the group receiving the ICDs compared to conventional therapy (19.9% versus 14.9% respectively).</p> <p>Ischemic cardiomyopathy only.</p> <p>5-year NNT = 6.</p>	<p>How and where patients recruited?</p> <p>Subset had MADIT I criteria.</p>	Weak
SCD-HeFT	RCT	<p>Statistically significant difference in β-blocker usage between treatment groups at last follow-up.</p> <p><u>Drug</u> arms double-blinded.</p>	<p>Shock-only single-lead device. Antitachycardia pacing not permitted.</p> <p>Ischemic <u>and</u> nonischemic cardiomyopathy.</p> <p>There was a statistically significant difference in terms of the NYHA prespecified subgroups analysis. The NYHA subgroups were prespecified a priori and</p>	<p>Direct.</p> <p>Study only evaluated conservatively programmed ICDs with a conservative detection algorithm and shock only therapy.</p> <p>ICD therapy may differ depending on the programming of the device – whether single-, dual-, or triple-chamber devices are used;</p>	Moderate

Trial	Design	Quality	Consistency	Directness†	Quality Grade
			<p>the results of the interaction tests were significant. Yet, ICD treatment had a significant benefit in patients in NYHA class II but not in those in NYHA class III. The general trend in prior trials had been for the relative treatment effect to be nearly constant in NYHA classes (e.g., MADIT II). The SCD-HeFT authors were unable to explain the results of the prespecified NYHA subgroup analysis.</p> <p>Prespecified HF subgroups showed no statistically significant difference in ICD versus placebo.</p> <p>Ischemic: 0.79 (0.60–1.04), $P = .05$ Nonischemic: 0.73 (0.50–1.07), $P = .06$.</p> <p>5-year NNT = 13.</p>	<p>whether antibradycardia pacing or rate responsive pacing is used; which detection algorithm is used and whether antitachycardia pacing maneuvers are used for VT.</p> <p>“ICD therapy cannot be considered a single intervention give the numerous possible permutations of the approach.”</p>	

*MADIT I: Multicentre Automatic Defibrillator Implantation Trial I; MADIT II: Multicentre Automatic Defibrillator Implantation Trial II; SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial.

†The 3 trials had 3 different sets of eligibility criteria for implantation of an ICD for primary prevention of SCD.

Conclusions

Overall, there is evidence that ICDs are effective for the primary prevention of SCD. Three trials have found a statistically significant decrease in total mortality for patients who prophylactically received an ICD compared with those who received conventional therapy in their respective study populations.

As per the GRADE Working Group, recommendations consider 4 main factors:

- The tradeoffs, taking into account the estimated size of the effect for the main outcome, the confidence limits around those estimates, and the relative value placed on the outcome;
- The quality of the evidence (Table 2);
- Translation of the evidence into practice in a specific setting, taking into consideration important factors that could be expected to modify the size of the expected effects, such as proximity to a hospital or availability of necessary expertise; and
- Uncertainty about the baseline risk for the population of interest

The GRADE Working Group also recommends that incremental costs of health care alternatives should be considered explicitly with the expected health benefits and harms. Recommendations rely on judgments about the value of the incremental health benefits in relation to the incremental costs. The last

column in Table 3 is the overall trade-off between benefits and harms and incorporates any risk or uncertainty.

For MADIT I, the overall GRADE and strength of the recommendation is “moderate” – the quality of the evidence is “moderate” (uncertainty due to methodological limitations in the study design), and risk/uncertainty in cost and budget impact was mitigated by the use of filters to help target the prevalent population at risk (Table 3).

For MADIT II, the overall GRADE and strength of the recommendation is “very weak” – the quality of the evidence is “weak” (uncertainty due to methodological limitations in the study design), but there is risk or uncertainty regarding the high prevalence, cost, and budget impact. It is not clear why screening for high-risk patients was dropped, given that in MADIT II the absolute reduction in mortality was small (5.6%) compared to MADIT I, which used electrophysiological screening (23%) (Table 3).

For SCD-HeFT, the overall GRADE and strength of the recommendation is “weak” – the study quality is “moderate,” but there is also risk/uncertainty due to a high NNT at 5 years (13 compared to the MADIT II NNT of 6 and MADIT I NNT of 2 at 5 years), high prevalent population (N = 23,700), and a high budget impact (\$770 million). A filter (as demonstrated in MADIT 1) is required to help target the prevalent population at risk and mitigate the risk or uncertainty relating to the high NNT, prevalence, and budget impact (Table 3).

The results of the most recent ICD trial (SCD-HeFT) are not generalizable to the prevalent population in Ontario (Table 3). Given that the current funding rate of an ICD is \$32,500 (Cdn), the estimated budget impact for Ontario would be as high as \$770 million (Cdn). The uncertainty around the cost estimate of treating the prevalent population with LVEF < 0.30 in Ontario, the lack of human resources to implement such a strategy and the high number of patients required to prevent one SCD (NNT = 13) calls for an alternative strategy that allows the appropriate uptake and diffusion of ICDs for primary prevention for patients at maximum risk for SCD within the SCD-HeFT population.

The uptake and diffusion of ICDs for primary prevention of SCD should therefore be based on risk stratification through the use of appropriate screen(s) that would identify patients at highest risk who could derive the most benefit from this technology.

Table 3: Overall GRADE and Strength of Recommendation for the Use of Implantable Cardioverter Defibrillators for the Primary Prevention of Sudden Cardiac Death

	Study Quality	Eligibility*	Estimated Number in Ontario	NNT†	Total Cost in Ontario, \$ millions	Overall Grade & Strength of Recommendation (Includes Uncertainty)
ICD	Moderate	MADIT I: Ejection fraction < 0.35, prior myocardial infarction, NSVT‡, inducible VT‡	~ 4,740	4	~ 156	Moderate
	Low	MADIT II: Ejection fraction < 0.30 and prior myocardial infarction	(greater than MADIT)	18	> 156	Very weak
	Moderate	SCD-HeFT: Ejection fraction < 0.35	~ 23,700	13	~ 770	Weak

*MADIT I: Multicentre Automatic Defibrillator Implantation Trial I; MADIT II: Multicentre Automatic Defibrillator Implantation Trial II; SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial.

†NNT indicates number needed to treat. The NNT will appear higher if follow-up is short. For ICDs, the absolute benefit increases over time for at least a 5-year period; the NNT declines, often substantially, in studies with a longer follow-up. When the NNT are equalized for a similar period as the SCD-HeFT duration (5 years), the NNT for MADIT-I is 2.2; for MADIT-II, it is 6.3.

‡NSVT indicates nonsustained ventricular tachycardia; VT, ventricular tachycardia.

Abbreviations

AECG	Ambulatory electrocardiogram
AMIOVIRT	Amiodarone versus Implantable Defibrillator in Patients With Nonischemic Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia
BEST-ICD	Beta-blocker Strategy plus ICD trial
CABG Patch	Coronary Artery Bypass Grafting Patch trial
CAD	Coronary artery disease
CAT	Primary Prevention of Sudden Cardiac Death in Idiopathic Dilated Cardiomyopathy
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
COMPANION	Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure trial
CRT	Cardiac resynchronization therapy
DEFINITE	Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation
DINAMIT	Defibrillators in Acute Myocardial Infarction Trial
ECG	Electrocardiogram
EF	Ejection fraction
EP	Electrophysiology
FDA	United States Food and Drug Administration
HR	Hazard ratio
HF	Heart failure
ICD	Implantable cardioverter defibrillator
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MADIT I	Multicentre Automatic Defibrillator Implantation Trial I
MADIT II	Multicentre Automatic Defibrillator Implantation Trial II
MI	Myocardial infarction
MIRACLE	Multicentre Insync Randomized Clinical Evaluation
MUSTT	Multicentre Unsustained Tachycardia Trial
MUSTIC	Multisite Stimulation in Cardiomyopathy
NICE	National Institute for Clinical Excellence
NNT	Number needed to treat
NSVT	Nonsustained ventricular tachycardia
NYHA	New York Heart Association
PTCA	Percutaneous transluminal coronary angioplasty
PVB	Premature ventricular beat
PVC	Premature ventricular contraction
RR	Relative risk
SCD	Sudden cardiac death
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Objective

The use of implantable cardiac defibrillators (ICDs) to prevent sudden cardiac death (SCD) in patients resuscitated from cardiac arrest or documented dangerous ventricular arrhythmias (secondary prevention of SCD) is an insured service. In 2003 (before the establishment of the Ontario Health Technology Advisory Committee), the Medical Advisory Secretariat conducted a health technology policy assessment on the prophylactic use (primary prevention of SCD) of ICDs for patients at high risk of SCD. The Medical Advisory Secretariat concluded that ICDs are effective for the primary prevention of SCD. Moreover, it found that a more clearly defined target population at risk for SCD that would be likely to benefit from ICDs is needed, given that the number needed to treat (NNT) from recent studies is 13 to 18, and given that the per-unit cost of ICDs is \$32,000, which means that the projected cost to Ontario is \$770 million.

Accordingly, as part of an annual review and publication of more recent articles, the Medical Advisory Secretariat updated the health technology policy assessment of ICDs.

Background

Clinical Need: Target Population and Condition

The true mortality burden of sudden cardiac death (SCD) is not well established. Various sources (7) have estimated the annual number of deaths in the United States to be between 184,000 and 462,000; this accounts for a mean of 1 to 2 deaths per 1,000 adults aged over 35 years annually, and 50% of all heart-related deaths. (8;9) Most SCDs are caused by acute, fatal arrhythmias, or abnormal heart rhythms: ventricular tachycardia (VT), a rhythm abnormality in which the ventricles cause the heart to beat too fast, and ventricular fibrillation (VF), an abnormal, rapid and erratic heart rhythm. Ventricular tachycardia degenerating first to VF and later to asystole (the absence of a heart beat) appears to be the most common pathophysiological cascade involved in fatal arrhythmias.

About 80% of fatal arrhythmias are caused by structural coronary arterial abnormalities and their consequences. (10) Dilated and hypertrophic cardiomyopathies account for the second largest number of SCDs. Most observational studies and interventional trials directed at preventing fatal ventricular arrhythmias have focused on patients with ischemic heart disease or heart failure (HF). (10)

The majority of SCDs are due to coronary artery disease (CAD); of these, 75% have evidence of prior myocardial infarction (MI). (11;12) A 26-year follow-up of the population of Framingham, Massachusetts, aged 30 to 59 years and free of identified heart disease at baseline observation, indicated that SCD accounted for 46% of deaths due to CAD among men and 34% among women. (13) Doyle et al. (14) combined data from Albany, New York and Framingham and identified SCD as the initial and terminal manifestation of CAD in more than 50% of all people who died from SCD.

Sudden death is the final event in about 35% to 50% of patients with chronic HF. (15) The risk of SCD is higher in patients with chronic HF than in any other definable subset of patients in cardiovascular medicine; it is fivefold higher than in the general population. (15) Recently, Cobb et al. (16) observed a major decline in the incidence of out-of-hospital VF and in all cases of treated cardiac arrest presumably due to heart disease in Seattle. It was suggested that the changes likely reflect the national (United States) decline in coronary heart disease mortality. The adjusted annual incidence of cardiac arrest with VF as the first identified rhythm decreased by about 56% from 1980 to 2000 (from 0.85 to 0.38 per 1000; relative risk, 0.44; 95% CI, 0.37–0.53). The incidence of VF in men far exceeded that of women, and the ratio of

male-to-female incidence rates decreased from only 4.0 to 3.5 in 20 years.

Survival rates following an outside-of-hospital cardiac arrest in Canadian cities have been reported to be less than 11%. (17) Similarly, survival rates after cardiac arrest remain low for communities in Ontario, ranging from no survivors to 11.8%. (17) These Ontario data were obtained from only some Ontario communities (including the Ontario Prehospital Advanced Life Support Study participants), and these communities may, if anything, be performing better than others for which data remain unavailable. (17)

New York Heart Association Functional Classification of Cardiac Disease

The New York Heart Association (NYHA) has provided a commonly used functional classification for the severity of HF:

- Class I: No limitation of physical activity. No symptoms with ordinary exertion.
- Class II: Slight limitations of physical activity. Ordinary activity causes symptoms.
- Class III: Marked limitation of physical activity. Less than ordinary activity causes symptoms. Asymptomatic at rest.
- Class IV: Inability to carry out any physical activity without discomfort. Symptoms at rest.

The National Heart, Lung, and Blood Institute estimates that 35% of patients with HF are in functional NYHA class I; 35% are in class II; 25%, class III; and 5%, class IV.

Indicators of Increased Risk of Sudden Cardiac Death from Arrhythmia

Ejection Fraction

For the design and clinical protocol of MADIT II, Moss et al. (18) stated that patients with coronary heart disease and an ejection fraction (EF) equal to or less than 0.30 have a 2-year mortality rate that is in the range of 20% despite appropriate therapy with ACE inhibitors, digoxin, β -blockers, and diuretics. It was also estimated that 50% of the deaths in patients with advanced LV dysfunction is due to VF. Therefore, MADIT II was designed to determine if ICD treatment would reduce mortality in high-risk coronary patients with an EF equal to or less than 0.30.

Bigger et al. (19) examined the relationships among ventricular arrhythmias, LV dysfunction, and mortality after the occurrence of MI in 766 patients who enrolled in a multicentre study. LVEF was determined by radionuclide ventriculography, a type of test that makes the ventricles and vessels of the heart more visible. The adjusted hazard ratio for death with an LVEF under 0.30 was 3.5 ($P < .001$). No confidence intervals were reported. The effect of LVEF on mortality was stronger in the first 6 months of follow-up (hazard ratio, 5.4) than after 6 months (hazard ratio, 1.9; $P < .01$). The study by Bigger et al. formed the rationale behind some of the primary prevention studies. (20)

The Multicenter Postinfarction Research Group (21) assessed the role of physiologic measurements of heart function in predicting mortality after MI. Eight hundred and sixty-six patients underwent 24-hour Holter monitoring of resting EF before discharge. (A Holter monitor records the heart rhythm – each and every heart beat – continuously for 24 hours.) Univariate analyses revealed a progressive increase in cardiac mortality during 1 year as the EF fell below 0.40, and as the number of ventricular ectopic depolarizations exceeded 1 per hour. Only 4 risk factors among 8 prespecified variables were independent predictors of mortality: an EF under 0.40, ventricular ectopy of at least 10 depolarizations per hour, advanced NYHA class before infarction, and rales heard in the upper two-thirds of the lungs while the patient was in the coronary care unit. Different combinations of the 4 factors identified subgroups with 2-year mortality rates ranging from 3% (no factors) to 60% (all factors).

The degree of functional impairment and left ventricular dysfunction, as measured by echocardiography, contrast angiography, or isotope techniques are strong predictors of death. (10) However, these methods have limitations as specific markers for the risk of death due to arrhythmia. As functional impairment increases, so do total mortality and the absolute number of sudden deaths, but the proportion of overall deaths due to cardiac arrhythmias decreases. (8) Therefore, the degree of functional impairment and left ventricular dysfunction lack specificity as predictors of death due to arrhythmia because they are also powerful measures of the risk of death from causes not due to arrhythmia.

The measurement of EF with the assessment of other risk factors for arrhythmia may improve the accuracy of prediction. (10) Many randomized controlled trials (RCTs) have used EF as an inclusion criterion risk factor. (2;3;22) Further trials examining the prophylactic use of ICDs and other antiarrhythmic therapies should more precisely define any role of LV dysfunction as a single risk factor for SCD. (10)

Nonsustained and Sustained Ventricular Tachycardia

The cutoff of what constitutes sustained versus nonsustained ventricular tachycardia (NSVT) is rather arbitrary. (23) In most literature describing induction of VT during programmed ventricular stimulation, a sustained tachycardia is defined as one that lasts at least 30 seconds or one that causes considerable hemodynamic compromise such that it needs termination by pacing or direct current cardioversion (i.e.,

an electric shock to the heart) before 30 seconds. (23) Tachycardias that terminate spontaneously in less than 30 seconds are considered nonsustained. (23)

Chronic HF is associated with an increased risk of sudden death. A patient with chronic HF is also susceptible to malignant ventricular arrhythmias. (15) The prevalence and complexity of ambulatory ventricular arrhythmias (for example, premature ventricular depolarizations and NSVT) increase as LV function deteriorates. In patients with an LVEF under 0.40, the prevalence of NSVT rises from 15% to 20% in patients with NYHA class I to II symptoms of HF, to 40% to 55% in patients with NYHA class II to III, to 50% to 70% in patients with NYHA class III to IV symptoms. (15) Furthermore, the prevalence of HF rises as ventricular arrhythmias become increasingly complex. In patients undergoing ambulatory electrocardiogram monitoring, HF is present in 6% of patients without ventricular arrhythmias; in 14% of patients with unifocal ventricular premature beats; in 29% of patients with ventricular couplets; and in 36% of patients with NSVT. (15) Similar to sudden death, the prevalence of ventricular arrhythmias is higher in patients with chronic HF than in any other subset of patients in cardiovascular medicine. (15)

Packer (15) suggested that there may be no relation between the prevalence and complexity of ambulatory ventricular arrhythmias and the risk of sudden death in patients with chronic HF. The presence of complex ambulatory ventricular arrhythmias (especially NSVT) on ambulatory monitoring predicts total cardiac mortality but does not identify patients who are destined to die suddenly. This suggests that the frequency and complexity of rhythm disturbances in patients with severe HF may reflect the severity of the underlying disease process rather than a specific arrhythmogenic state. (10;15) However, Packer notes that this is in contrast to the clinical and prognostic importance of symptomatic sustained ventricular arrhythmias in patients with LV dysfunction in whom VT has been shown to play a primary role in the occurrence of sudden death. As HF progresses, the prevalence of NSVT increases dramatically, but the risk of sudden death does not. When ambient ventricular arrhythmia is present in the absence of HF, long-term antiarrhythmic therapy for this condition is no longer considered a defined and proven strategy for preventing sudden death from cardiac causes. (10)

As HF progresses and enters the final stages, cardiac performance eventually becomes insufficient to sustain the circulation and malignant rhythm disturbances become increasingly common. The interplay between mechanical and electrical events is so complex that it may be nearly impossible to determine how these factors interact physiologically to lead to a patient's demise. (15) Even under close observation, it is difficult to determine if a terminal arrhythmia observed at the time of death played a primary or secondary role in the demise of the patient.

Non Sustained Ventricular Tachycardia

Some studies have indicated episodes of NSVT were associated with an increased risk of SCD among patients with HF or a recent MI. Doval et al. (24) conducted a prospective cohort study designed to evaluate the prognostic value of the presence or absence of NSVT in 24-hour Holter recordings obtained before randomization in 516 patients with severe HF and marked LV systolic dysfunction. Patients from the GESICA trial (33.4% with NSVT) were initially studied with the results of 24-hour Holter monitoring and 2 years of follow-up. Within 2 years, 87 (50.3%) of 173 patients with NSVT and 106 (30.9%) of 343 patients without NSVT died; relative risk (RR) was 1.69 (95% CI, 1.27–2.24; $P < .0002$). Sudden death increased from 8.7% (30/343) to 23.7% (41/173) in patients with NSVT (RR, 2.77; 95% CI, 1.78–4.44; $P < .001$). The rate of death due to progressive HF also increased: from 17.5% (60/343) to 20.8% (36/173) ($P = .22$).

When a combined dichotomous variable of couplets and/or NSVT was used, there was RR of 2.90 for total mortality (95% CI, 1.10–7.64; $P < .05$) and an RR of 10.1 for sudden death (95% CI, 1.91–52.7; $P < .01$). These RRs were statistically significant, however, the wide CIs especially for sudden death may

suggest questionable clinical conclusiveness. Accordingly, there was 89% sensitivity and 42% specificity for the prediction of sudden death, with a 21% positive predictive value. (24;25) Lack of a multivariate analysis did not permit the authors to assess if arrhythmias are independently useful in predicting sudden death. Furthermore, the GESICA patient population had more than 60% of patients with nonischemic cardiomyopathy, and patients with asymptomatic VT of at least 10 beats were excluded.

Maggioni et al. (26) examined the prevalence and prognostic value of ventricular arrhythmias in patients who had had an MI and been treated with fibrinolytic agents. They analyzed 24-hour Holter recordings obtained before discharge from the hospital in 8,676 post MI patients of the GISSI-2 study. Patients were followed-up for 6 months from the acute event. To assess the prevalence of ventricular arrhythmias and their prognostic significance, the patients were divided according to 3 criteria:

- Frequency of arrhythmias
 - < 1 premature ventricular beat (PVB) per hour
 - 1–10 PVBs per hour
 - > 10 PVBs per hour
- Presence or absence of complex arrhythmias, defined as >10 PVBs per hour and/or any number of couplets and/or runs of NSVT
- Presence or absence of runs of NSVT

Overall, 3,112 (35.9%) were free from ventricular arrhythmias, and 1,712 (19.7%) had more than 10 PVBs per hour. Furthermore, 2,892 (33.3%) patients had complex ventricular arrhythmias, and 586 (6.8%) patients had NSVT.

The multivariate analysis indicated that the presence of NSVT was not associated (RR 1.20; 95% CI, 0.80–1.79) with a worsened survival at 6 months after adjusting for age (< 70 or ≥ 70 years); sex; previous acute MI; history of diabetes or treated hypertension; site of acute MI; postdischarge treatment with antiarrhythmic drugs, digitalis, or β-blockers; presence of late (beyond day 4) clinical HF (presence of at least 2 of the following signs: presence of a third sound, rales, dyspnea, or radiological evidence of pulmonary congestion); or extensive LV damage in the absence of clinical HF (LVEF ≤ 0.35 or ≥ 45% injured myocardial segments).

In a Canadian study, Rouleau et al. (27) prospectively evaluated all patients aged under 75 years that presented with an acute MI between 1990 and 1992 at 9 hospitals. A total of 3,178 patients were recruited. One-year postdischarge cardiac mortality increased progressively with decreasing LVEF. The multivariate model for 1-year postdischarge total mortality revealed that LVEF was the most powerful predictor (inversely) of mortality ($P < .001$). Presumed arrhythmic death was not a frequent cause of in-hospital mortality (8%), but it was the most common cause of first-year postdischarge mortality (31%). However, because few patients died during the first year after hospital discharge, only 1.9% of all discharged patients died a presumed arrhythmic death. When premature ventricular contractions (Holter monitoring) were added to the multivariate model for 1-year postdischarge mortality (with LVEF excluded so as not to lose the 17% of patients without LVEF data), premature ventricular contraction frequency was not predictive of mortality.

Reports by Singh et al. (28) and Teerlink et al. (25) have suggested that ambient arrhythmias may not provide independent prognostic information in patients with advanced HF. In an early study, Singh et al. (29) determined the prevalence and clinical significance of NSVT in patients with premature ventricular contractions (PVCs) and HF treated with vasodilator therapy. Patients with documented HF and on vasodilator therapy were prospectively randomized to amiodarone or placebo in the Congestive Heart Failure Antiarrhythmic Trial (CHF STAT). (30) NSVT was defined as 3 consecutive premature beats in a row, at a rate of 100 beats per minute. Fast NSVT were episodes of at least 120 beats per minute. Long

NSVT was defined as episodes of at least 15 consecutive PVCs. Twenty-four-hour Holter recordings were done at randomization; 2 weeks; and 1, 3, 6, 9, and 12 months; and then every 6 months in 674 patients with HF.

There were 666 patients: 142 without NSVT and 524 with NSVT at baseline. (29) NSVT was present in 80% of all patients. There were no significant differences between the 2 groups with respect to age; NYHA class; CAD; atrial fibrillation; hypertension or diabetes; previous bypass surgery; smoking or alcohol use; cardiomyopathy; or use of diuretics, calcium channel blockers, or ACE inhibitors. However, patients with NSVT at baseline had significantly lower ($P < .01$) mean EF (0.25 [SD, 0.08] vs. 0.28 [SD, 0.07]), larger LV internal dimension, higher density of PVC per hour, and less β -blocker use.

There was an association between NSVT and increased overall mortality and SCD using a univariate model analysis. However, after adjusting for EF, NYHA class, diuretic use, type of cardiomyopathy, LV external dimension, PVC density, and use of β -blocker or amiodarone, only EF ($P = .001$) and NYHA class ($P = .01$) independently predicted survival. The suppression of NSVT by amiodarone had no effect on total survival or on SCD. NSVT showed a trend ($P = .07$) as an independent predictor for all cause mortality but not for sudden death. Only EF was an independent predictor for sudden death. There were no significant differences between patients with slow NSVT and those with fast NSVT in all-cause mortality or sudden death. Similarly, there were no differences in mortality between the groups with long versus short NSVT.

Separate retrospective analyses were conducted to classify NSVT over time, (subsequent Holter recordings after the baseline measurement). There were 33 study patients for whom NSVT was never documented on a Holter recording, and 162 patients had NSVT documented on every study Holter. The remaining 434 patients had NSVT documented on some of the Holter recordings (ever). Death rates of the 33 patients with no documented NSVT over time were similar to patients having NSVT (ever) for overall mortality (RR, 1.30 [95% CI, 0.69–2.45]; $P = .41$) and sudden death (RR, 2.30 [0.73–7.20]; $P = .14$). Survival of patients never having NSVT was significantly better than that of patients who had NSVT documented on every Holter recording for overall (RR, 2.3 [CI, 1.20–4.47]; $P = .01$) and sudden death survival (RR, 4.20 [CI, 1.37–13.66]; $P = .01$). However, Singh et al. noted that after adjusting for baseline variables, the rates of survival related to sudden death still did not differ between groups. They concluded that the prevalence of NSVT in HF is high if the baseline rate of PVCs is more than 10 per hour.

More recently, Teerlink et al. (25) examined the independent predictive value of ambulatory ventricular arrhythmias for sudden death and all-cause mortality in the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial. Ventricular arrhythmias were analyzed and quantified by use of prespecified criteria on baseline ambulatory echocardiograms (AECGs) from patients with NYHA class III/IV symptoms and an LVEF of at least 0.35. The AECGs included PVCs over 30 per hour, couplets, NSVT, NSVT over 10 beats, and NSVT across 5 episodes. All patients were required to receive treatment with a diuretic, ACE inhibitor, and digoxin. A total of 1,080 patients, in whom technically adequate 24-hour AECGs were recorded before randomization, received double-blinded treatment with either milrinone or matching placebo. Multivariate analyses, controlled for the presence of milrinone, were provided for each of the treatment groups. There were no significant baseline differences between the placebo and treatment groups. Two hundred and ninety (27%) patients died, of whom 139 (13%) were classified as sudden deaths.

Univariate and Multivariate Predictors of Overall and Sudden Death

Univariate Cox proportional hazard models indicated that many clinical and AECG variables predicted overall mortality, sudden death, and nonsudden mortality.

Multivariate general linear proportional hazards models were used to identify independent predictors of mortality. All of the selected clinical variables (age, NYHA class, presence of CAD, EF, systolic blood pressure, and treatment arm) were significant independent predictors of overall mortality. However, EF was the most powerful clinical predictor of sudden death for all patients combined (RR, 1.06 [CI, 1.03–1.09]; $P = .001$), and for the placebo group alone (RR, 1.05 [CI, 1.01–1.10]; $P = .027$).

Because the purpose of the study was to assess the additional predictive value of AECG variables in the context of clinical variables, AECG variables were included in multivariate general linear proportional hazards models with the clinical variables. When frequency of PVC, presence of NSVT, frequency of NSVT, and duration of longest run of NSVT were added individually to the clinical variables, each was a significant independent predictor of overall mortality and sudden death. The frequency of NSVT was the most powerful (no data provided). However, additional analysis was performed using forward and backward elimination procedures in a multivariate Cox proportional hazards model that included all of the clinical variables and the 4 AECG variables, and the backward elimination multivariate analysis revealed that of all the AECG variables, only the number of NSVT episodes significantly predicted overall mortality, sudden death *and* nonsudden death mortality.

Specificity of AECGs as Predictors of Sudden Cardiac Death

Although the number of NSVT episodes was a significant predictor of sudden death (as well as overall mortality and nonsudden death) in patients with HF, the sensitivity and specificity of this finding was the clinically relevant issue. Therefore, the number of NSVT episodes was analyzed in a univariate logistic survival model with sensitivity and specificity analyses. The univariate survival model yielded false positive rates of more than 80% at all sensitivity levels of more than 50% for predicting sudden death. The receiver operating characteristic curve indicated that NSVT episodes had poor sensitivity and specificity because the variable did not discriminate between sudden death and all-cause mortality:

Subsequently, multivariate logistic models were developed that used the clinical variables with and without the number of NSVT episodes to assess the incremental additive information from this specific variable. Sensitivity and specificity analyses were performed on both of these models, and receiver operating characteristic curves were generated. The addition of the number of NSVT episodes did not provide significant incremental prognostic information as revealed by analyses that included either all patients or the placebo group alone (the receiver operating characteristic curves of the 2 models were almost superimposable).

In summary, of the several measures of AECGs that were univariate predictors (PVCs per hour, couplets, NSVT, NSVT more than 10 beats, NSVT more than 5 episodes), only the frequency of NSVT episodes was the most powerful predictor of overall mortality, sudden death, and nonsudden death after inclusion with other clinical variables in backward elimination multivariate models. However, multiple logistic analysis with models, including the clinical variables with and without the NSVT episodes variable, indicated that the frequency of NSVT did not add significant information beyond the clinical variables.

Teerlink et al. concluded that AECGs are nonspecific predictors of mortality in HF patients. Ambulatory ventricular arrhythmias in patients with moderate to severe HF did not provide significant incremental prognostic information beyond the readily available clinical variables (age, NYHA class, CAD, EF, systolic blood pressure). They recommended that until results of other trials that refute these findings are available, the presence of asymptomatic NSVT should not guide therapeutic interventions.

The results of Teerlink et al. support the study by Singh et al. (29) and suggest that AECG is not an efficient approach to screening for sudden death candidates. The patients in the Teerlink et al. study were

in NYHA class III/IV with LVEFs less than or equal to 0.35. It can be argued that ventricular arrhythmias may be more specific predictors in patients with less severe HF. However, in CHF-STAT, more than 50% of patients were in NYHA class II. (29)

Most recently, Makikallio et al. (31) evaluated the utility of Holter-based risk variables in the prediction of SCD among survivors of MI treated with modern therapy. A total of 2,130 patients were treated with modern therapeutic strategies; 94% were on β -blockers, and 70% underwent coronary revascularization. Various risk parameters from Holter monitoring were analyzed. During a median follow-up of 1,012 days, cardiac mortality was 113/2,130, including 52 SCDs. All Holter variables predicted the occurrence of SCD ($P < .01$), but only reduced postectopic turbulence slope ($P < .001$) and NSVT ($P < .01$) remained as marked SCD predictors after adjustment for age, diabetes, and EF. In a subgroup analysis, none of the Holter variables predicted SCD among those with an EF under 0.35, but many variables predicted SCD among those with an EF over 0.35, particularly postectopic turbulence slope (hazard ratio, 5.9 [95% CI 2.9–11.7]; $P < .001$).

Sustained Ventricular Tachycardia

In the presence of heart disease, sustained VT is generally viewed as a marker of increased risk for SCD from arrhythmia. (8) In a case series, Buxton et al. (32) conducted electrophysiology (EP) studies in 83 consecutive patients with spontaneous NSVT. Sustained VT was inducible in 52 patients. During a mean follow-up of 33 months, 10 patients died suddenly, 5 with CAD and 5 with dilated cardiomyopathy. Sudden death occurred in 5/15 patients with inducible sustained VT, 2/37 patients with only NSVT, and 4/31 patients without inducible VT. Multivariate analysis revealed that patients with inducible sustained VT, or an EF under 0.40 had a threefold increased risk of sudden death. Patients with both factors had a sevenfold increased risk of sudden death. Buxton et al. concluded that the most powerful predictor of risk for SCD is an LVEF under 0.40, but the presence of inducible sustained VT is an independent risk factor for sudden death.

In a small case series, Cripps et al. (33) examined the prognostic significance of inducible sustained VT in relation to other prognostic markers including clinical assessment, signal-averaged ECG, Holter monitoring, EF, and exercise testing in 75 post-MI patients. Multivariate analysis revealed that of all of the variables examined, inducible sustained VT was the only independent predictor of arrhythmic events during the follow-up period. The sensitivity for predicting arrhythmic events by this response was 100%, the specificity was 97%, and the positive predictive accuracy was 75%. Individually, the other prognostic variables were less sensitive and less accurate predictors of arrhythmic events.

Bourke et al. (34) performed EP testing in survivors of acute MI. Of 3,286 consecutive patients treated for acute MI between 1980 and 1988, EP testing was conducted in 1,209 (37%) survivors who were free of significant complications at the time of hospital discharge. The remaining 2,077 (63%) patients did not undergo testing because of patient or physician refusal (35%), uncontrolled ischemia or HF (33%), age over 70 years (29%), or death within 7 days of their MI (3%). Ventricular tachycardia with a cycle length over 230 ms and lasting longer than 10 seconds was taken as an abnormal result. (34)

Sustained monomorphic VT was inducible by programmed electrical stimulation in 75 (6.2%) patients. Antiarrhythmic therapy was not routinely prescribed regardless of test results. Eighteen (24%) of the 75 patients with inducible VT were prescribed prophylactic drug therapy for the first year of follow-up (quinidine [$n = 6$]; mexiletine [$n = 3$]; disopyramide [$n = 1$]; sotalol [$n = 5$]; metoprolol [$n = 2$]; and amiodarone [$n = 1$]). In only 4 patients, therapy was able to suppress the induction of VT at repeat EP study.

In the first year after the index MI, 14 (19%) of the 75 patients with inducible VT were either witnessed

to die instantaneously or survived a documented spontaneous episode of VT or VF in the absence of new ischemic symptoms. When the follow-up was extended (median, 28 months), this figure increased to 19 (25%) patients. An electrical event was defined as a witnessed instantaneous death or documented sustained VT or VF without new ischemia. There was a statistically significant difference in the incidence of electrical events between the inducible and noninducible groups during the first year of follow-up.

Four hundred and twenty-three patients had EF measured close to the time of hospital discharge. The proportion of MI survivors requiring EP testing, and the proportion of positive tests as a function of total EP tests performed when such a strategy was used, were calculated. Based on these results, Bourke et al. recommended that EP study be restricted to MI survivors whose LVEF is less than 0.40.

Crandall et al. (35) did a retrospective study of 194 consecutive cardiac arrest survivors who were unable to have VT induced with EP. The efficacy of ICD therapy in these patients was assessed. In all patients, efforts were made to optimize therapy of HF and MI before EP study. All of the patients underwent coronary angiography. Coronary artery bypass graft (CABG) or angioplasty procedures were performed before EP study and when clinically indicated (12% of patients). After EP study, the use of β -blockers, class I antiarrhythmic drugs or amiodarone, and treatment with CABG or angioplasty procedures, were determined by each patient's physician. The use of ICD therapy was determined by the attending physician, patient preference, and the availability of devices.

Ninety-nine patients received an ICD, and 95 did not. There were no significant differences between the 2 groups in presenting rhythm, number of prior MIs, or use of antiarrhythmic drugs. Most of the patients on antiarrhythmic therapy were treated with class I antiarrhythmic drugs (Ia, Ib, Ic, or a combination). Ten (10%) ICD patients and 11 (12%) non-ICD patients received class III antiarrhythmic drugs after the index event. Seventy (70%) of the ICD patients and 60 (63%) of the non-ICD patients received no antiarrhythmic agents. Patients treated with an ICD were younger ($P = .03$), had a lower incidence of CAD ($P = .04$), and a lower EF ($P = .04$). The mean (SD) EF in the ICD group was 43% (16%) compared with 48% (18%) in the non-ICD group.

Patients treated with an ICD had an improvement in SCD-free survival, but the overall survival rate in this group did not differ from that of the patients not treated with an ICD ($P = .91$). Crandall et al. concluded that survivors of SCD in whom no arrhythmias could be induced remained at risk for arrhythmia recurrence. The secondary prevention study by Crandall et al. has many limitations due to the retrospective study design, including patient selection bias (ICD vs. no ICD) and the confounding effects of other therapies used by the patients.

Zoni-Berisso et al. (36) assessed programmed ventricular stimulation performed before hospital discharge in patients with recent MI preselected on the basis of 24-hour electrocardiographic recording, or signal-averaged ECG, or radionuclide ventriculography ($LVEF \leq 0.40$). These 3 noninvasive tests were performed in the absence of antiarrhythmic therapy. Patients with at least 1 of the 3 conditions were considered at risk and therefore eligible for programmed ventricular stimulation. Zoni-Berisso et al. evaluated 286 consecutive patients prospectively and followed-up these patients for 12 months. One hundred and three patients were eligible for EP study, and the remaining 183 patients were discharged without further evaluation.

To assess the independent importance of inducible sustained monomorphic VT in predicting late arrhythmic events, a linear discriminant analysis was performed. When sustained VT was compared with LVEF less than or equal to 0.40, late potentials and spontaneous complex ventricular arrhythmias (NSVT), sustained VT was the most important variable independently related to late arrhythmic events ($P < .00001$), followed by LVEF under 0.40 ($P < .01$), spontaneous complex ventricular arrhythmias ($P < .05$), and late potentials ($P = NS$), ($F = 9.76$; $P < .00001$).

Furukawa et al. (37) prospectively evaluated 101 consecutive patients with CAD who had survived a cardiac arrest unassociated with an MI and had had EP testing. The mean cycle length of induced sustained VT was 268 ms (range, 20–430 ms). Inducible VT occurred in 76 (75%) patients and was suppressed by antiarrhythmic drugs or surgery in 32 (42%) of 76 patients. During a mean follow-up of 27 months, cardiac arrest recurred in 21 patients (in 2 of the 25 patients in whom VT was not inducible, in 3 of the 32 in whom inducible VT was suppressed after treatment, and in 16 of the 44 in whom inducible VT could not be suppressed after treatment).

Cumulative actuarial curves of cardiac arrest recurrence in each of the 3 subgroups of VT inducibility were constructed. Patients who had VT that could not be suppressed had a significantly higher cardiac arrest recurrence rate than those with no inducible VT ($P = .0154$), or those with an inducible VT that was suppressible by treatment ($P = .0191$).

Multivariate Cox proportional hazards analysis identified an EF under 0.35 ($P = .0013$) and persistent inducibility of ventricular tachyarrhythmia ($P = .0025$) as independent predictors of cardiac arrest recurrence for the entire follow-up period. Separate analysis of variables within and after the first 6 months showed that an EF under 0.35 was the strongest predictor for early phase recurrence ($P = .0078$), but had only marginally significant predictive value for late phase recurrence ($P = .0516$). Persistent inducibility of ventricular tachyarrhythmia had no significant predictive value for early phase recurrence ($P = .1382$), but it was the strongest predictor for late phase recurrence ($P = .0061$).

Buxton et al. (22) reported that one of the secondary goals of MUSTT was to evaluate the usefulness of EP testing for risk stratification in patients with CAD, LV dysfunction, and NSVT. The rates of death due to arrhythmia and of death from any cause among patients in whom sustained VT was not induced on EP testing ($n = 1,397$) were compared with the rates among patients with inducible VTs who were randomly assigned to receive no antiarrhythmic therapy ($n = 353$). Patients without inducible VT were followed in a registry.

Patients were followed-up for a median of 39 months. In a Kaplan Meier analysis, the 2- and 5-year rates of cardiac arrest or death due to arrhythmia were 12% and 24%, respectively, among patients in the registry, versus 18% and 32% among patients with inducible VT who were assigned to no antiarrhythmic therapy (adjusted $P < .001$). Overall mortality after 5 years was 48% among the patients with inducible VT versus 44% among patients in the registry (adjusted $P = .005$). Deaths of patients without inducible VT were less likely to be classified as due to arrhythmia than those of patients with inducible VT (45% and 54%, respectively; $P = .06$). Buxton et al. concluded that patients with CAD, LV dysfunction, and asymptomatic NSVT in whom sustained VT cannot be induced have a significantly lower risk of sudden death or cardiac arrest and lower overall mortality than do similar patients with inducible sustained VT.

A documented MI was not required for entry in MUSTT: 87% of registry patients had a history of MI versus 94% of patients with inducible sustained VT who were assigned to no antiarrhythmic therapy. Buxton and colleagues suggested that the mechanism of death among patients with LV dysfunction but no history of MI may differ from patients with a previous MI, and that EP stimulation may not provoke VT in patients with no prior MI. They gave possible reasons as to why arrhythmic events may occur in patients without inducible sustained VT:

- The results for EP testing have been reported to vary from day to day and over the long term by 10%–50%.
- The progression of CAD may lead to re-entrant tachycardia or SCD due to recurrent ischemia.
- The progression of cardiac disease can lead to HF, with its attendant risk of SCD.

Buxton et al suggested that the problem of varying EP results might be remedied by periodic repetition of EP testing in patients who are identified as potentially at risk.

Existing Treatments Other than Technology Being Reviewed

Management of tachyarrhythmia includes pharmacotherapy, catheter ablation therapy, or direct VT surgery (and ICD, the subject of this review). β -blockers and angiotensin converting enzyme (ACE) inhibitors have shown a reduction of sudden death in patients with HF, and hypolipidemic therapy may contribute additional benefit in patients with HF due to coronary disease. (38) Pharmacotherapy for VT/VF includes drugs in classes I, II, and III of the Vaughn-Williams classification scheme of antiarrhythmic drugs:

- Class Ia: procainamide, quinidine
- Class Ib: lidocaine, mexiletine, tocainide
- Class Ic: flecainide, propafenone, encainide
- Class II: acebutalol, propranolol
- Class III: amiodarone, sotalol

Due to concern over toxicity of Class Ia and Ic drugs, amiodarone is a more recent pharmacological alternative for VT/VF. However, antiarrhythmic drugs may sometimes increase the risk of arrhythmias (pro arrhythmias) and may have adverse effects. Due to this, other nonpharmacological treatments have been explored.

Catheter ablation techniques in patients with VT due to CAD and prior MI are also under study. (39) The indications to ablate VT in this population have not been agreed upon, but generally include either incessant VT that is not controlled with pharmacotherapy or episodes of VT (in a patient with an ICD) that cause frequent device discharges. (40) Some centres have successfully ablated the target VT in these patients 60% to 70% of the time; however, further research is required to improve the rate of success. (41)

New Technology Being Reviewed

An ICD is a battery-powered device that monitors heart rhythm and can deliver an electric shock to restore normal sinus rhythm when malignant arrhythmias are detected.

The generator for the early ICDs was implanted beneath the skin of the abdomen, and open heart surgery was required to attach 3 to 4 electrodes to the heart. Newer models are similar in size to a pacemaker, weigh less than 80 grams, and are placed under the skin in the pectoral (chest) region. Intraoperative testing is performed to establish appropriate pacing thresholds and adequate sensing during sinus rhythm and VF. (42) The system's defibrillation capabilities are also tested, and the shocking lead configuration is optimized.

Implantable cardioverter defibrillators are available as a single-chamber or a dual-chamber device. A right ventricular lead is used for sensing and pacing. Defibrillators that are capable of dual-chamber pacing require an additional pacing lead in the right atrium. (42) Newer units that provide cardiac resynchronization therapy (CRT) for HF (i.e., biventricular pacing) require insertion of an additional lead into a coronary vein to achieve left ventricular capture.

Implantable cardioverter defibrillators can offer graded responses to a sensed ventricular arrhythmia. Antitachycardia pacing, low energy synchronized cardioversion, and high-energy defibrillation shocks

can be delivered by a single transvenous lead. (39) For example, if an ICD detects a minor arrhythmia, it activates a built-in conventional pacemaker to restabilize cardiac rhythm. If that fails, then the ICD can deliver a small, defibrillating electrical jolt to the heart. In the extreme, the device can deliver a stronger jolt to re-establish the normal heart rhythm. (43)

Devices last from 5 to 8 years before they need to be replaced. (44)

The concept of an implantable device that will recognize and immediately treat malignant arrhythmias has not changed since 1980 when the first ICD was implanted. A number of studies (45-47) have examined the use of ICDs to prevent recurrent SCD. A meta-analysis of 3 trials (AVID, CASH, CIDS) (48) examined ICD therapy versus medical treatment for the prevention of death in survivors of VF or sustained VT. Connolly et al. (48) reported that the 3 secondary prevention trials of ICD versus amiodarone yielded a 28% reduction in the relative risk of death with the ICD.

Traditionally, ICDs have been used for secondary treatment after an episode of VT or VF. Survival rates for out-of-hospital cardiac arrest are typically low, ranging from 2% to 25% in the United States. (49) Therefore, identification and preventive therapy for patients at high risk for SCD is desirable. Ziven and Bardy (50) stated that the combined incidence of sustained ventricular arrhythmias and sudden, 'presumably' arrhythmic death in MI survivors and patients with known coronary disease is 11% to 66% at 2 years, with the highest total mortality observed in patients with concomitant congestive HF.

Subgroups of patients with the highest relative risk for SCD include survivors of out-of-hospital cardiac arrest, HF, and patients with low LVEF. (8) However, these subgroups are a small proportion of the total population burden of SCD. This makes precise identification of patients that might benefit most from ICD difficult. (13) Information is lacking on specific markers of increased risk of death from ventricular arrhythmia in the general population and among those with nonspecific and intermediate risk profiles – who together account for the largest absolute number of events.

It is important to note that there is a trade-off in targeting progressively "higher risk" subgroups of patients for an ICD. To increase the confidence with which a fatal event can be predicted in the target group, an increasing number of patients at lesser risk are excluded from planned interventions. Therefore, as the target group becomes smaller, despite the high individual risk of fatal events, it will contain a progressively smaller number of the total fatal events experienced in the entire post-MI population. Fatalities in the excluded population, even though occurring at a much lower rate, will constitute a progressively greater share of the total events in the population. Although an intervention may save many lives in a targeted group, there would be only a small impact on overall survival in the entire population. (8;51)

Regulatory Status

The following ICDs are licensed by Health Canada as Class 4 devices:

Manufactured by ELA Medical, SA (Montrouge, France):

- ALTO 2 DR ICD (licence 35708)
- ALTO 2 VR ICD (licence 64225)

Manufactured by St. Jude Medical, Cardiac Rhythm Management Division (Sylmar, California, United States):

- Photon DR ICD (licence 24153)

- Atlas DR, Atlas VR, Atlas + DR, Atlas + HF, Atlas + VR (licence 36930 for all)
- Epic DR ICD, Epic VR ICD (licence 62204)
- Epic HF ICD (licence 62788)
- Epic + DR ICD, Epic VR + ICD (licence 62840 for both)

Manufactured by Biotronik GMBH & Co. (Berlin, Germany):

- Belos VR ICD, Belos DR, Belos DR-T, Belos VR, Belos VR-T, XELOS DR T ICD (licence 30461 for all)
- Cardiac airbag (licence 62933)
- Lexos A+, Lexos A+/T, Lexos DR, Lexos DR-T, Lexos VR, Lexos VR-T (licence 63521 for all)

Manufactured by Medtronic Inc. (Minneapolis, Minnesota, United States)

- Intrinsic 30 dual-chamber ICD with MPV pacing mode, Intrinsic dual-chamber ICD with MVP pacing mode (licence 65075 for both)
- Marquis DR dual-chamber ICD, Marquis VR single-chamber ICD (licence 35080 for both)
- Maximo DR dual-chamber ICD, Maximo VR single-chamber ICD (licence 63584 for both)
- OnyxVR single-chamber ICD (licence 65050)
- Gem II DR, Gem II VR (licence 2885 for both)
- Gem III (licence 26272)
- Gem active can electrode dual-chamber ICD, Gem DR active can electrode dual-chamber ICD (licence 20434 for both)
- Jewel AF arrhythmia management system (licence 13386)
- Jewel plus PCD arrhythmia management device, 7220B,C,D,E (licence 13387)

Manufactured by Cardiac Pacemakers Inc., a wholly owned subsidiary of Guidant (St. Paul, Minnesota, United States):

- VITALITY DR automatic ICD, VITALITY VR automatic ICD, VITALITY 2 AICD (licence 63154)
- VITALITY AVT AICD (licence 65811)
- VENTAK mini HE AICD, VENTAK mini AICD, VENTAK mini+ AICD, VENTAK mini III HE, VENTAK mini IV (licence 738 for all)
- VENTAK PRIZM AVT (system) (licence 62424)
- VENTAK AV AICD, VENTAK AV II DDD AICD, VENTAK AV II DR AICD, VENTAK AV III DR AICD, (licence 990)
- VENTAK VR (licence 4300)

Literature Review on Effectiveness

Objective

The aim of this literature review was to assess the effectiveness, safety, and cost effectiveness of ICDs for the primary prevention of SCD.

Methods

Inclusion criteria

- English-language articles (January 2003–May 2005). Journal articles that report primary data on the effectiveness or cost effectiveness of prophylactic ICD, treatment obtained in a clinical setting, or analysis of primary data maintained in registries or databases
- Clearly described study design and
- Systematic reviews, randomized controlled trials (RCTs), non-RCTs, and/or cohort studies that have ≥ 20 patients, and studies on cost-effectiveness

Exclusion criteria

- Studies that are duplicate publications (superseded by another publication by the same investigator group, with the same objective and data)
- Non-English-language articles
- Non-systematic reviews, letters, and editorials
- Animal and in vitro studies
- Case reports
- Studies that do not examine the outcomes of interest

Databases searched

- Cochrane database of systematic reviews
- ACP Journal Club
- DARE
- INAHTA
- EMBASE
- MEDLINE
- Reference section from reviews and extracted articles

Outcomes of Interest

- Mortality
- Adverse effects
- Quality of life
- Economics analysis data

GRADE Quality of Evidence and Strength of Recommendations

A modification of the GRADE approach (1) was used to make judgments about the quality of evidence

and strength of recommendations systematically and explicitly. GRADE provides a framework for structured reflection and can help to ensure that appropriate judgments are made. GRADE takes into account a study's design, quality, consistency, and directness in judging the quality of evidence for each outcome. The balance between benefits and harms, quality of evidence, applicability, and the certainty of the baseline risks are considered in judgments about the strength of recommendations.

Results of Literature Search

The Cochrane and INAHTA databases yielded 3 international health technology assessments on ICDs that had been done since the Medical Advisory Secretariat did its initial health technology policy assessment. A search of MEDLINE and EMBASE since the last review was conducted using key words implantable cardioverter defibrillator, cardiac arrest, sudden cardiac death, primary prevention, prophylactic, and randomized controlled trials yielded 3 RCTs and the quality of the included articles is presented in Table 1.

Table 1: Quality of Evidence

Study Design	Level of Evidence	Number of Eligible Studies
Large RCT, systematic reviews of RCTs*	1	3
Large RCT unpublished but reported to an international scientific meeting	1(g)†	
Small RCT	2	
Small RCT unpublished but reported to an international scientific meeting	2(g)	
Non-RCT with contemporaneous controls	3a	
Non-RCT with historical controls	3b	
Non-RCT presented at international conference	3(g)	
Surveillance (database or register)	4a	
Case series (multi-site)	4b	
Case series (single site)	4c	
Retrospective review, modeling	4d	
Case series presented at international conference	4(g)	

*RCT indicates randomized controlled trial.

†g refers to grey literature.

Updated Summary of Existing Health Technology Assessments

Table 2 shows an updated summary of international health technology assessments that examined the prophylactic use of ICDs. A detailed summary of each health technology assessment follows.

Table 2: Updated Summary of International Health Technology Assessments

Country	Organization	Date	Conclusion
United States	Blue Cross Blue Shield (52)	March 2005	Symptomatic ischemic or nonischemic cardiomyopathy, and ejection fraction \leq 0.35
United States	Centers for Medicare & Medicaid Services (6)	January 2005	Ischemic or nonischemic cardiomyopathy, NYHA* II/III heart failure, and ejection fraction \leq 0.35.
			(Allocated \$10 billion for ICD* primary prevention for 2005/06)

United Kingdom	National Institute for Clinical Excellence (53)	June 2005	Prior myocardial infarction and all of the following: - inducible VT* on electrophysiologic testing - ejection fraction \leq 0.35 - non-sustained VT on Holter monitoring - no worse than NYHA class III heart failure
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*ICD indicates implantable cardioverter defibrillation; NYHA, New York Heart Association; VT, ventricular tachyarrhythmia.

Blue Cross Blue Shield Association Technology Evaluation Center, March 2005

The Blue Cross Blue Shield Association Technology Evaluation Center (TEC) (52) divided primary prevention into 3 groups:

- Prior MI, reduced LVEF (i.e., chronic, ischemic cardiomyopathy)
 - MADIT, MADIT II, MUSTT, Coronary Artery Bypass Graft Patch Trial, SCD-HeFT and Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure trial (COMPANION)
- Recent MI, reduced LVEF (i.e., acute ischemic cardiomyopathy)
 - Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), Beta-Blocker Strategy Plus Implantable Cardioverter Defibrillator study, and the Immediate Risk Stratification Improves Survival study
- No prior MI, reduced LVEF (i.e., nonischemic dilated cardiomyopathy)
 - Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE), AMIOVIRT, SCD-HeFT, COMPANION, Primary Prevention of Sudden Cardiac Death in Idiopathic Dilated Cardiomyopathy (CAT), meta-analysis of these 5 trials by Desai et al. in 2004. (54)

“The assessment did not specifically address the use of ICD in patients with congenital syndromes and acquired disease that predispose to SCD such as long QT syndrome, the Brugada syndrome, LV hypertrophy, sarcoidosis, and arrhythmogenic right ventricular dysplasia. These conditions are uncommon and it is unlikely that RCTs will be conducted in these populations.” (52)

Blue Cross Blue Shield summarized the results of the trials that evaluated the role of ICDs in primary prevention (Tables 3 and 4). (52)

Table 3: Summary of Primary Prevention Studies Modified From Blue Cross Blue Shield Association Technology Evaluation Center*

Study†	Follow-up (Months)	Hazard Ratio for Mortality (95%CI)	Absolute Mortality Benefit, %	Number Needed To Treat
MADIT I	27	0.4 (0.26–0.82)	22.8	4.4
MADIT II	20	0.69 (0.51–0.93)	5.6	17.9
CABG Patch	32	1.07 (0.81–1.42)	–	–
DEFINITE	29	0.65 (0.40–1.06)	5.3	18.9
DINAMIT (Recent MI)	30	1.08 (0.76–1.55)	–	–
SCD-HeFT Total	60	0.77 (0.62–0.96)	7.2	13.9
SCD-HeFT Nonischemic	60	0.73 (0.50–1.07)	6.5	15.4
SCD-HeFT Ischemic	60	0.79 (0.60–1.04)	7.3	13.7

†MADIT I: Multicentre Automatic Defibrillator Implantation Trial I; MADIT II: Multicentre Automatic Defibrillator Implantation Trial II; CABG Patch: Coronary Artery Bypass Grafting Patch trial; DEFINITE: Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation; DINAMIT: Defibrillators in Acute Myocardial Infarction Trial; SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial.

*Modified with permission. Blue Cross Blue Shield Technology Evaluation Centre Assessment Program. Use of implantable cardioverter defibrillators for prevention of sudden death in patients at high risk for ventricular arrhythmia. Volume 19, Number 19. 2005. Blue Cross Blue Shield Association; Summary table, page 32. (52)

Table 4: Comparison of Studies on Implantable Cardioverter Defibrillators for Primary Prevention of Sudden Cardiac Death*

Study, Year†	N	Control Groups	LVEF‡	NYHA‡ Class	Cardiomyopathy	Ventricular Arrhythmia History		
						Asymptomatic NSVT‡	Noninvasive Tests	EPS Used
Prior MI‡								
MADIT II, 2002	1232	Best Med	≤ 30	1–3	Ischemic Prior MI	No	No	No
Stopped MADIT, 1996	196	Med	≤ 35	1–3	Ischemic Prior MI	√	Holter	√ Inducible VT/VF‡
MUSTT, 1999	704	Med	≤ 40	1–4	Ischemic CAD‡ ± MI	√		√ Inducible VT/VF
CABG Patch, 1997	900	Med	≤ 35	1–4	Ischemic CAD ± MI		SAECG	No
Recent MI								
DINAMIT 2004	674	Best Med	≤ 35	1–3	Ischemic Prior MI		Holter Depressed HR variability	
Prior MI or no prior MI								
SCD-HeFT 2005	2521	Placebo Amiodarone	≤ 35	2–3	Ischemic CAD ± MI		No	No
No prior MI								
DEFINITE, 2004	458	Best Med	≤ 35	1–3	Nonischemic dilated	√	√ Holter	No
AMIOVIRT, 2003	103	Best Med + Amiodarone	≤ 35	1–3	Nonischemic dilated	√		No
Stopped CAT, 2002	104	Meds	≤ 30	2–3	Nonischemic dilated Recent onset			√

† MADIT II: Multicentre Automatic Defibrillator Implantation Trial II; MADIT I: Multicentre Automatic Defibrillator Implantation Trial I; MUSTT: Multicentre Unsustained Tachycardia Trial; CABG Patch: Coronary Artery Bypass Grafting Patch trial; DINAMIT: Defibrillators in Acute Myocardial Infarction Trial; SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial; DEFINITE: Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation; AMIOVIRT: Amiodarone versus Implantable Defibrillator in Patients With Nonischemic Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia trial; CAT: Primary Prevention of Sudden Cardiac Death in Idiopathic Dilated Cardiomyopathy trial.

‡ LVEF indicates left ventricular ejection fraction; MI, myocardial infarction; CAD, coronary artery disease; NSVT, nonsustained VT; VT, ventricular tachycardia; VF, ventricular fibrillation; NYHA, New York Heart Association.

*Modified with permission. Blue Cross Blue Shield Technology Evaluation Centre Assessment Program. Use of implantable cardioverter defibrillators for prevention of sudden death in patients at high risk for ventricular arrhythmia. Volume 19, Number 19. 2005. Blue Cross Blue Shield Association; Table 3, p. 17. (52)

The TEC report concluded that the use of ICD devices meets the TEC criteria in the prevention of SCD in patients who have the following conditions:

- Symptomatic (defined as the presence of dyspnea (shortness of breath) on exertion, angina, palpitations, or fatigue) ischemic dilated cardiomyopathy with a history of MI at least 40 days before ICD treatment and EF equal to or less than 0.35; or
- Symptomatic (defined as the presence of dyspnea on exertion, angina, palpitations, or fatigue) nonischemic dilated cardiomyopathy for more than 9 months and EF equal to or less than 0.35.

The use of ICD devices does not meet the TEC criteria in the prevention of SCD in patients that:

- Have had an acute MI (fewer than 40 days before ICD treatment);
- Have NYHA class IV HF;
- Have had cardiac revascularization procedure in the past 3 months (CABG surgery or percutaneous transluminal coronary angioplasty (PTCA) or are candidates for a cardiac revascularization procedure; or
- Have noncardiac disease that would be associated with life expectancy less than or equal of 1 year.

Centers for Medicare and Medicaid Services, January 2005

The Centers for Medicare and Medicaid Services (CMS) (55) systematically reviewed the use of ICDs for the primary prevention of SCD. The June 2003 CMS systematic review was updated to include the following RCTs:

- CAT
- AMIOVIRT
- DEFINITE
- COMPANION
- DINAMIT
- SCD-HeFT

Studies That Examined Patients with Ischemic Dilated Cardiomyopathy and Patients with Nonischemic Dilated Cardiomyopathy

For the COMPANION trial, CMS arrived at the following conclusions:

- There were several issues with the design, conduct, and analysis of the trial.
- There was an unequal 1:2:2 randomization ratio weighted toward device therapy. An equal 1:1:1 randomization format is generally considered more neutral.
- The definition of hospitalization was changed during the course of the trial without notifying the United States Food and Drug Administration (FDA). This potentially had a direct impact on the primary outcome, because hospitalization was the dominating factor for the composite endpoint. Data should have been collected and reported using both definitions to determine if the change favoured one group over another.
- Many patients withdrew from the pharmacologic therapy group, many of whom obtained device therapy. Patients that were subsequently lost to follow-up were censored in the analyses, which may have led to an inaccurate estimation of the mortality rate.
- All of the above issues hamper the strength of the findings of the COMPANION trial.
- CMS stated, "Since it was the only trial to evaluate mortality for patients with CRT and CRT/ICD therapy, additional research is needed to support the findings of this trial."(55)

For the SCD-HeFT trial, CMS arrived at the following conclusions:

- The absolute reduction in mortality was modest for a trial with a median follow-up of 45.5 months.
- Several explanations were suggested for the modest overall effect compared to prior ICD trials:
 - In SCD-HeFT, appropriate medications for HF were recommended for all patients.
 - SCD-HeFT also included patients with nonischemic dilated cardiomyopathy. As with other studies on patients with nonischemic dilated cardiomyopathy, SCD-HeFT showed that overall

mortality is lower for patients with nonischemic dilated cardiomyopathy compared to patients with ischemic dilated cardiomyopathy,

- The follow-up period was extended by 1 year but the reason for doing so was not fully explained. This presents problems:
 - According to Newman. (56) SCD-HeFT recruited for a "...longer time period. The data and safety monitoring board of SCD-HeFT have prolonged the trial's followup phase so as to enrich the sample in outcome events." No further details of the extended follow-up were identified in the literature.
 - "Towards the scheduled end of a study, the investigator may find nearly statistically significant results. Therefore, an investigator may be tempted to extend or expand the trial in an effort to make the test significant. A strategy of extending assumes that the observed relative differences in rates of response will continue. The observed differences which are projected for a larger sample may not hold." (55)
 - "In addition, because of the multiple testing issue and the design change, the significance level should be adjusted downward." (55)
 - Adjustments to sample size or the length of follow-up should be made as early in the trial as possible. Early adjustments would diminish the criticism that the monitoring committee waited until the last minute to see if the results would achieve some prespecified significant level before changing the study design.
 - According to Klein et al., (57) the SCD-HeFT design had patients enrolled over 2.5 years, and after the end of enrollment, a minimum of 2.5 year follow-up is mandatory. The overall death incidence over a period of 2.5 years is hypothesized to be 25%. The study assumes a 90% power for detecting a 25% mortality reduction, assuming > 25% mortality within 2.5 years in the control group.
- CMS stated that overall, the results of SCD-HeFT provide evidence that a simple single-lead ICD has benefits.

In their review, CMS asked if there was enough evidence to conclude that ICDs decrease mortality for patients with ischemic dilated cardiomyopathy and reduced LVEF. In seeking to answer that question, they noted the following:

- MADIT II had an LVEF ≤ 0.30 as an inclusion criterion.
- SCD-HeFT included patients with an LVEF ≤ 0.35
 - The hazard ratio for LVEF ≤ 0.30 (n = 2098) was 0.73 (CI, 0.57–0.92)
 - The hazard ratio for LVEF ≥ 0.30 (n = 422) was 1.08 (CI, 0.57–2.07)
- The other trials reviewed had LVEF inclusion criteria that ranged from 0.30 to 0.35, but did not stratify their results by LVEF categories.
- Other previously reviewed trials (MADIT, MADIT II, MUST, CABG) had varying LVEF inclusion criteria from 0.30 to 0.40.

In evaluating studies that examined patients with nonischemic dilated cardiomyopathy, CMS asked if there was evidence to conclude that ICDs decrease mortality for patients with nonischemic dilated cardiomyopathy and reduced LVEF. In addressing this question, they noted the following:

- Fewer ICD trials have been conducted for nonischemic dilated cardiomyopathy than for ischemic dilated cardiomyopathy.
- AMIOVIRT, CAT, and DEFINITE did not demonstrate a clear role for the use of ICDs for patients with nonischemic dilated cardiomyopathy.
- SCD-HeFT enrolled 792 patients with nonischemic dilated cardiomyopathy as 1 prespecified subgroup and showed a reduction in the mortality hazard ratio for patients who received ICDs

compared with those in the control group, but it was not statistically significant (hazard ratio 0.73; 95% CI, 0.50–1.07).

- In COMPANION, which added prolonged PR and QRS interval as inclusion criteria, there were 678 patients with nonischemic dilated cardiomyopathy and a significant reduction in mortality in the CRT/ICD group compared with the optimal pharmacologic therapy group (hazard ratio 0.50; 95% CI, 0.29–0.88).
- Considered together, CAT, AMIOVIRT, DEFINITE, SCD-HeFT, and COMPANION present conflicting evidence in the use of ICDs for patients with nonischemic dilated cardiomyopathy and reduced LVEF.
- CAT, AMIOVIRT, and DEFINITE indicated need for further risk stratification of this population
 - CAT studied patients with recent-onset nonischemic dilated cardiomyopathy (≤ 9 months)
 - DEFINITE, COMPANION, and SCD-HeFT evaluated patients with chronic nonischemic dilated cardiomyopathy (mean duration 2.8 years, 3.6 years, and 2 years, respectively).
 - COMPANION supported the use of prolonged PR and QRS duration as risk stratifiers and showed that the mortality risk reduction was greatest in patients with prolonged QRS interval and nonischemic dilated cardiomyopathy.
- Of the 5 relevant studies, 2 (COMPANION, SCD-HeFT) showed a significant reduction in mortality overall but not specifically for patients with nonischemic dilated cardiomyopathy
 - SCD-HeFT presented evidence for a broad approach, but this evidence is tempered by the negative findings of AMIOVIRT, CAT, and DEFINITE and the restricted population of the COMPANION trial.

In conclusion, CMS stated, “based on the overall results of SCD-HeFT with support from COMPANION, there is evidence that ICDs decrease mortality for patients with NIDCM and reduced LVEF.” (55)

Evaluation of Patient Selection

- Although SCD-HeFT demonstrated a statistically significant reduction in mortality, the absolute reduction was modest. A relatively small proportion (21.4%) of the ICD group received an appropriate shock over the course of the trial. The firing rate was slightly higher than the overall firing rate (19%) seen in MADIT II, which had a shorter mean follow-up (20 months).
- A large proportion of patients who received an ICD never received any therapy from their device; therefore, consideration of additional risk stratification methods would be reasonable. During the follow-up period of SCD-HeFT, cardiac disease may have progressed, and other relevant characteristics likely changed in patients.

Drugs

- In SCD-HeFT, an attempt was made to ensure all patients received optimal medical therapy (β -blockers, ACE inhibitors, aldosterone blocking diuretics, aspirin, and statin therapy).
 - CMS suggested that optimal medical therapy likely had an important role in reducing overall mortality rates in all groups.
 - The mortality rate in the placebo group was lower than the rates in most prior trials.
 - CMS stated that optimizing medications for all patients should be emphasized.

NYHA Class

- Most ICD studies enrolled patients with NYHA class I–III symptoms.
- Although a subjective measure, it has been routinely used as a patient inclusion criterion
- Patients with NYHA class I and LVEF 0.30–0.35 were not included in MADIT or SCD-HeFT.

- Patients with NYHA class IV have been excluded in the large primary prevention trials such as SCD-HeFT and MADIT II.
- COMPANION was the only trial to include class IV patients. Separate subgroup analyses of class IV patients were not reported, but 14% of patients (219 of 1520) were identified as class IV.
- CMS stated, “due to the inclusion of patients with NYHA class IV HF in COMPANION and the industry and public comments that were received urging CMS to cover this population, we will expand ICD coverage to patients who meet all current CMS coverage requirements for cardiac resynchronization therapy.” (55)

Acute MI

- Based on the data from DINAMIT, an ICD should not be implanted within 40 days of an acute MI.

QRS Interval

- Given the body of evidence from ICD and CRT trials, prolonged QRS interval remains a potentially useful risk stratifier which could be considered for defining the level of baseline risk and likely benefit from an ICD. With further research on CRT and CRT-D devices, more information may be available.

Type of ICD

- In SCD-HeFT, single-lead ICDs with basic programming were used; they were not programmed for antitachycardia pacing.
- The evidence on the benefits of antitachycardia pacing is sparse and inconclusive.
- The number of adverse events, including lead fractures, increases with the number of leads implanted.
- CMS stated, “Since SCD-HeFT demonstrated a significant reduction in mortality from a single lead device and it enrolled by far the most patients of any trial, a single lead device is clinically appropriate and sufficient for primary prevention of SCD”. (55)
- Indiscriminate pacing may increase the risk of adverse events such as hospitalization for HF. This is consistent with the SCD-HeFT results which had a lower adverse event rate compared to prior trials such as the Dual Chamber and VVI Implantable Defibrillator trial and MADIT II.
- CMS did not limit coverage based on the type of ICD. However, providers must be able to justify the medical necessity of devices other than single lead devices.

Cardiac Resynchronization (Biventricular pacing) Plus ICD Therapy

- COMPANION examined CRT/ICD therapy; however, this trial had serious methodological limitations as mentioned previously.
- CMS stated, “Since there are no other published or reported trials powered to corroborate the findings of COMPANION on the outcome of mortality, the evidence on the benefit of adding CRT to ICD therapy is insufficient.” (55)
- “Since CRT alone did not significantly reduce mortality in COMPANION, the observed benefit from CRT/ICD was probably due to the defibrillator. Further research on CRT and CRT/ICD is needed.” (55)

National ICD Database

- Since CMS is concerned that the available evidence does not provide a high degree of guidance to providers to target these devices to patients who will clearly derive benefit, CMS requires that reimbursement for ICDs for primary prevention of SCD occur only if the beneficiary receiving the

ICD is enrolled in either an FDA-approved category B IDE clinical trial, a trial under the CMS clinical trial policy, or a qualifying data collection system including approved clinical trials and registries.

Microvolt T-Wave Alternans (MTWA)

- CMS “encourages the inclusion of MTWA in subsequent clinical trials, registries and other data collection protocols in order to further evaluate this promising risk stratification technology.” (55)

Conclusion of the Review by the Centers for Medicare and Medicaid Services

CMS will expand coverage as follows:

- CMS has determined that the evidence is adequate to conclude that an ICD is reasonable and necessary for the following:
 - Patients with ischemic dilated cardiomyopathy, documented prior MI, NYHA class II and III heart failure, and measured LVEF ≤ 0.35 ;
 - Patients with nonischemic dilated cardiomyopathy > 9 months, NYHA Class II and III heart failure, and measured LVEF ≤ 0.35 ;
 - Patients who meet all current CMS coverage requirements for a CRT device and have NYHA class IV heart failure;

For each of these groups, the following additional criteria must also be met:

- Patients must be able to give informed consent;
- Patients must not have:
 - Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm;
 - Had a CABG or PTCA within the past 3 months;
 - Had an acute MI within the past 40 days;
 - Clinical symptoms or findings that would make them a candidate for coronary revascularization;
 - Irreversible brain damage from preexisting cerebral disease;
 - Any disease, other than cardiac disease (e.g. cancer, uremia, liver failure), associated with a likelihood of survival less than one year;
- Ejection fractions must be measured by angiography, radionuclide scanning, or echocardiography;
- Myocardial infarctions must be documented and defined according to the consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction;
- The beneficiary receiving the ICD implantation for primary prevention is enrolled in either an FDA-approved category B IDE clinical trial, a trial under the CMS Clinical Trial Policy, or a qualifying data collection system including approved clinical trials and registries. Initially, an ICD database will be maintained using a data submission mechanism that is already in use by Medicare-participating hospitals to submit data to the Iowa Foundation for Medical Care – a Quality Improvement Organization contractor—for determination of reasonable, necessary, and quality improvement. Initial hypothesis and data elements are specified in this decision and are the minimum necessary to ensure the device is reasonable and necessary. Data collection will be completed using the ICDA (ICD Abstraction Tool) and transmitted via QNet (Quality Network Exchange) to the Iowa Foundation for Medical Care, which will collect and maintain the database. Additional stakeholder-developed data collection systems to augment or replace the initial QNet system, addressing at a minimum the hypotheses specified in this decision, must meet the following basic criteria:
 - Written protocol on file;
 - Institutional review board review and approval, if required;

- Scientific review and approval by 2 or more qualified individuals who are not part of the research team;
- Certification that investigators have not been disqualified.
- For purposes of this coverage decision, CMS will determine whether specific registries or clinical trials meet these criteria.
- Providers must be able to justify the medical necessity of devices other than single-lead devices. This justification should be available in the patient medical record.

CMS has determined that the evidence, though less compelling at this time, is adequate to conclude that an ICD is reasonable and necessary for patients with nonischemic dilated cardiomyopathy for more than 3 months, NYHA Class II or III heart failure, and measured LVEF ≤ 0.35 , only if the following additional criteria are also met:

- Patients must be able to give informed consent;
- Patients must not have:
 - Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm;
 - Had a CABG or PTCA within the past 3 months;
 - Had an acute MI within the past 40 days;
 - Clinical symptoms or findings that would make them a candidate for coronary revascularization;
 - Irreversible brain damage from pre-existing cerebral disease;
 - Any disease, other than cardiac disease (e.g. cancer, uremia, liver failure), associated with a likelihood of survival less than 1 year
- Ejection fractions must be measured by angiography, radionuclide scanning, or echocardiography;
- Myocardial infarctions must be documented and defined according to the consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction;
- The beneficiary receiving the ICD implantation for this indication is enrolled in either an FDA-approved category B IDE clinical trial, a trial under the CMS Clinical Trial Policy, or a prospective data collection system meeting the following basic criteria:
 - Written protocol on file;
 - Institutional review board review and approval;
 - Scientific review and approval by 2 or more qualified individuals who are not part of the research team;
 - Certification that investigators have not been disqualified.
- For purposes of this coverage decision, CMS will determine whether specific registries or clinical trials meet these criteria.
- Providers must be able to justify the medical necessity of devices other than single lead devices. This justification should be available in the patient medical record.
- There is still a considerable mortality rate for patients who have received ICDs:
 - Patients treated with an ICD in SCD-HeFT had a 22% mortality rate overall.
 - Patients treated with a CRT/ICD in COMPANION had a 17.6% mortality rate at 1 year.

“Since ICDs only treat VT, do not prevent death from other cardiac or noncardiac disease, and may cause adverse events, such as inappropriate shocks and worsening HF, they should not be perceived as or projected to be an ideal technology that eliminates significant health risks for patients with HF. Risk factor reduction and optimal medical therapy as encouraged in SCD-HeFT remain crucial in reducing overall mortality from SCD.”

Technology Assessment Report Commissioned by the HTA Programme on Behalf of the National Institute for Clinical Excellence, January 2004

Bryant et al (58) conducted a systematic review to examine the clinical effectiveness and cost-effectiveness of ICDs. At the time this report was being written, the document was considered a confidential draft on the Web site of the National Clinical Institute for Clinical Excellence (NICE).

The report summarized ICD studies; however, no definitive conclusions were reached. The appraisal consultation document corresponding to the systematic review provided preliminary recommendations from the committee. (53)

The committee understood that the evidence base for primary prevention had extended since the 2000 guidance, with the publication of the MADIT II, DEFINITE, and SCD-HeFT trials. The important difference between the recent trials and the older MADIT I/MUSTT trials is the lack of a requirement that patients must undergo EP testing to assess inducibility of their arrhythmia on enrolment, which was a requirement in MADIT I/MUSTT. This was also a requirement of the 2000 NICE guidance for the use of ICDs in primary prevention.

The committee discussed the need for EP testing. It carefully considered the new clinical evidence from MADIT II, DEFINITE, and SCD-HeFT. It was persuaded that patients in whom EP testing had shown inducibility of their arrhythmia were at higher baseline risk of subsequent SCD and had more to gain from implantation of an ICD. Conversely, patients in the trials in whom inducibility of the arrhythmia had not been tested were at lower risk of subsequent SCD. Consequently, the committee was also persuaded that the relative risk of death for patients who had shown inducibility of their arrhythmia was greater than that for patients who had not been tested.

The committee also concluded that the trials in which inducibility of the arrhythmia had not been tested included heterogeneous patient populations, as they comprised people who would have shown inducibility on an EP test and those who would not have done if they had the test. It therefore concluded that mixed populations of patients in the newer trials indicated that the average relative risk of SCD for the non-EP tested group might have been substantially lower if the people who would have been positive on testing had been stratified separately in the trial.

The committee also considered the cost of using EP testing to determine the need for an ICD would be a little over £1000 per person tested, and given that about one-third of people who have had an EP test show inducibility and receive an ICD the cost per implantation would be a little over £3000. It concluded that this additional cost would not influence the resulting ICERs significantly.

The committee heard from clinical experts that although EP testing was a relatively safe procedure, patients found it uncomfortable. The experts estimated that the rate of death associated with the procedure was about 1 in 3000. The experts stated that removing the need for EP testing would enable ICDs to be implanted at district general hospitals where EP facilities were not available, rather than only at health care facilities with specialist units.

Results from the final Buxton and Sharples model for the EP testing strategy (assuming 3 tests to identify 1 person) ranged from £21,000 to £23,000 per additional QALY for people with an LVEF of 0.35 when a lifetime horizon was assumed. The committee concluded that these estimates are within acceptable limits of cost-effectiveness.

The committee noted that the economic evaluation jointly submitted by the manufacturers (which was based on MADIT II criteria) suggested that the cost-effectiveness of primary prevention compared with medical management alone was about £39,000 per additional QALY. The Buxton and Sharples economic evaluation for this group, assuming a lifetime horizon, an LVEF less than 0.35, a replacement rate of 6%, and an ICD acquisition and implantation cost of £16,250, suggested that the incremental cost per QALY was between £33,000 and £46,000, depending on if the baseline risk of death was 7% or 12%.

Taking all recent and previous trial evidence into account, the committee was not persuaded that extending the use of ICDs for primary prevention to the MADIT II-type populations (that is, those in whom EP testing for arrhythmia inducibility had not been carried out) was a cost-effective use of NHS resources. It considered that neither the baseline risks (7% to 12%) of patients in this category, nor, more specifically, the patient's capacity to benefit as indicated by the relative risk reduction of SCD (25% to 30%), was sufficient to extend ICD implantation to all patients within this group. It discussed with the clinical experts the possibility of considering subgroups of this population, that is, patients with additional risk factors, such as very low LVEF (for example, < 20%), prolonged QRS duration, and clinical evidence of HF. However, it considered that the evidence relating to these risk factors has not been established, nor has it been evaluated for cost effectiveness. Thus, it concluded that, for now, the eligibility criteria to receive an ICD should not be expanded.

The committee discussed the potential importance of the use of CRT in patients who might also be eligible for ICD implantation. It was aware of evidence that, in the MADIT II study, the clinical baseline criteria of a sizeable proportion of patients significantly overlapped with those from more recent trials on the use of CRT (for example, the presence of overt HF and prolonged QRS duration). The committee considered that although it was not currently appraising the use of CRT, this was an important issue, as it meant that patients who were originally enrolled in the MADIT II trial might now be considered for CRT with or without ICD implantation. The clinical experts agreed with this. Accordingly, the committee concluded that its views, current deliberations and conclusions on the use of ICDs would not be affected by this but that review of the guidance would be necessary when CRT was being appraised at a later date.

The committee understood that the clinical evidence base relating to familial cardiac conditions with a high risk of SCD, including long QT syndrome (a disorder of the heart's electrical rhythm), hypertrophic cardiomyopathy (a form of heart disease that causes the muscle of the heart to thicken), Brugada syndrome (a congenital condition that causes unexpected sudden death in people who appear healthy), arrhythmogenic right ventricular dysplasia, and following repair of Tetralogy of Fallot (a type of congenital heart defect) has not changed since the publication of the previous NICE guidance. On this basis, the Committee concluded that this part of the guidance should not change.

Proposed recommendations for further research from NICE:

- Little research appears to be ongoing in the area of primary prophylaxis using ICDs for people with arrhythmias, although there are some small risk stratification studies in progress. Additionally, the MADIT-CRT study is measuring the impact of the earlier use of biventricular pacing in the context of the possible need for defibrillation.
- The clinical effectiveness of ICDs for primary prevention for people with LVEF < 0.35 and who have had a previous MI but who are not inducible on EP testing has not been established. It may be possible to do so by supplementary analysis of existing trial data; if not, more research in this area is needed.
- Up-to-date analysis is required to establish the risk factors that would lead to more clinically effective (and therefore more cost-effective) provision of ICDs. Again, it is possible that this work could be carried out by analyzing existing trial data.

NICE recommended the use of ICDs be routinely considered for patients in the following categories:

- Primary prevention – that is, for patients with: a history of previous MI and all of the following:
 - NSVT on Holter (24-hour ECG) monitoring
 - Inducible VT on EP testing
 - Left ventricular dysfunction with an LVEF < 0.35 and no worse than class III of the NYHA functional classification of heart failure.

- A familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular dysplasia, and following repair of Tetralogy of Fallot.

Summary of Updated Medical Advisory Secretariat Review: Studies Other Than Health Technology Assessments

In the 2003 health technology assessment, results for SCD-HeFT, DEFINITE, and DINAMIT were available only in the grey literature. Since the 2003 assessment, full, final published results have been available for SCD-HeFT, DEFINITE, and DINAMIT. These studies are described below.

Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)

Bardy et al. (4) randomly assigned 2521 patients with NYHA class II or III HF and a LVEF \leq 0.35 to conventional therapy for HF plus placebo (n = 847), conventional therapy plus amiodarone (n = 845), or conventional therapy plus a conservatively programmed shock-only single-lead ICD (n = 829). Placebo and amiodarone were administered in a double-blinded fashion. The primary endpoint was death from any cause.

Prespecified subgroups analyzed by the authors were cause of HF and NYHA class.

Similar to MADIT II, SCD-HeFT did not use any markers of arrhythmia to identify high risk patients. All patients were required to receive treatment with a β -blocker and an ACE inhibitor, as well as aldosterone, aspirin, and statins, when appropriate.

The median LVEF in patients was 0.25; 70% were in NYHA class II, and 30% were in NYHA class III. The cause of HF was ischemic in 52% and nonischemic in 48%. The median follow-up was 45.5 months.

There were 244 (29%) deaths in the placebo group, 240 (28%) in the amiodarone group and 182 (22%) in the ICD group.

Amiodarone Versus Placebo

Intent-to-treat analysis of mortality for amiodarone versus placebo yielded a hazard ratio of 1.06 (97.5% CI, 0.86–1.30; $P = .53$). When patients were analyzed according to NYHA class II or III, the hazard ratios were 0.85 (0.65–1.11) and 1.44 (1.05–1.97), respectively. Similarly, when patients were analyzed according to HF etiology, the hazard ratio for ischemic HF was 1.05 (0.81–1.36); for nonischemic HF, it was 1.07 (0.76–1.51).

Further subgroup analyses by gender, LVEF, age, QRS duration, enrolling country (United States and not the United States), use of β -blockers, and diabetes did not produce a statistically significant hazard ratio.

Implantable Cardioverter Defibrillator Versus Placebo

Intent-to-treat analysis of mortality for ICD versus placebo yielded a hazard ratio of 0.77 (0.62–0.96); $P = .007$. When patients were analyzed according to NYHA class II or III, the hazard ratios were 0.54 (0.40–0.74) and 1.16 (0.84–1.61), respectively. Similarly, when patients were analyzed according to HF etiology, the hazard ratio for ischemic HF was 0.79 (0.60–1.04); for nonischemic HF, it was 0.73 (0.50–1.04).

Bardy et al. concluded that in patients with class II or III HF, with an LVEF less than or equal to 0.35, and on good background drug therapy, the mortality rate for placebo-controlled patients is 7.2% per year over 5 years. He found that simple, shock-only ICDs decrease mortality by 23%, and that amiodarone, when used as a primary preventive agent, does not improve survival

Limitations to SCD-HeFT include the following:

- Similar to MADIT II, the investigators cast a wide net with regard to the patient inclusion criteria, and by doing such may have diluted the population at true risk of SCD. No attempt was made to optimize the selection process (markers of arrhythmia) to select the patients who might benefit the most.
- Subgroup benefits are considered credible if they are prespecified, have a significant interaction with treatment, and are considered biologically plausible.
 - The NYHA subgroups were prespecified, and the results of the interaction tests were significant. However, the subgroup effect was not anticipated before data analysis.
 - The general trend in prior trials had been for the relative treatment effect to be nearly constant and for the treatment benefit to be larger in absolute terms for sicker patients.
 - It's uncertain if the treatment differences that were observed in NYHA class subgroups are biologically plausible.
 - The effect of ICD therapy in patients with HF may differ substantially depending on the programming of the device; whether single-, dual-, or triple-chamber devices are used; whether antibradycardia pacing or rate responsive pacing is used; according to which detection algorithm is used; and whether antitachycardia pacing maneuvers are used for VT. Bardy et al. evaluated only very conservatively programmed ICDs with a conservative detection algorithm and shock-only therapy. Therefore, caution should be used in extrapolating the results of Bardy et al. to other approaches to ICD therapy such as those involving dual-chamber or biventricular pacing.

Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation Trial (DEFINITE)

The study population of DEFINITE (59) included 458 patients with nonischemic cardiomyopathy and LVEF < 0.35 and NSVT or PVCs. (59) All patients were treated with standard therapy. A total of 229 patients were randomly assigned to receive standard medical therapy, and 229 to receive standard medical therapy plus a single-chamber ICD. The primary endpoint was all-cause mortality. Secondary endpoints were quality of life and mechanism of death.

Patients were followed for a mean (SD) of 29.0 (14.4) months. Mean LVEF was 0.21. Most patients were treated with ACE inhibitors (86%) and β -blockers (85%).

There were 28 deaths in the ICD group and 40 deaths in the standard therapy group (hazard ratio, 0.65 [95% CI, 0.40–1.06]; $P = .08$). The mortality rate at 2 years was 14.1% in the standard therapy group (annual mortality rate, 7%), and 7.9% in the ICD group.

There were 14 sudden deaths from arrhythmia in the standard therapy group, and 3 in the ICD group (hazard ratio, 0.20 [95% CI, 0.06–0.71]; $P = .006$).

Limitations to DEFINITE include the following:

- On the basis of data available at the time the study was designed, more than 50% of the deaths were expected to be due to arrhythmia; therefore, the trial was powered to detect a 50% difference in the rates of death from any cause. However, about one-third of the deaths in the standard therapy group were due to arrhythmia.
- 85% of the patients in the study were treated with ACE inhibitors and β -blockers – a higher compliance than reported in other studies. The authors suggested that the lower-than-expected rate of sudden death from arrhythmia may have been due to the high rate of use of β -blockers and ACE inhibitors, which could have resulted in the nonsignificant reduction in deaths from any cause.
- Amiodarone use was discouraged owing to concern that its use would limit the ability to titrate β -blockers to the therapeutic doses.

Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)

DINAMIT (60) was an open, multicentre, randomized prospective study designed to assess the impact of ICD implantation plus optimal medical therapy (OMT) (n = 332), compared with only OMT (n = 342) on all-cause mortality in high risk patients within 40 days after MI.

Inclusion criteria were MI 6 to 40 days prior to enrollment, LVEF < 0.35, and signs of impaired cardiac autonomic modulation. Exclusion criteria were NYHA class IV HF, significant noncardiac disease-limiting life expectancy to under 2 years, CABG performed since index MI, 3 vessel PCI performed since index MI, and sustained VT/VF occurring more than 48 hours after index MI. The primary endpoint was all-cause mortality. Secondary endpoints were arrhythmic death and quality of life.

During a mean (SD) follow-up period of 30 (13) months, there was no difference in overall mortality between the 2 treatment groups. Of the 120 patients who died, 62 were in the ICD group, and 58 were in the control group (hazard ratio for death in the ICD group, 1.08 [95% CI, 0.76–1.55]; $P = .66$).

There were 12 deaths due to arrhythmia in the ICD group compared with 29 in the control group (hazard ratio in the ICD group, 0.42 [95% CI, 0.22–0.83]; $P = .009$). There were 50 deaths from nonarrhythmic causes in the ICD group and 29 in the control group (hazard ratio in the ICD group, 1.75 [95% CI, 1.11–2.76]; $P = .02$).

Hohnloser et al. concluded that prophylactic ICD therapy does not reduce overall mortality in high-risk patients who recently have had a MI. They noted that ICD therapy was associated with a lower rate of death due to arrhythmia, but this was offset by an increase in the rate of death from causes not due to arrhythmia.

Limitations to the study included the following:

- Coronary artery revascularization may have played a role in the outcomes. During the course of the study, more patients in the control group underwent revascularization procedures, compared with those in the ICD group (about 15% versus 10%).

Studies of Implantable Cardioverter Defibrillators in Progress

Beta-Blocker Strategy plus Implantable Cardioverter Defibrillator

The Beta-Blocker Strategy plus Implantable Cardioverter Defibrillator study (61) was launched in June 1998 and is expected to enroll 1,200 randomized patients after they have had an acute MI (within 5–21 days of the MI), who have an LVEF less than or equal to 0.35, and at least one additional risk factor: frequent ventricular premature beats, abnormal heart rate variability, or abnormal signal-averaged ECG (Holter). The conventional treatment arm requires β -blocker therapy. The EP-guided arm also requires treatment with β -blockers; however, patients with VT induced at EP study also receive an ICD. Patients who have a negative EP study will receive conventional medical therapy only.

Immediate Risk Stratification Improves Survival

This study (62) is comparing ICD therapy with optimal medical management in patients with MI 5 to 31 days before implantation of an ICD. Its authors plan to enroll 700 patients who have LVEFs ≤ 0.40 and abnormalities on noninvasive ECG testing.

Table 5 summarizes the key trials that have evaluated ICD therapy for primary prevention of SCD.

Table 5: Key Studies Examining the Use of Implantable Cardioverter Defibrillators for Primary Prevention Of Sudden Cardiac Death

Study, Year	Population	N	Follow-up, Months	Total Mortality, ICD* Group, %	Total Mortality, Control Group, %	Hazard Ratio (95% CI)	P	NNT*
MADIT, 1996 (2)	Ischemic Prior MI EF ≤ 0.35 NSVT EP+	196	27	15.8	38.6	0.46 (0.26–0.82) 54% relative reduction	.009	4
MADIT II, 2002 (3)	Ischemic Prior MI EF ≤ 0.30	1232	20	14.2	19.8	0.69 (0.51–0.93) 31% relative reduction	.016	18
SCD-HeFT, 2004 (4)	Ischemic & Nonischemic EF ≤ 0.35	2521	60	22	29	0.77 (0.62–0.96) 23% relative reduction	.007	13

*ICD indicates implantable cardioverter defibrillator; NNT, number needed to treat. The NNT will appear higher if follow-up is short. For ICDs, the absolute benefit increases over time for at least a 5-year period; the NNT declines, often substantially, in studies with a longer follow-up. When the NNT are equalized for a similar period as the SCD-HeFT duration (5 years), the NNT for MADIT-I is 2.2; for MADIT-II, it is 6.3.

GRADE Quality of Evidence

According to the GRADE Working Group criteria, (1) the quality of these 3 trials was examined (Table 6).

Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.

Consistency refers to the similarity of estimates of effect across studies. If there is important unexplained inconsistency in the results, our confidence in the estimate of effect for that outcome decreases.

Differences in the direction of effect, the size of the differences in effect, and the significance of the differences guide the decision about whether important inconsistency exists.

Directness refers to the extent to which the people interventions and outcome measures are similar to those of interest. For example, there may be uncertainty about the directness of the evidence if the people of interest are older, sicker or have more comorbidity than those in the studies.

As stated by the GRADE Working Group, the following definitions were used in grading the quality of the evidence:

- High: Further research is very unlikely to change our confidence on the estimate of effect.
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low: Any estimate of effect is very uncertain.

Table 6: Quality of Evidence - MADIT I, MADIT II, and SCD-HeFT*

Trial	Design	Quality	Consistency	Directness†	Quality Grade
MADIT I	RCT	<p>Imbalance in β-blocker usage between study arms.</p> <p>The overall number of patients from which the study was drawn was not reported.</p> <p>Selection bias may have occurred since patients were selected for randomization if they did not respond to procainamide, thereby introducing a potential bias into the medication arm.</p> <p>Specific details regarding allocation concealment and blinding procedures not provided.</p>	<p>Single-chamber ICD used in study.</p> <p>Trial started with transthoracic implants, and then switched to nontransthoracic implants.</p> <p>Ischemic cardiomyopathy only.</p> <p>5-year NNT = 2.</p>	<p>The overall number of patients from which the study was drawn was not reported.</p> <p>Selection bias may have occurred since patients were selected for randomization if they did not respond to procainamide, thereby introducing a potential bias into the medication arm.</p>	Moderate
MADIT II	RCT	<p>~90% of patients were recruited \geq 6 months post- MI; 20% of control group died after mean 20 month follow-up.</p> <p>How and where patients recruited?</p> <p>Specific details on allocation concealment/blinding procedures not provided.</p> <p>Subset had MADIT I criteria; post hoc analysis of incomplete data suggested "weak-moderate evidence that ICD effect greater in inducible than noninducible patients in MADIT II." (5;6)</p>	<p>First study to assess both single and dual chamber ICD devices for primary prevention. Programming of device and medications left to the discretion of the patients' physician.</p> <p>Higher rate of hospitalization for new or worsened heart failure in the group receiving the ICDs compared to conventional therapy (19.9% vs. 14.9%, respectively).</p> <p>Ischemic cardiomyopathy only.</p> <p>5-year NNT = 6.</p>	<p>How and where patients recruited?</p> <p>Subset had MADIT I criteria.</p>	Weak
SCD-HeFT	RCT	<p>Statistically significant difference in β-blocker usage between treatment groups at last follow-up.</p> <p>Drug arms double-blinded.</p>	<p>Shock-only single-lead device</p> <p>Antitachycardia pacing not permitted.</p> <p>Ischemic and nonischemic cardiomyopathy.</p> <p>There was a statistically significant difference in terms of</p>	<p>Direct</p> <p>Study only evaluated conservatively programmed ICDs with a conservative detection algorithm and shock only therapy.</p> <p>ICD therapy may differ depending on the programming of the device – whether single,</p>	Moderate

Trial	Design	Quality	Consistency	Directness†	Quality Grade
			<p>the NYHA prespecified subgroups analysis. The NYHA subgroups were prespecified a priori and the results of the interaction tests were significant. Yet, ICD treatment had a significant benefit in patients in NYHA class II but not in those in NYHA class III. The general trend in prior trials had been for the relative treatment effect to be nearly constant in NYHA classes (e.g., MADIT II). The SCD-HeFT authors were unable to explain the results of the prespecified NYHA subgroup analysis.</p> <p>Prespecified HF subgroups showed no statistically significant difference in ICD versus placebo. Ischemic: 0.79 (0.60 to 1.04), $P = .05$ Nonischemic: 0.73 (0.50 to 1.07), $P = .06$.</p> <p>5-year NNT = 13.</p>	<p>dual or triple chamber devices are used; whether antibradycardia pacing or rate responsive pacing is used; which detection algorithm is used and whether antitachycardia pacing maneuvers are used for VT.</p> <p>“ICD therapy cannot be considered a single intervention give the numerous possible permutations of the approach.”</p>	

*MADIT I: Multicentre Automatic Defibrillator Implantation Trial I; MADIT II: Multicentre Automatic Defibrillator Implantation Trial II; SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial.

†The 3 trials had 3 different sets of eligibility criteria for implantation of an ICD for primary prevention of SCD.

Economic Analysis

Literature Review: Update

In 2005, Sanders et al. (63) assessed the cost-effectiveness of ICDs in the populations represented in a number of primary prevention trials.

Use of an ICD increased lifetime costs in every trial. CABG Patch and DINAMIT found that the prophylactic implantation of an ICD did not reduce the risk of death; moreover, it was more expensive and less effective than control therapy.

For MADIT I, MADIT II, MUSTT, DEFINITE, COMPANION, and SCD-HeFT, the use of an ICD was projected to add between 1.01 and 2.99 QALYs, and between \$68,300 (US) and \$101,500 (US). Using base case assumptions, Sanders et al. found that the cost-effectiveness of an ICD compared with control therapy in these 6 populations ranged from \$34,000 (US) to \$70,200 (US) per QALY gained (Table 7). Sensitivity analyses showed that this cost-effectiveness ratio would remain below \$100,000 (US) per QALY as long as

the ICD reduced mortality for 7 or more years.

Limitations to the study by Sanders et al. included these:

- Overestimation of the benefits of ICDs by assuming that the rate of death from noncardiac causes after the implantation of an ICD would be the same as age- and sex-specific rates of death from noncardiac causes in the overall American population. Recipients of ICDs may be more likely to have smoked and have other atherosclerotic diseases. (64)
- Patients whose lives are saved by ICDs may otherwise be sicker than the survivors of MI whose data Sanders et al. used for their estimation of costs.
- Sanders et al. did not perform an uncertainty analysis in which all estimates are varied simultaneously within a reasonable range, the analysis is run 1000 or more times, and confidence intervals are created around every estimate.
- The baseline analysis assumed that the receipt of an ICD would not change a patient's quality of life, although such an event could decrease the quality of life of a patient who is bothered by implanted hardware or increase it by increasing a patient's self-assuredness. (64) Small changes in a patient's quality of life can drive cost-effectiveness. For example, the favourable cost-effectiveness of dual-chamber as compared with single-chamber pacing for sinus node dysfunction is critically dependent on small improvements in the quality of life. (64)

Table 7: Health and Economic Outcomes of the Prophylactic Implantation of an Implantable Cardioverter Defibrillator Compared With Control Therapy (63)

Trial and Strategy	Cost	Increase in Cost Related to ICD	Life Expectancy	Increase in Life Expectancy Related to ICD	QALY	Increase in QALY Related to ICD	Incremental Cost-Effectiveness of ICD†			
							\$/Life-Yr	Baseline Efficacy	High Efficacy \$/QALY	Low Efficacy
	\$			year						
MADIT I										
Control	38,300		4.06		2.98					
ICD	130,400	92,100	7.70	3.64	5.62	2.64	25,300	34,900	27,000	96,600
CABG Patch										
Control	78,600		8.41		6.13					
ICD	134,400	55,700	8.01	(0.40)	5.84	(0.29)	Dominated	Dominated	84,200	Dominated
MUSTT										
Control	44,300		4.72		3.46					
ICD	145,800	101,500	8.86	4.14	6.45	2.99	24,500	34,000	28,800	47,600
MADIT II										
Control	57,500		6.16		4.51					
ICD	136,900	79,400	8.20	2.03	5.98	1.47	39,000	54,100	37,200	213,900
DEFINITE										
Control	84,400		9.03		6.57					
ICD	184,900	100,500	11.75	2.73	8.53	1.96	36,800	51,300	34,500	Dominated
DINAMIT										
Control	88,300		9.44		6.87					
ICD	147,200	58,800	8.96	(0.48)	6.53	(0.34)	Dominated	Dominated	70,900	Dominated
COMPANION										
Control	37,800		4.01		2.95					
ICD	106,100	68,300	5.88	1.87	4.31	1.36	36,500	50,300	36,100	123,800
SCD-HeFT										
Control	57,800		6.19		4.53					
ICD	128,800	71,000	7.59	1.40	5.54	1.01	50,700	70,200	45,600	368,800

* The following eight trials were evaluated: the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), the Multicenter Automatic Defibrillator Implantation Trial I (MADIT I), MADIT II, the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial, the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, the Multicenter Unsustained Tachycardia Trial (MUSTT), the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), and the Coronary Artery Bypass Graft (CABG) Patch Trial.⁴⁻¹² Numbers in parentheses correspond to a decrease in the value and thus to an increase in the risk of death among patients who received an ICD. Costs and life expectancy are discounted at an annual rate of 3 percent. QALY denotes quality-adjusted life-year.

† Low efficacy and high efficacy correspond to the results obtained with the use of 95 percent confidence intervals for the efficacy of prophylactic ICD implantation as compared with control therapy in each clinical trial, except in the case of SCD-HeFT, which reported 97.5 percent confidence intervals. The term "dominated" means that the prophylactic implantation of an ICD was both more expensive and less effective than control therapy.

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Al-Khatib et al. (65) investigated the cost-effectiveness of implanting ICDs in patients who met MADIT II eligibility criteria and were enrolled in the Duke Cardiovascular Database between January 1986 and December 2001.

Their data sources were the published literature, databases owned by Duke University Medical Center, and Medicare data. Their target population was adults with a history of MI and an EF less than or equal to 0.30. The time horizon was lifetime, and the perspective was societal. The interventions of interest were ICD therapy compared versus conventional medical therapy. The outcome measures were cost per life-year gained and incremental cost-effectiveness.

Al-Khatib and colleagues found that, compared with conventional therapy, ICDs were projected to result in an increase of 1.8 discounted years in life expectancy and an incremental cost-effectiveness ratio of \$50,500 (US) per life-year gained. Cost-effectiveness varied with changes in the time horizons:

- 15 years: \$67,800 per life year gained
- 12 years: \$79,900 per life year gained
- 9 years: \$100,000 per life year gained
- 6 years: \$167,900 per life year gained
- 3 years: \$367,200 per life year gained

Changing the frequency of follow-up visits, complication rates, and battery replacements had less of an impact on the cost-effectiveness ratios than did reducing the cost of ICD placement and leads.

Al-Khatib and colleagues acknowledged that the number of patients meeting the MADIT II eligibility criteria is not small. In 2000, about \$1.3 million (US) inpatient cardiac catheterizations were performed in the United States. If the Duke cardiac catheterization experience was generalized, the results of Al-Khatib et al. suggest that about 32,000 (2.5% of \$1.3 million) of these patients meet MADIT II criteria. The overall number of ICDs implanted for any indication in 2000 was 34,000. Therefore, Al-Khatib et al. estimated that implanting ICDs in all MADIT II eligible patients would at least double the annual number of ICD implants in the United States (32,000 for any indication plus 34,000 for all MADIT II eligible patients).

In an accompanying editorial, Pauker et al. (66) noted that if the cost of placing an ICD was \$30,000 to \$40,000 (US), and if there were about 30,000 patients each year as Al-Khatib et al. suggested, then the annual burden would be roughly \$1 billion (US). If the number of new implants was 150,000 per year, then the annual burden would approach \$5 billion (US). If the number was 500,000 per year as McClellan and Tunis (67) have estimated, then the annual burden for implantations alone could exceed \$15 billion (US).

Limitations to the study by Al-Khatib et al. are as follows:

- The entire ICD group was extrapolated.
- The analysis was based on patients referred for a cardiac catheterization and involves referral bias.
- The difference in onset of enrollment between the Duke cohort and the MADIT II cohort probably resulted in a significant difference in medical therapy between the 2 groups. Adjusting for this difference did not alter the authors' findings.
- Potential addition of a biventricular pacemaker was not addressed.

Blue Cross Blue Shield Technology Evaluation Centre, April 2004

The Blue Cross Blue Shield Technology Evaluation Centre's (68) cost-effectiveness analysis compared ICD implantation with conventional medical management in the population represented by MADIT II.

The perspective was societal. The design used a Markov model cost-utility analysis to estimate the lifetime costs, life expectancy, quality adjusted life expectancy, and incremental cost-effectiveness. Estimates of survival, SCD, and the effectiveness of the ICD were from the MADIT II population and costs and utilities from the published literature. In terms of base case, clinical variables were based on MADIT II. Inpatient costs for conventional therapy and ICD use were derived from the Myocardial Infarction Triage and Intervention (MITI) patient registry. ICD implantation costs were estimated based on Diagnosis Related Groups, published costs, and a survey of northern California hospitals. Patient utilities were derived from the published literature. Total mortality was assumed to be 19.8%; arrhythmic mortality, 10%, in conventionally treated patients after the mean follow-up of 20 months. ICD was assumed to reduce arrhythmic mortality by 67%. It was assumed that no procedural death would occur with device implantation, that generator

replacement would occur every 7 years, and that there was 2% chance of lead problems requiring surgical intervention. Cost of the initial hospitalization for implantation (\$23,000 [US]) plus device (\$25,000 [US]) was estimated at \$48,000 (US). It was assumed that utilities for post-MI patients were the same with or without device implantation (0.88).

Results of base case analysis: ICD implantation improves life expectancy by 1.85 years or 1.33 QALYs at a cost of \$67,900 (US), relative to conventional therapy. The incremental cost-effectiveness ratios based on these data are \$36,700 (US) per life-year added and \$50,900 (US) per QALY added.

Sensitivity analysis: The most important determinants of the cost-effectiveness of the ICD in this population were the efficacy of the ICD in preventing SCD, the effect of the ICD on quality of life, the cost of the ICD, the age of patients, and the frequency of generator replacement. To reach a cost-effectiveness threshold of \$50,000 (US) per QALY gained, the ICD must prevent 68.5% of SCDs. If the cost of the ICD device were reduced from \$25,000 to \$10,000 (US), then the incremental cost-effectiveness of the ICD treatment relative to conventional therapy would improve from \$50,900 to \$33,500 (US) per QALY gained. Cost-effectiveness increased to \$44,300 (US) per QALY if the generator is replaced every 11 years, but decreased to \$58,100 (US) per QALY if the frequency is every 5 years. Each of these sensitivity analyses assumed all other variables remained constant, including the cost of conventional care.

Investigators have evaluated the usefulness of a variety of diagnostic tests or clinical markers to identify patients at high risk of SCD; to date, none has proven highly predictive. These indicators include EF, signal-averaged electrocardiography, T-wave alternans, heart rate variability, baroreceptor responsiveness, NSVT, and EP testing. Although ICDs should be more effective for patients at a higher risk of SCD, if patients at high risk of SCD are also at high risk of non-SCD, then the benefit of an ICD may be attenuated.

Other populations: In trials evaluating amiodarone's capacity to prevent mortality, the total mortality in untreated patients varies from 11.8% in post-MI patients (with a mean follow-up of 1.7 years) to 38.5% in survivors of cardiac arrest (with a mean follow-up of 2.3 years). In addition, the ratio of SCD to non-SCD varies from 1.33 in survivors of cardiac arrest to 1.61 among patients who have HF. The cost-effectiveness of the ICD is most favourable in patient populations with high rates of cardiac mortality and of SCD, especially when there is a low rate of noncardiac causes of death. Using the annual total cardiac mortality and the ratio of SCD to non-SCD, the authors estimated the cost-effectiveness of ICD implantation in known clinical populations. These calculations resulted in a cost-effectiveness of ICD versus conventional therapy of \$59,900, \$64,300, and \$48,400 (US) per QALY gained in the post-MI, HF, and survivors of SCD populations, respectively.

Limitations to the study included the following:

- The trial followed patients for a mean of 20 months; therefore, there is no long-term data to assess whether the relative risk reduction continues for the lifetime of the patient.

Ontario-Based Budget Impact Analysis

Notes and Disclaimer

The Medical Advisory Secretariat uses a standardized costing methodology for all of its economic analyses. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital costs: Ontario Case Costing Initiative (OCCI) cost data is used for all program costs when there are 10 or more hospital separations, or one-third or more of hospital separations in the Ontario Ministry of Health and Long-Term Care's data warehouse are for the designated International Classification of Diseases-10 diagnosis codes and Canadian Classification of Health Interventions procedure codes. Where appropriate,

costs are adjusted for hospital-specific or peer-specific effects. In cases where the technology under review falls outside the hospitals that report to the OCCI, PAC-10 weights converted into monetary units are used. Adjustments may need to be made to ensure the relevant case mix group is reflective of the diagnosis and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the Medical Advisory Secretariat normally defaults to considering direct treatment costs only. Historical costs have been adjusted upward by 3% per annum, representing a 5% inflation rate assumption less a 2% implicit expectation of efficiency gains by hospitals.

Non-hospital costs: These include physician services costs obtained from the Provider Services Branch of the ministry, device costs from the perspective of local health care institutions, and drug costs from the Ontario Drug Benefit formulary list price.

Discounting: For all cost-effective analyses, discount rates of 5% and 3% are used as per the Canadian Coordinating Office for Health Technology Assessment and the Washington Panel of Cost-Effectiveness, respectively.

Downstream cost savings: All cost avoidance and cost savings are based on assumptions of utilization, care patterns, funding, and other factors. These may or may not be realized by the system or individual institutions.

In cases where a deviation from this standard is used, an explanation has been given as to the reasons, the assumptions, and the revised approach.

The economic analysis represents an estimate only, based on assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied for the purpose of developing implementation plans for the technology.

Estimate of Patients Meeting SCD-HeFT Criteria in Ontario

- Budget impact for prevalent HF population: about \$770 million to \$2.4 billion (Cdn):
 - 23,700 patients $EF \leq 0.35$: This estimate is from David Alter (personal communication) at the Institute for Clinical Evaluative Sciences (ICES), where they examined a sample of echocardiography studies drawn from a diagnostic lab in 2001. They found that the prevalence of $EF \leq 0.35$ was 8.3%, and if generalized to all patients undergoing echocardiography, there would be 23,700 patients.
 - 86,400 patients with $EF \leq 0.30$: This estimate is from Redfield et al. (69) extrapolated to Ontario.
- An expert consultant (personal communication) believed that 23,700 is a more reasonable estimate for the prevalence in Ontario.
- Budget impact for incident HF population: about \$71 million (Cdn):
 - The incidence of HF in Ontario is about 9,575, as derived from Canadian Institute of Health Information database.
 - Of this HF incident population, about 2,488 people would be eligible for ICDs according to SCD-HeFT and MADIT II criteria.

Jauhar and Slotwiner (70) noted that about 150,000 ICDs were implanted in patients in the United States in 2003. They estimated that with no QRS restriction placed on MADIT II patients, this number could double. Moreover, if patients who met the inclusion criteria for SCD-HeFT were included, the number could double once again. Jauhar and Slotwiner estimated that several hundred thousand additional patients would be eligible for ICDs if only the SCD-HeFT criteria were applied. It was also estimated that if the penetration of ICDs into the eligible population, now estimated at 25%, were to increase, the number of implantations could rise further still.

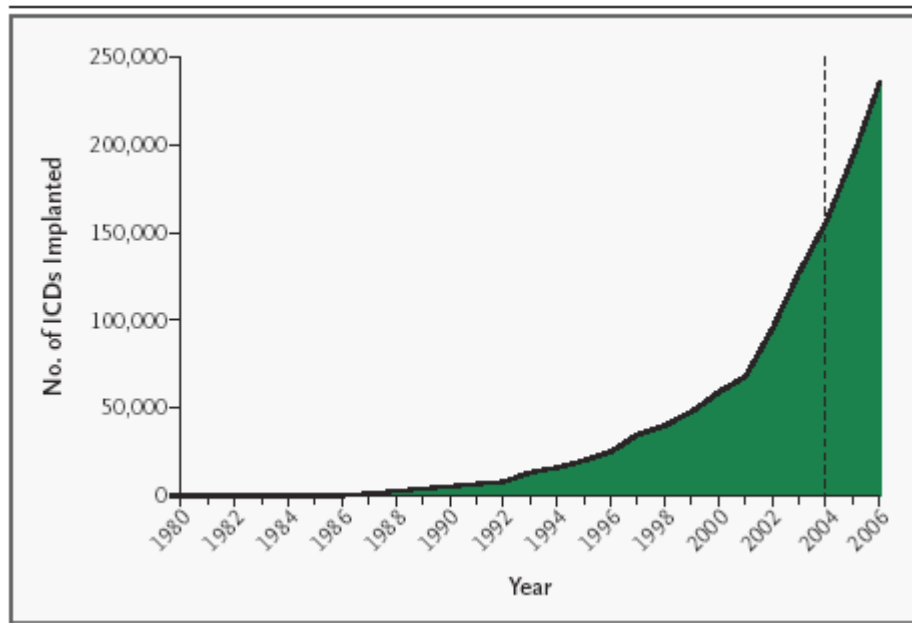


Figure 1: Increase in the Use of Implantable Cardioverter Defibrillators in the United States. Data are From Medtronic. Data for 2004 to 2006 are Estimates. (70)

Copyright © 2004. All rights reserved. Jauhar S, Slotwiner DJ. *The economics of ICDs. New England Journal of Medicine* 2004; 351:2542-2544.

McClellan and Tunis (67) estimated that Medicare beneficiaries account for 80% of SCDs in the United States. On the basis of results from SCD-HeFT, CMS proposed a further expansion of coverage for ICDs. This decision affects patients whose characteristics are similar to those of participants in SCD-HeFT including most patients with ischemic or nonischemic cardiomyopathy who have a LVEF less than or equal to 0.35.

McClellan and Tunis stated that aggregated data from several ICD trials suggest that patients with a normal QRS complex receive a smaller but still significant survival benefit, so such patients will have coverage as well. It is estimated that this CMS policy change could increase the number of Medicare beneficiaries who are eligible for an ICD to more than 500,000 – 2 to 3 times the number that are now eligible. Furthermore, Medicare proposes to use its expansion of coverage to support the development of additional practical evidence through one or more large-scale, prospective observational studies or registries. Medicare pays about \$30,000 (US) per case for ICDs.

Estimate of Patients Meeting MADIT II Criteria in Ontario

The number of acute MI patients (aged over 20 years) in Ontario surviving their index hospitalization in the 1996/1997 fiscal year was 15,773. (71) If MITI data (72) represent overall EF distribution among survivors of MI, then about 10% of survivors may be eligible (using a LVEF < 0.30) for a prophylactic ICD.

Therefore, about 1,578 patients in Ontario would be eligible each year based on MADIT II criteria. If an ICD was used for all patients who were eligible for primary prevention according to the MADIT II criteria, then the initial estimated costs would be $1,578 \times \$32,500$ (Cdn) = \$51 million (Cdn) for the first year alone.

The \$51 million for the first year does not include:

- All patients who would receive an ICD for secondary prevention already covered by the Ministry of Health and Long-Term Care (total budget of \$25 million).
- All patients diagnosed with *any past MI* and $LVEF < 0.30$.

Estimate of Patients Meeting MADIT I Criteria in Ontario

Using the estimate by Plummer et al., (73) the following number of patients would be eligible for an ICD using the inclusion criteria of MADIT I:

Post-MI patients



Estimate of LV function



16% will have $EF < 0.35$

Holter monitoring



16% will have NSVT

EP testing



16% will have inducible VT

ICD implantation

The number of acute MI patients (aged over 20 years) in Ontario surviving their index hospitalization in the 1996/1997 fiscal year was 15,773. (71) Using the estimate of Plummer et al., (73) about 2,524 patients ($15,773 \times 0.16$) have an EF less than 0.35. Of these, 404 ($2,524 \times 0.16$) patients would have NSVT; of these, about 65 patients (404×0.16) would have inducible VT. Therefore, the estimate by Plummer et al. suggests that 65 post-MI patients in Ontario would be eligible for primary prevention ICD implantation, based on incidence alone.

Using data collected as part of the CAST Registry, Every et al. (74) estimated the proportion of post-MI patients who would have been eligible for MADIT. Of the 94,797 CAST Registry patients, between 0.3% and 1.1% were at high enough risk to benefit from ICD placement as defined by MADIT I. Of the 94,797 patients who were enrolled in CAST, 79,838 (84.2%) met the MADIT age entry criteria and had had an acute MI within the qualifying period.

Applying MADIT clinical exclusion criteria (e.g., NYHA class IV HF, prior cardiac arrest, or symptomatic ventricular tachycardia) yielded 77,017 eligible patients. Of these, 17,812 (18.8%) CAST Registry patients had resting ventricular arrhythmia or high clinical suspicion of an arrhythmia resulting from a screening Holter monitor. Of these patients, 2,204 (2.3%) had an episode of asymptomatic ventricular tachycardia, and of patients with ventricular tachycardia, 1,101 (1.1%) had an EF less than 0.35. Of these patients, 303 were not suppressible using Holter monitor criteria. Therefore according to Every et al., 0.3% of 94,797 patients with MI entered into the CAST Registry would have met eligibility criteria for MADIT.

Using this estimate, of Every et al. (74), approximately 48 ($15,773 \times 0.3\%$) to 174 ($15,773 \times 1.1\%$) patients would meet the MADIT eligibility criteria, based on incidence alone.

Existing Guidelines for Use of Technology

AHA/ACC/NASPE 2005 Guideline Update

The AHA/ACC/ASPE's (75) classes of recommendation are as follows:

- Class I: Conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective.
- Class II: Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
- Class IIa: Weight of evidence/opinion is in favour of usefulness/efficacy.
- Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
- Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

Their levels of evidence are derived as follows:

- Level of evidence A: Data derived from multiple randomized clinical trials.
- Level of evidence B: Data derived from a single randomized trial or nonrandomized studies.
- Level of evidence C: Consensus opinion of experts.

Class I, Level of Evidence A:

"...ischemic heart disease who are at least 40 days post MI, have an LVEF <30% with NYHA II or III symptoms while undergoing chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year."(75)

Class I, Level of Evidence B:

"...nonischemic cardiomyopathy who have an LVEF <30%, with NYHA II or III symptoms while undergoing chronic optimal medical therapy and have reasonable expectation of survival with a good functional status for more than 1 year."(75)

Class IIa, Level of Evidence B:

"...LVEF of 30% to 35% of any origin with NYHA II or III symptoms who are taking chronic optimal medical therapy and who have reasonable expectation of survival with good functional status of more than 1 year."(75)

Class I, Level of Evidence C:

"Patients with refractory endstage HF and ICDs should receive information about the option to inactivate defibrillation." (75)

National Institute for Clinical Excellence Appraisal Committee's Recommendations (United Kingdom, 2006)

The National Institute for Clinical Excellence (NICE) Appraisal Committee's Recommendations (53) do not cover the use of ICDs for nonischemic dilated cardiomyopathy. The Committee advises that ICDs should be routinely considered for patients in the following 3 categories:

- As "secondary prevention" for patients who present in the absence of a treatable cause, with one of the following:
 - Having survived a cardiac arrest due to either VT or VF

- Spontaneous sustained VT causing syncope or significant hemodynamic compromise
 - Sustained VT without syncope/cardiac arrest and who have an associated reduction in EF (< 0.35) but are no worse than class 3 of the NYHA functional classification of HF
- As “primary prevention” for patients with a history of previous MI (more than 4 weeks) and:

Either:

- NSVT on Holter recording (24-hour ECG) monitoring, *and*
- Inducible VT on electrophysiological testing, *and*
- LV dysfunction with an EF less than 0.35 and no worse than class III of the NYHA functional classification of HF.

Or:

- LV dysfunction with an EF less than 0.30 and no worse than class III of the NYHA functional classification of HF, *and*
 - QRS duration equal to or more than 120 ms.
- A familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular dysplasia, or have undergone surgical repair of congenital heart disease.

European Society of Cardiology Guidelines for the Diagnosis and Treatment of Chronic Heart Failure 2005

The European Society of Cardiology’s (ESC’s) (76) classes of recommendations are as follows:

- Class I: Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective.
- Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment.
- Class IIa: Weight of evidence/opinion is in favour of usefulness/efficacy.
- Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
- Class III: Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful. (Note, the European Society of Cardiology discourages the use of this class.)

Their levels of evidence are as follows:

- Level of evidence A: Data derived from multiple RCTs or meta-analyses.
- Level of evidence B: Data derived from a single RCT or large nonrandomized studies.
- Level of evidence C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Class I, level of evidence A:

- ICD implantation is reasonable in selected symptomatic patients with LVEF < 0.30–0.35, not within 40 days of a MI, on optimal background therapy including ACE inhibitor, angiotensin receptor blocker, β -blocker, and an aldosterone antagonist where appropriate to reduce sudden death.

Class IIa, level of evidence B:

- Implantation of an ICD in combination with a biventricular pacemaker can be considered in patients who remain symptomatic with severe HF NYHA class III–IV with LVEF ≤ 0.35 and QRS duration ≥ 120 ms to improve morbidity or mortality.

Canadian Cardiovascular Society/Canadian Heart Rhythm Society Position Paper on ICD Use in Canada (2005)

The classes of recommendations from the Canadian Cardiovascular Society/Canadian Heart Rhythm Society Position Paper on ICD Use in Canada (77) are as follows:

- Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
- Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
- Class IIa: Weight of evidence/opinion is in favour of usefulness/efficacy.
- Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
- Class III: Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful.

Their levels of evidence are as follows:

- Level of evidence A: Data derived from multiple RCTs or meta-analyses.
- Level of evidence B: Data derived from a single RCT or large nonrandomized studies.
- Level of evidence C: Consensus of opinion of the experts, case studies or standard of care.

Class I recommendations:

(Note, it is recognized that each of these class I recommendations envelopes a broad group of patients. Subgroup analyses suggested that some may not benefit from an ICD. The decision to implant an ICD in any given patient must be individualized.)

- Cardiac arrest due to VF or VT not due to transient or reversible cause (level A)
- Spontaneous sustained VT in association with structural heart disease (level B)
- Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT, or VF induced at EP study (level B)
- Spontaneous sustained VT in patients who do not have structural heart disease that is not amenable to other treatments (level B)
- Patients with ischemic heart disease with or without mild to moderate HF symptoms and an EF < 0.30 , measured at least 1 month post-MI and at least 3 months after a coronary revascularization procedure (CABG or CI) (Level A)

Class IIa Recommendations:

- Patients with ischemic heart disease and EF 0.31–0.35, measured at least 1 month post-MI and 3 months after a coronary revascularization procedure with inducible VF/sustained VT at EP testing (level B)
- Patients with nonischemic cardiomyopathy present for at least 9 months, an EF < 0.30 and NYHA class II–III HF (level B)
- Patients with familial or inherited conditions including, but not limited to, long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, or arrhythmogenic right ventricular cardiomyopathy and patients at a high risk of life-threatening VT (level B)

Class IIb Recommendations:

- Patients with ischemic heart disease, prior MI, EF 0.31–0.35 either with no inducible VF/sustained VT at EP study or without an EP study (level C)
- Patients with nonischemic cardiomyopathy present for at least 9 months, EF 0.31–0.35, and NYHA functional class II–III HF (level C)
- Severe symptoms (e.g., syncope) attributable to sustained VT while awaiting cardiac transplantation (level C)

Class III Recommendations:

- Syncope of undetermined cause in a patient without structural heart disease (level C)
- Incessant VT or VF (level C)
- VF or VT resulting from arrhythmias due to a transient or reversible disorder (e.g., acute MI, electrolyte imbalance, drugs, trauma), or amenable to surgical or catheter ablation (e.g., right ventricular outflow tract VT, idiopathic LV tachycardia) (level C)
- Significant psychiatric illnesses that may be aggravated by device implantation or may preclude systematic follow-up (level C)
- Terminal illnesses with a projected life expectancy of less than 1 year (level C)
- NYHA class IV HF in patients who are not expected to improve with any further therapy and who are not candidates for cardiac transplantation (level C)

Canadian Cardiovascular Society Consensus Conference Recommendations on Heart Failure 2006

The following are the levels of evidence used by the Canadian Cardiovascular Society Consensus Conference recommendations on HF (78):

- Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
- Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
- Class IIa: Weight of evidence/opinion is in favour of usefulness/efficacy.
- Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
- Class III: Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful.

Their levels of evidence are as follows:

- Level of evidence A: Data derived from multiple RCTs or meta-analyses.
- Level of evidence B: Data derived from a single RCT or large nonrandomized studies.
- Level of evidence C: Consensus of opinion of the experts and/or small studies.

Recommendations

An ICD should be considered in patients with ischemic heart disease with or without mild to moderate HF symptoms and an LVEF less than or equal to 30%, measured at least one month postmyocardial infarction and at least 3 months postcoronary revascularization procedure (class I, level A).

An ICD may be considered in patients with nonischemic cardiomyopathy present for at least nine months, NYHA functional class II to III HF, and an LVEF less than or equal to 30% (class IIa, level B) or an LVEF of 31% to 35% (class IIb, level C).

An ICD may be considered in patient with ischemic heart disease, prior MI, 3 months postcoronary revascularization, LVEF 31% to 35%, and with inducible VF/sustained VT at EP study (class IIa, level B), or with either no inducible VF/sustained VT at EP study or without an EP study (class IIb, level C).

An ICD should not be implanted in patients with NYHA class IV HF who are not expected to improve with any further therapy and who are not candidates for cardiac transplantation (class II, level C).

Aetna, United States, March 2005

Aetna (79) considers FDA-approved ICDs (thoracotomy and non-thoracotomy systems) medically necessary for *any* of the following groups of individuals, except where contraindicated:

- Members after 1 or more episodes of spontaneously occurring and inducible VF or syncopal or hypotensive VT that is not associated with acute MI; not due to a remediable cause (e.g., drug toxicity, electrolyte abnormalities, ischemia); and neither controlled by appropriate drug therapy after serial testing nor amenable to definitive therapy (e.g., surgical ablation); or
- Members after spontaneously occurring but noninducible documented syncopal or hypotensive VT that was not due to acute MI; not controlled by appropriate drug therapy after serial testing; nor amenable to definitive therapy (e.g., surgical ablation); or
- Members after VT/VF cardiac arrest that was not associated with an inducible ventricular arrhythmia, and not due to acute MI; not controlled by appropriate drug therapy after serial testing; nor amenable to definitive therapy (e.g., surgical ablation); or
- Members after surgery for VT or VF if the ventricular arrhythmia remains inducible; *or*
- Members after one or more episodes of spontaneously occurring and inducible VF or syncopal or hypotensive VT that is associated with acute MI (greater than 2 days after the infarct but less than 1 month); not due to a remediable cause; and neither controlled by appropriate drug therapy after multiple trials nor amenable to definitive therapy; or
- Members after unexplained syncope, which by history and clinical circumstances was probably due to a ventricular tachyarrhythmia, and in the presence of reproducible inducible syncopal or hypotensive VT or VF that is not associated with acute MI (greater than 2 days after the infarct but less than 1 month); not due to a remediable cause; and neither controlled by appropriate drug therapy after multiple trials nor amenable to definitive therapy; or
- Members after VF or syncopal or hypotensive VT that is apparently controlled by drug, surgical, or ablative therapy, but in which the results of treatment are too unpredictable (e.g., when long-term effectiveness is in doubt or unknown; in the presence of adverse effects or toxicity leading to noncompliance; LVEF less than or equal to 0.30 despite drug control) to justify withholding ICD treatment; or
- Members with familial or inherited conditions with a high risk of life-threatening ventricular tachyarrhythmias such as long QT syndrome or hypertrophic cardiomyopathy; or
- Members with ischemic dilated cardiomyopathy with a LVEF less than or equal to 0.35 and NYHA class II or III HF who have a history of heart attack; or

- Members with nonischemic dilated cardiomyopathy greater than 9 months duration, NYHA class II or III HF, and a LVEF less than or equal to 0.35.

Contraindications: ICDs are *not* considered medically appropriate in *any* of the following situations:

- When other disease processes are present that clearly and severely limit the member's life expectancy; or
- Member has asymptomatic VT or symptomatic VT/VF that is associated with acute MI within 2 days, due to a remediable cause, controlled by appropriate drug therapy, and amenable to definitive therapy (e.g., ablative procedures, surgery); or
- Prophylactic use in members at high risk for SCD who have not experienced a life-threatening arrhythmia (other than members meeting the second-last and last criteria in the list above); or
- Use as a “bridge” to heart transplant.

Notes: Electronic analysis of defibrillator systems is required for long-term routine follow-up care of ICDs. Automatic defibrillator monitoring is considered medically necessary. Electrophysiologic assessment is a more complex evaluation of newly or chronically implanted ICDs, and is considered medically necessary.

Centers for Medicare and Medicaid Services

CMS (55) has determined that the evidence is adequate to conclude that an ICD is reasonable and necessary for the following groups:

- Patients with ischemic dilated cardiomyopathy, documented prior MI, NYHA class II and III heart failure, and measured LVEF ≤ 0.35
- Patients with nonischemic dilated cardiomyopathy > 9 months, NYHA class II and III heart failure, and measured LVEF ≤ 0.35
- Patients who meet all current CMS coverage requirements for a CRT device and have NYHA class IV heart failure

For each of these groups, the following additional criteria must also be met:

- Patients must be able to give informed consent.
- Patients must not have:
 - Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm;
 - Had a CABG or PTCA within the past 3 months;
 - Had an acute MI within the past 40 days;
 - Clinical symptoms or findings that would make them a candidate for coronary revascularization;
 - Irreversible brain damage from preexisting cerebral disease; or
 - Any disease, other than cardiac disease (e.g. cancer, uremia, liver failure), associated with a likelihood of survival less than 1 year.
- Ejection fractions must be measured by angiography, radionuclide scanning, or echocardiography.
- Myocardial infarctions must be documented and defined according to the consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction.
- The beneficiary receiving the ICD implantation for primary prevention is enrolled in either an FDA-approved category B IDE clinical trial, a trial under the CMS clinical trial policy or a qualifying data collection system, including approved clinical trials and registries. Initially, an ICD database will be maintained using a data submission mechanism that is already in use by Medicare participating hospitals to submit data to the Iowa Foundation for Medical Care – a Quality Improvement Organization contractor—for determination of reasonable and necessary and quality improvement. Initial hypothesis and data elements are specified in this decision and are the minimum necessary to ensure that the device is reasonable and necessary. Data collection will be completed using the ICDA (ICD Abstraction Tool)

and transmitted via QNet (Quality Network Exchange) to the Iowa Foundation for Medical Care who will collect and maintain the database. Additional stakeholder-developed data collection systems to augment or replace the initial QNet system, addressing at a minimum the hypotheses specified in this decision, must meet the following basic criteria:

- Written protocol on file;
- Institutional Review Board review and approval, if required;
- Scientific review and approval by at least 2 qualified people not part of the research team; and
- Certification that investigators have not been disqualified.

For purposes of this coverage decision, CMS will determine if specific registries or clinical trials meet these criteria. Providers must be able to justify the medical necessity of devices other than single-lead devices. This justification should be available in the patient's medical record.

CMS has determined that the evidence, though less compelling at this time, is adequate to conclude that an ICD is reasonable and necessary for patients who have nonischemic dilated cardiomyopathy for more than 3 months, NYHA Class II or III HF, and measured LVEF ≤ 0.35 , only if the following criteria are also met:

- Patients must be able to give informed consent.
- Patients must not have:
 - Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm;
 - Had a CABG or PTCA within the past 3 months;
 - Had an acute MI within the past 40 days;
 - Clinical symptoms or findings that would make them a candidate for coronary revascularization;
 - Irreversible brain damage from preexisting cerebral disease; or
 - Any disease, other than cardiac disease (e.g. cancer, uremia, liver failure), associated with a likelihood of survival less than 1 year.
- Ejection fractions must be measured by angiography, radionuclide scanning, or echocardiography.
- Myocardial infarctions must be documented and defined according to the consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction.
- The beneficiary receiving the ICD implantation for this indication is enrolled in either an FDA-approved category B IDE clinical trial, a trial under the CMS clinical trial policy, or a prospective data collection system meeting the following basic criteria:
 - Written protocol on file;
 - Institutional Review Board review and approval;
 - Scientific review and approval by at least 2 qualified people not part of the research team; and
 - Certification that investigators have not been disqualified.

For purposes of this coverage decision, CMS will determine whether specific registries or clinical trials meet these criteria. Providers must be able to justify the medical necessity of devices other than single-lead devices. This justification should be available in the patient's medical record.

Appraisal

Health Systems Implications

The number of people in Ontario estimated to have left ventricular HF that would fit the SCD-HeFT criteria (but with a lower LVEF of less than 0.30) is 23,700. The current funding rate for an ICD in Ontario (including insertion and follow-up costs) is \$32,500 (Cdn). Based on SCD-HeFT, the number of people needed to treat to prevent 1 SCD is 13 at 5 years follow-up at a total cost of \$770 million (Cdn).

The results of the most recent ICD trial are *not* generalizable to the prevalent population in Ontario, since the estimated budget impact for Ontario would be as high as \$770 million (Cdn). The uncertainty around the cost estimate of treating the prevalent population with LVEFs less than 0.30 in Ontario, the lack of human resources to implement such a strategy, and the high number of patients required to prevent 1 SCD (13) calls for an alternative strategy that allows the appropriate uptake and diffusion of ICDs for primary prevention for patients at maximum risk for SCD within the SCD-HeFT population.

The uptake and diffusion of ICDs for primary prevention of SCD should therefore be based on risk stratification through the use of appropriate screen(s) that would identify patients at highest risk who could derive most benefit from this technology.

From the literature, there are 2 possible risk stratifiers.

The first, identified through retrospective subset analysis of 2 major RCTs is the presence of a wide QRS interval on ECG (>120 ms) in patients with ischemic heart disease and an LVEF under 0.30. If this risk stratifier is used, then the number needed to treat to prevent 1 SCD is 4, as opposed to the generalized population in the SCD-HeFT population of 13. However, it is not considered advisable to develop policy based on a retrospective subset analysis, which has methodological weaknesses.

In a conference abstract, Zareba et al. (80) presented results from a noninvasive electrocardiology substudy of MADIT II. The 3 aims of the substudy were as follows:

- To determine the prognostic significance of noninvasive electrocardiology parameters in post-MI patients with EF < 0.30 for predicting mortality in patients randomized to conventional treatment;
- To determine the prognostic significance of noninvasive electrocardiology parameters for predicting arrhythmic events, defined as appropriate ICD therapy for VT/VF in patients randomized to ICD; and
- To identify patients who are more likely to benefit from ICD therapy and therefore provide recommendations regarding prioritization of patients for ICD therapy.

In multivariate analysis, after adjustment for relevant clinical covariates, atrial fibrillation and QRS duration over 120 ms were found to be independent and significant predictors of death in post-MI patients with EFs less than or equal to 0.30. Analysis of parameters for predicting ICD therapy for VT/VF indicated that prolonged QRS duration was the only ECG parameter significantly associated with the arrhythmic events.

Analysis of 364 MADIT II patients with a QRS over 120 ms (excluding paced patients) revealed a 63% reduction in mortality in ICD patients compared with the conventional treatment group (hazard ratio, 0.37; $P = .004$). In 530 MADIT II patients with a QRS of at least 120 ms (excluding paced patients), there was a 49% drop in mortality in ICD patients compared with those conventionally treated (hazard ratio, 0.51; $P = .07$). Complete data from the substudy of MADIT II by Zareba et al. has not been published.

The 2005 Canadian Cardiovascular Society/Canadian Heart Rhythm Society position paper (77) on ICD use in Canada stated that “the ultimate role of these criteria which are meant to further stratify patients for ICD

benefit, will depend on the results of future studies.”

The second potential risk stratifier is preselection by EP testing and inserting ICDs only for those patients with inducible VT. This resource is an intensive and time-consuming screen, would be difficult to standardize, and the original studies on which this potential screen is based include patients not consistent with the SCD-HeFT population.

The Medical Advisory Secretariat undertook an economic budget impact analysis for a number of scenarios in which ICDs could be used in the primary prevention of SCD over a 4-year period. The range of costs depending on approach varies dramatically.

Rather, a 2-year evaluation would identify the patients who would benefit the most from that would make ICD implantation for primary prevention of SCD more feasible.

Conclusions

Overall, there is evidence that ICDs are effective for the primary prevention of SCD. MADIT I, MADIT II, and SCD-HeFT all showed that there was a statistically significant decrease in total mortality for patients who prophylactically received an ICD compared with those who received conventional medical therapy.

As per the GRADE Working Group, (1) recommendations should consider 4 main factors:

- The tradeoffs, taking into account the estimated size of the effect for the main outcome, the confidence limits around those estimates, and the relative value placed on the outcome;
- The quality of the evidence (Table 6);
- Translation of the evidence into practice in a specific setting, taking into consideration important factors that could be expected to modify the size of the expected effects, such as proximity to a hospital or availability of necessary expertise; and
- Uncertainty about the baseline risk for the population of interest

The GRADE Working Group also recommends that incremental costs of health care alternatives should be considered explicitly alongside the expected benefits and harms. Recommendations rely on judgments about the value of the incremental health benefits in relation to the incremental costs. The last column in Table 9 is the overall trade-off between benefits and harms and incorporates any risk/uncertainty.

For MADIT I, the overall GRADE and strength of the recommendation is “moderate” – the quality of the evidence is “moderate” (uncertainty due to methodological limitations in the study design), and risk/uncertainty in cost and budget impact was mitigated by the use of filters to help target the prevalent population at risk (Table 9).

For MADIT II, the overall GRADE and strength of the recommendation is “very weak” – the quality of the evidence is “weak” (uncertainty due to methodological limitations in the study design), but there is risk/uncertainty regarding the high prevalence, cost, and budget impact. It is not clear why screening for high risk patients was dropped, given that in MADIT II the absolute reduction in mortality was small (5.6%) compared with that in MADIT I, which used EP screen (23%) (Table 9).

For SCD-HeFT, the overall GRADE and strength of the recommendation is “weak” – the study quality is “moderate,” but there is also risk/uncertainty due to a high NNT at 5 years (13 compared with that the MADIT II NNT of 6 and MADIT I NNT of 2 at 5 years), high prevalent population (N = 23,700) and a high budget impact (\$770 million [Cdn]). A filter (as demonstrated in MADIT I) is required to help target the prevalent population at risk and mitigate the risk/uncertainty relating to the high NNT, prevalence, and budget impact (Table 9).

Table 9: Overall GRADE and Strength of Recommendation for the Use of Implantable Cardioverter Defibrillators For Primary Prevention of Sudden Cardiac Death

	Study Quality	Eligibility*	Estimated No. in Ontario	NNT†	Total Cost in Ontario, \$ Millions	Overall Grade & Strength of Recommendation (Includes Uncertainty)
ICD	Moderate	MADIT I: Ejection fraction \leq 0.35, prior myocardial infarction, NSVT, inducible VT	~ 4,740	4	~ 156	Moderate
	Low	MADIT II: Ejection fraction \leq 0.30 and prior myocardial infarction	(greater than MADIT)	18	> 156	Very Weak
	Moderate	SCD-HeFT: Ejection fraction \leq 0.35	~ 23,700	13	~ 770	Weak

*MADIT I: Multicentre Automatic Defibrillator Implantation Trial I MADIT II: Multicentre Automatic Defibrillator Implantation Trial II; SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial.

†NNT indicates number needed to treat. NNT will appear higher if follow-up is short. For ICDs, the absolute benefit increases over time for at least a 5-year period; the NNT declines, often substantially, in studies with a longer follow-up. When the NNT are equalized for a similar period as the SCD-HeFT duration (5 years), the NNT for MADIT-I is 2.2; for MADIT-II, it is 6.3.

Glossary

Cardioverter defibrillator	A battery-powered device that monitors heart rhythm and can deliver an electric shock to restore normal rhythm when fatal arrhythmias are detected.
Ejection fraction	A measure of ventricular function. Low values indicate ventricular dysfunction.
Holter monitor	A Holter monitor records the heart rhythm – each and every heart beat – continuously for 24 hours.
Sudden cardiac death	Sudden death due to cardiac arrest; most SCDs are caused by acute, fatal ventricular arrhythmias.
Ventricular arrhythmia	Abnormal heart rhythm originating within the ventricles.

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