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### Implantable Cardiac Defibrillators for Primary Prevention of Sudden Cardiac Death in High Risk Patients: A Meta-Analysis of Clinical Efficacy, and a Review of Cost-Effectiveness and Psychosocial Issues



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**Canadian Agency for Drugs and Technologies in Health**

**Implantable Cardiac Defibrillators for Primary Prevention  
of Sudden Cardiac Death in High Risk Patients:  
A Meta-Analysis of Clinical Efficacy, and a Review of  
Cost-Effectiveness and Psychosocial Issues**

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As lead author, Chung Ho led the project protocol development, supervised the literature review, wrote the draft, revised the report, and prepared the report for publication. Karen Cimon worked with Chung Ho to evaluate the articles’ relevance, assess their quality, extract data, and complete the report. Huimin Li provided economic expertise, and contributed to the draft document and its subsequent revisions. Hussein Noorani was responsible for writing the psychosocial and ethical issues of the report. David Bernie and Anthony Tang provided clinical expertise, and contributed to the draft document and its subsequent revisions. Kaitryn Campbell was responsible for the design and execution of the literature search strategies, for writing the section and associated appendix on literature searching, and for verifying and formatting the bibliographic references.

## Acknowledgements

The authors are grateful to the CADTH staff members who helped us complete this report, and give special thanks to Amanda Hodgson for revising the references and providing valuable information.

## **Conflicts of Interest**

David Bernie received scientific grants from Medtronic Inc. Anthony Tang received education and research funding from Medtronic Inc., St. Jude Medical, and Guidant Corporation.

## Implantable Cardiac Defibrillators for Primary Prevention of Sudden Cardiac Death in High Risk Patients: A Meta-Analysis of Clinical Efficacy, and a Review of Cost-Effectiveness and Psychosocial Issues

### Technology

An implantable cardiac defibrillator (ICD) is a small electronic device implanted under the skin in the chest. It can be used to detect abnormal and potentially life-threatening heart rhythms, then to deliver a shock to restore normal rhythm.

### Condition

Sudden cardiac death (SCD) due to an abnormal heart rhythm is a leading cause of cardiac-related death. Only 5% of patients survive a cardiac arrest.

### Issues

The use of ICDs in patients who have survived an episode of SCD (secondary prevention) is established. ICDs may also be used to prevent a first episode of SCD in patients at risk (primary prevention) – but whether they should be used for these patients remains questionable. The costs associated with ICD use are high compared to those for antiarrhythmic medications, and psychosocial issues such as anxiety and depression may be associated with the use of ICDs. Questions about the allocation of health resources are raised when considering ICDs for the primary prevention of SCD, with the demand already outstripping capacity in many jurisdictions. To address these issues, the clinical effectiveness and cost-effectiveness of ICDs for the primary prevention of SCD in different patient groups must be determined.

### Methods and Results

We used systematic, defined literature searches to identify published and unpublished studies. Ten randomized controlled trials (RCTs) reporting clinical outcomes for ICDs in primary prevention were systematically reviewed. Psychosocial and ethical issues, and the cost-effectiveness of ICD treatment, were examined using the literature review, and a budget impact analysis was performed.

### Implications for Decision Making

- ICDs, with optimal pharmacologic therapy, significantly reduce SCD and all-cause death in patients at high risk.
- ICDs are effective in reducing SCD in patients with ischemic and non-ischemic heart disease.
- ICD therapy is expensive but some reviewed studies showed that ICDs are cost-effective if the willingness to pay is \$50,000 per quality-adjusted life year (QALY). More study with a broader target population is warranted.
- Poor psychosocial outcomes in ICD patients may occur as a result of their underlying cardiac condition, rather than as a direct response to ICDs.
- ICD therapy for primary prevention of SCD would result in a substantial budget impact. There are also infrastructure issues that would need to be addressed in order to meet demand

This summary is based on a comprehensive health technology assessment available from CADTH's web site ([www.cadth.ca](http://www.cadth.ca)): Ho C, Li H, Noorani H, Cimon K, Campbell K, Tang A, Birnie D. *Implantable cardiac defibrillators for primary prevention of sudden cardiac death in high risk patients: a meta-analysis of clinical efficacy, and a review of cost-effectiveness and psychosocial issues.*

# EXECUTIVE SUMMARY

## The Issue

The use of implantable cardiac defibrillators (ICDs) in patients who have survived an episode of sudden cardiac death (SCD) (secondary prevention) is established. ICDs may also be used to prevent a first episode of SCD in patients at risk (primary prevention) – but whether they should be used for these patients remains questionable. The costs associated with ICD use are high compared to those of antiarrhythmic medications, and psychosocial issues may be associated with the use of ICDs. Questions about the allocation of health resources are also raised when considering ICDs for the primary prevention of SCD, with demand already outstripping capacity in many jurisdictions. To address these issues, the clinical effectiveness and cost-effectiveness of ICDs for the primary prevention of SCD in different patient groups must be determined.

## Objectives

This report informs health care decision makers and others involved in the planning and delivery of ICD services about the evidence regarding the clinical effectiveness and cost-effectiveness of ICD therapy compared to conventional treatment for the primary prevention of SCD. The budget impact of ICD therapy for people at high risk for SCD is determined. The ethical and psychosocial issues related to ICD use are examined.

## Methods

Published and unpublished literature was identified through systematic searches of multiple databases and resources. Abstracts of conference proceedings and bibliographies of selected papers were also searched. Randomized controlled trials (RCTs) that reported clinical outcomes from the use of ICDs for primary prevention were systematically reviewed. The clinical outcomes investigated were the rates of all-cause death and SCD in ischemic and non-ischemic patients. Safety endpoints included the frequency of perioperative incidents and device-related complications. The cost-effectiveness of ICD treatment, and patients' psychosocial and ethical issues were examined using a literature review, and a budget impact analysis was done.

## Results

### *Clinical Review*

This systematic review of 10 RCTs of variable quality, which included over 7,000 patients, revealed three findings. First, the rate of death, either overall or cardiac in origin, was appreciable in patients who had no history of arrhythmia but who were considered to be at high risk. In the population treated with conventional therapy, the rates were 25% for all-cause death and 11% for SCD over a median time of 45 months' follow-up. In the population implanted with ICDs as an addition to conventional therapy, these rates were 19% and 4% respectively. Second, treatment with ICDs in addition to conventional therapy significantly reduced the relative risks (RRs) of all-cause death by 28% and of SCD by 67% [absolute risk reduction (ARR) 6% for all-cause death and 7% for SCD]. Third, subgroup analysis showed that patients with ischemic heart disease had higher rates of death than patients with non-ischemic heart disease. When the population was divided into ischemic and non-ischemic groups, the all-cause death risk reduction attributable to the use of ICDs failed to reach statistical significance in both groups (likely due to inadequate sample size) with RR reductions (RRRs) of 32% and 24%, respectively (ARRs 7% and 5% respectively). The RRRs for SCD with ICD use was statistically significant: 67% in ischemic patients and 74% in non-ischemic patients (ARR 9% and 4%

respectively). All-cause death is the more reliable clinical outcome because bias can be introduced if deaths are systematically misclassified, as is likely when studies are not double-blinded.

A number-needed-to-treat analysis showed that an ICD needed to be implanted into 14 patients to prevent one SCD, and in 12 and 28 patients to prevent one SCD in ischemic and non-ischemic patients respectively. The most common complications related to ICD therapy were infections associated with the surgical procedure and inappropriate shocks due to lead or generator problems.

### ***Economic Review***

Our review showed that ICDs generally cost more than conventional management of cardiac arrhythmia but were more effective in treating patients without prior clinical arrhythmia. If effectiveness was measured in life years, most of the incremental cost-effectiveness ratio (ICER) estimates were below or slightly above the commonly used willingness to pay threshold of US\$50,000 per life year gained. If effectiveness was measured by quality-adjusted life year (QALY), the ICER ranged from US\$34,000 to US\$97,863, for patients with an ejection fraction (EF)  $\leq 0.30$ . For patients with an EF of 0.31 to 0.40, the ICER increased to US\$195,700 per QALY gained.

### ***Budget Impact Analysis***

It is estimated that 85,000 untreated Canadians are candidates for ICD implantation in the primary prevention of a life-threatening arrhythmia, with the number of new cases expected to be 3,700 annually. Ideally, the budget impact analysis would be based on this number, but the infrastructure that is needed to implant tens of thousands of ICDs in a given year is limited. Thus, the budget impact analysis was based on the assumptions that the number of new ICDs in Canada would be 3,500 in fiscal year 2005-2006; 4,500 in 2006-2007; 5,500 in 2007-2008, and 6,500 in each of the four subsequent fiscal years.

A budget impact analysis usually assumes a time horizon of three to five years. For this analysis, we used a seven-year horizon to account for the initial implantation and device replacement or battery change five to six years later. For a patient receiving an ICD for the primary prevention of SCD, we estimated that during the seven-year period, the total cost was C\$48,119, largely due to the ICD implant in the first year and ICD or battery replacement in the sixth year.

From the health care system's perspective, if the cost associated with SCD was C\$300 per case, the estimated budget impact (relative to usual medical therapy) was C\$88.58 million, C\$332.37 million, C\$634.39 million, C\$834.40 million, and C\$1.04 billion respectively over one-, three-, five-, six-, and seven-year time horizons post ICD implant. Taking the same perspective, but assuming the cost associated with SCD prevention was C\$6,500 per case, the corresponding budget impact would be C\$330,000; C\$2.26 million; C\$6.37 million; C\$9.67 million, and C\$10 million less over the same time horizons than that seen when the cost of preventing SCD was assumed to be \$300.

### ***Ethical and Psychosocial Review***

The advent of ICD therapy poses emerging questions about the allocation of health care resources, because the need for ICDs exceeds the funded volumes in many Canadian jurisdictions. As a result of limited financial resources, physicians have been put into the difficult moral position of deciding who can receive an ICD. A transparent and fair decision-making process is required. This could consider guidelines that identify patients who are most likely to benefit from ICD therapy.



The impact of ICDs on quality of life (QoL) among patients for whom it is used for the primary prevention of sudden death requires more study. The available evidence is weak, and a poor psychosocial outcome in ICD patients may result from the underlying cardiac condition, rather than as a response to implantation of the device and therapy. The most common psychological problems reported in secondary reviews are anxiety and depression.

## Conclusions

Our review provides evidence that the use of ICDs, combined with optimized pharmacological therapy, can reduce all-cause death and SCD in patients at a high risk of ventricular arrhythmia. Treatment with ICDs reduces the relative risk of all-cause death by a third and of SCD by two-thirds compared to conventional treatment. ICD treatment is efficacious in reducing the risk of SCD in ischemic and non-ischemic patients, and may be shown to significantly reduce all-cause deaths for both groups as sample sizes grow. ICDs would need to be implanted in 14 patients to prevent one SCD, and in 12 and 28 patients to prevent one SCD in ischemic and non-ischemic patients respectively. These findings are consistent with those noted in reports from the UK and Australia. Our review excludes observational studies that could give an idea of real-world effectiveness, especially for safety issues. In the studies that were examined, complications were infections associated with the surgery and inappropriate shocks due to lead or generator problems.

The economic component of this review is limited in that no Canadian economic studies were identified. The seven identified economic studies provide ICER estimates that range from US\$24,500 to US\$63,300 per life-year gained or from US\$34,000 to US\$97,863 per QALY gained for patients with low EF. Whether the ICD treatment is cost-effective compared with conventional therapy depends on the threshold of willingness to pay for one life-year or one QALY gained. For Canada, if ICD policy was based on the joint recommendation of the Canadian Cardiovascular Society and the Canadian Heart Rhythm Society, the study populations in the reviewed papers provide an incomplete picture because the available cost-effectiveness studies are based on a subset of the population targeted by the joint recommendation. To more accurately determine the cost-effectiveness of ICD prophylactic use in Canada, a primary study with the broader target population is warranted.

ICD prophylactic use would result in a substantial impact on the Canadian health care system budget. Whether the cost associated with SCD was assumed to be a few hundred dollars or a few thousand dollars, the estimated budget impact of ICD implantation (relative to usual medical therapy) would be approximately C\$88 million, C\$330 million, C\$630 million, C\$830 million, and C\$1 billion over one-, three-, five-, six-, and seven-year time horizons post-implant. The budget impact is driven by the cost of the device, its future replacement cost, and the number of patients who would be eligible to receive the device. It is estimated that 85,000 untreated Canadians are candidates for ICD implantation in the primary prevention of a life-threatening arrhythmia, with the number of new cases expected to be 3,700 annually; however, the infrastructure that would be needed to implant tens of thousands of ICDs in a given year is limited. Our budget impact analysis was based on more realistic estimates of 3,500 to 6,500 ICDs being implanted annually over a seven-year time horizon.

The impact of ICDs on QoL among primary prevention patients requires more study; it is unknown whether the psychosocial issues (e.g., anxiety, depression) noted in ICD patients result from the underlying cardiac condition, or from a response to implantation of the device and therapy.

# ABBREVIATIONS

|       |  |
|-------|--|
| AEs   | adverse events                               |
| A&E   | accident and emergency                       |
| ARR   | absolute risk reduction                      |
| CABG  | coronary artery bypass graft                 |
| CER   | control event rate                           |
| CHF   | congestive heart failure                     |
| CI    | confidence interval                          |
| ECG   | electrocardiogram                            |
| EF    | ejection fraction                            |
| FDA   | Food and Drug Administration                 |
| ICD   | implantable cardiac defibrillator            |
| ICDER | implantable cardiac defibrillator event rate |
| ICER  | incremental cost-effectiveness ratio         |
| LVEF  | left ventricular ejection fraction           |
| MI    | myocardial infarction                        |
| NNT   | number needed to treat                       |
| NYHA  | New York Heart Association                   |
| QALY  | quality-adjusted life year                   |
| QoL   | quality of life                              |
| RCT   | randomized controlled trial                  |
| RR    | relative risk                                |
| RRR   | relative risk reduction                      |
| SCD   | sudden cardiac death                         |

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# 1 INTRODUCTION

## 1.1 Background

Sudden cardiac death (SCD) due to cardiac arrhythmia is a leading cause of cardiac-related death. An analysis of US national and state-specific SCD data determined that of 728,743 cardiac disease deaths that occurred in the US in 1999, 462,340 (63.4%) were SCDs.<sup>1</sup> Most sudden deaths are the result of ventricular fibrillation due to coronary artery disease. Primary ventricular arrhythmias, bradycardia or asystole, and electro-mechanical dissociation are the other causes of death. Most of those who die have cardiac pathology but a minority have other factors.<sup>2,3</sup> The Ontario Pre-hospital Advanced Life Support (OPALS) study found that 5.2% of people survive sudden cardiac arrest and are discharged from hospital. These people are at high risk of dying within a few years, and over half of these deaths are due to recurrent sudden cardiac arrest.<sup>4</sup>

Several approaches have been used to reduce arrhythmia mortality.<sup>5</sup> For patients at a low risk of SCD, managing coronary heart disease and placing automatic external defibrillators in the community are key interventions. Because the immediate recognition of an arrhythmia and instantaneous shock delivery are essential to a successful resuscitation, prophylactic intervention is often seen as being more practical, especially for patients at high risk, such as those with reduced left ventricular ejection fraction (LVEF) or with a history of cardiac arrest. This resulted in the invention of implantable cardiac defibrillators (ICDs) and the first surgical implantation in a human in 1980.

Initially, ICDs were used in the secondary prevention of SCD, for patients successfully resuscitated from ventricular fibrillation or ventricular tachycardia. Because only 5% of patients survive their first cardiac arrest,<sup>6</sup> there has been increasing interest over the last decade in using ICDs for patients with no history of ventricular fibrillation or tachycardia but who have a high risk of SCD (i.e., primary prevention). This would include patients with a prior myocardial infarction (MI) and advanced left ventricular dysfunction (LVEF  $\leq 35\%$ ), or patients with congestive heart failure (CHF), or a dilated cardiomyopathy. This translates into a population of more than three million patients in North America, with approximately 400,000 new patients each year.<sup>7</sup>

## 1.2 Technology

An ICD is a small electronic device that acts as a pacemaker and defibrillator. The technology and its indications have been reviewed.<sup>8-11</sup> ICDs consist of a pulse generator and have one or more leads. The generator contains a battery, capacitors, transformers, and electronics. When an abnormally fast and potentially life-threatening heart rhythm (ventricular tachycardia or ventricular fibrillation) is sensed, the capacitor begins to charge. During charging, low voltage from the battery is converted into high-voltage energy for rapid discharge to restore normal rhythm.

The electronic circuitry has many programmable features designed for sensing and defibrillation algorithms. The complexity of the generator depends on its purpose. The three types of ICDs are:

- single-chamber ventricular defibrillation device (right ventricle)
- ventricular defibrillation device with dual chamber pacing (right atrium and right ventricle)
- ventricular defibrillation device with atrioventricular sequential and biventricular pacing (defibrillation plus cardiac resynchronization).

ICDs are implanted under the skin in a procedure similar to that used to implant a permanent pacemaker. The procedure usually takes between one and two hours, and can be performed under general or local anesthesia. Since the first human implant in 1980 and Food and Drug Administration (FDA) approval in 1985, there have been changes to the ICD including weight, volume, and shape; and changes to the implantation location. These have occurred in response to perceived or actual improvement of the device and patients' comfort. Early devices were implanted by the trans-thoracic method, but now ICDs are placed under the skin in the pectoral region with the leads into the heart inserted through a vein while the patient is under local anesthesia.

The device costs about C\$20,000.<sup>12</sup> Hospital and physician costs are additional. Manufacturers claim a battery life of nine to 11 years. Empirical studies indicate battery life to be 4.0 to 4.7 years.<sup>13,14</sup> Several companies manufacture ICDs.<sup>15</sup>

## **2 THE ISSUE**

The use of ICDs for patients who have survived an episode of SCD (secondary prevention) is established.<sup>11</sup> ICDs may also be used to prevent a first episode of SCD in patients at risk (primary prevention), but whether they should be used for these patients remains questionable. The costs associated with ICD use are high compared to those of antiarrhythmic medications, and psychosocial issues such as anxiety and depression may be associated with ICDs. Questions about the allocation of health resources are also raised when considering ICDs for the primary prevention of SCD, with demand already outstripping capacity in many jurisdictions. To address these issues, the clinical effectiveness and cost-effectiveness of ICDs for the primary prevention of SCD in different patient groups must be determined.

## **3 OBJECTIVES**

This report informs health care decision makers and others who are involved in the planning and delivery of ICD services about the evidence regarding the clinical effectiveness and cost-effectiveness of ICDs compared with conventional treatment. The budget impact of ICD therapy for people at high risk for SCD will be determined. The ethical and psychosocial issues related to ICDs will also be examined.

The objectives will be achieved by addressing three questions:

- What is the evidence regarding the clinical effectiveness of ICDs for primary prevention in terms of reducing SCD or all-cause death?
- What is the demonstrated economic impact and impact on health budgets when ICDs are used compared with conventional treatment?
- What are the ethical and psychosocial considerations that should inform decisions about the use of ICDs for primary prevention?

## **4 METHODS**

### **4.1 Literature Search**

#### **4.1.1 Literature search strategy for clinical effectiveness studies**

Published literature was obtained by cross-searching MEDLINE<sup>®</sup>, BIOSIS Previews<sup>®</sup>, PASCAL, and EMBASE<sup>®</sup> databases from 1980 onwards, with no language restrictions. A search strategy (Appendix 1) with appropriate descriptors and keywords was used with a filter to restrict results to controlled trials, meta-analyses, and systematic reviews. Parallel searches were run on PubMed and The Cochrane Library.

The original search was performed in September 2005. Regular alerts were established on MEDLINE, BIOSIS Previews, and EMBASE databases to capture new studies until January 25, 2006, and searches in The Cochrane Library were updated regularly. The last Cochrane updates for this report were performed on February 6, 2006.

Grey literature was obtained by searching the web sites of regulatory agencies, and health technology assessment and near-technology assessment agencies. Specialized databases such as the University of York NHS Centre for Reviews and Dissemination and the Latin American and Caribbean Center on Health Sciences Information (LILACS) were also searched. The Internet was searched using the Google<sup>™</sup> and Dogpile search engines. The web sites of professional associations such as the Canadian Cardiovascular Society, the American College of Cardiology, the Heart and Stroke Foundation of Canada, and the American Heart Association, and their associated conference sites were searched for additional information. Hand-searching of the reference lists of included reports was also done.

#### **4.1.2 Literature search strategy for cost-effectiveness studies**

Published literature was obtained by cross-searching MEDLINE, BIOSIS Previews, PASCAL, and EMBASE databases from 1980 onwards, with no language restrictions. A search strategy (Appendix 2) with appropriate descriptors and keywords was used with an economic filter to restrict results to relevant records. Parallel searches were run on PubMed and The Cochrane Library.

The original search was performed in September 2005. Regular alerts were established on MEDLINE, BIOSIS Previews, and EMBASE databases to capture new studies until January 25, 2006, and updated searches in The Cochrane Library were done regularly. The last Cochrane updates for this report were performed on February 6, 2006. A search was run on the Health Economic Evaluations Database (HEED), using a parallel search strategy. Supplementary cost information for the economic model was obtained by contacting experts and searching formularies.

#### **4.1.3 Literature search strategy for ethical and psychosocial studies**

Information on ethical, legal, or psychosocial issues involving the use of ICD therapy was found by searching MEDLINE, BIOSIS Previews, PASCAL, EMBASE, and The Cochrane Library. Controlled vocabulary and keywords included terms for “behavio(u)ral/mental/psychological disorders/factors/issues/phenomena” or “discrimination” or “ethical aspects/issues” or “ethics” or “human rights” or “jurisprudence” or “legal aspects/issues” or “legislation” or “privacy” with the ICD terms in Appendix 1.

## 4.2 Selection Criteria and Method

### 4.2.1 Selection criteria

#### a) *Clinical studies*

Clinical studies were included if they satisfied each of the following criteria:

- study design was RCT
- population group was patients at high risk for SCD without a history of cardiac arrhythmia
- intervention was ICD
- comparator was conventional therapy
- outcomes included rates of death from any cause, rates of all-cause death in ischemic patients, rates of all-cause death in non-ischemic patients, rates of SCD, rates of SCD in ischemic patients, rates of SCD in non-ischemic patients.

Abstracts, letters, editorials, short notes, and duplicate publications were excluded.

#### b) *Economic studies*

An economic study was eligible for review only if it met the following criteria:

- design was full economic study (including cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis) or partial economic study including cost analysis, cost comparison, and cost-consequence analysis
- population group was patients at high risk for SCD without a history of cardiac arrhythmia
- intervention was ICD
- comparator was conventional therapy.

Abstracts, letters, editorials, short notes, and duplicate publications were excluded.

#### c) *Ethical and psychosocial studies*

Findings were restricted to published references, and analysis was limited to concepts and issues based on the results of the literature search. Ethical and psychosocial issues require a “big picture” discussion involving stakeholders, including relevant specialty societies. This was beyond our review’s scope.

Inclusion criteria specified reports that addressed the ethical and psychosocial issues pertaining to ICD therapy. Given the likelihood of finding only a few reports, the primary search was not restricted to primary prevention studies, and relevant studies of ICD therapy for secondary prevention were considered. Because of the advances in ICD technology, only those reports published from 1995 onward were included in this review. As a result of reviewers’ comments on a draft of this review, one report published in 1993 was included for the ethics section.

### 4.2.2 Selection method

Study selection was done in two stages: screening based on title, keywords, and abstract; then full-text review of those citations identified as being relevant. The reference lists of relevant reports were scanned for further documents, including general reviews that addressed issues associated with ICD therapy.

Two reviewers (CH and KC) independently selected the relevant clinical trials, two reviewers (CH and HL) independently selected the relevant economic studies, and two reviewers (CH and HN) independently selected the relevant ethical and psychosocial studies. Disagreements were resolved by discussion.



### 4.3 Data Extraction Strategy

Once relevant trials were selected, CH and KC extracted clinical outcome data using a form (Appendix 3) that was designed a priori to capture information on trial and publication characteristics (first author, year of publication, journal, publication status, period, country, number of centres, source(s) of funding, study design, sample size); patient characteristics [age, gender, New York Heart Association (NYHA) class, ischemic status]; intervention characteristics (treatment, concomitant medications); outcomes related to clinical benefit (all-cause death, all-cause death in ischemic patients, all-cause death in non-ischemic patients, SCD, SCD in ischemic patients, SCD in non-ischemic patients); and outcomes related to harm (procedure- and device-related complications). The reviewers verified the accuracy of this information.

A form (Appendix 4) was used to capture information on economic data (first author, year of publication, sponsor, year, and country); the evaluation type (methods and design of model, if appropriate); results of the base case analysis; and the sensitivity to changes in the assumptions and parameters of the evaluation. CH and HL extracted and verified data.

Because the ethical and psychosocial review is mainly qualitative, no separate data extraction form was used. HN and CH independently selected studies and verified the extracted data for accuracy.

### 4.4 Strategy for Quality Assessment

A quality appraisal assessment form that takes into account study design and study performance (Appendix 5), modified from Hailey *et al.*,<sup>16</sup> was used to assess the quality of all included clinical studies. This score was compared to that derived from application of the Jadad scale.<sup>17</sup> The 35-item BMJ checklist was used to assess the quality of included economic studies.<sup>18</sup> Studies included for the discussion of ethical and psychosocial issues were not subjected to quality assessment. In all cases, two reviewers independently assessed included studies and then compared responses; discrepancies were resolved through discussion.

### 4.5 Data Analysis Method

For the clinical review, the outcomes investigated were the numbers of patients with all-cause death or SCD after treatment with or without ICDs. Subanalysis included all-cause death or SCD in ischemic or non-ischemic patients. Safety endpoints included the number of complications caused by ICD therapy, such as death as a result of the implantation procedure, revision caused by device dislocation, bleeding, and infection.

To compare the binary outcomes in the different treatment arms, relative risks (RRs) with corresponding 95% confidence intervals (CIs) were computed. Forest plots were generated using Review Manager 4.2.4 software. RRs were computed such that a value <1 indicated that the ICD treatment was better. A chi-squared test was used to assess variance in effect size among trials, with  $p < 0.10$  indicating significant heterogeneity across trials. In all cases, the RRs were pooled using the random effects model so as to take into account between-study heterogeneity. RR reduction (RRR) and CIs were calculated from the RR and associated CIs ( $RRR = 1 - RR$ ; CIs for  $RRR = 1 - CIs$  for RR). To help interpret the clinical significance of the results, the number needed to treat (NNT) was calculated using Visual Rx for all outcomes. Statistical significance was defined as  $p < 0.05$  or 95% CI of the RR that excluded unity.

For the economic review, because of anticipated heterogeneity among studies, no attempt was made to pool the results. Instead, a qualitative systematic review was performed, and study characteristics and results were tabulated. Similarly, because the ethical and psychosocial review was principally qualitative, no data analysis was performed.

## 5 RESULTS

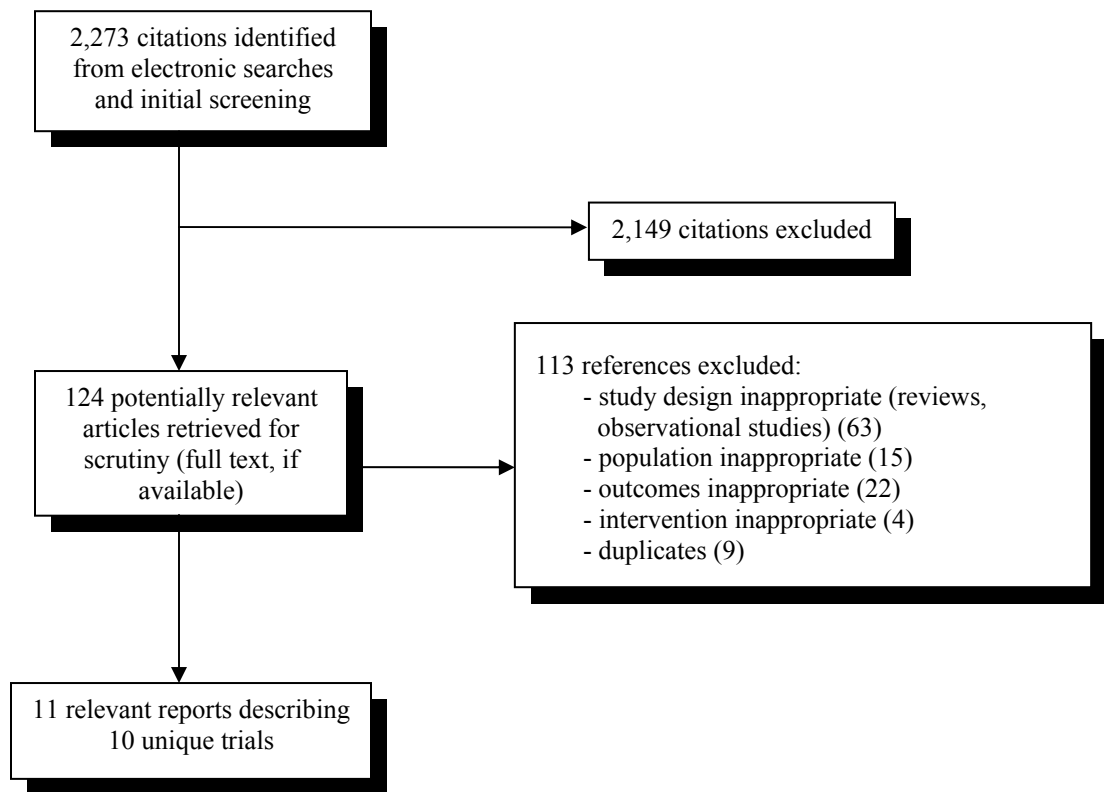
### 5.1 Quality and Quantity of Research Available

#### 5.1.1 Clinical studies

We identified 2,273 clinical citations in our original searches of multiple databases and retrieved 124 full reports. After eliminating reports that did not satisfy the selection criteria, we had 11 reports describing 10 unique trials (Figure 1).<sup>19-29</sup> The list of excluded clinical studies appears in Appendix 6.

According to the Jadad scale, included reports were of low quality with an average quality score of 2 out of 5, with blinding as the most common element not met or reported inadequately. This is to be expected because in the studies, the implantation of an ICD would be obvious. When the modified Hailey scale was used to assess study design and performance, the average quality score was 12.5, corresponding to category A high quality (high degree of confidence in study findings).

**Figure 1: Selected clinical reports**



### 5.1.2 Economic studies

Our original search identified 408 economic studies. After eliminating the reports that did not satisfy the selection criteria, we had seven economic reports<sup>30-36</sup> to include in this review.

Most of the included studies performed well based on the BMJ checklist, except for a lack of details of statistical tests and justification for choice of sensitivity analysis variables (items 26 and 28). Some studies detailed statistical tests but failed to provide the CI for stochastic data. Some did neither. Three studies<sup>30,31,35</sup> justified the choice of variables for sensitivity analysis while the remaining four did not or justified some of the variables.

### 5.1.3 Ethical and psychosocial studies

The original literature search strategy for this section identified 95 citations, of which 71 full reports were retrieved. After eliminating reports that did not satisfy the selection criteria, 18 studies were included in the review: seven for the ethics section<sup>11,37-42</sup> and 11 for the psychosocial section.<sup>29,43-52</sup> One additional report<sup>53</sup> for the ethics section was included based on an external reviewer's comments on a draft of this report.

## 5.2 Study Characteristics

### 5.2.1 Clinical studies

Of the 11 included reports, there were 10 randomized controlled trials (RCTs), with >7,000 patients enrolled (Table 1). One trial was conducted solely in the US,<sup>29</sup> two were conducted jointly in the US and Canada,<sup>20,22</sup> three were conducted jointly in the US and Europe,<sup>21,26,27</sup> one was conducted jointly in the US and Israel,<sup>25</sup> one was conducted in Germany,<sup>19</sup> one was conducted in Italy,<sup>28</sup> and one was multinational.<sup>24</sup> All studies were funded by industry.

Most studies included patients  $\geq 18$  years of age with NYHA class II or III CHF due to ischemic or non-ischemic causes, and LVEF of  $\leq 35\%$ . Patients did not have a history of sustained ventricular tachycardia or fibrillation. Appendices 7 and 8 outline the inclusion and exclusion criteria, and patients' characteristics.

### 5.2.2 Economic studies

Six full economic studies<sup>30-35</sup> and one partial economic evaluation<sup>36</sup> were included for review. In four full economic studies,<sup>31-33,35</sup> cost-effectiveness analyses and cost-utility analyses were done. The partial economic study<sup>36</sup> mislabelled itself as a cost-efficacy analysis. Because the study included no comparator, it was categorized as a partial economic evaluation.

One study<sup>34</sup> piggybacked a trial, and the remaining six were model-based evaluations.<sup>30-33,35,36</sup> Anderson *et al.*<sup>36</sup> developed a model that was flexible enough to allow the use of cost and survival figures derived from different sources. Insufficient detail was given about the model's structure. In the study by Chen *et al.*,<sup>30</sup> a decision analytic model was presented with clear structure. Three studies<sup>31,32,35</sup> adopted Markov models with the same structure for their analyses. Al-Khatib *et al.*<sup>33</sup> constructed a lifetime survival model for their health outcome estimation.

Five of the seven included studies<sup>30-33,35</sup> stated lifetime as their analysis horizon. The other two<sup>34,36</sup> used three- and four-year time horizons respectively. The five studies<sup>30-33,35</sup> with a lifetime horizon stated that their perspectives were societal, while the remaining two studies<sup>34,36</sup> did not state a perspective.

Economic outcomes were mainly reported as incremental cost per life year gained and incremental cost per quality-adjusted life year (QALY) gained (Table 2). Sanders *et al.*,<sup>31,35</sup> Al-Khatib *et al.*,<sup>33</sup> and one study for an insurance association<sup>32</sup> presented their results in both formats. Chen *et al.*<sup>30</sup> reported their evaluation of incremental cost per QALY of ICD compared with control therapy. The remaining two studies<sup>34,36</sup> estimated the economic value of ICDs in terms of incremental cost per life year gained.

### 5.2.3 Ethical and psychosocial studies

For ethical issues, no primary studies were identified. Of the eight studies included, four were review papers,<sup>11,37-39</sup> one was a commentary on adoption of new technologies,<sup>53</sup> one was an editorial on ethical uses with ICDs,<sup>40</sup> one was a textbook on biomedical ethics,<sup>41</sup> and one was a Canadian case report addressing the ethical implications associated with ICD therapy.<sup>42</sup> Two reviews<sup>11,38</sup> discussed the questions arising from the advent of ICD therapy about the allocation and rationing of scarce health care resources. One review was part of a larger technology report commissioned by CADTH (formerly CCOHTA) in 2000, which assessed the clinical, economic, ethical, and legal issues regarding the use of ICD therapy for secondary prevention.<sup>11</sup>

The main techniques for examining psychosocial issues were randomized clinical trials and systematic reviews. Six RCTs<sup>29,43-47</sup> and five reviews<sup>48-52</sup> were included. Two trials for quality of life (QoL) were for primary prevention.<sup>29,47</sup> One, the coronary artery bypass graft (CABG) Patch trial, is the largest QoL study among patients undergoing ICD therapy for primary prevention. Two of the five reviews were systematic: one meta-analysis of 20 studies<sup>48</sup> and one qualitative analysis of 42 studies.<sup>48</sup>

Observational studies have been limited by small study size, a lack of pre-morbid assessment, and the absence of randomization (i.e., dissimilar or no controls). These studies were conducted during the “learning curve” of ICD therapy and are of limited applicability now that less invasive implantation techniques are being used.

## 5.3 Data Analysis and Synthesis

### 5.3.1 Results of clinical studies

For the 10 RCTs (Table 1), patient outcomes were grouped into six categories: all-cause death, all-cause death in ischemic patients, all-cause death in non-ischemic patients, SCD, SCD in ischemic patients, and SCD in non-ischemic patients.

**Table 1: Characteristics of included clinical studies**

| Study  | Location      | Funding (organization, company)   | Number of Patients                           | Length of Study (years) | Length of Follow-up, Mean±SD | Jadad Score <sup>17</sup> (maximum=5) | Modified QA <sup>16</sup> (maximum=15) |
|--|---------------|---|--|-------------------------|------------------------------|---------------------------------------|--|
| Bänsch <sup>19</sup>                           | Germany       | Guidant Corporation   | 104  | 6                       | 22.8±4.3 months              | 2                                     | 13.0                                   |
| Bardy <sup>20</sup>                            | US, Canada    | Medtronic, Wyeth-Ayerst Laboratories; Knoll Pharmaceuticals; National Heart, Lung and Blood Institute; National Institutes of Health  | 2,521 (829 ICD, 845 amiodarone, 847 placebo) | 4                       | 45.5 months (median)         | 2                                     | 13.5                                   |
| Bigger <sup>21</sup>                           | US, Germany   | Guidant Corporation/CPI; National Heart, Lung and Blood Institute   | 900  | 4                       | 32±16 months                 | 3                                     | 12.5                                   |
| Buxton <sup>22</sup>                           | US, Canada    | Berlex Laboratories; Boehringer-Ingelheim Pharmaceuticals; Guidant Cardiac Pacemakers; Knoll Pharmaceutical; Medtronic, Searle, and Wyeth-Ayerst Laboratories; National Heart, Lung and Blood Institute | 351 randomized, 319 evaluated                | 6                       | 39 months (median)           | 2                                     | 12.5                                   |
| Hohnloser <sup>24</sup>                        | multinational | St. Jude Medical  | 674  | 5                       | 30±13 months                 | 3                                     | 14.5                                   |
| Kadish <sup>25</sup>                           | US, Israel    | St. Jude Medical  | 458  | 5                       | 29.0±14.4 months             | 2                                     | 13.0                                   |
| Moss <sup>27</sup>                             | US, Europe    | Guidant Corporation/CPI   | 196  | 5                       | 27 months (median)           | 2                                     | 11.5                                   |
| Moss <sup>26</sup> and Greenberg <sup>23</sup> | US, Europe    | Guidant Corporation   | 1232   | 4                       | 20 months (median)           | 2                                     | 12.5                                   |
| Raviele <sup>28</sup>                          | Italy         | Guidant Corporation   | 143 randomized, 138 evaluated                | 4.5                     | 540±403 days                 | 2                                     | 11.0                                   |
| Strickberger <sup>29</sup>                     | US            | Guidant Corporation   | 103  | 5                       | 2.0±1.3 years                | 2                                     | 11.0                                   |

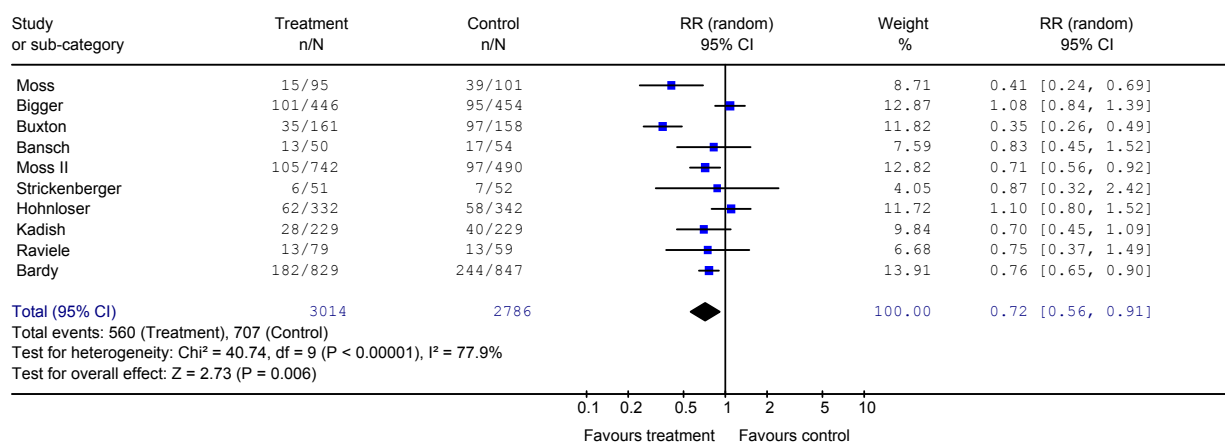
**Table 2: Characteristics of included economic studies**

| Author                                | Location and Funding Source                                      | Study Design  | Treatments  | Study Population   | Analysis Horizon | Study Perspective |
|---------------------------------------|--|---|---|--|------------------|-------------------|
| Al-Khatib <i>et al.</i> <sup>33</sup> | US, industry partially funded                                    | CEA and CUA with lifetime survival model                      | ICD versus conventional medical therapy                       | patients who met eligibility criteria for MADIT-II trial (i.e., age $\geq 21$ years, history of MI, EF $\leq 0.3$ , and cardiac catheterization)   | lifetime         | societal          |
| Anderson <i>et al.</i> <sup>36</sup>  | UK, NR   | model-based partial evaluation (cost and outcome description) | ICD   | patients meeting any of following criteria: survivors of out-of-hospital cardiac arrest; patients with non-sustained ventricular tachycardia; patients at high risk after MI; patients with low EF and positive signal average ECG; or patients awaiting cardiac transplantation | 3 years          | not stated        |
| Chen <i>et al.</i> <sup>30</sup>      | US, not funded by industry                                       | decision-model-based CEA and CUA                              | ICD versus standard CHF drug therapy                          | chronic heart failure patients with NYHA functional class II and III   | lifetime         | societal          |
| Mushlin <i>et al.</i> <sup>34</sup>   | US, research grant   | trial-tailed CEA  | ICD versus conventional therapy                               | patients with asymptomatic non-sustained ventricular tachycardia, prior MI, EF $\leq 35\%$ , and inducible ventricular tachyarrhythmia at electrophysiological testing not suppressed by procainamide  | 4 years          | not stated        |
| Sanders <i>et al.</i> <sup>31</sup>   | US, research grant   | Markov-model-based CEA and CUA                                | ICD versus amiodarone treatment versus no treatment           | patients with past MI who did not have sustained ventricular arrhythmia  | lifetime         | societal          |
| Sanders <i>et al.</i> <sup>32</sup>   | US, NR   | Markov-model-based CEA and CUA                                | ICD versus conventional therapy (no antiarrhythmic treatment) | patients who met eligibility criteria of MADIT-II trial (i.e., past MI and left ventricular dysfunction with EF $\leq 0.03$ )  | lifetime         | societal          |
| Sanders <i>et al.</i> <sup>35</sup>   | multiple locations (depending on trials), not funded by industry | Markov-model-based CEA and CUA                                | ICD versus control therapy (depending on referred trial)      | patients who respectively met eligibility criteria for 8 used clinical trials (MADIT-I, MADIT-II, CABG Patch, MUSTT, DEFINITE<DINAMIT, COMPANION, SCD-HeFT)  | lifetime         | societal          |

CEA=cost-effectiveness analysis; CUA=cost-utility analysis; ICD=implantable cardiac defibrillator; MI=myocardial infarction; EF=ejection fraction; ECG=electrocardiogram; CABG=coronary artery bypass graft; NR=not reported

## a) All-cause death

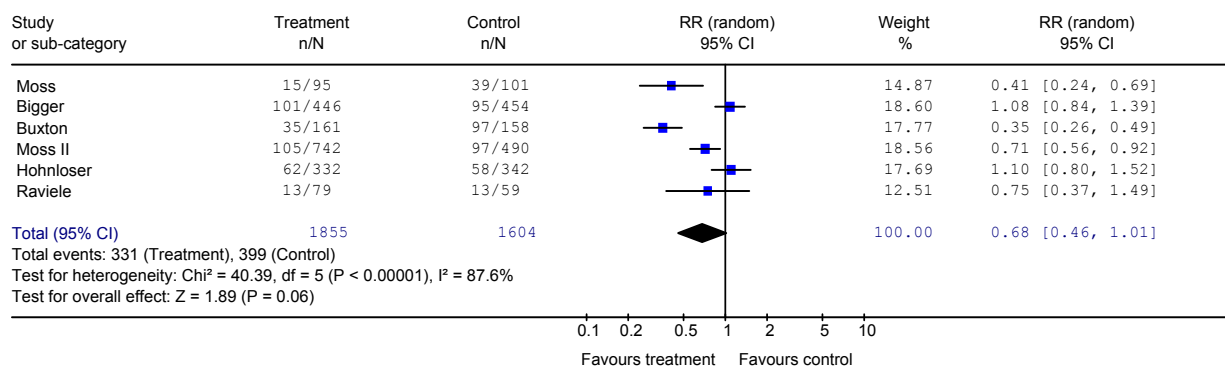
Review: Implantable cardiac defibrillator  
 Comparison: 01 Death  
 Outcome: 04 All cause death



Ten trials compared the number of patients who died from any cause after receiving an ICD (treatment group) with those who died from any cause after conventional treatment (control group). Most trials, except the studies by Bigger *et al.*<sup>21</sup> and Hohnloser *et al.*,<sup>24</sup> have RRs that favour treatment with ICDs. The overall estimate shows that treatment with ICDs yields a 28% decrease in risk of all-cause death (RR=0.72, ARR 6%) compared with the control treatment. The decrease in risk of all-cause death is statistically significant with RR 95% CI (0.56, 0.91). The chi-squared test shows heterogeneity ( $p < 0.00001$ ) across trials, meaning the differences between studies are not a consequence of sampling variation and not due to chance alone. For this reason, a random effects model was used to arrive at the pooled estimate of effectiveness. Although the study by Bardy *et al.*<sup>20</sup> included ischemic and non-ischemic patients, it did not provide the number of deaths for the subgroups other than Kaplan-Meier estimates. Therefore, we were unable to include the 1,676 patients from this study in all subgroup analyses.

## b) All-cause death in ischemic patients

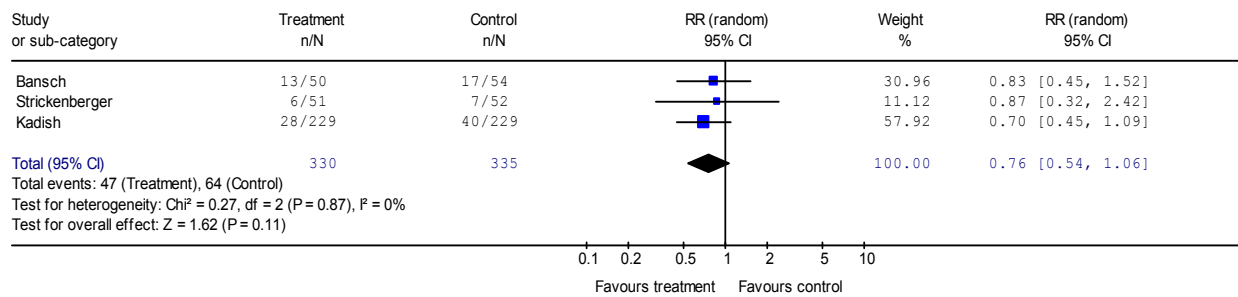
Review: Implantable cardiac defibrillator  
 Comparison: 01 Death  
 Outcome: 02 All cause death in ischemic patients



Six trials examined the number of all-cause deaths in ischemic patients after receiving an ICD (treatment group) or other therapy (control group). Four trials<sup>22,26-28</sup> have RRs that favour treatment with ICDs. The overall estimate shows that treatment with ICDs yields a 32% decrease in risk of all-cause death (RR=0.68, ARR 7%) compared with control treatment. The decrease in risk of death is not statistically significant with RR 95% CI (0.46, 1.01). Again, the chi-squared test shows heterogeneity ( $p < 0.00001$ ) across trials, meaning the differences between studies are not a consequence of sampling variation and not due to chance alone. For this reason, a random effects approach was used for the analysis.

### c) All-cause death in non-ischemic patients

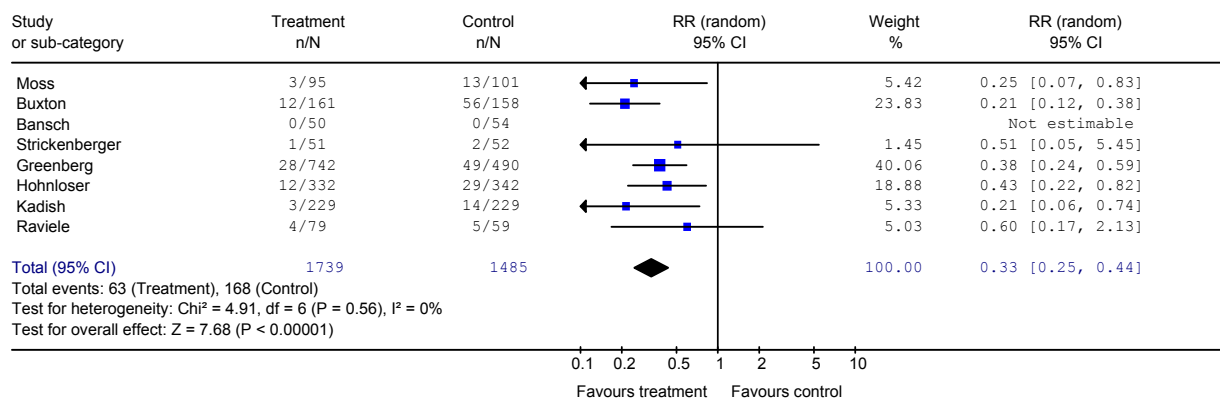
Review: Implantable cardiac defibrillator-rct  
 Comparison: 01 Death  
 Outcome: 03 All cause death in non-ischemic patients



Three trials examined the number of all-cause deaths in non-ischemic patients after receiving an ICD (treatment group) or other therapy (control group). All trials have RRs that favour treatment with ICDs. The overall estimate shows that treatment with ICDs yields a 24% decrease in risk of all-cause death [RR=0.76, absolute risk reduction (ARR) 5%] compared with control treatment. The decrease in risk of death is not statistically significant with RR 95% CI [0.54, 1.06]. Unlike the two previous analyses, the chi-squared test shows homogeneity ( $p = 0.87$ ) across trials, meaning the differences between studies may be due to chance alone.

### d) SCD

Review: Implantable cardiac defibrillator  
 Comparison: 01 Death  
 Outcome: 01 Sudden cardiac death

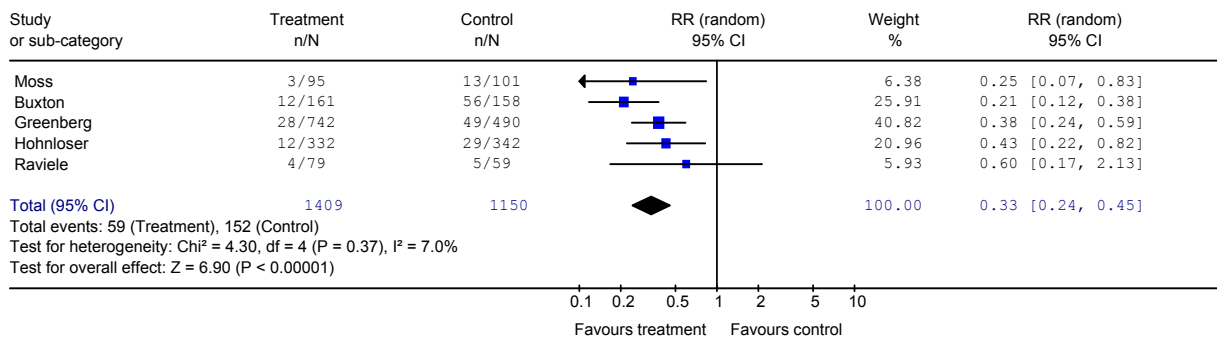




Eight trials examined the number of patients with SCD after receiving an ICD (treatment group) or other therapy (control group). All trials with detectable RR favour treatment with ICDs. There were no events in either arm of the trial by Bänsch<sup>19</sup> so the RR could not be computed. The overall estimate shows that treatment with ICDs yields a 67% decrease in risk of SCD (RR=0.33, ARR 7%) compared with control treatment. The decrease in SCD is statistically significant with RR 95% CI (0.25, 0.44). The chi-squared test shows homogeneity (p=0.56) across trials, meaning the differences between studies may be due to chance alone.

### e) Sudden cardiac death in ischemic patients

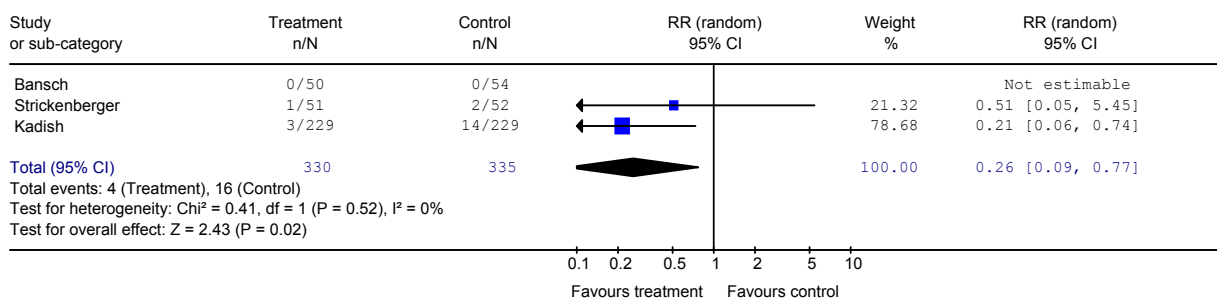
Review: Implantable cardiac defibrillator  
 Comparison: 01 Death  
 Outcome: 05 Sudden cardiac death in ischemic patients



Five trials<sup>22-24,27,28</sup> examined the number of SCD in ischemic patients after receiving an ICD (treatment group) or other therapy (control group). All trials have RRs that favour treatment with ICDs. The overall estimate shows that treatment with ICDs yields a 67% decrease in risk of SCD (RR=0.33, ARR 9%) compared with control treatment. The decrease in death is statistically significant with RR 95% CI (0.24, 0.45). The chi-squared test shows homogeneity (p=0.37) across trials, meaning the differences between studies may be due to chance alone.

### f) Sudden cardiac death in non-ischemic patients

Review: Implantable cardiac defibrillator  
 Comparison: 01 Death  
 Outcome: 06 Sudden cardiac death in non-ischemic patients



Three trials<sup>19,25,29</sup> examined the number of SCDs in non-ischemic patients after receiving an ICD (treatment group) or other therapy (control group). All trials with detectable RRs favour treatment with ICDs. The overall estimate shows that treatment with ICDs yields a 74% decrease in risk of SCD (RR=0.26, ARR 4%) compared with control treatment. The decrease in death is statistically

significant with RR 95% CI [0.09, 0.77]. The chi-squared test shows homogeneity ( $p=0.52$ ) across trials, meaning the differences between studies may be due to chance alone.

**g) Adverse events (AEs)**

Complications directly associated with ICDs can be categorized as perioperative- or device-related events (Appendix 9). Perioperative complications included thrombotic events, pulmonary embolism, bleeding, infection, hemothorax, pneumothorax, tissue perforation, cardiac tamponade, and post pericardiotomy syndrome. Device-related complications included dislocation of the leads, sensing or isolation defects, lead fractures, generator component malfunctions, conduction defects, and inappropriate shocks.

The most common perioperative complications were infections associated with the surgical procedure. A total of 77 infections were reported in five studies.<sup>19,21,25-27</sup> None of the most recent studies<sup>20,24,25,28,29</sup> reported AEs due to infection, except the Kadish study,<sup>25</sup> which reported one incidence of postoperative infection. Two studies<sup>21,27</sup> reported a combined 23 incidences of bleeding. Other perioperative complications were less frequent, with two studies<sup>25,27</sup> reporting four incidences of venous thrombosis, and three studies<sup>24,25,27</sup> reporting four incidences of pneumothorax (one study<sup>24</sup> did not report the number of events). There was one incidence of pulmonary embolism,<sup>27</sup> one incidence of post pericardiotomy syndrome,<sup>21</sup> one incidence of perforation,<sup>18</sup> one incidence of hemothorax,<sup>24</sup> and one incidence of cardiac tamponade<sup>25</sup> reported.

The device-related AE reported most often was that of inappropriate shock. Four studies<sup>20,24,25,28</sup> reported a total of 153 incidences of inappropriate shock (one study<sup>24</sup> did not report the number of events). There were 63 conduction defects reported in one study<sup>21</sup> and three defibrillator generator malfunctions in another study.<sup>27</sup> Lead problems accounted for a total of 33 AEs in five studies<sup>19,24-27</sup> (one study<sup>24</sup> did not report the number of events). Lead dislodgement, when it occurs, usually happens within the first few months after ICD implantation and is a concern due to the necessity for operative revision. One study<sup>22</sup> reported a death from infection during revision, 18 months after the initial device implantation.

One study<sup>26</sup> reported that patients receiving ICDs had a higher rate of new or worsening heart failure than those in the control arm of the study. This rate was not statistically significant ( $p=0.09$ ).

The other AEs reported occurred in both the control and intervention arms of the studies. These included atrial fibrillation, sinus bradycardia, heart failure, MI, ventricular arrhythmias, and syncope. The reporting of AEs in the included trials was mainly limited to listing the numbers of specific events. There was no indication of the seriousness of the events, or of the associated repeat hospitalizations and operative procedures.

**h) Summary of clinical results (Table 3)**

For patients at high risk of ventricular arrhythmia, the use of ICDs significantly reduced (by two-thirds) their risk of SCD compared with conventional treatment. ICDs were similarly efficacious in reducing the risk of cardiac death in ischemic and non-ischemic patients. ICD treatment significantly reduced the risk of all-cause death, by close to a third, in the overall population. Data indicated that ICDs needed to be implanted into 14 patients to prevent one SCD in the overall population, and in 12 and 28 ischemic and non-ischemic patients respectively. The most common complications were infections associated with the surgical procedure and inappropriate shocks due to lead or generator problems.

|   | <b>Number of Patients</b> | <b>RR</b> | <b>ARR</b> | <b>RRR (95% CI)</b> | <b>NNT (95% CI)</b> |
|---|---------------------------|-----------|------------|---------------------|---------------------|
| All-cause death                               | 5,800                     | 0.72      | 6%         | 28% (9%, 44%)       | 15 (10, 45)         |
| All-cause death in ischemic patients          | 3,459                     | 0.68      | 7%         | 32% (NS)            | 13 (NS)             |
| All-cause death in non-ischemic patients      | 665                       | 0.76      | 5%         | 24% (NS)            | 22 (NS)             |
| SCD   | 3,224                     | 0.33      | 7%         | 67% (56%, 75%)      | 14 (13, 17)         |
| Sudden cardiac death in ischemic patients     | 2,559                     | 0.33      | 9%         | 67% (55%, 76%)      | 12 (11, 14)         |
| Sudden cardiac death in non-ischemic patients | 665                       | 0.26      | 4%         | 74% (23%, 91%)      | 28 (22, 87)         |

ARR=absolute risk reduction; NNT=number of patients needed to treat to save one life; NS=not significant; RR=relative risk; RRR=relative risk reduction; SCD=sudden cardiac death.

### 5.3.2 Results of economic studies

This economic review addressed the main findings in a base-case analysis and a sensitivity analysis.

#### a) **Base-case results**

ICD therapy costs more and was more effective than conventional medical therapy. However, the incremental cost-effectiveness ratio (ICER) of ICD therapy over the comparator varied across studies (Table 4).

Most economic studies had ischemic samples with low LVEF. Their evaluated ICER of ICD compared with control therapy ranged from US\$24,500 per life year (US\$34,000 per QALY) (in the Sanders *et al.*<sup>35</sup> study for the MUSTT patients) to US\$63,300 per life year (US\$71,800 per QALY) (in the Sanders *et al.*<sup>31</sup> study for EF  $\leq 0.3$  group). There are two exceptions. For the CABG Patch trial and the DINAMIT populations, Sanders *et al.*<sup>35</sup> found that ICD treatment was dominated by control therapy. For the ischemic patients with higher LVEF, one identified economic study<sup>31</sup> provided the corresponding ICER evaluation. They reported that the ICER of ICD therapy over amiodarone was US\$173,400 per life year (US\$195,700 per QALY) for a group with EF 0.31 to 0.4 and US\$501,500 per life year (US\$557,900 per QALY) for a group with EF >0.4.

The Sanders *et al.*<sup>35</sup> study, based on the DEFINITE trial, was the only one identified specific to the non-ischemic population. The ICER of ICD over control therapy was estimated at US\$36,800 per life year (US\$51,300 per QALY) for the non-ischemic population. It is comparable to the results for ischemic patient cases.

The Sanders *et al.*<sup>35</sup> study involved an analysis of both non-ischemic and ischemic patients. For the SCD-HeFT population, they calculated the ICER of ICD compared with control therapy to be about US\$50,700 per life year (US\$70,200 per QALY). Another study, by Chen *et al.*,<sup>30</sup> had a hypothetical population of newly diagnosed US CHF patients, with NYHA functional classes II and III, that likely included both ischemic and non-ischemic patients. Their ICER could be as high as US\$97,863 per QALY.

The Anderson *et al.*<sup>36</sup> study calculated the amount of money that must be spent to give one ICD patient one extra year of life. No treatment seemed to be the comparator in their analysis, but this was unclear. They reported that the estimated cost was £42,500 for patients with non-sustained ventricular tachycardia (based on the MADIT trial strategy), £36,500 for those at high risk after MI,

£44,000 for those with low EF (e.g., EF <0.35) and positive signal-averaged ECG, and £16,000 for the patient group awaiting cardiac transplantation.

| Table 4: ICER of ICD use compared with control therapy by study |  |   |
|---|--|---|
| Study   | ICER Baseline Estimation   | Patients  |
| Al-Khatib <i>et al.</i> <sup>33</sup>                           | US\$50,500 per life year, US\$57,300 per QALY  | ischemic  |
| Anderson <i>et al.</i> <sup>36</sup>                            | £42,500 per life year (US\$77,404) for patients with non-sustained ventricular tachycardia<br>£36,500 per life year (US\$66,476) for patients at high risk after MI<br>£44,000 per life year (US\$86,135) for patients with low EF and positive signal average ECG<br>£16,000 per life year (US\$29,140) for patients awaiting cardiac transplantation   | ischemic<br>unclear<br>unclear<br>unclear   |
| Chen <i>et al.</i> <sup>30</sup>                                | US\$97,863 per QALY  | ischemic and non-ischemic   |
| Mushlin <i>et al.</i> <sup>34</sup>                             | US\$27,000 per life year   | ischemic  |
| Sanders <i>et al.</i> <sup>31</sup>                             | ICD versus amiodarone, with ICD moderate efficacy: US\$63,300 per life year, US\$71,800 per QALY for EF ≤0.3 group; US\$173,400 per life year, US\$195,700 per QALY for EF 0.31 to 0.4 group; US\$501,500 per life year, US\$557,900 per QALY for EF >0.4 group  | ischemic  |
| Sanders <i>et al.</i> <sup>32</sup>                             | US\$36,700 per life year, US\$50,900 per QALY  | ischemic  |
| Sanders <i>et al.</i> <sup>35</sup>                             | US\$24,500 per life year, US\$34,000 per QALY for MUSTT patients<br>US\$25,300 per life year, US\$34,900 per QALY for MADIT-I patients<br>US\$39,000 per life year, US\$54,100 per QALY for MADIT-II patients<br>US\$36,800 per life year, US\$51,300 per QALY for DEFINITE patients<br>US\$36,500 per life year, US\$50,300 per QALY for COMPANION patients<br>US\$50,700 per life year, US\$70,200 per QALY for SCD-HeFT patients<br><br>control therapy costs less and gives better result for CABG Patch patients<br>control therapy costs less and gives better result for DINAMIT patients | ischemic<br>ischemic<br>ischemic<br>non-ischemic<br>ischemic<br>ischemic and non-ischemic<br>ischemic<br>ischemic |

QALY=quality-adjusted life year; MI=myocardial infarction; EF=ejection fraction; ECG=electrocardiogram; ICD=implantable cardiac defibrillators; CABG=coronary artery bypass graft.

## b) Sensitivity results

The reviewed studies used several types of sensitivity analyses to examine the robustness of individual base-case results. These included one-way, threshold analysis, scenario analysis, and probabilistic sensitivity analysis. Some of the parameters tested in the sensitivity analysis were common among the studies while others were distinct. The results were consistent overall in terms of the direction of parameters influencing the economic value of ICD therapy; however, quantitative estimates of ICERs were significantly different, because the parameters varied between studies.

### One-way sensitivity analysis

Six studies used one-way sensitivity analysis.<sup>30-35</sup> The parameters examined were cost (e.g., ICD cost, implant procedure cost, battery replacement cost and frequency, ICD generator replacement cost and frequency, cost of ICD-related infection, and cost of CHF-related hospitalization), clinical parameters (e.g., ICD efficacy and effectiveness, ICD preoperative mortality, sudden death rate, cardiac mortality rate in the patient population, and all-cause mortality rate), utility parameters (e.g. post ICD utility and utility of left ventricular dysfunction), and study design (e.g., analysis horizon, discounting rate, and patient follow-up period). The three parameters that influenced the ICERs were ICD cost, ICD efficacy and effectiveness, and utility.

When the efficacy decreased, ICD treatment became less economically favourable<sup>32,35</sup> to different degrees. Mushlin *et al.*<sup>34</sup> indicated that a reduction of 21% of ICD effectiveness would yield an 8.5%

increase of ICER per life year gained. In the Sanders *et al.* study,<sup>35</sup> when ICD efficacy was changed from high to low, the ICER was reduced from 58.8% to 12.5%, depending on the corresponding trials. In another study by Sanders *et al.*,<sup>31</sup> the ICER of ICD versus no antiarrhythmic treatment declined from US\$59,800 per QALY to US\$46,100 per QALY for EF <0.3 patients when ICD treatment efficacy changed from low to high.

Five studies demonstrated how the cost of an ICD influences the estimated ICER.<sup>30-33,35</sup> If the cost of the ICD device dropped to \$10,000, the ICER would be more favourable, but with a degree of difference that varied from 60%<sup>31</sup> to 10%.<sup>30</sup> The most significant impact was reflected in the Mushlin *et al.* study,<sup>34</sup> where the ICER value of \$27,000 per life year decreased to \$3,300 per life year if a transvenous device was used and its cost was reduced by 50%.

If patients' QoL with ICDs increased, ICD therapy was more favourable. The Blue Cross study<sup>32</sup> indicated that if ICD utility increased to 0.94 (0.88 in the base case) and the utility of conventional therapy patients remained at 0.88, the ICER dropped to US\$39,600 per QALY, declining by 60% compared with their baseline result (US\$97,861 per QALY). The Chen *et al.* study<sup>30</sup> distinguished the post-ICD first year and subsequent years with respect to life quality. Their sensitivity analysis found that the cost-effectiveness ratio of ICD versus conventional therapy was not sensitive to utility in the first year after ICD implant, but was sensitive to utility in subsequent years. Compared with the base case, the ICER increased by 30% or declined by 18.75% if the second-year utility post-ICD decreased by 10% or increased by 10% respectively. If the first-year utility post-ICD implant varied ( $\pm 10\%$ ), the percentage change of ICER was less. This could be due to their assumption that the utilities of survival in subsequent years were computed directly based on the second-year utility and annual reduction rate.

### Threshold analysis

Five studies<sup>30-33,35</sup> performed a threshold analysis, identifying the cut-off value of selected parameters to reach certain ICER thresholds. The three parameters most commonly selected for this analysis were the efficacy of ICDs to prevent SCD, ICD cost, and utility.

The Blue Cross study<sup>32</sup> reported that ICDs must prevent 68.5% of SCDs to reach a cost-effectiveness of US\$50,000 per QALY and 31.2% for US\$100,000 per QALY. The corresponding cut-off values are 70% and 35% in the Sanders *et al.* study.<sup>31</sup>

Chen *et al.*<sup>30</sup> found that to reach the threshold of US\$50,000 per QALY gained, the cost of the initial ICD implant had to be as low as US\$9,600. The study of Al-Khatib *et al.*<sup>33</sup> estimated that with the hazard ratio of <0.72 (base case <0.69), if ICD placement cost was reduced to US\$10,000 (base case value=US\$19,370), the ICER of ICD versus medical therapy was <US\$50,000 per life year gained (base case ICER value=US\$57,500 per life year).

The cut-off value of utility for US\$50,000 per QALY gained varied. Chen *et al.*<sup>30</sup> observed that if other parameters did not change, the utility at the second year after ICD therapy had to be as high as 1.0 (base case utility=0.71). Sanders *et al.*<sup>35</sup> stated that in the SCD-HeFT trial, the ICD utility had to be increased to 0.95 (base case utility=0.88).

### Other types of sensitivity analysis

Sanders *et al.*<sup>31</sup> performed a probabilistic sensitivity analysis where all variables changed except for QoL with conventional therapy (amiodarone) or ICDs. For patients with EF  $\leq 0.30$ , amiodarone

dominated ICD therapy in 2.6% of their simulations, while ICD therapy cost more and was more effective in 97.4% of the simulations (median ICER value=US\$83,200 per QALY). No antiarrhythmic therapy dominated ICD in 0.02% of the simulations, while in the other simulations, the median ICER was US\$67,000 per QALY.

The study by Sanders *et al.*<sup>31</sup> conducted a multi-way sensitivity analysis in which they varied several utility-related parameters simultaneously. They originally assumed 0.88 utilities for all patients independent of their treatment. Then, they examined the ICER when utility was assumed to be 0.73 for amiodarone patients, 0.76 for ICD patients, and 0.8 for patients without any treatment. The ICER of ICD therapy compared with amiodarone decreased slightly from the baseline result of US\$71,800 per QALY gained to US\$70,000 for patients with EF  $\leq$ 0.30. When they continued to reduce utility for ICD therapy to 0.64, but retained 0.73 for amiodarone and 0.8 for patients without treatment, they observed that ICD therapy was dominated by both amiodarone and no antiarrhythmic therapy.

Best and worst scenario analyses were undertaken in the Blue Cross study,<sup>32</sup> which alternatively used favourable and unfavourable assumptions about ICD efficacy (45% or 90%), effect on QoL (0.80 or 0.95), and ICD cost (US\$60,000 or US\$10,000) to examine the ICER. The authors estimated the ICER of ICDs over conventional therapy at US\$311,700 per QALY under the worst scenario and US\$22,100 per QALY gained under the best scenario. The difference could be as much as 14 to one.

### **c) Summary of economic results (Appendix 10)**

This review showed that compared with control therapy, ICD therapy generally costs more, primarily because of expensive ICD implantation, but gained more life years and QALYs in treating patients without prior clinical arrhythmia. Subject to several assumptions, for patients with low EF, the ICER estimates of ICD prophylactic use varied from US\$24,500 to US\$63,300 per life year gained, or from US\$34,000 to US\$97,863 per QALY gained. For patients with a high EF, the ICER was higher (e.g., US\$195,700 or US\$557,900 per QALY gained in the Sanders *et al.* study<sup>31</sup> respectively for EF 0.31 to 0.4 and  $>$ 0.4). The sensitivity analyses in the reviewed studies indicated that the cost-effectiveness of ICD treatment was mainly driven by ICD efficacy, ICD implantation cost, and patients' life utility (if the effectiveness is measured using QALYs).

## **5.3.3 Results of ethical and psychosocial studies**

### **a) Ethical issues**

The use of ICDs is increasing as primary prevention trials identify the benefit for larger populations of patients, even though the benefit is confined to specific sub-populations.<sup>40</sup> Many of the ethical issues raised by the advent of ICD therapy are common to other health care interventions. They involve patients and their right to forgo, accept, be put on waiting lists for, and discontinue ICD therapy. Some unique issues about ICD therapy arise from the surgical implementation of a device that may malfunction or discharge inappropriately. For example, if an individual is prescribed a drug that has side effects, the patient can discontinue the drug, and the side effects often disappear. It is more complicated to discontinue ICD therapy.<sup>39</sup>

The advent of ICD therapy poses emerging questions about the allocation of resources, given its potentially heavy financial burden on the Canadian health care system.<sup>11</sup> The mandate of a health care system operated in the public interest is to maximize the population's health given the available resources and to seek extra resources only if the value of the health benefits to be obtained by expanding the health care budget exceeds the value (to society) of the resources put to another use. Demonstrating that an intervention is safe and effective is necessary but insufficient to indicate that

the public's welfare would be improved by diverting resources from other activities to pay for such an intervention.<sup>53</sup>

In the current situation, where the demand for ICDs exceeds the supply funded by many Canadian jurisdictions, there has been a tendency for “downward delegation” of allocation decisions to individual physicians.<sup>38</sup> According to Simpson *et al.*, this “bedside rationing” results in inconsistent resource allocation decisions because it creates a moral dilemma for physicians, who are torn between their traditional fiduciary role as “patient’s advocate” and the role of “gate-keeper.”<sup>38</sup> A more transparent and fair decision-making process includes guidelines that constrain resource allocation decisions about the use of ICD therapy.<sup>38</sup>

As part of the process of informed consent, a physician has the responsibility to discuss with every patient recommended for ICD therapy its advantages and disadvantages versus conventional medical care.<sup>37</sup> The specifics depend on the situation, but sufficient data are available from the randomized trials reported here. All potential ICD recipients should be advised that AEs, which occur in a minority of patients, may lead to lower QoL. They should also be informed that resources are available to ease their adjustment to the therapy. Physicians should encourage patients to critically measure the use of an ICD against the treatment objectives. This includes discussions about ICD deactivation and explantation in situations where the ICD is no longer desired by the patient or no longer medically appropriate.<sup>39,42</sup> These discussions should occur before a decision on ICD use is made.<sup>39</sup> QoL considerations are also relevant in resource allocation decisions. Individual physicians and hospital administrators will have to decide which patients will be offered ICD therapy.

### **b) Psychosocial issues**

Little work has been done on the psychosocial sequelae after ICD surgery. Individuals who receive their ICD for primary prevention must adjust to several changes and to the presence of a device for which they may not grasp the need. These changes require psychological, physical, and social adjustments. Some RCTs and systematic reviews examined psychosocial variables such as the psychological and physical aspects of QoL, mood constructs including anxiety and depression, and lifestyle changes such as restrictions on driving.

### **ICD implantation and QoL**

The impact of ICD therapy on QoL has been evaluated in two primary prevention trials (the CABG Patch trial<sup>47</sup> and AMIOVIRT<sup>29</sup>) (Table 5), and is the topic of one systematic review.<sup>49</sup>

| <b>Trial</b>             | <b>Sample Size (% of total)</b> | <b>Timing of QoL Assessment</b>    | <b>Instruments</b>   | <b>Results</b>                                    |
|--------------------------|---------------------------------|------------------------------------|--|---|
| CABG Patch <sup>47</sup> | 490 (54)                        | cross-sectional (6 months)         | SF-36 and disease-specific                                       | ICD associated with poorer QoL (several measures) |
| AMIOVIRT <sup>29</sup>   | 103 (100)                       | longitudinal (baseline, 12 months) | Quality of Well-Being Schedule and State Trait Anxiety Inventory | no significant difference in QoL                  |

QoL=quality of life; SF-36= Medical Outcomes Short-Form 36-item questionnaire; ICD=implantable cardiac defibrillator.

The CABG Patch trial<sup>47</sup> was an international, multi-centre, randomized trial. It failed to show that the prophylactic use of ICDs benefited patients with low EF and abnormal signal-averaged ECG who were undergoing CABG surgery. Six months after surgery, 490 of 900 patients completed a QoL assessment [Medical Outcomes Short-Form 36-item questionnaire (SF-36), and a disease-specific

questionnaire]. Compared with the ICD group, control patients in CABG Patch trial were significantly more likely to feel that their health status had improved over the preceding year, and that they had higher emotional role functioning and greater psychological well-being. On other measures of QoL, both groups performed similarly. ICD recipients who received a shock had poorer QoL in several domains compared with the control group, but not compared with ICD recipients who did not receive a shock.<sup>47</sup>

When interpreting the data from the CABG Patch trial, there are several considerations. Preventive therapy is unlikely to improve QoL, particularly in the short term. It is not surprising then, that the presence of an ICD – particularly if it delivered a shock – negatively affected QoL. The trial investigators proposed that ICD shock reinforced a sense of illness, decreasing the patients' QoL. An alternative explanation is that patients requiring ICD shock were sicker than patients who did not require a shock. Only 54% of patients completed QoL assessments, and the investigators noted several baseline differences between those who did and those who did not. Incomplete data acquisition and baseline differences could bias the data.<sup>52</sup> For example, receiving an unpleasant shock may motivate an individual to complete a QoL questionnaire that would bias results against ICD therapy. Although the generalizability of these findings is questionable, especially since open heart surgery is no longer required to perform CABG, this trial represents the largest QoL study among patients undergoing ICD surgery for primary prevention.

AMIOVIRT<sup>29</sup> was a US, multi-centre, randomized trial of amiodarone versus an ICD in patients with non-ischemic dilated cardiomyopathy and asymptomatic non-sustained ventricular tachycardia. QoL scores at baseline and at one year were similar between the two groups in this small study.<sup>29</sup>

The meta-analysis by Burke *et al.*<sup>49</sup> of 20 studies published between 1980 and 2001 found no significant differences in psychosocial outcome between ICD patients and pharmacologically maintained patients with ventricular arrhythmia, or between pre- and post-surgery ICD patients. ICD patients reported significantly worse psychological and physical functioning than other cardiac controls. There were two limitations to this meta-analysis. First, the studies involved primary and secondary prevention populations, and in only two studies were patients randomized between groups. Second, no subgroup analysis was performed to compare studies in which patients received an ICD as prophylaxis versus treatment for ventricular arrhythmia. The findings by Burke *et al.* suggest that poor psychosocial outcome in ICD patients may be a result of the underlying ventricular arrhythmia condition, rather than a response to device implantation and therapy.<sup>49</sup> The question of whether QoL changes in the long term (i.e., beyond one year) has not been evaluated. More study is needed to determine the impact of ICD therapy on QoL among patients in whom it is used for the primary prevention of sudden death.

### **ICD implantation and mood**

The most common psychological problems after ICD surgery are anxiety, depression, fear of shock, and fear of death.<sup>48,49,52</sup> Some anxiety or depression is experienced by 24% to 87% of patients, and up to 38% will experience anxiety of sufficient intensity and duration to meet diagnostic criteria for an anxiety spectrum disorder.<sup>48</sup> The frequency with which the ICD has fired and a recent shock are linked to anxiety. Other variables, including age, sex, family response, perception of control and predictability of shocks, and psychological attributions made by the patient regarding the device, are factors in the genesis of such disorders.<sup>48</sup>



The experience of shock has been regularly linked to poor psychological outcomes in the ICD literature. The results from the CABG Patch trial indicated that the ICD patients who had received shocks were responsible for the significantly worse mental and physical QoL outcome scores between the groups.<sup>47</sup> Similar findings have been reported from secondary prevention trials in which patients requiring frequent shocks self-reported lower QoL than patients who did not.<sup>45,46</sup> As shown in the meta-analysis by Burke *et al.*,<sup>49</sup> however, it is difficult to pinpoint causality in this regard (i.e., patients with the worst heart disease have lower QoL and more ICD shocks).

ICD recipients may have difficulties adjusting to having the device and coping with AEs. Resources are available to help patients adjust, and psychosocial interventions may be indicated in select patients. Most ICD recipients have access to support groups and have frequent telephone contact with health care professionals.<sup>48,54</sup> Evidence of the usefulness of interventions that may improve psychological outcome is lacking. Two randomized clinical trials,<sup>43,44</sup> including one published in abstract form, were identified for this review. They compare ICD recipients undergoing cognitive behavioural therapy with those receiving conventional medical care. Results suggest that cognitive behavioural therapy may prevent the development of psychological problems for up to one year in ICD recipients.<sup>43,44</sup> Evidence favouring specific interventions needs confirmation in larger randomized studies.

### **ICD implantation and lifestyle changes**

Recipients of ICDs will likely find that their lifestyles change after surgery. They will have restrictions on driving; marital and social relationships, and sexual intimacy may be challenging; and their participation in recreational activities may be limited. These changes can affect the recipient's psychological and emotional well-being.<sup>51</sup> The loss of driving privileges is the primary concern among recipients, because it reduces personal freedom, may threaten continued employment, and lowers overall QoL.

Driving restrictions are derived from the risk of partial or complete loss of consciousness due to ventricular arrhythmia before the ICD intervenes.<sup>51</sup> A secondary concern is the possibility that a sudden, unexpected shock might cause the driver to lose control of the vehicle even if she or he has not lost consciousness.<sup>51</sup> To address this issue, the Canadian Working Group on Cardiac Pacing has made recommendations for ICD follow-up in Canada.<sup>55</sup>

### **c) Summary of ethical and psychosocial results**

The advent of ICD therapy poses emerging questions about the allocation of health care resources, because the need for ICD devices exceeds the funding in many Canadian jurisdictions. As a result of limited financial resources, physicians have been put into the difficult moral position of deciding who can receive an ICD and who cannot. A more transparent and fair decision-making process is required. This should include guidelines that constrain resource allocation decisions on the use of ICD therapy. Ministry and institutional stakeholders must take responsibility for these decisions.

The impact of ICDs on QoL among patients in whom it is used for the primary prevention of sudden death requires more study. Available evidence is weak, and poor psychosocial outcome in ICD patients may result from the underlying cardiac condition, rather than as a response to implantation of the device and therapy. The most common psychological problems reported in secondary reviews are anxiety and depression.

## 6 BUDGET IMPACT ANALYSIS

The impact that ICD use for primary prevention of SCD would have on health care budgets was estimated. Based on the predictive nature of such an analysis, the results are not absolute values, but an indication of the likely impact.

### 6.1 Methods and Assumptions

Using a population-based approach, the budgetary impact of ICD therapy for the primary prevention of SCD was defined as the difference between budgets with or without ICD prophylactic use. Patients with ICDs also have usual medical therapy. They first survive ICD implantation or experience operative death. Then, the survivor may experience ICD-related complications and have the device removed or continue ICD treatment. Patients without ICDs may experience cardiac events that would have been reduced by an ICD implant. In this budget impact analysis, because of limited data and to simplify the issue, the budget for an ICD treatment scenario was determined by multiplying the per person cost due to ICD treatment with the total number of ICD candidates. For the scenario without ICD prophylactic use, the budget was the cost attributed to additional cardiac deaths that would have been prevented by ICD prophylactic use. The cost of those SCDs occurring with ICD therapy or with usual medical therapy was not considered, because it would be cancelled out in estimating the budget difference between the two scenarios. For the same reason, the cost of the usual medical therapy itself was excluded, as it would occur in both scenarios. Microsoft Excel was used to do the calculation.

Because of the limited data, several assumptions were made where necessary.

**Patient population:** Because patients without prior clinical arrhythmia were the target population, all were potential ICD candidates. The Gillis study<sup>56</sup> cited that the existing prevalence of untreated patients meeting the MADIT-II criteria for an ICD in Canada would be approximately 85,000, and the number of annual new cases would be about 3,700. Ideally, the budget impact analysis would be based on this number, but this is unlikely given that the infrastructure necessary to implant tens of thousands of ICDs in any year is limited.<sup>12</sup> Realistically, as presented by Simpson *et al.*,<sup>12</sup> the number of new ICD implants in Canada would be 3,500 in fiscal year 2005-2006; 4,500 in fiscal year 2006-2007; 5,500 in fiscal year 2007-2008, and 6,500 in fiscal year 2008-2009. These values were used in the budget impact analysis. Given a seven-year time horizon, it was assumed that in fiscal years 2009-2010, 2010-2011, and 2011-2012, the number of new ICD implants remained stable at 6,500 each fiscal year. Annual death rates were derived by using the estimated mortality rate in the literature.<sup>57</sup> The number of target patients in Canada was calculated (Appendix 11).

**Treatment comparators:** There is likely >1 alternative treatment for the primary prevention of SCD. Those without ICDs were grouped under “usual medical therapy” as the comparator in the analysis. The intervention was ICD plus usual medical therapy.

**Model perspectives:** In Canada, inpatient costs except for associated professional services are usually taken from the hospital budget. The professionals, including electrophysiologists, surgeons, and anesthesiologists, claim their service fees from the provincial ministry of health. This analysis took the health care system’s perspective and tended to include costs that were borne by the hospital and the provincial ministry of health.

**Analysis time horizon:** Usually, a budget analysis takes a horizon of three to five years. Considering the life expectancy of ICD candidates of around 10 years (shown in the reviewed economic studies with a lifetime horizon) and the lifespan of the ICD device or battery (approximately five years<sup>13,14</sup>), there was concern that a five-year time horizon might be misleading, because it would not incorporate ICD replacement or battery change during the life expectancy of patients with ICDs. The costs associated with ICD replacement or battery change should be considered in a budget impact analysis. So, a horizon of seven years was used to include the costs attributable to replacement of the ICD or battery. It was assumed that the lifespan of an ICD system was five years, that patients would need a replacement at the sixth year, and that within their life expectancy, one replacement would occur.

**Health care of concern:** With ICD use, there would be demanded health care during the implant procedure, care after implant, clinical follow-up, and treatment for ICD-related complications. The costs of each health service (Appendix 12) were estimated based on the consumed resources and professionals' time (Appendix 13), and unit cost (Appendix 14). The Ottawa Heart Institute provided relevant cost data for Ontario. Other information came from published literature. Without ICD use, the potential consumed health services due to cardiac events included ambulance use, accident and emergency (A&E) investigation of patient's death or admission into hospital, A&E attendance for patients dying on arrival, A&E observation unit care, emergency admission for arrhythmia, cardiac intensive care, and coronary care unit use. Because 5% of patients survive a cardiac arrest, it was assumed that the cost due to SCD was in the same range as that of cardiac events (Appendix 12). The difference of yearly death between the scenario with ICD prophylactic use and that with control therapy was assumed as the number of SCDs that would have been avoided by ICD treatment.

**Inflation rate and currency year:** An annual 3% inflation rate and the value of the 2005 Canadian dollar were used.

## 6.2 Results

For a patient receiving an ICD for primary prevention of SCD, it was estimated that during the seven-year period, the total cost was \$48,119 (Appendix 12), largely due to the ICD implant in the first year, and ICD or battery replacement in the sixth year. For an SCD that would have been prevented by ICD treatment, the cost ranged from C\$300 to C\$6,500 depending on what health care services were used (Appendix 14).

It is estimated that 85,000 untreated Canadians are candidates for ICD implantation in the primary prevention of a life-threatening arrhythmia, with the number of new cases expected to be 3,700 annually; however, the infrastructure that would be needed to implant tens of thousands of ICDs in a given year is limited. Our budget impact analysis, derived using the perspective of the health care system, was based on more realistic estimates of 3,500 to 6,500 ICDs being implanted annually over a seven-year time horizon (Appendix 11). It approximated C\$88.59 million, C\$332.48 million, C\$634.70 million, C\$834.87 million, and C\$1.05 billion in costs over one-, three-, five-, six-, and seven-year time horizons post-ICD implant respectively. For the scenario of usual medical therapy (Appendix 15), the cost associated with SCD was C\$15,750 (C\$341,250), C\$109,610 (C\$2.37 million), C\$308,310 (C\$6.68 million), C\$468,030 (C\$10.14 million), and C\$678,580 (C\$14.70 million) respectively for the time horizons. The estimated values presented in parentheses are derived when the SCD cost was assumed to be C\$6,500 instead of the baseline value of C\$300. When the cost of SCD was assumed to be C\$300, the corresponding budget impact figures were C\$88.58 million, C\$332.37 million, C\$634.39 million, C\$834.40 million and C\$1.04 billion. If the cost associated with SCD prevention was assumed to be C\$6,500 per case, the

corresponding budget impact of ICD implantation (relative to standard medical therapy) would be C\$330,000; C\$2.26 million; C\$6.37 million; C\$9.67 million, and C\$10 million less than that seen over those same time horizons when the cost of preventing SCD was assumed to be \$300.

These results showed that the budget impact increased in the first five years and then jumped at the sixth and seventh years. In the first five years, ICD implantation increased by only new ICD implants each year, but in the sixth year and seventh years, the survivors of the first cohort (2,505) and those of the second cohort (3,221) required ICD or battery replacement, increasing the total surgeries to 9,005 in fiscal year 2010-2011, in addition to the new ICD implants of 6,500 and 9,721 in fiscal year 2011-2012. Given the limited lifespan of the ICD device and battery, it is important to account for ICD patients requiring additional surgery several years later that might cost as much as the initial ICD implantation.

Varying the SCD-associated cost (C\$300 versus C\$6,500) did not significantly influence the evaluated value of the budget impact, but this is not surprising. In the first year of our analysis horizon, there were 3,500 patients in the ICD strategy scenario with the total budget of C\$88.59 million. Under the control therapy scenario, the budget was based on the cost due to an additional 53 deaths (in the first year) compared to the ICD treatment scenario. Their total costs were C\$15.75 thousand (or C\$341.25 thousand if the per case cost was C\$6,500). The 3,500 ICD implantations in the intervention scenario would result in the prevention of 53 deaths. With the large difference between per death cost and per ICD implantation cost, the variation of per death cost did not affect the budget impact.

In this analysis, the annual budget for the usual medical therapy scenario was based on the cost contributable to the difference of yearly death between two scenarios. The difference was calculated with the mortality rate data from the literature. So, the precision of the budget estimate for this scenario largely relied on the quality of that data. Because of the huge budget for the ICD treatment scenario, however, the budget impact would not vary significantly if the budget estimate of the usual medical therapy scenario changed.

The use of ICD therapy for the primary prevention of SCD would result in a substantial budget impact because of the device expense and its potential replacement within five to seven years. An evaluation of the budget impact requires data that include the number of SCDs that would have been avoided by ICD treatment and the SCD-associated cost. To understand the future budget impact of ICD prophylactic use, an appropriate time horizon must be selected.

## **7 DISCUSSION**

### **7.1 Clinical Review**

This study revealed three findings.

- The rate of death, either overall or cardiac in origin, was high in patients who had no history of arrhythmia but who were considered to be at high risk. In the population treated with conventional therapy, the rates were 25% for all-cause death and 11% for SCD. In the population using ICDs, the rates were 19% and 4% respectively.
- Subgroup analysis showed that patients with ischemic heart disease had higher rates of death than patients with non-ischemic heart disease. There is a 32% reduction in the risk of all-cause death

(ARR 7%) in ischemic patients and 25% risk reduction (ARR 5%) in non-ischemic patients using ICDs (though these results were shy of statistical significance). The risk reduction for SCD with ICD use was significant, with a reduction by 67% (ARR 9%) in ischemic patients and 74% (ARR 4%) in non-ischemic patients.

- Treatment with an ICD in addition to conventional therapy significantly reduced the risk of all-cause death (RRR 28%, ARR 6%) and SCD (RRR 67%, ARR 7%).

These findings lead to two clinical implications. First, the rate of death in patients at a high risk of ventricular arrhythmia with conventional medical treatment remains appreciable. Second, ICD therapy has a significant benefit in reducing death among high risk patients who have not experienced ventricular arrhythmia. Alternatives to standard ICDs, such as limited-use ICDs with different lead systems, were beyond this report's scope. Although biventricular pacing is beyond this report's purview, its potential role, especially when combined with an ICD, may be a future consideration.

AEs were poorly reported in the RCTs, but the potential for complications related to ICD implantation is substantial. A recent article by Gould *et al.*<sup>58</sup> described a retrospective Canadian study of complications associated with ICD replacements resulting from device advisories or recalls. Between October 2004 and October 2005, 2,915 patients were affected by device advisories in the 17 Canadian centres surveyed, and among them, 533 patients underwent device replacement. These numbers indicate that device advisories are a concern for patients with ICDs. The complication rates related to ICD replacement were observed to be similar to those with initial implantation in the large RCTs, ranging from 2.5% to 15.2%.

Maisel *et al.*<sup>59</sup> analyzed US FDA reports of ICD generator malfunctions from 1990 to 2002. They report that the three-year replacement rate of malfunctioning ICDs, from 2000 to 2002, was 26.8 per 1,000 implants, which is three times the replacement rate for the mid-1990s. They conclude that it is necessary to monitor device performance by reporting AEs and ensuring that defective devices are returned to the manufacturer for analysis.

This clinical review has several strengths: it is a systematic review, and the meta-analysis is independent of vested interest, with research questions and methods predefined in a protocol, and only the highest level of evidence is incorporated (RCTs). All included trials evaluated the use of ICDs compared with conventional treatment, not with placebo. Because patients with ICDs are also treated with conventional drugs, the difference in outcome findings demonstrates the incremental effect of ICD therapy.

The review has limitations. The reporting quality of included RCTs was low based on the Jadad scale.<sup>17</sup> This scale, however, assesses the quality of reporting (randomization, blinding, and withdrawal appropriately described) rather than the quality of the conduct of the trial. Because the Jadad scale includes a component to assess the extent of double-blinding, studies of devices and surgical techniques are unduly penalized because blinding is impossible. When study performance was evaluated with design and reporting, as measured using the modified Hailey scale,<sup>16</sup> the included trials were shown to have a higher degree of quality, thereby imparting a higher sense of confidence in their findings. While the study by Bardy *et al.*<sup>20</sup> included ischemic and non-ischemic patients, it did not provide the number of deaths for the subgroups. Therefore, the data from this study could not be used in the meta-analyses of ischemic and non-ischemic subgroups. Approximately 700 patients would have been added to each of the subgroup analyses, had the authors provided this information.

## 7.2 Economic Review

The review of seven economic studies showed a disparity in ICER likely due to between-study heterogeneity derived from the study populations, the model structure, and study assumptions. Their sensitivity analyses showed that three parameters influence the economic value of ICDs: ICD efficacy, ICD cost, and utility associated with ICD treatment.

### 7.2.1 ICD efficacy

In the studies with ischemic patients, the ICD efficacy used was statistically significant. For instance, the Mushlin *et al.* study<sup>34</sup> based their ICER of \$27 000 per life year on a survival analysis result that ICDs gained an extra 0.80 life years with 95% CI (0.41, 1.22) during a four-year period compared with conventional therapy. The Sanders *et al.* study<sup>35</sup> adopted 0.46 with 95% CI (0.26, 0.82), 0.45 with 95% CI (0.32, 0.63), and 0.69 with 95% CI (0.51, 0.93) as the input value of efficacy of ICDs in reducing total mortality in their analyses, particularly for the MADIT-I, MUSTT, and MADIT-II populations. The meta-analysis presented in this report found that ICD therapy yields a 32% decrease in risk of all-cause death (RR: 0.68), but the efficacy is not statistically significant [95% CI (0.46, 1.01)].

For the non-ischemic population, there seems to be one corresponding economic analysis available. Sanders *et al.*<sup>35</sup> based their ICER estimate for this population on the DEFINITE trial that reported an ICD efficacy of 0.65 with 95% CI (0.40, 1.06) in reducing all-cause death. The meta-analysis presented here, which involved two clinical trials and the DEFINITE trial, had a consistent estimation. Given this, the results of Sanders' economic analysis, based solely on the DEFINITE trial,<sup>35</sup> is likely to apply to other non-ischemic populations.

In the Sanders *et al.* study,<sup>35</sup> one analysis for the SCD-HeFT population included ischemic and non-ischemic patients. In the SCD-HeFT trial, ICD therapy reduced all-cause death by 0.65, but the 95% CI was not significant (0.40 to 1.06). This meta-analysis, however, showed that ICD efficacy is statistically significant [RRs 0.72 with 95% CI (0.56, 0.91)]. Thus, it is likely that the results presented in the Sanders *et al.* study<sup>35</sup> are specific to the SCD-HeFT population, and their findings that ICD therapy was possibly dominated by control therapy may not be generalizable to other ischemic and non-ischemic mixed groups.

Some of the reviewed studies were based on the assumption that ICD therapy affected only SCD. For example, in Sanders *et al.*,<sup>32</sup> the efficacy of ICD implantation for reduction of SCD in ischemic patients was 67% (range 30% to 100%). This was slightly higher than that in another Sanders *et al.* study<sup>31</sup> (ICD efficacy 60%; range 20% to 100%). The Chen *et al.* study<sup>30</sup> assumed that ICD implantation prevented all sudden death. In this meta-analysis, it was estimated that ICD prophylaxis for ischemic patients could decrease 67% of risk of SCD compared with control treatment (95% CI 55% to 76%). This estimate fits with the assumptions made in these economic studies.<sup>30,32</sup>

The ICD efficacy increased slightly when MADIT-I is compared to MADIT-II (the absolute difference was 0.23), while the ICER increased from US\$34,900 per QALY to US\$54,100 per QALY. Once the ICD was found to be less effective than control therapy (e.g., in the Sanders *et al.* study<sup>35</sup> for the CABG Patch population and DINAMIT population), the ICER evaluation accordingly favoured control therapy instead of ICD treatment. It was consistent with the findings in the one-way sensitivity analysis that ICER was sensitive to the ICD efficacy.

The continuity of any benefit is another aspect to consider. Three reviewed studies<sup>32,33,35</sup> addressed the potential influence of this parameter on the cost-effectiveness of ICD therapy. The Al-Khatib *et al.* study<sup>33</sup> reported that, if the efficacy of ICD therapy ended after three years instead of a lifetime, the ICER would jump from the baseline estimate of US\$50,500 per life year to US\$123,400 per life year, increasing by almost 2½ times. Similarly, the ICER in the Sanders *et al.* study<sup>32</sup> increased from US\$50,900 per QALY to US\$112,600 per QALY. To ensure that the ICER is <US\$75,000 per QALY, the Sanders *et al.* study<sup>32</sup> showed that ICD efficacy had to be retained for ≥6 years.

The ICD efficacy assumptions in the reviewed economic studies were consistent with the findings of the meta-analyses in this report. From this perspective, their economic evaluation results, except for the worst scenario of ICD efficacy, are likely to be generalizable to the corresponding subgroup patients (e.g., ischemic, non-ischemic, or combined). In 2005, the Canadian Heart Rhythm Society and the Canadian Cardiovascular Society developed a position paper<sup>60</sup> regarding ICD use in Canada. In this position paper, different class recommendations were given for ischemic or non-ischemic patients depending on patients' LVEF level and other characteristics including time post-MI. The populations in most of the studies reviewed for this report are likely subsets, so the relevant ICD efficacy assumptions may not represent the ICD benefit for the population recommended in the Canadian position paper. The ICER of ICD versus control therapy would change if the population in that recommendation was used in the economic evaluation.

### 7.2.2 ICD-related cost

In the short term (e.g., one year), the costs of an ICD and generator replacement are higher than other health care costs related to ICD treatment. In the Sanders *et al.* study,<sup>35</sup> ICD implantation and generator replacement are US\$27,975 (US\$10,000 to US\$60,000) and US\$18,390 (US\$5,000 to US\$30,000) respectively, while the year-around inpatient costs and outpatient costs are US\$5,928 (US\$1,020 to US\$30,000) and US\$600 (US\$0 to US\$1,200). In the reviewed studies, the life expectancy of ICD patients ranged from 7.08 to 13.5 years, while replacement of ICDs was required every five to seven years, making it difficult for costs to be adequately diffused over time.

One Canadian study<sup>57</sup> reported that for the McGill University Health Centre (MUHC), the total cost for one ICD device and electrodes averaged C\$22,863 (fiscal years 1999 to 2003), of which the unit cost for ICD was C\$20,000 and the electrode cost C\$2,500 or C\$3,000 depending on its type (single chamber or dual chamber). After incorporating the implant procedure cost, post-implant procedure cost, follow-up cost, treatment of complications, and professional service costs, ICD therapy resulted in an initial cost of C\$24,187, a complication treatment cost of C\$509 (in the first year), and a battery replacement cost of C\$24,170 (including the initial cost of C\$24,103 and follow-up of C\$67). The proportions of components in the cost of ICD treatment are similar as those in the economic studies reviewed for this report.

The costs for initial ICD implantation and generator replacement influence the cost-effectiveness of ICD therapy compared with other costs. The reported battery life of five to seven years did not affect the ICER value significantly.

### 7.2.3 ICD-related utility

Five studies<sup>30-33,35</sup> in this review measured the effectiveness of ICD treatment using QALYs; four<sup>31-33,35</sup> assumed that the QoL did not change as a result of an ICD implantation, and that the life utilities for patients with ICD and with control therapy were both 0.88 of optimal health (where optimal

health is scored as 1.0). The Chen *et al.* study,<sup>30</sup> however, assumed that for the ICD patients, the life utility was 0.639 in the first year after ICD surgery and returned to 0.71 afterward. For the conventional treatment patients, the life utility was a constant 0.71. Compared with the first four studies,<sup>31-33,35</sup> the Chen *et al.* study<sup>30</sup> assumed a lower life utility for their study population and recognized that ICD implantation decreased QoL in the first year of survival for ICD patients. Partially because of this, the ICER was more favourable in the first four studies<sup>31-33,35</sup> (from US\$34,000 to US\$71,800 per QALY) than in the Chen *et al.*<sup>30</sup> study (US\$97,863 per QALY gained).

In the review of ethical and psychosocial issues, two studies that evaluated the impact of ICD therapy on QoL in primary prevention trials were identified. One study<sup>47</sup> concluded that ICD therapy was associated with poorer QoL and another<sup>29</sup> found that QoL scores were similar between the patients with ICDs and those using amiodarone. Although the economic studies reviewed in this report did not refer to these studies, the QoL assumptions are consistent with those in the primary studies.

#### 7.2.4 Strength and limitation of review

Several economic reviews<sup>61-65</sup> have been published. They addressed the prophylactic use of ICDs and excluded the recent economic studies.<sup>30,32,33,35</sup> This review includes those studies with updated clinical findings (e.g. MADIT-II), and focuses on the issues of using ICDs for the primary prevention of SCD, systematically presenting the evidence, and highlighting the three drivers (ICD efficacy, ICD cost, and life utility) of the cost-effectiveness of ICD therapy, particularly for patients without prior clinical arrhythmia .

Most of the economic studies included in this review performed well, based on the BMJ checklist.<sup>18</sup> None of the reviewed studies entirely covered the target population. Most samples in the studies represented subsets. Nevertheless, because the ICER estimates were all likely to fall in a range of US\$20,000 to US\$70,000 per life year in the recent economic studies, it can be expected that the ICER for the overall population of interest may also lie in that range.

The clinical trials associated with the reviewed economic studies had follow-up periods ranging from 20 months to 45 months. The economic studies usually had a lifetime horizon. In our review, most studies estimated the life expectancy of patients as <14 years if in ICD treatment or as <10 years if in conventional therapy. It is difficult to say whether the short-term results would apply in the long term. More clinical evidence is needed regarding the long-term clinical outcomes of ICD patients.

Despite an extensive literature search, no primary Canadian economic study comparing ICDs with control therapy for the primary prevention of SCD was identified. A section of one Canadian report<sup>57</sup> examines the economic impact of 100 ICD implants in a university hospital, based on three scenarios. Compared with no ICD implant, the 100 ICD implants saved 72 life years (or 110 years or 154 years ) by the end of the 15<sup>th</sup> year, when the mortality rate was estimated to be 83% (or 76% or 68%). From the perspective of the health care system, the resulting ICER due to 100 ICD implants per year was C\$61,931 (or C\$42,070, or C\$31,256) per life year saved. Their calculation details in the report are unclear. The manner in which they estimated the cost of 100 ICD implants during the 15 years is unknown. It is also unknown whether they considered the cost of conventional treatment or whether the ICER estimate was based on the incremental cost of ICD implant compared with control therapy. So, to directly compare these values with those reported in the evidence reviewed in this report is inappropriate. Thus, the absence of Canadian cost studies remains a consideration when trying to determine the relevance of these findings in the Canadian context.



## 7.3 Ethical and Psychosocial Review

The increasing demand for ICDs in the face of a limited supply has raised moral questions about who should be recipients of the device. If everyone who would benefit received one, the financial toll on the Canadian health care system would be substantial.<sup>11</sup> Current demand is exceeding many jurisdictional health care budgets. As a result, physicians have been placed in the difficult position of rationing this resource, in opposition to their traditional role as patient's advocate. For ICDs to be distributed equitably, a transparent and fair decision-making process should include guidelines that constrain resource allocation decisions about the use of ICD therapy.<sup>11,38</sup> Such a process will need to account for competing demands placed by other expensive technologies and services on the health care system, including their costs and values. Macro- and meso-level decision makers, such as hospital administrators, must take responsibility for their part in such resource allocation decisions.

Few studies have looked at the impact that ICDs have on the QoL of patients who use them for the primary prevention of sudden death. This requires more examination, particularly in light of the poor psychosocial outcomes. Whether a result of their underlying cardiac condition or a direct response to having the device implanted, ICD patients in one primary prevention trial fared worse than control patients in terms of QoL.<sup>45-47,49</sup> The most common psychological problems reported in secondary reviews are anxiety and depression.<sup>48,49,52</sup> The results from RCTs show that patients requiring frequent shocks also self-report lower QoL.<sup>45-47</sup> It is difficult, however, to pinpoint why this is the case.

## 8 CONCLUSION

This report provides evidence that ICD use in patients at high risk for ventricular arrhythmia reduces by two-thirds the risk of SCD compared with conventional treatment. The report shows that ICD treatment is efficacious in reducing the risk of cardiac death in ischemic and non-ischemic patients. ICDs would need to be implanted in 14 patients to prevent one SCD, and in 12 and 28 patients to prevent one SCD in ischemic and non-ischemic patients respectively. These findings are consistent with those noted in reports from the UK<sup>66</sup> and Australia.<sup>67</sup> In the studies that were examined, complications were infections associated with the surgery and inappropriate shocks due to lead or generator problems. This review excludes observational studies (i.e., non-RCTs), which could give an idea of real-world effectiveness, especially for safety issues. Such issues could include those related to defective devices as reflected by a 2005 recall of nearly 50,000 defibrillators by a manufacturer. At the time of the recall, the company noted that they were aware of >45 reports of failures, two of which resulted in death.<sup>68</sup>

The economic component of this review is limited in that no Canadian economic studies were identified. The seven economic studies that examined the cost-effectiveness of ICD treatment and were included in this review did not reflect the Canadian context. In the seven studies, the estimated ICER values varied from US\$24,500 to US\$63,300 per life year gained or from US\$34,000 to US\$97,863 per QALY gained, for patients with low EF. The factors that determine the cost-effectiveness of ICD are ICD efficacy, ICD cost, and ICD-related utility changes. If Canadian ICD policy is to be based on the joint recommendation of the Canadian Cardiovascular Society and the Canadian Heart Rhythm Society, the study populations in the papers reviewed in this report provide an incomplete picture, because the available cost-effectiveness studies are based on a subset of the population included in the joint recommendation. To more accurately determine the cost-effectiveness of ICD prophylactic use in Canada, a primary study with a broader target population is warranted.

ICD prophylactic use would result in a substantial impact on the Canadian health care system budget. It is estimated that 85,000 untreated Canadians are candidates for ICD implantation in the primary prevention of a life-threatening arrhythmia, with the number of new cases expected to be 3,700 annually; however, the infrastructure that would be needed to implant tens of thousands of ICDs in a given year is limited. Our budget impact analysis was based on more realistic estimates of 3,500 to 6,500 ICDs being implanted annually over a seven-year time horizon. Whether the cost associated with SCD was assumed to be a few hundred dollars or a few thousand dollars, the estimated budget impact of ICD implantation (relative to usual medical therapy) would be approximately C\$88 million, C\$330 million, C\$630 million, C\$830 million, and C\$1 billion over one-, three-, five-, six-, and seven-year time horizons post-implant. The budget impact is driven by the cost of the device, its future replacement cost, and the number of patients who would be eligible for the device.

The impact of ICDs on the QoL in patients for whom it is used for the primary prevention of sudden death requires more study. Psychosocial issues in ICD patients may be a result of the underlying cardiac condition, rather than a response to implantation of the device and therapy. The most common psychological problems reported in secondary reviews are anxiety and depression.

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## **APPENDICES**

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