Canadian Cardiovascular Society/Canadian Heart Rhythm Society position paper on implantable cardioverter defibrillator use in Canada

Anthony S Tang MD FRCPC[1], Heather Ross MD FRCPC[2], Christopher S Simpson MD FRCPC[3], L Brent Mitchell MD FRCPC[4], Paul Dorian MD FRCPC[5], Ron Goeree MA[6], Barry Hoffmaster PhD[7], Malcolm Arnold MD FRCPC[7], Mario Talajic MD FRCPC[8], on behalf of the Canadian Heart Rhythm Society and the Canadian Cardiovascular Society

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The Canadian Heart Rhythm Society in conjunction with the Canadian Cardiovascular Society is committed to the promotion of evidence-based practice in Canada. Since the last Canadian guidelines on the management of sudden cardiac death were published in 2000, several well-conducted clinical trials evaluating the implantable cardioverter defibrillator have been completed and published. The Canadian Cardiovascular Society Council has granted permission to review and update guidelines for the indications for implantable cardioverter defibrillators. Furthermore, data are emerging on the potential benefits of biventricular pacing therapy (cardiac resynchronization) for heart failure; recommendations for the use of this therapy have been included in the present paper. Ethical considerations and the economic implications of these recommendations are also included. Canada's heart rhythm specialists, represented by the Canadian Heart Rhythm Society, have been joined by two heart failure specialists, a medical ethicist and an economist, to develop the present position paper. Members of the Canadian Heart Rhythm Society participated in the discussion of these recommendations in open forum meetings and by electronic communication.

Énoncé de position de la Société canadienne de cardiologie et de la *Canadian Heart Rhythm Society* sur l'utilisation des défibrillateurs implantables au Canada

En collaboration avec la Société canadienne de cardiologie (SCC), la *Canadian Heart Rhythm Society* se consacre à la promotion d'une pratique médicale fondée sur des preuves au Canada. Depuis la parution, en l'an 2000, des dernières directives sur la mort subite d'origine cardiaque, plusieurs essais cliniques rigoureux sur les défibrillateurs implantables ont été menés à terme et publiés. Le conseil de la SCC a donné son accord pour la révision et la mise à jour des directives et des indications relatives au défibrillateur implantable. En outre, depuis un certain temps, des données se font jour sur les avantages potentiels de la stimulation biventriculaire (resynchronisation cardiaque) dans l'insuffisance cardiaque; les recommandations relatives à cette modalité thérapeutique font partie du présent énoncé de position; on y retrouve en outre un survol des enjeux déontologiques et économiques de ces recommandations. Les électrophysiologistes du Canada, représentés par la *Canadian Heart Rhythm Society*, se sont adjoint la collaboration de deux spécialistes de l'insuffisance cardiaque, d'un éthicien et d'un économiste pour préparer le présent énoncé de position. Les membres de la *Canadian Heart Rhythm Society* ont pour leur part alimenté la discussion préparatoire aux recommandations par le biais de tribunes libres et de l'Internet.

Key Words: *ICD; Sudden death*

Each year, more than 40,000 Canadians die from a cardiovascular cause. Approximately one-half of these deaths are sudden, and they are usually due to the development of fatal ventricular arrhythmias. Implantable cardioverter defibrillators (ICDs) are life-saving in selected patients at high risk of sudden cardiac death (SCD) and have been the subject of previous national guidelines (Canadian Cardiovascular Society, American College of Cardiology/American Heart Association, North American Society for Pacing and Electrophysiology) (1,2). The recommendations from these guidelines focused mainly on secondary prevention of sudden death after a nonfatal ventricular arrhythmia, with fewer recommendations directed at primary prevention based on the literature available at that time. Since then, important new information has become available in the area of primary prevention of SCD, which forms the basis of the updated recommendations for ICD use in the present paper.

Evidence for ICD benefit in patients with a previous occurrence of sustained ventricular arrhythmia (secondary prevention)

Three large randomized studies have compared the use of an ICD with antiarrhythmic drug therapy (primarily amiodarone) in patients with a history of life-threatening ventricular arrhythmias (3-5). The largest of these studies, the

[1]*University of Ottawa Heart Institute, University of Ottawa, Ottawa;* [2]*University Health Network, University of Toronto, Toronto;* [3]*Queen's University, Kingston, Ontario;* [4]*Libin Cardiovascular Institute of Alberta, Calgary, Alberta;* [5]*St Michael's Hospital, University of Toronto, Toronto;* [6]*McMaster University, Hamilton;* [7]*University of Western Ontario, London, Ontario;* [8]*Montreal Heart Institute, University of Montreal, Montreal, Quebec*

Correspondence: Dr Anthony S Tang, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario K1Y 4W7. Telephone 613-761-4914, fax 613-761-4407, e-mail atang@ottawaheart.ca

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TABLE 1
Primary prevention of sudden death: Major entrance/exclusion criteria for implantable cardioverter defibrillator (ICD) trials

Study (reference), year	EF	Age (years)	NYHA	CAD	CABG	Nonischemic cardiomyopathy	Other criteria
MADIT (15), 1996	≤35%	25–80	I-III	Old MI (>3 weeks)	>3 months	Excluded	Spontaneous NSVT + inducible sustained VT not suppressed with intravenous procainamide
CABG-Patch (9), 1997	≤35%	<80	N/A	100%	100% needing CABG	Excluded	Abnormal SAECG/epicardial patches + ICD implant at the time of CABG
MUSTT (32), 2002	≤40%	<80	I-III	≥4 days post-MI	>4 days	Excluded	Spontaneous NSVT + inducible, sustained VT
MADIT-II (16), 1999	≤30%	≥21	I-III	Old MI (>1 month)	>3 months	Excluded	–
CAT (11), 2002	≤30%	18–70	II-III	Excluded	Excluded	Included	New onset (≤9 months) of CHF
AMIOVIRT (33), 2003	≤35%	≥18	I-IV	Excluded	Excluded	Included	Spontaneous NSVT
COMPANION (13), 2004	≤35%	≥18	III-IV	≥60 days post-MI	≥60 days post-CABG	Included	Sinus rhythm, QRS ≥120 ms, hospitalization for CHF in preceding 12 months
DEFINITE (14), 2004	≤35%	–	I-III	Excluded	Excluded	Included	Spontaneous NSVT or ≥10 PVC/h for 24 h
SCD-HeFT (12), 2005	≤35%	≥18	II-III	>30 days post-MI or percutaneous coronary angioplasty	>30 days	Included	History of CHF >3 months
DINAMIT (10), 2004	≤35%	18–80	I-III	Recent MI (6 to 40 days)	Excluded	Excluded	Depressed heart rate variability

AMIOVIRT Asymptomatic Nonsustained Ventricular Tachycardia; CABG Coronary artery bypass graft; CAD Coronary artery disease; CAT Cardiomyopathy Trial; CHF Chronic heart failure; COMPANION Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; DEFINITE Defibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT Defibrillator in Acute Myocardial Infarction; EF Ejection fraction; MADIT Multicenter Automatic Defibrillator Implantation Trial; MI Myocardial infarction; MUSTT Multicenter Unsustained Tachycardia Trial; N/A Not applicable; NSVT Non-sustained ventricular tachycardia; NYHA New York Heart Association functional class; PVC Premature ventricular contraction; SAECG Signal-averaged electrocardiogram; SCD-HeFT Sudden Cardiac Death in Heart Failure Trial; VT Ventricular tachycardia

Antiarrhythmics versus Implantable Defibrillators (AVID) study, demonstrated a statistically significant decrease in mortality associated with the use of an ICD (4). The other two studies (3,5) showed trends in the same direction. A subsequent meta-analysis estimated a 27% relative reduction of all-cause mortality with ICD use (6). These studies form the basis of recommendations for ICD use in patients after a nonfatal episode of sustained ventricular arrhythmia not associated with a reversible cause found in the present paper and in previous guidelines (1,2). However, the translation of this knowledge to clinical practice has been inadequate; in a recent review of 454 SCD patients who survived to hospital discharge in Ontario, only 58 (12.8%) received an ICD (7).

Subgroup analyses of these secondary prevention trials have suggested that most, if not all, of the benefit of ICD therapy for the prevention of all-cause mortality in patients who have experienced a sustained ventricular tachyarrhythmia is enjoyed by patients with a left ventricular ejection fraction (LVEF) of 35% or less (6).

Evidence for ICD benefit in high-risk patients without a prior history of sustained ventricular arrhythmia (primary prevention)

Ten randomized studies have evaluated the efficacy of an ICD to decrease the risk of death in patients thought to be at high risk of a life-threatening ventricular arrhythmia that has not yet been expressed. The entrance/exclusion criteria and principal results are summarized in Tables 1 and 2, respectively. A recent meta-analysis of these studies reports a 25% relative reduction and a 7.9% absolute reduction in all-cause mortality over an average follow-up of two to four years with ICD treatment in these trials (8). Four studies were negative, while six studies demonstrated benefit with ICD use. The negative studies were smaller and tended to study patient populations immediately after an acute event. For example, the Coronary Artery Bypass Graft Patch (CABG-Patch) trial (9), the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) (10) and the Cardiomyopathy Trial (CAT) (11) recruited patients shortly after coronary artery bypass graft surgery, an acute myocardial infarction and a new diagnosis of heart failure, respectively. In general, studies that recruited patients with chronic LV dysfunction have shown benefit from ICD use, with relative reductions in all-cause mortality between 23% and 51%. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) is the largest ICD trial with the longest follow-up reported to date (12). This trial randomized 2521 patients with chronic heart failure (New York Heart Association [NYHA] class II or III) and an LVEF of 35% or less to one of three strategies: optimal medical therapy alone; optimal medical therapy and amiodarone; or optimal medical therapy and a single-chamber ICD. The annual mortality in the control group was 7.2% per year and was unchanged by the addition of amiodarone. However, there was a 23% relative reduction in total mortality (a 7.2% absolute mortality reduction) over five years in patients receiving an ICD.

Subgroup analyses from SCD-HeFT (12) suggest similar benefits from ICD implantation in patients with and those without coronary artery disease. Additional support for ICD use in patients with nonischemic LV dysfunction comes from the results of the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial (13) and the Defibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) (14) trial (Tables 1 and 2).

The results of the SCD-HeFT (12) and the Multicenter Automatic Defibrillator Implantation Trial (MADIT and MADIT-II) (15,16) indicated that ICD therapy is associated

TABLE 2
Primary prevention of sudden death: Clinical and major results of implantable cardioverter defibrillator (ICD) trials

Study (reference), year	n	Age (years)	CAD (%)	Old MI (%)	CHF	QRS ≥120 ms	Average EF (%)	Average F/U (months)	Total annual mortality, % (control group)	RR reduction with ICD
MADIT (15), 1996	196	63	100	75 >6 months	N/R	N/R	26	27	17	54%
CABG-Patch (9), 1997	900	64	100	82	N/R	N/R	27	32	6	Negative study
MUSTT (32), 2002	704	66	100	62 >1 year	N/R	N/R	29	39	14	51%
MADIT-II (16), 1999	1232	64	100	88 >5 months	N/R	50%	23	20	10	31%
CAT (11), 2002	104	52	0	0	3 months	N/R	24	23	4	Negative study
AMIOVIRT (33), 2003	103	52	11	0	3.5 years	N/R	23	24	4	Negative study
COMPANION (13), 2004	1520	67	59	N/R	3.6 years	100%	22	15	19	36%*
DEFINITE (14), 2004	458	58	0	0	2.8 years	20%	21	29	7	35% total death (P=0.08), 80% sudden death (P=0.006)
SCD-HeFT (12), 2005	2521	60	52	N/R	2.0 years	41%	25	46	7	23%
DINAMIT (10), 2004	674	62	100	100	52% with CHF	N/R	28	30	8	Negative study

**All ICDs used biventricular stimulation. AMIOVIRT Asymptomatic Nonsustained Ventricular Tachycardia; CABG Coronary artery bypass graft; CAD Coronary artery disease; CAT Cardiomyopathy Trial; CHF Chronic heart failure; COMPANION Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; DEFINITE Defibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT Defibrillator in Acute Myocardial Infarction; EF Ejection fraction; F/U Follow-up; MADIT Multicenter Automatic Defibrillator Implantation Trial; MI Myocardial infarction; MUSTT Multicenter Unsustained Tachycardia Trial; N/R Not reported; SCD-HeFT Sudden Cardiac Death in Heart Failure Trial*

with greater benefit in patients with more severe LV dysfunction. Although SCD-HeFT included patients with an LVEF of less than 35%, the majority of patients had an LVEF of less than 30%, and subgroup analysis suggested that the benefit of ICD therapy was limited to this group. MADIT-II (16) only included patients with more severe LV dysfunction (LVEF of 30% or less). Thus, current data suggest that patients with more severe LV dysfunction derive the greatest benefit from ICD therapy irrespective of the underlying etiology of their structural heart disease.

It is important to consider that the absolute benefit from ICD therapy with respect to all-cause mortality depends on both the RR reduction from the ICD (approximately 25% to 30% risk reduction for the group as a whole) and the relevant population absolute mortality rate. The benefit will be greater if the absolute mortality is greater, even if the relative risk reduction is the same. Previous trials have demonstrated that QRS duration is a marker of a higher risk of mortality in patients with LV systolic dysfunction. Subgroup analyses of MADIT-II (16) and SCD-HeFT (12) have also suggested that the absolute benefit of ICD therapy may be greater in patients with ischemic heart disease and a wide QRS complex. Some authorities have accepted the use of a wide QRS to select patients with a potential for greater absolute benefit from an ICD, but others have rejected this notion. Additional criteria that could potentially be used to further stratify patients into lower and higher benefit groups include clinical parameters, other electrocardiogram measurements, and newer technologies such as microvolt T wave alternans measurement and heart rate variability determination. The ultimate role of these criteria, which are meant to further stratify patients for ICD benefit, will depend on the results of future studies.

It must be noted that the recommendations in the present paper reflect the current state of knowledge, based on published literature. Subgroup analyses may lead to reasonably derived hypotheses which, if proven, could lead to revisions of these recommendations.The current inclusion of any group in a class I recommedation should not impede further investigation that seeks to further refine subgroups which may derive most or potentially all of the benefit.

FACTORS TO CONSIDER WHEN APPLYING ICD RECOMMENDATIONS

Do the patient's characteristics correspond to the inclusion criteria of trials showing patient benefit?

All of the clinical trials mentioned above had important exclusion criteria. The following patient groups were not included in these trials: patients with significant comorbidity, such as advanced cerebrovascular disease or renal failure; patients with a predicted life expectancy of less than one year; patients for whom a revascularization procedure was planned; and patients with very severe heart failure symptoms (NYHA class IV). Furthermore, patients with no heart failure symptoms with usual activity (NYHA class I) are also under-represented in these trials.

In addition, most of the trials excluded patients during the recovery period of an acute event (acute myocardial infarction) or intervention (revascularization). The DINAMIT study (10) and secondary (post hoc) analyses of the MADIT II study (16) indicate that patients do not benefit from ICDs early after myocardial infarction (within 40 days in the DINAMIT study) (17). Therefore, in the case of a patient who is recovering from a recent myocardial infarction or revascularization procedure, adequate medical therapy should be utilized for at least one month before the determination of LVEF and assessment of the appropriateness of ICD therapy.

It is important to note that each patient's LVEF, a central criterion with respect to all prophylactic trials of ICDs, must be measured quantitatively. A qualitative echocardiographic estimate of LVEF is insufficient to assess the suitability of a patient for prophylactic ICD implantation.

Patients younger than 18 years of age were not included in any of these trials. When applying ICD recommendations to such young patients, the potential benefits (which are often magnified in conditions when presentation at a young age identifies higher risk and when a longer exposure to sudden

death risk in the absence of comorbid conditions may be anticipated) should be balanced against the increased complication rates of ICD therapy in young, small, active and growing patients (18). Octogenarians were either excluded or underrepresented in these trials (see Table 1). Therefore, the results of these trials may not be applicable to them.

Is the patient receiving optimal therapy for heart failure and his or her underlying disease?

In the clinical trials demonstrating benefit from prophylactic ICDs, patients were uniformly treated with state-of-the-art therapies for heart failure, including angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, beta-blockers, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, and spironolactone when indicated. Furthermore, the majority of patients with coronary artery disease had prior revascularization. It is not appropriate to implant a defibrillator until all of these therapies are considered and applied, if indicated and well-tolerated. Of note, drug therapies should be administered at their 'evidence-proven doses'.

Is the patient fully informed about the risks and benefits of ICD therapy?

ICDs are not innocuous; their use can expose the patient to potential complications. A combined analysis of the results of randomized ICD trials that have reported on ICD complications in over 2000 patients indicates a risk of early lead dislodgement of 2.3%, a risk of early ICD system infection of 1.9%, a risk of pneumothorax of 0.6%, a risk of device malfunction of 0.5%, a risk of serious bleeding of 0.4%, a risk of venous thrombosis of 0.2%, and a risk of cardiac perforation of 0.1% (19). Furthermore, approximately 20% of ICD recipients will experience an inappropriate shock on follow-up – usually as a consequence of sinus tachycardia or atrial fibrillation.

These potential nonfatal ICD therapy complications must be weighed against the absolute benefit of ICD therapy for the prevention of all-cause mortality, which is in the order of 1.5% to 3.0% per year. When a patient has been identified as a potential candidate for an ICD, the patient should be referred to an ICD centre for 'consideration of an ICD' without fostering undue patient expectations.

ECONOMICS

Evaluations addressing the cost-effectiveness of ICDs for secondary prevention can be divided into decision analytical models and trial-based analyses. Early decision analytical models were relatively consistent, with cost-effectiveness estimates ranging from $37,000 to $51,000 (20,21).

Two recent trial-based evaluations in secondary prevention (the Canadian Implantable Defibrillator Study [CIDS] and the AVID study) calculated cost-effectiveness estimates in the $98,000 to $237,000 per life-year gained range (Canadian dollars, 2004) (22,23). The only published trial-based analysis of the cost-effectiveness of ICD therapy in primary prevention is that of the MADIT trial, which estimated a cost-effectiveness of $39,000 per life-year gained (Canadian dollars, 2004) (24). In decision analytical modelling studies (24,25), cost-effectiveness estimates for primary prevention ICDs ranged from $47,000 to $317,000 per life-year gained (Canadian dollars, 2004). For the MADIT-II (16) population, arguably the best representation of primary prevention patient selection in Canada at the present time, a recent technology assessment document for a major insurance company (25) estimated a cost-effectiveness of $37,000 (United States dollars, currency value at the time of writing) per life-year gained, or $51,000 (United States dollars, currency value at the time of writing) per quality-adjusted life-year gained. These estimates are critically influenced by the cost of the ICD, the age of the patients, the frequency of generator replacement and the estimated efficacy of the ICD for the prevention of SCD.

NEED VERSUS RESOURCE AVAILABILITY

Patients can make voluntary, informed decisions about having ICDs implanted only if ICDs are first offered to them. Whether to offer an ICD to a patient is a decision that physicians have to make, but that decision can be difficult because the number of patients who fulfill the criteria for ICD implantation is greater than the number of ICDs currently available. The scientific data that identify patients who might benefit from ICD are rapidly evolving. The available funding tends to lag behind the demand. This discrepancy between available resources and need can lead physicians to exercise judgement in device allocation that may not be supported by scientific evidence. This kind of decision-making is problematic because of the inconsistency and arbitrariness that may result. A patient who presented in November, after the annual allocation of ICDs was exhausted, might have been offered this therapy if he or she had presented earlier in September. Economic constraints place physicians in an uncomfortable position. When they act as gatekeepers for society's health care resources, their medical duty to their patients may be compromised. In addition, economic constraints can create a culture of under-referral of appropriate patients.

An open, transparent process with disclosure of appropriate information leads to the implementation of legitimate institutional procedures and policies. Fair, consistent and objective decisions are the result. A cooperative, collaborative process that involves all stakeholders – patients, physicians, hospital administrators, program managers and ministries of health – confers legitimacy on some of the difficult decisions that must be made.

RECOMMENDATIONS FOR ICD IMPLANTATION – CANADIAN CARDIOVASCULAR SOCIETY/CANADIAN HEART RHYTHM SOCIETY GUIDELINES

In the present document, the authors adopted the American College of Cardiology/American Heart Association format for Classification of Recommendations and Level of Evidence (Table 3) as follows:

Classification of recommendations

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

IIa: Weight of evidence/opinion is in favour of usefulness/efficacy.

IIb: Usefulness/efficacy is less well-established by evidence/opinion.

TABLE 3
Classification of recommendations and levels of evidence for implantable cardioverter defibrillator (ICD) implantation

Recommendation	Level of evidence	Factors to consider when applying recommendations to an individual patient
Class I recommendations*		
1. Cardiac arrest due to VF or VT not due to a transient or reversible cause.	A	Subgroup analyses assign most of the benefit of ICD therapy to patients with LVEF ≤35%. Selected patients with LVEF >35% and/or significant comorbidity may choose alternate therapy such as amiodarone.
2. Spontaneous, sustained VT in association with structural heart disease.	B	In some instances, alternative therapy may be appropriate (eg, ablation for bundle branch re-entry VT).
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at EP study.	B	EP studies in patients with syncope NYD are usually most helpful in patients with evidence of structural heart disease.
4. Spontaneous, sustained VT in patients who do not have structural heart disease that is not amenable to other treatments.	B	ICD may be used if pharmacological treatment and/or ablation is not feasible or has failed.
5. Patients with ischemic heart disease with or without mild-to-moderate heart failure symptoms and LVEF of 30% or less, measured at least one month postmyocardial infarction and at least three months postcoronary revascularization procedure (CABG or PCI).	A	Patients with significant comorbidities may not benefit from an ICD. The use of additional risk stratifiers, such as QRS duration and T wave alternans, are under investigation.
Class IIa recommendations		
6. Patients with ischemic heart disease and LV dysfunction (LVEF 31% to 35%), measured at least one month post-myocardial infarction and three months postcoronary revascularization procedure with inducible VF/sustained VT at electrophysiology study.	B	Subgroup analyses of the primary prevention trials have suggested that the relative and absolute benefits of patients in the LVEF 31% to 35% range may be smaller. An EP study may help to select higher-risk patients in this group.
7. Patients with nonischemic cardiomyopathy present for at least nine months, an LVEF of 30% or less, and NYHA functional class II to III heart failure.	B	The LVEF in most patients in the trials assessing dilated cardiomyopathic patients was very low (average 21% to 25%); therefore, patients with higher LVEF measurements were under-represented in the trials showing benefit.
8. Patients with familial or inherited conditions including but not limited to long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic RV cardiomyopathy, and patients at a high risk of life-threatening ventricular tachyarrhythmias.	B	Factors such as family history of sudden death, inducibility of ventricular arrhythmias at EP study, patient preference and results of selected noninvasive testing may help to determine the appropriateness of ICD therapy.
Class IIb recommendations		
9. Patients with ischemic heart disease, prior myocardial infarction, LV dysfunction (LVEF 31% to 35%) either with no inducible VF/sustained VT at EP study or without an EP study.	C	Subgroup analyses of the primary prevention trials have suggested that the relative and absolute benefits of patients in the LVEF 31% to 35% range may be smaller. An EP study may help to select higher-risk patients in this group.
10. Patients with nonischemic cardiomyopathy present for at least nine months, LV dysfunction (LVEF 31% to 35%) and NYHA functional class II to III heart failure.	C	The LVEF in most patients in the trials assessing dilated cardiomyopathic patients was very low (average 21% to 25%); therefore, patients with higher EF measurements were under-represented in the trials showing benefit.
11. Severe symptoms (eg, syncope) attributable to sustained ventricular tachyarrhythmias while awaiting cardiac transplantation.	C	An ICD in this circumstance may be regarded as a 'bridge' to transplantation. Antiarrhythmic therapy may be regarded as a reasonable alternative in some cases.
Class III recommendations		
12. Syncope of undetermined cause in a patient without structural heart disease.	C	Efforts should be made to rule out syncope due to inherited electrical heart disease, particularly in patients with a family history of sudden death.
13. Incessant VT or VF.	C	An ICD may become appropriate if another treatment renders VF or VT nonincessant.
14. VF or VT resulting from arrhythmias due to a transient or reversible disorder (eg, AMI, electrolyte imbalance, drugs, trauma), or amenable to surgical or catheter ablation (eg, RV outflow tract VT, idiopathic LV tachycardia).	C	Recognizing the difficulty in identifying that VT/VF is due to a reversible cause, mild electrolyte abnormalities and small troponin rises may be insufficient evidence to withhold ICD therapy.
15. Significant psychiatric illnesses that may be aggravated by device implantation or may preclude systematic follow-up.	C	A formal psychiatric assessment may be helpful in cases where the potential impact of an ICD on a psychiatric condition is uncertain.

Continued on next page

TABLE 3 – CONTINUED
Classification of recommendations and levels of evidence for implantable cardioverter defibrillator (ICD) implantation

Recommendation	Level of evidence	Factors to consider when applying recommendations to an individual patient
Class III recommendations (continued)		
16. Terminal illnesses with a projected life expectancy of less than one year.	C	Such patients were excluded from all ICD trials.
17. NYHA class IV congestive heart failure in patients who are not expected to improve with any further therapy and who are not candidates for cardiac transplantation.	C	A CRT/ICD in highly selected patients with 'end stage' heart failure may be considered to be appropriate on the grounds that the CRT/ICD may improve the prognosis.

**It is recognized that each of these Class I recommendations includes a broad group of patients. Subgroup analyses have suggested that some may not benefit from an ICD. The decision to implant an ICD in any given patient must be individualized. AMI Acute myocardial infarction; CABG Coronary artery bypass graft; CRT Cardiac resynchronization therapy; EP Electrophysiology; LVEF Left ventricular ejection fraction; NYD Not yet diagnosed; NYHA New York Heart Association; PCI Percutaneous coronary intervention; RV Right ventricular; VF Ventricular fibrillation; VT Ventricular tachycardia*

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence
Level of Evidence A: Data are derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B: Data are derived from a single randomized trial, or nonrandomized studies.
Level of Evidence C: Only consensus opinion of experts, case studies or standard of care.

RECOMMENDATION FOR CARDIAC RESYNCHRONIZATION THERAPY

Heart failure is a significant health problem in Canada. There are over 500,000 Canadians living with this condition, and heart failure is the most frequent cause of hospitalization in those over 65 years of age. Quality of life is frequently impaired in patients with heart failure. The impact of heart failure therapies on quality of life is an important component of therapeutic efficacy.

Recent clinical trials in patients with heart failure have shown improved quality of life, heart failure symptoms (NYHA class) and exercise capacity with cardiac resynchronization therapy (CRT) devices (26-28). Improvements in quality of life with CRT devices appear to be more than what has been found with medical therapies for heart failure, although a significant proportion of this benefit may be placebo effect.

A recent meta-analysis of nine CRT trials that included 3216 patients demonstrated a 21% reduction in all-cause mortality (95% CI 4% to 24%) with CRT compared with that of controls (29). In these nine trials, the absolute risk of death was reduced by 4.2% over the course of three to 12 months of therapy. This translates into a need to treat 24 individuals to save one life over this time period. The reduction in mortality was largely related to a lower risk (40% relative reduction) of death from progressive heart failure. The impact of a combined CRT/ICD device would be anticipated to be greater than that of a CRT/pacemaker alone due to the risk of serious arrhythmias in these patients. In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial, a combined CRT/ICD device reduced mortality by 36% (7% absolute) when compared with medical therapy alone (13). This reduction was somewhat larger than that observed for a CRT/pacemaker versus optimal medical therapy (24% relative reduction and 4% absolute reduction). The relative benefit of a CRT/ICD versus an ICD alone is unknown and is the subject of ongoing randomized trials.

It is important to recognize the limitations of current data related to CRT. The majority of CRT studies have been based on limited (three to 12 month) follow-up (29). Most CRT trials have been restricted to patients in sinus rhythm with severe heart failure symptoms (NYHA class III and IV), with an LVEF of 35% or less, and with QRS durations of at least 130 ms. It is unclear whether the efficacy of CRT is similar in patients with chronic atrial fibrillation or in patients with more narrow QRS durations. While recent data indicate that CRT may be efficacious in patients with mechanical dyssynchrony regardless of QRS duration (30), long-term randomized data are required before this therapy can be recommended in these patients. All but one of the published CRT trials randomized patients after successful device implantation. In addition, these trials used clinical data only when patients were successfully followed for a period of time. Therefore, these results may overestimate the potential benefit of CRT. Data indicate that while most (75% to 80%) of the patients who receive CRT show clinical benefit in terms of NYHA symptoms, up to one-third of patients who receive an inactive CRT system also show clinical benefit (27,28). Thus, the rate of CRT response after adjusting for this placebo effect may be less than 50%.

CRT is resource-intensive and not without risk. Based on 18 studies that included a total of 3701 patients with CRT devices, the average implant success rate was 90%, and 0.4% of patients died during implantation (29). Over a median six-month follow-up, 9% of LV leads dislodged, and mechanical malfunctions occurred in 7% of CRT recipients. These rates of device malfunction are higher than the rates observed for non-CRT pacemakers or ICD systems. The cost of CRT is also substantial. A recent cost analysis found that CRT was associated with a median incremental cost of US$107,800 per additional quality-adjusted life-year. This median incremental cost was sensitive to changes in key variables such as comorbid illness, suggesting that CRT should not be considered in patients with a comorbid illness that shortens life expectancy (31).

Class IIa recommendation
Patients with ischemic or nonischemic LV dysfunction, in sinus rhythm, with NYHA functional class III to IV heart failure symptoms despite optimal medical therapy, with a left ventricular end-diastolic dimension greater than 60 mm, with an

LVEF of 35% or less, and with a QRS of at least 130 ms can be considered for CRT therapy. (Level of Evidence A).

In patients with ICD and CRT indications, a combined ICD/CRT device should be considered.

Currently, there is insufficient information to make recommendations for patients who otherwise meet the above criteria but have chronic persistent atrial fibrillation or for those who are on the waiting list for cardiac transplantation. Patients with narrow QRS with other evidence of ventricular dyssynchrony based on echocardiography may benefit from CRT, but the data are currently insufficient to recommend CRT. There are also insufficient data to make recommendations for patients with NYHA class II symptoms.

APPENDIX: The following Canadian cardiac electrophysiologists contributed to this position paper: S Connors, Memorial University, St John's, Newfoundland; M Basta, M Gardner, R Parkash, J Sapp, Dalhousie University, Halifax, Nova Scotia; L Blier, J Champagne, M Gilbert, F Molin, G O'Hara, F Philippon, Quebec Heart Institute, Sainte-Foy, Quebec; F Ayala-Paredes, F Scazzuso, Université de Sherbrooke, Sherbrooke, Quebec; P Costi, B Coutu, Pavillon Notre Dame, Université de Montréal, Montreal, Quebec; M Dubuc, P Guerra, C Guimond, P Lacombe, L Macle, D Roy, M Talajic, B Thibault, Montréal Heart Institute, Montreal, Quebec; M Rosengarten, M Sami, McGill University, Montreal, Quebec; D Birnie, M Gollob, M Green, R Lemery, A Tang, University of Ottawa Heart Institute, Ottawa, Ontario; R Gow, Children's Hospital of Eastern Ontario, Ottawa, Ontario; H Abdollah, C Simpson, G Veenhuyzen, Queen's University, Kingston, Ontario; P Dorian, V Korley, I Mangat, A Pinter, St Michael's Hospital, University of Toronto, Toronto, Ontario; D Cameron, V Chauhan, K Nanthakumar, M Waxman, University Health Network, University of Toronto, Toronto, Ontario; R Hamilton, J Kirsh, B Stephenson, Hospital for Sick Children, University of Toronto, Toronto, Ontario; E Crystal, Sunnybrook and Women's College Health Sciences Centre, University of Toronto, Toronto, Ontario; Y Khaykin, Z Wulffhart, South Lake Regional Health Centre, Newmarket, Ontario; A Janmohamed, Rouge Valley Centenary, Toronto, Ontario; D Newman, CAST, Toronto, Ontario; S Connolly, J Healey, C Morillo, G Nair, McMaster University, Hamilton, Ontario; G Klein, A Krahn, A Skanes, R Yee, University of Western Ontario, London, Ontario; K Wolfe, Health Sciences Centre, University of Manitoba, Winnipeg, Manitoba; H Duff, D Exner, A Gillis, K Kavanagh, B Mitchell, R Sheldon, G Wyse, Libin Cardiovascular Institute of Alberta, Calgary, Alberta; M Kantock, S Kimber, A Pantano, S Sivakumaran, University of Alberta, Edmonton, Alberta; C Kerr, S Sanatani, S Tung, J Yeung, University of British Columbia, Vancouver, British Columbia; R Leather, L Sterns, Victoria, British Columbia.

REFERENCES

1. Talajic M, Mitchell LB, Hadjis T. The role of prophylactic implantable cardioverter defibrillators to prevent sudden cardiac death. Can J Cardiol 2000;16(Suppl C):26C-8C.
2. Gregoratos G, Abrams J, Epstein AE, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines/North American Society for Pacing and Electrophysiology Committee to Update the 1998 Pacemaker Guideliness.ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). Circulation 2002;106:2145-61.
3. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000;101:1297-302.
4. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. N Engl J Med 1997;337:1576-83.
5. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: The Cardiac Arrest Study Hamburg (CASH). Circulation 2000;102:748-54.
6. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J 2000;21:2071-8.
7. Parkash R, Tang AS, Wells G, et al. Use of implantable cardioverter defibrillators after out-of-hospital cardiac arrest: A prospective follow-up study. CMAJ. (In press)
8. Nanthakumar K, Epstein AE, Kay GN, Plumb VJ, Lee DS. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: A pooled analysis of 10 primary prevention trials. J Am Coll Cardiol 2004;44:2166-72.
9. Bigger JT Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. N Engl J Med 1997;337:1569-75.
10. Hohnloser SH, Kuck KH, Dorian P, et al; DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 2004;351:2481-8.
11. Bansch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: The Cardiomyopathy Trial (CAT). Circulation 2002;105:1453-8.
12. Bardy GH, Lee KL, Mark DB, et al; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37.
13. Bristow MR, Saxon LA, Boehmer J, et al; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.
14. Kadish A, Dyer A, Daubert JP, et al; Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151-8.
15. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-40.
16. Moss AJ, Zareba W, Hall WJ, et al; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83.
17. Wilber DJ, Zareba W, Hall WJ, et al. Time dependence of mortality risk and defibrillator benefit after myocardial infarction. Circulation 2004;109:1082-4.
18. Link MS, Hill SL, Cliff DL, et al. Comparison of frequency of complications of implantable cardioverter-defibrillators in children versus adults. Am J Cardiol 1999;83:263-6.
19. Lee DS, Green LD, Liu PP, et al. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: A meta-analysis. J Am Coll Cardiol 2003;41:1573-82.
20. Kuppermann M, Luce BR, McGovern B, Podrid PJ, Bigger JT Jr, Ruskin JN. An analysis of the cost effectiveness of the implantable defibrillator. Circulation 1990;81:91-100.
21. Owens DK, Sanders GD, Harris RA, et al. Cost-effectiveness of implantable cardioverter defibrillators relative to amiodarone for prevention of sudden cardiac death. Ann Intern Med 1997;126:1-12.
22. Larsen G, Hallstrom A, McAnulty J, et al; AVID Investigators. Cost-effectiveness of the implantable cardioverter-defibrillator versus antiarrhythmic drugs in survivors of serious ventricular tachyarrhythmias: Results of the Antiarrhythmics Versus Implantable Defibrillators (AVID) economic analysis substudy. Circulation 2002;105:2049-57.
23. O'Brien BJ, Connolly SJ, Goeree R, et al. Cost-effectiveness of the implantable cardioverter-defibrillator: Results from the Canadian

Implantable Defibrillator Study (CIDS). Circulation 2001;103:1416-21.
24. Mushlin AI, Hall WJ, Zwanziger J, et al. The cost-effectiveness of automatic implantable cardiac defibrillators: Results from MADIT. Multicenter Automatic Defibrillator Implantation Trial. Circulation 1998;97:2129-35.
25. Special report: Cost-effectiveness of implantable cardioverter-defibrillators in a MADIT-II population. Technol Eval Cent Asses Program Exec Summ 2004;19:1-2.
26. Cazeau S, Leclercq C, Lavergne T, et al; Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873-80.
27. Abraham WT, Fisher WG, Smith AL, et al; MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-53.
28. Young JB, Abraham WT, Smith AL, et al; Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: The MIRACLE ICD Trial. JAMA 2003;289:2685-94.
29. McAlister FA, Ezekowitz JA, Wiebe N, et al. Systematic review: Cardiac resynchronization in patients with symptomatic heart failure. Ann Intern Med 2004;141:381-90.
30. Turner MS, Bleasdale RA, Vinereanu D, et al. Electrical and mechanical components of dyssynchrony in heart failure patients with normal QRS duration and left bundle-branch block: Impact of left and biventricular pacing. Circulation 2004;109:2544-9.
31. Nichol G, Kaul P, Huszti E, Bridges JF. Cost-effectiveness of cardiac resynchronization therapy in patients with symptomatic heart failure. Ann Intern Med 2004;141:343-51.
32. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 1999;341:1882-90.
33. Strickberger SA, Hummel JD, Bartlett TG, et al; AMIOVIRT Investigators. Amiodarone versus implantable cardioverter-defibrillator: Randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia – AMIOVIRT. J Am Coll Cardiol 2003;41:1707-12.