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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, CANADA

Scientific Update™

Preventing sudden death with prophylactic ICDs

A Report on a Presentation at the Late-breaking Trials Session at the 51st Annual Scientific Sessions of the American College of Cardiology

A portion of the material was originally presented by: A. J. Moss, MD

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A Report on a Presentation at the Canadian Cardiovascular Congress

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Tyrant King Dionysius lived in a fine palace surrounded by grandeur and happiness. Damocles, his friend, envied his fortune. The two decided to trade places for one day. Damocles was enjoying a grand feast, when he noticed, above his head, a sword hanging from the ceiling by a single horsehair. Horrified, he demanded from Dionysius the meaning of this. Dionysius explained that it is the "ever present peril" of his life as king. Never again, did Damocles envy the King.

Adapted from *Favorite Tales of Long Ago,*
retold by James Baldwin.

The Sword of Damocles

Implanted cardioverter defibrillators (ICDs) have become mainstream therapy for the prevention of sudden cardiac death from ventricular tachyarrhythmias. A decade of studies has confirmed the superiority of ICDs over anti-arrhythmic drug therapy in prolonging the life of patients with a prior history of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). Recent studies have compared ICD therapy to drugs or no antiarrhythmic therapy as 'primary prophylaxis' in patients considered at high risk for sudden death or with prior myocardial infarctions (MI). In selected patients, ICDs lead to important relative and absolute reductions in mortality in patients with no prior history of sustained VT or VF. Clinicians need to carefully consider these studies in their management of patients with coronary artery disease (CAD) and severe left ventricular (LV) dysfunction.

A 57-year-old patient consults you because of his exercise intolerance and concern about his prognosis. He has a history of two MIs, coronary artery bypass surgery 6 years ago, and now has New York Heart Association (NYHA) class II dyspnea on exertion. He does not have angina and has never had presyncope or syncope. A nuclear perfusion scan reveals nonreversible perfusion defects in two vascular territories, and the ejection fraction by MUGA scan is 26%. He is free of overt heart failure and is being treated with adequate doses of beta-blockers, an ACE inhibitor, aspirin, and a statin. The electrocardiogram shows sinus rhythm, prior anterior and inferior MIs, and left bundle branch block. He has never been hospitalized for heart failure.

Would you change his therapy or do any further investigations? What is his prognosis? He has read that patients with poor ventricular function have a high mortality rate. What should you advise him?

The understanding that cardiac death and, in particular, sudden cardiac death from fatal ventricular arrhythmias, is one of the most common causes of death in Western society is now widespread. Following the spectacular successes of thrombolytic, anti-ischemic, and revascularization therapies in the 1990s, focus has increasingly turned to the care of patients with the chronic consequences of CAD, chiefly LV dysfunction

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and heart failure, and the propensity for sudden arrhythmic death.

Although it has been very clearly established that patients with LV dysfunction, with or without symptomatic heart failure, are at high risk for out-of-hospital cardiac arrest and undocumented, but presumably arrhythmic sudden death, preventing such deaths has posed a major therapeutic challenge. First, it is difficult, if not impossible, to predict with any reasonable degree of certainty which patients are destined to suffer fatal arrhythmias, and which are destined to remain clinically stable, or at least free of serious ventricular arrhythmias. Of course, if such patients could be identified, then therapy could be targeted to only that select group whose destiny it is to suffer VT or VF (this represents approximately 40% to 60% of all patients with moderate to severe LV dysfunction).[1] Tests to identify patients at particularly high risk of sudden death have included:

- inducement of ventricular tachycardia or fibrillation at invasive electrophysiologic study;
- documentation of nonsustained ventricular tachycardia on Holter or in-hospital ECG monitoring;
- the presence of subtle (not visible to the naked eye) ECG abnormalities of depolarization and repolarization using the filtered, signal-averaged ECG, or the presence of microvolt T-wave alternans;
- the presence of abnormal autonomic modulation of cardiac function, by the registration of abnormally low heart rate variability (HRV), or depressed baroreceptor sensitivity.

Although each of these tests has some prognostic value, for practical clinical purposes, they are insufficiently accurate to direct therapy. Another expression of this difficulty is the "Bayesian conundrum" wherein patients with the above risk markers have a very high chance of dying suddenly, perhaps 20% to 40% per year, if several arrhythmic risk factors are present. However, such individuals represent only a small fraction of all of the patients with ventricular scarring who are potentially at risk of sudden death. On the other hand, the incidence of sudden death amongst all patients with prior MI is relatively low.

A second conceptual and practical problem is the inability to identify the timing, or proximate causes of sudden death from VT/VF. Such events appear to occur "out of the blue," and in most individuals, there are no clearly identifiable factors preceding sudden cardiac death. Although CAD is the most important etiologic factor leading to life-threatening ventricular arrhythmias, angina, other manifestations of myocardial ischemia, sudden worsening of heart failure, or behavioural factors such as stress or exercise, are rarely observed to immediately precede sudden death.

Improved acute and long-term therapies and survival for patients with MI have led to a relative increase in the number of the "walking wounded," ie, patients with chronic coronary disease and LV dysfunction who are nevertheless stable and not expected to suffer imminent recurrent infarction or progressive heart failure. Such patients usually feel relatively well, and may require some persuasion to consider prophylactic therapy for cardiac arrhythmias, which from a subjective standpoint can only decrease their quality of life in the short term.

In confronting these dilemmas, clinicians through the 1980s and 1990s were optimistic that sudden death could be prevented by administering antiarrhythmic drug therapy. This approach had the conceptual benefit that it could be delivered to a large group of patients at relatively low risk, as "chemoprophylaxis" for sudden cardiac death. With the spectacular failure of class I drugs (eg, flecainide) following MI, attention turned to drugs that prolong cardiac repolarization (class III drugs). The most extensively studied of these drugs is amiodarone. Several very large trials have examined in detail the potential usefulness of amiodarone in preventing sudden death in high-risk patients with CAD and LV dysfunction, the largest being the EMIAT study (European Myocardial Infarction Arrhythmia Trial)[2] and the CHF-STAT study (Congestive Heart Failure – Survival Trial of Antiarrhythmic Therapy).[3] The CAMIAT study (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial)[4] also included patients with prior MI, most of whom had at least moderate LV dysfunction, as well as frequent ventricular premature beats. All of these studies were randomized, placebo-controlled, clinical trials. None were able to show a statistically significant or a clinically meaningful reduction in all-cause cardiac mortality. Although meta-analyses of amiodarone have suggested a small and statistically significant reduction in all-cause mortality in high-risk populations, individual trials in patients with CAD and LV dysfunction provide scant hope that amiodarone is highly useful in this patient population. The progressively increasing burden of adverse effects from amiodarone is another barrier to its use. Given the paucity of evidence, there is no good reason to prescribe amiodarone as primary prophylaxis for VT or VF in patients with CAD and LV dysfunction and no symptoms of sustained ventricular arrhythmias.

Large studies have also examined the potential benefit from new class III antiarrhythmic drugs in the prevention of sudden death following MI or with heart failure, including studies of dofetilide (DIAMOND[5] and DIAMOND-CHF[6]), and azimilide (ALIVE[7]). These also failed to show any difference between drug- and placebo-treated patients in sudden or all-cause mortality. It is extremely important to note that beta-blocker therapy is of undoubted benefit in prolonging life in patients following MI, particularly in those with heart failure or extensive LV dysfunction. However, beyond the universal requirement for beta-blockers unless absolutely contraindicated, there is not much room for optimism that antiarrhythmic drugs, at least for the time being, will be even a partial solution to the problem of sudden cardiac death in susceptible coronary populations.

The implanted cardioverter defibrillator

An ICD represents an effective, if intellectually inelegant, therapy to prevent death from ventricular arrhythmias in that it does not prevent such arrhythmias, but treats them only after they occur. Shocks are painful and unpleasant, the devices are expensive, a surgical procedure is required for its implantation, and the follow-up of patients can be technically challenging. Where do we stand with respect to the evidence concerning implanted defibrillators and sudden death?

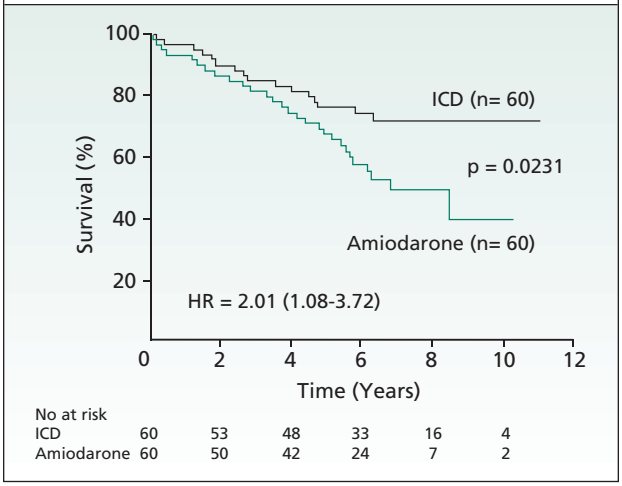
There is extensive information regarding the *efficacy* of ICD therapy. Appropriately tested devices have a 99% or greater probability of successfully restoring a perfusing rhythm in patients with VT or VF. Current devices can be implanted with <1% major morbidity or mortality, and with a surgical complexity and morbidity very similar to that of pacemaker implantation. Many of the life-threatening arrhythmias in patients with ICDs are due to sustained ventricular tachycardia that can usually be treated successfully with (painless) anti-tachycardia pacing. Improvements in ICD design will likely lead to improvements in tachycardia discrimination, which are also expected to lead to fewer ICD shocks, especially inappropriate shocks.

Studies in patients with a prior history of cardiac arrest or sustained ventricular tachycardia ("secondary prophylaxis"), have demonstrated convincingly that ICDs are both effective and superior to antiarrhythmic drug therapy in preventing all-cause mortality in such patients. The AVID,[8] CIDS,[9] and CASH[10] studies, and their meta-analysis,[11] have shown an approximate 20% to 30% reduction in all-cause mortality for such patients. The greatest relative benefit from defibrillators over antiarrhythmic therapy (primarily amiodarone) occurs in patients with the worst left ventricular function and in the elderly.[12]

The Canadian Implantable Defibrillator Study (CIDS) revealed non-significant risk reduction in overall mortality from an ICD compared to amiodarone.[9] A subset of CIDS patients were followed from 1991-2002. This subset consisted of patients who had been randomly assigned to receive either amiodarone (n=60) or an ICD (n=60) during the CIDS study at a single centre (St. Michael's Hospital, Toronto), and whose treatment was not altered after the formal study termination. The results of this study were presented at the Canadian Cardiovascular Congress in October, 2002.[13] Over 11 years, there were 28 deaths in the amiodarone group versus 16 deaths in the ICD group (Figure 1). In the amiodarone group, 49 patients (82%) had side effects related to amiodarone, of which 30 (50%) required discontinuation or dose reduction; 18 patients crossed over to ICD because of amiodarone failure (n=7) or adverse effects (n=11). In this study, the benefit of an ICD over amiodarone appears to increase with time since most of the amiodarone-treated patients experienced recurrences or adverse effects or died during the 11 years of follow-up.

Since the majority of sudden deaths occur in patients without a prior history of documented sustained VT or VF, studies have assessed the usefulness of defibrillators as "primary prophylaxis" of sudden cardiac death. The accumulated evidence from these studies is briefly reviewed below.

Figure 1: Long-term survival in patients randomized to an ICD versus amiodarone in CIDS[13]



Clinical trials of prophylactic ICDs

Initial trials focused on patients who were expected to be at particularly high risk of sudden cardiac death, based on a combination of low ejection fraction and an additional risk marker for sudden cardiac death.

MADIT I

The Multicenter Automatic Defibrillator Implantation Trial I (MADIT I) study assessed patients with CAD, poor LV function, and asymptomatic, nonsustained VT, with inducible VT or VF at electrophysiologic (EP) study that was not suppressible by antiarrhythmic drug therapy.[14] This study was the first to document a potential benefit from prophylactic ICDs, demonstrating a 54% reduction in mortality in patients with an ICD compared to those receiving "conventional medical therapy." Weaknesses in this trial included its relatively small size, inadequate therapy with beta-blockers and ACE inhibitors, and the clinically impractical sequence of EP study with the need for VT induction, followed by attempted VT/VF suppression with procainamide, which is required for risk stratification. Nevertheless, results from the MADIT I trial led to FDA approval of ICDs for the particular subset of patients meeting the inclusion criteria for this study.

CABG Patch

The Coronary Artery Bypass Graft (CABG Patch) study randomized patients to either an ICD or control therapy without ICD, immediately following successful aortocoronary bypass surgery, if they met the inclusion criteria of a low ejection fraction (<35%) and a positive signal-averaged ECG.[15] All devices were attached to the heart by means of epicardial defib-

rillator patches (which are no longer used during the CABG procedure).

This study failed to show any benefit whatsoever from the implanted defibrillator, but both defibrillator and no defibrillator patients had a low cardiac mortality (5.9% per year), suggesting that surgical revascularization has a very important protective effect against sudden death.

MUSTT

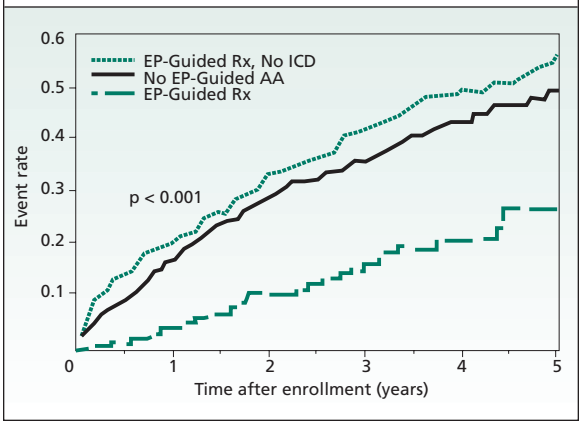
Like the MADIT study, the Multicenter UnSustained Tachycardia Trial (MUSTT) study also selected patients with CAD and an ejection fraction of <40% if they had asymptomatic nonsustained VT on Holter or in-hospital ECG monitoring, as well as inducible VT at EP study.[16] They were randomized to either "electrophysiologically-guided" (EP-guided) or no antiarrhythmic drug therapy. The EP-guided arm could include antiarrhythmic drugs designed to suppress the inducibility of VT, those that would render inducible arrhythmias hemodynamically stable, or an ICD. The choice between defibrillator versus drug therapy was not randomized.

Freedom at 5 years from sudden death was significantly lower in the EP-guided arm (25% vs 32%, $P = 0.04$), but all-cause mortality was not lower (48% vs 42%, $P = 0.06$, Figure 2). However, a secondary analysis comparing patients with no antiarrhythmic therapy to those with the ICD and antiarrhythmic drug therapy, showed some striking trends. The relative risk of death from all causes in the ICD group compared to the no antiarrhythmic therapy group was 0.45 (95%, CI, 0.32-0.63), and compared to EP-guided antiarrhythmic drug therapy was 0.40 (95% CI, 0.27-0.59). Although this is not strictly a randomized therapy assignment outcome, the study was widely interpreted, with reason, as showing superiority of the ICD to no antiarrhythmic therapy or antiarrhythmic drug therapy. As ICDs were increasingly used, it was observed that, over time, the EP-guided strategy was increasingly superior to no antiarrhythmic therapy. Furthermore, the fact that this strategy was relatively better in those centres where ICDs were used more frequently, lent plausibility to the belief that it was the defibrillator that contributed all of the observed benefit in the antiarrhythmic therapy arm.

As a consequence of the MUSTT study, expert bodies, including the Canadian Cardiovascular Society Consensus Guidelines for the treatment of ventricular arrhythmias, concluded that if patients with CAD, an ejection fraction < 40%, and nonsustained VT, had inducible ventricular tachycardia at EP study, they should preferably be treated with an ICD.[17]

Until very recently, the database above was sufficiently ambiguous and related to a sufficiently select subgroup of patients (all with CAD, low ejection fraction, nonsustained VT, and inducible VT/VF at EP studies), that these recommendations were not widely adopted into everyday clinical practice.

Figure 2: Total mortality in patients enrolled in the MUSTT study.[15] ICD therapy is associated with a lower mortality than either no antiarrhythmic therapy or EP-guided antiarrhythmic drug therapy.



MADIT II

The MADIT II study, published in March 2002,[18] took a simplified approach to testing the hypothesis that ICDs would reduce all-cause mortality in at-risk populations. The only "selection filters" to identify patients at-risk from sudden death were the presence of CAD, a prior MI, and an ejection fraction of < 30%. This study randomized 1232 patients to either the ICD (742 patients), or conventional medical therapy (490 patients, a 3:2 ratio). Neither nonsustained VT nor an EP study was required for entry into this study.

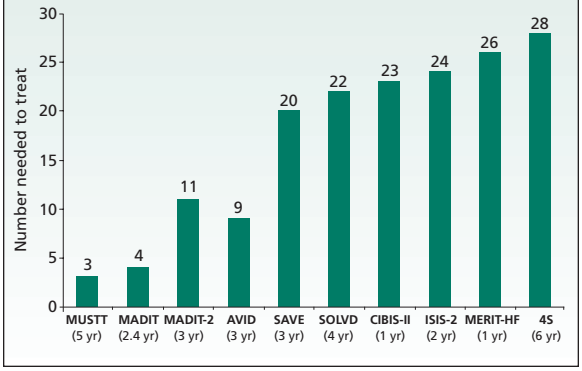
The patient population of MADIT II was reasonably representative of a potentially very large group of patients with chronic CAD and prior MI. The mean age was 65 years and 70% were either NYHA class I or II. A majority had a remote history of coronary artery bypass surgery (57%), or coronary angioplasty (44%). In the vast majority, more than 6 months had elapsed since their most recent MI.

Fortunately, the drug therapy was sufficiently "state-of-the-art" to allow generalizability in this trial: 70% were receiving ACE inhibitors, 70% beta-blockers, 57% digitalis, and 66% received statins. About 12% were receiving amiodarone at last contact (presumably most often for atrial fibrillation), only 9% were receiving calcium channel blockers, and 3% were receiving class I antiarrhythmic drugs.

Patients were followed to a common primary endpoint of death from any cause. The prespecified mortality efficacy boundary was achieved just over 4 years after the study began, after an average follow-up of 20 months.

Over time, defibrillator therapy resulted in an increasing mortality benefit compared to conventional therapy, with an

Figure 3: Numbers above each bar reflect number needed to treat (NNT) to prevent one death (over time frame indicated) in various studies of cardiovascular therapies.



NNT x years = 100 / (% mortality in control group – % mortality in treatment group).
SAVE and SOLVD are trials of ACE inhibitors.
CIBIS-II and MERIT-HF are trials of beta-blockers.
ISIS-2 is a trial of a thrombolytic agent.
4S is a trial of statin therapy.

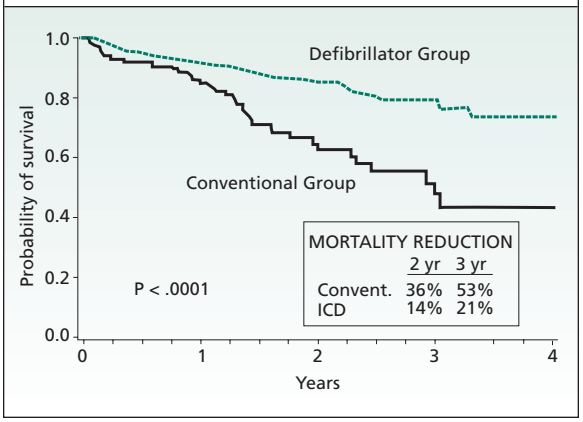
aggregate 31% reduction in the risk of death at any time interval, including a relative decrease in mortality of 12%, 28%, and 28% at 1, 2, and 3 years, respectively. In absolute terms, this meant a 1%, 6%, and 9% reduction in mortality at 1, 2, and 3 years; therefore, the number needed to treat (NNT) to prevent 1 death by 3 years was approximately 11. This NNT compares very favourably to other cardiovascular therapies in common use, for example beta-blockers (CIBIS 2, NNT = 23), statins (4S, NNT = 28), or ACE inhibitors (SAVE, NNT = 20, Figure 3). There was a slightly higher probability of hospitalization for heart failure in the ICD group (11 per 1000 months), versus the control group (9 per 1000 months, $P = 0.09$).

Further subsequent subgroup analysis showed that patients with QRS prolongation of >120 msec at baseline received a dramatic and particularly large benefit from the implantation of an ICD; mortality was reduced from 53% to 21% (a 63% reduction) at 3 years in these patients (Figure 4). This latter observation is consistent with a prior demonstration of QRS prolongation on the surface ECG as a particularly potent, simple marker for the probability of all-cause mortality and sudden death.

Where are we now?

The evidence indicating that ICDs prolong life in patients who are susceptible to sudden cardiac death is compelling. It is important to underline that the trials, thus far, pertain exclusively to patients with CAD (as opposed to those with dilated or other forms of cardiomyopathy), and are probably not applicable to patients immediately after bypass surgery. No study has shown that ICDs are superior

Figure 4: Survival in 364 patients in the MADIT-II study with QRS duration at baseline >120 msec (excluding paced patients), assigned to ICD (defibrillator group) or no antiarrhythmic therapy (conventional group).



HR = 0.37 (P = 0.004), 63% reduction in mortality.[17]

to medical therapy in patients with dilated cardiomyopathy; however, a large study of ICDs versus amiodarone (SCD-HeFT) will address this question. With these exceptions, patients with very poor ventricular function unquestionably benefit from implantation of a defibrillator, even if they are receiving optimal medical therapy. Although the MADIT and MUSTT trials did not systematically compare the ICD to "best" medical therapy (almost certainly amiodarone), the absence of clear proof that amiodarone is effective, along with its associated toxicity burden (which increases progressively over time), suggests that, for the moment, the ICD should be considered clearly superior to amiodarone therapy or no antiarrhythmic therapy for the prevention of sudden and all-cause mortality in susceptible populations.

Importantly, defibrillators in the MADIT and other studies were implanted with virtually no perioperative mortality and with a 2.5% incidence of nonfatal adverse events requiring surgical interventions (lead problems or infection).[18] The main barrier to more widespread use of prophylactic ICDs, at least in the Canadian context, seems to be resource limitations, both with respect to device and implantation costs and the availability of medical personnel to perform the procedures and follow the patients. In addition, the total number of years added to life, as well as the quality of these added years, has not been fully elucidated, given the relatively short follow-up time for all of the studies published thus far.

How is the clinician to deal with these ambiguities?

For the time being, it seems appropriate to at least *consider* a prophylactic ICD in all patients with a history of remote MI and an ejection fraction < 30%, provided they are

receiving, or have been considered for, evidence-based pharmacological therapies (ie, beta-blockers, ACE inhibitors, aspirin, statins, and spironolactone, as indicated). If revascularization is indicated and feasible, it should be performed. The presence of nonsustained VT during in-hospital or Holter monitoring probably adds some prognostic significance,[19] although the amount of information supplied by this finding is not clear. Performing an EP study for risk stratification is probably not required for most patients. The expectation of treatment benefit is amplified in patients with bundle branch block or QRS >120 msec.

Following these considerations, it is appropriate and advisable to inform the patient of the treatment options available, unless there are severe co-morbidities that reduce the expectation of treatment benefit. The belief that currently available resources are not sufficient to meet the potential demand for prophylactic ICDs should not be explicitly considered in the calculation of *individual* risk benefit for a particular patient. Clearly, the resource implications (both with respect to cost and indirect resource requirements) for widespread adoption of the practice of prophylactic ICDs are considerable. Scientific societies, advisory bodies, physicians, hospital administrators, and government bodies will have to carefully examine, collectively, all of these considerations in order to fairly distribute the resources that are and may become available to meet these challenges. It may be possible then to influence the "ever present peril" of sudden cardiac death and prevent the sword of Damocles from striking another patient.

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