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Prevention of Sudden Cardiac Death in Patients with Cardiomyopathy

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1. Introduction

Sudden cardiac death (SCD) is a major public health issue with an estimated annual incidence of 300,000 - 400,000 cases per year. The ACC/AHA/ESC 2006 guidelines define SCD as "death from an unexpected circulatory arrest, usually due to a cardiac arrhythmia occurring within an hour of the onset of symptoms"(Zipes et al. 2006). Most of the patients experiencing sudden cardiac arrest have an ejection fraction (LVEF) more than 50%, with the majority of these patients having a history of coronary artery disease (CAD). However, the risk of death in patients with LVEF of less than 35% is higher than patients with better preserved LVEF (Gorgels et al. 2003). Beta blocker therapy, Angiotensin enzymes inhibitors (ACE-I), angtiotensin receptor blockers as well as aldosteron antagonists have been shown to decrease the risk of sudden cardiac death especially in post myocardial infarction patients (Seidl et al. 1998; Domanski et al. 1999; Pitt et al. 2003; McMurray et al. 2005). In contrast antiarrhythmic drug therapy doesn't prevent sudden cardiac death in patients with cardiomyopathy. The focus of this chapter is to review the major implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy trials and their effects on sudden cardiac death prevention in patients with cardiomyopathy who are receiving optimal medical therapy.

2. Trials examining the benefits of ICD therapy in sudden cardiac death prevention

2.1 Secondary prevention trials of defibrillator therapy

The earlier trials examined the highest risk population of patients who had cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia (VT) and syncope. These trials helped establish the benefit of ICD therapy in prevention of sudden cardiac death as well as identify patients who are at high risk of dying suddenly and might benefit from ICD therapy as a primary prevention approach.

The first trial is the **Antiarrhythmic versus Implantable Defibrillators Trial (AVID)**. Patients were included if they were resuscitated from VT, had sustained VT with syncope or had sustained VT with LVEF < 40% and symptoms suggestive of hemodynamic compromise (angina or congestive heart failure or near syncope) (AVID 1997). Patients were excluded if the ventricular arrhythmia was due to a reversible cause, but those patients were followed in a registry. AVID enrolled 1016 patients and the primary end point was all cause mortality. Over

80% of the patients randomized to antiarrhythmic therapy (total of 509 patients) were on Amiodarone at end of follow up. AVID was terminated early when patients with ICD therapy (n=506) had a 38% reduction in all cause mortality compared to patients with antiarrhythmic drug therapy (HR 0.62, 95% CI of 0.47 to 0.81). Analysis of the AVID trial showed that patients with LVEF < 35% who received an ICD had significant reduction of sudden cardiac death while patients with LVEF > 35% who received an ICD did not see significant benefit compared to the antiarrhythmic drug therapy group (Domanski et al. 1999).

The patients with a reversible cause of ventricular arrhythmia who were not randomized were followed in a registry. These patients were in general younger, had a better mean LVEF and were more likely to have history of coronary artery disease and had underwent revascularization. Most of the reversible causes were due to ischemia or myocardial infarction (65%) or due to electrolytes imbalance (10%). Patients who were categorized as having VT/VF due to reversible causes had similar if not higher risk of sudden cardiac death compared to patients with no identifiable reversible cause(Wyse et al. 2001). Careful follow up and aggressive assessment for this patient group is advised.

The second study is the **Canadian Implantable Defibrillator Study (CIDS)**, which enrolled 659 patients who had VT, sustained VT with syncope or sustained VT with LVEF < 35%. Patients were excluded if they had recent myocardial infarction (MI) with in the past 72 hours or if they had electrolytes imbalance. Primary end point was all cause mortality. The patients were followed for an average of 36 months. There was a 20% relative risk reduction of death with ICD therapy compared to amiodarone (p=0.14)(Connolly et al. 2000). Analysis of CIDS showed that patients with low LVEF benefited from ICD therapy more than patient with better-preserved LVEF(O'Brien et al. 2001).

The third study is the **Cardiac Arrest Study Hamburg (CASH)**, which was a small trial randomizing 288 patients to ICD therapy with drug therapy. Inclusion criteria included patients successfully resuscitated from cardiac arrest due to documented sustained ventricular arrhythmia. Exclusion criteria included patients who had a cardiac arrest within 72 hours after MI or cardiac surgery or if they had a reversible cause due to electrolyte abnormality or proarrhythmic drug. There was a trend towards lower death with ICD therapy compared to drug therapy (23% relative risk reduction, p=0.16). Average follow up was 57 months. The lack of benefit in the CASH trial might be due to the fact that it had a small study population and better mean LVEF (45% ±18%) compared to the AVID trial(Kuck et al. 2000). Also, 44% of patient in CASH study had epicardial lead implantation as compared to only 4% in the AVID trial.

A pooled analysis of these trials demonstrated that all cause mortality was reduced by 27% (HR of ICD compared to Amiodarone of 0.73, 95% CI 0.60-0.87, p<0.001) (Connolly et al. 2000). Arrhythmic death was also reduced in the ICD group compared to the Amiodarone group (HR 0.49, 95% CI of 0.36 to 0.67, p<0.001). The metaanalysis also showed that patients with LVEF <35% had a significant benefit from ICD therapy compared to Amiodarone (HR 0.66, 95% CI of 0.53 to 0.83) while patients with LVEF >35% had no significant benefit from ICD therapy compared to Amiodarone therapy (HR of 1.2, 95% CI of 0.81 to 1.76). Furthermore, patients receiving epicardial lead systems had no benefit from ICD therapy compared to Amiodarone (HR 1.52, 95% CI of 0.92 to 2.50), while patients with transvenous lead had the most benefit (HR 0.69, 95% CI of 0.56 to 0.85). The three randomized trials examining the benefit of implantable cardioverter defibrillator (ICD) therapy in patients who survived cardiac arrest are summarized in Table 1.

Trial	N	Inclusion Criteria	Primary Endpoint	Age	Mean LVEF	HR (95% Confidence Interval)	P Value
Antiarrhythmics versus Implantable Defibrillators (AVID) (1016 patients)	1016	Resuscitated VF, sustained VT and syncope or sustained VT with LVEF < 40% and severe symptoms	All cause mortality	65	35%	0.62 (0.47-0.81)	0.02
Canadian Implatable Defibrillator Study (CIDS) (659 patients)	659	Resuscitated VF, sustained VT and syncope or sustained VT with LVEF < 35% or unmonitored syncope with subsequent inducible VT or sustained VT	All cause mortality	64	34%	0.82 (0.60 to 1.10)	0.14
Cardiac Arrest Study Hamburg (CASH)	288	cardiac arrest due to documented sustained ventricular arrhythmia	All cause mortality	58	45%		0.16

Table 1. Secondary prevention trials of ICD therapy. VT is for ventricular tachycardia, VF is for Ventricular Fibrillation, LVEF is for left Ventricular ejection Fraction. HR is for hazard Ratio, CI is confidence interval.

These trials established the benefits of ICD therapy in patients who survived cardiac arrest in the absence of reversible causes. Patients with reversible causes of the cardiac arrest remain high risk and should be followed closely. Even though the metaanalysis of these trials showed no benefits of ICD therapy in patients with LVEF >35%, this is not reflected in the guidelines due to the fact that LVEF was not an entry criterion in these trials. Furthermore, the mean time of cardiac arrest and measurement of LVEF was 3 days in the AVID trial, and the LVEF shortly after cardiac arrest might be depressed from myocardial injury and might improve over time. Table 2 lists current guidelines for ICD therapy.

Class I: (General agreement of benefit with ICD therapy)

1. ICD therapy is indicated in patients who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes.
2. ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable.
3. ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study.
4. ICD therapy is indicated in patients with LVEF less than or equal to 35% due to prior

MI who are at least 40 days post-MI and are in NYHA functional Class II or III.

5. ICD therapy is indicated in patients with nonischemic dilated cardiomyopathy who have an LVEF less than or equal to 35% and who are in NYHA functional Class II or III.

6. ICD therapy is indicated in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than or equal to 30%, and are in NYHA functional Class I.

7. ICD therapy is indicated in patients with nonsustained VT due to prior MI, LVEF less than or equal to 40%, and inducible VF or sustained VT at electrophysiological study.

Class IIa (Weight of evidence is in favor of usefulness of ICD therapy)

1. ICD implantation is reasonable for patients with unexplained syncope, significant LV dysfunction, and non-ischemic dilated cardiomyopathy.

2. ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function.

3. ICD implantation is reasonable for patients with hypertrophic cardiomyopathy (HCM) who have 1 or more major risk factors for SCD. [Major risk factors for SCD in patients with HCM are: prior cardiac arrest, spontaneous sustained VT, spontaneous non-sustained VT, Family history of SCD, LV thickness ≥ 30 mm and abnormal blood pressure response to exercise]

4. ICD implantation is reasonable for the prevention of SCD in patients with ARVD/C who have 1 or more risk factors for SCD. [Risk factors for SCD in patients with ARVD/C are: prior cardiac arrest, spontaneous sustained VT, spontaneous non-sustained VT, evidence of extensive RV disease, LV involvement, presentation with polymorphic VT and RV apical aneurysm and induction of VT during electrophysiologic testing]

5. ICD implantation is reasonable to reduce SCD in patients with long-QT syndrome who are experiencing syncope and/or VT while receiving beta blockers.

6. ICD implantation is reasonable for non hospitalized patients awaiting transplantation.

7. ICD implantation is reasonable for patients with Brugada syndrome who have had syncope.

8. ICD implantation is reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest.

9. ICD implantation is reasonable for patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving beta blockers.

10. ICD implantation is reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease.

Class IIb (Efficacy of the ICD therapy is less well established)

1. ICD therapy may be considered in patients with non-ischemic heart disease who have an LVEF of less than or equal to 35% and who are in NYHA functional Class I.

2. ICD therapy may be considered for patients with long-QT syndrome and risk factors for SCD.

3. ICD therapy may be considered in patients with syncope and advanced structural heart disease in whom thorough invasive and noninvasive investigations have failed

to define a cause.

4. ICD therapy may be considered in patients with a familial cardiomyopathy associated with sudden death.

5. ICD therapy may be considered in patients with LV noncompaction.

Class III (General agreement that an ICD is not effective and may be harmful)

1. ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria specified in the Class I, IIa, and IIb recommendations above.

2. ICD therapy is not indicated for patients with incessant VT or VF.

3. ICD therapy is not indicated in patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up.

4. ICD therapy is not indicated for NYHA Class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or CRT-D.

5. ICD therapy is not indicated for syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease.

6. ICD therapy is not indicated when VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, RV or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease).

7. ICD therapy is not indicated for patients with ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma).

Table 2. Recommendations for ICD therapy based on the ACC/AHA/HRS 2008 Guidelines for Device Based Therapy.

2.2 Primary prevention trials of defibrillator therapy
2.2.1 Primary prevention of SCD in patients with ischemic cardiomyopathy with and without prior myocardial infarction

The earlier primary prevention trials used electrophysiologic testing as well as a reduced LVEF as part of entry criterion. Electrophysiologic testing (EP study) was thought to be a reliable method of risk stratification of patients with coronary artery disease (CAD) who survived myocardial infarction.

The First of these trials is the **First Multicenter Automatic Defibrillator Implantation Trial (MADIT- I)** which compared ICD therapy to conventional care in 196 patients post MI, LVEF < 35%, non-sustained VT on ambulatory monitoring and inducible VT by programmed electrical stimulation and failure of intravenous procainamide to prevent inducibility (Moss et al. 1996). Patients were excluded if they had prior cardiac arrest or syncope due to ventricular tachycardia (VT) not related to myocardial infarction (MI). Patients were also excluded if they had suffered myocardial infarction within 3 weeks of randomization, had coronary artery bypass surgery within 2 months of randomization or if they had angioplasty within 3 months of randomization. MADIT I started enrolling patients in December 1990, with only transthoracic implantation of ICD was available at the time. Nonthoracotomy transvenous leads were implanted after being approved in August of 1993. Of the 196 patients enrolled, 95

patients were assigned to the ICD group and 101 patients were assigned to the conventional medical therapy group (which also included use of antiarrhythmic drugs). Primary endpoint was all cause mortality. After a mean follow up of 27 months, patients assigned to the ICD group had lower mortality than patients assigned to the conventional treatment group (Hazard Ratio (HR) of 0.46, 95% confidence interval (CI) 0.26 to 0.82, p=0.009). The interval from last MI was > 6 months in 75% of patients in each treatment group. The benefit of ICD was similar in patients with thoracotomy and non-thoracotomy ICD implantation (p=0.78). MADIT-I trail was the first trail to include patients who had purely low LVEF and inducible non-suppressible sustained ventricular arrhythmias during electrophysiologic testing.

The First Multicenter Unsustained Tachycardia Trial (MUSTT-I) trial was designed to determine whether inducibilty of VT identified risk of sudden cardiac death in patients with LVEF < 40%, prior myocardial infarction and non-sustained VT documented more than 4 days after MI. Patients were enrolled if they had a positive electrophysiology study (defined as an inducible monomorphic VT or inducible polymorphic VT with one or two extrastimuli). Those with negative EP study were followed in a registry. A total of 704 patients with positive EP study were randomized to electrophysiologic guided antiarrhythmic therapy (which included a drug or implantation of an ICD) versus best medial therapy (mainly beta blockers and angiotensin enzyme inhibitors but no antiarrhythmic drug therapy) (Buxton et al. 1999). Patients who failed suppression of inducibility of the ventricular arrhythmia after at least one antiarrhythmic drug trial could receive an ICD. The ICD implantation was not randomized in MUSTT-I. The primary endpoint was cardiac arrest or death from arrhythmia. Secondary endpoints included death from all causes, death from cardiac causes and spontaneous sustained VT. Over a follow up period of 39 months, patients assigned to electrophysiologic testing (n=351) had lower risk of arrhythmic death or cardiac arrest compared to patients receiving best medical therapy (n=353) (Relative risk 0.73, 95% CI 0.53 to 0.99, p =0.04). This is mostly attributable to lower risk of arrhythmic death or cardiac arrest in patients receiving an ICD compared to patients not receiving an ICD (relative risk 0.24, 95% CI of 0.13 to 0.45, p< 0.001). Patients who received an ICD had a lower risk of all cause mortality compared to patients with electrophysiology guided therapy who received antiarrhythmic drugs only (Relative risk 0.42, 95% CI of 0.29 to 0.61) This remained significant even after adjusting for all other clinical variables (Figure 1).

MUSTT-I showed that patients who had an inducible VT that was suppressed with antiarrhythmic drugs did not have any mortality benefit.

Patients who were screened for MUSTT-I but had a negative EP study were followed in a registry. Data was available for 1397 patients after 39 months of follow up. Total mortality was compared in this registry with the 353 patients in MUSTT-I with positive EP study that were assigned to best medical therapy. Only 35% of patients in the registry were on beta blockers compared to 51% of patients with inducible arrhythmias assigned to no antiarrhythmic therapy. The rate of used of ACE-I was similar (72% and 77% respectively). At 39 months, mortality was higher in patients with positive EP study assigned to best medical therapy (48%) compared to the patients with negative EP study in the registry (44%), (unadjusted p=0.09, adjusted p<0.001 for other clinical factors including use of beta blockers). Even though this difference was statistically significant, the absolute difference of 4% over 5 years is not clinically meaningful. Given these results as well as the consistency of LVEF <35% to predict a mortality benefit from ICD therapy, Electrophysiologic testing is not routinely performed in patients with coronary artery disease and LVEF < 35% as a risk stratifying tool. (Buxton et al. 2000).
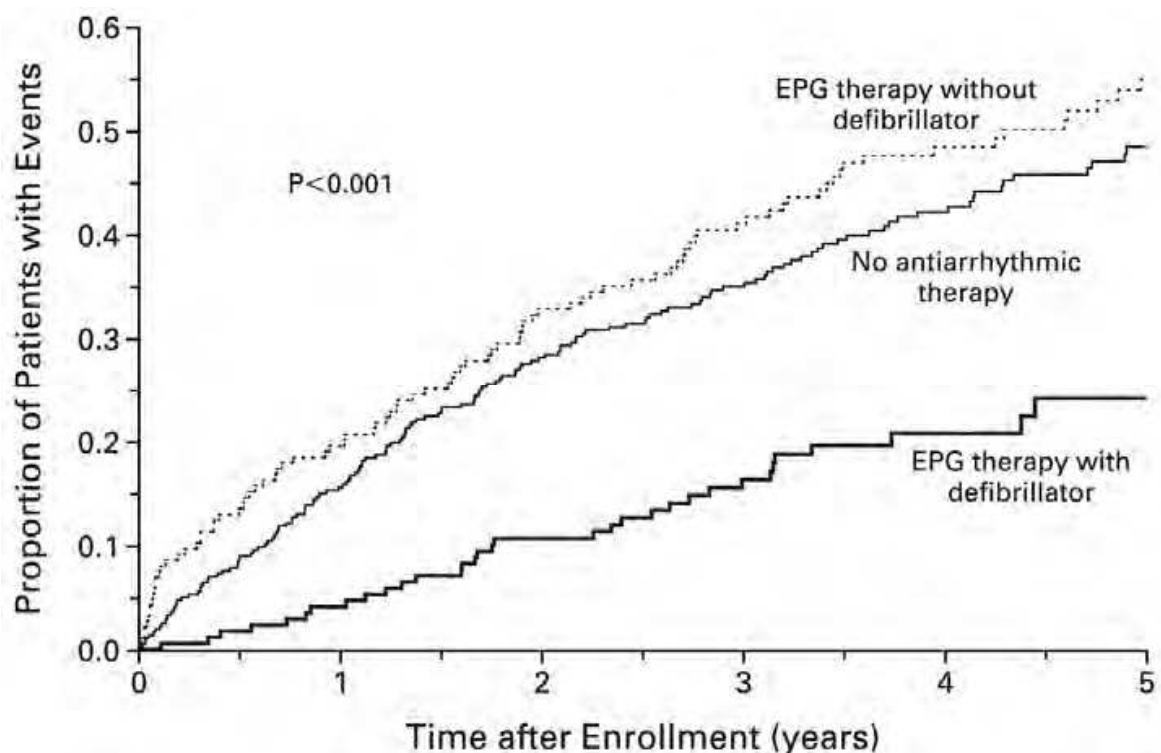
Fig. 1. Kaplan- Meier Estimates of the Rates of Death from All Causes. EPG denotes electrophysiologically guided. (From Buxton, A. E., Lee, K. L., Fisher, J. D., et al. (1999). "A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators." New England Journal of Medicine, Vol. 341, No.25, (December, 1999): pp. 1882-1890, ISSN 0028-4793, with permission)

The Coronary Artery Bypass Graft Patch and The Second Multicenter Automatic Defibrillator Implantation Trial (MADIT- II) trials examined the benefits of ICD therapy in patients with reduced LVEF months after myocardial infarction and did not include electrophysiologic testing or arrhythmia suppression as part of entry criterion. **The Coronary Artery Bypass Graft-Patch Trial (CABG-Patch)** randomized 1055 patients undergoing coronary artery bypass surgery, LVEF <36% and positive signal-averaged electrocardiograms to receive ICD therapy (n=446) or conventional medical therapy (n=454) (Bigger 1997). Only 50% of the patients had prior myocardial infarction but all the patients received epicardial ICD systems. ICD therapy showed no survival benefit over conventional medical therapy (HR 1.06, 95% CI of 0.81 to 1.42, p=0.64). The lack of benefit of ICD therapy in this trial could be due to the methods used for patient selection, but most likely is due to the effects of complete revascularization on the risk of sudden cardiac death. In a subanalysis of **Studies of Left Ventricular Dysfunction (SOLVD)** trial, CABG was found to be associated with a 36% relative risk reduction of all cause mortality and a 46% reduction of sudden cardiac death regardless of the severity of heart failure or the decrease in the LVEF. This might have contributed to the lack of benefit from ICD early after coronary artery bypass surgery (Veenhuyzen et al. 2001).

The Second Multicenter Automatic Defibrillator Implantation Trial (MADIT- II) randomized 1232 patients in a 3:2 fashion with LVEF < 30% and prior MI to receive an ICD (n=742) compared to medical therapy (n=490). Patients were excluded if they had a recent MI

(<1 month), if they had revascularization in the past 3 months prior to randomization or if they were New York Heart Association (NYHA) class IV at enrollment. Mean follow up was for 30 months and primary end point was all cause mortality. ICD therapy was associated with a 31% reduction in relative risk of death at 20 months (HR 0.69, 95% confidence interval of 0.53 to 0.93, p = 0.02) (Moss et al. 2002). There was no difference in subgroup analysis based on age, gender, ejection fraction, QRS duration as well as NYHA class in terms of ICD benefit.

All ICD implantations were transvenous lead systems. No deaths were related to the implantation procedure and the complication of lead implantation was 1.8% and infection rate was 0.7%. Analysis of the mortality events showed that ICD therapy mainly prevented sudden cardiac death (HR 0.33, 95% CI of 0.2 to 0.53, p<0.001) but did not affect non-sudden cardiac death (p=0.32).

Even though MADIT-II did not require electrophysiologic testing as an entry criterion, the investigators sought to evaluate the predictive value of EP study to predict mortality and ICD efficacy as a pre-specified secondary endpoint. Patients assigned to the ICD group were encouraged to undergo an EP study and they received the ICD regardless of the results of the electrophysiologic testing. Of the 720 patients who received an ICD, only 593 patients underwent EP testing. A positive EP study was defined as sustained monomorphic or polymorphic VT induced with 3 or fewer extrastimuli or VF induced with 2 or fewer extrastimuli. A positive EP study according to this standard protocol did not predict the pre-specified primary endpoint of spontaneous VT or VF requiring treatment by the ICD (p=0.28). Patients with inducible VT were more likely to have VT during follow up (0.023) compared to patients with no inducible VT (Daubert et al. 2006). This confirms the findings of MUSTT-I trial in regards to the utility of EP testing in risk stratifying patients with coronary artery disease and LVEF < 35%.

Another subanalysis of MADIT-II trial showed that patients with ICD therapy who underwent coronary revascularization within 6 months of randomization had no survival benefit from ICD therapy compared to patients in the conventional treatment group (HR = 1.19; p = 0.76), while patients with ICD therapy who were randomized > 6 months after coronary revascularization had significant survival benefit from ICD therapy (HR =0.64, p = 0.01) after adjusting for other important clinical variables (Goldenberg et al. 2006). Furthermore, mortality risk in patients in MADIT II was shown to be time dependent, with benefit extending even for patients who had remote MI (>15 years) (Wilber et al. 2004). Two studies were conducted examine the benefits of ICD therapy early after myocardial infarction (MI). The first is **The Defibrillators in Acute Myocardial Infarction Trial (DINAMIT) which** was designed to evaluate the potential for ICD benefit early (6 to 40 days) after a MI in patients with LVEF <35%, and abnormal autonomic tone [high resting heart rate over 80 beats per minutes (bpm) or low heart rate variability]. Patients were excluded if they had three-vessel coronary intervention, if they already had an ICD or if they were planned to undergo coronary artery bypass graft surgery (CABG). A total of 647 patients were randomized to optimal medical therapy (n=342) or ICD therapy (n=332) (Hohnloser et al. 2004). The primary end point was all cause mortality and the secondary end point was arrhythmic death. After a mean follow up of 30 months, there was no overall survival benefit attributable to early implantation of an ICD compared to medical therapy [HR 1.08; 95% confidence interval (CI), 0.76 to 1.55; P=0.66]. The ICD group had less arrhythmic death compared to the medical therapy group (HR in the ICD group, 0.42; 95% CI, 0.22 to 0.83; P=0.009). There was an increase in non-sudden cardiac

death in the ICD group compared to the medical therapy group (HR = 1.75; 95% CI, 1.11 to 2.76; P=0.02).

The second trial is **the Immediate Risk Stratification Improves Survival (IRIS) Trial**, which was a randomized, open label multicenter trial that studied the benefit of ICD therapy early after MI compared to optimal medical therapy. Patients were included if they had a history of myocardial infarction (5 to 31 days after MI), LVEF < 40% with either a baseline heart rate of > 90 bpm, non-sustained VT at >150 bpm on holter or both. A total of 898 patients were enrolled in the trial. Mean follow up was for 37 months, and almost 75% of the patients underwent revascularization. Most of the patients were on beta blockers (97% in the ICD group and 95% in the control group) and angiotensin receptor blockers (90% in ICD group and 91.1% in the control group). There was no difference in overall mortality between ICD group and the medical treatment group (HR 1.04, 95% CI of 0.81 to 1.35, p=0.78) (Steinbeck et al. 2009). Patients assigned to ICD therapy had lower incidence of sudden cardiac death (HR 0.55, 95% CI of 0.31 to 1.00, p = 0049) but higher incidence of non-sudden cardiac death (HR 1.92, 95% CI of 1.29 to 2.84).

The reasons for the lack of benefit of ICD therapy early after MI might never be known. Revascularization has a protective effect and leads to reverse remodeling especially if done in a timely fashion early after MI. Patients who died early in DINAMIT had pump failure. Other possibilities include side effects for ICD implantation early after MI or the negative effects of shocks or antitachycardia pacing on myocardial contractility.

In summary, the above trials support the use of ICD therapy for primary prevention of SCD in chronic ischemic cardiomyopathy. For patients who suffered a recent MI (<40 days), both IRIS and DINAMIT showed a decrease in arrhythmic death but no difference in all cause mortality. Currently, the guidelines support ICD therapy in patients with CAD who are > 40 days post MI and have LVEF < 35%.

Table 3 summarized the primary prevention trials in patients with coronary artery disease.

2.2.2 Primary prevention of SCD in patients with non-ischemic cardiomyopathy

The early trials examining the effects of ICD therapy compared to antiarrhythmic therapy in patients with non-ischemic cardiomyopathy (NICM) were small and not powered enough to show mortality benefit. The first trial is the **Amiodarone versus Implantable Cardioverter Defibrillator Trial (AMIOVERT)** which compared ICD therapy in 103 patients with NICM (with the diagnosis made > 6 months before enrollment) and non-sustained VT to amiodarone. The primary endpoint was all cause mortality. There was no difference in survival between the ICD group and the amiodarone group. The trial was terminated due to futility. The second trial is the **The Cardiomyopathy trial (CAT)** which was carried out in Germany and enrolled 104 patients with non-ischemic cardiomyopathy who were diagnosed within 9 months of enrollment. Mean follow up was 5.5 years and the primary end point was all cause mortality. Again there was no difference in survival between the ICD group and the control group. Both AMIOVERT and CAT trials were underpowered to detect a difference between groups, and in both of them the observed mortality was far lower than the predicted mortality used to design these trials.

Trial	N	Inclusion Criteria	Primary Endpoint	Age	Mean LVEF	NYHA Class	HR (95% CI)	P Value
First Multicenter Automatic Defibrillator Implantation Trial (MADIT-I)	196	NYHA I-III HF LVEF<35% MI > 4 weeks CABG > 3 months spontaneous NSVT and inducible VT	All cause mortality	63	26%	I, II and III	0.46 (0.26 to 0.82)	0.009
Multicenter Unsustained Tachycardia Trial (MUSTT)	704	NYHA I-III LVEF <40% MI>4 days spontaneous NSVT and inducible VT	Cardiac arrest or death from arrhythmia	65	28%	I, II and III	0.73 (0.53 -0.99)	0.04
The Coronary Artery Bypass Graft-Patch Trial (CABG-Patch)	1055	LVEF < 36%, Abnormal SAECG, undergoing CABG	All cause mortality	64	27%		1.06 (0.81 to 1.42)	0.64
Second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II)	1232	NYHA I-III, LVEF < 30% MI > 1 month	All Cause mortality	64	23%	I, II and III	0.69 (0.53 to 0.93)	0.02
Defibrillators in Acute Myocardial Infarction Trial (DINAMIT)	674	NYHA I-III LVEF <35% recent MI (6-40 days) with depressed heart rate variability or elevated average Hear rate over 24 hrs	All Cause mortality	62	28%	I, II and III	1.08 (0.76 to 1.55)	0.66
the Immediate Risk Stratification Improves Survival (IRIS)	898	NYHA I-III LVEF <40% Recent MI (5 to 31 days after MI), with either a baseline heart rate of > 90 (bpm) or NSVT at >150 bpm on holter or both	All Cause mortality	62	30%	I, II and III	1.04 (0.81 to 1.35)	0.78

Table 3. Primary prevention trials of ICD therapy in patients with coronary artery disease. VT is for ventricular tachycardia, VF is for Ventricular Fibrillation, NSVT is for non sustained VT, LVEF is for left Ventricular ejection Fraction. HR is for hazard Ratio, CI is confidence interval.

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation Trial (DEFINITE) studied the efficacy of ICD therapy to prevent all cause mortality in patients with LVEF < 35% and non-sustained VT or frequent premature ventricular contractions (PVCs) on ambulatory monitoring (Kadish et al. 2004). A total of 488 patients (229 in the ICD group and 229 in the conventional treatment group) were enrolled and the primary end point was death from any cause and the secondary endpoint was sudden cardiac death. Most of the patients were receiving beta blocker (85%) and ACE-I (86%) There was a 35% relative risk reduction in mortality in the ICD group compared to the medical therapy group (HR, 0.65; 95% CI, 0.40 to

1.06; P=0.08) but it did not reach statistical significance. A significant reduction in SCD was observed (HR 0.20; 95% CI, 0.06 to 0.71; P=0.006). The DEFINITE trial didn't specify duration of heart failure as an entry criterion and it only required absence of a reversible cause of cardiomyopathy for enrollment. Patients in DEFINITE who had a recent diagnosis of non-ischemic cardiomyopathy (Using a 3 months cut point or a 9 months cut point) had similar benefit from ICD therapy when compared to patients who had a remote diagnosis of non-ischemic cardiomyopathy (p0.25) (Kadish et al. 2006)

The largest trial conducted to examine the effects of ICD therapy on sudden cardiac death prevention in patients with ischemic and non-ischemic cardiomyopathy is the **Sudden Cardiac Death-Heart Failure (SCD-HeFT) trial**. This trial enrolled 2521 patients with LVEF < 35%, NYHA II-III and it had similar proportion of patients with ischemic cardiomyopathy (52%) and non-ischemic cardiomyopathy (48%). Patients were randomized to receive a single chamber ICD (n=829), Amiodarone (n=845) or placebo (n=847) (Bardy et al. 2005). Patients with recent MI or revascularization (<1 month) were not eligible. Nearly 96% of patients were on ACE-I or angiotensin receptor blockers and 69% were receiving beta-blocker therapy. The primary endpoint was all cause mortality. The ICD group was programmed to shock therapy only. After mean follow up of 45.5 months, the ICD group had lower mortality compared to placebo (HR 0.77, 95% CI of 0.62-0.96, p=0.007) while amiodarone had no effect on mortality compared to placebo (HR 1.06, 95% CI 0.86 to 1.30, p=0.53) (Figure 2). Annual rate of appropriate ICD shocks occurred in 68% of patients with an average annual rate of 5.1%. The absolute reduction in mortality was similar in patients with ischemic (7.2%) and non-ischemic cardiomyopathy (6.5%).
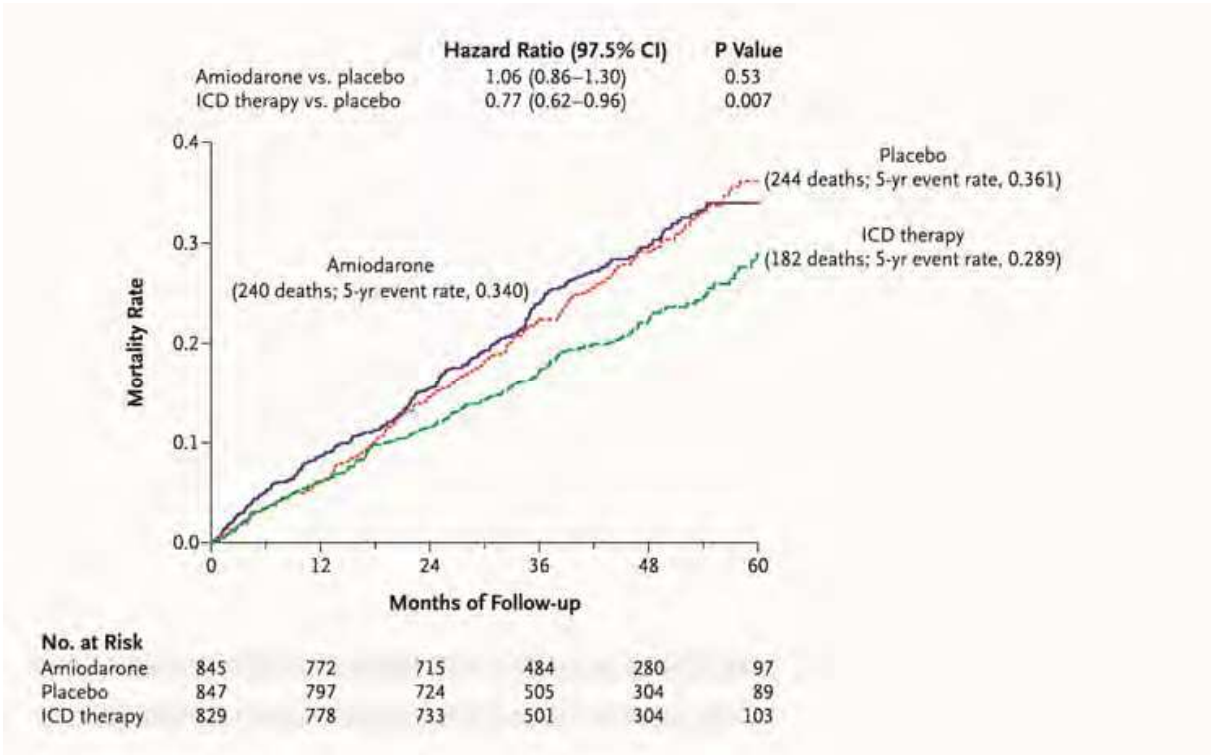

Fig. 2. Kaplan-Meier Estimates of Death from Any Cause. CI denotes confidence interval. (From Bardy, G. H., Lee, K. L., Mark, D. B., et al. (2005). "Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure." New England Journal of Medicine Vol. 352, No.3, (January, 2005): pp. 225-237, ISSN 1533-4406, with permission).

In a pooled analysis of 10 primary prevention trials (AMIOVERT, MADIT-I, MUSTT, MADIT-II, CABG PATCH, CAT, SCD-HeFT, COMPANION, DEFINITE and DINAMIT), ICD therapy was associated with 25% relative risk reduction of all cause mortality (RRR 9% to 37%, p=0.003) compared to the medical treatment group. The absolute risk reduction was 7.9%, which means 13 ICDs need to be implanted to save one life over about 3 years. This was not sensitive to removal of the any of the trials from the analysis. The benefit of ICD therapy in sudden cardiac death prevention is above and beyond the mortality benefit associated with use of beta blocker and ACE-I in patients with systolic heart failure (Nanthakumar et al. 2004). Table 4 summarized the primary prevention trials of ICD therapy in patients with non-ischemic cardiomyopathy.

Trial (N)	N	Inclusion Criteria	Primary Endpoint	Age	Mean LVEF	NYHA Class	HR (95% CI)	P Value
Amiodarone Versus Implantable Cardioverter Defibrillator Trial (AMIOVERT)	103	NYHA I-IV LVEF < 35% Dilated cardiomyopathy, NSVT	All cause mortality	52	23%	I, II ,III and IV		0.80
Cardiomyopathy Trial (CAT)	104	NYHA II-III, LVEF < 30%, Dilated cardiomyopathy, Recent onset heart failure < 9 months	All cause mortality	52	24%	II and III		0.54
The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation Trial (DEFINITE)	488	NYHA I-III, LVEF < 35%, Dilated cardioyopathy, NSVT or frequent PVCs (>10 PVC /hr)	All cause mortality	58	21%	I, II and III	0.65 (0.40 to 1.06)	0.08
Sudden Cardiac Death-Heart Failure (SCD-HeFT) trial	2521	NYHA II-III, EF< 35%, non-recent MI or revascularization (>1 month), non-recent heart failure onset (> 3 months)	All Cause mortality	60	25%	II and III	0.77 (0.62-0.96)	0.007

Table 4. Primary prevention trials of ICD therapy in patients with non-ischemic cardiomyopathy. VT is for ventricular tachycardia, VF is for Ventricular Fibrillation, PVC is for premature ventricular contractions, LVEF is for left Ventricular ejection Fraction. HR is for hazard Ratio, CI is confidence interval.

2.2.3 Cost effectiveness of ICD therapy

ICD therapy adds to the costs of care of patients with cardiomyopathy. Analysis of cost effectiveness in the SCD-HeFT trial showed that ICD therapy is cost effective, with incremental cost of $38,400 (95% CI of $25,217 to $80,160). This was similar in patients with ischemic and non-ischemic cardiomyopathy (Mark et al. 2006). In a pooled analysis of eight primary prevention trials, ICD therapy was not found to be cost effective in CABG PATCH

and in DINAMIT, which are the trials that showed no mortality benefit from ICD therapy compared to conventional medical therapy. When examining the primary prevention trials that showed mortality benefit (MADIT-I, MUSTT, MADIT-II, COMPANION, DEFINITE and SCD-HeFT), ICD therapy was found to be cost effective, adding between 1.01 and 2.99 quality-adjusted life years with costs ranging from $34,000 to $70,200. This analysis takes into account that the ICD generator will be replaced every 5 years and assumes that the mortality benefit persists throughout the patient's life time (Sanders et al. 2005). Careful patient selection with a focus on patients who best fit the trials and are likely to die from arrhythmia and not from other non cardiac causes is important to insure the best utilization of this important and life saving therapy.

3. Defibrillator therapy in less common types of cardiomyopathy

Some of the inherited cardiomyopathies carry an increased risk of sudden cardiac death. We will review in this section the data behind ICD therapy in patients with two inherited disorders, first is Hypertrophic cardiomyopathy (HCM) and the second is arrhythmogenic right ventricular dysplasia./ cardiomyopathy (ARVD/C).

3.1 Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is an autosomal dominant disorder diagnosed by two-dimensional echocardiography and is characterized by hypertrophied and non-dilated LV in the absence of other causes of hypertrophy (no history of hypertension or aortic stenosis or any other cardiac or systemic disease causing hypertrophy) (Maron 2002; 2003). Histologically, there is myocardial disarray, abnormal microvascular circulation with mismatch between myocardial mass and blood supply as well as interstitial fibrosis (Maron et al. 1986; Varnava et al. 2001). All of these predispose to ventricular tachycardia and ventricular fibrillation putting the patients at risk of sudden cardiac death (Varnava et al. 2001). The disease can present at any age in life. Earlier registries from tertiary care centers overestimated the risk of sudden cardiac death due to selection bias (with the annual risk of death thought to be 3 to 6%). More recent population studies of unselected patients from community centers suggest a more benign prognosis (annual risk of death of 1%) (Maron et al. 1999; Kofflard et al. 2003). Despite all recent data, there is a subset of patients with HCM who are at high risk of sudden cardiac death. In fact HCM remains the most common etiology for SCD in patients younger than 40 years and it can be the first presentation in patients with HCM (Maron 2003). Patients who survived a cardiac arrest are particularly at high risk of dying suddenly. Data from registries suggest a number of markers that increase the risk of sudden cardiac death. These markers include one or more of the following: LV wall thickness > 30 mm (Maron et al. 1999), syncope (particularly exertional syncope) (Kofflard et al. 2003), family history of SCD, non-sustained VT on ambulatory holter of > 120 bpm and a blunted blood pressure response to exercise. High LV outflow gradient (> 30 mmHg) has also been considered as risk marker for sudden cardiac death (Maron et al. 2003).

There are no randomized trials examining the benefits of ICD therapy in this patient population, so the data supporting ICD therapy is derived from registry data in patients with HCM who received an ICD when found to be high risk by their treating cardiologist / Electrophysiologist (Maron et al. 2000). The last update from the registry included 506 patients with HCM with a mean age of 42 years. Patients received and ICD if they had

survived a cardiac arrest due to ventricular tachycardia or ventricular fibrillation (secondary prevention cohort of 123 patients) or if they had one or more risk factors of sudden cardiac death: unexplained syncope, family history of sudden cardiac death in one or more first degree relatives, massive LV hypertrophy or non-sustained VT on holter monitoring (Primary prevention cohort of 383 patients) (Maron et al. 2007). Based on this registry, patients with HCM who survived cardiac arrest have a high appropriate ICD discharges (10.6% per year). This risk is lower in patients with HCM who had an ICD for primary prevention (3.6% per year). A third of these patients were 30 years or younger. Amiodarone was used based on the physicians judgment and it did not prevent arrhythmia occurrence (27% of patients who were on amiodarone had appropriate shocks). A third of the patients who received an ICD for primary prevention and had appropriate ICD discharges had one risk factor only for sudden cardiac death. There was no difference between the risk factors in the prediction of SCD. Since this is a young population of patients, they are at risk of inappropriate shocks, which occurred in 27% of the patients and were mainly due to sinus tachycardia, atrial fibrillation or lead malfunction. ICD implantation was shown to be safe with a rate of infection of 3.8% and the rate of lead fracture or dislodgement of 6.7%. Implantation of ICD has become an acceptable therapy in patients with HCM who survived cardiac arrest or who have two or more of the aforementioned risk factors of sudden cardiac death. For patients with only one risk factor of sudden cardiac death, the decision to implant an ICD is left to the physician's judgment and a careful discussion with the patient and his / her family in regards to the risks, benefits and alternatives of ICD therapy. In our experience, the presence of only one risk factor for SCD does not guarantee a recommendation for implanting an ICD. The clinical scenario is to be taken into account, as well as the patient's age and his / her wishes. The decision to implant is more favorable in a young patient with HCM with family history of sudden cardiac death or in a young patient with severe LV wall thickness (>30 mm) but still the discussion should take into account the young age of the patient and his / her wishes. On the other hand the discussion is more careful in an old patient with HCM in his / her 60s with history of non-exertional syncope that seems to be vasovagal in origin, the fact that the patient survived to that age without any major cardiac arrest indicates a more benign prognosis. Table 2 lists the current recommendations for ICD implantation for patients with hypertrophic cardiomyopathy.

3.2 Arrhythmogenic Right Ventricular Dysplasia / Cardiomyopathy (ARVD/C)

Arrhythmogenic right ventricular Dysplasia/ Cardiomyopathy (ARVD/C) is an inherited myopathy characterized by fibrofatty infiltration of the right ventricular (RV) wall, with left ventricular involvement over time in some patients (Gemayel et al. 2001; Sen-Chowdhry et al. 2004). The RV wall becomes thin, and the most areas affected are the RV inflow, apex and RV outflow, which form what is called the triangle of dysplasia. Ventricular tachycardia in general has left bundle branch morphology and is caused by macro-reentry and there is evidence that adrenergic stimulation acts as a trigger for these arrhythmias (Leclercq et al. 1996). ARVC/D accounts for 3 to 10% of death occurring in patients younger than 65 years (Tabib et al. 2003) and is one of the causes of sudden cardiac death in athletes (Maron 2003). The Most common presentation is with palpitations (due to frequent ventricular ectopy and ventricular tachycardia), chest pain, and syncope (mostly exertional). With time patients might develop RV dilatation, LV involvement and heart failure. Most of the data are obtained from registries in the United States and Europe (either single centers or multicenter registries). Diagnosis of

ARVD/C is based on the European Task Force criteria (McKenna et al. 1994). Risk factors of sudden cardiac death include prior cardiac arrest, hemodyamically unstable VT and prior syncope. Some studies suggested that LV involvement, development of heart failure and marked RV dilatation are risk factors for sudden cardiac death (Hulot et al. 2004). The role of electrophysiologic testing in risk stratification is less clear, with some studies showing a high positive predictive value and some showing low positive and low negative predictive values in predicting arrhythmias and appropriate ICD shocks (Corrado et al. 2003; Roguin et al. 2004). Beta blockers and sotalol were thought to be the best in suppressing these arrhythmias; however, this is challenged in more recent studies (Marcus et al. 2009). ICD therapy is clearly indicated in patients who survived cardiac arrest or have sustained VT and is a class IIa indication in patients with ARVD/C who have unexplained syncope. Some patients experience repetitive shocks requiring administration of antiarrhythmic drug therapy as well as VT ablation. Since this is a young population, they are also likely to experience inappropriate shocks due to sinus tachycardia or other supraventricular arrhythmias. In general ICD therapy is life saving and is well tolerated and has become accepted standard of care in patients with ARVD/C who experience cardiac arrest, sustained VT, unexplained syncope or marked RV dilatation or LV involvement (Epstein et al. 2008). Table 2 lists the current guidelines for ICD implantation in this patient population.

4. Cardiac Resynchronization Therapy (CRT) in patients with heart failure and its effects on mortality

Cardiac Resynchronization Therapy (CRT) aims at correcting mostly intraventricular dyssynchrony by stimulating the left ventricle (preferably basal stimulation) or by simultaneously stimulating the left and right ventricles after a sensed or paced atrial beat or during atrial fibrillation. CRT has been shown to improve the cardiac hemodynamics in patients with systolic heart failure, including improvements in the systolic blood pressure and decrease in the pulmonary capillary wedge pressure (by up to 20% in some patients) (Blanc et al. 1997). The early trials had endpoints related to heart failure functional status (including the 6 minute walk test, NYHA functional class), LV systolic function and improvement in the LV dimensions (including LVEF, LV end systolic volume and LV end systolic volume index as well as LV end diastolic dimension). Other studies relied on clinical composite score (which combines death from any cause, recent hospitalization for heart failure, NYHA class as well as the global assessment score) to define response to CRT (Chung et al. 2008). However, there is poor correlation between clinical and echocardiographic measurements of response and there is disagreement about the best way to measure response in patients with heart failure receiving CRT (Fornwalt et al.). So far QRS duration remains an important criterion for patient selection for CRT. Kass and colleagues demonstrated that baseline QRS duration correlated with enhancement in the isovolumetric dP/dt_{max} ($r = 0.6$, $p = 0.02$), while changes in the QRS duration with pacing did not predict hemodynamic response (Nelson et al. 2000). Most of the trials on CRT involved patients with systolic heart failure with LVEF < 35% and NYHA class III or IV as well as a QRS duration of > 120 msec. A trial studying patients with narrow QRS in patients with systolic heart failure failed to show any benefit. Later studies included patients with NYHA class I and class II heart failure with endpoints related to death or hospitalization. This section will focus mainly on the studies that included mortality as an endpoint.

4.1 Cardiac resynchronization therapy trials in patients with moderate to severe heart failure

The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial involved implanting a CRT only device (with biventricular pacing only, no Defibrillator component). Patients were randomized if they had an LVEF < 35% and NYHA functional class III or IV heart failure despite optimal medical therapy and QRS duration of > 130 milliseconds (msec). a total of 453 patients were randomized after successful implantation of a CRT device to CRT ON (228 patients) and CRT OFF (225 patients) status for a period of 6 months (Abraham et al. 2002). The primary endpoint included the 6 minute walk test, quality of life score and NYHA class. A total of 453 patients were enrolled in the study. Patients assigned to CRT ON had 13% improvement in the 6-minute walk and in the quality of life score. The secondary endpoints also improved in the CRT ON arm including improvement in LVEF as well as peak oxygen consumption (VO2). The protocol specified safety variables that included an analysis of death or worsening heart failure. There was no difference in overall mortality (HR 0.73, 95% CI 0.34 to 1.54, p=0.40) but there was a decrease in hospitalization (HR 0.50, 95% CI 0.28 to 0.88, p= 0.02). The study did not specify mortality as a primary end point and was not powered enough to show differences in mortality.

The Multicenter Insync ICD randomized Clinical Evaluation (MIRACLE ICD) trial had a similar design to the MIRACLE study. Patients were included if they had LVEF < 35%, NYHA class III to IV despite optimal medical therapy and QRS duration of > 130 milliseconds and were at high risk of death from ventricular arrhythmias (Young et al. 2003). Almost two thirds of patients had an ischemic etiology and at least 60% were on beta blockers. All patients received a CRT-D device (total of 369 patients) of whom 182 had CRT OFF (controls) and 187 had CRT ON. At 6 months follow up, all patients with the CRT ON showed an improvement in the NYHA class (p=0.007) and the quality of life score (p=0.02). There was no difference in 6-minute walk distance (p=0.36) compared to the control group. Of the secondary endpoints, There was an improvement in the peak VO2 (p=0.04) and a trend towards reductions in the LV end systolic and end diastolic dimensions (p=0.06 for both) compared to the control group. The study did not show any difference in mortality (p=0.96) or hospitalization (p=0.69) between the two groups. Similar the to MIRACLE study, the MIRACLE ICD study had short follow up and was not powered enough to detect difference in mortality.

The CONTACT CD Biventricular Pacing study enrolled 490 patients with LVEF <35%, QRS > 120 msec and NYHA class II to IV despite optimal medical therapy and conventional indications for ICD implantation. Patients were assigned to CRT ON (245 patients) and CRT OFF (245 patients) for up to 6 months (Higgins et al. 2003). The primary endpoint was progression of heart failure, defined as all cause mortality, hospitalization for HF and ventricular tachycardia or ventricular fibrillation requiring device intervention. Secondary endpoints included peak oxygen consumption (VO2), 6-minute walk, NYHA class, quality of life as well as echocardiographic analysis. Patients with CRT ON had a 15% reduction in the composite HF progression but this was not statistically significant (p=0.35). However, patients with NYHA class III and IV had an improvement in the peak VO2 (p=0.003), 6-minute walk (p=0.03), NYHA class (p=0.0006) and QOL (0.02). Patients who had NYHA class I or II didn't show any improvement in any of the secondary parameters. One important finding in CONTACT CD trial is that patients with CRT ON had significant reductions in LV internal diameter in diastole (LVIDd) (p<0.001) LV internal diameter in systole (LVIDs) (p<0.001), and LVEF (p=0.02). Even patients with NYHA II had significant

improvement in the LV dimensions with CRT ON. The study was not adequately powered to detect a statistical difference in the primary endpoint of composite HF progression. This was due to the fact that the observed event rates were half the expected while designing the trial.

The Comparison of Medical Therapy, Pacing and Defibrillation on Heart Failure Study (COMPANION) enrolled 1520 patients with LVEF< 35%, NYHA class III or IV heart failure despite optimal medical therapy and QRS duration of > 120 msec in a 1:2:2 fashion to medical therapy versus biventricular pacing alone (CRT only) versus biventricular pacing with defibrillation (CRT-D) (Bristow et al. 2004). Almost 59% of the patients had ischemic cardiomyopathy and 82% were NYHA class III. The primary endpoint was death or hospitalization for any cause while the secondary endpoints included death from any cause. As compared to the medical therapy group, patients with CRT only (Biventricular pacemaker only) decreased the risk of death or hospitalization from any cause (HR 0.81, p=0.014) as did CRT-D group (biventricular defibrillator group) (HR 0.80, p-0.01). CRT only decreased the risk of death by 24% (p=0.059) while CRT-D decreased the risk of death by 36% (p=0.003). COMPANION was the first trial to show that CRT improves the quality of life, symptoms as well as decrease the risk of death or hospitalization for heart failure.

The Cardiac Resynchronization-Heart Failure Study (CARE HF) randomized 813 patients with LVEF < 35%, NYHA class III to IV heart failure despite optimal medical therapy and QRS duration > 120 msec (patients with QRS between 120 to 149 msec had to have two of the three echocardiographic parameters of dys-synchrony: an aortic pre-ejection delay of > 140 msec, an interventricular mechanical delay of > 40 msec or delayed activation of the posterolateral wall of the LV (Cleland et al. 2005). Patients assigned to the CRT group received biventricular pacemaker (no defibrillators). The primary endpoint was the composite of death or unplanned hospitalization for a major cardiovascular event. Secondary endpoint was death from any cause. Other secondary endpoints included quality of life, improvement in NYHA class and echocardiographic parameters (mainly ventricular function, mitral regurgitation). After a mean follow up of 29.4 months, patients treated with CRT (total of 409 patients) had less death or hospitalization for cardiovascular event (HR 0.63, 95% CI 0.51 to 0.77, p< 0.001) compared to patients with medical therapy only (404 patients). CRT also improved survival (HR 0.64, 95% CI 0.48 to 0.85, p< 0.002) (Figure 3). Patients with CRT had improvement in NYHA class, better QOL, and showed smaller area of mitral regurgitation and an improvement in the LVEF at 3 and 18 months post CRT. CARE HF was the first CRT only trial to show that biventricular pacing alone can improve survival. The lack of mortality benefit from CRT only arm in COMPANION might be due to the fact that patients in COMPANION trial were sicker, with over 55% having ischemic cardiomyopathy with mean LVEF of 22% while patients in CARE HF had a mean LVEF of 25% and only a third of them had ischemic cardiomyopathy. The added benefits of CRT on survival will be examined later by the RAFT study.

The Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) study randomized 172 patients with history of NYHA class III heart failure, LVEF <35% despite optimal medical therapy and QRS duration of <130 msec with evidence of mechanical dys-synchrony on echocardiography (defined as septal to lateral or septal to inferior wall delay >65 msec as measured by tissue doppler or septal to posterior wall delay >130 msec as measured by M Mode echocardiography (Beshai et al. 2007). Primary outcome was the improvement of peak oxygen consumption of > 1 ml per kilogram of body weight
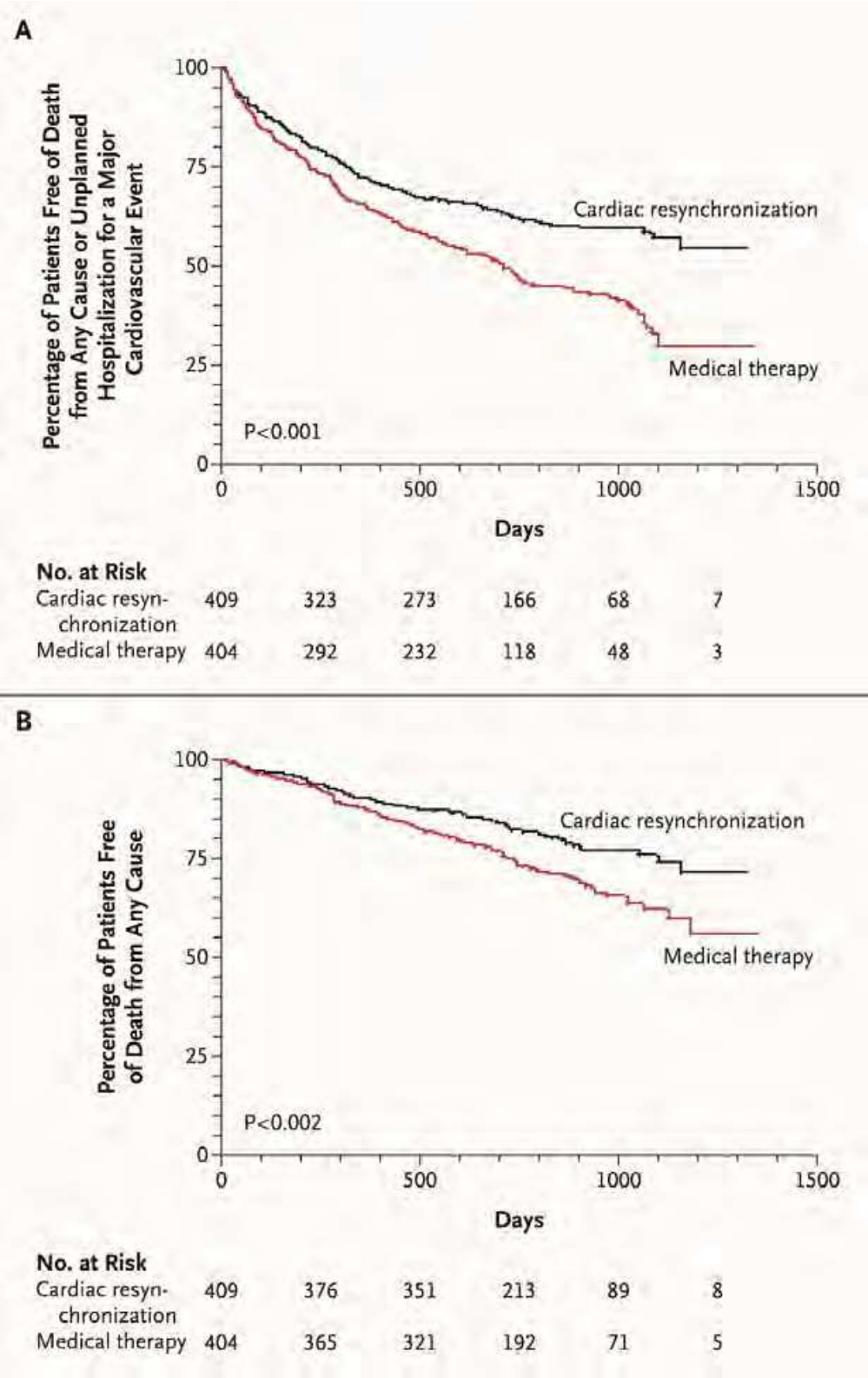
Fig. 3. Kaplan-Meier Estimates of the Time to the Primary End point of death or unplanned hospitalization for a major cardiovascular event (Panel A) and Death from any cause (Panel B). *(From Cleland, J. G., Daubert, J. C., Erdmann, E., et al. (2005). "The effect of cardiac resynchronization on morbidity and mortality in heart failure." New England Journal of Medicine, Vol. 352, No.15, (April, 2005): pp. 1539-1549, ISSN 1533-4406, with permission).*

per minute during cardiopulmonary exercise testing. The secondary outcomes were improvements in the 6 minute walk test, NYHA class and quality of life. All patients had a CRT device implantation and were assigned to CRT ON (n=76) or no CRT (n=80). After follow up of 6 months, there was no difference in the primary endpoint between patients with CRT and patients with no CRT (46% vs 44%, p=0.63). Patients in the CRT group with a QRS > 120 msec had significant improved in peak oxygen consumption at 6 months follow up (0.02) but patients in the CRT group with QRS <120 msec didn't have improvement in peak oxygen consumption at 6 months (p=0.45). There was no improvement in the quality of life measures (as measured by Minnesota living with Heart failure questionnaire) and in the 6-minute walk test in both groups of patients regardless of the QRS duration. Patients with CRT on had an improvement in the NYHA class at 6 months compared to patients with no CRT regardless of the QRS duration (p=0.006).

4.2 Cardiac resynchronization therapy trials in patients with mild heart failure

The Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction Study (REVERSE) trial was the first CRT trial to include patients with NYHA II and asymptomatic NYHA class I patients with LV dysfunction. A total of 610 patients underwent CRT device implantation and were randomized to CRT ON (419 patients) and CRT OFF (191 patients). Inclusion criteria included LVEF <40%, NYHA functional class I or II heart failure with a QRS 120 msec (Linde et al. 2008). Mean follow up was for 12 months. The primary end point was the heart failure (HF) clinical composite response (which included heart failure hospitalization, NYHA class and global assessment score). Secondary endpoints included LV end-systolic volume index and hospitalization for worsening HF. There was no difference between the two groups in the HF clinical composite score (which compared only the percent worsened) (p = 0.10). Patients assigned to CRT-ON experienced a greater improvement in LV end-systolic volume index (-18.4 ± 29.5 ml/m^2 vs. -1.3 ± 23.4 ml/m^2, p < 0.0001) and had a 53% relative risk reduction in time to first HF hospitalization (p=0.03). There was no difference between the two groups in the 6- minute walk test and in the quality of life scores. The improvement in LV end systolic volume index was similar in patients with NYHA I and NYHA II. The rate of LV lead implantation related complications was 10%. These complications were mostly due to LV lead dislodgement or diaphragmatic stimulation.

The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization therapy (MADIT-CRT) randomized 1820 patients with LVEF <30%, NYHA class I or II HF and QRS duration of > 130 msec in a 3:2 design to cardiac resynchronization therapy with defibrillation capacity (CRT-D) (1089 patients) and to ICD only group (731 patients). The primary endpoint was death from any cause or hospitalization for heart failure (Moss et al. 2009). Secondary endpoints included death from any cause and heart failure hospitalization alone. Follow up was for 4.5 years. Patients who received CRT-D had lower risk of death or hospitalization for heart failure (HR 0.66, 95% CI of 0.52 to 0.84, p=0.001) compared to the ICD only group. There was no difference in death from any cause between the two groups (HR 1.00, 95% CI of 0.69-1.44, p=0.99). The rate of hospitalization was significantly lower in the CRT-D group compared to the ICD only group (HR 0.59, 95% CI of 0.47 to 0.74, p<0.001). Patients with ischemic and non-ischemic cardiomyopathy benefited similarly from CRT. Subanalysis

of MADIT CRT showed that female patients (n=453, 25%) were more likely to have non-ischemic cardiomyopathy and left bundle branch block (LBBB) compared to male patients. Female patients were more likely to have reverse remodeling by echocardiography and had a 69% relative risk reduction of death or heart failure (HR of 0.31, p<0.001) (Arshad et al.). Patients with QRS duration > 150 msec had greater benefit from CRT (HR 0.48, 95% CI 0.37 to 0.64) compared to patients with QRS duration < 150 msec (HR 1.06, 95% CI 0.74 to 1.52, p=0.001 for interaction). Patients assigned to the CRT-D arm had significant reduction in LV end diastolic volume index (–26.2 versus –7.4 mL/m²), LV end systolic volume index (–28.7 versus –9.1 mL/m²) as well as improvement in LVEF (11% versus 3%) compared to the ICD only group. After adjusting for baseline variables, for every 10% reduction in the LV end diastolic volume index, there was a 40% reduction in the risk of death or heart failure hospitalization (Solomon et al.). Furthermore MADIT CRT measured echocardiographic response as a decrease in LV end systolic volume > 25%. Using this definition, 529 patients assigned to the CRT-D arm responded to CRT and were less likely to have ventricular tachyarrhythmia (VT or VF) and inappropriate shocks. Analysis of the data showed that for every 10% reduction in LV end systolic volume, there is a 20% decrease in the risk of ventricular tachyarrhythmias (p<0.001) even after adjusting for other clinical risk factors including age, QRS duration, left bundle branch block, and blood urea nitrogen (BUN) (Barsheshet et al.).

The Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) randomized 1798 patients with LVEF <30%, NYHA II to III heart failure and QRS duration of >120 msec or a paced QRS duration of > 200 msec to either ICD alone or Biventricular defibrillator (CRT-D) (Tang et al.). Mean follow up was for 40 months and the primary endpoint was death or hospitalization for heart failure while secondary endpoints included death from any cause, death from cardiovascular cause and heart failure hospitalization. Most of the patient had NYHA class II (80%) and had ischemic etiology (64%). Patients with CRT-D had less death and heart failure hospitalization compared to the ICD group (HR 0.75, 95% CI of 0.64 to 0.87, p <0.001). CRT-D also improved survival compared to ICD alone (HR 0.75, 95% CI 0.62-0.91, p=0.003) (Figure 4). There was less heart failure hospitalizations with CRT-D group compared to ICD only group (HR 0.68, 95% CI of 0.56 to 0.83, p<0.001). There was no difference in the primary and secondary endpoints in patients with ischemic and non-ischemic cardiomyopathy. Patients with wider QRS (>150 milliseconds) had better survival than patients with QRS < 150 msec. However, patients with CRT-D had more 30 days adverse events compared to the ICD alone group (p<0.001), these were mostly device related complications.

These trails established CRT as an important therapy for patients with heart failure, LVEF < 35% and NYHA class III to IV. The only measure of dys-synchrony that stood the test of time is the QRS duration. Even though there is disagreement in the literature in the measurement of "response". At least two thirds of patients with CRT show clinical improvement in their functional status. CRT has been proven to improve survival independently as shown in the CARE HF trial, and it also improves survival above and beyond ICD therapy as shown in the RAFT trial. The guidelines for implantation for CRT in patients with systolic heart failure are listed in Table 5. These guidelines were written in 2008, and do not reflect the recent evidence of the benefits of CRT in milder forms of heart failure that was found in the REVERSE, MADIT CRT and RAFT trials.
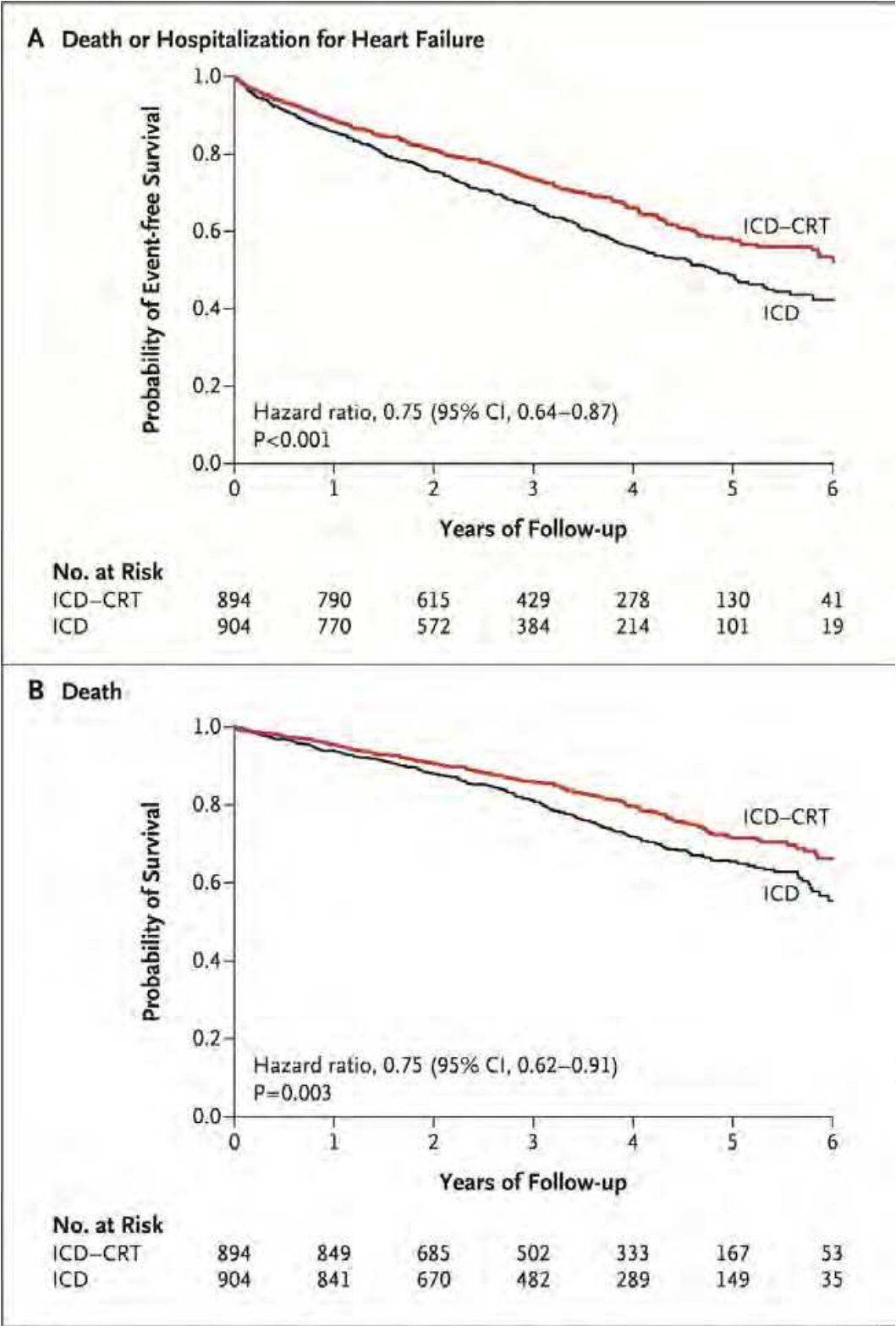
Fig. 4. Kaplan Meier Estimates of Death or Hospitalization for Heart Failure (Panel A) and Death from Any Cause (Panel B). (From Tang, A. S., Wells, G. A., Talajic, M., et al. "Cardiac-resynchronization therapy for mild-to-moderate heart failure." New England Journal of Medicine Vol. 363, No.25, (December, 2010): pp. 2385-2395, ISSN 1533-4406, with permission)

Class I (General agreement of benefit of CRT)

1. CRT with or without an ICD is indicated for the treatment of for patients are in sinus rhythm who have LVEF ≤ 35%, a QRS duration ≥ 120 milliseconds, NYHA functional Class III or ambulatory Class IV heart failure symptoms with optimal recommended medical therapy.

Class IIa (Weight of evidence is in favor of CRT)

1. CRT with or without an ICD is indicated for patients in sinus rhythm who have LVEF ≤ 35%, a QRS duration ≥ 120 msec, NYHA functional class III or ambulatory class IV heart failure symptoms with optimal recommended medical therapy.
2. CRT is reasonable for patients with LVEF ≤ 35%, QRS duration ≥120 milliseconds, NYHA functional Class III or ambulatory Class IV heart failure symptoms with optimal recommended medical therapy and who have frequent dependence on ventricular pacing.

Class IIb (Efficacy of CRT is less well established)

1. CRT may be considered for patients with LVEF ≤ 35% with NYHA functional Class I or II symptoms who are receiving optimal recommended medical therapy and who are undergoing implantation of a permanent pacemaker and/or ICD with anticipated frequent ventricular pacing.

Class III (General agreement that CRT is less effective and might be harmful)

1. CRT is not indicated for asymptomatic patients with reduced LVEF in the absence of other indications for pacing.
2. CRT is not indicated for patients whose functional status and life expectancy are limited predominantly by chronic non-cardiac conditions.

Table 5. Recommendations for cardiac resynchronization therapy based on the ACC/AHA/HRS 2008 Guidelines for Device Based Therapy. CRT: Cardiac Resynchronization Therapy. ICD: Implantable Cardioverter Defibrillator. NYHA: New York Heart Association

5. Defibrillator shocks, their impact on quality of life and prognosis

5.1 Impact of defibrillator shocks on quality of life

From all the studies presented earlier, it is clear that ICD therapy prevents sudden cardiac death. However, ICD shocks can be painful and have been shown to affect the quality of life in both primary and secondary prevention trials. Patients with ICD can receive inappropriate shocks due to atrial fibrillation (AF), supraventricular tachycardia (SVT) or inappropriate sensing from the device. The quality of life (QOL) was assessed in the AVID trial as a secondary endpoint using the Medical Outcomes Short Form 36 item questionnaire (SF-36). Of the 905 patients enrolled in QOL analysis, 800 survived for longer than 1 year. Both treatment groups (ICD group versus antiarrhythmic group) had significant impairment in both physical functioning and mental well-being(Schron et al. 2002). ICD shocks were independently associated with reduction in both physical functioning and mental well-being. The CIDS trial also measured QOL, in the 400 patients who survived for

> 1 year, patients assigned to the ICD group had an improvement in their quality of life scores compared to patients assigned to amiodarone. However, patients having frequent shocks (>5 shocks) had reduced QOL.

The SCD-HeFT trial also collected data on the quality of life using two different scales: The Duke Activity Scale Index (DASI) reflecting the overall physical functioning and the SF-36 Mental Health Inventory 5 which measures psychological well being (Mark et al. 2008). Data were collected at baseline, 3, 12 and 30 months of follow up. A total of 2479 patients (98%) enrolled in SCD-HeFT completed the quality of life portion of the study. Patients receiving ICD therapy and patients assigned to placebo had similar DASI scores and SF-36 MHI 5 scores at baseline. The psychological well being of patients receiving an ICD was significantly better at 3 months and 12 months compared to patients receiving placebo. There was no difference in the physical functioning at baseline or at 3, 12 or 30 months in the ICD group versus the placebo group. The quality of life of patients who received an ICD shock a month before the screening was significantly worse in multiple aspects (physical, psychological, social and self related health).

5.2 Impact of defibrillator shocks on prognosis

The SCD-HeFT Trial also evaluated the prognostic impact of ICD shocks in patients with ischemic and non-ischemic cardiomyopathy. Most of the patients received a single chamber ICD programmed to shock only therapy with no antitachycardia pacing involved. (Poole et al. 2008). Patients (n=811) were followed for 45.5 months and a third of patients (n=269) received ICD shocks. Patients who received appropriate ICD shock (n=128) were at increased risk of death (HR 5.68, 95% CI of 3.97 to 8.12, p < 0.001) compared to patients with no appropriate shocks. Patients who received inappropriate shocks were also at increased risk of death (HR 1.98, 95% CI of 1.29 to 3.05, p=0.002) compared to patients with no inappropriate shocks. Atrial fibrillation was the most common reason for inappropriate ICD shocks and the most common cause of death in patients receiving any shock was progressive heart failure.

Inappropriate shocks were examined in the MADIT-II trial. Of the 719 patients who received an ICD, inappropriate shocks occurred in 83 patients (11.5%). Inappropriate shocks represented a third (31.2%) of total shocks (Daubert et al. 2008). Independent predictors of inappropriate shocks included atrial fibrillation (HR = 2.9, P<0.01), smoking (HR 2.18, P=0.03), diastolic blood pressure of > 80 mmHg (HR = 1.61, P= 0.04) and antecedent appropriate shocks (HR = 2.25, P= 0.03). Again, inappropriate shocks were most likely due to AF (44%), SVT (36%) or abnormal sensing (20%). Implantation of a dual chamber ICD did not decrease the rate of inappropriate shocks compared to single chamber ICD implantation (38.6% versus 44% respectively, p=0.31). Any shock whether appropriate or inappropriate was associated with significant increase in mortality (HR 4.08, p<0.01). Inappropriate shocks were associated with a 2 fold increase in mortality (HR is 2.29, p=0.03) while appropriate shocks had a 3 fold increase in mortality (HR 3.36, p<0.01). Electrical instability in the form of VT or VF or atrial fibrillation could be markers of deteriorating heart function and pump failure(Obadah Al Chekakie 2009). It is unclear if the VT or VF that the patient experiences heralds progressive pump failure, or whether the fact that shocks my increase mortality due to their negative effect on contractility in this high risk population or if both assumptions are true.

5.3 Device programming studies: Safety, effectiveness and impact on quality of life

Since Shocks are associated with lower quality of life and increase mortality, attempts at reducing shocks (both appropriate and inappropriate) became the focus of several studies. Antitachycardia pacing (ATP) has been shown to terminate 78 to 94% of slow VTs (188 bpm) (Peinado et al. 1998). The PAINFREE RX II trial randomized 634 patients with ICDs to standardized ATP (n=313 patients) versus shocks (n=321 patients). The programming in the Standarized ATP arm included two main parameters: First programming ATP in the fast VT zone of 188 to 250 bpm, at 8 pulses and 88% of VT cycle length. Second is extending the detection to 18 of 24 beats to avoid shocking ventricular tachycardia that was going to terminate anyway. The primary objective was to demonstrate that ATP will not prolong treatment > 6 seconds compared to the shock arm. Secondary objectives included the QOL, ATP efficacy and acceleration and syncope (Sweeney et al. 2005). After mean follow up of 11+/- 3 months, 4230 ICD counters were retrieved, and electrograms were only available in 1827 episodes. A third of the shocks was deemed inappropriate and due to SVT and 0.2% were due to noise. Only 73% of total shocks were due to true ventricular arrhythmias. Of these, 431 (58%) were detected as VT, 32% as Fast VT and 10% as VF. ATP was successful as initial therapy in 81% of the episodes and failed in 54 episodes, of which 49 episodes were shocked while 5 were terminated by a second ATP therapy. ATP did not prolong therapy duration (median duration was 10 seconds in the ATP arm versus 9.7 seconds in the shock arm) and there was no significant difference in the acceleration of VT/VF between the two arms. Syncope was very rare in the two arms (2 in the ATP group and 1 in the shock arm) and the first shock success was identical between the two arms. There was no difference between the two groups at baseline in the QOL scores as assessed by the SF-36. Patients assigned to the shock arm had an improvement in the bodily pain scores at 12 months but no change in the other SF-36 subscales. While patients assigned to the ATP arm had significant improvement in 5 subscales (bodily pain, social functioning, role emotional, physical functioning and role physical). This trial established the safety and efficacy of ATP in the fast VT zone and the safety of extending the detection duration to 18 out of 24 beats, which led to a decrease in shocks (The patients assigned to the shock arm had 147 detected FVT episodes with only 99 episodes receiving therapy). This will be an important factor in the design and implementation of the PREPARE study.

The Primary Prevention Parameters Evaluation Study (PREPARE) study compared 700 patients who had received an ICD or Biventricular defibrillator for primary prevention within 6 months of enrollment (Wilkoff et al. 2008). The control group for the ICD patients was taken from the EMPIRIC trial while the control group for the Biventricular ICD (BiV ICD) arm was from the MIRACLE ICD trial. The cohort of the PREPARE study had the following programming parameters: Initial detection for VT at rate of >182 bpm, with ATP programmed to fast VT of 182 to 250 bpm, with detection prolonged to 30 of the 40 intervals to avoid shocking VT that was going to terminate anyway, programming SVT discriminators to arrhythmias < 200 bpm to prevent inappropriate shocks. The primary endpoint of the study was the morbidity index defined as 1) device related cardioversion or defibrillation whether appropriate or inappropriate, 2) syncope secondary to arrhythmia or presumed arrhythmia and 3) untreated sustained symptomatic VT/VF events. The PREPARE study patients were less likely to receive a shock for any cause in the first year as compared to the control cohort (8.5 % vs 16.9%, p<0.01) and were also less likely to receive inappropriate shocks even after correcting for differences in baseline variables including

mean LVEF, hypertension, history of ischemic heart disease, syncope and baseline use of beta blockers. The morbidity index incidence density was significantly lower in the PREPARE cohort compared to the control cohorts (HR 0.26 versus 0.69, 95% CI of 0.2 to 0.72, p=0.003). Importantly, only 12 of the 40 syncope episodes were judged to be due to arrhythmia, and of those, only 11 were due to PREPARE programming. The PREPARE study established the efficacy of empirically programming the ICD detection and therapy to minimize both appropriate and inappropriate shocks. This is true for patients receiving ICD therapy for primary prevention only.

In summary: ICD therapy prevents sudden cardiac death but patients who receive an ICD shock have increased morbidity and mortality and poor quality of life. Programming the device can help minimize ICD shocks, whether appropriate or inappropriate. Patients with ICD therapy who receive a shock should be followed closely since they are at increased risk of pump failure.

6. Conclusion

Implantable cardioverter defibrillator therapy is important in sudden cardiac death prevention in patients with ischemic and non-ischemic cardiomyopathy as well as survivors of cardiac arrest. Cardiac resynchronization therapy with and without an ICD improves the quality of life and leads to reverse remodeling and independently prevents sudden cardiac death in patients with QRS > 120 msec and LVEF < 35% who are on optimal medical therapy. Defibrillator shocks are associated with adverse outcomes and pump failure. Careful patient selection and sophisticated programming can help prevent sudden cardiac death without compromising the quality of life of the patients.

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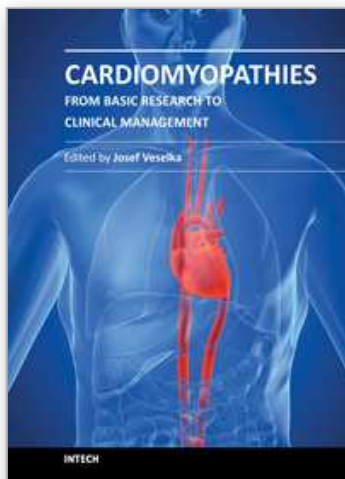
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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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