Review Article

Sudden Cardiac Death: A Race for Time

Mahyar Pourriahi¹, Mahbod Pourriahi², and John Kassotis*³

¹Department of Internal Medicine, SUNY Downstate Medical Center, Brooklyn, USA
²Department of Bioengineering, University of Toledo, Toledo, USA
³Division of Cardiovascular Medicine -Electrophysiology Section, SUNY Downstate Medical Center, USA

Abstract

Despite significant advances, the incidence of sudden cardiac death (SCD) remains high. With greater public awareness and ease of access to defibrillators (e.g. AEDs), we are hopeful that both the morbidity and mortality of SCD will improve significantly. However, we believe the greatest impact will be derived from focusing our attention on identifying and managing patient’s known to have a predisposition for SCD. Given the improvements in technology and refinements in implantation techniques, the placement of implantable cardioverter defibrillator has emerged as the standard of care for primary and secondary prevention. The purpose of this review is to identify for the reader which patients are at high risk for SCD and subsequent management.

INTRODUCTION

A sudden cardiac death (SCD) is responsible for over 300,000 to 400,000 deaths in the United States annually [1-3]. SCD is an unexpected fatality that occurs either an hour within the onset of symptoms or 24 hours within the patient’s last known well [4,5]. Despite advances in cardiopulmonary resuscitation (CPR) protocols, prognosis remains poor. 8% of patients who experience an out-of-hospital cardiac arrest (OHCA) survive until hospital discharge; whereas 21% of patients survive to discharge after an in hospital cardiac arrest [4,5]. A prompt initiation of effective CPR and defibrillation is instrumental in increasing survival after an OHCA; survival decreases 7-10% with each minute of delay in defibrillation, even if other elements of CPR have been initiated [1,5]. Further, 70% of the patients who experience an OHCA demonstrate substantial coronary artery disease (CAD). Therefore, the risk factors for SCD generally parallel those for CAD (e.g. diabetes mellitus, hyperlipidemia, and hypertension) [2-4,6]. Additionally, non-CAD related cardiomyopathies increase the risk of SCD [7]. A higher risk of ventricular arrhythmias occurs following a myocardial infarction (MI). This may be attributed not only to a reduction in left ventricular (LV) systolic function but also to alterations in the myocardium, including a presence of a scar, dispersion of ventricular refractoriness, and an alteration in conduction velocity. The resultant LV function, ejection fraction (EF) ≤ 35 %, is a major independent predictor of total and sudden cardiac mortality in patients with congestive heart failure secondary to systolic dysfunction [3]. Most commonly arrhythmic SCD is due to the degeneration from ventricular tachycardia (VT) to ventricular fibrillation (VF), with a transition to pulseless electrical activity (PEA) and/or a systole. Due to the rapid progression of SCD and its associated high mortality, a major emphasis has been placed on identifying and managing these patients before their first life-threatening event. In addition, a major emphasis has been placed on expanding the availability of CPR, increasing access to defibrillators (e.g. AEDs), and optimizing medical management after the return of spontaneous circulation (ROSC) [1,6].

Ventricular arrhythmias

Ventricular arrhythmias range from benign premature ventricular complexes (PVCs) to VT and VF. In general, PVCs are ectopic beats with a widened QRS complex morphologically distinct from the QRS found in sinus rhythm. The duration and morphology are essential features in the classification of VT. VT is defined as 3 or more ventricular complexes, occurring at a rate greater than 100 beats per minutes. Non-sustained VT (NSVT) is defined as a VT lasting less than 30 seconds. Sustained VT has a duration of more than 30 seconds and often requires emergent medical management due to hemodynamic compromise or degeneration to VF. When the VT exhibits a homogenous QRS morphology it is referred to as monomorphic VT, while polymorphic VT is characterized by QRS complexes with changing and variable morphologies. At the extreme end of the spectrum of ventricular arrhythmias is ventricular fibrillation, which shows no discernible QRS or P wave activity. VF shows no evidence of identifiable gross myocardial contraction and is characterized by multiple micro-reentrant pathways. VF can rapidly degenerate.

to either PEA and/or a systole. VF universally results in death unless emergent intervention (e.g. defibrillation) is undertaken.

Malignant ventricular arrhythmias result in SCD, with a substantial number of affected individuals having CAD [8]. Often times the first manifestation of an acute coronary syndrome is SCD. Alternatively, a small but interesting subgroup of patients experiencing SCD is those patients with a heritable disorder. Disorders including the long QT syndrome, short QT syndrome, catecholaminergic VT, arrhythmogenic RV dysplasia, Brugada syndrome, and Wolff-Parkinson-White syndrome can predispose an individual to SCD. While our understanding of these disorders has improved, much remains unknown. Many of these disorders exhibit a genetic predisposition due to polymorphisms and mutations leading to channelopathies that can result in the genesis of malignant ventricular arrhythmias.

SCD Risk Stratification

Recently, a prediction model utilizing 12 independent variables, risk factors derived from the Atherosclerosis Risk in Communities study (ARIC study), has been proposed as a tool for the risk stratification of SCD. The variables include: age, race, sex, active smoking, elevated systolic blood pressure, use of antihypertensive medications, diabetes mellitus, elevated serum potassium, reduced serum albumin, decreased estimated glomerular filtration rate, and an increased QT interval. Investigators, derived the prediction model from the ARIC cohort study and validated this model using the Cardiovascular Health Study (CHS). A 10 year follow up of the model exhibited a superior discrimination for predicting SCD risk compared to the 2013 American College of Cardiology/American Heart Association Pooled Cohort risk equation [9]. An improved SCD risk stratification model will enhance our ability to recognize currently unidentified patients for SCD primary prevention.

Assessment of Patients post-ROSC

Risk assessment of a patient with OHCA post-ROSC begins with a review of the data obtained from emergency medical services, including a continuous ECG, vital signs, and mentation. Attempts should be made to transport the patient to a center capable of performing percutaneous coronary interventions (PCI). The immediate evaluation of hemodynamics and continuous ECG monitoring should be established. With a high correlation between CAD and the presence of CAD, the first decision is to determine whether an immediate PCI and/or therapeutic hypothermia (TH) would benefit the patient. If available, a thorough history- including current angina, smoking status, and previous history of syncope, CAD, arrhythmia, heart failure, hypertension, and diabetes- should be obtained. In addition, every effort should be made to obtain a comprehensive family history. Additionally, history should be obtained regarding any unexplained deaths in family members younger than 35 years of age and sudden infant death syndrome. After a careful physical examination, diagnostic testing should include an evaluation of electrolytes, kidney function, cardiac biomarkers, and a 2D transthoracic echocardiography.

The role of genetic testing is controversial. Genetic testing and counseling should be recommended when a high-risk gene is identified in the patient with the phenotype of one of the aforementioned hereditary electrical diseases. It is the opinion of the authors that all first line family members should be screened and referred to a geneticist for counseling. In the absence of a herald event, the random use of genetic testing is not recommended primarily due to a low yield.

Immediate Management

The immediate goal in the hospital is to optimize cardio-cerebral perfusion/recovery. This includes an assessment of organ perfusion, and may require acute coronary intervention, therapeutic hypothermia, and neurological monitoring [10]. Patients who remain comatose (lack of meaningful response to commands) post-ROSC may receive TH. TH involves reducing the body temperature to 32-34°C for 12 to 24 hours after ROSC. An improved neurological recovery has been associated with early initiation of the TH protocol. The length of therapy ranges between 12-24 hours post VF or PEA/asystole [10-13]. The Hypothermia After Cardiac Arrest Study Group (2002) and Don (2009) both observed a statistically significant improvement in neurological function in patients who received TH post-ROSC after VF [12,13].

TH can be performed safely in conjunction with PCI [10]. While immediate PCI post-ROSC with a ST elevation myocardial infarction (STEMI) or a new left bundle branch block (regardless of mental status) is a class I-B indication, its utilization in all SCD cases without an obvious non-cardiac etiology is gaining support [10,14-16]. Dumas’s (2010) retrospective study examining the utilization of PCI for OHCA reported that 96% of patients with a STEMI post-ROSC and 58% of patients without ST-segment elevation had at least one significant coronary artery lesion. In addition, they observed an increase in survival after a successful PCI versus no PCI in both the EST-elevation (51% vs. 31%, p<0.001) and the non-STEMI elevation group (47% vs. 31%, p<0.001) [15].

Long term management

Long-term management of patients should focus on primary and secondary prevention. A thorough assessment of an ECG with short and long term trans-telephonic monitoring may shed light on possible electrical abnormalities and predisposing genetic findings that can sustain a malignant ventricular arrhythmia. Among the available pharmacological therapies, beta-blockers have become the cornerstone of post-MI therapy. However, the overall mortality benefit conferred by this class of drugs shows a limited role in decreasing SCD. Amiodarone, a class III antiarrhythmic agent, affects the sodium, potassium, and calcium channels, as well as antagonizing the adrenergic receptors [6]. Amiodarone has demonstrated benefits in the primary prevention of SCD; its use for secondary prevention is not well established. The CAMIAT and EMIAT trials demonstrated a statistically significant reduction in arrhythmic death (AD) with a relative risk reduction of 48.5% and 35%, respectively; there were limited to no effects on all-cause mortality [17,18]. Amiodarone’s use in secondary prevention remains limited with some studies
Amiodarone's role versus no treatment in secondary prevention was assessed in the OPTIC and ALPHEE trial. The OPTIC trial, Amiodarone plus beta-blocker significantly reduced the risk of shock as compared with beta-blocker alone, with a hazard ratio (HR) = 0.27 (p=0.001) [19]. ALPHEE trial assessed the HR for sudden death, which was found to be 4.46 (p=0.0207) [20]. The result from the amiodarone versus other antiarrhythmic drugs trials for the secondary prevention of SCD was inconclusive and statistically insignificant, as seen in Table (1) [20-22].

Implantable cardioverter-defibrillators (ICD) have taken on a primary role in the management/prevention of SCD, displacing pharmacological therapies as can be seen in Table (2) [23-34]. The vast majority of trials have exhibited a more favorable outcome of ICD as compared to pharmacological therapies. In the trials where ICD’s showed no benefit (e.g. CASH), the mean EF was considerably higher. An ICD is designed to identify and terminate dangerous ventricular arrhythmias. In the case of monomorphic VT, the ICD will attempt to use anti-tachycardia pacing, painless therapy, to terminate the arrhythmia. This is achieved by pacing at a higher rate, referred to as overdrive (OD) pacing compared to the VT. In the event that OD fails or the rhythm degenerates to VF, the devices will administer a shock (defibrillation). Both the MADIT-II and SCD-HeFT trials demonstrated a significant reduction in mortality in the ICD arm of the studies. Patient's post-MI with EF < 30% may qualify for ICD insertion based on MADIT-II criteria [23,24].

Patients with New York Heart Association (NYHA) class II, III and IV congestive heart failure, with EF < 35% and a QRS duration greater than 120 milliseconds, benefit from cardiac resynchronization therapy (CRT) as seen in the COMPANION and CARE-HF trials [6]. CRT reduces ventricular desynchrony by pacing either ventricles or a singular ventricle in patients with a bundle branch block. Patients with NYHA class IV HF are candidates for CRT pacing, without defibrillation therapy. The improvements in mortality and a decreased in hospitalizations are believed to be a caused by the synchronization of ventricles during systole with a resulting improvement in cardiac output [6].

Table 1: Amiodarone trials for primary or secondary prevention.

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<tr>
<th>Trial</th>
<th>Type</th>
<th>Inclusion criteria</th>
<th>Study divide</th>
<th>Results</th>
<th>Conclusion</th>
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<tr>
<td>CAMIAT17 Canadian Amiodarone Myocardial Infarction Arrhythmia Trial</td>
<td>Randomized double-blind placebo-controlled trial to assess the effect of amiodarone on the risk of VF or AD after aMI in patients experiencing frequent PVCs.</td>
<td>age ≥ 19, acute MI within the previous 6-45 days, 10 PVCs per hour or 1 run of VT</td>
<td>1202 patients (606 in the amiodarone group and 596 in the placebo group.)</td>
<td>In the efficacy analysis, resuscitated VF or AD; relative-risk reduction 48.5% [95% CI 4.5-72.2; p &lt;0.016].</td>
<td>Amiodarone reduced the incidence of VF/AD in post MI patients with frequent PVCs.</td>
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<td>EMIAT18 European Myocardial Infarct Amiodarone Trial</td>
<td>Randomized double-blind placebo-controlled trial to assess whether amiodarone reduced all-cause mortality in high risk patients.</td>
<td>18-75 years, post-MI, LVEF≤40%</td>
<td>1446 patients (743 in the amiodarone group and 743 in the placebo group)</td>
<td>All-cause mortality: [RR=0.99, p 0.96] Intention to treat arrhythmic deaths: 35% reduction in risk [p 0.05]</td>
<td>The results did not support prophylactic use of amiodarone in patients post MI and LV dysfunction. However, the reduction in AD support the use of amiodarone in patients for whom antarrhythmic therapy is indicated.</td>
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<td>Optic19 Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients</td>
<td>Randomized controlled trial with blinded adjudication of events of 412 patients to determine whether amiodarone plus beta-blocker or Sotalol are better than beta-blocker alone for prevention of ICD shocks.</td>
<td>Patients post ICD implantation within 21 days prior to randomization; LVEF≤40%, sustained VT, VF or CA; inducible VT or VF by programmed ventricular stimulation, or unexplained syncope with VT or VF</td>
<td>412 patients (140 in the amiodarone + beta-blocker, 138 beta-blockers alone, and 134 Sotalol group).</td>
<td>A reduction in risk of shock was observed with use of either amiodarone plus beta-blocker or Sotalol vs beta-blocker alone [HR = 0.44; 95% CI 0.28-0.68; P .001]. Amiodarone plus beta-blocker significantly reduced the risk of shock compared with beta-blocker alone [HR = 0.27; 95% CI 0.14-0.52; P .001].</td>
<td>Amiodarone plus beta-blocker is reduces the risk for shock and is more effective than Sotalol, but has an increased risk of drug-related adverse effects.</td>
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Role of Non-Invasive Diagnostic Testing

Autonomic nervous system (ANS) dysfunction seems to play a role in the genesis of SCD. The scarred myocardium demonstrates increased catecholamine sensitivity with a disproportionate shortening of myocardial tissue refractoriness. Changes in the conduction velocity and refractoriness are instrumental in the genesis of ventricular arrhythmia [3,8]. A means of non-invasively assessing the integrity of the ANS is Heart rate turbulence (HRT). HRV analyzes the temporal variation between heart beats and assesses the degree of autonomic desensitization, with patients with systolic dysfunction exhibiting unopposed sympathetic stimulation. HRV has been previously utilized for the conduction velocity and refractoriness are instrumental in the genesis of ventricular arrhythmia [8].

Heart rate turbulence (HRT) examines the RR interval time following PVC, which exhibits an acceleration followed by a deceleration. This variation is believed to be due to a baroreceptor response, a parasympathetic inhibition occurs due to a reduction in pulse pressure following PVC. This in turn results in a compensatory increase in heart rate (HR) due to the post-compensatory pause due to parasympathetic inhibition and sympathetic activation, resulting in an increased pressure [8]. The deviation of HRT from baseline is believed to be predictive of ventricular arrhythmia genesis and propagation.

T wave alternans (TWA) is a beat-to-beat measurement of amplitude, waveform, and duration of the repolarization in the ST-T wave complex. There are currently no gold standards for data processing, noise reduction, or utilization in SCD assessment [8].

Newer devices such as MARS® ambulatory ECG analysis system from GE analyzes a twenty-four-hour recording using turbulence correlation, frequency domain indices, and TWA algorithm to provide measurements for purposes of risk stratification. While the data derived from these non-invasive techniques is promising, their role in clinical practice remains to be established and lacks consensus.

CONCLUSION

Despite major advances in the acute management of patients following a cardiac arrest, SCD remains a major cause of morbidity and mortality. Increased accessibility to defibrillators, immediate catheterization, therapeutic hypothermia, and risk stratification for ICD placement has played an important role in the management of patients’ post-ROSC. Identification of high risk patients and their management, prior to sentinel events stands as the cornerstone for SCD prevention. In addition, implantation of an ICD, with and without CRT capabilities, is the therapeutic modality of choice in the primary and secondary prevention of SCD. Newer non-invasive diagnostic modalities show promise in enhancing our understanding of this disease process and may assist in further identification of an at-risk population.
Table 2: ICD and CRT Trials.

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<tr>
<th>Trial</th>
<th>Primary outcome tested</th>
<th>Method</th>
<th>Results</th>
<th>Conclusion</th>
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<tr>
<td>SCD-HeFT [23] The Sudden Cardiac Death in Heart Failure Trial</td>
<td>Does the insertion of an ICD for primary prevention affect the all-cause mortality in patients with mild-to-moderate congestive heart failure?</td>
<td>N=25,21 patients with NYHA class II or III CHF, LVEF $\leq 35$ were enrolled and randomized to conventional therapy for CHF plus placebo (n=874 patients), conventional therapy plus amiodarone (n=845 patients), or conventional therapy plus a conservatively programmed, shock only, single-lead ICD (n=829 patients).</td>
<td>As compared with placebo, amiodarone was associated with a similar risk of death [HR 1.06; 97.5% CI, 0.86-1.30; p=0.53] and ICD therapy was associated with a decreased risk of death of 23 percent [HR 0.77; 97.5% CI 0.62-0.96; p=0.007] and an absolute decrease in mortality of 7.2% after five years in the overall population. Results did not vary according to either ischemic or non-ischemic causes of CHF. In patients with NYHA class III CHF, there was a relative increase in the risk of death among patients in the amiodarone group, as compared placebo group [HR 1.44; 97.5% CI 1.05-1.97].</td>
<td>Amiodarone has no favorable effect on survival, whereas single-lead, shock-only ICD therapy reduces overall mortality by 23 percent.</td>
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<td>M ADIT-II [24] Multicenter Automatic Defibrillator Implantation Trial</td>
<td>Patients with reduced LV function after MI are at risk for life-threatening ventricular arrhythmias. Does ICD therapy for primary prevention improve all-cause mortality?</td>
<td>1232 patients with a prior myocardial infarction and a left ventricular ejection fraction of $\leq 30$ were randomized, using a 3:2 ratio; n= 742 patients in ICD arm, n=490 patients medical therapy arm</td>
<td>The mortality rates were 198 percent in the conventional-therapy group and 14.2 percent in the defibrillator group. The HR favored the ICD arm of the cohort [HR=0.69; 95% CI 0.51-0.93; P=0.016]. There were no significant differences in the effect of defibrillator therapy on survival in subgroups (age, sex, ejection fraction, New York Heart Association class, or the QRS interval).</td>
<td>In patients with a prior myocardial infarction and significant left ventricular dysfunction ($\leq 30$ %), prophylactic insertion of an ICD improves survival.</td>
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<td>MADIT-RIT [25,26] Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy</td>
<td>Does the programming of ICD intervention affect morbidity and mortality in patient who receive an ICD for primary prevention?</td>
<td>N=1,500 patients enrolled. Randomized to one of the three programming configurations: 1) high-rate therapy (with a 2.5-second delay before the initiation of therapy at a heart rate of $\geq 200$ beats per minute) 2) delayed therapy (with a 60-second delay at 170 to 199 beats per minute, a 12-second delay at 200 to 249 beats per minute, and a 2.5-second delay at $\geq 250$ beats per minute) 3) conventional programming (with a 2.5-second delay at 170 to 199 beats per minute and a 1.0-second delay at $\geq 200$ beats per minute).</td>
<td>High-rate therapy and delayed ICD therapy, as compared with conventional device programming were associated with reductions in a first occurrence of inappropriate therapy. High-rate therapy vs. conventional therapy: [HR 0.21; risk reduction of 79%; 95% CI 0.13-0.34; P=0.001] Delayed therapy vs. conventional therapy, [HR 0.24, risk reduction of 76%, 95% CI 0.15-0.40; P&lt;0.001] Reductions in all-cause mortality with high rate therapy: high-rate therapy vs. conventional therapy: [HR 0.45; 95% CI 0.24-0.85; P=0.01] Delayed therapy vs. conventional therapy: [HR 0.56; 95% CI 0.30-1.02; P=0.06].</td>
<td>Programming of ICD therapies for tachyarrhythmias of $\geq 200$ beats per minute or higher or with a prolonged delay in therapy at 170 beats per minute or higher, compared with conventional programming, was associated with a reduction in inappropriate therapy and all-cause mortality.</td>
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<td>DINAMIT [27] Defibrillator in Acute Myocardial Infarction Trial</td>
<td>Does ICD therapy improve survival early following a myocardial infarction, in patients with depressed LV function?</td>
<td>Randomized, open-label comparison of ICD therapy (n=332 patients) and no ICD therapy (n=342 patients) 6 to 40 days after a myocardial infarction, in patients with a LVEF $&lt; 35$; depressed HRV or an elevated average heart rate on 24 hour holter monitoring.</td>
<td>There was no difference in overall mortality between the two treatment groups. There was significantly less AD in the ICD arm [HR=0.42; 95% CI 0.22-0.83; P=0.009].</td>
<td>Prophylactic ICD therapy does not reduce overall mortality in high-risk patients after recent MI. Although ICD therapy was associated with a reduction in the rate of AD, this was offset by an increase in the rate of non-arrhythmic causes.</td>
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<td>DEFINITE [28] Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation</td>
<td>Does insertion of an ICD reduce the mortality risk of SCD in patients with a dilated non-ischemic (DCM) cardiomyopathy?</td>
<td>Randomized trial of N=458 patients with DCM, EF $\leq 36$, PVCs and/or NSVT. N=229 patients received standard medical therapy, while N=229 patients received standard medical therapy plus a single-channel ICD.</td>
<td>There were 68 deaths: 28 in the ICD group, as compared with 40 in the standard-therapy group [HR 0.65; 95% CI 0.40-1.06; P=0.08]. The mortality rate at 2 years was 14.1% in the standard-therapy group (annual mortality rate, 7 percent) and 7.9 percent in the ICD group. There were 17 sudden deaths from arrhythmia: 3 in the ICD group, as compared with 14 in the standard-therapy group [HR 0.20; 95% CI 0.06-0.71; P=0.006].</td>
<td>Prophylactic ICD insertion in a patient with a DCM, on medical therapy significantly reduced the risk of SCD but did not affect all-cause mortality.</td>
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<td>Study</td>
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<td>OBSERVO-ICD [29]</td>
<td>OBSERVational registry on long-term outcome of ICD patients</td>
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<td>CRT device</td>
<td>The purpose of this study was to test whether an aggressive ICD programming protocol can result in electrical storm (ES).</td>
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<td>CRT device</td>
<td>OBSERVO-ICD is a multicenter, retrospective registry enrolling consecutive patients undergoing ICD implantation. Clinical history and risk factors were collected for all patients. These were ICD therapy-related variables such as detection zones and delays. The total number of arrhythmic episodes and therapies delivered by the ICD were collected. The primary endpoint was detection of significant differences in ICD programming between patients experiencing ES, patients with unclustered VTs/VFs, and patients with no arrhythmic episodes. Of the 1319 consecutive patients, 62 (4.7%) experienced at least one episode of ES during a median follow-up of 39 months. Patients who experienced ES had a significantly lower VF detection zone (P = .002), more frequently had anti-tachycardia pacing therapies programmed off during capacitor charge (P = .001), and less frequently had an ICD set with delayed therapies for VT zones (P = .042) and VF zone (P = .036). Patients who experienced ES had a significantly higher incidence of death and heart failure-related death compared to patients with no ventricular arrhythmias and patients with unclustered VTs/VFs (P = .025 and P &lt; .001, respectively).</td>
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<td>COMPANION [30]</td>
<td>Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure</td>
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<td>CRT device</td>
<td>Does prophylactic CRT therapy reduce the risk of death and hospitalization among patients with advanced chronic systolic heart failure with an intraventricular conduction delay?</td>
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<td>CRT device</td>
<td>A total of 1520 patients with advanced heart failure (NYHA class III or IV), and QRS duration ≥ 120 msec were randomly assigned in a 1:2:2 ratio to receive optimal pharmacologic therapy, medical therapy in combination with CRT with either a pacemaker (CRT-P) or a pacemaker-defibrillator (CRT-D). The primary composite end-point was the time to death or hospitalization for any cause. As compared with optimal pharmacologic therapy alone, CRT-P decreased the risk of the primary end point [hazard ratio, 0.81; P = 0.014], as did CRT-D (HR 0.80; P &lt; .01). The risk of the combined end-point of death or hospitalization for heart failure was reduced by 34% in the CRT-P group (P &lt; .002), and by 40% in the pacemaker-D group (P &lt; .001) compared pharmacologic-therapy alone. CRT with pacing alone reduced the risk of death by 25% [HR 0.75; 95% CI 0.63-0.90; P &lt; .002], while CRT-D reduced the risk by 28% [HR 0.72; 95% CI 0.60 to 0.86; P &lt; .001], compared to medical therapy alone.</td>
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<td>MIRACLE-ICD [31]</td>
<td>Multicenter InSync ICD Randomized Clinical Evaluation</td>
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<td>CRT device</td>
<td>What are the outcomes of CRT (CRT-P, CRT-D) in patient with NYHA class III and IV HF, with a wide QRS, or on optimal guideline directed medical therapy?</td>
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<td>CRT device</td>
<td>Randomized, double-blind, parallel-controlled trial. N = 369 patients with EF ≥ 35%, QRS duration ≥ 120 ms, with either NYHA class III (n = 328) or IV (n = 41) despite optimal guideline directed medical therapy. N = 369 patients received CRT-D, n = 192 were controls (ICD activated, CRT off) and n = 187 were in the CRT-D group. Primary end points were changes between baseline and 6 months in quality of life, functional class, and distance covered during a 6-minute walk. Additional outcome measures included changes in exercise capacity, plasma neurohormone levels, LV function, and overall HF status. At 6 months, patients assigned to CRT had a greater improvement in median (95% CI) quality of life score (−17.5 [−21 to −14] vs −11.0 [−16 to −7], P = .02) and functional class (−1 to −1 to −1 vs 0 [−1 to 0], P = .007) compared to control but there was no difference in distance walked during a 6-minute walk test (55 m [44–79] vs 53 m [43–75], P = .36). Peak oxygen consumption increased by 1.1 mL/kg per minute (0.7–1.6) in the CRT group vs 0.1 mL/kg per minute (−0.1 to 0.8) in controls (P = .04), although treadmill exercise duration increased by 56 seconds (30–79) in the CRT group and decreased by 11 seconds (−55 to 12) in controls (P &lt; .001). No significant differences were observed in changes in left ventricular size or function, overall HF status, survival, and rates of hospitalization. No evidence of pro-arrhythmia was observed.</td>
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<td>CARE-HF [32]</td>
<td>Cardiac Resynchronization—Heart Failure</td>
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<td>CRT device</td>
<td>CRT reduces symptoms and improves LV function in patients with heart failure due to LV systolic dysfunction (HFpEF) and cardiac dyssynchrony. Does CRT affect morbidity and mortality?</td>
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<tr>
<td>CRT device</td>
<td>N = 813 patients with NYHA class III or IV heart failure due to HFpEF with evidence of electrical dyssynchrony, on standard pharmacologic therapy were randomized medical therapy alone or medical therapy with CRT. The primary end point was the time to death from any cause or an unplanned hospitalization for a major cardiovascular event. The CRT group exhibited a lower rate of the composite end-point 39% vs. 55% [HR 0.63; 95% CI 0.51–0.77; P &lt; .001]. There were 82 deaths in the CRT synchronization group, compared with 120 in the medical-therapy group (20% vs 30% [HR 0.64; 95% CI 0.48–0.85; P &lt; .002].</td>
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Patients with ES had a more aggressive ICD programming setup, including lower VF detection rates, shorter detection times, and no anti-tachycardia pacing therapies during capacitor charge. This kind of ICD programming potentially could increase the likelihood of ES and the related risk of death. In patients with advanced heart failure and a prolonged QRS interval, CRT therapy with and without defibrillation decreased the combined end-point of death and time to first hospitalization. CRT improved quality of life, functional status, and exercise capacity in patients with moderate to severe HF, with a wide QRS duration at risk for life-threatening arrhythmias. In patients with heart failure and cardiac dyssynchrony, cardiac resynchronization improves symptoms and the quality of life and reduces complications and the risk of death. The implantation of a CRT device should routinely be considered in such patients.
Does CRT reduce mortality? This trial was designed to determine whether cardiac-resynchronization therapy (CRT) with biventricular pacing would reduce the risk of death or heart-failure events in patients with mild cardiac symptoms, a reduced EF, and a wide QRS complex.

N=1820 patients with ischemic or non-ischemic cardiomyopathy, an EF ≤30%, QRS duration ≥ 120 msec, NYHA class I or II. Patients were randomly assigned in a 3:2 ratio to receive CRT-D (n=1089 patients) versus ICD alone (731 patients). The primary end point was death from any cause or a nonfatal heart-failure event (which ever came first).

The primary outcome occurred in 221 of 731 patients (30.2%) in the ICD group and 265 of 1089 patients (24.3%) in the CRT-D group ([HR] 0.75; 95% CI 0.64-0.87; P=0.001). There was no significant difference between patients with an ischemic versus non-ischemic cardiomyopathy. CRT resulted in a 41% reduction in heart-failure events, a finding that was evident primarily in a pre-specified subgroup of patients with QRS duration of ≥150 msec. CRT was associated with a significant reduction in left ventricular volumes and improved EF. There was no significant difference in the overall risk of death, with a 3% annual mortality rate in each treatment group.

The primary endpoint occurred in 187 of 1089 patients in the CRT–ICD group (17.2%) and 185 of 731 patients in the ICD-only group (25.3%) ([HR] in the CRT–ICD group 0.66; 95% CI 0.52-0.84; P=0.001). There was no significant difference between patients with an ischemic versus non-ischemic cardiomyopathy. CRT combined with ICD decreased the risk of heart-failure events in a relatively asymptomatic patient cohort with a low ejection fraction and wide QRS complex.

Among patients with NYHA class II or III HF, with a wide QRS complex, and left ventricular systolic dysfunction, the addition of CRT to an ICD significantly reduced death and HF hospitalizations.

REFERENCES
