

Device Therapies: New Indications and Future Directions

Prabhat Kumar and Jennifer D. Schwartz*

Center for Heart & Vascular Care, University of North Carolina at Chapel Hill, USA

Abstract: Implantable cardioverter-defibrillator (ICDs), cardiac resynchronization (CRT) and combination (CRT-D) therapy have become an integral part of the management of patients with heart failure with reduced ejection fraction (HFrEF). ICDs treat ventricular arrhythmia and CRTs improve left ventricular systolic function by resynchronizing ventricular contraction. Device therapies (ICD, CRT-D), have been shown to reduce all-cause mortality, including sudden cardiac death. Hospitalizations are reduced with CRT and CRT-D therapy. Major device related complications include device infection, inappropriate shocks, lead malfunction and complications related to extraction of devices. Improvements in device design and implantation have included progressive miniaturization and increasing battery life of the device, optimization of response to CRT, and minimizing inappropriate device therapy. Additionally, better definition of the population with the greatest benefit is an area of active research.

Keywords: Cardiac implantable electronic device, cardiac resynchronization therapy (CRT), heart failure (HF), implantable cardioverter-defibrillator (ICD), primary prevention, secondary prevention, sudden cardiac death (SCD).

INTRODUCTION

The two main causes of death in patients with heart failure with reduced ejection fraction (HFrEF) are progressive pump failure and sudden cardiac death (SCD). Published trials suggest that 30 to 50% of all cardiac deaths in patients with HFrEF are sudden, with or without preceding symptoms [1-4]. Sudden death occurs more frequently in patients with less symptomatic HFrEF compared to pump failure death [4].

In the current clinical management of HFrEF, implantable cardiac devices have become increasingly important for prevention of SCD. However, device therapy is associated with potential complications. Major device related complications include device infection, inappropriate shocks, lead malfunction and complications related to extraction of devices. Despite the potential problems with device therapy as discussed above, the benefits of these devices far outweigh the risks. Multiple prospective clinical trials have firmly established that implantable cardioverter-defibrillators (ICD), cardiac resynchronization therapy (CRT) and their combination (CRT-D) reduce all-cause and cardiac mortality in patients with HFrEF. Additionally, hospitalization is reduced with CRT and CRT-D therapy. This review focuses on the evidence supporting the use of these devices, patient selection, and ongoing efforts at refining device indications and reducing the risk of complications.

ICD THERAPY IN HEART FAILURE WITH REDUCED EJECTION FRACTION (HFREF)

Patients with HFrEF are prone to develop ventricular tachyarrhythmia (VA) leading to sudden cardiac death.

Large secondary prevention trials in patients with HFrEF and a history of VAs or aborted sudden cardiac death (SCD) and primary prevention trials in patients with heart failure with severe left ventricular (LV) systolic dysfunction have firmly established the role of ICD therapy in the prevention of SCD and reduction in all-cause mortality. The survival benefit first demonstrated in patients with an ischemic etiology has now been extended to patients with a nonischemic etiology as well. Primary and secondary prevention ICD trials, including number needed to treat (NNT) to prevent death, are described in Table 1.

SECONDARY PREVENTION ICD TRIALS

The benefit of ICDs was first studied in survivors of SCD. Although few out-of hospital cardiac arrest patients survive to hospital discharge, this patient population is at high risk for recurrent events. The Antiarrhythmics Versus Implantable Defibrillators trial (AVID), [5] the Canadian Implantable Defibrillator Study (CIDS) [6] and the Cardiac Arrest Study Hamburg (CASH) [7] enrolled patients with aborted SCD or patients with ventricular arrhythmias in the setting of reduced left ventricular ejection fraction (LVEF) (Table 1). The AVID trial was stopped early due to the benefit of ICD therapy over amiodarone. There was a 5.5% absolute risk reduction in all-cause mortality and a 3.6% absolute risk reduction in arrhythmic deaths. Although the CASH and CIDS trials were relatively underpowered to assess the reduction in all-cause mortality, they, still, showed consistent absolute risk reductions in arrhythmic death (3.6% and 1.5%, respectively). In a meta-analysis of these three randomized, prospective secondary prevention trials, there was a 28% relative reduction in all cause mortality and a 50% reduction in SCD in patients receiving ICDs [8]. Patients with LVEF < 35% derived the most benefit, hazard ratio 0.66 (95% CI 0.53-0.83) [8] and overall the number needed to treat to save a life per year of

*Address of correspondence to this author at the University of North Carolina at Chapel Hill, Heart and Vascular, 160 Dental Circle, CB 7075, Chapel Hill NC 27599, USA; Tel: 9199664743; Fax: 919-966-4366; E-mail: jennifer_schwartz@med.unc.edu

Table 1. ICD trials.

| Trial | Inclusion criteria | Etiology (ischemic, nonischemic) | N | LVE-Fmean | NNT (Mortality) | Follow up (years) |
|--|--|------------------------------------|------|-----------|----------------------|-------------------|
| <i>Secondary prevention ICD trials</i> | | | | | | |
| AVID [5] | VFib, VT with syncope, VT, LVEF \leq 40% | Both | 1016 | 32 | 14 | 2 |
| CIDS [6] | VFib, out-of-hospital cardiac arrest due to VFib or VT, VT with syncope, VT with symptoms and LVEF \leq 35%, unmonitored syncope with subsequent spontaneous or induced VT | Both | 659 | 34 | 17 | 2 |
| CASH [7] | VFib, VT | Both and structurally normal heart | 288 | 46 | 13 | 9 |
| <i>Primary prevention ICD trials</i> | | | | | | |
| MADIT [15] | Hx MI, LVEF \leq 35%, NSVT, inducible VT non-suppressible with IV procainamide; NYHA class I-III | Ischemic | 196 | 26 | 5 | 2 |
| MUSTT [14] | CAD, LVEF \leq 40%, NSVT, inducible VT; NYHA class I-III | Ischemic | 704 | 30 | 3 | 5 |
| MADIT II [16] | Hx MI (>1 month), LVEF \leq 30%; NYHA I-IV | Ischemic | 1232 | 23 | 17 | 2 |
| DEFINITE [18] | Nonischemic CM, Hx HF, LVEF \leq 35%, \geq 10 PVCs/hr or NSVT; NYHA I-III | Nonischemic | 458 | 21 | 17 | 2.5 |
| SCD-HeFT [17] | NYHA class II-III, EF \leq 35% | Both | 2521 | 25 | 14 | 5 |
| DINAMIT [13] | Recent MI (6-40 days), EF \leq 35%, abnormal HRV or mean 24-hr heart rate >80/min; NYHA class I-III | Post-MI | 674 | 28 | No mortality benefit | 2.5 |
| CABG Patch [12] | Coronary bypass surgery, EF <36%, SAECG (+) | Post-MI | 900 | 27 | No mortality benefit | 2 |

AAD: Antiarrhythmic Drug; **Vfib:** ventricular fibrillation; **LVEF:** Left ventricular ejection fraction; **VT:** Ventricular tachycardia; **NSVT:** Nonsustained ventricular tachycardia; **SAECG:** Signal averaged ECG; **CAD:** Coronary artery disease; **HF:** Heart failure; **PVC:** Premature ventricular complex; **CM:** Cardiomyopathy; **Hx:** history of; **MI:** Myocardial infarction; **NYHA:** New York Heart Association; **ICD:** Implantable cardioverter-defibrillator; **HRV:** heart rate variability; **NICM:** Non-ischemic cardiomyopathy; **ICM:** Ischemic cardiomyopathy; **NNT:** Number needed to treat. **AVID:** Antiarrhythmics Versus Implantable Defibrillators trial; **CIDS:** Canadian Implantable Defibrillator Study; **CASH:** Cardiac Arrest Study Hamburg; **MADIT:** Multicenter Automatic Defibrillator Implantation Trial; **MUSTT:** Multicenter Unsustained Tachycardia Trial; **DEFINITE:** SCD-HeFT: Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; **DINAMIT:** Defibrillator in Acute Myocardial Infarction Trial; **CABG:** Coronary Artery Bypass Graft.

follow-up was 29 [9]. These trials firmly established the benefit of ICDs over amiodarone as secondary prevention.

Subgroup analysis of these studies showed that the benefit of ICD therapy was largely restricted to patients with a lower LVEF. A subgroup analysis of 396 patients in the AVID trial with LVEF >35% failed to show a survival benefit. In addition a smaller group of 140 patients in this study with LVEF <20% did not show a statistically significant survival benefit. This was in contrast to the 473 patients with LVEF between 20% and 34% who had significantly improved survival with an ICD [10]. Similarly, in the CIDS trial the benefit of ICD therapy was restricted to the patients with high risk features (age >70 years, LVEF <35% and NYHA class III or IV) [11].

PRIMARY PREVENTION ICD TRIALS

Because the meta-analysis and further subgroup analysis of the secondary prevention trials showed the benefits were largely restricted to patients with lower LVEF, investigators were interested in whether patients with low LVEF

without documented VA would benefit from ICDs. Patients with HFrEF are a larger group of patients who are at a high risk of SCD based on epidemiological studies, but are at lower risk than patients who have survived a ventricular arrhythmia. The primary prevention trials included patients with an LVEF \leq 30-40%. Population characteristics and NNT are presented in Table 1. With the exception of implantation in close temporal proximity with coronary artery bypass surgery [12] or acute myocardial infarction [13], patients receiving ICD therapy for primary prevention live longer. These findings hold for both ischemic [14-17] and nonischemic etiologies [17, 18].

A meta-analysis of the primary prevention trials analyzing 5343 ischemic and non-ischemic patients with HFrEF showed a reduction in both arrhythmic deaths (relative risk: 0.40; 95% CI: 0.27-0.67) and all-cause mortality (relative risk: 0.73; 95% CI: 0.64-0.82). The benefit of ICD therapy was similar in ischemic (relative risk: 0.67; 95% CI: 0.51-0.88) and non-ischemic (RR: 0.74; 95% CI: 0.59-0.93) patients [19].

Although overall mortality for both men and women was similar (HR 0.96, 95% CI 0.67-1.39), women received appropriate ICD therapy less frequently compared to men (HR 0.63, 95%CI 0.49-0.82) and hence received less benefit from defibrillator therapy [20]. Another meta-analysis of primary prevention ICD trials showed a smaller benefit of ICD therapy in women with dilated cardiomyopathy compared to men. Despite increasingly older patients being the target group for ICD therapies, the majority of patients in these larger trials were younger. Two meta-analyses have suggested a benefit of ICD therapy in older patients [21, 22].

NEW DIRECTIONS IN RISK STRATIFICATION OF HEART FAILURE PATIENTS FOR SCD PREVENTION:

Despite the proven benefit of prophylactic ICD therapy in HF_{rEF} patients, the incidence of potentially lifesaving defibrillator therapy is relatively low. Only 14% of patients in the Multicenter Automatic Defibrillator Implantation Trial (MADIT II) and only 21% in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (SCD-HeFT) received appropriate ICD therapy. Because these studies relied on LVEF, investigators continue to search for a set of predictors to better differentiate between high and low risk patients. Data from MADIT II suggests that allocating risk scores using blood urea nitrogen, age, presence of atrial fibrillation and QRS duration may contribute to a better prediction model and may help physicians recommend ICD implantation in the patients who may derive the most benefit [23].

CARDIAC RESYNCHRONIZATION THERAPY (CRT)

A large subgroup of patients with HF_{rEF} exhibit cardiac dyssynchrony, the delayed contraction of the lateral left ventricular wall compared with the septum, which is usually associated with conduction abnormalities. Resynchronizing the septum and lateral left ventricular walls is the goal of cardiac resynchronization therapy (CRT). In a series of heart failure patients with severe LV systolic dysfunction, more than half had significant electrocardiographic LV dyssynchrony qualifying for CRT by current criteria [24]. Initially small clinical trials showed a benefit in left ventricular remodeling with improvement in LVEF and reduction in LV size. The benefit is most profound in patients with a left bundle branch block with a QRS duration of >150 msec. Subsequent larger trials have demonstrated an outcome benefit. (Table 2). However, approximately one-third of patients who receive CRT devices do not benefit symptomatically. There are ongoing efforts to better discriminate responders from non-responders and direct implants to patients who will receive the most benefit.

CRT TRIALS

Moderate to Severe Heart Failure

The initial trials of CRT were conducted in patients with severe LV systolic dysfunction and NYHA functional class III and IV. These studies demonstrated improvement in functional capacity (evaluated by 6-minute walk test), peak oxygen consumption, NYHA functional class and quality of life

Table 2. Major CRT trials.

| Study | N | NYHA Class | EF (%) | QRS (ms) | Outcome | NNT | Follow up (yrs) | |
|----------------|------|------------|--------|----------|---|-------|-----------------|---|
| COMPANION [33] | 1520 | III-IV | ≤35 | ≥120 | Mortality/hosp* | CRT-D | 8 | 1 |
| | | | | | | CRT-P | 8 | |
| | | | | | Mortality | CRT-D | 14 | |
| | | | | | Mortality/HF hosp | CRT-D | 6 | |
| | | | | | CRT-P | 7 | | |
| CARE-HF [34] | 814 | III-IV | ≤35 | ≥120 | Mortality/CV hosp* | CRT-P | 6 | 2 |
| | | | | | HF hosp | CRT-P | 6 | |
| | | | | | Mortality | CRT-P | 10 | |
| MADIT-CRT [36] | 1800 | I-II | ≤30 | ≥130 | Mortality/HF event* | CRT-D | 12 | 4 |
| | | | | | Heart Failure event | CRT-D | 11 | |
| RAFT [38] | 1798 | II-III | ≤30 | ≥130 | Mortality/ HF hosp* | CRT-D | 11 | 5 |
| | | | | ≥ 200 | Mortality | CRT-D | 14 | |
| | | | | paced | HF hospitalization | CRT-D | 15 | |
| BLOCK HF [39] | 691 | I-III | ≤50 | AV block | Mortality, HF urgent care or ≥15% increase in LVESVI* | CRT±D | 10 | 3 |

* Primary endpoint; ns not significant; NYHA: New York Heart Association; EF: Left ventricular ejection fraction; CRT: Cardiac resynchronization therapy; CRT-D: Cardiac resynchronization therapy with defibrillator; CRT-P: Cardiac resynchronization therapy without defibrillator; CV: Cardiovascular; LVESVI: Left ventricular end-systolic volume index; HF: Heart failure; Hosp: hospitalization; NNT: Number needed to treat; COMPANION: Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CARE-HF: Cardiac Resynchronization-Heart Failure; MADIT-CRT: Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; RAFT: Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; BLOCK HF: Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block.

[25-30]. Additional studies evaluating echocardiographic outcomes showed improvements in LVEF and reductions in LV volumes and dimensions [31, 32].

The pivotal Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial showed a mortality benefit of CRT combined with an ICD in patients with moderate to severe heart failure. A total of 1520 patients with class III or IV heart failure and an LVEF < 35% were enrolled and randomized to optimal medical therapy, CRT alone (CRT-P), or CRT-D. There was a significant reduction in the combined end point of mortality or HF hospitalization by 34% ($p < 0.002$) and 40% ($p < 0.001$) in patients receiving biventricular pacing only (CRT-P) and biventricular pacing plus defibrillator (CRT-D), respectively, as compared to patients receiving optimal pharmacological therapy alone [33]. Total mortality was significantly reduced only in the CRT-D group. In the Cardiac Resynchronization–Heart Failure (CARE-HF) study, 409 patients who received CRT alone had a lower mortality from any cause or unplanned hospitalization for a major cardiovascular event (39% vs. 55%, hazard ratio 0.63, 95% CI 0.51-0.77; $p < 0.001$). Total mortality was also significantly reduced. Additionally, patients in the CRT group had a reduction in inter-ventricular mechanical delay, a reduction in LV end-systolic volume index, a reduction in mitral regurgitation, an increase in LVEF, and an improvement in symptoms and quality of life [34, 35].

Less Severe Heart Failure

The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial studied 1820 patients with NYHA functional class I or II, LVEF $\leq 30\%$ and QRS duration ≥ 130 msec. Largely due to a reduction in heart failure events, the composite end point of all-cause mortality and nonfatal heart failure events was 34% less in patients with CRT-D compared to ICD alone [36]. Similarly, the REsynchronization reVERse Remodeling in Systolic left vEntricular dysfunction (REVERSE) study also enrolled patients with NYHA class I or II heart failure, but with an LVEF $\leq 40\%$, QRS duration of ≥ 120 ms and LV end-diastolic diameter ≥ 33 mm. Although there was no difference in the primary composite clinical end point after one-year, there was significant LV reverse remodeling with a reduction in LV end-systolic and end-diastolic volumes and a significant delay to first heart failure hospitalization. In a subgroup of these patients who had 2 years of follow up, there was significant decrease in the combined endpoint of heart failure hospitalization or death [37]. The Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) study enrolled patients with slightly more severe heart failure but the majority were NYHA functional class II (80%). Patients also had an LVEF $\leq 30\%$, and QRS prolongation (intrinsic ≥ 120 ms, paced ≥ 200 ms). The benefit of CRT included a significant decrease in all-cause mortality or heart failure hospitalization in the CRT group as compared to the control group (33.2% vs. 40.3%; hazard ratio 0.75, 95% CI 0.64-0.87, $p \leq 0.001$) [38].

CRT has also been shown to be beneficial in preventing the progression of LV systolic dysfunction and heart failure in patients who require frequent right ventricular (RV) pacing due to AV block. The Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) trial enrolled patients with LVEF $\leq 50\%$ and AV block requiring ventricular pacing. Patients received an ICD if they were eligible. The primary outcome of the time to death from any cause, an urgent care visit for heart failure that required intravenous therapy, or a 15% or more increase in the left ventricular end-systolic volume index was significantly reduced in the group who were randomized to biventricular pacing compared to RV pacing. Hospitalization for heart failure was also significantly reduced in the group of patients who received CRT alone (mean LVEF 43%) and were randomized to biventricular pacing [39].

Variables Determining Response to CRT

Although randomized controlled trials have shown the clear benefit of CRT in patients with mild and severe HFREF, studies have also highlighted that almost one-third of the patients receiving the device do not derive symptomatic benefit and are labeled *non-responders*. Various factors affect response rates including gender (women are more likely to respond), etiology of cardiomyopathy (nonischemic respond more than ischemic), degree of ventricular dyssynchrony, QRS morphology (left bundle branch block most responsive), QRS duration (≥ 150 ms most responsive), presence of atrial fibrillation (less response), lead position, degree of biventricular pacing and atrioventricular and inter-ventricular pacing delays.

Patients with an *ischemic etiology* have been shown to derive less benefit from CRT [40, 41]. Heart failure patients with ischemic heart disease generally have areas of left ventricular scarring. Patients may also experience progression of coronary artery disease. Subendocardial fibrosis with consequent tethering may result in electrical resynchronization with no recovery of mechanical function. Finally, placement of the LV lead in a scarred area may lead to a suboptimal response.

Degree and pattern of dyssynchrony is an important determinant of response to CRT. Baseline QRS width and QRS morphology have been shown to correlate with the response. MADIT-CRT, RAFT and REVERSE trials clearly demonstrated more benefit of CRT in patients with wider QRS at baseline (≥ 150 ms) [36-38, 42]. Additionally, the benefit was largely restricted to patients with left bundle branch block (LBBB). Patients with right bundle branch block or non-specific intra-ventricular conduction defect did not derive significant benefit [43].

Left ventricular lead position has been investigated extensively as a potential response modifier. Considering the mechanism of CRT, it is axiomatic to think that placement of the LV lead in the most delayed segment will give the best result. Many small studies demonstrated better results with implantation of the LV lead in a lateral or posterolateral segment of the left ventricular wall [44-46]. However, data from MADIT-CRT did not show any difference in response

between anterior lateral or posterior segmental position of the LV lead, although it did show worse outcome if the LV lead was placed in the apical segment as opposed to basal or midventricular segments [47]. Worse outcome with apical lead position was also shown in two other large studies [48, 49]. Placement of the LV lead in the most delayed segment as determined by echocardiographic tissue Doppler study [50, 51] or by recording the electrogram from the LV lead at the time of implantation have shown a more favorable outcome [52, 53]. However, this is not always possible. LV lead placement in an optimal position may be constrained by diaphragmatic pacing, coronary vein anatomy and presence of myocardial scar. Rarely, coronary venous access may not be possible due to anatomic variations or tortuosity. Surgical epicardial LV lead placement is done if transvenous LV pacing is not possible for these reasons, although it is more invasive.

Implantation of CRT devices in patients with *atrial fibrillation* and frequent *ventricular ectopy* poses another challenge. The response to CRT in these patients is suboptimal since they tend to have inconsistent true biventricular pacing [54]. Optimal management of atrial fibrillation and ventricular ectopy is critical to maximize CRT benefit in these patients.

Expansion of Indication of CRT

To date, the role of CRT is not well established in patients without a history of heart failure or in patients with heart failure and a narrow QRS and evidence of ventricular dyssynchrony on echocardiography [55, 56]. However, chronic right ventricular (RV) pacing in the setting of pre-existing LV systolic dysfunction may justify biventricular pacing to prevent deterioration of LV function and cause left ventricular dyssynchrony. Results from the BLOCK HF trial discussed above support the role of CRT in these patients [39].

Device Optimization

Device programmed atrioventricular and inter-ventricular pacing intervals can potentially affect the response to CRT. Although multiple small studies showed benefit of interval optimization, larger randomized trials have failed to show additional benefit [57-61].

Practice Guidelines and Approach to Patients with Heart Failure for Device Therapy

Current evidence has firmly established the role of ICDs and CRT devices in patients with HFrEF. Patients should receive guideline-directed medical therapy i.e. ACE-Inhibitor or angiotensin receptor blocker therapy plus a beta blocker for a minimum of 3-6 months prior to receiving device therapy. Reassessment of LVEF should be performed prior to device therapy. Figure 1 provides an algorithm based on current guidelines published by the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society, Heart Failure Society of America and European Society of Cardiology [62-64].

ICD therapy is recommended in patients with heart failure, LVEF $\leq 35\%$, and NYHA class II-III symptoms with a

life expectancy greater than 1 year and without a history of psychiatric disorder for SCD prevention. ICD therapy is also recommended in patients with an ischemic cardiomyopathy and NYHA class I symptoms if the LVEF is $\leq 30\%$. In patients with a history of non-sustained VT or inducible sustained VT/VF during electrophysiology study, ICD placement is recommended if the LVEF is $\leq 40\%$. Patients with a recent MI (< 40 days) or CABG do not benefit from ICD therapy.

CRT is recommended in patients with LVEF $\leq 35\%$ and a QRS duration ≥ 120 ms and NYHA functional class II-III and ambulatory class IV. Patients without a LBBB should have QRS duration > 150 msec. NYHA functional class IV patients should receive ICD only if eligible for concomitant CRT therapy.

Future Directions

Quadripolar LV Leads and Multisite LV Pacing

In order to maximize benefit and minimize complications of CRT (diaphragmatic pacing and high pacing thresholds), investigations continue to develop new pacing leads and pacing techniques. Quadripolar left ventricular leads give physicians the flexibility of choosing from multiple electrode pairs for pacing the left ventricle [65, 66]. These leads can also be used for multisite pacing, which may further enhance response to CRT [67]. Animal studies as well as recent small human studies have shown some promise for multisite pacing with a potential of better response to CRT [67, 68].

Endocardial LV Pacing

Left ventricular pacing for CRT has traditionally been achieved either through transvenous access of the coronary venous tree or surgical epicardial placement of an LV lead. Both of these pace the left ventricle from the epicardium and may predispose patients with CRT to ventricular arrhythmias. However, as the natural activation of the left ventricle is from the endocardium to epicardium and the fast conducting His-Purkinje system is endocardial in location, pacing the left ventricle endocardium may be more physiological. Small studies have evaluated endocardial pacing but due to the potential risk of thromboembolism, this exciting approach still requires further evaluation [69, 70].

Subcutaneous ICD

Lead malfunction and complications including device infections are unfortunate complications of cardiac implantable device therapy. Recently, rising use of defibrillators and recognition of lead-related complications has led to the development of a completely subcutaneous ICD [71, 72]. Safety and efficacy has been established and the device is now commercially available for implantation at some centers.

Reduction of Inappropriate and Unnecessary ICD Shocks

Since the inception of ICD therapy, concern has been raised about myocardial damage due to ICD shocks. There has been an ongoing effort to reduce the incidence of inappropriate and unnecessary shocks from supraventricular

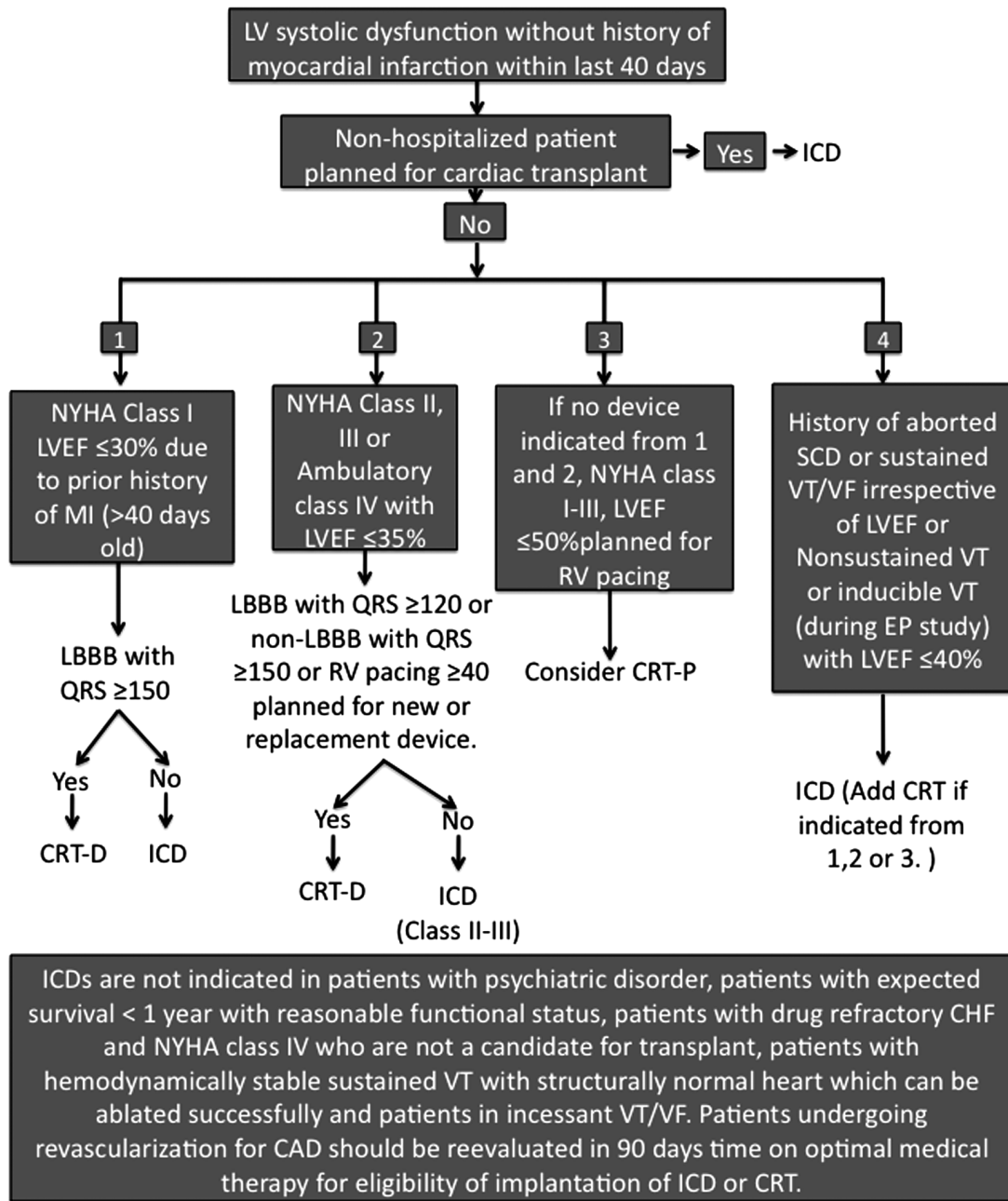


Fig. (1). Patient selection for device therapy.

tachycardia or nonsustained ventricular tachycardia. Recent studies have shown that conservative ICD programming including anti-tachycardia pacing during ICD charging, higher therapy cutoff rates and longer detection intervals have helped reduce the incidence of unnecessary ICD shocks while maintaining safety [73-75]. Appropriate ICD programming is an important aspect of management of patients with ICD.

CONCLUSIONS

Large clinical trials have established the role of cardiac implantable electronic devices in the management of patients with HFrEF. However, use of these devices requires careful

patient and device selection and implantation process. Various characteristics including LVEF, QRS width and morphology, requirement of pacing and other comorbidities should be taken into account in making the decision for implantation and the choice of the type of device. Follow-up for appropriate device management optimizes the benefit and prevents adverse and unpleasant effects of the device including unnecessary shocks. New implantation approaches and improvement in device programming algorithms have streamlined the management of these patients. Ongoing research in device design is under way to make more efficient systems with a goal to minimize the risks. Additionally, research continues to target device therapy for the most appropriate patients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomized trial. *Lancet* 1999; 353: 9-13.
- [2] Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA* 1995; 273: 1450-6.
- [3] Pitt B, Zannad F, Remme WJ, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; 341: 709-17.
- [4] Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). *Lancet* 1999; 353: 2001-7.
- [5] A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus implantable defibrillators (AVID) investigators. *N Engl J Med* 1997; 337: 1576-83.
- [6] Connolly SJ, Gent M, Roberts RS, *et al.* Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000; 101: 1297-302.
- [7] Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000; 102: 748-54.
- [8] Connolly SJ, Hallstrom AP, Cappato R, *et al.* Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. *Antiarrhythmics vs Implantable Defibrillator Study*. *Canad J Cardiol* 2000; 21: 2071-8.
- [9] Oseroff O, Retyk E, Bochoeyer A. Subanalyses of secondary prevention implantable cardioverter-defibrillator trials: antiarrhythmics versus implantable defibrillators (AVID), Canadian Implantable Defibrillator Study (CIDS), and Cardiac Arrest Study Hamburg (CASH). *Curr Opin Cardiol* 2004; 19: 26-30.
- [10] Domanski MJ, Sakseena S, Epstein AE, *et al.* Relative effectiveness of the implantable cardioverter-defibrillator and antiarrhythmic drugs in patients with varying degrees of left ventricular dysfunction who have survived malignant ventricular arrhythmias. AVID Investigators. *Antiarrhythmics Versus Implantable Defibrillators*. *J Am Coll Cardiol* 1999; 34: 1090-5.
- [11] Sheldon R, Connolly S, Krahn A, Roberts R, Gent M, Gardner M. Identification of patients most likely to benefit from implantable cardioverter-defibrillator therapy: the Canadian Implantable Defibrillator Study. *Circulation* 2000; 101: 1660-4.
- [12] Bigger JT, Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. *N Engl J Med* 1997; 337: 1569-75.
- [13] Hohnloser SH, Kuck KH, Dorian P, *et al.* Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004; 351: 2481-8.
- [14] Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999; 341: 1882-90.
- [15] Moss AJ, Hall WJ, Cannom DS, *et al.* Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996; 335: 1933-40.
- [16] Moss AJ, Zareba W, Hall WJ, *et al.* Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; 346: 877-83.
- [17] Bardy GH, Lee KL, Mark DB, *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; 352: 225-37.
- [18] Kadish A, Dyer A, Daubert JP, *et al.* Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004; 350: 2151-8.
- [19] Theuns DA, Smith T, Hunink MG, Bardy GH, Jordaens L. Effectiveness of prophylactic implantation of cardioverter-defibrillators without cardiac resynchronization therapy in patients with ischemic or non-ischaemic heart disease: a systematic review and meta-analysis. *Europace* 2010; 12: 1564-70.
- [20] Santangeli P, Pelargonio G, Dello Russo A, *et al.* Gender differences in clinical outcome and primary prevention defibrillator benefit in patients with severe left ventricular dysfunction: a systematic review and meta-analysis. *Heart Rhythm* 2010; 7: 876-82.
- [21] Kong MH, Al-Khatib SM, Sanders GD, Hasselblad V, Peterson ED. Use of implantable cardioverter-defibrillators for primary prevention in older patients: a systematic literature review and meta-analysis. *Cardiol J* 2011; 18: 503-14.
- [22] Santangeli P, Di Biase L, Dello Russo A, *et al.* Meta-analysis: age and effectiveness of prophylactic implantable cardioverter-defibrillators. *Ann Intern Med* 2010; 153: 592-9.
- [23] Goldenberg I, Vyas AK, Hall WJ, *et al.* Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. *J Am Coll Cardiol* 2008; 51: 288-96.
- [24] Ghio S, Constantin C, Klersy C, *et al.* Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration. *Eur Heart J* 2004; 25: 571-8.
- [25] Cazeau S, Leclercq C, Lavergne T, *et al.* Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001; 344: 873-80.
- [26] Abraham WT, Fisher WG, Smith AL, *et al.* Multicenter InSync Randomized Clinical Evaluation: Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002; 346: 1845-53.
- [27] Leclercq C, Walker S, Linde C, *et al.* Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* 2002; 23: 1780-7.
- [28] Auricchio A, Stellbrink C, Sack S, *et al.* Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002; 39: 2026-33.
- [29] Young JB, Abraham WT, Smith AL, *et al.* Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA* 2003; 289: 2685-94.
- [30] Auricchio A, Stellbrink C, Butter C, *et al.* Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol* 2003; 42: 2109-16.
- [31] Higgins SL, Hummel JD, Niazi IK, *et al.* Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003; 42: 1454-9.
- [32] Abraham WT, Young JB, Leon AR, *et al.* Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation* 2004; 110: 2864-8.
- [33] Bristow MR, Saxon LA, Boehmer J, *et al.* Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; 350: 2140-50.
- [34] Cleland JG, Daubert JC, Erdmann E, *et al.* The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; 352: 1539-49.
- [35] Cleland JG, Daubert JC, Erdmann E, *et al.* Longer-term effects of cardiac resynchronization therapy on mortality in heart failure the cardiac resynchronization-heart failure (CARE-HF) trial extension phase. *Eur Heart J* 2006; 27: 1928-32.
- [36] Moss AJ, Hall WJ, Cannom DS, *et al.* Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; 361: 1329-38.
- [37] Linde C, Abraham WT, Gold MR, *et al.* Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients

- and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008; 52: 1834-43.
- [38] Tang AS, Wells GA, Talajic M, *et al.* Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010; 363: 2385-95.
- [39] Curtis AB, Worley SJ, Adamson PB, *et al.* Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med* 2013; 368: 1585-93.
- [40] Woo GW, Petersen-Stejskal S, Johnson JW, Conti JB, Aranda JA, Jr, Curtis AB. Ventricular reverse remodeling and 6-month outcomes in patients receiving cardiac resynchronization therapy: analysis of the MIRACLE study. *J Interv Card Electrophysiol* 2005; 12: 107-13.
- [41] Barsheshet A, Goldenberg I, Moss AJ, *et al.* Response to preventive cardiac resynchronization therapy in patients with ischaemic and nonischaemic cardiomyopathy in MADIT-CRT. *Eur Heart J* 2011; 32: 1622-30.
- [42] Sipahi I, Carrigan TP, Rowland DY, Stambler BS, Fang JC. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. *Arch Intern Med* 2011; 171: 1454-62.
- [43] Sipahi I, Chou JC, Hyden M, Rowland DY, Simon DI, Fang JC. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. *Am Heart J* 2012; 163: 260.
- [44] Rossillo A, Verma A, Saad EB, *et al.* Impact of coronary sinus lead position on biventricular pacing: mortality and echocardiographic evaluation during long-term follow-up. *J Cardiovasc Electrophysiol* 2004; 15: 1120-5.
- [45] Thebault C, Donal E, Meunier C, *et al.* Sites of left and right ventricular lead implantation and response to cardiac resynchronization therapy observations from the REVERSE trial. *Eur Heart J* 2012; 33: 2662-71.
- [46] Wilton SB, Shibata MA, Sondergaard R, Cowan K, Semeniuk L, Exner DV. Relationship between left ventricular lead position using a simple radiographic classification scheme and long-term outcome with resynchronization therapy. *J Interv Card Electrophysiol* 2008; 23: 219-27.
- [47] Singh JP, Klein HU, Huang DT, *et al.* Left ventricular lead position and clinical outcome in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) trial. *Circulation* 2011; 123: 1159-66.
- [48] Merchant FM, Heist EK, McCarty D, *et al.* Impact of segmental left ventricle lead position on cardiac resynchronization therapy outcomes. *Heart Rhythm* 2010; 7: 639-44.
- [49] Foley PW, Chalil S, Ratib K, *et al.* Fluoroscopic left ventricular lead position and the long-term clinical outcome of cardiac resynchronization therapy. *Pacing Clin Electrophysiol* 2011; 34: 785-97.
- [50] Kristiansen HM, Vollan G, Hovstad T, Keilegavlen H, Faerstrand S. The impact of left ventricular lead position on left ventricular reverse remodelling and improvement in mechanical dyssynchrony in cardiac resynchronization therapy. *Eur Heart J Cardiovasc Imaging* 2012; 13: 991-1000.
- [51] Fung JW, Lam YY, Zhang Q, *et al.* Effect of left ventricular lead concordance to the delayed contraction segment on echocardiographic and clinical outcomes after cardiac resynchronization therapy. *J Cardiovasc Electrophysiol* 2009; 20: 530-5.
- [52] Singh JP, Fan D, Heist EK, *et al.* Left ventricular lead electrical delay predicts response to cardiac resynchronization therapy. *Heart Rhythm* 2006; 3: 1285-92.
- [53] Gold MR, Birgersdotter-Green U, Singh JP, *et al.* The relationship between ventricular electrical delay and left ventricular remodeling with cardiac resynchronization therapy. *Eur Heart J* 2011; 32: 2516-24.
- [54] Wilton SB, Leung AA, Ghali WA, Faris P, Exner DV. Outcomes of cardiac resynchronization therapy in patients with versus those without atrial fibrillation: a systematic review and meta-analysis. *Heart Rhythm* 2011; 8: 1088-94.
- [55] Beshai JF, Grimm RA, Nagueh SF, *et al.* Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007; 357: 2461-71.
- [56] Thibault B, Harel F, Ducharme A, *et al.* Cardiac resynchronization therapy in patients with heart failure and a QRS complex <120 milliseconds: the Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial. *Circulation* 2013; 127: 873-81.
- [57] Ellenbogen KA, Gold MR, Meyer TE, *et al.* Primary results from the SmartDelay determined AV optimization: a comparison to other AV delay methods used in cardiac resynchronization therapy (SMART-AV) trial: a randomized trial comparing empirical, echocardiography-guided, and algorithmic atrioventricular delay programming in cardiac resynchronization therapy. *Circulation* 2010; 122: 2660-8.
- [58] Abraham WT, Leon AR, St John Sutton MG, *et al.* Randomized controlled trial comparing simultaneous versus optimized sequential interventricular stimulation during cardiac resynchronization therapy. *Am Heart J* 2012; 164: 735-41.
- [59] Delnoy PP, Ritter P, Naegele H, *et al.* Association between frequent cardiac resynchronization therapy optimization and long-term clinical response: a post hoc analysis of the Clinical Evaluation on Advanced Resynchronization (CLEAR) pilot study. *Europace* 2013; 15(8): 1174-81.
- [60] Boriani G, Muller CP, Seidl KH, *et al.* Randomized comparison of simultaneous biventricular stimulation versus optimized interventricular delay in cardiac resynchronization therapy. The resynchronization for the hemodynamic treatment for heart failure management II implantable cardioverter defibrillator (RHYTHM II ICD) study. *Am Heart J* 2006; 151: 1050-8.
- [61] Rao RK, Kumar UN, Schafer J, Vilorio E, De Lurgio D, Foster E. Reduced ventricular volumes and improved systolic function with cardiac resynchronization therapy: a randomized trial comparing simultaneous biventricular pacing, sequential biventricular pacing, and left ventricular pacing. *Circulation* 2007; 115: 2136-44.
- [62] Epstein AE, DiMarco JP, Ellenbogen KA, *et al.* 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2013; 61: e6-75.
- [63] Daubert JC, Saxon L, Adamson PB, *et al.* 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. *Europace* 2012; 14: 1236-86.
- [64] Stevenson WG, Hernandez AF, Carson PE, *et al.* Indications for cardiac resynchronization therapy: 2011 update from the Heart Failure Society of America Guideline Committee. *J Card Fail* 2012; 18: 94-106.
- [65] Forleo GB, Mantica M, Di Biase L, *et al.* Clinical and procedural outcome of patients implanted with a quadripolar left ventricular lead: early results of a prospective multicenter study. *Heart Rhythm* 2012; 9: 1822-8.
- [66] Sperzel J, Danschel W, Gutleben KJ, *et al.* First prospective, multi-centre clinical experience with a novel left ventricular quadripolar lead. *Europace* 2012; 14: 365-72.
- [67] Thibault B, Dubuc M, Khairy P, *et al.* Acute haemodynamic comparison of multisite and biventricular pacing with a quadripolar left ventricular lead. *Europace* 2013; 15(7): 984-91.
- [68] Leclercq C, Gadler F, Kranig W, *et al.* A randomized comparison of triple-site versus dual-site ventricular stimulation in patients with congestive heart failure. *J Am Coll Cardiol* 2008; 51: 1455-62.
- [69] Padeletti L, Pieragnoli P, Ricciardi G, *et al.* Acute hemodynamic effect of left ventricular endocardial pacing in cardiac resynchronization therapy: assessment by pressure-volume loops. *Circ Arrhythm Electrophysiol* 2012; 5: 460-7.
- [70] Scott PA, Yue AM, Watts E, Zeb M, Roberts PR, Morgan JM. Transseptal left ventricular endocardial pacing reduces dispersion of ventricular repolarization. *Pacing Clin Electrophysiol* 2011; 34: 1258-66.
- [71] Bardy GH, Smith WM, Hood MA, *et al.* An entirely subcutaneous implantable cardioverter-defibrillator. *N Engl J Med* 2010; 363: 36-44.
- [72] Olde Nordkamp LR, Dabiri Abkenari L, Boersma LV, *et al.* The entirely subcutaneous implantable cardioverter-defibrillator: initial clinical experience in a large Dutch cohort. *J Am Coll Cardiol* 2012; 60: 1933-9.
- [73] Wathen MS, DeGroot PJ, Sweeney MO, *et al.* Prospective randomized multicenter trial of empirical antitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter-defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) trial results. *Circulation* 2004; 110: 2591-6.

[74] Wathen MS, Sweeney MO, DeGroot PJ, *et al.* Shock reduction using antitachycardia pacing for spontaneous rapid ventricular tachycardia in patients with coronary artery disease. *Circulation* 2001; 104: 796-801.

[75] Wilkoff BL, Williamson BD, Stern RS, *et al.* Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE (Primary Prevention Parameters Evaluation) study. *J Am Coll Cardiol* 2008; 52: 541-50.

Received: July 09, 2013

Revised: July 09, 2013

Accepted: September 27, 2013