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# **Implantable Cardioverter-Defibrillators in Sudden Cardiac Death Prevention: What Guidelines Don't Tell**

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## **1. Introduction**

A *guideline* is a statement by which to determine a course of action. A guideline aims to streamline particular processes according to a set routine or sound practice. By definition, following a guideline is never mandatory. Guidelines are not binding and are not enforced [5]. In effect guidelines are derived from 3 sources of data: 1. randomized clinical trials; 2. observational data from cohorts of high-risk patients with less common diseases; and 3. expert opinion on potential benefit for clinical condition or specific circumstances in which data are limited or uncertain. For all 3 categories of clinical guidance, there are limitations in available data that reinforce the importance of physician judgment in decision making, based on circumstances of individual cases or subgroups of patients [6]. Understanding the value and limitations of current information is important not only for the clinical electrophysiologist, but also for general cardiologists and primary care physicians because of their roles in referring appropriate patients for consideration of implantable cardioverter-defibrillator therapy and for the clinical management of patients at risk of sudden cardiac death. While the high stakes and unpredictable nature of sudden cardiac death justifiably provoke fear and uncertainty, emotional factors should not outweigh scientific evidence. In this context the obligation to adhere to guidelines could, in effects, to have paradoxically dulled our discriminatory senses as clinicians [7].

## 2. Sudden cardiac death

Sudden cardiac death (SCD) is generally defined as a sudden and unexpected death from a cardiovascular cause in a person with or without preexisting heart disease. The specificity of this definition varies depending on whether the event was witnessed; however, most studies include cases that are associated with a witnessed collapse, death occurring within 1 hour of an acute change in clinical status, or an unexpected death that occurred within the previous 24 hours [8-10]. Despite the significant decline in coronary artery disease (CAD), the overall burden of SCD in the population remains high. In the second half of the 20<sup>th</sup> century, SCD continues to claim 250,000 to 300,000 US lives annually [11,12]. In North America and Europe the annual incidence of SCD ranges between 50 to 100 per 100,000 in the general population [13-16]. However, even in the presence of advanced first responder systems for resuscitation of out-of-hospital cardiac arrest, the overall survival to hospital discharge was recently estimated to be only 7,9% [17]. In addition, the majority of SCDs occur at home, often where the event is unwitnessed [18,19]. SCD can manifest as ventricular tachycardia (VT), ventricular fibrillation (VF), that accounting for approximately three-quarters of cases, the rest 25% caused by bradyarrhythmias or asystole [20-22]. In a significant proportion of patients, SCD can present without warning or a recognized triggering mechanism. The mean age of those affected is in the mid 60s, and at least 40% of patients will suffer SCD before the age of 65 [14]. There is also strong evidence from studies in North America and Europe that there are significantly altered trends in the presenting arrhythmia observed by first responders among SCD cases [23,24]. The prevalence of SCD cases presenting with VF is decreasing with a corresponding increase in the proportion of cases presenting with pulseless electric activity (PEA). Given the extremes of resuscitation outcome based on presenting arrhythmia (>25% survival for VF and <2% for PEA) [14], it is important to improve our understanding of the determinants of these altered trends. Moreover for some segments of the population rate of SCD are not decreasing and may actually be increasing [23, 25].

More recent studies suggest that the incidence of VF or VT as the first recorded rhythm in out-of-hospital cardiac arrest has declined to perhaps even <30% in the past several decades [17,23,26]. The risk of SCD in myocardial infarction (MI) survivors has also declined significantly over the past 30 years, presumably due to early reperfusion and optimal medical therapy practices [27]. Recurrent ischemia may not be significantly associated with SCD, whereas heart failure due to MI markedly increases the risk of SCD [27]. Interestingly, acute ischemia is an established cause of VF and polymorphic VT [28], whereas cardiac death in patients with nonischemic dilated cardiomyopathy and functional class IV heart failure is more often due to bradyarrhythmia or electromechanical dissociation than due to ventricular tachyarrhythmias [29].

As a result, automated external defibrillators (ICD), which improve resuscitation rates for witnessed arrests only due to VT/VF [30], may have limited effectiveness on reducing overall mortality from SCD because SCD represent a current epidemic that is not exclusively due to ventricular tachyarrhythmias. These observations may have important implications when considering both secondary and primary SCD prevention by implantable ICDs [31].

### 3. Implantable cardioverter defibrillator

The ICD has emerged as a generally accepted therapy for prevention of SCD in selected categories of patients. Nearly 4 decades elapsed between the original notion that an ICD might be a useful clinical strategy, its subsequent development, and its current acceptance in various clinical settings based on randomized trial data. Each decade played a distinctive role in the evolution of ICD therapy. From the late 1960s until the first patient implant in 1980 [32], Mirowski's concept of a "standby automatic defibrillator" [33,34] met with skepticism [35] and concern about the practical difficulties in designing and manufacturing such a device [36,37]. After the first human device implant in 1980, clinical acceptance of the concept was initially slow, but began to accelerate after Food and Drug Administration approval in 1985 and Medicare coverage for limited indications in 1986. The early scientific support for the clinical value of the ICD was limited to a series of nonrandomized observational studies involving cohorts of high-risk patients. They were counterbalanced by contemporary interest in studies exploring the value of antiarrhythmic drug therapy guided by ambulatory arrhythmia monitoring or electrophysiological testing, and antiarrhythmic surgical techniques. This created uncertainty and intense debate in the electrophysiology community that continued even after the publication of the CAST (Cardiac Arrhythmia Suppression Trial) study [38,39] highlighted the potential dangers of empiric treatment with membrane-active antiarrhythmic drugs. Nonetheless, the CAST study was seminal in both constituting a turning point of the concept of antiarrhythmic drug therapy for prevention of SCD and serving as a catalyst for the recognition of the importance of randomized trial data to validate the potential for ICD benefit.

### 4. Secondary SCD prevention

The actual guidelines tell:

ICD in secondary prevention is indicated for survivors of cardiac arrest due to ventricular VF or VT and syncope and VF/VT inducible at electrophysiological study.

The first trial to investigate the use of ICD as first choice treatment in survivors of cardiac arrest compared with antiarrhythmic drugs was the Dutch study [40]. In a relatively small population of 60 patients, a strategy of ICD implantation as first-line treatment was shown to be preferable to medical therapy, conferring a significant reduction of a combined endpoint of main outcome events, included death, recurrent cardiac arrest, and cardiac transplantation. Three subsequent randomized clinical trials have evaluated the effect of ICD on overall mortality [41-43]. The AVID (Antiarrhythmics Versus Implantable Defibrillators) trial is the only trial to demonstrate statistically significant mortality reduction from ICD therapy in secondary prevention. After an interim analysis, the study was prematurely discontinued due to a 9% absolute increase in death in the antiarrhythmic group (mainly amiodarone) at 18 months (24.0% vs. 15.8%,  $p=0.02$ ).

What the guidelines don't tell is that, although statistical adjustments were attempted, it is difficult to overlook the >3-fold utilization of beta-blockers in the ICD group (38.1% vs. 11.0% at 1 year) and the 5% higher incidence of atrial fibrillation and NYHA functional class III heart failure in the antiarrhythmic group, and lower incidence of congestive heart failure in the ICD group as additive confounding variables that amplified net clinical benefit in favor of ICD therapy. Moreover, clinical benefit was not observed in patients with an EF >35% and <20% [44]. While the number needed to treat in this trial was 11 ICD implants to save 1 life, the unadjusted improvement in mean survival was only 0.21 year, or 2.6 months (31 vs. 29 months). This small difference was reduced by 15% when adjustments were made for heart failure and EF. This modest prolongation of life was valued at \$85,522 [45], which included the untoward costs of the 4% absolute increase in rehospitalizations in the ICD group (60% vs. 56%,  $p=0.04$ ).

Two smaller randomized trials, the CIDS (Canadian Implantable Defibrillator Study) and CASH (Cardiac Arrest Study Hamburg) trials, failed to demonstrate statistically significant reductions in mortality with ICD therapy for secondary prevention. These findings occurred despite similar inequities of beta-blockade therapy in ICD patients in the CIDS trial, with significantly higher event rates (44.4% in the CASH trial, 29.6% in the CIDS trial, and 24.0% in the AVID trial in control arms) and longer follow-up (57 months in the CASH trial, 36 months in the CIDS trial, and 18 months in the AVID trial). By current clinical trial standards, these trials, which did not meet conventional statistical significance, may not pass muster with the Food and Drug Administration. These nonsignificant trends in favor of ICD therapy prompted a meta-analysis that showed a significant difference in mortality in favor of ICD [46]. With a combined follow-up period of 6 years, patients with defibrillators lived only 4.4 months longer than those treated with antiarrhythmic therapy, and all statistically significant differences were nonsustained, narrowing at 4 years toward negligible after 6 years. As seen in the AVID trial, patients with an EF >35% did not experience survival benefit from ICD therapy. The skeptic, therefore, might interpret these results as suggesting that ICD confers a relatively small and rather transient survival benefit for secondary prevention in patients with EF of 35-40%, and this might be lost when  $\beta$ -blockers is implemented [31].

## 5. Primary SCD prevention

The actual guidelines tell:

ICD in primary prevention is indicated for patients with EF  $\leq$  35% due to prior MI (at least 40 days after infarct) with NYHA class II-III heart failure (and NYHA I if EF  $\leq$  30%); nonischemic dilated cardiomyopathy with EF  $\leq$  35% and NYHA class II-III heart failure; and ischemic cardiomyopathy with EF  $\leq$  40% and VF/VT inducible at electrophysiological testing. These findings arise from trials which have shown that prophylactic ICD therapy may improve survival in patients with increased risk of arrhythmic death.

What the guidelines don't tell is that:

### 5.1. Limitations of studies

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Multicenter Unsustained Tachycardia Trial (MUSTT) have demonstrated that prophylactic ICD therapy may improve survival in patients with increased risk of arrhythmic death [47,48]. The results of these trials may not be directly applicable to current medical practice, as the overall low rate of medication administration is not in compliance with current postmyocardial infarction treatment guidelines. For instance, in the MADIT only 8% of patients in the control group and 26% of patients in the ICD group were receiving  $\beta$ -blockers at 1 month of follow-up. Similarly in the MUSTT only 29% of the electrophysiologically guided therapy group was on  $\beta$ -blockers. Moreover the highly selected MADIT population is difficult to categorize as a primary prevention group. Induction of sustained ventricular arrhythmias and procainamide suppression is rarely, if ever, performed in current practice, and this feature may have been important for identifying patients more likely to experience adverse events (mortality rate 39%). The event rate in the control arm was higher than those seen in secondary prevention trials (25,3% in AVID vs 32% in MADIT, at 2 years). The larger MADIT II study demonstrated a 5,6% absolute mortality benefit (19,8% vs 14,2%) at 20 months of follow-up in ICD arm compared with patients in conventional medical therapy [49]. This difference, the smallest difference seen in any ICD trial demonstrating statistically significant benefit, was likely attenuated by a lower risk population enrolled without spontaneous ventricular arrhythmias or induced by the electrophysiological study. In addition, the equivalent high rate of  $\beta$ -blockers in both arms (70%) and low rate of amiodarone therapy (13% ICD vs 10% control) were likely factors that drove the event rates lower. Several insights often overlooked in MADIT II deserve mention. When examining the subgroup analysis, patients with QRS less than 150 msec, and EF greater than 25% did not derive benefit, suggesting that a sicker subpopulation within may be most optimal for selection. These data were confirmed in a MADIT II subanalysis that showed a U-shaped curve for ICD efficacy, demonstrating that patients with the lowest and highest risk scores had attenuated benefit from ICD therapy [50]. Another item of note are an unexpected 5% absolute increase in hospitalization for new or worsened congestive heart failure seen in the ICD group (19,9% vs 14,9%). Of note, this 5% trend in increased heart failure is the exact reverse of the mortality rates and absolute overall benefit. This observation confirmed some of the initial suspicion that right ventricular pacing and ICD discharges may have deleterious effects on myocardial function [51]. Furthermore, depriving a patient of sudden death may shift the mode of death to pump failure, which has the potential to be more costly and morbid [52]. Similar phenomena were observed in the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) in which the prevention of arrhythmic death with ICD was counterbalanced by excess death from nonarrhythmic causes [53]. The potential for causal harm from ICD shocks was again suggested by a substudy that showed the increased risk from nonarrhythmic death to be confined only to those that received ICD discharges. Due to the lack of mortality benefit seen immediately after myocardial infarction, the guidelines specify a 40-day blanking period during which ICD implantation is contraindicated. The findings of DINAMIT contradict the inferences from the VALIANT study (VALsartan in Acute myocardial iNfarcTion) [54], which showed that patients with reduced systolic function were at highest risk for sudden cardiac death in

the first 30 days after myocardial infarction. Interestingly, an analysis of the MADIT II results, with all the caveats that a subgroup analysis entails, has shown that patients who have recently had a MI do not benefit from an ICD, as opposed to those with old infarcts. The benefit is shown only for remote outside of 18 months that persisted up to 15 years after MI [55]. Although guidelines have adopted a 40-day blanking period from DINAMIT, the optimal timing of ICD implantation remains unknown.

Despite the inclusion of the nonischemic etiologies into class I ICD primary prevention recommendations, not a single trial has demonstrated a statistically significant mortality benefit from ICD in this group. The CAT (Cardiomyopathy Trial) and AMIOVIRT (Amiodarone Versus Implantable Cardioverter Defibrillator Trial) were both terminated prematurely due to futility [56,57]. The largest and only prospective trial of exclusively nonischemic patients was the DEFINITE (Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation) [58] that showed that the primary end point of all-cause mortality failed to reach statistical significance at 29 months. The low event rates in this study of relatively small sample size may also be attributed to the low usage of amiodarone in the control group, and high equitable rates of  $\beta$ -blockers (85%) and ACE inhibitor (95%) as background therapy. The SCD-HeFT (Sudden Cardiac Death Heart Failure Trial) was the largest primary prevention defibrillator trial to date, with a combination of ischemic (52%) and nonischemic (48%) etiologies [59]. Compared with placebo, ICD reduced all-cause mortality from 29% to 22% at 45 months. The 2-year mortality rate was approximately 20%, similar to the MADIT II population. Prespecified subgroup analysis was performed by NYHA class and etiology. Neither ischemic nor nonischemic subgroups met statistical significance. Of note benefit from ICD was seen only in NYHA II patients and amiodarone was harmful when compared with placebo in patients with NYHA III. In accordance with statistical dictum, subgroup analysis should be hypothesis generating, rather than leading to practice guidelines [52].

It's also fundamental to emphasize the drug therapy importance.  $\beta$ -Blockers use, which has been demonstrated to reduce arrhythmic and all-cause mortality in the postmyocardial infarction and chronic systolic dysfunction setting, can have an effect on the outcome of ICD trials. First, greater use of  $\beta$ -blockers decrease overall event rates, thereby diminishing the power of a study to demonstrate benefit of ICD therapy if the sample size is not increased. Furthermore, if patients randomized to ICD were disproportionately treated with higher rates of  $\beta$ -blockade, overall benefit seemingly from ICD would be accentuated. With the exception of SCD-HeFT, trial patients randomized to "control" received antiarrhythmic drug therapy. Although significant differences between randomized groups may be attributed to the superiority of the active treatment tested, the possibility of an inferior performance in the "control" arm, worse than that of placebo, must not be overlooked. The potential for harm from antiarrhythmic therapy has been well documented historically from trials like CAST (Cardiac Arrhythmia Suppression Trial) [39] and SWORD (Survival with Oral D-Sotalol) [60]. The propafenone active treatment arm had to be discontinued in CASH due to a 61% increase in mortality at 11 months [43]. In MADIT, patients in the control group had a 10% higher mortality rate if they were taking amiodarone at 1 month. Antiarrhythmic therapy resulted in a worse prognosis than standard therapy in SCD-HeFT and in MUSTT.



## 5.2. SCD risk predictors

As ICDs are by design effective in preventing sudden arrhythmic death, their ability to prolong overall survival is associated with the selection of a patient population with sufficiently high incidence of lethal arrhythmias and a sufficiently low incidence of death from all other causes combined. Thus, according to existing evidence, in the modern reperfusion and medical therapy era, a significant survival benefit has been demonstrated only in high-risk patients with ischaemic cardiomyopathy and with an EF of  $\leq 35\%$  usually due to a remote MI [31]. Therefore, substantial reductions in SCD incidence will require effective primary preventive interventions. Since the majority of SCDs occurs in the general population, the primary prevention goal is the identification of high-risk subsets. Numerous invasive and noninvasive techniques have been developed over the years to identify patients at risk for SCD [61-63]. Currently, assessment of left ventricular EF is commonly used to identify high-risk patients and to guide primary prevention of SCD [49]. EF is simple to evaluate, and has been a qualifying criterion of all the primary prevention trials. Concerns have been raised that EF is unlikely to be sufficient for effective SCD risk prediction, because it lacks both sensitivity and specificity [10]. Risk stratification for sudden cardiac death is an active field of investigation. Because of the dire consequences of the first clinical episode, there is a high degree of motivation in the medical community and patient community to identify individuals at risk for sudden cardiac death before its first manifestation. The Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction (CARISMA) study [64] performed a comprehensive analysis of a number of well-accepted risk markers for sudden cardiac death and compared them to each other. The findings are instructive, particularly in relation to the kind of information we can expect from any one of these risk stratification tests. To illustrate this concept, a new hypothetical risk stratification test will be proposed. The new test, a coin toss, will indicate that a patient is at high risk if the coin lands on "heads" and that a patient is at low risk if the coin lands on "tails." Intuitively, this test should provide absolutely no risk stratification. The positive and negative predictive values of this test are calculated in the CARISMA population. The positive predictive value of a coin toss is 8.3%; and the negative predictive value is 92.3%. As would be expected, the sensitivity and specificity of the coin toss approximate 50%. The coin toss performs minimally less well than left ventricular EF, the clinical parameter that is predominantly relied upon for risk stratification [65]. The same findings have been described in the Alternans Before Cardioverter Defibrillator (ABCD) Trial [66] which has repeated the coin toss experiment. Clinical decision-making is a complex process. Particularly when it comes to risk stratification for sudden cardiac death, it involves more than just a simple interpretation of a single test and implementation of therapy based on a single test. Yet, there are several important lessons from the coin toss experiment. When the overall incidence of events is low in the population (8.0% in CARISMA and 11.5% in ABCD), the negative predictive value of any test, even a coin toss, will be very high. This is because the number of true negatives far outweighs the number of false negatives. Although it is desirable to have a simple test to identify risk for sudden cardiac death, it can be seen that even with the use of currently available tests known to identify increased risk for sudden cardiac death, the ability to use these tests to make individual decisions is limited [67]. One option to improve risk stratification is to find some test that pro-

vides better discrimination. Taken together, the available experience suggests that multiple risk markers used in combination may provide a more robust prediction of events, which is not surprising when one considers the complexity and diversity of electro-anatomic substrates that underlie SCD.

The low predictive power of the EF in the community is well documented: less than a third off all SCD cases have severely decreased EF ( $\leq 35\%$ ) that would have qualified them as candidates for ICD therapy [68]. Conversely, an analysis of data from the MUSTT has shown that patients whose only risk factor is EF of  $\leq 30\%$ , and would qualify for ICD therapy according to current guidelines, may have a predicted 2-year arrhythmic death risk of  $<5\%$  [69]. Analysis of the MADIT II patients also indicates that the benefit of the ICD in the low EF population may not be uniform [50]. Depending on the presence of other risk factors, patients with EF from 30 to 40% may have total mortality and sudden death risks that exceed those of some patients with EF of  $\leq 30\%$  [69].

### 5.3. Comorbidity

Noncardiac comorbidity, such as diabetes mellitus, cerebrovascular disease, chronic obstructive pulmonary disease, and advanced renal failure, plays a pivotal role in the prognosis of a patient with arrhythmias. Despite the advances in medical therapy, the prognosis of heart failure patients is poor. The majority of heart failure patients has more than one condition affecting their health state. An increasing number of noncardiac comorbidities has the potential to blunt or negate the benefit of ICD therapy due to competing risks for death [52]. The potential futility of ICD efficacy in patients with chronic and end-stage renal disease has been suggested by multiple retrospective cohort analyses [70-73]. The Charlson comorbidity index (CCI) is widely used as an adjustment variable in prognostic models [74]. The index is based on comorbid conditions and cardiovascular risk factors of known prognostic value with varying assigned weights. A recent study showed that patients with a high comorbidity burden, defined as an age-adjusted CCI  $\geq 5$ , had an increased risk for mortality, independent from the prevention indication [4]. The majority of patients who died prior to appropriate ICD therapy had a primary prevention indication. Despite the effectiveness of terminating ventricular tachyarrhythmias by the ICD, competing non-cardiac comorbidity is associated with increased mortality [75]. Furthermore the effect of renal function on ICD efficacy was assessed in a retrospective analysis from MADIT II [76]. The study showed exceedingly high mortality rates (2-year Kaplan estimates of death of approximately 40%) in a relatively small subset of MADIT-II patients who had advanced renal dysfunction (estimated glomerular filtration rate [eGFR]  $<35 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ ). Death rates in patients with advanced renal disease were dominated by nonarrhythmic mortality. Accordingly, no ICD benefit was shown in MADIT-II patients with eGFR of less than 35 units, whereas the benefit of the ICD was pronounced in patients with eGFR of at least 35 units. These findings suggest caution when considering primary ICD implantation in patients with advanced renal dysfunction [77] and high burden of other noncardiac comorbidity.



#### 5.4. Age

Although elderly patients (> 70 years) remain at highest risk for SCD, comprising more than 65% of 465,000 out-of-hospital deaths in 1999 [78], routine ICD implantation in them is debatable. Patients older than 75 years were underrepresented in the landmark trials, those which have been drawn the guidelines, and patients older than 80 years were specifically excluded in MADIT (mean age  $62 \pm 9$  years). The median age of patients in SCD-HeFT was 61 and patients older than 65 years did not benefit from ICD therapy. The mean age of MADIT II was  $64 \pm 10$ , and only 16% of patients enrolled were older than 75 years. A meta-analysis of secondary prevention trials showed that patients older than 75 did not benefit from ICD implantation [79]. More recent meta-analysis of primary prevention trials showed that prophylactic ICD therapy in elderly patients was associated with a nonsignificant reduction in all-cause mortality compared with medical therapy [3]. Single-center ICD registries have demonstrated steep increases in both cardiac and noncardiac mortality in patients older than 75 years [80,81].

Advanced age clearly presents multiple competing risks for death, and age was also a significant independent predictor of mortality in the long-term follow-up of MADIT II. A recent study showed that age and GFR are the only independent predictors of survival in patients  $\geq 80$  years old, whereas ICD do not appear to influence the overall survival [82]. Of note, in none of the ICD recipients followed in this study there were any true instances of documented ventricular fibrillation, which adds to the evidence that ICDs are unlikely to influence survival in this patient population and is consistent with previous reports [83]. A consistent finding, however, is that older patients have an increased risk of death and an altered profile as to their cause of death. Indeed the ratio of SCD to all-cause mortality decreases over age groups such that the lowest ratio is found in patients > 80 years. Thus patients > 80 years old are more likely to die from nonarrhythmic or noncardiac causes for which an ICD is not helpful [84]. Other study [80,81] showed that given the increased probability of death from competing causes in elderly patients, patients older than a certain age cease to extract a survival benefit from an ICD. The problem therefore is reduced to identifying this specific age cutoff. Current guidelines do not preclude octogenarians and nonagenarians from receiving ICDs for primary prevention unless they have < 1-year life expectancy [1]. In primary prevention ICD trials, which constitute the basis for current clinical practice, more than 50% of enrolled patients were younger than 60 years [49,53,58,59,85]. In real-world practice, nearly 70% of ICDs are implanted in patients older than 60 years, and more than 40% are implanted in patients older than 70 years [83]. A primary prevention indication accounts for two thirds of cases in which such devices are used. The real-world extrapolation of data has resulted in 1 out of 6 Medicare ICD implants in patients older than 80 years, with a mean age of 70. The ACT registry (Advancements in ICD Therapy) showed that more than 40% of patients undergoing primary prevention ICD implantation were older than 70 years, with 12% older than 80 [83]. In light of this evidence and given of the cost and the potential risks associated with ICD implantation, the benefit of ICD therapy in the elderly are not well established. Of note, the benefit of cardiac resynchronization therapy (CRT), which reduces predominantly nonarrhythmic mortality (for example, heart failure mortality), seems consistent across dif-

ferent age groups. Subgroup analyses of CRT trials have reported a similar degree of CRT benefit in elderly and younger patients [86-88]. Taken together, these findings support that CRT alone may be the best device therapy in elderly persons with severe left ventricular dysfunction.

This upward drift in age representation in the real world not substantiated by trial data is concerning, not only on scientific grounds but from an ethic and philosophic viewpoint.

## 5.5. Gender

Different studies suggest that the incidences of various types of cardiac arrhythmia are different for women and men, although in many cases we still do not know why this should be. Two principle mechanisms have been proposed to explain these differences between the sexes differential: hormonal effects on the expression or function of ion channels or, conversely, differences in autonomic tone. It is also possible that a combination of these 2 mechanisms may be involved. A combined mechanism would lead to greater sympathetic activity and a lower baroreflex response in men of any age as well as to more pronounced parasympathetic or vagal activity in women. Experimental animal models studies, that used ovariectomized females treated with different gonadal steroids, suggest that the gonadal steroids are responsible for the differences, thanks to their effects on the ion channels of the cell membrane. These differences between sexes have some clinical implications, particularly for the therapeutic approach and clinical treatment of arrhythmias in women [89]. Differences in ventricular tachycardia and sudden death between the sexes were also reported in the Framingham study [90]. After a follow-up of 26 years, the incidence of sudden death increased with the age of the population, with a predominance in men in all age groups and an overall ratio in the incidence of approximately 3:1 compared to woman. This difference was explained by the epidemiology of the heart disease (in women, it appears 10 years to 20 years later). An analysis of survival in the VALIANT study, conducted in 14.703 patients with heart failure and ventricular dysfunction after myocardial infarction, revealed that 1067 cases of sudden death were reported during follow-up. Of these, 67% occurred in men and 33% in women [91]. The presence of gender differences in sudden cardiac death substrates and mechanisms has been reported also in epidemiological studies evaluating out-of-hospital cardiac arrest, which showed that women present more commonly with asystole and pulseless electrical activity, whereas men usually have ventricular tachycardia and ventricular fibrillation [92]. Subgroup analysis in several primary prevention trials revealed that the reduction of overall mortality achieved by ICD was more pronounced in male patients and it did not reach statistically significant levels in women [49,58,59]. In addition, a meta-analysis of 4 major primary prevention trials [93] found no mortality benefit of ICDs in women. After prophylactic ICD implantation, the mortality reduce significantly in men (HR 0,67, 95% CI 0,58-0,78,  $p < 0,001$ ), whereas in women the mortality reduction was inconclusive (HR 0,78, 95% CI 0,57-1,05,  $p = 0,1$ ) [94]. These data confirm that EF is not a reliable sudden death risk factor in women. At variance with ICD studies subgroup analyses of CRT trials suggest

that women may have a better response to CRT, with significantly lower incidence of the combined endpoint of first heart failure hospitalization or death, better degree of left ventricular reverse remodeling [88, 95-97].

## 6. Conclusions

The existing evidence does not support recommendations for ICD implantation by current guidelines on several occasions. We may over treat certain patients. As current guidelines have been broadened to include lower-risks groups with lower event rates, the cost-effectiveness of ICD therapy has become even less favorable. Implantable cardioverter-defibrillators are life-saving in high-risk population that, however, cannot be defined simply by the EF. The ICD does not confer immortality. It is most likely to result in meaningful prolongation of life in patients who are at high risk for lethal arrhythmias but low risk of death from hemodynamic failure or other organ system disease [98]. Further studies are necessary for identifying the most appropriately "at-risk" population for ICD therapies and the guidelines should be re-evaluated and updated. Serious comorbidities that limit the life expectancy of the patient, as well as gender and age should also be taken into account. The adoption of strict criteria for ICD implantation is a necessary step toward a rational use of our limited resources, particularly in an era of economic uncertainty and financial crises [31]. Finally, the ICD implantation should be preceded by a careful analysis of risk/benefit balance, shared with the patient and his family. Communication with these patients focused on a horizon of 5 years, during which for every 100 patients receiving devices, approximately 30 patients are predicted to die with or without an ICD, while 7 to 8 lives may be saved with the ICD. These estimates are presented in the context of adverse events, including unnecessary shocks, and the possibility that circumstances may arise for which the defibrillator may be inactivated to allow natural death [99]. Considerations of an individual's age comorbidity, and remaining life expectancy have a vital place not only in decision-making regarding expensive and invasive procedures such as ICD implantation, but also for "routine" health screenings. Many questions still remain open.

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## References

- [1] Epstein AE, Di Marco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Circulation* 2008;117: e350–e408.
- [2] Santangeli P, Di Biase L, Perlagonio G, et al. Outcome of invasive electrophysiological procedures and gender: Are Males and Females the same? *J CardiovascElectrophysiol* 2011; 22:605-612.
- [3] Santangeli P, Di Biase L, Dello Russo A, et al. Meta-analysis: Age and effectiveness of prophylactic implantable cardioverter-defibrillators. *Ann Intern Med* 2010;153:592-599.
- [4] Theuns DAMJ, Schaer BA, Soliman OI, et al. The prognosis of implantable defibrillator patients treated with cardiac resynchronization therapy: comorbidity burden as predictor of mortality. *Europace* 2011;13:62-69.
- [5] U.S. Dept. of Veterans Affairs, <http://www.va.gov/trm/TRMGlossaryPage.asp>.
- [6] Myerburg RJ, Reddy V, Castellanos A. Indications for Implantable Cardioverter-Defibrillators Based on Evidence and Judgment. *JACC* 2009;54:747-763.
- [7] Tung R, Zimetbaum P, Josephson ME. A Critical Appraisal of Implantable Cardioverter-Defibrillator Therapy for prevention of Sudden Cardiac Death. *JACC* 2008; 52:1111-1121.
- [8] Lopshire JC, Zipes DP. Sudden cardiac death: Better understanding of risks, mechanisms, and treatment. *Circulation*. 2006;114:1134 –1136.
- [9] Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association task force and the European Society of Cardiology committee for practice guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death): developed in collaboration with the European Heart Rhythm association and the Heart Rhythm Society. *Circulation*. 2006;114:e385– e484.
- [10] Fishman GI, Chugh S, DiMarco JP, et al. Sudden cardiac death prediction and prevention report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society workshop. *Circulation*. 2010;122:2335–2348.

- [11] Fox CS, Evans JC, Larson MG, et al. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: the Framingham Heart Study. *Circulation*. 2004;110:522–527.
- [12] Lloyd-Jones D, Adams RJ, Brown TM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2010 update: a report from the American Heart Association. *Circulation*. 2010;121:e46–e215.
- [13] Byrne R, Constant O, Smyth Y, et al. Multiple source surveillance incidence and aetiology of out-of-hospital sudden cardiac death in a rural population in the West of Ireland. *Eur Heart J*. 2008;29:1418–1423.
- [14] Chugh SS, Jui J, Gunson K, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. Community. *J Am CollCardiol*. 2004;44:1268–1275.
- [15] de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, et al. Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, characteristics and survival. *J Am CollCardiol*. 1997;30:1500–1505.
- [16] Vaillancourt C, Stiell IG. Cardiac arrest care and emergency medical services in Canada. *Can J Cardiol*. 2004;20:1081–1090.
- [17] Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA*. 2008;300:1423–1431.
- [18] de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, et al. Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, characteristics and survival. *J Am Coll Cardiol*. 1997;30:1500–1505.
- [19] Straus SM, Bleumink GS, Dieleman JP, et al. The incidence of sudden cardiac death in the general population. *J ClinEpidemiol*. 2004;57:98–102.
- [20] Luu M, Stevenson LW, Baron K, et al. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation* 1989;80:1675-1680.
- [21] Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J*. 1989;117:151-159.
- [22] Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: structure, function, and time-dependence of risk. *Circulation* 1992;85(1):I 1-10.
- [23] Cobb LA, Fahrenbruch CE, Olsufka M, et al. Changing incidence of out-of-hospital ventricular fibrillation, 1980–2000. *JAMA*. 2002;288:3008–3013.
- [24] Herlitz J, Andersson E, Bång A, et al. Experiences from treatment of out-of-hospital cardiac arrest during 17 years in Göteborg. *Eur Heart J*. 2000;21:1251–1258.

- [25] Zheng ZJ, Croft JB, Giles WH, et al. Sudden cardiac death in the United States, 1989 to 1998. *Circulation*. 2001;104:2158–2163.
- [26] Weisfeldt ML, Everson–Stewart S, Sitlani C, et al. Resuscitation Outcomes Consortium Investigators. Ventricular tachyarrhythmias after cardiac arrest in public versus at home. *N Engl J Med* 2011;364:313–321.
- [27] Adabag AS, Therneau TM, Gersh BJ, et al. Sudden death after myocardial infarction. *JAMA* 2008;300:2022–2029.
- [28] Myerburg RJ, Kessler KM, Mallon SM, et al. Life-threatening ventricular arrhythmias in patients with silent myocardial ischemia due to coronary artery spasm. *N Engl J Med* 1992;326:1451–1455.
- [29] Olshausen KV, Stienen U, Schwartz F, et al. Long-term prognostic significance of ventricular arrhythmias in idiopathic dilated-cardiomyopathy. *Am J Cardiol* 1988;61:146–151.
- [30] Hallstrom AP, Ornato JP, Weisfeldt M, et al. Public-access defibrillation and survival after out-of-hospital cardiac arrest. *N Engl J Med*. 2004;351:637–646.
- [31] Katritsis DG, Josephson ME. Sudden cardiac death and implantable cardioverter defibrillators: two modern epidemics? *Europace* 2012;14:787–794.
- [32] Mirowski M, Reid PR, Mower MM, et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *N Engl J Med* 1980;303:322–344.
- [33] Mirowski M, Mower MM, Staewen WS, et al. Standby automatic defibrillator. An approach to prevention of sudden coronary death. *Arch Intern Med* 1970;126:158–61.
- [34] Mirowski M, Mower MM, Mendeloff AI. Implanted standby defibrillators. *Circulation* 1973;47:1135–1136.
- [35] Lown B, Axelrod P. Implanted standby defibrillators. *Circulation* 1972;46:637–639.
- [36] Langer A, Heilman MS, Mower MM, et al. Considerations in the development of the automatic implantable defibrillator. *Med Instrum* 1976;10:163–167.
- [37] Mirowski M, Mower MM, Langer A, et al. A chronically implanted system for automatic defibrillation in active conscious dogs. Experimental model for treatment of sudden death from ventricular fibrillation. *Circulation* 1978;58:90–94.
- [38] The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321:406–412.
- [39] Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;324:781–788.



- [40] Wever EF, Hauer RN, van Capelle FL, et al. Randomized study of implantable defibrillators as first-choice therapy versus conventional strategy in postinfarct sudden death survivors. *Circulation* 1995;91:2195-2203.
- [41] The Antiarrhythmic versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576-1583.
- [42] 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;101:1297-1302.
- [43] Kuck KH, Cappato R, Siebels J, et al. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: The Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000;102:748-754.
- [44] Domanski MJ, Sakseena S, Epstein AE, et al., for the AVID Investigators. Relative effectiveness of the implantable cardioverterdefibrillator and antiarrhythmic drugs in patients with varying degrees of left ventricular dysfunction who have survived malignant ventricular arrhythmias. *Antiarrhythmics Versus Implantable Defibrillators*. *J Am CollCardiol* 1999;34:1090-1095.
- [45] Larsen G, Hallstrom A, McAnulty J. Cost-effectiveness of the implantable cardioverter-defibrillator versus antiarrhythmic drugs in survivors of serious ventricular tachyarrhythmias: results of the Antiarrhythmics Versus Implantable Defibrillators (AVID) economic analysis substudy. *Circulation* 2002;105:2049-2057.
- [46] Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. *Antiarrhythmics vs Implantable Defibrillator study*. *Cardiac Arrest Study Hamburg*. *Canadian Implantable Defibrillator Study*. *Eur Heart J* 2000;21:2071-2078.
- [47] 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. *Multi-center Automatic Defibrillator Implantation Trial Investigators*. *N Engl J Med* 1996;335:1933-1940.
- [48] Buxton AE, Lee KL, Fisher JD, et al. Randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341:1882-1890.
- [49] 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;346:877-883.
- [50] 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 CollCardiol* 8;51:288-296.

- [51] Mitchell, LB; Pineda, EA; Titus, JL; et al. Sudden Death in Patients With Implantable Cardioverter Defibrillators. The Importance of Post-Shock Electromechanical Dissociation. *JACC*, 2002;39:1323-1328.
- [52] Tung R, Josephson ME. Implantable Cardioverter-Defibrillator Therapy for Primary Prevention of Sudden Cardiac Death: An Argument for Restraint. *Card Electrophysiol Clin* 2009;1:105-116.
- [53] 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 : 2481-2488.
- [54] Solomon SD, Zelenkofske S, McVlurray JJ, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 2005;352;2581-2588.
- [55] Wilber DJ, Zareba W, Hall WJ, et al. Time dependence of mortality risk and defibrillator benefit after myocardial infarction. *Circulation* 2004;109:1082-1084.
- [56] Bansch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). *Circulation* 2002;105;1453-1458.
- [57] Strickberger SA, Hummel JD, Bartlett TG, et al. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia- AMIOVIRT. *J Am CollCardiol* 2003;41;1707-1712.
- [58] Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;350:2151-2158.
- [59] Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-237.
- [60] Waldo AL, Camm AJ, deRuyter H, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. *Survival with Oral D-Sotalol*. *Lancet* 1996;348:7-12.
- [61] Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation*. 1998;98:2334-2351.
- [62] Bailey JJ, Berson AS, Handelsman H, et al. Utility of current risk stratification tests for predicting major arrhythmic events after myocardial infarction. *J Am CollCardiol*. 2001;38:1902-1911.
- [63] Wilber DJ, Olshansky B, Moran JF, et al. Electrophysiological testing and nonsustained ventricular tachycardia: use and limitations in patients with coronary artery disease and impaired ventricular function. *Circulation*. 1990;82:350-358.
- [64] Huikuri HV, Raatikainen MJ, Moerch-Joergensen R, et al. Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction. *Eur Heart J* 2009;30:689-98.

- [65] Goldberger JJ. The coin toss: Implications for risk stratification for sudden cardiac death. *Am Heart J* 2010;160:3-7.
- [66] Costantini O, Hohnloser SH, Kirk MM, et al. The ABCD (AlternansBeforeCardioverter Defibrillator) Trial: strategies using T-wave alternans to improve efficiency of sudden cardiac death prevention. *J Am CollCardiol* 2009;53:471-9.
- [67] Goldberger JJ. Evidence-based analysis of risk factors for sudden cardiac death. *Heart Rhythm* 2009;6:S2-S7.
- [68] Stecker EC, Vickers C, Waltz J, et al. Populationbased analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study. *J Am CollCardiol* 2006;47:1161-1166.
- [69] Buxton AE, Lee KL, Hafley GE, et al. MUSTT Investigators. Limitations of ejection fraction for prediction of sudden death risk in patients with coronary artery disease: lessons from the MUSTT study. *J Am CollCardiol* 2007;50:1150-7.
- [70] Hreybe H, Razak E, Saba S. Effect of end-stage renal failure and hemodialysis on mortality rates in implantable cardioverter defibrillator recipients. *Pacing ClinElectrophysiol* 2007;30:1091-1095.
- [71] Lee DS, Tu JV, Austin PC, et al. Effect of cardiac and noncardiac conditions on survival after defibrillator implantation. *J Am CollCardiol* 2007;49:2408-2415.
- [72] Cuculich PS, Sanchez JM, Kerzner R, et al. Poor prognosis for patients with chronic kidney disease despite ICD therapy for the primary prevention of sudden death. *Pacing ClinElectrophysiol* 2007;30:207-213.
- [73] Bruch C, Sindermann J, Breithardt G, et al. Prevalence and prognostic impact of comorbidities in heart failure patients with implantable cardioverter defibrillator. *Europace* 2007;9:681-686.
- [74] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-383.
- [75] Koller MT, Schaer B, Wolbers M, et al. Death without prior appropriate implantable cardioverter-defibrillator therapy: a competing risk study. *Circulation*. 2008;117:1918-26.
- [76] Goldenberg I, Moss AJ, McNitt S, et al, for the Multicenter Automatic Defibrillator Implantation Trial-II Investigators: Relations among renal function, risk of sudden cardiac death, and benefit of the implanted cardiac defibrillator in patients with ischemic left ventricular dysfunction. *Am J Cardiol* , 2006;98:485-490.
- [77] Goldenberg I, Moss AJ. Implantable Device Therapy. *Progress in Cardiovascular Diseases* 2008;50:449-474.
- [78] Zheng ZJ, Croft JB, Giles WH, et al. State-specific mortality from sudden cardiac death-United States, 1999. *MMWR Morb Mortal Wkly Rep* 2002;51:123-126.

- [79] Healey JS, Hallstrom AP, Kuck KH, et al. Role of the implantable defibrillator among elderly patients with a history of life-threatening ventricular arrhythmias. *Eur Heart J* 2007;28:1746-1749.
- [80] Pellegrini CN, Lee K, Olgin JE, et al. Impact of advanced age on survival in patients with implantable cardioverter-defibrillators. *Europace* 2008;10:1296-1301.
- [81] Panotopoulos PT, Axtell K, Anderson AJ, et al. Efficacy of the implantable cardioverter-defibrillator in the elderly. *J Am CollCardiol* 1997;29:556-560.
- [82] Mezu U, Adelstein E, Jain S, et al. Effectiveness of Implantable Defibrillators in Octogenarians and Nonagenarians for Primary Prevention of Sudden Cardiac Death. *Am J Cardiol* 2011;108:718-722.
- [83] Epstein AE, Kay GN, Plumb VJ, et al. Implantable cardioverter-defibrillator prescription in the elderly. *Heart Rhythm* 2009;6:1136-1143.
- [84] Krahn AD, Connolly SJ, Roberts RS, et al. Diminishing proportional risk of sudden death with advancing age: implication for prevention of sudden cardiac death. *Am Heart J* 2004;147:837-840.
- [85] Steinbeck G, Andresen D, Seidl K, et al. Defibrillator implantation early after myocardial infarction. *N Engl J Med*. 2009;361:1427-1436.
- [86] Bristow MR, Saxon LA, Boehmer J, et al; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140-2150.
- [87] Cleland JG, Daubert JC, Erdmann E, et al; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539-1549.
- [88] Moss AJ, Hall WJ, Cannom DS, et al; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361:1329-1338.
- [89] Bernal O, Moro C. Cardiac Arrhythmias in Women. *Rev EspCardiol* 2006;59:609-618.
- [90] Kannel WB, Wilson PW, d'Agostino RB, et al. Sudden coronary death in women. *Am Heart J* 1998;136:205-212.
- [91] Solomon SD, Zelenkofske S, McMurray JV, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure or both. *N Engl J Med* 2005;352:2581-2588.
- [92] Wigginton JG, Pepe PE, Bedolla JP, et al. Sex related differences in the presentation and outcome of out-of-hospital cardiopulmonary arrest: A multiyear, prospective, population-based study. *Crit Care Med* 2002;30:S131-S136.
- [93] Ghanbari H, Dalloul G, Hasan R, et al. Effectiveness of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death in women with ad-

vanced heart failure: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2009;169:1500–1506.

- [94] 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;7:876-882.
- [95] Lilli A, Ricciardi G, Porciani MC, et al. Gender related differences in left ventricular reverse remodeling. *Pacing ClinElectrophysiol* 2007;30:1349-1355.
- [96] Woo GW, Petersen-Stejskal S, Johnson JW, et al. Ventricular reverse remodeling and 6-month outcomes in patients receiving cardiac resynchronization therapy: Analysis of the MIRACLE study. *J Interv Card Electrophysiol* 2005;12:107-113.
- [97] Di Biase L, Auricchio A, Sorgente A, et al. The magnitude of reverse remodelling irrespective of aetiology predicts outcome of heart failure patients treated with cardiac resynchronization therapy. *Eur Heart J* 2008;29:2497-2505.
- [98] Josephson M, Wellens HJ. Implantable defibrillators and sudden cardiac death. *Circulation* 2004;109:2685-2691.
- [99] Stevenson LW, Desai AS. Selecting patients for discussion of the ICD as primary prevention for sudden death in heart failure. *Journal of Cardiac Failure* 2006;12:407-412.

