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Chapter 4

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

Marzia Giaccardi, Andrea Colella, Giovanni Maria Santoro, Alfredo Zuppiroli and Gian Franco Gensini

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/52840

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 20th century, SCD continues to claim 250.000 to 300.000 US lives annualy [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 β-blockers is implemented [31].

5. Primary SCD prevention

The actual guidelines tell:

ICD in primary prevention is indicated for patients with EF ≤ 35% due to prior MI (at least 40 days after infarct) with NYHA class II-III heart failure (and NYHA I if EF ≤ 30%); nonischemic dilated cardiomyopathy with EF ≤ 35% and NYHA class II-III heart failure; and ischemic cardiomyopathy with EF ≤ 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. Limiations 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 this 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 infraction 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 β-blockers at 1 month of follow-up. Similarly in the MUSTT only 29% of the electrophysiologically guided therapy group was on β-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 β-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 was 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 off all-cause mortality failed to reach statistical significance at 29 months. The low event rates in this study of relatively small simple size may also be attributed to the low usage of amiodarone in the control group, and high equitable rates of β-blockers (85%) and ACE inibitor (95%) as background therapy. The SCD-HeFT (Sudden Cardiac Death Heart FailureTrial) 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 see 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. β-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 β-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 β-blockade, overall benefit seemingly from ICD would bee 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 ≤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 (≤ 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 ≤ 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 ≤ 30% [69].

5.3. Comorbidity

Noncardiac comorbidity, such as diabetes mellitus, cerebrovasular 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 ≥ 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 mL min^{-1} 1.73 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 ± 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 ± 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 e 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 indipendent predictors of survival in patients ≥ 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 unlike 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 like 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

http://dx.doi.org/10.5772/52840

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. Comunication 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 comordibity, 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.

Author details

Marzia Giaccardi[1], Andrea Colella[2], Giovanni Maria Santoro[1], Alfredo Zuppiroli[1] and Gian Franco Gensini[2]

1 Cardiology Department ASL 10, Florence, Italy

2 Heart and Vessels Department AOU Careggi, University of Florence, Italy

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