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Risk Stratification and Prevention of Sudden Death in Patients With Heart Failure

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Patients with heart failure can die of progressive refractory heart failure or sudden cardiac death. This article reviews the major clinical predictors of sudden death in patients with heart failure due to left ventricular systolic dysfunction. Although earlier studies have identified many independent univariate predictors of reduced survival in these patients, the positive predictive value of most of them is low. Cardioverter defibrillator implantation has been shown to be the most effective therapy in patients resuscitated after cardiac arrest caused by ventricular fibrillation or poorly tolerated ventricular tachycardia. Low left ventricular ejection fraction, low New York Heart Association functional class, unsustained ventricular tachycardia and inducibility of ventricular arrhythmia in electrophysiological studies may also identify high-risk patients who are candidates for cardioverter defibrillator implantation. The role of amiodarone in preventing sudden death in high-risk patients with heart failure seems to be small. Further studies are needed to improve risk stratification criteria to select patients with heart failure who are candidates for cardioverter defibrillator implantation.

Key words: *Heart failure. Sudden death. Risk stratification.*

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Estratificación del riesgo y prevención de la muerte súbita en pacientes con insuficiencia cardíaca

Los pacientes con insuficiencia cardíaca (IC) pueden fallecer como consecuencia de un fallo progresivo de bomba o de muerte súbita (MS). En este artículo analizaremos los predictores de MS en pacientes con IC secundaria a disfunción sistólica ventricular izquierda. Aunque en los estudios realizados en estos pacientes se han detectado distintos predictores univariados independientes relacionados con la supervivencia, la mayor parte de ellos ha demostrado tener un valor predictivo positivo muy limitado. El desfibrilador implantable ha confirmado ser el tratamiento más eficaz en pacientes resucitados de una parada cardíaca debida a fibrilación ventricular o a una taquicardia ventricular hemodinámicamente mal tolerada. La presencia de una fracción de eyección ventricular izquierda baja, un mal grado funcional, una taquicardia ventricular no sostenida y la inducibilidad de arritmias ventriculares en el estudio electrofisiológico ayudan a identificar a los pacientes candidatos al implante de un desfibrilador. El papel de la amiodarona a la hora de prevenir la MS en pacientes de riesgo elevado con fracaso cardíaco parece pequeño. Se necesitan más estudios que nos ayuden a conseguir una mejor estratificación del riesgo en pacientes con IC, con el fin de reconocer mejor a los candidatos a un desfibrilador implantable.

Palabras clave: *Insuficiencia cardíaca. Muerte súbita. Estratificación del riesgo.*

INTRODUCTION

Earlier chapters in this series have discussed the wide variety of diseases that can lead to heart failure (HF) and underlined the enormous importance of our knowledge of these when establishing adequate diagnosis, prognosis, and treatment for HF. Cardiac death is remarkably common among patients with HF. In Spain, HF is the third cause of cardiovascular death, responsible for 4% of all deaths in men and 8% in women in 2000.[1] Data from the Framingham study estimate a 5-year survival of approximately 50% following diagnosis of HF. Current treatment regimens have led to a decrease in this figure, paradoxically, due to the aging of the population, the number of patients with HF has increased considerably.[2-7]

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Patients with HF can die as a consequence of progressive pump failure (defined as death preceded by symptomatic or hemodynamic deterioration of the patients' status) or from sudden death (SD) (defined as death of a previously stable patient within 1 hour of the onset of symptoms).[8,9] Sudden cardiac death is defined as natural death due to cardiac causes in the form of sudden loss of consciousness within 1 hour of the onset of acute symptoms; a previous history of cardiopathy may be known but the moment and manner of death are unexpected.[10] In this chapter, we will try to learn precisely what can be considered predictors of SD in HF and how SD can be prevented.

Mechanisms of Sudden Death in Patients With Heart Failure

The HF population is heterogeneous which includes patients with preserved systolic function, severe conduction disturbances, severely depressed systolic function but a surprisingly good prognosis, and mildly depressed ventricular contractility that may lead to sudden death or death due to rapid clinical decompensation. The mechanisms that lead to SD in patients with HF are multifactorial and complex.[11] They depend to a great degree on the cause of HF: in ischemic etiologies, SD is fundamentally arrhythmic, due to ventricular tachycardia (VT) or ventricular fibrillation (VF) caused by reentry circuits in the infarcted area, acute ischemic episodes, or bradycardias; in non-ischemic etiologies, the percentage of arrhythmic SD seems lower. Published series report 30%-50% of all deaths in patients with HF are classified as SD[3] and the most frequent cause is arrhythmic. A small percentage (<2%) are considered due to nonarrhythmic causes (stroke, pulmonary, or systemic embolism, ruptured aortic aneurysm).[12] However, one study of SD in patients with implantable cardioverter defibrillators (ICD) showed most terminal events were precipitated by nonarrhythmic causes, simulating SD.[13]

It is often difficult to distinguish between patients who die suddenly and unexpectedly and those who present terminal arrhythmias in the context of progressive hemodynamic deterioration.[14] For example, the AIRE study reported that 45% of SD patients experienced deterioration of HF prior to death.[15] In fact, arrhythmia was the cause of death in only 39% of sudden deaths. In patients with HF, one third of deaths are assumed to correspond to SD, another third to SD during episodes of clinical worsening heart failure and the remaining third to pump failure.[16]

Risk of SD can be determined by the type of cardiopathy, degree of cardiac disease, presence of clinical evidence of acute or chronic pump failure and invasive or noninvasive procedures. However, identifying potential SD patients remains difficult as many are not in the most advanced stages of HF or do not present greater risk of initial arrhythmia. Rather, they belong to the group of patients who are in a better clinical status or who have not yet presented premonitory symptoms or serious arrhythmias (SD incidence is proportionately greater in New York Heart Association [NYHA] functional class II-III patients than in class IV patients) (Figure 1).[17-21] Logically, these patients are more likely to die of SD rather than pump failure.

Predictors of Sudden Death

Multiple neurohumoral factors and abnormalities in size, form and electrical activation of the heart have been shown to influence the natural history of HF. The role of genetic polymorphisms,[22] protein kinase activation,[23] Ca-channel conditions,[24] and alterations in myocardial protein expression[25] in arrhythmic susceptibility and risk of SD in HF are currently being studied.

Risk stratification for arrhythmic events in patients with HF differs substantially depending on whether the underlying cardiopathy is ischemic or non-ischemic. The prognostic significance of noninvasive studies and efficacy of therapeutic measures (drug regimes or devices) can also vary according to etiology. In patients with HF and advanced underl-
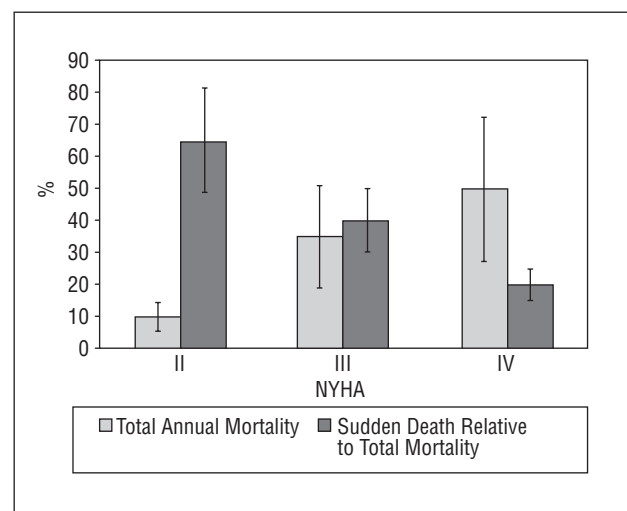

Fig. 1. Total annual mortality and percentage of sudden death compared with total causes of death in patients with heart failure, according to functional class. NYHA indicates New York Heart Association. Adapted from Uretsky and Sheahan.[21]

ying non-ischemic cardiomyopathy, SD occurrence is distributed uniformly over the 24 hours of the day; by contrast, in patients who present baseline ischemic cardiopathy, SD peaks in the 4 pm to 8 pm interval[26].

In patients with HF, developing VT that degenerates into VF is the most frequent cause of SD. Severe bradycardia or electromechanical dissociation (pulmonary embolism, massive acute myocardial infarction [AMI]) is the cause in 5%-33% of cases although the frequency can increase in patients with advanced HF (58%-68% in candidates for transplantation).[11] Too little is known of the prognostic factors that identify patients with HF at greater risk of SD, and the variables that predict the initiating mechanism (tachycardias or bradycardias).[21,27] The following factors have been found to associate with SD in patients with HF:

Left Ventricular Systolic Function

Left ventricular ejection fraction (LVEF), determined by echocardiography or contrast or radioisotopic ventriculography is an important predictor of long term post-AMI cardiac mortality (represented by SD in a high percentage of patients). Gosselink et al[28] analyzed patients with AMI treated with thrombolysis or primary angioplasty and found a mortality rate of 16% at 30±10 months if LVEF was <0.40 versus 2% if LVEF was >0.40. Prognosis is significantly worse when depressed LVEF is accompanied by clinical and radiological signs of congestive heart failure. In patients with LVEF ≤0.40 on admission, Nicod et al[29] found a 1-year mortality rate of 26% in those with clinical signs and symptoms of HF versus 12% in those without clinical signs and symptoms (*P*<.01). The same differences occurred if LVEF was 0.41-0.50 or >0.50 (19% vs 6%; *P*<.01, and 8% vs 3%; *P*<.02, respectively). Curtis et al[30] analyzed the association between ventricular function and mortality in non-hospitalized patients with stable HF. In patients with LVEF ≤45%, they found a linear reduction in mortality as LVEF increased (LVEF <15%, 51.7%; LVEF, 36%-45%, 25.6%; *P*<.0001); such association persisted in a multivariate analysis. In contrast, mortality was comparable in subgroups with LVEF>45% (LVEF, 46%-55%, 23.3%; LVEF>55%, 23.5%; *P*=.25). These authors also found progressive deterioration of systolic function associated with greater probability of arrhythmic death (LVEF>55%, 2.8%; LVEF, 46%-55%, 4.2%; LVEF, 26%-35%, 6.3%; LVEF≤15%, 13.9%; *P*<.01). This was confirmed in other studies such as TRACE[31] study. However**,** it remains controversial and is contradic-

ted by other studies, such as DIAMOND. In patients with LVEF<25% and LVEF, 26%-35%, DIAMOND[32] reported that ventricular dysfunction associated with increased overall mortality, but the frequency of arrhythmic cardiac death was similar (≥50%). As mentioned earlier, SD is more likely to occur in patients with NYHA functional class II-III than those with class IV, in whom the principal cause of death is progression of HF.[17-21] These findings contrast with results of randomized studies of prevention of SD by ICD implantation in which the device proves more effective in patients with lower EF.[33-35] Current thinking is that LVEF is a limited predictor and that often it is impossible to distinguish between patients with high arrhythmic mortality and those with high mortality due to pump failure.

Ventricular function also predicts post-AMI arrhythmic events. In fact, one third of patients with severely depressed LVEF die suddenly and incidence of ventricular tachyarrhythmias is greater.[36] The sensitivity, specificity, positive predictive value and negative predictive value of LVEF to detect arrhythmic events are 56%-71%, 74%-83%, 11%-22%, and 96%-98%, respectively[37]. Given the low positive predictive value, isolated systolic function is insufficient to detect patients at high risk of post-AMI arrhythmia so we must combine this with other diagnostic tests. For example, type B natriuretic peptide has recently been identified as an independent predictor of SD in patients with chronic heart failure.[38]

Ischemia

Although SD is frequently a result of ventricular arrhythmia, the role of ischemia is often underestimated. Prevalence of acute coronary syndrome and its relationship with SD were examined in the autopsies of 171 patients with HF.[39] Among patients with significant coronary heart disease, an acute coronary event was identified in 54% of sudden deaths and 32% of deaths from pump failure, although patients' coronary conditions might have been suspected prior to death. In contrast, an acute coronary syndrome was only found in 5% of SD patients and in 10% of those who died from heart failure among patients without previous coronary heart disease. Over 4 years, the Maastricht Circulatory Arrest Registry[40] recorded 492 cases of SD. In 59% of women and 52% of men, SD was the first evidence of heart disease. Among patients with a personal history of heart disease, 77% presented coronary heart disease (66% of whom had suffered at least one previous AMI) and

26% presented HF, with a mean latency period from the first episode of decompensated HF to SD of 4.3 years.

Electrocardiographic Monitoring

Ventricular extrasystoles (VE). Ventricular extrasystoles can be frequent and complex, occurring in 70%-95% of patients with HF.[41] Isolated VE have not been show to associate with worse prognosis nor has their pharmacologic suppression been demonstrated to reduce SD.[42] Therefore, administration of drugs to diminish VE (blockers or amiodarone) is only recommended in patients who have symptoms caused by arrhythmias or in whom the frequency of VE causes tachycardiomyopathy.[43]

Nonsustained ventricular tachycardia (NSVT). Bouts of NSVT are found in 50%-80% of patients with HF or cardiomyopathy.[41] Data suggest presence of NSVT cannot be considered an independent predictor of SD. The CHF-STAT study analyzed the effect of amiodarone in patients with frequent VE (71% with coronary heart disease) and found an apparent association between NSVT and increased SD. However, in multivariate analysis LVEF and NYHA functional class were independent predictors of mortality, NSVT was not.[44] Data from PROMISE[41] support these findings. Based on 1080 patients with functional class III-IV, NSVT frequency initially seemed an independent predictor of SD but, a change of statistical model showed it added no new prognostic information when clinical variables such as age, gender, blood pressure, functional class and LVEF were considered.

Accelerated idioventricular rhythm. Accelerated idioventricular rhythm, or slow VT (frequency range, 50-120 beats/min), is present in 8% of patients with HF or cardiomiopathy.[45] Treatment is not indicated unless it is highly symptomatic as a relationship with the development of VT or VF has not been demonstrated.

Sustained ventricular tachycardia. Sustained VT is infrequent and occurs in <5% of patients with HF or cardiomyopathy.[41] Most have inducible VT in the electrophysiological study (EPS) and remain inducible in spite of the use of antiarrhythmic drugs.[46] In contrast to other arrhythmias, sustained VT is a valued predictor of SD.[47] Consequently, as with those who survive SD from VT or VF, patients with sustained VT receive ICD implants.[48,49]

Other electrocardiographic findings. In patients with HF, studies analyzing presence of left bundle branch block,[50,51] QRS complex duration (120-150 ms),[52] prolonged QTc interval,[53] and atrial fibrillation[54] find these have no conclusive prognostic value for SD incidence.

Other Noninvasive Tests

Late potentials. Signal-averaged electrocardiograms can predict VT inducibility in patients with non-ischemic cardiomyopathy and NSVT.[55] However, both findings are rare and neither negative late potentials nor absence of VT inducibility ensures good prognosis. Consequently, signal-averaged electrocardiograms are not used in clinical decision-making.

Heart rate variability (HRV). HRV is obtained from beat-by-beat measurement and partly reflects the cycle of inspiration (increased vagal activity) and expiration (reduced vagal activity). Reduced HRV correlates with disturbance of the autonomous nervous system balance with a predominance of sympathetic over parasympathetic activity.[56] Various studies have shown low HRV to be a powerful predictor of mortality from any cause in patients with previous infarction and in those with dilated cardiomyopathy.[57,58] Reduced HRV has also been confirmed as a powerful predictor of VF and SD in patients with ischemic cardiomyopathy.[59] A recent study[60] analyzed the prognostic value of HRV with controlled respiration for arrhythmic SD in 202 patients with dilated cardiomyopathy and moderate-severe HF. Results showed that low-frequency power (LFP) HRV with controlled respiration ≤ 11 ms^2 and presence of ≥ 83 VE per hour in Holter monitoring were independent predictors of arrhythmic SD (relative risk [RR]=3.0 and RR=3.7, respectively). Although reduced HRV is a powerful predictor of SD independently of other noninvasive risk markers, when considered in isolation its positive predictive value remains quite limited ($\geq 30\%$). The best prognostic information is offered by the standard deviation of intervals between normal beats (SDNN) and the triangular index, which estimates mean variability. Although cutoff points have been clearly established, on the basis of published studies SDNN<50 ms or a triangular index <15 can be considered to identify patients with severely reduced HRV; SDNN values of 50-100 ms or triangular index values of 15-20 identify those with moderately reduced HRV. The predictive value of HRV alone is modest but can improve significantly when combined with other no-

ninvasive markers. However, the combination of usable noninvasive markers and optimal cutoff points to achieve maximum predictive capacity has yet to be defined. Moreover, HRV has substantial limitations: patients must be in sinus rhythm, interference from VE and its modification for posture, physical activity and respiratory cycle.

Baroreflex sensitivity (BRS). Autonomous nervous system activity can also be studied by evaluating the effect of pharmacologic stimulation of arterial baroreceptors (bradycardia reflected by increased blood pressure with epinephrine) on heart rate. The multicenter ATRAMI study enrolled 1284 patients with recent infarction to compare the possible additional prognostic value of baroreflex sensitivity with HRV. Presence of reduced BRS (slope of linear regression lines R-R vs blood pressure <3 ms/mm Hg) associates with increased risk of global cardiac mortality, independently of HRV. Reduced HRV (SDNN<70 ms) is also associated with greater mortality (RR=2.8 and RR=3.2, respectively)[61]. Moreover, combining reduced BRS and reduced HRV offers additional prognostic value (RR=8.5). Relative risk for LVEF<0.35 associated with reduced BRS was 8.7 and associated with low HRV, RR was 6.7. The study concluded that examining vagal baroreceptor reflexes in patients with recent infarction adds independent prognostic information on LVEF to that provided by HRV measurement. Principal limitations are the need to measure systolic blood pressure beat-by-beat and the difficulty of defining threshold values for use in clinical practice. Recently, a new measure has been designed to explore BRS. Turbulence of cardiac frequency reflects fluctuation of cardiac cycle duration in sinus rhythm after isolated VE. However, it does not provide adequate risk stratification for ventricular arrhythmia in patients with idiopathic dilated cardiomyopathy.[62]

T wave alternans (TWA). T wave alternans defines the electrocardiographic profile in which T wave morphology polarity changes from one beat to another indicating heterogeneity in repolarization (electrical vulnerability). Dependant on cardiac frequency, TWA presents maximum predictive capacity in the 100-120 beats/min range, attained through exercise or atrial stimulation. Averaged electrocardiography shows a subtle, invisible T wave variation: T wave microalternans.[63] In patients with HF, presence of TWA during exercise predicts arrhythmic events. A study of 107 patients in functional class II-III with LVEF≤45% and no previous history of ventricular arrhythmias evaluated the presence of TWA during exercise. At 14 months, patients with TWA presented more arrhythmic events than those with an indeterminate test or without TWA (21%, 9%, and 0%, respectively).[64] In a study that only included patients with dilated non-ischemic cardiomyopathy, TWA also showed a good correlation with presence of ventricular arrhythmias.[65] Some authors suggest that patients with non-ischemic dilated cardiomyopathy, LVEF<40%, NYHA functional class II-III, and positive TWA test should be indicated for ICD implant[66]. In patients with ischemic cardiopathy, presence of TWA shows high sensitivity and specificity to predict presence of inducible arrhythmias during EPS and to detect patients at low risk of arrhythmic events (sensitivity 93%, negative predictive value 98%, positive predictive value 28%).[67] T wave alternans can also help identify high-risk patients who fulfill MADIT II criteria.[68]

Electrophysiological Study

Various studies, generally involving patients with coronary heart disease, have shown the limitations of EPS when used to select antiarrhythmic drug treatment. Although they clearly suppress ventricular arrhythmia inducibility, clinical recurrence of arrhythmias is high. In the ESVEM study of patients with VT or survivors of cardiac arrest with mean LVEF 33%, 1-year arrhythmic recurrence was 20% with sotalol and >20% with other drugs on trial.[69] The principal use of EPS is in patients with coronary heart disease and left ventricular dysfunction who also present NSVT. Inducibility of ventricular arrhythmias in these patients identifies them as good candidates for ICD implant, as reported in MADIT I and MUSTT.[70,71]

The EPS has also been used in relatively small series of patients with idiopathic dilated cardiomyopathy.[72-74] Probability of pharmacologically suppressing inducible VT has been seen to vary, with rates <40% in some studies. Although patients in whom inducibility is suppressed generally evolve favorably, some series find that arrhythmias recur in ≤33% of patients.[75,76] Moreover, patients who are not inducible are at high risk. Consequently, most patients with non-ischemic cardiomyopathy and sustained VT or VF receive an ICD implant.

The study of new prognostic factors does not cease. One recent report on patients with ICD, most of whom have ischemic cardiopathy, demonstrated that physical and emotional (anger) stress are associated with discharges appropriate to a defibrillator for malignant ventricular arrhythmias.[77]

Risk Stratification

Preventing arrhythmic SD in patients with HF is one of the greatest challenges in HF treatment today. Arrhythmic risk stratification in patients with HF remains highly complex. Our ability to identify patients with HF at high risk is far from satisfactory. Many studies are small and populations differ from the patients we encounter in daily clinical practice. We need to develop precise, reproducible methods to identify patients at high risk of SD. EPS is expensive, invasive and imperfect, especially in HF with non-ischemic etiologies. On the other hand, studies that evaluate noninvasive tests occasionally differ in the parameters used to measure the same variable and in 20%-30% of patients they are not interpretable due to the presence of atrial fibrillation or other limitations intrinsic to the tests themselves. Moreover, the positive predictive value of these studies is greater in patients with ischemic cardiopathy than in those with idiopathic dilated cardiomyopathy. As shown earlier, the number of prognostic factors is high and we lack adequate knowledge of their interaction. Equally, prognostic significance of the variation in the time when results are obtained from different tests has barely been studied.[78] Nor do we know enough about the time and circumstances in which these are of greatest value as the association of these variables with SD may differ in the progressive evolving stages of HF, in relation to concomitant pharmacologic treatment, etc.

Consequently, a complete, individualized approach based on clinical and instrumental data is fundamental in dealing with each patient, as is the integration and use of results from invasive and noninvasive prognostic studies. Only thus will we gain access to adequate prognostic information and be capable of identifying high-risk patients who can benefit from optimal antiarrhythmic drug therapy and/or devices.

Recently published results of the Marburg Cardiomyopathy Study of 343 patients with dilated cardiomyopathy are in accordance with this approach to risk stratification. Patients underwent prospective evaluation of multiple potential predictors of arrhythmic risk including LVEF, left ventricle size, presence of late potentials, NSVT findings in ambulatory monitoring, QT interval dispersion, HRV, BRS, and TWA.[79] After 52 months of follow-up, 46 (13%) patients suffered serious arrhythmic events (VT, VF, or SD). In multivariate analysis, only LVEF was independently, statistically associated with arrhythmic risk in patients in sinus rhythm (RR=12.3 for a 10% reduction in LVEF). The combination of LVEF<30% and NSVT increased arrhythmic risk 8.2-fold by comparison with patients with LVEF≥30% without NSVT.

The Marburg results reflect the difficulty of definitively establishing the prognostic role of the multiple variables possibly involved in SD in patients with HF, despite the enormous research effort being employed in the field. Once again, the fundamental importance of classical risk factors such as left ventricular function is reinforced.

Therapeutic Recommendations

Secondary Prevention of SD: Patients Resuscitated After SD or Presenting Sustained VT

An ICD implant is the most frequent treatment of choice in these patients although exceptionally radiofrequency ablation, surgery, or transplant may be used. It is important to know that no antiarrhythmic drug offers sufficient protection in this clinical context and the use of drugs is reserved for patients who reject devices or are not candidates for ICD implantation. This has been demonstrated in 3 randomized studies (CASH, CIDS, and AVID) (Table 1) of ICD efficacy versus antiarrhythmic drugs (amiodarone, beta-blockers, sotalol, or propaphenone) in survivors of cardiac arrest or in patients at high risk of VT, 50% of these with HF.[80-82] Metaanalysis of all data found a statistically significant 25% reduction in mortality with ICD compared with amiodarone, due to a 50% reduction in sudden death.[83] The absolute reduction in all-cause mortality was 7%, meaning that 15 ICD implants would save 1 life.

Current ACC/AHA/NASPE 2002 recommendations establish the following as class I or IIa indications for ICD implantation as secondary prevention:[49]

– Cardiac arrest for VT or VF without transitory, reversible cause (class I, evidence A).

– Sustained spontaneous VT associated with structural cardiopathy (class I, evidence B).

– Sustained spontaneous VT in patients without structural cardiopathy that is not subsidiary to other treatments (class I, evidence C).

– Nonsustained VT in patients with coronary heart disease, previous AMI, ventricular dysfunction, and VT or VF inducible in the EPS that cannot be suppressed by class I antiarrhythmic drugs (class I, evidence A).

In ICD implanted patients, around a quarter of deaths are arrhythmic in origin. These may be due to arrhythmias that are untreatable despite multiple charges or electromechanical dissociation.[84]

TABLE 1. Randomized Clinical Trials Presenting Results on Secondary Prevention of Sudden Death With Implantable Cardioverter Defibrillator Implantation*

Study	n	Population	Inclusion Criteria	Treatment Groups	Sudden Death ICD
AVID[82]	1016	ICM+NICM	Cardiac arrest due to VF or cardioverted SVT+ LVEF≤40%+symptoms or cardioverted SVT+syncope, NYHA I-III	ICD vs antiarrhythmic drugs (d,l sotalol, amiodarone)	Reduction
CIDS[81]	659	ICM+NICM	Cardiac arrest due to SVT or VF, or syncope of probable/certain arrhythmic origin, NYHA I-IV	ICD vs amiodarone	Same
CASH[80]	349	ICM+NICM	Cardiac arrest due to SVT or VF, NYHA I-III	ICD vs antiarrhythmic drugs (metoprolol, propaphenone, amiodarone)	Reduction

*ICD: implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; ICM, ischemic cardiomyopathy; NICM, nonischemic cardiomyopathy; NYHA, New York Heart Association; SVT, sustained ventricular tachycardia.

These results show that patients with LVEF≤35% benefit most from ICD implantation and that in those with greater LVEF the benefits are practically inappreciable. These benefits extend to patients with severely depressed LVEF who are more likely to die from pump failure and for whom imperceptible benefits were predicted.[88]

Only antiarrhythmic drugs (amiodarone or sotalol) can be used in patients with severe ventricular dysfunction. Generally their use is recommended to diminish the number of episodes of VT (in patients with multiple ICD discharges) or treat other arrhythmias such as atrial fibrillation.[69,86-90] We cannot forget that these negative effects may also occur in patients: proarrhythmic capacity can increase the number of discharges; slowing of ventricular tachyarrhythmia frequency places this below the threshold for antitachycardia therapy; elevation of defibrillation thresholds, and possible incorrect detection of QRS complex morphology alteration.[91] In patients who present multiple ICD discharges, radiofrequency ablation of the VT responsible is also a good option. In these patients, induced tachycardias are very occasionally rapid. However, thanks to new navigation systems that facilitate localization of the circuits without the need for tachycardia, ablation can be successful. On the other hand, bundle branch reentrant VT can be present in ischemic and non-ischemic cardiomyopathy, usually in patients with advanced HF. This is relatively simple to treat by radiofrequency ablation of the branches of the His-Purkinje system.

Ablation of sustained VT by surgery is exceptional and is practically limited to patients with previous AMI associated with left ventricular aneurysm. In contrast, faced with the impossibility of controlling arrhythmia, heart transplants are frequently required.[92,93] In these cases, arrhythmic events are due to substantial deterioration of pump function[88]. Selective ICD implantation has been shown to reduce mortality in patients on heart transplant waiting lists.[93,94]

Syncope

The AVID study included patients with sustained VT with syncope, whereas CIDS studied patients with syncope of unknown origin in whom the presence of spontaneous sustained or induced VT was later determined.[81,82] This and other studies have also proved that patients with HF and syncope of unknown origin have a high risk of SD.[95-98] In a follow-up of almost 500 patients with HF and non-ischemic cardiomyopathy in functional class III or IV, 1-year incidence of SD was much higher in those with unexplained syncope (45% vs 12% in those without syncope).[95] Similarly, a 1-3 year follow-up of patients with cardiomyopathy and ICD implant, left ventricular dysfunction and unexplained syncope found that in one third of cases discharges appropriate to the ICD were produced by VT or VF[96,97]; this even occurred in patients with negative EPS.[98]

Current ACC/AHA/NASPE 2002 recommendations establish a class I indication for ICD implantation as secondary prevention of syncope when this is of unknown cause and sustained VT is induced with hemodynamic repercussions in the EPS and drug treatment is inefficient, not tolerated or not desired (evidence B). They do not establish any class IIa indication. To date, there is no proof of the benefit of ICD implantation in patients with syncope and negative EPS, so this therapeutic decision must be taken on an individual basis. Similarly, they establish a class IIb indication, evidence C, in patients with ventricular

TABLE 2. Principal Randomized Clinical Trials on the Benefit of Antiarrhythmic Drugs in Patients With Heart Failure*

Study	n	Population	Inclusion Criteria	Treatment Groups	Sudden Death With Antiarrhythmic Drugs
GESICA[100]	516	ICM+NICM	Dilatation or ventricular dysfunction left, symptomatic HF, NYHA II-IV	Amiodarone vs placebo	Reduction
CHF-STAT[44]	674	ICM+NICM	LVEF≤40%, VE, symptomatic HF, NYHA II-IV	Amiodarone vs placebo	Same
DIAMOND-CHF[32]	1518	ICM+NICM	LVEF≤35%, admission for HF 30 days previous, HF symptomatic, NYHA II-IV	Dofetilide vs placebo	Same
SCD-HeFT[102]	2500	ICM+NICM	LVEF≤35%, NYHA II-III	ICD vs amiodaronevs control	Same (control)

*ICD indicates implantable cardioverter defibrillator; VE, ventricular extrasystoles; LVEF, left ventricular ejection fraction; HF, heart failure; ICM, ischemic cardiomyopathy; NICM, nonischemic cardiomyopathy; NYHA, New York Heart Association.

dysfunction and syncope of indeterminate origin with stable ventricular arrhythmia inducible in the EPS, and in syncope in patients with severe structural cardiopathy in whom invasive and noninvasive tests are negative. They also establish as a class IIb indication, evidence C, ICD implantation for heart transplant waiting list patients and those who present severe symptoms (e.g. syncope) attributable to ventricular tachyarrhythmias.[49]

Primary Prevention of SD

Antiarrhythmic drugs. The role of antiarrhythmic drugs in preventing SD in patients with cardiomyopathy, HF and asymptomatic arrhythmias (VE or NSVT) seems limited and, usually, counterproductive (due to the proarrhythmic effect and worsening of left ventricular function).[32,99] Amiodarone, however, produces limited proarrhythmic activity and can even improve systolic function. It is the only drug to demonstrate positive results in some studies, especially in non-ischemic cardiomyopathy (Table 2).[32,100,101] Nevertheless, the SCD-HeFT study seems to show it has no beneficial effect at all in relation to prevention of death,[102] as well as carrying the potential risk of its now well known secondary effects.[103]

Beta-blockers. In several studies (MERIT-HF, metoprolol[19]; CIBISII, bisoprolol[104]; COPERNICUS, carvedilol[105,106]), beta-blockers have been found to improve global survival in patients with HF, partly because they reduce SD. This benefit is maintained even in patients in the worst functional class (NYHA III-IV) and with most severe left ventricular dysfunction (LVEF≤25%).[107] The COMET study showed greater chances of survival in patients administered carvedilol versus metoprolol, although these results are contro-

versial as doses administered are not considered equivalent.[108]

Consequently, assuming beta-blockers are tolerated, they should be administered to patients with HF regardless of functional class.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARA-II). It is fully accepted that these drugs prolong survival, prevent decompensation and progression of disease, and improve quality of life in patients with HF. However, their capacity to diminish incidence of arrhythmic SD in these patients is under debate due to contradictory results found in large clinical trials in patients with HF and post-AMI (CONSENSUS; SOLVD; V-HeFT II, enalapril[9,109,110]; SAVE, captopril[111]; AIRE, ramipril[15]; ATLAS, lisinopril[112]; ELITE II, losartan[113]; Val-HeFT, valsartan[114]; CHARM, candesartan[115,116]). It is generally believed that even though all studies of HF show they prolong survival, their capacity to avoid SD is limited.[117,118]

Aldosterone antagonists. Spironolactone[119] and eplerenone[120] have been proven to reduce total mortality and SD in patients with advanced HF.

Implantable cardioverter defibrillator. Most studies that evaluate the efficacy of ICD implantation have enrolled patients with previous AMI and severe left ventricular dysfunction (Table 3). The MADIT I and MUST studies enrolled patients with NSVT, LVEF≤35%-40% and inducible VT in the EPS. In MADIT II, inclusion criteria were less strict, calling only for LVEF ≤30%. We cannot forget that MADIT I, MUST, and other studies centered on patients with known ischemic cardiopathy and previous infarction; they did not directly address the problem of ICD use

in HF. The first 2 small-scale studies to study the benefit of ICD implantation on survival in patients with idiopathic or non-ischemic cardiomyopathy and severe left ventricular dysfunction (CAT[121], AMIOVIRT[122]) did not find positive results. The role of ICD implants in these patients continues to be debated. Recently, 2 larger studies underline their efficacy:

– DEFINITE: 458 patients with non-ischemic dilated cardiomyopathy, LVEF ≤35% and VE or NSVT were enrolled in this study[123]. Approximately 85% of patients received recommended optimal medical treatment (ACE inhibitors and beta-blockers). Patients were randomized to ICD or drug treatment only. At 2 years, an almost significant trend towards a reduction of total mortality in patients with ICD (8.1% vs 13.8%; *P*=.06) was found. This difference was statistically significant in patients in functional class III (13% vs 33%). Equally, the authors found a significant reduction in SD in patients with ICD implants, although the number of events was limited.

– SCD-HeFT trial: this study included 2521 patients with HF in functional class II (70%) and III (30%), with ischemic (52%) and non-ischemic (48%) cardiomyopathy, and with LVEF ≤35%, during a mean 45.5 month follow-up.[124] Patients had received optimal drug treatment (ACE inhibitors or ARA-II, 96%; beta-blockers, 69%; spironolactone, 19%). Three treatment groups were established: placebo, amiodarone, and ICD (VVI mode pacing). Total mortality at 3 years by group was ICD 17.1%, treatment with amiodarone 24%, and placebo 22.3%; at 5 years total mortality was 28.9%, 34.1%, and

35.8%, respectively. No differences were found between amiodarone and placebo (RR=1.06 [0.86-1.30]; *P*=.53), nor for beta-blockers. However, comparison of ICD and placebo showed a clear benefit in total mortality (RR=0.77 [0.62-0.96]; *P*=.007) with curves beginning to separate after 18 months of follow-up. Analysis of the benefit of ICD by functional class showed this was greater in class II than in class III (RR=0.54 [0.40-0.74] and RR=1.16 [0.84-1.61], respectively). Results also showed a non significant trend towards greater protection in non-ischemic (0.73 [0.50-1.04]) vs ischemic (0.79 [0.60-1.04]) cardiomyopathy. Presence of QRS complex duration ≥120 ms (RR=0.67), treatment with beta-blockers (RR=0.68) and absence of diabetes (RR=0.67) made treatment with ICD significantly more beneficial.

Severely depressed systolic function and NYHA functional class can help select patients with HF at risk of SD. But, if we only take account of these data, the population with HF subsidiary to ICD implantation is enormous. It is more and more obvious that ICDs are the only really efficient means of preventing SD. The problem is that of selecting candidates because ICD implantation is expensive and cannot be routinely offered to all patients as this would have an enormous impact on health care costs. We need to establish the most cost-efficient risk stratification strategy possible. Moreover, ICD implantation is not free from adverse effects, such as inappropriate discharges, problems with the cable or infections.[125] Both DDD and VVI mode pacing can increase right ventri-

TABLE 3. **Randomized Clinical Trials That Offer Results in Primary Prevention of Sudden Death With Implantation of an Implantable Cardioverter Defibrillator***

Study	n	Population	Inclusion Criteria	Treatment Groups	Sudden Death
MADIT[170]	196	ICM	LVEF<35%, previous AMI, NSVT, SMVT in EPS, NYHA I-III	ICD vs antiarrhythmic drug	Reduction
CABG Patch[129]	900	ICM	LVEF<36%, surgical revascularization, positive SAE, NYHA I-IV	ICD vs control	Reduction
MUSTT[71]	704	ICM	LVEF≤40%, previous AMI, NSVT, SMVT in EPS, NYHA I-III	Therapy guided by EPS (ICD or antiarrhythmic drug) vs control	Reduction
MADIT II[68]	1232	ICM	LVEF≤30%, previous AMI, NYHA I-III	ICD vs control	Reduction
CAT[121]	104	NICM	LVEF≤30%, recent onset of NICM (≤9 months), NYHA II-III	ICD vs control	Same
AMIOVIRT[122]	103	NICM	LVEF≤35%, NSVT, NYHA I-III	ICD vs amiodarone	Same
DEFINITE[123]	458	NICM	LVEF≤35%, NSVT or VE, NYHA I-III	ICD vs control	Reduction
SCD-HeFT[102]	2500	NICM+ICM	LVEF≤35%, NYHA II-III	ICD vs amiodarone vs control	Reduction

*ICD indicates implantable cardioverter defibrillator; EPS, electrophysiological study; SAE, signal-averaged electrocardiogram; VE, ventricular extrasystoles; LVEF, left ventricular ejection fraction; AMI, acute myocardial infarction; ICM, ischemic cardiomyopathy; NICM, nonischemic cardiomyopathy; NYHA, New York Heart Association; SMVT, sustained monomorphic ventricular tachycardia; NSVT, nonsustained ventricular tachycardia.

cular contraction asynchrony and contribute to HF decompensation.[35,126,127] Indiscriminate ICD use would entail low-risk patients accepting potential adverse effects without any ultimate benefit.

The ACC/AHA/NASPE 2002 recommendations for ICD implantation do not make express reference to patients with non-ischemic HF. Nor do they establish any class I indication in primary prevention. As class IIa indication, evidence B, we find patients with LVEF ≤30% at ≥1 month post-AMI or 3 months after surgical revascularization.[49]

Cardiac resynchronization therapy deserves a separate mention.[128] More than a third of patients with HF present delayed conduction in the atrioventricular node and His-Purkinje system. This gives rise to a deleterious effect in diastolic and systolic function (asynchrony in ventricular contraction) that can be remedied by a resynchronization device, leading to improved quality of life and functional capacity and lowering rehospitalizations.[129] The COMPANION study, unfinished at the time of writing, includes 1520 patients in sinus rhythm, functional class III-IV, with LVEF<35%, left ventricular end-diastolic volume ≥6 cm, PR interval >150 ms and QRS>120 ms. Patients are randomized in three treatment groups: optimal drug treatment, cardiac resynchronization therapy, or ICD with resynchronization. In an interim analysis, ICD with resynchronization presented a 43% relative reduction of mortality due to all causes in comparison with drug treatment.[130] As yet, we do not know the capability of cardiac resynchronization therapy to reduce SD in patients with HF, or which subgroup might benefit more, although research suggests therapy might improve some prognostic factors of SD.[131]

CONCLUSIONS

Risk stratification of SD in patients with HF is currently carried out using classical parameters such as clinical history, NYHA functional class and LVEF in the hope that we can better predict which patients are likely to suffer arrhythmic events.

In patients with HF who have been resuscitated after an SD event or who have suffered sustained VT or unexplained syncope, ICD implantation is the treatment of choice unless counterindicated or a heart transplant is needed. If functional class is poor despite optimal medical treatment, it is advisable to evaluate the use of an ICD capable of ventricular resynchronization. If functional class is acceptable, programmed ventricular stimulation should be avoided if possible using an ICD requiring 40 beat/min or algorhythms to impede stimulation. Antiarrhythmic drugs (amiodaro-

ne or sotalol) are only used in patients with ICD to treat arrhythmias such as atrial fibrillation or VT when these are frequent. In the latter case, radiofrequency ablation is a good option.

If NSVT has been determined in patients with HF and ejection fraction ≥40% due to ischemic cause, it is advisable to perform an EPS and consider ICD implantation if ventricular arrhythmias are induced. In patients with HF of any etiology with LVEF≥35% and functional class II-III, as in patients with LVEF≤30% due to ischemic cause, prophylactic ICD implantation can be seriously studied taking into account the risks and situation of each individual patient.

In patients with HF and LVEF>35%, nonsustained ventricular arrhythmia should not be treated as it has not been demonstrated to worsen prognosis because it is not symptomatic. If drug treatment is to be administered, amiodarone, and sotalol are the antiarrhythmic drugs of choice for patients with abnormal LVEF. In patients with HF and preserved LVEF, only symptomatic arrhythmias should be treated and there are no specific counterindications for antiarrhythmic drugs

Initially, risk stratification of arrhythmic death is carried out by determining LVEF and learning whether the cause of the HF is ischemic. To date, other diagnostic tests cannot be considered essential in establishing prognosis in these patients. Finally, we cannot forget that, independently of a good etiologic diagnosis and of the stratification criteria we have analyzed, patients with HF should receive beta blockers, vasodilators, spironolactone and anticoagulation therapy (if required to improve clinical condition or diminish the risk of embolism), assuming the drugs are well tolerated and that there is no counterindication to their use.[132,133] All of this, while we wait for new alternative therapies.[34]

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