More on the pathophysiology and prevention of sudden death - Part I

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IMPACT OF PSYCHOSOCIAL FACTORS ON VENTRICULAR ARRHYTHMIAS AND SUDDEN DEATH

Iván Mendoza Mujica, Juan Marques, Federico Moleiro, Iván Mendoza-Britto, Francesca Misticchio, Alvaro Matheus, Agustin Castellanos*

*Experimental Cardiology Section, Institute of Tropical Medicine, University Hospital of Caracas, Caracas, Venezuela, *Section of Cardiology, University of Miami, Miami, FL, USA*

Several studies provide convincing evidence that psychosocial factors contribute significantly to the genesis of malignant ventricular arrhythmias and sudden death. Recent prospective epidemiological and clinical studies, supported by experimental studies, suggested a link between factors such as anger, anxiety, depression, hostility, social supports and work characteristics and ventricular arrhythmias, cardiac autonomic nervous function and sudden death. The number of physicians providing cardiologic care who think about psychologic issues on an everyday basis is very low. Given the public health and clinical importance of the association between psychosocial factors and arrhythmic risk, further research is required to understand arrhythmia triggering by emotional factors.

Psychosocial factors such as anger, fear, stress, anxiety, depression and grief have been linked with precipitation of myocardial infarction, myocardial ischemia ventricular arrhythmias and sudden death[1-5].

Epidemiological and clinical studies have shown that sudden death increases in population experiencing emotionally devastating disasters such as war, earthquake, terrorist attacks, important sporting event, mud slidding[3-7]. In the case of the World Trade Center and Pentagon attacks, even people who were not in the vicinity of attacks responded viscerally, leading researchers to propose likely rose in response to the events, potentially responding to media coverage of the attacks[8]. A six-fold increase in the incidence of life threatening arrhythmias was observed in a population of 148 patients with implantable cardioverter defibrillators (ICD) shortly after the World Trade Center disaster on September 11 2001, presumably triggered by mental stress[8]. Proximity to the World Trade Center did not influence the frequency of events which suggests that media coverage of this catastrophe elicited stress at home watching events unfold that was equivalent to being close to the World Trade Center itself[8].

Several evidences have suggested that psychological factors may be an important factor in the development of malignant ventricular arrhythmias and sudden death[4,5-10]. Sympathetic arousal can trigger arrhythmic events. Ventricular tachycardia such as sudden death, occurs more frequently in the morning, at the time of peak of catecholamine level and lowest vagal tone as demonstrated in patients with ICD[10]. Ventricular tachycardia occurs more frequently on Monday in working patients with ICD[11]. In addition, ventricular and atrial arrhythmias increase during the stress of being on-call in medical interns[12].

The population of patients with ICD provides a unique opportunity to evaluate the effects of mental stress on human arrhythmias. Lampert et al.[13] reported that mental stress (anger recall and mental arithmetic) shortens cycle lengths and renders induced ventricular tachycardia more difficult to terminate. These alterations in ventricular tachycardia characteristics were associated with increased norepinephrine levels, which are known to rise during mental stress, but with no evidence of ischemia on ECG or

continuous ejection fraction monitoring. In these patients with defined arrhythmic substrate, anger destabilized the circuit, creating a potentially more dangerous arrhythmia[13]. In another publication from the same investigators anger triggered life-threatening ventricular arrhythmias in a group of 42 patients with ICD[5].

We examined a series of 57 consecutive victims of sudden death. Among them, we found anger as the most frequent trigger mechanism preceding the final event[14].

Summary of strength and consistency of evidence

Hemingway et al.[4] reviewed the evidence from prospective epidemiological and clinical studies, supported by experimental studies, that suggest a link between psychosocial factors such as anger, anxiety, depression, hostility, social supports and work characteristics and ventricular arrhythmias, cardiac autonomic nervous function and sudden death. Overall, 88/96 (92%) of identified published studies investigating psychosocial and social aspects of arrhythmic risk were positive. This remarkable consistency across different populations and study designs, lends cautions support to a casual association.

Pathophysiological mechanisms underlying the relationship between psychosocial factor and ventricular arrhythmias and sudden death

The precise mechanism and process by which psychosocial factors influence ventricular arrhythmia and sudden death are yet to be clarified. There are two main hypotheses[4]. One possibility is that psychosocial factors cause a severe perturbation in the autonomic cardiac nervous system. This may predispose susceptible individuals to lethal arrhythmias. Another possibility is that heightened sympathetic arousal, catecholamine secretion and decreases in parasympathetic tone induced by mental stressors are damaging the heart and its vasculature, and also play a role in the development of atherosclerosis lesions and provocation of ischemia[4].

Therapeutic implications

Given the public health and clinical importance of the association between psychosocial factors and arrhythmic risk, further research is required to understand arrhythmia triggered by emotional factors. This may help lead to therapeutic strategies that will decrease arrhythmia and the incidence of sudden death[1-5]. Avoidance of stress, anger or anxiety is not possible for individual leading a full life. However, integrative medicine including psychosocial and behavioral interventions, such as stress management, anger reducing interventions, development of specifically targeted behavioral interventions (based on profiling of patients factors[1-9]).

It has been suggested that the number of physicians providing cardiologic care who think about psychologic issues on an everyday basis is very low[15]. Most cardiologists are not equipped to deal with psychologic issues in cardiac patients[15]. That is why cardiovascular specialists need to collaborate with psychologists, psychiatrists, social workers and other mental health professionals. These experts can help cardiac patients to deal with psychological issues that may put them at risk for further cardiovascular problems[15].

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PRIMARY PREVENTION OF SUDDEN DEATH IN DILATED CARDIOMYOPATHY

Massimo Zecchin, Gianfranco Sinagra

Department of Cardiology, Cattinara Hospital, Trieste, Italy

Sudden death (SD) is a leading cause of death in western countries, and is estimated that about 300 000-400 000 people die suddenly in the United States every year[1]. In Italy there are 57 000 SD every year, meaning that 10.2% of total deaths are sudden (data from the Annuario ISTAT 2000).

Patients who already suffered of sustained ventricular tachyarrhythmias have a particularly high risk of SD. Unfortunately, the chances of surviving a first cardiac arrest are extremely low and patients who can benefit from secondary prevention therapies are few. On the other hand, the majority of subjects dying suddenly did not have any history of severe heart disease or were not considered at high risk before the event[2]. For this reason, pivotal issues for a significant reduction of SD in the general population are 1) the identification of patients at higher risk of SD, and 2) the development of treatments with an acceptable benefit/cost ratio.

In patients with ischemic heart disease no single parameter predicting SD has been identified; positive predictive value was generally low for most parameters considered, while negative predictive value was higher in some cases[3], meaning that it is generally possible to rule out patients at lower risk but is still difficult to identify subjects who will die suddenly. However, it is well established that some subgroups (i.e. patients with ejection fraction ≤ 30, ≤ 40%, non-sustained ventricular tachycardia and inducible ventricular tachyarrhythmias) have a better outcome if treated with implantable cardioverter-defibrillators (ICD)[4-6].

In patients without ischemic heart disease primary prevention of SD is also more difficult, probably because of the different mechanisms of ventricular arrhythmias and SD in this population.

A history of syncope is associated with a higher risk of SD also in patients with negative electrophysiological study[7]. Grimm et al.[8] found a high rate of appropriate interventions in patients with dilated cardiomyopathy and a history of syncope treated with ICD, and these data were confirmed also by our experience[9].

The role of severe left ventricular dysfunction in non-ischemic cardiomyopathy is controversial: although it has been recognized as a predictive factor of total mortality and SD[10-12], in the Cardiomyopathy Trial[13] patients with recent-onset dilated cardiomyopathy and ejection fraction ≤ 30% did not get any benefit from ICD in comparison with conventional treatment.

Neither the role of ventricular arrhythmias is clear: for some authors[8,14] the presence and number of ventricular arrhythmias were predictive of SD. However, in the Cardiomyopathy Trial patients with and without ventricular tachycardia on baseline Holter monitoring had similar survival after 2, 4 and 6 years and survival of patients with non-sustained ventricular tachycardia was not improved by ICD therapy[13]. Also in a recent analysis of a large population from our registry (n = 554) with a long follow-up (81 ± 58 months), non-sustained ventricular tachycardias were not associated with an increased risk of total mortality, SD and major arrhythmic events[15].

Finally, probably because of the different electrophysiological mechanisms of ventricular tachyarrhythmias in non-ischemic vs ischemic cardiomyopathy, electrophysiological evaluation is of little help for the identification of patients at higher risk of SD[16].

It is possible that the association of more parameters could help to increase sensitivity and specificity. Grimm et al.[11] found that an ejection fraction ≤ 30%, a left ventricular end-diastolic diameter ≥ 70 mm and the presence of non-sustained ventricular tachycardias were significantly correlated with a significantly higher risk of SD, and the association of ventricular tachycardia with left ventricular dilation or dysfunction identified patients with a 14-fold risk of arrhythmic events. In addition, patients with ventricular tachycardia and ejection fraction ≤ 30%, if treated with ICD, had a similar intervention rate (37% after a follow-up of 36 ± 22 months) as patients treated because of previous sustained ventricular tachyarrhythmias or syncope[8]. Our group[17] identified the association of ejection fraction ≤ 30% and left ventricular end-diastolic diameter ≥ 70 mm in patients with a long history of disease (68 ± 45 months) as the best predictor of SD in a large population with dilated cardiomyopathy, on optimal medical treatment, with a long follow-up. Patients treated with ICD for primary prevention because considered at high risk of SD according to clinical criteria had a 1-year rate of appropriate interventions similar to patients treated for secondary prevention. The rate of appropriate interventions was especially higher in patients with both severe left ventricular and dilation (76% after a follow-up of 21 ± 14 months)[17].

In the Cardiomyopathy Trial[13] ICD treatment did not significantly reduced total mortality in patients with ejection fraction ≤ 30%. A possible explanation was the low incidence of SD in the study population, all subjects with a recent diagnosis of disease (< 9 months). Patients with a recent-onset dilated cardiomyopathy may have an unpredictable outcome, and more than 50% of them can significantly improve left ventricular function in the next months[18]. In addition, the rate of SD, as shown recently by our group, is lower during the first years since diagnosis, but becomes the first cause of death in patients with a follow-up > 5-6 years, when the rate of heart failure death declines significantly[17].

In the AMIOVIRT patients with ejection fraction ≤ 35% and non-sustained ventricular tachycardia treat-

ed with ICD did not have a better survival than patients treated with amiodarone[19], but also in this study the SD rate was extremely low (3 out of 103 patients after 2.0 ± 1.3 years).

No definite data on the role of amiodarone for SD prevention in patients with dilated cardiomyopathy are available; however, it is possible that this drug could be more efficacious in patients with non-ischemic than ischemic cardiomyopathy[20,21]. Also in the AMIOVIRT an appropriate intervention for ventricular arrhythmias (mean rate of 218 ± 40 b/min) was delivered in 16 out of 51 (31%) patients of the ICD group[19], suggesting a role of the drug in preventing potentially lethal arrhythmias.

It is possible that new technologies, as T-wave alternans analysis[22], will help to stratify patients at higher risk who could benefit of more aggressive treatments and recently completed or ongoing trials[23,24] will help to identify the best strategy to prevent SD in patients with dilated cardiomyopathy; at the moment the selection of patients with dilated cardiomyopathy at higher risk of SD and the best therapeutic option for these patients are not well defined yet.

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PHARMACOLOGICAL APPROACH FOR THE PREVENTION OF SUDDEN DEATH IN PATIENTS WITH CONGESTIVE HEART FAILURE

Miran F. Kenda, Miran Šebeštjen*

*Department of Cardiology, *Department of Angiology, University Medical Center, Ljubljana, Slovenia*

Patients with heart failure (HF) are at increased risk of sudden cardiac death (SCD). This fact is not only a medical but also a great socio-economic problem. Despite of the significant progress in treatment and prevention of cardiovascular diseases, the incidence and prevalence of HF have been increasing especially in elderly. The most common cause of chronic HF as well as SCD is coronary artery disease (CAD) in about 70% of patients. The most frequent cause of SCD in HF are malignant ventricular arrhythmias, especially ventricular tachycardia caused by acute coronary event coupled with previous myocardial damage and pump failure. The degree of functional impairment classified by NYHA classification is the simplest variable to predict overall mortality. Left ventricular dysfunction in terms of ejection fraction has been established as a major predictor of outcome in studies evaluating CAD, secondary prevention of SCD as well as in multiple HF studies. Neurohormonal activity has also been related to prognosis. The signal-averaged ECG may have value in predicting SCD in post-myocardial infarction patients. Heart rate variability is reduced in patients with congestive HF and could be a useful predictor of death. Electrophysiologic studies have identified patients at higher risk for SCD in CAD groups. Unfortunately, there are not until now undisputedly accepted markers to identify the patients with HF who are most prone to die suddenly. Concerning therapeutic strategies in HF to prevent SCD, data about ACE-inhibitors, beta-blockers and amiodarone are well documented; ACE-inhibitors for preventing the progression of CAD and HF, beta-blockers with relief of ischemia, reduction of heart rate and maintenance of favorable autonomic balance, and amiodarone with its unique complex antiarrhythmic action, and also combination of amiodarone and beta-blockers. Implantable cardioverter-defibrillators in patients with HF are effective and should be probably considered for less functional impaired patients with HF at increased risk.

The scope of the problem

Sudden cardiac death (SCD) is one of the greatest problems in modern cardiology because of its dramatic presentation and the socio-economic implications due to a large number of cases that occur. Recent reports have shown that about 80% of cases take place in patients with coronary artery disease (CAD)[1]. Despite significant progress in the treatment and prevention of cardiovascular diseases the incidence and prevalence of heart failure (HF) have been increasing steadily in recent years, especially in the elderly. The most common cause of chronic HF is no longer hypertension or valvular heart disease, as it was in past decades, but rather CAD. In 13 multicenter HF treatment trials reported over the past 10 years, involving > 20 000 patients, CAD was the underlying etiology of HF in nearly 70% of the patients. The importance of CAD is nevertheless underestimated due to the fact that the prognosis of patients with HF and CAD is considerably worse than that of patients without CAD[2].

Reported incidence rates of SCD range between 0.36 to 1.28 per 1000 inhabitants per year. Age, sex, and the presence or absence of a history of cardiovascular disease are factors related with incidence of SCD. SCD rates as high as 8/1000/year have been reported in males between 60 and 69 years of age and a prior history of cardiac disease. With the assumption that 300 000 SCDs per year occur in the United States, the population incidence is expected to be > 1/1000/year. Therefore, 999/1000 individuals without risk for SCD per year should be treated to reduce the risk of only 1/1000 individual per year. In this regard, from the cost-benefit point of view it seems reasonable to give only general lifestyle advice on a population-wide basis. Of course, higher-risk subgroups of the population should be identified. Asymptomatic individuals with multiple risk factors for coronary disease are at higher risk than the population at large, while individuals with manifest CAD are at still greater risk. Identification and appropriate management of these patients is the interest of modern cardiology. However, subgroups with progressively greater annual risks of SCD comprise a progressively smaller proportion of the total numbers of SCDs in the population[3]. Therefore, the prevention and measures to decrease the prevalence of coronary disease is the mainstay of the reduction of the SCD burden on the society.

The mode of death in patients with HF as SCD has been reported in the range of 35-50%[4]. Many studies of patients with HF have described the incidence of SCD in HF according to the NYHA functional classification[5] (Table I).

Causes of sudden cardiac death in heart failure

Most studies of HF have described the major cause of SCD as arrhythmic. In some studies a small percentage of cases (< 2%) are the result of non-arrhythmic causes such as cerebral vascular accident or pulmonary embolisms. The myopathic ventricle is extremely arrhythmogenic, which in part may be related to

Table I. The percent of annual mortality and sudden cardiac death mortality regarding the NYHA functional classification.

NYHA class	Annual mortality (%)	Sudden cardiac death (%)
II	5-15	50-80
III	20-50	30-50
IV	30-70	5-30

mechanical factors, including chronic stretch, remodeling and other less well understood factors[6]. Meissner et al.[7] have estimated that in ischemic heart disease, monomorphic ventricular tachycardia from structural heart disease and reentrant tachycardia may account for 20 to 60% of all initiating arrhythmias, whereas polymorphic ventricular tachycardia or ventricular fibrillation may account for 20 to 40% and bradyarrhythmias for 5 to 25%. Our results also show that ventricular tachycardia is an important cause of SCD in our post-myocardial infarction (MI) patients (relative risk 2.38, p = 0.004)[1]. Pathologic examinations in patients with CAD dying suddenly have shown a potentially anatomic basis for an ischemically-mediated arrhythmia in more than 80% of cases (occlusive thrombus in 30%, mural thrombus in 44% and plaque fissure in only 8%)[8]. Particularly relevant for the patients with HF is the possibility that further myocardial necrosis, coupled with previous myocardial damage, may produce enough additional pump dysfunction that if SCD does not occur, rapidly developing myocardial failure will. This point is especially important in considering cardiogenic shock therapy where survival is measured in hours and days rather than in months and years.

Risk stratification for sudden cardiac death in heart failure

There are no undisputedly accepted markers to identify the patients with HF who are most prone to die suddenly. The degree of functional impairment, classified by the NYHA classification is the simplest variable to predict overall mortality[5]. Left ventricular dysfunction in terms of ejection fraction has been established as a major predictor of long-term outcome in many studies evaluating CAD, secondary prevention of SCD as well as in multiple HF studies[9]. Objective measurements of functional impairment particularly oxygen consumption at peak exercise predict mortality[10]. The level of plasma norepinephrine can be used to stratify the risk of death but it is used rarely because of the expense and technical requirements. Other neurohormones like plasma renin activity in some studies and atrial natriuretic peptide have also been related to prognosis[11,12]. Hyponatremia has also shown some prognostic value as a degree of activation of the renin-angiotensin system. All these blood levels tend to be abnormal in the most functionally impaired patients so they tend to separate the patients with a very bad prognosis from a bad prognosis.

The degree of activation of the sympathetic nervous system simply represents the resting heart rate. The extent of myocardial fibrosis and injury is seen by intraventricular conduction defects. Ventricular arrhythmias, especially non-sustained ventricular tachycardia and complex ventricular ectopy, portends a worse prognosis within that functional class for overall mortality rather than specifically for SCD. In a subgroup analysis of the GESICA trial, non-sustained ventricular tachycardia appeared to identify patients with a higher tendency to have SCD as well as total mortality[13]. Direct evaluation of electrical disturbances in the failing heart has provided conflicting data on the predictive value of various tests. Late potentials are considered to represent markers for the presence of an arrhythmogenic substrate. The signal-averaged ECG may have value in predicting SCD in post-MI patients; its value in patients with HF from ischemic cardiomyopathy is less clear. The signal-averaged ECG does not have clear prognostic value in patients with non-ischemic cardiomyopathy[5]. A decrease in heart rate variability has been demonstrated in patients who are susceptible for ventricular arrhythmias and SCD. Heart rate variability is decreased in patients with HF though the prognostic significance of these findings remains unclear. The consensus is that heart rate variability may be useful in the early stages of HF to predict SCD than in advanced HF. A potential explanation of this observation may be that progressive HF leads to atrial stretch. In clinical conditions where right atrial dilation occurs, there is reduced heart rate variability.

Electrophysiological studies by programmed ventricular stimulation have identified patients at higher risk for SCD in patients with CAD and ischemic cardiomyopathy. The utility of programmed ventricular stimulation is unclear in patients with non-ischemic cardiomyopathy. Some authors have reported that the combination of signal-averaged ECG and programmed ventricular stimulation has a greater prognostic value for SCD. We are left with a situation that the higher-risk patient can be easily determined clinically and that more sophisticated and expansive studies may improve risk stratification for overall mortality[5].

Therapeutic strategies in heart failure to prevent sudden cardiac death

Prevention of SCD is the prevention of CAD, since risk factors for both are the same[4,13].

ACE-inhibitors substantially decrease mortality in patients with varying degrees of HF. In addition, in post-MI patients both with and without HF symptoms have shown a decrease in mortality in long-term follow-up. The effect of ACE-inhibitors on SCD is less clear. In patients with less severe functional impairment in the SOLVD Treatment trial and in asymptomatic or minimally symptomatic patients in the SOLVD Prevention trial, there was a slight non-significant decrease in SCD[14,15]. The same results concerning SCD were shown in the SAVE study. The situation is somewhat different in post-MI patients. The TRACE study used the ACE-inhibitor trandolapril in post-MI patients (ejection fraction < 35%, with or without mild HF). A significant reduction in overall deaths, SCDs and myocardial fail-

ure deaths was seen[16]. The possibility of a small effect of ACE-inhibitors on the prevention of SCD is strengthened from data from the Veterans Administration HF Trial II (V-HeFT II) comparing enalapril with the combination of isosorbide dinitrate and hydralazine. An overall reduction in mortality with enalapril was significant at 2 years. There were fewer SCDs in the enalapril group[17]. On the basis of the latest findings of the ACE-inhibitor activities and the fact that CAD is the main reason of HF, we believe that ACE-inhibitors have preventing effects on CAD and HF progression and through this fact also at least a small reduction of SCD. HOPE[18] and EUROPA[19] studies in patients with multiple risk factors and in patients with CAD showed a decrease in overall mortality, which in part was probably influenced by SCD decrease, but no subgroup analyses are available.

Beta-blockers in post-MI studies have been shown to decrease mortality. The incidence of SCD also decreases. This effect is particularly striking in patients with presumed or documented left ventricular dysfunction. The benefits of beta-blockers are likely due to multiple effects, including relief of ischemia, prevention of cardiac rupture, reduction of heart rate and maintenance of favorable autonomic balance. It is important to underline that the favorable effects of beta-blockers are not tightly linked to the suppression of ventricular arrhythmias since beta-blockers suppress arrhythmias only at modest extents. Therefore, although beta-blockers do not act directly on ventricular arrhythmias, they have nevertheless a substantial effect by continuously modulating the arrhythmogenic influences on the substrate. By the opinion of several national consensus committees, those drugs are underused in patients after acute MI[20]. The combination of three trials using carvedilol in patients with mostly mild to moderate HF showed a significant reduction in all-case, HF and SCD mortality rates[21]. The meta-analysis of 3023 patients from 18 published randomized, double-blind, placebo-controlled trials of beta-blockers for HF showed that the risk of death was decreased by 49% in trials of non-selective beta-blockers (e.g. carvedilol) versus 18% in $beta_1$-selective agents (e.g. metoprolol); no other differences in outcomes were detected between the two types of beta-blockers[22]. Patients assigned to beta-blocker therapy were 32% more likely to experience an improvement in NYHA functional class. This study strengthens the case for beta-blockers, especially non-selective agents such as carvedilol, in patients with congestive HF[22]. Results from the CIBIS II trial with bisoprolol in patients with HF show a 32% reduction on total mortality and a 45% reduction in SCD[23]. Similar results – total mortality reduction 34% and SCD reduction 14% – are published for the MERIT-HF study with metoprolol CR/XL[24].

Amiodarone. No antiarrhythmic agent has shown evidence of preventing SCD in HF except amiodarone. Amiodarone is a unique antiarrhythmic drug originally class III agent which also exerts class I, II, and IV effects, with several antiarrhythmic action and unusual pharmacokinetics[25]. A number of randomized placebo-controlled trials have been done to evaluate the impact of amiodarone on total mortality in patients at risk for malignant ventricular arrhythmias and SCD. These trials have included two overlapping high-risk populations: survival of MI and patients with chronic congestive HF. In the GESICA[12], a placebo-controlled prospective randomized trial of amiodarone in patients with severe HF, the studied population was stratified according to the presence of non-sustained ventricular tachycardia. Patients treated with amiodarone had a risk reduction of total mortality of 28%. Furthermore, amiodarone was associated with significantly lower rate of SCD (27%) and death from progressive congestive HF (23%). In the CHF-STAT[26] placebo-controlled randomized trial that examined the effect of amiodarone on total mortality in patients with HF and ≥ 10 premature ventricular beats, amiodarone had no effect on total mortality at 2 years. Anyway there was a trend in favor of amiodarone among patients with idiopathic cardiomyopathy. The results of two largest amiodarone trials have raised much controversy and have not resolved the therapeutic dilemma regarding the use of amiodarone in post-MI patients. Both trials CAMIAT and EMIAT reported a substantial statistically significant reduction in risk of SCD (48 and 35% respectively), but both trials failed to detect significant differences in total and cardiac mortality between the amiodarone and placebo groups[27,28]. It is important to know that both CAMIAT and EMIAT showed that there was an important synergistic interaction between amiodarone and beta-blockers in reduction of total mortality. These findings suggest that the benefit of amiodarone is likely to be additive to that of beta-blockers. However a greater potential benefit of using a combination therapy with beta-blockers and amiodarone in reducing SCD and total mortality among post-MI patients is shown. The meta-analysis of 6500 post-MI patients in HF shows that prophylactic amiodarone would be a reasonable treatment in patients at particularly high risk. The effect results in an overall reduction of 13% in total mortality[29].

Only three groups of drugs have shown efficacy in preventing SCD in patients after acute MI: amiodarone, beta-blockers and ACE-inhibitors. The data from our own group of patients clearly show that a complete revascularization procedure prevents SCD (odds ratio 0.395, $p = 0.003$)[30].

Implantable cardioverter-defibrillators. There is much enthusiasm that implantable cardioverter-defibrillators (ICD) can prevent SCD in HF[31]. First, it must be admitted, even by the most enthusiastic advocate of ICD therapy, that scientific data for ICD use in primary prevention in the setting of HF are not available. Data used to suggest that ICD saves lives include studies in patients who have had a cardiac arrest or syncope,

studies using historic control patients and studies in which left ventricular function but not functional impairment from HF has been characterized. Published survival results have not uniformly favored the ICD. There are reasons to be concerned that the benefit from an ICD in HF setting may indeed be limited and probably considered to less functional impaired patients with HF at increased risk[32].

The results of the MADIT trial[33] showed that in the highly selected highrisk post-acute MI group, primary prevention of SCD could be achieved (with a risk reduction of 53% over an average of 27 months). This study points out that a very high-risk group can be obtained, which may help to maximize the life-saving potential of the ICD. The ICD as an initial treatment for secondary prevention in patients with severe symptomatic ventricular arrhythmias has been shown in the AVID trial[34] to decrease overall mortality in comparison with antiarrhythmic therapy. This study, which was interrupted early because of the favorable effect of ICD on mortality, showed a 38% reduction at 1 year and a 25% at 2 and 3 years in comparison with amiodarone or sotalol. Data from pharmacologic trials and secondary ICD prevention studies suggest that less functionally impaired patients with HF will have the greatest gain in overall survival from prophylactic ICD placement. This fact underscores the importance of developing a most exact risk profile for SCD in this large group of patients.

Amiodarone prevents supraventricular arrhythmias which could be reason for ICD inappropriate discharges. It also prevents non-sustained ventricular tachycardia or makes them slower and hemodynamic more effective[35].

In the study of Mitchell at al.[36] in patients with CAD who have received an ICD, lipid-lowering therapy was associated with reduction in the probability of ventricular tachycardia/ventricular fibrillation recurrence, suggesting that part of the benefit of lipid-lowering therapy may be due to an antiarrhythmic effect.

Data from studies on pharmacologic therapy suggest that the greatest benefit in preventing SCD occurs in patients with left ventricular dysfunction with at most mild to moderate symptoms. As functional impairment increases, drugs become less effective. ACE-inhibitors provide only modest protection against SCD in patients with established HF. In patients with asymptomatic left ventricular dysfunction after MI, a small benefit in decreasing SCD may be present. The possibility that beta-blockers and amiodarone decrease the risk of SCD is supported by some but not all data. Statins might act as antiarrhythmic therapy. This was shown in only one study, so further prospective studies are needed to confirm these results. Although several arrhythmic markers of SCD can be identified, the results of antiarrhythmic therapy aimed at primary prevention of SCD have been disappointing. The most encouraging prospect, at present, for preventing sudden death is the transvenous ICD, where technologic advances have been remarkable.

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