

Sudden cardiac death

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Abstract

Sudden death is a frequent event whose causes may not be anticipated, but often has a cardiac origin. Sudden cardiac death is the final consequence of many pathophysiological mechanisms which have caused acute or chronic arrhythmogenic disease. Single or multifactorial triggering factors may interact with the arrhythmogenic substrate to lead to lethal arrhythmias. Stratifying populations according to risk is feasible, but the immediate priority is prevention of triggering and disease-promoting factors.

ICD therapy is the best treatment for most survivors of sudden cardiac death. Drug therapy, catheter ablation, anti-tachycardia surgery or heart transplant are only first-choice treatments for very few patients. Choosing the best therapy is an individual decision based on the patient's clinical picture, the type of arrhythmia seen and hospital experience in the various techniques.

Key words: Sudden death, ventricular tachycardia, ventricular fibrillation, bradycardia, heart disease

Heart disease is the most frequent cause of death in the western world [1-4]. Among the various manifestations of this, sudden cardiac death is especially dramatic as are its social and economic repercussions [5].

The term *sudden death* has been used in a variety of ways by epidemiologists, clinicians and forensic pathologists. There is no consensus regarding the precise definition of *sudden* in terms of the time that must elapse from the onset of symptoms to death. From a clinical point of view, sudden death is generally considered to be attributable to natural causes (excluding therefore accidents, suicide, poisoning,

Resum

La mort sobtada representa un problema clínic per resoldre que succeeix amb molta freqüència. En un elevat percentatge de casos, l'origen es cardíac. La mort sobtada d'origen cardíac es la conseqüència final de múltiples mecanismes fisiopatològics possibles, que promouen un substrat arritmogènic de manera aguda o crònica. El desenvolupament d'un o múltiples factors desencadenants pot interactuar amb el substrat arritmogènic i facilitar l'aritmia final amb característiques letals. A pesar de que l'estratificació de risc de les poblacions es factible, la prevenció dels mecanismes desencadenants i promotors de malalties es la mesura més necessària i correcta.

El tractament amb el cardioversor-desfibril·lador implantable (ICD) és el més segur per la gran majoria de persones en les que s'ha pogut interrompre la mort sobtada cardíaca. Només en un petit subgrup de pacients molt seleccionats, la teràpia amb fàrmacs, l'ablació transcateter, la cirurgia antitaquicàrdica o el trasplantament de cor poden ésser considerades com el tractament electiu. La decisió del millor tractament per cada pacient cal considerar-la de forma individualitzada, tenint en compte les seves característiques, el tipus d'aritmia que ha sofert el pacient i la pròpia experiència de cada hospital en un tècnica determinada.

etc.) and appears within an hour of the onset of symptoms. In more than 90% of cases sudden death is caused by arrhythmias and is characterized by loss of consciousness and absence of an arterial pulse, without prior circulatory collapse; whereas sudden death due to heart failure involves progressive failure and leads to circulatory collapse before cardiac arrest occurs. If the patient is found dead, death is considered sudden if the subject was seen alive and well in the preceding 24 hours [6].

Epidemiology

According to a study by the WHO, the annual incidence of sudden death in industrialized countries ranges from 19 to 159 cases per 100,000 males and from 35 to 64 per 100,000

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females. Thus, it represents between 10 and 32% of all natural deaths, depending on the time that elapses from the onset of symptoms to death, making it the most common form of fatal cardiac disease. About 50% of patients with ischemic heart disease die suddenly [1-8].

Sudden death shows a clear circadian rhythm, occurring most frequently between 7 am and 11 am. This concurs with the higher incidence between these times of various manifestations of ischemic heart disease (infarction, coronary spasm, QTc variability, etc). As regards age, there are two peaks in the incidence of sudden death. The first peak is from birth to 6 months of life (infantile sudden death syndrome); the second peak occurs from 45 to 75 years and is characterized by an increasingly greater frequency of ischemic heart disease after the age of 40 [6]. A multivariate analysis carried out on the Framingham study, including all coronary risk factors, showed that age, systolic pressure, cigarette consumption, and relative body weight are all risk factors that are independently related to the incidence of sudden death. In females, besides age, only cholesterolemia and vital capacity were associated independently with increased risk of sudden death.

Pathophysiology

The pathophysiology of sudden death needs to be viewed as a multifactorial problem that is inseparable from associated diseases and that includes the precursors of sudden death, the final step responsible for sudden death as well as markers and triggering mechanisms of this event [9-15].

Associated diseases

In about 90% of cases, sudden death occurs in persons with heart disease. Most heart diseases may be associated with sudden death (Table I), as we outline below:

Ischemic Heart Disease

Although sudden death occurs in all forms of heart disease, in the west, ischemic heart disease is the most commonly occurring associated disease [1-5]. Several mechanisms can produce potentially fatal arrhythmias in patients with ischemic heart disease and it is often difficult to define the precise mechanism of a given episode [9,10,16-19]. At one extreme is the patient without a prior infarction who has an acute occlusion of a major epicardial coronary artery and develops ventricular fibrillation during the immediate phase of acute infarction [7,20-22]. This patient illustrates the role of acute severe transmural and persistent ischemia. At the other end of the spectrum lies the patient with a history of one or more previous myocardial infarctions, in whom postinfarction scarring has provided the anatomic substrate for a rapid reentrant ventricular tachycardia, triggering ventricular fibrillation, with a resultant hemodynamic collapse and sudden death; new ischemia does not necessarily have to be present [10,17,23-26]. The majority of sudden death

Table 1. Principal causes of sudden death *

Ischemic heart disease
Cardiomyopathies
Idiopathic dilated
Hypertrophic
Arrhythmogenic ventricular dysplasia
Valvular heart disease
Electrophysiologic abnormalities
Pre-excitation syndromes
Long-QT syndrome
Conduction system abnormalities
Brugada syndrome
Congenital cardiac abnormalities (e.g. abnormal coronary origin)
Other cardiovascular diseases (e.g. pulmonary embolism, dissecting aneurysm of the aorta)
Sudden death without apparent structural heart disease
Noncardiac diseases (e.g. massive gastrointestinal bleeding, cerebral hemorrhage)
Sudden infant death syndrome

* Heart failure is frequently present

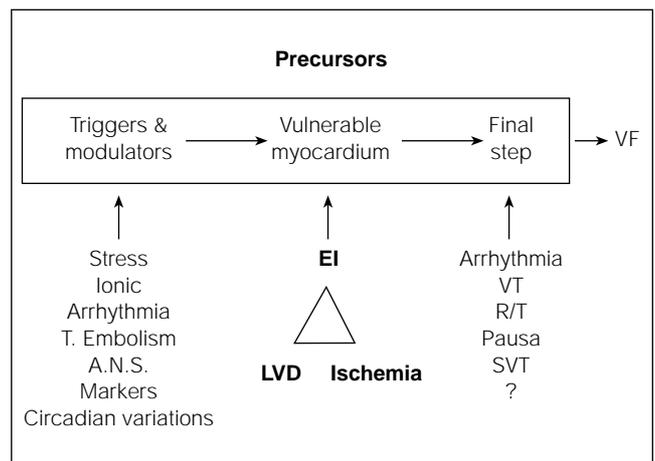


Figure 1. Cascade of factors leading to ventricular fibrillation (VF). ANS = autonomic nervous system, EI = Electrical instability, LVD = left ventricular dysfunction, VT = ventricular tachycardia, R/T = R-on-T phenomenon, SVT = supraventricular tachyarrhythmias.

victims with ischemic heart disease belong to these two groups. In these patients sudden death is usually produced by a complex interaction between several trigger-types – autonomic nervous system dysfunction, electrolyte imbalance, or drug toxicity among others – and the presence of different interactions between electrical instability, residual ischemia and left ventricular dysfunction (Figure 1) [10,27].

Autopsy and clinical studies differ in their findings of coronary thrombi and the evidence of new ischemia in sudden death patients. Evidence of coronary artery thrombi is reported in between 20% and 50% of sudden death victims. However, only about 25% of patients resuscitated from an out-of-hospital cardiac arrest will develop new Q-wave myocardial infarctions. While there may be persistent repolarization abnormalities and enzymatic evidence of necrosis in another 25% of patients, these changes are not specific for a

new infarction and may be caused by prolonged hypotension during a primary arrhythmia. There is also evidence suggesting a contributing role for acute ischemia without any signs or symptoms of infarction [9,10,21,22,27].

Coronary spasm and other diseases of the coronary arteries not due to atherosclerosis, such as an abnormal left coronary origin, may give rise to either myocardial infarction with late ventricular tachycardia or to arrhythmias mediated by acute intermittent ischemia and sudden death [6,7,27,28].

Cardiomyopathies

Idiopathic dilated cardiomyopathy is the primary cardiac diagnosis in 5-10% of resuscitated cardiac arrest victims. Sudden death accounts for about a half of all deaths in patients with this diagnosis. Sudden death often occurs relatively late in the course of dilated cardiomyopathy, after hemodynamic symptoms have been present for some time. Even with well-documented clinical episodes of ventricular tachycardia or fibrillation, similar arrhythmias are frequently not inducible at the time of electrophysiologic study [29,30]. In patients with dilated cardiomyopathy and very advanced heart failure, bradiarrhythmia, rather than tachyarrhythmia, is the final event that leads to sudden death.

In hypertrophic cardiomyopathy, sudden death often occurs in young adults who usually have had no prior cardiac symptoms. Polymorphic ventricular tachycardia or primary ventricular fibrillation appear to be the initial arrhythmia at the time of cardiac arrest. Patients with hypertrophic cardiomyopathy are also at risk from AV block and the severe hemodynamic compromise that may produce a cardiovascular collapse can occur during any rapid supraventricular tachycardia in these patients. In young athletes under 35, sudden death occurs fundamentally in patients with cardiomyopathy, usually, but not exclusively, of the hypertrophic variety. In contrast, sudden death in athletes over 35 is due to ischemic heart disease in 80% of victims [31,32].

Patients with arrhythmogenic right ventricular dysplasia may also account for a small number of cases of cardiac arrest and sudden death usually in young adults. The ventricular tachycardia that these patients typically present exhibits a left bundle branch block on the ECG, and a QRS pattern with negative T waves in the right precordial leads is usually seen auris sinus rhythm [33,34].

Valvular Heart Diseases

In mitral valve prolapse symptomatic atrial and ventricular arrhythmias are common but truly life-threatening arrhythmias are extraordinarily rare, except in the presence of certain complicating conditions such as long QT, electrolyte imbalance, or drug toxicity.

In young adults with congenital aortic stenoses sudden death is usually related to exertion probably due to sudden changes in either ventricular filling or aortic obstruction with a secondary arrhythmia. In the acquired forms of valvular heart disease, sudden death is usually a late occurrence seen in patients with advanced heart failure. Martínez-Rubio *et al.* demonstrated that any patient with valvular heart dis-

ease who presents with sustained ventricular tachyarrhythmias or syncope has to be considered as a very high risk patient because recurrence of sustained ventricular tachyarrhythmias or sudden death rate are high despite therapy [35]. In addition, the data provided by these authors suggest that such patients should be treated with implantable defibrillators while the mechanism of arrhythmias in them is particularly complex (multifactorial) [35].

Electrophysiological abnormalities

Supraventricular arrhythmias, if associated with very rapid ventricular rates, may cause hemodynamic collapse and degenerate to ventricular fibrillation. Atrial fibrillation with rapid conduction over an accessory pathway in a patient with Wolff-Parkinson-White syndrome is the supraventricular arrhythmia most frequently associated with sudden death [36].

Prolonged QT syndrome, leading to irregular repolarization, facilitates the appearance of malignant ventricular arrhythmias, usually 'torsade de pointes' leading to ventricular fibrillation. This phenomenon often occurs against a background of physical or mental stress [37].

Primary bradiarrhythmias may also be associated with sudden death [38]. In congenital complete heart block, the escape rhythm may deteriorate over time, with ventricular arrhythmias appearing as the patients bradycardia becomes more and more inappropriate. Rare cases of malignant vagal arrhythmias may also cause sudden death .

Idiopathic Ventricular fibrillation

In the absence of heart disease or other known casual factors, sudden death is exceptional. Idiopathic ventricular fibrillation represents about 1% of all cases of resuscitated out-of-hospital cardiac arrest. Many retrospective studies with a small number of patients confirm an unfavorable prognosis for these patients. The recurrence of ventricular fibrillation is observed in 33% of patients not treated in the appropriate manner, which would seem to be with an implantable defibrillator [39].

Precursors of sudden death

Cardiac sudden death occurs as a result of cardiac arrest due usually to ventricular fibrillation (VF) or more rarely to malignant bradiarrhythmias [38]. In both cases, a series of precursors may be identified before sudden death appears [9,18,24,40-43]. These include triggering mechanisms acting on a vulnerable myocardium to precipitate the appearance of the final step that terminates in either VF or, less frequently, cardiac arrest due to a malignant bradiarrhythmia though usually secondary to electromechanical dissociation in patients with severe heart failure.

Final step

Usually the final step leads to ventricular fibrillation. The sequence of events occurring in the final step that precipitate ventricular fibrillation can be called the 'ventricular fibrillation

cascade' (Figure 1). These include a final arrhythmia responsible for sudden death and the electrophysiological events that often precede sudden death. Below we describe the arrhythmias and events that constitute the final step in a range of clinical settings:

Pre-hospital phase of acute myocardial infarction

In patients whose sudden death is related to an acute myocardial infarction, records taken in mobile coronary units showed that the most frequent final arrhythmia was primary VF unpreceded by ventricular tachycardia (82%) (Figure 2A). In these patients, an R-on-T phenomenon was observed in 70% of cases. Characteristically, an increased heart rate, due to sympathetic overdrive, was seen before the lethal arrhythmia in patients with sudden death related to an acute myocardial infarction.

Ambulatory patients with out-of-hospital sudden death

We have published the results of a worldwide survey including 233 cases of patients who have died while wearing a Holter recorder [6,38]. The conclusions of this study are (Figure 2B):

- Sudden death occurs due to a ventricular tachyarrhythmia in 80% of cases and due a severe bradycardia in the remaining 20%.
- VF initiates abruptly in 10% of the individuals, in the rest it is triggered by classical sustained ventricular tachycardia (VT) or less often a 'torsade de pointes' ventricular tachycardia. The sustained VT leading to VF was often preceded by sinus tachycardia or a new supraventricular tachyarrhythmia.

On the other hand, in the group of patients with VF, only 12% of patients presented ischemic ST changes prior to the final event. However, the incidence of ischemic ST alterations requires further study using Holter instruments equipped with three leads or more, and should include observations on disturbances in the autonomic nervous system such as heart rate variability.

- In patients who died suddenly from bradycardia, the cause was more often sinus depression than atrioventricular block, and the incidence of previous ST changes was surprisingly high (>80%).

Patients with congestive heart failure

In patients with end-stage heart failure, Luu *et al.* [8] have demonstrated that the incidence of ventricular tachyarrhythmias as the final arrhythmia is much lower (40%) than the incidence obtained in ambulatory patients in our series (approximately 80%). Interestingly, all patients who died of VT/VF had a previous myocardial infarction, but previous myocardial infarction was present in fewer than half of the cases of the bradycardia/electromechanical dissociation group (Figure 2C). This finding, and hyponatremia in the latter group, were the only two parameters that differentiated between the bradycardia and tachyarrhythmia groups.

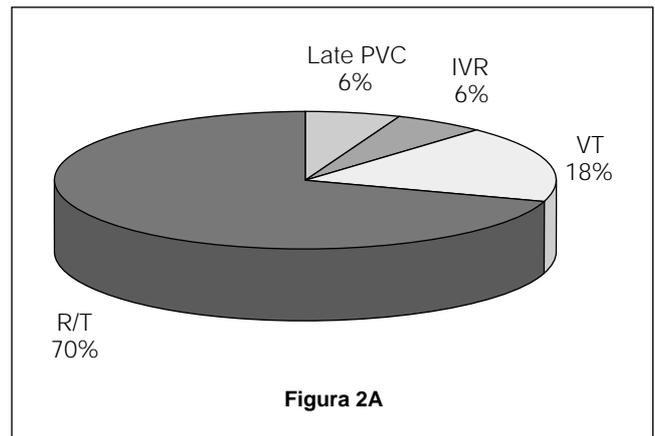


Figura 2A

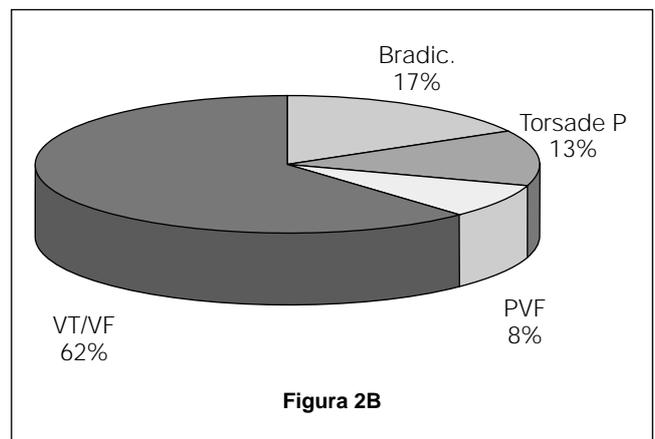


Figura 2B

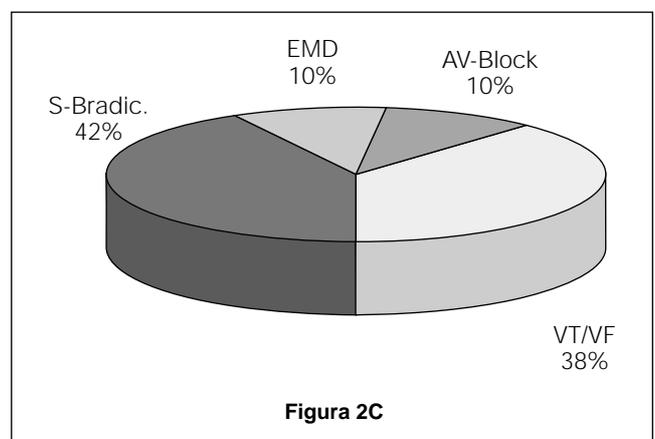


Figura 2C

Figure 2. In 2A we can see the proportions of final events in patients with ventricular fibrillation during the acute phase of myocardial infarction (modified from reference 2). 2B shows the causes of ambulatory sudden death recorded by Holter electrocardiography (modified from reference 8). Finally, in 2C there is the incidence of final events in patients with advanced heart failure who died suddenly (modified from reference 6). AV = atrioventricular, Bradic. = bradycardia, EMD = electromechanical dissociation, IVR = idioventricular rhythm, PVC = premature ventricular contractions, PVF = primary ventricular fibrillation, R/T = R-on-T phenomenon, S-Bradic. = sinus bradycardia, Torsade P = torsade de pointes, VF = ventricular fibrillation, VT = ventricular tachycardia

Electrophysiological disorders

In patients with Wolff-Parkinson-White syndrome who die suddenly it has been shown that the final trigger of VF leading to sudden death is a supraventricular tachyarrhythmia, usually atrial fibrillation with a very rapid ventricular rate [36].

In patients with long QT syndrome, there is evidence that adrenergic hyperactivity produced by physical and/or mental stress may be responsible for triggering malignant ventricular tachycardia of the *torsades de pointes* type [37]. In addition, several drugs might influence the occurrence of this electrophysiological disorder.

Patients with terminal noncardiac disease

Terminal cardiac activity has been described in adults who died with no apparent indication of heart disease, generally as a consequence of terminal malignancy present as bradycardia in 87% of patients and ventricular tachyarrhythmia in 17%. Agonal ST segment elevation was often observed.

Markers and Triggering Mechanisms of Sudden Death

The majority of patients who die suddenly present a vulnerable myocardium. Below we will discuss the different markers of this vulnerable myocardium and also the triggering factors, which acting on this vulnerable myocardium, may precipitate sudden death.

Postinfarction patients are the largest group, so we shall focus initially on them. The risk of sudden death in these patients is related especially to the presence of electrical instability and to its interaction with left ventricular dysfunction and residual ischemia. These three factors form the imaginary triangle of risk of postinfarction complications (Figure 3). In figure 4 we can see various parameters of electrical instability, ischemia and left ventricular dysfunction as markers that should alert us to the danger of a serious complication of myocardial infarction: malignant arrhythmias, new coronary events, and overt heart failure directly or indirectly increase the possibilities of triggering sudden death.

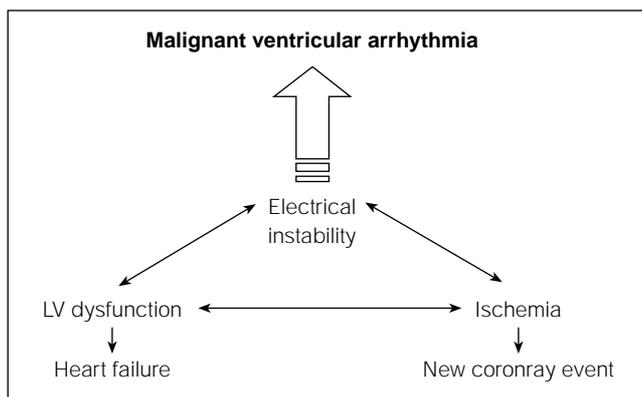


Figure 3. Triangle of risk factors. The three angles are the main factors related to major complications in the postmyocardial infarction patient. There is a strong interaction between these three factors. LV = left ventricular.

Various morphofunctional parameters (postinfarction scar, left ventricular hypertrophy, reduced ejection fraction), autonomic nervous system parameters (heart rate variability, QT interval, baroreflex sensitivity), and clinical and electrocardiographic findings (previous history, ST depression on surface ECG, number and nature of the ventricular arrhythmias, presence of ventricular late potentials) may be considered as markers of electrical instability and, therefore, of my-

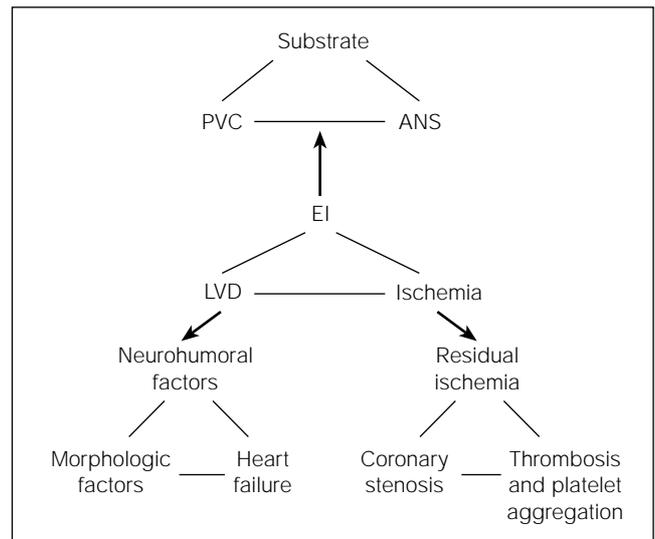


Figure 4. Triangle of risk factors with satellite triangles of markers. R = risk, ANS = autonomic nervous system, PVC = premature ventricular contraction, EI = electrical instability, LVD = left ventricular dysfunction.

ocardial vulnerability to sudden death [9,18,24,26,42,44-46]. The markers of ischemia and left ventricular dysfunction are also shown in figure 4.

The relationship between ischemia and sudden death depends to a great extent on the duration and severity of ischemia. It is evident that persistent and severe transmural ischemia may induce sudden death in acute infarction. However, in transitory transmural ischemia, such as Prinzmetal's angina and during PTCA, the relationship between ischemia and malignant ventricular arrhythmias is less certain. During moderate subendocardial ischemia, malignant ventricular arrhythmias are rare.

The five most important triggering factors which act on a vulnerable myocardium are: 1) physical or mental stress; 2) ionic or metabolic disorders; 3) acceleration of sinus rhythm or appearance of a supraventricular arrhythmia or a pause; 4) the arrhythmogenic effect of certain drugs and 5) interaction of electrical instability with ischemia and/or left ventricular dysfunction due to multiple causes [12,21,22,25,27,28,43,47,48].

When sudden death occurs in patients with nonischemic heart disease it is also conditioned by a vulnerable myocardium and certain triggering factors. Heart failure, left ventricular hypertrophy and electrical instability (ventricular arrhythmias, autonomic nervous system dysfunction) are usually the most important markers of vulnerable myocardium, while other factors such as physical or mental stress, ionic or metabolic disturbances, drug administration, etc, may also act as triggers.

Identification of high risk candidates

Patients at greatest risk from sudden death (table 2) are those who have previously experienced a malignant ventricular arrhythmia (sustained VT or out-of-hospital cardiac ar-

Table 2. Patients at high risk of sudden death

History of malignant ventricular arrhythmia (sustained ventricular tachycardia or out-of-hospital cardiac arrest)
Heart disease with markers of a vulnerable myocardium for malignant ventricular arrhythmias (depressed contractility, ischemia, electrical instability)
Severe bradyarrhythmias

rest). In patients without previous malignant ventricular arrhythmias, the risk of sudden death is related to the presence of different markers, described earlier and related with the evidence of advanced heart disease with left ventricular dysfunction or even heart failure, and/or evidence of electrical instability and/or residual ischemia when ischemic heart disease is present.

Clinical data are very useful both for risk stratification of patients who have presented severe arrhythmias and for the general population of postinfarction patients. Nonetheless, complementary studies using different technologies need to be undertaken to obtain more information about the triangle of risk (Table 3).

Table 3. Methods to identify a high-risk patient

Clinical history and physical examination (syncope, angina, etc)
Surface ECG (Q-waves, ventricular enlargement, QT interval, arrhythmias, etc.)
Exercise testing (ST-segment abnormalities, poor hemodynamic response, arrhythmias, etc.)
Ambulatory Holter ECG (arrhythmias, ischemia, autonomic tone, ventricular late potentials, etc.)
Electrophysiologic studies (induction of sustained ventricular tachyarrhythmias, anomalous pathways, sinus node dysfunction, etc.)
Echocardiography-Doppler (ventricular function, aneurysm, ischemia, valvular dysfunction, etc.)
Nuclear studies (ventricular function, aneurysm, ischemia, etc.)
Cardiac angiography (coronary artery lesions, ventricular function, aneurysm, biopsy, valvular abnormalities, etc.)

Pronostic stratification in the thrombolytic era

There are some indications that the prognosis of patients with or without fibrinolytic therapy following an acute myocardial infarction differs. In a study by Farrell *et al.* in non-thrombolized patients, the presence of ventricular premature beats (VPB) during the Holter recording, decreased heart rate variability (HRV), presence of late ventricular potentials, the results of exercise testing and the value of ejection fraction discriminated those patients at high risk of future arrhythmic events. However, in patients who received thrombolytic therapy, only the diminished HRV discriminated between the two groups. Nevertheless, the incidence of these risk markers (late ventricular potentials, low ejection

fraction, positive exercise testing, and decreased HRV) did not differ in the two groups [49].

Other results concerning the incidence of certain markers after thrombolysis are contradictory. Pedretti *et al.* demonstrated in post-myocardial infarction patients that thrombolysis significantly reduced the occurrence of arrhythmic events [46]. On the contrary, the GISSI-2 study showed that frequent premature ventricular beats, recorded by Holter monitoring, remained even in the fibrinolytic era as an independent risk factor of total and sudden death in the first 6 months following an acute myocardial infarction [26].

Prevention

The relatively low incidence of sudden death in Southern Europe is related to the lower incidence of ischemic heart disease, in comparison to Northern Europe and North America. Efforts to reduce risk factors and to treat the acute events as rapidly as possible are the best measures to reduce sudden death. The widespread use of recently developed therapies for acute events (thrombolysis, beta-blockers, aspirin, etc) and the global protection of the patient during follow-up are mandatory [15,50-59]. Undoubtedly, thrombolytic treatment has been crucial in decreasing mortality, though in the acute phase of myocardial infarction it is still relatively high. However, it should not be forgotten that a global cardioprotective approach has been very effective in reducing mortality particularly in the post-discharge phase [11,15,55]. Hämaläinen *et al.* [11] evaluated effectiveness before the thrombolytic era of a long-term multifactorial intervention program to reduce sudden and cardiac death by medication, cessation of smoking, physical exercise, diet, psychosocial support and optimal medical care. The patients included in the intervention group had an incidence of sudden death of 12.6% at 10 years as opposed to 23% in the group that received no standardized intervention.

We should point out that all patients already presenting a crisis of a malignant ventricular arrhythmia (sustained ventricular tachycardia or ventricular fibrillation) must be treated in a reference centre, because of the actual efficacy of non-pharmacological therapies (implantable cardioverter-defibrillator, ablation, etc.).

Another group of patients to mention are those who have not suffered a malignant arrhythmia, but who present high risk markers. In post-myocardial infarction patients with the following markers: low ejection fraction (<35%) + spontaneous non-sustained ventricular tachycardia on Holter monitoring + inducible ventricular arrhythmia inducible during the electrophysiologic study and non-suppressible due to drug therapy, the MADIT Trial [45] has demonstrated that the implantable cardioverter-defibrillator (ICD) is superior to conventional drug therapy (including amiodarone) for protecting against sudden death. The ICD may also offer the solution in the group of patients with cardiomyopathies at risk of sudden death (Figure 5). In some other cases, such as patients with WPW syndrome and paroxysmal tachyarrhyth-

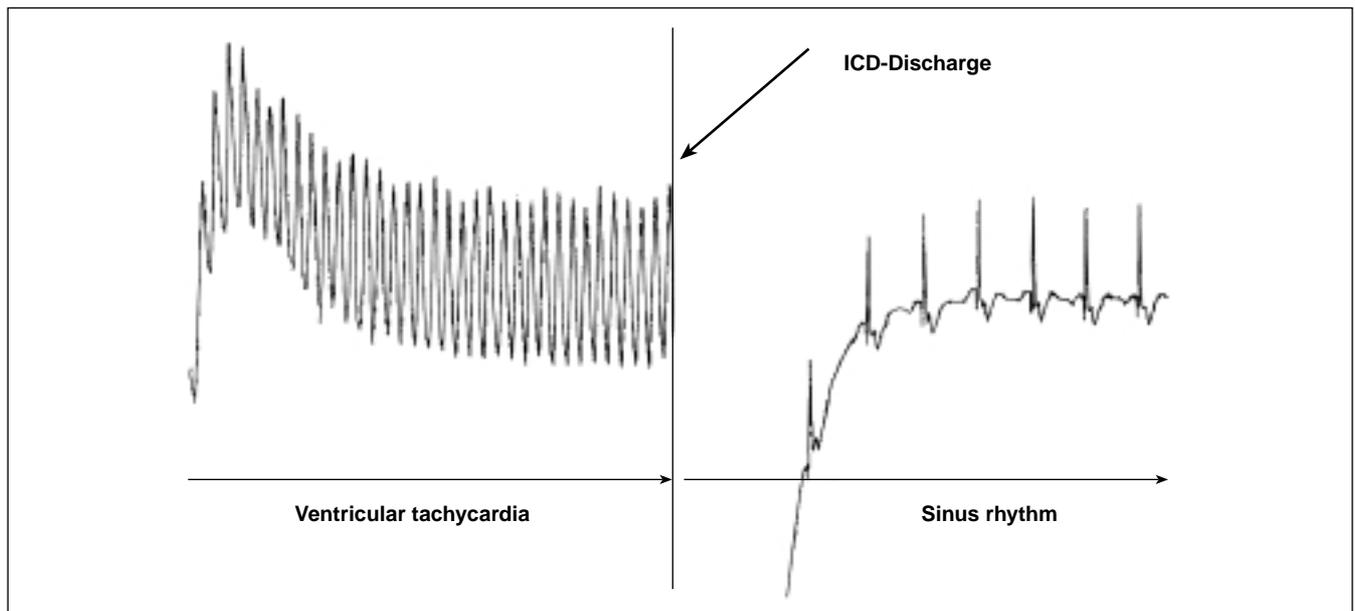


Figure 5. Example of a fast and hemodynamically unstable ventricular tachyarrhythmia reverted by an implantable cardioverter-defibrillator.

mias with electrophysiologic parameters of risk, radiofrequency catheter ablation may provide a definitive solution to the problem. In long QT syndrome a good protection may be achieved by blocking the adrenergic activation with beta-blockers or, even better, with left esterelectomy.

A large number of heart disease patients –currently more than half of post-infarction patients have a low risk of sudden death (without significant markers of electrical instability, ventricular dysfunction and/or ischemia). In these cases, the usual postinfarction treatment consists of acetylsalicylic acid, beta-blockers and control of risk factors (tobacco, high cholesterol levels, high blood pressure, etc). Recently, several studies [56-67] have firmly established the value of secondary (e.g. 4S Trial) and primary (e.g. WSO Trial) coronary prevention in reducing mortality by using inhibitors of the HMG CoA reductase. The inhibitors of the angiotensin converting enzyme have proven especially useful in patients with myocardial infarction and left ventricular dysfunction but are also recommended in all post-infarction patients after the ISIS-4 and GISSI-3 Trials. Amiodarone does not give significant advantages against placebo (EMIAT Trial) or has only been effective in some subsets of patients (CAMIAT Trial). Other antiarrhythmic agents have shown a significant increase in mortality (Class I agents –CAST Trial–; d Sotalol –SWORD Trial–).

Thus, although prognosis has improved, sudden death remains a frequent clinical occurrences and on unresolved multifactorial problem which needs further research.

References

- [1] Lopez AD. Assessing the burden of mortality from cardiovascular disease. *World Health Stat Q.* 1993; 46: 91-96.
- [2] Murray CJL, López AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997; 349: 1269-1276.
- [3] Murray CJL, Lopez AD. Global mortality, disability and the contribution fo risk factors: Global Burden of Disease Study. *Lancet* 1997; 349: 1436-42.
- [4] Murray CJL, López AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997; 349: 1498-1504.
- [5] Murray CJL, Lopez AD. Regional patterns of disability-free life expectancy and disability-adjusted life expectancy: Global Burden of Disease Study. *Lancet* 1997; 349: 1347-52.
- [6] Goldstein S, Bayés de Luna A, Guindo Soldevila J. *Sudden Cardiac Death*. Armonk, NY: Futura , 1994.
- [7] Adgey AA, Devlin JE, Webb SW, Mullholland HC. Initiation of ventricular fibrillation outside hospital in patients with acute ischemic heart disease. *Br Heart J* 47: 55-61; 1982.
- [8] Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation* 80: 1675-80; 1989.
- [9] Bayés de Luna A, Viñolas X, Guindo J, Bayés. Genís A. Risk stratification after myocardial infarction: role of electrical instability, ischemia and left ventricular function. *Cardiovasc Drug Ther* 8: 335-43; 1994.
- [10] Breithardt G, Borggreffe M, Martínez-Rubio A, Budde T. Pathophysiological mechanisms of ventricular tachyarrhythmias. *Eur Heart J* 1989; 10: 9-18.
- [11] Hämäläinen H, Luurila OJ, Kallio V, Knuts LR, Arstila M, Hakkila J. Long-term reduction in sudden death after a multifactorial intervention program in patients with myocardial infarction: 10-year results of a controlled investigation. *Eur Heart J* 10: 55-62; 1989.
- [12] Genest Jr, Cohn JS. Clustering of cardiovascular risk

- factors: targeting high-risk individuals. *Am J Cardiol.* 1995; 76: 8A-20A.
- [13] Folsom AR, Szklo M, Stevens J, Liao F, Smith R, Eckfeldt JH. A prospective study of coronary heart disease in relation to fasting insulin, glucose and diabetes: The Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care* 1997; 20: 935-42.
- [14] Folsom AR, Wu KK, Shahar E, Davis CE. Association of hemostatic variables with prevalent cardiovascular disease and asymptomatic carotid artery atherosclerosis. *Arterioscler Thromb* 1993; 13: 1829-36.
- [15] Martínez-Rubio A. Secondary prevention of coronary heart disease in clinical practice: special considerations for intensified lifestyle modification. *Eur J Clin Invest* 1999; 29: 365-8.
- [16] Bayés-Genis A, Viñolas X, Guindo J, Fiol M, Bayés de Luna A. Electrocardiographic and clinical precursors of ventricular fibrillation: chain of events. *J Cardiovasc Electrophysiol* 6: 410-417; 1995.
- [17] Martínez-Rubio A, Shenasa M, Borggrefe M, Chen X, Benning F, Breithardt G. Electrophysiologic variables characterizing the induction of ventricular tachycardia versus ventricular fibrillation after myocardial infarction: relation between ventricular late potentials and coupling intervals for the induction of sustained ventricular tachyarrhythmias. *J Am Coll Cardiol* 1993; 21: 1624-31.
- [18] Martínez-Rubio A, Borggrefe M, Shenasa M, Chen X, Wichter T, Fetsch T, Reinhardt L, Breithardt G. Are there gender differences in patients with coronary artery disease presenting with spontaneous sustained ventricular tachycardia or fibrillation ?. *Clin Cardiol* 1995; 18: 161-166.
- [19] Martínez-Rubio A, Stachowitz A, Borggrefe M, Reinhardt L, Cabrera-Santos A, Chen X, Willems S, Shenasa M, Breithardt G. Comparison of the results of programmed ventricular stimulation from the right ventricular apex and outflow tract: a randomized, prospective study. *Eur Heart J* 1995 16: 1234-43.
- [20] Fornes F, Lecomte D, Nicolas G. Mort subite coronaire extrahospitalière: étude autopsique comparative netre des sujeys avec et sans antécédents cardiovasculaires. *Arch Mal Coeur* 87: 319-24; 1994.
- [21] Davies MJ, Thomas A. Thrombosis and acute coronary artery lesions in sudden cardiac death. *N Engl J Med* 310: 1137-40; 1994.
- [22] Burke AP, Farb A, Malcolm GT, Liang YH, Smialek J, Virmani R: Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med* 1997;336:1276-82.
- [23] Borggrefe M, Chen X, Hindricks,G, Haverkamp W, Willems S, Kottkamp H, Rotman B, Martínez-Rubio A, Shenasa M, Block M, Breithardt G. Catheter ablation of ventricular tachycardia in patients with coronary heart disease. In: Zipes,DP and Jalife,J (eds.). *Cardiac electrophysiology, from cell to bedside.* Saunders, Philadelphia 1995; 1502-1517.
- [24] Borggrefe M, Fetsch T, Martínez-Rubio A, Mäkijärvi M, Breithardt G. Prediction of arrhythmia risk based on signal-averaged ECG in postinfarction patients. *Pacing Clin Electrophysiol* 1997; 20: 2566-76.
- [25] Haverkamp W, Martínez-Rubio A, Hief C, Lammers A, Mühlenkamp S, Wichter T, Breithardt G, Borggrefe M. Efficacy and safety of d,l-Sotalol in patients with ventricular tachycardia or survivors of cardiac arrest. *J Am Coll Cardiol* 1997; 30:487-95.
- [26] Maggioni AP, Zuanetti G, Franzosi MG, Rovelli F, Santoro E, Staszewsky L, Tavazzi L, Tognoni G. Prevalence and prognostic significance of ventricular arrhythmias after acute myocardial infarction in the fibrinolytic era: GISSI-2 results. *Circulation* 87: 31-22; 1993.
- [27] Borggrefe M, Haverkamp W, Martínez-Rubio A, Wichter T, Breithardt G. Management of patients with sustained ventricular tachyarrhythmias: different clinical studies, different patients. In Breithardt G, Borggrefe M, Camm,AJ, Shenasa M (eds.). *Antiarrhythmic drugs – Mechanisms of antiarrhythmic and proarrhythmic actions.* Springer Verlag, Berlin 1995; 122-143.
- [28] Krantz DS, Kop WJ, Gabbay FH, Rozanski A, Barnard M, Klein J, Pardo Y, Gottdiener JS. Circadian variation of ambulatory myocardial ischemia. Triggering by daily activities and evidence for an endogenous circadian component. *Circulation.* 1996; 93: 1364-71.
- [29] Chen X, Shenasa M, Borggrefe M, Block M, Hindricks G, Martínez-Rubio A, Haverkamp W, Willems S, Böcker D, Mäkijärvi M, Breithardt G. Role of programmed ventricular stimulation in patients with idiopathic dilated cardiomyopathy and documented sustained ventricular tachyarrhythmias: inducibility and prognostic value in 102 patients. *Eur Heart J* 1994; 15: 76-82.
- [30] Borggrefe M, Chen X, Martínez-Rubio A, Hindricks G, Haverkamp W, Block M, Breithardt G. The role of implantable cardioverter defibrillators in dilated cardiomyopathy. *Am Heart J* 1994; 127: 1145-50.
- [31] Prasad K, Frenneaux MP. Sudden death in hypertrophic cardiomyopathy: potential importance of altered autonomic control of vasculature. *Heart.* 1998 Jun; 79(6): 538-40.
- [32] Yi G, Elliott P, McKenna WJ, Prasad K, Sharma S, Guo XH, Camm AJ, Malik M. QT dispersion and risk factors for sudden cardiac death in patients with hypertrophic cardiomyopathy. *Am J Cardiol.* 1998 Dec 15; 82(12): 1514-9.
- [33] Marcus FI, Fontaine G. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: a review. *Pacing Clin Electrophysiol.* 1995 Jun; 18(6): 1298-314.
- [34] Corrado D, Basso C, Thiene G, McKenna WJ, Davies MJ, Fontaliran F, Nava A, Silvestri F, Blomstrom Lundqvist C, Wlodarska EK, Fontaine G, Camerini F. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. *J Am Coll Cardiol* 1997 Nov 15; 30(6): 1512-20.

- [35] Martínez-Rubio A, Schwammenthal Y, Schwammenthal E, Block M, Reinhardt L, Garcia-Alberola A, Sierra G, Shenasa M, Haverkamp W, Scheld HH, Breithardt G, Borggrefe M. Patients with valvular heart disease presenting with sustained ventricular tachyarrhythmias or syncope. Results of programmed ventricular stimulation and long-term follow-up. *Circulation* 1997; 96: 500-508.
- [36] Torner P, Brugada P, Smeets J et al. Ventricular fibrillation in the Wolff-Parkinson-White Syndrome. *Eur Heart J* 12: 144-50; 1991.
- [37] Galinier M, Vialette JC, Fourcade J, Cabrol P, Dongay B, Massabuau P, Boveda S, Doazan JP, Fauvel JM, Bounhoure JP. QT interval dispersion as a predictor of arrhythmic events in congestive heart failure. Importance of aetiology. *Eur Heart J* 1998 Jul, 19(7): 1054-62.
- [38] Bayés de Luna A, Coumel P, Leclercq JF et al. Ambulatory sudden death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 117: 151-59, 1989.
- [39] Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Ortiz Lopez R, Wang Z, Antzelevitch C, O'Brien RE, Schulze Bahr E, Keating MT, Towbin JA, Wang Q. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature*. 1998 Mar 19; 392(6673): 293-6.
- [40] Breithardt G, Borggrefe M, Martínez-Rubio A, Podczeck A. Prognostic significance of ventricular late potentials in the postmyocardial infarction period. *Herz* 1988, 13: 180-187.
- [41] Breithardt G, Martínez-Rubio A, Borggrefe M. Correlation between programmed ventricular stimulation and signal-averaged electrocardiograms in the identification of patients at high risk for serious ventricular arrhythmias. *Pacing Clin Electrophysiol* 1990, 13: 685-691.
- [42] Martínez-Rubio A, Borggrefe M, Guindo Soldevila J, Bayés de Luna A, Breithardt G. Potenciales tardíos ventriculares: que son, como se detectan y que representan. *Rev Lat Cardiol*. 1989, 10: 218-232.
- [43] Martínez-Rubio A, Shenasa M, Chen X, Wichter T, Breithardt G, Borggrefe M. Response to sotalol predicts the response to amiodarone during serial drug testing in patients with sustained ventricular tachycardia and coronary artery disease. *Am J Cardiol* 1994, 73: 357-360.
- [44] Breithardt G, Hackstein N, Borggrefe M, Podczeck A, Martínez-Rubio A, Trampisch HJ. Diagnostic value of electrocardiographic variables to predict the presence of ventricular late potentials. *J Am Coll Cardiol* 1990, 15: 152-8.
- [45] Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med*. 1996 Dec 26; 335(26): 1933-40.
- [46] Pedreti RFE, Colombo E, Braza SS, Caru B. Effect of thrombolysis on heart rate variability and life threatening ventricular-arrhythmias in survivors of acute myocardial infarction. *J Am Coll Cardiol* 23: 19-26, 1994.
- [47] Budde T, Borggrefe M, Podczeck A, Martínez-Rubio A, Breithardt G. Acute and long-term efficacy of oral propafenone in patients with ventricular tachyarrhythmias. *J Cardiovasc Pharmacol* 1991, 18: 254-260.
- [48] Hoffmann A, Pfiffner D, Hornung R, Niederhauser H. Psychosocial factors predict medical outcome following a first myocardial infarction. Working Group on Cardiac Rehabilitation of the Swiss Society of Cardiology. *Coron Artery Dis*. 1995, 6: 147-52.
- [49] Farrell T, Bashir Y, Poloniecki J, Ward D, Camm AJ. The effects of thrombolysis on risk stratification for arrhythmic events in post infarction patients. *J Am Coll Cardiol* 17: 17A, 1991.
- [50] De Faire U, Ericsson CG, Grip L, Nilsson J, Svane B, Hamsten A. Secondary preventive potential of lipid-lowering drugs. The Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT). *Eur Heart J*. 1996, 17 Suppl F: 37-42.
- [51] De Feyter PJ, Vos J, Deckers JW. Progression and regression of the atherosclerotic plaque. *Eur Heart J*. 1995, 16 Suppl I: 26-30.
- [52] Desmet W, Vrolix M, De Scheerder I, Van-Lierde J, Willems JL, Piessens J. Angiotensin-converting enzyme inhibition with fosinopril sodium in the prevention of restenosis after coronary angioplasty. *Circulation* 1994, 89: 385-92.
- [53] Enbergs A, Liese A, Heimbach M, Kerber S, Scheld HH, Breithardt G, Kleine-Katthofer P, Keil U. Evaluation of secondary prevention of coronary heart disease. Results of the EUROASPIRE study in the Munster region. *Z Kardiol*. 1997, 86: 284-91.
- [54] Gordon NF, Haskell WL. Comprehensive cardiovascular disease risk reduction in a cardiac rehabilitation setting. *Am J Cardiol*. 1997, 80: 69H-73H.
- [55] Haskell WL, Alderman EL, Fair JM, Maron DJ, Mackey SF, Superko HR, Williams PT, Johnstone IM, Champagne MA, Krauss RM, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Coronary Risk Intervention Project (SCRIP). *Circulation*. 1994, 89: 975-90.
- [56] Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyörälä K. Prevention of coronary heart disease in clinical practice. *Eur Heart J* 1998, 19: 1434-1503.
- [57] Reinhardt L, Mäkijärvi M, Fetsch T, Schulte G, Sierra G, Martínez-Rubio A, Montonen J, Katila T, Borggrefe M,

- Breithardt G. Noninvasive risk modeling after myocardial infarction. *Am J Cardiol* 1996, 78: 627-32.
- [58] Pepine CJ. Rationale for ACE inhibition as an anti-ischemic therapy. *Eur Heart J* 1998, 19 (suppl G): G34-G40.
- [59] Pepine CJ. Systemic hypertension and coronary artery disease. *Am J Cardiol* 1998, 82: 21H-24H.
- [60] Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study. *Lancet* 344: 1383-9, 1994.
- [61] Muntwyler J, Maschio Andrist M, Amann FW. Secondary prevention in patients before and after percutaneous transluminal coronary angioplasty: 5-year follow-up. *Schweiz Med Wochenschr* 1997, 127: 573-8.
- [62] ISIS-4 Collaborative Group. A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulfate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 345: 669-85, 1995.
- [63] Assmann G, Cullen P, Schulte H. The Münster Heart Study (PROCAM). Results of follow-up at 8 years. *Eur Heart J* 1998, 19 (suppl A): A2-A11.
- [64] Norris-RM. Amiodarone after myocardial infarction: EMIAT and CAMIAT trials. *Lancet*. 1997; 349(9067): 1767.
- [65] Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. *Lancet*. 1997; 349(9053): 675-82.
- [66] Obias Manno D, Friedmann E, Brooks MM, Thomas SA, Haakenson C, Morris M, Wimbush F, Somelofski C, Goldner F. Adherence and arrhythmic mortality in the cardiac arrhythmia suppression trial (CAST). *Ann Epidemiol*. 1996; 6(2): 93-101.
- [67] Pratt CM, Camm AJ, Cooper W, Friedman PL, MacNeil DJ, Moulton KM, Pitt B, Schwartz PJ, Veltri EP, Waldo AL. Mortality in the Survival With ORal D-sotalol (SWORD) trial: why did patients die?. *Am J Cardiol*. 1998; 81(7): 869-76.

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Professor Antonio Bayés de Luna was born at Vic (Barcelona) in 1936. He is a Cardiology specialist at the School of Cardiology at the University of Barcelona and at the Institute of Cardiology and Hammersmith Hospital in London. He is married to M. Clara Genis Piqueras and has five children. In 1971 he became Associate Lecturer at the Autonomous University of Barcelona and Head of the Unit of Electrocardiography and Arrhythmias at the Sant Pau Hospital. At present he is Professor of Cardiology at the Autonomous University of Barcelona and was Director of the Department of Cardiology and Cardiac Surgery at the Sant Pau Hospital from 1992 to 1998. He used this post to encourage essential research at the Sant Pau Hospital. At present he is Director of the Catalan Institute of Cardiology at the Sant Pau Hospital. Between 1973 and 1974 he was President of the Catalan Cardiology Association; 1983-1984, President of the Spanish Cardiology Association; 1983-1985, President of the Catalan Association of Aid to Cardiology (ACARD); and between 1983 and 1985, Vice-president of the Hispanic Foundation for Cardiology. He has been member of the Myocardiopathy Council of the International Society and Federation of Cardiology (ISFC) since 1991, and has been active in various ISFC heart disease campaigns. In September 1994 he was elected President of this Society, and ended his term as Executive President in January 1999. He has been deeply involved in activities of the European Society of Cardiology (ESC) as member of: nucleus of the working-group on Arrhythmias (1986-1993); Scientific Executive Committee (1986-1992); and the Nominations Committee of the ESC Council (1985-1991). In 1992 he was President of the XIV European Congress of Cardiology. He has represented the ESC on the Executive Committee of the European Board of Specialists in Cardiology, and at present is member of its Library and History Committee. He is also a member of the nucleus of the International Council of Electrocardiology, and of the Founder Nucleus of the International Society for Holter Monitoring, of which he is also Vice-president. He has received various prizes and honours, most notably «Catalan Doctor of the Year» (1991) and Spain's «Doctor of the Year» (1991 and 1994). He is Honorary Member or Correspondent of 19 National Cardiology associations and was made Doctor Honoris Causa by the University of Lisbon in 1997. In 1998 he was awarded the «Health Sciences» prize of the Uriach Foundation. In addition, he is on the editorial board of over 12 prestigious Spanish and international journals. He was also founder and editor of the journal *Revista Latina de Cardiología*. He has organised annual postgraduate courses and major meetings and symposia. He was President of the European Congress of Cardiology in 1992 and the Sixth International Congress on Ambulatory Monitoring in 1994, both held in Barcelona. He has been invited to lecture at major congresses and meetings in 39 countries round the world. His extensive scientific work has concentrated mainly on Electrocardiography, arrhythmias, sudden death, Holter technology, risk stratification and silent ischaemia. The fruit of this work is over 100 «peer review» original articles, many of them published in the most prestigious Cardiology journals (*Circulation*, *American Journal of Cardiology*, *American Heart Journal*, *Chest*, *European Heart Journal*, *Archives de Maladies du Coeur*, *Revista Española de Cardiología*, along with basic research studies already done in our country etc.). His impact on the Department of Cardiology of the Sant Pau Hospital, which he directs, led to around 200 articles in the last 4 years. He is also author of five books first published in English or Spanish. His book on *Clinical Electrocardiography*, first published in Catalan

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Antoni Martínez Rubio was born in Sabadell in 1961. After taking his degree in Medicine and Surgery at the Autonomous University of Barcelona (1985), he worked at the German universities of Düsseldorf and Münster, specialising in Internal Medicine and Cardiology. His basic research area was for many years the electrophysiology of the heart. He received a *magna cum laude* for his PhD. thesis (University of Münster) on: «Electrophysiological parameters that determine the induction of ventricular tachycardia versus ventricular fibrillation during programmed ventricular stimulation». Since the end of 1996 he has worked at the Sta. Creu and St. Pau Hospital in Barcelona as a clinical cardiologist and electrophysiologist. He has undertaken new lines of research in Arrhythmology and Ischaemic Cardiopathy, and received the Pfizer research grant from the Spanish Cardiology Association in 1999. He is author or co-author of over 250 papers to international congresses, chapters in books and articles in peer-review journals (*Circulation*, *Journal of the American College of Cardiology*, *European Heart Journal*, *European Journal of Clinical Investigation*, *American Journal of Cardiology*, *Pace*, *Zeitschrift für Kardiologie* etc.). He has received invitations to lecture in several countries and is a reviewer for several international journals. He is a member of, and participant in, various organisations: German Society of Cardiology, Spanish Cardiology Association, Working Group on Arrhythmias of the European Society of Cardiology, and the Scientific Committee of the European Society of Cardiology. He is assistant editor of *Timely Topics in Medicine – Cardiovascular*, Fellow of the European Society of Cardiology (F.E.S.C.), Fellow of the American College of Cardiology (F.A.C.C.), and lecturer at the School of Nursing of the Autonomous University of Barcelona. He is also a member of the committee of experts of the European Commission on: Evaluation of therapies through multinational large scale studies/trials taking into account advances in modern technology and optimised use of databases, registries, reagents and sample banks in «Chronic and degenerative diseases, cancer, diabetes, cardiovascular diseases and rare diseases»; «Quality of life and Management of Living Resources» of the Fifth Framework Programme for RTD and Demonstration Activities (European Commission, Brussels).

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