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Task Force Report

Task Force on Sudden Cardiac Death of the European Society of Cardiology

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The members of the Task Force on Sudden Death dedicate this paper to the memory of our former friend and colleague, Professor Ronald W. F. Campbell. Ronnie spent his life working in the field of sudden cardiac death; he contributed much and helped many. But his own life fell victim to this very problem, sadly illustrating its unexpected nature. With Ronnie's memory in mind the Task Force has worked diligently to describe the extent of our expanding knowledge in this field, hoping that our small contribution might help to appease his sad and sudden death.

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Why a Task Force on sudden cardiac death

This comprehensive, educational document on sudden cardiac death is an extensive review that was deemed necessary for two reasons: first, major studies have advanced our knowledge of the natural history, risk prediction and evaluation, and prevention of tachyarrhythmias and sudden death in patients with coronary artery disease or heart failure; second, in rare or previously unknown diseases, the recognition of high risk patients is more difficult since studies are either lacking or they are less likely to be performed.

Process followed for the creation of the Task Force

The procedure used for developing and issuing these guidelines was in accordance with the recently issued 'Recommendations for Task Force creation

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and report writing', (http://www.escardio.org/scinfo/guidelines_recommendations.htm) which is a position document of the ESC Committee for Practice Guidelines and Policy Conferences

Appointment of members

The Task Force was initiated by the former Committee for Scientific Initiatives chaired by Jean-Pierre Bassand. The experts were designated by this Committee and approved by the Board of the ESC. The Task Force was conducted under the supervision of the Committee for Practice Guidelines and Policy Conferences chaired by Werner Klein.

The panel of experts was composed of physicians and scientists involved in clinical practice in University and non-University hospitals and of basic scientists. Members were selected to represent experts of different European countries and to include members of the following Working Groups of the ESC whose activities and fields of interest were related to the topic of the Task Force: Working Group on Arrhythmias, Working Group on Cardiac Pacing, Working Group on Pericardial and Myocardial Diseases, Working Group on Coronary Circulation and Working Group on Cardiac Cellular Electrophysiology.

In addition, representatives from the following study groups were included: Study Group on Molecular Basis of Arrhythmias of the Working Group on Arrhythmias, and Study Group on the Indications for Implantable Cardioverter/Defibrillator of the Working Groups on Arrhythmias and on Cardiac Pacing. Two non-European members were included for their specific expertise in the fields of electrophysiology, and implantable cardioverter/defibrillators. A member of the European Resuscitation Council was also included. The Task Force was chaired by Silvia G. Priori.

Selection of evidence

The TF members have tried to provide evidence-based recommendations for the prediction and prevention of SCD: it should be reinforced, however, (as discussed in the text) that these recommendations cannot be intended as comprehensive 'guidelines for treatment' in those conditions such as myocardial infarction and failure in which sudden cardiac death is only one of the causes of death. In these conditions the objective of treatment has to be 'total mortality'. It is recognized that these guidelines do not consider the global management of all aspects of pathophysiological states associated with sudden cardiac death. However, interventions that are known to prevent SCD are identified and emphasized.

A literature review was performed through searching databases (Ovid, Medline). A large number of publications in English were reviewed by the committee members during the course of their discussions. The references selected for this document are mainly peer-reviewed papers that are representative but not all-inclusive. The committee reviewed and ranked the evidence supporting the current recommendations according to the ESC 'Recommendations for Task Force Creation and Report Writing' (http://www.escardio.org/scinfo/guidelines_recommendations.htm). The strength of evidence against or in favour of a diagnostic procedure or a particular treatment was ranked according to the following three levels.

Level of Evidence A=Data derived from multiple randomized clinical trials or meta-analyses.

Level of Evidence B=Data derived from a single randomized trial or non-randomized studies.

Level of Evidence C=Consensus opinion of the experts.

In some circumstances we have reported the opinion of the members of the Task Force and this is clearly stated in the Tables.

Class I=Conditions for which there is evidence and/or general agreement that a given procedure (or risk stratification parameter) is useful and effective.

Class II=Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the procedure or treatment (or risk stratification parameter).

IIa: Weight of evidence/opinion is in favour of usefulness/efficacy.

IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence or general agreement that the procedure/treatment is not useful/effective.

Observational registries and retrospective studies were ranked as level B or C, depending on the design and size of the study.

In controversial areas, or on issues without evidence other than usual clinical practice, a consensus was achieved by agreement in the expert panel after thorough deliberations.

This document was reviewed by the Committee for Practice Guidelines and Policy Conferences and by external reviewers. It was endorsed by the Board of the ESC and represents the official position of the ESC with regard to this subject. These guidelines will be reviewed two years after publication and considered as current unless the 'Guidelines' Committee revises or withdraws them from circulation.

The document consists of two parts: the first includes an overview of the most important clinical conditions associated with sudden cardiac death; the second is the presentation of recommendations for risk stratification and for prevention of sudden cardiac death.

This Task Force was financed by the budget of the former Committee for Scientific and Clinical Initiatives and of the Committee for Practice Guidelines and Policy Conferences of the ESC and was independent of any commercial, health or governmental authorities.

Recommendations for prevention of SCD of the European Society of Cardiology

At the end of each section of the document, recommendations for risk stratification and for prevention of SCD are provided. When reading the document it is important to remember that the recommendations are not for the comprehensive management of patients with any given condition but are only intended to highlight the value of different risk stratifiers to identify patients at risk of SCD and to rank the effectiveness of different interventions in preventing SCD. When treating patients this advice should be placed in the appropriate clinical context.

The Task Force wishes to remind the reader that in the Tables (as well as in the body of the document) the use of the terms 'primary' and 'secondary' prevention is unconventional as it refers to patients with/without a history of sustained ventricular arrhythmias/ventricular fibrillation.

Appendices 1 and 2 list acronyms and abbreviations used in the document.

Sudden cardiac death: the definition and its impact on clinical trials

The term sudden cardiac death has been used for several centuries and throughout this time different authors have debated how to define it most appropriately. SCD is defined as follows: 'Natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected.'[1]. A matter of debate has always been when an unexpected death should be called 'sudden' and 'how' the cardiac origin of the death should be ascertained. Several criteria have been proposed to link SCD to a specific 'mode' of death.

The clinical presentation of SCD is frequently used as a surrogate implying that a specific mechanism is involved. The more certain a specific mechanism is, the better preventive measures may be developed. Although it is true that in most cases of instantaneous death, such as after myocardial infarction, a tachyarrhythmia is the underlying cause, there are other mechanisms that may also lead to sudden death, for instance aortic rupture, rupture of a subarachnoidal aneurysm, cardiac rupture and tamponade, massive pulmonary embolism, and others. On the other hand, a death may still be arrhythmic in nature but may not occur suddenly, e.g. a patient who dies from an episode of sustained ventricular tachycardia after having been admitted to the hospital in haemodynamic collapse and subsequent complications.

The key concepts that are central in the definition of sudden death are the non-traumatic nature of the event and the fact that sudden death should be unexpected and instantaneous. In order to limit sudden death to heart diseases, the word 'cardiac' has been added to forge the term 'SCD'. A further subclassification has been proposed to distinguish 'coronary' and 'non-coronary' SCD. The time frame used to describe the duration of the terminal event initially was 24 hours but has subsequently been reduced to 1 hour or even to an instantaneous event to account for a more likely arrhythmic mechanism. As a consequence, there has been a large inconsistency in the definitions used in the different clinical trials. The problems associated with defining the mode of death have been a matter of concern for many authors[2–4]. A very difficult issue is the classification of deaths that occur unwitnessed, such as being found dead in bed. Most authors have erred in favour of classifying such events as SCDs, even though it is often impossible to define when the patient was last alive or for what duration he suffered any symptoms prior to death.

This document will propose recommendations for prevention of SCD that are based on results of trials and therefore will suffer from the unavoidable limitation of comparing studies that have used different definitions of sudden death. Furthermore, more recent trials have not analysed the effect of devices and interventions on 'sudden cardiac death' but have instead used 'arrhythmic death': as outlined above, the two terms are not identical as a patient may die because of arrhythmias even if the terminal event is not 'sudden' (i.e. instantaneous and unexpected). Conversely, not all sudden deaths are due to arrhythmias, specifically ventricular tachyarrhythmias.

In the analysis of trials, we have used, whenever possible, the data specifically obtained in the subgroup having SCD as an end-point. When this was not available, data classified as arrhythmic death were used or when only cardiac mortality was available, it was assumed that a significant proportion of cardiac mortality was represented by arrhythmic death.

Sudden cardiac death in the general population

Pathology

Although there is a tendency to ascribe all sudden non-traumatic deaths in middle-aged and elderly subjects to cardiac disease, autopsy studies in unselected subjects suggest that about 2/3 of such deaths are cardiac in origin, with coronary artery disease and its complications accounting for the overwhelming majority of deaths[5,6]. The accuracy of certification of out-of-hospital coronary heart disease death has been assessed by physician and autopsy review[7]. Reliance on death certificate diagnoses resulted in about 5% underestimation of the true CHD rates, whereas their use as a surrogate for SCD yielded a 16% overestimation of the true rates. The probability of finding an acute coronary lesion (plaque rupture or thrombosis) ranges widely in

published series, but increases with the duration of prodromal symptoms before death[6,8].

Epidemiology

The size of the problem

The single most important cause of death in the adult population of the industrialized world is SCD due to coronary disease. The first recorded rhythm in patients presenting with a sudden cardiovascular collapse is ventricular fibrillation (VF) in 75–80%, whereas bradyarrhythmias are thought to contribute to a minority of SCD. In about 5% to 10% of cases, SCD occurs in the absence of coronary artery disease or congestive heart failure.

Incidence rates of SCD ranging between 0·36 to 1·28 per 1000 inhabitants per year have been reported[9–12]. In these studies only witnessed victims seen or resuscitated by the emergency medical services are included; these data are therefore an underestimate of incidence of SCD in the general population.

The incidence of SCD occurring out-of-hospital varies with age, gender and presence or absence of a history of cardiovascular disease. In males between 60 and 69 years of age and a prior history of heart disease, SCD rates as high as 8 per 1000 per year have been reported[13]. In Maastricht[14] a population-based study monitored all cases of out-of-hospital cardiac arrest occurring in victims between 20 and 75 years of age. An overall yearly incidence of SCD of 1 per 1000 was recorded. Overall, 21% of all deaths were sudden and unexpected in men and 14·5% in women. Eighty percent of out-of-hospital cases occurred at home and about 15% on the street or in a public place. Forty percent of SCDs were unwitnessed.

Myerburg and colleagues[15] reviewed the issue of the risk of SCD in population subgroups, and their contribution to the overall burden of SCD. Based on a figure of 300 000 SCDs/annum in the United States, the population incidence was just over 1/1000/year. Any intervention applied to the general population to reduce the risk of SCD would therefore be given to the 999/1000 individuals per annum who will not die suddenly in order to prevent the death of one individual. The cost- and risk-benefit ratios imply that only general lifestyle advice could be given on a population-wide basis. Of course, higher risk subgroups of the population can be identified. Asymptomatic individuals with multiple risk factors for coronary disease are at higher risk than the population at large, while individuals with manifest coronary artery disease are at still greater risk. As will be discussed below, subgroups of patients with coronary disease at still greater risk of SCD are identifiable on the basis of previous myocardial infarction, ischaemia, impaired left ventricular function and previous life-threatening ventricular arrhythmias. Identification and appropriate management of these patients is at the heart of modern cardiology, and is the subject of much of this review. However, subgroups with progressively greater annual risks of SCD comprise a progressively smaller proportion of the total numbers of SCDs in the population. The logical conclusion of these figures is that the greatest opportunity to reduce the population burden of SCD lies in the reduction in the prevalence of coronary artery disease in the population at large[16].

Most Western populations have a high prevalence of coronary atherosclerosis in middle-aged and elderly subjects. Since coronary artery disease is commonly asymptomatic or unrecognized, the general population will contain an unknown proportion of individuals with advanced coronary disease. Epidemiological studies have also reported a high prevalence of unrecognized myocardial infarction and left ventricular dysfunction in the community[17,18]. Individuals with unrecognized coronary artery disease will, by definition, not be amenable to the preventive measures available to those with manifest disease. However, they may be identified if coronary risk factor screening is undertaken either in a systematic or opportunistic fashion.

Risk factors for sudden cardiac death in the community

Population studies in many industrialized countries have demonstrated that the risk factors for SCD are predominantly the same as those for atherosclerotic coronary disease, namely increasing age, male gender, family history of coronary artery disease, increased LDL cholesterol, hypertension, smoking and diabetes mellitus[19–22]. A number of studies have attempted to identify risk factors which may specifically predict SCD as opposed to acute myocardial infarction or other manifestations of coronary disease in population subsets without recognized heart disease. Among the specific risk factors studied, increased heart rate[20,23–25] and heavy alcohol consumption have been reported in several studies.

Hypertension and left ventricular hypertrophy

Hypertension is a well-established risk factor for coronary artery disease, but several epidemiological studies suggest that it plays a disproportionate role in increasing the risk of SCD[26,27]. The principal mechanism by which hypertension predisposes to SCD is via left ventricular hypertrophy (LVH). Other determinants of LVH include age, obesity, stature, glucose intolerance[28] and genetic factors. The greater prevalence of hypertension in black compared with white men may explain their greater incidence of SCD despite a lower prevalence of coronary artery disease[29]. The presence of electrocardiographic LVH as manifest by increased voltages and repolarization abnormalities was associated with a 5-year mortality of 33% in men and 21% in women[28]. The risk of SCD in the presence of electrocardiographic LVH was comparable to that of coronary artery disease or heart failure. Recent studies have indicated that increased left ventricular mass or LVH determined by

echocardiography also confers an increased risk of SCD. In the Framingham study, the hazard ratio for SCD was 1·45 (95% C.I. 1·10–1·92, $P=0·008$) for each 50 $g.m^{-2}$ increment in LV mass, after adjusting for other risk factors[30]. Left ventricular hypertrophy identified by echo- or electrocardiography contributes independently to cardiovascular risk, and the presence of LVH by both criteria confers a greater risk than having either alone.

The effect of blood pressure reduction on the incidence of SCD has been difficult to establish with certainty from randomized controlled trials, since individual trials have often been too small, or have studied populations at insufficiently high risk of cardiac death. Since elderly men with isolated systolic hypertension are known to be at high risk of SCD[27], it is important to note that an overview of the outcome trials in isolated systolic hypertension in the elderly identified a reduction in all-cause mortality of 17%, and myocardial infarction including SCD of 25%[31]. A meta-analysis of randomized controlled trials of blood pressure reduction mostly in middle-aged subjects with diastolic hypertension[32] found a risk reduction of 14% (95 C.I. 4–22%, $P<0·01$) in coronary death or non-fatal myocardial infarction.

There has been a downward trend in the prevalence of LVH in the last four decades, which has coincided with improved hypertension control. However, treated hypertensives still have a higher risk of SCD than those not treated for hypertension, even after correction for achieved blood pressure[26].

Lipids

The epidemiological association between elevated LDL-cholesterol and risk of all manifestations of coronary artery disease including SCD is well established[19–22]. Clinical trials of lipid lowering in the primary prevention of coronary artery disease have not looked specifically at SCD, and have not had sufficient statistical power to identify a significant reduction. If we assume that the reduction in risk of SCD occurs in parallel with that of coronary artery disease death and non-fatal myocardial infarction, then relative risk reductions of 30–40% would be expected from treatment with statins[33,34].

Dietary factors

Many epidemiological studies have associated a high dietary intake of saturated fat and a low intake of polyunsaturated fats with an increased risk of coronary heart disease, and hence indirectly with SCD[35]. There has been no evidence that high saturated fat intake specifically increases the risk of SCD. In contrast, the US Physicians Study of 20 551 males aged 40–84 years with no history of myocardial infarction showed that men who ate fish at least once per week had a relative risk of SCD of 0·48 (95% C.I. 0·24–0·96; $P=0·04$) compared with men who ate fish less than monthly. This effect was independent of other risk factors, and contrasted with the absence of a reduction in risk in total myocardial infarction or non-SCD[36]. Estimated dietary n-3 fatty acid intake from seafood was also associated with a reduced risk of SCD.

Physical activity

The association between strenuous exertion and sudden coronary death is well recognized, but the underlying mechanisms are unclear. An autopsy study of men who died suddenly compared 25 who died during strenuous activity or emotional stress with 116 age-matched men whose deaths occurred at rest. Evidence of plaque rupture was found in 17 (68%) of 25 men dying during exertion vs 27 (23%) of 116 men dying at rest ($P<0·001$). The majority of men dying during exertion (21/25) did not undertake regular exercise[37].

Because the risks of SCD and myocardial infarction are transiently increased during acute bouts of high-intensity activity, an important question from the public health perspective is whether regular participation in moderate-intensity activity confers overall protection from SCD. A population-based case-control study from King County, Washington, compared leisure-time physical activity in 333 victims of primary cardiac arrest with 503 age- and sex-matched controls from the same community[38]. All patients and controls were free from prior clinical heart disease, major co-morbidity, and self-reported poor health. After adjustment for other coronary risk factors, the odds ratio for SCD in subjects who performed moderate (e.g. gardening, walking) or high-intensity exercise for more than 60 min per week ranged from 0·27–0·34 compared with subjects who performed none of the activities. A study from Auckland, New Zealand, found that 43% (95% C.I. 26–60) of coronary events could be attributed to lack of physical activity after controlling for hypertension, cigarette smoking, and alcohol consumption[39].

Alcohol consumption

As in the case of exercise, there is an association between alcohol consumption and risk of SCD. Heavy alcohol intake, especially binge drinking, increases the risk of SCD[20,40]. This association may be explained by the finding of a prolonged QT interval in alcoholics[41]. In contrast, case-control studies have demonstrated a protective effect of moderate alcohol consumption against SCD[42]. In the prospective British Regional Heart Survey, moderate alcohol intake was associated with a reduction in the case fatality of a first major coronary event (odds ratio 0·61, $P<0·05$)[20].

Heart rate and heart rate variability

Increased heart rate has been reported as an independent risk factor for SCD in a number of studies[20,22–24]. The association between increased heart rate and SCD is seen both in individuals with and without known cardiac disease and is independent of body mass index and physical activity levels[25,43]. The underlying basis for this relationship is unknown, but may be due to reduced parasympathetic activity. In a study of 6693 patients who underwent ambulatory electrocardiographic recording, the heart rate variability in 245

subjects who died suddenly during the subsequent 2 years was compared with 268 randomly selected controls[24]. After adjusting for age, evidence of cardiac dysfunction, and history of myocardial infarction, the relative risk of SCD was 2·6 (95% C.I., 1·4–5·1) for patients with impaired short-term RR interval variability and 2·2 (95% C.I., 1·2–4·1) for long-term RR interval variability. The adjusted relative risk for a minimum heart rate ≥ 65 beats . min^{-1} was 2·1 (95% C.I., 1·3–3·6).

A community study in the Netherlands investigated the use of heart rate variability measurement from the routine 12-lead electrocardiogram[44] in the prediction of total and cardiac mortality. The 5-year age-adjusted relative rate of total mortality in men with heart rate variability (SDNN) < 20 ms vs 20–39 ms was 2·1 (95 C.I. 1·4–3·0) in the middle-aged and 1·4 (95% C.I. 0·9–2·2) in the elderly. However, while death from non-coronary causes, especially cancer, contributed significantly to this elevated risk, the association of low heart rate variability with SCD or coronary heart disease mortality was less consistent. The authors concluded that low heart rate variability is an indicator of compromised health in the general population.

Smoking

In community studies, cigarette smoking is an independent risk factor for SCD as it is for myocardial infarction[20,22,23]. This observation also applies to subjects without clinical evidence of coronary disease[45,46], where smoking appears to be a more important long-term than short-term risk factor[19]. A number of studies have addressed the question of whether smoking is a more powerful predictor of sudden than non-sudden coronary death. Evidence in favour of this hypothesis was obtained by a number of groups[21,47], but in other studies there was no significant evidence for a disproportionate effect of smoking on SCD[20,45]. Continued cigarette smoking is an independent risk factor for recurrent SCD in survivors of out-of-hospital cardiac arrest[48].

Diabetes mellitus

As in the case of cigarette smoking, there is controversy in the literature as to whether glucose intolerance or diabetes mellitus is an independent risk factor for SCD. In the Honolulu Heart Program, 8006 Japanese-American participants were followed-up for 23 years after enrolment. After adjustment for other baseline covariates, the relative risks for SCD within 24 h in individuals with asymptomatic hyperglycaemia (≥ 225 mg . dl^{-1}), and diabetes compared with those with values (<151 mg . dl^{-1}) were 2·22, and 2·76, respectively ($P \geq 0{\cdot}05$). Trends for SCD in 1 h were similar[49]. An Australian study found a history of diabetes mellitus to be a powerful risk factor for SCD (Odds Ratio=4·2, 95% C.I.: 1·39–12·81)[21], as did the Paris Prospective Study, which excluded men with known coronary disease[22]. In contrast, an American study of 18 733 SCDs found diabetes to be a risk factor for SCD only in individuals with known coronary disease[46], and even then it was not a specific risk factor for sudden vs non-sudden coronary death[47]. Diabetes mellitus was not an independent risk factor in other prospective studies in Finland or Great Britain[20,50].

ECG changes

The 12-lead electrocardiogram is a simple, non-invasive investigation, which can be applied widely in primary care for the assessment of cardiovascular risk. Development of computerized analysis algorithms makes interpretation available to non-cardiologists. Electrocardiographic abnormalities such as ST segment depression and T-wave changes are often indicative of unrecognized coronary artery disease or left ventricular hypertrophy. A number of prospective studies have reported an association between ST-segment depression or T-wave abnormalities and increased risk of cardiovascular death. For example, a Belgian study of 9117 men and women with no history of angina pectoris or myocardial infarction found that the age-standardized prevalence of an 'ischaemic' ECG (Minnesota codes 1-3, 4-1 to 4-3, 5-1 to 5-3 or 7-1) was 8·4% in men and 10·6% in women. After correction for other cardiovascular disease risk factors, the risk ratios for cardiovascular death were 2·45 (95% C.I. 1·70–3·53) for men and 2·16 (95% C.I.: 1·30–3·58) for women[51]. Other studies have confirmed the prognostic value of ST-segment depression or T-wave inversion as risk markers for cardiovascular death and SCD in particular[52]. In the Rotterdam Study of 5781 subjects, the hazard ratio for SCD risk associated with an abnormal T-wave axis was 4·4 (95% C.I. 2·6–7·4). Overall the cardiovascular risks associated with an abnormal T-wave axis were higher than for any other risk factors[52].

In view of the recognized risk of SCD in the congenital and acquired long QT syndromes, there has been interest in the use of the measurements of the QT interval or QT dispersion as risk markers in population studies. Interpretation of the data is confounded by the fact that the underlying heart disease or left ventricular hypertrophy may prolong the QT interval. Problems also exist in the measurement of QT interval and, particularly, dispersion[53,54], which may limit its interpretation. A further methodological problem is that the commonly used Bazett formula for heart rate correction does not fully remove the variance due to heart rate, and heart rate itself is a predictor of SCD, as discussed above. This limitation applies at very fast and very slow heart rates.

Prospective studies of subjects free from cardiac disease in the Netherlands have found a significant association between the prolonged QT interval and risk of SCD or cardiovascular death over a 15 to 28 year follow-up[55]. The Dutch Zutphen study found that men with a QT > 420 ms had a higher risk of a cardiovascular death relative to men with a shorter QTc[54]. The 28 year follow-up study of Dutch civil servants found that a QTc > 440 ms significantly predicted cardiovascular death with adjusted relative risks of 2·1[54]. Both studies

concluded that QTc contributes independently to cardiovascular risk.

Community studies of QT interval dispersion have not found this parameter to be of value in the prediction of SCD. In the Rotterdam study[56], QTc dispersion in the highest tertile carried a twofold increased risk of cardiac death (hazard ratio, 2·5; 95% C.I., 1·6–4·0) but the risk for SCD was only of borderline significance (Hazard Ratio, 1·9; 95% C.I., 1·0–3·7). A case-control analysis from the Helsinki Heart Study found that baseline QT dispersion was similar in patients suffering SCD or fatal myocardial infarction vs controls[57]. Analysis of the last ECG, on average 14 months before death, indicated that the risk of SCD could be predicted by measurement of QT dispersion to the peak of the T wave, but not to its end. The appearance of predictive changes close to the fatal event which were absent at baseline suggests that increased QT dispersion in this study may have been a marker for developing cardiac disease.

Genetic basis of sudden cardiac death

Sudden cardiac death may occur as a consequence of an inherited genetic abnormality affecting key proteins of the heart. Diseases such as Long QT Syndrome, Brugada Syndrome, Hypertrophic Cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy, Catecholaminergic Polymorphic Ventricular Tachycardia or Dilated Cardiomyopathy are the best known examples of monogenic diseases predisposing to SCD. While these conditions are described in detail in the following sections of this document, here we will evaluate current evidence in support of the existence of a genetic predisposition to SCD unrelated to a monogenic disease. Evidence supporting the existence of a genetic 'susceptibility factor' predisposing to SCD has emerged from large-scale epidemiological studies that have demonstrated a familial association of SCD. Two important studies[22,58] have recently been published that will impact SCD risk stratification. The first is designed as a case controlled study enrolling more than 500 SCD survivors and demonstrates that among 'conventional risk factors' family history is a relevant (Odds Ratio 1·57) independent predictor of SCD. The second study (Paris Prospective Study I) includes 7000 subjects followed for 23 years and including 118 SCD: the study confirms that family history is a strong independent predictor of susceptibility to SCD (Odds Ratio=1·8 after adjustment for conventional factors). Of interest is the observation that in families where a positive history for SCD was concomitantly present on the paternal and maternal side of the family the relative risk for SCD increased to 9·4. Therefore the two studies provide a major departure from the conventional view that biochemical and clinical markers are the most important predictors of SCD. Obviously the term 'familial association' suggests but does not prove that such a predisposition is genetically transmitted. It is possible that factors independent from DNA are responsible for the familial predisposition. The familial environment including 'dietary, psychological, and developmental factors' may all play a role in determining susceptibility clustered among family members. Among the genetic factors it is likely that what is genetically transmitted is not a 'rare' DNA variant as occurs in genetic diseases, but rather one or many 'polymorphisms' (common DNA variants) that may be present in a large proportion of the population yet create a disadvantaged profile toward susceptibility to SCD. Single nucleotide polymorphisms (SNPs) are DNA variants that may or may not be associated with a functional consequence: polymorphisms, such as those identified in the Beta2 adrenergic receptors, do not cause a specific disease instead they alter the function of the protein modulating its biological function. Since millions of SNPs are present in the DNA of each individual, it is likely that a risk factor derives from a specific 'combination' of polymorphisms of different genes that create a disadvantageous profile. Investigating the basis of genetic predisposition to SCD will be much more complicated than identifying the gene for a monogenic disease. It will imply developing technical tools to characterize thousands of polymorphisms in each individual to evaluate the association of the different combinations with susceptibility to SCD. The availability of chip technology is now rendering this type of study feasible.

It is important at this time to define the practical implications of our current knowledge of the genetic basis of SCD. It seems appropriate to encourage the assessment of family history in survivors of SCD. In the presence of familial clustering of cardiac arrests the presence of a monogenic disorder (Brugada Syndrome, Long QT Syndrome, hypertrophic cardiomyopathy . . ..) should be carefully evaluated, particularly in the presence of juvenile cardiac arrests. Unfortunately when the diagnosis of a genetically transmitted disease cannot be established little can be done to identify the possible cause of a genetic predisposition to SCD. In these families it remains advisable to inform family members that they may harbour vulnerability toward cardiac arrhythmias and that therefore they should actively pursue prevention of ischaemic heart disease.

SCD in myocardial infarction and heart failure

Causes and clinical findings for SCD in myocardial infarction

In patients with acute thrombotic occlusion of a major coronary artery branch in the absence of a previous myocardial infarction, cardiac arrest is most likely due to ventricular fibrillation but may also be caused by heart block or asystole especially if the right coronary artery is involved. However, although the terminal event

during SCD in patients after myocardial infarction is usually a cardiac arrhythmia[59] it may also be due to a new episode of ischaemia or another infarction in the presence of a scarred myocardium or a combination of these factors. The relative contribution of each mechanism can be indirectly estimated from pathology studies of the myocardium in SCD victims, from ambulatory monitoring of subjects with ischaemic heart disease who happened to die suddenly during recording and from epidemiological data of clinical studies on patients after AMI.

Epidemiology

In the pre-thrombolytic era, the expected mortality during the first 2·5 years following MI was a little greater than 15%[60], with three-quarters of all deaths being arrhythmic and about 70% of them being witnessed. Among arrhythmic deaths, symptoms of myocardial ischaemia preceded the terminal event in about 60% of cases. Thus, in patients convalescing from myocardial infarction, arrhythmic death may be as high as 10% in the following 2·5 years and new ischaemia may be an important cause.

Data from more recent studies conducted in the thrombolytic era have shown that the incidence of cardiac and arrhythmic deaths after MI have been substantially reduced, with figures of about 5% and 2%, respectively, at 2·5 years follow-up[61,62]. In addition, VT and VF without preceding ischaemia can be expected in 2·5% and 0·5% of patients.

In post-MI patients at high risk (EMIAT, CAMIAT, TRACE, SWORD and DIAMOND-MI), the cumulative incidence of arrhythmic mortality reached about 5% at 1 year and about 9% at 2 years, whereas the incidence of non-arrhythmic cardiac death was about 4% and 7% at the same time points. Of interest, the proportion of arrhythmic versus non-arrhythmic cardiac death does not appear to have changed with the introduction of effective thrombolysis.

Autopsy data

The reported frequency of active coronary lesions observed at autopsy in SCD victims has varied from <20% to >80%. In one study of 90 hearts, AMI was present in 21%, healed MI in 41% and no MI was seen in 38% of the hearts examined[63]. Active coronary lesions (plaque rupture and/or coronary thrombosis) were identified in 57% of the entire group of sudden coronary death victims. They were found in 89% of hearts with AMI, 46% of hearts with only healed MI, and 50% of hearts without acute or healed MI[63]. These data suggest that myocardial ischaemia is a major cause of SCD in patients with coronary artery disease. It may be the sole cause in the absence of a previous MI or it may trigger VF in its presence. Experimental studies have suggested an increased propensity to VF if ischaemia was induced at a site remote from a previous infarction[64]. However, in another series, macroscopically visible coronary artery thrombus was reported in only 13·4% of 500 cases of SCD due to coronary artery disease, and yet another study has reported acute coronary thrombus in 49% of 206 cases of SCD suspected of being ischaemic in origin[6,65].

The widely differing incidence of active coronary lesions in the reported series probably results from variable case selection, the definition SCD in terms of the time interval between the onset of symptoms and death, the autopsy protocol, and histopathology technique. Nevertheless, they provide insight into the causes of SCD in patients with coronary disease. Contemporary treatment may have reduced the incidence of active coronary lesions, as autopsy studies from the pre-thrombolytic era reported a consistently higher incidence of active coronary lesions (81 to 95%)[8,66].

Ambulatory electrocardiographic data

Recordings at the onset of collapse are rare. However, interpretation of ECG data obtained during resuscitation procedures is of limited value. For example, an episode of ventricular fibrillation recorded during resuscitation may have been precipitated by a bradyarrhythmia. Similarly, finding asystole at the time of cardiac arrest cannot exclude the possibility that it was preceded by ventricular fibrillation.

Among a total of 157 ambulatory patients who had SCD while undergoing Holter monitoring for clinical reasons, 62·4% of the deaths were due to ventricular fibrillation, 16·5% to bradyarrhythmia, 12·7% to TdP, and 8·3% to primary ventricular tachycardia[67]. Ischemic ST-segment changes preceding the arrhythmia were not common. Overall, ST-segment changes were seen in 12·6%. This small percentage may not represent the true frequency of acute ischaemic arrhythmia provocation because the study only included patients who underwent Holter monitoring for clinical reasons presumably for evaluation of arrhythmias and did not represent the general post MI population.

The incidence and importance of bradyarrhythmias as a mechanism of SCD is difficult to assess. Even the evaluation of memory logs of implanted cardioverter defibrillators will not help since these devices would normally pace asystolic hearts, thus, obscuring the full presentation of a bradyarrhythmia. Severe bradycardia, asystole or electro-mechanical dissociation is generally considered to account for about 25% of SCD[68]. In patients with advanced heart failure, who were scheduled for cardiac transplantation, this percentage may be as high as 62%[69]. The data supporting a bradyarrhythmia in a quarter of patients suffering SCD derive primarily from small groups of patients undergoing long-term ECG recordings at the time of death. Panidis and Morganroth[70] found complete heart block causing cardiac arrest in 3 of 15 patients during

ambulatory ECG recording. Roelandt *et al.*[71] found a bradyarrhythmia ending in asystole in 2 of 10 instances of SCD during ambulatory ECG recording, while Kempf and Josephson[72] found a bradyarrhythmia in 7 of 27 patients experiencing SCD during long-term ECG recording. Although the presence of a bifascicular and trifascicular bundle branch block is strongly predictive of SCD[73], the mechanism of death may not be bradycardia since the conduction system disease may merely reflect more extensive myocardial damage, thus increasing the chance of a tachyarrhythmia. In 2021 patients with permanent pacemaker implantation, 220 patients (11%) died over a mean pacing interval of $50{\cdot}5 \pm 7$ months. However, in patients with bifascicular and trifascicular bundle branch block, 35% died suddenly during the follow-up period compared with 18% of patients without bundle branch block.

Patients with severe bradycardia (SCD rate 28%), severe atrioventricular block (25%) or atrial fibrillation with slow ventricular rate (25%) before pacemaker implantation were more likely to suffer from SCD than patients with previous syncopal attacks (SCD rate 15%) or sick sinus syndrome (17%).

Causes and clinical findings for SCD in heart failure

The identification of the mechanisms and presentation of SCD in patients with heart failure is complicated by the fact that patients with heart failure comprise a mixed population of post MI patients, patients with primary DCM, and patients with a variety of other causes. To complicate the issue further, different studies have included variable proportions of individuals with idiopathic DCM and post-MI DCM. Recent data from the MERIT-HF study[74] showed a mortality in the heart failure group treated with standard pharmacological therapy (not including beta-blockers) of 11% per year which was reduced to 7% per year in those receiving beta-blockers. In this study, the population included 50% of patients with a previous MI, and SCD represented 60% of the total number of deaths. Although patients with heart failure may suffer SCD from both cardiac and non-cardiac causes most will die from a cardiac cause[75] Uretsky *et al.*[76] recently reported that in the ATLAS study, patients with heart failure due to IHD died suddenly as a consequence of reinfarction.

In an interesting subanalysis by the MERIT-HF investigators, the proportion of patients dying suddenly was higher in patients with less severe (lower NYHA class) chronic heart failure than in those with more advanced heart failure. Similar data have been reported in a large meta-analysis[77].

Risk stratification

Risk stratification after myocardial infarction (MI) aims at identifying patients who are at high risk of dying. The use of beta-blockers, HMG-CoA reductase inhibitors (statins) for hypercholesterolaemia and angiotensin-converting enzyme inhibitors for patients with low ejection fraction and/or clinical heart failure have been shown to reduce mortality after MI. This section will concentrate specifically on those patients at risk of arrhythmic or SCD who would warrant prophylactic treatment. Several simple clinical tests, some of which are routine, may help to predict arrhythmic events. i.e. SCD and life-threatening ventricular arrhythmias.

Modern post-MI therapy has reduced cardiac mortality and altered the predictive values of most of these risk factors. Hence it is no longer appropriate to extrapolate results obtained in the pre-thrombolytic era to the current situation. Accordingly, this document will focus on studies performed after introduction of thrombolysis. In addition, the lowered mortality rate reduces the possibility of finding markers with a high predictive value.

Demographic variables

Although complex risk parameters have improved the identification of patients at risk of SCD after MI, baseline demographic factors are also powerful predictors of SCD or arrhythmic events after MI but have largely been neglected. This is partly due to a lack of updated information since most studies on these factors were performed in the pre-thrombolytic era. Pooled data from placebo patients in the EMIAT, CAMIAT, SWORD, TRACE and DIAMOND-MI studies have shown that demographic features are significant predictors of arrhythmic events (including SCD) in patients after MI with $EF \leq 40\%$ or frequent ventricular premature beats[78] (Table 1). Of note, a history of a previous myocardial infarction or of a prior angina pectoris was related to a poor outcome, which probably reflects the significance of the presence of multivessel disease.

Left ventricular ejection fraction (LVEF)

Reduced LVEF remains the single most important risk factor for overall mortality and SCD. However, when LVEF is severely depressed (<15–20%), the prevailing mode of cardiac death is non-sudden, or when sudden it is often related to bradyarrhythmias or electromechanical dissociation rather than ventricular tachyarrhythmias.

The meta-analysis of pooled individual placebo patient data from EMIAT, CAMIAT, SWORD, TRACE and DIAMOND-MI studies, assessed the risk of death in patients who had survived at least 45 days after MI[78]. The prognostic value of EF was adjusted for treatment and other demographic factors associated with survival. The meta-analysis confirmed that LVEF significantly predicted 2-year all-cause, arrhythmic and cardiac mortality. A 10% absolute increase in EF

Table 1 Independent predictive value of risk factors for mortality at 2 years in patients surviving 45 days after MI

Risk factors	All-cause mortality		Arrhythmic mortality	
	HR (95% C.I.)	*P*-value	HR (95% C.I.)	*P*-value
Age (↑10 yr)	1·41 (1·26–1·57)	<0·001	1·28 (1·08–1·52)	0·005
Males	1·25 (0·99–1·58)	0·06	1·62 (1·10–2·38)	0·01
Smoker (current or ex-)*	1·25 (0·96–1·62)	0·1	1·04 (0·70–1·53)	0·9
Previous MI	1·63 (1·33–1·99)	<0·001	1·70 (1·25–2·30)	0·001
History of hypertension	1·35 (1·08–1·67)	0·006	1·70 (1·23–2·34)	0·001
History of angina*	1·63 (1·31–2·04)	<0·001	1·59 (1·13–2·23)	0·007
Diabetes*	1·29 (1·01–1·64)	0·004	1·30 (0·89–1·88)	0·2
Systolic BP (↑ by 10%)	0·91 (0·85–0·97)	0·002	0·84 (0·77–0·92)	<0·001
Heart rate (↑ by 10%)	1·14 (1·08–1·21)	<0·001	1·12 (1·03–1·22)	0·009
NYHA (compared to level 0)		<0·001		0·01
I	1·41 (0·83–2·39)		1·72 (0·80–3·73)	
II	2·18 (1·30–3·67)		2·77 (1·28–6·01)	
III	2·70 (1·53–4·75)		3·21 (1·38–7·47)	
IV	3·86 (1·86–8·02)		3·53 (1·09–11·45)	
Q-wave	0·68 (0·55–0·84)	<0·001	0·67 (0·49–0·92)	0·01
Atrial fibrillation*	0·90 (0·66–1·23)	0·5	0·99 (0·60–1·63)	0·99

*Data were only available for 4 out of 5 studies.
EF <35% had a 40% sensitivity, 78% specificity and 14% positive predictive accuracy[80].

reduced the mortality at 2 years with a hazard ratio of 0·61 (95% C.I.: 0·48–0·78, $P<0·001$) (Table 2)[78]. The rates of arrhythmic mortality per person-year were 3·2%, 7·7% and 9·4% for EF of 31–40%, 21–30% and <20%, respectively (Table 3). Another study showed that mortality for myocardial infarction survivors with EF <40% was 20% over 3·5 years and that half of the deaths were sudden[79]. For the prediction of cardiac death, a EF <35% had a 40% sensitivity, 78% specificity and 14% positive predictive accuracy[80].

EF is usually combined with other risk factors. While it is unclear which combination of non-invasive variables provides the strongest risk prediction in the current thrombolytic era, it seems logical to combine variables that reflect different factors linked to SCD, for example, the substrate (EF), the trigger (ventricular premature beats, non-sustained ventricular tachycardia) or the modulator (autonomic dysfunction). The ATRAMI study[81] demonstrated that a combination of low values of autonomic markers and reduced EF identified a group of post-MI patients at highest risk of sudden and non-SCD (see below).

The results from an earlier study[82] from the pre-thrombolytic era were recently confirmed showing that echocardiographic left ventricular end-systolic and end-diastolic volumes were strong predictors of mortality at 6 months after AMI[83]. Whether, as previously suggested, they are more superior to EF requires further study.

Table 2 EF and risk of mortality after MI[78]

Effect of 10% increase in EF on reduction in mortality	Mortality 45 days–2 years Hazard ratio (95% C.I.)
All-cause mortality	0·58 (0·49–0·68), $P<0·001$
Arrhythmic mortality	0·61 (0·48–0·78), $P<0·001$
Cardiac mortality	0·51 (0·39–0·66), $P<0·001$

Table 3 Rate of death for each mode of mortality at various dichotomy limits of EF[78]

EF	No. of patients	Rate (%) per person-year (total events)		
		All-cause	Arrhythmic	Cardiac
<20%	193	23·1%	9·4%	10·6%
21–30%	881	17·5%	7·7%	6·3%
31–40%	1432	6·8%	3·2%	2·2%

Ventricular premature beats

The prognostic value of ventricular arrhythmias in post-MI risk stratification, clearly demonstrated in the pre-thrombolytic era, has recently been reassessed by several studies. In one study[62], 680 patients of whom 379 received early thrombolytic therapy, underwent 24-hour Holter monitoring in a drug-free state between 6 and 10 days post-MI and were followed for 1 to 8 years. The mean PVC count was significantly higher in patients who died of cardiac causes, in those who died suddenly, and in those with arrhythmic events during the first year of follow-up. This finding was unaffected by thrombolysis but the positive predictive accuracy of PVC frequency was greater in thrombolysed patients. At a sensitivity level of 40%, the positive predictive accuracy of PVCs for cardiac mortality and arrhythmic events for the group with thrombolysis was 19·4% and 25·8%, respectively.

Table 4 Sensitivity and specificity for predicting arrhythmic events after MI

Study	n	Criteria	Sensitivity	Specificity
Farrell *et al.*[85]	416	PVCs >10/h	54	82
McClements & Adgey[86]	301	PVCs >10/h or repetitive	42	74
Richards *et al.*[87]	358	PVCs >60/h or repetitive	82	40

The GISSI-2 study indicated that frequent PVCs are independent risk factors for SCD in the first 6 months after MI in the thrombolytic era. After adjusting for other risk factors, the presence of PVCs $>10 \cdot h^{-1}$ remained a significant independent predictor of total mortality and SCD at 6 months after MI (total mortality: RR=1·62; 95% C.I.= 1·16–2·26; SCD: RR=1·20; 95% C.I.=0·80– 1·79)[84].

For PVCs $>10 \cdot h^{-1}$, the sensitivity and specificity were 42–54% and 74–82%, respectively, for the prediction of arrhythmic events after MI (Table 4). The specificity of PVCs can be improved by increasing the threshold number of PVCs $\cdot h^{-1}$ but at the expense of a reduced sensitivity.

Non-sustained VT

In the pre-thrombolytic era, non-sustained VT was a good predictor of all-cause and arrhythmic mortality post-MI. In the thrombolytic era, the risk associated with the presence of non-sustained VT has become uncertain. For instance, the large GISSI-2 study reported that the prevalence of non-sustained VT was only 6·8% and its presence was not predictive of SCD at 6 months post-MI[84]. In another study where 325 patients were followed-up for 30 ± 22 months, there was also a low prevalence (9%) of non-sustained VT shortly after AMI. At multivariate analysis, unlike HRV, EF or the status of the infarct artery, non-sustained VT was not an independent predictor[61]. Currently, there is a relative paucity of data regarding the prognostic value of non-sustained VT with modern post-MI therapy.

However, the combination of non-sustained VT with other variables including reduced EF and electrophysiological testing after AMI, was effective in identifying post-MI patients at high risk of arrhythmic death who subsequently benefited from prophylactic implantable cardioverter-defibrillator implantation, as demonstrated in the MADIT and MUSTT studies. In the Multicenter Automatic Defibrillator Implantation Trial (MADIT), prophylactic therapy saved lives in high-risk post-MI patients with EF $\leq$35%, non-sustained ventricular tachycardia and inducible ventricular tachycardia not suppressible by antiarrhythmic drugs at electrophysiological study (Hazard Ratio for overall mortality, 0·46; 95% C.I.: 0·26 to 0·82, P=0·009)[88]. The Multicenter Unsustained Tachycardia Trial (MUSTT)[89] demonstrated that in high risk coronary artery disease patients stratified with EF$\leq$40%, non-sustained ventricular tachycardia and an inducible ventricular tachycardia, the risk of cardiac arrest or death from arrhythmia was significantly reduced (76%) when they received an implantable cardioverter-defibrillator (Relative Risk, 0·24; 95% C.I.: 0·13–0·45, P<0·001). The 5-year estimate of overall mortality within the group treated by implantable cardioverter-defibrillators was 42% (relative risk, 0·80; 95% C.I., 0·64 to 1·01).

The number of high risk patients identified by a combination of depressed EF and non-sustained VT was as low as 3·2% among all post-MI survivors[90]. Nevertheless, the MADIT and MUSTT studies are the only definitive evidence that demonstrated the clinical value of risk parameter(s) based on the favourable survival impact of an intervention in patients selected using this parameter.

Late potentials

Most studies on the SAECG post-MI were performed in the pre-thrombolytic era. A meta-analysis of all available prospective studies, during the pre-thrombolytic era, on the use of SAECG after myocardial infarction showed that the SAECG predicted a sixfold increase in risk of arrhythmic events independent of left ventricular function, and an eightfold increase in risk of arrhythmic events independent of Holter results[91]. Thrombolysis reduced the frequency of SAECG abnormalities by 37%[92] and, in this setting, the predictive value of late potential was diminished[93].

More recent studies supported the concept that SAECG is an independent predictor of arrhythmic events after MI[86,93,94]. In a consecutive series of survivors of myocardial infarction, 68% of whom had received thrombolytic agents, 301 underwent SAECG examination[86]. At a median follow-up of approximately 1 year, 13 patients (4·3%) had an arrhythmic event (SCD or sustained VT). The SAECG at discharge had a sensitivity of 64% (95% C.I.: 36–92%), a specificity of 81% (95% C.I.: 76%–86%), a good negative predictive value of 98% (95% C.I.: 96–100%), and a low positive predictive value of 11% (95% C.I.: 3–19%) for prediction of arrhythmic events. In another prospective study of 222 patients with AMI in the thrombolytic era, the presence of late potential at discharge was predictive of arrhythmic events (SCD, sustained VT, syncope) during the first year after MI, with a sensitivity of 94% and a specificity of 72%[94].

The usefulness of SAECG[95] is limited by its low positive predictive value; by contrast, the absence of late potential has a high negative predictive accuracy.

Autonomic markers

These markers provide information about autonomic balance. Usually, risk is increased when there are signs of reduced vagal activity to the heart.

The time-honoured concept that an elevated heart rate increases the risk has been validated in the GISSI-2 study[96]. In 8915 post-MI patients, heart rate at hospital discharge was an independent predictor of total mortality of which SCD represents almost 50%.

Two markers were evaluated in the prospective ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study based on 1284 patients. HRV and BRS, determined in the first month post-MI, were found to be significant predictors of cardiac mortality[81]. ATRAMI demonstrated that during 21 months of follow-up, depressed HRV (SDNN <70 ms) and BRS (<3·0 ms mmHg) carried a significant multivariate risk of cardiac mortality of 3·2 and 2·8, respectively. The combination of low HRV and depressed BRS further increased the risk; 1-year mortality increased from 1% when both markers were well preserved to 15% when both were depressed. Of greater practical importance, the association of LVEF <35% with low HRV and even more with low BRS further increased the risk. Over age 65, the predictive power of BRS declined much more markedly than HRV; for this reason, the specific prognostic value was higher below age 65 for BRS and above age 65 for HRV.

ATRAMI has demonstrated that after MI, the analysis of autonomic markers has significant prognostic value independent of established clinical predictors such as EF and ventricular arrhythmias. The combination of low values of autonomic markers and reduced EF identifies a group of post-MI patients at high risk for sudden and non-SCD. This is further supported by the EMIAT data that in post-MI, patients with EF (40% low HRV) identified patients at increased risk of mortality, especially SCD. In such patients, amiodarone treatment significantly reduced the cardiac arrhythmic mortality by 66% compared with placebo (4·4% vs 12·8%, $P=0·005$)[97]. Although amiodarone also reduced all-cause mortality by 23·2%, it did not reach statistical significance (17·5% vs 22·8%, $P=$ns).

Heart rate turbulence (i.e. the variability in cycle length after a spontaneous post-extrasystolic pause) represents another measure of vagal activity and has been applied to the data from MPIP and EMIAT; retrospectively it represented a strong independent predictor of total mortality[98]. However, the MPIP data were from the pre-thrombolytic era and the EMIAT population comprised pre-selected patients with low EF. Thus, the prognostic value of heart rate turbulence in the general MI population will require an up-to-date prospective study.

The preliminary information further points to the importance of reduced vagal activity in increasing the risk for sudden and non-SCD.

Repolarization variables

Prolongation of the QT interval is associated with increased risk for SCD post-MI[99,100]. However, most of its prognostic value comes from repeated measurements, which has limited feasibility and validity and has led to the use of QT dispersion; a possible marker of heterogeneous repolarization has recently been investigated. The clinical and prognostic values of QT dispersion are undetermined by poor inter- and intra-observer reproducibility (a relative error of 25–42%) and a lack of standardized measurement techniques. To date, only one prospective study has been published, which indicated that QT dispersion had little value as a risk stratifier[101].

Microvolt T wave alternans, a pre-fibrillatory phenomenon, significantly predicted the first appropriate ICD therapy for documented ventricular tachycardia or fibrillation in a mixed cohort of cardiac patients with ICD[102]. Despite growing interest, microvolt T wave alternans has so far been tested in only a small cohort of post-MI patients. In a prospective cohort of 102 post-MI patients, univariate analysis showed that microvolt T wave alternans predicted sustained ventricular tachycardia or ventricular fibrillation at a follow-up period of 13 ± 6 months (sensitivity of 93%, negative predictive value of 98% and a positive predictive value of 28%). The highest positive predictive value was achieved when microvolt T wave alternans was combined with late potentials[103].

Electrophysiological testing

Electrophysiological testing, potentially still a useful invasive tool for early post-MI risk stratification, has progressively lost favour in the thrombolytic era. The end-point of the study is the induction of sustained monomorphic VT, which exceeded 5% in the pre-thrombolytic era but has now decreased considerably. Nearly half of all reported trials found the inducibility of sustained VT during programmed stimulation to be unhelpful in predicting later mortality or arrhythmic events[104]. Many post-MI patients with SCD have negative pre-discharge electrophysiological tests, resulting in a low negative predictive accuracy[105]. Furthermore, when used alone, EF is superior to electrophysiological testing in predicting arrhythmic events after AMI[106]. Thus, programmed ventricular stimulation alone as a predictor of SCD in the general MI population without spontaneous VT cannot be recommended[105].

A two-step strategy using EF $\leq$40% and ventricular arrhythmias on Holter monitoring ($\geq$20 PVCs . h^{-1}, $\geq$10 ventricular couplets/day or VT with cycle length

Table 5 Predictive values of occluded infarct-related artery and EF for combined VT and SCD[109]

	Sensitivity	Specificity	Pos. Pred. Value	Neg. Pred. Value
Occluded infarct-related artery	78%	61%	14%	97%
EF <40%	56%	83%	21%	96%

$\leq$600 ms), and then electrophysiological testing significantly improved the positive predictive accuracy of the risk stratification process, but only to a moderate level of 18·2%[107]. Nevertheless, the evidence from MADIT and MUSTT have confirmed that a two-step risk stratification procedure using reduced EF (<40%) and non-sustained VT as entry criteria, followed by electrophysiological testing was helpful in selecting a high risk subgroup of patients that benefited from prophylactic ICD implantation for the prevention of SCD, although the precise value of VT inducibility is uncertain.

Patency of infarct-related coronary artery

Successful reperfusion of the infarct-related artery reduces the incidence of ventricular tachyarrhythmias and SCD, possibly by increasing electrical stability at the border zone of the infarction. In a multivariate analysis of 173 post-MI patients examining the role of an occluded infarct-related artery, EF $\leq$40%, late potentials, ventricular arrhythmias and clinical variables, only the presence or absence of a patent infarct-related artery was an independent predictor of arrhythmic events (SCD, resuscitated VF, sustained VT) during a 12-month follow-up period[108]. In one study, an occluded infarct-related artery, as assessed by coronary angiography, was 78% sensitive and 58% specific for the prediction of arrhythmic events (SCD, sustained VT and unexplained syncope)[94]. Another study in 244 consecutive post-MI patients showed that an occluded infarct-related artery had similar predictive values for the combined end-point of VT and SCD, but suffered from a low positive predictive value and was worse than EF (Table 5)[109].

At present there is no direct evidence to support the routine use of coronary angiography after MI. The TIMI-IIb trial showed that routine cardiac catheterization resulted in three times the number of revascularization procedures but similar 1-year mortality and reinfarction rates compared with a conservative strategy[110]. Furthermore, a meta-analysis of randomized trials confirmed that revascularization with PTCA adjunctive to thrombolysis did not improve the 6-week and 1-year mortality or the non-fatal reinfarction rate, compared to thrombolytic therapy alone in post-MI patients[111]. Thus, coronary angiography after MI is not indicated solely for the assessment of the SCD risk.

Conclusions

Both non-invasive and invasive tests have been introduced to help stratify post-MI patients according to their risk for SCD. The decline in cardiac mortality in the thrombolytic era has enhanced a limitation inherent in risk stratification, namely the low positive predictive value. This limitation is partly overcome when these tests are not used alone, although an inevitable decrease in sensitivity results. Although a combination of different tests improves their predictive value, the positive predictive accuracy rarely reaches more than 40% at reasonable levels of sensitivity. An additional limitation is represented by the fact that some of these variables are inter-related (e.g. different autonomic markers all exploring aspects of vagal control of sinus node function); thus, they compete with each other when placed in a multivariate or regression model.

There are variables whose specific value increases when moving from the more general post-MI population to specific groups of patients. An example is represented by PES, which cannot be recommended for all post-MI patients but which acquires powerful prognostic value when used in patients with depressed EF and the presence of non-sustained VT, particularly in patients with large infarcts.

The available data suggest that strong combinations result from the association of a marker of structural damage, such as depressed EF, with markers of autonomic imbalance related to electrical instability, such as depressed HRV or BRS.

Clever and balanced use of risk stratification parameters will allow appropriate therapeutic strategies to be used successfully to reduce the incidence of SCD.

Recommendations for risk stratification for sudden cardiac death: myocardial infarction and heart failure

	Recommendations	Level of evidence	References
Demographic variables	Class I	A	[78]
Left ventricular ejection fraction	Class I	A	[78–80]
Heart rate variability or baroreflex sensitivity	Class I	A	[81,96,97]
Left ventricular volume	Class I	A	[83]
Ventricular premature beats	Class IIa	A	[62,84]
Non-sustained ventricular tachycardia	Class IIa	A	[61,88,89]
Resting heart rate	Class IIa	A	[84]
Late potential	Class IIb	A	[85,86,91,103]
QT interval	Class IIb	B	[99]
Electrophysiological study	Class IIb	A	[104–107]
T wave alternans	Class IIb	B	[61,103]
Heart rate turbulence	Class IIb	B	[98]
Patency of infarct-related artery	Class IIb	B	[108,109]
QT dispersion	Class III	B	[101]

This Table concerns risk stratification for SCD only; other clinical events are predicted using different stratification methods.

Prevention of SCD in post MI and HF

Due to the complex mechanisms leading to SCD, mainly due to ventricular tachyarrhythmias, a variety of therapeutic targets may be considered[112,113]. These may range from limitation of infarct size and prevention of new ischaemic events (resulting from progression of coronary artery disease and plaque instability) to modulation of neuroendocrine activation, antiarrhythmic and antifibrillatory actions, all designed to prevent or terminate ventricular tachyarrhythmias.

The terms 'primary' and 'secondary' prophylaxis are used unusually in the context of ventricular arrhythmia. Therapy that is given in order to prevent a sustained ventricular arrhythmia in patients who have not yet suffered a life-threatening ventricular arrhythmia, but who are at high risk of such an arrhythmia, is usually described as 'primary' prophylaxis. Similar prophylactic therapy recommended for patients who have already suffered a cardiac arrest or syncopal/hypotensive VT is known as 'secondary' prophylaxis.

It is important to point out that studies on the efficacy of drugs/interventions on specific 'modes' of death in MI and HF are dependent on the reliability and validity of the classification used. Differences in the classification of death adopted in different trials may be responsible for some of the discrepancies observed. Ziesche *et al.*[114] recently reported that when 10 narratives used to classify deaths in the V-HeFT trial[115] were independently classified by 21 SOLVD investigators[116], agreement was observed only in 50% of cases. They concluded that discrepant interpretations of the modality of death may account for the divergent data of the two trials on incidence of SCD and on the efficacy of enalapril to reduce it. Furthermore, the evidence supported by MERIT-HF that SCD is a more frequent cause of death in patients with less severe LV dysfunction is in contrast with the evidence that trials on the use of ICDs demonstrated that these devices are more effective in patients with more severe LV dysfunction[74]. It is intriguing to speculate that this discrepancy might also depend on the classification system used for attribution of the modality of death.

This discussion supports the view that total mortality is probably the only reliable end-point in MI and HF trials. As a consequence, the following section and the tables with recommendations reported at the end of the document, provide a review and a ranking of the data available on reduction of SCD and are therefore affected by the limitations described above: treatment of patients, however, should be aimed at reducing total mortality.

Primary prophylaxis

Drugs without electrophysiological properties

Several agents with no direct or only indirect effects on the cardiac electrophysiological substrate have shown potential for improving the clinical outcome in patients after MI or with CHF[112]. The primary end-point was all-cause mortality in most prospective controlled studies testing the efficacy of such agents.

Table 6 shows the results on all-cause mortality in different meta-analyses (modified from Hennekens *et al.*[117]) and in placebo-controlled trials on thrombolytic and antithrombotic agents (see paragraph below) presenting the effect of different non-antiarrhythmic drugs used for primary prevention.

Angiotensin converting enzyme inhibitors

The use of angiotensin converting enzyme (ACE) inhibitors has been investigated in patients with recent MI[128–134], as well as in patients with asymptomatic chronic left ventricular dysfunction[135], moderate[136]

Table 6 Impact of agents / interventions without direct cardiac electrophysiological properties on total or SCD of post-MI patients with and without left ventricular dysfunction

Drug category	No. of patients	Relative risk of death (95% C.I.)	Relative risk of SCD (95% C.I.)	References
ACE inhibitors				[113]
during MI	100 963	0·94 (0·8–0·98)		[117]
after MI	15 104	0·83 (0·71–0·97)	0·80 (0·70–0·92)	[118]
Aldosterone receptor blockers	1663	0·70 (0·60–0·82)	0·71 (0·54–0·95)	[119]
Lipid lowering agents				
statins	30 817	0·71 (0·64–0·80)		[120]
n-3 polyunsaturated fatty acids	11 324	0·70 (0·56–0·86)°°	0·55 (0·40–0·74)	[121]
Nitrates				
early treatment	81 908	0·94 (0·90–0·98)	na	[117]
Magnesium				
early treatment	61 860	1·02 (0·96–1·08)	na	[117]
Thrombolytics				
during MI	58 600	0·82 (0·77–0·87)	na	[122]
Aspirin				
after MI	17 187	0·75 (0·71–0·79)	na	[123]
Abciximab*	2399	0·43 (0·19–0·97)	na	[124]
Oral anticoagulants**	10 056	0·78 (0·69–0·87)	na	[125]
Heparin***	5130	0·90 (0·62–0·90)	na	[126]
PTCA****	2606	0·66 (0·46–0·94)	na	[127]

*after coronary stenting.
**significant reduction in mortality in high intensity oral anticoagulant therapy defined as 2·8>INR>4·8.
***overall data (high and low dosage) in the absence of aspirin.
****PTCA vs thrombolytic therapy.
°°death from all causes tested as one of more combined parameters accounting for the study's primary endpoint.

and advanced heart failure[116]. Treatment with ACE inhibitors resulted in a decreased progression to overt heart failure and a decrease in death due to progressive heart failure and SCD. Of note, reduction of SCD by ACE inhibitors ranges between 30% and 54%, which was statistically significant in some studies[128,131]. In other studies[132,135] the contribution of ACE inhibitors was probably underestimated, because patients who suffered a cardiac arrest during overt heart failure were regarded as having died due to progressive heart failure.

Aldosterone receptor blockers

During congestive heart failure, hyperstimulation of the renin-angiotensin-aldosterone system results not only in increased levels of plasma angiotensin II, but also of circulating aldosterone. Aldosterone levels are not suppressed by chronic ACE inhibitor therapy. The RALES[119] showed that spironolactone therapy in patients receiving diuretics, ACE inhibitors and, in most cases, digoxin was associated with a significant reduction in death due to progressive heart failure and SCD. The reason for the latter effect is unclear, but may include prevention of hypokalaemia and regression of aldosterone-related interstitial fibrosis[137].

Lipid lowering agents

The 4S (Scandinavian Simvastatin Survival Study)[138], the CARE study[139] and the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID)[140] trial did not recruit patients with overt heart failure but their post-MI population included patients with asymptomatic left ventricular dysfunction. In these studies, the reduction of all-cause mortality in patients assigned to treatment with lipid lowering agents was paralleled by a reduction in SCD. In the 4S, assignment to treatment with simvastatin was also associated with a reduction in heart failure which was largely attributable to prevention of recurrent MI[138]; although data on the specific contribution of SCD on total mortality are not provided, it is likely that part of the benefit among tested patients is related to the strong association between acute coronary occlusion and this mode of death[139].

Recently, supplemental n-3 polyunsaturated fatty acids (850/882 mg of eicosapentaenoic acid; EPA and docosahexaenoic acid; DHA as ethyl esters in the ratio of EPA/DHA 1:2), but not vitamin E (300 mg) were proven to be effective in improving the clinical outcome of patients with coronary artery disease[121,141].

Nitrates

Several studies have shown that the antiischaemic efficacy of nitrates does not translate into a reduction of mortality or morbidity in patients with acute MI. Indeed, data collected in the pre-thrombolytic era suggested a potential benefit of these drugs when administered intravenously in the early phase of acute MI, with

up to 35% reduction in all-cause mortality[142]. More recent data collected in the thrombolytic era have shown that nitrates minimally affect survival during the first month after acute myocardial infarction[134], with an estimated 3 to 4 fewer deaths for every 1000 patients treated[133]. Therefore, nitrates are not suggested for routine use in the post-MI patient, although these drugs are indicated for the relief of anginal pain and as a vasodilator in patients with MI associated with left ventricular failure.

Magnesium therapy

The efficacy of supplemental intravenous administration of magnesium is controversial. Meta-analysis of controlled trials in patients with suspected MI have shown a 45% risk reduction in all-cause mortality with early administration of magnesium[143,144]. In most such studies, the reduction in mortality appears to be mediated by a reduction in the development of congestive heart failure. More recent studies have failed to confirm a benefit from magnesium. The conflicting data between earlier and more recent studies appear to be associated with the low risk profile of selected patients[133] and the delayed treatment (median of 12 h) from the onset of symptoms[145,146] in the more recent studies.

Thrombolytic and antithrombotic therapy

During recent decades, it has become indisputable that thrombolytic treatment in the acute setting of myocardial infarction reduces the risk of future death by 18% to 50%[122,123,147–150]. The most relevant limitation of thrombolytic therapy is represented by the ineligibility to this treatment of about one-half to two-thirds of victims of acute myocardial infarction, mostly because of contraindications, late presentation, or non-diagnostic electrocardiographic abnormalities[123,147].

A variable proportion of the benefit of thrombolysis is secondary to a reduction of SCD, although specific data in this regard were not presented in the different trials. The benefit from thrombolytic therapy increases up to 25% when oral aspirin is also administered in the early phase[123], whereas additional use of heparin does not appear to be effective[151–153]. No major distinct advantage of any one among the available thrombolytic agents has emerged after direct comparisons in large trials[147,152–154].

Chronic treatment with aspirin is associated with a 25% reduction in all-cause mortality in post-MI patients. Although these results are substantiated by pooled data rather than by data from a single trial[155], routine use of aspirin after MI is justified by its additional impact on prevention of non-fatal reinfarction and stroke[156]. Although ticlopidine does not increase survival in patients with ischaemic heart disease, treatment with this drug appears justified whenever aspirin cannot be administered because it reduces the incidence of stroke[157]. Chronic anticoagulation appears to be less effective than antithrombotic therapy in the prevention of death, but not of future cardiovascular events[158–160].

Coronary revascularization

Revascularization can be beneficial in the reduction of SCD by two main mechanisms: prevention of acute ischaemia and modification of the myocardial substrate triggering ventricular arrhythmias. Revascularization may be performed either by percutaneous coronary interventions (PCI) or by coronary artery bypass grafting (CABG). In this section, revascularization will include both modalities of treatment with the selection based on patient- and lesion-related factors, which will not be discussed here.

Chronic stable angina. The only firm evidence that revascularization reduces the risk of death in chronic stable angina is derived from trials of medical vs surgical treatment carried out more than 20 years ago[161]. These trials did not look at SCD as distinct from all-cause mortality, but since the majority of late deaths in patients who have undergone revascularization therapy are cardiac, it is reasonable to assume that coronary bypass surgery reduces the risk of sudden as well as non-SCD.

Unstable angina. Recent trials have shown that aggressive management of these patients by early coronary arteriography and revascularization can further reduce the risk of the combined end-point of early death, myocardial infarction or recurrent ischaemia[162]. In one study, there was a significant reduction in mortality in the invasive group at 1 year[163], but SCD was not specifically reported. This would be expected to translate into a reduction in the prevalence of the substrate for late SCD related to post-MI left ventricular dysfunction. However, interpretation of these studies is complicated by the fact that the diagnostic criteria for myocardial infarction were different in the conservative and invasive groups, potentially biasing the myocardial infarction data in favour of the invasive strategy.

Acute myocardial infarction. Primary ventricular fibrillation in acute myocardial infarction usually occurs as an early event, typically within the first 2 hours of the onset of symptoms. Unless the patient presents to hospital very quickly, the role of reperfusion therapy in the prevention of primary ventricular fibrillation, whether by fibrinolytic drugs or mechanical revascularization, is limited. However, reperfusion therapy has a clear role in reduction of in-hospital mortality during MI, based on reduction both of arrhythmic death due to primary ventricular fibrillation, and of 'mechanical' death due to cardiogenic shock, secondary ventricular fibrillation or cardiac rupture. Furthermore, successful achievement of vessel patency and TIMI 3 flow results in preservation of left ventricular function, and reduction in ventricular enlargement[164,165] and the substrate for late ventricular tachyarrhythmias and SCD.

The recent classification of acute myocardial infarction proposed by a joint ESC/ACC committee[166] has considered the presence of greater than twofold elevation of CK-MB after PCI a sufficient criterion to be

considered AMI. These 'infarctlets' have been shown to be associated with higher rates of adverse events at follow-up, including increased mortality. SCD from VTs developing in areas of patchy necrosis after diffuse embolization during PCI has been proposed as one of the underlying mechanisms. The use of glycoprotein IIb-IIIa inhibitors reduces the incidence of post-intervention and 30 days adverse events and reduces in particular the incidence of non-Q-wave AMI. This effect may explain the sustained benefit of these drugs at long-term follow-up, shown up to 3 years after PTCA and up to 1 year after stent implantation[124,167] with significant reduction of cardiac death in general but likely involving a diminished incidence of SCD as well. The benefit of other methods to prevent distal embolization (embolectomy or aspiration systems, filters) when glycoprotein IIb-IIIa inhibitors appear insufficient because of too large a thrombus burden or degenerated plaque, such as in vein graft lesions, has still to be confirmed.

Although the randomized trials discussed above suggest a potential advantage of primary PCI, there is ongoing debate as to whether these benefits can be delivered in the general hospital population[168]. Two recent technical improvements have the potential for further improvement in clinical outcome. The use of stents has increased immediate success in complex lesions and reduced early occlusion[169] and late restenosis[170], but has not reduced late mortality[171]. Conversely, glycoprotein IIb-IIIa inhibitors improve myocardial perfusion and TIMI 3 flow and reduce left ventricular damage after PCI in acute MI[172–174]. Their effect on early and late mortality in this indication has not yet been studied in adequately sized trials. No study has separately analysed SCD after primary PTCA for AMI but, as PCI offer greater reduction of death than thrombolysis after AMI, it is likely that SCD, the main component of late mortality, is also affected.

Survivors of sudden cardiac death. Severe atherosclerotic coronary artery disease is a common pathological finding in survivors of SCD, and acute myocardial ischaemia is often a contributing factor. In patients with inducible polymorphic ventricular tachycardia or ventricular fibrillation or a known anatomical substrate for arrhythmias such as left ventricular aneurysms, successful revascularization can be insufficient to prevent recurrent episodes of cardiac arrest. Only 50% of sustained inducible ventricular arrhythmias will be suppressed by coronary revascularization alone[175] and a high risk also remains in patients with negative postoperative electrophysiological tests. Evidence from recordings obtained in survivors of cardiac death with implantable cardiac defibrillators indicates that appropriate discharges are frequent even if no sustained arrhythmias are inducible after myocardial revascularization[176].

Positive inotropic agents

Several positive inotropic agents have been investigated in patients with congestive heart failure. Controlled trials testing the efficacy of these agents have shown disappointing results, with some studies reporting a clear increase in all-cause mortality among patients assigned to drugs such as xamoterol and milrinone[177]. The mechanism of death associated with administration of positive inotropic agents does not appear to relate to a worsening of heart failure, but to an excess of SCDs. Digoxin appears to have a neutral effect on overall clinical outcome in patients with congestive heart failure. The Digitalis Investigation Group (DIG) study[178] reported a neutral effect on all-cause mortality and a significant reduction in the need for hospitalization for worsening cardiac failure. Of note, in this study a significant 14% increase in cardiac deaths not due to progressive heart failure was observed, although the number of SCDs was not reported.

Drugs with electrophysiological properties

In recent years, consistent evidence has been provided that suppression of spontaneous non-sustained ventricular arrhythmias by antiarrhythmic drugs[179] does not translate into risk reduction in the usual case[180]. In some instances, for example after myocardial infarction, administration of antiarrhythmic drugs such as sodium channel blockers may be distinctly harmful.

Table 7 summarizes the effects of antiarrhythmic drugs with electrophysiological properties on clinical outcome.

Sodium channel blockers

Intravenous administration of lidocaine during acute MI has not proven to be effective in preventing future fatal arrhythmias and indeed its use has caused some concern about possible drug-related harm when compared to placebo[181]. Prophylactic administration of sodium channel blockers is associated with an increased risk of all-cause mortality solely based on a pro-arrhythmic effect by this therapy. Although the most solid data refer to drugs such as encainide, flecainide[180] and moricizine[191], this harm does not appear to be confined to any one agent or subclass of agents (Table 7)[182]. The most harm of sodium channel blockers is observed during the first month of active treatment[180,191,192]; after this time, a residual excess mortality may still be present.

In summary, sodium channel blockers should be viewed as certainly providing no benefit and probably being potentially harmful in the prophylactic treatment of post-MI patients with documented ventricular arrhythmias.

Beta-blockers

Data collected during the last 20 years has convincingly proven that beta-blocking treatment is associated with an improved clinical outcome in several patient groups[60,183,193,194]. The efficacy of this treatment in post-MI patients relates to a drug-associated reduction in all-cause mortality and is not necessarily related to the

Table 7 Impact of agents with electrophysiological properties on death of post-MI patients with and without left ventricular dysfunction

Drug category	No. of patients	Relative risk of death (SCD in bold) (95% C.I.)	*P* value	References
Sodium channel blockers				
during MI				
lidocaine	9155§	1·38 (0·98–1·95)	<0·05	[181]
after MI				
class Ia	6582§	1·19 (0·99–1·44)	0·07	[182]
class Ib	14 033§	1·06 (0·89–1·26)	0·50	[182]
class Ic[1]	2538§	1·31 (895–1·79)	0·10	[182]
Flecainide and encainide	1455^	**3·6 (1·7–8·5)**	**0·0006**	[180]
Beta-blockers[2]				
during MI	28 970§	0·87 (0·77–0·98)	0·02	[183]
after MI	24 298§	0·77 (0·70–0·84)	<0·001	[183]
carvedilol[3]	1959	0·77 (0·60–0·98)	0·03	[184]
		0·74 (0·51–1·06)	**0·098**	**[184]**
in CHF				
carvedilol	1094	0·44 (0·28–0·69)	<0·001	[185]
		0·51 (0·28–0·92)	**na**	
bisoprolol	2647	0·66 (0·54–0·81)	<0·0001	[186]
		0·56 (0·39–0·80)	**<0·01**	
metoprolol	3991	0·66 (0·53–0·81)	0·0009	[74]
		0·59 (0·45–0·78)	**0·0002**	
Amiodarone	6500§	0·87 (0·78–0·99)	0·03	[187]
		0·71 (0·59–0·85)	**0·0003**	
Potassium channel blockers				
d-Sotalol	3121	1·65 (1·15–2·36)	<0·006	[188]
		1·77 (1·15–2·74)	**0·008**	
Dofetilide in HCF	1518	0·95 (0·81–1·11)	>0·05	[189]
Dofetilide in post MI		no significant reduction		[190]
Calcium channel blockers	20 342§	1·04 (0·95–1·14)	<0·41	[182]

[1]Data reported include CAST and other small trials[182].
^data on SCD from CAST[180].
[2]For comments on the effect of beta-blockers on SCD refer to the text.
[3]post MI with EF $\leq$40%.
§reflects data from meta-analysis studies.

time after the acute event when therapy is started[183]. A recent analysis of 31 beta-blockers trials[195,196] showed that only 13 trials reported data on reduction of SCD showing a reduction from 51% to 43% in patients treated with beta-blockers (n=7219) vs the untreated group (n=6956).

Recently the CAPRICORN trial in post MI patients with left ventricular dysfunction (EF$\leq$40%) demonstrated a beneficial effect of carvedilol on total mortality and a trend toward reduction in SCD[184].

Patients with a history of congestive heart failure[74,186,193,197–200] or depressed left ventricular function[201] tend to show the greatest benefit in mortality reduction. Although selectivity does not appear to be a critical determinant of benefit, selection of drug should take into account that most data come from studies investigating lipophilic agents[183]. A consistent contribution to the improved outcome by these drugs is related to a substantial reduction (between 40% and 55%) in SCD rates (see Table 7)[202]. Beta-blockers also reduce the risk of re-infarction[183]. The recent introduction of new categories of drugs, such as thrombolytics, ACE-inhibitors, aldosterone receptor blockers as well as concomitant revascularization or aspirin does not appear to limit the independent benefit on clinical outcome provided by beta-blockers, as suggested by the evidence of residual risk reductions between 30% and 50%[203].

In summary, beta-blockers should be regarded as mandatory in the prophylactic treatment of patients with acute MI, in the post-MI phase and in patients with congestive heart failure. Additional efforts are required to increase the about 35% reported drug administration rate in post-MI patients[203–205].

Amiodarone

Amiodarone has multiple actions including potassium and sodium channel blockade, antiadrenergic effects, coronary vasodilatation and effects on the thyroid hormone metabolism. It has a favourable safety profile as far as its effects on the electrophysiological substrate and on pump function are concerned[206]. Amiodarone

Table 8 Impact of ICD therapy or other therapies including ICD for the primary prevention of SCD

Trial	LV function	Other entry criteria	Control group	Study group	No. of patients	Risk of death (95% C.I.)	*P*
MADIT[231]	EF<36%	Clinical ns VT, sVT inducible at PES	EP-guided AA (80% amio)	ICD	196	0·46 (0·26–0·92)	0·009
MUSTT[89]	EF<40%	Clinical ns VT, sVT inducible at PES	no therapy	EP-guided (AA or ICD)	704	0·73 (0·53–0·99)	0·04
CABG Patch[232]	EF<36%	Late potentials, CABG	no treatment	ICD	900	1·07 (0·81–1·42)	0·64

AA=antiarrhythmic; CABG=coronary artery bypass graft; C.I.=confidence interval; EF=ejection fraction; EP=electrophysiologically; ICD=implantable cardioverter defibrillator; PES=programmed electrical stimulation; ns=nonsustained; s=sustained.

has been extensively investigated for the prophylactic treatment of patients at risk, including those with impaired left ventricular function. Although early studies had suggested a positive clinical outcome associated with amiodarone treatment, more recent randomized trials have shown that amiodarone has no or little effect on all-cause mortality[187]. This neutral effect does not appear to depend on patient selection, as similar results were shown in post-MI patients[207–211] and patients with congestive heart failure[212–215]. However, amiodarone provides substantial (about 30%) protection against SCD; but, for reasons still unknown, this benefit is counterbalanced by a drug-related increase in non-sudden death rate. The high drug discontinuation rates of up to 41% (in blinded trials, but not in the open-label trial GESICA) may underestimate the benefit of the drug. Retrospective analyses have suggested that most if not all benefit from amiodarone was derived from a combination with a beta-blocker in the primary prevention of death post-MI[208,216].

In summary, with regard to its neutral effect on total mortality, amiodarone may be safely administered in patients with symptomatic non-sustained ventricular arrhythmias, or atrial fibrillation even in the setting of CHF; its efficacy on clinical outcome in subsets of post-MI patients is the subject of ongoing prospective trials. However, it is not primarily indicated for the improvement of prognosis.

Potassium channel blockers

Potassium channel blockers have been extensively investigated and the evidence suggests that they are neutral with regard to total mortality in the case of dofetilide[189,190] or even harmful in the case of d-sotalol[188]. A surprisingly small mortality advantage was documented after myocardial infarction with d,l-sotalol, an antiarrhythmic drug with combined beta-blocking and potassium channel blocking, when compared to other class I antiarrhythmic agents; however, comparative data collected in patients with previous sustained ventricular tachycardia show that d,l sotalol is more effective (or less harmful?) than sodium channel blockers for the prevention of SCD[217]. Based on this information, use of d-l sotalol is a reasonable alternative to amiodarone whenever amiodarone is contraindicated or non-tolerated; however, its pro-arrhythmic potential to cause TdP tachycardia has to be taken into account[218].

Calcium channel blockers

Data collected from controlled trials show that, overall, assignment to calcium-channel blockers in post-MI patients may be associated with a small excess in all-cause mortality. Despite the experimental evidence for an antiischaemic effect of calcium channel blockers, conclusive data on the benefit of these agents in the treatment of acute myocardial infarction are lacking. Treatment of coronary artery disease with calcium channel blockers that slow heart rate appears to reduce the risk of future myocardial infarction, but with no effects on all-cause mortality[219–222]. Conversely, agents that increase heart rate given to similar patient populations show a trend towards a reduced all-cause mortality[182]. No data have been collected on the efficacy of these agents in patients with congestive heart failure. In summary, treatment with calcium channel blockers is not recommended for prophylactic treatments of patients at risk of life-threatening ventricular arrhythmias.

Implantable cardioverter defibrillator

The ICD was originally designed to prevent SCD in patients with life-threatening, sustained ventricular arrhythmias[223–226]. It was soon demonstrated that ICDs were effective in the reversion of sustained ventricular tachycardia and fibrillation[227–230]. However, the full clinical value of these devices was not shown until clinical trials, utilizing all-cause mortality as the primary end-point, were undertaken. Such trials were essential, because underlying conditions which themselves carry an ominous prognosis, such as disabling congestive heart failure or acute ischaemia, can be documented in about 30% and 55% of all patients dying of an arrhythmic death[60].

Table 8 summarizes the data from three prospective randomized trials (MADIT[231], CABG-Patch[232] and MUSTT[89]) that have investigated the impact of ICDs on primary prevention of SCD. In all studies, only patients with coronary artery disease, predominantly on

the basis of a prior myocardial infarction, were enrolled, with up to 60% of them suffering from heart failure.

The first controlled primary prevention trial, MADIT, selected patients with ejection fraction <36% and asymptomatic non-sustained VT. If sustained VT was induced and not suppressed by i.v. procainamide during programmed electrical stimulation, the patients were randomized to defibrillator implantation or best medical therapy. The study was terminated prematurely because the implantable defibrillator therapy was associated with a 54% reduction in total mortality. This was the first firm evidence of a beneficial effect of device therapy on mortality versus drugs.

The findings of MADIT were recently supported by those of MUSTT, which included patients with LV ejection fraction less than 40% plus non-sustained ventricular tachycardia. If VT was inducible, the patients were randomized to best medical therapy (antiarrhythmics selected by serial drug testing or ICD if drug selection failed) or no therapy. The hypothesis was that therapy guided by EP testing was superior to no therapy in reducing the incidence of arrhythmic death and cardiac arrest in this population. Of all patients assigned to EP testing, 46% finally received an ICD. The study showed an overall reduction of 27% of arrhythmic death and cardiac arrest (with a borderline statistical significance; $P=0{\cdot}04$) in patients assigned to EP testing. Noteworthy, a subgroup analysis comparing patients who received an ICD (finally implanted in 46% of all patients assigned to antiarrhythmic treatment) with controls or patients on drugs showed a very strong reduction in both arrhythmic death and total mortality in the ICD group. The use of beta-blockers and ACE inhibitors were equally distributed among the groups.

The CABG-patch study used the presence of late potentials on the signal averaged ECG and reduced left ventricular ejection fraction as risk markers and randomized patients scheduled for elective CABG to ICD or no therapy. The study was terminated prematurely, because an interim analysis showed no difference between the groups. The 2-year mortality was 18% compared to 32% in the MADIT trial and 28% in the MUSTT trial (control arms). The neutral outcome of this study raises questions about the value of late potentials as a risk marker. On the other hand, revascularization might play an important role in modifying arrhythmic risk.

In summary, the primary intervention trials of ICD vs best medical therapy provide convincing evidence for a reduction in all-cause mortality by ICD therapy vs drugs in selected high risk groups, i.e. patients with reduced left ventricular function, non-sustained VT and sustained VT inducibility by programmed stimulation. This reduction is due to a very significant decrease of arrhythmic death. The presence of late potentials does not indicate a sufficient risk of arrhythmic death to justify a prophylactic implantation of an ICD. Whether other risk markers (decreased heart rate variability, increased ventricular ectopy without inducibility or the presence of clinical heart failure)[81,91,233–237] combined with low ejection fraction identify groups at high risk of SCD favourable for ICD therapy will be clarified when ongoing trials (DINAMIT, MADIT II, SCD-HeFT, BEST plus ICD) have been completed.

Secondary prophylaxis

Drugs with electrophysiological properties

Patients suffering from sustained VT or resuscitated from VF after MI or CHF have been traditionally treated using drugs with electrophysiological properties. Drug treatment, not infrequently based on the ability to suppress VT occurrence or inducibility, has been undertaken using an empirical rather than a controlled approach. In the ESVEM study, a controlled trial that investigated the comparative efficacy of different antiarrhythmic agents guided by serial drug testing, either using PES or 24-h Holter monitoring, assignment to sotalol resulted in a significantly lower incidence of future arrhythmic events as compared to a number of class I antiarrhythmic agents in patients with prior documented or suspected ventricular arrhythmias[217]. Other data suggest that sotalol is effective against sustained ventricular tachycardia, but that it lacks efficacy in preventing SCD[238]. In the CASCADE trial, which enrolled high risk cardiac arrest survivors[239], the comparative efficacy of empirically administered amiodarone was prospectively tested against conventional drug therapy (mostly class IAA drugs) guided by serial drug testing. Although the evaluation of the clinical outcome in this trial was compromised by a decision to provide additional implantable defibrillation therapy in about 50% of enrolled patients, assignment to amiodarone was associated with a significant reduction of all-cause mortality and combined arrhythmic end-points.

In summary, these data, and others from randomized studies against ICDs[240–242], have led to the conclusion that amiodarone is the most effective drug for secondary prevention of SCD. Use of d-l sotalol is frequently regarded as a reasonable alternative to amiodarone. However, its true impact on survival in this category of patients cannot be estimated due to the lack of control groups. The use of antiarrhythmic drugs as a primary therapeutic option for the secondary prevention of SCD has been substantially limited by the recent evidence provided by implantable defibrillator therapy in these patients.

Implantable cardioverter defibrillator

Secondary prevention

The data from the three prospective randomized trials designed to investigate the impact of ICDs on the

Table 9 Impact of ICD therapy or other therapies including ICD for the secondary prevention of SCD

Trial	LV function	Other entry criteria	Control group	Study group	No. of patients	*P*
AVID[240]	Any if VF ≤40% if VT or symptoms	VF, non-tolerated VT	Amiodarone (and sotalol in <5%)	ICD	1016	0·009
CASH[242]	Any	Cardiac arrest	AA — Propafenone — Metoprolol — Amiodarone	ICD	289	0·081*
CIDS[241]	EF<36%	VF, non-tolerated VT, syncope & other VT	Amiodarone	ICD	659	0·142

*1-sided *P* value[241].

secondary prevention of patients at high risk of SCD are summarized in Table 9[240–242]. About 80% of patients in these studies had coronary artery disease (more than half of the cases had suffered a prior myocardial infarction), about 10% had a non-ischaemic cardiomyopathy (predominantly dilated), and about 5% had no underlying heart disease.

The largest of these studies, AVID, reported a 31% statistically significant reduction in mortality with ICD therapy compared with amiodarone (and sotalol in less than 5% of patients) during a 3-year follow-up[240]. On the other hand, although reductions in mortality with the ICD (18% during 5 years follow-up in CIDS and 23% during 9 years follow-up in CASH) were observed in the other two studies, neither reached statistical significance[241,242]. However, a recent meta-analysis, based on consolidation of individual patient data from the three studies into a single master database, compared 934 patients assigned to ICDs vs 932 assigned to amiodarone. It showed that the results from all three trials are consistent with each other[243]. In that study, the most precise estimate of the benefit of ICD over amiodarone for the prevention of all-cause mortality was a relative risk reduction of 0·27 (95% C.I., 0·11–0·41) over a follow-up of 6 years from the index event.

After its recent introduction in clinical practice, catheter ablation of the substrate for ventricular tachycardia has been curative in 60% to 90% of drug-refractory forms in post-MI patients; this therapy is associated with a recurrence rate of about 40% and an acute complication rate of about 2%[244,245]. This therapy is recommended in sustained, drug-refractory and haemodynamically tolerated VT, and its clinical success is unlikely to turn into an improved long-term survival.

Surgical treatment of ventricular tachycardia in the context of a coronary artery disease was initially introduced with the aim of possibly reducing the inherent risk of SCD associated with this condition. However, with the recent introduction of ICD therapy, the role of surgical ablation has been revisited. Because surgical ablation may lead to a good long-term quality of life, this therapy can be contemplated in patient categories at low surgical risk in whom the clinical arrhythmia has proven refractory to other therapies[246], although it is not expected to significantly affect the patients' prognosis[247].

Patients with syncope and otherwise documented VT and with stable VT

Data from the CIDS[248] and AVID[249] suggest that patients with syncope and otherwise documented VT as well as patients with haemodynamically stable VT present a high risk of all-cause mortality during the intermediate follow-up. In the former study, annual all-cause mortality was 13·4% in 91 patients with syncope and 8·7% in all other 568 patients. Although the excess was principally due to arrhythmic death (6·3% vs 3·4%), the benefit of ICD therapy over amiodarone was not evident in these patients (RR 0·94; 0·47–1·91). More recently, a review from the AVID registry[243] showed that the absence of severe symptoms with sustained VT did not predict a benign prognosis; on the contrary, the mortality at 3 years follow-up in 440 patients with stable VT tended to be greater than that observed in 1029 patients with unstable VT (33·6% vs 27·6%; RR 1·22), and remained so after adjustment for baseline and treatment differences (RR 1·25). These data suggest that further studies of ICD therapy in patients with syncope and otherwise documented VT as well as patients with stable VT are warranted.

Applicability to daily clinical practice of data from randomized ICD trials

Based on the data obtained from randomized trials, there is a wide consensus that ICD treatment improves the prognosis in appropriately selected patients at high risk of SCD. Effective primary prevention can be achieved in patients who have survived a prior myocardial infarction, but are left with a severely impaired left ventricular function, and an asymptomatic non-sustained ventricular tachycardia which can be induced in a sustained form at programmed electrical stimulation.

Data from MUSTT are consistent with those of MADIT and support the implantation of an ICD in post-MI patients with non-sustained VT and an ejection fraction $\leq 0{\cdot}35$. At present it is uncertain whether an EF between 0·36 and 0·40 justifies ICD treatment, and whether adequate risk stratification requires that sustained tachycardia is inducible and that antiarrhythmic drug suppression of tachycardia inducibility is not possible.

In survivors of sustained and haemodynamically non-tolerated ventricular arrhythmias, use of an ICD should usually be considered as the first treatment option for most cases. Exceptions to routine ICD treatment for secondary prevention are patients who refuse this therapy or in whom life-expectancy is limited by the presence of another disease. ICD treatment should also be discouraged in patients in whom the precipitating cause of the arrhythmia is due to a transient and correctable factor (e.g., electrolyte imbalance, ischaemia, drug-related adverse effects, etc.); this recommendation is based on intuition and may not always be correct. Observational data from the AVID registry suggest that the risk of future arrhythmic events in such a population remains high even after correction of the transient precipitating factor[243].

An important contribution to further knowledge on the therapeutic role of ICD therapy has been provided by the recent subanalyses from the AVID[250], CIDS[251] and MADIT trials[252]. The AVID data indicate that the significant survival improvement in the ICD arm is all carried by patients with a moderately (0·20–0·34) to severely impaired (<0·20) ejection fraction, with substantially no benefit in patients with relatively well preserved EF (> 0·35)[250]. Similarly, a 50% relative risk reduction in death was found in ICD subgroups representative of highest risk quartiles of the CIDS study, whereas no benefit was evident in the remaining risk quartiles; in CIDS, risk quartiles were identified based on reduced ejection fraction, advanced age and poor NYHA functional class[251]. Superimposable findings were reported in MADIT, when the relative risk was analysed based on subdivision of patients according to the median level of ejection fraction (0·26). The survival benefit from ICD therapy was significantly greater in the subgroup with an ejection fraction <0·26 than it was in the subgroup with a higher (0·26 to 0·35) ejection fraction[252].

Recommendations for primary prevention of sudden cardiac death: drugs without electrophysiological properties in patients with heart failure

Drugs	Recommendations	Level of evidence	References
Beta-blockers	Class I	A	[74,186,193,197,199,202,203,203]
ACE inhibitors	Class I	A	[116,117,128,133–136]
Aldosterone receptor blockers	Class I	B	[119]
Positive inotropic agents phosphodiesterase inhibitors	Class III	B	[177]
Digoxin	Class III	B	[178]

Primary prevention refers to prevention of SCD in patients who had not experienced sustained ventricular tachyarrhythmias prior to therapy.

Recommendations for primary prevention of sudden cardiac death: drugs without electrophysiological properties during and after myocardial infarction*

Drugs	Recommendations	Level of evidence	References
Beta-blockers	Class I	A	[74,186,193,199,202,203]
ACE inhibitors	Class I	B	[116,128,133–136]
Lipid lowering agents	Class I	A	[128,138–140]
PUFA (EPA+DHA)	Class IIa	B	[121,141]
Nitrates	Class III	A	[128,133,134,142]
Magnesium	Class III	A	[144–146]

*Only drugs evaluated in studies with SCD or arrhythmic death as primary or secondary end-points are considered in the Table, together with interventions that failed to demonstrate survival benefit or that worsened survival. As discussed in the text revascularization, antithrombotic, anticoagulants reduce total mortality and are therefore pivotal treatments.

Recommendations for primary prevention of sudden cardiac death: drugs with electrophysiological properties in post-myocardial infarction patients*

Drugs/interventions	Recommendations	Level of evidence	References
Amiodarone**	Class IIa	A***	[187,207–212]
Potassium channel blockers			
d-sotalol	Class III	B****	[188]
dofetilide	Class III	A	[189,190]
Calcium channel blockers	Class III	B	[182,219–222]
Sodium channel blockers	Class III	B	[180–182,191,192]

*Beta-blockers have been included in the previous tables (drugs without electrophysiological properties).
**Data refer also to patient with CHF.
***Reduces SCD, reduction of total mortality showed borderline significant reduction.
****Worsen prognosis.

Recommendations for the use of an implantable defibrillator for primary prevention in patients at risk of sudden cardiac death according to specific underlying clinical conditions

Condition	Recommendations	Level of evidence	References
Post-MI, EF <40%, clinical nsVT, sVA at PES	Class I	B*	[89,231]
Post-MI, EF <36%, late potentials, indication for CABG	Class III	B	[232]

*Data collected in post MI patients with stable IHD, and might not apply to patients with recent MI (<3 weeks).

Recommendations for the use of drugs with electrophysiological properties, implantable defibrillators, catheter ablation and surgery for secondary prevention in post MI patients with documented sustained ventricular arrhythmias according to their clinical presentation

Condition	Recommendations	Level of evidence	References
Resuscitated VT/VF, spontaneous sustained haemodynamically non-tolerated VT			
Implantable defibrillator	Class I	A	[240,242]
Beta-blockers	Class IIa	C*	[242]
Amiodarone	Class IIa	C*	[239–242]
Potassium channel blockers	Class III	C	[218,238]
Calcium channel blockers	Class III	Opinion of the Task Force Panel	
Sodium channel blockers	Class III	C	[217,242]
Spontaneous, sustained, well tolerated, monomorphic VT			
Beta-blockers	Class IIa	Opinion of the Task Force Panel**	
Amiodarone	Class IIa	Opinion of the Task Force Panel**	
Implantable defibrillator	Class IIb	B	[249]
Ablation	Class IIb	C**	[244,245]
Surgery	Class IIb	C	[246,247]
Potassium channel blockers	Class III	Opinion of the Task Force Panel	
Calcium channel blockers	Class III	Opinion of the Task Force Panel	
Sodium channel blockers	Class III	Opinion of the Task Force Panel	

*As an alternative to implantable defibrillators when the device is not implanted.
**Possibly reduces recurrence, unlikely to reduce SCD.
Note: Secondary prevention refers to prevention of SCD in patients who had already experienced a sustained ventricular tachyarrhythmia prior to the onset of therapy.

Hypertrophic cardiomyopathy

Causes and clinical findings

Hypertrophic cardiomyopathy (HCM) is an inherited heart muscle disorder caused by mutations in genes encoding cardiac sarcomeric proteins[253–255]. Its prevalence is estimated at 0·2% (1:500). HCM has a highly characteristic pathology (myocardial hypertrophy, myocyte disarray and fibrosis) which contributes to a broad spectrum of functional abnormalities that includes myocardial ischaemia, diastolic dysfunction and left ventricular outflow obstruction, resulting in congestive heart failure, clinically important arrhythmias (such as atrial fibrillation) and SCD in some patients[253,256–258]. Despite four decades of research, a number of challenges persist regarding the clinical management of the disease, the most important of which is perhaps the identification and treatment of patients at risk for SCD.

The natural history of HCM is diverse, but is relatively benign for most patients. SCD is most common in the young (<30 years of age), but may occur throughout life with an estimated annual frequency of 2–4% in referral centre cohorts[259–261] and about 1% in community-based populations[262–264]. SCD in the first decade of life appears to be uncommon, but data in this age group are limited.

Since most sudden deaths occur in young asymptomatic (or mildly symptomatic) individuals, a major focus in the management of HCM is the identification of those persons at increased risk for SCD. Indeed, HCM appears to be the most common cause of SCD in young people, including trained competitive athletes[265]. The inheritable nature of the disorder and the relative ease with which most HCM patients can be identified or suspected clinically (i.e. with 12 lead ECG and two dimensional echocardiography) also mandates cardiac evaluation of first degree relatives of probands.

SCD in HCM is probably a consequence of multiple interacting mechanisms, and the importance of each factor as a trigger or determinant is usually difficult to ascertain retrospectively. Myocyte disarray, myocardial ischaemia and replacement scarring contribute importantly to the underlying substrate responsible for SCD. Cardiac arrest may be triggered by intrinsic factors including ventricular arrhythmia, paroxysmal atrial fibrillation, atrioventricular block, rapid atrioventricular conduction via an accessory pathway, haemodynamic alterations or myocardial ischaemia or by other factors such as intense physical exertion[253,256,265]. The interaction of triggers and substrate may be modified by peripheral vascular responses and the development of ischaemia[266]. A small subset of HCM patients (5–10%) experience a rapid decline in left ventricular function with progressive congestive cardiac failure, often accompanied by development of atrial fibrillation[258,259,267].

Risk stratification

Genetic abnormalities

Molecular genetic studies in selected pedigrees have confirmed 9 disease causing genes and over 150 (usually missense) mutations[268]. Some genetic defects in cardiac troponin T and particular beta myosin heavy chain mutations (e.g., Arg403Gln, Arg453Cys) appear to be associated with higher risk for premature SCD[268,269]. These data, however, require confirmation in larger patient cohorts.

Family history

A detailed history aids in risk assessment and a family history of HCM-related SCD is present in approximately 10–20% of probands while less than 5% have a malignant family history with multiple premature deaths. Despite the low positive predictive accuracy of an adverse family history, this disease feature may have greater predictive power within selected individual pedigrees where the proportion of affected individuals who have died suddenly can be taken into account.

Symptoms

Unexplained syncope, particularly when recurrent, related to exertion, or occurring in children and adolescents with HCM, is an ominous symptom, especially when associated with other risk factors[259–261]. However, in adults, isolated syncopal events are of less prognostic significance. Children and adolescents with severe congestive symptoms may be at a greater risk, although available data do not substantiate that the severity of chest pain, dyspnoea and exercise limitation predicts SCD risk in adult patients[259,260,270].

Echocardiographic predictors

In most patients, echocardiographically determined morphological and haemodynamic features are not strong predictors of SCD[271–273]. Extreme wall thickening (maximum dimension $\geq$30 mm), particularly in the young, is usually associated with other risk factors and conveys greatly increased risk for SCD[272–274]; its prognostic value in the absence of other risk factors, however, is still debated.[271,274]. The precise distribution or pattern of left ventricular wall thickening has not been demonstrated to have an impact on prognosis. While it has been suggested that the apical form (with hypertrophy confined to the true left ventricular apex) is more benign, rigorous evidence for this assertion is lacking. In general, however, throughout the broad HCM disease spectrum, localized and mild left ventricular wall thickening is more favourable.

The natural history of gene carriers without hypertrophy is unresolved, but appears to be benign, except when there is a family history of premature SCD with mild or absent hypertrophy and commonly in those with proven troponin T disease[269,275].

The presence of a left ventricular outflow tract gradient is not associated with SCD although data on patients with particularly large gradients (>100 mmHg)

are limited[259,263]. Diastolic impairment with abnormal Doppler filling patterns and atrial enlargement may be associated with symptomatic limitation and poor prognosis but do not appear to be associated with premature SCD.

Exercise blood pressure responses

Twenty five percent of patients with HCM have either a flat (failure to rise by $\geq$20 mmHg) or, less commonly, a hypotensive blood pressure response during symptom-limited upright exercise testing[276–279]. This vascular response is useful in assessing SCD risk predominantly by virtue of a normal test result identifying the low risk young subset (high negative predictive accuracy). The finding of an abnormal exercise blood pressure response identifies the high risk young (<40 years of age) patient, but positive predictive accuracy is low and in isolation is insufficient to warrant prophylactic therapy[277]. In the majority of patients the underlying basis for the abnormal blood pressure response in HCM is inappropriate vasodilatation rather than a failure to maintain exercise cardiac output[276,278]. In a minority, pharmacological treatment (beta-blockers), chronotropic incompetence, left ventricular outflow tract obstruction or failure to increase cardiac output may be implicated.

Non-sustained ventricular tachycardia

The finding of non-sustained ventricular tachycardia during ambulatory Holter ECG provides a useful marker of increased risk in adults with HCM[280,281]. It is present in approximately 20% of adults, but is uncommon in adolescents and rare in children[260,282]. Similar to the clinical utility of a normal exercise blood pressure response, the absence of non-sustained ventricular tachycardia on Holter ECG in adults is of high negative predictive value, thereby providing a powerful tool for the identification of the low risk patient[283]. The presence of this arrhythmia, however, confers an increased risk of SCD[280–283]. The overall positive predictive accuracy of VTns is 22%[283] and is greater in the young as well as when associated with other risk factors, particularly syncope[273,274,284]. Some investigators have suggested that non-sustained ventricular tachycardia may be clinically important and convey greater risk in HCM patients when repetitive, frequent or prolonged[253,282], although data in this regard are very limited.

Cardiac arrest and sustained ventricular tachycardia

A few HCM patients who experience cardiac arrest (i.e. ventricular fibrillation) in the community are successfully resuscitated; in the pre-ICD era their subsequent annual mortality from SCD was approximately 4%[285,286]. Recent ICD data suggest appropriate intervention rates for secondary prevention of approximately 10% per year[287]. Clinical sustained ventricular tachycardia is uncommon in HCM, but should also be regarded as a significant risk factor.

Programmed electrical stimulation

Some studies have suggested that inducible VT/VF during programmed electrical stimulation in the electrophysiology laboratory in HCM is associated with a higher risk of cardiac events[286]. However, the response to programmed stimulation is highly dependent on the protocol used; aggressive protocols using $\geq$3 premature stimuli can be expected to produce sustained polymorphic ventricular tachycardia in up to 40% of patients with low predictive accuracy for SCD[288,289]. As most high-risk patients can be identified using non-invasive clinical markers, the inherent risks and inconvenience associated with programmed stimulation dictate that it should not be used routinely to assess risk in HCM.

Other risk factors

Anecdotal evidence suggests that myocardial ischaemia may be an important determinant of SCD risk, although there are practical limitations in identifying and discriminating the significance of potential electrocardiographic and perfusion evidence of ischaemia within the HCM patient population[290]. Preliminary data suggest that other non-invasive electrophysiological measures including QT dispersion, heart rate variability, signal-averaged ECG and T wave alternans add little to the identification of the high risk cohort[291,292].

Management of high risk patients

All patients should undergo non-invasive risk stratification and assessment for the presence of potential triggers for SCD which if identified, provide the basis for targeted therapy e.g. clinically identified sustained monomorphic ventricular tachycardia (pharmacological treatment and/or implantable cardioverter-defibrillator), conduction system disease (pacemaker), accessory atrioventricular pathways (radiofrequency ablation), exercise-related syncope with severe obstruction (myotomy-myectomy), and possibly myocardial ischaemia (verapamil) and paroxysmal atrial fibrillation (amiodarone). Exertion may also trigger SCD and competitive sport involving intense physical exercise should be avoided. Many patients who have recognized risk factors for SCD do not, however, have the obvious triggers amenable to specific therapies.

SCD prevention with the ICD is most strongly recommended for patients surviving prior cardiac arrest and for primary prevention in patients with two or more risk factors (identified during non-invasive risk stratification) in whom annual SCD rates are 3–6% or more[273,274,285,287]. The presence of a single risk factor is of lower positive predictive accuracy and in most patients decisions regarding prophylactic treatment for primary prevention should be individualized depending on patient age and the perceived severity of the risk factor[273,274,282]. Some data suggest that low dose amiodarone may also reduce SCD risk[293], but ICD provides more definitive treatment with greater efficacy[264,287,293,294]. Recent retrospective multicentre data report a 5% appropriate annual discharge rate in HCM patients implanted for primary prevention, with no SCDs[287].

There is no evidence that outflow gradient reduction with drugs, alcohol septal ablation, DDD pacing or myotomy-myectomy will reduce the risk for SCD. Though beta-blockers and calcium antagonists may improve symptoms, the data do not suggest they have a major role in the prevention of SCD[253,259].

Conclusions

HCM is a relatively common cardiac disorder (adult prevalence about 1:500) in which sudden unexpected death is the most devastating component, occurring throughout life, but particularly in young, often asymptomatic patients[295]. A major focus is directed toward the identification of the small subset of HCM patients who are at high-risk, so that therapeutic interventions to prevent SCD can be implemented. Prophylactic treatment for SCD prevention is most strongly warranted for those patients with either prior cardiac arrest or two or more risk factors. Decisions regarding prophylactic treatment for primary prevention in HCM patients with a single risk factor may be individualized as the positive predictive accuracy for SCD is relatively low. Based on observational data, the ICD would appear at present to be the most appropriate treatment modality for the HCM patient judged to be at high-risk, although amiodarone treatment may represent a pharmacological alternative to the ICD in some selected patients.

Although HCM is the most common genetic cardiovascular condition, it is nevertheless uncommon in comparison with coronary artery disease or systemic hypertension. Data sets to validate risk stratification and treatment strategies for SCD, therefore, are limited in comparison and most have been observational in design.

The evidence that led to the proposed recommendations is mainly based on retrospective studies, small prospective studies and on the opinion of experts.

Recommendations for risk stratification for sudden cardiac death: hypertrophic cardiomyopathy

	Recommendations	Level of evidence	References
Cardiac arrest (or sustained VT)	Class I	B	[285–287]
Family history of SD	Class IIa	B	[253,256,263,268,274]
Syncope*	Class IIa	B	[259260,261,273,274,284]
Extreme LVH ($\geq$3 cm max. wall thickness)**	Class IIa	B	[271–274]
Hypotensive blood pressure response to exercise	Class IIa	B	[273–279]
Non-sustained VT (Holter)	Class IIa	B	[260,273,274,280,281–284,295]
High-risk mutations	Class IIb	B	[253,256,268,269,275]
Inducible ventricular arrhythmias at PES	Class III	C	[284–289]
LV outflow gradient	Class III	B	[259]
Mitral regurgitation (moderate-severe)	Class III	C	[259]
Chest pain/dyspnoea	Class III	C	[259]
Paroxysmal atrial fibrillation	Class III	B	[266]

*Risk appears to be greatest when repetitive, or associated with exertion, or in children.
**Usually ventricular septum.
LVH=left ventricular hypertrophy; Max.=maximum; PES=programmed electrical stimulation; VT=ventricular tachycardia.

Recommendations for prevention of sudden cardiac death: hypertrophic cardiomyopathy

	Primary prevention		Secondary prevention		References
	Recommendations	Level of evidence	Recommendations	Level of evidence	
ICD	Class IIa	B	Class I	B	[285,287]
Amiodarone	Class IIb	B	—	—	[293,294]
Beta-blockers	Class III	C	—		[253,256,257,259]
Verapamil	Class III	C	—	—	[253,256,257]

Right ventricular cardiomyopathy

Causes and clinical findings

Right ventricular cardiomyopathy (RVC), originally termed arrhythmogenic right ventricular dysplasia[296], is a disease of the myocardium, characterized by regional or global fibro-fatty replacement of the right ventricular myocardium, with or without left ventricular involvement and with relative sparing of the septum[297,298].

The prevalence of RVC is not well defined, but is estimated to be between 1:1000–1:10 000. The post mortem features of RVC may be subtle and confined to regions of the right ventricle which may not have been routinely examined at post mortem. Recent data, however, suggest that like the other inherited cardiomyopathies, it is one of the major causes of SCD in those in the pre-coronary artery disease age group (<35 years), accounting for approximately 25% of deaths in young athletes[265,299–302].

The disease is familial in at least 30% of cases with an autosomal dominant inheritance and incomplete penetrance[303]. A recessive form with associated skin and hair abnormalities (Naxos disease) is recognized in which a 2 base pair deletion in plakoglobin causes disease[304]. Plakoglobin is an intercellular adhesion molecule which is involved with apoptosis. It is an important constituent of the cell to cell junction and as such provides potential insight into pathogenesis of autosomal dominant ARVC, the genes for which have not yet been identified.

The distinguishing electrocardiographic (ECG) pattern of RVC is that of inverted T-waves and prolonged QRS complex with epsilon waves in the right precordial leads. The disease manifests in adolescents or young adults with ventricular arrhythmias[305] while clinical presentation in children is rare or underreported. The initial presenting symptom may be syncope (29%) or cardiac arrest (7–23%)[306–308].

Monomorphic ventricular tachycardia with left bundle branch block morphology is the most common (70–92%) arrhythmia observed in RVC, but these may vary from asymptomatic premature ventricular beats to poorly tolerated polymorphic ventricular tachycardia[305,307,309,310]. Like hypertrophic cardiomyopathy, RVC may lead to cardiac failure[308], but it is more frequently associated with SCD[301,311,312] and if this can be prevented, life expectancy may be normal or near normal.

Risk stratification

Only limited information is available on risk assessment of SCD in RVC. Predictive markers of SCD in patients with RVC have not yet been defined in large prospective studies focusing on survival, and therefore, data reported here are based on small studies mainly derived from tertiary referral centres in patients who presented with arrhythmia. The risk profile of asymptomatic individuals who are identified during pedigree evaluation has not been systematically evaluated.

Family history and demographic variables

Analogous to other inherited arrhythmogenic disorders RVC is characterized by incomplete penetrance[312]. Pedigree studies suggest that the majority of gene carriers do not show diagnostic features. Manifestation at young age (<20 years of age) was suggested as a risk factor due to a high frequency of SCDs, compared to patients with a clinical manifestation at an older age[306]. This observation, however, was not supported by a series of autopsy cases[311]. The predictive accuracy of an adverse family history or of clinical presentation at a young age remains uncertain because of unavoidable selection biases and the heterogeneous nature of the disease.

Syncope

Although a less favourable prognosis is suspected for patients with syncope[309] a larger study was not able to demonstrate increased mortality[310]. Furthermore, syncope has a low negative predictive accuracy as almost 10% of patients without previous episodes subsequently died suddenly[310].

QT dispersion and ST T-wave complexity

QT and ST T-wave analysis are of uncertain value in risk stratification in RVC. The degree of QT dispersion failed to be a useful risk-marker for life threatening arrhythmias in one study[313], whereas principal component analysis of the ST T waves had a positive predictive value of 86% for occurrence of ventricular tachycardia in RVC patients in another study[314]. Since none of these observations have been confirmed in larger series, the use of these variables for risk stratification is premature.

Late potentials

The prevalence of late potentials during signal averaged ECG (SAECG) ranges between 47 and 91%[315–317]. In retrospective studies it has been shown that they correlate with the severity of the disease[315–318], and are an independent predictor of sustained ventricular tachycardia and of ventricular fibrillation when present in conjunction with right ventricular dysfunction[315].

Holter monitoring and exercise test

These tests aid diagnosis and assessment of antiarrhythmic drug efficacy for the prevention of ventricular tachycardia in selected patients[319]; however, they seem to have poor predictive accuracy to identify patients with sustained ventricular tachycardia[320] and/or SCD.

Right and left ventricular changes

SCD occurs more frequently in patients with diffuse right ventricular dilatation (55%) and in those with left ventricular involvement (36–56%) compared to right sided localized forms of the disease (8%)[308,311,321]. Left ventricular impairment appears to be a risk factor for

ventricular fibrillation and SCD with a sensitivity of 56% and specificity of 86%[321].

Clinical arrhythmias

The mechanism of SCD is most likely ventricular tachyarrhythmias since both ventricular tachycardia and ventricular fibrillation have been documented in patients with cardiac arrest[296,311,322,323]. Atrioventricular conduction disturbances are rare in patients with RVC[305,311].

The type of ventricular arrhythmia does not seem to be predictive of the occurrence of SCD[312]. The presence of sustained ventricular arrhythmia is associated with right ventricular and/or left ventricular morphological abnormalities. Such patients, if left untreated, appear to have an increased incidence of SCD. The prognostic significance of non-sustained ventricular arrhythmia is uncertain. It should be emphasized though that when present in combination, the various risk factors may modify their value in risk stratification.

Programmed electrical stimulation

The value of PES to predict the propensity for ventricular arrhythmias depends on the population studied and the protocol used. The rate of inducibility of sustained ventricular tachycardia is 57–94% in patients with sustained monomorphic ventricular tachycardia[307,320,324] and 50–82% in patients with localized forms or only right sided involvement, whereas it is low, 18%, in patients with ventricular fibrillation or left ventricular involvement[308,324]. Patients with (1) definite enlargement of the right ventricle, (2) reduced right ventricular ejection-fraction (<40%), (3) hypo- or akinesia of ≥ 3 right ventricular segments and outpouchings in >2 segments, presenting with inducible sustained ventricular arrhythmia during PES are at higher risk of SCD[321].

Management of high risk patients

Strenuous exercise, sport and acute mental stress are major triggering factors (23–100%) of SCD in patients with RVC[324–327]. Patients with RVC should therefore be strongly discouraged from practicing competitive sports. Evaluation for RVC in asymptomatic subjects who wish to participate in competitive sports or in first-degree relatives of patients with RVC, should include a 12-lead ECG, an SAECG, an exercise stress test and an echocardiographic study.

Data regarding efficacy of various drugs for the prevention of arrhythmias or SCD relies on retrospective[307,320,324] and prospective[319] non-randomized studies. Oral drug testing by PES identified an 'effective' antiarrhythmic drug in 74% of patients while use of Holter monitoring or treadmill exercise to assess efficacy of antiarrhythmic drugs in patients with non-sustained VT identified an 'effective' antiarrhythmic agent in 89% of patients[319]. In the same study long-term follow-up showed a recurrence rate of ventricular tachycardia of 10 and 12%, respectively, and no occurrence of SCD. Among all antiarrhythmic drugs tested, sotalol showed higher efficacy[319] and it is therefore recommended as a first choice drug to prevent recurrence of ventricular tachycardia. Patients with sustained monomorphic ventricular tachycardia are thus thought to have a more favourable prognosis when treated medically[307,320,324].

Radiofrequency catheter ablation is a potential adjunctive and palliative procedure for medically refractory ventricular tachycardia in selected patients[328,329]; however, there is no information regarding its efficacy in the prevention of SCD.

In patients with aborted SCD, ventricular tachycardia unresponsive to antiarrhythmic drug therapy, and in high risk patients with ventricular tachycardia and compromised right and left ventricular function, ICD therapy, though unproven, is likely to reduce mortality. Problems with low R wave amplitudes, high thresholds, and lead perforation are well recognized[330,331].

It is unclear whether ICD therapy is beneficial for primary prevention in high-risk patients.

Conclusions

RVC is one of the major causes of SCD in the pre-coronary artery disease age group. Although predictive markers of SCD have not yet been defined in large prospective studies, SCD occurs more frequently in patients with extensive right ventricular changes and in those with left ventricular involvement. Based on non-randomized studies, patients with sustained monomorphic ventricular tachycardia are thought to have a more favourable prognosis when treated medically. In patients with aborted SCD, ventricular tachycardia unresponsive to antiarrhythmic drug therapy, and in high risk patients with ventricular tachycardia, ICD therapy is probably appropriate. The evidence that led to the proposed recommendations is based on small studies or on the opinion of experts.

Recommendations for risk stratification for sudden cardiac death: right ventricular cardiomyopathy

	Recommendations	Level of evidence	References
Diffuse right ventricular dilatation	Class IIa	C	[308,311,321]
Left ventricular involvement	Class IIa	C	[308,311,321]
RV dysfunction/dilatation+inducible sustained VT	Class IIa	C	[308,311,321]
Previous cardiac arrest/VF	Class IIa	C	[308,311,321]
Family history of ARVC and SCD	Class IIb	C	[306,309–311,315]
Syncope	Class IIb	C	[306,309–311,315]
Late potentials+RV dysfunction	Class IIb	C	[306,309–311,315–318]
Ventricular tachycardia	Class IIb	C	[306,309–311,315,320,324,325]
Programmed electrical stimulation*	Class IIb	Opinion of the Task Force Panel	
QT dispersion and T wave complexity	Class III	C	[313,314]
PVCs	Class III	C	[313,314,324]

*PES inducibility identifies patients at high risk of SCD when associated with enlargement and RV dysfunction[321].

Recommendations for prevention of sudden cardiac death: right ventricular cardiomyopathy

Ventricular tachycardia	Recommendations	Level of evidence	References
Primary prevention			
ICD	Class IIa	Opinion of the Task Force Panel	
AA drugs*	Class IIb	C	[307,319,320,324]
RF ablation	Class III	C	[328,329]
Asymptomatic — high risk			
AA drugs*	Class III	C	[307,320,324]
ICD	Class III	C	[330,331]
Secondary prevention			
ICD	Class I	C	[330,331]
AA drugs	Class III	C	[307,319,320,324]
RF ablation	Class III	C	[328,329]

*Data on AA drugs are mainly retrospective analysis. In one prospective study sotalol treatment guided by acute oral drug testing during EP study demonstrated higher efficacy than other agents[319].

Dilated cardiomyopathy

Idiopathic dilated cardiomyopathy (DCM) is a chronic heart muscle disease characterized by left ventricular dilatation and impairment of systolic function. Epidemiological studies, which are probably an underestimate, report an incidence of approximately 20/100000/year and a prevalence of 38/100000[332]. Up to 40% of cases may be familial; inheritance patterns are predominantly autosomal dominant, but X-linked families are reported (2–5%)[333,334]. Five year mortality in DCM has gradually declined coincident with improvements in the management of cardiac failure from 70% in 1981[335] to approximately 20% according to more recent reports[336,337]. SCD accounts for at least 30% of all deaths in DCM and may occur in patients with advanced as well as mild disease and in those who appear clinically and echocardiographically to have recovered. Although the clinical challenges of DCM resemble those of cardiac failure in many respects, there are sufficient differences in terms of demographics, natural history, and utility of clinical testing to warrant discussion of risk stratification in DCM separately from other causes of heart failure.

Causes and clinical findings

In DCM, as in congestive cardiac failure of any aetiology, malignant ventricular arrhythmias are not the only cause of SCD. Reports vary on the extent to which other mechanisms are responsible for SCD. In advanced disease, bradyarrhythmias, pulmonary or systemic embolization, or electro-mechanical dissociation may

account for up to 50% of cardiac arrests[69,338,339]. However, malignant ventricular arrhythmia remains the commonest single cause of SCD in DCM, and deaths due to this mechanism account for the majority of SCDs in patients with less severe disease.

Risk stratification

The rate of SCD in DCM is closely related to the severity of disease and parallels the rate of death due to progressive heart failure. Thus the most severely affected patients are more likely to die by either mechanism. In heart failure in general and in DCM in particular, the proportion of deaths which is sudden is greater in the groups with less severe disease, but the majority of SCDs occur in patients with advanced disease[74,340]. Accordingly, many predictors of overall outcome in DCM might also be expected to predict SCD. Predictors of overall mortality include ejection fraction, end-diastolic dimension or volumes, male gender, older age, hyponatraemia, persistent third heart sound, sinus tachycardia, elevated pulmonary capillary wedge pressure, systemic hypotension and atrial fibrillation[337].

There are, however, few data which specifically examine the relationship of clinical variables and SCD. Ejection fraction has consistently emerged as a significant predictor of SCD in DCM[341–344], although predictive accuracy (for an EF <20%) has varied from as low as 13% to as high as 59%[344].

The major shortcoming of ejection fraction and other variables which reflect disease severity is lack of specificity for arrhythmic as opposed to non-arrhythmic mortality. Other investigations in this area have focused on syncope and ventricular arrhythmia.

Syncope

Syncope is a useful predictor of risk of SCD. In a prospective evaluation of 103 patients with DCM[345], during a mean follow-up of 24 months, 10 patients had sustained VT or episodes of SCD, of which 7(70%) had a prior history of syncope. The relationship of syncope to SCD was investigated in 491 patients with advanced heart failure (NYHA III and IV), of which approximately half had DCM[346]. Syncope was associated with a significantly increased risk of SCD at 1 year, regardless of the aetiology of the syncope. This risk factor was specific for SCD and did not predict risk of dying from progressive heart failure. Recently a report on the outcomes of 14 DCM patients with unexplained syncope treated with an implantable defibrillator[347] showed that 50% received appropriate shocks after a mean time from implantation of 32 months.

Ventricular arrhythmia

Ventricular arrhythmias are also common and are markers of disease severity. Non-sustained ventricular tachycardia during ECG monitoring is seen in approximately 20% of asymptomatic or mildly symptomatic patients and in up to 70% of severely symptomatic patients[339,348,349]. It has been reported that NSVT was a sensitive (80%) but not specific (31%) marker of SCD[348]. A significant association between the presence of couplets, VTns or PVCs >1000/day and SCD was reported in a study investigating 74 patients with DCM (class II/III) of whom 12 died suddenly[349]. The combination of ventricular ectopy and EF<40% was especially predictive of SCD. The prognostic significance of ventricular tachycardia, however, is controversial. Its presence early in the course of disease when left ventricular function is relatively preserved is probably an independent marker of SCD risk, whereas in general, markers of haemodynamic severity (e.g. ejection fraction, left ventricular end-diastolic dimension, filling pressures) are more predictive of disease-related mortality and SCD.

Programmed electrical stimulation

The utility of PES in DCM is limited by a low frequency of inducibility of sustained monomorphic VT and a low negative predictive accuracy[348]. In a meta-analysis of 6 programmed stimulation studies including a total of 288 DCM patients, PES failed to identify 75% of patients who died suddenly[350].

Other risk factors

Though there are studies, the information available does not suggest a major role for SAECG, QT dispersion, HRV, TWA, or heart rate in the identification of the high risk subset.

Management of high risk patients

Evidence-based therapy of cardiac failure, with few exceptions, has not specifically been evaluated in DCM in a randomized fashion. Initially clinical trials have been designed including either patients with DCM and patients with ischaemic cardiomyopathy based on the assumption that treatment efficacy is identical in the two groups[351]. Accordingly, CIBIS-II[186] and SOLVD[116] demonstrated that beta-blockers and angiotensin converting enzyme inhibitors and oral anticoagulants are equally effective in ischaemic and non-ischaemic HF patients. It has been suggested that amiodarone might be more effective in patients with idiopathic DCM than in patients with ischaemic HF. In the GESICA[213] study (60% of patients with idiopathic DCM) in fact amiodarone reduced the risk of SCD while a significant reduction was not observed in the STAT-CHF[212]. (29% of patients with idiopathic DCM). Secondary prevention trials with ICD in DCM patients with proven or suspected significant ventricular arrhythmia revealed 1, 3 and 5 year appropriate discharge rates of 15–20, 50–60 and >75%, respectively[241,352]. In addition, post-hoc analysis on pooled data from AVID, CIDS and CASH[243] suggest that patients with non-ischaemic cardiomyopathy are likely to receive more benefit from ICD than amiodarone treatment (hazard ratio 0·78;

0·45–1·37) The absence of a clear risk profile for SCD precludes primary prevention recommendations.

Conclusions

SCD due to malignant arrhythmias is the single most common cause of death in DCM. Few parameters have been identified as good predictors of SCD that can be reliably used for the risk stratification of DCM patients. Ejection fraction has been repeatedly identified as the most powerful predictor of outcome but its predictive accuracy has not been conclusively defined[343,344]. Occurrence of syncopal events is the other rather accurate indicator of risk of SCD[345–347].

Therapeutic strategies aimed at reduction of risk of SCD in patients with documented ventricular arrhythmias include ACE inhibitors, beta-blockers, amiodarone and the implantable cardioverter defibrillator[212,241,352]. Few studies have specifically investigated the role of non-antiarrhythmic drugs in DCM patients and it is commonly assumed (but not proven) that pharmacological treatment used in patients with progressive heart failure (with and without ischaemic substrate) is equally effective in patients with DCM.

The evidence that leads to the proposed recommendations is based on small studies or on the opinion of experts.

Recommendations for risk stratification for sudden cardiac death: dilated cardiomyopathy

	Recommendations	Level of evidence	References
Previous cardiac arrest/VF	Class I	B	[69,338,339]
Sustained VT	Class I	B	[345–347,349]
Syncope	Class IIa	B	[74,335–337,340–343,346,347]
EF	Class IIb	B	[74,335–337,340–344]
Non sustained VT	Class IIb	B	[340,341,348–350]
Inducibility at PES	Class III	B	[346–349]

Recommendations for prevention of sudden cardiac death: dilated cardiomyopathy

	Recommendations	Level of evidence	References
ACE inhibitors	Class I	B	[117]
Beta-blocker	Class I	B	[186]
ICD (secondary prevention)	Class I	Opinion of Task Force Panel	
ICD (primary prevention)	Class IIa	B	[241,352]
Aldosterone receptor blockers	Class IIa	B	[119]
Amiodarone	Class IIb	B	[212,213,241]

Long QT syndrome

Causes and clinical findings

The long QT syndrome (LQTS) is a familial disease characterized by an abnormally prolonged QT interval and, usually, by stress-mediated life-threatening ventricular arrhythmias[353]. Characteristically, the first clinical manifestations of LQTS tend to appear during childhood or in teenagers. Two variants of LQTS have been described: the rare recessive form with congenital deafness (Jervell and Lange-Nielsen syndrome, J-LN), and the more frequent autosomal dominant form (Romano-Ward syndrome, RW). Five genes encoding subunits of cardiac ion channels have been associated to LQTS and genotype–phenotype correlation have been established so that gene-specific epidemiology, risk stratification and management are emerging in LQTS.

Of the five genetic variants of LQTS currently identified[354–356], LQT1 and LQT2 subtypes involve two genes, *KCNQ1* and *HERG*, encoding major potassium currents (I_{Ks} and I_{Kr}). LQT3 involves *SCN5A*, the gene encoding the cardiac sodium current. LQT5 and LQT6 are rare subtypes also involving the I_{Ks} and I_{Kr} currents.

Risk stratification

Syncope and cardiac arrest

Syncope is the most common clinical manifestation in LQTS and its first occurrence is commonly between age 5 and 15. Males become symptomatic earlier than

females[357]. The age of occurrence of the first syncope has prognostic implications: when they commence before age 5 they predict a severe form of the disease, and syncope occurring in the first year of life is associated with extremely poor prognosis. A history of cardiac arrest increases by 13 times the probability of a cardiac arrest or SCD at follow-up, thus providing a rationale for the use of ICD in secondary prevention of SCD[358].

Family history

Conclusive data on the predictive accuracy of family history of SCD are not yet available. Given the high variability of clinical manifestations among family members[359] a negative family history for SCD cannot be safely regarded as a predictor of favourable outcome. On the other hand, anecdotal observations of malignant family histories suggest that within selected families previous occurrence of SD can have a strong positive predictive accuracy and increase risk.

Electrocardiographic parameters

The degree of QT prolongation (e.g., a QTc>600 ms) has been associated to risk[360]; thus, the longer the QTc, the greater the risk for cardiac events. However, other data from the same International Registry[353] show that 5% of family members with a normal QT interval (QTc <440 ms) had syncope or cardiac arrest.

Dispersion of QT interval on the 12-lead ECG may help risk stratification. Differences in QT interval duration almost always reflect the presence of notches on the T wave that are present only in selected leads (mainly V_1-V_4) producing regional prolongation of the QT interval. A QT dispersion exceeding 100 ms and a lack of shortening following beta-blockade have been proposed as risk factors for recurrent cardiac events[361]; however, their value in predicting SCD has not been defined.

The presence of macroscopic T Wave alternans (TWA) on the surface ECG was the first marker of severe electrical instability proposed for LQTS[362] and the available data support this concept[363]; however, quantification of the actual risk of SCD associated to TWA is still uncertain.

Finally, ECG changes during exercise stress test are not helpful for risk stratification.

Demographic variables

Events tend to occur earlier in males than in females, and males who are still asymptomatic at age 20 can be considered at lower risk for manifesting cardiac events. Females maintain the same risk of becoming symptomatic in adulthood. Since a higher risk of cardiac events has been observed in the first year after delivery[364], treatment at this time might be considered also in asymptomatic women.

Genetic defects

Risk stratification based on the individual genetic defect is still being defined but a few firm points have already been established[365].

LQT3 appears to be the most malignant variant and to be the one less effectively managed by beta-blockers[366]. LQT1 and LQT2 have a higher frequency of syncopal events but their lethality is lower and the protection afforded by beta-blockers, particularly in LQT1, is much higher[358,366]. The Jervell and Lange-Nielsen recessive variant is associated with very early clinical manifestations and a poorer prognosis than the Romano-Ward autosomal dominant form.

The presence of syndactyly seems to represent a different genetic variant of LQTS[367] also associated with a poor prognosis.

Recent genotype–phenotype correlation studies have demonstrated gene-specific 'triggers' for cardiac events[366]. Their identification may help in suggesting behavioral changes likely to reduce risk. LQT1 patients are at very high risk during exercise, particularly swimming. LQT2 patients are quite sensitive to loud noises, especially when they are asleep or resting.

Programmed electrical stimulation

Most LQTS patients are not inducible during programmed electrical stimulation[368]; therefore, PES should not be used for risk stratification.

Management of high risk patients

All patients (symptomatic, asymptomatic and silent gene carriers) should reduce physical stress, particularly competitive sports. While this is a 'must' for all LQT1 patients, some degree of greater flexibility for non-competitive physical activity might be cautiously considered for LQT3 patients.

All LQTS must avoid the use of drugs that prolong repolarization. It is especially important that their physicians are well aware of those non-cardiovascular drugs that contain IK_r blockers and that can easily precipitate TdP in patients affected by LQTS, even in the previously asymptomatic ones[369].

Pharmacological treatment of LQTS relies on the use of beta-blockers. However, their obvious clinical efficacy and the attendant ethical reasons have prevented a prospective, placebo-controlled, randomized study. Thus, a quantification of the actual prevention of SCD is missing and we have to rely on retrospective data obtained when due to insufficient medical knowledge many patients were left without treatment and when only the most severe cases were diagnosed. The largest of these retrospective analyses was conducted in 233 LQTS patients, all symptomatic for syncope or cardiac arrest, for whom precise data existed on the time of the first cardiac event[370]. Mortality 15 years after the first syncope was 9% for the patients treated by antiadrenergic therapy (β-blockers and/or left cardiac sympathetic denervation) and close to 60% in the group not treated or treated by miscellaneous therapies.

More recently, mortality data were analysed in a large group of LQTS patients, including many without symptoms, in whom beta-blockers had been prescribed[358]

but who did not necessarily remain on treatment. The 5-year incidence of cardiac arrest or SCD was below 1% for those asymptomatic at treatment initiation, 3% for those who had suffered syncope, and 13% for those who already had had a cardiac arrest. Approximately 25% of the patients who died had been off beta-blockers for a significant amount of time and many of the victims were below 1 year of age. The logical conclusion is that beta-blockers are, overall, very effective indeed; however, they cannot afford total protection and for the patients with a history of cardiac arrest the risk of SCD remains unacceptably high.

Left cardiac sympathetic denervation is indicated for patients who continue to have syncope despite full dose β-blocking therapy or who are not compliant with medical therapy[371].

Cardiac pacing is indicated in LQTS patients with A-V block and whenever there is evidence of bradycardia- or of pause-dependent malignant arrhythmias[372]. Pacemakers can also be considered in combination with β-blocking therapy to prevent the occurrence of excessive bradycardia in selected patients, such as those with the LQT3 variant[366,373].

While no data are yet available to demonstrate the efficacy of the ICD in preventing SCD in LQTS, its use is now recommended in survivors of cardiac arrest. It should also be considered in children with syndactyly, with complete A-V block, and in symptomatic JLN patients.

No data are available to define the role of prophylactic pharmacological therapy in asymptomatic individuals with prolonged QT intervals and in gene carriers with normal QT interval (silent carriers). However, the growing evidence of a significant risk of death at first episode strongly suggests the initiation of beta-blocker therapy in the asymptomatic patients with clear-cut QT prolongation.

Conclusions

Long QT syndrome is associated with high risk of SCD. Risk stratification is mainly based on history of syncopal events, TdP or cardiac arrest. The duration of the corrected QT interval is a weaker predictor of major events. The clinical variants presenting association of the cardiac phenotype with syndactyly or with deafness (Jervell and Lange-Nielsen syndrome) have a more severe prognosis. Genetic defects on the cardiac sodium channel gene (*SCN5A*) are also associated with higher risk of SCD.

Primary prevention is mainly based on treatment with beta-blockers; the implantable cardioverter defibrillator is recommended in secondary prevention (cardiac arrest survivors). No randomized trial is available. However, large prospective registries with very long follow-up are available and have provided the basis of most of the recommended strategies for risk stratification and management.

Recommendations for risk stratification sudden cardiac death: long QT syndrome

	Recommendations	Level of evidence	References
Syncope	Class I	B	[353,360]
TdP/VF/CA	Class I	B	[353,360]
JLN recessive variant	Class I	B	[353,360,366]
LQT3 genetic variant	Class I	C	[353,365,366]
QTc>600 msec	Class IIa	C	[360]
Cardiac events in infants	Class IIa	Opinion of the Task Force Panel	
Post partum period	Class IIa	C	[364]
Female gender	Class IIa	C	[357]
Syndactyly and AV block	Class IIa	C	[367]
T wave alternans (macroscopic)	Class IIa	C	[363]
Family history	Class IIb	Opinion of the Task Force Panel	
QT dispersion	Class IIb	C	[361]
Pogrammed electrical stimulation	Class III	C	[368]

Recommendations for prevention of sudden cardiac death: long QT syndrome

	Recommendations	Level of evidence	References
Primary prevention			
Avoidance of QT prolonging agents/K^+ lowering agents			
Symptomatic	Class IIa	C	[353]
Silent gene carriers	Class IIa	C	[353,369]
Asymptomatic	Class IIa	C	[353,369]
Avoidance of competitive sport/strenuous activity			
Symptomatic	Class I	C	[353]
Silent gene carriers	Class IIa	C	[353]
Asymptomatic	Class IIa	C	[353]
Beta-blockers			
Symptomatic	Class I	B	[358]
Asymptomatic	Class IIa	C	[358]
Left cardiac sympathetic denervation+beta-blockers			
Symptomatic with recurrences on beta-blockers	Class IIb	B	[371]
Pacemaker (plus beta-blockers)			
Symptomatic with pause- or bradycardia-dependent arrhythmias	Class IIb	C	[372,373]
ICD+beta-blockers			
Symptomatic with recurrences on beta-blockers	Class IIa	C	[353,365]
Secondary prevention			
ICD+beta-blockers	Class I	C	[353,358]
Avoidance of competitive sport/strenuous activity*	Class I	C	[353]
Avoidance of QT prolonging agents*	Class I	C	[353]

*Life-style measures to be adopted in conjunction with ICD implant in CA survivors.

Brugada syndrome

Causes and clinical findings

The Brugada syndrome [374] is an arrhythmogenic disorder associated with high risk of SCD in individuals with a structurally normal heart. The occurrence of cardiac arrest at 3 years follow-up has been shown to be 30% both in symptomatic and asymptomatic patients.

The disease is characterized by transient right bundle branch block and ST segment elevation in leads V_1-V_3. Genetic bases of one variant of BS have been identified and demonstrated that BS is an allelic disorder to LQT3 presenting mutations on the cardiac sodium channel (*SCN5A*). The disease is transmitted with an autosomal dominant pattern of inheritance. Cardiac events (syncope or cardiac arrest) occur mainly in males at a mean age of 38 years (range 6 months to 74 years)[375,376].

SCD is caused by rapid polymorphic ventricular arrhythmias mainly occurring at rest or during sleep. Fever has been reported as a possible risk factor for cardiac arrest in BS as few patients developed cardiac arrest during a febrile episode and at least one mutation has been shown to manifest severe functional impairment at higher temperature[377].

Risk stratification

Since the description of Brugada syndrome is relatively recent, its understanding is still incomplete and several areas of uncertainty remain as far as risk stratification algorithms and management strategies are concerned.

Demographic variables

Male gender and age in the third–fourth decade are risk factors for SCD[375,376] although paediatric cases have been reported as well.

Family history

A family history of SCD is considered a risk factor for SCD. In analogy with LQTS there are no data proving that family history predicts cardiac events among family members. The assumption that affected individuals without family history may be at lower risk for events could be misleading[375,376].

ECG

Identification of ST segment elevation on the surface ECG is the diagnostic marker of the disease. No data support a relationship between the severity of the ST segment elevation, the morphology of the ST segment, the presence or absence of right bundle branch block and the risk of developing SCD.

Pharmacological challenge

It has been reported that administration of i.v. sodium channel blockers such as flecainide ($2\ mg\ kg^{-1}$) and ajmaline ($1\ mg\ kg^{-1}$) unmasks ST segment elevation in concealed forms of the disease[378]. The sensitivity and specificity of the pharmacological challenge are unknown.

Programmed electrical stimulation

The role of PES for risk stratification is still debated. The initial experience showed[375] that PES has a pivotal

role in risk stratification as inducibility in the catheterization laboratory was a predictor of spontaneous occurrence of ventricular fibrillation. Recently[376], evidence has been presented to show that PES has a low predictive accuracy to identify individuals who will experience cardiac arrest.

Management of high risk patients

Some investigators[375] supported the view that both symptomatic patients (syncopal episodes or aborted SCD) and asymptomatic patients who are inducible by PES are best managed by the implantation of an ICD. More recent data, however[376], supported the view that given the low predictive accuracy of PES, cardiac arrest survivors and patients with a history of syncope or a family history of juvenile SCD should receive an ICD. Management of asymptomatic patients is still debated and no conclusive evidence exists to guide risk stratification in this subgroup. No drug has shown efficacy in the prevention of SCD.

Conclusions

Diagnosis of Brugada syndrome is established in the presence of spontaneous or induced ST segment elevation in leads V_1–V_3 with/without right bundle branch block. Risk stratification is still ill-defined. Cardiac arrest occurs mainly in males in the third–fourth decade of life: up to 80% of victims of cardiac arrest had experienced a syncopal event. The value of PES to predict occurrence of SCD is still debated. In survivors of cardiac arrest the implantation of an ICD is recommended. Given the limited number of studies on this disease, the evidence used to provide recommendations derives from small multicentre non-randomized studies with short follow-up and is therefore largely based on the opinion of experts.

Recommendations for risk stratification for sudden cardiac death: Brugada syndrome

	Recommendations	Level of evidence	
Family history for SCD	Class IIa	C	[375]
Syncope	Class IIa	C	[375,376]
VT/VF inducibility	Class IIb	C	[375,376]

Recommendations for prevention of sudden cardiac death: Brugada syndrome

	Recommendations	Level of evidence	
Primary prevention			
ICD			
Symptomatic for syncope/VT	Class I	B	[375,376]
Asymptomatic with inducible VT/VF	Class IIb	C	[375,376]
Asymptomatic with non-inducible VT/VF	Class III	C	[375,376]
AA drugs	Class III	C	[375,376]
Secondary prevention			
ICD	Class I	B	[375,376]
AA drugs	Class III	C	[375,376]

Catecholaminergic polymorphic ventricular tachycardia

Causes and clinical findings

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a clinical entity originally described by Coumel in 1978[379] and more extensively by Leenhardt in 1995[380]. This disease is characterized by adrenergically induced polymorphic ventricular tachycardia in the absence of structural cardiac abnormalities. Affected patients are usually referred to the cardiologist because of the occurrence of syncopal episodes, and a familial history of syncope and SCD is evident in approximately one third of the cases[380].

The electrocardiographic pattern of arrhythmias in CPVT is characterized by polymorphic ventricular tachycardia, that typically shows a bi-directional pattern of QRS complexes. The arrhythmias are reproducibly induced during exercise stress test or during isoproterenol infusion at heart rates above 120 beats . min[380]. The absence of structural abnormalities have been reported in the study by Leenhardt *et al.*[380] with a mean follow-up of 7 years, as well as in the previous

reports of CPVT[381,382], thus suggesting the presence of a primary electrical alteration.

No genetic analysis have been performed in the earlier studies on CPVT; however, the evidence of an autosomal pattern of inheritance suggests a genetic predisposition underlying the pathogenesis of CPVT. More recently, this concept has been further supported by Swan and co-workers[383] who demonstrated linkage between the CPVT phenotype and the chromosomal locus 1q42-q43 in two large affected families.

The clinical presentation of CPVT, which closely resembles the arrhythmias induced by intracellular calcium overload during digitalis toxicity, and the clear-cut evidence of adrenergically-mediated arrhythmias, point to delayed after-depolarizations (DAD) and triggered activity as the likely arrhythmogenic mechanism in these patients. Based on the published data, showing that DADs are caused by intracellular calcium overload[384] it was hypothesized that the human cardiac Ryanodine receptor gene (hRyR2), which maps to chromosome 1q42-43, could represent a likely candidate gene for CPVT. Indeed hRyR2 is a key protein for the regulation of calcium release from the sarcoplasmic reticulum and for the excitation–contraction coupling of the myocardial cells[385].

In a recent study Priori *et al.*[386] demonstrated the presence of hRyR2 mutations in four families affected with CPVT, thus showing that an altered hRyR2 protein is associated with the CPVT phenotype. These data strongly support the concept that arrhythmias of CPVT are caused by a genetically determined intracellular calcium overload, possibly due to a 'leakage' of Ca^{2+} from the sarcoplasmic reticulum.

Risk stratification

At the present time, because of the lack of controlled clinical trials, relatively little information is available for the risk stratification of patients with CPVT. The largest series available is the one reported in 1995 by Leenhardt *et al.*[380], showing a family history of SCD in 33% of cases and a mean age of $7{\cdot}8 \pm 4$ years at the first syncopal episode. A clear correlation between the age of first syncope and the severity of the disease has been observed, thus suggesting that an earlier onset may be considered as an adverse prognostic index.

CPVT patients are usually not inducible at PES[380], therefore inducibility should not be applied as an adequate risk stratifier. The assessment of the risk of developing severe clinical manifestation has to be based upon the clinical evaluation, the severity of the clinical history and upon the presence of severe history of sudden unexplained cardiac death among the relatives.

Management of high risk patients

Limited experience is available concerning the pharmacological treatment of CPVT patients. At the present time the only therapy that appears to be effective is antiadrenergic intervention with beta-blockers[380]. This concept is based on a retrospective analysis of published cases, which shows SCDs in 4/38 (10,5%) and 10/21 (48%) of patients with and without beta-blocker therapy, respectively[380]. The large majority of reported deaths are within the second decade of life in young otherwise healthy individuals.

Overall, these data are not to be considered conclusive given the lack of controlled studies. However, the evidence of a relatively high mortality even in the patients treated with beta-blockers (10·5%) may indicate the implantation of an ICD at least in those patients with early onset of symptoms and a positive family history of SCD.

Conclusions

The natural history of CPVT is still poorly defined because large studies are not available. The disease is associated with a high risk of SCD at young age but risk stratification parameters are missing. Inducibility at PES is not considered as an accurate predictor of outcome. History of syncope, previous occurrence of cardiac arrest, rapid and sustained runs of ventricular tachycardia at Holter recording or during exercise stress test are regarded as predictors of risk of major arrhythmic events. Treatment is based on beta-blockers even if a high rate of recurrence of ventricular arrhythmias has been reported; the implantable defibrillator has a role in secondary prevention while its value in primary prevention is unknown. Since no large prospective studies are available, the recommendations presented are based on the opinion of experts.

Recommendations for risk stratification for sudden cardiac death: catecholaminergic polymorphic ventricular tachycardia

	Recommendations	Level of evidence	References
Documented VF	Class I	C	[380]
Family history of SCD	Class IIa	C	[380]
Early onset of symptoms (paediatric age)	Class IIa	C	[380]
Syncope	Class IIb	C	[380]

Recommendations for prevention of sudden cardiac death: catecholaminergic polymorphic ventricular tachycardia

Recommendations	Level of evidence	References
Primary prevention		
Beta-blockers	Class IIa	C [380]
ICD	Class IIb	Opinion of the Task Force Panel
Secondary prevention		
ICD (plus beta-blockers)	Class I	Opinion of the Task Force Panel
Beta-blockers	Class IIa	C [380]

Aortic stenosis

Causes and clinical findings

Aortic stenosis (AS) can be either a congenital abnormality or acquired following acute rheumatic fever or due to an age-related degenerative process (senile AS). The natural history of AS is typically characterized by a long asymptomatic period during which the degree of stenosis increases. In 1968 Ross and Braunwald showed that the risk of SCD is low (3–5%) in asymptomatic patients[387]. More recently, a prospective study showed that SCD did not occur in any of 123 asymptomatic patients followed for 2·5 years[388]. The clinical manifestations of AS include syncope, angina pectoris and/or dyspnoea. Once symptoms develop, the prognosis worsens dramatically and the incidence of SCD among symptomatic patients ranges between 8 to 34% in different studies[387,389–391]. The mechanisms of SCD in aortic stenosis are not well documented, although substantial data attribute a possible role either to an abnormal Betzold-Jarisch reflex, ventricular tachyarrhythmias or to atrioventricular conduction disturbances. Analysis of Holter ECG in seven patients who died suddenly demonstrated the presence of ventricular tachyarrhythmia in six patients while only in one patient was death associated with bradyarrhythmia[392]. Both syncope and SCD are exertional in many patients but it is not clear if syncope is a predictor of SCD. Aortic stenosis is also associated with conduction disorders in the His bundle and the trifascicular system, which are more extensive when the valve is calcified[393].

Risk stratification

The difficulty is to predict the natural history of aortic stenosis in an asymptomatic patient since the risk of SCD is low. The degree of stenosis (systolic gradient, size of valve opening), amount of calcification and severity of left ventricular hypertrophy can be used to predict the speed of progression of stenosis requiring surgical intervention[389]. However, prediction of SCD based on the presence of frequent and/or complex ventricular arrhythmias, late potentials or reduced heart rate variability is still debated and not of sufficiently strong positive predictive accuracy to be used, e.g., for recommendation of aortic valve replacement[388,390–397]. In patients with spontaneous sustained ventricular arrhythmias, Martinez-Rubio *et al.*[397] pointed out that inducibility of ventricular tachycardia predicted a higher probability of recurrence of tachyarrhythmic events. Braunwald recommends surgery in asymptomatic patients when LV dysfunction, an abnormal response to exercise (e.g. syncope, hypotension) or significant ventricular arrhythmias are present[398]. It seems that aortic valve replacement should be considered if there is a significant left ventricular dysfunction, but such high-risk patients are rarely asymptomatic.

After aortic valve replacement, patients remain at some risk of SCD caused by cardiac arrhythmias, bundle branch block and complete heart block, impaired left ventricular function, residual left ventricular hypertrophy and fibrosis, coexistent coronary artery disease or prosthetic valve dysfunction. In this group of patients, SCD occurred with an incidence of 2–4% over a follow-up of 7 years[399–401]. A higher incidence of SCD was reported during the early recovery period (at 3 weeks) after valve replacement[402]. Transient complete AV block during the perioperative period does not predict late recurrence of conduction disorders[403]. The predictive factors of atrioventricular block requiring permanent pacing were: pre-existing conduction disorders, lower ejection fraction and calcification of the subaortic interventricular septum[404].

Management of high risk patients

Restriction of physical activity should be advised in patients with moderate and especially with severe aortic stenosis. Prevention of SCD is one of the goals of surgical treatment of AS. However, if surgery is considered to reduce the risk of SCD, the risk must be weighed against the surgical mortality and the known complications of prosthetic valves[390,399]. Most clinicians defer surgical intervention until symptoms occur. Patients should be educated about typical symptoms and the need for prompt surgery at the onset of symptoms. If a patient is undergoing coronary bypass grafting, concurrent aortic valve replacement may be considered to avoid early reoperation.

Patients presenting with sustained ventricular tachycardia or fibrillation who are inducible at electrophysiological study should be considered for cardioverter–defibrillator implantation[397]. The role of antiarrhythmic therapy with amiodarone is not clear.

Conclusions

Among all patients dying of AS, death is sudden in about 20%. In the absence of cardiac symptoms, survival is excellent without valve replacement. The prognostic value of different haemodynamic and electrophysiological testing is limited. This information comes only from small observational studies. Asymptomatic patients with haemodynamically severe AS should be followed-up frequently and carefully and surgical therapy should be undertaken as soon as the patient develops symptoms. In patients presenting with sustained ventricular tachyarrhythmias, implantation of ICD should be considered. Recommendations were based on small studies and on opinion of experts.

Recommendations for risk stratification for sudden cardiac death: aortic stenosis

	Recommendations	Level of evidence	References
Before aortic valve replacement			
Symptomatic patients	Class I	C	[387–391]
Asymptomatic patients			
Significant ventricular arrhythmia (patients presenting with VTs inducible at PES)	Class IIa	C	[397]
Left ventricular dysfunction	Class IIa	C	[398]
Abnormal response to exercise	Class IIa	C	[398]
Degree of stenosis	Class IIb	C	[388]
After aortic valve replacement			
Significant ventricular arrhythmia	Class IIa	C	[397]

Recommendations for prevention of sudden cardiac death in aortic stenosis

	Recommendations	Level of evidence	References
ICD (secondary prevention)	Class I	C	[397]
Aortic valve replacement	Class I	B	[390,399]
Amiodarone	Class IIa	Opinion of the Task Force Panel	

Mitral valve prolapse

Causes and clinical findings

Mitral valve prolapse (MVP) has been considered to be a highly prevalent abnormality mainly due to the initial use of non-specific echocardiographic criteria[405]. The prevalence has markedly decreased since the propositions of refined criteria. Recent data from the Framingham Study, of an unselected group of ambulatory patients, have suggested a prevalence of MVP as low as 1·3% in 3491 subjects[406]. MVP is mostly a benign condition[406–408]. SCD has been reported in association with MVP[408–410]. However, well-documented cases are rare and either clinical details or necropsy findings are absent or scanty. It is presumed that the basis of SCD in MVP is arrhythmic and ventricular fibrillation is probably responsible for SCD in most cases. Zuppiroli *et al.* reported the results of a prospective study in which 316 subjects were followed for a mean of 102 months[408]. During follow-up, only 6 patients died of cardiac causes, with only 3 cases of SCDs – 1 patient had mitral valve repair 14 months before death. However, it should be emphasized that due to the relatively high prevalence of MVP in the general population, even a low level of complications can result in a large number of affected people. Among 163 cases of sudden cardiovascular death in young people, MVP was the only cardiac pathology in 17 (10%)[410].

Risk stratification

Redundant and myxomatous leaflets are the most important echocardiographic findings associated with SCD. In the study of Nishimura *et al.* all 6 MVP patients who died suddenly were found to have redundant leaflets, whereas none of the 231 patients with non-redundant leaflets had SCD[411]. The relationship between the presence and the severity of mitral valve regurgitation and SCD is unclear[409,411–413]. Also, in the study by Zuppiroli mitral valve regurgitation was not an

evident risk factor for SCD[408]. Boudoulas *et al.*[412] and Campbell *et al.*[414] found that infero-lateral ST segment changes were associated with the presence of ventricular tachycardia or fibrillation. It was concluded from other studies that prolongation of QT interval and increased QT dispersion might be useful markers of arrhythmic mortality[415,416]. Frequent or complex premature ventricular beats were thought to be a risk factor for SCD but their prognostic role was not proven[417]. The SAECG may be helpful in the identification of MVP patients not predisposed to malignant arrhythmia[413]. Inducibility of ventricular tachycardia during PES does not seem to be helpful[413]. The most important prognostic markers for SCD in this group of patients are previous cardiac arrest, a family history of SCD at a young age, and mitral valve redundancy[409,411,412].

Management of high risk patients

No prospective studies have ever dealt with the efficacy of beta-blockers or antiarrhythmic drugs in preventing SCD. However, beta-blocking agents are generally considered as first choice therapy in the symptomatic patient. Patients with a history of cardiac arrest should be considered for ICD implantation.

Conclusions

MVP is usually benign, its link with SCD has been suggested but never conclusively demonstrated. Accordingly no data are available to define prophylactic interventions that may reduce the risk of SCD. No single finding is a consistent predictor for cardiac arrest. Most cases of SCD seem to involve patients with previous cardiac arrest or syncope, a family history of SCD at a young age, and mitral valve redundancy. Other clinical, echocardiographic and electrocardiographic markers, including electrophysiologic study, do not appear valuable in determining high risk subgroup. In survivors of cardiac arrest use of an ICD should be considered. These conclusions are based only on data from small observational studies and the consensus of experts.

Recommendations for risk stratification for sudden cardiac death: mitral valve prolapse

	Recommendations	Level of evidence	References
Cardiac arrest or VTs	Class I	C	[409,412]
Leaflet redundancy/mixomatous valve	Class IIa	C	[411]
Family history of SD	Class IIa	C	[409,412]
QT interval and QT dispersion	Class IIb	C	[415,416]
Frequent and complex ventricular arrhythmia	Class IIb	C	[417]
Mitral valve regurgitation	Class IIb	C	[408,411,412]
PES inducibility	Class IIb	C	[413]
Signal Averaged ECG	Class IIb	C	[413]

Recommendations for prevention of sudden cardiac death: mitral valve prolapse

	Recommendations	Level of evidence	References
ICD (secondary prevention)	Class I	Opinion of the Task Force Panel	
Beta-blockers*	Class III	Opinion of the Task Force Panel	

*Beta-blockers may be useful in reducing PVCs but their value in preventing SCD has not been demonstrated.

Anomalous origin of coronary arteries

Causes and clinical findings

Coronary artery anomalies are rare. The prevalence of these anomalies in the general population is unknown, ranging from 0·3% to 1·2% in patients referred for coronary angiography[418–421]. The most frequent coronary anomaly is the one of the circumflex artery — most commonly the vessel arises from the right coronary sinus. In this group of patients survival was not adversely affected[421]. However, origin of a left coronary artery from the right or non coronary aortic sinus of Valsalva appears to be associated with increased risk of SCD, particularly when the artery passes between the aortic and pulmonary artery roots[419,420]. Anomalous origin of the right coronary artery from the left sinus of Valsalva has also been reported to be associated with SCD but may not have the same risk as an anomalous origin of the left coronary

artery[419,420,422]. SCD is also the most common cause of death in patients with anomalous left coronary artery arising from the pulmonary artery who survive to adulthood[423,424].

Risk stratification

SCD typically occurs in males during or after physical activity. Unfortunately, data from the literature shows that diagnosis of these anomalies in life was possible in approximately 20% of patients. Presence of an anomalous origin of the coronary artery must be considered in young patients, particularly males, presenting with exertional chest pain or syncope accompanied by unexplained QRS or ST-T wave changes, or in those successfully resuscitated. Stress tests, Doppler colour flow mapping and transoesophageal echocardiography are useful non-invasive tests for diagnosing an anomalous origin of the left coronary artery[420,422,425,426]. However, coronary angiography is indicated, even in the case of a negative exercise test, in all young patients surviving cardiac arrest.

Management of high risk patients

In patients with an anomalous left coronary artery arising from the pulmonary artery, direct reimplantation of the left coronary artery into the aorta improves mortality and long-term morbidity[424]. In patients with aberrant origin of the left or right coronary artery who were successfully resuscitated from ventricular fibrillation, surgical intervention (usually bypass grafting) is appropriate. In the remaining symptomatic subjects with proven myocardial ischaemia, surgical therapy should be considered[419,420,422].

Conclusions

SCD occurs most commonly in individuals with anomalous origin of the left main coronary artery from the right or non-coronary sinus of Valsalva. Therefore special care should be taken to evaluate young patients with chest pain resembling angina. Surgical intervention appears to be the most appropriate treatment modality in patients who are at high risk for SCD. Data were derived from a limited number of small observational studies and consensus of experts.

Recommendations for risk stratification for sudden cardiac death: anomalous origin of coronary arteries

	Recommendations	Level of evidence	References
Cardiac arrest in history	Class I	C	[419,420,422,423]
Young patients, especially males with exertional chest pain or syncope and ECG changes	Class IIa	C	[419,420,422,423]

Recommendations for prevention of sudden cardiac death: anomalous origin of coronary arteries

	Recommendations	Level of evidence	References
Surgery	Class I	C	[419,420,422]

Myocardial bridging

Causes and clinical findings

Myocardial bridges consist of muscle fibre bundles overlying an epicardial coronary artery for a variable distance. The reported incidence of myocardial bridges observed at angiography (0·5%–4·5%) is far less than at pathological study (15%–85%)[427,428]. The left anterior descending artery is the vessel affected in almost all cases. Its typical angiographic presentation is systolic vessel narrowing due to transient myocardial compression. In a population of symptomatic patients, quantitative coronary angiography also demonstrated a delayed and incomplete vessel diameter gain during mid to late diastole[429]. Although most myocardial bridges are thought to be innocent, they may in some cases cause myocardial ischaemia, myocardial infarction, malignant ventricular arrhythmias, atrioventricular block and SCD[430–433].

Risk stratification

Identification of the presence and evaluation of the severity of myocardial bridges is of clinical importance. For the evaluation of the haemodynamic importance of myocardial bridges ECG exercise test, dobutamine stress echocardiography or myocardial perfusion scintigraphy may be useful. In selected cases, to obtain a functional insight into the myocardial bridging, intracoronary Doppler flow velocity measurement or angiography

during dobutamine stress are necessary[429,433]. Myocardial bridges occur in 30–50% of patients with hypertrophic cardiomyopathy and have been suggested as a possible cause of SCD in these patients[434].

Management of high risk patients

Patients symptomatic because of myocardial bridging usually improve with beta-blockers[435]. Beta-blockers work because of their negative inotropic and chronotropic effect. Nitrates increase the angiographic systolic narrowing and can lead to worsening of symptoms[429]. In refractory patients surgery (myotomy and/or coronary bypass), angioplasty or stenting can be considered[436,437].

Conclusions

Long-term prognosis of isolated myocardial bridges appears to be excellent but in some cases they may cause ventricular tachyarrhythmias and SCD. In symptomatic patients quantitative coronary angiography, Doppler flow analysis and intravascular ultrasound are used to characterize myocardial bridging. Medical treatment with beta-blockers, surgery, angioplasty or stenting may be the therapeutic alternatives.

This information is based on a limited number of small observational studies and a consensus opinion of experts was the primary source of recommendation.

Recommendations for risk stratification for sudden cardiac death in myocardial bridging

	Recommendations	Level of evidence	References
Cardiac arrest or symptomatic VT in history	Class I	C	[431,432]
Proven myocardial ischaemia	Class IIa	C	[433]

Recommendations for prevention of sudden cardiac death: myocardial bridging

	Recommendations	Level of evidence	References
Surgery in ischaemic patients	Class I	C	[436]
Beta-blockers	Class IIa	C	[435]
Nitrates	Class III	C	[429]

Wolff–Parkinson–White syndrome

Causes and clinical findings

The prevalence of the Wolff–Parkinson–White (WPW) ECG pattern varies from 0·1 to 0·3%. WPW can result in SCD when atrial fibrillation results in very rapid activation of the ventricles via an accessory AV pathway with a short anterograde refractory period and degenerates into ventricular fibrillation. SCD in the WPW syndrome is a rare but dramatic event in an otherwise healthy person. In symptomatic patients seen in tertiary referral centres, the prevalence of patients with a history of aborted SCD is 2–11%[438]. Population-based studies indicate a much lower incidence of SCD (0·15%/year)[439,440].

Risk stratification

Several studies in SCD survivors have revealed a higher incidence of the following markers: history of symptomatic tachycardia; short RR intervals between pre-excited beats during atrial fibrillation; multiple accessory pathways; postero-septally located pathways; familial occurrence and an increased incidence of Ebstein's anomaly[438,441–444]. A variety of non-invasive (Holter ECG, exercise testing, drug tests) and invasive tests (electrophysiological study) have been proposed to assess risk for SCD. An intermittent pattern of pre-excitation and an abrupt loss of pre-excitation during exercise indicate a low risk. Also loss of pre-excitation after intravenous administration of drugs like ajmaline or procainamide is used to identify patients at low risk[445]. However, sympathetic stimulation (exercise, anxiety, alcohol) may shorten the refractory period of the accessory pathway. Frequent conduction through an accessory pathway during atrial fibrillation has been accepted as a sensitive risk marker but its specificity and positive predictive value is low. However, a pre-excited RR interval >250 ms has a negative predictive value >95%[446].

Approximately 50% of patients with the WPW ECG pattern have no history of arrhythmias. Most asymptomatic patients with WPW have a good prognosis. Syncope has shown no predictive value for SCD in one study[446], but SCD may be the first manifestation of the disease[438]. At electrophysiological study, approximately 20% of asymptomatic patients will manifest a

rapid ventricular rate during induced atrial fibrillation[447,448]. However, the specificity and positive predictive value of this invasive prognostic indicator may be too low for routine use in asymptomatic WPW[442]. Thus, the use of electrophysiological study for risk stratification should be reserved for selected patients with a family history of SCD or individuals whose lifestyle or occupational activities require that risk is assessed. Detailed electrophysiological study is essential when RF ablation of accessory pathways is to be undertaken in symptomatic patients.

Management of high risk patients

Resuscitation from documented ventricular fibrillation or symptomatic atrial fibrillation with rapid ventricular response via the accessory pathway is unquestionably an indication for ablation of the accessory pathway[449]. Symptomatic tachyarrhythmias must be treated on their own merit. Asymptomatic WPW individuals should generally be offered catheter ablation only under special circumstances such as a family history of SCD, high risk profession (pilot, miner, operator of heavy industrial equipment, etc.) and in athletes. However, many physicians recommend that the majority of patients with a WPW ECG pattern should be treated by RF ablation on the grounds that risk stratification is uncertain and a therapy is available which is both effective and safe. This approach cannot be justified from a cost-effectiveness perspective.

Conclusions

In patients with WPW syndrome, natural history studies have reported an SCD rate of 0·15%/year which results from degeneration of atrial fibrillation with a rapid ventricular response into ventricular fibrillation. SCD survivors tend to be symptomatic, have short (<250 ms) RR intervals during atrial fibrillation, and multiple or postero-septally located accessory pathways. An electrophysiological study with induction of atrial fibrillation and determination of RR intervals between pre-excited QRS complexes has high sensitivity but limited specificity and positive predictive value. These data are derived from well-designed analyses of non-randomized studies. The non-invasive tests (intermittent pre-excitation, loss of pre-excitation during exercise or under antiarrhythmic agents) are not very helpful in risk stratification. This information is based on relatively small observational studies. Catheter ablation is recommended in patients at risk of SCD, especially those who were resuscitated from ventricular fibrillation or had clinical atrial fibrillation with rapid ventricular responses. Indications for procedure therapy are based on expert consensus and clinical experience.

Recommendations for risk stratification for sudden cardiac death: Wolff–Parkinson–White syndrome

	Recommendations	Level of evidence	References
Short (<250 ms) RR interval during atrial fibrillation	Class IIa	B	[441,443,444,446]
Short (<270 ms) anterograde refractory period of the accessory pathway	Class IIa	B	[438,439,444]
Multiple accessory pathways	Class IIa	C	[438,439,443,444]
Loss of pre-excitation ajmaline or procainamide test (lower risk)	Class IIb	C	[445]
Syncope	Class III	C	[446]

Recommendation for prevention of sudden cardiac death: Wolff–Parkinson–White syndrome

	Recommendations	Level of evidence	References
Catheter ablation — Secondary prevention	Class I	C	[449]
Catheter ablation: symptomatic patients with atrial fibrillation and rapid response via the accessory pathway	Class I	C	[449]
Catheter ablation: asymptomatic patients with family history of SCD, high risk professions, athletes	Class IIa	C	[449]
Amiodarone, class Ia, Ic AA drugs*	Class IIb	Opinion of the Task Force Panel	

*Alternative to ablation in asymptomatic patients.

Sinus node and atrioventricular conduction disturbances

Bradyarrhythmias account for approximately 20% of documented SCD[67,450,451].

The term 'bradyarrhythmia' is used to include the broad range of diseases affecting origin and propagation of cardiac excitation from the sinus node to the myocardium. In the paragraphs below the relationship between the conduction abnormalities and SCD is reviewed.

Sinus node dysfunction

Causes and clinical findings

Approximately 50% of pacemaker implants are due to sinus node dysfunction (SND)[452]. This disease presents a wide spectrum of arrhythmias, from inappropriate sinus bradycardia, sinus pauses and sino-atrial block to a variety of atrial tachyarrhythmias.

Pro gnosis is ill-defined but depends on the underlying or accompanying cardiac disorder. It has been suggested that permanent pacing does not modify the prognosis of patients with SND; however, these results derive mainly from a relatively old, non-randomized and non-prospective study[453]. Other trials have demonstrated poor quality of life, higher morbidity and even increased mortality of unpaced patients with sinus node disease[387,454]: systematic evaluation of the association with SCD, however, is lacking.

Risk stratification

Sinus node dysfunction, leading to serious bradycardia or pauses, is associated with dizziness, pre-syncopal or syncopal events and probably with SCD. The latter, when it occurs, mainly affects patients with left ventricular dysfunction. The pathophysiological mechanism that leads to death is usually a prolonged pause, with no escape rhythm or a ventricular tachyarrhythmia due to pause-dependent repolarization abnormalities.

Unfortunately, very few parameters are available for the evaluation of SCD in patients with sinus node dysfunction. Undoubtedly, a history of syncopal episodes, especially when accompanied with some form of injury, is considered an indication of the severity of the disease, while the electrocardiographic indexes, such as duration of pauses on Holter monitoring, correlate poorly with prognosis. More recently, the use of implantable loop recorders seems to have added some new information to the evaluation of the disease and they may contribute to improved risk stratification[455].

Management of high risk patients

Permanent atrial or dual-chamber pacing in patients with sinus node dysfunction relieves symptoms and improves quality of life, reduces morbidity and the incidence of atrial fibrillation. The value of ventricular pacing has repeatedly been shown to be less than atrial or dual chamber pacing. The effect of pacing on survival is not known[456].

Atrioventricular and intraventricular conduction disturbances

The natural history of atrioventricular and intraventricular conduction disturbances has been evaluated in non-randomized or observational studies performed in the past decades[457–459].

These conditions are frequently associated with presyncope or syncope and rarely with SCD. Permanent pacing leads to a marked improvement in the quality of life but its impact on reduction of SCD is debated.

Acquired AV nodal conduction abnormalities

First and second degree AV block type I (Wenckebach) are associated with a benign prognosis, whereas type II second degree AV block, either intra or infra Hissian, often progresses to third degree AV block and requires prophylactic permanent pacing[460–463].

Third degree AV block is most commonly associated with degenerative myocardial processes or ischaemic heart disease. A few non-randomized studies have suggested that permanent pacing improves survival in these patients[464,465].

Bifascicular and trifascicular block

Prospective studies in asymptomatic patients with chronic bifascicular block demonstrated that the disease slowly progressed to third degree AV block[458,466] and that the most frequent cause of SCD is ventricular tachyarrhythmia, mainly occurring in patients with a history of coronary artery disease, heart failure and/or advanced age[467]. Accordingly in these patients PES may be indicated to assess ventricular arrhythmia inducibility[468–472]. Patients with bifascicular or trifascicular block and syncope and those with intermittent third degree block have a higher incidence of SCD that is not significantly reduced by permanent pacing[473], supporting the concept that SCD may often result from ventricular tachyarrhythmias. Conflicting data exist concerning the value of HV prolongation to predict the risk of SCD due to bradyarrhythmias in these patients and it is commonly agreed that a prolonged HV interval (>75 ms) is poorly predictive of major events. On the other hand, some experienced authors indicate an HV interval exceeding 100 ms identifies a subgroup of extremely high-risk patients, in whom permanent pacing is essential[474–476].

The significance of bundle branch block as an independent marker for SCD is also controversial. The BBB has been implicated as a contributing factor in

SCD largely due to its frequent presence in high-risk patients. In patients with a normal heart, bundle branch block does not appear to reflect an adverse outcome. On the other hand, in patients with myocardial infarction receiving thrombolytic therapy, BBB identifies a subset of patients at high risk[477–479].

AV conduction disturbances during acute myocardial infarction

The long-term prognosis of acute myocardial infarction (AMI) survivors who develop conduction disturbances seems to be mainly related to the extent of the myocardial injury and the type of conduction disturbance. It is widely accepted that an anterior infarction and the appearance of persistent intraventricular conduction disturbances, with the exception of the left anterior fascicular block, have an unfavourable prognosis and an increased risk of SCD, attributable not only to advanced or complete heart block, but also to ventricular arrhythmia[480,481]. The prognosis for the combination of left bundle branch block with advanced or third degree AV block on the one hand or right bundle branch block in addition to left anterior or left posterior fascicular block on the other, is ominous[482]. Alternating fascicular block is also a condition with poor prognosis and requires urgent prophylactic pacing. Although the use of thrombolytic therapy reduces the incidence of AV block and the need for temporary pacing, it has no effect on the mortality of the patient population with AMI in whom atrioventricular block does develop. AV block in the setting of inferior myocardial infarction usually occurs at the level of AV node and has a favourable prognosis. Permanent pacing is seldom necessary unless the block persists for more than 14–16 days.

Congenital AV block

During the last few years, several studies have indicated that pacemaker implantation may improve long-term survival in complete congenital heart block (CCHB)[483–485].

SCD may be the initial manifestation of the CCHB in previously asymptomatic patients, even without structural heart disease and there is no definite safe period, either in fetal or postnatal life. The mechanism of SCD is attributed to either pauses without an escape pacemaker or pause mediated ventricular tachyarrhythmias. In the latter case and specifically in patients with CCHB and prolonged QT interval, early afterdepolarizations and dispersion of ventricular refractoriness, as a result of a pause or a long–short RR sequence, are the primary electrophysiological mechanism of fatal arrhythmias[486,487]. Undoubtedly, in patients with CCHB, a low heart rate (<50 beats . min $^{-1}$), the presence of a prolonged QT interval and the existence of structural heart disease, constitute risk for SCD and are indications for pacing.

Specific conditions of sinus node and conduction disturbances

SCD following orthotopic heart transplantation

The frequency of sinus node and conduction problems observed in the period following orthotopic heart transplantation is probably related to the ischaemic time and the severity of rejection. After hospital discharge, coronary atherosclerosis, acute and chronic allograft rejection, hypertension and non-specific fibrosis related to the use of cyclosporine, all affect the working myocardium and the conduction system. In a study by Patel *et al.*[488], who investigated 257 patient deaths, SCD had an incidence of 9·7% where 20% died <12 months after transplantation. There is a consensus that both bradyarrhythmias and tachyarrhythmias, due either to sinus node dysfunction or to complete heart block, are implicated in the early deaths[489].

Sudden death after AV nodal ablation and sudden death in paced patients

The occurrence of polymorphic ventricular tachyarrhythmias and SCD following complete ablation of the AV node, regardless of the use of DC or RF energy, is a clinically significant problem, because 2–3% of patients suffer SCD following the procedure[490,491]. The mechanism of SCD is still unclear, but may be due to bradycardia dependant prolongation of repolarization and refractoriness, mainly in the first 24 h after the procedure, particularly in those patients where the duration of repolarization is already prolonged[73,492].

Recommendations for dealing with this problem include pacing at relatively high rates and continuous ECG monitoring during the vulnerable period of the first 24 h after the procedure.

Considering the natural history of paced patients, it is estimated that 12–31% of these patients suffer sudden and unexpected death months or years after pacemaker implantation. Zehender *et al.* reported 23% incidence of SCD in paced patients[73]. The SCD rate was three times higher during the first year following pacemaker implantation than in subsequent years. The same authors suggested that sensing failure or asynchronous pacing might initiate malignant ventricular arrhythmias.

Conclusions

In general, SCD may be attributable to bradyarrhythmic mechanisms in as many as 15–20% of the cases. Importantly, significant numbers of bradyarrhythmic patients with impaired LV function suffer SCD due to the development of ventricular tachyarrhythmias.

Intraventricular conduction disturbances have been associated with bradyarrhythmic deaths but when the

conduction defect is caused by irreversible structural abnormalities SCD may be due to ventricular tachyarrhythmias. Intraventricular conduction disturbances have been associated with bradyarrhythmic deaths, while SCD could also be caused by ventricular tachyarrhythmias in those patients with conduction defects. Cardiac pacing undoubtedly improves the symptoms of bradyarrhythmic patients and may limit mortality.

Recommendations for risk stratification for sudden cardiac death: conduction system abnormalities

	Recommendations	Level of evidence	References
Acquired AV block in adults			
III° AV block	Class IIa	C	[464,465]
II° AV block type II	Class IIa	C	[461]
Syncope	Class IIa	B	[458,474]
Coexistent heart disease or heart failure	Class IIa	C	[465]
Congenital III° AV block			
Syncope	Class I	B	[484,485]
Prolonged QTc	Class I	B	[486,487]
Congenital heart disease	Class I	C	[486,487]
Chronic bifascicular and trifascicular block			
Coexistent heart disease or heart failure	Class I	B	[467]
Syncope	Class IIa	B	[469,471,472,474]
HV $\geq$ 100 ms or pacing induced infra-His block	Class IIa	C	[475,476]
PES inducibility	Class IIa	B	[468,469]

Recommendations for prevention of sudden cardiac death: conduction system abnormalities

	Recommendations	Level of evidence	References
Pacemaker in higher risk subgroups	Class I	C	[461–463,484,485]

Trained heart

Causes and clinical findings

Over the past several years, interest and concern in the medical community and with the lay public have heightened considerably regarding the causes of sudden and unexpected deaths in trained athletes[493–496]. Autopsy-based studies have documented the structural heart diseases responsible for SCD in competitive athletes or those with sports-related lifestyles[265,323,497–505]. Of note, these cardiovascular abnormalities should not be confused with the normal physiological adaptations of cardiac dimensions evident in many trained athletes[506], consisting of increased left ventricular mass due to cavity enlargement or increased wall thickness, or both[507–509]. Some caution is advised in assigning prevalence estimates for various cardiovascular diseases as the causes of SCD in athletes. Selection biases and geographic differences unavoidably influence the acquisition and interpretation of such data in the absence of systematic national registries. Furthermore, primary electrical diseases (due to ion channel gene mutations) such as long QT syndrome, Brugada syndrome and catecholaminergic polymorphic VT are not identifiable at routine autopsy, and can be reliably diagnosed clinically only through analysis of pre-existing ECGs.

The cardiovascular causes of SCD in athletes vary substantially with regard to age. In those over 35 years of age (largely engaged in distance running, rugby, squash or golf) the predominant cause of death is atherosclerotic coronary artery disease, often severe and diffuse in individuals with known risk factors or symptoms[505]. In contrast, in athletes younger than 35 years of age, a variety of about 20 largely congenital cardiac diseases which are uncommon in the general population, account for the SCDs.

Several studies show hypertrophic cardiomyopathy to be the single most frequent cause of SCD in young trained athletes, accounting for up to about one-third of the fatal events[254,256,265,501,503]. Second in importance and frequency to HCM are the congenital coronary artery anomalies of wrong aortic sinus origin, the most common of which is anomalous origin of the left main coronary artery from the right (anterior) sinus of Valsalva[265,422,510,511]. Coronary artery malformations may remain clinically silent for long periods of time and often lack premonitory symptoms (e.g., exertional

syncope or chest pain) and ECG abnormalities[511]. Also, atherosclerotic coronary artery disease with acute plaque rupture[37] may be responsible for SCD in youthful athletes[311].

While several autopsy studies of young athletes with SCD show RVC to be uncommon (i.e., <5%)[265,495,501–503], an exception are reports form the Veneto region of Italy where RVC is the single most common cause of SCD in young competitive athletes (and HCM is uncommon)[301,323]. Such geographic differences are possibly due to a unique genetic substrate or alternatively to the long-standing Italian national screening programme for competitive athletes[512] which has probably identified (and consequently disqualified) far greater numbers of athletes with HCM than with RVC[301].

Prevention of SCD in athletes

The purpose of pre-participation cardiovascular screening is to detect (or raise the suspicion of) clinically relevant abnormalities harbouring the potential to cause SCD or morbidity in a general population of apparently healthy athletes. Within a benevolent society, there is an implicit ethical obligation on the part of physicians and institutions (e.g., high schools, colleges/universities) to initiate and implement prudent, cost-effective strategies to assure that competitive athletes are not exposed to unacceptable and avoidable medical risks[513].

In the U.S. and many European countries, athletic screening has been performed customarily in the context of a personal and family history and physical examination[513–515]. Such standard pre-participation examinations are capable of raising the suspicion of cardiovascular abnormalities in some at-risk athletes. However, screening by history and physical examination alone (without non-invasive testing) does not possess sufficient power to identify many critical cardiovascular abnormalities in a large population of high school and college-aged student athletes[513–515].

Furthermore, no available screening design (even with diagnostic testing) is capable of reliably identifying all important lesions and affected athletes; some abnormalities (such as coronary artery anomalies) present particular challenges for detection. Haemodynamically significant congenital aortic valve stenosis is the lesion most likely to be reliably detected during routine screening due to the characteristically loud heart murmur. Detection of HCM by history or physical examination screening is generally unreliable because most patients have the non-obstructive form of this disease, typically expressed by no or only a soft heart murmur[422].

In general, however, personal and family history conveys a low specificity for the detection of many cardiovascular abnormalities that lead to SCD in young athletes. The addition of non-invasive testing (e.g., 12-lead ECG or echocardiography) to the screening process undoubtedly enhances detection of many of the lesions responsible for SCD; however, this strategy has not been considered cost-effective in most countries. An exception is in Italy where a national screening programme for the detection of potentially lethal cardiovascular abnormalities in competitive athletes has been in place since 1982, and administered annually by approved sports medicine examiners[512]. This programme is unique in routinely utilizing a 12-lead ECG and submaximal exercise test (in addition to a history and physical examination) to screen all young participants in organized sports. This process has been shown to be effective in the de novo identification of HCM in athletes[301]. Comprehensive and routine screening with DNA testing for genetic cardiovascular diseases such as HCM, Marfan syndrome, or long QT syndrome is not yet practical for large athletic populations, given the substantial genetic heterogeneity characteristic of those diseases, as well as the expensive and time-intensive methodologies required[516].

When a cardiovascular abnormality is identified in a competitive athlete two major considerations arise: (1) the magnitude of risk for SCD (or disease progression) potentially associated with continued participation in competitive sports; and (2) discerning criteria to dictate which individual athletes should be withdrawn from sports competition. In this regard, the 26th Bethesda Conference[493] affords prospective, consensus panel recommendations for athletic eligibility and disqualification, taking into account the severity of relevant cardiovascular abnormalities, as well as the intensity of potential sports training and competition. These recommendations are predicated on the assumption that intense physical exertion in the context of competitive sports may act as a trigger for SCD in certain predisposed athletes with underlying structural heart disease. While such risks cannot be quantified with precision, the temporary or permanent withdrawal of selected athletes with cardiovascular disease from participation in certain competitive sports is regarded as a prudent strategy for diminishing the risk of SCD[265,493].

Conclusions

Sudden and unexpected death in young trained athletes is due predominantly to underlying and usually unsuspected congenital cardiovascular disease. The most important of these appear to be hypertrophic cardiomyopathy, anomalous coronary artery of wrong aortic sinus origin, and right ventricular cardiomyopathy (in Italy). Screening strategies for asymptomatic normal populations of trained athletes can detect certain abnormalities, but the power of identification is enhanced considerably by the incorporation of non-invasive testing (i.e., 12-lead ECG or echocardiography). Removal of athletes with cardiovascular disease from competition and training may decrease risk. Consensus panel guidelines and criteria governing such clinical decision-making are available. Due to the nature of the subject matter much of the assembled data and conclusions have necessarily been made from uncontrolled, retrospective and inferential observations.

Recommendations for risk stratification for sudden cardiac death in young athletes*

	Recommendations	Level of evidence	References
12-lead ECG	Class I	A	[512]
Physical examination	Class IIa	B	[301,512]
Personal history	Class IIa	B	[513–515]
Family history	Class IIb	B	[513–515]

*These recommendations are offered solely in a scientific context, without particular consideration to other important issues concerning cardiovascular screening, such as implementation and cost-efficacy. Indeed, we understand that some European countries may not wish to formulate screening in the design offered here and that the inclusion of a 12-lead ECG to the protocol may not be regarded as feasible.

SCD in the normal heart

Causes and clinical findings

Data were collected from a large series of victims of cardiac arrest and show that ventricular fibrillation in the absence of structural heart disease, cardiotoxicity, electrolyte abnormalities, known heritable arrhythmogenic conditions and other transient conditions can be provoked by an appropriate challenge. The so-called idiopathic ventricular fibrillations (IVF), are more common than previously recognized, occurring in 1% of survivors of cardiac arrest and up to 8% of victims of SCD[68].

Risk stratification

Five years after cardiac arrest, IVF patients have 30% risk of recurrence of cardiac arrest[517]. This means that most (70%) remain free of symptoms during follow-up. Therefore it is extremely important to devise risk stratification protocols in order to identify high risk patients. Unfortunately at present no predictor of poor outcome has been identified.

Programmed electrical stimulation
Among the patients enrolled in the European registry, UCARE, only 50% were inducible by PES. Polymorphic sustained VT or VF were the most frequently observed rhythms but both positive and negative predictive values were low[518].

Body surface mapping
Peeters *et al.*[519] proposed that the 62-lead body surface QRST integral maps could help in the identification of patients at higher risk. In 17 patients with a first episode of IVF, 29% had a normal dipolar map, 24% had a dipolar map with an abnormally large negative area on the right side of the thorax, and 47% had a non-dipolar map. All subjects of a healthy control group had a normal dipolar QRST integral map. A recurrent arrhythmic event occurred in 7 patients (41%), all presenting an abnormal QRST integral map.

Sympathetic innervation
Schaefers *et al.*[520] evaluated pre-synaptic norepinephrine re-uptake in the heart in 15 IVF patients and 10 controls using iodine-labelled meta-iodobenzylguanidine (I-123-MIBG) uptake. Locally reduced I-123-MIBG uptake was found in 17 of 25 IVF patients (68%). However no data are available to define whether regional denervation is a predictor of outcome.

Pharmacological and ICD prevention

According to UCARE investigators, prevention of recurrence with antiarrhythmic agents and β-blockers failed[518]. A different view comes from the experience of Belhassen and Viskin[521], who reported a limited but positive experience with the use of sodium channel blockers in 15 patients. The UCARE registry does not confirm this result: 9% of the patients were treated with sodium channel blockers and this group had 30% recurrence rate with two SCDs. Long-term follow-up of all six IVF patients in whom PES had shown suppression of inducibility with sodium channel blockers suffered a recurrence of 100%[518].

IVF survivors should be regarded as candidates for an ICD[518].

Myocarditis

According to the definition of the World Health Organization 'myocarditis is an inflammatory heart muscle disease associated with cardiac dysfunction'. Myocarditis may occur as the consequence of a systemic infective disease or may be the consequence of a silent infection. Clinical diagnoses of myocarditis maybe difficult as the clinical manifestations are frequently non-specific ranging from chest pain to arrhythmias and from heart failure to SCD.

Myocarditis has been proposed as a major cause for unexpected arrhythmic death in young individuals. In 1996, Liberthson[503] reported that up to 44% of juvenile SCDs were associated to myocarditis. Similar data had been reported 10 years earlier from an autopsy series of US Army soldiers[522] that demonstrated histological signs of clinically silent myocarditis in a striking 42% of SCDs.

Much more conservative is the estimate reported by the Forensic Institute of Paris that found signs of myocarditis in 5% of out-of hospital cardiac arrests[523]. As recently pointed out by Fontaine *et al.*[524] the 'true prevalence' of myocarditis in a large 'control' group (such as road accident victims) is also lacking. Even when signs of myocarditis are identified in SCD victims, the causal relationship with death may be difficult to prove.

SCD may occur in the early phase of myocarditis or in the healing phase[524]: arrhythmias are most likely precipitated by inflammatory infiltrates and interstitial oedema. Bradyarrhythmias may also be a cause of SCD in myocarditis as the specialized tissue of the conduction system may be affected.

The offending agent can be viral or bacterial: molecular analysis recently played a major role in helping identify the aetiology of the infection[525,526]: data obtained so far would point to viral infection as the leading cause of myocarditis. Despite the presence of inflammatory infiltrates in a high percentage of SCD victims, it remains difficult to prove that myocarditis is the cause of SCD.

The view that inflammation may promote ventricular arrhythmias or act as a trigger in patients with concealed cardiomyopathy[265,524] or WPW[527] is an interesting hypothesis.

At the present time no data are available to provide recommendations for prevention of SCD associated with myocarditis or to allow adequate risk stratification for the risk of SCD.

Chest trauma

Causes and clinical findings

Cardiac arrest may result from a relatively modest and non-penetrating blunt blow to the chest, in the absence of underlying cardiovascular disease or structural injury to the chest wall or heart itself (i.e., commotio cordis). Such occurrences may be produced during sports activities either by a projectile (most commonly a baseball, softball or hockey puck), or by bodily contact, and result in virtually instantaneous collapse[528,529]. The blow to the chest is usually not perceived as unusual for the sporting event, nor of sufficient magnitude to result in a catastrophe. Most victims are young children (mean age 13 years; 70% are <16 years) and events after age 21 are very uncommon. While many of these events occur during organized sports, remarkably many of these events have occurred during recreational activities at home or on the playground (or in the course of daily activities unrelated to sports) with the fatal injuries being produced by family members or friends[530].

There appear to be four determinants of a commotio cordis event[528–532]: (1) location of chest impact directly over the heart; (2) relatively low-energy blow, in most instances; (3) a narrow, compliant chest wall, typical of young children; and (4) precise timing of the blow to a narrow 15 ms window within the repolarization phase of the cardiac cycle (just prior to the T wave peak), most vulnerable to potentially lethal ventricular tachyarrhythmias, and involving activation of the K^+_{ATP} channel with abrupt increase in left ventricular pressure.

Certain strategies aimed at prevention of commotio cordis events have been considered. Softer-than-standard (safety) baseballs reduced the risk for ventricular fibrillation in an experimental model of this syndrome[531], suggesting that a measure of SCD prevention may be achieved through the modification of athletic equipment. Wider use of chest barriers designed specifically to cover the precordium would theoretically offer protection against the occurrence of commotio cordis in young people competing in sports such as baseball, ice hockey, karate, lacrosse and football. However, the infrequency of commotio cordis events represents an obstacle to documenting the effectiveness of any protective intervention. Survival after commotio cordis is low: about 15% of the reported victims are known to have survived (after documented ventricular fibrillation), usually associated with prompt cardiopulmonary resuscitation and defibrillation[533]. With enhanced public awareness of this syndrome, emergency measures are likely to be implemented.

Drug-induced torsades de pointes and sudden cardiac death

A variety of drugs including antiarrhythmic drugs, antibiotics, antipsychotic drugs, antihistamines and prokinetic drugs have been recognized to possess substantial proarrhythmic potential by inducing an acquired long-QT syndrome (LQTS)[534]. With or without additional triggering conditions, the prolonged QT-interval can provoke torsades de pointes (TdP) arrhythmias that either resolve spontaneously or deteriorate into ventricular fibrillation. Therefore TdP represent a substantial risk for SCD unless adequately treated. As in congenital LQTS, the actual incidence of drug-induced TdP is low and that of proven drug-associated syncope or SCD is even lower. Nevertheless, the list of drugs recognized to cause acquired LQTS is increasing and has become a real concern for the medical community[534].

In congenital LQTS, the mechanisms responsible for QT prolongation have been identified. Mutations in the genes encoding for cardiac ion channels that are required for the cardiac action potential cause abnormal repolarization. These channels are putative targets for acquired LQTS and any drug that modifies them presents a potential risk for the development of arrhythmias. Almost all drugs with reported QT prolongation and TdP block the repolarizing outward potassium current I_{Kr}, encoded by HERG (*h*uman *e*ther-a-go-go *r*elated *g*ene). The HERG channel has been cloned and is sensitive to block by a surprisingly large variety of agents including drugs used for treating non-cardiac conditions[535]. However, not all selective I_{Kr} blockers exhibit the same propensity to induce TdP.

Besides underlying heart disease, several factors predispose for drug-induced TdP, these include female gender, long QT interval at baseline, bradycardia, low K^+ (and Mg^{2+}) plasma levels and old age. As mentioned above, drugs may act directly on ion channels or interact pharmacodynamically or pharmacokinetically with

other drugs that also affect channels. Although there appears to be no strict concentration–response relationship for triggering TdP, drug plasma concentrations should not be allowed to rise above the therapeutic level and interference with drug metabolism or excretion should be avoided. Aggravation of drug–drug interactions is particularly serious in individuals with a genetic predisposition related to congenital LQTS.

Cardiovascular drugs

Intuitively, cardiac drugs and in particular antiarrhythmics that prolong the action potential duration are expected to produce an increased risk not only because of their mechanism of action but also because they are given to patients with diseased hearts that are per se at a high risk for rhythm disturbances.

Class Ia and Ic antiarrhythmic drugs induce TdP. Most of these arrhythmias occur within the first few days after initiation of therapy, however, with encainide and flecainide that were part of the CAST study SCD did not occur shortly after the onset of therapy but was observed even after months of treatment[192]. With the class III antiarrhythmic amiodarone, the incidence of syncope and SCD is surprisingly low[536,537]. In fact, amiodarone may even be effective in patients with previous drug-induced TdP[538]. d-Sotalol on the other hand has been associated with dose-dependent proarrhythmias and increased mortality in patients after myocardial infarction[188]. TdP is also associated with the new selective I_{kr} blocker dofetilide[189].

The unselective calcium channel blockers bepridil and prenylamine, formerly used as antianginal drugs, have also been associated with polymorphous ventricular arrhythmias and TdP. Anecdotal reports exist about arrhythmias induced by other vasoactive agents including cocaine, the α-adrenoceptor blocker indoramin, sildenafil, vasopressin and vincamine.

Non-cardiac drugs

When serious arrhythmias or SCD occur during drug treatment of non-cardiac diseases, the event is more readily related to the severity of the underlying disease than associated with administration of a particular drug. Correct analysis of the causal relationship becomes more difficult with multi-drug therapy and when the incidence of proarrhythmic events is low.

Antihistamines

The non-sedating antihistamines terfenadine and astemizole are associated with acquired LQTS, in particular when the drugs were co-administered with antifungals that interfere both pharmacokinetically and pharmacodynamically. Terfenadine and astemizole block cardiac K^+ channels and thus prolong repolarization[539,540]. Terfenadine is rapidly metabolized to a cardio-inactive compound by the CYP 3A4 isoenzyme, a member of the cytochrome P450 enzyme family. If metabolism is impaired by co-administration of the antifungal ketoconazole, a potent inhibitor of CYP 3A4, plasma concentrations of terfenadine may reach toxic levels. Ketoconazole also blocks cardiac potassium channels and hence directly adds to the APD-prolonging effect of terfenadine. These combined effects are responsible for provocation of TdP. Similar interactions have been observed after co-administration of terfenadine and macrolide antibiotics[541], but even grapefruit juice may inhibit metabolism of terfenadine[542]. Most countries have restricted the use of terfenadine.

Pratt *et al.*[543] have examined the pharmacoepidemiological question whether terfenadine given alone to a population as a whole represents an increased risk of developing fatal arrhythmias. To this purpose they examined a large database (COMPASS) to identify subjects receiving terfenadine or comparison drugs such as over the counter antihistamines, ibuprofen or clemastine. It is not known whether the other non-sedating antihistamines (acrivastine, cetirizine, ebastine, fexofenadine, loratadine, mizolastine) are safe with respect to TdP. In fact, some cardiac deaths in the literature have been associated with the older antihistamines[544].

Macrolide antibiotics

In several casuistic reports, erythromycin has been associated with excessive lengthening of cardiac repolarization and TdP. Erythromycin directly blocks I_{Kr}[545]. Spiramycin, which is used for toxoplasmosis prophylaxis, has been associated with acquired LQTS in several cases including one cardiac arrest in a newborn[546], though direct effects on cardiac channels have not been reported. In addition, macrolide antibiotics compete with other drugs for reversible binding to cytochrome P450 in the liver leading to inhibition of metabolism of other drugs. The increased propensity to develop an acquired LQTS by co-administration of terfenadine with erythromycin has been explained by macrolide-induced inhibition of terfenadine metabolism leading to unduly high plasma concentrations of the cardioactive parent substance[541]; however, direct pharmacodynamic effects are likely to contribute to lengthening in action potential duration[547].

The sulfamethoxazole moiety of the antibiotic combination of trimethoprim–sulfamethoxazole may cause QT prolongation and TdP[548,549]. In a recent study of 98 patients with drug-induced arrhythmia, Sesti *et al.*[550] identified a patient with a genetic polymorphism that encoded for a potassium channel with normal electrophysiological properties under control conditions but several-fold more sensitive to block by sulfamethoxazole than the wild type. These results are important because they show that drug-induced LQTS can also occur in the presence of an additional disposition which by itself is silent.

Quinolone derivatives

For fluoroquinolones, a class effect of cardiotoxicity has been suggested[551]. Drug-related malignant arrhythmias have been described only in rare cases with sparfloxacin,

levofloxacin and gepraﬂoxacin. Only sparﬂoxacin, but not levofloxacin or ofloxacin, prolonged the action potential in Purkinje fibers[552]. The actual reporting rate for malignant arrhythmia is low, i.e. one per million for ciprofloxacin, 3 per million for clarithromycin and 14·5 per million for sparﬂoxacin[551]. These data suggest careful monitoring of all patients with additional risks for TdP arrhythmias.

Pentamidine
Pentamidine is used in the treatment of *Pneumocystis carinii* pneumonia in patients with acquired immune deficiency syndrome. Several cases of polymorphic ventricular arrhythmias have been reported with and without additional precipitating factors[553].

Antifungal drugs
The main cardiotoxic risk pertinent to ketoconazole and other imidazole antimycotic agents occurs by interference with metabolism of other QT prolonging drugs due to inhibition of cytochrome P450[554]. In addition, ketoconazole was shown directly to block cloned K^+ channels[555].

Antimalarial agents
For treatment of chloroquine-resistant malaria larger doses of quinidine are recommended than for antiarrhythmic therapy. Quinidine and its stereoisomer quinine induce QT interval prolongation[556,557]. SCD was reported after high doses of halofantrine used for treatment of *Plasmodium falciparum* malaria, leading to a prospective study in the course of which a sudden cardiac arrest occurred in a patient who had had a previous history of frequent syncope[558]. Children appear to be at high risk[559]. Chloroquine prolonged the QTc interval in 3 volunteers during curative doses[560].

Antiviral drugs. TdP arrhythmias occurred after a suicidal overdose of amantadine[561].

Antipsychotics. Many antipsychotic drugs including phenothiazines, butyrophenones, tricyclic antidepressants and serotonin reuptake blockers, show proclivity to arrhythmic events with SCDs reported for all drug classes.

Phenothiazines have repeatedly been associated with SCD in numerous case reports, though SCDs among patients treated with antipsychotic drugs also include non-cardiac reasons like drug-induced seizures or central nervous system depression. A large survey of SCD in autopsies in Finland over a period of 3 years revealed that 49 cases of SCD were associated with the use of phenothiazine and all but 3 with the use of thioridazine[562]. Haloperidol and droperidol are associated with several cases of TdP arrhythmias[563,564].

Antidepressants. Several cases of SCD attributable to tricyclic antidepressants have been reported[565]. Because of the underlying disease, these drugs are particularly prone to suicidal overdose and hence require careful assessment of cardiotoxicity. Since many tricyclic antidepressants (e.g. amitriptylin, desipramine, nortriptyline) and thioridazine are metabolized by cytochrome P450 enzymes, their plasma levels may rise unduly after co-administration with enzyme inhibitors (macrolide antibiotics, imidazoline fungicides, or psychotropic fluoxetine, fluvoxamine, haloperidol).

Prokinetics. Cisapride facilitates gastrointestinal motility and was used for the treatment of dyspepsia and gastrointestinal reflux disease in both children and adults. After at least 341 reports of arrhythmias including 80 deaths, the drug was withdrawn from the U.S. market[369,566,567].

Miscellaneous. Occasional reports on TdP arrhythmias have appeared for the following groups of drugs or single agents: diuretics (indapamide), muscle relaxants (suxamethonium), the lipid lowering agent (probucol), terodiline used for treatment of urinary incontinence, insecticide poisoning (organophosphates).

Conclusions

The steps to be recommended for increasing the awareness of proarrhythmic risks associated with established and new drugs include[534]: detailed list of all drugs associated with QT prolongation; For new drugs, mandatory data on block of K^+ channels (HERG, etc.); avoidance of co-administration of drugs prolonging the QT-interval; avoidance of drugs that interfere with metabolism and excretion; avoidance of drugs that produce TdP-promoting conditions (hypokalaemia, bradycardia). The absolute incidence of cardiotoxicity of any drug must be judged in relation to the severity of the treated disease: a high risk may be perfectly acceptable when treating a life-threatening condition whereas even a very low incidence as reported for non-sedating antihistamines is not acceptable as these drugs are widely prescribed for minor complaints.

Out-of-hospital resuscitation

Survival after cardiac arrest (CA) varies from less than 5% to 60% according to the characteristics of the cardiac arrest event (e.g. cardiac aetiology or not, witnessed or not, VF or not). The results of cardiopulmonary resuscitation (CPR) are influenced not only by the resuscitation efforts but also by the conditions before initiation of CPR. Outcome from cardiac arrest is a complex interplay of so-called 'fate factors' (e.g. age, underlying disease) and 'programme factors' (e.g. time interval to basic life support and to defibrillation). It is now generally accepted that the time to electrical defibrillation is the single most important determinant.

Emergency medical service (EMS) system

Before the introduction of automated external defibrillators, only some 15% of all out-of-hospital cardiac arrest victims had restoration of spontaneous circulation and reached the hospital alive. Of those, only 50% survived to discharge (= 5–7%). Considering only patients presenting with VF, survival to discharge is about double (15–20%). In areas where early defibrillation by ambulance personnel is implemented, more patients are found in VF (e.g. by short arrival times or use of the automated external defibrillator operated by ambulance personnel), more patients are found in VF at the time of the intervention resulting in a higher hospital discharge rate of 25–28%[568,569].

Cardiac arrest usually happens at home (about 2/3), in male patients aged >50 years of age (about 3/4) and during daytime (about 3/4 between 8–18 h). In most reports on out-of-hospital cardiac arrest presenting with VF, cardiac arrest has been witnessed in 2/3 of cases. This profile of the cardiac arrest patient is helpful to identify the profile of the potential bystander of a cardiac arrest event, and therefore the primary target group for teaching citizen CPR, i.e. the persons being close to male individuals aged >50 years, being at home during daytime, i.e. housewives, family members and relatives of cardiac patients[14,570–573].

Survival in out-of-hospital cardiac arrest: the 'chain of survival' concept

People are more likely to survive out-of-hospital cardiac arrest when activation of the Emergency Medical Service (EMS) system, basic cardiopulmonary resuscitation (CPR), defibrillation and advanced care occur as rapidly as possible. The concept of 'the chain of survival'[574] describes the interventions that are needed for optimal survival. This concept illustrates also that the weakness of any of these links condemns EMS to poor results.

- The first link in the chain of survival, 'early access' is essential to bring trained people and appropriate equipment, i.e. the defibrillator, quickly to the patient. This includes recognition of the collapse, decision to call, calling and dispatch, and can be strengthened by public education and availability of an efficient emergency communication system.
- The importance of the second link, 'early CPR' has been shown abundantly. Bystander CPR is able to keep the heart some 10–12 min longer in VF. Basic CPR is sufficient to sustain life until early arrival of trained and equipped people, and is therefore a bridge to first defibrillation.
- The most crucial link is 'early defibrillation'. Initially, out-of-hospital defibrillation was only performed by medical and paramedical personnel, but recently the automated external defibrillator (AED) has enabled reliable use by first-line trained ambulance personnel and laymen. First tier ambulances arrive many vital minutes before arrival of the second tier. Primary rescue teams, such as police, security personnel and fire fighters are present at the scene several minutes before the first tier ambulance of the EMS system. In remote areas (airplanes, cruise ships, trains) the delivery of a defibrillatory shock within seconds or minutes would be restricted to board personnel. To shorten the time to defibrillation, rescuers in the community other than doctors or paramedics should have access to defibrillation.
- Early defibrillation is of high value as long as the other links in the 'chain of survival' do not fail. In systems, where access time is excessively long, the usefulness of an early defibrillation program can be limited.
- The fourth link 'early advanced life support' implies early intervention of a well-trained and well-equipped team, working with specially equipped ambulances or rapid intervention vehicles. These teams consist of paramedics (in the U.S.A., U.K., and Scandinavia) or trained ambulance personnel, doctors and/or nurses (in most European countries).

Towards common international guidelines for resuscitation

In 1973 the AHA first published the 'Standards for Cardiopulmonary Resuscitation and Emergency Cardiac Care'. At the time only a few of the recommended measures were based on scientific evidence, but the medical world accepted them as the gold standard for resuscitation care. Since 1973, many national and supra-national guidelines have been developed and published to complement the AHA Standards. All new guidelines included detailed advice that was mostly scientifically unproven but was justified on the basis of clinical experience and tradition. Difficulties have arisen in implementation of these guidelines outside the U.S.A. because of medical considerations, medico-legal issues, ethical and religious matters[575].

The European Resuscitation Council (ERC), established in 1989 as an interdisciplinary council for resuscitation medicine and emergency medical care, produced in 1992–94–96–98 Guidelines for Basic, Advanced and Paediatric Life Support, for the use of automated external defibrillators (AEDs), for the Management of Peri-arrest Arrhythmias, for the Basic and Advanced Management of the Airway and Ventilation during Resuscitation[576].

Against this background, the International Liaison Committee On Resuscitation — ILCOR — was founded in 1992 and comprises representatives of the AHA, the ERC, the Australian Resuscitation Council, the Canadian Heart and Stroke Foundation, the Resuscitation Council of Southern Africa, and the Resuscitation Council of Latin America. The mission of ILCOR is: 'To provide a consensus mechanism by which the

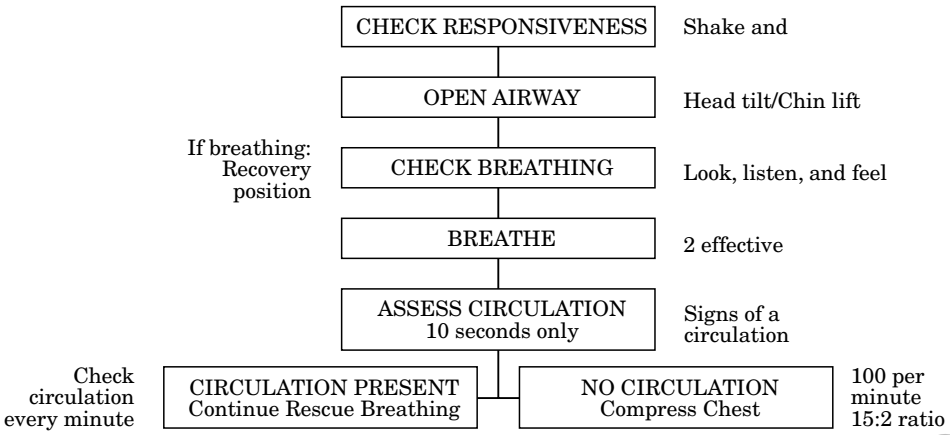

Figure 1 **Algorithm for Basic Life Support (BLS).**

international science and knowledge relevant to emergency cardiac care can be identified and reviewed. This consensus mechanism will be used to provide consistent international guidelines for basic life support, paediatric life support and advanced life support. These international guidelines will aim for a commonality supported by science for BLS, PLS and ALS.'

The constituent organizations agreed to make use of this resource so that all future guidelines will reflect the commonality of opinion that has evolved during the process[577].

In 2000, International Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) have been produced as a result of collaboration between the AHA and the other ILCOR member organisations. These International Guidelines are the result of a well-standardized evidence-based process, in which the scientific evidence supporting the aspects of CPR and ECC were investigated and classified (classes I, IIa, IIb, III, Indeterminate) according to the quality of the scientific evidence. As a result, today, all major resuscitation councils have now implemented the ILCOR advisory statements, so that in 2000, true international uniformity was finally achieved[578].

This publication, which serves as a consensus on science, contains complete references on all aspects of emergency care of sudden cardiorespiratory collapse.

Some key aspects of the International 2000 Guidelines for CPR and ECC will be highlighted in this overview (Figs 1 and 2).

The international 2000 guidelines for basic life support (BLS)

Moving towards simplicity

After 30 years of public CPR education most communities still do not train a sufficiently high proportion of the public to perform basic CPR. Increasing the efforts to teach CPR to the public is a vital priority for all communities.

There are many obstacles to lay CPR training. Psychomotor skills of CPR are too complex for the lay public and retention of skills by people who do not use them regularly has been disappointing.

There is scientific uncertainty within the literature regarding how good' CPR has to be in order to save a life. Any CPR (chest compression only) is clearly better than no CPR. Therefore a simple, basic, approach that can be effectively taught to the largest number of people will increase the number of individuals willing to attempt BLS.

Most important changes in the international 2000 guidelines:

Circulatory assessment and support. Until recently, all resuscitation guidelines required determination of absence of the carotid pulse as the diagnostic step which leads to the initiation of chest compression.

Recent studies suggest that the time needed to diagnose with confidence the presence or absence of a carotid pulse is far greater than the 5–10 s normally recommended. Even with prolonged palpation, 45% of carotid pulses may be pronounced absent even when present. Most of these studies were done in normotensive volunteers, a situation far different from finding a collapsed and cyanosed victim in the street, who is likely to be hypotensive and vasoconstricted.

As a result of these studies, the international scientific community advises 'de-emphasize' the carotid pulse check in training programmes for lay people and that it should only be taught to health care professionals. Therefore, other criteria should be used by lay people to determine the need for chest compression in an unresponsive, apnoeic, adult, patient. It was decided to use the expression: 'Look for signs of a circulation' which includes seeing for movement, coughing, respiration. The rescuer should limit the time for this check to no more than 10 s.

Chest compressions will be given at a rate of 100/min in adults and children, with the hands positioned at the lower half of the sternum.

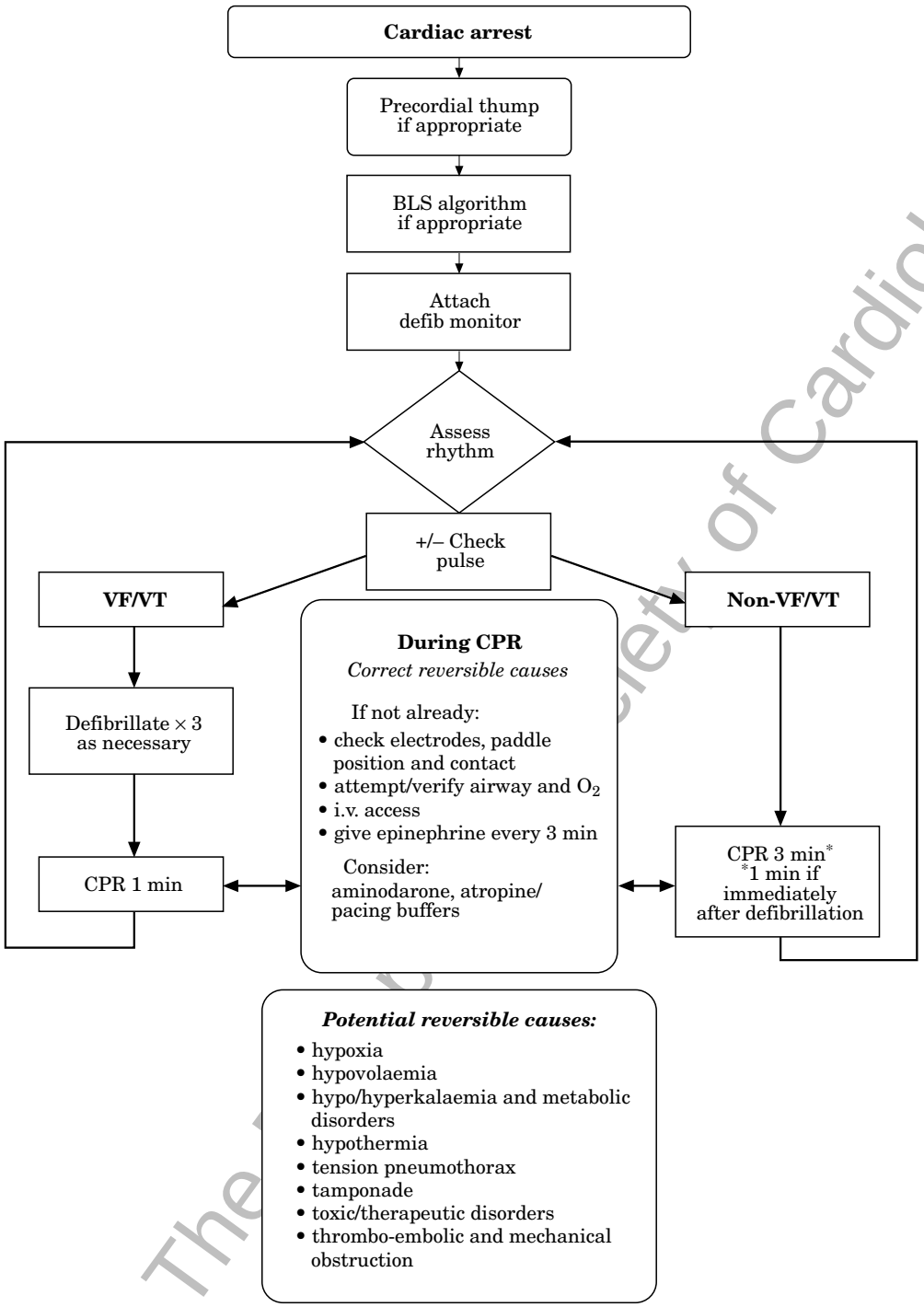

Figure 2 **Algorithm for Advanced Cardiac Life Support (ACLS).**

When combined with mouth-to-mouth ventilation, the ratio is 15 compressions and 2 ventilations. There is convincing evidence from research in animals and in humans, that coronary perfusion pressure during the previously recommended ratio of 5:1 in 2-rescuer CPR is insufficient. This 5:1 ratio is now abandoned in adult BLS CPR[579].

Volume and rate of ventilation. Rescue breathing is a well-accepted technique of airway management in BLS since 40 years. The recommended volume of air to be given with each inflation was usually 800–1200 cc, with each breath taking 1–1·5 s.

Artificial ventilation without airway protection (such as tracheal intubation) carries a high risk of gastric

inflation, regurgitation, and pulmonary aspiration. It has recently been shown that a smaller tidal volume is sufficient to give adequate ventilation in adult basic life support because CO_2 production during cardiac arrest is very low. The current recommendation is that a tidal volume of only 10 ml . kg^{-1} body weight will be given (700–1000 ml); this volume may even be smaller (7 ml . kg^{-1}) if additional oxygen is administered (400–600 ml). This is consistent with the accepted teaching that the tidal volume should be that which causes the chest to rise.

Call first — call fast. The optimum time during a CPR attempt to leave the victim and go for help will depend on whether the rescuer is alone, whether the victim has a primary respiratory or primary cardiac arrest, the distance to the nearest point of aid, the facilities of the EMS.

The importance of early defibrillation in the treatment of SCD is now accepted.

The International 2000 Guidelines advise that the rescuer should shout for assistance as soon as a victim is found to be unconscious, and that the lone rescuer should leave the victim to go for help as soon as respiratory arrest is diagnosed.

In children and in traumatic arrest (including drowning), respiratory arrest is far more common than cardiac arrest and survival will depend mainly upon the immediate delivery of effective rescue breathing, hence the recommendation of 1 minute rescue support before leaving and phoning for help.

Recovery position. The airway of an unconscious victim who is breathing spontaneously is at risk of obstruction by the tongue and from inhalation of mucus and vomit. Placing the victim on the side helps to prevent these problems, and allows fluid to drain easily from the mouth.

Principles for recovery position in the unconscious breathing victim:

1. The position should be a true lateral with the head dependant,
2. The position should be stable,
3. Any pressure of the chest that impairs breathing should be avoided,
4. It should be possible to turn the victim onto the side and return to the back easily,
5. Good observation of and access to the airway should be possible, and
6. The position should not give rise to injury to the victim.

The 1998 European Resuscitation Council guidelines for adult advanced life support

Defibrillation

In adults, the commonest arrhythmia at the onset of cardiac arrest is ventricular fibrillation or pulseless ventricular tachycardia. The majority of eventual survivors come from this group. The only interventions, which unequivocally improve long-term survival, are basic life support and defibrillation. VF is a treatable rhythm, but the chances of successful defibrillation decline substantially with time. The amplitude and waveform of VF deteriorate rapidly reflecting the depletion of myocardial high-energy phosphate stores. The rate of decline in success depends in part upon the provision and adequacy of BLS. As a result, the priority is to minimize any delay between the onset of cardiac arrest and the administration of defibrillating shocks.

At present, the most commonly used transthoracic defibrillation waveforms are damped sinusoidal. Newer techniques such as biphasic waveforms reduce the energy requirements for successful defibrillation. Automated biphasic waveform defibrillators are available and are being evaluated. Their use seems to increase the efficacy of individual shocks[580].

With conventional defibrillators, shocks are delivered in groups of three, the initial sequence having energies of 200J, 200J and 360J.

Other alternative waveforms and energy levels are acceptable if demonstrated to be of equal or greater net clinical benefit in terms of safety and efficacy.

A pulse check is required after a shock only if a change in waveform to one compatible with cardiac output is produced.

With modern defibrillators, charging times are sufficiently short for 3 shocks to be administered within one minute.

Airway management and ventilation

Oxygenation of the patient is the primary objective of ventilation and the aim should be to provide inspired oxygen concentrations (FiO_2) of 1·0.

Tracheal intubation remains the optimal procedure. The laryngeal mask airway (LMA), the pharyngotracheal lumen airway and the Combitube are alternatives but require more training and have specific problems in use. Correct tube placement should be confirmed by a measurement of end tidal CO_2.

The tidal volume with a bag/valve/mask should be 10 ml . kg^{-1} (700–1000 ml) delivered over 2 s (sufficient to make the chest rise clearly). Once supplementary oxygen is available this can be reduced to 7 ml . kg^{-1} (400–600 ml).

Once the patient's airway is secured (by a tube), ventilation need not be synchronized with chest compressions as uninterrupted chest compressions result in substantially higher coronary perfusion.

CPR techniques and adjuncts. There have been and are ongoing trials of new techniques, most notably with active compression–decompression (ACD) CPR, Vest CPR, interposed abdominal compression (IAC) and impedance threshold valve (ITV), but there are at

present no clinical data showing unequivocal improvement in outcomes[578,580].

Precordial thump: a single precordial thump may be performed by professional healthcare providers, in a witnessed or monitored arrest before the defibrillator is attached. It is unlikely to be successful after more than 30 seconds of arrest.

Vascular access: the central veins are the optimal route for delivering drugs rapidly into central circulation. Peripheral venous cannulation is often quicker, easier, and safer to perform. Drugs administered by this route should be followed by a flush of 10–20 ml 0·9% saline. When venous access is not available, adrenaline, atropine, and lidocaine may be given by the tracheal tube. In this case, use higher doses (2–3 times) and dilute the drug in 10 ml of sterile water.

Specific drug therapy

Vasopressors. Experimentally adrenaline improves myocardial and cerebral blood flow and resuscitation rates in animals, and higher doses are more effective than the 'standard' dose of 1 mg. There is no unequivocal clinical evidence that adrenaline improves survival or neurological recovery in humans irrespective of whether standard or high dose is used. Some clinical trials have reported slightly increased rates of spontaneous circulation with high dose adrenaline but without improvement in overall survival rate. Therefore, indications, dosage, and time interval between doses for adrenaline remain unchanged and 1 mg of adrenaline is given every 3 minutes.

Caution should be employed before routinely administering adrenaline in patients whose arrest is associated with solvent abuse, cocaine, and other sympathomimetic drugs.

Experimentally, vasopressin (40U) leads to significantly higher coronary perfusion pressures. Therefore, vasopressin is now accepted as a possible alternative for adrenaline[578].

Antiarrhythmic agents. The evidence supporting the prehospital use of antiarrhythmic drugs in VF or pulseless VT is weak and no agent has been found which improves survival to hospital discharge rates.

When considering the use of antiarrhythmic drugs, certain basic principles apply:

1. Immediate treatment will depend on whether the patient is stable or unstable.
2. Cardioversion is preferred when the patient is unstable.
3. All antiarrhythmic drugs have proarrhythmic properties.
4. The use of more than one antiarrhythmic drug is undesirable.
5. If a drug does not work, defibrillation/cardioversion should be considered.
6. If the patient has impaired myocardial function, most antiarrhythmic drugs will cause further impairment.

Amiodarone is the first choice in patients with VF/VT refractory to 3 initial shocks. 300 mg iv diluted in 20 ml 5% dextrose in bolus is the start dose. An additional 150 mg iv dose (also diluted) may be considered if VF/VT recurs, followed by an infusion of 1 mg . min^{-1} for 6 h and then 0·5 mg . min^{-1}, to a maximum of 2 g.

Magnesium (8 mmol) is recommended for refractory VF if there is a suspicion of hypomagnesaemia e.g. patients on potassium losing diuretics.

Lidocaine and *procainamide* are alternatives if amiodarone is not available but should not be given in addition to amiodarone. Procainamide is given at 30 mg . min^{-1} to a total dose of 17 mg . kg^{-1}. The necessity for this relatively slow rate of infusion makes it a less favoured option.

Bretylium is no longer recommended.

Atropine has a well-established role in the treatment of haemodynamically compromising bradyarrhythmias. Since any adverse effect is unlikely, its use can still be considered in a single dose of 3 mg iv. This dose is known to be sufficient to block vagal activity effectively in fit adults with a cardiac output.

Consider and treat reversible causes

In any cardiac arrest patient, potential causes or aggravating factors for which specific treatment exist should be considered ('the 4 H's and the 4 T's'):

Hypoxia
Hypovolaemia
Hyper/hypokalaemia, hypocalcaemia, acidaemia
Hypothermia
Tension pneumothorax
Cardiac tamponade
Thromboembolic or mechanical obstruction (e.g. pulmonary embolism)
Toxic or therapeutic substances in overdose

Peri-arrest arrhythmias

Specific attention is given to emergency management of arrhythmias that immediately precede or follow a cardiac arrest:

Bradycardias. Transvenous or transthoracic pacing may play a valuable role in patients with extreme bradyarrhythmias, but its value in asystole has not been established, except in cases of trifascicular block where P waves are seen. If external pacing is unavailable, a low dose adrenaline infusion is recommended instead of isoprenaline.

Atrial fibrillation and flutter. The patient is placed into one of three risk groups on the basis of heart rate and the presence of additional signs and symptoms rate >100, 100–150, <150 . min^{-1}; presence of chest pain; presence of breathlessness; presence of poor perfusion).

In high risk patients: attempt electrical cardioversion after heparinization.

In intermediate risk patients, the treatment options depend on the presence or absence of impaired

haemodynamics or structural heart disease and whether the onset of the atrial fibrillation is known to be within the last 24 h.

In low risk patients, cardioversion can be undertaken when the onset of the atrial fibrillation is known to be within the last 24 h. In fibrillation of more than 24 h duration, cardioversion should not be attempted until the patient has been anticoagulated for 3–4 weeks.

Narrow complex supraventricular tachycardia. If the patient is pulseless in association with a narrow complex tachycardia with a rate greater than $250 \cdot min^{-1}$, electrical cardioversion should be undertaken. Otherwise, vagal manoeuvres should be tried first (Valsava manoeuvre, carotid massage).

Adenosine is the first choice drug.

If the patient has adverse signs, attempt electrical cardioversion, supplemented, if necessary, with amiodarone.

In the absence of adverse signs chose one drug from esmolol, verapamil, amiodarone or digoxin.

Broad complex tachycardia. If there is no pulse follow the VF algorithm.

If the patient has adverse signs or the rhythm is unresponsive to drugs (amiodarone or lidocaine), attempt electrical cardioversion.

The international 2000 guidelines for the use of automated external defibrillators (AEDs) by EMS providers and first responders

Defibrillation of the heart is the only effective treatment of VF and pulseless VT. The time between the onset of VF and the first defibrillating shock is the most important variable of the efficacy of this treatment. The objective of the management of out-of-hospital cardiac arrest is to provide electrical defibrillation of the heart as soon as possible after collapse.

The introduction of the automated external defibrillator (AED) allowed less trained emergency medical technicians to deliver electric shocks in cases of out-of-hospital VF or VT, often many minutes before the arrival of the medical intervention team. This strategy is also known as 'first responder defibrillation'.

A first responders is defined as a trained individual, working in a medically supervised system.

First responders can be subdivided as

- traditional first responders: ambulance personnel
- non-traditional first responders: fire-fighter, police, security personnel, airline cabin crew, first aiders
- targeted lay first responders: trained citizens at worksites or public places, family of high risk patients

The AED incorporates an automated rhythm analysis system. The AED is attached to the patient by 2 adhesive pads to analyse the rhythm and to deliver a shock. The information is given by a voice prompt and/or on a visual display and the final delivery of the shock is triggered manually. The specificity of the diagnostic algorithm for VF is about 100%; sensitivity in case of coarse VF is about 90–92%, but is lower in cases of fine VF. Failures of the diagnostic algorithm have been documented when using an AED in patients carrying an implanted pacemaker.

Results of AED programs

Survival after cardiac arrest due to VF when non-medically qualified personnel use an AED have ranged between 0% and 54%[568,573]. These differences could be related to differences in characteristics of the population treated, differences in methodology and quality of registration or real differences in the performance of the AED program.

To be able to compare the reports on the efficacy of AED programs, data on outcome from cardiac arrest must be as uniform as possible[573,581] and should include the performance of the several links of the chain of survival.

Results of AED programs by non-traditional rescuers

In a recent survey of the survival data of 22 European EMS services it was shown that survival to discharge from all types of cardiac arrest ranged between 6% and 23%. Survival from witnessed cardiac arrest of cardiac origin found in VF ranged between 13% and 55% (7 centres reported a survival of more than 30%). Part of these impressive differences might be explained by selection bias and by non-uniformity of definitions. But even taking this caveat into account, high survival rates were obtained in areas where the prevalence of bystander CPR was high, time to defibrillation was short, and the level of training, exposure and experience of the 1st and 2nd tier rescuers was high[568].

These observations strongly suggest that AEDs should not be implemented in EMS systems as an isolated intervention, but should be linked with interventions that strengthen the other links of the chain of survival (early access to the EMS system, early basic CPR by the first witness, and early advanced life support).

AED by police

In many regions in the U.S.A. and Europe, police cars arrive at the site of a collapse several minutes before the arrival of the first ambulance. Encouraging results were obtained by equipping police cars with AEDs. Several authors confirmed that in cases of out-of-hospital cardiac arrest, the police are frequently the first responder

and that defibrillation by police results in shorter time to defibrillation and eventually improved survival[582,583].

AEDs in commercial aircraft

As many as 1000 lives are lost annually from cardiac arrest in commercial aircraft. Recently AEDs were installed in the aircraft of several airlines. Recent reports assessed the impact of making AEDs available for use in airlines for passengers with cardiac arrest. In a report on a 64-month period (Qantas airlines), AEDs were used 63 times for monitoring an acutely ill passenger and 46 times for cardiac arrest. Long-term survival from VF was achieved in 26%. It was concluded that AEDs in aircraft and terminals, with appropriate crew training, are helpful in the management of cardiac emergencies[584,585].

AED by members of the public

The next logical step could be the implementation of AED programs in the community (Public Access Defibrillation, PAD), with involvement of minimally trained lay individuals. Although this approach is technically feasible with the present technology, and seems economically attractive, evaluation of effectiveness and costs in controlled trials are mandatory[586].

Guidelines for the use of AEDs

In cases of sudden cardiac arrest, early defibrillation by the first responding professional rescuer is now well accepted as the standard of care.

In the International 2000 Guidelines for the use of AEDs by EMS providers and first responders it is recommended

- that every ambulance, which might respond to a cardiac arrest, must carry a defibrillator with personnel trained permitted to use it;
- that defibrillation should be one of the core competencies of doctors, nurses and other health care professionals;
- that defibrillators should be widely placed on general hospital wards;
- to investigate the feasibility and efficacy of allowing all those assigned to the management of cardiac arrest in the community to be trained and permitted to defibrillate. Refresher training should be carried out at least every 6 months. Specifically certified instructors working within a medically controlled system should give the training.

Slow implementation of AED in Europe

In Europe, the strategy of early defibrillation with AEDs by ambulance personnel is now implemented community-wide in the U.K., the Netherlands and Scandinavia, and in parts of Germany and Belgium. Pilot experiences are emerging in most other European countries. In some European countries, all ambulances are manned with experienced nurses and/or doctors and are equipped with manual defibrillators.

As a result of these experiences it was recognized that an early defibrillation programme was most likely to be successful if

- the programme is placed under medical control,
- the time interval between cardiac arrest and first CPR is usually <4 min,
- the time interval between cardiac arrest and defibrillation is usually <9 min,
- there is a critical number of interventions,
- there is a programme of training and retraining, and
- there is a programme for monitoring the performance of the programme.

Today AED programs are only partially implemented in Europe and in the U.S. less than 50% of ambulances are equipped with an AED. Major reasons for slow implementation are awareness, organization and legislation.

Electrical defibrillation is the single most important therapy for the treatment of VF. The time interval between the onset of VF and the delivery of the first defibrillating shock is the main determinant of survival. To achieve the goal of early defibrillation, it is mandatory to allow individuals other than doctors to defibrillate. The development of automated external defibrillators (AED) was a major breakthrough in the therapeutic possibilities, and became widely available. Current AEDs are simple, reliable and non-physicians can achieve training in their use in a short time, thus allowing implementation of defibrillation.

Overwhelming scientific and clinical evidence reinforces early defibrillation as the standard of medical practice. The international scientific community has issued guidelines for the use of AEDs by the first responding rescuers. However, in many countries, early defibrillation with an AED by other than physicians is not yet implemented on a nation-wide basis, due to a number of 'real' and 'perceived' obstacles such as law, structure, priorities, economics, tradition and inertia.

- The medical profession is urged to increase awareness of the public, of those responsible for emergency medical services and of those with regulatory powers, to permit changes in practice and legislation where necessary.
- It is essential to integrate the concept of early defibrillation into an effective emergency cardiac care system, which includes early access to the emergency medical services system (EMS), early CPR by the first witness, early defibrillation when indicated, and early advanced care.
- All emergency personnel, should be trained and permitted to operate a defibrillator if their professional activities require that they respond to persons with

cardiac arrest. This includes all first responding emergency personnel working in an organized EMS system, both in and outside the hospital.
- All emergency ambulances that respond to or transport cardiac patients should be equipped with a defibrillator.
- Defibrillation should be a core competence of all health care professionals including nurses, and defibrillators should be widely available on general hospital wards.
- All defibrillator programs must operate within medical control by qualified and experienced physicians. They should ensure that every link of the chain of survival is in place and should have access to all information required to permit system audit.
- To monitor the program, there must be appropriate registration of the interventions according to the Utstein style.

Recommendations for the use of AED in the prevention of sudden cardiac death

	Recommendations	Level of evidence	References
Use by EMS personnel	Class I	B	[568]
Use by police	Class I	C	[582,583]
Use in commercial aircraft	Class I	B	[584]
Use by family members of high risk individuals	Class IIb	C	[376,585]

Conclusions

Although SCD remains a serious public health hazard, major developments in risk stratification and therapy have now made it possible to identify many of those at risk and to provide effective prophylactic treatment. However, the implementation of novel and effective risk stratification and of therapies known to reduce the risk of SCD has been slow and inconsistent. The SCD Task Force has attempted to draw together in one document the substantial evidence-base both for risk stratification and for prophylactic treatment against SCD. The widespread introduction of these recommendations into clinical practice should reduce, but not eliminate SCD.

It is recognized that most of the success in defining risk and improving therapy has so far been achieved in patient groups with considerable pre-existing cardiac disease. Much more work is needed and anticipated in larger populations with less or no apparent heart disease. Effective identification and treatment of these subjects will then lead to a very substantial reduction in SCD in the general population. Epidemiological and clinical investigations in this arena are already underway and will provide much further information on which to base comprehensive strategies for the elimination of SCD.

The most effective treatment that is currently available for SCD is the implantable cardioverter defibrillator. This therapy is generally more effective than drug-based treatments but has not been uniformly adopted, probably because of differing medical priorities in communities that have limited resources. This document emphasizes the outstanding success of ICD therapy and provides cogent information and argument that supports investment in this treatment. It is recognized that ICD therapy cannot be proved against every other treatment in every condition. Obviously some sensible extrapolation is justifiable.

The Task Force expects further development in the therapy for the prevention and emergent treatment of SCD. Improvements in automatic external defibrillators, implantable cardioverter defibrillators and 'antiarrhythmic' drugs will certainly lead to even more effective treatment of those at risk of SCD. In due course it will clearly be necessary to reconvene the Task Force on SCD to reconsider the inevitably more comprehensive evidence base that will accumulate in the next several years.

Recommendations for the use of ICD, amiodarone and beta-blockers in the prevention of SCD

In this section a global view on the recommendation for the use of ICD, amiodarone and beta-blockers in the prevention of SCD is presented. This summary reflects the contents of the document and of the recommendations provided at the end of each section. The term 'primary' prevention and 'secondary' prevention are consistent with the use made throughout the document and refer to patients with/without history of sustained ventricular arrhythmias/ventricular fibrillation.

Implantable cardioverter defibrillator

Disease	Setting	Recommendations	Level of evidence	Reference
Post-MI	Resuscitated VT/VF, Spontaneous sustained haemodynamically non-tolerated VT	Class I	A	[240,242]
Post-MI	Primary prevention — EF <40%, nsVT clinical, sVA at PES	Class I	B	[89,231]
BS	Secondary prevention	Class I	B	[375,376]
BS	Symptomatic for syncope/VT	Class I	B	[375,376]
HCM	Secondary prevention	Class I	B	[285,287]
LQTS	Secondary prevention — ICD+Beta-blockers	Class I	C	[353,358]
AS	Secondary prevention	Class I	C	[397]
MVP	Secondary prevention	Class I	OTFP	
RVC	Secondary prevention	Class I	OTFP	[331]
DCM	Secondary prevention	Class I	OTFP	
CPVT	Secondary prevention (+beta-blockers)	Class I	OTFP	
HCM	Primary prevention	Class IIa	B	[285,287]
DCM	Primary prevention	Class IIa	B	[241,352]
ARVC	Primary prevention — ventricular tachycardia	Class IIa	C	[331,532]
LQTS	Primary prevention — symptomatic with recurrences on beta-blockers	Class IIa	C	[353,365]
BS	Asymptomatic with inducible VT/VF	Class IIb	C	[375,376]
Post-MI	Spontaneous, sustained, well tolerated, monomorphic VT	Class IIb	C	[249]
CPVT	Primary prevention (+beta-blockers)	Class IIb	OTFP	
Post-MI	Primary prevention — EF <36%, late potentials, indication for CABG	Class III	B	[232]
RVC	Primary prevention — asymptomatic -	Class III	C	[331,532]
BS	Asymptomatic with non-inducible VT/VF	Class III	C	[375,376]

RVC=Right Ventricular Cardiomyopathy.
AS=Aortic Stenosis.
BS=Brugada Syndrome.
CPVT=Catecholaminergic Polymorphic Ventricular Tachycardia.
DCM=Dilated Cardiomyopathy.
HCM=Hypertrophic Cardiomyopathy.
ICD=Implantable Cardioverter Defibrillator.
LQTS=Long QT Syndrome.
MVP=Mitral Valve Prolapse.
Post-MI=Post Myocardial Infarction.
OTFP=Opinion of the Task Force Panel.

Beta-blockers

Disease	Setting	Recommendations	Level of evidence	Reference
Post-MI	Primary prevention — in presence of heart failure	Class I	A	[184,193,74,186,197,199,202,203]
Post-MI	Primary prevention — during and post-MI	Class I	A	[74,186,193,199,202,203]
DCM		Class I	B	[186]
LQTS	Primary prevention — symptomatic	Class I	B	[353,358]
LQTS	Secondary prevention — beta-blockers+ICD	Class I	C	[353,358]
Post-MI	Resuscitated VT/VF, spontaneous sustained VT*	Class IIa	C	[242]
LQTS	Primary prevention — asymptomatic	Class IIa	C	[358]
MB		Class IIa	C	[435]
CPVT	Primary prevention	Class IIa	C	[380]
CPVT	Secondary prevention (consider also ICD)	Class IIa	C	[380]
RVC	Primary prevention	Class IIb	C	[319]
HCM	Primary Prevention	Class III	C	[253,256,257,259]

*: as alternative to implantable defibrillators when the device is not implanted.
RVC=Right Ventricular Cardiomyopathy.
CPVT=Catecholaminergic Polymorphic Ventricular Tachycardia.
DCM=Dilated Cardiomyopathy.
HCM=Hypertrophic Cardiomyopathy.
ICD=Implantable Cardioverter Defibrillator.
LCSD=Left Cardiac Sympathetic Denervation.
LQTS=Long QT Syndrome.
MB=Myocardial Bridging.
MVP=Mitral Valve Prolapse.
Post-MI=Post Myocardial Infarction.

Amiodarone

Disease	Setting	Recommendations	Level of evidence	Reference
Post-MI	Primary prevention	Class IIa	A*	[187,207–212]
Post-MI	Resuscitated VT/VF, spontaneous VT	Class IIa	C**	[239–242]
AS		Class IIa	OTFP	
HCM		Class IIb	B	[294,213,293]
DCM		Class IIb	B	[212,241]
RVC	Primary prevention	Class IIb	OTFP	
WPW		Class IIb	OTFP	

*Reduced SCD, modest impact on total mortality.
**As alternative to implantable defibrillators when the device is not implanted.
RVC=Right Ventricular Cardiomyopathy.
AS=Aortic Stenosis.
BS=Brugada Syndrome.
DCM=Dilated Cardiomyopathy.
HCM=Hypertrophic Cardiomyopathy.
Post-MI=Post Myocardial Infarction.
WPW=Wolff–Parkinson–White Syndrome.
OTFP=Opinion of the Task Force Panel.

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Appendix 1

List of acronyms of clinical cardiovascular trials quoted in the document

4S	Scandinavian Simvastatin Survival Study
AFCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
AIMS	APSAC Intervention Mortality Study
AIRE	Acute Infarction Ramipril Efficacy
ASPECT	Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) research group
ASSET	Anglo-Scandinavian Study of Early Thrombolysis
ATLAS	Assessment of Treatment with Lisinopril And Survival
ATRAMI	Autonomic Tone and Reflexes After Myocardial Infarction
AVID	Antiarrhythmics Versus Implatable Defibrillator
BASIS	Basel Antiarrhythmic Study of Infarct Survival
BBPP	Beta Blocker Pooling Project
BEST	Beta-blocker Evaluation of Survival Trial
CABG Patch	Coronary Artery By Pass Graft Patch Trial
CAMIAT	Canadian Amiodarone Myocardial Infarction Arrhythmia Trial
CAPRICORN	CArvedilol Post infaRct survIval COntrol in left ventRicular dysfuNction
CARDIA	Coronary Artery Risk Development In (Young) Adults
CARE	Cholesterol and Recurrent Events
CASCADE	Cardiac Arrest in Seattle: Conventional vs Amiodarone Drug Evaluation
CASH	Cardiac Arrest Study Hamburg
CAST	Cardiac Arrhythmia Suppression Trial
CHF-STAT	Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy
CIBIS	Cardiac Insufficiency Bisoprolol Study
CIDS	Canadian Implantable Defibrillator Study
CONSENSUS	COoperative New Scandinavian ENalapril SUrvival Study
DAVIT	DAnish Verapamil Infarction Trial
DIAMOND-HF	Danish Investigators of Arrhythmia and MOrtality oN Dofetilide — during Heart Failure
DIAMOND-MI	Danish Investigators of Arrhythmia and MOrtality oN Dofetilide — after Mycardial Infarction
DIG	Digitalis Investigation Group study
DINAMIT	Defibrillator IN Acute Myocardial Infarction Trial
EPIC	Evaluation of c7E3 for the Prevention of Ischemic Complications study group
EPISTENT	Evaluation of Platelet IIb/IIIa Inhibitor for STENting
EMIAT	European Myocardial Infarction Amiodarone Trial
EPAMSA	Argentine Pilot Study of Sudden Death and Amiodarone
ESVEM	The Electrophysiologic Study Vs Electrocardiographic Monitoring
FRISC	Fragmin during Instability in Coronary Artery disease Study
FTT	Fibrinolytic Therapy Trials
GEMICA	Grupo de Estudio Multicentrico de la Insuficiencia Coronaria en Argentina
GESICA	Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina
GISSI	Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto miocardico
GISSI-Prevenzione	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico
GUSTO-I	Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary Artery
GUSTO	Global Use of Strategies To open Occluded coronary arteries
ISAM	Intravenous Streptokinase in Acute Myocardial infarction
ISIS	International Study of Infarct Survival
LIPID	Long-term Intervention with Pravastatin in Ischemic Disease
LIMIT II	Leicester Intravenous Magnesium Intervention Trial
MADIT	Multicenter Automatic Defibrillator Trial
MERIT-HF	MEtoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure
MPIP	Multicenter Post Infarction Program
MUSTT	Multicenter Unsustained Tachycardia Trial Investigation
PAMI	Primary Angioplasty in Myocardial Infarction
PROMISE	Prospective Randomized Milrinome Survival Evaluation Trial
RALES	Randomized Aldactone Evaluation Study Investigators
RAPPORT	ReoPro and Primary PTCA Organization and Randomized Trial
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
SOLVD	Studies Of Left Ventricular Dysfunction

STENTIM	French Registry of Stenting in Acute Myocardial Infarction
SWORD	Survival With of ORal D-sotalol
TIMI	Thrombolysis In Myocardial Infarction
TRACE	TRAndolapril Cardiac Evaluation
UCARE	Unexplained Cardiac Arrest Registry of Europe

Appendix 2

List of abbreviations used in the document

AA	Antiarrhythmic Agent(s)
ACE	Angiotensin Converting Enzyme
AED	Automatic External Defibrillator
AMI	Acute Myocardial Infarction
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
AS	Aortic Stenosis
AV	Atrio Ventricular
BBB	Bundle Branch Block
BRS	Baro-Reflex Sensitivity
CA	Cardiac Arrest
CABG	Coronary Artery By-pass Graft
CCHB	Complete Congenital Heart Block
CI	Confidence Intervals
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
CPR	Cardiopulmonary Resuscitation
DHA	Docosahexaenoic acid
ECG	Eletrocardiogram
EF	Ejection Fraction
EMS	Emergency Medical Service
EPA	Eicosaperntaenoic acid
HV	His-Ventricle
HCM	Hypertophic Cardiomyopathy
HRV	Heart Rate Variability
ICD	Implantable Cardioverter Defibrillator
IHD	Ischaemic Heart Disease
IVF	Idiopathic Ventricular Fibrillation
LBBB	Left Bundle Branch Block
LCSD	Left Cardiac Sympathetic Denervation
LDL	Low Density Lipoproteins
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
LQTS	Long QT Syndrome
MI (post-MI)	Myocardial Infarction
MVP	Mitral Valve Prolapse
NPV	Negative Predictive Value
NYHA	New York Heart Association
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PES	Programmed Electrical Stimulation
PPV	Positive Predictive Value
PTCA	Percutaneous Transluminal Coronary Angioplasty
PVCs	Premature Ventricular Contractions
PUFA	Poly-Unsaturated Fatty Acids
QTc	Rate Corrected QT Interval (according to Bazzett formula)
RBBB	Right Bundle Branch Block
RF	Radio Frequency
RR	Relative Risk
RV	Right Ventricle
RVC	Right Ventricular Cardiomyopathy
SAECG	Signal Averaged Electrocardiogram
SCD	Sudden Cardiac Death
SND	Sinus Node Dysfunction
SDNN	Standard Deviation of Normal RR Intervals
sVA	Sustained Ventricular Arrhythmias
TdP	Torsades de Pointes
TWA	T Wave Alternans
VF	Ventricular Fibrillation
VTns	Non-sustained Ventricular Tachycardia
VTs	Sustained Ventricular Tachycardia
WPW	Wolff–Parkinson–White