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Sudden cardiac death: epidemiology and risk factors

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Abstract

Sudden cardiac death (SCD) is an important public-health problem with multiple etiologies, risk factors, and changing temporal trends. Substantial progress has been made over the past few decades in identifying markers that confer increased SCD risk at the population level. However, the quest for predicting the high-risk individual who could be a candidate for an implantable cardioverter-defibrillator, or other therapy, continues. In this article, we review the incidence, temporal trends, and triggers of SCD, and its demographic, clinical, and genetic risk factors. We also discuss the available evidence supporting the use of public-access defibrillators.

Introduction

Sudden cardiac death (SCD) is a common and devastating event, often occurring in the prime of life and having profound consequences for surviving members of the individual's family. Out-of-hospital SCD is the cause of more than 60% of all deaths from cardiovascular disease, which is the leading cause of death worldwide.[1–4] In the past few decades, substantial progress has been made in our understanding of SCD and in its prevention and management. Multiple clinical, structural, autonomic, and genetic risk factors have been identified and the use of automated external defibrillators (AEDs) and implantable cardioverter-defibrillators (ICDs) has increased. However, SCD continues to be an important public-health problem, largely because the majority of SCDs occur in individuals without previously diagnosed heart disease who do not meet the high-risk criteria defined by clinical trials and cohort studies.[5,6] Moreover, risk stratification of individuals lacks specificity and research into the genetics of sudden cardiac death is still at a very early stage. Thus, prevention of SCD hinges upon public-health interventions focused on the primary and secondary prevention of cardiovascular diseases.

The epidemiological, or population, approach to the investigation of cardiovascular disease was established in the 1940s and 1950s by Dawber and coworkers in the Framingham Heart

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Competing interests

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Study and by Keys and colleagues in the Seven Countries Study.[7] These investigations provided community-based data on the incidence, course, and prognosis of cardiovascular disease and helped to identify risk factors and gain insights into pathogenesis.[7] Much of the established knowledge on SCD, including its genetic origins, comes from epidemiological studies. Moreover, owing to temporal trends in the incidence and prognosis of coronary heart disease (CHD), diabetes mellitus, hyperlipidemia, and obesity, the epidemiology of SCD has also seen substantial fluctuation. In this article, we review the incidence, temporal trends, triggers, and time-dependency of SCD. We will also summarize the demographic, clinical, and genetic risk factors for SCD and the evidence supporting the use of public-access defibrillators.

Definition and incidence

The widely-accepted definition of SCD is unexpected death that occurs within 1 h from the start of symptoms when death is witnessed, and within 24 h of being seen alive and well when it is unwitnessed.[8] Most deaths that meet this definition are caused by cardiac arrhythmias, including those resulting from acute myocardial infarction. However, other potential causes, such as stroke, pulmonary embolism, aortic rupture, and drug or alcohol intoxication, need to be considered, although excluding these noncardiac causes of death is often difficult. The majority of SCDs are not witnessed and, if they are observed, the accounts obtained from witnesses may be unreliable. Furthermore, in many cases, medical records are unavailable, autopsy is not performed, and the cause of death given on the death certificate is speculative of the underlying event.[2,9,10]

The incidence of SCD has been estimated to be between 300,000 and 450,000 annually in the US.[1,3,11] These retrospective assessments are based on the assumption that all out-of-hospital deaths, for which CHD is given as the primary cause of death on the death certificate, are SCDs. This approach has been shown to be sensitive, but not specific, for identifying SCD.[11–14] Thus, these retrospective figures are likely to be an overestimate of the true SCD incidence in the community. Conversely, limiting the definition of SCD to deaths that occur within 1 h of symptom onset might be too restrictive and exclude many unwitnessed cases. The incidence figures obtained from studies of sudden cardiac arrest (range 40–90 SCDs per 100,000 individuals), which are based on data collected from first responders, could also be an underestimate because these statistics do not include unwitnessed SCDs or deaths not attended by emergency medical personnel.[15–17] Thus, multiple sources of ascertainment are needed in order to determine the true incidence of SCD.[5] Indeed, in two prospective community studies that used multiple sources to identify SCD, the annual incidence of SCD was lower than previously reported estimates—100 deaths per 100,000 among 20–75 year-old residents of Maastricht, the Netherlands,[18] and 53 deaths per 100,000 among residents of Multnomah County, OR, USA.[11] Data from community studies in China and Ireland, which also used multiple sources to identify SCD, indicate that SCD incidence is 40–50 per 100,000 persons annually.[19,20] Furthermore, SCD occurred in 6.8% of the ~5,000 individuals in the Framingham Heart Study over ~50 years of follow-up[13,21] and in 4.4% of the ~7,000 individuals in the Paris Prospective Study over 23 years of follow-up.[22] On the basis of these figures, the annual incidence of sudden

cardiac death in the US (total population ~320 million) would range between 180,000 and 250,000 cases per year.[2]

Deaths from CHD have declined markedly over the past several decades. This change is largely attributable to improvements in the primary and secondary prevention of CHD and to progress in acute treatment strategies.[23–25] The incidence of SCD has also declined, in parallel with the decline in CHD mortality.[14,21,23] A 49% decrease in the risk of SCD over 50 years was observed in the Framingham Heart Study.[21] The temporal decline in SCD was more pronounced among patients with known CHD than in those without CHD,[14] and was greater among men than women.[1] Despite the reduction in the absolute rate of SCD, the incidence of SCD as a proportion of overall cardiovascular deaths has increased, because in-hospital mortality has declined more rapidly than out-of-hospital mortality (Figure 1). Therefore, SCD now accounts for more than half of all CHD deaths.[1] These trends underscore the need for a renewed emphasis on primary prevention of CHD. Although survival after cardiac arrest has not changed appreciably in the past three decades, the long-term prognosis of those who survive to hospital discharge after a sudden cardiac arrest has improved.[26] In Olmsted County, MN, USA, the 5-year survival of patients who had an out-of-hospital cardiac arrest with ventricular fibrillation and survived to be discharged from the hospital was 79%, equal to age, sex, and disease-matched individuals without cardiac arrest.[26] These data highlight the successes of secondary prevention and ICD therapy.[27]

Age, sex, and race

The age distribution of SCD demonstrates peaks during infancy and after the age of 45 years (Figure 2). In adults, the risk of SCD increases with age and mirrors the incidence of CHD.[8,11] In the young (<30 years of age), however, the most common causes of SCD include cardiomyopathies, coronary anomalies, primary arrhythmogenic disorders, and drug abuse, rather than CHD.[28] Middle-aged men have a fourfold greater risk of SCD when compared with women of the same age.[8] However, this difference decreases with age, possibly as a result of the postmenopausal development of CHD in women. Furthermore, an increase in the proportion of out-of-hospital CHD deaths occurring in women has been observed since the 1970s.[11,29] This shift is attributed to a lower rate of decline in total mortality and SCD incidence among women in comparison with men, for reasons that are as yet unclear (Figure 1).[1,15]

Racial differences in the incidence of SCD have not been well investigated. The available data from death certificates suggest that, for both sexes, SCD is more common among black Americans than white and Hispanic Americans.[1,30] Moreover, in the US, black patients with in-hospital cardiac arrest are significantly less likely to survive to hospital discharge, are less likely to survive after cardiopulmonary resuscitation (CPR), and have lower rates of postresuscitation care than white patients.[31] This racial difference in outcomes substantially decreases after adjustment for the effect of the hospital site at which patients received care.[31]

Temporality and variation in rhythm

Approximately 80% of all SCDs occur in the home and around 60% are witnessed.[18,32–34] Several studies have demonstrated that there is a heightened risk of SCD on Mondays, in the early hours of the morning (0500 h to 0900 h), and during the winter months, with particular association with lower temperatures (<0 °C).[35–38] These temporal variations are thought to be secondary to increased ischemia owing to factors such as increased adrenergic activity. Overall, relatively few people who experience a sudden cardiac arrest receive CPR from a bystander, and this action is more likely to occur in public places than in the home.[18,32,39]

In most cases, SCD is thought to be the consequence of ventricular tachycardia, degenerating to ventricular fibrillation and subsequent asystole. In a study of confirmed cardiac arrest, where a defibrillator was used within 3 min of cardiac arrest, the initial rhythm was ventricular tachycardia or fibrillation in 71% of individuals, asystole in 18%, and pulseless electrical activity in 11%.[40] However, there was a 43% decline in the incidence of ventricular fibrillation as the causative rhythm disturbance between 1980 and 2000 among patients treated for out-of-hospital cardiac arrest in Seattle, WA, USA.[15] In the year 2000, only 41% of the cardiac arrests were due to ventricular fibrillation.[15] Similar reductions in the incidence of ventricular fibrillation in Finland and Sweden have also been reported.[41,42] The reasons for this change are speculative, but could be related to aging of the population with a higher prevalence of comorbidities, including heart failure. Whereas ventricular fibrillation can be a manifestation of ischemia, asystole is often the initial rhythm in cardiac arrest caused by heart failure.

SCD after myocardial infarction

Acute ST-segment elevation myocardial infarction (MI) is associated with ventricular arrhythmias and cardiac arrest. The risk of SCD is highest in the first 30 days after MI, and decreases gradually with time.[43–45] Among survivors of MI with left ventricular (LV) dysfunction or heart failure, the risk of SCD has been reported to be 1.4% in the first 30 days, but 0.14% per month after 2 years.[44] In a community-based cohort, the risk of SCD was 1.2% within the first month after MI, markedly exceeding the incidence in the general population[43] (Figure 3). Thereafter, however, the SCD risk declined markedly to 1.2% per year, which is lower than expected in the general population (~3% per year). This risk reduction is largely the result of secondary prevention measures, the early death of patients with severe disease, or both. Classic teaching is that arrhythmias in the first 12–24 h after MI do not predict SCD, although this notion has been challenged.[46] Current practice guidelines recommend assessing LV function 6 weeks after MI to determine whether ICD implantation for primary prevention of SCD is recommended. Zaman *et al.* showed that ventricular tachycardia, induced during programmed electrical stimulation (which was performed to risk stratify patients early after MI and subsequent revascularization), identifies those at high risk of SCD who are likely to benefit from ICD implantation.[47]

The incidence of SCD after MI has decreased over the years in parallel with the decline in CHD mortality and SCD in the general population.[43] In a study by Marcus and colleagues, which was conducted in the 1980s, approximately 10% of MI survivors died suddenly

during the 4-year follow-up period.[48] This rate has now decreased to less than 1% per year among patients who receive optimal medical therapy and revascularization.[49,50] Indeed, in Olmsted County, MN, USA, the risk of SCD after MI has declined by more than 40% over the past 25 years.[43] This decline predates the widespread use of ICDs, but parallels the increased use of reperfusion therapy and secondary prevention measures after MI. In the 1980s, 40–50% of deaths after MI were caused by sudden cardiac arrest,[48,51] but the proportion of SCDs has decreased to 20–30% in more contemporary cohorts.[43,49,50]

The concept of 'dynamic risk profiling' after MI relates to changes in the presence and power of risk markers over time, including LV remodeling, changes in the anatomical and electrophysiological properties of the myocardial scar, and progression of CHD.[6] Indeed, the risk of SCD beyond the first 30 days after MI is markedly increased by the presence of concomitant heart failure and ischemic events, which occur frequently during follow-up.[43,50–53] Among participants of MADIT-II[52] who were randomly assigned to receive an ICD, heart failure and recurrent ischemia were associated with a 2.5-fold and 1.5-fold higher risk of appropriate shocks for ventricular tachycardia or fibrillation, respectively. Also, among residents of Olmsted County, MN, USA who survived an MI, the occurrence of heart failure was associated with a fourfold increase in SCD risk, with the majority of SCDs occurring within 30 days of the heart failure episode.[43] These findings underscore the importance of continued surveillance and dynamic risk profiling of patients after MI.

Risk factors for SCD

Clinical risk predictors

Most people who suffer SCD have CHD. In around 50% of cases, SCD is the first clinical manifestation of heart disease.[18] Therefore, it is not surprising that clinical risk factors for SCD are also predictors of CHD-related death and all-cause mortality.[6] Indeed, risk factors such as, older age, male sex, cigarette smoking, hypertension, diabetes mellitus, hypercholesterolemia, obesity, and family history of CHD have all been associated with an increased risk of SCD.[8,22,53–55] Although these risk factors are powerful predictors at a population level, they are not specific enough to determine risk in an individual patient because of relatively low event rates (that is, low absolute risk). Additional SCD risk factors, such as LV dysfunction, history of heart failure, LV hypertrophy, poor functional status, elevated heart rate, an abnormal electrocardiogram, and abnormal autonomic markers, also lack the specificity to discriminate SCD from non-sudden death.[3,8,56–59] Only a small proportion of SCDs occur in patients with known markers of high-risk for arrhythmia[5] (Figure 4). Thus, in the absence of specific single markers, a multimarker strategy may be necessary to identify individuals with high SCD risk. Indeed, Buxton *et al.*[56,57] and others have created multivariable risk algorithms for SCD that are based on retrospective analyses of large clinical trials.[60–62] The markers in their algorithm were age, functional class, history of heart failure, nonsustained ventricular tachycardia, LV ejection fraction, LV conduction abnormalities, inducible sustained ventricular tachycardia, and atrial fibrillation. However, these algorithms are yet to be validated prospectively in large population studies.

Autopsy findings

Autopsy studies have shown that approximately 80% of adults who suffer SCD have severe CHD,[8,63] 10–15% have dilated or hypertrophic cardiomyopathy, and 5–10% have structurally normal hearts, suggesting that a primary arrhythmogenic disorder was the cause of death.[1] A substantial proportion (10–80%) of those with CHD have intracoronary plaque rupture, thrombus formation, or both, which are indicative of an acute coronary syndrome,[63–65] and around 30% have myocardial scar from a previous MI, creating a substrate for ventricular tachycardia.[65] LV hypertrophy, inflammation, infiltrative diseases (such as amyloidosis), and interstitial fibrosis are other structural abnormalities that create a potential substrate for ventricular arrhythmias.[66–68] Although clinical reports suggest that cardiac structural abnormalities are absent in up to 10% of survivors of sudden cardiac arrest and those who died suddenly,[2,3,8] careful evaluation of clinical history has revealed potential risks for SCD in the majority of these patients.[66] For example, Shen *et al.* reported that 33% of 20–40 year-olds who suffered SCD had a history of cocaine abuse.[28]

Heart failure

More than 5 million people in the US have heart failure, and around 600,000 new cases occur annually.[69] The process of remodeling in heart failure, which encompasses cellular, structural, and electrical changes in the myocardium, and neurohormonal activation, provide a suitable milieu for arrhythmogenesis.[70] Consequently, clinical heart failure leads to a fivefold increase in SCD risk.[43,71] Furthermore, SCD accounts for 30–50% of all deaths in patients with heart failure.[71] With advancing symptoms and decompensation of heart failure, however, the proportion of deaths that are classified as SCD decrease whereas those caused by heart failure itself increase. Reports suggest that 64% of patients with mild symptoms of heart failure die suddenly as opposed to 33% of those with severe symptoms.[5] Increased levels of brain natriuretic peptide—a biomarker secreted in response to ventricular stretch—was associated with an increased risk of SCD in patients with LV dysfunction and heart failure, and among women who participated in the Nurses' Health Study.[72–74]

Severe LV dysfunction, caused by ischemic or non-ischemic cardiomyopathy, is also a marker of elevated SCD risk.[75] In current practice guidelines, an LV ejection fraction of less than 35% is a major criterion for ICD therapy.[75] However, only 20–30% of ICD recipients in randomized clinical trials receive appropriate ICD shocks over 4 years of follow-up, reducing the positive predictive value of LV dysfunction as a marker.[76,77] Furthermore, in population cohort studies, approximately 65% of those who suffer SCD have either normal or mildly depressed LV function (that is, an ejection fraction of 35–50%).[18,78,79] Therefore, severe LV dysfunction alone is not a sufficiently specific marker for SCD, but could be useful when used with other predictors or as part of a multivariable risk score.[56,61,62]

Electrocardiographic risk predictors

Abnormalities on a 12-lead electrocardiogram raise the suspicion of underlying structural or genetic heart diseases associated with SCD (Box 1). Pathologic Q waves or dynamic ST-segment changes on electrocardiography are indicative of CHD, whereas increased R-wave voltage or prolonged QRS duration are signs of LV hypertrophy and cardiomyopathy, respectively. Left bundle (but not right bundle) branch block or LV hypertrophy on

electrocardiography are associated with a mildly increased risk of SCD (hazard ratio ~1.5 for both).[58,80] In addition, prolonged QRS duration was associated with SCD and ventricular tachyarrhythmias in two large clinical trials,[81,82] and Das *et al.* have suggested that fragmented QRS on electrocardiography is a marker of structural heart disease and predicts SCD.[83]

The electrocardiogram is particularly helpful in diagnosing primary arrhythmogenic disorders, such as the long and short QT syndromes, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and Wolff–Parkinson–White syndrome, all of which are associated with SCD.[8,84,85] These conditions are rare in the community; however, QT-interval prolongation and dispersion, which are more common and indicate prolonged repolarization, have also been associated with SCD in the general population.[2,86,87] Individuals with a corrected QT interval of greater than 440 ms have a 2.3-fold higher risk of SCD than those with corrected QT interval of less than 440 ms, independent of age, sex, heart rate, and drug use.[85] Furthermore, those with QT prolongation in the absence of QT prolonging drugs or diabetes have a fivefold increased risk of SCD.[87]

Abnormal heart rate profile on exercise electrocardiography, late potentials on signal-averaged electrocardiography, microvolt T-wave alternans, and reduced heart rate variability on Holter electrocardiography have all been shown to correlate with increased risk of SCD.[46,88,89] However, these specialized markers have a high negative predictive value and a low positive predictive value. Thus, SCD risk is low with a negative test, but indeterminate with a positive test.

Socioeconomic and psychosocial risk predictors

Low socioeconomic status is associated with an increased prevalence of risk factors for cardiovascular disease, CHD, and cardiovascular mortality.[90] The incidence of out-of-hospital cardiac arrest and SCD are also higher in areas of socioeconomic deprivation than in more affluent areas.[2,91,92] The effect of socioeconomic status on SCD is more marked among individuals younger than 65 years of age.[92] The mechanisms underlying the apparent association between socioeconomic status and SCD probably reflect a confluence of behavioral, environmental, and coronary risk factors, such as smoking and reduced access to health care.

Psychosocial risk factors, such as social isolation, a high degree of life stress, and substantial life changes have also been associated with SCD.[8,93] Among men with complex premature ventricular contractions after MI, those with lower educational status had threefold higher mortality than those who were better educated.[93] Furthermore, individuals who have suffered SCD have been reported to have experienced more life-changing events during the 6 months before SCD than controls.[8] Hostility and history of psychiatric diseases were also associated with an increased prevalence of SCD.[94] Whether the elevated risk of SCD is associated with the presence of CHD risk factors (such as smoking) in this population, or with the potential arrhythmic consequences of psychoactive medications, is yet to be established.[94]

Genetic risk predictors

The genetics of rare arrhythmogenic syndromes associated with SCD, such as long QT syndrome, have been recognized for several decades; however, the possibility of a genetic basis for SCD in the general population has only been proposed in the last 10 years.[22,95–97] Jouven *et al.* found that SCD risk was twofold higher if an individual had one parent who died suddenly, and ninefold higher if both parents died suddenly.[22] This effect was independent of parental history of MI. Dekker *et al.* reported that family history of SCD (odds ratio ~2.5) and cumulative ST-segment deviation (odds ratio ~1.5) were the only differences between patients who had cardiac arrest with acute MI and those who did not.[95] These data, therefore, indicate that heritable factors play an important role in determining SCD risk, possibly because of shared genes that increase vulnerability to life-threatening arrhythmias. The selective effect of family history on SCD risk, independent of MI, suggests that at least some genetic factors may specifically predispose the individual to fatal arrhythmias, rather than the effect being mediated through an increased risk of CHD. Furthermore, the increase in SCD risk with a greater number of relatives affected is consistent with a complex genetic architecture, in which susceptibility alleles increase risk additively.[98]

The genetic origins of complex events, such as SCD, can be explained either by rare variants with strong effects, rare variants with modest effects, or common variants with modest effects.[89] Rare variants with strong effects have been identified in genes that lead to uncommon inherited cardiac diseases associated with increased risk of ventricular arrhythmias and SCD, such as long and short QT syndromes, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia.[89] Molecular characterization of these diseases has provided the evidence that mutations in specific genes predispose the individual to SCD and has increased our understanding of the mechanisms of arrhythmogenesis. However, these rare mutations are subject to negative selection of allele frequency and contribute little to the burden of SCD in the general population.[89,98]

Rare variants with modest effect are ‘less malignant’ variations in the genes responsible for the arrhythmogenic disorders, such as long QT syndrome. These relatively unimportant changes could increase susceptibility to arrhythmias in the general population. Indeed, evidence from autopsy series suggests that those who have suffered apparently idiopathic SCD might harbor mutations in these candidate genes, particularly those described in long QT syndrome.[99–103] Chugh *et al.* identified a mutation in *KCNH2* (*HERG*), which encodes a voltage-gated potassium channel, in 16.7% of 12 adults who had suffered SCD.[99] Tester *et al.* showed that 30% of 49 individuals who died of unexplained sudden cardiac arrest harbored a mutation in one of the genes associated with long QT syndrome, and 14% had a mutation in the ryanodine receptor gene (*RYR2*).[100,101] Furthermore, in the Nurses’ Health Study, rare missense variants in *SCN5A*, which encodes the sodium channel alpha subunit, were detected in 10% of participants who died suddenly versus 1.6% of matched controls.[102] In a community-based study in Hennepin County, MN, USA, missense mutations in genes associated with long QT syndrome, all localized to *SCN5A*, were found in 6% of individuals who suffered SCD.[103] These data support the concept that rare variants with modest effects might not produce an identifiable clinical syndrome in isolation, but

could predispose the individual to acquired long QT syndrome and SCD after exposure to a secondary risk factor, such as a QT-interval-prolonging medication.[89]

Of potentially greater relevance to the general population are common genetic variants with modest effects that could contribute incrementally to SCD risk. Individuals with these gene variants may survive to reproductive age and, therefore, the variant remains unaffected by negative selection and can reach relatively high allele frequency in the population. Splawksi *et al.* identified the S1102Y variant of the sodium channel gene *SCN5A* in 57% of 23 black patients with an arrhythmia, syncope, and QT prolongation versus 13% of healthy control individuals.[104] This variant allele accelerates sodium-channel activation, potentially increasing the likelihood of arrhythmia. In a follow-up autopsy study, the S1102Y allele was found in the *SCN5A* gene of 28% of black individuals without structural heart disease who had suffered SCD, and in only 5.6% of controls who had died suddenly from non-cardiac causes.[105] Common genetic variants in isolation are unlikely to cause SCD because, if they did, strong selection pressure would reduce their allele frequency substantially.[89,98] More probably, these variants contribute only incrementally to the overall risk of SCD by reducing 'repolarization reserve' and predisposing some individuals to SCD through interactions with other risk factors such as ischemia, hypokalemia, or drug exposure.

As discussed above, QT prolongation is a consistent risk factor for SCD in the general population.[86,106] The QT interval—adjusted for heart rate, age, and sex—is normally distributed in the general population and around 35% of QT interval variability is attributable to genetic factors.[107] Common variants in the *KCNH2* (voltage-gated potassium channel) and *NOS1AP* (nitric oxide synthase 1 adaptor protein) genes influence QT interval duration.[106,108–110] However, these variants have a modest effect on QT interval at baseline (ranging from 6 to 12 ms) and an external influence is also likely to be necessary to prolong the QT interval to a degree where the SCD risk increases substantially. Therefore, the available evidence suggests that inheritable factors are partly involved in the pathogenesis of SCD, but the genetic basis of these events in the population is multifactorial and potentially includes the genetics of atherothrombosis and plaque stability, among other factors.[111,112]

Triggers of SCD

The current paradigm in SCD requires the presence of an abnormal myocardial substrate, such as CHD, and a transient external or internal factor that triggers cardiac arrest. While the abnormal substrate is identifiable in most cases of SCD, the transient triggers are not because a substantial proportion of deaths are unwitnessed or the accounts of the witnesses are biased. The majority of individuals who suffer a witnessed SCD report angina, dyspnea, nausea or vomiting, dizziness or syncope, and 'not feeling well' before cardiac arrest.[18,32] In a community-based SCD study in Hennepin County, MN, USA, we observed that 50% of those who died from a sudden cardiac arrest had taken analgesic and anti-inflammatory medications shortly before death, suggesting that they were not feeling well.[103] In the same study, around 30% of those who suffered SCD had smoked in the hours before death, and this risk factor may have acted as a trigger. Indeed, cigarette smoking promotes platelet aggregation and catecholamine surges, increasing the likelihood of plaque rupture, coronary vasospasm, and thrombus formation.[64,113] Symptoms, therefore, often seem to be present

before cardiac arrest, but are tolerated for prolonged periods of time (~75 min) particularly when the individual is at home.[32] These findings underscore the importance of educating patients with cardiovascular disease and their families about the warning signs of impending sudden cardiac arrest and promoting early intervention.

Public-access defibrillators

Prompt defibrillation of an individual who has suffered a sudden cardiac arrest is the most important determinant of survival. For every minute that passes between cardiac arrest and defibrillation, survival decreases by 7–10% without CPR, and by 3–4% with immediate CPR.[114] After 10 min or longer without defibrillation, 95% of patients die. The response times for emergency medical services in most areas of the US are typically 8–15 min; therefore, overall survival after sudden cardiac arrest in most communities is only 5–10%.[33,114] However, patients who are defibrillated within 10 min of cardiac arrest have a 40% chance of surviving to hospital discharge neurologically intact.[26] The long-term survival and quality-of-life scores of these patients are equal to age-matched and sex-matched individuals in the general population.[26]

AEDs are portable, computerized devices that can analyze cardiac rhythm accurately and deliver a biphasic electrical shock in cases of ventricular tachycardia or fibrillation. Studies have shown that AEDs can be easily operated by untrained lay persons.[115,116] Indeed, AED programs at airports and casinos have been associated with 50–75% survival among individuals who suffer an out-of-hospital cardiac arrest when immediate CPR is provided and defibrillation occurs within 3–5 min of cardiac arrest.[40,114,116,117] In the Public Access Defibrillation Trial,[118] volunteer responders from ~1,000 community locations, such as shopping malls or apartment complexes, were randomly assigned to undergo training in CPR alone or to training in CPR plus AED use. Individuals who suffered a cardiac arrest in these communities were twice as likely to survive to hospital discharge when the responder was trained in CPR plus AED use than if the responder was trained in CPR alone.[118] Currently, all federal buildings and airports in the US, and passenger airplanes run by US-based airlines, are legally required to have AEDs. Health and fitness facilities, and schools are also recommended to have AEDs, and many states are passing laws mandating AEDs in public places.

Since most SCDs occur in the home, the Home Automated External Defibrillator Trial[119] was performed to assess whether AED placement at homes of individuals who are at increased risk of SCD would save lives. About 7,000 patients with prior MI who were not candidates for an ICD were randomly assigned to have an AED in their home or to control response (calling the emergency medical services and performing CPR; both groups were trained in this response) in case of a cardiac arrest. After ~3 years, there was no difference in survival between the groups.[119] AEDs were used in only 32 patients, of whom 14 received an appropriate shock and four survived to hospital discharge.[119] Thus, at present, home usage of AEDs is not recommended as a general health policy. However, there is no reason why a strategy of AED use in the home should not work, when there is a willingness to use these devices in the household of the individual at risk.

Conclusions

In the last 60 years much progress has been made in the understanding of the mechanisms, risk factors, and management of SCD. However, despite the progress in knowledge and the temporal reduction in cardiovascular mortality, SCD remains a major public-health problem. One of the challenges is determining the true incidence of SCD in the community, a problem that is exacerbated by the inconsistency of the definition of SCD used by investigators. Thus, consensus on a specific definition for SCD and establishing prospective, community-based surveillance programs using multiple sources to identify cases of SCD would enable more accurate determination of SCD incidence. In addition, a statement by the AHA published in 2008 recommended that all out-of-hospital cardiac arrests should be reportable events.[120]

Another challenge is the accurate identification of the person at risk. Virtually all individual SCD risk markers, including LV ejection fraction, lack specificity. Multimarker SCD risk scores that include demographic, clinical, and laboratory variables could prove to be more useful in identifying persons at risk of SCD. Several such risk scores have been developed and retrospectively tested among participants of large clinical trials,[56,57,61,62,75] but prospective testing in the general population has not been performed. Perhaps the greatest challenge in identifying the high-risk individual lies in the observation that SCD is the first manifestation of cardiac disease for the majority of those who suffer a sudden cardiac arrest. Heart disease surveillance programs and community-wide interventions for risk-factor reduction (for example, smoking cessation) are, therefore, extremely important in reducing the incidence of SCD. Indeed, a slower reduction in mortality from out-of-hospital SCD than for in-hospital SCD, and among those without known CHD than in patients with CHD, suggest that there is room for improvement in the primary prevention of SCD. Finally, survival after sudden cardiac arrest continues to be dismal at ~5% and many individuals do not receive bystander CPR or timely defibrillation. Thus, educating the general public to perform CPR and use AEDs, and increasing their willingness and competence to do so, will be vital to increase survival after sudden cardiac arrest.

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Key points

- Sudden cardiac death (SCD) is a common public health problem that causes more than 60% of all deaths from cardiovascular disease
- Coronary heart disease underlies 80% of SCD cases; SCD is the first manifestation of heart disease in 50% of these individuals
- Prospective surveillance programs, using multiple sources to identify cases of SCD, would enable more accurate determination of SCD burden in the community
- Demographic, clinical, structural, laboratory, and genetic risk factors lack the specificity to identify individuals at high risk for SCD when used alone; multimarker SCD risk scores may improve SCD prediction
- The risk of SCD after a coronary event changes with time, therefore, dynamic risk-profiling is important
- Survival after sudden cardiac arrest is ~5% and many individuals do not receive cardiopulmonary resuscitation or defibrillation; educating the public to use automated external defibrillators will be important to improving survival

Box 1

Electrocardiographic markers of SCD risk

12-lead electrocardiography

- Pathologic Q waves or dynamic ST-segment changes
- Prolonged QRS duration
- Increased R-wave voltage
- Fragmented QRS
- Prolonged QT interval

Exercise electrocardiography

- Reduced heart-rate recovery
- Reduced functional capacity
- Increased ventricular ectopy
- T-wave alternans

Signal-averaged electrocardiography

- Late potentials

Ambulatory Holter electrocardiography

- Reduced heart-rate variability
- Nonsustained ventricular tachycardia

Review criteria

Articles were selected for inclusion in this Review by a search of the MEDLINE database. Key words used in the search were “sudden cardiac death”, and “epidemiology” in combination with additional keywords (such as “genetics”) relating to each subheading of the manuscript. The search was limited to English language articles and human data. No time limits were applied.

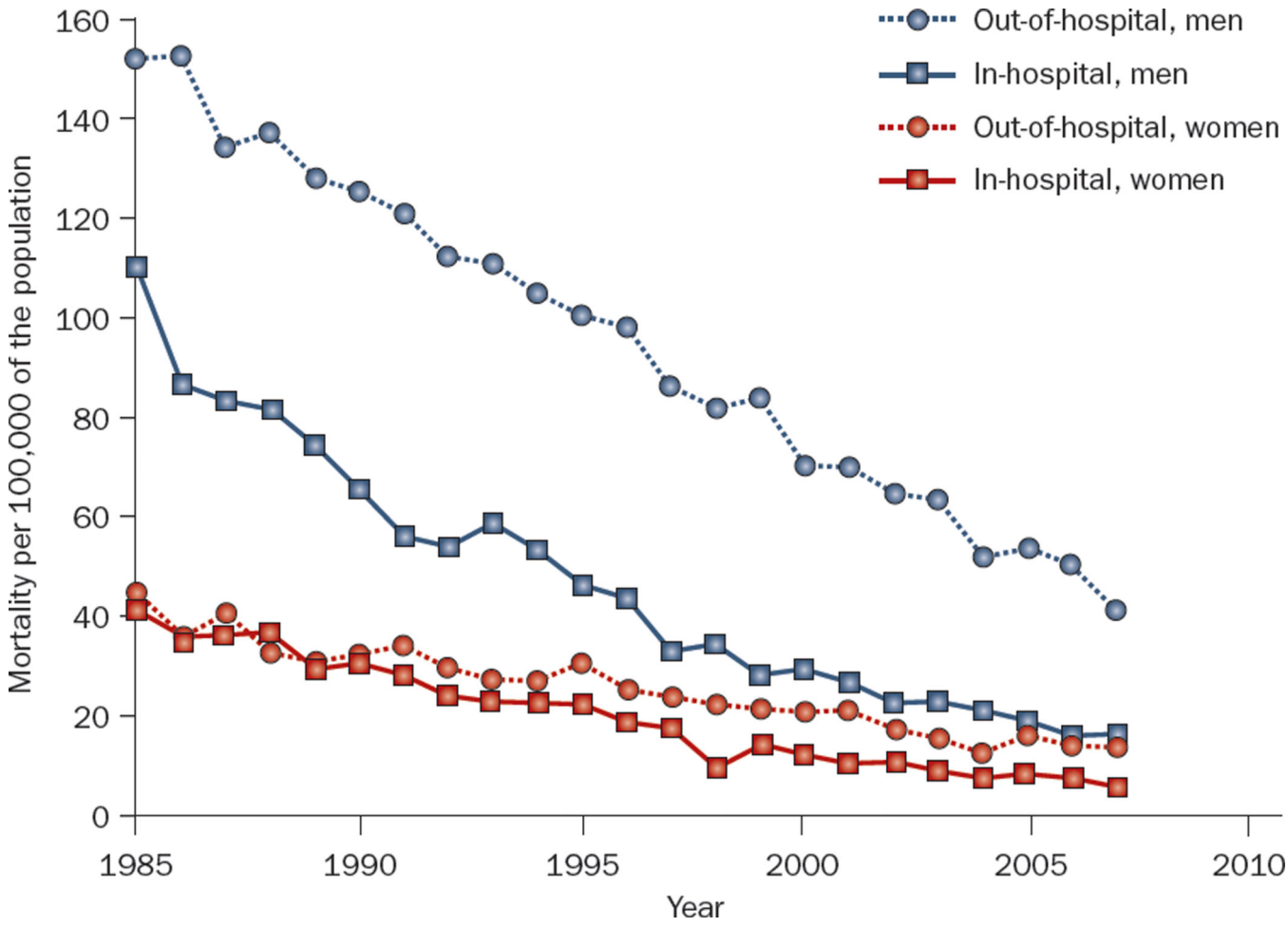

Figure 1.

Temporal trends in in-hospital and out-of-hospital cardiovascular mortality among men and women living in Minneapolis–St Paul, MN, USA.

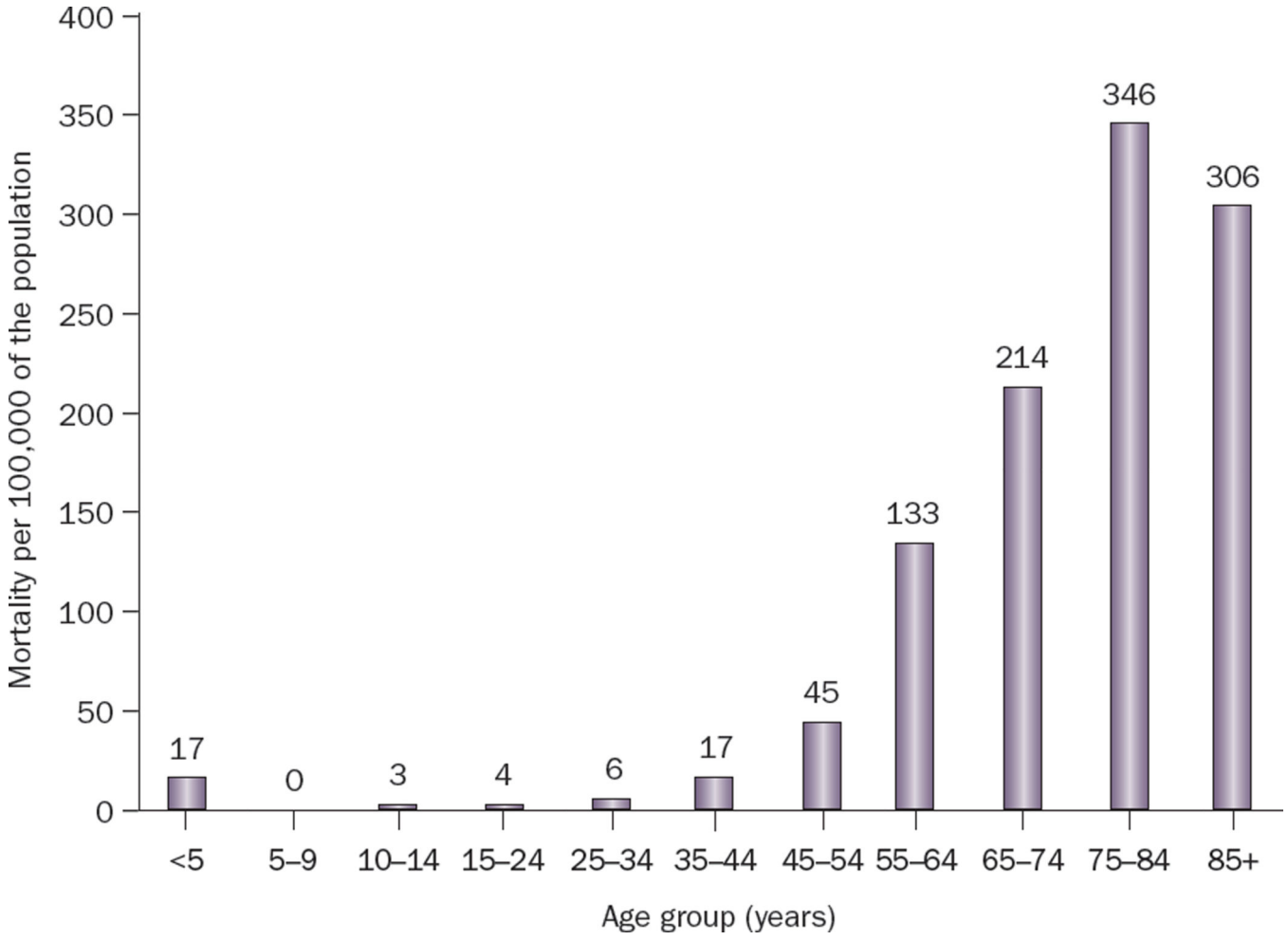

Figure 2.

Age distribution of sudden cardiac death among residents of Multnomah County, OR, USA (population 660,486) between 1 February 2002 and 31 January 2003. Reprinted from the *Journal of the American College of Cardiology*, 44(6), Chugh, S. S. *et al.* Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large US community. 1268–1275 © 2004 with permission from Elsevier and the American College of Cardiology.

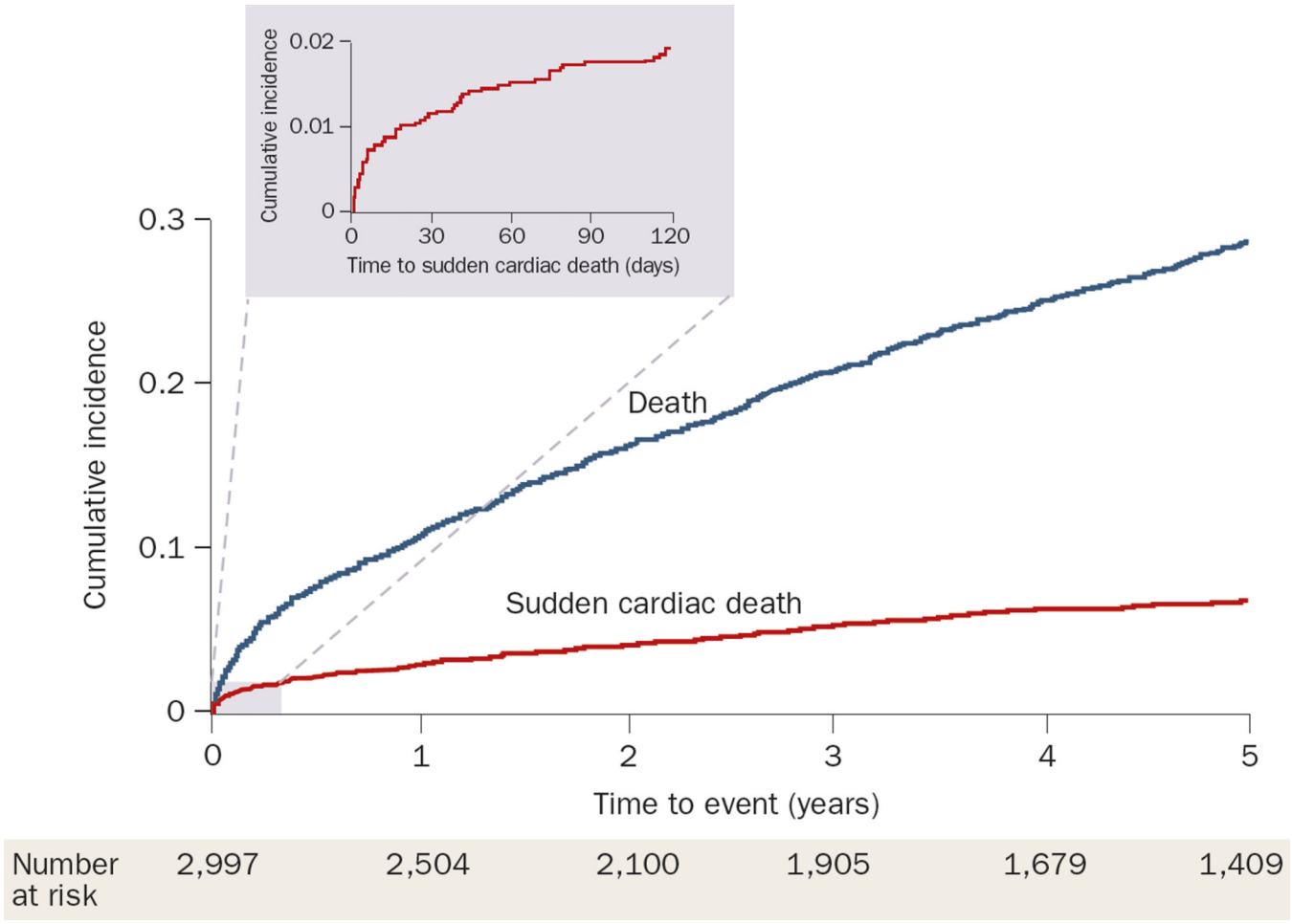

Figure 3.

Cumulative incidence of sudden cardiac death and all-cause mortality after myocardial infarction among residents of Olmsted County, MN, USA. The shaded area represents the cumulative incidence of sudden cardiac death during the first 120 days after the index myocardial infarction. Reproduced from Adabag, A. S. *et al.* Sudden death after myocardial infarction. *JAMA* 5 November 2008; 300(17), 2022–2029. © 2008 American Medical Association. All rights reserved.

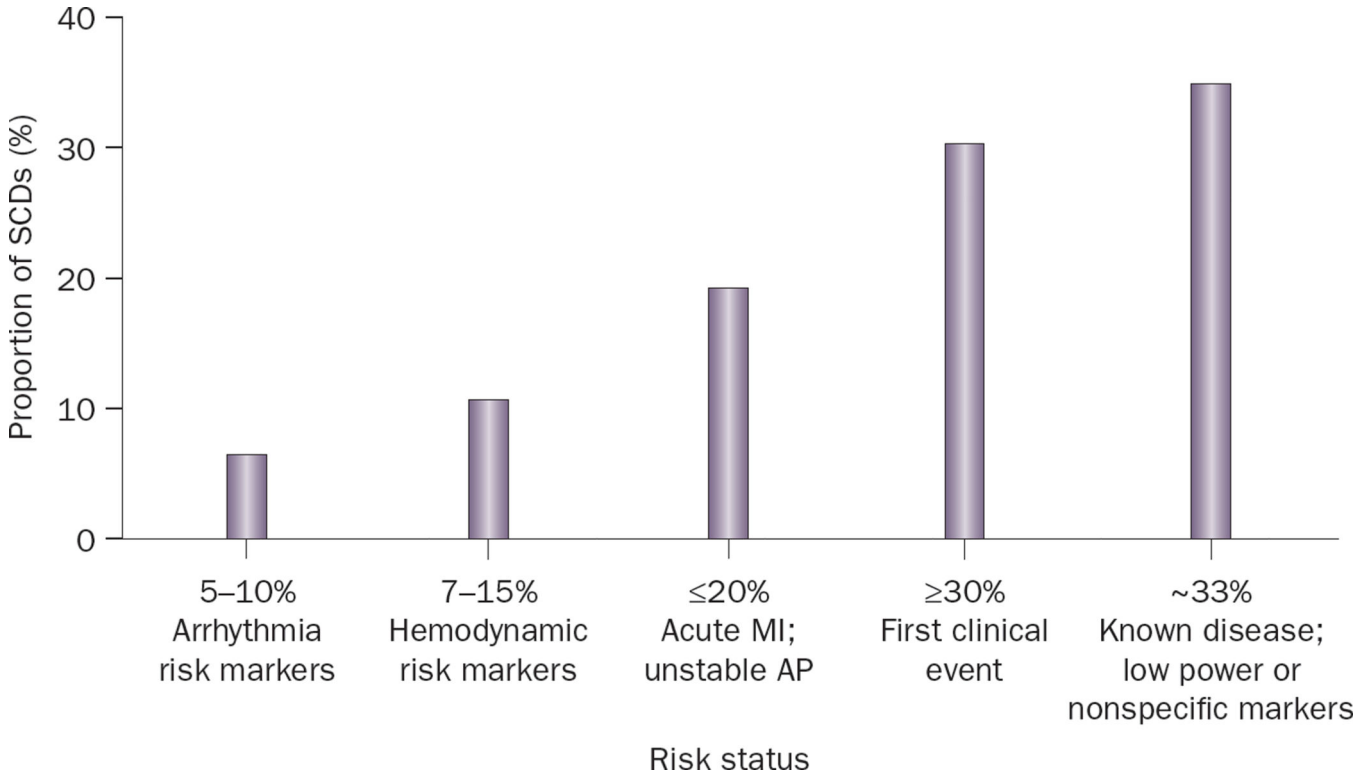

Figure 4.

Distribution of clinical status of individuals who suffer sudden cardiac death. Abbreviations: AP, angina pectoris; MI, myocardial infarction; SCD, sudden cardiac death. Reprinted from *Journal of the American College of Cardiology* 54(9), Myerburg, R. J., Reddy, V. and Castellanos, A. Indications for implantable cardioverter-defibrillators based on evidence and judgment. 747–763. Copyright (2009), with permission from Elsevier and the American College of Cardiology.