2 Epidemiology of Sudden Death

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CONTENTS

INTRODUCTION

Sudden death, mainly out-of-hospital death, is a major public health burden throughout the world. It accounts for 50 to 75% of all fatal cardiovascular disease (CVD) events in countries where data are collected. It is usually unexpected, affecting all age, gender, and ethnic groups *(1)*. The immediate mechanism of death is ventricular fibrillation or ventricular standstill, but the underlying cause is commonly ischemic coronary heart disease (CHD). However, other causes including different forms of cardiac pathology, genetic and environmentally induced, are also well recognized.

Classification of out-of-hospital death is deficient because of its sudden onset and lack of information from the victim. This lack of information limits the accuracy and extent of possible classification, as well as our understanding. Prospective epidemiological studies do provide more pre-event information but still face limited data on the circumstances surrounding the fatality and its causes. Although patients who undergo resuscitation from fatal events provide information, these events are uncommon and patients may be amnestic for the event. At the community or national level, the main sources of information are death certificates with their inherent limitations, and postmortem examination to confirm cause of death is infrequent in most areas.

This chapter will describe the population patterns, trends, and risk factors for out-of-hospital death in CVD. It will discuss the underlying pathophysiology in the population and ongoing attempts to better understand this common problem.

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INCIDENCE/PREVALENCE

Out-of-hospital CVD is the most common cause of death in much of the industrialized world. In the United States, almost 50% of deaths result from CVD and 60–70% of all cardiovascular deaths occur outside of hospitals *(1,2)*. Similar data are observed in the international MONICA study, which includes populations in Europe and Asia as well as North America *(3)*.

The age-adjusted annual rate for out-of-hospital death in the United States in 1998 was 410.6 per 100,000 for men and 274.6 per 100,000 for women *(1)*. These figures differed only modestly from those in the early 1980s as described by Gillum *(4)*.

The determination of rates of out-of-hospital death is based on death certificates. Site of death is a required part of this data collection. Although there may be some misclassification of those who are pronounced dead in the emergency room as in-hospital death, this proportion is thought to be modest at best *(5)*. Data on site of death from death certificates is felt to be of generally high quality.

The age-adjusted rates of out-of-hospital death differ for men and women and by race *(1)*. As shown in Fig. 1 for men, African Americans have the highest rates of out-of-hospital death. They are followed by white Americans and, at a much lower level, Native Americans and Asian Americans. Similar patterns are shown in Fig. 2 for women. However, the age-adjusted rates for women are much lower. This is a function of age-adjustment as out-of-hospital death is common in women but occurs at older ages. Again, African Americans have the highest rate of out-of-hospital death, followed by whites, Native Americans, and Asians.

The difference in out-of-hospital death and in-hospital fatality are shown in Fig. 3. At all the age levels in Scotland, out-of-hospital death exceeds rates of in-hospital death among both men and women *(6)*. Also observed in this study are slightly higher rates of out-of-hospital death for men. This is compensated by somewhat higher in-hospital rates of death for women. Women are more likely to reach the hospital with severe CVD, whereas men are more likely to die at home.

TRENDS

Overall age-adjusted CVD mortality has fallen steadily since the mid-1960s at 1–2% per year (Fig. 4; *7*). Out-of-hospital death rates are also falling in the United States as shown in Figs. 2 and 3. Over the past 30 years, there is a decline in age-adjusted rates of approx 1–2% per year for men and women in all major race and ethnic groups *(1)*.

Although the steady decline indicates progress is being made, it is significantly slower than the improvement of in-hospital mortality. In Fig. 5, data from Minnesota finds in-hospital mortality is falling much more rapidly (2–3% per year) than out-of-hospital death. These data suggest that much greater progress in improving survival is being made once people reach the hospital. The result is that out-of-hospital death constitutes a growing proportion of the burden. This shift is particularly evident among women (Fig. 5).

DEFINITIONS

Although the fact and site of out-of-hospital death are based on reliable data, other information surrounding the event is less available and reliable. Other potentially important data are shown in Table 1. The victim cannot supply much of this data. The data relate

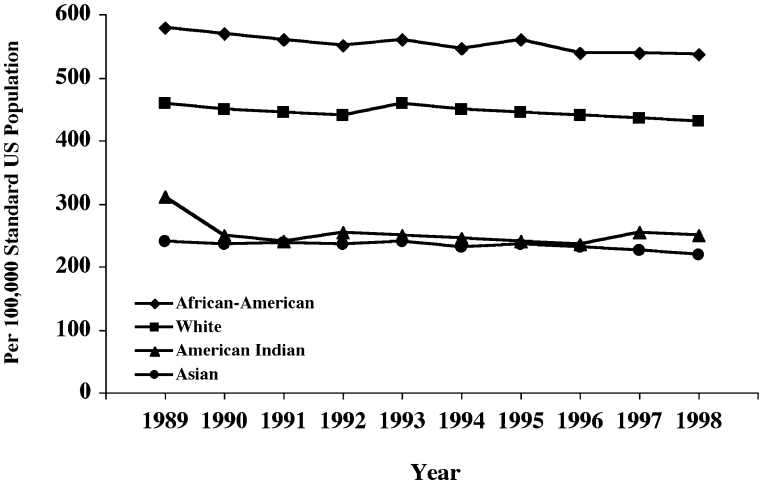

Fig. 1. Men and sudden death trends.

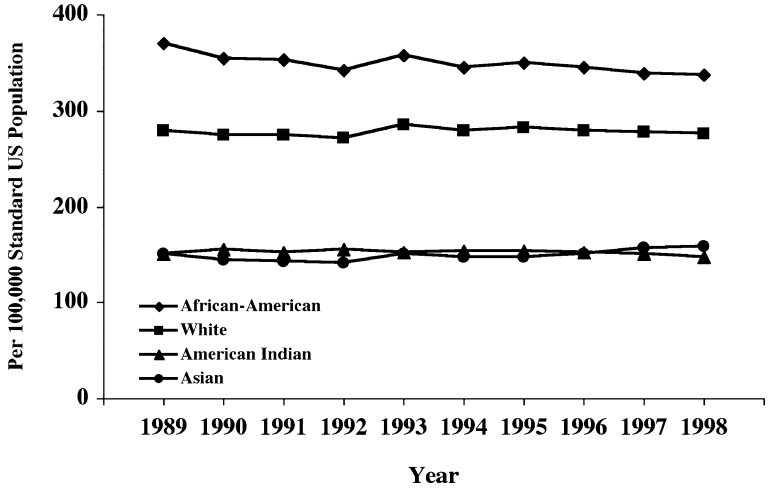

Fig. 2. Women and sudden death trends.

to the circumstances surrounding the event and medical history. Among the most important factors has been timing. Although the classic popular version of out-of-hospital death is sudden and dramatic without early symptoms, such circumstances are probably uncommon. Determining the onset of symptoms to demise is difficult even when the person is under observation. The definition of *sudden*—commonly viewed as less than 1 hour since last seen alive—obscures the nature of the problem.

Many epidemiologists now suggest that a 24-hour window from onset of symptoms or when the victim was last seen alive should define sudden out-of-hospital death.

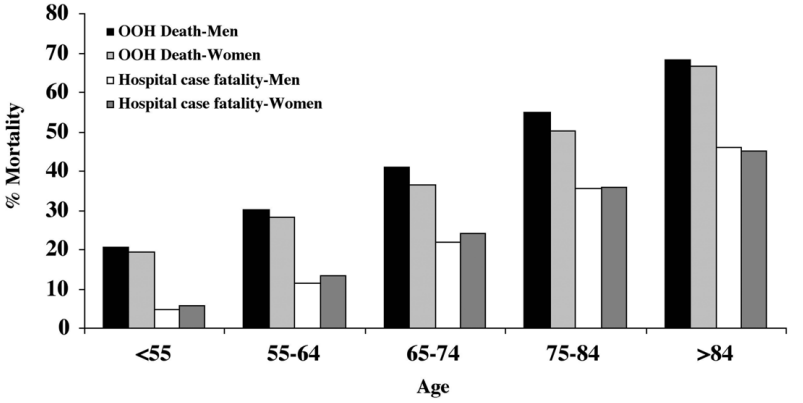

Fig. 3. Survival in acute myocardial infarction, Scotland 1986–1995.

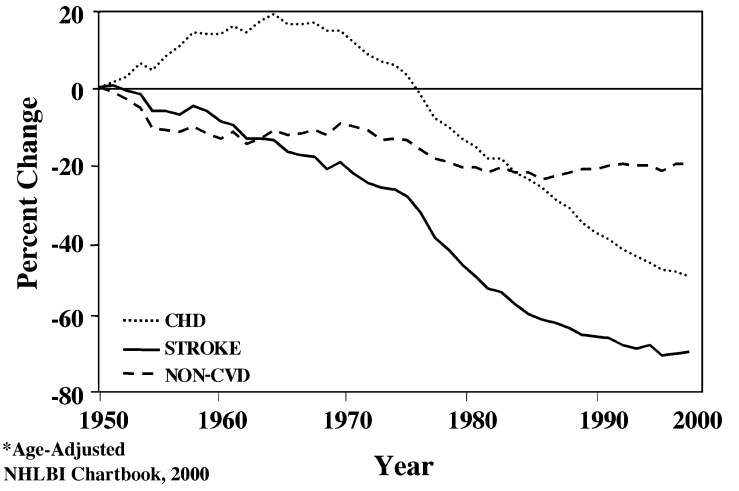

Fig. 4. Percent change in death rates (age adjusted) since 1950.

SITE OF SUDDEN DEATH

The site of sudden death is available on death certificates. In a study by Kuller et al., 70% of out-of-hospital deaths occurred at home *(8)*. A much smaller proportion occurred while the victim was at work (12%) and while traveling (7%). Only 1% occurred while participating in recreational activities and 2% while observing recreational activities. This distribution by site roughly approximates the amount of time an individual spends at each of these places. It is skewed toward events at home and not at work partly because many of the victims are retired. The Kuller study also observed that women (84%) were more likely than men (65%) to die at home, which may be a function of the earlier presentation and work status of this disease among males. Also observed in this study is a similar distribution of sites for whites and African Americans. A more recent study by Tunstall-Pedoe et al. in Scotland showed a similar distribution of site of death *(9)*.

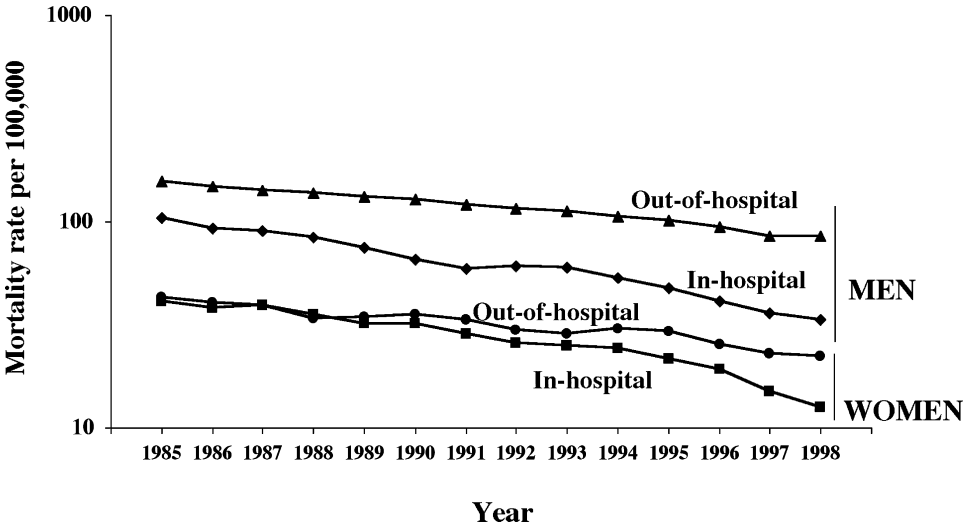

Fig. 5. Time trends (1985–1998) in congestive heart disease mortality rates in Twin Cities residents, ages 30–74. Years, by location of death.

Table 1
Definitions

- Observed or unobserved
- Symptomatic or not
- CPR or not
- Timing
  - 15 minutes
  - 1 hour
  - 6 hours
  - 24 hours

As one considers acute interventions for out-of-hospital death, the preponderance of events at home, as opposed to public places, should influence planning.

PATHOLOGY

Postmortem examination at autopsy is the well-accepted arbiter of underlying cause of death pathology. Unfortunately, sudden out-of-hospital death is usually an electral event resulting in ventricular tachycardia and fibrillation. The process is quite sudden and may leave no macro- or microscopic clues for the examining pathologist. Additionally, the autopsy rate in the United States and internationally has fallen to very low levels. This is particularly true in the older adult population because the cause of death is not of forensic interest, and families will not give permission.

Nonetheless, there are studies of sudden out-of-hospital deaths attributed to cardiac causes based on postmortem autopsy findings. They tend to be highly selected in cases in which the cause of death is not suspected from prior medical history. A recent study by Chugh et al. found that a group of hearts referred for specialized examination in the setting of sudden out-of-hospital death resulted in the discovery of a number of common findings *(10)*. In that select group of hearts, approximately two-thirds (65%) had anatomical evidence of CHD. A second subgroup (23%) had congenital conditions including arrhythmogenic right ventricular dysplasia and hypertrophic obstructive cardiomyopathy. Myocarditis was found in 11%. There were a number of other much less common abnormalities and some hearts had more than one pathology.

In a group of 76 hearts referred for specialized examination because they were apparently normal on gross examination, 79% had cardiac pathology when examined microscopically. This included local myocarditis and conduction system disease in most cases. Only a small proportion had a structurally normal heart without any evidence of pathology *(11)*.

It is apparent from these and other postmortem studies that most out-of-hospital deaths have evidence of CHD either clinically manifest or unknown to the victim.

The current thinking about the pathophysiology of acute coronary syndrome implicates thrombosis formation in the setting of a disrupted plaque. Pathologists have begun to look more systematically for this phenomenon in sudden out-of-hospital death. The work of Davies demonstrated 81% of postmortem cases with disrupted plaque and/or active thrombosis *(12)*. Others have found lower rates. Farb et al. described 57% active lesions in their study *(13)*. These differences are not surprising given the differences in selection factors for those hearts available for examination by cardiac pathologists. Atherosclerotic plaque rupture with resultant ischemia appears to be a common underlying event.

ETIOLOGY

Although the death certificate and autopsy provide clues to the causes of sudden out-of-hospital death, there are additional epidemiologic data providing substantial information. It is clear that most cases are associated with CHD. Congestive heart failure, an increasingly prevalent condition associated with out-of-hospital death, is most commonly the result of chronic ischemic CHD as well. Other factors are less common but some are well studied. For example, congenital heart disease including hypertrophic cardiomyopathy, arrhythmic right ventricular dysplasia, and other malformations of the heart and blood vessels are associated with sudden out-of-hospital death, particularly among younger individuals. Cardiomyopathies of congenital, infectious, and other etiology are also more commonly associated. Other genetic abnormalities that are increasingly studied are those of the conduction system.

It is also apparent that there are factors that provoke sudden out-of-hospital death particularly in the population in which atherosclerotic CHD is common as in industrialized societies. These factors include environmental issues such as air pollution and a wide variety of medications known to cause long QT abnormality. Recently, more attention has been paid to acute risk factors such as stress, anger, physical activity, and others as triggers of acute myocardial infarction and out-of-hospital death.

The growing body of observational data based on prospective epidemiologic studies, patient histories, and medical records allows a better picture of out-of-hospital sudden cardiac death (CD).

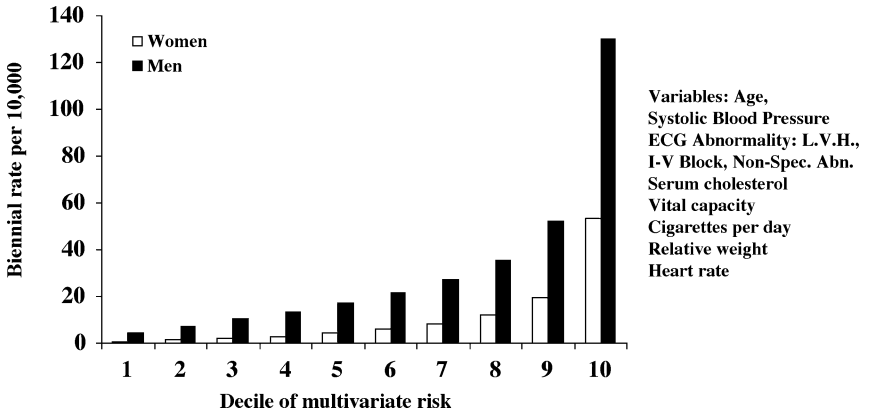

Fig. 6. Risk of sudden cardiac death by decile of multivariate risk: 26-year follow-up: Framingham Study.

Atherosclerotic CHD

A growing number of prospective epidemiologic studies have evaluated the predictive power of risk factors for atherosclerosis and sudden out-of-hospital CD. Among these is the Framingham study, which demonstrated increasing multivariate risk of out-of-hospital death is associated with age, systolic blood pressure, ECG abnormalities, serum cholesterol, vital capacity, cigarettes, relative weight, and heart rate *(14)*. A relative risk of 25 or more is found for men and women between the lowest and highest declines of risk (Fig. 6). The Pooling Project showed similar relationships using serum cholesterol, diastolic blood pressure, and cigarette smoking *(15)*. The more recent Paris Prospective Study of middle-aged men found that those who suffered sudden out-of-hospital death had significantly higher body mass index, tobacco consumption, diabetes, systolic and diastolic blood pressure, blood cholesterol, and blood triglycerides than the controls. These levels were also somewhat, although not always, significantly higher than men who suffered fatal myocardial infarctions in the hospital *(16)*. It is clear that traditional cardiovascular risk factors are associated with sudden out-of-hospital death in large prospective studies just as they are for other forms of atherosclerotic CHD.

Medications and Food Intake

Medications have the ability to affect the QT interval, prolonging it. A long QT is associated with fatal arrhythmias. This acquired long QT syndrome has been associated with numerous agents including antihistamines, antimicrobials, psychotropic agents, food supplements, and anti-arrhythmic agents *(14)*. The well-described association of a high-protein diet with sudden out-of-hospital death is another example. Antipsychotic drugs, particularly in high doses have also been associated with an increased rate ratio (2.39) of sudden out-of-hospital CD *(17)*. This effect was particularly high in those with known prior CVD *(17)*.

Most recently, usual diet has been suspected as an etiologic factor. Intake of n-3 polyunsaturated fatty acids from seafood was observed to be protective in cardiac arrest

(18). However, studies such as this require significantly more exploration and confounding factors may play an important role in explaining the results.

Acute Risk Factors

The observation that out-of-hospital sudden death had an increased incidence in the morning has increased our understanding of the role of a number of acute risk factors or triggers *(19)*. Key factors include time of day, strenuous physical activity, anger, stress, alcohol excess, and sexual intercourse *(20–23)*. There is evidence that commonly used medications such as aspirin and β-blockers blunt this effect. Acute risk factors present an intriguing new approach to out-of-hospital sudden CD. However, it must be remembered that this phenomenon occurs in the context of widespread atherosclerotic CVD in the population.

GENETIC FACTORS

Genetic abnormalities leading to sudden CD are an area of increased interest and speculation as methods to explore genes improve *(24,25)*. Much interest has centered on inherited electrical abnormalities rather than traditional structural abnormalities of congenital heart disease. The long QT syndrome, Brugada syndrome and Lev's syndrome are among the best known. There are currently ten identifiable genetic variants of long QT syndrome associated with out-of-hospital sudden CD. It is anticipated that more will be discovered as the human genome is further understood *(26)*. These and the recently described Brugada syndrome affect potassium and sodium regulation mechanisms in the heart. Most of the genetic variances are thought to be rare although there is growing interest and debate about their prevalence.

In addition to the identification of genetic conduction abnormalities, there is also growing interest on the interaction of these factors with environmental characteristics. It appears intuitive that a lethal conduction system defect would be manifest early and fatally. However, interaction between the environment and genes may provide some insight into their effects among mature adults. For example, studies of long QT syndrome show that exercise, emotion, sleep, and other circumstances are variably associated with long QT-1, long QT-2, and long QT-3 *(27)*. For example, long QT-1 is associated with cardiac events during exercise, whereas association is much less common with other variants. These observations suggest that more will be learned on gene–environment interactions.

CONCLUSION

Out-of-hospital sudden CD is a common and major public health problem accounting for approx 25% of all mortality in the United States. Although overall age-adjusted CVD mortality is falling in most industrialized countries, the rate of improvement is less for out-of-hospital sudden CD. Patients are more likely to survive a cardiovascular event including sudden death once they reach the hospital and the many therapies it provides. Atherosclerotic CHD is the underlying substrate for the overwhelming majority of cases. Given its ubiquity in the adult population, it is not surprising that primary prevention through risk factor modification is an important strategy as the traditional risk characteristics predict out-of-hospital sudden death. However, there is also an interest in identifying the portion of the adult population that has atherosclerosis and is at higher risk.

Methods for identifying these victims are still lacking as approximately half of the out-of-hospital sudden death have no diagnosed CVD.

Acute risk factors are emerging and may provide an insight into prevention. More will be learned about this along with the emergence of genetic factors and their interaction with environmental stressors.

We do know something about the pathophysiology of sudden CD. It is based on diseased tissue either acquired or genetic with local electrical instability. Treatments are emerging as we learn about the effects of aspirin and β-blockers. Additionally, for the most severe identifiable cases, intracardiac defibrillators are becoming more widely used. These may provide insights into the events preceding sudden death as their discharge may be lifesaving. Unfortunately, many of these devices and treatments are too late for most. Primary prevention of CVD remains the best population-wide approach to confront this difficult health problem.

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