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Sudden Cardiac Death:
Exploring the Limits of Our Knowledge

ROBERT J. MYERBURG, M.D.

From the Division of Cardiology, University of Miami School of Medicine, Miami, Florida

Sudden Cardiac Death. Despite progress in epidemiology, clinical profiling, and interventions, sudden cardiac death remains a major clinical and public health problem. There remain important unresolved issues that are challenges for future progress. Among these are a better understanding of the magnitude of the problem and methods of profiling risk for individuals, the etiology and mechanisms of cardiac arrest in individuals with and without previously identified structural heart disease, clinical strategies for primary and secondary prevention of sudden cardiac death, and further development of community programs for improving cardiac arrest survival in the out-of-hospital environment. Each of these areas of endeavor and potential progress are reviewed and discussed. *(J Cardiovasc Electrophysiol, Vol. 12, pp. 369-381, March 2001)*

implantable defibrillators, out-of-hospital cardiac arrest, automated external defibrillators, risk factors, genetics

Introduction

The second half of the twentieth century was a watershed of progress in the medical sciences. Among the successes in the various disciplines of cardiovascular medicine was the evolution of a knowledge base for understanding causes and mechanisms of sudden cardiac death (SCD) and the development of clinical strategies for intervention. Beginning with little more than a general appreciation of an association between arteriosclerotic cardiovascular disease and SCD in the middle part of the century,[1-3] a series of cognitive and technological advances followed upon one another, leading to meaningful insights and intervention strategies by the end of the century. With the dawn of the twenty-first century, the term "prevention of SCD" has begun to take on more than theoretical meaning.

Despite the series of successes, there still remain important unresolved issues. The limits of the progress achieved define the challenges that remain for the future. These can by analyzed in the context of new insights required from the underlying basic and clinical sciences, the strategies needed for further progress in prevention, and the identification of reasonable expectations for improving outcomes.

The challenges begin with a more precise definition of the incidence of SCD and move to epidemiologic strategies that will predict fatal arrhythmic events more precisely. Beyond these, the development of better treatment strategies for individuals at risk must be sought, as well as more comprehensive and effective community intervention systems. New paradigms of predicting risks will have to integrate the various disciplines and interventions that may lead to reductions in the risk of SCD, combining both clinical strategies and community-based actions. Undoubtedly, progress will be incremental and cumulative; it is unrealistic to consider that a single strategic approach will have a meaningful impact on the complexities of SCD.

Epidemiology of SCD: Population and Clinical Perspectives

The magnitude of SCD as a public heath problem is self-evident, but the precise incidence remains uncertain. For more than 20 years, SCD has been stated to have an incidence of 300,000 deaths annually in the United States, with other estimates ranging from as low as

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Address for correspondence: Robert J. Myerburg, M.D., Division of Cardiology, University of Miami School of Medicine, P.O. Box 016960, Miami, FL 33101. Fax: 305-585-7085; E-mail: rmyerbur@med.miami.edu

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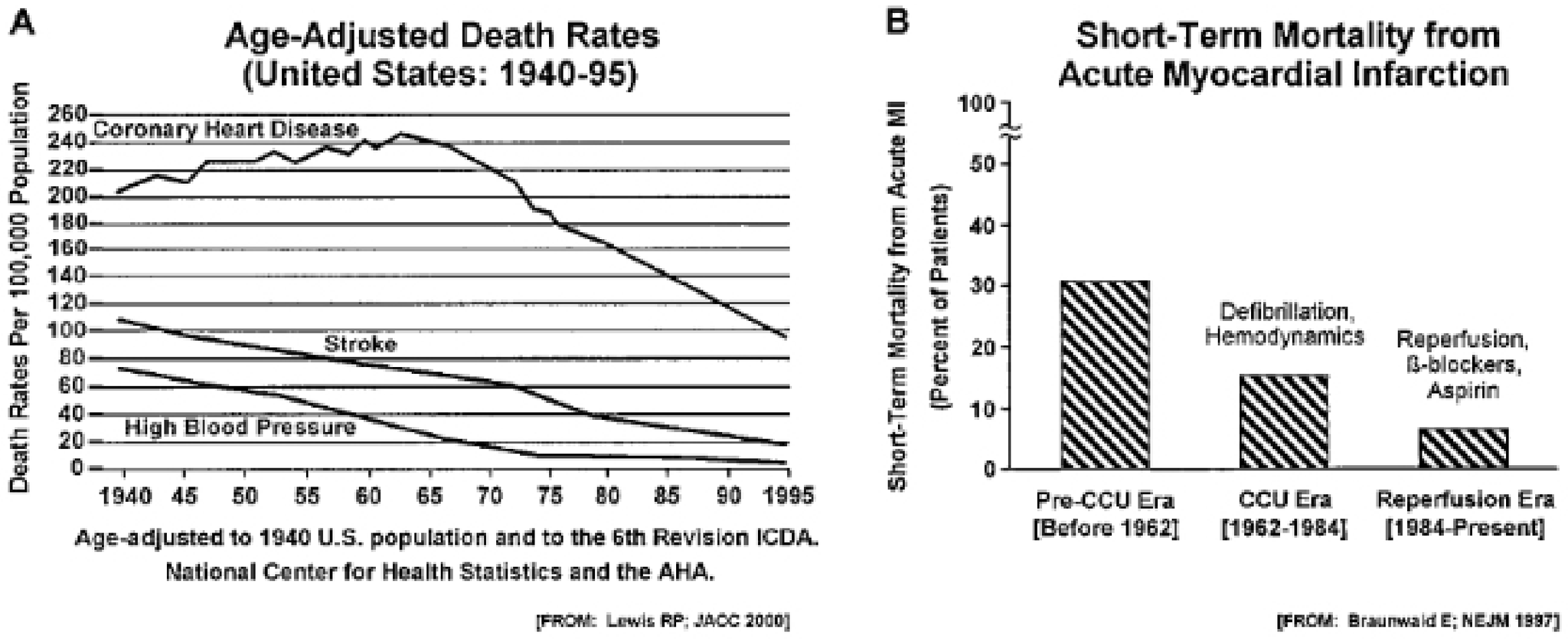

Figure 1. *Factors influencing estimate of the public health burden of sudden cardiac death. (A) Age-adjusted death rates from coronary heart disease, stroke, and high blood pressure, from 1940 to 1995. (Modified with permission from the American Journal of Cardiology [Journal of the American College of Cardiology], 2000;35:1061-1066). Decreasing age-adjusted risk does not inherently provide information on incidence or prevalence. (B) Estimates of the reduction in short-term mortality due to acute myocardial infarction during the second half of the twentieth century. Short-term mortality benefit results in increased population of survivors with chronic ischemic heart disease (Modified with permission from Braunwald E: Cardiovascular medicine at the turn of the millennium: Triumphs, concerns, and opportunities. N Engl J Med 1997;337:1360-1369. Copyright © 1997 Massachusetts Medical Society. All rights reserved.)*

250,000 to 400,000 or more.[4-8] This figure of 300,000 deaths accounts for an average of 1 to 2 deaths per 1,000 adults over the age of 35 per year and represents 50% of all heart-related deaths.[8,9] Although the 50% proportion seems to hold up from a number of sources of data, the estimate of 300,000 SCDs per year is a derived figure, based on an assumption of 600,000 cardiovascular deaths per year in the mid-1970s. Although much has changed in the population substrate and interventional capabilities in cardiovascular diseases during the past 25 years, the estimates that formed the basis for the 300,000 SCDs annually have remained unchallenged.

An example of how changing clinical and epidemiologic patterns can influence SCD risk without being immediately apparent is shown in Figure 1. The decrease in age-adjusted risk of coronary heart disease death from the 1940s to 1995 (Fig. 1A) has been applauded as a statement of medical and public health progress.[10] During the same period of time, there was a marked reduction in early mortality from acute myocardial infarction, initially thought to be related to the development of the coronary care unit and its effect on electrical and, to a more limited extent, mechanical deaths, and recently by more advanced therapies[11,12] (Fig. 1B). The interaction between these two sources of data is complex. The age-adjusted risk curve expresses the fact that deaths from cardiovascular disease are occurring at older ages; it does not inherently state that the prevalence of heart disease or absolute numbers of death have changed. In addition, the short-term acute myocardial infarction mortality experience infers the establishment of a population of survivors who entered the pool of aging patients with cardiovascular disease. These factors combine with the general growth of the older population pool, because of increased birth rates during the middle part of the century. These several observations come together to suggest that, in an aging population with a lower short-term morality rate and a shifting age-adjusted risk, there is likely a growing population of patients at risk for various cardiovascular events.[12] The events include the development of heart failure and the risk of SCD. Finally, the 300,000 figure does not factor in the suggestion that there are now estimated to be 750,000 cardiovascular deaths annually.[12] In the absence of a properly designed survey that would allow a direct measure of SCD rates, the actual numerical magnitude of the risk of SCD remains speculative.

The magnitude of the risk of SCD is both age and cause related (Fig. 2), and these two factors interact. The general assumption of a risk of 0.1% to 0.2% per year among the population aged 35 and older is an average figure for patients across that age range. Among that segment of the general population, however, the risk of SCD is strongly age related, with the most marked increase in risk between the ages of 40 to 65 years.[8] In that segment of the population, coronary artery disease is by far the most common cause of SCD (Fig. 3), accounting for approximately 80% of all SCDs. The collective cardiomyopathies, dominated by the dilated cardiomyopathies, account for another 10% to 15%. Once coronary heart disease or cardiomyopathies are in advanced stages, they dominate and largely neutralize the age-related component of SCD risk. Among patients with advanced structural heart disease, silent or recognized, it is the extent of disease rather than the age that determines risk; therefore, age-related risk curves tend to blunt in that subgroup of the population (Fig. 2).

At the other end of the age spectrum, adolescents and young adults (ages 10 to 30), the order of magnitude of SCD risk is about 1/100th that of the general adult

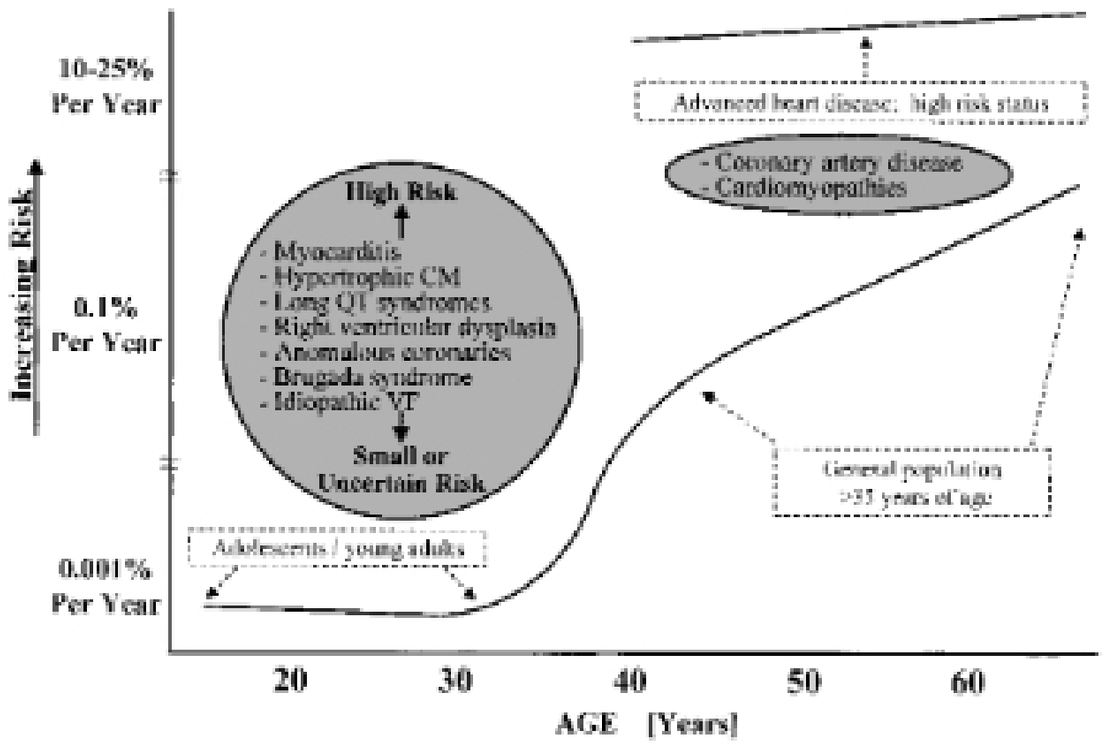

Figure 2. *Age-related risk of sudden cardiac death, with influence of preexisting heart disease on magnitude of risk in middle-aged and older adults. The prevalent etiologies are a function of age. See text for details. (Modified with permission from Myerburg RJ, Castellanos A: Cardiac arrest and sudden cardiac death. In Braunwald E, ed: Heart Disease: A Textbook of Cardiovascular Medicine. Sixth Edition. WB Saunders, Philadelphia, 2001, pp. 890-931.)*

population (1 per 100,000 individuals annually), and there appears to be a modest inverse age relationship, with the adolescent group having a higher mortality risk than young adults. It is likely that the risk of lethal arrhythmia in the genetically controlled disorders tend to express more commonly in the adolescent years.[13] This is particularly evident for hypertrophic cardiomyopathy.[14]

The group of disorders responsible for SCD in the adolescent and young adult group is distinctly different from those in the middle-aged to elderly group. Coronary atherosclerosis is an uncommon cause, with myocarditis, hypertrophic cardiomyopathy, long QT syndromes, right ventricular dysplasia, anomalous coronary arteries, Brugada syndrome, and idiopathic ventricular fibrillation (VF) accounting for the majority of these deaths. Mortality risks for any one of these diagnoses is quite variable and may, in fact, have genetic predetermination of the magnitude of risk for sudden death as an expression of the specific mutation (see later).

The inverse relationship between the incidence of SCD and absolute numbers of events in the various epidemiologic or clinical categories is important to appreciate (Fig. 4), particularly in relationship to the impact of therapeutic interventions.[15] Among the general population aged 35 years and older, the nominal incidence of 0.1% to 0.2% per year incorporates all of the estimated 300,000 sudden deaths that occur in the United States annually. With profiles of increasing risk from patients who fall into categories of high risk for development of coronary atherosclerosis, to those who have survived a coronary event, and beyond that to those with heart failure or ejection fractions <35%, cardiac arrest survivors and the specific high-risk post-myocardial infarction patients, the escalating risk accounts for a decreasing absolute number of events annually. The importance of recognizing this principle relates to the magnitude of population benefit for various preventative interventions. For example, the very high-risk patient categories studied in the clinical trials of implantable defibrillators (Fig. 4) represent only a very small part of the universe of SCD risk, and the reported benefits apply only to those small subgroups. This highlights the importance of finding specific risk markers for more general segments of the population from which the potential for greater public health impact can emerge.

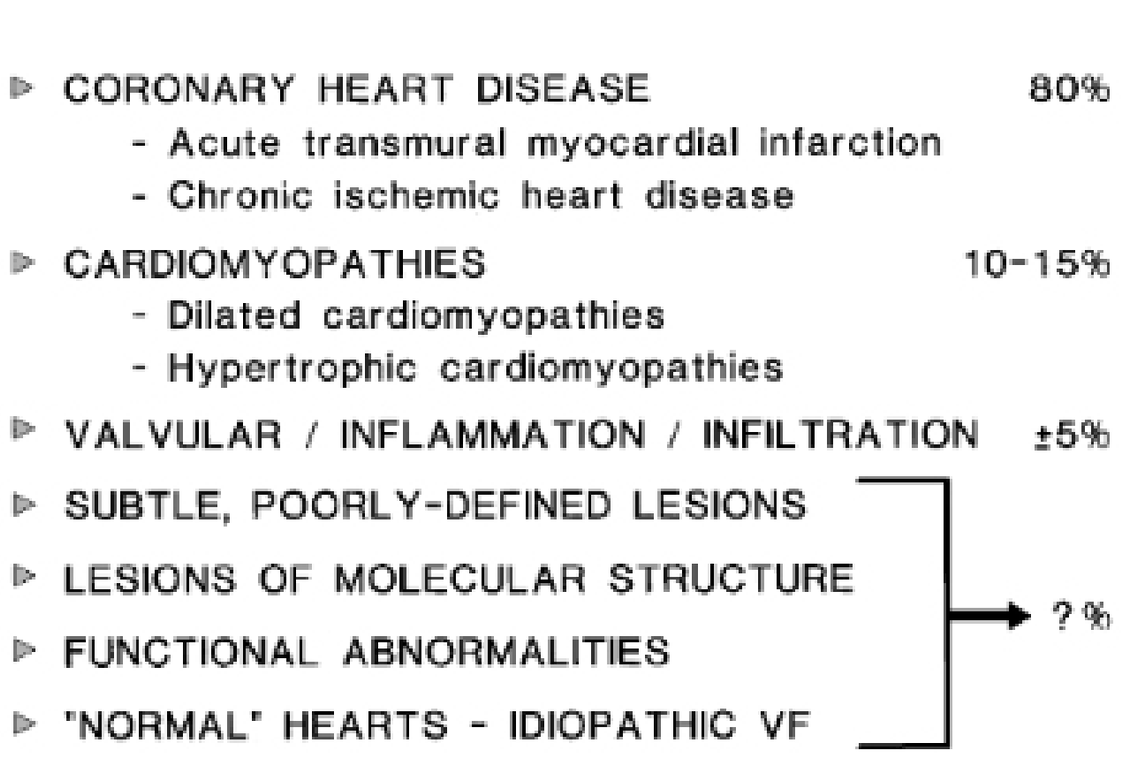

Figure 3. *Etiologic basis of sudden cardiac death. Coronary heart disease and the cardiomyopathies collectively account for >90% of all sudden cardiac deaths. (Modified from American Journal of Cardiology, Volume 80, Myerburg RJ, Interian A, Mitrani RM, Kessler KM, Castellanos A: Frequency of sudden cardiac death and profiles of risk, pages 10F-19F, Copyright 1997, with permission from Excerpta Medica, Inc.)*

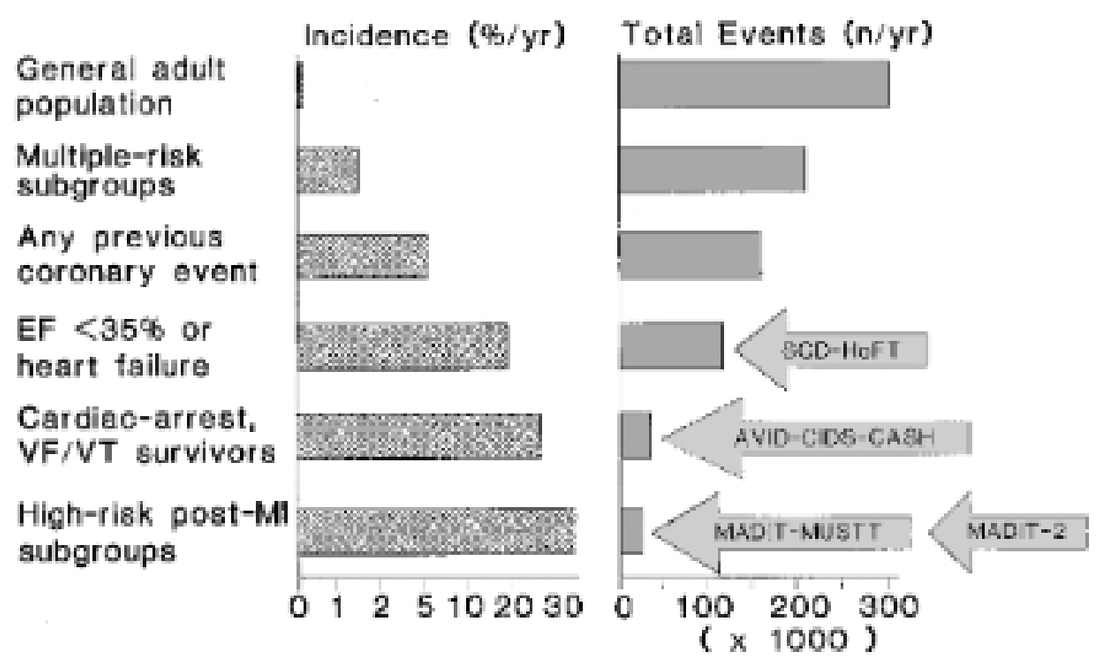

Figure 4. *Relationship between population subsets, incidence of sudden cardiac death, and total population burden for each group. With increasing incidence, based on subgroup profiling, there is a decreasing proportion of the total sudden death burden. This relates to the population impact of the outcomes of ICD trials. (Modified from American Journal of Cardiology, Volume 80, Myerburg RJ, Interian A, Mitrani RM, Kessler KM, Castellanos A: Frequency of sudden cardiac death and profiles of risk, pages 10F-19F, Copyright 1997, with permission from Excerpta Medica, Inc.)*