Section one:
Epidemiology and mechanisms

CHAPTER 1
Epidemiology of cardiac arrest

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Epidemiological studies related to sudden cardiac death (SCD) remain challenging for both theoretical and practical reasons. There are persisting fundamental questions about definition, inconsistencies in access to data, variations in pathophysiological mechanisms and their clinical recognition, and distinctions between population risk and individual risk. In addition, the emerging field of genetic epidemiology adds a new dimension for study, and there is need for focus on interventional epidemiology, the latter being a term coined to define the population dynamics of therapeutic outcomes. This chapter will provide an overview of each of these components of the epidemiology of SCD.

Basic definitions of SCD

A generally accepted definition of SCD is natural death due to cardiac causes, heralded by abrupt loss of consciousness within an hour of the onset of acute symptoms. Preexisting heart disease may or may not have been previously recognized, but the time and mode of death are unexpected [1]. The term "unexpected" is the hallmark of the definition because it permits inclusion of a broad range of preceding clinical states, having different levels risk.

Four time elements must be considered in the construction of a definition of SCD to satisfy clinical, scientific, legal, and social considerations: prodromes, onset, cardiac arrest, and progression to biological death. The proximate cause of SCD is an abrupt cessation of blood flow that is incompatible with maintaining life if allowed to persist. The 1-h definition is arbitrary and refers to the duration of the "terminal event," which defines the interval between the onset of symptoms signaling the pathophysiological disturbance leading to cardiac arrest and the onset of the cardiac arrest itself. A 24-h definition may be used as a SCD definition for *unwitnessed deaths* of victims known to be alive and functioning normally prior to being found, and this is appropriate within obvious limits. However, the temporal definition used affects the relative incidence of cardiac causes of sudden death and the frequency of specific cardiac disorders [1].

Biological death was viewed as an immediate consequence of cardiac arrest in the past, usually occurring within minutes. However, since the development of community-based interventions and life support systems, patients may now remain biologically alive for a long period of time after the onset of a pathophysiological process that has caused irreversible damage. In this circumstance, the causative pathophysiological and clinical event is the cardiac arrest itself, rather than the factors responsible for the delayed biological death. However, for legal, forensic, and certain social considerations, biological death is the absolute definition, in contrast to cardiac arrest, which retains survival potential.

Clinical definitions of cardiac arrest and SCD are categorized as "primary" or "secondary." These classifications are used in many clinical trials and some epidemiological surveys. "Secondary" refers to a cardiac arrest or SCD in an individual who has survived a prior cardiac arrest or its equivalent. Common use of the term "primary" is more complex, generally referring to an event in an individual who has not had a prior cardiac arrest, regardless of the clinical severity of the underlying disease. The term also refers to arrthythmic collapse as an initial or isolated feature of the disease (primary cardiac arrest – PCA), in the absence of a recognized acute state (such as acute myocardial infarction) that is an identified trigger for the event. By strict epidemiological definitions, however, none of these usages of "primary" is correct, since the term refers to the prevention of the underlying disease state, rather than of a clinical manifestation. Conversely, all cardiac arrests associated with underlying diseases are "secondary" events. Despite these differences epidemiologically, the common usage remains ingrained in clinical medicine.

General epidemiology of SCD

Overview

The worldwide incidence of SCD is difficult to estimate because it varies largely as a function of prevalence of coronary heart disease in different countries [2,3]. Estimates for the United States, largely based upon retrospective death certificate analyses [4–6] and an emergency rescue database in one study [7] range from less than 200 000 to more than 450 000 SCDs annually, with the most widely used estimates in the range of 300 000–350 000 SCDs [8]. This accounts for an incidence of 0.1–0.2% per year among the population >35 years of age. Event rates in Europe are similar to those in the United States [9]. These ranges of estimates are based, in part, on the definition of sudden death and inclusion criteria used in individual studies, and the correct number can only be defined from a carefully designed prospective epidemiological study. A recent study in a single city in the United States, using a prospective design for data collection, suggested a significantly lower national incidence when extrapolated to the entire country [10]. Because of geographic population variations [11], however, such extrapolations must be viewed with caution.

Approximately 50% of all coronary heart disease deaths are sudden and unexpected, often occurring shortly after the onset of symptoms. Because coronary heart disease is the dominant cause of both sudden and nonsudden cardiac deaths in the United States and Europe, the fraction of total cardiac deaths that are sudden is similar to the fraction of coronary heart disease deaths that are sudden. It is also of interest that the age-adjusted decline in coronary heart disease mortality in the United States during the past half-century has not changed the fraction of coronary deaths that are sudden and unexpected [12,13]. Furthermore, the decreasing age-adjusted mortality does not imply a decrease in absolute numbers of cardiac or sudden deaths because of the growth and aging of the population and the increasing prevalence of chronic heart disease [14,15].

Population subgroups and SCD

When the more than 300 000 adult SCDs that occur annually in the United States are viewed as a global incidence in an unselected adult population, the overall incidence is 1 to 2/1000 (0.1–0.2%) per year. This large population base includes those victims whose SCDs occur as a first cardiac event, as well as those whose SCDs can be predicted with greater accuracy because they are included in higher-risk subgroups. Any intervention designed for the general population must be applied to the 999/1000 who will not have an event, in order to reach and possibly influence the 1/1000 who will have. The cost and risk-to-benefit uncertainties limit the nature of broad-based interventions and demand a higher resolution of risk identification. Figure 1.1(a) highlights this problem by expressing the incidence (percent/year) of SCD among various subgroups and comparing the incidence figures to the total number of events that occur annually in each subgroup. By moving from the total adult population to a subgroup at higher risk because of the presence of selected coronary risk factors, there may be a 10-fold or greater increase in the incidence of events annually, with the magnitude of increase dependent on the number of risk factors operating in the subgroup [15]. The size of the denominator pool, however, remains very large, and implementation of interventions remains problematic, even at this heightened level of risk. Higher resolution is desirable and can be achieved by identification of more specific subgroups. However, the corresponding absolute number of deaths become progressively smaller as the subgroups become more focused, limiting the potential benefit of interventions to a much smaller fraction of the total number of patients at risk. Various estimates suggest that at least two-third of all SCDs due to coronary heart disease occur as a first clinical event or among subgroups of patients thought to be at relatively low risk for SCD [12] (Figure 1.1(b)).

Time-dependence of risk

Temporal influences on the risk of SCD have been analyzed in the context of both biological and clinical chronology. In the former, epidemiological analyses of SCD risk among populations have identified three patterns: diurnal,

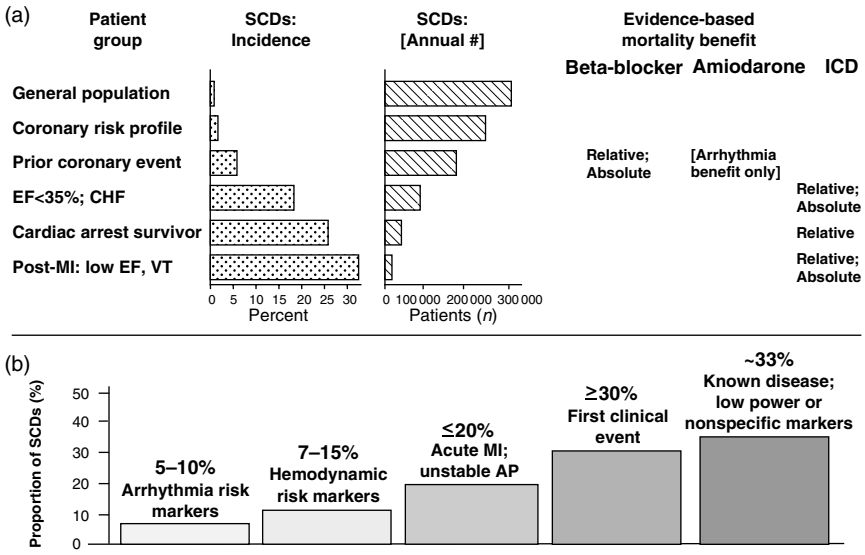


Figure 1.1 Distribution of SCD risk According to clinical and population profiles. (a) The figure shows estimates of incidence (percent/year) and the total number of events per year for the general adult population in the United States, and for increasingly higher-risk subgroups. With the identification of increasingly powerful markers of risk, the incidence increases progressively, accompanied by a progressive decrease in the total number of events contained within each successive subgroup. Successful interventions among larger population subgroups will require identification of new markers, specific for high risk of a future event. Modified from Reference 15; reproduced with permission of the American Heart Association, Inc. (b) The figure demonstrates the distribution of clinical status of victims at the time of SCD. Nearly two-third of cardiac arrests occur as the first clinically manifest event or in the clinical setting of known disease in the absence of strong risk predictors. Modified from Reference 12.

weekly, and seasonal. General patterns of heightened risk during the morning hours, on Mondays, and during the winter months have been described [15,16]. In the clinical paradigm, risk of SCD is not linear as a function of time after changes in cardiovascular status. Survival curves after major cardiovascular events, which identify risk for both sudden and total cardiac death, usually demonstrate that the most rapid rate of attrition occurs during the first 6–18 months after the index event. Thus there is a time-dependence of risk that focuses the opportunity for maximum efficacy of an intervention during the early period after a conditioning event [15]. Curves that have these characteristics have been generated from among survivors of out-of-hospital cardiac arrest, new onset of heart failure, and unstable angina, and from high-risk subgroups of patients having recent myocardial infarction [8,15]. Even though attrition rates decrease over time, an effective intervention can still cause late

diversion of treated versus control risk curves, indicating continuing benefit. The patterns of early and late separation of curves reflect two different dimensions of time-dependent risk.

Age, heredity, gender, and race

Age

There are two ages of peak incidence of sudden death: between birth and 6 months of age (the sudden infant death syndrome) and between 45 and 75 years of age. Among the general adult population, the *incidence* of sudden death increases dramatically as a function of advancing age [17], in parallel with the age-related increase in incidence of total coronary heart disease deaths. For subgroups with advanced heart disease, the higher risk associated with the disease state blunts the impact of age. The incidence is 100-fold less in adolescents and adults below 30 years of age [18–20] (1 in 100 000 per year), than it is in adults above 35 years age of (1 in 1000 per year) [12].

Heredity

Among the less common causes of SCD, hereditary patterns have been reported for specific syndromes, such as the congenital long-QT-interval syndromes, hypertrophic cardiomyopathy, right ventricular cardiomyopathy, the Brugada syndrome, "idiopathic" ventricular tachycardia/fibrillation, and yet-to-be-defined patterns of familial SCD in children and young adults (see Chapter 9). Mutations and functioning polymorphisms are being mapped to genes located on many chromosomes, as the molecular bases for the entities are being defined. In addition, these observations may provide screening tools for individuals at risk for SCD due to more common causes, such as coronary heart disease [21] (see Section on Genetic Epidemiology). To the extent that SCD is an expression of underlying coronary heart disease, hereditary factors that contribute to coronary heart disease risk have been thought to operate nonspecifically for the SCD syndrome. However, recent studies have identified mutations and polymorphisms along multiple steps of the cascade from atherogenesis to plaque destabilization, thrombosis, and arrhythmogenesis, many of which are associated with altered risk of coronary events [22–25].

Gender

The risk of SCD is four to seven times greater in males compared with females during the young adult and early middle-age years because of the protection females enjoy from coronary atherosclerosis before menopause [26]. As coronary event risk increases in postmenopausal women, SCD risk increases, perhaps disproportionately, and the excess in males fades. Even though the overall risk is much lower in younger women, the classic coronary risk factors are still predictive of events among women [1,26], including cigarette smoking, diabetes, use of oral contraceptives, and hyperlipidemia.

Race

A number of early studies comparing racial differences in relative risk of SCD in whites and African Americans with coronary heart disease in the United States had yielded conflicting and inconclusive data. However, recent studies have demonstrated excess risk of cardiac arrest and SCD among African Americans compared with whites [27,28]. SCD rates among Hispanic populations were smaller. The differences were observed across all age groups.

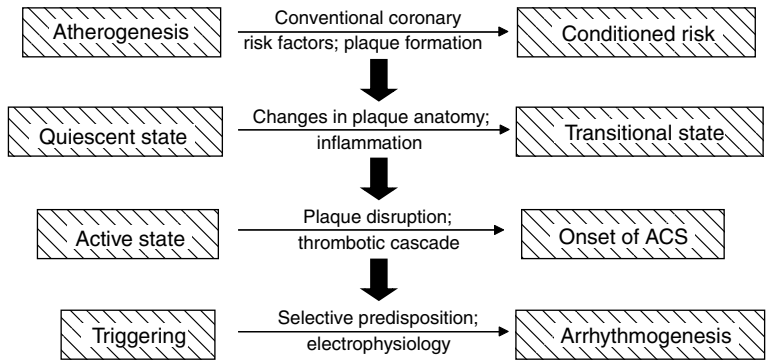
Conventional coronary risk factors and SCD

Risk profiling for coronary atherogenesis is useful for identifying levels of population risk and individual risk [29], but cannot be used to distinguish individual patients at risk for SCD from those at risk for other manifestations of coronary heart disease. Multivariate analyses of selected risk factors (i.e. age, systolic blood pressure, heart rate, electrocardiographic abnormalities, vital capacity, relative weight, cigarette smoking, diabetes mellitus, and serum cholesterol) have determined that approximately one-half of all SCDs occur among the 10% of the population in the highest risk decile, based upon multiple risk factors. Thus, the cumulative risk derived from multiple risk factors exceeds the simple arithmetic sum of the individual risks [29]. In addition, angiographic and hemodynamic patterns discriminate SCD risk from non-SCD risk only under limited circumstances. In contrast, familial clustering of SCD as a specific manifestation of the disease may lead to identification of specific genetic abnormalities that predispose to SCD [30,31].

Hypertension is a clearly established risk factor for coronary heart disease and also emerges as a highly significant risk factor for incidence of SCD [32]. However, there is no influence of increasing systolic blood pressure levels on the ratio of sudden deaths to total coronary heart disease deaths. No relationship has been observed between cholesterol concentration and the proportion of coronary deaths that are sudden. Neither the electrocardiographic pattern of left ventricular (LV) hypertrophy nor nonspecific ST–T-wave abnormalities influence the proportion of total coronary deaths that are sudden and unexpected; only intraventricular conduction abnormalities are suggestive of a disproportionate number of SCDs [1]. The latter is an old observation that was recently reinforced by data from device trials that suggests the importance of QRS duration as a risk marker [33].

The conventional risk factors used in early studies of SCD are the risk factors for evolution of coronary artery disease. The rationale is based on two facts: (1) coronary disease is the structural basis for 80% of SCDs in the United States and Europe, and (2) the coronary risk factors are easy to identify because they tend to be present continuously over time (Figure 1.2). However, risk factors specific for fatal arrhythmias are dynamic pathophysiological events and occur transiently [13,15]. Transient pathophysiological events are being modeled epidemiologically [21], in an attempt to express and use them as clinical risk factors for both profiling and intervention.

(a) Cascade for sudden death in coronary heart disease



(b)

VARIABLES	EXAMPLES	MEASURES	SENSITIVITY
• **Conventional risk factors**	• Framingham risk index	• Predict evolution of disease	• Very low
• **Anatomic screening**	• Electron beam tomography	• Identify CAD	• Very low
• **Clinical markers**	• EF; angiography	• Extent of disease	• Variable; extent of disease; low specificity
	• Ambulatory monitors; EPS	• Arrhythmic markers	• Low-to-intermediate for screening; high in specific groups
• **Transient risk predictors**	• EKG markers	• T-wave alternans; Q-T dispersion	• Primary predictive value unknown
	• Pathophysiological controls (e.g. HRV)	• Autonomic regulation	• Uncertain; some measures may be useful
	• Inflammatory markers	• Predict unstable plaques	• Unknown; potentially high

Figure 1.2 Cascade for sudden cardiac death in coronary heart disease and levels of clinical prediction. (a) The figure demonstrates the cascade from conventional risk factors for coronary atherosclerosis to arrhythmogenesis in SCD due to coronary heart disease. The cascade identifies four levels of evolution, beginning with lesion initiation and development, progressing to the transition to an active state, then to acute coronary syndromes, and finally to the specific expression of life-threatening arrhythmias. Modified from Reference 21 with permission. (b) The figure demonstrates categories of risk factors. *Conventional risk factors* and *anatomic disease screening* have general use for predicting risk but with low sensitivity. They are not specific for arrhythmic deaths. *Clinical predictors* have variable power, some of which are useful as predictors for cardiac arrest and SCD, and have been widely used in the design of arrhythmia intervention trials. *Transient risk predictors* and *individual risk prediction* (see Figure 1.4) offer the hope for more powerful individual prediction of risk of SCD. Modified from Reference 12.

Lifestyle and psychosocial factors

Lifestyle

There is a strong association between *cigarette smoking* and all manifestations of coronary heart disease. The Framingham Study demonstrates that cigarette smokers have a two-fold to three-fold increase in sudden death risk in each decade of life at entry between 30 and 59 years, and that this is one of the few risk factors in which the proportion of coronary heart disease deaths that are sudden increases in association with the risk factor [34]. In addition, in a study of 310 survivors of out-of-hospital cardiac arrest, the recurrent cardiac arrest rate was 27% at 3 years of follow-up among those who continued to smoke after their index event, compared with 19% in those who stopped [35] ($p < .04$).

Obesity is a second factor that appears to influence the proportion of coronary deaths that occur suddenly [34]. With increasing relative weight, the percentage of coronary heart disease deaths that were sudden in the Framingham Study increased linearly from a low of 39% to a high of 70%. Total coronary heart disease deaths increased with increasing relative weight as well. Associations between levels of physical activity and SCD have been studied, with variable results. Epidemiological observations have suggested a relationship between *low levels of physical activity* and increased coronary heart disease death risk. The Framingham Study, however, showed an *insignificant* relationship between low levels of physical activity and incidence of sudden death and a high proportion of sudden to total cardiac deaths at higher levels of physical activity [34]. A case-crossover cohort study demonstrated a 17-fold relative increase in vigorous exercise-associated SCD, compared to lower-level activity or inactive states [36]. However, the absolute risk for events was very low (1 event per 1.5 million exercise sessions). Habitual vigorous exercise attenuated risk. In contrast, SCD among young athletes has a higher incidence than among young nonathletic individuals in the same age range [37]. Information about physical activity relationships in various clinical settings, such as overt and silent disease states, is still lacking.

Psychosocial factors

The magnitude of recent life changes in the realms of health, work, home and family, and personal and social factors have been related to myocardial infarction and SCD [38,39]. There is an association between significant elevations of life-change scores during the 6 months before a coronary event, and the association is particularly striking in victims of SCD. Among women, those who die suddenly are less often married, had fewer children, and had greater educational discrepancies with their spouses than did age-related controls living in the same neighborhood as the sudden death victims. A history of psychiatric treatment, cigarette smoking, and greater quantities of alcohol consumption than the controls also characterized the sudden death group. Controlling for other major prognostic factors, risk of sudden and total deaths, and other

coronary events, is impacted by social and economic stresses [40]. Alteration of modifiable lifestyle factors has been proposed as a strategy for reducing risk of SCD in patients with coronary heart disease, although a study of treatment of depression following myocardial infarction failed to demonstrate an effect on event rates [1]. Acute psychosocial stressors have been associated with risk of cardiovascular events, including SCD. The risk appears to cluster around the time of the stress, and appear to occur among victims at preexisting risk, with the stressor simply advancing the time of an impending event [41].

Risk prediction and the coronary heart disease cascade

The cascade of evolution and clinical manifestations of coronary artery disease leading to risk of SCD can be viewed as a four-stage process: atherogenesis, transition, acute coronary syndromes, and arrhythmogenesis (see Figure 1.2(a)). The initial stage occurs over a long period of time and must be viewed from the perspective of population risk, rather than clinical risk, because event rates are relatively low, even among the higher-risk categories. Risk markers identified with the transitional state, those factors responsible for evolution of changes in atherosclerotic plaque anatomy and pathophysiology, are applicable to subgroups with established disease, even though it may not yet be clinically expressed. Recent interest in markers of plaque inflammation as a predictor of risk is an example of the application of pathophysiologic states in more concentrated population groups. The target is prediction of the transition of the disease to an active state over shorter time periods. The next level of the cascade is the onset of an acute coronary syndrome as the proximate trigger of SCD, or other manifestations of the underlying disease. An example is the variations in response of the thrombotic cascade to onset of the syndrome.

At the final stage of arrhythmogenesis, there is an interaction between the ischemic consequences of the earlier stages of the cascade and the generation of cardiac arrhythmias. This may be related to ion channel behavior at the single cell level and interactions between ion channel responses, or between ischemic and nonischemic regions. As one moves along the cascade of risk, there is the potential for increasing sensitivity and specificity in exchange for decreasing size of the population denominator. The challenge presently is to determine how markers of risk at each level of the cascade can be identified prospectively in order to seek subgroups at especially high risk of events prior to the onset of acute coronary syndromes. An example of such strategies is the current interest in the use of inflammatory markers as a predictor of acute coronary syndromes. The ultimate goal is to use predictors of transient risk to identify those individuals at risk for the events that trigger fatal arrhythmias [12,21] (Figure 1.2(b)). Viewed in broad perspective, these may include such pathophysiologic control mechanisms as autonomic nervous system functions (e.g. heart-rate variability, baroreceptor sensitivity, measures of alteration of repolarization, inflammatory markers, and thrombotic cascade markers).

Risk prediction in dilated cardiomyopathy

Sudden cardiac death among patients with the cardiomyopathies is even more difficult to predict. While LV ejection fraction (EF) is a strong mortality risk predictor generally among patients who have dilated cardiomyopathies, it is not as useful for specifically predicting SCD. It appears that there is a better association with functional capacity. For example, among patients with dilated cardiomyopathy who are classified as functional class I, the risk of dying is small, but the proportional probability that a death will be sudden, if it occurs, is relatively high. The fact that this category encompasses a large number of patients at relatively low risk limits the predictive power for benefit from interventions. At the other end of the spectrum, functional class III and IV patients are generally at a higher risk of mortality and a higher risk of absolute numbers of SCDs [42], although the proportional risk of sudden death is somewhat lower. This statement does not incorporate the possible impact of long-term medical therapy for heart failure on the balance between sudden and nonsudden deaths.

Interventional epidemiology

The outcomes of clinical trials, observational therapeutic data, and the results of epidemiological surveys all contribute to the management of risk for SCD [12]. However, the application of the knowledge gained from each of these sources of data may differ in terms of its population impact, compared to individual clinical impact. For example, mining of existing large databases can identify risk factors or strong associations. Observations are generally expressed in terms of relative risk statements, and often based on low absolute event rates. Low event rates with large relative differences identify effects, but usually with limited individual patient impact (Figure 1.3(a)). In contrast, randomized clinical trials with large absolute differences in outcomes are able to better define individual patient benefits. Observational studies are limited by their dependence on anticipated, rather than actual, comparison outcomes.

Studies of the benefit of the implantable cardioverter-defibrillator (ICD) for individuals at high risk of SCD are instructive. From the time of the first implant in 1980 until the publication of the first clinical trial in 1996, their use was initially prescribed on the basis of observational data and clinical judgment, and their use compared to drugs and surgery. This scientific limitation impeded their initial acceptance. With the publication of a number of randomized trials since 1996, the ICD has moved into the position of preferred therapy for specifically defined high-risk patients. The clinical trials of ICDs have included both primary and secondary prevention strategies. While the usage of the term "primary prevention" for ICD trials is technically incorrect (see above), it does serve the purpose of subgrouping patients into two general categories, the study design and outcomes of which might be interpreted and applied differently.

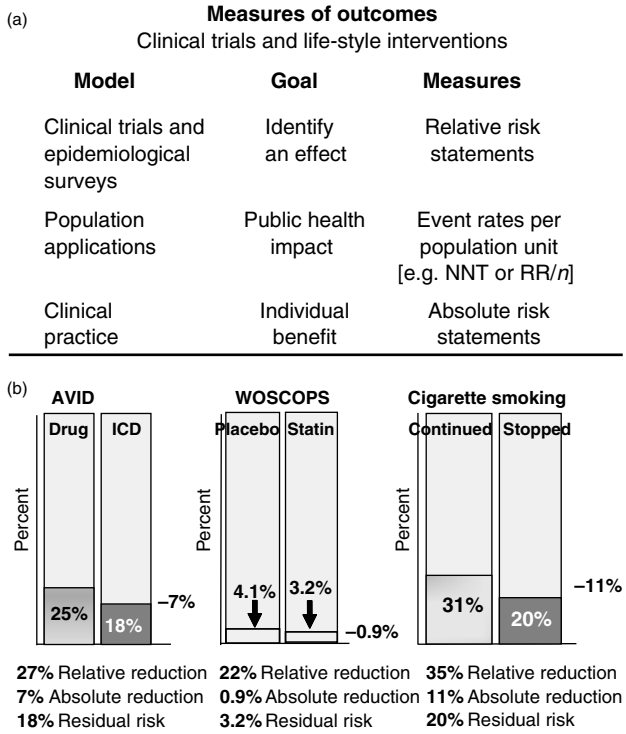


Figure 1.3 Outcomes of clinical trials can be expressed as relative risk and absolute risk improvements, as well as normalized to numbers needed to treat (NNT) or relative risk (RR) divided by the number of observations (n). (a) Here the clinical trial or epidemiological survey model, population applications, and practical clinical applications are related to the goals of identifying an effect, public health impact, or individual benefit, and the appropriate measures to express outcome in relation to those goals. (b) Here the relative and absolute risk reductions are demonstrated for three practical clinical models: the AVID trial [43] the West of Scotland Coronary Prevention Study (WOSCOPS) [44] demonstrating the effect of statins on mortality outcome, and the effect of continued cigarette smoking on outcomes after survival from an initial cardiac arrest [35]. Modified from Reference 45.

All studies of group outcomes of therapy for complex pathophysiological states must take four factors into account (Figure 1.3(b)): (1) relative risk reduction, (2) absolute risk reduction, (3) residual risk, and (4) cumulative benefits of multiple interventions. The primary endpoint reports for all clinical trials of ICD therapy, and most other large clinical trials, focus on reduction in relative risk [45,46] since this measure identifies the *effect* of the intervention. However, relative risk reduction does not quantify the benefit for the individual patient. To do so, a measure of absolute risk reduction is required, such as the absolute numerical difference in risk observed in the test and control

groups, or calculations of a number of patients needed to be treated (NNT) in order to save a life [47].

Other measures of group impact that do not commonly receive attention include residual risk and cumulative benefit. The former refers to the absolute outcome among the treated group or test group in a clinical trial population, which identifies the component of total mortality risk that does not respond to the tested therapy. If residual risk is very high, the absolute and relative risk reduction benefits are correspondingly limited. Cumulative benefit refers to the increment in benefit from integration of multiple interventions. Despite its importance [45,48], this is rarely stratified in clinical trial designs because it requires larger study populations, and has not been used prospectively in any of the ICD or antiarrhythmic trials. *Post hoc* subgroup analysis can be used to suggest added benefit of a secondary strategy, but this does not replace stratifying the multiple interventions.

A comparison of the various measures of outcomes from an ICD trial, contrasted with another cardiovascular intervention, is shown in Figure 1.3(b). The relative and absolute outcomes observed in the Antiarrhythmics Versus Implantable Device (AVID) study [47] at 2 years of follow-up are compared to the West of Scotland Coronary Prevention Study (WOSCOPS) [48], a study of the impact of Pravachol versus placebo in a population of men without known preexisting coronary artery disease. While the relative risk reduction for total mortality (at 2 years of follow-up in AVID and 5 years of follow-up in WOSCOPS), was reasonably close (27% versus 22%), the absolute risk reduction and residual risks were very different. The absolute benefit in AVID was 7% over 2 years, whereas in the WOSCOPS, the absolute total mortality benefit was 0.9% over a study period of 5 years. In addition, the residual risk in AVID was considerably higher than in the WOSCOPS population, as might be expected for the populations in the two studies. The high residual risk in AVID dwarfs, to some extent, the absolute risk reduction.

In another comparison, ICD use versus amiodarone (AVID), and cessation of cigarette smoking among survivors of out-of-hospital cardiac arrest [35], both identify absolute and relative risk benefits of the same general order of magnitude. However, these two separate observations leads us to question of whether there is a positive interaction between cigarette smoking cessation and the ICD (Figure 1.3(b)). Subgroup analyses are not sufficient to answer these questions. Cessation of cigarette smoking is but one of a number of interventions that could be tested in parallel with ICD therapy, seeking positive interactions. The general principle has been suggested for amiodarone and beta-blockers in post-myocardial infarction patients.

A final consideration in the epidemiology of interventions is the comparison of entry criteria to actual enrollment. In many of the ICD trials, the range of EFs and functional classifications were unintentionally biased toward certain values, limiting the interpretation and proper application of the outcomes (see Table 1.1). EF entry criteria were largely in the range of $\leq$30 to $\leq$40%,

Table 1.1 Comparison of entry criteria to actual enrollment

	Reference	Ejection fraction		Time from qualifying event	
		Entry criterion	Actually enrolled	Entry criterion	Actually enrolled
MADIT	49	≤35%	26% (±7%) (Mean ± SD)	≥3 weeks	75% ≥6 months
MUSIT	50	≤40%	30% (21%, 35%) (Median; 25th, 75th percentile)	≥4 days	39% ≤1 year 50% ≥3 years
MADIT-2	51	≤30%	23% (±5%) (Mean ± SD)	>1 month	88% ≥6 months
SCD-HeFT	52	≤35%	25% (20%, 30%) (Median; 25th, 75th percentile)	Not specified	24 months (28, 25) (Median; 25th, 75th percentile)
COMPANION	53	≤35%	21% (±5%) (Mean ± SD)	Not specified	43 months (CHF) (Median)
DEFINITE	54	≤35%	21% (7–35%) (Mean, range)	Not specified	32 months (CHF)

but enrollment was dominated by lower ranges. Therefore, the benefit to those with the higher end of the EF range is not clear.

Genetic epidemiology of SCD

Limitations in identifying the *individual* at risk of SCD from among the general population is a major reason why SCD remains an important public health problem. The ability to identify individual-specific predisposition to expression of plaque disruption-thrombosis, and of electrophysiological responses leading to life-threatening arrhythmias, could lead to preventive actions in anticipation of the potentially fatal disturbances. New insights into specific risk at all levels of the cascade offer hope for better individual risk prediction, expressed in terms of higher orders of *single-patient probabilities*, in contrast to less specific general population risks [21].

Interest in the evolving constellation of information on genetic control of ion channel function (see Chapter 9) is reinforced by recent epidemiological studies, suggesting that SCD may be a patient-specific response in acute coronary syndromes. Two studies have demonstrated a pattern of familial clustering of SCD, with an excess risk of sudden death as the specific initial manifestation of an acute coronary syndrome when there is family history of SCD in one parent [30,31], and even higher when both sides of the family are affected [31]. While such familial clustering could be either genetic or environmental, studies on genetically-based arrhythmia syndromes provide a series of candidate

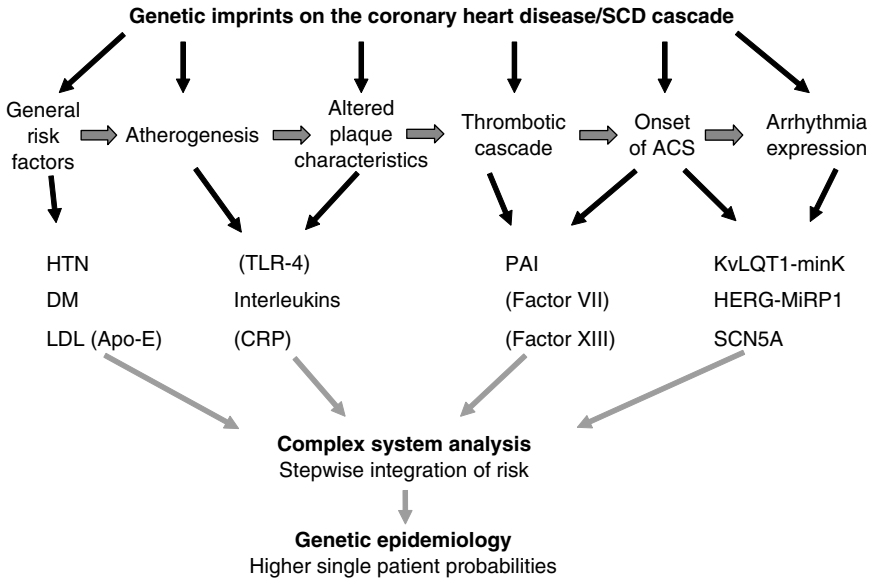


Figure 1.4 Genetic imprints on the cascade from coronary atherogenesis to sudden cardiac death. Influences of genetic variations on individual risk prediction have been identified for elements of atherogenesis, plaque evolution, the thrombotic cascade, and arrhythmia expression. Stepwise integration of these characteristics for individuals through complex system analysis methods offers the hope of a field of genetic epidemiology that may lead to higher single-patient probabilities for SCD risk prediction. Modified from Reference 21, with permission.

genes that could be the targets of studies seeking polymorphisms or mutations carried by such families. An example is a genetic variant in the cardiac sodium channel gene (*SCN5A*) observed among the African American population (carrier rate = 13.2%) that appears to predispose to arrhythmias, even though it does not express as a prototypic long-QT syndrome under control conditions [55]. Its role in predicting risk of SCD awaits clarification. Although still in its infancy, the potential impact on predicting and preventing sudden death could be huge.

A major paradigm shift in the epidemiology of coronary heart disease may emerge from new insights into the cause and expression of the multiple elements in the cascade of lesion formation, initiation of acute coronary syndromes, and triggering of cardiac arrest and SCD (Figure 1.4). Conceptually, nonexpressed variations of DNA sequences in genes encoding ion channel structure may transpose into an abnormal phenotype under pathophysiologic conditions, thus integrating with the pathophysiology of the acute coronary syndrome.

As data applicable to an expanded epidemiological approach evolves, it will call for a conceptual transformation of the sequential pathophysiologic cascade

into a complex system analytic model [21,56]. The value of this approach derives from the fundamental limitation of the ability of conventional risk factors to identify specific individuals at high risk for SCD (or other manifestations of coronary artery disease) from among the *general* population. Because the majority of SCDs occur in individuals without easily identifiable high absolute risks for cardiovascular or total mortality (Figure 1.1), and risk is multifactorial, more precise predictors of *single-patient probabilities* of risk of coronary heart disease generally, and SCD in particular, must be sought. This will have to come from mathematical analyses of the interactions between multiple risks or complex system analysis.

When viewed from the perspective of a complex system, containing voluminous bioinformation, both the difficulty and the opportunity become evident. Genetic, environmental, and acquired pathophysiological states all may play roles. The value of genetically-based analysis of risk is the fact that it provides predetermined patterns far in advance of clinical events. Higher-order *single-patient probabilities*, derived from integration of properties at multiple levels of pathophysiology, will complement the power of risk expression for individual components of the SCD cascade (Figure 1.4). The ultimate goal is to profile individual risk at multiple steps in the SCD cascade, generating probability figures that are powerful enough to be useful for preventive strategies far in advance of clinical events. The degree to which analysis of genetic interactions can achieve this goal remains speculative [21,57]. However, it is clear that answering the question can be achieved only by new epidemiological models, requiring large investments into both the specialized personnel and computing power needed by a new community of science within the field of bioinformatics. Closing the gap between the numerator and denominator for SCD among the general population will offer the hope of having a far greater impact on the problem of SCD than any other approach has offered in the past, or will offer in the future, by conventional risk profiling [57].

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