Out-of-Hospital Cardiac Arrest
Getting Beyond the Tip of the Iceberg

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Sudden Cardiac Death: The Scope
Sudden cardiac death (SCD), which is responsible for approximately 300,000 deaths in the United States, refers to an unexpected death from a cardiovascular cause in a person with or without preexisting heart disease. Most studies include cases that are associated with death occurring within 1 hour of an acute change in clinical status or an unexpected death that occurred within the previous 24 hours, but this definition is not specific for sudden arrhythmic death. The most common sequence of events leading to arrhythmic SCD is the degeneration of ventricular tachycardia (VT) into ventricular fibrillation (VF), often followed by asystole or pulseless electric activity. The transition of shockable rhythms (VT/VF) to more ominous rhythms such as asystole or pulseless electric activity depends on various factors, but is highly dependent on time; the longer the time interval, the more likely the VT/VF degenerates to pulseless electric activity or asystole. Although VF and VT together represent the initial rhythm in half of all outpatient cardiac arrests, data suggest that with each passing minute of untreated VF, the likelihood of survival is reduced by 7% to 10%. Preexisting coronary artery disease and its sequelae (eg, acute myocardial ischemia, scarring from previous myocardial infarction, heart failure) are manifest in 80% of SCDs. Dilated nonischemic and hypertrophic cardiomyopathies account for the second largest number of SCDs, whereas other cardiac disorders such as congenital heart disease and underlying genetically determined ion channel anomalies account for 5% to 10% of SCDs. Although the cascade of events triggering SCD are complex and are currently active areas of investigation, the general goals of reducing SCD are focused on (1) identifying and preventing sudden death in high-risk individuals by using efficacious therapies such as medications and implantable cardioverter defibrillators (ICDs), (2) organizing resuscitation services to improve response to and efficiency and effectiveness of treatments directed to individuals who experience cardiac arrest, and (3) improving survival rates for individuals who experience SCD by implementing and organizing specialized services at hospitals that deliver postresuscitation care.

SCD Prevention
Response to OHCA
Hulleman et al4 assess the role of ICDs in reducing the incidence of resuscitation for out-of-hospital cardiac arrest (OHCA) caused by lethal ventricular arrhythmias, the specific target for ICD therapy. They found that the incidence of VF-OHCA decreased during a 10-year period in north Holland from 21.1/100,000 inhabitants per year to 17.4/100,000 inhabitants per year, and that ICD therapy likely explained approximately one third of this decrease (1.2/100,000 inhabitants per year). Interestingly, the incidence of non-VF-OHCA increased during the same time period from 12.2/100,000 inhabitants per year to 19.4/100,000 inhabitants per year, leading to an overall increased rate of OHCA.

Although many assumptions are made in this report, any one of which could affect the results, the sensitivity analyses as well as concordance with other data suggest that these estimates have substantial validity. This validity enables us to use these important data to provide a global perspective on the tremendous efforts that have been put forth during the past several decades on prevention of SCD.

Multifaceted approaches have been implemented to reduce the number of SCDs. In this issue of Circulation, Hulleman et al4 assess the role of ICDs in reducing the incidence of resuscitation for out-of-hospital cardiac arrest (OHCA) caused by lethal ventricular arrhythmias, the specific target for ICD therapy. They found that the incidence of VF-OHCA decreased during a 10-year period in north Holland from 21.1/100,000 inhabitants per year to 17.4/100,000 inhabitants per year, and that ICD therapy likely explained approximately one third of this decrease (1.2/100,000 inhabitants per year). Interestingly, the incidence of non-VF-OHCA increased during the same time period from 12.2/100,000 inhabitants per year to 19.4/100,000 inhabitants per year, leading to an overall increased rate of OHCA.

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have limited effectiveness in reducing overall mortality from SCD. Delays in emergency medical services (personnel reaching a witnessed SCD individual, not having an automated external defibrillators readily available, and not initiating immediate cardiopulmonary resuscitation) may contribute to rapid deterioration of a life-threatening ventricular tachyarrhythmia to asystole. More important, unwitnessed SCD carries a grave prognosis, largely because the time to resuscitative efforts is delayed and resuscitative efforts may not even be initiated in one third of cases. It is important to note that improvement in postarrest therapies and approaches are not likely to influence the number of OHCAs, only the outcome.

Although there are significant limitations in delivering optimal services to individuals with OHCA, some metropolitan areas that have adopted organized approaches to resuscitative medicine have shown that overall rates of survival from OHCA—in particular, witnessed VF—can improve over time. Time to first shock has averaged 6 minutes in Rochester, MN, and between 2006 and 2008, survival to hospital discharge for bystander-witnessed events in which individuals presented with VF exceeded 50%.9

**Prevention of OHCA**

These coordinated efforts to provide rapid response to SCD individuals are complemented by approaches to prevent SCD. Prevention requires a synergy of efforts, including proper medical therapy and ICD placement in appropriate high-risk individuals. The work by Hulleman et al4 is important because it, specifically, places into context the role of ICDs in reducing VF-OHCA in light of important changes in the epidemiology of disease and other factors in north Holland. Because ICD use explained only 33% of the reduced incidence of VF-OHCA in this study, the implication is that additional factors are significant contributors to the decline in VF-OHCA incidence.

**Medication Use**

Improved use of medical therapies such as β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, potassium-sparing diuretics, and polyunsaturated fatty acids that may affect SCD likely have had an impact on the declining incidence of VF-OHCA. These therapies most likely confer their antiarrhythmic potential indirectly by inhibiting or delaying adverse structural remodeling in a diseased heart, and by modulating upstream inflammatory and neurohormonal pathways, thereby contributing to electrophysiological stability. Specifically, Hulleman et al4 point out that β-blocker use, which has been reported to decrease sudden death by as much as 50%, may have reduced the incidence of VF. Yet, there are potentially important ramifications of these therapies, particularly in light of the reported increase in non-VF-OHCA. Individuals taking β-blockers who experienced OHCA were 5 times more likely to present with non-VF than VF as the first documented rhythm. A recent trial using implantable loop recorders in myocardial infarction patients with left ventricular dysfunction reported that VF and bradyarrhythmias accounted for equal proportions of recordings at the time of death. Even though VT/VF was the terminal rhythm and was associated primarily with SCD, intermittent high-degree atrioventricular block was also a strong predictor of cardiac death.14 It is conceivable that β-blockers not only reduce the incidence of VT/VF, but also may alter the electrophysiological milieu in such a manner as to convert VF-OHCA events to non-VF events. Further efforts to ensure proper medical therapy and to understand the interactions of medical therapy with the diverse mechanisms of SCD are necessary.

**Declines in Coronary Heart Disease Rates**

A second potential reason for reduction in VF-OHCA incidence is a concomitant decline in coronary heart disease (CHD) burden over time. This decline can likely be explained by improvements in diagnosis and treatment of comorbidities associated with CHD, such as diabetes mellitus, hypertension, and dyslipidemia, and improved targeted therapies and interventions for CHD. Because CHD is the leading cause of SCD in the world, a decline in CHD rates should parallel the reduction in VF-OHCA rates to some degree. As Hullemen et al4 note, the decline in VF-OHCA may also be attributed to other changing biological mechanisms in the population at risk for VF.

**Future Approaches to OHCA**

The impact of the ICD in reducing the population-based problem of SCD is clearly significant, but is far from enough. Certainly one of the factors limiting the population impact of ICDs is the consistent finding that most individuals who experience SCD fall outside the current guidelines for consideration of an ICD. Substantial impact on VF-OHCA can be achieved by improving our ability to identify individuals at risk for SCD prior to them experiencing a life-threatening event. More important, enhancing our risk stratification armamentarium of tools, genetic markers, and other techniques to provide adequate discriminatory power to manage individuals requires rigorous and ongoing research.15

Although the field of risk stratification for the prevention of SCD is currently focused on using certain approaches to identify appropriate ICD candidates, the importance of this research endeavor transcends this specific treatment. Individuals found to be at significant risk for SCD could be treated with a host of therapies, including lifestyle modifications (ie, exercise, diet), more aggressive medical therapy, and newer medical or other novel therapies. Examples of the latter could include vagus nerve stimulators or spinal cord stimulators meant to modulate the autonomic nervous system effects on the heart.

The final challenge in addressing the vast public health problem of SCD is that, in a sizable percentage of individuals, SCD is the first manifestation of cardiac disease. Improved public education and screening for cardiovascular disease are modalities that may impact SCD in this subpopulation. Because of the number of susceptible individuals who would not be identified as candidates for an ICD using current guideline approaches, it remains important to continue to focus on rapid identification and efficient response systems to OHCA, and successful restoration of spontaneous circulation. Continued improvements in this field, such as greater dissem-
ination of automated external defibrillators, rapid and early cardiopulmonary resuscitation, the development and implementation of hypothermia protocols, and other systems of care will also further impact SCD outcomes and lead to improved survival rates in OHCA. In Philadelphia, for example, a comprehensive multidisciplinary treatment protocol for patients resuscitated from OHCA and its implementation led to survival rates that improved from 22% to >50%.9

The future clearly holds significant opportunity to reduce the population burden of OHCA (Figure). Our greatest opportunity appears to stem from unlocking the mechanisms and triggering events leading to VF in at-risk individuals and disseminating appropriate therapies to limit this risk. Our greatest challenge may be in preventing and treating non-VF-OHCA, for which the triggering events for SCD remain elusive. Because non-VF-OHCA represents a sizable portion of all OHCA’s, a better understanding of this mode of SCD and its precursors is required to have a tangible impact. The future, as suggested by Hullemann et al., may bring further shifts in OHCA from VF to non-VF cases.

Improvements in risk stratification and identification of individuals as appropriate candidates for medical and device therapy, advancements in medical therapy to limit progression of cardiac disease, and enhancements in resuscitative services collectively will lead to incremental and continued declines in the incidence of VF-OHCA and overall SCD rates. Further studies are necessary to continue to track the epidemiological impact of all these efforts on OHCA.

Disclosures
Dr Goldberger is director of the Path to Improved Risk Stratification, a not-for-profit think tank on risk stratification for prevention of sudden cardiac death, which has received unrestricted educational grants from Medtronic, Boston Scientific, and St. Jude Medical. Dr Goldberger has received past honoraria from Medtronic, Biotronik and St. Jude Medical. Dr Ilkhanoff has received past honoraria from Biotronik and St. Jude Medical.

References


Key Words: Editorials ■ death ■ sudden ■ ventricular fibrillation ■ ventricular tachycardia
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Circulation. 2012;126:793-796; originally published online August 6, 2012;
doi: 10.1161/CIRCULATIONAHA.112.123588

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World Wide Web at:
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