Predicting and Preventing Sudden Cardiac Death

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Case presentation: A 61-year-old moderately obese (body mass index 28.1 kg/m²) hypertensive diabetic man without any prior cardiac history collapsed suddenly at a town meeting. Bystander cardiopulmonary resuscitation was initiated, an automated external defibrillator available at the town hall was deployed, and a single shock was delivered. He regained a pulse and spontaneous respirations. He was transported to the local hospital, where he was stabilized, but remained comatose. The patient was immediately transferred to a tertiary hospital, where a therapeutic hypothermia protocol was initiated. No ECG or laboratory evidence of a transmural myocardial infarction (MI) was present. He regained consciousness 2 days after resuscitation. Coronary angiography demonstrated significant obstruction of 3 major coronary arteries, with mild global impairment of left ventricular function with an ejection fraction of 45%. Coronary bypass surgery was performed, and after implantable cardioverter-defibrillator (ICD) placement, he was discharged on a statin, a β-blocker, aspirin, and an angiotensin-converting enzyme inhibitor. The patient has no residual neurological or cognitive deficits. He has done well clinically in a cardiac rehabilitation program stressing exercise, diet, and lifestyle changes to achieve an ideal body weight.

Overview

Sudden cardiac death (SCD) from cardiac arrest is the most common cause of death worldwide, accounting for >50% of all deaths from cardiovascular disease. SCD results in ∼250 000 to 300 000 deaths annually in the United States, and is characterized by unexpected cardiovascular collapse due to an underlying cardiovascular cause. SCD represents a major challenge for the clinician because most episodes occur in individuals without previously known cardiac disease. Because most individuals experiencing SCD currently are not identifiable as being at high risk, community-based public access to defibrillation programs is essential to save lives and improve neurological and functional outcomes for cardiac arrest victims. Although there has been a recent decline in the incidence of SCD paralleling the decline in the decrease in cardiovascular mortality, the burden of SCD remains substantial. On average, only 8% of those receiving community-based resuscitation are discharged from the hospital alive. There are many opportunities for clinicians to improve outcomes of cardiac arrest through preventive measures in their practice, resuscitation programs in their community, and postresuscitation care protocols in their hospital.

Pathophysiology

Ventricular fibrillation is the mechanism underlying most sudden cardiac arrest episodes. Survival declines by ∼10% per minute for patients in ventricular fibrillation. This underscores the critical importance of early and definitive intervention with defibrillation. Other cardiac tachycardias, bradycardias, or pulseless electric activity can also result in cessation of cardiac mechanical activity with absence of signs of circulation. Other causes of SCD include stroke, pulmonary embolism, aortic rupture, and other noncardiac causes. Cardiac arrest typically arises suddenly in an individual with the appropriate anatomic or electrophysiological substrate without an identifiable trigger (Table 1). Although the current paradigm for the pathophysiology of SCD includes an abnormal myocardial substrate and transient factors that trigger the cardiac arrest, in most instances a clinical trig-
ger cannot be identified (Table 2).1–4 There has been a notable decrease in the incidence of cardiac arrest from ventricular fibrillation recently.2–4 Multiple factors are likely to contribute to this decline. These include improvements in prevention of sudden death and cardiovascular disease as well as community approaches to resuscitation and care after out-of-hospital cardiac arrest.2–4

**Prevention of Sudden Cardiac Death**

Multiple strategies have evolved to predict and prevent SCD. One strategy receiving recent emphasis is primordial prevention of coronary artery disease.5 This approach stresses prevention of development of risk factors for cardiovascular disease and stroke, as represented in the term primordial prevention.3 Optimization of blood pressure, weight, glucose, cholesterol, smoking, diet, and physical activity, through lifestyle interventions, is the focus of this approach.5 Although it is intuitive that this strategy will reduce cardiovascular disease and SCD, robust evidence supporting this notion is currently lacking.5

Primary prevention of SCD with risk stratification and intervention in those individuals with established cardiovascular disease placing them at high risk is another strategy to improve outcomes.1–4 The most common underlying cardiovascular condition predisposing to SCD is coronary artery disease. In ~50% of cases, SCD is the first manifestation of the coronary disease.1–5 Risk factors for SCD include advanced age, male sex, cigarette smoking, hypertension, diabetes mellitus, hypercholesterolemia, obesity, and a family history of coronary artery disease.3 These risk factors for SCD are also predictors of coronary heart disease–related death and all-cause mortality.1–4 Impaired left ventricular function as well as multiple other genetic, anatomic, and electrophysiological risk factors for sudden death have been identified.1–4 These risk factors are temporally dynamic and vary by anatomic and electrophysiological substrate, age, sex, and race.1–4 Although risk stratification is useful to identify populations of individuals at risk for SCD, current techniques to identify high-risk individuals lack sufficient predictive value to have clinical utility because of the relatively low event rates or absolute risk (Figure 1).1–4

**Pharmacological interventions demonstrated to reduce the risk of sudden cardiac arrest in patients with impaired left ventricular function from coronary disease or cardiomyopathy include β-blockers, angiotensin-converting enzyme inhibitors, and statins.**1 Suppression of spontaneous ventricular arrhythmias with antiarrhythmic agents has been shown to have a neutral or negative effect on mortality in prospective, randomized trials.1 By contrast, use of the ICD has been demonstrated to reduce sudden death and improve total mortality in selected patient populations, including those with impaired ventricular function and those with ischemic or nonischemic cardiomyopathy.6 Multiple clinical tri-
als randomizing several thousand patients have demonstrated that the ICD prevents sudden death and significantly reduces overall mortality among patients with left ventricular dysfunction due to dilated nonischemic cardiomyopathy or ischemic heart disease (Table 3).6

Secondary prevention refers to clinical intervention in patients who have survived a prior cardiac arrest or sustained ventricular tachycardia.6 In these patients, the ICD has proven superior to antiarrhythmic drug therapy for prolonging survival.6 Recommendations for ICD therapy apply only to patients who are receiving optimal medical therapy and have a reasonable expectation of survival with good functional status for >1 year (Table 4).6 When indicated for primary and secondary prevention, ICD use is beneficial and cost-effective.7 Unfortunately, studies suggest that most patients who have indications for this therapy for primary or secondary prevention of SCD are not receiving ICDs.7

### Table 3. Clinical Trials of Use of Implantable Cardioverter-Defibrillator to Prevent Sudden Cardiac Death and Reduce Overall Mortality in Patients With Left Ventricular Dysfunction

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Patients, n</th>
<th>LVEF, %</th>
<th>Additional Study Features</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADI I</td>
<td>1996</td>
<td>196</td>
<td>≤35</td>
<td>NSVT and EP positive</td>
<td>0.46</td>
<td>(0.26–0.82)</td>
<td>0.009</td>
</tr>
<tr>
<td>MADI II</td>
<td>2002</td>
<td>1232</td>
<td>≤30</td>
<td>Prior MI</td>
<td>0.69</td>
<td>(0.51–0.93)</td>
<td>0.016</td>
</tr>
<tr>
<td>MUSTT</td>
<td>2000</td>
<td>1397</td>
<td>≤40</td>
<td>Prior MI, NSVT, inducible VT</td>
<td>0.77</td>
<td>(0.62–0.94)</td>
<td>0.005</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>2006</td>
<td>1676</td>
<td>≤35</td>
<td>Prior MI or NICM</td>
<td>0.77</td>
<td>(0.62–0.96)</td>
<td>0.007</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>2004</td>
<td>485</td>
<td>≤35</td>
<td>NICM, PVCs, or NSVT</td>
<td>0.65</td>
<td>(0.40–1.06)</td>
<td>0.08</td>
</tr>
<tr>
<td>CABB-Patch</td>
<td>1997</td>
<td>900</td>
<td>≤36</td>
<td>Positive SAECG and CABG</td>
<td>1.07</td>
<td>(0.81–1.42)</td>
<td>0.63</td>
</tr>
<tr>
<td>DINAMIT</td>
<td>2004</td>
<td>674</td>
<td>≤35</td>
<td>6–40 d post-MI and impaired HRV</td>
<td>1.08</td>
<td>(0.76–1.55)</td>
<td>0.66</td>
</tr>
<tr>
<td>IRIS</td>
<td>2009</td>
<td>898</td>
<td>≤40</td>
<td>&lt;30 d post-MI, HR &gt;90, or NSVT</td>
<td>1.04</td>
<td>(0.81–1.35)</td>
<td>0.78</td>
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<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVID</td>
<td>1997</td>
<td>1016</td>
<td>Prior cardiac arrest</td>
<td>NA</td>
<td>0.62</td>
<td>(0.43–0.82)</td>
<td>NS</td>
</tr>
<tr>
<td>CASH</td>
<td>2000</td>
<td>191</td>
<td>Prior cardiac arrest</td>
<td>NA</td>
<td>0.766</td>
<td>1-sided</td>
<td>0.081</td>
</tr>
<tr>
<td>CIDS</td>
<td>2000</td>
<td>659</td>
<td>Prior cardiac arrest, syncope</td>
<td>NA</td>
<td>0.82</td>
<td>(0.06–1.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

AVID indicates Antiarrhythmics vs Implantable Defibrillators; CABB, coronary artery bypass grafting; CABB-Patch, Coronary Artery Bypass Graft–Patch; CASH, Cardiac Arrest Study Hamburg; CI, confidence interval; CIDS, Canadian Implantable Defibrillator Study; DEFINITE, Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator in Acute Myocardial Infarction Trial; EP, electrophysiological study; HR, heart rate; HRV, heart rate variability; LVEF, left ventricular ejection fraction; MADI I, Multicenter Automatic Defibrillator Implantation Trial I; MADI II, Multicenter Automatic Defibrillator Implantation Trial II; MI, myocardial infarction; MUSTT, Multicenter Unsustained Tachycardia Trial; NICM, nonischemic cardiomyopathy; NSVT, nonsustained ventricular tachycardia; PVCs, premature ventricular complexes; SAECG, signal-averaged electrocardiogram; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; and VT, ventricular tachycardia.

### Prevention of Sudden Cardiac Death After Myocardial Infarction

SCD in the immediate period after MI represents a particular clinical challenge.8–10 With widespread advances in the treatment of ST-segment elevation MI with primary percutaneous coronary intervention and pharmacological therapy, sudden death and total mortality after MI have decreased.8–10 Despite optimal therapy, the risk of SCD is highest in the first 30 days among patients with left ventricular dysfunction.1–4,8–10 Two recent trials showed no improvement in mortality with early placement of an ICD in patients at high risk of SCD after MI.9,10 Recent autopsy evaluation of patients experiencing sudden cardiac arrest in the immediate post-MI period indicates that there is a high frequency of cardiac rupture or recurrent MI in the first month after the index MI, whereas arrhythmic deaths become more likely subsequently.11 These findings may help to explain the lack of benefit of early ICD therapy after MI.

Current clinical guidelines restrict ICD implants to patients at least 40 days after MI with continued impairment of left ventricular function while on optimal medical therapy.6 The strategy of home automated external defibrillator use in high-risk post-MI patients failed to improve survival compared with conventional resuscitation methods.12 Prior studies using risk stratification with programmed ventricular stimulation in high-risk patients immediately after MI have also failed to demonstrate any survival benefit.13 Although the short-term use of noninvasive vest defibrillation is a reasonable approach with high-risk post-MI patients, it remains to be evaluated in appropriately designed prospective trials.13 It is evident that additional research is needed to identify risk stratification and intervention strategies to prevent SCD immediately after MI. In the meantime, clinicians should optimize and individualize therapy in the immediate post-MI patient while carefully considering the
The Chain of Survival

The concept of the chain of survival was developed to underscore the critical importance of the time-sensitive steps that each independently improve the outcome of cardiac arrest. These stepwise links include early activation of emergency medical services, early cardiopulmonary resuscitation, early defibrillation, and timely advanced care. The chain of survival includes a strategy of training and equipping members of the lay population to perform cardiopulmonary resuscitation and defibrillation with an automated external defibrillator when a cardiac arrest occurs through local public access to defibrillation programs. A prospective, randomized trial demonstrated that this approach is medically effective and cost-effective. However, the benefits were limited to

Table 4. Indications for ICDs*

Class I

ICD therapy is indicated for:
- Survivors of cardiac arrest
- Patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable
- Patients with syncope of undetermined origin with clinically relevant, hemodynamically significant induced sustained VT or VF
- Patients with LVEF <35% due to prior MI who are at least 40 d post-MI and are in NYHA functional class II or III
- Patients with nonischemic dilated cardiomyopathy with NYHA class II or III heart failure with LVEF ≤35%
- Patients with LVEF <30% due to prior MI who are at least 40 d post-MI
- Patients with nonsustained VT due to prior MI, LVEF <40%, and inducible VF or sustained VT

Class IIa

ICD therapy is reasonable for:
- Patients with unexplained syncope, significant LV dysfunction, and nonischemic dilated cardiomyopathy
- Patients with sustained VT and normal or near-normal ventricular function
- Patients with hypertrophic cardiomyopathy who have ≥1 major risk factor for SCD
- Patients with arrhythmogenic right ventricular dysplasia cardiomyopathy who have ≥1 risk factor for SCD
- Patients with long-QT syndrome who are experiencing syncope and/or VT while receiving β-blockers
- Nonhospitalized patients awaiting transplantation
- Patients with Brugada syndrome who have had syncope or VT
- Patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving β-blockers
- Patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease

Class IIb

ICD therapy might be considered for:
- Patients with nonischemic heart disease with NYHA class I heart failure and LVEF ≤35%
- Patients with long-QT syndrome and risk factors for SCD
- Patients with syncope of unknown origin and advanced structural heart disease
- Patients with a familial cardiomyopathy associated with sudden death
- Patients with LV noncompaction

Class III

ICD therapy is not indicated for:
- Patients without a reasonable expectation of survival with an acceptable functional status for at least 1 y
- Patients with incessant VT or VF
- Patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up
- NYHA class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or cardiac resynchronization therapy defibrillators
- Patients with syncope of undetermined cause without inducible ventricular tachyarrhythmias and without structural heart disease
- Patients with VF or VT amenable to surgical or catheter ablation
- Patients with ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease

ICD indicates implantable cardioverter-defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; MI, myocardial infarction; and SCD, sudden cardiac death.

*All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for ≥1 y.

risks of sudden death and mortality from other causes. The Chain of Survival

The concept of the chain of survival was developed to underscore the critical importance of the time-sensitive steps that each independently improve the outcome of cardiac arrest (Figure 2). These stepwise links include early activation of emergency medical services, early cardiopulmonary resuscitation, early defibrillation, and timely advanced care. The chain of survival includes a strategy of training and equipping members of the lay population to perform cardiopulmonary resuscitation and defibrillation with an automated external defibrillator when a cardiac arrest occurs through local public access to defibrillation programs. A prospective, randomized trial demonstrated that this approach is medically effective and cost-effective. However, the benefits were limited to
those cardiac arrests occurring in public locations. The limitations of this approach are evident because only one third of cardiac arrests occur in public locations. Randomized trials have failed to demonstrate benefit of the use of automated external defibrillators by lay responders in residential locations. However, these trials lacked sufficient power to detect a clinically significant improvement in outcomes. Importantly, public policy initiatives have encouraged public access to defibrillation programs and automated external defibrillator use with broad legal protection of lay individuals and trained first-responders with Good Samaritan legislation.

A recent retrospective observational study suggests that targeted deployment in locations with a high incidence of cardiac arrest could improve outcomes in a more cost-effective manner. There is a >5-fold regional variation in survival after cardiac arrest, with the worst outcomes in neighborhoods with the lowest education level, highest population density, and lowest socioeconomic status. Prospective assessment of selective interventions in these high-risk communities and other approaches to improve outcomes while reducing disability, death, and disparity are needed.

The Importance of Postresuscitation Care
Survival rates vary widely among patients resuscitated from cardiac arrest by emergency medical services, ranging from as low as 10% to >50%. There is a growing body of evidence that effective hospital-based interventions can improve functional survival. Many patients who are initially resuscitated from cardiac arrest and admitted to the hospital die before discharge or have impaired neurological outcomes. Although immediate resuscitation has been the traditional focus of clinical investigation and treatment guidelines, more recent efforts have demonstrated the importance of post–cardiac arrest care. Some of the important elements of an effective post–cardiac arrest care strategy are delivery of therapeutic hypothermia to selected comatose patients, coronary angiography when there is a high degree of suspicion of an acute ischemic trigger, early hemodynamic stabilization of the patient with the ability to effectively treat re-arrest, reliable prognostication, and appropriate cardiac electrophysiological assessment and treatment before discharge. Multiple studies demonstrate the efficacy of multifaceted hospital-based interventions in patients resuscitated from cardiac arrest.

Improving Outcomes in Clinical Practice and the Community
There are many opportunities for clinicians to predict and prevent SCD in their practices and their communities (Table 5). Prevention of risk factors for coronary artery disease is one clinical strategy. Identification and appropriate treatment of individuals at risk for SCD with primary and secondary prevention represents another useful approach. Robust evidence supports reduction in sudden death and reduced mortality with pharmacological and ICD therapy in many patient populations at high risk for SCD. Although there has been considerable progress in understanding the mechanisms, risk factors, and epidemiology of sudden cardiac arrest, it is evident that much remains unknown. Further basic, translational, clinical, and population research is needed to develop novel strategies to reduce the burden of SCD. Clinician leadership is essential to ensuring that all stakeholders develop a well-integrated chain of survival in their community. Similarly, physicians should ensure that regionalized systems of hospital care are optimized for the post–cardiac arrest patient. Successful implementation of these strategies for prevention and improved resuscitation and postresuscitation care will save lives and improve the neurological and functional outcomes of pa-

Table 5. Clinical Strategies to Improve Outcomes From Sudden Cardiac Death

| Prevention of risk factor development for coronary artery disease |
| Primary prevention and secondary prevention of sudden cardiac death |
| Appropriate use of β-blocker, ACE inhibitor, and statin therapy |
| Implantable cardioverter-defibrillator use in selected patients |
| Community-based public access to defibrillation programs |
| Regionalized systems of postresuscitation hospital care |

ACE indicates angiotensin-converting enzyme.
tients in our practice and individuals in our community.

Disclosures
Dr Estes has received consulting fees (modest) from Boston Scientific.

References


