Sudden Cardiac Death: Epidemiology and Temporal Trends

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Sudden cardiac death (SCD) now accounts for more than half of all coronary heart disease deaths in the United States. The majority of cases are due to underlying coronary artery disease, and deaths from both coronary artery disease and SCD have declined markedly over the past several decades due to improved primary and secondary prevention and treatment strategies. This review examines the current statistics on the prevalence of SCD, and identifies those patients at greatest risk. It also discusses existing tests and treatments, including medication that results in neurohormonal antagonism, and devices such as the implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy with a defibrillator (CRT-D). Along with increased public awareness of SCD as a major health risk, physicians are advised to implement proven effective drug and devices that can improve survival.
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The majority of cases of sudden cardiac death (SCD) occurring in the United States are due to coronary artery disease and 20% to 40% of all patients experiencing SCD do not have a history of heart disease.[1-5] Deaths from coronary artery disease have declined markedly over the past several decades due to improved primary and secondary prevention, and treatment strategies.[4] It also appears that the risk of SCD has declined in tandem.[5]

Data from the Framingham Heart Study comparing decade-specific risk ratios for coronary heart deaths due to sudden and non-sudden causes found a 49% decline in the risk of SCD from 1990 to 1999 as compared to 1950 to 1969. The risk of non-sudden death decreased even more dramatically by 64% over the same intervals.[5] A Seattle study of patients treated for out-of-hospital cardiac arrest also demonstrated a 43% decline in the incidence of cardiac arrest due to ventricular fibrillation between 1980 and 2000.[6] Interestingly, the proportion of cardiovascular deaths that are sudden has actually increased and SCD now accounts for more than half of all coronary heart disease deaths.[7]

Various methods exist to estimate the absolute number of sudden deaths occurring yearly in the United States.[1,5,8-10] Current estimates of the annual incidence range from 184,000 to 400,000[1-12] (Table 1). Analysis of death certificate information or data from first responder agencies may over- or underestimate the incidence of SCD. Ideally, multiple sources of ascertainment should be utilized to determine the true annual incidence.[8,9,12] In one community-based population study performed in Oregon, multiple sources of ascertainment were used, including emergency medical services, medical examiner records, and hospital records. The study found that SCD accounted for 5.6% of all deaths.[8]

The use of only death certificate data results in an overestimation of the incidence of SCD. The incidence of SCD most likely ranges between 50 to 90 per 100,000 persons.[8-11] Use of death certificate data alone would estimate the event rate at between 150 to 170 per 100,000 persons.[8,11,12]

The majority of SCD occurs in the home and most events are not witnessed.[8] These sudden deaths occur in patients older than age 65 years, and women account for nearly half of these patients.[7,8,13] However, the decline in SCD may be less in women than men.[6,7] Survival after cardiac arrest remains dismal, especially for out-of-hospital cardiac arrest.[7-13] Survival estimates range from 2% to 29%.[8-13] Risk factors associated with death include asystole or pulseless electrical activity and non-witnessed SCD.[6,8,10-13]

Table 1
Sudden Death in the United States

Annual incidence	184,000–400,000
Percentage of all coronary heart deaths	62–75
Percentage of sudden cardiac death with no known history of coronary heart disease	20–40
Percentage of sudden death due to transmural myocardial infarction	20
Average age of sudden death:	
Men	70 (years)
Women	82 (years)

Heart Failure Due to Systolic Dysfunction—A High-Risk Subgroup

While the greatest number of sudden deaths occurring annually in the United States happen in patients not considered to be in high-risk subgroups (30% with first clinical manifestation of coronary heart disease, 20% with acute myocardial infarction, 15% with minor risk factors), up to one third of sudden deaths occur in patients with depressed left ventricular ejection fraction (LVEF) due to both ischemic heart disease and non-ischemic etiologies of left ventricular (LV) dysfunction.[9,13,14]

The rate of SCD in this population is expected to rise as the incidence of heart failure (HF) prevalence doubles or triples in the next 2 to 3 decades.[15] This increase is attributed to the aging population and the prolonged survival of patients with chronic cardiovascular diseases that result in LV dysfunction.[16]

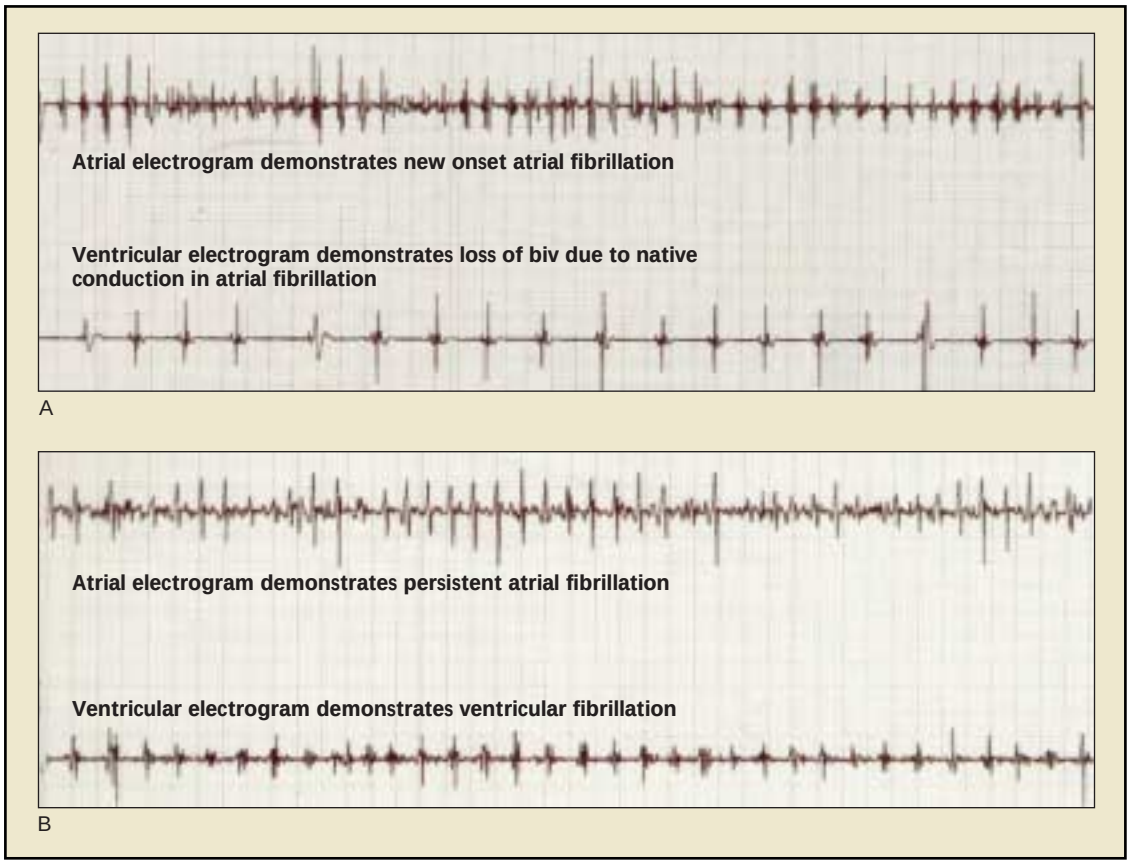
In absolute terms, the prevalence of HF in the United States is estimated at 4 to 5 million persons, with 400,000 to 700,000 new cases yearly.[13,14] The number of yearly deaths attributed to HF is 250,000, and approximately one third to one half of these deaths may be SCD.[10,13]

Sustained ventricular tachycardia or fibrillation are the rhythm disorders thought to cause the majority of SCD in HF patients. This is supported by the primary prevention implantable cardioverter defibrillator (ICD) trials performed in patients with LV dysfunction and symptomatic HF that demonstrate survival benefit within the ICD-treated groups.[17-22] However, a significant proportion of these deaths are due to other

mechanisms such as malignant bradyarrhythmias or electromechanical dissociation. The etiologies of these causes of SCD may be diverse and include acute ischemia, pulmonary embolism, acute neurophysiologic alterations, drug toxicities, or electrolyte abnormalities.[2,23,24] Figure 1 shows electrograms retrieved postmortem from a cardiac resynchronization therapy (CRT) pacemaker in a patient who died in his sleep. The electrograms demonstrate atrial fibrillation with a rapid native ventricular response that degenerates to ventricular fibrillation. Clearly, the ability to promptly defibrillate, as is present in a CRT with a defibrillator (CRT-D) device was needed. Figure 2 demonstrates the terminal rhythm of a patient with a CRT-D device, obtained by paramedics. The patient experienced SCD within an hour of the onset of acute shortness of breath. The rhythm strip shows acute ST elevation and lower rate pacing, and subsequently electromechanical dissociation. In this case, there was no history of coronary artery disease and the patient's HF symptoms had been stable. The patient was on warfarin therapy, but the differential diagnosis includes an acute embolic event, electrolyte disturbance, or drug toxicity. In this example, lower rate pacing was not able to sustain blood pressure and there was no ventricular tachyarrhythmia to defibrillate.

The proportion of deaths due to SCD in HF decreases as HF becomes more severe, as assessed by measures of functional status such as New York Heart Association Functional Class (NYHA FC) or exercise duration.[9,25] In the MERIT-HF Trial of the β-receptor-blocking agent metoprolol CR/XL (controlled release/extended release) in patients with NYHA FC II-IV heart failure, a 41% reduction in the risk of SCD was observed in metoprolol-treated patients. Interestingly, while mortality risk increased with increasing severity of HF, SCD was identified

Figure 1. *A comparison of a cardiac resynchronization therapy (CRT) device recording taken* **(A)** *24 hours before a patient's death and* **(B)** *at the time of death. The atrial electrogram demonstrates new onset of atrial fibrillation that becomes persistent at the time of death. The ventricular electrogram demonstrates loss of biventricular pacing (biv) due to native conduction in atrial fibrillation, and at the time of death, it demonstrates ventricular fibrillation. ICD, implantable cardioverter defibrillator. Patient file, LA Saxon, MD.*



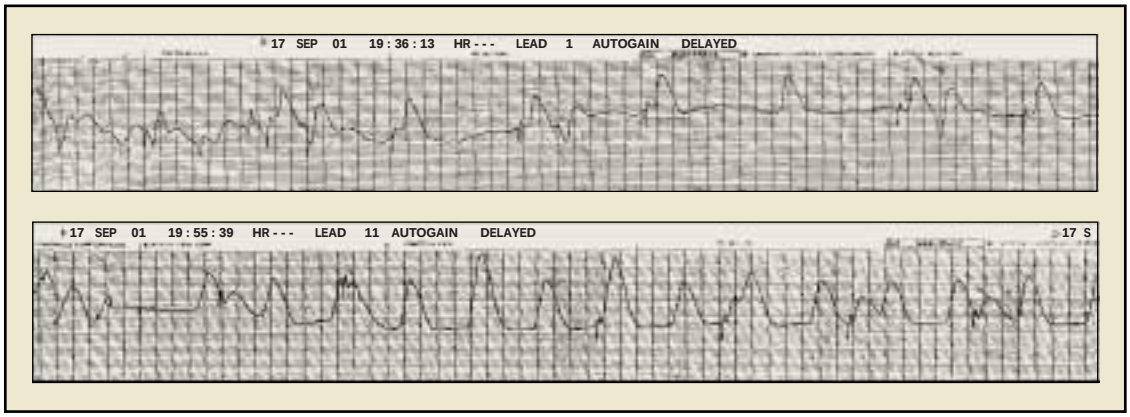


Figure 2. *Sudden cardiac death with a cardiac resynchronization therapy with a defibrillator device (device programmed VDD [ventricular sense, dual pace, dual response] 40 beats per minute). This rhythm strip was obtained shortly before the patient became pulseless and hypotensive. Patient file, LA Saxon, MD.*

as the cause of death in 33% of NYHA FC IV patients and accounted for 64% of deaths in NYHA FC II patients.

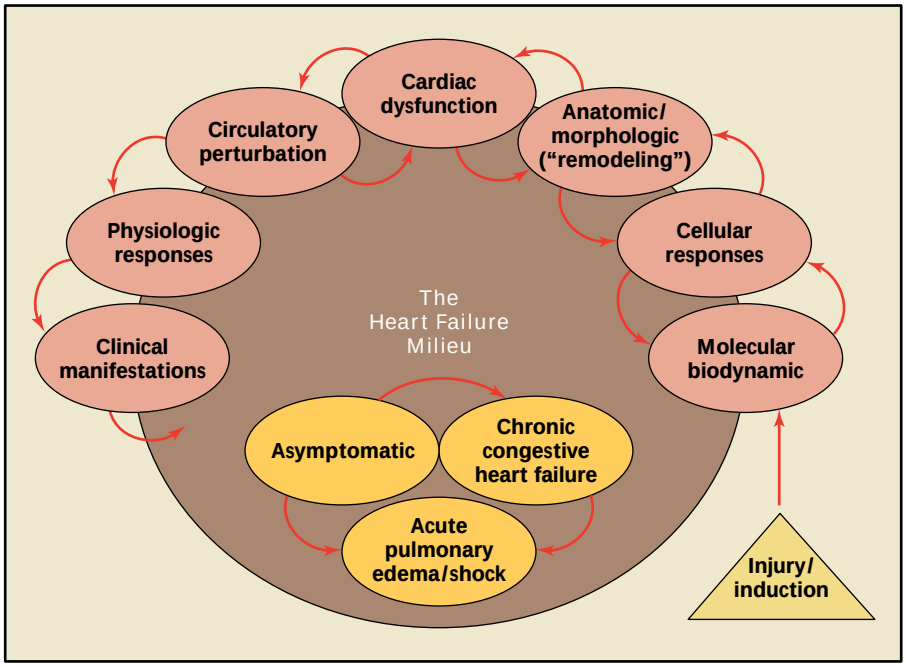
This data illustrates the issue of competing risks in HF. Those with less advanced LV dysfunction, such as the NYHA FC II patients, are more likely to experience SCD versus death due to pump dysfunction. As pump function worsens, the risk of significant morbidity or mortality resulting directly from reduced LV function predominates, and the absolute risk of both SCD and pump failure death is highest in this group.

Sudden Death in Heart Failure—The Pathologic Substrate

The term "cardiac remodeling" encompasses many of the changes that are associated with the HF syndrome.[26] Furthermore, the extent of remodeling predicts risk and is directly and indirectly associated with peripheral circulatory responses and activation of neurohormonal and other mediator pathways.[13,26,27] These responses, in addition to cellular changes in the myocardium that underlie the remodeling process, provide the milieu for arrhythmogeneis and other mechanisms of SCD occurring in the HF setting. Figure 3 illustrates the complex interplay of the various responses that comprise the HF syndrome.[27]

Electrical remodeling in HF results from the changes cited above and causes prolongation of the action potential duration and alterations in calcium homeostatis. Long action potential durations and dispersion in action potential duration predispose to the development of afterdepolarizations that can lead to polymorphic ventricular tachycardia. Alterations in cell-to-cell coupling resulting from gap junction remodeling can promote conduction delay and block and lead to the development of monomorphic ventricular tachycardias.[28]

Figure 3. *Schematic illustrating the complexity of the multifaceted heart failure syndrome. Adapted with permission from Saxon and DeMarco.[27]*



In the setting of these electrophysiologic baseline abnormalities present in HF, alterations in electrolytes, such as the development of hypo- or hyperkalemia, or use of class III antiarrhythmic agents, can result in a much heightened risk of a malignant tachyarrhythmia or bradyarrhythmia.[28] Prolongation of the QRS duration further worsens HF status and may increase the tendency toward development of re-entrant ventricular arrhythmias.[29] Figure 4 illustrates the electrophysiologic changes that promote arrhythmogenesis in HF. Figure 5 demonstrates the 2 primary types of sustained ventricular tachycardias that may occur in HF.

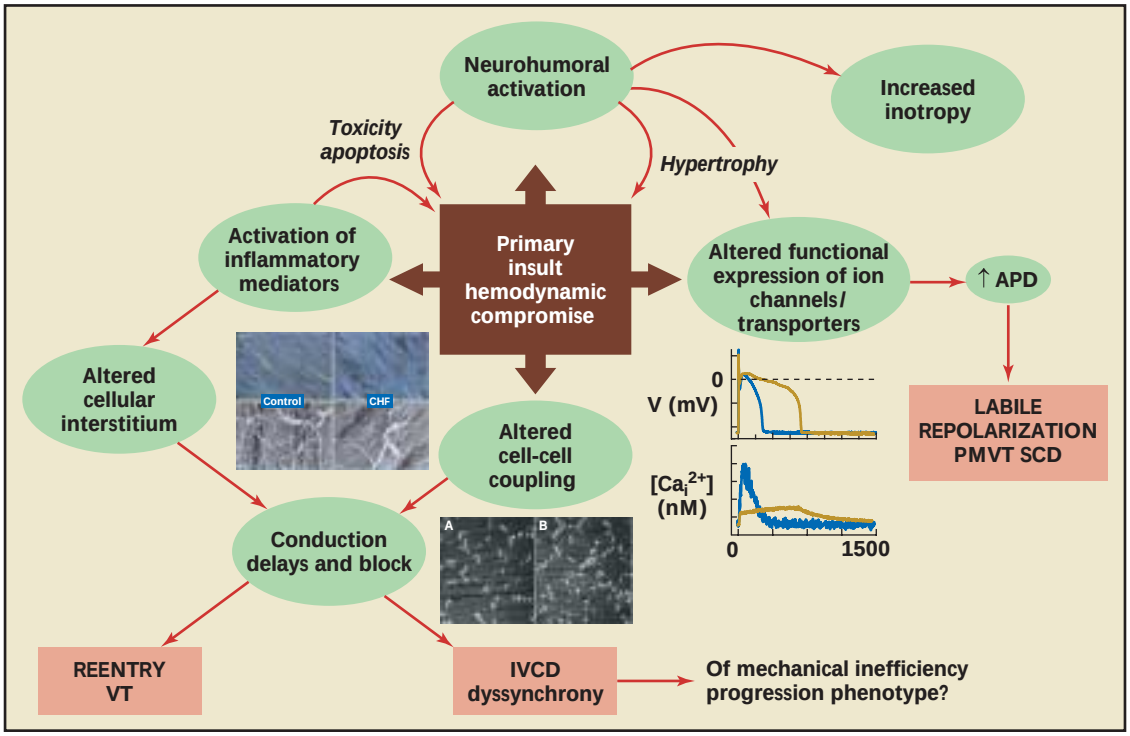
Preventing and Predicting Sudden Death in Heart Failure

Dramatic improvements in survival in HF patients have occurred over the past decade. Yearly survival now ranges from 98% to 81% for ambulatory patients with NYHA FC I-IV heart failure.[13,14,21,25,30-32] This improvement is due to the ability of current HF medications to attenuate the neurohormonal activation that occurs. This is most dramatically illustrated with improvements in both pump failure and SCD survival with β-receptor-blocker therapy.[25,31] Additional improvements in survival and functional status can be obtained with ICD and CRT-D devices.[17-22] Table 2 summarizes the reductions in mortality that have been achieved with the major classes of medical therapies consisting of angiotensin-converting-enzyme inhibitors, β-receptor-blocker therapy, aldosterone antagonism, and CRT-D therapy. Therefore, the first step in preventing SCD in HF is to ensure that patients are receiving those drug and device therapies that have been shown to improve outcomes.

The clinical assessment of patients presenting with the signs and symptoms of HF should include identification and documentation of the structural abnormality.[14] The risk of SCD can be estimated from a measure of ejection fraction and the electrocardiogram. Evaluation of the cause of LV dysfunction is also critical, particularly to assess the status of the coronary arteries. Coronary artery disease is responsible for approximately two thirds of HF cases resulting in LV dysfunction.[9,14]

The risk for acute coronary syndromes needs to be evaluated on an ongoing basis in HF patients. Use of endomyocardial biopsy may be indicated in the evaluation of patients with LV dysfunction and normal coronary arteries. Ongoing assessment of functional status, volume

Figure 4. *Heart failure factors promoting arrhythmogenesis. APD, action potential duration; IVCD, intraventricular conduction delay; PMVT, polymorphic ventricular tachycardia; SCD, sudden cardiac death; VT, ventricular tachycardia. Adapted with permission from Saxon and DeMarco.*[27]



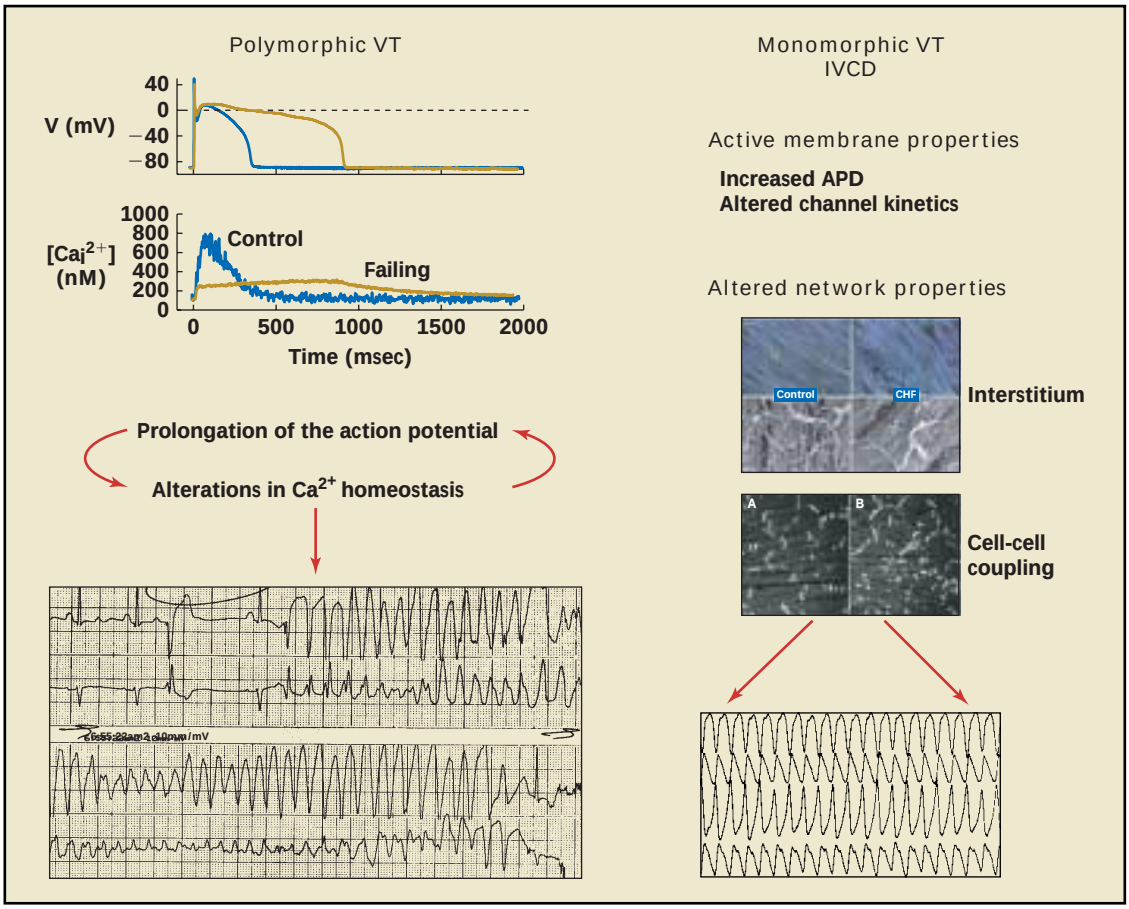


Figure 5. *The 2 primary types of sustained ventricular tachycardia (VT) that may occur in heart failure: polymorphic and monomorphic. APD, action potential duration; IVCD, intraventricular conduction delay. Adapted with permission from Saxon and DeMarco.*[27]

status, and laboratory assessment are also critical, as abnormalities in these measurements can promote the likelihood of arrhythmias and SCD.

Adequate treatment of comorbidities such as hypertension, pulmonary disease, cancer, diabetes, renal dysfunction, and conditions that can cause cardiac injury are also critical to halting the progression of HF and minimizing SCD risk. Attention to special populations, such as women, racial minorities, and the elderly, who may respond differently to medication or have distinct risks, is also necessary.[13]

The majority of patients with symptomatic HF due to systolic dysfunction have frequent premature ventricular complexes or non-sustained ventricular tachycardia. These arrhythmias do not appear to predict SCD risk.[33] The use of antiarrhythmic drugs to suppress non-sustained ventricular tachycardias is therefore unwarranted in the asymptomatic patient. This is particularly true for antiarrhythmic agents of class IA and IC, as use of these drugs (quinidine, procainamide, flecainide, encainide, propafenone) can result in lethal proarrhythmia in the HF setting.[34]

For patients with symptomatic non-sustained ventricular arrhythmias and supraventricular arrhythmias, low-dose amiodarone is the safest and most effective antiarrhythmic agent.[35] Low-dose amiodarone for primary prevention of SCD has not been consistently or definitively shown to improve survival.[18,19,22]

Early ICD clinical trials for primary prevention of SCD in the setting of ischemic LV dysfunction, evaluated the use of the signal-averaged electrocardiogram and Holter monitor to detect non-sustained ventricular tachycardia and electrophysiologic studies to detect inducible ventricular arrhythmias. The purpose of these screening studies was to identify a higher risk subgroup for sudden death and ICD placement.[18,19,36] While these studies, particularly inducibility at electrophysiologic study,

Table 2
Improvement in Survival With Drug and Device Therapy for Heart Failure

Trial (Background Rx)	Active Rx	Follow-Up Period (mo)	Sample Size	Mortality (Control)	Mortality (Active Rx)	Relative Reduction (%)
CONSENSUS I[30] (Diuretics + Digoxin)	Enalapril (ACEI)	12	253	52%	36%	↓ 31%
MERIT-HF[25] (ACEI +)	Metoprolol (β-blocker)	12	3991	11%	7%	↓ 34%
COPERNICUS[31] (ACEI +)	Carvedilol (β-blocker)	10.4	2289	18%	12%	↓ 35%
RALES[32] (ACEI +)	Spironolactone (aldosterone antagonist)	24	1663	46%	35%	↓ 30%
COMPANION[21] (ACEI, β-blockers, spironolactone +)	CRT-D	12	1520 (total both arms + placebo)	19%	12%	↓ 36%
	CRT-P	12		19%	15%	↓ 24%
MADIT II (ACEI, β-blocker +)	ICD	20	1232	20%	14%	↓ 31%
SCD-HeFT[22] (ACEI, β-blocker +)	ICD (Amiodarone)	45	2521	36.1%	28.9%	↓ 23%

ACEI, angiotensin-converting enzyme inhibitors; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; CRT-D, cardiac resynchronization therapy with a defibrillator; CRT-P, CRT with a pacemaker; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure; RALES, Randomized Aldactone Evaluation Study; Rx, therapy; MADIT II, Multicenter Defibrillator Implantation Trial II; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

may predict a high-risk subgroup for SCD, lack of a positive screening test does not necessarily predict low risk. This is especially true if HF severity worsens. Furthermore, all of these screening studies lack predictive value in HF not due to ischemic heart disease. For these reasons, the newer generation of ICD and CRT-D trials have not used these studies, preferring instead the measurement of LVEF, HF symptoms status, and QRS duration, as "risk enhancers." QRS duration appears to be a marker of HF severity and is a negative predictor of outcome.[37,38] Use of microvolt T-wave alternans, a dynamic electrocardiographic method of determining susceptibility to ventricular arrhythmias based upon changes in repolarization, may have predictive value in assessing risk of a malignant ventricular arrhythmia in HF patients and is under study.[39,40] The primary driver toward identification of a noninvasive marker of SCD risk is to decrease the number of primary prevention ICDs that need to be implanted to save 1 life.[9] Table 3 summarizes the baseline evaluation of patients with LV dysfunction that should be performed to help assess the risk of SCD, as well as factors that need to be considered in the ongoing management.

Conclusions

Prevention of SCD in the setting of HF associated with LV dysfunction requires a knowledge and understanding of the established and newly identified indications for drug and device therapies shown to improve overall and sudden death survival. Importantly, these include medical therapy agents that result in neurohormonal antagonism and ICD and CRT-D devices.[13,14,17-22]

In order to prevent a secondary cardiac arrest in the HF patient, physicians should continually assess for volume and functional status. Scrupulous attention to maintaining normal electrolyte status and avoiding drug toxicities is also critical. The use of traditional electrophysiologic screening studies other than the electrocardiograph do not have proven benefit over an assessment of LVEF and functional status for primary prevention indications.[19,22]

Improving the awareness of SCD as a major health risk and educating the public, patients, and physician groups about proven effective therapies is a major challenge. While analysts acknowledge a rapid growth in the ICD and CRT-D market for primary prevention devices, there are an estimated 1 to 2 million Americans who now qualify for such a device.[41] Additionally, even with the

Table 3
Assessment of the Risk of Sudden Death in Heart Failure

Identification of the structural abnormality
• LVEF
• Heart size
• Hemodynamics
• Valve status
Evaluation of the cause of LV dysfunction
• Endomyocardial biopsy (selected cases)
Electrocardiogram
• Microvolt T-wave alternans (investigational)
Coronary artery status
Identification of co-morbid conditions
Attention to special populations
• Women
• Racial minorities
• Elderly
Ongoing assessment of
• Functional status
• Laboratory values
• Volume status

LV, left ventricular; LVEF, left ventricular ejection fraction.

publication of HF treatment guidelines, medical therapies of proven benefit are underutilized.[13,14]

One of the difficulties encountered in developing strategies directed toward increasing public awareness of SCD risk is what has been termed "the many faces of sudden death." This term describes the lack of a single disease entity or condition to which "sudden" refers. An additional impediment is the fact that many HF patients are never referred for consideration for an ICD or to a HF specialist. This may be due to the fact that physicians fear losing control of their patients to a subspecialty cardiologist, or due to geographic or payer circumstances.[42,43]

There also is debate as to whether there are enough cardiac electrophysiologists available to implant the number of devices that are needed. This concern has recently been addressed by the issuance of new training pathways for ICD and

Main Points

- The majority of sudden cardiac death (SCD) cases occurring in the United States are due to coronary artery disease. Deaths from both coronary artery disease and SCD have declined markedly over the past several decades due to improved primary and secondary prevention and treatment strategies. The proportion of cardiovascular deaths that are sudden has actually increased, and SCD now accounts for more than half of all coronary heart disease deaths.
- Up to one third of SCD cases occur in patients with depressed left ventricular ejection fraction (LVEF) due to both ischemic heart disease and non-ischemic etiologies of left ventricular (LV) dysfunction.
- Yearly survival rates for ambulatory patients with New York Heart Association Functional Class (NYHA FC) I-IV HF now range from 98% to 81%. This improvement is associated with current heart failure (HF) medication (primarily β-receptor blocker therapy) that attenuates the neurohormonal activation occurring in HF. Also playing a significant role in improving survival rates are device therapies, such as implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy with a defibrillator (CRT-D) devices.
- The clinical assessment of patients presenting with the signs and symptoms of HF should include identification and documentation of the structural abnormality. The risk of SCD can be estimated from a measure of ejection fraction and electrocardiogram. Evaluation of the cause of LV dysfunction is also critical, particularly to assess the status of the coronary arteries.
- Whereas mortality risk increases with increasing severity of HF, SCD is identified as the cause of death in 33% of NYHA FC IV patients, 59% of FC III patients, and 64% of FC II patients.
- The first step in preventing SCD in HF is to ensure that patients are receiving those drug and device therapies that have been shown to improve outcomes.

CRT-D implantation from the Heart Rhythm Society of America.[44] Clearly, progress will need to occur in each of these areas to reach those heart failure patients in whom SCD can be prevented. ■

References

1. American Heart Association. 2003 Heart and Stroke Statistical Update. Dallas, TX: American Heart Association;2002.
2. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: epidemiology, transient risk, and intervention assessment. *Ann Intern Med*. 1993;119:1187-1197.
3. McGovern PG, Jacobs DR Jr, Shahar E, et al. Trends in acute coronary heart disease mortality, morbidity, and medical care from 1985 through 1997: the Minnesota heart survey. *Circulation*. 2001;104:19-24.
4. Capewell S, Morrison CE, McMurray JJ. Contribution of modern cardiovascular treatment and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. *Heart*. 1999;81:380-386.
5. Fox CS, Evans JC, Larson MG, et al. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: the Framingham Heart Study. *Circulation*. 2004;110:522-527.
6. Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK. Changing incidence of out-of-hospital ventricular fibrillation, 1980-2000. *JAMA*. 2002;288:3008-3013.
7. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. *Circulation*. 2001;104:2158-2163.
8. Chugh SS, Jui J, Gunson K, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. *J Am Coll Cardiol*. 2004;44:1268-1275.
9. Myerburg RJ. Scientific gaps in the prediction and prevention of sudden cardiac death. *J Cardiovasc Electrophysiol*. 2002;13:709-723.
10. Josephson M, Wellens HJ. Implantable defibrillators and sudden cardiac death. *Circulation*. 2004;109:2685-2691.
11. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, et al. Out-of-hospital cardiac arrest in the 1990s: a population-based study in the Maastricht area on incidence, characteristics and survival. *J Am Coll Cardiol*. 1997;30:1500-1505.
12. Tokashiki T, Muratani A, Kimura Y, et al. Sudden death in the general population in Okinawa: incidence and causes of death. *Jpn Circ J*. 1999;63:37-42.
13. HFSA Practice Guidelines for Management of Patients with Heart Failure Caused by Left Ventricular Systolic Dysfunction. *J Card Fail*. 1999;5:357-382.
14. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *Circulation*. 2001;104:2996-3007.
15. Eriksson H. Heart failure: a growing public health problem. *J Intern Med*. 1995;237:135-141.
16. Massie BM, Shah NB. Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management. *Am Heart J*. 1997;133: 703-712.
17. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Am Heart J*. 2000;101:1297-1302.
18. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary artery disease at high risk for ventricular arrhythmia. *N Engl J Med*. 1996;335:1933-1940.
19. Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med*. 1999;341:1882-1890.
20. Moss AJ, Zareba W, Hall WJ, et al, for the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877-883.
21. Bristow MR, Saxon LA, Boehmer J, et al, for the Comparison of Medical Therapy, Pacing, and Defibrillationin Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140-2150.
22. Bardy GH, Lee KL, Mark DB, et al. Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352:225-237.
23. Stevenson WG, Stevenson LW, Middlekauff HR, et al. Improving survival for patients with advanced heart failure: a study of 737 consecutive patients. *J Am Coll Cardiol*. 1995;26:1417-1423.
24. Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. In: Braunwald E, Zipes DP, Libby P, eds. *Heart disease: A textbook of cardiovascular medicine*, 6th ed. Philadelphia, PA: WB Saunders Company; 2001:890-931.
25. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). *Lancet*. 1999;353:2001-2007.
26. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol*. 2000;35:569-582.
27. Saxon LA, DeMarco T. Executive Summary: Resynchronization Therapy for Heart Failure, Executive Consensus Conference-May 8, 2002. NASPE 2002. Available at: http://www.hrsonline.org/uploadDocs/CRT_12_3.pdf.
28. Tomaselli GF, Marban E. Electrophysiological remodeling in hypertrophy and heart failure. *Cardiovasc Research*. 1999;42:270-283.
29. Horwich T, Lee, SJ, Saxon LA. Usefulness of QRS prolongation in predicting risk of inducible monomorphic ventricular tachycardia in patients referred for electrophysiologic studies. *Am J Cardiol*. 2003;92:804-809.
30. The CONSENSUS Trial Study Group: Effects of enalapril on mortality in severe congestive heart failure: Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-1435.
31. Packer M, Coats AJ, Fowler MB, et al. Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651-1658.
32. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709-717.
33. Packer M. Lack of relation between ventricular arrhythmias and sudden death in patients with chronic heart failure. *Circulation*. 1992;85: 150-156.
34. Pratt CM, Eaton T, Francis M, et al. The inverse relationship between baseline left ventricular ejection fraction and outcome of antiarrhythmic therapy: a dangerous imbalance in the risk-benefit ratio. *Am Heart J*. 1989;118:433-440.
35. Connolly SJ. Meta-analysis of antiarrhythmic drug trials. *Am J Cardiol*. 1999;84:90R-93R.
36. Gomes JA, Cain ME, Buxton AE, et al. Prediction of long-term outcomes by signal-averaged electrocardiography in patients with unsustained ventricular tachycardia, coronary artery disease, and left ventricular dysfunction. *Circulation*. 2001;104:436-441.
37. McAnulty HJ, Rahimtoola HS, Murphy E, et al. Natural history of "high-risk" bundle-branch block. *N Engl J Med*. 1982;307:137-143.
38. Shenkman HJ, McKinnon JE, Khandelwal AK, et al. Determinants of QRS prolongation in a generalized heart failure population: Findings from the Conquest Study. *Circulation*. 2000; 102(18 Suppl II):617.
39. Klingenheben T, Zabel M, D'Agostino RB, et al. Predictive value of T-wave alternans for arrhythmic events in patients with congestive heart failure. *Lancet*. 2000;356:651-652.
40. Rashba EJ, Cooklin M, MacMurdy K, et al. Effect of selective autonomic blockade on T-wave alternans in humans. *Circulation*. 2002;105: 837-842.
41. Morgan Stanley. Equity Research - North America - Industry: Hospital Supplies and Medical Technology. September 2004.
42. Saxon LA. An insider's view: The emerging role of devices. *eCardiologyNews*. 2004;2(8):10.
43. Saxon LA. An insider's view: costs, patient selection. *eCardiologyNews*. 2004;2(9):10.
44. Curtis AB, Ellenbogen KA, Hammill SC, et al. Heart Rhythm Society clinical competency statement: Training pathways for implantation of cardioverter defibrillators and cardiac resynchronization devices. This document has been endorsed by the American College of Cardiology Foundation. *Heart Rhythm*. 2004; 3:371-375.