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Sudden Cardiac Death in Heart Failure

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KEYWORDS

• Heart failure • Implantable cardiac defibrillators • Ischemic heart disease
• Nonischemic cardiomyopathy • Sudden death • Ventricular tachycardia

KEY POINTS

- Sudden cardiac death is common in patients with heart failure and depends on ejection fraction.
- Although several techniques exist for risk stratification, they are imperfect.
- Several pharmacologic strategies exist to prevent sudden death in patients with heart failure.
- Implantable cardioverter-defibrillators, cardiac resynchronization therapy defibrillators, and wearable cardioverter-defibrillators are the most effective tools to prevent sudden death in patients with heart failure and systolic dysfunction.

INTRODUCTION

Heart failure (HF) is a clinical syndrome resulting from structural and functional myocardial abnormalities leading to impaired ability to circulate blood at a rate sufficient to maintain the metabolic needs of internal organs and peripheral tissues. These abnormalities are consequences of long-standing ischemia caused by coronary artery disease or loss of myocardial mass because of prior infarction, myocardial remodeling, and structural damage from long-standing hypertension, valvular disease, or direct toxin exposure (eg, alcohol abuse, illicit substances, chemotherapeutic agents).[1] The prevalence of HF in the United States is around 5.7 million patients, of whom approximately 45% have reduced ejection fraction/systolic dysfunction.[2] There are more than half a million cases of HF newly diagnosed every year and there are more than 1 million hospitalizations yearly with HF as the primary diagnosis.[3] More than 80% of deaths in patients with HF have cardiovascular causes, with most being either sudden cardiac deaths (SCDs) or deaths caused by progressive pump failure.[4]

In general, SCD events are defined as unexpected deaths from cardiovascular causes that are preceded by a witnessed collapse, occur within 1 hour of an acute change in clinical condition, or occur not more than 24 hours after the deceased individuals were known to be in their usual state of health.[5] It is estimated that 350,000 to 380,000 SCD cases occur every year in the adult population in the United States, and that most of these individuals have preexisting heart disease.[6] If the American College of Cardiology/American Heart Association stage-based system for the classification of HF were applied, most patients presenting with SCD could be classified as stage A to D (**Fig. 1**). This classification adds a useful dimension to the understanding of the magnitude of SCD in HF by recognizing that there

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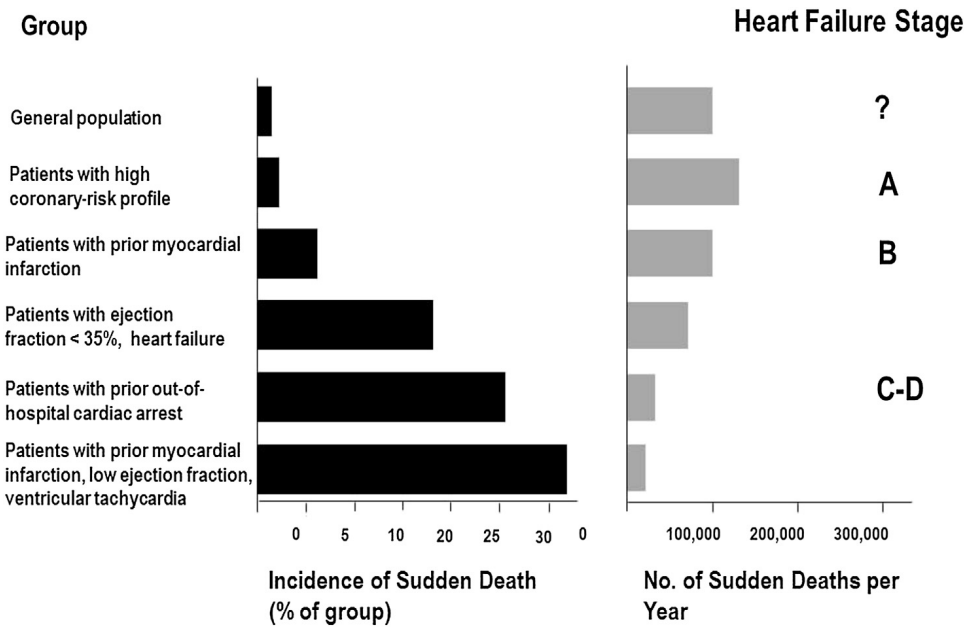

Fig. 1. Relation between incidence of sudden death and heart failure stages. (*Modified from* Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med 2001;345:1474; with permission.)

are established risk factors and structural prerequisites for the development of SCD and that therapeutic interventions used early after the development of left ventricular dysfunction can prevent the occurrence of SCD.

PATHOPHYSIOLOGY

The mechanisms of SCD in patients with HF are complex and require the chance interaction between a transient event and underlying pathologic substrate. In arrhythmic SCD, the process induces electrical instability and ventricular arrhythmias followed by hemodynamic collapse and death. This event happens more frequently in patients with ischemic cardiomyopathy, and can occur in 2 settings: (1) acute myocardial ischemia (with or without infarction), and (2) structural alterations (scar formation) secondary to prior myocardial infarction or chronic myocardial ischemia. In the setting of acute myocardial ischemia, the electrical instability generates ventricular fibrillation that degenerates to asystole over the course of several minutes. Thus, most SCD cases show asystole or pulseless electric activity when first examined by the emergency medical response teams. In cases in which there has been a short time between collapse and the initial rhythm determination, the proportion with documented ventricular tachycardia/fibrillation increases to 75% to 80%.[7] After experiencing an acute coronary event, women and men have a 4-fold and 10-fold higher risk of SCD, respectively.[8] Although the absolute rate of SCD is highest in the first 30 days after the event and decreases gradually with time,[9] rates are still high in certain subsets of postinfarction patients, and the degree of left ventricular systolic dysfunction and symptoms (New York Heart Association [NYHA] class) are powerful predictors for SCD in these patients.[10] In the chronic stage of ischemic cardiomyopathy (months and years after the initial infarction), the presumed mechanism of SCD is an electrical event caused by ventricular arrhythmias often originating from areas of prior infarcted myocardium that are adjacent to dense scar that has formed over time. Residual endomyocardial fibers survive, probably because of perfusion from the ventricular cavity or retrograde perfusion through sinusoidal channels. These surviving myocytes become embedded within regions of fibrosis that constitute substrate for abnormal nonuniform anisotropy with conduction block and propagation barrier that promote reentry and the ensuing ventricular arrhythmias.

In patients with systolic dysfunction after a myocardial infarction, nonarrhythmic SCD occurs frequently during the first 4 to 6 weeks. Within hours of infarction, extracellular matrix is digested and results in wall thinning and infarct expansion that may result in ventricular rupture that can manifest as SCD.[11] In addition, autopsy data from Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL), Assessment of Treatment with Lisinopril and Survival

(ATLAS), and Valsartan In Acute myocardial Infarction Trial (VALIANT) showed that recurrent myocardial infarctions may account for as much as 40% to 50% of the SCD in this population.[12–14] It seems that the proportions of arrhythmic and nonarrhythmic SCD cases become equivalent approximately 1 to 3 months after the initial infarct.[14] These observations are important, because they influence the choice of therapy to prevent SCD after myocardial infarction and explain the time differential effect of therapies (ie, β-blockers and mineralocorticoid receptor blockers vs implantable cardioverter-defibrillators [ICDs]) in this setting.

In contrast with ischemic cardiomyopathy, ventricular myocardium in nonischemic cardiomyopathy often has multiple patchy areas of fibrosis and myofibril disarray with various degrees of myocyte hypertrophy and atrophy. Autopsy studies in patients with idiopathic dilated cardiomyopathy showed that there was a high incidence of myocardial fibrosis without significant visible scar.[15] Myocardial scar-based reentry accounts for only half of the mechanisms of ventricular arrhythmias in patients with nonischemic cardiomyopathy, with the rest having focal initiation of ventricular tachycardia from triggered activity with early afterdepolarizations and delayed afterdepolarizations.[16] Irrespective of the HF cause, patients with advanced HF (stage D) have a different distribution of arrhythmias that may be triggered primarily by pump failure. One series showed that 62% of such patients had severe bradycardia or electromechanical dissociation as the underlying cause for their SCD and only 38% had ventricular tachycardia/ventricular fibrillation.[17]

In other uncommon causes of nonischemic cardiomyopathies, such as infiltrative (sarcoidosis), genetic (arrhythmogenic right ventricular cardiomyopathy), and inflammatory/immunologic (acute myocarditis or Chagas disease), SCD is almost always caused by ventricular arrhythmias. In patients with sarcoidosis, myocardial involvement may be multifocal and the sarcoid granulomas become foci of abnormal automaticity and increase the likelihood of reentrant arrhythmias.[18] In arrhythmogenic right ventricular cardiomyopathy, the infiltration of fibrous tissue and fat into regions of normal myocardium, analogous to infarct-related aneurysms in ischemic heart disease, forms the arrhythmogenic basis for development of reentrant ventricular tachycardia.[19] The anatomic substrate for ventricular tachycardia in Chagas disease is primarily located epicardially and/or at the inferolateral base of the left ventricle. Histologic examinations show patches of focal and diffuse fibrosis of the myocardium, suggesting that VT resulting from this disease may also be caused by a reentrant mechanism.[20]

EPIDEMIOLOGY

Compared with the general population, SCD occurs 6 to 9 times more frequently in patients with HF and is present in patients with both depressed and preserved ejection fraction.[21] Before effective therapies became available, the incidence of SCD in patients with HF and ejection fraction less than 30% was greater than 20% per year.[22] However, with current medical and nonpharmacologic interventions, the incidence of SCD has decreased to about 3% per year.[1] In patients with systolic HF, SCD accounts for about 40% to 45% of all deaths[23] and the proportion of SCD is higher in patients with milder symptoms; two-thirds of patients with NYHA functional class II experience SCD, compared with only a third of those with NYHA functional class IV symptoms, who die preponderantly from progressive pump failure.[24]

Although for a long time patients with diastolic HF were thought to be at low risk for SCD, recent studies have shown an increased risk in this population as well. In the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-PRESERVE) trial[25] and the Candesartan in Heart Failure Assessment of Reduction in Mortality (CHARM) Preserved study,[26] a little more than a quarter of the deaths were deemed to be arrhythmic SCD, highlighting the need for strategies to prevent the high burden of SCD in these patients with diastolic HF.

RISK STRATIFICATION

The highest risk for SCD seems to be in patients who have a depressed ejection fraction and HF symptoms. Several risk factors for SCD have been identified and proposed in patients who have structural heart disease, but developing a comprehensive risk stratification strategy remains a challenging task (**Table 1**).

Left Ventricular Ejection Fraction

Left ventricular ejection fraction remains the most consistent predictor of SCD in patients with structural heart disease, irrespective of the cause. For instance, patients after myocardial infarction enrolled in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) with ejection fractions less than 30% had an annual rate of SCD of approximately 5.5%,[27] whereas patients after myocardial infarction with ejection fractions greater than 35% had a risk of SCD of only 1.8%.[28] Although left ventricular ejection fraction has a powerful role in predicting future ventricular arrhythmia and sudden death, it remains an imperfect tool for risk stratification because most

Table 1
Summary of risk stratification tools for sudden death in patients with heart failure

Technique	Findings
Left ventricular ejection fraction	Most studied and proven predictor of sudden death Imperfect in identifying the patients who will benefit most from defibrillators
MTWA	Several trials suggest limited use to direct decisions on defibrillator implantation Combination of MTWA and electrophysiologic studies seem to have some predictive value but limited clinical applicability
Ambulatory electrocardiography	Conflicting data on the predictive value of nonsustained ventricular tachycardia in patient with heart failure Heart rate variability, baroreflex sensitivity, and signal-averaged ECG do not reliably predict sudden death and have limited applicability in the absence of clinical trials
Cardiac imaging	Presence and extent of scar on cardiac magnetic resonance imaging have predictive value Abnormal washout rate of I-123 metaiodobenzylguanidine is associated with arrhythmic events

Abbreviations: ECG, electrocardiogram; MTWA, microvolt T-wave alternans.

patients enrolled in MADIT-II or Sudden Cardiac Death in Heart Failure trial (SCD-HeFT) did not receive ICD therapy for primary prevention.[27,29]

Ventricular Ectopy

The presence of ventricular ectopy in patients with HF also has prognostic significance. In patients with prior myocardial infarction, frequent premature ventricular complexes (>10/h) or nonsustained ventricular tachycardia were associated with an increased risk of SCD.[30] Nonsustained ventricular tachycardia was associated with SCD in patients with nonischemic cardiomyopathy in the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) trial.[31]

Microvolt T-wave Alternans

Microvolt T-wave alternans (MTWA) is a noninvasive test that detects beat-to-beat oscillations in the T-wave amplitude recorded on electrocardiogram (ECG) for the purpose of detecting arrhythmia vulnerability. Although MTWA has been promoted as a predictor of ventricular events, its value is controversial because prospective trial results have been inconsistent[32–34] and the optimal population in which it can be used for risk stratification is yet to be determined.

Heart Rate Variability and Baroreflex Sensitivity

Depressed heart rate variability (HRV) and baroreflex sensitivity (BRS) reflect the autonomic nervous system health, and have been shown in some studies to be predictors of arrhythmic events in patients who have myocardial infarctions.[35,36] However, such altered autonomic parameters have been associated with increased total non–sudden death mortality in most studies. Because of the inconsistent results, they are not routinely used in clinical practice.

Signal-averaged ECG

The signal-averaged ECG (SAECG) is a high-resolution recording technique designed to measure the low-amplitude, high-frequency surface ECG signals in the terminal QRS complex that cannot be detected by a standard ECG machine. These late potentials have been correlated with localized areas of delayed endocardial activation and reflect the substrate for ventricular reentry. In patients with ischemic cardiomyopathy, SAECG has a high negative predictive value (more than 96%), but its usefulness as prognostic tool remains controversial in patients who have idiopathic nonischemic cardiomyopathy.[37,38]

Electrophysiology Studies

The prognostic value of electrophysiology studies and programmed ventricular stimulation depends on the underlying substrate and the arrhythmia presentations. The inducibility of monomorphic ventricular tachycardia is a powerful marker of risk for SCD only in patients who have a history of prior myocardial infarction and reduced ejection fraction or syncope. In patients with nonischemic cardiomyopathies, the usefulness of electrophysiology

studies to determine prognosis and to guide therapy remains limited. The clinical outcomes do not correlate with arrhythmia inducibility, and suppression of induced arrhythmia does not predict a good prognosis.[39,40]

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging has provided unique capabilities to identify morphologic changes in the cardiac structure in both ischemic and nonischemic cardiomyopathies. Applications of gadolinium-enhanced imaging provide detailed characterization of cardiac tissues and identification of areas of scar, with several studies showing inducibility of ventricular arrhythmias and appropriate defibrillator discharge in patients with higher scar burden.[41]

I-123 Metaiodobenzylguanidine

Abnormal washout rate of I-123 metaiodobenzylguanidine (MIBG) (an analog of norepinephrine used for estimating cardiac adrenergic nerve activity) has been correlated with increased risk of SCD and appropriate defibrillator shocks.[42,43]

PREVENTION AND TREATMENT OF SUDDEN DEATH

Pharmacologic Therapies

The most striking benefit of therapies with angiotensin-converting enzyme (ACE) inhibitors is the dramatic increase in survival seen in patients with NYHA functional class II to IV and in all patients with systolic dysfunction after an acute myocardial infarction, even in those without symptoms or signs of HF. Although all the ACE inhibitors studied decreased mortality caused by progressive HF, in patients after myocardial infarction, these agents decreased the SCD rate in only 2 studies, by 24% and 30%.[44,45] The angiotensin receptor blockers (ARBs) have been shown to increase SCD mortality by 30% compared with ACE inhibitors, especially in the post–myocardial infarction setting.[46,47]

In addition to the neurohormonal modulation benefits in the management of patients with HF, β-blockers have been shown to be antiarrhythmic. The total mortality reduction with these agents is approximately 35%, with approximately a 40% to 45% reduction in the incidence of SCD in patients with chronic HF and around 25% in the immediate post–myocardial infarction period.[48–50]

The mineralocorticoid receptor blockers spironolactone and eplerenone have been shown not only to decrease total mortality across the HF spectrum (patients with NYHA functional class II-IV) but also to significantly decrease the risk for SCD by 21% to 29%.[51–53] Even more importantly, starting eplerenone within a week after a myocardial infarction led to a significant 30% decrease in SCD within 2 weeks after the initiation of therapy. These data are of paramount importance, because this represents the vulnerable period in which the ICDs have been shown not to reduce mortality.[54,55]

All antiarrhythmic drugs possess potential proarrhythmic toxicity and class IA and IC drugs, as well as dronedarone, are contraindicated in patients with HF. Amiodarone is the only antiarrhythmic drug that may reduce the risk of SCD in patients after myocardial infarction and represents a viable alternative in patients who are not eligible for, refuse, or who do not have access to ICD therapy for the prevention of SCD.[56]

Although a post hoc analysis from the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) showed that, among patients treated with ICD, those with background statin therapy had a lower rate of ventricular arrhythmias,[57] 2 prospective studies of statins in systolic HF showed no benefit in terms of preventing or reducing SCD compared with placebo.[58,59] In addition, although it was thought that fish oil containing omega-3 polyunsaturated fatty acids could reduce SCD in patients with ischemic HF by reducing the risk of recurrent acute coronary syndrome, this hypothesis was not confirmed in a large randomized trial.[60]

Coronary Revascularization

It is clear that immediate revascularization decreases the risk of SCD in the setting of ST elevation myocardial infarction. Recently, analyses from the Surgical Treatment for Ischemic Heart Failure (STICH) trial showed that in patients with ischemic systolic HF, surgical revascularization decreases the risk of SCD by 27%.[61] Interestingly, there was time dependency on the protective effect of surgical revascularization, with the SCD risk being significantly affected only 24 months after coronary artery bypass grafting.

ICDs

The initial studies using ICDs were targeted at survivors of SCD (secondary prevention) and showed a significant survival benefit in total mortality and SCD mortality. When combined, the results of the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial,[62] Canadian Implantable Defibrillator Study (CIDS),[63] and the Cardiac Arrest Study Hamburg (CASH)[64] showed a 57% decrease in the risk of arrhythmic death along with a 30% decrease in all-cause mortality in survivors of SCD. Over the last 15 years, several major trials

have evaluated the role of ICDs in the primary prevention of SCD in patients with ischemic and nonischemic cardiomyopathies with reduced ejection fraction (Table 2). All these trials showed a clear reduction in SCD and in all-cause mortality in patients with HF and reduced ejection fraction. Based on these trial results, the current guidelines recommend ICD as primary prevention in all patients with systolic dysfunction, NYHA functional class II and III symptoms and ejection fraction less than 35%, or NYHA functional class I and ejection fraction less than 30%.[65]

Although ICDs improve survival in these high-risk patients, there is the potential morbidity associated with inappropriate shocks and the significant increase in the rate of hospitalization for worsening HF. As such, judicious programming is needed to minimize the untoward side effects and improve survival.[66] Simple clinical variables, such as NYHA functional class greater than II, age greater than 70 years, BUN greater than 26 mg/dL, QRS duration greater than 0.12 seconds, and atrial fibrillation, can be used to identify the subset of patients with ischemic ventricular dysfunction who may not benefit from primary ICD implantation.[67] In addition, careful timing is needed for ICD implantation to avoid the early lack of benefit in the immediate post–myocardial infarction period.

Cardiac Resynchronization Therapy

In patients with systolic HF and electrical dyssynchrony (QRS >120 milliseconds), cardiac resynchronization therapy (CRT) has been used successfully to improve ventricular remodeling, patients' symptoms, functional capacity, and survival. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and the Cardiac Resynchronization Heart Failure (CARE-HF) trials have shown a 36% and 46% decrease in SCD, respectively.[68,69]

Table 2
Implantable cardioverter defibrillator trials for prevention of sudden death

Trial	Inclusion Criteria	Intervention	Results
Primary Prevention			
DEFINITE	Nonischemic cardiomyopathy, EF <36%, NSVT	Placebo vs ICD	80% decrease in SCD Insignificant decrease in all-cause mortality
MADIT-I	MI, EF <35%, NSVT, inducible/ nonsuppressible arrhythmias	Placebo vs ICD	54% decrease in overall mortality
MADIT-II	MI, EF <30%	Placebo vs ICD	31% decrease in overall mortality
MUSTT	CAD, EF <40%, NSVT	EP vs non–EP-guided treatment, antiarrhythmic drugs vs ICD	55%–60% decrease in all-cause mortality in ICD vs drugs at 39 mo 73%–76% decrease in SCD in ICD vs drugs
SCD-HeFT	EF <35% and NYHA functional class II and III	Placebo vs amiodarone vs ICD	23% decrease in all-cause mortality in ICD vs drugs at 5 y Amiodarone does not improve survival
Secondary Prevention			
AVID	VF, VT/syncope, VT with EF $\leq$40%	Amiodarone vs sotalol vs ICD	31% decrease in all-cause mortality in ICD vs drugs at 3 y
CASH	Survivors of VF (no EF requirement)	Metoprolol vs amiodarone vs propafenone vs ICD	37% decrease all-cause mortality in ICD vs drugs at 2 y 85% decrease in SCD in ICD vs drugs
CIDS	VF, VT/syncope, VT/EF $\leq$35%, CL <400 ms	Amiodarone vs ICD	20% decrease all-cause mortality in ICD group vs amiodarone at 3 y

Abbreviations: CAD, coronary artery disease; CL, cycle length; DEFINITE, Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation; EF, ejection fraction; ICD, implantable cardioverter defibrillator; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MI, myocardial infarction; MUSTT, Multicenter Unsustained Tachycardia Trial; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 3
Summary of pharmacologic, electrical and surgical treatment strategies for sudden death in patients with heart failure

Strategy	Decreases Sudden Death (Clinical Trials)	No Effect on Sudden Death (Clinical Trials)
ACE inhibitors	AIRE, TRACE	CONSENSUS, SAVE, SOLVD, SMILE
Mineralocorticoid receptor blocker	EMPHASIS, EPHESUS, RALES	—
β-Blockers	CAPRICORN, CIBIS II; MERIT-HF	—
Statins	—	CORONA, GISSI-HF
Fish oil	—	GISSI-HF
ICDs	AVID, CIDS, CASH DEFINITE, MADIT I and II, MUSTT, SCD-HeFT	—
CRT	CARE-HF, COMPANION	—
Surgical coronary revascularization	STICH	—

Abbreviations: ACE, angiotensin converting enzyme; AIRE, Acute Infarction Ramipril Efficacy; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; CARE-HF, Cardiac Resynchronization Heart Failure; CIBIS II, Cardiac Insufficiency Bisoprolol Study II; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; CRT, cardiac resynchronization therapy; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insuffi cienza cardiaca; ICD, implantable cardioverter defibrillator; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; RALES, Randomized Aldactone Evaluation Study; SAVE, Survival and Ventricular Enlargement; SMILE, Survival of Myocardial Infarction Long-Term Evaluation; SOLVD, Studies of Left Ventricular Dysfunction; STICH, Surgical Treatment for Ischemic Heart Failure; TRACE, Trandolapril Cardiac Evaluation.

Based on these benefits, CRT is recommended in the guidelines for patients with systolic HF, ejection fraction less than 35%, NYHA functional class II to IV, left bundle branch block, and QRS (preferably) more than 150 milliseconds.[65]

Wearable Cardioverter-Defibrillators

The wearable cardioverter defibrillator represents an alternative approach to prevent SCD until either ICD implantation is clearly indicated or the arrhythmic risk is considered significantly lower or absent. Recent studies show a benefit in the early post–myocardial infarction period or after revascularization, with about 1.5% of patients having an appropriate defibrillation.[70] Because it has been shown that as many as 28% of patients can improve their function significantly using appropriate neurohormonal antagonists,[71] it is reasonable to use this strategy as SCD protection while giving the chance for myocardial recovery. A summary of pharmacologic and electrical treatment strategies for SCD prevention in patients with heart failure is listed in **Table 3**.

SUMMARY

Sudden death is responsible for most deaths in patients with HF, irrespective of the ejection fraction. In most cases, SCD is arrhythmic, but it can be caused by recurrent myocardial infarction or myocardial rupture. Although several strategies have been developed for risk assessment and to improve patient selection for ICDs, left ventricular ejection fraction is still the best qualifier. Besides ICDs and CRTs, pharmacologic therapy plays an important role in reducing the risk of SCD.

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