Contemporary ICD Use in Patients with Heart Failure

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ABSTRACT

Despite constant breakthroughs in heart failure (HF) therapy, the population of HF patients resume to grow and is linked to increased mortality and morbidity. Ventricular arrhythmias (VA) are one of the leading causes of mortality in HF subjects. Implantable cardioverter-defibrillators (ICDs) are currently the gold standard in treatment, preventing arrhythmic sudden cardiac death (SCD) episodes. However, the death rates related to HF remain elevated, as not all HF subjects benefit equally. Cardiac resynchronization therapy (CRT) has emerged as a novel approach for HF patients. These devices have been thoroughly investigated in major randomized controlled studies but continue to be underutilized in various countries. This review discusses the use of ICD in HF populations on top of treatments.

Keywords: Heart failure; Implantable cardioverter-defibrillator; Ventricular arrhythmias; Cardiac resynchronization therapy; Sudden cardiac death

Key Summary Points
ICDs and CRTs are the cornerstone of current therapy of HF patients, reducing mortality and morbidity.
Despite these proven benefits, ICD and CRT therapies continue to be underutilized in various countries.
It is important to maintain medical education and conduct prospective randomized clinical trials in order to maximize patient selection and benefit.
Novel advances involve refining present treatments with leadless and subcutaneous devices.

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INTRODUCTION

The European Society of Cardiology (ESC) guidelines categorize heart failure (HF) into HF with preserved ejection fraction (EF > 50%, HFpEF), moderate EF (EF 40–49%, HFmrEF), and reduced ejection fraction (EF < 40%, HFrHF) [1]. The main etiology of death in HF patients is not only hemodynamic failure but life-threatening rhythm disturbances such as ventricular tachycardia (VT) and ventricular fibrillation (VF). Implantable cardioverter-defibrillators (ICDs) have become the standard of care in preventing arrhythmic sudden cardiac death (SCD), and cardiac resynchronization therapy (CRT) has evolved as an established treatment approach that improves a patient's quality of life and mortality [1].

Despite these proven benefits, the mortality and morbidity related to HF continue to be elevated [2]. Furthermore, ICDs therapy continues to be underutilized in various countries [2]. We will discuss the use of ICDs in HF with a primary focus on SCD prevention and CRT, including current literature and breakthrough advancements. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

HF AND SCD

The knowledge regarding the susceptibility to SCD in HF is still scarce, hindering optimal risk stratification for the use of ICDs [2, 3]. Ventricular arrhythmias (VA) are frequent in HF patients and range in severity from asymptomatic premature ventricular contractions (PVCs) to sustained rhythm disturbances such as VT, ventricular fibrillation (VF), or SCD [2, 3].

The most often seen arrhythmia causing SCD in HF is VT degenerating into VF [2, 3].

SCD is defined as death resulting from sudden unexpected circulatory collapse caused by a cardiovascular cause [2, 3]. SCD episode verification is generally difficult for clinical and research goals, affecting community-level estimates of SCD and resulting in variability in clinical trial reporting based on event definitions and ascertainment [2, 3]. Cardiovascular deaths are characterized as SCD when the collapse causing death is witnessed and occurs within 1 h of an alteration in health status, or when the death is not witnessed and occurs within the preceding 24 h [2, 3]. In addition, not all SCD are of arrhythmic etiology, and many are caused by pump failure or mechanical complications of myocardial infarction [2, 3]. One-third of cardiovascular deaths in HF patients is caused by gradual hemodynamic collapse, while the other two-thirds are caused either unexpectedly or in the context of progressing clinical HF [2, 3]. Overall mortality rates of SCD rise as the HF disease progresses, but the percentage of SCD deaths to total deaths decreases as the New York Heart Association (NYHA) functional class progresses [2, 3]. As HF advances, it is possible that more deaths are caused by pump failure rather than rhythm disturbances [2, 3]. MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) showed that the 1-year mortality rates for NYHA functional groups II, III, and IV were 6.3, 10.5, and 18.6%, respectively. However, the percentage of SCD deaths to total deaths was 64, 59, and 33%, respectively. Additionally, only 40% of SCD in HF are attributed to rhythm disturbances, a finding made mainly in HF patients after myocardial infarction [2, 3].

DEVICE THERAPY FOR PRIMARY AND SECONDARY PREVENTION OF SCD

HF subjects with EF < 35% are at an elevated risk of SCD due to VA [3]. This risk is greater in subjects with past VA episodes [3]. In secondary prevention, where no reversible trigger, such as

an acute myocardial infarction, could be detected, an ICD with a class IA recommendation is suggested (if survival is greater than 1 year with good functional status), according to ESC recommendations [1]. Although existing recommendations suggest ICD implantation in HF patients with an EF of less than 35% after at least 3 months of optimal medical therapy, NYHA class II–IVa, and a projected lifespan of more than 1 year, there appears to be a difference in the positive impact of an ICD based on the underlying cardiac condition in primary prevention [1]. Subjects with ischemic cardiomyopathy (ICM) have an indication level of IA, while those without ICM have an indication level of IB [1]. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) tried to determine the function of a transvenous defibrillator in primary prevention [4, 5]. Both studies demonstrated an advantage in survival in subjects with an EF impairment (30% in the MADIT-II study and 35% in the SCD-HeFT trial) [4, 5]. In MADIT-II, which recruited subjects with ICM and a prior myocardial infarction, the transvenous defibrillator resulted in a 31% decrease in relative mortality over a 5-year period [4, 5]. On the other side, SCD-HeFT enrolled a combined group of patients with ICM and non-ICM (NICM) [4, 5]. Subgroup studies revealed little disparity in the outcome of overall mortality decrease among ICM and NICM, suggesting that all patient populations benefited from the same impact [4, 5]. In comparison, the most up-to-date randomized Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) examined the function of primary prevention ICDs only in NICM and showed a large decrease in SCD in subjects with NICM and an EF of 35% [6].

While a new study conducted by the European Heart Rhythm Association (EHRA) revealed that approximately 50% of clinicians reversed their existing practice of implanting a transvenous defibrillator in a NICM individual 4 months after the completion of the DANISH study, a meta-analysis demonstrated an advantage of primary preventive ICDs even in terms of overall mortality [7, 8]. Optimizing patient selection of NICM patients could be the best approach to enhance the value of a transvenous defibrillator [7, 8]. Subgroup examinations of the DANISH study revealed that patients less than 70 years old or those with mild HF (as determined by lower NT-proBNP concentrations) did not experience a decrease in all-cause mortality [7–9]. Such findings suggest that relying solely on the EF to determine when a patient dies from hemodynamic collapse or VA could be inadequate [10–12]. The Seattle Heart Failure Model integrates a variety of risk factors, including age and laboratory criteria for HF prognosis, and can be an alternative strategy approach for optimal ICD patient selection [13]. Another interesting approach is to evaluate the myocardial substrate that could be proarrhythmogenic [13]. On cardiac magnetic resonance imaging (MRI), late gadolinium enhancement (LGE) highlights regions of myocardial fibrosis, and studies indicate that patients with LGE are at an elevated risk of SCD and VA [13, 14]. In subjects with dilated cardiomyopathy (DCM) and an EF of 40%, mid-wall LGE was correlated with a significant elevation in the risk of SCD [15]. Electroanatomical mapping (EAM) is a relatively popular technique for invasively examining myocardial scarring [16]. Local electrical properties may be used to distinguish scar tissue from healthy myocardium during an electrophysiological (EP) examination [16]. While both imaging modalities show tremendous potential, their utility must be evaluated prospectively in randomized controlled studies [15, 16]. Numerous other indicators of elevated arrhythmia risk, including genetic analysis, circulating biochemical markers, and non-invasive EP analysis, can be integrated into the ICD decision-making method [15, 16].

The decrease of SCD associated with an ICD in this population might not be attributed solely to an excess of non-arrhythmogenic fatalities but rather to device-related complications and morbidity [17]. As a result, further research and development in the area of device technologies are critical [17]. The subcutaneous ICD (S-ICD) is an innovative ICD intended to reduce the incidence and related morbidity and mortality linked to infection [17]. Infection is

Table 1 Landmark trials of defibrillators for the prevention of sudden cardiac death [3–7, 31, 58–61]

Study	SCD prevention	Number of subjects	Population	Study arms	Hazard ratio
AVID	Secondary	1016	Resuscitated VF, cardioverted VT, VT and syncope or VT and EF ≤ 40% and hemodynamic compromise	ICD versus class III AAD	0.62 (P < 0.02)
CASH	Secondary	288	Resuscitated cardiac arrest from documented VA	ICD versus amiodarone versus metoprolol	0.77 (P = NS)
CIDS	Secondary	659	Resuscitated VF or VT or unmonitored syncope	ICD versus amiodarone	0.80 (P = NS)
MADIT	Primary	196	Prior MI and EF ≤ 35% and NSVT and inducible sustained VT or VF on EP study (> 3 weeks post-MI, > 2 months post-CABG, > 3 months post-PCI)	ICD versus conventional medical therapy	0.46 (P = 0.009)
MUSTT	Primary	704	CAD and EF ≤ 40% and asymptomatic NSVT and Inducible sustained VA (34 days post-MI or PCI)	EP-guided therapy with AADs or ICD or no AADs	0.40 (P < 0.001)
MADIT II	Primary	1232	Prior MI and EF ≤ 30% (> 1 month post-MI, > 3 months post-PCI)	ICD versus conventional medical therapy	0.69 (P = 0.02)
DEFINITE	Primary	458	NICM EF < 36% and PVC or NSVT	ICD and standard medical therapy versus medical therapy alone	0.65 (P = 0.08)
SCDHeFT	Primary	2521	NYHA II-III and EF ≤ 35% (> 3 months HF)	ICD versus amiodarone versus placebo	0.77 (P = 0.007)
DANISH	Primary	1116	NICM EF ≤ 35% and NYHA II or III, or IV if CRT was scheduled and NT-pro BNP > 200 pg/ml	ICD versus standard care CRT received in 58% in both groups	0.87 (P = 0.28)

SCD sudden cardiac death, *AVID* Antiarrhythmics Versus Implantable Defibrillator, *VF* ventricular fibrillation, *VT* ventricular tachycardia, *EF* ejection fraction, *ICD* implantable cardioverter defibrillator, *AAD* antiarrhythmic drug, *CASH* Cardiac Arrest Survival in Hamburg, *VA* ventricular arrhythmias, *CIDS* Canadian Implantable Defibrillator Study, *MADIT* Multicenter Automatic Defibrillator Implantation Trial, *MI* myocardial infarction, *NSVT* non-sustained ventricular tachycardia, *EP* electrophysiological, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention, *MUSTT* Multicenter Unsustained Tachycardia Trial, *CAD* coronary artery disease, *MADIT-II* Multicenter Automatic Defibrillator Implantation II Trial, *DEFINITE* Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation, *NICM* non-ischemic cardiomyopathy, *PVC* premature ventricular complex, *SCD-HeFT* Sudden Cardiac Death in Heart Failure Trial, *NYHA* New York Heart Association, *HF* heart failure, *DANISH* Danish Study to Assess the Efficacy of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality, *CRT* cardiac resynchronization therapy, *BNP* brain natriuretic peptide

the most significant lifelong threat related to transvenous devices [17]. In an S-ICD, the generator is situated on the left mid-axillary position, between the anterior serratus and latissimus dorsi muscles [17]. The lead is tunneled beneath the skin into the xiphoid process

and then progressed cranially alongside the sternum [17]. The PRAETORIAN trial showed that S-ICD avoids major complications associated with the transvenous ICD, including serious infection and lead-related complications, establishing S-ICD as an appropriate and potentially attractive option for primary and secondary prevention in subjects who do not require pacing [18]. Recent ESC recommendations propose that, in the absence of contraindications, an S-ICD with a class IIa sign can be used instead of a transvenous ICD [19]. An S-ICD is not appropriate for subjects that need pacing, cardiac resynchronization therapy, and overdrive pacing [18, 19]. Resolving the majority of these issues seems to be achievable in the near future when a mixture of S-ICD and a leadless pacemaker would reach clinical trials [18]. Additionally, subjects must perform preprocedure sensing vector testing to achieve sufficient sensing of the QRS complex and T wave in order to prevent both undersensing or oversensing of the T wave [18]. At least one of the three sensing vectors must provide adequate sensing in the supine and sitting or standing positions [18]. Table 1 summarizes the landmark trials of defibrillators for the prevention of SCD.

CRT DEFIBRILLATOR

CRT has essentially altered how HF patients are handled [20]. Left ventricular dysfunction often leads to ventricular conduction disorder, which, consequently, causes electrical and mechanical dyssynchrony of the ventricle, disrupting the ventricle's hemodynamics even more [20]. The aim of biventricular pacing is to break this vicious cycle [20].

CRT is recommended in subjects with NYHA II–IVa status HF after 3 months of optimum medical therapy, EF of 35%, and QRS complex of 130 ms [20]. The recommendation is based on the findings of two major trials investigating the impact of CRT in subjects with advanced HF (mainly NYHA III) with QRS complex of 120 ms; the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and the Cardiac Resynchronization-

Heart Failure (CARE-HF) trials [21, 22]. These trials established that biventricular pacing decreased total mortality in this population by up to 36%, a finding that was eventually validated by databases and meta-analyses [23–25]. CRT has also been investigated in people with minor HF symptomatology (NYHA II) [26]. The MADIT-CRT trial examined HF subjects with EF less than 30%, NYHA score of I-II, and a QRS complex greater than 130 ms [26]. Total mortality was 34% lesser in the CRT population relative to the conservatively treated group [26]. This result is corroborated by evidence from the Resynchronization-Defibrillation for Ambulatory Heart Failure (RAFT) study, which demonstrated that CRT decreases overall mortality by 25% in subjects with an EF of 30%, a QRS complex greater than 120 ms, and NYHA II–III [27].

There is inadequate evidence from the MADIT-CRT and RAFT studies to suggest CRT in subjects with NYHA class I [26, 27]. Although CRT devices minimize mortality in appropriately chosen individuals, they have little advantage and can inflict damage if they are used in incorrect subjects [28]. The EchoCRT study showed little advantage and an enhanced risk of death when a CRT system is inserted in individuals with a narrow QRS (even though mechanical dyssynchrony of the ventricle was validated by echocardiogram) [27].

CRT system implant in subjects with left bundle branch block (LBBB) is classified as a class I recommendation (IA if the QRS duration is greater than 150 ms, IB if the QRS width is 130–149 ms), while non-LBBB cases are classified as a class II indication [29, 30]. LBBB subjects seem to have a more serious form of left ventricle electrical dyssynchrony than those without LBBB and are thus more likely to gain from CRT [29, 30]. A subgroup study in the MADIT-CRT study demonstrated that only LBBB individuals benefited from resynchronization therapy in terms of HF event-free survival [26, 27, 31]. This result is corroborated by a meta-analysis of these studies, which concluded that CRT has little effect in non-LBBB individuals [25].

The overwhelming majority of CRT studies excluded subjects with atrial fibrillation (AF),

notwithstanding the possibility that AF and HF often co-exist and |HF subjects with AF had a poorer prognosis [32, 33]. Due to the rapid, erratic conduction, AF often hinders the benefit of resynchronization therapy in comparison to sinus rhythm [34]. When AF though is disrupted by atrioventricular junction ablation, the advantage of resynchronization therapy is comparable to that of individuals without AF in several meta-analyses [35, 36].

On the other hand, it is important to keep in mind that up to one-third of individuals treated with resynchronization therapy do not experience a long-term gain (non-responders) [37, 38]. There is, however, no universally accepted concept of response and non-response [20, 39]. Although several studies utilize clinical criteria (mortality, HF hospital admissions, and NYHA status) [20, 39], many utilize echocardiographic measures (improved EF, decreased end-systolic volume) or a mixture of the two [40]. Occasionally, a difference in clinical and echocardiographic responses occurs [41]. Individuals with ICM do not have a good echocardiographic response to resynchronization therapy [42, 43]. Nevertheless, the value of resynchronization therapy was not contingent on the underlying heart disease in the landmark studies (CARE-HF and COMPANION) [21, 22]. On the opposite, since ICM subjects have poorer survival rates and a greater absolute incidence of new episodes, their overall risk reduction could be much greater, resulting in a much lower amount needed to treat [44].

The absence of marked change in EF and health condition following resynchronization therapy could cause clinicians to overlook resynchronization therapy as a viable method of reducing mortality and morbidity, resulting in a reduction in the overall utilization percentages [37]. Physicians often overlook in such instances that HF is a relentlessly progressing, chronic condition and that stabilization of its path indicates a major advantage of CRT for this susceptible subject group.

Certain individuals profit enormously from CRT and can even achieve normal left ventricular function (super-responders) [37]. While echocardiographic evaluation of ventricular dyssynchrony is not a good predictor of response, pre-procedural imaging can become more critical in deciding the optimal location for the left ventricular lead [45–48]. This may be accomplished by CMR and computed tomographic imaging of the coronary sinus to assess LGE or by speckle tracking echocardiography to measure strain and late mechanical activation sites [45–48]. It is critical to position the lead at the location with the latest activation, if necessary, in order to have a better degree of resynchronization [49]. Surgical epicardial lead positioning is currently restricted by its invasive existence and the possibility of scarring, which can result in the lead performing suboptimal over time [49].

Additionally, optimal application programming by cardiac device specialists and troubleshooting post-procedure and during follow-up is critical to maximizing gain [50]. Optimizing systems regularly after implantation has not been found to be clinically beneficial, but it could be applicable to non-responders, negative responders, and those undergoing clinical episodes and complications [51]. Additionally, device-based applications for optimizing CRT response, such as AdaptivCRT or SyncAV, can gain prominence in the future [52–54]. Quadripolar left ventricular leads, which were introduced only recently, have greater programming versatility by allowing for more pacing vector variations while eliminating phrenic capture and apical pacing [52–54].

Along with biventricular stimulation, additional pacing strategies are being investigated that may increase the performance of HF individuals [55, 56]. His-bundle pacing has been found to be an effective alternative for subjects with a need of constant ventricular pacing when used in conjunction with bradycardia indications [55]. His-bundle pacing in HF individuals is currently being examined in a number of studies (HOPE-HF trial, His-SYNC trial) [55, 56]. His-bundle pacing is considered a viable option for individuals undergoing CRT who have undesirable coronary sinus anatomy [55, 56]. The potential role of His-bundle pacing in non-responders, though, is still unknown [55, 56]. The His-SYNC trial concluded that subjects receiving His-bundle pacing on top of treatments showed improved electrical

resynchronization and a tendency toward greater echocardiographic response than standard resynchronization therapy [57].

NOVEL CONCEPTS IN DEFIBRILLATOR THERAPY IN HF

In a post hoc study of SCDHeFT, it was discovered that ICD shocks, whether appropriate or not, were correlated with a lower rate of survival in ICD patients [58–60]. Much research has shown that shocks can be minimized by proper programming, which allows for longer detections and durations before shock initiation [60]. Furthermore, a randomized trial (MADIT-RIT) demonstrated that such programming is correlated with increased patient survival [60]. As a result, strategic programming is highly advised [60].

Wearable cardioverter-defibrillators were newly launched as a bridge to ICD or as a bridge to decision [61]. Wearable cardioverter-defibrillators can be beneficial in individuals with elevated SCD risk but do not want to undergo ICD implantation [61]. These devices have been demonstrated to be as effective as ICD in terminating VA [61]. However, they are hindered by their lack of stimulation and their failure to provide antitachycardia pacing [61]. In the early post-myocardial infarction era, these defibrillators greatly reduced the risk of arrhythmic SCD in individuals with EF of 35%, as determined by the VEST (Vest Prevention of Early Sudden Death Trial) [61]. Due to initial enrollment difficulties, the study's goal sample size was limited, and the primary endpoint was revised from all-cause to arrhythmic SCD, raising some bias issues [61]. Additionally, adherence with the wearable defibrillators was lower than predicted, which may have an effect on the power estimate [61].

Intravascular lead complications have resulted in the leadless systems boom [61]. While their usage in HF individuals is currently minimal, single leadless pacing devices (Nanostim from St Jude Medical, Inc and Micra Transcatheter Pacing System from Medtronic, Inc) could have potential use in these patients, especially when utilized together with subcutaneous devices [17, 18, 61]. However, multicomponent leadless devices are now being used in HF subjects [17, 18, 61]. The WiSE-CRT research (Wireless Stimulation Endocardially for CRT) evaluated the efficacy of leadless endocardial left ventricular pacing using ultrasound in CRT individuals [61]. A subcutaneous pulse generator and a tiny receiver electrode are inserted in the left ventricular endocardium as part of the multicomponent system [61]. The results from the study were positive, but the research was prematurely terminated for safety concerns [61]. The SELECT-LV research (Safety and Performance of Electrodes Implanted in the Left Ventricle) demonstrated both efficacy and potential clinical progress utilizing this method [61]. This method, though, is not completely lead-free, since it requires the existence of RV defibrillation lead [61].

ICDs, today, allow remote data collection via data transmission to a computer, which then transmits data to an encrypted server and then to the responsible physician [61]. The details presented relate to both patient management and system operation monitoring [61]. The number of metrics that may be tracked continues to expand [61]. It also incorporates information regarding heart rate, patient activity, the percentage of biventricular stimulation, the frequency of rhythm disturbances, alterations in thoracic impedance as an indicator of pulmonary congestion, and heart rate variability [61]. The expectation is that this type of surveillance will predict preclinical symptoms of acute HF, leading to therapies that will minimize hospitalization and enhance the quality of life [61].

Device features and, more specifically, lead warnings can also be monitored remotely [61, 62]. This is critical for devices to resume providing effective life-sustaining treatments [61, 62]. Numerous reported investigations advocate the usage of remote monitoring for lead failure diagnosis [61, 62]. As such, the Heart Rhythm Society and the Canadian Heart Rhythm Society have issued consensus statements endorsing the importance of remote monitoring in diagnosing lead failure and monitoring at-risk leads [61, 62].

CONCLUSIONS

ICDs and CRTs are critical components of current HF therapy, significantly lowering mortality and morbidity in the community. Continuous medical education is critical for optimizing patient selection and benefit based on pathophysiological mechanisms, epidemiology, clinical study outcomes, and advanced technology. Current and prospective research and scientific advancements hope to enhance individuals' prognoses further. Only by joint efforts of all parties, such as cardiologists, primary care physicians, and, progressively, the patient, would we be able to advance science and research and better establish strategies for improving the survival rate of HF individuals.

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