ESC European Society of Cardiology

European Journal of Heart Failure (2025)
doi:10.1002/ejhf.3641

POSITION PAPER

Cardiac rhythm devices in heart failure with reduced ejection fraction – role, timing, and optimal use in contemporary practice. *European Journal of Heart Failure* expert consensus document

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Received 19 December 2024; revised 10 February 2025; accepted 23 February 2025

Guidelines for management of heart failure with reduced ejection fraction (HFrEF) emphasize personalized care, patient engagement, and shared decision-making. Medications and cardiac rhythm management (CRM) devices are recommended with a high level of evidence. However, there are significant disparities: patients who could benefit from devices are frequently referred too late or not at all. Misconceptions about device therapy and the notion that the needs of patients (especially the prevention of sudden cardiac death) can now be met by expanding drug therapies may play a role in these disparities. This state-of-the-art review is produced by members of the DIRECT HF initiative, a patient-centred, expert-led educational programme that aims to advance guideline-directed use of CRM devices in patients with HFrEF. This review discusses the latest evidence on the role of CRM devices in reducing HFrEF mortality and morbidity, and provides practical guidance on patient referral, device selection, implant timing and patient-centred follow-up.

Keywords Patient-centred heart failure care • Sudden cardiac death • Cardiac dyssynchrony • Cardiac implantable electronic device • Implantable cardioverter-defibrillator • Cardiac resynchronization therapy

Introduction

Guidelines for management of heart failure with reduced ejection fraction (HFrEF) emphasize personalized care, patient engagement, and shared decision-making between patients and clinicians. Current guidelines make strong recommendations with a high level of evidence for the use of pharmacological treatment and cardiac rhythm management (CRM) devices in patients with HFrEF.

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However, there are significant gaps in the implementation of both treatment modalities, and patients who could benefit from devices are frequently referred too late or not at all. Misconceptions about device therapy (indications, risks, impact of comorbidities), the historical sequential utilization of device therapy after optimization of guideline-directed medical therapy (GDMT), as well as challenges in care coordination and access to care play a role in these disparities. In addition, a misplaced belief that the needs of all patients with HFrEF (especially the prevention of sudden cardiac death [SCD]) can now be met by pharmacological options alone is further disadvantaging patients who are in need of these therapies.

This state-of-the art review has been produced through the DIRECT HF educational programme with the aim of advancing optimal use of CRM devices in patients with HFrEF. DIRECT HF is a global initiative led by internationally recognized HF specialists and electrophysiologists with expert input from HF patient advocacy groups. As well as summarizing guideline recommendations and the latest evidence on the efficacy and safety of implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) in patients with HFrEF, this review provides practical guidance on patient referral, device selection, implant timing, and patient-centred follow up.

Cardiac rhythm management devices: cornerstones of comprehensive, patient-centred management of heart failure with reduced ejection fraction

According to current estimates, there are 60 million individuals with heart failure (HF) worldwide, and approximately one in four persons will develop HF during their lifetime.[1–3] HF is a leading cause of hospitalization and its mortality remains high, with a 1-year risk of 15–30% post-hospital discharge.[1] Half of the patients diagnosed with HF die within 5 years of diagnosis.[4] Across European Society of Cardiology (ESC) member countries, HF accounts for 5.8% of total deaths (14.6% of cardiovascular disease deaths) in females and for 4.4% of total deaths (12.5% of cardiovascular disease deaths) in males.[5] HF can affect quality of life (QoL) and the ability to carry out activities of daily living, as well as mental health and psychosocial well-being.[6] A patient-centred, multidisciplinary approach is needed to achieve timely, evidence-based and comprehensive care, optimizing the use of all therapeutic options including medications, medical devices, surgery or other procedures, lifestyle modifications, and regular patient monitoring, while considering patients' clinical characteristics and preferences.[7,8]

Heart failure with reduced ejection fraction is characterized by a left ventricular ejection fraction (LVEF) ≤40%[9] and affects 40% to 50% of patients with HF.[2] Current HF guidelines make strong recommendations for quadruple drug therapy in HFrEF, namely (1) angiotensin receptor–neprilysin inhibitors (ARNi) (or angiotensin-converting enzyme inhibitors [ACEi]/angiotensin receptor blockers [ARB]), (2) beta-blockers, (3) mineralocorticoid receptor antagonists (MRA), and (4) sodium–glucose co-transporter 2 inhibitors (SGLT2i).[7,8,10,11] Rapid initiation of foundational pharmacological therapy is recommended, and survival advantages support early initiation of comprehensive treatment over sequential initiation and titration to target doses.[12–15] Practitioners are encouraged to personalize treatment based on patient characteristics and comorbidities.[16,17] After initiation and optimization of quadruple therapy, additional drug therapies can be considered in selected patients.[7,8,10,11]

Heart failure guidelines also provide strong recommendations for the use of ICDs and CRT in eligible patients.[7,8,10,11,18–20] Although pivotal trials of CRM devices were conducted before the introduction of ARNi and SGLT2i into clinical practice, recent evidence continues to show the benefits of combining contemporary GDMT with device therapy.[21,22] It is of vital importance to recognize that there is significant residual risk of cardiovascular mortality and morbidity even among the individuals treated with newer therapies such as SGLT2i.[23,24] The mortality rates in patients with HFrEF remain high, even in contemporary trials,[3,25] underlying the importance of comprehensive and complete therapies to prevent residual risk.

There is clear evidence of substantial benefit with CRM device therapy in contemporary registries of real-world patients. In an analysis of >40 000 patients with HF and LVEF ≤35%, both the number of GDMT classes prescribed and ICD/CRT-defibrillator (CRT-D) implantation were independently associated with a lower mortality risk.[22] In patients implanted with a primary prevention ICD or CRT-D, the number of GDMT medications prescribed was associated with the 2-year risk of death, with a nearly four-fold lower risk in patients with three or four drugs compared with those with none of the four drugs.[21] In England, data from a large national database show improved survival and decreased HF hospitalizations among CRT recipients over the past decade, despite an increasing comorbidity burden.[26]

Pharmacological and device therapy play complementary roles in the management of HFrEF patients. However, guideline-recommended medications[27–34] and devices such as ICDs[35–37] and CRT[38–40] are widely underused in clinical practice. Similar to standard cancer therapies that entail different modalities such as radiation, surgery as well as immune and chemotherapies, management of HFrEF also entails comprehensive, integrated drug and device therapies. This concept is relatively new to many clinicians and needs to be put into clinical practice.

Integration of implantable device therapy in comprehensive heart failure care

Recent scientific statements emphasize the need to implement a personalized approach to combining pharmacological and device therapies in patients with HF.[41,42] It is recommended that patients be evaluated at diagnosis to establish a clear treatment plan that prioritizes GDMT initially and rapidly integrates device therapy tailored to the patient's phenotype as soon as maximum tolerated

pharmacological treatment is achieved, with a well-defined strategy for timing.[41] Efforts should be maximized to optimize medical therapy before or following device placement. Of note, the treatment plan must be reevaluated and updated continuously to adapt to changing conditions during HF.

Before initiating device therapy, a multidisciplinary team (MDT) should discuss all available options to ensure adequate device implementation. As part of the HF MDT, HF nurses and advanced practice providers play an important role in screening patients for device eligibility and help patients and their families prepare for device implantation by providing information about implantation procedures, device functionality, and associated risks. Such information can help patients cope with the device after implantation, set realistic expectations, and prevent possible fears and misconceptions – thus enabling shared decision-making.[43]

After implantation, the HF team including allied professionals can assist in monitoring the effects and potential side effects/adverse events related to device function and optimizing HF treatment when appropriate. During their assessment, they may review results from remote monitoring or device readings and provide further education on the implications of device implantation for daily life, for example handling alarms, driving restrictions, changes in body image, sexual function, pregnancy planning, social activities, or self-care.[44,45] Remote monitoring is recommended as part of the standard of care in patients with implantable cardiac devices[46] and device-based HF clinical pathways can help improve disease management and patient outcomes.[47–49] Some healthcare systems have pharmacist-led HF clinics to screen for device eligibility, optimize medical therapies, and provide information to patients.[50] Cardiac device technicians may also be involved in device optimization, for example by recognizing patients needing escalation of care.

To better implement devices in routine care, it is important to raise awareness of device therapy options among cardiologists, general practitioners, nurses, allied health professionals, and patients (*Figure 1*). Early referral and collaboration between primary and expert centres are necessary to overcome the current inadequate or delayed care that many patients face. Therefore, hospital referral networks should be created to ensure all patients have timely access to device therapies.

Overview of cardiac rhythm management devices and evolving techniques

Implantable cardioverter-defibrillators

An ICD may be implanted alone or in combination with a CRT. Five types of commercially available implantable ICDs exist, characterized by the position of the ICD lead within the body (*Figure 2*). The subcutaneous ICD was created to avoid inserting the ICD lead into the venous system and the complications it can induce.[51–53] The subcutaneous ICD eliminates the risk of device-associated endocarditis and substantially reduces the incidence of lead dysfunction, thereby addressing two weaknesses of the transvenous ICD. Furthermore, the development of a modular pacing-defibrillator system comprising a leadless pacemaker in wireless communication with a subcutaneous ICD has demonstrated that a subcutaneous ICD may safely provide antitachycardia and bradycardia pacing.[54] The extravascular ICD has an ICD lead implanted in the substernal space just behind the sternum and connected to a pulse generator located in the lateral chest wall, and can provide shocks, antitachycardia pacing, and cardiac pacing in case of cardiac pause – but not in the context of continuous bradycardia – without an intracardiac lead.[55,56] A wearable cardioverter-defibrillator may be used for a temporary ICD indication or as a bridge to definitive ICD implantation.[57]

Cardiac physiological pacing

Cardiac physiological pacing refers to any form of cardiac pacing intended to restore or preserve ventricular synchronicity; it encompasses CRT with biventricular (BiV) pacing and conduction system pacing (CSP) (*Figure 3*).[58] CRT with BiV pacing has been extensively studied in randomized controlled trials (RCTs) for the treatment of patients with HFrEF and prolonged QRS duration, and is most effective for patients with left bundle branch block (LBBB). However, not all patients with HFrEF and a wide QRS complex achieve improvement of electrical ventricular dyssynchrony.[59] In addition, approximately 12% of patients with right ventricular pacemakers may develop pacing-induced cardiomyopathy.[60] Therefore, there has been a search for a more physiological solution to pace patients who need a conventional pacemaker and those who need a CRT device.

Ideally, physiological pacing should engage the intrinsic conduction system, activating the ventricles in a more normal and synchronous manner. CSP involves recruitment of the intrinsic conduction fibres, for example by His bundle pacing or left bundle branch area pacing, providing a more physiological approach to pacing.[58,59,61–63]

Implantable cardioverter-defibrillators for the prevention of sudden cardiac death in patients with heart failure with reduced ejection fraction

Implantable cardioverter-defibrillators have been widely used for the prevention of SCD in patients with HFrEF. SCD is a major public health issue, with an estimated global annual burden of 4–5 million cases.[64,65] In patients with HFrEF, several pathophysiological mechanisms can trigger sudden death; the most common is an arrhythmic event resulting from acute electrical or mechanical failure in the ventricles with extensive remodelling and fibrosis.[66] GDMT, devices, and surgical interventions that improve cardiac function can help prevent the occurrence of SCD, while only defibrillator therapy is effective at terminating life-threatening ventricular tachyarrhythmias.[7,66] Following recent advances in pharmacological therapy for HFrEF, the perception that SCD is no longer a

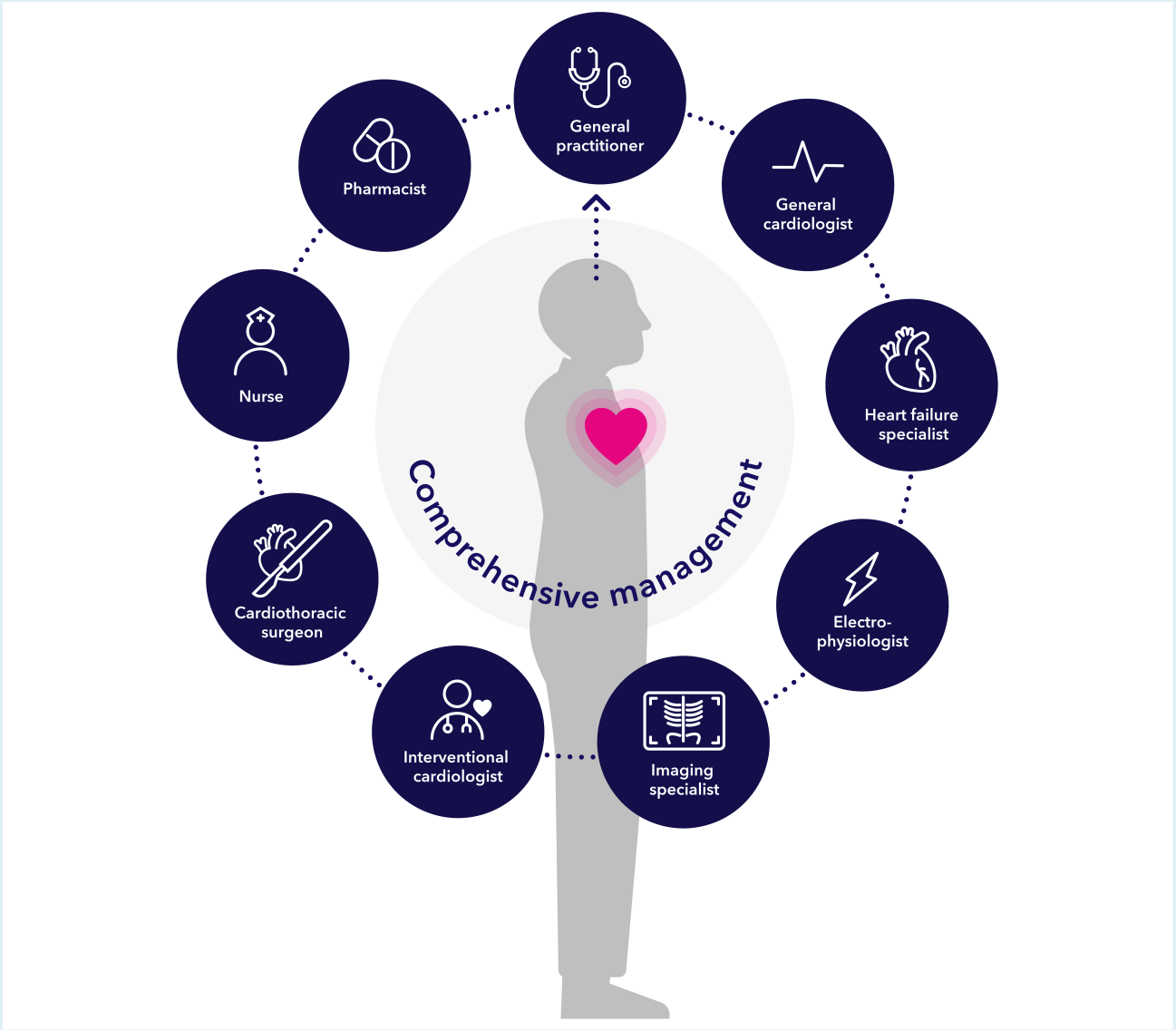

Figure 1 Patient-centred, multidisciplinary and integrated heart failure care. Imaging specialist: echocardiographist, multimodality imaging cardiologist; nurse: heart failure specialist nurse, cardiac device specialist nurse, nurse with cardiology training, general nurse practitioner. Essential support is provided by caregivers as well as patient groups and organizations.

significant risk for patients on GDMT has unfortunately become widespread, and current patient selection criteria for ICD therapy have been questioned.[67]

Risk of sudden cardiac death in heart failure with reduced ejection fraction in the current era of pharmacological therapy

Pivotal clinical trials showed that disease-modifying medical therapies for HFrEF decrease the risk of SCD.[68,69] In a meta-analysis of over 40 000 patients with HFrEF from 12 RCTs carried out between 1995 and 2014, the risk of sudden death declined by 44% over 19 years.[70] However, the residual SCD risk remained at a non-negligible 3.75% per year (considerably higher than the 1.2% threshold adopted for ICD indications in hypertrophic cardiomyopathy[67]) and in each trial the cumulative incidence of sudden death at 180 days was approximately double that found at 90 days.[70] The results from this meta-analysis should be interpreted with caution as several studies were excluded due to incomplete or unobtainable data, trial populations differed regarding disease severity, with substantial heterogeneity in SCD risk in early trials, and patients with ICDs were excluded from the analysis, leaving the interaction of ICD therapy with medical therapy unexplored.[67]

A post hoc analysis of the DAPA-HF trial showed a 21% reduction in the incidence of the composite outcome of serious ventricular arrhythmia (VA), resuscitated cardiac arrest, or sudden death in

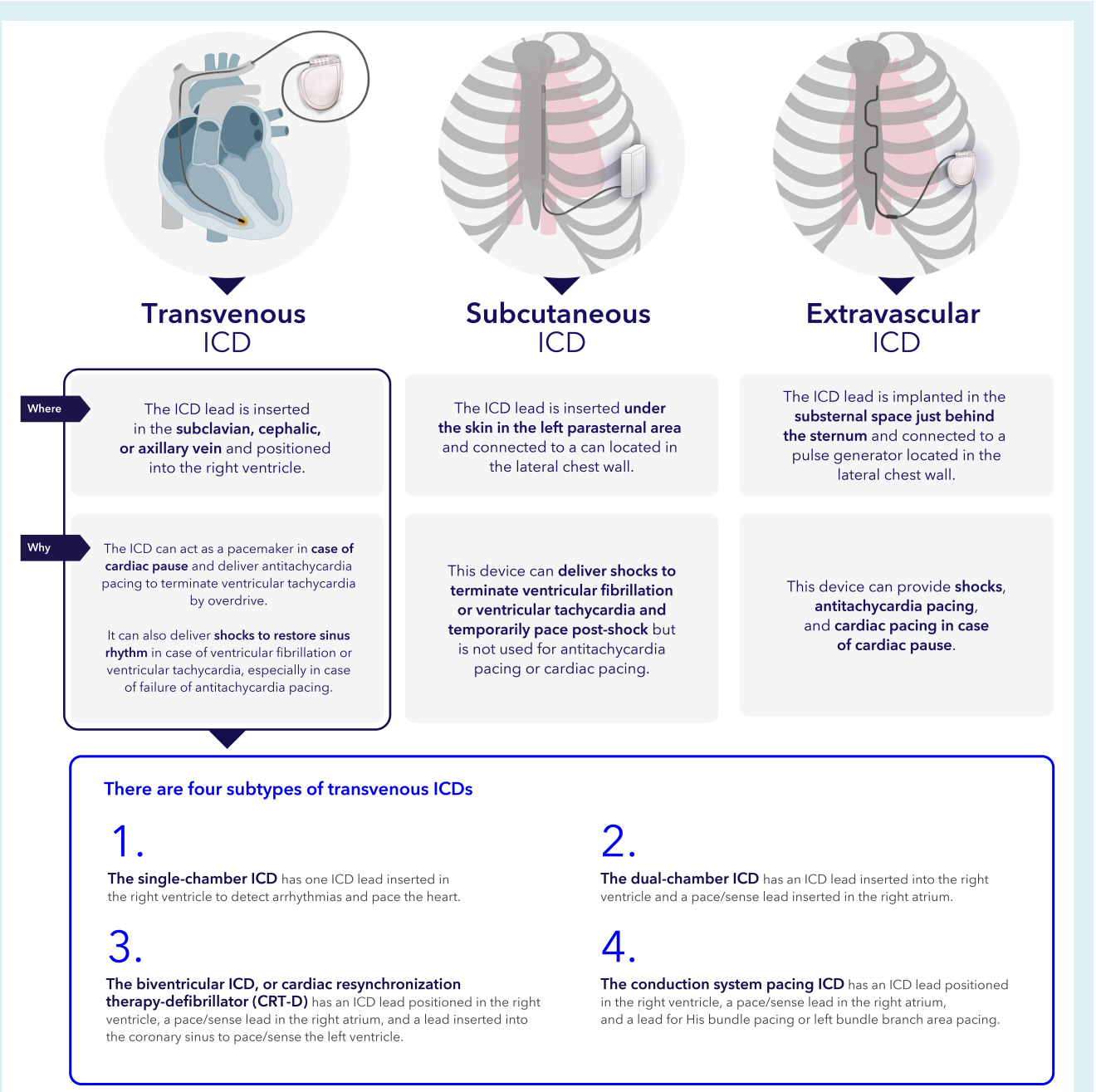

Figure 2 Overview of implantable cardioverter-defibrillators (ICD).

patients receiving dapagliflozin versus placebo.[71] In the dapagliflozin group, this composite outcome occurred in 5.9% of patients during the 2-year follow-up period with an annualized incidence of SCD of 2.7%.[71] An analysis of the PARADIGM-HF trial found that randomization to sacubitril/valsartan significantly reduced SCD risk in HFrEF patients with or without an ICD, with risk reductions of 51% and 17%, respectively.[35] Among patients without an ICD, the annualized SCD rate as a percentage of total mortality was 39.1%. In a propensity score-adjusted analysis, the use of ICD was associated with a 56% lower risk of SCD in patients meeting eligibility criteria for primary prevention irrespective of HF aetiology. Across regions, an inverse relationship was observed between ICD implantation and SCD rates. The residual annualized rate of SCD was 3.5% among patients who were ICD-eligible but did not have an ICD.[35] These results suggest that ICDs and sacubitril/valsartan reduce the risk of SCD in different ways and work synergistically.

Sudden cardiac death rates in recent trials of GDMT remain significant, both in absolute terms and as a proportion of all deaths. However, the most important question is whether GDMT has reduced the incidence of SCD in real-world patients. Evidence

Figure 3 Overview of cardiac physiological pacing techniques. CRT, cardiac resynchronization therapy; HFrEF, heart failure with reduced ejection fraction.

from registries and observational studies reveal significantly higher rates of SCD compared to clinical trial population. These higher SCD rates can partially be attributed to lower rates of GDMT in real-world patient populations,[15,29–31] not only due to provider inertia but also to patient-related physiological factors limiting optimization of GDMT.[72] In the Postmortem Systematic Investigation of Sudden Cardiac Death (POST SCD) study, only 3 of the 54 patients with HFrEF and autopsy-confirmed sudden arrhythmic death were on triple GDMT.[73]

Among 1.5 million patients with HF from 60 community-based studies, SCD accounted for a median 22% of all deaths from 2007 to 2017, with no apparent reduction of SCD rates over time.[74] A recent analysis of US administrative data from death certificates identified over 1 million deaths attributed to the combined effects of cardiac arrest and HF between 1999 and 2020, with an age-adjusted mortality rate decreasing from 27.7 per 100 000 in 1999 to 22.8 per 100 000 in 2020.[75] Mortality associated with both cardiac arrest and HF declined steadily between 1999 and 2011 but rose again between 2011 and 2020, and continues to increase since 2020.[3,76]

Therefore, it is incorrect to assume that current pharmacological therapy has eliminated the risk of SCD in patients with HFrEF or that real-world adherence to GDMT is adequate to match the levels of SCD reduction seen in clinical trials.

Efficacy and safety of implantable cardioverter-defibrillator therapy in heart failure with reduced ejection fraction

The effect of ICD therapy on all-cause mortality in patients with HFrEF at risk of SCD has been widely studied.[69] Trials evaluating ICD therapy for secondary prevention in survivors of ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) and for primary prevention in patients with or without ischaemic heart disease have shown that ICD therapy reduces patient mortality.

Secondary prevention trials

In a patient-level meta-analysis of three secondary prevention trials comparing ICD therapy and amiodarone, ICD therapy reduced death from any cause by 28% and arrhythmic death by 50% in 1866 patients.[77] Patients with LVEF ≤35% derived significantly more benefit from ICDs than those with a better preserved LVEF.

Primary prevention trials in patients with ischaemic cardiomyopathy

Implantable cardioverter-defibrillator therapy for primary prevention in patients with ischaemic cardiomyopathy and no recent myocardial infarction has been shown to significantly reduce all-cause mortality. In a meta-analysis of 2967 patients enrolled in four trials published between 1996 and 2005 in which ICD implantation was carried out as a dedicated procedure, it reduced mortality by 24%.[78]

Primary prevention trials in patients with non-ischaemic cardiomyopathy

Implantable cardioverter-defibrillators for primary prevention have also been shown to reduce all-cause mortality in patients with non-ischaemic cardiomyopathy. In a meta-analysis of data from six studies published between 2002 and 2016 that included 3128 patients without ischaemic heart disease, ICD implantation reduced mortality by 24%.[78] In the largest and most recent of these trials (DANISH), ICD therapy did not reduce all-cause mortality despite a 50% reduction in the risk of SCD.[79] These results were consistent regardless of the baseline New York Heart Association (NYHA) functional class.[80] A prespecified subgroup analysis of the DANISH trial found that the all-cause mortality benefit from ICD therapy was limited to patients aged 70 years or younger.[81]

Observational studies

In an analysis of data from the Swedish HF registry (2000–2016) that included 1305 patients with HFrEF who received an ICD and 1305 who did not, all-cause mortality within 1 and 5 years was reduced by 27% and 12%, respectively, in patients with an ICD.[82] Results were consistent across subgroups, including patients with and without ischaemic heart disease, men and women, those aged <75 and ≥75 years, and patients with and without CRT.[82]

EU-CERT-ICD, a prospective controlled cohort study conducted in 44 centres and 15 European countries, recruited 2327 patients with ischaemic cardiomyopathy or dilated cardiomyopathy and used multivariable models and propensity scoring for adjustment to compare mortality in patients with and without an ICD. Adjusted mortality was 27% lower in the ICD group than in the control group, with a significant reduction in the risk of SCD.[83] Subgroup analyses indicated that ICD therapy had no benefit in patients with diabetes or older than 75.

In the HINODE study, which included 354 patients with VAs and HF in Japan, followed up for a minimum of 12 months, propensity-matched ICD and CRT-D cohorts showed comparable VA and mortality rates to those seen in patients in the Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT) study, thus suggesting that mortality and VA event rates in major trials in Western populations are applicable to patients who have ICD for primary prevention in Japan.[84]

In a contemporary real-world study that used electronic health record data from 25 296 US patients with an indication for primary prevention ICD therapy between 2012 and 2020, the all-cause mortality in 2118 patients who received an ICD within a year was 24.3% lower than in those with no ICD.[36] There was no detectable difference in ICD benefit between patients with ischaemic and non-ischaemic heart disease.

In conclusion, there is thus good evidence of the efficacy and safety of ICD therapy for secondary or primary prevention in patients with ischaemic or non-ischaemic HFrEF.

Eligibility criteria for implantable cardioverter-defibrillator therapy in clinical practice guidelines

Many clinical guidelines consider eligibility for ICD implantation according to primary (Supplementary Material) and secondary prevention.

Secondary prevention refers to patients who have survived a life-threatening VA and remain haemodynamically unstable in the absence of reversible causes or later than 48 h after myocardial infarction.[7,85–87] Clinicians should ensure the patient has a good functional status and an estimated life expectancy of more than 1 year.

Primary prevention is recommended in symptomatic patients (NYHA class II–III) with an LVEF ≤35%.[7,8,19,85,86,88,89] Patients should have an estimated life expectancy of more than 1 year, have good functional status, and be on optimal medical therapy. Recent guidelines recommend the use of risk prediction models for those – often younger – patients with inheritable arrhythmogenic diseases.[88,90] The 2023 ESC cardiomyopathy guidelines recommended that patients with a secondary prevention ICD indication who are temporarily ineligible for ICD implantation may be provided with a wearable cardioverter-defibrillator.[85]

What determines the mortality benefit of implantable cardioverter-defibrillator therapy?

Clarifying the determinants of ICD benefit in patients with HFrEF is crucial for optimizing patient selection and improving outcomes.

The risk of life-threatening VT and/or VF should be weighed against the competing risk of non-arrhythmic mortality and the risk of potential device-related side effects. The mortality benefit of ICD therapy is influenced by a complex interplay of patient-related factors, device programming strategies, underlying cardiac and non-cardiac conditions, and procedural considerations. Patients with more advanced HF (NYHA class III–IV) and more severe left ventricular dysfunction have an increased risk of SCD and, therefore, are more likely to benefit from ICD therapy. Furthermore, advanced age and the presence of comorbidities such as diabetes and chronic kidney disease can reduce the effectiveness of ICD therapy since patients with multiple comorbidities may have a higher risk of non-SCD, which can significantly lower the overall mortality benefit of ICDs.[69,91]

In hospitalized patients with HF, the incidence of non-cardiovascular death is high, and its proportion increases with time after discharge.[92] A shift in modes of death has been observed over the last two decades: fewer sudden deaths are recorded in patients with HF and more patients die as a result of non-cardiovascular causes, mainly cancer.[93] The proportion of non-cardiovascular deaths varies depending on the cause of HF.[94] Additionally, genotype and socioeconomic factors may impact response to therapy.[89] Optimal device programming is important to maximize the efficacy of ICDs.[95] Technical aspects of ICD implantation and complications can impact outcomes.[96] It is also important to bear in mind that the mortality benefit of ICD therapy can diminish as HF progresses to end-stage disease.

Personalized sudden cardiac death risk stratification

The broad eligibility criteria for primary prevention ICD therapy in current guidelines have been questioned as they may lead to overtreatment, that is a significant proportion of recipients never experience a life-threatening arrhythmia. Conversely, limited implementation of ICD therapy may result in undertreatment and failure to prevent SCD in high-risk patients. In addition to guideline-recommended eligibility criteria, assessment of myocardial fibrosis, genetic testing, biomarkers and clinical variables may be used to individualize SCD risk stratification in patients with HFrEF.

Myocardial fibrosis confirmed by late gadolinium enhancement (LGE) using cardiac magnetic resonance (CMR) has been repeatedly demonstrated as an independent predictor of malignant VAs (MVAs), SCD, and mortality in patients with both ischaemic and non-ischaemic cardiomyopathy on top of LVEF.[97–103] Fibrosis pattern and size generally contribute to risk prediction, with the highest risk in the presence of mid-wall fibrosis.[103–105] Myocardial fibrosis on visual assessment and quantification of total fibrosis were found to be strong predictors of SCD, VT or VF, with a total fibrosis mass >10 g associated with a nine-fold increased risk compared with no myocardial fibrosis on visual assessment.[103]

Genetic testing significantly contributes to SCD risk stratification in non-ischaemic cardiomyopathy. Lamin A/C (LMNA), filamin C (FLNC), RNA-binding motif protein 20 (RBM20), and phospholamban (PLN) gene variants/mutations help identify patients at particularly elevated risk of SCD and MVA, irrespective of LVEF.[68] SCD/MVA risk prediction according to genotype and LGE have performed better than each approach separately.[106]

Biomarkers might contribute to risk stratification for SCD. Levels of natriuretic peptides, galectin-3, and ST2 have been associated with a higher risk of SCD and MVA. Natriuretic peptides, which reflect wall stress, were more likely to predict death due to pump failure in patients with HF and LVEF ≤35%, whereas novel biomarkers better enhanced SCD prediction.[107–112]

Demographics and patient characteristics predict the risk of SCD. Beyond a lower LVEF, better functional class, younger age, male sex, and higher body mass index predict a higher risk. Diabetes mellitus, hyper/hypotension, higher creatinine level, and hyponatraemia predict a lower risk. These variables were used to derive and validate the Seattle Proportional Risk Model (before the implementation of newer HF medications such as ARNi and SGLT2i).[113] This score combined with the Seattle Heart Failure Model predicting all-cause mortality[114] helped identify a subgroup of patients more likely to benefit from primary prevention ICD (i.e. at higher risk of SCD and lower risk of all-cause mortality).[37,115] However, in a Mediterranean cohort of outpatients with HF, the proportion of SCD was lower than expected based of the Seattle score.[116] The MADIT-ICD benefit score evaluates the risk of VT/VF against the competing risk of non-arrhythmic mortality based on simple clinical variables.[117] Further scores have been derived and validated, with most incorporating fibrosis assessed by LGE on CMR beyond clinical variables, LVEF, and electrocardiogram parameters in patients with non-ischaemic cardiomyopathy.[118–120] However, surprisingly, in the contemporary and prospective PROFID project, no multivariable model including clinical and CMR data significantly improved risk stratification in a heterogeneous cohort of approximately 4000 patients with ischaemic cardiomyopathy.[121] Although an LVEF threshold of 35% identified subpopulations at higher versus lower risk, LVEF as a continuous variable did not improve risk stratification within the LVEF ≤35% subgroup.[121]

In the future, artificial intelligence may have an important role in SCD risk stratification by improving prediction models, integrating multimodal data and tailoring preventive strategies to the unique profiles of individual patients.[69,122,123] It may also help optimize patient selection for primary prevention ICD therapy by identifying patients with a high risk of non-SCD mortality usually associated with comorbidities.[124]

A holistic and patient-centred approach that includes the assessment of clinical and genetic profiles and the characterization of the myocardial and arrhythmic substrate is a promising strategy for tailoring decision-making on ICD implantation. At present, however, guideline recommendations based on current evidence should be followed while further investigation is underway.

Timing of referral for implantable cardioverter-defibrillator implantation: the need for an individualized approach

Implantable cardioverter-defibrillator therapy is part of guideline-directed and evidence-based care and should not be

delayed. The timing of ICD implantation may vary according to patient characteristics. After initiation of GDMT, patients may have improved LVEF and left ventricular volumes, with LVEF reassessment helping to determine device indications.[8,125,126] The ESC HF guidelines recommend the consideration of ICD after 3 months of treatment with GDMT[7] while US HF guidelines do not specify a certain time frame and underscore the individualization of ICD timing.[8,14] The urgency of ICD implementation should be determined based on an individualized assessment of SCD risk.

Implantable cardioverter-defibrillator implantation may be considered earlier than 3 months after GDMT initiation in patients with a high risk of VAs and SCD (e.g. patients with arrhythmogenic cardiomyopathy), with very low LVEF (i.e. LVEF <20%), with irreversible aetiologies (e.g. recurrent myocardial infarction), with extensive myocardial scarring, or with a low likelihood of recovery of LVEF to >35% (very low LVEF along with advanced and long-standing HF with marked left ventricular remodelling).

Furthermore, certain patients – especially those with advanced HF and/or patients with hypoperfusion – may not tolerate initiation and up-titration of medical therapies despite attempts. An indicated ICD should not be delayed in these patients as they are at very high risk for SCD.

Cardiac resynchronization therapy in patients with heart failure with reduced ejection fraction

Among patients with HFrEF, 35–40% have QRS prolongation (QRS >120 ms), and 20–30% have an LBBB.[127] CRT with BiV pacing is a well-established therapy for patients with HFrEF who have a wide QRS complex. However, despite solid evidence and strong recommendations across guidelines, CRT is widely underused in clinical practice.[38–40,128] As an example, data from Europe indicate than approximately 50% of eligible patients followed up at specialist HF clinics and 25% of patients receiving general HF care received CRT.[38] Registry data show that factors associated with non-referral for CRT include older age (>75 years), lack of CRT implant centres, shorter duration of HF, absence of an HF nurse, and non-cardiology follow-up.[127]

Underuse of CRT is associated with excess mortality and morbidity. In an analysis of 30 134 eligible patients treated in 1377 US hospitals, CRT-D implantation ranged from 0% to 100% with a median of 89%, and lower rates of CRT-D utilization were associated with increased hospital mortality and readmissions.[40] In Japan, an analysis of 3447 consecutive symptomatic patients with chronic HF found that the cumulative incidence of cardiovascular death and HF hospitalizations, as well as that of HF death and HF hospitalizations, was significantly higher in eligible patients who did not have CRT compared to those who had CRT.[128]

Underutilization of CRT has been attributed to a poor understanding of the true benefits of CRT, suboptimal care pathways, and a lack of integrated cardiology and non-specialist care.[129] Disparities in use of HF therapies, particularly underuse of CRT-D therapy in women, have also been described.[130,131] Geographic and ethnic differences in CRT implantation rates have also been reported.[127] Improved implementation of Class I recommendations for CRT requires the education of both primary and secondary care physicians, nurses, and allied health professionals. The Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) published a joint position paper with a call for action for referral and optimization of care in CRT.[127]

Efficacy and safety of cardiac resynchronization therapy in heart failure with reduced ejection fraction

Cardiac resynchronization therapy has been subject to unprecedented scrutiny despite its firmly established benefits for morbidity and mortality in patients with HFrEF and a wide QRS (>130 ms). Multiple RCTs have unequivocally demonstrated that CRT with BiV pacing reduces HF hospitalizations and mortality and improves symptoms, QoL, exercise capacity, and left ventricular reverse remodelling in selected patients with HFrEF and cardiac dyssynchrony.[132,133] In four of the largest, appropriately powered studies (COMPANION, CARE-HF, MADIT-CRT, and RAFT), CRT led to important reductions in mortality and HF hospitalizations in patients with QRS duration ≥120 ms, especially in patients with LBBB.[134–137] In contrast, CRT was associated with worse outcomes in patients with echocardiographic evidence of left ventricular dyssynchrony without prolonged QRS (<130 ms).[138] In the RAFT Long-Term Study, the survival benefit of CRT-D therapy over ICD alone in HF patients with NYHA class II or III, LVEF ≤30%, and QRS duration ≥120 ms was sustained during a median of nearly 14 years of follow-up.[139]

In a patient-level meta-analysis of 6264 patients from eight pivotal CRT trials, CRT was associated with a 23% reduction in all-cause death.[140] In terms of number needed to treat (NNT) for 3-year all-cause mortality, the benefits of CRT when given on top of optimal medical therapy are comparable with those of HF medications such as beta-blockers and MRA, with NNTs of 8 for CRT when given in addition to medical treatment, 9 for beta-blockers and 6 for MRA.[8]

A recently completed trial highlights the valuable research still being conducted in this therapeutic arena. With over 3600 patients randomized in 27 countries, AdaptResponse is the largest global RCT of CRT conducted to date.[141] It compared standard CRT and adaptative CRT with timed left ventricular stimulation in patients with HF, LBBB, and intact atrioventricular conduction, a population expected to achieve significant disease modification after CRT. At the 5-year follow-up, adaptative CRT did not significantly reduce the incidence of all-cause death or interventions for HF decompensation compared with standard CRT, but the overall mortality (16.5% over 5 years) was much lower than reported in previous CRT trials and remained low during follow-up,[141] reflecting a high percentage of optimized HF and the relatively young mean age of the trial participants. Higher mortality rates reported in previous CRT trials may thus not indicate a lack of disease modification but rather reflect different patient populations and medical treatments.

In view of the relatively small numbers of trial patients in device compared to medical therapy trials, patient level meta-analysis has helped discern benefits of CRT in relation to conduction disturbance type. A patient-level meta-analysis of eight trials shows that the benefits of CRT are present in patients with QRS ≥150 ms and LBBB or with intraventricular conduction delay, but are reduced in those with right bundle branch block.[140] CRT is effective in both ischaemic and non-ischaemic cardiomyopathy, increasing the time to death or HF hospitalization in both patient populations, though with a greater extent of reverse remodelling in patients with non-ischaemic cardiomyopathy.[142] CRT is effective in people with a wide range of comorbidities.[143] Thus, comorbidities should not be barriers to referral for CRT.

Beneficial effects of CRT are seen in both men and women, but post hoc analyses and registry studies suggest that effects on clinical outcomes and left ventricular reverse remodelling may be greater in women than men, which probably relates to the differences in QRS width for volume (i.e. less left ventricular dilatation in women).[144] Pooled data from three trials comparing CRT-D and ICD implantation in over 4000 patients – predominantly with NYHA class II HF – with a 3-year follow-up showed that women with LBBB benefited from CRT-D at a shorter QRS duration than men with LBBB.[145] A patient-level meta-analysis of seven CRT trials showed a greater reduction in HF hospitalizations or death in women, irrespective of body size.[146] Thus, both female sex and smaller body size may explain the greater benefit of CRT in women.

In contrast to CRT with BiV pacing, there is currently limited randomized data demonstrating the benefit of CSP – His bundle pacing or left bundle branch area pacing – in patients who have CRT indications.[147] However, retrospective and prospective cohort studies suggest that CSP improves outcomes such as functional status and LVEF in HF patients with an indication for pacing, and multiple randomized trials are ongoing.[148,149]

Eligibility criteria for cardiac resynchronization therapy in clinical practice guidelines

There is broad agreement on eligibility criteria for CRT across major HF guidelines.[7,8,18,19] In patients with HFrEF in sinus rhythm, eligibility criteria are as follows: symptomatic HF, LVEF ≤35%, optimal medical therapy, QRS duration ≥150 ms (with weaker recommendations for QRS duration 120/130–149 ms), and LBBB QRS morphology (with weaker recommendations for non-LBBB QRS morphology). CRT is also recommended for HF patients with an indication for ventricular pacing for high-degree atrioventricular block, irrespective of NYHA class, and – in some but not all guidelines – for atrial fibrillation patients with LVEF ≤35%. Most HF guidelines recommend against using CRT in patients with a QRS duration <120/130 ms.[138]

The recently updated HRS/APHRS/LAHRS cardiac pacing guideline takes account of the greater benefits of CRT in women and includes a Class I recommendation for CRT in women with LVEF ≤35%, sinus rhythm, LBBB and QRS duration 120–149 ms, and NYHA class II–IV symptoms on GDMT.[58] The ESC guidelines on cardiac pacing and CRT have recommendations for CRT in patients with HF, LVEF ≤35%, NYHA class III or IV despite optimal medical therapy, atrial fibrillation, and QRS ≥130 ms, provided a strategy to ensure BiV capture is in place (Class IIa), and in patients with symptomatic atrial fibrillation and uncontrolled heart rate who are candidates for atrioventricular junction ablation (irrespective of QRS duration) and have HFrEF (Class I) or HF with mildly reduced ejection fraction (Class IIa).[150]

The 2023 HRS/APHRS/LAHRS guideline supports indications for CSP in specific situations such as using it as a potential substitute for CRT if effective resynchronization cannot be achieved with BiV pacing based on anatomical or functional criteria.[58] At present, the only Class I indication for cardiac physiologic pacing in patients with HF is for CRT using BiV pacing.[58]

A common misconception: the concept of 'non-responder'

A common misconception that may hamper optimal use of CRT is the definition of 'response'. A variety of methods to assess CRT response have been used in clinical trials, evaluating different aspects of HF status using outcomes such as functional, echocardiographic, or hard clinical outcome measures. Response rates to CRT may vary dramatically depending on the endpoints chosen.[151]

A binary classification of 'responder' versus 'non-responder', mainly based on criteria for reverse remodelling, has been widely used because the responder classification usually interacts or associates with clinical outcomes.[127,152,153] The traditional non-responder classification is mainly based on LVEF trajectory and includes both patients who worsen and those who remain stable (i.e. unchanged) after CRT implantation at 6 months. However, those who remain stable have better survival rates than those who worsen.[153] The simple binary definition of response has therefore been challenged.[127,152–154]

The placebo effect of an implant on functional outcomes is often underestimated, as noted after implantation during the run-in phase before left ventricular-only pacing was switched on in the GREATER-EARTH study.[155]

The REVERSE trial systematically evaluated survival, clinical outcomes, patient-related outcomes, death, and QoL in groups of deteriorated, stabilized, and responding patients.[156,157] This analysis showed that the widely used classification based on reverse remodelling following CRT implantation predicts clinical and patient-related outcomes in a complex and sometimes unreliable way, and therefore challenges the view that separation into responders and non-responders is meaningful.[157]

The success of CRT should not be defined as the degree of reverse remodelling it induces, but rather as the extent of disease modification it provides. As HF is a progressive disease, the stabilization of left ventricular function and the patient's clinical condition should be considered as a treatment success.[127]

This aligns with previous data showing a lack of agreement between clinical response and echocardiographic reverse remodelling.[158] Composite clinical endpoints such as the Packer score or those encompassing a wide range of responses[159] have been used in landmark trials.[156,160] However, the systematic use of the score reveals different results (69% response rates) compared to when

criteria are defined by investigational sites (80% response rates).[161] Overall, there is a clear discrepancy in clinical trials in the definition of non-response by clinical outcomes, remodelling measures, functional measures and clinical composite outcome measures. With evaluation of remodelling measures, a higher non-response rate is detected. Thus, it appears that trials systemically overestimate non-response rates when the binary morphological classification is used.[154]

Importantly, CRT outcomes depend on (i) pre-implant patient selection criteria, (ii) intra-procedure lead positioning, and (iii) post-implant device programming and arrhythmia control. To achieve maximal effectiveness, BiV pacing frequency should be maximized (>98%).

In summary, 'non-response' to CRT is complex and multifactorial. A binary classification into non-response and response according to reverse remodelling criteria appears to be unjustified and may lead to underutilization of life-saving therapy.

Reverse cardiac remodelling by guideline-directed medications in patients eligible for cardiac resynchronization therapy

Referral of HFrEF patients for CRT is generally considered only after GDMT optimization, based on the assumption that medication-induced reverse remodelling may prevent the need for CRT in some patients. As a result, many patients are not implanted when the device could have the greatest effect in synergy with GDMT.

The medications that form the basis of current GDMT – ACEi, ARB, beta-blockers, MRA, ARNi, and SGLT2i – have all been shown to improve remodelling indices.[162,163] A meta-analysis that did not include SGLT2i found that the combination of beta-blockers, MRA, and ARNi was the most effective.[162] In the PROVE-HF study, 5.2% and 9.4% improvements in LVEF were observed at 6 and 12 months, respectively, in patients treated with ARNi on a background of beta-blocker (95%) and MRA (35%) therapy, and 25% of the patients experienced an LVEF increase ≥13% at 12 months.[164]

While GDMT is linked to improvement in LVEF in patients with HFrEF, the effects on remodelling are significantly less in patients with wide than with narrow QRS. In a study of GDMT in 659 patients with LBBB, QRS duration >120 ms without LBBB, or QRS duration <120 ms, the adjusted mean increase in LVEF over 3 to 6 months was 2.0%, 5.3%, and 8.0%, respectively.[165] Additionally, an analysis of more than 1100 patients with HFrEF in the TAROT-HF trial showed that patients who met eligibility criteria for CRT implantation but did not have CRT had less left ventricular structural and functional improvement after initiation of ARNi than those with a narrow QRS complex who were not eligible for CRT.[166]

Timing of referral for cardiac resynchronization therapy implantation

Delaying the CRT implant in eligible patients has been associated with less reverse remodelling, more HF hospitalizations, and increased all-cause mortality.[127] Importantly, early use of CRT may improve the adverse haemodynamics (low cardiac output, low blood pressure, brady-arrhythmias) seen in HF and facilitate the optimization of medical therapy.[127]

In a nationwide retrospective analysis of 64 968 patients who underwent CRT implantation in the UK, the best outcomes were observed in those with no previous HF hospitalization and those undergoing CRT implantation during their first HF hospitalization.[167] Each year's delay in CRT implantation after a first HF hospitalization was associated with a 21% increase in total mortality and a 34% greater risk of HF hospitalization. In a retrospective cohort study in patients with LBBB-associated idiopathic non-ischaemic cardiomyopathy, those who had CRT within 9 months after diagnosis were more likely to have a post-CRT LVEF >35% than those who waited more than 9 months.[168]

The latest ESC guidelines on pacing and multiple scientific position statements encourage clinicians not to postpone CRT implantation, particularly in patients with LBBB and QRS ≥150 ms.[127,150] CRT implantation should be considered early in the disease trajectory of HF patients, as soon as maximum tolerated pharmacological treatment is achieved. Thus, the timing of CRT therapy is crucial, and referrals should not be delayed.

Cardiac resynchronization therapy (CRT)-defibrillator versus CRT-pacemaker in patients with heart failure with reduced ejection fraction

As CRT-D combines CRT and ICD therapy, it must in theory be indicated for patients who meet eligibility criteria for both therapies. However, CRT alone reduces the risk of VA and SCD, mainly through reverse left ventricular remodeling,[169] although this benefit may be limited to patients with LBBB.[170] CRT-pacemaker (CRT-P) and CRT-D reduce all-cause mortality compared to medical therapy alone in patients with HFrEF, but no RCTs directly compared CRT-P and CRT-D.[171] Some evidence suggests that CRT-D may improve survival more than CRT-P,[134,171] but CRT-D is more complex and is associated with a greater risk of ICD-specific risks such as lead failure and inappropriate shocks, late complications such as device-related infection, and additional costs.[150,169,172]

In the COMPANION trial, which included patients with advanced HF, both CRT-P and CRT-D significantly reduced the risk of mortality and hospitalization compared to medical therapy alone at a mean 16-month follow-up, but only CRT-D significantly reduced the risk of death from any cause.[134] In a subsequent analysis, patients with non-ischaemic cardiomyopathy had lower all-cause mortality with CRT-D than with CRT-P, but no between-device difference was observed in patients with ischaemic cardiomyopathy.[173] CRT-D treatment was associated with a greater reduction in the risk of SCD in both ischaemic and non-ischaemic cardiomyopathy, but there was excess mortality of non-cardiac and unknown causes with CRT-D in ischaemic cardiomyopathy – thus attenuating the overall survival benefit of

CRT-D.[174] In a network meta-analysis of 13 HF RCTs ($n = 12\,638$), unadjusted analyses showed that CRT-D reduced mortality more than CRT-P.[171]

Observational studies have presented conflicting results. A single-centre study in which 1122 CRT devices (693 CRT-P and 429 CRT-D) were implanted in patients with HFrEF showed no overall benefit of CRT-D compared to CRT-P during a median 28-month follow-up.[175] In patients with ischaemic cardiomyopathy, CRT-D was associated with a 30% risk reduction in all-cause mortality compared with CRT-P, whereas there was no mortality benefit of CRT-D over CRT-P in patients with non-ischaemic cardiomyopathy.[175] In a 5-year follow-up analysis of Medicare claims data on 1236 CRT-P versus 4359 CRT-D devices implanted in patients with non-ischaemic cardiomyopathy, outcomes did not differ between matched CRT-P and CRT-D recipients.[176] In a contemporary HFrEF cohort of 1988 patients from the Swedish HF registry, CRT-D was associated with lower 1- and 3-year all-cause mortality than CRT-P.[177] In an analysis of health insurance claims data for 847 patients who received CRT-P and 2722 who received CRT-D, adjusted for age and comorbidity, CRT-P was not associated with inferior survival compared with CRT-D during a median follow-up of 2.35 years.[178]

In the absence of conclusive evidence, current guidelines recommend that the choice of CRT-P or CRT-D should be guided by shared decision-making between patients and clinicians, taking into account age and comorbidities and patient values.[150] Guidelines suggest that CRT-D should be particularly considered in younger patients with a good survival prognosis, ischaemic aetiology, and a favourable comorbidity profile or presence of myocardial fibrosis on CMR.[150] CRT-P may be more appropriate in patients with dilated cardiomyopathy in the absence of myocardial scar, a short life expectancy, major comorbidities, poor renal function, or with a preference for non-defibrillator devices.[150]

The patient's perspective

In the international REVOLUTION HF survey, at least two-thirds of patients valued the time spent with healthcare professionals discussing symptoms, general HF information, lifestyle management, test results, and treatment decisions.[179] Most patients requested more information about their prognosis and HF treatments (74% and 77%, respectively).

Heart failure patients with implantable cardiac devices frequently raise the issue of inadequate patient information and its potential effects on QoL. The French Association of Cardiac Electrical Device Wearers (APODEC) survey found that 61% of patients were not sufficiently informed about ICDs before implantation, and shocks were associated with major stress for patients.[180] Indeed, a Swedish study found the worry about a potential/future shock may cause patients more distress than actual shocks.[181]

In EHRA's 'Living with an ICD' study of more than 1800 patients, 46% reported a significant improvement in QoL after device implantation, 37% had unchanged QoL, and 10% reported a deterioration.[182] Although the annual incidence of inappropriate shocks was less than 2.5%, most respondents expressed their greatest fear was the possibility of having an ICD shock or device-related complications. Nonetheless, 80% of patients felt safer with an ICD, and 69% accepted ICD limitations and necessary lifestyle changes. Patients often described the ICD as a 'life-saving' device. The study authors stressed the importance of a detailed ICD informed consent process and patient involvement in decision-making.

Shared decision-making can help to ensure the inclusion of patient goals for care, and their values and preferences into healthcare choices.[183,184] Collaborative decision-making is associated with greater emotional well-being and perceived control over illness among patients with HF.[185] Shared decision-making can also facilitate patient understanding of the importance of self-care, including nutrition, physical activity, symptom monitoring, and medication adherence.[45] Patients and family members also require improved communication concerning the decision to deactivate an ICD in the advanced stages of illness.[186]

Patient decision aids (PDA) are widely used to facilitate shared decision-making, though evidence of their effectiveness in cardiovascular care is limited. PDAs for decision-making about ICD and CRT-D therapy in patients with HF are available from the American College of Cardiology through CardioSmart (https://www.cardiosmart.org/assets/decision-aid/icds-for-patients-with-heart-failure) and the Colorado Program for Patient Centered Decisions (https://patientdecisionaid.org/decision-aids).

Integration of cardiac rhythm management devices in heart failure management: practical recommendations

The patient characteristics, comorbidities and HF medications, clinical investigations and laboratory tests that can be used to identify potential candidates for implantable cardiac devices are summarized in *Figure 4*. From the outset, it is important to be aware that patients with HFrEF benefit from ICD implantation and those with HFrEF with wide QRS benefit from CRT. Both therapies can be life-saving and CRT is a disease-modifying intervention. With this in mind, patients with HFrEF need to be carefully assessed, including medical history, ejection fraction, biomarker and genetic testing, and closely followed up to ascertain eligibility for these life-saving therapies.

Figure 5 shows the importance of personalizing timing of referral for ICD or CRT according to patient criteria such as whether they are hospitalized with HF, newly diagnosed with symptomatic HF, have a high degree of atrioventricular block, or already have a conventional pacemaker or ICD. Referral should not be delayed beyond 3 months in most patients. Some patients may require earlier referral, including high-risk patients such as those with arrhythmogenic cardiomyopathies or features that represent a sicker population whose ejection fraction is unlikely to improve without CRT implantation. Indeed, the likelihood of needing an ICD can be predicted by looking at the baseline ejection fraction and aetiologies so that timing of referral for implantation can be personalized for each patient. For example, an individual with a

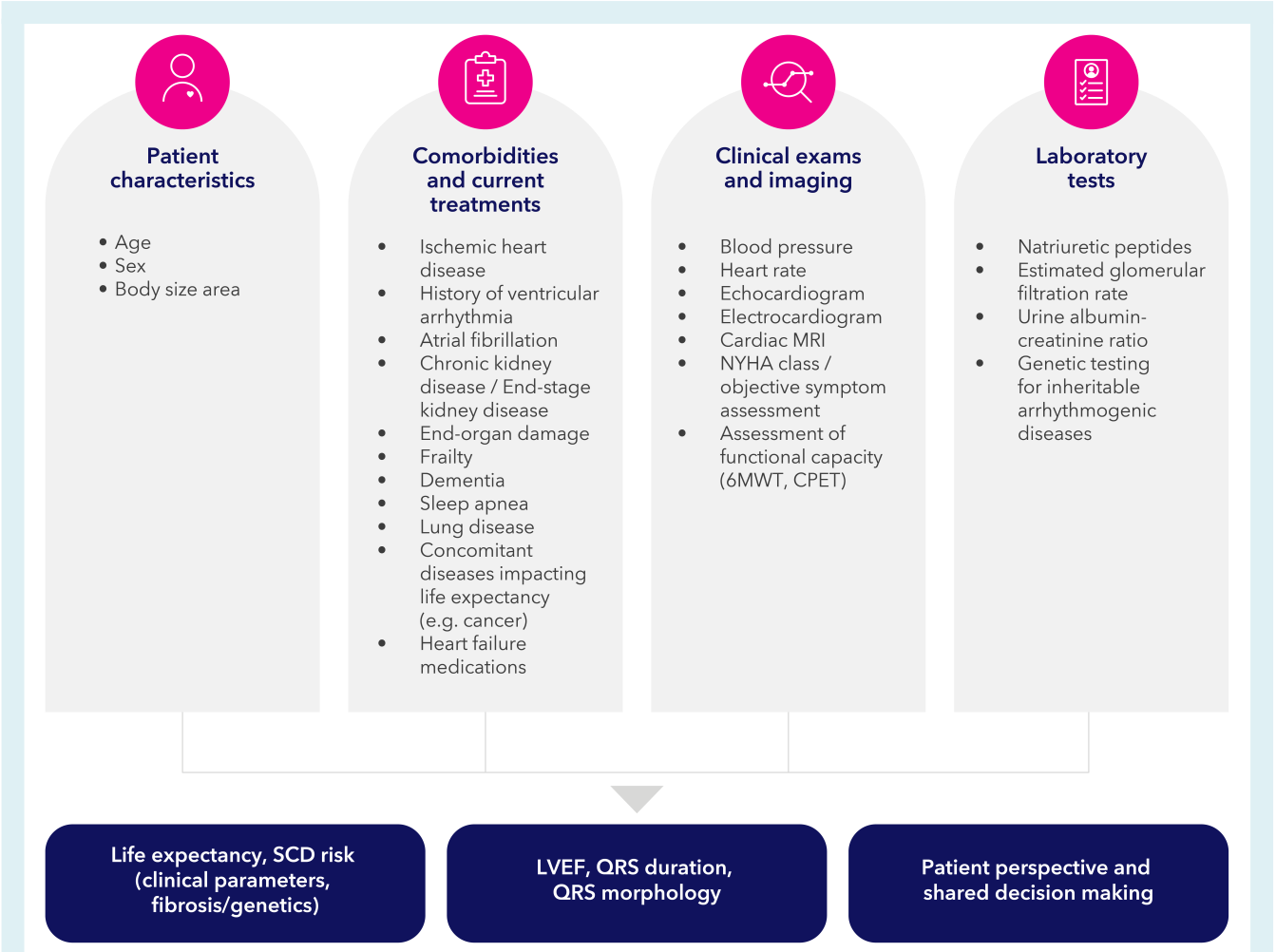

Figure 4 Information needed to identify potential candidates for implantable cardiac devices. Patient characteristics, clinical and current pharmacological history, instrumental and laboratory exams could be useful to identify potential candidates for implantable cardiac devices, in particular defining three fundamental aspects: overall mortality and sudden cardiac death risk, left ventricular ejection fraction and QRS duration and morphology, and the patient perspective. 6MWT, 6-min walk test; CPET, cardiopulmonary exercise test; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NYHA, New York Heart Association; SCD, sudden cardiac death.

baseline LVEF <20% with ischaemic cardiomyopathy and recurrent myocardial infarction is unlikely to achieve a recovery to an LVEF >35%. In such patients, referral for device implantation at the same time as starting GDMT would be the optimal route.

Any decision about referral for device assessment/implantation should be carried out in full consultation with the patient, as part of shared decision-making, and take account of each patient's preferences and concerns, addressing any misconceptions. Patients are likely to be anxious about the shocks they may receive with ICDs. Despite knowing that device implantation may be life-saving, some patients may be concerned about the potential impact of a device on their lifestyle. Patient education is essential for shared decision-making, and information needs to be provided in a timely way, tailored to the needs of each patient and taking account of their health awareness and understanding, and should be repeated and reinforced as often as needed.

Multidisciplinary post-implantation monitoring of patients with CRM devices is also important for successful long-term care. Regular monitoring of patient progress including the impact of both device and GDMT on symptoms and QoL, as well as side effects/adverse events, will help to identify issues at an early stage, so that clinical adverse effects and patient concerns can be addressed before they develop into more significant problems.

Conclusion and future perspectives

Cardiac rhythm management devices are an integral part of the management of HFrEF, with Class I recommendations for their use in multiple clinical guidelines. Current pharmacological therapies have not eliminated the risk of SCD in patients with HFrEF and it

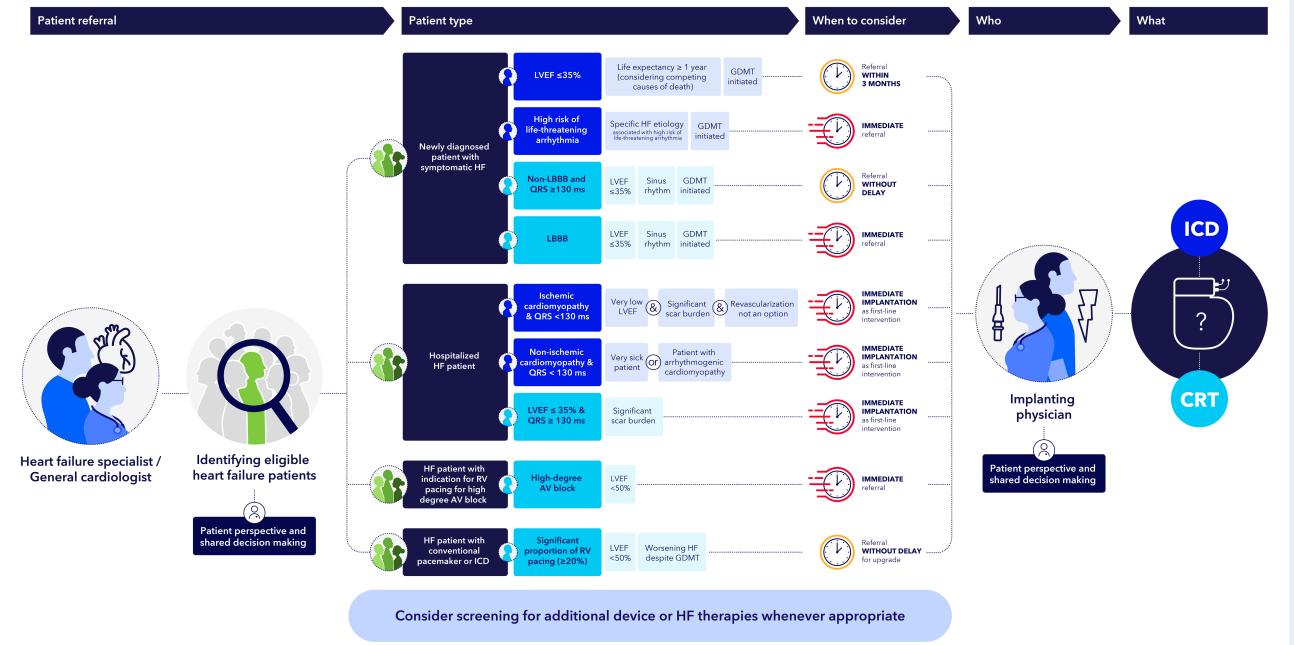

Figure 5 Algorithm for the identification of patients with heart failure who are eligible for cardiac rhythm management device therapy. AV, atrioventricular; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RV, right ventricle.

cannot be assumed that real-world adherence to GDMT is sufficient to achieve the levels of SCD reduction seen in clinical trials. ICD therapy reduces mortality in patients with HFrEF at risk of SCD in both primary and secondary prevention and in patients with and without ischaemic heart disease. The mortality and morbidity benefits of CRT in patients with HFrEF and QRS prolongation are well established, and the success of treatment should be defined by the grade of disease modification or stabilization of left ventricular function, not according to the degree of reverse remodelling that is induced. CRT implantation should be considered early in the trajectory of HFrEF to improve adverse haemodynamics and facilitate optimization of medical therapy. A patient-centred approach to assessment for a CRM device is recommended, and timing of implantation should be based on risk assessment, LVEF, comorbidities and patient preference.

Future opportunities for reducing mortality and morbidity in patients with HFrEF, and improving their QoL, will depend on implementation of evidence-based recommendations for the use of both GDMT and CRM devices in a patient-centred, personalized and timely manner. This will require high-quality educational programmes addressing the needs of healthcare professionals and patients, overcoming barriers to optimal use of device therapy.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

The DIRECT HF educational programme is coordinated by MedEd Global Solutions, Paris, France. Editorial support was provided by Jenny Bryan.

Funding

The DIRECT HF educational programme is supported by Medtronic.

Conflict of interest: B.B. has served as consultant or advisory committee member for Abbott, Abiomed/Johnson and Johnson, Bayer, Boehringer Ingelheim, Cardurion, Cytokinetics, Eli Lilly, Medtronic, Merck, Idorsia, Novo Nordisk, Regeneron, Renovacor, Roche, Salubris, Sanofi-Aventis, scPharmaceuticals, CSL Vifor, and Zoll Respicardia. W.M. has nothing to disclose. Ch.L. has received consulting and speaker fees from Medtronic and Biotronik. A.M.R. has received research grants from Abbott, Boston Scientific, Medtronic; honoraria or consulting fees from Abbott, Biotronik, Boston Scientific, Medtronic, and PaceMate; fellowship support from Medtronic; and royalties from UptoDate. G.S. has received grants and personal fees from CSL Vifor, Boehringer Ingelheim, AstraZeneca, Servier, Novartis, Cytokinetics, Pharmacosmos, Bayer, and Medtronic; personal fees from Roche, Abbott, Edwards Lifesciences, TEVA, INTAS, Hikma, and Menarini; and grants from Boston Scientific and Merck. M.B. is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation) and has received personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Medtronic, Novartis, Servier, and CSL Vifor. L.H. has received speaker fees from AstraZeneca, CSL Vifor, and Medtronic. K.K. has received consulting fees from Otsuka, Abiomed, Novartis, Medtronic, Boehringer Ingelheim, Abbott and Bayer; speaker fees from Otsuka, Abiomed, Novartis, Medtronic, Boehringer Ingelheim, Abbott, Daiichi-Sankyo, Alnylam, Nipro, AstraZeneca, Ono, and

Bayer; writing fees from Otsuka; research support from Ono, Kowa, and Boehringer Ingelheim; and scholarship funds from Otsuka and Ono. N.S. has received speaker and consulting fees from Otsuka, Novartis, BMS, Bayer, Terumo, Boehringer Ingelheim, Daiichi-Sankyo, Ono, Medtronic, AstraZeneca, Taisho, and Kowa. W.T.A. has received consulting or speaker fees from Boehringer Ingelheim, CVRx, Impulse Dynamics, Medtronic, Sensible Medical, Vectorious, V-Wave, and Zoll Respicardia. A.B.G. has received speaker or consulting fees from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Novo Nordisk, Roche Diagnostics, and CSL Vifor. A.M. has received research grants from Roche, 4TEEN4, Sphyngotec, Abbott Diagnostics, and Windtree; consulting fees from Roche, Adrenomed, Corteria, and Fire1; speaker honoraria from Merck, Novartis, Roche, and Bayer; and lab supplies by Sphyngotec; and is an advisory board member for Secret-HF, S-Form Pharma, and Implicity. G.M.C.R. has received grants and personal fees from AstraZeneca, Boehringer Ingelheim, Medtronic, Novartis, and CSL Vifor; and has received grants from Bayer, Cytokinetics, Menarini, and Servier. S.Z. has received research grant support, served on advisory boards for, or had speaker engagements with Abbott, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, CSL Vifor, Cytokinetics, Edwards, Eli Lilly, GSK, Medtronic, Merck, Novartis, Novo Nordisk, and Pfizer; serves on a clinical trial committee for studies sponsored by AstraZeneca, Boehringer Ingelheim, Cytokinetics, Merck, Novartis, Pfizer, Salubris Bio; and has received non-industry fees from Canadian Medical and Surgical KT Group, CCS, CHFS, Charité, EOCI, Liv, Medscape, Ology, PACE-CME, Radcliffe, Reach MD, Translational Medicine Academy, and Voxmedia. Ce.L. has received research grants from the Swedish Heart Lung Foundation, the Swedish Council of Science, and the Stockholm County Council. J.B. has received consulting fees from Abbott, Adaptyx, American Regent, Amgen, Applied Therapeutic, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, Cardior, CSL Behring, CVRx, Cytokinetics, Edwards, Element Science, Faraday, Foundry, Innolife, Impulse Dynamics, Imbria, Inventiva, Ionis, Lexicon, Lilly, LivaNova, Janssen, Medtronic, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, PharmaIN, Pfizer, Prolaio, Regeneron, Renibus, Roche, Salamandra, Sanofi, SC Pharma, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vifor, and Zoll.

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