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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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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

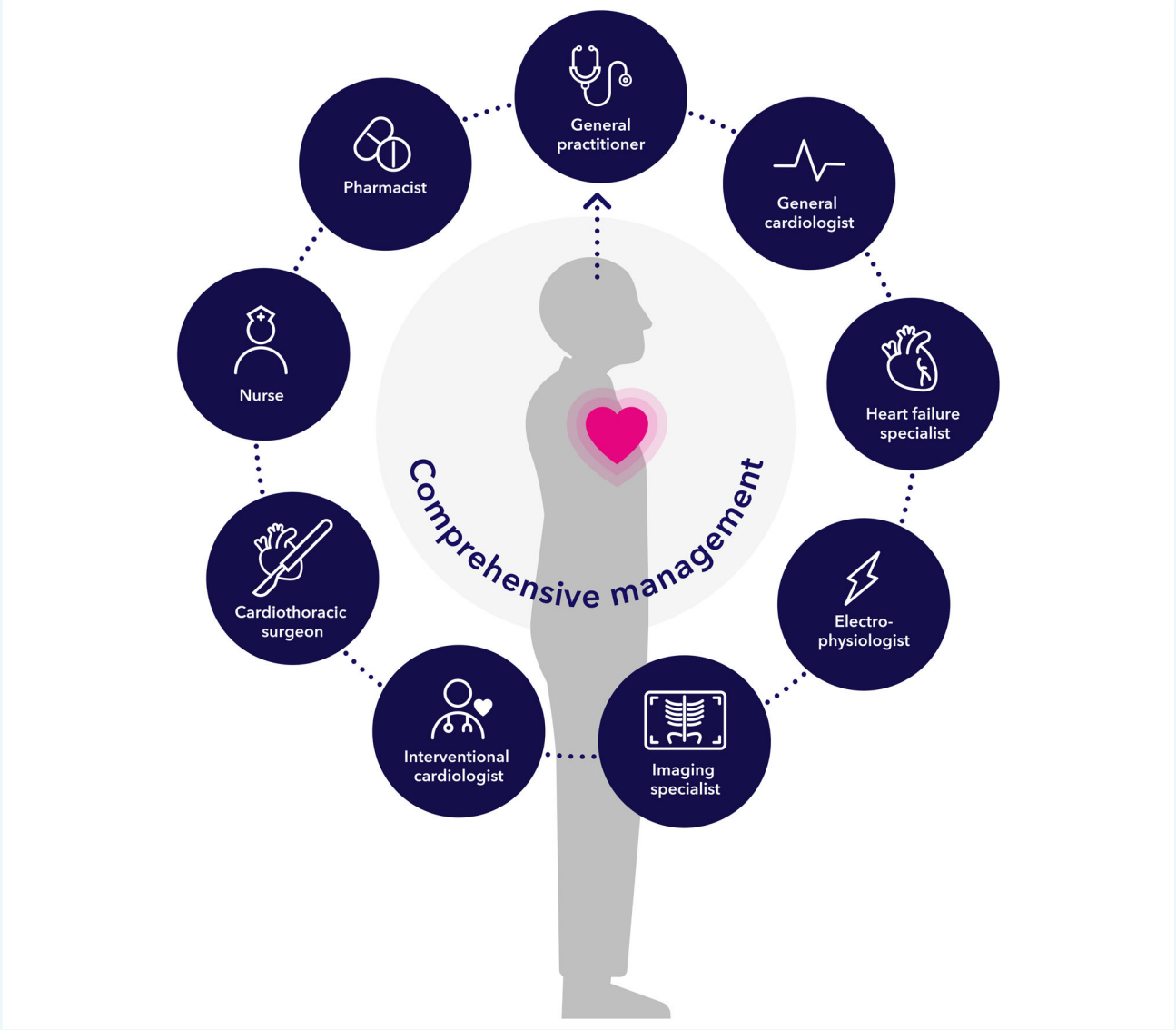

Figure 1 Patient-centred, multidisciplinary and integrated heart failure care. Imaging specialist: echocardiographist, multimodality imaging cardiologist; nurse: heart failure specialist nurse, cardiac device specialist nurse, nurse with cardiology training, general nurse practitioner. Essential support 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

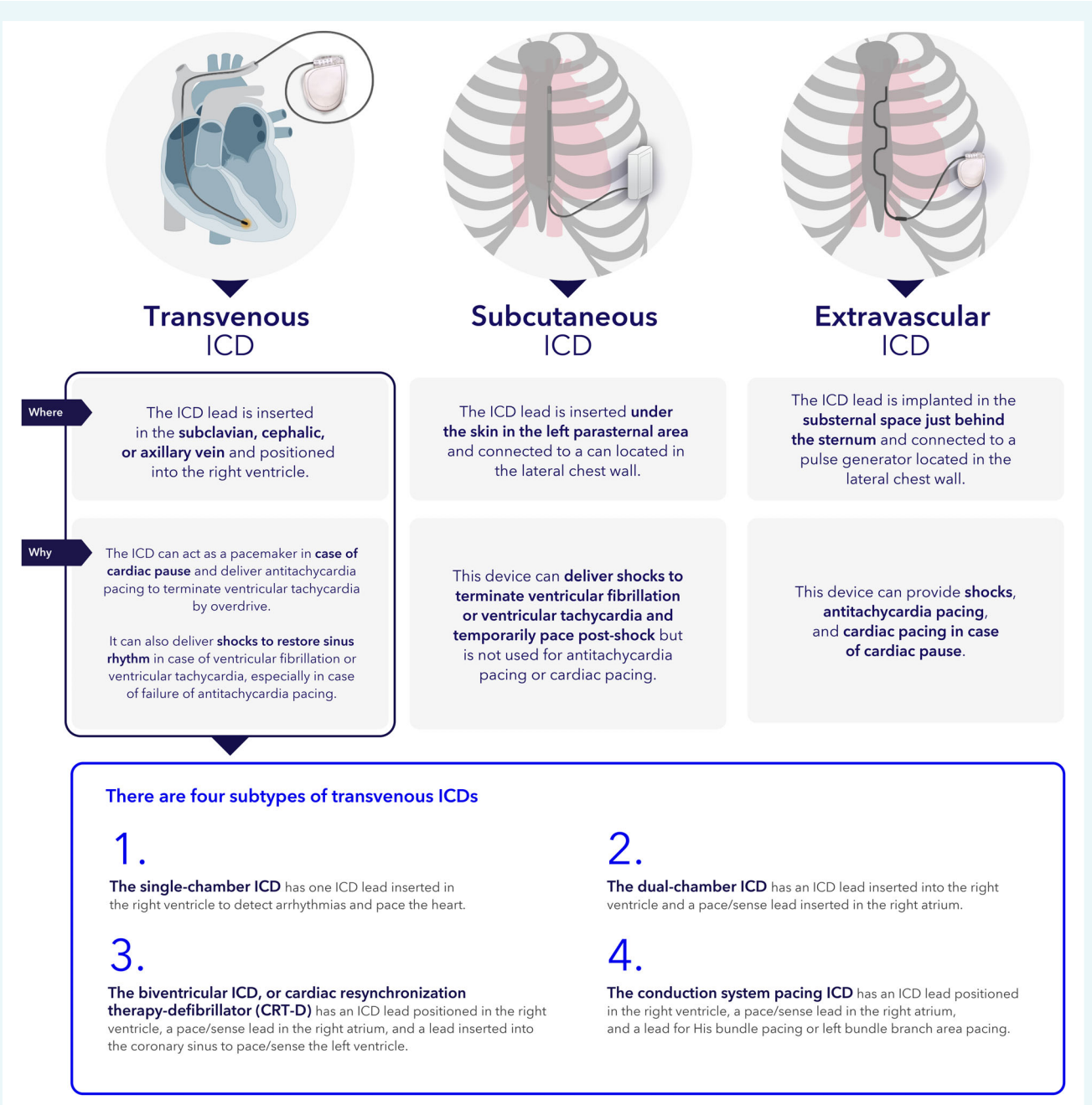

Figure 2 Overview of implantable cardioverter-defibrillators (ICD).

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 REWOLUTION 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

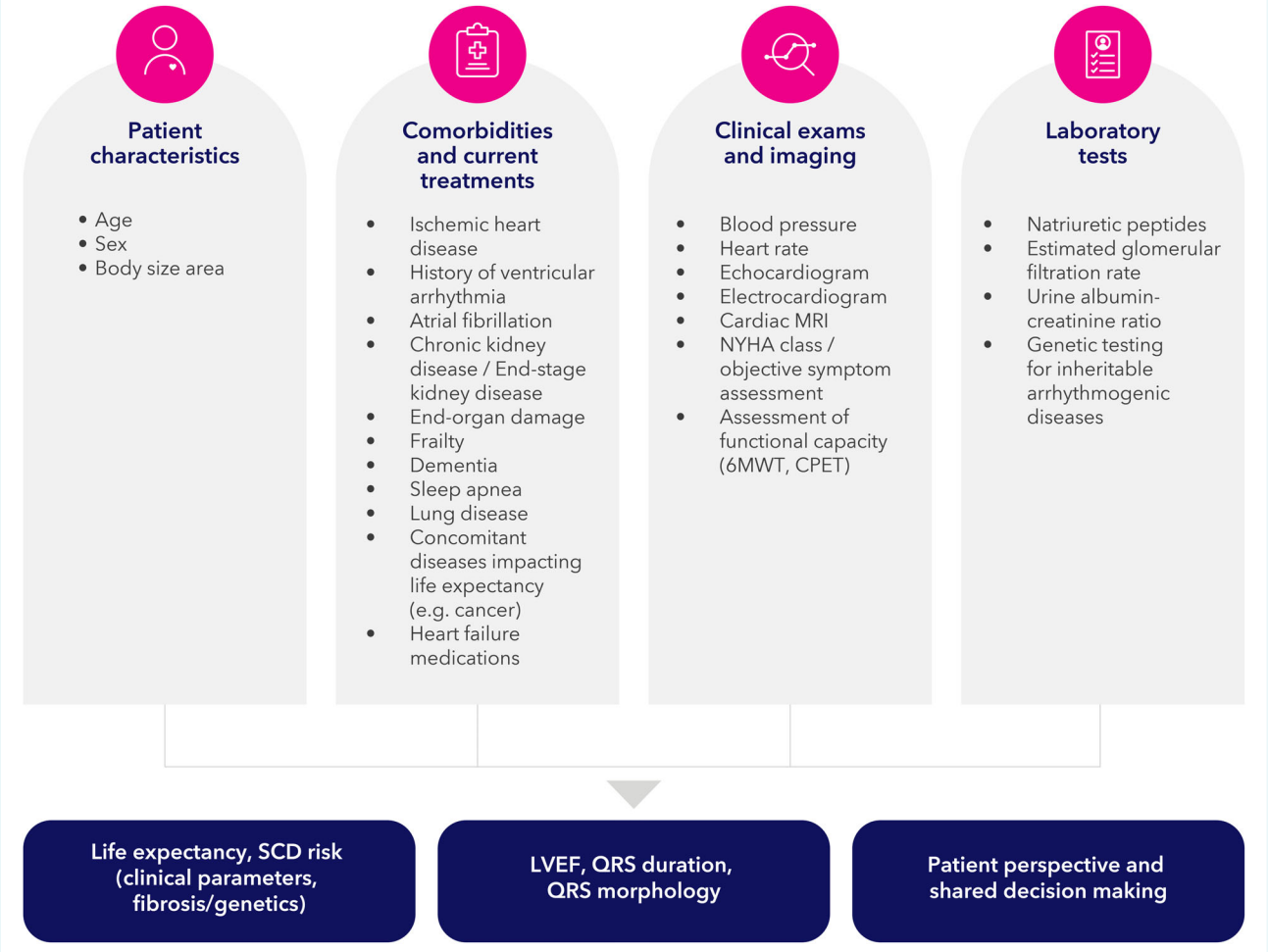

Figure 4 Information needed to identify potential candidates for implantable cardiac devices. Patient characteristics, clinical and current pharmacological history, instrumental and laboratory exams could be useful to identify potential candidates for implantable cardiac devices, in particular defining 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

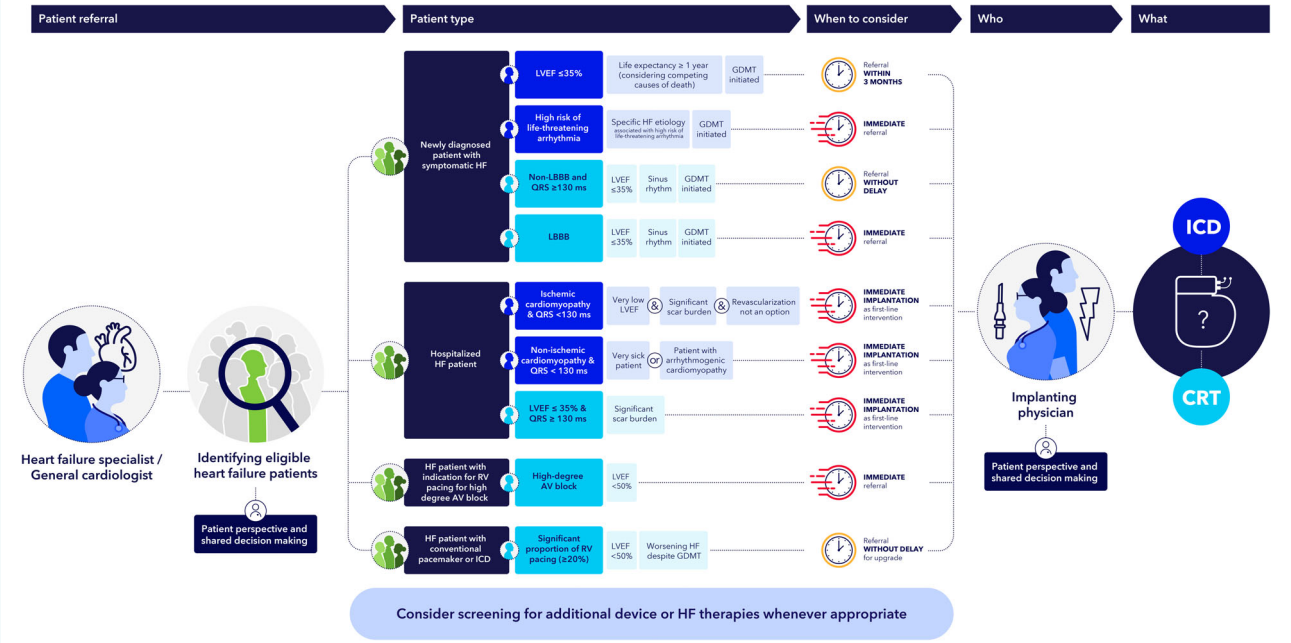

Figure 5 Algorithm for the identification of patients with heart failure who are eligible for cardiac rhythm management device therapy. AV, atrioventricular; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; 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.

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References

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: A comprehensive and updated review of epidemiology. *Cardiovasc Res* 2023;**118**:3272–3287. https://doi.org/10.1093/cvr/cvac013
2. Khan MS, Shahid I, Bennis A, Rakisheva A, Metra M, Butler J. Global epidemiology of heart failure. *Nat Rev Cardiol* 2024;**21**:717–734. https://doi.org/10.1038/s41569-024-01046-6
3. Bozkurt B, Ahmad T, Alexander K, Baker WL, Bosak K, Breathett K, *et al.*; Writing Committee Members. HF STATS 2024: Heart failure epidemiology and outcomes statistics – an updated 2024 report from the Heart Failure Society of America. *J Card Fail* 2025;**31**:66–116. https://doi.org/10.1016/j.cardfail.2024.07.001
4. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, *et al.* Heart disease and stroke statistics – 2023 update: A report from the American Heart Association. *Circulation* 2023;**147**:e93–e621. https://doi.org/10.1161/CIR.0000000000001123
5. Timmis A, Aboyans V, Vardas P, Townsend N, Torbica A, Kavousi M, *et al.* European Society of Cardiology: The 2023 Atlas of cardiovascular disease statistics. *Eur Heart J* 2024;**45**:4019–4062. https://doi.org/10.1093/eurheartj/ehae466
6. Rubio R, Palacios B, Varela L, Fernandez R, Camargo Correa S, Estupinan MF, *et al.* Quality of life and disease experience in patients with heart failure with reduced ejection fraction in Spain: A mixed-methods study. *BMJ Open* 2021;**11**:e053216. https://doi.org/10.1136/bmjopen-2021-053216
7. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
8. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;**79**:e263–e421. https://doi.org/10.1016/j.jacc.2021.12.012
9. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, *et al.* Universal definition and classification of heart failure: A report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail* 2021;**23**:352–380. https://doi.org/10.1002/ejhf.2115
10. McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz JA, Giannetti N, *et al.* CCS/CHFS heart failure guidelines update: Defining a new pharmacologic standard of care for heart failure with reduced ejection fraction. *Can J Cardiol* 2021;**37**:531–546. https://doi.org/10.1016/j.cjca.2021.01.017
11. Tsutsui H, Ide T, Ito H, Kihara Y, Kinugawa K, Kinugawa S, *et al.*; Japanese Circulation Society and the Japanese Heart Failure Society Joint Working Group. JCS/JHFS 2021 guideline focused update on diagnosis and treatment of acute and chronic heart failure. *Circ J* 2021;**85**:2252–2291. https://doi.org/10.1253/circj.CJ-21-0431
12. Tromp J, Ouwerkerk W, van Veldhuisen DJ, Hillege HL, Richards AM, van der Meer P, *et al.* A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. *JACC Heart Fail* 2022;**10**:73–84. https://doi.org/10.1016/j.jchf.2021.09.004
13. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, *et al.* Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): A multinational, open-label, randomised, trial. *Lancet* 2022;**400**:1938–1952. https://doi.org/10.1016/S0140-6736(22)02076-1
14. Bozkurt B. Contemporary pharmacological treatment and management of heart failure. *Nat Rev Cardiol* 2024;**21**:545–555. https://doi.org/10.1038/s41569-024-00997-0
15. Greene SJ, Ayodele I, Pierce JB, Khan MS, Lewsey SC, Yancy CW, *et al.* Eligibility and projected benefits of rapid initiation of quadruple therapy for newly diagnosed heart failure. *JACC Heart Fail* 2024;**12**:1365–1377. https://doi.org/10.1016/j.jchf.2024.03.001
16. Rosano GMC, Moura B, Metra M, Bohm M, Bauersachs J, Ben Gal T, *et al.* Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2021;**23**:872–881. https://doi.org/10.1002/ejhf.2206
17. Rosano GMC, Allen LA, Abdin A, Lindenfeld J, O'Meara E, Lam CSP, *et al.* Drug layering in heart failure: Phenotype-guided initiation. *JACC Heart Fail* 2021;**9**:775–783. https://doi.org/10.1016/j.jchf.2021.06.011
18. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, *et al.* 2017 Comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure. *Can J Cardiol* 2017;**33**:1342–1433. https://doi.org/10.1016/j.cjca.2017.08.022
19. Tsutsui H, Isobe M, Ito H, Ito H, Okumura K, Ono M, *et al.*; Japanese Circulation Society and the Japanese Heart Failure Society Joint Working Group. JCS 2017/JHFS 2017 guideline on diagnosis and treatment of acute and chronic heart failure – Digest version. *Circ J* 2019;**83**:2084–2184. https://doi.org/10.1253/circj.CJ-19-0342
20. Nogami A, Kurita T, Abe H, Ando K, Ishikawa T, Imai K, *et al.*; JCS/JHRS Joint Working Group. JCS/JHRS 2019 guideline on non-pharmacotherapy of cardiac arrhythmias. *Circ J* 2021;**85**:1104–1244. https://doi.org/10.1253/circj.CJ-20-0637
21. Dhande M, Rangavajla G, Canterbury A, Hamandi M, Boricha H, Newhouse D, *et al.* Guideline-directed medical therapy and the risk of death in primary prevention defibrillator recipients. *JACC Clin Electrophysiol* 2022;**8**:1024–1030. https://doi.org/10.1016/j.jacep.2022.05.001
22. Mignone JL, Alexander KM, Dobbles M, Eberst K, Fonarow GC, Ellenbogen KA. Outcomes with guideline-directed medical therapy and cardiac implantable electronic device therapies for patients with heart failure with reduced ejection fraction. *Heart Rhythm O2* 2024;**5**:168–173. https://doi.org/10.1016/j.hroo.2024.01.004
23. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, *et al.*; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008. https://doi.org/10.1056/NEJMoa1911303

24. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, *et al.*; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424. https://doi.org/10.1056/NEJMoa2022190
25. Bozkurt B. Concerning trends of rising heart failure mortality rates. *JACC Heart Fail* 2024;**12**:970–972. https://doi.org/10.1016/j.jchf.2024.04.001
26. Leyva F, Zegard A, Patel P, Stegemann B, Marshall H, Ludman P, *et al.* Improved prognosis after cardiac resynchronization therapy over a decade. *Europace* 2023;**25**:euad141. https://doi.org/10.1093/europace/euad141
27. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, *et al.* Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. *J Am Coll Cardiol* 2018;**72**:351–366. https://doi.org/10.1016/j.jacc.2018.04.070
28. Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM, *et al.* Titration of medical therapy for heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2019;**73**:2365–2383. https://doi.org/10.1016/j.jacc.2019.02.015
29. Tromp J, Ouwerkerk W, Teng TK, Cleland JGF, Bamadhaj S, Angermann CE, *et al.* Global disparities in prescription of guideline-recommended drugs for heart failure with reduced ejection fraction. *Eur Heart J* 2022;**43**:2224–2234. https://doi.org/10.1093/eurheartj/ehac103
30. Savarese G, Kishi T, Vardeny O, Adamsson Eryd S, Bodegard J, Lund LH, *et al.* Heart failure drug treatment – inertia, titration, and discontinuation: A multinational observational study (EVOLUTION HF). *JACC Heart Fail* 2023;**11**:1–14. https://doi.org/10.1016/j.jchf.2022.08.009
31. Tomasoni D, Pagnesi M, Colombo G, Chiarito M, Stolfo D, Baldetti L, *et al.* Guideline-directed medical therapy in severe heart failure with reduced ejection fraction: An analysis from the HELP-HF registry. *Eur J Heart Fail* 2024;**26**:327–337. https://doi.org/10.1002/ejhf.3081
32. Fujihashi T, Nochioka K, Yasuda S, Sakata Y, Hayashi H, Shiroto T, *et al.* Underuse of heart failure medications and poor long-term prognosis in chronic heart failure patients with polypharmacy – a report from the CHART-2 study. *Int J Cardiol Heart Vasc* 2024;**50**:101345. https://doi.org/10.1016/j.ijcha.2024.101345
33. Pierce JB, Vaduganathan M, Fonarow GC, Ikeaba U, Chiswell K, Butler J, *et al.* Contemporary use of sodium-glucose cotransporter-2 inhibitor therapy among patients hospitalized for heart failure with reduced ejection fraction in the US: The Get With The Guidelines-Heart Failure Registry. *JAMA Cardiol* 2023;**8**:652–661. https://doi.org/10.1001/jamacardio.2023.1266
34. Hess PL, Langner P, Heidenreich PA, Essien U, Leonard C, Swat SA, *et al.* National trends in hospital performance in guideline-recommended pharmacologic treatment for heart failure at discharge. *JACC Heart Fail* 2024;**12**:1059–1070. https://doi.org/10.1016/j.jchf.2024.02.014
35. Rohde LE, Chatterjee NA, Vaduganathan M, Claggett B, Packer M, Desai AS, *et al.* Sacubitril/valsartan and sudden cardiac death according to implantable cardioverter-defibrillator use and heart failure cause: A PARADIGM-HF analysis. *JACC Heart Fail* 2020;**8**:844–855. https://doi.org/10.1016/j.jchf.2020.06.015
36. Ahmed A, Auricchio A, Mittal S, Pickett RA, Wilkoff BL, Jacobsen LD, *et al.* Mortality benefit among primary prevention implantable cardioverter-defibrillator recipients on contemporary heart failure treatment. *JACC Clin Electrophysiol* 2024;**10**:916–926. https://doi.org/10.1016/j.jacep.2024.102334
37. Schrage B, Lund LH, Benson L, Dahlstrom U, Shadman R, Linde C, *et al.* Predictors of primary prevention implantable cardioverter-defibrillator use in heart failure with reduced ejection fraction: Impact of the predicted risk of sudden cardiac death and all-cause mortality. *Eur J Heart Fail* 2022;**24**:1212–1222. https://doi.org/10.1002/ejhf.2530
38. Gatti P, Linde C, Benson L, Thorvaldsen T, Normand C, Savarese G, *et al.* What determines who gets cardiac resynchronization therapy in Europe? A comparison between ESC-HF-LT Registry, SwedeHF Registry, and ESC-CRT Survey II. *Eur Heart J Qual Care Clin Outcomes* 2023;**9**:741–748. https://doi.org/10.1093/ehjqcco/qcad024
39. Curtis AB, Manrodt C, Jacobsen LD, Soderlund D, Fonarow GC. Guideline-directed device therapies in heart failure: A clinical practice-based analysis using electronic health record data. *Am Heart J Plus* 2022;**16**:100139. https://doi.org/10.1016/j.ahjo.2022.100139
40. Chui PW, Lan Z, Freeman JV, Enriquez AD, Khera R, Akar JG, *et al.* Variation in hospital use of cardiac resynchronization therapy-defibrillator among eligible patients and association with clinical outcomes. *Heart Rhythm* 2023;**20**:1000–1008. https://doi.org/10.1016/j.hrthm.2023.03.022
41. Mullens W, Dauw J, Gustafsson F, Mebazaa A, Steffel J, Witte KK, *et al.* Integration of implantable device therapy in patients with heart failure. A clinical consensus statement from the Heart Failure Association (HFA) and European Heart Rhythm Association (EHRA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2024;**26**:483–501. https://doi.org/10.1002/ejhf.3150
42. Estep JD, Salah HM, Kapadia SR, Burkhoff D, Lala A, Butler J, *et al.* HFSA scientific statement: Update on device based therapies in heart failure. *J Card Fail* 2024;**30**:1472–1488. https://doi.org/10.1016/j.cardfail.2024.07.007
43. Fried TR. Shared decision making – Finding the sweet spot. *N Engl J Med* 2016;**374**:104–106. https://doi.org/10.1056/NEJMp1510020
44. Itzhaki Ben Zadok O, Ben-Avraham B, Jaarsma T, Shaul A, Hammer Y, Barac YD, *et al.* Health-related quality of life in left ventricular assist device-supported patients. *ESC Heart Fail* 2021;**8**:2036–2044. https://doi.org/10.1002/ehf2.13282
45. Jaarsma T, Hill L, Bayes-Genis A, La Rocca HB, Castiello T, Celutkiene J, *et al.* Self-care of heart failure patients: Practical management recommendations from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2021;**23**:157–174. https://doi.org/10.1002/ejhf.2008
46. Ferrick AM, Raj SR, Deneke T, Kojodjojo P, Lopez-Cabanillas N, Abe H, *et al.* 2023 HRS/EHRA/APHRS/LAHRS expert consensus statement on practical management of the remote device clinic. *Heart Rhythm* 2023;**20**:e92–e144. https://doi.org/10.1016/j.hrthm.2023.03.1525
47. Varma N, Braunschweig F, Burri H, Hindricks G, Linz D, Michowitz Y, *et al.* Remote monitoring of cardiac implantable electronic devices and disease management. *Europace* 2023;**25**:euad233. https://doi.org/10.1093/europace/euad233
48. Feijen M, Beles M, Tan YZ, Cordon A, Dupont M, Treskes RW, *et al.* Fewer worsening heart failure events with HeartLogic on top of standard care: A propensity-matched cohort analysis. *J Card Fail* 2023;**29**:1522–1530. https://doi.org/10.1016/j.cardfail.2023.04.012
49. Ahmed FZ, Sammut-Powell C, Martin GP, Callan P, Cunnington C, Kahn M, *et al.* Association of a device-based remote management heart failure pathway with outcomes: TriageHF plus real-world evaluation. *ESC Heart Fail* 2024;**11**:2637–2647. https://doi.org/10.1002/ehf2.14821
50. Shah SP, Dixit NM, Mendoza K, Entabi R, Meymandi S, Balady-Bouziane N, *et al.* Integration of clinical pharmacists into a heart failure clinic within a safety-net hospital. *J Am Pharm Assoc* 2022;**62**:575–579.e2. https://doi.org/10.1016/j.japh.2021.11.012
51. Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, *et al.* An entirely subcutaneous implantable cardioverter-defibrillator. *N Engl J Med* 2010;**363**:36–44. https://doi.org/10.1056/NEJMoa0909545
52. Knops RE, Olde Nordkamp LRA, Delnoy PHM, Boersma LVA, Kuschyk J, El-Chami MF, *et al.*; PRAETORIAN Investigators. Subcutaneous or transvenous defibrillator therapy. *N Engl J Med* 2020;**383**:526–536. https://doi.org/10.1056/NEJMoa1915932
53. Healey JS, Krahn AD, Bashir J, Amit G, Philippon F, McIntyre WF, *et al.*; ATLAS Investigators. Perioperative safety and early patient and device outcomes among subcutaneous versus transvenous implantable cardioverter defibrillator implantations: A randomized, multicenter trial. *Ann Intern Med* 2022;**175**:1658–1665. https://doi.org/10.7326/M22-1566
54. Knops RE, Lloyd MS, Roberts PR, Wright DJ, Boersma LVA, Doshi R, *et al.*; MODULAR ATP Investigators. A modular communicative leadless pacing-defibrillator system. *N Engl J Med* 2024;**391**:1402–1412. https://doi.org/10.1056/NEJMoa2401807
55. Friedman P, Murgatroyd F, Boersma LVA, Manlucu J, O'Donnell D, Knight BP, *et al.*; Extravascular ICD Pivotal Study Investigators. Efficacy and safety of an extravascular implantable cardioverter-defibrillator. *N Engl J Med* 2022;**387**:1292–1302. https://doi.org/10.1056/NEJMoa2206485
56. Friedman P, Murgatroyd F, Boersma LVA, Manlucu J, Knight BP, Clementy N, *et al.*; Extravascular ICD Pivotal Study Investigators. Performance and safety of the extravascular implantable cardioverter-defibrillator through long-term follow-up: Final results from the Pivotal study. *Circulation* 2025;**151**:322–332. https://doi.org/10.1161/CIRCULATIONAHA.124.071795
57. Piccini JP, Allen LA, Kudenchuk PJ, Page RL, Patel MR, Turakhia MP. Wearable cardioverter-defibrillator therapy for the prevention of sudden cardiac death: A science advisory from the American Heart Association. *Circulation* 2016;**133**:1715–1727. https://doi.org/10.1161/CIR.0000000000000394
58. Chung MK, Patton KK, Lau CP, Dal Forno ARJ, Al-Khatib SM, Arora V, *et al.* 2023 HRS/APHRS/LAHRS guideline on cardiac physiologic pacing for the avoidance and mitigation of heart failure. *Heart Rhythm* 2023;**20**:e17–e91. https://doi.org/10.1016/j.hrthm.2023.03.1538
59. Ellenbogen KA, Auricchio A, Burri H, Gold MR, Leclercq C, Leyva F, *et al.* The evolving state of cardiac resynchronization therapy and conduction system pacing: 25 years of research at EP Europace journal. *Europace* 2023;**25**:euad168. https://doi.org/10.1093/europace/euad168
60. Somma V, Ha FJ, Palmer S, Mohamed U, Agarwal S. Pacing-induced cardiomyopathy: A systematic review and meta-analysis of definition, prevalence, risk factors, and management. *Heart Rhythm* 2023;**20**:282–290. https://doi.org/10.1016/j.hrthm.2022.09.019

61. Tan NY, Witt CM, Oh JK, Cha YM. Left bundle branch block: Current and future perspectives. *Circ Arrhythm Electrophysiol* 2020;**13**:e008239. https://doi.org/10.1161/CIRCEP.119.008239
62. Vijayaraman P, Bordachar P, Ellenbogen KA. The continued search for physiological pacing: Where are we now? *J Am Coll Cardiol* 2017;**69**:3099–3114. https://doi.org/10.1016/j.jacc.2017.05.005
63. Burri H, Jastrzebski M, Cano O, Curila K, de Pooter J, Huang W, *et al.* EHRA clinical consensus statement on conduction system pacing implantation: Endorsed by the Asia Pacific Heart Rhythm Society (APHRS), Canadian Heart Rhythm Society (CHRS), and Latin American Heart Rhythm Society (LAHRS). *Europace* 2023;**25**:1208–1236. https://doi.org/10.1093/europace/euad043
64. Marijon E, Narayanan K, Smith K, Barra S, Basso C, Blom MT, *et al.* The Lancet Commission to reduce the global burden of sudden cardiac death: A call for multidisciplinary action. *Lancet* 2023;**402**:883–936. https://doi.org/10.1016/S0140-6736(23)00875-9
65. Empana JP, Lerner I, Valentin E, Folke F, Bottiger B, Gislason G, *et al.*; ESCAPE-NET Investigators. Incidence of sudden cardiac death in the European Union. *J Am Coll Cardiol* 2022;**79**:1818–1827. https://doi.org/10.1016/j.jacc.2022.02.041
66. Packer M. What causes sudden death in patients with chronic heart failure and a reduced ejection fraction? *Eur Heart J* 2020;**41**:1757–1763. https://doi.org/10.1093/eurheartj/ehz553
67. Leyva F, Israel CW, Singh J. Declining risk of sudden cardiac death in heart failure: Fact or myth? *Circulation* 2023;**147**:759–767. https://doi.org/10.1161/CIRCULATIONAHA.122.062159
68. Polovina M, Tschope C, Rosano G, Metra M, Crea F, Mullens W, *et al.* Incidence, risk assessment and prevention of sudden cardiac death in cardiomyopathies. *Eur J Heart Fail* 2023;**25**:2144–2163. https://doi.org/10.1002/ejhf.3076
69. Yehya A, Lopez J, Sauer AJ, Davis JD, Ibrahim NE, Tung R, *et al.* Revisiting ICD therapy for primary prevention in patients with heart failure and reduced ejection fraction. *JACC Heart Fail* 2025;**13**:1–13. https://doi.org/10.1016/j.jchf.2024.09.014
70. Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, *et al.* Declining risk of sudden death in heart failure. *N Engl J Med* 2017;**377**:41–51. https://doi.org/10.1056/NEJMoa1609758
71. Curtain JP, Docherty KF, Jhund PS, Petrie MC, Inzucchi SE, Kober L, *et al.* Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. *Eur Heart J* 2021;**42**:3727–3738. https://doi.org/10.1093/eurheartj/ehab560
72. Jarjour M, Henri C, de Denus S, Fortier A, Bouabdallaoui N, Nigam A, *et al.* Care gaps in adherence to heart failure guidelines: Clinical inertia or physiological limitations? *JACC Heart Fail* 2020;**8**:725–738. https://doi.org/10.1016/j.jchf.2020.04.019
73. Ramakrishna S, Salazar JW, Olgin JE, Moffatt E, Tseng ZH. Heart failure burden by autopsy, guideline-directed medical therapy, and ICD utilization among sudden deaths. *JACC Clin Electrophysiol* 2023;**9**:403–413. https://doi.org/10.1016/j.jacep.2022.10.018
74. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: A systematic review and meta-analysis. *Eur J Heart Fail* 2019;**21**:1306–1325. https://doi.org/10.1002/ejhf.1594
75. Jain V, Rao B, Knijnik L, Shah AD, Lloyd MS, El-Chami MF, *et al.* Rising burden of cardiac arrest- and heart failure-related mortality in the United States from 1999 to 2020. *Heart Rhythm* 2024;**O2**:254–255. https://doi.org/10.1016/j.hroo.2024.03.001
76. Martin SS, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, *et al.*; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. 2024 Heart disease and stroke statistics: A report of US and global data from the American Heart Association. *Circulation* 2024;**149**:e347–e913. https://doi.org/10.1161/CIR.0000000000001209
77. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, *et al.* Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. *Eur Heart J* 2000;**21**:2071–2078. https://doi.org/10.1053/euhj.2000.2476
78. Shun-Shin MJ, Zheng SL, Cole GD, Howard JP, Whinnett ZI, Francis DP. Implantable cardioverter defibrillators for primary prevention of death in left ventricular dysfunction with and without ischaemic heart disease: A meta-analysis of 8567 patients in the 11 trials. *Eur Heart J* 2017;**38**:1738–1746. https://doi.org/10.1093/eurheartj/ehx028
79. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, *et al.*; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230. https://doi.org/10.1056/NEJMoa1608029
80. Karacan MN, Doi SN, Yafasova A, Thune JJ, Nielsen JC, Haarbo J, *et al.* New York Heart Association functional class and implantable cardioverter-defibrillator in non-ischaemic heart failure with reduced ejection fraction: Extended follow-up of the D ANISH trial. *Eur J Heart Fail* 2024;**26**:1423–1431. https://doi.org/10.1002/ejhf.3239
81. Elming MB, Nielsen JC, Haarbo J, Videbaek L, Korup E, Signorovitch J, *et al.* Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure. *Circulation* 2017;**136**:1772–1780. https://doi.org/10.1161/CIRCULATIONAHA.117.028829
82. Schrage B, Uijl A, Benson L, Westermann D, Stahlberg M, Stolfo D, *et al.* Association between use of primary-prevention implantable cardioverter-defibrillators and mortality in patients with heart failure: A prospective propensity score-matched analysis from the Swedish Heart Failure Registry. *Circulation* 2019;**140**:1530–1539. https://doi.org/10.1161/CIRCULATIONAHA.119.043012
83. Zabel M, Willems R, Lubinski A, Bauer A, Brugada J, Conen D, *et al.*; EU-CERT-ICD Study Investigators. Clinical effectiveness of primary prevention implantable cardioverter-defibrillators: Results of the EU-CERT-ICD controlled multicentre cohort study. *Eur Heart J* 2020;**41**:3437–3447. https://doi.org/10.1093/eurheartj/ehaa226
84. Aonuma K, Ando K, Kusano K, Asai T, Inoue K, Inamura Y, *et al.*; HINODE Investigators. Primary results from the Japanese Heart Failure and Sudden Cardiac Death Prevention Trial (HINODE). *ESC Heart Fail* 2022;**9**:1584–1596. https://doi.org/10.1002/ehf2.13901
85. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, *et al.* 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;**44**:3503–3626. https://doi.org/10.1093/eurheartj/ehad194
86. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, *et al.* 2020 ESC Guidelines for the management of adult congenital heart disease. *Eur Heart J* 2021;**42**:563–645. https://doi.org/10.1093/eurheartj/ehaa554
87. Terasaki F, Azuma A, Anzai T, Ishizaka N, Ishida Y, Isobe M, *et al.*; Japanese Circulation Society Joint Working Group. JCS 2016 guideline on diagnosis and treatment of cardiac sarcoidosis – Digest version. *Circ J* 2019;**83**:2329–2388. https://doi.org/10.1253/circj.CJ-19-0508
88. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, *et al.* 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;**43**:3997–4126. https://doi.org/10.1093/eurheartj/ehac262
89. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, *et al.* 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation* 2018;**138**:e272–e391. https://doi.org/10.1161/CIR.0000000000000549
90. Wahbi K, Ben Yaou R, Gandjbakhch E, Anselme F, Gossios T, Lakdawala NK, *et al.* Development and validation of a new risk prediction score for life-threatening ventricular tachyarrhythmias in laminopathies. *Circulation* 2019;**140**:293–302. https://doi.org/10.1161/CIRCULATIONAHA.118.039410
91. Varga CR, Cleland JGF, Abraham WT, Lip GYH, Leyva F, Hatamizadeh P. Implantable cardioverter defibrillator and resynchronization therapy in patients with overt chronic kidney disease: JACC state-of-the-art review. *J Am Coll Cardiol* 2024;**84**:1342–1362. https://doi.org/10.1016/j.jacc.2024.05.081
92. Wakabayashi K, Ikeda N, Kajimoto K, Minami Y, Keida T, Asai K, *et al.*; ATTEND Investigators. Trends and predictors of non-cardiovascular death in patients hospitalized for acute heart failure. *Int J Cardiol* 2018;**250**:164–170. https://doi.org/10.1016/j.ijcard.2017.09.004
93. Moliner P, Lupon J, de Antonio M, Domingo M, Santiago-Vacas E, Zamora E, *et al.* Trends in modes of death in heart failure over the last two decades: Less sudden death but cancer deaths on the rise. *Eur J Heart Fail* 2019;**21**:1259–1266. https://doi.org/10.1002/ejhf.1569
94. Amara N, Boveda S, Defaye P, Klug D, Treguer F, Amet D, *et al.* Implantable cardioverter-defibrillator therapy among patients with non-ischaemic vs. ischaemic cardiomyopathy for primary prevention of sudden cardiac death. *Europace* 2017;**20**:65–72. https://doi.org/10.1093/europace/euw379
95. Stiles MK, Fauchier L, Morillo CA, Wilkoff BL. 2019 HRS/EHRA/APHRS/LAHRS focused update to 2015 expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. *J Interv Card Electrophysiol* 2020;**59**:135–144. https://doi.org/10.1007/s10840-019-00662-4
96. Freeman JV, Wang Y, Curtis JP, Heidenreich PA, Hlatky MA. Physician procedure volume and complications of cardioverter-defibrillator implantation. *Circulation* 2012;**125**:57–64. https://doi.org/10.1161/CIRCULATIONAHA.111.046995
97. Cojan-Minzat BO, Zlibut A, Muresan ID, Cionca C, Horvat D, Kiss E, *et al.* Left ventricular geometry and replacement fibrosis detected by cMRI are associated with major adverse cardiovascular events in nonischemic dilated cardiomyopathy. *J Clin Med* 2020;**9**:1997. https://doi.org/10.3390/jcm9061997

98. Masci PG, Doulaptsis C, Bertella E, Del Torto A, Symons R, Pontone G, *et al.* Incremental prognostic value of myocardial fibrosis in patients with non-ischemic cardiomyopathy without congestive heart failure. *Circ Heart Fail* 2014;**7**:448–456. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000996
99. Perazzolo Marra M, De Lazzari M, Zorzi A, Migliore F, Zilio F, Calore C, *et al.* Impact of the presence and amount of myocardial fibrosis by cardiac magnetic resonance on arrhythmic outcome and sudden cardiac death in nonischemic dilated cardiomyopathy. *Heart Rhythm* 2014;**11**:856–863. https://doi.org/10.1016/j.hrthm.2014.01.014
100. Wu KC, Weiss RG, Thiemann DR, Kitagawa K, Schmidt A, Dalal D, *et al.* Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. *J Am Coll Cardiol* 2008;**51**:2414–2421. https://doi.org/10.1016/j.jacc.2008.03.018
101. Gao P, Yee R, Gula L, Krahn AD, Skanes A, Leong-Sit P, *et al.* Prediction of arrhythmic events in ischemic and dilated cardiomyopathy patients referred for implantable cardiac defibrillator: Evaluation of multiple scar quantification measures for late gadolinium enhancement magnetic resonance imaging. *Circ Cardiovasc Imaging* 2012;**5**:448–456. https://doi.org/10.1161/CIRCIMAGING.111.971549
102. Di Marco A, Anguera I, Schmitt M, Klem I, Neilan TG, White JA, *et al.* Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: Systematic review and meta-analysis. *JACC Heart Fail* 2017;**5**:28–38. https://doi.org/10.1016/j.jchf.2016.09.017
103. Hammersley DJ, Zegard A, Androulakis E, Jones RE, Okafor O, Hatipoglu S, *et al.* Arrhythmic risk stratification by cardiovascular magnetic resonance imaging in patients with nonischemic cardiomyopathy. *J Am Coll Cardiol* 2024;**84**:1407–1420. https://doi.org/10.1016/j.jacc.2024.06.046
104. Gulati A, Japp AG, Raza S, Halliday BP, Jones DA, Newsome S, *et al.* Absence of myocardial fibrosis predicts favorable long-term survival in new-onset heart failure. *Circ Cardiovasc Imaging* 2018;**11**:e007722. https://doi.org/10.1161/CIRCIMAGING.118.007722
105. Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M, *et al.* Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol* 2006;**48**:1977–1985. https://doi.org/10.1016/j.jacc.2006.07.049
106. Mirelis JG, Escobar-Lopez L, Ochoa JP, Espinosa MA, Villacorta E, Navarro M, *et al.* Combination of late gadolinium enhancement and genotype improves prediction of prognosis in non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail* 2022;**24**:1183–1196. https://doi.org/10.1002/ejhf.2514
107. Scott PA, Barry J, Roberts PR, Morgan JM. Brain natriuretic peptide for the prediction of sudden cardiac death and ventricular arrhythmias: A meta-analysis. *Eur J Heart Fail* 2009;**11**:958–966. https://doi.org/10.1093/eurjhf/hfp123
108. Ahmad T, Fiuzat M, Neely B, Neely ML, Pencina MJ, Kraus WE, *et al.* Biomarkers of myocardial stress and fibrosis as predictors of mode of death in patients with chronic heart failure. *JACC Heart Fail* 2014;**2**:260–268. https://doi.org/10.1016/j.jchf.2013.12.004
109. Lupon J, Cediel G, Moliner P, de Antonio M, Domingo M, Zamora E, *et al.* A bio-clinical approach for prediction of sudden cardiac death in outpatients with heart failure: The ST2-SCD score. *Int J Cardiol* 2019;**293**:148–152. https://doi.org/10.1016/j.ijcard.2019.05.046
110. Skali H, Gerwien R, Meyer TE, Snider JV, Solomon SD, Stolen CM. Soluble ST2 and risk of arrhythmias, heart failure, or death in patients with mildly symptomatic heart failure: Results from MADIT-CRT. *J Cardiovasc Transl Res* 2016;**9**:421–428. https://doi.org/10.1007/s12265-016-9713-1
111. Medina A, Moss AJ, McNitt S, Zareba W, Wang PJ, Goldenberg I. Brain natriuretic peptide and the risk of ventricular tachyarrhythmias in mildly symptomatic heart failure patients enrolled in MADIT-CRT. *Heart Rhythm* 2016;**13**:852–859. https://doi.org/10.1016/j.hrthm.2015.12.024
112. Pascual-Figal DA, Ordonez-Llanos J, Tornel PL, Vazquez R, Puig T, Valdes M, *et al.* Soluble ST2 for predicting sudden cardiac death in patients with chronic heart failure and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2009;**54**:2174–2179. https://doi.org/10.1016/j.jacc.2009.07.041
113. Shadman R, Poole JE, Dardas TF, Mozaffarian D, Cleland JG, Swedberg K, *et al.* A novel method to predict the proportional risk of sudden cardiac death in heart failure: Derivation of the Seattle Proportional Risk Model. *Heart Rhythm* 2015;**12**:2069–2077. https://doi.org/10.1016/j.hrthm.2015.06.039
114. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, *et al.* The Seattle Heart Failure Model: Prediction of survival in heart failure. *Circulation* 2006;**113**:1424–1433. https://doi.org/10.1161/CIRCULATIONAHA.105.584102
115. Bilchick KC, Wang Y, Cheng A, Curtis JP, Dharmarajan K, Stukenborg GJ, *et al.* Seattle Heart Failure and Proportional Risk Models predict benefit from implantable cardioverter-defibrillators. *J Am Coll Cardiol* 2017;**69**:2606–2618. https://doi.org/10.1016/j.jacc.2017.03.568
116. Codina P, Zamora E, Levy WC, Cediel G, Santiago-Vacas E, Domingo M, *et al.* Sudden cardiac death in heart failure: A 20-year perspective from a Mediterranean cohort. *J Card Fail* 2023;**29**:236–245. https://doi.org/10.1016/j.cardfail.2022.11.016
117. Younis A, Goldberger JJ, Kutyifa V, Zareba W, Polonsky B, Klein H, *et al.* Predicted benefit of an implantable cardioverter-defibrillator: The MADIT-ICD benefit score. *Eur Heart J* 2021;**42**:1676–1684. https://doi.org/10.1093/eurheartj/ehaa1057
118. Pontone G, Guaricci AI, Fusini L, Baggiano A, Guglielmo M, Muscogiuri G, *et al.* Cardiac magnetic resonance for prophylactic implantable-cardioverter defibrillator therapy in ischemic cardiomyopathy: The DERIVATE-ICM international registry. *JACC Cardiovasc Imaging* 2023;**16**:1387–1400. https://doi.org/10.1016/j.jcmg.2023.03.015
119. Marume K, Noguchi T, Tateishi E, Morita Y, Kamakura T, Ishibashi K, *et al.* Mortality and sudden cardiac death risk stratification using the noninvasive combination of wide QRS duration and late gadolinium enhancement in idiopathic dilated cardiomyopathy. *Circ Arrhythm Electrophysiol* 2018;**11**:e006233. https://doi.org/10.1161/CIRCEP.117.006233
120. Li X, Fan X, Li S, Sun W, Shivkumar K, Zhao S, *et al.* A novel risk stratification score for sudden cardiac death prediction in middle-aged, nonischemic dilated cardiomyopathy patients: The ESTIMATED score. *Can J Cardiol* 2020;**36**:1121–1129. https://doi.org/10.1016/j.cjca.2019.11.009
121. Peek N, Hindricks G, Akbarov A, Tijssen JGP, Jenkins DA, Kapacee Z, *et al.* Sudden cardiac death after myocardial infarction: Individual participant data from pooled cohorts. *Eur Heart J* 2024;**45**:4616–4626. https://doi.org/10.1093/eurheartj/ehae326
122. Kolk MZH, Ruiperez-Campillo S, Wilde AAM, Knops RE, Narayan SM, Tjong FVY. Prediction of sudden cardiac death using artificial intelligence: Current status and future directions. *Heart Rhythm* 2025;**22**:756–766. https://doi.org/10.1016/j.hrthm.2024.09.003
123. Chrispin J, Merchant FM, Lakdawala NK, Wu KC, Tomaselli GF, Navara R, *et al.* Risk of arrhythmic death in patients with nonischemic cardiomyopathy. *J Am Coll Cardiol* 2023;**82**:735–747. https://doi.org/10.1016/j.jacc.2023.05.064
124. Kolk MZH, Ruiperez-Campillo S, Deb B, Bekkers EJ, Allaart CP, Rogers AJ, *et al.* Optimizing patient selection for primary prevention implantable cardioverter-defibrillator implantation: Utilizing multimodal machine learning to assess risk of implantable cardioverter-defibrillator non-benefit. *Europace* 2023;**25**:euad271. https://doi.org/10.1093/europace/euad271
125. Felker GM, Butler J, Ibrahim NE, Pina IL, Maisel A, Bapat D, *et al.*; PROVE-HF Investigators. Implantable cardioverter-defibrillator eligibility after initiation of sacubitril/valsartan in chronic heart failure: Insights from PROVE-HF. *Circulation* 2021;**144**:180–182. https://doi.org/10.1161/CIRCULATIONAHA.121.054034
126. Veltmann C, Duncker D, Doering M, Gummadi S, Robertson M, Wittlinger T, *et al.* Therapy duration and improvement of ventricular function in de novo heart failure: The Heart Failure Optimization study. *Eur Heart J* 2024;**45**:2771–2781. https://doi.org/10.1093/eurheartj/ehae334
127. Mullens W, Auricchio A, Martens P, Witte K, Cowie MR, Delgado V, *et al.* Optimized implementation of cardiac resynchronization therapy: A call for action for referral and optimization of care: A joint position statement from the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:2349–2369. https://doi.org/10.1002/ejhf.2046
128. Hayashi H, Yasuda S, Nakano M, Sakata Y, Nochioka K, Shiroto T, *et al.* Utilization and efficacy of cardiac resynchronization therapy in patients with chronic heart failure – A report from the CHART-2 study. *Circ Rep* 2022;**4**:264–273. https://doi.org/10.1253/circrep.CR-22-0036
129. Patwala A, Barker D, Da Costa A, Bayard G, Brunner-La Rocca HP, Fontes-Carvalho R, *et al.* Optimizing heart failure pathways to enhance patient care: The Program to Optimize Heart Failure Patient Pathways (PRO-HF). *ESC Heart Fail* 2024;**11**:2578–2590. https://doi.org/10.1002/ehf2.14911
130. Yancy CW, Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, *et al.* Influence of patient age and sex on delivery of guideline-recommended heart failure care in the outpatient cardiology practice setting: Findings from IMPROVE HF. *Am Heart J* 2009;**157**:754–762. https://doi.org/10.1016/j.ahj.2008.12.016
131. De Silva K, Nassar N, Badgery-Parker T, Kumar S, Taylor L, Kovoor P, *et al.* Sex-based differences in selected cardiac implantable electronic device use: A 10-year statewide patient cohort. *J Am Heart Assoc* 2022;**11**:e025428. https://doi.org/10.1161/JAHA.121.025428
132. Jaffe LM, Morin DP. Cardiac resynchronization therapy: History, present status, and future directions. *Ochsner J* 2014;**14**:596–607.
133. Packer M. Electrophysiological interventions in the treatment of chronic heart failure: A comparison of the strength of evidence supporting cardiac resynchronization for electrical conduction delay and catheter ablation for atrial fibrillation. *Eur J Heart Fail* 2019;**21**:398–401. https://doi.org/10.1002/ejhf.1447

134. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, *et al.*; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150. https://doi.org/10.1056/NEJMoa032423
135. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, *et al.*; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549. https://doi.org/10.1056/NEJMoa050496
136. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, *et al.*; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–1338. https://doi.org/10.1056/NEJMoa0906431
137. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, *et al.*; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–2395. https://doi.org/10.1056/NEJMoa1009540
138. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, *et al.*; EchoCRT Study Group. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013;**369**:1395–1405. https://doi.org/10.1056/NEJMoa1306687
139. Sapp JL, Sivakumaran S, Redpath CJ, Khan H, Parkash R, Exner DV, *et al.*; RAFT Long-Term Study Team. Long-term outcomes of resynchronization-defibrillation for heart failure. *N Engl J Med* 2024;**390**:212–220. https://doi.org/10.1056/NEJMoa2304542
140. Friedman DJ, Al-Khatib SM, Dalgaard F, Fudim M, Abraham WT, Cleland JGF, *et al.* Cardiac resynchronization therapy improves outcomes in patients with intraventricular conduction delay but not right bundle branch block: A patient-level meta-analysis of randomized controlled trials. *Circulation* 2023;**147**:812–823. https://doi.org/10.1161/CIRCULATIONAHA.122.062124
141. Wilkoff BL, Filippatos G, Leclercq C, Gold MR, Hersi AS, Kusano K, *et al.*; AdaptResponse Investigators. Adaptive versus conventional cardiac resynchronisation therapy in patients with heart failure (AdaptResponse): A global, prospective, randomised controlled trial. *Lancet* 2023;**402**:1147–1157. https://doi.org/10.1016/S0140-6736(23)00912-1
142. Sudesh S, Abraham WT, Cleland JGF, Curtis AB, Friedman D, Gold MR, *et al.* Cardiac resynchronization therapy in ischemic versus nonischemic cardiomyopathy: Patient-level meta-analysis of 7 randomized clinical trials. *JACC Heart Fail* 2024;**12**:1915–1924. https://doi.org/10.1016/j.jchf.2024.08.010
143. Zeitler EP, Friedman DJ, Daubert JP, Al-Khatib SM, Solomon SD, Biton Y, *et al.* Multiple comorbidities and response to cardiac resynchronization therapy: MADIT-CRT long-term follow-up. *J Am Coll Cardiol* 2017;**69**:2369–2379. https://doi.org/10.1016/j.jacc.2017.03.531
144. Chyou JY, Qin H, Butler J, Voors AA, Lam CSP. Sex-related similarities and differences in responses to heart failure therapies. *Nat Rev Cardiol* 2024;**21**:498–516. https://doi.org/10.1038/s41569-024-00996-1
145. Zusterzeel R, Selzman KA, Sanders WE, Canos DA, O'Callaghan KM, Carpenter JL, *et al.* Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. *JAMA Intern Med* 2014;**174**:1340–1348. https://doi.org/10.1001/jamainternmed.2014.2717
146. Friedman DJ, Olivas-Martinez A, Dalgaard F, Fudim M, Abraham WT, Cleland JGF, *et al.* Relationship between sex, body size, and cardiac resynchronization therapy benefit: A patient-level meta-analysis of randomized controlled trials. *Heart Rhythm* 2024;**21**:845–854. https://doi.org/10.1016/j.hrthm.2024.01.058
147. Herweg B, Welter-Frost A, Vijayaraman P. The evolution of cardiac resynchronization therapy and an introduction to conduction system pacing: A conceptual review. *Europace* 2021;**23**:496–510. https://doi.org/10.1093/europace/euaa264
148. Derndorfer M, Kollias G, Martinek M, Pürerfellner H. Is conduction system pacing going to be the new gold standard for cardiac resynchronization therapy? *J Clin Med* 2024;**13**:4320. https://doi.org/10.3390/jcm13154320
149. König S, Hilbert S, Bode K. Conduction system pacing: Hope, challenges, and the journey forward. *Curr Cardiol Rep* 2024;**26**:801–814. https://doi.org/10.1007/s11886-024-02085-8
150. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, *et al.* 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021;**42**:3427–3520. https://doi.org/10.1093/eurheartj/ehab364
151. Daubert JC, Saxon L, Adamson PB, Auricchio A, Berger RD, Beshai JF, *et al.* 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: Implant and follow-up recommendations and management. *Heart Rhythm* 2012;**9**:1524–1576. https://doi.org/10.1016/j.hrthm.2012.07.025
152. Gold MR, Rickard J, Daubert JC, Zimmerman P, Linde C. Redefining the classifications of response to cardiac resynchronization therapy: Results from the REVERSE study. *JACC Clin Electrophysiol* 2021;**7**:871–880. https://doi.org/10.1016/j.jacep.2020.11.010
153. Chung ES, Gold MR, Abraham WT, Young JB, Linde C, Anderson C, *et al.* The importance of early evaluation after cardiac resynchronization therapy to redefine response: Pooled individual patient analysis from 5 prospective studies. *Heart Rhythm* 2022;**19**:595–603. https://doi.org/10.1016/j.hrthm.2021.11.030
154. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: A practical guide. *Eur Heart J* 2017;**38**:1463–1472. https://doi.org/10.1093/eurheartj/ehw270
155. Thibault B, Ducharme A, Harel F, White M, O'Meara E, Guertin MC, *et al.*; Evaluation of Resynchronization Therapy for Heart Failure (GREATER-EARTH) Investigators. Left ventricular versus simultaneous biventricular pacing in patients with heart failure and a QRS complex ≥120 milliseconds. *Circulation* 2011;**124**:2874–2881. https://doi.org/10.1161/CIRCULATIONAHA.111.032904
156. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C; REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;**52**:1834–1843. https://doi.org/10.1016/j.jacc.2008.08.027
157. Gold MR, Rickard J, Daubert JC, Cerkvenik J, Linde C. Association of left ventricular remodeling with cardiac resynchronization therapy outcomes. *Heart Rhythm* 2023;**20**:173–180. https://doi.org/10.1016/j.hrthm.2022.11.016
158. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, *et al.* Results of the predictors of response to CRT (PROSPECT) trial. *Circulation* 2008;**117**:2608–2616. https://doi.org/10.1161/CIRCULATIONAHA.107.743120
159. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail* 2001;**7**:176–182. https://doi.org/10.1054/jcaf.2001.25652
160. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, *et al.*; IN-TIME Study Group. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): A randomised controlled trial. *Lancet* 2014;**384**:583–590. https://doi.org/10.1016/S0140-6736(14)61176-4
161. Varma N, Boehmer J, Bhargava K, Yoo D, Leonelli F, Costanzo M, *et al.* Evaluation, management, and outcomes of patients poorly responsive to cardiac resynchronization device therapy. *J Am Coll Cardiol* 2019;**74**:2588–2603. https://doi.org/10.1016/j.jacc.2019.09.043
162. Bao J, Kan R, Chen J, Xuan H, Wang C, Li D, *et al.* Combination pharmacotherapies for cardiac reverse remodeling in heart failure patients with reduced ejection fraction: A systematic review and network meta-analysis of randomized clinical trials. *Pharmacol Res* 2021;**169**:105573. https://doi.org/10.1016/j.phrs.2021.105573
163. Dhingra NK, Mistry N, Puar P, Verma R, Anker S, Mazer CD, *et al.* SGLT2 inhibitors and cardiac remodelling: A systematic review and meta-analysis of randomized cardiac magnetic resonance imaging trials. *ESC Heart Fail* 2021;**8**:4693–4700. https://doi.org/10.1002/ehf2.13645
164. Januzzi JL Jr, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, *et al.*; PROVE-HF Investigators. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA* 2019;**322**:1085–1095. https://doi.org/10.1001/jama.2019.12821
165. Sze E, Samad Z, Dunning A, Campbell KB, Loring Z, Atwater BD, *et al.* Impaired recovery of left ventricular function in patients with cardiomyopathy and left bundle branch block. *J Am Coll Cardiol* 2018;**71**:306–317. https://doi.org/10.1016/j.jacc.2017.11.020
166. Huang HT, Huang JL, Lin PL, Lee YH, Hsu CY, Chung FP, *et al.* Clinical impacts of sacubitril/valsartan on patients eligible for cardiac resynchronization therapy. *ESC Heart Fail* 2022;**9**:3825–3835. https://doi.org/10.1002/ehf2.14107
167. Leyva F, Zegard A, Patel P, Stegemann B, Marshall H, Ludman P, *et al.* Timing of cardiac resynchronization therapy implantation. *Europace* 2023;**25**:euad059. https://doi.org/10.1093/europace/euad059
168. Wang NC, Li JZ, Adelstein EC, Althouse AD, Sharbaugh MS, Jain SK, *et al.* New-onset left bundle branch block-associated idiopathic nonischemic cardiomyopathy and time from diagnosis to cardiac resynchronization therapy: The NEOLITH II study. *Pacing Clin Electrophysiol* 2018;**41**:143–154. https://doi.org/10.1111/pace.13264
169. Linde C. CRT-P or CRT-D in heart failure patients: The RESET-CRT project – a prelude to the randomized controlled RESET-CRT study. *Eur Heart J* 2022;**43**:2600–2602. https://doi.org/10.1093/eurheartj/ehac136
170. Goldenberg I, Aktas MK, Zareba W, Tsu-Chau Huang D, Rosero SZ, Younis A, *et al.* QRS morphology and the risk of ventricular tachyarrhythmia in cardiac resynchronization therapy recipients. *JACC Clin Electrophysiol* 2024;**10**:16–26. https://doi.org/10.1016/j.jacep.2023.09.018
171. Woods B, Hawkins N, Mealing S, Sutton A, Abraham WT, Beshai JF, *et al.* Individual patient data network meta-analysis of mortality effects of implantable

cardiac devices. *Heart* 2015;**101**:1800–1806. https://doi.org/10.1136/heartjnl-2015-307634
172. Barra S, Providencia R, Boveda S, Duehmke R, Narayanan K, Chow AW, *et al.* Device complications with addition of defibrillation to cardiac resynchronisation therapy for primary prevention. *Heart* 2018;**104**:1529–1535. https://doi.org/10.1136/heartjnl-2017-312546
173. Doran B, Mei C, Varosy PD, Kao DP, Saxon LA, Feldman AM, *et al.* The addition of a defibrillator to resynchronization therapy decreases mortality in patients with nonischemic cardiomyopathy. *JACC Heart Fail* 2021;**9**:439–449. https://doi.org/10.1016/j.jchf.2021.02.013
174. Chatterjee NA, Poole JE. Cardiac resynchronization therapy in nonischemic cardiomyopathy: To D or P? *JACC Heart Fail* 2021;**9**:450–452. https://doi.org/10.1016/j.jchf.2021.04.001
175. Kutyifa V, Geller L, Bogyi P, Zima E, Aktas MK, Ozcan EE, *et al.* Effect of cardiac resynchronization therapy with implantable cardioverter defibrillator versus cardiac resynchronization therapy with pacemaker on mortality in heart failure patients: Results of a high-volume, single-centre experience. *Eur J Heart Fail* 2014;**16**:1323–1330. https://doi.org/10.1002/ejhf.185
176. Saba S, McLaughlin T, He M, Althouse A, Mulukutla S, Hernandez I. Cardiac resynchronization therapy using pacemakers vs defibrillators in patients with nonischemic cardiomyopathy: The United States experience from 2007 to 2014. *Heart Rhythm* 2019;**16**:1065–1071. https://doi.org/10.1016/j.hrthm.2019.04.028
177. Schrage B, Lund LH, Melin M, Benson L, Uijl A, Dahlstrom U, *et al.* Cardiac resynchronization therapy with or without defibrillator in patients with heart failure. *Europace* 2022;**24**:48–57. https://doi.org/10.1093/europace/euab233
178. Hadwiger M, Dagres N, Haug J, Wolf M, Marschall U, Tijssen J, *et al.* Survival of patients undergoing cardiac resynchronization therapy with or without defibrillator: The RESET-CRT project. *Eur Heart J* 2022;**43**:2591–2599. https://doi.org/10.1093/eurheartj/ehac053
179. Jankowska EA, Liu PP, Cowie MR, Groenhart M, Cobey KD, Howlett J, *et al.* Personalized care of patients with heart failure: Are we ready for a REVOLUTION? Insights from two international surveys on healthcare professionals' needs and patients' perceptions. *Eur J Heart Fail* 2023;**25**:364–372. https://doi.org/10.1002/ejhf.2798
180. Halin A, Hamelin JL, Defaye P, Deharo JC, Fauchier L, Marijon E, *et al.* Information provision and follow-up of French patients with implantable cardioverter-defibrillators: The APODEC survey. *Arch Cardiovasc Dis* 2023;**116**:572–579. https://doi.org/10.1016/j.acvd.2023.10.005
181. Thylen I, Moser DK, Stromberg A, Dekker RA, Chung ML. Concerns about implantable cardioverter-defibrillator shocks mediate the relationship between actual shocks and psychological distress. *Europace* 2016;**18**:828–835. https://doi.org/10.1093/europace/euv220
182. Januszkiewicz L, Barra S, Providencia R, Conte G, de Asmundis C, Chun JKR, *et al.* Long-term quality of life and acceptance of implantable cardioverter-defibrillator therapy: Results of the European Heart Rhythm Association survey. *Europace* 2022;**24**:860–867. https://doi.org/10.1093/europace/euac011
183. Perpetua EM, Palmer R, Le VT, Al-Khatib SM, Beavers CJ, Beckman JA, *et al.* JACC: Advances expert panel perspective: Shared decision-making in multidisciplinary team-based cardiovascular care. *JACC Adv* 2024;**3**:100981. https://doi.org/10.1016/j.jacadv.2024.100981
184. Dennison Himmelfarb CR, Beckie TM, Allen LA, Commodore-Mensah Y, Davidson PM, Lin G, *et al.* Shared decision-making and cardiovascular health: A scientific statement from the American Heart Association. *Circulation* 2023;**148**:912–931. https://doi.org/10.1161/CIR.0000000000001162
185. Ozdemir S, Teo I, Bundoc FG, Malhotra C, Yeo KK, David Sim KL, *et al.* Role in decision making among congestive heart failure patients and its association with patient outcomes: A baseline analysis of the SCOPAH study. *Patient Educ Couns* 2021;**104**:496–504. https://doi.org/10.1016/j.pec.2020.08.033
186. Hill LM, McIlfatrick S, Taylor B, Dixon L, Fitzsimons D. Implantable cardioverter defibrillator (ICD) functionality: Patient and family information for advanced decision-making. *BMJ Support Palliat Care* 2022;**12**:e219–e225. https://doi.org/10.1136/bmjspcare-2019-001835