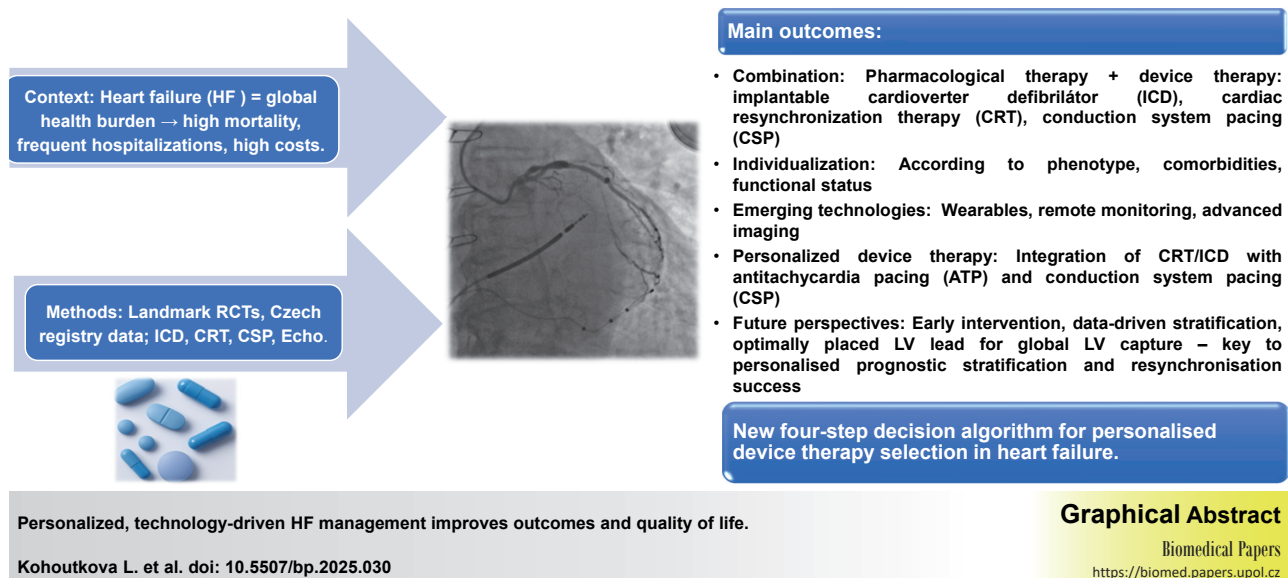


# Personalised treatment strategies in heart failure: A literature review and new proposed algorithm for device therapy selection

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Heart failure remains a major global health challenge, characterized by high morbidity, mortality, and economic burden despite continuous advances in therapy. This review summarizes landmark clinical trials that have shaped current approaches to device therapy in heart failure, including implantable cardioverter-defibrillators, cardiac resynchronization therapy, and emerging conduction system pacing. In addition, it discusses novel prognostic and monitoring methods such as impedance cardiography and dobutamine stress echocardiography, which enable more precise patient assessment. Based on the available clinical data, we propose a new four-step decision algorithm for personalised device therapy selection in heart failure, integrating etiology-specific risk stratification, electrical and functional evaluation, and prognostic modifiers. The integration of evidence-based interventions and phenotype-driven decision-making supports a proactive and individualized approach to improving outcomes and quality of life in patients with heart failure.

## PERSONALISED TREATMENT STRATEGIES IN HEART FAILURE: A LITERATURE REVIEW AND NEW PROPOSED ALGORITHM FOR DEVICE THERAPY SELECTION



**Key words:** heart failure, implantable cardioverter-defibrillator, cardiac resynchronization therapy, conduction system pacing, impedance cardiography, prognosis, personalised medicine

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## INTRODUCTION

Heart failure is among the most prevalent chronic diseases of the 21st century. Its incidence continues to rise despite major advancements in both pharmacological and non-pharmacological therapies. The disease remains as-

sociated with high morbidity, frequent hospitalizations, and unsatisfactory prognosis. In developed European countries, heart failure accounts for approximately 1–2% of total healthcare expenditure, with a prevalence of 1–2% in the adult population and up to 10% among individuals older than 70 years (ESC 2021, 2023 update<sup>1</sup>).

In compensated heart failure, symptoms may temporarily improve due to compensatory mechanisms or therapy. Improvements in cardiac function, including an increase in left ventricular ejection fraction (LVEF) and reductions in ventricular dimensions, may be achieved with effective therapy.

According to the current guidelines from the European Heart Rhythm Association (EHRA), heart failure is classified based on LVEF as follows:

- **HFrEF** (Heart Failure with Reduced Ejection Fraction): LVEF  $\leq$  40%
- **HFmrEF** (Heart Failure with Mildly Reduced Ejection Fraction): LVEF 41–49%
- **HFpEF** (Heart Failure with Preserved Ejection Fraction): LVEF  $\geq$  50%

Due to the high prevalence of HF and its heterogeneous presentation, there is an urgent need for reliable methods of prognostic stratification to optimize management and improve long-term outcomes.

## MATERIALS AND METHODS

This narrative review was conducted through a structured search and critical appraisal of landmark randomized controlled trials and observational studies addressing device-based therapies and prognostic methods in heart failure.

Studies were selected for inclusion if they met the following criteria:

- randomized controlled design or large prospective observational registry,
- patient population with symptomatic or asymptomatic left ventricular dysfunction,
- endpoints related to mortality, hospitalization, left ventricular remodeling, or quality of life.

Priority was given to trials with high methodological rigor and substantial clinical impact, such as MADIT II, COMPANION, MIRACLE, and DANISH. In addition, Czech national registry data and institutional studies (e.g., IKEM cohort) were reviewed to provide real-world context.

The following sections summarize key trials, including study design, patient characteristics, methodology, main findings, and clinical significance.

### MADIT II Study

#### Design and Objectives

The MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) was a randomized, multicenter, controlled study aimed at evaluating the effect of implantable cardioverter-defibrillators (ICDs) on overall survival in patients with ischemic heart disease, left ventricular dysfunction (ejection fraction  $\leq$  30%), and no prior history of malignant ventricular arrhythmias<sup>2</sup>.

### Patient Population and Methodology

A total of 1,232 patients were randomized into two groups:

- **ICD Group:** Received an implantable cardioverter-defibrillator.
- **Control Group:** Received standard pharmacological treatment for heart failure and ischemic heart disease without ICD implantation.

### Key Findings

- **Mortality:** ICDs reduced all-cause mortality by 31%.
- **Sudden Cardiac Death:** ICDs significantly reduced the incidence of sudden cardiac death.
- **Hospitalizations:** Fewer heart failure-related hospitalizations occurred in the ICD group.
- **Quality of Life:** No significant improvement in quality of life was observed in ICD recipients.

### Clinical Significance

The results established ICD therapy as a cornerstone for primary prevention of sudden cardiac death in this high-risk population. The results of MADIT II firmly established ICD therapy as the standard of care for primary prevention in ischemic cardiomyopathy and it has since been incorporated into all major guidelines.

### DANISH Study

#### Study Design and Objectives

The DANISH (Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality) trial was a multicenter, randomized, controlled clinical study designed to evaluate whether ICD implantation improves survival in patients with non-ischemic heart failure and reduced ejection fraction (LVEF  $\leq$  35% (ref.<sup>3</sup>).

### Patient Population and Methodology

A total of 1,116 patients with symptomatic, non-ischemic systolic heart failure were randomized into two groups:

- **ICD Group:** Received an implantable cardioverter-defibrillator.
- **Control Group:** Received standard heart failure therapy without ICD implantation.

### Key Findings

- **Sudden Cardiac Death:** ICD therapy significantly reduced the incidence of sudden cardiac death.
- **Overall Mortality:** No statistically significant reduction in all-cause mortality was observed in the ICD group compared to the control group.
- **Risk Stratification:** Subgroup analysis using the Seattle Proportional Risk Model (SPRM) revealed that patients at higher risk of sudden cardiac death derived greater benefit from ICD therapy.

### Clinical Significance

The DANISH study highlighted the importance of individualized risk stratification when considering ICD

implantation in patients with non-ischemic heart failure. While ICDs effectively prevent sudden cardiac death, their impact on overall survival in this population is uncertain, underscoring the need for refined patient selection strategies. The neutral findings of the DANISH trial have sparked considerable debate and are frequently cited in contemporary guidelines as a rationale for more careful patient selection in non-ischemic heart failure.

## COMPANION Study

### Study Design and Objectives

The COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) study was a prospective, randomized, multicenter clinical trial evaluating the impact of cardiac resynchronization therapy (CRT) with or without an implantable cardioverter-defibrillator (ICD) on survival and hospitalization in patients with advanced heart failure<sup>4</sup>.

### Patient Population and Methodology

A total of 1,520 patients with NYHA class III-IV symptoms, LVEF < 35%, QRS duration > 120 ms, and prolonged PR interval were randomized into three groups:

- **Pharmacological Therapy Alone:** Standard heart failure medical management.
- **CRT Alone:** Received CRT-P (without defibrillator capabilities).
- **CRT + ICD Group:** Received CRT-D (with defibrillator capabilities).

### Key Findings

- **Survival:** CRT-D significantly reduced all-cause mortality compared to medical therapy alone. CRT-P alone also improved survival, although to a lesser extent.
- **Hospitalizations:** Both CRT groups experienced fewer heart failure-related hospitalizations compared to medical therapy alone.
- **Quality of Life:** Notable improvements in functional capacity and patient-reported quality of life were observed, especially in the CRT-D groups.
- **Sudden Cardiac Death:** The CRT-D group had a significantly lower incidence of sudden cardiac death.

### Clinical Significance

The COMPANION study demonstrated that CRT, particularly when combined with ICD therapy, enhances survival, reduces hospitalizations, and improves quality of life in patients with advanced systolic heart failure and electrical dyssynchrony. The COMPANION trial paved the way for widespread adoption of CRT-D, demonstrating the additive benefits of combining resynchronization with defibrillation and shaping international guideline recommendations.

## MIRACLE Study

### Study Design and Objectives

The MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study was a prospective, randomized, controlled trial designed to assess the effects of cardiac resynchronization therapy (CRT) on symptoms, exercise

capacity, and quality of life in patients with symptomatic heart failure and electrical dyssynchrony<sup>5</sup>.

### Patient Population and Methodology

Participants included patients with NYHA class III-IV heart failure, LVEF ≤ 35%, and QRS duration ≥ 130 ms. Subjects were randomized into:

- **CRT Group:** Received biventricular pacing via a CRT device.
- **Control Group:** Received standard pharmacological treatment without device implantation.

### Key Findings

- **Functional Improvement:** The CRT group showed significant improvements in NYHA class and a 30% increase in 6-minute walk distance.
- **Hospitalizations:** Fewer hospital admissions for worsening heart failure were noted in the CRT group.
- **Quality of Life:** Patients receiving CRT reported improved quality of life scores and overall well-being.
- **Cardiac Function:** CRT led to an increase in LVEF and evidence of reverse ventricular remodeling.

### Clinical Significance

The MIRACLE study was pivotal in establishing CRT as a therapeutic option for patients with symptomatic systolic heart failure and ventricular dyssynchrony. The improvements in exercise tolerance, quality of life, and cardiac function laid the groundwork for expanded indications and future trials examining survival outcomes. These findings supported the expansion of CRT indications and highlighted symptomatic and functional improvements as clinically meaningful endpoints, later confirmed by subsequent trials.

## MIRACLE ICD Study

### Study Design and Objectives

The MIRACLE ICD (Multicenter InSync Randomized Clinical Evaluation ICD) study was a randomized, controlled, multicenter trial designed to evaluate the additive effect of implantable cardioverter-defibrillator (ICD) therapy in patients receiving cardiac resynchronization therapy (CRT) for advanced heart failure with intraventricular conduction delay<sup>6</sup>.

### Patient Population and Methodology

Patients with NYHA class III-IV heart failure, left ventricular ejection fraction ≤ 35%, and QRS duration ≥ 130 ms were randomized into two groups:

- **CRT + ICD Group:** Received biventricular pacing with ICD capability (CRT-D).
- **Pharmacological Therapy Group:** Received standard medical treatment for heart failure without device implantation.

### Key Findings

- **Mortality and Hospitalization:** The CRT + ICD group showed a significant reduction in the combined endpoint of all-cause mortality and heart failure hospitalizations.

- **Symptom Relief and Exercise Capacity:** Patients receiving CRT + ICD experienced marked improvements in NYHA functional class and 6-min walk distance (6MWT).
- **Quality of Life:** Significant enhancements in physical and emotional well-being were observed in the device group.
- **Left Ventricular Function:** CRT-D therapy improved left ventricular ejection fraction and promoted reverse remodeling.

### Clinical Significance

The MIRACLE ICD study confirmed the dual benefit of CRT and ICD in patients with symptomatic systolic heart failure and ventricular dyssynchrony. The addition of ICD functionality to CRT not only reduces sudden cardiac death risk but also enhances functional outcomes and quality of life, supporting the adoption of CRT-D as standard therapy in appropriately selected patients.

### DEFINITE Study

#### Study Design and Objectives

The DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) study was a randomized, controlled, multicenter trial aimed at evaluating whether ICD therapy reduces mortality in patients with non-ischemic dilated cardiomyopathy (NIDCM) and left ventricular ejection fraction  $\leq 35\%$  without a prior history of malignant ventricular arrhythmias<sup>7</sup>.

#### Patient Population and Methodology

A total of 458 patients with NIDCM and reduced LVEF were enrolled and randomized into two groups:

- **ICD Group:** Received standard heart failure medical therapy plus an ICD.
- **Control Group:** Received standard heart failure medical therapy alone.

#### Key Findings

- **Mortality:** A non-significant trend toward reduced all-cause mortality was observed in the ICD group; however, there was a significant reduction in sudden cardiac death.
- **Hospitalizations:** Fewer heart failure hospitalizations occurred in the ICD group, although not statistically significant.
- **Quality of Life:** ICD recipients showed modest improvements in functional status and symptom burden.

### Clinical Significance

The DEFINITE study supported the role of ICDs for the primary prevention of sudden cardiac death in patients with non-ischemic cardiomyopathy. While the reduction in all-cause mortality did not reach statistical significance, the benefit in preventing sudden death contributed to subsequent guideline recommendations endorsing ICD use in this population.

### REVERSE Study

#### Study Design and Objectives

The REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) study was a randomized, controlled trial aimed at evaluating the impact of CRT on asymptomatic or mildly symptomatic heart failure patients with preserved or mildly reduced ejection fraction<sup>8</sup>.

#### Patient Population and Methodology

Patients with NYHA class I-II heart failure, LVEF  $\leq 40\%$ , and QRS duration  $\geq 120$  ms were randomized into:

- **CRT Group:** Received CRT device implantation.
- **Control Group:** Received optimal pharmacologic therapy alone.

#### Key Findings

- **Ventricular Remodeling:** CRT significantly improved left ventricular volumes and systolic function.
- **Clinical Status:** Trends toward improvement in clinical composite scores and delayed disease progression.
- **Exercise Capacity and Symptoms:** Modest improvements in 6-min walk test and patient-reported symptoms.

### Clinical Significance

The REVERSE study extended the potential utility of CRT to earlier stages of heart failure. Although mortality benefit was not the primary endpoint, the results demonstrated that CRT favorably affects cardiac remodeling and may delay clinical deterioration in patients with milder symptoms. The REVERSE trial influenced the extension of CRT indications toward earlier stages of heart failure and is often referenced in guideline discussions on treating mildly symptomatic patients.

### AVID Study

The AVID (Antiarrhythmics Versus Implantable Defibrillators) study was a prospective, multicenter, randomized controlled trial designed to compare the efficacy of implantable cardioverter-defibrillators (ICDs) versus antiarrhythmic drug therapy in preventing sudden cardiac death in patients with malignant ventricular arrhythmias, such as hemodynamically significant ventricular tachycardia or ventricular fibrillation<sup>9</sup>.

A total of 1,016 patients were enrolled and randomly assigned to:

- **ICD Group:** Received an implantable cardioverter-defibrillator.
- **Antiarrhythmic Group:** Received antiarrhythmic medications, primarily amiodarone.

The study was prematurely terminated after showing a 38% reduction in mortality at one year and a 31% reduction at three years in the ICD group.

#### Key Findings:

- **Survival:** The ICD group had a 27% lower risk of overall mortality compared to the antiarrhythmic group.

- **Sudden Cardiac Death:** ICDs significantly reduced the risk of sudden cardiac death.
- **Recurrence of Arrhythmias:** Fewer recurrences were seen in the ICD group.
- **Quality of Life:** Some improvement was noted, though not a primary endpoint.
- **Complications:** ICD-related issues (e.g., infection, dislodgement) occurred but were outweighed by the survival benefit.

### PainFREE Rx II Study

#### Study Design and Objectives

The PainFREE Rx II trial was a multicenter, randomized study comparing the efficacy and safety of antitachycardia pacing (ATP) versus shock therapy in patients with implantable cardioverter-defibrillators (ICDs) experiencing ventricular tachycardia<sup>10</sup>.

#### Patient Population and Methodology

634 patients with ICDs and spontaneous ventricular tachycardia (188–250 bpm) were randomized into:

- **ATP Group:** Received empiric antitachycardia pacing.
- **Shock Group:** Received immediate shock therapy.

#### Key Findings

- **Efficacy:** ATP successfully terminated 81% of arrhythmias.
- **Shock Reduction:** ATP reduced the number of shocks by 70%.
- **Safety and Outcomes:** No difference in syncope or sudden death between groups.

#### Clinical Significance

PainFREE Rx II demonstrated that ATP is a safe and effective alternative to shocks in ICD patients, significantly enhancing patient comfort and reducing the burden of shock-related anxiety without compromising clinical safety.

### IKEM Study

#### Study Design and Objectives

The IKEM (Institute for Clinical and Experimental Medicine) study was designed as a prospective, observational analysis aimed at assessing the prognostic value of contractile reserve in patients with ischemic heart disease (IHD). Specifically, the study investigated whether dynamic changes in left ventricular (LV) volumes and ejection fraction (LVEF) during low-dose dobutamine stress echocardiography (DSE) could serve as early predictors of heart failure progression and adverse remodeling<sup>11</sup>.

This concept builds on the landmark work of Kitaoka et al., who demonstrated that low-dose dobutamine echocardiography reliably predicts the recovery of LV systolic function in patients with dilated cardiomyopathy<sup>12</sup>. By applying this methodology in a cohort with ischemic etiology, the IKEM study sought to determine whether similar predictive principles hold true in structurally different myocardial substrates, thus extending the applicability of DSE from non-ischemic to ischemic populations.

### Patient Population and Methodology

A total of approximately 66 patients with chronic heart failure, the majority with ischemic etiology, were prospectively enrolled. All participants underwent low-dose dobutamine stress echocardiography at infusion rates of 5 and 10 µg/kg/min. Echocardiographic assessment included measurements of left ventricular end-diastolic volume (EDV), end-systolic volume (ESV), and left ventricular ejection fraction (LVEF). Standardized imaging protocols and blinded offline analysis were applied to ensure reproducibility and minimize observer bias.

#### Key Findings

- **Contractile Reserve:** A significant increase in LVEF accompanied by a reduction in ESV during low-dose stress identified patients with preserved contractile reserve and predicted subsequent reverse remodeling.
- **Prognostic Value in IHD:** These predictive responses were most pronounced in patients with ischemic heart disease, suggesting that functional reserve assessment is particularly relevant in this subgroup.
- **Risk Stratification:** Patients without demonstrable contractile reserve exhibited progressive ventricular dilation and poorer long-term outcomes, underscoring the adverse prognostic implications of absent dobutamine response.

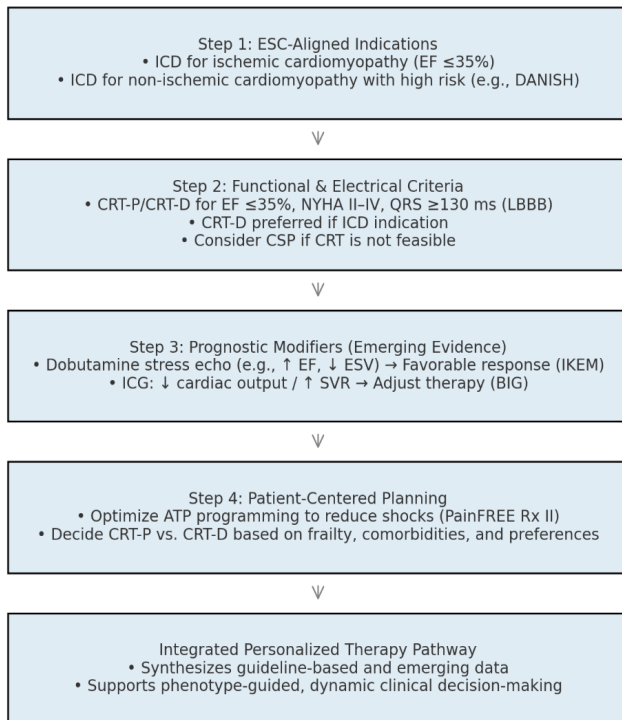
#### Clinical Significance

The IKEM study demonstrated that low-dose dobutamine echocardiography provides both diagnostic and prognostic information in the evaluation of patients with ischemic heart disease and heart failure. Assessment of contractile reserve enables early identification of patients likely to benefit from targeted therapeutic strategies, while also flagging those at higher risk of disease progression. These findings support the incorporation of stress echocardiography into routine clinical evaluation and risk stratification algorithms in IHD-related heart failure.

## DISCUSSION

#### Comparative insights from major trials:

While numerous randomized trials (see Table 1) have confirmed the efficacy of device-based therapy in heart failure, outcomes vary significantly depending on underlying etiology, QRS morphology, and left ventricular ejection fraction (LVEF). For instance, MADIT II demonstrated a 31% reduction in mortality with ICD implantation in ischemic cardiomyopathy, while the DANISH study in non-ischemic patients showed reduced sudden death but no overall mortality benefit. These contrasting results highlight the importance of etiology-specific risk stratification. Similarly, the COMPANION trial showed superior survival outcomes with CRT-D compared to CRT-P alone in patients with LBBB and wide QRS complexes. In contrast, the REVERSE study – focused on patients with milder symptoms – showed structural and symptomatic improvements without a conclusive mortal-



**Fig. 1.** Proposed phenotype-driven clinical decision algorithm for advanced device therapy in heart failure.

ity benefit. These findings highlight the importance of QRS morphology and duration as key predictors of CRT responsiveness.

These insights support a shift from uniform treatment models toward personalized therapy management. Future studies should emphasize multimodal selection strategies incorporating electrical, structural, and functional markers to enhance clinical outcomes.

In addition, implanted devices may serve as prognostic tools by monitoring parameters such as lead impedance, arrhythmic burden, or intrathoracic impedance, providing early warning signals of heart failure deterioration.

#### Trends from Czech national registries:

Data from the Czech Registry of Permanent Cardiac Stimulation provide real-world insight into evolving device therapy adoption<sup>13</sup>. Notably, conduction system pacing (CSP) – including His bundle and left bundle branch area pacing – accounted for 14% of initial implantations in 2023, rising sharply from 5% in 2022. This shift reflects growing clinical recognition of CSP as a physiologically superior alternative to traditional biventricular pacing in select patients.

CSP offers several advantages: better preservation of native conduction pathways, reduced pacing-induced cardiomyopathy, and improved ventricular synchrony. Its growing use in Czech clinical practice mirrors broader European trends and illustrates the flexibility of national centers in adopting evidence-based innovations.

Simultaneously, CRT-D and CRT-P implant rates have declined, especially in cases where CSP restores conduction effectively and with fewer complications.

Comparative analyses using benchmarks from the EHRA White Book support efforts to align national practice with international standards and inform training and resource allocation strategies.

These national findings underscore the dynamic nature of device therapy adoption in smaller European countries. Projections indicate that CSP could represent up to half of all implantations by 2025, depending on the capacities and expertise of individual centers, reinforcing the need for updated clinical pathways and integration into guidelines. These local trends provide a unique insight into real-world European practice and may be generalizable to similar healthcare systems.

#### Proposed algorithm for device therapy selection

To improve precision in heart failure management, we propose a simplified decision algorithm that integrates key parameters identified across major trials:

##### Step 1: Etiology-Based Risk Stratification

- Ischemic cardiomyopathy: Consider ICD for primary prevention in patients with LVEF  $\leq 35\%$  (MADIT II).
- Non-ischemic cardiomyopathy: ICD may be considered in selected high-risk patients, particularly those with elevated SPRM score (DANISH<sup>4</sup>).

##### Step 2: Functional and Electrical Assessment

- LVEF  $\leq 35\%$  and NYHA class II–IV → Evaluate for CRT-P or CRT-D.
- QRS  $\geq 130$  ms with LBBB morphology → Recommend CRT-D (COMPANION, MIRACLE); CSP may be considered as an alternative or adjunct.
- QRS  $< 130$  ms or non-LBBB → Consider CSP or optimized pharmacological therapy (REVERSE trial, CSP registries).

##### Step 3: Prognostic and Structural Modifiers

- Positive dobutamine stress echocardiography (e.g.,  $\uparrow$  EF,  $\downarrow$  ESV) → Indicates favorable remodeling potential (IKEM study).
- Impedance cardiography (ICG):  $\downarrow$  cardiac output or  $\uparrow$  systemic vascular resistance (SVR) → Supports intensification or adjustment of therapy<sup>14</sup>.

##### Step 4: Patient-Centered Planning

- Consider anti-tachycardia pacing (ATP) programming to reduce shocks and improve comfort (PainFREE Rx II).
- Choose between CRT-P and CRT-D based on frailty status, comorbidities, and individual patient preferences and goals.

An algorithm synthesizes ESC guideline-based indications with trial evidence and novel clinical markers<sup>1</sup>. It aims to improve risk stratification and optimize device selection in a phenotype-driven, patient-centered manner. A simplified decision algorithm is presented in Fig. 1. By synthesizing data from major international trials and reflecting real-world shifts in clinical practice – such as

**Table 1.** Overview of landmark trials evaluating device-based therapies and monitoring strategies in heart failure.

Study	Population	Intervention	Key Results	Clinical Significance
<b>MADIT II</b>	Ischemic HF, EF ≤ 30%, n = 1232	ICD vs. standard therapy	↓ Mortality (31%), ↓ sudden death, no QoL change	ICDs for primary prevention in ischemic HF
<b>DANISH</b>	Non-ischemic HF, EF ≤ 35%, n = 1116	ICD vs. standard therapy	↓ Sudden death; no mortality benefit overall	ICD benefit depends on arrhythmic risk
<b>COMPANION</b>	Advanced HF, EF < 35%, n = 1520	CRT, CRT+ICD, or medical therapy	CRT+ICD: ↓ mortality, hospitalizations, improved QoL	CRT and CRT-D beneficial in advanced HF
<b>MIRACLE</b>	HF with wide QRS, EF ≤ 35%, n = 453	CRT vs. standard care	↑ NYHA class, ↑ 6MWT, ↑ EF	CRT improves symptoms and function
<b>MIRACLE ICD</b>	HF with wide QRS, EF ≤ 35%, n = 369	CRT+ICD vs. pharmacotherapy	↓ Mortality + hospitalizations, ↑ EF, improved QoL	CRT-D improves outcomes in high-risk HF
<b>DEFINITE</b>	Non-ischemic HF, EF < 35%, n = 458	ICD vs. medical therapy	↓ Sudden death; trend to ↓ mortality	Supports ICD use in non-ischemic HF
<b>REVERSE</b>	Mild HF, EF ≤ 40%, n = 610	CRT vs. standard care	↓ Remodeling, trend to delayed progression	CRT useful in early-stage HF
<b>AVID</b>	Post-VT/VF patients, n = 1016	ICD vs. antiarrhythmic drugs	↓ Overall mortality (27%), ↓ sudden death	ICDs superior to drug therapy in high-risk patients
<b>PainFREE Rx II</b>	ICD patients with VT, n = 634	ATP vs. shock	↓ Shocks (70%), ↑ comfort	ATP preferred for patient quality of life
<b>IKEM</b>	Chronic HF, mostly IHD, n = 66	Dobutamine echo to predict remodeling	↑ EF and ↓ ESV predictive in IHD	Stress echo useful for prognosis

the increasing adoption of CSP – this framework supports a more dynamic, phenotype-driven approach to device therapy selection and may serve as a basis for future prospective validation and implementation in national and international registries.

## CONCLUSION

The integration of evidence-based pharmacological strategies with advanced device therapies and individualized monitoring methods has led to substantial progress in heart failure management. However, therapy optimization remains complex and requires tailoring based on patient phenotype, comorbidities, and functional status. Emerging technologies – including wearable sensors and remote monitoring platforms – together with evidence from clinical trials and registries, continue to refine risk stratification and expand indications for device-based therapy. One key innovation is the transition from a reactive to a proactive model of care. Early identification of high-risk patients using multimodal monitoring – such as impedance cardiography, echocardiographic contractile reserve, and electrophysiologic assessment – enables timely and targeted intervention.

The integration of CRT and ICD with antitachycardia pacing (ATP) programming and physiological pacing techniques like CSP represents a move toward less invasive and more personalized care. These findings support a feedback-guided approach, where real-time hemodynamic and electrophysiologic data inform continuous management decisions.

Ultimately, personalized medicine and early intervention remain central to improving outcomes and quality of life in heart failure. The integration of global evidence, including the 2023 ESC Guidelines (Focused Update<sup>1</sup>), national registry data, and structured decision-making tools supports a more precise and effective care pathway. This review highlights the need for phenotype-driven, feedback-guided management of heart failure incorporating contemporary pharmacotherapy, advanced device therapy, and multimodal monitoring.

## Scientific summary and future perspectives

Evidence from the reviewed studies supports the use of advanced device therapies and non-invasive monitoring in heart failure management. Landmark trials such as MADIT II, MIRACLE, and COMPANION confirmed the prognostic and therapeutic value of ICDs and CRT, particularly in patients with reduced EF and wide QRS complexes.

More recent investigations, including REVERSE and RESYNC (*Resynchronization in Pediatric and Congenital Heart Disease* trial), expanded CRT indications to patients with preserved or mildly reduced EF. These findings suggest potential for CRT in earlier disease stages, though long-term mortality benefits remain uncertain.

Concurrently, tools like impedance cardiography (ICG) and dobutamine stress echocardiography have shown promise for real-time hemodynamic assessment and risk stratification. The BIG and IKEM studies underscore the value of dynamic parameters such as cardiac output, systemic vascular resistance, and volume changes in guiding management.

**Future research should focus on:**

1. Refining CRT selection criteria, especially in HF with preserved or mid-range EF, potentially using machine learning or risk scores.
2. Longitudinal studies on ICG, dobutamine stress echocardiography (particularly in ischemic etiology), and related modalities to guide therapy escalation or de-escalation.
3. Integrating device therapy with digital tools for symptom, fluid, and rhythm monitoring.
4. Evaluating novel pacing techniques (e.g., CSP) versus conventional CRT.
5. Comprehensive assessment of cost-effectiveness, incorporating quality-of-life outcomes and real-world registry data, to support broader implementation and health policy decisions.
6. Leveraging device-derived metrics – such as LV lead impedance – for early detection of remodeling.
7. Addressing ethical issues like ICD deactivation in end-of-life care through early counseling and collaboration between cardiology and palliative care.

Taken together, these studies underscore a paradigm shift toward personalized, technology-driven heart failure management.

**Search strategy and selection criteria**

Relevant studies were identified through electronic databases (PubMed, Web of Science, and Scopus) using the search terms “heart failure,” “device therapy,” “implantable cardioverter-defibrillator,” “cardiac resynchronization therapy,” “conduction system pacing,” “impedance cardiography,” and “dobutamine stress echocardiography.” Only randomized controlled trials, large prospective registries, and guideline documents published between 1995 and 2024 were included. Reference lists of key articles were also screened to identify additional relevant studies. No language restrictions were applied.

The preparation of this review manuscript involved the use of large language models (LLMs) for language editing and reference formatting.

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**Data availability:** This article is a narrative review based solely on publicly available clinical trials, peer-reviewed publications, and registry data. No new data were generated or analyzed during the preparation of this manuscript.

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