European Journal of Internal Medicine 145 (2026) 106633

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

The changing landscape of heart failure: translating management into the modern era

Cristina Madaudo [a,b], Wasyla Ibrahim [a], Daniela Noakes [a,c], Daniel Bromage [a,c], Gianfranco Sinagra [d], Theresa McDonagh [a,c], Antonio Cannata [a,c,*]

[a] British Heart Foundation Centre of Research Excellence, School of Cardiovascular Medicine, Faculty of Life Science, King's College London, London, UK
[b] Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, Cardiology Unit, University of Palermo, University Hospital P. Giaccone, 90127, Palermo, Italy
[c] Cardiology Department, King's College Hospital NHS Foundation Trust, London, UK
[d] Azienda Sanitaria Universitaria Giuliano-Isontina, Universita' di Trieste, Trieste, Italy

ARTICLE INFO

Keywords:
Heart failure
Ejection fraction
Guideline-directed medical therapy
Ventricular remodeling
Precision medicine

ABSTRACT

Heart failure (HF) is a complex clinical syndrome associated with high morbidity and mortality, accounting for approximately 2 % of total healthcare expenditures. Despite advances in pharmacological and device-based therapies, HF continues to affect over 70 million people globally, with an increasing prevalence driven by an aging population. The classification remains imperfect due to the pathophysiological complexity of the syndrome. Recent attention has focused on aetiological characterisation, particularly in non-ischaemic cardiomyopathies, where genetic testing may provide diagnostic, prognostic, and therapeutic insights. Left ventricular reverse remodeling (LVRR) and the recognition of HF with improved ejection fraction (HFimpEF) have highlighted the dynamic nature of HF and the importance of continued therapy despite apparent recovery. Guideline-directed medical therapy (GDMT), based on four foundational drug classes for HFrEF, has demonstrated significant benefit, yet its implementation remains suboptimal. For HFpEF, all effective drugs have however failed to reduce mortality. Device therapy, including implantable cardioverter-defibrillators (ICDs), cardiac resynchronisation therapy (CRT) and valve replacement offers additional benefit in select patients and may facilitate optimisation of medical therapy. New avenues such as multiomic profiling, gene therapy, and artificial intelligence (AI) are expanding our ability to phenotype HF, predict disease progression, and personalize treatment strategies. This viewpoint summarises the current understanding of HF, with an emphasis on the classification, aetiology, phenotypes and evidence-based management including newer therapies and their scope of use across the spectrum of LVEF.

1. Introduction

Heart Failure (HF) is a complex clinical syndrome characterised by symptoms and/or signs of congestion caused by a structural or functional cardiac abnormality. Its diagnosis is usually corroborated by elevated natriuretic peptide levels [1–3].

HF affects approximately 70 million people worldwide. It has an incidence of approximately 5 per 1000 person-years in adults, and its prevalence is about 2 % of the global population [4]. Although the incidence has remained stable in the last decades, given the aging of the world population, its prevalence has increased, and it is expected to continue increasing. To date, the prevalence of HF reaches approximately 10 % in the elderly (i.e. >65 years of age) [4].

From a health economic perspective, HF is a massive burden on healthcare systems. The annual economic burden of HF reaches $108 billion per year, and in the UK, it consumes >2 % of the entire NHS budget [1].

Over the past few decades, the management of HF has dramatically changed. Nowadays, a range of medications and devices are part of standard care, leading to a substantial improvement in quality of life and long-term mortality [5]. However, despite these advancements, HF is still a major cause of morbidity and mortality worldwide. This review aims to summarise the current management of HF, highlighting the gaps in evidence and the potential future avenues of research.

* Corresponding author.
E-mail address: antonio.cannata@kcl.ac.uk (A. Cannata).

https://doi.org/10.1016/j.ejim.2025.106633
Received 13 August 2025; Received in revised form 9 November 2025; Accepted 1 December 2025
Available online 5 December 2025

Table 1
Classification of HF based on LVEF and other echocardiographic evidence.

Subtype of HF	HFrEF	HFmrEF	HFpEF	HFimpEF
Signs and symptoms	Present	Present	Present	Present/absent
NTproBNP	Elevated	Elevated	Elevated	Variable
Left Ventricle Ejection Fraction	≤40 %	41–49 %	≥50 %	≥10-point increase from baseline and LVEF >40 %
Echocardiographic evidence	LV systolic dysfunction	Mildly reduced LV systolic function	Structural or functional abnormalities consistent with diastolic dysfunction/raised filling pressures. Common (LA enlargement, LV hypertrophy)	Evidence of prior LV systolic dysfunction with subsequent improvement. Structural heart disease may persist despite LVEF recovery

Abbreviations: EF: ejection fraction; HF: heart failure; HFrEF: HF with reduced ejection fraction; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFimpEF: heart failure with improved ejection fraction; LV: Left ventricle; NTproBNP: N-terminal pro-brain natriuretic peptide.

2. Gaps in classification of HF

Traditionally, HF has been categorized based according to the degree of left ventricular (LV) systolic dysfunction measured by the left ventricular ejection fraction (LVEF) on echocardiography [1,2,6]. Beyond LVEF, emerging approaches to HF classification incorporate functional and biomarker-based phenotyping, including exercise capacity, natriuretic peptide levels, and novel markers such as ST2 and galectin-3, which may offer a more comprehensive assessment of disease severity and prognosis [3]. Currently, HF with reduced LVEF (HFrEF) is defined as LVEF ≤ 40 %, and HF with preserved LVEF (HFpEF) as LVEF > 50 %. The grey area between 41 % and 49 % is defined as HF with mildly reduced LVEF (HFmrEF) [7,8]. However, the 2025 Canadian Cardiovascular Society/Canadian HF Society guidelines have recently proposed a unified classification of all patients with LVEF >40 % under the term HF with nonreduced EF (HFnrEF), reflecting evidence of similar clinical outcomes and therapeutic responses across this spectrum [9]. The classification of HF phenotypes based on LVEF and other echocardiographic parameters is summarized in Table 1. Historically, this classification derives from the inclusion criteria of early randomised clinical trials (RCTs) in HF, which showed a greater benefit from treatment in subjects with LVEF≤ 40 % and the notion of the higher risk of adverse events with a reduced LVEF [1,2,6].

The concept of HFpEF was later introduced in the CHARM trial, which evaluated candesartan across the full LVEF spectrum. In this trial, patients with an LVEF greater than 40 % were classified as having 'preserved' ejection fraction, since this value was above the threshold commonly used at that time to define "reduced" systolic function [10]. Although LVEF is normally distributed in the general population, in patients with HF its distribution becomes bimodal, and normal reference values vary by age, sex, and ethnicity [11]. According to the European Association of Cardiovascular Imaging (EACVI), systolic dysfunction is defined as LVEF < 52 % in men and < 54 % in women [12]. However, even among patients with HFpEF, some degree of LV systolic dysfunction is present. Some HFpEF patients may have mildly reduced systolic function, which makes the distinction between categories unclear. This dichotomisation has created the grey area of HFmrEF, in which the strength of the evidence for treatment is weaker and can be mostly derived from post-hoc analysis of large RCTs. Although now a distinct category, HFmrEF shares several similarities with HFrEF, potentially suggesting a unified phenotype. It overlaps with HFrEF in terms of aetiology and comorbidities, such as prevalence of ischaemic heart disease (IHD) and chronic kidney disease (CKD) [6]. At the same time, it exhibits traits more typical of the HFpEF phenotype, such as a high prevalence of metabolic syndrome, hypertension, diabetes, and obesity. Geographical differences have also been described: in U.S. cohorts, HFmrEF patients more closely resemble those with HFpEF, being older, with higher BMI, and more frequent hypertension and atrial fibrillation (AF) [13–15]; whereas, in Europe, patients with HFmrEF more closely resemble those with HFrEF, particularly in being younger, predominantly male, having a higher prevalence of IHD, and a lower prevalence of AF [16]. HFmrEF shares pathophysiological features with HFrEF and has a similar therapeutic approach. Recent registry data show that medical therapy effective for HFrEF, in particular beta-blockers and angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), are also beneficial in patients with HFmrEF highlighting the overlap between these two categories[17,18]. In the future, perhaps a simplified classification using a LVEF cut-off of 50 % may partially resolve this conundrum.

Table 2
Aetiologies of non-ischaemic heart failure.

Aetiology		Estimated prevalence/ incidence in HF population
Hypertensive heart disease	Long-standing hypertension leading to LV hypertrophy and dysfunction	Accounts for ~30–40 % of HF cases; incidence rises with age and hypertension prevalence
Valvular heart disease	Aortic stenosis, mitral regurgitation	~10–15 % of HF cases; incidence 1–2 % per year in ≥65 years
Infiltrative cardiomyopathy	Amyloidosis, sarcoidosis	<5 % of HF cases; cardiac amyloidosis prevalence ~1 % in HFpEF ≥65 years
Inherited cardiomyopathies	Dilated (DCM), hypertrophic (HCM), arrhythmogenic (ARVC)	DCM 10–20 %; HCM 0.2–0.5 % in general population; ARVC 1:2000–1:5000
Toxin-induced cardiomyopathy	Chemotherapy (e.g. anthracyclines), alcohol, recreational drugs	1–5 % of all HF; up to 9 % in oncologic populations exposed to anthracyclines
Tachycardia-mediated cardiomyopathy	Due to persistent atrial or ventricular tachyarrhythmias	~5–10 % of new-onset non-ischemic HF

Abbreviations: ARVC: arrhythmogenic right ventricular cardiomyopathy; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; LV: left ventricle.

In clinical practice, however, LVEF should be interpreted as a continuum rather than as discrete categories. Rather than relying on rigid cut-offs for the initiation of guideline-directed medical therapy (GDMT), treatment should perhaps target all patients whose LVEF falls below the normal reference range [19] This approach promotes a more continuous and individualized view of HF management across the LVEF spectrum.

Regarding mortality across the range of LVEF, contemporary registry data suggest that overall mortality rates are largely comparable between HFpEF and HFrEF, although cardiovascular mortality remains higher in HFrEF, while non-cardiovascular causes account for a growing proportion of deaths in HFpEF [4,20,21]. In the nationwide Swedish HF Registry, crude 1-year mortality rates among 42,061 outpatients were 15.4 % in HFrEF, 17.4 % in HFpEF and 14.2 % in HFmrEF [22]. In both groups, non-cardiovascular comorbidities and systemic inflammation, further amplified during the COVID-19 era, significantly contribute to hospitalisations and long-term outcomes [23–25]. The main differences between phenotypes are therefore reflected in hospitalization burden

and quality-of-life impact rather than mortality, underscoring the need for improved management strategies particularly in HFmrEF and HFpEF [4].

3. Aetiological characterisation and continuous reclassification of heart failure

HF is a complex clinical syndrome with multiple aetiologies. Although HF is usually classified into ischaemic and non-ischaemic, the latter encompasses several different causes with important prognostic implications [26].

Non-ischaemic HF encompasses a wide range of conditions leading to the overt phenotype (Table 2). These includes hypertensive heart disease, valvular heart disease (VHD), infiltrative conditions such as amyloidosis, inherited cardiomyopathies such as dilated and hypertrophic cardiomyopathies, toxin-induced phenotypes due to chemotherapy or alcohol and tachycardia-mediated systolic dysfunction [27,28]. Proper diagnosis of the aetiology of HF is important for predicting the natural history of the disease and for prognostic implications.

However, the definition of cardiomyopathies and their underlying aetiologies remains heterogeneous. This heterogeneity complicates comparison across studies and may downplay prognostic nuances. Notably, data on the prognostic impact of HF aetiology remain inconsistent. Identifying the underlying cause of HF has clear diagnostic and a potential prognostic value in specific subgroup of patients. However, in clinical practice, most patients with HFrEF are managed according to standardized, guideline-based treatment protocols, regardless the aetiological subtype [29].

While most earlier studies associated ICM with poorer outcomes, more recent evidence has reported comparable or even improved survival in ischaemic versus non-ischaemic HF, suggesting that advances in revascularization and contemporary GDMT may have attenuated this gap [27,30]. This variability, together with the lack of uniform etiological definitions, underscores the need for standardized classification frameworks. Beyond the identification of aetiology, it is increasingly recognized that HF is a dynamic condition rather than a static state of dysfunction [31]. Structural and functional changes in the LV may occur over time in response to therapy or disease progression [31]. In this context, left ventricular reverse remodeling (LVRR) has emerged as an important marker of therapeutic response and prognosis [32]. Indeed, patients with non-ischaemic HFrEF are more likely to undergo LVRR and improve or even recover their LVEF [33]. LVRR reflects the dynamic nature of HF and has gained increasing attention for its prognostic implications. LVRR has been defined as either an increase in LVEF of $\geq$10 % and a decrease in LV end-diastolic diameter index of $\geq$10 % or $\leq$33 mm/m, or by an improvement in LVEF alone [32,34]. LVRR has been reported in approximately 30 % to 50 % of patients with HFrEF, with rates of around 37 % in those with idiopathic dilated cardiomyopathy (DCM) [35]. Patients with myocarditis have an even higher rate of LVRR [36]. Although the overall rate of LVRR appears comparable between sexes, women who achieve LVRR tend to experience the most favourable long-term outcomes compared to both men and women without LVRR [37].

In a prospective study, this sustained improvement over time was associated with reduced mortality (17 % at 5 years) and a lower rate of HF hospitalisations (12 %) [38]. Consistently, another study conducted in 346 patients with dilated cardiomyopathy (DCM) and hypokinetic non-DCM reported that HF rehospitalisation (hazard ratio [HR], 0.47; 95 % CI, 0.24–0.91; $P = 0.026$) and cardiovascular death (HR, 0.18; 95 % CI, 0.04–0.82; $P = 0.026$) were significantly lower in patients who experienced LVRR [39,40]. Therefore, LVRR could have a role as a marker of therapeutic efficacy and improvement of long-term outcomes in patients with HF.

The recognition of HF with improved ejection fraction (HFimpEF) naturally derives from these observations, as etiological factors and the capacity for LVRR determine the likelihood of LVEF recovery and subsequent reclassification over time.

After the recovery of LVEF, patients with HFrEF may be reclassified as HFimpEF. This has emerged as a distinct phenotype within the spectrum of HF, defined by an initial LVEF$\leq$40 % that subsequently improves to >40 %, with varying thresholds depending on specific guidelines [41]. This entity reflects the dynamic nature of HF and is increasingly recognized, likely due to greater adherence to guideline-directed medical therapy and the establishment of standardized diagnostic criteria [42]. Although patients with HFimpEF exhibit significant LVRR and improved clinical status, they remain at risk for adverse outcomes, including HF recurrence and arrhythmias [41,43].

Patients with HFimpEF present with lower HF severity, reflected by milder neurohormonal activation, better functional capacity, and less advanced LV dysfunction, as well as higher exercise capacity and lower cardiovascular mortality compared to those with persistently reduced LVEF (26.6 vs 46.9 per 1000 person-years, $p < 0.001$). However, their long-term prognosis remains similar. This highlights that HFimpEF represents a partially recovered but still vulnerable phenotype within the HF spectrum [44]. The TRED-HF trial, a pilot, open-label, randomized, controlled, single-arm crossover study, investigated the effects of phased withdrawal of GDMT in 51 patients with recovered DCM. The trial demonstrated that 65 % of patients ($n = 33$) experienced at least one episode of relapse over a six-year follow-up period [45]. Therefore, despite the limitations of TRED-HF, such as the open-label, single-center study design with a small sample size and short-term follow-up, this study demonstrates that routine GDMT discontinuation in patients with DCM and recovered LVEF should currently be avoided unless necessary [46]. Management strategies remain uncertain, with few therapies specifically studied in this subgroup [41,43]. Current guidelines recommend continuation of GDMT, as there is no current evidence supporting safe withdrawal [41]. Ongoing clinical trials are exploring the safety of medication withdrawal (With-HF NCT04367051; WEAN—HF NCT06128980; PROSPER-HF NCT04803175), predictors of relapse, and the utility of advanced imaging and biomarkers in monitoring and risk stratification [41]. Ultimately, this represents a heterogeneous group with a variable risk of LVEF deterioration and outcomes largely dependent on the underlying aetiology of HF. Genetic background and the presence of persistent symptoms also play an important role, further emphasizing the need to identify specific etiological mechanisms. In this context, genetic testing has emerged as a key tool for improving etiologic characterisation and guiding personalized management, particularly in non-ischaemic HF [41,47] From a therapeutic perspective, distinguishing between partial and complete recovery has important clinical implications. Patients with partial recovery remain at significant risk of relapse and should continue full-dose GDMT indefinitely, whereas those with complete recovery may be considered for cautious de-escalation under specialist supervision and close follow-up, given the risk of recurrent LV dysfunction.

4. The importance of genetic testing in non-ischaemic HF

Genetic testing plays a crucial role in the diagnosis and management of non-ischaemic HF, particularly in the context of dilated cardiomyopathy (DCM), where a monogenic cause is identified in up to 40 % of cases [26,48]. Contemporary evidence supports the implementation of genetic testing to uncover pathogenic variants that not only aid in etiologic classification but also inform prognosis, therapeutic choices, and family screening. Notably, truncating variants in the TTN gene (TTNtv) represent the most prevalent genetic cause of DCM and have been associated with increased risk of arrhythmias and poor reverse remodelling response [49,50]. Conversely, LMNA mutations carry a high arrhythmic burden and often necessitate early implantable cardioverter-defibrillators (ICDs) implantation, even in patients with modest systolic dysfunction[48]. The integration of genetic data with clinical and imaging findings enhances risk stratification, allowing for more personalized management[51,52]. Moreover, cascade screening in

first-degree relatives enables early identification of preclinical disease, guiding surveillance and intervention strategies[48]. Despite its growing relevance, genetic testing remains underutilized, highlighting the need for broader implementation in clinical practice and improved access to genetic counselling services[53].

5. Current treatment options in heart failure

GDMT of HFrEF is based on robust evidence from RCTs. The mainstay of treatment is based on counteraction of the neurohormonal axis to reduce the vascular remodelling, vasoconstriction and fluid retention that occurs in response to reduced cardiac output [7,42]. In addition to diuretics to relieve congestion, foundational pharmacological therapy is based on four drug classes: ACE-i or ARBs with or without neprilysin inhibition (ARNI), beta-blockers, mineralocorticoid receptor antagonists (MRAs) and SGLT2-inhibitors (SGLT2-I) [29,42]. These agents, often referred to as the "four pillars" of HFrEF management, should be initiated promptly and concurrently when possible, even at low doses, with subsequent individualized uptitration to maximally tolerated target doses[29]. Early initiation and rapid sequencing of these therapies has been associated with improved outcomes, including reduced mortality and hospitalisations, supporting a shift from stepwise to simultaneous treatment strategies. This paradigm is supported by recent trials and expert consensus, emphasizing that even starting low doses of all four classes can confer early benefit, particularly within the first 30 days of treatment initiation [54].

5.1. Treatment of HFmrEF and HFpEF

The evidence of benefit for guideline-directed treatment in HFrEF is clear and well defined. However, most of the trials showing a significant benefit in survival, recruited patients with LVEF<40 %. The evidence of use of these medications in HFmrEF is less strong and largely comes from post-hoc analysis of RCTs or observational data[55]. In the TOPCAT trial which investigated the role of spironolactone (Aldactone) in patients with an LVEF ≥45 %, the post-hoc analysis suggested greater reduction in HF hospitalisations in those with a lower LVEF [56]. Similarly, the subgroup analysis in the PARAGON—HF trial showed that for patients with HFmrEF/HFpEF and LVEF below the median (i.e. 57 %), the use of sacubitril/valsartan was associated with fewer CV deaths or HF hospitalisations [57]. SGLT2is currently represent the only recommended class of drugs across the entire LVEF spectrum, including patients with HFpEF [29,58]. Although strong evidence supports their benefit in LVEF <40 %—as demonstrated in the DAPA-HF and EMPEROR-Reduced trials—their efficacy in LVEF >40 % has been demonstrated in terms of a reduction in HF hospitalisations, as observed in the EMPEROR-Preserved and DELIVER trials[59]. However, no drug to date, including SGLT2i, has demonstrated a significant benefit on mortality in patients with HFpEF [58]. Similarly, there is new emerging data on the benefits of MRA's in patients with HFpEF. The FINEARTS- trial examined the use of Finerenone vs placebo in patients with LVEF>40 % and showed a significant reduction in the composite endpoint of CV death and total worsening HF events [60]. In a recent prespecified individual patient-level meta-analysis including 13,846 patients from four major randomized trials (RALES, EMPHASIS-HF, TOPCAT, and FINEARTS-HF), the effects of MRAs were evaluated across the spectrum of LVEF. This analysis demonstrated that MRAs significantly reduced the composite outcome of cardiovascular death or heart failure hospitalisation (HR 0.77; 95 % CI 0.72–0.83). While the benefit was more pronounced in patients with HFrEF (HR 0.66; 95 % CI 0.59–0.73), a significant reduction in HF hospitalisations was also observed in those with HFmrEF and HFpEF (HR 0.82; 95 % CI 0.74–0.91). However, no significant reduction in cardiovascular or all-cause mortality was seen in the HFmrEF/HFpEF subgroup [61]. These findings suggest that steroidal MRAs reduce the risk of cardiovascular death or HF hospitalisation in patients with HFrEF, while non-steroidal MRAs may reduce this risk in patients with HFmrEF or HFpEF.

Collectively, these findings reinforce the pivotal role of MRAs as a cornerstone of neurohormonal blockade in HFrEF and suggest a potential class effect extending into HFmrEF and HFpEF. The introduction of non-steroidal MRAs such as finerenone, with a more favourable renal and metabolic profile, may broaden the therapeutic applicability of this class across the HF spectrum, warranting further investigation in real-world and outcome-driven studies.

Therefore, it may be appropriate to consider a selective benefit of MRAs depending on the underlying LVEF phenotype [61]. This highlights an ongoing challenge in HF management: the lack of a clear and consistent phenotypic definition for HFmrEF, which complicates both clinical decision-making and trial design [62].

5.2. Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

GLP-1 RA have emerged as a promising therapeutic option in patients with HFPEF and obesity. Initially shown to reduce cardiovascular events in patients with type 2 diabetes mellitus [63] and promote significant weight loss in obesity [64], they have since been evaluated in several HFPEF RCTs. The STEP-HFpEF trial was the first to demonstrate improved quality of life and exercise capacity in patients with HFPEF and obesity (BMI ≥30) treated with semaglutide. This was in the context of significant weight loss with a mean reduction in body weight of 13.3 % in the semaglutide arm versus 2.6 % in the placebo arm [65]. These benefits were confirmed in patients with type 2 diabetes in STEP-HFpEF DM [66] Although secondary outcomes from STEP-HFpEF suggested reduced heart failure events and NT-proBNP levels, the SUMMIT trial provided more definitive evidence. In SUMMIT, tirzepatide—a dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist—reduced the risk of cardiovascular death or worsening heart failure in patients with HFpEF and obesity [67] This was further supported by the pre-specified analysis of the SELECT trial which showed that semaglutide reduced major adverse cardiovascular events (MACE) and composite heart failure outcomes in patients with atherosclerotic cardiovascular disease and a BMI of ≥27 regardless of heart failure subtype [68]. After years of limited treatment options in HFpEF we now have several therapies that we can tailor to our individual patients depending on their comorbidities. Beyond their metabolic effects, GLP-1 RAs and dual GIP/GLP-1 agonists are emerging as effective medications in obese HFpEF, offering a combined benefit on weight loss, and cardiovascular risk. Their integration into HFpEF management shifts its treatment to a phenotype-specific, comorbidity-driven therapy, particularly for patients with coexisting obesity and diabetes. In addition, SGLT2-i and non-steroidal MRAs, such as finerenone, may represent a potential first-line options for all eligible patients. ARNI therapy is appropriate for those with "LVEF below normal", reflecting the emerging continuum-based classification, while GLP-1 receptor agonists are particularly indicated for obese HFpEF, where they improve symptoms, exercise tolerance, and cardiometabolic risk [69]. This individualized strategy integrates the main evidence-based treatments according to pathophysiologic phenotype.

5.3. Vericiguat

Vericiguat, an oral soluble guanylate cyclase stimulator, targets the impaired nitric oxide–sGC–cGMP pathway and has been evaluated as a potential therapeutic option for patients with HFrEF. In the VICTORIA trial, which enrolled 5050 patients with worsening HFrEF (median NT-proBNP 3377 pg/ml; 64 % hospitalized within 3 months), Vericiguat reduced the composite endpoint of cardiovascular (CV) death or HF hospitalization compared with placebo (HR 0.90; 95 % CI 0.82–0.98; $p = 0.02$) over a median follow-up of 10.8 months. This benefit was primarily driven by a reduction in HF hospitalizations (HR 0.90; 95 % CI 0.81–1.00), while the effect on CV mortality was neutral (HR 0.93; 95 % CI 0.81–1.06) [70]. Subgroup analyses suggested that Vericiguat might

provide greater benefit in more stable patients. This hypothesis was tested in the VICTOR trial, which enrolled 6105 stable ambulatory HFrEF patients (NT-proBNP ≤6000 pg/ml and no recent hospitalisation). Although the primary composite endpoint of CV death or HF hospitalization was not significantly reduced (HR 0.93; 95 % CI 0.83–1.04; $p = 0.22$), a signal toward lower CV mortality was observed (HR 0.83; 95 % CI 0.71–0.97), confirmed in a post-hoc analysis showing reduced all-cause mortality at two years (7.3 % vs 8.6 % per year; HR 0.84; 95 % CI 0.74–0.97; $p = 0.01$) [71]. Overall, Vericiguat appears most beneficial in patients with high-risk or recently decompensated HFrEF, while its role in stable, lower-risk patients remains uncertain. In clinical practice, its use should be tailored to individuals who tolerate vasodilatory therapy and are most likely to experience symptomatic and prognostic benefit [29,42,70]. In the VICTORIA trial, a significant interaction was observed between treatment effect and baseline NT-proBNP levels (p for interaction =0.002)[70]. Patients with NT-proBNP ≤4000 pg/mL experienced a 23 % relative risk reduction in the composite endpoint of cardiovascular death or HF hospitalization (HR 0.77; 95 % CI 0.68–0.88), whereas no benefit was seen in those with values >8000 pg/mL [72]. However, the effect of Vericiguat in patients with heart failure is small and inconsistent across the two trials and its use should be reserved for specific subgroup of patients.

5.4. Strategies to implement medical treatment

The recent STRONG-HF trial showed that rapid optimisation of GDMT in patients following a hospital admission with acute HF reduced the risk of HF hospitalisation and all-cause mortality at 6 months [8]. These results highlight the importance of a rapid initiation and uptitration of GDMT in patients with HF. Despite the demonstrated benefits of GDMT, its implementation in clinical practice remains suboptimal due to therapeutic inertia [73]. This is often linked to clinical factors (e.g., hypotension, renal insufficiency, hyperkalaemia), organizational factors, and the patient's perceived frailty or advanced age, leading to delays or failure to optimize therapy [73]. Furthermore, adherence is often compromised by polypharmacy, comorbidity burden, and socioeconomic barriers. Educational strategies and structured follow-up can improve therapy adoption, particularly in elderly or frail patients [73]. Management by HF specialists is associated with a higher likelihood of discharge with complete therapy, a reduced need for diuretics, and a significant improvement in long-term survival [30]. Patients followed by specialist teams also show a lower incidence of HF-related rehospitalisations[30]. Moreover, the simultaneous or near-simultaneous introduction of these agents is considered both safe and feasible in the majority of patients, with flexible sequencing tailored to clinical status, blood pressure, renal function, and comorbidities [54]. Recent evidence supports an 'ARNI-first' initiation strategy, which may accelerate reverse remodeling and improve outcomes when tolerated [74]. In patients with intolerance due to hypotension, renal impairment, or hyperkalaemia, gradual up-titration, dose adjustments, or sequencing strategies can optimize therapy while maintaining all four foundational drug classes whenever possible [75].

5.5. Diuretic strategies to relieve congestion in heart failure

Loop diuretics remain the cornerstone of management of congestion in both acute and chronic HF [76]. The aim of treatment is to improve symptoms by achieving decongestion using the lowest possible dose and therefore minimising side effects [42]. In case of diuretic resistance, sequential nephron blockade, involving the addition of agents such as thiazides, MRAs, SGLT2-I or acetazolamide to loop diuretics, is an emerging strategy aimed at enhancing diuresis, improving decongestion and reducing hospitalisation duration [10,77]. The ADVOR trial showed that adding intravenous acetazolamide to loop diuretics in patients with acute decompensated HF improved early diuresis and shortened length of stay [11]. Similarly, the CLOROTIC trial demonstrated that adding hydrochlorothiazide to intravenous furosemide led to faster weight loss in acute HF patients but increased the risk of renal dysfunction and electrolyte abnormalities [12]. Of note, these trials were powered for in-hospital endpoints of decongestion and there is no indication that sequential nephron blockade may improve survival in patients with HF. In a large multicenter prospective study, continuous intravenous infusion (CiV) of furosemide was associated with greater reductions in NT-proBNP (>30 % in 63 % vs 45 % with bolus administration, $p < 0.001$) and more pronounced weight loss, but at the cost of longer hospital stay and higher adverse event rates [78]. Consistently, continuous infusion and sequential nephron blockade strategies enhanced diuretic response compared with bolus furosemide alone, although at the expense of an increased risk of worsening renal function and electrolyte disturbances [77].

5.6. Device therapy in heart failure

In patients with a reduced LVEF despite optimal GDMT, evidence supports the use of devices to prevent sudden cardiac death (SCD) and restore ventricular synchrony. Early trials showed the benefit of ICDs on the reduction of SCD in patients with LVEF≤35 % compared to amiodarone or placebo [79].

The SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) trial evaluated 2521 patients with NYHA class II or III HF and a LVEF≤35 %, randomly assigned to receive amiodarone, an ICD, or placebo. The study demonstrated that amiodarone conferred no survival benefit, whereas single-lead, shock-only ICD therapy significantly reduced all-cause mortality by 23 % (0.77; 97.5 % CI, 0.62 to 0.96; $P = 0.007$) compared to placebo with an absolute decrease in mortality of 7.2 % after 5 years in the overall population. Although the incidence of SCD in HFrEF has substantially declined over time, the indication for primary prevention ICD therapy now varies by aetiology [29]. In ischaemic cardiomyopathy, patients with LVEF ≤35 % despite optimal GDMT retain a Class I indication for ICD implantation [29]. In contrast, in non-ischaemic cardiomyopathy, the recommendation has been downgraded to Class IIa following the DANISH trial, which failed to demonstrate a significant mortality reduction despite a lower rate of SCD [80]. In this setting, a multidisciplinary and multiparametric arrhythmic risk assessment, integrating cardiac MRI and genetics, is essential to guide individualized decision-making beyond LVEF alone [81–83]. In particular, individuals with additional arrhythmic risk markers, such as the presence of myocardial fibrosis on cardiac MRI (e.g., late gadolinium enhancement) or pathogenic variants in genes like LMNA, FLNC, or PLN, may derive the greatest benefit [81]. Nevertheless, in the current therapeutic era, we need further evidence to guide us on who will benefit from primary prevention ICD therapy and there are several ongoing trials in this sphere in both ischaemic and non-ischaemic cardiomyopathy – the BRITISH (NCT05568069) study, PRO FID EHRA (NCT05665608) and CONTEMP-ICD (NCT06543446).

Similarly, cardiac resynchronisation therapy (CRT) has well established mortality and symptomatic benefits in HFrEF patients with prolonged QRS duration (>130 msec) in addition to optimal GMDT [84,85]. More recently, conduction system pacing (e.g. implanting leads into the Bundle of His or left bundle branch) has emerged as an alternative to traditional biventricular pacing as it aims to restore physiological ventricular activation [86]. Cardiac contractility modulation (CCM) has also shown potential in selected patients with symptomatic HFrEF, narrow QRS complexes, and LVEF between 25 % and 45 %, who are not candidates for CRT[87]. Both CSP and CCM represent evolving device-based strategies that may expand therapeutic options in patients with heart failure and conduction abnormalities or who do not respond to conventional therapies.

5.7. Transcatheter edge-to-edge repair (TEER) of the mitral and tricuspid valve

For patients with symptomatic HFrEF and severe mitral regurgitation (MR), transcatheter edge to edge repair (TEER) of the mitral valve may be a feasible option. Although the MITRA-FR, which included 304 patients, showed no significant reduction in all-cause mortality or HF hospitalisations with mitral TEER [88], the COAPT trial, which enrolled 614 symptomatic patients, demonstrated that mitral TEER in patients with functional MR and LVEF between 20–50 % resulted in a 47 % reduction in HF hospitalisations and a 38 % reduction in all-cause mortality[89]. The difference in results may be related to patient selection, with COAPT recruiting patients with higher LVEF but more severe MR, mandatory pre-enrolment GMDT optimisation and longer follow up duration. More recently, the RESHAPE-HF2 trial, a multicentre RCT comparing TEER versus medical therapy in patients with functional MR and LVEF 20–50 %, confirmed the benefit of TEER in reducing the composite endpoint of total HF hospitalisations and cardiovascular death, along with significant symptomatic improvement [90].

In addition to mitral valve interventions, tricuspid TEER could be an option for HF patients. The recently published TRISCEND II trial randomized 402 patients with severe and symptomatic tricuspid regurgitation (TR) in a 2:1 ratio to patients on optimal medical therapy alone [91]. The primary hierarchical composite outcome, analysed using the win ratio statistical method, included all-cause mortality, implantation of a right ventricular assist device or heart transplantation, further tricuspid-valve intervention, hospitalisation for heart failure, improvement in the Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS), New York Heart Association (NYHA) functional class and the 6-min walk distance[91]. The study demonstrated that tricuspid TEER was superior to medical therapy alone for the primary composite outcome with a win ratio of 1.48 (95 % CI, 1.13 to 1.96; $P = 0.005$), driven primarily by improvements in symptoms and quality of life[91]. These findings build upon prior evidence from the TRISCEND study, which had already shown sustained TR reduction, significant increases in stroke volume and cardiac output, as well as high survival and low hospitalisation rates, with improved clinical, functional, and quality-of-life outcomes at one year, further supporting the evolving role of transcatheter tricuspid therapies [92].

Similarly, the TRILUMINATE trial investigated the use of tricuspid TEER in 572 patients with severe and symptomatic TR compared to GDMT. Initial data after 12 months follow up showed a reduction in TR severity and significant improvement in quality of life with the extended 2 years follow up showing that T-TEER may be associated with lower rate of HF hospitalisations [93,94]. Therefore, while recent findings are encouraging, they should be interpreted with caution. To date, no adequately powered and definitive evidence demonstrates that tricuspid TEER reduces cardiovascular mortality or HF hospitalisations. Patient selection remains crucial, and individualized clinical evaluation is essential before considering T-TEER as a standard therapeutic strategy in heart failure management.

5.8. Device treatment as drug facilitator

The evidence supporting the use of prognostic HF medications is based on the administration of optimal or maximum tolerated doses, as this improves outcomes in HF patients. However, in clinical practice, a significant proportion of HF patients are unable to tolerate these doses due to common side effects such as renal impairment, symptomatic hypotension, bradycardia, or electrolyte imbalances[95]. To partially overcome these barriers, specific devices may be used to facilitate uptitration of GDMT. The effect of CRT on optimisation of HF medications was examined in the Swedish HF registry [96]. They compared patients who had CRT implanted to a control group who met the criteria for implantation but did not have a device inserted [96]. All patients had HF for a minimum of 3 months to allow maximum tolerated titration of prognostic medications[42]. They showed that in the CRT group patients had significant improved use of beta-blockers (higher doses) and reduced doses of loop diuretics based on intention to treat analysis but also improvement in use of ACEi/ARB/ARNI and MRA's using per-protocol analysis[96]. Similarly, there is registry data to suggest that TEER in functional MR also allows for up-titration of prognostic medications and that this was in turn independently linked to reduced all-cause mortality and HF hospitalisations [97]. Thus, device therapy may facilitate up-titration and optimisation of these prognostic medications in patients who have historically struggled to achieve optimal doses due to significant side effects and may further improve mortality in patients with HFrEF [97]. Although this is promising, more research is likely required before this is translated into international HF guidelines.

6. Cancer and heart failure

Advancements in cancer therapy have significantly improved survival rates in recent decades[98]. Cancer patients and cancer survivors are at an increased risk of cardiovascular disease, including HF [99–101]. This is a result of both baseline cardiovascular risk factors and cancer therapies causing cardiotoxicity[102]. In 2022, the Cardio-oncology ESC Guidelines defined cancer therapeutics–related cardiac dysfunction (CTRCD) as a spectrum ranging from asymptomatic myocardial injury, detected by biomarkers or reductions in global longitudinal strain (GLS) on echocardiography, to overt HF [103,104]. Anthracycline chemotherapies (doxorubicin, daunorubicin, epirubicin and idarubicin) are used primarily to treat breast and haematological malignancies [105]. Up to 5 % of patients treated with anthracyclines develop clinical heart failure, involving either left, right, or biventricular dysfunction[106,107]. The risk increases proportionally with the cumulative anthracycline dose received [108,109]. Trastuzumab is a monoclonal antibody used in the treatment of human epidermal growth factor receptor 2 (HER-2) positive breast cancers [110]. Its mechanism of cardiotoxicity is different to anthracyclines; LV dysfunction is often reversible on withdrawal of the Trastuzumab and is not dose related [110,111].

The importance lies in early detection of cardiotoxicity, prior to the development of overt HF symptoms [112,113].

Regular echocardiographic monitoring including 3D LVEF and global longitudinal strain (GLS) is recommended based on baseline cardiovascular risk, with the aim of identifying subclinical cardiotoxicity before progression to symptomatic and potentially irreversible LV dysfunction[104,114]. GLS is now an established technique for identifying subclinical cardiotoxicity with a relative reduction of >15 % from baseline identified as the cut off for predicting subsequent LVEF decline [104]. Cardiac biomarkers such as troponin have also shown value in predicting subsequent development of cancer therapy-related cardiac dysfunction (CTRCD), particularly with anthracyclines and trastuzumab [110,115].

Early recognition of cardiotoxicity allows for the initiation of cardioprotective therapy such as neurohormonal blockade which may prevent further decline in cardiac function. In a prospective study by Cardinale et al., enalapril significantly prevented the decline in LVEF in high-risk patients with elevated troponin I following high-dose chemotherapy (mean ΔLVEF −1 % vs −11 %, $p < 0.001$), with no cases of symptomatic HF in the enalapril group compared to 17 % in controls [116]. Similarly, Georgakopoulos et al. reported preserved LVEF at 36 months in patients treated with enalapril and metoprolol (mean LVEF 62 % vs 50 %, $p = 0.001$)[117]. However, more recent trials such as the PRADA and CECCY trials have yielded mixed results (83, 86) and no trial to date has demonstrated a reduction in symptomatic HF incidence with neurohormonal therapy in this setting. Although no randomized trials have yet evaluated SGLT2 inhibitors specifically for cardiotoxicity prevention in cancer patients, emerging real-world data and small observational studies suggest a potential cardioprotective role, particularly in

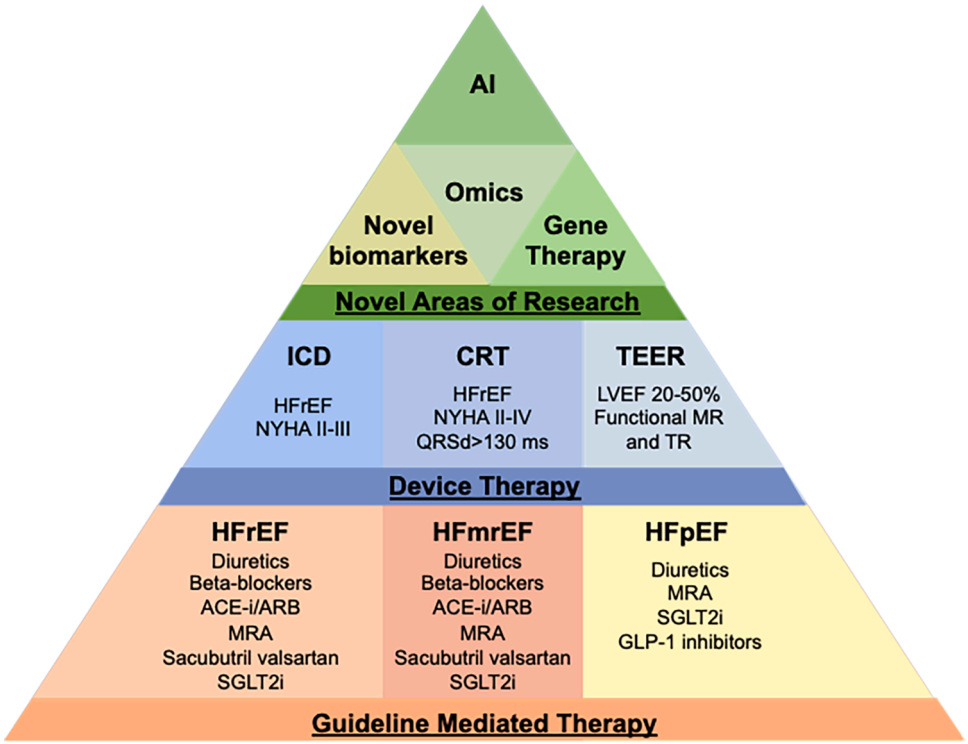

Fig. 1. Current management and future perspective of treatment for heart failure.
Abbreviations:ACE-I: angiotensin-converting enzyme inhibitor; AI: artificial intelligence; ARB: angiotensin II receptor blocker; CRT: cardiac resynchronization therapy; GLP-1: glucagon-like peptide-1; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; MR: mitral regurgitation; NYHA: New York Heart Association; SGLT2i: sodium-glucose cotransporter-2 inhibitor; TEER: transcatheter edge-to-edge repair; TR: tricuspid regurgitation.

patients with diabetes or pre-existing cardiovascular risk factors[118,119]. Their favourable effects on ventricular loading conditions, inflammation, and myocardial metabolism may offer additional benefits in this vulnerable population, warranting further investigation in prospective trials[118].

Dexrazoxane remains the only pharmacological agent conclusively demonstrated to confer cardioprotection against anthracycline-induced CTRCD [120]. However, its clinical use is restricted to patients at very high risk of cardiotoxicity due to high cumulative anthracycline exposure, primarily because of concerns regarding a potential increased risk of secondary malignant neoplasms [120].

7. New avenues in heart failure

HF is a heterogeneous condition that increasingly requires a personalized approach for each individual patient [121]. Growing evidence confirms that inflammation may play a significant role in heart failure, beyond myocarditis, increasing the potential use of biomarkers to aid diagnosis and assess disease progression, as well as anti-inflammatory drugs to potentially improve outcomes [122]. The use of C-reactive protein (CRP) as a biomarker in HF remains controversial, primarily due to its low specificity for cardiac pathology [123]. While elevated CRP levels may reflect systemic inflammation, they are not specific to myocardial injury or dysfunction [123]. However, high-sensitivity CRP (hsCRP) has emerged as a marker of low-grade inflammation and may provide additional prognostic information in patients with HF. Despite this, its clinical utility remains limited by the same lack of disease specificity that affects conventional CRP measurements [124]

Therefore, reliance on CRP or hsCRP alone offers limited value in guiding clinical decision-making. In this context, the identification and application of novel inflammatory biomarkers with greater specificity are essential to enable more accurate risk stratification and the development of targeted therapeutic strategies [122] In addition, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a simple and inexpensive index of systemic inflammation, with established diagnostic and prognostic value in myocarditis. When interpreted alongside cardiac-specific biomarkers, NLR may also provide complementary information for risk stratification in patients with HF [125,126]

Gut dysbiosis and gut-derived metabolites, may also contribute to systemic inflammation and adverse cardiac remodeling and are associated with worse outcomes [127,128]. These findings support the emerging concept of a gut–heart axis, suggesting that modulation of the intestinal microbiome could represent a novel therapeutic target in HF management.

Recent progress in the field of omics—which includes genomics, proteomics, transcriptomics, metabolomics, and epigenomics—holds great promise for the identification of novel biomarkers and therapeutic targets in HF. These approaches allow for in-depth molecular characterisation of disease mechanisms, enabling more precise diagnosis, prognosis, and treatment selection. A notable example is a large-scale study involving >420,000 individuals from the Million Veteran Program, which used integrative genomic and transcriptomic data with Mendelian randomisation to identify 70 therapeutic targets for HFrEF and 10 for HFpEF, of which 58 had not been previously reported [129]. Importantly, the identified targets were non-overlapping between the two HF subtypes, emphasizing the biological divergence and the need for subtype-specific therapeutic strategies [129].

Omics could support therapeutic prioritisation by combining efficacy, safety, novelty, and pharmacology into actionable profiles [130]. Among the most promising targets were IL6R, ADM, and EDNRA for HFrEF, and LPA for both HFrEF and HFpEF [130]. These findings highlight the potential of omics not only for discovering new molecular pathways, but also for refining clinical decision-making—for instance,

by identifying patients who may benefit more from specific pharmacologic agents or advanced therapies such as device implantation [131].

Moreover, the integration of multiomics with polygenic risk scores (PRS) and polygenic response predictors (PRP) may further enhance personalized risk stratification and prediction of therapeutic response [132].

Gene therapy represents one of the emerging therapeutic strategies in cardiovascular medicine, offering the potential to directly target molecular mechanisms of disease [51]. Initially explored in the setting of IHD and cardiomyopathy, its theoretical advantages include disease-modifying effects, long-term efficacy after a single administration, and the ability to address conditions with limited pharmacological options [51]. However, several limitations have so far hindered clinical success, including challenges in vector delivery, transient gene expression, safety concerns, and insufficient understanding of cardiac pathophysiology [51]. Despite these hurdles, ongoing advances in gene editing technologies and delivery systems continue to strengthen its promise, particularly for monogenic cardiomyopathies and selected high-risk populations.

Artificial intelligence (AI) is expected to play an increasingly central role in cardiovascular medicine, particularly in the diagnosis and phenotyping of HF through advanced analysis of imaging, biomarkers, and electronic health records [133,134]. AI-driven tools may enable earlier identification of subclinical dysfunction and more accurate patient stratification [135]. Furthermore, AI can support personalized therapy by predicting treatment response and optimizing clinical decision-making, thus enhancing the precision and efficiency of care in complex patient populations [134].

8. Conclusion

HF is a complex and heterogeneous syndrome with significant clinical and economic implications worldwide. Despite significant advances in the treatment of HFrEF through guideline-based medical therapy and the use of devices, evidence gaps persist for HFmrEF and HFpEF. New concepts such as reverse remodeling, HFimpEF, and the role of genetic testing in non-ischemic HF reflect a shift toward individualized understanding and management of the disease. Looking ahead, omics-based profiling has shown promise in identifying novel therapeutic targets and stratifying patients across HF phenotypes. Gene therapy and AI are also emerging as potential tools, improving the precision and efficiency of care. Further research will be essential to improve HF outcomes. The future of HF management lies in precision and accurate medicine, ensuring equitable access to novel therapies and technologies across healthcare systems.

Fig. 1

Declaration of competing interest

The authors have Nothing to declare.

References

[1] Cook C, Cole G, Asaria P, et al. The annual global economic burden of heart failure. Int J Cardiol 2014;171:368–76. https://doi.org/10.1016/j.ijcard.2013.12.028.

[2] Chen Q-F, Chen L, Katsouras CS, et al. Global burden of heart failure and its underlying causes in 204 countries and territories, 1990-2021. Eur Heart J Qual Care Clin Outcomes 2025;11:493–509. https://doi.org/10.1093/ehjqcco/qcae110.

[3] Parlati ALM, Madaudo C, Nuzzi V, et al. Biomarkers for congestion in heart failure: state-of-the-art and future directions. Card Fail Rev 2025;11:e01. https://doi.org/10.15420/cfr.2024.32.

[4] Savarese G, Becher PM, Lund LH, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res 2023;118:3272–87. https://doi.org/10.1093/cvr/cvac013.

[5] Jordan-Rios A, Cannatà A, Bromage D, et al. Challenges in the implementation of medical therapy in heart failure. JACC Heart Fail 2023;11:607–9. https://doi.org/10.1016/j.jchf.2023.04.001.

[6] Tromp J, Westenbrink BD, Ouwerkerk W, et al. Identifying pathophysiological mechanisms in heart failure with reduced versus preserved ejection fraction. J Am Coll Cardiol 2018;72:1081–90. https://doi.org/10.1016/j.jacc.2018.06.050.

[7] Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992;20:248–54. https://doi.org/10.1016/0735-1097(92)90167-l.

[8] Mebazaa A, Davison B, Chioncel O, 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 Lond Engl 2022;400:1938–52. https://doi.org/10.1016/S0140-6736(22)02076-1.

[9] Virani S, Zieroth S, Aleksova N, et al. Canadian Cardiovascular society/canadian heart failure society 2025 guideline update for pharmacologic management of heart failure with nonreduced ejection fraction (LVEF >40%). Can J Cardiol 2025;41:1857–74. https://doi.org/10.1016/j.cjca.2025.07.027.

[10] Bromage DI, Cannata A, McDonagh TA. Combination diuretic therapy for acute heart failure: "alone we can do so little; together we can do so much. Eur J Heart Fail 2022;24:1611–3. https://doi.org/10.1002/ejhf.2634.

[11] Mullens W, Dauw J, Martens P, et al. Acetazolamide in acute decompensated heart failure with volume overload. N Engl J Med 2022;387:1185–95. https://doi.org/10.1056/NEJMoa2203094.

[12] Trullàs JC, Morales-Rull JL, Casado J, et al. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. Eur Heart J 2023;44:411–21. https://doi.org/10.1093/eurheartj/ehac689.

[13] Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF registry. J Am Coll Cardiol 2007;50:768–77. https://doi.org/10.1016/j.jacc.2007.04.064.

[14] Shah KS, Xu H, Matsouaka RA, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. J Am Coll Cardiol 2017;70:2476–86. https://doi.org/10.1016/j.jacc.2017.08.074.

[15] Sweitzer NK, Lopatin M, Yancy CW, et al. Comparison of clinical features and outcomes of patients hospitalized with heart failure and normal ejection fraction (>or =55%) versus those with mildly reduced (40% to 55%) and moderately to severely reduced (<40%) fractions. Am J Cardiol 2008;101:1151–6. https://doi.org/10.1016/j.amjcard.2007.12.014.

[16] Chioncel O, Lainscak M, Seferovic PM, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC heart failure long-term registry. Eur J Heart Fail 2017;19:1574–85. https://doi.org/10.1002/ejhf.813.

[17] Straw S, Cole CA, McGinlay M, et al. Guideline-directed medical therapy is similarly effective in heart failure with mildly reduced ejection fraction. Clin Res Cardiol 2023;112:111–22. https://doi.org/10.1007/s00392-022-02053-8.

[18] Schupp T, Bertsch T, Reinhardt M, et al. Effect of heart failure pharmacotherapies in patients with heart failure with mildly reduced ejection fraction. Eur J Prev Cardiol 2024;31:1347–60. https://doi.org/10.1093/eurjpc/zwae121.

[19] Solomon SD, Vaduganathan M, Claggett L B, et al. Sacubitril/Valsartan across the spectrum of ejection fraction in heart failure. Circulation 2020;141:352–61. https://doi.org/10.1161/CIRCULATIONAHA.119.044586.

[20] Landucci L, Faxén UL, Benson L, et al. Characterizing heart failure across the spectrum of the preserved ejection fraction: does heart failure with supranormal ejection fraction exist? Data from the swedish heart failure registry. J Am Heart Assoc 2025:e037502. https://doi.org/10.1161/JAHA.124.037502.

[21] Stolfo D, Lund LH, Benson L, et al. Persistent high burden of heart failure across the ejection fraction spectrum in a nationwide setting. J Am Heart Assoc 2022;11:e026708. https://doi.org/10.1161/JAHA.122.026708.

[22] Koh AS, Tay WT, Teng THK, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. Eur J Heart Fail 2017;19:1624–34. https://doi.org/10.1002/ejhf.945.

[23] Cannata A, Mizani MA, Bromage DI, et al. A nationwide, population-based study on specialized care for acute heart failure throughout the COVID -19 pandemic. Eur J Heart Fail 2024;26:1574–84. https://doi.org/10.1002/ejhf.3306.

[24] Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med 2015;175:996. https://doi.org/10.1001/jamainternmed.2015.0924.

[25] Tsao CW, Lyass A, Enserro D, et al. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. JACC Heart Fail 2018;6:678–85. https://doi.org/10.1016/j.jchf.2018.03.006.

[26] Merlo M, Cannatà A, Gobbo M, et al. Evolving concepts in dilated cardiomyopathy. Eur J Heart Fail 2018;20:228–39. https://doi.org/10.1002/ejhf.1103.

[27] Merlo M, Cannatà A, Pio Loco C, et al. Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy. Eur J Heart Fail 2020;22:1111–21. https://doi.org/10.1002/ejhf.1914.

[28] Di Lisi D, Cadeddu Dessalvi C, Zito C, et al. Management of cancer patients at high and very-high risk of cardiotoxicity: main questions and answers. Curr Probl Cardiol 2024;49:102229. https://doi.org/10.1016/j.cpcardiol.2023.102229.

[29] McDonagh TA, Metra M, Adamo M, et al. 2023 Focused update of the 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 Heart J 2023;44:3627–39. https://doi.org/10.1093/eurheartj/ehad195.

[30] Cannata A, Mizani MA, Bromage DI, et al. Heart failure specialist care and long-term outcomes for patients admitted with acute Heart failure. JACC Heart Fail 2025;13:402–13. https://doi.org/10.1016/j.jchf.2024.06.013.
[31] Hulot J, Ter Maaten JM, Bayes-Genis A, et al. Heart failure improvement, remission, and recovery: a *European Journal of Heart Failure* expert consensus document. Eur J Heart Fail 2025;27:1807–19. https://doi.org/10.1002/ejhf.3732.
[32] Hnat T, Veselka J, Honek J. Left ventricular reverse remodelling and its predictors in non-ischaemic cardiomyopathy. ESC Heart Fail 2022;9:2070–83. https://doi.org/10.1002/ehf2.13939.
[33] Boulet J, Mehra MR. Left ventricular reverse remodeling in heart failure: remission to recovery. Struct Heart 2021;5:466–81. https://doi.org/10.1080/24748706.2021.1954275.
[34] Kuchynka P, Podzimkova J, Marek J, et al. Long-term outcomes and reverse remodelling in recently diagnosed unexplained left ventricular systolic dysfunction. ESC Heart Fail 2024;11:859–70. https://doi.org/10.1002/ehf2.14643.
[35] Merlo M, Pyxaras SA, Pinamonti B, et al. Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment. J Am Coll Cardiol 2011;57:1468–76. https://doi.org/10.1016/j.jacc.2010.11.030.
[36] Topkara VK, Garan AR, Fine B, et al. Myocardial recovery in patients receiving contemporary left ventricular Assist devices: results from the Interagency Registry for mechanically assisted circulatory support (INTERMACS). Circ Heart Fail 2016;9:e003157. https://doi.org/10.1161/CIRCHEARTFAILURE.116.003157.
[37] Cannata A, Manca P, Nuzzi V, et al. Sex-specific prognostic implications in dilated cardiomyopathy after left ventricular reverse remodeling. J Clin Med 2020;9:2426. https://doi.org/10.3390/jcm9082426.
[38] Kuchynka P, Podzimkova J, Marek J, et al. Long-term outcomes and reverse remodelling in recently diagnosed unexplained left ventricular systolic dysfunction. ESC Heart Fail 2024;11:859–70. https://doi.org/10.1002/ehf2.14643.
[39] Verdonschot JAJ, Hazebroek MR, Wang P, et al. Clinical phenotype and genotype associations with improvement in left ventricular function in dilated cardiomyopathy. Circ Heart Fail 2018;11:e005220. https://doi.org/10.1161/CIRCHEARTFAILURE.118.005220.
[40] Merlo M, Cannatà A, Sinagra G. Dilated cardiomyopathy: a paradigm of revolution in medicine. J Clin Med 2020;9:3385. https://doi.org/10.3390/jcm9113385.
[41] Riccardi M, Pabon MA, Bhatt AS, et al. Heart failure with improved ejection fraction: definitions, epidemiology, and management. J Am Coll Cardiol 2025;85:2401–15. https://doi.org/10.1016/j.jacc.2025.03.544.
[42] McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599–726. https://doi.org/10.1093/eurheartj/ehab368.
[43] Kodur N, Tang WHW. Management of heart failure with improved ejection fraction. JACC Heart Fail 2025;13:537–53. https://doi.org/10.1016/j.jchf.2025.02.007.
[44] Agostoni P, Pluchinotta FR, Salvioni E, et al. Heart failure patients with improved ejection fraction: insights from the MECKI score database. Eur J Heart Fail 2023;25:1976–84. https://doi.org/10.1002/ejhf.3031.
[45] Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. The Lancet 2019;393:61–73. https://doi.org/10.1016/s0140-6736(18)32484-x.
[46] Cheng L, Hammersley D, Ragavan A, et al. Long-term follow-up of the TRED-HF trial: implications for therapy in patients with dilated cardiomyopathy and heart failure remission. Eur J Heart Fail 2025;27:113–23. https://doi.org/10.1002/ejhf.3475.
[47] Wilcox JE, Fang JC, Margulies KB, et al. Heart failure with recovered left ventricular ejection fraction. J Am Coll Cardiol 2020;76:719–34. https://doi.org/10.1016/j.jacc.2020.05.075.
[48] Garoia F, Capovilla TM, Reginato A, et al. Genetic testing in cardiomyopathies: updates and future perspectives. J Cardiovasc Med 2025;26:386–97. https://doi.org/10.2459/jcm.0000000000001750.
[49] Cannatà A, Merlo M, Dal Ferro M, et al. Association of Titin variations with late-onset dilated cardiomyopathy. JAMA Cardiol 2022;7:371–7. https://doi.org/10.1001/jamacardio.2021.5890.
[50] Porcari A, De Angelis G, Romani S, et al. Current diagnostic strategies for dilated cardiomyopathy: a comparison of imaging techniques. Expert Rev Cardiovasc Ther 2019;17:53–63. https://doi.org/10.1080/14779072.2019.1550719.
[51] Cannatà A, Ali H, Sinagra G, et al. Gene therapy for the heart lessons learned and future perspectives. Circ Res 2020;126:1394–414. https://doi.org/10.1161/CIRCRESAHA.120.315855.
[52] Merlo M, Cannatá A, Vitagliano A, et al. Clinical management of dilated cardiomyopathy: current knowledge and future perspectives. Expert Rev Cardiovasc Ther 2016;14:137–40. https://doi.org/10.1586/14779072.2016.1125292.
[53] Hershberger RE, Cowan J, Jordan E, et al. The complex and diverse genetic architecture of dilated cardiomyopathy. Circ Res 2021;128:1514–32. https://doi.org/10.1161/circresaha.121.318157.
[54] Malgie J, Wilde MI, Brunner-La Rocca H-P, et al. Newly diagnosed heart failure with reduced ejection fraction: timing, sequencing, and titration of guideline-recommended medical therapy. Eur Heart J 2025;46:2394–405. https://doi.org/10.1093/eurheartj/ehaf244.
[55] Madaudo C, Bromage D, Cannata A. Current and future landscape of heart failure management: understanding the present, unraveling the future. Future Cardiol 2025;21:405–9. https://doi.org/10.1080/14796678.2025.2490403.
[56] Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–92. https://doi.org/10.1056/NEJMoa1313731.
[57] Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–Neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381:1609–20. https://doi.org/10.1056/nejmoa1908655.
[58] Cannata A, McDonagh TA. Heart failure with preserved ejection fraction. N Engl J Med 2025;392:173–84. https://doi.org/10.1056/nejmcp2305181.
[59] Greene SJ, Butler J, Kosiborod MN. Chapter 3: clinical trials of sodium-glucose Co-transporter-2 inhibitors for treatment of heart failure. Am J Med 2024;137:S25–34. https://doi.org/10.1016/j.amjmed.2023.04.019.
[60] Solomon SD, McMurray JJV, Vaduganathan M, et al. Finerenone in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2024. https://doi.org/10.1056/NEJMoa2407107. NEJMoa2407107.
[61] Jhund PS, Talebi A, Henderson AD, et al. Mineralocorticoid receptor antagonists in heart failure: an individual patient level meta-analysis. The Lancet 2024;404:1119–31. https://doi.org/10.1016/S0140-6736(24)01733-1.
[62] Palazzuoli A, Beltrami M. The need to understand distinct phenotypes. Front Cardiovasc Med 2021;8:676658. https://doi.org/10.3389/fcvm.2021.676658.
[63] Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus: systematic review and meta-analysis of cardiovascular outcomes trials. Circulation 2019;139:2022–31. https://doi.org/10.1161/CIRCULATIONAHA.118.038868.
[64] Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384:989–1002. https://doi.org/10.1056/NEJMoa2032183.
[65] Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med 2023;389:1069–84. https://doi.org/10.1056/NEJMoa2306963.
[66] Kosiborod MN, Petrie MC, Borlaug BA, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. N Engl J Med 2024;390:1394–407. https://doi.org/10.1056/NEJMoa2313917.
[67] Packer M, Zile MR, Kramer CM, et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. N Engl J Med 2025;392:427–37. https://doi.org/10.1056/NEJMoa2410027.
[68] Deanfield J, Verma S, Scirica BM, et al. Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: a prespecified analysis of the SELECT trial. The Lancet 2024;404:773–86. https://doi.org/10.1016/S0140-6736(24)01498-3.
[69] Inciardi RM, Riccardi M, Savarese G, et al. Tailoring medical therapy for heart failure with preserved ejection fraction. Eur J Heart Fail 2025;27:190–3. https://doi.org/10.1002/ejhf.3558.
[70] Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med 2020;382:1883–93. https://doi.org/10.1056/NEJMoa1915928.
[71] Butler J, McMullan CJ, Anstrom KJ, et al. Vericiguat in patients with chronic heart failure and reduced ejection fraction (VICTOR): a double-blind, placebo-controlled, randomised, phase 3 trial. The Lancet 2025;406:1341–50. https://doi.org/10.1016/S0140-6736(25)01665-4.
[72] Ezekowitz JA, O'Connor CM, Troughton RW, et al. N-terminal Pro-B-type natriuretic peptide and clinical outcomes. JACC Heart Fail 2020;8:931–9. https://doi.org/10.1016/j.jchf.2020.08.008.
[73] Savarese G, Lindberg F, Cannata A, et al. How to tackle therapeutic inertia in heart failure with reduced ejection fraction. a scientific statement of the heart failure association of the ESC. Eur J Heart Fail 2024;26:1278–97. https://doi.org/10.1002/ejhf.3295.
[74] Robles-Mezcua A, Januzzi JL, Pavón-Morón FJ, et al. Effects of sacubitril/valsartan on cardiac remodeling in heart failure with reduced ejection fraction: an integrated study of molecular biomarkers and imaging techniques. Biomed Pharmacother 2025;183:117874. https://doi.org/10.1016/j.biopha.2025.117874.
[75] Skouri H, Girerd N, Monzo L, et al. Clinical management and therapeutic optimization of patients with heart failure with reduced ejection fraction and low blood pressure. a clinical consensus statement of the heart failure association (HFA) of the ESC. Eur J Heart Fail 2025;27:707–22. https://doi.org/10.1002/ejhf.3618.
[76] Simonavičius J, Knackstedt C, Brunner-La Rocca H-P. Loop diuretics in chronic heart failure: how to manage congestion? Heart Fail Rev 2019;24:17–30. https://doi.org/10.1007/s10741-018-9735-7.
[77] Cannatà A, Anastasia G, De Marzo V, et al. Diuretic strategies in acute heart failure: a systematic review and network meta-analysis of randomized clinical trials. Eur Heart J - Cardiovasc Pharmacother 2025:pvaf067. https://doi.org/10.1093/ehjcvp/pvaf067.
[78] Palazzuoli A, Pirrotta F, Stefanini A, et al. Different loop diuretic dosing and administration in acute heart failure (DIUR-AHF): a multicenter prospective observational open-label study. Eur J Intern Med 2025;138:121–8. https://doi.org/10.1016/j.ejim.2025.05.026.
[79] Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–37. https://doi.org/10.1056/NEJMoa043399.

[80] Butt JH, Doi SN, Thune JJ, et al. Long-term effect of ICDs in nonischemic heart failure with reduced ejection fraction. JACC 2025. https://doi.org/10.1016/j.jacc.2025.08.089. S0735109725077654.
[81] Cannatà A, De Angelis G, Boscutti A, et al. Arrhythmic risk stratification in non-ischaemic dilated cardiomyopathy beyond ejection fraction. Heart 2020;106:656–64. https://doi.org/10.1136/heartjnl-2019-315942.
[82] Shen L, Jhund PS, Petrie MC, et al. Declining risk of sudden death in heart failure. N Engl J Med 2017;377:41–51. https://doi.org/10.1056/NEJMoa1609758.
[83] Artico J, Ceolin R, Franco S, et al. ICD replacement in patients with intermediate left ventricular dysfunction under optimal medical treatment. Int J Cardiol 2019;293:119–24. https://doi.org/10.1016/j.ijcard.2019.06.072.
[84] Zusterzeel R, Selzman KA, Sanders WE, et al. Cardiac resynchronization therapy in women: US food and drug administration meta-analysis of patient-level data. JAMA Intern Med 2014;174:1340–8. https://doi.org/10.1001/jamainternmed.2014.2717.
[85] Bozkurt B, Mullens W, Leclercq C, et al. 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. Eur J Heart Fail 2025. https://doi.org/10.1002/ejhf.3641.
[86] Whinnett ZI, Shun-Shin MJ, Tanner M, et al. Effects of haemodynamically atrio-ventricular optimized his bundle pacing on heart failure symptoms and exercise capacity: the his optimized pacing evaluated for heart failure (HOPE-HF) randomized, double-blind, cross-over trial. Eur J Heart Fail 2023;25:274–83. https://doi.org/10.1002/ejhf.2736.
[87] Pipilas DC, Hanley A, Singh JP, et al. Cardiac contractility modulation for heart failure: current and future directions. J Soc Cardiovasc Angiogr Interv 2023;2:101176. https://doi.org/10.1016/j.jscai.2023.101176.
[88] Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018;379:2297–306. https://doi.org/10.1056/NEJMoa1805374.
[89] Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018;379:2307–18. https://doi.org/10.1056/NEJMoa1806640.
[90] Anker SD, Friede T, von Bardeleben R-S, et al. Transcatheter valve repair in heart failure with moderate to severe mitral regurgitation. N Engl J Med 2024;391:1799–809. https://doi.org/10.1056/NEJMoa2314328.
[91] Hahn RT, Makkar R, Thourani VH, et al. Transcatheter valve replacement in severe tricuspid regurgitation. N Engl J Med 2025;392:115–26. https://doi.org/10.1056/NEJMoa2401918.
[92] Kodali S, Hahn RT, Makkar R, et al. Transfemoral tricuspid valve replacement and one-year outcomes: the TRISCEND study. Eur Heart J 2023;44:4862–73. https://doi.org/10.1093/eurheartj/ehad667.
[93] Tang GHL, Hahn RT, Whisenant BK, et al. Tricuspid transcatheter edge-to-edge repair for severe tricuspid regurgitation: 1-year outcomes from the TRILUMINATE randomized cohort. J Am Coll Cardiol 2025;85:235–46. https://doi.org/10.1016/j.jacc.2024.10.086.
[94] Kar S, Makkar RR, Whisenant BK, et al. Two-year outcomes of transcatheter edge-to-edge repair for severe tricuspid regurgitation: the TRILUMINATE pivotal randomized controlled trial. Circulation 2025;151:1630–8. https://doi.org/10.1161/CIRCULATIONAHA.125.074536.
[95] Greene SJ, Fonarow GC, DeVore AD, et al. Titration of medical therapy for heart failure with reduced ejection fraction. J Am Coll Cardiol 2019;73:2365–83. https://doi.org/10.1016/j.jacc.2019.02.015.
[96] Tomasoni D, Benson L, Gatti P, et al. Cardiac resynchronization therapy for enabling guideline-directed medical therapy optimization in heart failure. Eur J Heart Fail 2025. https://doi.org/10.1002/ejhf.3719.
[97] Varshney AS, Butler J, Vaduganathan M. The enabling potential of device therapy for heart failure. J Card Fail 2022;28:1227–9. https://doi.org/10.1016/j.cardfail.2022.02.005.
[98] Dell'Aquila E, Zeppola T, Stellato M, et al. Anti-EGFR therapy in metastatic small bowel adenocarcinoma: myth or reality? Clin Med Insights Oncol 2020;14:1179554920946693. https://doi.org/10.1177/1179554920946693.
[99] Cleland JGF, Pfeffer MA, Clark AL, et al. The struggle towards a universal definition of heart failure-how to proceed? Eur Heart J 2021;42:2331–43. https://doi.org/10.1093/eurheartj/ehab082.
[100] Di Lisi D, Madaudo C, Macaione F, et al. Cancer survivors and cardiovascular diseases: from preventive strategies to treatment. J Cardiovasc Med Hagerstown Md 2025;26:8–17. https://doi.org/10.2459/JCM.0000000000001681.
[101] Strongman H, Gadd S, Matthews A, et al. Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study using multiple linked UK electronic health records databases. Lancet Lond Engl 2019;394:1041–54. https://doi.org/10.1016/S0140-6736(19)31674-5.
[102] Di Lisi D, Madaudo C, Alagna G, et al. The new HFA/ICOS risk assessment tool to identify patients with chronic myeloid leukaemia at high risk of cardiotoxicity. ESC Heart Fail 2022;9:1914–9. https://doi.org/10.1002/ehf2.13897.
[103] Metra M, Coats AJS. Why we love heart failure: an introduction to the universal definition of heart failure. Eur J Heart Fail 2021;23:350–1. https://doi.org/10.1002/ejhf.2168.
[104] Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European hematology association (EHA), the European society for therapeutic radiology and oncology (ESTRO) and the international cardio-oncology society (IC-OS). Eur Heart J 2022;43:4229–361. https://doi.org/10.1093/eurheartj/ehac244.
[105] Bozkurt B, Coats AJS, Tsutsui H, 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;23:352–80. https://doi.org/10.1002/ejhf.2115.
[106] Di Lisi D, Manno G, Madaudo C, et al. Chemotherapy-related cardiac dysfunction: the usefulness of myocardial work indices. Int J Cardiovasc Imaging 2023;39:1845–53. https://doi.org/10.1007/s10554-023-02897-9.
[107] Rossetto L, Di Lisi D, Madaudo C, et al. Right ventricle involvement in patients with breast cancer treated with chemotherapy. Cardio-Oncol Lond Engl 2024;10:24. https://doi.org/10.1186/s40959-024-00224-2.
[108] Henriksen PA. Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. Heart Br Card Soc 2018;104:971–7. https://doi.org/10.1136/heartjnl-2017-312103.
[109] Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of Anthracyclines. Front Cardiovasc Med 2020;7:26. https://doi.org/10.3389/fcvm.2020.00026.
[110] Cardinale D, Colombo A, Torrisi R, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of Troponin I evaluation. J Clin Oncol 2010;28:3910–6. https://doi.org/10.1200/JCO.2009.27.3615.
[111] Heidenreich PA, Bozkurt B, Aguilar D, 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. Circulation 2022;145:e895–1032. https://doi.org/10.1161/CIR.0000000000001063.
[112] Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015;131:1981–8. https://doi.org/10.1161/CIRCULATIONAHA.114.013777.
[113] Clerico A, Cardinale DM, Zaninotto M, et al. High-sensitivity cardiac troponin I and T methods for the early detection of myocardial injury in patients on chemotherapy. Clin Chem Lab Med CCLM 2021;59:513–21. https://doi.org/10.1515/cclm-2020-0362.
[114] Artico J, Abiodun A, Shiwani H, et al. Multimodality Imaging for cardiotoxicity: state of the art and Future perspectives. J Cardiovasc Pharmacol 2022;80:547–61. https://doi.org/10.1097/FJC.0000000000001281.
[115] Bannister C, Tam To B, Patel T, et al. The use of high sensitivity troponin T as a biomarker of anthracycline cardiotoxicity. Eur Heart J 2023;44. https://doi.org/10.1093/eurheartj/ehad655.2718.
[116] Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation 2006;114:2474–81. https://doi.org/10.1161/CIRCULATIONAHA.106.635144.
[117] Georgakopoulos P, Roussou P, Matsakas E, et al. Cardioprotective effect of metoprolol and enalapril in doxorubicin-treated lymphoma patients: a prospective, parallel-group, randomized, controlled study with 36-month follow-up. Am J Hematol 2010;85:894–6. https://doi.org/10.1002/ajh.21840.
[118] Dabour MS, George MY, Daniel MR, et al. The cardioprotective and anticancer effects of SGLT2 inhibitors: JACC: CardioOncology State-of-the-art review. JACC CardioOncology 2024;6:159. https://doi.org/10.1016/j.jaccao.2024.01.007.
[119] Novo G, Madaudo C, Cannatà A, et al. Effects of sodium-glucose cotransporter 2 inhibitors in patients with cancer and diabetes mellitus: a systematic review and meta-analysis. Eur Heart J Cardiovasc Pharmacother 2025;11:343–52. https://doi.org/10.1093/ehjcvp/pvaf028.
[120] de Baat EC, Mulder RL, Armenian S, et al. Dexrazoxane for preventing or reducing cardiotoxicity in adults and children with cancer receiving anthracyclines. Cochrane Database Syst Rev 2022;9:CD014638. https://doi.org/10.1002/14651858.CD014638.pub2.
[121] Shen L, Jhund PS, Docherty KF, et al. Accelerated and personalized therapy for heart failure with reduced ejection fraction. Eur Heart J 2022;43:2573–87. https://doi.org/10.1093/eurheartj/ehac210.
[122] Murphy SP, Kakkar R, McCarthy CP, et al. Inflammation in heart failure. J Am Coll Cardiol 2020;75:1324–40. https://doi.org/10.1016/j.jacc.2020.01.014.
[123] Lichtenauer M, Jirak P, Wernly B, et al. A comparative analysis of novel cardiovascular biomarkers in patients with chronic heart failure. Eur J Intern Med 2017;44:31–8. https://doi.org/10.1016/j.ejim.2017.05.027.
[124] Ferreira JP, Claggett BL, Liu J, et al. High-sensitivity C-reactive protein in heart failure with preserved ejection fraction: findings from TOPCAT. Int J Cardiol 2024;402:131818. https://doi.org/10.1016/j.ijcard.2024.131818.
[125] Cannata A, Segev A, Madaudo C, et al. Elevated neutrophil-to-lymphocyte ratio predicts prognosis in acute myocarditis. JACC Heart Fail 2025. https://doi.org/10.1016/j.jchf.2024.11.003. S2213177924008655.
[126] Madaudo C, Segev A, Bobbio E, et al. Neutrophil-to-lymphocyte ratio for risk stratification in acute myocarditis across the left ventricular ejection fraction spectrum. Eur J Heart Fail 2025:ejhf.70072. https://doi.org/10.1002/ejhf.70072.
[127] Albulushi A, Taha T. Gut microbiome dysbiosis in heart failure: updated evidence, mechanisms, and therapeutic directions. Am Heart J Plus Cardiol Res Pract 2025;59:100633. https://doi.org/10.1016/j.ahjo.2025.100633.
[128] Lupu VV, Adam Raileanu A, Mihai CM, et al. The implication of the gut microbiome in heart failure. Cells 2023;12:1158. https://doi.org/10.3390/cells12081158.
[129] Rasooly D, Giambartolomei C, Peloso GM, et al. Large-scale multi-omics identifies drug targets for heart failure with reduced and preserved ejection fraction. Nat Cardiovasc Res 2025;4:293–311. https://doi.org/10.1038/s44161-025-00609-1.
[130] Lteif C, Huang Y, Guerra LA, et al. Using omics to identify novel therapeutic targets in heart failure. Circ Genomic Precis Med 2024;17. https://doi.org/10.1161/circgen.123.004398.

[131] Bayes-Genis A, Liu PP, Lanfear DE, et al. Omics phenotyping in heart failure: the next frontier. Eur Heart J 2020;41:3477–84. https://doi.org/10.1093/eurheartj/ehaa270.
[132] Jung H, Jung H-U, Baek EJ, et al. Integration of risk factor polygenic risk score with disease polygenic risk score for disease prediction. Commun Biol 2024;7. https://doi.org/10.1038/s42003-024-05874-7.
[133] Madaudo C, Parlati ALM, Di Lisi D, et al. Artificial intelligence in cardiology: a peek at the future and the role of ChatGPT in cardiology practice. J Cardiovasc Med 2024;25:766–71. https://doi.org/10.2459/JCM.0000000000001664.
[134] Yoon M, Park JJ, Hur T, et al. Application and potential of artificial intelligence in heart failure: past, present, and future. Int J Heart Fail 2024;6:11. https://doi.org/10.36628/ijhf.2023.0050.
[135] Xie Y, Zhang L, Sun W, et al. Artificial intelligence in diagnosis of heart failure. J Am Heart Assoc 2025;14. https://doi.org/10.1161/jaha.124.039511.