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Precision Medicine in Heart Failure: from Phenotype-Based Classification to Individualized Therapy

Short title: Precision Medicine in Heart Failure

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Abstract

Heart failure (HF) is a complex and heterogeneous clinical syndrome characterized by substantial variation in etiology, pathophysiology, clinical presentation, and treatment response. Traditional management approaches often fail to account for this diversity, highlighting the need for more individualized strategies. Objective was to review and integrate the concepts of precision medicine, personalized care, and phenotyping in heart failure, and to examine their roles in advancing individualized diagnosis, risk stratification, and therapeutic decision-making. A narrative review of the contemporary literature was conducted, focusing on studies, guidelines, and expert perspectives addressing precision medicine, personalized care models, and phenotypic classification in heart failure. Most studies described as personalized HF care employed individualized treatment adjustment based on clinical status, physiological monitoring, treatment tolerance, or patient-specific management plans rather than biological phenotypes or molecular targets. Relatively few investigations fulfilled criteria for precision medicine, and among these, evidence for improved clinical outcomes remained limited. Genomic studies, biomarker-guided strategies, and machine-learning approaches have enhanced disease classification, risk stratification, and understanding of HF heterogeneity, but their translation into effective phenotype-directed therapies has been inconsistent. Furthermore, many phenotyping frameworks identify statistically distinct subgroups without clear therapeutic implications. Personalized care, precision medicine, and phenotyping represent related but distinct paradigms in HF management. Current evidence shows data on phenotype-guided therapeutic benefit remains limited. Future progress will require biologically validated phenotypes linked to actionable treatment strategies and improved patient outcomes.

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Introduction

Heart failure (HF) is term for structural or functional cardiac abnormalities that impair ventricular filling and/or ejection of blood [1]. HF represents a major global public health challenge that is affecting more than 64 million people globally and imposing a considerable socioeconomic burden on healthcare systems [2]. The prevalence of HF continues to rise despite improvements in cardiovascular care, largely owing to population ageing, increasing survival after myocardial infarction, and advances in evidence-based therapies that prolong life [3]. Epidemiological data suggest that although age-adjusted HF incidence has stabilized or declined in many high-income countries, the overall number of affected individuals is increasing because of demographic transitions and the growing burden of cardiometabolic risk factors [4]. Furthermore, HF is associated with frequent hospitalizations, reduced quality of life, and persistently high mortality rates despite therapeutic advances [5, 6]. The epidemiological profile of HF has evolved with growing proportion of patients presenting with heart failure with preserved ejection fraction (HFpEF), particularly among older adults and women [7].

The American College of Cardiology/American Heart Association (ACC/AHA) staging system categorizes HF progression from individuals at risk (Stage A) to advanced disease (Stage D), whereas the New York Heart Association (NYHA) functional classification assesses symptom severity and exercise limitation from Class I to IV [8, 9]. In addition, HF is commonly classified according to left ventricular ejection fraction into heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF) [10, 11]. HF can be clinically classified using the Stevenson bedside hemodynamic framework into “wet” (congested) or “dry” (non-congested) states and “warm” (adequately perfused) or “cold” (hypoperfused) states, generating four profiles: warm–dry, warm–wet, cold–dry, and cold–wet [12, 13]. Congestion is the dominant presentation in acute HF, with approximately 70–95% of hospitalized patients exhibiting a

“wet” profile, while the warm–wet phenotype is the most frequent clinical presentation [14, 15]. The wet–cold profile is associated with the worst prognosis, whereas warm–dry patients generally experience the most favorable outcomes [12, 15]. From an epidemiological perspective, HF affects more than 64 million people worldwide, making it a major global public health challenge [16, 17].

Recent literature has recognized the marked heterogeneity of the syndrome and studies are seeking tailored treatment according to clinical phenotype, comorbidities, biomarkers, patient preferences, and risk profile [18, 19]. Patient-centered heart failure management integrates guideline-directed medical therapy with individualized assessment of congestion, frailty, renal function, and lifestyle goals, thereby improving outcomes while supporting shared decision-making [20, 21]. In addition, precision approaches, including phenotype-guided treatment selection [18], the use of advanced risk stratification tools and digital technologies [22], and targeted management of specific heart failure subgroups, can help optimize therapeutic benefit and reduce unnecessary interventions [19, 20].

The growing recognition that heart failure encompasses multiple biological and clinical entities has challenged the traditional “one-size-fits-all” management paradigm. Precision medicine, personalized care, and phenotyping have emerged as interconnected frameworks that seek to align therapeutic decisions with individual disease characteristics and patient needs. However, these concepts are often used interchangeably despite important distinctions in their scope and application. An integrated review is therefore needed to clarify their relationships.

Trials of Personalized/Individualized Care in Heart Failure

Although popular trials are frequently done and described as examples of personalized or individualized care, their personalization strategies differ substantially from phenotype-driven precision medicine (Table-1). Across studies such as myPACE, ALLEViate-HF, IT-HEART, and POLY-HF and study of Shen *et al.* treatment adaptation was

primarily based on individual clinical characteristics, physiological monitoring, treatment tolerance, risk alerts, or patient-specific management plans rather than on biological phenotypes, genetic profiles, molecular biomarkers, omics data, or formal subgroup classification. In other words, personalization was operational and management-oriented adjusting therapies, pacing settings, medication sequences, dosing, or monitoring intensity according to a patient’s evolving clinical status—rather than mechanistically targeting distinct biological disease pathways. These studies therefore represent individualized care delivery and treatment optimization, but not precision medicine in the contemporary sense. Personalization in these studies was generally achieved through individualized treatment adjustment rather than formal phenotyping. Shen *et al.* tailored treatment sequencing and titration to patients’ clinical status, tolerance, and expected benefit, representing treatment-sequencing personalization rather than phenotype-driven care [23]. The myPACE trial individualized pacemaker settings using patient-specific physiological characteristics but did not stratify patients into HFpEF subgroups [24]. Similarly, ALLEVIATE-HF and INTER-

VENE-HF used continuous physiologic monitoring and risk-based alerts to guide individualized diuretic and medication adjustments according to predefined patient-specific plans [25, 26]. The IT-HEART trial personalized care through tailored self-management plans and telemonitoring-guided interventions [27]. In POLY-HF, personalization was limited to individualized beta-blocker dosing, without formal phenotyping or predictive classification [28]. The Yee *et al.* [29] study evaluated device-based personalization through automated intrinsic antitachycardia pacing (iATP) and TriageHF risk monitoring algorithms that adapt therapy according to sole real-time physiological and device-derived data. ASSIST-HF shifts the focus from biological personalization to personalized care delivery. A generative AI-supported virtual assistant guided GDMT optimization through frequent remote interactions delivered by non-physician staff. This model recognizes an often overlooked reality: many HF patients do not receive precision medicine because evidence-based therapies are inadequately implemented. However, ASSIST-HF should not be confused with biological precision medicine. The AI system did not identify genetic

Table 1. Characteristics of Personalized Care Strategies in Heart Failure Clinical Trials

Study	Year	HF Type	Personalization Target	Personalization Method	Data Used
Shen <i>et al.</i> [23]	2022	HFrEF	Therapy sequencing	Accelerated GDMT titration	Clinical status, tolerability
myPACE [24]	2023	HFpEF	Pacing rate	Personalized backup HR	Height, EF, resting HR
ALLEVIATE-HF [25]	2026	HF	Diuretic therapy	Risk-triggered escalation	ICM physiologic signals
INTERVENE-HF [26]	2021	HFrEF	PRN medication	Risk-guided intervention	TriageHF score, device metrics
IT-HEART [27]	2026	HF	Self-management	Tailored telemonitoring	Symptoms, vitals, self-care data
POLY-HF [28]	2026	HFrEF	Drug dosing	Tailored β -blocker dose	Clinical assessment
Yee <i>et al.</i> [29]	2025	HF/ICD patients	ATP & HF monitoring	Automated device algorithms	iATP, TriageHF, device signals
ASSIST-HF [30]	2026	HFrEF	Clinical status	GDMT Optimization	Virtual assistance based on clinical data
GUIDE-IT [30]	2017	HFrEF	Therapy titration	NT-proBNP-guided care	NT-proBNP levels

subgroups, molecular pathways, or therapeutic responders. Instead, it individualized care processes and treatment intensification [30]. Abbreviations: HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; GDMT, guideline-directed medical therapy; HR, heart rate; EF, ejection fraction; ICM, insertable cardiac monitor; PRN, pro re nata (as needed); iATP, intrinsic antitachycardia pacing.

Phenotype-guided trails of Precision Medicine in Heart Failure

The promise of precision medicine in HF is to move beyond broad syndromic classifications such as HFrEF or HFpEF and instead identify biologically meaningful subgroups that can receive targeted therapies. The literature provided represent several major approaches to precision medicine (Table-2); but precision medicine ideally requires confirmation that the therapeutic target is present in the individual patient before treatment, that is not mainly targeted by literature. Among the studies reviewed, GENETIC-AF arguably comes closest to a true precision medicine trial design. Patients were prospectively selected based on the ADRB1 Arg389Arg genotype and randomized to bucindolol or metoprolol [31]. The genotype had prior biological plausibility because bucindolol's pharmacological effects were believed to interact with β 1-adrenergic receptor signaling. Investigators subsequently identified additional "precision therapeutic phenotypes" involving disease chronology, including time from HF diagnosis and timing of AF onset relative to HF onset. This finding is revealing. A single genetic marker proved insufficient to explain treatment response. Instead, meaningful heterogeneity emerged only when genetic information was combined with clinical trajectory data [31]. This suggests that precision medicine in HF may require multi-dimensional phenotyping integrating genomics with disease evolution rather than relying on isolated variants.

The prospective validation of CoDE-HF represents a different precision medicine paradigm. Rather than identifying therapeutic targets, the algorithm improves diagnostic

classification by integrating NT-proBNP with multiple clinical variables to estimate individualized probabilities of acute HF. Compared with conventional natriuretic peptide thresholds, CoDE-HF demonstrated improved discrimination and calibration, particularly among patients without prior HF and among those with pre-existing HF where standard NT-proBNP thresholds perform poorly [32]. The CUPID-2 trial represents one of the earliest attempts to apply mechanism-based precision medicine in HFrEF. The intervention was designed around a specific molecular abnormality: reduced activity of sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA2a), a key regulator of intracellular calcium handling in failing myocardium. Rather than targeting symptoms or neurohormonal pathways, investigators attempted to correct a presumed causal molecular defect through intracoronary delivery of AAV1/SERCA2a gene therapy [33]. However, from a precision medicine perspective, the trial's phenotyping strategy was surprisingly crude. Patients were selected based on conventional clinical criteria, reduced ejection fraction, NYHA class II–IV symptoms, elevated natriuretic peptides, and recent HF hospitalization, rather than direct evidence of SERCA2a deficiency or impaired calcium cycling [33]. Consequently, the trial assumed that all enrolled patients shared the same pathogenic mechanism and the intervention was biologically targeted, but the population was not biologically stratified.

The ATTRIBUTE-CM trial evaluating acoramidis represents one of the most successful examples of precision medicine in cardiovascular disease. Patients were selected based on a clearly defined molecular disease entity: transthyretin amyloid cardiomyopathy (ATTR-CM). They demonstrated significant improvements in hierarchical clinical outcomes, functional status, and biomarkers [34]. Unlike CUPID-2, patient selection was directly linked to the therapeutic mechanism. Acoramidis stabilizes transthyretin tetramers, preventing dissociation and amyloid formation [34]. All enrolled patients had documented ATTR-CM, meaning the target pathology was present by design. However, ATTR-CM differs fundamentally from common HFrEF and HFpEF. It is a relatively discrete molec-

ular disease with a single dominant pathogenic pathway. The Genetic Risk Assessment of Heart Failure in African Americans (GRAHF) substudy of A-HeFT moved beyond conventional clinical phenotyping by investigating the CYP11B2 aldosterone synthase promoter polymorphism. McNamara *et al.* demonstrated that carriers of the -344C allele had significantly worse HF outcomes and higher mortality than TT homozygotes [35]. Furthermore, treatment response to fixed-dose isosorbide dinitrate-hydralazine appeared greater among TT genotype carriers [35]. Although A-HeFT successfully addressed a historically underrepresented population, race is an imperfect surrogate for genetic diversity. Using African American identity as a biological category risks conflating social, environmental, and genetic determinants of disease. Modern precision medicine increasingly favors direct molecular characterization over race-based stratification.

GUIDE-IT [36] incorporated a biomarker into treatment personalization by using serial NT-proBNP measurements to guide therapy intensification. However, patients were not classified into distinct biological or clinical phenotypes, and the same NT-proBNP target was applied across all participants. Therefore, the trial represents biomarker-guided management rather than true phenotype-driven precision medicine. The CHARM pharmacogenomic analysis illustrates both the potential and limitations of genome-wide approaches in HF. Investigators identified rs66886237 near GFRA2 as strongly associated with progression of HFpEF but found no significant genetic predictors of candesartan efficacy or safety [37].

Genome-wide assessments in heart failure

(HF) for phenotyping

Large-scale genomic studies have demonstrated that patients classified within the same HF phenotype frequently exhibit substantial biological heterogeneity that suggests that conventional clinical phenotypes often represent aggregated syndromes rather than discrete disease entities. For example, genome-wide association analyses from the HERMES consortium revealed distinct genetic architectures across HFrEF, HFpEF, and non-ischemic HF, indicating that current classifications may obscure important mechanistic differences that influence disease progression and therapeutic responsiveness [38]. Similarly, integrative genomic and imaging studies have shown that genetic variants associated with ventricular remodeling, myocardial structure, and cardiac function do not uniformly distribute across clinically defined HF populations, reinforcing the concept that molecular endotypes may be more informative than traditional phenotypes for understanding disease biology [39]. However, while these findings support a transition toward genomically informed phenotyping, it is important to recognize that genetic variation alone explains only a modest proportion of HF risk and clinical variability. The multifactorial nature of HF, involving complex interactions among genetic, environmental, metabolic, and social determinants, limits the ability of genomic data to fully characterize disease heterogeneity. Consequently, genome-wide assessments should be viewed not as replacements for conventional phenotyping but as complementary tools that refine disease classification by uncovering latent biological mechanisms that are invisible to routine clinical evaluation.

The concepts of personalized care and precision medicine, although frequently used inter-

Table 2. Major operationalized strategies of precision medicine in HF

Strategy	trials	Strength	Major Limitation
Molecular targeting	CUPID-2, ATTRIBUTE-CM	Targets disease biology directly	Often lacks molecular confirmation in individual patients
Pharmacogenomics	A-HeFT, GENETIC-AF, CHARM	Identifies genetic heterogeneity	Limited replication and weak clinical actionability
Machine-learning phenotyping	CoDE-HF	Individualized risk estimation	Limited mechanistic insight

changeably, represent distinct yet overlapping objectives within HF management. Personalized care traditionally emphasizes tailoring treatment to the individual patient's preferences, comorbidities, and clinical circumstances, whereas precision medicine seeks to align therapeutic decisions with measurable biological characteristics, including genomic profiles and molecular pathways. Genome-wide assessments have advanced precision medicine by enabling identification of genetically defined subgroups with differential prognostic trajectories and therapeutic implications. The clearest example is observed in inherited cardiomyopathies, where pathogenic variants in genes such as *LMNA*, *FLNC*, and *DSP* directly influence decisions regarding implantable cardioverter-defibrillator placement and family screening strategies [40]. Nevertheless, the broader application of precision medicine in HF remains constrained by several challenges. Polygenic risk scores and GWAS-derived biomarkers have demonstrated statistically significant associations with disease susceptibility, yet their incremental clinical utility beyond established risk factors remains modest and insufficient for routine implementation [38, 41]. Furthermore, there is a persistent risk of genetic determinism, whereby complex disease processes are oversimplified through an excessive focus on genomic information while underestimating environmental exposures and dynamic disease evolution. Therefore, the true value of genome-wide assessments may not lie in predicting individual outcomes with certainty but rather in redefining HF as a spectrum of biologically distinct disorders that require mechanism-based rather than symptom-based management. From this perspective, precision medicine should be interpreted not as the delivery of individualized genomic therapy to every patient, but as the progressive integration of genomic, clinical, imaging, and multi-omic data to improve the accuracy, specificity, and biological relevance of clinical decision-making.

Limitations of Precision Medicine in Heart Failure Care

A central limitation across the literature is the persistent gap between improved prognostic discrimination and demonstrable improve-

ment in patient outcomes. The American Heart Association scientific statement emphasized that multi-omics technologies have substantially expanded mechanistic understanding of HF, yet robust evidence demonstrating routine clinical utility of omics-guided therapeutic decision-making remains scarce, reflecting a recurring challenge throughout precision medicine research in HF management [42]. Among precision medicine approaches, patient phenotyping and risk stratification have received the greatest methodological attention. Nagai *et al.* argued that conventional risk prediction models inadequately capture HF heterogeneity because they rely on static clinical variables and often demonstrate inconsistent external validity across populations [43]. Similarly, American Heart Association scientific statement indicate that genomic and molecular signatures frequently explain only a fraction of observed clinical variability that might be limiting their predictive value when applied independently from clinical and environmental factors [42]. These concerns are reinforced by contemporary HFpEF literature, where phenotype clustering has been proposed as a means of overcoming the limitations of LVEF-based classifications. Rasalam *et al.* noted that HFpEF represents a collection of distinct syndromes rather than a single disease entity and argued that therapeutic response may be more strongly determined by underlying phenotypic clusters than by traditional LVEF thresholds alone [44]. However, Marut *et al.* critically questioned whether machine learning-derived phenotypes genuinely improve clinical decision-making or merely generate statistically distinct groups lacking therapeutic implications; this effort showed that the risk of data-driven overclassification exists without biological validation [45]. Consequently, while phenomapping improves disease characterization, evidence that it consistently changes outcomes remains limited. Comparable challenges are evident in studies examining statistical treatment optimization. Virkud *et al.* applied random forests, residual weighted learning, and efficient augmentation relaxed learning algorithms to identify individualized treatment rules among HF patients using Medicare claims data [46]. Their analysis suggested that precision treatment

allocation could increase survival free from HF readmission by approximately nine days compared with universal treatment strategies. While statistically innovative, the clinical significance of such gains remains debatable. Natriuretic peptides are among the most extensively validated prognostic biomarkers in HF and have repeatedly demonstrated strong associations with mortality and hospitalization risk. However, prognostic utility has not translated into therapeutic utility. The GUIDE-IT trial, one of the largest biomarker-guided HF studies, found no significant difference between NT-proBNP-guided therapy and usual care for the primary endpoint of cardiovascular mortality or HF hospitalization (HR 0.98, 95% CI 0.79–1.22; $P=0.88$) [36]. The study was terminated early for futility, underscoring a critical lesson for precision medicine: biomarkers capable of predicting outcomes are not necessarily effective tools for guiding treatment decisions. Consistent with these findings, Allach *et al.* concluded that despite substantial advances in biomarker discovery, evidence supporting routine biomarker-guided treatment strategies remains insufficient, and the field continues to rely primarily on biomarkers for risk stratification rather than therapeutic personalization [47]. Recent attempts to integrate multimodal monitoring and AI-driven analytics seek to overcome these limitations by combining biomarkers, imaging, hemodynamic monitoring, and electronic health records into unified decision-support systems. Zhang *et al.* proposed that multimodal AI frameworks may improve risk prediction, phenotyping, diagnosis, and therapeutic selection by leveraging complementary information across diverse data streams [48]. Similarly, Allach *et al.* advocated combining serial biomarker measurements with invasive and non-invasive monitoring technologies to create dynamic rather than static models of disease progression [47]. However, the literature remains dominated by retrospective validation studies reporting discrimination metrics such as C-statistics and area under the receiver operating characteristic curve rather than prospective evidence demonstrating improved clinical outcomes. Petrescu *et al.* argued that arterial stiffness and ventricular–vascular coupling represents

critical determinants of HF pathophysiology that are largely ignored by current precision medicine models [49]. Their proposed integration of pulse wave velocity into multidimensional phenotyping frameworks is conceptually attractive because vascular dysfunction contributes substantially to HF progression, particularly in HFpEF. However, much of the supporting evidence remains associative rather than interventional. The ability of vascular phenotyping to improve risk prediction does not automatically imply that modifying vascular parameters will improve outcomes. Similar concerns apply to broader omics-based precision medicine approaches, where biological plausibility frequently exceeds therapeutic evidence [42,43, 49].

Statistical considerations in precision medicine

Advanced statistical approaches have become central to the evolution of precision medicine in heart failure, moving beyond conventional average treatment effect analyses toward individualized treatment estimation and patient-specific decision-making. Li *et al.* employed a sophisticated causal machine-learning framework to emulate the DAPA-HF trial using electronic health record data, combining Cox proportional hazards models with a Meta-S learner and decision tree-based heterogeneous treatment effect (HTE) stratification. Although no significant treatment effect was observed in the overall cohort (HR 1.681, 95% CI 0.828–3.413; $P=0.1507$), HTE analysis uncovered a subgroup with substantial benefit from dapagliflozin (HR 0.203, 95% CI 0.087–0.476; $P=0.0002$) and another with significantly increased mortality risk (HR 6.680, 95% CI 2.759–16.171; $P<0.0001$), illustrating how conventional trial analyses may obscure clinically meaningful treatment heterogeneity [50]. Similarly, Virkud *et al.* integrated causal inference principles with machine-learning algorithms, including random forests, residual weighted learning, and efficient augmentation relaxed learning, to derive individualized treatment rules from Medicare claims data. Their findings suggested that tailored treatment allocation improved survival free from heart failure readmission compared with uni-

versal treatment strategies, highlighting the potential of dynamic treatment regime methodology to optimize therapeutic selection at the individual level [46]. Extending precision medicine beyond treatment allocation, Qian *et al.* applied large-scale in silico electrophysiological modelling to 2,627 UK Biobank participants and 359 patients with ischemic heart disease, creating virtual populations to evaluate sex-specific cardiac resynchronization therapy (CRT) eligibility criteria. Through simulation-based statistical modelling of conduction abnormalities and cardiac geometry, the investigators demonstrated that conventional QRS duration thresholds systematically misclassified women, whereas height-indexed QRS duration improved diagnostic performance and reduced sex-related selection bias [51].

Discussion

Our findings provide a deep interpretation of the evolving concepts of precision medicine, personalized care, and phenotyping in HF than many contemporary reviews. While recent narrative reviews have portrayed HF management as increasingly transitioning toward precision medicine through integration of genomics, biomarkers, digital health technologies, and artificial intelligence, the actual evidence base remains substantially less mature than often implied. For example, Palaparthi *et al.* emphasized molecular diagnostics, pharmacogenomics, biomarker-guided management, and technology-enabled interventions as transformative components of personalized HF care that is suggesting a paradigm shift away from conventional population-based treatment approaches; however, their review largely highlights emerging tools and future opportunities rather than demonstrating consistent clinical outcome benefits from phenotype-directed therapies in routine practice [52]. Similarly, recent reviews of HF therapeutics have positioned genetic testing, advanced imaging, and biomarker-guided strategies as central pillars of individualized management, yet simultaneously acknowledge persistent implementation barriers, limited validation, and uncertainty regarding real-world effectiveness, findings

that align closely with our observation that most so-called “precision” approaches currently function primarily as enhanced risk stratification or disease characterization tools rather than mechanisms for selecting proven phenotype-specific therapies. The distinction between precision medicine and personalized care is particularly important. Our review found that the majority of studies described as personalized HF care actually involve individualized treatment adjustment based on symptoms, physiological monitoring, treatment tolerance, comorbidities, patient preferences, or multidisciplinary management plans rather than biologically defined phenotypes. This contrasts with the conceptual framework proposed by Ahmad *et al.*, who argued that true precision care should be founded on the “trifecta” of biology, biomarkers, and big data, moving beyond conventional classifications such as ejection fraction toward mechanistically informed disease subgroups. Their commentary on the BIoSTAT-CHF analyses demonstrated that biomarker-network approaches can reveal distinct molecular signatures between HF_rEF and HF_pEF, supporting the biological heterogeneity of HF, yet they also acknowledged that such discoveries remain largely exploratory and have not yet translated into actionable therapeutic algorithms [53]. Likewise, Shah [54] highlighted HF_pEF as a prototypical condition for precision medicine because of its marked heterogeneity and repeated failures of one-size-fits-all therapeutic strategies, advocating deep phenotyping, machine learning, genomics, and novel trial designs to identify biologically meaningful subgroups. Nearly a decade later, however, many proposed HF_pEF phenotypes remain statistically derived constructs with uncertain mechanistic validity and limited therapeutic implications, reinforcing our conclusion that phenotyping alone should not be equated with precision medicine. Similar themes emerge in the recent review by Wu *et al.* [55] focusing on HF with mildly reduced ejection fraction (HF_{mr}EF), where advanced imaging, biomarkers, genomics, and artificial intelligence are proposed as foundations for future precision-based management. Although the authors correctly emphasize the heterogeneity of HF_{mr}EF and the potential value of

phenotype-specific assessment, they also acknowledge that much of the current evidence is extrapolated from broader HF populations and that direct evidence supporting precision-guided interventions remains sparse.

Conclusion

Literature demonstrates substantial progress in understanding HF heterogeneity and in developing increasingly sophisticated methods of patient classification, but they also reveal a recurring gap between identification of phenotypes and demonstration of improved clinical outcomes through phenotype-targeted treatment. Our findings therefore extend prior literature by emphasizing that personalized care, phenotyping, and precision medicine represent overlapping but distinct concepts. Current HF management has clearly advanced toward greater individualization; however, most clinical applications remain personalized rather than truly precision-based, and the evidence supporting phenotype-guided

therapeutic benefit remains limited. Future progress will depend not merely on generating increasingly complex phenotypic classifications but on validating biologically coherent phenotypes linked to actionable treatment strategies and demonstrable improvements in patient-centered outcomes.

Conflict of Interest

The authors declare no conflict of interest.

AI Disclosure Statement

During the preparation of this manuscript, the authors used ChatGPT, OpenAI company for language editing, grammar improvement, and liboberry.com for reference management. After its use, the authors thoroughly reviewed, verified, and revised all AI-assisted content to ensure accuracy and originality. The authors take full responsibility for the integrity and final content of the published article.

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