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REVIEW

Mildly symptomatic heart failure with reduced ejection fraction: diagnostic and therapeutic considerations

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Abstract

Aims Whereas up to about half of patients with heart failure with reduced ejection fraction (HFrEF) report no or only mild symptoms and are considered as clinically stable, the progressive nature of HFrEF, often silent, renders clinical stability a misleading situation, especially if disease progression is unrecognized. We highlight the challenges in the definition of clinical stability and mild symptomatic status in HFrEF, outline clinical characteristics and available diagnostic tools, and discuss evidence and gaps in the current guidelines for the management of these patients.

Methods and Results This is a state-of-the-art review that focuses on clinical, diagnostic, and therapeutic aspects in mildly symptomatic HFrEF patients; summarizes the challenges; and proposes directions for future research in this group of patients. The New York Heart Association classification has been widely used as a measure of prognosis in HFrEF, but it lacks objectivity and reproducibility in terms of symptoms assessment. The definition of clinical stability as described in current guidelines is vague and may often lead to underdiagnosis of disease progression in patients who appear to be 'stable' but in fact are at an increased risk of clinical worsening, hospitalization, or death. Although an increasing number of clinical trials proved that the efficacy of HFrEF therapies was unrelated to the symptomatic status of patients and led to their implementation early in the course of the disease, clinical inertia in terms of under-prescription or underdosing of guideline-recommended medications in mildly symptomatic HFrEF patients is still a challenging issue to deal with.

Conclusions Mildly symptomatic status in a patient with HFrEF is very frequent; it should not be ignored and should not be regarded as an index of disease stability. The application of risk scores designed to predict mortality and mode of death should be engaged among mildly symptomatic patients, not only to identify the most suitable HF candidates for cardioverter defibrillator implantation, but also to identify patients who might benefit from early intensification of medical treatment before the implementation of more interventional approaches.

Keywords Heart failure with reduced ejection fraction; Mildly symptomatic status; Clinical stability

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Introduction

Heart failure with reduced ejection fraction (HFrEF) is a chronic progressive condition with an overall prevalence of 1–2% among adults, characterized by an ongoing structural and functional deterioration.[1] Despite significant therapeutic advances in the past two decades, mortality in HFrEF remains high even among mildly symptomatic patients, with a 2 year mortality of ~14%.[2] Although about half of patients with HFrEF have no or only mild symptoms, approximately one-quarter of outpatients with stable HFrEF will either die or need an advanced therapeutic option, such as implantable

cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) within 3 years.[3] Interestingly, although patients with New York Heart Association (NYHA) class I–II symptoms have better prognosis than have those with class III–IV symptoms, disease progression is also evident among these mildly or non-symptomatic patients.[3] Therefore, the progressive nature of HFrEF, silent at times, renders clinical stability elusive, especially if disease progression is unrecognized.[4]

In this review, we (i) highlight the challenges in the definition of clinical stability and the notion of mild symptomatic status of patients with HFrEF; (ii) outline the clinical characteristics of the mildly symptomatic patient with HFrEF; (iii) summarize the available diagnostic tools (and the associated caveats) for early symptom detection and clinical worsening assessment; and (iv) discuss evidence (and gaps thereof) in the current guidelines for the management of these patients. Finally, we summarize the challenges and directions for future research in this group of patients.

Challenges in the definition of clinical stability and symptomatic status

In the complex course of HF, patients often transition between periods of stability ('chronic HF') and periods of decompensation, usually requiring hospitalization ('decompensated' or 'acute' HF).[5] According to the European Society of Cardiology (ESC) HF guidelines, a patient is 'stable' under HF treatment when symptoms and signs are unchanged for ≥1 month and is 'decompensated' when HF deteriorates, either suddenly or slowly, often leading to hospitalization.[1] In the American Heart Association (AHA) HF guidelines, the terms 'chronic' or 'clinically stable' HF are widely used, mainly to characterize ambulatory patients with HF of different duration and on stable medication doses; however, these terms are not consistently defined.[6] *Table* 1 summarizes all the definitions and their inconsistences and ambiguities regarding HFrEF patients' clinical status according to the ESC and American College of Cardiology Foundation/American Heart Association (AHA) guidelines.

The definition of clinical stability in both guidelines is vague and may lead to underdiagnosis of disease progression in patients who appear to be 'stable', but in fact are at increased risk of clinical worsening, hospitalization, or death. Consequently, despite the need for a comprehensive and operational definition for clinical stability, the line between chronic and acute HF is often blurred. Large HF registries use the term 'outpatients' to characterize clinically stable HF patients. However, about three to four out of 10 'ambulatory' patients in these registries were severely symptomatic with signs of decompensation,[7–9] while the treatment adherence to HF guidelines was low.[8] In the PINNACLE HF study, one out of six patients with 'chronic stable' HFrEF developed clinical worsening within 18 months of HF diagnosis and had a higher risk for 2 year mortality and recurrent HF hospitalizations.[10] The use of standard-of-care therapies both before and after the onset of worsening HF was low, with a great proportion of patients receiving monotherapy.[10]

Clinical trial data suggest that the elevated mortality risk persists for at least 90 days after an admission for HF in patients with HFrEF.[11] However, neither the absence of a prior HF hospitalization nor a mildly symptomatic status can ensure clinical stability.[12,13] In the PARADIGM-HF trial, 20% of patients without prior HF hospitalization experienced a primary endpoint of cardiovascular death or HF hospitalization during the course of the trial. Those apparently 'stable' patients were undertreated in comparison with HFrEF patients who were hospitalized at least once within 12 months.[13] Once these previously 'stable' patients are hospitalized, their stability is disrupted and the risk for further admissions and death is increased thereafter.[12,13] Furthermore, in the recently published DAPA HF trial, 67.5% of enrolled patients were in NYHA II functional class, yet 18.7% of these mildly symptomatic patients experienced clinical worsening or cardiovascular death over a median follow-up of 18.2 months.[14]

Quantification of functional status is often less than straightforward in patients with HFrEF. The NYHA functional classification has been widely used as an inclusion criterion for clinical trials, as a measure of prognosis, and as an eligibility criterion for certain medical and device therapies.[15] However, the NYHA classification lacks objectivity and reproducibility and changes frequently over time.[15,16] There is no specific definition of 'ordinary physical activity', 'slight', and 'marked limitation of physical activity', leading the clinician to place each patient into one of the four groups according to a subjective judgement based on arbitrary questions (*Table* 2).

The presence and severity of reported symptoms are influenced not only by physical status, but also by emotional and psychological well-being. A patient cannot impartially report the physical aspects of a disease in the setting of emotional stress and therefore appears to be more severely affected by atypical symptoms and exaggerates psychological and somatic complaints. Once the psychological impact of the disease is addressed, patients may report improved functional capacity even when the burden of symptoms has remained unchanged.[17] Perception of symptoms may vary markedly among patients and particularly between men and women. For the same symptomatic burden of HF, women tend to report a worse NYHA class than do men.[18]

Mildly symptomatic patients may underestimate their symptoms. Many patients with HF conduct sedentary lives and therefore are expected to report an asymptomatic status, as a level of physical exertion is required for manifestation of symptoms. But even patients who perform some physical activity tend to subconsciously adjust to lower

Table 1 Current definitions of heart failure clinical status according to European Society of Cardiology and American College of Cardiology Foundation/American Heart Association guidelines and relevant inconsistencies or ambiguities

ESC HF Guidelines 2016[1]			ACCF/AHA HF Guidelines 2013[6]		
HF clinical status	Definition	Inconsistencies/ ambiguities	HF clinical status	Definition	Inconsistencies/ ambiguities
Asymptomatic LV systolic dysfunction	Patients with a reduced LVEF who have never exhibited the typical symptoms and/or signs of HF	- Mild symptoms may be underestimated or attributed to other co-morbidities. - Asymptomatic patients are unlikely to seek medical care.	Stage B Asymptomatic LV systolic dysfunction	Structural heart disease without signs or symptoms of HF	- No clarification on the severity of structural heart disease. - The same limitations with the ESC guidelines definition.
Chronic HF	Patients who have had HF for some time	- The exact duration of HF is not clarified. - NYHA classification cannot clearly define the symptomatic status of certain patients. - A patient can be rendered asymptomatic after prompt treatment.	Stage C	Structural heart disease with prior or current symptoms of HF	- This stage includes NYHA II–IV patients, clinically stable, or unstable. - No discrimination in disease severity and patients' clinical status.
Clinically Stable HF	A treated patient with symptoms and signs that have remained 'generally unchanged' for at least 1 month	- The term 'generally unchanged' is subjective to physician's judgement. - Clinical stability should not be interpreted the same way: 1. among stable patients without any HF hospitalization, 2. after patients' first discharge, or 3. among patients with multiple HF hospitalizations.	Stage D	'Refractory', 'advanced', or 'end-stage' HF requiring specialized interventions	- A table with a thorough definition from an ESC position statement is displayed in AHA guidelines.
Decompensated HF	Sudden or slow deterioration of HF, often leading to hospitalization	- The terms 'decompensation/ deterioration' are not clarified/ quantified. - Underdiagnosis of decompensation signs prevents from early treatment escalation and leads to increased hospitalizations. - No clear line between clinically stable and decompensated HF.	Chronic HF or chronic stable HF	Ambulatory patients in stages C and D	- No clear definition for chronic HF. - The term 'ambulatory patients' discriminates them from patients who need hospitalization, but it is too vague to describe patients' clinical status.
Advanced HF	Patients with severe symptoms, recurrent decompensation, and severe cardiac dysfunction	- An ESC position statement on advanced chronic heart failure with a clear definition is cited.	Acute decompensated HF	De novo presentation of HF Worsening of previously chronic stable HF that requires hospitalization	- This general term includes various aetiologies of decompensated HF.
Acute HF	Rapid onset or worsening of symptoms and/or signs of HF First occurrence (de novo) or acute decompensation of chronic HF	- Frequently, the term 'acute HF' is used to describe the 'chronic decompensated HF'.			

ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ESC, European Society of Cardiology; HF, heart failure; LV, left ventricle; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

intensity in order to avoid symptoms and thus, they do not seek medical assistance.[19] Furthermore, patient-reported NYHA class I and II may reflect patients, whose symptoms have a small impact on their already poor functional capacity, such as older patients and patients with severe co-morbidities. The main challenge thus for the physicians is to differentiate HFrEF patients between NYHA classes II and III, because there is no consistent method to assess functional classification. There are neither standard questions that physicians could use nor a proposed way that these are integrated into the consultation with the patient. According to a survey, physicians agreed for only 54% of the assessed patients on the reported NYHA class, a concordance that would be accepted merely by chance.[16] Consequently, there is an urgent need for objective methods to assess functional capacity, such as wearable activity trackers that count patients'

Table 2 New York Heart Association functional classification and definition inconsistences

Class	NYHA functional classification	Inconsistences/ambiguities	Proposal
I	- Patients have cardiac disease but without the resulting limitations of physical activity. - Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea, or anginal pain.	- How is 'ordinary physical activity' defined? - Physical activity varies among different sex, age, body mass indices, and personalities and is also influenced by pulmonary, neurological, or musculoskeletal diseases.	- A specific questionnaire should be created and validated among healthy individuals to determine and quantify ordinary physical activity (duration, intensity, etc.) in order to use as a reference tool.
II	- Patients have cardiac disease resulting in slight limitation of physical activity. - They are comfortable at rest. - Ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain.	- How is 'slight limitation of physical activity' determined? - How is the term 'comfortable' explained? - Many mildly symptomatic patients are familiarized with HF symptoms and feel comfortable up to a significant extent.	- Physical activity should be quantified. - Sex-adjusted, age-adjusted, and BMI-adjusted cut-off values for 'slight' and marked' 'limitation' of physical activity should be provided after validation in a large HF cohort.
III	- Patients have cardiac disease resulting in marked limitation of physical activity. - They are comfortable at rest. - Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.	- How is 'marked limitation of physical activity' determined? - How is 'less than ordinary physical activity' measured?	
IV	- Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. - Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. - If any physical activity is undertaken, discomfort is increased.	- Compared with the previous definitions, NYHA IV class is quite well defined. However, the quantification of 'any physical activity' is necessary. - Does a symptom or sign of acute or chronic low cardiac output syndrome correspond to NYHA IV class?	

NYHA, New York Heart Association.

daily steps under free-living conditions.[20] A more precise definition of NYHA class is also warranted.

Another challenge is that physicians are sometimes influenced by the general clinical status of their patients and the severity of the underlying disease, and thus they use NYHA classification system as an 'HF severity score' and not as a measure of symptom severity.[18] For instance, patients hospitalized for HF worsening may report being mildly symptomatic a few days after receiving intense intravenous diuretics. Clinicians must then decide whether to apply NYHA class IV therapies or only class II therapies, which leads to some uncertainty. This approach may result in misinterpretation of disease severity and lead patients not to receive the maximal guideline-recommended medical therapy.

Clinical characteristics of clinically stable mildly symptomatic heart failure with reduced ejection fraction

According to current guidelines, a clinically stable mildly symptomatic patient with HFrEF is one who has HF with a left ventricular EF (LVEF) of $<$40% for some time, who has been receiving guideline-recommended treatment, and whose NYHA II symptoms and signs have remained unchanged for at least 1 month.[1,6] Such patients constitute 41.5% of real-world chronic HF patients seen at European and Mediterranean outpatient clinics and represents ~69% of all HFrEF symptomatic counterparts, with the remaining 31% having more severe symptoms.[7]

Clinical trials and real-world registries agree that the clinically stable mildly symptomatic HFrEF patient is a young-old (65–74 years old), overweight, male person with HF mainly due to ischaemic heart disease.[21,22] Despite the more favourable co-morbidity profile, this patient carries a considerable burden of coexisting conditions, more commonly coronary artery disease, hypertension, diabetes, atrial fibrillation, and chronic kidney disease.[9,23,24] The main symptom is dyspnoea on exertion and fatigue and less frequently overt signs or symptoms of HF, such as orthopnoea, paroxysmal nocturnal dyspnoea, dyspnoea at rest, peripheral oedema, and jugular vein distention.[25,26] Most of these patients are in sinus rhythm, with one-third of the mild symptomatic population having atrial fibrillation or flutter.[24,27] In terms of intraventricular conduction, QRS duration is shorter than that of NYHA class III/IV patients. In a Swedish registry, about two out of three NYHA II patients had QRS duration of $<$120 ms, while this ratio was lower for the more symptomatic NYHA III/IV patients (63% vs. 56%, $P < 0.001$).[27]

Overall, this is a patient population that physicians encounter in their outpatient practice and is prone to disease severity underestimation because of the relative silent clinical picture. Despite a more benign clinical profile, the mildly

symptomatic patient with HFrEF continues to experience considerable hospitalizations and mortality burden,[10,12,13] with sudden cardiac death being the most prevalent mode of death, while death from worsening HF rises as symptoms worsen.[28] Whether sudden cardiac death represents the main mode of death for both ischaemic and non-ischaemic mildly symptomatic systolic HF patients remains unclear.[29,30]

Diagnostic tools to reduce clinical uncertainties

HF is characterized by a variety of symptoms and signs that may sometimes be nonspecific or resemble those of lung disease, chronic kidney disease, anaemia, obesity, and thyroid disease. The combination of a detailed medical history followed by a thorough physical examination constitutes the cornerstone of HF diagnosis. Additional diagnostic investigations, such as chest X-ray, electrocardiography, transthoracic echocardiography (TTE), natriuretic peptides, and cardiopulmonary exercise testing (CPET) may improve the detection of HF, especially in its early stages (*Table* 3). In a large unselected group of stable primary care outpatients suspected of having HF, diagnostic uncertainty of HF was minimized by means of a detailed medical history and a thorough physical examination. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels further improved the diagnostic accuracy, leading to the diagnosis of HF in 28.7% of the patients with more than one-third of them having systolic HF.[31]

The elderly represent a subgroup of HF patients whose diagnostic assessment may be difficult and often delayed. Clinical manifestations of HF in older adults are often subtle and thus underdiagnosed. Dyspnoea on exertion is easily attributed to ageing or manifests as dry cough and nonspecific complaints of general weakness, insomnia, and palpitations. Peripheral oedema hiding behind age-related venous and renal insufficiency is often ignored, perceived as non-significant

Table 3 Symptoms and signs of patients with heart failure and reduced ejection fraction in New York Heart Association II functional class, who can be underdiagnosed or misinterpreted and diagnostic tools that may increase diagnostic accuracy

Clinical presentation	Diagnostic uncertainties	Diagnostic tools
Dyspnoea on exertion	- May be non-cardiac in origin: • Pulmonary disease • Obesity • Ageing • Pulmonary infection • Psychological factors - May be underestimated: • Reduced physical activity • Subconsciously	- Detailed medical history: • Ischaemic heart disease • Hypertension • Diabetes mellitus • Arrhythmias • Valvular heart disease • Cardiomyopathies • Cardiotoxic drugs • Radiation
Fatigue	- May be non-cardiac in origin: • Anaemia • Obesity • Ageing • Thyroid disease - May be underestimated: • Reduced physical activity • Subconsciously	- Physical examination: • Laterally displaced apex beat • S3 gallop • Increased heart rate • Jugular venous distention • Bilateral ankle oedema • Hepatomegaly
Rales	- May be non-cardiac in origin: • Pulmonic atelectasis • COPD • Pulmonary infection - May be obscured by: •Pulmonic atelectasis • Cardiac asthma • Wheezes and stridor	- Chest X-ray: • Pulmonary congestion • Cardiomegaly • Kerley lines - Electrocardiography: • Any abnormality
Peripheral oedema	- May be non-cardiac in origin: • Medications • Obesity • Renal insufficiency • Venous insufficiency • Deep vein thrombosis	- Transthoracic echocardiography: • LV systolic dysfunction and/or diastolic dysfunction • Valvular dysfunction • Structural heart disease
Palpitations	- May be non-cardiac in origin: • Thyroid disease • Anaemia • Drug toxicity • Psychological factors	- Laboratory tests: • Natriuretic peptides - CPET • Assessment of functional capacity at baseline and during follow-up

CPET, cardiopulmonary exercise testing; NYHA, New York Heart Association; HFrEF, heart failure with reduced ejection fraction.

or as a side effect of pharmacotherapy. An S3 gallop is difficult to distinguish, while pulmonic atelectasis or cardiac asthma obscures pulmonary rales. Jugular venous distention and its correlation with elevated filling pressures and consequently HF underline the importance of a meticulous clinical examination in the elderly.[32] Among 405 older adults with a diagnosis of chronic pulmonary disease from a general practitioner, 20% were newly diagnosed with HF (half of them with systolic HF) when a systematic diagnostic investigation was performed. A medical history of ischaemic heart disease, a laterally displaced apex beat, a high body mass index (BMI), and an elevated heart rate were clinical variables that were highly indicative of concomitant HF, while higher levels of NT-proBNP and an abnormal electrocardiogram further improved the diagnostic accuracy.[33]

Younger patients, on the other hand, have a completely different clinical profile that could also lead to a delayed or even false diagnosis. Despite having more severe LV systolic dysfunction, they report a better NYHA class, probably due to the low burden of co-morbidities.[34] They usually report less dyspnoea at level ground and present less often with peripheral oedema. But when thoroughly examined, signs of HF, such as an S3 gallop, increased heart rate, and even hepatomegaly, are more prevalent and are almost always combined with an abnormal electrocardiogram.

Because NYHA class is a subjective tool for assessing functional status, some alternative outcomes could be used as measures of stability in patients who are enrolled in clinical trials. 'Days alive and out of hospital' (DAOH) or percentage of 'follow-up time alive and out of hospital' (%DAOH) combine together morbidity and mortality by incorporating the components of 'days in hospital' (total of index hospitalization and subsequent hospitalizations), 'days alive and not in hospital', and 'days dead' (the day of the follow-up period that the patient died) into a single measure over a defined time frame (e.g. 30 or 60 days).[5] Patient symptoms and changes in therapy can be incorporated into this measure, forming a clinically composite outcome of 'patient journey', which is virtually a symptom-adjusted DAOH. By the adoption of DAOH and %DAOH, the CHARM trial demonstrated that the treatment benefit of candesartan was mainly due to the reduction of cardiovascular mortality, although the reduction of HF hospitalizations was also significant and consistent across all years of follow-up. In addition, the 'patient journey' revealed that patients in the candesartan group spent more time in a mildly symptomatic or even asymptomatic status.[35]

Furthermore, patient-reported outcome measures could be useful tools for the quantification of the symptom burden in HF. The Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ) are two of the most widely used and validated questionnaires for assessing heart failure-specific quality of life.[36] They have primarily been used in clinical research rather than clinical practice, owing to their time-consuming nature. However, recent data suggest that these scores are independent predictors of major clinical outcomes, such as hospitalization, progression of heart failure, and death, and may provide incremental value to NYHA class.[36,37]

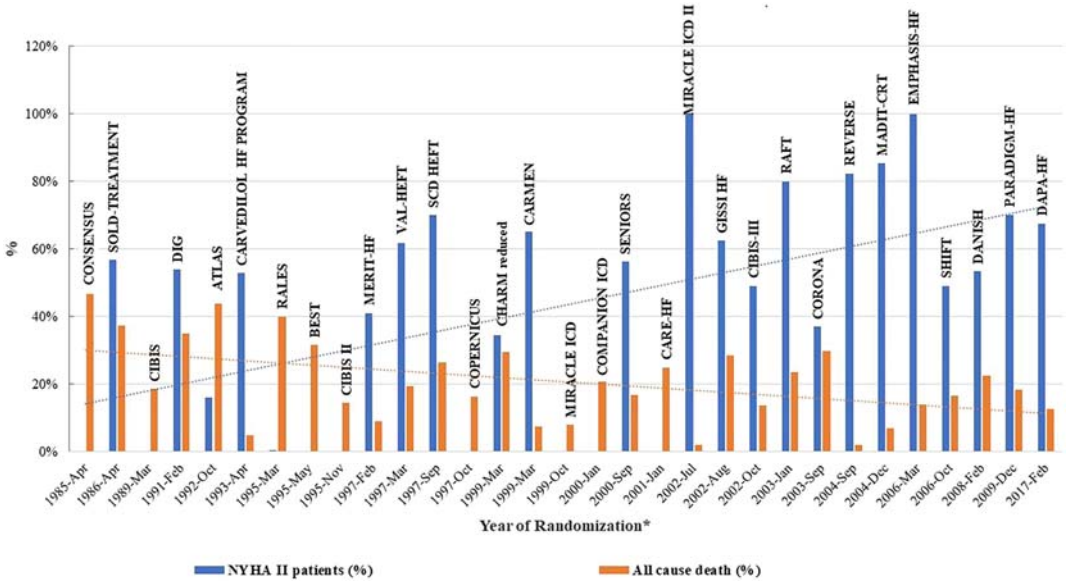
CPET could also play a vital role as an objective tool in assessing functional capacity in HFrEF patients and could serve in diagnosis, risk stratification, and prognosis of this population.[38] It could be applied even in mildly symptomatic elderly patients with co-morbidities, by evaluating symptom-limited CPET parameters derived from submaximal exercise testing, because these patients are usually unable to achieve maximal aerobic power. Repeated tests could predict clinical worsening and guide therapeutic management to prevent major events.

Apart from clinical and patient-reported markers of disease severity, TTE could also play a vital role in the diagnosis, long-term assessment, and prognosis of mildly symptomatic HFrEF patients. Several studies presented LV global longitudinal strain and measures of LV filling pressure and left atrial function, as early markers and independent predictors of all-cause mortality in stable HFrEF patients.[39–41] Furthermore, assessing the increase in inferior vena cava diameter and the trans-tricuspid systolic gradient could predict adverse outcomes, such as HF hospitalization and cardiovascular death.[42] A prospective study also revealed the clinical utility of non-invasive haemodynamic parameters, such as stroke volume and LV filling pressure, in guiding up-titration of HF evidence-based medications and therefore reducing rehospitalizations.[43]

Therapeutic considerations

Evidence-based therapies for HFrEF improve symptoms and quality of life and reduce also morbidity and mortality.[1,6] Although initial trials aimed at more advanced HF, subsequent trials enrolled less symptomatic patients with better functional classification (*Figure* 1, Supporting Information S1). These studies proved that the efficacy of these therapies was unrelated to symptomatic status,[28] leading to their subsequent implementation early in the disease process, including thus, the mildly symptomatic NYHA II patients. Interestingly, a prespecified analysis of the DAPA-HF trial demonstrated that NYHA II patients had a higher benefit from dapagliflozin versus placebo in terms of the primary composite endpoint of worsening heart failure or cardiovascular death in comparison with NYHA III/IV patients.[14] This finding may result in a modified therapeutic approach of the disease, which includes intensified treatment of mildly symptomatic patients to prevent clinical worsening. Furthermore, upfront combination therapy with angiotensin-converting enzyme (ACE) inhibitors/angiotensin

Figure 1 Percentage of NYHA II patients with HFrEF and rate of all-cause death in randomized controlled trials. Initial trials included patients with more advanced HF, while subsequent trials enrolled less symptomatic patients. Blue dotted line depicts the increasing trend of the proportion of NYHA II patients enrolled in randomized clinical trials over the years. Orange dotted line depicts the trend in progressive reduction of all-cause mortality in HFrEF. *Year of randomization represents the date of enrollment of the first patient in each trial. NYHA, New York Heart Association; HFrEF, heart failure with reduced ejection fraction.



receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor agonists (MRAs) is recommended for these 'less sick' patients to counteract as many mechanisms responsible for cardiac dysfunction as possible.

In the context of this compound approach, novel therapies were recently approved for patients with mild symptoms. Among them, sacubitril/valsartan, a combined angiotensin receptor and neprilysin inhibitor (ARNI), proved superior to ACE inhibition,in reducing hard endpoints, such as mortality and HF hospitalizations, not only among all NYHA subgroups,[44] but also across the spectrum of risk in this mostly mildly symptomatic population.[45] The benefit of sacubitril/valsartan over enalapril in patients with no prior or only remote HF hospitalization supports the guideline recommendation to up-titrate HF medications to the maximum tolerated dose and to switch from conventional renin–angiotensin inhibitors to ARNIs, even in the presence of mild HF symptoms.[1,13,46] Similarly, ivabradine should be initiated early in the course of the disease in HFrEF patients who are in sinus rhythm with a heart rate $\geq$ 70 b.p.m. to maintain clinical stability.[47]

Clinical inertia in the form of under-prescription or underdosing of recommended medications in mildly symptomatic patients is a challenging issue.[48] This is even more prominent when combination therapy is considered. Combination therapies with ARNI + beta-blockers + MRAs and ACE inhibitors + beta-blockers + MRAs are more efficacious regarding reduction of all-cause mortality than are double therapies and monotherapies with disease-modifying drugs.[49] However, in HF registries, only half of HFrEF patients receive triple therapy with ACE inhibitors/ARBs, beta-blockers, and MRAs, primarily because of underuse of MRAs, which is often encountered in patients with NYHA class II symptoms.[21] Furthermore, in real-world practice, patients with clinically stable mildly symptomatic HFrEF are being treated at a great extent by non-cardiologists,[21] especially older patients with a higher co-morbidity burden.[9] As a result, these patients may not receive guideline-recommended treatment (and therefore may not have survival benefit), despite the fact that therapy is more amenable to optimization among patients with NYHA class II symptoms.[50]

Devices in HF patients seem to follow the same 'inertia pattern' as disease-modifying drugs, although they have been shown to improve outcomes in selected patients.[51] In the current era of lifesaving evidence-based medication, sudden death has become less frequent in recently diagnosed HFrEF patients, casting doubts on the widespread use of ICDs in this population.[52] Furthermore, the effectiveness of ICDs in reducing all-cause mortality has been in doubt for non-ischaemic HFrEF.[29] On the other hand, in clinically stable mildly symptomatic HFrEF patients with wide QRS, CRT in addition to optimal medical treatment further modifies disease progression and improves survival,[53] mainly in patients with a

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left bundle branch block electrocardiogram morphology.[54] These mildly symptomatic device recipients could also benefit from remote monitoring of their fluid status via intrathoracic impedance, which represents a useful adjunctive clinical tool for the early detection of patients at greater risk for re-hospitalization and predicts all-cause mortality.[55]

Future perspectives

The application of novel risk scores that are designed to predict mortality and mode of death should be engaged among mildly symptomatic patients, not only to identify the most suitable HF candidates for ICD implantation but also to identify patients who might benefit from early intensification of medical treatment before the implementation of more interventional approaches.[56] Several prediction models have been developed in ambulatory HFrEF patients, such as the CHARM (Candesartan in Heart Failure-Assessment of Reduction in Mortality), the GISSI-HF (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure), the MAGGIC (Meta-analysis Global Group in Chronic Heart Failure), the EMPHASIS (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), and the SHFM (Seattle Heart Failure Model) score.[57]

Sudden death is the most prevalent mode of death among NYHA II patients with lower SHFM score, while pump failure contributed most to the mortality of patients with the highest score.[58] In PARADIGM-HF, stable patients with NYHA class II symptoms were at greater risk in terms of cardiovascular mortality and/or HF hospitalizations according to the EMPHASIS-HF and MAGGIC risk score and derived a large absolute benefit from sacubitril/valsartan compared to enalapril, over a relatively short treatment period.[45] These mildly symptomatic stable patients at higher risk should be identified and their heart failure treatment optimized. Nonetheless, even low-risk patients have considerable residual risk, which can further be reduced when evidence-based therapies are implemented.[45] However, these scores are not routinely used in clinical practice, primarily because of their poor reliability at the individual patient level. Recent data from the ESC Heart Failure Long-Term Registry demonstrate the limited performance of major HF risk models in predicting 1-year mortality.[57]

Current HF guidelines do not stratify patients according to risk and propose the same treatment plan for all NYHA II patients, as treatments that specifically fit different levels of risk have not yet been established.[1,6] More prospective studies are warranted to establish the possible benefits that may arise from the early identification of high-risk mildly symptomatic patients and subsequent intensification of HF therapy.

In addition, genetic testing could be useful in the identification of patients at risk of SCD, despite an apparently mild HFrEF phenotype, who could benefit from ICD implantation. For example, patients with non-ischaemic dilated cardiomyopathy due to LMNA, RBM20, and PLN mutations present with higher risk for malignant arrhythmic events than do their counterparts and may have a more rapid course towards advanced heart failure that demands heart transplantation, irrespective of their baseline functional status.[59,60] Consequently, the inclusion of genetic variants in risk stratification algorithms would intensify preventive and therapeutic management in these patients.

Conclusion

Mildly symptomatic status in a patient with HFrEF is frequent, should not be ignored, and should not be regarded as an indicator of disease stability. In the current era, physicians have at their disposal a great arsenal of effective HF treatments that promote clinical stability. Thus, clinicians should be alert in order to promptly recognize these patients and implement evidence-based therapies in a timely fashion and at optimal doses, with the ultimate goal to achieve the best clinical results, until new treatments or new lines of evidence emerge.

Conflict of interest

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Supporting information

Supporting Information S1

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

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