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REVIEW

Implementation of guideline-recommended medical therapy for patients with heart failure in Europe

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Abstract

Physicians' adherence to guideline-recommended heart failure (HF) treatment remains suboptimal, especially regarding the target doses. In particular, there is evidence that non-cardiologists are less compliant with HF guideline recommendations. This is likely to have a detrimental impact on patients' survival, readmissions and quality of life. Thus, the present document aims to address the reasons underlying low implementation and under-dosing of guideline-directed medical therapy in HF and to update a guidance for the initiation and rapid titration of HF drugs. In particular, aim of this document is to provide practical indications for drug implementation, to be applied not only by cardiologists but also by GPs and internal medicine doctors.

Keywords guideline-directed medical therapy; heart failure; phenotypes; worsening heart failure

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Introduction

Heart failure (HF) is a long-term disease, affecting around 63 million people worldwide,[1] with increasing prevalence that mirrors the ageing of the population.[2] Although treatment strategies and overall outcomes of HF patients have improved over time,[3] HF mortality and hospitalization rates remain high, especially in high-risk subgroups.[4] Under-prescription and suboptimal dosing of guideline-directed medical therapy (GDMT) are one of the main reasons. This phenomenon may be due to several clinical and non-clinical factors, such as concerns of side effects, contraindications or even an off-label and subjective physician's choice.[5] In particular, general practitioners (GPs) were found to be less compliant with HF guideline recommendations.[5–7]

Taking into account these issues, this document has been developed in order to assist health professionals to optimize HF medical therapy.

Specifically, aims of this statement are follows: (a) to update the current status of GDMT for the treatment of HF and to discuss its barriers; (b) to highlight implementation strategies, drawing updated indications regarding HF drug initiation and titration. This practical guidance is hopefully applicable to all physicians dealing with HF patients, not just cardiologists.

Current status of HF treatment implementation

Both the two latest major HF guidelines, endorsed by the ESC[3] and the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA),[8] recommend starting from the four major pillars of pharmacological treatment [i.e., angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor-neprilysin inhibitors (ARNi),

beta-blockers, mineralocorticoid receptor antagonists (MRAs) and a sodium-glucose cotransporter 2 inhibitor (SGLT2i)]. Thus, both European and American guidelines recommend *early* initiation and titration of multiple GDMTs.

However, studies on adherence to the dose of recommended drugs showed that a huge percentage of patients were under titrated.[5,9,10] The QUALIFY registry[6] and the ESC-HF Pilot Survey[10] revealed that less than one-third of patients achieved the GDMTs in target doses (TDs). The TSOC-HFrEF registry[9] showed that more than 75% of HF patients did not achieve TDs of ACEI/angiotensin receptor antagonists (ARBs) and β-blockers.

The Evolution HF Study[11] further clarified that initiation of novel GDMTs (dapagliflozin or sacubitril/valsartan) after HF hospitalization is delayed compared with other GDMTs. Pooled data from Japan, Sweden and the United States (n = 266 589 patients) indicated the following percentages of patients discontinuing therapy within 12 months: 23.5% (dapagliflozin), 26.4% (sacubitril/valsartan), 38.4% (ACEi), 33.4% (ARBs), 25.2% (beta-blockers) and 42.2% (MRAs). Corresponding TD achievements were 75.7%, 28.2%, 20.1%, 6.7%, 7.2% and 5.1%, respectively. Thus, persistence of therapy was higher for dapagliflozin than other GDMTs. Consistently, a former study[12] pooling data from Sweden, the United Kingdom and the United States showed similar patterns of dose titration and discontinuation of ACEi, ARB, beta-blockers, MRA and ARNi. Despite high risk of clinical events following hospitalization, new initiation of GDMT was followed by low uptitration and early GDMT discontinuation in the three countries despite different healthcare systems.

Further, an analysis from the Swedish Registry[13] investigated the association between combination, dose and use of current guideline-recommended TDs of renin–angiotensin system inhibitors (RASi), ARNi and β-blockers, and outcomes in patients with heart failure with reduced ejection fraction (HFrEF). Higher doses of RASi or ARNi and β-blockers were associated to lower risk of cardiovascular death or HF hospitalization. Combination of two drug classes at 50%–99% of TD was associated with lower risk than one drug class at 100% of TD.

Considering all these data, improving dose uptitration of life-saving drugs in HF in the *short term* is recommended.

Regarding the initiation of ARNI in HFrEF patients being on ACEi/ARB, switching on the drug can be started in stable outpatients, as well as in patients during the stabilization period (after cardiovascular decompensation) during hospitalization—with systolic RR $\geq$ 100 mmHg and potassium concentration $\leq$ 5.4 mmol/L.[14] The initiation of ARNI in HFrEF patients being on ACEi/ARB should follow the principle of safe conversion, that is, 36 h interval before the first dose of sacubitril/valsartan and the last dose of ACEI (but not in the case of ARB). Before starting treatment, kidney and liver function, serum potassium concentration, blood pressure and volume status should be assessed; contraindications to ARNI are very similar to those to ACEI. Practical indications regarding starting dose and uptitration modalities are described in Box 1.

BOX 1 Practical indications for starting and uptitrating the four major pillars of pharmacological treatment in HF.

ACEi/ARNI

- Before starting treatment, kidney and liver function, serum potassium concentration, blood pressure and volume status should be assessed.
- To minimize the risk of hypotension, treatment can be started in the evening, before bedtime.
- Urea, creatinine and serum potassium should be measured 1–2 weeks after starting treatment and 1–2 weeks after escalation of the dose; subsequent control tests should be performed every 4 months (more often in patients with renal impairment and/or a tendency to electrolyte disturbances);
- Starting dose for ARNI should be 49 mg/51 mg twice daily; it is possible to start with a dose of 24 mg/26 mg twice daily when the patient has not been previously treated with ACEI/ARB, has taken low doses of ACEI/ARB or presents with systolic pressure of 100–110 mmHg, moderate or severe renal impairment [glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2] or moderate hepatic impairment.
- If well tolerated, the initial dose of the drug should be doubled after 2–4 weeks until the target dose is reached.
- Control of serum potassium and creatinine 1–2 weeks after the onset of treatment and after reaching the target dose, subsequent control every 4 months.
- Monitoring potential increase in urea, creatinine and potassium levels (see indications in Box 1).
- Monitoring plasma concentration of NT-proBNP (ARNi).
- A 36-hour interval should be maintained between the last dose of ACEI (but not ARB if previously used) and the first dose of sacubitril/valsartan when switching from one drug to another; the drug can be administered with or without food.

BB

- Before starting treatment, kidney function and electrolyte concentration should be assessed.
- Treatment requires gradual escalation of doses with control of the chronotropic effect and arterial pressure:

1 Bisoprolol 1 × 1.25 mg → 1 × 10 mg
2 Carvedilol 2 × 3.125 mg → 2 × 25 mg (in patients >85 kg–2 × 50 kg)
3 Metoprolol succinate 1 × 12.5 mg → 1 × 200 mg
4 Nebivolol 1 × 1.25 mg → 1 × 10 mg

- HF patients should ultimately achieve an average heart rate over the course of a day in the range of 60–69/min.

MRAs

- Levels of serum potassium and eGFR should be measured in all patients before the initiation of treatment.

5. In the case of potassium >5.5 mmol/L or creatinine >221 μmol/L (2.5 mg/dL)/estimated GFR < 30 mL/min/1.73 m^2, the MRA dose should be reduced by half and the patient should be carefully monitored. In the case of potassium >6.0 mmol/L or creatinine >310 μmol/L (3.5 mg/dL)/estimated GFR < 20 mL/min/1.73 m^2, MRA should be withheld immediately. K-binders should be initiated in order to allow timely re-initiation of MRAs.

- Other agents likely to increase serum potassium should be avoided during treatment.

SGLT2i

- Starting dapagliflozin or empagliflozin at doses of 1 × 10 mg/day, without the need for adjustment
- Monitoring hypoglycaemia, osmotic diuresis and natriuresis

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARBs, use of angiotensin receptor antagonists; ARNi, angiotensin receptor-neprilysin inhibitors; BB, beta-blockers; MRAs, mineralocorticoid receptor antagonists; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Barriers to implementation

It is useful to clarify the incidence of low implementation but even more the reasons for this phenomenon, for example, factors influencing follow-up referral decisions and their prognostic implications. Barriers to be overcome for implementing GDMT in HFrEF have been described elsewhere.[15]

Main patient-related factors are advanced age, comorbidities, frailty, cognitive impairment, poor adherence and low socioeconomic status. Healthcare-related factors influence the availability and accessibility of HF care as well. As for treatment-related factors, intolerance and side effects are relevant clinical barriers. Caution and contraindications to the four pillars of HF therapy are listed in Box 2.

BOX 2 Caution or contraindications of the four major pillars of pharmacological treatment in HF.

CEi/ARNi

- The indication for dose reduction or discontinuation are intolerable hypotension, volume overload/haemodynamic congestion, clinically significant and untreatable hyperkalaemia or renal impairment (stenosis of the renal artery of the only active or dominant kidney, kidney dysfunction), liver dysfunction.
- A slight increase in urea, creatinine, and potassium levels after therapy initiation is observable (caution. Not to be discontinued).
- Cough may be reported for ACEi (caution. Not to be discontinued).

BB

- The indication for dose reduction or discontinuation are severe volume overload/haemodynamic congestion, intolerable hypotension or bradycardia worsening heart failure.
- A decrease in exercise tolerance in the initial period of use is observable (caution. Not to be discontinued).

MRAs

- The indication for dose reduction are renal impairment and Severe hyperkalaemia (caution. Not to be discontinued: see cut-off values below).
- eGFR cut-off values are: 45 mL/min/1.73 m^2 for spironolactone, 30 mL/min/1.73 m^2 for eplerenone, 25 mL/min/1.73 m^2 for finerenone.
- When estimated potassium $\geq$6 mEq/L, initiation of MRA therapy is contraindicated.

SGLT2i

- Contraindicated in patients with eGFR $<$20 mL/min/1.73 m^2 (empagliflozin) and $<$25 mL/min/1.73 m^2 (dapagliflozin).
- SGLT2i increases the risk of fungal infections of the external genitourinary organs of mild or moderate severity (not to be discontinued).
- An increased in osmotic diuresis and natriuresis is observable (caution. Not to be discontinued)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor-neprilysin inhibitors; BB, beta-blockers; MRAs, mineralocorticoid receptor antagonists; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Age is one of the main documented reasons for low implementation. A large nationwide cohort study, based on the Swedish HF Registry,[16] investigated the implementation of GDMT in HFrEF across different age strata showing that elderly patients were less likely treated with TDs or combinations of HF medications. Similarly, older patients were less likely treated with cardiac resynchronization therapy and less likely implanted with cardioverter defibrillator. Thus, gaps persist in the use of medications as well as for devices in older patients with HFrEF.

Similarly, the Dutch PHARMO Database Network on 22 476 patients with a diagnosis of HF at hospital discharge showed that the probability of being prescribed HF drug combinations decreased with increasing age. A study from the Swedish HF registry between 2000 and 2018, identifying the independent predictors of planned follow-up in specialty versus primary care across the EF spectrum,[17] found that referral to specialty care was associated to male sex, younger age, lower ejection fraction (EF), lower comorbidity burden, better socioeconomic environment and optimized HF care.

Considering this evidence, a more individualized approach for implementing use of GDMTs in HF is required, particularly in older patients and those with high-risk profile, as described below. On the other hand, follow-up improves implementation: monitoring patients over time is one of the main predictors of persistence and uptitration as shown by data collected 1 year after the publication of Atlas.[18]

In a real-world cohort,[19] 20% of patients were eligible for ARNi but only 13% received the treatment. Despite sacubitril/valsartan was well tolerated, 41% of the patients did not reach TD. Another study showed its implementation to be slow, especially in elderly and females.[20] Under-prescription of sacubitril/valsartan was observed in Italy, during the COVID-19 pandemic, due to the lockdown measures.[21]

Therefore, as for drug compound sacubitril/valsartan, early initiation during hospitalization or immediately

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post-discharge is recommended. Of note, there is evidence[22] that the most commonly used dose of the drug in clinical practice (i.e., 24/26 mg twice daily) provides substantial clinical benefits. Indeed, favourable mechanistic outcomes in terms of prognostic biomarkers, health status and cardiac remodelling were found across various sacubitril/valsartan doses, from even low doses.

Other factors linked to low prescription and low titration of HF drugs are chronic kidney disease (CKD), hypotension and socio-economic status. From the physician point of view, CKD is a major trigger for underuse. In the Swedish HF Registry in 2009–2018,[23] patients with CKD were less likely to initiate HF medications and less likely to adhere to and persist on ACEi/ARB/ARNi, MRA and triple therapy. Among stoppers, CKD patients were less likely to restart these medications. Another analysis from the Swedish HF registry[24] showed that underuse of MRAs in HFrEF was due to impaired renal function, even in the creatinine clearance 30–59.9 mL/min range where they are not contraindicated. MRA underuse may be further related to non-specialist care, milder HF and no use of other HF therapies. Thus, greater awareness in non-specialist care regarding MRAs use in HFrEF patients with impaired renal function is needed, and their prescription should be implemented. Notably, as shown in Box 2, there are no estimated glomerular filtration rate (eGFR) limits for ACEi, ARNI and beta-blockers.

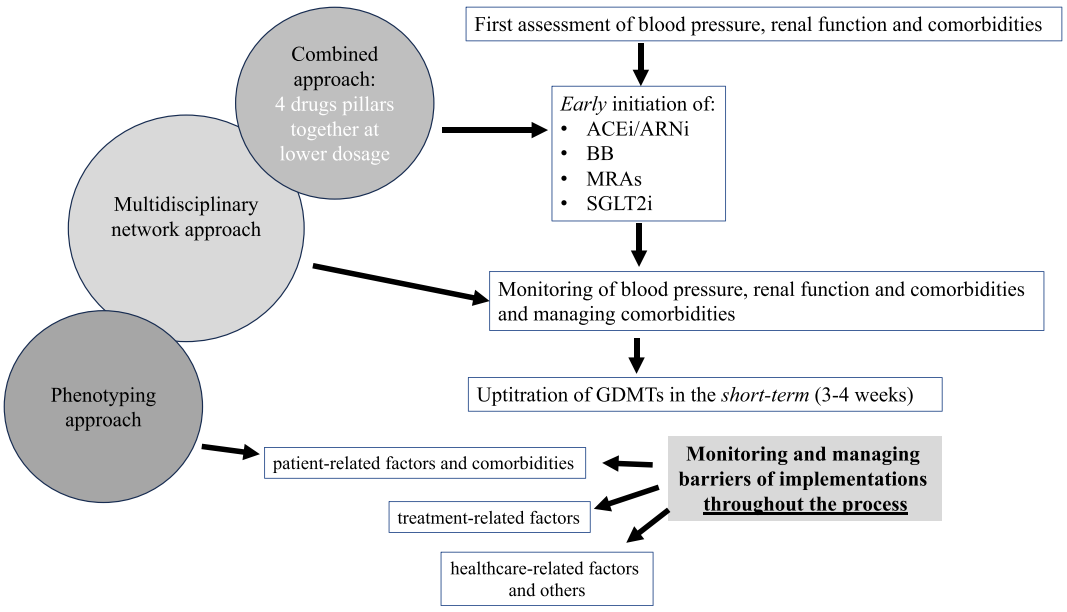
As discussed elsewhere,[25] safety concerns often lead to discontinuations of GDMTs in dialysis-dependent patients, thereby compromising the management of HF in this population. First, an assessment of renal function should be performed before starting treatments, and renal parameters should be controlled over treatment. Clinicians should avoid discontinuations of GDMT unless otherwise necessary. Down-titration should be preferred over discontinuation.[25] Cardiologists and nephrologists are asked to collaborate in managing this complex phenotype. Clinical trial evidence is warranted to ascertain the safety of GDMT in HF patients on dialysis.

Strategies for uptitration

There is evidence that HF patients achieve better outcomes with a combination approach than using one TD (i.e., sequential approach).[11,13] Thus, the combined approach, that is, using the four drug pillars together at lower dosages and then starting with uptitration, is recommended. On the contrary, it is not advisable to prescribe less drugs at higher doses. The indication is to initiate with low dosage of multiple drugs with short-term uptitration (3–4 weeks) after monitoring blood pressure, renal function and comorbidities (*Figure* 1). Threshold for uptitration is defined as the maximum tolerate dose. Thus, there is the urgent need for moving away from long sequential approach when initiating HF treatment towards a combination approach, following current guidelines. Also, using fixed dose combinations to improve adherence is pivotal.

Further, multidisciplinary network approach is of utmost importance for drug implementation, as indicated by results

Figure 1 Strategies of uptitration and implementation of GDMTs in HF patients. ACEi, angiotensin-converting enzyme inhibitors; ARNi, angiotensin receptor-neprilysin inhibitors; BB, beta-blockers; GDMTs, guideline-directed medical therapy; HF, heart failure; MRAs, mineralocorticoid receptor antagonists; SGLT2i, sodium-glucose cotransporter 2 inhibitor.



from the HFA Atlas survey.[26] As aforementioned, it has been observed that non-cardiologists are those more likely to discontinue HF drugs because of safety concerns. Thus, communication among cardiologists and GPs or internal medicine physicians is pivotal. Development of a simple tool, such as a checklist, to assess the need to optimize HF therapy by GPs or internal medicine doctors may be useful. In particular, HF patients with high-risk profiles should be identified.

To this aim, phenotyping is a currently accepted strategy in Europe and represents the most relevant change in HF care.[27] Following current European and American guidelines, there are differences regarding the assessment of HF phenotype and management optimization, as reviewed elsewhere.[28] Briefly, according to the ACC/AHA/HFSA guidelines,[8] pharmacological approach is based on the combination of the four pillars in HFrEF and, as a second step, on their short-term dose uptitration. The ESC guidelines recommend the prescription of the four pillars in all patients with HFrEF to reduce mortality and HF hospitalizations, although using a phenotype-based approach for either initiation or uptitration of therapy.

Tailored-treatment strategies based on phenotypes (such as difference in aetiology and presence of comorbidities) are currently available for HFrEF only.[27] However, broader categories for phenotyping are still to be considered. For instance, the ESC HF Long-Term Registry[29] showed that left ventricular EF (LVEF) identifies different phenotypes as for demography, clinical features, aetiology and 1 year outcomes.

This document proposes to define main profiles according to major clinical features such as ageing, heart rate, blood pressure, diabetes, CKD and obesity. Beyond left ventricular dysfunction and comorbidities, a useful approach is characterizing patients according to their setting (e.g., patients ready to be discharged, frail patients, outpatients and chronic patients). In particular, distinguishing patients with new onset HF versus chronic patients is indicated. Patients with cardiac dysfunction identified by imaging techniques and even just by elevated concentrations of natriuretic peptides may benefit from HF treatment, even if still asymptomatic (so called per-HF stage according to the universal definition of HF).[30–33] In addition, patients recently hospitalized for HF and with worsening HF may have peculiar characteristics and deserve proper treatment, as outlined in recent HFA statements.[34,35]

In-hospital and outpatients HF patients: SGLT2 inhibitors as foundational therapies for HF patients regardless ejection fraction

SGLT2 inhibitors are the only drugs that have demonstrated an improvement in clinical outcomes in an overall population with HF. In addition, SGLT2 inhibitors have been shown to have cardioprotective and renoprotective effects in other diseases including type 2 diabetes and CKD, making these medications, in addition to other treatments according to each patient's clinical profile, the most effective method of improving clinical outcomes.

In patients with HF, the clinical benefits of SGLT2 inhibitors were first established in those with reduced EF,[36,37] and then evidence has been extended to those with mildly reduced and preserved EF.[38,39] These four trials provide compelling evidence of the benefits of dapagliflozin and empagliflozin in reducing HF clinical events and improving quality of life in patients with HF in the full spectrum of EF regardless age, diabetes status, eGFR and body mass index. Clinical guidelines were recently updated to incorporate these new data, with a class IA indication for dapagliflozin or empagliflozin in HFrEF, HF with mid-range EF and HF with preserved EF, marking these medications as the foundational therapy for patients with HF regardless the EF.[3,8,40]

In a pre-specified patient-level pooled meta-analysis, which analysed the data of all 11 007 HF patients previously enrolled in the DAPA-HF and DELIVER trials, dapagliflozin showed to significantly reduce the risk of death from CV causes, as well death from any cause, and total (first and repeat) hospital admissions for HF.[41] This provides compelling evidence of a beneficial effect of SGLT2 inhibitors in managing the complexity of HF and reducing the burden of complications. Interestingly, the beneficial effects of dapagliflozin on mortality risk were consistently significant also in patients with CKD enrolled in the DAPA-CKD trial.[42] Two additional peculiarities of dapagliflozin that make it eligible in many patient's clinical profile are its efficacy in HF patients with improved LVEF who remained symptomatic despite treatment; and its beneficial effects extend to those subpopulations at the highest end of the EF spectrum (EF $>$ 60%).[43]

Defining worsening HF: An update

Identifying worsening HF is pivotal in order to made decisions on uptitration. This document proposes an expanded definition of worsening HF that takes into account not only signs and symptoms requiring intensification of medical therapy but also based on a series of adjunctive criteria as outlined in a recent HFA consensus paper.[35]

In addition to the four pillars of HFrEF treatment, guidelines recommend intravenous iron repletion therapy for the patients with iron deficiency and vericiguat in patients with HFrEF who had recent worsening HF. According to ESC guidelines, vericiguat may be considered in HFrEF patients in New York Heart Association class II–IV with worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA, to reduce the risk of cardiovascular mortality or HF

hospitalization.[3] This class 2b recommendation is based on data from the VICTORIA study,[44] which assessed the efficacy and safety of vericiguat in a high-risk population with HFrEF post-worsening HF events who were optimized on background HF therapy. Rates of the primary endpoint of cardiovascular death or HF hospitalization were lower among patients who received vericiguat than among those under placebo. Thus, although a significant difference in the composite of cardiovascular death and hospitalization due to HF, the trial did not show a difference in the secondary endpoint of cardiovascular death, plausibly due to the high-risk population enrolled and short follow-up. Despite not explicitly stated in these guidelines, a higher level of recommendation may have not been acknowledged to vericiguat for this reason.[45,46]

The evidence-based recommended doses are 2.5 mg as starting dosage, which should be doubled as tolerated every 2 weeks until achieving a TD of 10 mg once daily. There is no need for discontinuation or washout periods of background HF therapies.

Vericiguat has a favourable safety profile and is generally well-tolerated in HFrEF patients, even in those with advanced renal disease; it may result in minimal hypotension or syncope.[46] Despite its safety and efficacy, potential barriers against the prescription of vericiguat in clinical practice in eligible patients might be identified. Main factors hindering its implementation are providers' lack of familiarity, clinical inertia, limited knowledge about monitoring response and concerns about potential adverse effects.[46] Standardized protocols to identify eligible patients and support prescribing may be helpful to overcome such barriers. There is therefore the need to develop better strategies for implementation of this GDMT in a real-world HF population. Data from the ongoing phase 3 randomized, placebo-controlled VICTOR trial (NCT05093933) will provide additional data on safety and efficacy of vericiguat in patients with and without recent worsening HF, including patients with broader uses of other class 1 recommended novel background therapies.

Conclusions

Implementation of the life-saving HF drugs needs to be improved, to reduce HF burden. A combined approach of the four pillars and their short-term uptitration are the recommended strategies; vericiguat may be considered in addition to background therapies in selected high-risk patients with HFrEF who had recent worsening HF. In order to reduce exacerbations, hospital readmission rates, morbidity and mortality and to improve the overall quality of life, an interdisciplinary approach to treatment is mandatory for HF patients. In particular, GPs and internal medicine physicians should be aware of their pivotal role in HF care, particularly for follow-up referral decisions and their prognostic implications.

The treatment strategy must be individualized for each HF patient, periodically monitored and reviewed by the healthcare team. To phenotype a patient, beyond comorbidities, age and LVEF, the present document proposes to consider three main settings: in-hospital, outpatients, worsening HF. Understanding the alarming signs and symptoms of worsening HF is a pivotal action that needs to be urgently implemented in HF management. Finally, it is possible to observe worsening HF in the acute setting and future research should aim to define trajectories of patients for each phenotype.

Conflict of interest statement

All the authors declare that they have no conflict of interest.

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