

Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology

Giuseppe M.C. Rosano^{1†}, Brenda Moura^{2,3*†}, Marco Metra⁴, Michael Böhm⁵, Johann Bauersachs⁶, Tuvia Ben Gal⁷, Stamatis Adamopoulos⁸, Magdy Abdelhamid⁹, Vasiliki Bistola¹⁰, Jelena Čelutkienė¹¹, Ovidiu Chioncel^{12,13}, Dimitrios Farmakis¹⁴, Roberto Ferrari^{15,16}, Gerasimos Filippatos¹⁷, Loreena Hill¹⁸, Ewa A. Jankowska¹⁹, Tiny Jaarsma^{20,21}, Pardeep Jhund²², Mitja Lainscak^{23,24}, Yuri Lopatin²⁵, Lars H. Lund²⁶, Davor Milicic²⁷, Wilfried Mullens^{28,29}, Fausto Pinto³⁰, Piotr Ponikowski³¹, Gianluigi Savarese²⁶, Thomas Thum³², Maurizio Volterrani¹, Stefan D. Anker³³, Petar M. Seferovic^{34,35}, and Andrew J.S. Coats³⁶

¹IRCCS San Raffaele Pisana, Rome, Italy; ²Armed Forces Hospital, Porto, Portugal; ³Faculty of Medicine, University of Porto, Porto, Portugal; ⁴Department of Medical and Surgical Specialities, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; ⁵Saarland University Hospital, Homburg, Germany; ⁶Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; ⁷Department of Cardiology, Rabin Medical Centre, Petah Tikva, Israel; ⁸Onassis Cardiac Surgery Center, Athens, Greece; ⁹Faculty of Medicine, Department of Cardiology, Cairo University, Giza, Egypt; ¹⁰Department of Cardiology, Attikon University Hospital, University of Athens Medical School, Athens, Greece; ¹¹Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania; ¹²University of Medicine Carol Davila, Bucharest, Romania; ¹³Emergency Institute for Cardiovascular Diseases 'Prof. C.C. Iliescu', Bucharest, Romania; ¹⁴University of Cyprus Medical School, Nicosia, Cyprus; ¹⁵Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy; ¹⁶Centro Cardiologico Universitario di Ferrara, University of Ferrara, Ferrara, Italy; ¹⁷National and Kapodistrian University of Athens, School of Medicine, University Hospital Attikon, Athens, Greece; ¹⁸School of Nursing and Midwifery, Queen's University Belfast, Northern Ireland, UK; ¹⁹Department of Heart Diseases, Wrocław Medical University and Center for Heart Diseases, University Hospital in Wrocław, Wrocław, Poland; ²⁰Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden; ²¹Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; ²²Institute of Cardiovascular and Medical Sciences, Glasgow, UK; ²³Division of Cardiology, General Hospital Murska Sobota, Murska Sobota, Slovenia; ²⁴Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; ²⁵Volgograd State Medical University, Regional Cardiology Centre Volgograd, Volgograd, Russian Federation; ²⁶Department of Medicine, Karolinska Institutet, and Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden; ²⁷University of Zagreb School of Medicine, Zagreb, Croatia; ²⁸Faculty of Medicine and Life Sciences, BIOMED - Biomedical Research Institute, Hasselt University, Diepenbeek, Belgium; ²⁹Department of Cardiology, Ziekenhuis Oost, Genk, Belgium; ³⁰Cardiology Department, University Hospital Santa Maria (CHULN), CAML, CCUL, Faculty of Medicine, University of Lisbon, Lisbon, Portugal; ³¹Centre for Heart Diseases, Faculty of Health Sciences, Wrocław Medical University, Wrocław, Poland; ³²Hannover Medical School, Institute of Molecular and Translational Therapeutic Strategies, Hannover, Germany; ³³Department of Cardiology (CVK); and Berlin Institute of Health Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Berlin, Germany; ³⁴Department Faculty of Medicine, University of Belgrade, Belgrade, Serbia; ³⁵Serbian Academy of Sciences and Arts, Belgrade, Serbia and ³⁶University of Warwick, Coventry, UK

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Despite guideline recommendations and available evidence, implementation of treatment in heart failure (HF) is poor. The majority of patients are not prescribed drugs at target doses that have been proven to positively impact morbidity and mortality. Among others, tolerability issues related to low blood pressure, heart rate, impaired renal function or hyperkalaemia are responsible. Chronic kidney disease plays an important role as it affects up to 50% of patients with HF. Also, dynamic changes in estimated glomerular filtration rate may occur during

*Corresponding author. Armed Forces Hospital, Av. Boavista, 4050-115, Porto, Portugal. Tel: +351 913 636848, Email: brenamoura.c@gmail.com

†These authors contributed equally to this manuscript.

the course of HF, resulting in inappropriate dose reduction or even discontinuation of decongestive or neurohormonal modulating therapy in clinical practice. As patients with HF are rarely naïve to pharmacologic therapies, the challenge is to adequately prioritize or select the most appropriate up-titration schedule according to patient profile. In this consensus document, we identified nine patient profiles that may be relevant for treatment implementation in HF patients with a reduced ejection fraction. These profiles take into account heart rate (<60 bpm or >70 bpm), the presence of atrial fibrillation, symptomatic low blood pressure, estimated glomerular filtration rate (<30 or >30 mL/min/1.73 m²) or hyperkalaemia. The pre-discharge patient, frequently still congestive, is also addressed. A personalized approach, adjusting guideline-directed medical therapy to patient profile, may allow to achieve a better and more comprehensive therapy for each individual patient than the more traditional, forced titration of each drug class before initiating treatment with the next.

Keywords

Heart failure • Guideline-directed medical therapy • Clinical profiles • Heart rate • Blood pressure • Chronic kidney disease • Hyperkalaemia • Atrial fibrillation • Pre-discharge patient

Introduction

Treatment of patients with heart failure (HF) and a reduced ejection fraction (HFrEF) is supported by large-scale randomized clinical trials (RCT) that are reflected in the European Society of Cardiology/Heart Failure Association (ESC/HFA) guidelines,¹ and their updates.^{2–4} However, despite guideline recommendations and available evidence, treatment implementation is poor.⁵ The majority of patients do not receive treatment with all drugs (or do so only at below target doses) and recommended devices that have been proven to positively impact morbidity and mortality. This may be due to tolerability issues related to low blood pressure, heart rate, impaired renal function or hyperkalaemia^{6–10} (Table 1). Limited access to specialist care,^{11,12} physician inertia and organization of care¹³ also contribute to the observed lack of optimal penetration of medical and device therapy in clinical practice. Additionally, other factors such as poor socioeconomic status, lack of social support and poor medication adherence can also lead to undertreatment in HF.¹⁴

Treatment of HF patients has evolved over the last few years, with new evidence supporting novel therapies. Never before has there been such an opportunity to positively impact prognosis with drug therapy for patients with HFrEF. This comes, however, with increased complexity in management. For years, treating HFrEF patients required dealing with angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) if ACEi were not tolerated due to cough, beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), digoxin, diuretics, and devices. However, over the past decade, ivabradine, sacubitril/valsartan, sodium–glucose co-transporter 2 inhibitors (SGLT2i), ferric carboxymaltose and, to a lesser extent, vericiguat and omecamtiv mecarbil, have all demonstrated a positive impact on mortality and/or morbidity in HFrEF patients.

Implementation and up-titration of guideline-directed medical therapy (GDMT) in HFrEF is complex, as many drugs have an impact on blood pressure, renal function and potassium levels. Not infrequently patients may not tolerate all the therapies, at least at their target dose, and a decision may need to be made concerning which drugs will benefit the individual patient the

most.^{5,15,16} Furthermore, HF patients are frequently elderly, with several comorbidities requiring pharmacotherapy, and with this the potential for adverse effects and drug interactions increases significantly (for impact of comorbidities in the use of GDMT see Table 2).

The aim of this position paper is to identify patient profiles that may be relevant for treatment implementation in patients with HFrEF. This implies first the identification of the causes of undertreatment and, second, proper implementation of treatment when possible. Causes of undertreatment may be those related to 'non-medical factors' such as low socioeconomic status, lack of social support and poor adherence, and those related to medical, biological factors, such as low blood pressure, renal dysfunction and, congestion.

Through inclusion and exclusion criteria of RCTs, subgroup analyses and meta-analyses, and taking into consideration specific patient profiles that may limit the implementation of medical therapy, it is possible to personalize specific treatment options.

All efforts should be made to have all GDMT and devices offered to every patient, and treatment personalization should be seen as a means to achieve this, or to achieve as close to full GDMT as possible in patients that are intolerant to any drugs.

Barriers to implementation of medical therapy

Patients admitted to hospital because of HF decompensation pose a unique challenge at the time of their hospital discharge. This is the phase when they have the greatest likelihood to be readmitted or even die. The discharge plan plays an important role in the transition from hospital to outpatient care, and it should describe the schedule for up-titration and monitoring of GDMT, indications for reviewing the need and timing for device therapies, the form of an exercise or rehabilitation programme and lifestyle changes. It also must include scheduling of primary care visits during the first week post-discharge, and home visits by specialist nurses (where available) as well as specialist follow-up. There is evidence that in a patient with HFrEF, GDMT taken at discharge improves

Table 1 Common side effects of guideline-directed medical therapy

Drug	Common side effects
Diuretics	Hypotension; hypokalaemia; hypomagnesaemia; hyponatraemia; hyperuricemia; hypovolaemia/dehydration; rise in creatinine, urea
ACEi/ARB	Cough; hypotension; rise in urea, creatinine, potassium
ARNI	Hypotension; rise in creatinine, potassium; angioedema
Beta-blockers	Worsening HF; low heart rate; hypotension
Ivabradine	Low heart rate; visual phenomena
MRA	Rise in creatinine, potassium; breast discomfort or gynaecomastia
SGLT2i	Genital infection (in diabetic patients)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

Table 2 Common comorbidities seen in heart failure and impact on use of guideline-directed medical therapy

Comorbidity	GDMT	Precaution	Comment
Coronary artery disease and angina	✓		Beta-blockers and ivabradine may help control symptoms
Diabetes	✓		GDMT have shown similar benefits in diabetic patients
Lung disease		Asthma is a relative contraindication to beta-blocker; starting with low doses of cardio-selective beta-blocker may allow its use	Beta-blockers can be given in COPD
Depression	✓		Depression is associated with low adherence to medication
Erectile dysfunction	✓		Thiazides, spironolactone and beta-blockers (nebivolol preferred) may aggravate erectile dysfunction
Iron deficiency/anaemia	✓		
Kidney dysfunction		ACEi, ARB, ARNI, MRA may have some limitations (see text)	Diuretics may need higher doses to be effective
Cachexia		ACEi, ARB, ARNI should be up-titrated carefully because of orthostatic hypotension	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; GDMT, guideline-directed medical therapy; MRA, mineralocorticoid receptor antagonist.

outcomes, with a lower mortality rate both at 90 days and 1 year. Recently, angiotensin receptor–neprilysin inhibitors (ARNI) have shown they can be safely introduced prior to discharge, and SGLT2i introduced during hospitalization have shown to reduce rehospitalizations and mortality.^{17–20}

In the transition phase, approximately in the first 2 months after hospitalization for decompensated HF, there is an unmet need to implement and titrate GDMT. This results from inadequate knowledge of guideline recommendations, and a failure to integrate guideline and RCT evidence with clinical practice.¹³ This is especially relevant for general practitioners (GPs), who are most frequently in charge of the patient's follow-up. The fact that in the HART trial, the highest physician non-adherence to guidelines was in older patients, with more comorbidities, and in minorities,²¹ may also reveal the gaps in evidence.

Nonetheless, there is clear evidence that adherence to medication is associated with lower cardiovascular mortality and fewer

hospitalizations for HF in chronic outpatients^{22–24}. The contributions of multidisciplinary team professionals and patient/family members' education and interactions are fundamental to overcome poor adherence to medication.^{25,26} These programmes provide tailored education and exercise, lifestyle advice, and education for symptom monitoring and self-care including adherence. Also, they have the ability to function across hospital and primary care sectors of care, providing a seamless path of treatment. Enrolment in disease management programmes, with a multidisciplinary team approach, is recommended especially in high-risk patients, following the ESC/HFA guidelines.

Intolerance to GDMT, particularly in very symptomatic patients, should prompt evaluation for referral to a specialized HF centre.

In summary, there are physician, patient and organizational barriers to the implementation of therapy, and the post-discharge or transition phase represents a particularly vulnerable time for HF patients.

Optimization of medical therapy in patients with chronic kidney disease

Chronic kidney disease (CKD), with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², affects 4.5% of the general population, but up to 50% of patients with HF.²⁷ CKD carries a double risk for all-cause mortality, making it a stronger prognostic predictor than left ventricular ejection fraction (LVEF). Dynamic changes in eGFR may occur during the course of HF, and its interpretation should take into consideration the evolving clinical context. Misinterpretation of the evolution of eGFR often results in inappropriate dose reduction or even discontinuation of decongestive or neurohormonal modulating therapy in clinical practice (i.e. a drop in eGFR with ongoing diuresis and improvement in HF status in acute HF, and an eGFR drop during up-titration of GDMT in chronic HF; in both situations medication should not be withheld^{9,27}).

Patients with baseline CKD (who are at higher risk for dynamic changes in eGFR) might actually benefit the most in absolute terms from treatment with neurohormonal blockers, as CKD is associated with a higher event rate. An analysis of the RALES trial showed a 30% relative risk reduction for mortality regardless of baseline eGFR, but a higher absolute risk reduction for mortality in patients with worse baseline eGFR, when treated with spironolactone compared to placebo.²⁸ If worsening renal function occurs during renin–angiotensin–aldosterone system inhibitor (RAASi) up-titration (described as ‘pseudo worsening renal function’), there is indication to temporarily discontinue medication if an increase of $>100\%$ of serum creatinine occurs, or potassium levels rise to >5.5 mEq/L. RAASi doses can be reduced if serum creatinine increases by $<50\%$ above baseline levels and is still <3 mg/dL, with eGFR >25 mL/min/1.73 m². Re-administration is advised, when the adverse reaction has resolved.

It is important to keep in mind that eGFR declines with age, and more so in HF patients (2–3 mL/min/1.73 m²/year above the age of 50) and diabetic HF patients (5 mL/min/1.73 m²/year above the age of 50). When RAASi are started, there is an expected drop in eGFR, but this does not portend a poorer prognosis. In fact, HF patients medicated with RAASi have a lower mortality despite a lower eGFR.^{29,30}

An initial drop in eGFR is also observed in patients started on SGLT2i, but this drop is not associated with established worsening of renal dysfunction. Conversely, these drugs have been shown to be reno-protective in patients with HF and/or diabetes mellitus and/or CKD.^{31–33}

Phenotyping patients for targeted therapies

With the introduction of effective new drugs for the treatment of HF, the demand for patient phenotyping has become increasingly important, as some patients cannot tolerate all medications. Stratifying HF patients is challenging, as there is an overlap of clinical

phenotypes along the spectrum of HF. Given the heterogeneity of HF patients, any subdivision of the spectrum by a single biomarker is inaccurate, and demands a combination of clinical characterization, biomarkers and imaging technologies to improve patient stratification.^{34,35}

The increasing knowledge about the different HF phenotypes, based on either aetiology or disease mechanisms, or on outcomes and bio-profiling, may allow an evolution from large-scale clinical trials performed in heterogeneous LVEF-classified patients, to personalized mechanistic trials on small populations of homogeneous HF patients.

A combination of biomarkers and imaging technologies will be needed to improve patient stratification. ‘Omics’, artificial intelligence, and machine learning approaches will play a major role in the future.^{36,37} Biomarker-guided approaches can have further benefits, as in evaluating toxicity, dose ranging, patient stratification and therapy monitoring.

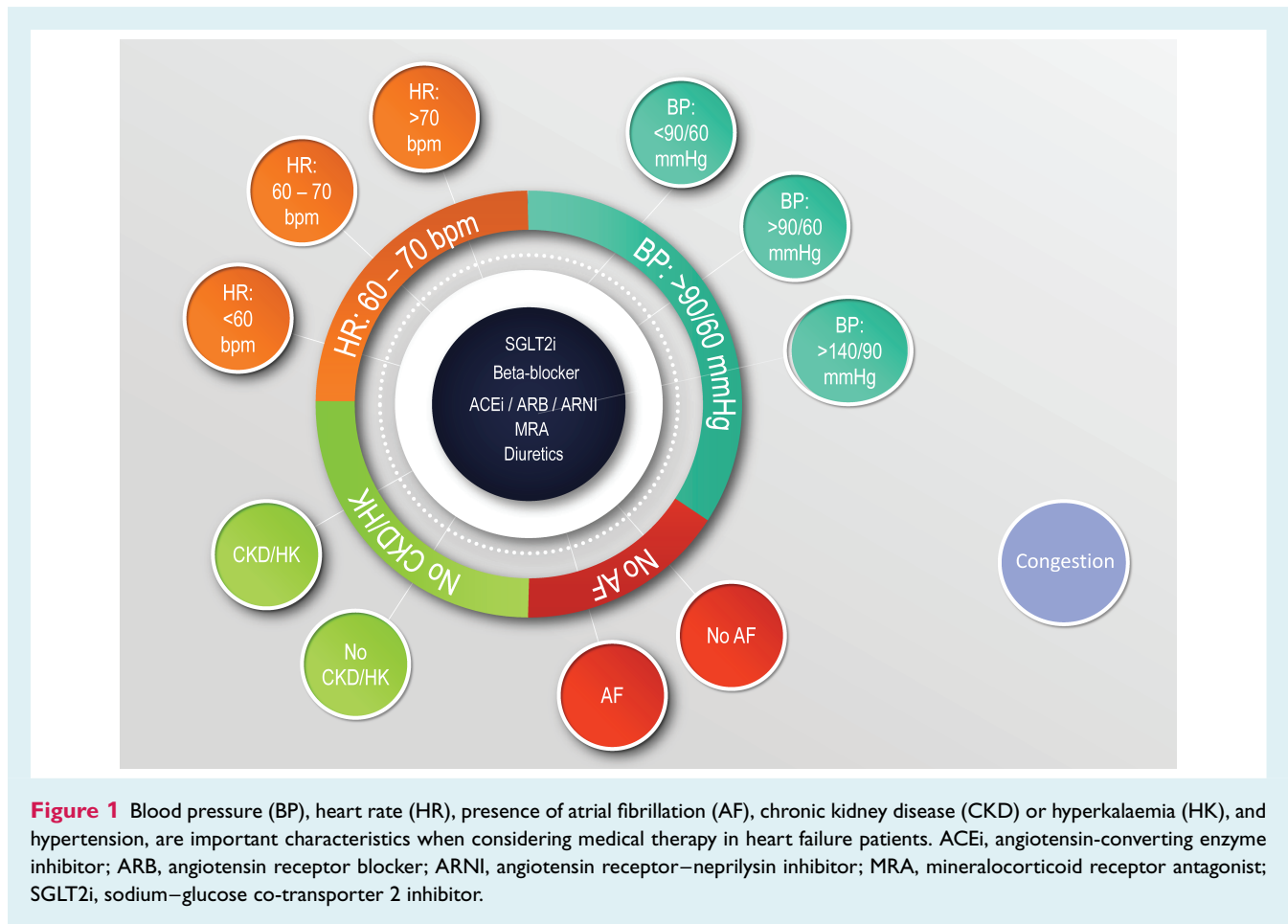
Multi-omics integration together with imaging technology advances and new machine learning and artificial intelligence algorithms may, in the future, lead to an improved understanding of the disease pathology, to a better patient stratification and to the optimized use of current and future drug candidates in cardiovascular disease.³⁸

Therapy according to patient profiles

Several therapies improve outcomes in patients with HF_{rEF}, as established by large RCTs. Questions could arise about the translation of these benefits to real-world practice, involving less selected populations, such as older patients, women, frail, multimorbid patients who are often not included in RCTs.³⁹ Surveys and registries are important to fill this gap in evidence.

An analysis of IMPROVE HF, with a population of 4128 patients from the longitudinal cohort, showed a survival benefit at 24 months with incremental use of GDMT, reaching a potential plateau at four to five therapies.⁴⁰ In this analysis, some of these therapies had a survival estimate advantage at 2 years greater than that observed in RCTs. Eventually, this real-world group of HF patients, less selected than those of RCT populations, may derive greater benefit from these drug therapies. Recently, data from the EPICAL2 study showed that long-term adherence to guideline-recommended drugs was associated with lower 3-year all-cause and cardiovascular mortality in HF_{rEF} patients.⁴¹ In the QUALIFY registry examining 6118 ambulatory HF_{rEF} patients, adherence was assessed for five classes of recommended HF medications and dosages. Cardiovascular and HF deaths were significantly associated with physicians’ adherence to guidelines.²² So, despite lack of evidence from RCTs, registries seem to suggest benefits of GDMT in a broader population.^{12,42–44}

Patients with HF have many different presentations, regarding congestion, haemodynamic status and kidney function. Therefore, adjusting or prioritizing drugs according to the patient profile appears as a reasonable way to give each individual patient the benefit of GDMT.



Patients with HF are rarely naïve regarding pharmacologic therapies. Most frequently, patients with HF are already on ACEi, and/or BB or diuretic because of concomitant hypertension, ischaemic heart disease, atrial fibrillation or other conditions. The challenge is to correctly prioritize or select the most appropriate titration schedule according to the patient profile. Another frequent clinical scenario is the patient admitted for HF, whether due to *de novo* HF or decompensated chronic HF, in whom GDMT was reduced or withdrawn, needing guidance on how to start medical therapy, or how to perform up-titration at discharge.

The drugs used in HF patients to improve prognosis impact blood pressure, heart rate, renal function and potassium levels, although differently. Taking this into account, efforts should be made towards a personalized approach for the treatment of HF (Figure 1).

The core of HF treatment includes ACEi/ARB/ARNI, BB, MRA, and SGLT2i. These medications should be started in all patients with HF.

Presence of congestion should be assessed, and diuretic implemented in the correct regimen in order to achieve an euvoaemic state. Apart from symptoms, congestion may negatively impact appropriate titration of GDMT. Proper utilization of diuretics in HF will not be addressed here, as it has already been the focus of another paper.⁴⁵

All patients should receive the core treatment for HF, as it will reduce hospitalizations and mortality as well as the need for devices. The question raises on how this therapy can be implemented, as all core therapies but SGLT2i affect either blood pressure and heart rate or potassium levels, and require dose adjustments and gradual up-titration. Therefore, while SGLT2i can be more easily implemented in the complex HF therapy, the identification of patient phenotypes can help to determine tailored treatment strategies (Figure 2). We suggest that nine phenotypes of patients with individual needs for up-titration can be identified. We acknowledge that the chosen patient profiles are broad but physicians need advice on how best implement therapies in the identified patient profiles. Of course, physicians will recognize patients cannot always be characterized accurately by simple demographics, so that advice may need to be sought by comparison and combinations of the advice for one or more profiles.

Profile 1: Patients with low blood pressure and high heart rate

There is no clear definition of what is low blood pressure in HF. Nonetheless, a systolic blood pressure <90 mmHg is frequently used. However, in patients with underlying coronary artery disease,



Figure 2 Tailoring of medical therapy according to clinical profiles. According to some patient characteristics – blood pressure (BP), heart rate (HR), presence of atrial fibrillation (AF), chronic kidney disease (CKD) or hypertension, some drugs may have to be reduced, discontinued, or added. Black—drugs that should be given to patients; red—drugs that should be reduced or discontinued; blue—drugs that should be added. *In patients with predominant chronic coronary syndrome, BP threshold is 120/80 mmHg. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

a systolic blood pressure >120 mmHg is recommended.⁴⁶ This profile is not frequent in outpatient clinical practice, and its presentation should trigger an evaluation of causes of low blood pressure, such as hypovolaemia, bleeding, or infection. All non-HF medications should be reviewed, and the need for nitrates, calcium channel blockers and other vasodilators should be reconsidered, and whenever possible stopped as they have no prognostic benefit. If the patient is euvoemic, reduction or discontinuation of diuretics can be attempted, and careful monitoring in the following days is necessary to avoid fluid retention. Modifying GDMT or its dosage needs to be addressed only if the patient has symptomatic hypotension. Lower heart rate is associated with improved survival in HFrEF and sinus rhythm, and the most favourable outcome is observed with a heart rate around 60 bpm.⁴⁷ BB are part of the core of HFrEF therapy, and should be up-titrated to the target or maximal tolerated dose. In the COPERNICUS trial, among patients with a systolic blood pressure of 85 to 95 mmHg, there was no evidence of any decline in systolic blood pressure after BB treatment, compared to placebo. These patients were at highest risk of an event, and experienced the greatest absolute benefit from treatment with BB.⁴⁸ In the CARVIVA HF trial, the combination of a BB with ivabradine allowed patients to reach higher doses of both drugs, than isolated up-titration.⁴⁹ In patients with symptomatic hypotension,

and after considering withdrawal of unnecessary blood pressure lowering medications, the reduction or even discontinuation of BB may be necessary. In this situation, ivabradine, whose sole mode of action is to reduce heart rate with no effect on blood pressure, represents an important therapeutic resource. MRAs and SGLT2i have a very modest impact on blood pressure, so their discontinuation is not mandatory or rarely necessary.^{50–52} Use of sacubitril/valsartan is contraindicated in patients with systolic blood pressure <100 mmHg. Omecamtiv mecarbil seems a very interesting treatment option in more severely affected patients within this phenotype.

Profile 2: Patients with low blood pressure and low heart rate

Consider other causes of hypotension, and other medications as in profile 1. Modifying GDMT or its dosing needs to be addressed only if the patient has symptomatic hypotension. MRAs and SGLT2i have a very modest effect on blood pressure, so their withdrawal is not necessary. Reduction of BB may be necessary if the patient has a heart rate <50 bpm, or symptomatic bradycardia. Omecamtiv mecarbil is a viable treatment option in these patients where limited GDMT can be used.

Profile 3: Patients with normal blood pressure and low heart rate

Drugs with a negative chronotropic effect should be carefully reconsidered and if possible discontinued, such as non-dihydropyridine calcium channel blockers (diltiazem and verapamil), digoxin, or antiarrhythmic drugs. If the patient is on ivabradine, its dose should be reduced or suspended if the heart rate remains <50 bpm or the patient has symptomatic bradycardia. Furthermore, patients with bradycardia or heart rate <50 bpm will also require down-titration of BBs.

Profile 4: Patients with normal blood pressure and high heart rate

These patients should be treated with target doses of BB. If high heart rate (>70 bpm) in sinus rhythm persists, the use of BBs in combination with ivabradine results in better heart rate control and better up-titration of BBs in a lower incidence of side effects. ACEi/ARB or ARNI should be up-titrated to target dose in HFrEF patients, as this was always the aim in RCTs, and higher doses have provided greater benefit than lower doses.^{53,54} In hospitalized patients, initiation of vericiguat should be considered before discharge.

Profile 5: Patients with atrial fibrillation and normal blood pressure

The optimal resting ventricular rate in HF patients with atrial fibrillation remains to be clearly determined but may be between 60–80 bpm.⁵⁵ In contrast to patients in sinus rhythm, heart rate is not a predictor of mortality in HFrEF patients with atrial fibrillation. There is no clear evidence for a prognostic benefit of BBs in HF patients with AF.^{56,57} Attempts to up-titrate BBs to the maximal tolerated dose may have a detrimental effect, as ventricular rates <70 bpm have been associated with a worse outcome. Anticoagulation is always indicated for patients with AF unless risks exceed the potential benefits or these drugs have specific contraindication.

Profile 6: Patients with atrial fibrillation and low blood pressure

As stated previously, evidence for the benefit of BBs on mortality and morbidity is less strong, so BB may be reduced or discontinued if necessary. Digoxin may be used in this situation as an alternative to BB for heart rate control, as it has no effects on blood pressure. A heart rate >70 bpm should be maintained. This strategy may allow the introduction or up-titration of drugs with an impact on mortality and morbidity, such as ACEi or ARNI. MRAs and SGLT2i have a very modest effect on blood pressure, so their withdrawal is not mandatory nor necessary. HF patients with AF should always be anticoagulated, preferably with non-vitamin K antagonist oral anticoagulants unless contraindicated.

Profile 7: Patients with chronic kidney disease

Most RCTs have excluded patients with severe CKD, limiting available evidence on the benefit and safety of drugs in this setting. Data from registries show that patients who may benefit from GDMT are precluded from its use for unspecified reasons, or invalid reasons, such as CKD with eGFR >30 mL/min/1.73 m². ACEi/ARBs/ARNI should only be stopped if creatinine increases by >100% or to >3.5 mg/dL, or eGFR <20 mL/min/1.73 m². BBs can be safely given to patients down to an eGFR of 30 mL/min/1.73 m², with a clear benefit in mortality. MRAs can also be given down to eGFR of 30 mL/min/1.73 m², provided potassium is ≤5.0 mEq/L, with a low risk of hyperkalaemia and clinically important rise in creatinine. Blood testing for potassium levels should be performed at 1 and 4 weeks after starting or increasing MRA dose, and periodically thereafter. Sacubitril/valsartan can be used until an eGFR <30 mL/min/1.73 m². Dapagliflozin and empagliflozin have been shown to be effective and safe in improving cardiovascular and renal endpoints in patients with an eGFR >20–25 mL/min/1.73 m². However, there is evidence of benefit from dapagliflozin also in patients with eGFR <20 mL/min/1.73 m². The minor fall in eGFR in the first days after initiation of an SGLT2i should not lead to cessation of this therapy, as this reversible reduction in eGFR is associated with a long-term beneficial effect on renal function.⁵⁸ The novel agents vericiguat and omecamtiv mecarbil can be given to patients with an eGFR >15 mL/min/1.73 m² and eGFR >20 mL/min/1.73 m², respectively. Other drugs may worsen renal function (i.e. non-steroidal anti-inflammatory drugs), so it is important to be sure that they are not unnecessarily being taken by the patient.²⁷ Potassium binders (patiomer and sodium zirconium cyclosilicate) have shown efficacy in reducing serum potassium in HF patients and CKD treated with RAASi.^{59,60} Nevertheless, there is still no evidence of their positive impact on prognosis.

Profile 8: Pre-discharge patient

During hospitalization, patients may get stabilized while still remaining congestive. A proportion of 30% of hospitalized HF patients are discharged with clinical signs of residual congestion, particularly patients with tricuspid regurgitation, diabetes, or anemia.⁶¹ If these patients are BB naïve, or not on BB treatment at the time, these should not be the first-line treatment, as starting BB in a congestive patient may lead to clinical deterioration. ACEi or ARNI in patients who had already received an ACEi at adequate dose, should be started in patients with a systolic blood pressure of >90 or >100 mmHg, respectively.¹⁸ MRAs and SGLT2i can be introduced safely, even in the congestive and low blood pressure patient.

Empagliflozin was well tolerated in these patients, and reduced the combined endpoint of worsening HF, rehospitalization for HF or death at 60 days. In diabetic patients hospitalized for HF,²⁰ sotagliflozin, a SGLT1 and SGLT2 inhibitor, reduced the combined endpoint of cardiovascular mortality, and hospitalizations and urgent visits for HF, when initiated before or just after discharge.²¹ Omecamtiv mecarbil and vericiguat can be used in selected patients

before discharge as they have been shown to reduce events. These drugs can contribute to decongestion, eventually allowing a safer initiation of BB.

Profile 9: Patient with hypertension despite guideline-directed medical therapy

In patients with a hypertensive profile, it is important to ensure the patient is not taking any medication that may increase blood pressure (i.e. non-steroidal anti-inflammatory drugs, corticoids, or bronchodilators). Patient adherence to medication has to be assured, and that the higher recommended doses are being used. If the patient is still hypertensive despite GDMT at optimal doses, the combination of isosorbide dinitrate and hydralazine should be used to achieve a controlled blood pressure profile.

Conclusion

Guideline-directed medical therapy has a major impact on mortality and morbidity of HF patients. Therefore, all efforts should be made to initiate and up-titrate foundational therapy. A personalized patient approach, adjusting GDMT to the patient's haemodynamic profile (blood pressure, heart rate, congestion) and kidney function, may allow to achieve a better and more comprehensive therapy for each individual patient better than the more traditional hierarchical, step by step, standardized forced titration of each drug class before initiating treatment with the next, in a misguided 'one size fits all' approach.

Randomized clinical trials have so far excluded patients with low blood pressure, heart rate and eGFR, and have addressed titration of medication in a standardized way. There is an unmet need for RCTs including more real-life patients, and testing different strategies to achieve a comprehensive medication.

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