Optimisation of treatments for heart failure with reduced ejection fraction in routine practice: a position statement from a panel of experts

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Optimización de los tratamientos de la insuficiencia cardiaca con fracción de eyección reducida en la práctica diaria: propuesta de un grupo de expertos

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ABSTRACT

Although treatment of patients with heart failure with reduced ejection fraction (HFrEF) with a combination of 4 medication classes is now recommended in major international practice guidelines, these guidelines do not specify how these treatments should be introduced and up-titrated. In consequence, many patients with HFrEF do not move on to an optimised treatment regimen. The objective of this review is to propose a pragmatic algorithm for treatment optimisation designed to be as easy as possible for practicing physicians to apply in routine practice. The first treatment goal is to ensure that all 4 recommended classes of medication are initiated as early as possible, in order to establish effective therapy, even at a low dose. This is considered preferable to starting fewer medications at a maximal dose. The second goal is to ensure that the intervals between introduction of different medications and between different titration steps are as short as possible, consistent with ensuring the safety of the patient. Specific proposals are made for older patients (> 75 years) who are frail, and for those with cardiac rhythm disorders. Application of this algorithm should allow an optimal treatment protocol to be achieved within a 2-month time-frame in the vast majority of patients. This needs to be our treatment goal in HFrEF and every effort must be undertaken to achieve it.

Keywords:

Heart failure

Treatment optimisation

Titration

Practice guidelines treatment algorithm

Cardiovascular diseases

RESUMEN

El tratamiento de los pacientes con insuficiencia cardiaca con fracción de eyección reducida (IC-FEr) con una combinación de cuatro clases de fármacos se recomienda actualmente en las principales guías de práctica clínica internacionales. Sin embargo, estas guías no especifican cómo deben introducirse y ajustarse estos tratamientos. En consecuencia, muchos pacientes con IC-FEr no pasan a un régimen de tratamiento optimizado. El objetivo de esta revisión es proponer un algoritmo pragmático para optimizar el tratamiento, diseñado para que sea lo más fácil posible de aplicar en la práctica diaria. El primer objetivo del tratamiento es garantizar que las cuatro clases de medicación recomendadas se inicien lo antes posible, con el fin de establecer una terapia eficaz, incluso a dosis bajas. Esto se considera preferible a iniciar menos medicamentos a una dosis máxima. El segundo objetivo es garantizar que los intervalos entre la introducción de los distintos medicamentos y entre los distintos pasos de titulación sean lo más breves posible, en consonancia con la seguridad del paciente. Se hacen propuestas específicas para los pacientes de edad avanzada (> 75 años) que son frágiles, y para aquellos con trastornos del ritmo cardiaco. La aplicación de este algoritmo debería permitir alcanzar un protocolo de tratamiento óptimo en un plazo de 2 meses en la gran mayoría de los pacientes. Este debe ser nuestro objetivo en el tratamiento de la IC-FEr y debemos hacer todo lo posible por conseguirlo.

Palabras clave:

Insuficiencia cardiaca

Optimización del tratamiento

Titulación

Algoritmo de tratamiento de guías de práctica clínica

Enfermedades cardiovasculares

ABBREVIATIONS

HF: heart failure

BB: beta-blockers

ARNI: angiotensin receptor-neprilysin inhibitors

ACEI: angiotensin-converting enzyme inhibitors

MRI: mineralocorticosteroid receptor antagonist

SGTL2I: type 2 sodium-glucose cotransporter inhibitor

GDMT: guideline-directed medical therapy

ABREVIATURAS

IC: insuficiencia cardiaca

BB: bloqueadores beta

ARNI: inhibidores del receptor la angiotensina y de la neprilisina

IECA: inhibidores de la enzima de conversión de la angiotensina

ARM: antagonistas del receptor de mineralocorticoides

ISGTL2: inhibidores del cotransportador de sodio-glucosa tipo 2

GDMT: guideline-directed medical therapy

INTRODUCTION

Heart failure (HF) is a major cause of hospitalisation, morbidity and mortality, notably in older patients, with an estimated worldwide prevalence of around 2%.[1] Nonetheless, appropriate management effectively prevents disease aggravation, acute decompensations and saves lives,[2] although optimisation is rarely obtained in real-life. New international practice guidelines have been published recently,[3,4] which recommend the use of a combination of 4 medication classes as the platform therapy for HF with reduced ejection fraction (Class I recommendation). These are certain beta-blockers (BB), angiotensin receptor-neprilysin inhibitors (ARNIs) or angiotensin-converting enzyme inhibitors (ACEIs), mineralocorticoid receptor antagonists (MRAs) and sodium-glucose co-transporter 2 inhibitors (SGLT2Is). However, how to introduce such guideline-directed medical therapy (GDMT) in a given patient remains a matter of debate.[5-12]

Important factors limiting the introduction and titration of HF medications include worsening renal function,[13] low blood pressure[14] and low heart rate.[15] Concomitant initiation of multiple drugs which carry a risk of these adverse events can be a hurdle, and this needs to be considered when choosing a therapeutic strategy. Likewise, rapid treatment optimisation, ideally within a 2-month timeframe, is also a challenge.

In the present article, we propose a pragmatic approach designed to be as easy as possible for practicing physicians to apply in routine practice. We have tried to take into consideration recent guidelines, the notion of early implementation and its difficulties, and the need to tailor management to individual patient requirements. This position statement was prepared through a collaboration between experts from the Heart Failure Working Group of the French Society of Cardiology, with the aims of promoting treatment optimisation and facilitating the practical implementation of the ESC HF guidelines.[4]

FACTORS TO CONSIDER WHEN DESIGNING AN ALGORITHM FOR MEDICATION OPTIMISATION IN CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION

Pharmacological considerations

The different classes of GDMT target different pathophysiological mechanisms: ARNIs/ACEI and MRAs inhibit the renin-angiotensin-aldosterone system,[16] with ARNIs also specifically blocking the degradation of natriuretic peptides and other vasoactive hormones.[17] BBs principally target the autonomic nervous system, but also inhibit renin synthesis.[18] Finally, SGLT2Is were originally developed to prevent glucose and sodium reabsorption in the kidney, but their beneficial effects in HF probably involve extrarenal mechanisms which are not yet fully elucidated.[19] From a pharmacological perspective, it appears reasonable to target the maximum number of physiopathological mechanisms in parallel, rather than attempting to achieve maximal inhibition of a single pathway.

Efficacy considerations

Historically, classes of GDMT were introduced sequentially, following demonstration of their efficacy from well-designed randomized clinical trials spanning a period of over thirty years. For this reason, each novel class has usually been evaluated compared to placebo over a platform therapy of previously available medication, and direct head-to-head comparative studies have not been performed (except for ARNIs vs ACEIs).[20]

To address the limited amount of data from direct comparisons, the relative efficacy of different HF treatments has been addressed in a recent metaanalysis of 75 randomized clinical trials.[21] Unsurprisingly, the most effective option in reducing all-cause death relative to placebo was the concomitant use of an ARNI, a BB, a MRA and a SGLT2I.[21] Importantly, there is no evidence for

interactions between classes of HF medication and the available data strongly suggest that each class has an independent impact on clinical outcomes, regardless of the other drugs with which the patient is treated.[8,22]

As well as the absolute treatment effect sizes of the different medication classes, the order in which they are introduced may also be important. For example, in a recent study in which different treatment sequences were modelled using data from 6 pivotal trials,[10] some differences in mortality outcomes were observed between sequences. However, the most important factor in reducing mortality was the rapidity of treatment up-titration.[10]

Early introduction of therapy following diagnosis or an acute exacerbation is recommended to optimise the prognosis. *Post hoc* findings from recent trials have consistently demonstrated a rapid reduction of risk following initiation of therapy. For example, in a large randomised trial comparing sacubitril/valsartan to enalapril,[20] and in recent trials of SGLT2i,[23,24] rehospitalizations were significantly reduced within 1 month of treatment initiation. Recently, in the STRONG-HF trial,[25] 900 hospitalised patients were randomised to management either with 'usual care' or 'high-intensity care'. The latter group received rapidly up-titrated 4-drug therapy to achieve optimal doses within 2 weeks of discharge. This approach was feasible and safe, and the trial demonstrated that rapid-titration of GDMT significantly reduced the risk of 180-day all-cause death or HF hospitalisation.[25] Acute hospitalisations provide a window of opportunity to initiate and optimise treatments for HF, and this window of opportunity will be lost if patients are discharged untreated.

Safety considerations

Low blood pressure, low heart rate, impairment of renal function and electrolyte disturbances, principally hyperkalaemia with MRAs, are the principal adverse events which limit the optimisation of GDMT.[26] In this respect, SGLT2Is appear to have the best safety profile as their effect on blood pressure is minimal and they do not generally cause orthostatic hypotension in those without hyperglycaemia (which can easily be rectified with intensification of other treatments for diabetes).[27]

However, SGLT2Is may expose patients to a higher risk of ketoacidosis,[28] especially if the patient becomes haemodynamically unstable and goes into shock. In such cases, SGLT2I treatment should be delayed or discontinued.[27] These drugs also may increase the risk of urinary infections in patients with a urinary catheter in place.[28]

Low blood pressure is principally an issue for BBs, ACEIs and ARNIs. Impaired renal function, due to reversible hemodynamic effects, is observed with MRAs, ACEIs and ARNIs.[13,29] While SGLT2I treatment may lead to a small early rise in serum creatinine, these drugs provide significant renal protection in the mid-term.[13] It should be noted that little information is available on medication risk in patients with very severe HF (ejection fraction < 25%), and these may require more conservative management. Of note, difficulties related to low blood pressure and impairment of renal function can be attenuated with recently proposed management algorithms.[14,29]

Another factor that influences how quickly GDMT can be optimised is persistence of congestion, which is associated with poor prognosis after discharge.[30] Apart from BB, which may need to be introduced later or titrated more slowly, persistent congestion should not prevent optimisation of GMDT prior to discharge. Indeed, ACEIs, ARNIs and SGLT2Is have been shown to improve decongestion.[31-33] However, the question of managing congestion is a complex one and deserves lengthier treatment elsewhere.

Comorbidities

Comorbidities are frequent in HF, especially diabetes, chronic respiratory diseases, and chronic kidney disease.[1] Many of the medications used for the treatment of HF are also effective in these other conditions or diseases such as hypertension or longstanding coronary artery disease. In patients with diabetes, the use of SGLT2Is in HF may improve glycaemic control as well as improving cardiac function. This class of drug has also more recently been shown to reduce disease progression and mortality in patients with chronic kidney disease.[34] Moreover, ARNIs have also been shown to improve diabetes control[35] and renal function in patients with HF.

PROPOSED ALGORITHM FOR OPTIMISATION OF HEART FAILURE MEDICATION

On the basis of the available evidence, we propose an algorithm for the initiation or optimisation of treatments for HF (figure 1). Our goal is to provide a simplified approach to the heterogeneous clinical presentations of patients, focusing on key factors that may influence drug tolerability (figure 2). The algorithm proposed can be applied to most patients. However, we appreciate that there are other patient groups whose clinical presentations are more complex. Our algorithm may be adapted in these cases for a more sophisticated comorbidity-based approach.[36] It should be noted that we focus here on a practical approach to optimise GDMT, and do not discuss other important aspects of HF management, such as second-line treatments, non-pharmacological management, and management of comorbidities.

The underlying principles of this algorithm (figure 2) are the following:

a) To ensure that all 4 recommended classes of GDMT are initiated as early as possible, in order to establish effective therapy, even at a low dose. This is considered preferable to starting fewer medications at a maximal dose, and has been identified as the most effective strategy in the network metaanalysis.[21]

b) To ensure that the intervals between introduction of different medications and between different titration steps are as short as possible, consistent with ensuring the safety of the patient. Again, rapid titration has been shown to provide mortality benefits in the STRONG-HF trial.[25]

c) To ensure that the time from first treatment initiation to reaching the target dose for all 4 GDMT components[4] does not exceed 30 days and that the patient is stabilised on optimal medication dosing within 2 months.

The algorithm proposed is a general one, developed for use in all patients with HF, except for 2 specific populations who may require different treatment strategies. The needs of these patients are addressed separately below. This concerns:

a) Patients aged > 75 years who are frail (defined as a Triage Risk Screening Tool score ≥ 2)[37,38]

b) Patients with certain cardiac rhythm disorders

The algorithm proposes specific management pathways depending on the number of current HF medication classes used, on whether the patient is hospitalised or not, and on the presence of low blood pressure (systolic blood pressure < 100 mm Hg) or impaired renal function (estimated glomerular filtration rates [eGFR] < 30 ml/min/1.72 m²).

Management of patients aged > 75 years

The prevalence of HF rises steeply with age, reaching between 15% and 20% in individuals aged ≥ 80 years.[39] These patients are more likely to develop adverse events to medication, are likely to be already polymedicated, and to present unfavorable prognostic factors, such as renal failure, cognitive disorders, a risk of falls and malnutrition. These considerations need to be considered when deciding how to optimize treatment in such patients. Moreover, frailty is very common in older people with HF (45%)[40] and this increases the risk of mortality and hospitalisations.[41]

All patients aged > 75 years should undergo frailty evaluation using validated frailty scales. We recommend using the Triage Risk Screening Tool (TRST),[38] which is a very simple and rapid test considering multiple dimensions of frailty. Recently a Cardiology/Geriatrics consensus group proposed using the TRST as a frailty screening tool in the cardiology setting.[37] Patients with a TRST score ≥ 2 should be considered frail and treated in a more conservative manner. However, others frailty scales can also be used, including the FRAIL scale,[42] the Clinical Frailty Score,[43] or the Fried criteria,[44] although these scales cover less dimensions of frailty than the TRST.

For the frail patients, treatment escalation should be more gradual than that proposed in the general HF treatment algorithm. Starting doses of all drug classes should be ¼ the full dose, with the

exception of SLGT2Is, which can be given at the full dose. The dosing interval should be extended to 1-2 weeks between each change in medication and the dose increased in incremental steps of a ¼ dose. The final dose of all medications will more often be below the usual targets specified in treatment guidelines for all drugs, apart from SGLT2Is. Nonetheless, titration to maximally tolerated doses in the elderly should be attempted whenever possible. An algorithm illustrating the proposed treatment escalation sequences for frail patients > 75 years old according to their baseline blood pressure and kidney function status is provided in figure 3.

In addition, the presence of frailty should trigger the management of comorbidities and geriatric syndromes by a comprehensive geriatric assessment.[37,45] This multidimensional assessment should take into account comorbidities, cognitive function, autonomy, walking disorders, the risk of falls, nutritional status, depression, polypharmacy, vaccination status (notably influenza, pneumococcus and COVID) and social isolation.[37,45] Such multidisciplinary management has been shown to reduce mortality in older patients with HF.[45] Any medical needs identified during this assessment should be addressed promptly in parallel to HF treatment. Wherever appropriate, specific comorbidities should be managed, home help (nurses and social support) and cognitive stimulation offered, physical activity adapted, and physiotherapy or psychotherapy provided as needed. Medications and vaccination status should be checked, and vitamin D supplementation, oral nutritional supplements and antidepressant treatment provided when justified. Finally, an environmental assessment should be made.

Management of patients with cardiac rhythm disorders

Cardiac rhythm disturbances, such as supraventricular and ventricular arrhythmias, bradycardia and conduction disturbances (mainly left-bundle branch block) are commonly observed in patients with HF, and contribute to the increased mortality and morbidity of these patients.[4] For these reasons, it

is important to ensure a specific diagnostic work-up for rhythm disorders and their appropriate management in all patients diagnosed with HF. Associated rhythm disorders can have an impact on the titration strategy, as in patients with ventricular tachycardia or premature ventricular contractions, BB should be introduced in the first treatment step, in preference to ACEIs or ARNIs, due to their beneficial effect on rate control.

In addition, the decision to implant a cardioverter-defibrillator should be made after drug optimization, according to ESC practice guidelines,[4] in all patients with symptomatic HF (NHYA class II-III) and a left ventricular ejection fraction ≤ 35% with ischemic cardiomyopathy (Class IA recommendation) and non-ischemic cardiomyopathy (Class IIa A). Rapid initiation of HF drugs is advisable to ensure timely implementation of cardioverter-defibrillators in patients in whom left ventricular ejection fraction remains ≤ 35%. In patients with HF and wide QRS and conduction disorders, cardiac resynchronization therapy should be considered, the level of recommendations depending on the QRS width and the type of conduction disorder (presence or absence of left-bundle branch block).[4]

Atrial fibrillation (AF) is a common comorbidity in patients with HF, its prevalence increasing with the severity of HF.[46] Around half of all patients with HF either have pre-existing AF at the time of diagnosis of HF or develop AF subsequently.[47] Comorbid AF may aggravate underlying HF,[48] for example due to the development of tachycardia-mediated cardiomyopathy which impairs ventricular contractility.[46] Patients with AF should be proposed cardioversion and antiarrhythmic drugs (limited to amiodarone in patients with reduced ejection fraction), or catheter ablation, the latter having been shown to be more effective in reducing the risk of HF exacerbation.[49]

HEALTHCARE ORGANISATION

Once the 4 classes of GDMT have been initiated, the doses will require optimisation in the community setting and regular monitoring, with adjustment where necessary to avoid acute exacerbations which may be fatal, and generally require rehospitalisation.

Following discharge from the hospital after an episode of worsening HF, patients enter a vulnerable period, during which transition care programmes are advocated to avoid early HF re-admissions.[50] A randomized clinical trial is currently underway to document the effectiveness of such programmes.[51]

However, a majority of HF patients are not followed-up promptly, when they are still at high risk.[52] The dose optimisation phase is crucial and it is recommended that detailed instructions on implementation be provided in the discharge letter for patients going home from hospital.[52] In the absence of dedicated follow-up, treatment optimisation may not be implemented correctly, and the long-term consequences of this are likely to be more deleterious to prognosis than how the treatments were introduced initially. Unfortunately, many patients discharged from hospital never move on to an optimised treatment regimen due to the inertia of the system.[11,52-56] Establishing structured post-discharge follow-up is crucial, ideally through a dedicated disease management programme.[57,58] Trained and dedicated HF nurses are usually the cornerstone of rapid treatment optimisation as they can titrate HF drugs, provide therapeutic education, ensure a personalised contact with the patient and identify early any signs of deterioration. In a recent randomised clinical trial evaluating the role of nurses in up-titrating HF medication, HF nurses achieved higher doses of BB and ACE-Is over a 4-month period than did HF cardiologists, principally because nurses were able to see the patient much more frequently.[59] In addition, multidisciplinary management involving a dedicated HF nurse has been shown to improve adherence to practice guidelines[60] and clinical outcomes.[61]

Telemedicine programmes can be especially useful to ensure timely modifications of treatment or other interventions should the patient's state deteriorate.[62-64] However, telemedicine may not be appropriate for all patients, notably those with cognitive impairment or poor adherence.

Following an episode of acute decompensation, cardiac rehabilitation involving exercise training associated with psychosocial support and dietary counselling is useful for reducing the risk of rehospitalisation.[65] Currently, patients are not sufficiently referred to cardiac rehabilitation centres from community care.[66]

In primary care, delays in referral to specialist HF physicians, limited consultation time and lack of communication between health professionals can lead to inadequate implementation of optimal treatment and inappropriate follow-up.[67] To avoid a silo approach to care of HF patients in the community, multidisciplinary management involving a dedicated HF nurse and both hospital and community cardiologists is essential. Education of healthcare professionals is critical in this respect and provision of online medical expertise could be a powerful way for centres of excellence for HF care to reach out to community healthcare providers.

It is important to emphasise that differences in the organisation of care for patients with HF between regions and countries clearly exist, and these need to be considered when considering how to optimise treatment pathways. However, it is also the responsibility of national decision-makers to ensure that the best quality of care can be offered to all patients and that inequalities in care provision are minimised.

CONCLUSIONS

In this position paper, we propose a pragmatic algorithm for the implementation and optimisation of GDMT for the treatment of HF with reduced ejection fraction. We believe that the sequential

introduction and titration of these '4 pillars of heart failure' within 2 months of an acute exacerbation of pre-existing HF or a recent diagnosis can be achieved routinely in most patients with HF. This needs to be our treatment goal and every effort must be undertaken to achieve it. The algorithm proposed above should help hospital and community physicians achieve this goal in everyday practice.

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AUTHORS' CONTRIBUTIONS

NG and FR coordinated the manuscript.

NG, CL, OH, FR drafted parts of the manuscript.

NG, CL, OH, ABG, JLJ, TD, BL, CM, PS and FR provided critical reviewing and editing of the initial draft.

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FIGURES

Figure 1. Proposed treatment algorithm for patients with heart failure.

1. In patients with an eGFR between 30 and 40 ml/min/1.73m², kidney function and serum electrolytes should be monitored more closely.

2. Particular attention should be paid to regular monitoring of serum potassium in this group.

3. ARNIs are to be preferred to ACEIs, as this will allow the treatment to be optimised most rapidly. However, ACEIs can be used as an alternative, notably if ARNIs are contra-indicated. A ¼ dose of the ARNI sacubitril/valsartan corresponds to 24/26 mg *bid* and a ½ dose to 49/51 mg *bid*.

4. In patients with ventricular tachycardia or premature ventricular contractions, a BB should be preferred to an ACEI as a first step. Caution should be exerted in patients with either very low BP or clinical instability.

5. Titration should not be considered definitive, and medication should be reassessed at each follow-up visit in function of the general medical condition of the patient. Even in patients whose ejection fraction improves after treatment, guideline-directed medical therapy should be pursued.

ACEI, angiotensin-converting enzyme inhibitor; AE, adverse events; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blockers; BP, blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SGLT2I, sodium-glucose like transporter type 2 inhibitor; VT, ventricular tachycardia.

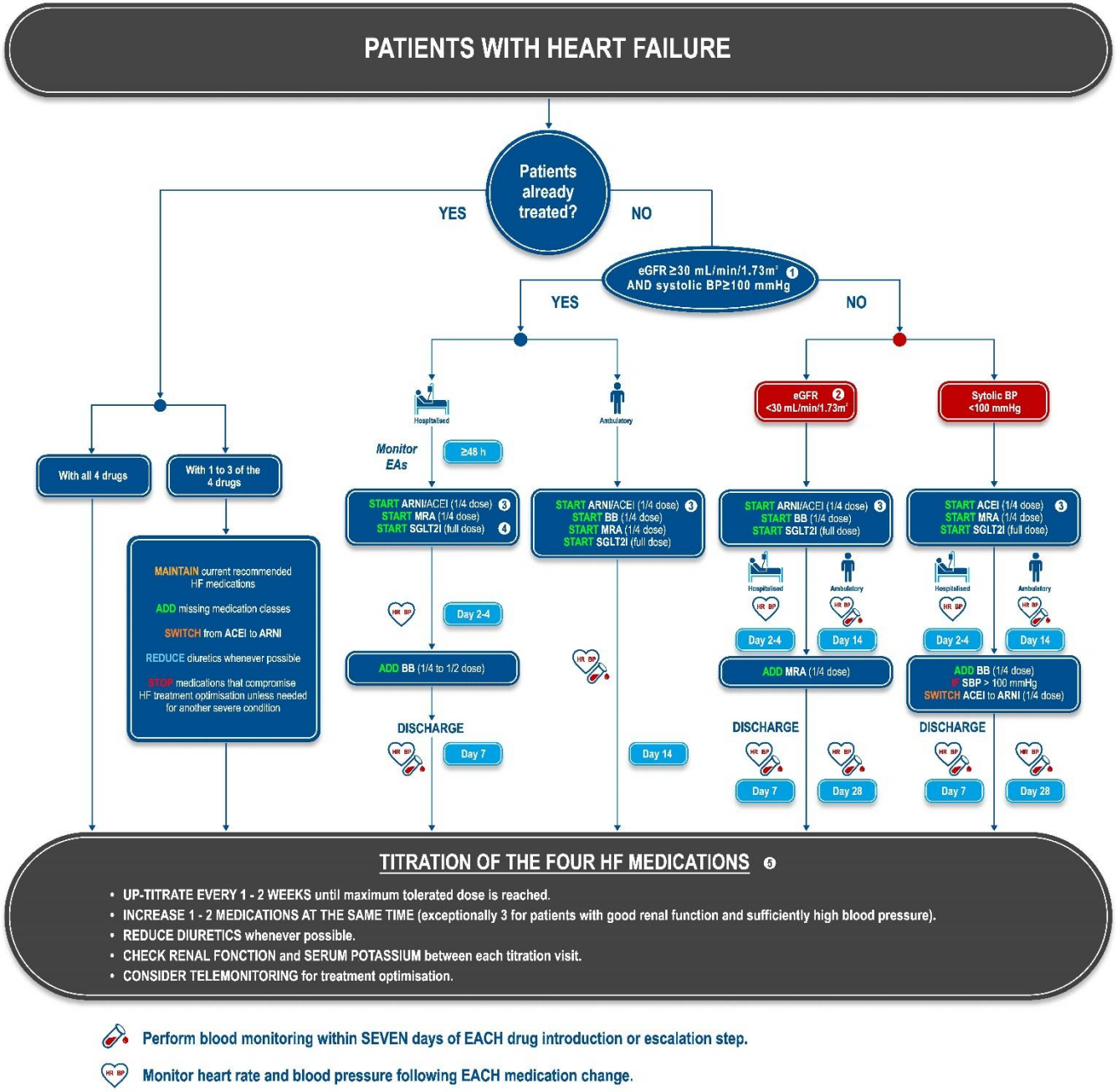
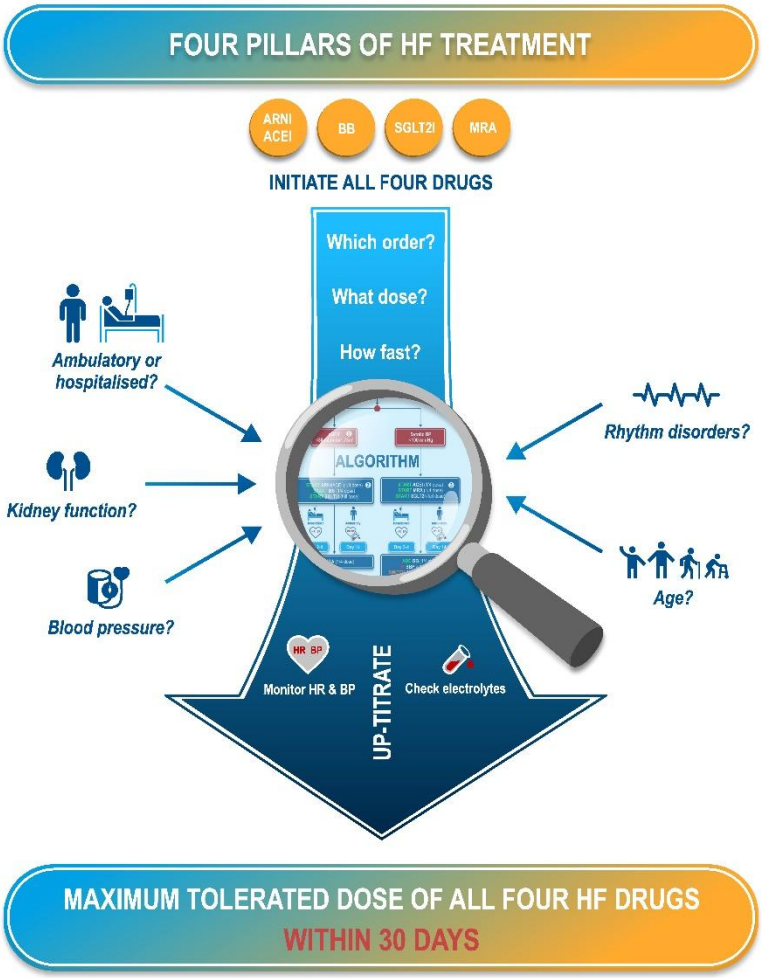

PATIENTS WITH HEART FAILURE
Patients already treated?
YES
NO
eGFR ≥30 mL/min/1.73m² 1 AND systolic BP≥100 mmHg
YES
NO
With all 4 drugs
With 1 to 3 of the 4 drugs
MAINTAIN current recommended HF medications
ADD missing medication classes
SWITCH from ACEI to ARNI
REDUCE diuretics whenever possible
STOP medications that compromise HF treatment optimisation unless needed for another severe condition
Hospitalised
Ambulatory
Monitor EAs
≥48 h
START ARNI/ACEI (1/4 dose) 3
START MRA (1/4 dose)
START SGLT2I (full dose) 4
START ARNI/ACEI (1/4 dose) 3
START BB (1/4 dose)
START MRA (1/4 dose)
START SGLT2I (full dose)
Day 2-4
ADD BB (1/4 to 1/2 dose)
DISCHARGE
Day 7
Day 14
eGFR 2 <30 mL/min/1.73m²
Sytolic BP <100 mmHg
START ARNI/ACEI (1/4 dose) 3
START BB (1/4 dose)
START SGLT2I (full dose)
START ACEI (1/4 dose) 3
START MRA (1/4 dose)
START SGLT2I (full dose)
Day 2-4
Day 14
ADD MRA (1/4 dose)
ADD BB (1/4 dose)
IF SBP > 100 mmHg
SWITCH ACEI to ARNI (1/4 dose)
DISCHARGE
DISCHARGE
Day 7
Day 28
Day 7
Day 28
TITRATION OF THE FOUR HF MEDICATIONS 5
• UP-TITRATE EVERY 1 - 2 WEEKS until maximum tolerated dose is reached.
• INCREASE 1 - 2 MEDICATIONS AT THE SAME TIME (exceptionally 3 for patients with good renal function and sufficiently high blood pressure).
• REDUCE DIURETICS whenever possible.
• CHECK RENAL FONCTION and SERUM POTASSIUM between each titration visit.
• CONSIDER TELEMONITORING for treatment optimisation.
Perform blood monitoring within SEVEN days of EACH drug introduction or escalation step.
Monitor heart rate and blood pressure following EACH medication change.

Figure 2. Central illustration. An algorithm is proposed on how to introduce and optimise the 4 GDMT medications based on factors that influence drug tolerability, giving recommendations for monitoring and titration to achieve optimal dosing within 30 days. ACEI, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blockers; BP, blood pressure; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SGLT2I, sodium-glucose like



transporter type 2 inhibitor.

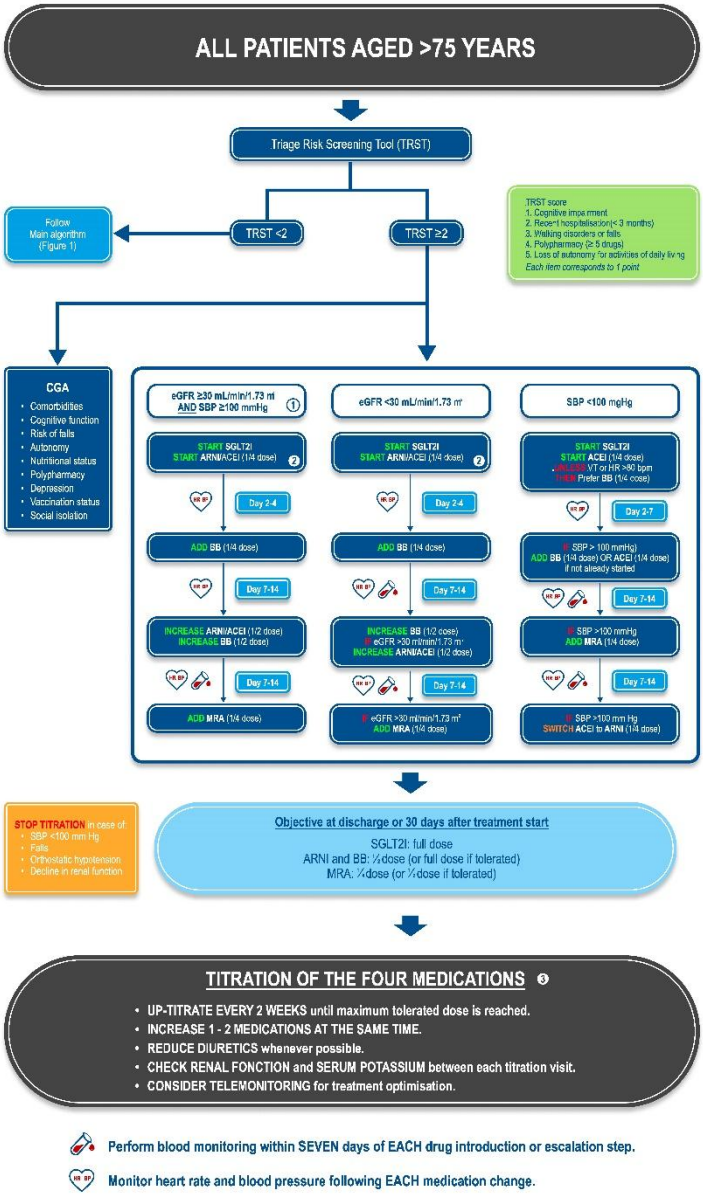
Figure 3. Proposed treatment algorithm for patients aged >75 years with heart failure.

1. In patients with an eGFR between 30 and 40 ml/min/1.73m², kidney function and serum electrolytes should be monitored more closely.

2. ARNIs are to be preferred to ACEIs, as this will allow the treatment to be optimised most rapidly. However, ACEIs can be used as an alternative, notably if ARNIs are contra-indicated. A ¼ dose of the ARNI sacubitril/valsartan corresponds to 24/26 mg *bid* and a ½ dose to 49/51 mg *bid*.

3. Titration should not be considered definitive, and medication should be reassessed at each follow-up visit in function of the general medical condition of the patient. Even in patients whose ejection fraction improves after treatment, guideline-directed medical therapy should be pursued.

ACEI, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blockers; CGA, Comprehensive Geriatric Assessment; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; SGLT2I, sodium-glucose like transporter type 2 inhibitor; TRST, Triage Risk Screening Tool; VT, ventricular tachycardia.


ALL PATIENTS AGED >75 YEARS
Triage Risk Screening Tool (TRST)
TRST score
1. Cognitive impairment
2. Recent hospitalisation(< 3 months)
3. Walking disorders or falls
4. Polypharmacy (≥ 5 drugs)
5. Loss of autonomy for activities of daily living
Each item corresponds to 1 point
TRST <2
Follow Main algorithm (Figure 1)
TRST ≥2
CGA
Comorbidities
Cognitive function
Risk of falls
Autonomy
Nutritional status
Polypharmacy
Depression
Vaccination status
Social isolation
eGFR ≥30 mL/min/1.73 m² AND SBP ≥100 mmHg
eGFR <30 mL/min/1.73 m²
SBP <100 mgHg
START SGLT2i
START ARNI/ACEI (1/4 dose)
START ACEI (1/4 dose)
UNLESS VT or HR >80 bpm
THEN Prefer BB (1/4 dose)
Day 2-4
Day 2-7
ADD BB (1/4 dose)
IF SBP > 100 mmHg
ADD BB (1/4 dose) OR ACEI (1/4 dose) if not already started
Day 7-14
INCREASE ARNI/ACEI (1/2 dose)
INCREASE BB (1/2 dose)
INCREASE BB (1/2 dose)
IF eGFR >30 ml/min/1.73 m²
INCREASE ARNI/ACEI (1/2 dose)
IF SBP >100 mmHg
ADD MRA (1/4 dose)
ADD MRA (1/4 dose)
IF eGFR >30 ml/min/1.73 m²
ADD MRA (1/4 dose)
IF SBP >100 mm Hg
SWITCH ACEI to ARNI (1/4 dose)
STOP TITRATION in case of
SBP <100 mm Hg
Falls
Orthostatic hypotension
Decline in renal function
Objective at discharge or 30 days after treatment start
SGLT2I: full dose
ARNI and BB: ½ dose (or full dose if tolerated)
MRA: ¼ dose (or ½ dose if tolerated)
TITRATION OF THE FOUR MEDICATIONS
UP-TITRATE EVERY 2 WEEKS until maximum tolerated dose is reached.
INCREASE 1 - 2 MEDICATIONS AT THE SAME TIME.
REDUCE DIURETICS whenever possible.
CHECK RENAL FONCTION and SERUM POTASSIUM between each titration visit.
CONSIDER TELEMONITORING for treatment optimisation.
Perform blood monitoring within SEVEN days of EACH drug introduction or escalation step.
Monitor heart rate and blood pressure following EACH medication change.