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Patients profiling in Heart Failure for tailoring medical therapy

A consensus document of the Heart Failure Association of the European Society of Cardiology

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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 ESC/HFA Guidelines[1], and its updates[2-4]. However, despite the recommendations and evidence, 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, proven to positively impact morbidity and mortality. This may be because of tolerability issues related to low blood pressure, heart rate, impaired renal function or hyperkalaemia[6-10](table 1). Poor access to specialist care[11,12], physician inertia and organization of care [13] 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 lack of adherence are also cause of undertreatment in HF[14].

The treatment of patients with HF has evolved over the last few years, with new evidence for novel therapies. Never before has there been such an opportunity to positively impact prognosis with drug therapy for patients with heart failure with reduced ejection fraction (HFREF). This comes, however, with increased complexity in management. For years, treating HFREF patients required dealing with Angiotensin Converting Enzyme Inhibitors (ACE-i), Angiotensin receptor Blockers (ARB) if ACEi were not tolerated due to cough, Beta-blockers (BB), Mineralocorticoid Receptor Antagonists (MRA), digoxin, diuretics and devices. But over the past decade Ivabradine, Sacubitril/Valsartan, Sodium-glucose Cotranspoter-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 needing 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 poor socioeconomic status, lack of social support, lack of adherence, and those related to medical, biological factors, such as low blood pressure, renal dysfunction, congestion.

Through inclusion and exclusion criteria of RCT's, subgroup analyses, and meta-analyses, and taking in consideration specific patient profiles that may limit the implementation of medical therapy, it is possible to personalise specific therapeutic options.

All efforts should be made to have all GDMT and devices offered to every patient, and personalization should be seen as a means to achieve this, or in the patient who cannot tolerate all drugs, to achieve as close to full GDMT as is achievable.

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 to review the need and timing for device therapies, the form of an exercise or rehabilitation program and life style changes. It also must include the scheduling of primary care visits within the first week after 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 therapies taken at discharge improve outcomes, with a lower mortality rate both at 90 days and 1 year. Recently, ARNI have shown that they can be safely introduced prior to discharge, and SGLT2i introduced during hospitalisation have shown to reduce rehospitalizations and mortality. [17-20]

In the transition phase, approximately the first two months after hospitalization for decompensated HF, there is an unmet need to implement and titrate GDMT. This results from inadequate knowledge of Guidelines (GL) recommendations, and a failure to integrate GL 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 GL was in older patients, with more comorbidities, and from a minority group[21], may also reveal the gaps in evidence.

Nonetheless, there is clear evidence that adherence to medication is associated with lower cardiovascular (CV) mortality and fewer hospitalizations for HF in chronic outpatients [22-24,]. The contributions of multi-disciplinary team professionals and patient/family members' education

and interactions are fundamental to overcome poor adherence to medication[25,26]. These programs 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 ESC/HFA Guidelines.

Intolerance to GDMT specially in very symptomatic patients, should prompt evaluation for the need to referral to a specialised HF Centre.

In summary, there are physician, patient and organizational barriers for 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 eGFR < 60 ml/min/1,73 m^2, 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 needs to be done while considering 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 of treatment with neurohormonal blockers, as the presence of 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 an absolute risk

reduction for mortality higher in patients with worse baseline eGFR, when treated with spironolactone compared to placebo[28]. If worsening renal function (WRF) occurs during RAASi up-titration (described as "pseudo WRF"), there is indication to temporarily discontinue medication if an increase of more than 100% of serum creatinine occurs, or potassium levels rise to more than 5.5mEq/L. RAASi doses can be reduced if serum creatinine increases by less than 50% of baseline levels, and is still <3 mg/dL and eGFR> 25 ml/min/1,73 m^2. Re-administration is advised, when the adverse reaction has resolved.

It is important to keep in mind that GFR declines with age, and more so in HF patients (2-3ml/min/1,73m^2 /year above the age of 50) and HF and DM patients (5 ml/min/1,73 m^2/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 in renal dysfunction. Conversely, these drugs have been shown to be reno-protective in patients with HF and/or DM and/or CKD [31-33].

Phenotyping patients for targeted therapies

With effective new drugs for the treatment of HF, the demand for patient phenotyping has become increasingly important, as some patients will not 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 (AI), and machine learning approaches will play a major role in the future[36,37]. Biomarker-guided approaches can have further benefits, as evaluating toxicity, in dose ranging, patient stratification and therapy monitoring.

Multi-omics integration together with imaging technology advances and new machine learning and AI 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 for patients with HFrEF, as established by the large RCT's. Questions could arise about the translation of these benefits to real-world practice, involving less selected population, such as older patients, women, frail, multimorbid patients who are often not included in RCT[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 that a survival benefit at 24 months was seen with the incremental use of GDMT, reaching a potential plateau at 4 to 5 therapies[40]. In fact, in this analysis, some of these therapies had a survival estimate advantage at two years greater than that observed in RCT. Eventually, this real-world group of HF patients, less selected than those in the RCT population, may derive greater benefit from these drug therapies. Data from EPICAL2 study recently showed that long term adherence to guideline-recommended drugs was associated with lower 3-year all-cause and CV mortality, in HFrEF patients[1]. In the Qualify Registry examining 6118 ambulatory HFrEF patients, adherence was assessed for five classes of recommended HF medications and dosages. Cardiovascular and HF deaths were significantly negatively associated with physician's

adherence to guidelines[22]. So, despite absence of evidence from RCT's, there is, through registries, suggestions of 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 patients' 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, because of hypertension, ischaemic heart disease, atrial fibrillation or other conditions, patients with HF are already on ACEi, and/or BB or diuretic. The challenge is to adequately prioritize or choose the most adequate up titration of drugs according to the patients' profile. Another frequent clinical scenario is the patient admitted for HF, whether due to de novo HF or to decompensated chronic HF patients in whom GDMT was reduced or suspended, needing guidance on how to start medical therapy, or how to perform up titration at discharge

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 heart failure (Figure 1).

The core of HF treatment includes ACEi/ARB/ARNI, Beta-blockers, MRA andSGLT2i. These medications should be started in all patients with heart failure.

Presence of congestion should be assessed, and diuretic implemented in the correct regimen in order to achieve an euvolemic state. Apart from symptoms, congestion may negatively impact proper titration of GDMT. Proper utilization of diuretics in HF will not be addressed here, at 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, and also the need for devices. The question raises on how this therapy can be implemented, as all core therapies but SGLT2i affect either blood pressure, 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 helps to identify tailored therapeutic 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 recognise patients can frequently not 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.

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 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 hypovolemia, bleeding or infection. All non-HF medication 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 euvolemic, reduction or suspension of diuretics can be attempted, and careful monitoring in the following days is necessary to avoid fluid retention. Modifying GDMT medication or their doses needs to be addressed only if the patient has symptomatic hypotension. Lower heart rate (HR) is associated with improved survival in HFREF and sinus rhythm, and the most favourable outcome is observed with a HR around 60 bpm [47]. BB are part of the core of HFREF therapy, and should be up titrated to the target dose, or maximal tolerated dose. In the Copernicus trial, in patients with a systolic blood pressure between 85 and 95 mmHg, there was no evidence of decline in systolic blood pressure when treated with BB, compared to placebo. These patients were at a highest risk of an event, and experienced a greater absolute benefit from treatment with BB[48]. In the CARVIVA 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 stopping unnecessary blood pressure lowering medications, the reduction or even suspension of BB may be necessary. In this situation, Ivabradine, which has an action solely on heart rate with no impact on blood pressure represents an important therapeutic resource. MRAs and SGLT2i have a very modest impact on

blood pressure, so their suspension is not mandatory or necessary[50-52]. Use of sacubitril/valsartan is contraindicated in patients with systolic blood pressure <100 mmHg. Omecamtiv mecarbil seems a very interesting therapeutic option in more severely affected patients within this phenotype.

2- **Patients with low blood pressure and low HR** – Consider other causes of hypotension, and other medications as in profile 1. Modifying GDMT medication or their doses needs to be addressed only if the patient has symptomatic hypotension. MRAs and SGLT2i have a very modest impact on blood pressure, so their suspension is necessary. Reduction of BB may be necessary if the patient has a heart rate <50 bpm, or symptomatic bradycardia. Omecamtiv mecarbil is a viable therapeutic option in these patients where limited GDMT can be used.

3- **Patients with normal blood pressure and low HR** – drugs with a negative chronotropic effect should be carefully reconsidered and if possible suspended, 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 HR remains <50 bpm or the patient has symptomatic bradycardia. Furthermore, patients with bradycardia or HR<50 bpm will also require a down-titration of beta-blockers.

4-**Patients with normal blood pressure and high HR** – these patients should be treated with target doses of BB. In case high heart rate in sinus rhythm persists (HR>70bpm) the concurrent use of beta-blockers and ivabradine leads to a better HR control and better up-titration of beta-blockers with a lower incidence of side effects. ACEi/ARB or ARNI need to be up titrated to target dose in HFrEF patients, as this was always the aim in RCT, and higher doses have provided greater benefit than lower doses[53,54]. In hospitalised patients initiation of vericiguat should be considered before discharge.

5- **Patients with atrial fibrillation and normal blood pressure** - The optimal resting ventricular rate in patients with AF and HF has not been clearly determined but may be between 60- 80 bpm[55]. In contrast to patients in sinus rhythm, HR is not a predictor of mortality in HFrEF patients with atrial fibrillation. There is no clear evidence for a prognostic benefit of

BBs in heart failure patients with AF [56,57]. Attempts to up titrate BB to maximal dose may have a detrimental effect, as ventricular rates below 70 bpm have been associated with a worse outcome. Anticoagulation (NOAC) is always indicated in patients with AF unless risks exceed the potential benefits or these drugs have specific contra indication.

6- **Patients with atrial fibrillation and low blood pressure** – As stated previously, evidence for the benefit of BB's on mortality and morbidity is less strong, so BB may be reduced or suspended 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 uptitration of drugs with an impact on mortality and morbidity, as ACEi or ARNI. MRAs and SGLT2i have a very modest impact on blood pressure, so their suspension is not mandatory nor necessary. Patients with AF and HF should always be anticoagulated preferably with NOACs unless contra indicated.

7- **Patients with chronic kidney disease-** Most RCT exclude patients with severe CKD, limiting the evidence available regarding benefit and safety of drugs in this situation. Data from registries show that patients who could potentially benefit from GDMT, are precluded from its use for unspecified reasons, or invalid reasons, such as CKD with eGFR>30ml /min/1,73 m^2. ACEis/ARBs/ARNI only need to be stopped when creatinine increases by >100% or to >3.5 mg/dL or eGFR <20 mL/min/1.73 m^2. Beta-blockers can be safely given to patients down to an eGFR of 30 ml/min/1,73 m^2, with a clear benefit in mortality. MRAs can also be given down to eGFR of 30 ml/min/1,73 m^2, 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 m^2. Dapagliflozin and empagliflozin have been shown to be efficacious and safe and to improve cardiovascular and renal end points in patients with an eGFR>20-25 mL/min/1.73 m^2. However, there is evidence of benefit from dapagliflozin also in patients with eGFR <20 mL/min/1.73 m^2. 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 m^2 and eGFR > 20 ml /min/1,73 m^2 respectively. Other drugs may worsen renal function (i.e. NSAIDs), so it is important to be sure that they are not unnecessarily being taken by the patient[27]. Potassium binders (patiromer and sodium zirconium cyclosilicate) have shown efficacy reducing serum potassium in HF patients and CKD treated with RAASi [59,60]. Nevertheless, there is still no evidence of their positive impact in prognosis.

8- Pre-discharge patient –During hospitalization, patients may get stabilized while still remaining -congestive. In fact, 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 of 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 full dose, should be started first, provided the patient has 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 heart failure, when initiated before or just after discharge[21]. Omecamtiv mecarbil and vericiguat can be used in selected patients before discharge as they have shown to reduce events. These drugs can contribute to decongestion, eventually allowing a safer initiation of BB.

9- Patient with hypertension despite GDMT - in the patient with a hypertensive profile, it is important to ensure the patient is not taking any medication that may increase blood pressure, as NSAID, corticoids or bronchodilators. Patients adherence to medication has to be assured,

and that the higher recommended doses are being used. If, despite GDMT on optimal doses, the patient is still hypertensive, the combination of isosorbide dinitrate and hydralazine should be used to achieve a controlled blood pressure profile.

Conclusion

GDMT has a major impact on the mortality and morbidity of patients with heart failure. Therefore, all efforts should be made to initiate and up-titrate foundational therapy. A personalized patient approach, adjusting GDMT to the patient's hemodynamic 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 class before adding the next, in a misguided "one size fits all" approach.

RCTs have so far patients 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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Figure 1- blood pressure, heart rate, presence of AF, of CKD or hyperkalaemia, and hypertension, are important characteristics when considering medical therapy in HF patients.

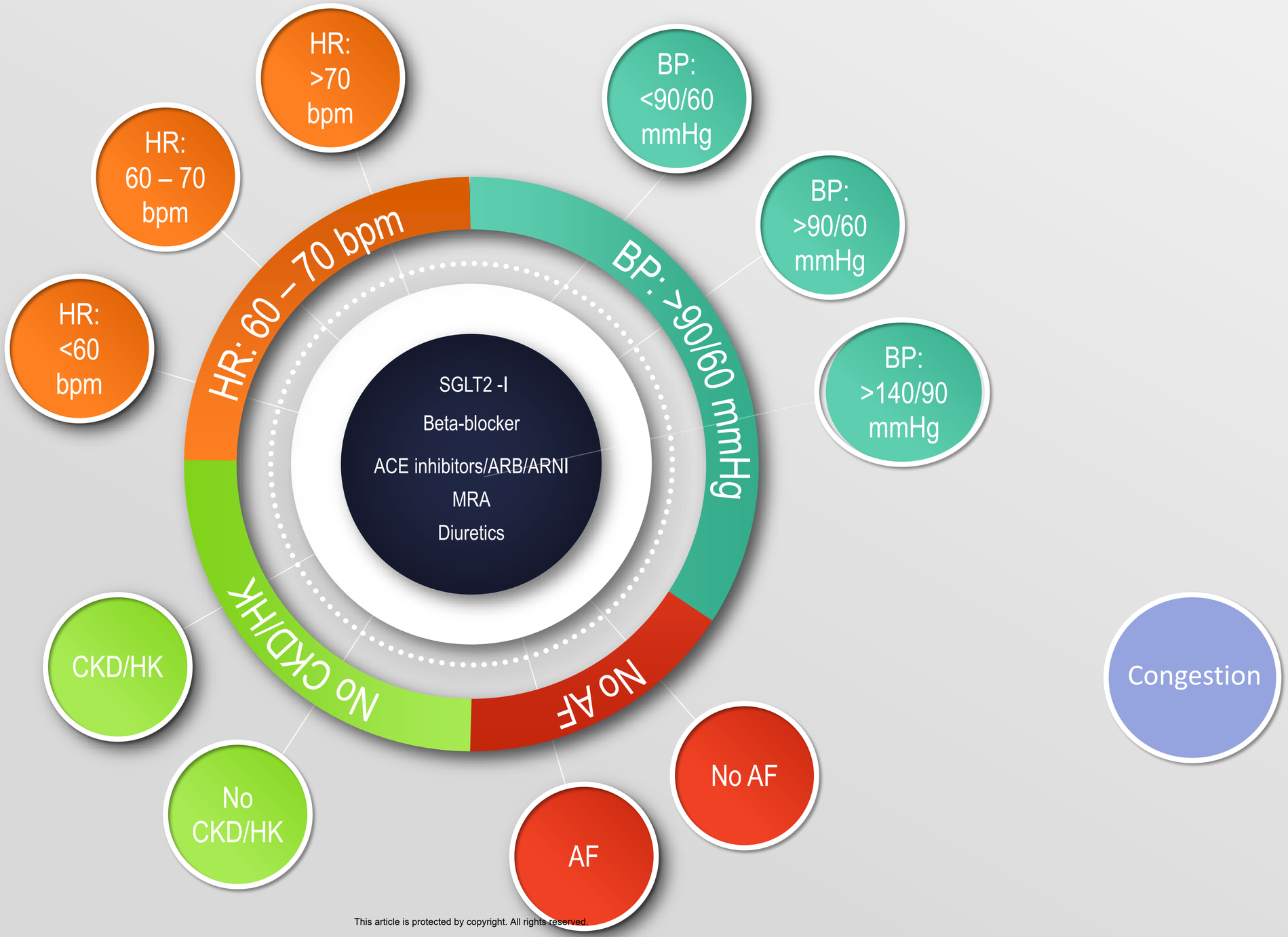
Figure 2- tailoring of medical therapy according to clinical profiles. According to some patients' characteristics – blood pressure, heart rate, presence of AF, of CKD or hypertension, some drugs may have to be reduced, suspended, or added

black- drugs that should be given to patients

red – drugs that need to be reduced or suspended

blue - drugs that need to be added

*For patients with predominant CCS threshold of BP is 120/80 mmHg



Drug	Common side effects
Diuretics	Hypotension; hypokalaemia; hypomagnesaemia; hyponatraemia; hyperuricemia; hypovolemia/dehydration; rise in creatinine, urea.
ACE inhibitors/ 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
SGLT2 inhibitor	Genital infection (in diabetic patients)

Table 1. Common side effects of GDMT

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 BB; 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/anemia	✓		
Kidney dysfunction		ACEi, ARB, ARNI, MRA may have some limitations- see text	Diuretics may need higher doses to be effective
Cachexia		ACEi, ARB, ARNI need to be uptitrated carefully because of orthostatic hypotension	

Table 2. Common comorbidities seen in HF and impact in use of GDMT