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BCS Editorial

European Society of Cardiology Heart Failure Guidelines 2021: What should we be doing in current practice?

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Take Home Messages

The recommendations for clinicians from ESC HF Guidelines 2021 most likely to impact management of the heart failure patient:

- Aim to start all patients with heart failure and a reduced ejection fraction (HeFREF) on "quadruple therapy" – with one of either an angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), or sacubitril valsartan) **plus** mineralocorticoid receptor antagonist (MRA) **plus** β-blocker **plus** sodium glucose co-transporter 2 inhibitors (SGLT2I).
- Treatment with ACEI, ARB, β-blocker, MRA or sacubitril valsartan now has a class IIb indication - "may be considered" - for patients with a left ventricular ejection fraction of 40-49%.
- Primary prevention implantable cardioverter defibrillator for patients with non-ischaemic cardiomyopathy, and cardiac resynchronisation therapy for patients with left bundle branch block and QRS duration 130-149ms have been downgraded from a class I indication "recommended" to a class IIa indication "should be considered".
- Patients admitted to hospital with HeFREF should have oral treatment "optimised" pre-discharge.
- Patient education and self-management advice has been given a class I indication so as to help patients manage their condition, and stay well.

Introduction

The 2012 European Society of Cardiology (ESC) Heart Failure (HF) guidelines recommended, in its 61 pages, the use of three different drug classes for the treatment of "systolic" HF while acknowledging "diastolic" HF as a separate and untreatable entity (1). The 2021 ESC-HF guidelines, in its 128 pages, cover a period of scientific study during which the understanding and treatment of HF has advanced more than for any other chronic condition (2).

HF is increasingly treated by a wide range of clinicians and this editorial attempts to distil the most recent guideline into 5 key "take-home" messages.

"All at once" heart failure treatment

The 2021 guideline marks a significant change in HF management. It advises that once diagnosed, patients with HF and a reduced ejection fraction (HeFREF) should be treated with two renin-angiotensin-aldosterone-system inhibitors (either an angiotensin converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), or sacubitril-valsartan; and a mineralocorticoid receptor antagonist (MRA)); a beta-blocker; and a sodium-glucose co-transporter-2 inhibitor (SGLT2I); plus diuretic for those with venous congestion (**Table 1**).

About the author

Joe Cuthbert graduated from the Hull York Medical School (HYMS) in 2012 and completed foundation and core medical training in and around the East Riding of Yorkshire. After completing his MD entitled "Venous Congestion in Humans" in 2018, he is now a Clinical Lecturer and Honorary Specialty Registrar in Cardiology at HYMS and the Hull University Teaching Hospitals Trust.

Treatment with all four drug classes is associated with an extra 3 years of life free from HF hospitalisation or death for an 80 year old, and an extra 8 years for a 55 year old with HeFREF compared to treatment with an ACEI or ARB and beta-blocker alone (3). Each treatment has additive prognostic benefit independent of the others (3),3 and the guidelines thus recommend abandoning the notion that drugs such as MRA or ARNI should only be introduced in patients with ongoing symptoms despite treatment with an ACEI or ARB, plus beta-blocker (4).

While the improvements in prognosis are remarkable and very welcome, it presents several questions such as; in what order and over what time scale should each drug be introduced? Different approaches might include low dose beta-blocker plus SGLT2I followed by sacubitril-valsartan and MRA; an alternative might be low dose sacubitril-vasartan and SGLT2I followed by beta-blocker and MRA (**figure 1**) (5-7).

While the exact order is likely to be unimportant – and is not discussed in the guideline – those caring for the patient must not lose sight of the ultimate goal of achieving quadruple therapy, despite apparent clinical stability.

Another relevant question is who should take the lead for medicines optimisation? Heart failure specialist nurses are trained for just such a role but their availability is patchy nationally (8). Primary care specialists have enormously high workloads, and specialist hospital clinics lack capacity (9). Additionally, the increasing use of remote consultations, which make assessment of clinical status, blood pressure, heart rate and rhythm, and renal function difficult, present another barrier to adequate medicines optimisation.

An additional problem is that a patient recently diagnosed with HeFREF who is tolerant of all four medications is likely to be taking 5-6 tablets per day, not including diuretics or treatments for co-morbidities. Polypharmacy and its consequences, such as non-adherence (10), will be unavoidable for patients with HeFREF.

Heart Failure Phenotype Definitions

The 2016 ESC-HF guidelines introduced the new concept of HF with a mid-range ejection fraction to describe those lying in the grey zone between an obviously normal left ventricular ejection fraction (LVEF) on echocardiography, and an obviously reduced LVEF.

Table 1. "Quadruple Therapy" for HeFREF (adapted from McDonagh et al, 2021) (2)

Treatment	Drug class	Drug	Starting dose	Target dose
1	ACEI	Enalapril	2.5mg BD	10-20mg BD[a]
		Ramipril	2.5mg BD	5mg BD[b]
	ARB	Candesartan	4mg OD	32mg OD
		Losartan	50mg OD	150mg OD
	ARNI	Sacubitril-Valsartan	49/51mg BD[c]	97/103mg BD
2	β-Blocker	Carvedilol	3.125mg BD	25mg BD[d]
		Bisoprolol	1.25mg OD	10mg OD
3	MRA	Spironolactone	25mg OD[e]	50mg OD
		Eplerenone	25mg OD	50mg OD
4	SGLT2I	Dapagliflozin	10mg OD	
		Empagliflozin	10mg OD	

[a] Although the ESC list other ACEI as being licenced for the treatment of HeFREF, only trials of enalapril are listed in the supplementary appendix of the 2021 guidelines
[b] Commonly used but with little evidence to support its use *over* enalapril in patients with HeFREF
[c] Starting doses of 24/26mg BD permissible in "selected patients" – in practice, those most likely to experience side effects such as symptomatic hypotension
[d] Target dose should be 50mg BD in patients weighing >85mg
[e] Optional starting dose of 12.5mg OD in patients in whom there are concerns regarding renal function or hyperkalaemia.
Abbreviations used: ACEI – angiotensin receptor blocker; ARB – angiotensin receptor antagonist; ARNI – angiotensin receptor neprilysin inhibitor; MRA – mineralocorticoid receptor antagonist; SGLT2I – sodium glucose co-transporter-2 inhibitor; mg – milligram; OD – once daily; BD – bis in die (twice daily)

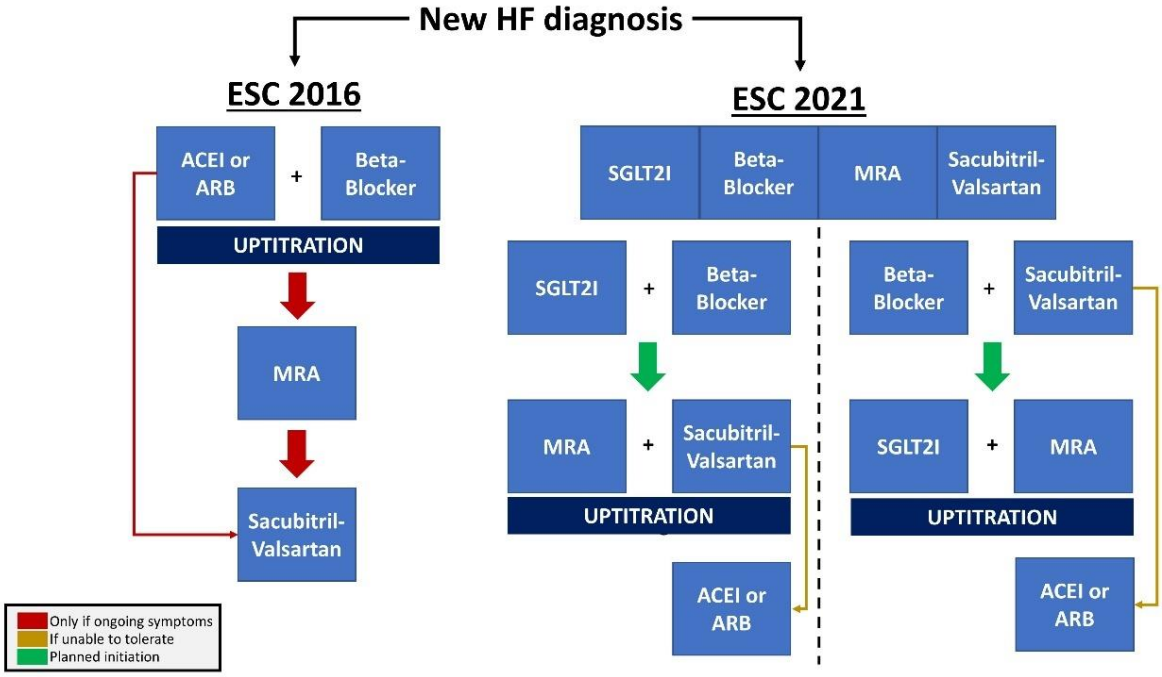

Figure 1. Comparison of ESC-HF 2016 and 2021 recommendations for medical treatment of HeFREF (adapted from Packer and McMurray, 2020; and Straw et al, 2021) (6, 7) . ESC – European Society of Cardiology, HF – Heart Failure, HeFREF – Heart Failure and a Reduced Ejection Fraction

The 2021 iteration renames this "HF with a mildly reduced ejection fraction (HeMREF)" and gives weak recommendations for medical therapies for patient with an LVEF between 40-50% (**figure 2**).

While based on some clinical data (11-17), this is also an attempt to mitigate two concerns with basing treatment decisions on LVEF measured by transthoracic echocardiography:

- dividing a continuous variable (LVEF) into groups based on arbitrary cut-offs will lead to misclassification, which may mean some patients do not receive treatments that may benefit them
- there is much inter- and intra-observer variability when measuring LVEF: a patient who has an LVEF of 42% measured one day by one operator, may have an LVEF of 38% another day (18).
- no trial has actually deliberately set out to investigate patients in this specific subset of patients with heart failure: all studies in patients with heart failure and normal ejection fraction have shown that the benefit of intervention increases with decreasing initial left ventricular ejection fraction

Although not in the 2021 guideline, the recent EMPEROR-Preserved study which showed a reduction in HF hospitalisations (but not total hospitalisations) amongst patients with an LVEF <50% will almost certainly add SGLT2I to the list of treatments for patients with HeFMREF (**figure 2**) (14).

The term to describe patients with the HF syndrome and an LVEF >50% is controversial and, after being put to a vote, the guideline committee adopted the term "HF with a preserved ejection fration" rather than "HF with a normal ejection fraction", despite being inaccurate. For example: a patient with an LVEF of 70% has a heart attack and later presents with breathlessness and is diagnosed with HF, an echocardiogram finds an LVEF of 55% - the LVEF cannot be described as "preserved", but it would lie within the normal range.

Changes to Device Recommendations

<u>Primary prevention ICD for patients with non-ischaemic cardiomyopathy</u>

None of the landmark studies that established the prognostic benefit of implantable cardioverter defibrillator (ICD) implantation in patients with HeFREF specifically enrolled patients with non-ischaemic cardiomyopathy (19-22). Those that did were either neutral (23), or were closed early (24, 25).

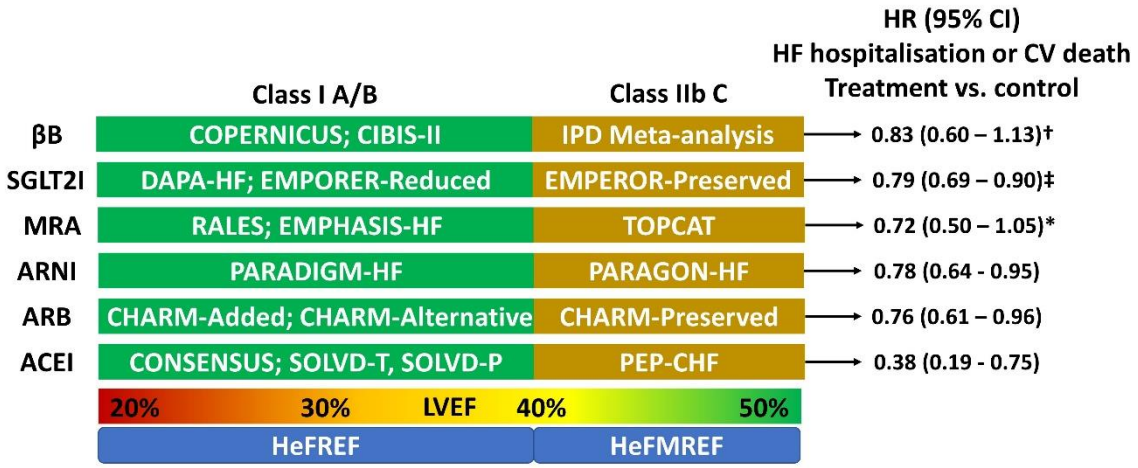

Figure 2. Medical management of HeFREF and HeFMREF (adapted from McDonagh et al, 2021) (2). † - Although the combined endpoint was not statistically significant, there was a significant reduction in CV mortality with βB in patients with HeFMREF vs. placebo; ‡ - The EMPEROR-Preserved data does not feature in the 2021 ESC-HF guideline and is likely to carry a greater recommendation than level C in the next iteration; * - there was a significant reduction in the primary outcome of HF hospitalisation, aborted cardiac arrest, or CV mortality with spironolactone vs. placebo for patients enrolled in the Americas. HeFREF – heart failure and a reduced ejection fraction; HeFMREF – heart failure and a mildly reduced ejection fraction; βB – beta-blocker; SGLT2I – sodium-glucose co-transporter-2 inhibitor; MRA – mineralocorticoid receptor antagonist; ARNI – angiotensin receptor neprilysin inhibitor; ARB – angiotensin receptor blocker; ACEI – angiotensin converting enzyme inhibitor; HR – hazard ratio; CI – confidence interval; HF – heart failure; CV – cardiovascular; IPD – individual patient data.

The DANISH trial, which recruited only patients with non-ischaemic cardiomyopathy, found no reduction in all-cause mortality with ICD over usual care (although there was a signal that ICD implantation may reduce the risk of all-cause mortality in those aged 68 or younger (16% in the ICD arm vs. 21% in the control arm; HR = 0.64 (95% CI 0.45-0.90; P=0.01) (26). Only 70 out of 1116 patients recruited had sudden cardiac death (SCD) over a 5 year follow up period (26). Although patients with an ICD were 50% less likely to die suddenly, more patients in the ICD group had inappropriate shocks (N=34; 6%) than had SCD (N=24; 4%) (26). Thus, the level of recommendation for *primary prevention* ICD in patients with HeFREF has been downgraded.

It is worth noting that the trials of primary prevention ICD are nearly twenty years old. In that time the rate of SCD in patients with HeFREF has fallen by 44% (27), with reductions in SCD seen with ACEI, beta-blocker, MRA (27), ARNI (28), and SGLT2I (29). ICD implantation has a complication rate between 3-9% (3); although it remains a major part of HF treatment, the real prognostic benefit of primary prevention ICDs in the age of quadruple therapy is unknown.

<u>CRT for patients with LBBB and QRS duration 130-149ms</u>

Two individual patient-data meta-analyses from the landmark trials of CRT have suggested the prognostic benefit of CRT was less certain with a QRS duration 130-149ms, with a signal towards potential harm in patients with a QRS <130ms (**table 2**) (31, 32).

Although the strength of the recommendation has changed between 2016 and 2021, the data on which they are based in the referenced meta-analyses remain the same. This perhaps reflects the dilemma facing all guideline committees: should recommendations be based on the effect seen in sub-groups within a trial; or should they be based on the overall observed effect of treatment? In the case of the former, sub-group analysis may be statistically underpowered. In the case of the latter, some patients who might benefit from the treatment are excluded.

Table 2. Estimated HR for mortality and mortality or HF hospitalisation based on QRS duration derived from an individual patient data meta-analysis in the landmark CRT clinical trials (Cleland et al, 2013) (31)

QRS duration (ms)	All cause mortality HR (95% bootstrap CI)	All cause mortality or HF hospitalisation HR (95% bootstrap CI)
<120	1.20 (0.90 – 1.70)	1.50 (0.90 – 1.80)
120-139	1.00 (0.90 – 1.40)	1.1 (0.90 – 1.5)
140-159	0.90 (0.80 – 1.10)	0.90 (0.80 – 1.10)
>160	0.80 (0.70 – 0.90)	0.70 (0.60 – 0.80)

Abbreviations used: HR – hazard ratio; CRT – cardiac resynchronisation therapy; CI – confidence interval; HF – heart failure

Downgrading the recommendation acknowledges the weaknesses in the evidence bases while accepting that there may be subgroups of patients who lie outside of the study entry criteria who may also benefit from the treatment.

Oral treatment on discharge

Only ~50% of patients with HeFREF admitted to hospital in the UK are discharged on triple therapy (33). The reasons for this are unknown although it is probable that some patients are unable to tolerate multiple drugs that reduce blood pressure after a prolonged period of diuresis. However, the National HF Audit has consistently found that patients discharged from specialist wards are more likely to be prescribed an ACEI, ARB, MRA and beta-blocker than patients discharged from general medical wards (**table 3**) and the absence of specialist knowledge or experience may be a factor (33). Registry data also consistently suggests that under-treatment is a common problem in patients with HF and likely to be a result of a degree of clinical inertia (34). The 2021 ESC-HF guidelines recommend that all patients admitted with heart failure are prescribed "evidence-based oral treatment" and have their oral medications "optimised" pre-discharge. It is unknown if this is realistic in practice, but it is a logical goal as those who have the most to gain from HF medications are those most at risk. For example, the readmission and mortality rates are 23% and 15% within 1 month of discharge (33, 35) and the prognostic benefit of HF medical therapy is seen within 30 days of initiation (36-38). However, "medicines optimisation" in patients with HeFREF is often complicated, and takes many weeks to achieve. It may be more practical to develop and invest in systems that allow optimisation to take place over a series of out-patient visits shortly after discharge.

The National Institute for Health and Clinical Excellence HF guideline (and now also the ESC-HF guideline) recommend that patients are seen in clinic within 2 weeks of discharge following admission with HF; one purpose of this clinic visit is to initiate or up-titrate medications (2, 39). However, many HF services do not meet this target (33), and efforts will be further complicated by the barriers to out-patient care as a result of the COVID-19 pandemic. Initiating quadruple therapy before discharge in patients with HeFREF may be the best opportunity to do so, whilst also providing a chance to assess tolerance.

Encouraging self-management

Self-management has been an important part of HF guidelines for years, yet 2021 is the first year to give self-management advice to patients a class I level A recommendation (**figure 4**) alongside specific goals of patient education and how this might be achieved (**table 4**).

Table 3. Medications at discharge by place of care (adapted from The National Heart Failure Audit Summary Report 2018-19) (33)

Ward	ACEI/ARB	Beta-blocker	MRA	Triple therapy
Cardiology	88%	92%	62%	55%
General Medical	80%	85%	45%	35%

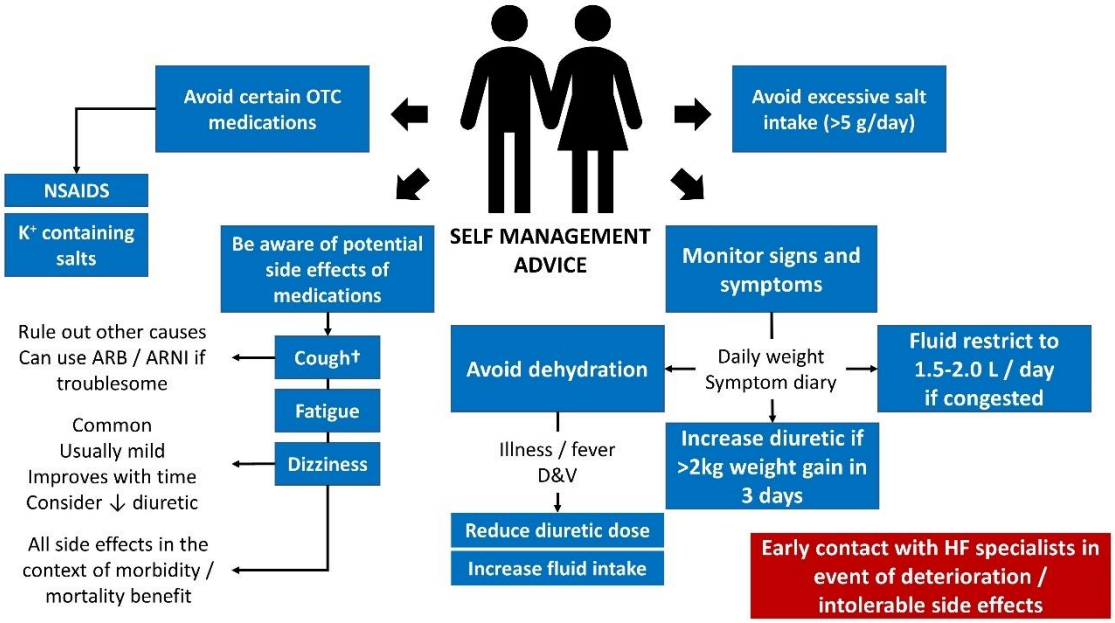

Figure 4. Self management advice for patients with heart failure (adapted from McDonagh et al, 2021)[2]. † - only seen with ACEI. OTC – over the counter; NSAIDS – non-steroidal anti-inflammatory drugs; ARB – angiotensin receptor blocker; ARNI – angiotensin receptor neprilysin inhibitor; D&V – diarrhoea and vomiting; g – grams; L – litre; kg – kilograms; HF – heart failure

Heart failure is a diagnosis for life and the specialist-patient relationship is long-term; empowering the patient through education and self-management advice at an early stage can help ensure it is, at least at the beginning, a happy one [a].

Conclusions

The 2021 ESC-HF guideline has been delivered 'with little fanfare' but deserve recognition for its effort to incorporate recent rapid scientific advances in the field into a logical guideline for clinical practice. While the practicalities of some of the recommendations may require further discussion, for example around quadruple therapy, the rationale is persuasive. Patients with HF, and those that care for them, are being well served.

Disclosures

None

Table 4. Patient education goals and how to achieve them (adapted from McDonagh et al, 2021)[2]

Patient goals	How to achieve it
Understand the cause of heart failure	• Give a clear description tailored to the patient's level of understanding and educational background at diagnosis
Understand the cause of symptoms	
Understand the prognosis	
Understand reason for treatment	• Provide written **and** oral information on benefits, dosing and potential side effects. • Discuss barriers to compliance (e.g. avoidance of urinary frequency with diuretics for social reasons)
Understand common side effects	
Understand the importance of regular exercise	• Emphasise the prognostic benefits • Tailor advice to current physical status • Discuss potential barriers / opportunities • Refer to exercise programme (if available)

[a] Some useful websites include: https://www.bhf.org.uk/informationsupport/conditions/heart-failure; https://www.pumpingmarvellous.org/heart-failure-toolkit/. However, online content may not be suitable for some patients and should not replace a clear and concise explanation from the specialist.

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