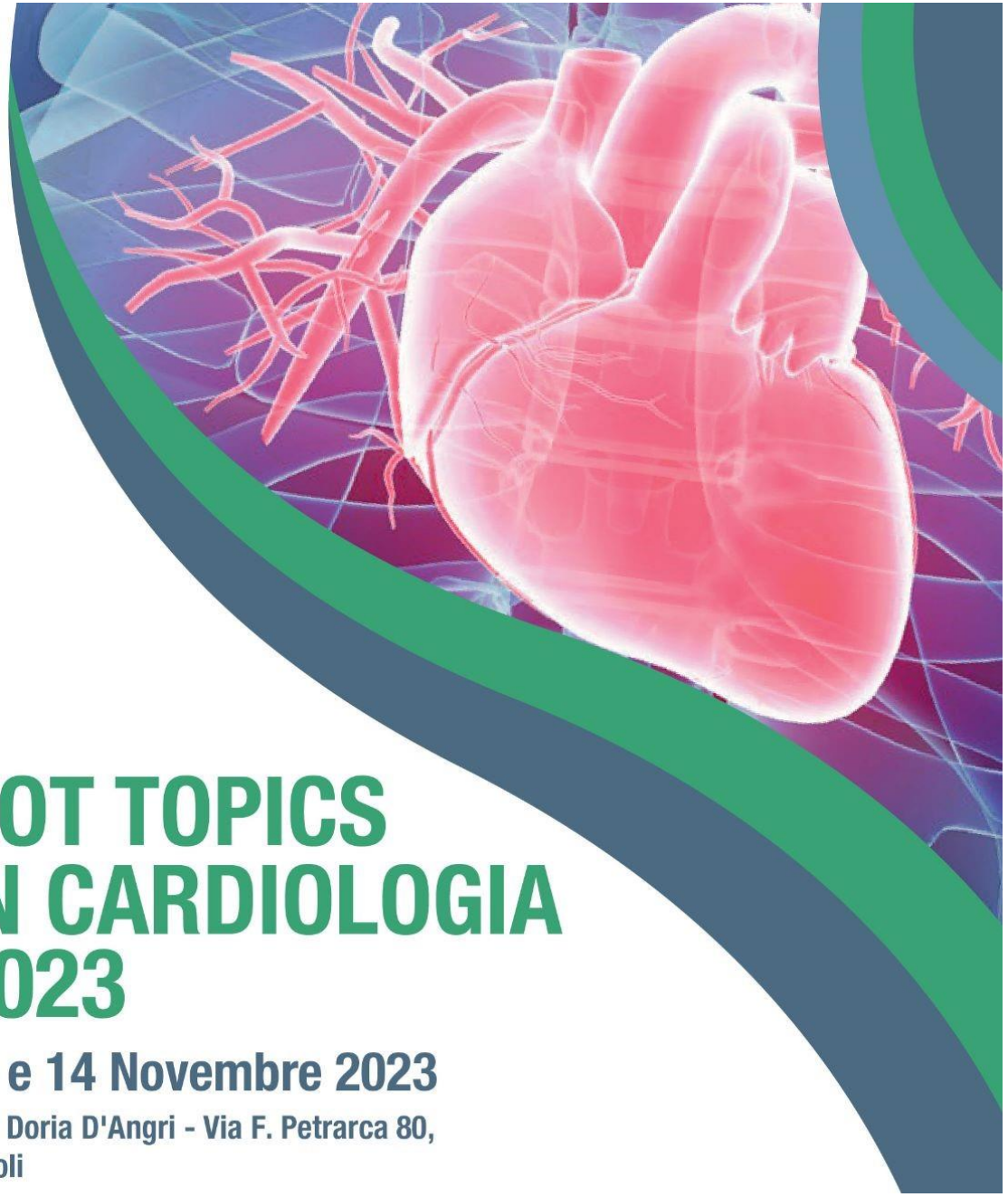

HOT TOPICS IN CARDIOLOGIA 2023

13 e 14 Novembre 2023

Villa Doria D'Angri - Via F. Petrarca 80, Napoli

DALLE RACCOMANDAZIONI ALLA PRATICA CLINICA: DIFFICOLTA' QUOTIDIANE E SUGGERIMENTI PER LA PRESCRIZIONE E/O OTTIMIZZAZIONE DELLA TERAPIA FARMACOLOGICA DELLO SCOMPENSO

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AORN OSPEDALI DEI COLLI - OSPEDALE MONALDI

Definition of heart failure

Heart failure is not a single pathological diagnosis, but a **clinical syndrome** consisting of cardinal symptoms (e.g. breathlessness and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in **elevated intracardiac pressures and/or inadequate cardiac output** at rest and/or during exercise.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Table 3 Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction, and preserved ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms ± signs[a]	Symptoms ± signs[a]	Symptoms ± signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle; LVEF, left ventricular ejection fraction.

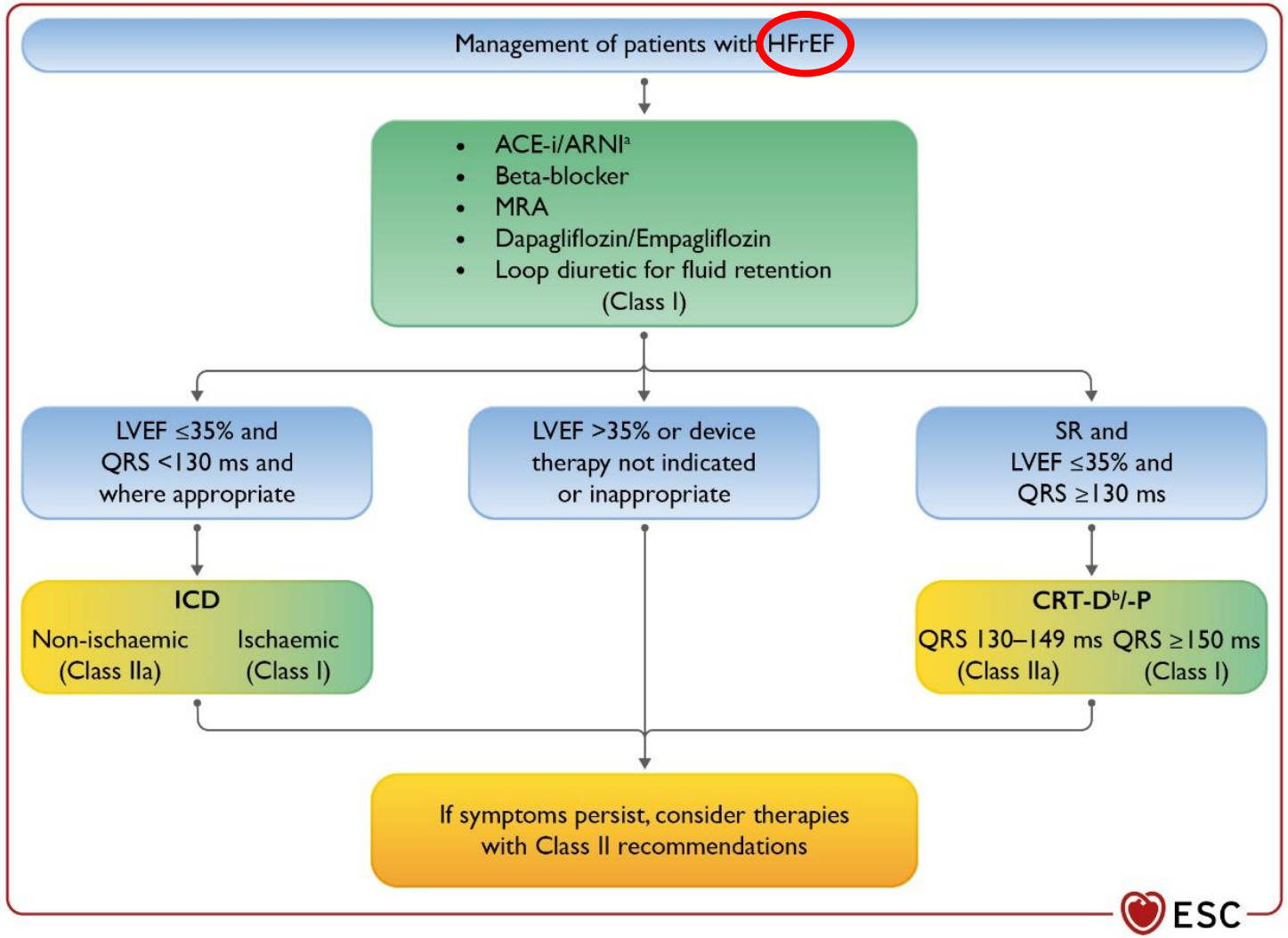
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

[b]For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy, or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.

[c]For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Therapeutic algorithm of Class I Therapy Indications for a patient with heart failure with reduced ejection fraction



ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; ICD = implantable cardioverter-defibrillator; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; QRS = Q, R, and S waves (on a 12-lead electrocardiogram); SR = sinus rhythm.
[a]As a replacement for ACE-I.
[b]Where appropriate. Class I=green. Class IIa=Yellow.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Pharmacological treatments indicated in patients with (NYHA class II-IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class	Level
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

ACE-I = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA= New York Heart Association.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Other pharmacological treatments indicated in selected patients with NYHA class II-IV heart failure with reduced ejection fraction (LVEF ≤40%) (1)

Recommendations	Class	Level
Loop diuretics		
Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity, and reduce HF hospitalizations.	I	C
ARB		
An ARB[a] is recommended to reduce the risk of HF hospitalization and CV death in symptomatic patients unable to tolerate an ACE-I or ARNI (patients should also receive a beta-blocker and an MRA).	I	B

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CV = cardiovascular; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA= New York Heart Association.

[a]The ARBs with evidence in HFrEF are candesartan, losartan, and valsartan.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Other pharmacological treatments indicated in selected patients with NYHA class II-IV heart failure with reduced ejection fraction (LVEF ≤40%) (2)

Recommendations	Class	Level
I_f-channel inhibitor		
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I/(or ARNI), and an MRA, to reduce the risk of HF hospitalization and CV death.	IIa	B
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. who are unable to tolerate or have contraindications for a beta-blocker to reduce the risk of HF hospitalization and CV death. Patients should also receive an ACE-I (or ARNI) and an MRA.	IIa	C

ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; b.p.m. = beats per minute; CV = cardiovascular; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA= New York Heart Association; SR = sinus rhythm.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Other pharmacological treatments indicated in selected patients with NYHA class II-IV heart failure with reduced ejection fraction (LVEF ≤40%) (3)

Recommendations	Class	Level
Soluble guanylate cyclase receptor stimulator		
Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.	IIb	B
Hydralazine and isosorbide dinitrate		
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated left ventricle in NYHA class III-IV despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.	IIa	B
Hydralazine and isosorbide dinitrate may be considered in patients with symptomatic HFrEF who cannot tolerate any of an ACE-I, an ARB, or ARNI (or they are contraindicated) to reduce the risk of death.	IIb	B

ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CV = cardiovascular; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA= New York Heart Association.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Other pharmacological treatments indicated in selected patients with NYHA class II-IV heart failure with reduced ejection fraction (LVEF ≤40%) (4)

Recommendations	Class	Level
Digoxin		
Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF hospitalizations).	IIb	B

ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

5.2.2 General principles of pharmacotherapy for heart failure with reduced ejection fraction

Modulation of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems with angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonists (MRA) has been shown to improve survival, reduce the risk of HF hospitalizations, and reduce symptoms in patients with HFrEF. These drugs serve as the foundations of pharmacotherapy for patients with HFrEF. The triad of an ACE-I/ARNI, a beta-blocker, and an MRA is recommended as cornerstone therapies for these patients, unless the drugs are contraindicated or not tolerated.[103–105] They should be uptitrated to the doses used in the clinical trials (or to maximally tolerated doses if that is not possible). This guideline still recommends the use of ARNI as a replacement for ACE-I in suitable patients who remain symptomatic on ACE-I, beta-blocker, and MRA therapies; however, an ARNI may be considered as a first-line therapy instead of an ACE-I.[106,107] The recommended doses of these drugs are given in *Table 8*. Angiotensin-receptor blockers (ARBs) still have a role in those who are intolerant to ACE-I or ARNI.

The sodium-glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin added to therapy with ACE-I/ARNI/beta-blocker/MRA reduced the risk of CV death and worsening HF in patients with HFrEF.[108,109] Unless contraindicated or not tolerated, dapagliflozin or empagliflozin are recommended for all patients with HFrEF already treated with an ACE-I/ARNI, a beta-blocker, and an MRA, regardless of whether they have diabetes or not.

5.3.1 Angiotensin-converting enzyme inhibitors

ACE-Is were the first class of drugs shown to reduce mortality and morbidity in patients with HFrEF.[110–113] They have also been shown to improve symptoms.[111] They are recommended in all patients unless contraindicated or not tolerated. They should be uptitrated to the maximum tolerated recommended doses.

5.3.2 Beta-blockers

Beta-blockers have been shown to reduce mortality and morbidity in patients with HFrEF, in addition to treatment with an ACE-I and diuretic.[114–120] They also improve symptoms.[123] There is consensus that ACE-I and beta-blockers can be commenced together as soon as the diagnosis of symptomatic HFrEF is established. There is no evidence favouring the initiation of a beta-blocker before an ACE-I and vice versa.[124] Beta-blockers should be initiated in clinically stable, euvolaemic, patients at a low dose and gradually uptitrated to the maximum tolerated dose. In patients admitted with AHF, beta-blockers should be cautiously initiated in hospital, once the patient is haemodynamically stabilized.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Therefore, it is recommended that an ACE-I or ARB is replaced by sacubitril/valsartan in ambulatory patients with HFrEF, who remain symptomatic despite optimal treatment outlined above. Two studies have examined the use of ARNI in hospitalized patients, some of whom had not been previously treated with ACE-I. Initiation in this setting appears safe and reduces subsequent CV death or HF hospitalizations by 42% compared to enalapril.[106,107,131] As such, initiation of sacubitril/valsartan in ACE-I naive (i.e. *de novo*) patients with HFrEF may be considered (class of recommendation IIb, level of evidence B). Patients being commenced on sacubitril/valsartan should have an adequate blood pressure (BP), and an eGFR ≥30 mL/min/1.73 m^2. A washout period of at least 36 h after ACE-I therapy is required in order to minimize the risk of angioedema.

5.3.3 Mineralocorticoid receptor antagonists

MRAs (spironolactone or eplerenone) are recommended, in addition to an ACE-I and a beta-blocker, in all patients with HFrEF to reduce mortality and the risk of HF hospitalization.[121,122] They also improve symptoms.[121] MRAs block receptors that bind aldosterone and, with different degrees of affinity, other steroid hormones (e.g. corticosteroid and androgen) receptors. Eplerenone is more specific for aldosterone blockade and, therefore, causes less gynaecomastia.

Therefore, dapagliflozin or empagliflozin are recommended, in addition to OMT with an ACE-I/ARNI, a beta-blocker and an MRA, for patients with HFrEF regardless of diabetes status. The diuretic/natriuretic properties of SGLT2 inhibitors may offer additional benefits in reducing congestion and may allow a reduction in loop diuretic requirement.[135]

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction (1)

	Starting dose	Target dose
ACE-I		
Captopril[a]	6.25 mg *t.i.d.*	50 mg *t.i.d.*
Enalapril	2.5 mg *b.i.d.*	10–20 mg *b.i.d.*
Lisinopril[b]	2.5–5 mg *o.d.*	20–35 mg *o.d.*
Ramipril	2.5 mg *b.i.d.*	5 mg *b.i.d.*
Trandolapril[a]	0.5 mg *o.d.*	4 mg *o.d.*
ARNI		
Sacubitril/valsartan	49/51 mg *b.i.d.*[c]	97/103 mg *b.i.d.*

ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptorneprilysin inhibitor; b.i.d. = bis in die; o.d. = omne in die (once daily); t.i.d. = ter in die (three times a day).
[a]Indicates an ACE-I where the dosing target is derived from post-myocardial infarction trials.
[b]Indicates drugs where a higher dose has been shown to reduce morbidity/mortality compared with a lower dose of the same drug, but there is no substantive randomized, placebo-controlled trial and the optimum dose is uncertain. [c]Sacubitril/valsartan may have an optional lower starting dose of 24/26 mg b.i.d. for those with a history of symptomatic hypotension.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction (2)

	Starting dose	Target dose
Beta-blockers		
Bisoprolol	1.25 mg *o.d.*	10 mg *o.d.*
Carvedilol	3.125 mg *b.i.d.*	25 mg *b.i.d.*[e]
Metoprolol succinate (CR/XL)	12.5–25 mg *o.d.*	200 mg *o.d.*
Nebivolol[d]	1.25 mg *o.d.*	10 mg *o.d.*
MRA		
Eplerenone	25 mg *o.d.*	50 mg *o.d.*
Spironolactone	25 mg *o.d.*[f]	50 mg *o.d.*

b.i.d. = bis in die (twice daily); CR = controlled release; MRA = mineralocorticoid receptor antagonist; o.d. = omne in die (once daily); XL = extended release.
[d]Indicates a treatment not shown to reduce CV or all-cause mortality in patients with heart failure (or shown to be non-inferior to a treatment that does).
[e]A maximum dose of 50 mg twice daily can be administered to patients weighing over 85 kg.
[f]Spironolactone has an optional starting dose of 12.5 mg in patients where renal status or hyperkalaemia warrant caution.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction (3)

	Starting dose	Target dose
SGLT2 inhibitor		
Dapagliflozin	10 mg *o.d.*	10 mg *o.d.*
Empagliflozin	10 mg *o.d.*	10 mg *o.d.*
Other agents		
Candesartan	4 mg *o.d.*	32 mg *o.d.*
Losartan	50 mg *o.d.*	150 mg *o.d.*
Valsartan	40 mg *b.i.d.*	160 mg *b.i.d.*
Ivabradine	5 mg *b.i.d.*	7.5 mg *b.i.d.*
Vericiguat	2.5 mg *o.d.*	10 mg *o.d.*

b.i.d. = bis in die (twice daily); o.d. = omne in die (once daily); SGLT2 = sodium-glucose co-transporter 2; t.i.d. = ter in die (three times a day.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction (3)

	Starting dose	Target dose
Other agents (continued)		
Digoxin	62.5 µg *o.d.*	250 µg *o.d.*
Hydralazine/ Isosorbide dinitrate	37.5 mg *t.i.d.*/ 20 mg *t.i.d.*	75 mg *t.i.d.*/ 40 mg *t.i.d.*

b.i.d. = bis in die (twice daily); o.d. = omne in die (once daily); SGLT2 = sodium-glucose co-transporter 2; t.i.d. = ter in die (three times a day.

Recommendations for Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendations**
1	A	1. In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality.[1–5]
1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible.[6–13]
1	A	3. In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality.[14–18]
Value Statement: High Value (A)		4. In patients with previous or current symptoms of chronic HFrEF, in whom ARNi is not feasible, treatment with an ACEi or ARB provides high economic value.[19–25]
1	B-R	5. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality.[1–5]
Value Statement: High Value (A)		6. In patients with chronic symptomatic HFrEF, treatment with an ARNi instead of an ACEi provides high economic value.[26–29]

2022 AHA/ACC/HFSA Heart Failure Guidelines

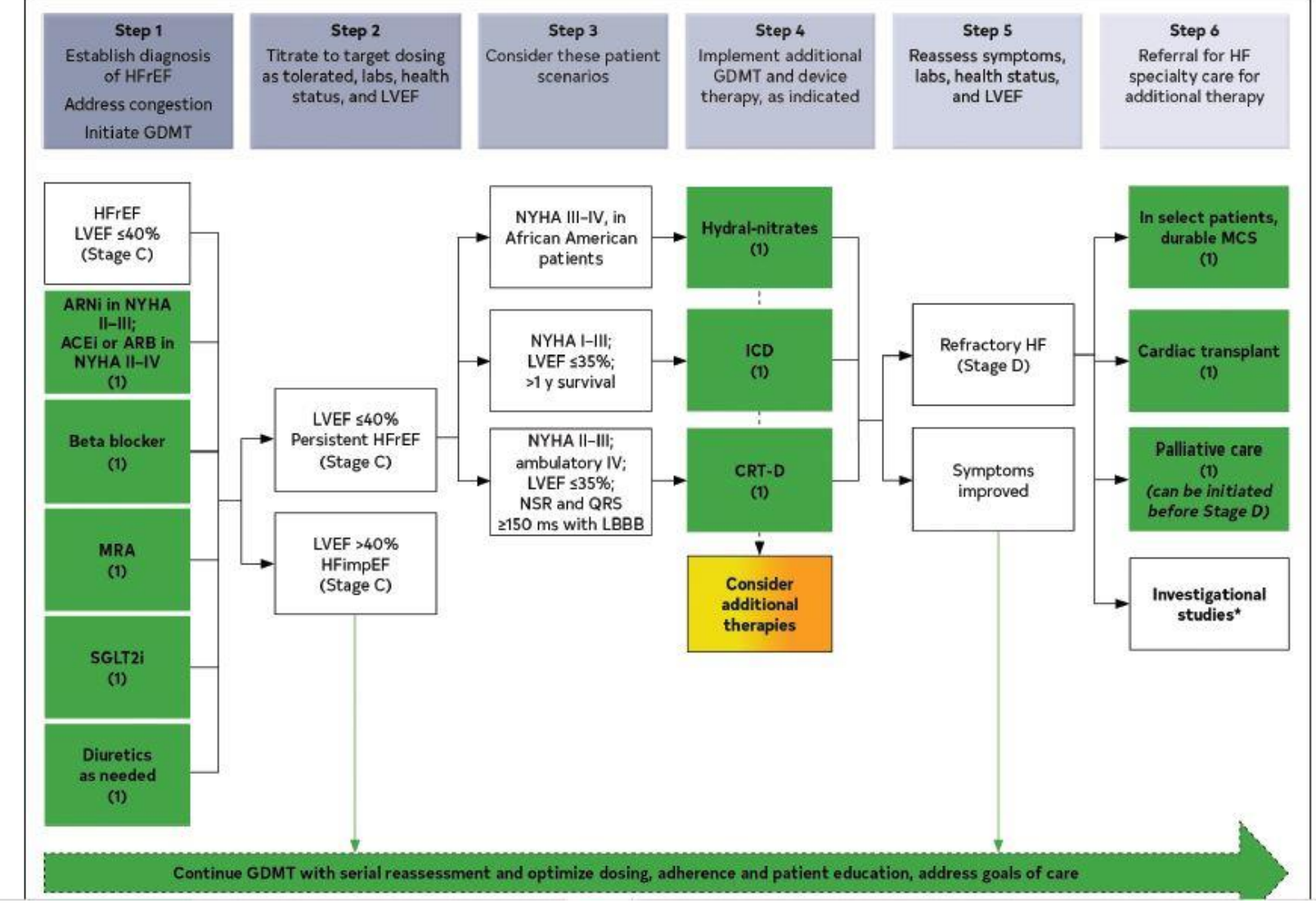


Figure 6. Treatment of HFrEF Stages C and D.

Colors correspond to COR in Table 2. Treatment recommendations for patients with HFrEF are displayed. Step 1 medications may be started simultaneously at initial (low) doses recommended for HFrEF. Alternatively, these medications may be started sequentially, with sequence guided by clinical or other factors, without need to achieve target dosing before initiating next medication. Medication doses should be increased to target as tolerated. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; COR, Class of Recommendation; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter-defibrillator; hydral-nitrates, hydralazine and isosorbide dinitrate; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle branch block; MCS, mechanical circulatory support; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; NYHA, New York Heart Association; and SGLT2i, sodium-glucose cotransporter 2 inhibitor. *Participation in investigational studies is appropriate for stage C, NYHA class II and III HF.

2022 AHA/ACC/HFSA Heart Failure Guidelines

SUGGERIMENTI PER LA PRESCRIZIONE E/O OTTIMIZZAZIONE DELLA TERAPIA PER LO SCOMPENSO CARDIACO CRONICO

2017 ACCF/AHA Heart Failure Guidelines

How to implement GDMT...

Issue 1. Initiate, Add, or Switch

Treatment algorithm for GDMT including novel therapies (*Figures 2* and *3*)

Issue 2. Titration

Target doses, indications, contraindications, and other considerations of select GDMT for HFrEF (*Tables 1, 2, 3, 4, 5*)

Considerations for monitoring

How to address challenges with...

Issue 3. Referral

Triggers for referral to HF specialist (*Table 6*)

Issue 4. Care Coordination

Essential skills for an HF team (*Table 7*)

Infrastructure for team-based HF care (*Table 8*)

Issue 5. Adherence

Causes of nonadherence *(Table 9)*

Considerations to improve adherence *(Table 10)*

Issue 6. Specific Patient Cohorts

Evidence-based recommendations and assessment of risk for special cohorts: African Americans, older adults, and the frail (*Table 11*)

Issue 7. Medication Cost and Access

Strategies to reduce patients' cost of care (*Table 12*)

Helpful information for completion of prior authorization forms (*Table 13* and *Supplemental Appendix 2)*

How to manage...

Issue 8. Increasing Complexity

Twelve pathophysiological targets in HFrEF and treatments (*Table 14*)

Ten principles and actions to guide optimal therapy

Issue 9. Comorbidities

Common cardiovascular and noncardiovascular comorbidities with suggested actions (*Table 15*)

Issue 10. Palliative/ Hospice Care

Seven principles and actions to consider regarding palliative care

GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction.

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

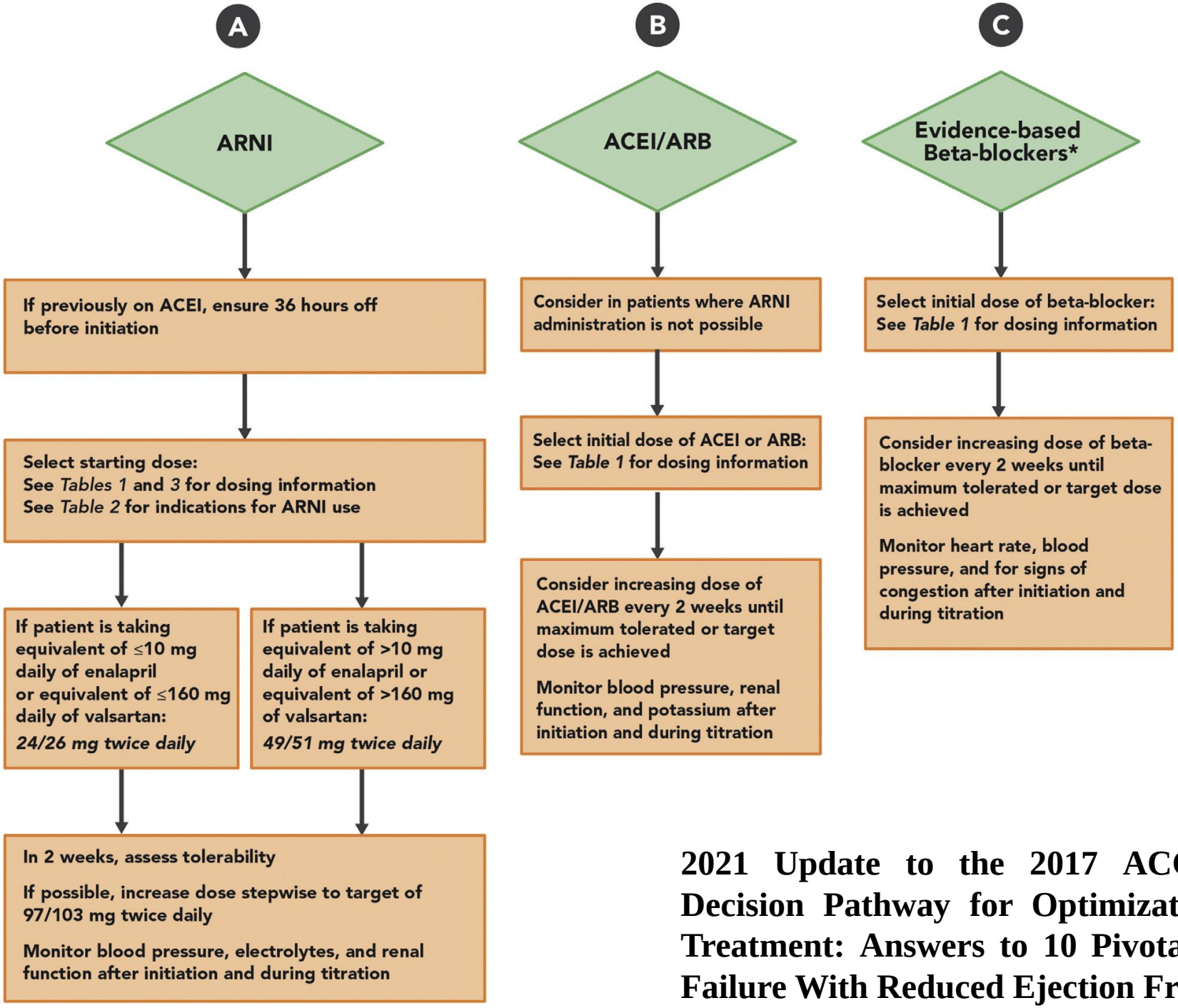
In some cases, an ARNI/ACEI/ARB and a beta-blocker can be started at the same time. Regardless of the initiation sequence, both classes of agent should be up-titrated to the maximum tolerated or target doses in a timely fashion (e.g., every 2 weeks). Initiation of an ARNI/ACEI/ARB is often better tolerated when the patient is still congested ("wet"), whereas beta-blockers are better tolerated when the patient is less congested ("dry") with an adequate resting heart rate.

As there is no existing predicate data to suggest an aldosterone antagonist is mandatory before ARNI therapy, lack of treatment with an aldosterone antagonist should not delay initiating or switching a patient to an ARNI.

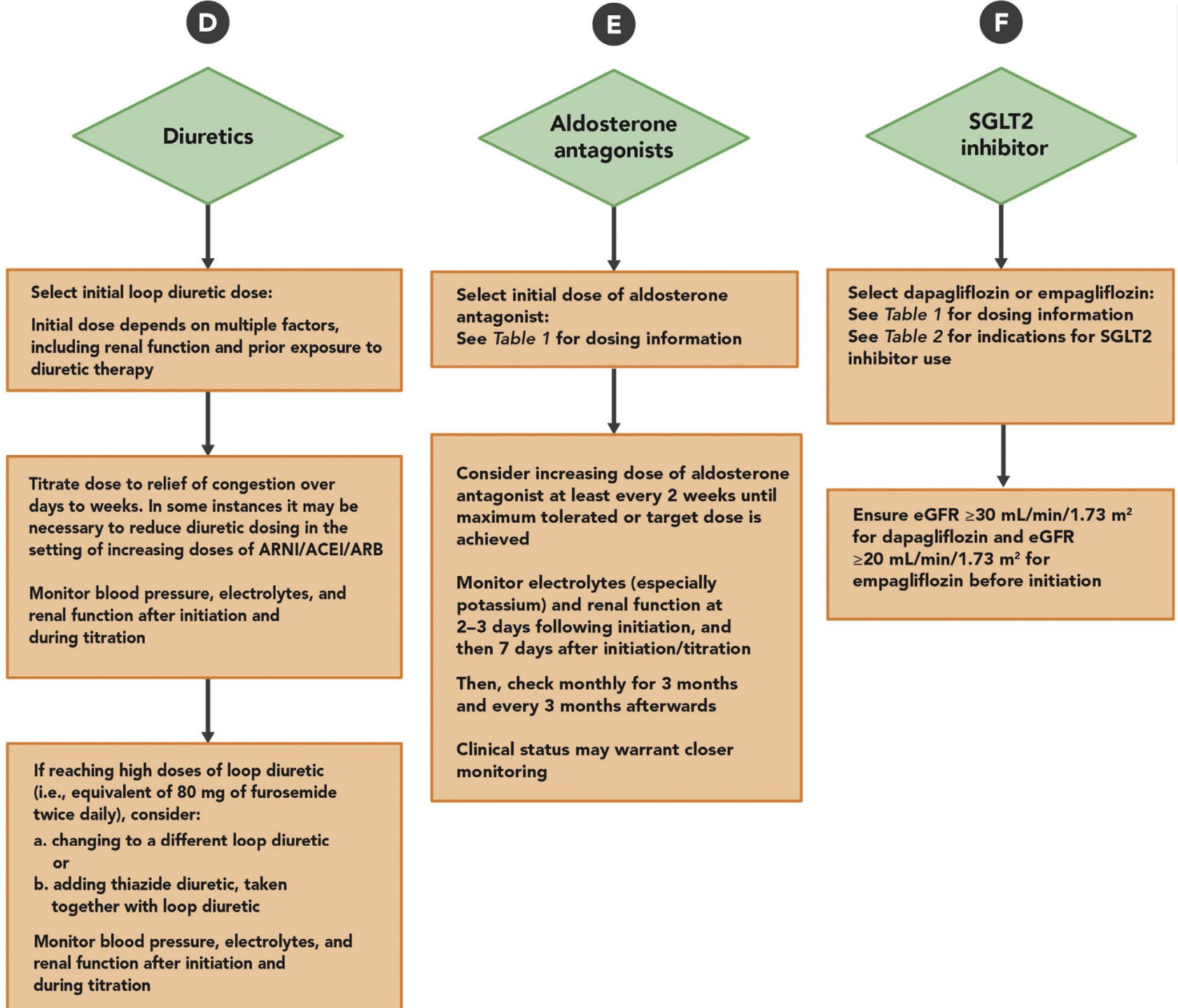
The investigators compared titration of ARNI to a target dose between 3 and 6 weeks. Both approaches were tolerated similarly, but the gradual titration (6 weeks) approach maximized attainment of the target dose of sacubitril/ valsartan in patients previously receiving low doses of an ACEI/ARB.
Clinicians should be advised that sacubitril/valsartan may exert a more noteworthy effect on blood pressure when compared with ACEIs/ARBs. In noncongested patients with otherwise stable clinical profiles, empiric modest lowering of loop diuretic agents has been found to mitigate the hypotensive effects of sacubitril/valsartan.

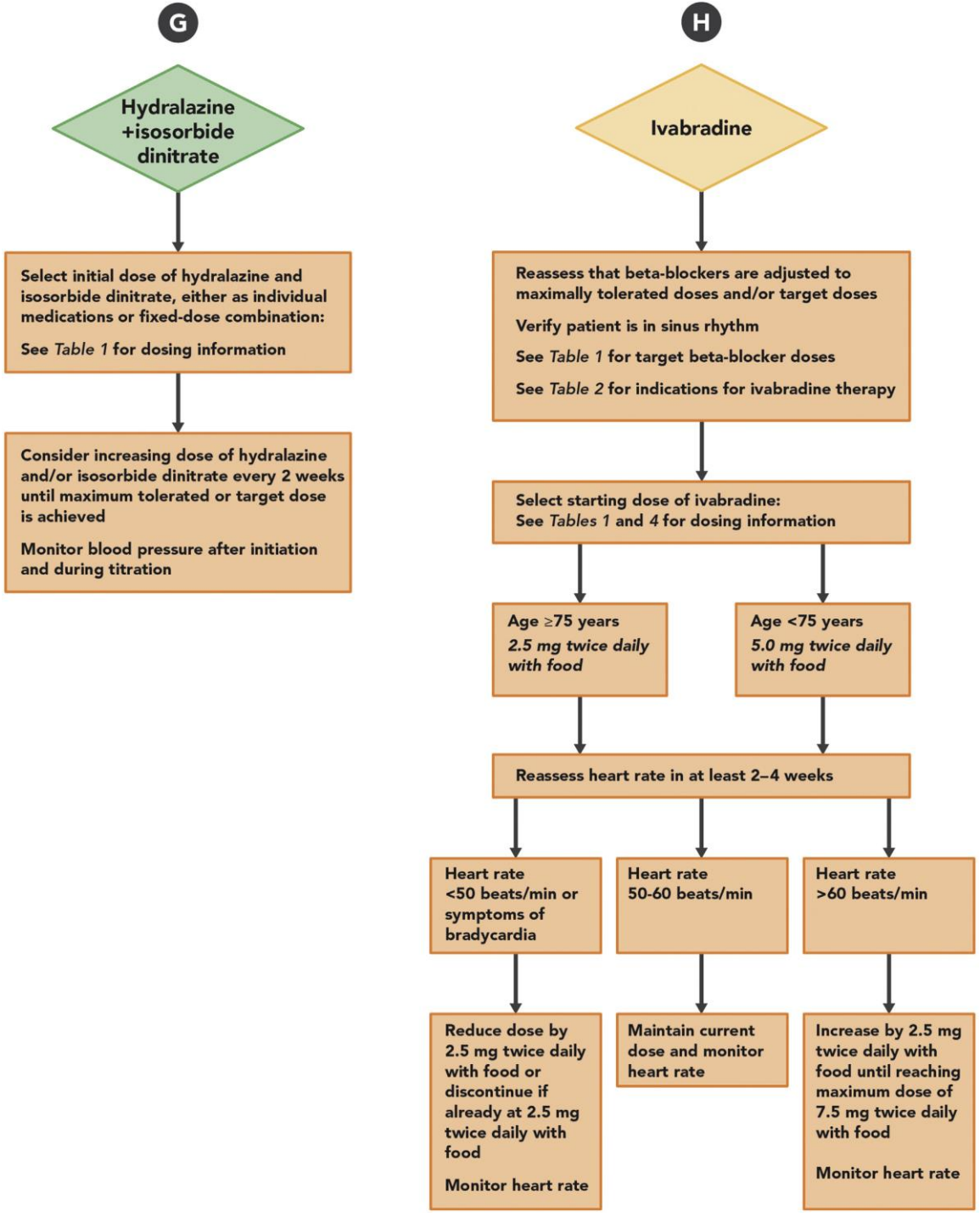
An ideal time to consider therapy optimization is during hospitalization for HFrEF: the PIONEER-HF (Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute HF Episode) trial established that the initiation of ARNI during an acute decompensated HF hospitalization is feasible after the patient has been hemodynamically stabilized.

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction



2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction


D
Diuretics
Select initial loop diuretic dose:
Initial dose depends on multiple factors, including renal function and prior exposure to diuretic therapy
Titrate dose to relief of congestion over days to weeks. In some instances it may be necessary to reduce diuretic dosing in the setting of increasing doses of ARNI/ACEI/ARB
Monitor blood pressure, electrolytes, and renal function after initiation and during titration
If reaching high doses of loop diuretic (i.e., equivalent of 80 mg of furosemide twice daily), consider:
a. changing to a different loop diuretic
or
b. adding thiazide diuretic, taken together with loop diuretic
Monitor blood pressure, electrolytes, and renal function after initiation and during titration
E
Aldosterone antagonists
Select initial dose of aldosterone antagonist:
See Table 1 for dosing information
Consider increasing dose of aldosterone antagonist at least every 2 weeks until maximum tolerated or target dose is achieved
Monitor electrolytes (especially potassium) and renal function at 2–3 days following initiation, and then 7 days after initiation/titration
Then, check monthly for 3 months and every 3 months afterwards
Clinical status may warrant closer monitoring
F
SGLT2 inhibitor
Select dapagliflozin or empagliflozin:
See Table 1 for dosing information
See Table 2 for indications for SGLT2 inhibitor use
Ensure eGFR ≥30 mL/min/1.73 m²
for dapagliflozin and eGFR
≥20 mL/min/1.73 m² for
empagliflozin before initiation


G
Hydralazine +isosorbide dinitrate
Select initial dose of hydralazine and isosorbide dinitrate, either as individual medications or fixed-dose combination:
See Table 1 for dosing information
Consider increasing dose of hydralazine and/or isosorbide dinitrate every 2 weeks until maximum tolerated or target dose is achieved
Monitor blood pressure after initiation and during titration
H
Ivabradine
Reassess that beta-blockers are adjusted to maximally tolerated doses and/or target doses
Verify patient is in sinus rhythm
See Table 1 for target beta-blocker doses
See Table 2 for indications for ivabradine therapy
Select starting dose of ivabradine:
See Tables 1 and 4 for dosing information
Age ≥75 years
2.5 mg twice daily with food
Age <75 years
5.0 mg twice daily with food
Reassess heart rate in at least 2–4 weeks
Heart rate <50 beats/min or symptoms of bradycardia
Heart rate 50-60 beats/min
Heart rate >60 beats/min
Reduce dose by 2.5 mg twice daily with food or discontinue if already at 2.5 mg twice daily with food
Monitor heart rate
Maintain current dose and monitor heart rate
Increase by 2.5 mg twice daily with food until reaching maximum dose of 7.5 mg twice daily with food
Monitor heart rate

PROBLEMI DI PIU' FREQUENTE RISCONTRO NELLA PRATICA CLINICA QUOTIDIANA

In some instances, it may not be possible to titrate GDMT to the target doses achieved in clinical trials. Patients seen in clinical practice may differ substantially from those enrolled in trials. For example, patients seen in clinical practice are typically older, may experience more side effects including hypotension, and are likely to have more comorbidities that will limit titration. Although data are lacking, it is logical to assume that below-target doses of multiple classes of GDMT are likely more effective in reducing risk than large doses of 1 or 2 agents.

Abnormal renal function and/or hyperkalemia are common barriers to initiation and titration of GDMT. In patients with hyperkalemia, education regarding a low potassium diet should be provided. In addition, newer potassium binders (patiromer and sodium zirconium cyclosilicate) are now approved by the Food and Drug Administration and may be considered.

For patients with established renal disease, caution may be necessary when starting GDMT. In patients with moderate renal impairment (eGFR >30 mL/min/1.73 m2 and <60 mL/min/1.73 m2), no adjustment is needed when deciding the starting dose of the ARNI sacubitril/valsartan. In those with severe renal impairment (eGFR <30 mL/ min/1.73 m2), the starting dose of sacubitril/valsartan should be reduced to 24/26 mg twice daily. ACEIs/ARBs are generally considered safe in patients with severe renal impairment, although definitive data are lacking. Aldosterone antagonists are contraindicated in patients with severe renal impairment (eGFR <30 mL/ min/1.73 m2, or creatinine >2.5 mg/dL in men or creatinine >2 mg/dL in women) or with potassium >5.0 mEq/L may be considered.

During the initiation and titration of agents that affect renal function, a decrease in eGFR of >30% or the development of hyperkalemia should alert the clinician that a reduction in doses may be necessary.

In patients with evidence of hypovolemia, the dose of diuretic agents should be reduced.

Socioeconomic barriers to care may undermine the ability to achieve GDMT. For example, the cost of therapies poses a substantial barrier to care, particularly for an ARNI, SGLT2 inhibitor, and ivabradine. In such cases, if all solutions are exhausted, optimizing care with the most financially manageable program is recommended. Similarly, some patients (for example, homebound patients) have a limited ability to attend frequent office visits for GDMT optimization. In these cases, options such as virtual care and home visiting nurse services may aid in remote optimization of GDMT limited ability to travel may be unable to have blood pressure, heart rate, or renal function assessed in a timely fashion.

After GDMT is initiated and titrated with the goal of achieving clinical trial doses or maximally tolerated doses, patients with chronic HFrEF should be evaluated on a regularly scheduled basis. For most patients, a reasonable interval is every 3 to 6 months.

Estimates of significant nonadherence in patients with HFrEF vary from 20% to 50% .
Such nonadherence is associated with worse outcomes in HF. In addition to nonadherence, a large proportion of patients with HFrEF do not receive target doses of medical therapies, even in the absence of documented intolerance.
Reasons for nonadherence are complex.

TABLE 9 Reasons for Nonadherence (World Health Organization)

Patient	■ Perceived lack of effect ■ Poor health literacy ■ Physical impairment (vision, cognition) ■ Mental health conditions (depression, anxiety) ■ Social isolation ■ Cognitive impairment (dementia)
Medical condition	■ High HF regimen complexity ■ Impact of comorbidities (e.g., depression) ■ Polypharmacy due to multiple comorbidities
Therapy	■ Frequency of dosing ■ Polypharmacy ■ Side effects
Socioeconomic	■ Out-of-pocket cost ■ Difficult access to pharmacy ■ Lack of social support ■ Homelessness
Health system	■ Poor communication ■ Silos of care ■ No automatic refills ■ Difficulty navigating patient assistance programs

HF = heart failure.

Pharmacological treatments to be considered in patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction

Recommendations	Class	Level
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.	I	C
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA= New York Heart Association.

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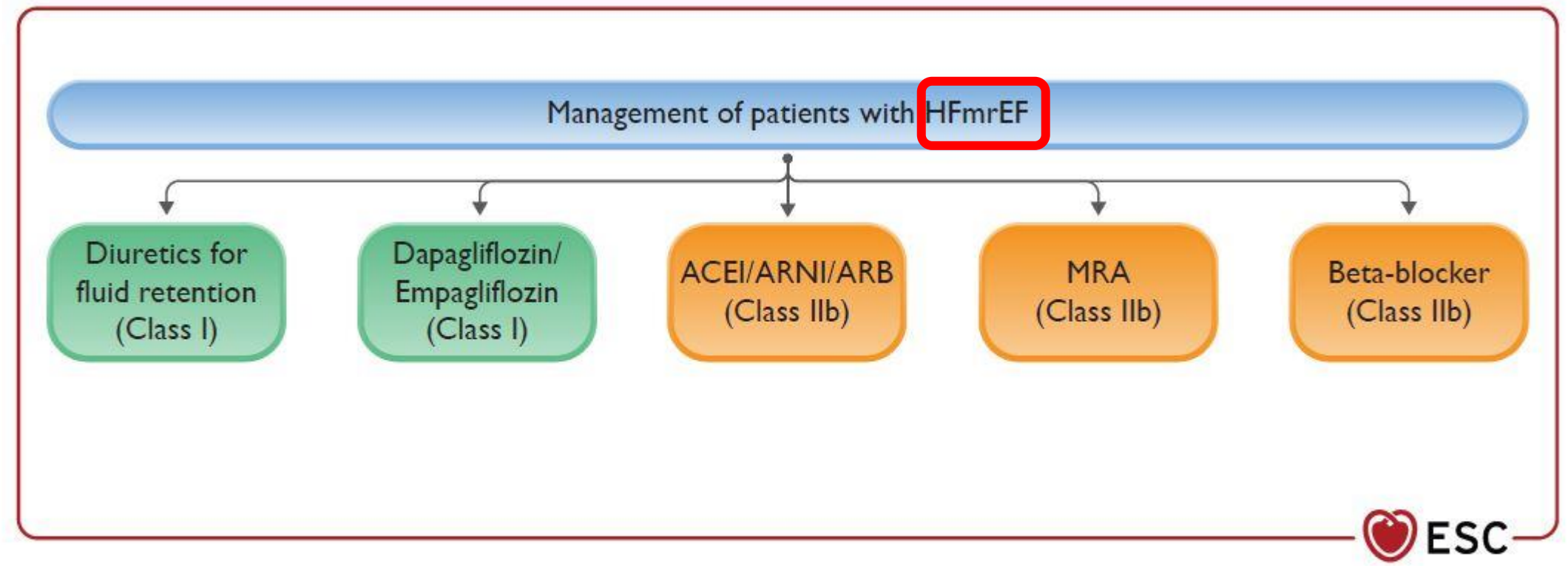

Figure 1 Management of patients with heart failure with mildly reduced ejection fraction. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HFmrEF, heart failure with mildly reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

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Recommendations for the treatment of patients with heart failure with preserved ejection fraction

Recommendations	Class[a]	Level[b]
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.[137]	I	C

HFpEF = heart failure with preserved ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.

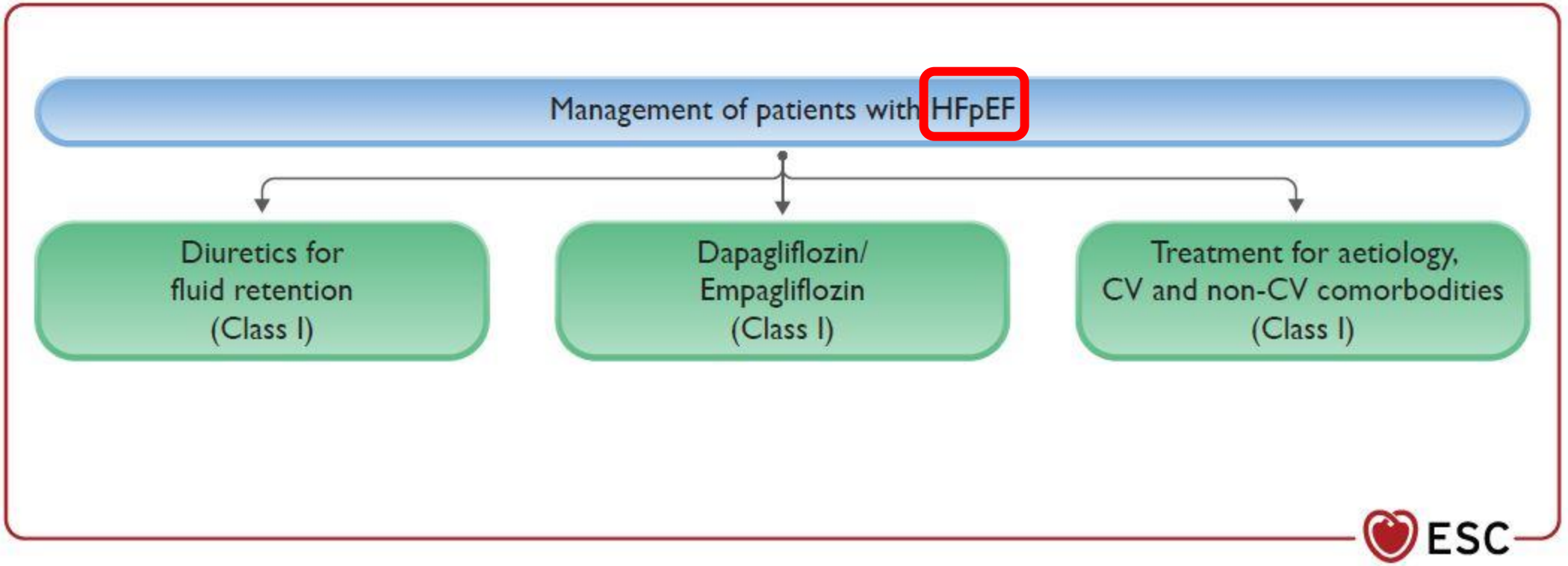

Figure 2 Management of patients with heart failure with preserved ejection fraction. CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction.

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Recommendation Table 1 — Recommendation for the treatment of patients with symptomatic heart failure with mildly reduced ejection fraction

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; SGLT2, sodium–glucose co-transporter 2.
[a]Class of recommendation.
[b]Level of evidence.
[c]This recommendation is based on the reduction of the primary composite endpoint used in the EMPEROR-Preserved and DELIVER trials and in a meta-analysis. However, it should be noted that there was a significant reduction only in HF hospitalizations and no reduction in CV death.

Recommendation Table 2 — Recommendation for the treatment of patients with symptomatic heart failure with preserved ejection fraction

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; SGLT2, sodium–glucose co-transporter 2.
[a]Class of recommendation.
[b]Level of evidence.
[c]This recommendation is based on the reduction of the primary composite endpoint used in the EMPEROR-Preserved and DELIVER trials and in a meta-analysis. However, it should be noted that there was a significant reduction only in HF hospitalizations and no reduction in CV death.

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