The 3rd Indonesian Symposium on Heart Failure and Cardiometabolic Disease 2023

Foundational therapy in HFrEF: Maximizing patient benefits in clinical practice

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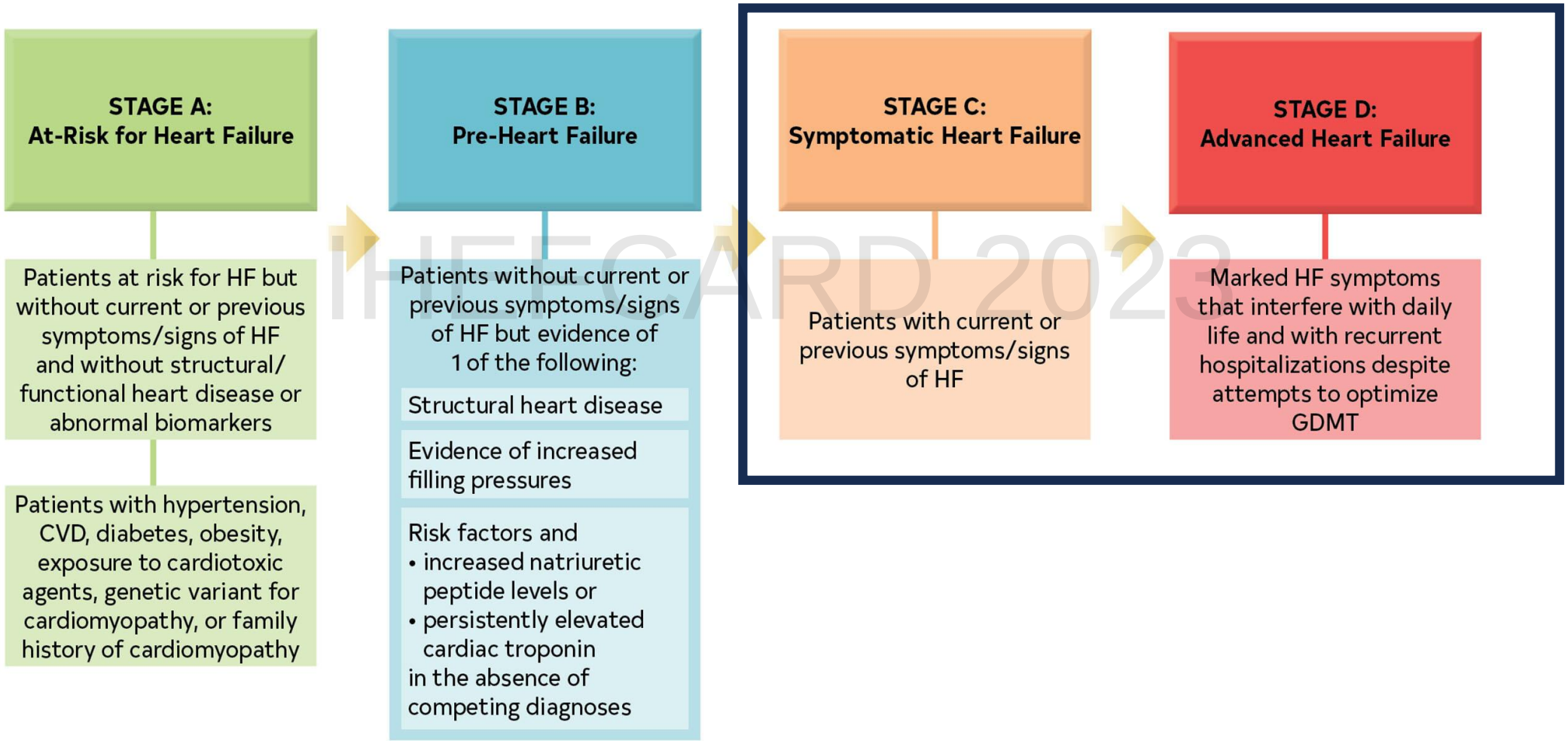
Heart failure: a complex clinical syndrome with symptoms and signs result from structural or functional impairment of ventricular filling or ejection of blood.



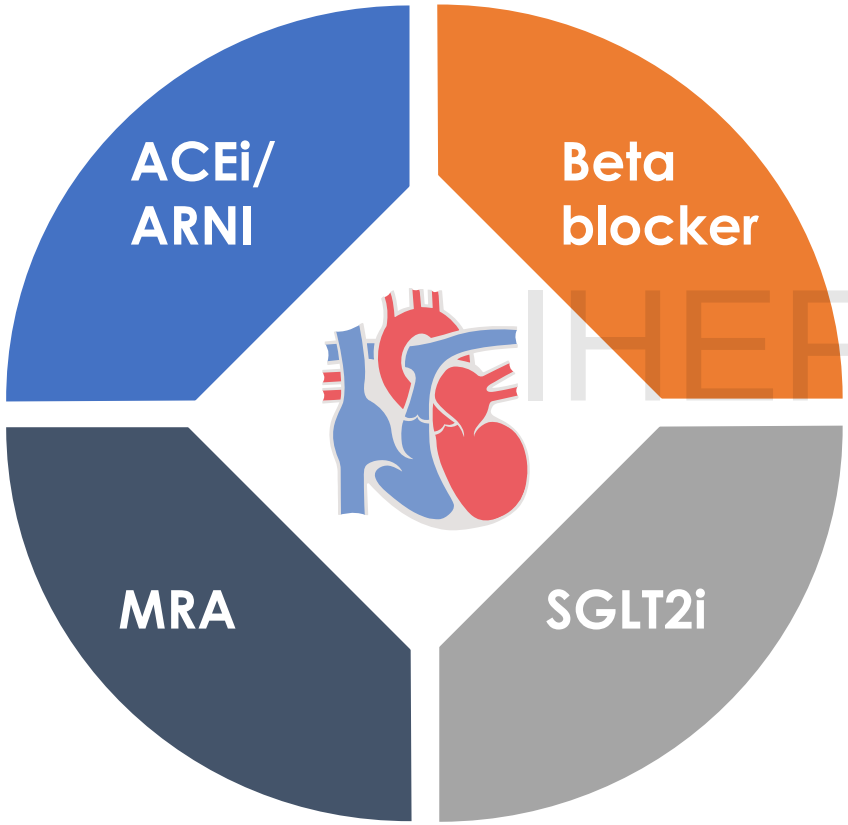
Definition of HF with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction

≤40%	41–49%	≥50%
HF with reduced EF (HFrEF)	HF with mildly reduced EF (HFmrEF)	HF with preserved EF (HFpEF)

HF with improved EF (HFimpEF)

HF with a baseline LVEF ≤40%, a ≥10-point increase from baseline LVEF, and a second measurement of LVEF >40%

Four foundational therapies for the treatment of patients with HFrEF



Evidence-Based Therapy	Relative Risk Reduction in All-Cause Mortality in Pivotal RCTs, %	NNT to Prevent All-Cause Mortality Over Time*
ACEi or ARB	17	22 over 42 mo
ARNi†	16	36 over 27 mo
Beta blocker	34	28 over 12 mo
Mineralocorticoid receptor antagonist	30	9 over 24 mo
SGLT2i	17	43 over 18 mo

Circulation. 2022;145:e895–e1032.

1. Maddox TM *et al. J Am Coll Cardiol.* 2021;77:772; 2. McDonald M *et al. Can J Cardiol.* 2021;37:531; 3. McDonagh TA *et al. Eur Heart J.* 2021;42:3599.

ACEi/ ARNi

- Inhibition of RAAS is recommended to reduce morbidity and mortality for patients with HFrEF.
- ARNi, ACEi, or ARB are recommended as first-line therapy
- If patients have chronic symptomatic HFrEF with NYHA class II or III symptoms and they tolerate an ACEi or ARB, they should be switched to an ARNi because of improvement in morbidity and mortality

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]
3: Harm	B-R	7. ARNi should not be administered concomitantly with ACEi or within 36 hours of the last dose of an ACEi.[30,31]
3: Harm	C-LD	8. ARNi should not be administered to patients with any history of angioedema.[32–35]
3: Harm	C-LD	9. ACEi should not be administered to patients with any history of angioedema.[36–39]

*See Section 7.2, "Diuretics and Decongestion Strategies in Patients with HF," for diuretic recommendations.

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ACEi		
Captopril	6.25 mg 3 times daily	50 mg 3 times daily
Enalapril	2.5 mg twice daily	10–20 mg twice daily
Fosinopril	5–10 mg once daily	40 mg once daily
Lisinopril	2.5–5 mg once daily	20–40 mg once daily
Perindopril	2 mg once daily	8–16 mg once daily
Quinapril	5 mg twice daily	20 mg twice daily
Ramipril	1.25–2.5 mg once daily	10 mg once daily
Trandolapril	1 mg once daily	4 mg once daily
ARB		
Candesartan	4–8 mg once daily	32 mg once daily
Losartan	25–50 mg once daily	50–150 mg once daily
Valsartan	20–40 mg once daily	160 mg twice daily
ARNi		
Sacubitril-valsartan	49 mg sacubitril and 51 mg valsartan twice daily (therapy may be initiated at 24 mg sacubitril and 26 mg valsartan twice daily)	97 mg sacubitril and 103 mg valsartan twice daily

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Beta blockers

- Beta blockers reduces the risk of death and the combined risk of death or hospitalization in patients with HFrEF.
- Beta blockers can improve LVEF, lessen the symptoms of HF, and improve clinical status.
- Beta blockers should be prescribed to all patients when HFrEF is diagnosed, including in-hospital, unless contraindicated or not tolerated

COR	LOE	Recommendation
1	A	1. In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality (eg, bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations.[1–3]
Value Statement: High Value (A)		2. In patients with HFrEF, with current or previous symptoms, beta-blocker therapy provides high economic value.[4–8]

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Betablockers

Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25–50 mg twice daily
Carvedilol CR	10 mg once daily	80 mg once daily
Metoprolol succinate extended release (metoprolol CR/XL)	12.5–25 mg once daily	200 mg once daily

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MRA

- MRA (aldosterone antagonists or anti-mineralocorticoids) improved all-cause mortality, HF hospitalizations, and SCD in patients with HFrEF.
- Patients at risk for renal dysfunction or hyperkalemia require close monitoring.
- An eGFR ≤30 mL/min/1.73 m^2 or serum potassium ≥5.0 mEq/L are contraindications to MRA initiation.

COR	LOE	Recommendations
1	A	1. In patients with HFrEF and NYHA class II to IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency.[1-3]
Value Statement: High Value (A)		2. In patients with HFrEF and NYHA class II to IV symptoms, MRA therapy provides high economic value.[4-7]
3: Harm	B-NR	3. In patients taking MRA whose serum potassium cannot be maintained at <5.5 mEq/L, MRA should be discontinued to avoid life-threatening hyperkalemia.[8,9]

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MR Antagonist

Spironolactone	12.5–25 mg once daily	25–50 mg once daily
Eplerenone	25 mg once daily	50 mg once daily

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SGLT2i

- In the DAPA-HF and EMPEROR-Reduced trials, SGLT2i compared with placebo reduced the composite of cardiovascular death or HF hospitalization by approximately 25%.
- The benefit in reduction of HF hospitalization was greater (30%) in both trials.
- Sotagliflozin, a dual inhibitor of sodium-glucose co-transporters 1 and 2, reduced the combined endpoint of cardiovascular death, HF hospitalization, or urgent HF visits by 33%

COR	LOE	Recommendation
1	A	1. In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.[1,2]
Value Statement: Intermediate Value (A)		2. In patients with symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value.[3,4]

SGLT2i	
Dapagliflozin	10 mg once daily
Empagliflozin	10 mg once daily

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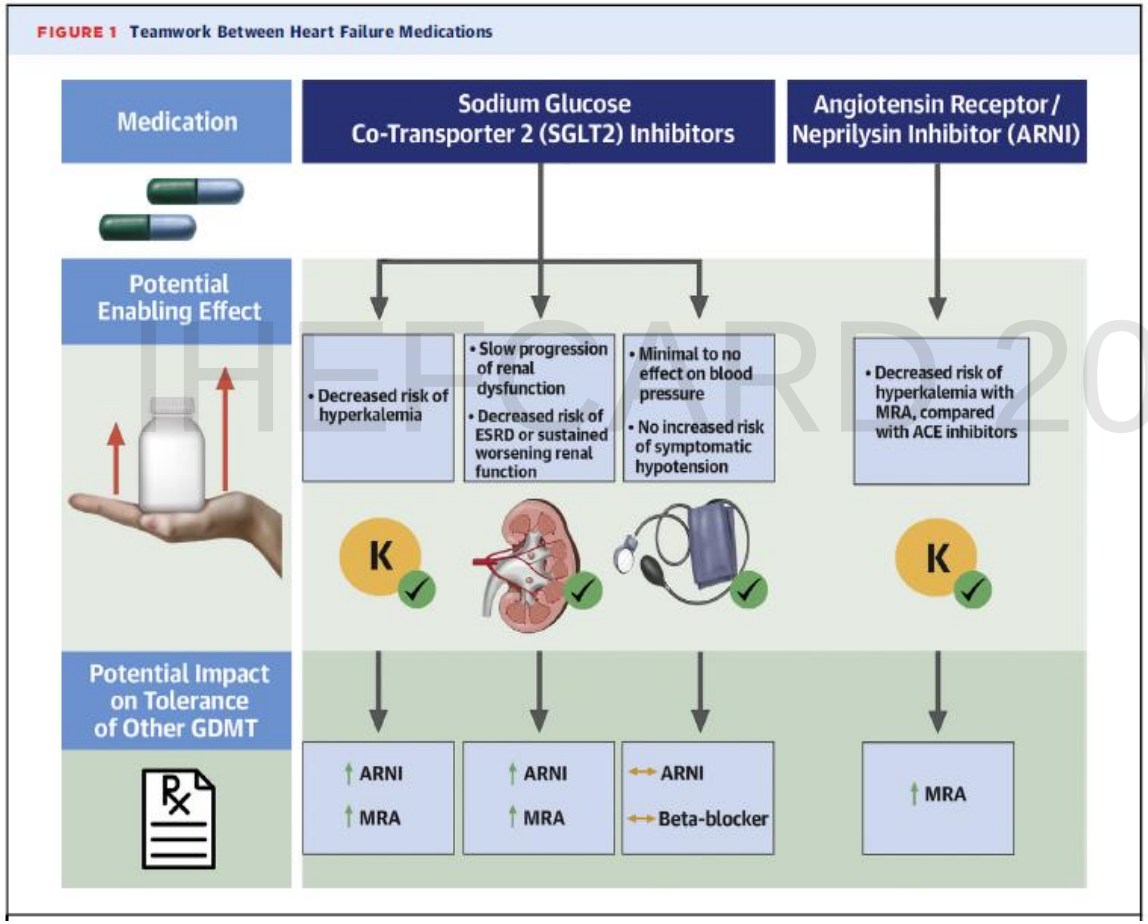
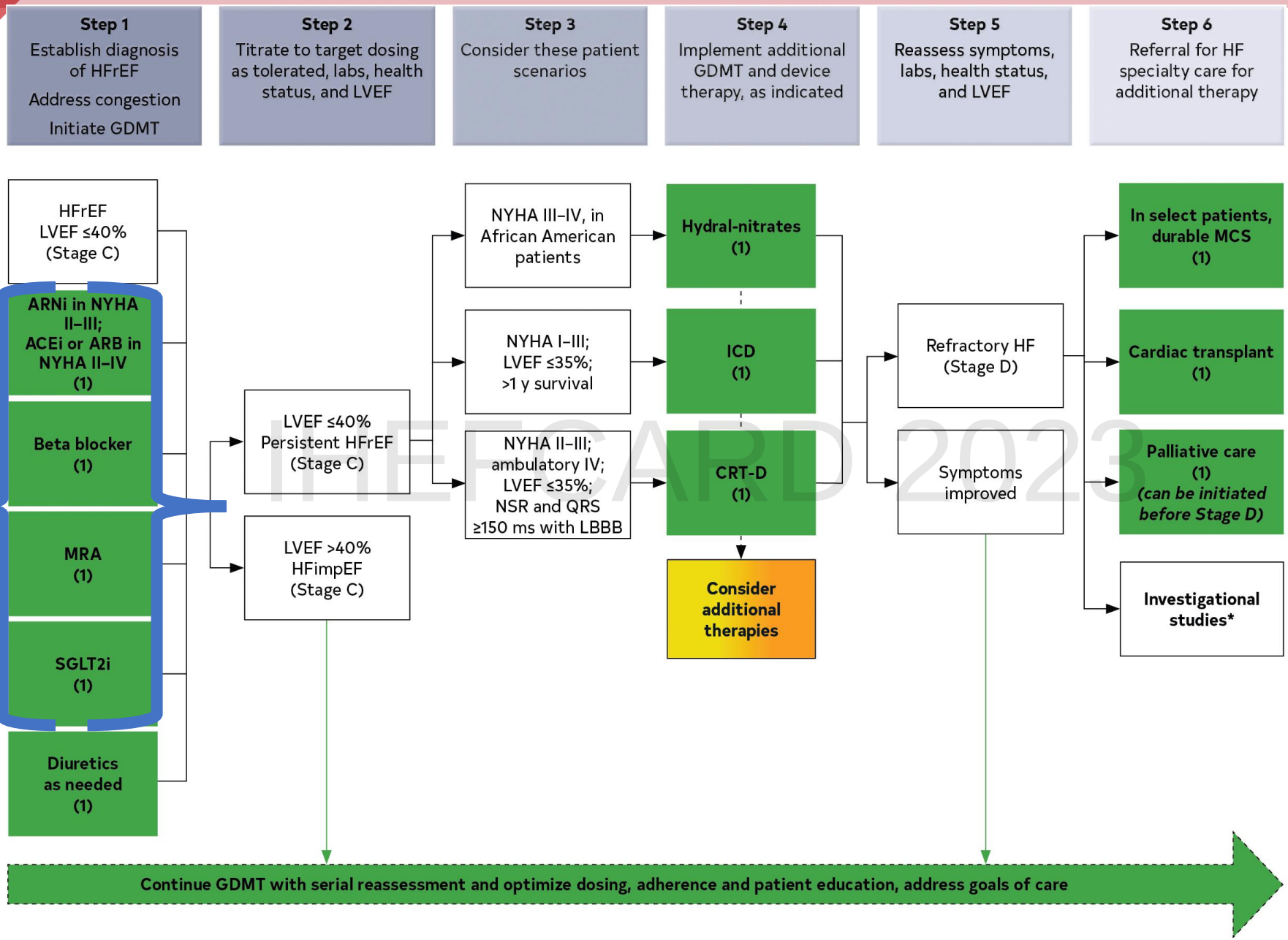
SGLT2-i Works with Other Background Foundation



Greene SJ, Butler J, Metra M. European Journal of Heart Failure 2021;23(9):1525-1528



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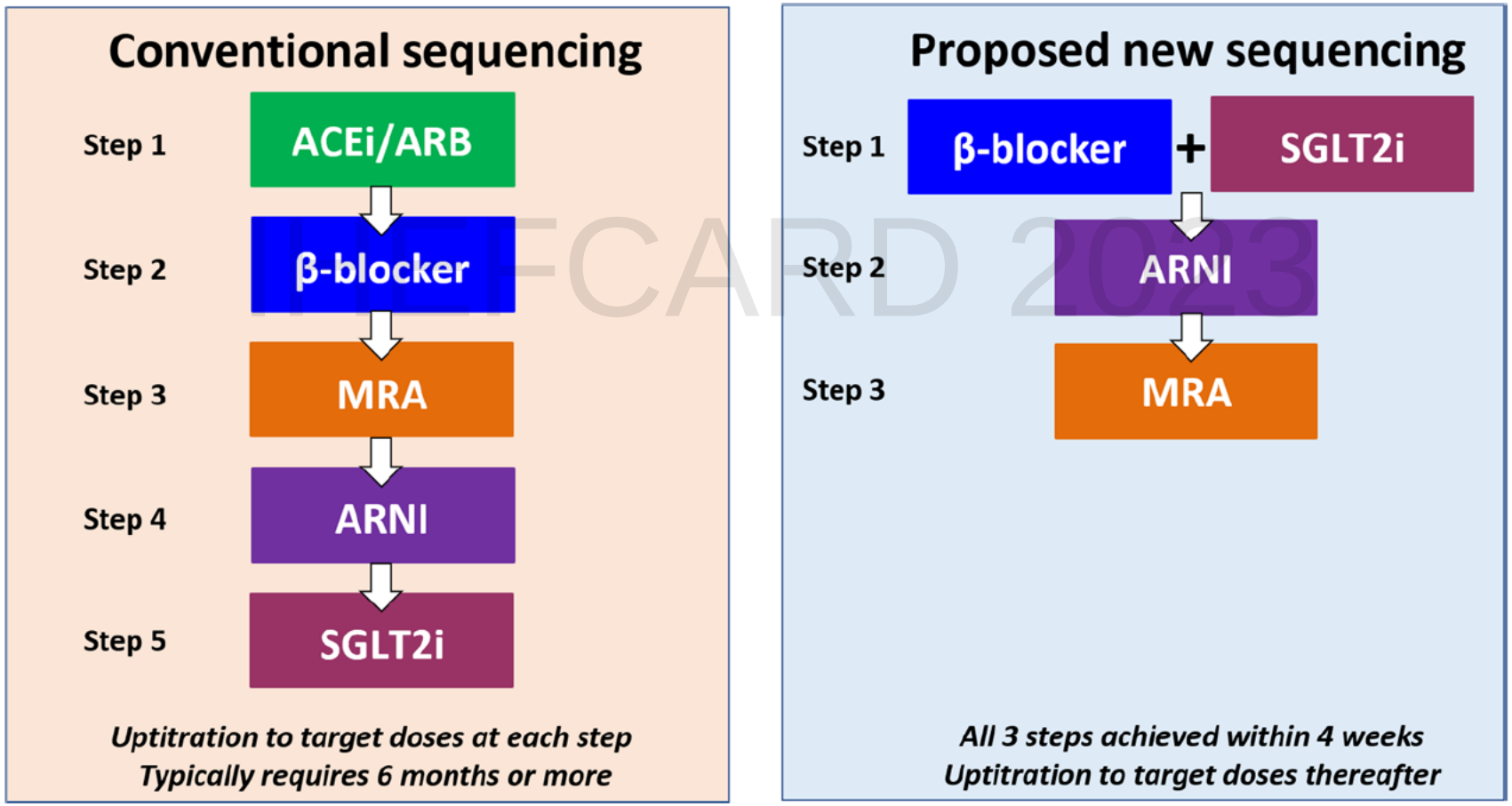
Sequencing the foundation therapy → quick strategy, more benefit



Circulation. 2021;143:875–877.

Strategies to Anticipate GDMT Related Adverse Events

4 Therapies on Board in 4 Weeks

Acute HF	Chronic HF	De Novo HF
STOP ACEI • ARB	STOP ACEI • ARB	INITIATE ARNI • β-blocker
CONTINUE β-blocker	CONTINUE β-blocker	INITIATE in 2-4 weeks SGLT2i • MRA
INITIATE in hospital ARNI • SGLT2i	INITIATE ARNI • SGLT2i	
INITIATE at discharge MRA	INITIATE in 2 weeks MRA	

Start low dose ARNI/BB - Uptitrate over time to guideline-directed or maximally-tolerated doses after all 4 foundational therapies have been introduced

Anticipate potential side effects

Hypotension	Declining eGFR	Hyperkalemia
a. Assess volume status and diuretic dose b. Consider spacing medications during the day c. Discontinue therapies that do not offer CV benefits (e.g. CCBs)	Anticipate an early decline in eGFR (~20%) that will recover and stabilize with time	Consider K^+ binders (e.g. patiromer and sodium zirconium cylosilicate)

Sharma et al. 2022. Optimizing Foundational Therapies in Patients With HFrEF. https://doi.org/10.1016/j.jacbts.2021.10.018

Thank you