Prioritizing GDMT in HFrEF: What Matters Most

St. Michael's Hospital Virtual Cardiology Day

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Disclosures

PROGRAM DISCLOSURE OF COMMERCIAL SUPPORT

I have relationships with for-profit and not-for-profit organizations over the past two years:

Nature of Relationship	Name of the for-profit of not-for-profit organization	Description of Relationship
Any direct financial payments including receipt of honoraria	Roche Diagnostics, Canadian Heart Failure Society	Honoraria for conferences
Membership on advisory boards or speakers' bureaus	Abbott, Boehringer Ingelheim, CHEP Plus, CSL, GSK, Novo Nordisk	Member of advisory board, speaker bureaus, moderator of CME events
Funded grants of clinical trials	N/A	
Patents on a drug, product or device	N/A	
All other investments/relationship that could be seen as having the potential to influence the content of the educational activity	N/A	

Case: Ms. Wynded

- 75 year old woman
- DM2 treated with metformin 1000 mg BID and glyburide 5 mg BID
- History of HF due to previous MI and AF
- LVEF 33%, declined ICD therapy
- Used to walk 30 min daily without shortness of breath
- Now NYHAIII for the past 2 weeks with orthopnea

- In clinic:
  - On perindopril 8 mg/day, bisoprolol 10 mg/day, spironolactone 12.5 mg/day
  - Creatinine 131 µmol/L, eGFR 36 mL/min/1.73 m2, K+ 5.2 mmol/L
  - HR 83 bpm, atrial fibrillation
  - BP 120/78 mmHg

BID, twice a day; BP, blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HR, heart rate; ICD, implantable cardioverter defibrillator; K+, potassium; MI, myocardial infarction; NYHA, New York Heart Association Functional Classification; T2DM, type 2 diabetes mellitus

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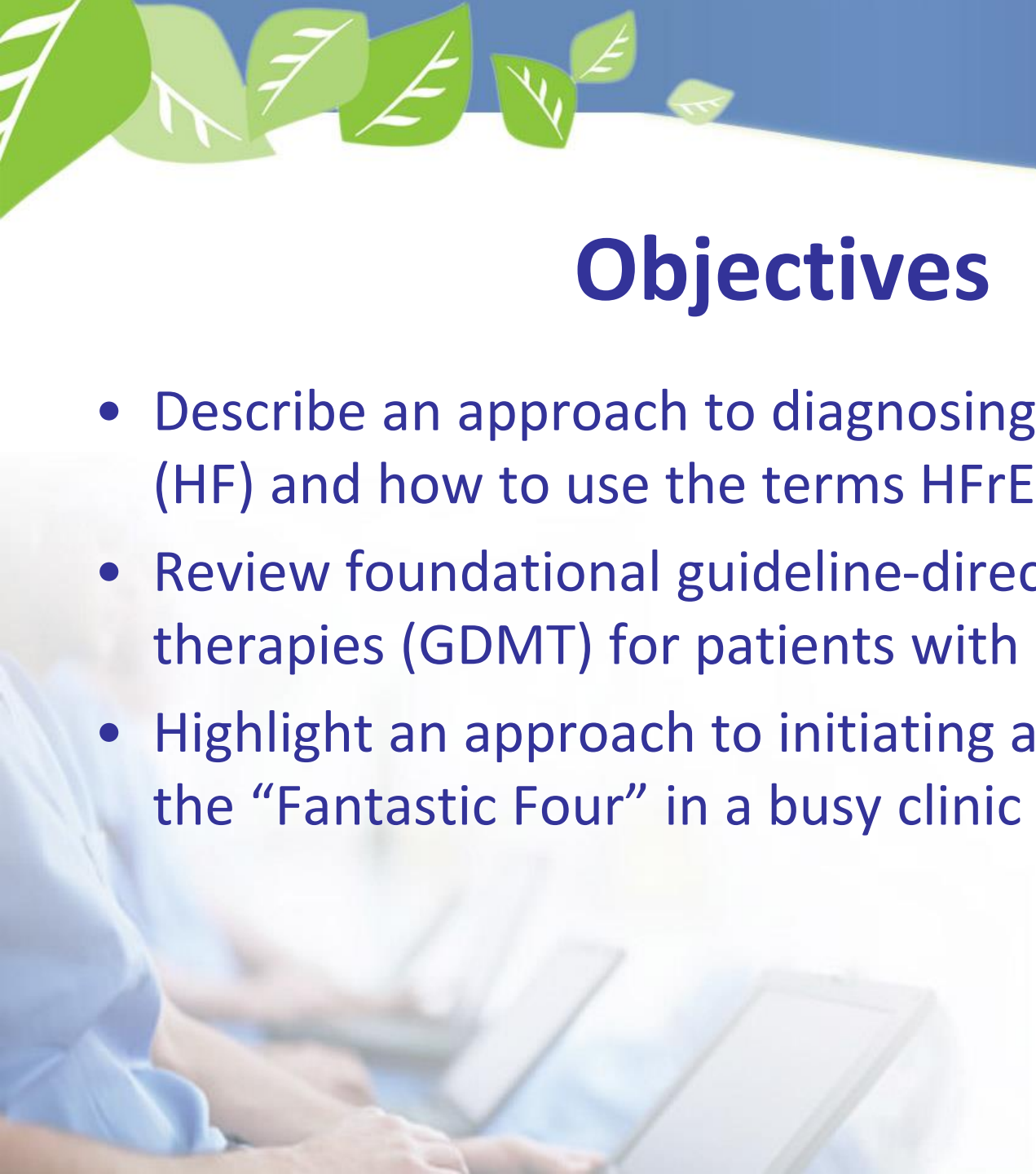
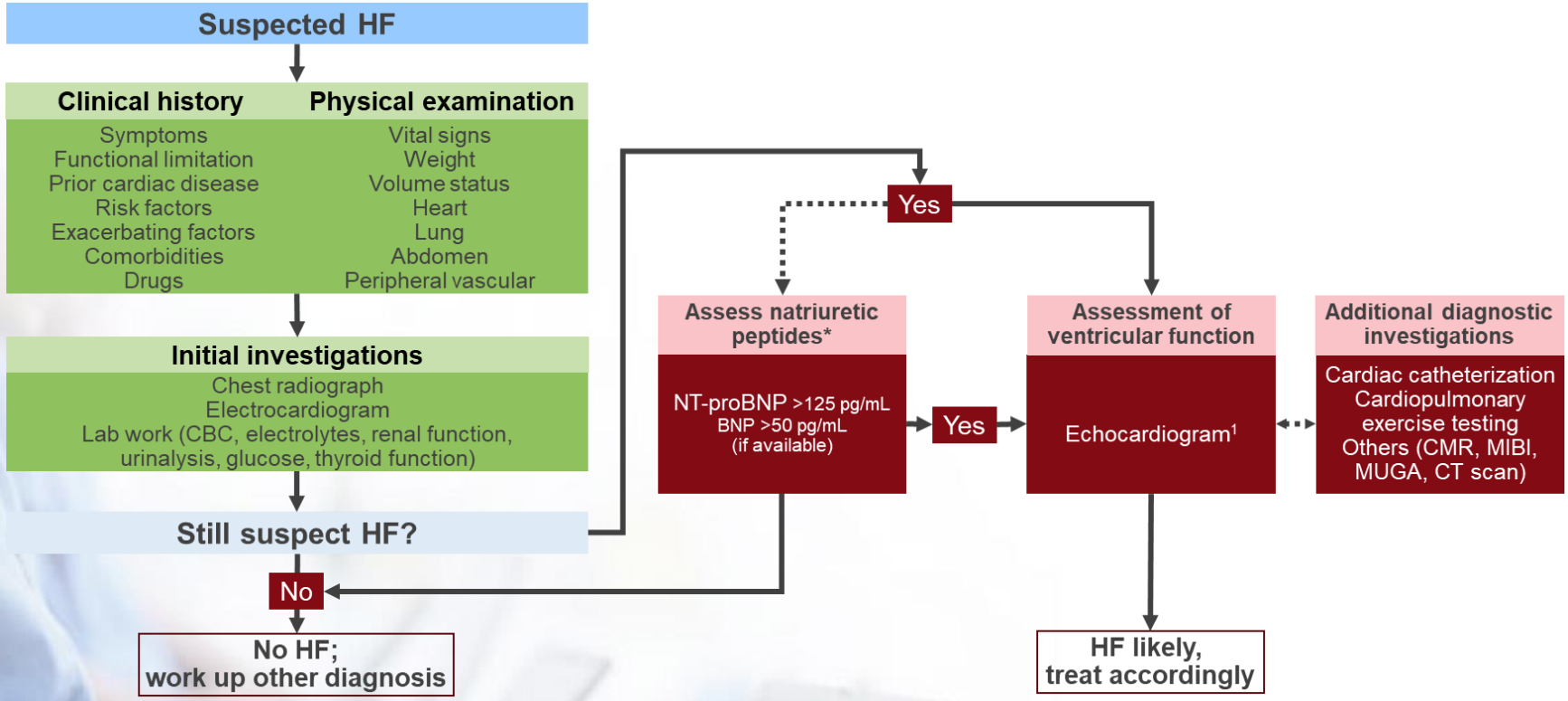
Objectives

- Describe an approach to diagnosing heart failure (HF) and how to use the terms HFrEF and HFnrEF
- Review foundational guideline-directed medical therapies (GDMT) for patients with HFrEF
- Highlight an approach to initiating and maintaining the “Fantastic Four” in a busy clinic



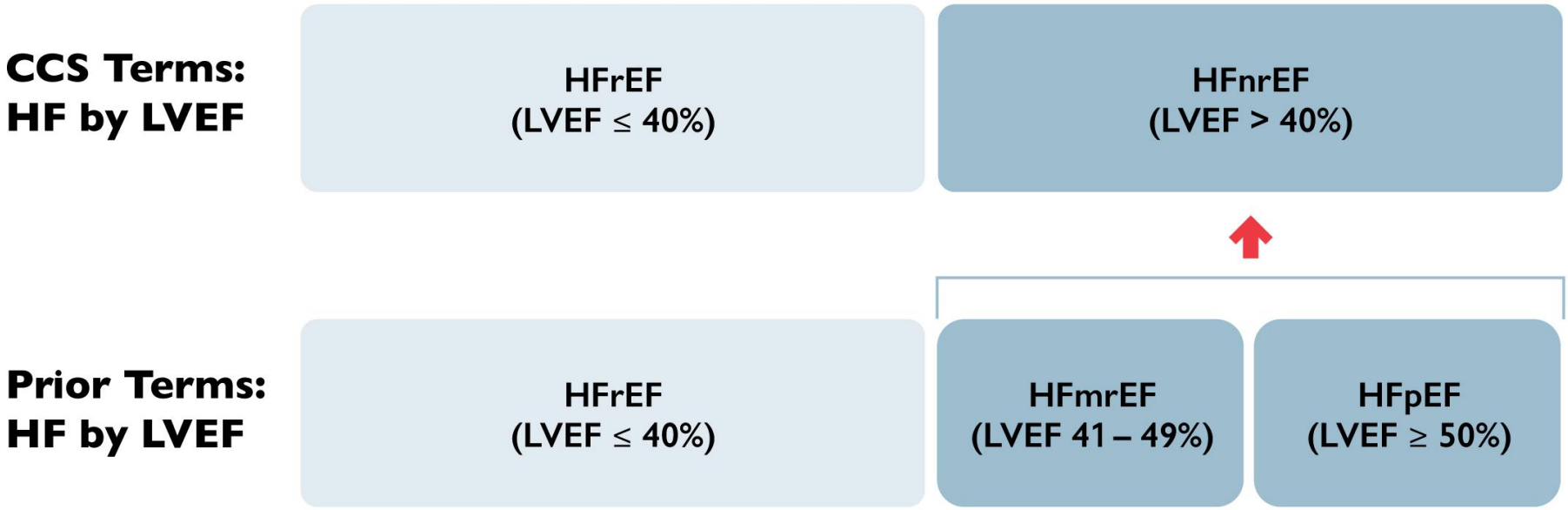
CCS Diagnosis Algorithm for HF



CCS, Canadian Cardiovascular Society

Ezekowitz JA. Can J Cardiol. 2017;33(11):1342-1433.

Definition of HFrEF



Virani S et al. Can J Cardiol. 2025;41(10):1857-1874

CCS/CHFS 2021 HF Guidelines

- We recommend that in the absence of contraindications, patients with HFrEF be treated with combination therapy including 1 evidence-based medication from each of the following categories *(Strong Recommendation; Moderate-Quality Evidence)*:
  - **a.** ARNI (or ACEI/ARB);
  - **b.** β-blocker;
  - **c.** MRA; and
  - **d.** SGLT2 inhibitor.
- *The Committee acknowledges lack of evidence favouring one particular titration strategy for guideline-directed medical therapy (GDMT) over another.*

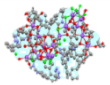
Sacubitril/valsartan simultaneously promotes the NP pathway and inhibits the RAAS pathway

Natriuretic and other vasoactive peptides*

Neprilysin

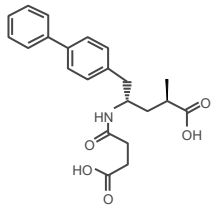
Inactive fragments

ARNI

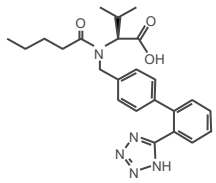


Sacubitril
(AHU377; pro-drug)

LBQ657
(NEP inhibitor)



Valsartan



RAAS

Angiotensinogen
(liver secretion)

↓

Ang I

↓

Ang II

↓

AT_1 Receptor

Enhancing

Vasorelaxation
- ↓ Blood pressure
- ↓ Sympathetic tone
- ↓ Aldosterone levels
- ↓ Fibrosis
- ↓ Hypertrophy
- ↑ Natriuresis/diuresis

Inhibiting

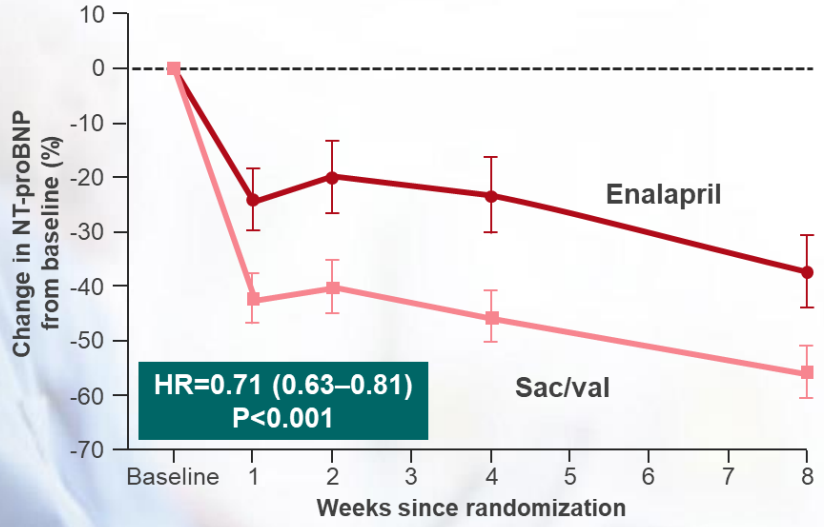
Vasoconstriction
- ↑ Blood pressure
- ↑ Sympathetic tone
- ↑ Aldosterone
- ↑ Fibrosis
- ↑ Hypertrophy

*Neprilysin substrates listed in order of relative affinity for NEP: ANP, CNP, Ang II, Ang I, adrenomedullin, substance P, bradykinin, endothelin-1, BNP

Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Schrier & Abraham N Engl J Med 2009;341:577–85; Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9;
Feng et al. Tetrahedron Letters 2012;53:275–6

Sacubitril/Valsartan: Early separation in HFrEF and acute decompensated HF

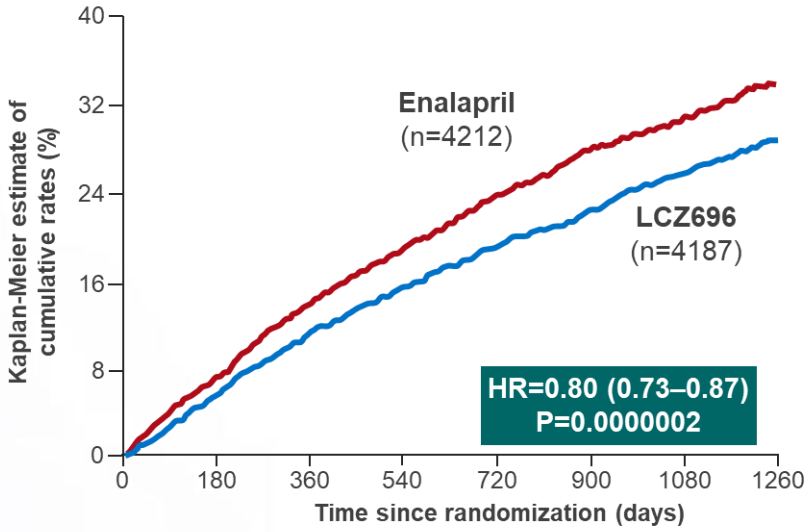
PIONEER-HF (acute decompensated inpatients): Primary efficacy outcome (change in the NT-proBNP concentration)[2]



No. at risk

Sac/val	397	355	363	365	349			
Enalapril	394	359	351	350	348			

PARADIGM-HF (outpatients): Primary endpoint (CV death or HF hospitalization)[1]



Patients at risk

LCZ696: 4187	3822	3663	3018	2257	1544	896	249	
Enalapril: 4212	3883	3579	2922	2123	1488	853	236	

CV, cardiovascular; HR, hazard ratio; NT-pro-BNP, N-terminal pro b-type natriuretic peptide; sac/val, sacubitril/valsartan

1. McMurray JJ et al. N Eng J Med 2014;371(11):993-1004; 2. Velazquez EJ et al. N Eng J Med 2019;280(6): 539-548.

SGLT2i IMPROVES CARDIAC FUNCTIONS

- Decreases intravascular volume and blood pressure by reducing preload and afterload through osmotic diuresis and natriuresis
- Enhances myocardial efficiency
- Reverses cardiac remodeling through anti-inflammatory and antifibrotic effects, reduced oxidative stress, and improved endothelial function

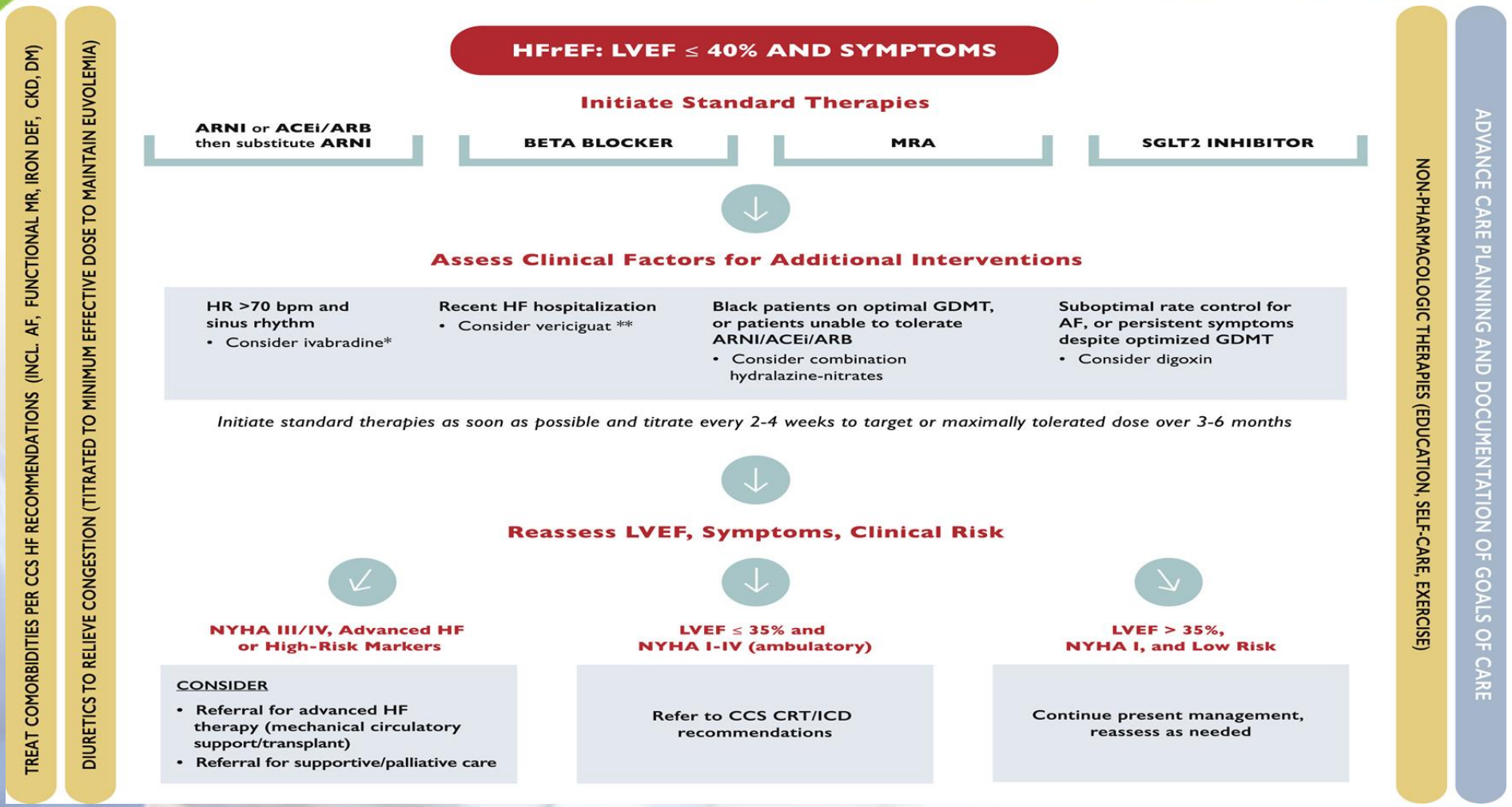
Early RCTs showed
reduced risk of HFH and CV death

SGLT2 inhibitors in HFrEF

	DAPA-HF	EMPEROR-Reduced
SGLT2 inhibitor	Dapagliflozin 10 mg daily	Empagliflozin 10 mg daily
No. of patients	4,744	3,730
Inclusion criteria	LVEF ≤40% +/-DM (42%)	LVEF ≤40% +/-DM (50%)
eGFR	>30	>20
Median follow-up	18.2 months	16 months
Primary outcome	CV death + HF composite (HF hosp + urgent HF visit)	CV death + HF hosp
Results	HR 0.74 (0.65-0.85); P<0.001	HR 0.75 (0.65-0.86); P<0.001

Consistent regardless of DM status, age, sex, baseline ARNI

McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008.
Packer M et al. *N Engl J Med*. 2020;383:1413-1424.



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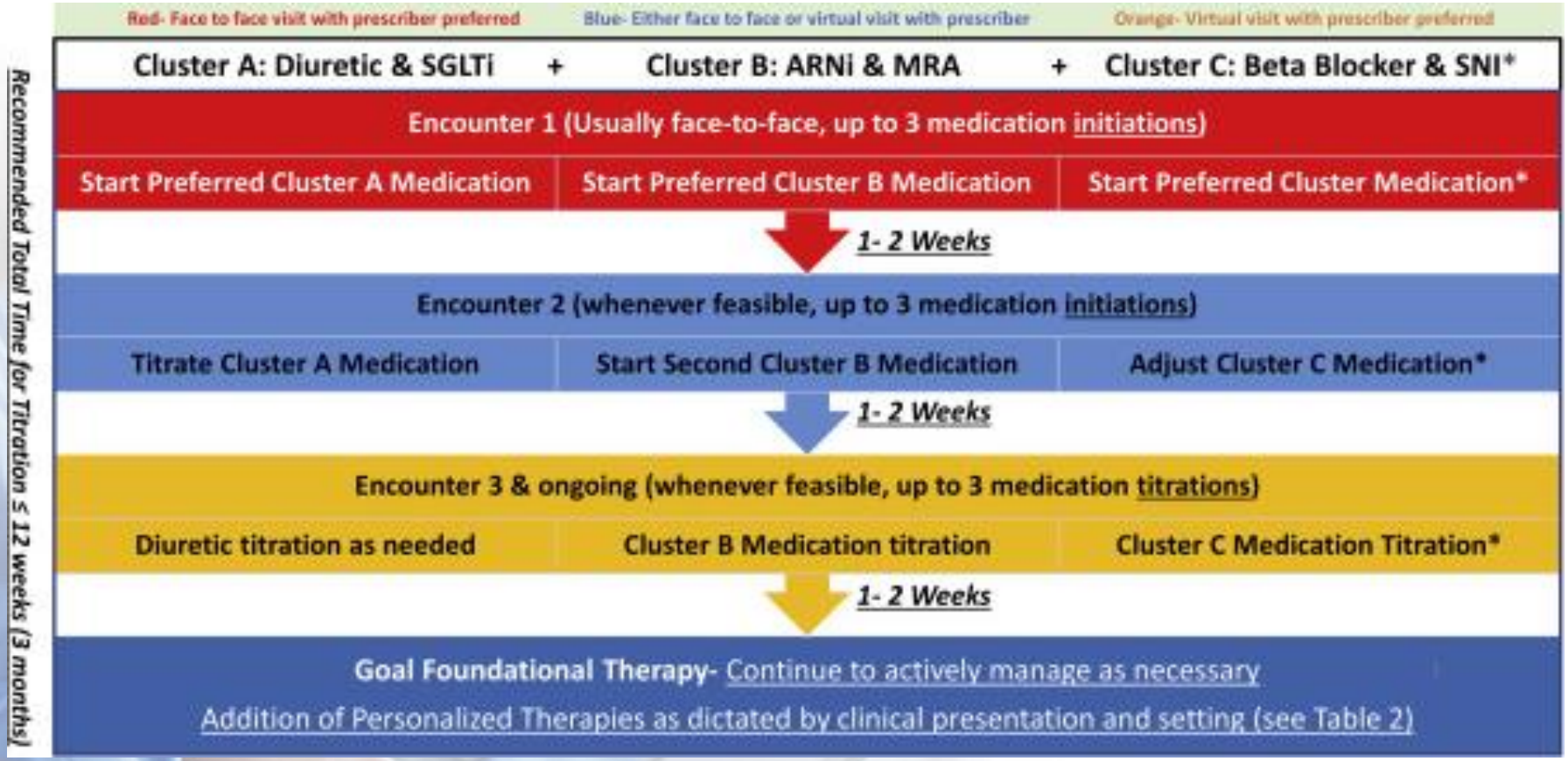
Cluster Scheme:
Initiation and Titration of HFrEF GDMT



How to Follow Up a Patient Initiated on Sacubitril Valsartan

✓	**Do replace ACE or ARB in the management of HFrEF**	• Leverage both suppression of RAAS pathway and increased NP levels • Stop ACE for 36 hours (if ARB, start at next dose) • Start sac/val at 49/51 mg (or 24/26 mg based on patient profile) • Increase dose 4 weeks after initiation if labs/BP adequate* • If ARNI, ACE/ARB inadequate, try nitrates + hydralazine
✓	**Do watch K^+/Cr for 2–3 weeks post initiation**	• Cut down if hyperkalemia or significant rise in Cr occurs • Recall that with ACE/ARB/diuretic or sac/val – ↑ Cr of 30% is acceptable* • No visit with specialist or GP required
✓	**Do follow BP for 2–3 weeks post initiation**	• Anticipate BP-lowering effect • No visit with specialist or GP required
	**Use caution if SBP <100 mmHg and/or eGFR <30 mL/min/1.73 m^2**	PARADIGM-HF trial excluded patients with eGFR <30 mL/min/1.73 m^2 or symptomatic hypotension with SBP <100 mmHg
✗	**Do NOT start an ACE when already on sac/val**	Risk of angioedema with combined use
✗	**Do NOT start an ARB when already on sac/val**	Redundant, as there is ARB already in it

*If initial dose is 24/26 mg, add one addition step during the titration

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BP, blood pressure; CR, creatinine; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; K+, potassium; NP, natriuretic peptide; RAAS, renin-angiotensin-aldosterone system; sac/val, sacubitril/valsartan; SBP, systolic blood pressure

Howlett JG. Can J Cardiol 2015;32(3):296-310. Consult product monograph.

How to Follow Up a Patient Initiated on SGLT2i

✓	**Glucose-lowering effects beneficial in patients with comorbid diabetes**	• No changes in most diabetic medications given low risk of hypoglycemia
		• If on insulin or sulfonylurea:
		  • No dose reduction if A1c >8.5 or unknown
		  • Consider 25–50% dose reduction if A1c <8.5

✓	**Volume contraction/diuresis effects**	• If euvolemic, reduce loop diuretic by 25–50% • If hypervolemic, no dose adjustment in loop diuretic required • If hypovolemic, defer initiation of SGLT2is
✓	**Indicated for eGFR ≥30%**	Early drop in eGFR by 20% (relative) acceptable; stabilizes, and reduces further decline
✗	**Sick day management**	Hold for dehydrating illness
✗	**Genital mycotic infections (GMIs)**	• SGLT2is do not cause GMIs but they do not prevent them; manage according to general guidelines for candidiasis • No effect on urinary tract infections (UTIs)

How to Follow Up a Patient Initiated on Ivabradine

✓	**Do try to achieve target doses of BBs prior to initiation**	• If HR remains ≥70 bpm, consider initiation of ivabradine
✓	**Do start with low dose and modify dose based on patient's resting HR**	• In patients >75 years of age, 2.5 mg BID starting dose may be used • Aim for targeted dose, or highest tolerated dose based on resting HR (50–60 bpm target) • Titration can usually be accomplished in 2–4 weeks
✓	**Do follow-up with 12-lead ECG**	• HR fluctuates considerably over time • Assess HR prior to dose modifications
	**Use with caution if symptomatic hypotension (<90/50 mmHg)**	While ivabradine has no effect on BP, caution is advised when used in patients with BP <90/50 mmHg
	**Do NOT use if HR <70 bpm or not in sinus rhythm prior to treatment**	Titrate dose downward if bradycardia develops (HR <50 bpm) or patient experiences symptoms of dizziness, fatigue or hypotension
	**Do NOT use if severe cirrhosis**	Titrate dose downward if bradycardia develops (HR <50 bpm) or patient experiences symptoms of dizziness, fatigue or hypotension

BB, beta-blocker; BID, twice a day; BP, blood pressure; bpm, beats per minute; ECG, electrocardiogram; HR, heart rate

Howlett JG. Can J Cardiol 2015;32(3):296-310; Ponikowski P et al. Eur Heart J, 2016;37(27):2129-2200. Consult product monograph.

Nonpharmacologic Strategies for All HF Patients

- Typical sodium intake ≤2000 mg/day
- Fluid restriction in selected patients
- Daily weight monitoring with diuretic sliding scale
- Regular exercise may improve quality of life
- Achieving and maintaining healthy body weight
- Smoking cessation
- Annual influenza, periodic pneumococcal pneumonia immunizations and current/future vaccines relevant to this high-risk population (e.g. COVID-19)
- Close follow-up and disease management
- Patient and caregiver education

I-NEED-HELP Mnemonic: Referral to HF Specialist

- **I** = inotropes
- **N** = NYHA class/natriuretic peptides
- **E** = end-organ dysfunction (renal, liver)
- **E** = LVEF ≤25%
- **D** = defibrillator shock
- **H** = at least 1 HF hospitalization in the prior 12 months
- **E** = edema, escalating diuretics
- **L** = low blood pressure
- **P** = prognostic medications (inability to increase or need to decrease)

Baumwol J. "I NEED HELP": a mnemonic to aid timely referral in advanced heart failure. *J Heart Lung Transplant.* 2017;36:593–594.

Takeaway Messages

- HFrEF is highly treatable
  - Use all 4 pillars early (ARNI/ACEi/ARB, beta-blocker, MRA, SGLT2i)
  - Benefits are additive and rapid
- Time matters
  - Initiate and uptitrate within weeks, not months
  - Early optimization reduces hospitalizations and mortality
- Don’t let barriers delay therapy
  - Renal dysfunction, hypotension, hyperkalemia are oftentimes manageable, and not contraindications
  - Adjust, monitor, and keep patients on therapy
- Care beyond medications
- Recognize risk early and when to refer