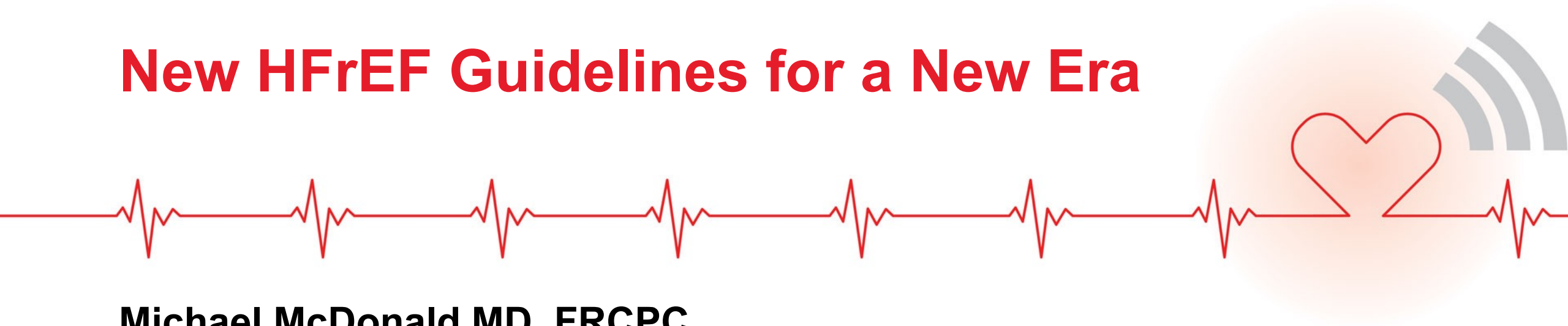
New HFrEF Guidelines for a New Era



Michael McDonald MD, FRCPC

Associate Professor, University of Toronto

Medical Director, Ted Rogers Centre of Excellence in Heart Function

Medical Director, Ajmera Heart Transplant Program, University Health Network

Disclosures

- **Grants/research support**: Novartis, Abbott
- **Consulting fees**: Novartis, Servier, BI-Lilly, AstraZeneca, Merck, Otsuka
- **Speaker fees**: Novartis, Servier

Objectives

- Review key highlights from the 2021 heart failure guidelines
- Incorporate new drugs for patients with acute or chronic heart failure
- Discuss options for medication titration in HFrEF

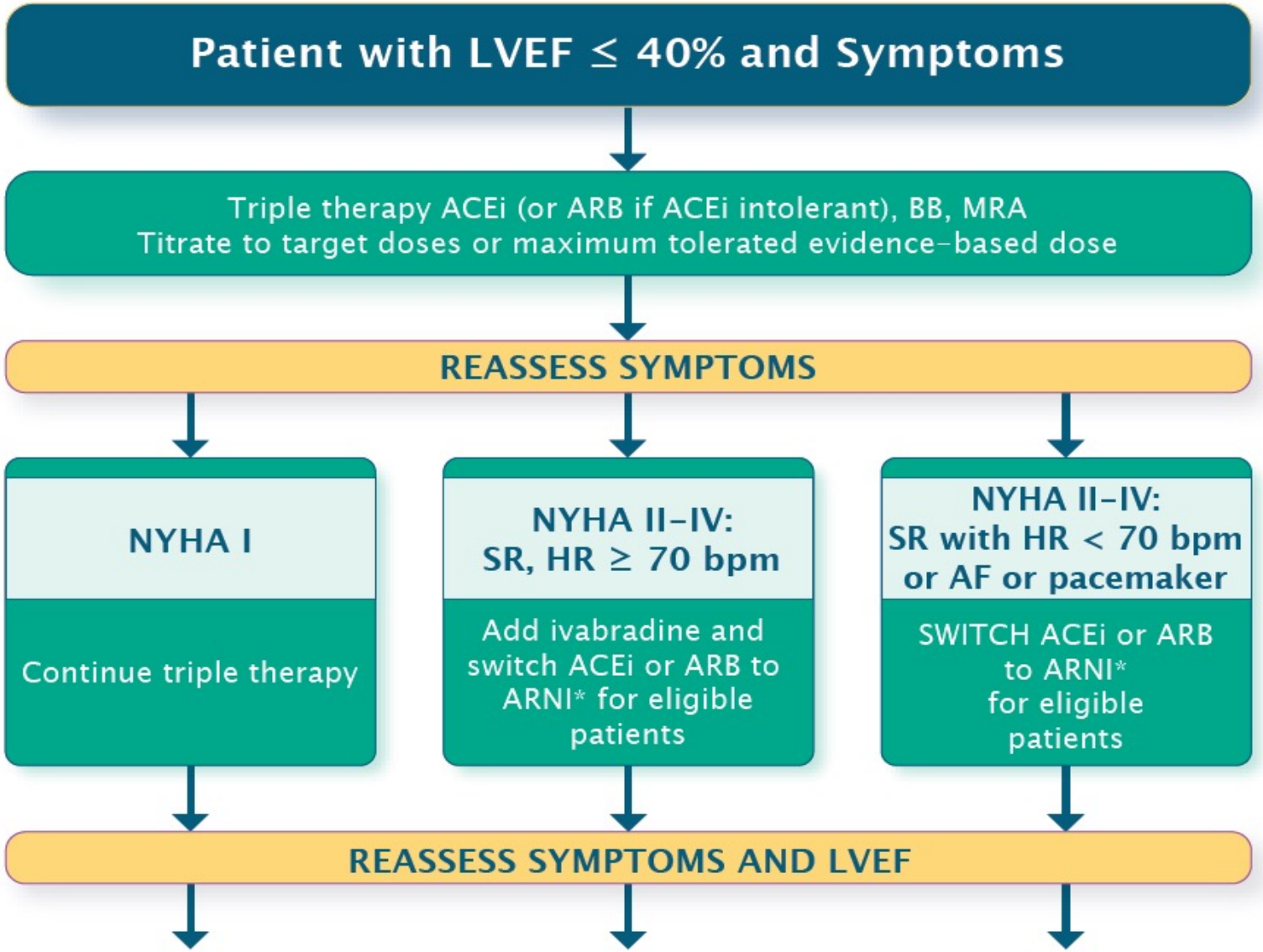
CCS/CHFS Heart Failure Guideline Updates

- 2017: Comprehensive Update for the Management of Heart Failure
- 2020: Focus on Functional MR, SGLT2 inhibitors, ARNI in HFpEF, and Cardiac Amyloidosis
- **2021: Updated Standard of Care for Heart Failure with Reduced Ejection Fraction**
  - Incorporating new evidence for ARNI in different settings, SGLT2 inhibitors, vericiguat
  - Updated evidence review for all pharmacologic therapies in HF
  - Update HFrEF treatment algorithm

Therapeutic approach to patients with HFrEF (circa 2017)

"Triple therapy"

Substitute for ARNI, add ivabradine



Ezekowitz et al, Can J Cardiol 2017

Some new evidence for decision making in HFrEF

Study	Drug	Patients	Primary Outcome	Study Implications
PIONEER-HF (and extension study)	Sac-val vs Enalapril	Stabilized after admission with with worsening HF; 35% with de novo HF	Change in NT-proBNP values at 8 weeks	Broader use of ARNI in hospitalized and de novo HF patients

Some new evidence for decision making in HFrEF

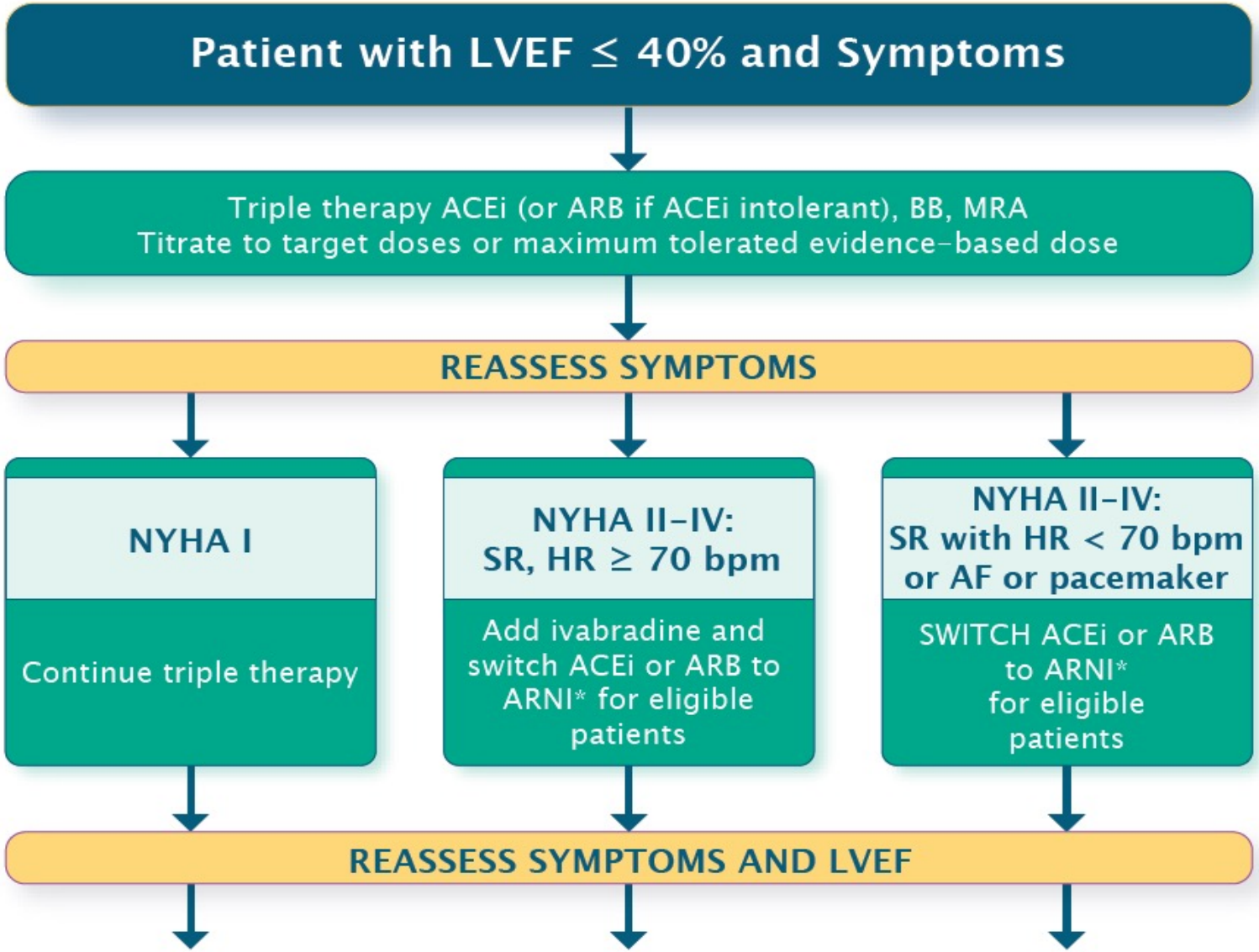
Study	Drug	Patients	Primary Outcome	Study Implications
PIONEER-HF (and extension study)	Sac-val vs Enalapril	Stabilized after admission with with worsening HF; 35% with de novo HF	Change in NT-proBNP values at 8 weeks	Broader use of ARNI in hospitalized and de novo HF patients
DAPA HF	Dapagliflozin vs placebo	NYHA II-IV, chronic HF, with or without DM2	CV death or worsening HF	Addition of SGLT2 inhibitors improves outcomes in broad spectrum of HFrEF patients with or without DM2
EMPEROR Reduced	Empagliflozin vs placebo	High risk NYHA II-IV, chronic HF, with or without DM2	CV death or worsening HF	

Some new evidence for decision making in HFrEF

Study	Drug	Patients	Primary Outcome	Study Implications
PIONEER-HF (and extension study)	Sac-val vs Enalapril	Stabilized after admission with with worsening HF; 35% with de novo HF	Change in NT-proBNP values at 8 weeks	Broader use of ARNI in hospitalized and de novo HF patients
DAPA HF	Dapagliflozin vs placebo	NYHA II-IV, chronic HF, with or without DM2	CV death or worsening HF	Addition of SGLT2 inhibitors improves outcomes in broad spectrum of HFrEF patients with or without DM2
EMPEROR Reduced	Empagliflozin vs placebo	High risk NYHA II-IV, chronic HF, with or without DM2	CV death or worsening HF	
VICTORIA	Vericiguat vs placebo	NYHA II-IV, recent worsening HF requiring admission or IV diuretic	CV death or worsening HF	Addition of vericiguat in stabilized high risk patients further improves outcomes

Opportunities with some challenges

- **Where do we now put ARNI… and SGLT2 inhibitors?**
- **Where do we put sGC stimulators?**
- **What about older HF therapies like digoxin and vasodilators?**
- **When should we refer for ICD and CRT?**



Vignette #1

- 55 F, admitted with new onset HF
  - Anterior wall MI, 12 weeks prior with PCI to LAD
  - LVEF 35-40%
- PMHx:
  - HTN
- Meds
  - Ramipril 1.25 mg bid
  - Spironolactone 25 mg/d
  - Bisoprolol 5 mg/d
  - Atorvastatin 80 mg/d
  - ASA, Ticagrelor 90mg bid

- BP 155/95, HR 76 bpm (admission)
- JVP 7 cm, bibasilar crepitations
- ECG: sinus rhythm, anterior Qs (QRS 120ms)

- Decongested with IV furosemide x 48h
  - BP 118/66, HR 72 bpm

- ***So now what?***

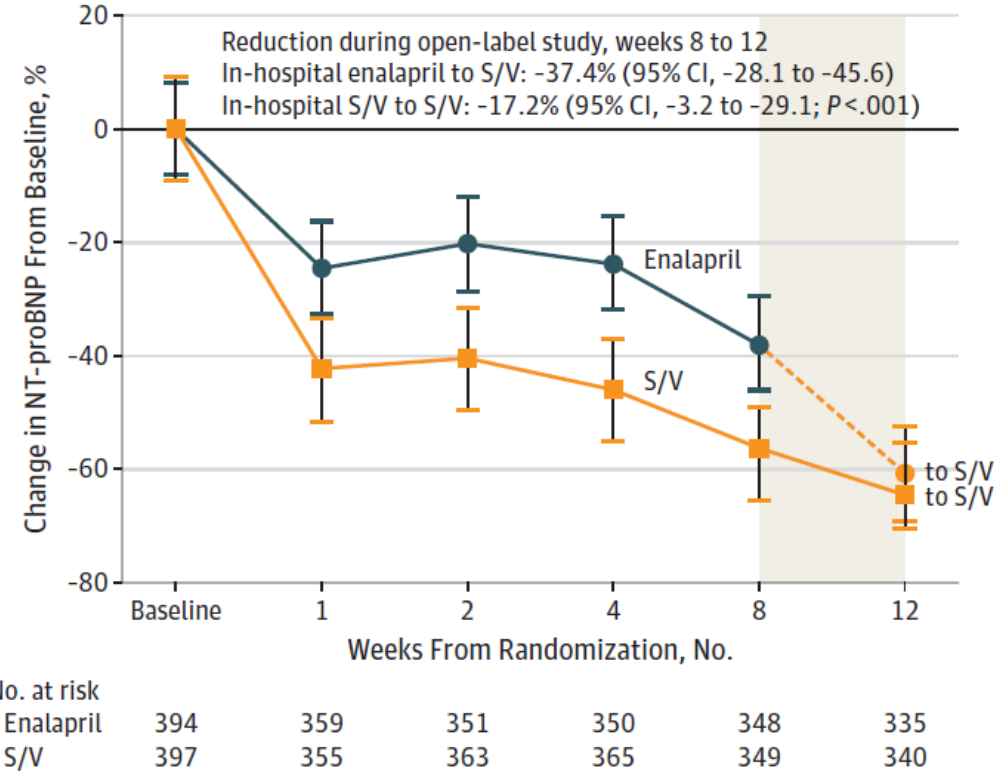
a) Titrate ramipril dose?

b) Stop ramipril x 36h, start sacubitril-valsartan?

c) Add ivabradine?

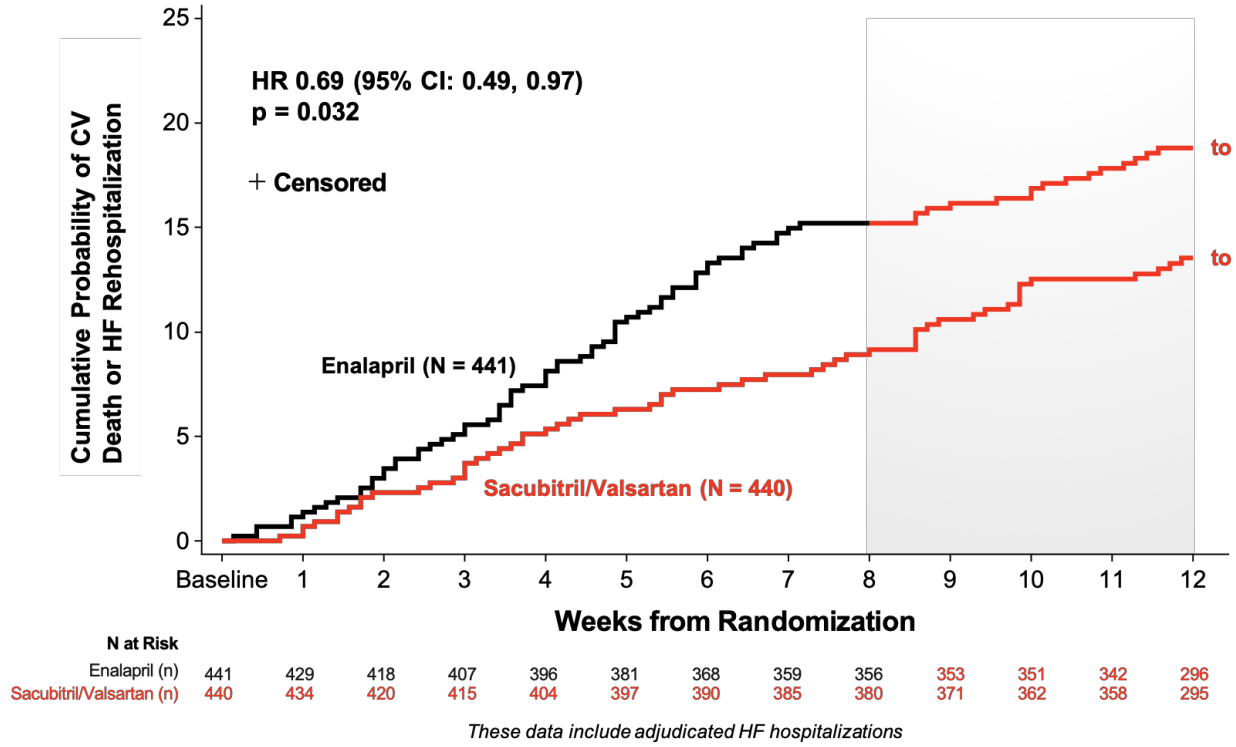
d) Refer for ICD?

PIONEER-HF Study and Analysis of Open Label Extension



No. at risk

Enalapril	394	359	351	350	348	335
S/V	397	355	363	365	349	340



N at Risk

Enalapril (n)	441	429	418	407	396	381	368	359	356	353	351	342	296
Sacubitril/Valsartan (n)	440	434	420	415	404	397	390	385	380	371	362	358	295

These data include adjudicated HF hospitalizations

880 patients, hospitalized for worsening HF randomized to enalapril vs sac-val once stabilized, 1/3 de novo HF

- Primary study: Sac-val initiation associated with greater reduction in NTproBNP
- Open label extension:
  - Further reduction in NTproBNP (both groups);
  - In-hospital sac-val group experienced lower incidence of death or re-hospitalization

Velazquez et al, N Engl J Med 2019
Devore et al, JAMA Cardiol 2020

Recommendations

- We recommend that an ARNI be used in place of an ACEI or ARB, in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses of GDMT to decrease CV death, HF hospitalizations, and symptoms

  (Strong Recommendation; High- Quality Evidence)

- We recommend that patients admitted to hospital for acute decompensated HF with HFrEF should be switched to an ARNI, from an ACEI or ARB, when stabilized and before hospital discharge

  (Strong Recommendation; Moderate-Quality Evidence)

- We suggest that patients admitted to hospital with a new diagnosis of HFrEF should be treated with ARNI as first-line therapy, as an alternative to either an ACEI or ARB

  (Weak Recommendation; Moderate-Quality Evidence)

Vignette #2

- 66 F, seen in HFC (virtual visit) following admission for newly diagnosed HFrEF
- PMHx: non-hodgkins lymphoma, completed R-CHOP therapy 2 months earlier
- LVEF 25%, moderate functional MR
- Normal coronaries
- Discharge meds:
  - Sacubitril-valsartan 50mg bid
  - Carvedilol 3.125mg bid
  - Spironolactone 25 mg/d
  - Furosemide 40mg/d

- NYHA III sx, occasional lightheadedness when standing
- No volume overload symptoms at present
- BP 102/65, HR 68 bpm, weight unchanged from discharge

- ***So now what?***

  a) Titrate sac-val dose?

  b) Titrate carvedilol?

  c) Add digoxin?

  d) Add SGLT2 inhibitor?

DAPA-HF and EMPEROR-Reduced

DAPA-HF

Outcome	Dapagliflozin	Placebo	
	Events/100 patient-yr	Events/100 patient-yr	HR (95%CI)
Primary outcome	11.6	15.6	0.74 (0.65-0.85)
HHF	6.9	9.8	0.70 (0.59-0.83)
CV death	6.5	7.9	0.82 (0.69-0.98)

EMPEROR-Reduced

Outcome	Empagliflozin	Placebo	
	Events/100 patient-yr	Events/100 patient-yr	HR (95%CI)
Primary outcome	15.8	21.0	0.75 (0.65-0.86)
HHF	10.7	15.5	0.69 (0.59-0.81)
CV death	7.6	8.1	0.92 (0.75-1.12)

- In these trials, dapagliflozin and empagliflozin, respectively, significantly reduced combined endpoint of CV death or HF hospitalization compared to placebo, with very few adverse events
- Differences in trials relate to baseline characteristics; EMPEROR Reduced patients with both higher risk and more aggressively treated with HF therapies
- Magnitude of benefit observed in both trials similar in patient WITH an WITHOUT diabetes

McMurray JJV, et al. N Engl J Med. 2019

Packer M, et al. N Engl J Med. 2020

Recommendation

- We recommend an SGLT2 inhibitor, such as dapagliflozin or empagliflozin, be used in patients with HFrEF, with or without concomitant type 2 diabetes, to improve symptoms and quality of life and to reduce the risk of HF hospitalization and/or CV mortality

  (Strong Recommendation; High-Quality Evidence).

Vignette #3

- 69 M, recurrent admissions with HF, discharged 2 weeks prior
- PMHx:
  - CABG x 3 2009
  - HTN
  - CKD (baseline creat 200-210)
  - ICD in situ

- Meds:
  - Ramipril 2.5 mg bid
  - Carvedilol 25 mg bid
  - Furosemide 120mg bid
  - metolazone 2.5 mg prn

- NYHA III
- BP 108/56, HR 60 bpm, mild leg edema
- ECG: sinus with RBBB, LAFB, anterior Qs
- BNP 550 pg/mL, creat 229, k 5.0

- ***So now what?***

a) Add low dose digoxin?

b) Add SGLT2 inhibitor?

c) Upgrade to CRT ?

d) Consider vericiguat?

VICTORIA Trial: Vericiguat, a soluble guanylate cyclase stimulator

"Chronic HF" ***after*** ***"Worsening event"***

- NYHA class II–IV
- **LVEF < 45%**
- Guideline based HF therapies

- Recent hospitalization or IV diuretic use
- With elevated natriuretic peptides

BNP ≥ 300 & pro-BNP ≥ 1000 pg/ml NSR
BNP ≥ 500 & pro-BNP ≥ 1600pg/ml AF

- 5050 high-risk patients randomized to vericiguat vs placebo
- Primary outcome: composite of CV death or first HF hospitalization
- Median f/u 10.8 months

Armstrong et al. JACC Heart Fail. 2018

VICTORIA: Primary and Secondary Outcomes

	Vericiguat (N=2526)		Placebo (N=2524)		Treatment Comparison	
	%	Events/ 100 Pt-Yrs	%	Events/ 100 Pt-Yrs	HR (95%)*	P-value†
PRIMARY COMPOSITE OUTCOME	35.5	**33.6**	38.5	**37.8**	0.90 (0.82–0.98)	**0.019**
HF hospitalization	27.4		29.6			
Cardiovascular death‡	8.2		8.9			
SECONDARY OUTCOMES						
Cardiovascular death	16.4	**12.9**	17.5	**13.9**	0.93 (0.81–1.06)	0.269
HF hospitalization	27.4	**25.9**	29.6	**29.1**	0.90 (0.81–1.00)	**0.048**
Total HF hospitalizations		**38.3**		**42.4**	0.91 (0.84–0.99)	**0.023**
Secondary composite outcome	37.9	**35.9**	40.9	**40.1**	0.90 (0.83–0.98)	**0.021**
HF hospitalization	27.4		29.6			
All-cause mortality‡	10.5		11.3			
All-cause mortality	20.3	**16.0**	21.2	**16.9**	0.95 (0.84–1.07)	0.377

Armstrong et al. N Engl J Med 2020

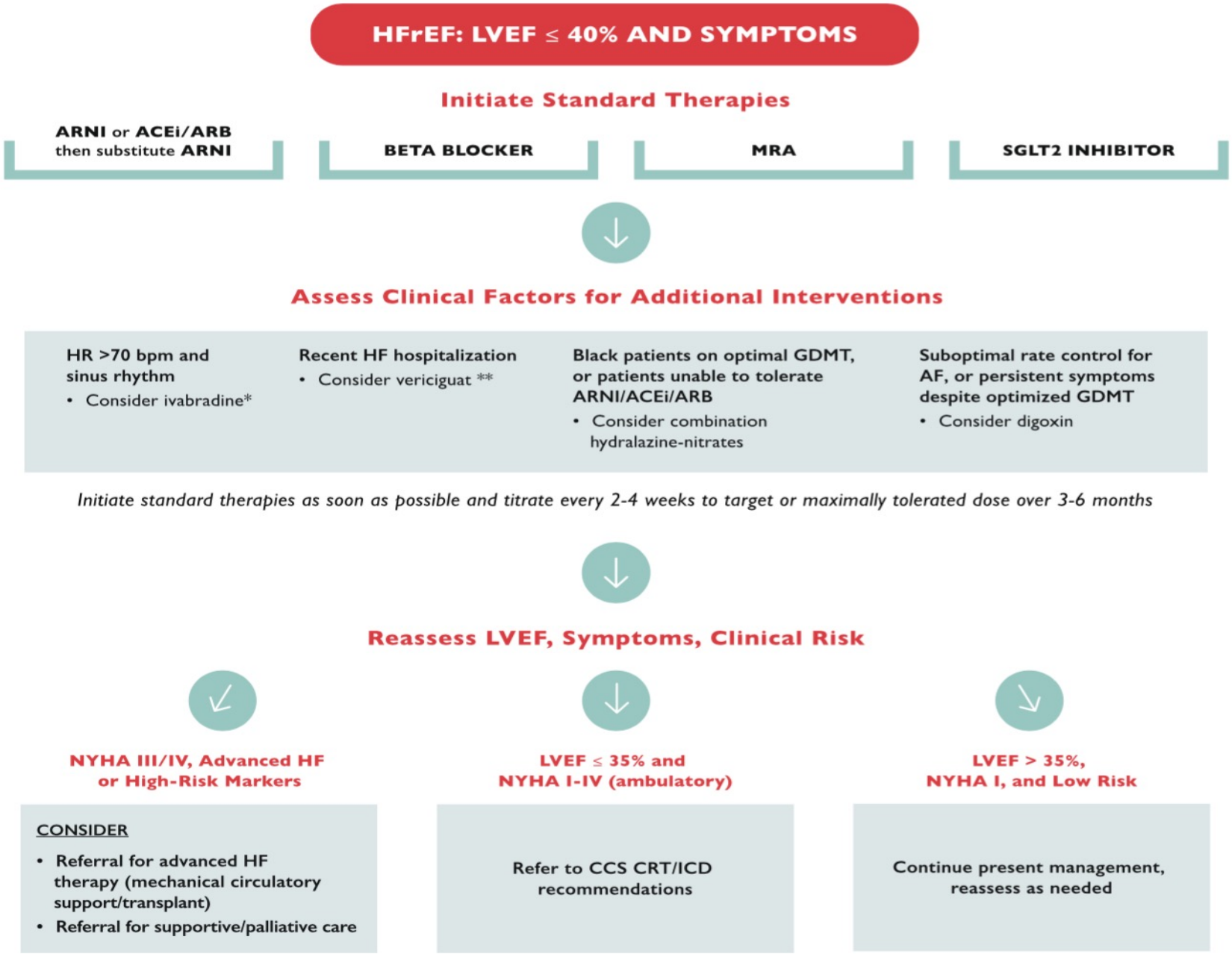
Recommendation

- We recommend that vericiguat, an oral sGC stimulator, be considered in addition to optimal HF therapies for HFrEF patients with worsening symptoms and heart failure hospitalization in the past 6 months, to reduce the risk of subsequent HF hospitalization

  (Conditional Recommendation; Moderate-Quality Evidence).

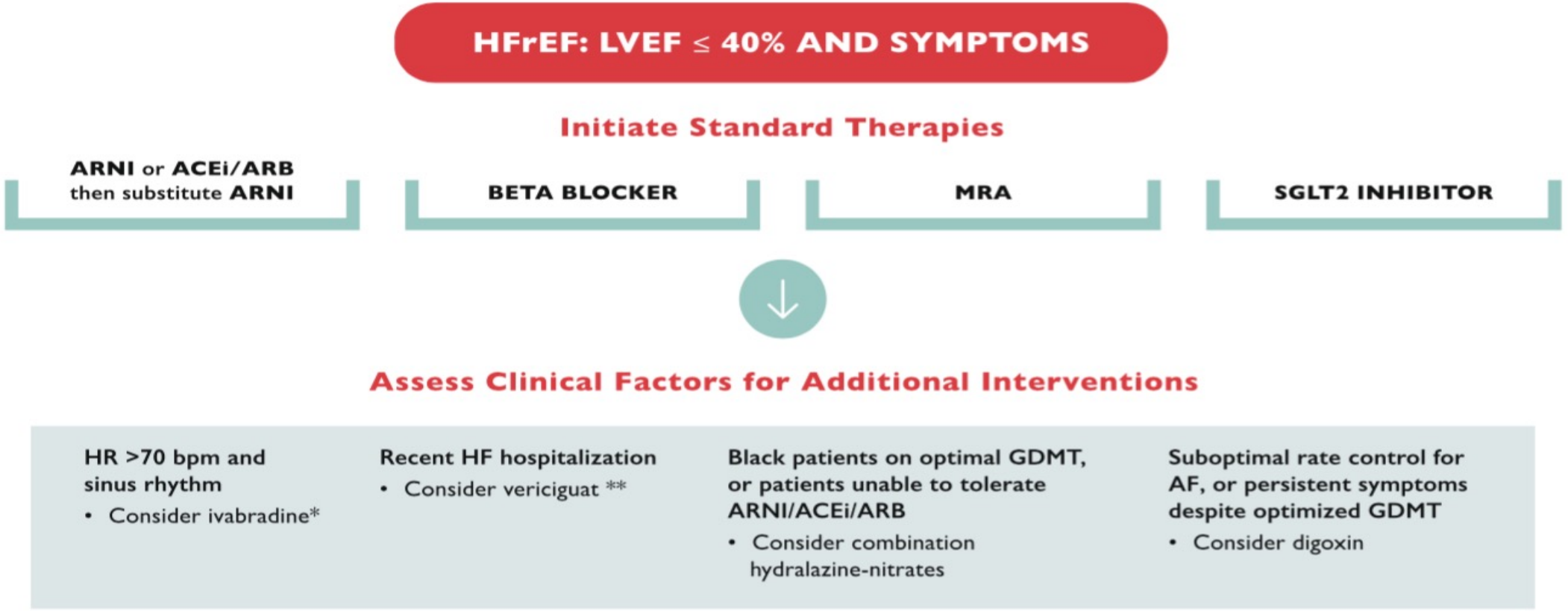
- This recommendation places value on the use of an additional medication to reduce the risk of hospitalization in a high-risk patient population despite the relatively modest relative benefits observed in the VICTORIA trial.

How best to prescribe?



Key points:

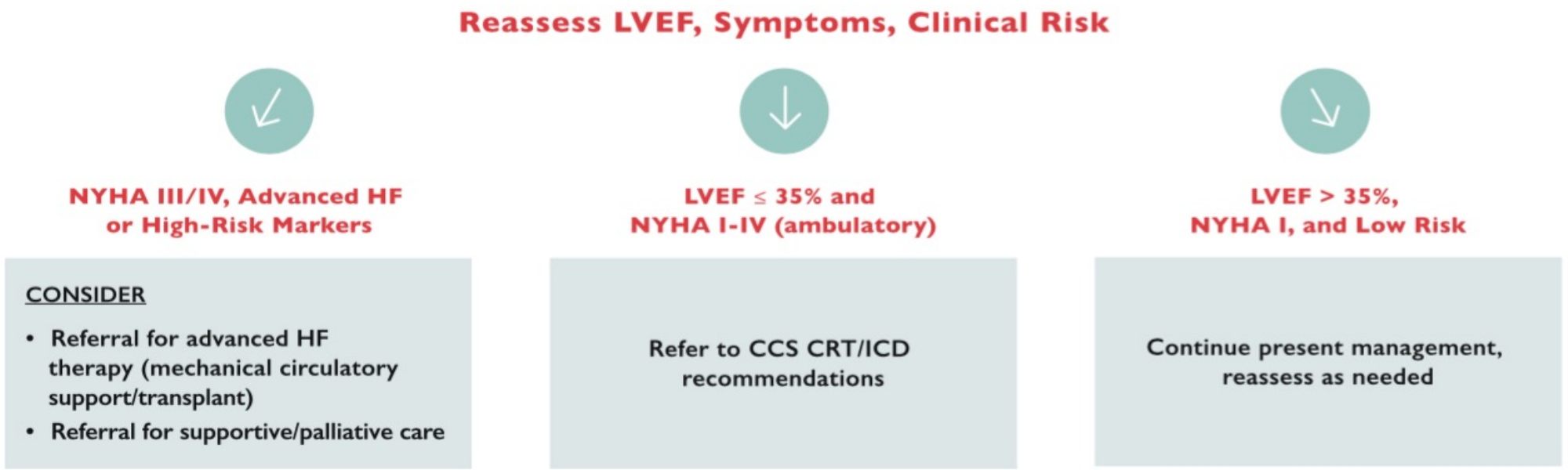
- 4 drugs should now be considered ‘foundational therapy’ in the absence of contraindications
- Reasonable to prescribe ARNI for de novo HFrEF patients if tolerability is anticipated
- Clinical factors should determine which order medications are prescribed/titrated
- These therapies apply to broad HFrEF population; non-specialists should be expected to prescribe



Key points:

- Additional clinical factors (or phenotypes) can determine what additional therapies should be considered on top of standard 4 drugs
- Every attempt should be made to titrate all indicated therapies 3-6 months following diagnosis
- These therapies apply to subgroups of HFrEF patients; specialist input may be helpful

After titration of medications



Recommendation:

We recommend that after a diagnosis of HFrEF, standard medical therapy should be initiated and titrated to target or maximally tolerated doses with a repeat assessment of LVEF before referral for ICD or CRT

(Strong Recommendation; Moderate-Quality Evidence)

Summary

- New clinical trial evidence has driven the need for HFrEF Guidelines Update
- 4 drugs should now be considered standard therapies for the majority of patients
  - ARNI/beta blocker/MRA/SGLT2 inhibitor
- Personalization of care allows for incorporation of new/additional therapies based on clinical factors
  - ivabradine, vericiguat, H-ISDN, digoxin
- Optimization is a challenge that should be tackled by both generalists and specialists