Treating HFrEf, what comes after the Big Four?

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Disclosures

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- **Consulting/speaker fees**: Novartis, Servier, Amgen, Merck, Astra, Boehringer Ingelheim

Objectives

- How to approach patients with persistent symptoms after foundational therapy has been optimized
- Evidence for medical therapy “after the big four”
- Recommendations from the 2021 heart failure guidelines: after foundational therapy

Vignette 1

- 72 F, admitted with acute on chronic HF without clear precipitant
  - Remote Anterior wall MI
  - Prior HF admission 2 months ago, compliant with meds and diet, no clear precipitant
  - LVEF 20% at baseline
  - Remote CRT-D
- PMHx
  - HTN
- Meds
  - Sacubitril-Valsartan 96-103mg PO BID
  - Spironolactone 25mg/d
  - Bisoprolol 10mg/d
  - Empagliflozin 10mg/d
  - Furosemide 40mg/d
  - Atorvastatin 80mg/d
  - ASA

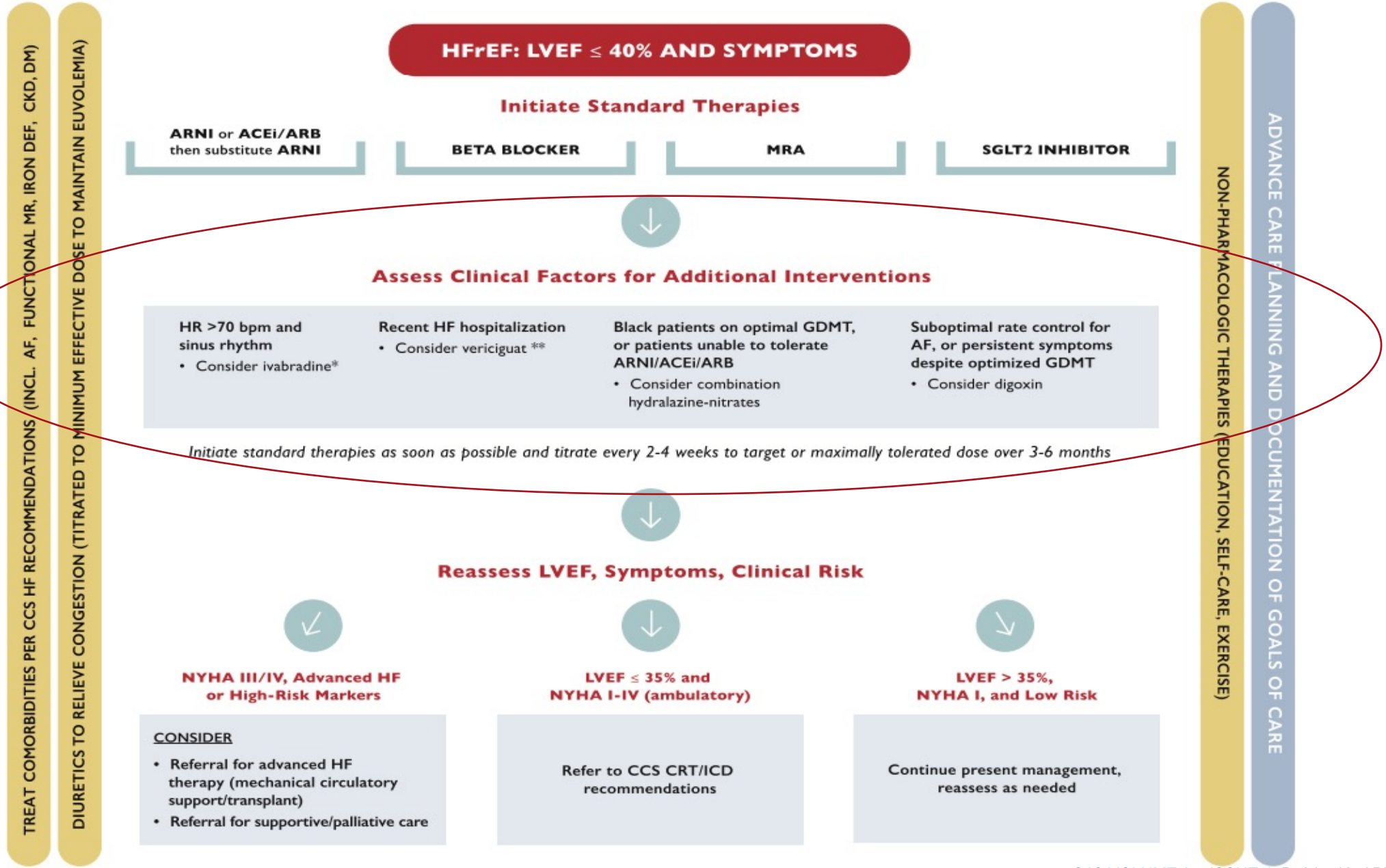
- BP 110/75, HR 62 bpm (2 days post-admission)
- JVP 10 cm, bibasilar crepitations at presentation, now chest is clear
- ECG: CRT paced 62bpm (98% pacing)
- Creat 128mmol/L, K 5.0 mmol/L

- Decongested with IV furosemide x 48h

- ***So now what?***

  a) DC home on same meds?

  b) Add a new medication?



CJC VOLUME 37, ISSUE 4, P531-546, APRIL 01, 2021

Personalizing therapy

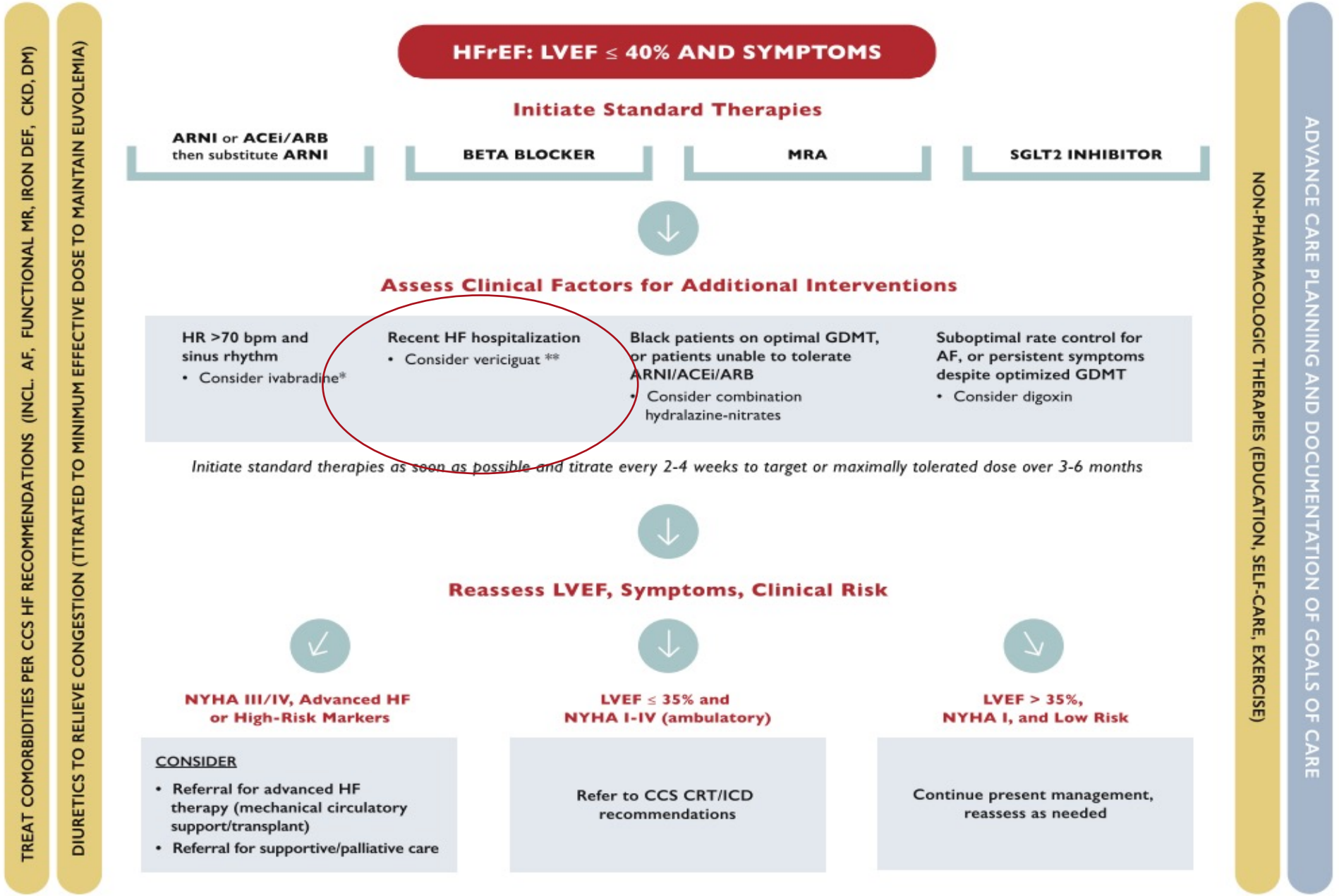
- Elevated HR in Sinus rhythm
- Recurrent hospitalizations
- Renal failure
- Black patient
- A fib
- Persistent symptoms on maximally tolerated GDMT

Evidence on therapy

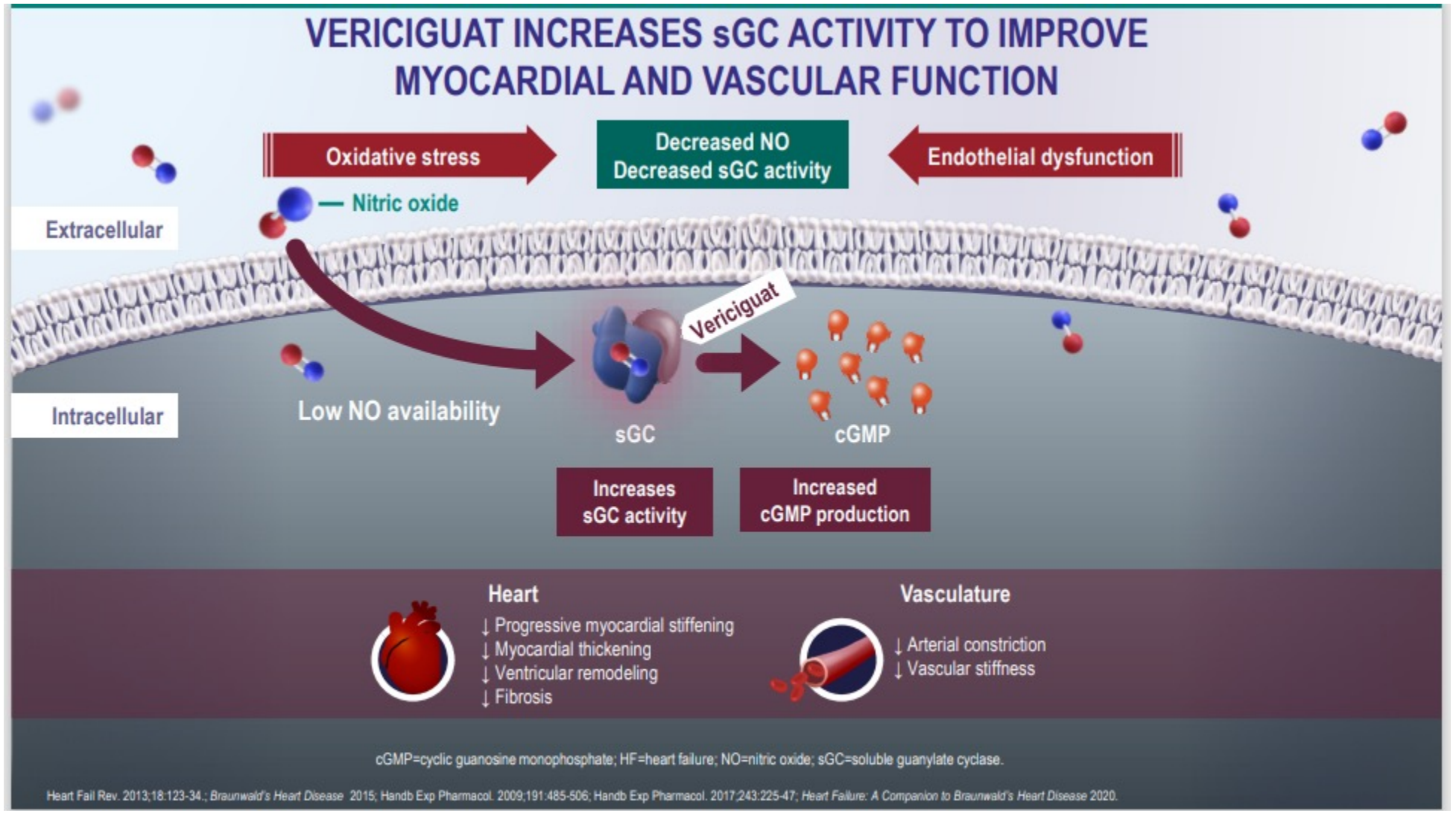
Table 1. Quality of available evidence to support the use of each HFrEF therapy according to clinical setting

	Quality of evidence supporting recommendation		
HFrEF drug therapy	Chronic ambulatory HF	New-onset HF	HF hospitalization*
Sacubitril-valsartan	High	Low	Moderate
ACEI/ARB	High	High	High†
β-blockers	High	High	High
MRAs	High	High	High†
SGLT2 inhibitors	High	N/A	N/A†
Ivabradine	High	N/A	N/A
Vericiguat	Moderate	N/A	NA
Digoxin	Moderate	Low	Low
H-ISDN	Moderate	Low	Low

CJC VOLUME 37, ISSUE 4, P531-546, APRIL 01, 2021


TREAT COMORBIDITIES PER CCS HF RECOMMENDATIONS (INCL. AF, FUNCTIONAL MR, IRON DEF, CKD, DM)
DIURETICS TO RELIEVE CONGESTION (TITRATED TO MINIMUM EFFECTIVE DOSE TO MAINTAIN EUVOLEMIA)
HFrEF: LVEF ≤ 40% AND SYMPTOMS
Initiate Standard Therapies
ARNI or ACEi/ARB then substitute ARNI
BETA BLOCKER
MRA
SGLT2 INHIBITOR
Assess Clinical Factors for Additional Interventions
HR >70 bpm and sinus rhythm
• Consider ivabradine*
Recent HF hospitalization
• Consider vericiguat **
Black patients on optimal GDMT, or patients unable to tolerate ARNI/ACEi/ARB
• Consider combination hydralazine-nitrates
Suboptimal rate control for AF, or persistent symptoms despite optimized GDMT
• Consider digoxin
Initiate standard therapies as soon as possible and titrate every 2-4 weeks to target or maximally tolerated dose over 3-6 months
Reassess LVEF, Symptoms, Clinical Risk
NYHA III/IV, Advanced HF or High-Risk Markers
CONSIDER
• Referral for advanced HF therapy (mechanical circulatory support/transplant)
• Referral for supportive/palliative care
LVEF ≤ 35% and NYHA I-IV (ambulatory)
Refer to CCS CRT/ICD recommendations
LVEF > 35%, NYHA I, and Low Risk
Continue present management, reassess as needed
NON-PHARMACOLOGIC THERAPIES (EDUCATION, SELF-CARE, EXERCISE)
ADVANCE CARE PLANNING AND DOCUMENTATION OF GOALS OF CARE

Vericiguat



Soluble guanalate cyclase stimulators (sGCs), such as vericiguat, directly enhance cyclic GMP production and also enhance endogenous sGC sensitivity to nitric oxide. This results in a cascade of adaptive effects on the heart, blood vessels and kidneys providing the physiological rationale for their use in patients with HF.

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 TRIAL OBJECTIVES

- To assess whether vericiguat reduces the primary composite outcome of cardiovascular (CV) death or first HF hospitalization
- Secondary outcomes were:
  - Components of the primary composite endpoint
  - Total HF hospitalizations; first and recurrent
  - Composite of all-cause mortality or first HF hospitalization
  - All-cause mortality
- To evaluate the safety and tolerability of vericiguat in this high-risk population with HF with reduced EF (HFrEF)

VICTORIA TRIAL BASELINE CHARACTERISTICS

Index event — no. (%)			
Hospitalization for heart failure in previous 3 mo	1673 (66.2)	1705 (67.6)	3378 (66.9)
Hospitalization for heart failure in previous 3–6 mo	454 (18.0)	417 (16.5)	871 (17.2)
Intravenous diuretic for heart failure (without hospitalization) in previous 3 mo	399 (15.8)	402 (15.9)	801 (15.9)
Mean body-mass index‡	27.7±5.8	27.9±6.1	27.8±5.9
Mean ejection fraction at screening — %	29.0±8.3	28.8±8.3	28.9±8.3
Ejection fraction <40% — no. (%)	2158 (85.8)	2158 (85.6)	4316 (85.7)
NYHA class — no./total no. (%)			
I	0	2/2523 (0.1)	2/5046 (<0.1)
II	1478/2523 (58.6)	1497/2523 (59.3)	2975/5046 (59.0)
III	1010/2523 (40.0)	993/2523 (39.4)	2003/5046 (39.7)
IV	35/2523 (1.4)	31/2523 (1.2)	66/5046 (1.3)
Mean time from initial diagnosis of heart failure with reduced ejection fraction to randomization — yr	4.7±5.5	4.8±5.4	4.8±5.4

NEJM 382;20 May 14, 2020

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

VICTORIA TRIAL ADVERSE EVENTS

Patients with Adverse Events of Clinical Interest

	Vericiguat		Placebo		Difference in % vs. Placebo	
	No.	(%)	No.	(%)	Estimate (95% CI)*	P-value
Patients in population	2519		2515			
Symptomatic hypotension	229	(9.1)	198	(7.9)	1.2 (-0.3 to 2.8)	0.121
Syncope	101	(4.0)	87	(3.5)	0.6 (-0.5 to 1.6)	0.303

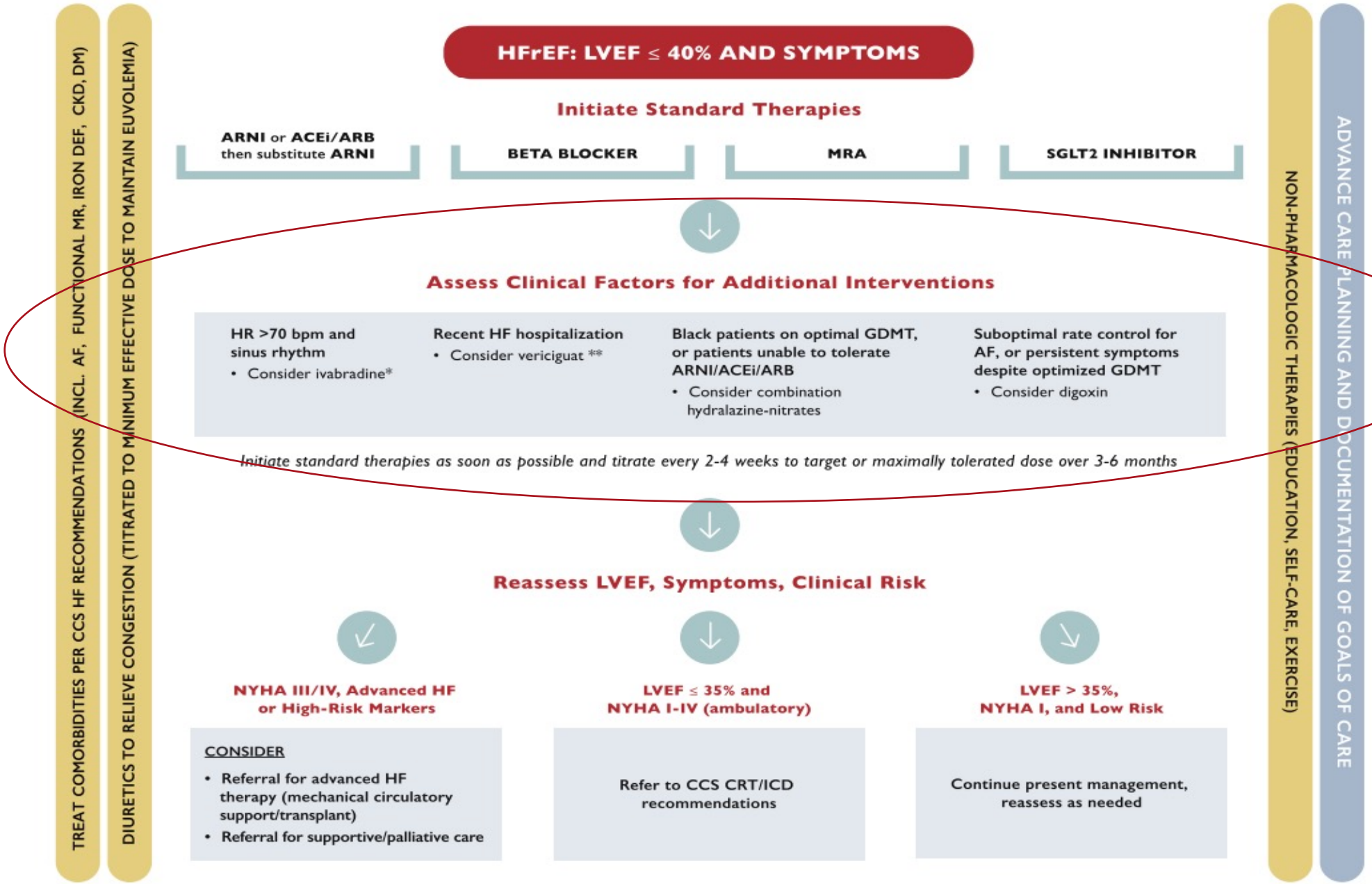
**Based on the Miettinen & Nurminen method.*
Note: Includes events/measurements from the day of first dose of study drug to 14 days after the last dose of study drug.
Based on data up to the primary analysis cutoff date (18Jun2019).
CI indicates confidence interval.

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.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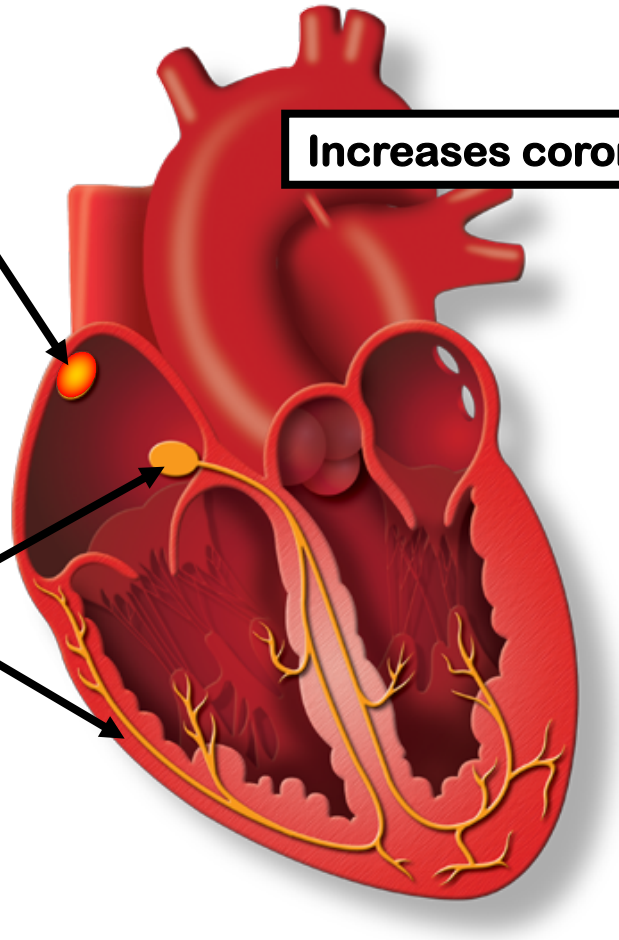
Ivabradine

Selective HR reduction



Increases coronary flow[2]

Improves myocardial O_2 supply

Decreases myocardial O_2 consumption without:

Effecting conduction

Effecting contractility

Increases stroke volume & preserves cardiac output

1. Monnet X, Ghaleh B, Colin P, et al. *Eur Heart J.* 2004 2. Simon L et al. *J Pharmacol Exp Ther*. 1995. 3. De Ferrari GM, Tavazzi L. et al. ESC 2006 (Abstract), 4. **Colin P et al.** ***Am J Physiol Heart Circ Physiol*****. 2002. Vilaine JP, Bidouard JP, Lesage L et al. J** ***Cardiovasc Pharmacol*****. 2003;42**

SHIFT Trial

- Randomized, double-blind, placebo-controlled trial in 6505 patients to test the hypothesis that heart rate slowing with the I_f inhibitor ivabradine improves cardiovascular outcomes in patients with:
  - Moderate to severe chronic heart failure (HF)
  - Hospitalization for worsening HF within the 12 months prior to randomization
  - Left ventricular ejection fraction ≤35%
  - Sinus rhythm and heart rate ≥70 bpm
  - Receiving guidelines-based background HF therapy

Lancet 376, 2010

SHIFT Trial

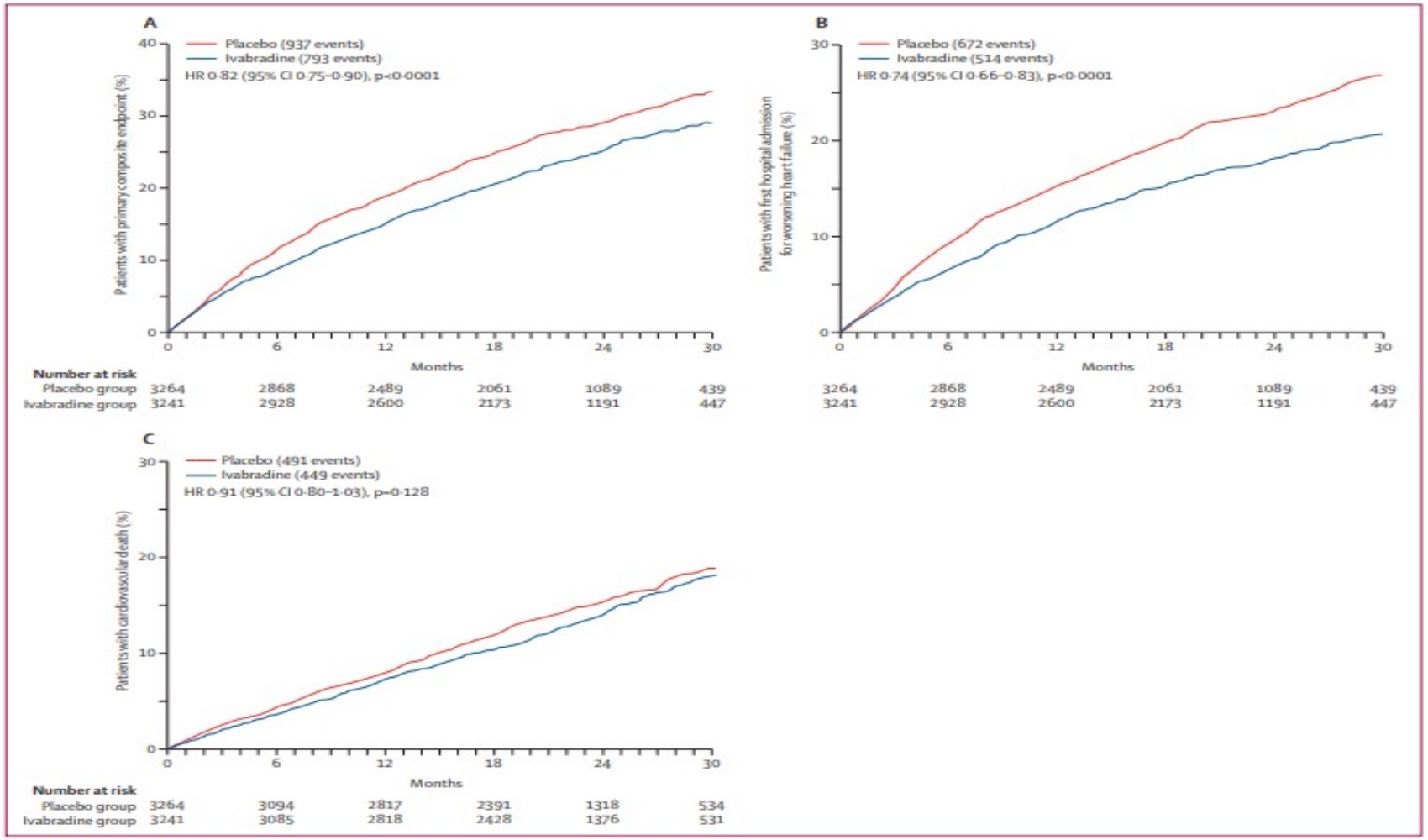


Figure 3: **Kaplan-Meier cumulative event curves for (A) the primary composite endpoint of cardiovascular death or hospital admission for worsening heart failure, (B) hospital admission for worsening heart failure, and (C) cardiovascular death**

Lancet 376, 2010

Ivabradine

- **Recommendation**s:
  - We recommend that ivabradine be used for patients with HFrEF and symptoms despite treatment with GDMT for the prevention of cardiovascular death and HF hospitalization
    - a resting heart rate > 70 beats per minute (bpm)
    - sinus rhythm, for the prevention of cardiovascular death and HF hospitalization

    - *(Strong Recommendation; High- Quality Evidence).*

- **Practical tips:**
  - Ivabradine has no direct effect on BP, myocardial contractility or renal function
  - Typical reductions in resting sinus HR following treatment with b-blockers range from 10-14 bpm

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 11, 2004 VOL. 351 NO. 20

Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure

Anne L. Taylor, M.D., Susan Ziesche, R.N., Clyde Yancy, M.D., Peter Carson, M.D., Ralph D'Agostino, Jr., Ph.D., Keith Ferdinand, M.D., Malcolm Taylor, M.D., Kirkwood Adams, M.D., Michael Sabolinski, M.D., Manuel Worcel, M.D., and Jay N. Cohn, M.D., for the African-American Heart Failure Trial Investigators*

A-HEFT TRIAL

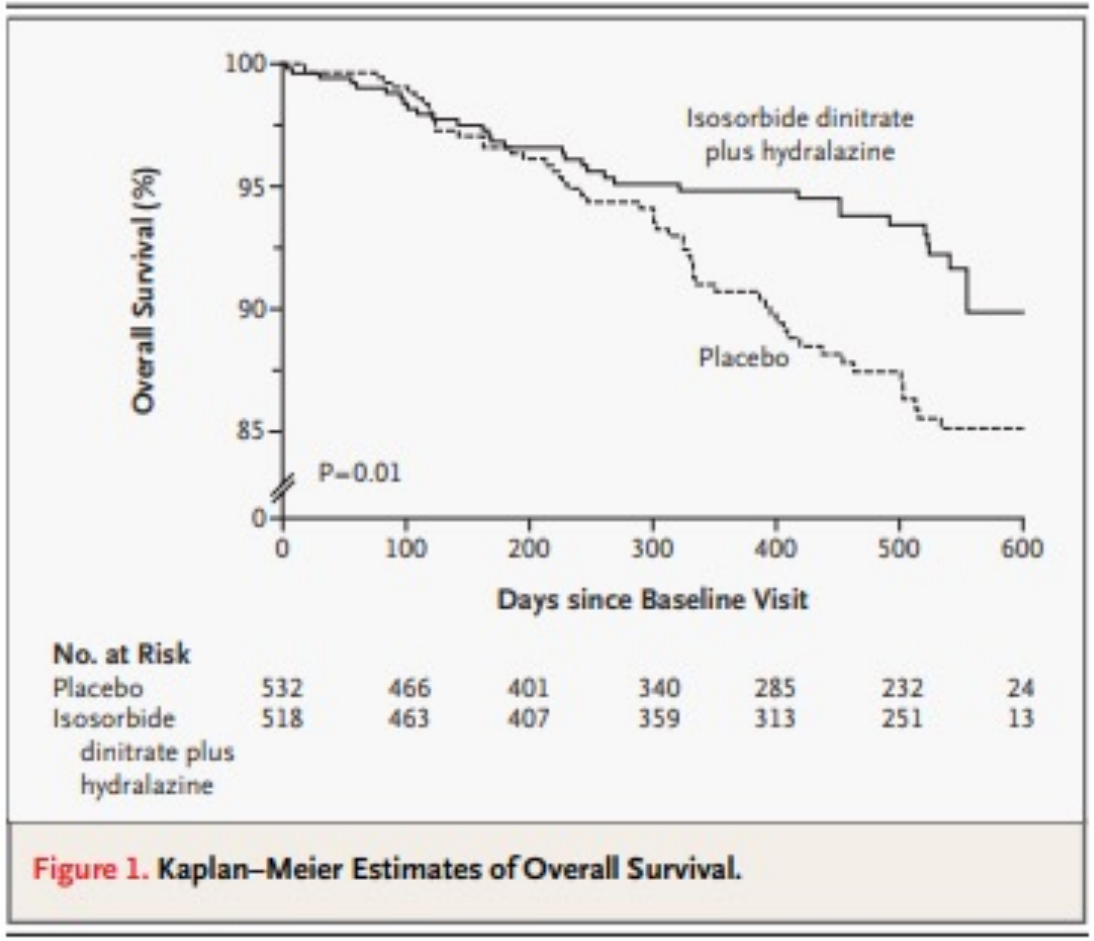


Figure 1. Kaplan–Meier Estimates of Overall Survival.

NEJM 351, 2004

Hydralazine-nitrate

- We recommend the combination of hydralazine and isosorbide dinitrate (H-ISDN) be considered in patients with HFrEF who are unable to tolerate an ACEi, ARB, or ARNI because of hyperkalemia, renal dysfunction or other contraindications, in the following settings:
  - *Chronic HF (Strong Recommendation, Moderate-Quality Evidence)*
  - *New onset HF (Weak Recommendation, Low-Quality Evidence)*
  - *HF hospitalization (Weak Recommendation, Low-Quality Evidence)*

- We recommend the combination of hydralazine and isosorbide dinitrate (H-ISDN) be considered in addition to standard GDMT at appropriate doses for black patients with HFrEF and advanced symptoms *(Strong Recommendation; Moderate-Quality Evidence).*
-

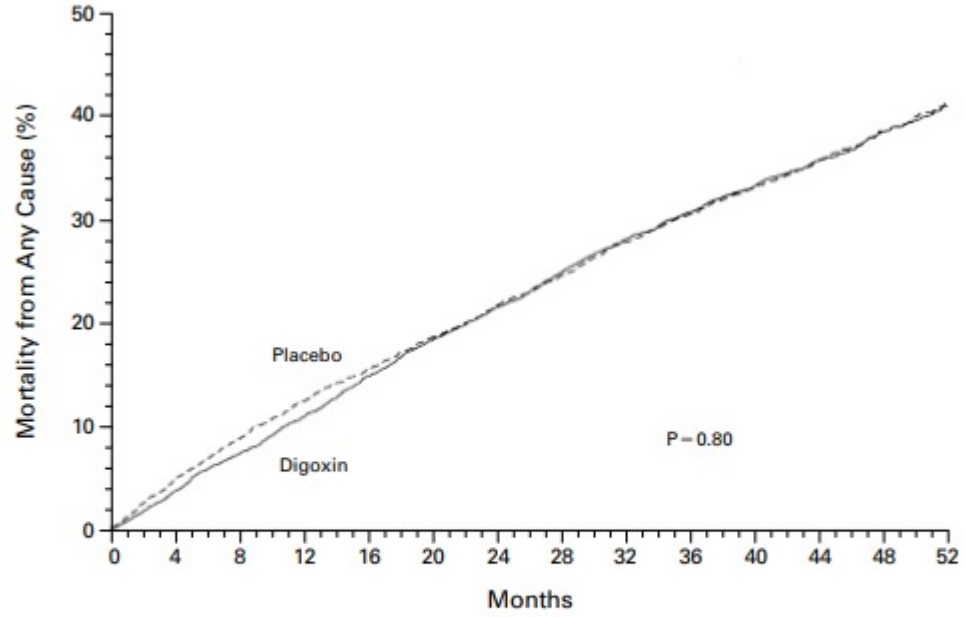
The New England
Journal of Medicine

VOLUME 336 FEBRUARY 20, 1997 NUMBER 8

THE EFFECT OF DIGOXIN ON MORTALITY AND MORBIDITY IN PATIENTS WITH HEART FAILURE

THE DIGITALIS INVESTIGATION GROUP*

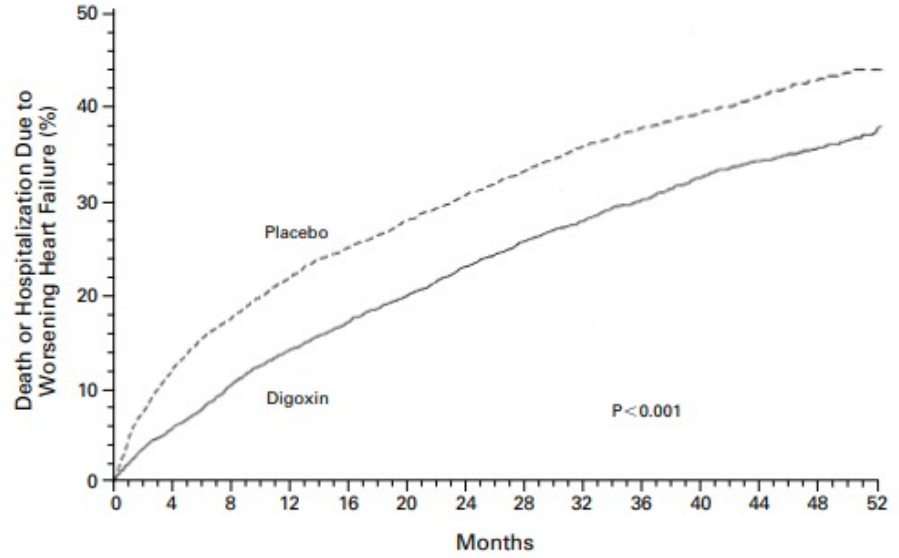
DIG-trial



No. of Patients at Risk

Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

Figure 1. Mortality in the Digoxin and Placebo Groups.
The number of patients at risk at each four-month interval is shown below the figure.



No. of Patients at Risk

Placebo	3403	2915	2674	2473	2328	2197	2071	1954	1659	1397	1111	859	546	250
Digoxin	3397	3120	2888	2696	2544	2392	2241	2115	1825	1521	1188	916	578	255

Figure 3. Incidence of Death or Hospitalization Due to Worsening Heart Failure in the Digoxin and Placebo Groups.
The number of patients at risk at each four-month interval is shown below the figure.

NEJM 336,8 1997

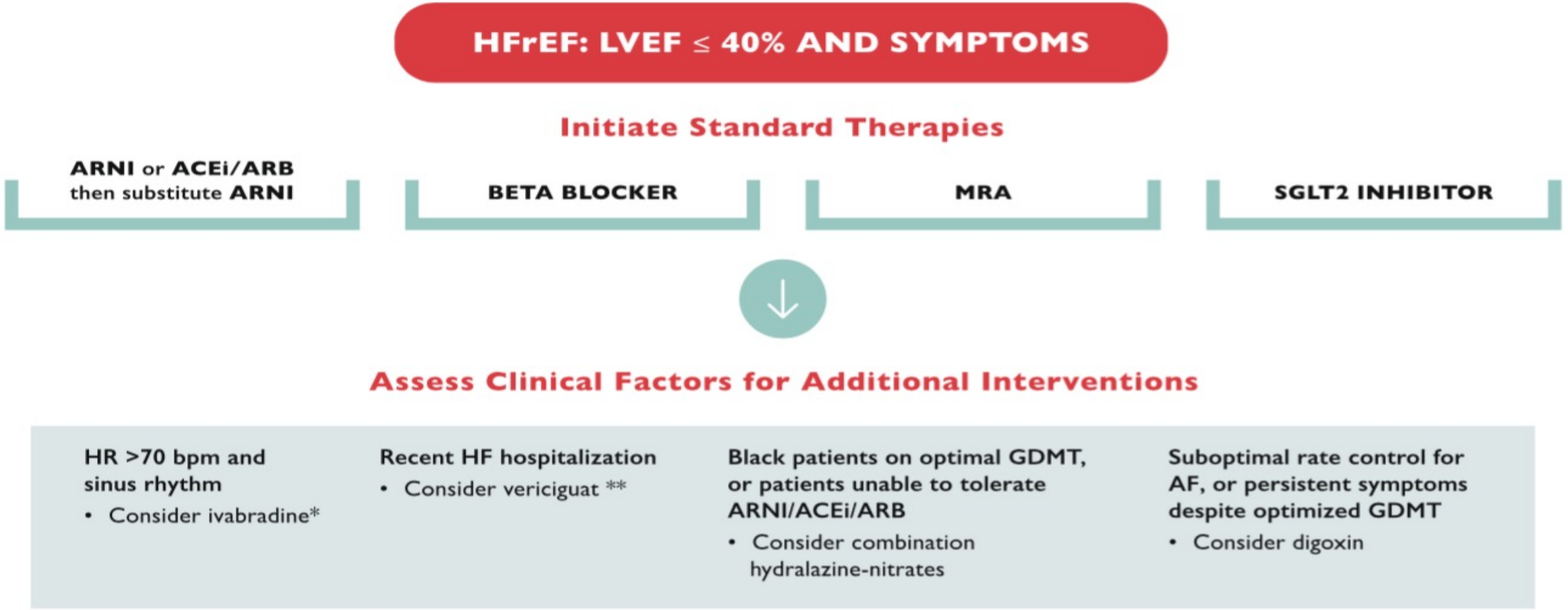
Digoxin

- We suggest digoxin be considered in patients with HFrEF and atrial fibrillation, with poor control of ventricular rate and/or persistent symptoms despite optimally tolerated β-blocker therapy *(Weak Recommendation; Low-Quality Evidence).*
- We suggest digoxin be considered in patients with HFrEF in sinus rhythm who continue to have moderate to severe symptoms despite GDMT to relieve symptoms and reduce hospitalizations *(Weak Recommendation; Moderate-Quality Evidence).*

- **Practical tip.** Serum concentrations of digoxin < 1.2 ng/mL are associated with less treatment-related morbidity.

- **Practical tip.** Digoxin can cause atrial and ventricular arrhythmias particularly in the presence of hypokalemia and/or worsening renal function and levels should be monitored accordingly.

Note: There is also a role for ablation in select patients with Afib

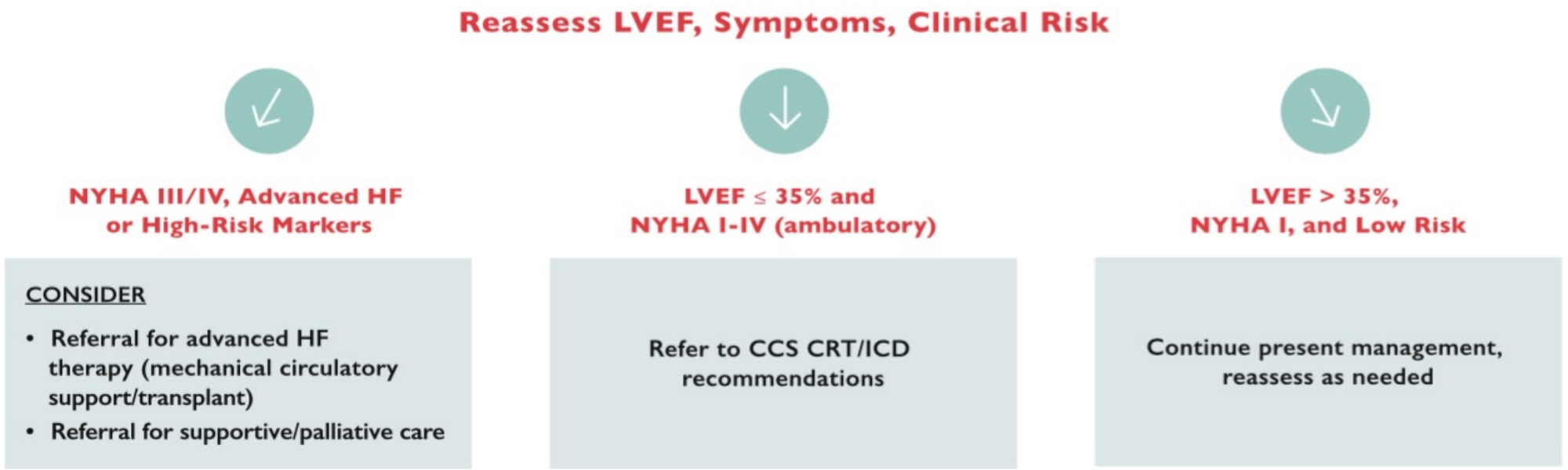


Key points:

- 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

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 for therapies

- **Values and preferences.** High value is placed on prescribing a combination of individual therapies that reduce CV mortality and HHF in well conducted randomized controlled trials.

- The complementary mechanisms of action of these agents in patients with HFrEF provides further rationale for a multidrug approach.

- The Committee acknowledges lack of evidence favouring one particular titration strategy for guideline-directed medical therapy (GDMT) over another.

Summary

- New clinical trial evidence has driven the need for HFrEF Guidelines Update
- After the foundational 4 therapies are optimized, further treatment options should be considered in patients who remain symptomatic
- Personalization of care allows for additional therapies based on clinical factors
  - ivabradine, vericiguat, H-ISDN, digoxin
- Reassessment of ejection fraction and should be done in all patients prior to device consideration

Take away slide

- In patients who remain symptomatic after optimization of foundational therapies, further medical therapy can be considered.
- This additional therapy, based on individual patient factors, includes ivabradine, vericiguat, hydralazine-nitrates and digoxin
- Medical therapy should be optimized in the first 3-6 months post-diagnosis of heart failure
- Reassessment of ejection fraction and should be done in all patients prior to device consideration