CCS/CHFS Heart Failure Guidelines –
Evidence to support innovation in practice

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Conflict of Interest Disclosures

- **Grants/research support**: Abbott, AstraZeneca, Boehringer Ingelheim, Medtronic, Novartis, Pfizer

- **Consulting and Speaker Fees**: Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS/Pfizer Alliance, Medtronic, Merck, Novartis, Pfizer, Servier

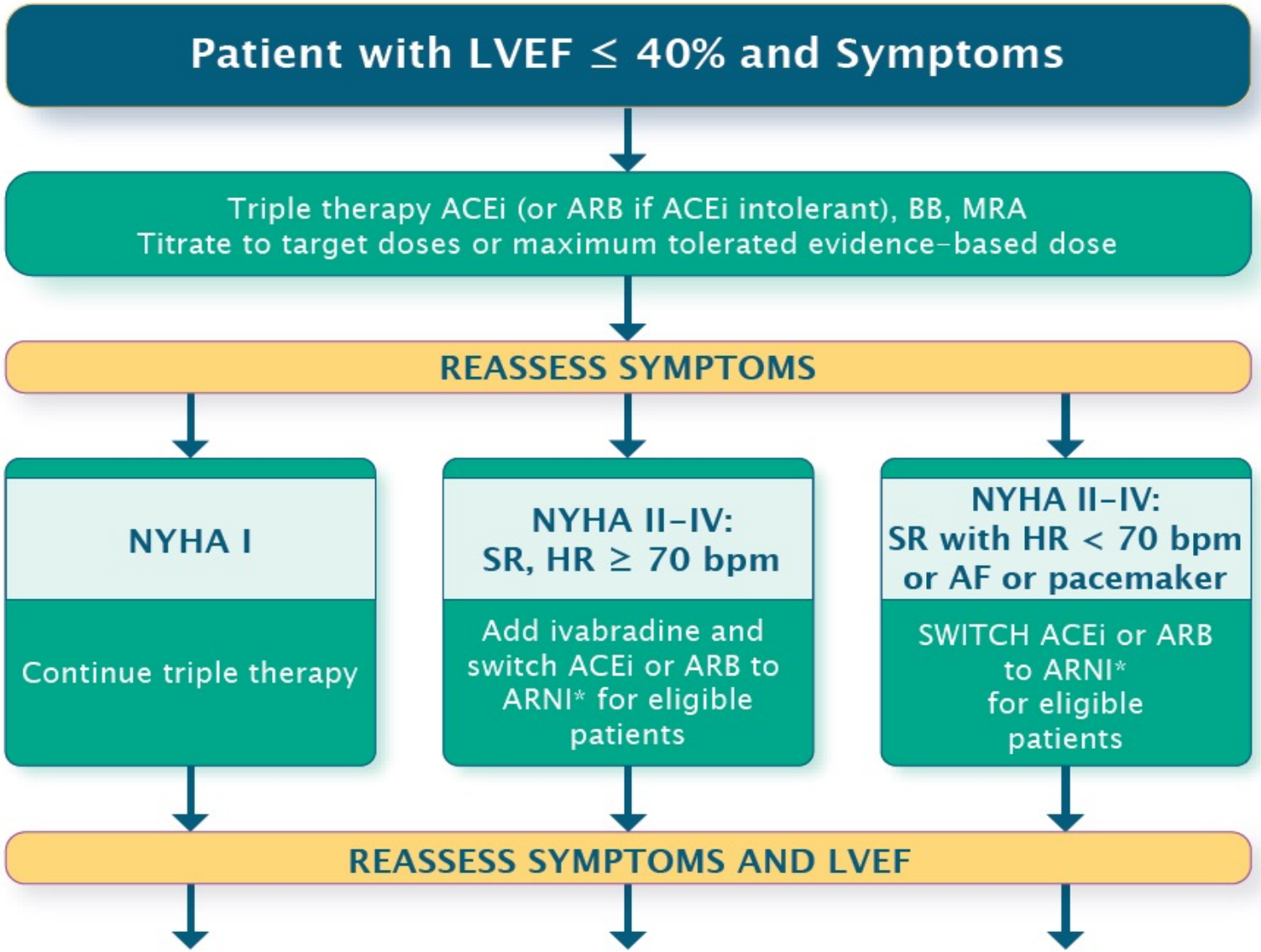
Canadian Cardiovascular Society

CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacological Standard of Care for Heart Failure with Reduced Ejection Fraction

Primary Panel: Michael McDonald (Co-chair), Sean Virani (Co-Chair), Eileen O'Meara, Michael Chan, Anique Ducharme, Justin A. Ezekowitz, Nadia Giannetti, Adam Grzeslo, George A. Heckman, Jonathan G. Howlett, Sheri L. Koshman, Serge Lepage, Lisa Mielniczuk, Gordon W. Moe, Elizabeth Swiggum, Mustafa Toma, Shelley Zieroth

Secondary Panel: Kim Anderson, Sharon A. Bray, Brian Clarke, Alain Cohen-Solal, Michel D'Astous, Margot Davis, Sabe De, Andrew D. M. Grant, Jodi Heshka, Sabina Keen, Simon Kouz, Douglas Lee, Frederick A. Masoudi, Robert McKelvie, Marie-Claude Parent, Stephanie Poon, Miroslaw Rajda, Abhinav Sharma, Kyla Siatecki, Kate Storm, Bruce Sussex, Harriette Van Spall, Amelia Ming Ching Yip

Therapeutic approach to patients with HFrEF (circa 2017)



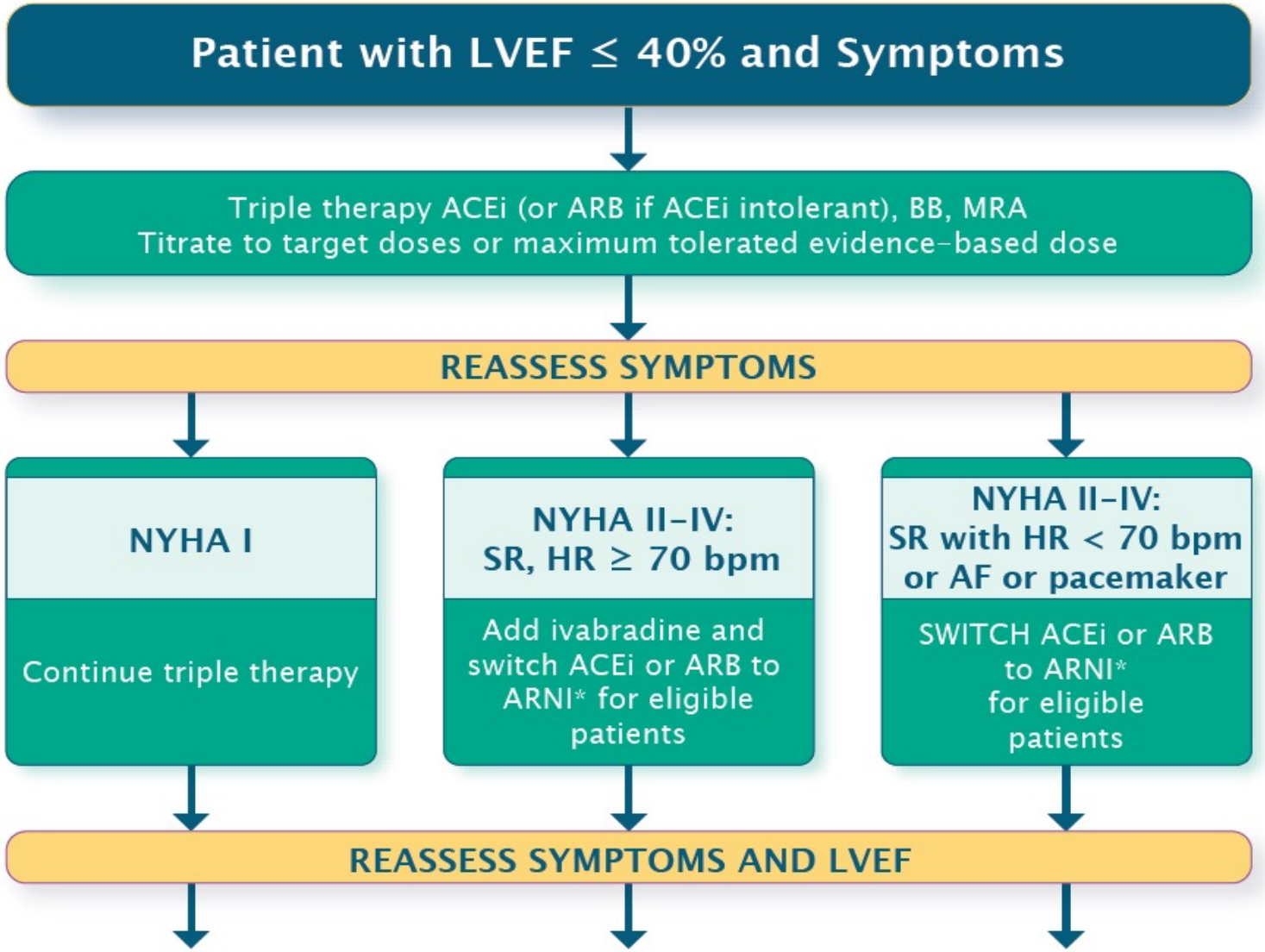
Ezekowitz et al, Can J Cardiol 2017

Some new evidence for decision making in HFrEF

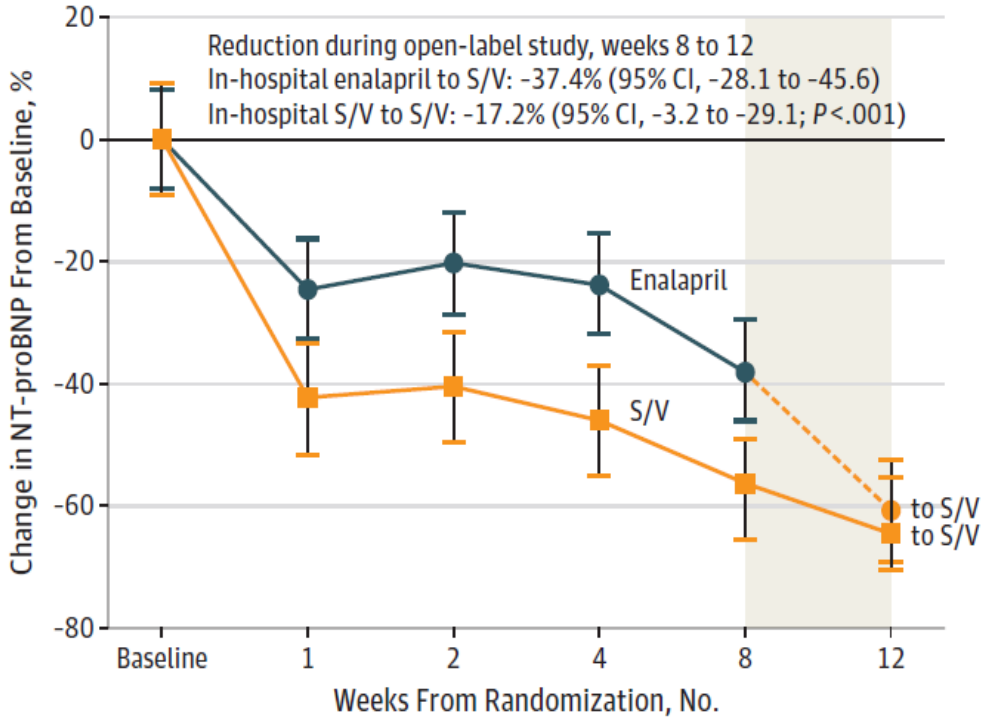
Study	Drug	Patients	Primary Outcome	Study Implications
PIONEER-HF (and extension study)	Sac-val vs Enalapril	Stabilized after admission with with worsening HF; 35% with de novo HF	Change in NT-proBNP values at 8 weeks	Broader use of ARNI in hospitalized and de novo HF patients
DAPA HF	Dapagliflozin vs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

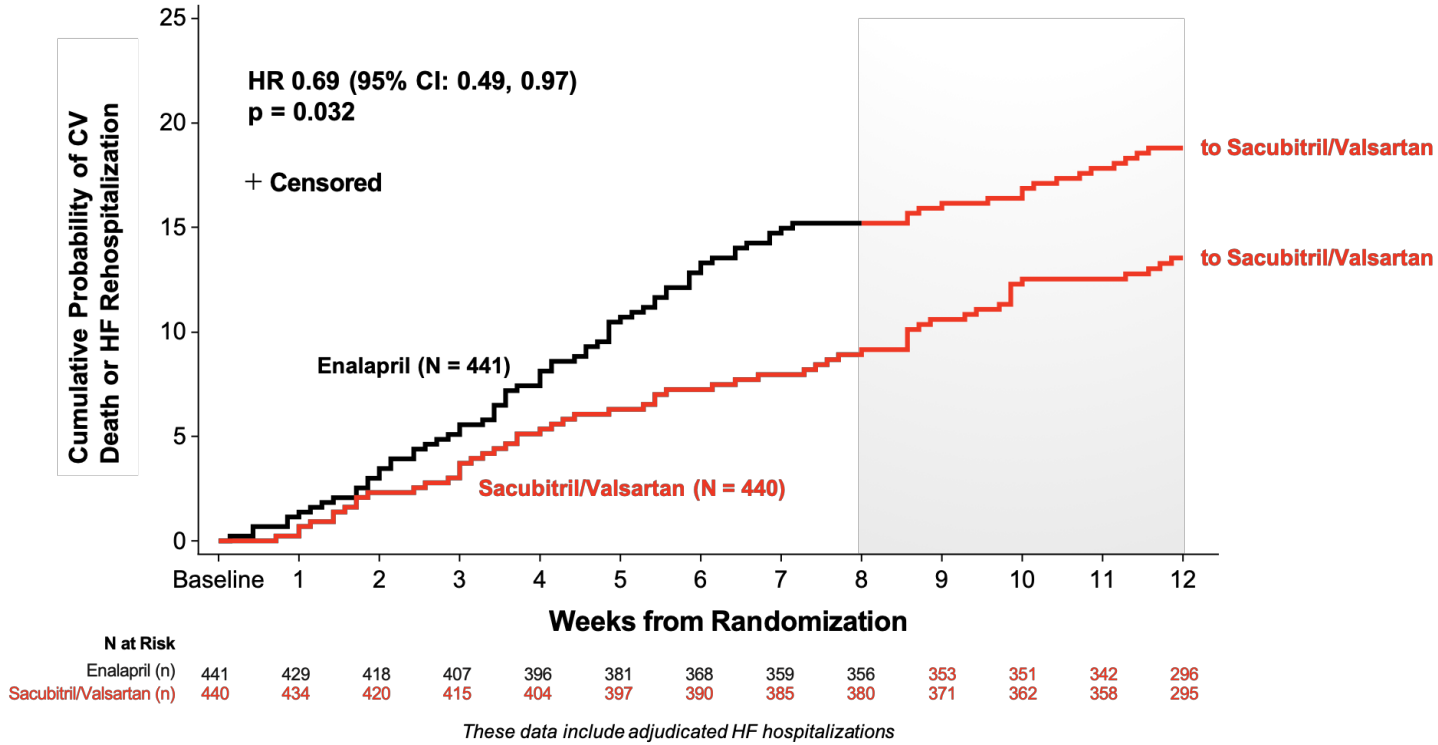


PIONEER-HF Study and Open label extension



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

- Open label extension:
  - Further reduction in NTproBNP (both groups)
  - In-hospital sac-val group experienced lower incidence of death or re-hospitalization over 12 weeks follow-up

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

Updated 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)

McDonald M, Virani S, et al. Can J Cardiol 2021

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

Updated Recommendation

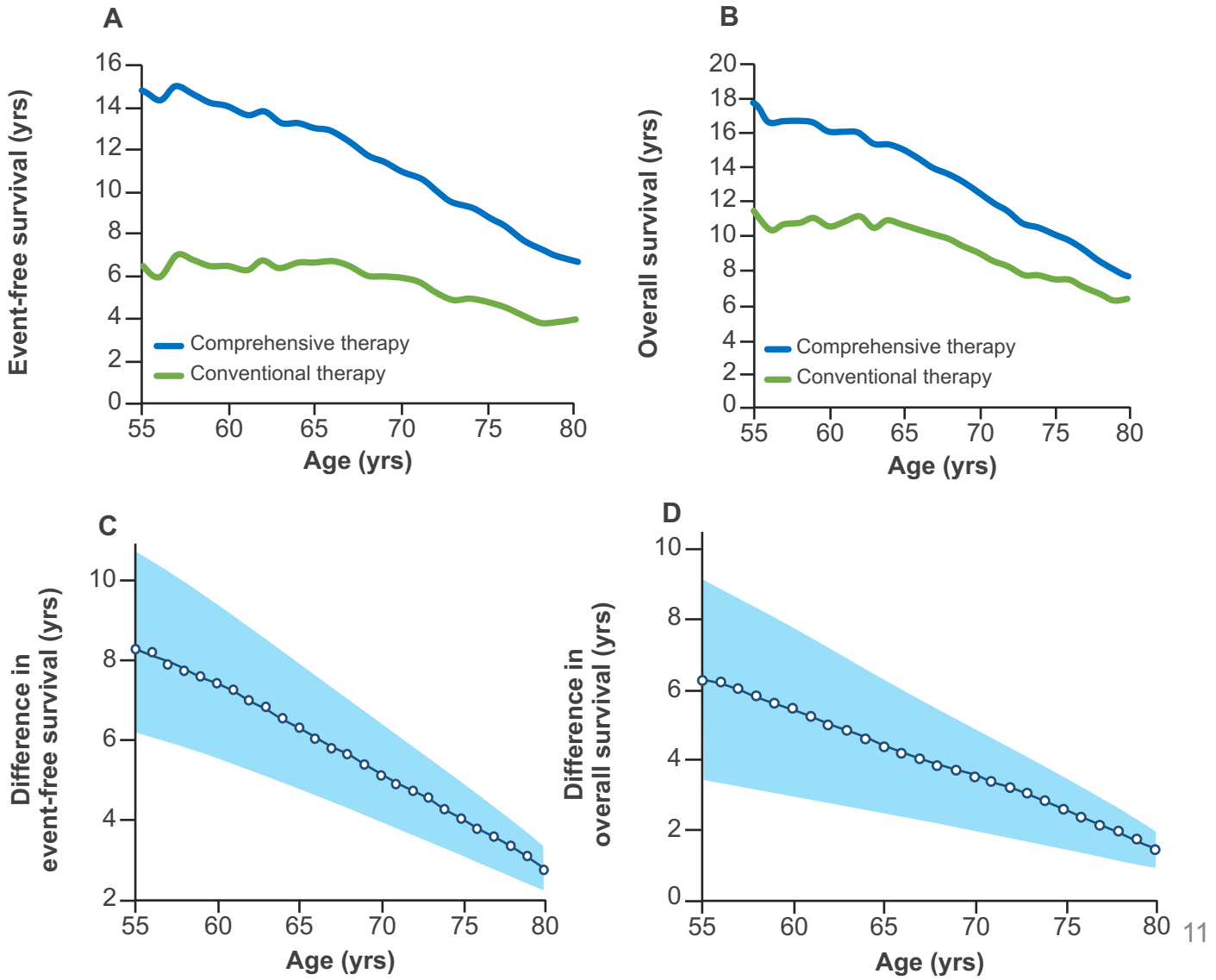
- We recommend an SGLT2 inhibitor, such as dapagliflozin or empagliflozin, be used in patients with HFrEF, with or without concomitant type 2 diabetes, to improve symptoms and quality of life and to reduce the risk of HF hospitalization and/or CV mortality

  (Strong Recommendation; High-Quality Evidence).

McDonald M, Virani S, et al. Can J Cardiol 2021

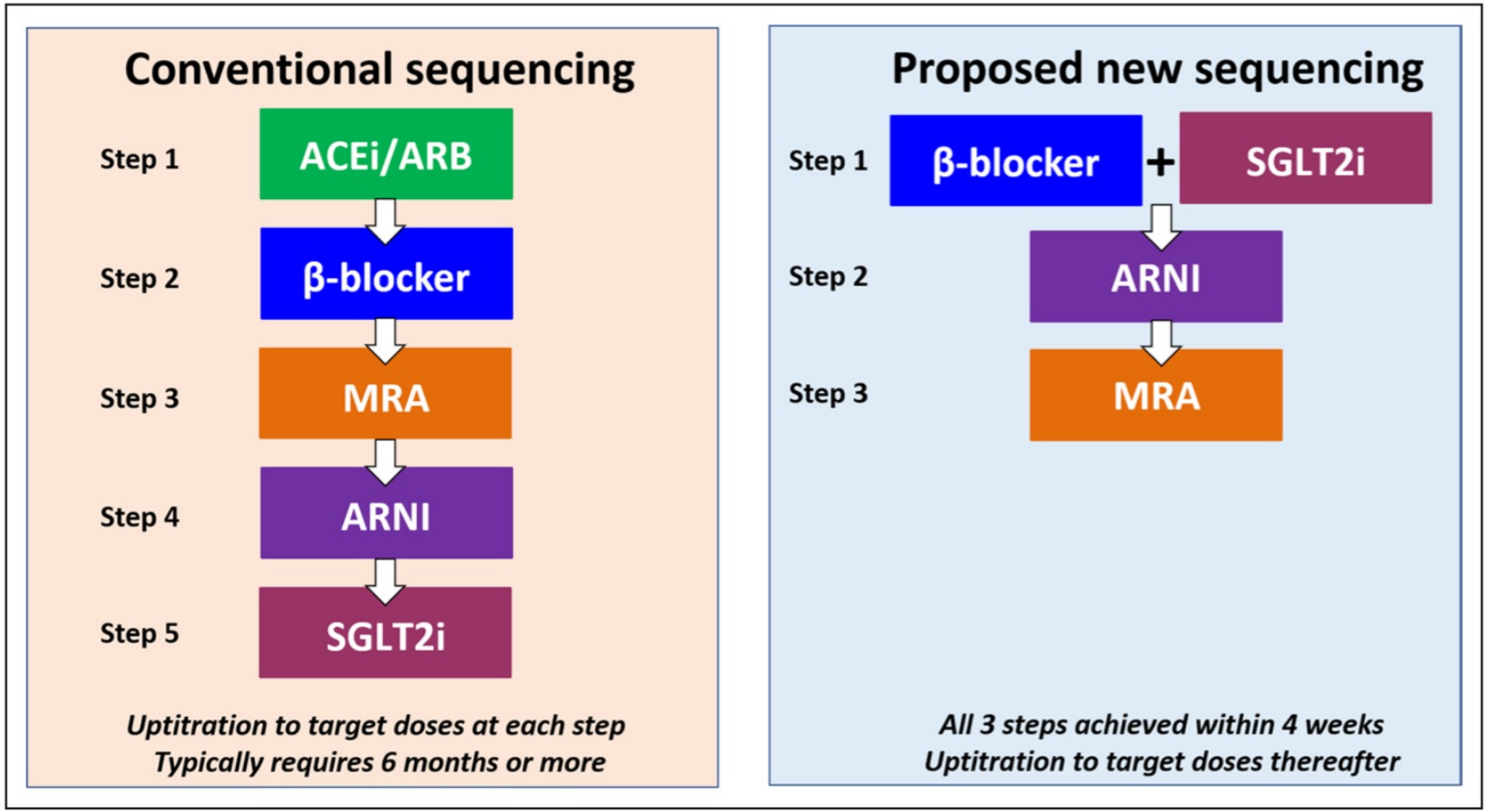
Why guideline therapy matters: Comprehensive treatment improves survival in HFrEF

- In HFrEF, treatment effects of comprehensive therapy (ARNI, beta-blocker, MRA, SGLT2i) was compared to conventional therapy (ACEI/ARB, beta-blocker) in cross trial analyses
- Significant improvement with comprehensive therapy observed in both overall survival and event-free survival across all age groups
- In a 55-year-old man, comprehensive therapy would improve event-free survival by 8.3 years and overall survival by 6.3 years



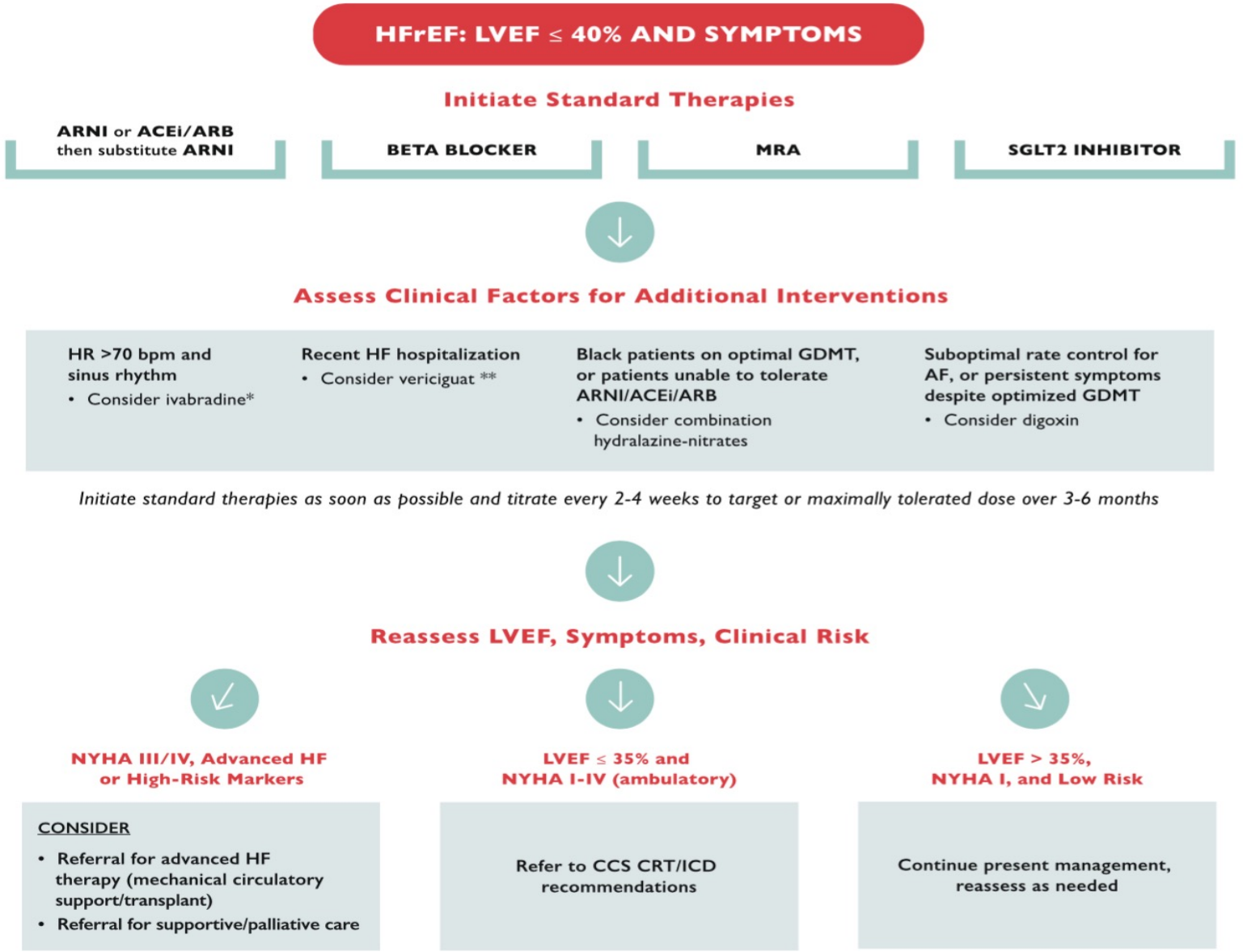
Vaduganathan M et al. Lancet 2020

What people are talking about: how best to prescribe ?



McMurray and Packer, Circulation 2021

The new CCS HFrEF Treatment Algorithm



Step 1

Step 2

Step 3

New Recommendation:

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:

a. ARNI (or ACEI/ARB);
b. beta-blocker;
c. MRA;
d. SGLT2 inhibitor

(Strong Recommendation; Moderate-Quality Evidence).

Case

- 65 year old male
  - NYHA II for past year
  - no hospitalizations
  - LVEF 40%
- Meds:
  - Sacubitril-valsartan 49/51mg bid
  - Bisoprolol 10 mg/d
  - Empagliflozin 10mg/d
  - Developed hyperkalemia with spironolactone
- At baseline HR 81 bpm, BP 112/80
- Euvolemic
- Baseline SCr 160 µmol/L, K^+ 5.2
- ECG shows NSR with QRS of 136ms

- Presents to ED after flu-like illness
- More SOBOE, weight up 3kg
- HR 108bpm, BP 108/78
- JVP elevated, moderate edema to shins
- BNP 799pg/mL, SCr 220 µmol/L
- Admitted for IV lasix
- Discharged after 8 days
  - Sac-val reduced to low dose
  - Furosemide 80mg daily added
  - Other meds unchanged
  - SCr 180 µmol/L at discharge, K^+ 4.9
  - Back to NYHA II

How can we further optimize in this setting?

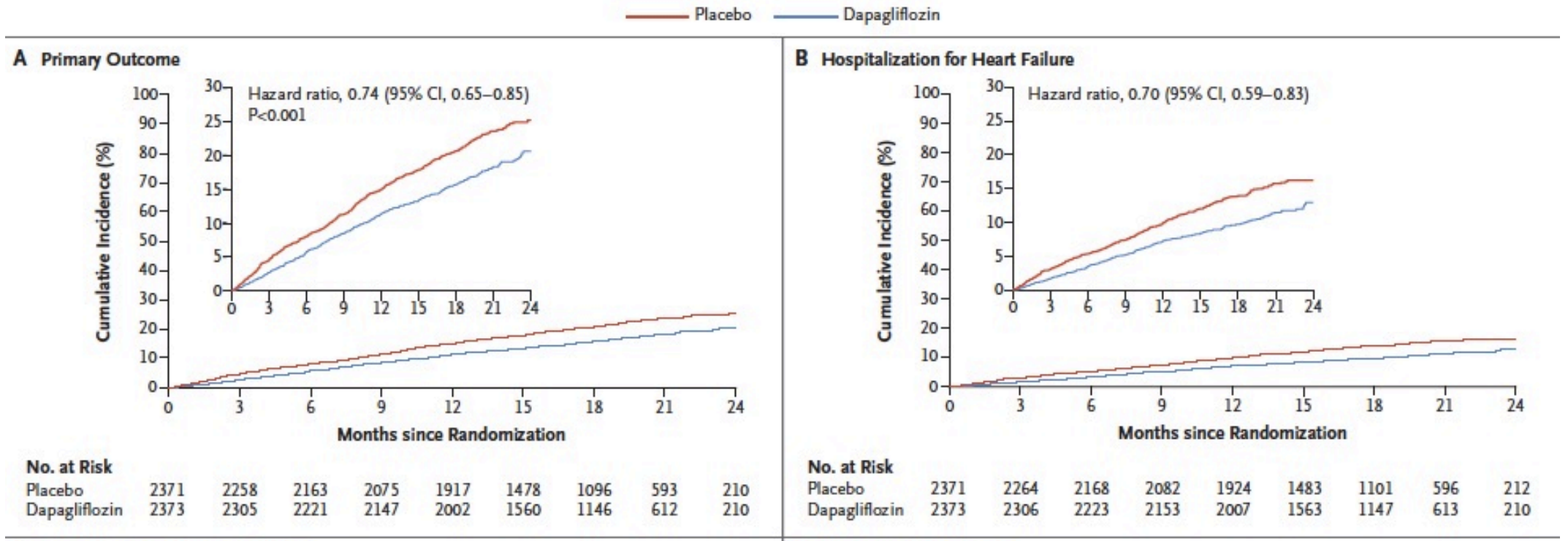
Optimizing Treatment Beyond “Foundational” Therapies

- Quadruple Therapy is an important first step in achieving GDMT, but where applicable additional therapies must be considered:
  - (1) There is a significant residual risk of adverse events even when quadruple therapy is utilized
  - (2) Not all patients will be able to achieve (or tolerate) all four therapies at target doses
- We must consider additional approaches and treatments to mitigate risk

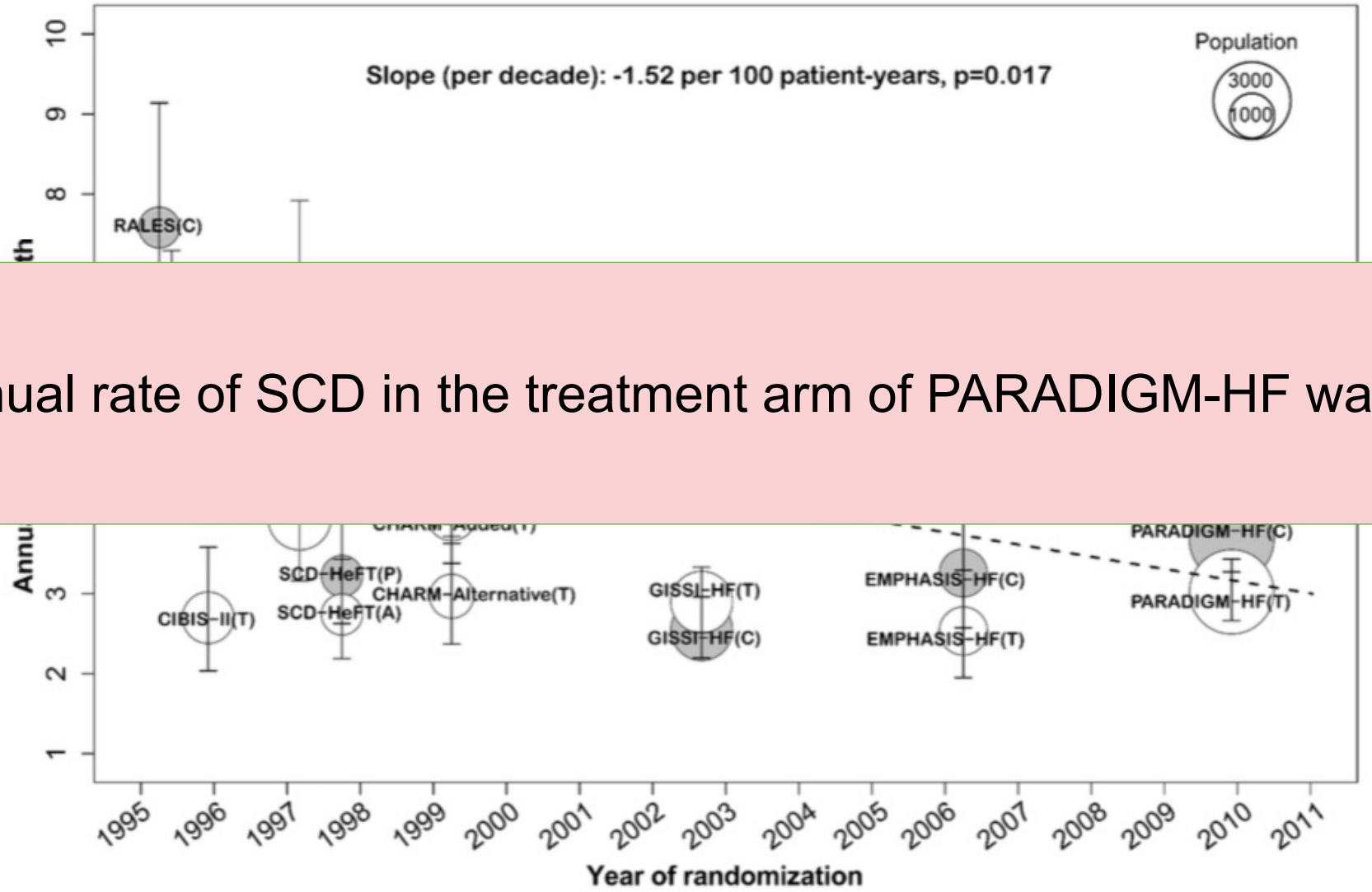
Baseline Medical and Device Therapies
SGLT2i Heart Failure Trials

	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin	Placebo	Dapagliflozin	Placebo
Heart failure medications				
ACE inhibitor	867 (46·5%)	836 (44·8%)	1332 (56·1%)	1329 (56·1%)
ARB	451 (24·2%)	457 (24·5%)	675 (28·4%)	632 (26·7%)
Mineralocorticoid receptor antagonist	1306 (70·1%)	1355 (72·6%)	1696 (71·5%)	1674 (70·6%)
ARNI	340 (18·3%)	387 (20·7%)	250 (10·5%)	258 (10·9%)
Device therapy				
ICD or CRT-D	578 (31·0%)	593 (31·8%)	622 (26·2%)	620 (26·1%)
CRT-D or CRT-P	220 (11·8%)	222 (11·9%)	190 (8·0%)	164 (6·9%)

Zannad F et al: Lancet Aug 30


Placebo
Dapagliflozin
A Primary Outcome
Hazard ratio, 0.74 (95% CI, 0.65–0.85)
P<0.001
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2258 2163 2075 1917 1478 1096 593 210
Dapagliflozin 2373 2305 2221 2147 2002 1560 1146 612 210
B Hospitalization for Heart Failure
Hazard ratio, 0.70 (95% CI, 0.59–0.83)
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2264 2168 2082 1924 1483 1101 596 212
Dapagliflozin 2373 2306 2223 2153 2007 1563 1147 613 210
C Death from Cardiovascular Causes
Hazard ratio, 0.82 (95% CI, 0.69–0.98)
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2330 2279 2230 2091 1636 1219 664 234
Dapagliflozin 2373 2339 2293 2248 2127 1664 1242 671 232
D Death from Any Cause
Hazard ratio, 0.83 (95% CI, 0.71–0.97)
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2330 2279 2231 2092 1638 1221 665 235
Dapagliflozin 2373 2342 2296 2251 2130 1666 1243 672 233

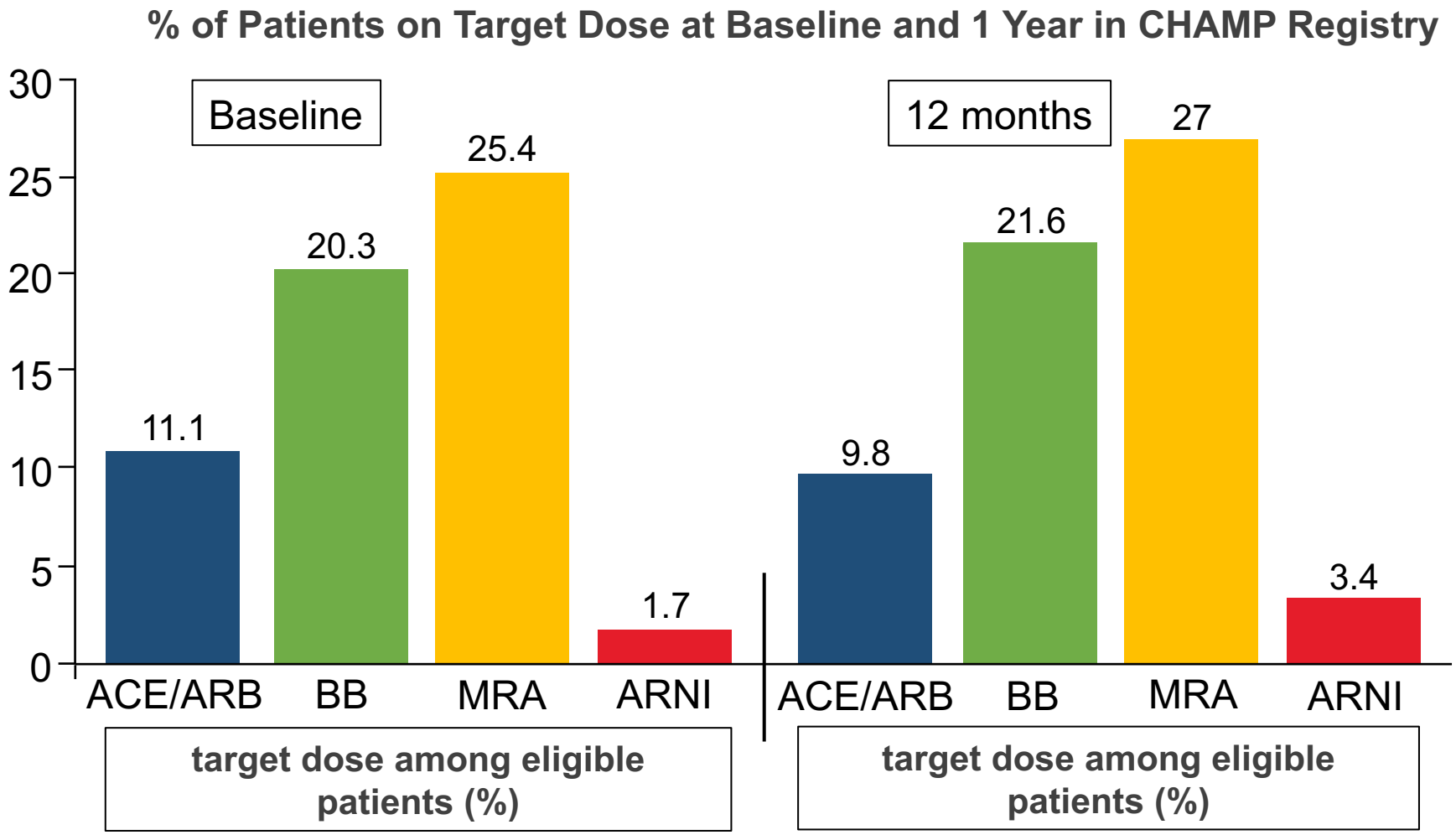
Sudden Cardiac Death in HF Trials



The annual rate of SCD in the treatment arm of PARADIGM-HF was 3.0%

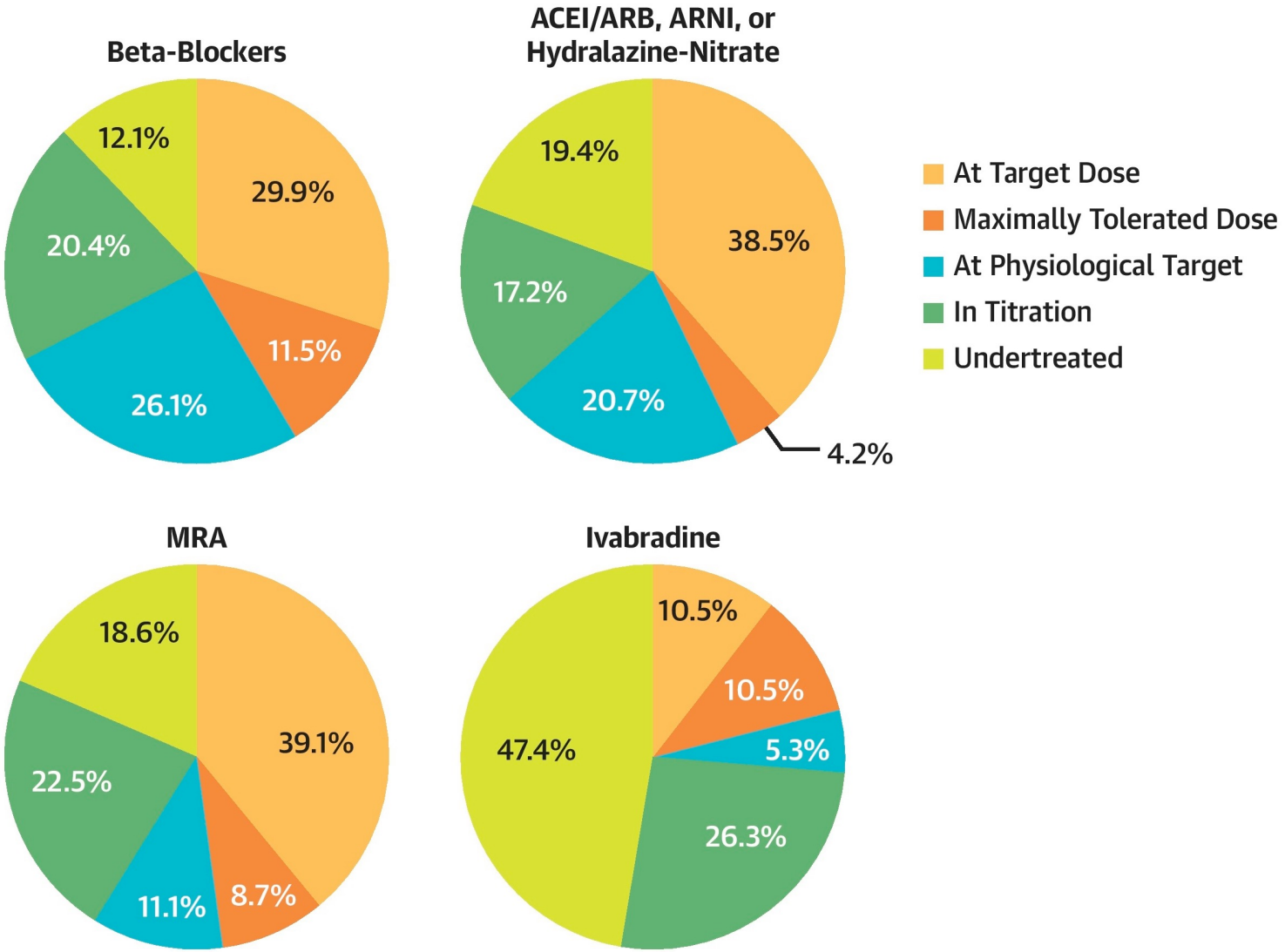
Shen et al. N Engl J Med 2017;377:41-50

Therapeutic inertia:
Missed opportunity to optimize medical therapy



Bozkurt B. J Am Coll Cardiol 2019.

Achieving GDMT in Canadian Ambulatory HF Patients



Jarjour et al. JACC HF 2020 Sep 8 (9) 725-38.

Is this patient a candidate for Individualized Therapies?

- 65 year old male
  - NYHA II for past year
  - no hospitalizations
  - LVEF 40%

- Meds:
  - Sacubitril-valsartan 49/51mg bid
  - Bisoprolol 10 mg/d
  - Empagliflozin 10mg/d
  - Developed hyperkalemia with spironolactone

- At baseline HR 81 bpm, BP 112/80
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- Presents to ED after flu-like illness
- More SOBOE, weight up 3kg
- HR 108bpm, BP 108/78
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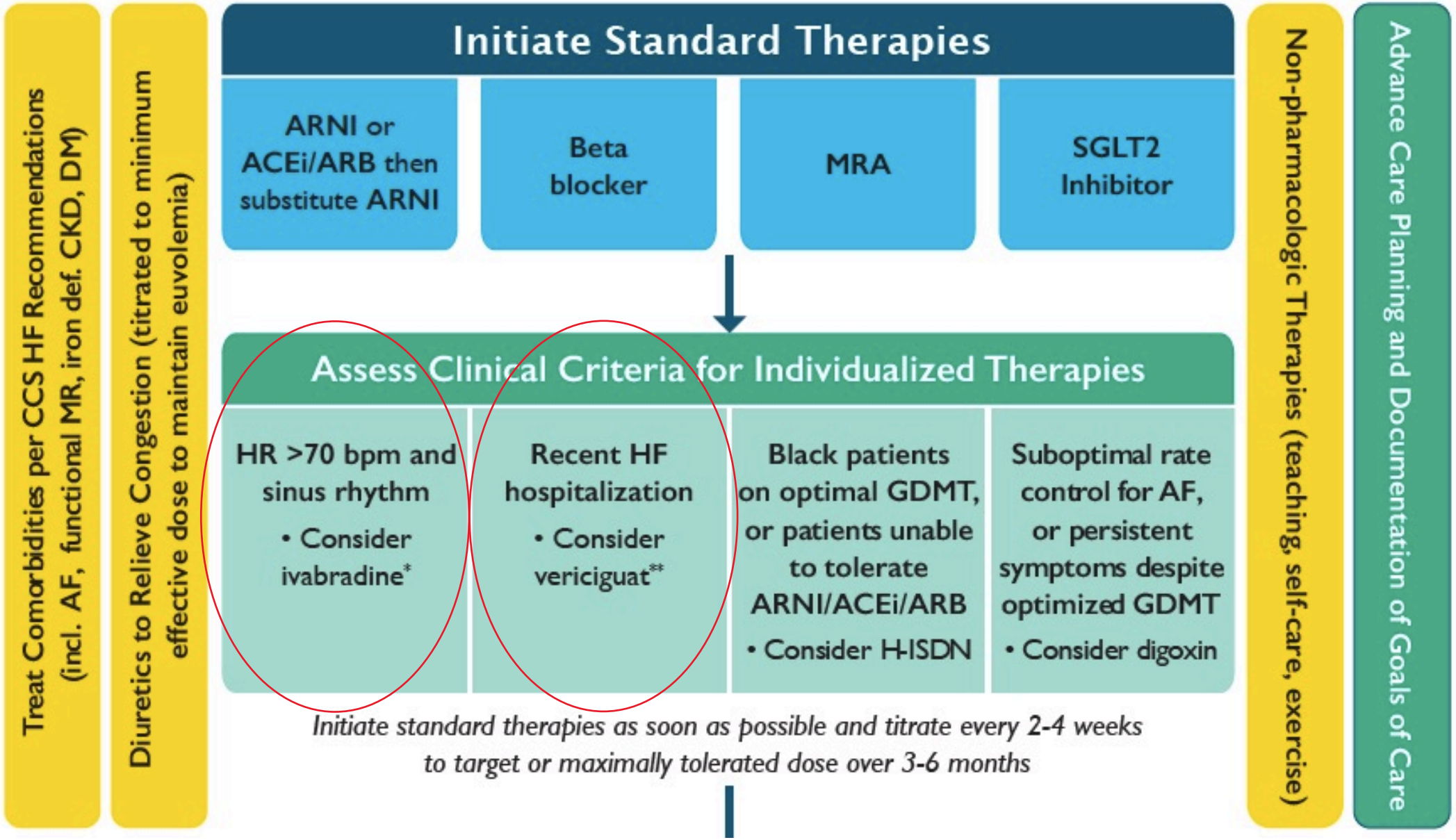
- BNP 799pg/mL, SCr 220 µmol/L
- Admitted for IV lasix

- Discharged after 8 days
  - Sac-val reduced to low dose
  - Furosemide 80mg daily added
  - Other meds unchanged
  - SCr 180 µmol/L at discharge, K^+ 4.9
  - Back to NYHA II

How can we further optimize in this setting?

HFrEF: LVEF ≤ 40% and Symptoms



Clinical Factors for Consideration with Individualized Therapies

Drug	Main Indication	Heart Rate and Blood Pressure	Renal Function	Notes
Ivabradine	• Sinus rhythm • HR ≥ 70 bpm despite beta-blocker optimization	• Minimum effect on blood pressure • Contraindicated in bradycardia	• Use in patients with severe renal dysfunction not well studied • No safety data for patients on dialysis or eGFR<15mL/min?1.73m^2	• Subgroup with HR ≥ 77bpm most likely to benefit • Can be initiated in hospital prior to discharge once clinical stability has been achieved • Potential side effects include visual disturbances (phosphenes) and bradycardia
Vericiguat	• Worsening HF symptoms and/or heart failure hospitalization in prior 6 months	• Avoid in patients with SBP <100mmHg or symptomatic hypotension • Minimal effect on HR	• No contraindication • No safety data for patient on dialysis or eGFR <15mL/min/1.73 m^2	• Should not be combined with nitrate therapy • Patients with very high NT-proBNP levels (>8000pg/mL) unlikely to benefit • Potential side effects include symptomatic hypotension and anemia

CCS HF Booklet 2021

VICTORIA Trial

- 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)

Armstrong et al. NEJM 2020, doi: 10.1056/NEJMoa1915928

Hospitalization remains a major risk factor for adverse events

“Chronic HF”

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

after

“Worsening event”

- Recent HFH or IV diuretic use
- With very elevated natriuretic peptides (BNP or NT-proBNP)

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

Armstrong et al. JACC Heart Fail. 2018 Feb;6(2):96-104. doi: 10.1016/j.jchf.2017.08.013.

VICTORIA: 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. NEJM 2020, doi: 10.1056/NEJMoa1915928

New Recommendation

- We recommend that vericiguat, an oral soluble guanylate cyclase stimulator, be considered in addition to optimal heart failure therapies for HFrEF patients with worsening symptoms and hospitalization for HF in the past 6 months, to reduce the risk of subsequent heart failure hospitalization
  - (Conditional Recommendation; Moderate-Quality Evidence)

- Practical Tip
  - Subgroup analysis from the VICTORIA Trial suggests that clinical response to vericiguat may be attenuated in patients with very elevated natriuretic peptide levels.

McDonald M, Virani S, et al. Can J Cardiol 2021

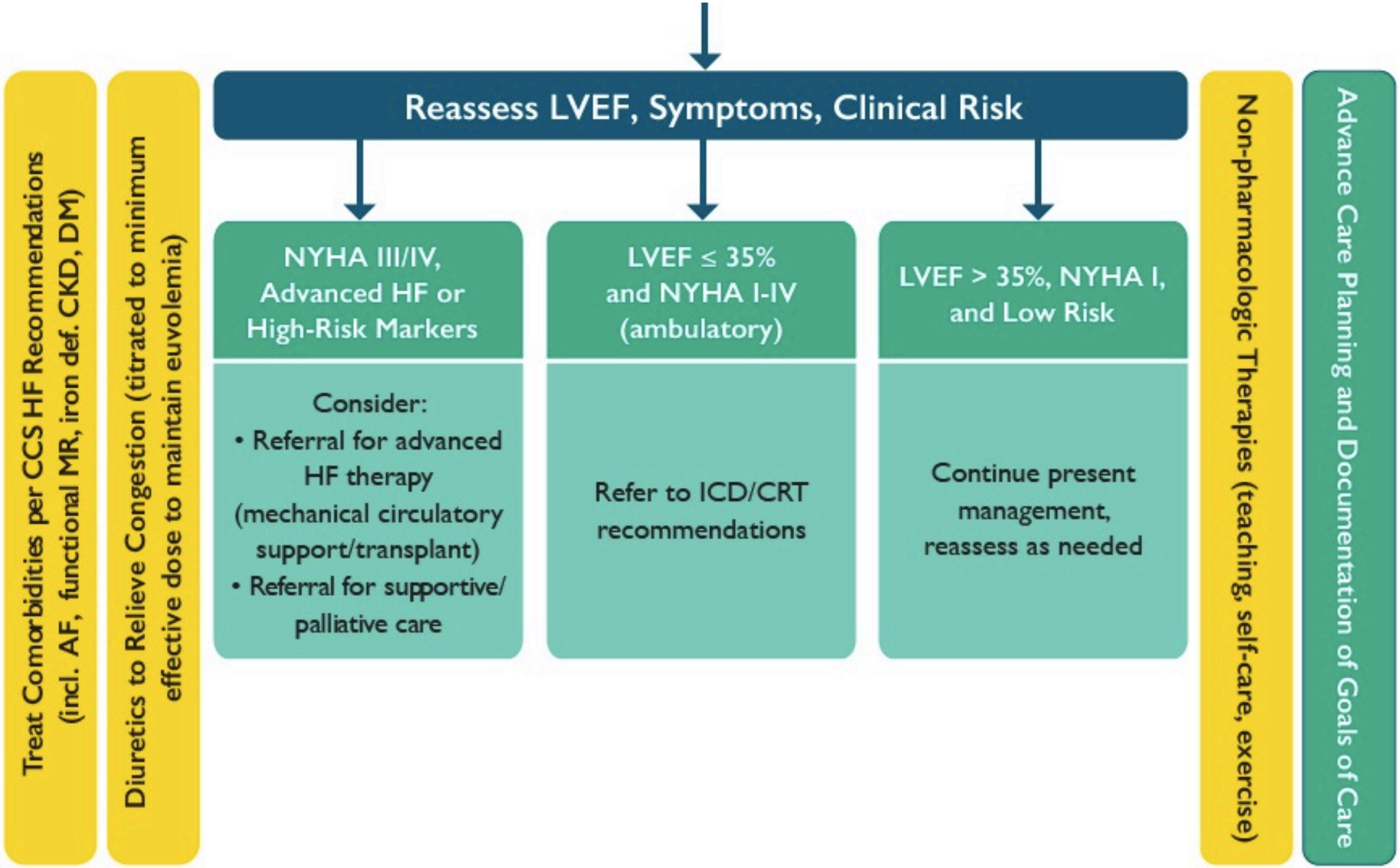
Is this patient a candidate for Advanced HF Therapies or a Device?

- 65 year old male
  - NYHA I since hospitalization
  - One hospitalization in the last year
  - LVEF 40%

- Meds:
  - Sacubitril-valsartan 49/51 mg bid
  - Bisoprolol 10 mg daily
  - Empagliflozin 10m daily
  - Spironolactone 6.25 mg daily
  - Ivabradine 5 mg po bid
  - Furosemide 80 mg po daily

- HR 61 bpm, BP 90/65 mmHg
- Euvolemic
- Baseline SCr 185 µmol/L, K^+ 5.2
- ECG shows NSR with QRS of 135ms

Can we further optimize in this setting?


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)
Reassess LVEF, Symptoms, Clinical Risk
NYHA III/IV, Advanced HF or High-Risk Markers
LVEF ≤ 35% and NYHA I-IV (ambulatory)
LVEF > 35%, NYHA I, and Low Risk
Consider:
• Referral for advanced HF therapy (mechanical circulatory support/transplant)
• Referral for supportive/ palliative care
Refer to ICD/CRT recommendations
Continue present management, reassess as needed
Non-pharmacologic Therapies (teaching, self-care, exercise)
Advance Care Planning and Documentation of Goals of Care

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 prior to referral for ICD or CRT
  - (Strong Recommendation; Moderate-Quality Evidence)

- Practical Tips
  - Reassessment of ejection fraction should be performed 3 months after the achievement of target or maximally tolerated doses of GDMT.
  - An assessment of arrhythmic and non-arrhythmic SCD risk should be performed to estimate the risk/benefit of an ICD/CRT.
  - Specific HF therapies may contribute to improvements in LVEF and should be considered prior to referral for ICD or CRT:
    - For eligible patients, switching to ARNI therapy should be considered prior to referral for ICD or CRT.
    - Adding ivabradine, where otherwise indicated after beta-blocker optimization, should be considered prior to referral for ICD or CRT.
  - Referral for ICD or CRT should not be unduly delayed if timely titration of pharmacologic therapies is infeasible or impractical.

McDonald M, Virani S, et al. Can J Cardiol 2021

Sean's Editorial Comments:

(1) These guidelines are remarkable for highlighting the breadth and depth of existing therapies for HFrEF

- There is still more to come, both in terms of new agents/technologies and new indications/clinical settings
- For the first time, in a long time, we will have lots of tools in the tool box and clinicians will need guidance on how to "mix and match"

(2) These guidelines serve as a reminder to clinicians about the evidence basis for treatment initiation by clinical setting

What is the quality of evidence for HFrEF therapies based on clinical setting?

	Quality of evidence supporting recommendation		
HFrEF Drug Therapy	**Chronic ambulatory HF**	**New-onset HF**	**HF hospitalization**
Sac-Val	High	Low	Moderate
ACEi/ARB	High	High	High*
B-Blockers	High	High	High
MRAs	High	High	High*
SGLT2i	High	N/A	N/A
Ivabradine	High	N/A	N/A
Vericiguat	Moderate	N/A	N/A
Digoxin	Moderate	Low	Low
H-ISDN	Moderate	Low	Low

McDonald M, Virani S, et al. Can J Cardiol 2021

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(2) These guidelines serve as a reminder to clinicians about the evidence basis for treatment initiation by clinical setting

(3) These guidelines represent a more nuanced and personalized treatment strategy, which represents a "transitional" approach to HFrEF management

- A hybrid approach which aims to balance population health with personalized care

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