Heart Failure Guidelines

McGill Refresher Course

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Dr. Nadia Giannetti

Medical Director, Heart Failure and Heart Transplant Program

McGill University Health Centre

Centre universitaire de santé McGill
Institut de recherche
McGill University Health Centre
Research Institute

Disclosures of potential conflicts of interest

Nadia Giannetti

Consulting Fees/Honoraria: Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS/Pfizer, Merck, Novartis, Pfizer, Servier, Hemostemix, Area-19

Clinical Trials: Abbott, AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Servier

Canadian Journal of Cardiology 36 (2020) 159–169

Society Guidelines

CCS/CHFS Heart Failure Guidelines: Clinical Trial Update on Functional Mitral Regurgitation, SGLT2 Inhibitors, ARNI in HFpEF, and Tafamidis in Amyloidosis

Primary Panel and Secondary Panel Writing Members: Eileen O'Meara, MD,[a,*] Michael McDonald, MD,[b,*] Michael Chan, MBBS,[c] Anique Ducharme, MD,[a] Justin A. Ezekowitz, MBBCh,[d] Nadia Giannetti, MD,[e] Adam Grzeslo, MD,[f] George A. Heckman, MD,[g] Jonathan G. Howlett, MD,[h] Sheri L. Koshman, PharmD,[d] Serge Lepage, MD,[i] Lisa M. Mielniczuk, MD,[j] Gordon W. Moe, MD,[k] Elizabeth Swiggum, MD,[l] Mustafa Toma, MD,[m] Sean A. Virani, MD,[m] Shelley Zieroth, MD,[n] Sabe De, MD,[o] Sylvain Matteau, MD,[i,p] Marie-Claude Parent, MD,[a] **External Reviewers and Co-authors:** Anita W. Asgar, MD,[a] Gideon Cohen, MD,[q] Nowell Fine, MD,[r] Margot Davis, MD,[m] Subodh Verma, MD,[s] David Cherney, MD,[t] **Secondary Panel:** Howard Abrams, MD,[u] Abdul Al-Hesayen, MD,[k] Alain Cohen-Solal, MD,[v] Michel D'Astous, MD,[w] Diego H. Delgado, MD,[u] Olivier Desplantie, MD,[x] Estrellita Estrella-Holder, RN,[y] Lee Green, MD,[d] Haissam Haddad, MD,[z] Karen Harkness, RN,[aa] Adrian F. Hernandez, MD,[bb] Simon Kouz, MD,[cc] Marie-Hélène LeBlanc, MD,[dd] Douglas Lee, MD,[u] Frederick A. Masoudi, MD,[ee] Robert S. McKelvie, MD,[ff] Miroslaw Rajda, MD,[gg] Heather J. Ross, MD,[b] and Bruce Sussex, MBBS[hh]

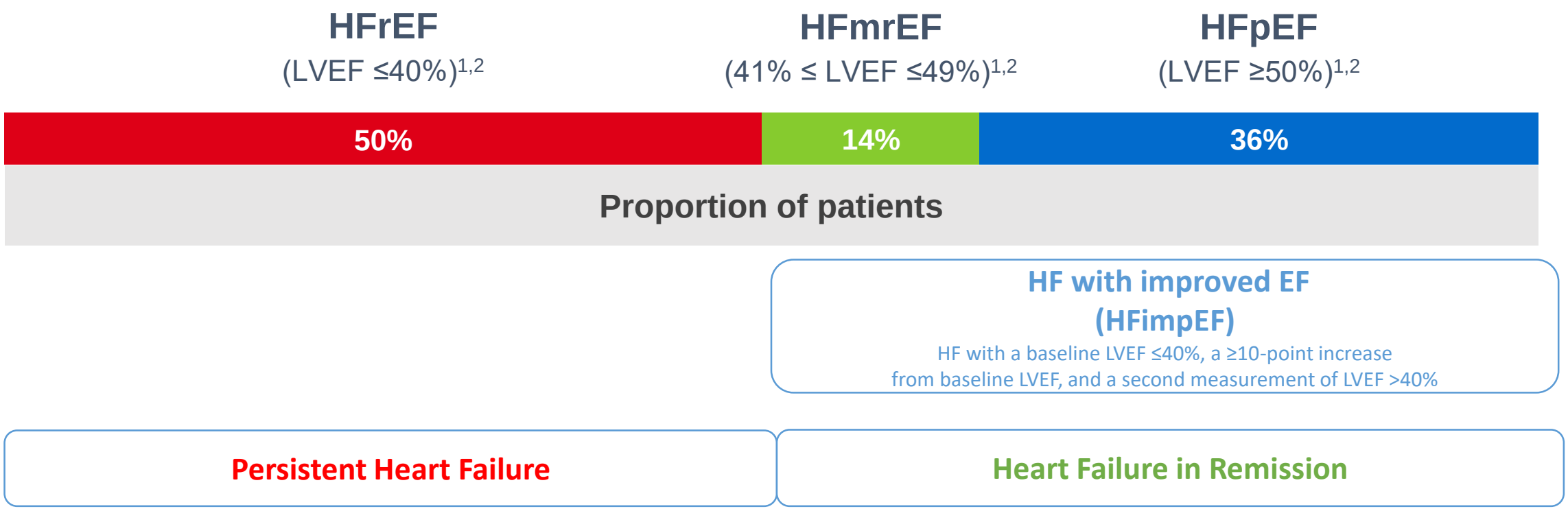
CCs.ca

Burden of HF in Canada

It is estimated that about 750,000 Canadians are living with heart failure.

https://www.heartandstroke.ca/heart-disease/conditions/heart-failure

The new universal definition of heart failure classifies the different phenotypes according to LVEF



EF, ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction.
Bozkurt B *et al*. *Eur J Heart Fail.* 2021;23:352.

Cardiac remodeling, a major risk factor in the progression of HF[1-3]

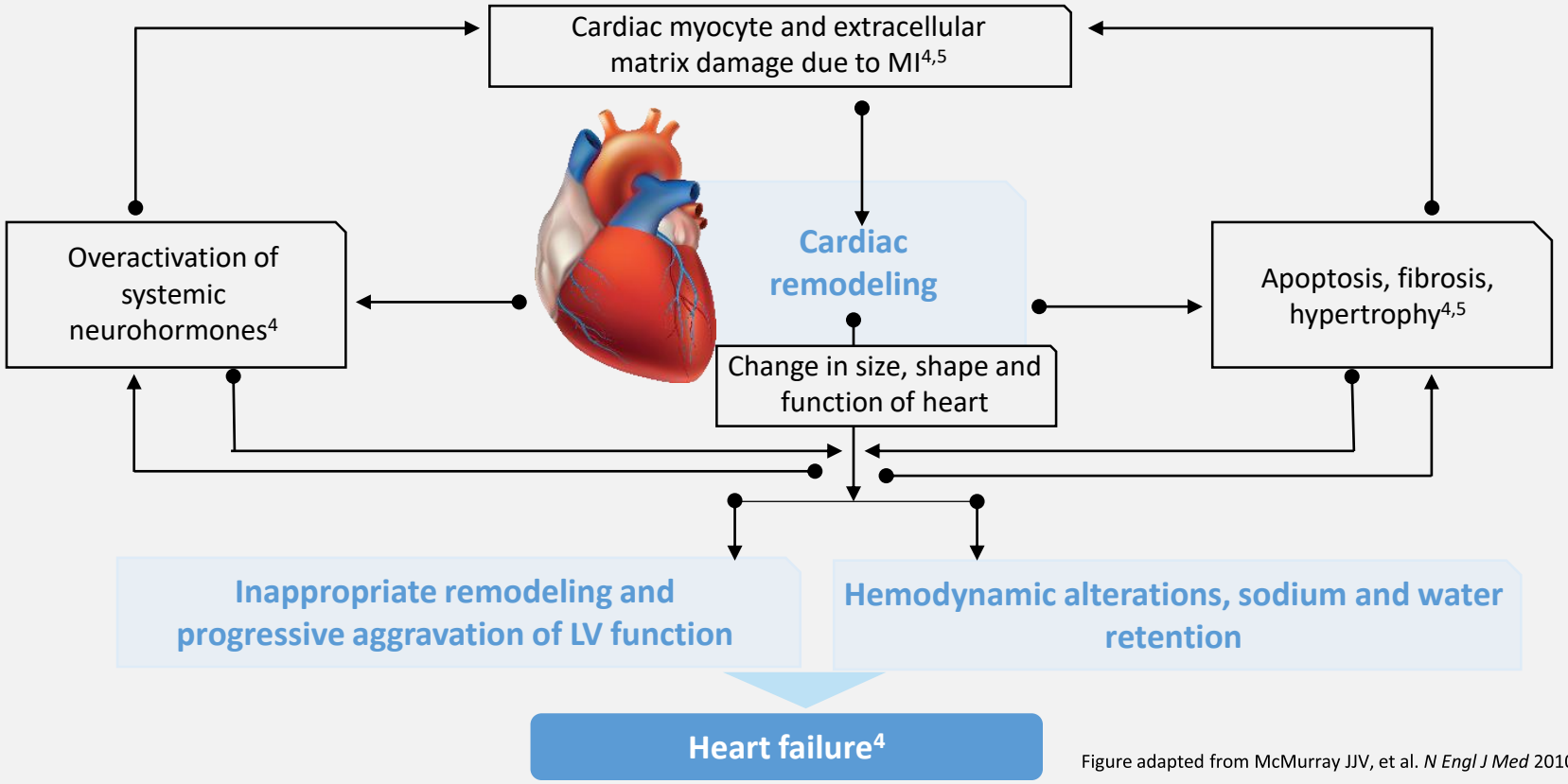


Figure adapted from McMurray JJV, et al. *N Engl J Med* 2010;362:228-238

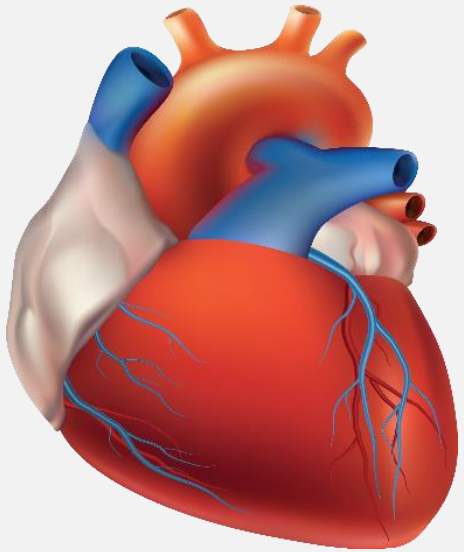
HF, heart failure; LV, left ventricle; MI, myocardial infarction

1. Vasan RS, et al. N Engl J Med 1997;336:1350-1355; 2. Almufleh A, et al. Am J Cardiovasc Dis 2017;7:108-113; 3. Cohn JN, et al. J Am Coll Cardiol 2000;35:569-582; 4. McMurray JJV, et al. N Engl J Med 2010;362:228-238; 5. Kemp CD and Conte JV. Cardiovasc Pathol 2012;21:365-371

An increase in LVEDV and LVESV corresponds to poor clinical outcomes

VALIANT ECHO study[a]: The risks of HF hospitalization or death increased significantly with increases in LVEDV and LVESV

Death or hospitalization for HF associated with LVEDV and LVESV[b]



LVEDV
10 mL

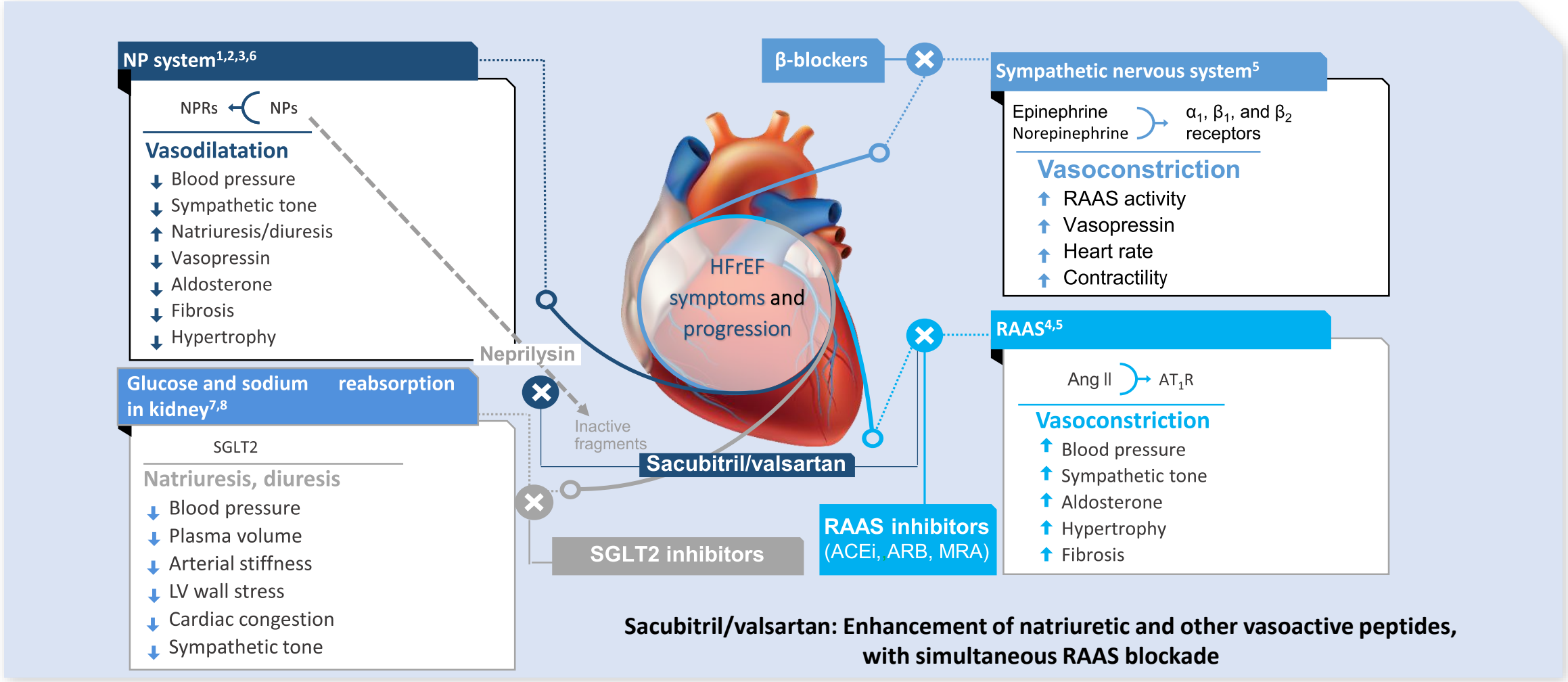
Death or HF hospitalization
9%
HR 1.09 (1.05–1.14; *P*<0.001)

LVESV
10 mL

Death or HF hospitalization
15%
HR 1.15 (1.09–1.21; *P*<0.001)

[a]Patient population: 10 post-MI patients from the total VALIANT population (14,703) were enrolled in VALIANT Echo; [b]Secondary outcome
HF, heart failure; HR, hazard ratio; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MI, myocardial infarction
Solomon SD, et al. *Circulation* 2005;111:3411-3419

Majority of the HF drug classes recommended by HFrEF guidelines can improve cardiac remodeling by reducing cardiac hypertrophy[1–5]



Sacubitril/valsartan: Enhancement of natriuretic and other vasoactive peptides, with simultaneous RAAS blockade

1. Levin ER, et al. *N Engl J Med* 1998;339:321-328; 2. McMurray JJV, et al. *Eur J Heart Fail* 2013;15:1062-1073; 3. Nathisuwan S and Talbert RL. *Pharmacotherapy* 2002;22:27-42; 4. Kemp CD and Conte JV. *Cardiovasc Pathol* 2012;21:365-371; 5. Schrier RW and Abraham WT. *N Engl J Med* 1999;341:577-585; 6. McMurray JJV, et al. *N Engl J Med* 2014;371:993–1004; 7. Indranee N, et al. Chapter 18 - Novel pharmacotherapies for heart failure. Available at https://doi.org/10.1016/B978-0-12-813706-2.00018-X (Accessed August 26, 2021); 8. Omar M, et al. *JAMA Cardiol* 2021;6(7):836-840

HFrEF 76 yo man

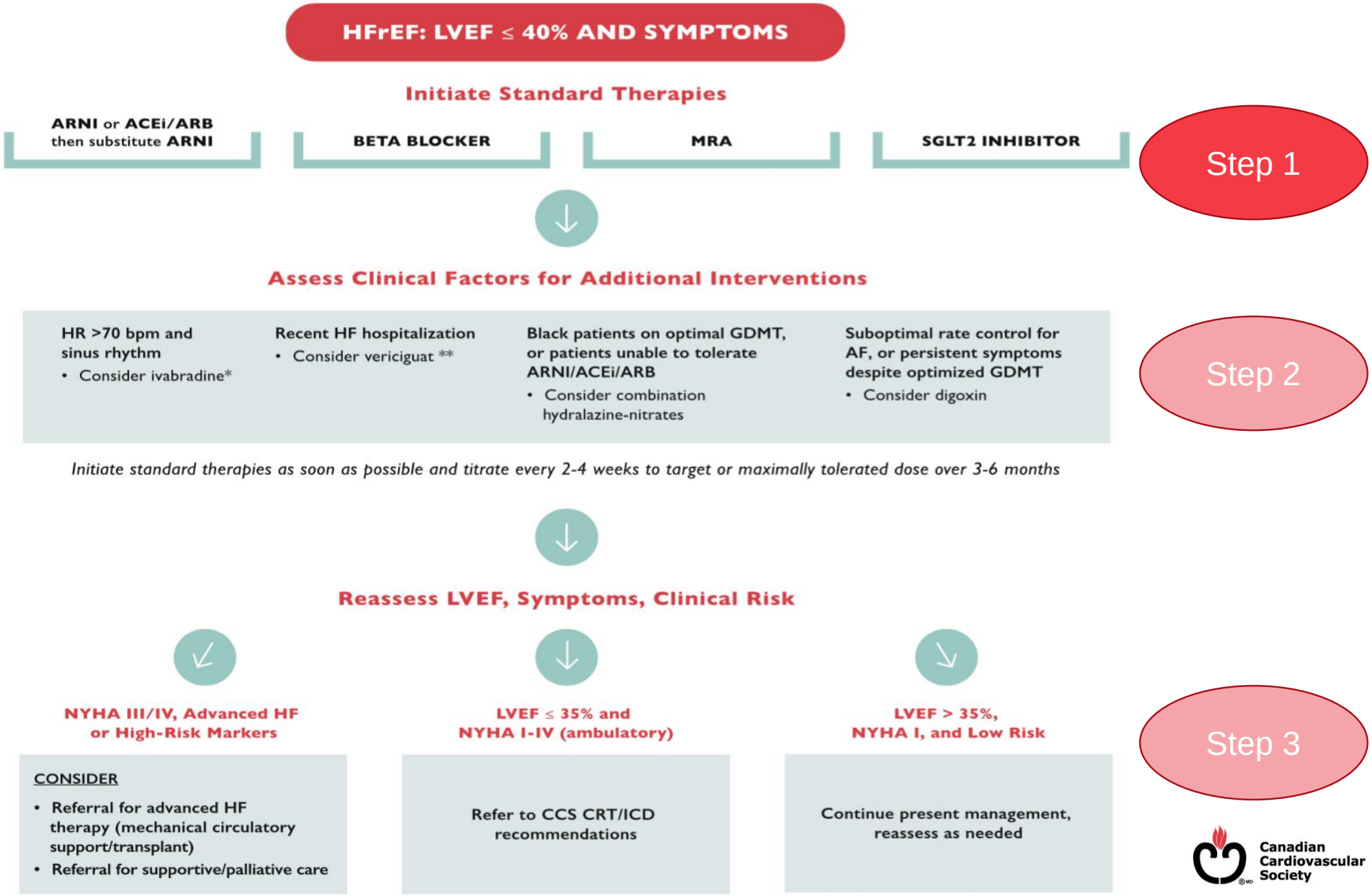
Previous medical condition(s)	Treatments
• Ischemic cardiopathy NYHA 2/4 never hospitalized • CRT-D • No DM • HTN • DLPD (LDL at target)	• Perindopril 6mg od • Spironolactone 25 mg od • Carvedilol 25 mg bid • Furosemide 20mg bid

Urgency visit
• Sob for a week, edema • No chest pain, no palpitation, 2 pillow orthopnea • Compliant with meds, diet • Weight gain 4 Kg

P/E
• Bp 110/70 , HR 88bpm NSR. • JVP 8, S3 + , holosystolic 2/6 murmur • Creps over ½ lungs fields, 2+ pitting oedema

Canadian Cardiovascular Society

New Standard: Foundational 4



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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:

1. ACEI/ARB or ARNI;
2. beta-blocker;
3. MRA;
4. SGLT2 inhibitor

(Strong Recommendation; Moderate-Quality Evidence).

Some new evidence for decision making in HFrEF

Study	Drug	Patients	Primary Outcome	Study Implications
PIONEER-HF (and extension study) 2019/2020	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 2019	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 2020	Empagliflozin vs placebo	High risk NYHA II-IV, chronic HF, with or without DM2	CV death or worsening HF	

DAPA-HF and EMPEROR-Reduced

DAPA-HF 4744 pts

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)

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

EMPEROR-Reduced 3730 pts

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)

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

- 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
- Magnitude of benefit observed in both trials similar in patient WITH and WITHOUT diabetes
- Differences in trials relate to baseline characteristics

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, Virani, et al, Can J Cardiol 2021

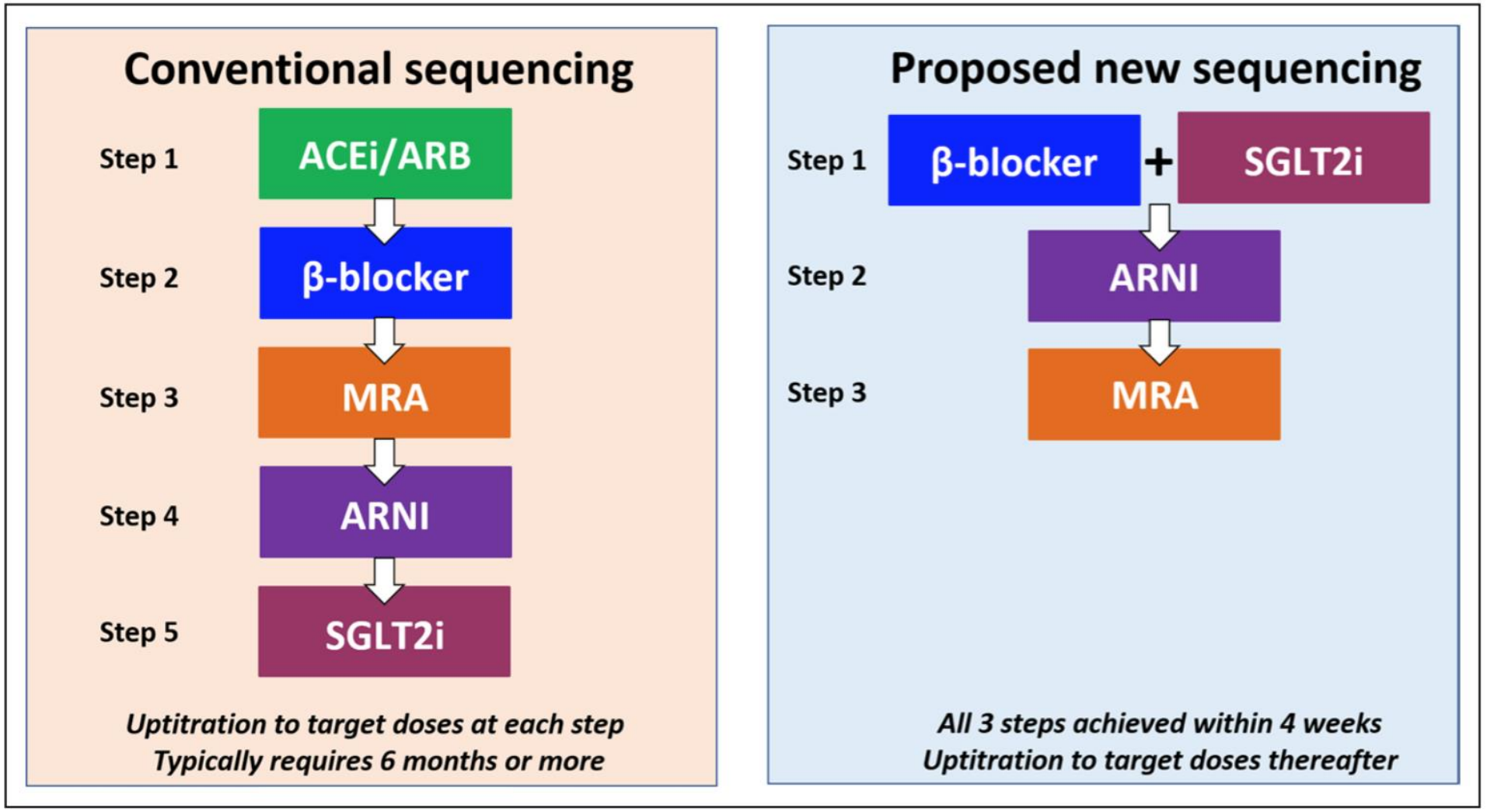
Updated Recommendation

- 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, Virani, et al, Can J Cardiol 2021

What people are talking about: How best to prescribe? Combination therapy first *then* titration



McMurray and Packer, Circulation 2021

After the Big-4

A more personalized approach

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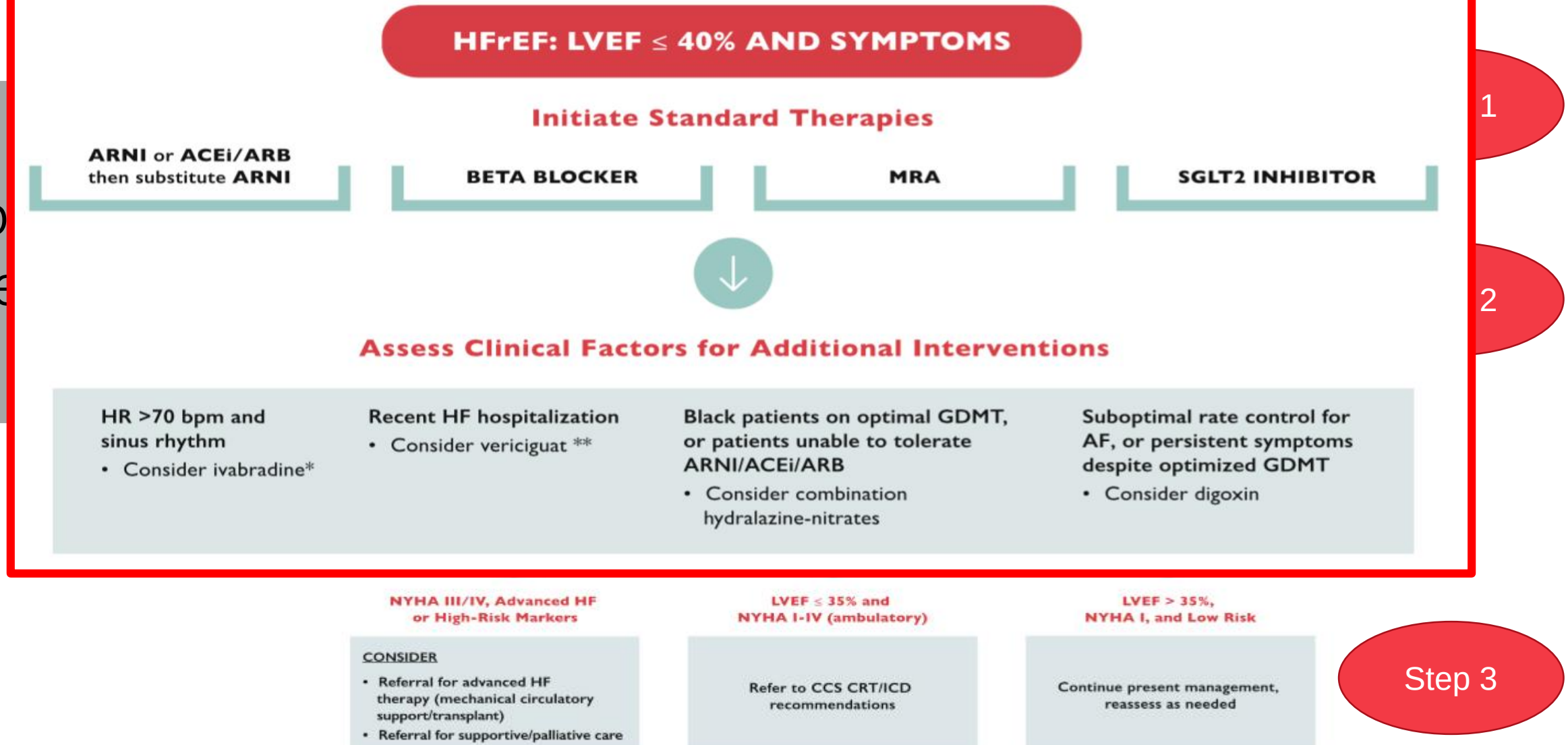
pre



1

2

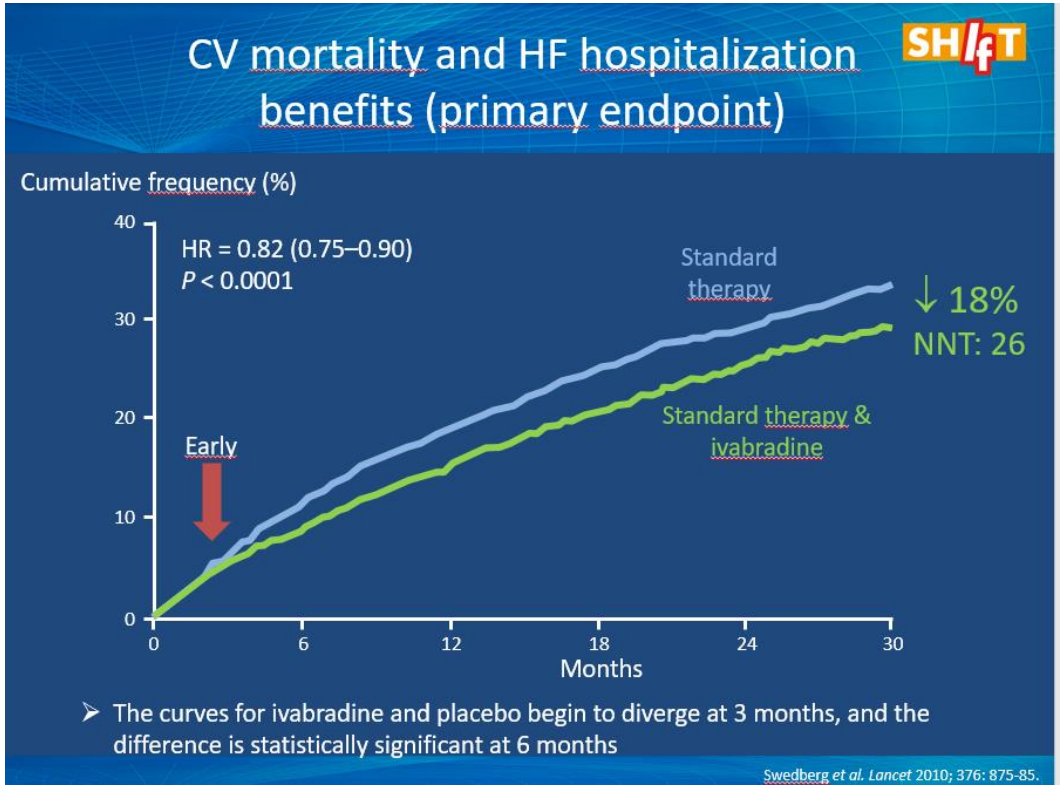
Step 3

Recommendation: Ivabradine

Recommendation 34: We recommend that ivabradine be considered in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses of GDMT, with a resting heart rate > 70 bpm, in sinus rhythm and a prior HF hospitalization within 12 months, for the prevention of cardiovascular death and HF hospitalization (Strong Recommendation, Moderate Quality Evidence).

Values and preferences:

High value is placed on the improvement of cardiovascular death and HF hospitalizations as adjunctive therapy to standard HF medication treatments in a selected HF population. The health economic implications are unknown. Differing criteria for heart rate eligibility have been approved by various regulatory authorities ranging from 70 to 77 beats per minute with the trial entry criteria of 70 bpm.



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: Isordil and Hydralazine

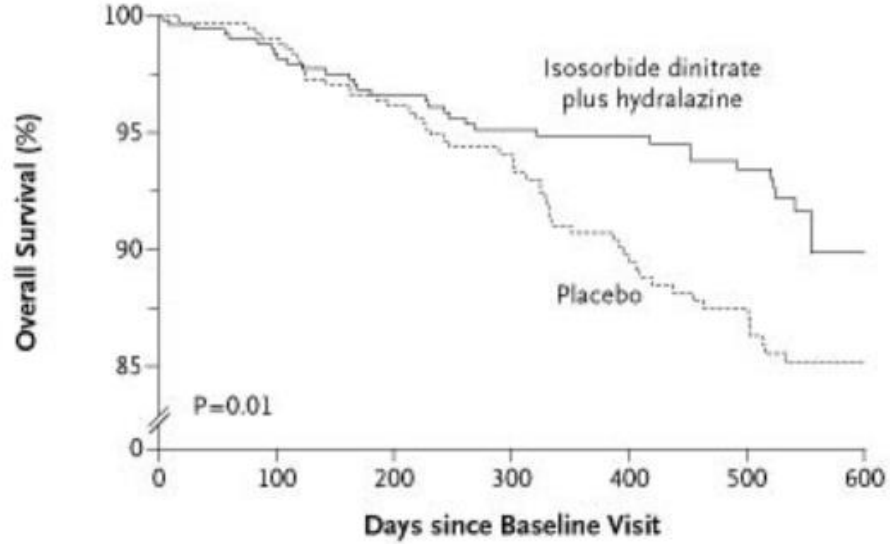
Recommendation 35: We recommend the combination of H-ISDN be considered in addition to standard GDMT at appropriate doses for black patients with HFrEF and advanced symptoms (Strong Recommendation, Moderate Quality Evidence).

Recommendation 36: We recommend that H-ISDN be considered in patients with HFrEF unable to tolerate an ACE inhibitor, ARB or ARNI because of hyperkalemia or renal dysfunction (Strong Recommendation, Low Quality Evidence).

ORIGINAL ARTICLE

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*



No. at Risk							
Placebo	532	466	401	340	285	232	24
Isosorbide dinitrate plus hydralazine	518	463	407	359	313	251	13

Taylor et al. N Engl J Med 2004; 351:2049-2057

Recommendation: Digoxin

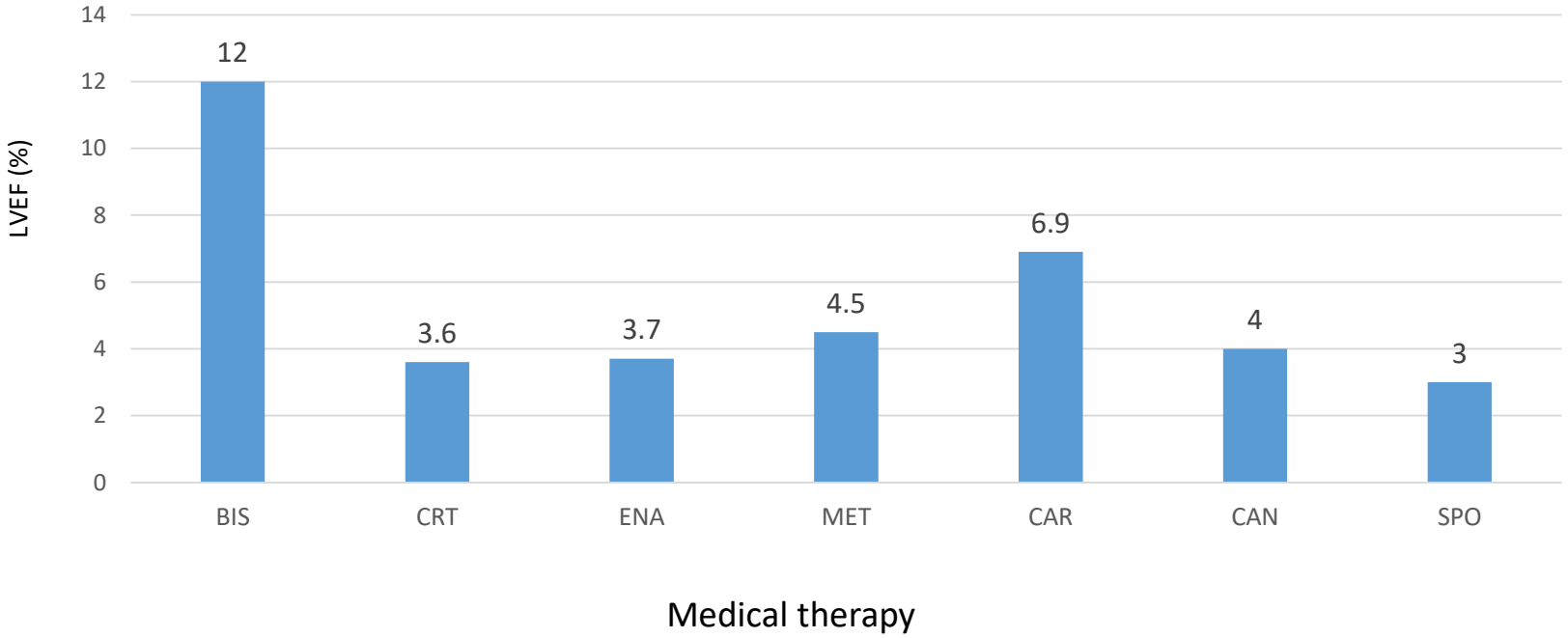
Recommendation 37: We suggest digoxin be considered in patients with HFrEF in sinus rhythm who continue to have moderate to severe symptoms, despite appropriate doses of GDMT to relieve symptoms and reduce hospitalizations (Weak Recommendation, Moderate Quality Evidence).

After titration of medications

Key Points:

- LVEF should be reassessed after optimization of medical therapy and prior to referral for primary prevention ICD or CRT
- Titrate medical therapies as soon possible to avoid delays in referral for ICD or CRT
- Repeat LVEF, clinical risk, goals of care should be used to determine appropriate next steps

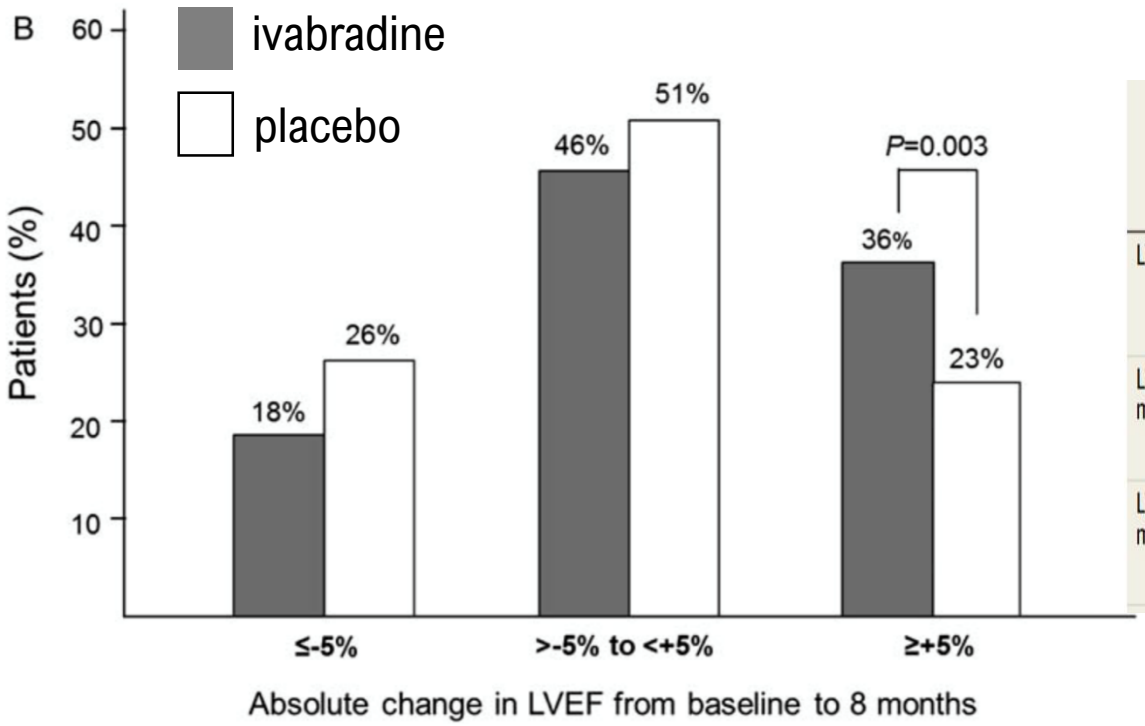
Conventional HF therapies increase LVEF (reverse remodeling) compared to placebo



A 5% increase in LVEF corresponded to a 14% mortality reduction*

Data are based on the results of a meta-analysis of 30 mortality trials including a total of 69,766 patients who were followed for a median of 17 months.*95% CI (0.77, 0.96)
BIS: Bisoprolol, CAR: Carvedilol; CAN: Candesartan, CRT: Cardiac resynchronization therapy; ENA, enalapril; MET: Metoprolol, SPO: Spironolactone.
Kramer JACC 2010 July 27: 392-406. Katsi V. Heart Fail Rev 2017;641-655.

Additional medical therapy improvements in LVEF



Echo sub-study of 411 patients in the SHIFT Trial;
Baseline vs 8 month follow up

Tardif et al, Eur Heart J 2011

PROVE HF :
LV evaluation after starting sacubitril-valsartan

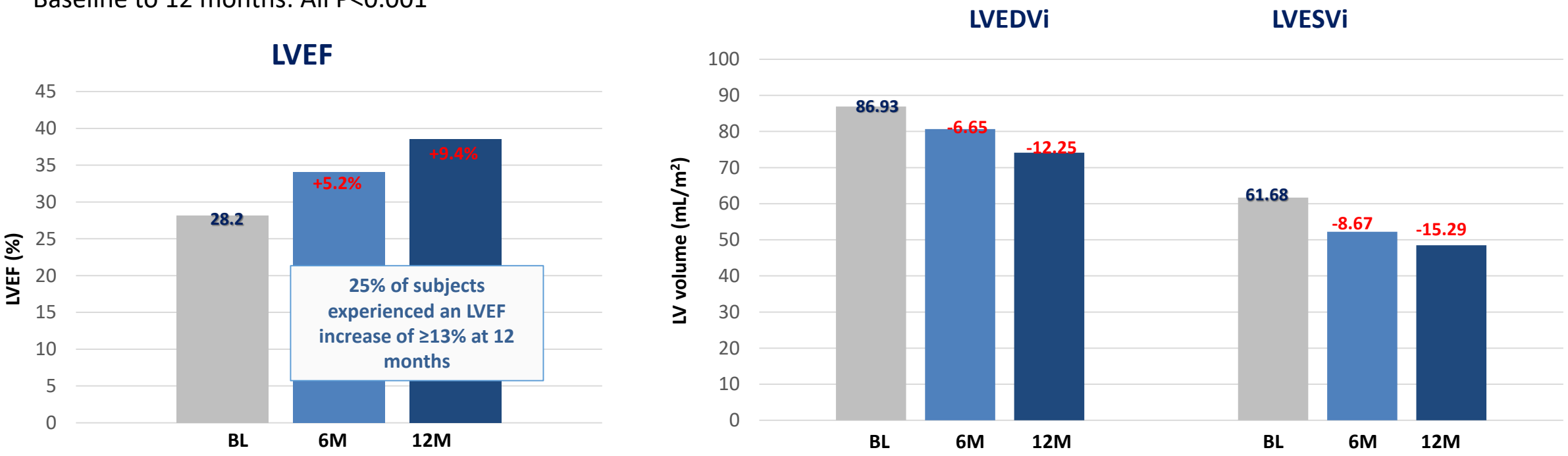
	All Patients				
	Baseline Value, Median (25th to 75th Percentile)	6-mo Value, Median (25th to 75th Percentile)	LS Mean Change From Baseline at 6 mo (95% CI)	12-mo Value, Median (25th to 75th Percentile)	LS Mean Change From Baseline at 12 mo (95% CI)
LVEF, %	n = 757	n = 716		n = 648	
	28.2 (24.5 to 32.7)	34.1 (29.0 to 39.65)	5.2 (4.8 to 5.6)	37.8 (32.3 to 45.2)	9.4 (8.8 to 9.9)
LVEDVI, mL/m^2	n = 756	n = 716		n = 648	
	86.93 (76.17 to 100.43)	79.50 (69.34 to 93.52)	−6.65 (−7.11 to −6.19)	74.15 (63.46 to 86.30)	−12.25 (−12.92 to −11.58)
LVESVI, mL/m^2	n = 756	n = 716		n = 648	
	61.68 (51.95 to 75.00)	52.25 (42.34 to 65.25)	−8.67 (−9.18 to −8.15)	45.46 (34.84 to 57.56)	−15.29 (−16.03 to −14.55)

LVEF and remodeling improves at 6 and 12 months
in a prospective observational study

Januzzi et al, JAMA 2019

Significant reverse remodeling after 6 and 12 months of sacubitril/valsartan treatment in PROVE-HF

Baseline to 12 months: All P<0.001



At baseline 95% of patients were on beta-blocker, 76% on ACEi/ARB, and 35% on MRA; observed improvements were on top of this background medical therapy.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BL, baseline; M, month; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; MRA, mineralocorticoid receptor antagonist

1. Januzzi JL, et al. *JAMA* 2019; DOI: 10.1001/jama.2019.128. 2 Januzzi JL, et al. Late Breaker ESC 2019. Paris, France August 31-September 4, 2019.
3. Schaer B et al. Swiss Med Wkly. 2016;146:w14300.

Patients with improved EF after initiation of sacubitril/valsartan may no longer be eligible for ICD

The impact of sacubitril/valsartan therapy on ICD eligibility was investigated in PROVE-HF

- Among a cohort of patients with HFrEF who met primary prevention ICD eligibility criteria at baseline (N=661) and who were initiated on sacubitril/valsartan:
  - **32% improved EF to >35% by 6 months**
  - **62% improved EF to >35% by 12 months**
- There were 23 deaths during follow-up:
  - 8 with improved EF and 15 without improved EF

In patients without ICD at the time of sacubitril/valsartan initiation, many patients may have sufficient favorable cardiac remodeling to no longer qualify for primary prevention ICD therapy; improvements in LVEF may continue for at least 12 months

EF, ejection fraction; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction

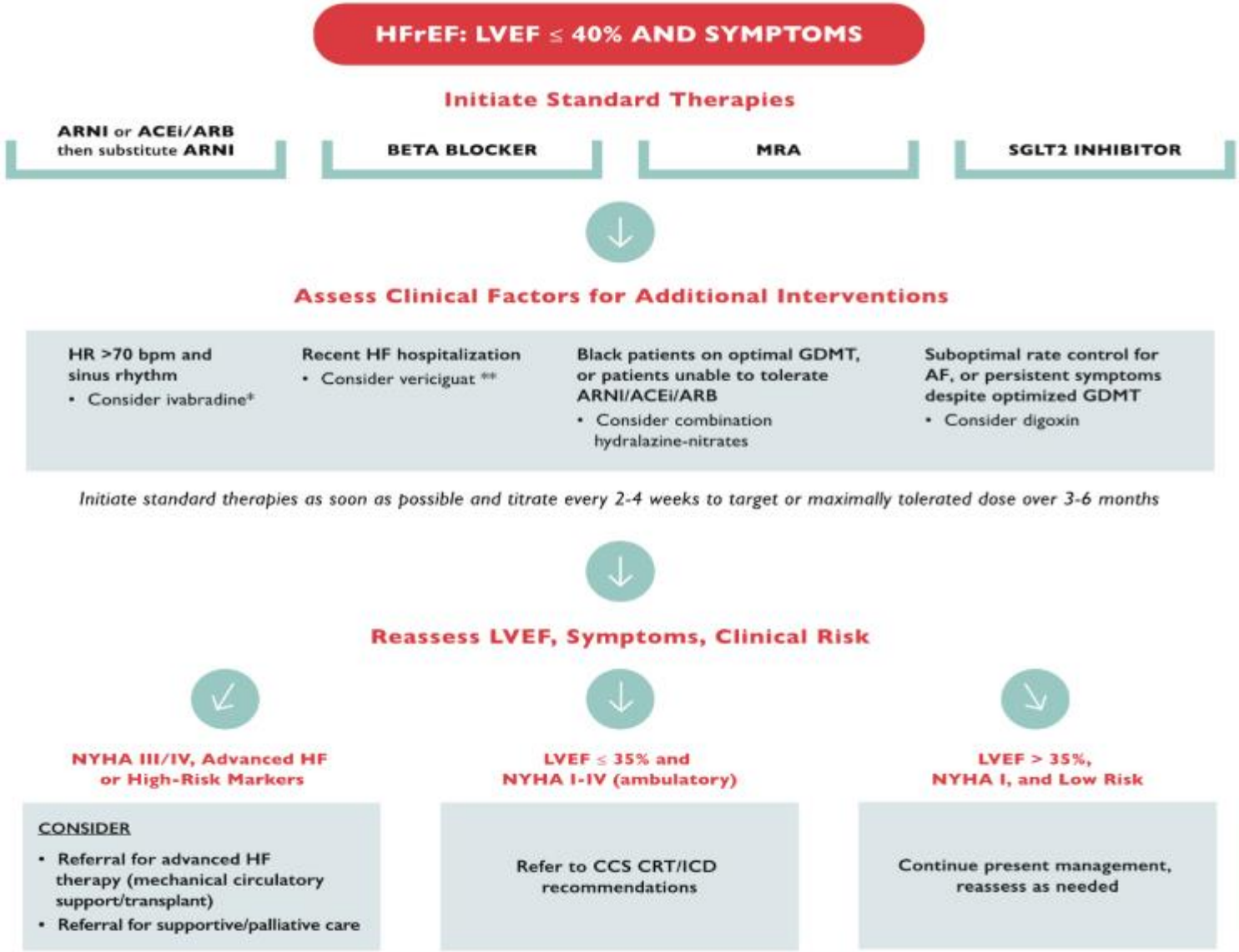
Felker GM, Butler J, Ibrahim NE, et al. Circulation. 2021;144(2):180-182. doi:10.1161/CIRCULATIONAHA.121.054034

Early initiation of therapy

New clinical evidence has driven the definition of contemporary HF care

4 drugs should now be considered standard therapy

Initiate and then titrate medical therapy as soon as possible



Step 1

Step 2

Step 3

Canadian Cardiovascular Society

HFrEF 76 yo man

Previous medical condition(s)	Treatments
• Ischemic cardiopathy NYHA 2/4 never hospitalized • CRT-D • No DM • HTN • DLPD (LDL at target)	• Perindopril 6mg od • Spironolactone 25 mg od • Carvedilol 25 mg bid • Furosemide 20mg bid

Urgency visit
• Sob for a week, edema • No chest pain, no palpitation, 2 pillow orthopnea • Compliant with meds, diet • Weight gain 4 Kg

P/E
• Bp 110/70 , HR 88bpm NSR. • JVP 8, S3 + , holosystolic 2/6 murmur • Creps over ½ lungs fields, 2+ pitting oedema

Canadian Cardiovascular Society

Summary

- Despite standard medical therapy, the burden of HF remains high
- There is underutilization of medical therapy in HF patients
- Life-style and medical therapy can improve QOL and CV outcomes in HF patients
- Beyond standard therapy, medication can be individualized depending on patient volume status, heart rhythm and hemodynamics