ECHO IDAHO

Managing Heart Failure in Primary Care

Managing ARNI/ACEI/ARB and Beta-Blockers in HF

11/20/2025

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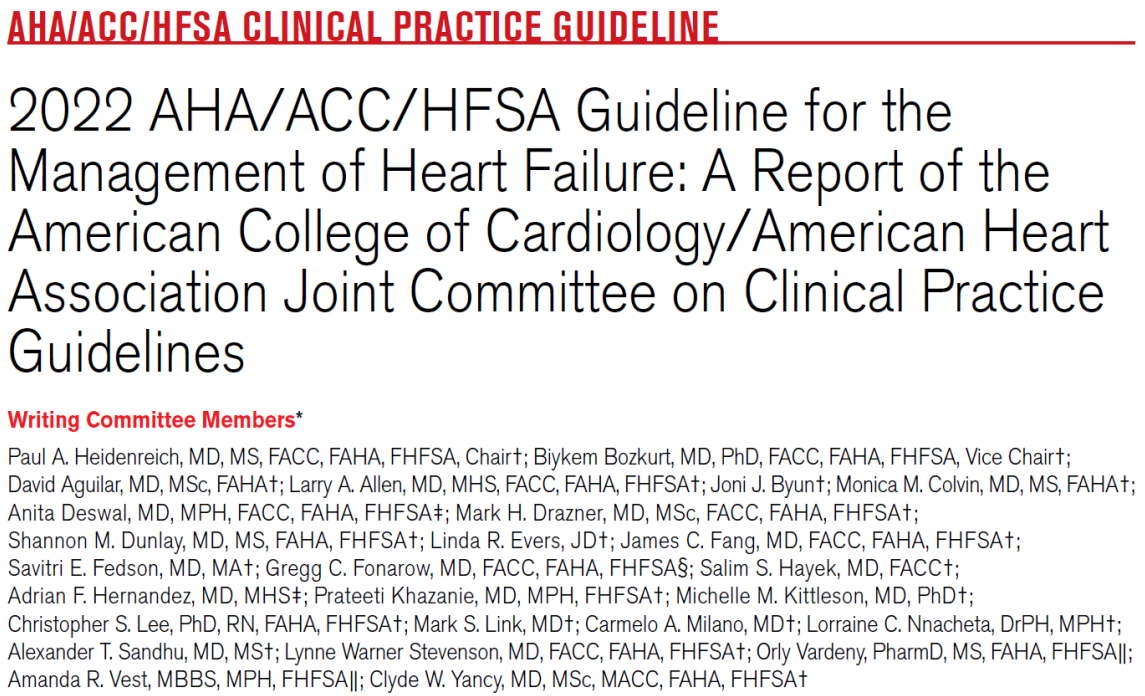
Project ECHO

No Financial Conflicts of Interest

- Promote views of
  - American College of Cardiology
  - American Heart Association
  - Heart Failure Society of America



AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

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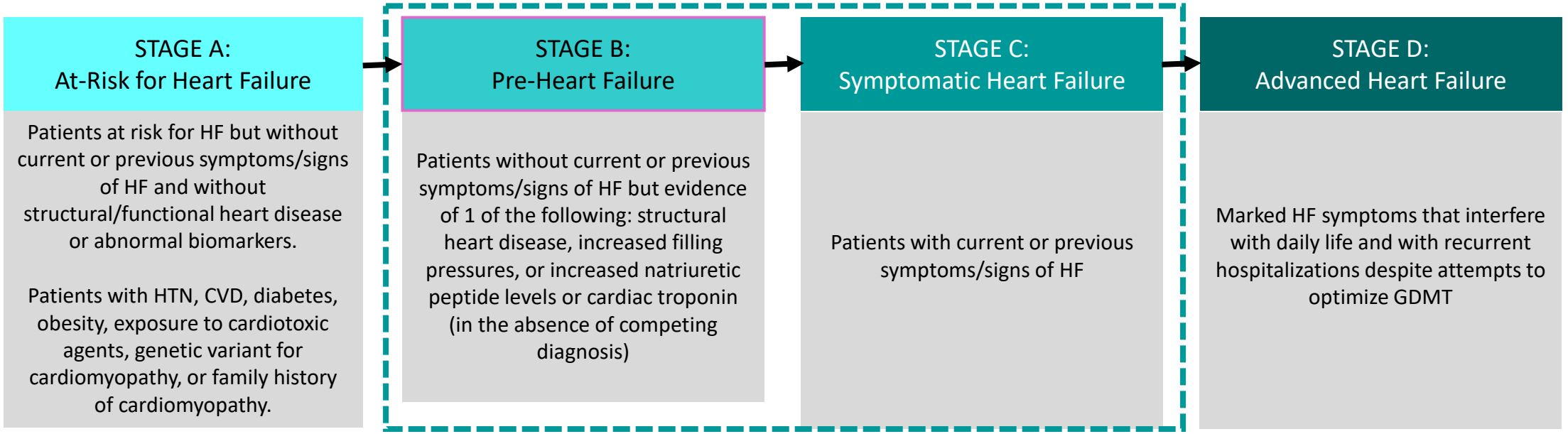
Learning Objectives

- Be comfortable prescribing ARNI and Beta-blockers for HF
- Know what change in glomerular filtration rate (creatinine) is a concern
- Understand contraindications to ARNI, ACEi, ARB and Beta-blockers

Outline

- Pre-Heart Failure
- Heart Failure
  - HFrEF
  - HFmrEF
  - HFpEF

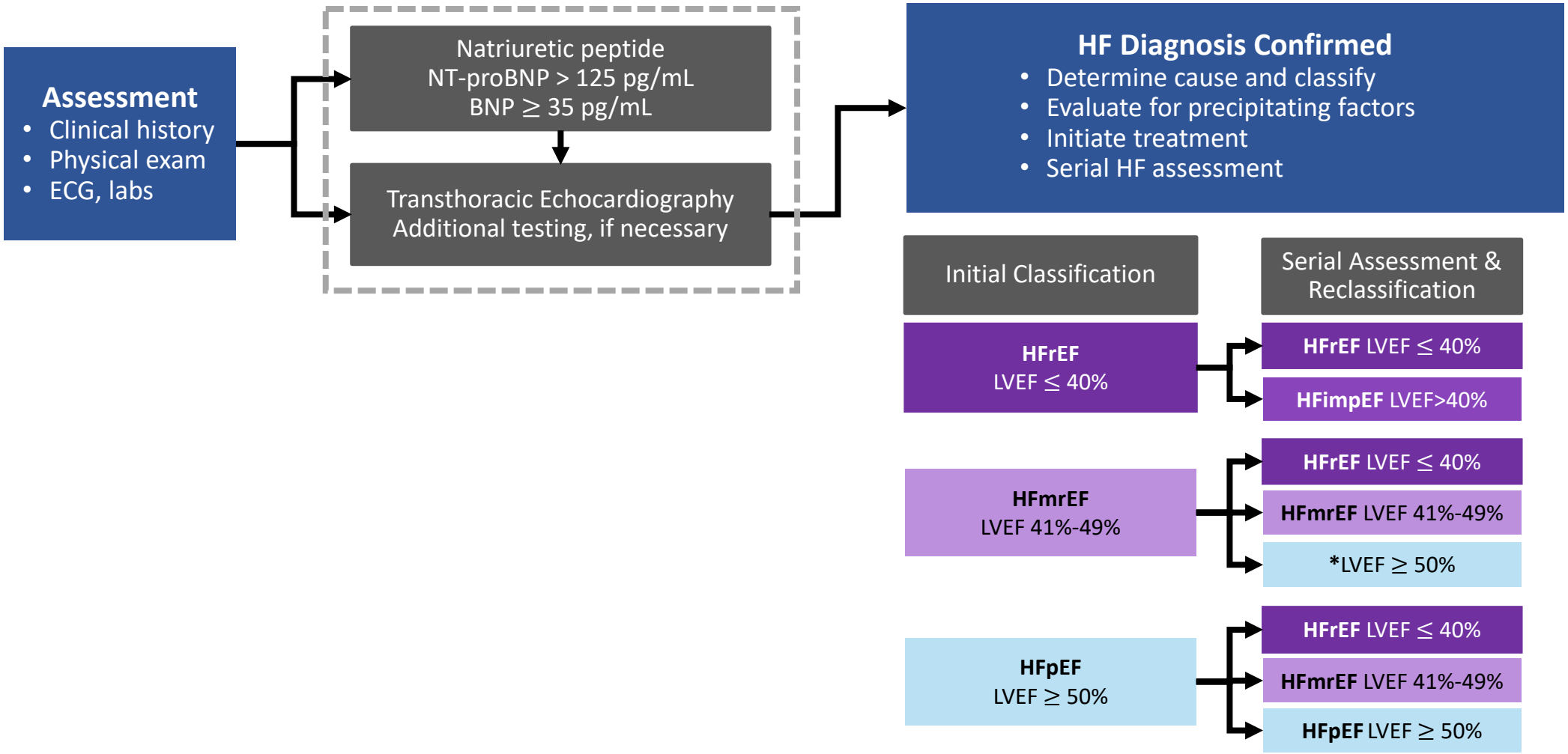
STAGES OF HEART FAILURE



Abbreviations: CVD indicates cardiovascular disease; GDMT, guideline-directed medical therapy; HF, heart failure; HTN, hypertension; and NYHA, New York Heart Association.

Heidenreich, Circulation, 2022

DIAGNOSTIC ALGORITHM FOR HF AND LVEF BASED ON HF CLASSIFICATION



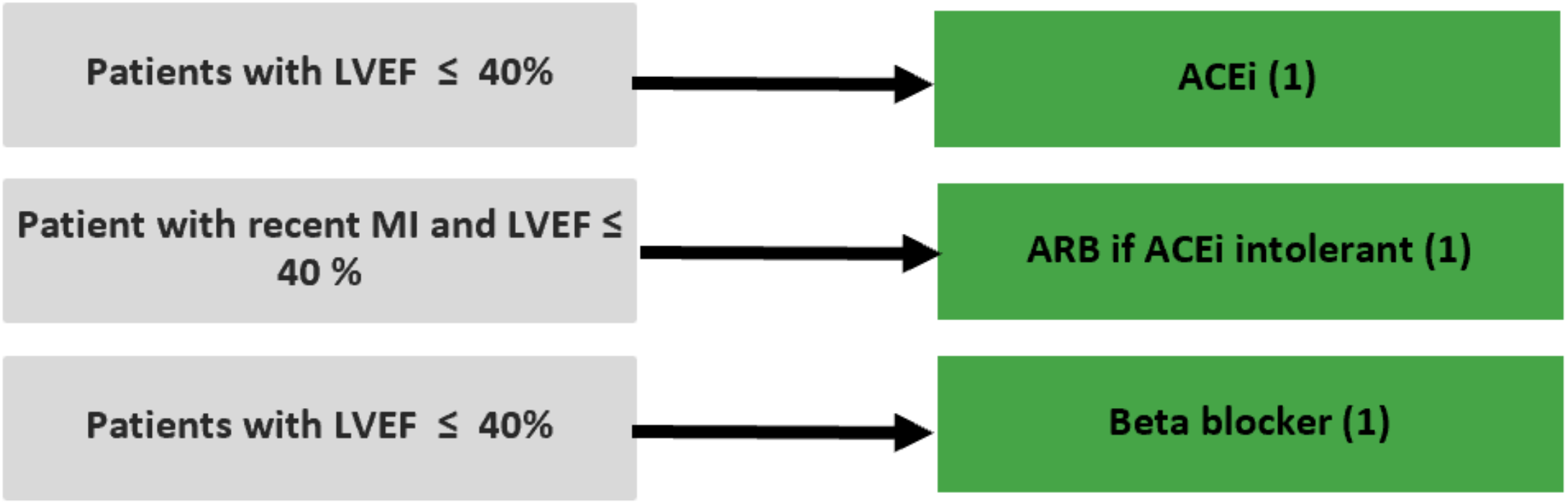
American Heart Association.

Heidenreich, Circulation, 2022

HFpEF
LVEF ≥ 50%

Pre-HF (Stage B)

Preventing the Syndrome



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ACEi/ARB for Pre-HF: Evidence

- In **survivors of acute MI with asymptomatic LV dysfunction** (LVEF <35%–40%), RCTs have shown that **captopril reduced mortality, HF hospitalizations, and progression to severe HF** compared with placebo.
- In those individuals with **asymptomatic LV dysfunction** in the SOLVD (Studies of Left Ventricular Systolic Dysfunction) prevention trial, which included approximately 20% without ischemic heart disease, **enalapril reduced HF hospitalization and mortality** compared with placebo.

Circulation, 2022 ACC/AHA/HFSA Guideline

ARB if ACEi Intolerant: Evidence

- The VALIANT (**Valsartan** in Acute Myocardial Infarction) trial, which included approximately 25% of patients with asymptomatic LV dysfunction, showed that the benefits of valsartan on mortality and other adverse cardiovascular outcomes were comparable to captopril.
- In the OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) trial, **losartan did not meet he noninferiority criteria** for mortality compared with captopril.
- No clinical trials have specifically evaluated ARB in patients with asymptomatic reduced LVEF in the absence of previous MI.

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Beta-Blockers for Pre-HF: Evidence

- Among patients with **asymptomatic LV systolic dysfunction** in the SOLVD prevention trial (which included 80% with previous MI) and the SAVE (Survival and Ventricular Enlargement) trial, **secondary analyses** showed that the **administration of beta blockers in addition to ACEi reduced mortality and hospitalization.**

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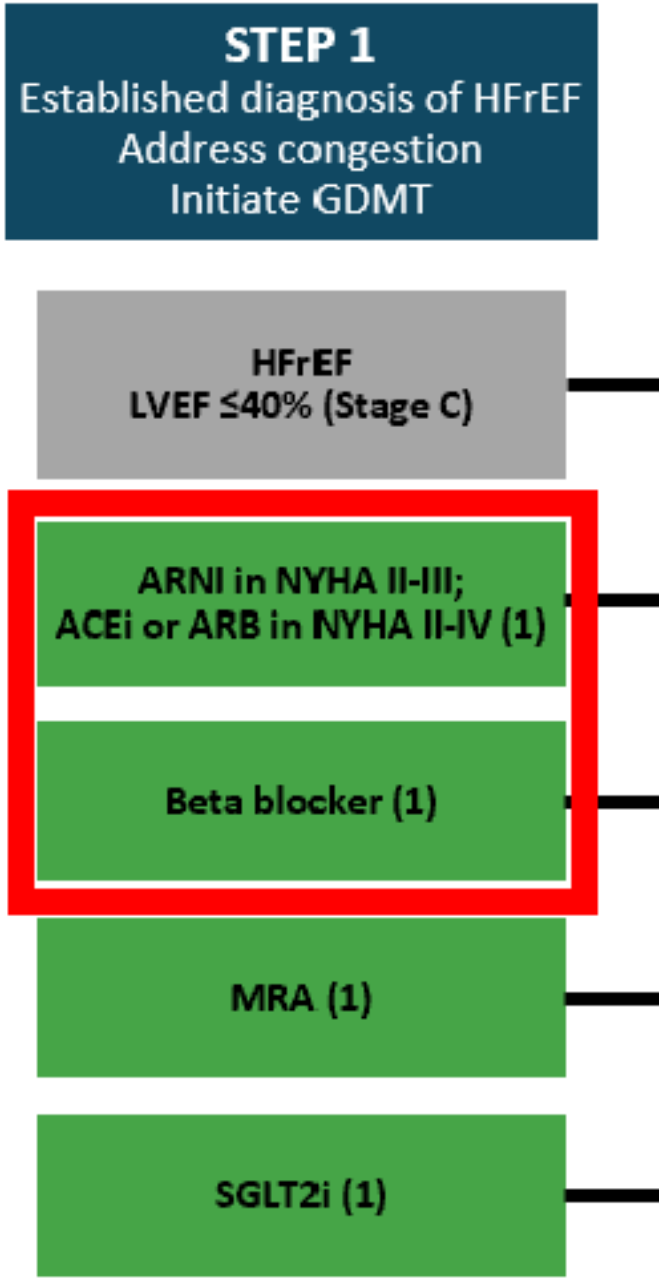
Heart Failure (Stage C)

HFrEF, HFmrEF, HFpEF

HFrEF Treatment



Heidenreich, Circulation, 2022

Already on ACEi/ARB: Switch to ARNi

1	B-R	5. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality.[1–5]
Value Statement: High Value (A)		6. In patients with chronic symptomatic HFrEF, treatment with an ARNi instead of an ACEi provides high economic value.[26–29]

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Not On Any Therapy, ARNi Preferred

Recommendations for Renin-Angiotensin System Inhibition With ACEI or ARB or ARNI Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendations**
1	A	1. In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality.[1–5]
1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible.[6–13]
1	A	3. In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality.[14–18]
Value Statement: High Value (A)		4. In patients with previous or current symptoms of chronic HFrEF, in whom ARNi is not feasible, treatment with an ACEi or ARB provides high economic value.[19–25]

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Angiotensin Receptor Blocker with Neprilysin Inhibitor (ARNi): Evidence

Angiotensin Receptor blocker Neprilysin Inhibitor (ARNI)						
Pivotal Trials						
Study Name (year)	**Active**	**Control**	**Primary Endpoint**	**HR (95% CI) for primary outcome**	**Mean/median eGFR**	**Renal function exclusion (Creatinine (mg/dL) /eGFR)**
PARADIGM-HF (2014)[77]	Sacubitril / Valsartan	Enalapril	CV Death or HF Hospitalization	0.80 (0.73-0.87)	70	< 30 mL/min/1.73m²
PIONEER (2019)[81]	Sacubitril / Valsartan	Enalapril	Change in NTproBNP	NA	58	< 30 mL/min/1.73m²

Beldhuis, Circulation 2022

Heart Failure Medication Titration Protocol for ARNi

	SACUBITRIL/VALSARTAN (ENTRESTO®)	
	No prior ACEi/ARB, or on **LESS THAN OR EQUAL TO** lisinopril 10mg/day or losartan 50mg/day or equivalent dose‡	On **GREATER THAN** lisinopril 10mg/day or losartan 50mg/day or equivalent dose‡
Step 1: Starting Dose*	24mg/26mg BID	49mg/51mg BID
Step 2: Week 3	49mg/51mg BID	97mg/103mg BID
Step 3: Week 5	97mg/103mg BID	----

Titration Protocol for Angiotensin Receptor Blocker/Neprilysin Inhibitor (ARNi)
***Must allow 36-hour washout period if patient previously on ACEi (not necessary for ARBs)**

‡**Equivalent doses**:
Enalapril 10mg/day = Lisinopril 10mg/day
Valsartan 160mg/day = Losartan 50mg/day

Used for VA Clinician Guidance

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First Drug: ARNi or Beta-Blocker

- ARNi better tolerated if “wet”
- Beta-blocker better tolerated if “dry”
  - OK to continue beta-blocker if decompensated
  - Do not initiate beta-blocker if decompensated

Maddox, JACC 2024

Contraindications and Cautions: ARNi

Contraindications	Cautions
A. Sacubitril/Valsartan	
■ Within 36 h of ACE inhibitor use ■ Any history of angioedema ■ Pregnancy ■ Lactation (no data) ■ Severe hepatic impairment (Child-Pugh class C) ■ Concomitant aliskiren use in patients with diabetes ■ Known hypersensitivity to either ARBs or ARNIs	■ Kidney impairment: • Mild-to-moderate (eGFR 30-59 mL/min/1.73 m^2): no starting dose adjustment required • Severe* (eGFR <30 mL/min/1.73 m^2): reduce starting dose to 24 mg/26 mg twice daily; double the dose every 2-4 weeks to target maintenance dose of 97 mg/103 mg twice daily, as tolerated ■ Hepatic impairment: • Mild (Child-Pugh class A): No starting dose adjustment required • Moderate (Child-Pugh class B): Reduce starting dose to 24/26 mg twice daily; double the dose every 2-4 weeks to target maintenance dose of 97/103 mg twice daily, as tolerated ■ Renal artery stenosis ■ Systolic blood pressure <100 mm Hg ■ Volume depletion

Maddox, JACC 2024

Angiotensin Converting Enzyme Inhibitors *(*ACEis)

Angiotensin Receptor Blockers (ARBs)

ACE Inhibitors (ACEi): Evidence

ACE Inhibitors (ACEi)						
Pivotal Trials						
Study Name (year)	**Active**	**Control**	**Primary Endpoint**	**HR (95% CI) for primary outcome**	**Mean/median eGFR / CrCl**	**Renal function exclusion (Creatinine (mg/dL))**
CONSENSUS (1987)[20]	Enalapril	Placebo	ACM	0.73	45	> 3.4 mg/dL
SOLVD T (1991)[21]	Enalapril	Placebo	ACM	0.84 (0.74-0.95)	66	> 2.0 mg/dL
SAVE (1992)[35]	Captopril	Placebo	ACM	0.81 (0.68-0.97)	70	> 2.5 mg/dL
AIRE (1993)[36]	Ramipril	Placebo	ACM	0.73 (0.60-0.89)	NA	NA
TRACE (1995)[37]	Trandolapril	Placebo	ACM	0.78 (0.61-0.91)	NA	> 2.3 mg/dL

Beldhuis, Circulation 2022

Angiotensin Receptor Blockers (ARB):Evidence

Angiotensin II Receptor Blockers (ARB)						
Pivotal Trials						
Study Name (year)	**Active**	**Control**	**Primary Endpoint**	**HR (95% CI) for primary outcome**	**Mean/median eGFR**	**Renal function exclusion (Creatinine (mg/dL))**
ValHeFT (2001)[24]	Valsartan	Placebo	ACM	1.02 (0.88-1.18)	58	> 3.4
CHARM-Added (2003)[40]	Candesartan	Placebo	CV Death or HF Hospitalization	0.85 (0.75-0.96)	74	> 3.0
CHARM-Alternative (2003)[41]	Candesartan	Placebo	CV Death or HF Hospitalization	0.77 (0.67-0.89)	68	> 3.0
HEAAL (2009)[42]	Losartan 100 mg	Losartan 50 mg	ACM or HF Hospitalization	0.90 (0.82-0.99)	69	> 2.5

Beldhuis, Circulation 2022

Heart Failure Medication Titration Protocol for ACEis, ARBs

ACEi

	Lisinopril	Captopril	Enalapril	Fosinopril	Ramipril (increase every 3 weeks)
Step 1: Starting Dose	2.5mg daily	6.25mg TID	2.5mg daily	10mg daily	2.5mg daily
Step 2: Week 3	5mg daily	12.5mg TID	5mg daily	20mg daily	7.5mg daily
Step 3: Week 5	10mg daily	25mg TID	10mg daily	40mg daily	7.5mg daily
Step 4: Week 7	20mg daily	50mg TID	10mg BID	-	10mg daily (or 5 mg BID)
Step 5: Week 9	40mg daily	100mg TID	20mg BID	-	-

Titration Protocol for Angiotensin Converting Enzyme Inhibitors (ACEis)

ARB

	Losartan	Valsartan	Candesartan
Conservative Starting Dose*	12.5mg daily	20mg BID	-
Standard Starting Dose*	25mg daily	40mg BID	4mg daily
Step 2: Week 3	50mg daily	80mg BID	8mg daily
Step 3: Week 5	100mg daily	80mg QAM / 160mg QPM	16mg daily
Step 4: Week 7	150mg daily	160mg BID	32mg daily

Titration Protocol for Angiotensin II Receptor Blockers (ARBs)

* Consider conservative starting dose if patient at higher risk for hypotension (elderly, DM, etc.)

Used for VA Clinician Guidance

University of Idaho School of Health and Medical Professions

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Worsening Renal Dysfunction

- "Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose"*
- Increase in creatinine of > 30%.
  - Consider underlying causes that can be reversed.
  - If none are reversible then reduce dose or stop ACE inhibitor.

Reasons for Increased Creatinine with ACEi/ARB/ARNi
Renal artery stenosis
Volume depletion
polycystic kidney disease
Severe heart failure
Worsening cirrhosis
Intercurrent illness
Acute renal disease (ATN)
Intrarenal vascular disease

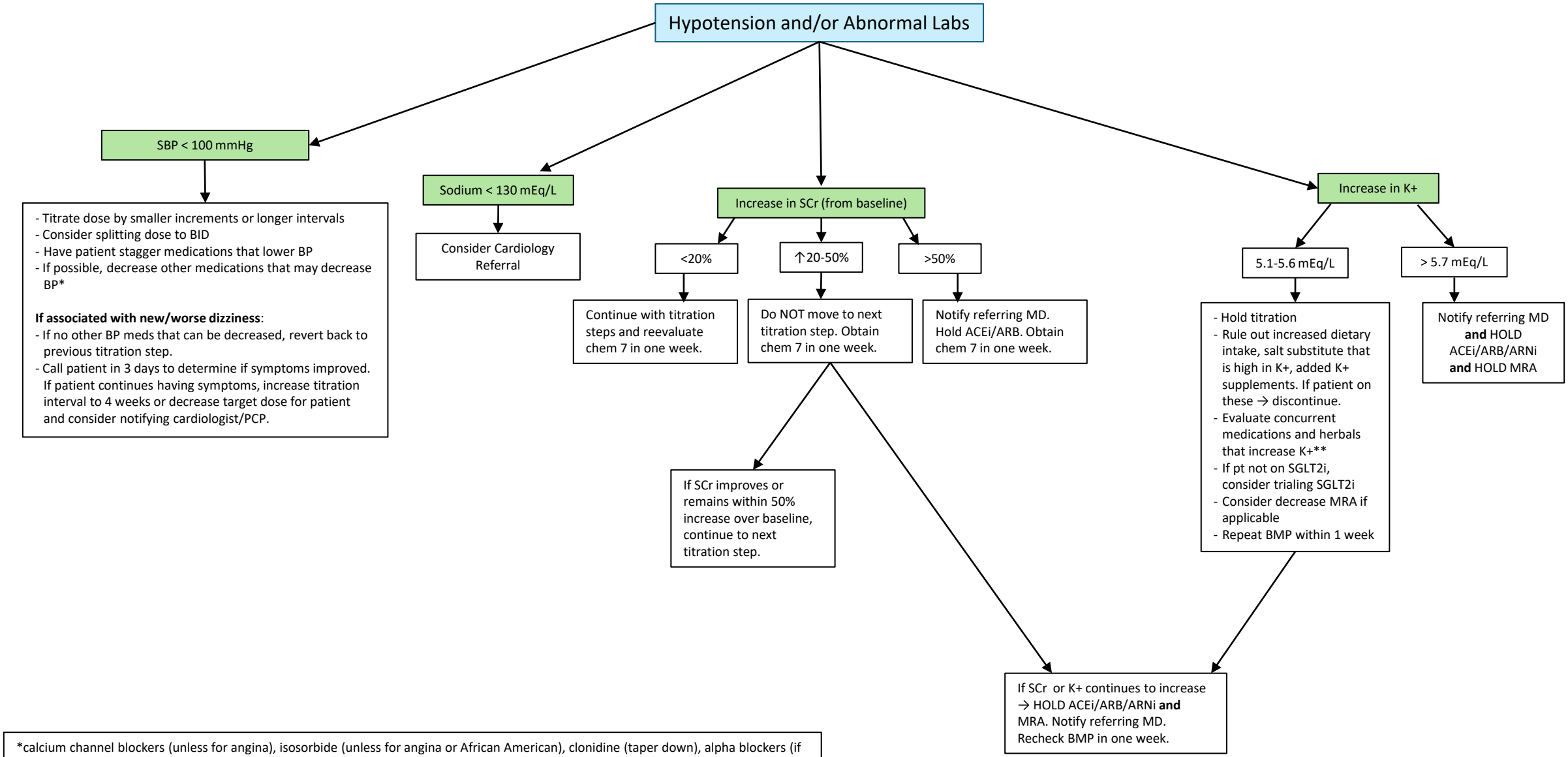
*KDIGO 2024 Treatment Guideline for Chronic Kidney Disease, Kidney Int, 2024.

Less Conservative Approach to Decrease in Kidney Function:

Δ serum creatinine (%)	Max serum creatinine (mg/dL)	Min eGFR mL/min/1.73m²	Max serum potassium (mmol/L)	Action advised
< 50	2.5 mg/dL	30	5.0	None, uptitrate and evaluate renal function and electrolytes
50-100	3.5 mg/dL	20	5.5	Evaluate clinical status and other causes of WRF. Consider halving med and re-evaluate
> 100	> 3.5 mg/dL	< 20	> 5.5	Evaluate clinical status and other causes of WRF. Consider stopping med and re-evaluate
Rechallenge after 2-4 weeks (if possible at lower dose) when dosing reduced or stopped all together if renal function has improved				

Adapted from Beldhuis, Circulation 2022

Managing Hypotension or Abnormal Labs: ACEis, ARBs, and ARNi



*calcium channel blockers (unless for angina), isosorbide (unless for angina or African American), clonidine (taper down), alpha blockers (if doxazosin, switch to tamsulosin). Consider reducing these non-GDMT meds for any patient with SBP<120 to allow room for uptitration of GDMT.
**Including but not limited to triamterene, amiloride, NSAIDs, TMP/SMX, & select herbals (noni juice, alfalfa, dandelion, horsetail, nettle, chan su, milkweed, lily of the valley, siberian ginseng, hawthorn berry)

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Beta-Blockers

Beta-Blockers for Symptomatic Heart Failure

Recommendation for Beta Blockers Referenced studies that support the recommendation are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendation**
1	A	1. In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality (eg, bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations.[1–3]
Value Statement: High Value (A)		2. In patients with HFrEF, with current or previous symptoms, beta-blocker therapy provides high economic value.[4–8]

Circulation, 2022 ACC/AHA/HFSA Guideline

Beta-Blockers in HF and Reduced LVEF: Evidence

Trial	Year	Type of β-Blockers	n° of Patients	Inclusion Criteria	Effects on Mortality
CIBIS	1994	Bisoprolol	641	LVEF < 40%, NYHA class III-V	No significant difference in mortality between the two groups
MERIT HF	1999	Metoprolol	3991	LVEF < 40%, NYHA class II-IV	34% relative risk reduction in all-cause mortality
CIBIS II	1999	Bisoprolol	2647	LVEF < 35%, NYHA class III-IV	34% relative risk reduction in all-cause mortality
CAPRICORN	2001	Carvedilol	1959	Previous AMI and LVEF < 40%	23% relative risk reduction in all-cause mortality
COPERNICUS	2001	Carvedilol	2289	LVEF < 25% and NYHA class III-IV	31% relative risk reduction in all-cause mortality
COMET	2003	Metoprolol vs Carvedilolo	2309	LVEF < 35% and NYHA class II-IV	17% relative risk reduction in all-cause mortality in carvedilol group
SENIORS	2005	Nebivolol	2128	LVEF < 35%, NYHA class II-IV, age > 7o years	No significant difference in mortality between the two groups

Masarone J Cardiovas Develop Dis 2021

Heart Failure Medication Titration Protocol for Beta-Blockers

Contraindications:

- 2nd or 3rd degree heart block, sick sinus syndrome, or severe bradycardia (without pacemaker)
- Decompensated heart failure requiring inotropic therapy

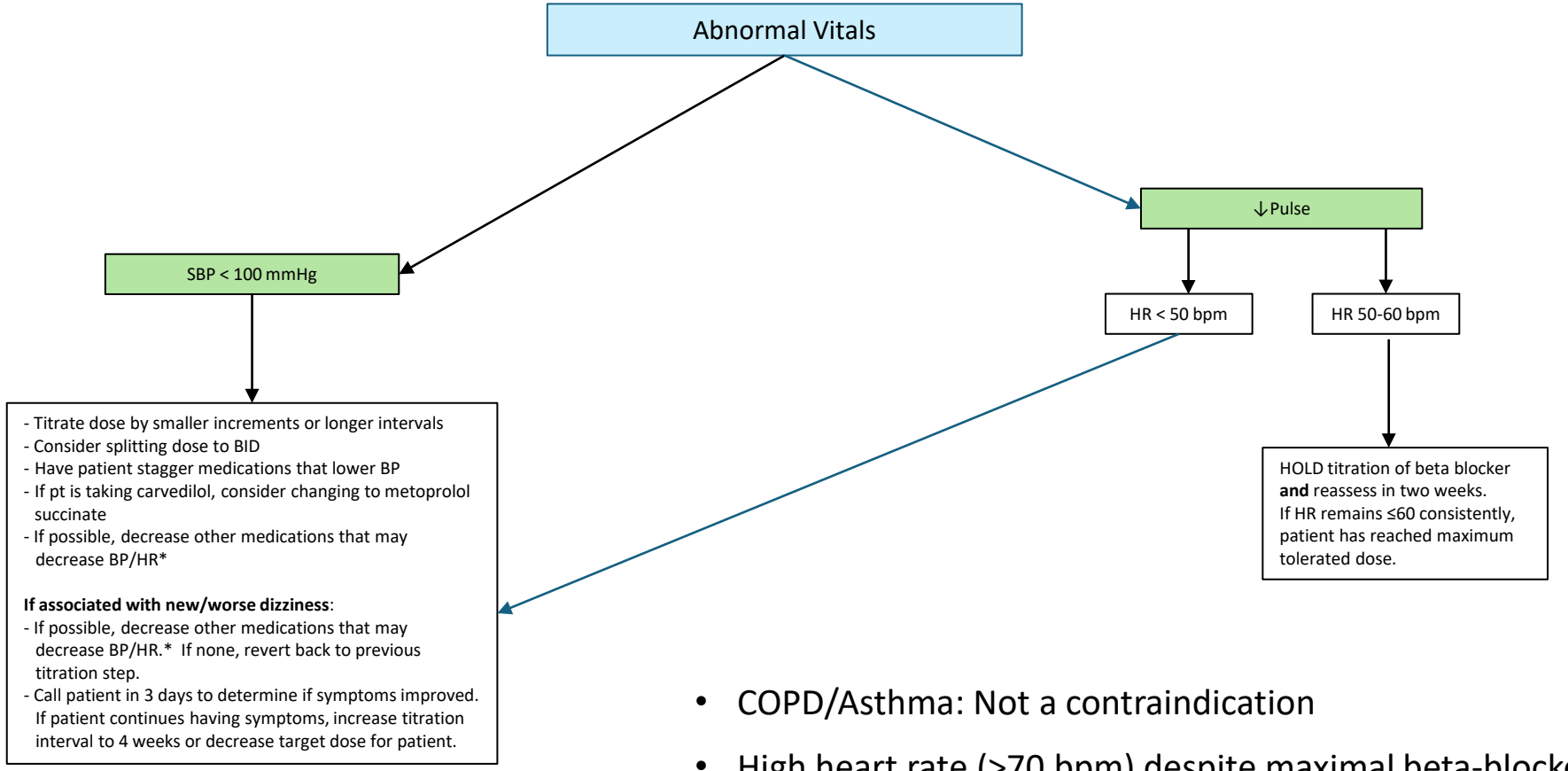
Monitoring:

- Electrocardiogram (prior to initiation, within two years)
- Depression: If depression *worsens* after starting/increasing BB 1) offer Mental Health Services- discuss continued titration 3) assess for suicidality.

	Carvedilol	Metoprolol Succinate	Bisoprolol
Step 1: Starting Dose	3.125mg BID	12.5mg daily	1.25mg daily
Step 2: Week 3	6.25mg BID	25mg daily	2.5mg daily
Step 3: Week 5	12.5mg BID	50mg daily	5mg daily
Step 4: Week 7	25mg BID	100mg daily	10mg daily
Step 5: Week 9	50mg BID (if > 85 kg)	200mg daily	-

Used for VA Clinician Guidance

Beta-Blockers with Hypotension, Bradycardia



- COPD/Asthma: Not a contraindication
- High heart rate (>70 bpm) despite maximal beta-blocker: ivabradine

*calcium channel blockers (unless necessary for angina, etc.), isosorbide (unless for angina or African American), clonidine (titrate down), alpha blockers (if doxazosin, switch to tamsulosin). Consider reducing these non-GDMT meds for any patient with SBP<120 to allow room for uptitration of GDMT.

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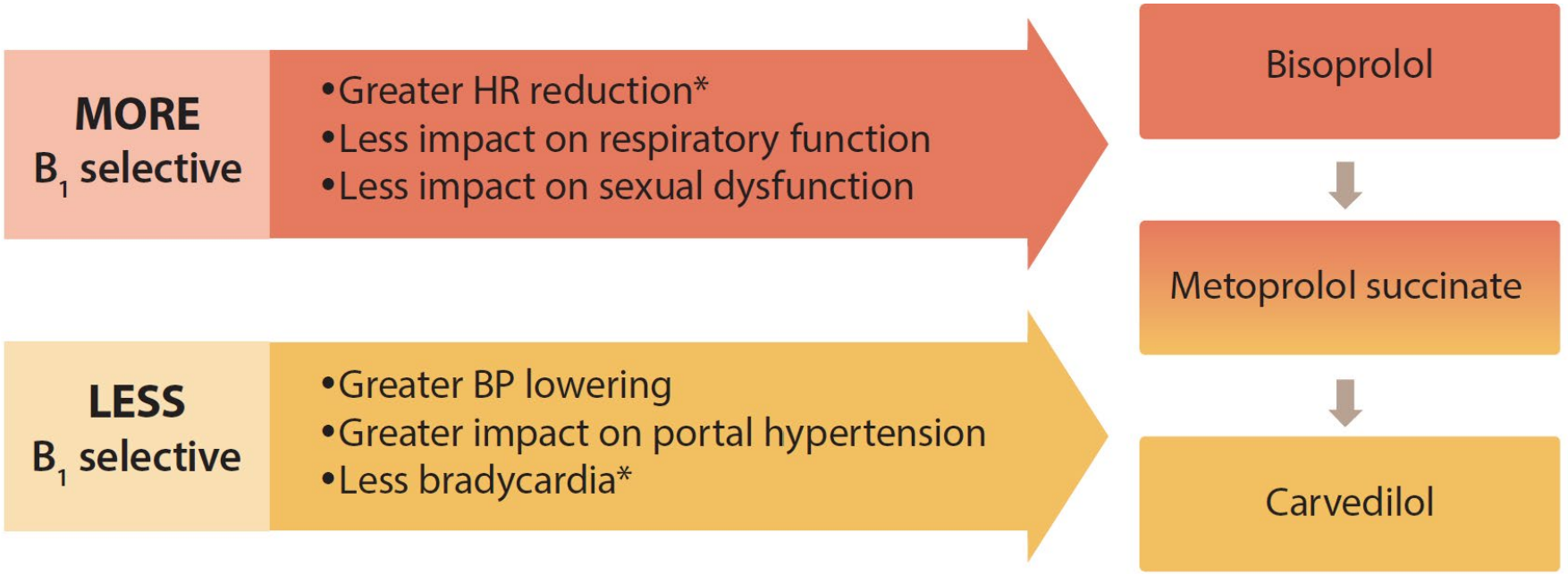
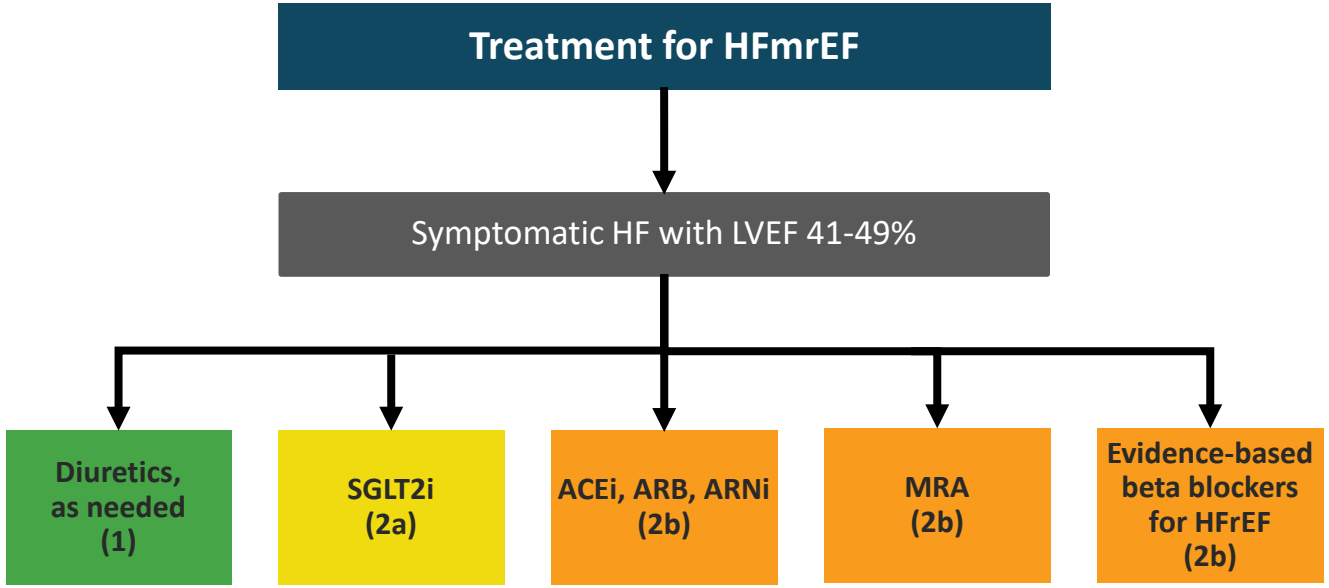
Beta-Blockers



Bristow, Circulation 2000

HFmrEF and HFpEF

RECOMMENDATIONS FOR PATIENTS WITH MILDLY REDUCED LVEF



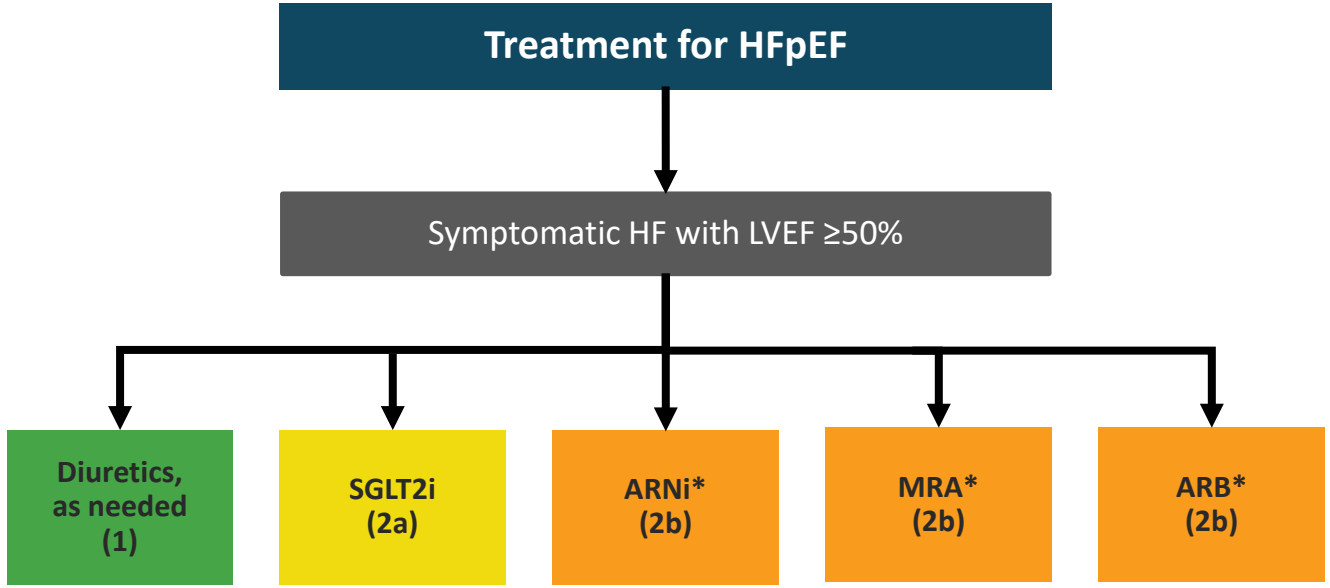
Patients With HFimpEF

COR	RECOMMENDATIONS
1	1. In patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (1)

American Heart Association.

Heidenreich, Circulation, 2022

RECOMMENDATIONS FOR PATIENTS WITH PRESERVED LVEF

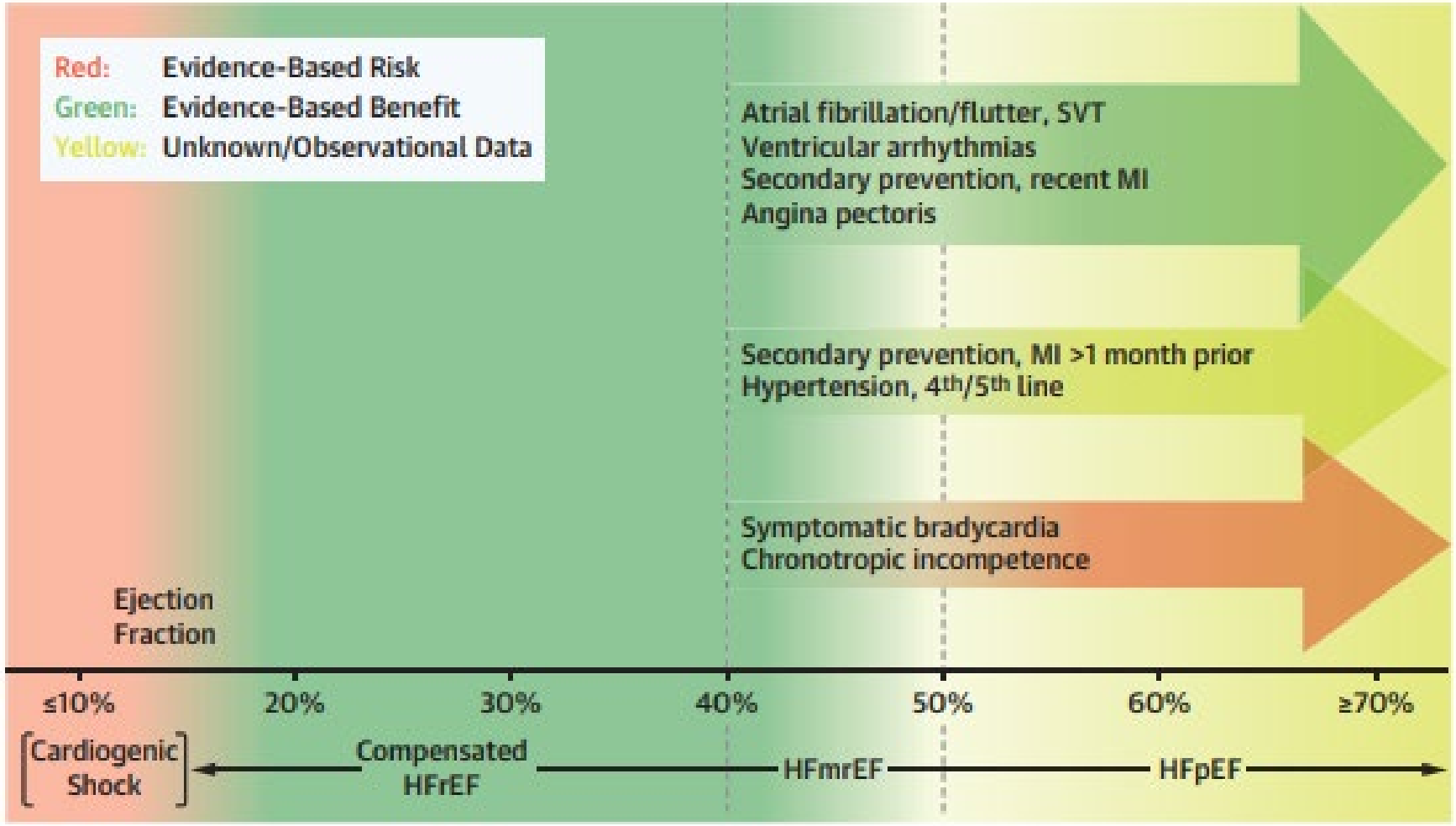


NOTE: *Greater benefit in patients with LVEF closer to 50%

Abbreviations: ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium- glucose cotransporter 2 inhibitor.

Heidenreich, Circulation, 2022

Beta-Blockers Effect by LVEF



Arnold SV, et al. J Am Coll Cardiol HF. 2023;11(8):893-900.

When to Consider Referral to Cardiology?

- Persistent NYHA functional class III-IV symptoms of congestion or profound fatigue
- Systolic blood pressure <90 mm Hg or symptomatic hypotension
- Creatinine >1.8 mg/dL or BUN >43 mg/dL
- Onset of atrial fibrillation, ventricular arrhythmias, or repetitive ICD shocks
- 2 or more emergency department visits or hospitalizations for worsening HF in the prior 12 months
- Inability to tolerate optimally doses of medications.

Key Points

- ARNi first line (good value at current prices)
  - Best choice for fluid overloaded patients with adequate blood pressure
- Small creatinine bump (<30%) is OK (do not need to cut dose).
- Titration of medications at least every 2 weeks.
- Side effects are common but usually manageable without medication withdrawal.
- Consider use of pharmacists and other clinical staff to assist.

THANK YOU

References

- 2022 ACC/AHA/HFSA Heart Failure Guideline: https://pubmed.ncbi.nlm.nih.gov/35363499/
- 2023 ACC Expert Clinical Guidance for HFpEF: https://pubmed.ncbi.nlm.nih.gov/37137593/
- 2024 ACC Expert Clinical Guidance for HFrEF: https://pubmed.ncbi.nlm.nih.gov/38466244/