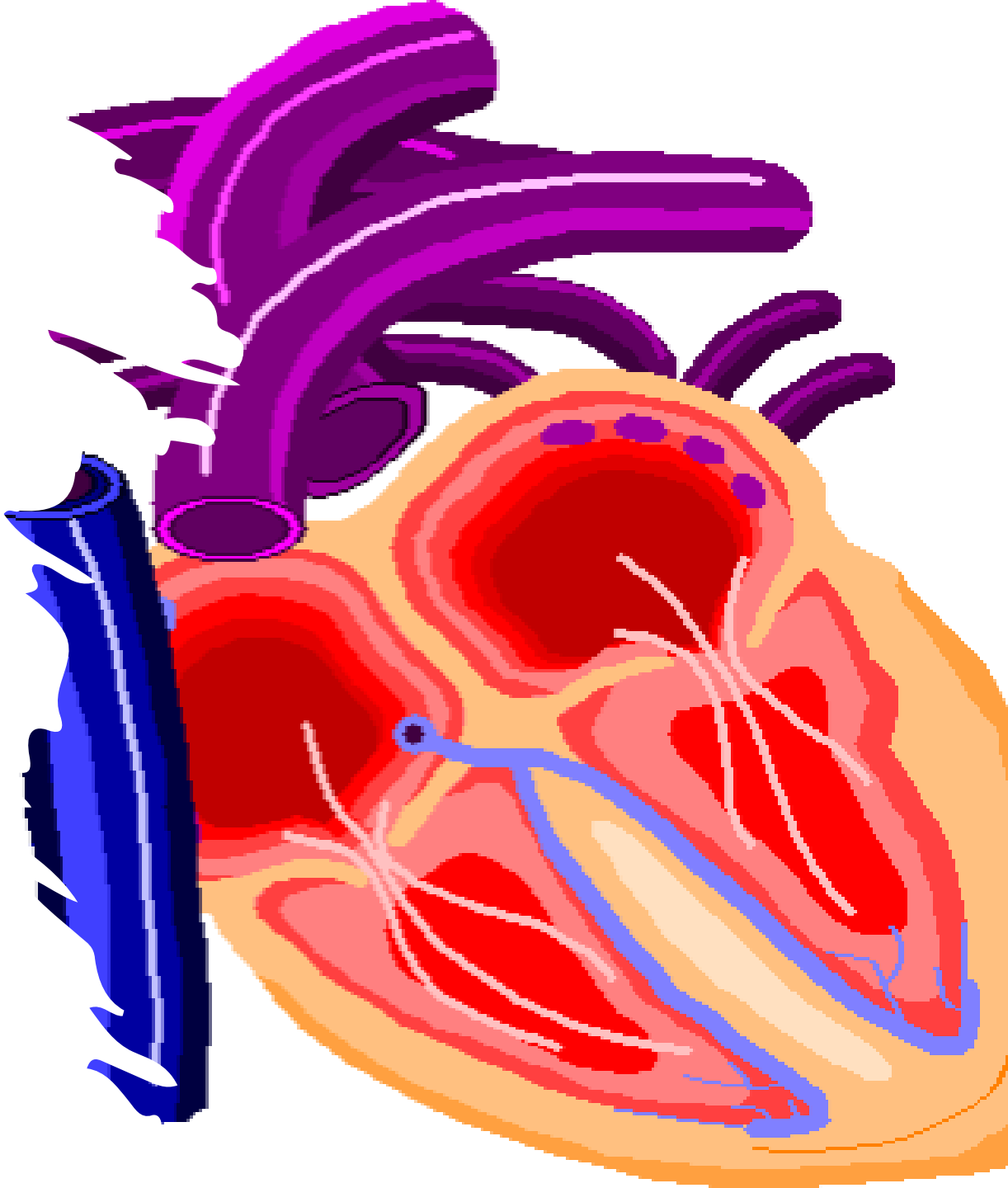
Update on the Pharmacologic Management of Heart Failure

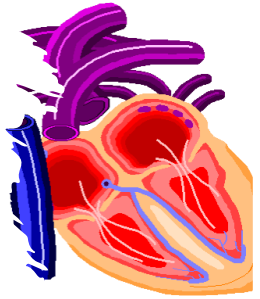
Adrienne Z Ables, PharmD, MS (MedEdL), FNAOME

SCAFP Annual Assembly

June 10, 2022

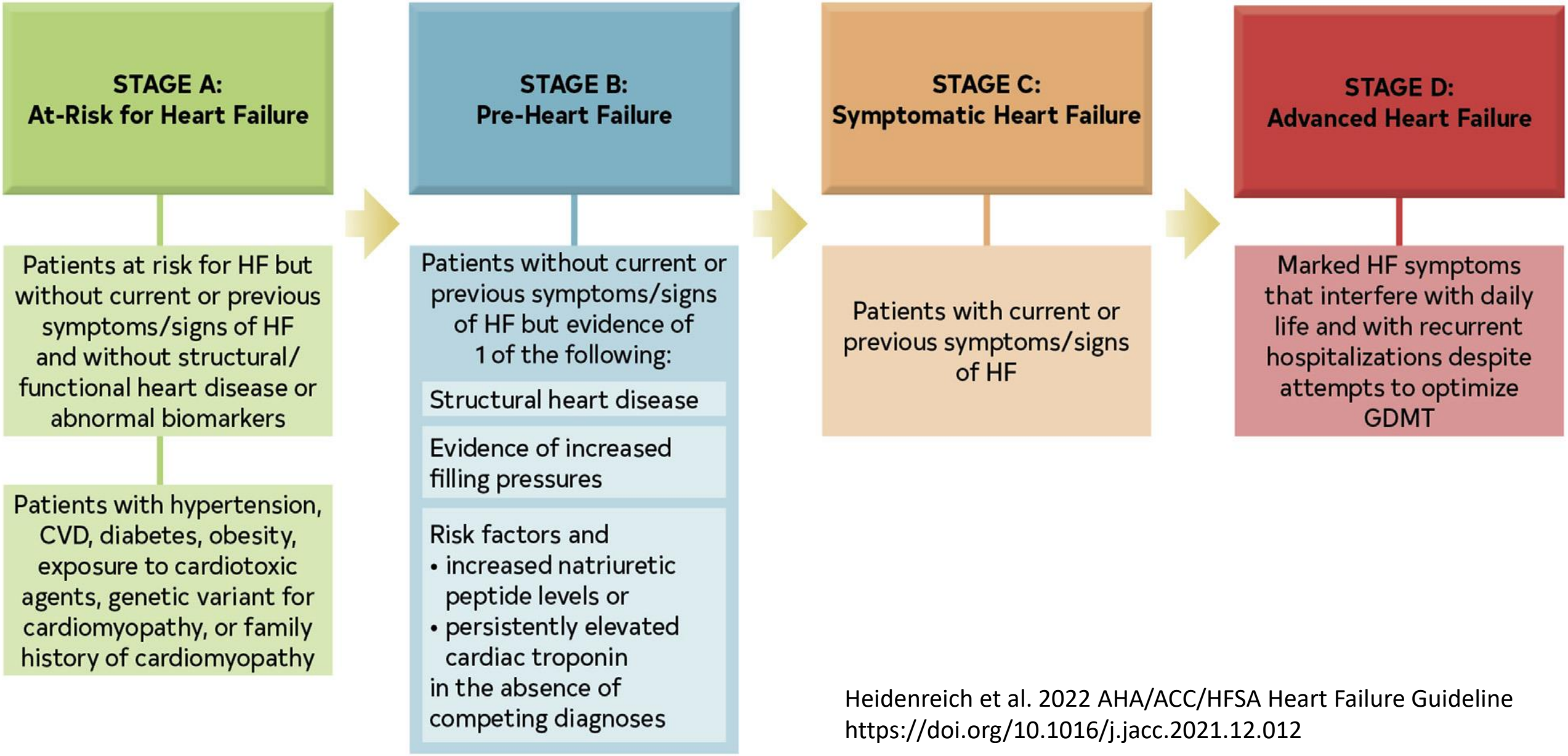


Learning Outcomes



- Identify drugs that are of benefit in patients with heart failure with reduced ejection fraction (HFrRF), with a focus on newer agents.
- Optimize treatment of patients with heart failure using Guideline-Directed Medical Therapy (GDMT)
- Recognize adverse effects, drug interactions, and monitoring parameters for patients on GDMT for heart failure

ACC/AHA Stages of HF



Heidenreich et al. 2022 AHA/ACC/HFSA Heart Failure Guideline
https://doi.org/10.1016/j.jacc.2021.12.012

Table 2. Clinical Classifications of Heart Failure Severity.*

NYHA Functional Classification		ACC–AHA Stages of Heart Failure	
Class I	No limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea	Stage A	At high risk for heart failure; no identified structural or functional abnormality; no signs or symptoms
Class II	Slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea	Stage B	Developed structural heart disease that is strongly associated with the development of heart failure but without signs or symptoms
Class III	Marked limitation of physical activity; comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea	Stage C	Symptomatic heart failure associated with underlying structural heart disease
Class IV	Unable to carry on any physical activity without discomfort; symptoms present at rest; if any physical activity is undertaken, discomfort is increased	Stage D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy

* The American College of Cardiology (ACC)–American Heart Association (AHA) classification is from Hunt et al.[8] The New York Heart Association (NYHA) functional classification is from the Criteria Committee of the New York Heart Association.[12]

New Engl J Med. 2010;362:228-38.

Desired outcomes

- Improve quality of life
- Relieve or reduce symptoms
- Prevent or minimize hospitalizations
- Slow disease progression
- Prolong survival

Renin-Angiotensin System Inhibition

What we know

- RCTs clearly establish the benefits of ACE inhibition in patients with mild, moderate, or severe symptoms of HF

- ARBs have been shown to reduce mortality and HF hospitalizations in patients with HFrEF in large RCTs

What's new (-ish)?

- In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality

Sacubitril

- **MOA:** inhibits neprilysin which increases levels of peptides that are normally degraded by neprilysin

- more vasodilation and sodium loss; less cardiac and vascular hypertrophy and remodeling

- Available in combination with valsartan

- **Indicated** to reduce the risk of cardiovascular death and hospitalization for heart failure
- **Contraindicated** with history of ACEI-angioedema
- **AEs: hypotension**, hyperkalemia, cough, dizziness, and renal failure
- **DIs:** K+ sparing drugs, NSAIDs, Lithium

The Evidence: sacubitril/valsartan

- Prevents one CV death or heart failure hospitalization for every 21 patients treated over 2 years versus enalapril 10mg bid

BUT

- 1 in 21 patients have hypotension symptoms with *Entresto* versus enalapril
- 1 in 77 have a systolic BP < 90mmHg

McMurray JJ, Packer M, Desai AS, et al. *N Engl J Med*. 2014;371:993–1004.

Prescribing sacubitril/valsartan

- Allow a washout period of 36 hours when switching from an ACEi to ARNi
- Starting dose: 49/51 mg orally twice-daily
  - Start with half dose if eGFR < 30 mL/min/1.73 m2
- Double the dose after 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated

- Observe for signs and symptoms of angioedema and hypotension
- Monitor renal function and potassium
- When pregnancy is detected, discontinue as soon as possible

Target doses

Drug	Initial Daily Dose(s)	Target Doses(s)	Mean Doses Achieved in Clinical Trials
ACEI			
Captopril	6.25 mg 3 times daily	50 mg 3 times daily	122.7 mg total daily
Enalapril	2.5 mg twice daily	10–20 mg twice daily	16.6 mg total daily
Fosinopril	5–10 mg once daily	40 mg once daily	NA
Lisinopril	2.5–5 mg once daily	20–40 mg once daily	32.5–35.0 mg total daily
Perindopril	2 mg once daily	8–16 mg once daily	NA
Quinapril	5 mg twice daily	20 mg twice daily	NA
Ramipril	1.25–2.5 mg once daily	10 mg once daily	NA
Trandolapril	1 mg once daily	4 mg once daily	NA
ARB			
Candesartan	4–8 mg once daily	32 mg once daily	24 mg total daily
Losartan	25–50 mg once daily	50–150 mg once daily	129 mg total daily
Valsartan	20–40 mg once daily	160 mg twice daily	254 mg total daily
ARNi			
Sacubitril-valsartan	49 mg sacubitril and 51 mg valsartan twice daily (therapy may be initiated at 24 mg sacubitril and 26 mg valsartan twice daily)	97 mg sacubitril and 103 mg valsartan twice daily	182 mg sacubitril and 193 mg valsartan total daily

Beta-Blockers

What we know

- Treatment reduces the risk of death and the combined risk of death or hospitalization in patients with HFrEF
- Use of 1 of 3 beta blockers is recommended to reduce mortality and hospitalizations
  - Bisoprolol
  - Carvedilol
  - Metoprolol succinate (sustained-release)

Cardiac Insufficiency Authors. Lancet. 1999;353:9–13.
MERIT-HF Study Group. Lancet. 1999;353:2001–2007.
Packer M, et al. Circulation. 2002;106:2194–2199.

Target doses

Beta blockers			
Bisoprolol	1.25 mg once daily	10 mg once daily	8.6 mg total daily
Carvedilol	3.125 mg twice daily	25–50 mg twice daily	37 mg total daily
Carvedilol CR	10 mg once daily	80 mg once daily	NA
Metoprolol succinate extended release (metoprolol CR/XL)	12.5–25 mg once daily	200 mg once daily	159 mg total daily

Mineralocorticoid Receptor Antagonists (MRAs)

What we know

- In patients with HFrEF who are symptomatic despite RAS inhibition and beta blockade, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality
  - eGFR is >30 mL/min/1.73 m^2
  - Serum potassium is <5.0 mEq/L

Pitt B, Zannad F, Remme WJ, et al. *N Engl J Med*. 1999;341:709–717.
Zannad F, McMurray JJ, Krum H, et al. *N Engl J Med*. 2011;364:11–21.

Target doses

Mineralocorticoid receptor antagonists			
Spironolactone	12.5–25 mg once daily	25–50 mg once daily	26 mg total daily
Eplerenone	25 mg once daily	50 mg once daily	42.6 mg total daily

SGLT2 inhibition

What we know

- Type 2 diabetes mellitus – glycemic control
- Type 2 diabetes mellitus with CV disease – decrease hospitalizations for HF
- Chronic kidney disease at risk of progression

What's new?

- In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality
  - Irrespective of the presence of type 2 diabetes

SGLT2 inhibitors

- **MOA:** Inhibit renal glucose reabsorption facilitated by sodium glucose co-transporter 2
- **Indications:** to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with HFrEF
- **CIs**: Do not start with eGFR < 25 ml/min/1.73 m2
- **AEs:** genital fungal infections, urinary tract infection, increased urination, hypotension

The Evidence: SGLT2i

DAPA-HF

- Reduced the composite endpoint of worsening HF (hospitalization or urgent visit requiring intravenous therapy) or CV death
- NNT = 21
- NNT ~18 patients with DM
- NNT ~22 patients without DM

EMPEROR

- Reduced the composite endpoint of hospitalizations for HF or CV death
- NNT = 19
- NNT ~14 patients with DM
- NNT ~26 patients without DM

Prescribing SGLT2i

- Before initiating SGLT2i assess volume status and renal function
  - elderly
  - renal impairment
  - low systolic blood pressure
  - patients on diuretics

- Starting dose = target dose
- Monitor blood pressure
- Not recommended in pregnancy

Target doses

SGLT2i			
Dapagliflozin	10 mg once daily	10 mg once daily	9.8 mg total daily
Empagliflozin	10 mg once daily	10 mg once daily	NR

Hydralazine/Isosorbide Dinitrate

What we know

- For patients self-identified as African American with NYHA class III-IV HFrEF who are receiving optimal medical therapy, the combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality

Taylor AL, Ziesche S, Yancy C, et al. *N Engl J Med.* 2004;351:2049–2057.

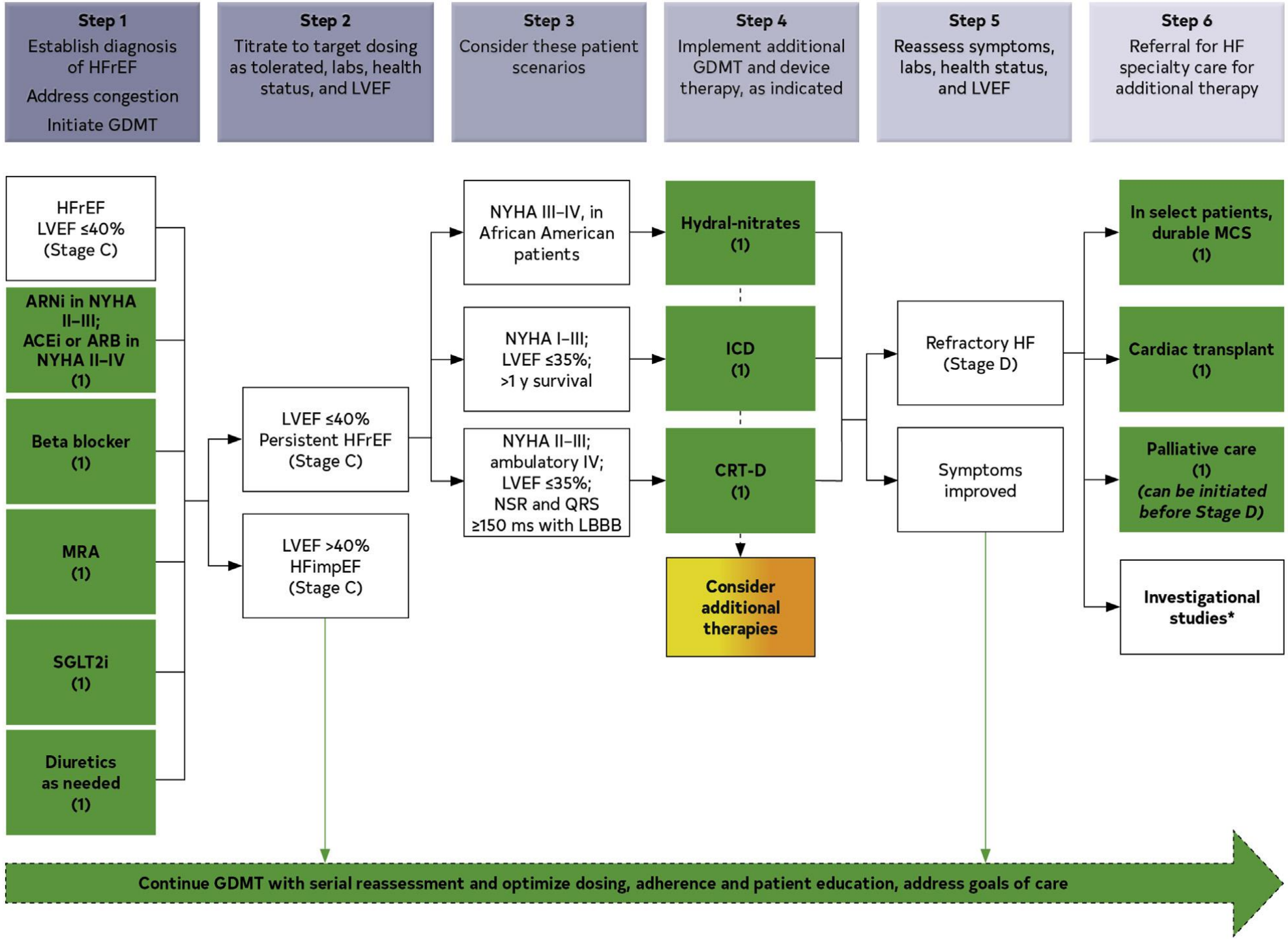
Target doses

Isosorbide dinitrate and hydralazine			
Fixed dose combination	20 mg isosorbide dinitrate and 37.5 mg hydralazine 3 times daily	40 mg isosorbide dinitrate and 75 mg hydralazine 3 times daily	90 mg isosorbide dinitrate and ~175 mg hydralazine total daily
Isosorbide dinitrate and hydralazine	20–30 mg isosorbide dinitrate and 25–50 mg hydralazine 3–4 times daily	120 mg isosorbide dinitrate total daily in divided doses and 300 mg hydralazine total daily in divided doses	NA

Diuretics

What we know

- In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF (LOE = B)
- Loop diuretics are the preferred diuretic agents for use in most patients with HF
- Effects of diuretics on morbidity and mortality are uncertain


Step 1
Establish diagnosis of HFrEF
Address congestion
Initiate GDMT
Step 2
Titrate to target dosing as tolerated, labs, health status, and LVEF
Step 3
Consider these patient scenarios
Step 4
Implement additional GDMT and device therapy, as indicated
Step 5
Reassess symptoms, labs, health status, and LVEF
Step 6
Referral for HF specialty care for additional therapy
HFrEF
LVEF ≤40%
(Stage C)
ARNi in NYHA II–III;
ACEi or ARB in NYHA II–IV
(1)
Beta blocker
(1)
MRA
(1)
SGLT2i
(1)
Diuretics as needed
(1)
LVEF ≤40%
Persistent HFrEF
(Stage C)
LVEF >40%
HFimpEF
(Stage C)
NYHA III–IV, in African American patients
NYHA I–III;
LVEF ≤35%;
>1 y survival
NYHA II–III;
ambulatory IV;
LVEF ≤35%;
NSR and QRS ≥150 ms with LBBB
Hydral-nitrates
(1)
ICD
(1)
CRT-D
(1)
Consider additional therapies
Refractory HF
(Stage D)
Symptoms improved
In select patients, durable MCS
(1)
Cardiac transplant
(1)
Palliative care
(1)
(can be initiated before Stage D)
Investigational studies*
Continue GDMT with serial reassessment and optimize dosing, adherence and patient education, address goals of care

Cost comparison

Triple Therapy

ACEi/ARB + BB + MRA =

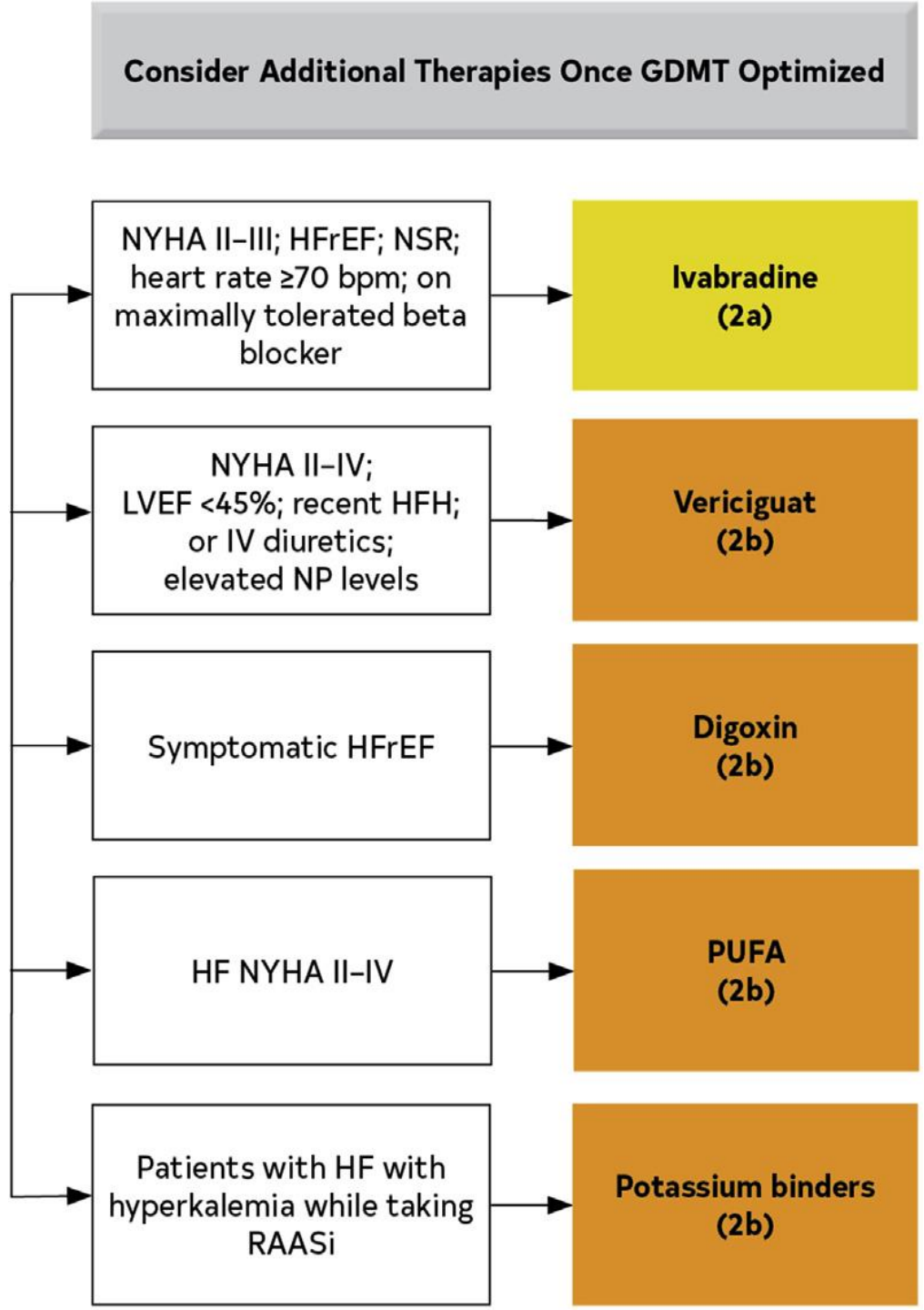
< $30/month

QUAD Therapy

- ARNi + BB + MRA + SGLT2i =
- > $1,200/month

Recommendations - HFrEF

- Continue to focus on optimizing traditional triple therapy
  - Aim for target doses
- If patients still have heart failure symptoms, consider switching from an ACEI or ARB to ARNi (sacubitril/valsartan)
- If symptomatic patients are already on optimized triple therapy with sacubitril/valsartan consider adding an SGLT2 inhibitor, esp. if they have diabetes
  - May want to lower diuretic dose
- Avoid NSAIDs, diltiazem, alogliptin, saxagliptin, pioglitazone, verapamil, nifedipine, sotalol, dronedarone, alpha-1 blockers


Consider Additional Therapies Once GDMT Optimized
NYHA II–III; HFrEF; NSR; heart rate ≥70 bpm; on maximally tolerated beta blocker
Ivabradine (2a)
NYHA II–IV; LVEF <45%; recent HFH; or IV diuretics; elevated NP levels
Vericiguat (2b)
Symptomatic HFrEF
Digoxin (2b)
HF NYHA II–IV
PUFA (2b)
Patients with HF with hyperkalemia while taking RAASi
Potassium binders (2b)

Ivabradine

What we know

- For patients with symptomatic chronic HFrEF on GDMT
  - including a beta blocker at maximum tolerated dose AND
  - in sinus rhythm with a heart rate of ≥70 bpm at rest
- Ivabradine may reduce HF hospitalizations and cardiovascular death

Ivabradine

- **MOA:** Inhibits the I_f or “funny” current
- Decreases heart rate
- Does not affect blood pressure
- **AEs:** Atrial fibrillation NNTH = 100; bradycardia
- May cause a temporary brightness in the field of vision
  - “phosphenes” usually occur within the first 2 months of therapy
  - resolve on their own even with continued use

- **DIs:** CYP3A4 inhibitors
- **Target dose:** 7.5 mg BID

The Evidence: Ivabradine

- Evidence: may reduce hospitalizations in patients with **HF*r*EF** who still have symptoms AND a heart rate ≥ 70 bpm
- NNT_2 = 25 hospitalization
- NNT_2 = 50 HF death

- *LOE B*

Vericiguat

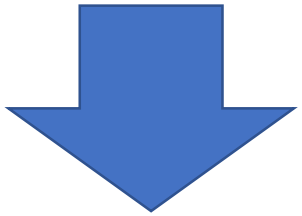
What's new?

- In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator may be considered to reduce HF hospitalization and CV death

- *LOE B*

Vericiguat

- **MOA:** directly binds and stimulates sGC and increases cGMP production



- vasodilation, improvement in endothelial function, decrease in fibrosis and remodeling of the heart

- **CIs:** Pregnancy
- **AEs:** hypotension, anemia
- **DIs:** PDE-5 inhibitors – hypotension

- **Target dose:** 10 mg once daily

The Evidence: VICTORIA

- n= 5050 higher-risk patients with worsening HFrEF (LVEF <45%, NYHA class II to IV) to vericiguat versus placebo
- On GDMT
- Elevated natriuretic peptides (BNP ≥ 300 pg/mL or NTproBNP ≥ 1000 pg/mL
- Recent HF worsening
  - Hospitalized within 6 months
  - Recently received intravenous diuretic therapy without hospitalization
- Median follow-up 10.8 months

VICTORIA

Primary outcome: CV death or HF hospitalization

- 35.5% with vericiguat
- 38.5% with placebo

- NNT = 33

All-cause mortality:

- 20.3% with vericiguat
- 21.2% with placebo

- NNT = 111

Digoxin

What we know

- In patients with symptomatic HFrEF despite GDMT (or who are unable to tolerate GDMT), digoxin might be considered to decrease hospitalizations for HF

- *LOE B*

The Evidence: Digoxin

- Treatment with digoxin for 2 to 5 years had no effect on mortality but modestly reduced the combined risk of death and hospitalization
  - 0.5 – 0.9 ng/mL therapeutic in HF

- Predated current GDMT

Digitalis Investigation Group. *N Engl J Med*. 1997;336:525–533.

Digoxin

TABLE 4-13 Signs and Symptoms of Digoxin Toxicity

Noncardiac (mostly CNS) adverse effects

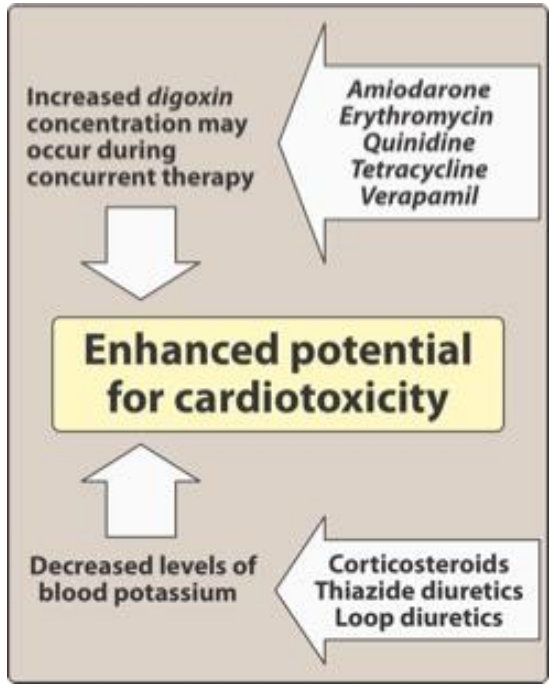
Anorexia, nausea, vomiting, abdominal pain
Visual disturbances
Halos, photophobia, problems with color perception (i.e., red-green or yellow-green vision), scotomata
Fatigue, weakness, dizziness, headache, neuralgia, confusion, delirium, psychosis

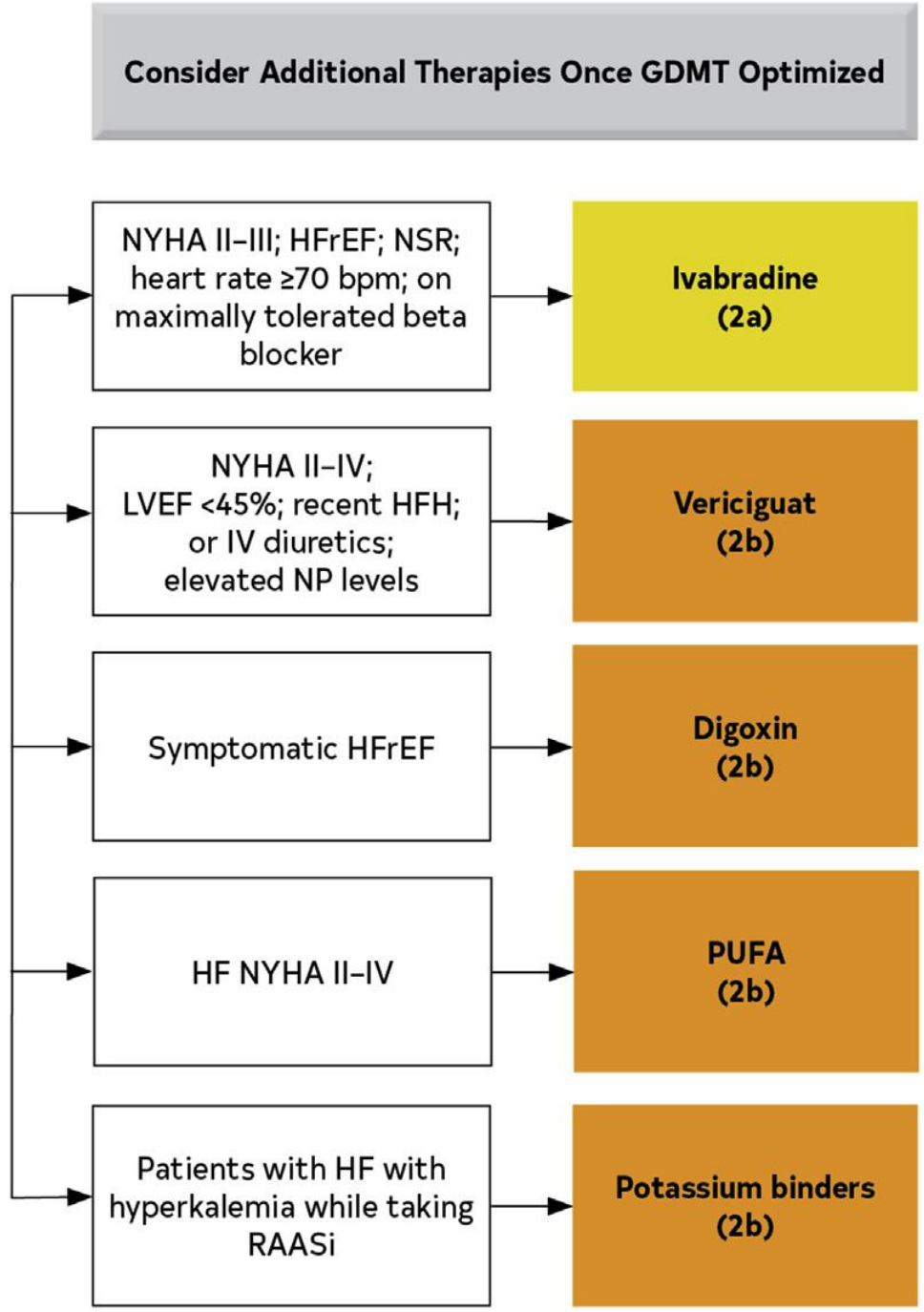
Cardiac adverse effects[a,b]

Ventricular arrhythmias
Premature ventricular depolarizations, bigeminy, trigeminy, ventricular tachycardia, ventricular fibrillation
Atrioventricular (A-V) block
First degree, second degree (Mobitz type I), third degree
A-V junctional escape rhythms, junctional tachycardia
Atrial arrhythmias with slowed A-V conduction or A-V block particularly paroxysmal atrial tachycardia with A-V block
Sinus bradycardia

[a]Some adverse effects may be difficult to distinguish from the signs/symptoms of heart failure.
[b]Digoxin toxicity has been associated with almost every known rhythm abnormality (only the more common manifestations are listed).

- Eliminated unchanged via kidneys
- Large V_D (body stores in the skeletal muscle)
- Narrow therapeutic window

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Medication adherence apps

MyMedSchedule Plus 12+

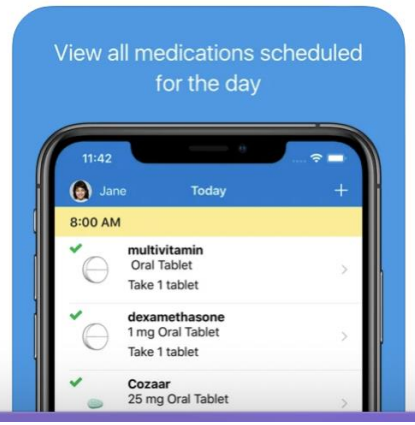
Med Reminder & Pill Organizer

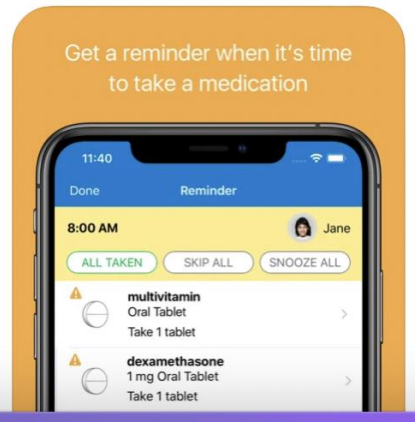
MedActionPlan.com

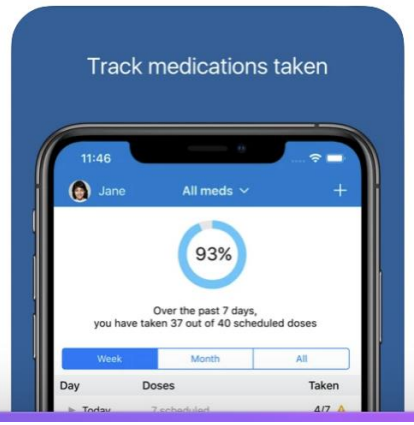
★★★★☆ 3.9 • 62 Ratings

Free

iPhone Screenshots







Non-Pharmacologic Interventions

- Multidisciplinary care team
- Vaccinations
- Exercise

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Summer Break Away & Annual Assembly

June 9-12, 2022

Wild Dunes Resort, Isle of Palms, SC