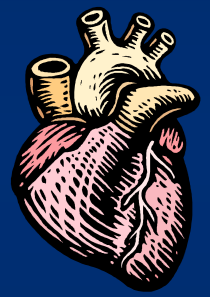
Heart Failure Medication Management



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Objectives

- Define heart failure and review classifications
- Summarize key drug therapy recommendations from the American College of Cardiology Foundation/ American Heart Association guidelines
- Evaluate drug therapy options in the outpatient management of heart failure

Heart Failure Guidelines

- American College of Cardiology Foundation/American Heart Association (ACCF/AHA) (2013)
  - Available at www.acc.org and www.americanheart.org
- Heart Failure Society of America (2010)
  - Available at www.hfsa.org

Heart Failure
Definition

- Complex clinical syndrome that results from any structural or functional impairment of ventricular filing or ejection of blood

- Cardinal manifestations: dyspnea, fatigue, and fluid retention

ACCF/AHA 2013

Definition of Heart Failure

Classification	Ejection Fraction	Description
I. Heart Failure with Reduced Ejection Fraction (HF*r*EF)	≤40%	Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HF*r*EF and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart Failure with Preserved Ejection Fraction (HF*p*EF)	≥50%	Also referred to as diastolic HF. Several different criteria have been used to further define HF*p*EF. The diagnosis of HF*p*EF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HF*p*EF, Borderline	41% to 49%	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patient with HF*p*EF.
b. HF*p*EF, Improved	>40%	It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

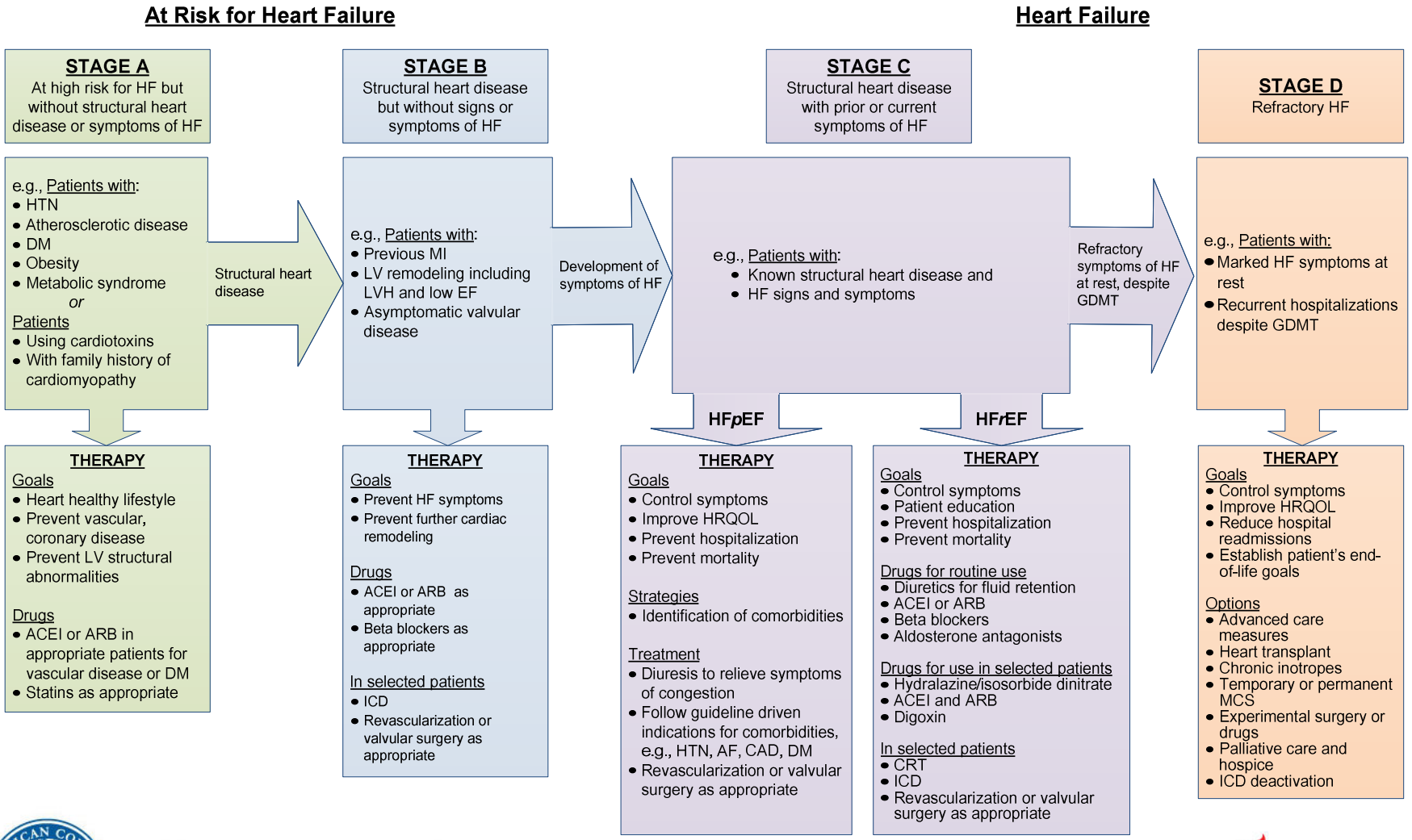
Heart Failure Classifications

Important: Guides Place in Therapy for Medications

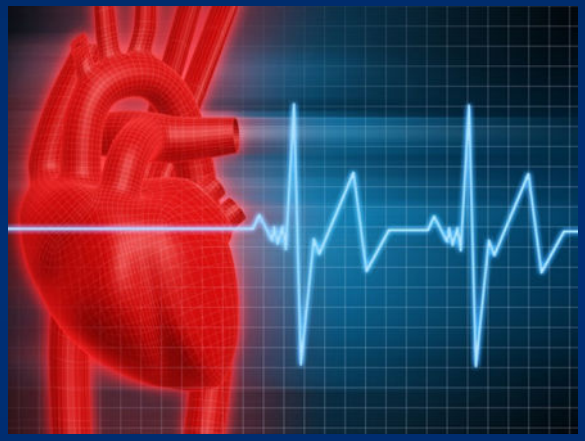
Classification of Heart Failure

ACCF/AHA Stages of HF		NYHA Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of HF.	None	
B	Structural heart disease but without signs or symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
D	Refractory HF requiring specialized interventions.		

Stages, Phenotypes and Treatment of HF



Treatment of Stages A to C



Guideline-Directed Medical Therapy (GDMT):
Represents optimal medical therapy as defined by ACCF/AHA guideline-recommend therapies (primarily Class I)

Classification of Recommendations and Levels of Evidence

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B It is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/ efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

Recommendations for the Treatment of Stage A HF

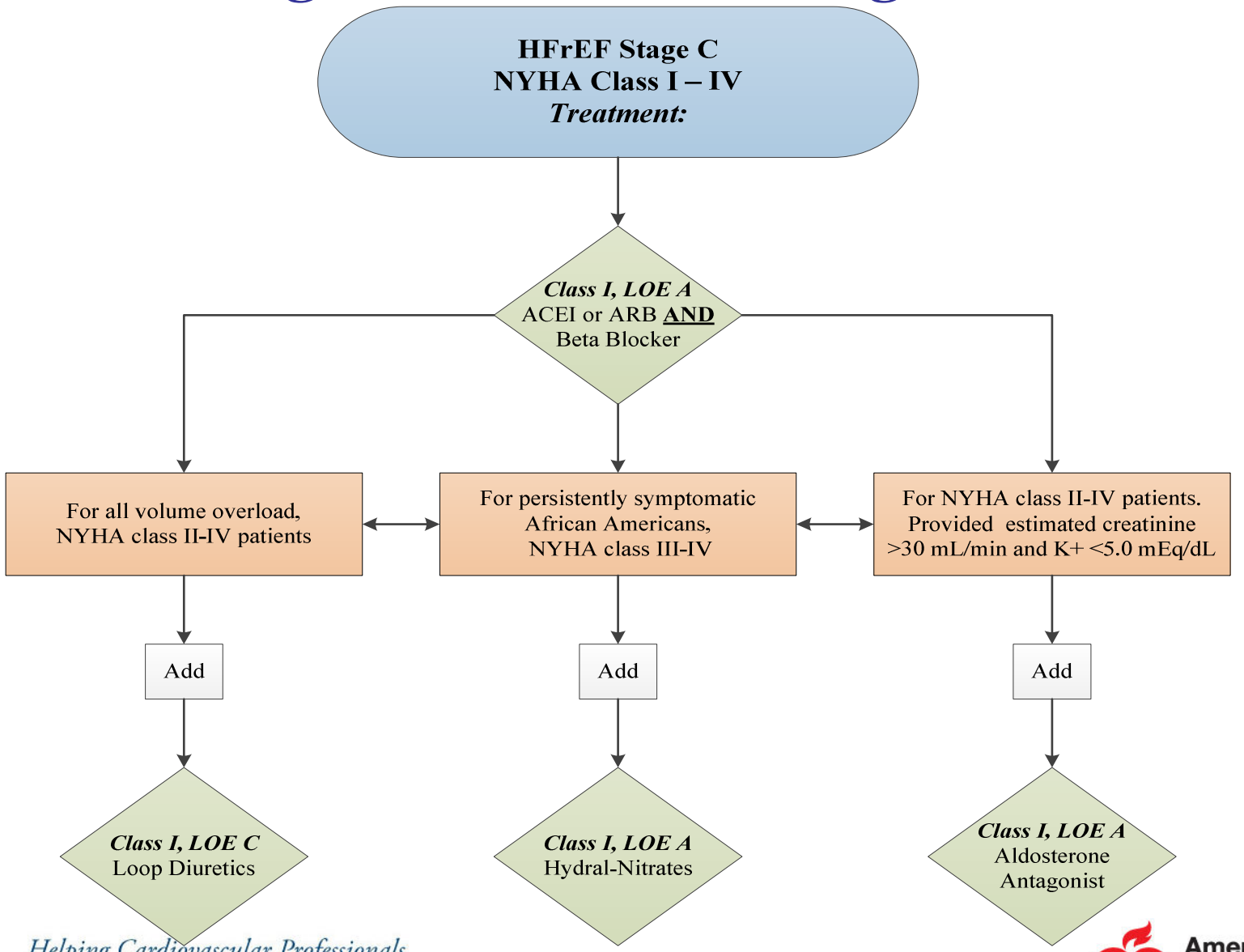
- Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines (COR I/LOE A)
- Other conditions that may lead to or contribute to HF, such as obesity, diabetes, tobacco use, and known cardiotoxic agents, should be controlled or avoided (COR I/LOE C)
- Use ACEI/ARB and statins in appropriate patients

Recommendations for Treatment of Stage B HF

Recommendations	COR	LOE
In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF	I	A
In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF	I	B
In patients with MI, statins should be used to prevent HF	I	A
Blood pressure should be controlled to prevent symptomatic HF	I	A
ACE inhibitors should be used in all patients with a reduced EF to prevent HF	I	A
Beta blockers should be used in all patients with a reduced EF to prevent HF	I	C
An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on GDMT	IIa	B
Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF	III: Harm	C

Recommendations for the Treatment of Stage C HF*r*EF

Pharmacologic Treatment for Stage C HF*r*EF



Pharmacological Therapy for Management of Stage C HF*r*EF

Recommendations	COR	LOE
Diuretics		
Diuretics are recommended in patients with HFrEF with fluid retention	I	C
ACE Inhibitors		
ACE inhibitors are recommended for all patients with HFrEF	I	A
ARBs		
ARBs are recommended in patients with HFrEF who are ACE inhibitor intolerant	I	A
ARBs are reasonable as alternatives to ACE inhibitor as first line therapy in HFrEF	IIa	A
The addition of an ARB may be considered in persistently symptomatic patients with HFrEF on GDMT	IIb	A
Routine *combined* use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful	III: Harm	C

Pharmacological Therapy for Management of Stage C HF*r*EF (cont.)

Recommendations	COR	LOE
Beta Blockers		
Use of 1 of the 3 beta blockers proven to reduce mortality is recommended for all stable patients	I	A
Aldosterone Antagonists		
Aldosterone receptor antagonists are recommended in patients with NYHA class II-IV HF who have LVEF ≤35%	I	A
Aldosterone receptor antagonists are recommended in patients following an acute MI who have LVEF ≤40% with symptoms of HF or DM	I	B
Inappropriate use of aldosterone receptor antagonists may be harmful	III: Harm	B
Hydralazine and Isosorbide Dinitrate		
The combination of hydralazine and isosorbide dinitrate is recommended for African-Americans, with NYHA class III–IV HFrEF on GDMT	I	A
A combination of hydralazine and isosorbide dinitrate can be useful in patients with HFrEF who cannot be given ACE inhibitors or ARBs	IIa	B

Pharmacologic Therapy for Management of Stage C HF*r*EF (cont.)

Recommendations	COR	LOE
Digoxin		
Digoxin can be beneficial in patients with HFrEF	IIa	B
Anticoagulation		
Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy*	I	A
The selection of an anticoagulant agent should be individualized	I	C
Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but without an additional risk factor for cardioembolic stroke*	IIa	B
Anticoagulation is not recommended in patients with chronic HFrEF without AF, prior thromboembolic event, or a cardioembolic source	III: No Benefit	B
Statins		
Statins are not beneficial as adjunctive therapy when prescribed solely for HF	III: No Benefit	A
Omega-3 Fatty Acids		
Omega-3 PUFA supplementation is reasonable to use as adjunctive therapy in HFrEF or HFpEF patients	IIa	B

Pharmacological Therapy for Management of Stage C HF*r*EF (cont.)

Recommendations	COR	LOE
Other Drugs		
Nutritional supplements as treatment for HF are not recommended in HFrEF	III: No Benefit	B
Hormonal therapies other than to replete deficiencies are not recommended in HFrEF	III: No Benefit	C
Drugs known to adversely affect the clinical status of patients with HFrEF are potentially harmful and should be avoided or withdrawn	III: Harm	B
Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation	III: Harm	C
Calcium Channel Blockers		
Calcium channel blocking drugs are not recommended as routine in HFrEF	III: No Benefit	A

Recommendations for the Treatment of Stage C HF*p*EF

Treatment of HF*p*EF

Recommendations	COR	LOE
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines	I	B
Diuretics should be used for relief of symptoms due to volume overload	I	C
Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT	IIa	C
Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF	IIa	C
Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF	IIa	C
ARBs might be considered to decrease hospitalizations in HFpEF	IIb	B
Nutritional supplementation is not recommended in HFpEF	III: No Benefit	C

Pharmacotherapy Options for HF*r*EF

Heart Failure Management

HF Severity	Treatment Options
Stage B Class I	ACE Inhibitor or ARB Beta-blocker
Stage C Class I-IV	ACE Inhibitor or/and ARB Beta-blocker Diuretic Aldosterone antagonist Hydralazine/isosorbide dinitrate Digoxin CRT; ICD
Stage D Class IV	All Stage C medications Inotropic agents; vasodilators Experimental drugs/surgery ICD deactivation Transplant Mechanical circulatory support Pallative care and hospice

Diuretics

- Goal of treatment is to eliminate clinical evidence of fluid retention
- No long-term studies for morbidity and mortality
  - Use in patients to improve symptoms
  - Use in combination with GDMT

ACCF/AHA 2013
HFSA 2010

Diuretics

- Diuretic of choice: loop

- Available agents:
  - Furosemide 40 mg = bumetanide 1mg = torsemide 20 mg = ethacrynic acid 50 mg
  - Furosemide most commonly used
  - Bumetanide and torsemide have increased oral bioavailability

Loop Diuretics

Loop Diuretic	Initial Daily Dose(s)	Max Daily Dose	Duration of Action
Bumetanide	0.5 – 1.0 mg qd/bid	10 mg	4-6 hours
Furosemide	20 – 40 mg qd/bid	600 mg	6-8 hours
Torsemide	10 – 20 mg qd	200 mg	12-16 hours

All available in generic
Cost per month <$20 per www.goodrx.com (9/14)

ACCF/AHA 2013

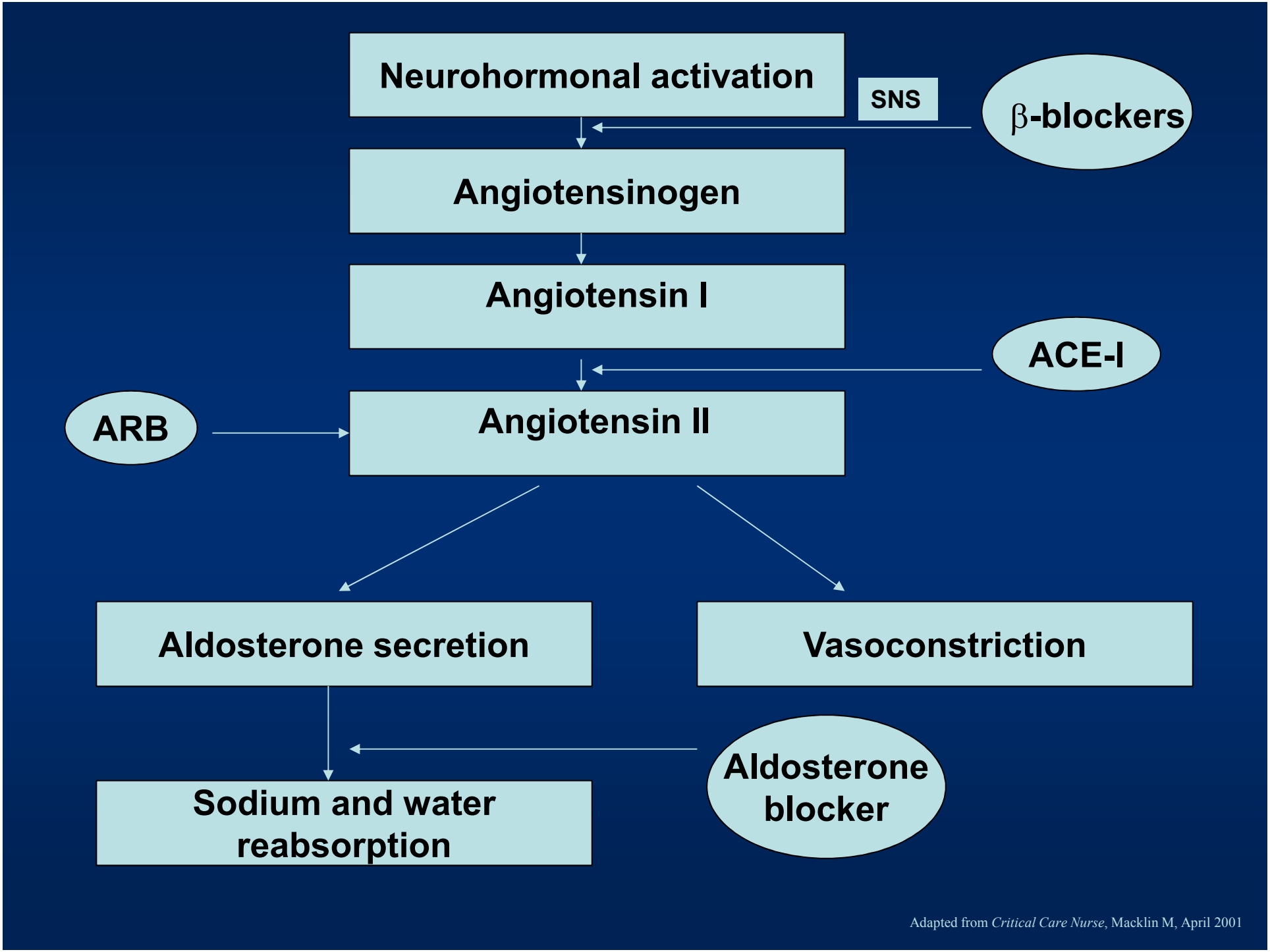
Diuretics

- Dosing
  - PRN based on weight
  - Initiate starting dose, then double dose until desired diuresis
  - Appropriate use is a key element in the success of other drugs used in treating HF
- Watch for electrolyte imbalances, volume depletion, hypotension, and renal insufficiency

ACCF/AHA 2013
HFSA 2010

Diuretics

- Patients may become refractory
  - Due to increased dietary sodium intake, administration of NSAIDS, gut wall edema (↓ furosemide absorption up to 50%), significant impairment of renal function or perfusion, etc.
- Resistance can be overcome by:
  - IV administration
  - Combination of loop and thiazide diuretic
    - Metolazone (2.5-10 mg qd) is the thiazide of choice



Adapted from *Critical Care Nurse*, Macklin M, April 2001

ACE Inhibitors

- **Use in all ACCF/AHA Stages and NYHA Classes of HF, unless contraindicated**
- Decreases cardiovascular morbidity, mortality, and recurrence of MI (in pts with or without LV dysfunction)

ACCF/AHA 2013
HFSA 2010

ACE Inhibitors

- Benefit considered class effect
  - Consider cost/convenience in choosing agent
- Use target doses, if possible
  - Recommend using highest tolerable dose during concomitant up titration of beta-blockers
- Use with caution if low SBP (<80 mm Hg), increased serum creatinine (>3 mg/dL), bilateral RAS, or elevated K^+ levels (> 5 mEq/L)

ACCF/AHA 2013
HFSA 2010

ACE Inhibitor	Target Dose
Captopril (Capoten®)	50 mg TID
Enalapril (Vasotec®)	10 mg BID
Lisinopril (Prinivil®, Zestril®)	20 mg QD
Quinapril (Accupril®)	20 BIDΨ
Ramipril (Altace®)	10 mg QDΨ
Trandolapril (Mavik®)	4 mg QDΨ
Fosinopril (Monopril®)	40 mg QDΨ
Perindopril (Aceon®)	8 mg QDΨ

All available in generic
Cost per month <$20 per www.goodrx.com (9/14)
Ψ No study data on dose

ACCF/AHA 2013
HFSA 2010

ACE Inhibitors

- Adverse effects
  - Hypotension, renal insufficiency, hyperkalemia, cough (up to 20%), angioedema (0.1-0.5%)
- Monitor serum creatinine and potassium at baseline, 1-2 weeks after initiation, and after dosage changes

ACCF/AHA 2013
HFSA 2010

Alternatives to ACE Inhibitors

- Use one of the following medications if a patient is intolerant to an ACE inhibitor:
  - Angiotension receptor blocker (ARB)
  - Hydralazine + isosorbide dinitrate combination
- ACE inhibitors remain preferred over both options due to morbidity and mortality data

ACCF/AHA 2013
HFSA 2010

Angiotensin Receptor Blockers

- Morbidity and mortality data available
- Alternative when intolerant to an ACE inhibitor, primarily due to cough
- May consider use in patients that experienced angioedema while on an ACE inhibitor
  - Use caution - evaluate underlying risk and recognize angioedema has been reported with ARBs

ACCF/AHA 2013
HFSA 2010

Angiotensin Receptor Blockers

- Alternative as first-line therapy, especially if already taking an ARB for another indication
- Consider combination with ACE inhibitor and a beta blocker in patients that are persistently symptomatic in whom an aldosterone antagonist is not indicated or tolerated
- Triple combination (ACE inhibitor + ARB + aldosterone antagonist) is **not** recommended due to high risk of hyperkalemia

ACCF/AHA 2013
HFSA 2010

Angiotensin Receptor Blockers

- Use recommended ARBs at target doses

ARB	Target Dose	Cost/month*
Candesartan (Atacand®)	32 mg qd	$50-110
Valsartan (Diovan®)	160 mg bid	$110-230
Losartan (Cozaar®)	150 mg qd	$8-35

All available in generic

*www.goodrx.com (9/14)

ACCF/AHA 2013
HFSA 2010

Angiotensin Receptor Blockers

- Same precautions as ACE inhibitors
- Adverse effects
  - Hypotension, renal insufficiency, hyperkalemia, angioedema (lower incidence than with ACEIs)
- Monitor serum creatinine and potassium at baseline, 1-2 weeks after initiation, and after dosage changes

ACCF/AHA 2013
HFSA 2010

Beta-Blockers

- **Use in ACCF/AHA Stages B – D and all NYHA Classes of HF, unless contraindicated**
- Decreases cardiovascular morbidity, mortality, and recurrence of MI
- Recommended even if pt has concomitant DM, asthma/COPD, or PVD

ACCF/AHA 2013
HFSA 2010

Beta-Blockers

- Use caution in pts with diabetes with recurrent hypoglycemia, reactive airway disease, or resting limb ischemia
  - Do not use in asthma patients with active bronchospasm
- Use considerable caution in pts with marked bradycardia (<55 beats/min) or marked hypotension (SBP < 80 mmHg)

Beta-Blockers

- Not considered a class effect - use agents studied
  - Carvedilol, metoprolol succinate, bisoprolol
    - Similar efficacy in trials
    - Most data in Class II-III
  - Consider carvedilol over other agents in pts with EF <25% or those needing additional BP lowering

ACCF/AHA 2013
HFSA 2010

Beta-Blockers

- Dosing
  - Start low and go slow
  - Titrate at 2-week intervals (adjust as necessary)
  - Use target doses, if possible
- Adverse effects
  - Bradycardia, hypotension, fatigue, fluid retention
  - Patients usually feel worse for a while

ACCF/AHA 2013
HFSA 2010

Beta-Blocker	Target Dose	Cost/month*
Bisoprolol (Zebeta®)	10 mg qd	$20-25
Carvedilol (Coreg®)	25 mg bid (<85 kg) 50 mg bid (>85 kg)	<$15
(Coreg CR®)	80 mg qd	$180-200
Metoprolol succinate (Toprol XL®)	200 mg qd	$15-25

*www.goodrx.com (9/14)

All available in generic, except Coreg CR

ACCF/AHA 2013
HFSA 2010

Which Beta Blocker is Best?

- Guidelines do not recommend one agent over another
- No head-to-head mortality comparisons
- Comparative data has suggested superiority of carvedilol; however, studies had flaws
- Recent cohort study comparing carvedilol and metoprolol succinate found no significant difference in all cause mortality

JAMA Intern Med. Published online August 31, 2014.
doi:10.1001/jamainternmed.2014.3258

Beta-Blockers During Decompensation of HF

- Can be used in pts with recent decompensation after optimization of fluid status and d/c of IV diuretics, vasodilators, and inotropic support

- Avoid abrupt discontinuation. Continue therapy in most pts during an exacerbation, if possible.
  - May require temporary reduction in dose or discontinuation. Reinstate or gradually increase before hospital discharge.

ACCF/AHA 2013
HFSA 2010

Aldosterone Antagonists

- Decreases morbidity and mortality
- Recommended in patients with NYHA Class II – IV HF and who have LVEF ≤35%, unless contraindicated
  - Pts with NYHA Class II HF should have a h/o prior CV hospitalization or elevated plasma natriuretic peptide levels

  .
- Recommended following an acute MI in patients who have LVEF ≤40% who develop HF symptoms or who have a history of diabetes, unless contraindicated

ACCF/AHA 2013
HFSA 2010

Aldosterone Antagonists

- Consider adding to patients who are already on ACE inhibitors (or ARBs) and beta blockers
- Limited data to support or refute that available agents (spironolactone and eplerenone) are interchangeable

ACCF/AHA 2013
HFSA 2010

Aldosterone Antagonists

- **Eplerenone (**Inspra®)
  - Selective mineralo-corticoid antagonist
  - HF post MI, HTN, mild to moderate HF (NYHA class II)
  - Target: 50 mg qd
  - Drug interactions (3A4)
  - No gynecomastia
  - Expensive: generic $50-90/month*
- **Spironolactone (**Aldactone®)
  - Nonselective mineralo-corticoid antagonist
  - Moderate to severe HF (NYHA class III-IV)
  - Target: 25 mg qd
  - Gynecomastia
  - Inexpensive: generic <$10/month*

*www.goodrx.com (9/14)

Aldosterone Antagonists

- Adverse effects
  - Renal insufficiency, hyperkalemia
- Adjust initial regimen to every-other-day dosing if CrCl 30-49 mL/min
- Potassium supplements should be discontinued or dose reduced
- Stop during an episode of diarrhea or dehydration or while loop therapy is interrupted

ACCF/AHA 2013
HFSA 2010

Aldosterone Antagonists

- Not recommended when:
  - SCr >2 (females) or >2.5 (males) mg/dL **OR**
  - CrCl <30 mL/min
  - K^+ >5 mEq/L
- Monitor serum creatinine and potassium
  - ACCF/AHA: baseline, 3 days, 1 week, monthly x 3 months, every 3 months
  - HFSA: baseline, 1 week, 1 month, every 3 months

ACCF/AHA 2013
HFSA 2010

Hydralazine and Isosorbide Dinitrate

- Morbidity and mortality data available
- Recommended in African Americans with NYHA Class III-IV HF receiving optimal therapy with an ACE inhibitor and beta blocker, unless contraindicated
- Benefit in non-African Americans is unknown
  - HFSA states that you may consider use in non-African Americans who remain symptomatic despite optimal therapy

ACCF/AHA 2013
HFSA 2010

Hydralazine and Isosorbide Dinitrate

- Alternative to ACE inhibitors and ARBs
  - Due to drug intolerance, hypotension, hyperkalemia, or renal insufficiency
  - ACE inhibitors have demonstrated greater benefits in comparative trial

ACCF/AHA 2013
HFSA 2010

Hydralazine and Isosorbide Dinitrate

- Dosing
  - Generic (~$100/month*)
    - Hydralazine 75 mg qid + isosorbide dinitrate 40 mg qid
  - BiDil® (~$400/month*)
    - Hydralazine 37.5mg / isosorbide dinitrate 20mg
    - Target dose: 2 tabs tid
- Adverse effects: HA, hypotension, dizziness, and GI complaints

*www.goodrx.com (9/14)

Digoxin

- Decreases symptoms and hospitalizations; No effect on mortality
- Consider as add–on therapy to standard therapy (GDMT) to improve symptoms
- May also be added to initial regimen in pts with severe symptoms, who have not yet responded to GDMT

ACCF/AHA 2013
HFSA 2010

Digoxin

- Dosing
  - 0.125 mg - 0.25 mg QD (generic $10-35/month*)
  - Adjust dose with renal dysfunction
- Monitoring
  - Digoxin levels as needed; target <1 ng/mL
    - 0.5-0.9 ng/mL per ACCF/AHA
    - 0.7-0.9 ng/mL per HFSA
  - Serum creatinine and potassium
- Use caution in the elderly
- Watch for drug interactions

*www.goodrx.com (9/14)

Digoxin

- Adverse effects
  - Arrhythmias, nausea, vomiting, anorexia, visual halos, photophobia, fatigue, weakness, dizziness, HA, confusion
- Overt toxicity associated with levels >2 ng/mL
- Hypokalemia, hypomagnesemia, and hypothyroidism may increase risk of toxicity at lower digoxin levels

ACCF/AHA 2013
HFSA 2010

Calcium Channel Blockers

- Not recommended as routine treatment for patients with HF*r*EF and should generally be avoided
- May consider amlodipine in the management of HTN or IHD in pts with HF because it is well tolerated and had neutral effects on morbidity and mortality in trials
  - If use, monitor for peripheral edema

ACCF/AHA 2013
HFSA 2010

Future Medication Options

- Ivabradine
  - FDA fast track designation for chronic heart failure
  - Inhibits the I_f (pacemaker) current in the sinoatrial node to decrease heart rate
  - SHIFT trial demonstrated a reduction in CV death or hospitalization for worsening heart failure
- Valsartan/sacubitril
  - ARB + neprilysin inhibitor
  - PARADIGM-HF trial demonstrated superiority over enalapril to reduce risk of death and hospitalization

Lancet 2010;376(9744):875-885.
New Engl J Med 2014;371:993-1004.

Pharmacotherapy Options for HF*p*EF

Heart Failure with Preserved Ejection Fraction

- Very limited outcome studies available
- No randomized, controlled trials have shown a delay in disease progression or reduction in mortality
- Treatment goals focus on reducing symptoms, managing associated disease(s), reducing risk factors, and modifying underlying pathophysiology

Goals of Therapy

- Reduce the congestive state
- Maintain atrial contraction and prevent tachycardia
- Slow HR to allow for adequate filling of left ventricle
- Treat and prevent myocardial ischemia
- Control hypertension
- Promote regression of hypertrophy and prevent myocardial fibrosis

N Engl J Med 2004;351:1097-1105.

ACCF/AHA Recommendations

- Control blood pressure according to guidelines
- Use diuretics to relieve symptoms of volume overload
- Coronary revascularization in appropriate pts
- Manage atrial fibrillation according to guidelines
- Use beta-blockers, ACE inhibitors, and ARBs for hypertension
- Use of ARBs may be considered to decrease hospitalizations
- Routine use of nutritional supplements not recommended

HF*p*EF Treatment Options
Per HFSA

- Diuretics
- ACE Inhibitors or ARBs
- Beta-Blockers (non-ISA)
- Calcium Channel Blockers
  - Diltiazem
  - Verapamil

Diuretics

- For all patients with HF*p*EF and fluid overload
  - Begin with thiazide or loop diuretic
  - Loop preferred in severe volume overload or if inadequate response to thiazide
  - Avoid excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function

ACE Inhibitors and ARBs

- Consider an ACE inhibitor or ARB in the absence of other indications
- ACE inhibitors should be considered in all patients who have:
  - Symptomatic atherosclerotic disease OR
  - Diabetes and one additional risk factor
- In patients who meet the above criteria but are intolerant to ACE inhibitors, ARBs should be considered

Beta-Blockers

- Recommended in patients who have HF*p*EF and:
  - Prior MI
  - Hypertension
  - Atrial fibrillation (requiring rate control)

Calcium Channel Blockers

- Consider in patients with HF*p*EF and:
  - Atrial fibrillation (requiring rate control) and intolerance to beta-blockers
    - Options: diltiazem and verapamil
  - Symptom limiting angina
  - Hypertension

Chronic Heart Failure
Conclusions

- Heart failure is associated with significant morbidity and mortality
- Follow guideline recommendations regarding drug therapy, which are supported by evidence
- ACE inhibitors (ARBs) and beta-blockers should be used in all patients, if possible
- Close follow-up and adherence to therapy is important

Questions?

Additional Charts for Reference

Strategies for Achieving Optimal GDMT
(ACCF/AHA 2013)

1. Uptitrate in small increments to the recommended target dose or the highest tolerated dose for those medications listed in Table 15 with an appreciation that some patients cannot tolerate the full recommended doses of all medications, particularly patients with low baseline heart rate or blood pressure or with a tendency to postural symptoms.

2. Certain patients (eg, the elderly, patients with chronic kidney disease) may require more frequent visits and laboratory monitoring during dose titration and more gradual dose changes. However, such vulnerable patients may accrue considerable benefits from GDMT. Inability to tolerate optimal doses of GDMT may change after disease-modifying interventions such as CRT.

3. Monitor vital signs closely before and during uptitration, including postural changes in blood pressure or heart rate, particularly in patients with orthostatic symptoms, bradycardia, and/or “low” systolic blood pressure (eg, 80 to 100 mm Hg).

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4. Alternate adjustments of different medication classes (especially ACE inhibitors/ARBs and beta blockers) listed in Table 15. Patients with elevated or normal blood pressure and heart rate may tolerate faster incremental increases in dosages.

5. Monitor renal function and electrolytes for rising creatinine and hyperkalemia, recognizing that an initial rise in creatinine may be expected and does not necessarily require discontinuation of therapy; discuss tolerable levels of creatinine above baseline with a nephrologist if necessary.

6. Patients may complain of symptoms of fatigue and weakness with dosage increases; in the absence of instability in vital signs, reassure them that these symptoms are often transient and usually resolve within a few days of changes in therapy.

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7. Discourage sudden spontaneous discontinuation of GDMT medications by the patient and/or other clinicians without discussion with managing clinicians.

8. Carefully review doses of other medications for HF symptom control (eg, diuretics, nitrates) during uptitration.

9. Consider temporary adjustments in dosages of GDMT during acute episodes of noncardiac illnesses (eg, respiratory infections, risk of dehydration, etc).

10. Educate patients, family members, and other clinicians about the expected benefits of achieving GDMT, including an understanding of the potential benefits of myocardial reverse remodeling, increased survival, and improved functional status and HRQOL.

Drugs Commonly Used for HF*r*EF (Stage C HF)

Drug	Initial Daily Dose(s)	Maximum Doses(s)	Mean Doses Achieved in Clinical Trials
ACE Inhibitors			
Captopril	6.25 mg 3 times	50 mg 3 times	122.7 mg/d (421)
Enalapril	2.5 mg twice	10 to 20 mg twice	16.6 mg/d (412)
Fosinopril	5 to 10 mg once	40 mg once	---------
Lisinopril	2.5 to 5 mg once	20 to 40 mg once	32.5 to 35.0 mg/d (444)
Perindopril	2 mg once	8 to 16 mg once	---------
Quinapril	5 mg twice	20 mg twice	---------
Ramipril	1.25 to 2.5 mg once	10 mg once	---------
Trandolapril	1 mg once	4 mg once	---------
ARBs			
Candesartan	4 to 8 mg once	32 mg once	24 mg/d (419)
Losartan	25 to 50 mg once	50 to 150 mg once	129 mg/d (420)
Valsartan	20 to 40 mg twice	160 mg twice	254 mg/d (109)
Aldosterone Antagonists			
Spironolactone	12.5 to 25 mg once	25 mg once or twice	26 mg/d (424)
Eplerenone	25 mg once	50 mg once	42.6 mg/d (445)

Drugs Commonly Used for HF*r*EF (Stage C HF) (cont.)

Drug	Initial Daily Dose(s)	Maximum Doses(s)	Mean Doses Achieved in Clinical Trials
Beta Blockers			
Bisoprolol	1.25 mg once	10 mg once	8.6 mg/d (118)
Carvedilol	3.125 mg twice	50 mg twice	37 mg/d (446)
Carvedilol CR	10 mg once	80 mg once	---
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once	159 mg/d (447)
Hydralazine & Isosorbide Dinitrate			
Fixed dose combination (423)	37.5 mg hydralazine/ 20 mg isosorbide dinitrate 3 times daily	75 mg hydralazine/ 40 mg isosorbide dinitrate 3 times daily	~175 mg hydralazine/90 mg isosorbide dinitrate daily
Hydralazine and isosorbide dinitrate (448)	Hydralazine: 25 to 50 mg, 3 or 4 times daily and isosorbide dinitrate: 20 to 30 mg 3 or 4 times daily	Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate 120 mg daily in divided doses	---

Review of the Evidence

Drug or Drug Class	NNT	Outcome Prevented
ACE Inhibitors	6 100	One death over 1 year; NYHA Class III-IV One death over 1 year; NYHA Class I-II
Beta-Blockers	23 13	One death over 1 year One hospitalization over 1 year
Spironolactone	9	One death over 2 years; NYHA Class III - IV
Hydralazine + isosorbide dinitrate	14	One death over 1 year
Digoxin	9	ED visits or hospitalizations

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Review of the Evidence

Drug or Drug Class	NNT	Outcome Prevented
Candesartan (ACEI intolerant)	14	One CV death or hospital admission over ~3 years
(ACEI + ARB)	23	One CV death or hospital admission over ~3 years
Valsartan (ACEI + ARB)	23	One hospitalization over 23 months
Hydralazine/isosorbide dinitrate (BiDil®)	25	One death from any cause over 18 months
-In African Americans	12	One hospitalization over 18 months

Review of the Evidence

Drug or Drug Class	NNT	Outcome Prevented
Eplerenone -Post MI	44 30	One death from any cause over 16 months One CV death or hospitalization over 16 months
Eplerenone -NYHA Class II	13 33	One death from CV causes or hospitalization for heart failure over 21 months One death from any cause over 21 months

HF*p*EF
Clinical Trials

Trial (Therapy)	n	EF (%)	Outcome/Benefit
PEP-CHF (perindopril)	852	~40	•No change in composite endpoint •Reduced hospitalization for HF
CHARM-Preserved (candesartan)	3023	>40	•No change in composite endpoint •Reduced hospitalization for HF
I-PRESERVE (irbesartan)	4128	>45	•No change in composite endpoint
SENIORS trial (nebivolol)	2128	>35	•Reduced all-cause mortality or CV hospitalization
DIG trial (digoxin)	988	>45	•No change in primary or secondary end points

Adapted from PSAP-VII Chronic Heart Failure, 2011