

Guidelines for Medical Therapy Chronic Systolic Congestive Heart Failure with Reduced Ejection Fraction

Definitions:

<u>Classification:</u>	<u>EF (%)</u>
Heart failure with reduced ejection fraction (HFrEF)	< 40%
Heart failure with preserved ejection fraction (HFpEF)	> 50%
Heart failure with preserved ejection fraction, borderline	41-49
Heart failure with recovered left ventricle (LV) systolic function	> 50%

Asymptomatic Subjects with Reduced LV Systolic Function (ACC/AHA Class B Heart Failure)

Subjects with Class B heart failure have reduced LV systolic function, but report no symptoms with regular activity. This may be due to a sedentary lifestyle or adequate compensatory mechanisms. Subjects with asymptomatic LV systolic dysfunction have a 10% annual risk of developing symptoms of congestive heart failure and 8% risk of mortality or hospitalization annually. Medical therapy should be used to prevent progression to symptomatic heart failure.

Recommendations:

- 1) All patients with a history of remote or recent myocardial infarction (MI) or ACS WITH reduced EF (<40%) should be treated with ACE inhibitors to prevent symptomatic heart failure and reduce mortality. Patients intolerant of ACE inhibitors should be treated with ARBs unless contraindicated.
- 2) ACE inhibitors (or ARB) and beta-blockers should be used in all patients with reduced EF (<40%), irrespective of etiology to prevent symptomatic heart failure.
- 3) Non-dihydropyridine calcium channel blockers (Diltiazem and Verapamil) are considered harmful to patients with LV EF < 40% due to their negative inotropic effects and should be avoided.

The only drugs that have been tested in Class B heart failure are Captopril (SAVE), enalapril (SOLVD), and candesartan (CHARM-Preserved).

Medications accepted as evidence-based treatment of Class C heart failure are believed to be effective in Class B heart failure including:

ACEIs: Captopril, Enalapril, Fosinopril, Lisinopril, Perindopril, Quinapril, Ramipril, Trandolapril

ARBs: Candesartan, Losartan, Valsartan

Beta-blockers: Carvedilol, Metoprolol succinate, bisoprolol

In patients with asymptomatic LV systolic dysfunction, functional testing may be considered to assess whether exercise capacity is low for patient age/sex. This may include six-minute walk testing, with a total walk distance < 300 meters, indicating a high risk of hospitalization and mortality from heart failure, or cardiopulmonary stress testing.

Symptomatic Heart Failure with Reduced LV Systolic Function (ACC/AHA Class C Congestive Heart Failure)

Subjects with symptomatic heart failure and reduced LV systolic function are at higher risk of hospitalization and mortality from congestive heart failure. Medical therapy can modify the course of the disease and prevent these events.

Baseline therapy with evidence-based ACE inhibitor or ARB and Beta-blocker are recommended. The evidence-based medications are listed above.

Angiotensin Converting Enzyme Inhibitors, ARBs, and Afterload Reducing Agents:

ACE inhibitors reduce mortality from systolic congestive heart failure by 17%. Subjects who have low systolic blood pressure (<85 mm Hg), severely impaired renal function (Cr <3), hyperkalemia (K⁺ >5), or bilateral renal artery stenosis should not be treated with ACE inhibitors.

ARBs may be substituted for ACE inhibitors in subjects who are truly intolerant. However, ACE inhibitors remain the first choice for afterload reduction therapy.

A cough occurs in up to 20% of patients treated with ACE inhibitors due to increased levels of bradykinin, which may also produce beneficial vasodilation. Angioedema to ACE inhibitors is a serious side effect occurring in < 1% of subjects and is more likely to occur in African Americans and women. Similar angioedema can occur with ARBs.

Despite the initially positive clinical trial findings in heart failure (CHARM-ADDED), the use of **ACE inhibitors in combination with ARBs is not recommended** due to a higher incidence of renal insufficiency with treatment.

The use of the renin inhibitor **Aliskiren**, in addition to standard medical therapy, is **not recommended** in subjects with systolic congestive heart failure. Aliskiren treatment, in addition to beta-blocker and ACE inhibitor treatment, was not beneficial (ASTRONAUT) in reducing death or hospitalization for congestive heart failure. In addition, it may be potentially harmful in subjects with co-morbid

diabetes mellitus, as an increase in death was reported in these subjects. The addition of aliskiren to enalapril (ATMOSPHERE) resulted in more adverse events including hypotension, decreased renal function and hyperkalemia without protection from death or admission for congestive heart failure treatment.

The combination of hydralazine and isosorbide dinitrate (BiDil) is recommended to reduce morbidity and mortality in African American subjects with NYHA Class III-IV heart failure, with reduced LV function receiving optimal therapy, with ACE inhibitors and beta blockers. A fixed-dose combination pill BiDil contains hydralazine 37.5 mg and ISDN 20 mg, and should be administered three times daily. The dosage can be uptitrated to two tablets per day as tolerated. This combination resulted in an additional 43% reduction in death compared with standard medical therapy (A-HeFT).

Hydralazine and isosorbide dinitrate can be useful to reduce morbidity and mortality in patients with current or prior heart failure, with reduced LV systolic function, who cannot be treated with an ACE inhibitor or ARB due to drug intolerance, hypotension, or renal insufficiency (VA Cooperative Study).

Beta-Adrenergic Receptor Antagonists:

Specific beta-blockers have been proven to reduce mortality by 34% in subjects with symptomatic heart failure, with reduced ejection fraction. They include **Carvedilol, metoprolol succinate, and bisoprolol**. Beta-blockers not tested in subjects with systolic congestive heart failure (atenolol, propranolol, nadolol) are less favored in the treatment of systolic congestive heart failure.

Vasodilating beta-blockers (carvedilol (several), bisoprolol (CIBIS-II) and nebivolol (SENIORS)) are favored in subjects with systolic congestive heart failure based on the available trial evidence.

Metoprolol tartrate is less effective than carvedilol in systolic heart failure based on the results of the COMET trial and does not have a role in systolic congestive heart failure management.

Uptitration of carvedilol is particularly useful in subjects with **non-ischemic cardiomyopathy** (MOCHA Trial) and will result in **dose-dependent improvement in LV EF**. Subjects with ischemic cardiomyopathy did not have a significant improvement in LV EF with uptitration of beta-blocker dosing.

Uptitration of beta-blocker therapy is frequently associated with increased symptoms of shortness of breath. Symptoms should be treated with additional doses of loop diuretic and not with a decrease in dose of beta-blocker. Uptitration of beta-blockers should also occur slowly over a 7-14 day period at each dose.

In subjects with co-morbid COPD, bisoprolol may be better tolerated than carvedilol or metoprolol succinate (JACC 2010; 55 (17): 1780-7).

Diuretic Therapy:

Subjects with symptoms of congestion should be treated with loop diuretic medications including Bumetanide, Furosemide, Torsemide.

Bumetanide and torsemide are favored over furosemide due to more reliable oral bioavailability. The lowest dosage necessary to achieve relief of symptoms should be utilized to minimize untoward side effects, including hearing loss.

Ethacrynic acid may be substituted in subjects who have a true allergy to sulfa drugs that cross-react with bumetanide, furosemide or torsemide.

Those with a poor or variable response to loop diuretic treatment may be supplemented with sequential nephron blockade agents, including metolazone, hydrochlorothiazide (high dosage 25-100 mg), before administration of loop diuretic.

Mineralocorticoid Antagonists:

Aldosterone receptor antagonists are recommended in subjects with NYHA Class II-IV symptoms of systolic heart failure AND who have LVEF <35% to reduce morbidity and mortality as much as 30%.

Patients with NYHA Class II heart failure should have a history of prior hospitalization for heart failure OR elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonist therapy.

Aldosterone receptor antagonists are recommended in patients following an acute MI, who have LV EF < 40% with symptoms of congestive heart failure or diabetes mellitus

Aldosterone receptor antagonists can have harmful effects, including renal insufficiency and hyperkalemia. It is recommended that aldosterone receptor antagonists be used in subjects who have creatinine levels < 2.5 mg/dL in men or 2.0 mg/dL or less in women (eGFR > 30 mL/min/1.73 m²). Serum potassium levels should be less than 5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize the risk of hyperkalemia and renal insufficiency.

Use of an aldosterone antagonist in combination with ACE inhibitors and ARB is contraindicated.

Digoxin:

Digoxin, in addition to guideline-directed medical therapy, can be beneficial in patients with heart failure and reduced LV systolic function to decrease hospitalizations. Digoxin is best added in patients who either have not yet

responded to guideline-based medical therapy, or remain symptomatic after treatment. Digoxin should not be used alone or in place of beta blockers and ACE inhibitors.

Digoxin may be useful when used in combination with beta-blockers in subjects with atrial fibrillation and reduced LV systolic function to control ventricular response rate.

Digoxin should not be given to patients with significant sinus or atrioventricular block in the absence of a pacemaker.

Digoxin should be initiated at low dosages (0.125 mg daily or every other day) in older patients (> 70 years of age), impaired renal function, or low lean body mass. Plasma levels of digoxin between 0.5 to 0.9 ng/mL are recommended, and higher plasma levels are not beneficial.

Concomitant use of clarithromycin, dronedarone, erythromycin, amiodarone, itraconazole, cyclosporine, propafenone, verapamil, and quinidine can increase serum digoxin levels and the likelihood of digoxin toxicity.

Angiotensin Receptor/Nepriylsin Inhibitor (ARNI) Therapy:

The recently published PARADIGM-HF trial documented the effectiveness of a novel strategy in congestive heart failure. Sacubitril is an inhibitor of an enzyme called neprolysin, which breaks down brain-derived natriuretic peptide, bradykinin, adrenomedullin and other vasoactive peptides. The combination of medications containing valsartan/sacubitril reduced cardiovascular death and hospitalization for congestive heart failure by 20% relative to enalapril.

ARNI therapy (valsartan/sacubitril) is recommended in patients with NYHA Class II or III systolic congestive heart failure, who can tolerate an ACE inhibitor or ARB as disease modifying therapy with:

- 1) Elevated brain-derived natriuretic peptide > 150 pg/mL or NT-pro-BNP > 600 pg/mL
- 2) Elevated brain-derived natriuretic peptide > 100 pg/mL or NT-pro-BNP > 400 pg/mL **WITH** a prior hospitalization for congestive heart failure in the past 12 months

Substitution of an ACE inhibitor or ARB with an ARNI (valsartan/sacubitril) is indicated. **ARNI should not be administered concomitantly with ACE inhibitors or ARBs within 36 hours of the last dosage.** The dosage of ARNI should be uptitrated to dosages used in the clinical trial (97/103 mg twice daily) as tolerated by blood pressure.

Valsartan/sacubitril is not intended for subjects with low systolic blood pressure < 100 mm Hg, eGFR < 30 mL/min/1.73m², or potassium > 5.2 mmol/L. Hypotension and angioedema are potential effects of the drug.

Prior history of angioedema after treatment with an ACE inhibitor is a **contraindication for the use of Valsartan/sacubitril**. African Americans and smokers are at particular risk of angioedema with ARNIs. The incidence of angioedema in PARAGON-HF was rare.

Ivabradine is a new agent that acts to reduce heart rate by inhibiting the “funny channel” known as I_f . Ivabradine may be used to reduce heart failure hospitalizations in patients with symptomatic (NYHA Class II-III) systolic congestive heart failure already receiving guideline-directed medical therapy. This includes the use of a beta blocker at maximum tolerated dosage. Ivabradine should be considered only in subjects in sinus rhythm, and when heart rate is greater than 70 bpm at rest. It is important to stress that given the proven mortality benefits obtained with beta blockers provided at dosages used in clinical trials, this approach should be exhausted first before considering the use of ivabradine. Ivabradine may be started at 5 mg twice daily and uptitrated to 7.5 mg twice daily. Patients with conduction defects should be started at 2.5 mg twice daily.

Important contraindications for the use of Ivabradine include:

- Myocardial infarction within the past 2 months
- Sick sinus syndrome, or pacemaker dependent rhythm
- Concomitant use with Cytochrome P450 3A4 including azole antifungals (ketoconazole), macrolide antibiotics, nefazodone, nelfinavir, and ritonavir
- Use with verapamil or diltiazem is contraindicated
- Acute decompensated heart failure
- Blood pressure less than 90/50 mm Hg
- Severe hepatic impairment
- AFib