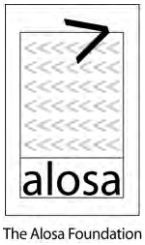
A Guide to Outpatient Management of Congestive Heart Failure



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These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.

Contents

Introduction

Congestive heart failure (CHF) is a major cause of morbidity and mortality in the U.S. It affects almost 6 million people, with 670,000 new diagnoses made each year. The prevalence of CHF increases with age, with a male predominance in most age groups (Figure 1). About 20% of people with CHF will die within a year of diagnosis and the mortality rate is highest in those over age 65. One in eight death certificates in the U.S. contains CHF as a contributing cause. [1] CHF hospitalizations continue to rise, increasing from about 870,000 to 1.1 million annually (from 1996 to 2006) (Figure 2). CHF costs the U.S. $34 billion a year in medications, health care, and lost productivity.[2]

Although the morbidity and mortality associated with CHF are extremely high, the appropriate use of evidence-based treatments can prolong life and improve its quality. This module will review the evidence-based management of acute and chronic CHF and common co-morbid conditions.

Figure 1: Prevalence of heart failure by age and sex[1]

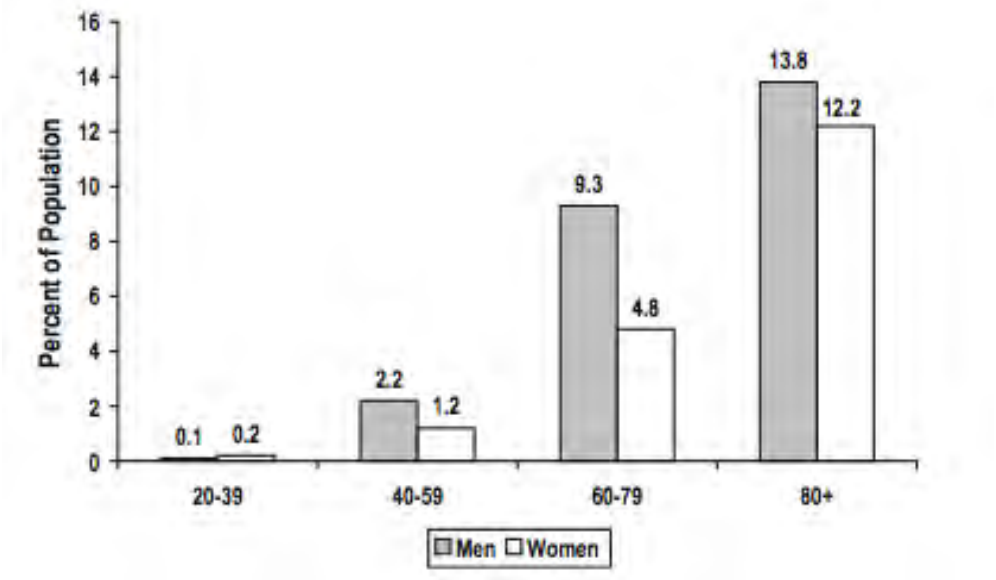
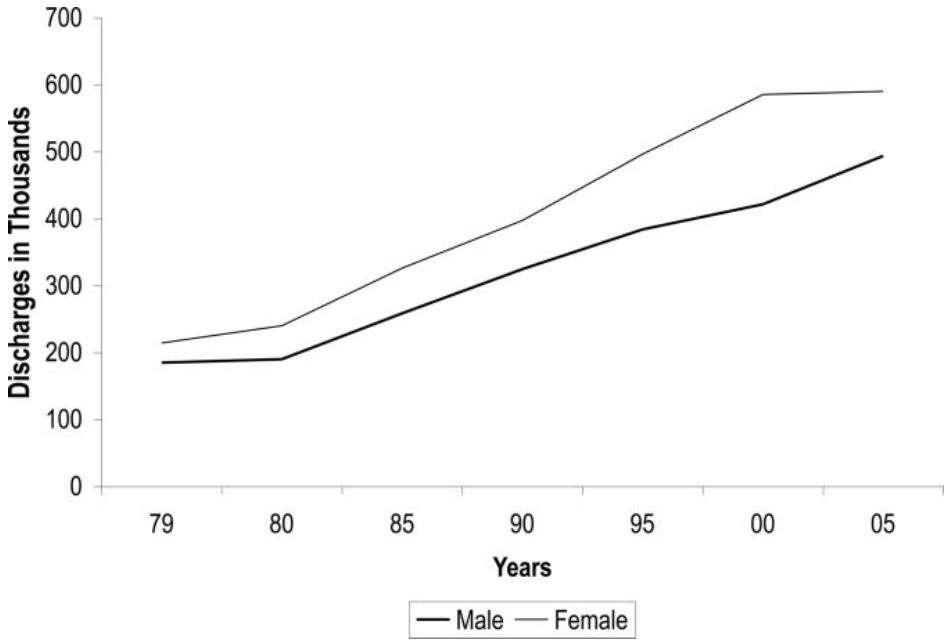


Figure 2: CHF hospital discharges, by year and sex[1]



Pathophysiology

CHF is characterized by the inability of the heart to provide adequate blood flow. It is triggered by an event or series of events (such as acute myocardial infarction, or longstanding hypertension; see more under "etiologies"), which also activate several neurohormonal systems. The two primary systems involved with CHF are the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS).

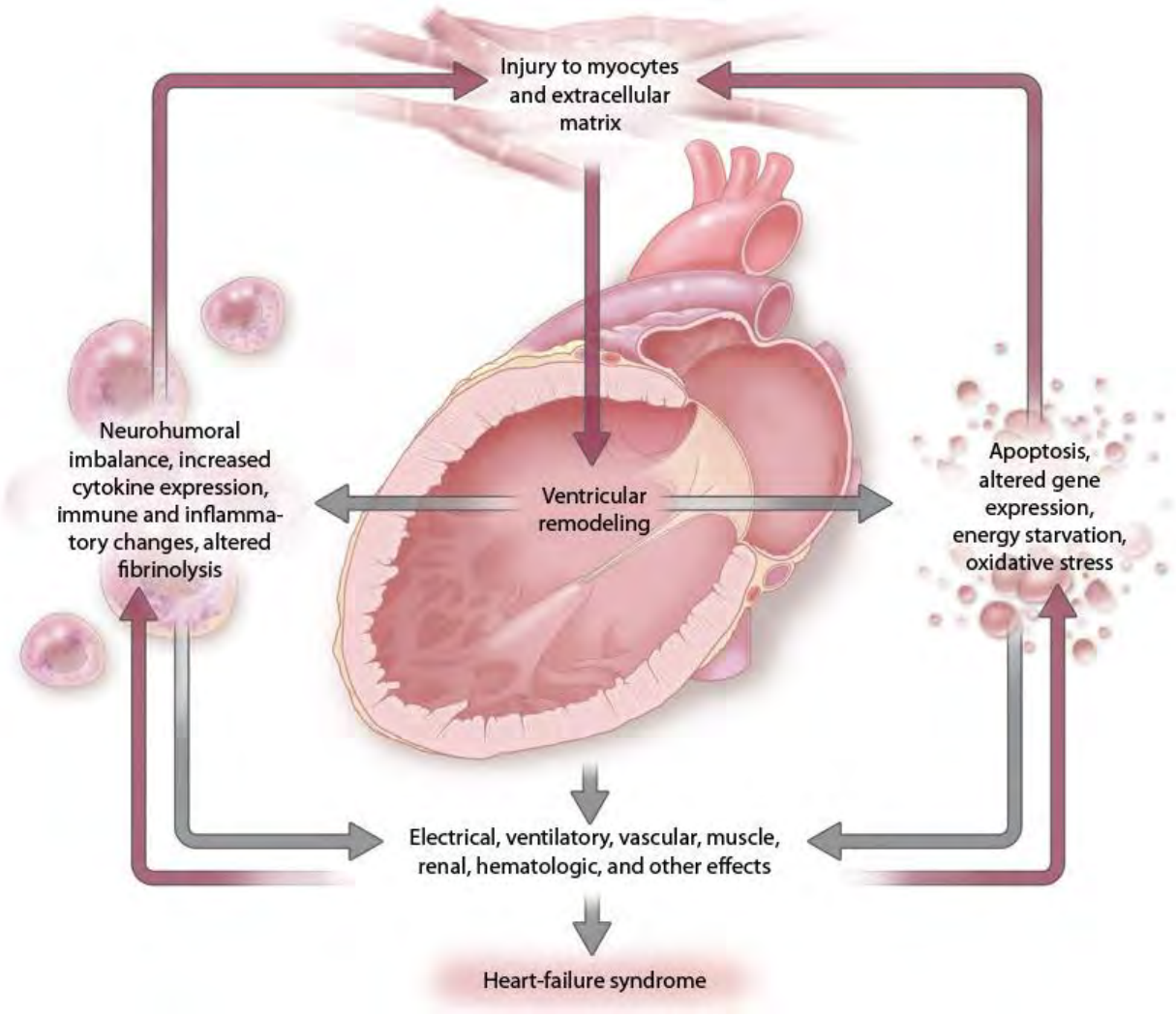
Sympathetic nervous system hormones related to CHF (including epinephrine and norepinephrine) increase heart rate, blood pressure, the risk of arrhythmias, and also exert direct myocardial toxicity. RAAS hormones promote sodium and water reabsorption from the kidneys, as well as the release of a complex system of inflammatory cytokines (which also exert direct myocardial toxicity). Acting together, these two systems lead to further myocardial dysfunction (in the contraction or relaxation of the heart, or both) and volume overload.

Fortunately are a number of counter-regulatory hormones can combat the changes noted above. These primarily include atrial natriuretic peptides and B-type natriuretic peptides, which are released in response to myocardial stress or "stretch", and promote natriuresis (renal excretion of sodium) and diuresis (renal

excretion of water). They also inhibit the effects of the sympathetic hormones and RAAS hormones, reducing heart rate, blood pressure, and the risk of arrhythmias.

In CHF, these protective counter-regulatory hormones can become "overwhelmed" by the sympathetic and RAAS hormones, leading to a vicious cycle of renal hypoperfusion and volume retention. In addition, the volume retention results in a leaking of fluid into interstitial spaces such as the lungs and lower extremities, which eventually overwhelms the lymphatic system's ability to drain this interstitial fluid. The resultant clinical syndrome manifests as dyspnea or pulmonary edema and peripheral edema (or dependent areas in bed-bound patients). The pathophysiology of CHF is outlined in Figure 3 below.

Figure 3: Pathophysiology of congestive heart failure[3]



Many of the effective pharmacologic therapies used in CHF work by inhibiting some component of the sympathetic nervous system (e.g. beta blockers) or the RAAS system (e.g. ACE-inhibitors or aldosterone antagonists). Other agents, such as diuretics, work by increasing sodium and water loss through the kidneys (i.e. natriuresis/diuresis). When used correctly, these agents can effectively reduce the morbidity and mortality associated with CHF.

BOTTOM LINE: CHF can lead to and be exacerbated by results from an imbalance of sympathetic and RAAS hormones. Most effective medical therapies target one or more of these systems, to counteract their effects.

Classification and etiologies of heart failure

Systolic versus diastolic dysfunction

Patients with congestive heart failure can be categorized based on whether their ejection fraction (EF) is "preserved" or "not preserved". The EF is the percentage of blood that is ejected out of the left ventricle with each ventricular contraction. CHF with preserved EF is also referred to as "diastolic dysfunction" since the heart in unable to appropriately relax during diastole, leading to high filling pressures within the heart. CHF with "not preserved," or "systolic dysfunction," reflects the inability of the heart to appropriately contract.

Systolic and diastolic heart failure can be difficult to distinguish by history, physical exam, and many diagnostic tests (including EKG, chest x-ray, and laboratory testing). An echocardiogram is usually required to make a definitive distinction. There is no absolute cut point to distinguish systolic from diastolic heart failure, although an EF of 55% is often used. Currently in the US about half of all cases of heart failure are categorized as systolic and half as diastolic. Morbidity and mortality rates for systolic and diastolic CHF are similar, with 1 year hospital admission rates ~50% and 1 year mortality rates ~22-29%.[4]

Systolic and diastolic heart failure differ importantly in demographics, etiologies, and management, outlined in Table 1 below.

Table 1: Differences in systolic and diastolic CHF[4]

CHF type	Typical demographics	Common etiologies and co-morbidities	Evidence based management
Diastolic	Older Female	Obesity Hypertension Atrial fibrillation	Few randomized controlled trials to guide management
Systolic	Younger Male	Coronary artery disease Smoking Diabetes Hyperlipidemia	Many randomized controlled trials to guide management

BOTTOM LINE: Systolic and diastolic heart failure are often clinically indistinguishable by history, physical exam, basic testing, and prognosis. They differ in echocardiographic features, typical demographics, etiologies, and evidence- based management.

Right versus left sided heart failure

The pathophysiology of CHF (depicted in Figure 3) can affect both the left and right ventricle; chronic left ventricular dysfunction with high left ventriclular and pulmonary pressures will eventually lead to structural changes and right ventricular dysfunction. Isolated right ventricular CHF (without left ventricular CHF) is frequently associated with chronic lung disease (such as COPD, chronic pulmonary emboli, or pulmonary hypertension).

Functional symptoms class

The severity of symptoms can be used to classify patients with CHF; the two most commonly used classification systems are listed in Table 3. Most of the randomized controlled trials discussed in this evidence document include or exclude patients based on their New York Heart Association (NYHA) functional class.

Table 3: Congestive heart failure symptom classification schemes

New York Heart Association (NYHA) Functional Classification[3]	American College of Cardiology – American Heart Association (ACC-AHA) Stages of Heart Failure[5]
Class I: No limitation of functional 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 less than ordinary activity results in fatigue, palpitation, or dyspnea	**Stage B:** Developed structural heart disease that is strongly associated with progression to 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 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

Etiologies

The most common causes for CHF are listed in Table 4 below.

Table 4: CHF etiologies

Primary cardiovascular disease 1. Ischemia 2. Valvular dysfunction 3. Hypertension 4. Myocarditis/pericarditis 5. Cardiomyopathy (dilated/hypertrophic/restrictive)
Primary pulmonary disease 1. Pulmonary hypertension 2. COPD 3. Chronic thromboembolic disease 4. Obstructive sleep apnea
Drug use 1. Alcohol 2. Cocaine
Anemia
Infiltrative diseases: 1. Amyloid 2. Glycogen storage diseases
Endocrinopathies 1. Thyroid disease 2. Cushing's disease
Other 1. Peripartum 2. HIV 3. Connective tissue diseases 4. Chemotherapy (e.g. doxorubicin)

Presentation and diagnostic workup

History

Patients with symptoms of new heart failure should be interviewed about past and present symptoms, when symptoms occur, and how/when the symptoms started. They should be queried about present and past use of alcohol, drugs, or

chemotherapy agents, and all co-morbid conditions (e.g. ischemic heart disease, hypertension, obstructive sleep apnea, HIV, COPD, etc).

Patients with CHF usually present with one or more of the three cardinal symptoms: [6,7]

1. Shortness of breath (dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea)
2. Fatigue
3. Edema (lower extremity edema, weight gain, or increase in abdominal girth).

The most sensitive symptom is dyspnea on exertion, but the most specific is paroxysmal nocturnal dyspnea.

Exam findings

The following physical exam findings are common in patients with CHF, although no one finding is particularly sensitive or specific:[6,7]

1. Neck: elevated jugular venous pressure
2. Heart: tachycardia, S3/S4, diffuse point of maximal intensity
3. Lungs: rales/crackles, hypoxia, or tachypnea
4. Abdomen: ascites (or dependent edema in bed bound patients)
5. Extremities: peripheral edema

The physical exam should also include height/weight/BMI, routine vitals, and orthostatic blood pressure

Laboratory testing

Lab tests that should be done during the initial workup of patients with CHF include those that help determine the etiology, or help guide management, and should include:[6,7]

1. Complete chemistries (including liver function tests)
2. Complete blood count
3. Thyroid function tests
4. Cardiac enzymes (troponin I or T)
5. Urinalysis
6. Lipid profile

Other lab testing should only be done if the history or exam suggests an unusual cause of CHF (such as Cushing's disease, HIV, or an infiltrative disease). Check cardiac enzymes (troponin I or T) if acute ischemia is suspected.

B-type natriuretic peptide (BNP) testing

Overview:

BNP is a hormone released in response to myocardial stress or "stretch". It can be measured in serum, to help determine if symptoms are due to congestive heart failure. There are currently 2 tests available, which measure different sections of the same hormone: the BNP test and the N-terminal pro-BNP test.

Efficacy:

Both of these tests are sensitive for determining if a patient's symptoms (such as shortness of breath) are due to CHF or due to another cause. The *BNP trial* found a sensitivity of 90% and specificity of 74%. The BNP level increased with higher levels of NYHA class.[8]

Class 1: Mean BNP 150
Class 2: Mean BNP 250
Class 3: Mean BNP 550
Class 4: Mean BNP 900

Based on clinical trials, the cut-point for suspecting CHF should be:

- 100pg/mL (29 pmol/L) for BNP
- 450pg/mL (53 pmol/L) for N-terminal pro-BNP (twice the cut point is recommend for those > age 50, eg 900 pg/mL, 106 pmol/L). [8,9]

These lab tests should be used in concert with the history and physical exam, to increase or decrease the suspicion for CHF, but should never be used as an isolated diagnostic test.

In patients with known CHF, BNP measurements can also be used to guide medical management and reduce CHF hospitalizations. A randomized trial (*TIME-CHF*) compared the effect of managing CHF patients based on symptoms alone, compared to including serum BNP levels. The trial randomized almost 500 patients, age >60 years old, with an EF <45% (Class II-IV symptoms), with elevated baseline BNP to one of the two management groups. At 18 months, there was no significant difference between the groups in all-cause hospitalizations or quality of life, but there was a significant increase in survival free of CHF hospitalization, which occurred in:[10]

72% of those in the BNP group, vs.
62% of those in the symptom-based management group (relative risk reduction 32%, p=0.01)[10]

A subsequent meta-analysis of 8 randomized trials including 1726 patients (including TIME-CHF) found BNP-guided therapy reduced all cause mortality by 24% (relative risk reduction 0.76, 95% CI 0.63-0.91, p=0.003), but did not find a difference in hospitalizations. The benefit was more pronounced in patients <age 75, with limited benefit in those > age 75. [11]

Safety:

In the above trial, serious adverse events were no different between the 2 groups overall, although hypotension and renal failure were more common in the BNP-guided group, in those age 60-74 (15% versus 12%) and those ≥ age 75 (18% versus 13%) (p=0.01).[10]

BOTTOM LINE: Patients with new or suspected CHF should undergo a thorough history, physical exam, echocardiography and basic lab testing. BNP testing is highly sensitive and specific for diagnosing new CHF, when used in conjunction with history and physical exam. For patients with known CHF, BNP-guided therapy reduces mortality and some hospitalizations, but may increase adverse events (e.g., hypotension and renal failure), especially in the elderly.

Pulmonary disease work up

Patients with a history suggestive of obstructive sleep apnea (OSA) should be referred for a diagnostic sleep study, and for OSA management if sleep results are positive. Pulmonary function tests should be ordered on those with symptoms of COPD (chronic cough or sputum production, especially in smokers or those exposed to second hand smoke). Work up for chronic thromboembolic disease should be undertaken for those with suspected or history of venous thromboembolic disease.

Non-invasive testing (EKG, chest X-ray, echocardiogram, MRI, CTA, perfusion scans)

An EKG, Chest X-ray, and echocardiogram are all routinely performed in patients with new or worsening CHF signs/symptoms. The EKG is valuable in determining the heart rate and rhythm (which may affect management). The chest X-ray is valuable in ruling in or ruling out CHF as the etiology of the patient's symptoms (the typical findings in CHF include interstitial edema and vascular congestion). The echocardiogram is valuable in assessing a number of

structural cardiac elements that can affect patient management, including the left ventricular ejection fraction (EF), diastolic dysfunction, valvular function (stenosis or regurgitation), ventricular filling pressures, pericardial size/effusions, and inferior vena caval pressures. All of these tests are routinely available, non-invasive, and relatively low cost to perform.[12]

More sensitive cardiac imaging should be performed only in selected patient situations. Cardiac MRI is a good diagnostic test for suspected myocardial pathology (such as infiltrative diseases) or pericardial pathology (such as malignant effusions) but does not provide useful clinical information for most CHF patients. Cardiac CT (with or without CT angiogram) can detect cardiac vascular calcifications/stenosis, although the significance of these findings for management is not always clear and the testing carries the risks of radiation and contrast. A number of different types of cardiac nuclear perfusion scans can be performed if cardiac ischemia is suspected, the type of which will depend on locally available technology and cardiology preferences. These should be performed in patients whose CHF etiology is not known after physical exam, laboratory testing, and EKG/echocardiography.

Invasive testing (Cardiac catheterization, myocardial biopsy)

Further invasive testing for patients with new or worsening CHF should be dictated by the suspicion of the etiology of the CHF. For patients with suspected or confirmed cardiac ischemia (despite medical therapy), cardiac catheterization may be pursued for diagnostic and/or therapeutic purposes. For patients with suspected myocarditis or myocardial infiltrative diseases, a myocardial biopsy may be appropriate. Both should be performed by qualified cardiac specialists.

BOTTOM LINE: Additional work up for all new CHF should include EKG, chest x-ray, and echocardiogram. Further diagnostic testing should be targeted based on suspicion of pulmonary, cardiac, or other diseases causing the CHF.

Non-pharmacologic management

Dietary management (sodium and fluid)

Sodium restriction is routinely recommended in patients with symptomatic CHF.[3,13] The degree of sodium restriction recommended should correlate with the degree of CHF symptoms and edema. The US Department of Health and Human Services recommends <2,300 mg of sodium a day for most Americans,

noting that the average daily intake of sodium currently is 3,400 mg a day.[13] A few easy tips for patients on reducing salt intake include:

1. Do not salt any foods
2. Avoid canned foods
3. Eat primarily fresh and home-prepared foods
4. Learn how to read a label to determine how much sodium is in a serving of food (example food label in Appendix 1)

Many patients with CHF will also need to restrict the amount of fluid they take in. The fluid restriction will correlate with the degree of CHF symptoms and edema, ranging from 1-2 liters a day.[14] This will usually require patients to keep a log of their fluid intake (e.g. any intake of liquids). Prescribers must be cautious not to limit fluid intake *too* much, especially in elderly patients with a reduced thirst mechanism. Volume depletion can also exacerbate CHF, especially in patients with diastolic CHF, which *requires* high left ventricular filling pressures to maintain adequate cardiac output.

Weight monitoring

Patients with CHF should weigh themselves daily on the same scale at the same time daily, ideally first thing in the morning, with instructions to phone the physician or use extra diuretic if weight exceeds a given level. Daily weights can often be used in concert with a telemonitoring program, to adjust the regimen based on the results. An example weight log is provided in Appendix 2.

Vaccines

Influenza (annually) and pneumococcal (when indicated) vaccines are indicated in all patients with CHF.

Lifestyle

Exercise:

Exercise training is can be safe and modestly effective in reducing adverse outcomes in patients with CHF. A large trial evaluated 2,331 stable outpatients with systolic CHF (median EF 25%) who were randomized to 36 sessions (over 3 months) of supervised exercise training or usual care. After 30 months of follow up, the exercise group had slightly lower rates of the primary and secondary outcomes, although none of which were statistically significantly different (Table 5).[15]

Table 5: Benefits of exercise training versus usual care in patients with systolic CHF[15]

Outcome	Exercise group	Usual care group	P value
Death or hospitalization	65%	68%	0.13
Death	16%	17%	0.70
CV death or hospitalization	55%	58%	0.14
CV death or CHF hospitalization	30%	34%	0.06

Exercise training has been less well studied in those with diastolic dysfunction, but does appear to be safe and modestly effective. A small randomized trial of older women with diastolic CHF found that a 12 week home-based exercise program improved their 6 minute walk test by about 300 feet, and significantly increased their quality of life, with no adverse events.[16]

In contrast, cardiac rehabilitation has been shown to clearly reduce mortality by 45% in patients who participate after undergoing percutaneous coronary intervention (PCI). Therefore most patients with CHF and concomitant coronary artery disease should undergo cardiac rehabilitation after PCI.[17]

Smoking and alcohol:

Smoking cessation counseling and medical therapy should be offered to all patients with CHF currently smoking. Medical therapy consists of nicotine replacement (in any form, eg patch, gum, inhaler, etc) and either buproprion or varenicline. Buproprion is safe and effective in patients with heart disease, but varenicline is currently undergoing further investigation based on preliminary data suggesting a possible increase in the risk of cardiovascular events related to its use (primarily ischemic events). Until this association is better elucidated, varenicline should not be used in patients with existing cardiovascular disease.

All patients with CHF should refrain from excessive alcohol intake (>1-2 drinks a day).[14] Those with alcoholic cardiomyopathy should refrain completely.

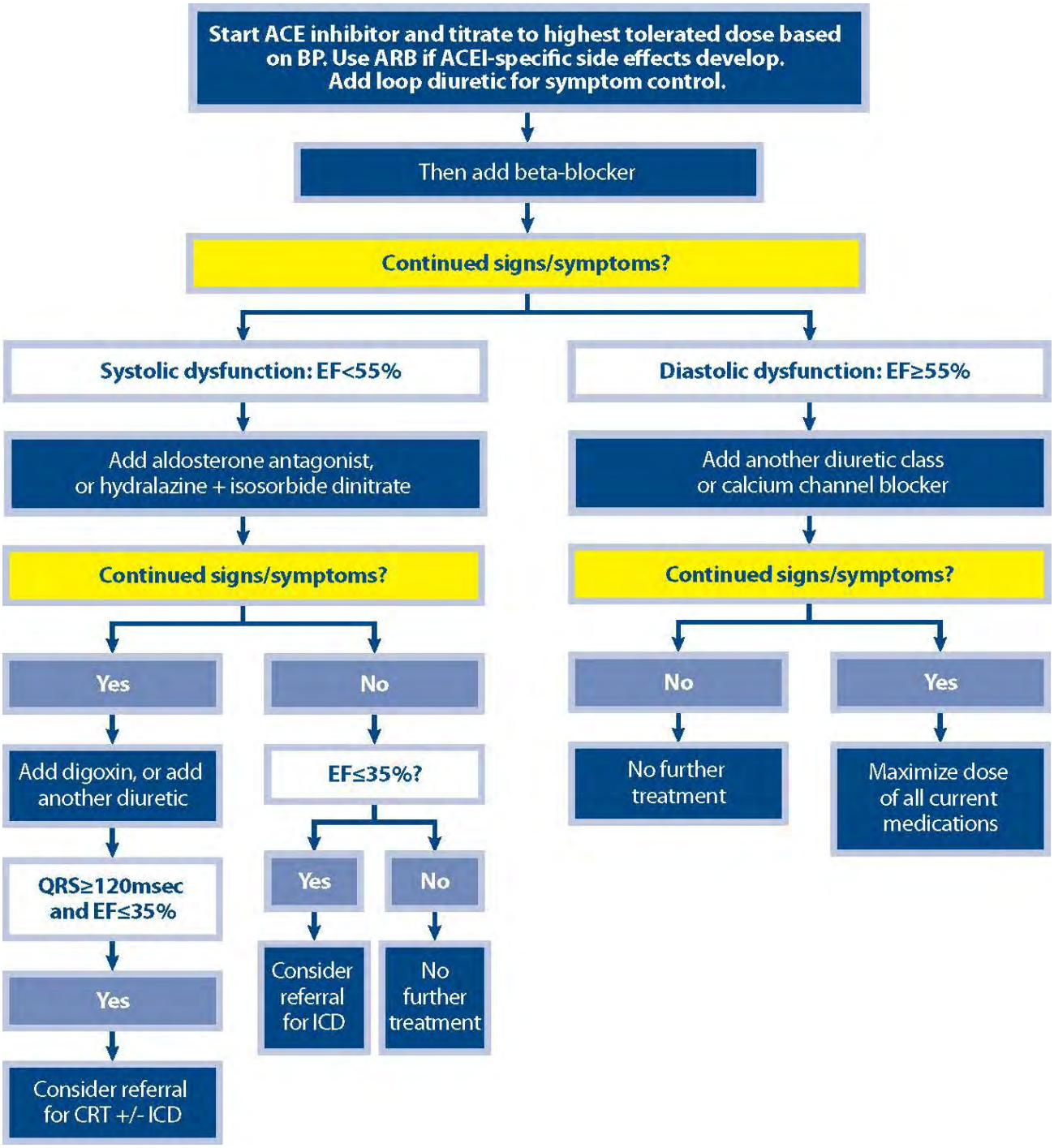
BOTTOM LINE: Both sodium restriction (2-4g/day) and fluid restriction (1-2L/day) are recommended for most CHF patients, depending on their degree of symptoms. Exercise programs are safe, and modestly effective in reducing adverse outcomes and improving walking distance and quality of life. Influenza and pneumococcal vaccinations should be updated (influenza annually; pneumococcal when indicated). Smoking and alcohol use should be discouraged.

Chronic medical management by drug class

Goals of treatment and overview

The goals of CHF treatment are reducing symptoms, and preventing hospitalizations and avoidable death. While some pharmacologic therapies only reduce symptoms (e.g. diuretics), others can reduce hospitalizations and death (e.g. beta blockers and ACE inhibitors) and thus form the cornerstones of medical management. There is much more evidence for the treatment of systolic failure than diastolic failure; the former is outlined in Figure 4.

Figure 4: Suggested treatment algorithm for heart failure



ACE inhibitors

Efficacy:

ACE inhibitors are first line therapy for all patients with heart failure; with the highest benefit in those with symptomatic systolic heart failure. In a landmark study (CONSENSUS trial), patients with NYHA class IV CHF randomized to enalapril (2.5mg to 40mg daily) had significantly lower 6-month mortality than those randomized to placebo (26% versus 44%, 40% relative reduction, p=0.002).[18] A subsequent large randomized trial of patients with less symptomatic CHF and EF <35% (SOLVD trial) found a significant reduction in mortality and heart failure hospitalizations in those randomized to enalapril versus placebo (Figures 4-5).[19]

Figure 4: Percent mortality in patients with reduced EF (<35%) in enalapril versus placebo (SOLVD trial)[19]

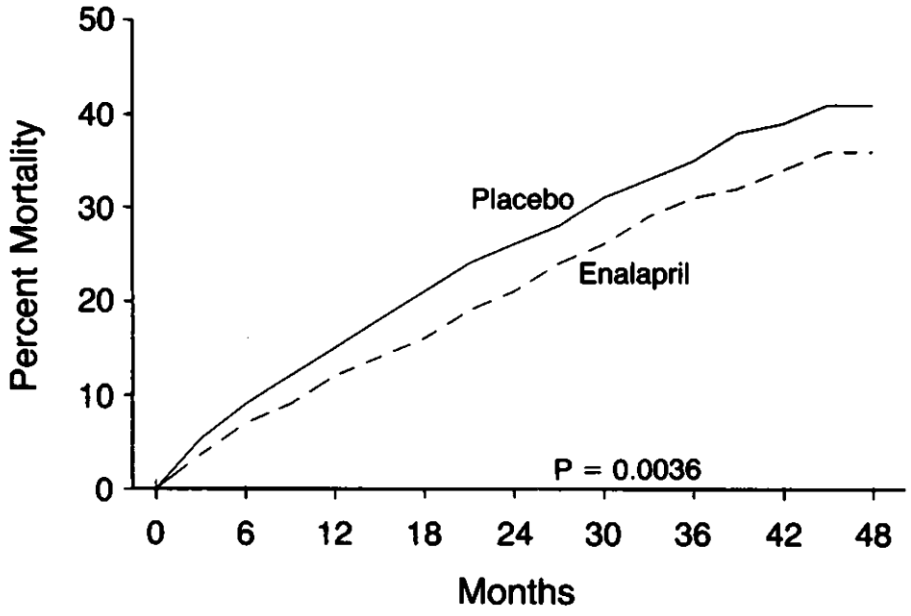
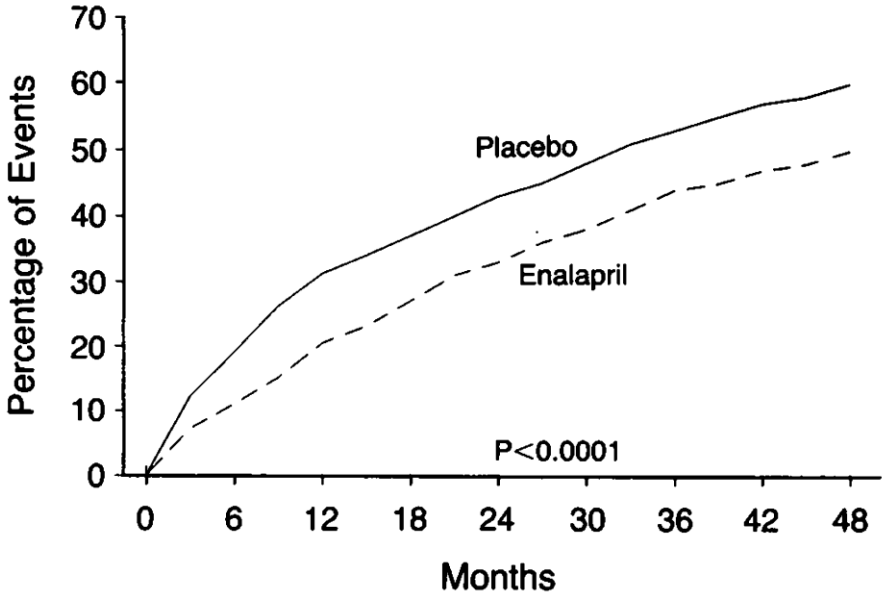
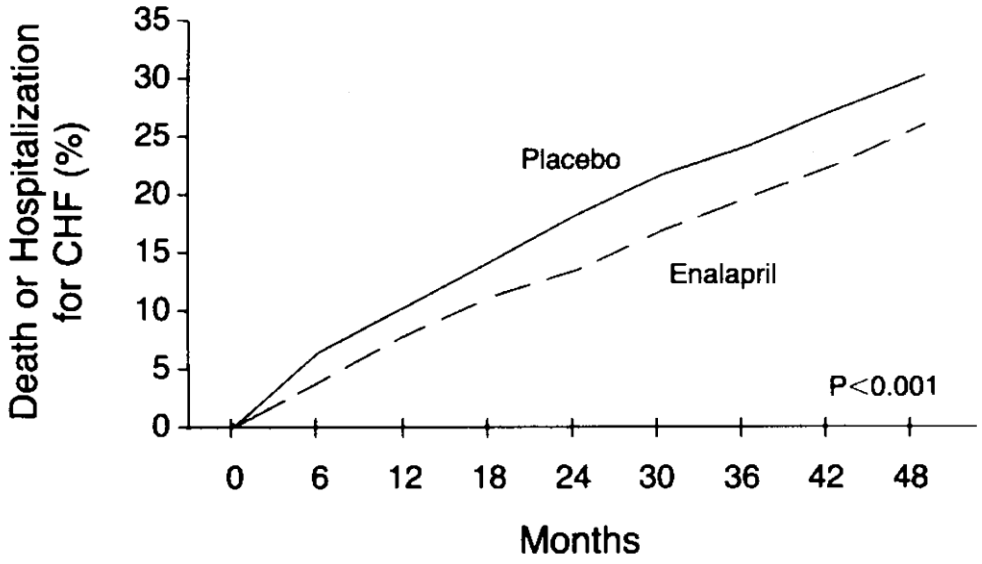


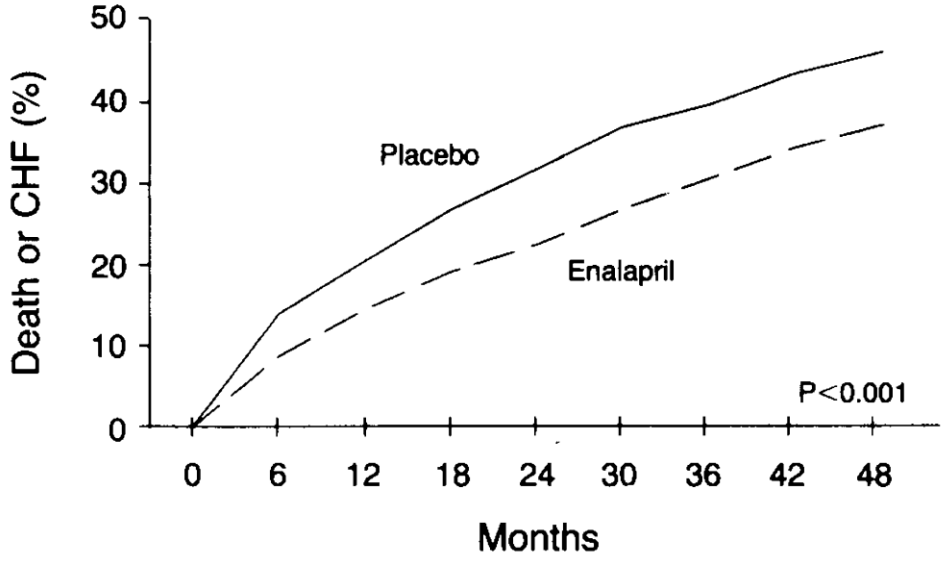
Figure 5: Percent mortality or CHF hospitalization in patients with reduced EF (<35%) in enalapril versus placebo (SOLVD trial)[19]



ACE inhibitors also significantly reduce mortality, CHF hospitalizations, and incidence of CHF symptoms in patients with asymptomatic reductions in their EF (<40%).[20] (Figure 6)

Figure 6: Reduction in mortality, CHF hospitalizations, and incidence of new CHF symptoms in asymptomatic patients with low EF (<40%) with enalapril versus placebo[20]





However, sub-group analysis from the *SOLVD trials* found no benefit of ACE inhibitors for mortality, CHF hospitalizations, or blood pressuring lower among black patients.[21] This is discussed more below in the section "hydralazine-Isosorbide."

The benefits of ACE inhibitors in those with preserved EF are less well established. The *PEP-CHF trial* randomized >800 patients with CHF with preserved EF to ACE inhibitor or placebo, and did not find any difference in the primary outcome (death or CHF hospitalization), or most of the secondary outcomes. There were some improvements in functional class and six minute walk testing in the ACE group, as indicated in Table 8 below:

Table 8: Selected outcomes in ACE versus placebo[22]

	Placebo	Perindopril	
NYHA I	47 (12.4%)	75 (20.3%)	
NYHA II	268 (70.5%)	235 (63.7%)	*P*=0.030*
NYHA III/IV	65 (17.1%)	59 (16%)	
Six-min walk distance (m)	*n*=324	*n*=318	Mean difference in change [95% CI]
Mean (SD)	309 (132)	328 (126)	14 m [3 to 25]
			P=0.011**

*Fisher's exact test **Analysis of covariance

Dose and type:

Any dose of ACE-inhibition is effective in reducing morbidity and mortality in those with reduced EF. Several studies have shown a significant benefit in reducing CHF hospitalizations with high dose ACE versus low dose ACE, although higher doses also increased the risk of adverse events (such as renal insufficiency and hyperkalemia). Given this, patients should be titrated to the highest tolerable dose (without adverse effects), being mindful that any dose is beneficial. [23,24] There is no data to support the superiority of any one ACE inhibitor over another.

Safety:

In the *SOLVD trial*, ACE inhibitors were significantly more likely than placebo to cause a significant increase in serum creatinine and potassium, as outlined in Table 9 below.

Table 9: Risk of adverse events with ACE inhibitors versus placebo in SOLVD trial[19]

Adverse event	Enalapril	Placebo	P value
Creatinine> 2mg/dL	10.7%	7.7%	<0.01
Potassium > 5.5 mmol/L	6.4%	2.5%	<0.01
Dizziness / Fainting	57%	50%	NA
Cough	37%	31%	NA

BOTTOM LINE: ACE inhibitors are should be first- line therapy for most patients with CHF. In patients with reduced EF, regardless of symptoms, ACE inhibitors reduce morbidity and mortality. In patients with preserved EF, ACE inhibitors improve functional class and walking distance. Any dose and any type of ACE inhibitor is beneficial; higher doses may reduce hospitalizations, but present a are associated with higher risk of adverse events.

Angiotensin Receptor Blockers (ARBs)

Efficacy:

ARBs are also effective in reducing mortality and hospitalizations in patients with CHF, primarily systolic CHF. A series of *CHARM trials* found candesartan beneficial compared to placebo as listed in table 10 below. Similar to ACE inhibitors, the benefits of ARBs for those with preserved EF are less well established. The *CHARM-preserved trial* (Table 10) found a marginal benefit for candesartan in patients with normal EF, and a meta-analysis that combined the *CHARM-preserved trial* with the *I-PRESERVE trial* did not find a benefit of ARBs for mortality or CHF hospitalizations in patients with normal EF.[25]

Table 10: CHARM trial outcomes[25]

Trial	Patient type studied	Primary outcome: CV death or CHF hospitalization (candesartan versus placebo)	Secondary outcome: CHF hospitalization (candesartan versus placebo)
CHARM-alternative[33]	EF<40% NYHA II-IV Intolerant to ACE	33% vs 40% (p<0.0001)	20% vs 28% (p<0.0001)
CHARM-Added[34]	EF<40% NYHA II-IV Already on ACE	38% vs 42% (p=0.01)	24% vs 28% (p=0.02)
CHARM-preserved[35]	EF>40% NYHA II-IV	22% vs 24% (p=0.05)	16% vs 18% (p=0.05)
CHARM-overall[36]	All 3 above studies combined	All cause mortality 23% vs 25% (p=0.03)	20% vs 24% (p<0.0001)

A randomized controlled trial of the angiotensin receptor blocker (ARB) valsartan in patients with NYHA class II-IV produced findings similar to those of the CHARM-overall study, with significant reductions in the combined outcome

measure (morality, cardiac arrest, CHF hospitalization, or IV inotrope/vasodilator for 4 hours) compared to placebo.[30]

Dose and type:

As with ACE-inhibitors, any ARB dose is effective in reducing morbidity and mortality. One study found a significant benefit in reducing CHF hospitalizations with high dose ARB versus low dose ACE, although the higher the dose, the higher the risk of adverse events (such as renal insufficiency and hyperkalemia). Given this, patients should be uptitrated to the highest tolerable dose (without adverse effects), being mindful that any dose is beneficial.[31]

Safety:

In the *CHARM-overall trial*, ARBs were significantly more likely than placebo to cause hypotension, and a significant increase in serum creatinine and potassium, as outlined in Table 11 below.

Table 11: Risk of discontinuation due to adverse events with ARB versus placebo in *CHARM-overall trial*[29]

Cause of discontinuation	Candesartan	Placebo	P value
Hypotension	3.5%	1.7%	<0.0001
Increase in creatinine	6.2%	3.0%	<0.0001
Hyperkalemia	2.2%	0.6%	<0.0001
Any adverse event or laboratory abnormality	21%	16.7%	<0.0001

ACE or ARB or both?

A meta-analysis of trials comparing ACE and ARBs in CHF found no significant differences between ACE and ARBs in mortality or hospitalization rates. [32] The ACC/AHA recommends ARBs in patients who cannot tolerate an ACE.[5]

Both the *CHARM-added* study and the *Val-HeFT* found that the combination of ACE and ARB significantly reduce morbidity and mortality in patients with systolic dysfunction, compared to an ACEI alone.[27] However, given the risk of adverse events (hyperkalemia and renal dysfunction), the ACC/AHA and HFSA recommend against routinely combining ACEIs and ARBs.[7,33]

BOTTOM LINE: In patients with symptoms and reduced EF, ARBs reduce morbidity and mortality. In patients with preserved EF, the benefit of ARBs is less well established. Any dose and any type of ARB is beneficial; higher doses may reduce hospitalizations, but are associated with higher risk of adverse events. Guidelines recommend ACE as first line therapy, and ARBs in those who cannot tolerate an ACE. ACE and ARB's should not routinely be combined to due to the risk of adverse events.

Beta blockers

Efficacy:

Beta blockers are routinely recommended in all patients with systolic CHF who are already on an ACE and still symptomatic. This is based on several randomized controlled trials, as outlined in Table 6 below:

Table 6: Efficacy of beta blockers in heart failure by trial and outcome

Trial (drug)	Patient type studied and mean follow up	Primary outcome: All cause mortality (beta blocker versus placebo)	Secondary outcomes (beta blocker versus placebo)
CIBIS-II (bisoprolol)[17]	EF<35% NYHA class II-IV 15 months	12% vs 17% (p<0.0001)	Sudden cardiac death 4% vs 6% (p=0.001)
MERIT-HF (metoprolol CR/XL)[18]	EF<40% NYHA class II-IV 12 months	7% vs 11% (p=0.006)	Sudden cardiac death 4% vs 7% (p=0.0002)
Carvedilol Prospective Randomized Cumulative Survival Study Group (carvedilol) [19]	EF<25% NYHA class III-IV 10 months	11% vs 17% (p=0.001)	Death or hospitalization 37% vs 45% (p<0.001)

The role of beta-blockers in patients with diastolic CHF has been less rigorously studied. The largest trial enrolled elderly patients recently hospitalized for CHF (SENIORS trial) and randomized them to the beta blocker nebivolol or placebo. Two subgroups of patients were analyzed: those with EF <35% or > 35% (with actual median EF values of 30% versus 46%). The analysis found the beneficial

effects of nebivolol on all outcomes were similar between the high and low EF groups; outcomes included mortality, CV hospitalizations, CHF hospitalizations, all-cause hospitalizations and sudden cardiac death. However, the trial has been criticized for not truly answering the question of the value of beta blockers in those with preserved EF, as the median EF value in the "preserved" group was only 46%.[37]

An ongoing trial (beta-PRESERVE) is randomizing patients with normal EF to metoprolol or placebo, with the primary outcome measure of CV death or CHF hospitalization, which should more definitively define the role of beta blockers in CHF patients with preserved EF. [38]

Dose and type:

If a beta-blocker is started, there is evidence that its dose should be titrated to the highest tolerated, in relation to heart rate and blood pressure. One randomized trial found a benefit of higher versus lower dosing of carvedilol on left ventricular function and mortality. [39] Mortality rates at 6 months were:

Placebo:	16%
Low-medium dose carvedilol (6.25mg-12.5mg BID):	6-7%
High dose carvedilol (25mg BID):	1%

A recent meta-analysis of randomized controlled trials (95% of which enrolled patients with systolic CHF) found that heart rate, not beta-blocker dose, was the best predictor of death. For every 5 beats per minute reduction in heart rate, the risk of death was reduced by 18% (95% CI 6% to 29%). [40]

The ACC/AHA recommends using a beta-blocker with proven mortality benefit (e.g. metoprolol CR/XL, bisoprolol, or carvedilol).[7]

There is indirect evidence that carvedilol (which has vasodilating effects) may be superior to non-vasodilating beta blockers (e.g. bisoprolol or metoprolol). A meta-analysis of 21 trials in almost 6,000 CHF patients found overall mortality reduction was greater with carvedilol than the other beta blockers (54% versus 27%, p=0.007), particularly in patients without ischemic heart disease.[41] However, carvedilol lowers blood pressure more than the other agents, and may the best agent in patients who also have hypertension.

Safety:

In the MERIT-CHF trial, metoprolol was very well tolerated, with discontinuation rates of the study drug lower than those for placebo (14% versus 15%). The mean daily dose was 159mg, with almost 90% of patients receiving at least 100mg of

the drug (and 2/3 receiving 200 mg a day). Mean changes in heart rate and systolic blood pressure are noted in Table 7 below.[35] In the carvedilol study, discontinuation rates due to adverse effects were also lower than for placebo.[36]

Table 7: Mean decrease in blood pressure and heart rate by metoprolol CR/XL[35]

Drug	metoprolol CR/XL	Placebo
Mean change in heart rate	-14 points	-3 points
Mean change in systolic blood pressure	-2.1 mmHg	+3.5 mmHg

BOTTOM LINE: Beta-blockers reduce mortality and morbidity in patients with systolic CHF. There is less evidence of benefit for beta blockers in diastolic CHF. Guidelines recommend carvedilol, metoprolol CR/XL, or bisoprolol, the former of which may have the greatest mortality benefit in CHF. Dose should be titrated to the lowest tolerated heart rate. Beta blockers are well tolerated, with discontinuation rates similar to placebo in clinical trials.

Aldosterone-blocking agents

Spironolactone

Efficacy:

The RALES study showed that spironolactone reduces mortality in patients with reduced EF (<35%) and NYHA class III-IV symptoms, who are already on an ACE, loop diuretic, and in most cases digoxin (about ¾ of patients). Patients in the RALES study were randomized to spironolactone (25mg) or placebo. At 2-year follow up, all-cause mortality was significantly lower in the spironolactone group (35% versus 46%, relative risk reduction 30%, p<0.001). [42] The role of spironolactone in patients with CHF and preserved EF has not been established; however, the TOPCAT study is an ongoing study which is randomizing CHF patients (EF>45%) to spironolactone or placebo, which should clarify the role of spironolactone in patients with (relatively) preserved EF.[43]

Safety:

The primary safety concern with aldosterone blocking agents is renal function decline and hyperkalemia. In the *RALES trial*, the median creatinine increase

was 0.05 to 0.10 mg/dL and the median potassium increase was 0.30 mmol/L (at a mean study dose of 25mg). In this trial, serious hyperkalemia occurred in 2% of the study group and 1% of the placebo group. However, a population-based study of routine care found that after the publication of the *RALES trial,* as the rate of spironolactone use increased from 34 to 149 (per 1,000 CHF patients), hospitalizations due to hyperkalemia also increased from 2 to 11 (per 1,000 patients) from 1994 to 2001.[44]

Spironolactone can also cause endocrine side effects, which occurred in 10% of the treatment group (versus 3% of the placebo group). These included gynecomastia, breast pain, menstrual irregularities, impotence, and decreased libido. Discontinuation rates due to adverse events occurred in 8% of the treatment group and 5% of the placebo group.

The ACC/AHA recommends against starting aldosterone antagonists in patients with:

1. Creatinine>2.5 mg/dL (in men); >2.0 mg/dL (in women)
2. Serum potassium >5.0 mEq/L[7]

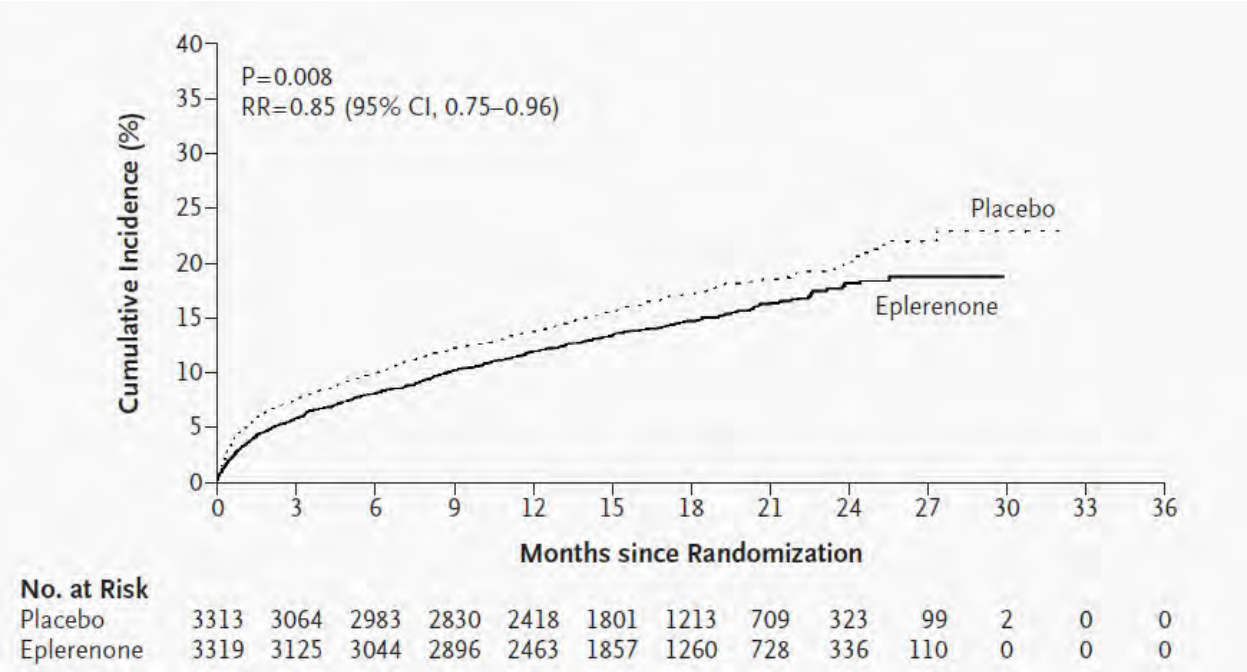
Eplerenone

Efficacy:

Eplerenone is an aldosterone-blocker that selectively blocks the mineralocorticoid receptor and not the glucocorticoid, progesterone, or androgen receptors.

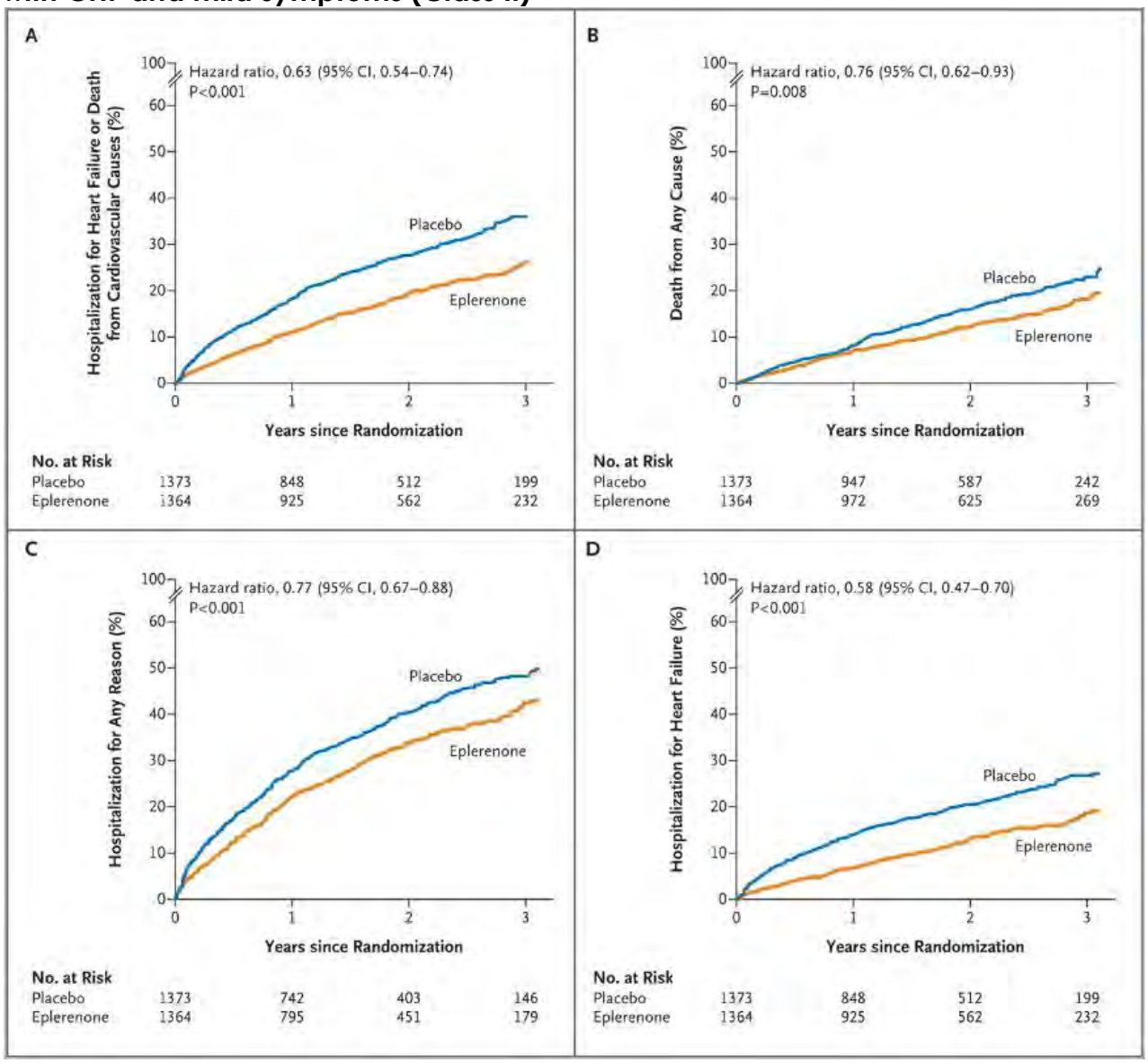
In a randomized trial (*EPHESUS trial*) >6,000 patients within 3-14 days after an acute MI with reduced EF (<40%) were randomized to eplerenone (starting dose 25mg, mean dose by end of trial, 43mg) or placebo. All three primary endpoints occurred significantly less often in the eplerenone group (figure 7 below):[45]

Figure 7: Death from any cause in eplerenone versus placebo in patients with CHF post-acute MI[45]



Eplerenone has also demonstrated benefit in reducing morbidity and mortality in CHF patients with mild symptoms (Class II). In a randomized trial >2,700 patients with mild CHF symptoms and EF ≤ 35% were randomized to eplerenone (starting dose 25mg, mean dose by end of trial, 39mg) or placebo. All primary endpoints occurred significantly less often in the eplerenone group (figure 8 below):[46]

Figure 8: Selected clinical outcomes in eplerenone versus placebo in patients with CHF and mild symptoms (Class II)[46]



Safety:

Overall adverse events rates were the same in the treatment and placebo groups in the *EPHESUS trial*, but the eplerenone group had a higher rate of renal dysfunction and hyperkalemia.

Serum creatinine increased by a mean of:

Placebo:	0.02 mg/dL
Eplerenone:	0.06 mg/dL

Serious hyperkalemia (≥ 6 mmol/L) occurred in:

Placebo (CrCl>50cc/min): 4%
Eplerenone (CrCl>50cc/min): 6%
Placebo (CrCl<50cc/min): 6%
Eplerenone (CrCl<50cc/min): 10% [45]

A large retrospective database analysis found that only 33% of patients with CHF who met criteria to benefit from aldosterone antagonists actually received them, indicating that physicians may have limited understanding of their efficacy, or excessive concerns about their safety. [47]

The ACC/AHA recommends the following to reduce the risk of hyperkalemia and renal dysfunction associated with aldosterone antagonists:

- Use the lowest effective dose
- Avoid NSAIDs
- Reduce or discontinue all potassium supplements
- Closely monitor potassium and creatinine levels (check in 3 days, then 1 week, then monthly for the first 3 months)[5]

BOTTOM LINE: Spironolactone reduces mortality in patients with reduced EF (<35%) and class III-IV symptoms. Eplerenone (which selectively blocks only the mineralocorticoid receptor) reduces mortality in patients with reduced EF (<35%) and class II symptoms. Both increase creatinine and potassium levels in a dose dependent fashion, and should not be used in those with creatinine >2.5 mg/dL (in men; >2.0 mg/dL in women) or serum potassium >5 meq/L. Spironolactone is less expensive, but may cause more endocrine side effects than eplerenone.

Digoxin

Efficacy:

The only large randomized trial of digoxin enrolled patients with an EF<45% who were already on combinations of ACE inhibitors and diuretics. After about 3 years of follow up, overall mortality and cardiac mortality were no different between the groups, but significantly fewer patients in the digoxin group versus the placebo group were hospitalized for worsening heart failure (27% versus 35%, p<0.001). This reduction was most pronounced in the sub-group of patients with EF<35%, enlarged ventricular size, or NYHA class III-IV symptoms.[48] The only large randomized trial of digoxin in patients with diastolic CHF did not find any benefit

on the primary outcome (hospitalization or CHF death). [49] Current guidelines recommend against the use of digoxin in patients with low EF, sinus rhythm, and no symptoms of CHF.[7]

Safety:

In the above trial, suspected digoxin toxicity (based on physician suspicion) occurred in 12% of the digoxin group and 8% of the placebo group ($p<0.001$), although only 2% of patients had digoxin levels exceeding 2 ng/mL, indicating the symptoms of toxicity are non-specific and difficult to attribute to increased drug levels.[48] Digoxin toxicity occurs more commonly in patients with advanced age, low BMI, and renal insufficiency. Symptoms of digoxin toxicity include:

1. Cardiac arrhythmias (re-entrant rhythms and heart block)
2. GI symptoms (anorexia, nausea, vomiting)
3. Neurologic symptoms (visual disturbances, confusion)

BOTTOM LINE: Digoxin can reduce hospitalizations in patients with systolic CHF, but not diastolic CHF, and has no effect on mortality. Digoxin toxicity occurs more commonly in those with advanced age, low BMI, and renal insufficiency; the drug should be used with caution in those patients.

Diuretics

Goals of therapy:

The goal of diuretics in patients with heart failure is to achieve a "dry weight" and reduce symptoms of shortness of breath. "Dry weight" is generally the lowest measured weight of the patient, performed first thing in the morning, on a day when functional status is at its best: this should be the daily target weight. Patients should be encouraged to check their weight daily, and manage their diuretics based on this. The diuretic regimen should be variably managed, based on weight and symptoms of heart failure.[3] This plan can be determined in advance (e.g., "If you gain more than 1 kg in weight in a day, take an extra dose of x mg of furosemide"). The plan may involve a telemedicine component, discussed further below. Diuretics should be combined with salt and fluid restriction for maximal efficacy.[7]

Efficacy:

Loop diuretics (eg furosemide, torsemide, bumetanide) are the first-line diuretics since they produce more natriuresis (sodium loss through the kidneys) than any other diuretic type. These drugs act on the "loop" of the nephron by blocking reabsorption of sodium, thus leaving more sodium within the nephron to be

excreted (Figure 9). Other diuretics useful in CHF include the thiazides, potassium sparing diuretics, and carbonic anhydrase inhibitors.

Thiazide diuretics act on the distal tubule and connecting segment of the nephron to block sodium and water reabsorption there (Figure 9). Potassium sparing diuretics act on the collecting duct, and the carbonic anhydrase inhibitors act on the proximal tubule. Different diuretic types can therefore be combined for synergistic effect. A meta-analysis of randomized placebo-controlled trials of diuretics (primarily loop or thiazide diuretics) found that these drugs reduce the risk of death, although sample sizes were small and confidence intervals wide. Diuretics also improved exercise capacity, and reduced the risk of worsening CHF (odds 0.31, 95% CI 0.15 to 0.62, p = 0.001).[50]

Loop diuretics:

The loop diuretics cause the patient to excrete more filtered sodium than any other diuretic type. Furosemide is most commonly used, based on its low cost and effectiveness in most patients. Torsemide and bumetanide have better and more predictable oral absorption than furosemide, and can be used in patients with poor oral absorption, such as that caused by right sided heart failure and bowel edema. Dosing of loop diuretics needs to be higher with higher creatinine, but generally starts at 20-40mg, with higher dosing given for non-response; see Table 12. Ethacrynic acid is a loop diuretic but not a sulfonamide, so it can be used in patients with sulfa allergy, although it is rarely used otherwise due to higher risk of ototoxicity and inability to deliver in IV form.

Table 12: Initial and maximum dosing of loop diuretics

Drug	Initial dose	Maximum daily dose
furosemide	20-40 mg	600 mg
torsemide	5-10 mg	200 mg
bumetanide	0.5-1 mg	10 mg

Thiazides:

If patients continue to have hypervolemia despite adequate doses of loop diuretics, a thiazide can be added temporarily, or on an as-needed basis (based on weight or symptoms). Chronic daily use of thiazides combined with a loop diuretic is discouraged, given the risk of electrolyte depletion and volume depletion, and these patients should be very closely followed.[33] Hydrochlorothiazide or metolazone are the most commonly used; the latter may work better in patients with renal insufficiency, but the data supporting this is limited.

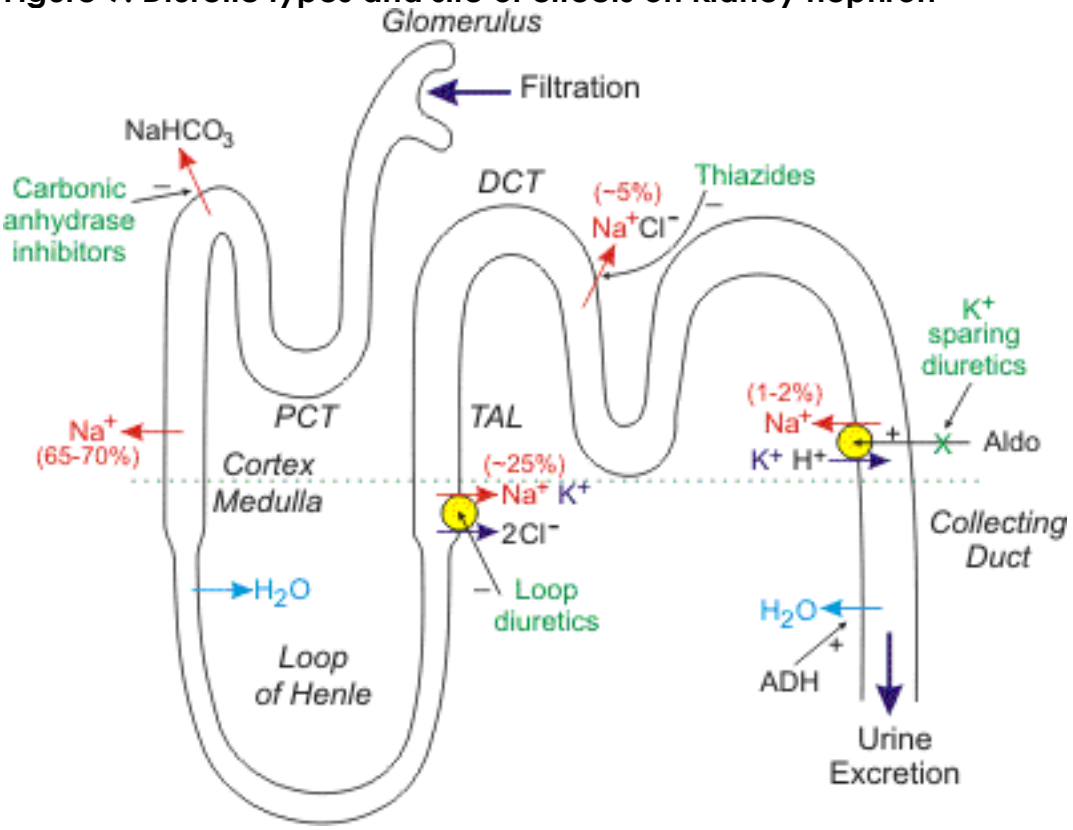
Potassium sparing diuretics:

Amiloride and triamterene excrete about the same amount of sodium as the thiazide diuretics, so can also be combined with a loop diuretic or thiazide in CHF patients. The primary advantage is that they reduce potassium loss. However, if potassium sparing is needed, the use of aldosterone antagonist agents is more beneficial (e.g., spironolactone or eplerenone) since they have a proven mortality advantage in CHF (see "aldosterone antagonists").

Carbonic anhydrase inhibitors:

Acetazolamide produces little sodium and fluid restriction, and therefore has a limited role in the treatment of volume overload in CHF patients.

Figure 9: Diuretic types and site of effects on kidney nephron



Safety:

All diuretics can cause metabolic disturbance, which is generally dose-dependent; these are summarized in Table 13.

Table 13: Diuretics and common adverse effects

Diuretic type	Common adverse effects
Loop diuretics	Hypokalemia Hypochloremia Hypomagnesemia Hyponatremia Hyperuricemia Increased BUN/creatinine Ototoxicity (high dose)
Thiazide diuretics	Hypokalemia Hyperuricemia Hyperglycemia Increased BUN/creatinine
Potassium sparing diuretics	Hyperkalemia Impotence Gynecomastia

Combination therapy:

The different diuretic types can be combined in patients whose dry weight cannot be maintained on a single diuretic. Since different diuretics block different areas of the nephron, they can be additive in their diuretic effect. [3]

BOTTOM LINE: Diuretics can reduce mortality, hospitalizations, and symptoms in patients with CHF. Loop diuretics are the first-line category; torsemide and bumetanide may have better oral absorption than furosemide, and ethacrynic acid can be used for sulfonamide allergic patients. This class can be combined with thiazides to enhance diuresis, but patients should be closely monitored for volume depletion and electrolyte disturbances. If a potassium-sparing diuretic is needed, the aldosterone antagonists are preferable. Patients should be monitored for adverse effects of diuretics, primarily electrolyte derangements and renal dysfunction.

Hydralazine + Isosorbide dinitrate

Efficacy:

A large randomized trial of patients with CHF found that patients given a combination of hydralazine + isosorbide dinitrate had a significantly higher mortality rate at 2 years than those given ACE inhibitors (25% versus 18%, p=0.02).[51] However, sub-group analysis from the *SOLVD trials* found no benefit of

ACE inhibitors (mortality, CHF hospitalizations, or blood pressure lower) among black patients.[28] This led to a trial that randomized black patients with NYHA class III-IV CHF (with EF <35%, or <45% with ventricular dilation) to placebo or hydralazine + isosorbide dinitrate (in addition to ACEI and beta blocker, with or without an aldosterone antagonist). The results at ten months are presented in Table 14 below.[52]

Table 14: Outcomes of hydralazine + isosorbide versus placebo in black patients with symptomatic CHF[52]

Outcome	Hydralazine + Isosorbide	Placebo	P value
All cause mortality	6.2%	10.2%	0.02
CHF hospitalization	16%	24%	0.001
Change in quality of life at 6 months (lower better)	-5.6	-2.7	0.02

Another smaller trial randomized patients of different races who were already taking either an ACEI or ARB to receive hydralazine + Isosorbide dinitrate or placebo therapy (with reduced EF). Results of this trial were similar, as seen in Table 15 below:

Table 15: Benefits of hydralazine + Isosorbide dinitrate, added to ACE/ARB therapy, in all races, compared to placebo[53]

Outcome	Hydralazine + isosorbide	Placebo	P value
All cause mortality	34%	41%	p=0.04
All cause mortality or CHF admission	70%	95%	P=0.03

Conclusion: hydralazine + isosorbide reduce mortality and hospitalization and can benefit patients with reduced EF who are already taking an ACEI or ARB, regardless of race.

Safety:

Adverse events that occurred significantly more often in the hydralazine + isosorbide dinitrate group versus placebo were:

- headache (48% vs 19%, p<0.001)
- dizziness (29% vs 12%, p<0.001) [52]

BOTTOM LINE: Hydralazine + isosorbide dinitrate reduces mortality and hospitalization in patients with reduced EF already on standard medical therapy (including ACE) regardless of race. This combination was well tolerated in clinical trials.

Calcium channel blockers

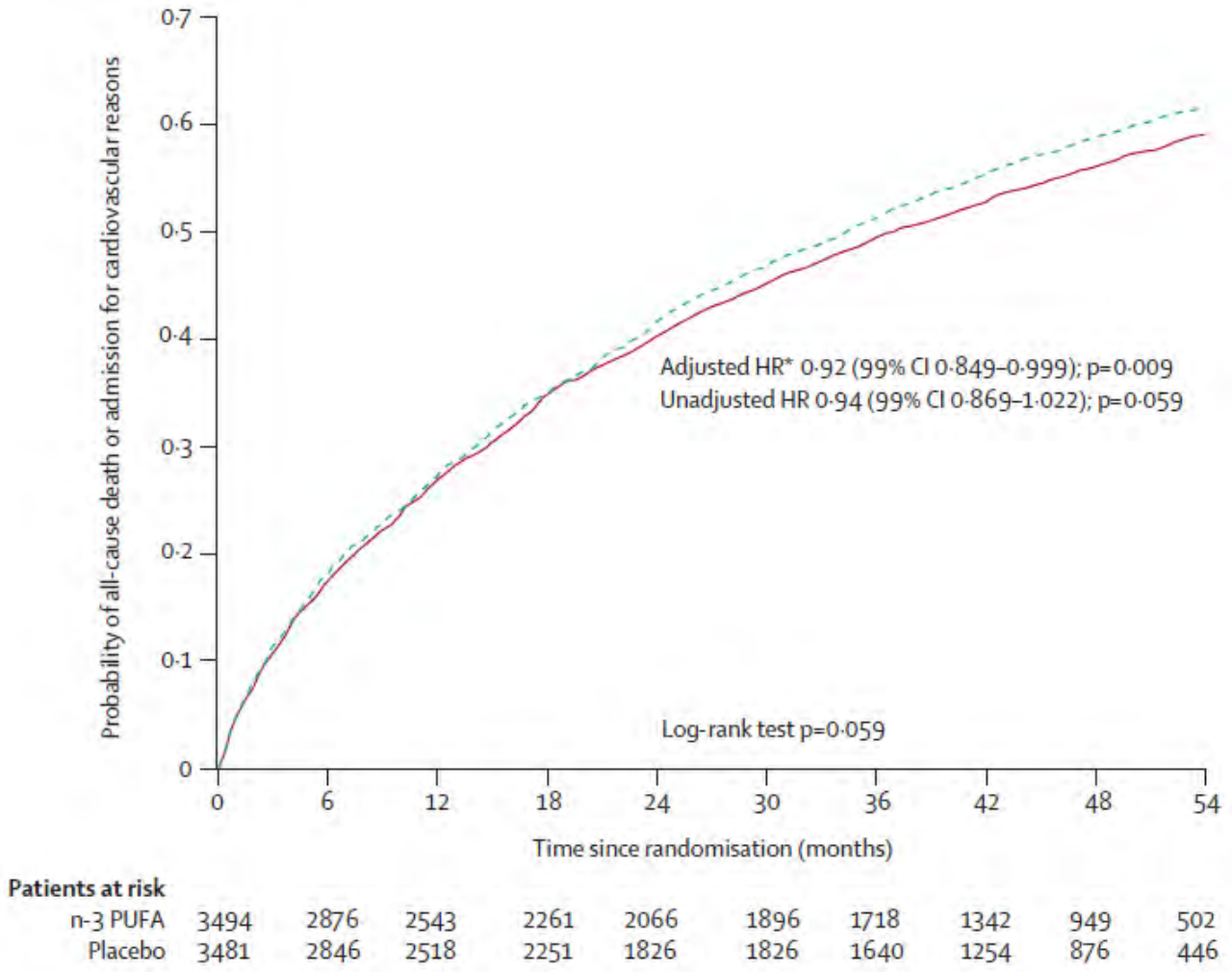
Calcium channel blockers have a limited role in the treatment of CHF. In the *PRAISE trial*, patients with severe systolic CHF were randomized to amlodipine or placebo; there was no significant difference in the primary endpoint of all cause death or CV hospitalization, but there was a reduction in mortality among the subgroup of patients with non-ischemic CHF. [54] Therefore, amlodipine is a reasonable addition to a regimen in patients with non-ischemic CHF, if all other first line therapies have been used or excluded.[7]

n-3 polyunsaturated fatty acids (PUFA)

Efficacy:

Polyunsaturated fatty acids reduce inflammation, platelet activation, and autonomic tone; their role in reducing malignant arrhythmias and sudden cardiac death has recently been investigated. A large randomized controlled trial of >7,000 patients with symptomatic CHF (NYHA class II-IV) randomized patients to 1 gram of n-3 PUFA (850-882mg eicosapentaenoic acid and docosahexaenoic acid as ethyl esters) or placebo. The primary outcome (time to death or CV hospital admission) occurred in 57% of patients in the treatment group and 59% in the control group, which represents a 8% relative reduction (p=0.009)(Figure 10).[55]

Figure 10: Time to death or CV hospital admission in CHF patients randomized to PUFA versus placebo[55]



Safety:

In this trial, there were no differences between PUFA and placebo in rates of discontinuation (29% in each group) or rates of discontinuation due to an adverse event (3% in each group, the majority of which were gastrointestinal upset).[55]

BOTTOM LINE: PUFA is safe and has a modest benefit in reducing the risk of death and hospitalizations in patients with symptomatic CHF.

Management of acute decompensated CHF

Background:

Acute decompensated heart failure is the leading cause of hospital admissions for patients >age 65 and the most costly cardiac condition in the US. The likelihood of death within 60 days after a hospitalized CHF event is as high as 20%. About half of these patients have a preserved EF. [12] Signs and symptoms of acute heart failure are discussed in the section on clinical presentation.

Triggers

A list of the most common triggers for CHF exacerbation is outlined in Table 16.

Table 16: Common CHF exacerbation triggers[12]

Primary cardiac
• Progressive cardiomyopathy with remodeling
• Acute cardiomyopathy (myocarditis, postpartum cardiomyopathy)
• Myocardial ischemia
• Arrhythmia (tachy- or bradyarrhythmia)
• Valvular dysfunction (stenosis or regurgitation)
• Pericadiral syndrome (tamponade, constriction)
Pressure overload
• Hypertensive urgency or emergency
Volume overload
• Sodium or volume load
• Decreased compliance with diuretics
• Renal dysfunction
• Hepatic dysfunction
High output
• Shunt (intra- or extracardiac)
• Anemia
• Septicemia
• Thyroid disease
Other
• Inflammation or infection
• Major surgery
• Lack of compliance with heart failure medications
• New medications (excess β-blockade)
• Substance abuse (alcohol, stimulants)

Indications for hospitalization

Several factors increase the need for hospitalization in CHF, although individual differences in patients' functional status, home and caregiver situation, and resources will help shape the decision to admit or treat at home.[56]

Table 17: Relative indications for hospital admission for CHF[57]

CHF symptoms with end-organ decompensation 3. hypoxia (saturations <90%) 4. altered mental status 5. worsening renal function 6. acute coronary syndrome
Worsened dyspnea, especially dyspnea at rest
Hypotension
New or hemodynamically significant arrhythmia (such as atrial fibrillation)
Major electrolyte abnormality
Significant weight gain (usually >5kg above baseline) or worsening edema
Repeated ICD firings

In addition to vital signs, at least daily monitoring should be done during the hospital stay, as described below:

Table 18: Ongoing daily inpatient assessments for CHF hospitalizations[57]

Laboratory testing (basic chemistries with electrolytes and renal function)
Weight, total intake, and total outputs
Signs (edema, ascites, pulmonary rales, hepatomegaly, increased JVP, hepatojugular reflux, liver tenderness)
Symptoms (orthopnea, dyspnea, fatigue, lightheadedness, cough, PND)
Assessment of fluid restriction (<2 liters/day) and sodium restriction (<2g/day)

Medical management

The medical management of patients with acute decompensated CHF should generally include those medications that the patient takes at home (such as beta-blockers, ACE/ARBs, aldosterone antagonists, etc.). These should usually not be stopped unless an acute problem (such as hyperkalemia, hypotension, bradycardia, or renal failure) necessitates their discontinuation. Doses should be titrated upwards or downwards based on the patient's stability, vital signs, and laboratory findings. For example, the ACE inhibitor and/or beta blocker dose may need to be reduced in the setting of severe decompensation, and these drugs may need to be temporarily held in the setting of cardiogenic shock. Abrupt discontinuation of beta-blockers should be avoided, and only done in

patients with hemodynamic instability.[5] Diuretic doses usually need to be increased in the acute setting, and additional diuretic classes may need to be added. In addition to the home medical regimen, other specialized medications and management options should be considered, discussed below.[12]

Diuretics:

Here too, diuretics are a mainstay of therapy. As with chronic management, first line therapy should be a loop diuretic, which can be combined with other diuretic classes for additional benefit.

A recent randomized trial of patients hospitalized with CHF found furosemide given by intermittent IV bolus was just as effective as that given by continuous infusion, and there was no difference in symptoms if furosemide was given in low doses (eg equivalent to patient's home dose) or high dose (eg 2.5 times the home dose).[58] Therefore, there is little evidence-based guidance on the dose or frequency of intravenous furosemide that should be administered during an acute exacerbation of CHF. ACC/AHA recommends an initial IV dose of loop diuretic that equals or exceeds the home chronic oral dose. [7] If diuresis is inadequate, 2 options are available:

1. increase the dose of the loop diuretic
2. add a second diuretic type (thiazide or potassium sparing diuretic)

Inotropes:

Adrenergic inotropic therapy is usually reserved for patients with hemodynamic instability, when these agents may be required for survival. Otherwise, using these agents without symptomatic hypotension remains controversial and is not well supported by research evidence. These agents should only be used in an intensive care unit (ICU) setting (in most hospitals) under the supervision of an experienced team. A summary of these agents is outlined in Table 19.

Table 19: Inotropes by type of action, clinical use, and limitations[7,12]

Agent and type of action	Appropriate clinical use	Limitations
dobutamine and milrinone (inotrope*, chronotrope**, and vasodilator)	Acute CHF unresponsive to all other medical therapies or worsening renal function	Increases arrhythmias and risk of death
Dopamine and norepinephrine (inotrope*, chronotrope**, and vasoconstrictor)	Cardiogenic shock	Increases arrhythmias and risk of hypotension

*inotrope = increases heart contractility **chronotrope=increases heart rate

Venous vasodilators:

The two available venous vasodilators include morphine and nitroglycerin. Both should be used only in patients with adequate blood pressure. Both significantly reduce symptoms of breathlessness, but have not been shown to reduce morbidity or mortality.[7,12] A systematic review found the use of nitrates in patients with acute pulmonary edema was better in improving hemodynamics and reducing the need for intubation compared to furosemide.[59]

Arterial vasodilators:

The 2 available arterial vasodilators are nitroprusside and nitroglycerin (which is also a venodilator), both of which can be delivered via continuous IV infusion during an acute CHF exacerbation. They are indicated only in patients with hypertension and can usually be delivered only in an ICU setting. These agents should be switched to an oral agent (such as ACE or hydralazine/isosorbide dinitrate) as soon as the patient has stabilized and can take medications by mouth. [7,12]

Natriuretic peptides:

Natriuretic peptides are naturally occurring proteins released in response to atrial stretch, which act on the kidney to induce excretion of sodium. Nesiritide is a synthetic recombinant B-type natriuretic peptide, FDA approved in 2001 for use in hospitalized acute CHF patients. In early randomized trials, it was found to reduce pulmonary capillary wedge pressure, dyspnea scores, and 30 day readmission rates. However, a subsequent meta-analysis found that it also causes a significant increase in the risk of renal dysfunction and mortality. A subsequent large trial enrolled >7000 patients hospitalized with acute CHF who were randomized to nesiritide or placebo. There were no significant differences in dyspnea scores, readmission rates, or mortality rates between the groups, but there were higher rates of hypotension in the nesiritide group.[60] Based on this, nesiritide should not be routinely used in patients hospitalized with acute CHF.

BOTTOM LINE: In acute decompensated CHF, patients should be continued on their home oral agents, with doses adjusted upwards or downwards, depending on their clinical condition. Loop diuretics are a mainstay in acute CHF; they can be given IV, and can be combined with other diuretic classes for maximum effect. Other supportive therapies (such as inotropes, vasodilators, and natriuretic peptides) should only be used by experienced physicians in ICU settings, are primarily used for symptom management, and have not been shown to reduce the risk of death.

Invasive management (revascularization, NIPPV, intubation)

Ultrafiltation:

Peripheral ultrafiltration is a promising new therapy for patients with acute decompensated CHF. A randomized trial (*UNLOAD trial*) of patients hospitalized with acute CHF randomized to ultrafiltration versus diuretics alone found the following benefits of ultrafiltration: [61]

- Improved weight loss at 48 hours (5 versus 3 kg, p<0.001)
- Decreased need for vasoactive drugs (3% versus 13%, p=0.02)
- Reduced 90-day readmission rate (18% versus 32%, p=0.02)

It requires the insertion of a venous access line, and specialized monitoring of the patient and the equipment. It is not yet clear if this therapy will become standard practice for patients hospitalized with CHF.[61]

Non-invasive positive pressure ventilation (NIPPV):

In patients with acute CHF and hypoxia, the use of NIPPV has been shown to reduce the need for invasive mechanical ventilation and to reduce mortality. NIPPV can consist of either continuous positive airway pressure (CPAP) or biPAP (bilevel positive airway pressures). Both modalities act by reducing venous return to the heart, and improve oxygenation levels. CPAP delivers a continuous positive airway pressure, whereas biPAP delivers a "bi-modal" pressure (more during inspiration and less during expiration). These can be applied by nasal prongs (for CPAP) or fitted mask over the nose and mouth (for CPAP or biPAP). A meta-analysis of randomized trials in acute CHF found CPAP and biPAP(compared to standard therapy) significantly reduced:[62]

- the need for mechanical intubation by 22% and 18% respectively
- the risk of mortality by 13% and 7% respectively

In that review, the differences between CPAP and biPAP were not significantly different; therefore either is appropriate, depending on local availability and/or patient/provider preference.[62]

Discharge Planning

Quality Measure Reporting:

The Centers for Medicare and Medicaid services (CMS) established a voluntary public reporting program for patients hospitalized with heart failure. Participating hospitals may choose to submit their performance of CHF-related quality measures, which are publicly reported at www.hospitalcompare.org. The

currently available measures are listed in Table 20, which summarize many important aspects of CHF care, and should be addressed before discharging the patient.

Table 20: Publicly reported quality measures for hospitalized CHF

Left ventricular function measure
ACE or ARB at discharge
Beta blocker at discharge
Discharge instructions including 3. diet 4. weight monitoring 5. discharge medications (doses, when to uptitrate) 6. adherence 7. activity 8. follow up appointments 9. what to do if symptoms worsen (what meds to take, who to call)
30 day mortality
30 day readmission rate

Reconciliation of all medications must also be performed on admission and discharge, required for hospital accreditation by the Joint Commission National Patient Safety Goal program.[63]

Discharge documentation:

Inpatient stay and discharges for patients with CHF have changed significantly in the last 15 years (Table 21).[64] This makes discharge planning vital to ensure that CHF patients understand their care plan and follow-up plan.

Table 21: Changes in length of stay, discharge to home, and 30 day readmission rates from 1993 to 2006 in CHF Medicare patients[64]

Outcome	Year 1993	Year 2006
Mean length of stay	8.8 days	6.3 days
Discharge to home	74%	67%
30 day readmission	17%	20%

In a large observational study of Medicare patients discharged after an episode of CHF, only 38% of patients had a follow up visit within 7 days of discharge. Those hospitals with the highest rate of early follow-up had the lowest 30 day readmission rates.[65] The Heart Failure Society of America recommends that the following criteria be documented before discharge:

Table 22: Suggested documentation for CHF hospital discharge[57]

Exacerbating factors have been addressed and treated (e.g. ischemia, arrhythmia, non-compliance, etc.)
Near optimal volume status and medical management have been attained
Transition back to oral medications (e.g. diuretics) has been completed
Patient and family education has been completed
EF documented
Smoking cessation addressed (if relevant)
Ambulatory functional status assessed
Follow up clinic visit arranged (within 7-10 days)

Management of common co-morbid conditions

Patients with CHF often have many other co-morbid conditions that can affect the management of their heart disease. According to Medicare claims data, about 40% of patients with CHF have 5 or more co-morbid conditions. [62] Many older patients with CHF are already taking multiple medications for their cardiac disease; the mean number of medications in all Medicare patients recently discharged is 7, with a mean of 10 daily doses. [66] Therefore, careful attention must be paid to managing other co-morbid conditions without inducing unnecessary polypharmacy. This section will briefly discuss the most commonly associated co-morbid conditions, and how they impact the management of CHF.

Hyperlipidemia:

Two large randomized trials (*GISSI-HF trial and CORONA trial)* in patients with symptomatic systolic CHF found no benefit in any of the outcomes in patients randomized to rosuvastatin versus placebo.[67,68] There are no randomized trials of statin therapy in patients with diastolic dysfunction. Therefore statin therapy should not be initiated in CHF patients for the purpose of improving outcomes, in the absence of other indications for statin therapy (e.g., ischemic heart disease). For further information on the diagnosis and management of hyperlipidemia, see the monograph on lipid-lowering therapy at www.rxfacts.org.

Hypertension:

Concomitant hypertension can worsen the symptoms of CHF; blood pressure should be controlled at least to goal levels based on JNC-7 standards (BP<140/90 for most patients, and <130/80 in those with renal dysfunction). Some recommend lower targets (<130/80) for all patients with CHF.[69] Many medications used to treat CHF are effective anti-hypertensives, including ACE's,

ARB's, beta blockers, and diuretics. For more information on the diagnosis and management of hypertension, see the monograph on antihypertensive treatment at www.rxfacts.org.

Diabetes:

Many patients have concomitant CHF and diabetes. Insulin management is relatively unchanged with or without CHF, but the use of oral agents is more complicated. All glitazones are relatively contraindicated in CHF, as they can exacerbate CHF symptoms. Metformin should not be used in the setting of acute decompensated CHF, as it can increase the risk of metabolic acidosis, but can be used in chronic stable CHF. The oral sulfonylureas do not need to be adjusted in the setting of CHF, unless patients develop concomitant renal failure. For more information on the diagnosis and management of diabetes, see the monograph on type II diabetes at www.rxfacts.org.

Atrial fibrillation:

The most common arrhythmia in patients with CHF is atrial fibrillation, which occurs in 30% to 40% of CHF patients admitted to the hospital. Atrial fibrillation can exacerbate CHF symptoms by reducing the "atrial kick", or amount of blood that fills the ventricle during diastole, and therefore the cardiac output. For further discussion on the acute and chronic management of atrial fibrillation, see the module on this topic at www.rxfacts.org

Arthritis

Patients with concomitant CHF and arthritis should avoid non-steroidal anti-inflammatory drugs (NSAIDs), as they can increase the risk of CHF exacerbations, and increase blood pressure. No NSAIDs are considered safe for patients with cardiac disease, but the COX-2 inhibitors pose more risk than the COX-1 inhibitors. Of all NSAIDs, naproxen is the safest alternative if an NSAID is essential in patients with cardiac disease. Acetaminophen is safe and effective for arthritis pain in patients with CHF. For more information on the treatment of chronic pain, including a discussion of the risk of NSAIDs with cardiac disease, see the module on chronic pain at www.rxfacts.org.

Anemia

Iron-deficiency anemia commonly occurs in patients with systolic CHF, estimated in one study at 37% of patients, with higher prevalence in women, worse CHF functional class, and higher BNP levels.[70] One small randomized trial found that giving IV iron improved patient outcomes, including symptoms and health-related quality of life scores, with no apparent adverse effects. [71]

It is not currently known if correction of anemia improves outcomes in patients with CHF. A current trial is randomizing patients with symptomatic CHF and concomitant anemia to placebo or erythropoiesis-stimulating agent (egdarbepoetin-alpha, the *RED-HF trial)*. This industry-sponsored trial is expected to complete enrollment shortly.

Depression and anxiety

According to Medicare claims data, 8% of CHF patients also have depression and 3% have anxiety.[66] Both co-morbid conditions have been associated with lower compliance and higher cost, hospitalization rates, and mortality rates in patients with CHF. Both cognitive behavioral therapy and anti-depressants are recommended for these patients. The selective serotonin reuptake inhibitors (SSRIs) are most commonly utilized, as they appear to be effective and have few drug interactions.[13] The tricyclic antidepressants are relatively contraindicated in patients with cardiac disease and should generally be avoided. [66] For more information on the diagnosis and treatment of depression, see the monograph on this topic at www.rxfacts.org.

Renal dysfunction

About 40% of CHF patients also have chronic renal dysfunction, defined as creatinine clearance <60 ml/min. [66] This is likely a consequence of low cardiac output state and decreased renal perfusion with intrarenal vasoconstriction. About 1/3 of patients admitted with CHF have a significant increase in their serum creatinine (eg>0.3 mg/dL over baseline), which is associated with higher morbidity and mortality compared to patients without an increase over baseline. [66] Many of the medications used to treat CHF will have to be adjusted for renal dysfunction. ACEIs and ARBs both cause a transient reduction in creatinine clearance rates, although both are beneficial in patients with renal dysfunction -- especially that associated with proteinuria. The aldosterone antagonists should be used with caution in patients with renal dysfunction, with close monitoring of renal function and electrolytes (primarily potassium), and are contraindicated with creatinine clearance <10 ml/min.[66] Doses of loop diuretics generally must be increased as the creatinine clearance is decreased. The use of digoxin should be limited in those with renal dysfunction, and the dose should be appropriately decreased based on the creatinine clearance. Digoxin dosing calculators can help determine appropriate daily dosing. [73] Beta blocker doses generally do not have to be adjusted for creatinine clearance, although atenolol, which is renally cleared, should be avoided.

Cachexia

Some patients with advanced heart failure will have weight loss or muscle wasting, known as "cardiac cachexia". These patients will need an evaluation

by a nutritionist to determine their nutritional and caloric needs, current intake, and a nutritional plan to fulfill their needs. Caloric supplements may be needed, but anabolic steroids are not recommended. Daily multivitamins may be needed, but specific evaluation for nutritional deficiencies are rarely needed.[14]

Sexual dysfunction

It is recommended that sexual dysfunction be discussed openly with patients who have CHF. This is a common side effect of beta-blockers and other anti-hypertensive medications, and their risks/benefits should be reviewed in those with significant sexual dysfunction. The use of phosphodiasterase-5 inhibitors is reasonable in those with stable chronic CHF, but is contraindicated in patients taking nitrate preparations.[14]

Sleep Apnea

Approximately 11% of patients with CHF have obstructive sleep apnea and up to 40% have central sleep apnea. Apneic episodes can trigger the activation of sympathetic nervous system hormones that are detrimental to patients with CHF, as they increase heart rate and blood pressure. Treatment of sleep apnea can improve cardiac function and symptoms. A trial of >250 patients with systolic CHF (mean EF 25%) and sleep apnea randomized them to CPAP or no CPAP; the CPAP group had modest but significant increases in six minute walk tests (by about 20 meters) and ejection fraction (by about 2%), but there were no significant differences between the groups in CHF hospitalizations or mortality.[74]

Pulmonary disease

A third of all patients with CHF also have a diagnosis of COPD. [66] This can make it difficult to differentiate the etiology of shortness of breath in patients presenting for medical care, as several symptoms and physical exam signs may be similar. Laboratory testing with BNP may be helpful in making this distinction. Most of the cardiac medications should be continued despite the COPD, including beta-blockers. An observational study of >2,000 patients with COPD found the risk of mortality and COPD exacerbations were lower in those on beta-blockers than those not on beta-blockers, indicating that beta-blockers are not harmful, and may be helpful in patients with COPD. [75] For more information on the diagnosis and management of COPD, see the monograph on this topic at www.rxfacts.org.

BOTTOM LINE: Co-morbid conditions are common in patients with CHF, complicating its management. Medications that commonly need to be avoided include NSAIDs and glitazones, which can worsen CHF. Careful attention should be paid to treating these co-morbid conditions, to avoid polypharmacy and drug interactions.

Invasive management of CHF

Revascularization

Some patients with systolic CHF and coronary artery disease will benefit from revascularization. A large trial of patients with systolic CHF (EF<35%) and coronary artery disease amenable to coronary artery bypass grafting (CABG) surgery were randomized to surgery or medical therapy. There were no differences between the groups in the primary outcome measure between the groups (death from any cause), but there was a small benefit in the CABG group in the secondary outcomes, including:[76]

- CV death (28% of surgical group, 33% of medical group, p=0.05)
- Death from any cause or CV hospitalization (58% of surgical group, 68% of medical group, p<0.001)[76]

Valve surgery

Significant valvular dysfunction (either stenosis or regurgitant lesions) can complicate the management of CHF, and can lead to worsening of symptoms. For patients with severe dysfunction of any valve, valvular repair should be considered, with appropriate and timely referral to a cardiologist or cardiac surgeon.[7]

Cardiac resynchronization

Efficacy:

Delays of the intraventricular conduction system occur in about 1/3 of patients with systolic CHF, identifiable by a QRS duration of >120 milliseconds.[3] This delay results in asynchronous contraction of the left atria and ventricle, and resultant reduction of the cardiac output (due to mitral regurgitation). Cardiac resynchronization therapy works by placing pacing wires into 3 locations: the right atria, the right ventricle, and the left ventricle, thereby re-synchronizing the contraction of both atria and both ventricles. This therapy has been shown to improve symptoms and quality of life and reduce CHF hospitalizations and mortality, as indicated by the trials below.

A randomized controlled trial evaluated >1,500 patients with class III-IV CHF with EF<35%, and QRS>120 msec who were randomized to conventional therapy, biventricular pacing, or biventricular pacing with an ICD. At 12 months, the primary endpoint, death or hospitalization for any cause, occurred in:[77]

- 68% of pharmacologic therapy group
- 56% of both the pacer and pacer-ICD groups (20% reduction, p=0.01)

In that same trial, 12 month mortality was 19% in the pharmacologic treatment group. Compared to this group, mortality reductions were:

- 24% lower in the pacer group (p=0.06)
- 36% lower in the pacer-ICD group (p=0.004)[77]

A subsequent randomized controlled trial enrolled >800 patients with class III-IV CHF with EF<35% and QRS>120 msec, who were randomized to standard medical therapy or cardiac resynchronization therapy. After a mean of 29 months, the primary endpoint, death or unplanned cardiac hospitalization, occurred in:[78]

- 55% of the medical group
- 39% of the cardiac resynchronization group (37% relative risk reduction, p<0.001)

In addition, death occurred in:

- 30% of the medical group
- 20% of the cardiac resynchronization group (36% relative risk reduction, p<0.002).

In addition to reducing the morbidity and mortality, cardiac resynchronization significantly improved the ejection fraction (by ~ 7%), improved symptom class (by -0.6 point), and improved quality of life (by 0.08 on a 0 -1 scale). [78]

Based on these trials, current guidelines recommend cardiac resynchronization therapy in all patients with the combination of:

1. reduced EF (<35%)
2. class III-IV symptoms despite optimal medical therapy
3. sinus rhythm with a QRS>120 msec.[5,79]

In patients with less severe symptoms (Class I-II) but with EF<35% and QRS >120 msec, cardiac resynchronization also improves ventricular function, CHF

hospitalizations, and mortality. A recent meta-analysis in patients with Class I-II symptoms found that compared to ICD therapy, CRT was beneficial in the following outcomes: [80]

- Mortality: 8% in CRT versus 12% in ICD
  - (19% relative risk reduction, p=0.04)
- CHF hospitalizations: 12% in CRT versus 18% in ICD
  - (32% relative risk reduction, p<0.001)

Outcomes were more pronounced in those with Class II versus Class I status, and there was no mortality benefit in patients with Class I symptoms. [80]

CRT is not routinely recommended in patients with Class I-II symptoms according to the most recent clinical guidelines from the 2008 American College of Cardiology/ American Heart Association / Heart Rhythm Society, but it is endorsed by the European Society of Cardiology 2010 guidelines, and it has been approved for use in these patients by the US Food and Drug Association (FDA).[81] Before referral for CRT, symptom class should be assessed 3 months after initiation of recommended CHF medications. These recommendations are summarized in the table below.

Table 23: Guideline indications for cardiac resynchronization therapy[82]

	NYHA Class 1	NYHA Class 2	NYHA Class 3	NYHA Class 4 (ambulatory)	NYHA Class 4 (inotrope)
Ischemic	LVEF ≤ 30% QRS ≥ 130 ms (LBBB)	LVEF ≤ 30% QRS ≥ 130 ms (LBBB)	LVEF ≤ 35% QRS ≥ 120 ms	LVEF ≤ 35% QRS ≥ 120 ms	No
Nonischemic	No	LVEF ≤ 30% QRS ≥ 130 ms (LBBB)	LVEF ≤ 35% QRS ≥ 120 ms	LVEF ≤ 35% QRS ≥ 120 ms	No

Green and red sections are endorsed by the American College of Cardiology/American Heart Association/Heart Rhythm Society 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. Yellow section is an approved indication, not yet incorporated into guidelines. NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; LBBB = left bundle branch block.

Safety:

Device and procedure-related adverse effects occur at the following rates:

Table 24: Device and procedure-related adverse effects associated with cardiac resynchronization devices[78]

Adverse effect	% patients affected
Lead displacement	6%
Coronary sinus dissection	2%
Pocket erosions	2%
Pneumothorax	1%
Device-related infections	<1%

Satisfactory lead position can be obtained in about 90% of patients. Alternative placement can be achieved by the placement of an epicardial lead, if the transvenous approach can be achieved. [82] Most patients can not undergo MRI imaging after the insertion of such a devise. The actual procedure lasts between 2-4 hours, may require an overnight hospital stay for monitoring, and may require general anesthesia. Most patients will also need regular long-term follow up with an cardiac electrophysiology doctor, for assessments of the device (typically every 3-12 months). [82]

BOTTOM LINE: Cardiac resynchronization therapy reduces morbidity and mortality in patients with class III-IV systolic CHF with QRS>120 msec. Less symptomatic patients (class I-II) derive less benefit, but CRT is approved by the FDA for these patients, and is endorsed by some professional societies. Device and procedure related adverse effects occur in up to 10% of patients, and these must be considered when weighing the risks and benefits of CRT.

Implantable Cardiac Defibrillators (ICDs)

Efficacy:

ICD's can reduce the risk of sudden cardiac death due to malignant ventricular arrhythmias, although (unlike CRT), they have no effect on the structure or function of the ventricles. However, since about half of deaths in patients with reduced EF are due to ventricular arrhythmias, ICD's have been shown to reduce mortality in high-risk patients.

A randomized trial enrolled >2,500 patients with class II-III CHF (about half of which were ischemic) and an EF <35% who were randomized to one of three arms, in addition to conventional therapy: placebo, amiodarone, or ICD. At a median follow up of 45 months, the primary endpoint, death from any cause, occurred in:[83]

- 29% of placebo
- 28% of amiodarone (p=0.53 compared to placebo)
- 22% of ICD (p=0.007 compared to placebo)[83]

A follow up study from the same patient population found that having an ICD did not have any detrimental effect on quality of life, which was better than that seen in the medical therapy group at 12 months, but the same as medical therapy at 30 months. [84]

ICDs are therefore recommended for

- secondary prevention of sudden cardiac death in patients with CHF who survive an episode of unprovoked ventricular fibrillation or sustained ventricular tachycardia, regardless of EF.
- patients with EF<35% on maximal medical therapy who have a life expectancy of >1 year.[7]

A recent trial did not find any overall benefit for ICDs in patients post-MI who had EF<40% or non-sustained ventricular tachycardia (or both). [85]
ICDs are often inserted in patients who do not meet evidence-based criteria to have an ICD. One large registry found 23% of patients with an ICD did not meet criteria for insertion. [86]

Safety:

In the above trial, the average annual rate of ICD shocks was 7.5%, of which 5.1% were appropriate shocks (e.g. for ventricular fibrillation or sustained ventricular tachycardia). ICD complications (e.g. those requiring surgery, hospitalization, or new drug therapy) occurred in 5% of patients at the time of implantation, and 9% of patients over the course of the trial.[83] ICD recalls have become more common as the number of inserted ICDs has risen. There have been over 30 FDA recalls of ICDs (affecting >300,000 devices) since 1990. Patients should be made aware of the risks of ICD recalls, which may necessitate revisions or replacements of the device.[87]

Insertion of ICDs should be performed by experienced cardiac electrophysiologists. A retrospective cohort found that insertion by other specialists was associated with higher complication rates. [88]

BOTTOM LINE: Implantable cardiac defibrillators (ICDs) are indicated for all patients with a history of ventricular fibrillation or sustained ventricular tachycardia, and those with EF<35% on maximal medical therapy. Similar to CRT devices, ICD complications occur in about 10% of patients, the risk of which is lower if performed by an experienced electrophysiologist.

Cardiac transplant / Ventricular Assist Devices (VADs)

Cardiac transplant is a last resort for patients with CHF and refractory symptoms. Patients must be carefully screened for their ability to endure the surgery, and to emotionally and logistically comply with all post-transplant medications and other therapies. Given the scarcity of heart donors, some patients may need a ventricular assist device for a period of time while awaiting a transplant. These devices have become smaller and more manageable for ambulatory patients, but must be carefully monitored by cardiac specialists.[3,89]

Newer agents on the horizon

Direct renin inhibitor

The direct renin inhibitor aliskiren has been studied in patients with CHF, although its role is not yet clearly defined. The *ALOFT trial* randomized patients already taking an ACEI to aliskiren or placebo, and found the aliskerin group had significantly lower BNP serum levels than the placebo group, but did not assess clinical outcomes.[90] Another trial (*ASPIRE trial*) randomized post-MI patients with CHF to aliskerin or placebo, and found no benefit on any of the studied clinical outcome measures (systolic or diastolic volume, EF, CV death/CHF hospitalization). However, the treatment did produce higher rates of adverse events (hypotension, hyperkalemia, and increased creatinine).[91] Two future studies may further clarify the role of direct renin inhibition on outcomes in patients with CHF, compared to placebo, summarized in Table 25:

Table 25: Clinical trials of aliskerin, by patient type, randomized treatment, and outcomes [92,93]

Trial name	Patient types being recruited	Randomized treatment groups	Outcomes
ASTRONAUT [92]	Post-CHF hospitalization and EF<40%	Aliskerin or placebo	CV death or CHF admission
ATMOSPHERE [93]	EF<40%	Aliskerin or ACE (enalapril) or both	CV death or CHF admission

Vasopressin antagonist

Tolvaptan is a vasopressin receptor antagonist, which directly enhances diuresis without affecting electrolytes. The *EVEREST trial* randomized patients hospitalized with CHF to tolvaptan or placebo, and found significantly greater reductions in mean body weight on day 1 (1.7 vs 1.0 kg) and on day 7 (3.4 vs 2.7kg) in the tolvaptan vs placebo groups.[94] However, there was no difference between tolvaptan and placebo in meaningful clinical outcomes such as CV death, CHF hospitalizations, or worsening heart failure.[95]

SA node inhibitor

Ivabradine selectively inhibits a channel that controls the responsiveness of the sinoatrial (SA) node, and therefore directly reduces the heart rate, with no other cardiovascular effects. This agent was evaluated in the *SHIFT trial*, which randomized recently hospitalized CHF patients (EF<35%) to ivabardine or placebo (most of which were already on a beta-blocker). At 2 years, ivabradine significantly reduced:

- CHF admissions (16% vs 21%, p<0.0001)
- CHF deaths (3% vs 5%, p=0.01)

However, it did not reduce overall mortality, and caused significantly more symptomatic bradycardia (5% vs 1%, p<0.0001). Further analysis of the trial found the least benefit in those patients with higher beta blocker doses and lower baseline heart rates, indicating that this agent may only have a role in improving outcomes in patients who cannot tolerate, or cannot reduce their heart rate, on a beta blocker. [96] It is currently not FDA approved.

Stem cell transplants

Intracoronary stem cell transplants have shown some promise in the treatment of CHF. A small randomized trial in patients post-MI with an EF<40% found mean EF increased by 8% in the intervention group (with no change in the control group) with no reported adverse effects. Further studies will help define the safety and efficacy of this treatment.[97]

Patient education / Disease management / counseling

Elements of patient education

Patients should be educated on their disease, symptoms, medications, diet, and weight management, as outlined in Table 26.

Table 26: Elements of CHF patient education[33]

Disease	What is CHF, what are the triggers, how can medications make CHF better (symptoms, hospitalizations, and mortality)
Symptoms	What are the symptoms of CHF, how can I recognize the symptoms, and when should I call for help (eg a clinician)
Medications	What medications am I on, why am I taking them, what are the doses, how often do I take them, what are the common side effects, and what happens if I skip doses?
Dietary and weight	When and how often should I weigh myself, how do I limit my salt and fluid intake?

Considerations (literacy, culture, resources, social support)

Education should consider the patient's literacy level, cultural context, resources, and social support levels. The patient should be asked to demonstrate understanding of the concepts listed above, by reiterating the elements and demonstrating their understanding of each of the elements. Difficulty in affording medications, getting transportation to pick up medications, and any other barriers should be addressed. Support for dietary and weight management from family and friends should be assessed.

Modality / frequency (visits, videos, handouts, internet, home visit)

Patient education can be done in many ways, and should be re-addressed at each patient visit. It can be accomplished with videotapes in the office or at

home, one-on-one or group discussion, reading materials at the appropriate reading level, over the internet, or during home or clinic visits.

Remote management (telephone, telemedicine)

Many outpatient and hospital systems have instituted telemonitoring systems to remotely monitor and manage CHF patients for physical signs (such as weight, vital signs, or urine output), symptoms (such as edema or shortness of breath), laboratory values (such as creatinine or BNP), and medication/dietary compliance (by self-report or by use of more sophisticated devices). The purported benefit of telemedicine programs is the early detection and management of disease deterioration. It is generally accomplished by the transmission of information to a provider, who uses standard guidelines and operating procedures to direct the patients on how to best proceed. Several of these goals can be met much more readily with regular telephone contact with the patient.

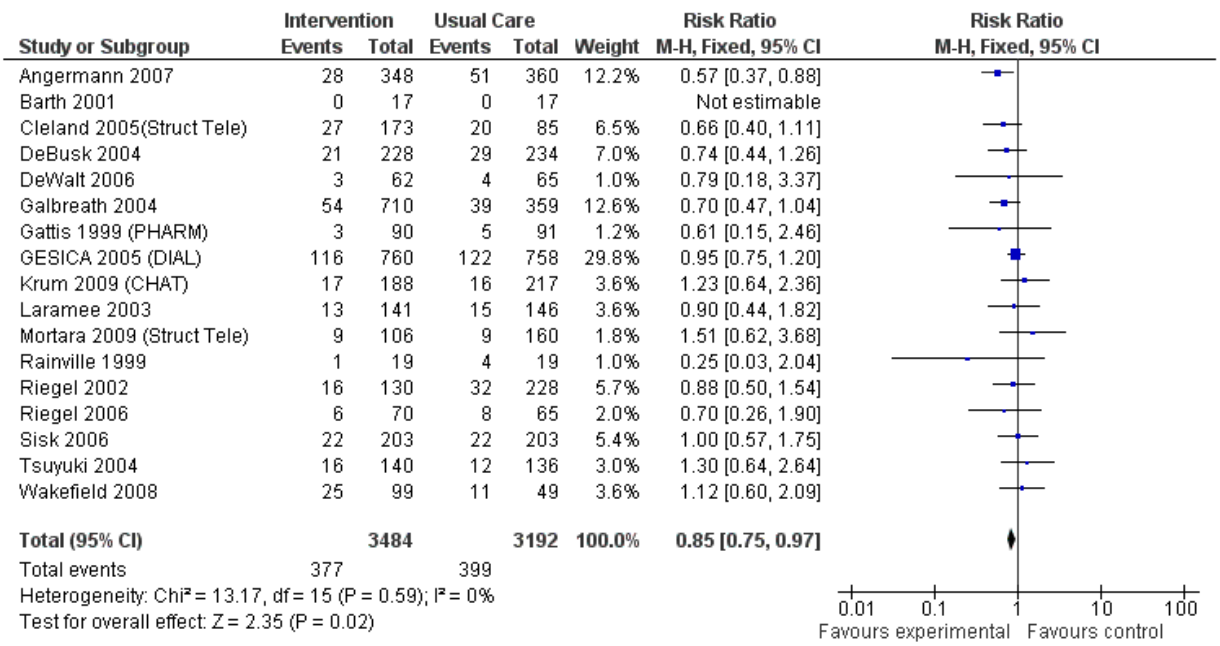
There is controversy as to how beneficial formal telemedicine programs are to individual or populations of patients with CHF. A systematic review of 56 articles found the following improvements in telemonitoring in randomized trials, based on the type of monitoring, listed in Table 27:

Table 27: Efficacy of telemonitoring technologies in CHF[98]

Type of telemonitoring modality	Outcomes improved in randomized trials
Device-based: Participants enter data into a device, which is transmitted to a monitoring station	Decreased mortality Decreased hospitalizations Decreased anxiety / depression scores Increased self-efficacy scores Increased exercise adherence Increased QOL
Telephone touch-pad-based: Participants enter data into a telephone, which is transmitted to a monitoring station	Decreased hospitalizations Decreased time to target beta blocker
Video consultation-based: Participants were monitored by video conferences manned by nurses	No improvements
Website-based: Participants enter data into a website, which was monitored by healthcare professionals	Decreased hospital days
Combinations	Decreased ED visits and charges Decreased readmission rates Decreased hospital days Decreased mortality Decreased cardiac claims (eg cost)

A Cochrane review found a modest but statistically significant improvement in mortality with telemonitoring programs in CHF patients, outlined in Figure 11.[99]

Figure 11: Impact of structured telephone support and telemonitoring in CHF on all-cause mortality.[99]



Study or Subgroup	Intervention Events	Intervention Total	Usual Care Events	Usual Care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Angermann 2007	28	348	51	360	12.2%	0.57 [0.37, 0.88]
Barth 2001	0	17	0	17		Not estimable
Cleland 2005(Struct Tele)	27	173	20	85	6.5%	0.66 [0.40, 1.11]
DeBusk 2004	21	228	29	234	7.0%	0.74 [0.44, 1.26]
DeWalt 2006	3	62	4	65	1.0%	0.79 [0.18, 3.37]
Galbreath 2004	54	710	39	359	12.6%	0.70 [0.47, 1.04]
Gattis 1999 (PHARM)	3	90	5	91	1.2%	0.61 [0.15, 2.46]
GESICA 2005 (DIAL)	116	760	122	758	29.8%	0.95 [0.75, 1.20]
Krum 2009 (CHAT)	17	188	16	217	3.6%	1.23 [0.64, 2.36]
Laramee 2003	13	141	15	146	3.6%	0.90 [0.44, 1.82]
Mortara 2009 (Struct Tele)	9	106	9	160	1.8%	1.51 [0.62, 3.68]
Rainville 1999	1	19	4	19	1.0%	0.25 [0.03, 2.04]
Riegel 2002	16	130	32	228	5.7%	0.88 [0.50, 1.54]
Riegel 2006	6	70	8	65	2.0%	0.70 [0.26, 1.90]
Sisk 2006	22	203	22	203	5.4%	1.00 [0.57, 1.75]
Tsuyuki 2004	16	140	12	136	3.0%	1.30 [0.64, 2.64]
Wakefield 2008	25	99	11	49	3.6%	1.12 [0.60, 2.09]
Total (95% CI)		**3484**		**3192**	**100.0%**	**0.85 [0.75, 0.97]**
Total events	377		399			

Heterogeneity: Chi² = 13.17, df = 15 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.35 (P = 0.02)

A recent large trial in 1,653 patients with a recent CHF hospitalization randomized them to telemonitoring or usual care. The telemonitoring program consisted of a telephone-based interactive voice-response system that collected daily patient information about weight and symptoms, which was reviewed by the clinical team daily. There were no differences in any of the primary or secondary outcome measures between the groups, including all cause death or readmissions.[100]

Two subsequent trials have evaluated the effect of more invasive telemonitoring on patient results. The *SENSE-HF trial* found the results of an intrathoracic impedence device could not predict the risk of CHF hospitalizations;[101] but the *CHAMPION trial* found patients randomized to an invasive pulmonary artery pressure monitoring/management plan had a 39% reduction in CHF hospitalizations compared to the control group ($p<0.0001$).[102]

The success of a telemonitoring program may depend on many factors including (but not limited to):

- Practitioners: availability (e.g. nights and weekends), amount of time it takes for them to render a care plan, lack of reimbursement, lack of a clear standardized operating procedure.
- Patients: compliance with the data submission, compliance with the care plan, availability to receive the care plan (by phone, etc).

- Technology: Cost, device failures, technology failures, user misunderstandings, etc.

BOTTOM LINE: Telemonitoring programs have become widespread in use, but not all have demonstrated improvements in morbidity or mortality. The success of these programs likely depends on many practitioner, patient, and technology factors, and may be expensive to initiate and maintain.

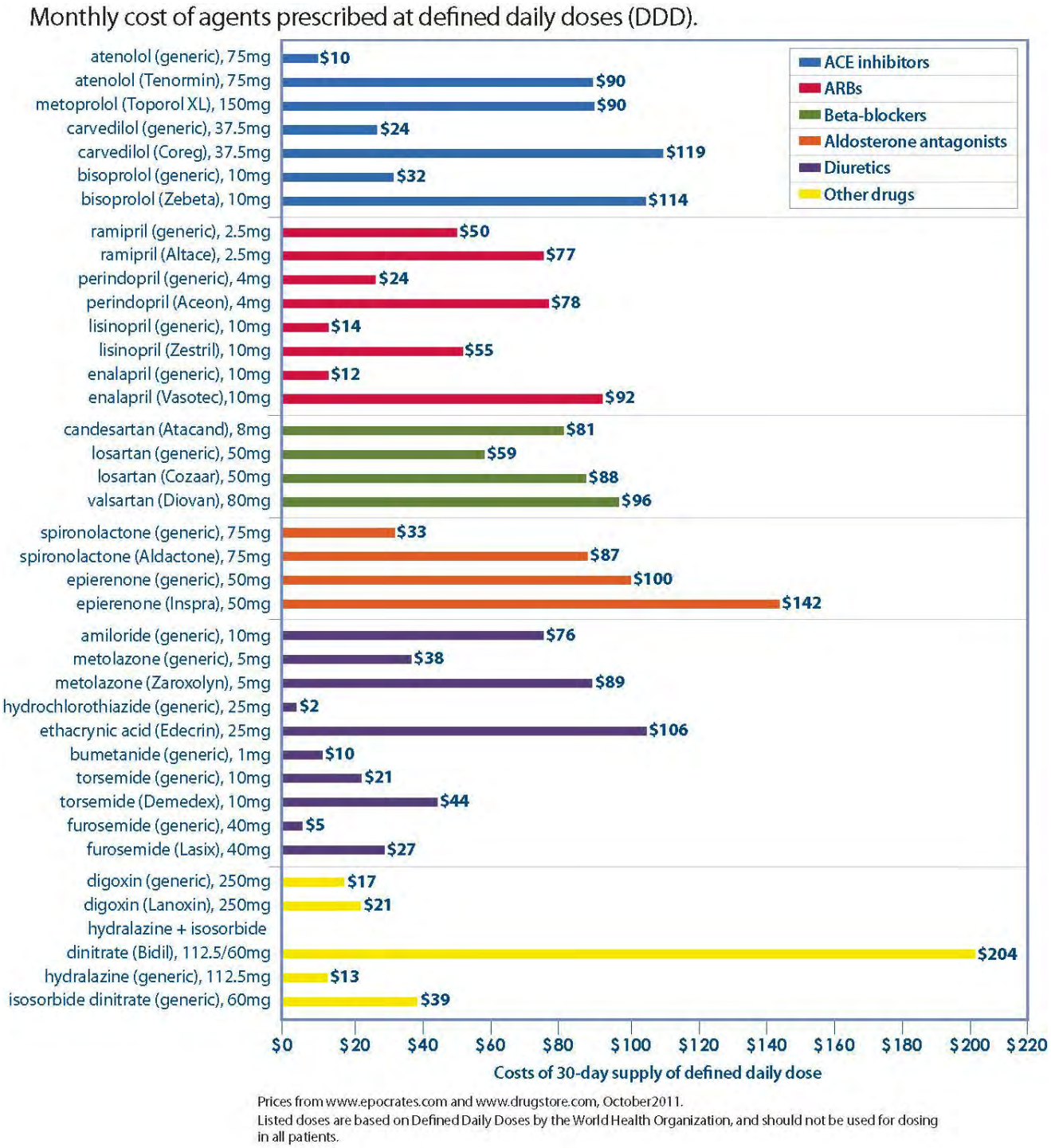
End of Life

Many patients with CHF undergo invasive and non-beneficial treatments near the end of life. A recent analysis of Medicare beneficiaries found that 80% of those with CHF were hospitalized within the last 6 months of life, with a significant increase in ICU days and overall costs during the last 6 months of life. However, the same analysis found the use of hospice increased from 19% of patients (before the last 6 months of life) to 40% of patients (within the last 6 months of life).[103] End of life care should be discussed with all patients/families who have class IV symptoms despite maximal medical therapy. This discussion should involve:[7]

- symptomatic therapy for dyspnea (including oxygen therapy)
- symptomatic therapy for anxiety or depression (if present)
- information on how to prepare a medical power of attorney, living will, and "do not resuscitate" orders
- discussion of the potential futility of invasive management at the end of life (eg ICUs, ventilators, cardiac resuscitation)
- discussion of the potential benefits of hospice care (at home or in a facility)
- discussion of inactivating an ICD (if present).

Initiation of discussions about patient wishes for end of life care can also be helpful for patients at less advanced stages of CHF, allowing them time to consider their preferences and discuss their decisions with family members and/or a health care proxy.

Cost



Prices from www.epocrates.com and www.drugstore.com, October2011.
Listed doses are based on Defined Daily Doses by the World Health Organization, and should not be used for dosing in all patients.

Putting it all together

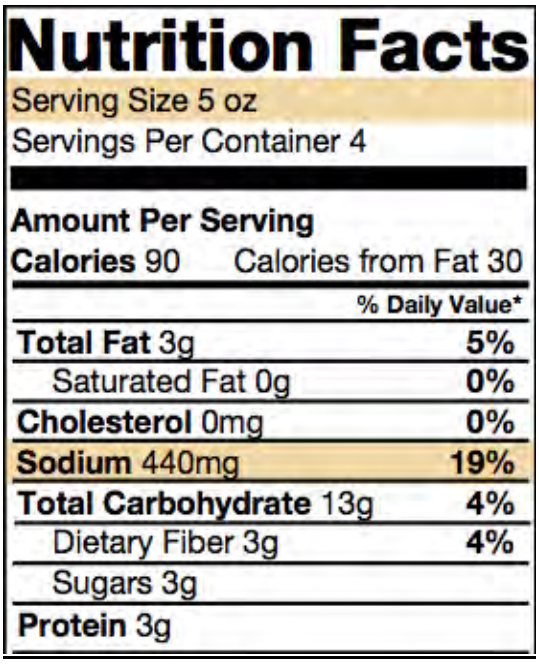
All patients with chronic systolic heart failure should be maintained on a diuretic to achieve their appropriate volume, and started on an ACE inhibitor as first line therapy, then a beta blocker. For those who remain symptomatic, next line agents should be either an ARB or aldosterone antagonist (spironolactone for those with Class III-IV symptoms, or eplerenone for those with Class II-IV symptoms). Aldosterone antagonists are generally preferable to combining an ACE and ARB, based on a lack of mortality benefit for this combination, and the increased risk of adverse effects (e.g. renal insufficiency, hypotension, and hyperkalemia). The combination of hydralazine with isosorbide dinitrate should be considered for black patients, who do not response as well to ACE or ARB therapy, as well as white patients who require additional therapy for symptom management. Digoxin is usually reserved for patients who remain symptomatic despite all of the above medical therapies, to reduce the risk of hospitalization. Additional diuretics can also be added in those with continued symptoms. Invasive therapies, including LVADs, transplantation, ICDs, and CRT should be considered depending on the patient's ejection fraction and QRS duration, as outlined in Figure 4.

For those with CHF and preserved EF, guidelines recommend the following medications to reduce volume overload and hypertension, generally in this order:[96]

- Diuretics (thiazide or loop) for volume overload
- ACEI (or ARB) (especially with prior MI, CAD, or diabetes)
- Beta blocker (especially with prior MI, CAD, angina or atrial fibrillation)
- Calcium channel blockers (especially with angina or atrial fibrillation)

Non-pharmacologic therapy should consist of sodium and fluid restriction, commensurate with the degree of symptoms and edema. Patients should avoid smoking and alcohol, and be educated on vaccines, and exercise. Co-morbid conditions are common and should be carefully addressed to avoid polypharmacy and drug interactions. Acute exacerbations should be managed with diuretics, with more aggressive interventions reserved for unstable patients. Patient education is an important component of CHF care, and should include end of life care in class IV patients.

APPENDIX 1



Nutrition Facts

Serving Size 5 oz

Servings Per Container 4

Amount Per Serving

Calories 90 Calories from Fat 30

	% Daily Value*
Total Fat 3g	**5%**
Saturated Fat 0g	**0%**
Cholesterol 0mg	**0%**
Sodium 440mg	**19%**
Total Carbohydrate 13g	**4%**
Dietary Fiber 3g	**4%**
Sugars 3g	
Protein 3g	

APPENDIX 2

Weight Log

Name:

Month	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	Date: Wt:	Date: Wt:	Date: Wt:	Date: Wt:	Date: Wt:	Date: Wt:	Date: Wt:
	Date: Wt:	Date: Wt:	Date: Wt:	Date: Wt:	Date: Wt:	Date: Wt:	Date: Wt:
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	Date: Wt:	Date: Wt:	Date: Wt:	Date: Wt:	Date: Wt:	Date: Wt:	Date: Wt:

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