

# Clinical Evidence Handbook

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## Heart Failure

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Heart failure occurs in 3 to 4 percent of adults older than 65 years, usually as a consequence of coronary artery disease or hypertension, and causes breathlessness, effort intolerance, fluid retention, and increased mortality.

- The five-year mortality rate in persons with systolic heart failure ranges from 25 to 75 percent, often from sudden death following ventricular arrhythmia. Risk of cardiovascular events is increased in persons with left ventricular systolic dysfunction (LVSD) or heart failure.

Multidisciplinary interventions may reduce hospital admissions and mortality in persons with heart failure compared with usual care. Exercise may reduce hospital admissions because of heart failure compared with usual care. However, long-term benefits of these interventions remain unclear.

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and beta blockers reduce mortality and hospital admissions from heart failure compared with placebo, with greater absolute benefits in persons with more severe heart failure.

- Combined treatment with angiotensin II receptor blockers and ACE inhibitors may lead to a greater reduction in hospital admissions for heart failure compared with ACE inhibitor treatment alone.

Aldosterone receptor antagonists (spironolactone, eplerenone, and canrenoate) may reduce all-cause mortality in persons with heart failure, but increase the risk of hyperkalemia.

Digoxin slows the progression of heart failure compared with placebo, but may not reduce mortality.

Hydralazine/isosorbide dinitrate may improve survival and quality-of-life scores compared with placebo in persons with chronic congestive heart failure.

We do not know whether amiodarone, anticoagulants, or antiplatelet agents are effective at reducing mortality or hospital readmission rates.

*Caution:* Positive inotropic agents (other than digoxin), calcium channel blockers, and antiarrhythmic drugs (other than amiodarone and beta blockers) may all increase mortality and should be used with caution, if at all, in persons with systolic heart failure.

Implantable cardiac defibrillators and cardiac resynchronization therapy can reduce mortality in persons with heart failure who are at high risk of ventricular arrhythmias. However, studies evaluating cardiac resynchronization therapy were performed in centers with considerable experience, which may have overestimated the benefits.

We do not know how coronary revascularization and drug treatment compare for reducing mortality in persons with heart failure and left ventricular dysfunction. All of the trials assessing this comparison were conducted before ACE inhibitors, aspirin, beta blockers, and statins were in routine use, thus limiting their applicability to current clinical practice.

ACE inhibitors delay the onset of symptomatic heart failure, reduce cardiovascular events, and improve long-term survival in persons with asymptomatic LVSD compared with placebo.

- Angiotensin II receptor blockers and ACE inhibitors seem equally effective at reducing all-cause mortality and cardiovascular mortality in persons at high risk of heart failure.

- The combination of angiotensin II receptor blockers and ACE inhibitors seems no more effective than ACE inhibitors alone and causes more adverse effects.

ACE inhibitors or angiotensin II receptor blockers seem no more effective at reducing mortality or rate of hospital admissions for

cardiovascular events in persons with diastolic heart failure compared with placebo.

- We do not know whether treatments other than angiotensin II receptor blockers are beneficial in reducing mortality in persons with diastolic heart failure because we found only one trial.

**Definition**

Heart failure occurs when abnormal cardiac function causes failure of the heart to pump blood at a rate sufficient for metabolic requirements under normal filling pressure. It is characterized clinically by breathlessness, effort intolerance, fluid retention, and poor survival. Fluid retention and the congestion related to this can often be relieved with diuretic therapy. However, diuretic therapy generally should not be used alone and, if required, should be combined with the pharmacologic treatments outlined in this review.

Heart failure can be caused by systolic or diastolic dysfunction, and is associated with neurohormonal changes. LVSD is defined as a left ventricular ejection fraction of less than 0.4. It may be symptomatic or asymptomatic. Defining and diagnosing diastolic heart failure can be difficult. Proposed criteria include: (1) clinical evidence of heart failure; (2) normal or mildly abnormal left ventricular systolic function; (3) evidence of abnormal left ventricular relaxation, filling, diastolic distensibility, or diastolic stiffness; and (4) evidence of elevated N-terminal-probrain natriuretic peptide. However, assessment of some of these criteria is not standardized.

**Incidence and Prevalence**

Both incidence and prevalence of heart failure increase with age. Studies of heart failure in the United States and the United Kingdom found the annual incidence in persons older than 45 years to be between 29 and 32 cases per 1,000. In those older than 85 years, the incidence was considerably higher, at 45 to 90 cases per 1,000 persons per year. The study carried out in the United States reported a decline in the incidence of heart failure (all age groups) over a 10-year period, with the incidence falling from 32.2 cases per 1,000 persons per year in 1994 to 29.1 cases per 1,000 persons per year in 2003. However, analysis of

those 65 years or older indicated an increase in prevalence of heart failure (from 89.9 cases per 1,000 persons in 1994 to 121 cases per 1,000 persons in 2003). Prevalence of heart failure was higher in men (130 cases per 1,000) compared with women (115 cases per 1,000).

In persons 65 years or older, the incidence of heart failure after a myocardial infarction is on the rise, with one study finding a 25.1 percent increase in in-hospital heart failures from 1994 to 2000 (from 31.4 to

**Clinical Questions**

**What are the effects of multidisciplinary interventions for heart failure?**

Beneficial                      Multidisciplinary interventions

**What are the effects of exercise in persons with heart failure?**

Likely to be beneficial      Exercise

**What are the effects of drug treatments for heart failure?**

Beneficial                      ACE inhibitors  
   Angiotensin II receptor blockers  
   Beta blockers  
   Digoxin (improves morbidity in persons already receiving diuretics and ACE inhibitors)

Likely to be beneficial      Aldosterone receptor antagonists  
   Hydralazine/isosorbide dinitrate

Unknown effectiveness      Amiodarone  
   Anticoagulation  
   Antiplatelet agents

Likely to be ineffective or harmful      Antiarrhythmics other than amiodarone  
   Calcium channel blockers  
   Positive inotropes other than digoxin

**What are the effects of devices for treatment of heart failure?**

Beneficial                      Implantable cardiac defibrillators in persons at high risk of arrhythmia

Likely to be beneficial      Cardiac resynchronization therapy

**What are the effects of coronary revascularization for treatment of heart failure?**

Unknown effectiveness      Coronary revascularization

**What are the effects of drug treatments in persons at high risk of heart failure?**

Beneficial                      ACE inhibitors in persons with asymptomatic left ventricular dysfunction or other risk factors

Likely to be beneficial      Angiotensin II receptor blockers

**What are the effects of treatments for diastolic heart failure?**

Unknown effectiveness      Treatments other than angiotensin II receptor blockers

Unlikely to be beneficial      ACE inhibitors or angiotensin II receptor blockers

ACE = angiotensin-converting enzyme.

39.3 percent;  $P = .001$ ). Furthermore, the study noted that 76 percent of persons who survived a myocardial infarction had developed heart failure at five years' follow-up. Prevalence of asymptomatic LVSD is 3 percent in the general population, and the mean age of persons with asymptomatic LVSD is lower than that of symptomatic persons. Both heart failure and asymptomatic LVSD are more common in men. Prevalence of diastolic heart failure in the community is unknown. Prevalence of heart failure with preserved systolic function in hospitalized patients with clinical heart failure varies from 13 to 74 percent. Less than 15 percent of persons with heart failure who are younger than 65 years have normal systolic function, whereas the prevalence is about 40 percent in persons older than 65 years.

### Etiology and Risk Factors

Coronary artery disease is the most common cause of heart failure. Other common causes include hypertension and idiopathic dilated congestive cardiomyopathy. After adjustment for hypertension, the presence of left ventricular hypertrophy remains a risk factor for the development of heart failure. Other risk factors include cigarette smoking, hyperlipidemia, and diabetes mellitus. The common causes of left ventricular diastolic dysfunction are coronary artery disease and systemic hypertension. Other causes are hypertrophic cardiomyopathy, restrictive or infiltrative cardiomyopathies, and valvular heart disease.

### Prognosis

The prognosis of heart failure is poor, with five-year mortality rates ranging from 26 to 75 percent. Up to 16 percent of patients are readmitted with heart failure within six months of first hospital admission. In the United States, heart failure is the leading cause of hospital admission among persons older than 65 years. In persons with heart failure, a new myocardial infarction increases the risk of death

(relative risk [RR] = 7.8; 95% confidence interval [CI], 6.9 to 8.8). About one-third of all deaths in persons with heart failure are preceded by a major ischemic event. Sudden death, mainly caused by ventricular arrhythmia, is responsible for 25 to 50 percent of all deaths, and is the most common cause of death in persons with heart failure. Women with heart failure have a 15 to 20 percent lower risk of total and cardiovascular mortality compared with men with heart failure (risk after adjustment for demographic and social economic characteristics, comorbidities, cardiovascular treatments, and left ventricular ejection fraction).

The presence of asymptomatic LVSD increases a person's risk of having a cardiovascular event. One large prevention trial found that the risk of heart failure, hospital admission for heart failure, and death increased linearly as ejection fraction fell (for each 5 percent reduction in ejection fraction: RR for mortality = 1.2 [95% CI, 1.13 to 1.29]; RR for hospital admission = 1.28 [95% CI, 1.18 to 1.38]; RR for heart failure = 1.2 [95% CI, 1.13 to 1.26]). The annual mortality for persons with diastolic heart failure varies in observational studies (1 to 18 percent). Reasons for this variation include age, presence of coronary artery disease, and variation in the partition value used to define abnormal ventricular systolic function. The annual mortality rate for left ventricular diastolic dysfunction is lower than that in persons with systolic dysfunction.

EDITOR'S NOTE: Canrenoate is not available in the United States.

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