The American College of Cardiology/American Heart Association guidelines recommend that patients with asymptomatic left ventricular systolic dysfunction or with congestive heart failure (CHF) be treated with angiotensin-converting enzyme (ACE) inhibitors plus beta-blockers unless there are contraindications to the use of these drugs. Beta-blockers have been demonstrated to significantly reduce all-cause mortality associated with abnormal or normal left ventricular ejection fraction in older and younger patients with CHF. An angiotensin receptor blocker should not be administered to patients with CHF who are being treated with a beta-blocker plus ACE inhibitor, but should be given to patients with CHF treated with beta-blockers who cannot tolerate ACE inhibitors due to cough, angioneurotic edema, rash or altered taste sensation.

Key words: congestive heart failure, left ventricular ejection fraction, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers.

Introduction
The American College of Cardiology/American Heart Association guidelines recommend that all patients with left ventricular systolic dysfunction or with congestive heart failure (CHF) be treated with angiotensin-converting enzyme (ACE) inhibitors plus beta-blockers, unless there are contraindications to the use of these drugs. Beta-blockers have been demonstrated to significantly reduce all-cause mortality associated with abnormal left ventricular ejection fraction in older and younger patients with CHF. An angiotensin receptor blocker should not be administered to patients with CHF who are being treated with a beta-blocker plus ACE inhibitor, but should be given to patients with CHF treated with beta-blockers who cannot tolerate ACE inhibitors due to cough, angioneurotic edema, rash or altered taste sensation.

Evidence for Benefit of Beta-blockers in Older People

Effect on Incidence of New CHF
A study of 477 older patients (mean age 79 years) with prior myocardial infarction and a mean abnormal LVEF of 31% found that the use of ACE inhibitors alone and beta-blockers alone significantly reduced the incidence of new CHF by 32% and 41%, respectively, compared with no ACE inhibitors or no beta-blockers at 34-month follow-up. At 41-month follow-up, use of ACE inhibitors plus beta-blockers significantly reduced the incidence of new CHF by 61% compared to no ACE inhibitors or beta-blockers. The significantly longer follow-up time in patients treated with ACE inhibitors plus beta-blockers indicates that this combination delayed as well as reduced the incidence of new CHF in older adults with prior myocardial infarction and an abnormal LVEF.

Effect on Mortality Rates
Beta-blockers are effective in significantly reducing mortality in patients with CHF associated with abnormal LVEF or with normal LVEF (diastolic heart failure). In the U.S. Carvedilol Heart Failure Study, 1,094 patients with New York Heart Association (NYHA) class II-IV CHF and LVEF ≤ 35% were randomized to receive carvedilol or placebo, in addition to their usual medication (diuretics, ACE inhibitors and digoxin). Compared to the placebo group, carvedilol was found to significantly reduce mortality by 65% and reduced the combined risk of mortality or hospitalization for cardiovascular causes by 38% (Table). The reduction in mortality due to carvedilol was similar regardless of sex; in patients 59 years or older, carvedilol caused a 62% significant reduction in all-cause mortality.

The Cardiac Insufficiency Bisoprolol Study II randomized 2,647 patients with NYHA class III or IV CHF and a LVEF of ≤ 35% to either bisoprolol or placebo. Treatment also had to include a diuretic and an ACE inhibitor; the use of digoxin was optional. At 1.3 years follow-up, bisoprolol significantly reduced mortality by 34%, and significantly reduced hospitalization for worsening CHF by 36%. This study included patients up to age 80 at study entry.

A total of 3,991 patients taking a diuretic and ACE inhibitor (63% were also taking digoxin) for NYHA class II-IV CHF and a LVEF of ≤ 40% were randomized to metoprolol CR/XL or placebo. Treatment also had to include a diuretic and an ACE inhibitor; the use of digoxin was optional. At 1.3 years follow-up, bisoprolol significantly reduced mortality by 34%, and significantly reduced hospitalization for worsening CHF by 36%. This study included patients up to age 80 at study entry.

Evidence for the Use of Beta-blockers in Congestive Heart Failure Treatment in Older Persons

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Beta-blockers in CHF

The Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) randomized 2,289 patients with severe CHF and a LVEF < 25% to either carvedilol or placebo. Patients were followed for 10.4 months, during which standard treatment for heart failure (diuretic and ACE inhibitors or angiotensin receptor blockers) was continued. Compared with placebo, carvedilol significantly reduced all-cause mortality by 35% (Figure 2).10 Carvedilol also significantly reduced combined risk of mortality or hospitalization for any reason by 24%. The significant reduction in mortality in this study occurred in patients both older and younger than 65 years of age.

A prospective study of 158 older persons (mean age 81 years; 70% women) with prior myocardial infarction, NYHA class II or III CHF and a LVEF of ≥40% treated with diuretics plus ACE inhibitors for two months, randomized 79 subjects to propranolol and 79 to no propranolol.11 The initial dose of propranolol was 10mg daily, which was increased by 10mg increments at 10-day intervals until a dose of 30mg t.i.d. was administered. At a mean of 32 months follow-up, propranolol significantly reduced all-cause mortality by 35% and all-cause mortality plus nonfatal myocardial infarction by 37%, compared with no propranolol. At one-year follow-up, propranolol significantly increased the mean LVEF from 57% to 63%, and significantly reduced left ventricular mass by 11%.

Are All Beta-blockers Equal?

Not all beta-blockers have been demonstrated to cause a significant reduction in mortality in patients with CHF. At two year follow-up of 2,708 patients with NYHA class III or IV CHF and a LVEF of ≤35% in the Beta-Blocker Evaluation of Survival Trial (BEST), bucindolol resulted in a non-significant 10% reduction in all-cause mortality compared with placebo.13 As this drug has not been shown to be efficacious in the treatment of heart failure, it has not been approved for this purpose in any country.

Recently published data from the Carvedilol or Metoprolol European Trial (COMET) found that carvedilol significantly reduced mortality by 17% compared with metoprolol.14 This study randomized 3,029 patients (mean age 62 years) with NYHA class II-IV CHF, a LVEF of ≤35% and receiving treatment with diuretics and ACE inhibitors unless not tolerated, to carvedilol, with a target dose of 25mg twice daily, or to metoprolol, with a target dose of 50mg twice daily. However, the mean dose of metoprolol 85mg daily used in COMET did not reduce the resting heart rate as much as carvedilol 50mg daily, raising the question of whether the dose of metoprolol used in this study caused a similar degree of beta-1 blockade as that of carvedilol.15

Summary of Evidence

Prospective, randomized studies have demonstrated that beta-blockers significantly decrease mortality in patients with CHF associated with abnormal7-10 or normal11 LVEF (Table). Beta-blockers reduce all-cause mortality, cardiovascular mortality, sudden death and death from worsening CHF in patients with existing CHF.7-11 Significant reductions in mortality have been found among all subgroups of patients with CHF examined, including African-Americans7,9,10,16 and Caucasians,7-11 both women7-11 and men,7-11 older7-11 and younger7-10 patients, diabetics7-11 and nondiabetics,7-11 and in patients with severe CHF7-10.
Beta-blockers in CHF

Summary of Evidence for Reduction in Mortality with Beta-blockers in Patients with Congestive Heart Failure

<table>
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<td>158 older patients with NYHA class II or III CHF and LVEF ≥ 40%</td>
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and with mild or moderate CHF. Beta-blockers should be used to treat older patients with CHF and abnormal LVEF or normal LVEF, unless there are contraindications to their use.

Mechanism of Action

Beta-blockers are effective in antagonizing neurohormonal systems that cause myocyte apoptosis, myocyte necrosis, myocyte hypertrophy, fetal gene program activation, extracellular matrix alterations and beta-receptor uncoupling. Beta-blockers may prevent or reverse increased systemic vascular resistance and increased afterload caused by excessive sympathetic nervous system activation (Figure 3). Beta-blockers also decrease levels of atrial natriuretic peptide, brain natriuretic peptide and tumour necrosis alpha levels, and are effective in preventing cardiovascular events due to their antihypertensive, anti-ischemic, antiarrhythmic and anti-atherogenic effects.

Beta-blockers are also beneficial in the treatment of patients with diastolic CHF by reducing the ventricular rate to less than 90 beats/minute—thereby increasing LV diastolic filling time and increasing LV end-diastolic volume—by reducing myocardial ischemia, elevated blood pressure and LV mass, and by improving LV relaxation. In these patients beta-blockers are well tolerated despite sinus bradycardia at rest. The increase in ventricular rate that occurs after exercise also can be prevented with modest doses of beta-blockers, especially in older patients.

Recommendations for Administration of Beta-blockers

Before initiating beta-blocker therapy in patients with HF, patients should be treated with an ACE inhibitor or angiotensin receptor blocker (ARB) and should be in a relatively stable condition without the need for intravenous inotropic therapy and without signs of marked fluid retention. Beta-blockers should be initiated at a low dose, such as carvedilol 3.125mg twice daily or metoprolol CR/XL 12.5mg daily if there is NYHA class III or IV heart failure or 25mg daily if there is NYHA class II heart failure. The beta-blocker dose should be doubled at two-to-three-week intervals, with the maintenance dose reached over three months (carvedilol 25mg twice daily or metoprolol CR/XL 200mg once daily). The patient may experience fatigue during the initiation or up-titration of the dose, but this effect will dissipate over time. The need to continue the treatment in patients with CHF must be stressed due to the proven efficacy of beta-blockers in reducing mortality.

During titration, the patient should be monitored for CHF symptoms, fluid retention, hypotension and bradycardia. If there is worsening of CHF symptoms, the dose of the diuretic or ACE inhibitor should be increased and, if necessary, the dose of the beta-blocker temporarily reduced. If there is hypotension, a reduction in the dose of vasodilator should be made and, if necessary, of the beta-blocker temporarily. In the presence of bradycardia, it is recommended to decrease or discontinue drugs that may reduce heart rate. Contraindications to the use of beta-blockers in patients with CHF are bronchial asthma, severe bronchial disease, symptomatic bradycardia and symptomatic hypotension.

In the Losartan Heart Failure Survival Study ELITE II, 3,152 patients aged ≥ 60 years with NYHA class II-IV CHF and a LVEF of ≤ 40% were randomized to receive the ARB losartan 50mg daily or the ACE inhibitor captopril 50mg t.i.d. After a median follow-up of 555 days, significantly
Beta-blockers in CHF

Figure 3: Beta-blockers' Mechanism of Action

Control
Beta-adrenergic receptors remain inactive prior to the binding of a neurotransmitter.

When the heart begins to fail, the body activates the sympathetic nervous system in order to increase cardiac output.

Sympathetic effect
Sympathetic nerves secrete norepinephrine, which, when bound to the $\beta_1$-adrenergic receptor, causes:
- the heart rate to increase
- the force of the heart’s contraction to increase
- an increase in blood pressure

$P$ = phosphorylation (by the protein kinase)

Beta-blocker effect
Beta-blockers reduce the workload of the heart and lower blood pressure by blocking certain actions of the sympathetic nervous system.
Beta-blockers in CHF

more patients discontinued captopril because of adverse effects (14.7%) compared with those in the losartan group (9.7%). However, there were no significant differences in mortality rate between the two treatment groups. Mortality was 77% significantly lower in patients treated with captopril plus beta-blockers than in patients treated with losartan plus beta-blockers, and 5% insignificantly lower in patients treated with captopril without beta-blockers than in patients treated with losartan without beta-blockers.21 As recommended by The American College of Cardiology /American Heart Association, an ARB should be given to patients with CHF only if they cannot be treated with an ACE inhibitor due to cough or angioneurotic edema with a class Ila recommendation.1

The Valsartan Heart Failure Trial (Val-HeFT) randomized 5,010 patients with NYHA class II-IV CHF and an abnormal LV ejection fraction to the ARB valsartan 160mg daily or placebo.22 Of these, 93% were treated with ACE inhibitors, 85% with diuretics, 67% with digoxin and 35% with beta-blockers. At 23 month follow-up, mortality was similar in the two treatment groups. The incidence of the combined endpoint, mortality plus morbidity, was significantly reduced by 85% with diuretics, 67% with digoxin and 35% with beta-blockers.21 As recommended by The American College of Cardiology / American Heart Association, an ARB should be given to patients with CHF only if they cannot be treated with an ACE inhibitor due to cough or angioneurotic edema with a class Ila recommendation.1

These unexpected results were not confirmed by two recent studies.23,24 If a patient with CHF cannot tolerate an ACE inhibitor because of cough, angioneurotic edema, rash or altered taste sensation, they may be treated with an ARB in addition to the beta-blocker.

No competing financial interests declared.

References


