CLINICAL PRACTICE

Systolic Heart Failure

John J.V. McMurray, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 74-year-old man with a history of hypertension and myocardial infarction that occurred 5 years previously presents with breathlessness on exertion. His current medications include a statin and aspirin. On examination, his pulse is 76 beats per minute and regular, and his blood pressure is 121/74 mm Hg. There is jugular venous distention, lateral displacement of the apex beat, and edema in his lower limbs. The lung examination is normal. An echocardiogram shows left ventricular dilatation, globally reduced contractility, and an ejection fraction of 33%. How should his case be managed?

THE CLINICAL PROBLEM

Approximately 1 to 2% of the population in developed countries has heart failure, with the prevalence rising to 10% or more among persons 70 years of age or older.¹ At least half the patients with heart failure have a low ejection fraction (40% or less).¹ This review focuses on the recommended treatment for ambulatory patients with systolic heart failure; heart failure with preserved ejection fraction was reviewed previously in this series.²

Coronary artery disease is the cause of approximately two thirds of cases of systolic heart failure, although hypertension and diabetes are likely to be contributing factors in many cases. Dilated cardiomyopathy may also result from a genetic cause, previous viral infection (recognized or unrecognized), alcohol abuse, or occasionally, chemotherapy (e.g., doxorubicin or trastuzumab).²

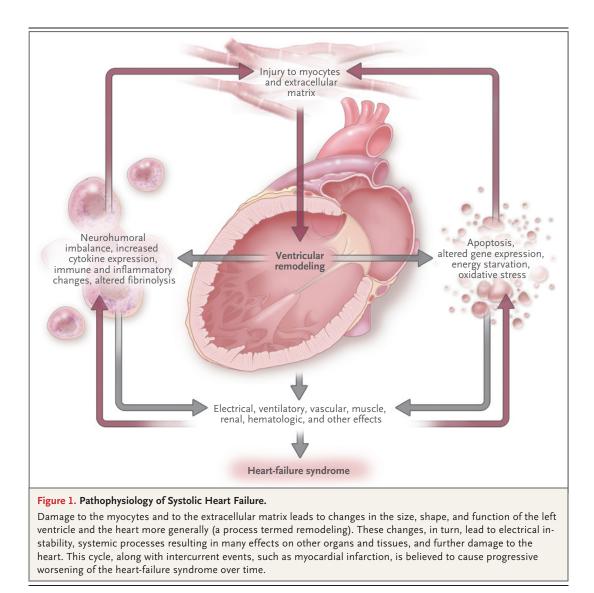
The maladaptive changes that occur in surviving myocytes and in the extracellular matrix after myocardial injury lead to pathologic remodeling of the left ventricle, with dilatation and impaired contractility. If these changes are left untreated, they worsen over time, exacerbated by additional injury (e.g., myocardial infarction)³ and by systemic responses to left ventricular systolic dysfunction, notably activation of the sympathetic and renin-angiotensin-aldosterone systems.⁴ All these responses have detrimental systemic effects, accounting for the clinical manifestations of the syndrome of heart failure, including the development and worsening of symptoms, declining functional capacity, episodes of frank decompensation that result in the need for hospitalization, myocardial electrical instability, and premature death, usually due to pump failure or a ventricular arrhythmia (Fig. 1). Since the limited cardiac reserve of patients with systolic heart failure depends on atrial contraction and synchronized contraction of the left ventricle, events that affect these functions (e.g., the development of atrial fibrillation or left bundle-branch block) or that impose an additional hemodynamic load on the failing heart (e.g., anemia) can lead to acute deterioration. Interruption of left ventricular remodeling and of the systemic responses to it is the basis of much of the effective treatment of heart failure.

From the Western Infirmary and the British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom. Address reprint requests to Dr. McMurray at the British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Pl., Glasgow G12 8TA, United Kingdom, or at j.mcmurray@bio .gla.ac.uk.

N Engl J Med 2010;362:228-38. Copyright © 2010 Massachusetts Medical Society.

> An audio version of this article is available at NEJM.org

ପର



Before 1990, as many as 60 to 70% of patients died within 5 years after the diagnosis of systolic heart failure, and hospitalization owing to the exacerbation of symptoms was frequent.⁵ Effective treatment has improved both outcomes, with a relative reduction in mortality in recent years of 20 to 30%.⁶

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

The cardinal symptoms (i.e., dyspnea and fatigue) and signs (i.e., peripheral edema) of heart failure are nonspecific and must be evaluated in light of the patient's history, the findings on examination,

and the results of additional testing.^{1,7,8} Other symptoms (e.g., orthopnea and paroxysmal nocturnal dyspnea) and signs (e.g., jugular venous distention, cardiac enlargement, and a third heart sound) have 70 to 90% specificity for the diagnosis but only 11 to 55% sensitivity.⁹

Routine cardiac investigations, such as electrocardiography and chest radiography, are also insensitive, although they may provide other useful information (Table 1).^{7,8} For example, left ventricular systolic dysfunction may be seen without cardiomegaly on a chest radiograph. Measurement of the plasma concentration of natriuretic peptides is recommended, since natriuretic peptides are secreted in increased amounts by the failing heart,

N ENGLJ MED 362;3 NEJM.ORG JANUARY 21, 2010

Table 1. Possible Findings in Patients with Left Ventricul	ar Systolic Dysfunction and Recommendations for Treatment.*
Test and Possible Finding	Recommendation
Electrocardiography	
Atrial fibrillation or flutter	Slow the ventricular rate if it is rapid, and consider prophy- lactic anticoagulation therapy for thromboembolism.
QRS duration ≥120 msec	Consider cardiac-resynchronization therapy.
Sinus bradycardia	Administer beta-blocker and digoxin with caution.
Chest radiography	
Pulmonary congestion, edema, or pleural effusion	Provide adequate diuresis.
Primary pulmonary pathology (e.g., COPD, fibrosis, or tumor)	Look for alternative cause of dyspnea and provide therapy specific to that cause.
Hematologic tests	
Anemia	Perform a diagnostic workup; treat iron deficiency, if present.
Biochemical tests	
Increased creatinine	Administer RAAS blockers with caution.
Hypokalemia	Add or increase the dose of RAAS blocker; consider potassi- um replacement.
Hyperkalemia	Stop potassium replacement and supplements; reduce dose of or withdraw RAAS blocker.
Hyponatremia	Reduce the dose of or discontinue use of thiazide diuretic; reduce water intake; consider treatment with tolvaptan, if hyponatremia is severe.
Hyperuricemia	Consider reducing the dose of the diuretic as much as possible; administer prophylaxis for gout with a xanthine oxidase inhibitor.

* COPD denotes chronic obstructive pulmonary disease, and RAAS renin-angiotensin-aldosterone system.

and a normal concentration virtually rules out a diagnosis of heart failure (although this observation may not hold true in the case of obese persons).¹⁰

Transthoracic Doppler echocardiography allows for confirmation of the diagnosis, provides information on myocardial and valvular structure and function, and may reveal other important findings, such as the presence of a thrombus in a cardiac chamber.^{7,8} Cardiac magnetic resonance imaging is an alternative to echocardiography in difficult cases, such as those in which the quality of the ultrasonic image is poor, or in cases in which characterization of the tissue is particularly important (e.g., when myocarditis or an infiltrative myocardial disease is suspected).¹¹ Investigations that are recommended routinely, as well as those that are useful in selected circumstances, are summarized in Table 1.^{7,8}

Patients' symptoms, including limitations in activity, can be quantified with the use of the New York Heart Association (NYHA) functional classification or the more recent American Heart Association–American College of Cardiology classification (Table 2).^{7,8,12}

Coexisting conditions that are common in patients with heart failure and that may influence the prognosis and affect treatment decisions should be routinely assessed (Table 1). These include conditions that may have led to the heart failure (e.g., ischemic heart disease, hypertension, or diabetes) or that may result from either the heart failure itself (e.g., atrial fibrillation, cachexia, or depression) or the treatment (e.g., gout induced by diuretics). Other common coexisting conditions include renal impairment, anemia, and sleep-disordered breathing.

TREATMENT OPTIONS

The goals of treatment are the reduction in symptoms, a decrease in the rate of hospitalization, and the prevention of premature death. The cornerstone of treatment is pharmacologic therapy

Table 2. Cl	inical Classifications of Heart Failure Severity.*		
NYHA Fur	nctional Classification	ACC–AHA	Stages of Heart Failure
Class I	No limitation of physical 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; com- fortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea	Stage B	Developed structural heart disease that is strongly associated with the develop- ment of heart failure but without signs or symptoms
Class III	Marked limitation of physical activity; com- fortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea	Stage C	Symptomatic heart failure associated with underlying structural heart disease
Class IV	Unable to carry on any physical activity without discomfort; symptoms present at rest; if any physical activity is under- taken, discomfort is increased	Stage D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy

* The American College of Cardiology (ACC)-American Heart Association (AHA) classification is from Hunt et al.⁸ The New York Heart Association (NYHA) functional classification is from the Criteria Committee of the New York Heart Association.¹²

(Fig. 2). Lifestyle modification such as exercise this treatment requires close monitoring of blood levels of electrolytes because of the risk of disturbances such as hyponatremia. Patients with

PHARMACOLOGIC THERAPY

Pharmacologic agents include those that provide relief of symptoms only (i.e., diuretics) and those that also modify the course of the disease (see below). The dosing and key side effects of medications that have been shown in randomized trials to be effective are listed in Table 3. The randomized trials are summarized in Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. Detailed information that provides guidance on prescribing and monitoring treatments is available.³²

Diuretics for Relief of Symptoms

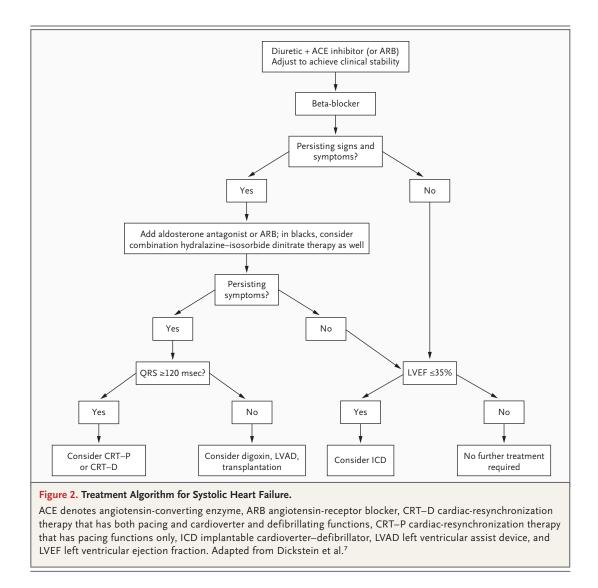
Diuretics provide rapid relief of dyspnea and fluid retention.^{7,8} The lowest dose of diuretic needed to achieve an edema-free state ("dry weight") is used. The patient's weight should be measured daily, and the dose of the diuretic adjusted to maintain the dry weight. Patients can alter the timing of the doses for social convenience.

The combination of a loop diuretic and a thiazide-like diuretic (e.g., metolazone), often in conjunction with an aldosterone antagonist — treatment that is termed sequential nephron blockade — may be needed to control fluid retention in cases of severe heart failure, although

this treatment requires close monitoring of blood levels of electrolytes because of the risk of disturbances such as hyponatremia. Patients with refractory edema often have impaired absorption of oral diuretics and require intravenous therapy. The requirement for diuretics may decrease as the patient's condition improves. Although patients who have recently presented with symptoms may quickly become symptom-free with diuretic therapy, treatment with agents that also modify the course of the disease is needed to reduce the risk of progression of the disease.

Agents That Modify the Course of the Disease

Angiotensin-Converting–Enzyme (ACE) Inhibitors ACE inhibitors are the first-line therapy for patients with systolic heart failure; therapy should be initiated promptly after diagnosis and continued indefinitely. ACE inhibitors reduce ventricular size, increase the ejection fraction modestly, and reduce symptoms.7,8 Two large trials showed that when patients with NYHA class II, III, or IV heart failure were treated with enalapril, as compared with placebo, in addition to diuretics and digoxin, the rates of admission to the hospital were reduced, and there was a relative risk reduction for death of 16 to 40%.^{14,15} In a placebo-controlled trial, enalapril therapy reduced the risk of the development of symptomatic heart failure among asymptomatic (NYHA class I) patients with left ventricular systolic dysfunction³³ and was su-



perior to the combination of hydralazine and isosorbide dinitrate in a head-to-head trial assessing mortality (18% vs. 25% mortality at 2 years, P<0.02).³⁴ ACE inhibitors also reduce the risk of myocardial infarction.^{15,33} Treatment with ACE inhibitors is recommended for all patients who have left ventricular systolic dysfunction, irrespective of the cause of the condition or the severity of the symptoms (i.e., whether they are in NYHA class I, II, III, or IV).

Angiotensin-Receptor Blockers (ARBs)

The efficacy of ARBs is similar to that of ACE inhibitors, as evidenced by findings from a single large trial in which candesartan was used²⁴ and a subgroup analysis from a study of valsartan ther-

apy (Table 1 in the Supplementary Appendix).²⁶ Since ARBs are generally more expensive than ACE inhibitors, they are used as an alternative to ACE inhibitors primarily in patients in whom a cough develops as a result of ACE-inhibitor therapy.

ARBs are also used as additional therapy in patients who have symptoms that persist (i.e., patients who remain in NYHA class II, III, or IV) despite receiving an optimal dose of an ACE inhibitor and a beta-blocker. In two placebo-controlled, randomized trials (one in which valsartan was used²⁶ and one in which candesartan was used²⁵), the addition of an ARB reduced the rate of hospitalization for heart failure by 17 to 22%; candesartan also reduced cardiovascular mortality by 16%.²⁵

Downloaded from www.nejm.org by JOHN VOGEL MD on January 20, 2010 . Copyright © 2010 Massachusetts Medical Society. All rights reserved.

No. of Dose No. of Target Total Mean Total Daily Dose Achieved in Dose Achieved i	Starting Dose Dose DoseNo. of Target Total Dose Achieved in Dose Achieved in ScienceMean Total Daily Dose Achieved in Be: Cor Cor ScienceMean Total Daily Dose Achieved in Be: Dose Achieved in Be: Dose Achieved in Dose	No. of bose No. of Target Total Mean Total Daily Doses Dose Achieved in Dose Achieved in Dose Achieved in Dose Achieved in 2.5 mg Mean Total Daily Dose Achieved in Dose Achieved in 12.5 mg Mean Total Daily Dose Achieved in Na; 6.25 mg 3 150 mg 16.6 mg 2.5-5.0 mg 1 20–35 mg NA; 2.5-5.0 mg 1 20–35 mg NA; 2.5 mg 1 20–35 mg NA; 3.15 mg 1 20–35 mg 3 mg 1.0 mg 1 20–35 mg 3 mg 3.125 mg 1 200 mg 37 mg¶ 1.25 mg 1 10 mg 7.7 mg* 3.125 mg 1 10 mg 7.7 mg* 1.25 mg 1 200 mg 129 mg 1.25 mg 1 100 mg 7.7 mg* 3.125 mg 1 200 mg 24 mg* 3.125 mg 1 200 mg 24 mg* 3.15 mg 1 250 mg 26 mg 3.7.5 mg 1 250 mg 24 mg* 3.7.5 mg 25 mg 25 mg <td< th=""><th>Treatment</th><th></th><th></th><th>Dosing</th><th></th><th>Contraindications, Cautions, and Adverse Events</th></td<>	Treatment			Dosing		Contraindications, Cautions, and Adverse Events
6.25 mg 3 150 mg 121 mg 8.9 2.5 mg 2 20-40 mg 16.6 mg pos 2.5-5.0 mg 1 20-35 mg NA 2.5-5.0 mg 1 20-35 mg NA 2.5-5.0 mg 1 20-35 mg NA 2.5 mg 1 0 r2 10 mg 8.7 mg 1.0 mg 3.7 mg 3.125 mg 1 10 mg 6.2 mg 86 3.125 mg 1 200 mg 159 mg 1.25 mg 1 200 mg 129 mg 50 mg 1 150 mg 129 mg 50 mg 2 320 mg 24 mg 7.7 mg** 60 mg 25 mg 1 255 mg 905 25 mg 1 255 mg 129 mg 3.7 mg 86 3.7 mg 905 3.7	6.25 mg 3 150 mg 121 mg Bei 2.5 mg 2 20-40 mg 16.6 mg Pos 2.5-5.0 mg 1 2 20-40 mg 16.6 mg Pos 2.5-5.0 mg 1 2 20-40 mg 16.6 mg Pos 2.5-5.0 mg 1 2 20-40 mg 16.6 mg Pos 2.5-5.0 mg 1 2 20-40 mg 16.6 mg Pos 2.5-5.0 mg 1 20-35 mg 1 20-35 mg Pos 1.0 mg 1 4 mg 3 mg 3 mg Cor 1.25 mg 1 200 mg 37 mg Pos 1.25 mg 1 10 mg 57 mg Pos 1.25 mg 1 200 mg 7.7 mg** Cor 1.25 mg 1 10 mg 7.7 mg** Cor 1.25 mg 1 10 mg 24 mg†† Bei 40 mg 2 320 mg 254 mg Pos 50 mg 1 150 mg 129 mg ‡‡ Cor 25 mg 1 255 mg 26 mg Pos 37.5 mg 3 255 mg 143 mg Pos 37.5 mg 3 120 mg 133 mg <td< th=""><th>ACT inhibuts Carpany of any of a</th><th></th><th>Starting Dose</th><th>No. of Doses per Day'j</th><th>Target Total Daily Dose†</th><th>Mean Total Daily Dose Achieved in Outcome Studies</th><th></th></td<>	ACT inhibuts Carpany of any of a		Starting Dose	No. of Doses per Day 'j	Target Total Daily Dose†	Mean Total Daily Dose Achieved in Outcome Studies	
6.25 mg 3 150 mg 121 mg Bei 2.5 mg 1 2 20-40 mg 16.6 mg Pos 2.5 mg 1 2 20-40 mg 16.6 mg Pos 2.5 mg 1 2 20-40 mg 16.6 mg Pos 2.5 mg 1 2 20-35 mg NA‡ Pos 2.5 mg 1 or 2 10 mg 8.7 mg% S.7 mg% Pos 1.0 mg 1 4 mg 3 mg Cor Cor 1.25 mg 1 10 mg 5.7 mg% Pos Pos 3.125 mg 1 10 mg 3.7 mg% Pos Cor 1.25 mg 1 10 mg 7.7 mg** Cor Cor 1.25 mg 1 10 mg 7.7 mg** Cor Cor 1.25 mg 1 10 mg 159 mg †* Pos Cor 1.25 mg 1 10 mg 159 mg †* Pos Cor 50 mg 1 150 mg 129 mg †* Pos Cor 51 mg 1 1 <	6.25 mg 3 150 mg 121 mg Bei 2.5 mg 1 2 20-40 mg 16.6 mg Pos 2.5 -5.0 mg 1 1 20-35 mg NA‡ Pos 2.5 -5.0 mg 1 2 20-40 mg 16.6 mg Pos 2.5 -5.0 mg 1 2 20-35 mg NA‡ Pos 2.5 mg 1 or 2 10 mg 8.7 mg% Pos 2.5 mg 1 4 mg 3 mg Cor 1.25 mg 1 10 mg 6.2 mg Pos 3.125 mg 1 200 mg 37 mg% Pos 1.25 mg 1 10 mg 7.7 mg** Cor 1.25 mg 1 200 mg 159 mg% Pos 1.25 mg 1 32 mg 24 mg% Pos 1.25 mg 1 32 mg 25 mg Pos 50 mg 1 150 mg 25 mg Pos 50 mg 1 25 mg 25 mg Pos 25 mg 1 25 mg 26 mg Pos 37.5 mg 3 225 mg 143 mg Pos 37.5 mg 3 120 mg 143 mg Pos 37.5 mg 3	Capapalitie 6.55 mg 130 mg 121 mg 6.6 mg Reard for sense common patistions of symptomatic hypotension or systolic blood pressure <50 mm (Jitts computed mathema and symptomatic hypotension or systolic blood pressure <50 mm (Jitts computed mathema and symptomatic hypotension or systolic blood pressure <50 mm (Jitts computed mathema and symptomatic hypotension or systolic blood pressure <50 mm (Jitts computed mathema and symptomatic hypotension or systolic blood pressure <50 mm (Jitts computed mathema and symptomatic hypotension or systolic blood pressure <50 mm (Jitts computed mathema and symptomatic hypotension or systolic blood pressure <50 mm (Jitts computed mathema and symptomatic hypotension). Rampolicits 1.2.5-50 mg 1.2.0 mg 3.mg Contraindications include bathanal and symptomatic hypotension. Rampolicits 1.2.5-50 mg 1.2.5 mg 1.2.0 mg 3.mg Contraindications include bathanal and symptomatic hypotension. Rampolicits 3.1.25 mg 1.2.0 mg 2.mg 1.0 mg 2.mg Responder 3.1.25 mg 1.2.0 mg 2.mg 1.0 mg 2.mg Responder 3.1.25 mg 1.2.0 mg 2.mg 1.0 mg 2.mg Responder 1.2.2 mg 1.2.2 mg 2.mg 1.2.2 mg 2.mg 1.2.2 mg Responder 1.2.2 mg 2.mg <td>ACE inhibitors</td> <td></td> <td></td> <td></td> <td></td> <td>Contraindications include a history of angioedema and bilateral renal-artery stenosis.</td>	ACE inhibitors					Contraindications include a history of angioedema and bilateral renal-artery stenosis.
2.5 mg 2 20-40 mg 16.6 mg Pos 2.5 -5.0 mg 1 20-35 mg NA‡ Pos 2.5 mg 1 or 2 10 mg 8.7 mg§ Pos 2.5 mg 1 or 2 10 mg 8.7 mg§ Pos 2.5 mg 1 or 2 10 mg 8.7 mg§ Pos 1.0 mg 1 4 mg 3 mg Cor 1.25 mg 1 10 mg 6.2 mg Pos 3.125 mg 1 200 mg 37 mg¶ Pos 1.25 mg 1 200 mg 159 mg Pos 1.25 mg 1 200 mg 159 mg Pos 1.25 mg 1 200 mg 159 mg Pos 1.25 mg 1 10 mg 7.7 mg** Cor 40 mg 2 320 mg 254 mg Pos 26 25 mg 1 150 mg 129 mg ‡‡ Pos 26 25 mg 1 1 25 mg 26 mg Pos 37.5 mg 3 25 mg 120 mg 26 mg Pos <td>2.5 mg 2 20-40 mg 16.6 mg Pos 2.5 -5.0 mg 1 20-35 mg NA; Pos 2.5 -5.0 mg 1 20-35 mg NA; Pos 2.5 mg 1 or 2 10 mg 8.7 mg/s Pos 2.5 mg 1 or 2 10 mg 8.7 mg/s Pos 1.0 mg 1 4 mg 3 mg Pos 3.125 mg 1 200 mg 37 mg/s Pos 3.125 mg 1 200 mg 37 mg/s Pos 1.25 mg 1 200 mg 37 mg/s Pos 12.5 or 25 mg 1 200 mg 7.7 mg*s Cor 1.25 mg 1 200 mg 24 mg/s Pos 1.25 mg 1 32 mg 25 mg Pos 50 mg 1 10 mg 26 mg Pos 25 mg 1 25 mg Pos 25 mg Pos 25 mg 1 25 mg 25 mg Pos 26 mg Pos 25 mg 37.5 mg 25 mg 143 mg Pos 20 mg<</td> <td>Endlapril1 5.0 mg 2.4-dmg 16.6 mg Stift Function of protection of protection of protection. Stift in cardination of protection. Trandolapril* 2.5-5 mg 1 or 2.5-3 mg NA; regen, hyperlatents, and symptomatic hypotension. Ang Rampin* 2.5-5 mg 1 or 2.5-4 mg 3 mg Containdications include subma and second-or third-dgree actionentricular block. Banapolo¹ 2.5-5 mg 1 or 3 mg Containdications include subma and second-or third-dgree actionentricular block. Banapolo¹ 1.15 mg 1 mg 7 mg Containdications include subma and second-or third-dgree actionentricular block. Banapolo¹ 1.15 mg 1 mg 7 mg Name Name or third block. Andorentricular block 1 mg 7 mg Name Name or third block bloc</td> <td>Captopril¹³</td> <td>6.25 mg</td> <td>3</td> <td>150 mg</td> <td>121 mg</td> <td>Be alert for serum potassium >5.0 mmol/liter, serum creatinine >2.5 mg/dl (220 µmol/</td>	2.5 mg 2 20-40 mg 16.6 mg Pos 2.5 -5.0 mg 1 20-35 mg NA; Pos 2.5 -5.0 mg 1 20-35 mg NA; Pos 2.5 mg 1 or 2 10 mg 8.7 mg/s Pos 2.5 mg 1 or 2 10 mg 8.7 mg/s Pos 1.0 mg 1 4 mg 3 mg Pos 3.125 mg 1 200 mg 37 mg/s Pos 3.125 mg 1 200 mg 37 mg/s Pos 1.25 mg 1 200 mg 37 mg/s Pos 12.5 or 25 mg 1 200 mg 7.7 mg*s Cor 1.25 mg 1 200 mg 24 mg/s Pos 1.25 mg 1 32 mg 25 mg Pos 50 mg 1 10 mg 26 mg Pos 25 mg 1 25 mg Pos 25 mg Pos 25 mg 1 25 mg 25 mg Pos 26 mg Pos 25 mg 37.5 mg 25 mg 143 mg Pos 20 mg<	Endlapril1 5.0 mg 2.4-dmg 16.6 mg Stift Function of protection of protection of protection. Stift in cardination of protection. Trandolapril* 2.5-5 mg 1 or 2.5-3 mg NA; regen, hyperlatents, and symptomatic hypotension. Ang Rampin* 2.5-5 mg 1 or 2.5-4 mg 3 mg Containdications include subma and second-or third-dgree actionentricular block. Banapolo ¹ 2.5-5 mg 1 or 3 mg Containdications include subma and second-or third-dgree actionentricular block. Banapolo ¹ 1.15 mg 1 mg 7 mg Containdications include subma and second-or third-dgree actionentricular block. Banapolo ¹ 1.15 mg 1 mg 7 mg Name Name or third block. Andorentricular block 1 mg 7 mg Name Name or third block bloc	Captopril ¹³	6.25 mg	3	150 mg	121 mg	Be alert for serum potassium >5.0 mmol/liter, serum creatinine >2.5 mg/dl (220 µmol/
2.5-5.0 mg 1 20-35 mg NA‡ 2.5 mg 1 or 2 10 mg 8.7 mg 1.0 mg 1 or 2 10 mg 8.7 mg 1.0 mg 1 0 mg 8.7 mg 1.25 mg 1 4 mg 3 mg 3.125 mg 1 200 mg 159 mg 1.25 mg 1 200 mg 159 mg 1.25 mg 1 200 mg 24 mg† 4 mg 2 320 mg 24 mg† 9 mg 50 mg 1 10 mg 24 mg† 8 e 50 mg 1 20 mg 254 mg 90s 50 mg 1 20 mg 26 mg 90s 25 mg 1 25 -50 mg 26 mg 90s 20 mg 37.5 mg 3 225 mg 143 mg 860 20 mg 2 1 25 mg 143 mg 800 20 mg 2 120 mg 90s 20 mg 2 120 mg 90s 20 mg 1 25 mg 10 mg 90s 20 mg 2 120 mg 90s 20 mg 9	2.5-5.0 mg 1 20–35 mg NA‡ 2.5 mg 1 or 2 10 mg 8.7 mg% 1.0 mg 1 or 2 10 mg 8.7 mg% 1.0 mg 1 or 2 3 mg 3.125 mg 1 10 mg 6.2 mg Bei 3.125 mg 1 200 mg 159 mg 1.25 mg 1 200 mg 159 mg 1.25 mg 1 200 mg 24 mg†† Bei 4 mg 2 320 mg 24 mg†† Bei 4 mg 2 320 mg 254 mg pos 50 mg 1 25 mg 129 mg‡‡ 25 mg 1 255 mg 129 mg‡‡ 20 mg 3 120 mg 60 mg pos 20 mg 3 120 mg 60 mg pos	Lationplif 2.5-50 mg 1 2.0-35 mg NA3 regen, hyperlaienia, and sympfomanic hypotension. Ramiphif 1.0 mg 1 4 ms 3 mg Amgent interactions include asthm and second or third degree antoentricular block. Respondels 1.0 mg 1 4 ms 3 mg Contraindications include asthm and second or third degree antoentricular block. Respondels 3.125 mg 1 10 mg 3 mg Sample astronom second block. Mebiooloi (CK)(L1 1.25 mg 1 10 mg 3 mg Sample astronom second block. Amgoeneris-receptor blockers 3.125 mg 2 90 mg 3 mg/s Sample astronom second block. Amgoeneris-receptor blockers 3.125 mg 1 20 mg 3 mg/s Sample astronom second block. Sample astronom second block. Carrendio 3.125 mg 1 20 mg 3 mg/s Sample astronom second block. Sample astronom second block. Carrendio 3 mg/s 2 mg/s 2 mg/s Sample astronom second block. Sample astronom second block. Carrendio 2 mg/s 2 mg/s 2 m	Enalapril ^{14,15}	2.5 mg	2	20-40 mg	16.6 mg	iiter), or symptomatic hypotension or systolic biood pressure <90 mm Hg. Possible adverse events include cough: angioedema: a rise in creatinine or blood urea ni-
2.5 mg 1 or 2 10 mg 8.7 mg% 1.0 mg 1 4 mg 3 mg 1.0 mg 1 4 mg 3 mg 3.125 mg 1 10 mg 6.2 mg 86 3.125 mg 1 10 mg 7.7 mg** 1.25 mg 1 200 mg 159 mg 1.25 mg 1 200 mg 129 mg 4 mg 1 32 mg 24 mg 40 mg 2 320 mg 129 mg 1 50 mg 1 50 mg 43 mg 86 25 mg 1 25-50 mg 26 mg 905 37.5 mg 3 225 mg 143 mg 86 37.5 mg 3 225 mg 143 mg 86 37.5 mg 3 225 mg 143 mg 86 1.25 mg 1 25-50 mg 26 mg 905 2.5 mg 1 25-50 mg 26 mg 905 3.75 mg 3 225 mg 143 mg 86 3.75 mg 3 225 mg 10 mg 60 mg 905 3.75 mg 3 225 mg 90 mg 900 mg 905 3.75 mg 3 225 mg 90 mg 900	2.5 mg 1 or 2 10 mg 8.7 mg% 1.0 mg 1 4 mg 3 mg 1.0 mg 1 4 mg 3 mg 1.25 mg 1 10 mg 6.2 mg 86: 3.125 mg 1 10 mg 6.2 mg 86: 3.125 mg 1 10 mg 5.2 mg 86: 1.25 or 25 mg 1 200 mg 159 mg/h 90: 12.5 or 25 mg 1 200 mg 159 mg/h 86: 1.25 mg 1 32 mg 7.7 mg** Cor 1.25 mg 1 32 mg 24 mg/h 86: 4 mg 1 10 mg 2.4 mg/h 86: 40 mg 2 320 mg 254 mg 90: 50 mg 1 150 mg 129 mg/h 86: 25 mg 1 25 mg 120 mg 90: 37.5 mg 3 25 mg 143 mg 86: 37.5 mg 3 120 mg 60 mg 90: 37.5 mg 3 120 mg 60 mg 90:	Ramipli 25 mg 1 or 2 10 mg 3 mg Trandolprilim 10 mg 1 4 mg 3 mg Trandolprilim 10 mg 1 1 mg 3 mg Trandolprilim 10 mg 1 1 mg 3 mg Resublockers 88 optolo ¹¹ 13 mg 2 50-100 mg 3 mg Respondel ¹² 13.2 mg 1 10 mg 2 mg/s Possible adverse events include projecnitions of treatment or increase in dosage, and symp. Metoprolof Styll ¹¹ 1.35 mg 1 2 mg/s S0-100 mg 3 mg Contraindications include satifiare during initiation of treatment or increase in dosage, and symp. Metoprolof 1.125 mg 1 10 mg 2 mg/s S1 mg/s Contraindications include satifiare during initiation of treatment or increase in dosage, and symp. Metoprolof 1.125 mg 1 1.00 mg 2 mg/s S1 mg/s Contraindications include satifiare during initiation of treatment or increase in dosage, and symp. Metoprolof 1.125 mg/s 1.130 mg 2 mg/s S1 mg/s Metoprolof montintintintime S1 mg/s Mm	Lisinopril ¹⁶	2.5-5.0 mg	1	20–35 mg	₩A	trogen, hyperkalemia, and symptomatic hypotension.
1.0 mg 1 4 mg 3 mg 1.25 mg 1 10 mg 6.2 mg 8e 3.125 mg 2 50-100 mg 37 mg¶ Pos 3.125 mg 1 200 mg 159 mg¶ Pos 3.125 mg 1 200 mg 159 mg¶ Pos 1.25 mg 1 200 mg 159 mg¶ Pos 1.25 mg 1 32 mg 24 mg°† 8e 4 mg 1 32 mg 24 mg°† 8e 40 mg 1 150 mg 129 mg°‡ Cor 50 mg 1 150 mg 129 mg°‡ Cor 25 mg 1 150 mg 43 mg 8e 37.5 mg 3 25 mg 12 129 mg°‡ 37.5 mg 1 25 mg 13 26 mg Pos 37.5 mg 3 25 mg 13 26 mg Pos 37.5 mg 3 25 mg 143 mg Pos 37.5 mg 3 120 mg 60 mg Pos	1.0 mg 1 4 mg 3 mg 1.25 mg 1 10 mg 6.2 mg 86. 3.125 mg 2 50-100 mg 37 mg 905 3.125 mg 1 200 mg 37 mg 905 1.25 mg 1 200 mg 159 mg 905 1.25 or 25 mg 1 200 mg 159 mg 905 1.25 mg 1 200 mg 129 mg 905 1.25 mg 1 32 mg 24 mg 86 4 mg 1 32 mg 254 mg 905 50 mg 1 32 mg 254 mg 905 50 mg 1 100 mg 254 mg 905 50 mg 1 150 mg 129 mg † 60 mg 37.5 mg 1 25-50 mg 26 mg 905 37.5 mg 3 225 mg 143 mg 866 37.5 mg 3 120 mg 60 mg 905	Trandolaprilla 10mg 1 4 mg 3 mg Trandolaprilla 10mg 1 0 mg 2 mg/s Beschlöckers 2 mg/s 10 mg 2 mg/s Postbadzerda and atmoventricular block, bronchostsam, sorsening fraut failure and fraet rate 455 pm. Beschlöckers 31.25 mg 2 so-00 mg 37 mg/s Postbadzerda and atmoventricular block, bronchostsam, sorsening fraut failure and fraet rate 55 pm. Meteopolic (CKNL ¹ 1.25 mg 1 10 mg 2 mg/s Postbadge attrovice receiption e.25	Ramipril ¹⁷	2.5 mg		10 mg	8.7 mg(
1.25 mg 1 10 mg 6.2 mg Be: 3.125 mg 2 50-100 mg 37 mg¶ Pos 12.5 or 25 mg 1 200 mg 159 mg¶ Pos 12.5 or 25 mg 1 200 mg 159 mg¶ Pos 12.5 or 25 mg 1 200 mg 159 mg¶ Pos 12.5 or 25 mg 1 10 mg 7.7 mg** Cor 1.25 mg 1 32 mg 24 mg†† Bei 4 mg 1 32 mg 24 mg†† Bei 40 mg 2 320 mg 129 mg ‡† Cor 50 mg 1 150 mg 129 mg ‡‡ Pos 25 mg 1 150 mg 129 mg ‡‡ Pos 25 mg 1 25 mg 129 mg ‡‡ Pos 37.5 mg 3 25 mg 129 mg ‡‡ Pos 37.5 mg 3 25 mg 130 mg Pos 37.5 mg 3 25 mg 143 mg Pos 37.5 mg 3 120 mg Pos Pos	1.25 mg 1 10 mg 6.2 mg Bei 3.125 mg 2 50-100 mg 37 mg Poss 3.125 mg 1 200 mg 159 mg Poss 12.5 or 25 mg 1 200 mg 159 mg Poss 1.25 mg 1 200 mg 159 mg Poss 12.5 or 25 mg 1 200 mg 159 mg Poss 1.25 mg 1 32 mg 24 mg Poss 40 mg 1 32 mg 24 mg Poss 50 mg 1 32 mg 254 mg Poss 50 mg 1 150 mg 129 mg Poss 25 mg 1 25 mg 129 mg Poss 25 mg 1 25-50 mg 26 mg Poss 37.5 mg 3 225 mg 143 mg Poss 20 mg 3 120 mg 60 mg Poss 20 mg 3 120 mg 60 mg Poss	Betabolicks Contraindications include safety and activity accord entromersular block. Respondio 1.25 mg 1 10 mg 5.7 mg/l Possible adverse entris include bardward and hear time. S5 bm. Revoluoio 3.12 mg 2 s-100 mg 3.7 mg/l Possible adverse entris include bardward and hear time. S5 bm. Revoluoio 1.25 mg 1 0 mg 7.7 mg/l Possible adverse entris include bardward and hear time. S5 bm. Ampointeristreeptor blocks: 1.25 mg 1.25 mg 2.9 mg 1.27 mg/l Angointeristreeptor blocks: 1.25 mg 2.10 mg 7.7 mg/r Non-stational and hear time. S5 bm. 1.0 mg Angointeristreeptor blocks: 1.25 mg 2.4 mg/r 1.20 mg 2.4 mg/r Non-stational and hear time. S5 bm. 1.25 mg/l Andosterone blocks: 0 mg 2.7 mg/r 2.4 mg/r Non-stational and hear time. S5 bm. 1.25 mg/l Addosterone blocks: 2.1 mg 2.3 mg/r 2.4 mg/r Non-pole pression. 2.5 mg/l 1.2 mg/l Addosterone blocks: 2.3 mg/r 2.4 mg/r 2.4 mg/r 2.4 mg/r 2.4 mg/r 2.5 mg/l	Trandolapril ¹⁸	1.0 mg	1	4 mg	3 mg	
1.25 mg 1 10 mg 6.2 mg Bei 3.125 mg 2 50-100 mg 37 mg Pos 12.5 or 25 mg 1 200 mg 159 mg Pos 12.5 or 25 mg 1 200 mg 159 mg Pos 12.5 or 25 mg 1 200 mg 159 mg Pos 12.5 or 25 mg 1 10 mg 7.7 mg** Cor 4 mg 1 32 mg 24 mg†† Bei 40 mg 2 320 mg 254 mg Pos 50 mg 1 150 mg 129 mg‡‡ Cor 25 mg 1 150 mg 129 mg‡‡ Pos 25 mg 1 150 mg 129 mg‡‡ Pos 37.5 mg 1 25 mg 129 mg‡‡ Pos 37.5 mg 3 25 mg 130 mg Pos 37.5 mg 3 25 mg 143 mg Pos 37.5 mg 3 120 mg 60 mg Pos	1.25 mg 1 10 mg 6.2 mg Bei 3.125 mg 2 50-100 mg 37 mg Pos 12.5 or 25 mg 1 200 mg 159 mg Pos 12.5 or 25 mg 1 200 mg 159 mg Pos 12.5 or 25 mg 1 200 mg 159 mg Pos 12.5 or 25 mg 1 200 mg 7.7 mg** Cor 1.25 mg 1 10 mg 7.7 mg** Cor 4 mg 1 32 mg 24 mg†† Bei 40 mg 2 320 mg 254 mg Pos 50 mg 1 150 mg 129 mg ‡‡ Cor 25 mg 1 150 mg 129 mg ‡‡ Pos 25 mg 1 25 mg 132 mg Bei 25 mg 1 255 mg 143 mg Bei 37.5 mg 3 225 mg 143 mg Pos 37.5 mg 3 120 mg 60 mg Pos	Bisoproloi ³ 11.55 mg 1 0.0 mg 3.7 mg ⁴ consensition that rate vision that rate vision tables, bonchoppending, bonch production and attriorent vision bonch. Network production 1.12 mg 2 9.0 mg 3.7 mg ⁴ consensity pertained uning initiation of treatment or increase in dosage, and symp. Networkol ¹³ 1.25 mg 1 0 mg 7.7 mg ⁴⁺ constant (protension. 25 mg (dd) symptomatic (protension. 26 mg (gd) symptomatic	Beta-blockers					Contraindications include asthma and second- or third-degree atrioventricular block.
3.125 mg 2 50-100 mg 37 mg ¹⁰³ 12.5 or 25 mg 1 200 mg 159 mg ¹⁰³ 1.25 mg 1 200 mg 159 mg ¹¹ 1.25 mg 1 10 mg 7.7 mg ^{**} Cor 4 mg 1 32 mg 24 mg ¹¹ ¹⁰ ¹⁰ ¹⁰ ¹⁰ ¹⁰ ¹⁰ ¹⁰	3:125 mg 2 50-100 mg 37 mg ¹⁰³ 12.5 or 25 mg 1 200 mg 159 mg 1 1.25 mg 1 200 mg 159 mg ¹ 1.25 mg 1 20 mg 7.7 mg ** 4 mg 1 32 mg 24 mg †† 8e ⁴ 40 mg 2 320 mg 254 mg pos 50 mg 1 150 mg 129 mg †† 25 mg 1 50 mg 43 mg 8e ⁵ 25 mg 1 25-50 mg 26 mg pos 37.5 mg 3 225 mg 143 mg 8e ⁵ 20 mg 3 120 mg 60 mg pos	Carreeliolo ¹⁰ 3125 mg 2 s0-100 mg 37 mg ^{+s} Possine everyage regist failure induces and structer or increase in dosage, and symphonatic Webholo ¹² Nebholo ¹² 1.25 or 37 mg 1 10 mg 7.7 mg ^{+s} For sum possint-score during indiation of freatment or increase in dosage, and symponatic molecular structure structu	Bisoprolol ¹⁹	1.25 mg	1	10 mg	6.2 mg	Be alert for recent decompensated heart failure and heart rate <55 bpm.
12.5 or 25 mg 1 200 mg 159 mg 1.25 mg 1 10 mg 7.7 mg** 1.25 mg 1 10 mg 7.7 mg** 4 mg 1 32 mg 24 mg†† ^{Bei} 40 mg 2 320 mg 254 mg pos 50 mg 1 150 mg 129 mg‡‡ 25 mg 1 50 mg 43 mg ^{Bei} 25 mg 1 25-50 mg 26 mg pos 37.5 mg 3 225 mg 143 mg ^{Bei} 37.5 mg 3 225 mg 143 mg ^{Bei} 20 mg 50 mg	12.5 or 25 mg 1 200 mg 159 mg∥ 1.25 mg 1 10 mg 7.7 mg** 1.25 mg 1 10 mg 7.7 mg** 4 mg 1 32 mg 24 mg†† ^{Be} 40 mg 2 320 mg 254 mg pos 50 mg 1 150 mg 129 mg ‡‡ 25 mg 1 50 mg 43 mg ^{Be} 25 mg 1 25-50 mg 26 mg pos 37.5 mg 3 225 mg 143 mg ^{Be} 20 mg 3 120 mg 60 mg ^{Pos}	Metopolol (CR/L1 ¹ 12.5 or 25 mg 1 20 mg 77 mger tomatic hypotension. 95 mgl tomatic hypotension. Nebvolol ³ 1.35 mg 1 10 mg 77 mger Amgiouristic receive hole (and state) state (and state) state) state (and state) state) state (and state) state (and state) state) state) state) state (and state)	Carvedilol ²⁰	3.125 mg	2	50-100 mg	37 mg¶	Possible adverse events include bradycardia and atrioventricular block, bronchospasm, worsening heart failure during initiation of treatment or increase in dosage, and symp-
1.25 mg 1 10 mg 7.7 mg** 4 mg 1 32 mg 24 mg†† 40 mg 2 320 mg 25 mg 50 mg 1 150 mg 129 mg‡‡ 25 mg 1 50 mg 26 mg 25 mg 1 25-50 mg 26 mg 37.5 mg 3 225 mg 143 mg 37.5 mg 3 225 mg 143 mg	1.25 mg 1 10 mg 7.7 mg** 4 mg 1 32 mg 24 mg†† 40 mg 2 320 mg 254 mg 40 mg 2 320 mg 254 mg 50 mg 1 150 mg 129 mg ‡‡ 25 mg 1 50 mg 43 mg 25 mg 1 25-50 mg 26 mg 37.5 mg 3 225 mg 143 mg 20 mg 3 120 mg 60 mg	Nebiologia 1.25 mg 1 0 mg 7.7 mg** Angiotensin-receptor blockers 4 mg 1 32 mg 4 mg1 8 mg/mpotension or systellic blood pressum >5.0 mmol/liter, semon castinine >2.5 mg/di, symptomatic values rata and symptomatic molyanes in or systellic blood pressum of blood urea nitrogen, hyperklarmia, using the adverse events include a rise in creatinine of blood urea nitrogen, hyperklarmia, Losartan ^{7,13} 50 mg 1 32 mg 54 mg1 Psole adverse and provide a rise in creatinine of blood urea nitrogen, hyperklarmia, using the adverse events include a rise in creatinine of blood urea nitrogen, hyperklarmia, a disymptomatic pytomatic molecters Addostreone ¹² 25 mg 1 25-50 mg 24 mg Psole adverse events include a rise in creatinine or blood urea nitrogen, hyperklarmia, rise in creatinine or blood urea nitrogen, hyperklarmia, rise in creatinine or blood urea nitrogen, so and synchomatic molecters Addostreone ¹² 25 mg 1 25-50 mg 24 mg Psole adverse events include hyperklarmia, rise in creatinine or blood urea nitrogen, hyperklarmia, rise in creatinine or blood urea nitrogen, hyperklarmia, rise in creatinine or blood urea nitrogen, hyperklarmia, rise in creatinine 20 mg/di (175 mol/liter, adverse events include hyperklarmia, rise in creatinine or blood urea nitrogen, rathragia, and urganice mag, recent adverse recents include hyperklarmia, rise in creatinine or blood urea nitrogen, hyperklarmia, rise in creatinine or blood urea nitrogen, rathradia adverse adverse recent in the radverse recent adverse recent	Metoprolol CR/XL ²¹	12.5 or 25 mg		200 mg	159 mg	tomatic hypotension.
4 mg 1 32 mg 24 mg†† 40 mg 2 320 mg 254 mg 50 mg 1 150 mg 129 mg ‡ 25 mg 1 50 mg 43 mg 25 mg 1 25-50 mg 26 mg 37.5 mg 3 225 mg 143 mg 20 mg 3 120 mm 60 mm	4 mg 1 32 mg 24 mg†† 40 mg 2 320 mg 254 mg 40 mg 1 150 mg 129 mg‡‡ 50 mg 1 150 mg 129 mg‡‡ 25 mg 1 50 mg 43 mg 25 mg 1 25-50 mg 26 mg 37.5 mg 3 225 mg 143 mg 20 mg 3 120 mg 60 mg	Argiotensin-receptor blockers 4 mg 1 32 mg 24 mg/rit Realerfor screm potassium - 50 mm/offler; scrum centainine -2.5 mg/dl, symptomatic Valsartan ^{3,1,3} Candesartan ^{3,1,4,3,1} 4 mg 1 32 mg Psysible adore scenary potassium - 50 mm/offler; scrum centainine -2.5 mg/dl, symptomatic Valsartan ^{3,1,4,4,4,4,4,4,4,4,4,4,4,4,4,4,4,4,4,4,}	Nebivolol ²³	1.25 mg		10 mg	$7.7 \mathrm{mg^{**}}$	
4 mg 1 32 mg 24 mg†† 40 mg 2 320 mg 24 mg†† 50 mg 1 150 mg 129 mg ‡‡ 25 mg 1 50 mg 43 mg 25 mg 1 25-50 mg 26 mg 37.5 mg 3 225 mg 143 mg 20 mg 3 120 mg 60 mg	4 mg 1 32 mg 24 mg†† 40 mg 2 320 mg 254 mg 50 mg 1 150 mg 129 mg ‡‡ 50 mg 1 50 mg 43 mg 25 mg 1 25-50 mg 26 mg 37.5 mg 3 225 mg 143 mg 20 mg 3 120 mg 60 mg	Candesartan ^{3,4,3} 4 mg 1 32 mg 24 mg ⁺ be alert for serum possisum s.05 mmol/lifer, serum creatinine >.25 mg/dl, symptomatic Valsartan ^{3,5} 6 mg 1 30 mg 24 mg possible adverse events include a rise in creatinine >.20 mg/dl, symptomatic Valsartan ^{3,5} 6 mg 1 30 mg 11 30 mg 11 30 mg 11 30 mg 31 mg possible adverse events include a rise in creatinine >.20 mg/dl (175 µmol/ Mdsterone 10 mg 23 mg 11 30 mg 31 mg 81 mill calerors events include a rise in creatinine >.20 mg/dl (175 µmol/ Milto: 25 mg 11 25 mg 11 25 mg 11 mon/liter and 25 mg 11 mon/liter and 25 mg/dl, symptomatic Aldasterone ¹⁸ 25 mg 1 25 mg 1 25 mg 1 25 mg/dl, symptomatic Aldasterone ¹⁸ 25 mg 1 25 mg 13 mg 8 elert for serum potassium >.45 mol/liter and serum creatinine >.20 mg/dl 175 µmol/ mol Aldasteron 375 mg 3 25 mg 13 mg 8 elert for serum potassium >.45 mol/liter and serum creatinine >.20 mg/dl 175 µmol/ milge; Hydralazine 375 mg 3	Angiotensin-receptor blockers					Contraindications include bilateral renal-artery stenosis.
40 mg 2 320 mg 254 mg 50 mg 1 150 mg 129 mg ‡ ; 25 mg 1 50 mg 43 mg 25 mg 1 25-50 mg 26 mg e dinitrate∬ 37.5 mg 3 225 mg 143 mg	40 mg 2 320 mg 254 mg 50 mg 1 150 mg 129 mg ‡ ‡ 25 mg 1 50 mg 43 mg 25 mg 1 25 mg 26 mg admitrate{\} 37.5 mg 3 225 mg 143 mg te ^{3o} 20 mg 3 120 mg 60 mg	Valsartan ⁴⁶ 40 mg 2 320 mg 139 mg posible duverse events include a rise in creatinine or blood urea nitrogen, hyperkalemia, Losartan ³⁷ Losartan ³⁷ 50 mg 1 150 mg 129 mg ±± and symptomatic hypotension. Losartan ³⁷ 50 mg 1 150 mg 129 mg ±± and symptomatic hypotension. Adosterone blockers 25 mg 1 25 mg 1 25 mg 10 mg Hydralazine - lossobide dinitrate{§] 25 mg 1 25 mg 1 25 mg 10 mg Hydralazine - lossobide dinitrate{§] 25 mg 1 25 mg 1 25 mg 1 mg Hydralazine - lossobide dinitrate 37.5 mg 3 1 24 mg possible adverse events include headache, symptomatic hypotension or and treas print Hydralazine - lossobide dinitrate ¹ 37.5 mg 3 1.3 mg Be alert for symptomatic hypotension or and treas print 1.0 mg possible adverse events include headache, symptomatic hypotension or or the loss of adpoint in the post adplant and breas point in the intogen. Hydralazine - lossobide dinitrate ¹⁰ 37.5 mg 1.0 mg 1.0 mg breaseveneevents include headache, symptomatic hypotension or	Candesartan ^{24,25}		1	32 mg	24 mg††	Be alert for serum potassium >5.0 mmol/liter, serum creatinine >2.5 mg/dl, symptomatic
50 mg 1 150 mg 129 mg ‡‡ 25 mg 1 50 mg 43 mg 25 mg 1 25–50 mg 26 mg e dinitrate∬ 37.5 mg 3 225 mg 143 mg	50 mg 1 150 mg 129 mg ‡‡ 25 mg 1 50 mg 43 mg 25 mg 1 25-50 mg 26 mg edinitrate∭ 37.5 mg 3 225 mg 143 mg te ³⁰ 20 mg 3 120 mg 60 mg	Losartan ⁷⁵ 50 mg 1 150 mg 129 mg ¹ ; and symptomatic hypotension. Addosterone blockers Eplerenone ⁴⁸ 25 mg 1 25 mg 1 25-50 mg 26 mg Pasible adverse events include hyperkalemia, rise in creatinine or blood urea mirrogen, and gymonactic hypotension. Hydralazine-isosobide dinitrate ¹⁸ 25 mg 1 25-50 mg 26 mg Possible adverse events include hyperkalemia, rise in creatinine or blood urea mirrogen, and gymonactic hypotension. Hydralazine-isosobide dinitrate ¹⁰ 37.5 mg 3 225 mg 143 mg Possible adverse events include hyperkalemia, rise in creatinine or blood urea mirrogen, and gymonact hypotension or syntolic blood pressure <00 mm With	Valsartan ²⁶	40 mg	2	320 mg	254 mg	hypotension, or systolic blood pressure <90 mm Hg. Possible adverse events include a rise in creatinine or blood urea nitrogen. Hyperkalemia
25 mg 1 50 mg 43 mg 25 mg 1 25–50 mg 43 mg 26 mg adinitrate∬ 37.5 mg 3 225 mg 143 mg	25 mg 1 50 mg 43 mg 25 mg 1 25–50 mg 43 mg e dinitrate∬ 37.5 mg 3 225 mg 143 mg te ³⁰ 20 mg 3 120 mg 60 mg	Aldosterone blockers Contraindications include serum potassium >5.0 mmol/liter. Eplerenone ³⁸ 25 mg 1 50 mg 8a alert for serum potassium >4.0 mg Be alert for serum potassium >4.0 mg/liter and serum creatinine >2.0 mg/ld (1.75 µmol/) Spironolactone ³⁸ 25 mg 1 25-50 mg 26 mg Possible adverse events include hyperkalemia, rise in creatinine >2.0 mg/ld (1.75 µmol/) Hydralazine-isosobide dinitrate ¹⁰ 37.5 mg 1 25-50 mg 143 mg Hydralazine 37.5 mg 3 1.2 symboand core). Possible adverse events include hyperkalemia, rise in creatinine or blood urea nitrogen, and gmecomata and breast pain in men (more common with spironolactone). Hydralazine 37.5 mg 3 1.43 mg Be alert for symptomatic hypotension or systolic blood pressure <90 mm Hg.	Losartan ²⁷	50 mg	1	150 mg	129 mg ‡‡	and symptomatic hypotension.
25 mg 1 50 mg 43 mg 25 mg 1 25-50 mg 26 mg 37.5 mg 3 225 mg 143 mg 20 mg	25 mg 1 50 mg 43 mg 25 mg 1 25-50 mg 26 mg 37.5 mg 3 225 mg 143 mg 20 mg 3 120 mg 60 mg	Eplerenone ²⁸ 25 mg 1 50 mg 43 mg Be alert for serum potassium >4.5 mmol/liter and serum creatinine >2.0 mg/dl (175 µmol/ Spironolactone ²⁸ 25 mg 1 25-50 mg 26 mg Posible adverse events include hyperkalemia, rise in creatinine >2.0 mg/dl 17.5 µmol/ stand Hydralazine-isosohide dinitrate ⁵⁰ 25 mg 1 3.7,5 mg 26 mg Posible adverse events include lupus syndrome. Hydralazine-isosohide dinitrate ⁵⁰ 3.7,5 mg 3 225 mg 143 mg Be alert for symptomatic hypotension or systolic blood pressure <90 mm Hg.	Aldosterone blockers					Contraindications include serum potassium >5.0 mmol/liter.
25 mg 1 25–50 mg 26 mg 37.5 mg 3 225 mg 143 mg 20 mg 3 120 mg 60 mg	25 mg 1 25–50 mg 26 mg 37.5 mg 3 225 mg 143 mg 20 mg 3 120 mg 60 mg	Spironolactone ³³ 25 mg 1 25-50 mg 26 mg Possible adverse events include hyperkalemia, rise in creatinine or blood urea nitrogen, and gynecomastia and breast pain in men (more common with spironolactone). Hydralazine isosobide dinitrate ³⁰ 37.5 mg 13 mg Possible adverse events include lupus syntomatic hypotension, arthralgia, and lupus-like syntome. The information in this table is based on randomized, controlled trials involving patients with chronic heart failure or with heart failure, left ventricular systolic dysfunction, or both inservated and lose, taken as one pill daily or split into two or three equal portions (e.g., the target total daily dose, taken as one pill daily or split into two or three equal portions (e.g., the target total daily dose of captopril is 150 mg, taken as 50 mg three times a day on the basis of results of the Sunvival (ATLAS) trial compared high-dose lisinopril (32.5 to 35.0 mg); guidelines recommer times table is based on the results of the Sunvival (ATLAS) trial compared high-dose lisinopril (32.5 to 35.0 mg); buy which the target total daily dose of 10 mg). ¹⁷ This value is based on the results of the Sunvival (ATLAS) trial compared ligh-dose lisinopril (32.5 to 35.0 mg); buy which the target total daily dose of 10 mg). ¹² This value is based on the results of the Sunvival (EGNET) study, in which the target total daily dose of 10 mg). ¹² This value is based on the results of the Carvediol Prospective Randomized Cumulative Sunvival (COPERNUCUS) study, in whi	Eplerenone ²⁸	25 mg	1	50 mg	43 mg	Be alert for serum potassium >4.5 mmol/liter and serum creatinine >2.0 mg/dl (175 µmol/ liter
37.5 mg 3 225 mg 143 mg 20 مبر 3 120 مبر 60 مبر	37.5 mg 3 225 mg 143 mg 20 mg 3 120 mg 60 mg	 Hydralazine –isosorbide dinitrate§ Hydralazine –isosorbide dinitrate§ Hydralazine –isosorbide dinitrate§ Hydralazine 37.5 mg 37.5 mg 143 mg suff or symptomatic hypotension or systolic blood pressure <90 mm Hg. Hydralazine 20 mg 37.5 mg 37.5 mg 120 mg 60 mg leaderse events include lupus syndrome. The information in this table is based on randomized, controlled trials involving patients with chronic heart failure. Ieft ventricular systolic of syndrome. The systolic denotes angiotensin-converting enzyme, metoprolol CR/XL metoprolol succinate, controlled release, and NA not available. Dose sare based on rhe total daily dose, taken as one pill daily or split into two or three equal potions (e.g., the target total daily dose of results of the Survival and Ventricular Enlargement [SAVE] study).¹³³ The systesment of Treatment with Lisinopril and Survival (ATLAS) trial compared high-dose lisinopril (3.2.5 to 3.5.0 mg) to low-dose lisinopril (2.5 to 5.0 mg); guidelines recommer this value is based on the results of the Survival and Ventricular Enlargement [SAVE] study).¹³³ This value is based on the results of the Cardediol prospective Randomized Cumutative Survival (COPERNICUS) study, in with the target total daily dose was 5.0 mg.²⁰³ This value is based on the results of the Cardelol Prospective Randobol European Trial (COMET) showed that low doses of methorol latine (SEN MG.²⁰³) This value is based on the results of the Cardediol or Metoprolol European Trial (COMET) showed that low doses of methorol latine (SEN MG.²⁰³) This value is based on the results of the Cardediol or Metoprolol European Trial (COMET) showed that low doses of metoprolol tartate are inferior to carvello²⁰³) This value is based on the results of the Cardes of Nebivolol Intervention on Outcomes and Rehostifisation in Seniors with Heart Failure (SEN MG.²⁰³) This value is based on the results of the Card	Spironolactone ²⁹	25 mg	г	25–50 mg	26 mg	Possible adverse events include hyperkalemia, rise in creatinine or blood urea nitrogen, and ovnecomastia and hreast pain in men (more common with spironalactone)
37.5 mg 3 225 mg 143 mg اماندونوعن 20 mg 3 120 mg 60 mg	37.5 mg 3 225 mg 143 mg initrate ³⁰ 20 mg 3 120 mg 60 mg	 Hydralazine 37.5 mg 3 225 mg 143 mg Be alert for symptomatic hypotension or systolic blood pressure <90 mm Hg. lsosorbide dinitrate³⁰ 20 mg 3 120 mg 60 mg lupus-like syndrome. Isosorbide dinitrate³⁰ 20 mg 3 120 mg 60 mg lupus-like syndrome. The information in this table is based on randomized, controlled trials involving patients with chronic heart failure or with heart failure, left ventricular systolic dysfunction, or both term so as one pill daily or split into two or three equal portions (e.g., the target total daily dose of captopril is 150 mg, taken as 50 mg three times a day on the basis of results of the Survival and Ventricular FlATE study).¹³ The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial compared high-dose lisinopril (3.5 to 5.0 mg) to low-dose lisinopril (2.5 to 5.0 mg); guidelines recommen 20 mg daily as a single dose.¹⁶ The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial compared high-dose lisinopril (3.5 to 5.0 mg) to low-dose lisinopril (2.5 to 5.0 mg); guidelines recommen 20 mg daily as a single dose.¹⁶ This value is based on the results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) showed that low doses of metoprolol surcinate. The Carvedilol or Metoprolol European Trial (COMET) showed that low doses of metoprolol surcinate. The Carvedilol or Metoprolol European Trial (COMET) showed that low doses of metoprolol surcinate solution on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial.²³ This value is based on the results of the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospital station in Seniors with Heart Failure (SENIORS) trial.²³ This value is based on the results of the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial.²³ This value is based on the results of the Ratudy of the Effects of Nebivolol Int	Hydralazine–isosorbide dinitrate(IJ				Contraindications include lupus syndrome.
20 mg 3 120 mg 60 mg	20 mg 3 120 mg 60 mg	 Isosorbide dinitrate³⁰ 20 mg 3 120 mg 60 mg lupus-like syndrome. The information in this table is based on randomized, controlled trials involving patients with chronic heart failure or with heart failure, left ventricular systolic dysfunction, or both termycardial infarction. ACE denotes and verse events include release, and NA not available. Doses are based on the total daily dose, taken as one pill daily or split into two or three equal portions (e.g., the target total daily dose of captopril is 150 mg, taken as 50 mg three times a day on the basis of reactures the basis of reacture into Xival and Ventricular Enlargement [SAVE] study).¹³ The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial compared high-dose lisinopril (3.2.5 to 35.0 mg) to low-dose lisinopril (2.5 to 5.0 mg); guidelines recommen 20 mg daily as a single dose.¹⁵ This value is based on the results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study, in which ramipil was prescribed twice daily (with a target total daily dose was 50 mg.²⁰ This value is based on the results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) showed that low doses of metoprolol tartrate are inferior to carvedilol.²² This value is based on the results of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENORS) riral.²³ This value is based on the results of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENORS) riral.²³ This value is based on the results of the Heart Failure Endocin in Mortality and Morbidity (CHARN)-Added trial (CincalTrial-gov number, NCT00634309) This value is based on the results of the Heart Failure Endocine no of Angiotensin II Antagonist Losartan trial (HEAAL; NCT00090259), in which doses of 50 and 150 mg of isoartan once daily were compared.²³ Thes data	Hydralazine	37.5 mg	3	225 mg	143 mg	Be alert for symptomatic hypotension or systolic blood pressure <90 mm Hg.
		The information in this table is based on randomized, controlled trials involving patients with chronic heart failure or with heart failure, left ventricular systolic dysfunction, or both ter myocardial infarction. ACE denotes angiotensin-converting enzyme, metoprolol CR/XL metoprolol succinate, controlled release or extended release, and NA not available. Doses are based on the total daily dose, taken as one pill daily or split into two or three equal portions (e.g., the target total daily dose of captopril is 150 mg, taken as 50 mg three times a day on the basis of results of the Survival and Ventricular Enlargement [SAVE] study). ¹³ The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial compared high-dose lisinopril (32.5 to 35.0 mg) to low-dose lisinopril (2.5 to 5.0 mg); guidelines recommen 20 mg daily as a single dose. ¹⁶ This value is based on the results of the Acute Infarction Ramipril Efficacy (AIRE) study, in which ramipril was prescribed twice daily (with a target total daily dose of 10 mg). ¹⁷ This value is based on the results of the Cardesartan in Heart Failure Efficacy (AIRE) study, in which ramipril was prescribed twice daily (with a target total daily dose of 10 mg). ¹³ This value is based on the results of the Study of the Effects of Neutonion on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial. ²³ This value is based on the results of the Heart Failure Endpoint Evaluation on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial. ²³ This value is based on the results of the Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan trial (HEAML; NCT00090259), in which dose of 50 and 150 mg of losartan once daily were compared. ²⁷	lsosorbide dinitrate ³⁰	20 mg	З	120 mg	60 mg	Possible adverse events include headache, symptomatic hypotension, arthraigia, and lupus-like syndrome.
ter myocardial marcuon. Ace denotes anglotensin-converting enzyme, metoproiol CK/AL metoproiol succinate, controlled refease of extended refease, and Doses are based on the total daily dose, taken as one pill daily or split into two or three equal portions (e.g., the target total daily dose of captopril is 150 ms		20 mg daily as a single dose. ¹⁶ This value is based on the results of the Acute Infarction Ramipril Efficacy (AIRE) study, in which ramipril was prescribed twice daily (with a target total daily dose of 10 mg). ¹⁷ This value is based on the results of the Acute Infarction Ramipril Efficacy (AIRE) study, in which the target total daily dose was 50 mg. ²⁰ This value is based on the results for metoprolol succinate. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study, in which the target total daily dose was 50 mg. ²⁰ This value is based on the results for metoprolol succinate. The Carvedilol Prospection in Mortality and Monbidity (ARM).Added trial (ENORS) trial. ³² This value is based on the results of the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial. ³³ This value is based on the results of the Heart Failure Assessment of Reduction in Mortality and Monbidity (CHARM).Added trial (ClinicalTrials.gov number, NCT000634309) This value is based on the results of the Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan trial (HEAL; NCT00090259), in which doses of 50 and 150 mg of losartan once daily were compared. ²⁷ These data are based on the African-American Heart Failure Trial (A-HEFT; NCT00047775) ³⁰ , this combination was given four times daily in the 1st Vasodilator Heart Failure (Y-HEFT I). ³¹	times a day on the basis of ru The Assessment of Treatmer	esults of the Su nt with Lisinopri		ntricular Enlarg	gement [SAVE] stud	y). ¹³ se lisinopril (32.5 to 35.0 mg) to low-dose lisinopril (2.5 to 5.0 mg); guidelines recommend
		 * This value is based on the results of the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial.²³ † This value is based on the results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Added trial (ClinicalTrials.gov number, NCT00634309) ‡ This value is based on the results of the Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan trial (HEAAL; NCT00090259), in which doses of 50 and 150 mg of losartan once daily were compared.²⁷ These data are based on the African-American Heart Failure Trial (A-HET; NCT00047775)³⁰, this combination was given four times daily in the 1st Vasodilator Heart Failure Trial (V-HETI).³¹ 	20 mg daily as a single dose. This value is based on the re This value is based on the re This value is based on results	s for metoprolol	te Infarction /edilol Prosp succinate. Th	Ramipril Effica ective Random le Carvedilol or	cy (AIRE) study, in ized Cumulative Su Metoprolol Europe	which ramipril was prescribed twice daily (with a target total daily dose of 10 mg). ¹⁷ rvival (COPERNICUS) study, in which the target total daily dose was 50 mg. ²⁰ an Trial (COMET) showed that low doses of metoprolol tartrate are inferior to carvedilol. ²²
ter myocardial million. ALE denotes angrouens Doses are based on the total daily dose, taken as times a day on the basis of results of the Survival The ASsessment of Treatment with Lisinopril and 20 mg daily as a single dose. ¹⁶ This value is based on the results of the Acute Infi This value is based on the results of the Carvedilo This value is based on results for metoprolol succi	day on the basis of results of the Survival and Ventricular Enlargement [SAVE] study). ¹³ essment of Treatment with Lisinopril and Survival (ATLAS) trial compared high-dose lisinopril (32.5 to 35.0 mg) to low-dose lisinopril (2.5 to 5.0 mg); guidelines recomme laily as a single dose. ¹⁶ ue is based on the results of the Acute Infarction Ramipril Efficacy (AIRE) study, in which ramipril was prescribed twice daily (with a target total daily dose of 10 mg). ¹⁷ ue is based on the results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study, in which the target total daily dose was 50 mg. ²⁰ ue is based on results for metoprolol succinate. The Carvedilol or Metoprolol European Trial (COMET) showed that low doses of metoprolol tartrate are inferior to carvedilol. ²²	These data are based on the African-American Heart	* This value is based on the re This value is based on the resu This value is based on the re	sults of the Studuts of the Cander ults of the Cander sults of the Hea	dy of the Effe sartan in Hea irt Failure En	cts of Nebivolo art Failure: Asse dpoint Evaluati	I Intervention on C ssment of Reduction on of Angiotensin	outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial. ²³ n in Mortality and Morbidity (CHARM)-Added trial (ClinicalTrials.gov number, NCT00634309). ²³ II Antagonist Losartan trial (HEAAL; NCT00090259), in which doses of 50 and 150 mg of
 This value is based on the results of the Study of the Effects of Networking enzyme, metoprolocies and portions (e.g., the target total daily dose of captopril is 150 mg times a say on the basis of results of the Survival and Ventricular Enlargement [SAVE] study).¹³ The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial compared high-dose lisinopril (32.5 to 35.0 mg) to low-dose lisinopril (2.5 to 5.0 mg 20 mg daily as a single dose.¹⁶ This value is based on the results of the Carvediol Prospective Randomized Cumulative Survival (COPERNICUS) study, in which the target total daily dose of captopril is 150 mg 20 mg daily as a single dose.¹⁶ This value is based on the results of the Carvediol Prospective Randomized Cumulative Survival (COPERNICUS) study, in which the target total daily dose of metoprolol succinate. The Carvediol or Metoprolol European Trial (COMET) showed that low doses of metoprolol tartrate are this value is based on the results of the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SE). This value is based on the results of the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SE). This value is based on the results of the Heart Failure Edgent of Angiotensin II Antagonist Losartan trial (HEAAL; NCT00090259), in which dos and the results of the Heart Failure Edgent of Angiotensin II Antagonist Losartan trial (HEAAL; NCT00090259), in which dos and the results of the Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan trial (HEAAL; NCT00090259), in which dos and the results of the Heart Failure Edgent of Angiotensin II Antagonist Losartan trial (HEAAL; NCT00090259), in which dos and the results of the Heart Failure Edgent of Angiotensin II Antagonist Losartan trial (Heaved trial (ClinicalTrials.gov) 	day on the basis of results of the Survival and Ventricular Enlargement [SAVE] study). ¹³ essment of Treatment with Lisinopril and Survival (ATLAS) trial compared high-dose lisinopril (32.5 to 35.0 mg) to low-dose lisinopril (2.5 to 5.0 mg); guidelines recomme laily as a single dose. ¹⁶ ue is based on the results of the Acute Infarction Ramipril Efficacy (AIRE) study, in which ramipril was prescribed twice daily (with a target total daily dose of 10 mg). ¹⁷ ue is based on the results of the Carvediol Prospective Randomized Cumulative Survival (COPERNICUS) study, in which the target total daily dose was 50 mg. ²⁰ ue is based on the results of the Study of the Effects of Netionol European Trial (COMET) showed that low doses of metoprolol tartrate are inferior to carvedilol. ²¹ ue is based on the results of the Study of the Effects of Netionol European Trial (COMET) showed that low doses of metoprolol tartrate are inferior to carvedilol. ²² ue is based on the results of the Study of the Effects of Netiovolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial. ²³ Le is based on the results of the Landesartan in Heart Failure: Assessment of Reduction in Montality and Monbidity (CHARM)-Added trial (ClinicalTrials.gov number, NCT0063430) Le is based on the results of the Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan trial (HEALL; NCT00090259), in which doses of 50 and 150 mg on the comparison of the Heart Failure for and the intervalue of the compared to and 150 mg of the compared to and 150 mg of the compared to and the compared to a second to a compare of the compared to a compared to a second to a compare of the condesartan in Heart Failure (SENIORS) to compare to a second to a compare of the condesartan in Heart Failure for the compared to a compare of the condesartan in the conditione of the condesartan in the conditione of Angiotensin II Antagonist Losartan trial (HEAAL; NCT00090259), in which doses of 50 and 150 mg of the conditione of t			ipareu. Giore Amorico I				

N ENGLJ MED 362;3 NEJM.ORG JANUARY 21, 2010

Beta-Blockers

Along with ACE inhibitors, beta-blockers are essential first-line therapy in patients with heart failure and left ventricular systolic dysfunction, regardless of the cause of the condition.^{7,8,19-21} Treatment with beta-blockers improves systolic function, resulting in an increase in ejection fraction of 5 to 10%, and reduces symptoms. In three placebocontrolled trials, beta-blocker therapy (with bisoprolol,19 carvedilol,20 or metoprolol CR/XL [metoprolol succinate, controlled release or extended release]²¹) reduced the rate of hospital admissions and reduced mortality by 34%, when it was added to an ACE inhibitor, diuretic, and digoxin among patients with NYHA class II, III, or IV symptoms. Among patients hospitalized with acute decompensation who are not already taking a betablocker, beta-blocker therapy should be deferred until the patient's condition improves but should be initiated before the patient's discharge from the hospital. Long-term beta-blocker therapy should not be stopped during episodes of decompensation unless the patient has severe systemic underperfusion, in which case it should be withdrawn until the patient is hemodynamically stable and his or her condition is improved.35

Aldosterone Antagonists

In a large, placebo-controlled, randomized trial in which patients received spironolactone in addition to a diuretic, digoxin, and an ACE inhibitor, a reduction in symptoms and in hospital admissions, and a 30% reduction in mortality, were seen among patients with severe systolic heart failure (NYHA class III or IV).²⁹ Therefore, the addition of an aldosterone antagonist should be considered for any patient who remains in NYHA class III or IV despite treatment with a diuretic, an ACE inhibitor (or ARB), and a beta-blocker. Either an aldosterone antagonist or an ARB (but not both, because of the risk of renal dysfunction and hyperkalemia) may be added to an ACE inhibitor.

Hydralazine and Isosorbide Dinitrate

Retrospective subgroup analyses from two trials of hydralazine and isosorbide dinitrate³⁶ (one a placebo-controlled trial³¹ and the other a comparison of hydralazine–isosorbide dinitrate with enalapril³⁴) and from the Studies of Left Ventricular Dysfunction³⁷ (in which enalapril was compared with placebo) suggested that black patients did not have as good a response to an ACE inhibitor as did white patients, but had a better response to hydralazine–isosorbide dinitrate than did white patients. In a subsequent randomized, placebo-controlled trial involving patients with NYHA class III or IV heart failure who self-identified as African American,³⁰ treatment with hydralazine–isosorbide dinitrate, when added to an ACE inhibitor, a betablocker, and, in some cases, an aldosterone antagonist, resulted in a reduced rate of hospitalization for heart failure, improved quality of life, and increased survival.³⁰

Other Medications

In the single large trial involving patients with systolic heart failure who were in sinus rhythm, digoxin, when added to a diuretic and an ACE inhibitor, had no effect on mortality but reduced the risk of hospitalization for heart failure by 28% (Table 1 in the Supplementary Appendix).³⁸ A recent study showed that treatment with 1 gram of n-3 polyunsaturated fatty acid per day (850 to 852 mg of eicosapentaenoic acid and docosahexaenoic acid as ethyl esters in the average ratio of 1:1.2) led to a small reduction in cardiovascular complications and death in patients with heart failure (Table 1 in the Supplementary Appendix).39 The exact mechanism of action of this treatment is uncertain, although it may have beneficial antiinflammatory and electrophysiological effects (the latter reducing the risk of arrhythmias). Some conventional cardiovascular drugs (e.g., aspirin,⁴⁰ statins,⁴¹ and erythropoiesis-stimulating agents⁴²) are of uncertain benefit in patients with heart failure, and some drugs can be harmful, including thiazolidinediones, nonsteroidal antiinflammatory drugs, and most antiarrhythmic drugs (including dronedarone43). Vitamin K antagonists reduce the risk of thromboembolism in patients with atrial fibrillation but have not been shown to be of value in other patients with heart failure.7,8,40 Pneumococcal and influenza vaccinations are recommended.7,8

ORGANIZATION OF CARE

A multidisciplinary intervention that is focused on both the patient and the caregiver results in a reduction in the rate of hospital admissions and has also been shown in a meta-analysis of trials to reduce mortality.⁴⁴ Educating patients, their families, and caregivers about heart failure, its treatment, and the early recognition of and response to clinical deterioration (e.g., new or wors-

Downloaded from www.nejm.org by JOHN VOGEL MD on January 20, 2010 . Copyright © 2010 Massachusetts Medical Society. All rights reserved. ening symptoms or weight gain) appears to be of central importance. The importance of adhering to treatment should be emphasized, and guidance on flexible dosing of diuretics should be provided. These disease-management programs also provide the framework for optimizing evidence-based pharmacologic therapy and encouraging regular exercise. End-of-life palliative care should also be available for patients with end-stage heart failure.⁴⁵

LIFESTYLE AND EXERCISE

Restriction of sodium intake is routinely recommended, although this recommendation is based on little evidence.^{7,8} A recent trial showed that tailored, structured, aerobic exercise was safe and improved functional capacity and quality of life in patients with heart failure (Table 1 in the Supplementary Appendix).⁴⁶ That trial and a meta-analysis of smaller studies also suggested that exercise may reduce the risk of death and of hospitalization for heart failure.⁴⁶ The intervention used in the study, however, was labor-intensive.

DEVICES

Implantable Cardioverter–Defibrillators

About half the deaths that occur among patients with systolic heart failure are attributed to ventricular arrhythmias; the proportion is higher among patients with mild symptoms, whereas patients with severe heart failure are more likely to die from pump failure. An implantable cardioverter–defibrillator reduces the risk of sudden death in patients with left ventricular systolic dysfunction,⁴⁷ with no adverse effect on quality of life,⁴⁸ although the benefit is not apparent until a year or more after implantation of the device (Table 1 in the Supplementary Appendix).⁴⁷

An implantable cardioverter–defibrillator is indicated for secondary prevention, in the case of any patient who survives an unprovoked episode of ventricular fibrillation or sustained ventricular tachycardia,^{7,8} and for primary prevention, in the case of patients in NYHA functional class II or III who have an ejection fraction that is persistently 35% or less despite optimal medical therapy and who are expected to survive for at least 1 year with a reasonable quality of life and functional status.^{7,8,47}

Cardiac-Resynchronization Therapy

Intraventricular conduction delays, identified by a QRS interval of 120 msec or more on a 12-lead

electrocardiogram, occur in up to a third of patients with severe systolic heart failure and are associated with dyssynchronous contraction of the left ventricle, leading to impaired emptying and, in some patients, mitral regurgitation.49,50 Abnormal atrioventricular coupling (identified by a prolonged PR interval) and interventricular dyssynchrony, identified on an echocardiogram, may also occur. Cardiac-resynchronization therapy with atrial-synchronized biventricular pacing often improves cardiac performance immediately, by increasing stroke volume and reducing mitral regurgitation.^{7,8} Randomized trials involving patients with severe heart failure showed that cardiacresynchronization therapy resulted in a reduction in symptoms and improved functional capacity, a reduction in the number of hospitalizations for worsening heart failure, and increased survival.49,50 On the basis of these trials, current guidelines recommend cardiac-resynchronization therapy for patients with severe symptoms (NYHA class III or IV), an ejection fraction that is persistently 35% or below, sinus rhythm, and a QRS duration of 120 msec or more.7,8 Although cardiacresynchronization therapy was not shown to be beneficial in patients with NYHA class III symptoms and a narrow QRS interval (<120 msec),⁵¹ a recent randomized trial involving patients with NYHA class I or II symptoms, ejection fractions of 30% or less, and wide QRS intervals (≥130 msec) showed that cardiac-resynchronization therapy in addition to an implantable cardioverter-defibrillator, as compared with an implantable cardioverter-defibrillator alone, improved ventricular function and reduced the risk of worsening heart failure; these effects were most pronounced in patients with a QRS interval of 150 msec or more (Table 1 in the Supplementary Appendix).⁵² Cardiac-resynchronization therapy did not reduce the risk of death in this population with a relatively low mortality.52

SURGERY

Although coronary revascularization is performed frequently, its role, especially in patients who do not have angina or reversible myocardial ischemia, is uncertain; this surgical treatment is currently being evaluated in a randomized trial.⁵³ Other procedures, such as repair of the mitral valve, are used empirically in selected patients. A recent trial showed that surgical ventricular reconstruction provided no benefit with respect to symptoms or rates of death or hospitalization for cardiac causes.⁵⁴

Cardiac transplantation is a last resort for patients with refractory heart failure. The patient must be otherwise fit for surgery and must be able to adhere to the intensive medical treatment and follow-up that are required postoperatively. Given the scarcity of donor organs,^{7,8} there has been interest in left ventricular assist devices as a bridge to transplantation or even as definitive therapy. Whereas older pulsatile volume-displacement ventricular assist devices were not shown to improve 2-year survival in patients with endstage heart failure who were ineligible for transplantation (Table 1 in the Supplementary Appendix) and were associated with relatively high rates of bleeding, infection, stroke, and repeat surgery to repair or replace the device,55 newer ventricular assist devices appear to be more effective and safer.7,8 In a recent trial comparing a continuousflow device with an older pulsatile volume-displacement device in patients with end-stage heart failure who were ineligible for transplantation,56 the 2-year survival without disabling stroke or the need for repeat surgery to repair or replace the device was significantly greater with the new device than with the older device (46% vs. 11%).

AREAS OF UNCERTAINTY

Randomized trials (e.g., the Reduction of Events with Darbepoetin Alfa in Heart Failure trial [RED-HF; NCT00358215]⁴² and the Surgical Treatment for Ischemic Heart Failure trial [STICH; NCT00023595]53) are in progress to assess the benefit of an aldosterone antagonist as treatment for patients who are categorized as NYHA functional class II and to define the roles that correction of anemia and coronary revascularization play in the treatment of patients with systolic heart failure. The optimal content of disease-management programs is uncertain.44 It is not known whether telemonitoring, implanted monitoring devices, or therapy guided by the measurement of natriuretic peptides improves the outcomes.57,58 Whether persons with a narrow QRS interval, mild symptoms, or atrial fibrillation benefit from cardiac-resynchronization therapy is uncertain, nor is it clear which patients benefit from cardiacresynchronization therapy alone and which patients need a device that provides both cardiacresynchronization therapy and implantable cardioversion–defibrillation. The effectiveness and cost-effectiveness of ventricular assist devices require further evaluation.

GUIDELINES

The recommendations in this article are consistent with international guidelines.^{7,8}

CONCLUSIONS AND RECOMMENDATIONS

The patient in this vignette presented with typical symptoms and signs of heart failure. Although systolic dysfunction is the likely diagnosis, given the patient's previous myocardial infarction, confirmation by echocardiography (or other imaging) is essential. In cases in which heart failure is a less likely diagnosis, measurement of natriuretic peptides may be useful as a first step, since a normal concentration suggests an alternative diagnosis.

A diuretic will quickly alleviate the patient's dyspnea and edema, but it is insufficient therapy alone. Both an ACE inhibitor and a beta-blocker should be prescribed at doses that have been shown in randomized trials to be effective; if symptoms persist, an aldosterone antagonist or ARB should be added. With these treatments, I would expect the patient's ejection fraction to improve over the course of 3 to 6 months, but if it remains at 35% or below, an implantable cardioverter-defibrillator should be considered. If the patient's 12-lead electrocardiogram shows QRS prolongation, I would consider a device that provides both cardiac-resynchronization therapy and implantable cardioversion-defibrillation instead, especially if he continues to have functional limitations owing to his symptoms.

Close monitoring is warranted, particularly during the initiation of therapy and the adjustment of the doses. I would encourage participation in a disease-management program, which would provide him and his family education^{59,60} regarding heart failure and appropriate dietary, exercise, and other self-care interventions.

Dr. McMurray reports receiving consulting fees from the Menarini Group, Bristol-Myers Squibb, Roche, Novocardia (now part of Merck), Boehringer Ingelheim, Novartis, Boston Scientific, and bioMérieux, lecture fees from AstraZeneca, Solvay, Takeda, Novartis, and Bristol-Myers Squibb–Sanofi, and grant support from Bristol-Myers Squibb, Novartis, Amgen, AstraZeneca, F. Hoffmann–La Roche, Pfizer, GlaxoSmithKline, and Scios. No other potential conflict of interest relevant to the article was reported.

REFERENCES

1. Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348:2007-18.

2. Aurigemma GP, Gaasch WH. Diastolic heart failure. N Engl J Med 2004;351: 1097-105.

3. Abrahamsson P, Dobson J, Granger CB, et al. Impact of hospitalization for acute coronary events on subsequent mortality in patients with chronic heart failure. Eur Heart J 2009;30:338-45.

4. Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. The neurohumoral axis in congestive heart failure. Ann Intern Med 1984;101:370-7.

5. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. N Engl J Med 1971;285:1441-6.

6. Jhund PS, Macintyre K, Simpson CR, et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. Circulation 2009:119:515-23.

7. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology: developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008; 10:933-89.

8. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119(14):e391-e479.

Mant J, Doust J, Roalfe A, et al. Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care. Health Technol Assess 2009;13:1-207.
 Maisel A, Mueller C, Adams K Jr, et al. State of the art: using natriuretic peptide levels in clinical practice. Eur J Heart Fail 2008;10:824-39.

11. Karamitsos TD, Francis JM, Myerson S, Selvanayagam JB, Neubauer S. The role of cardiovascular magnetic resonance imaging in heart failure. J Am Coll Cardiol 2009;54:1407-24.

12. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston: Little, Brown, 1994:253-6.

13. Pfeffer MA, Braunwald E, Moyé LA, et

al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement trial. N Engl J Med 1992;327: 669-77.

14. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429-35.

15. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.

16. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensinconverting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation 1999;100:2312-8.

17. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993;342:821-8.

18. Køber L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensinconverting–enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1995;333:1670-6.

19. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9-13.

20. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344:1651-8.

21. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353:2001-7.

22. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003;362:7-13.

23. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26:215-25.

24. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003; 362:772-6.

25. McMurray JJ, Ostergren J, Swedberg

K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003; 362:767-71.

26. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.

27. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet 2009; 374:1840-8.

28. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309-21. [Erratum, N Engl J Med 2003;348:2271.]

29. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.

30. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2049-57. [Erratum, N Engl J Med 2005;352:1276.]

31. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. N Engl J Med 1986; 314:1547-52.

32. McMurray J, Cohen-Solal A, Dietz R, et al. Practical recommendations for the use of ACE inhibitors, beta-blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. Eur J Heart Fail 2005;7:710-21.

33. *Idem.* Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685-91. [Erratum, N Engl J Med 1992;327:1768.]

34. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine–isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303-10.

35. Jondeau G, Neuder Y, Eicher JC, et al. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. Eur Heart J 2009;30:2186-92.

36. Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the vaso-dilator-heart failure trials. J Card Fail 1999;5:178-87.

37. Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-

237

converting–enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. N Engl J Med 2001;344:1351-7.

38. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525-33.

39. GISSI-HF Investigators, Tavazzi L, Maggioni AP, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1223-30.

40. Massie BM, Collins JF, Ammon SE, et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplate-let Therapy in Chronic Heart Failure (WATCH) trial. Circulation 2009;119: 1616-24.

41. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007; 357:2248-61.

42. McMurray JJ, Anand IS, Diaz R, et al. Design of the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF): a Phase III, anaemia correction, morbiditymortality trial. Eur J Heart Fail 2009;11: 795-801.

43. Køber L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358:2678-87.

44. Sochalski J, Jaarsma T, Krumholz HM, et al. What works in chronic care management: the case of heart failure. Health Aff (Millwood) 2009;28:179-89.

45. Jaarsma T, Beattie JM, Ryder M, et al. Palliative care in heart failure: a position statement from the palliative care workshop of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2009;11:433-43.

46. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439-50.

47. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37. [Erratum, N Engl J Med 2005;352:2146.]
48. Mark DB, Anstrom KJ, Sun JL, et al. Quality of life with defibrillator therapy or amiodarone in heart failure. N Engl J Med 2008;359:999-1008.

49. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.

50. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.

51. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. N Engl J Med 2007;357:2461-71.

52. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329-38.

53. Velazquez EJ, Lee KL, O'Connor CM, et al. The rationale and design of the Sur-

gical Treatment for Ischemic Heart Failure (STICH) trial. J Thorac Cardiovasc Surg 2007;134:1540-7.

54. Jones RH, Velazquez EJ, Michler RE, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med 2009;360:1705-17.

55. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med 2001;345:1435-43.

56. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241-51.

57. Pfisterer M, Buser P, Rickli H, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA 2009;301:383-92.

58. Maric B, Kaan A, Ignaszewski A, Lear SA. A systematic review of telemonitoring technologies in heart failure. Eur J Heart Fail 2009;11:506-17.

59. Educational modules on heart failure. St. Paul, MN: Heart Failure Society of America. (Accessed December 29, 2009, at http://www.hfsa.org/heart_failure_ education_modules.asp.)

60. Heart Failure Matters home page. (Accessed December 29, 2009, at http://www.heartfailurematters.org/EN/Pages/index.aspx.)

Copyright © 2010 Massachusetts Medical Society.

COLLECTIONS OF ARTICLES ON THE JOURNAL'S WEB SITE

The Journal's Web site (**NEJM.org**) sorts published articles into more than 50 distinct clinical collections, which can be used as convenient entry points to clinical content. In each collection, articles are cited in reverse chronologic order, with the most recent first.