Chapter 10

Heart Failure

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INTRODUCTION

This chapter presents data on the efficacy, effectiveness, and cost-effectiveness of priority heart failure–related interventions. Heart failure is a clinical syndrome in which the heart is unable to meet the metabolic demands of the body because of functional limitations in ventricular filling (diastole), ejection (systole), or both (Yancy and others 2013). Heart failure is a heterogeneous, progressive, chronic disease with protean symptoms, including fatigue; breathlessness at rest or with exertion; and fluid retention in the lungs, abdomen, or extremities. The stages and functional classes of heart failure are detailed in box 10.1.

Causes of Heart Failure

Often, heart failure is an end-stage manifestation of other forms of heart disease, such as ischemic heart disease, usually the result of reduced or obstructed blood flow to the heart; hypertensive heart disease, associated with cardiac damage resulting from high blood pressure; or valvular heart disease, characterized by damage to one or more of the four cardiac valves. There are marked differences according to geographic region (Callender and others 2014; Sliwa and Stewart 2014).

Other causes include the following:

- Primary heart muscle abnormalities known as cardiomyopathies, for example, dilated, familial, peripartum, and infiltrative cardiomyopathies
- Heart muscle toxins, for example, alcohol or cocaine use, as well as cancer therapies
- Specific or severe inflammation, for example, myocarditis, AIDS (acquired immune deficiency syndrome), and Chagas disease.

Diagnosis

Heart failure is diagnosed through a careful history and physical examination, but additional diagnostics—including B-type natriuretic peptide and echocardiography—are frequently performed (McMurray and others 2012; Yancy and others 2013). Five-year mortality rates continue to be estimated at 50 percent in high-income countries (HICs) (Loehr and others 2008), reflecting the severity of a heart failure diagnosis. Long-term outcome data are not available for individuals living in low- and middle-income countries (LMICs) but are assumed to be similarly high, if not higher. Hospitalization for acute heart failure symptoms that typically require intravenous diuretic therapy is a particularly high-risk event, with one-year mortality estimates of 30 percent among older adults in the United States; this rate has not changed substantially between 1998 and 2008 (Chen and others 2011).

BURDEN OF DISEASE

Global Burden

Global estimates of the disease burden of heart failure are difficult to capture, in part because heart failure may be considered both a mode of death (for example, heart

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Box 10.1

Stages and Functional Classes of Heart Failure

The American Heart Association and the American College of Cardiology have developed a system to classify heart failure into one of four stages. This classification scheme describes the inviolate progression of clinical manifestations of heart failure based on risk for subsequent fatal and nonfatal events, including hospitalization due to acute heart failure.

- Stage A applies to individuals with heart failure risk factors.
- Stage B applies to individuals with cardiac structural abnormalities without symptoms.
- Stage C applies to individuals with current or previous heart failure symptoms.
- Stage D applies to individuals with end-stage heart failure.

This classification scheme is complemented by the New York Heart Association functional classification scheme, which is widely used by clinicians for risk stratification and treatment decision making. The New York Heart Association functional classification is restricted to patients with stages B, C, or D heart failure:

- Class I applies to individuals with no functional limitations.
- Class II applies to individuals with slight functional limitations.
- Class III applies to individuals with marked functional limitations.
- Class IV applies to individuals with severe limitations upon undertaking any activity or while at rest.

Source: Yancy and others 2013.

failure in a patient with end-stage ischemic heart disease, valvular heart disease, or hypertensive heart disease) and an underlying disease process that causes death or disability (for example, cardiomyopathy or primary heart muscle disorder) (Stevens, King, and Shibuya 2010). Mortality data are generally limited to deaths attributable to underlying disease processes.

According to the World Health Organization (WHO), an estimated 482,000 individuals (0.8 percent of total deaths) died as the result of cardiomyopathy, myocarditis, or endocarditis in 2015 (WHO 2015a) (table 10.1). The majority of these deaths occurred among men compared with women (58 percent versus 42 percent), and among individuals living in LMICs compared with individuals living in HICs (88 percent versus 12 percent). Because of population growth and aging, the estimated number of deaths is projected to reach 576,000 by 2030, which would be 0.8 percent of total deaths. This estimate does not reflect the burden and costs of heart failure caused by other, more common causes, including ischemic heart disease, hypertensive heart disease, and valvular heart disease.

Hypertensive heart disease is categorized separately and caused an estimated 1,137,000 deaths (2.0 percent of total deaths) in 2015 (table 10.1). The majority of these deaths occurred among women compared with men (57 percent versus 43 percent), and among individuals living in LMICs compared with individuals living in HICs (80 percent versus 20 percent). Because of population growth and aging, this estimate is projected to reach 1.5 million by 2030, which would be 2.1 percent of total deaths.

The Global Burden of Disease Study Investigators estimated that 61.7 million individuals had symptomatic heart failure from any cause in 2013, which is a substantial increase from 31.4 million estimated in 1990 (table 10.2) (GBD Study 2013 Collaborators 2015). The investigators used all available hospital-based data, a literature review, and a DisMod state transition model to create this estimate in total and for individual causes.

Regional Burden of Disease

A systematic review of the same Global Burden of Disease Study methodology describes the geographic variation in major risk factors (figure 10.1) (Khatibzadeh and others 2012). Although the presence of multiple risk factors was common, hypertension was reported as a risk factor in 17 percent of cases, with a higher age- and gender-adjusted prevalence in Eastern and Central Europe (35 percent, 95 percent confidence interval [CI] 33–37 percent) and Sub-Saharan Africa (33 percent, 95 percent CI 30–36 percent). Ischemic heart disease was reported as a risk factor in 52 percent of patients with heart failure in HICs but only 5 percent of patients with

Table 10.1 Population and Mortality Estimates (2015) and Projections (2030) for Cardiomyopathy, Myocarditis, Endocarditis, and Hypertensive Heart Disease

	2015			2030		
	Population	Deaths attributable to cardiomyopathy, myocarditis, or endocarditis	Deaths attributable to hypertensive heart disease	Population	Deaths attributable to cardiomyopathy, myocarditis, or endocarditis	Deaths attributable to hypertensive heart disease
Global men	3,655,810,000	278,055	488,881	4,170,366,000	327,081	625,483
Global women	3,592,760,000	203,664	648,049	4,113,006,000	248,470	831,823
Global total	*7,248,570,000*	*481,720*	*1,136,930*	*8,283,372,000*	*575,551*	*1,457,306*
High-income men	555,410,000	50,239	84,763	591,660,000	56,048	100,911
High-income women	563,034,000	38,565	137,564	595,773,000	41,888	150,650
High-income total	*1,118,444,000*	*88,804*	*222,327*	*1,187,434,000*	*97,936*	*251,561*
LMI-AFR men	472,224,000	36,361	25,818	657,536,000	58,455	41,185
LMI-AFR women	628,815,000	30,527	69,171	653,881,000	48,459	119,186
LMI-AFR total	*943,520,000*	*66,888*	*94,989*	*1,311,417,000*	*106,914*	*160,372*
LMI-AMR men	303,611,000	21,803	55,680	341,868,000	26,098	75,542
LMI-AMR women	311,305,000	16,548	67,153	352,013,000	20,358	88,349
LMI-AMR total	*614,917,000*	*38,351*	*122,834*	*693,881,000*	*46,456*	*163,892*
LMI-SEAR men	979,685,000	74,042	127,215	1,119,437,000	91,416	177,272
LMI-SEAR women	941,076,000	44,754	139,359	1,085,709,000	59,256	198,416
LMI-SEAR total	*1,920,761,000*	*118,796*	*266,574*	*2,205,146,000*	*150,672*	*375,687*
LMI-EUR men	196,322,000	44,314	37,641	200,123,000	34,826	37,175
LMI-EUR women	214,911,000	27,805	51,344	218,087,000	24,257	50,072
LMI-EUR total	*411,234,000*	*72,119*	*88,985*	*418,210,000*	*59,083*	*87,247*
LMI-EMR men	304,165,000	21,136	34,596	381,747,000	29,556	51,076
LMI-EMR women	298,489,000	18,251	42,108	376,438,000	27,095	67,407
LMI-EMR total	*602,655,000*	*39,387*	*76,703*	*758,185,000*	*56,651*	*118,483*
LMI-WPR men	844,393,000	30,160	123,168	877,995,000	30,682	142,321
LMI-WPR women	792,647,000	27,214	141,350	831,104,000	27,157	157,743
LMI-WPR total	*1,637,040,000*	*57,375*	*264,518*	*1,709,099,000*	*57,839*	*300,064*

Source: WHO 2015a.
Note: AFR = Africa; AMR = the Americas; EMR = Eastern Mediterranean Region; EUR = Europe; LMI = low- and middle-income; SEAR = South-East Asia Region; WPR = Western Pacific Region.

Table 10.2 Prevalence and Causes of Symptomatic Heart Failure in 1990 and 2013 Based on Estimates Derived from the Global Burden of Disease Study

	Prevalence (%), 1990	Prevalence (%), 2013
Ischemic heart disease	10,298,900 (32.8)	20,372,600 (33.0)
Hypertensive heart disease	5,128,400 (16.3)	10,906,900 (17.7)
Other cardiovascular disease	4,117,600 (13.1)	95,421,000 (15.5)
Cardiomyopathy and myocarditis	4,077,600 (13.0)	7,629,900 (12.4)
Chronic obstructive pulmonary disease	3,036,500 (9.7)	5,846,400 (9.5)

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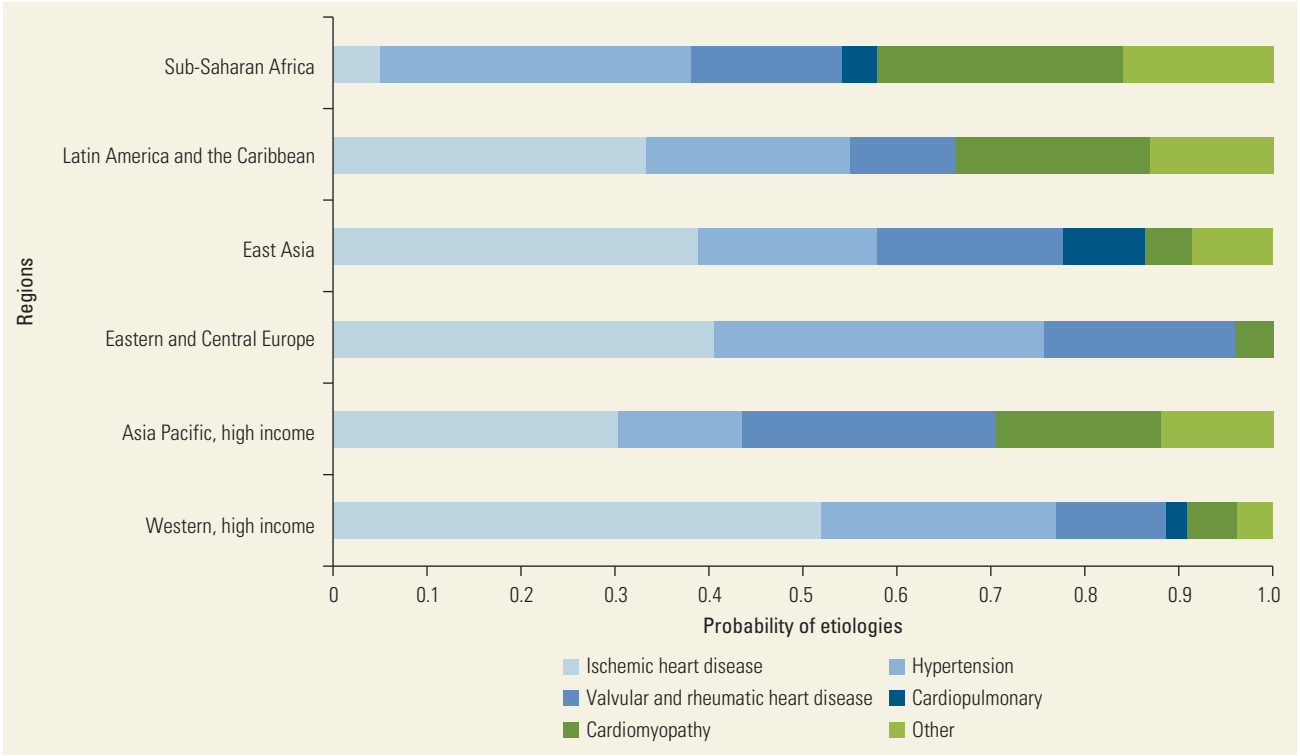
Table 10.2 Prevalence and Causes of Symptomatic Heart Failure in 1990 and 2013 Based on Estimates Derived from the Global Burden of Disease Study (continued)

	Prevalence (%), 1990	Prevalence (%), 2013
Rheumatic heart disease	2,837,800 (9.0)	4,274,000 (6.9)
Endocrine, metabolic, blood, and immune disorders	338,200 (1.1)	852,400 (1.4)
Congenital heart anomalies	495,900 (1.6)	621,700 (1.0)
Iron-deficiency anemia	373,200 (1.2)	446,600 (0.7)
Chagas disease	280,100 (0.9)	383,900 (0.6)
Endocarditis	136,200 (0.4)	250,200 (0.4)
Other hemoglobinopathies and hemolytic anemias	93,000 (0.3)	216,600 (0.4)
Thalassemias	96,400 (0.3)	117,800 (0.2)
Interstitial lung disease and pulmonary sarcoidosis	51,300 (0.2)	102,100 (0.2)
Other pneumoconiosis	16,200 (0.1)	37,700 (0.1)
Glucose-6-phosphate dehydrogenase deficiency	8,100 (<0.1)	20,400 (<01)
Silicosis	10,800 (<0.1)	16,200 (<0.1)
Coal workers' pneumoconiosis	5,800 (<0.1)	9,000 (<0.1)
Iodine deficiency	4,300 (<0.1)	6,900 (<0.1)
Asbestosis	2,400 (<0.1)	4,100 (<0.1)
Total	31,408,500	61,657,600

Source: GBD 2015.

Figure 10.1 Age- and Gender-Adjusted Proportional Contribution of Six Heart Failure Risk Factors



Source: Khatibzadeh and others 2012.
Note: Regions of the world are according to the Global Burden of Disease 2005 classifications.

heart failure in Sub-Saharan Africa. The diversity of causes and the relative weights across regions suggest that optimal prevention and treatment strategies may vary substantially.

HEART FAILURE INTERVENTIONS

Methods

To evaluate potential individual, health system, and health policy interventions to reduce the burden and costs of heart failure, we performed a systematic review of interventions by searching MEDLINE through September 15, 2013, with the assistance of an information specialist. Our search strategy was based on Khatibzadeh and others (2012). We restricted our search to the English language and to those studies published after 1980. Our initial search produced 12,747 results. Restricting the search to *systematic* reviews by filtering with the term systematic produced 396 results. One author reviewed titles and abstracts from these results and selected full-text reports based on perceived relevance, quality, and scalability. We did not include strategies targeting distal heart failure risk factors, such as the prevention and control of ischemic heart disease or rheumatic heart disease or their risk factors (stage A heart failure), because these topics are covered in other chapters of this volume. (See chapters 8 and 11 in this volume [Dugani and others 2017; Watkins and others 2017]).

The MEDLINE search was complemented by another search in August 2014 on http://www.healthsystemsevidence.org, using the term *heart failure*. This search produced 49 systematic reviews of effects of interventions (1997–2003) and 44 economic evaluations (2003–14), all of which were reviewed by one author. Two studies were reported in both categories (N = 91). Individual reports were included on the basis of their publication date (more recent publications were selected over reports from earlier years if the topics were similar) and quality (reports with higher ratings using the A Measurement Tool to Assess Systematic Reviews [AMSTAR] instrument, a reliable and valid tool for assessing systematic review quality [Shea and others 2009], were selected over reports with lower AMSTAR ratings if the topics were similar). The systematic reviews of effects of interventions fell into the broad domains of telemonitoring and self-monitoring, disease management programs, and clinic-based arrangements. Among the economic analyses, only one report came from an upper-middle-income country (China). No results from low- or lower middle-income countries were retrieved.

Recommended Pharmacologic Interventions

Pharmacotherapy for heart failure has demonstrated benefits for individuals with heart failure with reduced left-ventricular ejection fraction (ejection fraction < 40 percent). Individuals with heart failure with preserved ejection fraction (ejection fraction ≥ 40 percent) may derive symptomatic benefit from diuretics for management of intravascular volume, but other agents have largely failed to improve clinical outcomes in these patients. This threshold for ejection fraction was initially based on the concept that heart failure could be attributable only to a low ejection fraction, or low pumping function of the heart. Later research demonstrated the high prevalence of heart failure attributable to poor filling of the heart (Redfield and others 2003). Each of the drug classes outlined in subsequent sections is included in the most recent version of the WHO's Model List of Essential Medicines, reflecting the expectation of the general availability of these drugs, even in LMICs (WHO 2015b).

Diuretics

Diuretics work by promoting water loss through the kidneys, thereby increasing urine output and decreasing intravascular volume. Common side effects include electrolyte disturbances and abnormalities in renal function, particularly at higher doses. Diuretics have become a mainstay in the treatment of heart failure. Diuretics have substantial effects in key areas:

- Reducing mortality (odds ratio [OR] 0.24, 95 percent CI 0.07–0.83; three trials, 202 participants)
- Reducing hospital admissions for worsening heart failure (OR 0.07, 95 percent CI 0.01–0.52; two trials, 169 participants)
- Increasing exercise capacity (weighted mean difference 0.72 units, 95 percent CI 0.40–1.04; four trials, 91 participants) in patients with chronic heart failure symptoms.

However, trials have been generally few, small, and of short duration (4–24 weeks) (Faris and others 2012). Diuretics are widely available and relatively inexpensive.

Beta Blockers

Beta blockers work by reducing the effects of neurohormonal stress that develops from heart failure with reduced ejection fraction, helping the heart strengthen over time. Beta blockers have become an integral part of chronic pharmacotherapy for patients with heart failure who have reduced ejection fraction. Data from 22 randomized controlled trials that included 10,480 participants demonstrated a reduction in all-cause mortality

with beta blockers compared with placebo (458 deaths out of 5,657 participants [8 percent] versus 635 deaths in 4,951 participants [13 percent]; OR 0.63, 95 percent CI 0.55–0.72). Similar reductions have been demonstrated for heart failure–related hospitalizations (11 percent versus 17 percent; OR 0.63, 95 percent CI 0.56–0.71) (Shibata, Flather, and Wang 2001). Some beta blockers appear to be more effective than others in head-to-head trials (Poole-Wilson and others 2003). However, a network meta-analysis suggests that the effects of atenolol, bisoprolol, bucindolol, carvedilol, metoprolol, and nebivolol may be similar in their effects on mortality and ejection fraction (Chatterjee and others 2013).

In patients with Chagas cardiomyopathy, only two trials evaluated the effects of beta blockers in 69 participants; both trials had a high risk of bias. There was no evidence that beta blockers lowered all-cause mortality compared with placebo (two deaths among 34 participants [5.9 percent] versus three deaths among 35 participants [5.9 percent]; relative risk [RR] 0.69, 95 percent CI 0.12–3.88, heterogeneity measured by $I^2 = 0$ percent) (Hidalgo and others 2012). These trials did not report the effects on cardiovascular disease mortality or nonfatal events and should not be considered conclusive.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Angiotensin-converting enzyme inhibitors (ACEi) also work by reducing the effects of neurohormonal stress that develop from heart failure with reduced ejection fraction and help the heart to strengthen over time. ACEi are another integral part of the chronic pharmacotherapy regimen for patients with heart failure who have reduced ejection fraction. Among patients with heart failure with reduced ejection fraction, data from 32 trials randomizing 7,205 participants demonstrated a reduction in all-cause mortality (15.5 percent versus 21.9 percent; OR 0.77, 95 percent CI 0.67–0.88). ACEi have demonstrated a similar effect on the risk of heart failure–related hospitalizations (OR 0.65, 95 percent CI 0.57–0.74), compared with placebo (Garg and Yusuf 1995).

Even among individuals with left-ventricular systolic dysfunction or reduced ejection fraction without symptoms of heart failure (stage B heart failure), ACE inhibitors have been demonstrated to reduce the incidence of heart failure among 4,228 participants randomized to ACEi compared with control (20.7 percent versus 30.2 percent) (SOLVD Investigators 1992).

For patients who cannot tolerate ACEi because of side effects—including allergic reactions such as angioedema, elevated serum potassium levels, or abnormal renal function—angiotensin receptor blockers (ARBs) are frequently recommended, although similar side effects can occur (Yancy and others 2013). Among patients with heart failure, data from nine trials randomizing 4,643 participants demonstrated a reduction in all-cause mortality with ARBs (RR 0.87, 95 percent CI 0.76–1.00) (Heran and others 2012). Among patients with heart failure who have reduced ejection fraction, candesartan has been shown to reduce the risk of heart failure–related hospitalization (RR 0.71, 95 percent CI 0.61–0.82). However, candesartan increased the risk of hospitalization for other causes (RR 1.12, 95 percent CI 1.00–1.25) (Heran and others 2012).

Combination therapy with ACEi and ARBs is not recommended because it is associated with increased risk of hyperkalemia, hypotension, and renal failure, without reducing all-cause mortality (Makani and others 2013). Some evidence indicates that this combination may reduce heart failure–related hospitalizations (RR 0.83, 95 percent CI 0.71–0.97) (Shibata, Tsuyuki, and Wiebe 2008).

Mineralocorticoid Receptor Antagonists

A systematic review and meta-analysis of 19 trials demonstrated a 20 percent reduction in all-cause death from mineralocorticoid receptor antagonists in patients with left-ventricular systolic dysfunction (RR 0.80, 95 percent CI 0.74–0.87) compared with placebo (Ezekowitz and McAlister 2009). Although these drugs have potent effects, are widely available, inexpensive, and cost effective (Glick and others 2002; Zhang and others 2010), they require echocardiography for demonstrating a reduced ejection fraction and monitoring of serum electrolytes and serum creatinine because of increased risks for hyperkalemia and acute kidney injury. Similar monitoring is typically recommended for ACEi and ARBs. Side effects also include gynecomastia. Early detection of these laboratory abnormalities, usually through blood testing one week after initiation of treatment, helps minimize clinical adverse events, including arrhythmia and renal failure. However, the need for laboratory monitoring may limit the scalability of these drugs.

Other Potential Pharmacological Interventions

Digoxin

Digoxin works by blocking ion channel pumps to improve the heart's function. Digoxin does not have an effect on mortality in individuals with heart failure (OR 0.98, 95 percent CI 0.89–1.09; eight studies, 7,755 participants). However, evidence suggests that digoxin reduces heart failure–related hospitalization

rates (OR 0.68, 95 percent CI 0.61–0.75; four studies, 7,262 participants) (Hood and others 2014). These trials were largely performed before widespread neurohormonal blockade with beta blockers and ACE inhibitors in patients with left-ventricular systolic dysfunction. The independent effect of digoxin in patients treated with beta blockers and ACEi is uncertain.

Digoxin is widely available and relatively inexpensive, but the high frequency of adverse effects severely limits its widespread use. Digoxin is largely reserved for rate control of atrial fibrillation when other agents are ineffective or contraindicated (for example, calcium channel blockers in patients with left-ventricular systolic dysfunction). Investigators have become interested in its potential for treatment of acute heart failure (Gheorghiade and Braunwald 2009), but large-scale trials of this strategy have yet to be performed.

Anticoagulants

Anticoagulants work by thinning the blood and preventing the development of clots. They are commonly used for individuals with abnormal heart rhythms for stroke prevention but have been considered in patients with heart failure with reduced ejection. Only two small randomized trials (N = 324 participants) with substantial heterogeneity (I^2 = 82 percent) have reported results on the potential effects of anticoagulation in patients with heart failure in normal sinus rhythm. Compared with placebo, there is no convincing evidence that anticoagulation reduces all-cause mortality (RR 0.66, 95 percent CI 0.36–1.18) or cardiovascular disease mortality in patients with heart failure (RR 0.98, 95 percent CI 0.58–1.65) (Lip, Wrigley, and Pisters 2012). However, anticoagulation is associated with a substantial increase in major bleeding (RR 5.98, 95 percent CI 1.71–20.93). Accordingly, it is not recommended for the prevention of thromboembolic events in patients with heart failure. It is unlikely that further trials evaluating anticoagulation in patients with heart failure in sinus rhythm will be performed. Similarly, routine aspirin use is not recommended in patients with heart failure because of the lack of efficacy in preventing thromboembolic events, unless the patients have a comorbid condition for which aspirin is recommended, for example, ischemic heart disease (Yancy and others 2013).

Inotropes

Inotropes work by increasing the heart's pumping function or rate, by reducing the pressure inside the heart so it can pump more easily, or by increasing blood pressure when it is low. For patients who are hospitalized with severe left-ventricular systolic dysfunction and low blood pressure attributable to low cardiac output, short-term use of intravenous inotropes can be considered to preserve end-organ function (Yancy and others 2013). However, trials have not demonstrated improvements in fatal or nonfatal events with inotropes (Cuffe 2002; Schaink 2012). Outside of these conditions, inotropes can be harmful.

Recommended Nonpharmacologic Interventions

Noninvasive Positive Pressure Ventilation

Compared with standard medical care, noninvasive positive pressure ventilation has been associated with lower rates of in-hospital mortality (RR 0.66, 95 percent CI 0.48–0.89) and endotracheal intubation (RR 0.52, 95 percent CI 0.36–0.75) in patients hospitalized for heart failure based on data from 32 trials enrolling 2,916 participants (Vital, Ladeira, and Atallah 2013). Noninvasive positive pressure ventilation was also associated with fewer adverse events, including respiratory failure and coma, compared with usual care. This intervention requires specialized personnel (respiratory therapist) and equipment, but it is less invasive than endotracheal intubation and more scalable as an adjunct to medical therapy for hospital-based management of acute heart failure. The availability of noninvasive positive pressure ventilation equipment and personnel in LMICs is uncertain. However, data on stable, outpatient heart failure patients with reduced ejection fraction (less than 45 percent) and predominantly central sleep apnea have not demonstrated benefits from this intervention (Cowie 2015).

Exercise-Based Rehabilitation

Exercise-based rehabilitation for patients with heart failure has been studied in 25 trials enrolling 1,871 participants. There is no evidence of overall reduction in all-cause mortality (RR 0.93, 95 percent CI 0.67–1.27). In trials with more than one year of follow-up (six trials, 2,845 participants), the effect size was modestly increased (RR 0.88, 95 percent CI 0.75–1.01) (Taylor and others 2014). Exercise training reduced hospitalization in 12 trials that included 1,036 participants (RR 0.61, 95 percent CI 0.46–0.80). Exercise training also improved the health-related quality of life in 13 trials that included 1,270 participants (weighted mean difference in Minnesota Living with Heart Failure −5.8 points, 95 percent CI −9.2 to −2.4) (Taylor and others 2014). An incremental cost-effectiveness ratio of US$1,773 (1998 U.S. dollars) per life year gained was reported in one trial with 15.5 years of follow-up among 99 participants. The HF-ACTION trial of 2,331 participants with heart failure in the United States demonstrated lower expenditures from high-cost inpatient procedures for individuals randomized to the

exercise group (US$4,300 in 2008); however, these savings were offset by increased costs related to participants' time, travel, and parking (Reed and others 2010).

Devices

Implantable cardioverter defibrillators continuously detect heart rhythm and have the capacity to charge and shock when potentially fatal heart rhythm abnormalities are detected. Compared with usual care, implantable cardioverter defibrillators are associated with a 31 percent (95 percent CI 21–40 percent) lower risk of all-cause mortality in patients with heart failure with reduced ejection fraction ≤ 35 percent (10 studies enrolling 8,606 participants) (Uhlig and others 2013). Although adverse events such as device or lead infection occur in fewer than 5 percent of patients, approximately 20 percent of patients who receive an implantable cardioverter defibrillator will receive at least one inappropriate shock, meaning that the device will deliver an electrical shock to the patient at a time when it is not needed.

Patients with heart failure with reduced ejection fraction and evidence of ventricular dyssynchrony (when the electrical conduction systems of the right and left ventricles depolarize at least 120 milliseconds apart from one another) benefit from cardiac resynchronization therapy, which uses a pacemaker lead in both the left and right ventricles to synchronize ventricular depolarization and thereby contraction. Rivero-Ayerza and others (2006) evaluated five trials of 2,371 patients and found that, compared with the control, cardiac resynchronization was associated with a reduction in all-cause mortality (17 percent versus 21 percent; OR 0.71, 95 percent CI 0.57–0.88) and heart failure–associated mortality (7 percent versus 10 percent; OR 0.62, 95 percent CI 0.45–0.84). However, data on the availability of device-based therapies in LMICs are limited.

Advanced Heart Failure Therapies

Advanced heart failure therapies for patients with end-stage heart failure, such as ventricular reconstruction, implantable ventricular assist devices, or heart transplantation, have very limited availability in most LMICs and are beyond the scope of this chapter.

HEALTH SERVICE ARRANGEMENTS

Takeda and others (2012) evaluated three types of health service arrangements for patients with heart failure across 25 trials of nearly 6,000 patients:

- Case management with telephone and home visit support from specialty nurses (17 studies)
- Clinic-based interventions, including vertical, specialized heart failure clinics (six studies)
- Multidisciplinary care by a team of physicians, nurses, dieticians, and pharmacists (two studies).

Case Management Interventions

Case management interventions were associated with a reduction in all-cause mortality reduction at 12 months (OR 0.66, 95 percent CI 0.47–0.91) but not at six months. Case management was associated with a reduction in heart failure readmission rates at both six months (OR 0.64, 95 percent CI 0.46–0.88) and 12 months (OR 0.47, 95 percent CI 0.30–0.76). There was no evidence that vertical-type heart failure clinic-based interventions improved mortality or heart failure readmissions. Multidisciplinary interventions to bridge the gap between hospital admission and discharge home care were associated with reductions in heart failure readmission rates (OR 0.46, 95 percent CI 0.46–0.69). A systematic review demonstrated that weekly, but not monthly, heart failure clinics were associated with reductions in unplanned hospitalizations (RR 0.42, 95 percent CI 0.27–0.65; three studies); these reports were from HICs (Thomas and others 2013).

Inglis and others (2011) performed a systematic review of the potential effects of telemonitoring (11 studies, 2,710 participants) and structured telephone support (16 studies, 5,613 participants). Telemonitoring was associated with a reduction in all-cause mortality (RR 0.66, 95 percent CI 0.54–0.81) and heart failure–related hospitalizations (RR 0.79, 95 percent CI 0.67–0.94). Costs related to hospital admissions or health care were lower in individuals randomized to telemonitoring compared with usual care (range 14–86 percent). Structured telephone support demonstrated a less robust effect on mortality but similar effect on hospitalization. Both strategies appear to increase evidence-based prescribing as the mechanism of effect.

Quality Improvement through Care Pathways

Heart failure quality-improvement programs are typically multifaceted strategies to improve evidence-based medication prescribing. One such strategy includes care pathways, or algorithms. A systematic review of seven randomized and quasi-randomized trials in HICs that included 3,690 participants with heart failure demonstrated a 55 percent reduction in in-hospital mortality (RR 0.45, 95 percent CI 0.21–0.94) and a 19 percent reduction in readmission (RR 0.81, 95 percent

CI 0.66–0.99) with the use of care pathways. The weighted mean length of hospital stay was reduced by 1.9 days (95 percent CI 1.3–2.4), but costs were similar (Kul and others 2012). There are no reports of similar randomized or quasi-randomized trials in LMICs, but data in box 10.2 demonstrate the current state of the science.

Box 10.3 provides a recent, specific example of presentation, management, and outcomes among individuals hospitalized for heart failure in India, a middle-income country.

Box 10.2

Systematic Review of Heart Failure Presentation, Management, and Outcomes in Low- and Middle-Income Countries

Callender and others (2014) described data on heart failure presentation, management, and outcomes among low- and middle-income countries (LMICs) from 1995 to 2014, including 42 studies of acute (hospitalized) heart failure (25 LMICs; N = 232,500 patients) and 11 studies of chronic heart failure (14 LMICs; N = 5,358 patients). Mean ejection fraction was 38 percent (range 27–57 percent) and 48 percent (range 29–55 percent) among acute and chronic heart failure patients, respectively. Ischemic heart disease was the most common cause of heart failure in all regions except Sub-Saharan Africa and the Americas, where hypertension was the most common cause. Mean length of hospital stay was 10 days (range 3–23 days), and mean in-hospital mortality was 8 percent (95 percent CI 6–10 percent). Diuretics were prescribed in 69 percent of patients (range 60–78 percent); ACE inhibitors were prescribed in 57 percent of patients (range 49–64 percent); beta blockers were prescribed in 34 percent of patients (range 28–41 percent); and mineralocorticoid receptor antagonists were prescribed in 32 percent (range 25–39 percent).

For context, in the EuroHeart Failure II Survey (Nieminen and others 2006) of acute heart failure patients admitted to hospitals across 30 European countries, discharge medication rates for patients with heart failure with reduced ejection fraction were generally higher (ACE inhibitors 71 percent; beta blockers 61 percent; mineralocorticoid receptor antagonists 48 percent) than the rates reported by Callender and others (2014). However, those rates may have changed over the ensuing decade.

Box 10.3

Case Study: Trivandrum Heart Failure Registry

Harikrishnan and others (2015) described the in-hospital and short-term outcomes among 1,205 consecutive admissions from 13 urban and 5 rural hospitals in Trivandrum, India, with a primary diagnosis of heart failure from January to December 2013. Ischemic heart disease was the underlying etiology of 72 percent of admissions, and heart failure with preserved ejection fraction (> 45 percent) constituted 26 percent of the sample. The median length of hospital stay was 6 days (interquartile range = 4–9 days), and in-hospital mortality rate was 8.5 percent (95 percent CI 6.9–10.0 percent). The all-cause mortality rate at 90 days was 2.43 deaths per 1,000 person-days (95 percent CI 2.11–2.78). Older age, lower education, poor ejection fraction, higher serum creatinine, New York Heart Association functional class IV, and not receiving guideline-based medical treatment were associated with higher risk of 90-day mortality.

These data demonstrate opportunities for improving in-hospital heart failure care in a low- and middle-income country setting.

Integration and Prioritization

The interventions discussed can be viewed through the lens of the WHO's building blocks for health systems framework (http://www.who.int/healthinfo/systems/monitoring/en/) to help guide their integration and prioritization (box 10.4, table 10.3). Because of the morbid nature of heart failure, early diagnosis and medical therapy are crucial to altering the natural history, particularly in patients with reduced ejection fraction in whom the majority of the interventions have been shown to be more effective compared with individuals with preserved ejection fraction.

Box 10.4

Health System Capacity Needs for Integrating and Prioritizing Interventions for Patients with Heart Failure, According to the World Health Organization's Building Blocks for Health Systems Framework

Service delivery

- Clinic and hospital facilities are required for initial diagnosis and treatment of patients with heart failure.
- Self-management supported by telemonitoring, ideally with multidisciplinary teams, improves outcomes, primarily through prescription of evidence-based drugs.
- Quality improvement programs that use care pathways have substantial potential to improve in-hospital quality of care and outcomes.

Health workforce

- Key staff members include physicians and nurses, particularly those with training in echocardiography. Ancillary staff members, including dieticians, psychologists, and pharmacists, can improve general self-care and self-management in a team-based care model.

Health information systems

- Information systems need to identify heart failure as an underlying disease process and mode of death for estimating disease burden.
- Ejection fraction, typically derived from echocardiography, is essential for matching drug therapy with underlying disease process.

Access to essential medicines and technologies

- Several medications have independently demonstrated improvements in survival among patients with heart failure with reduced ejection fraction, highlighting how important pharmacologic therapy is for such patients. Strategies to improve adherence to medication regimens, including fixed-dose combination therapies, are important to optimize their use and effectiveness.
- Echocardiography, which can be performed by both doctors and nurses, is an essential technology for diagnosis of heart failure.
- Noninvasive positive pressure ventilation is a relatively low-cost and effective, yet underutilized, option for preventing death and the need for intubation among patients with acute (stage C or D) heart failure.

Financing

- Strategies to reduce the financial burden of access to clinicians, echocardiography, and essential medicines, with an emphasis on reducing point-of-service costs, will likely lead to improved process and outcome measures.

Leadership and governance

- Patients with heart failure are cared for by primary care physicians and specialists, where available, and their teams in both inpatient and outpatient settings. Leadership and governance structures of health systems will need to rely upon these groups to execute any proposed health service changes.

Table 10.3 Priority Interventions for Patients with Heart Failure

Intervention	Effect on mortality (range)	Effect on heart failure hospitalization (range)	Study
Pharmacologic			
Diuretics	OR = 0.27 (0.07–0.83)	OR = 0.07 (0.01–0.52)	Faris and others 2012
Beta blockers*	OR = 0.63 (0.55–0.72)	OR = 0.63 (0.56–0.71)	Shibata, Flather, and Wang 2001
ACE inhibitors*	OR = 0.77 (0.67–0.88)	OR = 0.65 (0.57–0.74)	Garg and Yufus 1995
Mineralocorticoid receptor antagonists*	RR = 0.80 (0.74–0.87)	RR = 0.77 (0.68–0.87)	Ezekowitz and McAlister 2009
Nonpharmacologic			
Noninvasive positive pressure ventilation	RR = 0.66 (0.48–0.89)	Not applicable	Vital, Ladeira, and Atallah 2013
Implantable cardioverter defibrillator*	RR = 0.69 (0.60–0.89)		Uhlig and others 2013
Cardiac resynchronization therapy*	RR = 0.71 (0.57–0.88)		Rivero-Ayerza and others 2006
Health system arrangements			
Multidisciplinary team management		OR = 0.40 (0.30–0.76)	Thomas and others 2013
Telemonitoring	RR = 0.66 (0.54–0.81)	RR = 0.79 (0.67–0.94)	Inglis and others 2010
Care pathways	RR = 0.45 (0.21–0.94)	RR = 0.81 (0.66–0.99)	Kul and others 2012

Note: ACE = angiotensin-converting enzyme; OR = odds ratio; RR = relative risk.
*Denotes interventions wherein benefits are limited to patients with heart failure with reduced ejection fraction.

COST-EFFECTIVENESS AND EXTENDED COST-EFFECTIVENESS OF POTENTIAL INTERVENTIONS

Screening for Suspected Heart Failure

Kwan and others (2013) developed a nurse-led, echocardiographic screening method for heart failure diagnosis and treatment in rural Rwanda for patients suspected of having heart failure. Nurses were provided with diagnostic criteria to categorize patients as either having cardiomyopathy, hypertensive heart disease, mitral stenosis, other valvular abnormalities, or isolated right heart failure. Beyond volume management for all patients, the investigators provided a general therapeutic plan based on the underlying heart failure etiology and estimated the annual cost to be US$315 in 2010 U.S. dollars per patient (table 10.4).

Treatment for Heart Failure

Diuretics

The mainstay for heart failure includes diuretics in patients with heart failure with either reduced or preserved ejection fraction. While diuretics have been shown to be cost-effective for managing hypertension in HICs (Tran and others 2007) and LMICs (Alefan and others 2009), they have not been evaluated in a cost-effectiveness analysis for heart failure. However, given that patients with heart failure have much higher risk and costs associated with the condition, and that the

Table 10.4 Annual Costs of Heart Failure Diagnostics and Treatment in Rwanda

Program costs	Annual cost per patient (2010 US$)
Typical medical regimen	40
• Furosemide 40 mg twice daily	
• Lisinopril 20 mg daily	
• Carvedilol 25 mg twice daily	
Laboratory testing and imaging (including point-of-care chemistries and echocardiography)	59
Transport subsidy ($3 per visit, 12 visits)	36
Community health worker ($30 per month divided among five patients)	72
Advanced NCD clinician salary ($10,000/year)	33
Marginal cost of hospitalization (five days/year at $15 per day)	75
Total	*315*

Source: Kwan and others 2013.
Note: mg = milligram; NCD = noncommunicable disease.

relative risk reduction for heart failure is similar to that for those with hypertension, it is safe to infer their overall cost-effectiveness. All other agents for heart failure have then been compared with a baseline of diuretic therapy.

ACE Inhibitors

ACE inhibitors are an integral part of the treatment of patients with heart failure, both reducing costly admissions and prolonging life (table 10.5). Cost-effectiveness studies dating back to the 1990s have shown ACE inhibitors to be either highly cost-effective or cost saving in HICs (Butler and Fletcher 1996; Paul and others 1994; Tsevat and others 1995). Further work in LMICs has confirmed the use of ACE inhibitors as cost saving when added to diuretics in all six LMIC regions (Gaziano 2005) or extremely cost-effective (US$50 per disability-adjusted life year [DALY] averted) when access to hospitals was limited.

Beta Blockers

Beta blockers are equally integral for the management of patients with heart failure with reduced ejection fraction. In HICs, similar cost-effectiveness results for carvedilol were seen in the late 1990s (Delea and others 1999) and for metoprolol in the early 2000s (Levy and others 2001) of less than US$30,000 per quality-adjusted life year (QALY) to as low as US$4,000 per QALY. However, these studies used costs of up to US$500–US$1,000 per year. When analyses were repeated using generic pricing in all six LMIC regions, the incremental cost-effectiveness ratios were extremely favorable, ranging from US$124 to US$219 per DALY averted in all regions (Gaziano 2005).

Mineralocorticoid Agents

Mineralocorticoid agents have a favorable health profile in patients with reduced systolic function heart failure, reducing both all-cause mortality and hospitalizations. Although eplerenone has proven to be cost-effective in HICs (McKenna and others 2010; Weintraub and others 2005), it has not been evaluated for cost-effectiveness in LMICs. One limitation to its use is an additional requirement for blood monitoring of renal function and electrolytes.

Devices

Devices such as the implantable cardioverter defibrillator for those with advanced heart failure have been cost-effective in HICs. When implantable cardioverter defibrillators were compared with best medical therapy for those with heart failure in Brazil, the cost was US$50,000 per QALY for those with advanced heart failure (Ribeiro and others 2010). When implantable cardioverter defibrillators for those with heart failure were evaluated, the incremental cost-effectiveness ratio dropped to US$32,000 per QALY (Bertoldi and others 2013). When implantable cardiac resynchronization therapy (CRT) was compared with medical therapy in Brazil in those with advanced heart failure, CRT was even more cost-effective, at US$17,700 per QALY in 2012 U.S. dollars. When implantable cardioverter defibrillator and CRT capabilities were combined in the same device for those with heart failure, the incremental cost-effectiveness ratio was nearly US$33,000 per QALY. Similar values for CRT of US$34,000 per QALY were observed in Argentina (Poggio and others 2012).

CONCLUSIONS

Heart failure is a progressive, highly morbid condition that can result from underlying cardiovascular diseases, such as ischemic heart disease or hypertensive heart disease, or from underlying heart muscle abnormalities, such as cardiomyopathies. The predominant underlying causes of heart failure vary substantially by region. Several inexpensive therapies can improve the natural history of heart failure, particularly in the presence of left-ventricular systolic dysfunction. While the

Table 10.5 Incremental Cost-Effectiveness Ratios for Heart Failure Treatment, Compared with No Treatment, by Region

US$/DALY averted

	Medical therapy for AMI compared with baseline of no treatment				Medical therapy and CABG for IHD compared with baseline of no treatment, hospital access				Medical therapy and CABG for IHD compared with baseline of no treatment, limited hospital access			ACEi and BBs for CHF compared with baseline of diuretics, hospital access		ACEi and BBs for CHF compared with baseline of diuretics, limited hospital access	
Region	ASA	ASA, BB	ASA, BB, SK	ASA, BB, TPA	ASA, BB	ASA, BB, ACEi	ASA, BB, ACEi Statin	CABG	ASA, BB	ASA, BB, ACEi	ASA, BB, Statin	ACEi	ACEi, MET	ACEi	ACEi, MET
East Asia and the Pacific	13	15	672	15,867	Cost saving	781	1,914	33,846	461	942	2,220	Cost saving	189	27	274
Europe and Central Asia	19	21	722	15,878	Cost saving	866	2,026	47,942	530	1,097	2,470	Cost saving	144	30	275
Latin America and the Caribbean	20	22	734	15,887	Cost saving	821	1,942	62,426	545	1,111	2,497	Cost saving	124	31	275
Middle East and North Africa	17	20	715	15,893	Cost saving	672	1,686	72,345	527	996	2,305	Cost saving	128	29	275
South Asia	9	11	638	15,860	Cost saving	715	1,819	24,040	386	828	2,034	Cost saving	219	25	273
Sub-Saharan Africa	9	11	634	15,862	Cost saving	660	1,720	26,813	389	783	1,955	Cost saving	218	25	273

Source: Gaziano and others 2006.

Note: ACEi = angiotensin-converting enzyme inhibitors; AMI = acute myocardial infarction; ASA = aspirin; BB = beta blocker; CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; DALY = disability-adjusted life year; IHD = ischemic heart disease; MET = metoprolol; SK = streptokinase; TPA = tissue plasminogen activator. The intervention in the first column of each set of strategies is compared with the baseline of no treatment; each successive intervention for each set of strategies is compared with the intervention immediately to its left.

prevention of heart failure is ideal, we propose a resource-stratified approach to integrate and adopt interventions, including coprimary strategies to diagnose patients early in the disease course and to improve initiation and adherence to medication regimens.

Effective Strategies

Nurse-based screening with echocardiography and biomarker testing for diagnosis of heart failure appears promising, but human resource availability and economic costs are likely to be variable.

Diuretics are inexpensive, effective therapies that should be available for all patients with heart failure. Diuretics should be complemented by medical therapy using beta blockers, ACE inhibitors, and mineralocorticoid receptor antagonists in patients with heart failure with reduced ejection fraction.

Noninvasive positive pressure ventilation is an effective, yet likely underutilized, therapy for patients with acute respiratory distress secondary to heart failure, particularly in middle-income countries. Effectiveness and cost-effectiveness of cardioverter defibrillators require further study.

Beta blockers, ACE inhibitors, and mineralocorticoid receptor antagonists generally should be favored over digoxin for treatment of heart failure because of their superior mid- and long-term effectiveness compared with digoxin, and because of the narrow therapeutic index and high adverse event rate associated with digoxin.

Strategies to Avoid

Inotropic agents are frequently used in patients hospitalized with heart failure and cardiogenic shock, yet they have failed to demonstrate benefits.

Routine oral anticoagulation in patients with severe left-ventricular systolic dysfunction has not been demonstrated to improve outcomes. Anticoagulation should be reserved for patients with evidence of ventricular thrombi.

Future Directions

Policies related to the prevention, treatment, and control of cardiovascular risk factors and cardiovascular disease may favorably influence age-adjusted heart failure incidence and prevalence. Whether these policies lead to overall reductions in heart failure and heart failure–related costs, particularly in the presence of aging populations, remains uncertain.

Heart failure screening is generally restricted to patients presenting with symptoms. However, the influence of health system arrangements for screening and ultimately diagnosing patients with heart failure, including the availability of advanced diagnostic services such as biomarker testing and echocardiography at various health system levels, warrants further study to understand where best to place available diagnostics. Facilities or systems that can link patients from diagnostics to treatment will likely be effective for longitudinal care.

Long-term heart failure treatment is based on the provision and use of essential medications that need to be available, accessible, and affordable. Long-term adherence to complex medication regimens remains difficult for most patients, and strategies that use nonphysician health workers, that lower out-of-pocket spending, or that lower the number of pills used each day (such as fixed-dose combinations) appear to improve adherence (Nieuwlaat and others 2014). Updated local and regional health policy and cost-effectiveness models may be useful methods for evaluating the effect of health system arrangements for acute and chronic treatment on outcomes and costs.

NOTE

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  (a) lower-middle-income = US$1,046 to US$4,125
  (b) upper-middle-income (UMICs) = US$4,126 to US$12,745
- High-income countries (HICs) = US$12,746 or more.

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