DCP3 Chapter 11. Heart Failure

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Introduction

Heart failure is a clinical syndrome whereby the heart is unable to meet the metabolic demands of the body due to 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 or extremities. Details of the stages and functional classes of heart failure are detailed in box __.

<<Insert box 11.1 about here>>

Causes of Heart Failure

Heart failure causes are varied and include the following:

- In most cases, 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.

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, acquired immunodeficiency syndrome, and Chagas disease.

Diagnosis

Heart failure is diagnosed through a careful history and physical examination, but additional diagnostics, including B-type natriuretic peptide (BNP) 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 represents a particularly high-risk event, with one-year mortality estimates equal to 30 percent among older adults in the United States; this rate has not changed substantially in the past decade (Chen and others 2011).

Box __.1. Stages and Functional Classes of Heart Failure

The American Heart Association and American College of Cardiology classify heart failure according to four stages. This classification scheme describes the inviolate progression of clinical manifestations of heart failure based on risk for subsequent fatal and non-fatal events, including hospitalization due to acute heart failure.

- Stage A represents individuals with heart failure risk factors.
- Stage B represents individuals with cardiac structural abnormalities.
- Stage C represents individuals with current or prior heart failure symptoms.
- Stage D represents 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, and D:

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

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 as a mode of death—for example, heart failure in a patient with end-stage ischemic heart disease, valvular heart disease, or hypertensive heart disease—as well as 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 due to underlying disease processes.

According to World Health Organization (WHO 2015), an estimated 482,000 individuals (0.8 percent of total deaths) died as the result of cardiomyopathy, myocarditis, or endocarditis (table 11.1). 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). Due to population growth and aging, this estimate is projected to reach 576,000 by 2030, which represents 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 11.1). The majority of these deaths occur among women compared with men (57 percent versus 43 percent) and individuals living in LMICs compared with individuals living in HICs **(80 percent**

Box __.1. Stages and Functional Classes of Heart Failure

The American Heart Association and 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 non-fatal events, including hospitalization due to acute heart failure.

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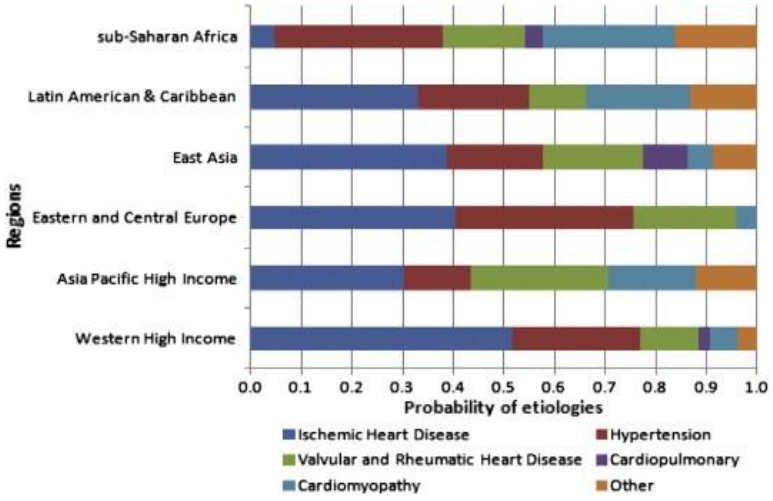
versus 20 percent). Due to population growth and aging, this estimate is projected to reach 1.5 million by 2030, which represents 2.1 percent of total deaths.

Regional Burden of Disease

A systematic review describes the geographic variation in major risk factors (figure 11.1) (Khatibzadeh, Farzadfar, Oliver, Ezzati, & Moran, 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% [95% CI: 33, 37]) and Sub-Saharan Africa (33% [95% CI: 30, 36]). 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 heart failure in Sub-Saharan Africa. The diversity of causes and the relative weights across regions suggests that optimal prevention and treatment strategies may vary substantially.

Figure 11.1. Age- and Sex-Adjusted Proportional Contribution of Six Heart Failure Risk Factors



Source: Khatibzadeh and others 2012.

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 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 (MDH) 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. <<cross-references can be added when chapter numbering is final>>

The MEDLINE search was complemented by another search in August 2014 on http://www.healthsystemsevidence.org, using the team "heart failure." This search produced 49 systematic reviews of effects of interventions (1997-2003) and 44 economic evaluations (2003-14), which were reviewed by one author. Two studies were reported in both categories (N=91). Individual reports were included based on their publication date (more recent publications were selected over reports from earlier years if the topics were similar) and quality (reports with higher AMSTAR rating 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/self-monitoring, disease management programs, and clinic-based arrangements. Among the economic analyses, only one report came from an upper-middle-income country (UMIC) (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 (HFrEF, or ejection fraction < 40 percent). Individuals with heart failure with preserved ejection fraction (HFpEF, or 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 only be due to a low ejection fraction, or low pumping function of the heart. Later research demonstrated the high prevalence of heart failure due to poor filling of the heart. However, each of these drug classes is included in the most recent version of the Model List of Essential Medicines, reflecting the expectation of the general availability of these drugs, even in LMICs (WHO 2015)

Commented [MH1]: Add Reference: Redfield MM, et al JAMA 2003

Commented [MH2]: WHO 2015

Diuretics
Diuretics work by promoting water loss through the kidney and thus increasing urine output. They have become a mainstay in the treatment of heart failure. Diuretics have substantial effects in key areas:

- Reducing mortality (OR [95% CI]: 0.24 [0.07, 0.83]; three trials, 202 participants)
- Reducing hospital admissions for worsening heart failure (OR [95% CI]: 0.07 [0.01, 0.52]; two trials, 169 participants)
- Increasing exercise capacity (weighted mean difference [95% CI]: 0.72 units [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 to 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 and help 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 [95% CI]: 0.63 [0.55, 0.72]). Similar reductions have been demonstrated for heart failure-related hospitalizations (11 percent versus 17 percent, OR [95% CI]: 0.63 [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 terms of effects on mortality and ejection fraction (Chatterjee and others 2013).

In patients with Chagas cardiomyopathy, only two trials evaluated the effects of beta-blockers on 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 in 34 participants (5.9 percent) versus three deaths among 35 participants (5.9 percent); RR [95% CI]: 0.69 [0.12, 3.88], I^2=0%) (Hidalgo and others 2012). These trials did not report the effects on cardiovascular disease mortality or non-fatal events and should not be considered conclusive.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers
Angiotensin-converting enzyme (ACE) inhibitors also work by reducing the effects of neurohormonal stress that develops from heart failure with reduced ejection fraction and help the heart strengthen over time. Angiotensin-converting enzyme (ACE) inhibitors 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 [95% CI]: 0.77 [0.67, 0.88]). ACE-inhibitors have demonstrated a similar effect on the risk of heart failure-related hospitalizations (OR [95% CI]: 0.65 [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 ACE-inhibitors, compared with control (20.7 percent vs. 30.2 percent) (SOLVD Investigators 1992**)**

For patients who cannot tolerate ACE-inhibitors due to side effects, angiotensin receptor blockers (ARBs) are frequently recommended (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 [95% CI]: 0.87 [95% 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 hospitalizations (RR [95% CI]: 0.71 [0.61, 0.82]). However, candesartan increased the risk of hospitalization for other causes (RR [95% CI]: 1.12 [95% CI]: [1.00, 1.25]) (Heran and others 2012).

Combination therapy with ACE-inhibitors 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 [95% CI]: 0.83 [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 blockade in patients with left ventricular systolic dysfunction (RR [95% CI]: 0.80 [0.74, 0.87]) compared with placebo (Ezekowitz and McAlister 2008). Although these drugs have potent effects, are widely available, and are relatively inexpensive, monitoring of serum electrolytes and serum creatinine are recommended because of increased risks for hyperkalemia and acute kidney injury. Early detection of these laboratory abnormalities, usually through blood testing one week after initiation of treatment, helps to 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 (eight studies; 7,755 participants; OR [95% CI]: 0.98 [0.89, 1.09]). However, evidence suggests that digoxin reduces heart-failure-related hospitalization rates (four studies; 7,262 participants; OR [95% CI]: 0.68 [0.61, 0.75]) (Hood and others 2014). These trials were largely

performed prior to 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 ACE-inhibitors is uncertain.

Digoxin is widely available and relatively inexpensive, but the high frequency of adverse drug effect 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. Only two small, randomized trials (n=324 participants) with substantial heterogeneity (I^2=82%) 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 [95% CI]: 0.66 [0.36, 1.18]) or cardiovascular disease mortality in patients with heart failure (RR [95% CI]: 0.98 [0.58, 1.65].(Lip, Wrigley, & Pisters, 2012). However, anticoagulation is associated with a substantial increase in major bleeding (RR [95% CI]: 5.98 [1.71, 20.93]. Accordingly, anticoagulation 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. Routine aspirin use is similarly not recommended in patients with heart failure because of the lack of efficacy

Box__.2. Systematic review of heart failure presentation, management, and outcomes in LMIC

Callender and others (2011) 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% to 57%) and 48 percent (range: 29% to 55%) 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 stay was 10 days (range 3 to 23 days), and mean in-hospital mortality was 8 percent (95% CI: 6% to 10%). Diuretics were prescribed in 69 percent of patients (range: 60% to 78%); ACE-inhibitors were prescribed in 57 percent of patients (range: 49% to 64%); beta-blockers were prescribed in 34 percent of patients (range: 28% to 41%); and mineralocorticoid receptor antagonists were prescribed in 32 percent (range: 25% to 39%).

For context, in the EuroHeart Failure II Survey (Nieminen 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-I 71%; beta blocker 61%; mineralocorticoid receptor antagonist 48%) than what was reported by Callender. However, these rates may have changed over the ensuing decade.

in preventing thromboembolic events, unless the patients have a **comorbid condition** for which aspirin is recommended, for example, for 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 an individuals' blood pressure when it is low. For patients who are hospitalized with severe left ventricular systolic dysfunction and low blood pressure due to low cardiac output, short-term use of intravenous inotropes can be considered to preserve end-organ function.(Yancy et al., 2013) However, trials have not demonstrated improvements in fatal or non-fatal events with inotropes (Cuffe 2002; Schaink and Ontario 2012). Outside of these conditions, inotropes can be harmful.

Recommended Nonpharmacologic Interventions

Noninvasive Positive Pressure Ventilation

Compared to standard medical care, noninvasive positive pressure ventilation has been associated with lower rates of in-hospital mortality (RR [95% CI]: 0.66 [0.48, 0.89]) and endotracheal intubation (RR [95% CI]: 0.52 [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. However, the availability of noninvasive positive pressure ventilation equipment and personnel in LMICs is uncertain.

Exercise-Based Rehabilitation

Exercise-based rehabilitation for patients with heart failure has been studied in 25 trials including 1,871 participants. There is no evidence of overall reduction in all-cause mortality (RR [95% CI]: 0.93 [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 [95% CI]: 0.88 [0.75, 1.01]) (Taylor and others 2014). Exercise training reduced hospitalization in 12 trials that included 1,036 participants (RR [95% CI]: 0.61 [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% CI: -9.2, -2.4).(Taylor et al., 2014) An incremental cost effectiveness ratio of 1998 US$1,773 per life years 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 (USD$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% CI: 21% to 40%) lower risk of all-cause mortality in patients with heart failure with a reduced ejection fraction less than or equal to 35 percent (10 studies, 8,606 participants) (Uhlig and others **2013).** Although adverse events such as device or lead infection occur in less 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 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 [95% CI]: 0.71 [0.57, 0.88] and heart failure-associated mortality (7 percent versus 10 percent; OR [95% CI]: 0.62; [0.45, 0.84]). However, data on the availability of device-based therapies in LMICS are limited.

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 [95% confidence intervals]: 0.66 [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 [95% CI]: 0.64 [0.46, 0.88]) and 12 months (OR [95% CI]: 0.47 [0.30, 0.76]). There was no evidence that **vertical-type**, heart failure clinic-based

Box__. 2. 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 (EF > 45%) constituted 26 percent of the sample. The median length of hospital stay was six days (IQR = four to nine days), and in-hospital mortality rate was 8.5 percent (95% CI: 6.9 to 10.0). The all-cause mortality rate at 90 days was 2.43 deaths per 1,000 person-days (95% CI: 2.11 to 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.

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 [95% CI]: 0.46 [0.46, 0.69]). A systematic review demonstrated that weekly, but not monthly, heart failure clinics were associated with reductions in unplanned hospitalizations (three studies, RR [95% CI]: 0.42 [0.27, 0.65]); these reports were from HICs (Thomas and others 2013).

Inglis and others performed a systematic review of the potential effects of telemonitoring (11 studies, 2,710 participants) and structured telephone support (16 studies, 5,613 participants) (Inglis and others 2011). Telemonitoring was associated with a reduction in all-cause mortality (RR [95% CI]: 0.66 [0.54, 0.81]) and heart failure-related hospitalizations (RR [95% CI]: 0.79 [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 percent to 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 [95% CI]: 0.45 [0.21, 0.94]) and a 19 percent reduction in readmission (RR [95% CI]: 0.81 [0.66, 0.99]) with the use of care pathways. The weighted mean length of hospital was reduced by 1.9 days (95% 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 below demonstrate the current state of the science (box 11.2)

Integration and Prioritization

The aforementioned interventions can be viewed through the lens of the WHO's building blocks for health systems framework to help guide their integration and prioritization (box 11.3, table 11.2). Because of the morbid nature of heart failure, early diagnosis and medical therapy are crucial to alter 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 __.3. Health system capacity needs for integrating and prioritizing interventions for patients with heart failure according to the World Health Organization's health system building blocks 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 at 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 is an essential technology for diagnosis of heart failure that can be performed by doctors, nurses, or both.
- 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 financial burden on 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/governance

- Patient 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.

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 dollars per patient (table11. 3).

Table 11.3 Annual Costs of Heart Failure Diagnostics and Treatment in Rwanda

Program costs	**Annual cost per patient (2010 US$)**
Typical medical regimen: • Furosemide 40 mg twice daily • Lisinopril 20 mg daily • Carvedilol 25 mg twice daily	$40
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 $72 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: **NCD = non-communicable disease**

Treatment for Heart Failure

The mainstay for heart failure includes diuretics. While diuretics have been shown to be cost-effective for managing hypertension both in HICs (Tran et al) and in LMICs (Alefan et al), they have not been evaluated in a cost effectiveness analyses for heart failure. However, given patients with heart failure have much higher risk and costs associated with the condition, and that the 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 to a baseline of diuretic therapy. ACE-inhibitors are an integral part of the treatment of patients with heart failure, both reducing costly admissions and prolonging life. 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 et al 1994, Tsevat 1995). Further work in LMICs confirms the use of ACE-inhibitors as cost-saving when added to diuretics in all 6 LMIC World Bank regions (Gaziano Circ) or extremely cost-effective ($50/DALY averted) when there was limited access to hospitals.

Beta-blockers are equally integral for the management of patients with heart failure with reduced ejection fraction. Similar cost-effectiveness results for carvedilol were seen in the late 1990s (Delea 1999 Am J Card) and early 2000s for metoprolol (Levy, 2001 Am Heart J) for HICs of less than $30000/QALY to as low as $4000/QALY. However these used costs of up to $500 to $1000 per year. When analysis were repeated using generic pricing in all 6 LMIC World Bank regions, the incremental cost-effectiveness ratios were extremely favorable ranging from $124-$219/DALY averted in all regions (Gaziano Circ). Mineralocorticoid agents have a favorable health profile in patients with reduced systolic function heart failure both reducing all-cause mortality and hospitalizations. Although, eplerenone has proven to be cost-effective in HICs (Weintraub, CIRC 2005, McKenna, NIHR HTA Exec Summary 2010), they have not been evaluated for cost-effectiveness in LMICs. One limitation to their use is an additional requirement for blood monitoring of renal function and electrolytes.

Devices such as the implantable cardioverter defibrillators for those with advanced heart failure have been seen as cost-effective in HICs. In LMICs they have been evaluated in Brazil. When implantable cardioverter defibrillators were compared to best medical therapy for those without heart failure it was found to be $50,000/QALY in Brazil for those with advanced heart failure. (Rodrigo 2010) When implantable cardioverter defibrillators for those with heart failure were evaluated the incremental cost-effectiveness ratio dropped to $32,000/QALY. (Bertoli 2011) When implantable cardiac implantable resynchronization therapy (CRT) was compared with medical therapy in Brazil in those with advanced heart failure, CRT was even more cost-effective at $17700/QALY in 2012 $US. When ICD and CRT capabilities were combined in the same device for those with CHF the ICER was nearly $33,000/QALY. Similar values for CRT of $34,000/QALY were found in Argentina (Poggio Int J Tech Ass Helath Care 2012).

Table __.4 ICERs for Treatment Compared with No treatment, by Region

Table 33.2 ICERs for Treatment Compared with No Treatment, by Region
US$/DALY

	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			ACE inhibitors and beta-blockers for CHF compared with baseline of diuretics, hospital access		ACE inhibitors and beta-blockers 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: Authors' calculations.
ASA = aspirin, BB = atenolol, SK = streptokinase, TPA = tissue plasminogen activator, ACEI = enalapril, Statin = lovastatin, MET = metoprolol.
Note: The intervention in the first column of each set of strategies is compared with the baseline; each successive intervention for each set of strategies is compared with the intervention immediately to its left.

Source:
Note: ICERs = incremental cost-effectiveness ratio; US$ per disability-adjusted life year.

Conclusions and Recommendations

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. We propose a resource-stratified approach to integrate and adopt interventions, including co-primary 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 with 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 implantable cardioverter defibrillators requires further study.

Strategies to Avoid

Inotropic agents are frequently used in patients hospitalized with heart failure and cardiogenic shock, yet these 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.

Beta-blockers, ACE inhibitors, and mineralocorticoid receptor antagonists should be generally favored over digoxin for treatment of heart failure because of the narrow therapeutic index and high adverse event rate of digoxin.

Policies related to the prevention, treatment, and control of cardiovascular risk factors and cardiovascular disease likely 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 availability of advanced diagnostic services (biomarker testing, 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 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 non-physician health workers, lower out-of-pocket spending, or 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 to evaluate the effect of health system arrangements for acute and chronic treatment on outcomes and costs.

Table 11.1. Population and mortality estimates (2015) and projections (2030) for cardiomyopathy, myocarditis, and endocarditis and hypertensive heart disease.

	2015			2030		
	Population	**Deaths due to cardiomyopathy, myocarditis, or endocarditis**	**Deaths due to hypertensive heart disease**	**Population**	**Deaths due to cardiomyopathy, myocarditis, or endocarditis**	**Deaths due 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, 2015

Note: LMIC = low- and middle-income country; AFR = Africa; AMR = Americas; SEAR = Southeast Asia region; EUR = Europe; EMR = Eastern Mediterranean; WPR = Western Pacific.

Table 11.2. Priority Interventions For Patients With Heart Failure In Patients With Reduced Ejection Fraction, Unless Otherwise Noted.

		Effect on mortality	Effect on heart failure hospitalization
Pharmacologic			
	Diuretics[a]	OR = 0.27 (0.07, 0.83)	OR = 0.07 (0.01, 0.52)
	Beta-blockers[b]	OR = 0.63 (0.55, 0.72)	OR = 0.63 (0.56, 0.71)
	ACE-inhibitors[c]	OR = 0.77 (0.67, 0.88)	OR = 0.65 (0.57, 0.74)
	Mineralocorticoid receptor antagonists[d]	RR = 0.80 (0.74, 0.87)	RR = 0.77 (0.68, 0.87)
Non-pharmacologic			
	Non-invasive positive pressure ventilation[e]	RR = 0.66 (0.48, 0.89)	Not applicable
	Implantable cardioverter defibrillator[f]	RR = 0.69 (0.60, 0.89)	
	Cardiac resynchronization therapy[g]	RR = 0.71 (0.57, 0.88)	
Health system arrangements			
	Multi-disciplinary team management[h]		OR = 0.40 (0.30, 0.76)
	Telemonitoring[i]	RR = 0.66 (0.54, 0.81)	RR = 0.79 (0.67, 0.94)
	Care pathways[j]	RR = 0.45 (0.21, 0.94)	RR = 0.81 (0.66, 0.99)

Sources:

a. Faris and others 2012
b. Shibata, Flathers, and Wang 2001
c. C. Garg an Yufus 1995
d. D. Ezekowitz and McAlister 2008
e. E. Vital, Ladeira, and Atallah 2013
f. Uhlig and others **2013**
g. Rivero-Ayerza and others 2006
h. Thomas and others 2013
i. Inglis and others 2010
j. Kul and others 2012

[Authors: Because each figure and table can appear apart from the chapter online, we need to provide the sources to make it as self-contained as possible.]

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