



NANCY M. ALBERT, MSN, RN, CCRN, CNA*

Clinical outcomes researcher, clinical nurse specialist, Kaufman Center for Heart Failure, Cleveland Clinic

JAMES B. YOUNG, MD*

Medical Director, Kaufman Center for Heart Failure; Head, Section of Heart Failure and Cardiac Transplant Medicine, Department of Cardiology, Cleveland Clinic

Heart failure disease management: A team approach

ABSTRACT

Patients with heart failure do better if they are treated in a formal heart failure disease-management program than if they receive standard care: their hospitalization rates and costs of treatment are lower, and their functional status is higher. The programs feature close coordination between primary care givers, subspecialty consultants, and nurses with specialty training in the nuances of heart failure management. Aggressive medical therapy must be coupled with patient education and rapid response to early identified problems. This article reviews the principles of heart failure disease-management programs and cites evidence that they are beneficial.

KEY POINTS

If crises are to be avoided, the management of heart failure patients must shift from simply ameliorating symptoms to more complex disease management.

The optimal approach to treating heart failure uses an interdisciplinary team: a primary care provider, cardiologist (heart failure specialist), nurse, pharmacist, dietary personnel, and others.

Heart failure treatment requires a synchronized pharmacologic and nonpharmacologic approach.



to keep your heart failure under control, page 63

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O TREAT HEART FAILURE effectively you need a team and you need a plan. In short, you need a program.1

Although some may decry such an approach as "cookbook medicine," the proof is in the outcomes. Studies show that patients treated in formal programs have lower hospitalization rates, fewer emergency visits, and a higher quality of life, functional status, and level of satisfaction with their care. They also incur less cost.

With a team in place, you can delegate work. Nurses keep in contact with the patients at home on a regular basis, heading off problems before they become crises. Heart failure specialists and others are available if you need them. Furthermore, with a formal plan you know that you are following evidence-based guidelines, 2-5 and not just shooting from the hip. And with a program you can be proactive instead of reactive: you can concentrate on keeping patients healthy, instead of dealing only with acute exacerbations.

A team approach to heart failure management can be implemented in most traditional or managed-care outpatient settings.

WHAT'S WRONG WITH THE TRADITIONAL APPROACH?

In the traditional approach, the patient comes to the physician (or, too often, to the emergency department of the local hospital) with symptoms such as worsening fatigue or shortness of breath, which the physician tries to resolve. Then the patient goes home, and nobody gives him or her much thought until the next bout of worsening symptoms.

This approach does not work very well. Despite advances in understanding the bio-

TABLE 1

Common errors and omissions in treating heart failure

Medication-related

Failure to prescribe angiotensin-converting enzyme inhibitors or beta-blockers, or use in suboptimal doses

Suboptimal dosing of diuretics when volume overload (which may be subclinical) persists

Failure to remove detrimental medications from the regimen

Inappropriate heart failure treatment in patients with normal systolic left ventricular function (diastolic dysfunction)

Related to concomitant diseases

Failure to control ischemia, hypertension, diabetes, thyroid dysfunction, anemia, or electrolyte disturbances

Uncontrolled atrial fibrillation; excessive tachycardia or bradycardia

Failure to discuss and promote cardiovascular and general "disease prevention" strategies (eg, flu shots, lipid-lowering drugs, alcohol or substance abuse withdrawal) when needed

Related to management strategy

Inadequate patient education, eg, inadequate self-care instructions, especially on how to manage new or worsening symptoms

Failure to recognize or address patient noncompliance

Failure to assess the option of revascularization if the patient has coronary artery disease

Failure to consider the option of mitral valve repair if the patient has mitral valve insufficiency

Delay in referring the patient for cardiac transplantation if indicated

Delay in obtaining a consult with a heart failure specialist when the patient has had multiple hospital readmissions or symptoms refractory to maximum medical therapy

Inadequate promotion of cardiac rehabilitation or active exercise

Inadequate use of specialty community programs for heart failure (eg, a home health care program) when the patient meets inclusion criteria

Failure to respond promptly and intervene early when the patient initiates contact

for a worsening condition

Physicians often do not address chronic issues that affect outcome

> chemical abnormalities in heart failure and in its treatment, the morbidity and mortality rates have not budged over the past decade. Further, hospitalization rates and costs have increased. Why should this be?

> The focus is on symptoms. The primary goal of the traditional approach is to alleviate symptoms. Decreasing morbidity and improving survival are also goals, but get short shrift. Most physicians do not intently focus on nonacute issues such as psychosocial problems, poverty, poor nutrition, poor function, low education level, poor prognosis, problems with self-management, or cardiovascular risk factors such as dyslipidemia.^{6,7} Yet these factors can affect compliance and outcomes.

Patients may not be able to comply with their treatment. The treatment of heart failure is complex and includes both lifestyle changes (such as exercise and limiting the amount of sodium in the diet) and complicated multidrug regimens. Without ongoing support and encouragement, many patients cannot or will not comply, owing to comorbid conditions, drug side effects, complexity of the regimen, psychosocial issues, physical limitations (due to heart failure or aging or both), or cognitive dysfunction.¹

Physicians may not follow guidelines. Although evidence-based guidelines exist,^{2–5} they can be time-consuming to follow and require ongoing follow-up monitoring, which



Heart failure disease management program used at the Cleveland Clinic

REFERRAL

Patient is referred to the heart failure program:

- Upon hospital discharge
- After an emergency department visit
- After an outpatient visit
- Upon **new onset** of heart failure in a current patient

PHYSICIANS

- Primary care physician Provides most of the care for patients with heart failure
- Cardiologist Provides additional expertise for patients with particularly difficult problems
- Heart failure specialist Provides expertise in aggressive care of very advanced heart failure



CARDIAC NURSE CLINICIAN

Under the supervision of a physician, the cardiac nurse clinician plays a comprehensive role, providing much of the patient care and acting as a facilitator and communicator among team members

Disease management tools used by the cardiac nurse clinician include:

- Diagnosis and care algorithms
- Vigilance monitoring systems
- Patient education programs
- Outcomes assessment

SUPPORT SERVICES

Support services provide specific care and advice, usually for a limited time, and generally involve education. These include:

- Cardiac rehabilitation specialist
- Pharmacist
- Dietitian
- Social worker



ANCILLARY SERVICES

Specific heart failure programs in the following settings can improve exercise tolerance and quality of life, alleviate or prevent symptoms, and optimize treatment:

- Emergency department
- Clinical decision unit
- Subacute care facility
- Rehabilitation unit
- Palliative care/home care
- "Nurse-on-call" phone service
- · Home health care

may not be feasible in a traditional outpatient office practice. Furthermore, it is likely that many physicians do not know about the guidelines.

Use of ACE inhibitors. For instance, angiotensin-converting enzyme (ACE) inhibitors—indicated in all patients with left ventricular systolic dysfunction who have no contraindications to them-tend to be underprescribed or used in suboptimal doses. Philbin⁸ and Gattis et al⁹ found that ACE inhibitors were underused in the community setting, primarily in the elderly and in patients with perceived (but not actual) contraindications to these drugs. Even though patients older than 74 years were similar to younger patients in their baseline characteristics, they differed in the medications they were prescribed. Of importance, elderly patients who were receiving target doses of ACE inhibitors (ie, those used in clinical trials—generally the equivalent of 20 mg of enalapril daily) appeared to have fewer morbid heart failure events.9 Other studies confirmed that heart failure medications are generally used in doses lower than those used in clinical trials.¹⁰

Other problems. Other errors or omissions include suboptimal use of other heart failure medications and failure to control concomitant conditions or to address other issues (TABLE 1).11,12

HEART FAILURE DISEASE MANAGEMENT DEFINED

In an effort to provide better care, doctors, nurses, and others at a number of hospitals set up special disease-management programs for patients with heart failure.¹³ Results were good: in general, hospitalizations and emergency visits for heart failure decreased, and functional status, peak oxygen consumption, and quality-of-life scores improved.^{14–17}

The programs had key elements in common:

- A multidisciplinary team
- Practice guidelines developed by consensus
- Adjunctive programs
- Patient education
- Systems for following patients at home ("vigilance monitoring")
- Data collection at regular intervals to measure outcomes.

A multidisciplinary team

The heart failure team comprises a number of players. Of note: the lines of authority and communication among these people need to be agreed on and drawn up in the program plan, as should the paths that patients will follow from one team member to the other (FIGURE 1). Good communication is essential among the team members and the patient.

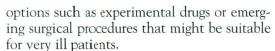
The primary care physician is the anchor of the team, the person with whom the patients have the strongest relationship, and the person who orchestrates care decisions that the other team members carry out.

As the "gatekeeper" in managed care, the primary care physician traditionally controls access to specialists. In a heart failure diseasemanagement program, the primary care physician also plays this role, but with the help of algorithms and protocols to improve outcomes. Primary care physicians provide most of the care for patients with heart failure. Even in the hospital, cardiologists care for fewer than one third of all patients admitted for congestive heart failure. In fact, the cardiologist may refer patients to the primary care physician once guideline recommendations are implemented. In this way, patient referrals move both to and from specialty and primary care physicians.

In developing the program, the primary care physician must assure that the program is flexible and can respond to environmental, cultural, and individual patient diversity. For example, if the patients seen in a particular practice are mostly poor, they may need a formal social work program; if they are mostly frail and elderly with multiple comorbidities, they may need office-based pharmacist support; if they tend to consume a lot of salt in the diet, they may benefit from dietitian support.

The cardiologist. It is important to have access to a cardiologist with additional training and expertise in managing patients with particularly difficult problems, such as those with multiple hospital admissions over a short period. Heart failure specialists generally have much experience in the aggressive care of very advanced heart failure syndromes, since the cornerstone of their practice is usually patient referral for heart transplantation. In addition, they are more likely to promote alternative

ACE inhibitors tend to be underused, or used in suboptimal doses



Since cardiologists who specialize in heart failure are still relatively rare, networks should be developed that allow primary care physicians or general cardiologists ready access to this additional consultation resource.

The heart failure specialist can be instrumental in developing and updating the clinical practice guidelines or care pathways used in the outpatient setting by the primary care provider. In helping develop the protocol, the heart failure specialist should help interpret and communicate published guidelines and ensure that the program is research-based and aggressive and provides the best opportunity to improve outcomes.

The cardiac nurse. Many successful programs use cardiac-trained nurses to assist in patient management. 13-17 In one inpatient program, 18 total hospital costs were significantly lowered and length of hospital stay decreased in the year after a nurse practitioner was added to the team. Cardiac nurses have also been incorporated into programs at cardiomyopathy clinics, and the reported outcomes have been good. 14,15,17,19 In an aggressive, nurse-assisted management program, outpatient visits and communication should increase, whereas hospital readmission rates will likely decrease.

Under the supervision of the primary care physician, an advanced-practice nurse (clinical nurse specialist or nurse practitioner) can have a comprehensive role on the team, providing much of the patient care as guided by protocols and guidelines, and acting as the facilitator and communicator between the other team members (TABLE 2).

Other team members include emergency medicine specialists, pharmacists, nutritionists, dietitians, cardiac rehabilitation personnel, social workers, home health care aides, and palliative care specialists.

Practice quidelines

The protocols should be based on national guidelines and cover the following areas.

Seeking evidence of underlying disease, such as coronary artery disease or cardiomyopathy.

TABLE 2

Role of the advanced-practice nurse in disease management for heart failure

Ensures that primary and secondary atherosclerosis prevention strategies are in place

Assesses the patient's knowledge of heart failure and its management, and patient education needs

Provides patient education

Assesses patient compliance with therapy, and reviews patient management and compliance issues with the primary care physician

Determines need for medication changes on the basis of symptoms

Ensures therapeutic dosing of drugs is appropriate

Performs routine follow-up care and monitoring

Supervises data collection and performs outcomes analysis

Troubleshoots worsening symptoms

Schedules frequent (weekly or biweekly) patient visits to assess readiness for medication up-titration

Consults with the primary care physician regarding problems, and facilitates ad hoc consultation with the heart failure specialist

Facilitates referral of patients from the heart failure specialist to the primary care physician for continued follow-up, surveillance, and implementation of general preventive health care guidelines, such as screening for lipid abnormalities or malignancy and administration of appropriate vaccines

Nonpharmacologic therapy such as diet, fluid management, activity and exercise, and lifestyle modifications.

Pharmacologic therapy, including ACE inhibitors (FIGURE 2) and beta blockers (FIGURE 3), if indicated, in the right doses. Numerous reports14,17,20-24 document the benefit of polypharmacy protocols.

Indications for obtaining a consult with a heart failure specialist and for hospitalization (TABLE 3).

Adjunctive programs

The program should have access to a subacute care facility, a rehabilitation unit, an emergency center clinical decision unit, and a heart failure intensive care unit. Specific heart failure protocols should be developed for

ACE inhibitor therapy algorithm used at the Cleveland Clinic

DOES THE PATIENT HAVE SYSTOLIC HEART FAILURE?

NO Individualize vasodilator therapy on the basis of restrictive physiology (diastolic dysfunction), renal function, and blood pressure

YES Does the patient have any of the following?

- Serum creatinine ≥ 3.0 mg/dL
- History of intolerance to ACE inhibitors (eg, angioedema, severe hypotension, hyperkalemia, severe persistent cough)
- Already taking ACE inhibitor at target dose or maximum tolerated dose

YES Begin hydralazine-nitrate combination:

- Hydralazine (Apresoline) 25 mg three or four times a day, increased to maximum of 100 mg four times a day in 25-mg increments every 24 hours as necessary,
- Isosorbide dinitrate (Isordil) 10 mg three times a day increased to maximum of 80 mg three times a day in 20-mg increments every 24 hours as necessary. If tolerating isosorbide dinitrate, may switch to isosorbide mononitrate (Imdur) 30 mg daily, increased to maximum of 240 mg daily in increments every week in doses as follows: 30, 60, 90, 120, 180, 240 mg

Note: If renal function is adequate, may consider an angiotensin II receptor blocker in addition to an ACE inhibitor or as substitute for hydralazine-nitrate combination or for ACE inhibitor intolerance

NO Is serum sodium < 134 mg/dL?

YES Assess for volume overload; if present:

- Give diuretic
- Reassess sodium, potassium, and magnesium levels
- Restrict fluids and free water to 1,500 cc/day for 3 days

Note: Hypotension with ACE inhibitors is less likely when serum sodium is > 134 mg/dL

NO Is systolic blood pressure < 80 mm Hg, or does patient have signs of orthostasis with vasodilator therapy?

YES Do not begin new vasodilator therapy or increase dose of current therapy

NO Begin ACE inhibitor or increase dose using incremental table below until target is reached

ACE inhibitor incremental dosing schedule

SELECTED AGENTS*	DOSES PER DAY				INTERVAL			
		STEP 1	STEP 2	STEP 3	TARGET	STEP 5	MAXIMUM	BETWEEN STEPS
Captopril (Capoten)	3	6.25	12.5	25	50	75	100	48 hours
Enalapril (Vasotec)	2	2.5	5.0	7.5	10	15	20	1 week
Lisinopril (Prinivil, Zestril)	1	5	10	15	20	30	40	1 week
Quinapril (Accupril)	2	5	10	15	20	_	20	1 week
Ramipril (Altace)	1	1.25	2.5	5	10		10	1 week

Note: Aspirin may diminish ACE inhibitor response; low-dose aspirin (eg, 81 mg) may be reasonable

*Not shown: benazepril (Lotensin), fosinopril (Monopril), moexipril (Univasc), trandolapril (Mavik), which are not approved by the FDA for treating heart failure

FIGURE 2. Angiotensin-converting enzyme (ACE) inhibitor therapy algorithm and incremental dosing schedule for patients with systolic heart failure.

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use in these settings to ensure aggressive and effective therapies that are congruent with the disease-management objectives and ensure ongoing communication and collaboration.

Patient education, compliance, and self-management

Patients should learn the warning symptoms of worsening heart failure and what to do should these occur (see the Patient Information page,"What you can do to keep your heart failure under control," page 63). They should be encouraged to use alternatives to emergency facilities. The goal is to prevent crises by carefully following patients and intervening early when fluid retention and other symptoms first develop.

Sodium retention due to inadequate dietary restriction is a leading cause of hospitalization in heart failure.25 Butler et al26 found that over half of heart failure admissions to a university medical center were for dyspnea without other life-threatening complications. These patients were thought to be at low risk and could likely have been cared for in a nonacute care setting, had that been available. These reports reinforce the need for programs that offer aggressive advice and comprehensive education about patient selfmanagement. Program-specific written material is particularly useful.

Management outside the office

Comprehensive management does not necessarily have to be carried out in the traditional office setting.

Telemanagement is simple and inexpensive and provides a means of collecting data for measuring outcomes. The information gathered may lead to adjustments to the patient's plan of care or help optimization of program objectives.

One group²⁷ carried out weekly telephone contact for 6 weeks after an initial home nursing visit. Program objectives were to promote optimal doses of vasodilators and other heart failure drugs, keep patients compliant with a low-sodium diet, and watch them for worsening heart failure or clinical instability as reflected by weight gain, edema, or symptoms. At 6 months, dietary sodium intake had fallen, average medication doses had increased,

TABLE 3

Indications for referral or for hospitalization

Indications for referral to a heart failure specialist

Frequent decompensation to New York Heart Association (NYHA) class III or IV

Refractory NYHA III or IV heart failure without obvious contraindications to heart transplantation

Poor quality of life (patient may be a candidate for research medication protocols)

Persistent symptoms despite an optimized medication regimen (which may require home inotrope therapy or surgery)

Frequent hemodynamic instability, electrolyte imbalance, arrhythmias, bouts of mental obtundation, or emergency room visits

Refractory angina with heart failure

Frequent bouts of respiratory fatigue

Acute pulmonary edema

Acute hospitalization in a coronary care unit with pulmonary artery catheter insertion to guide aggressive therapy.

Indications for hospitalization

Hypotension with organ dysfunction

Severe dyspnea or periodic respirations

Profound fluid retention states

Severe renal or hepatic insufficiency

Hemodynamic instability requiring intravenous inotropes

Arrhythmias requiring intravenous antiarrhythmic treatment or malignant arrhythmias

Decompensated heart failure with refractory angina

Elevated cardiac enzymes or electrocardiographic signs of myocardial ischemia, injury, or new necrosis

functional status and exercise capacity had improved, and hospitalization and emergency department visits had decreased.

e-Management. Telemanagement can be time-intensive and may not be practical in a busy outpatient practice. Technology may provide an answer: healthcare companies now provide computer programs for communicating with patients. For example, patients may log on to the hospital's web site every day and fill out a form that includes their weight and

Beta-blocker therapy algorithm used at the Cleveland Clinic

DOES THE PATIENT HAVE SYSTOLIC HEART FAILURE?

NO Individualize beta-blocker therapy on the basis of restrictive physiology (diastolic dysfunction), hypertension, coronary artery disease, tachyarrhythmias

YES What is the patient's New York Heart Association class?

- I (asymptomatic). Does the patient have any of the following?
 - Marked left ventricular dysfunction (ejection fraction < 35%)
 - History of hypertension
 - Coronary artery disease or previous myocardial revascularization
 - YES Consider beta-blocker therapy after stabilizing therapy with an ACE inhibitor or other vasodilator, a diuretic, and digoxin for 2–3 weeks
 - NO Beta-blocker use is unclear but possibly beneficial
- II (mild) or III (moderate). Is the patient taking an ACE inhibitor, other vasodilator, a diuretic, and digoxin?
 - NO Stabilize therapy with an ACE inhibitor or other vasodilator, diuretic, and digoxin for 2–3 weeks before considering a beta-blocker

YES Does the patient have a contraindication to beta-blockers, eg, any of the following?

- Significant hepatic impairment
- Hospitalization or major cardiovascular event in the last 7 days that involved hypervolemia or Killip class
 ≥ 2 as part of problem
- Significant hypotension
- Currently receiving an intravenous inotrope
- Current light-headedness or dizziness
- History of clinically significant asthma, bronchitis, or other bronchospastic condition
- Resting heart rate < 50 or a consistent heart rate < 60–65 with symptoms
- History of sick sinus syndrome or 2nd or 3rd degree AV block without a permanent pacemaker in place
- YES Do not begin beta-blockers; if the patient is already taking a beta-blocker, do not increase the dose—consider decreasing the dose
- NO Begin carvedilol* at 3.125 mg twice a day for 2 weeks, regardless of weight and age Have patient take with food and take first dose at bedtime to minimize orthostatic hypotension; provide proper instruction on signs and symptoms of congestive heart failure and what to report
 - If dose is tolerated, increase to 6.25 mg twice a day for 2 weeks
 - Double the dose every 1-4 weeks, to a target dose of 25 mg twice a day for patients weighing
 ≤ 85 kg or 50 mg twice a day for patients weighing > 85 kg
- IV (severe). Begin a beta-blocker following the guidelines above only if patient is eurolemic; up-titrate drug slowly; monitor patient closely

Beta-blocker incremental dosing schedule

SELECTED AGENTS*	DOSES PER DAY	INITIAL	MG PER DOSE TARGET	MAXIMUM	SIDE EFFECTS
Carvedilol (Coreg)	2	3.125	25 (≤ 85 kg) 50 (> 85 kg)	25 (≤ 85 kg) 50 (> 85 kg)	Bradycardia, hypotension, AV block, worsening heart failure, bronchospasm, dyspnea, diarrhea
Metoprolol (Toprol XL)	1	25 [†]	150-200	200	Same as for carvedilol, but not diarrhea
Metoprolol (Lopressor)	2	25 [†]	50	100	Same as for carvedilol, but not diarrhea
Bisoprolol (Zebeta)	1	1.25	5 (≤ 85 kg) 10 (> 85 kg)	20	Same as for metoprolol, plus vivid dreams

^{*}Carvedilol is currently the only beta-blocker approved by the Food and Drug Administration (FDA) for treating heart failure, but clinical trials of bisoprolol and metoprolol^{33,34} indicate morbidity and mortality benefit as well [†]One tablet cut in half

FIGURE 3. Beta-blocker therapy algorithm and incremental dosing schedule for patients with systolic heart failure.



yes-or-no questions about their symptoms and self-management. Registered nurses monitor the data and notify the patient's care providers immediately if they encounter any "alarm" values.

Home visits. In one study,²⁸ patients received either unstructured usual care or a single home visit 1 week after hospital discharge. A nurse and pharmacist assessed their knowledge of medications and the extent of medication compliance. If problems were identified, incremental monitoring and other resources were focused on the patient. Patients in the home-intervention group had significantly fewer unplanned readmissions and a trend toward decreased mortality.²⁸

Mailings. Another strategy is to mail educational material to the patient every month. These should be easy to read and understand. In one study,²⁹ patients received mailings on heart failure, medications, risk factors, and behavioral health issues that reinforced key behavioral objectives and provided information on emotional health and the chronic nature of heart failure. Compared with a control group, the group receiving the mailings complied better with their dietary salt restriction and medications, and they felt more confident about their self-management abilities. Perhaps most importantly, readmission rates were reduced by 51% in the intervention group.

"Group therapy" has also been used successfully to reduce adverse outcomes in patients with heart failure. In one study,³⁰ patients randomized to a lifestyle modification program consisting of structured exercise, cognitive-behavioral therapy, and dietary modification had significant improvement in exercise tolerance, weight loss, and depression and anxiety scores.

Rapid-response medical advice systems provide 24-hour access

Patients with chronic heart failure may benefit from a telephone-based rapid response program that provides 24-hour access to medical advice and interventions. This program adjunct uses algorithms or protocols to treat new or worsening symptoms after assessing the patient's medical, medication, diet, fluid, and exercise history.

A rapid-response program may decrease the need for emergency care and emergent inpatient hospitalization, especially if patients are instructed to use the program for early symptoms of worsening condition. If so, this would be a good trend: the hospital admission rate for patients with heart failure actually increased in the 1990s, making heart failure (DRG 127) the number-one hospital discharge diagnosis in the elderly and the most costly Medicare diagnosis to treat.³¹

There are many ways to set up a rapidresponse system. In an established nurse-oncall program, algorithms can include care options that move beyond the standard advice to have the patient seek emergency department care or contact the office for a next-day appointment. An algorithmic program can also be developed for use with a pager system monitored by a cardiac nurse. A local emergency department can place a dedicated telephone line in the triage area. The triage nurse would offer advice to patients by following written protocols. Based on available evidence of telemanagement program benefits, it seems reasonable to recommend a rapid-response intervention system to augment services for heart failure patients during off-duty hours.

Measuring outcomes

The following data should be gathered at regular intervals to measure the effectiveness of the program:

Baseline information such as age, gender, race, education level, social resources, etiology of heart failure, comorbidities, signs, and symptoms.

What was done? Did the team comply with quality-of-care definitions? What medications were used? What were the reasons for discontinuing, changing, or failing to uptitrate drugs? How were worsening symptoms treated? Were multidisciplinary services used? Were hemodynamic parameters measured?

What were the outcomes? Examples: changes in functional class, costs of care, hospitalization rates (number of admissions, number of repeat admissions, length of stay, use of the emergency department), changes in patient practices (eg, use of a rapid-response system rather than the emergency department; changes in sodium intake), proportion

Without a plan, needed care may be omitted

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of patients eligible for therapies who actually received them, quality-of-life data (eg,

Minnesota Living With Heart Failure questionnaire),³² symptoms, survival rates.

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ADDRESS: James B. Young, MD, Cardiac Catheterization Laboratory, F25, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail youngj@ccf.org.