Management of Chronic Heart Failure in Adults: Synopsis of the National Institute for Health and Clinical Excellence Guideline

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Description: The National Institute for Health and Clinical Excellence released its first clinical guideline on heart failure in 2003. This synopsis describes the update of that guideline, which was released in August 2010 and discusses the diagnosis, treatment, and monitoring of heart failure.

Methods: Guideline developers considered clinical evidence, health economic analyses, clinical expert opinion, and patient views. Systematic literature searches were performed, and an original decision model assessed the cost-effectiveness of serial measurement of serum natriuretic peptide to monitor patients with chronic heart failure.

Recommendations: First, this guideline update describes the role of serum natriuretic peptide measurement, echocardiography, and specialist assessment in the diagnosis of heart failure. Second, it presents a pathway for pharmacologic treatment, rehabilitation, and pacing therapy (including implantable cardioverter-defibrillator and cardiac resynchronization therapy) for patients with heart failure and left ventricular systolic dysfunction and patients with heart failure and preserved ejection fraction. Finally, it explains the recommendation to monitor patients with heart failure by using serial measurement of serum natriuretic peptide.

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RATIONALE

Chronic heart failure is a complex clinical syndrome with increasing prevalence (1, 2). This condition causes high hospitalization and mortality rates and carries a substantial economic burden. The National Institute for Health and Clinical Excellence (NICE), which develops clinical practice guidelines for the National Health Service of England and Wales, published its first guideline on heart failure in 2003 (3).

Every 3 years, NICE evaluates the need for guideline updates by using 2 key sources of information. First, literature searches are performed to identify new evidence, warnings issued by licensing agencies, and major changes in costs. Second, the National Clinical Guideline Centre seeks the views of health care professionals and patients. As a result of this process, NICE issued a partial update of the guideline on the management of chronic heart failure in adults in August 2010 (4, 5).

Guideline Focus

The update summarized in this synopsis focuses on the role of symptoms and signs, B-type serum natriuretic peptides (BNP) (specifically, BNP and *N*-terminal fragment of prohormone BNP [NT-proBNP]) levels, and echocardiography in the diagnosis of heart failure. It also focuses on pharmacologic treatment of heart failure and incorporating recommendations from the NICE Technology Appraisal Committee on the roles of cardiac resynchronization therapy and implantable cardioverter-defibrillators (ICDs) in the management of heart failure (6, 7). Finally, this update focuses on disease monitoring, specifically the serial measurement of serum natriuretic peptide and telemonitoring.

See also:

Print
Summary for Patients I-42

Web-Only
Appendix
CME quiz
Conversion of graphics into slides

Target Population

The guideline applies to nonpregnant adults with symptoms of chronic heart failure. It does not apply to persons with acute heart failure or acute exacerbations of chronic heart failure.

Guideline Development Process

The guideline was developed in accordance with the methods described in the 2009 NICE guidelines manual (8) and summarized in previous publications (9, 10). In brief, systematic literature searches identified published literature relevant to the clinical issues previously described. The cutoff date for all searches was October 2009. The databases, search dates, and search terms varied for each question. The guideline development group (GDG) posed several questions designed to cover the topics included in the scope of the review and aimed to explore the new emerging evidence base. The search strategies are outlined in Appendix D of the full guideline (11).

Table 1 provides the MEDLINE search strategy for chronic heart failure. Only articles published in English were included. Systematic reviews or randomized, con-

* Members of the guideline development group are listed in the **Appendix** (available at www.annals.org).

trolled trials were included, but lower-quality evidence, such as cohort studies, were included only if these trials were unavailable.

In addition to the systematic literature reviews, an original decision model was constructed to assess the cost-effectiveness of using serial measurement of serum natriuretic peptide to monitor patients with chronic heart failure, because the cost-effectiveness of this intervention versus that of current practice is uncertain. The GDG included general practitioners, specialist nurses, a consultant physician consultant cardiologists, and 2 members representing patients and caregivers.

The technical team that supported guideline development included a chair, clinical advisor, project manager, information scientist, research fellow, and health economist. The technical team attended each GDG meeting and met approximately 2 weeks before each GDG meeting to discuss the draft review of the clinical and health economic evidence. Each GDG member completed a declaration of potential conflicts of interest form, updated this form throughout the development process, and managed potential conflicts of interest in accordance with NICE policy (9).

Evidence Grading

The guideline developers evaluated the strength of evidence by using an adaptation of the Grading of Recommendations Assessment, Development and Evaluation Working Group's toolbox (www.gradeworkinggroup.org/) (8). **Table 2** summarizes this method for grading the quality of evidence.

Stakeholder Review, Public Comment, and Modification

A clinician with expertise in heart failure reviewed the draft of the guideline. The guideline was also available on the NICE Web site for 8 weeks, during which registered stakeholders, including patient groups, were invited to comment. The guideline was modified on the basis of these reviews.

RECOMMENDATIONS AND RATIONALE

The full NICE chronic heart failure guideline (5) contains the complete list of recommendations, as well as the evidence underpinning these recommendations. Appendix E of the guideline (11) includes evidence tables that summarize studies comprising the clinical and health economic evidence.

Table 1. **MEDLINE Search Strategy for Chronic Heart Failure**

1. Heart Failure/
2. Cardiomyopathy, Dilated/
3. Shock, Cardiogenic/
4. exp Ventricular Dysfunction/
5. Cardiac Output, Low/
6. ((heart or cardiac or myocardial) adj2 (failure or decompensation)).ti.
7. ((congestive or chronic) adj2 "heart failure").ti,ab.
8. ((dilated or congestive) adj2 cardiomyopath$).ti.
9. "cardiogenic shock".ti.
10. ((ventricular or ventricle$) adj2 (failure or insufficien$ or dysfunction$)).ti.
11. (("left ventricular" or "left ventricle") adj2 (failure or insufficien$ or dysfunction$))ti,ab.
12. lvsd.ti,ab.
13. or/1-12.

Table 2. **Summary of the Modified Grading of Recommendations Assessment, Development and Evaluation System Used by the National Institute for Health and Clinical Excellence**

Quality of Evidence	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Diagnosis of Heart Failure

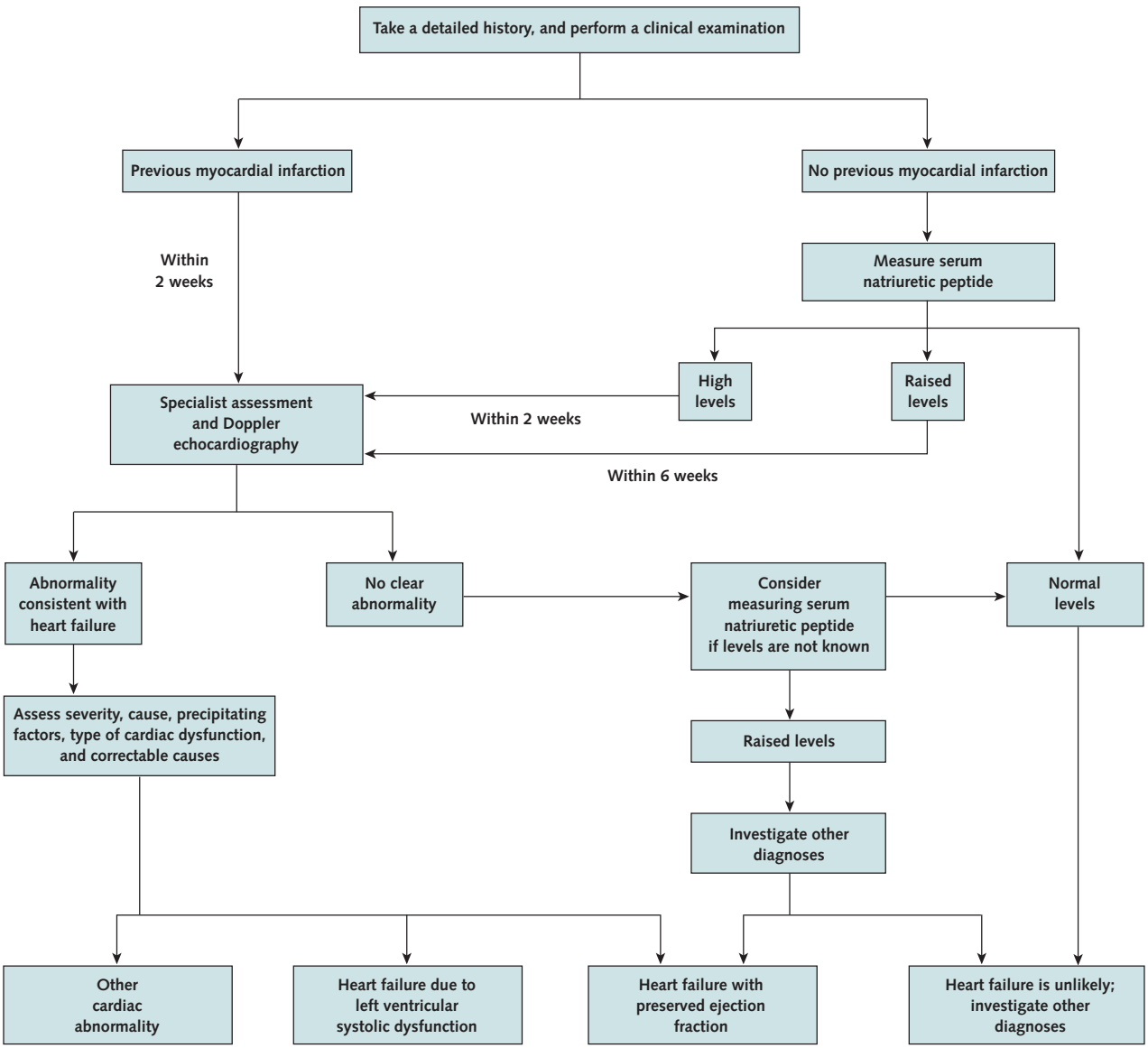
Figure 1 summarizes the recommendations for diagnosis of heart failure. Diagnosis should begin with a detailed history and physical examination if heart failure is suspected. Other investigations include electrocardiography and consideration of chest radiography, peak flow measurement or spirometry, and blood tests (including renal, liver, and thyroid function studies; a lipid profile; complete blood count; and measurement of blood glucose). These studies and the history and physical examination are performed in part to consider possible aggravating factors and alternative diagnoses.

Patients without previous myocardial infarction should undergo measurement of serum natriuretic peptide with subsequent echocardiography, and specialist evaluation is indicated if these levels are elevated. Patients with a history of myocardial infarction should proceed directly to echocardiography and specialist evaluation; if the echocardiogram is normal, then clinicians should consider measuring serum natriuretic peptide.

Heart failure is associated with a poor prognosis, poor quality of life, and high health care costs. Pharmacologic therapy can improve these outcomes. Prompt diagnosis enables appropriate use of effective treatment. Thus, echocardiography and specialist evaluation should be available within 2 weeks of presentation if patients have a history of myocardial infarction or high serum natriuretic peptide levels and no later than 6 weeks after presentation if the serum natriuretic peptide levels are increased but not high (**Figure 1**).

Clinical signs and symptoms are of limited use in the diagnosis of heart failure. Moderate- to high-quality evidence shows that measurement of serum natriuretic peptide levels (both BNP and NT-proBNP) has high sensitivity but only moderate specificity for diagnosis of heart failure. The GDG noted that the consensus-based recommendations of the European Society of Cardiology (12)

Figure 1. **National Institute for Health and Clinical Excellence recommendation for diagnosis of heart failure.**



Normal serum natriuretic peptide levels are defined as BNP levels <100 ng/L or NT-proBNP levels <400 ng/L. Raised serum natriuretic peptide levels are defined as BNP levels between 100 ng/L and 400 ng/L or NT-proBNP levels between 400 ng/L and 2000 ng/L. High serum natriuretic peptide levels are defined as BNP levels >400 ng/L or NT-proBNP levels >2000 ng/L. BNP = B-type natriuretic peptide; NT-proBNP = *N*-terminal fragment of prohormone BNP.

were consistent with cutoff levels proposed in an economic analysis that was appraised for the NICE guideline (13) and therefore adopted the same levels recommended by the European Society of Cardiology (**Figure 1**).

Economic analysis suggested that it was more cost-effective to directly refer patients with a higher probability of heart failure for echocardiography without first measuring serum natriuretic peptide (13). The GDG reviewed the evidence for possible indicators of high probability of heart failure from the history and clinical features and considered that a history of myocardial infarction was the most reliable of the clinical features predictive of heart failure when ascertained by a generalist. Patients with normal serum natriuretic peptide levels are unlikely to have heart failure and therefore do not require referral for echocardiography; however, therapy with diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), or β-blockers will reduce these levels.

Echocardiography also has an important role in excluding valve disease, assessing systolic and diastolic function, and detecting intracardiac shunts. The National Institute for Health and Clinical Excellence recommends that

echocardiography be performed on high-resolution equipment by experienced operators trained in the relevant professional standards. Specialist involvement is recommended to accurately identify the cause of heart failure, including correctable causes.

Treatment of Heart Failure

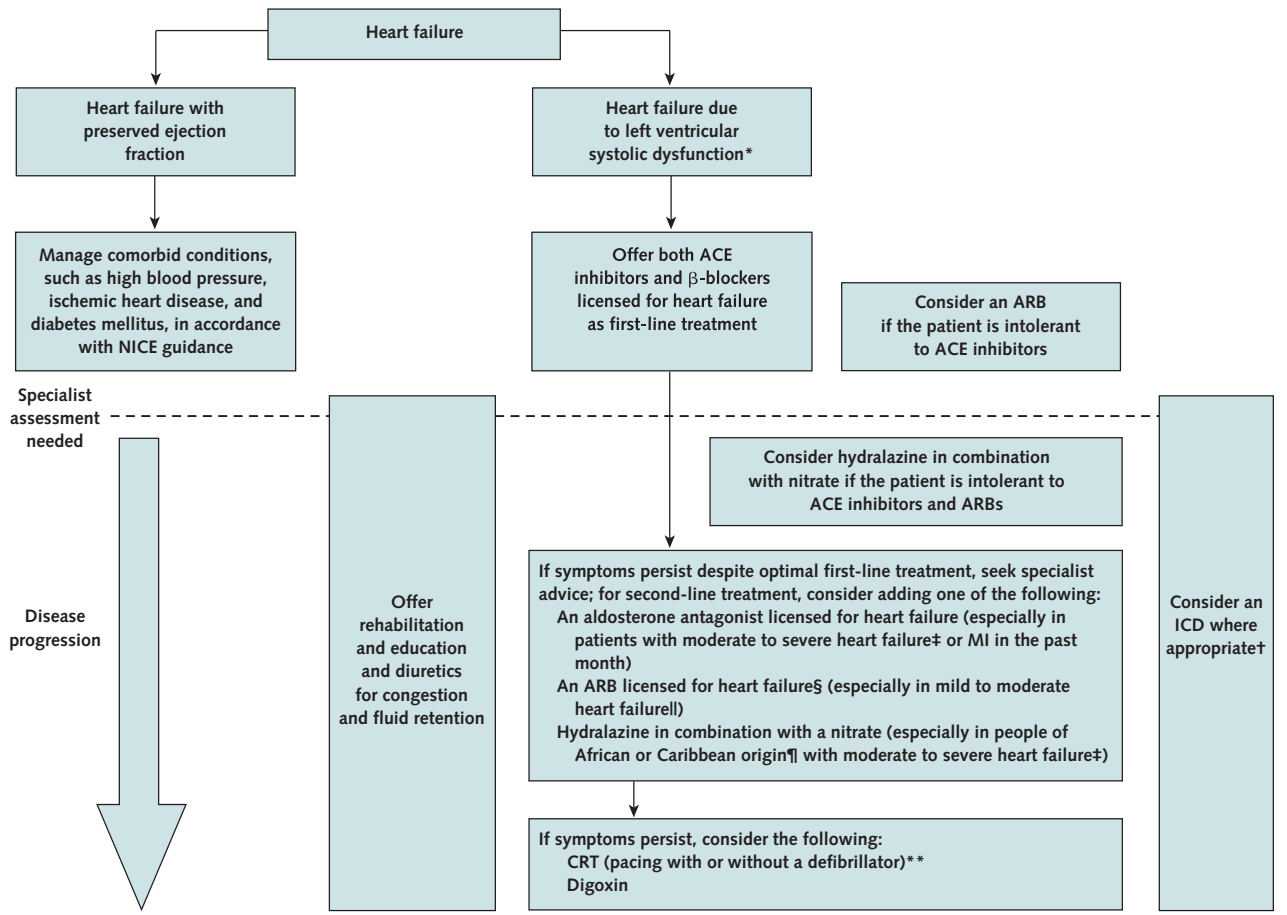
Figure 2 summarizes the recommendations for treatment of heart failure. Clinicians should focus on managing comorbid conditions, such as hypertension, ischemic heart disease, and diabetes mellitus, in patients with preserved ventricular function. Patients with left ventricular systolic dysfunction should receive both an ACE inhibitor and a β-blocker as first-line therapy.

If ACE inhibitors are not tolerated, ARBs are an alternative. Patients who are intolerant of both ACE inhibitors and ARBs should receive combination therapy with hydralazine and a nitrate. In patients with persistent symptoms, specialist referral is warranted for consideration of additional drug therapy, cardiac resynchronization therapy, and an ICD.

Heart Failure With Preserved Ejection Fraction

The GDG found insufficient evidence to recommend specific therapies for heart failure with preserved ejection fraction, other than treatment of comorbid conditions and diuretic therapy to manage fluid retention. Although most trials evaluating rehabilitation recruited only patients with

Figure 2. **NICE recommendation for treatment of heart failure.**



The term "licensed for heart failure" refers to drugs that have been approved for use for the given indication by regulatory agencies in the United Kingdom. ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; NICE = National Institute for Health and Clinical Excellence.

* For more information on drug treatment, see Appendix J to the NICE clinical guideline on heart failure (11) and the NICE clinical guideline on chronic kidney disease (14).

† Consider using an ICD according to the recommendations described in the NICE technology appraisal on ICDs (7).

‡ New York Heart Association class III to IV.

§ Not all ARBs are licensed for use in heart failure in combination with ACE inhibitors.

‖ New York Heart Association class II to III.

¶ This does not include persons of mixed race. For more information, see the full NICE chronic heart failure guideline (5).

** Consider using a CRT according to the recommendations described in the NICE technology appraisal on CRT (6).

left ventricular systolic dysfunction, the GDG recommended offering rehabilitation to patients with heart failure with preserved ejection fraction, because the symptoms and prognosis of this condition are similar to those of left ventricular systolic dysfunction.

Pharmacologic Treatment of Heart Failure With Left Ventricular Systolic Dysfunction

High-quality evidence shows that ACE inhibitors and β-blockers reduce morbidity and increase survival in patients with left ventricular systolic dysfunction (14–17). New low-quality evidence shows that β-blockers reduce mortality in older adults (age ≥65 years) but do not lead to statistically significant differences in quality of life or number of hospitalizations in this age group (18). High-quality evidence shows that no difference exists between selective β-blockers (for example, metoprolol) and nonselective β-blockers (for example, carvedilol) on the combined end point of mortality and hospitalization, and moderate-quality evidence from 1 trial shows lower mortality when the nonselective β-blocker carvedilol is used (19). High-quality evidence shows that the same outcomes are achieved whether ACE inhibitor or β-blocker therapy is started first (20).

Moderate-quality evidence demonstrates that ARBs reduce hospitalizations for heart failure and improve quality of life but do not have a statistically significant effect on survival (21). Low-quality evidence shows that adding ARBs to ACE inhibitors reduces the risk for first hospitalization, and moderate-quality evidence shows that ARBs improve quality of life but do not affect mortality (22, 23). High-quality evidence shows that combination therapy with ARBs and ACE inhibitors increases the risk for hyperkalemia, and low-quality evidence demonstrates that it increases serum creatinine levels (23). High-quality evidence also demonstrates that adding ARBs to ACE inhibitors and β-blockers reduces the composite outcome of cardiovascular mortality and hospitalization for heart failure (24).

First-line therapy with β-blockers and ACE inhibitors is indicated for all patients with heart failure with left ventricular systolic dysfunction, regardless of the severity of their symptoms. However, concern remains that β-blockers are still underutilized in certain subgroups; therefore, the GDG recommended that these agents be considered for all patients with left ventricular systolic dysfunction, including older adults and persons with peripheral vascular disease, erectile dysfunction, diabetes mellitus, interstitial pulmonary disease, and irreversible chronic obstructive pulmonary disease. β-Blockers should be introduced in a "start-low, go-slow" manner, with heart rate, blood pressure, and clinical status reviewed after each dose titration to avoid adverse effects, such as symptomatic bradycardia and hypotension.

The GDG considered that the lower mortality associated with the nonselective β-blocker carvedilol versus the selective β-blocker metoprolol tartrate may be related to the short-acting metoprolol tartrate used in that trial (19). Selective β-blockers, such as bisoprolol and metoprolol succinate, used in other randomized clinical trials have a similar effect on heart failure mortality as carvedilol (25–27). Because the evidence base for β-blockers in heart failure has been established only for some β-blockers (bisoprolol, metoprolol succinate, carvedilol, and nebivolol), the GDG recommended that therapy in patients who develop heart failure while already receiving treatment for a comorbid condition should be switched to one of these β-blockers.

The GDG noted the current practice of readily switching from ACE inhibitor to ARB therapy whenever patients experience adverse effects. It considered the stronger evidence base for ACE inhibitors than for ARBs and therefore recommended this switch only if the adverse effects of ACE inhibitor therapy are intolerable. Regardless of which drug is used, monitoring renal function in patients receiving these drugs is important.

There are 3 choices for second-line treatment for patients with heart failure with left ventricular systolic dysfunction: aldosterone antagonists (28), ARBs, and combination therapy with hydralazine and a nitrate (29). Deciding which agent to use should take into account the severity of heart failure, the ethnicity of the patient, and comorbid conditions. The addition of aldosterone antagonists or ARBs requires close monitoring of potassium levels and renal function.

Invasive Therapy

Separate NICE committees reviewed evidence for cardiac resynchronization therapy and for ICDs, and their recommendations were incorporated into the treatment algorithm (**Figure 2**) (6, 7). Patients with heart failure with left ventricular systolic dysfunction who remain symptomatic despite first- and second-line therapy should be considered for advanced electrical therapy (cardiac resynchronization therapy) if they fulfill the indications given in the NICE technology appraisal on cardiac resynchronization therapy (6). These criteria are a left ventricular ejection fraction less than 35% and a QRS duration on electrocardiography of 150 ms or higher or between 120 ms and 149 ms in patients with mechanical dyssynchrony on echocardiography.

Implantable cardioverter-defibrillators can be considered for patients at any stage of heart failure who have left ventricular systolic dysfunction if the patients fulfill the criteria in the NICE technology appraisal on ICDs (7). These criteria are sustained ventricular tachycardia or nonsustained ventricular tachycardia that is inducible on electrophysiologic testing if the left ventricular ejection fraction is less than 35%, or a QRS duration of 120 ms or higher on electrocardiography if the left ventricular ejection fraction is less than 30%.

Rehabilitation

Moderate-quality evidence shows that exercise rehabilitation reduces hospital admissions for heart failure and increases long-term quality of life almost exclusively in patients with heart failure with left ventricular systolic dysfunction. However, the GDG considered that a supervised group exercise–based rehabilitation program that includes psychological and educational components should be offered to all patients with heart failure, provided that they are stable and do not have a condition or device that would preclude an exercise-based program.

Monitoring Patients With Heart Failure

Heart failure is a chronic, progressive syndrome with an unpredictable and sometimes fluctuating clinical course. Monitoring this clinical course is potentially important to ensure that patients are receiving optimal therapy (which may require up-titration or down-titration). Developers of the 2003 NICE guideline on heart failure agreed on general principles of monitoring (3). However, since then, new evidence has emerged on serial monitoring of serum natriuretic peptide levels and use of telemonitoring. The guideline update included 1 new recommendation about monitoring, namely, that clinicians should consider specialist monitoring of serum natriuretic peptide levels in some patients (for example, persons in whom up-titration of pharmacologic therapy with such agents as ACE inhibitors and β-blockers is problematic or those with a history of hospitalization for exacerbations of heart failure).

Serial Monitoring of Serum Natriuretic Peptide Levels

Moderate-quality evidence demonstrates that therapy guided by serum natriuretic peptide levels results in a medium-term (defined as 9 to 15 months) reduction in hospitalizations for heart failure. Moderate-quality evidence demonstrates that serum natriuretic peptide–guided therapy does not reduce mortality, change quality of life, or reduce hospitalizations for any cause. However, evidence shows different effects of this therapy in different age groups. Moderate-quality evidence shows that serum natriuretic peptide–guided therapy reduces mortality in persons younger than 75 years of age but not in persons older than 75 years. A cost-effectiveness analysis specifically performed for this guideline demonstrated that serial serum natriuretic peptide monitoring was cost-effective when used by specialists (11).

Telemonitoring

Moderate-quality evidence shows that telemonitoring reduces mortality and hospitalization for any reason but does not improve quality of life or decrease hospitalization for heart failure. Significant heterogeneity was observed among the results of different trials. It was unclear whether the observed benefits associated with telemonitoring were due to the telemonitoring itself or to the improved access to care related to telemonitoring. As such, the guideline does not include a recommendation for telemonitoring. Nevertheless, studies show the potential for this technique to be used to extend specialist monitoring to a larger proportion of persons with heart failure.

Discussion

The partial update of the NICE guideline on chronic heart failure made important changes to the previous guideline in England and Wales in diagnosis and treatment. In diagnosis, the guideline focuses on using both a history of myocardial infarction and an increase in serum natriuretic peptide levels to guide further assessment. It also recommends time limits within which patients should receive both echocardiography and clinical assessment by a specialist.

In treatment, the guideline encourages increased use of β-blockers and ACE inhibitors as first-line therapy in patients with heart failure and left ventricular systolic dysfunction and proposes options for second-line therapy (aldosterone antagonists, ARBs, or combination therapy with a nitrate and hydralazine). It also recommends offering group exercise–based rehabilitation programs to all patients with heart failure with stable symptoms and no definite contraindications. The GDG did not believe that sufficient evidence existed to recommend any specific pharmacologic therapies for heart failure with preserved ejection fraction or to recommend telemonitoring. Serial measurement of serum natriuretic peptide levels is only recommended for selected patients receiving specialist care.

New Evidence Since the Guideline Was Published

Evidence has continued to emerge since the publication of the 2010 update of the NICE clinical guideline on heart failure. EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) studied patients with chronic heart failure due to left ventricular systolic dysfunction with mild symptoms (defined as New York Heart Association class II heart failure). It found significant reductions in hospitalization and mortality when eplerenone therapy is started in patients hospitalized during the preceding 6 months or with persistent moderate elevation in serum natriuretic peptide levels (defined as BNP levels ≥250 ng/L, or NT-proBNP levels ≥500 ng/L in men and 750 ng/L in women) (30). SHI_fT (Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial) showed that ivabradine, a blocker of the I_f channel in the sinoatrial node, significantly reduced unplanned hospitalization and mortality in patients with heart failure due to left ventricular systolic dysfunction whose heart rate remains higher than 70 beats/min (31).

A large trial of telemonitoring for patients with a recent hospitalization for heart failure found no evidence that this intervention reduced hospital readmission or mortality (32). The RAFT (Resynchronisation/Defibrillation for Ambulatory Heart Failure Trial) reported that addition of cardiac resynchronization therapy in patients with an

ICD with mild to moderate heart failure reduced all-cause mortality and hospitalization but increased adverse events (33).

It is unclear what effect, if any, these trials would have had on the recommendations if their results had been available before the guideline was published. The continuing emergence of new evidence emphasizes the importance of regular reviews and updates of the evidence base underpinning national guidelines and that clinicians should be alert to potential new advances that have not been captured in guidelines.

Comparison With Other International Guidelines

The NICE guidelines are broadly consistent with other international guidelines, including those of the European Society of Cardiology and the American College of Cardiology/American Heart Association (12, 34). Minor differences in recommendations reflect the target audience, methodology, and importance attached to cost-effectiveness. For example, the European Society of Cardiology guidelines on diagnosis recommend that all patients with symptoms suggestive of heart failure undergo echocardiography and measurement of serum natriuretic peptide levels, whereas NICE recommends selective use of these investigative tools. The American College of Cardiology/American Heart Association guidelines focus on evaluating patients with heart failure rather than determining whether a patient has this syndrome.

The recommendations for treatment from each of these 3 guidelines are very similar. This fact is perhaps not surprising because the guidelines are all based on a substantial evidence base of high-quality randomized, controlled trials for which there is less scope for differing interpretations or consensus-based opinion.

Problems With Implementation and Applicability

A key obstacle to full implementation of the updated NICE clinical guideline on chronic heart failure is concern about its effect on health care expenditure. However, heart failure will be diagnosed earlier and more accurately in patients who are managed according to this guideline, and these patients will receive earlier therapy with agents known to improve survival and substantially reduce hospitalization rate. In England and Wales, NICE published an implementation document based on the chronic heart failure guideline that showed a net savings of £19 000 per 100 000 persons if all of the recommendations were implemented (35). A key priority in implementation is that all clinicians have access to measurement of serum natriuretic peptide to facilitate diagnosis of heart failure.

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Appendix: Guideline Development Group Members

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