2012 Guidelines of the Taiwan Society of Cardiology (TSOC) for the Diagnosis and Treatment of Heart Failure

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INTRODUCTION

Heart failure is the major terminal pathway for most cardiovascular disease. Initial heart failure guidelines were published by American College of Cardiology (ACC) and American Heart Association (AHA) in 1995,[1] and revised guidelines followed in 2001.[2] Subsequently, there were another two update guidelines for diagnosis and management of heart failure published by ACC/AHA in 2005[3] and 2009[4] respectively.

In Europe, initial guidelines for the diagnosis of heart failure were announced in 1995.[5] Guidelines for the treatment of heart failure were published in 1997.[6] From then on, several European Society of Cardiology (ESC) update guidelines have been published including guidelines for the diagnosis and treatment of chronic heart failure in 2001,[7] guidelines on the diagnosis and treatment of acute heart failure in 2005,[8] the ESC guidelines for cardiac pacing and cardiac resynchronization therapy (CRT) in 2007,[9] the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure in 2008,[10] and the focused update of ESC guidelines on device therapy in heart failure in 2010.[11] Later on, both Heart Failure Society of America (HFSA) and National Institute for Health and Clinical Excellence (NICE) launched their guidelines for heart failure in 2010 and 2011, respectively.[12,13]

This paper from the Heart Failure Committee of the Taiwan Society of Cardiology is to provide an updated guideline based on the above guidelines as well as Taiwanese domestic statistics and researches on the diagnosis and management of heart failure. We hope this practice guideline will be useful in the management of heart failure patients not only for cardiologists but also for all medical professionals.

DEFINITION

Heart failure is a complex clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or

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eject blood. The clinical syndrome of heart failure may result from disorders of the pericardium, myocardium, endocardium, or great vessels. In fact, any kind of heart disease may lead to heart failure. The majority of patients with heart failure have symptoms due to an impairment of left ventricular myocardial function. Heart failure may be associated with a wide spectrum of left ventricular functional abnormalities, which may range from patients with normal left ventricular size and preserved left ventricular ejection fraction (LVEF) to those with severe left ventricular dilatation and markedly reduced LVEF. More than half the patients with heart failure syndrome do not have left ventricular dysfunction.[14] The term heart failure with preserved ejection fraction (HFpEF) is used to describe patients with heart failure and normal/near-normal LVEF. Whether the dysfunction is primarily systolic or diastolic, it leads to neurohormonal activation and circulatory abnormalities. The cardinal manifestations of heart failure are fluid retention, dyspnea and fatigue, especially on exertion.

Asymptomatic structural or functional abnormalities of the heart (myocardial remodeling) are usually progressive disorders and considered as precursors of symptomatic heart failure. Moreover, treatment is available for these conditions. These conditions are included in the guideline for early diagnosis and preventive treatment. Heart failure should never be a sole diagnosis. The underlying etiology and cause should always be sought.

DIAGNOSIS OF HEART FAILURE

The diagnosis of heart failure is based on symptoms typical of heart failure, and signs typical of heart failure and an objective evidence structural or functional abnormality of the heart.

Symptoms and signs of heart failure

The symptoms and signs of heart failure are the key to early detection because that is what causes patients to seek medical attention. Breathlessness, exercise intolerance, fatigue and fluid retention are the most common symptoms.[15] They are non-specific and may be difficult to assess particularly in the elderly.

The signs of heart failure include an elevated jugular venous pressure, tachycardia, third heart sound, displaced apex beat, peripheral edema, hepatomegaly, ascites and rales.[16,17] The clinical signs of heart failure should be assessed in a careful clinical examination, including observation, palpation, and auscultation. Like symptoms, the signs of early heart failure can be difficult to interpret, especially in elderly patients and in obese patients. The clinical suspicion of heart failure must then be confirmed by more objective diagnostic tests particularly targeting assessment of cardiac function.

Symptoms and severity of heart failure

There is a poor relationship between symptoms and the severity of cardiac dysfunction. Symptoms if persistent after therapy relate more closely to prognosis and can then be used to classify the severity of heart failure and to monitor the effects of therapy. The severity of heart failure is most often classified using the New York Heart Association (NYHA) functional classification. A more recent classification is based on both the structural change of the heart and symptoms is suggested by AHA/ACC. (Table 1)

Algorithm for the diagnosis of heart failure

An algorithm for the diagnosis of heart failure or left ventricular dysfunction is shown in Figure 1. The diagnosis of heart failure is not sufficient alone. Appropriate investigations are required to establish of the underlying abnormality of the heart, the severity of the syndrome, the etiology, precipitating and exacerbating factors, identification of concomitant disease relevant to the management, and an estimation of prognosis.

DIAGNOSTIC TOOLS

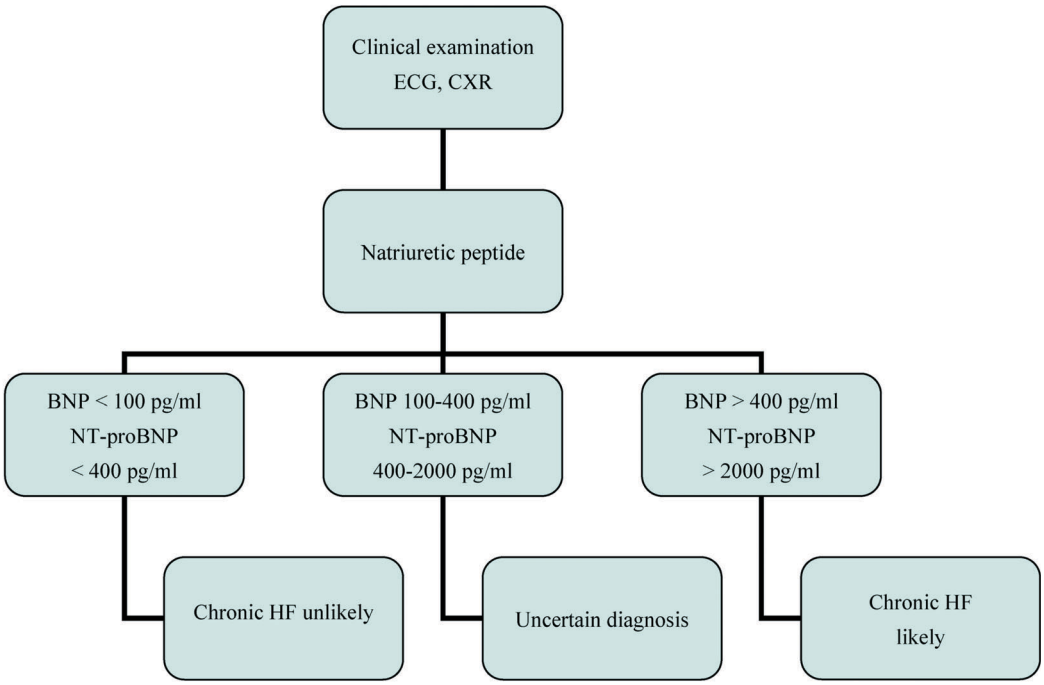
Diagnostic tests in heart failure

Several diagnostic tests are employed routinely to confirm or rule out the diagnosis of heart failure. Diagnostic tests are usually most sensitive for the detection of patients with heart failure and reduced EF. Diagnostic findings are often less pronounced in patients with HFpEF. Echocardiography is the most useful method for evaluating systolic and diastolic dysfunction. The following investigations are considered appropriate in patients with heart failure. However, the recommendations

Table 1. Classification of heart failure

AHA/ACC staging classification		NYHA functional classification	
A	At high risk for developing heart failure. No identified structural or functional abnormality; no signs or symptoms.	I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
B	Developed structural heart disease that is strongly associated with the development of heart failure, but without signs or symptoms.	II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
C	Symptomatic heart failure associated with underlying structural heart disease.	III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea.
D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy.	IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

AHA, American Heart Association; ACC, American College of Cardiology; NYHA, New York Heart Association.



ECG, electrocardiogram; CXR, chest X-ray; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; HF: heart failure.

Figure 1. *Algorithm for initial diagnosis of heart failure.*

largely represent expert consensus opinion without adequate documented evidence.

Electrocardiogram (ECG)

An ECG should be performed in every patient with suspected heart failure. Electrocardiographic changes are common in patients suspected of having heart failure. An abnormal ECG has little predictive value for the presence of heart failure. If the ECG is completely normal, heart failure, especially with systolic dysfunction, is unlikely (< 10%).

Chest X-ray

Chest X-ray is an essential component of the diagnostic work-up in heart failure. It permits assessment of pulmonary congestion and may demonstrate important pulmonary or thoracic causes of dyspnea. The chest X-ray (in two planes) is useful to detect cardiomegaly, pulmonary

congestion, and pleural fluid accumulation, and can demonstrate the presence of pulmonary disease or infection causing or contributing to dyspnea. Apart from congestion, findings are predictive of heart failure only in the context of typical signs and symptoms. Cardiomegaly can be absent not only in acute but also in chronic heart failure.

Laboratory tests

A routine diagnostic evaluation of patients with suspected heart failure includes a complete blood count (hemoglobin, leukocytes, and platelets), serum electrolytes, serum creatinine, estimated glomerular filtration rate, glucose, liver function tests, and urinalysis. Additional tests should be considered according to the clinical picture. Marked hematological or electrolyte abnormalities are uncommon in untreated mild to moderate heart failure, although mild anemia, hyponatremia, hyperkalemia, and reduced renal function are common, especially in patients treated with diuretics and renin-angiotensin-aldosterone antagonist therapy. Appropriate laboratory monitoring is essential during the initiation, titration, and follow-up phases in patients receiving drug therapy for heart failure.

Natriuretic peptides

Plasma concentrations of natriuretic peptides are useful biomarkers in the diagnosis of heart failure and in the management of patients with established chronic heart failure. Evidence exists supporting their use for diagnosing, staging, making hospitalization/discharge decisions, and identifying patients at risk for clinical events. The evidence for their use in monitoring and adjusting drug therapy is less clearly established. A normal concentration in an untreated patient has a high negative predictive value and makes heart failure an unlikely cause of symptoms. This may play an important role especially in primary care. High levels of natriuretic peptides despite optimal treatment indicate a poor prognosis. B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) measurements were introduced as tools for diagnosis and management of heart failure (Figure 1). They rise in response to an increase in myocardial wall stress. Usually, lower levels are observed in patients with preserved left ventricular systolic function. There is no definitive cut-off value recognized for either of the two natriuretic peptides commonly assessed for the diagnosis of heart failure in the emergency department. Due to the relatively long half-lives of natriuretic peptides, abrupt changes in left ventricular filling pressures may not be reflected by rapid changes in peptides. Conditions other than heart failure associated with elevated natriuretic peptide levels include: left ventricular hypertrophy, tachycardia, right ventricular overload, myocardial ischemia, hypoxemia, renal dysfunction, advanced age, liver cirrhosis, sepsis, and infection. Obesity and treatment may decrease natriuretic peptide levels. Natriuretic peptides may also be useful in assessing prognosis prior to hospital discharge and in monitoring the effectiveness of heart failure therapy.

Troponins

Troponin I or T should be sampled in suspected heart failure when the clinical picture suggests an acute coronary syndrome. An increase in cardiac troponins indicates myocyte necrosis and, if indicated, the potential for revascularization should be considered and an appropriate diagnostic work-up performed. An increase in troponin also occurs in acute myocarditis. Mild increases in cardiac troponins are frequently seen in severe heart failure or during episodes of heart failure decompensation in patients without evidence of myocardial ischemia due to acute coronary syndrome and in situations such as sepsis. An elevated troponin is a strong prognostic marker in heart failure, especially in the presence of elevated natriuretic peptides.

Echocardiography

The term echocardiography is used to refer to all cardiac ultrasound imaging techniques, including pulsed and continuous wave Doppler, color Doppler and tissue Doppler imaging. Confirmation by echocardiography of the diagnosis of heart failure and/or cardiac dysfunction is mandatory and should be performed shortly following suspicion of the diagnosis of heart failure, especially when the blood natriuretic peptide level in high. Echocardiography is widely available, rapid, non-invasive, and safe, and provides extensive information on cardiac anatomy (volumes, geometry, and mass), wall motion, and valvular function. The study provides essential information on the etiology of heart failure. In general, a diagnosis of heart failure should include an echocar-

diogram. The most practical measurement of ventricular function for distinguishing between patients with systolic dysfunction and patients with preserved systolic function is the LVEF (normal: 45-50%). This cut-off is somewhat arbitrary. LVEF is not synonymous with indices of contractility as it is strongly dependent on volumes, preload, afterload, heart rate, and valvular function. Stroke volume may be maintained by cardiac dilatation and increased volumes.

Assessment of left ventricular diastolic function

Assessment of diastolic function using evaluation of the ventricular filling pattern is important for detecting abnormalities of diastolic function or filling in patients with heart failure. This can be the predominant functional abnormality of the heart, thus fulfilling the third component necessary for the diagnosis of heart failure. This is especially true in symptomatic patients with preserved LVEF. A recent consensus paper from the Heart Failure Association has focused on the assessment of diastolic dysfunction in HFpEF.[18] There are three types of abnormal filling patterns recognized conventionally in patients in sinus rhythm.

- A pattern of 'impaired' myocardial relaxation with a decrease in peak transmitral E-velocity, a compensatory increase in the atrial-induced (A) velocity, and therefore a decrease in the E/A ratio may be seen at an early stage of diastolic dysfunction; it is frequently seen in hypertension and in the normal elderly subject, and is generally associated with normal or low left ventricular filling pressures.
- In patients with elevated left atrial pressure, (decreased left ventricular compliance, volume overload, mitral insufficiency), there may be a pattern of 'restrictive filling', with an elevated peak E-velocity, a short E-deceleration time, and a markedly increased E/A ratio.
- In patients with an intermediate pattern between impaired relaxation and restrictive filling, the E/A ratio and the deceleration time may be normal, and a so-called 'pseudo-normalized filling pattern' may be seen. This pattern may be distinguished from normal filling by analysis of other Doppler variables such as pulmonary venous flow or tissue Doppler imaging of the mitral plane motion.

Doppler echocardiography allows estimation of the systolic pulmonary artery pressure. This is derived from calculation of the right ventricular systolic pressure estimated from the peak velocity of the tricuspid regurgitant jet velocity present in most subjects. It also permits an assessment of stroke volume and cardiac output by measurement of the velocity time integral of the aortic flow.

Assessment of heart failure with preserved ejection fraction (HFpEF)

Echocardiography plays a major role in confirming the diagnosis of HFpEF. The diagnosis of HFpEF requires three conditions to be satisfied:

- Presence of signs and/or symptoms of chronic heart failure.
- Presence of normal or only mildly abnormal left ventricular systolic function (LVEF 45-50%).
- Evidence of diastolic dysfunction (abnormal left ventricular relaxation or diastolic stiffness).

Transesophageal echocardiography

Transesophageal echocardiography is recommended in patients who have an inadequate transthoracic echo window (obesity, ventilated patients), in complicated valvular patients (especially aortic, mitral, and mechanical valves), in suspected endocarditis, in congenital heart disease, or to exclude a thrombus in the left atrial appendage in patients with atrial fibrillation.

Stress echocardiography

Stress echocardiography (dobutamine or exercise echo) is used to detect ventricular dysfunction caused by ischemia and to assess myocardial viability in the presence of marked hypokinesis or akinesis. It may also be useful in identifying myocardial stunning, hibernation, and in relating heart failure symptoms to valvular abnormalities. In patients with heart failure, stress echo may have a lower sensitivity and specificity due to left ventricular dilatation or the presence of bundle branch block.

Additional non-invasive imaging tests

In patients whom echocardiography at rest has not provided adequate information and in patients with suspected coronary artery disease, further non-invasive imaging may include cardiac magnetic resonance imaging, cardiac computerized tomography, or radionuclide imaging.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging is a versatile, highly accurate, reproducible, non-invasive imaging technique for the assessment of left and right ventricular volumes, global function, regional wall motion, myocardial thickness, thickening, myocardial mass and tumors, cardiac valves, congenital defects, and pericardial disease.[19,20] It has become the gold standard of accuracy and reproducibility for assessment of volumes, mass, and wall motion. The use of paramagnetic contrast agents such as gadolinium can provide evidence of inflammation, infiltration, and scarring in patients with infarction, myocarditis, pericarditis, cardiomyopathies, infiltrative and storage diseases. Limitations include cost, availability, patients with dysrhythmia or an implanted device and patient intolerance.

Computed tomography scan

In patients with heart failure, non-invasive diagnosis of coronary anatomy might be of value and assist in decisions concerning coronary angiography. Computed tomography angiography may be considered in patients with a low or intermediate pre-test probability of coronary artery disease and an equivocal exercise or imaging stress test.[20] The demonstration of atherosclerosis on a computed tomography scan confirms coronary artery disease but does not necessarily imply ischemia.

Radionuclide ventriculography

Radionuclide ventriculography is recognized as a relatively accurate method of determining LVEF and is most often performed in the context of a myocardial perfusion scan providing information on viability and ischemia. It has limited value for assessing volumes or more subtle indices of systolic or diastolic function.

Pulmonary function tests

Measurements of pulmonary function are of limited value in the diagnosis of heart failure. However, these tests are useful in demonstrating or excluding respiratory causes of breathlessness and assessing the potential contribution of lung disease to the patient's dyspnea. Routine spirometry evaluates the extent of obstructive airway disease. The presence of pulmonary congestion may influence the test results. Blood gases are normal in well-compensated chronic heart failure. A reduction of arterial oxygen saturation should lead to a search for other diagnoses.

Exercise testing

Exercise testing is useful for the objective evaluation of exercise capacity and exertional symptoms, such as dyspnea and fatigue. The 6-min walk test is a simple, reproducible, readily available tool frequently employed to assess submaximal functional capacity and evaluate the response to intervention. A normal peak exercise test in a patient not receiving treatment excludes the diagnosis of symptomatic heart failure. Either a cycle ergometer or treadmill may be used with a modified heart failure protocol employing a slow increase in workload. Gas exchange analysis during exercise is preferable as it provides a highly reproducible measurement of exercise limitation and insights into the differentiation between cardiac or respiratory cause of dyspnea, assesses ventilatory efficiency, and carries prognostic information. Peak oxygen uptake (peak VO2) and the anaerobic threshold are useful indicators of the patient's functional capacity, and peak VO2 and the minute ventilation/carbon dioxide production slope (VE/VCO2) is a major prognostic variable. The peak respiratory exchange ratio is a useful index of the degree of anaerobiosis achieved. There is a poor correlation between exercise capacity, LVEF, and most hemodynamic measures at rest.

Ambulatory ECG (Holter) monitoring

Ambulatory ECG monitoring is valuable in the assessment of patients with symptoms suggestive of an arrhythmia (e.g. palpitations or syncope) and in monitoring ventricular rate control in patients with atrial fibrillation. It may detect and quantify the nature, frequency, and duration of atrial and ventricular arrhythmias and silent episodes of ischemia which could be causing or exacerbating symptoms of heart failure. Episodes of symptomatic, non-sustained ventricular tachycardia (VT) are frequent in heart failure and are associated with a poor prognosis.

Cardiac catheterization

Cardiac catheterization is unnecessary for the routine diagnosis and management of patients with heart failure. Invasive investigation is frequently indicated to elucidate etiology, to obtain important prognostic in-

formation, and if revascularization is being considered.

Coronary angiography

Coronary angiography should be considered in heart failure patients with a history of exertional angina or suspected ischemic left ventricular dysfunction, following cardiac arrest, and in those with a strong risk factor profile for coronary heart disease, and may be urgently required in selected patients with severe heart failure (shock or acute pulmonary edema) and in patients not responding adequately to treatment.[21-23] Coronary angiography and left ventricular ventriculography are also indicated in patients with refractory heart failure of unknown etiology[21-23] and in patients with evidence of severe mitral regurgitation or aortic valve disease potentially correctable by surgery.

Right heart catheterization

Right heart catheterization provides valuable hemodynamic information regarding filling pressures, vascular resistance and cardiac output. Its role in the diagnosis of heart failure is, in clinical practice, limited. It forms the basis for the Forrester classification and is the most accurate method to evaluate hemodynamics in patients refractory to treatment, prior to cardiac transplantation, or in clinical research evaluating interventions.

Monitoring of hemodynamic variables by means of a pulmonary arterial catheter may be considered in hospitalized patients with cardiogenic or non-cardiogenic shock or to monitor responses to therapy in patients with severe heart failure. However, the use of a pulmonary arterial catheter has not been shown to improve outcomes.

Endomyocardial biopsy

Specific myocardial disorders may be diagnosed by endomyocardial biopsy. Clinical decisions must be made from available case-controlled studies and expert opinion statements. A recently published AHA/ACC/ESC joint statement for the indications of endomyocardial biopsy suggested that the procedure should be considered in patients with acute or fulminant heart failure of unknown etiology who deteriorate rapidly with ventricular arrhythmias and/or heart block, or in patients who are unresponsive to conventional heart failure therapy.[24] Endomyocardial biopsy might be also considered in chronic heart failure with suspected infiltrative processes such as amyloid, sarcoid, and hemochromatosis, as well as in eosinophilic myocarditis and restrictive cardiomyopathy of unknown origin.

Prognosis

Determining prognosis in heart failure is complex. Diverse etiologies, age, frequent co-morbidities, variation in individual progression and outcomes (sudden vs. progressive heart failure death) must be considered. The impact on prognosis of specific treatments in individual patients with heart failure is often difficult to predict. The variables most consistently cited as independent outcome predictors are old age, ischemic etiology, resuscitated sudden death, hypotension, NYHA functional class III-IV, prior heart failure hospitalization, wide QRS complexes, ventricular arrhythmias, low peak VO2, marked elevation of BNP/NTpro-BNP, hyponatremia, neurohumoral activation, elevated troponin, and low LVEF.

Recommendations

- Take a careful and detailed history, and perform a thorough clinical examination in a patient presented with of heart failure.
- Measure BNP or NT-proBNP in patients with suspected heart failure.
- Patients with suspected heart failure and a BNP level between 100 and 400 pg/mL, or a NT-proBNP level between 400 and 2000 pg/mL should be further evaluated with transthoracic echocardiography or other modality to confirm/exclude diagnosis of heart failure.
- Perform transthoracic echocardiography to exclude important valvular diseases, assess the volume, mass, geometry and systolic/diastolic function of the (left) ventricle, and detect intracardiac shunts.
- Consider alternative methods of imaging the heart (for example, radionuclide ventriculography, cardiac magnetic resonance imaging or transesophageal echocardiography) when a poor image is produced by transthoracic echocardiography.
- Perform an ECG and consider the following tests to evaluate possible aggravating factors and/or alternative diagnoses: chest X-ray, blood tests (electrolytes, urea and creatinine, estimated glomerular filtration rate, thyroid function tests, liver function tests, fasting

lipids, fasting glucose, and complete blood count), urinalysis.

- Perform a coronary angiography in patients presenting with heart failure who have angina or significant ischemia unless the patient is not eligible for revascularization of any kind. Perform a noninvasive imaging to detect myocardial ischemia and viability in patients presenting with heart failure who have known coronary artery disease and no angina unless the patient is not eligible for revascularization of any kind.

ANGIOTENSIN CONVERTING ENZYME INHIBITOR (ACEI)/ANGIOTENSIN RECEPTOR BLOCKER (ARB) THERAPY

Heart failure is a cardiovascular disease with high risk of morbidity and mortality, particularly in patients with previous myocardial infarction. Two classes of agents have become the recommended cornerstones of therapy to delay progression of cardiac dysfunction and to improve survival: ACEI and beta-blockers. ACEI plays a major role in treating patients with either systolic or diastolic heart failure because evidences in randomized controlled trials support its use to improve symptoms, reduce hospitalization, and improve survival.[25] ACEI dosage should be up-titrated slowly to the target doses used in randomized controlled trials. However, escape phenomenon of ACEI with elevation of angiotensin II levels may be detected 3 to 6 months after initiation of its treatment. ARB was therefore started to be used in patients with heart failure.

Recommendations for patients with heart failure and low LVEF

There is compelling evidence that ACEI should be used to inhibit the renin-angiotensin-aldosterone system in all heart failure patients with reduced LVEF, whether they are symptomatic or not (Table 2). A number of large clinical trials, including CONSENSUS,[26] SOLVD & ATLAS[27] have demonstrated improvement in morbidity and mortality in heart failure patients with reduced LVEF, both chronically and post-myocardial infarction.

- ACEIs are recommended for all patients with current or prior symptoms of heart failure with reduced LVEF ($\leqq$ 40%), unless contraindicated.
- ACEI should be titrated to doses used in clinical trials, as tolerated during concomitant up-titration of beta-blockers.

Recommendations for alternatives to ACEI

ACEI can have some troublesome side effects, including cough and angioedema, which may limit therapy with these agents. According to the results of trials for ARBs in heart failure (RESOLVD: candesartan, enalapril; ELITE: losartan, placebo; ELITE II: losartan, captopril; VAL-HeFT:[28] valsartan/ACEI, ACEI; CHARM:[29] candesartan/ACEI, ACEI; OPTIMAAL:[30] losartan, captopril; VALIANT: valsartan, captopril, both), ARB has no beneficial effect on mortality when combined with ACEI. However, a 17% reduction in hospitalizations could be seen when ARB was used in heart failure. According to CHARM-Added study (candesartan/ACEI), the major decision to achieve better primary outcome is dependent on whether recommended or maximal doses of ACEI were used. Partial blockage of angiotensin II by ACEI reduced morbidity and mortality in high risk patients.

According to the 2009 ACCF/AHA update guideline for heart failure,[4] ARBs are recommended in patients with current or prior symptoms of heart failure and reduced LVEF who are ACEI-intolerant. ARBs are reasonable to use as alternatives to ACEI as first-line therapy

Table 2. ACEI/ARB in heart failure with low LVEF

Generic Name	Initial Daily Dose (mg)		Target Dose (mg)	
ACEI				
Captopril	6.25	tid	50	tid
Enalapril	2.5	bid	10	bid
Fosinopril	5-10	qd	80	qd
Lisinopril	2.5-5.0	qd	20	qd
Quinapril	5	bid	80	qd
Ramipril	1.25-2.5	qd	10	qd
ARB				
Candesartan	4-8	qd	32	qd
Losartan	12.5-25	qd	150	qd
Valsartan	40	bid	160	bid
Aldosterone Antagonists				
Spironolactone	12.5-25	qd	25	qd
Eplerenone	25	qd	50	qd

LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

for patients with mild to moderate heart failure and reduced LVEF, especially for patients already taking ARBs for other indications. ARBs have been demonstrated to be well tolerated in randomized trials enrolling patients judged to be intolerant of ACEI. Both drugs have similar effects on blood pressure, renal function, and potassium. Thus, patients intolerant of ACEI for these reasons may also be intolerant to ARBs, and the combination of hydralazine and oral nitrates should be considered for these patients.

It is recommended that other therapy be substituted for ACEI in the following circumstances:

- In patients who cannot tolerate ACEI due to cough, ARBs are recommended.
- ARBs are recommended in patients with current or prior symptoms of heart failure with reduced LVEF, who are ACEI intolerant.
- ARBs are reasonable to use as alternatives to ACEIs as first line therapy for patients with mild to moderate heart failure and reduced LVEF, especially for patients already taking ARBs for other indications.
- The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are on conventional therapy.
- The combination of hydralazine and an oral nitrate may be considered in patients not tolerating ARB therapy.
- Patients intolerant to ACEI from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered.

Recommendations for heart failure in the setting of ischemic heart disease

A series of well-designed clinical trials, including SAVE[31] (captopril), TRACE (trandolapril), AIRE (ramipril), have evaluated the effects of long-term and short-term ACEI therapy in post-myocardial infarction patients. Based on the data from the SAVE studies, the long-term benefits of ACEI therapy are clear. In patients with evidence of left ventricular dysfunction (LVEF $\leqq$ 40%) within 2 weeks following acute myocardial infarction, ACEI group was associated with significant risk reductions in mortality (20%), heart failure hospitalization (20%) and recurrent ischemia events (25%). Some large clinical trials (GISSI-3,[32] ISIS-4, SMILE) have shown a small but significant improvement in survival with early ACEI therapy (within 24 hours) in patients with acute myocardial infarction. At 1 month follow-up, significant reduction of mortality (10%) and progression to severe heart failure (30%) were observed. Additionally, short-term treatment resulted in reduction of 1-year long-term mortality (29%).

Two large clinical trials have evaluated the role of ARBS as an alternative renin-angiotensin-aldosterone system blocking agent in post-myocardial infarction patients with left ventricular dysfunction: OPTIMAAL[30] (losartan), VALIANT (valsartan). There were no significant differences between ARB & ACEI groups in all cause mortality, even in cardiovascular deaths, recurrent myocardial infarction or heart failure hospitalization. Nevertheless, it also documented decrease tolerability and lack of additional morbidity or mortality benefit when combined ACEI and ARB therapy was used in patients with post-myocardial infarction left ventricular dysfunction.

- ACEI is recommended in all patients with either reduced or preserved LVEF after a myocardial infarction.
- ARB should be administered to post-myocardial infarction patients who are intolerant of ACEI and have a low LVEF.
- It is recommended that ACEI and beta blocker therapy be initiated early (< 48 hour) during hospitalization in hemodynamically stable post-myocardial infarction patients with reduced LVEF or heart failure.

BETA-BLOCKER THERAPY

Background

The level of adrenergic and neurohormonal activation correlates strongly with the risk of heart failure progression and death.[33-35] Blocking or limiting neurohormonal activation and its effects is especially important in retarding heart failure progression. ACEIs, ARBs, aldosterone blockade and beta-blockers have been proven to provide cardiovascular benefit to patients at any point during heart failure development. Beta-blockers have been shown to attenuate the remodeling and systemic effects of adrenergic activation.

Treatment guidelines based on clinical study results

The HFSA, the ESC, and the ACC/AHA published similar treatment guidelines that made strong recommendations based on clinical study results published at the time.[4,10,12] Whereas the HFSA and ESC guidelines use the familiar NYHA functional class system (classes I-IV) based on signs and symptoms of dyspnea, the ACC/AHA has identified four separate stages of heart failure, paraphrased as followings:

Stage A: High risk for heart failure with no structural damage or heart failure symptoms.

Stage B: Structural damage without heart failure symptoms.

Stage C: Structural damage with previous or current heart failure symptoms.

Stage D: Refractory heart failure, specialized intervention.

Patient categorization by stages focused attention on customization of therapy to achieve optimal, evidence-based treatments across the heart failure continuum. Beta-blockers are important in treating heart failure and have been proven useful in reducing the likelihood of progression through the continuum of heart failure. They should be included in the therapeutic regimens of patients with asymptomatic left ventricular systolic dysfunction to prevent progression to symptomatic heart failure, to slow or prevent remodeling of the ventricle, and to improve survival. Beta-blockers have been used to treat patients with stage A heart failure with hypertension. Beta-blockers are standard therapy for the patient with stage B heart failure who has had a myocardial infarction, but few data are available concerning use in asymptomatic patients with left ventricular dysfunction. Additionally, beta-blockers are part of the core therapy for stage C heart failure and selected patients with stage D heart failure.[4,10,12,36]

Beta-blockers are valuable for treatment of heart failure; however, the class is heterogeneous, and proper beta-blocker selection for each heart failure stage is important. Three beta-blockers (bisoprolol, carvedilol, and metoprolol succinate) have been shown to reduce mortality and morbidity in patients with heart failure resulting from left ventricular systolic dysfunction are available in Taiwan.[37-39] Evidence-based beta-blocker therapy in combination with standard therapy is strongly recommended by current guidelines as a mainstay of treatment in all symptomatic patients with left ventricular systolic dysfunction. The trial results support benefit from both β1 selective and nonselective beta-blockers, whether ancillary properties are present or not. Beta-blockers with intrinsic sympathomimetic activity are likely to worsen survival and should be avoided in patients with heart failure.[4,10,12,36]

Clinical practice recommendations

Current heart failure guidelines have established the beta-blockers studied in clinical trials as routine therapy in patients with reduced LVEF. However, beta-blockers have been underused, possibly because of perceptions of complex management, adverse events, a contraindication in patients with left ventricular dysfunction, or negative effects on short-term clinical outcomes.[39,40] Optimizing heart failure outcomes will require both the expansion of the evidence base for treating the highest-risk patients as well as the development of effective strategies to assure that eligible high-risk patients receive all appropriate therapies.[4,10,12,40,41]

Trial data, though valuable, often do not give direction for individual patient management. From a practical point of view, it is recommended that beta-blockers be initiated at low doses and uptitrated gradually, typically at 2-week intervals in patients with reduced LVEF, and after 3-10 day intervals in patients with reduced LVEF following newly diagnosed myocardial infarction.[4,10,12,40,41]

This therapy is well tolerated by a large majority of patients with heart failure, even those with co-morbid conditions like diabetes mellitus, chronic obstructive lung disease, and peripheral vascular disease. It is recommended that beta-blocker therapy be continued in most patients experiencing a symptomatic exacerbation of heart failure during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload, or symptomatic bradycardia. A temporary reduction of dose in this setting may be considered. Abrupt discontinuation in patients with symptomatic exacerbation should be avoided, unless the situation is life-threatening. If discontinued or reduced, beta-blockers should be reinstated before the patient is discharged. In general, doses should be uptitrated to the previous well-tolerated dose as soon as safely possible.[4,10,12,40,41]

Beta-blocker therapy should be used with caution in patients with diabetes with recurrent hypoglycemia, with

asthma, or with resting limb ischemia. Considerable caution should be used if beta-blockers are initiated in patients with marked bradycardia (< 55 beats/min) or marked hypotension (systolic blood pressure < 80 mmHg). Beta-blockers are not recommended in patients with asthma with active bronchospasm.[4,10,12,40,41]

Special considerations in Taiwanese and Chinese population

The recently published 2010 Canadian Cardiovascular Society heart failure guidelines update focuses on an increasing issue in the western world – heart failure in ethnic minorities, including the Chinese population, provide practicing clinicians with recommendations and practical tips from a clinical perspective.[42] The guidelines indicate that Chinese community are lack of awareness of symptoms of stroke and myocardial infarction and risk factors for heart disease. This lack of knowledge, combined with social and ethnocultural factors, may confound the management of Chinese patients with heart failure or at risk of developing heart failure.

Although there are no large-scale randomized controlled trials of pharmacological and device therapy conducted specifically among Chinese patients with heart failure, current recommendations from the Chinese guidelines on the diagnosis and treatment of chronic heart failure closely resemble those contained in guidelines in the western world.[43]

In Taiwan, data regarding beta-blocker therapy in heart failure patients are lacking. Limited data demonstrated that the use of beta-blocker therapy in patients with heart failure remains low. In the study of Hu et al.[44] from a tertiary medical center, the mean stable dose of beta-blockers in Taiwanese heart failure patients with carvedilol was 12 ± 8 mg/day which was significantly lower than those reported in the literatures.

DIURETIC THERAPY

Diuretics should not be the sole therapy for patients with signs of volume overload, and the cornerstone of treatment for heart failure is the use of beta-blockers and ACEIs. Loop diuretics are more effective in severe heart failure than thiazide diuretics, and the combination therapy with thiazide (or thiazide-like medications) and loop diuretics are effective in refractory cases of volume overload. Aldosterone blocking agents (spironolactone, eplerenone) reduce mortality in patients with NYHA functional class II-IV heart failure, left ventricular dysfunction and on stable doses of digoxin and ACEIs. However, for all types of heart failure, diuretics should be routinely used for the relief of congestive symptoms and fluid retention in patients with heart failure, and titrated (up and down) according to need (Table 3).[45,46]

Heart failure due to left ventricular systolic dysfunction

Recommendations for optimal use of multi-drug therapy

Multi-drug therapy is required for optimal management to slow progression and improve outcome in patients with heart failure and reduced LVEF. An ACEI plus a beta-blocker is standard background therapy. Additional pharmacological therapy should be considered in patients with heart failure and reduced LVEF who are unable to tolerate a beta-blocker and have persistent symptoms or progressive worsening despite optimized therapy with an ACEI. The choice of specific agent will

Table 3. Diuretic treatment for heart failure

Medication	Beneficial Subsets	Initial Daily Dose	Maximal Daily Dose
Diuretics	Fluid overload (edema, ascites, dyspnea, weight gain)	Furosemide 40 mg	Furosemide 160~200 mg
		Bumetanide 1.0 mg	Bumetanide 4~8 mg
		Torsemide 10 mg	Torsemide 100~200 mg
		Chlorothiazide 500 mg	Chlorothiazide 1,000 mg
		Hydrochlorothiazide 25 mg	Hydrochlorothiazide 50 mg
Aldosterone Antagonists	NYHA functional class II-IV	Spironolactone 12.5 mg	Spironolactone 25 mg
		Eplerenone 25 mg	Eplerenone 50 mg

be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure and volume status. The triple combination of an ACEI, an ARB, and an aldosterone antagonist is not recommended due to high risk of hyperkalemia.

Addition of an aldosterone antagonist have been shown to reduce mortality in patients with NYHA functional class II-IV heart failure for patients on stable doses of digoxin and ACEIs.[47-50] For patients who have had an acute myocardial infarction and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, treatment with an aldosterone antagonist licensed for post-myocardial infarction treatment should be initiated within 3-14 days of the myocardial infarction, preferably after ACEI therapy.[48,49] Patients who have recently had an acute myocardial infarction and have clinical heart failure and left ventricular systolic dysfunction, but who are already being treated with an aldosterone antagonist for a concomitant condition (for example, chronic heart failure), should continue with the aldosterone antagonist or an alternative, licensed for early post-myocardial infarction treatment.[12,46] Addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of heart failure and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be 2.5 mg/dL or less in men or 2.0 mg/dL or less in women, and potassium should be less than 5.0 mEq/L. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists.[4]

Recommendations for diuretic therapy

- Loop and distal tubular diuretics are necessary adjuncts in the medical therapy for heart failure when symptoms are the result of sodium and water retention. Diuretics reduce congestive symptoms and signs and can be titrated as needed to restore euvolemia and to reach an estimated "dry" weight goal for the patient. Relief of signs and symptoms must be achieved without causing side effects, particularly symptomatic hypotension or worsening renal function.
- Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms (orthopnea, edema, and shortness of breath), or signs of elevated filling pressures (jugular venous distention, peripheral edema, pulsatile hepatomegaly, and, less commonly, rales). Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure.
- The initial dose of diuretic may be increased as necessary to relieve congestion. Restoration of normal volume status may require multiple adjustments over many days and occasionally weeks in patients with severe fluid overload evidenced by massive edema or as cites. After a diuretic effect is achieved with short-acting loop diuretics, increasing administration frequency to twice or even three times per day will provide more diuresis with less physiologic perturbation than larger single doses. Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present, particularly those with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. Intravenous administration of diuretics may be necessary to relieve congestion. Diuretic refractoriness may represent patient non-adherence, a direct effect of diuretic use on the kidney, or progression of underlying cardiac dysfunction.
- Addition of chlorothiazides or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high dose loop diuretic therapy. But chronic daily use, especially metolazone, should be avoided if possible because of the potential for electrolyte shifts and volume depletion.[51] These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer-acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used.
- Careful observation for the development of side effects, including electrolyte abnormalities, symptomatic hypotension, renal dysfunction, or worsening renal function, is recommended in patients treated with diuretics, especially when used at high doses and in

combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. Diuretics should be used, in the smallest doses necessary, to control fluid retention. Care should be taken to avoid hypokalemia, hypomagnesemia, prerenal azotemia, or orthostatic hypotension. Diuretic doses may need to be reduced in order to introduce or optimize treatment with ACE inhibitors and beta-blockers.

- Patients requiring diuretic therapy to treat fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or even discontinuing diuretics may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention.
- It is recommended that patients and caregivers be given education that will enable them to demonstrate understanding of the early signs of fluid retention and the plan for initial therapy. Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload (typically short-term weight gain of 1 to 2 Kg).

Heart failure with preserved ejection fraction

Diuretic treatment is recommended in all patients with heart failure and clinical evidence of volume overload and edema, including those with preserved LVEF. Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. Patients who do not respond to this treatment will require further specialist advice.[12,46]

Acute decompensated heart failure

It is recommended that patients admitted with acute decompensated heart failure and evidence of fluid overload be treated initially with loop diuretics – usually given intravenously rather than orally. When congestion fails to improve in response to diuretic therapy, the following options should be considered:

- Reevaluation if presence or absence of congestion.
- Restriction of sodium and fluid.
- Increasing doses of a loop diuretic.
- Continuous infusion of a loop diuretic.
- Addition of a second diuretic orally or intravenously.
- Ultrafiltration

Recommendations for patients with hypertension and asymptomatic left ventricular dysfunction with left ventricular dilatation and a low LVEF

Prescription of an ACEI is recommended. Addition of a beta-blocker is recommended even if blood pressure is controlled. If blood pressure remains >130/80 mmHg then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium channel blockers or other antihypertensive drugs.

Recommendations for patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilatation and low LVEF

Prescription of target doses of ACEIs, ARBs, beta-blockers, aldosterone inhibitors, and hydralazine/isosorbide dinitrate in various combinations (with a loop diuretic if needed) is recommended, based on doses used in large-scale outcome trials. If blood pressure remains > 130/80 mmHg, a dihydropyridine calcium channel blockers may be considered or other antihypertensive medication doses increased.

Heart failure in special populations

As in all patients, but especially important in the elderly, careful attention to volume status during therapy with ACEIs, beta-blockers and diuretics is recommended to avoid the possibility of postural hypotension and cerebral hypoperfusion.

INOTROPIC THERAPY

Recommendations of digoxin

In the DIG trial,[52] 6800 patients with an LVEF < 45% and in NYHA functional class II-IV were random-

ized to placebo or digoxin (0.25 mg/day), added to a diuretic and ACEI. Treatment with digoxin does not alter all-cause mortality but lead to an relative risk reduction for hospitalization for worsening heart failure of 28% within an average of 3 years after starting treatment. The absolute risk reduction is 7.9%, equating to NNT (for 3 years to postpone 1 patient admission) of 13. These findings are supported by another meta-analysis, but not supported entirely by the DIG trial where quality of life was not improved and there was no advantage in patients with HFpEF.[53] Potential adverse effects of digoxin include sinoatrial and atrioventricular block, atrial and ventricular arrhythmias (especially in the presence of hypokalemia). Signs of digoxin toxicity include confusion, nausea, anorexia, and disturbance of color vision.

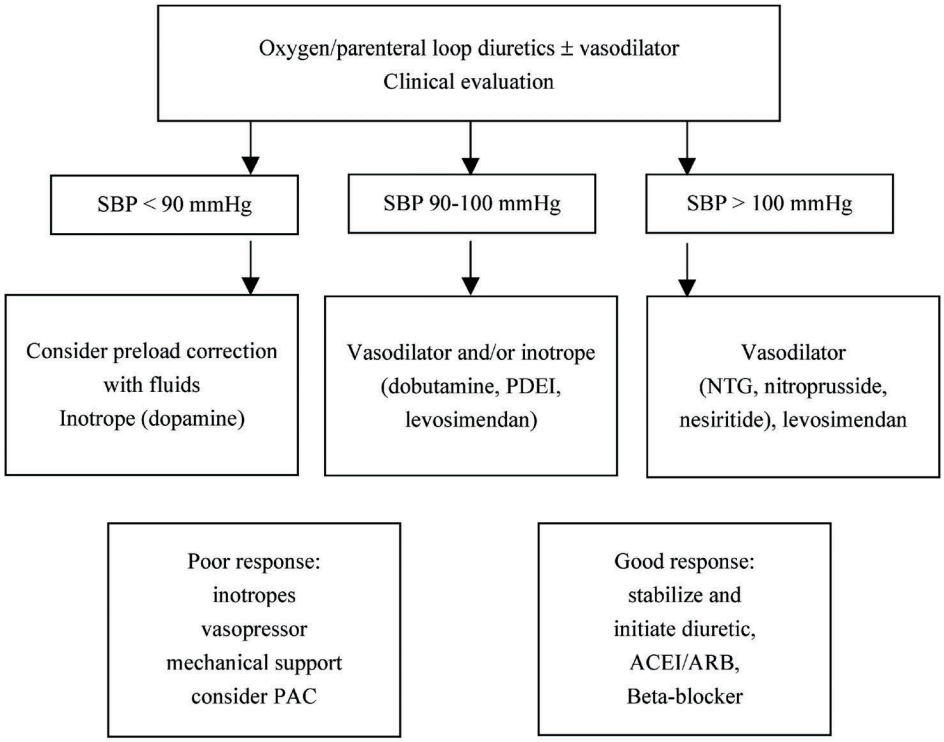
- Digoxin should be used for rate control in symptomatic heart failure and atrial fibrillation prior to beta-blocker for decompensated heart failure, or combined with beta-blocker in LVEF ≤ 40%, or combined with diltiazem or verapamil in LVEF > 40%.[4,10,12,45,46]
- Digoxin is recommended to be used in symptomatic heart failure (NYHA functional class II-IV) with LVEF < 40% with sinus rhythm (in addition to optimal dose of ACEI and/or an ARB, beta-blocker and aldosterone antagonist, if indicated) improves ventricular function and patient well-being, reduces hospitalization for worsening heart failure, but has no effect on survival).[10,12,45,46]
- Serial monitoring of serum electrolytes and renal function is mandatory in the use of digoxin.[10]
- Single daily maintenance dose of 0.25 mg is commonly given in adults with normal renal function. In the elderly and/or in patients with renal impairment, a reduced dose of 0.125 or 0.0625 mg QD should be used.[10,12,45]
- The therapeutic serum concentration (8-12 hours after last dose) should be between 0.6 and 1.2 ng/mL (toxicity might still occur). Drug-drug interaction issue should be considered. Certain drugs may increase plasma digoxin levels; e.g. amiodarone, diltiazem, verapamil, certain antibiotics, quinidine, laxatives and diuretics.[10,12,45,46,54,55]

Recommendations of other inotropes

- Inotropes (Table 4) should be considered in patients with low systolic blood pressure or low LVEF as well as low perfusion signs (including cold, clammy skin, in patients who are vasoconstricted with acidosis, renal impairment, liver dysfunction, or impaired mental status).[56-63] Moreover, inotropes should be administered as early as possible and withdrawn as soon as adequate organ perfusion is restored and/or congestion reduced. They may induce arrhythmia, causing further myocardial injury and leading to increased mortality. In heart failure patients without low perfusion, use of inotropes is not recommended.[4,10]
- In patients with cardiogenic shock or end-stage heart failure, inotropes should be considered to stabilize patients in cardiogenic shock or serve as a life-sustaining bridge to more definitive therapy such as mechanical circulatory support, ventricular assist devices, or cardiac transplantation.[10,64] (Figure 2)
- Type III phosphodiesterase inhibitors, e.g. milrinone and enoximone, increase cardiac output and stroke volume, decrease pulmonary artery pressure, pulmonary wedge pressure, and systemic and pulmonary vascular

Table 4. Dosage of inotropic agents in acute heart failure

	Bolus	Infusion rate
Epinephrine	1 mg can be given i.v. during resuscitation, repeated every 3-5 min	0.05-0.5 μg/kg/min
Norepinephrine	No	0.2-1.0 μg/kg/min
Levosimendan	12 μg/kg over 10 min (optional)	0.1 μg/kg/min which can be decreased to 0.05 or increased to 0.2 μg/kg/min
Enoximone	0.25-0.75 mg/kg	1.25-7.5 μg/kg/min
Milrinone	25-75 μg/kg over 10-20 min	0.375-0.75 μg/kg/min
Dopamine	No	< 3 μg/kg/min: renal effect (δ+) 3-5 μg/kg/min: inotropic effect (β+) > 5 μg/kg/min: (β+), vasopressor effect (α+)
Dobutamine	No	2-20 μg/kg/min (β+)



SBP, systolic blood pressure; PDEI, phosphodiesterase inhibitor; NTG, nitroglycerin; PAC, pulmonary artery catheter; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Figure 2. *Algorithm for the treatment of acute heart failure.*

resistance They might be used with caution in coronary artery disease, as they may increase mid-term mortality.[4,10,45,47]

- Vasopressors like norepinephrine are only indicated in cardiogenic shock when the combination of an inotropic agent and fluid challenge fails to restore SBP > 90 mmHg, with inadequate organ perfusion. Epinephrine should be restricted to use as rescue therapy in cardiac arrest.[10] (Figure 2)

ANTITHROMBOTIC THERAPY

Chronic heart failure is associated with an increased risk of thromboembolic complication. In the Framingham Heart Study, the risk of stroke was 4.1% per year for men and 2.8% per year for women with heart failure.[65] According to a meta-analysis of 26 studies by Witt et al, the incidence of ischemic stroke of heart failure patients was 18 per 1000 people in the first year of heart failure diagnosis and increased to 47 per 1000 people at the end of five years.[66]

Heart failure carries a hypercoagulable state and predisposes to thrombosis by fulfillment of Virchow's triad for thrombogenesis. Based on this theory, low cardiac output with aberrant flow from the dilated cardiac chambers, endothelial dysfunction, as well as abnormal hemostasis, platelet dysfunction, neuroendocrine activation, chronic oxidative stress, excessive cytokine production and proinflammatory process would all lead to the thrombosis in heart failure.[67]

Retrospective analysis or post hoc analysis of several clinical trials including SAVE (Survival and Ventricular Enlargement trial), CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study), SOLVD (Studies of Left Ventricular Dysfunction) and PRIME-II (Promotion of Reperfusion in Myocardial Infarction Evolution-II) showed that warfarin or antiplatelet therapy could reduce the stroke risk, mortality rate, hospitalization and improved the prognosis of patients with advanced heart failure.[68]

Three randomized controlled trials have investigated the optimal preventive regimen of antithrombotic therapy for preventing thromboembolic events in heart fail-

ure. The WASH (Warfarin/Aspirin Study in Heart Failure) study compared Warfarin (INR target 2.5), aspirin 300 mg, or placebo in 279 patients with LVEF < 35% over a mean period of 27 months and no difference was found among these three groups in the combined primary endpoints of all cause mortality, non-fatal myocardial infarction and non-fatal stroke. However, patients on warfarin therapy did have fewer cardiovascular hospitalizations than those on aspirin or placebo.[69] In the WATCH (Warfarin and Antiplatelet Therapy in Chronic Heart Failure) study, 587 patients with LVEF < 35% were randomized to receive warfarin (INR 2.5) vs. blinded antiplatelet therapy (aspirin 162 mg, or clopidogrel 75 mg). No difference was seen in the composite endpoint of death/non-fatal myocardial infarction/stroke in the three treatment groups. However, warfarin therapy was associated with fewer non-fatal strokes than aspirin or clopidogrel and fewer hospitalizations than aspirin.[70] The HELAS (Efficacy of Antithrombotic Therapy in Chronic Heart Failure) study, randomized 197 patients with heart failure and LVEF < 35% to aspirin 325 mg vs. warfarin in patients with ischemic heart disease and to warfarin vs. placebo in patients with idiopathic dilated cardiomyopathy. No difference has been found between the treatments in ischemic heart failure group in terms of primary endpoints (non-fatal stroke, peripheral or pulmonary embolism, myocardial infarction, re-hospitalization with heart failure or death due to heart failure). However there was a trend towards benefit for warfarin over placebo for the primary composite endpoint in the non-ischemic cardiomyopathy group.[71] These studies were underpowered due to poor recruitment and the ongoing WARCEF (Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction) trial probably could answer our questions in the near future.[72]

In the absence of definitive trials, it is not clear how anticoagulants should be prescribed in patients with heart failure. The available heart failure guidelines (ACCF/AHA, ESC, HFSA, NICE, SIGN)[4,10,12,45,46] recommend warfarin (or an alternative oral anticoagulant) therapy in patients with heart failure and permanent, persistent, or paroxysmal atrial fibrillation without contraindication to anticoagulation or a history of systemic or pulmonary emboli, including stroke or transient ischemic attack. Long-term treatment with an antiplatelet agent, generally aspirin in doses of 80-150 mg, is recommended for patients with heart failure due to ischemic cardiomyopathy whether or not they are receiving ACEIs.

However, according to a nationwide descriptive study by Lin et al., the compliance of antithrombotic agent prescribing in patients with atrial fibrillation was lower in Taiwan.[73] Again, those patients after mechanical valve replacement under vitamin K antagonist treatment and the low intensity anticoagulant therapy (INR < 2.0) in Taiwanese patients was not associated with increased thromboembolic and bleeding rates as compared with higher intensity anticoagulant therapy in western countries.[74] Under this context, the warfarin maintenance dose (INR 2-3) might not be suitable for Taiwanese as Asians may be less vulnerable to thrombotic events than Caucasians that might be related to the great inter-individual and inter-ethnic differences of the warfarin effect.

ANTIARRHYTHMIC DRUG THERAPY

Ventricular arrhythmias are common in heart failure patients, and sudden cardiac death continues to account for a significant proportion of the mortality in heart failure patients. Many antiarrhythmic drugs have adverse hemodynamic effects sufficient to have negative consequences in patients with heart failure. Patients with heart failure are at higher risk of proarrhythmic effects when using antiarrhythmic agents. The major role for the use of antiarrhythmic agents in heart failure is to reduce recurrences of symptomatic atrial or ventricular arrhythmias, usually in patients who have an ICD.

Although nonsustained VT may play a role in triggering ventricular tachyarrhythmias, antiarrhythmic drugs to suppress premature ventricular depolarizations and nonsustained ventricular arrhythmias have not improved survival. Furthermore, most antiarrhythmic drugs have negative inotropic effects and can increase the risk of serious arrhythmia; these adverse cardiovascular effects are particularly prone to occur in patients with low LVEF. This risk is especially high with the use of class IA agents (quinidine and procainamide), class IC agents (flecainide and propafenone), and some class III agents

(d-sotalol), which have increased mortality in post-myocardial infarction trials. Amiodarone is a class III antiarrhythmic agent but differs from other drugs in this class in having a sympatholytic effect on the heart. Amiodarone has been associated with overall neutral effects on survival when administered to patients with low LVEF and heart failure.

Recommendations for use of antiarrhythmic drug therapy in heart failure

- Drugs known to adversely affect the clinical status of patients with heart failure and reduced LVEF should be avoided or withdrawn whenever possible; e.g., nonsteroidal anti-inflammatory drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs.[75-77]
- Antiarrhythmic drugs, including amiodarone, are not recommended for the primary prevention of sudden death in patients with heart failure.
- Routine, prophylactic use of antiarrhythmic drugs in patients with asymptomatic, non-sustained ventricular arrhythmia is not recommended. In heart failure patients, class Ic agents should not be used.
- In patients with heart failure and an ICD, amiodarone may be considered to reduce the frequency of recurrent symptomatic arrhythmias causing ICD shocks.[78]
- It is recommended that when amiodarone therapy is initiated, the potential for interactions with other drugs be reviewed. The maintenance doses of digoxin, warfarin, and some statins should be reduced when amiodarone is initiated and then carefully monitored. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended.
- Routine use of amiodarone therapy for asymptomatic arrhythmias that are not contributing to heart failure or ventricular dysfunction is not recommended.
- If beta-blockers are ineffective or contraindicated in patients with atrial fibrillation and heart failure, amiodarone may be a useful alternative for rate control of atrial fibrillation.[79] Also, amiodarone remains the agent most likely to be safe and effective when antiarrhythmic therapy is necessary to prevent recurrent atrial fibrillation.
- Dronedarone is contraindicated in patients with NYHA functional class IV heart failure or symptomatic heart failure with recent decompensation requiring hospitalization because it doubles the risk of death.[80]
- Dronedarone is contraindicated in patients with permanent atrial fibrillation and heart failure. Dronedarone doubles the risk of cardiovascular death (largely arrhythmic) and heart failure events in patients with permanent atrial fibrillation. Patients treated with dronedarone should undergo monitoring of cardiac rhythm no less than every 3 months. Cardiovert patients who are in atrial fibrillation (if clinically indicated) or discontinue dronedarone.[80]

ACUTE HEART FAILURE THERAPY

The goals of acute heart failure therapy are to improve clinical symptoms, stabilize hemodynamic status and minimize cardiac and other vital organ damage.[10]

Hospitalization

Hospitalization should be considered in acute heart failure patients presenting with severe clinical symptoms and sign which outpatient management seems to be less effective, and in patients who present significantly unstable hemodynamic status.[12] Moreover, hospitalization also is recommended in acute heart failure patients who require invasive or surgical interventions for diagnosis or treatment.

Monitoring

Acute heart failure patients should be monitoring carefully.[10] Non-invasive monitoring for vital signs, oxygenation, urine output and ECG is advised. Arterial line insertion is recommended in patients with unstable hemodynamics or when frequent blood samples are required. Central venous catheter should be considered for evaluating central venous pressure and venous oxygen saturation. Furthermore, it is useful in delivery of fluids or drugs.[10] Pulmonary arterial catheter is not recommended to implant routinely unless in patients whose diagnosis of cardiogenic etiology is questionable or who are not respond traditional management toward to heart failure. Moreover, hemodynamic data from monitoring devices should be interpreted carefully. Incorrect interpreting of hemodynamic data may result in inverse outcomes.[81]

Predisposing factors

It is recommended to evaluate the potential predisposing factors which lead to deterioration of cardiac function rapidly in acute heart failure patients. Identification and treatment for predisposing factors is important in management of acute heart failure and may prevent recurrence of acute heart failure.[12]

Recommendations of non-pharmacological therapies in acute heart failure

Water and sodium restriction

Hyponatremia in patients with acute heart failure mainly resulted from volume overload and it was demonstrated that hyponatremia was correlated with prolonged hospitalization and increased mortality.[82-84] However, it is hard to correct hyponatremia only by administrating sodium. In acute heart failure patients with refractory volume overload or moderate to severe hyponatremia (less than 125 mEq/L), adjuvant managements with water restriction (2 L/day) and/or strict sodium restriction (2 g/day) is considered.

Oxygen supplement

Oxygen supplement is recommended for acute heart failure with hypoxia and the goal of oxygen supplement is to keep arterial saturation up to 95% or up to 90% in patients with chronic obstructive pulmonary disease.[10] Acute heart failure patients without hypoxia don't need oxygen supplement routinely.[12]

Non-invasive ventilation

The efficacy of non-invasive ventilation on reducing the proportion of intubation and short-term mortality in acute heart failure patients with pulmonary edema has been documented.[85,86] It is recommended that non-invasive ventilation should be initiated as early as possible in acute heart failure patients with dyspnea and respiratory distress if no obvious contraindication.[10] A positive end-expiratory pressure of 5 cmH_2O is applied initially and is titrated up to 10 cmH_2O based on clinical response. Moreover, the delivery of the fraction of O_2 should be more than 40%. Potential adverse effect of non-invasive ventilation included worsening of right heart function, hypercapnia, anxiety, or aspiration.

Ultrafiltration

Ultrafiltration should be considered in the management of fluid retention and congestion in acute heart failure patients with poor response to diuretics or co-existing renal dysfunction.[10] Some studies had demonstrated the efficacy of ultrafiltration in reduction of fluid retention and in acute heart failure patients.[12,87]

Recommendations of pharmacological therapies in acute heart failure

Diuretics

Diuretics are indicated in acute heart failure patients with congestion and fluid overload. Loop diuretics with bolus or continuous infusion are recommended for symptom relief. In acute heart failure patients with impaired renal function or with chronic oral diuretic use, higher dose of intravenous diuretics is considered.[10] Combination therapy with loop diuretics and non-loop diuretics is reasonable for patients with diuretic resistance.[10,12] The recommended dosage and potential side effects are summarized in Table 5.

Vasodilators

Intravenous nitrates or sodium nitroprusside help to relieve congestion and reduce the necessary of high dose of diuretics use.[10,12] Vasodilator should not be used in patient with low systolic blood pressure (SBP < 90 mmHg). The recommended dosage and potential side effects are summarized in Table 5.

Inotropes

In acute heart failure patients with low cardiac output or congestion despite the use of diuretics and/or vasodilators use, inotropes use is reasonable.[10] However, dopamine use in patients with tachycardia is not recommended. Moreover, dobutamine should be gradually tapering and simultaneously oral therapy while the conditions of the patients improve. The recommended dosage and potential side effects are summarized in Table 5.

Vasopressors

Vasopressors are considered in acute heart failure patients with cardiogenic shock or inadequate organ perfusion despite the use of inotropes and adequate fluid repletion.[10,12] The recommended dosages and potential

Table 5. Recommended pharmacological therapies in acute heart failure

Medication	Beneficial Subset	Initial Dose	Recommended Maximal Dose	Potential Side Effects
Diuretics	Fluid overload (congestion; ascites; dyspnea; weight gain)	Furosemide: 20-40 mg intravenous infusion Bumetanide: 0.5-1.0 mg intravenous infusion	Up to clinical symptoms; intermittent bolus or continuous infusion	Hypokalemia; Hyponatremia; Hyperuricemia
Vasodilators	Fluid overload	Intravenous nitrates: 10-20 μg/kg/min Sodium nitroprusside: 0.3 μg/kg/min Nesiritide: 0.015 μg/kg/min	Intravenous nitrates: up to 200 μg/kg/min Sodium nitroprusside: up to 5 μg/kg/min Nesiritide: up to 0.03 μg/kg/min	Headache; Hypotension; Tachyphylaxis
Inotropes	Low cardiac output; Poor response to diuretics and/or vasodilators	Dobutamine: 2-3 μg/kg/min Dopamine: 2-3 μg/kg/min Milrinone: 0.3 μg/kg/min	Dobutamine: up to 20 μg/kg/min Dopamine: up to 20 μg/kg/min Milrinone: up to 0.7 μg/kg/min	Atrial or ventricular arrhythmia; Hypotension
Vasopressors	Cardiogenic shock; inadequate organ perfusion after inotropes use	Norepinephrine: 0.2 μg/kg/min Epinephrine: 0.05 μg/kg/min	Norepinephrine: up to 10 μg/kg/min Epinephrine: 0.5 μg/kg/min; bolus dose with 1 mg is considered during resuscitation	Atrial and ventricular arrhythmia; inversely impair organ perfusion due to severe vasoconstriction effect

side effects are summarized in Table 5.

ACEI/ARB

ACEI/ARB is considered in acute heart failure patients who have high risk to develop chronic heart failure or in acute heart failure patients with acute myocardial infarction. Initiation of ACEI/ARB therapy is suggested before discharge if indicated.[10]

Beta-blockers

The dose of beta-blocker should be reduced temporarily in patients with acute heart failure. Beta-blocker should be considered to resume or start before discharge if no contraindication.[10]

HEART FAILURE WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION

Approximately 40% to 50% of patients with heart failure have preserved LVEF, variably defined as LVEF > 40%, > 45%, or > 50%.[88-90] In the past, HFpEF has been classified as "diastolic" heart failure in opposition to "systolic" heart failure, which frequently been referred to heart failure with reduced ejection fraction (HFrEF). It is important to identify and treat HFpEF patients early because long-term prognosis was equally poor in both HF types, as well as both men and women.

Diagnosis

Most of clinical doctors used to pay attention and focused on the importance of HFrEF, even though the morbidity and mortality in HFpEF are similar to HFrEF.[90] To date, no diagnostic 'gold standard' exists for HFpEF. In clinical practice, its diagnosis is largely based on the finding of typical symptoms and signs of heart failure in a patient who is shown to have a "normal" LVEF and no significant valvular abnormalities on echocardiography.

The cardinal symptoms of dyspnea and fatigue when combined with signs of fluid retention – lung crackles, elevated jugular venous pressure and peripheral edema – usually lead one to the diagnosis. With echocardiographic measures, the findings in HFpEF may be characterized by left atrial enlargement, elevated filling pressures, left ventricular hypertrophy, and abnormal left ventricular filling kinetics on mitral flow velocity. However, HFpEF is more prevalent in the elderly, in women, in obese people and in patients with a history of long-standing hypertension, less often, coronary artery disease. Activation of the neurohormonal milieu, including the

renin-angiotensin system and the sympathetic nervous system, is rather common in HFpEF. Some studies have reported that BNP or NT-proBNP levels are less elevated (or only marginally elevated) in HFpEF than in HFrEF.

Recommendations for management of HFpEF

In general, the treatment of HFpEF remains difficult and often unsatisfactory. The transfer of HFpEF patients to an expert should be encouraged. First step is to confirm the diagnosis and to exclude out other diseases presenting similar symptoms and signs. It is very important to identify and correct the comorbidities, such as hypertension and tachyarrhythmia, that are often associated with HFpEF. Counseling on the use of a low-sodium diet is recommended for all HFpEF patients. The prognosis and quality of life for patients with HFrEF has been markedly improved by the implementation of evidence-based treatments including therapy with beta-blockers and inhibitors of the renin-angiotensin-aldosterone system. On the other hand, no treatment has been proven to alter the natural history of HFpEF. Treatment remains empirical, and is aimed at controlling associated conditions and symptoms and signs of fluid retention. Diuretic, beginning with either a thiazide or loop diuretic, may be necessary when episodes with fluid overload are present, but should be used cautiously so as not to decreases in cardiac output and compromise of renal function. In a recent analysis of the very large ALLHAT trial[91] of patients with hypertension and aged over 55 years, antihypertensive treatment with chlorothiazide was associated with a lower risk of developing HFpEF when compared with treatment with lisinopril, amlodipine or doxazosin. Therapeutic trials of other drug classes in HFpEF have been limited, and generally disappointing.

Unlike in HFrEF, ACEI or ARB in PEP-CHF,[92] CHARM-Preserved,[88] and I-PRESERVE[89] did not show convincing evidence for a prognostic benefit in HFpEF patients. However, CHARM-Preserved observed fewer heart failure hospitalizations in the candesartan-treated patients. Beta-blockers may be promising. The SENIORS study[93] showed similar beneficial benefits of nebivolol, a vasodilating beta-blocker, in older patients with either HFpEF or HFrEF; however, the definition of HFpEF in that study was a LVEF of greater than 35%. The OPTIMIZE-HF analysis reported that among HFpEF patients, compared with HFrEF patients, treatment with ACEIs, ARBs, or beta-blockers didn't improve 1 year mortality or hospitalization rates.[94] Thus, the potential therapeutic effect of beta-blockers remains uncertain despite these trials, and there should be equipoise for a randomized clinical trial. In practice, beta-blocker treatment may be particularly useful in patients with HFrEF who have prior myocardial infarction or atrial fibrillation requiring control of ventricular rate. Verapamil-type calcium antagonists may be used to lower heart rate and increase the diastolic period. Some studies with verapamil have shown a functional improvement in patients with hypertrophic cardiomyopathy.[95] Clearly, more trials are needed.

DEVICE THERAPY

Heart failure is a chronic and debilitating disease in Taiwan and cardiovascular disease remains the No. 2 cause of death. Chronic heart failure has become an epidemic in Taiwan. It is evident that incidence was highly dependent on age in either sex and was especially high in elderly subjects aged > 65 years.[96] Patients with heart failure generally die of one of two causes: progressive heart failure or unexpected cardiac death. In the progress of heart failure, electrical-conduction disturbances are now recognized to be important causes of left ventricular dysfunction. CRT can restore more-normal electrical contraction and, when combined with defibrillation, can have a major impact on the mortality and morbidity of heart failure.[97,98] Implantable cardioverter-defibrillator (ICD) therapy has had a major impact on the treatment of heart failure. The ICD has been shown to decrease mortality relative to the best medical therapy in patients who have survived an episode of sustained VT or ventricular fibrillation (VF) and accepted as a guideline therapy for patients with left ventricular dsyfunciton.[99] Unfortunately, only a small minority of patients who experience an out-of-hospital cardiac arrest are successfully resuscitated. Thus, ICD therapy has been applied for the primary prevention of sudden death in patients at high risk of cardiac arrest in the developed countries such as American and European countries. However, there are many regulations of device reimbursement by the national health insurance bureau in Taiwan because

of economical consideration. Although there remain many limitations and challenges to the appropriate application of ICDs or CRT defibrillators in Taiwan, there is no question that device therapy has had a major impact on the management of patients with left ventricular dysfunction. While a number of pharmacologic therapies have shown effectiveness, we will discuss about the advances in the treatment of chronic heart failure in this chapter.

Recommendation for CRT in chronic heart failure

The clinical effects of long-term CRT have been evaluated in a large number of randomized multi-center trials with crossover or parallel treatment assignment, using CRT pacemakers or CRT defibrillators.[11,97-99] The clinical effects of long-term CRT have been evaluated in a large number of randomized multi-centre trials. In the COMPANION trial,[100] CRT with or without an ICD, lowered the combined endpoint of all-cause mortality and rehospitalization for heart failure by 35-40%, mainly driven by the 76% lower rate of hospitalizations. In CARE-HF trial,[101] CRT pacemaker lowered the proportion of unplanned hospitalizations for worsening heart failure by 52%, and the number of unplanned hospitalizations for major cardiovascular events by 39%. Numerous single-center studies indicated that the assessment of mechanical dyssynchrony helps predict response to CRT. However, two multi-center studies disprove the idea that the conventional assessment of mechanical dyssynchrony is useful for CRT patient selection.[102]

Practice with regard to the choice of the CRT device varies widely between countries. In current regulations of national health insurance bureau in Taiwan, the criteria of complete left bundle branch block is mandatory for CRT application. CRT pacemaker rather than CRT defibrillator is reimbursed by the insurance if the patient has no evidence of VT or VF before application. According to the recommendations of ACC/AHA/HRS/ESC,[11,99] the indications are listed in Table 6.

Recommendations of ICD for heart failure

ICD therapy for secondary prevention is recommended for survivors of VF and also for patients with documented hemodynamically unstable VT and/or VT with syncope. ICD will be reimbursed by the insurance on the existence of VT or VF in the regulations of national health insurance bureau in Taiwan. In Taiwan registry, clinical presentations included sudden cardiac death due to VT/VF in 38% patients, syncopal VT in 27%, drug refractory non-syncopal VT in 29%, and unexplained syncope with inducible sustained VT/VF in 6%. The mean age was significantly younger than that in CIDS or AVID (59 ± 16 vs. 63 ± 9 years in CIDS, $p = 0.02$; vs. 65 ± 11 years in AVID, $P < 0.001$).[103]

For primary prevention, a patient with LVEF ≦ 40% due to myocardial infarction or ≦ 35% due to non-ischemic cardiomyopathy in NYHA functional class II or III, on optimal medical therapy, and with an expectation of survival with good functional status for over 1

Table 6. Indications for cardiac resynchronization therapy in heart failure

Class I	Class IIa	Class IIb	Class III
• NYHA Fc III or ambulatory Class IV • Optimal medical therapy • Sinus rhythm • QRSd ≧ 120 ms • CLBBB* • LVEF ≦ 35%	• NYHA Fc III or ambulatory Class IV • Optimal medical therapy • AF or pacing dependent • QRSd ≧ 120 ms • CLBBB* • LVEF ≦ 35%	• NYHA Fc I-II • Optimal medical therapy • QRSd ≧ 120 ms • LVEF ≦ 35%	• Asymptomatic with reduced LVEF in the absence of other indications for pacing • Functional status and life expectancy are limited by chronic noncardiac conditions
ESC gudieline (2010) • NYHA FC II • QRSd ≧ 150 ms • LVEF ≦ 35%			

CLBBB, complete left bundle branch block; Fc, functional class; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; QRSd, QRS duration.

year. Others include structural heart diseases with high risk factors which will lead to sudden cardiac death such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia/cardiomyopathy, long QT syndrome, Brugada syndrome, cardiac sarcoidosis, giant cell myocarditis, or Chagas disease.

SURGERY & SURGICAL DEVICES

Despite advances in medical management of heart failure, there remain circumstances in which surgical procedures are the only or the best treatment option. To simply the surgical options, we arbitrarily divided into two groups for each according to reversibility and pathology of heart failure as the followings: acute potentially reversible vs. chronic irreversible; and ischemic vs. non-ischemic.

Recommendations for surgical treatments of heart failure

Acute, potentially reversible mechanism

- If refractory to maximal medical treatment, intraaortic balloon pump is the first option unless contraindicated.
- If hemodynamics deteriorate with intraaortic balloon pump support, extracorporeal membrane oxygenation may be considered as a "bridge to recovery".
- If cardiac function does not recover after 7 days of extracorporeal membrane oxygenation support and no other anatomically correctable etiologies exist, listing to heart transplant should be considered.[104]
- If contraindicated to transplant temporarily because of compromised systemic organs, short-term ventricular assist device should be considered as a "bridge to decision."
- If contraindicated to transplant due to age limitation but preserved systemic organs, permanent implantable ventricular assist device may be considered as a "destination therapy".

Chronic, irreversible mechanism

- If refractory to maximal medical treatment and conventional surgical treatment, listing to heart transplant should be considered if fulfilling the criteria and not contraindicated.
- If contraindicated to heart transplant due to age limitation but preserved systemic organs, permanent implantable ventricular assist device may be considered as a "destination therapy".
- If hemodynamics crash and burn while awaiting heart transplant, extracorporeal membrane oxygenation or short-term ventricular assist device should be considered as a "bridge to transplant".
- If patients, awaiting heart transplant and associated with severe mitral regurgitation secondary to ventricular dilatation, who need repeated hospitalizations for intravenous inotropic therapy because of pulmonary hypertension, mitral repair or replacement may be considered to prolong waiting time in transplant list.

Ischemic etiology

- Revascularization, either percutaneous coronary intervention or coronary artery bypass grafting, should be considered if myocardial viability proved.
- If impaired LVEF, high SYNTAX score, combined severe mitral regurgitation and/or apical aneurysm, coronary artery bypass grafting should be provided as the first revascularization option.
- Partial left ventricular resection "Batista procedure" is not recommended but surgical ventricular restoration may be considered if fulfilling the "original STICH trial" criteria and performed only by experienced surgeons after cardiac magnetic resonance imaging study.
- If heart failure symptom/sign persisted with debilitating refractory angina and/or ventricular arrhythmia and repeated revascularization therapy is not feasible, listing to heart transplant should be considered.
- ICD should be provided while awaiting heart transplant if fulfilling the current government insurance criteria.

Non-ischemic etiology

- CRT should be considered if fulfilling the criteria.
- If patients are CRT non-responders and have severe mitral regurgitation secondary to ventricular dilatation, while experiencing repeated hospitalizations for intravenous inotropic and diuretic therapy because of pulmonary hypertension, mitral repair or replacement may be considered before listing to transplant.[105]

- If heart failure symptom/sign persists and deteriorates after maximal medications and conventional surgical operations, listing to heart transplant should be considered.
- ICD should be provided while awaiting for transplant if fulfilling the current government insurance criteria.
- If contraindicated to heart transplant due to age limitation but preserved systemic organs, permanent implantable ventricular assist device may be considered as a "destination therapy" in highly selected patients, particularly those who need repeated hospitalizations for intravenous inotropic support at an experienced heart failure center.

Heart transplantation

Wei et al.[106] reported their heart transplantation experiences in a single medical center in 2008. Since 1987, they have performed 288 heart transplantation. Actuarial survival rates at 1, 5, and 10 years are 86%, 76%, and 61%, respectively. Heart transplantation remains a definitive therapy for patients with end-stage heart failure.

Because of this critical organ shortage, the recipient selection process and the donor allocation system have become both ethical and clinical issues.

Absolute contraindication

Increased pulmonary vascular resistance - The major hemodynamic factor excluding cardiac transplantation is a pulmonary vascular resistance greater than 4 to 6 Wood units (normal ≤ 1.5 Wood units). Patients with an elevated pulmonary vascular resistance or a transpulmonary gradient (mean pulmonary artery pressure minus mean pulmonary capillary wedge pressure) above 15 mmHg have an increased risk of right ventricular failure in the immediate postoperative period.

Infection - Active infection can be worsened by the immunosuppressive therapy given to prevent transplant rejection.

Malignancy - Even without preexisting disease, the incidence of malignancy is increased following transplantation. However, patients with a remote history of cured malignancy, many of whom develop their cardiomyopathy as a consequence of chemotherapy for the malignancy, are considered reasonable candidates for transplantation.

Relative contraindication

Age - Age has historically been a major factor of relative contraindication. Many programs have routinely excluded patients over the age of 60 to 65, but most feel that physiologic age is more important than chronologic age.

Diabetes mellitus - Diabetes mellitus particularly with evidence of significant end-organ damage, is a relative contraindication to heart transplantation.

Advanced obstructive and/or restrictive lung disease - Advanced obstructive and/or restrictive lung disease is associated with a higher incidence of postoperative lung complications, including infection associated with immunosuppressive therapy. Objective exclusion criteria include a forced one-second expiratory volume (FEV1) of less than 1.0 liter, a forced vital capacity of less than 50 percent of predicted, or a forced expiratory volume-to-vital capacity ratio of less than 1.0.

Recent pulmonary embolism - Recent pulmonary embolism with or without infarction should delay transplantation, because secondary infection in the affected lobe may occur postoperatively.

Advanced hepatic disease - Advanced hepatic disease can limit survival and increase perioperative morbidity, particularly if a coagulopathy is present.

CARDIAC REHABILITATION

Introduction

Heart failure, the end stage heart disease of heterogeneous etiologies, was characterized with low cardiac pumping ability, low aerobic capacity and exercise intolerance. Investigators have now shown that regular exercise in heart failure patients produces positive effects with minimal risks. Regular physical activity is recommended for all patients when medically stable, using a tailored cardiac rehabilitation program based on the result of cardiopulmonary exercise test and individualized factors. The main focus is to avoid "disability" and improve "wellness".

For most patients, exercise prescription should include an aerobic (endurance) exercise performed at least 3 times per week (and preferably on most days of the week) and a resistant (strength) training twice per week with low to moderate intensity.

Encourage patients to join cardiac rehabilitation programs

Exercise instruction should be included as a part of a comprehensive heart failure program. Referral to a cardiac rehabilitation program is recommended as soon as possible for bedside intervention to prevent from complications associated with immobilization, and will contribute to patients' compliance with exercise, functional improvement and quality of life. Patients join an advanced cardiac rehabilitation program for 36 supervised exercise sessions after a cardiopulmonary test, which provides the starting point of a tailored cardiac rehabilitation program.

Design a safe and tailored cardiac rehabilitation program (Table 7)

Adequate monitoring is needed. Emergent medial support facilities should be readily available. To set cardiac rehabilitation unit nearby cardiology ward is strongly recommended. Furthermore, a formal cardiac rehabilitation program should also contain the education for life-style modification. Disease manager plays a critical role in this component.

Three basic types of exercise

- Flexibility exercise (stretch exercise): Stretching muscles could be the choice in warm-up and cool-down phase.
- Aerobic exercise: The part of aerobic exercise should be emphasized. It includes any activity that preferentially uses large muscle groups and can be maintained for a prolonged period (e.g., walking).
- Strengthening training (needs professionals to design): Isometric physical activity with heavy straining should be avoided, as it may increase left ventricular afterload. Isokinetic muscle-strengthening physical activity has been used safely in patients with heart failure.

General exercise recommendations[107-110]

- Wait at least 90 minutes after a meal before aerobic exercise.
- Gradually increase the activity level, especially if the patient has not been exercising regularly.
- Remember to have fun! Choose an activity that the patient enjoys – exercising should be fun and not a chore, so that the patient will be more likely to stick to an exercise program. Here are some questions your patients can think about before choosing a routine exercise program:
  - What physical activities do I enjoy?
  - Do I prefer group or individual activities?
  - What programs best fit my schedule?
  - Do I have physical conditions that limit my choice of exercise?
  - What goals do I have in mind? (losing weight, strengthening muscles or improving flexibility, for example)
- Every exercise session should include a warm-up, conditioning phase, and a cool-down (at least 15 minutes for warm-up and cool-down phase). It allows your body to gradually prepare for and recover from the conditioning phase.
- When drinking liquids during exercise, remember to follow the fluid restriction guidelines.
- Dress for the weather conditions and wear protective footwear.
- Schedule exercise into the daily routine. Plan to exercise at the same time every day (such as in the mornings when your patients have more energy). Add a variety of exercises so that your patients do not get bored.
- Exercise at a steady pace that is effective.
- Exercise does not have to put a strain on patients' wallet. Think twice before buying expensive equipment or health club memberships unless your patients are certain that they will use them regularly. There are

Table 7. Benefits and concerns of regular exercise

Benefits of regular exercise:
1. strengthen the heart and cardiovascular system
2. reduce risk factors
3. improve circulation and ventilation efficacy
4. decrease symptoms
5. do more activity of daily life without dyspnea
6. lower blood pressure
7. improve muscle strength and tone
8. improve balance and flexibility
9. strengthen bones
Questions need to ask before exercise
1. amount of exercise in a day
2. frequency of exercise in a week
3. kind of exercise to do
4. kind of exercise to avoid
5. medication considerations for exercise
6. necessity of pulse rate monitoring during exercise

plenty of other activities that can be done with no extra cost (e.g., walking).
- Keep an exercise record. This will allow your patients to see their progress.

Duration and frequency of exercise

Duration of exercise
- Initially, multiple 10-minute bouts distributed throughout the day may be optimal for some patients.
- During the first two to six weeks of participation, exercise duration could be gradually increased from 30 minutes to 45 minutes or more. This does not include the warm-up, cool-down or stretching periods.
- Duration should be increased before intensity is increased.

Frequency of exercise

To achieve maximal benefits, your patients should gradually work up to an aerobic session lasting 20 to 30 minutes, at least 3 times per week (and preferably on most days of the week).

Items to be alerted when doing exercise
- If the patient does not feel well.
- If the patient has unusual cough or wheezing.
- Extreme weather (too cold or too hot): consider indoor exercise.
- Deterioration in a patient's clinical status may necessitate a reduction in the dose of physical activity until clinical stability is achieved.

Items to stop exercise
- Abnormal responses to exercise, such as lightheadedness, chest pain, marked dyspnea, or unusual fatigue.
- Unusual shortness of breath, or palpitation.
- Extreme tiredness or any unusual symptoms.
- Acute exacerbation of heart failure, or unstable conditions.

THERAPEUTIC LIFE-STYLE MODIFICATIONS

Individualized education on heart failure knowledge before hospital discharge[111-115]

Medications

Patient should be able to (1) tell the name, dosage, purpose, and adverse effects of all prescribed guideline-based medications; (2) identify which drug is diuretic, and understand the timing of using additional diuretics; and (3) know and can tell the behavior that could worsen the condition of heart failure: for example, should avoid nonsteroidal anti-inflammatory drugs, unexpected discontinuation of heart failure medications, and avoid taking herb drugs.

Diet

Patients themselves or assisted by their caregiver should know their nutritional status, can tell the allowed amount of food and water intake for a day, and know how to calculate the sodium content of food, so as to discriminate high and low salt diet.

Daily record

Patients themselves or assisted by their caregiver should be able to (1) record their blood pressure, pulse rate, body weight, and intake amount everyday in a regular booklet; (2) know the time to return to the clinic, and to bring their record booklet to the clinic; and (3) know the target body weight that should maintained at home, and when they should contact the heart failure team based on the changes in body weight.

Familiarity with the symptoms of deteriorated heart failure

Patients should be able to independently tell the symptoms indicating heart failure deterioration. Furthermore, in response to a condition simulating a status of deteriorated heart failure, patients should be tested whether they themselves or assisted by their caregiver are able to contact the team member for further handling. Patients should know their own risk factors associated with heart failure deterioration, and know the therapeutic target for each risk factor, such as "should quit smoking", "should lower cholesterol level less than 200 mg/dL", and "daily exercise program and duration".

Self care at home[111,114-120]

Medications

Patients should know that they should regularly take the prescribed medications every day and how to

take medicine when they miss the last dose; for example, they should avoid overdose. It's better to have a 2-hour break before the next dose. Patients should know that the up-titration in medication dosage by doctor is to strengthen the cardiovascular protective effect. To comply with the adjustment of drug dosage in the beginning, the patient should be aware of monitoring blood pressure, heart rate, and the timing to contact the heart failure team if there are any discomfort, such as dizziness, chest tightness, breathless feeling, wheezing, and decrease in activity. Do not inappropriately withdraw all medications without notifying the team member.

They should know when to put diuretics on hold if there is poor appetite, decreased intake amount, diarrhea, and body weight loss. In the meantime, they should contact the heart failure team to monitor electrolyte imbalance and kidney dysfunction. Importantly, they should refuse using non-qualified herb drugs. If they have to, ask the patients to discuss with the heart failure team to avoid the side effect on kidney derived from combined use of Chinese and Western medicines.

Diet[12,116]

Patients should (1) control the amount of food and water intake within the suggestion of doctors and nutritionists. Take recordings in detail and control the body weight within 2 kg of the targeted body weight set by doctors; (2) learn how to calculate the salt content of boxed, canned, frozen, and bagged food. Patient should know how to choose a low salt diet appropriate for heart failure; (3) make the initiative to ask the restaurant to prepare dishes with less salt or monosodium glutamate when having dinner with family or friends in a restaurant. If the dishes are accompanied with sauce, gravy, or salad dressing, please request that the sauce is put aside for individualized use; and (4) take the initiative to refuse food with high salt content, such as processed or smoked food, pickles, tomato sauce, stock, instant soup, and fast food

Daily record

Patients should be able to (1) record the blood pressure, pulse rate, body weight, and intake amount everyday in a regular booklet; (2) measure body weight before breakfast with empty bladder in the morning to compare the target body weight set by the cardiologist. Patients should notify the heart failure team if there are 2 kg of body weight increase or decrease;[12] (3) take a record for all the details regarding to the predisposing and relieving factors, and all the associated information if there are any symptoms related to heart failure deterioration such as chest pain or tightness, dizziness, fainting, or leg edema. Discuss with the cardiologist regarding the records, and the possible treatment plan; and (4) take a record in detail with respect to the reasons and frequency if the patient takes extra dose of medications, such as diuretics, or rate-controlling or blood pressure controlling medications.

Familiarity with the symptoms of deteriorated heart failure

Patients themselves should observe any symptoms or signs suggesting "worsening", such as increased respiratory rate during regular activity at home, and leg edema, etc. They should also be educated to observe and identify any symptoms associated with deteriorated coronary artery disease, such as chest pain and tightness. If flu or a cold is noted or suspected, patients may visit heart failure unit to have a management with cautions specifically to avoid fluid accumulating effects of NSAID, anti-histamines and analgesics. If patients search for medical assistance at a general practitioner, they should notify doctors the history of heart failure to avoid fluid overload and possible pulmonary edema complicated by massive intravenous fluid supplementation. Patients should be aware of the acceptable and safety range of their blood pressure, pulse rate, and body weight. Based on this understanding, they can identify any abnormalities, such as hypotension, abnormal heart rate, or body weight changes related to deteriorated heart failure, so that they can notify the heart failure team on the first hand.

Cardiac rehabilitation

When stabilized (approximately one month after an acute episode), patients should get started with a full course of cardiac rehabilitation (36 times a course) to avoid disability, improve wellness, and tolerate basic requirement of activity at home and at work. In addition, patients should discuss with their doctors if they will take works or loads over the range of their allowed regular activity.

Regular follow-up at clinic

Patients should take regular exams such as echocardiogram to estimate the effect of ongoing treatment strategy. When developing deteriorated symptoms and signs, patients should take extra-exams as early as possible, including ECG, Chest X-ray, echocardiogram, kidney function and electrolytes assessment.

Vaccinations

Pneumococcal and influenza immunization have been shown to lower the re-hospitalization rate and shorten the length of stay in hospital in the elderly with heart failure.[122]

Multidisciplinary heart failure team

Heart failure patient education is an essential component at assisting patients to conduct self-care. Several randomized studies have demonstrated the beneficial effects of organizing a multidisciplinary team on the prevention and management of symptoms, decrease in re-hospitalization, and decrease in morbidity and mortality rates. Team members include cardiologist, well-trained disease manager, pharmacist, dietician, cardiac rehabilitation specialist, physical therapist, psychiatrist, and social worker.[111,114,119]

Taiwan experiences

Based on the report in Taiwan with respect to heart failure self-care behavior,[122] 70%~80% of patients did not perform daily body weight record or monitor lower limbs edema, 51.2% of patients were unable to identify the symptoms related to worsening heart failure (such as dyspnea or lower limbs edema), and only 18.6% of patients had the initiative to take low salt diet in a restaurant.

After in-hospital individualized disease education, patients' heart failure-related knowledge improved from 43 ± 27 to 84 ± 14 (Dutch Heart Failure Knowledge score), and self-care behavior improved as well. Under the multidisciplinary disease management program, more than 90% of patients clearly know the target body weight set by the cardiologist, and the appropriate timing of taking diuretic and calling for help. Furthermore, this kind program remarkably lowers the 3-month heart failure-related re-hospitalization rate (Table 8), and significantly improves patients' health-related life quality.

According to the official report from Taiwan National Healthcare Bureau in 2005, the age in the heart failure population in Taiwan was similar to the data in United States (The rate of heart failure patients with age > 65 years old was 78.4% in Taiwan and 80% in America). Tseng et al. found that the average length of stay in hospital in Taiwan was longer than that in United States (15.8 days versus 5.7 days). The in-hospital mortality was also higher in Taiwan (4.2% versus 3.7% in United States).[96] Clinical outcomes, use of medications, and heart failure related expenses in three domestic hospitals with heart failure disease management programs are shown in Table 8.

NUTRITIONAL RECOMMENDATIONS

Comprehensive nutritional care includes management of risk factors for the development of heart failure, dietary modifications for the clinical syndrome of heart failure, and the prevention of malnutrition. Dietary instructions regarding sodium and fluid intake are recom-

Table 8. Clinical outcomes, use of medications, and heart failure related expenses in 3 hospitals with heart failure center services

Variables	Results (%)
In-hospital mortality rate	9.67
Mortality rate in a year	10.6~12.5
Re-hospitalization rate	
HF-related in 30 days	3.1~14.5
All cause-related in 30 days	9.8~17.2
HF-related in 90 days	12.2~23.3
All cause-related in 90 days	27.6~30.3
HF-related in 1 year	18.7~34.2
All cause-related in 1 year	39~45.1
Medications	
ACEI/ARB	75~98.9
Beta-blockers	62~92.3
HF clinic follow-up	97.5~100
HF-related expenses (NTD/per person/yr)	95,903~143,147

Because the data are from two medical centers and one regional hospital, the interpretation should be referred to different backgrounds in different areas.
HF, heart failure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NTD, New Taiwan dollars.

mended for all patients with heart failure. For patients with heart failure and the comorbidity of hypertension, diabetes or dyslipidemia, further dietary modifications should be considered.

Energy and macronutrients

The energy requirement of patients with heart failure is in the range of 25-35 kcal/kg body weight/day and needs to be modified for the patient's activity levels, nutritional status or medical conditions. While obesity is known to increase the risk of cardiovascular disease, evidence shows that increasing body mass index is associated with higher survival rate among patients with heart failure. If body mass index is below 30 kg/m^2, weight loss should not be encouraged. For intensive care unit patients, energy provided in excess of 25 kcal/kg body weight/day may be associated with a less favorable outcome. Furthermore, carbohydrates should not exceed 6 g/kcal/kg body weight/day and lipids should not exceed 2.5 g/kcal/kg body weight/day in critically ill patients. Providing 1.2-1.5 g/kg body weight/day of protein is generally recommended[124] and adjustment for impaired renal function should be considered.

For management of risk factors involving the development of heart failure, including hypertension, hyperlipidemia and diabetes, dietary suggestions should follow DASH,[125] NCEP-TLC,[126] JNC-7,[127] AHA,[128] ADA[129] and HFSA[12] guidelines. These components are summarized as followings:

- Limit saturated fat to < 7% of energy; trans fat to < 1% of energy; total fat to within 25%-35% of energy.
- Limit cholesterol to < 200 mg/day.
- Consume oily fish (high ω-3 fatty acids) at least twice a week; intake of EPA/DHA to 1-2 g/day for hypertriglyceridemia (200-499 mg/dL) and 2 to 4 g (capsules) daily for hypertriglyceridemia (> 500 mg/dL).
- Select whole grains, more vegetables and fruits to ingest 20-30 g/day (or 14 g/1000 kcal) of fiber; limit added sugar to < 10% of energy and fructose to < 100 g/day; limit carbohydrates to within 45-60% of energy – a lower limit is suggested for patients with poorly controlled blood sugar or very high serum triglyceride level.
- Restrict ethanol alcohol to 15 ml (women) or 15-30 ml (men) equivalents/day (Alcohol should be prohibited for patients with established heart failure or severe hypertriglyceridemia).

[Notes: DASH, dietary approaches to stop hypertension; JNC-7, joint national committee -7 report; ADA, American diabetes association; NCEP, national cholesterol education program; TLC, therapeutic lifestyle changes; HFSA, heart failure society of America; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.]

Sodium and fluid

Maintaining body fluid balance is the essential dietary intervention for heart failure. Dietary instructions to promote self-care and adherence to sodium and fluid restrictions can help minimize the risk of acute congestive episodes and hospitalization. A daily sodium restriction of 2400 mg is generally recommended for prevention of cardiovascular diseases. While limit sodium to the range of 2000-3000 mg/day is recommended by major guidelines,[12] a recent prospective follow-up study showed that high sodium intake (≧ 2800 mg/day) had a higher incidence of acute decompensated heart failure in ambulatory heart failure patients compared to lower intake groups (2000-2700 mg or ≦ 1900 mg).[130] Thus, limiting daily sodium to 2400 mg for patients with heart failure is appropriate. Further restrictions (< 2000 mg sodium/day) may be considered in moderate to severe heart failure. Suggestions for fluid intake can be made according to the balance of intake/output or daily body weight monitoring. A fluid restriction to below 2000 ml/day is recommended for severe hyponatremia (< 130 mEq/L).[12] For severely decompensated patients, a more restrictive fluid intake, 1000-1500 ml/daily, may be needed for adequate diuresis.[131] Fluid restrictions that include food sources, drinks and intravenous fluid should be carefully assessed.

Weight loss and cardiac cachexia

Severe weight loss or cardiac cachexia is associated with an increased mortality in patients with heart failure. There is no consensus on the definition of cardiac cachexia at the present time. A diagnostic criteria for cachexia in adults with chronic illness includes: 1) underlying disease, 2) weight loss of at least 5% in 12 month or less (or body mass index < 20 kg/m^2), and 3) at

least 3 of 5 clinical signs, such as decreased muscle strength, fatigue, anorexia, low fat-free mass index, abnormal biochemistry (inflammation/anemia/low serum albumin).[132] Another definition that has been used includes nonedematous weight loss of > 6% of the previous normal weight over a period of 6 months.[133] It has been estimated that around 15% of patients with advanced heart failure develop cachexia.[133] The physiological and metabolic changes of intestinal ischemia, malabsorption, anorexia, activated inflammatory cascades and hypercatabolism may contribute to malnutrition and cachexia in heart failure.[134]

Aggressive nutritional assessment and adequate nutrition support for heart failure are recommended to prevent cachexia. The levels of serum albumin, pealbumin and other biochemical markers of nutritional status are influenced by body fluid balance, therefore, other methods of nutritional assessment should be considered. The measurement of mid-upper arm circumference and triceps skin folds can be used for assessing protein-energy malnutrition in heart failure.[131] In general, small and frequent meal planning is tolerated well than large meal in patients with heart failure. For poor intake cases, caloric supplements with balanced nutrients and being concentrated given between meals are beneficial for nutrition support and fluid control.[135]

Micronutrients and nutraceuticals

Multivitamin-mineral supplementation to ensure adequate intake of the recommended daily value of essential nutrients is recommended.[12] Poor dietary intake and multiple drug therapies for heart failure can lead to electrolyte disturbances and/or micronutrients deficiency and may affect disease prognosis. Potassium, magnesium, thiamin, vitamin D, calcium and zinc are all important candidate for monitoring and supplementation.[134] The ω-3 fatty acids from fish oils have shown a beneficial triglyceride reduction[136] and a lower incidence of heart failure.[137] Fish oil may present a novel therapeutic approach in cardiac cachexia.[138] Avoid using natural or synthetic products containing ephedra (ma huang), ephedrine, or its metabolites because of an increased risk of mortality and morbidity.

PALLIATIVE/HOSPICE CARE FOR PATIENTS WITH ADVANCED HEART FAILURE

Heart failure is a progressive disease with significant morbidity and mortality, but prognostication often is difficult. Palliative/hospice care referral was recommended for end-stage heart failure (Level of Evidence 1A) in 2005 ACC/AHA heart failure guidelines.[3] Palliative care aims to relieve suffering by a multidisciplinary and holistic approach that addresses patients' and caregivers' physical, emotional, spiritual, and logistical needs. Heart failure is associated with a notoriously variable prognosis, which is a barrier to timely hospice referral.[139] Lack of hospice referral by providers is also related to many factors, including a lack of understanding of the role of hospice, lack of an identifiable terminal phase, and concerns about meeting hospice referral criteria.[140]

Before a patient is considered to be in refractory heart failure, physicians should confirm the accuracy of the diagnosis, identify precipitating factors, and ensure that all conventional medical strategies including medications or even electrical/mechanical devices which are indicated and helpful have been optimally employed. Although it is difficult to predict a palliative phase with a 6-month timeline in patients with end-stage heart failure, such patients are eligible for hospice enrollment. Reference criteria are shown in Table 9 to assist healthcare providers in determining the appropriateness of hospice care. Each of the criteria, including a diminished LVEF, refractory symptoms, and functional decline, is documented to ensure hospice coverage.

Table 9. Reference hospice referral criteria for end-stage heart failure (modified) [141]

1. The patient has persistent symptoms despite optimal pharmacologic and device therapies by cardiologists.
2. The patient has refractory symptoms with rest or minimal activity despite optimal therapy modalities (NYHA functional class IV or ACC/AHA stage D).
3. The patient has poor quality of life with an ejection fraction of left ventricle being less than 20%.
4. The patient has advanced, persistent heart failure with repeated hospitalization, or in need for continuous intravenous inotropic therapy, but is not candidate of heart transplantation.

Although heart failure patients are often assumed principally to suffer from fatigue, dyspnea and edema, a majority have insomnia, anxiety, depression, confusion, anorexia, and constipation. Palliative therapies gradually expand as illnesses progress. Hospice is ultimately administered according to the patient's wishes or when the harm of therapies outweighs their benefits. Regarding the end of life, issues of sudden death and living with uncertainty are pertinent to all patients with heart failure. The opportunity to discuss these issues should be available at all stages of care. The palliative needs of patients and caregivers should be identified, assessed and managed at the earliest opportunity. Patients with heart failure and their caregivers should have access to professionals with palliative care skills within the heart failure team.[46]

Hospice and palliative care focuses on meeting the physical, psychosocial, and spiritual needs of patients and their families. In end-stage heart failure, care is enhanced when there is collaboration between the cardiologist, who is an expert in heart failure, and palliative care providers, who are expert at dealing with terminal illness.[142] Hospice care allows family and friends -with the aid of nurses, social workers and trained volunteers – to care for and comfort a loved one at home or in hospice residences. For people who stay in a hospital, specialists in end-of-life care can provide comfort, compassionate care and dignity. An interdisciplinary approach is used, with the patient at the center of care. Fundamental goals include managing symptoms effectively and decreasing the burden of illness for patients, family members and the healthcare expense.

CONCLUSION

Heart failure population is growing in Taiwan because of aging population and improved care of underlying cardiovascular diseases. Heart failure is one of the most studied and best understood chronic diseases. Recent randomized clinical trials clearly indicate which pharmacological, non-pharmacological treatments and therapeutic strategies are beneficial in heart failure. The present guideline represents the commitment of the Taiwan Society of Cardiology to recognize heart failure as a major health care challenge and to provide advices and resources for clinicians and related health care providers. With guideline recommendations, we hope that the management of heart failure can be improved.

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Key Words: Heart failure • Guidelines

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