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專題報導

Current Trends from Diagnosis to Treatment in Heart Failure

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Abstract

In the past few decades, heart failure (HF) becomes a heavy burden to healthcare system globally because of rapid aging population in developing countries. Although many strategies are applied for HF treatment, it still leads to significant mortality and morbidity. The updated ESC and ACC/AHA guidelines and several recent randomized control trials suggest novel agents and new concepts for HF treatment to further improve clinical outcome. This mini-review will outline the diagnostic protocol and management of patients with different types of heart failure. (J Intern Med Taiwan 2017; 28: 115-123)

Key Words: Heart Failure, Healthcare System, Aging

Introduction, Epidemiology, Prognosis

Heart failure (HF) is the most prevalent cardiac disease in modern clinical practice with estimated prevalence of 1-2% of the adult population in developed countries and ranges from 1.3% to 6.7% in East Asian countries[1,2]. Patients with HF have a poor prognosis. In total 5029 participants in ECHOES study, the 5-year and 10-year mortality rate was 38% & 73.3% in all HF patients and 47% and 72.6% in HF patients with LVEF<40%, respectively.[3]

Definition of Heart Failure

HF is a complex clinical syndrome that results from structural disorders or functional impairment, resulting in reduced cardiac output and/or increased ventricular filling pressure and leading to systemic perfusion inadequate to meet body's metabolic demands.

Algorithm for the Diagnosis of Heart Failure

The algorithm for diagnosis of HF is shown in Figure 1. For patients presenting with suspected

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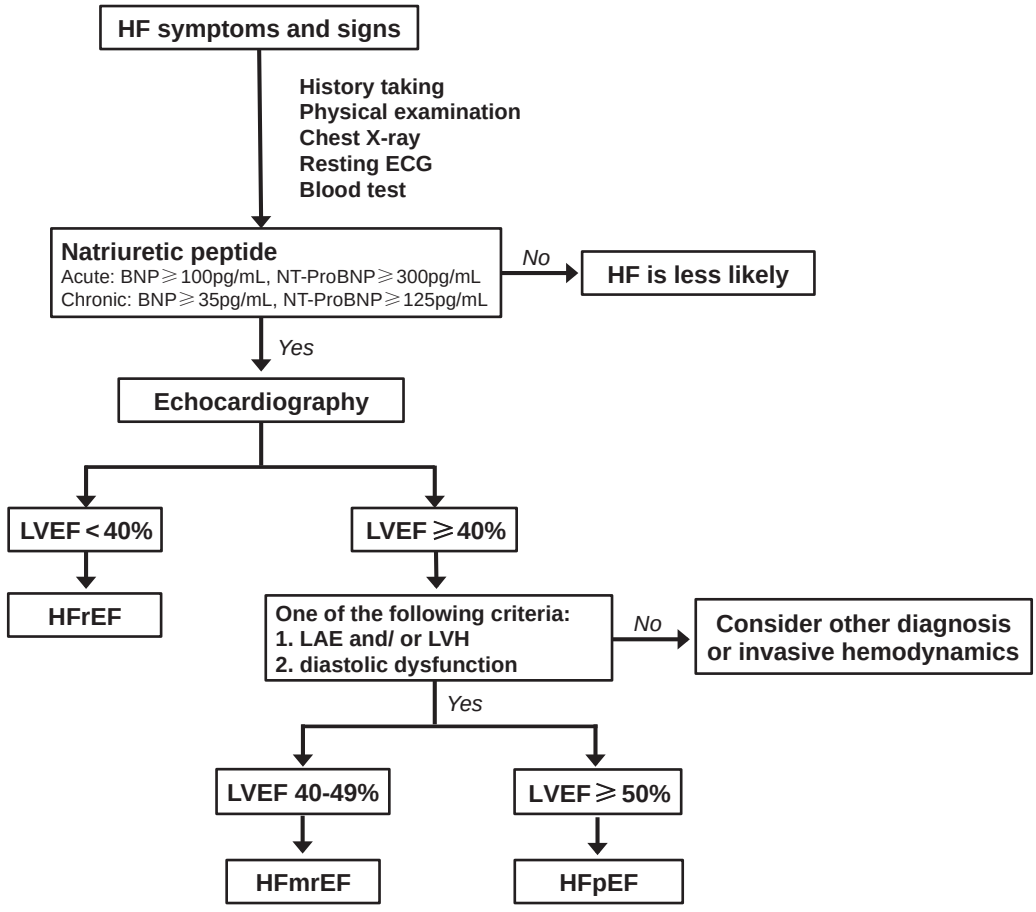
HF, the diagnosis should be made carefully based on comprehensive history taking, physical examination, resting ECG, blood test (natriuretic peptite, TSH, hemoglobin, liver function, renal function, electrolyte, glucose, HbA1c, lipid profile), chest X-ray, cardiac echocardiograph. HF is further classified into three groups based on ejection fraction documented in echocardiography: HF with reduced ejection fraction (HFrEF, LVEF≤40%), HF with mid-range ejection fraction (HFmrEF, LVEF 40-49%), HF with preserved ejection fraction (HFpEF, LVEF≥50%).

Cardiac MRI is recommended in HF patients with suspected myocarditis, Fabry disease, sarcoidosis, amyloidosis, and non-compaction cardiomyopathy. HF patients presented with angina refractory to optimal medical therapy or evidence of ischemia in non-invasive stress tests may undergo invasive coronary angiography. Myocardial biopsy is used to diagnose rejection after heart transplantation, myocarditis, or certain types of cardiomyopathy such as Fabry disease and cardiac amyloidosis.

Invasive hemodynamic measurement provides valuable information for cardiac function in HF patients. Ejection fraction is the most widely used parameter for cardiac contractility; however, it is less specific because cardiac contractility is very sensitive to cardiac load and chamber size.



The diagnostic algorithm for HF is modified based on 2016 ESC HF guideline[1]
HF: heart failure; LVEF: left ventricular ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; LAE: left atrial enlargement; LVH: left ventricular hypertrophy.

Figure 1. Diagnostic algorithm of heart failure.

Invasive hemodynamics may provide more specific measurements of systolic and diastolic function in HF patients.[4] Invasive hemodynamic is also necessary for patients with refractory HF who need heart transplantation or mechanical circulatory support.

Etiology and Precipitation Factors for Heart Failure

Various underlying factors cause HF including coronary artery disease, hypertension, diabetes mellitus, valvular heart disease, arrhythmia, myocarditis, congenital heart disease, drugs (alcohol, cocaine, doxorubicin), idiopathic cardiomyopathy, hypertrophic cardiomyopathy, endocrine disorders, autoimmune disease, severe anemia, or pregnancy. Exacerbations of HF are frequently associated with precipitating factors, including acute coronary syndrome, hypertensive emergency, arrhythmia, acute mechanical cause (cardiac rupture, ventricular septal defect, acute mitral regurgitation after acute

Table 1. Evidenced-based drugs and dose suggestions in randomized controlled trial of heart failure with reduced ejection fraction

	Initial dose	Target dose	Trial name
Angiotensin converting enzymes (ACEI)			
Captopril	6.25mg tid	50mg tid	SAVE
Enalapril	2.5mg bid	20mg bid	CONSENSUS, V-HeFT II, SOLVD
Lisinopril	2.5-5mg qd	20-35mg qd	ATLAS
Ramipril	2.5mg qd	10mg qd	AIRE
Trandolapril	0.5mg qd	4mg qd	TRACE
Beta-blocker (BB)			
Bisoprolol	1.25mg qd	10mg qd	CIBIS-II
Carvedilol	3.125mg bid	25mg bid	COPERNICUS
Metoprolol	12.5-25mg qd	200mg qd	MERIT-HF
Nebivolol	1.25mg qd	10mg qd	SENIORS
Angiotensin receptor blocker(ARB)			
Candesartan	4-8mg qd	32mg qd	CHARM
Valsartan	40mg bid	160mg bid	VALIANT, Val-HeFT
Losartan	50mg qd	150mg qd	ELITE-II
Minoralcorticoid receptor antangonist (MRA)			
Eplerenone	25mg qd	50mg qd	EPHESUS
Spironolactone	25mg qd	50mg qd	RALES
Angiotensin receptor-Neprilysin inhibitor (ARNI)			
Sacubitril/valsartan	49/51mg bid	97/103mg bid	PARADIGM-HF
If-channel inhibitor			
Ivabradine	5mg bid	7.5mg bid	SHIFT

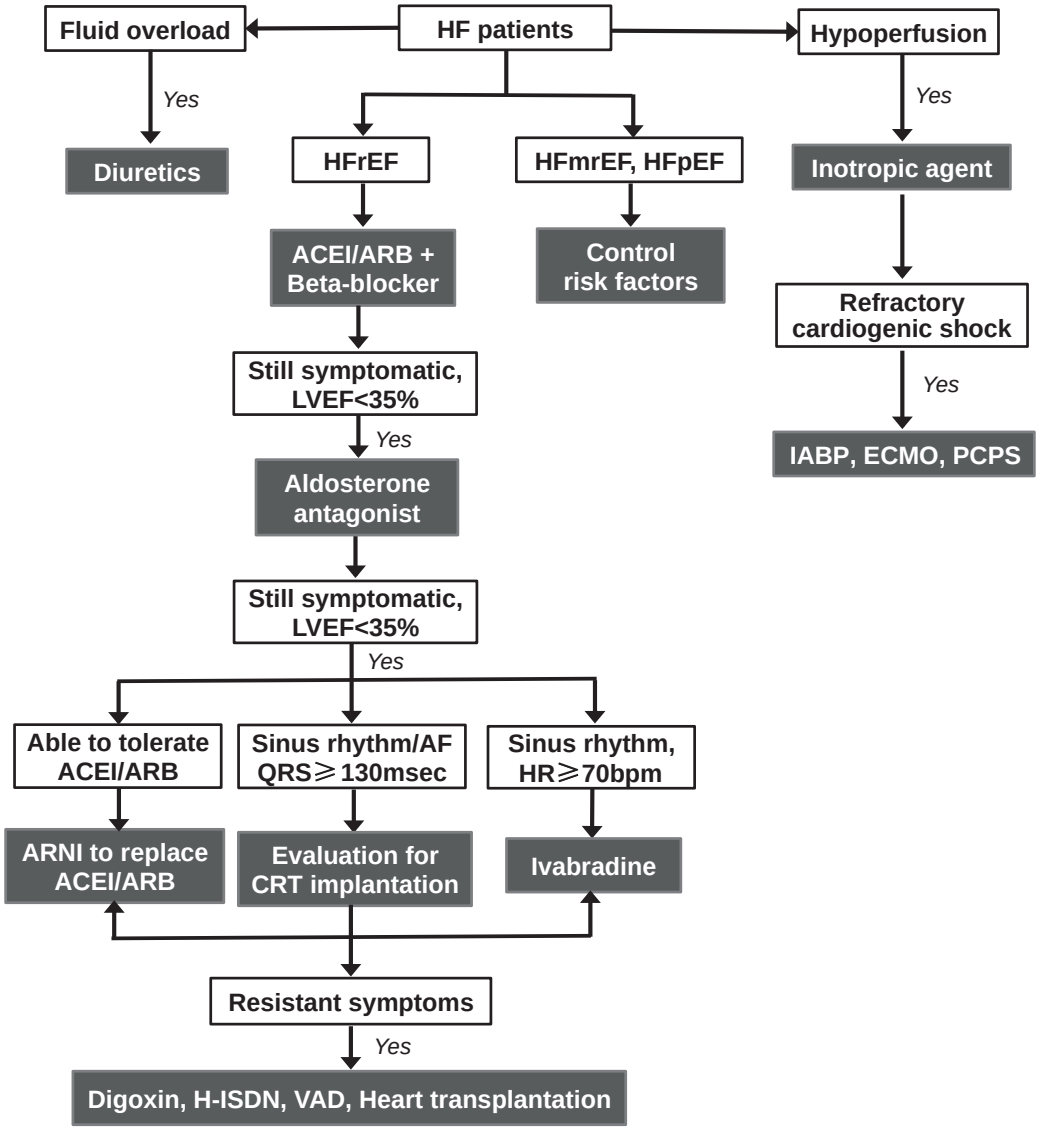
myocardial infarction), pulmonary embolism, poor compliance with diet and HF medication.

Treatment of Heart Failure with Reduced Ejection Fraction

The treatment protocol for HF patients with HFrEF was summarized in Figure 2.

Pharmacological treatment

Several endogenous neurohormonal mechanisms involve in HFrEF: renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, and natriuretic peptide system. RAAS induces vasoconstriction, ventricular hypertrophy, increased sodium and water retention. Angiotensin



The algorithm for HF treatment is modified based on 2016 ESC HF guideline[1]
HF: heart failure; LVEF: left ventricular ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; IABP: intra-aortic balloon pump; ECMO: extracorporeal membrane oxygenation; PCPS: percutaneous cardiopulmonary support; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor block; AF: atrial fibrillation; HR: heart rate; ARNI: angiotensin receptor-nephrilysin inhibitor; CRT: cardiac resynchronization therapy; H-ISDN: hydralazine–isosorbide dinitrate ; VAD: ventricular assist device.

Figure 2. Algorithm for management of patients with heart failure.

converting enzymes inhibitor (ACEI), angiotensin receptor blocker (ARB), mineralocorticoid receptor antagonist (MRA) primarily inhibit RAAS and showed mortality benefit. Sympathetic activation accelerates heart rate, increases vascular resistance, and enhances cardiac contractility that are harmful for long-term cardiac structure and performance. Beta-blockers (BB) inhibit adrenergic sympathetic activity and significantly improve morbidity and mortality in HFrEF. Nitriuretic peptide system protects against RAAS and reduces negative effects of sodium and water retention. Neprilysin inhibitor increases bioavailability of natriuretic peptide and contributes to a novel agent, LCZ 696 (Sacubitril/valsartan), for the treatment of HFrEF.[5]

Angiotensin converting enzymes inhibitor (ACEI)

ACEIs show cardiovascular mortality benefit and significantly reduce hospitalization in patients with HFrEF. ACEI is usually recommended before BB therapy and initiated at a low dose with gradual titration to a maximum target dose. When compared to patients with HFrEF who received a lower dose of ACEI, those who took higher dose of ACEI was associated with significant reduction of all-cause mortality and HF hospitalization.[6]

Beta-blocker

The results emerged from various randomized controlled trials demonstrate that BB significantly reduce HF mortality and improve symptoms in chronic HF patients with reduced ejection fraction.[7-9] BB are recommended after ACEI therapy in patients with HFrEF. There is consensus that BB should be initiated at a tolerated dose and gradually up-titrated to the maximum dose. However, there is paucity of evidence regarding the effects of BB in acute decompensated HF. Many physicians choose to discontinue BB owing to concerns about its potential negative inotropic effects on cardiovascular hemodynamics in acute decompensated HF. Nevertheless, a recent meta-analysis showed continuation of BB in patients with acute decompensated HF was associated with significant reduction of in-hospital and short-term mortality, but the long-term outcome remains uncertain[10]

Angiotensin receptor blocker (ARB)

ARBs are recommended as alternative choices when the patients with HFrEF who are intolerant to ACEIs. ARBs and ACEIs undergo different pathways in RAAS. ARB do not inhibit kinase and therefore cause lower incidence of dry cough and angioedema than ACEIs. ARBs is recommended at lower dose initially and up-titrate to maximum tolerated dose gradually to achieve greater benefit in mortality. [11,12]

Minerocorticoid antagonist (MRA)

An MRA is recommended for symptomatic patients with HFrEF and LVEF≤35% despite ACEI and BB therapy to reduce HF hospitalization and all-cause mortality (Class I). The use of MRAs should be cautious in patients with serum creatinine ≥2.5mg/dL in men and ≥2.0mg/dL in women and/or hyperkalemia.[1] Both spironolactone and eplerenone have significantly reduced mortality in patients with HFrEF. There are substantial differences between these two agents. In RALES, spironolactone has proven mortality benefit in patients with advanced ischemic and non-ischemic HF (LVEF≤35%, NYHA III-IV). In EPHESUS, eplerenone produced reduction in overall mortality in symptomatic patients with HF (LVEF≤40%) caused by myocardial infarction.[13] Furthermore, spironolactone causes more gynecomastia or breast pain (10%) than eplerenone (0.5%) in male.[14,15]

Angiotensin receptor- Neprilysin inhibitor (ARNI)

LCZ 696 is the most promising agent in HF treatment that is composed of sacubitril (nephrilysin-inhibitor) and valsartan (angiotensin receptor blocker). PARADIGM-HF trial showed LCZ 696 is superior to enaparil in reduction of HF hospitalization and mortality in patients with HFrEF.[16] In symptomatic patients with HFrEF, ACEI or ARB is recommended to be replaced by LCZ 696 together

with BB and MRA to further reduce the risk of HF hospitalization and mortality.

I_f channel inhibitor

Ivabradine acts on I_f channel in sinus node and slows the heart rate in patients with sinus rhythm. Ivabradine is recommended in stable patients with HFrEF (LVEF≤35%) and sinus rhythm with resting heart rate ≥70 bpm despite BB therapy or those who are intolerant to BB to reduce HF hospitalization and mortality. However, Ivabradine therapy may increase the risk of atrial fibrillation development.[17]

Digoxin

Digoxin reduce the risk of all cause and HF hospitalization but does not improve survival and may be considered in symptomatic patients with sinus rhythm and HFrEF despite treatment with an ACEI/ARB and beta-blocker.[18] Digoxin may also be an alternative to slow heart rate in patients with HFrEF and atrial fibrillation with rapid ventricular response when the other appropriate anti-arrhythmic drugs fail to control heart rate.

Nitrates plus hydralazine (H-ISDN)

ESC and ACC/AHA guidelines recommend that therapy with hydralazine and isosorbide dinitrate showed benefit in mortality and reduction of hospitalization in patients with LVEF≤35% or symptomatic advanced heart failure (NYHA Class III-IV) with LVEF≤45% and dilated LV despite treatment with ACEI, BB, and MRA. Hydralazine and isosorbide dinitriate may be an alternative for patients with HFrEF who are intolerant to ACEI/ARB to reduce the risk of hospitalization.[19]

Diuretics

Diuretic therapy is very effective to relieve the symptoms and signs of HF patients with congestion. Loop diuretics are stronger diuretics to remove the overload fluid than thiazide diuretics though thiazide diuretics have greater influence on blood pressure. However, several studies showed the effect of diuretics on clinical HF outcome have been disappointing. Diuretics may deteriorate renal function and cause electrolyte imbalance, which poses certain threat to HF treatment.

Non-surgical device treatment

Sudden cardiac death is a major threat to patients with HFrEF. An implantable cardioverter-defibrilllator (ICD) is recommended in patients with history of unstable ventricular arrhythmia, asymptomatic ischemic HF patients with LVEF ≤30% or symptomatic ischemic HF patients with LVEF ≤35% at least 40 days after acute myocardial infarction. ICD is also recommended in patients with non-ischemic heart failure with LVEF ≤30% despite optimal medical therapy or dilated cardiomyopathy to prevent sudden cardiac death and improve survival. ICD implantation is not recommended within 40 days of acute myocardial infarction or in patients with refractory heart failure unless they are candidates for heart transplantation, CRT, or ventricular assist device.[1]

Cardiac resynchronized therapy (CRT) improves symptoms, reduces mortality and morbidity in selected patients with HFrEF and bundle branch block. CRT may be considered in selected HF patients with LVEF ≤35% and bundle branch block (LBBB and non-LBBB QRS morphology). Previous studies showed patients with HFrEF and LBBB have significantly lower mortality and higher prevalence of symptomatic and echocardiographic response to CRT than those with non-LBBB.[20] CRT rather than RV pacing is also recommended in patients with HFrEF who have high degree AV block. It is noteworthy that the Echo-CRT trial suggested CRT implantation may increase mortality in patients with HFrEF and QRS duration <130 msec.[21]

Treatment of Heart Failure with Preserved Ejection Fraction

No treatment has been proven to improve the mortality in patients with HFmrEF or HFpEF; however, aggressive controls of risk factors and

comorbidities are recommended. Diuretics are helpful to ameliorate congestion and improve symptoms and signs in those patients with HFmrEF or HFpEF.

Treatment Not Recommended in Heart Failure

Diltiazem and verapamil pose negative inotropic effect on heart function and increase the risk of HF worsening thus not recommended in patients with HFrEF. Moxonidine is not recommended in hypertensive patients with HFrEF as it increases mortality.[22] Alpha-adrenoceptor antagonist causes neurohormonal activation, fluid retention and deteriorate heart function and is not recommended in patients with HFrEF.[23] Thiazolidinediones (glitazones) increase the risk of HF hospitalization and are not recommended in HF patients with diabetes.[24] NSAIDs or COX-2 inhibitors are not recommended in HF patients because they increase the risk of HF worsening and hospitalization.[25] In patients with HFrEF and sleep apnea, adaptive servo-ventilation therapy is associated with increases all-cause and cardiovascular mortality.[26]

Acute Heart Failure

Acute decompensated HF means rapid onset of worsening HF symptoms and signs resulting from pumping failure and/or congestion. Diuretics therapy are effective to remove the overload fluid when HF patients have symptoms and signs of congestion. If HF patients present with hypoperfusion, inotropic agent may be necessary to increase ventricular contractility and restore adequate cardiac output. It is also important to identity the precipitating factors leading to acute heart failure and correct these factors promptly.

Refractory Heart Failure

The patients with severe heart failure refractory to optimal medical therapy may need interventional therapy including implantable left ventricular assist device (LVAD) or heart transplantation. LVAD was used as bridge therapy for patients on the heart transplant waiting list or destination therapy because heart transplantation is limited by the availability of donors.

For those patients with refractory HF who are not suitable for specialized intervention therapy, hospice care improves the HF symptoms, clinical outcomes, and both patient and family satisfaction. The patients with end-stage HF who had hospice care lived 81 days longer compared with those who received aggressive HF therapy.[27]

Life Style Modification

Making life style modification is very helpful to relieve the symptoms and signs of HF and prevent disease progression. Sodium is recommended to restrict <3g daily. If patients with acute decompensated HF, fluid restriction is recommended <2 liter daily to restore euvolemia. Smoking cessation, alcohol limitation, and maintenance of ideal body weight are also very important in HF treatment.

Multi-Discipline Therapy

Both ESC and ACC/AHA guidelines recommended multidisciplinary involvement for HF therapy, including cardiologists, HF case manager, dietician, pharmacologists, social workers, rehabilitation department to provide intensive follow-up and telephone contact. The systemic review of 29 randomized control trials showed a specialized multidisciplinary HF team significantly reduced mortality and all-cause hospitalization.[28]

Conclusion

HF is one of the most rapid growing cardiovascular disease and is associated with significant risk of mortality and hospitalization in Taiwan. New novel agent LCZ 696 and Ivabradine are effective to further reduce HF mortality and hospitalization. For

large-population of HF patients, specialized multidisciplinary teams are very cost-effective in HF treatment and associated with mortality benefit.

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心衰竭診斷及治療新趨勢

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摘 要

近年來全球人口老化，導致心臟衰竭快速成長，變成全世界健康照護上重大的威脅。雖然心臟衰竭已有明確的治療指引，但還是造成相當高比例的心血管併發症及死亡率。最新的歐洲以及美國心臟學會發表新一代心衰竭藥物以及跨團隊治療，可更加改善病人症狀及增加存活率。本文簡要地整理不同類型心臟衰竭的診斷和治療流程，以供臨床醫師治療之參考。