

Guidelines

2019 Focused Update of the Guidelines of the Taiwan Society of Cardiology for the Diagnosis and Treatment of Heart Failure

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Heart failure is a growing epidemic, especially in Taiwan because of the aging population. The 2016 Taiwan Society of Cardiology – Heart Failure with reduced Ejection Fraction (TSOC-HFrEF) registry showed that the guideline-recommended therapies were prescribed suboptimally both at the time of hospital discharge and during follow-up. We, therefore, conducted this 2019 focused update of the guidelines of the Taiwan Society of Cardiology for the diagnosis and treatment of heart failure to reinforce the importance of new diagnostic and therapeutic modalities of heart failure.

The 2019 focused update discusses new diagnostic criteria, pharmacotherapy, non-pharmacological management, and certain co-morbidities of heart failure. Angiotensin receptor neprilysin inhibitor and *If* channel inhibitor is introduced as new and recommended medical therapies. Latest criteria of cardiac resynchronization therapy, implantable cardioverter-defibrillator, heart transplantation, and ventricular assist device therapy are reviewed in the non-pharmacological management chapter. Co-morbidities in heart failure are discussed including chronic kidney disease, diabetes, chronic obstructive pulmonary disease, and sleep-disordered breathing. We also explain the adequate use of oxygen therapy and non-invasive ventilation in heart failure management. A particular chapter for chemotherapy-induced cardiac toxicity is incorporated in the focused update to emphasize the importance of its recognition and management. Lastly, implications from the TSOC-HFrEF registry and post-acute care of heart failure are discussed to highlight the importance of guideline-directed medical therapy and the benefits of multidisciplinary disease management programs.

With guideline recommendations, we hope that the management of heart failure can be improved in our society.

Key Words: Biomarkers • Cardiac resynchronization therapy • Cardio-oncology • Co-morbidities • Guidelines • Heart failure • Pharmacotherapy • Post-acute care • Transplantation • Ventricular assist device

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The Taiwan Society of Cardiology (TSOC) Heart Failure Committee provides periodic reviews of new data to produce focused updates that address clinically essential advances in heart failure (HF) management. This 2019 Focused Update deals with the following topics: (1) Diagnosis: echocardiography; (2) Diagnosis: biomarkers; (3) Pharmacotherapy: angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs)/angiotensin receptor neprilysin inhibitor (ARNI); (4) Pharmacotherapy: beta-blockers; (5) Pharmacotherapy: mineralocorticoid receptor antagonists; (6) Pharmacotherapy: *If* channel inhibitors; (7) Non-pharmacological management: cardiac resynchronization therapy and implantable cardioverter-defibrillators; (8) Non-pharmacological management: surgery; (9) Comorbidities in HF: chronic kidney disease, diabetes, chronic obstructive pulmonary disease, sleep-disordered breathing; (10) Oxygen therapy in acute HF; (11) Chemotherapy-induced cardiac toxicity; (12) Implications from the Taiwan Society of Cardiology – Heart Failure with reduced Ejection Fraction (TSOC-HFrEF) registry; and (13) Post-acute care of HF.

DIAGNOSIS – ECHOCARDIOGRAPHY

Echocardiography is a term encompassing all cardiac ultrasound imaging techniques. We will focus on the use of three-dimensional (3D) echocardiography, tissue Doppler imaging (TDI), deformation imaging (strain and strain rate) and transthoracic echocardiography in the current guidelines to carefully assess the myocardial systolic and diastolic function of both left and right ventricles.

Assessment of systolic function, classification of heart failure

To assess systolic function, we recommend the modified biplane Simpson's rule. Left ventricular ejection fraction (LVEF) should be obtained from apical four- and two-chamber views. Contrast agents can also add to the diagnostic accuracy for patients with poor quality images.¹ In contrast, the Teichholz and Quinones methods of calculating LVEF from linear dimensions are not recommended in the setting of HF, especially for those with regional wall motion abnormalities. In recent years, some studies have shown that 3D echocardiography, tis-

sue Doppler parameters (such as S wave) and deformation imaging techniques (strain and strain rate) can be used to detect subtle, earlier changes in some HF patients and they are suggested in selected cases.^{2,3} In a retrospective study enrolling 330 HFrEF Taiwanese patients, the authors assessed the predictive value of the ratio of transmitral early filling velocity (E) to early diastolic tissue velocity (E') and the early diastolic strain rate (E'sr). They concluded that the E/E'sr ratio was better able to predict the prognosis of HFrEF than the E/E' ratio. In addition, combined assessments of global longitudinal strain and E/E'sr by speckle-tracking longitudinal strain could facilitate risk stratification of these patients.⁴

In patients with clinical HF, the definition of HF with preserved ejection fraction (HFpEF) varies widely in previous studies.⁵⁻⁷ In most patients, abnormalities of systolic and diastolic dysfunction coexist. Because ejection fraction (EF) is the most common selection criteria in clinical trials, echocardiographic EF is considered necessary to classify patients with HF. In the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) HF guidelines, HF was classified as HFrEF, HFpEF, and borderline HFpEF according to an EF \leq 40%, 41~49% and \geq 50%, respectively, with one subcategory of "HFpEF, improved" to describe a subset of HFrEF patients with improvement or recovery in EF above 40% after treatment.⁸ In the 2016 European Society of Cardiology (ESC) HF guidelines, "gray zone" HF (EF between 40~49%) was defined as HF with mid-range ejection fraction (HFmrEF).⁹ HFmrEF has been suggested to be a transitional zone for HFpEF and HFrEF in some recent studies.^{10,11} In the current guidelines, we also define patients with HF as HFpEF, HFmrEF, and HFrEF according to LVEF $<$ 40%, 40% to 49%, and LVEF \geq 50% (Table 1).

Evaluation of diastolic function

After an initial clinical diagnosis of HFpEF, further objective evidence of echocardiographic cardiac dysfunction is required to validate the diagnosis. Patients with suspected HFpEF or HFmrEF should have the following objective structural and/or functional alterations of the heart:

- Key structural alterations including left atrial volume index (LAVI) $>$ 34 mL/m² or a left ventricular (LV) mass index \geq 115 g/m² for males and \geq 95 g/m² for females.⁹

Table 1. Types of heart failure

Types of heart failure	HFpEF	HFmrEF	HFrEF
Clinical expression	Symptoms and/or signs	Symptoms and/or signs	Symptoms and/or signs
Echocardiographic ejection fraction	LVEF \geq 50%	LVEF between 40 and 49%	LVEF $<$ 40%
Objective evidence	Elevated natriuretic peptides* and echocardiographic cardiac structural change or diastolic dysfunction [#]	Elevated natriuretic peptides* and echocardiographic cardiac structural change or diastolic dysfunction [#]	

* B-type natriuretic peptide $>$ 100 pg/mL and/or N-terminal pro-B type natriuretic peptide $>$ 300 pg/mL. [#] Refer to Figure 1 for structural and function change and diastolic dysfunction grading.

HFmrEF, HF with mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced EF; LVEF, left ventricular ejection fraction.

- Key functional alterations including an average $E/e' >$ 14, a septal e' velocity $<$ 7 cm/s or a lateral e' velocity $<$ 10 cm/s.¹²
- Other indirect echocardiographically derived measurements including longitudinal strain or tricuspid regurgitation velocity (TRV; TRV $>$ 2.8 m/s).¹²
- A recent recommendation from the American Society of Echocardiography and the European Association of Cardiovascular Imaging has focused on the assessment of diastolic dysfunction in HFpEF.¹² There are three types of abnormal filling patterns recognized conventionally in patients in sinus rhythm.
- When the mitral inflow pattern shows an E/A ratio \leq 0.8 as well as a peak E velocity of \leq 50 cm/s, then mean left atrial pressure is considered low. The corresponding grade of diastolic dysfunction is grade I.
- When the mitral inflow pattern shows an E/A ratio \geq 2, mean left atrial pressure is elevated and is considered to be grade III diastolic dysfunction.
- When mitral inflow shows an E/A \leq 0.8 and a peak E velocity $>$ 50 cm/s, or if the E/A ratio is $>$ 0.8 but $<$ 2, other criteria should be evaluated including peak TRV $>$ 2.8 m/s, average $E/e' >$ 14 or LAVI $>$ 34 mL/m². In patients in whom one of the three main criteria is not available, the ratio of pulmonary vein peak systolic to peak diastolic velocity or systolic time velocity integral to diastolic time-velocity integral $<$ 1 supports the presence of elevated LV filling pressure. If these three parameters are available and none or only one exceeds the cutoff value, the patient is considered to have grade I diastolic dysfunction. If two of the three or all three parameters exceed the cutoff values, then the patient is considered to have grade II diastolic dysfunction. Otherwise, the diastolic dysfunction grade cannot be evaluated and should not be reported.

A diagnostic algorithm for HFpEF and diastolic cardiac dysfunction is shown in Figure 1A, and the grade of diastolic dysfunction is shown in Figure 1B. A recent retrospective study including 451 Taiwanese HFpEF patients evaluated their risks of outcomes based on the 2016 and 2009 diastolic dysfunction grading algorithm. After a follow-up period of 2,976 days, the net reclassification index increased significantly after grading with the 2016 algorithm (10.6%, $p <$ 0.001). Therefore, the 2016 diastolic dysfunction grading algorithm appears to improve the prognostic value in Taiwanese patients with HFpEF.

Evaluation of right ventricular function and pulmonary artery pressure

Echocardiography should also address right ventricular (RV) size and function, as well as right atrial size and dimensions.⁸ RV function is a useful parameter to predict mortality and morbidity in patients with HF.^{13,14} To measure RV function, the following parameters are especially useful:

- Tricuspid annular plane systolic excursion (TAPSE; abnormal TAPSE $<$ 17 mm indicates RV systolic dysfunction).
- Tissue Doppler-derived tricuspid lateral annular systolic velocity (s') (s' velocity $<$ 9.5 cm/s indicates RV systolic dysfunction).^{1,15,16}
- RV fractional area change, which is expressed as a percentage change in the RV chamber area from end-diastole to end-systole, rather than changes in volume.¹⁶
- Systolic pulmonary artery pressure derived from an optimal recording of the maximal systolic tricuspid pressure gradient.
- Estimation of right atrial or central venous pressure (CVP) based on inferior vena cava size and its breath-

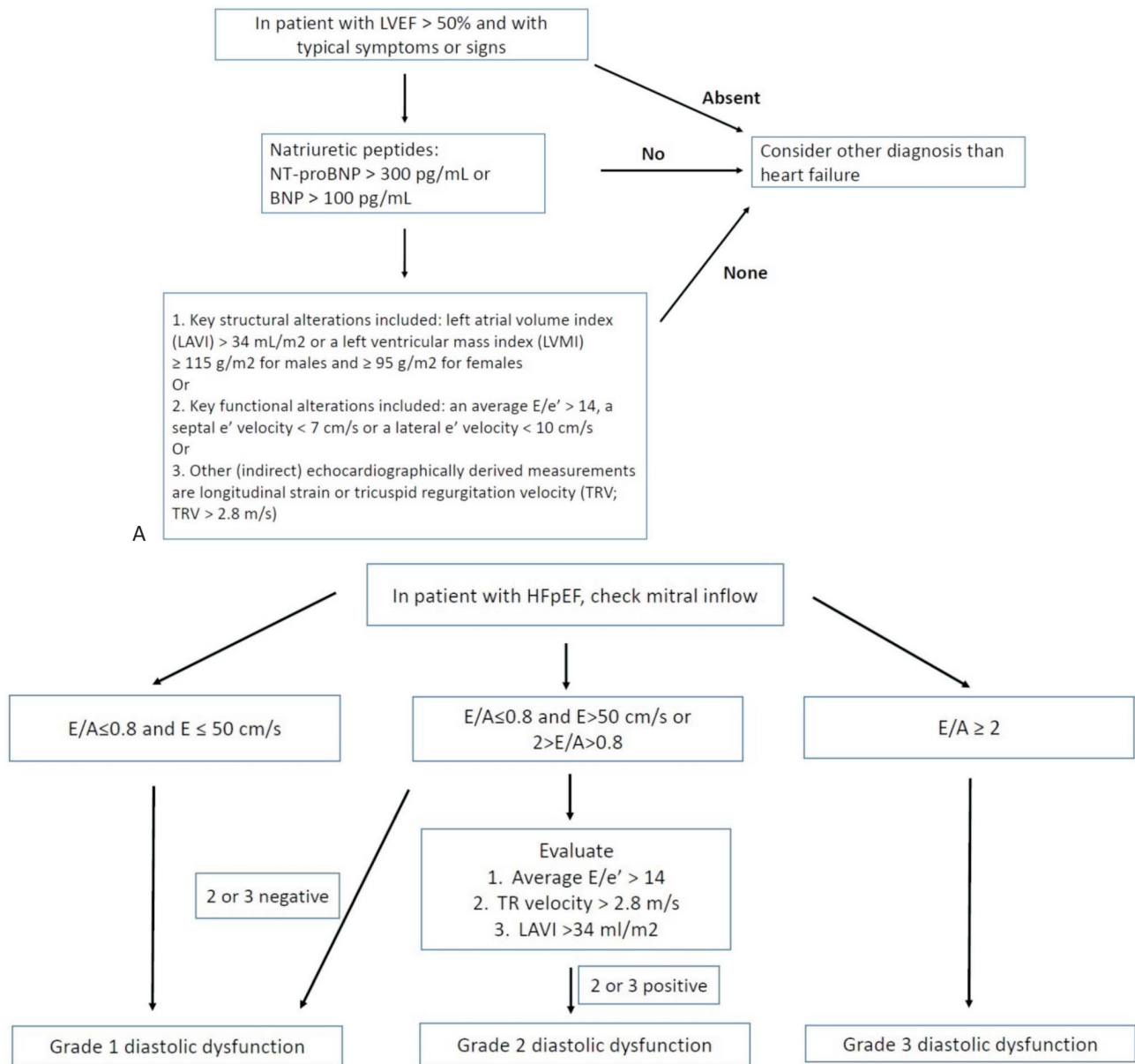


Figure 1. (A) Diagnosis of heart failure with preserved ejection fraction. (B) Grading of diastolic dysfunction. BNP, B-type natriuretic peptide; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide.

ing-related collapse.

For patients with severe HF and cardiologists with experience in 3D echocardiography, 3D measurements of RV volume may be more accurate and clinically relevant.³ Newer techniques to assess RV function include 3D speckle-tracking echocardiography, pulsed-wave TDI, color TDI, and strain imaging.^{16,17}

Transesophageal echocardiography and stress echocardiography

Transesophageal echocardiography is recommended in patients with an inadequate thoracic echo window, in patients with complicated valvular disease which cannot be distinguished from transthoracic echo or does not match the patients' symptoms using transthoracic echo alone, in suspected aortic dissection, suspected endo-

carditis or congenital heart disease, and to rule out intracavitary thrombi in patients with atrial fibrillation (AF) requiring cardioversion. Stress echocardiography, on the other hand, can be used to assess the severity of ischemic heart disease and myocardial viability.¹⁸ Stress echocardiography can also detect exercise diastolic dysfunction for HFpEF patients with an inconclusive diagnosis at rest.¹⁹

DIAGNOSIS – BIOMARKERS

Routine diagnostic evaluations for HF should include laboratory tests, including biomarkers for HF, which can be used to assist in the diagnosis and as prognostic predictors. The use of biomarkers to diagnose HF is more convenient than echocardiography as a first line tool at outpatient service or emergency departments. However, these biomarkers can also be elevated in conditions other than HF. Therefore, biomarkers should be used cautiously and be limited to exclusion, especially in patients with atypical presentations.

We recommend measuring B-type natriuretic peptide (BNP) or N-terminal proB-type natriuretic peptide (NT-proBNP) to assist in confirming or excluding the diagnosis of HF (Figure 2). Natriuretic peptides (NPs) are biomarkers associated with stretched myocardial myocytes²⁰ which can counteract stress by inducing vasodilation, natriuresis, diuresis, and inhibition of cardiac and vascular myocyte growth. Evidence from some large cohort studies supports the use of NPs, especially BNP and NT-proBNP,²¹ to predict and diagnose new-onset HF. Other studies also support the potential for predicting the prognosis of HF including hospitalization and overall mortality. Recent studies from Taiwan with regards to patients with acute decompensated HF have reported that a higher BNP was associated with worse function class and a two-fold increased risk of in-hospital mortality.²² In patients with HFpEF, elevated NP levels have also been shown to be a marker associated with a poor prognosis, including mortality and HF-related hospitalization.^{23,24}

We also suggest the use of NPs as a prognostic predictor to monitor the effectiveness of HF therapy before hospital discharge. However, the effectiveness and benefits of serial follow-up measurements or targeting a

specific NP reduction as a treatment goal are still unclear. Although some smaller studies have shown an improvement in clinical outcomes,^{25,26} further studies are required to elucidate the benefits.

Besides HF, ischemic heart disease, uncontrolled hypertension, increasing age, renal dysfunction, anemia, pulmonary diseases, and sepsis can also increase NP levels. The grey zone of BNP as a diagnostic tool for HF is 100-400 pg/mL, and 300-450 pg/mL for NT-proBNP. In elderly patients (age > 75 years), the grey zone of NT-proBNP can be extended to 300-1800 pg/mL.²⁷ Because the level can also be elevated in various conditions other than HF, NPs are preferred as an exclusion tool in first-line screening. A normal concentration in an untreated patient has a high negative predictive value for the diagnosis of HF. Moreover, the level of NPs can be lower in patients with a higher body mass index (BMI) (> 35 kg/m²) due to increased clearance receptors in adipocytes,²⁸ thus the use of NPs in these groups of patients should be applied with caution. For patients receiving treatment with ARNI, NP-proBNP is preferred to evaluate the patient's prognosis because the mechanism of action of ARNI elevates the level of BNP.

Cardiac troponins should also be sampled in patients with suspected or newly diagnosed HF. Cardiac troponins are an established marker of cardiac injury. Several factors are associated with elevated troponins, including subendocardial ischemia, cardiomyocyte necrosis, cardiomyocyte damage from inflammatory cytokines, oxidative stress, apoptosis, and leakage of troponins from the cytosolic pool due to increased membrane permeability.²⁹ For patients with newly diagnosed HF, troponins can be measured to evaluate the possible etiology and also to predict the prognosis. Patients with acute coronary syndrome-induced HF should consider revascularization. Nevertheless, cardiac troponins can also be elevated in patients with myocarditis and severe HF. An elevated cardiac troponin level in HFpEF patients is significantly associated with mortality and cardiovascular (CV) events.³⁰⁻³² However, data on the prognostic value in patients with HFpEF are limited.^{33,34}

In addition to NPs and cardiac troponins, other markers are also associated with HF (Figure 3). Markers of cardiomyocyte remodeling such as ST-2 and Galectin-3 have been shown to be predictors and markers of HF. An elevated level of soluble ST-2 suggests de-

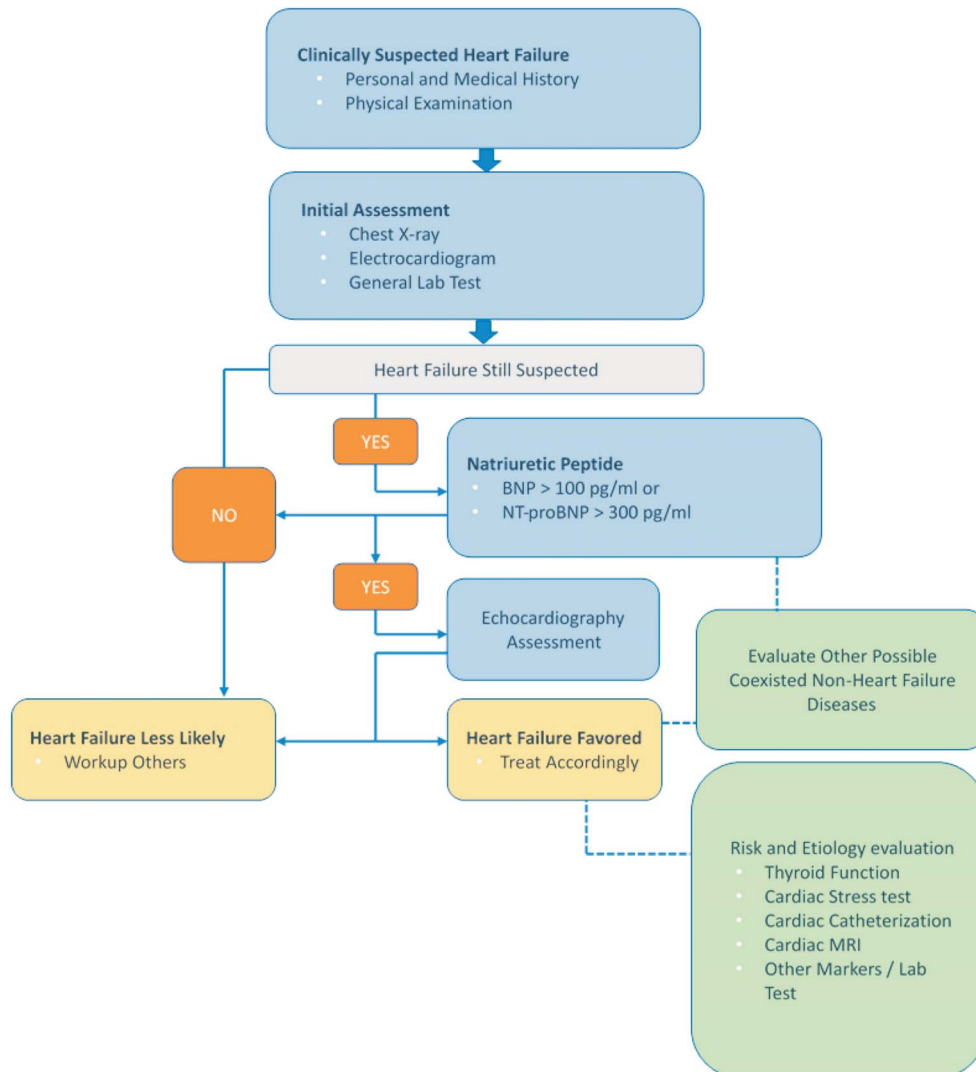


Figure 2. Algorithm of B-type natriuretic peptide (BNP) or N-terminal proB-type natriuretic peptide (NT-proBNP) to assist in the differential diagnosis of HF. HF, heart failure; MRI, magnetic resonance imaging.

creased cardiac protection in cardiac injuries. Studies have also shown that ST-2 can be an independent marker to predict HF hospitalizations and mortality.³⁵ Among patients with acute myocardial infarction (AMI), a high serum ST-2 level has also been shown to be a predictor of HF.³⁶ Macrophages secrete Galectin-3, and this is associated with cardiac fibrosis. Accordingly, studies have suggested that elevated Galectin-3 could be a prognostic indicator of HF. Urinary albumin to creatinine ratio (UACR) and neutrophil gelatinase-associated lipocalin (NGAL) have been used as markers for kidney injury. Recent studies have also suggested that UACR and NGAL can be markers to assess the prognosis of HF.^{33,36}

These kidney biomarkers can reflect nephrotoxic injury and systemic endothelial dysfunction. Although the direct mechanism in HF is unclear, these markers may be an early indicator of kidney injury in HF.³⁷ Furthermore, the occurrence of pneumonia in patients with acute HF is a commonly discussed issue, and initiating appropriate antibiotic therapy is essential. Procalcitonin is a valuable diagnostic marker for infection in the setting of acute exacerbations of HF. The combination of multiple biomarkers may have potential benefits for the diagnosis and prognostic prediction for patients with HF. However, further validation for clinical cohorts is required.

Major Markers and Important Labs in Heart Failure

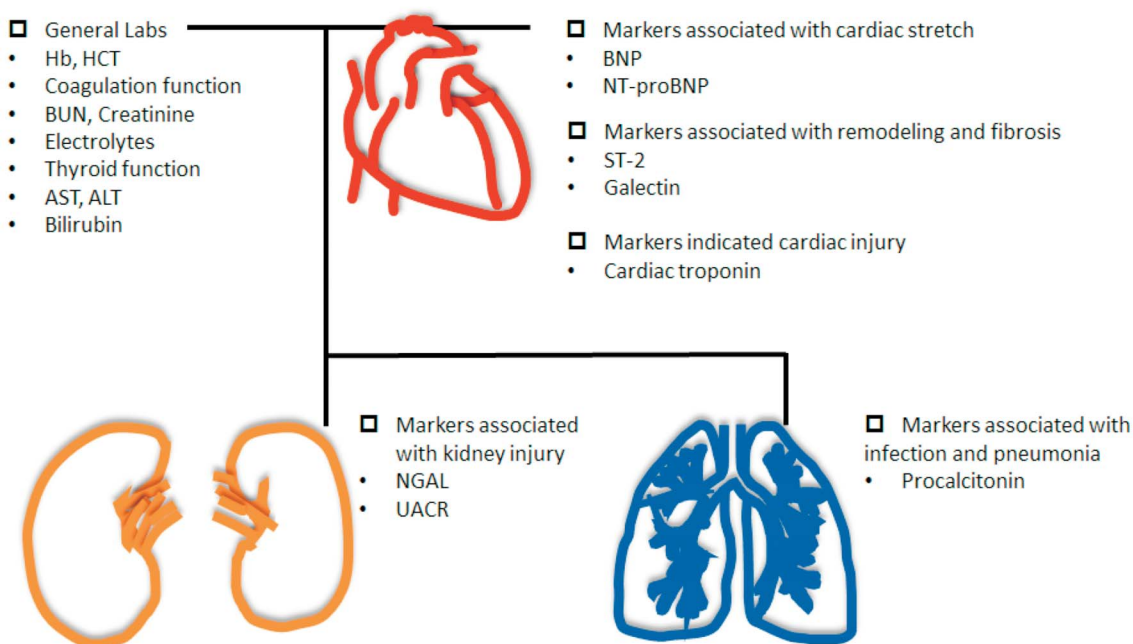


Figure 3. Key biomarkers and necessary laboratory parameters in the differential diagnosis of HF. ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; Hb, hemoglobin; HCT, hematocrit; HF, heart failure; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-terminal proB-type natriuretic peptide; UACR, urinary albumin to creatinine ratio.

PHARMACOTHERAPY – ANGIOTENSIN CONVERTING ENZYME INHIBITORS/ANGIOTENSIN RECEPTOR BLOCKERS/ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITOR

HF is the final common pathway of various cardiac diseases and is characterized by high morbidity and mortality. A major issue in the treatment of HF is cardiac remodeling after either acute or chronic myocardial injury.³⁸ The renin-angiotensin-aldosterone (RAA) system is deeply involved in cardiac remodeling. Numerous large clinical trials have demonstrated that successfully blocking the RAA axis both reduces morbidity and also improves the survival of HF patients.

Although ACEIs and ARBs have been incorporated into guidelines of international cardiology societies, including the ACC/AHA and ESC, for the management of HF, the prescription rate of RAA system blockers is relatively low. According to the TSOC registry,³⁹ the prescription rates of ACEIs and ARBs are 27.5% and 34.6%, respectively. The combined prescription rate of 62.1% for either an ACEI or ARB is lower than that in Western countries. The doses of both ACEIs and ARBs should be

up-titrated to the target doses used in randomized controlled trials (RCTs) if tolerable.⁴⁰

The development of ARNI has caused a paradigm shift from “add-on” to “replacement” in RAA axis blockers. Although pivotal trials for sacubitril/valsartan are still lacking, the overwhelming superiority of ARNI to ACEIs in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial⁴¹ led to the incorporation of ARNI into the revised ESC guidelines for HF in 2016.⁴²

Angiotensin converting enzyme inhibitors

Multiple large-scale RCTs have clearly established the benefits of angiotensin converting enzyme inhibition in patients with mild, moderate, or severe symptoms of HF and in patients with or without coronary artery disease (CAD) [Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS): enalapril, 1987; Studies of Left Ventricular Dysfunction (SOLVD): enalapril, 1991; Survival And Ventricular Enlargement trial (SAVE): captopril, 1992; Acute Infarction Ramipril Efficacy study (AIRE): ramipril, 1993; Trandolapril Cardiac

Evaluation study (TRACE): trandolapril 1995; Assessment of Treatment with Lisinopril and Survival trial (ATLAS): lisinopril, 1999].

No significant differences among the available ACEIs have been reported with regards to their effects on symptoms or survival. (ACC/AHA 2017)

- ACEIs reduce morbidity and mortality in HFrEF.
- ACEIs should be started at low doses and titrated upward to doses shown to reduce the risk of CV events in clinical trials.
- ACEIs can produce angioedema and should be given with caution to patients with low systemic blood pressure, renal insufficiency, or elevated serum potassium ($[K] > 5.0$ mEq/L). The dose of ACEIs should be reduced or held temporarily if serum K > 5.5 mEq/L and be discontinued if K > 6.0 mEq/L.
- If maximal doses are not tolerable, moderate doses should be tried; abrupt withdrawal of ACE inhibition can lead to clinical deterioration and should be avoided. (ACC/AHA 2017)
- Although the use of an ARNI instead of an ACEI for HFrEF is superior, for the patients for whom ARNI is not appropriate, the continued use of an ACEI for all classes of HFrEF remains strongly advised. (ACC/AHA 2017)

Angiotensin receptor blockers

ACEIs are associated with side effects including cough and angioedema, which may compromise its clinical implication. Moreover, escape phenomenon with an elevation in angiotensin II levels may be detected 3 to 6 months after the initiation of ACEI treatment. ARBs were developed with the rationale that angiotensin II production continues in the presence of ACE inhibition, driven through alternative enzyme pathways. ARBs do not inhibit kininase and are associated with a much lower incidence of cough and angioedema than ACEIs.

The findings of multiple large-scale RCTs have shown that long-term therapy with ARBs reduces mortality and morbidity, especially in ACEI-intolerant patients. [Evaluation of Losartan in The Elderly II study (ELITE II): losartan, captopril, 2000; Valsartan in Heart Failure trial (Val-HeFT): valsartan, 2001;^{43,44} Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity trial (CHARM): candesartan, 2003;^{45,46} Heart failure Endpoint evaluation of All-Antagonist Losartan study (HEAAL): losartan, high vs. low dose 2009⁴⁷]. However,

ARBs have no beneficial effects on mortality when combined with ACEIs, and may increase the risk of hypotension or hyperkalemia (VAL-HeFT: valsartan/ACEI, ACEI, 2001;⁴³ CHARM add-on: candesartan/ACEI, ACEI, 2003;⁴⁸ VALsartan In Acute myocardial Infarction Trial (VALIANT): valsartan, captopril, or both, 2003; ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET): telmisartan, ramipril, or both, 2008⁴⁹).

- An ARB is recommended to reduce the risk of HF hospitalization and CV death in symptomatic patients intolerant to ACEIs (because of cough or angioedema); (Class A, Level I for ACC/AHA 2017; Class A, Level B for ESC 2016).
- An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate a mineralocorticoid receptor antagonist (MRA) (Class IIb, Level C for ESC 2016).
- Patients already tolerating ARBs for other indications may be continued on ARBs if they subsequently develop HF.
- ARBs should be started at low doses and titrated upward, with an attempt to use doses shown to reduce the risk of CV events in clinical trials.
- ARBs should be given with caution to patients with low systemic blood pressure, renal insufficiency, or elevated serum potassium (> 5.0 mEq/L). The dose of ARBs should be reduced or held temporarily if serum K > 5.5 mEq/L and be discontinued if K > 6.0 mEq/L.

Angiotensin receptor neprilysin inhibitor

The benefits of ACEIs regarding decreased morbidity and mortality have been shown consistently for HF patients across the clinical spectrum, from asymptomatic to severely symptomatic. Similar benefits have been shown for ARBs in populations with mild-to-moderate HF who are unable to tolerate ACEIs.

In ARNI, a single molecule with dual action, the ARB valsartan, blocks the action of angiotensin II at AT1 receptors, thus inhibiting activation of the RAA system and preventing vasoconstriction, renal sodium and fluid retention and cardiac remodeling. On the other hand, the active metabolite in sacubitril LBQ657 inhibits neprilysin and thereby increases NPs, which in turn leads to vasodilation.

In the PARADIGM-HF study, patients with mild-to-moderate HF characterized by either (1) a mildly elevated BNP (> 150 pg/mL) or NT-proBNP (≥ 600 pg/mL), or (2)

BNP \geq 100 pg/mL or NT-proBNP \geq 400 pg/mL with a prior hospitalization in the preceding 12 months who were able to tolerate both a target dose of enalapril (10 mg twice daily) and then subsequently an ARNI (sacubitril/valsartan; 200 mg twice daily), were randomized. Compared with the enalapril group, sacubitril/valsartan significantly reduced the combined risk of the primary endpoint (death from a CV cause or first hospitalization for HF) [21.8% vs. 26.5%; hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.73-0.87; $p < 0.001$]. In particular, the risk of CV death was reduced by 20%, death due to worsening HF by 21%, and sudden cardiac death (SCD) by 20%.

Sacubitril/valsartan therapy is recommended to replace ACEI therapy to further reduce the risk of HF hospitalization and mortality in ambulatory HFrEF patients who remain symptomatic despite optimal therapy with an ACEI, a beta-blocker, and an MRA, and who fit trial criteria.

- The use of an ARNI is associated with hypotension and a low-frequency incidence of angioedema.
- The target dose is 97/103 mg twice daily. Clinical experience will provide further information about the optimal titration and tolerability of ARNI, particularly regarding blood pressure, adjustments in concomitant HF medications, and the rare complication of angioedema.
- ARNI should not be administered concomitantly with an ACEI or within 36 hours of the last dose of an ACEI.
- ARNI should not be administered to patients with a history of angioedema.

Recently, the comparison of sacubitril/valsartan versus Enalapril on Effect on nt-pro-bnp in patients stabilized from an acute Heart Failure episode trial (PIONEER-HF)⁵⁰ showed promising results in HFrEF patients who were hospitalized for acute decompensated HF. The initiation of sacubitril/valsartan therapy after hemodynamic stabilization resulted in a significantly greater reduction in NT-proBNP concentration than enalapril therapy, with no significant difference in the rate of renal dysfunction, symptomatic hypotension, hyperkalemia, or angioedema. However, the role of ARNI in the setting of acute HF should be confirmed in a more extensive prospective study.

PHARMACOTHERAPY – BETA-BLOCKERS

Beta-blockers are recommended as first-line therapy

for HF. The mortality and morbidity in patients with HF resulting from LV systolic dysfunction have been shown to be reduced by three beta-blockers (bisoprolol, carvedilol, and metoprolol succinate).⁵¹⁻⁵⁴ Nebivolol, a beta-blocker with vasodilating properties, has been shown to be effective and well-tolerated in older patients with HF.⁵⁵ Beta-blockers have also been shown to improve LV function and outcomes in Taiwanese studies,^{56,57} and also in long-term hemodialysis patients with HF in a National Health Insurance Research Database study.⁵⁸

The TSOC-HFrEF multicenter registry collected data from 21 medical centers or teaching hospitals in Taiwan, and showed that only 59.6% of patients with HF received beta-blocker therapy at discharge,³⁹ which is lower than in Northern America Organized Program To Initiate life-saving treatMent In HospitalIZed Patients with Heart Failure registry (OPTIMIZE-HF)⁵⁹ and Europe ESC Heart Failure Pilot survey (ESC-HF Pilot)⁶⁰ studies. At 12 months of follow-up, the prescription rate increased to 66.3%,⁶¹ and the percentage of patients receiving > 50% of the target dose of beta-blockers increased from 20.6% at discharge to 26.3% at 1-year follow-up.⁵¹ However, these results were lower than in the QUALIFY global survey, which reported that the percentages of patients receiving the target dose and > 50% of the target dose of beta-blockers were 14.8% and 51.8%, respectively.⁶² The mean heart rate in the TSOC-HFrEF registry at 1-year follow-up was 80.7 ± 16.0 bpm, indicating that there was still a need for further drug up-titration or medications.^{51,61} A multidisciplinary disease management program reported an increase in beta-blocker prescription rate to 77% at discharge in a Taiwan single-center study.⁶³

The prevalence of chronic obstructive pulmonary disease (COPD) and/or asthma in the TSOC-HFrEF registry was 11%,⁶² which is lower than the 31% in the Acute De-compensated HEart failure national REgistry (ADHERE) and 19% in the EuroHeart Failure Survey II (EHFS-II).^{64,65} Cardioselective β -blockers, including bisoprolol, carvedilol, and metoprolol, were recommended for patients with coexisting HF and COPD in the 2015 Taiwan cardiologist-pulmonologist consensus handbook and previous studies.⁶⁶⁻⁷¹ In the Val-HeFT study, cardioselective β -blockers were shown to have a better 23-month mortality rate than non-selective β -blockers^{66,70} in patients with coexisting HF and COPD. In a Taiwan nationwide study, beta-blockers were shown to reduce mortality, HF exacerbations, and

the need for hospitalization in patients with coexisting HF and COPD.⁷² Moreover, beta-blockers were not shown to be associated with COPD exacerbations.⁷² However, the suboptimal use of beta-blockers has also been shown in patients with concurrent HF and COPD in Taiwan.^{72,73}

PHARMACOTHERAPY – MINERALOCORTICOID RECEPTOR ANTAGONISTS

- MRAs are recommended in patients with chronic symptomatic HFrEF and New York Heart Association (NYHA) functional class II-IV who are already receiving ACEIs or ARBs and beta blockers to reduce mortality and HF hospitalization.
- In patients following an AMI who have reduced LV function and develop symptoms of HF or have a history of diabetes, treatment with MRAs in addition to optimal medical therapy is recommended to reduce mortality and hospitalizations from a CV cause.
- MRAs should be avoided in patients with advanced chronic kidney disease (CKD) (creatinine > 2.5 mg/dL or estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) or hyperkalemia (potassium level > 5.0 mEq/L).

The benefits of MRA treatment in patients with HFrEF were investigated in two landmark studies: the Randomized Aldactone Evaluation study (RALES)⁷⁴ and the Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure trial (EMPHASIS-HF).⁷⁵

The RALES trial randomly assigned patients with NYHA functional class III or IV and an LVEF of no more than 35% who had been treated with an ACEI or loop diuretic to receive spironolactone (25 mg daily) or placebo. After a mean follow-up of 24 months, patients in the spironolactone group showed a 30% reduction in all-cause mortality compared with the placebo group, as well as 29% reduction in SCD and a 35% reduction in the frequency of hospitalizations for worsening HF. The EMPHASIS-HF trial enrolled patients with mild symptoms (NYHA functional class II) and an LVEF of no more than 35% to receive eplerenone (a selective MRA) or placebo, in addition to recommended optimal medical therapy (an ACEI, an ARB, or both and a beta-blocker). After a mean follow-up period of 21 months, the eplerenone group showed a 37% reduction in the composite of CV death or hospitalization for HF

as well as a 24% reduction in all-cause mortality.

The effects of MRAs on morbidity and mortality among patients with AMI complicated by LV dysfunction and HF were evaluated in the Eplerenone post-acute myocardial infarction Heart failure Efficacy and SURvival Study (EPHESUS).⁷⁶ Patients with LV dysfunction (LVEF ≤ 40%) following AMI who developed symptoms of HF or had a history of diabetes mellitus were randomly assigned to receive eplerenone (25 mg per day initially, titrated to a maximum of 50 mg daily) or placebo in addition to optimal medical therapy (ACEIs, ARBs, diuretics and beta-blockers). After a mean follow-up duration of 16 months, the rates of all-cause mortality, CV death, and hospitalizations for CV events were significantly lower in the eplerenone group.

Of note, patients with hyperkalemia (defined as a serum potassium level > 5.0 mEq/L) or advanced CKD (defined as a serum creatinine concentration > 2.5 mg/dL or eGFR < 30 mL/min/1.73 m²) were all excluded from these randomized trials to avoid life-threatening hyperkalemia in patients with HFrEF.

Dosages of mineralocorticoid receptor antagonists and laboratory monitoring

Spironolactone and eplerenone should be initiated at a dose of 25 mg daily and up-titrated to 50 mg daily after 4~8 weeks. In patients at risk of hyperkalemia or worsening renal function (patients aged ≥ 75 years, with diabetes mellitus, or eGFR < 60 mL/min/1.73 m²),⁷⁷ an initial regimen of spironolactone 25 mg or eplerenone 25 mg every other day is advised.

The most significant risk related to MRA treatment is hyperkalemia (defined as a potassium level more than 5.5 mEq/L), which occurred in 19.0% of the spironolactone group in the RALES trial and 11.8% of the eplerenone group in the EMPHASIS-HF trial. The development of hyperkalemia is associated with morbidity and mortality.⁷⁸ However, the treatment benefits of spironolactone were maintained at least until the potassium level exceeded 5.5 mEq/L, and this benefit lost statistical significance as the potassium level approached 6.0 mEq/L.⁷⁹ Routine follow-up of potassium level and renal function is recommended 1 week and 1 month after starting or increasing the dose of MRAs. Subsequent monitoring should occur at least monthly for the first 3 months and every 3-6 months thereafter according to

the baseline renal function. Patients should be educated to avoid foods high in potassium once potassium levels are higher than 5.0 mEq/L. The dose of MRAs should be reduced if potassium levels rise above 5.5 mEq/L. If potassium levels rise above 6.0 mEq/L, MRAs should be withheld. The potassium level should be rechecked within 3-7 days, and MRAs should only be restarted if the follow-up potassium level is less than 5.0 mEq/L.

PHARMACOTHERAPY – *I_f* CHANNEL INHIBITORS

Ivabradine is a new therapeutic agent that explicitly inhibits ion movement through the f-channel, thereby inhibiting the *I_f* current in the sinoatrial node slowing diastolic depolarization, the sole effect being heart rate reduction, without altering other cardiac functions.⁸⁰

The Systolic Heart failure treatment with the *I_f* inhibitor ivabradine Trial (SHIFT) demonstrated the efficacy of ivabradine in reducing the composite endpoint of CV death or HF hospitalization. Ivabradine reduced the composite endpoint for HF in patients with symptomatic HFrEF and LVEF \leq 35%, in sinus rhythm and with a heart rate \geq 70 beats bpm who had been hospitalized for HF within the previous 12 months, receiving treatment with an evidence-based dose of beta-blockers (or maximum tolerated dose), an ACEI (or ARB), and an MRA.⁸¹ Heart rate reduction with ivabradine has been shown to be safe in severe HF and to improve clinical outcomes independently of disease severity.⁸² Patients receiving ivabradine have been shown to spend fewer days in the hospital as they benefit from a reduction in recurrent hospitalizations,⁸³ which is an essential marker of prognosis and remains a primary objective to reduce healthcare costs. The initiation of ivabradine before discharge has been shown to reduce the risk of rehospitalization during the vulnerable phase after hospitalization for HF.⁸³

Ivabradine treatment is associated with a marked reduction in LV volume and a significant improvement in LVEF, therefore suggesting that it modifies disease progression in patients with HF.⁸⁴ A great deal of clinical evidence has shown that the use of ivabradine can address unmet needs in the management of systolic HF, as it improves symptoms, increases exercise capacity, improves the quality of life, prevents re-hospitalization, and prolongs survival.⁸⁵

Ivabradine should be considered to attenuate the

risk of CV death and HF hospitalization in HFrEF patients (LVEF \leq 35%) with NYHA functional class II to IV in sinus rhythm and a resting heart rate \geq 70 bpm who are receiving a maximal dose of beta-blockers or cannot tolerate or have contraindications for a beta-blocker after receiving an ACEI (or ARB) and an MRA. A high resting heart rate is not only a well-validated risk marker but also a modifiable risk factor in HF.^{81,86} The magnitude of heart rate reduction with a beta-blocker plus ivabradine, rather than background beta-blocker dose, primarily determines the subsequent effect on outcomes,⁸⁷ since a substantial proportion of patients with HF cannot tolerate the doses of beta-blockers used in large clinical trials. The most common reasons for patients not receiving target doses include hypotension and fatigue, and contraindications to beta-blockers such as asthma, frequent hypoglycemic episodes or others. Therefore, patients who cannot tolerate optimal beta-blocker doses may benefit from the addition of ivabradine.^{81,88}

Although both beta-blockers and ivabradine are known to reduce resting heart rate, beta-blockers likely reduce ventricular arrhythmias by blocking beta-1 receptors throughout the myocardium. It is therefore likely that beta-blockers have a more pronounced benefit by reducing sudden death,^{52,89} whereas ivabradine has an isolated effect on sinoatrial nodal tissue and increases diastolic time without affecting blood pressure,⁹⁰ resulting in improvements in myocardial perfusion and stroke volume and maintaining cardiac output.⁹¹ Ivabradine has been shown to have a significant effect on pump failure death with no effect on SCD; these differences in effect indicate that combining the two may result in further benefits and cancel unwanted effects.⁹² However, bradycardia has been reported to be found more common in ivabradine-treated patients.⁹³ Moreover, in a meta-analysis study, patients receiving ivabradine were shown to have more AF than controls.⁹⁴ Close follow-up is therefore suggested to monitor these effects.

NON-PHARMACOLOGICAL MANAGEMENT – CARDIAC RESYNCHRONIZATION THERAPY & IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

Cardiac resynchronization therapy for HF

Cardiac resynchronization therapy (CRT) has been

shown to improve cardiac performance in appropriately selected patients and to improve symptoms and well-being⁹⁵⁻⁹⁷ and reduce morbidity and mortality.⁹⁸ Of the improvements in quality-adjusted life years with CRT among patients with moderate to severe HF, two-thirds may be attributed to improved quality of life and one-third to increased longevity.⁹⁹ The indications are listed in Figure 4.

Left ventricular dysfunction

Only the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION)¹⁰⁰ and the Cardiac RESynchronization in Heart Failure (CARE-HF)^{101,102} trials have compared the effect of CRT to guideline-directed medical therapy (GDMT). Most other trials have compared CRT therapy with defibrillation backup (CRT-D) to implantable cardioverter defibrillators (ICDs), and a few have compared CRT-pacemaker (CRT-P) to backup pacing. Most studies of CRT have specified that the LVEF should be < 35%, but the RAFT¹⁰³ and MADIT-

CRT^{104,105} trials specified an LVEF < 30%, while the REVERSE¹⁰⁶⁻¹⁰⁸ trial specified < 40% and the BLOCK-HF¹⁰⁹ trial < 50%. Relatively few patients with an LVEF of 35-40% have been randomized. However an individual participant data meta-analysis suggested no reduction in the effect of CRT in this group. The results of CRT trials about remodeling and HF events support a standard threshold of 35% to achieve benefits from CRT in patients with NYHA functional class II through IV HF symptoms.¹¹⁰

QRS morphology and duration

The prevalence of mechanical dyssynchrony has been documented in 40% of patients with dilated cardiomyopathy and QRS duration ≥ 120 ms, and up to 70% of patients with QRS duration ≥ 150 ms and intraventricular mechanical delay, as identified by several echocardiographic techniques.^{111,112} The COMPANION¹⁰⁰ and CARE-HF trials^{101,102} included patient with a QRS duration ≥ 120 ms, and LVEF ≤ 35% and compared GDMT to

Indications for CRT

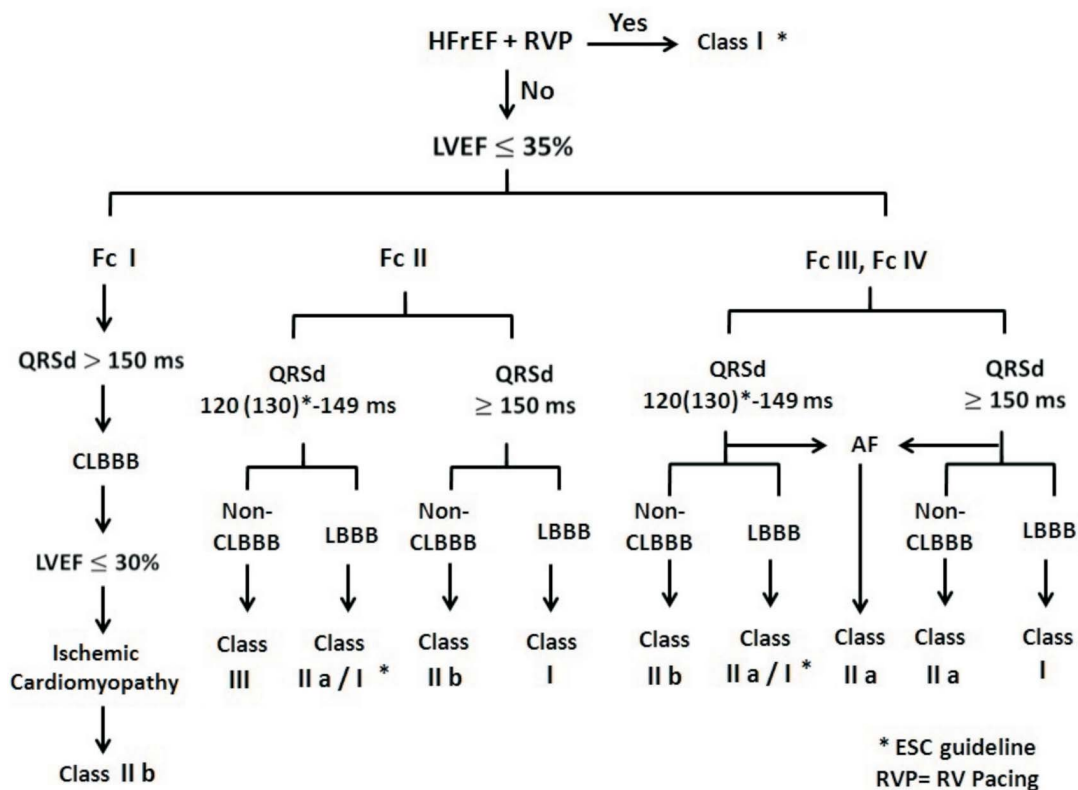


Figure 4. Indications for cardiac resynchronization therapy. AF, atrial fibrillation; CLBBB, complete left bundle branch block; CRT, cardiac resynchronization therapy; Fc, functional class; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; QRSd, QRS duration; RVP, right ventricular pacing.

CRT pacing therapy without backup defibrillation (CRT-P) and to CRT-D. Both CRT-P and CRT-D reduced the risk of the primary composite endpoint by approximately 20% compared with GDMT alone. The CARE-HF trial enrolled subjects with a QRS duration ≥ 150 ms (89% of the patients) or a QRS duration 120 to 150 ms with echocardiographic evidence of dyssynchrony (11% of the patients) and was the first study to show a significant (36%) reduction in death rate. The prospective EchoCRT trial^{113,114} suggested possible harm from CRT in patients with a QRS duration < 130 ms, and therefore CRT is not recommended if the QRS duration is < 130 ms in the ESC guidelines.^{98,113,114} However, randomization in the Echo-CRT trial was not stratified by QRS duration and only in subgroup analysis so that unmeasured residual confounding was possible.¹¹⁴

QRS morphology has also been associated with a beneficial response to CRT. Several studies have shown that patients with left bundle branch block (LBBB) morphology are more likely to respond favorably to CRT, whereas there is less certainty about patients with non-LBBB morphology.^{98,115} Therefore, the Taiwan National Health Insurance Administration only reimburses CRT for patients with a QRS duration ≥ 120 ms, LBBB, and LV dysfunction.

HFrEF with ventricular pacing dependent

When LVEF is reduced, RV pacing may exacerbate cardiac dyssynchrony. LV dyssynchrony can be prevented by CRT, which might improve patient outcomes.^{109,116-118} CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA functional class who are indicated for ventricular pacing in order to reduce morbidity.¹⁰⁹ Upgrading to CRT should be considered in patients with HF and a high proportion of RV pacing despite optimal medical therapy.

Cardiac resynchronization in patients with atrial fibrillation

A subgroup analysis of patients with AF from the RAFT study found no benefit from CRT-D compared with ICD, although less than half of the patients had $> 90\%$ biventricular capture.¹¹⁹ Observational studies have reported that when biventricular capture is $< 98\%$, the prognosis of patients with CRT declines.¹¹⁶ Large observational studies have investigated the optimal level of biventricular pacing percentage and found that a higher percentage is associ-

ated with more obvious CRT benefits. Optimal CRT benefits have been observed with a biventricular pacing percentage as close to 100% as possible.¹²⁰⁻¹²³

The roles of imaging tests

Not all patients respond favorably to CRT.⁹⁵ Several characteristics can predict improvements in morbidity and mortality, and the extent of reverse remodeling is one of the most important mechanisms of action of CRT. Patients with an ischemic etiology have been shown to have less improvement in LV function due to myocardial scar tissue, which is less likely to undergo favorable remodeling.¹²⁴ Imaging tests with echocardiography for dyssynchrony have not yet been shown to be of value in selecting patients for CRT.¹²⁵ Patients with extensive myocardial scarring have been shown to have less improvement in LV function with CRT.¹²⁶⁻¹²⁸ Optimizing the site of the LV lead can be achieved using imaging studies.^{128,129} Pacing thresholds are higher in scarred myocardium and, if possible, placing the pacing lead in such regions should be avoided.^{130,131}

Recommendations

- CRT is indicated for patients with LV dysfunction (LVEF $\leq 35\%$), LBBB (QRS ≥ 120 ms) and HF NYHA functional class II-IV.
- CRT is indicated for patients with HFrEF and RV pacing dependent regardless of functional class.
- High biventricular pacing percentage ($\geq 98\%$) is beneficial in patients with CRT and AF.
- Imaging studies can provide information regarding optimal sites for the LV lead.

Implantable cardioverter-defibrillators

A high proportion of deaths among patients with HF, especially those with milder symptoms, occur suddenly and unexpectedly. Many of these are due to electrical disturbances, including ventricular arrhythmias, bradycardia, and asystole, although some are due to coronary, cerebral or aortic vascular events. Treatments that improve or delay the progression of cardiovascular disease (CVD) will reduce the annual rate of sudden death. ICDs are effective in preventing bradycardia and correcting potentially lethal ventricular arrhythmias. Some antiarrhythmic drugs may also reduce the rates of tachyarrhythmias and sudden death. However they do not reduce overall mortality and may actually increase it. Indi-

cations are listed in the algorithm in Figure 5.

Secondary prevention of sudden cardiac death

Compared with amiodarone treatment, ICDs reduce mortality in survivors of cardiac arrest and in patients who have experienced sustained symptomatic ventricular arrhythmias. Therefore, the Taiwan National Health Insurance Administration reimburses indications for secondary prevention. An ICD is recommended in such patients when the intent is to increase survival; the decision to implant should take into account the patient's wishes and their quality of life, the LVEF (survival benefit is uncertain when the LVEF is > 35%) and the absence of other diseases likely to cause death within the following year.¹³²⁻¹³⁴

Primary prevention of sudden cardiac death

Although amiodarone may have been shown to reduce mortality in older trials of HF,^{135,136} contemporary

studies conducted since the widespread introduction of beta-blockers suggest that it does not reduce mortality in patients with HFrEF.¹³⁷⁻¹³⁹ Dronedarone^{140,141} and class I antiarrhythmic agents^{140,142} should not be used to prevent arrhythmias in this population. Some guideline-recommended therapies including beta-blockers, MRAs, sacubitril/valsartan, and CRT-Ps have been shown to reduce the risk of sudden death.¹⁴³

Sudden death has been shown to be strongly reduced by beta-blockers (41-65%).^{54,144,145} However, ACEIs and ARBs do not fully suppress aldosterone synthesis and do not provide significant benefits with regards to a decrease in SCD. MRAs prevent SCD by controlling potassium loss, blocking the effect of aldosterone on the formation of collagen, and by increasing the myocardial uptake of norepinephrine, which decreases sympathetic activation.¹⁴⁶

Spironolactone treatment has been shown to result in a 31% reduction in cardiac death, and eplerenone treatment

ICD Class I Indications

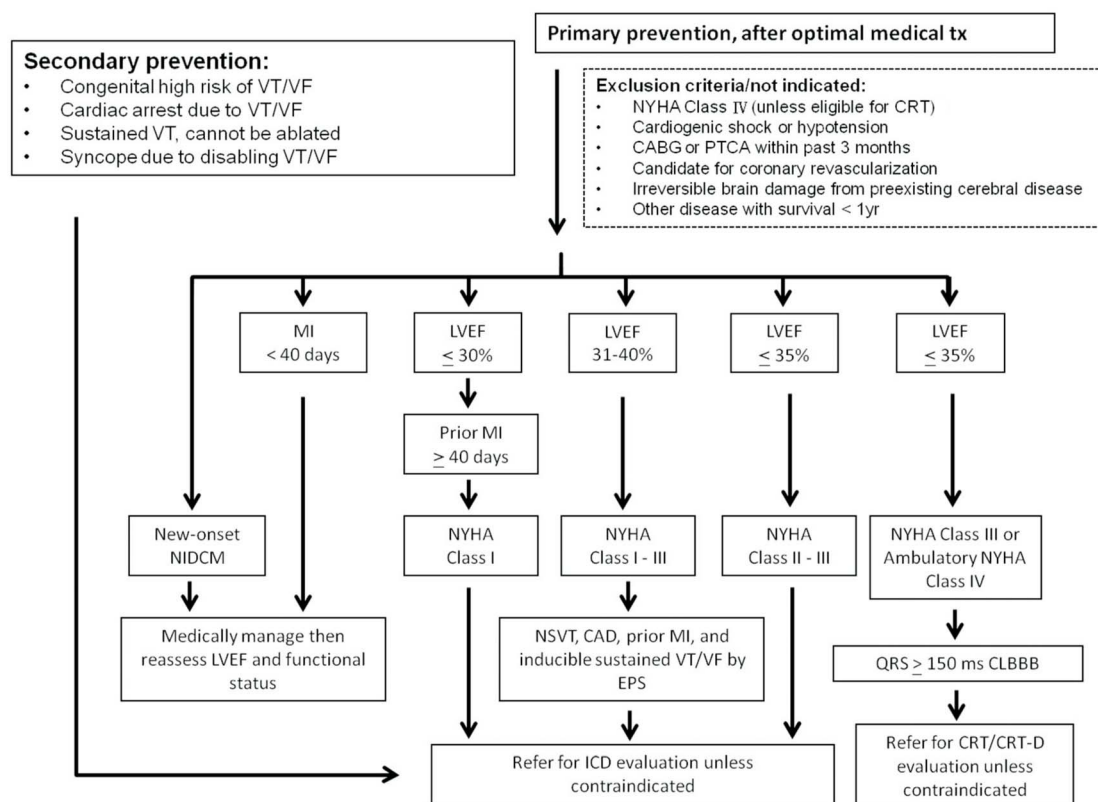


Figure 5. ICD class I indications. CABG, coronary artery bypass graft; CAD, coronary artery disease; CLBBB, complete left bundle branch block; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; EPS, electrophysiologic study; ICD, implantable cardioverter-defibrillator; LVEF left ventricular ejection fraction; MI, myocardial infarction; NIDCM, non-ischemic dilated cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NYHA, New York heart association; PTCA, percutaneous transluminal coronary angioplasty; tx, treatment; VF, ventricular fibrillation; VT, ventricular tachycardia.

has been shown to result in a reduction in death from CV causes or hospitalization for CV events (relative risk, 0.83; 95% CI, 0.72-0.94; $p = 0.005$). A reduction in sudden death from cardiac causes (relative risk, 0.79; 95% CI 0.64-0.97; $p = 0.03$) has also been reported.^{147,148}

An ICD can reduce the rate of SCD in patients with symptomatic ventricular arrhythmia.^{149,150} In patients with moderate or severe HF, a reduction in sudden death may be partially or wholly offset by an increase in death due to worsening HF.¹³⁷ In patients with mild HF (NYHA functional class II-III), an ICD will prevent about two deaths per year for every 100 devices implanted.¹³⁷ On average, patients with ischemic heart disease are at a greater risk of sudden death than patients with dilated cardiomyopathy, and, therefore, although the relative benefits are similar, the absolute benefit is greater in patients with ischemic heart disease.¹⁵⁰ Patients with a longer QRS duration may also benefit more from an ICD. However, these patients should often receive a CRT device.^{137,151} ICD therapy is not recommended in patients with NYHA functional class IV with severe symptoms refractory to pharmacological therapy who are not candidates for CRT, a ventricular assist device or cardiac transplantation, because such patients have a very limited life expectancy and are likely to die from pump failure. Patients with serious co-morbidities who are unlikely to survive for more than 1 year are unlikely to obtain substantial benefits from an ICD.¹⁵²⁻¹⁵⁶

Compared with traditional pharmacological therapy, several large RCTs including the Multicenter Automatic Defibrillator Implantation Trial (MADIT), MADIT II, and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) all showed significant benefits and cost-effectiveness in the primary prevention of SCD by ICD implantation in patients with HF_{rEF}.¹⁵⁷ Subgroup analysis of the MADIT and MADIT II trials also showed the same outcome of primary prevention of SCD with ICDs in an Asian population.^{158,159} Of 313 Taiwanese patients without ICD implantation who satisfied the MADIT II criteria, 152 (49%) died after 4.60 ± 4.31 years of follow-up. Of these patients, 68 (45%) died of SCD, similar to the conventional group in the MADIT II study (51%), and survival during the first 2 years in this cohort was inferior to the conventional group in the MADIT II study.¹⁵⁸ Two other RCTs showed no benefits in patients who had an ICD implanted within 40 days after myocardial infarction (MI).^{160,161} Although sudden arrhythmic

deaths were reduced, this was offset by an increase in non-arrhythmic deaths. Accordingly, an ICD is contraindicated during this period. A wearable defibrillator may be considered if the patient is deemed to be at high risk of ventricular fibrillation, although evidence from randomized trials is lacking.¹⁶²⁻¹⁶⁴

Recommendations

- Secondary prevention is indicated and reimbursed by the Taiwan National Health Insurance Administration.
- SCD is an important issue for patients with LV dysfunction, especially for those after an MI. An ICD is recommended.
- SCD can be reduced with MRAs, beta-blockers, and ARNI rather than ACEIs/ARBs.
- Anti-arrhythmic agents (amiodarone, dronedarone) cannot decrease the incidence of SCD in HF.

NON-PHARMACOLOGICAL MANAGEMENT – SURGERY

Guidelines for heart transplantation listing were established in 2006 and modified in 2016; the two versions of the guidelines are compared with the indications in Taiwan in Table 2. More recent studies have adopted stricter cardiopulmonary stress tests and emphasized the importance of anaerobic threshold to ensure the accuracy of the test results.

The current trend is more toward durable mechanical support. The suggested indications and contraindications for mechanical support are shown in Table 3.

The suggested timing of mechanical circulatory (MCS) support is based on the INTERagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) patient profiles as shown in Table 4.

The current algorithm for stage D HF and HF_{rEF}, in which transplantation is the first consideration. In the future, the shortage of organs and improvements in durable LV assist device (LVAD) may change the algorithm (Figure 6).^{167,168}

Surgery for heart failure

The standard surgery for stage D HF is still heart transplantation. For stage D HF and HF_{rEF}, temporary or permanent mechanical support can also be considered.

Table 2. Comparison of the Taiwan and International Society for Heart and Lung Transplantation 2006 vs. 2016 guidelines for heart transplantation listing¹⁶⁵

	2006 Guideline recommendations	2016 Guideline recommendations
Heart transplantation indications in Taiwan¹⁶⁶		
1.1. Cardiopulmonary stress testing to guide transplant listing		
HF and maximal $V_{O_2} < 10$ mL/Kg/min.	A maximal cardiopulmonary exercise test is defined as one with a respiratory exchange ratio (RER) > 1.05 and achievement of an anaerobic threshold on optimal pharmacologic therapy (Class I, Level of Evidence: B).	Continuing approval without change.
NYHA functional class IV and maximal $V_{O_2} < 14$ mL/Kg/min.	In patients intolerant of a β -blocker, a cutoff for peak oxygen consumption (V_{O_2}) of ≤ 14 mL/kg/min should be used to guide listing (Class I, Level of Evidence: B).	The presence of a CRT device does not alter the current peak V_{O_2} cutoff recommendations (Class I, Level of Evidence: B).
Congestive HF Radionuclide examination (RNA) LVEF $< 20\%$, maximal medical treatment for more than 6 months with persisted HF symptoms (medications including ACEIs, digoxin, diuretics). Severe mitral regurgitation with radionuclide examination (RNA) LVEF $< 25\%$.	In the presence of a β -blocker, a cutoff for peak V_{O_2} of ≤ 12 mL/kg/min should be used to guide listing (Class I, Level of Evidence: B).	Continuing approval without change.
Severe ischemic heart disease with radionuclide examination (RNA) LVEF $< 20\%$, thallium scan and cardiac catheterization revealing non-suitable viable revascularizable myocardium.	In young patients (< 50 years) and women, it is reasonable to consider using alternate standards in conjunction with peak V_{O_2} to guide listing, including percent of predicted ($\leq 50\%$) peak V_{O_2} (Class IIa, Level of Evidence: B).	Continuing approval without change.
NYHA functional class IV, continuous use of dopamine or dobutamine > 5 mcg/Kg/min for more than 7 days, with radionuclide examination (RNA) LVEF $< 25\%$ or cardiac index < 2.0 L/min/m ² .	In the presence of a sub-maximal cardiopulmonary exercise test (RER < 1.05), use of ventilation equivalent of carbon dioxide (VE/V_{CO_2}) slope of > 35 as a determinant in listing for transplantation may be considered (Class IIb, Level of Evidence: C).	Continuing approval without change.
HF depending on mechanical support such as extracorporeal membrane oxygenation (ECMO) and ventricular assist device.	In obese (BMI > 30 kg/m ²) patients, adjusting peak V_{O_2} to lean body mass may be considered. A lean body mass-adjusted peak V_{O_2} of < 19 mL/kg/min can serve as an optimal threshold to guide prognosis (Class IIb, Level of Evidence: B).	Continuing approval without change.
Recurrent symptomatic ventricular arrhythmia which cannot be adequately controlled.	Listing patients based solely on the criterion of a peak V_{O_2} measurement should not be performed (Class III, Level of Evidence: C).	Continuing approval without change.
Other end-stage HF, cannot be treated by conventional operation methods.		
1.2. Use of heart failure prognosis scores		
	In circumstances of ambiguity (e.g., peak $V_{O_2} > 12$ and < 14 mL/kg/min), an HF Survival Score (HFSS) may be considered, and it may add discriminatory value to determining the prognosis and guide listing for transplantation for ambulatory patients (Class IIb, Level of Evidence: C).	HF prognosis scores should be performed along with a cardiopulmonary exercise test to determine the prognosis and guide listing for transplantation for ambulatory patients. An estimated 1-year survival as calculated by the Seattle HF Model (SHFM) of $< 80\%$ or an HF Survival Score (HFSS) in the high/medium risk range should be considered as reasonable cutoff points for listing (Class IIb, Level of Evidence: C). Listing patients solely on the criteria of HF survival prognostic scores should not be performed (Class III, Level of Evidence: C).

Table 2. Continued

1.3. Role of diagnostic right-heart catheterization	
Right heart catheterization (RHC) should be performed on all candidates in preparation for listing for cardiac transplantation and annually until transplantation (Class 1, Level of Evidence: C).	RHC should be performed in all adult candidates in preparation for listing for cardiac transplantation and periodically until transplantation (Class 1, Level of Evidence: C). Periodic RHC is not advocated for routine surveillance in children (Class III, Level of Evidence: C). Continuing approval without change.
RHC should be performed at 3- to 6-month intervals in listed patients, especially in the presence of reversible pulmonary hypertension or worsening HF symptoms (Class I, Level of Evidence: C).	Continuing approval without change.
A vasodilator challenge should be administered when the pulmonary artery systolic pressure is ≥ 50 mmHg and either the transpulmonary gradient is ≥ 15 , or the pulmonary vascular resistance (PVR) is > 3 Wood units while maintaining a systolic arterial blood pressure > 85 mmHg (Class I, Level of Evidence: C).	Continuing approval without change.
When an acute vasodilator challenge is unsuccessful, hospitalization with continuous hemodynamic monitoring should be performed, as the PVR will often decline after 24 to 48 hours of treatment consisting of diuretics, inotropes and vasoactive agents such as inhaled nitric oxide (Class I, Level of Evidence: C).	Continuing approval without change.
If medical therapy fails to achieve acceptable hemodynamics, and if the left ventricle cannot be effectively unloaded with mechanical adjuncts, including an intra-aortic balloon pump (IABP) and/or LV assist device (LVAD), it is reasonable to conclude that pulmonary hypertension is irreversible (Class IIb, Level of Evidence: C).	If medical therapy fails to achieve acceptable hemodynamics and if the left ventricle cannot be effectively unloaded with mechanical adjuncts, including an IABP and/or LVAD, it is reasonable to conclude that the pulmonary hypertension is irreversible. After LVAD, reevaluation of hemodynamics should be done after 3 to 6 months to ascertain reversibility of pulmonary hypertension (Class IIA, Level of Evidence: C).

ACEIs, angiotensin converting enzyme inhibitors; CRT, cardiac resynchronization therapy; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Valvular surgery does not provide any survival benefits for patients with stage D HF. In selected patients with stage B and stage C HF, revascularization or valvular surgery is appropriate.¹⁷²

CO-MORBIDITIES IN HEART FAILURE

Chronic kidney disease

With the implementation of The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, CKD is clinically defined as an eGFR < 60 mL/min/1.73 m² and/or the presence of albuminuria (high 30-300 or very high > 300 mg albumin/1 g of

urine creatinine) and eGFR < 30 mL/min/1.73 m² as severe renal dysfunction. Worsening renal function is defined as an increase in serum creatinine by 25% or 0.3 mg/dL increase or eGFR drop by $> 20\%$.

CKD is one of the most common comorbidities of HF.¹⁷³ The prevalence of moderate to severe renal dysfunction has been reported to be around 30% to 60%,¹⁷⁴ and the incidence of worsening renal function in acute HF has been estimated to be around 45%. The extent of renal dysfunction affects the risk of CVD,^{175,176} and patients with HF and moderate renal dysfunction have been reported to have a more than 2-fold risk of total mortality.¹⁷⁷ The survival of patients on hemodialysis has also been reported to be lower in patients with HF

Table 3. Indications and contraindications for mechanical support**Durable mechanical support indications and contraindications**¹⁶⁷⁻¹⁶⁹

Indications: combination of the following:

- Frequent hospitalizations for HF
- NYHA functional class IIIB*-IV functional limitations despite maximal therapy
- NYHA functional class IIIB*-IV
- Intolerance to neurohormonal antagonists
- Increasing diuretic requirement
- Symptomatic despite CRT
- Inotrope dependence
- Low peak VO₂ (< 14-16)
- End-organ dysfunction attributable to low cardiac output

Contraindications

Absolute

- Irreversible hepatic disease
- Irreversible neurological disease
- Medical nonadherence
- Severe psychosocial limitations

Relative

- Age > 80 years for destination therapy
- Irreversible renal disease
- Obesity or malnutrition
- Musculoskeletal disease that impairs rehabilitation
- Active systemic infection or prolonged intubation
- Untreated malignancy
- Severe peripheral vascular disease
- Active substance abuse
- Impaired cognitive function
- Unmanaged psychiatric disorder
- Lack of social support

CRT, cardiac resynchronization therapy; HF, heart failure; NYHA, New York heart association; * NYHA functional class IIIB refers to Interagency registry for mechanically assisted circulatory support (INTERMACS) patient profiles 6 (exertion limited) symptoms.

than in those without HF before starting end-stage renal disease (ESRD) therapy.¹⁷⁸ Interactions between the heart and kidneys are so tightly involved that they affect the outcome of patients.^{179,180} Therefore, the term “cardiorenal syndrome” has been coined to indicate the relationship between renal dysfunction and HF.

Many factors contributing to the impairment of renal function in patients with HF have been proposed, including reduced cardiac output, intra-abdominal pressure and CVP, sympathetic overactivity, a maladaptive RAA system, oxidative injury, endothelial dysfunction, and anemia.^{179,181,182} Reduced cardiac output in HF is considered to be the main factor leading to a decrease in renal function. However, data analysis from the Evaluation Study of Congestive heart failure And Pulmonary artery catheterization Effectiveness trial (ESCAPE) showed that cardiac output was not the only risk factor causing impaired renal function, and a weak correlation between the cardiac index and eGFR was shown.^{183,184} Nonetheless, CVP level can affect eGFR and mortality.

Damman et al. reported that increased CVP was associated with impairment of renal function and independently associated with all-cause mortality during a 10-year follow-up period in patients with CVD.¹⁸⁵ In addition, a high CVP level has been reported to be the most important hemodynamic factor leading to renal dysfunction in decompensated patients with advanced HF.^{185,186}

A previous clinical study reported that, when the intra-abdominal venous pressure increased up to approximately 20 mmHg, the GFR decreased by 28%.¹⁸⁷ Therefore, the appropriate use of diuretics may reduce renal venous pressure and thus improve GFR. RV dysfunction may also contribute to central venous congestion and impairment of renal function, and thus improving RV function may decrease the extent of renal dysfunction. Along with the hemodynamic factors, HF can activate the RAA system that would subsequently increase sodium reabsorption, water retention, sympathetic overactivity, peripheral vascular contraction, and LV remodeling. Renal function may decline after RAA system activation. Previous studies have shown that ACEIs and ARBs can protect against the deterioration of renal function in diabetic nephropathy.^{188,189}

The metabolism of BNP/NT-proBNP is affected by renal function, and thus caution should be used when using these biomarkers to diagnosis or evaluate patients with acute kidney injury or CKD. However, the level of BNP itself still has a similar diagnostic value to predict LV hypertrophy in dialysis patients as in the general population.¹⁹⁰ It is essential to use an echocardiogram to evaluate cardiac function. Foley et al. reported that 73.4% of patients with ESRD before hemodialysis had LV hypertrophy, 35.8% had LV dilatation, and 14.8% had LV dysfunction function.¹⁹¹ The prevalence of LV diastolic dysfunction has been reported to be higher in patients with CKD than in patients without CKD.¹⁹² The KDOQI guidelines recommend that echocardiograms should be performed in all patients at the initiation of dialysis, once patients have achieved a dry weight within 1-3 months, and at 3-yearly intervals thereafter.¹⁹³

Most HF randomized clinical trials have excluded patients with severe renal dysfunction (eGFR < 30 mL/min/1.73 m²). Therefore, there is a lack of evidence-based therapy in these patients. In general, HF patients with eGFR > 30 mL/min/1.73 m² should receive standard therapy with an ACEI, ARB and MRA.¹⁹⁴ Worsening of re-

Table 4. INTERMACS patient profiles and mechanical support timing^{170,171}

Level	Definition	Description	Time to MCS
1	“Crash and burn”	Critical cardiogenic shock Patients with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels.	Within hours
2	“Sliding on inotropes”	Progressive decline Patients with declining function despite intravenous inotropic support may be manifested by worsening renal function, nutritional depletion, and an inability to restore volume balance.	Within a few days
3	“Dependent stability”	Stable but inotrope dependent Patients with stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both), but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction.	Within a few weeks
4	“Frequent flyer”	Resting symptoms Patients can be stabilized close to normal volume status but experience daily symptoms of congestion at rest or during activities of daily living (ADL). Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy.	Within weeks to months
5	“Housebound”	Exertion intolerant Comfortable at rest and with ADL but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms but may have underlying refractory elevated volume status, often with renal dysfunction.	Variable
6	“Walking wounded”	Exertion limited Patients without evidence of fluid overload are comfortable at rest, and with ADL and minor activities outside the home but fatigue after the first few minutes of any meaningful activity.	Variable
7	“Placeholder”	Advanced NYHA functional class III Includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.	Not a candidate for MCS

INTERMACS, Interagency registry for mechanically assisted circulatory support; MCS, mechanical circulatory support; NYHA, New York Heart Association.

nal function is often encountered in patients with HF at initiation or up-titration of ACEI or ARB therapy, especially under conditions of dehydration or diuretic usage. It is necessary to increase the frequency of monitoring serum creatinine and electrolytes when up-titrating the doses of ACEIs, ARBs, and diuretics. Although worsening renal function increases mortality in HF patients during therapy, decreasing the doses of ACEIs and ARBs or discontinuing therapy should only be considered when serum creatinine increases or eGFR decreases by more than 30% from the baseline level, since long-term outcomes are not affected by ACEIs or ARBs with a mild de-

crease in eGFR.¹⁹⁵ Furthermore, Brisco et al. reported that an increased serum creatinine level after diuretic therapy did not increase the mortality rate in patients with acute HF.¹⁹⁶ In HF patients with renal dysfunction, beta-blockers have been shown to decrease CV mortality by 34% and all-cause mortality by 28%, but increase the risk of hypotension and bradycardia by 5-fold.¹⁹⁷ Digoxin should be avoided in patients with acute renal injury and an eGFR < 30 mL/min/1.73 m². MRAs are also contraindicated in patients with severe renal dysfunction with an eGFR < 30 mL/min/1.73 m². However, patients with HF undergoing chronic hemodialysis are still

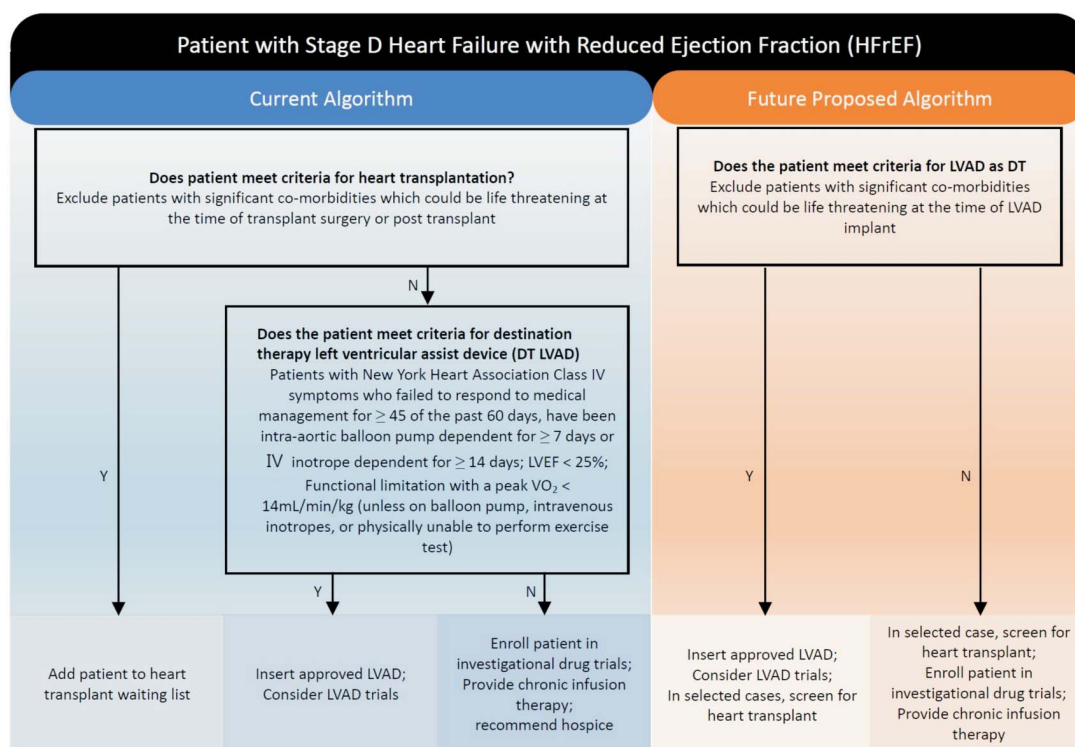


Figure 6. Algorithm changes for stage D heart failure. DT, destination therapy; IABP, intra-aortic balloon pump; IV, intravenous; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; VO₂, oxygen uptake.

recommended to receive ACEI, ARB and beta-blocker therapy.¹⁹⁸⁻²⁰⁰

It is recommended to use loop diuretics to remove fluid overload in acute HF with CKD effectively. Ultrafiltration is considered to those with complications and poor response to high dose diuretics. Theoretically, ultrafiltration therapy could remove fluid faster and sodium efficiently. However, there are potential complications with ultrafiltration therapy including bleeding, hemolysis, hypotension, allergic reaction, air emboli, and worsening renal function. In the Relief for Acutely fluid-overloaded Patients with Decompensated Congestive Heart Failure trial (RAPID-CHF) and the Ultrafiltration versus intravenous diuretics for patients hospitalized for Acute Decompensated heart failure trial (UNLOAD), ultrafiltration therapy could early remove body fluid, improve symptoms and decrease 90-day readmission rate, but no effects on creatinine level and days of hospitalization.²⁰¹⁻²⁰³ In CARDiorenal RESCue Study in acute decompensated Heart Failure (CARESS-HF) trial, it is demonstrated that stepped pharmacologic therapy is preferred to the preservation of renal function and fewer complications than ultrafiltration therapy in acute decompensated HF.²⁰⁴

Diabetes

It is very common for diabetes and dysglycemia in HF patients. Diabetes in HF is associated with poorer LV function and prognosis, and a higher glycohemoglobin (HbA1c) is associated with a higher risk of CV events in HF patients who have not been treated for diabetes.²⁰⁵

It is not clear whether intensive glycemic control alters the risk of CV events, so HF patients with diabetes should be individually assessed for his or her optimal glycemic target for the prevention of macrovascular events.^{206,207} Metformin is considered to be first-line pharmacological therapy for type 2 diabetes, but it is contraindicated in patients with severe renal or hepatic dysfunction.²⁰⁶⁻²⁰⁸ Empagliflozin and canagliflozin, inhibitors of sodium-glucose cotransporter 2 (SGLT-2 inhibitors), were shown to significantly reduce CV death and hospitalizations for HF in the Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients (EMPA-REG OUTCOME)²⁰⁸ and the Canagliflozin cardiovascular assessment study (CANVAS program)²⁰⁹ trials. They should be considered as second-line pharmacological therapy for HF patients with type 2 diabetes. In addition, dapagliflozin reduced the rates of CV

death and hospitalizations for HF in the Dapagliflozin Effect on Cardiovascular Events trial (DECLARE-TIMI 58) trial.²¹⁰ To date, the DECLARE-TIMI 58 trial is the only diabetic CV outcome trial that has included HF as a primary endpoint. The results of this trial indicated durable protection against HF in those with underlying CVD, and probably in those without a history of CVD. Reliable protection against renal decline was also shown with dapagliflozin, with similar risk estimates in the DECLARE-TIMI 58 trial as previously reported for empagliflozin and canagliflozin in the EMPA-REG OUTCOME and CANVAS program trials.

There is no firm evidence of the additional benefits of long-acting glucagon-like peptide-1 and dipeptidyl peptidase-4 inhibitors (DPP4is) in patients with HF.^{206,207,211} However, clinicians should be aware of the potential of an increased risk of hospitalization for HF in patients taking DPP4is, particular for saxagliptin, but less for sitagliptin.²¹²⁻²¹⁵ Thiazolidinedione can increase the risk of HF and should be avoided in HF patients.^{206,207} Insulin may exacerbate fluid retention and worsen HF. Sulfonylurea derivatives can also increase the risk of worsening HF.²⁰⁷

Chronic obstructive pulmonary disease

COPD and HF may coexist, and about 20-32% of COPD patients have HF.²¹⁶ Due to overlap in symptoms and signs, the diagnosis of COPD in a patient with HF may be difficult. BNP/NT-proBNP levels and echocardiography can be used to confirm the diagnosis of HF in COPD patients. COPD should be suspected if HF patients have the following: smoking history; age > 40 years; dyspnea; chronic productive cough; disproportionate dyspnea or body weight loss for an unknown reason; electrocardiogram showing P-pulmonale, atrial flutter, AF or incomplete RBBB; chest X-ray showing increased lung marking, emphysema or hyperinflation; echocardiogram showing right atrial dilation or pulmonary hypertension for an unknown reason. Spirometry should be performed when HF patients have been stable and euvolemic for at least 3 months. If the FEV% (FEV1/FVC) is < 0.7 after inhalation of a bronchodilator, COPD can be diagnosed.²¹⁷

Beta-blockers are not contraindicated in patients with COPD, and only relatively contraindicated in those with asthma. Starting with a low dose of more selective β_1 -adrenoceptor antagonists (bisoprolol, metoprolol

succinate or nebivolol) combined with close monitoring for signs of airway obstruction is considered to be appropriate to treat COPD patients with HF.²⁰⁷ A study on patients with coexisting COPD and HF using the Taiwan National Health Insurance Research Database showed a dose-response survival benefit of bisoprolol.⁷³ All ACEIs, ARBs, diuretics and MRAs are also suitable treatments for COPD patients with HF.²¹⁸ Inhaled bronchodilators are preferred for HF patients with COPD rather than the oral forms.²¹⁹ Long-acting β_2 -agonists (LABAs), long-acting muscarinic antagonists (LAMAs), or a combination of both have not been associated with an increased risk of CV events.²²⁰ Oral corticosteroids can cause sodium and water retention, but is not for inhaled form.²²¹ After LABA or LAMA, combining with low dose theophylline (100-200 mg/day) might be considered for HF patients with COPD. However, the toxicity of theophylline is dose-related and should be closely monitored.^{219,221}

Sleep-disordered breathing

More than one-third of HF patients suffer from sleep-disordered breathing (SDB). The most common types are central sleep apnea (CSA), obstructive sleep apnea (OSA), and a mixed pattern of the two. CSA and HFrEF are closely linked, and OSA is associated with an increased risk of incident HF in men. It is clinically important to distinguish OSA from CSA, given the different responses to treatment. Overnight polysomnography can be used to distinguish the type of sleep apnea in HF patients with suspected SDB or excessive daytime sleepiness.^{40,207} In patients with CVD and OSA, continuous positive airway pressure (CPAP) may improve sleep quality and daytime sleepiness.²²² In patients with paroxysmal AF, the use of CPAP for OSA has been shown to reduce the risk of progressing to more permanent forms.²²³ Although CPAP, bi-level positive airway pressure (BiPAP) and adaptive servo-ventilation (ASV) can be considered to treat nocturnal hypoxemia in patients with OSA, none of them has been proven to improve the major outcomes in HFrEF.^{40,206,207,222,224} CPAP has been shown to alleviate CSA, improve LVEF and 6-minute walk test distance, but not to improve the prognosis or the rate of HF-related hospitalizations.²²⁵ ASV is not recommended in patients with HFrEF and predominantly CSA due to increases in both all-cause and CV mortality.^{40,206,207,226}

OXYGEN THERAPY IN ACUTE HEART FAILURE

Supplemental oxygen is considered to be a standard treatment for all patients with heart disease, especially for hypoxemia. However, compelling clinical evidence is lacking for the beneficial effect of oxygen therapy in patients with heart disease. It could be life-saving, but it may also be harmful if the inappropriate concentration is given.

Oxygen is an integral part of the maintenance of normal cellular function and tissue survival. Hypoxemia can cause tissue hypoxia that subsequently impairs tissue function. It is reasonable to provide supplemental oxygen in this situation to recover hypoxemia; however excessive oxygen supplementation would have adverse effects on the circulatory system. Most clinical studies on patients with acute coronary syndrome or healthy populations have shown that oxygen therapy decreases cardiac output and stroke volume but increases systemic vascular resistance in normal oxygen saturation ($\text{SaO}_2 > 90\%$).²²⁷⁻²²⁹ Oxygen therapy in patients with ST-segment-elevation MI without hypoxemia may also increase early myocardial injury and MI size.²³⁰ A registry-based study did not support the routine use of supplemental oxygen in patients with suspected MI without hypoxemia.²³¹ Another study showed that hyperoxemia increased the generation of reactive oxygen species which then damaged pulmonary alveolar cells in animal studies and that this injury could be alleviated with antioxidants.²³² In other animal studies, exposure to a very high oxygen concentration ($\text{FIO}_2 > 0.9$) for more than 72-96 hours or even $\text{FIO}_2 > 0.8$ for a week induced lung injury.^{233,234} Therefore, appropriate oxygen supplementation should maintain cellular function and improve tissue hypoxia. Hyperoxemia may cause unnecessary burden and even injury to tissue.

Peripheral pulse oximetry (SpO_2) is a standard clinical tool to continuously monitor oxygenation. The exact prevalence of hypoxemia in acute HF is unclear. Theoretically, tissue hypoxia in acute HF results from low cardiac output and decreased tissue perfusion even with normal SpO_2 . To improve tissue hypoxia in acute HF, it is important to focus on increases in cardiac output and tissue perfusion. Simply providing supplementation with a high oxygen concentration does not seem to be of much help in this condition. Masip et al. demonstrated that measuring baseline oxygen saturation with pulse

oximetry in patients with acute HF could enhance the diagnosis of the severity and prognostic implications.²³⁵ In their study, baseline oxygen saturation decreased progressively according to the presence and severity of acute HF after acute MI. Another study demonstrated that baseline pO_2 , pCO_2 , and pH were not significantly associated with mortality in patients with acute decompensated HF after multivariate analysis.²³⁶

A target SpO_2 range within 94-98% is recommended in patients with acute HF. In addition, a target SpO_2 range of 88-92% should be used for patients at risk of hypercapnic respiratory failure, such as those with COPD.²³⁷ A sudden decline in $\text{SpO}_2 \geq 3\%$ in a patient within the target saturation range and acute illness should prompt a comprehensive assessment. Oxygen supplementation should be considered if the oxygen desaturation is $< 94\%$ (or 88% in patients at risk of hypercapnic failure) in patients with acute HF. The routine use of supplemental oxygen in patients without obvious hypoxemia is not recommended.

There is evidence of the efficacy of non-invasive ventilation (NIV) in patients with acute HF and pulmonary edema to reduce the intubation rate and decrease short-term mortality.^{238,239} However, the routine use of NIV is not advisable. An analysis from the Three Interventions in Cardiogenic Pulmonary Oedema trial showed no differences in intubation rate, 7-day mortality rate, 30-day mortality rate, or admission to an intensive care unit (ICU) among three study groups of CPAP, NIV, or standard oxygen therapy.²⁴⁰ Therefore, NIV (BiPAP or CPAP) is recommended for patients with acute pulmonary edema with a high respiratory rate (> 25 breaths per minute) and persistent systemic hypoxemia ($< 90\%$) despite high-flow oxygen supplementation.²⁴¹ NIV has the potential risks of worsening hypercapnia, aspiration, right HF, and pneumothorax.

In most acute HF patients, oxygen therapy has to be reduced gradually when they become clinically stable and achieve oxygen saturation above the target range of 94-98% (or 88-92% in patients at risk of hypercapnic failure). Weaning or discontinuing oxygen supplementation should be considered and stopped once a patient is clinically stable on low-concentration oxygen (nasal cannula 2 L/min oxygen). Once the patient can breathe on room air after discontinuing oxygen supplementation, SpO_2 and vital signs should be continuously monitored for at least 5 minutes. If oxygen saturation is maintained within the normal

range, it is recommended to recheck SpO₂ 1 hour later.

Recommendations

1. Oxygen therapy is not routinely recommended for patients with acute HF without hypoxemia.
2. Keep SpO₂ within 94-98% (88-92% in patients at risk of hypercapnic respiratory failure).
3. Supply oxygen if SpO₂ < 94% (88% in patients at risk of hypercapnic respiratory failure).
4. Taper the oxygen concentration if SpO₂ > 98% (> 92% in patients at risk of hypercapnic respiratory failure).
5. NIV (BiPAP or CPAP) should not routinely be used (only for patients with acute pulmonary edema with a high respiratory rate (> 25 breaths per minute) and persistent systemic hypoxemia (< 90%) despite high-flow oxygen supplementation.

CHEMOTHERAPY-INDUCED CARDIAC TOXICITY

Introduction

- With advances in cancer therap, the survival of patients with cancer has improved. However, the morbidity and mortality due to treatment side effects have increased.²⁴²
- Both traditional, targeted and even immune-therapies can affect the CV system, resulting in hypertension, HF, myocarditis, arrhythmias, vascular disease, and thrombosis.^{243,244}
- Even though the recurrence of cancer causes most cancer-related deaths in cancer survivors, CVD is also responsible for substantial morbidity and mortality.^{244,245}

- According to previous studies, the incidence of chemotherapy-induced cardiotoxicity varies.^{246,247} In previous retrospective studies, the overall incidence of anthracycline-induced cardiotoxicity is 4-5% for cumulative doses of up to 500 mg/m², and 11-31% for cumulative doses greater than 500 mg/m².²⁴⁷⁻²⁴⁹
- Among the cases of chemotherapy-induced cardiotoxicity, 98% have been reported to occur within the first year and to be asymptomatic.²⁴⁷ However, the effects on the CV system may last for years after exposure, particularly among children.

Mechanism and clinical manifestation

- There are two types of cardiotoxicities (Table 5).
- Type I includes anthracyclines (e.g., doxorubicin and epirubicin), alkylating agents, antimetabolites and antimicrotubule agents, which cause permanent cell death and irreversible myocardial damage in a dose-dependent manner.²⁵⁰ For example, doxorubicin has been shown to affect cardiac function mainly through mechanisms that involve the formation of reactive oxygen species, induction of apoptosis, deoxyribonucleic acid (DNA) damage through interactions with topoisomerase II, and inhibition of protein synthesis.²⁵⁰ Subsequently, the production of toxic oxygen-free radicals and the topoisomerase II-beta-doxorubicin-DNA complex can also induce DNA breaks and cell death in cardiomyocytes, resulting in cardiotoxicity.²⁵⁰
- Type II includes monoclonal antibodies, tyrosine kinase inhibitors (TKIs) and protease inhibitors, are their effects are mostly reversible.²⁵¹ The use of TKIs requires

Table 5. Two types of chemotherapy-induced cardiac dysfunction

	Type I	Type II
Medications	Anthracyclines (Doxorubicin, Idarubicin, Epirubicin) Alkylating agents (Cyclophosphamide, Ifosfamide) Antimetabolites (Clofarabine) Antimicrotubule agents (Docetaxel, Paclitaxel)	Monoclonal antibodies (Trastuzumab, Bevacizumab, Pertuzumab) TKIs (Sunitinib, Pazopanib, Sorafenib) Protease inhibitors (Carfilzomib, Bortezomib)
Incidence	1-48%	0.2-20%
Mechanism	Cellular death	Cellular dysfunction
Dose	Dose dependent	Grossly dose independent
Pathology	Biopsy findings (+)	Biopsy findings (-)
Reversibility	Permanent damage	Mostly reversible
Risk factors	Concurrent radiotherapy Age (< 18 or > 65 y/o) Female Previous cardiac disease Hypertension Renal failure Genetic factors	Concurrent anthracyclines Age Previous cardiac disease Obesity Genetic factors

an understanding of mechanism-based (on-target) and bystander-based (off-target) toxicity.^{251,252} Off-target effects result from non-selective redundancy in essential signaling cascades targeting cancer cell proliferation. Unlike in conventional chemotherapy, off-target toxicity is less common with TKIs.²⁵¹

Diagnosis

- Cancer therapeutic-related cardiac dysfunction is defined as a reduction of LVEF > 10% to a value below 50%.^{244,253,254}
- Imaging strategies to screen and detect cardiotoxicity include echocardiography, nuclear imaging, and cardiac magnetic resonance examinations.²⁴⁴
- Novel modalities such as speckle-tracking echocardiography have also been used to detect cardiac dysfunction.²⁴⁴ A relative percentage reduction in global longitudinal strain > 15% from baseline may suggest the risk of cardiotoxicity.²⁵⁵
- Biomarkers including troponins and NPs may increase the diagnostic value using the same assays during fol-

low-up measurements.²⁵⁶ The choice of modalities depends on local expertise and availability.

- According to the European Society for Medical Oncology guidelines, patients receiving anthracyclines and/or trastuzumab in an adjuvant setting should receive serial monitoring of cardiac function at baseline, 3, 6 and 9 months during treatment, and then at 12 and 18 months after the initiation of treatment.²⁵⁷ Monitoring should be repeated during or following treatment as clinically indicated.
- Patients with a decreased LVEF at baseline should be evaluated with repeated cardiac imaging 2-3 weeks after showing the initial decrease in LVEF.²⁵⁸ If a reduced LVEF is found at baseline, a multidiscipline consultation between cardiologists and oncologists is required.²⁴⁴

Other cardiac comorbidity associated with chemotherapy

- In addition to HF, chemotherapy is involved in other CV complications such as CAD, arrhythmia, arterial hypertension, valvular disease and venous thrombosis (Table 6).^{243,244}

Table 6. Cancer drug-associated other cardiac comorbidities including arrhythmia, coronary artery disease, and arterial hypertension

Arrhythmia	
Medications	Risks
Anthracyclines, arsenic trioxide, bortezomib, alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), 5-FU, ifosfamide, IL-2, methotrexate, mitoxantrone, paclitaxel, rituximab, thalidomide.	Bradycardia
Anthracyclines, arsenic trioxide, bortezomib, cyclophosphamide, 5-FU, mitoxantrone, rituximab, taxanes, thalidomide.	Atrioventricular block (high risk as a combination of radiotherapy)
Alkylating agents, amsacrine, anthracyclines, antimetabolites, bortezomib, IL-2, interferons, paclitaxel	Supraventricular tachycardias (most atrial fibrillation)
Alkylating agents, amsacrine, antimetabolites, arsenic trioxide, doxorubicin, interferons, IL-2, methotrexate, paclitaxel, proteasome inhibitors	Ventricular tachycardia/fibrillation
Anthracyclines (14%), histone deacetylase inhibitors (depsipeptide, vorinostat) (10-14%), TKIs* (3-15%), arsenic trioxide (35.4%, risk of Torsade de pointes)	QTc prolongation
Coronary artery disease	
Medications	Risks
Fluoropyrimidines (5-FU, capecitabine, gemcitabine)	Symptomatic myocardial ischemia (18%), silent myocardial ischemia (7-10%)
VEGF inhibitors [#] (bevacizumab)	Risk of arterial thrombosis (1.4-3.8%)
Radiotherapy	2-7-fold increased relative risk of myocardial infarction, especially in Hodgkin lymphoma survivors. Dose-dependent
Arterial hypertension	
Medications	Risks
VEGF inhibitors [#]	Incidence of HTN up to 23.6%
TKIs*	Incidence of HTN up to 15.3-21.6%

* Tyrosine kinase inhibitors (TKIs), e.g., ponatinib, sorafenib, sunitinib, and ibrutinib; [#] Vascular endothelial growth factor (VEGF) inhibitors, e.g., bevacizumab. HTN, hypertension.

- For example, kinase inhibitors (e.g., nilotinib or ponatinib) may contribute to hypertension and vascular disease.²⁵⁹
- Angiogenesis-inhibitors (vascular endothelial growth factor [VEGF] inhibitors, e.g., bevacizumab or pazopanib) may induce hypertension, thrombosis, and cardiomyopathy.²⁶⁰
- Proteasome inhibitors (e.g., carfilzomib) are associated with hypertension and thrombosis.²⁶¹
- Cancer immunotherapies may cause myocarditis and vascular toxicity.²⁶²
- Chemotherapeutic agents do not directly affect cardiac valves, but they may be observed in patients post radiotherapy for decades.^{258,263}
- Patients with cancer may experience a broad spectrum of cardiac arrhythmias, including bradyarrhythmias, tachyarrhythmias, and conduction defects at a baseline incidence of 16-36%.²⁶⁴
- Post-chemotherapy, treatment-induced QT prolongation can lead to life-threatening arrhythmias such as torsade de pointes.²⁶⁴ The duration of the QT interval and risk factors for QT prolongation should be monitored before, during and post cancer treatment.²⁴⁴
- Among different drugs, arsenic trioxide, which is mostly used in leukemia and myelomas, has been associated with the high occurrence of QTc prolongation in 26-93% of patients, and subsequent life-threatening ventricular tachyarrhythmias have frequently been reported.²⁶⁵

The management of chemotherapy-induced cardiotoxicity

- Strategies to prevent chemotherapy-induced cardiotoxicity include prevention before treatment, monitoring during treatment and treatment after the development of cardiotoxicity (Figure 7).
- Before chemotherapy, the risk factors which increase the incidence of cardiotoxicity should be evaluated and managed carefully. When choosing antineoplastic regimens, analogs (epirubicin, pixantrone) or liposomal formulations can be used instead of doxorubicin in the delivery of continuous infusions (up to 48-96 h) to decrease peak plasma levels.^{266,267}
- Most importantly, the cumulative dose should be carefully monitored to below 400 mg/m².²⁴⁴ When there is evidence of similar efficacy or superiority with non-anthracycline regimens, they should be considered,

particularly in patients with established CV risk factors or previous exposure to anthracyclines.²⁴⁴

- A reliable method to evaluate cardiac function should be performed through periods of treatment and follow-up. Clinicians should be aware of newly developed HF symptoms or asymptomatic reductions in LVEF. A careful review of medications is crucial for further discussion with an oncologist regarding the chemotherapy plan.
- If cardiac dysfunction develops, early interventions for HF management should be initiated, with beta-blockers and ACEIs/ARBs being regarded as the most beneficial medications.^{244,268}
- Chemo- or target therapy regimens should be discontinued if significant complications occur. It remains unclear whether these regimens should be reinstated once these complications have been managed. The subsequent use of traditional chemotherapies (e.g., fluorouracil) has been associated with an increased risk of serious complications,²⁶⁹ while target therapies (e.g., VEGF inhibitors) should be reinstated at the same or lower dose to achieve a maximum effect on the tumor once the complications have been controlled.²⁷⁰

Taiwanese data and future perspectives

- Cardio-oncology, a new field in Taiwan with many unmet needs, requires close collaboration between oncologists and cardiologists. With the advances in knowledge in cardio-oncology, some local studies have been performed.

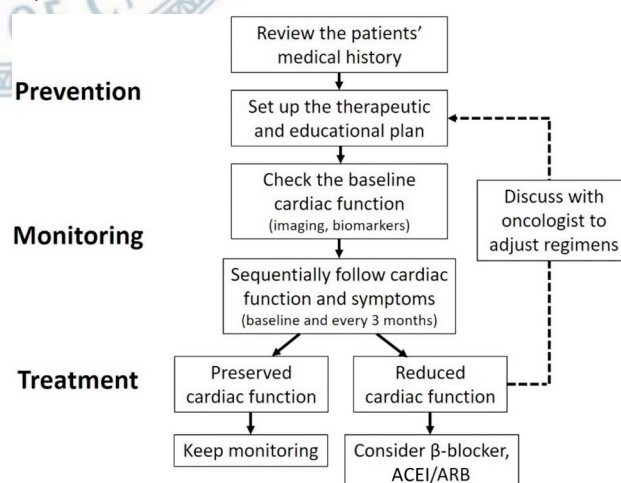


Figure 7. Strategies to reduce chemotherapy-induced cardiotoxicity. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

- An increased systemic vascular fluorodeoxyglucose uptake has been observed in serial positron-emission tomography/computed tomography examinations after cisplatin-based concurrent chemoradiotherapy in patients with head/neck cancer.²⁷¹
- In addition, using speckle-tracking imaging, RV longitudinal strain sensitively has been shown to predict the development of dyspnea in breast cancer patients receiving epirubicin therapy.²⁷² The future points to further joint research to provide evidence-based strategies in cardio-oncology.

IMPLICATIONS FROM THE TAIWAN HFrEF REGISTRY

Although more than 20,000 patients are hospitalized for HF annually, local data of “real-world practice” are scarce. Adherence to guideline-driven HF treatment and multi-disciplinary HF care has not received much attention in Taiwan. Therefore, a nationwide registration program, the Taiwan Society of Cardiology - Heart Failure with reduced Ejection Fraction (TSOC-HFrEF) registry was established to improve awareness of HF management status in Taiwan.

Study design and population

The TSOC-HFrEF registry was a prospective, multi-center, observational survey of patients presenting to 21 hospitals in Taiwan. Hospitalized patients with either acute new-onset HF or acute decompensation of chronic HFrEF were enrolled. Only patients with an LVEF < 40% were enrolled.

Baseline characteristics and management

A total of 1509 patients were enrolled in the registry between May 2013 and October 2014, with a mean age of 64 years (72% were male). The most common etiology of HF was ischemic cardiomyopathy (44.1%), followed by dilated cardiomyopathy (32.9%) and valvular heart disease (7.9%). Diabetes (43.6%), CAD (41.8%), hypertension (34.5%), and chronic renal insufficiency (31.5%) were the most common comorbid conditions. Acute coronary syndrome (31.3%), non-compliance to treatment (24.6%), and concurrent infection (17.0%) were the major precipitating factors for acute decompensation.

After excluding 102 patients who received cardiac implantable electronic device (49 patients with pacemakers, 25 with ICDs and 29 with CRT pacemakers or defibrillators), sinus rhythm was noted in 65.6% and atrial fibrillation/flutter in 27.4% of the patients. Prolonged QRS duration > 120 ms was detected in 25.8% of the patients (25.9% of them showed an LBBB pattern).

The median length of hospital stay was 8 days. During hospitalization, 33% of the patients were admitted to an intensive care unit with a median stay of 4 days. Intravenous diuretics and inotropes were given in 62.6% and 36.5% of the patients, respectively. Mechanical ventilator support for respiratory failure was used in 12.9% of the cases, and including an intra-aortic balloon pump (IABP) and extracorporeal membrane oxygenation (ECMO) were applied in 2.7% and 0.5% of the patients, respectively. A total of 33 patients (2.2%) received either an ICD or CRT during the index hospitalization. At discharge, 62.1% of the patients were prescribed with either an ACEI or ARB, 59.6% with a beta-blocker, and 49% with an MRA.

Patient characteristics, medications, and outcomes of the TSOC-HFrEF registry compared with recent large-scale acute HF registries are shown in Table 7. Several differences were noted among these registries. The patients in Taiwan were younger than those in Western countries, Japan and Korea, but older than those in the Middle East and Africa. Moreover, compared with other cohorts, patients in the TSOC-HFrEF registry were more often male, less frequently had a history of hypertension and more frequently had a history of diabetes mellitus and CKD. The percentage of severe HF (NYHA functional class III-IV) on admission was highest in Taiwan among these registries. Concerning medications at discharge, adherence to using a renin-angiotensin system blocker was lower, but adherence rates to beta-blockers and MRAs were similar compared with the other registries. The utilization of electronic device therapy in Taiwan during the index hospitalization was low compared with that in Europe and Japan.

Pharmacological therapy: dosage and up-titration

The prescription rate of guideline-recommended medical therapy was suboptimal in the TSOC-HFrEF registry, and the prescription dosage of these medications was also low. Table 8 shows the types and doses of guideline-recommended medications at discharge and

Table 7. Comparison of patients' characteristics among recent HF registries

	GWTG*	ESC-HF-LT [#]	Gulf CARE [†]	THESUS-HF [‡]	ATTEND*	CHINA-HF [§]	KorHF*	Hong Kong HF Registry*	TSOC-HFrEF Registry
Patients' characteristics									
Year of enrollment	2005~11	2011~13	2012	2007~10	2007~11	2012~15	2004~09	2005~12	2013~14
Region	USA	Europe	Middle East	Africa	Japan	China	Korea	Hong Kong	Taiwan
Patient numbers, n	15,716	4,449	5,005	1,006	2,585	4,882	1,527	383	1,509
Age, years	79	69.4	59	52.3	69.7	60	69.1	72.2	63.9
Male	60%	62.6%	63%	49.2%	67.9%	69.8%	55.9%	59.8%	72.4%
BMI, kg/m ²	25.7	28.7	27	25.2	23.2	23.7	23.2	-	25.2
LVEF, %	25	40.4	35	39.5	-	-	28.7	-	28.5
SBP at admission, mmHg	132	133.5	137	130.4	143.1	121	129.3	-	130.9
HR at admission, bpm	82	90.8	97	103.7	103.7	83	93.9	-	92.7
NYHA III-IV at admission, %	-	85.2	75	34.6	84.6	85.8	59.6	-	88.2
Median length of stay, day	-	-	7	7	21	11	8	-	8
Hypertension	73.1%	65.6%	61%	45.4%	65.2%	41.2%	42.0%	60.3%	34.5%
Diabetes mellitus	39.3%	39.0%	50%	11.4%	35.1%	20.1%	31.4%	36.0%	43.6%
Chronic renal failure	20.9%	25.3%	15%	7.7%	70.2%	36.4%	7.3%	8.9%	31.5%
Coronary artery disease	58.0%	53.8%	47%	7.7%	39.8%	42.9%	40.1%	34.2%	41.8%
Atrial fibrillation	36.1%	44.0%	12%	18.3%	31.2%	23.4%	20.8%	31.3%	26.0%
COPD	26.7%	20.1%	-	-	10.8%	-	3.5%	-	11.0%
Guideline-directed therapy at discharge									
ACEI or ARB	88.0%	77.0%	78%	81%	81.2%	67.5%	68.0%	68.6%	62.1%
ACEI	-	-	61%	-	36.6%	48.4%	45.6%	-	27.5%
ARB	-	-	17%	-	44.6%	19.1%	24.5%	-	34.6%
Beta-blocker	73.4%	72.6%	71%	30%	78.9%	70.0%	40.9%	48.2%	59.6%
Aldosterone antagonist	24.9%	53.9%	43%	72%	53.9%	74.1%	37.5%	12.2%	49.0%
In hospital implantation of CRT/ICD	-	8.8%	1.7%	-	9.9%	1.4%	3.7%	-	2.2%
Outcomes after discharge									
Follow-up period	1 year	1 year	1 year	180 days	1 year	Ongoing	1 year	1 year	1 year
All-cause mortality	37.5%	23.6%	20.2%	17.8% (180 days)	24.8%	-	9.2%	19.5%	15.9%
Re-hospitalization	42.4%	18.7%	40%	9.1% (60 days)	42.4% (death & readmission)	-	9.8%	NA	38.5%

* Subgroup of patients with LVEF < 40%. [#] Includes 41.6% of patients with LVEF > 40%. [†] Includes 31% of patients with LVEF > 40%. [‡] Percentage of HFrEF unknown. [§] Subgroup of patients with LVEF < 45%.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York heart association; SBP, systolic blood pressure.

Table 8. Prescribed pharmacological treatments for heart failure over time

	At discharge			At 12 months		
	Rate of use	Dose (mg/day)	≥ 50% of target dose	Rate of use	Dose (mg/day)	≥ 50% of target dose
ACEIs/ARBs	62.1%		24.4%	57.7%		24.3%
ACEIs	27.5%		27.1%	16.9%		36.2%
Ramipril	33.8%	4.5 ± 4.2	34.6%	44.2%	4.6 ± 4.4	36.1%
Captopril	30.3%	29.0 ± 22.9	14.8%	15.3%	31.1 ± 20.8	12.0%
Enalapril	23.6%	8.1 ± 8.9	31.6%	20.2%	12.3 ± 11.9	54.5%
ARBs	34.6%		22.3%	40.8%		20.0%
Candesartan	39.7%	7.2 ± 5.0	14.4%	32.9%	6.8 ± 5.2	10.0%
Valsartan	35.0%	114.1 ± 62.0	39.0%	40.3%	112.4 ± 61.8	34.4%
Losartan	16.4%	41.4 ± 29.1	6.0%	16.5%	40.5 ± 18.8	4.6%
Beta-blockers	59.6%		20.6%	66.2%		26.3%
Bisoprolol	57.9%	2.5 ± 2.0	21.7%	62.0%	2.7 ± 1.9	27.4%
Carvedilol	37.5%	13.6 ± 14.1	20.7%	33.7%	15.0 ± 13.5	25.3%
Metoprolol	1.3%	40.0 ± 26.2	18.2%	2.8%	48.6 ± 36.1	27.8%
MRA	49.0%		86.2%	40.8%		86.6%
Spirolactone	98.7%	28.9 ± 14.2	86.0%	99.5%	32.8 ± 29.3	86.6%
Eplerenone	1.3%	52.8 ± 19.5	100%	0.5%	75.0 ± 35.4	100%
Diuretics	82.2%			75.9%		
Digitalis	25.9%			24.0%		
Nitrate	36.4%			32.2%		
Hydralazine	4.9%			4.2%		

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

after 1 year of follow-up. In the TSOC-HFrEF registry, the proportions of patients at the target dose and $\geq 50\%$ of the target dose were 5% and 24.4% for ACEIs/ARBs, 3.6% and 20.6% for beta-blockers, and 21.6% and 86.2% for MRAs at discharge, respectively, which were significantly lower than those reported in the recent QUALIFY global survey. Kaplan-Meier survival curves showed that patients who received two or three classes of guideline-recommended medications with $\geq 50\%$ of the target dose had a better prognosis than those who received $< 50\%$ of the target dose and those who received fewer than two classes of guideline-recommended medical therapy (Figure 8). Current guidelines recommended that these medications should be up-titrated to the maximum tolerated evidence-based doses in order to reduce mortality and morbidity in patients with HFrEF, but at 1 year of follow-up, the prescription rates and dosages of guideline-recommended medications in the TSOC-HFrEF registry were not significantly increased.

One-year outcome: comparison with other heart failure registries

The all-cause mortality rate in the TSOC-HFrEF registry was 15.9%, and the CV mortality rate was 10.5% 1 year after hospital discharge. The 1-year re-hospitalization rate for HF was 38.5%, and 9.7% of the patients were admitted more than once within 1 year. Overall, 46.4% of the patients were free from death, hospitalization for HF, implantation of an LVAD and heart transplantation at 1 year. The 1-year mortality rate was comparable to those from Asia registries and better than those from the Middle East and Africa. The older patient populations might explain the high rates of mortality in European and American registries. Nevertheless, the 1-year re-hospitalization rate of 38.5% in Taiwan is very high compared with other registries. Underutilization of guideline-recommended therapies and device therapies, a high prevalence of precipitating factors such as acute coronary syndrome and non-compliance, and proximity to a relatively low-cost healthcare system may contribute to this high rate of re-hospitalization.

Implications of the TSOC-HFrEF registry

The TSOC-HFrEF is the largest Taiwanese database to date involving acute decompensated HFrEF patients. There are several important implications of this registry:

- Significant underutilization of the RAA system blockers at discharge compared to registries in other countries.
- The guideline drugs were used at suboptimal dosages, and there was a reluctance to up-titrate these drugs to the target dose during follow-up.
- The implantation of CRT devices and ICDs remained uncommon.
- The severity of HF in Taiwanese hospitalized patients was high. Acute HF care was aggressive, as one-third of the patients were admitted to an intensive care unit and some of them received invasive cardiopulmonary support. Nevertheless, post-acute HF care did not attract much attention, and the 1-year rehospitalization rate remained high. Prominent efforts should be made to overcome the barriers to guideline adherence, and improve care and reduce the cost of HF.

POST-ACUTE CARE

After discharge for decompensated HF, many patients require post-acute care (PAC) to maximize their functional progress, reduce disability, and make it possible for them to return to their home and community. PAC is also called intermediate care and transitional care. It involves a community-based multidisciplinary team.

The pre-discharge period, post-discharge period,

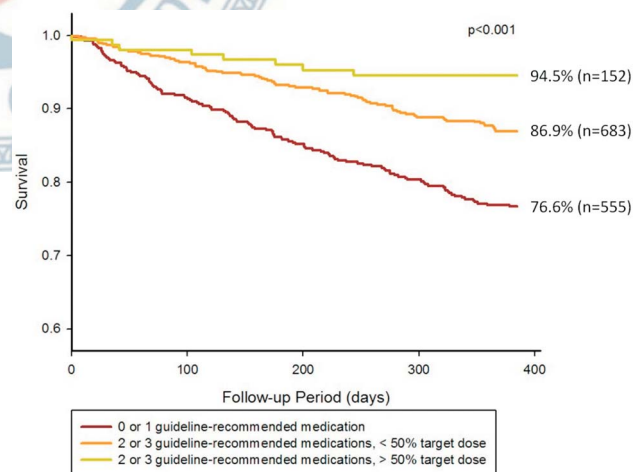


Figure 8. Kaplan-Meier survival curves in registry patients presenting with different types and dosages of guideline-recommended medications. Adapted from “Gap between guidelines and clinical practice in heart failure with reduced ejection fraction: results from TSOC-HFrEF registry”, by Chang HY, Wang CC, Wei J, et al., *J Chin Med Assoc* 2017;80:750-7. Adapted with permission.

and long-term chronic phase occur after the acute phase. PAC involves these pre- and post-discharge periods for approximately 3 to 6 months (Figure 9).

Figures 10 and 11 depict the recommended items for the pre- and post-discharge periods, respectively.

Annotations:

(* in Figure 10) **Contents of education, self-care learning, and a guide to decision making**²⁰⁷

(A) Symptom monitoring and self-care

1. Monitor and recognize changes in signs and symptoms.
2. Know how and when to contact a healthcare professional.
3. In line with professional advice, know when to self-manage diuretic therapy and fluid intake. For example, in the case of increasing dyspnea or edema or a sudden unexpected weight gain of > 2 Kg in 3 days, patients may increase their diuretic dose and/or

alert their healthcare team.

(B) Diet and alcohol

1. Avoid excessive fluid intake.
2. Recognize the need for altered fluid intake such as:
 - (1) Increase intake during periods of high heat and humidity, nausea/vomiting.
 - (2) Fluid restriction of 1.5-2 L/day (including fluid in food) may be considered in patients with severe

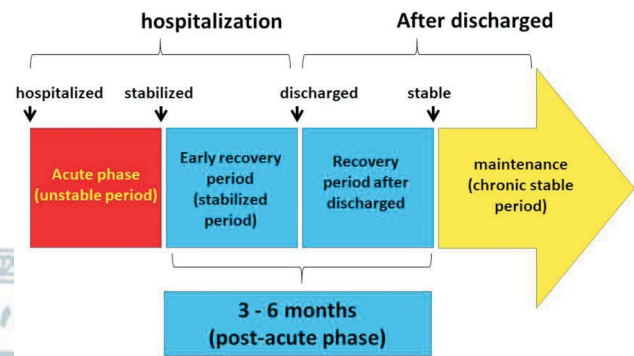


Figure 9. Periods from acute, post-acute to chronic phases.

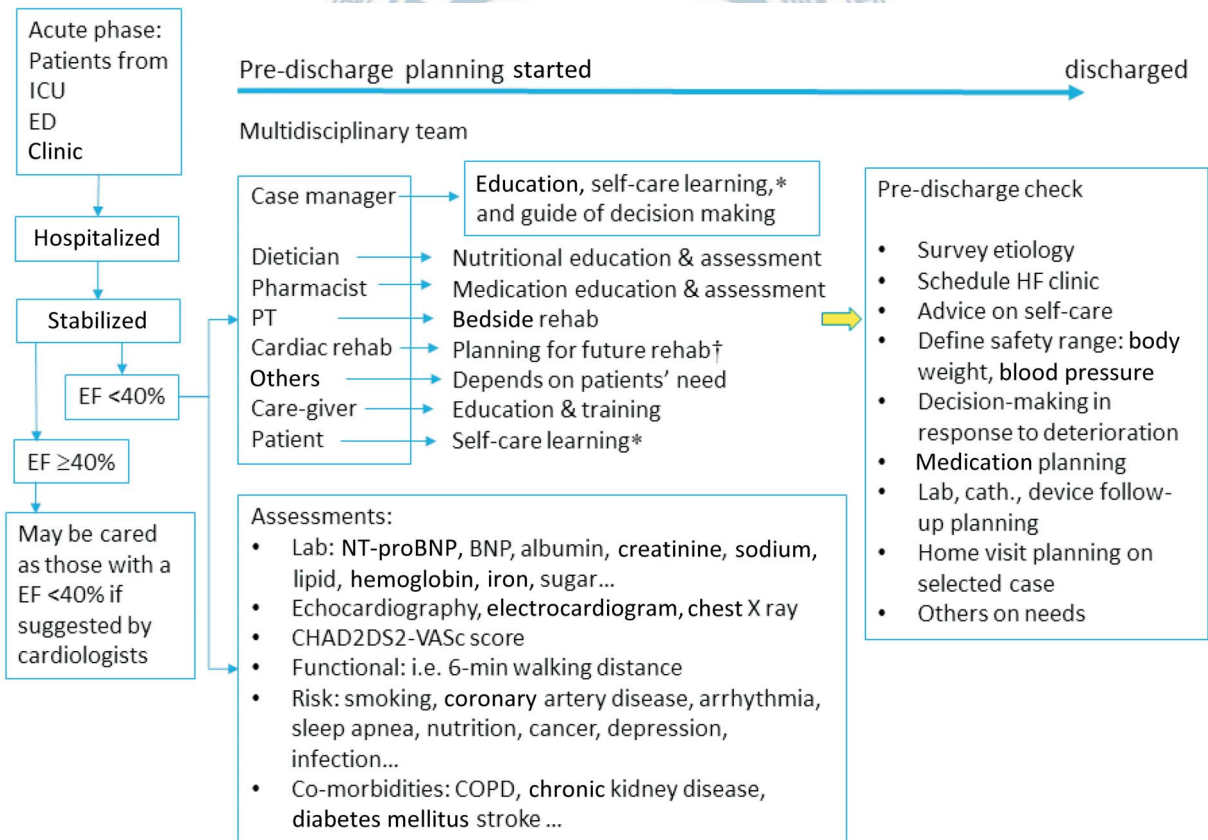


Figure 10. Programs before discharge. Cath, cardiac catheterization; COPD, chronic obstructive pulmonary disease; ED, emergency department; EF, ejection fraction; HF, heart failure; ICU, intensive care unit; Lab, laboratory tests; PT, physical therapist; rehab, rehabilitation.

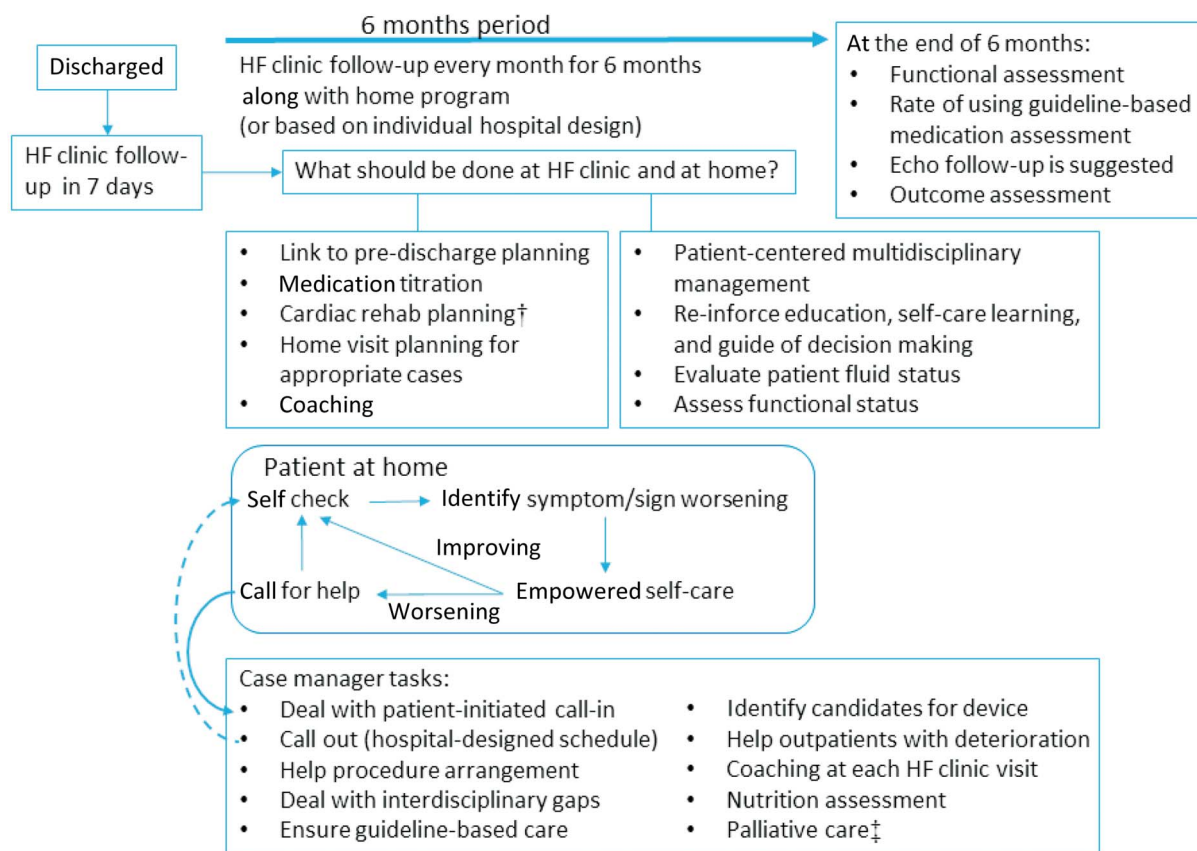


Figure 11. Programs after discharge. Echo, echocardiograms; HF, heart failure; rehab, rehabilitation.

- HF to relieve symptoms and congestion.
3. Monitor body weight and prevent malnutrition.
 4. Eat healthily, avoid excessive salt intake (> 5 g/day).
 5. Abstain from or avoid excessive alcohol intake.
- (C) Psychosocial aspects
1. Depressive symptoms and cognitive dysfunction are found more frequently in people with HF, and that may affect adherence.
 2. Recognize psychological problems which may occur in the course of the disease in relation to a changed lifestyle, pharmacotherapy, implanted devices, and others. Patients do not always accept the changes associated with the treatment plan, leading to poor outcomes.
- (D) Definition, etiology, and trajectory of HF (including prognosis).
- (E) Pharmacological treatment.
- (F) Implanted devices and percutaneous/surgical interventions.
- (G) Immunization: annual influenza vaccination.
- (H) Quit smoking and recreational substance use.
- (I) Exercise regularly.
- (J) Travel and leisure.
- (K) Sleep and breathing: optimize sleep duration and quality.
- (L) Sexual activity.
- Benefits**
- A few meta-analyses have consistently shown that multidisciplinary disease management programs (MDP) reduce all-cause and HF-related readmission rates.^{63,273-275} For example, Roccaforte et al. reported that MDP programs significantly reduced all-cause readmission rates by 24% (odds ratio [OR], 0.76; 95% CI, 0.69-0.94) and HF readmission rates by 42% (OR, 0.58; 95% CI, 0.50-0.67).²⁷³ MDP was also associated with a significant reduction in mortality by 20% (OR, 0.80; 95% CI, 0.69-0.93) although less robust, along with improved medication prescription and adherence, improved quality of life, and reduced cost of care.

(† in Figures 10 and 11) **Activity, exercise prescription, and cardiac rehabilitation: recommendations**²⁷⁶

1. Exercise training (or regular physical activity) is recommended as being safe and effective for patients with HF who can participate in improving functional status. (Class I, Level of Evidence: A)
2. Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, health-related quality of life, and mortality. (Class IIa, Level of Evidence: B)

(‡ in Figure 11) **Palliative care**²⁰⁷

The primary focus is on improving or maintaining the quality of life of a patient and the patient's family as much as possible until the patient dies. Hospice care also includes advanced care planning, taking into account preferences for the place of death and resuscitation.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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