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Clinical Practice Guideline

Korean Society of Heart Failure Guidelines for the Management of Heart Failure: Management of the Underlying Etiologies and Comorbidities of Heart Failure

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AUTHOR'S SUMMARY

The current review article discussed the impact of comorbidities on patients with heart failure (HF), which incorporates cardiovascular and non-cardiovascular comorbidities. It recommends treatment for patients with hypertension and left ventricular hypertrophy, measurement of pulmonary vascular resistance for candidates of mechanical circulatory support devices, coronary angiography for patients with HF and angina pectoris refractory to antianginal medications, and long-term anticoagulants for patients with HF and atrial fibrillation. It also recommends medical and surgical treatment for valvular heart diseases and appropriate management for patients with diabetes mellitus, chronic kidney and pulmonary diseases, iron deficiency and anemia, and sleep apnea.

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ABSTRACT

Most patients with heart failure (HF) have multiple comorbidities, which impact their quality of life, aggravate HF, and increase mortality. Cardiovascular comorbidities include systemic and pulmonary hypertension, ischemic and valvular heart diseases, and atrial fibrillation. Non-cardiovascular comorbidities include diabetes mellitus (DM), chronic kidney and pulmonary diseases, iron deficiency and anemia, and sleep apnea. In patients with HF with hypertension and left ventricular hypertrophy, renin-angiotensin system inhibitors combined with calcium channel blockers and/or diuretics is an effective treatment regimen. Measurement of pulmonary vascular resistance via right heart catheterization is recommended for patients with HF considered suitable for implantation of mechanical circulatory support devices or as heart transplantation candidates. Coronary angiography remains the gold standard for the diagnosis and reperfusion in patients with HF and angina pectoris refractory to antianginal medications. In patients with HF and atrial fibrillation, long-term anticoagulants are recommended according to the CHA_2DS_2-VASc scores. Valvular heart diseases should be treated medically and/or surgically. In patients with HF and DM, metformin is relatively safer; thiazolidinediones cause fluid retention and should be avoided in patients with HF and dyspnea. In renal insufficiency, both volume status and cardiac performance are important for therapy guidance. In patients with HF and pulmonary disease, beta-blockers are underused, which may be related to increased mortality. In patients with HF and anemia, iron supplementation can help improve symptoms. In obstructive sleep apnea, continuous positive airway pressure therapy helps avoid severe nocturnal hypoxia. Appropriate management of comorbidities is important for improving clinical outcomes in patients with HF.

Keywords: Heart failure; Guideline; Comorbidity; Disease management

INTRODUCTION

Most patients with heart failure (HF) have multiple cardiovascular and non-cardiovascular comorbidities, which often complicate the diagnosis and management of the condition.[1)2)] Cardiovascular comorbidities include systemic and pulmonary hypertension, ischemic and valvular heart diseases, atrial fibrillation and ventricular arrhythmia, and conduction disorders.[3)] Non-cardiovascular comorbidities include diabetes mellitus (DM), chronic kidney disease, obesity, pulmonary disease, iron deficiency and anemia, sleep apnea, mood disorders, pregnancy, and cancer-related issues (**Figure 1**).[4)] These comorbidities impact patients' quality of life (QoL), aggravate HF, and result in increased mortality; however, these are yet to be fully understood and may be overlooked during HF management. Although the evidence-based data of several clinical trials are incorporated into real-world practice, comprehensive information on the management comorbidities of HF are lacking. Proper management of comorbidities are important in improving clinical outcomes in HF patients.[5)] Herein, the appropriate diagnostic approaches and management of the various causative diseases and comorbidities of HF have been discussed on the basis of recent evidences and current guidelines of major cardiovascular societies including the Korean Society of Heart Failure.

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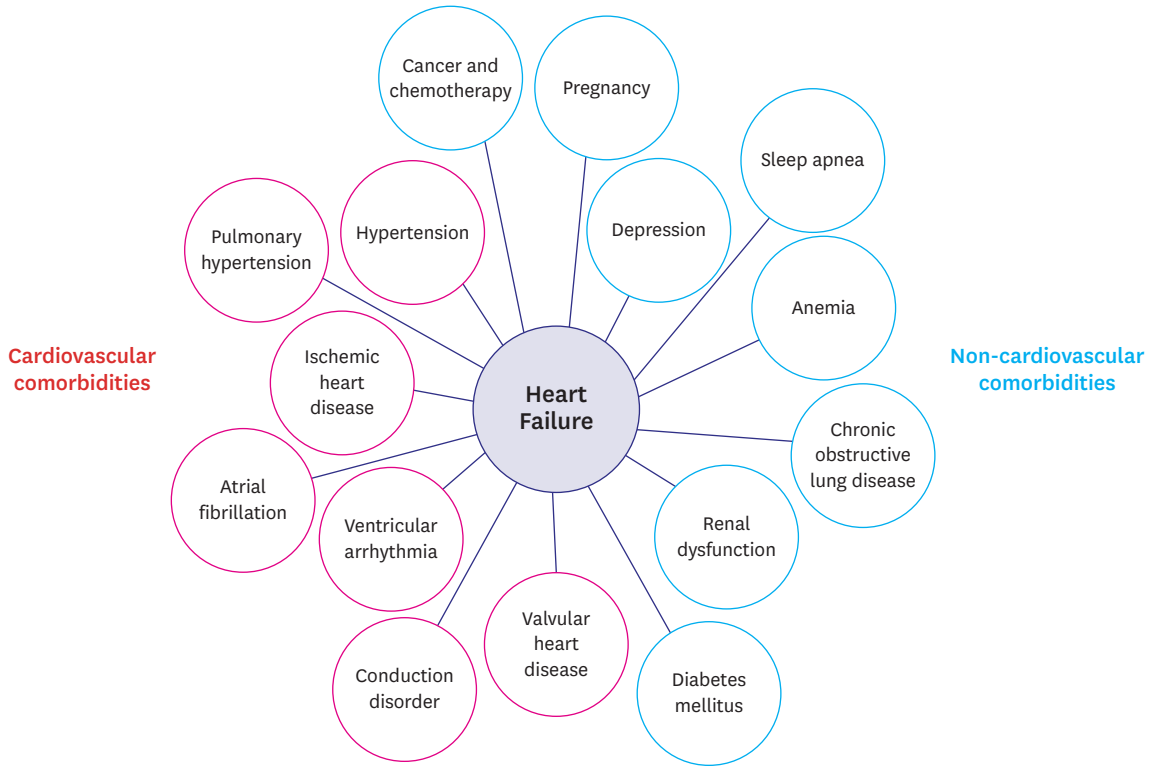

Figure 1. Various cardiovascular and non-cardiovascular underlying etiologies and comorbidities of heart failure.
Red and blue circles indicate cardiovascular and non-cardiovascular comorbidities respectively.

HYPERTENSION

1. Regardless of the left ventricular (LV) ejection fraction (EF), antihypertensive medication may be helpful if the blood pressure is greater than 140/90 mmHg in patients with HF. (Class IIa, Level of Evidence B)
2. In patients with heart failure with reduced ejection fraction (HFrEF), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), beta-blockers, diuretics and aldosterone antagonists is recommended. (Class I, Level of Evidence A)
3. In patients with heart failure with preserved ejection fraction (HFpEF), it is reasonable to make the similar criteria and target blood pressure of hypertension to that of patients with heart failure with ejection fraction reduced. (Class IIa, Level of Evidence B)
4. If accompanied by LV hypertrophy, a combination of renin-angiotensin inhibitors with calcium channel blockers (CCBs; dihydropyridine) and/or diuretics is recommended. (Class I, Level of Evidence A)
5. If accompanied by LV hypertrophy, it is helpful to reduce systolic blood pressure to the range of 120–130 mmHg. (Class IIa, Level of Evidence B)

Hypertension is a representative underlying etiology and comorbidity of HF.[1-3] It is the most important cardiovascular risk factor found in most patients with HF; the proportion of patients with hypertension in the Korean Heart Failure and Korean Acute Heart Failure (KorAHF) registries is 46.5% and 62.2% respectively[6,7]; Hypertension increases LV afterload,

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leads to systolic and diastolic dysfunction, and subsequently, induces ventricular remodeling. In addition, it increases oxygen consumption by increasing LV wall stress and aggravates myocardial ischemia through endothelial microcirculatory dysfunction. Furthermore, in patients with myocardial infarction (MI), neurohormonal system activation aggravates hypertensive ventricular remodeling and increases the occurrence of HF.[6]

Regardless of the LVEF, antihypertensive medications may be beneficial if blood pressure is >140/90 mmHg in patients with HF (Class IIa, Level of Evidence B). The Systolic Blood Pressure Intervention Trial reported that patients with strict control of systolic blood pressure <120 mmHg had a reduced risk (38%) of combined cardiovascular events, including HF development, compared with the standard treatment groups with systolic blood pressure <140 mmHg.[8] In patients with HFrEF, the treatment goal is a reduction in systolic blood pressure to <130 mmHg,[9][10] a recommendation endorsed by the Korean hypertension practice guidelines as well.[11]

The choice of an appropriate antihypertensive agent is based on the principle of reduced blood pressure and combined treatment for HF. In patients with HFrEF, ACEIs or ARBs, diuretics, and aldosterone antagonists are recommended for the treatment of hypertension (Class I, Level of Evidence A). ACEIs are the first-line therapeutic agents for patients with HFrEF and hypertension. ARBs can be used when ACEIs are not tolerated or contraindicated.[12] If the blood pressure is not well-controlled (to the target value), dihydropyridine-based CCBs may be added (Class IIb, Level of Evidence C). In the presence of fluid retention, thiazide diuretics can be added at an early stage. In the absence of fluid retention, amlodipine or felodipine may be considered to further lower the blood pressure.[13] However, verapamil, diltiazem, and moxonidine (a centrally-acting antihypertensive drug) are not recommended because they are associated with a poor prognosis in patients with HF.[14] Compared with beta-blockers or diuretics, ACEIs, ARBs, and CCBs are more effective in reducing LV hypertrophy.[15]

In patients with HFpEF and hypertension, the target blood pressure level may be set to a similar level as that for patients with HFrEF (Class IIa, Level of Evidence B). A combination of renin-angiotensin system (RAS) inhibitors with CCBs and/or diuretics is recommended for patients with hypertensive LV hypertrophy (Class I, Level of Evidence A). Furthermore, reducing the systolic blood pressure to 120–130 mmHg may be beneficial in such patients (Class IIa, Level of Evidence B). In patients with HFpEF and LV hypertrophy, overtreatment should be avoided because excessive lowering of blood pressure may reduce the preload and cause hypotension, indicated by symptoms such as dizziness, and increase mortality.[7][12]

PULMONARY HYPERTENSION

1. Measurement of pulmonary artery pressure in patients with pulmonary hypertension is recommended because it can reflect symptoms and prognosis in patients with HFrEF and/or HFpEF. (Class I, Level of Evidence A)
2. It is recommended to perform right heart catheterization to measure the pulmonary vascular resistance in patients with HF who are considered heart transplant recipients or need a mechanical circulatory assist device. (Class I, Level of Evidence B)
3. Mitral valvular plasty with clips may help reduce pulmonary hypertension in HF patients with mitral regurgitation(MR), thereby alleviating symptoms and improving prognosis. (Class IIa, Level of Evidence B)

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At the 6th World Symposium on Pulmonary Hypertension in 2018, a mean pulmonary artery pressure >20 mmHg was proposed as the updated hemodynamic definition of pulmonary hypertension (PH), and pulmonary vascular resistance (PVR) ≥3 Wood units was used for the definition of precapillary pulmonary hypertension.[16] Pulmonary hypertension due to left heart disease (PH-LHD) has an incidence of 65%.[17] Moreover, the presence or absence of PH in patients with HFrEF and HFpEF is related to the prognosis.[18] Therefore, evaluation of pulmonary arterial pressure is recommended because it may reflect symptoms and prognosis in these patients (Class I, Level of Evidence A). Measurement of PVR via right heart catheterization is recommended in patients with HF who are being considered for the implantation of mechanical circulatory support devices or as heart transplantation candidates (Class I, Level of Evidence B). Therefore, if PH is suspected in severe HF, right heart catheterization should be performed to determine an appropriate treatment strategy (**Figure 2**). The presence of combined precapillary and postcapillary pulmonary hypertension (Cpc-PH), a form of PH-LHD, in patients with advanced severe HF is a contraindication for heart transplantation because of a high risk of adverse outcomes postoperatively.[19] In patients with severe PH-LHD, especially those who are heart transplantation candidates, implantation of a left ventricular assist device (LVAD) reduces pulmonary arterial wedge pressure, mean pulmonary arterial pressure, and PVR by consistently reducing LV filling pressure regardless of Cpc-PH. Therefore, LVAD can be a bridge to transplantation and a destination therapy in patients with Cpc-PH.[20-22]

Mitral valve repair with clips may help reduce PH in patients with HF and MR, thereby alleviating symptoms and improving prognosis (Class IIa, Level of Evidence B). Percutaneous mitral valve repair with clips improved left heart function in patients with severe MR and improved PH-LHD-related hemodynamics, reduced tricuspid valve regurgitation, lowered pulmonary artery systolic pressure, and increased tricuspid planar systolic movement.[23]

Dedicated treatment regimens for pulmonary arterial hypertension are available for patients with HF and Cpc-PH (Class IIa, Level of Evidence C). Targeted therapeutics include phosphodiesterase type 5 inhibitor, guanylate cyclase stimulators, prostacyclin analogs,

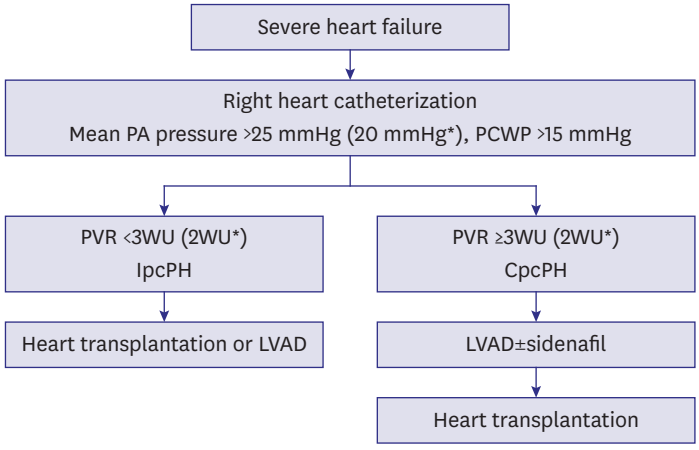

Figure 2. Algorithm for right heart catheterization in patients with severe heart failure.
Cpc-PH = combined postcapillary and precapillary pulmonary hypertension; Ipc-PH = isolated postcapillary pulmonary hypertension; LVAD = left ventricular assist device; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; WU = Wood units.
*Values for recently updated 2022 European Society of Cardiology and the European Respiratory Society guideline for pulmonary hypertension.

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and endothelin receptor antagonists (ERAs). Several studies have reported conflicting and controversial results regarding their effects and side effects. However, other studies on targeted therapies for various indications are ongoing and the use of these therapies is expected to expand in the future, depending on the results. Patients with Cpc-PH scheduled for heart transplantation who received sildenafil had significantly improved postoperative pulmonary hemodynamics compared with those who did not receive it.[24] In PH-LHD, prostacyclin analogs and guanylate cyclase stimulators did not demonstrate a proven benefit in most studies.[25-28] Furthermore, trials using ERAs have only demonstrated an increase in peripheral edema, a side effect.[29-31]

ISCHEMIC HEART DISEASE

1. Coronary angiography is recommended primarily for diagnosis and severity assessment and reperfusion of coronary artery disease (CAD) in patients with HF who have angina and do not respond to drug treatment. (Class I, Level of Evidence C)
2. In patients with HF, cardiac computed tomography (CT), cardiac magnetic resonance imaging, single photon emission CT are appropriate to diagnose ischemic heart disease (IHD). (Class IIa, Level of Evidence C)
3. As a reperfusion treatment of IHD, it is appropriate to decide on percutaneous coronary intervention (PCI) or coronary artery bypass according to the clinical situation. (Class IIa, Level of Evidence B)
4. If cardiogenic shock caused by acute coronary syndrome occurs and immediate reperfusion is difficult, temporary mechanical circulatory assistive devices (ex. extracorporeal membrane oxygenation) may be considered. (Class IIa, Level of Evidence C)

Large-scale studies from the world-wide registry, including Korean data, have revealed that IHD or CAD is the most common etiology of the acute HF. CAD is present in 50–60% of patients with acute decompensated HF.[32][33] Moreover, CAD is a common exacerbating factor in progressive acute decompensated HF; hence, its treatment is important for the prevention and better prognosis of HF and improving the symptoms of angina pectoris.[34][35]

Coronary angiography is preferentially recommended for the diagnosis, severity assessment, and reperfusion of CAD in patients with HF with angina pectoris refractory to antianginal medications (Class I, Level of Evidence C).[35][36] In addition, non-invasive tests should be considered when CAD is moderate–severe (Class IIa, Level of Evidence C). In patients with HF with suspected CAD, cardiac CT, cardiac magnetic resonance imaging, and single photon emission CT (Class IIa, Level of Evidence C) are appropriate non-invasive diagnostic modalities. Current global practical guidelines suggest that when the likelihood of CAD is mild–moderate or ambiguous, cardiac (CT) may help rule out CAD (Class IIa, Level of Evidence C).

Therapeutic strategies to improve the prognosis of patients with HF caused or accompanied by CAD include lifestyle changes, optimal medical treatment (OMT), and invasive revascularization. Medical therapeutics include diuretics, digoxin, RAS inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRAs; spironolactone), hydralazine, nitrates, CCBs, and amiodarone. Thiazide diuretics reduce the risk of MI and left HF.[37][38]

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Excluding digoxin in patients with dilated cardiomyopathy revealed exacerbations in exercise capacity and LVEF; however, it did not increase the risk of clinical deterioration in patients with HF due to CAD.[39] Conversely, MI and mortality tended to increase after the use of digoxin; therefore, more research is needed to evaluate the clinical effects of digoxin in HF patients with CAD.[40] ACEIs reduce mortality in patients with HF by reducing MI-induced LV remodeling.[41] The prevailing hypothesis for preventing vascular events is that ACEI improves the function of endothelial cells by enhancing the action of bradykinin and prostaglandin in the arterial walls and reduces the rupture of sclerotic plaques.[41][42] Beta-blockers reduce myocardial ischemia in patients with HF due to IHD and restore stunned or hibernating myocardium, leading to reverse remodeling of the left ventricle.[43][44] They are contraindicated in respiratory diseases such as asthma and their use is restricted in bradycardia or hypotension with systolic blood pressure of ≤90 mmHg. In patients with limited use of beta-blockers, ivabradine is an effective alternative in controlling angina pectoris and an essential component of HFrEF treatment. Moreover, ivabradine may be used to relieve angina pectoris in patients with HFpEF.[36] CCBs such as amlodipine have been used safely in patients with HF and can be administered to manage angina; however, it is unlikely to expect improvement in mortality rates. In a study conducted in only patients with dilated cardiomyopathy, diltiazem demonstrated improvements in symptoms and exercise capacities; however, there was no effect on the prognosis, and caution is required because it may worsen HF after MI.[45]

For the treatment CAD in the patients with HF, antithrombotic drugs should be used appropriately in situations where blood clots can form. Atrial fibrillation, a common comorbidity of HF, is detected in approximately 20% of patients with HF. Anticoagulants such as warfarin or non-vitamin K antagonist oral anticoagulants (NOAC) help prevent cerebral infarction. Although aspirin has safety concerns in patients with HF, it remains the primary treatment for CAD. However, long-term use of aspirin for treating CAD in HF patients did not demonstrated the reduced mortality.[46-48] Although the safety of clopidogrel has not been literally established for treating CAD in patients with HF,[49-51] unlike aspirin it does not inhibit prostaglandin production; therefore, it is considered safe for use in patients with HF.[48] Statins are the cornerstones of primary and secondary prevention in patients with CAD; however, the exact effect of statins on patients with HF is unclear.[52] The Scandinavian Simvastatin Survival Study reported that simvastatin slowed the progression of HF in patients with LV dysfunction,[53] while two large trials revealed that rosuvastatin did not have a good long-term prognosis and failed to reduce cardiovascular mortality.[54][55]

As for the role of revascularization with PCI in HF patients, recently, REVIVED-BCIS2 evaluated whether PCI can improve event-free survival and LV function in 700 patients with HF with LV dysfunction (LVEF <35%). PCI groups did not improve mortality and HF hospitalization compared to the optimal medical therapy group. In addition, PCI was not associated with LVEF improvement except for the short-term QoL score.[56]

PCI or coronary artery bypass graft surgery (CABG) as a reperfusion treatment for IHD may be decided according to the clinical situation (Class IIa, Level of Evidence B). Few studies have examined the effects of PCI in patients with HF; hence, further prospective studies are needed. In the Surgical Treatment for Ischemic Heart Failure study, the clinical effects of OMT only versus OMT with CABG in patients with ischemic cardiomyopathy with an LVEF of <35% were examined and compared. The 30-day mortality was 3.12-times higher in the OMT with CABG group, and the overall mortality was not reduced even at the long-term clinical follow-up period of 4.6 years, regardless of the cause.[57]

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In cases of cardiogenic shock accompanying ischemic cardiomyopathy, such as acute MI, rapid improvement in coronary blood flow is the treatment goal.[7] When the cardiogenic shock is caused by acute coronary syndrome and reperfusion cannot be performed immediately, temporary mechanical percutaneous circulatory and pulmonary support such as an extracorporeal membrane oxygenation may be considered (Class IIa, Level of Evidence C). In patients with acute MI accompanied with cardiogenic shock, CABG is performed in only a few select cases, probably because the mortality rate of patients undergoing CABG is relatively high at 14%.[58] If immediate revascularization of the occluded vessels in patients with non-ST segment elevation acute MI is difficult, short "door-to-support" time may help improve prognosis by optimizing systemic circulation and peripheral organ perfusion and attenuating metabolic shock.[59][60]

ATRIAL FIBRILLATION

1. Long-term anticoagulation treatment is recommended for male with CHA_2DS_2-VASc score of 2 or higher and female patients with 3 points or more in patients with HF and atrial fibrillation. (Class I, Level of Evidence A)
2. In patients with HF and atrial fibrillation, except in special cases (moderate or severe mitral valve stenosis or mechanical valve), direct oral anticoagulants are more recommended than vitamin K antagonistic anticoagulant. (Class I, Level of Evidence A)
3. In patients with HF and atrial fibrillation, male patients with CHA_2DS_2-VASc score of 1 and female patients with 2 points long-term anticoagulation is feasible. (Class IIa, Level of Evidence B)
4. In people with HF and atrial fibrillation, beta-blockers may be helpful for acute and long-term heart rate control. (Class IIa, Level of Evidence B)
5. If beta-blockers are contraindicated or if the pulse rate is still high even after beta-blockers, digoxin use may be helpful. (Class IIa, Level of Evidence C)
6. Early electronic cardioversion is recommended for patients with acute exacerbations of HF with rapid beats and hemodynamically unstable atrial fibrillation. (Class I, Level of Evidence C)
7. In patients with HF and atrial fibrillation, if atrial fibrillation contributes to worsening HF symptoms and persists despite medication, catheter ablation is helpful. (Class IIa, Level of Evidence B)

In the KorAHF registry study, approximately 30% of patients with HF had atrial fibrillation. Thus, in the patients with HF and atrial fibrillation, appropriate treatment strategies should be considered.[61] Treatment of atrial fibrillation in these patients should be comprehensive in terms of identifying the etiology, managing HF, preventing stroke, and controlling rhythm.[12] Long-term anticoagulation is recommended for the prevention of stroke and embolism in all patients with HF and concomitant atrial fibrillation, if it is not contraindicated.[12]

In patients with HF with atrial fibrillation, NOACs are recommended rather than warfarin, except in cases such as moderate or severe mitral valve stenosis or mechanical valves (Class I, Level of Evidence A).[62] Regarding stroke risk score, long-term anticoagulation therapy is strongly recommended for male and female patients with CHA_2DS_2-VASc scores ≥2 and ≥3, respectively (Class I, Level of Evidence A). Recently, CHA_2DS_2-VASc scores of 1 and 2

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in male and female patients, respectively, have been considered sufficient for long-term anticoagulation therapy (Class IIa, Level of Evidence B).

In patients with atrial fibrillation, a heart rate of <110 beats/min at rest is targeted. However, the data is limited because the two clinical studies supporting this target included only 10% and 17% of patients with HF, respectively.[61)63)] In patients with HF and atrial fibrillation, beta-blockers may be helpful for acute and long-term heart rate control, and some therapeutic potential associated with the role of beta-blockers according to basal heart rate in patients with atrial fibrillation is gradually emerging in the Korean population (Class IIa, Level of Evidence B). Although beta-blockers are preferred, digoxin may be further considered when beta-blockers are contraindicated or if the pulse rate remains high after beta-blockers are administered (Class IIa, Level of Evidence C).[64-66)] In hemodynamically unstable patients, intravenous infusion of amiodarone may be used for heart rate control.[67)]

Early electrical cardioversion for sinus rhythm conversion is recommended for patients with acute exacerbations of HF accompanied by rapid ventricular rate and hemodynamically unstable atrial fibrillation (Class I, Level of Evidence C). In addition, sinus rhythm conversion may be considered when worsening HF symptoms due to atrial fibrillation that persists despite medication are suspected (Class IIb, Level of Evidence B).

In patients with HF and atrial fibrillation, catheter ablation may be helpful if atrial fibrillation contributes to worsening HF symptoms and persists despite drug treatment (Class IIa, Level of Evidence B). Atrioventricular node ablation may be considered for rhythm control in patients who are unresponsive to medical therapy, those who are not qualified for rhythmic control indication, or those who are undergoing biventricular pacing.[68-70)] However, whether rhythm control is superior to rate control and whether the catheter ablation is superior to the use of only antiarrhythmic medication for rhythm control in patients with HF and atrial fibrillation remains controversial and research on these topics are ongoing. In the Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation trial, which compared catheter ablation with drug therapy in patients with New York Heart Association (NYHA) functional grade >II, the catheter ablation group had 36% lower risk of death, severe stroke, and sudden cardiac death compared with the drug therapy only group.[71)] The 2020 European Society of Cardiology guidelines for the diagnosis and management of atrial fibrillation recommends catheter ablation without prior drug treatment in patients with atrial fibrillation and HFrEF. Accordingly, device therapies such as catheter ablation and cryoablation for atrial fibrillation could be considered for the patients with HF.[12)]

VENTRICULAR ARRHYTHMIA AND DISORDERS

Ventricular arrhythmias, including ventricular fibrillation, ventricular tachycardia, and premature ventricular contractions, occur in several patients with HF. Ventricular arrhythmias must be recognized and promptly treated because of the high risk of mortality. Immediate direct current (DC) cardioversion or defibrillation is recommended if hemodynamically unstable ventricular tachycardia or ventricular fibrillation occurs in patients with HF.[72)] Conversely, DC cardioversion or intravenous administration of amiodarone should be considered if hemodynamically stable ventricular tachycardia occurs.[73)74)] Amiodarone is recommended for patients with ventricular tachycardia and ventricular fibrillation unresponsive to DC cardioversion or defibrillation, or recurrence.[73)74)]

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In hemodynamically stable states, administration of beta-blockers may help prevent recurrence of ventricular tachycardia and ventricular fibrillation in patients with HF.[75] Catheter ablation may be helpful in patients with HF and monomorphic ventricular tachycardia unresponsive to pharmacological treatment, based on the type of arrhythmia.[76] Implantable cardioverter-defibrillators (ICDs) may be considered for the secondary prevention of hemodynamically unstable ventricular tachycardia and ventricular fibrillation in patients with HF. Furthermore, ICDs should be used for secondary prevention of acute cardiac death in patients experiencing hemodynamically unstable ventricular arrhythmias.[77] Administration of amiodarone is recommended to reduce the frequency of ventricular arrhythmias in patients with multiple ICD therapies,[78] and catheter ablation may be helpful in those with ICDs and ventricular arrhythmias unresponsive to medical treatment.[79]

Premature ventricular contractions are the cause of LV dysfunction and HF. In addition, frequent premature ventricular contractions increased the risk of cardiovascular disease (CVD) and mortality.[80][81] Amiodarone and beta-blockers may be helpful to reduce the frequency of premature ventricular contractions that exacerbate HF.[82][83] Catheter ablation can be considered in patients with premature ventricular contractions unresponsive to medical treatment (**Figure 3**).[84][85]

The standards for pacemaker insertion for conduction disorders may be applied to patients with HF. If a pacemaker is to be implanted for sinus node dysfunction, the ventricular pace

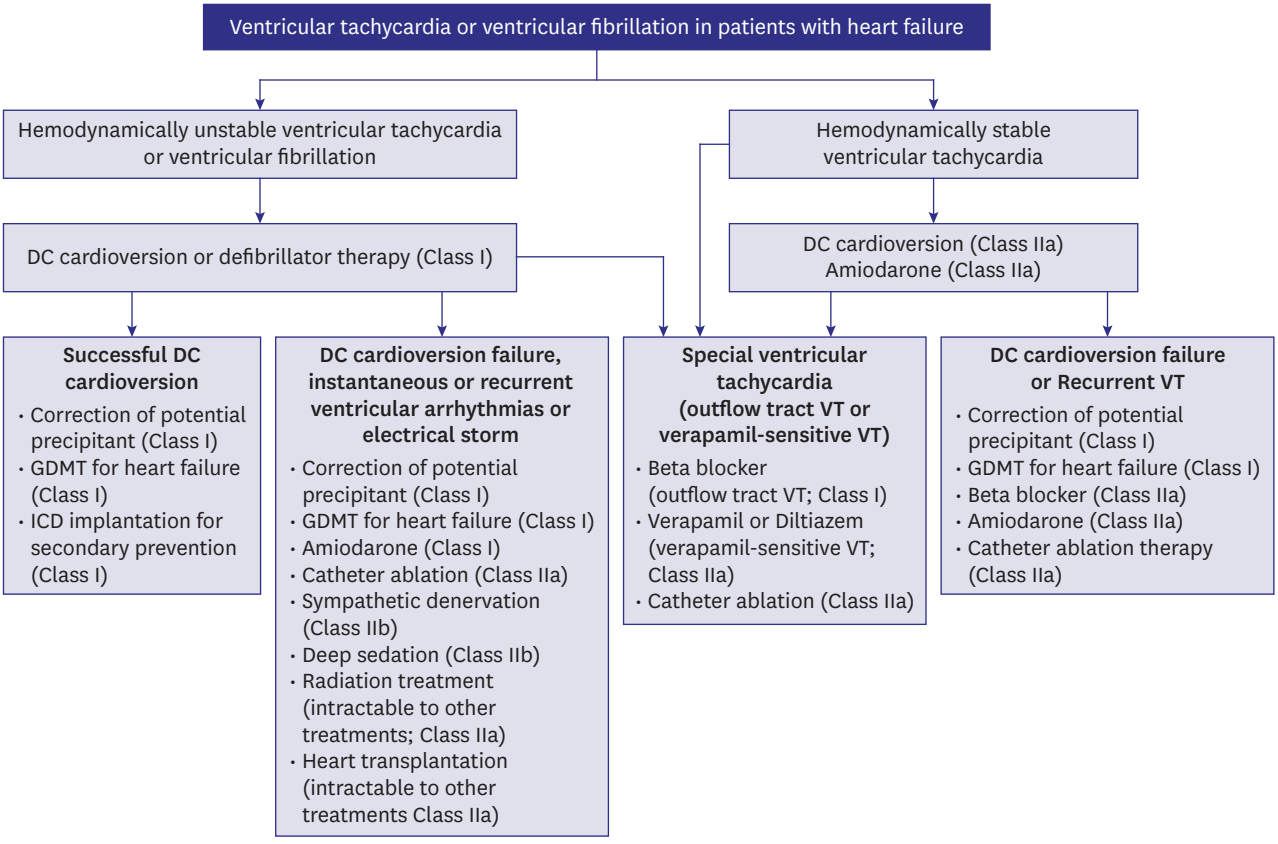

Figure 3. Recommendations for the treatment of ventricular arrhythmia in patients with heart failure.
DC = direct current; GDMT = guideline-directed medical therapy; ICD = implantable cardioverter-defibrillator; VT = ventricular tachycardia.

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should be reduced as much as possible.[86-88] In patients with HFrEF (LVEF ≤40%) requiring ventricular pacing, bi-ventricular pacing is recommended rather than right ventricular pacing.[89-92]

VALVULAR HEART DISEASE

1. In patients with suspected low-flow/low gradient severe aortic stenosis (AS) with reduced EF, low-dose dobutamine stress echocardiography or measurement of aortic valve calcium score by cardiac tomography imaging is reasonable to further define severity and assess contractile reserve. (Class IIa, Level of Evidence B)
2. In symptomatic patients with severe AS, surgical or transcatheter aortic valve replacement is indicated. (Class I, Level of Evidence B)
3. In asymptomatic patients with severe AS, and an EF <50%, surgical or transcatheter aortic valve replacement is indicated. (Class I, Level of Evidence B)
4. Transcatheter edge-to-edge repair should be considered in carefully selected patients with chronic severe secondary MR, not eligible for surgery and not needing coronary revascularization, who are symptomatic, despite optimal medical treatment including cardiac resynchronization therapy for HF. (Class IIa, Level of Evidence B)

Aortic valve

AS is an increasingly prevalent valvular heart disease among the aging population. It is associated with significant morbidity and mortality. In patients with HF with reduced LVEF and AS, accurate assessment of stenosis severity is crucial for clinical decision-making. Low-dose dobutamine stress echocardiography or cardiac CT may help assess severity of stenosis and contractile reserve for patients with low-flow/low-gradient AS. Surgical or transcatheter aortic valve replacement is recommended for symptomatic patients with severe AS[93)94)] and for asymptomatic patients with severe AS and LV systolic dysfunction (LVEF <50%).[93)94)]

No specific drug therapy has been proven to improve the clinical course of chronic aortic regurgitation. Surgical treatment is recommended in patients with acute and chronic HF due to severe aortic regurgitation, regardless of the LVEF.[95)96)]

Mitral valve

Primary MR is caused by valvular abnormalities and leads to HF. If acute or chronic HF is caused by severe primary MR, mitral valve repair is recommended when durable results are expected.[93)94)96)]

Secondary MR is caused by mitral annulus dilatation and associated with poor prognosis in patients with HF. Mitral valve surgery is recommended for patients with severe secondary MR who have an indication for CABG.[93)94)] In patients without CAD, if symptomatic secondary severe MR persists despite OMT including cardiac resynchronization therapy, surgery or transcatheter edge-to-edge repair may be considered to reduce HF-related hospitalization.[97)98)] A multidisciplinary team discussion based on the detailed echocardiographic evaluation of valve structure and cardiac function is essential.

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Tricuspid valve

Secondary tricuspid regurgitation (TR) is more common and occurs as a result of tricuspid annulus dilation caused by right ventricular enlargement and dysfunction as a consequence of PH, left-sided heart disease, or atrial fibrillation. Diuretic therapy treats the systemic congestion in patients with severe symptomatic TR. Tricuspid valve repair (or replacement) is recommended for patients with severe TR undergoing left-sided heart surgery. Transcatheter interventions for severe TR are under clinical development.[99]

DIABETES MELLITUS

1. In patients with type 2 diabetes mellitus (T2DM) and either established CVD or at high cardiovascular risk, sodium-glucose cotransporter-2 (SGLT2) inhibitor is recommended to prevent hospitalizations for HF, and cardiovascular death. (Class I, Level of Evidence A)
2. In patients with T2DM and HFrEF, SGLT2 inhibitor is recommended to reduce hospitalizations for HF and cardiovascular death. (Class I, Level of Evidence A)

The KorAHF registry study reported that 40% of patients with HF had concomitant diabetes.[100] In general, the glycated hemoglobin of patients with diabetes is maintained <7.0%. However, individualized control is recommended according to comorbidities, frailty, and risk of hypoglycemia.[100] The cardiorenal benefits of different SGLT2 inhibitors have been reported in numerous large clinical trials, in patients with and without diabetes.[101-109] The SGLT2 inhibitors are recommended for patients with T2DM and HFrEF and at risk of cardiovascular events or with CVD to reduce HF-related hospitalizations and cardiovascular mortality.[100][110] Moreover, recently published large-scale trials showed that SGLT2 inhibitors reduced the risk of cardiovascular death and hospitalizations for HF with mildly reduced or preserved EF in patients with and without diabete.[102][106] Thiazolidine derivatives should not be administered in symptomatic HF patients.

RENAL FAILURE AND ELECTROLYTE IMBALANCE

Cardiorenal syndrome refers to a condition in which HF and renal dysfunction interact (**Table 1**). After treatment with RAS inhibitors, angiotensin receptor-neprilysin inhibitors (ARNIs), or SGLT2 inhibitors are initiated, the initial decrease in the glomerular filtration pressure may decrease the glomerular filtration rate and increase serum creatinine. However, these changes are generally transient and occur despite improved patient outcomes in the long term.[111-113] Diuretics should be used continuously when there is evidence of congestion

Table 1. Types of cardiorenal syndrome

Type	Description
Type 1	Acute deterioration in cardiac function, which leads to acute kidney injury
Type 2	Chronic abnormalities of cardiac function leading to chronic kidney disease
Type 3	Acute kidney injury leading to acute cardiac injury and/or dysfunction
Type 4	Chronic kidney injury leading to chronic cardiac dysfunction
Type 5	Systemic disorders causing cardiac and renal dysfunction

Adopted from Jang and Yang. *Int J Heart Fail* 2022;4:75-90.[113]

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indicated by an elevation of serum creatinine. Ultrafiltration may be considered for removal fluid excess refractory to diuretic therapy.[114][115]

RESPIRATORY DISORDERS

The KorAHF registry study reported that 11% of patients with HF had chronic lung disease at the time of admission.[7] Generally, most HF treatments do not significantly affect the course of chronic obstructive pulmonary disease[116]; however, beta-blockers may worsen lung function in some patients.[117] However, beta-blockers are not contraindicated in chronic obstructive pulmonary disease or asthma in the guidelines.[118][119] In clinical practice, when cardiac selective beta-blockers are initiated at a low dose and up-titrated, patients need to be closely monitored for signs of airway obstruction.

IRON DEFICIENCY AND ANEMIA

1. Erythropoiesis-stimulating agents are not recommended in patients with chronic HF accompanied by anemia without a specific cause. (Class III, Level of Evidence B)
2. Intravenous administration of iron supplements (ferric carboxymaltose) is reasonable for HF patients with iron deficiency anemia. (Class IIa, Level of Evidence A)
3. In patients with iron deficiency with a LVEF of less than 50% who were recently hospitalized for acute HF, intravenous iron supplementation may help reduce hospitalization due to HF. (Class IIa, Level of Evidence B)

Iron deficiency and anemia are common in patients with chronic HF. Previous studies reported that 50% of patients had iron deficiency (absolute iron deficiency: serum ferritin <100 ng/mL; functional iron deficiency: serum ferritin 100–299 ng/mL and transferrin saturation <20%) and 14–60% had anemia (hemoglobin <13 g/dL and <12 g/dL in men and women, respectively).[120][121] In Korea, 36% of patients with HF were reported to have anemia.[122] Anemia increases mortality in patients with HF and is associated with reduced exercise capacity, high readmission rates, and poor QoL.[123][124] Iron deficiency could be found independent of anemia and is associated with reduced exercise capacity and decreased QoL and poor prognosis of HF.[120][125-127]

Iron is mainly stored in the liver and reticuloendothelial system. Ferritin stores iron in tissues, and transferrin moves stored iron into the plasma and extracellular fluid. There are two types of iron deficiency; "absolute iron deficiency," which is caused by insufficient iron absorption and "functional iron deficiency," which develops when the amount of iron in the body is sufficient, whereas iron homeostasis is abnormal, resulting in iron deficiency than the required amount of the target tissue.[128] Absolute iron deficiency can be diagnosed by measuring serum ferritin levels as the amount of iron decreases. Functional iron deficiency can be diagnosed by measuring both ferritin and transferrin saturation (TSAT). Notably, TSAT is decreased in functional iron deficiency. However, ferritin is an acute phase reactant; hence, ferritin levels may increase non-specifically due to infection or inflammation.

In several small-scale studies, erythropoiesis stimulators exhibited anemia correction and improvement in exercise capacity.[129][130] A subsequent large-scale randomized clinical study,

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which evaluated the efficacy of darbepoetin, reported no improvement in performance or LVEF; nevertheless, several QoL indices were improved. However, 6 out of 110 patients treated with darbepoetin died, which raised safety concerns over erythropoiesis-stimulating agents.[131] In addition, although safety concerns were not raised in the Study of Anemia in Heart Failure Trial, treatment efficacy was not proven.[132] A randomized clinical trial (the Reduction of Events by Darbepoetin Alfa in Heart Failure trial) that evaluated the efficacy and safety of darbepoetin in 1,142 patients with HF and anemia reported that darbepoetin did not significantly improve anemia, while the frequency of thromboembolic events was significantly increased.[133] Therefore, erythropoiesis-stimulating agents are not recommended in patients with HF.

Intravenous administration of iron supplements is effective in patients with HF and iron deficiency anemia. Intravenous administration of iron sucrose improved hemoglobin levels, QoL, 6-minute walk test distance, exercise capacity, and symptoms.[134][135] Large-scale clinical trials mainly researched ferric carboxymaltose administration. The Ferinject Assessment in patients with IRon deficiency and chronic Heart Failure study, a randomized clinical trial, compared intravenous ferric carboxymaltose and placebo in 459 patients with systolic HF and iron deficiency (hemoglobin 9.5–13.5 g/dL) and reported that intravenous ferric carboxymaltose improved symptoms and 6-min walk test distance.[136] The CONFIRM-HF study demonstrated the effectiveness of long-term intravenous ferric carboxymaltose administration in patients with HF and iron deficiency (LVEF <45%; hemoglobin <15 g/dL). Intravenous administration of ferric carboxymaltose improved the 6-minute walk test distance and reduced hospitalization due to HF exacerbation compared with the placebo.[137] The AFFIRM-HF study, which compared intravenous administration of ferric carboxymaltose and placebo, reported no significant reduction in the primary endpoint of total HF hospitalization and cardiovascular mortality (rate ratio, 0.79; 95% confidence interval [CI], 0.62–1.01; p=0.059). However, total HF hospitalization (rate ratio, 0.74; 95% CI, 0.58–0.94; p=0.013) and first HF hospitalization or cardiovascular mortality (hazard ratio, 0.80; 95% CI, 0.66–0.98; p=0.030) were significantly lower in the intravenous ferric carboxymaltose group than in the placebo group.[138] Thus, in patients with iron deficiency and an LVEF <50% who were recently hospitalized for acute HF, intravenous iron supplementation may help reduce HF-related hospitalization (Class IIa, Level of Evidence B).

Conversely, oral iron supplements did not significantly increase ferritin and only increased TSAT by 3.3%, despite administration for 16 weeks in patients with HF with LVEF <40% and iron deficiency. In addition, the exercise capacity or 6-minute walk test distances were not improved.[139] This may be due to reduced iron absorption in patients with HF due to concomitant medications or functional changes in the digestive tract.[140]

SLEEP APNEA DISORDERS

Sleep apnea or hypopnea occurs when breathing is paused for more than >10 seconds during an hour of sleep and is defined as an apnea-hypopnea index ≥5. Sleep apnea increases the morbidity and mortality of CVD by three-fold; it is diagnosed through polysomnography.[141] Epidemiologically, approximately 9% and 24% of women and men, respectively, aged >30 years have sleep apnea.[142] The prevalence of sleep apnea is much higher in patients with HF (>50%).[143]

Sleep apnea is classified as obstructive (OSA), central (CSA), and mixed sleep apneas. Obstructive sleep apnea is mostly observed in otherwise healthy individuals. Although it is

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observed in patients with HF, CSA and Cheyne-Stokes respiration (CSR), defined as "periodic breathing in HF," is more frequently observed. Such periodic breathing is observed in HFrEF and HFpEF, and is associated with a decrease in cardiac output and is closely related to left ventricular dysfunction and atrial fibrillation.[144] In a supine position, accumulated fluids migrate into the upper airway and induce upper airway edema, which can cause or worsen apnea.[145]

The typical symptoms of sleep apnea, such as snoring and excessive daytime sleepiness, appear less typically in patients with HF than in the general population, despite severe sleep apnea and less total sleep duration.[146] Therefore, patients can be assessed (via questionnaires) for sleep quality, the sleep maintenance status, and nocturia, especially in cases of men or those frequently hospitalized for HF.

Nevertheless, since a diagnosis cannot be made based on a questionnaire, a full-night polysomnography is required for accurate diagnosis. This will help accurately determine the presence of sleep apnea and its type (OSA or CSA). Distinguishing between both types is important for deciding treatment options. In addition, polysomnography can determine low oxygen concentration, apnea severity, arousal during sleep, and sleep depth.

In cases of OSA, continuous positive airway pressure (CPAP) therapy can improve stroke volume and cardiac output by suppressing upper airway obstruction, reducing changes in intrathoracic pressure or blood pressure, and preventing an increase in left ventricular afterload. Several studies have reported that CPAP therapy increased the LVEF in patients with HF, and demonstrated an improvement in sympathetic nerve activation and myocardial oxygen metabolism.[147][148]

Appropriate treatment for CSA with HF is yet to be established. In many cases, the appropriate pharmacological treatment of HF concomitantly improves CSA.[149] In particular, diuretics may prevent aggravation of sleep apnea by preventing upper airway edema during sleep. However, in a large-scale Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure study, which included 1,325 patients with HFrEF (LVEF <35%) and CSA-CSR, although the apnea exhibited improvement when treated with Adaptive Servo-Ventilation (ASV), increased occurrence of sudden death in the ASV group resulted in a statistically significant increase in overall and cardiovascular mortalities.[150] Therefore, ASV is no longer recommended for patients with HFrEF and CSA.

DEPRESSION AND COGNITIVE IMPAIRMENT

The prevalence of major depression in patients with chronic HF is approximately 20–40%, which is 4–5% higher than in the normal population, and half of these are severe. Depression in HF is a major problem as the burden of HF continues to rise, and many studies have reported a poorer prognosis in patients with HF and comorbid depression.[151][152] Depression significantly affects cognitive function and treatment adherence in patients with HF. Therefore, it is important to consider depression as a treatable disorder that is common in older adults with chronic conditions including HF. When depression is clinically suspected, a screening test should be performed using validated questionnaires, such as the Beck Depression Inventory II and Cardiac Depression Scale. In addition, the Geriatric Depression Scale, Hamilton Depression Rating Scale, and Hospital Anxiety and Depression Scale may be considered.

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The optimal treatment for HF patients with depression is yet to be established. Psychosocial intervention can improve depressive symptoms; however, it may not affect the prognosis.[151][152] Although selective serotonin reuptake inhibitors were hypothesized to improve depressive symptoms, actual clinical trials revealed no significant results in symptom and prognosis improvement compared with the placebo. Sertraline and escitalopram exhibited medication safety in patients with HF.[153] Tricyclic antidepressants cause hypotension, worsening HF, and arrhythmia and should be avoided in patients with HF.

Cognitive decline, an independent prognostic factor in patients with HF, is reported in 45–80% of patients hospitalized for acute decompensated HF.[154] Cerebral hypoperfusion, blood-brain barrier damage, oxidative damage, and brain-derived cytokines are considered to be pathologically related. White matter hyperintensity, lacunar infarction, and general volume loss are common neuroimaging features of cognitive decline. Assessment of cognitive function via simple screening tests should be part of the routine clinical examination in patients with HF. The screening tests in an outpatient setting include the Mini-Mental State Examination and Montreal Cognitive Assessment. However, these tests may not be sufficient to identify subtle cognitive impairments; hence, more detailed neuropsychological tools may be needed. No drugs have been specifically approved for patients with HF and cognitive impairment. Acetylcholinesterase inhibitors and memantine are reportedly effective in vascular dementia; however, the effectiveness and safety of these drugs in patients with HF are yet to be elucidated.[155]

PREGNANCY

Pregnant women with chronic HF have a high mortality rate, and a normal pregnancy and delivery may be difficult. Pregnant women with hemodynamically unstable acute HF are at high risk of maternal mortality and morbidities and indicated or spontaneous preterm birth. Even in cases of mild chronic HF, pregnancy may worsen HF; therefore, a detailed explanation and counseling sessions with a doctor are essential if the patient desires pregnancy. In the case of pregnant women with HF with the NYHA functional class II–IV, close observation is required from the 20th week of pregnancy. Pregnant women with an LVEF ≤40% are a high-risk group and require intensive observation at a higher-level medical institution. Pregnant women with an LVEF ≤20% have an extremely high maternal mortality rate; hence, pregnancy termination should be considered based on the patient's condition.[156]

Pregnant patients with HF are treated similar to non-pregnant patients with HF, with the exception of some medications that are contraindicated during pregnancy. Medications such as ACEI, ARBs, ARNI, MRAs (aldosterone antagonists), ivabradine, and SGLT2 inhibitors are contraindicated during pregnancy due to fetal toxicity (Class III, Level of Evidence B). For the treatment of HF, continuation of beta-blockers already in use are recommended throughout pregnancy, and bisoprolol or metoprolol, which have high ß-1 selectivity may be recommended (Class IIa, Level of Evidence B). Hydralazine and nitrates may be used instead of ACEI or ARBs to reduce afterload. Direct oral anticoagulants for treating atrial fibrillation are contraindicated (Class III, Level of Evidence B). Therefore, low-molecular-weight heparin can be used throughout pregnancy (Class I, Level of Evidence B), and warfarin can be used during the second trimester (Class IIa, Level of Evidence B).[157][158]

Peripartum cardiomyopathy is defined as HF with an LVEF ≤45% that occurs in the last trimester of pregnancy or within 5 months after delivery, without an obvious cause.[159][160] It

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has been reported to occur 1 month after delivery. According to one cohort study using the Korean National Health Insurance Service data, 52% of peripartum cardiomyopathy occurred after delivery (46% within 1 week), and 8.1% occurred between 5 and 12 months after delivery. Caesarean sections were more common in patients with perinatal cardiomyopathy. Moreover, birth-related complications such as premature placental abruption, uterine artery embolization, and hysterectomy were more frequent. Prognosis prediction depends on whether LV size and function normalize within six months after delivery (LVEF ≥50%). In general, irreversible LV dysfunction can be expected if cardiac function does not recover 3–6 months after the initial diagnosis; however, in rare cases, cardiac function and size are completely normalized after 2 years. The degree of recovery varies across countries, ranging from >50% to 75%.[159][161][162]

MALIGNANCY OR CHEMOTHERAPY ASSOCIATED WITH HEART FAILURE

In patients with malignant tumors, HF may occur due to interactions between the underlying CVD risk factors, the tumor itself, and anticancer drugs. Anticancer drugs can cause HF by inducing myocardial cell damage, myocarditis, systemic/pulmonary arterial hypertension, arrhythmia, or IHD due to immune responses or side effects on blood vessels.[163] The clinical manifestations are diverse, and the causal relationship of certain drugs is yet to be accurately proven (**Table 2**).

Anthracycline, an anticancer drug used to treat breast cancer, lymphoma, leukemia, or sarcoma, might cause HF. Since anthracycline-related HF often causes irreversible myocardial damage, a chelating agent such as dexrazoxane may be needed in patients with administration of doxorubicin or epirubicin is more than a specific dose (≥300 mg/m^2 or ≥540 mg/m^2, respectively) or in patients with concomitant heart disease. Trastuzumab, a human epidermal growth factor receptor 2-targeted therapy, frequently causes HF. Thus, the cardiac function should be checked at regular intervals before, during, and after anticancer drug administration. In patients receiving anticancer drugs, if the LVEF decreases by >10% compared with the baseline LVEF or LVEF <50%, ACEIs or beta-blockers are primarily used. If LVEF decreases <40%, discontinuation of anticancer drugs should be considered.[164] Myocardial strain value is gaining attention as an early predictor of anticancer cardiotoxicity.[165][166] In the case of high-risk populations, preemptive use of ACEIs or beta-blockers might be helpful for the prevention of cardiotoxicity.[167] Immune checkpoint inhibitors, which are increasing prescribed for various tumors, might cause myocarditis in approximately 1.1%, and prompt treatment with intravenous injection of high-dose steroids and immunoglobulins is important for early recovery of HF.[166] Owing to the rapid development of various anticancer drugs and the increased survival rate of patients with malignant tumors, managing CVD and prevent cardiovascular complications, even in cancer

Table 2. Major anticancer drugs causing heart failure

Agents	Drugs
Anthracycline	Doxorubicin, Epirubicin, Idarubicin
HER2 targeted therapy	Trastuzumab, Pertuzumab, T-DM1
VEGF inhibitor	Sunitinib, Pazopanib, Lenvatinib, Bevacizumab, Ramucirumab
Proteasome inhibitor	Carfilzomib, Bortezomib
Immune checkpoint inhibitor	Pembrolizumab, Nivolumab, Ipilimumab, Atezolizumab

Adopted from Kim et al. *J Cardiovasc Ultrasound* 2018;26:1-25.[163]
HER2 = human epidermal growth factor receptor 2; VEGF = vascular endothelial growth factor.

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patients is the current necessity. Stratifying the risk of HF according to the patient's underlying CVD and type of anticancer drug being administered are needed and regular cardiac function monitoring and heart protection strategies should be performed accordingly.

CONCLUSION

Managing comorbidities in patients with HF is important to determine HF outcome substantially. The strong impact of comorbidities on prognosis of HF complicates management of patients with HF. Despite the recent and major advances in HF treatment, research that evaluate the effect of controlling the comorbidities have not demonstrated significant improvements. Moreover, managing non-cardiovascular comorbidities in patients with HF has become increasingly complex. Despite this, novel therapies in the field of AF, DM, iron deficiency, valvular heart disease, and CAD have been introduced. Therefore, a multidisciplinary approach in various non-cardiovascular conditions is strongly needed to optimally treat patients with HF. These comorbidities directly contribute to the clinical outcomes of HF and are key determining factors of HF; therefore, further studies are needed to elaborate the impact of multiple comorbidities on HF and HF-related mortalities.

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