Clinical Practice Guideline

Heart Failure Council of Thailand (HFCT) 2019 Heart Failure Guideline: Comorbidity in Heart Failure

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In addition to screening for and presence of cardiovascular comorbidity, non-cardiovascular comorbidity screening is recommended in all heart failure patients (Figure 1), and all identified conditions should be promptly treated.

Hypertension

Hypertension is one of the most important risk factors for heart failure. Blood pressure lowering therapies significantly reduce the occurrence of heart failure. A recent trial demonstrated that intensive blood pressure control with a goal of systolic blood pressure control of less than 120 mmHg significantly reduced the incidence of heart failure and cardiovascular death among non-diabetic patients at high cardiovascular risk[(1)]. Office blood pressure is typically 5 to 10 mmHg higher than blood pressure measured in a research setting. Therefore, target blood pressure of less than 130/80 mmHg in patients at risk for heart failure (stage A heart failure) is recommended (Table 1). Although the optimal blood pressure target in patients with stage C heart failure [in both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF)] with concomitant hypertension has not yet been conclusively established, a systolic blood pressure target of less than 130 mmHg in this population is consistent with the recent evidence and seems to be appropriate.

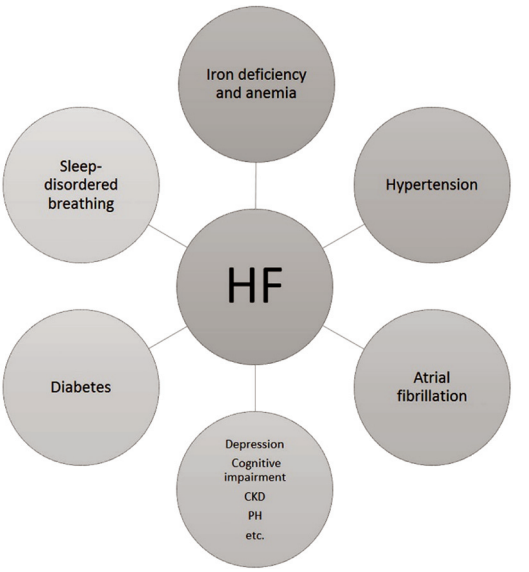

Figure 1. Comorbidity in heart failure.

HF, heart failure; CKD, chronic kidney disease; PH, pulmonary hypertension

Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, angiotensin receptor-neprilysin inhibitor, beta-blocker, or mineralocorticoid receptor antagonist is recommended as first-line blood pressure lowering agent in patients with HFrEF

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Table 1. Summary of recommendations regarding treatment targets in heart failure patients with hypertension

Recommendations	COR	LOE
1. In hypertensive patients at risk for heart failure, the recommended target blood pressure is less than 130/80 mmHg.	I	A
2. In patients with HFrEF and hypertension, the recommended target systolic blood pressure is less than 130 mmHg.	I	C
3. In patients with HFpEF and hypertension, the recommended target systolic blood pressure is less than 130 mmHg.	I	C

COR=class of recommendation; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; LOE=level of evidence

due to observed mortality and morbidity benefits in this population. Thiazide diuretic, amlodipine[2], felodipine[3], or hydralazine[4-6] can be safely used to lower blood pressure in HFrEF patients. Since they are harmful, alpha-receptor antagonist[7-9] and non-dihydropyridine antagonist (including verapamil and diltiazem)[10] should not be used to treat hypertension in patients with HFrEF. Although clinical trials in patients with HFpEF are limited, nitrate is not recommended for use in HFpEF due to its negative impact on exercise capacity[11].

Iron deficiency and anemia

Iron deficiency is common in heart failure, and it is independently associated with reduced exercise capacity and worse prognosis regardless of hemoglobin level[12,13]. Intravenous iron replacement may improve functional capacity and quality of life. Two randomized controlled trials using intravenous ferric carboxymaltose in symptomatic patients with HFrEF and iron deficiency (defined as serum ferritin of less than 100 ng/mL or serum ferritin between 100 and 299 ng/mL and transferrin saturation of less than 20%) was shown to improve New York Heart Association (NYHA) Functional Class and quality of life, and to reduce N-terminal pro-B-type natriuretic peptide levels in those with and without anemia[14,15]. In the Ferric Carboxymaltose evaluation on performance in patients with iron deficiency in combination with chronic Heart Failure (CONFIRM-HF) study, the secondary endpoint of heart failure readmission was found to be significantly reduced[15]. A meta-analysis of prospective controlled studies showed statistically significant improvement in functional capacity, heart failure hospitalization, and left ventricular ejection fraction, but not for reducing mortality[16]. There is limited long-term data regarding the efficacy and safety of intravenous iron therapy in those with HFpEF, in those with heart failure with mid-range ejection fraction, and in heart failure patients with hemoglobin level of more than 15 g/dL.

There is limited data regarding the effect of oral iron supplementation in heart failure patients. The Iron Repletion Effects on Oxygen Uptake in Heart Failure (IRONOUT HF) trial, which is a recently published randomized controlled trial, reported that oral iron polysaccharide did not demonstrate improvement in exercise capacity measured by peak oxygen consumption in symptomatic HFrEF patients with iron deficiency when compared to placebo[17].

Anemia, defined as hemoglobin level of less than 12 g/dL in female and less than 13 g/dL in male, is common in heart failure population, and is independently associated with poor exercise capacity and worse outcome. Several small prospective cohort studies and small controlled trials reported the benefit of erythropoietin-stimulating agent for improving functional capacity, improving quality of life, and decreasing heart failure admission[18-21]. In the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) trial, darbepoietin alpha failed to improve clinical outcomes, and it increased thromboembolic complications[22]. Therefore, routine use of erythropoietin stimulating agents in HFrEF patients with anemia to improve exercise capacity and quality of life is not recommended (Table 2).

Diabetes mellitus

Diabetes mellitus is common in patients with heart failure, and it is associated with worse prognosis and poor functional status[23]. Although high glycated hemoglobin level is associated with worse outcomes, the evidence is inconsistent relative to the benefit of strict glycemic control in type 2 diabetes on long-term cardiovascular outcomes[24-28]. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are associated with better outcomes. Two recently conducted large randomized controlled trials [Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME)[29] and Canagliflozin

Table 2. Summary of recommendations regarding treatment of heart failure patients with iron deficiency and anemia

Recommendations	COR	LOE
1. Assessment of anemia and iron deficiency should be performed in heart failure patients who remain symptomatic after receiving optimized guideline-directed medical therapy.	IIa	B
2. Intravenous iron should be considered to improve functional status and quality of life in symptomatic heart failure patients with NYHA Functional Class II and III and iron deficiency (serum ferritin <100 ng/mL, or serum ferritin 100 to 299 ng/mL and transferrin saturation <20%).	IIa	B
3. Routine use of erythropoietin-stimulating agents to improve functional status and quality of life in heart failure patients with anemia is not recommended.	III	A

COR=class of recommendation; LOE=level of evidence; NYHA=New York Heart Association

Table 3. Summary of recommendations regarding treatment of HF patients with diabetes mellitus

Recommendations	COR	LOE
1. Metformin should be used as a first-line therapy in heart failure patients with diabetes, unless contraindicated.	IIa	C
2. SGLT-2 inhibitors should be considered in CVD patients with diabetes type 2 to reduce heart failure hospitalization.	IIa	A
3. Thiazolidinediones are not recommended in patients with heart failure due to the increased risk of worsening heart failure and hospitalization.	III	A

COR=class of recommendation; CVD=cardiovascular disease; LOE=level of evidence; SGLT-2=sodium/glucose cotransporter-2

Table 4. Summary of recommendations regarding the treatment of heart failure patients with sleep-disordered breathing

Recommendations	COR	LOE
1. Polysomnography should be considered in symptomatic heart failure patients with NYHA Functional Class II-IV with suspected sleep-disordered breathing.	IIa	C
2. CPAP may be reasonable for use in CVD patients with obstructive sleep apnea to improve sleep quality and daytime sleepiness.	IIb	B
3. Adaptive servo-ventilation is not recommended in symptomatic HFrEF patients with central sleep apnea due to the increased risk of all-cause and cardiovascular mortality.	III	B

COR=class of recommendation; CPAP=continuous positive airway pressure; CVD=cardiovascular disease; HFrEF=heart failure with reduced ejection fraction; NYHA=New York Heart Association; LOE=level of evidence

cardioVascular Assessment (CANVAS)[30] studies] showed that empagliflozin and canagliflozin significantly reduced long-term cardiovascular death and heart failure hospitalization, respectively, in type 2 diabetes with established cardiovascular disease (CVD) and/or at high cardiovascular risk over the median follow-up of approximately three years. Although the Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) trial is still ongoing, the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD REAL) study demonstrated the beneficial effect of dapagliflozin on cardiovascular outcomes in real-life clinical practice[31]. Therefore, SGLT-2 inhibitors should be used in CVD patients with concomitant type 2 diabetes to prevent heart failure. Thiazolidinediones have been shown to increase the risk of worsening heart failure in established CVD patients, so they are not recommended in patients with history of heart failure[32,33] (Table 3).

Sleep-disordered breathing

Sleep-disordered breathing, including central and obstructive sleep apnea, is prevalent in patients with heart failure, and is associated with worse outcomes[34]. Polysomnography should be considered in patients with heart failure that are suspected of having sleep apnea. Continuous positive airway pressure (CPAP) in CVD patients with obstructive sleep apnea was shown to improve sleep quality and daytime sleepiness,

but no benefit was observed relative to prevention of cardiovascular events[35,36]. Adaptive servo-ventilation in HFrEF patients with central sleep apnea is associated with increased mortality and should be avoided in this population[37] (Table 4).

Conflicts of interest

The authors declare no conflict of interest.

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