Clinical Practice Guideline

Heart Failure Council of Thailand (HFCT) 2019 Heart Failure Guideline: Pharmacologic Treatment of Chronic Heart Failure - Part I

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Heart failure with reduced ejection fraction (HFrEF)

Heart failure (HF) can be divided into different stages according to risk factors for heart failure, alteration of cardiac structure/function (cardiac remodeling), and the presence of symptoms. HF is a progressive condition in which neurohormonal activation plays a central role. Without appropriate treatment, patients with HFrEF will generally develop worsening of symptoms and increased risk of cardiovascular morbidity and mortality. Medications that modify this neurohormonal activation can delay HF progression, reduce symptoms, and/or prolong the survival of patients with HFrEF. These medications include angiotensin converting enzyme inhibitors (ACEIs) angiotensin II receptor blockers (ARBs), beta blockers (BB), and mineralocorticoid receptor antagonist (MRA) (Figure 1). Recently, an angiotensin II receptor blocker neprilysin inhibitor (ARNI) (sacubitril/valsartan)[1] and a sodium/glucose cotransporter-2 (SGLT-2) inhibitor[2] (e.g., empagliflozin) were shown to benefit specific subgroups of patients with HF and patients at risk for developing HF, respectively. The goals of treatment in HFrEF are to improve clinical status, functional capacity, and quality of life, prevent hospital admission, and, ultimately, to reduce mortality. Staging of heart failure and New York Heart Association (NYHA) functional classifications are shown in Table 1.

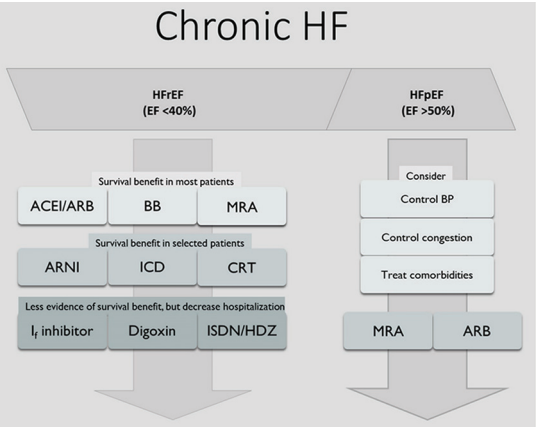

Figure 1. Pharmacologic treatment of chronic heart failure according to survival benefit.

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor neprilysin inhibitor; BB=beta blockers; CRT=cardiac re-synchronization therapy; EF=ejection Fraction; HFrEF=heart failure with reduced ejection fraction; ICD=implantable cardioverter defibrillator; ISDN=isosorbide dinitrate; HDZ=hydralazine; MRA=mineralocorticoid receptor antagonist

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Table 1. Stages of HF and NYHA functional classifications

Stage of HF and definition		NYHA functional classification		Symptom of HF
A	At high risk for HF, but without structural heart disease or symptoms of HF	I	No limitation of physical activity Ordinary physical activity does not cause symptoms of HF	Absent
B	Structural heart disease, but without signs or symptoms of HF	I	No limitation of physical activity Ordinary physical activity does not cause symptoms of HF	Absent
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity Ordinary physical activity does not cause symptoms of HF	Absent
		II	Slight limitation of physical activity Comfortable at rest, but ordinary physical activity results in symptoms of HF	Present
		III	Marked limitation of physical activity Comfortable at rest, but less than ordinary activity causes symptoms of HF	Present
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest	Present
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest	Present

HF=heart failure; NYHA=New York Heart Association

Table 2. Summary of recommendations regarding the use of ACEIs in patients with HF

Recommendations	COR	LOE
ACEIs are recommended in all patients with asymptomatic LV systolic dysfunction regardless of etiology in order to prevent or delay the onset of symptomatic HF unless contraindicated.	I	A
ACEIs are recommended in all patients with HFrEF and current or prior HF symptoms to reduce HF hospitalization and mortality.	I	A
In patients intolerant to ACEIs, angiotensin-receptor blockers (ARBs) are recommended unless contraindicated.	I	A
ACEIs should be initiated in clinically stable patients at a low dose, and then gradually uptitrated to the maximum tolerated dose.	I	A

ACEIs=angiotensin converting enzyme inhibitors; ARBs=angiotensin II receptor blockers; COR=class of recommendation; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; LOE=level of evidence; LV=left ventricle

Angiotensin-converting enzyme inhibitors (ACEIs)

ACEIs reduce mortality and morbidity in symptomatic patients with HFrEF[3-6], and they are recommended unless contraindicated or not tolerated (Table 2). In asymptomatic patients with chronically reduced left ventricular ejection fraction (LVEF), ACEIs can reduce the risk of HF hospitalization regardless of its etiology[7,8]. ACEIs should be uptitrated to the maximum tolerated dose to attain clinical benefits similar to those observed in clinical trials (Table 2). Concurrent use of diuretics should be modulated according to the clinical status of the patient (i.e., symptoms and signs of congestion). This is done to avoid hypotension and acute renal insufficiency after initiation of ACEIs if the patient became hypovolemic due to over-diuresis.

Angiotensin-receptor blockers (ARBs)

Some ARBs have been shown to reduce mortality in patients with HFrEF. Candesartan reduces cardiovascular mortality in HF patients who are intolerant to ACEIs[9]. Valsartan reduces HF hospitalization, but not all-cause hospitalization in patients with HFrEF that are receiving background ACEIs[10]. Use of ARBs should be restricted to patients intolerant to ACEIs[9-12]. Combination of ACEIs and ARBs has a limited role in this population. If ACEI or ARB is used, renal function and serum potassium should be monitored at appropriate

Table 3. Summary of recommendations regarding the use of ARBs in patients with HF

Recommendations	COR	LOE
ARBs are recommended in all patients with HFrEF with current or prior HF symptoms who are intolerant to ACEIs (unless contraindicated) to reduce morbidity and mortality. Patients should also receive a beta-blocker and an MRA.	I	A
ARBs should be initiated in clinically stable patients at a low dose, and then gradually uptitrated to the maximum tolerated dose.	I	A
ARBs are a reasonable alternative to ACEIs as a first-line therapy for reducing morbidity and mortality in patients with HFrEF, especially in patients already taking ARBs for other indications, unless contraindicated.	IIa	A
Routine combined use of ACEIs, ARBs, and MRA is harmful in patients with HFrEF.	III	C

ACEIs=angiotensin converting enzyme inhibitors; ARBs=angiotensin II receptor blockers; COR=class of recommendation; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; LOE=level of evidence; MRA=mineralocorticoid receptor antagonist

Table 4. Summary of recommendations regarding the use of beta-blockers in patients with HF

Recommendations	COR	LOE
Beta-blockers are recommended in all patients with asymptomatic LV systolic dysfunction and history of myocardial infarction in order to prevent or delay the onset of symptomatic HF and to reduce mortality.	I	B
Beta-blockers are recommended in all patients with asymptomatic LV systolic dysfunction, including those with no history of myocardial infarction, in order to prevent or delay the onset of symptomatic HF.	I	C
A beta-blocker (bisoprolol, carvedilol, sustained-release metoprolol succinate, or nebivolol) is recommended in addition to ACEIs in all stable patients with current or prior symptoms of HFrEF to reduce the risk of HF hospitalization and death.	I	A
Beta-blockers should be initiated in clinically stable patients at a low dose, and then gradually uptitrated to the maximum tolerated dose.	I	A

ACEIs=angiotensin converting enzyme inhibitors; COR=class of recommendation; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; LV=left ventricle; LOE=level of evidence

intervals, especially in patients with impaired renal function. Recommended uses of ARBs in HFrEF are in (Table 3).

Beta-blockers

Beta-blockers are recommended in patients with history of myocardial infarction and asymptomatic LV systolic dysfunction to reduce mortality (Table 4). Beta-blockers reduce mortality and morbidity in patients with symptomatic HFrEF, despite treatment with ACEIs and diuretic. Four beta-blockers (bisoprolol, carvedilol, sustained-release metoprolol succinate, and nebivolol) have been extensively studied in patients with symptomatic HFrEF, and those studies showed reduction in morbidity and mortality[13-17]. A beta-blocker should be initiated in clinically stable patients at a low dose, and then gradually uptitrated to the maximum tolerated dose (Table 4). The clinical effects of beta-blockers and ACEIs are complementary. Initiation of either beta-blocker or ACEIs with subsequent initiation of the other has demonstrated similar benefits[18]. Beta-blocker and ACEIs can be started together as soon as HFrEF is diagnosed. Beta-blockers should be considered for heart rate control in patients with HFrEF and atrial fibrillation, especially in those with high heart rate. However, there is no evidence of additional benefit relative to HF hospitalization or mortality in this specific setting[19].

Conflicts of interest

The authors declare no conflict of interest.

References

1. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
2. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31-9.
3. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316:1429-35.

Table 5. Common drugs and recommended dose for patients with symptomatic HFrEF

Drug class	Drug	Initial dose (mg)	Target dose (mg)	Mean dose achieved in clinical trials
ACEIs	Captopril	6.25 mg b.i.d.	50 mg t.i.d.	122.7 mg/day
	Enalapril	2.5 mg b.i.d.	10 to 20 mg b.i.d.	16.6 mg/day
	Lisinopril	2.5 to 5 mg o.d.	20 to 40 mg o.d.	32.5 to 35 mg/day
	Perindopril	2 mg o.d.	8 to 16 mg o.d.	n/a
	Quinapril	5 mg b.i.d.	20 mg b.i.d.	n/a
	Ramipril	1.25 to 2.5 mg o.d.	10 mg o.d.	n/a
ARBs	Candesartan	4 to 8 mg o.d.	32 mg o.d.	24 mg/day
	Losartan	25 to 50 mg o.d.	50 to 150 mg o.d.	129 mg/day
	Valsartan	20 to 40 mg b.i.d.	160 mg b.i.d.	254 mg/day
Beta-blockers	Bisoprolol	1.25 mg o.d.	10 mg o.d.	8.6 mg/day
	Carvedilol	3.125 mg b.i.d.	25 mg b.i.d.	37 mg/day
	Metoprolol succinate extended release	12.5 to 25 mg o.d.	200 mg o.d.	159 mg/day
	Nebivolol	1.5 mg o.d.	10 mg o.d.	7.7 mg/day

ACEIs=angiotensin-converting enzyme inhibitors; ARBs=angiotensin-receptor blockers; b.i.d.=bis in die (twice daily); n/a=not available; o.d.=omne in die (once daily); t.i.d.=ter in die (three times a day)

4. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 1995;273:1450-6.
5. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
6. Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685-91.
7. Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet 2003;361: 1843-8.
8. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327:669-77.
9. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772-6.
10. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.
11. Maggioni AP, Anand I, Gottlieb SO, Latini R, Tognoni G, Cohn JN. Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. J Am Coll Cardiol 2002;40:1414-21.
12. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893-906.
13. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-7.
14. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9-13.
15. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26: 215-25.
16. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA 2000;283:1295-302.
17. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344: 1651-8.
18. Willenheimer R, Van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krum H, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the

randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation 2005;112:2426-35.
19. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet 2014;384:2235-43.