

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

Yingchoncharoen T, MD¹, Kanjanavanich R, MD²

¹ Cardiology Unit, Department of Internal Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

² Cardiovascular Unit, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

J Med Assoc Thai 2019;102(3):368-72

Website: <http://www.jmatonline.com>

Mineralocorticoid receptor antagonist (MRA)

Aldosterone activation in heart failure (HF) promotes myocardial fibrosis and progressive cardiac remodeling. Low (non-diuretic) dose MRA effectively blocks the harmful effect of aldosterone on the myocardium. MRA has been shown to markedly reduce mortality and rehospitalization in symptomatic (Fc II-IV) HF with reduced ejection fraction HFrEF (LVEF 35% or less) patients, despite prior treatment with an Angiotensin converting enzyme inhibitors (ACEI) and a beta-blocker (Table 1).

Every effort should be exercised to avoid life-threatening hyperkalemia, which is a relatively common serious side effect of MRA. Serum potassium level should be checked at least every three months, and at least seven days after initiation or dose up-titration. High-dose MRA (spironolactone of more than 50 mg per day) should be avoided, and it should never be used in combination with ACEIs and Angiotensin II receptor blockers (ARBs) due to the high-risk of hyperkalemia. MRA should not be initiated if serum creatinine (Cr) level is greater than 2.5 mg/dL in men or greater than 2.0 mg/dL in women or estimated glomerular filtration rate (eGFR) is less than 30 mL per minute per 1.73 m², and those with baseline serum K⁺ of more than 5.0 mEq/L.

Correspondence to:

Yingchoncharoen T.

Cardiology Unit, Department of Internal Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Phone: +66-2-2011612, **Fax:** +66-2-2011618

Email: teerapatmdcu@gmail.com

Physicians should be extremely careful if potassium supplementation is needed in patients receiving MRA, and more frequent potassium level monitoring is recommended.

Angiotensin Receptor Nephilysin Inhibitor (ARNI) (Table 2)

In addition to RAAS blockade, promoting natriuretic peptide (NP) system activation has shown beneficial effect (i.e., vasodilatory, natriuretic, and anti-remodeling) in HFrEF patients. In the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial, LCZ696 (a salt complex comprising valsartan and sacubitril in 1:1 molar ratio that was the first agent in the ARNI drug class) was shown to be superior to ACEI (enalapril 10 mg b.i.d.) for reducing hospitalizations for worsening HF, cardiovascular mortality, and overall mortality in ambulatory symptomatic HFrEF patients with left ventricular ejection fraction (LVEF) of 40% or less⁽¹⁾. Since the PARADIGM-HF trial consisted of three consecutive run-in periods that included only patients who were able to tolerate moderate dose of ACEI and ARNI, physicians should be cautious about potential ARNI side effects, such as increased risk of hypotension and angioedema, in real-life clinical practice. ARNI should be avoided in patients with hypotension [systolic blood pressure (SBP) of less than 90 mmHg], eGFR of less than 30 mL per minute per 1.73 m², serum K⁺ of more than 5.2 mmol/L, and history of angioedema. Pregnancy is also an absolute contraindication. ARNI must not be used

How to cite this article: Yingchoncharoen T, Kanjanavanich R. Heart Failure Council of Thailand (HFCT) 2019 Heart Failure Guideline: Pharmacologic Treatment of Chronic Heart Failure - Part II. J Med Assoc Thai 2019;102:368-72.

Table 1. Summary of recommendations regarding MRA use in patients with HF

| Recommendations | COR | LOE |
|---|-----|-----|
| Unless contraindicated, low-dose MRA (spironolactone) is recommended in symptomatic chronic HFrEF patients, preferably after treatment with ACEI/ARBs and BB, to further reduce HF hospitalization and mortality. | I | A |

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

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

| Recommendations | COR | LOE |
|--|-----|-----|
| Replacement of ACEIs (or ARBs) with ARNI (sacubitril/valsartan) to further reduce the risk of HF hospitalization and mortality in chronic HFrEF (LVEF <40%) patients who remain symptomatic despite guideline-directed medical therapy with an ACEI (or ARB), a beta-blocker, and an MRA is recommended. | I | B |
| Initiation of ARNI (sacubitril/valsartan) may be considered in ACEI/ARB naïve patients who have no vulnerable characteristics (e.g., systolic BP <100 mmHg, age >75 years). Low-dose ARNI should be carefully initiated and slowly uptitrated to the target dose. | IIb | C |

ACEI=angiotensin converting enzyme inhibitors; ARBs=angiotensin II receptor blockers; ARNI=angiotensin receptor-neprilysin inhibitor; BP=blood pressure; COR=class of recommendation; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; LOE=level of evidence; LVEF=left ventricular ejection fraction

Table 3. Recommended initial dose of ARNI

| Current dose RAAS blockade | | Initial dose of ARNI | Titration |
|----------------------------|------------------------|----------------------|---|
| ACEIs | ARBs | Sacubitril/valsartan | |
| Enalapril ≥10 mg/day | Losartan ≥50 mg/day | 49/51 mg b.i.d. | Increase over 3 to 4 weeks to target dose of 97/103 mg b.i.d. |
| Lisinopril ≥10 mg/day | Valsartan ≥160 mg/day | | |
| Perindopril ≥4 mg/day | Candesartan ≥16 mg/day | | |
| Ramipril ≥5 mg/day | Irbesartan ≥150 mg/day | | |
| | Olmесartan ≥10 mg/day | | |
| | Telmisartan ≥40 mg/day | | |
| Low-dose RAAS blockade | | 24/26 mg b.i.d. | Increase over 6 weeks to target of 97/103 mg b.i.d. |
| RAAS blockade naïve | | 24/26 mg b.i.d. | |
| High risk of hypotension | | | |

ACEI=angiotensin converting enzyme inhibitors; ARBs=angiotensin II receptor blockers; b.i.d.=bis in die (twice daily); RAAS=renin-angiotensin-aldosterone system

concomitantly with an ACEI due to the increased risk of excessive hypotension and angioedema. When switching from ACEIs to ARNI, discontinue ACEIs for at least 36 hours before starting ARNI (Table 3). In contrast, no discontinuation of ARBs is required before switching to ARNI⁽¹⁾.

Ivabradine (Table 4)

Ivabradine is a selective I_f channel inhibitor that produces negative chronotropic effect without negative inotropic effect. The clinical benefit of ivabradine in HFrEF was demonstrated in the Systolic HF treatment with the I_f inhibitor ivabradine Trial (SHIFT) study. That study found that ivabradine

significantly reduced cardiovascular death or hospital admission for worsening HF by 18% compared with placebo treatment⁽²⁾. Therefore, the Thai FDA approved ivabradine for treatment of chronic HF to reduce cardiovascular events (cardiovascular mortality or hospitalization for worsening HF) in adults in sinus rhythm with symptomatic chronic HF with heart rate of 70 bpm or more, despite maximum tolerated dose of beta-blocker⁽²⁾.

Hydralazine and isosorbide dinitrate (Table 4)

The benefit of hydralazine and isosorbide dinitrate combination in HFrEF was shown in the Veterans Administration Cooperative Vasodilator-Heart Failure

Table 4. Summary of recommendations regarding the use of ivabradine, hydralazine, isosorbide dinitrate, and digoxin in patients with HF

| Recommendations | COR | LOE |
|--|-----|-----|
| Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35% that are in sinus rhythm and that have a resting heart rate ≥70 bpm despite guideline-directed medical therapy that included the maximum tolerated dose of a beta blocker, an ACEI (or ARB), and an MRA. | Ila | B |
| Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who are unable to tolerate or have contraindications for ACEIs or ARBs to reduce HF symptoms. | Ilb | B |
| Digoxin may be considered in HFrEF patients with sinus rhythm who are still symptomatic despite guideline-directed medical therapy with an ACEI (or ARB), a beta-blocker, and an MRA to reduce the risk of heart failure hospitalization. | Ilb | B |

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

Table 5. Summary of recommendations regarding vaccines and multidisciplinary care in patients with HF

| Recommendations | COR | LOE |
|---|-----|-----|
| Annual influenza vaccine is recommended in all patients with HF. | I | B |
| Combined pneumococcal vaccine and influenza vaccine are recommended in all patients with HF. | Ila | B |
| Multidisciplinary care management program is recommended for patients with high-risk HF to reduce the risk of HF hospitalization and mortality. | I | A |
| Routine use of coenzyme Q10 is not recommended in patients with HFrEF due to insufficient data | III | B |

COR=class of recommendation; HF=heart failure; LOE=level of evidence

Trial (V-HeFT I). The results of that study revealed that this drug combination led to a relative risk reduction in mortality of 22%, but the level of significance was only borderline⁽³⁾. The later result of the V-HeFT II trial showed the mortality rate associated with combination hydralazine and isosorbide dinitrate to be higher than the mortality rate associated with enalapril (25% versus 18% at two years)⁽⁴⁾. Post-hoc analysis of the V-HeFT trials revealed significant benefit of this drug combination in African-American population. The hypothesis that there would be incremental benefit of this combination in non-African-American patients when added to background treatment of ACEIs and/or beta-blocker has not yet been tested⁽³⁾.

Digoxin (Table 4)

Evidence from the Digitalis Investigation Group (DIG) mortality trial found that the use of digoxin reduced hospitalization in patients with HFrEF, especially in patients with more advanced symptoms, but no survival benefit was demonstrated⁽⁵⁾. Digoxin has a narrow therapeutic index, and serum digoxin level should be followed closely, especially in patients with unstable renal function. The results of the DIG trial suggest that risk-adjusted mortality increases when plasma concentration exceeds 1.0 ng/mL,

although overt toxicity is not often observed until plasma concentration exceeds 2 ng/mL⁽⁵⁾.

Vaccines (Table 5)

The recommendation for anti-influenza vaccination in HF is based on data from a limited number of large observational studies⁽⁶⁾. Those results showed that timely vaccination during influenza season reduced hospitalization mainly due to acute HF as the cause of hospital admission. However, the quantitative data relative to myocardial function prior to the event are lacking. Recent sub-analysis from the PARADIGM-HF trial showed that patients with symptomatic HF with reduced LVEF who received anti-influenza vaccination had lower risk for all-cause mortality when compared to the non-vaccinated group⁽⁷⁾.

Given the acceptable safety profile of influenza vaccines and the World Health Organization's recommendation for their use in high-risk populations, influenza immunization appears to be a safe and cost-effective strategy for decreasing influenza burden in HF.

Coenzyme Q10

Coenzyme Q10 (CoQ10) may be considered to

Table 6. Summary of recommendations regarding treatment of patients with HFpEF

| Recommendations | COR | LOE |
|---|-----|-----|
| Recommended optimal treatment of patients with hypertension and HFpEF is in accordance with published clinical practice guidelines, with a target systolic BP <130 mmHg ^(11,12) . | I | B |
| The following cardiovascular and non-cardiovascular comorbidities should be actively screened and optimally treated in all patients with HFpEF: | I | C |
| <ul style="list-style-type: none"> • Cardiovascular diseases <ul style="list-style-type: none"> ○ Coronary artery disease ○ Hypertension ○ Atrial fibrillation ○ Pulmonary hypertension • Non-cardiovascular diseases <ul style="list-style-type: none"> ○ Diabetes mellitus ○ Chronic kidney disease ○ Anemia, iron deficiency ○ Chronic obstructive pulmonary disease ○ Obesity ○ Obstructive sleep apnea | | |
| Diuretics are recommended in HFpEF patients who have evidence of volume overload to improve symptoms and reduce hospitalization. When diuretics are used, care must be taken to avoid overdiuresis ^(13,14) . | I | C |
| Concomitant coronary artery disease should be screened as a possible cause of exertional dyspnea and/or acute decompensation in HFpEF patients. | IIa | C |
| ARBs may be considered to decrease hospitalizations in HFpEF patients. | IIb | B |
| Low-dose MRA may be considered to decrease hospitalizations in HFpEF patients with elevated natriuretic peptides or history of recent HF hospitalization ⁽¹⁰⁾ . | IIb | B |
| Routine use of nitrates to improve functional capacity in HFpEF patients is not recommended ⁽¹⁵⁾ . | III | B |
| Routine use of phosphodiesterase-5 (PDE5) inhibitors to improve symptoms in HFpEF is not recommended ⁽¹⁶⁾ . | III | B |

ARBs=angiotensin II receptor blockers; BP=blood pressure; COR=class of recommendation; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; LOE=level of evidence; MRA=mineralocorticoid receptor antagonist

improve survival in patients with HFrEF⁽⁸⁾. However, the benefit of CoQ10 on HF outcomes is still unclear, so its routine use cannot be recommended at this time.

Heart failure with preserved ejection fraction (HFpEF) (Table 6)

HFpEF is a complex and difficult to define condition that has heterogenous pathophysiology, and that is associated with diverse concomitant cardiovascular and non-cardiovascular comorbidities. Disappointingly, randomized controlled trials of numerous treatment options have so far have failed to convincingly reduce morbidity and mortality in HFpEF patients. Cautious use of diuretics is an important strategy for improving congestive symptoms without causing low cardiac output. Blood pressure should be controlled in accordance with published guidelines.

Candesartan, an ARB, was shown in the Candesartan in HF: Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved trial to have moderate impact in preventing HF

hospitalization in HFpEF patients⁽⁹⁾. MRA use in HFpEF was investigated in the Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist (TOPCAT) trial. The TOPCAT trial demonstrated that among patients with HFpEF, spironolactone does not reduce the composite endpoint of cardiovascular mortality, aborted cardiac arrest, or HF hospitalizations when compared to placebo. However, it is associated with small reduction in HF hospitalizations.

Post hoc analysis showed significant composite endpoint reduction in the North American subgroup (HR: 0.83), but not in the Russian/Georgian subgroup (HR: 1.10). The Russian/Georgian population had an unusually low event rate, no expected increased rate of hyperkalemia, and some patients had non-detectable levels of spironolactone metabolite despite being in the active treatment arm.

After acknowledging the limitation of subgroup interpretation, it is suggested that selected patients with symptomatic HFpEF and elevated B-type natriuretic peptide (BNP) level may benefit from spironolactone use⁽¹⁰⁾.

Extended-release isosorbide mononitrate (a long-acting nitrate) was shown in the Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) trial to have no benefit on daily activity level, exercise capacity, quality of life, or NT-proBNP levels in patients with HFpEF and it may have adverse effects on exercise tolerance. Therefore, routine use of nitrates to improve functional capacity in HFpEF patients is not recommended⁽¹⁵⁾.

Phosphodiesterase-5 (PDE5) inhibitor sildenafil was shown in Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People with Diastolic Heart Failure (The RELAX Study) to have no benefit on exercise capacity or clinical status. Therefore, routine use of PDE5 inhibitors to improve symptoms in HFpEF is not recommended⁽¹⁶⁾.

Conflicts of interest

The authors declare no conflict of interest.

References

- 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.
- Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;376:875-85.
- Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;314:1547-52.
- Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; 325:303-10.
- Gheorghiade M, Pitt B. Digitalis Investigation Group (DIG) trial: a stimulus for further research. *Am Heart J* 1997;134:3-12.
- Kadoglou NPE, Bracke F, Simmers T, Tsiodras S, Parissis J. Influenza infection and heart failure-vaccination may change heart failure prognosis? *Heart Fail Rev* 2017;22:329-36.
- Vardeny O, Claggett B, Udell JA, Packer M, Zile M, Rouleau J, et al. Influenza vaccination in patients with chronic heart failure: The PARADIGM-HF Trial. *JACC Heart Fail* 2016;4:152-8.
- Fotino AD, Thompson-Paul AM, Bazzano LA. Effect of coenzyme Q(1)(0) supplementation on heart failure: a meta-analysis. *Am J Clin Nutr* 2013;97:268-75.
- Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;362:777-81.
- Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; 370:1383-92.
- Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996;275:1557-62.
- Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013;31:1281-357.
- Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol* 2002;82:149-58.
- Faris R, Flather MD, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. *Cochrane Database Syst Rev* 2006;(1):CD003838.
- Redfield MM, Anstrom KJ, Levine JA, Koepp GA, Borlaug BA, Chen HH, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med* 2015;373:2314-24.
- Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2013;309:1268-77.