Consensus on Clinical Application of Echocardiography and Angiotensin Receptor-Neprilysin Inhibitors for Post Percutaneous Coronary Intervention Patients

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Abstract

Purpose: To establish consensus on the clinical application of echocardiography and angiotensin receptor-neprilysin inhibitor (ARNI) for patients treated with percutaneous coronary intervention (PCI).

Method: The consensus statements were established by PCI experts based on their most updated clinical evidence and experience.

Results: Ischemic heart disease is an important mortality and morbidity risk factor for heart failure (HF). Left ventricular (LV) remodeling plays a critical role in the prognosis of post-infarct HF. Routine echocardiographic examination can identify HF patients with LV remodeling and assist in individualizing their treatment. Thus, for post PCI patients with acute coronary syndrome (ACS) and non-ACS and baseline LVEF < 40%, echocardiographic follow-up should be performed within 3-6 months of the first year post PCI and every 6-12 months starting in the second year. For ACS patients post PCI and with baseline LVEF of 40-50%, echocardiographic follow-up should be performed within 3-6 months of the first year post PCI and every 6-24 months starting in the second year. Growing evidence supports that ARNI reverses LV remodeling in HF patients with reduced ejection fraction (HFrEF) and improves subsequent cardiovascular recovery. Gradual increase of ARNI dosage to a target of 200-400 mg per day is recommended for post PCI HFrEF patients.

Conclusion: For PCI patients, routine echocardiography check-up is recommended. Furthermore, a targeted ARNI dosage is recommended for post PCI HFrEF patients.

Keywords: HF, echocardiography, left ventricle remodeling, angiotensin receptor-neprilysin inhibitor, acute coronary syndrome, percutaneous coronary intervention

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1. Introduction

Percutaneous coronary intervention (PCI) has revolutionized the prognosis of acute coronary syndrome (ACS). However, post-infarct left ventricular (LV) remodeling with subsequent heart failure (HF) occurs in nearly one half of patients within a year, leading to increased mortality and morbidity.[1] Currently, there are no well-identified predictors for the development of LV remodeling. Thus, routine LV function echocardiography follow-up seems to be a reasonable strategy to identify high risk patients and individualize their treatment.

For years, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), and beta-blockers have been medications listed in HF patients' routine treatment guidelines for their ability to reverse LV remodeling.[2,3] Yet, in recent years, angiotensin receptor-neprilysin inhibitor (ARNI) has been found to additionally reduce mortality and morbidities in HFrEF patients, compared to the medications mentioned above.[4]

Growing evidence from clinical trials, preliminary research, and real-world studies is revealing ARNI benefits and its property of reversing LV remodeling in patients with ischemic HF.[5-9]

With the aim of improving quality of care for patients post PCI, the Taiwan Society of Cardiovascular Interventions has appointed an expert panel to discuss and recommend the timing of echocardiographic follow-ups and use of ARNI for patients after PCI treatment. As of now, no clear guideline or recommendations have been established or published. In this consensus statement, recommendations are supported by evidence and expert experience.

2. Timing of echocardiographic follow-up in patients after PCI

Recommendation Table

Patient group	Etiology	ACS		Non-ACS
	Baseline LVEF	< 40%	40-50%	< 40%
Recommended echocardiographic follow-up	Within the first year after PCI	Every 3-6 months	Every 3-6 months	Consider periodic follow-up
	From the second year after PCI	Consider periodic follow-up		

Consensus Statements

- Echocardiography, or other studies which evaluate LV systolic function (e.g. myocardial perfusion scan and coronary CT angiography) should be obtained in patients with ACS during hospital stay or symptomatic patients with suspected coronary artery disease (CAD).
- For ACS patients post PCI and baseline LVEF < 40%, echocardiographic follow-up should be performed within 3-6 months within the first year post PCI and periodic follow-up should be considered starting in the second year.
- For ACS patients post PCI and baseline LVEF of 40-50%, echocardiographic follow-up should be performed within 3-6 months within the first year post PCI and periodic follow-up should be considered starting in the second year.
- For post PCI patients with no ACS and baseline LVEF < 40%, periodic echocardiographic follow-up should be considered, especially in those with symptoms or clinical deterioration.

Role of echocardiography in ACS

Echocardiography is a widely used tool in patients with ACS. It can be used to detect regional wall motion abnormalities (RWMAs) so as to assist diagnosis of ACS. Location and extent of infarction and coexisting valvular heart disease can also be evaluated by echocardiography, which may influence the type of revascularization and pharmacological therapies.[10] Shortly after the infarct, echocardiography is also useful to detect mechanical complications, such as ventricular septal defect and papillary muscle rupture.

Therefore, echocardiography should be obtained before PCI in patients with ACS.

In post-infarct patients, echocardiography provides prognostic information and helps guide management. The 2013 ACC/AHA guideline for ST-elevation MI recommended evaluating left ventricular ejection fraction (LVEF), since LV systolic dysfunction is one of the strongest predictors of mortality risk after STEMI.[11] In the CORE trial, LVEF of 1137 post-infarct patients was evaluated and their association with 6-month mortality tested. Those with an LVEF of < 30% had the highest 6-month mortality (11%), in contrast to 0.7% in HFpEF.[12] The TIMI II trial revealed similar results. A total of 3197 post-infarct patients were stratified by LVEF and 1-year all-cause mortality analyzed in each group. Those with an LVEF of < 30% had a 1-year all-cause mortality of 9.9%, higher than the 3.1% with LVEF 30-39%, 2.2% with LVEF 40-49%, and 1.2% with LVEF 50-59%.[13] Besides systolic function, diastolic dysfunction of the LV is also an independent predictor of post-infarct mortality. In a meta-analysis including 3396 post-infarct patients, those with restrictive mitral filling pattern (RFP), the most severe form of diastolic dysfunction, had a 2.67-fold hazard of all-cause mortality, compared to those without RFP.[14] In addition, left atrial volume, ischemic mitral regurgitation and wall motion score index have all been shown to be of prognostic value in post-infarct patients.[15-17]

Because of its availability and capability to detect multiple abnormalities, including systolic and diastolic dysfunction, left atrial volume, and valvular heart disease, echocardiography is the most commonly used modality to evaluate LVEF. It is suggested to use the biplane Simpson's method in patients with RWMAs.[18]

Clinical significance of LV remodeling and HF in ACS patients post PCI

Post-infarct HF is a common complication in patients with ACS, and especially characterized by poor prognosis. In a population-based cohort study including 7,733 elderly patients hospitalized for myocardial infarction (MI), 37% were diagnosed with HF during hospitalization. Among those who survived MI without HF during hospitalization, 64% developed HF in the first year and 71% developed HF within 5 years.[19] In addition, poor prognosis in post-infarct HF was evident in a large cohort study including 4,137 discharged patients diagnosed with ACS. Patients with de novo HF had more than four-fold mortality compared to those without.[20]

In ACS, LV remodeling is caused by inflammatory response and mediated by neurohormones resulting in architectural change. The initial LV remodeling post infarction usually presents with an (adapted) increase in volume. However, in later phases, the remodeled LV is characterized by hypertrophy, myocyte cell death, and myocardial extracellular matrix degradation causing chamber dilatation and contraction dysfunction leading to HF.[1,21] Presence of LV remodeling represents a risk factor for ACS patients. In a study following 1,995 STEMI patients, 48% had LV remodeling (defined as an increase in left ventricle end diastolic volume (LVEDV) ≥ 20% within one year). The remodelers had lower LVEF and higher incidence of HF hospitalization.[1] In the VALIANT study, echocardiographic analysis showed positive association between post-infarct LV remodeling and multiple cardiovascular outcomes (including mortality and HF hospitalization).[22] Medications such as ACEi, ARB, or beta-blockers have been well recognized in slowing or reversing LV remodeling and reducing mortality.[23] Also, the HEART study followed 352 patients with Q-wave anterior MI. It was demonstrated that LV remodeling is inversely related to improvement in LVEF over 90 days.[24] Aside from reduction in mortality and HF hospitalization, post-MI LV remodeling is also associated with increased cardiovascular morbidities; including patients with re-infarction, stroke, and resuscitated cardiac arrest.[21,25]

LV remodeling developed in 48% of STEMI patients treated with primary PCI within one

year. Of these remodelers, 64% developed within 3 months post infarction, 23% became mid-term remodelers (development of remodeling within the 3rd to 6th month post infarction), and 13% became late remodelers (development of remodeling within the 6th to 12th month).[1] Also, it was recommended by ESC that a reassessment of LV function within the first 8-12 weeks after revascularization should be considered in ACS patients who have LV systolic dysfunction.[26] Thus, the expert panel recommends ACS patients receive echocardiography within 3 to 6 months post infarction.

Recurrent cardiovascular events develop in a substantial amount of ACS patients, resulting in mortality and disabilities. In the HORIZONS AMI trial, the 3-year risks of all-cause mortality, CV mortality and re-infarction in STEMI patients post PCI were 5.9%, 2.9%, and 6.2%, respectively.[27] Therefore, the expert panel recommends that periodic assessment for risk stratification and guidance of coexisting HF treatment should be considered to improve the long-term outcomes.

Role of echocardiography in chronic coronary syndrome

Echocardiography is an important clinical tool for confirming the diagnosis of chronic coronary syndrome. It helps to detect alternative causes of chest tightness and coexisting cardiac disease, including valvular heart disease or cardiomyopathy, and to evaluate a baseline LVEF for risk stratification. In a study comparing outcomes from various baseline LVEF in non-ACS patients post PCI, those with an LVEF > 50% (Group I) had a one-year mortality rate of 1.9% - compared to 4.5% in those with LVEF 41-49% (Group II) and 11.0% in those with LVEF < 40% (Group III). Group III also had the highest rate (20.9%) of adverse cardiovascular events (death, MI, and requirement of coronary artery bypass grafting (CABG) within one year), when compared with 14.2% in Group II, and 11.8% in Group I.[28] Because of these benefits, a resting echocardiogram is recommended as a part of initial evaluation by ESC in all symptomatic patients with suspected CAD.[26]

Lifelong treatment and surveillance is required for patients with chronic coronary syndrome. In a 5-year follow-up data from the CLARIFY registry revealed 11.6% of patients developed new-onset HF symptoms, and 2.8% required admission due to HF.[29] This indicated a substantial proportion of CCS patients would develop various CV complications. Thus, the expert panel recommends that periodic echocardiography to reassess LV function and coexisting cardiac disease can be considered, especially in those with related symptoms or clinical deterioration.

3. Use of ARNI in post PCI patients with low LVEF

Consensus statements

- ARNI is recommended for ischemic HFrEF patients before or after PCI treatment.
- Substitution of an ACEi/ARB with an ARNI in HFrEF patients with stable symptoms can be considered.

In the course of extensive research, ARNI has been shown to improve multiple outcomes in HFrEF patients. In the pivotal PARADIGM-HF trial, ARNI reduced the incidence of composite cardiovascular (CV) outcomes (HF hospitalization and CV deaths) by 21% compared to enalapril in HFrEF patients; the majority of patients were on optimal HF therapy using ACEI/ARB, beta-blockers, and MRA. Substitution of an ACEi/ARB with an ARNI provided an additional reduction in all-cause mortality by 20%.[30] The 2021 update to the ACC expert consensus decision pathway for the optimization of HF treatment also pointed out that for patients with stage C HFrEF, ARNI is preferable to ACEi/ARB.[31] The clinical benefit of ARNI with regard to HF is consistent in patients with ischemic etiology. In the PARADIGM-HF trial, 43% of the patients had a history of MI and 57.1% had coronary artery disease. Subgroup analysis showed no confounding between etiologic

categories and primary composite outcome.[30]

The clinical benefit of ARNI as regards ischemic HF may stem from its ability to reverse LV remodeling. PROVE-HF is a single-arm study investigating the effects of ARNI in reversing LV remodeling in HFrEF patients. It is known that the reduction of N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations during current goal-directed medical therapy (GDMT) is associated with the reversing of LV remodeling, thus researchers obtained levels of NT-proBNP and echocardiographic parameters from 794 ARNI-treated patients in a one-year follow-up. Among these patients, 41% had a history of MI and 53.7% had an HF ischemic etiology. Rapid reduction of NT-proBNP level was observed within 2 weeks post ARNI initiation and continued to gradually decrease thereafter. Meanwhile, echocardiography exams revealed a constant improvement of LVEF and reduced LV chamber size. Statistically significant correlations between lowering of NT-proBNP levels and changes in LVEF, LVEDVI and LVESVI outcomes were observed.[6]

Activation of the natriuretic peptide (NP) system may also provide further benefits in reversing LV remodeling than ACEi therapy alone. In EVALUATE-HF, Desai et al. compared the effect of ARNI versus enalapril on aortic stiffness and reversing cardiac remodeling. Patients with HFrEF were randomly assigned to either ARNI or enalapril groups. From baseline to 12 weeks, patients on ARNI had similar changes in aortic characteristic impedance to those on enalapril. However, the ARNI group had greater reduction of left side chamber sizes and lower NT-proBNP level. The results suggest that other than renin-angiotensin system (RAS) blockades, activation of the NP system can also enhance LV remodeling reversion and reduce congestion.[7] Iborra-Egea et al. also pointed out that combinations of sacubitril and valsartan may provide synergistic effects to reduce LV extracellular matrix remodeling (LVEMR) (Figure 1).[32]

The mechanism by which ARNI reverses remodeling involves multiple pathways. First, systematic biology research has revealed that valsartan inhibits hypertrophy of cardiomyocytes, while sacubitril reduces death of cardiomyocytes as well as lowering LVEMR. Second, ARNI increases levels of C-type natriuretic peptide (CNP), leading to relaxation of coronary artery tone and increased blood flow.[33,34] Torrado et al. conducted animal model experiments, showing the efficacy of sacubitril/valsartan in rabbits with surgically induced MI. These rabbits experienced 45 minutes of ischemia followed by 72 hours of reperfusion. Administration of sacubitril/valsartan

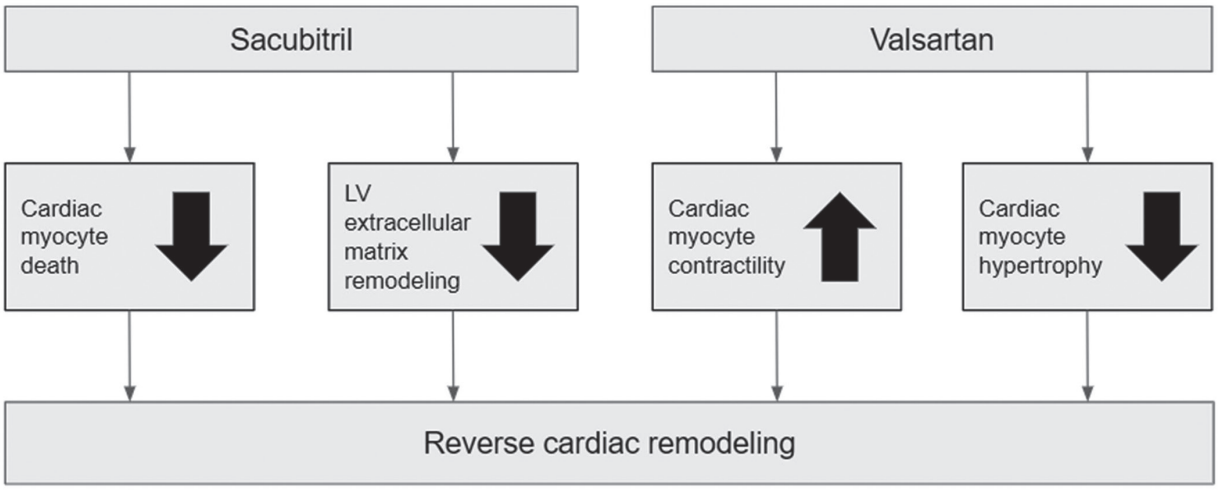

Figure 1. The benefits of ARNI's dual-mechanism in reversing cardiac remodeling.

at the beginning of reperfusion reduced infarction size and plasma troponin levels.[5] Sacubitril/valsartan has been shown to reduce TGF-ß levels (leading to smaller fibrotic area after MI) in rabbits with surgically-induced MI on regular ARNI therapy and yielded lower scar sizes and lower decline of LVEF, suggesting the possibility of HF prevention.[35] Among the rabbits that developed HFrEF, administration of ARNI was associated with improved LVEF and reduction in chamber size.[5]

Real-world studies of ARNI-treated HFrEF patients revealed similar results to clinical trials and preliminary research. In local studies in Taiwan, use of ARNI was associated with better LVEF and size reduction in LV and LA.[9,36]

In conclusion, evidence supports the efficacy of ARNI in patients with HFrEF and ischemic heart disease. ARNI can reverse LV remodeling and improve CV outcomes, and is therefore recommended by the expert panel.

Consensus statements

- Patients in stable condition with normal systolic blood pressure can increase ARNI titration until reaching a target dosage of 200-400 mg per day.
- ARNI should not be discontinued despite LVEF recovery.

No clinical trial has been designed to directly compare the efficacy of different ARNI dosages in HFrEF patients. However, secondary analysis of the PARADIGM-HF report shows that patients with reduced dosage were associated with poorer CV outcome.[37] Real-world study has also suggested that maintenance of a constant ARNI dosage is associated with higher LVEF, lower CV mortality rate, and HF rehospitalization 8. Increasing titration of > 200 mg per day is associated with superior outcome.[38] These associations may reflect the fact that patients with advanced HF are less likely to tolerate higher dosages of ARNI and thus have poorer outcomes. Nevertheless, patients who can tolerate higher ARNI dosage (increasing titration up to a target of 200-400 mg per day) may benefit from better outcomes. Thus the panel experts recommend to increase the dose of ARNI to reach the maximal dose if possible.

Discontinuation of HFrEF standard therapy, including RASi (i.e. ACEi/ARB), beta-blockers, MRA in patients with dilated cardiomyopathy during LVEF recovery has been proven to lead to deteriorating symptoms, LVEF, and biomarker profiles.[39] In a multicenter study comparing consistent and discontinued sacubitril/valsartan in 427 HFrEF patients, those who discontinued ARNI had a higher CV and all-cause mortality.[40] In another Taiwanese retrospective study comparing two ARNI dosage strategies during LVEF recovery (consistent or decreasing titration dosage), those with consistent dosage had better LVEF and lower rate of HF hospitalization.[8]

Consensus statements

- Maintain close blood pressure monitoring when increasing ARNI titration. If hypotension (i.e. systolic blood pressure (SBP) < 90-95 mmHg or presence of symptoms) is noted, first check volume status then correct hypovolemia when present. If ARNI is tolerated, consider up-titrating the dose monthly.

From real-world experience, hypotension is the most commonly reported adverse event of ARNI and causation for ARNI intolerance.[9,40,41] Therefore, most experts on the panel have emphasized close monitoring of blood pressure when increasing ARNI titrating dosage.

As of now, there is no definite definition of hypotension caused by ARNI titration. Nevertheless, the expert panels agree that hypotension can be regarded as the presence of related symptoms or when SBP < 90-95 mmHg. The guideline is based on the protocol of PARADIGM-HF. In this trial, patients were randomly selected, and those with SBP < 95 mmHg were excluded. Although patients with advanced HF benefited from ARNI, some still showed difficultly in sustaining normal blood pressure. Therefore, treatment strategy should always be tailored accordingly.

Correction of hypovolemia may be the first step in managing hypotension in ARNI-treated patients. Reduction was demonstrated to be the strongest predictive factor to achieve target dosage. Given that symptomatic hypotension is the most common causation for intolerance, accurate volume assessment is key to achieving successful ARNI titration.[42] If hypotension persists after correction of hypovolemia, the expert panel suggests to discontinue HF medication in the order of diuretics, MRA, beta-blocker and then ACEi/ARB/ARNI, consistent with the TRED-HF trial protocol.[39]

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