EDITORIAL

Angiotensin Receptor–Neprilysin Inhibition (ARNI) Therapy and Reverse Remodeling in Heart Failure With Reduced Ejection Fraction

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In patients with heart failure with reduced ejection fraction (HFrEF), adverse cardiac remodeling leads to deleterious changes in cardiac structure and function, including progressive left ventricular dilatation and reduced contractile function. Adverse cardiac remodeling is central to the pathophysiology of HFrEF. The effect of pharmacologic interventions on the remodeling process mirrors their therapeutic efficacy on clinical outcomes assessed in clinical trials of patients with HFrEF in most but not all cases.[1] Early studies of neurohormonal antagonists exemplify this relationship. Angiotensin-converting enzyme (ACE) inhibitors and β-adrenergic receptor blockers attenuate[2] or reverse[3] the remodeling process, respectively, and both agents improve survival of patients with HFrEF.[4]

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Angiotensin receptor-neprilysin inhibition (ARNI) therapy now has a class 1 indication for the treatment of patients with HFrEF.[4] This recommendation was based on the PARADIGM-HF trial, which demonstrated important clinical benefits of sacubitril-valsartan vs enalapril therapy, including a reduction in the risk of heart failure hospitalization and death.[5] Additionally, ARNI therapy vs enalapril therapy in PARADIGM-HF led to greater reductions in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels.[6] However, neither the PARADIGM-HF trial or studies that preceded it nor the PIONEER-HF trial,[7] which demonstrated sacubitril-valsartan efficacy over enalapril in reducing natriuretic peptide levels in patients with HFrEF hospitalized with heart failure, assessed the effect of ARNI on cardiac structure and function. Thus, there has been an evidence gap in the data assessing how ARNI improves outcomes in patients with HFrEF.

Following the PARADIGM-HF trial, several studies have attempted to fill this evidence gap. In animal models of myocardial infarction[8] or ischemia-reperfusion injury,[9] ARNI had favorable effects on ventricular remodeling. Additionally, studies based on serial echocardiograms in patients with HFrEF treated with ARNI have begun to appear. A recent meta-analysis[10] that included retrospective studies concluded that ARNI therapy was associated with an absolute left ventricular ejection fraction increase of approximately 5% vs placebo and approximately 5% more than ACE inhibitors. In this issue of *JAMA*, Januzzi et al[11] and Desai et al[12] present data that substantially advance the current understanding of how ARNI therapy exerts favorable actions in patients with HFrEF.

Januzzi et al[11] conducted the PROVE-HF study,[11] an open-label multicenter investigation that enrolled 794 patients with HFrEF who primarily had New York Heart Association class II or III status, were taking β-blockers (95%) and ACE inhibitors or angiotensin receptor blockers (76%), and were candidates for ARNI per standard of care. The primary end points were the correlation coefficients between change in NT-proBNP concentration levels and change in markers of cardiac remodeling (left ventricular end-systolic volume index [LVESVI], left ventricular end-diastolic volume index [LVEDVI], left ventricular ejection fraction, and left atrial volume index) after 12 months of ARNI therapy. Patients were treated with escalating dosages of sacubitril-valsartan, targeting a dosage of 97/103 mg twice daily. Serial echocardiograms at baseline, 6 months, and 12 months were performed locally and sent to a core laboratory where they were interpreted in a blinded fashion to clinical status or temporal acquisition.

In the PROVE-HF study, NT-proBNP levels declined rapidly, with most reduction already present 14 days after ARNI initiation. There were significant, albeit modest, correlations between change in NT-proBNP level and change in left ventricular ejection fraction (r = −0.381), LVESVI (r = 0.405), LVEDVI (r = 0.320), and left atrial volume index (r = 0.263) at 12 months. The correlations between changes in NT-proBNP levels and cardiac remodeling at 6 months, while statistically significant, were even less robust. Additionally, the correlation of changes in NT-proBNP levels and markers of cardiac remodeling were present in 3 subgroups not well represented in the PARADIGM-HF trial: patients with new-onset heart failure or not taking an ACE inhibitor or angiotensin receptor blocker at baseline; those who had NT-proBNP levels lower than inclusion criteria for PARADIGM-HF; and those who did not achieve target dosages of sacubitril-valsartan.

In post hoc analyses that assessed the ability of ARNI to promote reverse remodeling, sacubitril-valsartan was associated with an increase in the mean left ventricular ejection fraction of 5.2% at 6 months and 9.4% at 12 months. There also were significant reductions in both LVEDVI and LVESVI, evident already at 6 months but of greater magnitude at 12 months. In addition, there was evidence of reverse remodeling of other cardiac structures (reductions in left ventricular mass index and left atrial volume index), as well as improved diastolic function (reduction in E/e′ ratio, the ratio of mitral peak velocity of early filling [E] to early diastolic mitral annular velocity [e′]).

The PROVE-HF study was not a randomized trial because of the ethical concerns of withholding ARNI for 12 months in patients with HFrEF. Rather, ARNI was initiated in all study participants, then NT-proBNP levels and echocardiographic markers of remodeling were measured over time. Given the lack of a control group, an important question is whether ARNI caused the subsequent reverse remodeling. Echocardiographic interpretation in a core laboratory blinded to temporal acquisition should minimize the potential of unintentional bias or drift over time. Most patients had a diagnosis of heart failure of at least 15 months, so the reverse remodeling observed seems likely related to recovery of new-onset heart failure. Nevertheless, the absence of a control group remains a notable limitation and allows the possibility that some component of the reverse remodeling in PROVE-HF was due to another therapy, such as β-blockers, started prior to study enrollment.

In this context, the accompanying study by Desai et al,[12] the EVALUATE-HF trial, provides complementary information. EVALUATE-HF was a multicenter, double-blind, randomized trial with a primary objective of assessing the effect of ARNI vs ACE inhibitors on central aortic stiffness in 464 participants with HFrEF. As in PARADIGM-HF, a target dosage of sacubitril-valsartan, 97/103 mg twice daily (n = 231 patients), was compared with enalapril, 10 mg twice daily (n = 233 patients). Randomization to ACE inhibitor therapy was thought to be acceptable given the short study duration of 12 weeks. The primary outcome, the between-group difference in change in aortic characteristic impedance (a measure of proximal aortic stiffness) from baseline to 12 weeks, was not significantly different between the treatment groups. Aortic characteristic impedance decreased from 223.8 to 218.9 dyne × s/cm^5 in the sacubitril-valsartan group and increased from 213.2 to 214.3 dyne × s/cm^5 in the enalapril group, for a between-group treatment difference of −2.2 dyne × s/cm^5 (95% CI, −17.6 to 13.2 dyne × s/cm^5; P = .78). These data are an informative null result and suggest that the mechanism of ARNI benefit in HFrEF is not mediated via remodeling of the aorta.

As with the PROVE-HF study, there is important information in the EVALUATE-HF trial beyond the primary end point. Sacubitril-valsartan, compared with enalapril, did not improve left ventricular ejection fraction or global longitudinal strain at 12 weeks, but there was evidence of reverse remodeling via other measures, including significant reductions in LVESVI, LVEDVI, left atrial volume index, and E/e′ ratio, mirroring those findings in PROVE-HF. Importantly, these data were demonstrated within the context of a randomized trial, albeit as secondary end points, buttressing the PROVE-HF results that were observed in the absence of a control group. Additionally, in post hoc analyses in EVALUATE-HF, changes in NT-proBNP levels correlated significantly with changes in cardiac structure and function, replicating the primary outcome of PROVE-HF and also extending this observation to the earlier time point of 3 months after ARNI initiation.

There are clinical implications from these 2 studies. Guidelines recommend that patients with new-onset HFrEF should have an implantable cardioverter-defibrillator only after a trial of guideline-directed medical therapy.[13] Based on these 2 studies, it stands to reason that ARNI should be implemented before determining a patient's eligibility for an implantable cardioverter-defibrillator. Furthermore, reverse remodeling, while detectable within 3 months, appears progressive for at least 12 months, a time course also reported following β-blocker administration.[14] In addition, the results of these 2 studies add supportive evidence to a rapidly growing database of ARNI efficacy and provide further impetus for the need for widespread dissemination of this therapy to applicable patients with HFrEF.

In conclusion, the PROVE-HF study and the EVALUATE-HF trial reported in this issue of *JAMA* together strongly suggest that ARNI therapy can promote cardiac reverse remodeling in patients with HFrEF. Although neither investigation assessed this question as its primary end point, and one study was observational in nature, the replication of the reduction in left ventricular volumes, left atrial volumes, and E/e′ ratio in these 2 reports, as well as the large, progressive increase in left ventricular ejection fraction in PROVE-HF, are important. As with β-blockers and ACE inhibitors, it thus appears that the benefits of ARNI therapy on clinical outcomes in patients with HFrEF are mediated, at least in part, by their favorable effects on the adverse cardiac remodeling that characterizes this condition.

ARTICLE INFORMATION

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REFERENCES

1. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. *J Am Coll Cardiol*. 2010;56(5):392-406. doi:10.1016/j.jacc.2010.05.011

2. Greenberg B, Quinones MA, Koilpillai C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction: results of the SOLVD echocardiography substudy. *Circulation*. 1995;91(10):2573-2581. doi:10.1161/01.CIR.91.10.2573

3. Krum H, Sackner-Bernstein JD, Goldsmith RL, et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation*. 1995;92(6):1499-1506. doi:10.1161/01.CIR.92.6.1499

4. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136(6):e137-e161. doi:10.1161/CIR.0000000000000509

5. McMurray JJ, Packer M, Desai AS, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077

6. Zile MR, Claggett BL, Prescott MF, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. *J Am Coll Cardiol*. 2016;68(22):2425-2436. doi:10.1016/j.jacc.2016.09.931

7. Velazquez EJ, Morrow DA, DeVore AD, et al; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380(6):539-548. doi:10.1056/NEJMoa1812851

8. von Lueder TG, Wang BH, Kompa AR, et al. Angiotensin receptor neprilysin inhibitor LCZ696 attenuates cardiac remodeling and dysfunction after myocardial infarction by reducing cardiac fibrosis and hypertrophy. *Circ Heart Fail*. 2015;8(1):71-78. doi:10.1161/CIRCHEARTFAILURE.114.001785

9. Suematsu Y, Miura S, Goto M, et al. LCZ696, an angiotensin receptor–neprilysin inhibitor, improves cardiac function with the attenuation of fibrosis in heart failure with reduced ejection fraction in streptozotocin-induced diabetic mice. *Eur J Heart Fail*. 2016;18(4):386-393. doi:10.1002/ejhf.474

10. Wang Y, Zhou R, Lu C, Chen Q, Xu T, Li D. Effects of the angiotensin-receptor neprilysin inhibitor on cardiac reverse remodeling: meta-analysis. *J Am Heart Assoc*. 2019;8(13):e012272. doi:10.1161/JAHA.119.012272

11. Januzzi JL Jr, Prescott MF, Butler J, et al; PROVE-HF Investigators. Association of change in N-terminal pro–B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction [published online September 2, 2019]. *JAMA*. doi:10.1001/jama.2019.12821

12. Desai AS, Solomon SD, Shah AM, et al; EVALUATE-HF Investigators. Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: a randomized clinical trial [published online September 2, 2019]. *JAMA*. doi:10.1001/jama.2019.12843

13. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm*. 2018;15(10):e73-e189. doi:10.1016/j.hrthm.2017.10.036

14. Hall SA, Cigarroa CG, Marcoux L, Risser RC, Grayburn PA, Eichhorn EJ. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. *J Am Coll Cardiol*. 1995;25(5):1154-1161. doi:10.1016/0735-1097(94)00543-Y