Editorial

Is it time to adopt angiotensin receptor-neprilysin inhibitors (ARNI) therapy as standard of care for the management of hypertension?

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Hypertension is the most potent and prevalent risk factor contributing to cardiovascular disease (CVD), stroke and all-cause mortality worldwide (1,2). The expanded use of evidence-based medical therapies, particularly in the management of hypertension have contributed to the reduction in CVD mortality in the United States over the last two decades (3,4). However, when examining mortality trends within subgroups of CVD, death due to heart failure and other heart diseases have been rising, emphasizing the continued need for innovations in CVD risk reduction (3,5). Opportunely, Japan has recently joined other nations in the approval the angiotensin receptor-neprilysin inhibitors (ARNI) sacubitril/valsartan for the treatment of primary hypertension due its actions of increased diuresis and natriuresis, systemic vasodilation and decreased peripheral vasoconstriction (6). While sacubitril/valsartan is widely used as guideline-directed medical therapy for patients with heart failure with reduced ejection fraction (HFrEF), there is growing evidence supporting expanded use for the indication of hypertension (6,7). This is in part the subject of Imamura and Kinugawa's study, "*Implication of sacubitril/valsartan on N-terminal pro B-type natriuretic peptide levels in hypertensive patients*", which provides novel considerations for ARNI therapy in patients with hypertension, as well as insight on possible cardioprotective properties that would be unsurprising if found to improve long term CVD outcomes for this indication.

Imamura and Kinugawa's work revealed several interesting and important findings. In this retroactive study, consecutive patients received sacubitril/valsartan for treatment of hypertension to determine effect on blood pressure and clinical biomarkers. A change in plasma N-terminal pro B-type natriuretic peptide (NT-pro BNP) levels during a 3-month treatment period with sacubitril/valsartan was compared with pre-treatment levels. Patients with a history of heart failure and those with acute decompensated heart failure were excluded. The study found that after three months of ARNI, patients had a significant reduction in systolic blood pressure (138 to 130 mmHg, P<0.001), and plasma NT-pro BNP levels (207 to 118 pg/mL, P=0.001) (6). These two key findings have separate but related implications on downstream cardioprotective benefits that may make ARNI a superior antihypertensive than the current standard of care.

The natriuretic peptides are involved in volume homeostasis and are secreted from cardiomyocytes in response to atrial and/or ventricular wall stretch (6,8,9). There is an established association between increased NT-pro BNP levels and increased rates of major adverse cardiovascular events (MACE) and may be an important goal for CVD risk reduction in patients with hypertension (6). Even when NT-pro BNP levels are within normal limits,

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slight increases are still associated with incremental overall CVD risk (6). In clinical practice, measurement of plasma natriuretic peptides has frequently focused on their diagnostic and prognostic utility in patients with heart failure (7,9,10). For example, the PIONEER-HF study was a biomarker-endpoint trial that revealed ARNI was associated with a greater reduction in NT-pro BNP than enalapril (–47% *vs.* –25%) in adults with acute decompensated HFrEF (7). Additionally, increased plasma NT-pro BNP levels predict a wide range of CVD outcomes including increased rates heart failure, atrial fibrillation, stroke, transient ischemic attack and death from any cause in patients without heart failure (9). The findings of Imamura and Kinugawa's study lend opportunity for further investigation to determine whether this reduction in NT-pro BNP with ARNI leads to clinically significant reduction in MACE in patients with hypertension.

Early activation of the renin angiotensin aldosterone system and the sympathetic nervous system promotes vasoconstriction and retention of salt and water, resulting in maladaptive cardiac remodeling that causes increased cardiac chamber volumes, increased muscle mass and interstitial fibrosis (11). This atrial and ventricular remodeling due to abnormal neurohormonal regulation is a consequence of many CVD and mitigated with sacubitril/valsartan therapy (12). The Imamura and Kinugawa's study offers discussion for further investigation on whether ARNI will reduce adverse cardiac remodeling and future downstream consequences of hypertension such as heart failure, cardiomyopathies and ischemic heart disease. This notion has already been shown to improve outcomes in HFrEF. The practice-changing PARADIGM-HF (Prospective Comparison of ARNI with angiotensin-converting enzyme inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) study showed that ARNI was superior to enalapril in improving mortality, likely by the aforementioned pathophysiology (13,14). Other studies have also demonstrated that ARNI therapy in patients with HFrEF results in improvement in health status, reverse cardiac remodeling, reduction in the prognostic biomarker NT pro-BNP and improved left ventricular size and hypertrophy when compared with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (12-14). Therefore, improvements in cardiac remodeling may be a way by which sacubitril/valsartan reduces CVD and all-cause mortality.

While sacubitril/valsartan is a class 1A recommendation in patient with HFrEF and New York Heart Association (NYHA) class II to III HFrEF and standard guideline-directed medical therapy, countries such as Japan, China and Russia are expanding its use for primary hypertension given the new emerging data that have demonstrated its superior protective effect on target end organs (6,15). This study adds to our understanding of how ARNI therapy improves hypertension and surrogate end-points like reductions in NT pro-BNP (6). These novel findings stress the importance of future research to determine if this surrogate endpoint leads to clinical significance in patients with hypertension. There are some limitations to consider in this study. As mentioned by the authors, the sample size of the study was small, including 33 patients. Additionally, further investigation will be critical in a diverse patient population, as Japan is ethnically homogenous and unlikely reflect the demographics of other countries. As the pathophysiology of primary hypertension is complex with substantial associated morbidity and mortality, there is need for new antihypertensive pharmacotherapy that are cardioprotective against the other CVD. As clinicians, we strategically use blood pressure therapies to treat other comorbid conditions and perhaps this study and others will further elucidate the value of sacubitril/valsartan in improving CVD outcomes, irrespective of the diagnosis of heart failure. In the future, it would not be surprising if ARNI therapy may become standard therapy for hypertension.

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References

1. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol 2020;16:223-37.
2. Writing Group Members; Mozaffarian D, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation 2016;133:e38-360.
3. Ferdinand KC, Maraboto C. Improved pathways to hypertension control and elimination of disparities: Are we there yet? J Clin Hypertens (Greenwich) 2019;21:499-501.
4. Sidney S, Quesenberry CP Jr, Jaffe MG, et al. Recent Trends in Cardiovascular Mortality in the United States and Public Health Goals. JAMA Cardiol 2016;1:594-9.
5. Sidney S, Quesenberry CP Jr, Jaffe MG, et al. Heterogeneity in national U.S. mortality trends within heart disease subgroups, 2000-2015. BMC Cardiovasc Disord 2017;17:192.
6. Imamura T, Kinugawa K. Implication of sacubitril/valsartan on N-terminal pro B-type natriuretic peptide levels in hypertensive patients. Ann Palliat Med 2022;11:2856-61.
7. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. N Engl J Med 2019;380:539-48.
8. Doi Y, Ninomiya T, Hata J, et al. N-terminal pro-brain natriuretic peptide and risk of cardiovascular events in a Japanese community: the Hisayama study. Arterioscler Thromb Vasc Biol 2011;31:2997-3003.
9. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655-63.
10. Vasan RS, Benjamin EJ, Larson MG, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. JAMA 2002;288:1252-9.
11. Greenberg B. Angiotensin Receptor-Neprilysin Inhibition (ARNI) in Heart Failure. Int J Heart Fail 2020;2:73-90.
12. Wang Y, Zhou R, Lu C, et al. Effects of the Angiotensin-Receptor Neprilysin Inhibitor on Cardiac Reverse Remodeling: Meta-Analysis. J Am Heart Assoc 2019;8:e012272.
13. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
14. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e895-1032.
15. Sun N. The World's First Published Expert Consensus on ARNI Treatment For Hypertension. J Am Coll Cardiol 2021. Available online: https://www.acc.org/latest-in-cardiology/articles/2021/05/11/16/16/the-worlds-first-published-expert-consensus-on-arni-treatment-for-hypertension

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