JACC: ASIA VOL. 4, NO. 9, 2024

EDITORIAL COMMENT

Angiotensin Receptor Neprilysin Inhibition

An Overlooked Frontier in the Treatment of Hypertension

Magnus O. Wijkman, MD, PhD

Randomized placebo-controlled cardiovascular outcomes trials of pharmacological blood pressure lowering were performed already in the 1960s, and the scientific evidence supporting the use of antihypertensive drugs as a cornerstone for cardiovascular protection has grown ever since.[1] Today, 4 classes of antihypertensive drugs are considered the most rational drugs of choice because of their proven ability to reduce the incidence of cardiovascular events: inhibitors of the renin-angiotensin system (angiotensin converting enzyme inhibitors and angiotensin receptor blockers), calcium channel blockers, thiazides and related diuretics, and beta blockers. Emerging drug classes that appear on the horizon include selective aldosterone synthase inhibitors, dual blockers of endothelin receptors A and B, and injectable blockers of hepatic angiotensinogen mRNA synthesis.[2]

Another promising approach to pharmacological blood pressure lowering is to inhibit neprilysin, an endopeptidase which cleaves and inactivates natriuretic peptides. The combined angiotensin receptor neprilysin inhibitor sacubitril/valsartan, which today is indicated for treatment of chronic heart failure, was initially evaluated for efficacy as an antihypertensive drug[3] and has shown favorable short-term effects also on central aortic systolic blood pressure.[4]

In this issue of *JACC: Asia*, Zhang et al[5] report the results from a randomized, double-blind multicenter trial performed in China in which 1,197 patients with hypertension were randomized to treatment with either the angiotensin receptor blocker olmesartan (20 mg daily) or to 1 of 2 doses (240 or 480 mg daily) of the novel angiotensin receptor neprilysin inhibitor sacubitril/allisartan. Patients were included based on their systolic office blood pressure, which was required to be 150 to 179 mm Hg at study initiation, following a wash-out period during which participants on prior antihypertensive therapy (approximately 90% of the study cohort) terminated their treatment. After 12 weeks of treatment, the baseline-adjusted changes in office systolic blood pressure (which was the primary outcome) was −23 mm Hg with olmesartan 20 mg daily, −25 mm Hg with sacubitril/allisartan 240 mg daily, and −28 mm Hg with sacubitril/allisartan 480 mm Hg daily, corresponding to a statistically significant ($P < 0.001$) olmesartan-corrected difference of −2 mm Hg and −5 mm Hg for the 2 doses of sacubitril/allisartan, respectively. The proportions of patients who experienced at least 1 adverse event during the 12 weeks of treatment was numerically lower in the sacubitril/allisartan groups than in the olmesartan group, suggesting a reassuring short-term safety profile, but it will of course be necessary to evaluate the safety of this novel drug in dedicated and adequately powered outcomes-trials with longer follow-up.

The magnitude of the comparator-corrected blood pressure reduction is similar to that which was observed in a post hoc analysis of the PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction) trial, in which treatment with sacubitril/valsartan lowered office systolic blood pressure 4 mm Hg more than treatment with valsartan in patients with heart failure with preserved ejection fraction who also had apparent resistant hypertension.[6] If sustained over

From the Department of Internal Medicine and Department of Health, Medicine and Caring Sciences, Linköping University, Norrköping, Sweden.

The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2024.07.001

time, such a blood pressure reduction is likely to be clinically meaningful: in a recent meta-analysis of randomized clinical outcomes trials of hypertension, a reduction of office systolic blood pressure of 5 mm Hg was associated with about 10% lower risk for major cardiovascular events.[7]

In the present study, patients with a prior diagnosis of type 1 diabetes or type 2 diabetes with poor glycemic control were excluded. Considering the many shared pathophysiological characteristics of patients with hypertension and diabetes[8] and the fact that angiotensin receptor neprilysin inhibition has been associated with improved glycemic control in patients with heart failure and diabetes,[9] it would be of great interest to include patients with hypertension from a broader spectrum of dysglycemia in future clinical trials of sacubitril/allisartan. Likewise, the efficacy and safety of sacubitril/allisartan used against a background therapy of commonly used antihypertensive drugs should be explored in future trials.

The worldwide prevalence of hypertension in adults has doubled between 1990 and 2019, and a sizeable proportion of the persons living with high blood pressure remain uncontrolled.[10] This exposes them for a major health risk because failure to control blood pressure is an independent long-term risk factor for incident cardiovascular events and death.[11] Global improvements in the rates of blood pressure control should be a prioritized endeavor for the cardiovascular health care community. In this struggle, novel drugs that are safe, tolerable, and efficacious are more than welcomed and should be evaluated in well-conducted clinical trials. Zhang et al[5] should be congratulated for their contribution to this important research field. However, while awaiting longer outcomes trials of sacubitril/allisartan as well as of other promising but novel antihypertensive drugs, it should not be forgotten that certain tools are available to the practicing clinician already today: spironolactone effectively lowers blood pressure in many patients with resistant hypertension,[12] as does reductions in dietary sodium intake.[13] Only by choosing proven and cost-effective treatments can we hope to achieve the goal of truly sustainable hypertension care globally.[14]

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Wijkman has served on advisory boards or lectured for AstraZeneca, MSD, Lilly, Novo Nordisk, and Sanofi; and has organized a professional regional meeting sponsored by Lilly, Rubin Medical, Sanofi, Novartis, and Novo Nordisk.

ADDRESS FOR CORRESPONDENCE: Dr Magnus O. Wijkman, Department of Internal Medicine, Vrinnevi Hospital, 601 82 Norrköping, Sweden. E-mail: magnus.wijkman@liu.se.

REFERENCES

1. Pfeffer MA, McMurray JJ. Lessons in uncertainty and humility — clinical trials involving hypertension. *N Engl J Med*. 2016;375(18):1756–1766.

2. Redon J, Carmena R. Present and future of drug therapy in hypertension: an overview. *Blood Press*. 2024;33(1):2320401.

3. Ruilope LM, Dukat A, Bohm M, Lacourciere Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet*. 2010;375(9722):1255–1266.

4. Williams B, Cockcroft JR, Kario K, et al. Effects of sacubitril/valsartan versus olmesartan on central hemodynamics in the elderly with systolic hypertension: the PARAMETER study. *Hypertension*. 2017;69(3):411–420.

5. Zhang W, Zhang J, Yan J, et al. Efficacy and safety of sacubitril/allisartan for the treatment of primary hypertension. *JACC Asia*. 2024;4(9):697–707.

6. Jackson AM, Jhund PS, Anand IS, et al. Sacubitril-valsartan as a treatment for apparent resistant hypertension in patients with heart failure and preserved ejection fraction. *Eur Heart J*. 2021;42(36):3741–3752.

7. Blood Pressure Lowering Treatment Trialists Collaboraton. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet*. 2021;397(10285):1625–1636.

8. Jia G, Sowers JR. Hypertension in diabetes: an update of basic mechanisms and clinical disease. *Hypertension*. 2021;78(5):1197–1205.

9. Wijkman MO, Claggett B, Vaduganathan M, et al. Effects of sacubitril/valsartan on glycemia in patients with diabetes and heart failure: the PARAGON-HF and PARADIGM-HF trials. *Cardiovasc Diabetol*. 2022;21(1):110.

10. Collaboration NCDRF. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet*. 2021;398(10304):957–980.

11. Wijkman MO, Malachias MVB, Claggett BL, et al. Resistance to antihypertensive treatment and long-term risk: the Atherosclerosis Risk in Communities study. *J Clin Hypertens (Greenwich)*. 2021;23(10):1887–1896.

12. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. 2015;386(10008):2059–2068.

13. Gupta DK, Lewis CE, Varady KA, et al. Effect of dietary sodium on blood pressure: a crossover trial. *JAMA*. 2023;330(23):2258–2266.

14. Nilsson PM. Sustainable hypertension care — how can it be achieved? *J Intern Med*. 2023;294(3):242–244.

KEY WORDS ambulatory blood pressure, angiotensin receptor neprilysin inhibitor, blood pressure reduction, hypertension, phase 3 randomized controlled trial