SCIENCE BEHIND THE STUDY

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Aldosterone and Treatment-Resistant Hypertension

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Aldosterone has long been a pharmacologic target for the treatment of hypertension. Thus, an article by Freeman et al.[1] and an accompanying editorial by Azizi[2] in this issue of the Journal are of keen interest. Freeman et al. describe a trial of a new small-molecule drug (see Key Concepts) called baxdrostat that inhibits aldosterone synthase in patients with treatment-resistant hypertension.

WHAT IS HYPERTENSION, AND WHY SHOULD WE CARE?

The definition of ideal or "normal" blood pressure, which is presently based on population-level data, is a blood pressure of 120/80 mm Hg or lower in adults.[3,4] Hypertension is defined as blood pressure of 130/80 mm Hg or higher; this definition is based on evidence from epidemiologic studies and clinical trials that examined the relationship between higher blood pressures and major adverse cardiovascular events.[3,4] According to the Centers for Disease Control and Prevention, 116 million adults in the United States, or 47% of adults in the population, have hypertension. The prevalence of hypertension is higher among men than among women, among non-Hispanic Black adults than among non-Hispanic White or Asian adults, and among persons in the southeastern United States than among those in the rest of the country.[3,4]

We should care about hypertension because it contributes to disparities in health care, and disparities in economic resources, environmental conditions, and access to health care surely contribute to the prevalence of hypertension. Hypertension is associated with increased risks of stroke, coronary artery disease, and other cardiovascular diseases; heart failure; atrial fibrillation; chronic kidney disease; and death.[3,4] The death rate attributable to hypertension has increased by 34.2% over the past decade; in 2020, hypertension was a primary or contributing cause of more than 670,000 deaths, or 20% of all deaths in the United States.[3,4] Furthermore, although hypertension is a modifiable risk factor, only 24% of adults with hypertension have adequately controlled blood pressure, which is defined as a blood pressure of less than 130/80 mm Hg in persons who have received lifestyle interventions and medications. These numbers point to a substantial unmet need — the effective management of hypertension.

HOW IS TREATMENT-RESISTANT HYPERTENSION DEFINED?

For several reasons, blood pressure in a patient with hypertension may not be lowered to ideal target levels, despite the use of antihypertensive

Key Concepts

Small-molecule drug

A chemical compound with a low molecular weight (typically 0.1 to 0.6 kD). Small-molecule drugs are smaller than biologic drugs, such as monoclonal antibodies (typically 150 kD) and oligonucleotides (typically 4 to 10 kD). Because of their small size, they can penetrate the cell membrane and bind intracellular targets. They are generally more stable than biologic drugs and can be administered orally.

Small (or short) interfering RNA (siRNA)

A short, double-stranded regulatory RNA molecule of 21 to 23 nucleotides that interferes with the expression of a specific gene by binding to a complementary sequence in the messenger RNA of that gene and targeting it for enzymatic degradation. Chemically modified siRNAs are the basis of some approved drugs and drugs in development.

Antisense oligonucleotide

A short single strand (typically 12 to 30 nucleotides) of chemically modified RNA that targets messenger RNA (mRNA) to prevent translation into protein. Antisense oligonucleotides can bind directly to mRNA, leading to mRNA degradation; they can inhibit generation of mature mRNA by blocking splicing of precursor forms of mRNA; or they can block ribosome recruitment to inhibit protein translation. Antisense oligonucleotides can also be designed to target other RNAs, such as microRNAs and long noncoding RNAs. They are the basis of some approved drugs and drugs in development.

An expanded illustrated glossary is available at NEJM.org

medications. These reasons include nonadherence to prescribed medications, "white-coat hypertension" (hypertension that is present only during clinic visits but not at other times), mismeasured blood pressure, or concomitant use of medications or substances that can elevate blood pressure. Treatment-resistant hypertension is defined as hypertension in a patient who is taking three or more medications, including a diuretic, to lower blood pressure,[5] and for whom misdiagnosis (owing to nonadherence, mismeasurement, and so on) has been ruled out.

ABSENT A MISDIAGNOSIS, WHAT CAUSES TREATMENT-RESISTANT HYPERTENSION?

Treatment-resistant hypertension may be attributable to volume overload, untreated obstructive sleep apnea, and renovascular disease. It may also occur in patients with hormonal dysregulation associated with hyperparathyroidism, thyroid disease, or rare conditions such as pheochromocytoma, paraganglioma, or reninoma. Treatment-resistant hypertension also occurs in patients with undiagnosed primary aldosteronism (Conn's syndrome) or hypercortisolism (Cushing's syndrome). Some patients with treatment-resistant hypertension have been found to have increased aldosterone production, even though they do not have primary aldosteronism (Fig. 1).

IS SODIUM RETENTION A MAJOR FEATURE OF TREATMENT-RESISTANT HYPERTENSION?

Yes. Many patients with treatment-resistant hypertension have salt-sensitive hypertension, a condition in which increased sodium intake results in increased blood pressure through sodium and water retention. This process occurs because of activation of the sympathetic nervous system that impairs the suppression of the renin–angiotensin–aldosterone system; consequently, levels of aldosterone increase (Fig. 1). Aldosterone increases sodium reabsorption and thus passive water reabsorption across the distal tubule of the nephron, thereby contributing to hypertension. Although a decrease in salt intake may reduce blood pressure, it is usually insufficient to achieve normotension.

CAN MEDICATION TARGET OR TREAT IT?

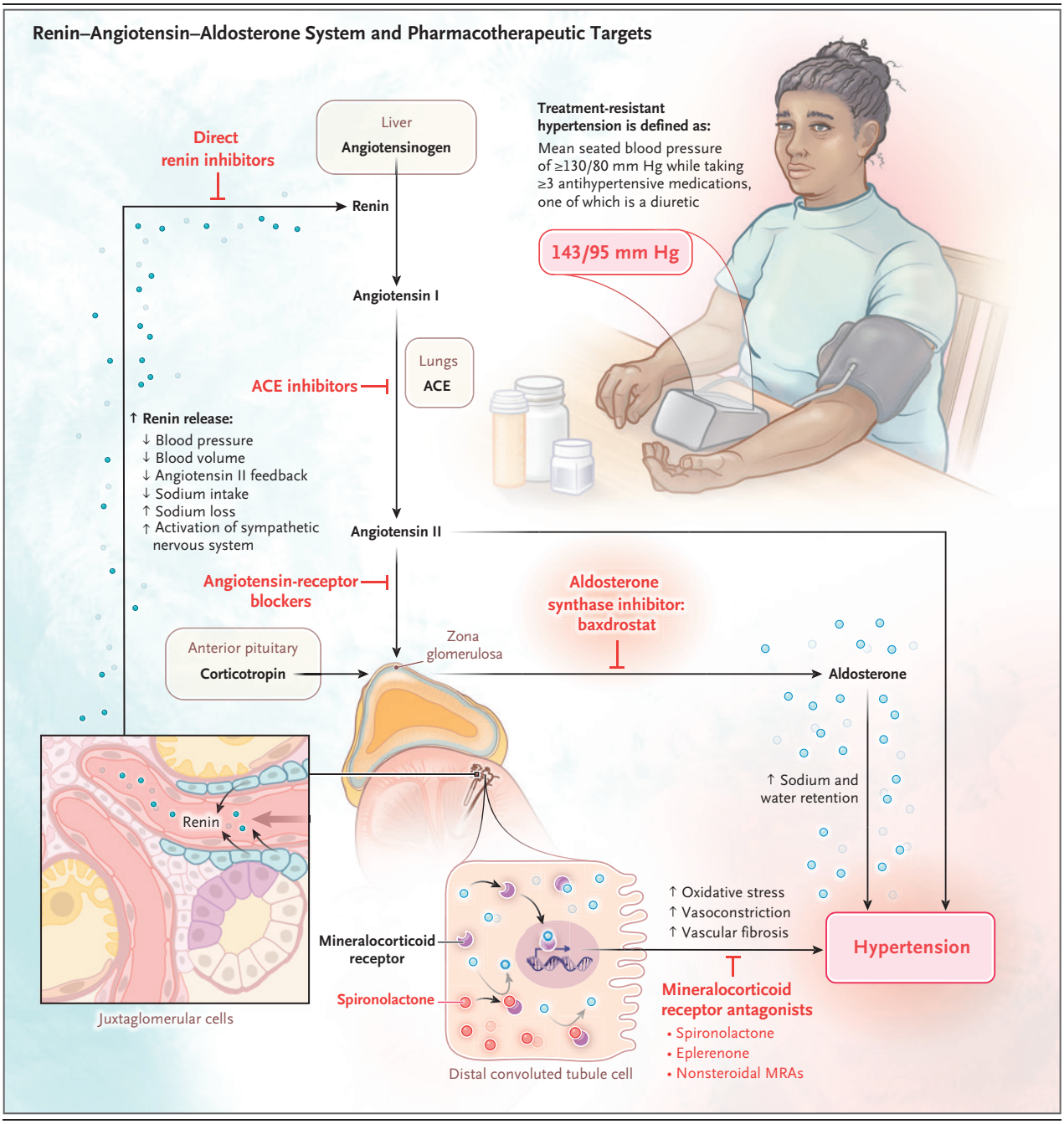
Fortunately, yes. The Prevention and Treatment of Hypertension with Algorithm-based Therapy–2 (PATHWAY-2) trial showed that spironolactone is effective. These findings provide support for the concept that high dietary sodium intake and elevated levels of aldosterone mediate treatment-resistant hypertension.

HOW DOES SPIRONOLACTONE WORK?

Spironolactone competes with aldosterone to bind to the mineralocorticoid receptor (also known as the aldosterone receptor), which is expressed in the distal convoluted tubule cells of the kidney. The binding of spironolactone to the receptor inhibits aldosterone-dependent sodium–potassium exchange, leading to excretion of sodium and water and retention of potassium. Spironolactone is considered to be a weak diuretic and is usually administered with another drug that targets the proximal tubules in order to increase diuresis. In some patients, the use of spironolactone may cause hyperkalemia. Spironolactone is nonselective — it binds androgen and progesterone receptors, leading to off-target effects such as gynecomastia.

Figure 1 (next page). Treatment-Resistant Hypertension and Aldosterone Synthesis.

Treatment-resistant hypertension is defined as a blood pressure that is higher than the goal of less than 130/80 mm Hg in patients who are receiving at least three medications, including a diuretic. The synthesis of aldosterone, a pharmacologic target for the treatment of hypertension, is regulated by the proteins renin and angiotensin. In response to stimuli, the juxtaglomerular cells of the kidney secrete renin, which cleaves angiotensinogen into two fragments, one of which is angiotensin I. Angiotensin I is converted to angiotensin II, primarily in the lungs, by angiotensin-converting enzyme (ACE). Angiotensin II, a potent vasoconstrictor, stimulates cells in the zona glomerulosa of the adrenal gland to synthesize and secrete aldosterone. Corticotropin released by the pituitary gland also stimulates adrenal aldosterone production, albeit to a lesser degree than angiotensin II. Drug classes that are commonly used to treat hypertension and their sites of action in the renin–angiotensin–aldosterone system are shown. Baxdrostat blocks aldosterone synthase (also known as CYP11B2), thereby inhibiting the synthesis of aldosterone. Other drugs used to block the actions of aldosterone (e.g., spironolactone, eplerenone, and nonsteroidal mineralocorticoid receptor antagonists [MRAs]) inhibit the activation of the mineralocorticoid receptor by aldosterone.



HOW DOES BAXDROSTAT AFFECT ALDOSTERONE LEVELS?

Baxdrostat decreases levels of aldosterone by inhibiting its synthesis. It does so by inhibiting the CYP11B2 enzyme (also known as aldosterone synthase) that catalyzes the final steps of aldosterone synthesis from cholesterol (Fig. 2). Moreover, it is highly selective for CYP11B2. This selectivity is good because the CYP11B2 enzyme has 93% sequence similarity with CYP11B1 (also known as 11β-hydroxylase), the final enzyme in the cortisol-synthesis pathway. This high degree of similarity led to cross-reactivity and suppression of cortisol synthesis by earlier aldosterone

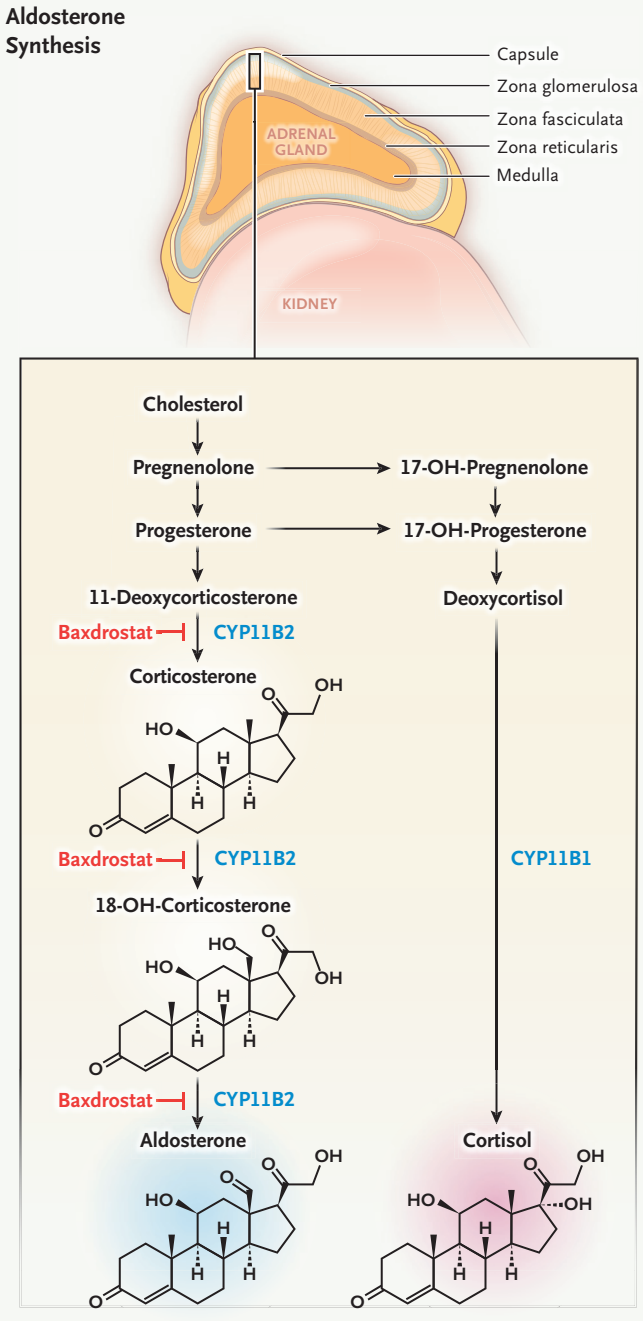


Figure 2. Aldosterone Synthesis in the Zona Glomerulosa.

In the zona glomerulosa of the adrenal gland, the CYP11B2 enzyme (also known as aldosterone synthase) catalyzes the synthesis of aldosterone. CYP11B2 and CYP11B1 (also known as 11β-hydroxylase, which synthesizes cortisol and is the final enzyme in the cortisol-synthesis pathway) share 93% sequence similarity, and drugs that block CYP11B2 have the potential to block CYP11B1.

synthase inhibitors, which rendered these compounds inappropriate as antihypertensive agents. Freeman et al. found that in addition to lowering plasma aldosterone levels and blood pressure, baxdrostat had no substantive effect on plasma cortisol levels.

WHAT'S NEXT?

Among the new therapeutic agents that target the renin–angiotensin–aldosterone system in patients with treatment-resistant hypertension are nonsteroidal mineralocorticoid receptor antagonists and antisense oligonucleotide or small interfering RNA therapies. Nonsteroidal mineralocorticoid receptor antagonists such as finerenone and esaxerenone have a longer plasma half-life than spironolactone and are specific for the mineralocorticoid receptor, with no evident hormonal side effects.[6] Antisense oligonucleotides and RNA-interference oligonucleotides that are designed to target the synthesis of angiotensinogen in the liver are under investigation in patients with treatment-resistant hypertension.[6]

Inhibition of aldosterone synthesis with baxdrostat may expand the possible choices of therapeutic agents for treatment-resistant hypertension. The benefits of inhibiting aldosterone synthesis may also extend beyond treatment-resistant hypertension, because elevated levels of aldosterone have been implicated in the pathobiology of pulmonary hypertension, obesity, and insulin resistance and metabolic syndrome.

Disclosure forms are available with the full text of this editorial at NEJM.org.

1. Freeman MW, Halvorsen Y-D, Marshall W, et al. Phase 2 trial of baxdrostat for treatment-resistant hypertension. N Engl J Med 2023;388:395-405.
2. Azizi M. Decreasing the effects of aldosterone in resistant hypertension — a success story. N Engl J Med 2023;388:461-3.
3. World Health Organization. Guideline for the pharmacological treatment of hypertension in adults. 2021 (https://apps.who.int/iris/bitstream/handle/10665/344424/9789240033986-eng.pdf).
4. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics — 2022 update: a report from the American Heart Association. Circulation 2022;145(8):e153-e639.
5. Acelajado MC, Hughes ZH, Oparil S, Calhoun DA. Treatment of resistant and refractory hypertension. Circ Res 2019;124:1061-70.
6. Salvador VD, Bakris GL. Novel antihypertensive agents for resistant hypertension: what does the future hold? Hypertens Res 2022;45:1918-28.

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