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Editorial

Newer alternatives for resistant hypertension: Beyond 2022 paradigms



A B S T R A C T

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Given the increased incidence of resistant hypertension and no novel agents to manage hypertension for more than 15 years, there has been an increase in the development of newer agents with unique mechanisms that will hopefully aid in getting this subset of patients under control. More recent classes of agents include nonsteroidal mineralocorticoid receptor blockers, aminopeptidase A inhibitors, dual endothelin A and B antagonists and aldosterone synthetase inhibitors, and novel agents affecting angiotensinogen mRNA in the liver. All these agents are under different levels of development and, if all goes well, should be available to the public within the next 2–5 years. In addition to these agents, renal denervation is anticipated to be approved in the United States within the next 6–9 months, whereas it has already been authorized in certain European countries. Thus, by 2025 and later, we will have a more extensive armamentarium to help quell the rise in resistant hypertension.

From early actuarial data associating elevated blood pressure with mortality to the first trials of blood pressure-lowering medications to contemporary American and European hypertension guidelines, the beneficial impact of blood pressure lowering in individuals with hypertension is well established^{1,2-4}. Population-level decreases in incident cardiovascular disease and mortality over the past 50 years reflect this well-established impact. Yet, the year-over-year decline in the incidence of cardiovascular disease has now plateaued, and concomitantly rates of uncontrolled hypertension have increased^{5,6}. Additionally, how the global COVID-19 pandemic impacts cardiovascular disease and hypertension-related outcomes is yet to be determined, but early data suggests population-level increases in blood pressure⁷.

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1. Current paradigms and ongoing investigations

Hypertension diagnosis and treatment standards remain relatively uniform globally, although thresholds defining hypertension differ in American and European blood pressure guidelines⁸. Agreement exists regarding factors such as the use of out-of-office blood pressure to confirm a diagnosis of hypertension, the emphasis on lifestyle interventions for adequate blood pressure lowering, encouraging clinicians to use single-pill fixed-dose combination pharmacotherapy as often as possible, standard first-line pharmacotherapy for primary hypertension (a blocker of the renin–angiotensin system, with either a dihydropyridine calcium channel blocker or a thiazide-type diuretic), and the use of a mineralocorticoid receptor antagonist for the treatment of resistant hypertension. Notably, the Diuretic Comparison Program pragmatic open-label randomized trial of chlorthalidone and hydrochlorothiazide among elderly veterans with hypertension demonstrated no differences in cardiovascular outcomes between chlorthalidone and hydrochlorothiazide, with a benefit of chlorthalidone among patients with prior myocardial infarction or stroke, but higher rates of hypokalemia⁹. Yet, the application of these and other recommendations in the “real world” is variable at best, as is the efficacy of

these strategies when applied to various patient populations. This variable efficacy is dependent on adherence to lifestyle recommendations such as low sodium diets, exercise, and proper sleep, as well as concomitant conditions such as advanced kidney disease. This has prompted clinicians and researchers to explore new solutions.

The most relevant recent advance in the evaluation and diagnosis of hypertension is the increasingly recognized prevalence of autonomous aldosterone production as a contributor to primary hypertension, coupled with gross undertesting and thus underdiagnosis of primary hyperaldosteronism^{10,11}. Clinician and patient education on the role of autonomous aldosterone production are clear priorities to more readily identify this patient population. Treatment options beyond standard mineralocorticoid receptor antagonists for this patient population are being evaluated, particularly a novel class of blood pressure-lowering medications, aldosterone synthase inhibitors.

Additional classes of blood pressure-lowering medications are under active clinical investigation and have promise, particularly in patients with resistant hypertension with and without chronic kidney disease. These include the dual endothelin receptor antagonist, apocritentan¹², nonsteroidal mineralocorticoid receptor antagonists such as ocedurenone¹³, and brain aminopeptidase A inhibitor, firibastat¹⁴ (Fig. 1).

Perhaps the most intriguing novel pharmacotherapies involve using RNA-based therapeutics, namely, antisense oligonucleotides

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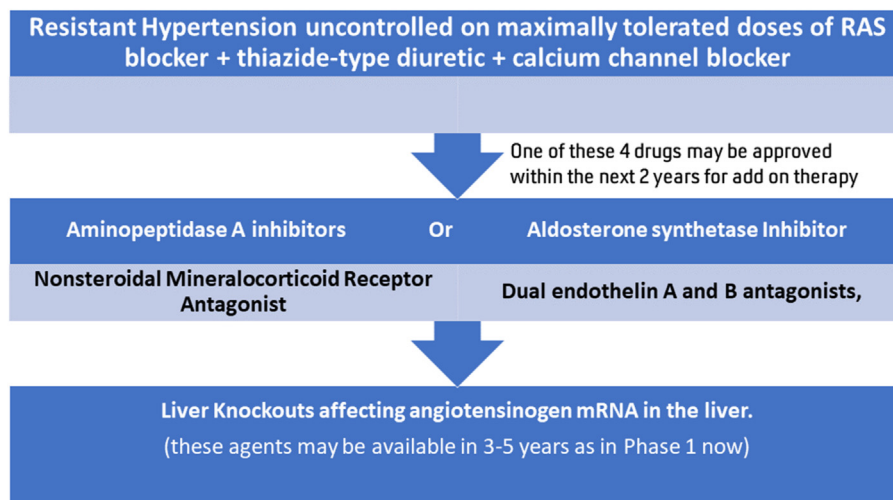


Figure 1. Current and future outlook on antihypertensive treatment.

and small interfering RNAs (siRNAs), to treat hypertension. This class of therapeutics is already in use in Europe and the United States to treat hypercholesterolemia, and the drug inclisiran is an example. Solutions targeting angiotensinogen production in the liver are currently in phase 2 trials¹⁵. These represent a solution to medication nonadherence inherent in chronic disease processes requiring multiple medications, among other potential benefits¹⁶.

Although the momentum for device-based therapy to treat hypertension dampened after the results of SYMPLICITY HTN-3 in 2015, a new impetus for renal denervation has emerged, given more recent data showing modest but significant blood pressure lowering in selected populations using an updated and more perfected catheter and procedure as shown in the SPYRAL HTN-ON MED, RADIANCE-HTN SOLO, and TRIO trials^{17–19}. Regulatory approval of renal denervation to treat hypertension is anticipated shortly and represents another treatment strategy, likely as an adjunct to medications and perhaps driven by evolving patient preferences for one-time procedures rather than daily medications¹⁹.

2. Future directions for hypertension management

To truly impact blood pressure control rates worldwide, public health entities must play a vital role and prioritize hypertension as they did before to acknowledge it is one of the top 10 noncommunicable diseases contributing to cardiovascular events. The United States Surgeon General declared hypertension a national priority²⁰, but how this declaration translates to clinical impact and outcomes is to be determined. Population-level strategies clearly can play a role in reducing blood pressure and subsequent cardiovascular disease – the Salt Substitute and Stroke Study being a prime example²². This open-label, cluster-randomized trial involved persons from 600 villages in rural China randomly assigning villages in a 1:1 ratio to the intervention group, in which the participants used a salt substitute (75% sodium chloride and 25% potassium chloride by mass), or to the control group, in which the participants continued to use regular salt (100% sodium chloride). Almost 21,000 participants were enrolled, and the rates of stroke, major adverse cardiovascular events, and death were significantly lower with the salt substitute than with regular salt²¹. The United States Food and Drug Administration has taken small steps in this direction through its publication *Guidance for Industry: Voluntary Sodium Reduction Goals* (FDA-2014-D-0055). It will be

incumbent upon jurisdictions worldwide to prioritize implementing and measuring the efficacy of similar public health interventions.

Scalable team-based care delivery to treat hypertension is also crucial. Although highly publicized trials of community-level interventions for BP management exist²¹, the ability to scale such interventions remains elusive, and technology-based automated solutions will play a key role. In early 2022, the American Heart Association released a report on the self-measured blood pressure digital health platform provider landscape. No platform meets *all* the standards set forth by the American Heart Association; hence, the potential for innovation and further growth in this area is large²³.

Even with decades of experience diagnosing and treating hypertension, population levels of blood pressure control are poor. Continued study of new therapies and effective ways to implement proven therapies remains crucial to improving hypertension management worldwide.

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The impact of hypertension on worldwide health outcomes is profound. Although numerous diagnostic and therapeutic strategies to address hypertension are available, applying these strategies still leaves much to be desired. Hypertension management is evolving and must continue to manage patient preferences, technological advances, and increasing prevalence in developing countries.

Conflict of Interest

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