Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/tcm

Emerging concepts for patients with treatment-resistant hypertension

*Alfonso Eirin, MD, Stephen C. Textor, MD, and Lilach O. Lerman, MD, PhD**

Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN

ABSTRACT

Treatment-resistant hypertension (TRH) is defined as elevated blood pressure despite treatment with three properly dosed antihypertensive drugs, and is associated with adverse cardiovascular and renal outcomes and increased mortality. Treatment of patients with TRH focuses on maximizing the doses of antihypertensive drugs and adding drugs with complementary mechanisms of action, including a combination of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, calcium channel blockers, and thiazide-like diuretics. Randomized clinical trials have demonstrated the efficacy of the mineralocorticoid receptor antagonist spironolactone as a fourth-line therapy for patients with TRH. Other pharmacologic considerations include adding α-blockers, combined α–β-blockers, centrally acting α-agonists, or direct vasodilators. However, a small, but important subset of patients remain hypertensive despite combination regimens with multiple antihypertensive drugs, underscoring the need for novel blood pressure-lowering therapies. Over recent years, alternative approaches for treating TRH have emerged, including agonists of natriuretic peptides, endothelin-receptor antagonists, and additional vasoactive drugs. Lastly, device-based interventions, such as renal denervation or carotid baroreflex activation, may supplement drug therapy for these patients. This review summarizes current knowledge on the management of TRH, with focus on novel therapeutic strategies designed to achieve optimal blood pressure control.

Key words: Resistant hypertension, Uncontrolled hypertension renal denervation.

Introduction

Hypertension affects approximately 75 million adults in the United States and more than 1 billion people worldwide, and is responsible for as many as 9 million deaths each year [1]. Although multiple clinical studies have demonstrated the efficacy of antihypertensive drugs to both decrease blood pressure (BP) and reduce mortality rates, many hypertensive subjects fail to achieve goal BP and become a major challenge for physicians involved in their care [2].

According to the European society of hypertension/cardiology guidelines, treatment-resistant hypertension (TRH) is defined as BP > 140/90 mmHg despite adequate lifestyles and treatment with full doses of >3 antihypertensive drugs (including a diuretic) [3]. The American Heart Association extends the definition to include "controlled" resistant hypertension, thereby considering those requiring four or more antihypertensive drugs as being "treatment resistant" [4]. The reported prevalence of TRH ranges from 9% to 27%, and increased over the past decades [2]. Importantly, its presence is associated with a substantially increased risk of adverse renal and cardiovascular outcomes. A large randomized trial showed that TRH is associated with an increased risk for congestive heart failure, stroke, cardiovascular disease, end-stage renal disease, and all-cause mortality [5], consistent with additional data from a recent retrospective, longitudinal cohort study of 470,386 Kaiser Permanente members [6].

Partly supported by NIH, United States Grants DK106427, HL123160, DK104273, DK100081, and DK76308.
The authors have indicated that there are no conflicts of interest.
* *Corresponding author*. Tel.: +1 507 266 9376; fax: +1 507 266 9316.
E-mail address: Lerman.Lilach@Mayo.Edu (L.O. Lerman).

http://dx.doi.org/10.1016/j.tcm.2016.05.004
1050-1738/

This review summarizes current approaches for treating patients with TRH, and the emergence of novel pharmacologic and device-based therapeutic strategies designed to more effectively achieve goal BP in this group.

Fluid expansion, salt sensitivity, and sympathetic activation

The precise mechanisms responsible for TRH remain uncertain and are likely multifactorial. Risk factors for TRH include obesity, male gender, older age, African–American origin, insulin resistance, increased dietary sodium intake, and renal dysfunction, conditions all associated with excess fluid retention. Indeed, prospective studies suggest that inadequate diuretic administration is a common feature in TRH. Serial hemodynamic and impedance measurements in patients with TRH revealed its association with increased thoracic fluid content, supporting occult volume expansion as a mediator of antihypertensive drug resistance [7]. Addition of mineralocorticoid receptor blockade in patients with TRH regularly reduces BP and volume overload, supporting the contention that fluid retention is a major contributor to TRH.

Excessive dietary sodium ingestion also contributes to resistance to antihypertensive treatment. In subjects with TRH, a low-salt diet decreases BP, increases plasma renin activity, and decreases creatinine clearance and body weight, consistent with a reduction in intravascular volume [8]. Additionally, renin–angiotensin system blockade may partially contribute to increase "salt-sensitivity," the tendency for BP to decrease during salt reduction and rise during salt repletion. Multiple genetic and environmental factors including age, body mass index, and ethnicity modulate the effects of dietary sodium on BP. Furthermore, potassium modulates the BP-elevating effects of sodium, as its dietary supplementation can abolish sodium sensitivity in both normotensive and hypertensive subjects [9].

Increased sympathetic activation may also contribute to some forms of TRH. Patients with hypertension associated with renal dysfunction, left ventricular hypertrophy, impaired left ventricular diastolic function, or systolic heart failure have greater sympathetic activation compared to those with uncomplicated hypertension. Furthermore, sympathetic activation is higher in patients with TRH than in individuals with elevated BP who respond to antihypertensive drug administration. In a recent study, Dudenbostel et al. [10] found increased 24-h urinary normetanephrine levels in patients with uncontrolled TRH, suggesting that heightened sympathetic tone might be partly responsible for antihypertensive treatment failure. Importantly, these findings support expanded efforts to design denervation device-based interventions to treat TRH.

Current approaches for management of TRH

As with all forms of complex hypertension, initial steps in the management of patients with TRH should confirm the diagnosis and identify secondary contributing factors (Fig.). A detailed assessment of the medical history should address the time of the first diagnosis, duration, severity, and progression of arterial hypertension, predisposing factors (lifestyle, cardiovascular risk factors, family history, etc.), current and past BP measurements, treatment adherence, response to prior medications, adverse reaction to antihypertensive therapies, history or current symptoms of target organ damage, and symptoms of possible secondary causes of hypertension.

A large fraction of failure to achieve goal BP is attributable to poor adherence, inadequate antihypertensive dosing, and "pseudoresistance," which results from discrepancies between BP measurements using different methods. Poor medication adherence is an important cause of "pseudoresistance" among patients with TRH, and might be falsely interpreted as treatment resistance. In a recent study, either

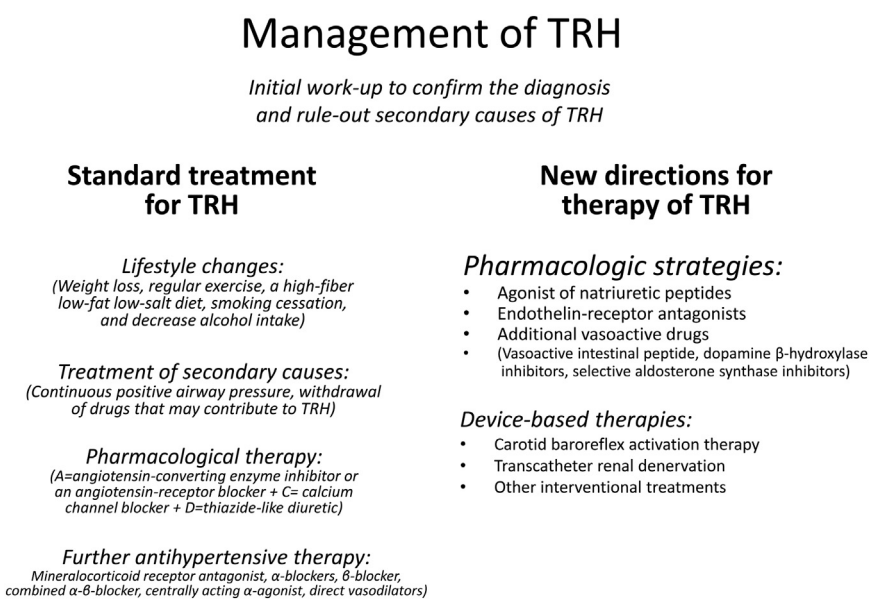

Fig – Current approaches and new directions for treatment-resistant hypertension (TRH).