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TITLE

Resistant hypertension: Novel insights

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ABSTRACT

Hypertension is the most common chronic disease and the leading risk factor for disability and premature deaths in the world, accounting for more than 9 million deaths annually. Resistant hypertension is a particularly severe form of hypertension. It was described 50 years ago and since then has been a very active field of research. This review aims at summarizing the most recent findings on resistant hypertension.

The recent concepts of apparent- and true-resistant hypertension have stimulated a more precise definition of resistant hypertension taking into account not only accuracy of blood pressure measurement and pharmacological class of prescribed drugs but also patient adherence to drugs and life-style recommendations.

Recent epidemiological studies have reported a 10% prevalence of resistant hypertension among hypertensive subjects and demonstrated the high cardiovascular risk of these patients. In addition, these studies identified subgroups of patients with an even higher morbidity and mortality risk, probably requiring a more aggressive medical management.

In the meantime, guidelines provided more standardized clinical work-up to identify potentially reversible causes for resistant hypertension such as secondary hypertension. Debate is however still ongoing on which would be the optimal method(s) to screen for non-adherence to hypertension therapy, recognized as the major cause for (pseudo)-resistance to treatment.

Recent randomized clinical trials have demonstrated the strong benefit of anti-aldosterone drugs (mostly spironolocatone) as fourth line therapies in resistant hypertension whereas clinical trials with device-based therapies displayed contrasting results. New trials with improved devices and more carefully selected patients with resistant hypertension are ongoing.

KEYWORDS

Hypertension, resistant hypertension, secondary hypertension, blood pressure measurement, antihypertensive drugs, adherence to therapy, medical devices

INTRODUCTION

Hypertension is the most common chronic disease and the leading risk factor for disability and premature deaths in the world. It affects nearly 1 billion adults, accounts for about 9% of global disability-adjusted life years and is associated with more than 9 million deaths annually [1–3]. Resistant hypertension (RHTN), a particularly severe form of hypertension, has been described and extensively studied during the last 50 years. This review summarizes recent findings on epidemiology, diagnosis, and treatment of RHTN.

1. THE BURDEN OF RESISTANT HYPERTENSION

1.1. Definition of Resistant Hypertension

Despite availability of a large number pharmacological classes, treatment of hypertensive patients do not always lead to optimal blood pressure (BP) control. This observation led more than 50 years ago to define resistant or refractory hypertension as a form of the disease in which hypertensive patients keep elevated BP levels despite utilization of medications [4, 5].

First consensus definitions of RHTN were published in 2007 and 2008. The 2007 European Guidelines defined RHTN as failure to lower systolic and diastolic BP to goal despite attention to life styles measures and prescription of 3 or more antihypertensive drugs in adequate doses, including a diuretic [6]. One year later, the American consensus statement on RHTN extended this definition to patients with four or more antihypertensive medications, irrespective of their BP level [7].

Numerous observations challenged these definitions in the last 10 years, as patients matching with these initial definitions certainly represent a heterogeneous population with highly variable morbid risks, depending on other characteristics.

White coat hypertension refers to patients with elevated office BP but controlled home BP monitoring (HBPM) or ambulatory BP monitoring (ABPM) [8, 9]. In 2011, de la Sierra et al. reported that 37.5% patients matching the 2007 European definition for RHTN had in fact normal ABPM values. Also, patients with ABPM-confirmed RHTN were having higher rate of target organ damage and cardiovascular disease [9]. Inaccurate BP measurement can also mis-classify hypertensive patients as resistant [10]. Interestingly, inaccurate office BP measurement does not systematically lead to

overestimation of BP levels. If BP levels are defined using office BP measurement only, diagnosis of RHTN can be missed in patient with masked hypertension, a situation in which BP levels exceed goals when evaluated with ABPM but not with office BP measurement [11]. Overall, these studies clearly evidenced that office BP measurement alone was not sufficient to rule in (and probably to rule out) RHTN and suggested that ABPM and/or HBPM should be used to properly diagnose resistant hypertensive patients.

Many patients defined as resistant do not follow recommended life styles guidelines and/or do not take some (or all) of the prescribed medications. Based on 24h sodium urinary excretion as a surrogate for daily sodium intake, Galletti showed that 73% patients defined as resistant did not follow recommendations on sodium consumption [12]. Also, pharmacological analyses can now provide with accurate evaluation of the burden of non-adherence to hypertension medications [13–15]. In 2013, Strauch et al. used liquid chromatography-mass spectrometry to detect antihypertensive drugs in the serum of 339 patients referred for RHTN [15]. Interestingly, no antihypertensive drug was found in the serum of 24% of the patients and some but not all drugs were detected for 23% additional patients, indicating that almost one half of the patients were totally or partially non-adherent to prescribed medications. Doxazosine, spironolactone and hydrochlorothiazide were linked to the highest rate of non-adherence. Even if these patients match the initial ESH/ESC and AHA definitions of RHTN, it is likely that they are not subjects with a resistant disease.

All these findings lead to the conclusion that numerous patients classified as resistant according to the initial European or American definitions did not really correspond to the idea of ‘resistance to therapy’. These data shed a new light on RHTN definition and management as these patients may represent up to two-thirds of RHTN in some hypertensive patient cohorts [16]. Therefore, the terms ‘apparent treatment-resistant’ hypertension (ATRH), ‘true-resistant’ hypertension (true-RHTN) and ‘pseudo-resistant’ hypertension (pseudo-RHTN) were introduced to better reflect this complexity (Figure 1). Accordingly, the American and European recommendations on arterial hypertension have been recently updated [17–19]. They emphasize the importance to detect pseudo-resistance related to (1) BP measurement technique issues, to (2) white-coat hypertension, and to (3) medication/life style non-compliance. For

example, the 2018 European guidelines definition for RHTN requires inadequate control of BP to be confirmed by ABPM or HBPM and adherence to therapy to be validated.

If some differences persist between the different recommendations (Table 1), new data will be challenging RHTN definition. In the 2017 American guidelines, following the publication of the SPRINT trial [20], BP threshold for identification of non-optimal BP levels was set from 140/90mmHg to 130/80mmHg. This change will mechanically increase the prevalence of RHTN [17]. However, it will not impact the strategy of management of RHTN. More importantly, anticipated changes in therapeutic strategies will more dramatically challenge our actual definition of RHTN. The 2018 European guidelines massively recommended utilization of lower dose combination of 2 antihypertensive drugs as first line therapy in many patients [21]. Furthermore, more complex combination of multiple classes of antihypertensive drugs are being tested in clinical trials with favorable outcome and may be recommended in the future [22]. Therefore, it is not clear if we will still be able to identify RHTN patient according to the number of prescribed medications. As detection of these patients who are at higher risk for morbid CVD events and death is crucial, there is a need for an improved RHTN definition that will not depend on the number of prescribed medications.

1.2. Refractory Hypertension: a Specific Sub-Group of Patients with Resistant Hypertension

First used concurrently with RHTN, the term refractory hypertension has been redefined ten years ago to characterize a different group of patients with a more severe form of RHTN [23].

Its definition has been proposed as follows: (1) uncontrolled RHTN after at least three visits at the clinic [24] or (2) hypertension that remained uncontrolled after co-prescription of five or more drugs from different classes [25]. In 2017, definition of refractory hypertension was updated by the American guidelines as failure to control BP despite the use of at least 5 antihypertensive agents of different classes, including a long-acting thiazide-type diuretic, such as chlorthalidone, and a mineralocorticoid receptor antagonist (MRA), such as spironolactone [17]. Refractory hypertension subjects have increased cardiovascular risk, target organ damage, coronary heart disease prevalence, and a greater level of hormonal alterations such as increase in aldosterone and a worse pattern of adipokines blood

concentration [25–29]. This suggests that these patients may at least require a greater medical attention among patients with RHTN.

1.3. Epidemiology of Resistant Hypertension

Numerous studies reported RHTN prevalence. However, because of study-to-study variations in analyzed populations and methodologies, including the definition of RHTN, the range of estimated RHTN prevalence remains quite broad. The 2018 American statement on RHTN indicates that prevalence of ATRH is likely to be between 12 and 18%, whereas the 2018 European hypertension guidelines states that the prevalence of true-RHTN (after exclusion of pseudo-resistance) is likely to be <10% of treated hypertensive patients. Table 2 summarizes a selection of studies that have reported prevalence of RHTN and analyzes the impact of RHTN definitions and measures aiming at detecting pseudo-resistance on calculated prevalence [9, 12, 30–35].

A meta-analysis that included 961,035 individuals reported a mean prevalence of RHTN in 20 observational studies of 13.7% (95% CI 11.2-16.2) and a mean prevalence in four randomized trials of 16.3% (95% CI 10.7-21.9); however, pseudo-resistance caused by suboptimal drug dosing, poor medication adherence and the white-coat effect were not ruled out in these studies [36].

More recently, another meta-analysis on 91 studies performed between 1991 and 2017 was published. It reported data of a pooled sample of more than 3 million patients with treated hypertension. The prevalence of true-RHTN, ATRH and pseudo-RHTN hypertension were 10.3% (95% CI 7.6% to 13.2%), 14.7% (95% CI 13.1% to 16.3%) and 10.3% (95% CI 6.0% to 15.5%), respectively [16].

Indeed, more epidemiological studies are needed to better ascertain the prevalence of RHTN according to the most recent definitions, including assessment of medication adherence and ABPM [37]. However, actual data clearly show the high prevalence of pseudo-RHTN and stress the need for its systematic detection when dealing with ATRH.

1.4. Prognostic of Patients with Resistant Hypertension

RHTN is strongly associated with adverse health outcomes and more particularly cardiovascular events. In a retrospective study that included more than 200,000 patients in the United States during a median

follow-up of 3.8 years, RHTN was significantly associated with increased major cardiovascular events (myocardial infarction, congestive heart failure or stroke) (HR 1.47, 95% CI 1.33-1.62, $p < 0.001$) [35]. A prospective cohort study of 470,386 individuals with hypertension enrolled in the Kaiser Permanente Southern California health-care program, found significant associations between RHTN and all-cause mortality (HR 1.06, 95% CI 1.03-1.08), ischemic heart events (HR 1.24, 95% CI 1.20-1.28), congestive heart failure (HR 1.46, 95% CI 1.40-1.52), cerebrovascular accident (HR 1.14, 95% CI 1.10-1.19) and end-stage renal disease (HR 1.32, 95% CI 1.27-1.37) [38]. This RHTN-associated higher risk for cardiovascular events was found in numerous other studies [39, 40] including in the sub-group of hypertensive patients with subclinical or established atherothrombotic [41]. Interestingly, similar findings could not be found in pseudo-RHTN [42]. Overall, RHTN has a very morbid outcome pattern and specific approaches are needed to identify risk factors for RHTN to promote early detection and surveillance of patients at risk.

1.5. Risk Factor to Develop Resistant Hypertension and Detection of Patients at Risk.

Risk factors to develop RHTN have been reported in post-hoc analyses of clinical trial or in longitudinal follow-up of cohorts of hypertensive patients (Table 3) [39, 40, 43, 44]. Based on these findings, Buhnerkempe et al. were able to propose 2 prediction models based on 5 or 6 common clinical data (ethnicity, body-mass index, diabetes, systolic BP level, estimated glomerular filtration rate (eGFR), and number of prescribed antihypertensive medications) [44]. The models displayed good prediction capabilities (area under curve values were 0.82 and 0.77) and excellent negative predictive values (94% and 95%). Prediction power of these models should be further validated in replication cohorts. Nevertheless, if validated, these prediction tests could be very easy to implement and will be very helpful to timely detect patients at risk for RHTN and set up specific surveillance and therapeutic management.

1.6. Resistant Hypertension in Specific Populations: Diabetes and Chronic Kidney Disease:

In specific populations such as patients with diabetes or with chronic kidney disease (CKD), RHTN seem to be more prevalent and with a greater impact on patients' outcome.

Association of CKD and ATRH is frequent. In a recent meta-analysis, the prevalence of true-RHTN was 22.9% (95% CI 19.1% to 27.0%) and 56.0% (95% CI 52.7% to 59.3%) in CKD patients and renal transplantation recipients, respectively [16]. In RHTN population, the presence of reduced eGFR and/or albuminuria is predictive of a 2-to-3-fold increase in cardiovascular and all-cause mortality [45]. Conversely, in cohorts of CKD patients, presence of RHTN increased all-cause mortality, cardiovascular events and incidence of end-stage renal disease by 1.5-to-2 fold.[46, 47]. In patients with type-2 diabetes, hypertension and baseline eGFR > 60ml/min/1.73m² [48], presence of ATRH was associated to a 1.43-fold greater risk of kidney function deterioration at 4 years, as compared to non-resistant hypertensive patients. Interestingly, tight BP control was also associated with a greater risk of kidney function deterioration in ATRH patients. This observation is in line with a previous report and therefore questions optimal BP target and optimal use of renin-angiotensin system (RAS) blockers in this specific population [49]. Overall, this suggests that detection and treatment of RHTN is even more crucial in specific population such as diabetic and/or CKD patients. Whether these patients may benefit from tailored target BP values remains to be elucidated.

2. DIAGNOSIS OF RESISTANT HYPERTENSION

2.1. Accurate Blood Pressure Measurement

ABPM is the current gold standard for BP measurement. Both the US Preventive Services Task Force [50] and the European Society of Hypertension [51] recommend ABPM as the method of choice for the diagnosis of hypertension. When ABPM is not feasible, HBPM may be substituted and has been shown to correlate closely with daytime ABPM readings [52].

Self-measured home BP shares some of the advantages of ABPM compared with office BP measurement, such as the greater number of readings and identification of the white-coat effect [53]. However, HBPM cannot replace 24-hour ABPM as the gold standard to assess BP levels because HBPM will not provide recording of night BP levels, a period during which BP is most predictive of adverse cardiovascular outcomes [54]. Only ABPM permits detection of non-dipping pattern, defined as <10% nocturnal drop in BP [55] and isolated nocturnal hypertension which confers a cardiovascular risk equal to that of an elevated daytime or 24-hour ABPM [56]. This is an important limitation of HBPM given

that the prevalence of isolated nocturnal hypertension is 7% among white individuals and 10-11% among black individuals and Asians [55, 56]. Finally, use of HBPM instead of 24-hour ABPM can also lead to mis-diagnose masked or sustained hypertension, which is associated with high cardiovascular risk, in over 25% of patients [57].

Thus, 24-hour ABPM is the cornerstone of the diagnosis and management of RHTN, although self-measurement of BP might be used, in addition to ABPM, to aid optimization of drug treatment [53]. For example, self-measurement of BP might be considered in patients who resent ABPM because the BP measurements disturb their sleep quality or interfere with strenuous physical labour at work.

2.2. Secondary hypertension screening

RHTN is one of the most frequent conditions requiring secondary hypertension screening. Such screening is also recommended for patients showing signs suggesting secondary hypertension (such as symptoms of pheochromocytoma or hypokalemia), for patients with hypertension onset before the age of 30 (American guidelines) or 40 (European guidelines), patient with sudden onset of hypertension, or patient with disproportionate end-organ damage [18, 58]. In practice, it is recommended to first exclude pseudo-RHTN and RHTN related to drugs, such as oral contraceptive pills, stimulant (illicit) drugs, immunosuppressive medications, anti-inflammatory drugs or glycyrrhizic acid-based products or alcohol. Rare genetic etiologies must be suspected in young patients, particularly in case of familial history of hypertension.

The latest guidelines stratify the routine screening and the additional investigations. Routine screening is based on physical examination, routine blood and urine tests, abdominal ultrasound, and echocardiography for aortic coarctation screening [18]. If one or more of them is positive, “referral to a specialized center is recommended for additional investigations to confirm a suspected diagnosis of secondary hypertension and for clinical management” [18].

In detail, among the most prevalent etiologies, renal ultrasound will help to diagnose renal parenchymal disease, completed with duplex doppler ultrasound to diagnose renovascular diseases. Computed tomography (CT) and magnetic resonance imaging (MRI) angiographies are alternatives to duplex doppler ultrasound, without any preference in the guidelines to one or the other. The choice depends

actually on the patient characteristics (such as obesity, renal failure) and local availability. Then, referral to a bilateral selective renal angiography can help confirm the diagnosis and if appropriate treat renovascular diseases.

Obstructive sleep apnea is also a common cause in patients with RHTN, with prevalence rate as high as 70% to 90% [59, 60]. Clinicians should vigorously screen patients for symptoms of obstructive sleep apnea (loud snoring, frequent nocturnal arousals, witnessed apnea and excessive daytime sleepiness) and use scoring such as the Epworth score or the Berlin questionnaire to consider overnight oxymetry and polysomnography for confirmation [61]. European guidelines add ambulatory polygraphy to this routine screening, when American guidelines recommend polysomnography to confirm the diagnosis.

Hyperaldosteronism is the most common endocrine cause of RHTN. Plasma aldosterone and renin sampling and aldosterone/renin ratio are recommended for the screening but require particular measurements conditions. Hypokalemia can depress aldosterone levels and must be corrected before measurements [62]. A switch to antihypertensive drugs neutral to the RAS is necessary prior to blood sampling. Beta-blockers, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) must be stopped for 2 weeks and MRAs for 6 weeks prior to blood sampling. Calcium channel blockers (CCB), alpha-blockers, centrally acting agents can be used to maintain acceptable BP level during the washout period.

Among the rare endocrine causes of hypertension, pheochromocytoma and paraganglioma should be explored by 24-hour urinary fractionated metanephrines or free plasma metanephrines collected in a supine position. Additional tests recommended in the hypertension guidelines are CT or MRI scans [63]. According to the Endocrine Society guidelines, meta-iodobenzylguanidine scintigraphy and positron emission tomography/CT should be used in patients with metastatic pheochromocytoma [63].

Some differences can be seen between guidelines for Cushing syndrome diagnosis. Cushing's disease screening differs between American and European guidelines, with overnight 1-mg dexamethasone suppression test for the former and 24-hour urinary free cortisol for the latter. Both can be easily managed with an ambulatory screening. Midnight salivary cortisol can also help to confirm the diagnosis.

Thyroid diseases and hyperparathyroidism may be screened by thyroid function tests (Thyroid-stimulating hormone (TSH) and free thyroxin) and serum calcium, respectively. Additional uncommon diseases cited by the American guidelines can also be revealed by hypertension such as congenital adrenal hyperplasia, mineralocorticoid excess syndromes (other than primary aldosteronism) and acromegaly [58].

2.3. Drug Adherence Evaluation

Poor drug adherence is a major issue in patients with RHTN [64, 65]. Non-adherence to antihypertensive therapy is an indicator of poor prognosis and correlates with poor cardiovascular outcomes. This is the main reason for treatment failure and repeated hospital admissions [66]. Conversely, good adherence to BP-lowering therapy is associated with a reduction of adverse cardiovascular outcomes [66]. Unfortunately, up to 40% of clinical appointments fail to address adherence [67].

A recent analysis suggests that non-adherence is the dominant type of pseudo-RHTN in patients referred for renal denervation [68]. Thus, addressing non-adherence is of critical importance in the management of patients diagnosed with RHTN [69].

Poor drug adherence in hypertensive patients is influenced by multiple factors including number of medications prescribed, low level of education, younger age and being female [70, 71]. Other causes of non-adherence include socioeconomic barriers, medication side effects and cognitive dysfunction. Psychological factors have been also associated with an increased likelihood of medication non-adherence [70, 72]. Poor drug adherence is particularly frequent in patients with RHTN [73]. Partial adherence ranges from 17 to 46%, and complete non-adherence from 9 to 35% [73].

To detect poor or non-adherence to treatment is very difficult. Several studies demonstrated that physicians are generally not good judges to state if their patients are taking their medication as prescribed. Physicians' perception of non-adherence correlated with an objective measure in less 40% of cases. Moreover, 40% of diagnoses of non-adherence based on clinical judgment results in treatment escalation that, through augmentation of polypharmacy, may further compromise adherence [74]. There are many validated questionnaires to diagnose adherence, the most used being the four-item Morisky Medication Adherence Questionnaire (MAQ). However, these questionnaires are responsible for an up-

to-20% over-declaration of adherence when compared to an objective measure [75]. Other objective indirect methods have been evaluated such as pill counts, electronic pillbox, evaluation of heart rate with beta-blockers or activation of the RAS with ACEi or ARB but their sensitivity remains low.

The gold-standard objective method for assessing drug adherence is to measure drug or their metabolites in body fluids [14]. For example, in the DENER-HTN study, while poor compliance was systematically sought by interview and questionnaire at each monthly consultation, drug-testing at 6 months found 52% of non-adherent patients, 13% of whom were not taking any treatment [71].

However, if urine or blood measurement of drug or metabolites with mass spectroscopy reliably determines whether a drug is present or absent, it does not determine whether it was taken regularly or at a therapeutic level. A novel approach, urine fluorometry, was recently reported as a safe, easy, and reliable method to assess adherence [76].

Many methods can be attempted to limit non-adherence to treatment. It seems necessary to limit the total number of tablets by promoting the use of agents that are dosed once daily, combinations antihypertensive drugs, low-cost and generic antihypertensives (particularly when cost of care is a barrier), dispensing of pillbox. It is essential to generalize and develop therapeutic education that must be repeated at each consultation [77]. Finally, some authors suggest to repeat regularly drug dosages in patients initially non-adherents, in order to favor better adherence and improve BP control [78]. Many clinicians may also benefit from training to enhance communication skills and to increase cultural competence in their interactions with patients [19].

3. TREATMENT OF RESISTANT HYPERTENSION

3.1. Target Blood Pressure

Whether optimal BP targets in resistant and non-resistant hypertension differs remains unknown and this probably explains the difference between American and European guidelines. Tight BP control may lead to adverse events in sub-groups of RHTN patients [48, 49]. However, a recent pooled analysis of data from SPRINT and ACCORD studies indicated that intensive BP control was similarly beneficial in patients with resistant and non-resistant hypertension [79].

3.2. Medical Therapy

RHTN implies that patients are already on 3 or more different antihypertensive medication at the time of resistance diagnosis. The first 3 prescribed drugs should ideally act through complementary mechanisms and are usually a combination of RAS blockers (ACEi or ARB), a CCB, and a diuretic [18, 19, 58]. Drugs should be prescribed at maximally tolerated doses. However, in specific medical conditions, such as atrial fibrillation or heart failure, the initial triple therapy may be different [18].

Before adding a fourth medication, several adaptations are suggested, including (i) combination of all drugs in a single pill so as to improve adherence to treatment [18], (ii) modification of the timing of drug dosing in order to comprise nighttime dosing for at least one drug [58], or (iii) switch to a different diuretic. Thiazide-type diuretics, such as hydrochlorothiazide, chlorthalidone or indapamide, are equally considered as first-line diuretic in hypertension. However, HCTZ or indapamide may be switched to chlorthalidone in case of $eGFR < 45 \text{ ml/min/1.73m}^2$ [19]. If renal function is more severely decreased ($eGFR < 30 \text{ ml/min/1.73m}^2$), loop diuretics (furosemide, bumetanide or torsemide) should be preferred as first-line diuretic drug [18, 19].

In case of uncontrolled RHTN after triple therapy adjustment, increasing amount of evidence indicates spironolactone as the fourth drug of choice. Excess fluid and sodium retention have been described as a key mechanisms in RHTN pathophysiology [80] and diuretics combination have shown superiority over RAS blockers combination to improve BP control in this setting [81]. In patients with normal or mildly decreased renal function, potassium sparing diuretics have demonstrated a significant reduction of BP [82]. Among those, the greater reduction on BP in RHTN was obtained with spironolactone. Several non-randomized [83, 84] and randomized [85–87] studies on a small number of patients with RHTN demonstrated that low-dose (25mg per day) spironolactone significantly improved BP control as compared to placebo. These findings were also confirmed by Dahal et al. in a 15-study meta-analysis on 1204 patients investigating reduction in BP induced by MRAs (spironolactone or eplerenone) [88]. In 2015, Williams et al. reported the results of the PATHWAY-2 trial [89]. This randomized, double-blind, crossover study tested, in 335 patients with RHTN, spironolactone as a 4th-line treatment as compared to placebo and to 2 other alternative drugs: the beta1-blocker bisoprolol, the alpha2-blocker

doxazosin. Pseudo-RHTN was excluded after HBPM and validation of treatment compliance. At baseline, all patients were on a combination of a RAS blocker (ACEi or ARB), a CCB, and a diuretic. Each study drug was given for 12 weeks with a forced up-titration after 6 weeks. The primary end-point was decrease of home systolic BP values with spironolactone as compared to placebo and as compared to the other drugs. All 3 tested drugs significantly reduced BP at 12 weeks as compared to placebo, from 4.2mmHg for bisoprolol to 4.9mmHg for doxazosin, to 10.2mmHg for spironolactone. Systolic BP reduction obtained with spironolactone was significantly greater than reductions obtained with bisoprolol or doxazosin and up-titration of spironolactone to 50mg daily further decreased BP level, as compared to 25mg.

As well, additional data were obtained from the same patients and helped further decipher the relationship between drugs mechanisms of action and BP response to treatment in RHTN [90]. BP response to spironolactone strongly depended on blood aldosterone-to-renin ratio and blood renin levels, patients with the lowest baseline renin blood level being better spironolactone responders. This suggested that renin level as a predictor of spironolactone efficacy. Furthermore, hemodynamics data revealed that spironolactone was the only drug to reduce significantly thoracic fluid content, a surrogate marker for intravascular volume. As excess fluid/sodium is a hallmark of the majority of patient with RHTN [80], this finding may explain, at least in part, the superiority of spironolactone over the other tested drugs. In a subset of patients, amiloride, another potassium-sparing diuretic, was tested in an open label design as another candidate fourth-line therapy. Amiloride reduced systolic BP with a magnitude similar to spironolactone and, on a patient-to-patient analysis, BP response to amiloride and spironolactone strongly correlated. Overall, PATHWAY-2 provided strong evidence that spironolactone was the drug of choice as a fourth-line treatment in RHTN and this has been translated in all recent guidelines [18, 19, 58].

Amiloride might represent the main alternative drug to spironolactone and bisoprolol and doxazosin may be also considered as alternative to spironolactone or amiloride, or as 5th-line therapy if needed.

In addition, 2 recent studies compared renal denervation and spironolactone in RHTN and reported a more favorable effect of spironolactone on BP control [91, 92].

However, if low/moderate dose spironolactone was effective to reduce BP over a 12 weeks of treatment, long-term effect of spironolactone on cardiovascular and renal end-points remains largely unknown in the setting of RHTN. As well, PATHWAY-2 mostly enrolled Caucasians patients; therefore, these findings may not be extended to patients with other ethnic origin [89].

Also, utilization of spironolactone has several limitations and contra-indications, reducing the number patients that may benefit from this drug in real practice. Spironolactone is not recommended in patients with $eGFR < 45 \text{ ml/min/1.73m}^2$ and/or potassium $> 4.5 \text{ mEq/L}$, as it may lead to renal function worsening and hyperkalemia. Indeed, these patients were excluded from the PATHWAY-2 trial [89], as in most of the studies published in RHTN. As amiloride has a lower tendency to hyperkalemia, it may be used as an alternative to spironolactone. Recently, potassium binders such as patiromer have been developed to increase persistence of drugs such as MRAs or RAS blockers[93]. Utilization together with spironolactone in patients with RHTN and CKD is under evaluation and may represent an important solution to increase persistence of spironolactone [94].

Hormonal side-effects of spironolactone such as gynecomastia and erectile dysfunction in men and menstrual irregularities in women are also frequent. In this situation, amiloride and eplerenone may be used. However, use of eplerenone might be also limited if concomitantly used with CYP3A4 inhibitors such as amiodarone or verapamil and need to be taken every 12h due to its shorter half-life.

3.3. Device-Based Therapies

The last decade has seen the emergence of interventional devices in alternative to medications in the treatment of RHTN. The most advanced techniques will be described below, but other devices like the carotid body ablation procedures give some interesting preliminary results [95].

3.3.1. Renal denervation (RDN)

Briefly, renal denervation aims at interrupting the renal sympathetic activity by destroying sympathetic nerves localized close to the renal arteries. Most of the evidence concerning renal denervation are about patient with RHTN. Until recently, patients with drug-resistant hypertension were the only target

population. Demonstration of an activated renal sympathetic outflow in RHTN does corroborate the selection of these patients in studies, but the uncertainty of the benefit/risk ratio in the first SYMPPLICITY trials was the true reason to target this population [96, 97]. Earlier studies focused on severe hypertension, with systolic hypertension exceeding 160 mmHg [98]. Greater severity means in general longer history of hypertension and more non-reversible end organ damages and arterial stiffness, both adding confounding factors to the blood BP response to RDN. This might be a part of the explanation for the failure of SYMPPLICITY-HTN3 trial [99]. The proven safety shown in the different studies and registries allows widening of the indications for denervation. More recent sham-controlled projects reflect this, and patients with BP higher than 140/90 mmHg with or without drugs are now recruited. The latest data seem to confirm the efficacy of renal denervation in less severe hypertension [100–102].

RHTN is perhaps not the best target population to confirm RDN efficacy but it does not mean that RDN should not be used in RHTN. People who might respond to RDN should be identified first. Further, the possible value of renal denervation extends beyond the hypertension field, for example to benefits in atrial fibrillation [103, 104] and in reducing heart failure recurrence [105].

3.3.2. Carotid baroreceptor stimulation

Baroreflex activation therapy (BAT) devices have been designed to artificially strain the carotid baroreceptor and to induce a decrease of BP. A first generation of implantable pulse generator confirmed the efficacy of the technic to lower BP in RHTN. However, concerns about periprocedural and the long-term safety, linked to the implantation of complex electrodes around both carotid artery, lead to the development of a second-generation devices. The first results of unilateral stimulation on ABPM were similar to bilateral stimulation with a better safety profile [106]. Clinical trials are still ongoing. Similarly, a new technic based on a stent-like device implanted in the carotid to stretch the carotid bulb gave positive preliminary results [107].

3.3.3. Arteriovenous fistula

The third potential device-based option for the treatment of RHTN is the creation of an arteriovenous fistula to unload the arterial vascular bed in the venous system [108]. The fistula is sustained by a stent-like nitinol device. First studies have confirmed the efficacy to decrease arterial BP with an immediate effect [109]. The results at one year seem to be sustained but with 33% of venous stenosis, all successfully treated by venous stenting [110]. If there were no major events in these studies, the risk of right heart failure or high-output cardiac failure justify a longer follow-up [18].

To summarize, some devices will certainly help the physician to treat RHTN in the future. But, the latest guidelines [18] still exclude device-based therapies for the routine treatment of HTN. These devices must be reserved for clinical studies to confirm their efficacy and their safety.

CONCLUSION

To summarize, the last 10 years of research in hypertension helped better defined RHTN with the identification of true- and pseudo-RHTN, two clearly different forms of the disease with distinct management and prognosis. Management of patients with pseudo-RHTN should mainly focus on promoting adherence to drug therapy and life style recommendations. Patients with true-RHTN probably account for 10% or less of all hypertensive subjects but sub-groups of patients are at higher risk of true-RHTN such as patients with diabetes or CKD. True-RHTN patients have a high rate of cardiovascular and renal complications and should benefit from aggressive medical surveillance. A large body of evidence indicates that spironolactone should be the preferred fourth line of treatment for true-RHTN after failure of an optimally-dosed triple antihypertensive therapy ideally comprising a RAS blocker, a CCB and a thiazide-type diuretic. Device therapy for true-RHTN is an active field of clinical research and may emerge in the next years as a therapeutic option for carefully selected true-RHTN patients.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table 1

Diagnostic criteria for resistant hypertension	ESH/ESC 2018	AHA 2018	ACC/AHA 2017
BP control not achieved despite the concurrent use of three antihypertensive drugs	✓	✓	✓
Concurrent use of 4 antihypertensive agents irrespective of BP control	-	✓	✓
Preferential combination of an ACE inhibitor or an ARB, a CCB, and a diuretic	✓	✓	-
Mandatory use of a diuretic	✓	-	-
All drugs up-titrated to maximal or maximally-tolerated doses	✓	✓	-
BP level confirmed by ABPM or HBPM	✓	✓	-
Adherence to therapy assessed and confirmed	✓	✓	-
Adherence to life style recommendation assessed and confirmed	✓	-	-
Secondary hypertension excluded	✓	-	-

Table 2

Prevalence of ATRH among hypertensive patients					
study	population (n=)	definition	ATRH prevalence		
Bangalore et al. [30]	10001	AHA 2008	11.1%		
Gijon-Conde et al. [31]	63167	AHA 2008	9.9%		
de Beus et al. [32]	6191	AHA 2008	9.1%		
Sarganas et al. [33]	2205	AHA 2008 ESC 2007	11.6% 6.0%		
Prevalence of RHTN among hypertensive patients before and after exclusion of white-coat hypertension (WC HTN) with ABPM					
study	population (n=)	definition	ATRH prevalence	prevalence after WC HTN exclusion	
Brambilla et al. [34]	1312	AHA 2008	32.2%	19.4%	
de la Sierra et al. [9]	68045	ESC 2007	12.2%	7.6%	
Prevalence of RHTN among hypertensive patients before and after exclusion of non-adherence					
study	population (n=)	definition	ATRH prevalence	prevalence after partial non-adherence exclusion	adherence measure
Daugherty et al. [35]	205750	AHA 2008	17.9%	16.2%	prescription fills
Galletti et al. [12]	1177	ESC 2007	8.2%	2.2%	24h urinary sodium

Table 3

Risk factors for resistant hypertension

Factors related to hypertension history

- level of systolic blood pressure at the time of treatment onset and/or during follow-up
- time from hypertension onset
- number of drug classes prescribed

Factors reflecting organ damage

- history of arterial disease
- left ventricular hypertrophy
- heart failure
- reduced glomerular filtration rate

Factors reflecting metabolic syndrome and/or life habits

- type 2 diabetes
- elevated fasting glucose
- raised body mass index
- alcohol intake
- high sodium intake (reflected by 24h urinary sodium)

Unmodifiable factors

- male sex
- African-American ethnic origin

TABLES AND FIGURE LEGENDS

Table 1-

Diagnostic criteria for resistant hypertension according to recent American and European recommendations.

Table 2-

Measured prevalence of apparent treatment-resistant hypertension, white-coat hypertension, and non-adherence in cohort studies.

Table 3-

Risk factors to develop resistant hypertension

Figure-

Simplified diagnostic flow-chart algorithm for true-resistant hypertension focusing on pseudo-resistance detection

