CMHC Cardiometabolic Health Congress

CLINICAL BRIEF

The Burden of Resistant Hypertension in Women: Novel and Emerging Approaches to Improve Outcomes

The Burden of Hypertension and Resistant Hypertension In Women

Hypertension is an important cardiovascular disease risk factor that causes more than 7 million deaths worldwide per year, and accounts for 54% of strokes and 47% of coronary heart disease.[1] In the US, almost half of the population (45%) have hypertension, and this number is higher in individuals with existing CVD or increased CVD risk, such as in those with diabetes, chronic kidney disease, and older adults.[1]

Hypertension remains under-treated and difficult to control. Clinicians are challenged with knowing at what blood pressure (BP) level to start medication, at what level to maintain medication, and what medications should be used to get to the BP goal. Despite the improvements in hypertension awareness and treatment, a large proportion of hypertensive adults still fail to achieve their BP targets, despite continuous and persistent therapy.[2,3] In particular, individuals who fail to achieve BP targets on 3 antihypertensive medications or require ≥4 medications to achieve their targets are designated as having treatment-resistant hypertension, a condition that poses increased risks for organ damage, morbidity and mortality.[2]

For these patients, controlling blood pressure is extremely challenging, as options are very limited. Furthermore, there are data to suggest that this is a bigger challenge in women compared to men. Until recently, there was limited information about sex differences in hypertension control and related outcomes, however, studies have shown that even though the prevalence of HTN is similar and women are more likely to be treated with antihypertensive therapy, women are less likely than men to achieve BP control, particularly in aging and older populations.[4] It has been suggested that despite having higher rates of resistant HTN, women have lower risk of adverse cardiovascular events, however, this latter part has been disputed by other studies showing the opposite.[4-6] These disparities, both in the prevalence of resistant HTN and increased CV risk, are more pronounced in hypertensive women from certain racial and ethnic groups, such as non-Hispanic black women.[1,6,7]

In addition, BP thresholds at which CVD develops are lower in women compared to men, highlighting the need for stricter BP targets in women.[1,8] Furthermore, in addition to conventional risk factors, women also have gender-specific risk factors that can increase the risk of resistant hypertension, such as the use of oral contraceptives, postmenopausal hormone replacement therapy, and history of adverse pregnancy outcomes.[2,9]

Initial Assessment and Treatment of Patients with Resistant Hypertension

Resistant hypertension is typically defined as BP that remains elevated despite the concurrent use of 3 antihypertensive agents, most commonly being a combination of the following: a long-acting calcium channel blocker (CCB), an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and a diuretic.[2] Because errors in BP measurement can contribute to the misdiagnosis and suboptimal treatment of hypertension and RH, it is critical to ensure that accurate BP measurements are made before establishing a diagnosis.[2] The white-coat effect is important in diagnosing resistant hypertension as some degree of BP rise is seen with in-office measurement in most individuals, but this effect can be greater in individuals diagnosed with hypertension, women, and older individuals.[2] Additionally, non-adherence in taking prescribed medications must be evaluated and excluded before true RH is diagnosed, given that as many as 50-80% of hypertensive patients demonstrate suboptimal adherence.[2] As discussed above, women can also have sex-specific risk factors for resistant hypertension, in addition to conventional risk factors, and these should be taken into account when getting a comprehensive medical history.[2,9]

When it comes to the management of RH, lifestyle interventions, including weight loss, dietary salt restriction, and exercise, as well as optimization of current antihypertensive medications are critical.[2] In a 2018 statement on RH published by the American Heart Association, a treatment algorithm was released, which involves constant re-evaluations if BP remains elevated and practical steps to continue to address RH.[2]

Management of Resistant Hypertension

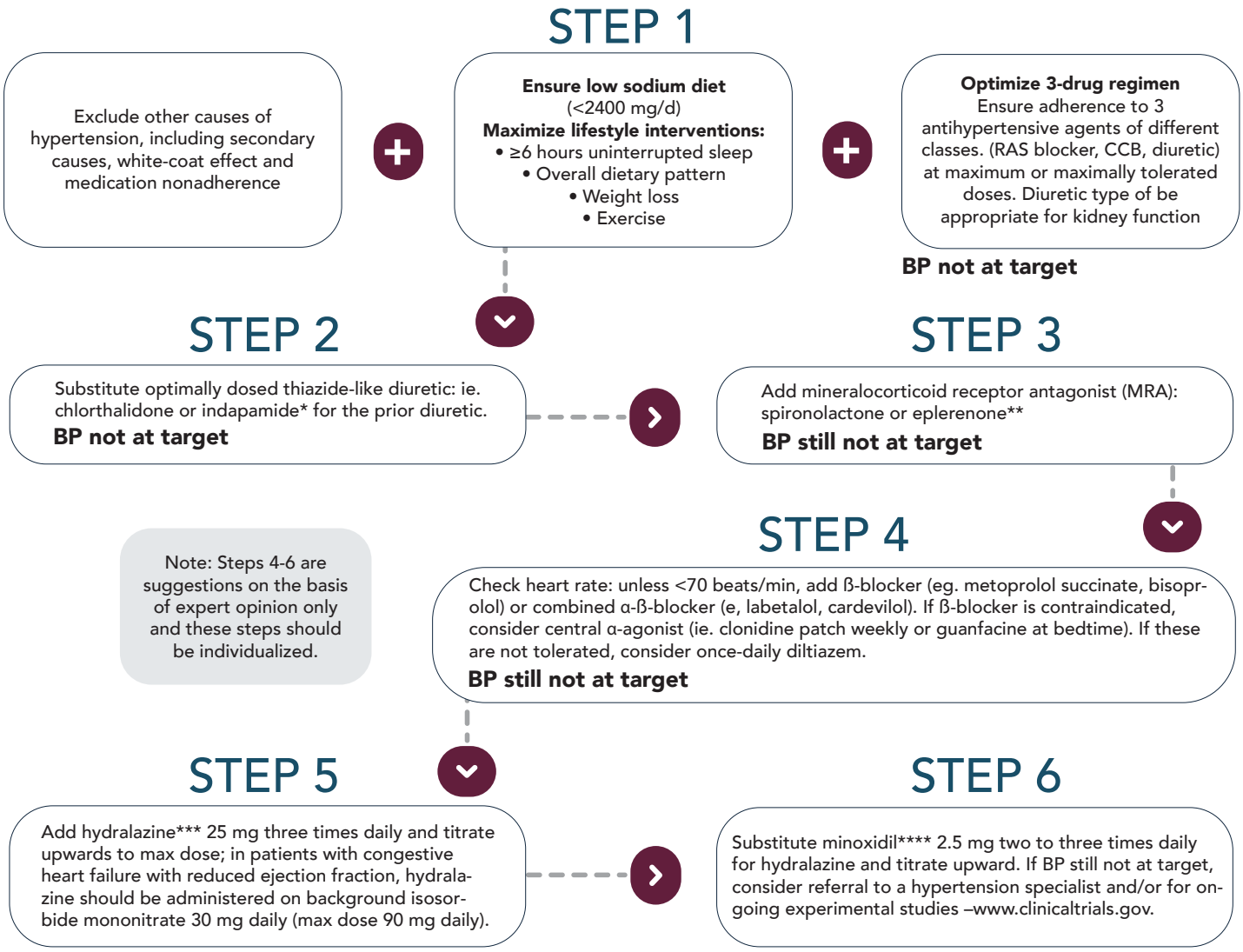

Figure 1 – Management of Resistant Hypertension – 2018 AHA Scientific Statement[2]

Additionally, in 2023, the European Society of Hypertension published new guidelines for the management of HTN, including specific recommendations for the diagnosis and treatment of true resistant hypertension, delineating a simple algorithm for treatment intensification in this setting that now includes renal denervation (Figure 2).[10]

Emerging pharmacological treatments for resistant hypertension

As part of the cardiovascular outcomes' trials, several SGLT-2 inhibitors, including canagliflozin, empagliflozin, and dapagliflozin have been shown to decrease blood pressure, however, they are not indicated for BP reduction and additional studies in this area are needed.[11] In addition, multiple agents targeting the renin-angiotensin-aldosterone pathway are in advanced clinical development for RH.[12] An overview of key evidence with these agents is outlined below.

Several selective nonsteroidal MRAs, such as KBP-5074, esaxerenone, apararenone, and AZD9977 are in development.[13-15] Of these, KBP-5074 is at the most advanced stage, currently being evaluated in a phase 3 trial. Phase 2 studies showed that KBP-5074 effectively lowers BP with some risk of hyperkalemia in patients with advanced CKD and uncontrolled blood pressure.[16] A phase 3 trial evaluating this agent in patients with uncontrolled hypertension and moderate or severe CKD is ongoing.[17]

Aprocitentan, a novel dual endothelin-receptor antagonist, was evaluated in a phase III trial (PRECISION trial) for its ability to lower blood pressure when added to other antihypertensive drugs in patents with resistant hypertension.[18] The study was recently concluded and the results showed that aprocitentan was well-tolerated and superior to placebo in lowering BP in patients with resistant HTN.[19] The study also enrolled a significant proportion of women (41%).[19]

Baxdrostat, which lowers aldosterone production by blocking aldosterone synthase, was shown to lead to dose-dependent reductions in BP in patients with resistant HTN in the phase 2 BrigHTN study.[20] The results of another phase II study, HALO, showed that treatment with baxdrostat did not result in a significant reduction of BP compared to placebo in patients with uncontrolled hypertension.[21] However, a larger than expected placebo effect was noted and low adherence was observed in some study sites, which can account for the discrepancies observed between the BrigHTN and HALO trials.[21] Despite this, experts remain confident about the viability of this approach and a phase 3 trial is currently being planned. Additionally, lorundrostat (formerly MLS-101), another aldosterone synthase inhibitor, is currently being evaluated in a phase 2 trial for resistant hypertension.[22] Recently, results from another phase 2 trial with lorundrostat were published, showing effective BP lowering with treatment vs. placebo in patients with uncontrolled hypertension.[23]

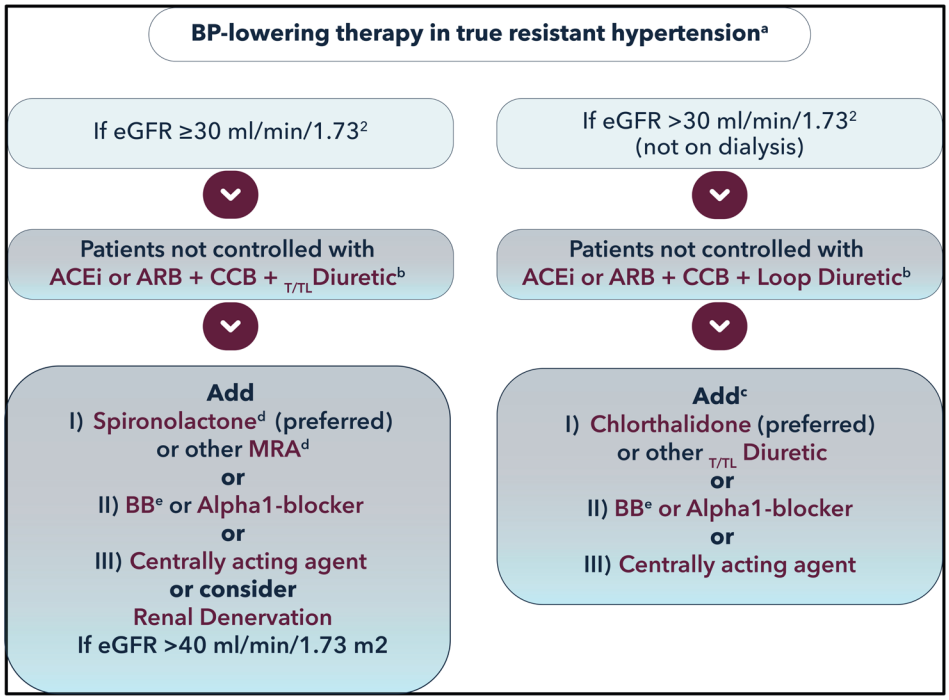

Figure 2. Treatment for true resistant hypertension – 2023 ESH guidelines[10]

Another novel approach for resistant hypertension involves using RNA-based therapeutics, such as antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs).[13] Several approaches that fall under this category are in phase 2 trials, including with zilebesiran (RNAi against angiotensinogen) and ION904 (ASO against angiotensinogen).[24,25] Results from a phase 1 study with zilebesiran showed dose-dependent decreases in serum angiotensinogen levels and 24-hr ambulatory BP, which were sustained for up to 24 weeks after a single subcutaneous injection of zilebesiran (200mg or more).[26]

Renal Denervation: Basics and Newer Clinical Data

Several device-based therapies have been studied in RH, however, the one that is more extensively investigated is catheter-based renal sympathetic denervation, which aims to interrupt the activity of afferent and efferent renal sympathetic nerves by applying radiofrequency energy, ultrasound energy, or injection of alcohol in the perivascular space.[3]

Renal denervation (RDN) first emerged as a potential treatment for RH more than a decade ago, but has recently re-emerged as an alternative for effective blood pressure lowering in these patients.[3] Early on, its utility was not fully clear due to conflicting study results, however, recent developments, improved technology and study designs have provided adequate evidence that renal denervation can be an effective treatment option.[3,27,28]

In 2019, 3 sham-controlled trials, SPYRAL HTN-ON MED, SPYRAL-HTN-OFF MED, and RADIANCE-HTN SOLO, showed that RDN (radiofrequency-based in the SPYRAL trials, and ultrasound energy in the RADIANCE-HTN trial) was effective in reducing blood pressure in patients with RH in the presence or absence of antihypertensive medications.[29-31] Additionally, data from the Global SYMPLICITY Registry, which represents the largest real-world study of hypertensive patients receiving RDN, has demonstrated the efficacy and safety of this procedure with significant and sustained office and ambulatory BP reductions in patients with RH for up to 3 years.[32,33] Furthermore, these data have also shown the efficacy of RDN in high-risk patients, including those with chronic kidney disease, high cardiovascular risk, diabetes, atrial fibrillation, RH, and in older adults;[34,35] with data also suggesting that there is a benefit of RDN in decreasing left ventricular mass, albumin-to-creatinine ratio, and albuminuria in patients with RH.[36-38] Based on these data, prediction models have suggested a potential for RDN to reduce the risk of adverse cardiovascular events in high-risk patients, including stroke, all-cause mortality, and MACE, although more studies are needed in this setting.[35]

Several trials with RDN have been published recently. Data presented at the 2021 American College of Cardiology (ACC) from the RADIANCE-HTN TRIO trial, showed that ultrasound renal denervation reduced blood pressure at 2 months in patients with hypertension and resistant to a standardized triple combination pill.39 Data from the SPYRAL HTN-ON trial showed that renal denervation produced a clinically meaningful and lasting BP reduction up to 36 months of follow-up, independent of concomitant antihypertensive medications and without major safety concerns.[40] Additionally, recent topline results from RADIANCE II trial showed that ultrasound renal denervation significantly reduced daytime ambulatory systolic blood pressure when with a sham procedure at 2 months in patients with mild to moderate uncontrolled hypertension.41 Furthermore, data from the SPYRAL HTN-ON MED trial were presented at the 2022 AHA meeting, showing that it met some important secondary endpoints compared to sham controls, such as improvements in office-based systolic blood pressure, as well as meeting its primary safety endpoint, however, the primary efficacy endpoint of a change in 24-hr systolic ambulatory BP monitoring at sixth months was not met.42 More recently, data from the 36-month follow up of the SYMPLICITY study (SIMPLICITY HTN-3) were published, further supporting the efficacy and safety of this procedure, including reductions in mean office and 24-hr BP measurements compared to sham

(-22.1 mmHg vs. sham at 36 months with office measurements; -16.5mmHg vs. sham at 36 months with 24-hr ABPM).[43]

A patient-level analysis of the RADIANCE II, RADIANCE-HTN SOLO, AND RADIANCE-HTN trial trials showed that BP reductions with renal denervation were consistent across HTN severity compared to sham control at 2 months, with consistency across trials.[44] In terms of safety, the totality of the studies to date have shown that RDN intervention preserved renal function and re-interventions are rare, with low incidence of renal stenting.[27, 45-47]

In addition, there have been questions about any sex-related differences in response to renal denervation. A recent expert perspective highlighted that no clear sex-based evidence can be generated due to the under-representation of women in clinical trials, limited data, and lack of pre-specified sex-based analysis, and concluded that more data are needed, including increasing enrollment of women in clinical trials.[48]

Renal Denervation: Updates to guidelines and position statements

In 2018, the ESC/ESH guidelines for the management of hypertension did not recommend RDN as a routine treatment, citing the need for additional evidence in this setting, and the 2017 US. guidelines do not even mention RDN.[49,50] However, recent position statements, such as that from the European Society of Hypertension, as well as from the ESC Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) state that RDN is an evidence-based option to treat HTN in addition to lifestyle changes and BP-lowering pharmacotherapy, as it expands the therapeutic options for HTN treatment, is relatively safe, and it is a viable alternative or additive strategy in this setting.[27, 51]

As mentioned above, the new 2023 ESH guidelines now have included RDN as part of the treatment algorithm for true resistant hypertension (Figure 2).[10] They recommend that RDN can be considered as an additional treatment option in patients with resistant hypertension if eGFR >40 ml/min/1.73m2, and patient selection for RDN should be done in a shared decision-making process (Figure 3).[10]

In addition, based on this evidence, in November 2023, the FDA approved both the ReCor and Medtronic renal denervation devices for the treatment of HTN as adjunctive to lifesstyle changes and pharmacotherapy.[52,53] The approval for the ReCor ultrasound device was based on the data from RADIANCE II, RADIANCE-HTN SOLO and RADIANCE-HTN TRIO, and the approval of the Medtronic Symplicity system on data from the SPYRAL clinical program.

Recommendations and statements	CoR	LoE
RDN can be considered as a treatment option in patients an eGFR >40 mil/min/1.73^2 who have uncontrolled BP despite the use of antihypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life.	II	B
RDN can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 ml/min/1.73m^2.	II	B
Selection of patients to whom RDN is oddered should be done in a shared decision-making process after objective and complete patient's information.	I	C
Renal denervation should only be performed in experienced specialized centers to guarantee appropriate selection of eligible patients and completeness of the denervation procedure.	I	C

Figure 3 – Use of renal denervation – 2023 ESH guidelines[10]

Conclusion

Resistant hypertension is a major challenge and has significant implications for increased cardiovascular risk in women, who are more likely than men to develop resistant hypertension. Conventional hypertension treatment options are often not successful in this setting, and several approaches are currently in development that may help address some of these treatment gaps in the near future. However, additional studies are needed to better inform the potential role of these emerging therapies for the treatment of RH. These treatments will most likely be in addition to current pharmacotherapy, particularly in the case of RDN, which may address the current gaps in pill burden and adherence concerns in difficult to treat patients.[54]

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