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Guidelines

Hypertension Canada's 2020 Evidence Review and Guidelines for the Management of Resistant Hypertension

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ABSTRACT

We present Hypertension Canada's inaugural evidence-based recommendations for the diagnosis and management of resistant hypertension. Hypertension is present in 21% of the Canadian population, and among those with hypertension, resistant hypertension has an estimated prevalence from 10% to 30%. This subgroup of hypertensive individuals is important, because resistant hypertension portends a high cardiovascular risk. Because of its importance, Hypertension Canada formed a Guidelines Committee to conduct a review of the evidence and develop recommendations for the diagnosis and management of resistant hypertension. The Hypertension Canada Guidelines Committee recommends that patients with blood pressure above target, despite use of 3 or more blood pressure-lowering drugs at optimal doses, preferably including a diuretic, be identified as those with apparent resistant hypertension. Patients identified with apparent

RÉSUMÉ

Nous présentons ici les premières recommandations d'Hypertension Canada, basées sur des données probantes, pour le diagnostic et la prise en charge de l'hypertension résistante. L'hypertension est présente dans 21 % de la population canadienne, et parmi les personnes souffrant d'hypertension, l'hypertension résistante a une prévalence estimée entre 10 % et 30 %. Ce sous-groupe d'individus hypertendus est important, car l'hypertension résistante laisse présager un risque cardiovasculaire élevé. Compte tenu de son importance, Hypertension Canada a formé un comité des lignes directrices pour effectuer un examen des données probantes disponibles et élaborer des recommandations pour le diagnostic et la prise en charge de l'hypertension résistante. Le comité des lignes directrices d'Hypertension Canada recommande que les patients dont la pression artérielle est supérieure à la valeur cible, malgré l'administration d'au moins trois médicaments

Elevated BP is the most robust risk factor for many adverse cardiovascular (CV) outcomes, including stroke, heart failure, and CV mortality. In particular, those with RHT have an even greater risk for adverse CV outcomes. Among patients with established hypertension, the prevalence of RHT has been estimated to be up to 10%-30%.[1] Risk factors for RHT include diabetes, obesity, and other adverse lifestyle factors, which are increasing in prevalence worldwide.[2,3] RHT is predominantly associated with an increased sodium intake and sodium retention, inappropriately elevated aldosterone levels, and to a lesser degree, sympathetic nervous system activation.[1] In addition, BP targets have become lower in recent years with the publication of data from large prospective randomized controlled trials (RCTs) that have shown improved outcomes with stricter BP control.[4-7] Taken together, the prevalence of RHT is therefore expected to increase, along with the higher risk of consequent adverse clinical outcomes, including CV morbidity and mortality.

On the basis of these factors, Hypertension Canada's target audience expressed a need for guidance on the management of RHT. In response, a Resistant Hypertension Subgroup was formed in 2018 to synthesize the evidence on RHT and develop BP management guidelines. These inaugural Hypertension Canada guidelines for RHT are intended to provide a framework for evidence-based care of RHT. As with all

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resistant hypertension should be assessed for white coat effect, nonadherence, and therapeutic inertia, investigated for secondary hypertension, and referred to a provider with expertise in hypertension. There is no randomized controlled trial evidence for better cardiovascular outcomes with any class of antihypertensive agent at this time, so recommendations for a preferred drug class cannot be made. Furthermore, we provide a summary of the current evidence concerning the role of device therapy in the management of resistant hypertension. We will continue updating the guidelines as additional high-quality evidence with relevance to daily practice becomes available.

hypotenseurs à des doses optimales, incluant de préférence un diurétique, soient identifiés comme souffrant d'hypertension résistante apparente. Les patients identifiés comme présentant une hypertension résistante apparente doivent être évalués pour l'effet blouse blanche, la non-observance, l'inertie thérapeutique, doivent faire l'objet d'une investigation pour une hypertension secondaire et être référés à un prestataire de soin spécialisé dans l'hypertension. Il n'existe pas à l'heure actuelle de données issues d'essais contrôlés randomisés ayant de meilleurs résultats cardiovasculaires avec une quelconque classe d'antihypertenseurs, de sorte qu'il n'est pas encore possible de faire des recommandations pour une classe de médicaments privilégiée. En outre, nous présentons un condensé des données actuelles concernant le rôle des thérapies par dispositifs d'assistance dans la gestion de l'hypertension résistante. Nous continuerons à mettre à jour les lignes directrices au fur et à mesure que des données probantes supplémentaires de haute qualité et pertinentes pour la pratique quotidienne seront disponibles.

guidelines, practitioners should use their own clinical judgement and are advised to consider patient preferences, values, and clinical circumstances when determining how to best apply these guidelines to individual patients.

Methods

The Hypertension Canada guidelines are developed annually through a highly structured and systematic process designed to minimize bias. Hypertension Canada's guideline process has been externally reviewed and is in concordance with the **A**ppraisal of **G**uidelines for **Re**search and **E**valuation (AGREE) II instrument for guideline development (guidelines.hypertension.ca/about/overview-process).[8,9] The Hypertension Canada Guidelines Committee (HCGC) is comprised of a multidisciplinary panel of content as well as methodological experts divided into 7 sections, which include 16 subgroups in total in distinct areas of hypertension (see Supplemental Appendices S1 and S2 for list of members and conflicts of interest, respectively).[10] The RHT subgroup consisted of 7 members, experts in hypertension with a broad range of expertise, including general internal medicine and nephrology. The comprehensive literature search was performed by a highly trained medical librarian on the basis of key words and terms provided by the subgroup. The initial literature search was performed in April 2019 up until that date (details of search strategies and retrieved articles are available upon request). Additional literature review of related guidelines on RHT, review articles on the topic, as well as citations from these articles was then subsequently conducted. The literature was reviewed independently by subgroup members and graded using the standardized method developed by Hypertension Canada and according to the Hypertension Canada guidelines established process.[11] The process for grading evidence takes into account the types of study design, and reported outcomes. Specific for pharmacotherapy, a guideline statement requires supporting evidence from an RCT with clinically relevant outcomes, in addition to change in BP. The proposed guidelines were then reviewed by the RHT section chair and presented to the Central Review Committee, comprised of unbiased methodological experts, to ensure that the guidelines reflected the evidence and to verify proposed grading. The draft guidelines and supporting evidence were presented to the HCGC in Edmonton, Alberta, on September 25, 2019. After the discussions, the guidelines were further revised and finalized for an electronic vote by all 81 members of the HCGC, with $>$ 70% support required for approval of each new guideline. Guidelines for the diagnosis, assessment, prevention, and treatment of hypertension in adults and children are published separately.[10]

Key Messages

- Resistant hypertension (RHT) is defined as blood pressure (BP) above target despite 3 or more BP-lowering drugs at optimal doses preferably including a diuretic.
- Accurate office and out-of-office BP measurement is essential.
- Other reasons for apparent RHT should be eliminated before diagnosing true RHT, including nonadherence, white coat effect, and secondary hypertension.
- Optimize drug therapy, using longer-duration medications and a diuretic, preferably thiazide-like (ie, chlorthalidone or indapamide). Increase the doses to the highest tolerated level.
- Review adherence and consider obstructive sleep apnea in patients with suspected RHT.
- Health behaviour modification, including a reduction in dietary sodium intake, might still be beneficial in patients with suspected RHT.
- Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone.
- The evidence for device therapy is currently inconclusive to make any recommendation.

Hypertension Canada's 2020 Guidelines on Resistant Hypertension

Epidemiology of RHT

RHT is defined as having a BP above target with use of at least 3 medications, at optimal doses, including a diuretic. True RHT is diagnosed when causes of pseudoresistance and secondary causes are further excluded. Causes of pseudoresistance, also termed "apparent treatment-resistant hypertension" include medication nonadherence, white coat effect, and treatment inertia. Population studies mostly do not exclude causes of pseudoresistance, and the outcomes reported in the literature thus relate to what is termed apparent treatment-resistant hypertension in the following section.

Prevalence of RHT

A systematic review of 91 studies including 3,207,911 patients being treated with hypertension estimated the prevalence of apparent treatment-resistant hypertension at 14.7%, and of true RHT at 10.3%.[12] The prevalence was higher in the elderly (12.3%), those with chronic kidney disease (22.9%), and kidney transplant recipients (56.0%).[12] In a longitudinal study from the United Kingdom it was estimated that the incidence of RHT among hypertensive individuals increased from 0.93 per 100 patient years to 2.07 per 100 patient years from 1996 to 2004, accompanied by a similar increase in prevalence.[13] The prevalence also depends on the definition of RHT, as illustrated in this analysis of the National Health and Nutrition Examination Survey, which reported a prevalence of 17.7% with the BP threshold of $>$ 140/90 and a higher estimate of 19.7% using the 2018 revised guideline of $>$ 130/80 from the American Heart Association/American College of Cardiology.[5,14,15]

RHT is associated with CV and renal outcomes

Apparent treatment-resistant hypertension is associated with a higher risk of adverse CV outcomes compared with patients without RHT, from large epidemiological studies, as summarized in Table 1.[16-21] A registry analysis of 205,750 patients with incident hypertension reported that the risk of CV outcomes was higher in patients with apparent treatment-resistant hypertension, with a hazard ratio (HR) of 1.47 (95% confidence interval [CI], 1.33-1.62).[17] Another study of 9974 patients with apparent treatment-resistant hypertension reported an HR of 6.32 (95% CI, 4.30-9.30) for incident end stage kidney disease.[21] Even for patients with controlled RHT (defined as BP $<$ 140/90 with use of 4 or more BP-lowering drugs), there was a higher risk of CV (HR, 1.86; 95% CI, 1.10-3.15) and all-cause mortality (HR, 1.64; 95% CI, 1.07-2.52).[20] This study also reported a higher risk of the same outcomes for uncontrolled vs controlled RHT.[20]

Diagnosis of Resistant Hypertension

The diagnosis of RHT should take into account proper office and out-of-office BP measurement, optimization of pharmacotherapy taking into consideration clinical inertia, and an assessment of adherence, in addition to other factors as described in Table 2 and Figure 1.

BP measurement

Cohort studies that have evaluated prognosis as well as some RCTs in this population have most commonly used office BP measures to identify patients with RHT. However, in a study of 8295 patients with RHT on the basis of office BP being above target, 24-hour ambulatory BP monitoring (ABPM) revealed that 37.5% had controlled BP.[13] Thus, the

Table 1. Summary of cardiovascular risk associated with resistant hypertension

Reference	Patient population	Cardiovascular risk (95% CI)
Bangalore et al.[16]	10,001 patients with CAD enrolled in Treating to New Targets Trial, RHT defined as: (1) BP $>$ 140 mm Hg despite use of 3 anti-HTN medications; or (2) BP $<$ 140 mm Hg with $\geq$ 4 anti-HTN medications	MACE (1) HR, 1.64 (1.39-1.94) (2) HR, 1.49 (1.15-1.95)
Daugherty et al.[17]	Retrospective cohort study including 205,750 patients, 2 health plans within Cardiovascular Research Network hypertension registry in 2002-2006, RHT defined as use of $\geq$ 3 anti-HTN medications	MACE and CKD HR, 1.47 (1.33-1.62)
Smith et al.[19]	927 Women with ischemic heart disease, RHT defined as BP $\geq$ 140/90 mm Hg with use of $\geq$ 3 anti-HTN medications or BP $<$ 140/90 mm Hg using $\geq$ 4 anti-HTN medications	MACE HR, 3.25 (1.94-5.43)
Tanner et al.[21]	9974 Patients with HTN without ESKD at baseline, older than 45 years, RHT defined as BP $\geq$ 140/90 mm Hg with use of $\geq$ 3 anti-HTN medications (including diuretic) or BP $<$ 140/90 mm Hg using $\geq$ 4 anti-HTN medications	ESKD incidence HR, 6.32 (4.30-9.30)
van der Sande et al.[20]	6191 Patients with controlled RHT defined as BP $<$ 140/90 mm Hg using $\geq$ 4 anti-HTN medications, uncontrolled RHT as BP $\geq$ 140/90 mm Hg with use of $\geq$ 3 anti-HTN (including diuretic) medications	• Controlled RHT vs controlled HTN HR, 1.86 (1.10-3.15) CV mortality HR, 1.64 (1.07-2.52) all-cause mortality • Uncontrolled RHT vs controlled HTN HR, 1.36 (1.01-1.83 CV mortality) HR, 1.27 (1.01-1.60 all-cause mortality)

BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; ESKD, end stage kidney disease; HR, hazard ratio; HTN, hypertension; MACE, major adverse cardiovascular event; RHT, resistant hypertension.

Table 2. Diagnostic aspects in suspected resistant hypertension

- Accurate office BP measurement
- Out-of-office BP measurement, preferably with a 24-hour ABPM
- Optimize BP-lowering drug choice and dosages
- Evaluation of target organ damage
- Review adherence
  - Indirect measures (eg, pill counts, pharmacy refill data)
  - Direct measures as appropriate (therapeutic drug monitoring, direct observed testing)
- Assess for sleep apnea

ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

measurement of out-of-office BP, preferably ABPM, in addition to an accurate, standardized, office BP measurement, should be undertaken to exclude white coat effect. If access to ABPM is not feasible, home BP monitoring may be used to exclude white coat effect.

Optimization of pharmacotherapy

The first-line drugs recommended for management of hypertension are renin angiotensin system blockade (either angiotensin converting enzyme inhibitors or angiotensin receptor blockers), dihydropyridine calcium channel blockers, and thiazide-like diuretics with longer-acting diuretics preferred (ie, indapamide or chlorthalidone).[4] Choice of these 3, the so-called "A-C-D" combination drug classes is commonly, though not exclusively, used as an inclusion criterion for RCTs in RHT populations.[22] However, no RCT has been done to establish that these 3 drug classes used in combination are superior to other combinations (especially with other diuretic agents) in patients with RHT, particularly for reducing CV outcomes. Additionally, the choice of other BP-lowering drugs might be dictated by intolerance to one of the first-line drugs. Hence, there is inadequate evidence to support specific drug classes, and dosages for the diagnosis of RHT.

Another cause of pseudoresistance is the use of exacerbators of hypertension and clinical inertia. Drug exacerbators of hypertension are listed in Table 3, and whenever possible, should be discontinued to help in improvement in BP. Clinical or therapeutic inertia and improper drug choice or dosage might also contribute to apparent RHT. Clinical inertia is relatively common and is defined as whenever the care provider does not initiate or intensify therapy appropriately when therapeutic goals are not reached.[23] Inertia might be deliberate, particularly in cases of severe clinical and/or social complexity, however it remains a significant contributor to pseudoresistance.

Adherence

The prevalence of nonadherence in apparent RHT is quite high, with a systematic review of 24 studies reporting a pooled prevalence of 31.2% nonadherence.[24] In a trial of a fourth-line agent in patients with RHT, from the 1597 participants enrolled with apparent RHT, only 187 were eligible for randomization, because 72% of the original cohort actually had controlled hypertension after good adherence was assured.[25] Supporting the higher estimate for nonadherence are granular data from a systematic review, which reported very high heterogeneity ($I^2 = 99.5\%$) with the range of reported nonadherence in individual studies ranging from 3% (assessed with medication possession ratio) to 86% (assessed with therapeutic drug monitoring). Direct measures of nonadherence such as direct observed therapy and therapeutic drug monitoring might provide a more accurate assessment of adherence but are resource-intensive and not widely available

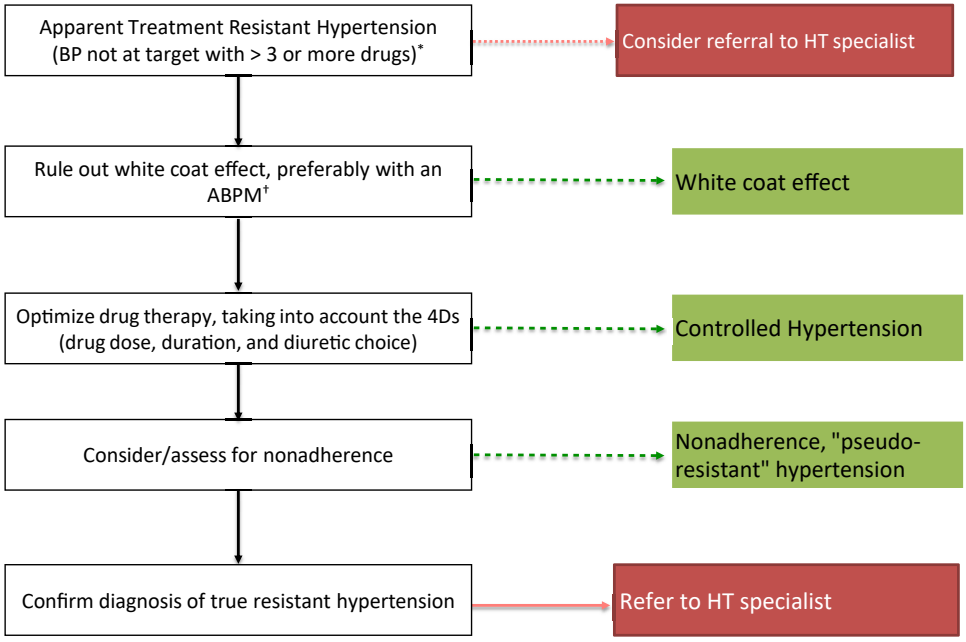

Figure 1. Diagnostic algorithm for a patient with suspected resistant hypertension. ABPM, ambulatory blood pressure monitoring; BP, blood pressure; HT, hypertension. *Three or more drugs, at optimally tolerated dosages, and preferably including a diuretic. †Home BP monitoring can be performed if ABPM is not accessible.

Table 3. Therapeutic strategies in resistant hypertension

Review and reiterate lifestyle measures (sodium and potassium intake, stress, exercise, alcohol)
Improve adherence
When possible, eliminate drugs and substances causing higher blood pressure (eg, calcineurin inhibitors, licorice, erythropoietin, tyrosine kinase inhibitors, nonsteroidal anti-inflammatory drugs, cocaine, amphetamines, oral contraceptive agents, sympathomimetics, corticosteroids)
Add pharmacotherapy; evidence of significant blood pressure-lowering exists for:
• Spironolactone, eplerenone, amiloride
• α- and β-adrenergic antagonists
• Clonidine
Evaluate and refer if secondary hypertension suspected:
• Primary hyperaldosteronism (see Hypertension Canada guidelines[10] on endocrine hypertension)
• Renovascular hypertension (see Hypertension Canada guidelines[10] on renovascular hypertension)
• Pheochromocytoma and paraganglioma (see Hypertension Canada guidelines[10] on endocrine hypertension)
• Other causes of secondary hypertension

in most centres.[24,26] Use of pharmacy prescription databases or self-reported nonadherence questionnaires are options, however, they might underestimate the true extent of nonadherence (see data in Table 4). Thus, although it is agreed that nonadherence is an important contributor to pseudo-RHT, there is little consensus on the preferred method for assessment of adherence.

Diagnostic thresholds

Although most previous studies (and other guideline bodies) have used BP of 140/90 mm Hg as the cutoff in the definition of RHT (Table 5), we elected not to use a single threshold for the following reasons: (1) the BP readings depend on the measurement method, being commonly lower when automated office BP is used; and (2) the target for BP varies on the basis of associated CV risk (ie, BP < 140/90 mm Hg for those with no compelling indications, < 130/80 mm Hg in those with diabetes, and systolic BP [SBP] < 120 mm Hg for those at high CV risk; Table 6).[4] Hence the definition for diagnosis of RHT should take these factors into account. For these reasons we, therefore, refrained from providing a specific single cutoff value in the definition of RHT.

With the recent recommendation for intensification of BP-lowering to < 120 mm Hg systolic for high-risk patients on the basis of the **S**ystolic Blood **Pr**essure **In**tervention **T**rial (SPRINT), additional patients now do meet the definition for RHT.[7] A subanalysis of SPRINT provides insight on the ramifications of this aspect. It was performed comparing 1397 participants with RHT with 7698 without, with the target BP of intensive SBP of < 120 vs < 140 mm Hg.[27] Intensified BP-lowering led to an improvement in major adverse CV event rates in patients with RHT with a HR of 0.62 (95% CI, 0.40-0.96; $P = 0.03$). Less than 2% of the patients in the intensive-treated group were receiving 5 or more medications. Mean follow-up was 3.1 years and major adverse CV event rates were > 50% higher in patients with RHT. Of interest, the benefit of intensified BP-lowering was mostly limited to those patients who were able to achieve the SBP target of < 120 mm Hg. This suggests that additional therapy to achieve intensive BP targets is appropriate in a high CV risk patient, similar to those included in SPRINT, but those who do not respond are at higher risk and it is not known whether further intensifying therapy beyond 4 antihypertensive agents will improve their outcomes, or just add to iatrogenic complications.

Last, according to the previous discussion, it is clear that a multidisciplinary team, involving nurses and pharmacists might be more appropriate for the assessment and the complex care of an individual with suspected or confirmed RHT. The proper establishment of the diagnosis of true RHT requires resources that are more likely to be available in a referral practice with providers having expertise in hypertension management.

Guidelines

1. We recommend patients with RHT, defined as BP above target despite use of 3 or more BP-lowering drugs at optimal doses preferably including a diuretic, be referred to a provider with expertise in hypertension management, for diagnostic (Table 2) and therapeutic (Table 3) purposes (grade D).

Management

The literature around nonpharmacological as well as pharmacological management in patients with RHT is

Table 4. Adherence assessment methods and estimates in resistant hypertension

Method	Estimate of nonadherence*	Comments
Indirect method		
Medication possession ratio	3 (1-12)	This is the sum of the days' supply for all fills of a given drug in a particular time period, divided by the number of days in the time period
Self-report	13 (5-28)	Self-explanatory; easy to assess
Physician interview	13 (8-21)	Self-explanatory; easy to perform
Medical event monitoring system	16 (4-49)	Usually is a cap that fits on standard medicine bottles and records the time and date each time the bottle is opened and closed; usually used in research settings
Prescription refill	19 (2-69)	Requires some time and resources
Direct method		
Direct observed therapy	45 (24-67)	Requires significant time and resources; see details
Serum/urine assay	49 (37-61)	Mostly performed in research settings; expensive

*Data from Durand et al.[24]; numbers refer to pooled nonadherence estimate reported (ie, 0% = perfect adherence and 100% = perfect nonadherence) with 95% confidence intervals in parenthesis.

Table 5. Comparison of existing guidelines for diagnosis of resistant hypertension with Hypertension Canada 2020 guidelines

Guideline	ESH 2018[6]	AHA-ACC 2018[5]	Hypertension Canada 2020 (current document)
BP threshold	SBP > 140 mm Hg and/or DBP > 90 mm Hg	SBP > 130 mm Hg and/or DBP > 80 mm Hg	Above target
Number of antihypertensive medications	≥ 3 Optimally tolerated or best tolerated	≥ 3 Maximum or maximally tolerated, appropriate dosing intervals	≥ 3 Drugs from different classes, at optimally tolerated dosages, used simultaneously
Class of antihypertensive medications	ACEi/ARB, CCB, diuretic	3 Different classes, commonly ACEi/ARB, CCB, diuretic	≥ 3 Drugs of different classes, preferably including a diuretic
Method of BP measurement	Confirmed with ABPM or HBPM	Consider ABPM or HBPM	Confirm with ABPM
Adherence	Confirmed	Assess	Assess

ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin converting enzyme inhibitor; AHA-ACC, American Heart Association-American College of Cardiology; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; ESH, European Society of Hypertension; HBPM, home blood pressure monitoring; SBP, systolic blood pressure.

discussed in this section. As previously mentioned, a recommendation for pharmacotherapy requires RCT-level evidence of clinically relevant outcomes, which have not been undertaken in the RHT population. Even in the absence of a specific guideline, the literature in this area is discussed in the following sections, and summarized in Tables 6 and 7 and in Figure 2.

Nonpharmacological management

In all patients with hypertension, the Hypertension Canada guidelines recommend a reduction in sodium intake and an increase in dietary potassium as well as a diet concordant with the dietary approaches to stop hypertension, reduction in stress, reduction in weight, and decreasing alcohol intake for decreasing BP.[4] Specifically, in the RHT population, these factors still play a role and are worth reviewing with the patient.[1] In terms of evidence, there is 1 small trial of 12 patients with RHT whose sodium intake decreased from a mean of 252 mmol/d to 46 mmol/d with an accompanying BP reduction of 22.7/9.1 mm Hg.[23] There are no RCTs that have reported clinically relevant outcomes with health behaviour modifications in the RHT population.

Pharmacological management

There are few high-quality data from RCTs as well as systematic reviews that have evaluated the fourth agent, summarized in Table 7. Most trials are limited because they are short-term and assess efficacy in BP-lowering but not CV end points or mortality. Systematic reviews indicate that spironolactone reduces BP to a greater extent than other antihypertensive agents. However, there is significant variability in the form of BP measurements, clinical outcomes, and patient populations (eg, unselected RHT, RHT and diabetes only, or end-stage kidney disease). Additionally, from the clinical trial data, doxazosin, bisoprolol, amiloride, and clonidine also reduce BP more than placebo in this population. Hence the HCGC does not provide a guideline for a preference to use a specific drug as the fourth agent in the RHT population. The literature supporting the BP reduction strategies is discussed in the following section in detail and might be helpful to the clinician for decision-making with respect to drug choice.

Table 6. Blood pressure thresholds for diagnosis of resistant hypertension

Description	BP threshold
Diabetes	Systolic BP > 130 mm Hg or diastolic BP > 80 mm Hg
High cardiovascular risk Age older than 75 years Age older than 50 years and GFR 20-59 mL/min/1.73 m^2 Clinical or subclinical CV disease Estimated 10-year global risk* > 15%	Systolic BP > 120 mm Hg
No other compelling indication	Systolic BP > 140 mm Hg or diastolic BP > 90 mm Hg

BP, blood pressure; CV, cardiovascular; GFR, glomerular filtration rate.
*On the basis of Framingham Risk Score.

Choice of fourth agent: effect on BP. The **P**revention **a**nd **T**reatment of **H**ypertension **W**ith **A**lgorithm Based Therap**y-2** (PATHWAY-2) trial evaluated the effect on home BP control of 3 different antihypertensive agents as add-on therapy.[22] The trial included 314 patients with RHT who were randomized to sequentially taking spironolactone, bisoprolol, doxazosin, or placebo in 12-week crossover periods on a background of baseline BP-lowering drugs.[22] The outcome was a reduction in home SBP compared with placebo, which was greatest with spironolactone (−8.70 mm Hg [95% CI, −9.72 to −7.69]), compared with doxazosin (−4.03 mm Hg [94% CI, −5.04 to −3.02]) and vs bisoprolol (−4.48 mm Hg [95% CI, −5.50 to −3.46]); doxazosin and bisoprolol also lowered SBP significantly compared with placebo. An open-label extension of this trial also showed a similar SBP reduction with amiloride (at a 10-mg daily dose) of 20.4 mm Hg compared with spironolactone (25 mg daily), which reduced SBP by 18.3 mm Hg.[28] The **A**ddition of **Sp**ironolactone **i**n Patients With **R**esist**an**t Arterial Hyper**t**ension-**Ext**ension (ASPIRANT-EXT) RCT also compared spironolactone with placebo in 161 patients with RHT, and is notable for reporting ABPM, with a decrease in 24-hour SBP of 10.5 mm Hg and diastolic BP (DBP) of 3.5 mm Hg with spironolactone compared with placebo.[27] The **Re**sistant **Hy**pertension **O**ptimal **T**reatment (ReHOT) trial included 187 patients with RHT randomized to spironolactone compared with clonidine as additional therapy.[25] At 3 months, the mean change from baseline in office BP (in mm Hg) was similar between spironolactone (−15.1 for SBP and −7.7 for DBP) and clonidine (−13.7 and −6.4, respectively). However, the

Table 7. Summary of major trials of pharmacotherapy in resistant hypertension

Study	Patient population	Intervention	Outcomes	Comments
PATHWAY-2[22]	N = 314 RHT on the basis of A-C-D combination	12-Week crossover of spironolactone, bisoprolol, doxazosin, and placebo	Greater BP reduction with spironolactone compared with placebo (−8.70 mm Hg), doxazosin (− 4.03 mm Hg), and bisoprolol (−4.48 mm Hg)	Open-label trial, relied on home BP for outcome assessment; 2% of patients developed hyperkalemia (K^+ > 6 mmol/L) with spironolactone
PATHWAY-2 extension[28]	N = 146 Open-label run-out substudy of PATHWAY-2	Amiloride 10 mg compared with spironolactone 25 mg orally daily	BP change similar Amiloride: 20.4 mm Hg (95% CI, 18.3-22.5) Spironolactone: 18.3 (95% CI, 16.2-20.5)	
ReHOT trial[25]	N = 187 patients with RHT	Spironolactone 12.5-50 mg (mean dose 40 mg) vs clonidine 0.1-0.3 mg twice daily (mean dose, 0.35 mg)	Office BP reduction similar with spironolactone (15.1/7.7 mm Hg) vs clonidine (13.7/6.4 mm Hg)	Greater reduction in 24-hour ABPM with spironolactone (11.8 vs 7.3 mm Hg)
Sinnott et al.[29]	Systematic review Included 5 studies, 755 patients	AAs compared with active comparators	AAs reduced BP more than active comparator (7.5 mm Hg; 95% CI, 3.2-11.6)	Pooled analysis of nonrandomized studies shows greater BP-lowering with AAs (11.9 mm Hg; 95% CI, 9.3-14.4)
Sinnott et al.[32]	Propensity matched study N = 8639 with apparent RHT n = 5420 (α-blockers) n = 350 AAs n = 2869 (β-blockers)	AAs compared with α- and β-adrenergic antagonists	CV outcomes worse with AAs HR, 0.81 (95% CI, 0.55-1.19) vs β-blockers HR, 0.68 (95% CI, 0.46-0.96) vs α-blockers	Likely residual confounding; BP change was 2 mm Hg lower with AAs compared with α/β blockers at 12 weeks, but not significant at 2 years

AA, aldosterone antagonist; ABPM, ambulatory blood pressure monitoring; A-C-D, angiotensin converting enzyme inhibitor/angiotensin receptor blocker with calcium channel blocker and diuretic; BP, blood pressure; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; PATHWAY-2, **P**revention **a**nd **T**reatment of **H**ypertension **W**ith **A**lgorithm Based Therap**y-2**; ReHOT, **Re**sistant **H**ypertension **O**ptimal **T**reatment; RHT, resistant hypertension.

decrease in 24-hour ABPM (in mm Hg) was greater with spironolactone (−11.8 for SBP and −6.3 for DBP) than with clonidine (−7.3 and −3.9, respectively). These findings are confirmed in several systematic reviews, which all report a high degree of statistical heterogeneity, but overall a greater BP-lowering effect of spironolactone compared with placebo (−17 mm Hg [95% CI, 25.0-9.0]), and also with active comparators (−7.4 mm Hg [95% CI, 3.2-11.6]).[29,30]

Choice of fourth agent: effect on clinical outcomes. As is apparent, the RCTs discussed in the previous section are all of a short duration, up to 3 months, and hence there are scant data on the benefit of specific pharmacotherapy on clinically relevant outcomes (eg, CV morbidity and mortality). Further, they all reported lower BP with additional medication, but the greatest lowering with spironolactone. Additional use of spironolactone with a baseline regimen including renin-angiotensin system blockade represents dual blockade of the renin-angiotensin-aldosterone system, with potentially downstream increased risk of hyperkalemia or acute kidney injury in the long term.[31] A large epidemiological study including 8639 patients with RHT, used propensity score matching to compare outcomes across aldosterone antagonists as reference with α- and β-adrenergic antagonists.[32] The study reported that the latter 2 classes had a lower risk of adverse CV outcomes, with an HR of 0.68 for α-adrenergic antagonists and an HR of 0.81 for β-blockers. This result is likely due to residual confounding, as the authors acknowledge, but does not engender confidence in the long-term benefit of specific drug classes in patients with RHT. Additionally, there exists a probability that the RHT population is enriched with patients having hitherto undiagnosed primary aldosteronism, which partially explains the superior BP-lowering effect shown with spironolactone. In this line, subsequent analysis from the PATHWAY-2 study reported 25% of patients having an inappropriately elevated plasma aldosterone concentration, with a strong correlation between BP-lowering effect and the aldosterone-renin concentration ($r^2 = 0.13$; $P < 0.0001$).[28] However, the superior benefits of spironolactone in PATHWAY-2 extended across the range of renin levels except among those with very high renin levels in whom β-blockers were more effective. Nevertheless, the overall literature supports that pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone. Of note, there have been no head to head comparisons of eplerenone with spironolactone. None of the studies assessed whether there were racial or sex differences in the response to these agents. Hence, the absence of longer-term clinical outcome data from RCTs does not support a preference of a specific drug choice, with individualization to be on the basis of clinical judgement and adverse effect profile.

Device Therapy

In this section, the HCGC considered all interventions including renal sympathetic denervation, arteriovenous fistula, and baroreceptor activation therapy. Although there are several ongoing clinical trials, as of the writing of this article, none of these interventions have been approved for use in Canada.

Lumbar sympathectomy was known to effectively lower BP, and was performed in the era before availability of pharmacotherapy, however, because it was associated with serious adverse effects, it rapidly fell out of favour since the

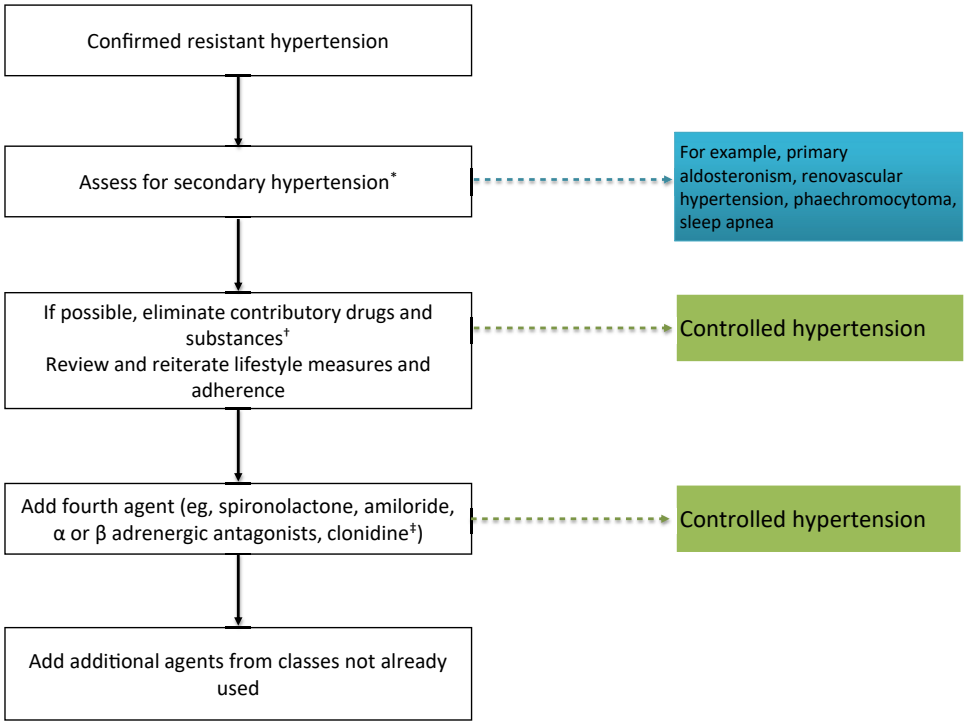

Figure 2. Management algorithm for resistant hypertension. *Refer to detailed Hypertension Canada guidelines[10] for diagnosis of specific causes of secondary hypertension. †Refer to Table 2 for details. ‡The greatest decrease in blood pressure is reported with spironolactone compared with the others.

advent of safer and effective BP-lowering drugs.[33] In the past decade, the technique of ablation of sympathetic afferents in the renal artery was developed (renal denervation [RDN]) with initial pilot studies showing a decrease of 20-30 mm Hg in SBP in office BP in patients with RHT.[34] However, the largest sham-controlled RCT, Symplicity HTN-3, did not report a significant difference between the sham and RDN arms.[35] Subsequent analysis identified several factors to contribute to this discrepancy, including aspects of study design in the previous studies (regression to mean in the uncontrolled studies, varying adherence in between arms, and information bias in the open-label, controlled studies) as well as high variance from adherence and possibly inadequate ablation in Symplicity HTN-3.[36] A subsequent meta-analysis confirmed that the pooled effect from the 3 sham controlled RCTs was not different between arms (ABPM: −1.8 for SBP [95% CI, − 4.5 to 0.9] and −0.6 for DBP [95% CI, −2.3 to 1.2]).[37] These aspects informed the design of the more recent trials that have used different multielectrode catheter designs or techniques (eg, ultrasound) to ensure more complete ablation.[38-40] Additionally, these trials have included patients with mild hypertension, either receiving no BP medications, or 1-3 medications, with observed administration of BP-lowering medications in the later design, to minimize the effect of adherence on variance. These trials do report a significant decrease in ABPM with RDN controlled for sham, albeit at a lower magnitude of 4-6 mm Hg. Notably, the follow-up in these RCTs is short (2-6 months), and there are no data on reduction in clinical outcomes from sham controlled RCTs, yet. Hence, at present, there are insufficient data to recommend the use of RDN in patients with RHT.

Baroreceptor activation therapy relies on the activation of the myogenic stretch reflex in the carotid body, which results in reduction in sympathetic activity and lowering of BP. After the initial promising pilot RCT data, the pivotal double blind Rheos RCT did not show a significant BP-lowering.[41] The proportion of responders in the group in whom the device was activated was 54% compared with 46% in the control arm ($P = 0.97$). Similarly, the decrease in office SBP was 16 ± 29 mm Hg in the active group and 9 ± 29 mm Hg for the control ($P = 0.08$). Additionally, 25% of participants had procedural adverse events.[41] Subsequently, a second-generation device has been developed; this has a single electrode, is inserted unilaterally with a potentially safer safety profile, and is undergoing ongoing trials, although focused in the heart failure population. An endovascularly delivered implant device, MobiusHD (Vascular Dynamics Inc, Irvine CA), which increases wall strain in the carotid sinus, has similarly shown promise in a pilot RCT (lowering of ABPM by 21 mm Hg) with a larger double blind RCT currently under way.[42] Arteriovenous fistula creation with a central anastomotic device was reported to reduce BP significantly in a small open-label RCT of 83 patients; however, the technique was associated with significant procedural complications in a third of the participants and is not being developed further as of the time of this writing.[43]

Thus, overall, device therapy shows promise of being an effective strategy in the future for management of RHT, but the literature presently does not support its use outside the setting of clinical research. Because of the inconclusive existing evidence at present and in the quest of forthcoming information, there was no consensus to proceed with a guideline for the use of device therapy for RHT.

Summary and Future Direction

The present guidelines summarize the best available evidence to guide clinicians in the diagnosis and management of RHT and represents 2 years of work by the RHT subgroup/section with the support of the HCGC. Some practical aspects for the clinician are presented in the Key Messages box. The next update for Hypertension Canada's guidelines related to RHT will be on the basis of a systematic review of the evidence that will be performed on an annual basis. Research priorities that have been identified include but are not limited to:

- Determine optimal initial triple drug therapy for patients with RHT including a diuretic;
- Robust long-term CV outcome data with fourth and subsequent drug effectiveness in patients with RHT;
- Role of patient partnership in assessment and management of adherence, including health behaviour;
- Economic analyses of the implications of RHT diagnosis, balancing extra referrals and investigations against the benefit of improved BP control.

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Disclosures

Please see Supplemental Appendix S2 for potential conflicts of interest.

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Supplementary Material

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