



Clinical Research

Epidemiology of Resistant Hypertension in Canada

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See editorial by Salvador and Bakris, pages 555–556 of this issue.

ABSTRACT

Background: Resistant hypertension is associated with cardiovascular morbidity and mortality. The objective of this study was to estimate the prevalence of apparent treatment-resistant hypertension in Canadian adults and examine the characteristics of those affected.

Methods: A nationally representative cross-sectional study was conducted with the use of Canadian Health Measures Survey (2007–2017) data. The frequency of respondents with uncontrolled blood pressure despite 3 or more antihypertensive medications of different drug classes (and at least 1 agent being a diuretic), or treatment with 4 or more agents regardless of blood pressure, was determined.

Results: A total of 245,700 people were identified to have apparent treatment-resistant hypertension, representing 5.3% (95% confidence interval [CI] 4.5%–6.2%) of adults treated for hypertension in Canada. Respondents who had uncontrolled blood pressure with 3 or more

RÉSUMÉ

Contexte : L'hypertension résistante au traitement est associée à une morbidité et une mortalité cardiovasculaires. L'objectif de cette étude était d'estimer la prévalence de l'hypertension apparemment résistante au traitement chez les adultes canadiens et d'examiner les caractéristiques des personnes qui en étaient affectées.

Méthodes : Une étude transversale représentative, à l'échelle nationale, a été menée à l'aide des données de l'Enquête canadienne sur les mesures de la santé (2007–2017). On a déterminé la fréquence des participants dont la pression artérielle n'était pas maîtrisée malgré la prise de trois médicaments antihypertenseurs ou plus comprenant différentes classes de médicaments (dont au moins un agent étant un diurétique), ou le traitement avec quatre agents ou plus, quelle que soit la pression artérielle.

Blood pressure (BP) control is of enormous clinical and public health importance owing to the high prevalence of hypertension, detrimental consequences of uncontrolled BP, and proven benefits of reducing high BP in terms of lowering the risks of cardiovascular disease, kidney failure, and death.^{1,2} Even so, there has been a growing care gap over the past decade in Canada, with BP control dropping from nearly 70% to less than 60% in recent years,¹ a finding associated with a corresponding rise in the rate of cardiovascular death since 2010.³ As such, a better understanding of the factors contributing to uncontrolled BP in Canada is urgently needed.⁴

Patients who are treated yet remain uncontrolled represent an important segment of the population. Apparent treatment-resistant hypertension (aTRH) may be the result of inaccurate BP measurement, suboptimal medication regimens, medication nonadherence, or unrecognised secondary causes of hypertension, all of which may be potentially amenable to targeted interventions.^{5,6} Compared with other forms of hypertension, the presence of aTRH is associated with an increased risk of cardiovascular morbidity and mortality, making identification of these individuals all the more important.^{7–9}

Accordingly, it is critical to understand the characteristics of Canadians who have difficult-to-control hypertension so that targeted interventions can be provided to improve BP control in this important subgroup to reduce sequelae. Addressing this, we used the Canadian Health Measures Survey (CHMS) to estimate the prevalence of aTRH among Canadian adults aged 20 to 79 years, and examined the characteristics of those affected in order to determine who may potentially benefit from specialised diagnostic workup, specific treatments, or targeted interventions.

Received for publication November 10, 2021. Accepted January 27, 2022.

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See page 686 for disclosure information.

antihypertensive drugs were more likely women (55.8%, 95% CI 41.1%-70.4%), 70 years of age or older (45.3% 95% CI 32.8%-57.9%), and overweight or obese (84.2%, 95% CI 72.3%-96.1%). Respondents with apparent treatment-resistant hypertension also had a high likelihood of chronic kidney disease (36.0%, 95% CI 21.4%-50.6%), diabetes (35.2%, 95% CI 21.7%-48.7%), dyslipidemia (68.0%, 95% CI 55.2%-80.8%), and history of heart attack (9.9%, 95% CI 4.8%-15.1%) or stroke (7.1%, 95% CI 0-14.4%).

Conclusions: Despite being prescribed at least 3 antihypertensive drugs, a considerable proportion of Canadians, especially women, have difficulty achieving blood pressure control, predisposing them to a higher risk of cardiovascular complications and death.

Methods

Data source

The CHMS is an ongoing cross-sectional survey designed to provide nationally representative estimates of common medical conditions by means of complex stratified sampling.^{10,11} The sampling frame covers more than 96% of the Canadian population (excluding full-time members of the Canadian Armed Forces, persons living on reserves or other aboriginal settlements, the institutionalised, and those living in some remote regions of Canada).¹⁰ Sociodemographic and health information data were collected through in-person household interviews, followed by visits to mobile examination centers for direct physical measures.^{11,12} Data for this study were from the first (2007-2009), second (2009-2011), third (2012-2013), fourth (2014-2015), and fifth (2016-2017) cycles of the CHMS.¹³⁻¹⁷ The response rates for the cycles 1 to 5 were, respectively, 51.7%, 55.5%, 51.7%, 53.7%, and 48.5%. The resulting analytic sample size was 16,602 for adults aged 20 to 79 years.

Measures and definitions

Hypertension. Respondents were considered to be hypertensive if their mean systolic blood pressure (SBP) was ≥ 140 mm Hg or diastolic blood pressure (DBP) was ≥ 90 mm Hg, or if they reported taking an antihypertensive medication in the past month.^{1,18-20} Among those with hypertension, individuals who reported using an antihypertensive medication in the past month were defined as treated, and those with a mean SBP < 140 mm Hg and DBP < 90 mm Hg were classified as controlled. Respondents with uncontrolled BP despite reporting the use of 3 or more antihypertensive medications of different drug classes (and at least 1 of them being a diuretic), or those treated with 4 or more agents regardless of BP, were defined as having aTRH, to be as consistent as possible with other studies.²¹ We also used the

Résultats : Au total, 245 700 personnes ont été identifiées comme souffrant d'une hypertension apparemment résistante au traitement, ce qui représente 5,3 % (intervalle de confiance [IC] à 95 % : 4,5 %-6,2 %) des adultes traités pour hypertension au Canada. Les participants dont la pression artérielle n'était pas contrôlée par au moins trois médicaments antihypertenseurs étaient le plus souvent des femmes (55,8 %, IC à 95 % : 41,1 %-70,4 %), étaient âgés de 70 ans ou plus (45,3 %, IC à 95 % : 32,8 %-57,9 %) et présentant une surcharge pondérale ou une obésité (84,2 %, IC à 95 % : 72,3 %-96,1 %). Les participants présentant une hypertension apparemment résistante au traitement avaient également une forte probabilité de souffrir d'une maladie rénale chronique (36,0 %, IC à 95 % : 21,4 %-50,6 %), de diabète (35,2 %, IC à 95 % : 21,7 %-48,7 %), de dyslipidémie (68,0 %, IC à 95 % : 55,2 %-80,8 %) et d'antécédents de crise cardiaque (9,9 %, IC à 95 % : 4,8 %-15,1 %) ou d'accident vasculaire cérébral (7,1 %, IC à 95 % : 0-14,4 %).

Conclusions : Bien qu'au moins trois médicaments antihypertenseurs leur ait été prescrits, une proportion considérable de Canadiens, surtout des femmes, ont de la difficulté à contrôler leur pression artérielle, ce qui les prédispose à un risque plus élevé de complications cardiovasculaires et de décès.

preferred term aTRH ("apparent treatment-resistant hypertension") rather than "resistant hypertension" because the possibility of treatment nonadherence could not be ruled out, as medication use was self-reported and adherence was not verified through assessment of pharmacologic concentrations and/or directly observed therapy.

Blood pressure. BP was measured by means of an automated office BP method using calibrated BpTRU BPM-200 and BPM-300 oscillometric devices (BpTRU Medical Devices, Coquitlam, BC).^{22,23} After 5 minutes of rest, 6 sequential measurements at 1-minute intervals were taken while unattended. The last 5 readings were then used to calculate the mean SBP and DBP for each person.²²

Medications. Antihypertensive medications were classified into drug classes according to their Anatomical Therapeutic Chemical (ATC) codes (Supplemental Table S1).^{1,18,24} Analysis was based on these discrete classes, but the final reporting was aggregated according to broader categories (eg, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers were collectively grouped into "renin-angiotensin system inhibitors").

Other factors. Diabetes was defined by self-report, a glycated hemoglobin A_{1c} of 6.5% or higher, or the use of a glucose-lowering medication (ATC code A10). Chronic kidney disease was based on a glomerular filtration rate less than 60 mL/min/1.73 m², estimated with the use of the 4-variable Modification of Diet in Renal Disease equation.²⁵ Participants who had a body mass index of 25.0 kg/m² or more were classified as overweight or obese. Personal history of dyslipidemia, heart attack, stroke, smoking, usual physical activity, and typical consumption of fruit and vegetables were based on self-report. Family history of high BP or early cardiovascular disease (ie, heart disease or stroke before the age of 60 years) was also based on self-report.

Table 1. Characteristics of Canadian adults, aged 20 to 79 years, with hypertension

Characteristics	Hypertension		Apparent treatment-resistant hypertension		
	All	Treated	All	Uncontrolled with ≥ 3 medications	Taking ≥ 4 medications
No. represented, rounded to nearest 100	5,820,400	4,605,400	245,700	109,750	135,950
Proportion among those treated, %	—	100	5.3 (4.5-6.2)	2.4 (1.7-3.1)	3.0 (2.3-3.6)
Baseline sociodemographics					
Age, years	60.4 (59.9-60.9)	61.7 (61.1-62.4)	67.5 (65.5-69.5)	66.8 (64.5-69.1)	68.1 (64.8-71.4)
Age category, %					
20-59 y	43.1 (40.7-45.5)	37.9 (35.0-40.8)	18.1 (9.5-26.7)	18.3 (4.5-32.1)	17.9 (5.4-30.3)
60-69 y	33.8 (31.7-35.9)	36.4 (34.0-38.9)	31.8 (23.4-40.2)	36.3 (23.8-48.9)	28.2 (15.8-40.6)
70-79 y	23.1 (21.3-24.9)	25.7 (23.7-27.7)	50.1 (40.8-59.3)	45.3 (32.8-57.9)	53.9 (39.9-67.9)
Men, %	53.1 (50.7-55.4)	53.3 (50.6-55.9)	58.1 (46.6-69.5)	44.2 (29.6-58.9)	69.3 (54.3-84.2)
White race, %	84.9 (80.3-89.5)	85.2 (80.3-90.2)	89.3 (81.3-97.2)	90.6 (80.6-100)	88.2 (76.5-99.9)
Marital status, %					
Married or common-law	71.7 (68.9-74.6)	72.9 (70.1-75.7)	68.9 (61.3-76.4)	73.1 (61.8-84.4)	65.5 (53.9-77.0)
Other (single, widowed, separated, or divorced)	28.3 (25.4-31.1)	27.1 (24.3-29.9)	31.1 (23.6-38.6)	26.9 (15.6-38.2)	34.5 (23.0-46.1)
Less than secondary school graduation, %	41.9 (39.4-44.5)	43.3 (40.3-46.4)	44.1 (34.2-54.1)	45.4 (31.3-59.6)	43.1 (30.8-55.5)
Anthropometrics					
Overweight or obese, %	80.5 (77.7-83.3)	82.6 (79.9-85.2)	90.7 (85.0-96.3)	84.2 (72.3-96.1)	95.9 (92.3-99.5)
Systolic blood pressure, mm Hg	127.6 (126.6-128.7)	122.9 (122.0-123.8)	132.6 (128.1-137.2)	150.8 (147.3-154.2)	118.0 (113.7-122.3)
Diastolic blood pressure, mm Hg	76.9 (76.3-77.6)	73.7 (73.1-74.4)	71.8 (69.5-74.1)	79.1 (76.2-82.0)	65.8 (63.5-68.2)
Heart rate, beats/min	67.6 (66.9-68.4)	66.9 (66.1-67.6)	63.2 (60.9-65.5)	64.9 (61.9-67.9)	61.9 (58.7-65.1)
Medications					
No. of antihypertensive medications taken in the past month	1.4 (1.4-1.5)	1.8 (1.7-1.8)	3.8 (3.6-4.0)	3.5 (3.3-3.8)	4.0 (3.8-4.3)
Antihypertensive medications by drug class, %					
Beta-blockers	20.9 (19.1-22.7)	24.6 (22.6-26.6)	69.3 (60.2-78.3)	57.4 (44.0-70.9)	78.8 (65.1-92.5)
Renin-angiotensin system inhibitors	65.3 (63.1-67.6)	75.3 (73.1-77.5)	98.4 (96.7-100.0)	NR*	NR*
Diuretics	35.7 (33.2-38.1)	42.0 (39.6-44.5)	90.7 (84.3-97.2)	100 [†]	83.2 (72.7-93.8)
Potassium-sparing diuretics	3.1 (2.4-3.8)	3.7 (2.8-4.5)	7.1 (3.4-10.8)	8.0 (1.2-14.7)	6.4 (1.9-10.8)
Calcium channel blockers	21.9 (20.1-23.7)	25.8 (23.7-27.9)	72.6 (63.1-82.2)	54.6 (39.0-70.1)	87.2 (78.1-96.4)
Other antihypertensive drugs	7.0 (5.8-8.3)	8.9 (7.3-10.4)	37.8 (27.2-48.5)	10.5 (3.5-17.5)	59.9 (47.1-72.7)
Comorbidities, %					
Chronic kidney disease	13.1 (11.7-14.6)	15.5 (13.7-17.4)	31.6 (23.2-40.0)	36.0 (21.4-50.6)	28.1 (18.5-37.7)
Diabetes	24.2 (22.3-26.1)	28.8 (26.5-31.0)	46.7 (35.3-58.0)	35.2 (21.7-48.7)	55.9 (43.1-68.8)
Dyslipidemia	52.2 (49.8-54.6)	59.6 (57.0-62.3)	79.4 (73.0-85.8)	68.0 (55.2-80.8)	88.6 (84.1-93.0)
Heart attack	8.8 (7.6-10.1)	11.0 (9.4-12.6)	22.8 (14.2-31.4)	9.9 (4.8-15.1)	33.1 (18.8-47.4)
Stroke	2.5 (1.9-3.1)	3.1 (2.4-3.9)	5.8 (2.2-9.3)	7.1 (0-14.4)	4.7 (0.4-8.9)
Family history, %					
High blood pressure	61.0 (58.7-63.4)	62.7 (60.2-65.2)	73.1 (64.5-81.7)	69.9 (54.1-85.6)	75.8 (67.8-84.0)
Early cardiovascular disease	45.6 (42.5-48.8)	46.5 (43.2-49.8)	62.0 (49.6-74.5)	64.4 (45.0-83.8)	60.1 (42.8-77.5)
Other factors, %					
Active smoking	16.1 (14.3-17.8)	15.3 (13.4-17.2)	18.4 (9.9-26.9)	11.6 (1.2-22.0)	23.8 (10.7-37.0)
< 150 min moderate to vigorous physical activity per week [‡]	81.4 (78.4-84.4)	81.9 (78.7-85.0)	88.9 (84.5-93.4)	NR*	NR*
Fruit and vegetable consumption < 5 times per day	87.0 (85.4-88.7)	87.0 (85.4-88.7)	88.0 (83.4-92.6)	87.2 (80.5-93.9)	88.7 (83.4-94.0)
Regular medical doctor	92.6 (91.1-94.0)	95.5 (94.1-96.9)	94.3 (90.5-98.1)	95.8 (91.3-100.0)	93.1 (86.6-99.6)
Framingham risk score for 10-year risk of cardiovascular disease, [§] %					
$\leq 19\%$	65.7 (63.7-67.6)	62.9 (60.6-65.1)	33.8 (22.3-45.3)	24.2 (10.6-37.7)	43.9 (23.2-64.6)
$\geq 20\%$	34.3 (32.4-36.3)	37.1 (34.9-39.4)	66.2 (54.7-77.7)	75.8 (62.3-89.4)	56.1 (35.4-76.8)

Ranges in parentheses are 95% confidence intervals. Percentages, means, and confidence intervals based on weighted estimates.

* Not reported due to small cell sizes (eg, nearly all respondents with treatment-resistant hypertension were taking a renin-angiotensin system inhibitor, and therefore very few people were not prescribed a medication from this drug class).

[†] Use of thiazide/thiazide-like diuretics was part of the definition (ie, uncontrolled blood pressure despite ≥ 3 drugs and at least 1 of them being a diuretic).

[‡] Physical activity was available only for cycles 3, 4, and 5.

[§] Framingham risk score was not calculated for individuals with known cardiovascular disease.

Statistical analysis

Data from all available cycles of the CHMS were pooled by applying respondent-specific survey weights to generate population-representative estimates, and variances were determined with the use of bootstrapping to account for the complex survey design.^{13-15,26} The proportion of respondents with aTRH was calculated and descriptive statistics of their characteristics reported. In adherence with Statistics Canada's policy, absolute numbers were rounded to the nearest 100, and estimates based on sample sizes of fewer than 5 respondents were suppressed. These cases were handled either by omitting the corresponding cells or by combining multiple subgroups together to satisfy the requirements for data release and publication. We conducted 2 sensitivity analyses to facilitate comparisons^{1,18,19}: first, recognising that BpTRU SBP and DBP measurements may be slightly lower than conventional manual BP readings,²⁷ we applied a validated correction²⁷ and used the adjusted values to determine the prevalence of hypertension and aTRH (defined by a mean SBP of ≥ 140 mm Hg or DBP of ≥ 90 mm Hg); second, we examined the proportion of people with hypertension and aTRH according to the BP threshold provided by the American College of Cardiology and American Heart Association guidelines (a mean SBP of ≥ 130 mm Hg or DBP of ≥ 80 mm Hg based on unadjusted BpTRU measurements).²⁸

We then assessed for predictors for aTRH among those who were treated for hypertension. Potential risk factors were selected *a priori* based on clinical reasoning and previous reports.²⁹ Logistic regression modelling was used to estimate risk ratios (RRs), adjusting for other covariates, and stratified according to sex. The candidate variables were all dichotomous, except age, which was modelled as a multicategorical variable (with age bands corresponding to 20-59, 60-69, and 70-79 years) to allow for the possibility of nonlinear associations. All statistical analyses were performed using Stata 16.0 (StataCorp, College Station, TX).

Results

There was a total of 26,041,200 Canadian adults represented in the survey (rounded to the nearest 100) and 5,820,400 of them had hypertension (23.2%, 95% CI 22.1%-24.4%). Of these, 79.1% (95% CI 76.4%-81.8%) were treated with at least 1 antihypertensive drug. Treated patients had a mean SBP and DBP of 122.9 and 73.7 mm Hg, respectively, and they were taking an average of 1.8 antihypertensive medications in the past month (Table 1). The mean age of treated individuals was 61.7 years, approximately half were men, and the majority were white. Being overweight or obese, engaging in less than 150 minutes of moderate to vigorous physical activity per week, and consuming fruits and vegetables less than 5 times per day were common: present in more than 80% of those treated. More than half had dyslipidemia, nearly one-third had diabetes, and more than 1 in 10 had chronic kidney disease.

Overall, aTRH was present in 245,700 of the sample, representing 5.3% (95% CI 4.5%-6.2%) of adults who were treated for hypertension in Canada, and the prevalence was similar in each cycle of the survey (Table 2). Slightly less than

half of these people with aTRH had uncontrolled BP even though they reported taking at least 3 antihypertensive medications, while the remainder were taking at least 4 antihypertensive medications in the past month. In our sensitivity analyses, the prevalence of aTRH and its individual components were broadly similar after adjusting for possible differences in measurements obtained using automatic oscillometric devices vs traditional manual BP measurements, as well as when a threshold of 130/80 mm Hg for high BP was applied (Supplemental Table S2).

Adults with aTRH had mean SBP and DBP of 132.6 and 71.8 mm Hg, respectively (Table 1). Those who had uncontrolled BP despite taking 3 or more antihypertensive drugs had mean SBP and DBP of 150.8 and 79.1 mm Hg, and those who were taking 4 or more antihypertensive drugs (regardless of BP) had mean SBP and DBP of 118.0 and 65.8 mm Hg, respectively. Nearly all respondents were taking diuretics and renin-angiotensin system inhibitors in the past month, and more than a third were also taking beta-blockers and calcium channel blockers. Respondents with aTRH were typically older and more commonly men compared with those with treated hypertension in general. Being overweight or obese and engaging in less than 150 minutes of moderate to vigorous physical activity per week were nearly 10% more frequent in those with aTRH. Respondents with aTRH, compared with those with treated hypertension in general, were twice as likely to have diabetes, chronic kidney disease, heart attack, stroke, or a family history of high blood pressure or premature cardiovascular disease. In contrast to most patients with hypertension (where the risk of incident cardiovascular disease was estimated to be low to moderate), two-thirds of those with aTRH were at high cardiovascular risk based on the Framingham risk score.

There were notable differences between respondents with uncontrolled BP despite taking 3 or more antihypertensive drugs vs those taking 4 or more drugs regardless of BP achieved. The former were more commonly women (55.8% vs 30.7%), were less likely to be overweight or obese (84.2% vs 95.9%), and were more likely to have chronic kidney disease (36.0% vs 28.1) and stroke (7.1% vs 4.7%), but had considerably lower prevalence of diabetes (35.2% vs 55.9%), dyslipidemia (68.0% vs 88.6%), and heart attack (9.9% vs 33.1%). While there were high levels of use of every major antihypertensive drug class (including renin-angiotensin system inhibitors, diuretics, calcium channel blockers, and beta-blockers), the use of antihypertensive drugs from other categories was considerably less common among respondents who had uncontrolled BP on 3 or more drugs vs those who were taking 4 or more drugs (10.5% vs 59.9%).

After covariate adjustment, 4 risk factors were significantly associated with aTRH in adult men (Supplemental Table S3): age from 70 to 79 years (compared with men aged 20 to 59 years: RR 5.0, 95% CI 1.6-16.2), being overweight or obese (RR 2.5, 95% CI 1.1-5.9), chronic kidney disease (RR 1.9, 95% CI 1.1-3.2), and diabetes (RR 2.5, 95% CI 1.5-4.4). Among adult women, age from 70 to 79 years was the only statistically significant predictor of aTRH (RR 2.7, 95% CI 1.1-6.7). Similarly to men, however, women with chronic kidney disease and diabetes appeared to be at a 2-fold higher risk of aTRH, but these latter associations were not statistically significant.

Table 2. Prevalence of apparent treatment-resistant hypertension

Cycle	Years	Total no.	Uncontrolled BP with ≥ 3 medications, %	Taking ≥ 4 medications, %	Apparent treatment-resistant hypertension, %
1	2007-2009	43,700	3.3 (2.0-4.6)	2.3 (1.5-3.0)	5.6 (4.3-6.8)
2	2009-2011	76,500	2.7 (0.5-5.0)	4.6 (2.5-6.8)	7.3 (4.3-10.3)
3	2012-2013	40,400	2.4 (0.8-4.0)	1.8 (0.2-3.3)	4.2 (2.7-5.7)
4	2014-2015	46,650	2.0 (1.0-3.0)	2.9 (1.8-4.1)	4.9 (3.3-6.5)
5	2016-2017	38,450	1.6 (0.6-2.5)	2.9 (1.9-3.9)	4.5 (3.3-5.7)
All	2007-2017	245,700	2.4 (1.7-3.1)	3.0 (2.3-3.6)	5.3 (4.5-6.2)

The denominator is number of people with treated hypertension. Note that people with uncontrolled blood pressure (BP) despite taking 3 or more medications and those taking 4 or more medications are not mutually exclusive, and there may occasionally be small numbers of people that overlap. Therefore, the sum of the 2 categories does not necessarily equal the final percentage of people with apparent treatment-resistant hypertension.

Discussion

In this study, aTRH was present 1 in 20 adults treated for high BP (representing nearly a quarter million people) in Canada; aTRH occurred most frequently in the elderly and commonly coexisted with being overweight or obese, having diabetes, and the presence of chronic kidney disease. Affected adults were at very high cardiovascular risk, with one-fourth reporting a history of heart attack and more than 1 in 20 having suffered a stroke. Those with uncontrolled BP despite the use of 3 or more antihypertensive drugs were more often women, a finding consistent with known sex disparities in the treatment and control of hypertension in Canada.^{1,24,30}

The findings of our study extend those of previous reports. The true prevalence of resistant hypertension around the world remains uncertain, owing to large differences in disease definitions, BP measurement techniques, and populations between studies.³¹ In a recent systematic review and meta-analysis, Noubiap et al. estimated that resistant hypertension was present in approximately 10% of patients treated for high BP globally (ranging from 1.2% to 25.5%), but there was a large amount of unexplained statistical heterogeneity between studies, even when restricted to those of highest quality and lowest risk of bias ($I^2 = 94.4\%$), thus limiting the interpretability of the pooled prevalence.³¹ In contrast to our study, where we used an unattended automated office BP measurement, many previous studies measured BP by auscultation without an out-of-office component, which likely accounted for the higher rates of aTRH in other studies. Previous Canadian-specific estimates were reported by Gee et al., dating back over a decade, placing the prevalence of aTRH at 4% to 8% among hypertensive adults.³⁰ The consistency of their findings with ours is expected because they also used the CHMS as their data source (ie, cycle 1), but they were limited by small sample size (of fewer than 1000 people) and therefore could not provide detailed characteristics about those affected. In contrast, we found that the majority of Canadians with uncontrolled BP with 3 or more medications were women and nearly half were aged 70 years or older. Our findings bear similarities with other Western countries. Reports from the National Health and Nutrition Examination Survey have also indicated that American women aged 75 years or older have the lowest rates of general hypertension treatment and control (at 43% and 34%, respectively),^{32,33} with women representing more than 60% of people with uncontrolled hypertension taking 3 or more medications in the United States.²⁹ While the prevalence of aTRH also increases with age in the United Kingdom, no major sex differences have been observed,³⁴ suggesting that differences in North America may be at least

partly driven by social determinants of health, organisations of care, underrecognition, and/or therapeutic inertia.

The factors underlying aTRH are complex and multifactorial. Medication nonadherence, inaccurate BP measurement, suboptimal treatment regimens, and unrecognised secondary causes of hypertension are among the leading causes.^{21,35} Indeed, medication nonadherence is thought to be present in a third of cases (with rates as high as 50% when chemical tests are used to verify drug exposure).³⁶ Possible strategies to improve adherence include the adoption of simplified medication regimens (eg, single-pill fixed-dose combinations of antihypertensive drugs), preferential use of generic or low-cost drugs, and enhanced communication with patients about potential adverse effects and benefits of treatment.²¹ Furthermore, undertreatment (eg, inadequate medication dosing) and underrecognition of secondary causes are other important factors leading to apparent treatment resistance.³⁵ Addressing these, adoption of standardised treatment algorithms (eg, guidance for specific drugs, doses, and titration schedules)³⁷ and promotion of healthy behaviours (eg, dietary sodium reduction in those who are salt sensitive, working toward a healthy weight in those who are overweight or obese)³⁸ have proven to be effective at improving BP control. Moreover, given that resistant hypertension is often volume mediated,^{39,40} the use of potassium-sparing diuretics (eg, spironolactone) is increasingly recognised to have a central role in treatment,⁴¹ but few Canadians with aTRH (7%) reported taking these (with similarly low rates in the U.S.).⁴² Collectively, these interventions could potentially improve the health of hundreds of thousands of Canadians.

Study limitations

While there are many strengths to this study (eg, it was comprehensive and used high-quality data with blood pressure measurements collected by means of a standardised automated technique), there are also some limitations. First, inherent to all surveys, if nonrespondents were systematically different than those who participated, unknown bias may have been introduced. Addressing this, we applied survey weights so that respondents would be representative of the underlying population of interest according to sociodemographic characteristics (eg, age and gender), but it was not possible to ensure that their clinical characteristics (eg, BP and medication usage) were also similar. Second, treatment exposure was based entirely on self-report. We were unable to account for treatment nonadherence by patients (eg, missed doses) or undertreatment by physicians (eg, inadequate dosing or selection of

medication combinations that are less likely to be effective). As such, we could not report on rates of resistant hypertension, but only aTRH. Third, we could not confirm the primary indication for taking an antihypertensive drug (ie, whether it was prescribed for high BP or for another condition, such as heart failure). Therefore, our estimated treatment rates may have been subject to some degree of misclassification, though this likely would have been small.⁴³ Fourth, we could not completely rule out misclassification from a single visit office-based BP measurement. Still, unattended automated office BP measurements are thought to largely mitigate the white-coat effect,^{27,44} and compared with the criterion standard of 24-hour ambulatory blood pressure measurements, they have high specificity (81%-91%) for detecting elevated BP.⁴⁵ Fifth, we did not factor more intensive treatment goals for certain groups (eg, BP < 130/80 mm Hg in people with diabetes, or SBP < 120 mm Hg in high-risk adults),⁴⁶ but rather assumed a common BP target for all respondents because treatment decisions are frequently nuanced. Applying a lower BP target would doubtlessly have raised the prevalence of aTRH, which may have been one of the reasons why our estimates were slightly lower than others.^{30,31} Finally, we identified a number of risk factors associated with aTRH, but causal relationships could not be established because data were cross-sectional. Further study is needed to determine if treatment of modifiable risk factors leads to improved long-term BP control.³⁸

Conclusion

Apparent treatment-resistant hypertension is associated with a significantly higher frequency of cardiovascular disease compared with treatment-responsive hypertension. Despite being prescribed multiple BP-lowering medications, a considerable proportion of Canadians, especially women, have difficulty achieving long-term BP control, thus predisposing them to a greater risk of cardiovascular complications and death. Strategies to effectively control BP in high-risk populations, such as the elderly, people who are overweight or obese, and those with chronic kidney disease or diabetes, as well as to narrow sex-based care gaps are urgently needed.

Funding Sources

This study was funded by the Canadian Institutes of Health Research (project grant no 159533). Dr Leung is supported by a Heart and Stroke Foundation National New Investigator Award.

Disclosures

Dr Padwal is CEO of mmHg Inc, a digital health company that creates cloud-based solutions for remote patient monitoring and management. The other authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at <https://doi.org/10.1016/j.cjca.2022.01.029>.