Refractory Hypertension and Risks of Adverse Cardiovascular Events and Mortality in Patients With Resistant Hypertension: A Prospective Cohort Study

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BACKGROUND: The long-term prognosis of refractory hypertension (RfHT), defined as failure to control blood pressure (BP) levels despite an antihypertensive treatment with ≥5 medications including a diuretic and mineralocorticoid receptor antagonist, has never been evaluated.

METHODS AND RESULTS: In a prospective cohort study with 1576 patients with resistant hypertension, patients were classified as refractory or nonrefractory based on uncontrolled clinic (or office) and ambulatory BPs during the first 2 years of follow-up. Multivariate Cox analyses examined the associations between the diagnosis of RfHT and the occurrence of total cardiovascular events (CVEs), major adverse CVEs, and cardiovascular and all-cause mortality, after adjustments for other risk factors. In total, 135 patients (8.6%) had RfHT by uncontrolled ambulatory BPs and 167 (10.6%) by uncontrolled clinic BPs. Over a median follow-up of 8.9 years, 338 total CVEs occurred (288 major adverse CVEs, including 124 myocardial infarctions, and 96 strokes), and 331 patients died, 196 from cardiovascular causes. The diagnosis of RfHT, using either classification by clinic or ambulatory BPs, was associated with significantly higher risks of major adverse CVEs, cardiovascular mortality, and stroke incidence, with hazard ratios varying from 1.54 to 2.14 in relation to patients with resistant nonrefractory hypertension; however, the classification based on ambulatory BPs was better in identifying higher risk patients than the classification based on clinic BP levels.

CONCLUSIONS: Patients with RfHT, particularly when defined by uncontrolled ambulatory BP levels, had higher risks of major adverse CVEs and mortality in relation to patients with resistant but nonrefractory hypertension, supporting the concept of refractory hypertension as a true extreme phenotype of antihypertensive treatment failure.

Key Words: ambulatory blood pressure monitoring ■ cardiovascular events ■ cohort study ■ mortality ■ refractory hypertension ■ risk factors

Resistant hypertension (RHT) is the most extensively studied phenotype of patients with difficult-to-control hypertension. RHT is defined as the failure to achieve recommended clinic (office) blood pressure (BP) goals despite the concurrent use of 3 antihypertensive medications of different classes at optimal dosages—commonly including a long-acting calcium channel blocker, a blocker of the renin–angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic—or achieving BP goals with ≥4 drugs after causes of pseudoresistance were ruled out.1 RHT has a prevalence of 15% to 18% of the general treated hypertensive population1,2; patients with RHT typically have higher prevalence of target-organ damage3-4 and worse cardiovascular prognosis than those with non-RHT.5-7 A small subgroup of patients with RHT with a most extreme phenotype of antihypertensive treatment failure, called refractory hypertension (RfHT), was described recently.8 RfHT is currently defined as the failure to
control high BP despite the use of ≥5 antihypertensive drugs including a long-acting thiazide or thiazide-like diuretic and a mineralocorticoid receptor antagonist. In initial studies, the prevalence of RfHT seemed to vary from 5% to 10% of patients with RHT, although prevalence as high as 31% has been reported, and from 0.5% to 1.4% of those with general treated hypertension. Patients with RfHT seemed to be younger and more frequently of African ancestry and to have more end-organ damage, particularly chronic kidney disease (CKD), than patients with RHT. However, their prognosis in contrast to the more common phenotype of RHT is still completely unknown. As far as we know, no previous longitudinal prospective study evaluated cardiovascular or mortality outcomes specifically in people with RfHT. Therefore, we took advantage of a large cohort of patients with RHT and aimed to classify them as having RfHT or non-RfHT, based on treatment and BP levels during the first 2 years of follow-up, and then to assess whether the diagnosis of RfHT was associated with worse prognosis in terms of adverse cardiovascular and mortality outcomes in relation to those with resistant but non-RfHT. We used separated, attended, clinic (office) and ambulatory BPs, with both the traditional and the new 2017 American College of Cardiology/American Heart Association (ACC/AHA) lower BP cutoff values, to classify RfHT.

**METHODS**

The data that support the findings of this study are available from the corresponding author on reasonable request. The corresponding author had full access to all data in the study and takes responsibility for data integrity and the data analysis.

**Study Overview**

This prospective cohort study included 1726 patients with RHT enrolled between 2000 and 2016 and followed up until 2018 in the outpatient clinics of our university hospital; this approach resulted from the joining of 2 independent cohorts. All participants fulfilled the 2008 criteria for RHT: clinic BP ≥140/90 mm Hg using 3 antihypertensive medications, always including a diuretic, or using ≥4 drugs regardless of having controlled or uncontrolled BP levels; and considered to be at least moderately adherent to treatment by a validated questionnaire. All participants gave written informed consent, and the local ethics committee previously approved the study protocols. The characteristics of both cohorts, the baseline procedures, and the diagnostic definitions have been described elsewhere. None of the patients had secondary hypertension (surgical primary aldosteronism and renovascular hypertension) except sleep apnea syndromes. Adrenal adenomas were investigated by a serum aldosterone-to-renin ratio, followed by an adrenal computed tomography scan and saline loading test; renovascular hypertension was assessed by renal artery duplex scan or renal isotope scintigraphy, complemented by arteriography when needed. All participants underwent a routine protocol at baseline that comprised a thorough clinical examination, a laboratory evaluation, and 24-hour ambulatory BP monitoring (ABPM). Attended clinic BP was measured twice with a suitably sized cuff, using a digital oscillometric BP monitor (HEM-907XL; Omron Healthcare), and BP considered was the mean between the 2 readings.
ABPM was recorded with Mobil-O-Graph equipment (version 12, DynaMAPA; Cardios). All patients used their prescribed antihypertensive medications during ABPM. A reading was taken every 15 minutes throughout the day and every 30 minutes at night. The nighttime period was ascertained for each patient from registered diaries. Parameters evaluated were mean 24-hour, daytime, and nighttime systolic and diastolic BPs, and their respective nocturnal BP fall as the night-to-day BP ratio. The mean white-coat effect was estimated as the difference between mean clinic and daytime BPs. ABPM quality was considered satisfactory if it had at least 70% valid measurements of all anticipated measurements during daytime and nighttime; if not, the examination was discarded and repeated as soon as possible, usually in the same week. Laboratory evaluation included fasting glycemia, serum creatinine, and lipids. Presence of CKD at baseline was defined by an estimated glomerular filtration rate ≤60 mL/min per 1.73 m², using the Chronic Kidney Disease Epidemiology Collaboration equation.

Diagnosis of RfHT

We used the first 2 years of follow-up to establish the diagnosis of RfHT. Patients who used at least 5 antihypertensive drugs, including a diuretic and a mineralocorticoid receptor blocker (spironolactone is the only one available in Brazil) and whose uncontrolled BP levels persisted during this period were considered to have RfHT. During this initial 2-year period, patients performed at least one more ABPM examination (median of 2 exams) and had 3 to 6 annual clinic visits. We used mean clinic and ambulatory BPs separately to establish an RfHT diagnosis: uncontrolled clinic and ambulatory 24-hour BPs were defined by traditional criteria (≥140/90 mm Hg and ≥130/80 mm Hg) and also by the new 2017 ACC/AHA criteria (≥130/80 mm Hg and ≥125/75 mm Hg). We excluded from analysis 150 participants who had any of the end points during this 2-year period, totaling 1576 individuals with RHT in the current study.

Follow-Up and Outcome Assessment

All patients were followed up regularly with 3 to 6 annual medical visits, and the observation period for each participant was the number of months from the baseline evaluation to the date of the last clinical visit or the first end point, whichever came first. Overall, 107 patients (6.8%) were lost to follow-up and were considered censored observations at the date of their last hospital visit. There was no differential loss to follow-up between fatal and nonfatal end points. The primary outcomes were a composite of total fatal or nonfatal cardiovascular events (CVEs), major adverse CVEs (MACE), and all-cause and cardiovascular mortalities. Definitions of end points have been detailed previously. In brief, CVEs were fatal or nonfatal myocardial infarction (MI), sudden cardiac death, new-onset heart failure (needing hospitalization and echocardiographic confirmation of an ejection fraction <40%), death from progressive heart failure, any myocardial revascularization procedure (surgical or endovascular), fatal or nonfatal stroke, any aortic or lower limb revascularization procedure, amputation above the ankle, and death from aortic or peripheral arterial disease. The classic 3-point MACE was nonfatal MI and stroke plus all cardiovascular deaths. MIs and strokes separately were considered secondary outcomes. End points were adjudicated from medical records (most nonfatal and fatal in-hospital events were attended at our hospital), death certificates, and interviews with the attending physicians and patients’ families, using a standard questionnaire reviewed by an independent observer.

Statistical Analysis

Continuous data were expressed as means and SDs if normally distributed or as medians and interquartile ranges if asymmetrically distributed. Baseline characteristics of patients divided according to having RfHT or non-RfHT in the first 2 years of follow-up were compared by unpaired t test, Mann–Whitney test, or χ² test, as appropriate. Kaplan-Meier curves of cumulative end-point incidence during follow-up, compared by log-rank tests, were performed to estimate different incidence of outcomes between patients with and without RfHT. To assess the risks associated with the diagnosis of RfHT by any criteria (ambulatory or clinic BPs, using traditional or 2017 ACC/AHA cutoff values), a time-to-event Cox analysis for each outcome was performed. Cox analyses were adjusted for age and sex and then further adjusted for all potential confounders and risk factors (per capita income, body mass index, smoking status, physical inactivity, presence of diabetes mellitus and cardiovascular diseases at baseline, estimated glomerular filtration rate, and serum total and HDL [high-density lipoprotein] cholesterol). Results were presented as hazard ratios (HRs; in relation to patients with resistant non-RfHT) with their respective 95% CIs. The proportional hazards assumption was tested by inspection of log-minus-log curves, and no violation was observed. A separate analysis excluding 317 patients using 3 antihypertensive drugs and with controlled ambulatory BP levels at baseline (ie, including only those who would be considered as resistant hypertensive under the 2018 AHA Scientific Statement) was also undertaken. In sensitivity and
interaction analyses, interactions between the presence of RfHT and age (<60 versus ≥60 years), sex, and presence of diabetes mellitus, cardiovascular diseases, and CKD at baseline were tested for all outcomes, and whenever there would be evidence of interaction (P<0.10 for the interaction term), a further stratified analysis for that specific characteristic would be performed. In all analyses, a 2-tailed probability value <0.05 was considered significant. Statistics were performed with SPSS v19.0 (IBM Corp).

RESULTS

Baseline Characteristics and Prevalence of RfHT During the First 2 Years of Follow-Up

Overall, RfHT was identified in 135 patients (prevalence rate, 8.6%; 95% CI, 7.2%–10.1%) by the uncontrolled ambulatory BP criterion (mean 24-hour BP ≥130/80 mm Hg) and in 167 (prevalence rate, 10.6%; 95% CI, 9.1%–12.3%) by the uncontrolled clinic BP criterion (≥140/90 mm Hg) during the first 2 years of follow-up. Only 4 patients (3.0% of those classified as RfHT by ambulatory BP) had masked RfHT (ie, uncontrolled ambulatory BPs and controlled clinic BPs), whereas 36 individuals (21.6% of those classified as RfHT by clinic BPs) had white-coat RfHT (ie, uncontrolled clinic and controlled ambulatory BPs). Using the lower BP cutoff values proposed by the 2017 ACC/AHA guideline increased the prevalence of RfHT using the ambulatory BP criterion to 10.1% (95% CI, 8.6%–11.8%; 159 patients) and using the clinic BP criterion to 11.5% (95% CI, 9.9%–13.3%; 181 patients). Table 1 shows the baseline characteristics during the first 2 years of follow-up of all 1576 patients with RHT and of those divided according to having RfHT or non-RfHT using the traditional ambulatory and clinic BP criteria. Patients with RfHT by either criterion were younger, were more obese, had lower prevalence of diabetes mellitus and greater prevalence of current smoking and CKD than their counterparts with non-RfHT. The use of statins (58% at baseline and 77% during follow-up) was equivalent for patients with and without RfHT. As expected by the RfHT definition, those patients used more antihypertensive medications and had higher clinic and ambulatory BPs than those who had resistant non-RfHT. Of note, there were no differences in the nocturnal BP fall and in the white-coat effect between patients with RHT both with and without RfHT when classified by ambulatory BPs. Moreover, the prevalence of white-coat RHT in patients with RfHT defined by the clinic BP criterion was lower than in those without RfHT (21.6% versus 35.3%). In addition, patients with RfHT had a heart rate that, significantly, was 3 beats/min higher than those with non-RfHT, although patients with RfHT used β-blockers and centrally acting sympatholytic agents more frequently.

End Point Occurrence During Follow-Up

Including the first 2 years of follow-up, patients were followed up for a median of 8.9 years (interquartile range, 5.5–11.8 years; maximum of 18 years), which corresponds to 13 679 person-years (PY) of follow-up. After the second year of follow-up, 338 total CVEs occurred (crude incidence, 26.1 per 1000 PY), with 288 MACE (21.8 per 1000 PY), including 124 MIs and 96 strokes. Overall, 331 patients died (24.2 per 1000 PY), 196 from cardiovascular causes (14.3 per 1000 PY). Patients with RfHT by either criterion had greater incidence of adverse cardiovascular outcomes than those without RfHT, except for MIs and total CVEs for the clinic BP definition (Table 1, bottom). This is also demonstrated in Kaplan-Meier estimation of cumulative incidence of end points during follow-up shown in Figures 1 and 2.

Risks Associated With RfHT

Table 2 outlines the excess risks of each outcome associated with the diagnosis of RfHT in the first 2 years of follow-up for both RfHT definitions, using the traditional cutoff-value criteria. Using mean ambulatory BPs, the presence of RfHT was associated with increased risk of all adverse outcomes except MI, with HRs ranging from 1.44 for total CVEs to 2.14 for stroke occurrence in fully adjusted analyses. Using clinic BPs instead of ambulatory BPs to define RfHT somewhat attenuated the risks associated with RfHT, but they remained significant for most adverse outcomes except for total CVEs and MI. Table 3 presents the same analyses using the new 2017 ACC/AHA BP cutoff values to define RfHT. For the clinic BP criterion, the risks associated with the lower cutoff values were equivalent to the traditional ones. However, for the ambulatory BP criterion, the risks associated with the lower cutoff-value definition of RfHT were smaller than those derived from the traditional BP cutoffs, without any superiority in using ambulatory BPs instead of clinic BPs to detect RfHT. Using ambulatory daytime BPs (≥135/85 mm Hg) to define RfHT, instead of mean 24-hour BPs, did not materially change any results.

Excluding those 317 individuals who used 3 antihypertensive drugs and had controlled ambulatory BPs at baseline did not materially change any results but slightly attenuated the risks associated with the presence of RfHT. For example, the HRs for MACE occurrence changed from 1.68 to 1.58 (95% CI, 1.08–2.30)
Table 1. Baseline Characteristics and Crude Incidence Rates of Outcomes in All 1576 Patients With RHT and Grouped According to RFHT or non-RfHT, Defined by Uncontrolled Ambulatory Mean 24-Hour BPs (≥130/80 mm Hg) and by Uncontrolled Mean Clinic BPs (≥140/90 mm Hg) During the First 2 Years of Follow-Up

| Characteristic or Outcome | All Patients (n=1576) | Mean Ambulatory BP (≥130/80 mm Hg) | Mean Clinic BP (≥140/90 mm Hg) |
|---------------------------|-----------------------|-----------------------------------|-------------------------------|
|                           | Non-RfHT (n=1441)     | RFHT (n=135)                      | Non-RfHT (n=1409)             | RFHT (n=167) |
| Demographic/anthropometric|                       |                                   |                               |              |
| Female sex, %             | 69.4                  | 69.3                              | 71.1                           | 69.3          | 70.7          |
| Age, y                    | 61.9 (11.3)           | 62.4 (11.2)                       | 56.5 (11.4)*                  | 62.4 (11.2)   | 57.7 (11.4)*  |
| Body mass index, kg/m²    | 30.3 (5.8)            | 30.1 (5.8)                        | 31.8 (5.8)*                   | 30.1 (5.8)    | 31.7 (6.1)*   |
| Abdominal circumference, cm| 101 (12)              | 101 (12)                         | 104 (12)*                     | 101 (12)      | 104 (12)*     |
| Per capita income (No. of minimum wage) | 1.0 (0.7-1.7) | 1.0 (0.7-1.7) | 1.0 (0.6-1.8) | 1.0 (0.7-1.7) | 1.0 (0.7-1.8) |
| Cardiovascular risk factors, % |                       |                                   |                               |              |
| Physical inactivity       | 75.3                  | 75.4                              | 73.3                           | 75.6          | 72.5          |
| Diabetes mellitus         | 52.5                  | 53.2                              | 45.9                           | 53.5          | 44.3†         |
| Current smoking           | 8.4                   | 7.9                               | 14.1†                          | 7.9           | 13.2†         |
| Dyslipidemia              | 75.3                  | 76.1                              | 66.7†                          | 76.0          | 69.5          |
| Established CVD, %        |                       |                                   |                               |              |
| Previous CVDs             | 40.6                  | 40.0                              | 46.7                           | 40.0          | 45.5          |
| Coronary heart disease    | 22.7                  | 22.3                              | 26.7                           | 22.2          | 26.3          |
| Stroke                    | 14.5                  | 14.4                              | 15.6                           | 14.3          | 16.2          |
| Heart failure             | 4.2                   | 4.2                               | 4.4                            | 4.3           | 3.6           |
| Peripheral artery disease | 11.7                  | 11.9                              | 10.4                           | 11.9          | 10.2          |
| CKD§                      | 43.3                  | 42.3                              | 54.1*                          | 42.4          | 50.9†         |
| Antihypertensive treatment|                       |                                   |                               |              |
| No. of drugs in use       | 4 (3–4)               | 4 (3–4)                           | 5 (5–6)*                       | 4 (3–4)       | 5 (5–6)*      |
| Diuretics                 | 100                   | 100                               | 100                            | 100           | 100           |
| Spironolactone            | 47.5                  | 42.5                              | 100*                           | 41.3          | 100*          |
| ACEI/ARB, %               | 94.2                  | 93.9                              | 97.8                           | 94.0          | 96.4          |
| β-Blockers, %             | 82.0                  | 81.1                              | 91.9†                          | 80.9          | 91.6†         |
| Calcium channel blockers, %| 71.1                  | 69.0                              | 93.3*                          | 68.5          | 92.8*         |
| Direct vasodilators, %    | 33.4                  | 32.8                              | 39.3                           | 31.5          | 49.1*         |
| Central α-agonists, %     | 18.5                  | 16.8                              | 36.3*                          | 17.2          | 29.3*         |
| Systolic BPs, mm Hg       |                       |                                   |                               |              |
| Mean clinic               | 158 (19)              | 157 (19)                          | 172 (21)*                      | 156 (19)      | 170 (19)*     |
| Mean ambulatory 24-h      | 132 (14)              | 131 (14)                          | 145 (14)*                      | 131 (14)      | 141 (16)*     |
| Mean ambulatory daytime   | 134 (14)              | 133 (14)                          | 148 (14)*                      | 133 (14)      | 143 (16)*     |
| Mean ambulatory nighttime | 125 (15)              | 124 (15)                          | 137 (16)*                      | 124 (15)      | 133 (17)*     |
| White-coat effect         | 23 (18)               | 23 (18)                           | 24 (18)                        | 23 (18)       | 27 (17)†      |
| Night-to-day rate          | 0.93 (0.06)           | 0.93 (0.06)                       | 0.93 (0.05)                    | 0.93 (0.06)   | 0.93 (0.06)   |
| Nondipper, %              | 68.5                  | 68.3                              | 70.7                           | 68.0          | 70.1          |
| Diastolic BPs, mm Hg      |                       |                                   |                               |              |
| Mean clinic               | 85 (13)               | 84 (13)                           | 96 (15)*                       | 84 (13)       | 94 (15)*      |
| Mean ambulatory 24-h      | 75 (10)               | 74 (10)                           | 84 (11)*                       | 74 (10)       | 81 (12)*      |
| Mean ambulatory daytime   | 76 (11)               | 76 (10)                           | 86 (11)*                       | 76 (10)       | 83 (12)*      |
| Mean ambulatory nighttime | 69 (10)               | 69 (10)                           | 78 (11)*                       | 69 (10)       | 75 (11)*      |
| White-coat effect         | 9 (10)                | 9 (10)                            | 10 (11)                        | 9 (10)        | 11 (10)†      |
| Night-to-day rate          | 0.91 (0.07)           | 0.91 (0.07)                       | 0.91 (0.06)                    | 0.91 (0.07)   | 0.91 (0.06)   |
| Nondipper, %              | 55.7                  | 55.4                              | 59.2                           | 55.7          | 58.1          |

(Continued)
when defined by ambulatory BPs and from 1.54 to 1.44 (95% CI, 1.01–2.05) when defined by clinic BPs. There were significant interactions between age and the RfHT diagnosis by ambulatory BPs for MACE (P = 0.087 for interaction) and for cardiovascular mortality (P = 0.085 for interaction), for which the HRs were higher in younger (≤ 60 years) than in older patients (MACE: HR, 2.13 [95% CI, 1.28–3.55] and 1.28 [95% CI, 0.69–2.37], respectively; cardiovascular mortality: HR, 2.72 [95% CI, 1.44–5.11] and 1.35 [95% CI, 0.66–2.79], respectively). No other evidence of interaction was found between RfHT diagnosis by either criterion and sex, diabetes mellitus, or the presence of cardiovascular diseases and CKD at baseline or between RfHT diagnosis by clinic BP criterion and age (all P > 0.10 for interaction).

**DISCUSSION**

As far as we know, this is the first prospective study to evaluate the risks of adverse cardiovascular and mortality outcomes associated with the presence of RfHT in patients with RHT. We demonstrated that the diagnosis of RfHT, defined either by ambulatory or clinic BP levels, in the first 2 years of follow-up was associated with significant excess risks of these adverse outcomes, particularly MACE, cardiovascular mortality, and stroke incidence, in relation to patients with resistant but non-RfHT. Moreover, we showed that the RfHT classification based on uncontrolled mean ambulatory BP levels better identified patients with RfHT at increased risk than the classification based on uncontrolled clinic BP levels. Otherwise, when classified by the new lower BP cutoff values proposed by the 2017 ACC/AHA guideline, the risks associated with RfHT defined by ambulatory BPs attenuated and became roughly equal to those derived from the RfHT classification defined by clinic BP levels. Consequently, the best criterion to define RfHT, in terms of cardiovascular and mortality risk stratification, was that based on uncontrolled ambulatory mean 24-hour BP levels, using the traditional cutoff values (≥130/80 mm Hg).

Since the pioneering description in 2012 by Calhoun and colleagues of a small subgroup of 29 individuals (9.5% of a group of 304 patients with RHT) who persisted with uncontrolled clinic BPs despite apparent maximum therapy (average of 6 antihypertensive medications, 83% with a mineralocorticoid antagonist) as an extreme phenotype of antihypertensive
treatment failure, named RIHT (a term formerly used interchangeably with RHT); several other studies reported on RIHT, particularly its prevalence and patients’ characteristics, in addition to a few mechanistic studies. The prevalence of RIHT appeared to vary between 5% and 10% of patients with
RfHT; this range was corroborated by the present study (8.6% and 10.6% respectively, using the criteria of ambulatory and clinic BP levels). Patients with RfHT were younger and more obese, with greater prevalence of CKD (reduced estimated glomerular filtration rate) than patients who were resistant with non-RfHT, as reported.

Figure 2. Kaplan–Meier estimation of cumulative incidence of CV deaths (A and B) and strokes (C and D) in 1576 patients with resistant hypertension categorized as having RfHT or non-RfHT, defined by ambulatory mean 24-hour BPs (≥130/80 mm Hg, A and C) and by clinic BPs (≥140/90 mm Hg, B and D) during follow-up. HRs were from fully adjusted models. BP indicates blood pressure; CV, cardiovascular; HR, hazard ratio; and RfHT, refractory hypertension.
previously. More important, a few previous studies suggested that sympathetic overactivity, and not intravascular volume overload, as has been demonstrated for RHT, may be the main physiopathologic mechanism underlying RfHT. Patients with RfHT had similar serum aldosterone and plasma renin activity and equal serum B-type natriuretic peptide and cardiac volumes but higher urinary metanephrines, heart rates, and peripheral vascular resistance and low heart rate variability than patients with controlled resistant hypertension; all these results suggest increased sympathetic tonus but not volume overload. Recently, this hypothesis was further supported by a small proof-of-concept study that showed an impressively large BP reduction of 29/22 mm Hg in clinic and 24/15 mm Hg in ambulatory 24-hour BPs following 4-week treatment with reserpine, a potent sympatholytic agent, in 6 patients with RfHT. Therefore, the current study, by providing the first evidence that patients with RfHT had significantly higher risk of cardiovascular diseases and mortality than patients with resistant non-RfHT completed the full-blown clinical picture of RfHT as a relatively rare but true extreme phenotype of antihypertensive treatment failure.

### Table 2. Risks of Adverse Cardiovascular Outcomes and Mortality Associated With the Diagnosis of RfHT (Defined by Clinic and by Ambulatory BPs, Using the Traditional Criteria) During the First 2 Years of Follow-Up in 1576 Patients With RHT

| Outcomes                      | RfHT (n=135)     | RHT (n=167)        |
|-------------------------------|------------------|--------------------|
|                               | Model 1*         | Model 2*           | Model 1*         | Model 2*         |
| Total CVEs (n=338)            | 1.63 (1.14–2.32) | 1.44 (1.01–2.07)   | 1.45 (1.03–2.03) | 1.31 (0.93–1.84) |
| MACE (n=288)                  | 1.87 (1.29–2.70) | 1.68 (1.16–2.45)   | 1.68 (1.19–2.39) | 1.54 (1.08–2.29) |
| Cardiovascular mortality (n=196) | 2.06 (1.32–3.21) | 1.85 (1.18–2.90)   | 1.86 (1.22–2.83) | 1.69 (1.10–2.60) |
| All-cause mortality (n=331)   | 1.62 (1.10–2.37) | 1.50 (1.02–2.20)   | 1.55 (1.09–2.21) | 1.46 (1.02–2.09) |
| MI (n=124)                    | 1.62 (0.90–2.90) | 1.52 (0.84–2.75)   | 1.28 (0.71–2.28) | 1.21 (0.67–2.19) |
| Stroke (n=96)                 | 2.30 (1.27–4.17) | 2.14 (1.17–3.93)   | 2.14 (1.22–3.75) | 2.03 (1.15–3.60) |

Values are hazard ratios (95% CIs), estimated in relation to resistant non-RHT. BP indicates blood pressure; CVE, cardiovascular event; MACE, major adverse cardiovascular events; MI, myocardial infarction; RfHT, refractory hypertension; and RHT, resistant hypertension.

*Model 1 is adjusted for age and sex, and model 2 is further adjusted for per capita income, body mass index, smoking, physical inactivity, diabetes mellitus, preexistent cardiovascular diseases, estimated glomerular filtration rate, and serum total and HDL (high-density lipoprotein) cholesterol.

†p<0.01.
‡p<0.05.
§p<0.001.

### Table 3. Risks of Adverse Cardiovascular Outcomes and Mortality Associated With the Diagnosis of RfHT (Defined by Clinic and by Ambulatory BPs, Using the ACC/AHA 2017 Criteria) During the First 2 Years of Follow-Up in 1576 Patient With RHT

| Outcomes                      | RfHT (n=159)     | RHT (n=181)        |
|-------------------------------|------------------|--------------------|
|                               | Model 1*         | Model 2*           | Model 1*         | Model 2*         |
| Total CVEs (n=338)            | 1.45 (1.02–2.05) | 1.27 (0.89–1.81)   | 1.42 (1.02–1.98) | 1.29 (0.92–1.80) |
| MACE (n=288)                  | 1.68 (1.17–2.40) | 1.50 (1.04–2.16)   | 1.66 (1.18–2.34) | 1.52 (1.08–2.16) |
| Cardiovascular mortality (n=196) | 1.93 (1.26–2.96) | 1.72 (1.11–2.66)   | 1.90 (1.26–2.85) | 1.75 (1.15–2.64) |
| All-cause mortality (n=331)   | 1.58 (1.18–2.37) | 1.45 (1.01–2.10)   | 1.54 (1.09–2.21) | 1.46 (1.03–2.07) |
| MI (n=124)                    | 1.35 (0.75–2.42) | 1.26 (0.70–2.27)   | 1.29 (0.73–2.26) | 1.22 (0.69–2.16) |
| Stroke (n=96)                 | 1.92 (1.06–3.49) | 1.78 (0.97–3.27)   | 1.97 (1.12–3.45) | 1.86 (1.05–3.28) |

Values are hazard ratios (95% CIs), estimated in relation to resistant non-RHT. ACC/AHA indicates American College of Cardiology/American Heart Association; BP, blood pressure; CVE, cardiovascular event; MACE, major adverse cardiovascular events; MI, myocardial infarction; RfHT, refractory hypertension; and RHT, resistant hypertension.

*Models 1 and 2 were adjusted for the same covariates as in Table 2.

†p<0.05.
‡p<0.01.
BP levels) in individuals with RfHT. The first description of ABPM in patients with RfHT suggested that white-coat RfHT was rare (only 2 of 31 patients with RfHT, 6.5%). However, an analysis of a large Spanish database on ABPM reported a prevalence of 26.7% of white-coat RfHT among 955 individuals with RfHT, albeit lower than the 37.1% prevalence among those with RHT. Our data corroborated this study by showing a prevalence of 21.6% of white-coat RfHT in 167 individuals classified as RfHT based on clinic BP levels, which was lower than in patients with resistant non-RfHT (35.3%). These data support the use of ambulatory BP levels to define and classify RfHT, as it is currently recommended. Moreover, we demonstrated that classifying RfHT by ambulatory BP levels better identified people with higher cardiovascular risk than classification based on clinic BP levels.

Our results of the analyses on the prognostic importance of RfHT when classified by the new lower BP thresholds proposed by the 2017 ACC/AHA guideline should be considered with caution. In almost all patients, the first 2-year follow-up period, when RfHT diagnosis was made, occurred before the guideline publication—when attending physicians were satisfied with a clinic BP <140/90 mm Hg and a 24-hour ambulatory BP <130/80 mm Hg, without making any effort to reduce BP levels. These new patients with RfHT were reclassified retrospectively, and we did not know how many would truly have RfHT if the attending physician had increased their antihypertensive regimens toward reaching the new lower BP thresholds. Otherwise, it is clear by comparing the HRs in Tables 2 and 3 that the reclassification based on the 2017 ACC/AHA BP cutoffs decreased the risks associated with RfHT when classified by ambulatory BPs but did not change the risks associated with RfHT defined by clinic BPs.

This study has some limitations that warrant discussion. First, we assessed only antihypertensive treatment adherence at baseline and by indirect questionnaire methods, which are widely known to overestimate adherence. Moreover, treatment-adherence changes during follow-up were not assessed at all and might have affected the prognosis. Regarding medication adherence in patients with RfHT, a unique previous study shows that at least half of the patients were totally or partially nonadherent when directly tested by urinary drug assays—a picture similar to those with resistant non-RfHT. At least part of the antihypertensive drug treatment failure in RfHT individuals might be due to treatment nonadherence and to other behavioral factors related either to the physician (clinical inertia) or to the healthcare system, and not to true biological causes. Second, most of our patients (~80%), either RfHT or non-RfHT, used hydrochlorothiazide, and not chlorthalidone, as the thiazide diuretic because hydrochlorothiazide is freely available in Brazil from Ministry of Health pharmacies, whereas chlorthalidone is not. Chlorthalidone is generally recommended as the thiazide diuretic of choice because of its longer half-life and greater effectiveness, particularly in RHT. However, a recent large study using a network of databases and with >730,000 individuals questioned the superiority of chlorthalidone over hydrochlorothiazide for cardiovascular protection. Otherwise, it is possible that the prevalence of RfHT in our study might have been somewhat overestimated by preferentially using hydrochlorothiazide instead of chlorthalidone. Third, we had a large cohort of patients with RHT followed up for a long period of time, with a relatively large number of end points; nevertheless, because of the low prevalence of RfHT, our sample size might have been insufficient to demonstrate some more subtle increases in risk, such as those associated with MI occurrence. Fourth, as in all observational cohort studies, no direct inferences can be made regarding cause-and-effect relationships or physiopathologic mechanisms. Furthermore, although we used a comprehensive set of adjusting covariates, residual confounding due to unmeasured or unknown factors cannot be ruled out. In particular, we had no information on current or past psychiatric history, particularly major depression, which might have affected the prognosis. Finally, this cohort was from a tertiary care specialized referral center; therefore, our results might not be generalizable to patients with RfHT followed up at primary care or nonspecialized centers.

In conclusion, this study showed, for the first time, that patients with RfHT had worse cardiovascular and mortality outcomes than patients who had resistant but non-RfHT. This study completed the clinical picture of RfHT as a true extreme phenotype of antihypertensive treatment failure. Future interventional studies, ideally multicenter, using peripherally acting (β- and α-blockers) and/or centrally acting (clonidine) sympatholytic agents and with rigorous adherence measures, should be performed in this subgroup of patients with RfHT to assess their effectiveness in reducing BP levels and providing cardiovascular protection.
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Disclosures
None.
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