ORIGINAL RESEARCH

# Prevalence and Clinical Characteristics of Refractory Hypertension

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***Background*—**We aimed to estimate the prevalence of refractory hypertension (RfH) and to determine the clinical differences between these patients and resistant hypertensives (RH). Secondly, we assessed the prevalence of white-coat RfH and clinical differences between true- and white-coat RfH patients.

***Methods and Results*—**The present analysis was conducted on the Spanish Ambulatory Blood Pressure Monitoring Registry database containing 70 997 treated hypertensive patients. RH and RfH were defined by the presence of elevated office blood pressure (≥140 and/or 90 mm Hg) in patients treated with at least 3 (RH) and 5 (RfH) antihypertensive drugs. White-coat RfH was defined by RfH with normal (<130/80 mm Hg) 24-hour blood pressure. A total of 11.972 (16.9%) patients fulfilled the standard criteria of RH, and 955 (1.4%) were considered as having RfH. Compared with RH patients, those with RfH were younger, more frequently male, and after adjusting for age and sex, had increased prevalence of target organ damage, and previous cardiovascular disease. The prevalence of white coat RfH was lower than white-coat RH (26.7% versus 37.1%, $P<0.001$). White-coat RfH, in comparison with those with true RfH, showed a lower prevalence of both left ventricular hypertrophy (22% versus 29.7%; $P=0.018$) and microalbuminuria (28.3% versus 42.9%; $P=0.047$).

***Conclusions*—**The prevalence of RfH was low and these patients had a greater cardiovascular risk profile compared with RH. One out of 4 patients with RfH have normal 24-hour blood pressure and less target organ damage, thus indicating the important role of ambulatory blood pressure monitoring in guiding antihypertensive therapy in difficult-to-treat patients. **(*J Am Heart Assoc.* 2017;6:e007365. DOI: 10.1161/JAHA.117.007365.)**

**Key Words:** refractory hypertension • resistant hypertension • target organ damage • white coat refractory hypertension

Resistant hypertension (RH) is defined as the persistence of high blood pressure (BP) ≥140 mm Hg of systolic BP or ≥90 mm Hg of diastolic BP, despite a therapeutic plan with 3 or more antihypertensive drugs, at the full tolerated doses, 1 of them diuretic, in subjects in whom secondary hypertension has been ruled out, as well as poor adherence to antihypertensive therapy.[1] Several studies have observed a prevalence of around 12% to 14% of treated hypertensives.[2,3] Compared with subjects with controlled hypertension with 3 or less antihypertensive drugs, patients with RH more frequently have target organ damage[4,5] and a higher incidence of cardiovascular events.[6] We have previously reported that more than one third of RH patients have normal 24-hour BP (white-coat RH) and they exhibit a better cardiovascular risk profile compared with those with elevated 24-hour BP.[2]

The term refractory hypertension (RfH) has been recently proposed to define subjects who do not achieve BP control with 5 or more antihypertensive drugs.[7,8] Its prevalence has been reported to be around 3% of RH subjects, and it has been associated with male sex, black race, obesity, and a higher prevalence of cardiovascular and renal alterations.[8,9] As in RH, 24-hour ambulatory blood pressure monitoring (ABPM) is of interest in RfH patients, considering that the magnitude of the white-coat effect could also be involved in

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## Clinical Perspective

### What Is New?

- The prevalence of the white-coat effect is reported for the first time in a wide sample of refractory hypertensive patients.

### What Are the Clinical Implications?

- One out of 4 patients with refractory hypertension have normal 24-hour blood pressure measurements and they also have less target organ damage.
- Ambulatory blood pressure monitoring should be encouraged for all subjects not achieving office blood pressure control, as it can help identify patients who will require additional therapies.

RfH. A recent report[10] has suggested the white-coat effect was very uncommon in RfH patients, although results were based on a small group of patients attending a highly specialized hypertension clinic. This situation could be different when examining a broader spectrum of clinical care, which includes primary care centers.

In the present study, we aimed to assess the prevalence of RfH and white-coat RfH. Furthermore, we compared clinical characteristics between RfH and RH patients, as well as between true and white-coat RfH in a large sample of treated hypertensive patients seen in real-world (primary care and specialized hypertension units) clinical practice.

## Patients and Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

### Study Design

The Spanish Ambulatory BP Monitoring (ABPM) Registry was initiated in 2004 to promote the use of ABPM in clinical practice. Details of physician recruitment and characteristics of the registry have been reported elsewhere.[11,12] Briefly, physicians and nurses received specific training in the technique of ABPM and used the internet-based platform that receives ABPM records, together with their corresponding medical charts. Physicians then obtained a report in real time, and these registries were stored in the database of an external clinical research organization. The practice guidelines of the European Society of Hypertension for BP measurements were used to establish general indications for ABPM.[13,14]

The present analysis was conducted on the Spanish ABPM Registry database containing 70 997 treated patients who had enough information regarding office BP measurements, ABPM of good quality, and complete clinical information.

Clinical resistant hypertension was considered as an office systolic and diastolic BP ≥140 and/or 90 mm Hg, respectively, despite a prescribed therapeutic schedule with an appropriate combination of ≥3 antihypertensive drugs, including a diuretic. Clinical RfH was considered as an office systolic and diastolic BP ≥140 and/or 90 mm Hg, respectively, despite a prescribed therapeutic schedule with an appropriate combination of ≥5 antihypertensive drugs, including a diuretic. Patients with suspected poor adherence to antihypertensive therapy were excluded, and secondary causes of hypertension were evaluated according the clinical criteria.

The local Institutional Ethic Committees approved the study protocol. Written informed consent was obtained from all participants. The investigation conforms to the principles outlined in the declaration of Helsinki.

### BP Measurements

The methodology of office BP measurements and 24-hour ABPM has been previously described by our group.[2,4,11,12] Briefly, BP was measured at the office with a calibrated mercury sphygmomanometer or a validated oscillometric device, after 5 minutes rest in a sitting position. BP values were estimated as the mean of 2 readings. Thereafter, 24-hour ABPM was performed using Spacelabs 90207 automated noninvasive oscillometric device, programmed to register BP at 20-minute intervals for the 24-hour period. Valid registries had to fulfill a series of pre-established criteria, including ≥80% of systolic and diastolic BP successful recordings during the daytime and nighttime periods, 24-hour duration, and ≥1 BP measurement per hour. Daytime and nighttime periods were defined individually according to the patients' self-reported data of going-to-bed and getting-up times. Circadian patterns were defined by calculating night-to-day ratios for systolic and diastolic BP. According to this, patients were classified as systolic or diastolic extreme dippers (night-to-day ratio <0.8), dippers (night-to-day ratio 0.8–0.9), nondippers (night-to-day ratio 0.9–1), and risers (night-to-day ratio >1).

### Study Variables

Variables of each patient collected from the interview and physical examination obtained at the routine visit and from clinical records were defined and measured in accordance with international guidelines. These included age, sex, weight, body mass index, duration of hypertension, known cardiovascular risk factors, biochemical values of creatinine, and lipid profile, target organ damage including urinary albumin excretion (microalbuminuria defined as values >30 mg/g of creatinine), ECG (left ventricular hypertrophy defined as a

Sokolow-Lyon voltage >38 mm and/or Cornell duration/voltage index >2440 mm/ms), and clinical cardiovascular disease: coronary heart disease, congestive heart failure, or cerebrovascular disease.[15] The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease-Epidemiology Collaborative equation.[16] Diabetes mellitus was diagnosed using the medical history if the patient was under antidiabetic treatment or by 2 or more fasting plasma glucose determinations ≥7.0 mmol/L (126 mg/dL). Dyslipidemia was considered to be present if patients were being treated with lipid-lowering drugs and/or total cholesterol was >5 mmol/L (190 mg/dL), low-density lipoprotein cholesterol was >3.0 mmol/L (115 mg/dL), high-density lipoprotein cholesterol was <1.0 mmol/L (40 mg/dL) in men or <1.2 mmol/L (46 mg/dL) in women, or triglycerides were >1.7 mmol/L (150 mg/dL). Moreover, details about antihypertensive treatment (including number and types of drugs) were also collected.

## Statistical Analysis

Data are presented as absolute frequencies and percentages for qualitative variables and as mean (SD) or median (interquartile range) for quantitative variables. Differences in study variables between groups were assessed with the Pearson $\chi^2$ test for qualitative variables and the Student *t* test (or Mann–Whitney test) for quantitative data. In addition, general linear models for quantitative variables and multiple logistic regression for qualitative variables were used for the assessment of differences after adjusting for age and sex. The SPSS Windows version 19.0 software (SPSS Inc, Chicago, IL) was used for statistical analysis.

## Results

A total of 11 972 (16.9%) patients fulfilled the standard criteria of RH (office systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mm Hg despite the use of ≥3 antihypertensive drugs), and 955 (7.9% of RH; 1.4% of the entire treated group) were considered as having RfH (elevated office BP despite the simultaneous use of 5 or more antihypertensive agents).

Compared with RH, patients with RfH were younger, more frequently males, had a longer duration of hypertension, and higher prevalence of obesity, diabetes mellitus, and dyslipidemia. The prevalence of chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 $m^2$) was also higher in RfH patients. Regarding organ damage, after adjusting for age and sex, microalbuminuria, ECG-based left ventricular hypertrophy and previous history of a cardiovascular event were also significantly higher in RfH, compared with RH patients (Table 1).

All groups of antihypertensive drugs were more commonly used in RfH versus RH patients, including mineralocorticoid receptor antagonists, which amounted to 11.5% of RfH (n=111; 88 with spironolactone and 22 with eplerenone), and to 1.4% in RH (*P*<0.001 for the comparison between groups) (Table 2).

**Table 1.** Clinical Features in RfHs in Comparison With RH Subjects

| | RfH (n=955) | RH (n=11 017) | *P* Value | *P* Adjusted for Age and Sex |
|---|---|---|---|---|
| Age, y | 63.9 (11.0) | 64.9 (11.6) | 0.007 | |
| Sex, % men | 56.3 | 51.3 | 0.003 | |
| Duration hypertension, y | 13.3 (9.2) | 10.9 (8.5) | <0.001 | <0.001 |
| BMI, kg/$m^2$ | 31.6 (4.8) | 30.7 (4.8) | <0.001 | <0.001 |
| Obesity (BMI ≥30), % | 59.6 | 51.4 | <0.001 | <0.001 |
| Diabetes mellitus, % | 48.1 | 33.5 | <0.001 | <0.001 |
| Smokers, % | 15.1 | 12.9 | 0.056 | 0.290 |
| Dyslipidemia, % | 61.9 | 51.7 | <0.001 | <0.001 |
| LVH by ECG, % | 27.6 | 14.9 | <0.001 | <0.001 |
| Serum creatinine, mg/dL | 1.20 (0.69) | 1.02 (0.42) | <0.001 | <0.001 |
| eGFR <60 mL/min per 1.73 $m^2$, % | 32.1 | 23.6 | <0.001 | <0.001 |
| UAE, mg/g | 14.2 [4–58.5] | 8.9 [3.3–28] | <0.005 | 0.101 |
| UAE ≥30 mg/g, % | 38.3 | 24.5 | <0.001 | <0.001 |
| Previous cardiovascular disease, % | 20.5 | 14.7 | <0.001 | <0.001 |

Values are mean (SD) or median [interquartile range]. BMI indicates body mass index; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy; RfH, refractory hypertension; RH, resistant hypertension; UAE, urinary albumin excretion.

**Table 2.** Antihypertensive Drug Classes in Patients With RfH or RH

| Drug Class | RfH | RH | *P* Value |
|---|---|---|---|
| Diuretics* | 100% | 100% | |
| RAS blockers | 99.4% | 95.5% | <0.001 |
| CCB | 84.9% | 58.3% | <0.001 |
| β-Blockers | 77.2% | 43.0% | <0.001 |
| α-Blockers | 62.4% | 17.4% | <0.001 |
| Central blocking agents | 12.1% | 1.4% | <0.001 |
| Aldosterone antagonists | 11.5% | 1.4% | <0.001 |
| Vasodilators | 2.2% | 0.2% | <0.001 |

Central blocking agents include clonidine, moxonidine, reserpine, and α-methyldopa. Vasodilators include hydralazine and minoxidil. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; RAS, renin–angiotensin system; RfH, refractory hypertension; RH, resistant hypertension. *Required for definition. RAS blockers include ACE inhibitors, ARB, and aliskiren.

Table 3 shows office and ambulatory BP values in patients with RfH and RH. After adjusting for age and sex, the former group had significantly higher values for office, 24-hour, daytime and nighttime systolic BP, and for nighttime diastolic BP. RfH was also associated with higher night-to-day ratios for both systolic and diastolic BP. As a consequence, the proportion of reduced dippers/risers was increased in RfH, compared with RH patients ($P<0.001$ for both systolic and diastolic pattern distribution) (Figure).

**Table 3.** Differences in Office, 24-H, Daytime, and Nighttime BP, as Well as Night-to-Day Ratios, in Patients With RfH Compared With RHs

| | RfH (n=955) | RH (n=11 017) | *P* Value | *P* Adjusted for Age and Sex |
|---|---|---|---|---|
| Office systolic BP | 164.8 (19.3) | 160.8 (17.3) | <0.001 | <0.001 |
| Office diastolic BP | 87.8 (13.7) | 88.1 (12.2) | 0.645 | 0.093 |
| 24-h systolic BP | 139.7 (17.4) | 134.2 (15.7) | <0.001 | <0.001 |
| 24-h diastolic BP | 75.2 (12.5) | 74.5 (11.2) | 0.122 | 0.885 |
| Daytime systolic BP | 141.6 (17.5) | 136.7 (15.9) | <0.001 | <0.001 |
| Daytime diastolic BP | 77.2 (13.1) | 76.9 (11.7) | 0.580 | 0.274 |
| Nighttime systolic BP | 134.2 (20.5) | 126.9 (18.0) | <0.001 | <0.001 |
| Nighttime diastolic BP | 69.5 (12.6) | 67.8 (11.1) | <0.001 | 0.001 |
| Systolic BP night/day ratio | 0.95 (0.09) | 0.93 (0.09) | <0.001 | <0.001 |
| Diastolic BP night/day ratio | 0.90 (0.10) | 0.88 (0.09) | <0.001 | <0.001 |

Values are mean (SD). BP indicates blood pressure; RfH, refractory hypertension; RH, resistant hypertension.

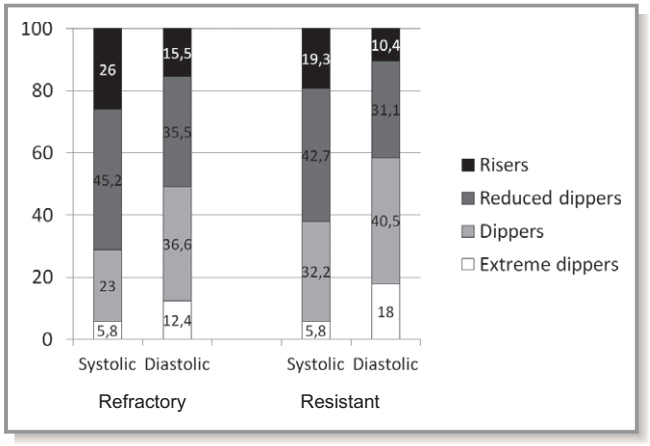


**Figure.** Distribution of circadian patterns in refractory and resistant hypertensive patients. The former group has a higher proportion of reduced dippers and risers for both systolic and diastolic BP ($P<0.001$ for both comparisons). BP indicates blood pressure.

A total of 255 patients among 955 with RfH (26.7%) had normal 24-hour BP (<130/80 mm Hg). The prevalence of white-coat RfH was significantly lower when compared with RH (37.1% with normal 24-hour BP; $P<0.001$). When comparing patients with true, versus white-coat RfH (Table 4), the former group were more frequently males, with a longer duration of hypertension, and more frequently had left ventricular hypertrophy on ECG or microalbuminuria.

## Discussion

The main findings of the present study were, firstly, that the prevalence of this particular phenotype of RfH was low (1.4% of treated hypertensive) but still accounts for a significant part of the population of RH (7.9%). Secondly, cardiovascular risk was higher in the group of RfH in comparison to RH. Thirdly, the prevalence of white-coat RfH was lower than the prevalence of white-coat RH, but still high: 26.7% of them had a 24-hour controlled BP, and fourthly, white-coat RfH was associated with less target organ damage, compared with RfH with elevated 24-hour BP.

In the present study, only 1.4% of treated hypertensive patients had RfH. The prevalence of RfH observed in the participants in the REGARD (Reasons for Geographic And Racial Differences in Stroke) Study was even lower (0.5%).[8] In the present study, 7.9% of RH had RfH. Dudenbostel et al[9,17] reported that the prevalence of RfH in a referral hypertension

**Table 4.** Clinical Features in RfHs With or Without Elevated 24-H BP

| | True RfH (n=700) | White-Coat RfH (n=255) | *P* Value |
|---|---|---|---|
| Age, y | 63.9 (11.0) | 63.9 (10.7) | 0.984 |
| Sex, % men | 58.4 | 50.6 | 0.033 |
| Duration hypertension, y | 13.7 (9.2) | 12.3 (9.3) | 0.040 |
| BMI, kg/m$^2$ | 31.6 (4.9) | 31.5 (4.8) | 0.703 |
| Obesity (BMI ≥30), % | 60.1 | 58.0 | 0.602 |
| Diabetes mellitus, % | 48.9 | 45.9 | 0.422 |
| Smokers, % | 16.3 | 11.8 | 0.102 |
| Dyslipidemia, % | 63.7 | 56.9 | 0.060 |
| LVH by ECG, % | 29.7 | 22.0 | 0.018 |
| eGFR <60 mL/min per 1.73 m$^2$, % | 32.0 | 32.2 | 0.962 |
| Serum creatinine, mg/dL | 1.21 (0.69) | 1.16 (0.66) | 0.475 |
| UAE, mg/g | 16.8 [5.0–99.0] | 8.0 [3.1–32] | 0.010 |
| UAE ≥30 mg/g, % | 42.9 | 28.3 | 0.047 |
| Previous cardiovascular disease, % | 20.6 | 20.4 | 0.952 |

Values are mean (SD) or median [interquartile range]. BMI indicates body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy; RfH, refractory hypertension; UAE, urinary albumin excretion.

unit was ≈5%, and Calhoun et al[8] estimated a prevalence of RfH of 3.6% of subjects with controlled or uncontrolled RH. The slightly higher prevalence observed in our study could be explained by 2 reasons: first, because low BP control is one of the main indications for ABPM, it is possible that the Spanish Registry was selecting more subjects with difficult-to-treat hypertension than other population-based studies. Secondly, the prevalence of RfH depends critically on the definition used, and thus our study may have overestimated the actual prevalence because in our definition we did not specifically require the mandatory use of chlorthalidone and spironolactone, which are associated with higher BP control rates.[9] In fact, it is noteworthy that only 11% of our patients were treated with mineralocorticoid receptor antagonists. The use of this drug in RfH observed by Calhoun et al[8] was higher (18%), but still lower than expected. A meta-analysis of studies in which mineralocorticoid receptor antagonists with or without random allocation were used has shown that low-dose spironolactone is an effective and safe additional drug to achieve BP control in many RH patients, although it is required that renal function is preserved, or only slightly or moderately reduced.[18] The results of the PATHWAY-2 (The Prevention and Treatment of Hypertension With Algorithm based therapy) study,[19] the first randomized study evaluating different therapeutic options (spironolactone, doxazosin, bisoprolol, or placebo) as the fourth step in the management of patients with RH, have unequivocally demonstrated that spironolactone is the best option, at least in the short term, to improve BP control in RH subjects. The open-label, randomized clinical trial DENERVHTA (DENERVación en HiperTensión Arterial) study[20] has shown that allocation to spironolactone treatment (25–50 mg daily) in true RH subjects was more effective in reducing systolic and diastolic 24-hour BP than renal denervation. These results support that, except if a contraindication exists, mineralocorticoid receptor antagonists should be included in the therapeutic regimen of subjects with RH.

This phenotype of RfH shares some similarities but also some differences with respect to subjects with RH. In our study, patients with RfH had a significantly higher prevalence of diabetes mellitus, obesity, target organ damage, and previous history of cardiovascular disease, as well as a longer duration of hypertension, as previously reported by other authors.[8,21]

Differences between RfH and RH go in the same direction as those observed when comparing RH versus controlled patients,[4] thus suggesting that, when markedly present, the same characteristics leading to RH would be responsible for treatment failure and development of RfH, as an extreme phenotype.[9]

Another important novel feature in RfH patients is the worse circadian profile in comparison to RH. Not only are office and ambulatory systolic blood pressure higher, but also differences are more important in nighttime BP, and the nocturnal decline in BP is lower. Both nocturnal BP elevation and reduced nocturnal dipping have been associated with increased prevalence of target organ damage and a worse cardiovascular outcome in patients with RH.[22–24]

We have also reported here that 1 out of 4 RfH patients in the present study show normal 24-hour BP, suggesting that the white-coat effect accounts for a quite high rate of patients with apparent treatment failure. Although its prevalence was considerably lower than that of RH,[2] it is surprising that those patients were still receiving 5 or more drugs based only on clinic BP, without considering ABPM in earlier steps of management. A recent report[10] has found that normal ABPM of RfH was present only in 2 out of 31 patients with RfH. Besides differences in sample size, discrepancies between studies are probably derived from patients' origin, a highly specialized clinic in the report from Siddiqui and coworkers[10] and a nationwide Registry in the current report. We can speculate that perhaps a previous normal ABPM has prevented an increase in antihypertensive treatment in patients attending a specialized hypertension clinic, thus selecting only those with a true resistance to 5 drugs. In addition, the report from Siddiqui et al[10] used automated office BP monitoring, which has been claimed to results in lower values than daytime BP obtained through ABPM.[25] In contrast, our data derive from the implementation of ABPM in clinical settings where this tool was

previously unavailable. We can also speculate that most patients were uptitrated to 5 or more antihypertensive drugs without considering ABPM.

Differences in ambulatory in RfH were associated with differences in the cardiovascular risk profile, as left ventricular hypertrophy and microalbuminuria were more common in true- versus white-coat RfH patients. It seems reasonable to advocate for ABPM to guide therapeutic decisions, at least in those patients not achieving BP control with 3 antihypertensive drugs.

Our study has some limitations. First, it is a cross-sectional study that allows only descriptive associations, but this was the main objective of the present report; secondly, like other registries, the Spanish registry was not directly focused on RfH.

Another limitation we must mention is that the diagnosis of RH or RfH is probable, but not absolutely confirmed, since we cannot ensure that all secondary causes of hypertension have been discarded in such a large database, not just the suboptimal adherence. We must remark that according to the study-accepted definition, the criterion used to define refractory hypertension required the use of a diuretic, but not necessarily a mineralocorticoid receptor antagonist. Most patients were included in this database before the publication of the results of the PATHWAY-2 Study.[19] Certainly, in the light of recent evidence, the percentage of patients with noncontrolled BP that receive a mineralocorticoid receptor antagonist in our cohort is low. In addition, only whites have been included in the present study, and our results cannot be extrapolated to other populations; other previous studies have shown that RfH was more common among patients of black ancestry.[8]

In conclusion, 1.4% of treated hypertensive patients are not controlled even they are treated with 5 or more antihypertensive drugs. These RfH patients, in comparison to RH, have some distinctive clinical features of a worse cardiovascular risk profile and more target organ damage, probably associated with higher ambulatory BP and more pronounced circadian alterations. One in 4 RfH patients have normal 24-hour BP (white-coat RfH) also exhibiting less organ damage than those with true RfH. Our findings are relevant for clinical practice because given the magnitude of white-coat RfH, physicians should be aware of avoiding overdiagnosing and overtreating these patients, based only on clinic BP if the decisions rely exclusively on clinic BP. Standardized repeated BP measurement obtained by patients at home during several days has also been recommended in clinical practice, but in patients with RH and RfH 24-hour ABPM is more reliable and also provides relevant information about nighttime BP and circadian pattern. Moreover, given the low use of the effective-proven mineralocorticoid antagonist receptor drugs in RfH, a large room for improvement in BP control remains as a simple, reasonable perspective.

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## Disclosures

None.

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