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ARTICLE

Prevalence, predictors, and outcomes of both true- and pseudo-resistant hypertension in the action to control cardiovascular risk in diabetes trial: a cohort study

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Abstract

Resistant hypertension (RH) has been poorly studied due to the difficulty in distinguishing it from nonadherence—the exclusion of which is necessary to accurately diagnose RH. Therefore, little is known about the prevalence, predictors, and outcomes of true RH. We evaluated 1838 patients from the standard blood pressure (BP) arm of the Action to Control Cardiovascular Risk in Diabetes Trial. We classified patients into three groups: "true RH", "pseudo-RH" (i.e., patients with BP levels that would classify them as RH but who were non-adherent), and "other" (i.e., those who could not be classified as having "true RH" or "pseudo-RH"). We examined predictors of true and pseudo-RH and the relationship between true RH and the composite outcome of nonfatal MI, nonfatal stroke, or cardiovascular death. Among 1838 participants with complete information, 489 (26.6%) met the definition of true RH, and 94 (16.1%) RH patients had "pseudo-RH" on ≥1 visit over the first 12 months. Predictors of RH included: baseline SBP ≥ 160 mmHg (OR = 8.79; 95% CI: 5.70–13.68) and baseline SBP between 140–159 (OR = 2.91; 95% CI: 2.13–4.00) compared to SBP < 140, additional baseline BP medication (OR = 3.40; 95% CI: 2.83–4.11), macroalbuminuria (OR = 2.35; 95% CI: 1.50–3.67), CKD (OR = 1.53; 95% CI: 0.99–2.33), history of stroke (OR = 1.73; 95% CI: 1.04–2.82), and black race (OR = 1.39; 95% CI: 1.02–1.88); the cross-validated C-statistic was 0.80. "True RH" patients had a 65% increased hazard in composite outcome (HR = 1.65; 95% CI: 1.13–2.42). In conclusion, the majority of patients classified as having RH had "true RH," which was more common among those who are black, have macroalbuminuria, CKD, stroke, higher baseline SBP, and are taking more baseline antihypertensives. These patients are at increased risk for cardiovascular and mortality events.

Keywords Hypertension · diabetes · resistant hypertension · adherence

Introduction

Hypertension affects ~1 billion adults worldwide [1, 2] and accounts for more cardiovascular deaths in the United States than any other modifiable cardiovascular risk factor [3]. Among US adults with hypertension, only 53% have adequate blood pressure (BP) control [4]. There are a number of factors that contribute to poorly controlled hypertension, including medication nonadherence and physician inertia to up-titrate medications. However, some individuals do not achieve adequate BP control despite appropriate clinician behavior and optimal patient adherence.

Consistent with this, the most recent 2018 American Heart Association Scientific Statement on Resistant Hypertension (RH) defines RH as the failure to achieve BP targets in an individual on ≥3 antihypertensive medications (of which one is a diuretic) or achieving BP goal but requiring ≥4 medications [5, 6]. This definition requires that nonadherence to prescribed antihypertensive medications be excluded before "true" RH can be diagnosed.

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Accurate data on RH are limited in part because of the difficulty in conducting suitable studies in which there are strict per-protocol up-titration of BP medication, appropriate BP measurement methods, and careful monitoring of adherence [7, 8]. Prior studies have been unable to separate true RH from "pseudoresistance", a term used to describe scenarios in which a patient would meet the conventional definition of RH but for whom nonadherence, errors in measurement, or white-coat effect cannot be confidently ruled out [6]. Few studies on RH have required that perfect adherence be a condition for the classification of true RH. As such, the prevalence, predictors, and outcomes of true RH patients free from misclassification due to nonadherence are not well elucidated. We used data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure trial to address these knowledge gaps.

Methods

Participants

The design, rationale, and main results of the ACCORD trial have been previously published [9, 10]. Briefly, the ACCORD Blood Pressure trial randomly assigned 4733 high-risk participants with type 2 diabetes mellitus to either intensive (SBP ≤ 120 mmHg) or standard blood-pressure control (SBP ≤ 140 mmHg) and was a multicenter trial at 77 sites organized into seven networks in the United States and Canada. All participants were also randomly assigned to either intensive or standard glycemic control.

Eligible participants had type 2 diabetes, glycated hemoglobin A1c (HbA1c) ≥ 7.5%, and were ≥40 years with cardiovascular disease or ≥55 years with evidence of substantial atherosclerosis, albuminuria, left ventricular hypertrophy, or ≥2 additional risk factors for cardiovascular disease. Participants were eligible for the blood-pressure trial if they had SBP from 130 to 180 mmHg, were taking ≤3 antihypertensives, and had a 24-h protein excretion rate of <1.0 g. Exclusion criteria included body mass index (BMI) > 45 kg/m^2, serum creatinine >1.5 mg per deciliter, and other serious illnesses.

The IRB was approved by the Partners Human Research Committee.

Overall design

Our analysis focused on patients randomized to a standard SBP target of 140 mmHg. We chose the 140 mmHg target to conduct our analysis for several reasons: first, per-protocol up-titration in the 120 mmHg group was much more stringent, requiring frequent office visits unlikely to be represented in real clinical practice and thus affecting generalizability; second, the difference in per-protocol instructions for uptitration and office visits would represent a confounder in our analysis combining patients from both groups; and finally, we felt that the standard SBP target would more accurately reflect general real-world population estimates based on prior practice patterns from historical guideline recommendations. After randomization, patients in the standard group were scheduled for regular visits at months 1 and 4 and every 4 months thereafter (Appendix 1). We included only patients who had complete medication and adherence information throughout the first 12 months, as well as complete baseline covariate information and were on ≥1 BP medication at baseline. BP measurements and adherence to antihypertensives were used to identify the prevalence of true RH at each visit and within the first 12 months of study initiation. Cardiovascular outcomes were assessed beginning 12 months after randomization (i.e., beginning immediately after defining patients as having true RH) until the end of the study period of 7 years. The ACCORD approach to treatment intensification has been described elsewhere [9].

Adherence definition

Perfect adherence to any individual medication was defined as per the ACCORD trial definition, in which a participant takes his or her medication as prescribed ≥80% of the time. Consistent with other hypertension treatment trials, the adherence definition in ACCORD was prespecified and based on patient self-report [11, 12]. Any patient who did not reach this 80% level of self-reported adherence to any one medication in his or her prescribed regimen over the time period between the prior visit and current visit was classified as non-adherent to said individual medication at the current visit month. We assessed adherence status at each scheduled visit within the study's initial 12-month period, with visits at 1, 4, 8, and 12 months. We chose 4-month intervals to allow time for the effects of non-adherence to BP medications to be reflected in physiologic BP readings.

Resistant hypertension definition

We classified patients into three mutually exclusive groups: (1) 'true RH,' defined as the failure to achieve BP target (≥140 mmHg systolic) while perfectly adherent to ≥3 antihypertensive medications (including a diuretic) or achieving the BP goal while perfectly adherent to ≥4 medications (including diuretic); (2) 'pseudo-RH', which included those who would be incorrectly classified as having resistant hypertension under a definition that neglects to consider adherence; specifically, this was defined as participants who were prescribed ≥3 medications and had SBP > 140 mmHg

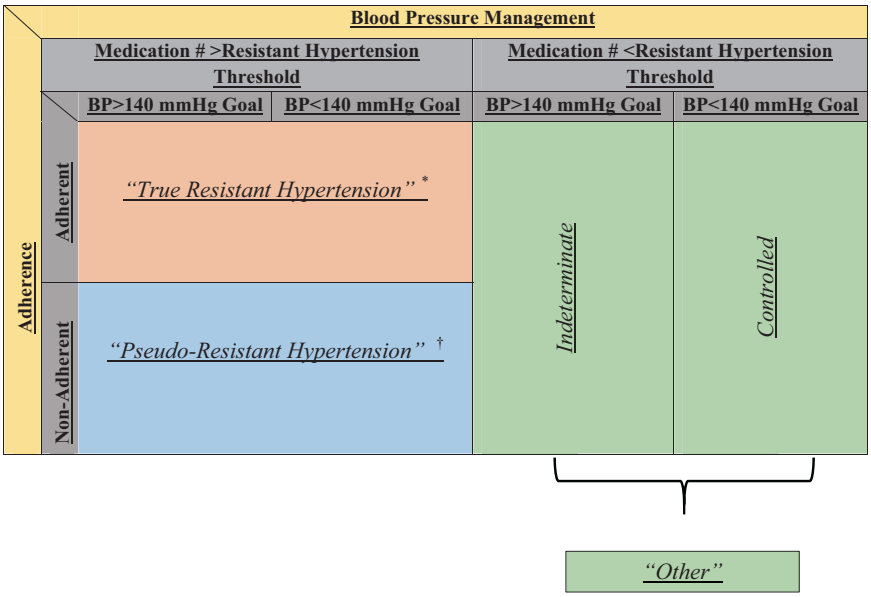

Fig. 1 Definitions of hypertension categories. * Participants with SBP above goal (≥140 mmHg systolic) despite perfect adherence to ≥3 antihypertensives, including a diuretic, and those with BP controlled (<140 mmHg systolic) with perfect adherence to ≥4 medications, including a diuretic. †Participants who were prescribed ≥3 medications and had SBP > 140 mmHg but were adherent to fewer than 3 of them, or participants who were prescribed ≥4 medications and had SBP ≤ 140 mmHg but were adherent to fewer than 4 of them

but were adherent to fewer than 3 of them, or participants who were prescribed ≥4 medications and had SBP ≤ 140 mmHg but were adherent to fewer than 4 of them; and (3) 'other' patients, defined as those who did not meet the definition of true or pseudo-RH. A visual depiction of the 3 groups and how they were defined is displayed in Fig. 1. In addition, a flowchart of participants and how they were categorized is displayed in Fig. 2.

Prevalence of RH classification over time

To estimate the proportion of patients with different types of RH over time, we reported the proportion of patients classified as true RH, pseudo-RH, and other at 1, 4, 8, and 12 months. We additionally reported on the proportions of patients *ever* classified as true- or pseudo-RH within the initial 12-month period. Finally, to more finely elucidate the phenomena of true vs. pseudo-RH, we reported the proportion of conventionally resistant hypertension patients (under a definition that neglects adherence) who were in fact pseudo-RH due to nonadherence at each visit month as well as non-adherent at least once within the 12-month period.

Predictors of true RH

For prediction modeling, we used each participant's hypertension classification at 12 months as the outcome of interest to allow time for appropriate physician per-protocol medication titration and stabilizing of the participants' physiologic responses to their BP regimens. The candidate variables considered for predictors of true RH were selected based on clinical judgment and included sex, age, race (black, Hispanic, and other race; White as reference), baseline SBP ≥ 160 mmHg and baseline SBP between 140–159 mmHg (SBP < 140 mmHg as reference) and DBP ≥ 90 mmHg (DBP < 90 mmHg as reference), HbA1c, total cholesterol, triglycerides, VLDL, LDL, fasting plasma glucose, chronic kidney disease (CKD), macroalbuminuria, number of antihypertensives at the baseline post-randomization visit, education, heart failure, depression, alcohol, insurance coverage, smoking status, BMI, and history of cardiovascular disease, myocardial infarction (MI), or stroke.

Clinical outcomes

We examined ACCORD's primary outcome, a composite of nonfatal MI, nonfatal stroke, or cardiovascular death.

Secondary outcomes examined included a combination of the primary outcome plus revascularization or hospitalization for congestive heart failure ("expanded macrovascular outcome") and a combination of a fatal coronary event, nonfatal MI, or unstable angina ("major coronary disease events"). Details and corresponding results are detailed in the Appendix.

Statistical analysis

We used descriptive statistics to estimate the prevalence of true RH, pseudo-RH, and other. To predict variables associated with true RH as compared to all other groups of patients, we fit multivariable logistic regression models including a fully fitted model with all candidate variables and a reduced model condensed via backwards section procedure. In backwards selection, covariates that did not reach a predefined 0.10 level of significance were removed

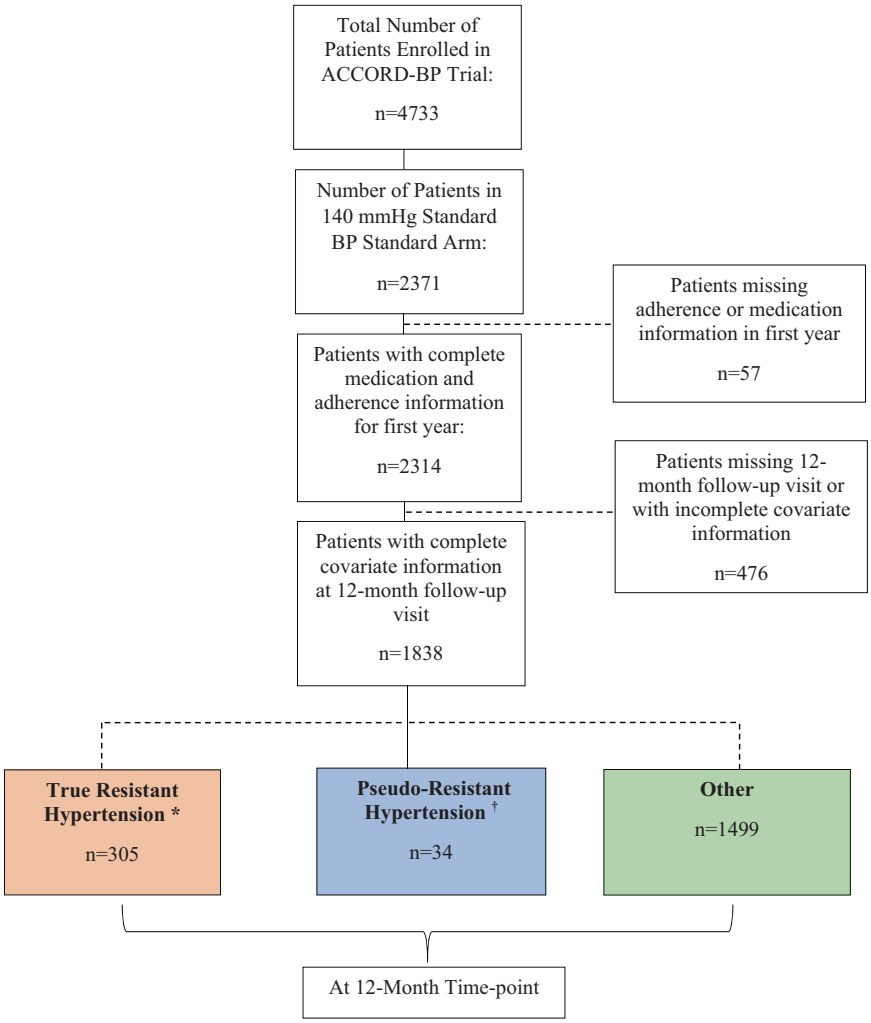

Fig. 2 Flowchart of study participants used for analysis. * SBP > 140 mmHg while adherent to ≥ 3 blood pressure medications (including a diuretic); OR SBP ≤ 140 mmHg while adherent to ≥4 blood pressure medications (including a diuretic). †Prescribed ≥ 3 medications and SBP > 140 mmHg goal but not perfectly adherent to ≥ 3 medications prescribed OR prescribed ≥ 4 medications and SBP ≤ 140 mmHg but adherent to < 4 medications

one-by-one in order of highest *p*-value until all covariates were below the 0.10 threshold. We then fit models excluding variables inherently part of the definition of RH (i.e., baseline BP measurements and number of medications at the baseline post-randomization visit). From this modified, fully fitted model that excluded definitional components, we assessed another reduced model condensed via backwards selection procedure. Overall, we produced six models; each model's discrimination was assessed through a cross-validated C-statistic.

The relationship between true RH status and time to primary and secondary outcomes was analyzed using multivariable Cox proportional hazards modeling. To align the exposure definition time period with the beginning of the outcome assessment period, those who had outcomes prior to 12 months were excluded from our outcome analyses. A multivariable Cox model was used to adjust for the baseline differences and potential confounders based on clinical knowledge. A 2-sided *p*-value of <0.05 was considered statistically significant.

All analyses were conducted in R 3.51 statistical software.

Sensitivity analyses

Boosted regression for predicting true RH

In sensitivity analysis, we used a generalized boosted regression approach to evaluate the model identifying the strongest predictors from a list of all candidate variables. We evaluated another boosted model from all variables except those that included definitional components of RH (i.e., number of BP medications and baseline SBP).

Generalized boosted regression models create a prediction model by building many small regression trees that collectively can provide highly accurate classification [13]. Using this regression tree approach offers advantages over standard logistic regression in improving prediction accuracy by identifying nonlinear associations between predictors and outcomes as well as deep

Table 1 Demographics and medication information

Baseline characteristics	True resistant hypertension $n = 305$ (16.6%)	Pseudo-resistant hypertension $n = 34$ (1.8%)	Other $n = 1499$ (81.6%)
Age, mean (SD), years	63.7 (7.0)	66.7 (7.1)	62.6 (6.8)
Male sex, %	51.5%	44.1%	53.3%
Race			
White	49.8%	32.4%	60.0%
Black	33.1%	32.4%	22.4%
Hispanic	6.6%	29.4%	6.8%
Other	10.5%	5.9%	11.1%
Education			
Less than high school	15.4%	26.5%	14.7%
High school graduate	30.2%	32.4%	27.4%
Some college or technical school	29.8%	23.5%	33.2%
College graduate	24.6%	17.6%	24.7%
Uninsured, %	11.8%	17.6%	15.5%
Current smokers, %	9.5%	5.9%	11.6%
Weekly alcohol consumption, mean (SD)	0.9 (2.9)	0.2 (0.7)	1.0 (2.8)
Depression, %	20.0%	11.8%	26.0%
BMI, mean (SD)	32.9 (5.3)	31.8 (5.4)	32.1 (5.3)
Baseline SBP, mean (SD), mmHg	149.8 (16.4)	152.6 (17.8)	138.5 (14.2)
Baseline DBP, mean (SD), mmHg	76.6 (11.1)	76.6 (13.4)	76.0 (10.0)
Cardiovascular history, %	41.3%	38.2%	34.0%
HbA1c, mean (SD)	8.4 (1.1)	8.6 (1.2)	8.3 (1.1)
Fasting glucose, mean (SD)	173.4 (59.1)	180.8 (72.3)	175.2 (57.7)
Cholesterol, mean (SD)			
Total	187.3 (38.8)	202.2 (43.8)	191.0 (44.9)
VLDL	35.3 (24.9)	33.7 (19.6)	36.9 (29.1)
LDL	105.8 (31.7)	125.0 (38.6)	108.4 (36.2)
HDL	46.2 (13.4)	43.5 (10.9)	45.9 (13.7)
Triglycerides, mean (SD)			
Serum creatinine, mean (SD)	0.94 (0.23)	0.94 (0.25)	0.89 (0.24)
eGFR, mean (SD)	87.0 (25.3)	83.7 (22.1)	92.4 (27.7)
Macroalbuminuria (UACR > 300 mg/g), %	15.7%	17.6%	4.9%
Heart failure, %	7.9%	8.8%	3.7%
Hx MI, %	18.0%	8.8%	14.6%
Hx stroke, %	9.8%	8.8%	5.1%
Hx angina, %	12.8%	8.8%	12.3%
CABG, %	12.1%	17.6%	11.7%
PTCI, %	13.4%	8.8%	10.4%
Medications at baseline post-randomization			
# Prior BP meds at baseline, mean (SD)	3.2 (0.4)	3.1 (0.3)	1.7 (0.7)
≥4 BP medications, %	23.1%	9.1%	0.1%
≥5 BP medications, %	0.0%	0.0%	0.0%

Table 1 (continued)

Baseline characteristics	True resistant hypertension $n = 305$ (16.6%)	Pseudo-resistant hypertension $n = 34$ (1.8%)	Other $n = 1499$ (81.6%)
Diuretics, %	100%	100%	32.4%
ACE/ARB, %	89.7%	90.9%	74.9%
Beta-blocker, %	51.9%	54.5%	28.3%
CCB, %	41.7%	27.3%	19.0%
Alpha-blocker, %	3.8%	0.0%	3.6%
Reserpine, %	0.6%	9.1%	0.0%
Hydralazine, %	0.0%	0.0%	0.2%
Other, %	1.9%	9.1%	4.3%
Medications at 12 months			
Number of BP medications, mean (SD)	3.8 (0.8)	3.5 (0.6)	1.8 (0.8)
≥4 BP medications, %	60.0%	41.2%	0.3%
≥5 BP medications, %	13.1%	5.9%	0.0%
Diuretics, %	100%	100%	48.8%
ACE/ARB, %	77.4%	79.4%	77.9%
Beta-blocker, %	72.1%	67.6%	29.0%
CCB, %	53.1%	38.2%	13.5%
Alpha-blocker, %	8.2%	5.9%	2.4%
Reserpine, %	5.6%	8.8%	0.0%
Hydralazine, %	2.3%	0.0%	0.0%
Other, %	2.0%	0.0%	0.8%

interactions among predictors [13]. We assessed the boosted models' discriminative abilities using a fivefold cross-validated C-statistic, which quantifies model prediction accuracy as applied to a new set of patients by randomly partitioning the cohort into 5 samples of approximately equal size [14].

Predictors of pseudo-RH

In further sensitivity analysis, we examined predictors for "pseudo-RH" compared to "True RH" (reference group) using multivariable logistic regression and stepwise backwards selection. The cross-validated C-statistic was used to assess discrimination.

Results

Baseline characteristics and blood pressure medication information

Baseline characteristics of patients within all three groups and details of the antihypertensives they were on at the baseline post-randomization visit and at 12 months are described in Table 1.

Prevalence of RH classifications over time

The proportion of patients classified as true RH, pseudo-RH, and other at each visit month are displayed in Fig. 3. Over the first year, the proportion of patients classified as true RH increased from each visit until the 12-month visit, with 9.2% of patients classified as true RH in the first month, then 12.8%, 14.8%, and 16.6% by 4, 8, and 12 months, respectively (Fig. 3A). At the 1-, 4-, 8-, and 12-month visits, 8.7%, 8.5%, 8.2%, and 10.0% of patients, respectively, who would conventionally be classified as RH in actuality had pseudo-RH due to nonadherence (Fig. 3B). Over the entire 12-month period, 489 patients (26.6%) fit the criteria for true RH for at least one visit (Fig. 3C). Over the full 12-month period, 16.1% of RH patients were "pseudo-RH" for at least one visit (Fig. 3D).

Prediction models for resistant hypertension and nonadherence

A total of 1838 patients had complete medication, adherence, and baseline covariate information as well as a documented 12-month visit for prediction modeling. Table 2 shows the 6 models that we examined to identify predictors of true RH. All models that included all baseline

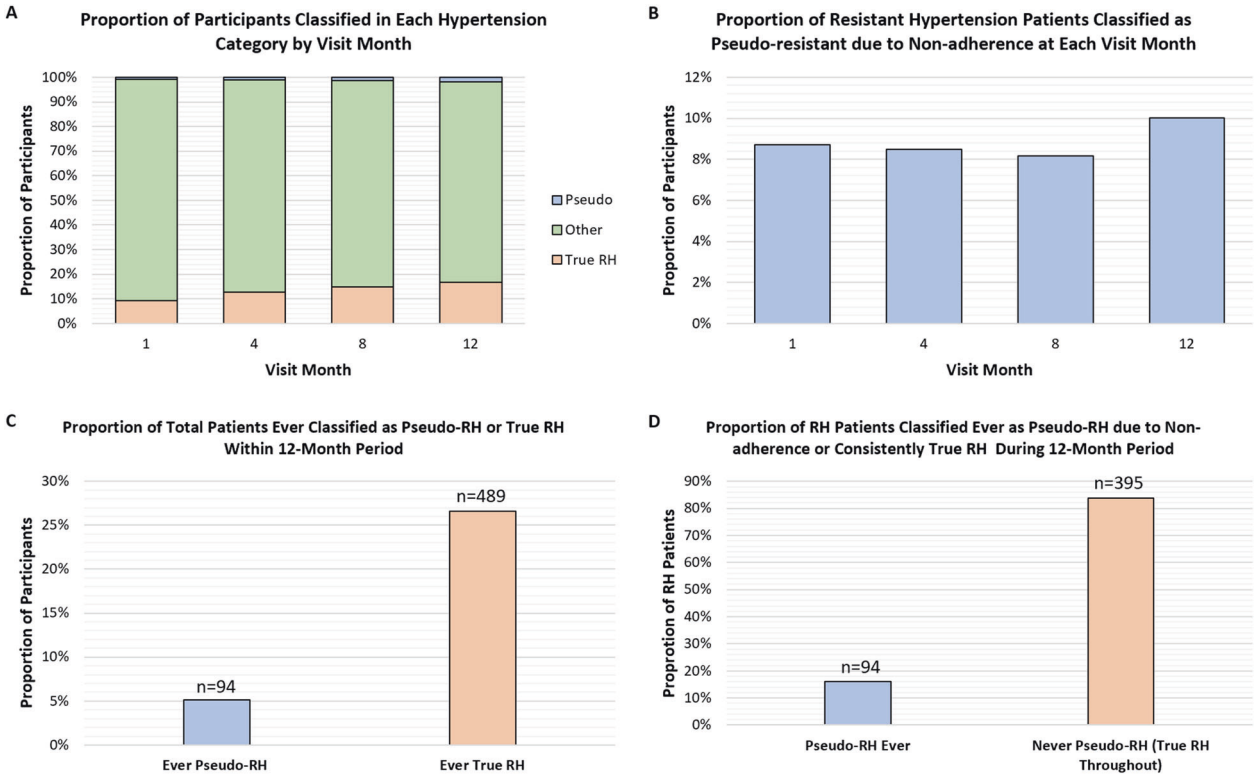

Fig. 3 Prorportions of patients with "True RH," "Pseudo-RH," and "Other" classifications. **A** Proportion of participants who are classified as either "True RH," "Pseudo-RH," or "Other" at each visit month (1, 4, 8, 12 months); **B** The proportion of conventionally resistant hypertensive patients (under definition that neglects adherence) who are in fact "Pseudo-RH," due to nonadherence to BP medications at each visit month (1, 4, 8, 12 months); **C** The proportion of total participants who have ever been classified as "Pseudo-RH," and "True RH," within the 12-month study period. **D** Proportion of conventionally resistant hypertensive patients (under a definition that neglects adherence) who have ever been classified as "Pseudo-RH," due to nonadherence or who have been consistently classified as True RH within the 12-month study period

characteristics accurately discriminated patients with true RH from those without (cross-validated C-statistic, 0.80–0.83). Predictors identified via stepwise backwards selection included: baseline SBP ≥ 160 mmHg (OR = 8.79; 95% CI: 5.70–13.68), baseline SBP between 140–159 (OR = 2.91; 95% CI: 2.13–4.00), each additional baseline BP medication (OR = 3.40; 95% CI: 2.83–4.11), macroalbuminuria (OR = 2.35; 95% CI: 1.50–3.67), history of stroke (OR = 1.73; 95% CI: 1.04–2.82), and black race (OR = 1.39; 95% CI: 1.02–1.88); DBP > 90 mmHg decreased the risk for RH (OR = 0.59; 95% CI: 0.34–0.99). The associated generalized boosted regression considering all the same candidate variables yielded an even higher fivefold cross-validated C-statistic of 0.83, indicating very high prediction discrimination. This model identified the same variables as the stepwise backwards selection model (Model 2) except for DBP and additionally identified heart failure, BMI, age, weekly alcohol consumption, HbA1c, and high and borderline total cholesterol as additional predictors for true RH.

The three models that considered variables that were not inherently a component of the definition of RH had moderate discriminative ability (cross-validated C-statistic, 0.64–0.68). Predictors identified via stepwise backward selection (Model 5) included black race, CKD, macroalbuminuria, history of stroke, depression, heart failure, BMI, and age. The generalized boosting regression model in the sensitivity analysis (Model 6) identified the same predictors as Model 5 but additionally identified a lack of insurance, weekly alcohol consumption, cardiovascular history, and HbA1c.

Finally, an additional sensitivity analysis examining predictors for "pseudo-RH" compared to "True RH" (reference group) identified older age and Hispanic race as the only two variables after backwards selection that met the criteria for inclusion in the model predicting a classification of "pseudo-RH." The cross-validated C-statistic for this model was 0.69. The results for this model can be found in the Appendix.

Outcomes

Among 1838 total patients, 32 had cardiovascular or mortality events prior to 12 months, leaving 1806 (98.3%)

Table 2 Adjusted odds ratios (With 95% confidence intervals) for logistic regression models and relative influence % for generalized boosted regression predicting for true RH[a] presented together with explanatory power

	Models including definitional components of RH (i.e. BP meds and baseline BP)			Models excluding definitional components of RH (i.e. No BP meds and baseline BP)		
	Model 1: full model with logistic regression	Model 2: logistic model after stepwise backwards selection of Model 1[b]	Model 3: generalized boosted regression	Model 4: full model with logistic regression	Model 5: logistic model after stepwise backwards selection of Model 4[b]	Model 6: generalized boosted regression
Patient variables[c]						
Race[d]						
Black	1.42 (0.99, 2.03)	1.39 (1.02, 1.89)	1.9%	1.75 (1.26, 2.42)	1.65 (1.25, 2.18)	12.9%
Hispanic	1.04 (0.55, 1.89)			1.2 (0.68, 2.03)		
Other	1.34 (0.80, 2.20)			1.31 (0.83, 2.01)		
CKD[e]	1.57 (1, 2.43)	1.53 (0.99, 2.33)	1.4%	1.79 (1.19, 2.66)	1.80 (1.21, 2.65)	11.2%
Macroalbuminuria[e]	2.41 (1.51, 3.81)	2.35 (1.50, 3.67)	1.2%	3.15 (2.08, 4.73)	2.99 (2.00, 4.43)	6.8%
History of stroke[e]	1.67 (0.93, 2.94)	1.73 (1.04, 2.82)	1.4%	1.66 (0.97, 2.78)	1.79 (1.12, 2.81)	2.5%
Depression[e]	0.70 (0.48, 0.99)	0.72 (0.51, 1.01)	1.2%	0.73 (0.53, 1.01)	0.72 (0.52, 0.98)	2.2%
Baseline blood pressure[f]						
SBP 140–159 mmHg	2.98 (2.17, 4.12)	2.91 (2.13, 4.00)	6.1%			
SBP ≥ 160 mmHg	9.50 (6.04, 15.02)	8.79 (5.70, 13.68)	24.9%			
DBP > 90 mmHg	0.57 (0.32, 0.96)	0.59 (0.34, 0.99)				
Number of baseline BP medications	3.32 (2.75, 4.05)	3.40 (2.83, 4.11)	34.3%			
Heart failure[e]	1.11 (0.6, 1.98)		0.6%	1.67 (0.97, 2.8)	1.88(1.11, 3.08)	7.4%
BMI	1.02 (0.99, 1.05)		4.2%	1.04 (1.01, 1.06)	1.03 (1.01, 1.06)	5.9%
Age	1.00 (0.98, 1.02)		8.9%	1.02 (1, 1.04)	1.02 (1.00, 1.04)	27.3%
Female sex[e]	1.00 (0.72, 1.39)			1 (0.75, 1.35)		
Education[g]						
Less than high school	0.77 (0.47, 1.24)			0.79 (0.51, 1.22)		
High school graduate	0.86 (0.58, 1.28)			0.95 (0.67, 1.36)		
Some college or technical school	0.81 (0.55, 1.19)			0.83 (0.59, 1.18)		
Uninsured[e]	0.74 (0.46, 1.17)			0.76 (0.5, 1.14)		1.2%
Current smoker[e]	1.19 (0.72, 1.91)			0.89 (0.57, 1.36)		
Weekly alcohol consumption	1.00 (0.95, 1.05)		1.1%	1.00 (0.95, 1.05)		4.1%
Cardiovascular history[e]	1.09 (0.73, 1.6)			1.19 (0.82, 1.69)		3.5%
HbA1c	1.10 (0.94, 1.28)		10.9%	1.09 (0.95, 1.26)		14.9%
Total cholesterol (mg/dL)[h]						
High (≥240)	0.87 (0.49, 1.50)		1.5%	0.78 (0.47, 1.26)		
Borderline (200–239)	1.00 (0.70, 1.43)		0.4%	0.86 (0.62, 1.18)		
LDL (mg/dL)[i]						
Borderline LDL (70–189)	1.17 (0.74, 1.88)			1.28 (0.84, 2)		
High LDL (≥190)	0.69 (0.18, 2.26)			0.73 (0.21, 2.16)		
High HDL (>40 mg/dL)[e]	1.02 (0.72, 1.45)			1.02 (0.75, 1.39)		
Triglycerides (mg/dL) [j]						
High triglycerides (≥500)	0.72 (0.27, 1.72)			0.99 (0.41, 2.19)		
Borderline triglycerides (≥150–499)	1.00 (0.72, 1.4)			1.07 (0.8, 1.44)		

Table 2 (continued)

	Models including definitional components of RH (i.e. BP meds and baseline BP)			Models excluding definitional components of RH (i.e. No BP meds and baseline BP)		
	Model 1: full model with logistic regression	Model 2: logistic model after stepwise backwards selection of Model 1[b]	Model 3: generalized boosted regression	Model 4: full model with logistic regression	Model 5: logistic model after stepwise backwards selection of Model 4[b]	Model 6: generalized boosted regression
History of myocardial infarction	1.05 (0.66, 1.67)			1.09 (0.71, 1.67)		
Explanatory power						
Cross-validated C-statistic	0.81	0.80	0.83	0.67	0.64	0.68

[a]Each model shown in Table 2 predict for "True Resistant Hypertension" and use all other individuals as the reference group

[b]These models contain only variables identified after stepwise backwards selection of full models displayed in columns immediately to the left

[c]Unless otherwise indicated, variables were included as continuous linear predictors

[d]White race is the reference variable

[e]Reference for these variables is the lack of the specified condition

[f]Baseline SBP < 140 mmHg, and baseline DBP < 90 mmHg are the respective reference variables

[g]College graduate is the reference variable

[h]Low cholesterol (<200 mg/dL) is the reference variable

[i]Low LDL (<70 mg/dL) is the reference variable

[j]Low triglycerides (<150 mg/dL) is the reference variable

patients for our outcome analysis from 1-year post-randomization to the end of the study period.

Patients with "true RH" had a 65% increased hazard in primary outcome (HR = 1.65; 95% CI: 1.13–2.42) (Fig. 4). Further testing of secondary outcomes can be found in the Appendix.

Discussion

We used data from the ACCORD trial to evaluate the prevalence, predictors, and outcomes of "true RH"—a definition that newly distinguishes RH from "pseudoresistance" due to nonadherence. Our study serves to clearly elucidate the phenomena of "true RH" free from misclassification due to nonadherence. We demonstrate a notable prevalence of true RH at 12 months (16.6%) and a large proportion of patients who were ever classified as true RH at any point within 1 year of careful antihypertensive management (26.6%). We also find that among those classified as having RH based on prior guideline definitions, up to 16.1% were in fact "pseudoresistant" due to nonadherence at some point within 12 months of treatment even in a carefully monitored trial setting, where the setting for optimal adherence should be ideal. We additionally provide the most robust analysis of predictors for RH to date using both classical and novel modeling techniques. Our analysis identified several strong predictors of true RH, including higher baseline SBP, higher number of baseline BP medications, macroalbuminuria, CKD, history of stroke, and black race, using a model that achieved very strong discriminative capacity (cross-validated C-statistic = 0.80). Patients with true RH were also at significantly increased risk for long-term cardiovascular outcomes. These findings demonstrate a notable prevalence and poor prognosis for high-risk diabetic patients with true resistant hypertension.

A notable strength of our study is the study design of ACCORD, which had stringent per-protocol instructions on BP monitoring, medication intensification, and strict documentation of medication adherence. As our study was able to exclude the effect of medication nonadherence, we were able to document the prevalence of true RH and pseudo-RH over time. We showed a robust set of predictors for true RH that are distinct from those of pseudo-RH, which suggests that these two groups are heterogeneous. While limited studies have attempted to account for pseudo-RH in their analyses [15, 16], these studies do not further characterize pseudo-RH patients.

It is somewhat surprising that among patients classified as having resistant hypertension under a definition that neglects adherence, only 10% were "pseudoresistant" at 12 months. This number increased to 16.6% when considering whether such patients ever qualified as pseudo-RH

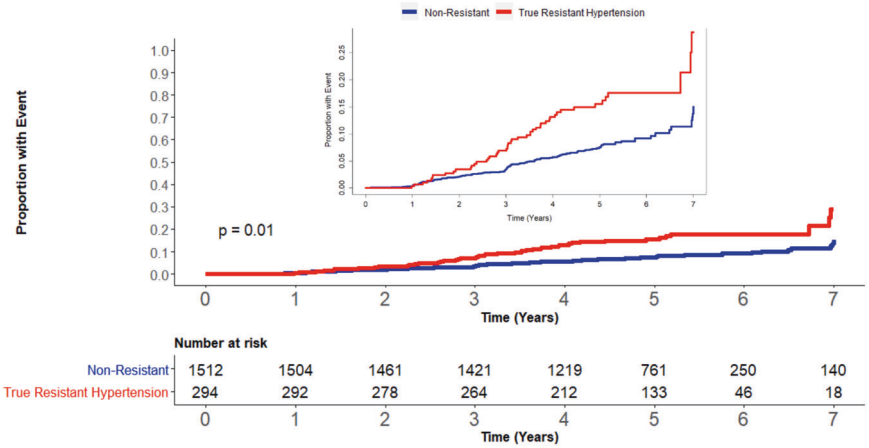

Fig. 4 Primary outcome of true resistant hypertensives vs. non-resistant patients. Patients with "True RH" had a 65% increased hazard in primary outcome (HR = 1.65; 95% CI: 1.13–2.42). Primary outcome was a composite of nonfatal MI, nonfatal stroke, or cardiovascular death. To align the exposure definition time period with the beginning of the outcome assessment period, those who had outcomes prior to the 12-month follow-up were excluded for the purposes of our outcomes analyses. Multivariable Cox proportional hazard regression model was adjusted for the baseline differences between the groups as outlined in Table 1 and based on clinical judgment

within 12 months; however, this nonadherence estimate is still lower than that reported in cohort studies of hypertension patients [17, 18]. Moreover, self-reported adherence has been documented as often overestimating adherence.[x] As such, our report may underreport the number of patients who in fact have pseudo-RH. Given careful monitoring of adherence in ACCORD, one could reasonably project the proportion of "pseudoresistant" patients to be much higher than 10% of resistant hypertension patients in a real-world setting. Future pragmatic trials and studies using nationally representative data would help to more accurately estimate the prevalence of "pseudoresistance" among the general population.

Our models showed strong discriminative ability to distinguish between those with true RH and those without. Few studies have examined the clinical predictors of treatment-resistant hypertension in multivariate models, and because our study is the first to distinguish true RH from pseudo-RH, our models enabled more accurate identification of actual predictors for true RH. Prior single-cohort studies have identified several demographic predictors, including older age, black race, and male sex [5, 19]. In addition, multiple comorbidities have been associated with RH, including obesity [20, 21], CKD [19, 20], OSA [22], and albuminuria [23, 24]. Our study is consistent with some of these observations. In particular, we found that black race was associated with a 39% increased odds of true RH, and macroalbuminuria was associated with a greater than two-fold increased odds of treatment resistance.

We further noted that baseline DBP > 90 mmHg was associated with lower odds of treatment resistance when compared with baseline DBP ≤ 90 mmHg. The presence of depression was also associated with lower odds of RH. These protective factors against RH have not been documented in prior literature on RH; however, it is worth noting that multiple studies have observed decreased BP in depressed patients [25–28]. A physiologic mechanism for this observed association has been proposed, which implicates the central monoamine system as a possible source of an underlying factor independently increasing both the risk for depression and the likelihood of maintaining a low BP level [29, 30]. However, much research is necessary to elucidate the underlying mechanisms contributing to low BP in depressed patients.

Overall, our results suggest that individuals with diabetes who have true RH experience a similarly poor prognosis as suggested by estimates from other populations [31–34]. In line with these studies, we observed a 65% increased hazard for the primary outcome. Further studies should assess effect modification by diabetes status to investigate whether diabetic patients with true resistant hypertension differ in their cardiovascular and renal risk from nondiabetic patients. This will aid clinicians in better risk-stratifying patients and approach treatment intensification decisions. Moreover, our results highlight the need for better ascertainment of adherence on the part of physicians to better distinguish pseudoresistant from true RH.

Our study has several limitations. First, we cannot rule out the possibility of selection bias in our outcome analysis from potential unmeasured confounders. Nevertheless, to mitigate selection bias, our Cox model was adjusted for baseline covariates and potential clinically relevant confounders. We also cannot rule out pseudoresistance due to white-coat hypertension, nor can we comment on resistant hypertension as evaluated via out-of-office BP measurement, which may be more reflective of a patient's true BP

than office BP measurements as conducted in the ACCORD trial; however, given that the BP readings recorded were the averages of three repeated measures, pseudoresistance due to errors was likely mitigated. In addition, we were unable to compare outcomes between those who had pseudoresistant versus true RH, as our sample size and event rate within the pseudoresistant group was not sufficiently adequate to make meaningful statistical comparisons and would lead to imprecise estimates in this type of analysis. This would be a clinically meaningful question for future research in population studies. A further limitation is that adherence was assessed using self-reports; this may not be a sufficiently sensitive measure of actual nonadherence, resulting in misclassification and affecting our reported rates of true RH. Finally, our study is a post hoc analysis of a population of higher-risk individuals with diabetes mellitus; as such, our results may not be generalizable to other populations, and our prevalence estimates cannot be extended to the national population. In addition, generalizability is limited due to the study population, which reflects a population of patients enrolled in an RCT where monitoring was more stringent than would be observed in regular clinical practice.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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References

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2224–60.
2. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. JAMA 2017;317:165–82.
3. Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJL, et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med. 2009;6:e1000058.
4. Yoon SS, Fryar CD, Carroll MD. Hypertension prevalence and control among adults: United States, 2011–2014. Hyattsville, MD, USA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics 2015.
5. Correction to: 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;72:e33.
6. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American heart association. Hypertension 2018;72:e53–90.
7. Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. J Am Coll Cardiol. 2008;52:1749–57.
8. Sarafidis PA, Bakris GL. State of Hypertension Management in the United States: Confluence of Risk Factors and the Prevalence of Resistant Hypertension. J Clin Hypertens. 2008;10:130–9. https://doi.org/10.1111/j.1751-7176.2008.07309.x.
9. Cushman WC, Grimm RH Jr, Cutler JA, Evans GW, Capes S, Corson MA, et al. Rationale and design for the blood pressure intervention of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol. 2007;99:44i–55i.
10. Cushman WC, Evans GW, Byington RP, Goff Jr DC, Grimm Jr RH, Cutler JA, et al.. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N. Eng. J. Med. 2010;362:1575–85.
11. Haley WE, Gilbert ON, Riley RF, Newman JC, Roumie CL, Whittle J, et al. The association between Self-Reported Medication Adherence scores and systolic blood pressure control: a SPRINT baseline data study. J Am Soc Hypertens. 2016;10:857–64.e2.
12. Kronish IM, Lynch AI, Oparil S, Whittle J, Davis BR, Simpson LM, et al. The Association Between Antihypertensive Medication Nonadherence and Visit-to-Visit Variability of Blood Pressure: Findings From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Hypertension 2016;68:39–45.
13. Friedman J, Hastie T, Tibshirani R. Additive logistic regression: a statistical view of boosting (with discussion and a rejoinder by the authors). Ann. Stat. 2000;28:337–407.
14. Efron B, Gong G. A Leisurely Look at the Bootstrap, the Jackknife, and Cross-Validation [Internet]. Am Statistician. 1983;37:36. https://doi.org/10.2307/2685844.
15. Daugherty SL, David Powers J, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, et al. Incidence and Prognosis of Resistant Hypertension in Hypertensive Patients [Internet]. Circulation. 2012;125:1635–42. https://doi.org/10.1161/circulationaha.111.068064.
16. Sinnott S-J, Smeeth L, Williamson E, Douglas IJ. Trends for prevalence and incidence of resistant hypertension: population based cohort study in the UK 1995-2015. BMJ 2017;358:j3984.
17. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. J Hypertens. 2013;31:766–74.
18. Irvin MR, Shimbo D, Mann DM, Reynolds K, Krousel-Wood M, Limdi NA, et al. Prevalence and correlates of low medication adherence in apparent treatment-resistant hypertension. J Clin Hypertens. 2012;14:694–700.
19. Sim JJ, Bhandari SK, Shi J, Liu ILA, Calhoun DA, McGlynn EA, et al. Characteristics of Resistant Hypertension in a Large, Ethnically Diverse Hypertension Population of an Integrated Health System [Internet]. Mayo Clin Proc. 2013;88:1099–107. https://doi.org/10.1016/j.mayocp.2013.06.017.
20. Acharya T, Tringali S, Singh M, Huang J. Resistant Hypertension and Associated Comorbidities in a Veterans Affairs Population [Internet]. J Clin Hypertension. 2014;16:741–5. https://doi.org/10.1111/jch.12410.
21. Holecki M, Duława J, Chudek J. Resistant hypertension in visceral obesity [Internet]. Eur J Intern Med. 2012;23:643–8. https://doi.org/10.1016/j.ejim.2012.04.012.

22. Demede M, Pandey A, Zizi F, Bachmann R, Donat M, McFarlane SI, et al. Resistant Hypertension and Obstructive Sleep Apnea in the Primary-Care Setting. Int J Hypertens. 2011;2011:1–5. https://doi.org/10.4061/2011/340929.
23. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension 2011;57:1076–80.
24. Oliveras A, Armario P, Hernández-del Rey R, Arroyo JA, Poch E, Larrousse M, et al. Urinary albumin excretion is associated with true resistant hypertension [Internet]. J Hum Hypertension. 2010;24:27–33. https://doi.org/10.1038/jhh.2009.35.
25. Hildrum B, Romild U, Holmen J. Anxiety and depression lowers blood pressure: 22-year follow-up of the population based HUNT study, Norway. BMC Public Health. 2011;11:601.
26. Licht CMM, de Geus EJC, Seldenrijk A, van Hout HPJ, Zitman FG, van Dyck R, et al. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. Hypertension 2009;53:631–8.
27. Hildrum B, Mykletun A, Holmen J, Dahl AA. Effect of anxiety and depression on blood pressure: 11-year longitudinal population study. Br J Psychiatry. 2008;193:108–13.
28. Paterniti S, Alperovitch A, Ducimetiere P, Dealberto M-J, Lepine J-P, Bisserbe J-C. Anxiety But Not Depression Is Associated With Elevated Blood Pressure in a Community Group of French Elderly [Internet]. Psychosom Med. 1999;61:77–83. https://doi.org/10.1097/00006842-199901000-00013.
29. Head GA. Central monoamine neurons and cardiovascular control. Kidney Int Suppl. 1992;37:S8–13.
30. Stahl SM. Blue genes and the monoamine hypothesis of depression. J Clin Psychiatry. 2000;61:77–8.
31. Tsioufis C, Kasiakogias A, Kordalis A, Dimitriadis K, Thomopoulos C, Tsiachris D, et al. Dynamic resistant hypertension patterns as predictors of cardiovascular morbidity: a 4-year prospective study. J Hypertens. 2014;32:415–22.
32. Pierdomenico SD, Lapenna D, Bucci A, Di Tommaso R, Di Mascio R, Manente BM, et al. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. Am J Hypertens. 2005;18:1422–8.
33. Salles GF, Cardoso CRL, Muxfeldt ES. Prognostic Influence of Office and Ambulatory Blood Pressures in Resistant Hypertension [Internet]. Arch Intern Med. 2008;168:2340. https://doi.org/10.1001/archinte.168.21.2340.
34. Muxfeldt ES, Cardoso CRL, Salles GF. Prognostic Value of Nocturnal Blood Pressure Reduction in Resistant Hypertension [Internet]. Arch Intern Med. 2009;169:874. https://doi.org/10.1001/archinternmed.2009.68.