Prognostic Importance of Resistant Hypertension in Patients With Type 2 Diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study

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OBJECTIVE

To evaluate the prognostic importance of resistant hypertension (RHT) for the development of complications in a cohort of individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS

A total of 646 patients had the diagnosis of apparent treatment-resistant hypertension (aRHT) based on mean office blood pressure (BP) levels during the 1st year of follow-up. They were reclassified as white-coat/controlled or true/uncontrolled RHT according to 24-h ambulatory BP monitoring (ABPM), using the traditional BP cutoffs and the new 2017 American College of Cardiology (ACC)/American Heart Association (AHA) criteria. Multivariate Cox analyses examined the associations between RHT diagnoses and the occurrence of microvascular and cardiovascular complications and all-cause and cardiovascular mortality.

RESULTS

During a median follow-up of 10 years, 177 patients had a cardiovascular event (145 major ones); 222 patients died (101 from cardiovascular diseases); 200 had a renal event; 156 had a retinopathy event; and 174 patients had a neuropathy event. In relation to non-RHT individuals, aRHT (present in 44.6% and 50% by the traditional and new criteria, respectively) predicted all cardiovascular and mortality outcomes, with hazard ratios (HRs) between 1.64 and 2.16, but none of the microvascular outcomes. True RHT increased the HRs (from 1.81 to 2.25) and additionally predicted renal outcomes. White-coat/controlled RHT implied an increased risk (HRs 1.33–1.86) that was intermediate between non-RHT and true RHT individuals. Classifications using the traditional and the new ACC/AHA criteria were equivalent.

CONCLUSIONS

In patients with type 2 diabetes, the presence of aRHT implied an increased risk of cardiovascular and mortality outcomes, and classification based on ABPM predicted renal outcomes and improved cardiovascular/mortality risk stratification.

Apparent treatment-resistant hypertension (aRHT) is defined as the failure to achieve the recommended office blood pressure (BP) goals despite the concurrent use of three antihypertensive medications of different classes on optimal dosages, or achieving BP goals with four or more drugs (1). Additionally, true resistant hypertension (RHT) is

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defined when an exaggerated white-coat effect is ruled out by out-of-office BP measurements in contrast to white-coat/controlled RHT (1). aRHT is associated with increased risks of cardiovascular morbidity and mortality in longitudinal studies in hypertensive populations (1–6). Individuals with type 2 diabetes have a higher prevalence of RHT (1,2) and also an increased mortality that is mainly because of cardiovascular diseases (7). Nonetheless, there were scarce studies exploring the prognostic impact of RHT specifically in type 2 diabetes (8–10), with controversial findings. Furthermore, 24-h ambulatory BP monitoring (ABPM) has been consistently demonstrated to be a better predictor of several adverse outcomes than office BP measurements (11,12). However, no previous study to date has examined the prognostic importance of true/uncontrolled and white-coat/controlled RHT as defined by 24-h ABPM.

Another point that needs investigation is which BP level, in terms of RHT definition, better stratifies cardiovascular risk in individuals with type 2 diabetes: the traditional criteria (≥140/90 and ≥130/80 mmHg for office and 24-h ambulatory BPs, respectively) that was recently reaffirmed by the European Societies of Cardiology and Hypertension in 2018 (13) or the lately proposed lower values (≥130/80 and ≥125/75 mmHg for office and 24-h ambulatory BPs, respectively) by the American College of Cardiology (ACC) and the American Heart Association (AHA) in 2017 (14). Only one study performed in hypertensive individuals with diabetes evaluated the predictive importance of these two different office BP cutoffs, and it found that aRHT was not a predictor of all-cause mortality by either cutoff (8).

Therefore, the current study aimed to investigate the prognostic impact of the baseline diagnosis of aRHT (based on office BP levels) and of true/white-coat RHT (based on 24-h ambulatory BP levels) for mortality and for the development of macro- and microvascular complications in a ongoing cohort of patients with type 2 diabetes from the Rio de Janeiro Type 2 Diabetes (RIO-T2D) Cohort Study. Additionally, we evaluated whether the two BP cutoff values for defining aRHT and true RHT, the traditional values (13) and the new lower ones (14), differ in their ability to predict adverse outcomes.

RESEARCH DESIGN AND METHODS

Study Overview

It was a prospective follow-up investigation, the RIO-T2D Cohort Study, with 646 patients with type 2 diabetes enrolled between August 2004 and December 2008 and followed-up until December 2018 in the diabetes outpatient clinic of our tertiary-care university hospital. All participants gave written informed consent, and the local ethics committee had previously approved the study protocol. The characteristics of this cohort, the baseline procedures and the diagnostic definitions have been described elsewhere (15–20). In summary, inclusion criteria were all adult patients with type 2 diabetes up to 80 years old with either any microvascular (retinopathy, nephropathy, or neuropathy) or macrovascular (coronary, cerebrovascular, or peripheral artery disease) complication, or with at least two other modifiable cardiovascular risk factors. Exclusion criteria were morbid obesity (BMI ≥40 kg/m^2), advanced renal failure (serum creatinine >180 μmol/L or estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2) or the presence of any serious concomitant disease limiting life expectancy. Diagnostic criteria for chronic complications for patients with diabetes were detailed previously (15–20). In brief, coronary heart disease was diagnosed by clinical, electrocardiographic, or echocardiographic criteria, or by positive ischemic stress tests. Cerebrovascular disease was defined by a previous history of stroke or transient ischemic attacks or by evidence of significant carotid artery stenosis on clinical examination (carotid bruits or decreased carotid pulses) or on carotid ultrasonography (carotid plaques with stenosis >50%). The diagnosis of nephropathy needed at least two albuminurias ≥30 mg/24 h or confirmed reduction of eGFR to ≤60 mL/min/1.73 m^2, as estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, or serum creatinine >130 mol/L. Peripheral neuropathy was determined by clinical examination (knee and ankle reflex activities, feet sensation with the Semmes-Weinstein monofilament, vibration with a 128-Hz tuning fork, pinprick, and temperature sensations), and neuropathic symptoms were ascertained by a standard validated questionnaire (17,20). Office BP was measured three times in each visit using a digital oscillometric BP monitor (HEM-907XL; Omron Healthcare, Kyoto, Japan) with a proper-sized cuff. The first measure was discarded, and the BP considered was the mean between the last two readings (15). ABPM was recorded within the first 6 months of follow-up using Mobil-*O*-Graph, version 12 equipment (Dynamapa; Cardios LTDA., São Paulo, Brazil), and average 24-h systolic BP and diastolic BP were registered (15,18,19). Laboratory evaluation included fasting glycemia, glycated hemoglobin (HbA_{1c}), serum creatinine, and lipids. Albuminuria was evaluated in two nonconsecutive sterile 24-h urine collections. Laboratory examinations and office BP measurements were repeated two to four times each year during follow-up, except albuminuria, which was repeated once annually.

RHT Classification Criteria

RHT classifications were based on mean office BPs obtained during the 1st year of follow-up (median of four clinical visits, eight BP measurements), on ambulatory mean 24-h BPs, and on the number of antihypertensive drugs in use during the ABPM recording. Antihypertensive treatment adherence was evaluated by a standard questionnaire (21) and by pill counting during the 3-month period previous to ABPM. Only patients considered at least moderately adherent (<20% of returned pills) were included. Antihypertensive medication changes during the 1st year of follow-up occurred only during this time period of adherence monitoring and were only drug dosage optimizations, not the addition of any new antihypertensive medication. Therefore, clinic and ambulatory BPs were measured as close as 6 months apart and under the same antihypertensive regimen, except for possible small dosage titration. aRHT was defined as uncontrolled office BPs in patients using three antihypertensive drugs and all patients using greater than or equal to four drugs regardless of controlled/uncontrolled office BP levels (1). True/uncontrolled RHT was defined as uncontrolled ambulatory mean 24-h BPs in patients using greater than or equal to three antihypertensive drugs (1), thus excluding patients with white-coat RHT (uncontrolled office but controlled ambulatory BP levels) and including those with masked RHT (controlled office but uncontrolled ambulatory BPs). In the

same way, white-coat/controlled RHT was defined as all aRHT with controlled ambulatory 24-h BP levels. We used two cutoff values for defining controlled/uncontrolled office and ambulatory BP levels: the traditional one (13) (≥140/90 and ≥130/80 mmHg for office and ambulatory BPs, respectively) and the new 2017 ACC/AHA criteria (14) (≥130/80 and ≥125/75 mmHg for office and ambulatory BPs, respectively).

Follow-Up and Outcomes Ascertainment

The patients were followed-up regularly at least three to four times per year until December 2018 under standardized treatment. The observation period for each patient was the number of months from the date of the first clinical examination to the date of the last clinical visit in 2018 or the date of the first end point, whichever came first. The primary end points were the occurrence of any macro- or microvascular outcomes. Macrovascular outcomes were total cardiovascular events (CVEs; fatal or nonfatal myocardial infarctions [MIs], sudden cardiac deaths, new-onset heart failure, death from progressive heart failure, any myocardial revascularization procedure, fatal or nonfatal strokes, any aortic or lower limb revascularization procedure, any amputation above the ankle, and deaths from aortic or peripheral arterial disease), major adverse CVEs (MACE; nonfatal MIs and strokes plus all cardiovascular deaths), and all-cause and cardiovascular mortalities (15,16). Microvascular outcomes, previously defined, were the following: retinopathy development or worsening (18); a composite renal outcome (19), defined as new microalbuminuria development or new renal failure development (defined as doubling of serum creatinine or end-stage renal failure needing dialysis or death from renal failure); and peripheral neuropathy development or worsening (17,20). Retinopathy and renal outcomes were evaluated by annual examinations (18,19), whereas peripheral neuropathy was evaluated on two serial specific examinations performed after a median of 6 and 10 years from the baseline examination (17,20).

Statistical Analyses

Continuous data were described as means (SD) or as medians (interquartile range [IQR]). Baseline characteristics of patients with non-RHT/aRHT and white-coat/true RHT were compared by *t* test, Mann-Whitney, or χ^2 tests, when appropriate. Kaplan-Meier curves of cumulative end points incidence during follow-up, compared by log-rank tests, were used for assessing different incidences of outcomes between patients with nonapparent RHT and aRHT and with non-RHT, white-coat RHT, and true RHT (three categories). For assessing the prognostic value of aRHT and of true and white-coat RHT in relation to the non-RHT subgroup (the reference one) for each macrovascular and microvascular outcome (except for peripheral neuropathy), a time-to-event Cox analysis was undertaken. First, analyses were only adjusted for age and sex, and then they were further adjusted for other potential confounders/risk factors (diabetes duration; BMI; smoking; physical activity; presence of micro- and macrovascular complications at baseline; serum mean 1st-year HbA_{1c}; HDL- and LDL-cholesterol; and use of insulin, statins, and aspirin). These results were presented as hazard ratios (HRs) with 95% CIs. For the analysis of peripheral neuropathy, a multiple logistic regression was used with the same statistical adjustments, except that height (instead of BMI) and the time interval between the baseline and the other two neuropathy evaluations were included as adjusting covariates. These results were reported as odds ratios with 95% CIs. In the sensitivity and interaction analyses, interactions between each RHT classification and age (<65 vs. ≥65 years old), sex, diabetes duration (<10 vs. ≥10 years long), presence of micro- and macrovascular complications at baseline, and glycemic control (mean HbA_{1c} <7.5 vs. ≥7.5%, <58.5 vs. ≥58.5 mmol/mol) were tested for all end points. Finally, to examine possible reverse causality between RHT and outcomes, separate analyses excluding patients who had any of the end points during the first 2 years of follow-up were performed. In all analyses, a two-tailed probability value <0.05 was considered significant. Statistics were performed with SPSS version 19.0 (SPSS Inc, Chicago, IL).

RESULTS

Baseline Characteristics According to RHT Classification

Six-hundred and forty-six patients with type 2 diabetes were evaluated with office and 24-h ABPM during the 1st year of follow-up. Using the traditional cutoff values for classifying RHT, 288 patients (44.6%) had aRHT; 118 patients (18.3%) had white-coat controlled RHT; and 190 (29.4%) had true uncontrolled RHT by ABPM. Only 20 individuals (3.1%) were reclassified as true RHT because of masked RHT on ABPM. Using the 2017 ACC/AHA criteria increased the prevalence of aRHT to 50% (323 patients) and of true RHT to 36.2% (234 individuals). However, it reduced the prevalence of white-coat controlled RHT to 15.3% (99 individuals). Only 10 patients (1.6%) were reclassified as true RHT because of masked RHT on ABPM with the ACC/AHA criteria. Table 1 outlines the baseline characteristics of those classified as nonapparent RHT, aRHT, white-coat/controlled, and true/uncontrolled RHT by the traditional criteria. Patients with aRHT and with white-coat and true RHT were older and more frequently women, and they had greater BMI and longer diabetes duration than those classified as non-RHT. They also had higher prevalences of diabeties-related micro- and macrovascular complications at baseline, except for peripheral neuropathy, and more frequently used insulin, statins, and aspirin than non-RHT individuals. As expected by the classification criteria, they had higher office and ambulatory BP levels and used more antihypertensive drugs than non-RHT patients. Otherwise, RHT patients had poorer glycemic control, higher albuminuria, and lower eGFR than non-RHT individuals. In general, the characteristics of white-coat RHT and true RHT patients were similar, except that true RHT patients had a higher prevalence of cerebrovascular disease and nephropathy due to diabetes as well as poorer glycemic control than white-coat RHT individuals (in addition to the expected differences in ambulatory BPs). Supplementary Table 1 shows the same baseline characteristics of patients classified by the 2017 ACC/AHA criteria. In general, it follows the same patterns of the traditional cutoff criteria.

End Points Incidence During Follow-Up

During a median follow-up of 10.3 years (maximum of 16 years), which corresponded to 6,286 patient-years (PY) of follow-up, 177 patients had a CVE (crude incidence of 31.2 events per 1,000 PY), and 145 patients had a MACE (24.7 events per 1,000 PY). Two-hundred

Table 1—Baseline characteristics and end points incidence for patients with diabetes

Characteristics	Nonapparent RHT (n = 358)	Apparent RHT (n = 288)	White-coat controlled RHT (n = 118)	True uncontrolled RHT (n = 190)
Age (years)	58.7 (10.2)	62.1 (8.2)*	62.9 (7.5)*	61.3 (8.6)†
Male sex (%)	42.2	34.0‡	34.7	33.2‡
BMI (kg/m^2)	29.1 (4.9)	30.6 (4.7)*	30.6 (4.8)*	30.7 (4.7)*
Smoking, current/past (%)	47.5	40.6	42.4	38.6‡
Physical activity (% active)	22.7	21.9	22.0	20.6
Diabetes duration (years)	7 (2.5–15)	9 (4–16)†	10 (4.5–18)†	8 (4–15)
Chronic diabetes-related complications (%)				
Cerebrovascular disease	6.1	13.9†	8.5	17.4*
Coronary artery disease	10.1	23.3*	24.6*	22.1*
Peripheral artery disease	13.4	21.6†	19.7	21.6‡
Retinopathy	28.9	36.6‡	35.9	37.4‡
Nephropathy	25.7	38.4†	25.0	44.7*
Peripheral neuropathy	25.9	32.9	29.1	33.3
Diabetes treatment (%)				
Metformin	87.2	88.5	90.7	87.4
Sulfonylureas	42.7	45.1	53.4‡	39.5
Insulin	45.5	51.7	44.1	55.8‡
Aspirin	87.7	95.4†	95.7‡	94.7†
Dyslipidemia (%)	86.0	89.9	89.8	90.0
Statins use	73.5	83.2†	83.8‡	82.0‡
BPs (mmHg)				
Office SBP	133 (17)	162 (24)*	155 (23)*	163 (26)*
Office DBP	78 (11)	87 (14)*	84 (13)*	87 (14)*
Ambulatory 24 h SBP	125 (12)	134 (17)*	118 (7)*	143 (13)*
Ambulatory 24 h DBP	73 (9)	75 (11)†	67 (6)*	81 (10)*
Number of antihypertensive drugs	2 (1–2)	4 (3–4)*	4 (3–4)*	4 (3–4)*
Laboratory variables				
Fasting glycemia (mmol/L)	7.9 (2.7)	8.4 (2.8)‡	7.8 (2.3)	8.8 (3.0)†
HbA_{1c} (%)	7.5 (1.4)	7.9 (1.6)†	7.5 (1.3)	8.2 (1.8)*
HbA_{1c} (mmol/mol)	60 (15.3)	63 (17.5)	60 (14.2)	66 (19.7)
Triacylglycerol (mmol/L)	1.8 (1.3)	2.0 (1.8)	1.9 (1.8)	2.1 (1.8)†
HDL-cholesterol (mmol/L)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)
LDL-cholesterol (mmol/L)	2.7 (0.8)	2.8 (0.9)	2.6 (0.8)	2.9 (0.9)‡
eGFR (mL/min/1.73 m^2)	86 (19)	76 (20)*	76 (20)*	75 (20)*
Albuminuria (mg/24 h)	12 (7–30)	16 (7–70)‡	11 (6–25)	21 (8–134)*
Outcomes§				
Total CVEs	75 (22.5)	102 (43.6)*	37 (36.5)‡	69 (46.0)*
MACE	61 (17.8)	84 (34.2)*	29 (27.2)	58 (36.9)*
Cardiovascular mortality	38 (10.7)	63 (24.5)*	22 (19.8)‡	44 (26.7)*
All-cause mortality	98 (27.6)	124 (48.2)*	43 (38.7)‡	87 (52.8)*
Renal composite	105 (35.1)	95 (43.4)	28 (29.5)	71 (52.1)†
Retinopathy (incident/worsening) (n = 526)	86 (49.4)	70 (53.7)	28 (49.1)	43 (51.2)
Peripheral neuropathy (incident/worsening) (n = 510)	92 (31.2%)	82 (38.1%)	28 (28.9%)	59 (43.7%)‡

Values are proportions, means (SDs), or medians (IQR). Patient groups are divided according to the presence or absence of aRHT and of white-coat (controlled) and true (uncontrolled) RHT, which are defined according to the traditional criteria (office BP ≥140/90 mmHg and ambulatory 24-h BP ≥130/80 mmHg, respectively). DBP, diastolic BP; SBP, systolic BP. *$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$ for bivariate comparisons with the nonapparent RHT subgroup. §Values are absolute numbers (incidence rate per 1,000 PYs of follow-up), except for peripheral neuropathy, which are absolute numbers (proportions).

and twenty-two patients died (36.3 deaths per 1,000 PY), 101 of them from cardiovascular causes (16.5 cardiovascular deaths per 1,000 PY). Two-hundred patients presented a renal outcome (crude incidence of 38.8 per 1,000 PY); 119 had new microalbuminuria development; and 81 had deteriorated renal function. A total of 156 patients had new or worsening retinopathy, and 174 had new or worsening peripheral neuropathy. Table 1 and Supplementary Table 1 present the incidences of each outcome in patients classified as non-RHT, aRHT, white-coat, and true RHT according to both criteria. Patients with aRHT and true RHT had higher incidences of all cardiovascular end points and of all-cause mortality than non-RHT individuals. However, only patients with true RHT had higher incidences of renal outcomes and of peripheral neuropathy than non-RHT patients. Patients with white-coat RHT had incidences of cardiovascular and mortality outcomes intermediary between non-RHT and true RHT individuals. The incidence rates of retinopathy were similar in the four subgroups. Kaplan-Meier curves of cumulative incidences over time for patients classified as nonapparent RHT and aRHT (Fig. 1) and for the three categories (non-RHT, white-coat

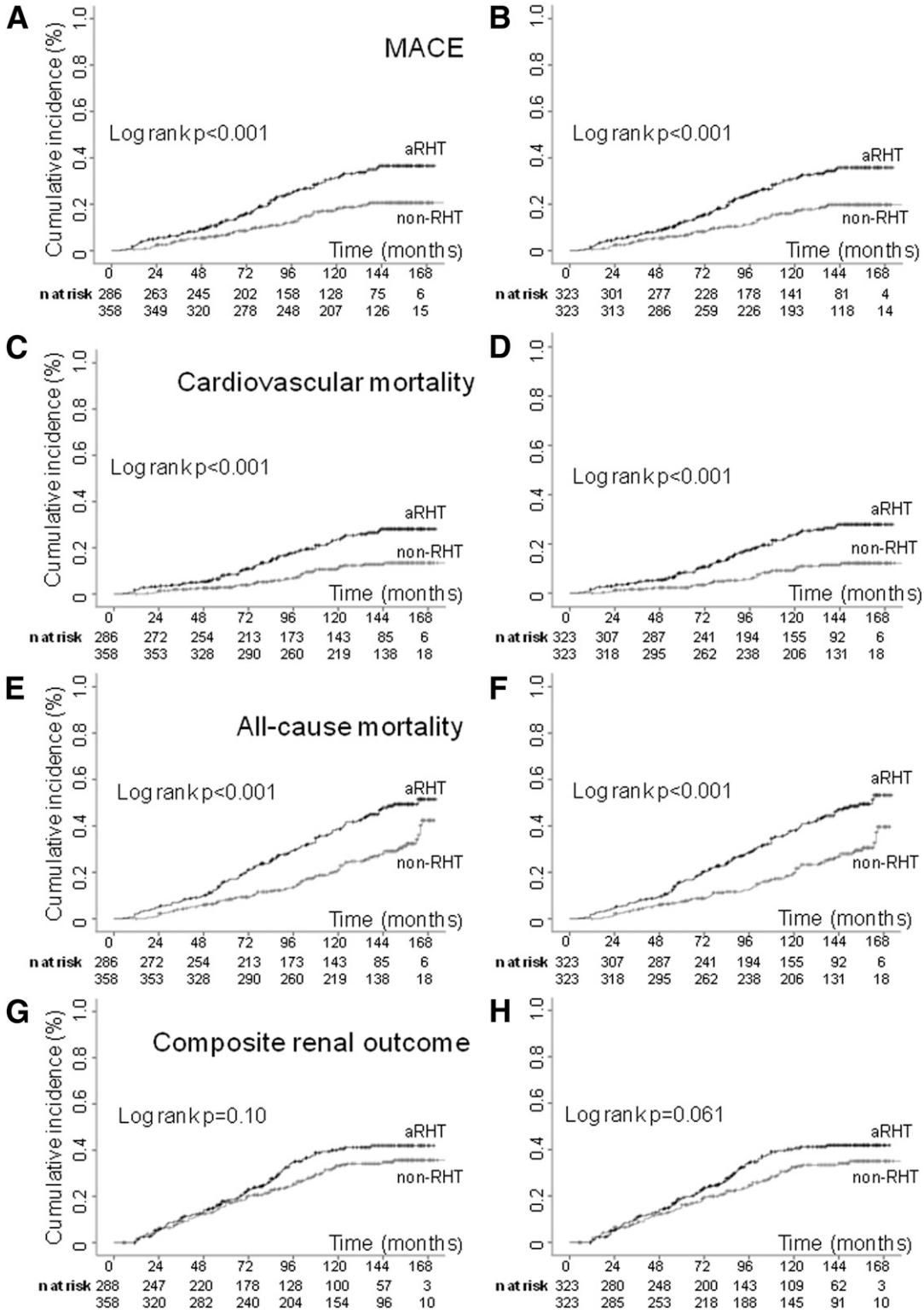

Figure 1—Kaplan-Meier estimation curves of cumulative events incidence during follow-up on the basis of BP levels. The BP levels are defined by the traditional cutoff value (≥140/90 mmHg) and by the new 2017 ACC/AHA cutoff value (≥130/80 mmHg). Curves are shown for MACEs outcome for the traditional (*A*) and new (*B*) cutoff values; for cardiovascular mortality for the traditional (*C*) and new (*D*) cutoff values; for all-cause mortality for the traditional (*E*) and new (*F*) cutoff values; and for the composite renal outcome for the traditional (*G*) and new (*H*) cutoff values in patients classified as aRHT and non-RHT by office BP levels.

RHT, and true RHT) (Supplementary Fig. 1), defined by both criteria, confirmed these findings: patients with aRHT had significantly higher incidences of cardiovascular and mortality end points than nonapparent RHT patients, which was observed both in the white-coat and true RHT subgroups. However, only the true RHT patients had worse renal outcomes.

Table 2—Results of Cox survival analyses for the prognostic value of aRHT

	Traditional criteria		2017 ACC/AHA criteria	
Outcomes	Age/sex adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)§	Age/sex adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)§
Total CVEs ($n = 177$)	1.93 (1.42–2.62)*	1.69 (1.22–2.36)†	1.97 (1.44–2.70)*	1.75 (1.24–2.46)*
MACE ($n = 145$)	1.89 (1.35–2.65)*	1.77 (1.23–2.56)†	1.98 (1.40–2.81)*	1.86 (1.28–2.72)*
CV mortality ($n = 101$)	2.17 (1.44–3.26)*	1.89 (1.21–2.95)†	2.49 (1.62–3.84)*	2.16 (1.36–3.45)*
All-cause mortality ($n = 222$)	1.77 (1.35–2.32)*	1.64 (1.22–2.21)*	1.93 (1.46–2.55)*	1.79 (1.32–2.42)*
Renal composite ($n = 200$)	1.30 (0.98–1.73)	1.15 (0.85–1.57)	1.36 (1.02–1.81)‡	1.21 (0.89–1.65)
Retinopathy ($n = 156$)	1.12 (0.81–1.55)	0.92 (0.64–1.31)	1.10 (0.80–1.52)	0.90 (0.64–1.1.29)
Peripheral neuropathy ($n = 174$)¶	1.13 (0.75–1.71)	0.97 (0.62–1.51)	1.04 (0.69–1.56)	0.90 (0.58–1.40)

aRHT is defined by office BP levels according to the traditional criteria (office BP ≥140/90 mmHg) and to the new 2017 ACC/AHA criteria (office BP ≥130/80 mmHg). CV, cardiovascular. §Adjusted for age; sex; BMI; diabetes duration; smoking; physical activity; presence of micro- and macrovascular diseases at baseline; mean HbA_{1c}; HDL- and LDL-cholesterol levels during the 1st year of follow-up; and use of insulin, statins, and aspirin. ¶Neuropathy outcomes are odds ratios and 95% CIs, adjusted for the same covariates (height instead of BMI) and further to the time interval between neuropathy assessments. *$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$.

Risks Associated With Different RHT Classifications

Tables 2 and 3 show multivariable-adjusted HRs for the associations of aRHT and white-coat/true RHT classifications, respectively, by both criteria with the outcomes. The presence of aRHT as defined by the traditional cutoff criteria significantly increased the risks of cardiovascular outcomes and all-cause mortality, with excess risks ranging from 64 to 89%. However, it was not associated with excess risks for any of the microvascular outcomes. Using the lower 2017 ACC/AHA cutoffs slightly increased the excess risks for cardiovascular and mortality outcomes (Table 2). Otherwise, the presence of true RHT (Table 3) was similarly associated with significantly higher risks of cardiovascular outcomes and all-cause mortality (with HRs higher than those for aRHT, ranging from 1.81 to 2.21), without any notable differences between the traditional and the ACC/AHA criteria of classification. White-coat RHT presented excess risks varying from 33 to 65% when defined by the traditional criteria and from 49 to 86% defined by the 2017 ACC/AHA criteria for cardiovascular and mortality outcomes. Only the true RHT classification was associated with significantly increased risks of adverse renal outcomes, with excess risks of 38 and 37% for the traditional and the 2017 ACC/AHA criteria, respectively. None of the RHT classifications were associated with retinopathy or peripheral neuropathy outcomes.

In interaction and sensitivity analyses, no evidence of interaction was detected between any of the RHT classifications and age, sex, diabetes duration, presence of micro- or macrovascular complications at baseline, and glycemic control, indicating that the prognostic effects of RHT was similarly observed in older and younger individuals, men and women, patients with longer or shorter diabetes duration, with and without previous complications due to diabetes, and with better or poorer controlled diabetes. Also, excluding those individuals who had any of the end points in the first 2 years of follow-up did not change any of the results, signifying that there was no reverse causation between RHT classification and adverse outcomes.

CONCLUSIONS

The present prospective study investigated the importance of aRHT and of white-coat/true RHT as predictors of micro- and macrovascular outcomes

Table 3—Results of Cox survival analyses for the prognostic value of white-coat controlled RHT and of true uncontrolled RHT in relation to non-RHT individuals

	Traditional criteria		2017 ACC/AHA criteria	
Outcomes	White-coat controlled RHT ($n = 118$)	True uncontrolled RHT ($n = 190$)	White-coat controlled RHT ($n = 99$)	True uncontrolled RHT ($n = 234$)
Total CVEs ($n = 177$)	1.54 (1.01–2.36)‡	1.81 (1.25–2.61)†	1.49 (0.93–2.38)	1.82 (1.27–2.61)*
MACE ($n = 145$)	1.51 (0.93–2.43)	1.88 (1.25–2.81)†	1.53 (0.90–2.61)	1.98 (1.33–2.95)*
CV mortality ($n = 101$)	1.65 (0.93–2.43)	2.21 (1.36–3.59)*	1.86 (1.01–3.42)‡	2.25 (1.38–3.69)*
All-cause mortality ($n = 222$)	1.33 (0.91–1.96)	1.90 (1.37–2.63)*	1.56 (1.04–2.34)‡	1.86 (1.35–2.58)*
Renal composite ($n = 200$)	0.88 (0.57–1.34)	1.38 (1.01–1.87)‡	0.99 (0.63–1.54)	1.37 (1.01–1.86)‡
Retinopathy ($n = 156$)	0.85 (0.53–1.35)	0.81 (0.54–1.21)	1.03 (0.65–1.65)	0.77 (0.52–1.14)
Peripheral neuropathy ($n = 174$)¶	0.78 (0.43–1.41)	1.05 (0.64–1.75)	0.79 (0.43–1.47)	0.89 (0.55–1.45)

Values are HRs (95% CI) adjusted for age; sex; BMI; diabetes duration; smoking; physical activity; presence of micro- and macrovascular diseases at baseline; mean HbA_{1c}; HDL- and LDL-cholesterol levels during the 1st year of follow-up; and use of insulin, statins, and aspirin. The traditional criteria are used for white-coat controlled RHT (office BP ≥140/90 mmHg and ambulatory 24 h BP < 130/80 mmHg) and true uncontrolled RHT (office BP ≥140/90 mmHg and ambulatory 24 h BP ≥130/80 mmHg). The 2017 ACC/AHA criteria are used for white-coat controlled RHT (office BP ≥130/80 mmHg and ambulatory 24 h BP < 125/75 mmHg) and true uncontrolled RHT (office BP ≥130/80 mmHg and ambulatory 24 h BP ≥125/75 mmHg). Non-RHT individuals are the reference group. CV, cardiovascular. ¶Neuropathy values are odds ratios (95% CI) adjusted for the same covariates (height instead of BMI) and further to the time interval between neuropathy assessments. *$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$.

and all-cause mortality in high-risk individuals with type 2 diabetes. It demonstrated that aRHT, either diagnosed by the traditional BP cutoff or by the new 2017 ACC/AHA criteria, was associated with increased risks of all macrovascular outcomes (total CVEs, MACE, and cardiovascular mortality) and of all-cause mortality with similar relative risks. However, the aRHT diagnosis, either defined by the traditional criteria or by the new criteria, did not predict any of the microvascular outcomes. Otherwise, the diagnosis of true RHT by both ABPM criteria was shown to be a predictor of all macrovascular outcomes and all-cause mortality, with relative risks higher than those attributed to aRHT, and additionally, it was associated with adverse renal outcomes but not with retinopathy or neuropathy outcomes. Finally, we demonstrated that patients with white-coat RHT (i.e., classified as aRHT by office BPs but as nontrue RHT by ambulatory BPs) still had an increased cardiovascular and mortality risk but equal renal risk compared with non-RHT patients. Overall, this study supports that the new lower cutoff BP values proposed by the 2017 ACC/AHA guideline are, at least, equivalent to the older traditional criteria in terms of the prognostic importance of RHT diagnoses and that using 24-h ABPM to diagnose white-coat/true RHT refines the risk stratification for macrovascular complications and mortality in relation to the aRHT diagnosis based on office BP levels. Also, it improves renal disease risk stratification in patients with type 2 diabetes.

aRHT has been previously demonstrated as a predictor of cardiovascular morbidity and mortality and of renal outcomes in hypertensive populations (3–6,22). However, only two previous observational cohort studies investigated aRHT specifically in type 2 diabetes, and both had results different from ours (8–10). One of them showed that aRHT was not an independent predictor of all-cause mortality after adjusting for the presence of degenerative complications at baseline (8), whereas in the other cohort (9,10), the presence of aRHT was associated with renal function deterioration. In these reports (8–10), an aRHT diagnosis was based on only a few office BP measurements; hence, some misclassification of aRHT might explain, at least partially, the different findings. In our study, aRHT classification was based on mean office BPs during the 1st year of follow-up, hence, using a minimum of six to eight BP measurements over time. Our study advanced in contrast to these previous ones (8–10) by addressing a more comprehensive setting of outcomes that encompassed micro- and macrovascular end points and mortality, with a longer follow-up. We also included the true and white-coat RHT diagnoses based on ABPM, which provided a more accurate measure of actual BP levels than casual office BP measurements (13,14,23).

Notably, we observed that the true RHT diagnosis, based on joining the office and 24-h ambulatory BPs, provided higher estimated HRs for cardiovascular and mortality outcomes than the aRHT diagnosis based solely on office BP measurements. Indeed, we have previously reported (15) in this cohort, but with a shorter follow-up, that ambulatory BPs were better cardiovascular and mortality risk markers than office BPs. Moreover, the true RHT status was the only RHT-based classification that predicted adverse renal outcomes in relation to non-RHT individuals. We had also previously reported on the superiority of ambulatory BPs in contrast to office BP levels as predictors of adverse renal outcomes in a competing risk analysis with mortality (19). Otherwise, we demonstrated, as far as we know, for the first time in diabetes that patients classified as white-coat/controlled RHT still had increased cardiovascular and mortality risks that were intermediary between non-RHT and true RHT individuals. In our cohort, ABPM mostly reclassified patients as white-coat RHT (118 individuals, 41% of those 288 individuals initially classified as aRHT by office BP levels by the traditional criteria; and 99 individuals, 31% of those 323 patients initially classified as aRHT by the ACC/AHA criteria). The opposite reclassification, masked true RHT, was very rare (only 20 patients, 6% of those 358 individuals initially classified as nonapparent RHT by the traditional criteria; and 10 patients, 3% of those 323 originally classified as nonapparent RHT by the ACC/AHA criteria). We had previously reported in a cross-sectional analysis (24) that in hypertensive patients with type 2 diabetes the presence of isolated uncontrolled office-measured hypertension (i.e., white-coat hypertension) was independently associated with higher aortic stiffness and left ventricular mass, two well-known preclinical markers of cardiovascular disease, in comparison with patients with sustained controlled hypertension, suggesting that the white-coat effect is not benign in patients with diabetes. The higher risk of individuals with white-coat hypertension has recently been confirmed in a large prospective cohort of hypertensive individuals from Spain (12). Hence, in patients with type 2 diabetes, the simpler classification of nonapparent RHT/aRHT based only on office BP levels might be sufficient for initial cardiovascular and mortality risk stratification. Otherwise, the ABPM reclassification of patients with aRHT clearly improved cardiovascular/renal and mortality risk prediction. Overall, our findings support the wider use of ABPM in clinical type 2 diabetes management. Otherwise, we did not find any prognostic value of any RHT classification for the development/worsening of diabetes-related retinopathy or peripheral neuropathy. This probably reflects the preponderant importance of glycemic control over BP levels for the development of these microvascular complications (17,18) because all analyses were adjusted for mean HbA_{1c} levels.

Regarding the best BP cutoff values to classify RHT, we demonstrated that the higher traditional cutoffs (13) and the lower new ones proposed in the 2017 ACC/AHA guideline (14) were roughly equivalent in their capacity to predict adverse renal, cardiovascular, and mortality outcomes. As expected, using the lower BP cutoffs increased the prevalences of aRHT and of true RHT. However, this did not affect their predictive ability. Indeed, the new RHT classification yielded slightly higher HRs than the classification based on the traditional BP cutoffs, particularly in relation to an aRHT diagnosis based on office BP levels. Hence, at least in patients with type 2 diabetes, the new ACC/AHA classification of RHT can be used interchangeably with the traditional RHT classification in terms of cardiovascular/renal and mortality risk stratification. Furthermore, it is important to note that the new cutoffs for ambulatory BPs proposed by the 2017 ACC/AHA guideline were mainly based on simple correlations between office and ambulatory BPs in epidemiological studies, but they were not ascertained in outcome-based

trials. So, from this perspective, our study was the first to demonstrate that this new lower 24-h ambulatory BP cutoff was validated against hard cardiovascular outcomes and mortality, at least for the classification of RHT phenotypes in patients with type 2 diabetes.

This study has some limitations that should be noted. First, the diagnosis of white-coat/true RHT was based on a single ABPM performed during the 1st year of follow-up, thus possibly limiting its prognostic power. Also, we had previously shown in a cohort of hypertensive individuals with an aRHT diagnosis that most patients with white-coat RHT developed true RHT in the following years (25); hence, the white-coat/true RHT categories should be faced as a nonfixed dynamic status. Moreover, there was a small time lag (not >6 months) between clinic and ambulatory BP measurements, with some possible small antihypertensive drug titration, which might have affected RHT classifications. Second, this is an observational cohort study on the prognostic value of RHT, and thus, no direct inference can be made regarding cause-and-effect relationships or physiopathological mechanisms. Third, as with any cohort study, residual confounding due to unmeasured or unknown factors cannot be ruled out. Moreover, the RHT subgroups had a higher baseline cardiovascular disease burden than the non-RHT subgroup. Although we have adjusted our analyses as much as possible for these disparities between non-RHT and RHT individuals, some residual confounding was still possible. Finally, this cohort enrolled mostly middle-aged to elderly individuals with a long duration of type 2 diabetes who were treated at a tertiary-care center. Hence, our findings might not be generalized to younger individuals with recent-onset diabetes or treated at primary care.

In conclusion, in patients with type 2 diabetes, the diagnoses of aRHT and of white-coat and true RHT were associated with increased cardiovascular morbidity and mortality and with all-cause mortality, but only the diagnosis of true RHT was capable of predicting worse renal outcomes. The traditional and the new ACC/AHA BP cutoff values to define aRHT and true RHT were equivalent in terms of cardiovascular/renal and mortality risk prediction. In patients with type 2 diabetes and aRHT, ABPM not only allows better BP management, but also improves the stratification risk for cardiovascular/renal outcomes, and it should be regularly performed whenever clinically indicated. Interventional studies of intensive risk factor management in these high-risk patients are warranted to verify whether such increased cardiovascular and renal risks could be reduced.

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