Original Article

# Resistant hypertension in patients with type 2 diabetes: clinical correlates and association with complications

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**Objective:** The phenotype of resistant hypertension in patients with type 2 diabetes has been poorly characterized. This cross-sectional analysis of the large cohort from the Renal Insufficiency and Cardiovascular Events (RIACE) study was aimed at assessing the clinical correlates and association with complications of resistant hypertension in patients with type 2 diabetes.

**Methods:** The RIACE study enrolled 15 773 patients consecutively visiting 19 diabetes clinics during the years 2007–2008. Resistant hypertension, defined as BP values not on target (i.e. >130/80 mmHg, respectively) with three antihypertensive agents, was detected in 2363 individuals (15% of the whole RIACE cohort, 17.4% of hypertensive individuals, and 21.2% of treated hypertensive patients). Patients without resistant hypertension [nonresistant hypertension (NRH)], that is on target with one ($n = 1569$), two ($n = 1369$), and three ($n = 803$) drugs, and individuals with uncontrolled hypertension, that is untreated or not on target with less than three drugs ($n = 7440$), served as controls.

**Results:** As compared with NRH and uncontrolled hypertension patients, patients with resistant hypertension were older and more frequently women and had significantly higher waist circumference, albuminuria, and serum creatinine, and lower glomerular filtration rate. Prevalence values of chronic kidney disease and advanced retinopathy were significantly higher in resistant hypertension than in both nonresistant hypertension and uncontrolled hypertension individuals, whereas cardiovascular disease was more frequent in resistant hypertension versus uncontrolled hypertension, but not nonresistant hypertension patients, especially those on 2–3 drugs.

**Conclusions:** Resistant hypertension is relatively common in patients with type 2 diabetes. In these individuals, age, female sex and waist circumference are independent correlates of resistant hypertension, which is strongly associated with microvascular (especially renal) disease, whereas relation with macrovascular complications is unclear.

**Keywords:** cardiovascular disease, chronic kidney disease, diabetic retinopathy, resistant hypertension, type 2 diabetes

**Abbreviations:** AER, albumin excretion rate; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey; NPDR, nonproliferative diabetic retinopathy; NRH, nonresistant hypertension; OR, odds ratio; PDR, proliferative diabetic retinopathy; RIACE, Renal Insufficiency And Cardiovascular Events

## INTRODUCTION

Resistant hypertension is defined as blood pressure (BP) that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes at optimal dose amounts, one of which should ideally be a diuretic [1].

Resistant hypertension is often overdiagnosed by including patients with 'apparent or pseudo-resistant hypertension', that is those with 'white-coat' hypertension, nonadherence to medications, inappropriately prescribed antihypertensive regimen and incorrect BP measurement

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due to cuff-related artifacts. However, resistant hypertension is also frequently underdiagnosed because of exclusion of patients with uncontrolled hypertension, that is those untreated or receiving two drugs or less, that comprise patients who would fail to achieve BP goal if treated with three drugs [2,3]. Data from the National Health and Nutrition Examination Survey (NHANES) and the Framingham Heart Study showed that only 53 and 48%, respectively, of treated individuals were controlled to less than 140/90 mmHg [4,5].

As a consequence, the real prevalence of 'true resistant hypertension ' is unknown, with huge differences between observational studies and intervention trials. In fact, an analysis of the NHANES from 2003 through 2008 showed that 8.9% of patients with hypertension and 12.8% of those on antihypertensive treatment met the criteria for resistant hypertension [6], and comparison of three time periods revealed an alarmingly increasing prevalence of resistant hypertension [7]. Data from the NHANES are consistent with those from a large Spanish database, in which 37.5% of patients who met criteria for resistant hypertension had 'white-coat' hypertension on the basis of ambulatory BP monitoring [8]. In contrast, prevalence values of 25–30% were observed in randomized controlled trials [9–11], mainly due to forced titrated treatment, which reduces the number of patients with uncontrolled hypertension, though likelihood to achieve BP goal is diminished by restricted use of specific medication combinations.

The clinical features of patients with resistant hypertension include older age, female sex, and Afro-American ethnicity [6,12]. Moreover, these individuals have higher prevalence of target organ damage, cardiovascular disease (CVD) and chronic kidney disease (CKD), and are more frequently obese and diabetic [1–3,6,13,14]. Several pathophysiologic links may justify the association between resistant hypertension and diabetes; among others, excess aldosterone impairs insulin signaling thus leading to insulin resistance [15,16]. However, so far, no study has addressed the prevalence and clinical features of resistant hypertension in large samples of diabetic individuals.

This prespecified analysis of the cohort from the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter Study was aimed at assessing the independent correlates of resistant hypertension and the association of this condition with long-term complications in patients with type 2 diabetes.

# METHODS

## Study cohort

For this analysis, we used the baseline data from the RIACE Italian Multicenter Study (registered with Clinical Trials.gov; URL: http://www.clinicaltrials.gov/ct2/show/NCT00715481), an observational, prospective cohort study on the impact of estimated glomerular filtration rate (eGFR) on CVD morbidity and mortality in type 2 diabetes. The study protocol was approved by the locally appointed ethics boards.

The RIACE cohort consisted of 15 933 Caucasian patients with type 2 diabetes consecutively attending 19 hospital-based Diabetes Clinics of the National Health Service throughout Italy between 2007 and 2008 who were initially recruited. Exclusion criteria were dialysis or renal transplantation. Quality and completeness of data were controlled and 160 patients were excluded due to implausible or missing values, and the remaining 15 773 patients were subsequently analyzed.

## Measurements

The following data were recorded by a structured interview: age, smoking status, known diabetes duration, current antihyperglycaemic, antihypertensive and lipid-lowering treatment.

Body weight and height were measured and BMI was calculated from them. BP was measured manually using a mercury sphygmomanometer. Two consecutive readings were taken 10 min apart with the patients seated with the arm at the heart level and the cuff correctly placed on the arm circumference. Standard adult cuffs were used (9–13 inches), except for severely obese patients, in whom large cuffs (13–17 inches) were employed. Waist circumference was measured in 4618 patients and predicted from BMI in the remaining 11 155 individuals using sex-specific linear regression equations [17].

Hemoglobin $A_{1c}$ ($HbA_{1c}$) was measured by HPLC Diabetes Control and Complications Trial (DCCT)-aligned methods; triglycerides, total and high-density lipoprotein (HDL) cholesterol were determined by standard analytical methods; low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula.

The presence of CKD was assessed by measuring albuminuria and serum creatinine. As previously reported in detail [18], albumin excretion rate (AER) was obtained from 24-h urine collections or calculated from albumin/creatinine ratio in first-morning urine samples, in the absence of interfering clinical conditions. Albuminuria was measured in one-to-three fresh urine samples for each patient by immunonephelometry or immunoturbidimetry, and, in case of multiple measurements, the geometric mean was used for analysis. In patients with multiple measurements (4062 with at least two and 2310 with three values), concordance rate between the first value and the geometric mean was above 90% for all classes of albuminuria [19]. Serum (and urine) creatinine was measured by the modified Jaffe method. One-to-three measurements were obtained for each patients and eGFR was calculated by the four-variable Modification of Diet in Renal Disease study equation, using the mean serum creatinine value in case of multiple measures [18].

The presence of diabetic retinopathy was assessed by an expert ophthalmologist by dilated fundoscopy [20].

Prevalent CVD was assessed from medical history by recording previous major acute CVD events, which were adjudicated based on hospital discharge records by an ad hoc committee in each center [18].

## Categorization of patients

Resistant hypertension was defined as SBP and/or DBP values not on target (i.e. >130 and/or 80 mmHg, respectively) in patients on three antihypertensive agents ($n = 2363$) [1]. Patients without resistant hypertension [nonresistant hypertension (NRH)], that is on target with

one (NRH1, $n=1569$), two (NRH2, $n=1369$) and three drugs (NRH3, $n=803$), and individuals with uncontrolled hypertension, that is not on target with less than three drugs [$n=7440$; 2395 (32.2%) with 0, 2634 (35.4%) with 1, and 2411 (32.4%) with three drugs] served as control groups. Subsequently, we excluded patients who did not meet BP targets, and were not on a diuretic ($n=273$, 11.6% of resistant hypertension patients). Additionally, we repeated the analyses categorizing patients according to the BP targets recently proposed by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) (i.e. ≤140/85 mmHg) [21]. Using these goals, 3183 patients (20.2%) were normotensive, 1925 (12.2%) had resistant hypertension, 2477 (15.7%) were NRH1, 2138 (13.6%) were NRH2, 1241 (7.9%) were NRH3, and 4809 (30.5%) had uncontrolled hypertension. However, data were collected several years ago from patients treated according to more stringent goals which likely required a higher number of drugs to be achieved. For this reason, the primary analyses were conducted using the previous BP targets.

Patients were then assigned to one of the following categories of albuminuria (mg/24 h): normoalbuminuria (AER <30), microalbuminuria (AER 30–299), or macroalbuminuria (AER >300). In addition, normoalbuminuric patients were further classified as having normal (AER <10) or low albuminuria (AER <10–29). Patients were assigned to one of the following categories of eGFR (ml/min per 1.73 $m^2$): 1 (>90); 2 (60–89); 3 (30–59); 4 (15–29); and 5 (<15). Finally, patients were classified as having no CKD or CKD stages 1–5, according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative [22]. Patients assigned to CKD stages (and GFR classes) 4 and 5 were pooled together. As previously reported [18], CKD patients were further classified as having one of the following CKD phenotypes: albuminuria alone (stages 1–2 CKD), reduced eGFR alone (stage >3 CKD without albuminuria), or both (stage >3 CKD with albuminuria).

Patients were classified into absent diabetic retinopathy, mild, moderate or severe nonproliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), or maculopathy, according to the Global Diabetic Retinopathy Project Group [23]. For further analysis, patients with mild or moderate NPDR were classified as having nonadvanced diabetic retinopathy, whereas those with severe NPDR, PDR, or maculopathy were grouped into the advanced, sight-threatening diabetic retinopathy category. Diabetic retinopathy grade was assigned based on the worst eye [20].

Previous major acute CVD events were classified as either myocardial infarction, stroke, and foot ulcer/gangrene/amputation, or coronary, cerebrovascular, and peripheral events by including also coronary, carotid, and lower limb revascularization, respectively [16].

### Statistical analysis

Data are reported as mean ± SD for continuous variables and $n$ (%) for categorical variables.

Comparisons between groups were performed using the analysis of variance (ANOVA) one-way test for parametric (post-hoc analysis by the Scheffe's test) or the corresponding Kruskal–Wallis test (post-hoc analysis by the Mann–Whitney $U$ test) for nonparametric continuous variables, and the chi-square test for categorical variables.

Logistic regression analyses with backward variable selection (probability for removal >0.10) were performed to assess independent correlates of resistant hypertension versus NRH or uncontrolled hypertension. Covariates were age, sex, smoking habits, diabetes duration, $HbA_{1c}$, BMI, waist circumference, triglycerides, total and HDL cholesterol, and eventually SBP and DBP in model 1, and CKD (albuminuria and eGFR categories or CKD phenotypes) and diabetic retinopathy in model 2, and CVD in model 3. Results of these analyses were expressed as odd ratios (ORs) with their 95% confidence interval (CI).

All $P$ values were two-sided, and a $P$ value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

In the whole RIACE cohort, 14.1% of the patients were normotensive, whereas 15.0% (17.4% of all hypertensive individuals and 21.2% of treated hypertensive patients) fulfilled the criteria for resistant hypertension, 23.7% had NRH, and 47.2% had uncontrolled hypertension. Prevalence of resistant hypertension was approximately double in patients with than in those without any CKD, whereas that of uncontrolled hypertension was higher in patients without CKD (Fig. 1). Of patients with resistant hypertension, 1426 (60.35%), 778 (32.92%), 137 (5.80%) and 22 (0.93%) were on three, four, five and six antihypertensive agents, respectively; moreover, 2057 (87.05%) were not on target for SBP and/or DBP, whereas 306 (12.95%) were on target with at least four drugs. Since most (88.4%), but not all, resistant hypertension patients were on a diuretic, these figures would be slightly lower if diuretic treatment is used as an additional criterion for resistant hypertension definition (13.2% of the cohort, 15.4% of hypertensive patients, and 18.7% of treated hypertensive patients), whereas using the new ESH/ESC criteria the number of resistant hypertension patients falls to 1925 (12.2% of the cohort, 14.2% of hypertensive patients, and 17.3% of treated hypertensive patients).

Clinical characteristics of patients are shown in Table 1. As compared with NRH and uncontrolled hypertension patients, patients with resistant hypertension were older, less frequently men and, except when compared with NRH3, more former versus current smokers. Moreover, they had significantly higher diabetes duration (versus NRH1 and uncontrolled hypertension only), BMI (except versus NRH3), waist circumference, triglycerides (versus NRH1 and uncontrolled hypertension only), albuminuria, and serum creatinine, and lower eGFR. As compared with patients with uncontrolled hypertension, resistant hypertension patients had also lower total, HDL, LDL and non-HDL cholesterol, and diastolic and mean BP levels, whereas SBP was similar and pulse pressure was higher. Finally, patients with resistant hypertension were on a more aggressive pharmacological treatment than those with NRH (except NRH3) or uncontrolled hypertension, as shown by the higher percentage of patients on insulin (both alone

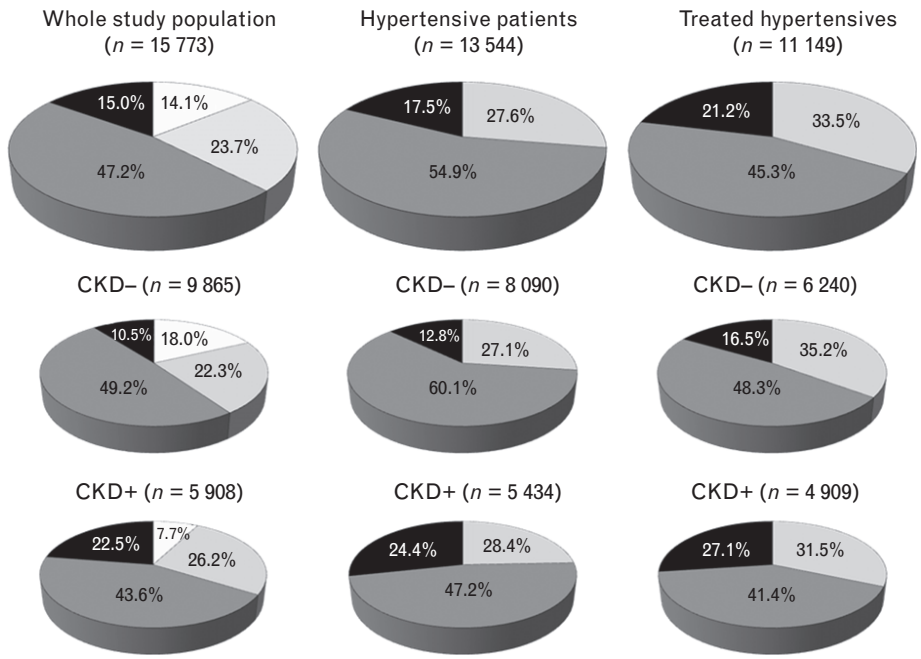


**FIGURE 1** Prevalence of hypertension categories in the whole Renal Insufficiency And Cardiovascular Events cohort and in the subset of hypertensive patients and treated hypertensive patients, total and stratified according to the absence or presence of chronic renal disease (CKD– and CKD+, respectively). White, normotensive individuals; light gray, patients with nonresistant hypertension; dark gray, patients with uncontrolled hypertension; black, patients with resistant hypertension.

or combined with oral agents) and lipid-lowering agents. As compared with NRH3 individuals, resistant hypertension patients were more often on blockers of the renin–angiotensin system (especially angiotensin-converting enzyme inhibitors), diuretics (particularly thiazides), dihydropyridine calcium channel blockers and α-blockers.

Table 2 shows the prevalence of micro and macrovascular complications in the RIACE cohort stratified as indicated above. As compared with NRH and uncontrolled hypertension patients, patients with resistant hypertension had higher prevalence of advanced diabetic retinopathy, and microalbuminuria and macroalbuminuria (and also of low albuminuria versus uncontrolled hypertension). As a consequence, prevalence of both any diabetic retinopathy and any CKD (especially stage ≥3 with and without albuminuria) was higher in resistant hypertension than in NRH or uncontrolled hypertension patients. Prevalence of any CVD, myocardial infarction and any coronary event was significantly higher in resistant hypertension versus NRH patients as a group (35.4 versus 30.4%, 19.4 versus 16.9%, and 25.2 versus 22.3%; $P<0.0001$, $P=0.012$, and $P<0.0001$, respectively), but not when NRH patients were stratified by number of antihypertensive drugs. In fact, values were similar between resistant hypertension and NRH2 patients, and lower in resistant hypertension than in NRH3 patients. Interestingly, resistant hypertension patients who were also not on target had a much lower prevalence of CVD than those on target (34.0 versus 44.4%; $P<0.0001$), again due to a lower prevalence of myocardial infarction (17.9 versus 29.4%; $P<0.0001$) and any coronary event (23.3 versus 37.6%; $P<0.0001$). Conversely, frequency of CVD, either total or by vascular bed, was significantly higher in resistant hypertension than in uncontrolled hypertension patients.

In regression models investigating the independent correlates of resistant hypertension versus NRH, age, female sex, former smoking status, diabetes duration, waist circumference and triglycerides entered in model 1; the same variables (except diabetes duration) and advanced diabetic retinopathy, low to macroalbuminuria, eGFR below 60 ml/min per 1.73 $m^2$, and, to a lesser extent, CKD stage at least 3 (not shown) entered in model 2; and CVD entered in model 3 at borderline significance (Table 3). The independent correlates of CVD were similar in resistant hypertension and NRH individuals except for male sex, which was associated only with NRH, and waist circumference, nonadvanced retinopathy, and albuminuria, which were associated only with resistant hypertension, consistent with the relation of resistant hypertension with female sex, adiposity, and microvascular complications. Interestingly, when SBP and DBP were included as covariates, association with advanced retinopathy was of borderline significance (OR 1.311, 95% CI 1.003–1.712, $P=0.047$) and that with CVD became significant (OR 1.524, 95% CI 1.275–1.821, $P<0.0001$), whereas albuminuria did not enter in the regression model (not shown).

When such analysis was repeated in patients with and without CKD, age, diabetes duration, waist circumference, and microvascular disease (low to macroalbuminuria, GFR <90 ml/min per 1.73 $m^2$ and advanced diabetic retinopathy), but not CVD, were independent correlates of resistant hypertension in patients with CKD (Supplemental Table 1, http://links.lww.com/HJH/A395), whereas age, female sex, waist circumference and low albuminuria, but not eGFR 60–89 ml/min per 1.73 $m^2$ and CVD, were associated with resistant hypertension in those without any CKD (Supplemental Table 2, http://links.lww.com/HJH/A395). Similarly to the whole cohort, when SBP and DBP values were introduced as covariates, advanced diabetic

**TABLE 1. Clinical characteristics of patients with resistant hypertension and control individuals on target with one (NRH1), two (NRH2), or three (NRH3) drugs and not on target with no or less than three drugs (UH)**

| Variables | RH | NRH1 | NRH2 | NRH3 | UH | *P* |
|---|---|---|---|---|---|---|
| *N* | 2363 | 1569 | 1369 | 803 | 7440 | |
| Men [*n* (%)] | 1246 (52.7) | 943 (60.1)* | 766 (56.0) | 422 (52.6) | 4201 (56.5)* | <0.0001 |
| Age (years) | 69.0 ± 8.7 | 65.6 ± 10.4* | 67.5 ± 9.6* | 67.7 ± 9.7*** | 66.3 ± 10.0* | <0.0001 |
| Diabetes duration (years) | 14.4 ± 10.2 | 13.2 ± 10.2*** | 13.4 ± 10.4 | 13.3 ± 9.9 | 13.4 ± 10.3** | <0.0001 |
| Smoking [*n* (%)] | | | | | | <0.0001 |
| Never | 1333 (56.4) | 822 (52.4)*** | 797 (58.2) | 465 (57.9) | 4274 (57.4) | |
| Former | 753 (31.9) | 453 (28.9)*** | 391 (28.6)*** | 246 (30.6) | 2054 (27.6)* | |
| Current | 277 (11.7) | 277 (11.7) | 181 (13.2) | 92 (11.5) | 1112 (14.9)* | |
| $HbA_{1c}$ (%) | 7.61 ± 1.50 | 7.52 ± 1.55 | 7.55 ± 1.57 | 7.42 ± 1.45 | 7.56 ± 1.46 | 0.041 |
| $HbA_{1c}$ (mmol/mol) | 60.1 ± 16.4 | 59.2 ± 16.9 | 59.5 ± 17.2 | 58.2 ± 15.8 | 58.9 ± 11.4 | 0.041 |
| BMI (kg/m$^2$) | | | | | | |
| Men | 29.8 ± 4.7 | 27.9 ± 4.3* | 28.5 ± 4.3* | 29.5 ± 4.8 | 28.4 ± 4.4* | <0.0001 |
| Women | 31.5 ± 6.1 | 29.4 ± 5.8* | 30.1 ± 5.8* | 30.4 ± 5.7*** | 29.6 ± 5.6* | <0.0001 |
| Waist circumference (cm) | | | | | | |
| Men | 105.8 ± 10.9 | 101.2 ± 10.2* | 102.9 ± 9.7* | 104.8 ± 10.4*** | 102.4 ± 10.2* | <0.0001 |
| Women | 106.0 ± 12.2 | 101.8 ± 11.7* | 103.4 ± 11.9** | 103.7 ± 12.4*** | 102.6 ± 11.5* | <0.0001 |
| Triglycerides (mmol/l) | 1.67 ± 0.94 | 1.54 ± 0.99** | 1.57 ± 0.97 | 1.69 ± 0.98 | 1.57 ± 1.02** | <0.0001 |
| Total cholesterol (mmol/l) | 4.69 ± 0.96 | 4.70 ± 1.00 | 4.62 ± 1.01 | 4.62 ± 0.99 | 4.86 ± 0.99* | <0.0001 |
| HDL cholesterol (mmol/l) | | | | | | |
| Men | 1.19 ± 0.32 | 1.21 ± 0.32 | 1.16 ± 0.32 | 1.15 ± 0.33 | 1.23 ± 0.33** | <0.0001 |
| Women | 1.34 ± 0.35 | 1.37 ± 0.36 | 1.36 ± 0.37 | 1.30 ± 0.37 | 1.41 ± 0.36* | <0.0001 |
| LDL cholesterol (mmol/l) | 2.67 ± 0.82 | 2.73 ± 0.83 | 2.67 ± 0.85 | 2.63 ± 0.84 | 2.85 ± 0.85* | <0.0001 |
| Non-HDL cholesterol (mmol/l) | 3.42 ± 0.93 | 3.43 ± 0.95 | 3.37 ± 0.96 | 3.40 ± 0.96 | 3.55 ± 0.96* | <0.0001 |
| Dyslipidemia [*n* (%)] | 2032 (86.0) | 1278 (81.5)* | 1110 (81.1)* | 684 (85.2) | 6122 (82.3)* | <0.0001 |
| SBP (mmHg) | 147.2 ± 17.5 | 122.3 ± 8.3* | 121.9 ± 8.4* | 122.2 ± 8.5* | 148.2 ± 13.9 | <0.0001 |
| DBP (mmHg) | 80.5 ± 9.7 | 73.7 ± 6.9* | 72.8 ± 7.6* | 72.7 ± 7.4* | 82.5 ± 8.9* | <0.0001 |
| Mean BP (mmHg) | 102.7 ± 10.2 | 89.9 ± 6.2* | 89.1 ± 6.5* | 89.3 ± 6.7* | 104.4 ± 8.2* | <0.0001 |
| Pulse pressure (mmHg) | 66.7 ± 16.7 | 48.6 ± 8.5* | 49.2 ± 8.9* | 49.4 ± 8.9* | 65.7 ± 14.8*** | <0.0001 |
| Albuminuria (mg/24 )h | 138.6 ± 442.2 | 65.6 ± 444.5* | 68.9 ± 267.7* | 100.1 ± 399.2 | 64.2 ± 271.4* | <0.0001 |
| Serum creatinine (μmol/l) | 95.5 ± 44.2 | 84.0 ± 30.1* | 87.5 ± 29.2* | 90.2 ± 37.1* | 83.1 ± 32.7* | <0.0001 |
| eGFR (ml/min per 1.73 m$^2$) | 70.5 ± 23.9 | 80.2 ± 22.7** | 76.3 ± 23.7* | 74.4 ± 25.7** | 80.6 ± 22.7* | <0.0001 |
| Antihyperglycaemic treatment [*n* (%)] | | | | | | <0.0001 |
| Diet | 228 (9.6) | 197 (12.6)** | 180 (13.1)** | 110 (13.7)** | 1017 (13.7)* | |
| OHAs | 1375 (58.2) | 979 (62.4)** | 822 (60.0) | 462 (57.5) | 4717 (63.4)* | |
| OHAs + insulin | 301 (12.7) | 145 (9.2)** | 152 (11.1) | 82 (10.2) | 659 (8.9)* | |
| Insulin | 459 (19.4) | 248 (15.8)** | 215 (15.7)** | 149 (18.6) | 1047 (14.1)* | |
| Lipid-lowering treatment [*n* (%)] | 1382 (58.5) | 761 (48.5)* | 732 (53.5)** | 463 (57.7) | 3269 (43.9)* | <0.0001 |
| Antihypertensive treatment [*n* (%)] | | | | | | <0.0001 |
| RAS blockers | 2245 (95.0) | 1085 (69.2)* | 1170 (85.5)* | 734 (91.4)* | 3931 (52.8)* | <0.0001 |
| ACE-Is | 1436 (60.8) | 761 (48.5)* | 780 (57.0)*** | 474 (59.0) | 2671 (35.9)* | <0.0001 |
| ARBs | 1150 (48.7) | 324 (20.7)* | 438 (32.0)* | 333 (41.5)* | 1350 (18.1)* | <0.0001 |
| Diuretics | 2090 (88.4) | 87 (5.5)* | 674 (49.2)* | 663 (82.6)*** | 1169 (15.7)* | <0.0001 |
| Aldosterone antagonists | 302 (12.8) | 15 (1.0)* | 62 (4.5)* | 99 (12.3) | 100 (1.3)* | <0.0001 |
| Thiazide diuretics | 1395 (59.0) | 14 (0.9)* | 433 (31.6)* | 386 (48.1)* | 798 (10.7)* | <0.0001 |
| Loop diuretics | 805 (34.1) | 58 (3.6)* | 213 (15.6)* | 286 (35.6) | 382 (5.1)* | <0.0001 |
| Non-DHP CCBs | 260 (11.0) | 45 (2.9)* | 112 (8.2)** | 92 (11.5) | 286 (3.8)* | <0.0001 |
| DHP CCBs | 1249 (52.9) | 124 (7.9)* | 301 (22.0)* | 286 (35.6)* | 872 (11.7)* | <0.0001 |
| α-blockers | 507 (21.5) | 50 (3.2)* | 57 (4.2)* | 93 (11.6)* | 240 (3.2)* | <0.0001 |
| β-blockers | 1103 (46.7) | 178 (11.3)* | 342 (25.0)* | 360 (44.8) | 757 (10.2)* | <0.0001 |

Values are mean ± SD for continuous variables and *n* (%) for categorical variables. ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BP, blood pressure; CCBs, calcium channel blockers; DHP, dihydorpyridine; eGFR, estimated glomerular filtration rate; $HbA_{1c}$, hemoglobin $A_{1c}$; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NRH, nonresistant hypertension; OHAs, oral hypoglycaemic agents; RAS, renin–angiotensin system; RH, resistant hypertension; UH, uncontrolled hypertension. *P* values for comparison between groups using the ANOVA one-way test for parametric (post-hoc analysis by the Scheffe's test) or the corresponding Kruskal–Wallis test (post-hoc analysis by the Mann–Whitney *U* test) for nonparametric (triglycerides, albuminuria, serum creatinine and eGFR) continuous variables, and the chi-square test for categorical variables:
*$P<0.001$.
**$P<0.01$.
***$P<0.05$ versus RH.

retinopathy and albuminuria were excluded from regression, whereas CVD was significantly associated with resistant hypertension in both patients with (OR 1.372, 95% CI 1.084–1.736, $P=0.009$) and without (OR 1.712, 95% CI 1.307–2.242, $P<0.0001$) CKD.

Logistic regression analysis comparing resistant hypertension and uncontrolled hypertension patients confirmed results of comparison between resistant hypertension and NRH patients, except that, in model 2, eGFR 60–89 ml/min per 1.73 m$^2$ also correlated with resistant hypertension and particularly, in model 3, CVD was strongly associated with resistant hypertension (Supplemental Table 3, http://links.lww.com/HJH/A395). However, association with micro and macrovascular complications did not change

**TABLE 2. Microvascular complications and cardiovascular disease patients with resistant hypertension and control individuals on target with one (NRH1), two (NRH2), or three (NRH3) drugs and not on target with no or less than three drugs**

| Variables | RH | NRH1 | NRH2 | NRH3 | UH | *P* |
|---|---|---|---|---|---|---|
| *n* | 2363 | 1569 | 1369 | 803 | 7440 | |
| Albuminuria | | | | | | <0.0001 |
| Normal albuminuria | 656 (27.8) | 620 (39.5)* | 538 (39.3)* | 283 (35.2)* | 2862 (38.5)* | <0.0001 |
| Low albuminuria | 766 (32.4) | 497 (31.7) | 456 (33.3) | 265 (33.0) | 2703 (36.3)* | <0.0001 |
| Microalbuminuria | 709 (30.0) | 391 (24.9)* | 318 (23.2)* | 211 (26.3)*** | 1558 (20.9)* | <0.0001 |
| Macroalbuminuria | 232 (9.8) | 61 (3.9)* | 57 (4.2)* | 44 (5.5)* | 317 (4.3)* | <0.0001 |
| eGFR | | | | | | <0.0001 |
| ≥90 ml/min per 1.73 $m^2$ | 455 (19.3) | 469 (29.9)* | 324 (23.7)** | 184 (22.9)*** | 2254 (30.3)* | |
| 60–89 ml/min per 1.73 $m^2$ | 1122 (47.5) | 828 (52.8)* | 725 (53.0)* | 393 (48.9) | 4006 (53.8)* | |
| 30–59 ml/min per 1.73 $m^2$ | 694 (29.4) | 253 (16.1)* | 297 (21.7)* | 208 (25.9) | 1084 (14.6)* | <0.0001 |
| <30 ml/min per 1.73 $m^2$ | 92 (3.9) | 19 (1.2)* | 23 (1.7)* | 18 (2.2)*** | 96 (1.3)* | <0.0001 |
| CKD phenotype | | | | | | <0.0001 |
| No CKD | 1032 (43.7) | 966 (61.6)* | 796 (58.1)* | 433 (53.9)* | 4863 (65.4)* | <0.0001 |
| Stages 1–2 CKD | 545 (23.1) | 331 (21.1) | 253 (18.5)* | 144 (17.9)** | 1397 (18.8)* | <0.0001 |
| Stage >3 CKD without albuminuria | 390 (16.5) | 151 (9.6)* | 198 (14.5)*** | 115 (14.3) | 702 (9.4)* | <0.0001 |
| Stage >3 CKD with albuminuria | 396 (16.8) | 121 (7.7)* | 122 (8.9)* | 111 (13.8) | 478 (6.4)* | <0.0001 |
| Retinopathy [*n* (%)] | | | | | | <0.0001 |
| No retinopathy | 1696 (71.8) | 1235 (78.7)* | 1043 (76.2)** | 610 (76.0)*** | 5792 (77.8)* | <0.0001 |
| Nonadvanced retinopathy | 329 (13.9) | 194 (12.4) | 197 (14.4) | 108 (13.4) | 931 (12.5) | <0.0001 |
| Advanced retinopathy | 338 (14.3) | 140 (8.9)* | 129 (9.4)* | 85 (10.6)** | 717 (9.6)* | <0.0001 |
| Any cardiovascular disease [*n* (%)] | 836 (35.4) | 364 (23.2)* | 462 (33.7) | 310 (38.6) | 1464 (19.7)* | <0.0001 |
| Acute myocardial infarction [*n* (%)] | 459 (19.4) | 176 (11.2)* | 263 (19.2) | 192 (23.9)** | 600 (8.1)* | <0.0001 |
| Any coronary event [*n* (%)] | 595 (25.2) | 235 (15.0)* | 356 (26.0) | 244 (30.4)** | 876 (11.8)* | <0.0001 |
| Stroke [*n* (%)] | 127 (5.4) | 49 (3.1)** | 54 (3.9) | 45 (5.6) | 212 (2.8)* | <0.0001 |
| Any cerebrovascular event [*n* (%)] | 301 (12.7)* | 127 (8.1) | 132 (9.6)** | 90 (11.2) | 574 (7.7)* | <0.0001 |
| Ulceration/gangrene [*n* (%)] | 116 (4.9) | 54 (3.4)*** | 46 (3.4)*** | 48 (6.0) | 217 (2.9)* | <0.0001 |
| Any lower limb event [*n* (%)] | 197 (8.3) | 96 (6.1)** | 91 (6.6) | 76 (9.5) | 366 (4.9)* | <0.0001 |

Values are *n* (%). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate. *P* values for comparison between groups using the chi-square test:
*$P < 0.001$.
**$P < 0.01$.
***$P < 0.05$ versus RH.

depending on whether BP values were included (Supplemental Table 3, http://links.lww.com/HJH/A395) or not included (not shown) in the regression models.

Results did not change when only the subset of resistant hypertension patients receiving a diuretic was analyzed (data not shown). Conversely, when analyses were conducted using the current BP targets, the association of resistant hypertension with CVD became significant, whereas that with age, female sex, waist circumference, triglycerides, advanced diabetic retinopathy and measures of CKD was maintained (Table 4).

## DISCUSSION

Compared with data from the general population or hypertensive individuals [6,8,12,13], a high frequency of resistant hypertension was observed in the RIACE cohort of patients with type 2 diabetes, though true prevalence values could not be derived from our analysis. Our finding is consistent with the high percentage of diabetic patients detected among resistant hypertension individuals, ranging from 18 to 35% [6,8,12,13]. Also the relation with age, sex and waist circumference confirms previous findings from samples from the general population or hypertensive patients [6,8,12,13]. In particular, the association between resistant hypertension and waist circumference is consistent with the hypothesis that adipocytes produce an as-yet unidentified mineralocorticoid-releasing factor that stimulates adrenal production of aldosterone, which in turn is associated with insulin resistance, the metabolic syndrome, and type 2 diabetes, as well as with resistant hypertension and related CVD and CKD risk [24].

The most relevant finding of our stu (UH) dy is the diverging relationship of resistant hypertension with micro and macrovascular complications. In fact, patients with resistant hypertension had higher albuminuria, lower eGFR and higher prevalence of any CKD and advanced diabetic retinopathy than NRH patients. Moreover, these variables were independently associated with resistant hypertension versus NRH, and resistant hypertension was twice more prevalent in patients with than in those without CKD. This is the first evidence on an association between diabetic retinopathy and resistant hypertension, though it is in keeping with the high frequency of retinal lesions in nondiabetic patients with resistant hypertension [14]. Conversely, renal data are consistent with the long recognized relationship between resistant hypertension and CKD, the nature of which is likely bidirectional, with both resistant hypertension adversely impacting upon renal function [25] and CKD reducing response to antihypertensive treatment, due to sodium retention, and increased activity of the renin–angiotensin and the sympathetic nervous systems [26]. In contrast, CVD data are at odds with cross-sectional [8] and longitudinal [27] analyses showing a higher prevalence and incidence of CVD in patients with than in those without resistant hypertension, as well as with evidence that eGFR reduction and/or albuminuria amplify CVD risk correlated to resistant hypertension in the general hypertensive

**TABLE 3. Independent correlates of resistant hypertension ($n = 2363$), defined according to the 2007 guidelines, versus nonresistant hypertension (obtained pooling NRH1, NRH2 and NRH3; $n = 3741$)**

| Variables | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* | OR | 95% CI | *P* | OR | 95% CI | *P* |
| Age, × year | 1.034 | 1.027–1.040 | <0.0001 | 1.027 | 1.021–1.034 | <0.0001 | 1.026 | 1.020–1.033 | <0.0001 |
| Sex, male | 0.880 | 0.785–0.986 | 0.028 | 0.818 | 0.727–0.920 | 0.001 | 0.820 | 0.726–0.926 | 0.001 |
| Smoking | | | 0.012 | | | 0.013 | | | 0.022 |
| Never | 1.0 | | | 1.0 | | | 1.0 | | |
| Former | 1.152 | 1.016–1.307 | 0.028 | 1.128 | 0.993–1.282 | 0.063 | 1.119 | 0.984–1.272 | 0.087 |
| Current | 0.901 | 0.762–1.066 | 0.225 | 0.869 | 0.733–1.031 | 0.107 | 0.875 | 0.737–1.037 | 0.124 |
| Diabetes duration, × year | 1.006 | 1.000–1.011 | 0.037 | – | – | – | – | – | – |
| Waist circumference, × 1 cm | 1.035 | 1.030–1.040 | <0.0001 | 1.033 | 1.028–1.038 | <0.0001 | 1.034 | 1.028–1.039 | <0.0001 |
| Triglycerides, × 0.0113 mmol/l | 1.001 | 1.000–1.002 | 0.004 | – | – | – | – | – | – |
| Retinopathy | | | | | | 0.008 | | | 0.012 |
| No retinopathy | | | | 1.0 | | | 1.0 | | |
| Nonadvanced retinopathy | | | | 0.983 | 0.840–1.152 | 0.834 | 0.971 | 0.829–1.138 | 0.717 |
| Advanced retinopathy | | | | 1.301 | 1.096–1.543 | 0.003 | 1.283 | 1.081–1.524 | 0.004 |
| Albuminuria | | | | | | <0.0001 | | | <0.0001 |
| Normal albuminuria | | | | 1.0 | | | 1.0 | | |
| Low albuminuria | | | | 1.340 | 1.173–1.531 | <0.0001 | 1.343 | 1.176–1.535 | <0.0001 |
| Microalbuminuria | | | | 1.569 | 1.360–1.810 | <0.0001 | 1.568 | 1.359–1.809 | <0.0001 |
| Macroalbuminuiria | | | | 2.637 | 2.074–3.352 | <0.0001 | 2.612 | 2.054–3.322 | <0.0001 |
| eGFR | | | | | | <0.0001 | | | <0.0001 |
| ≥90 ml/min per 1.73 $m^2$ | | | | 1.0 | | | 1.0 | | |
| 60–89 ml/min per 1.73 $m^2$ | | | | 1.135 | 0.987–1.305 | 0.077 | 1.136 | 0.987–1.307 | 0.075 |
| 30–59 ml/min per 1.73 $m^2$ | | | | 1.425 | 1.205–1.685 | <0.0001 | 1.430 | 1.208–1.693 | <0.0001 |
| <30 ml/min per 1.73 $m^2$ | | | | 1.692 | 1.169–2.449 | 0.005 | 1.704 | 1.175–2.470 | 0.006 |
| CVD | | | | | | | 1.126 | 1.000–1.268 | 0.050 |
| Variables not in regression | BMI, total cholesterol, $HbA_{1c}$, HDL cholesterol | | | BMI, total cholesterol, $HbA_{1c}$, HDL cholesterol, diabetes duration | | | BMI, total cholesterol, $HbA_{1c}$, HDL cholesterol, diabetes duration, triglycerides | | |

CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; $HbA_{1c}$, hemoglobin $A_{1c}$; HDL, high-density lipoprotein; NRH, nonresistant hypertension; OR, odds ratio.

**TABLE 4. Independent correlates of resistant hypertension ($n = 2363$), defined according to the 2013 guidelines, versus nonresistant hypertension (obtained pooling NRH1, NRH2 and NRH3; $n = 3741$)**

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variables** | **OR** | **95% CI** | ***P*** | **OR** | **95% CI** | ***P*** | **OR** | **95% CI** | ***P*** |
| Age, × year | 1.026 | 1.020–1.033 | <0.0001 | 1.019 | 1.013–1.026 | <0.0001 | 1.018 | 1.011–1.024 | <0.0001 |
| Sex, male | 0.736 | 0.589–0.919 | 0.007 | 0.678 | 0.540–0.850 | 0.001 | 0.670 | 0.535–0.840 | 0.001 |
| Smoking | | | 0.045 | | | 0.035 | | | 0.061 |
| Never | 1.0 | | | 1.0 | | | 1.0 | | |
| Former | 1.123 | 0.991–1.272 | 0.068 | 1.110 | 0.978–1.259 | 0.106 | 1.094 | 0.964–1.242 | 0.164 |
| Current | 0.912 | 0.770–1.080 | 0.285 | 0.882 | 0.743–1.047 | 0.150 | 0.884 | 0.745–1.049 | 0.159 |
| Diabetes duration, × year | 1.006 | 1.001–1.012 | 0.021 | – | – | – | – | – | – |
| Waist circumference, × 1 cm | 1.103 | 1.029–1.183 | 0.006 | 1.107 | 1.031–1.188 | 0.005 | 1.109 | 1.034–1.190 | 0.004 |
| BMI, × 1 kg/m$^2$ | 0.877 | 0.761–1.010 | 0.068 | 0.867 | 0.751–1.001 | 0.051 | 0.864 | 0.749–0.997 | 0.046 |
| Triglycerides, × 0.0113 mmol/l | 1.001 | 1.001–1.002 | <0.0001 | 1.001 | 1.000–1.001 | 0.082 | – | – | – |
| Total cholesterol | 0.999 | 0.997–1.000 | 0.050 | 0.999 | 0.997–1.000 | 0.059 | – | – | – |
| Retinopathy | | | | | | 0.006 | | | 0.010 |
| No retinopathy | | | | 1.0 | | | 1.0 | | |
| Nonadvanced retinopathy | | | | 1.085 | 0.930–1.267 | 0.299 | 1.073 | 0.919–1.253 | 0.373 |
| Advanced retinopathy | | | | 1.304 | 1.106–1.538 | 0.002 | 1.288 | 1.092–1.520 | 0.003 |
| Albuminuria | | | | | | <0.0001 | | | <0.0001 |
| Normal albuminuria | | | | 1.0 | | | 1.0 | | |
| Low albuminuria | | | | 1.217 | 1.063–1.392 | 0.004 | 1.219 | 1.066–1.395 | 0.004 |
| Microalbuminuria | | | | 1.550 | 1.343–1.789 | <0.0001 | 1.550 | 1.344–1.788 | <0.0001 |
| Macroalbuminuiria | | | | 2.487 | 1.987–3.113 | <0.0001 | 2.468 | 1.973–3.087 | <0.0001 |
| eGFR | | | | | | <0.0001 | | | <0.0001 |
| ≥90 ml/min per 1.73 m$^2$ | | | | 1.0 | | | 1.0 | | |
| 60–89 ml/min per 1.73 m$^2$ | | | | 1.184 | 1.027–1.365 | 0.020 | 1.185 | 1.028–1.366 | 0.019 |
| 30–59 ml/min per 1.73 m$^2$ | | | | 1.534 | 1.297–1.815 | <0.0001 | 1.525 | 1.290–1.804 | <0.0001 |
| <30 ml/min per 1.73 m$^2$ | | | | 1.580 | 1.120–2.229 | 0.009 | 1.581 | 1.121–2.229 | 0.009 |
| CVD | | | | | | | 1.183 | 1.051–1.330 | 0.005 |
| Variables not in regression | $HbA_{1c}$, HDL cholesterol | | | $HbA_{1c}$, HDL cholesterol, diabetes duration | | | Total cholesterol, $HbA_{1c}$, HDL cholesterol, diabetes duration, triglycerides | | |

CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; $HbA_{1c}$, hemoglobin $A_{1c}$; HDL, high-density lipoprotein; NRH, nonresistant hypertension; OR, odds ratio.

population [28]. Indeed, a longitudinal retrospective survey did confirm a significantly higher rate of CVD events in patients with versus those without resistant hypertension (18.0 versus 13.5%), which, however, was largely driven by CKD, which was included in the composite CVD outcome [15]. Moreover, ambulatory, but not office BP was associated with CVD morbidity and mortality in patients with resistant hypertension, thus highlighting the confounding role of pseudo-resistant hypertension [8,27].

Blood pressure levels might explain the deleterious effect of resistant hypertension on the kidney and the retina. In fact, in diabetic patients, high BP is associated with development and progression of CKD, and diabetic retinopathy and antihypertensive treatment is effective in reducing the burden from both complications [29]. Moreover, in a relatively small cohort of Japanese patients with type 2 diabetes, an increased frequency of hypertension requiring more drugs to be treated has been recently shown to be coupled with CKD progression [30]. This view is supported by the finding that association of microvascular complications with resistant hypertension became less strong or disappeared when adjusted for the higher BP levels of resistant hypertension patients. In addition, the higher prevalence of renal dysfunction and advanced retinal lesions in resistant hypertension versus NRH patients might be due to the higher pulse pressure values, which were shown to be associated with disease of small blood vessels in the kidney [31] and retina [32]. Conversely, the observation that, despite higher BP values, resistant hypertension was not associated with increased CVD risk versus NRH2 and NRH3 has no obvious explanation, though, in a cross-sectional analysis, this paradoxical finding might be due to an 'indication effect', that is patients with CVD events were treated more effectively to achieve BP targets than those without. Another possible reason is that a significantly lower percentage of NRH patients were on a blocker of the renin–angiotensin system than resistant hypertension patients, thus being less protected from CVD [33]. In addition, NRH patients (and on-target resistant hypertension patients) could have been exposed to the detrimental effect of low BP levels on coronary circulation, according to recent randomized controlled studies and meta-analysis, showing an increased risk for coronary events in patients treated more aggressively to lower SBP below 120 mmHg [34,35], the so-called J-shaped risk curve [36]. That the J effect might explain the higher CVD prevalence detected in NRH2 and NRH3 than in resistant hypertension patients and, among resistant hypertension patients, in those on target than in those not on target, is supported by several lines of evidence. Firstly, the higher CVD prevalence in

on-target patients was driven by coronary events; secondly, the percentage of patients with SBP 120 mmHg or less was high among NRH patients (~50%) and particularly among resistant hypertension patients on target with at least four drugs (60.5%); thirdly, CVD correlated strongly with resistant hypertension versus NRH when association was adjusted for the higher BP values of resistant hypertension patients; and, fourthly, the independent association of resistant hypertension versus NRH became significant for CVD when the analyses were conducted using the new BP targets. In fact, inclusion of patients with higher BP values (i.e. SBP 130–139 mmHg and DBP 80–84 mmHg) among the NRH patients, diluted the effect of low BP (which increased from ~122/73 to ~128/75 mmHg on average) on CVD, as shown by the lower prevalence of this complication.

Finally, the finding that prevalence of all complications was much higher in resistant hypertension than in uncontrolled hypertension patients might reflect differences in the CVD risk profile and possibly in the accumulated BP burden due to differences in duration and severity of hypertension.

A major strength of this study is that this is the first analysis of resistant hypertension in a large cohort of contemporary patients with type 2 diabetes, well characterized for clinical features and status of long-term complications. Limitations include the lack of appropriate methods for identifying patients with pseudo-resistant hypertension, such as ambulatory BP monitoring and adherence assessment, and, as in other observational studies [4,5], the lack of forced titrated treatment, which resulted in a high prevalence of uncontrolled hypertension patients. Another limitation was the cross-sectional design of the study which did not allow to examine the impact of resistant hypertension on the development and progression of complications. Hopefully, the follow-up of the RIACE study would clarify whether and to what extent resistant hypertension is associated with morbidity and mortality from complications, particularly CVD, either per se or by virtue of increased BP levels.

In conclusion, this study shows that resistant hypertension is relatively common in patients with type 2 diabetes and identifies age, female sex and waist circumference as independent correlates of this hypertensive phenotype in diabetic patients. In addition, this analysis reveals a strong relation of resistant hypertension with microvascular complications, especially CKD, but not with CVD, though this finding needs to be confirmed by longitudinal studies.

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### Conflicts of interest

The authors declare no conflict of interest.

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## Reviewers' Summary Evaluations

### Referee 1

Strengths: Important topic and large cohort. Weaknesses: Completed some years ago, today we have other guidelines; Cross-sectional design of the study; Nonadherence to medication has not been ruled out among the patients

### Referee 2

This is an interesting observational study on a large patient population demonstrating that resistant hypertension (BP>130/80mmHg) is common in diabetic patients particularly in those with chronic renal involvement. Old age, female gender and increased waist circumference are correlates of hypertension resistance. In addition, patients with resistant hypertension have greater incidence of diabetic retinopathy, suggesting that resistant hypertensive diabetic patients are more prone to develop microvascular disease. In contrast, treated patients appear to have a greater risk of macrovascular disease, namely myocardial infarction suggesting a J curve phenomenon and possible recommendation to avoid significant BP reduction in this group of patients.