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Prevalence and clinical characteristics of apparent therapy-resistant hypertension in patients with cardiovascular disease: a cross-sectional cohort study in secondary care

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ABSTRACT

Objectives Our aim was to investigate the prevalence of apparent therapy-resistant hypertension (aTRH) in patients with clinical manifest cardiovascular disease (CVD), and to study clinical characteristics related to aTRH in this population.

Setting The SMART (Second Manifestations of ARTerial disease) study is a large, single-centre cohort study in secondary care.

Participants Office blood pressure (BP) at inclusion was used to evaluate BP control in 6191 hypertensive patients with clinical manifest (cardio)vascular disease. Therapy-resistant hypertension was defined as BP ≥140/90 mm Hg despite use of antihypertensive drugs from ≥3 drug classes including a diuretic or use of ≥4 antihypertensive drugs irrespective of BP. Logistic regression analysis was used to explore the relationship between clinical characteristics measured at baseline and presence of aTRH.

Results The prevalence of aTRH was 9.1% (95% CI 8.4 to 9.8). Prevalence increased with age and when albuminuria was present and was higher in patients with lower estimated glomerular filtration rate (eGFR). Presence of aTRH was related to diabetes, female sex, duration and multiple locations of vascular disease, body mass index and waist circumference. Carotid intima-media thickness was higher (0.99±0.28 vs 0.93±0.28 mm) and ankle-brachial index lower (1.07±0.20 vs 1.10±0.19) in patients with aTRH compared with patients without aTRH.

Conclusion aTRH is prevalent in patients with clinical manifest CVD and is related to clinical factors known to be related with increased vascular risk, and with lower eGFR.

INTRODUCTION

Elevated blood pressure (BP) is strongly related to the occurrence of cardiovascular disease (CVD).[1 2] In patients with clinical manifest CVD, the risk of a recurrent cardiovascular event is very high.[3] Hypertension has been shown to increase risk of recurrent cardiovascular events[4] and BP-lowering drugs decrease the risk.[5 6] Therefore, BP control is strongly advised in these patients.[7] Although

Strengths and limitations of this study

► In this observational study in a large, well-defined population of patients with a history of cardiovascular disease the prevalence and clinical characteristics of apparent therapy-resistant hypertension were investigated.
► Measurements were done using a standardised protocol, vouching for reliability of the associations found. Use of antihypertensive drug was carefully recorded.
► Inclusion was regardless of the site of clinically manifest vascular disease making the information relevant for all physicians involved in cardiovascular disease care.
► An important limitation of the study is that 24-hour ambulatory blood pressure measurement was not part of the protocol. White coat hypertension and masked hypertension leading to over and underestimation of the prevalence of resistant hypertension were therefore not excluded.

awareness and control of hypertension have improved in the last decade, the proportion of patients meeting BP targets remains low.[8] Also for secondary prevention, control rate is only slightly over 50%, and antihypertensive medication is still underused, even in very high-risk patients.[9 10] With the emergence of new device-based BP-lowering therapies, such as percutaneous renal denervation[11–13] and implantable devices for barostimulation,[14] the concept of (apparent) therapy-resistant hypertension (aTRH) has regained attention.[15 16] Yet, detailed information on the prevalence and determinants of therapy-resistant hypertension is limited, in particular among patients with a history of a cardiovascular event. Such information creates more awareness among clinicians and potentially leads to investigations into modifiable causes.

We therefore set out to investigate the age and sex specific prevalence of therapy-resistant hypertension in patients with clinically manifest CVD. Second, we investigated clinical characteristics associated with aTRH in these patients.

METHODS
Study design
The SMART (Second Manifestations of ARTerial disease) study is an ongoing prospective cohort study including 18–79 year-old patients referred to the University Medical Center Utrecht with atherosclerotic CVD or for treatment of cardiovascular risk factors. Design and rationale of the SMART study have been described in detail previously.[17] For this study, we selected patients referred for treatment of symptomatic CVD or for treatment of CVD risk factors with a history of manifest vascular disease. These patients were referred for coronary heart disease, cerebral vascular disease, peripheral artery disease, abdominal aortic aneurysm (AAA) or for CVD risk factor management with a history of CVD. Coronary artery disease was defined as myocardial infarction, angina pectoris or coronary revascularisation. Patients with cerebrovascular disease had experienced a transient ischaemic attack (TIA), ischaemic stroke, amaurosis fugax, retinal infarction or a history of carotid surgery. Peripheral artery disease was defined as a symptomatic and documented obstruction of distal arteries of the leg or interventions (Fontaine classification II–IV confirmed with ankle brachial index (ABI) ≤0.90 in rest or decrease of ABI >20% after exercise, percutaneous transluminal angioplasty, bypass or amputation). Patients with AAA had a suprarenal or infrarenal aneurysm of the aorta or a history of AAA surgery. Diabetes mellitus was defined as fasting serum glucose ≥7.0 mmol/L, self-reported diabetes and/or the use of oral antihyperglycaemic agents or insulin.

Participants are subjected to an extensive vascular disease screening including a questionnaire on history and symptoms of CVD and risk factors for CVD, measurement of office BP and anthropometrical characteristics, and laboratory tests including serum lipids, glucose and creatinine and urinary albumin and creatinine excretion. Blood pressure was measured on a single occasion in the office: with a semiautomatic oscillometric device during 25 min in supine position with measurement every 4 min and the mean taken as the BP until 1999 and, thereafter, in sitting position, three times at both upper arms with the highest mean of the last two measurements on one arm taken as the BP. Height and weight were measured without shoes and in light clothing. Waist and hip circumferences were measured in duplicate. Laboratory values were measured in venous blood using commercial enzymatic chemistry kits. For albuminuria, albumin/creatinine ratios (ACR) were calculated in a random urine sample. Normoalbuminuria is defined as an ACR <3 mg/mmol, 3–29 mg/mmol is classified as microalbuminuria and an ACR ≥30 mg/mmol as macroalbuminuria. Glomerular filtration rate was estimated from the measured serum creatinine by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[18] Ankle-brachial index (ABI) was calculated from the highest systolic BP measured at the posterior tibial and dorsal pedal arteries by Doppler and at both brachial arteries by a semiautomatic oscillometric device in supine position. Carotid intima-media thickness was measured three times at the left and right common carotid arteries with the mean of all measurements being reported. Physical activity was quantified using a questionnaire on the usual pattern of leisure time physical activity in a week and expressed as metabolic equivalents (METs)/week (one MET is the rate of energy expenditure for an individual at rest, activities are assigned a MET intensity, weekly energy expenditure is calculated by multiplying hours spent on an activity by the activities' MET intensity). Details on these measurements can be found in previous publications.[17 19] Medication use was recorded at the baseline visit using a questionnaire. Use of antihypertensive drugs was recorded as use of an ACE inhibitor, angiotensin receptor blocker, beta blocker, calcium channel blocker, diuretics including subclasses, aldosterone antagonist, alpha blocker, central acting antihypertensive or direct acting vasodilator. For this study, these cross-sectional data were used to define BP control as no hypertension (below 140/90 mm Hg not using any antihypertensive drugs), controlled hypertension (below 140/90 mm Hg while using less than four antihypertensive drugs), uncontrolled but not therapy-resistant hypertension (≥140/90 mm Hg while using less than three antihypertensive drugs or less than four drugs not including a diuretic) or aTRH. aTRH was defined as BP ≥140/90 mm Hg while using ≥3 antihypertensive drugs including a diuretic or use of ≥4 antihypertensive drugs regardless of BP. For this study, we used data of all 7223 patients with CVD included from September 1996 to February 2014. The SMART study was approved by the Medical Ethics Committee of the Utrecht University Medical Center and written informed consent was obtained from all patients.

Data analyses
Patient characteristics were evaluated according to BP control group with means with SD reported, median with 25%–75% range for non-normally distributed data and proportions for categorical data. Prevalence of aTRH was reported in age and sex groups and in strata of estimated glomerular filtration rate (eGFR) and albuminuria as a proportion with corresponding 95% CIs. Prevalence of aTRH according to eGFR and albuminuria was adjusted for age and sex using UNIANOVA analyses (estimated marginal means). Clinical factors possibly related to presence of aTRH were entered in a univariate logistic regression model first, second in an age and sex adjusted model and finally in a multivariable model containing all variables. Measurements of signs of vascular disease (carotid intima-media thickness, albuminuria and ankle-brachial index) were related to presence of aTRH. For direct comparison of the magnitude of the relationships with

aTRH, ORs for 1 SD change in the continuous clinical factors were analysed. These results are presented as online supplementary material. Change of the prevalence of aTRH depending on the year of inclusion was investigated in a separate logistic regression analysis. Because of significant loss of participants due to missing data, imputation was used for the logistic regression analyses. Imputation was performed using bootstrapping and predictive mean matching (aregimpute in R, Hmisc package), assuming that these values were missing at random. Imputed variables included systolic and diastolic BP (0.6%), body mass index (BMI, 0.7%), waist circumference (4.0%), glucose (1.1%), hsCRP (0.8%), lipid levels (1.0%), albuminuria (7.2%), eGFR (1.0%), pack-years (1.1%), alcohol use (1.2%), and carotid intima-media thickness (3.5%). Analyses were performed in SPSS V.21. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript and its final contents.

RESULTS
Study population
Of 7223 patients with clinically manifest vascular disease, 985 did not have hypertension and were excluded (14%). In the remaining 6191 patients, mean age was 61 ± 10 years and 75% was male. The first manifestation of vascular disease occurred less than 1 year earlier in 57%, between 1 and 5 years ago in 19%, between 6 and 15 years earlier in 15% and over 15 years ago in 9%. Locations of vascular disease were coronary artery disease in 66%, cerebral vascular disease in 27%, peripheral arterial disease in 17% and aneurysm of the abdominal aorta in 9%. More than one of these sites were clinically effected in 16% of patients. The majority was referred for CVD, with 10% of patients referred for treatment of cardiovascular risk factors only with a history of vascular disease.

Prevalence of aTRH
BP was controlled on less than four drugs in 41% of the patients. aTRH was present in 9.1% (95% CI 8.4% to 9.8%). BP was uncontrolled but not therapy resistant in 50%. Patient characteristics according to BP control are shown in table 1.

The prevalence of aTRH increased with age in both sexes (figure 1). aTRH prevalence also increased with decrease in eGFR: at an eGFR above $90\,mL/min/1.73\,m^2$ aTRH was present in 6.0% of patients, and in patients with an eGFR between 75 and $90\,mL/min/1.73\,m^2$, this was 6.2%. At an eGFR between 60 and $74\,mL/min/1.73\,m^2$ 8.2% had aTRH. Between 45 and $60\,mL/min/1.73\,m^2$ and below $45\,mL/min/1.73\,m^2$, 15.1% and 26.8% of the patients fulfilled the criteria of aTRH, respectively. Albuminuria was related to aTRH: in patients without albuminuria 8.0% had aTRH, in patients with microalbuminuria this was 14.8% and in patients with macroalbuminuria 15.5% had aTRH. The age and sex adjusted prevalence estimates are presented in figure 2.

Determinants of aTRH
Antihypertensive drug use in the BP groups is shown in table 2. In the aTRH group, use of renin-angiotensin-aldosterone system inhibitors was virtually universal just as use of diuretics (the latter being part of the aTRH definition). A beta blocker was used by the majority of patients with aTRH (84%). Use of calcium channel blockers was much lower (54%). Aldosterone antagonists were used by 15% of the patients with aTRH.

Age and sex adjusted analyses showed that female sex, higher age, diabetes mellitus, duration and multiple locations of vascular disease, BMI and waist circumference and eGFR and albuminuria were related to aTRH as were lower total, high-density lipoprotein and low-density lipoprotein cholesterol and higher triglycerides (table 3). To facilitate comparison of the ORs of the different factors, these are expressed for 1 SD change instead of 1 unit change as online supplementary table S1. Important relationships were for higher age (OR 1.38 per 10 years, 95% CI 1.25 to 1.51), diabetes mellitus (OR 2.31, 95% CI 1.92 to 2.80), BMI (OR 1.09 per kg/m^2, 95% CI 1.07 to 1.12), eGFR (OR 0.77 for $10\,mL/min/1.73\,m^2$ higher eGFR, 95% CI 0.73 to 0.81) and albuminuria (OR 1.78, 95% CI 1.43 to 2.22 for microalbuminuria and OR 1.75, 95% CI 1.07 to 2.85 for macroalbuminuria, both compared with no albuminuria). Carotid intima-media thickness was significantly higher (0.99 ± 0.28 vs 0.93 ± 0.28 mm) and ABI lower (1.07 ± 0.20 vs 1.10 ± 0.19) in patients with aTRH compared with patients without aTRH. Results from the full multivariable model are shown in table 3.

The prevalence of aTRH increased with 8.8% (95% CI 6.7-11.0) for every year later a participant was included in the study (logistic regression analysis), from 4.8% in those included before 2000 (n=1300) to 13.9% in those included in 2010 or thereafter (n=891). Adjustment for the location of the vascular disease the participant had suffered from (cardiac, cerebral, peripheral or aneurysmatic vascular disease) did not change this result. When all variables in the multivariable analysis where adjusted for, the increase per year was 11.6% (95% CI 8.8-14.5).

DISCUSSION
Therapy-resistant hypertension was present in 9.1% of hypertensive patients with clinically manifest vascular disease and 49.5% had uncontrolled but non-resistant hypertension. Clinical characteristics related to aTRH were higher age, female sex, BMI and waist circumference, diabetes mellitus and duration and multiple locations of vascular disease, lower eGFR and albuminuria. Patients with aTRH had greater carotid intima-media thickness and lower ABI representing greater burden of subclinical vascular damage.

The prevalence of aTRH has been reported to be 9%–13% in the general hypertensive population.[20–22] In patients with chronic kidney disease (CKD), known for their high cardiovascular risk, a much higher prevalence of 25%–35% has been found, often using a

Table 1 Patient characteristics in BP control groups

	Controlled hypertension (n=2564)	Uncontrolled hypertension (n=3063)	Resistant hypertension (n=564)
Sex (male)	77%	74%	69%
Age (years)	59 (10)	62 (10)	64 (9)
Diabetes mellitus (yes)	15%	19%	33%
History of coronary heart disease	81%	54%	71%
History of cerebral vascular disease	18%	33%	29%
History of peripheral arterial disease	10%	23%	18%
History of abdominal aortic aneurysm	7%	10%	12%
Duration of vascular disease (years)	0 (0–4)	0 (0–4)	1 (0–10)
Body mass index (kg/m²)	27.0 (3.9)	26.9 (3.9)	28.3 (4.4)
Waist circumference (cm)	96 (12)	96 (12)	100 (13)
Office systolic BP (mm Hg)	124 (10)	156 (16)	152 (23)
Office diastolic BP (mm Hg)	75 (8)	88 (11)	85 (13)
Pulse pressure (mm Hg)	50 (9)	68 (16)	67 (18)
Fasting blood glucose (mmol/L)	6.1 (1.6)	6.4 (1.8)	6.8 (2.1)
HbA1c (%)	5.9 (0.9)	6.1 (1.0)	6.2 (1.0)
Total cholesterol (mmol/L)	4.6 (1.1)	5.0 (1.3)	4.7 (1.1)
LDL cholesterol (mmol/L)	2.7 (0.9)	3.0 (1.1)	2.7 (1.0)
HDL cholesterol (mmol/L)	1.2 (0.3)	1.3 (0.4)	1.2 (0.4)
Triglycerides (mmol/L)	1.4 (1.0–2.0)	1.4 (1.0–2.0)	1.5 (1.1–2.3)
HsCRP (mg/L)	1.9 (0.9–4.0)	2.2 (1.0–4.6)	2.3 (1.1–4.8)
eGFR (mL/min/1.73m²)	77 (17)	75 (18)	66 (20)
eGFR category (mL/min/1.73m²)			
<45	4%	6%	17%
45–60	11%	14%	22%
60–75	27%	31%	26%
75–90	35%	29%	21%
>90	23%	21%	14%
Albuminuria			
None	91%	82%	75%
Micro	8%	16%	21%
Macro	1%	3%	4%
Pack-years	14 (3–31)	16 (3–33)	16 (0–35)
Alcohol use (any)	84%	81%	78%
Physical exercise score (METs*hours/week)	36 (16–63)	32 (14–60)	31 (14–55)
Carotid intima-media thickness (mm)	0.89 (0.26)	0.97 (0.29)	0.99 (0.28)
Ankle-brachial index	1.13 (0.17)	1.07 (0.20)	1.07 (0.20)

Data are expressed as a proportion, mean with corresponding SD or median with IQR if not normally distributed.
Controlled hypertension is defined as BP <140/90 mm Hg while using 1-3 antihypertensive drugs.
Uncontrolled non-resistant hypertension is defined as ≥140/90 mm Hg while using <3 antihypertensive drugs or <4 antihypertensive drugs not including a diuretic.
Apparent therapy-resistant hypertension is defined as BP ≥140/90 mm Hg while using ≥3 antihypertensive drugs including a diuretic or using ≥4 antihypertensive drugs regardless of BP.
Albuminuria is absent if ACR is <3 mg/mmol, microalbuminuria is defined as ACR 3–29 mg/mmol, macroalbuminuria is defined as ACR ≥30 mg/mmol, eGFR (mL/min/1.73m²) was calculated using the CKD-EPI formula.
ACR, albumin-creatinine ratio; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent.
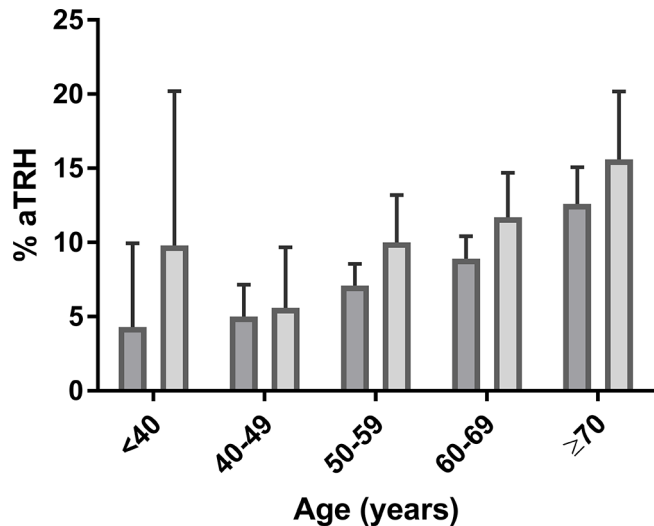
Figure 1 Prevalence of aTRH according to age and sex. Whiskers indicate 95% CIs. Legend: dark gray, male; light grey, female. aTRH, apparent therapy-resistant hypertension.

Figure 2 Prevalence of aTRH according to eGFR (A) and albuminuria (B). Prevalences adjusted for age and sex. Whiskers indicate 95% CIs . ACR, albumin-creatinine ratio; aTRH, apparent therapy-resistant hypertension; eGFR, estimated glomerular filtration rate using the CKD-EPI formula.

more stringent BP definition of <130/80 mm Hg.[23–25] Although several reports have shown a higher prevalence of vascular disease in those with aTRH in hypertensive populations,[21 22 26–28] the exact aTRH prevalence in patients with clinical manifest vascular disease has not been established. In the REGARDS study, 26% of 1694 hypertensive patients with a history of stroke or TIA were assigned the label of aTRH, with a definition not including diuretic use (and only 59% using one).[29] The smaller (n=927) WISE study in women suspected of coronary artery disease, with less than halve having obstructive coronary artery disease confirmed, found a much lower prevalence of 10.4%.[30] Information on patients with coronary artery disease was also reported from the INVEST and TNT trials (comparing two antihypertensive drugs and high/low dose statin use) with a prevalence of aTRH of 37.8% and 11.1% found, respectively.[31 32] However, the prevalence of aTRH might well be very different in patients participating in a trial compared with that in daily practice. Evidence comparable with this study comes from the REACH registry, mainly including patients with established (cardiac, cerebral and peripheral) arterial vascular disease (80%), that reported a prevalence of aTRH of 11.8%. Adding controlled BP while using ≥4 antihypertensive drugs led to an increase in aTRH to 21.6%.[33] The current study adjusts the estimate downwards, at least for patients with clinically manifest vascular disease of European descent. Black race has been found to be related to aTRH,[29 34] and apart from REACH, which is a worldwide study, all previous estimates were from US studies naturally including more black participants, or even deliberately oversampling them (REGARDS). In this study, most (57%) patients had their first CVD event within 1 year prior to inclusion. In the subgroup of patients with a duration of vascular disease longer than 1 year, the prevalence of aTRH was higher at 12% (95% CI 11%
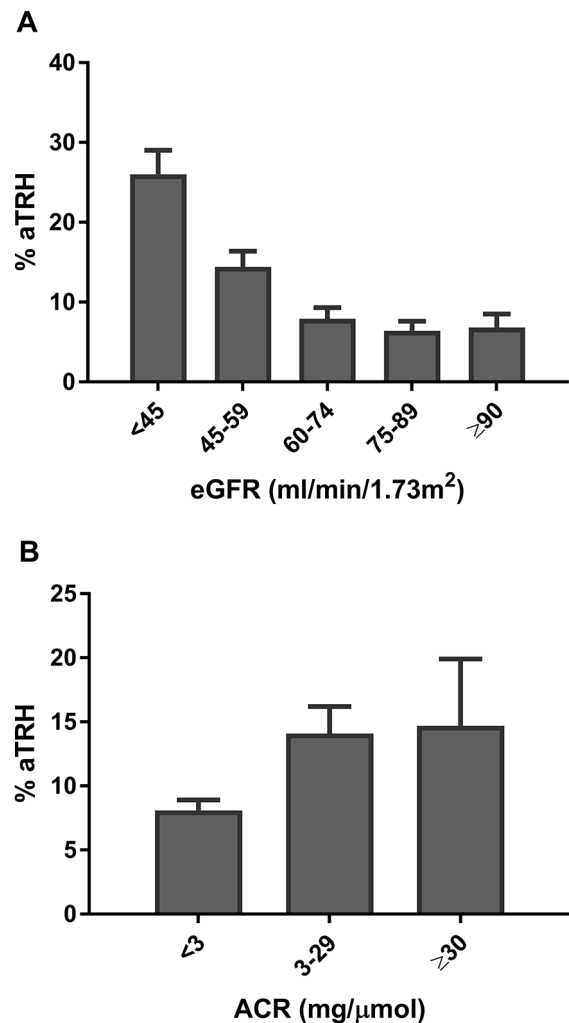
to 14%). Also important is that the prevalence of aTRH was 15% (95% CI 13% to 18%) in patients with more than one manifestation of vascular disease. The prevalence of aTRH can now be concluded to be 10%–20% in patients with clinically manifest CVD, with a strong influence of characteristics such as race, age and sex. In this study, we add detailed age and sex specific prevalence data to the literature. During the study, the prevalence of aTRH increased in participants newly included in the cohort. Adjustment for the clinical characteristics found to be related to aTRH and for location of vascular disease did not change this. A true increase in the prevalence of aTRH therefore exists. This confirms findings from NHANES[35] in a well-defined and carefully investigated cohort of patients with clinically manifest vascular disease. Patients with aTRH were found to have a worse cardiovascular risk profile with a higher

Table 2 Use of antihypertensive drugs in blood pressure control groups

	Controlled hypertension n=2564	Uncontrolled hypertension n=3063	Resistant hypertension n=564
Number of classes of antihypertensive drugs	1.7±0.7	1.1±0.9	3.6±0.7
Number of antihypertensives ≥3	17%	6%	100%
Number of antihypertensives ≥4	0%	0%	51%
ACE inhibitor	38%	26%	66%
ARB	11%	9%	34%
Beta blocker	77%	45%	84%
Calcium channel blocker	24%	19%	54%
Alpha blocker	0,3%	1%	5%
Diuretic	20%	11%	98%
Thiazid diuretic	11%	7%	55%
Loop diuretic	9%	3%	43%
Potassium sparing diuretic	2%	2%	6%
Aldosterone antagonist	2%	1%	15%
Centrally acting antihypertensive	0,1%	0,2%	0.9%
Direct acting vasodilator	0%	0%	0,4%

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

prevalence of diabetes mellitus and albuminuria, higher age and BMI and lower eGFR as compared with patients with prior CVD with controlled or non-resistant uncontrolled BP. Patients with aTRH also had a longer duration of vascular disease and multiple locations of vascular disease more often. The clinical factors related to the presence of aTRH have been very consistent and similar in the previous studies in hypertensive populations. Higher age, higher BMI and/or waist circumference, presence of diabetes and prior vascular disease have been reported to be related to aTRH in most studies.[21 26–28 34 36] Two cohorts with an ethnically diverse population found black race to be related to aTRH.[29 34] Longer duration of hypertension has also been shown to be related to presence of resistant hypertension both in general hypertensive populations and in the REGARDS patients with cerebrovascular disease.[26 29 36] Information on the duration of hypertension was not available in the SMART cohort. Sex differences have been less clear, with some studies reporting female predominance[27 32 33] just as in the present study, some finding no difference,[26 28] and others a higher prevalence in men.[21 34] In conclusion, the clinical picture of patients with aTRH is no different in patients with prior vascular disease than in those without.

Impaired kidney function and albuminuria were strongly related to resistant hypertension in patients with CVD. This is in accordance with the previous studies in the general hypertensive population[21 26–28 34 36] and also with the much higher prevalence of resistant hypertension found in patients with CKD. In the MASTERPLAN cohort investigating patients with CKD under nephrologist care, we found 34% to have resistant hypertension using a more

stringent CKD adjusted target BP of <130/80 mm Hg, and around one-quarter when using 140/90 mm Hg as target BP.[23] A similarly high prevalence was reported in a recent review summarising the state of knowledge on resistant hypertension in CKD.[25] Analyses from the Chronic Renal Insufficiency Cohort disclosed an even higher prevalence of 40% using a slightly different definition of aTRH.[37] Clinical characteristics related to resistant hypertension were reported to be similar to the general hypertensive population in CKD.[24 37] The patients with stroke/TIA and aTRH studied in REGARDS also had a greater chance of having aTRH if microalbuminuria or eGFR $<60\,mL/min/1.73\,m^2$ was present, and in REACH an eGFR $<60\,mL/min/1.73\,m^2$ was more frequent in aTRH.[29 33] This study adds detailed age and sex adjusted prevalence data according to eGFR and albuminuria. We feel this is an important aspect of aTRH especially for patients with prior CVD like we studied. As CKD is an independent risk factor for CVD, clustering with resistant hypertension can be expected to add up to a greatly increased CVD risk. For the patients we studied who have already suffered from CVD, the associated vascular risk may even be greater as well as the risk for end-stage kidney disease.[22 23 37 38] Hypertension/vascular nephropathy is one of the most common causes of end stage renal disease (ESRD).[39]

aTRH has also been shown to increase risk for CVD in both the general hypertensive population[22 36 40–42] and in patients with CKD[23 24 37 43] by 25%–90% after adjustment for other cardiovascular risk factors. The REACH investigators reported a 20% increase in risk for a composite endpoint of cardiovascular death, myocardial infarction or stroke in patients with a history of vascular disease and aTRH in 4 years of follow-up.[33] Patients with aTRH,

Table 3 Factors related to presence of aTRH

	Univariate analysis		Age and sex adjusted analysis		Multivariable-adjusted analysis	
	OR	95% CI	OR	95% CI	OR	95% CI
Sex (female)	1.33	1.11 to 1.61	1.34	1.11 to 1.62	1.53	1.18 to 1.99
Age (years)	1.03	1.02 to 1.04	1.03	1.02 to 1.04	1.01	0.99 to 1.02
Diabetes mellitus	2.42	2.00 to 2.92	2.31	1.92 to 2.80	1.66	1.28 to 2.16
History of cardiac vascular disease	1.26	1.04 to 1.52	1.34	1.10 to 1.62	0.98	0.54 to 1.78
History of cerebral vascular disease	1.18	0.98 to 1.43	1.13	0.93 to 1.37	0.97	0.53 to 1.77
History of peripheral vascular disease	1.13	0.90 to 1.40	1.08	0.86 to 1.35	0.77	0.42 to 1.41
History of abdominal aneurysmatic disease	1.60	1.23 to 2.09	1.44	1.10 to 1.89	1.09	0.59 to 2.01
Multiple locations of vascular disease	2.12	1.74 to 2.59	1.99	1.63 to 2.44	1.53	0.77 to 3.01
Duration of vascular disease (years)	1.03	1.02 to 1.04	1.03	1.02 to 1.04	1.01	1.00 to 1.02
Body mass index (kg/m²)	1.08	1.06 to 1.10	1.09	1.07 to 1.12	1.04	1.00 to 1.08
Waist circumference (cm)	1.03	1.02 to 1.03	1.03	1.03 to 1.04	1.01	1.00 to 1.03
Total cholesterol (mmol/L)	0.92	0.86 to 0.99	0.91	0.84 to 0.98	0.95	0.87 to 1.04
LDL cholesterol (mmol/L)	0.83	0.76 to 0.91	0.83	0.76 to 0.91	0.88	0.79 to 0.97
HDL cholesterol (mmol/L)	0.83	0.65 to 1.06	0.64	0.49 to 0.84	1.04	0.77 to 1.40
Triglycerides (mmol/L)	1.09	1.04 to 1.15	1.13	1.07 to 1.19	1.07	1.02 to 1.13
Fasting glucose (mmol/L)	1.15	1.10 to 1.19	1.15	1.10 to 1.19	1.02	0.96 to 1.08
hsCRP (mg/L)	1.00	0.99 to 1.01	1.00	0.99 to 1.01	0.99	0.98 to 1.00
eGFR (mL/min/1.73m²)	0.97	0.97 to 0.98	0.97	0.97 to 0.98	0.98	0.97 to 0.98
Albuminuria (no)	Ref		Ref		Ref	
Microalbuminuria	1.97	1.59 to 2.45	1.78	1.43 to 2.22	1.27	0.99 to 1.63
Macroalbuminuria	1.91	1.18 to 3.10	1.75	1.07 to 2.85	1.03	0.59 to 1.81
Pack-years	1.00	1.00 to 1.01	1.00	1.00 to 1.01	1.00	1.00 to 1.01
Alcohol use (any)	0.76	0.61 to 0.94	0.85	0.68 to 1.06	0.99	0.78 to 1.27
Physical exercise score (METs*hours/week)	1.00	1.00 to 1.00	1.00	1.00 to 1.00	1.00	1.00 to 1.00
Carotid intima-media thickness (mm)	1.84	1.41 to 2.40	1.49	1.11 to 2.00	1.20	0.85 to 1.68
Ankle-brachialis index	0.42	0.28 to 0.65	0.54	0.35 to 0.84	0.54	0.31 to 0.96

In the second model, age was adjusted only for sex, sex was adjusted only for age.
In the multivariate analysis, total cholesterol was used for the other factors. HDL, LDL cholesterol and triglycerides were entered separately.
aTRH, apparent therapy-resistant hypertension; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent.

whether CKD, hypertensive only or with a history of CVD, should be followed closely and every effort to increase BP control should be made. Awareness of a high prevalence of aTRH in certain patient groups and clinical factors related to it might help improve vascular and renal outcomes.

Strengths of this study are the large, well-defined population studied without restriction to one location of vascular disease, providing information for all physicians involved in CVD care. As the SMART study has been running for over 20 years now, change in the aTRH prevalence could also be studied. Risk factors were screened for with use of a standardised protocol. Office BP was calculated from the mean of several measurements. The most important limitation of the study, apart from the limitations inherent to the cross-sectional design with BP and medication use recorded

at a single time point, is that ambulatory BP measurement was not part of the protocol. White coat hypertension and masked hypertension leading to over- and underestimation of the prevalence of resistant hypertension, respectively, were therefore not excluded. As patients were often included shortly after the time of referral, the effect of adjustments made in antihypertensive drug treatment on the prevalence of aTRH was not assessed. For example, increase in the relatively low use of aldosterone antagonists detected in the study could have decreased aTRH. The effect on the prevalence of aTRH however is uncertain: reduction of undertreatment would decrease BP decreasing aTRH, but increase in number of antihypertensive drugs would also increase aTRH based on the criterion of ≥4 drugs regardless of BP. Also, although use of antihypertensive drugs was carefully recorded, prescription refill

data confirming adherence were not collected. Non-adherence has been shown to be an important cause of aTRH.[44]

In conclusion, 1 of every 11 patients in a hospital-based population of patients with clinically manifest CVD has aTRH. Risk factors are higher age, female sex, diabetes mellitus, duration and multiple locations of vascular disease, higher BMI and waist circumference, lower eGFR and albuminuria. Patients with aTRH deserve optimal treatment of cardiovascular risk factors in order to lower cardiovascular risk as well as the risk for end-stage renal disease. Increased attention to aTRH could be an important effect of the new device-based hypertension therapies introduced the last decade.

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