Clinical characteristics, antihypertensive medication use and blood pressure control among patients with treatment resistant hypertension: the SPIRIT study

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ABSTRACT

Objective: We evaluated the characteristics of patients with treatment resistant hypertension (TRH) and the prevalence of TRH in a large multi-country sample of specialist tertiary centres.

Methods: The Survey of PatIents with treatment ResIstant hyperTension (SPIRIT) study was a retrospective review of medical records of patients seen at tertiary centres located in Western Europe, Eastern Europe, North America, South America, Australia and Asia. Data on demographics, medical history and medication use were extracted from medical records. Prevalence and incidence of TRH were based upon estimated catchment populations.

Results: 1555 patients from 76 centres were included, mostly from centres that specialise in hypertension (55%), cardiology (11%) or nephrology (19%). Mean age was 64, 60% were male, 62% were Caucasian, 36% had chronic kidney disease, 41% had diabetes, 12% were smokers and 31% had a previous cardiovascular event. Daytime and night time ambulatory blood pressure (BP) was the most frequently used measurement for diagnosis (82%). 95% patients were prescribed diuretics, 93% an inhibitor of the renin-angiotensin system, 86% a calcium channel blocker, 74% a beta-blocker and 36% an aldosterone antagonist. The overall estimated mean incidence of TRH was 5.8 per 100,000 per year (ranging between 2.3 and 14.0 across regions) and the corresponding estimated mean prevalence of TRH was 23.9 per 100,000 (ranging between 7.6 and 90.5 across regions).

Conclusion: Observed variation likely reflects real differences in patient characteristics and physician management practices across regions and specialities but may also reflect differences in patient selection and errors in estimation of catchment population across participating centres.

CONDENSED ABSTRACT

Data on clinical characteristics and management of patients with treatment resistant hypertension (TRH) by specialty clinic is limited. We found differences which are likely the consequence of the significant number of centres in the study that identified cardiology and nephrology as their specialty. Despite being prescribed 3 and ≥ 4 antihypertensive classes, TRH patients continue to have poorly controlled BP. There may be under utilization of aldosterone antagonists in some patients. These data suggest the need for optimization of treatment and the development of more effective therapeutic strategies.

Key words: hypertension, treatment-resistant, prevalence, incidence, region, specialty

INTRODUCTION

Globally, over 1.4 billion people have hypertension with the proportion diagnosed and treated varying considerably between continents and countries.[1, 2] Fewer than one third of those prescribed treatment have their blood pressure (BP) controlled. This occurs despite extensive knowledge about how to make the diagnosis of hypertension, the availability of numerous antihypertensive drug classes and widespread consensus about management guidelines.[3-5] Treatment resistant hypertension (TRH) is a diagnosis made for a subset of individuals with uncontrolled BP levels.[6] TRH is present amongst individuals in which secondary causes of hypertension have been excluded when either BP levels remain above thresholds while the patient is using three or more different anti-hypertensive drug classes including a diuretic at optimal or maximum tolerated doses, or when BP levels are controlled only by the use of four or more different antihypertensive drug classes including a diuretic.[3, 5-8]

In a recent meta-analysis of 961,035 hypertensive individuals managed at specialist centres around the world, the prevalence of TRH was estimated as 13.7% in observational studies and 16.3% in clinical trials.[9] Amongst the studies contributing to the overview, the repeated measures of BP required to obtain a robust estimate of true average BP for an individual were not always available and it was recognised that over-estimation of the prevalence of TRH was likely.[9] It is also of note that this prevalence estimate applies only to a high risk subset of hypertensive patients who have been referred to a specialist centre.

Individuals with TRH are more likely to be male, obese, diabetic and to have previous cardiovascular disease.[10, 11] There have also been reported differences in the strategies used for diagnosis and treatment between centres, though most prior studies of patient characteristics have been either single centre investigations done in primary care[12, 13] or have been conducted in populations of limited diversity.[11, 14]

Accordingly, there remains some uncertainty about the prevalence of TRH, the characteristics of patients with TRH and the way that patients with TRH are managed around the world. Almost certainly TRH affects only a small proportion of individuals with hypertension but because hypertension is in itself very common it may nonetheless affect a substantial number of individuals.

The objectives of this study were to quantify and compare the characteristics of patients with TRH in a large multi-country sample of specialist clinical centres and to make estimates of the incidence and prevalence of TRH in the general populations of different countries.

METHODS

The Survey of Patients with treatment Resistant hyperTension (SPIRIT) study was a retrospective review of medical records relating to patient consultations at clinical centres with particular expertise in the diagnosis and management of TRH. The SPIRIT study protocol was approved by the Ethics Committees at participating institutions. All data collected were de-identified. Patient consent was only required in some countries, as directed by the responsible Ethics Committees. Requests for access to the de-identified data that underlie the study results should be made to datasharing@georgeinstitute.org. We will provide data to researchers with a methodologically sound proposal, and will work with interested parties to define and operationalise a data access agreement.

Centre selection

The study was conducted in 76 clinical centres in 15 countries divided into regions described as Western Europe (Belgium, France, Germany, The Netherlands, Switzerland and the United Kingdom), Eastern Europe (the Czech Republic, Poland and Hungary), North America (the United States and Canada), South America (Argentina), Asia (China and South Korea) and Australia. Potential clinical centres were included or excluded based upon a feasibility

assessment that assessed expertise in the diagnosis and management of TRH. A trained interviewer administered a standardised feasibility questionnaire, which included the collection of information regarding the estimated numbers of TRH patients managed by the centre, the estimated numbers of new TRH patients managed by the centre each year, and the estimated population catchment from which the centre draws the patients.

Participant identification and eligibility

The clinical centres identified medical records of patients using standardised medical record eligibility criteria. Medical records of potentially eligible patients were reviewed for eligibility on the basis of satisfying the following criteria: 1) No documented secondary cause of hypertension 2) Age ≥ 18 years 3) Reviewed for management on at least two occasions, the last of which was after 1 Jan 2016 4) Most recent ABPM, HBPM or AOBP measured after 1 Jan 2016 5) Antihypertensive medications prescribed at optimal or maximum tolerated doses in the opinion of the responsible physician 6) Exclusion of patients who were non-adherent to medication7) Diuretic prescribed 8) Most recent systolic blood pressure measured by ABPM, AOBP or HBPM while using at least three different classes of antihypertensive agent is uncontrolled and indicative of resistant hypertension 9) Alternatively, currently using four or more different classes of antihypertensive to achieve controlled blood pressure.The exclusion of secondary causes of uncontrolled BP was based upon medical record review alone and patients were eligible for inclusion in the survey so long as there was no record of a secondary or other cause of uncontrolled BP documented in the medical notes. Chronic kidney disease (CKD) was not deemed a secondary cause of hypertension so long as an established secondary renal cause such as renal artery stenosis was not present and estimated glomerular filtration rate was > 30ml/min/1.73m2.

Data collection

Data were extracted using a standardised process and entered into an electronic case record form. Data on demographics, medical history, laboratory values, qualifying BP and medication use were extracted from the medical records of patients at the participating clinical centres with no requirement for patient contact. Medications used at the time of the medical record review were recorded with the antihypertensive drug classes specified for data collection being angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), direct renin inhibitors, beta blockers, calcium channel blockers (CCB), diuretics (including subclasses), aldosterone antagonists, alpha adrenergic receptor blockers, central adrenergic agonists and direct vasodilators.

Blood pressure criteria for definition of TRH

BP criteria for the definition of uncontrolled TRH were ABPM daytime (or awake) ≥135 and/or ≥85 mm Hg; ABPM night time (or asleep) ≥120 and/or ≥70 mm Hg; ABPM 24-hour ≥130 and/or ≥80 mm Hg; AOBPM ≥135 and/or ≥85 mm Hg; and/or HBPM ≥135 and/or ≥85 mm Hg.[3-5] AOBPM referred to BP measurement obtained using a fully automated electronic sphygmomanometer that recorded multiple BP readings with the patient resting undisturbed in a quiet place without medical staff being present.

Statistical analysis

Descriptive statistics (means, standard deviations, ranges, proportions) were utilized to describe baseline characteristics, methods of BP measurement and current medications used by the study population. Estimates of these factors were made overall, by specialty and by the geographic region in which the participating centre was located. Prevalence was calculated as the number of patients managed in a year divided by the estimated catchment population from which each centre recruited. Likewise, incidence was calculated by dividing the new cases of TRH in a year by the estimated catchment population from which each

centre recruited. All analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC).

RESULTS

The study identified and collected medical record data on 1555 patients with TRH retrieved from 76 centres across 15 countries (Supplementary Table 1) between May and August 2017. Patients were drawn from specialist centres in hypertension, (55%), cardiology (11%), nephrology (19%) and other (14%), which included neurology, endocrinology, internal medicine, primary care and surgery. The specialties of participating sites varied across geographic regions (Supplementary Table 2).

Patient characteristics

A total of 1232 (80%) patients had uncontrolled BP while using three or more different anti-hypertensive drug classes including a diuretic, and 323 (20%) patients had controlled BP while using four or more different antihypertensive drug classes including a diuretic. The mean number (range) of drug classes used in each group was similar at 4.6 (2.0 to 10.0) and 4.7 (3.0 to 9.0) respectively.

The mean age of patients was 64 (SD, 12.7), 60% were males, mean body mass index (BMI) was 32kg/m^2, 62% were Caucasian, and 41% had diabetes, 25% CKD, 66% dyslipidaemia and 31% had a previous cardiovascular event (myocardial infarction, 8.5%; unstable angina,3.4%; heart failure,9.4%; or stroke, 10%;Table 1). Some participant characteristics differed by centre speciality and region with the variability explained in part by the distribution of different types of centres across regions (Supplementary Table 3).

BP measurements methods and BP levels

The most widely used measurement method, AOBPM, was reported for 65% of participants particularly in North America and Australia. Daytime, night time and/or 24hr ABPM was

used across all regions and specialities except for the North American centres. HBPM was used to make the diagnosis in only 17% of participants. Mean and range BP levels varied across regions and specialties with anticipated patterns of higher and lower levels observed according to the method used and whether patients were uncontrolled or controlled according to the definition of TRH (Table 2, Figure 1 and Supplemental Table 4).

Antihypertensive therapies

The most frequently used BP lowering drug class was diuretics (95%) closely followed by the renin-angiotensin system (RAS) inhibitors (93%), CCB (86%) and beta blockers (74%) (Table 3). Among the diuretic class, thiazides were most widely used (75%) and amongst the RAS inhibitors, ARBs (61%) were used twice as frequently as ACE inhibitors (33%). The most widely used combination was a diuretic, RAS inhibitor, CCB and beta-blocker (27%) and the next most frequent was the five class combination of a RAS inhibitor, diuretic, CCB, beta blocker and aldosterone antagonist (10%) (Supplementary Table 5). Overall, 14% of patients were prescribed three different classes of antihypertensive medications, 39% four classes, 27% five and 20% six or more classes (Supplementary Table 6). The majority of SPIRIT study patients (86%) were using 4 or more different types of antihypertensive agents and many were using 5 different drug classes.

There was moderate variation in the choice of drug therapies across different medical specialties with patients recruited from cardiology centres the most likely to use ARBs and the least likely to use loop diuretics, aldosterone antagonists and central adrenergic agonists (Table 3, Figure 2a). There were wide variations in the prescription of ARBs, beta blockers, alpha adrenergic receptor blockers and aldosterone antagonists across regions. Beta blockers were more common in Eastern Europe (85%), North America (76%) and Asia (76%) while aldosterone antagonists were more frequent in Western (56%) and Eastern Europe (53%) (Supplementary Table 7, Figure 2b).

Prevalence and incidence

The overall estimated prevalence of TRH was 23.9/100,000 with the range extending from 7.6/100,000 in Asia to 91.0/100,000 in Eastern Europe (Table 4). The estimated incidence of new cases of uncontrolled TRH in the populations served by the clinical sites ranged between 2.3 and 14.0 (mean 5.8) per 100,000. The estimates of incidence were smallest for Asia and greatest for Eastern Europe.

DISCUSSION

Patients with TRH included in the SPIRIT study exhibited the anticipated elevated levels of known risk factors, such as old age, male gender and high body mass index, as well as highly prevalent coexistent risk factors for CVD, such as diabetes, dyslipidaemia, chronic kidney disease and prior stroke. The differences in patient characteristics compared to prior studies of TRH , while mostly small,[10, 11, 15-17] are likely a consequence of the significant number of centres within the SPIRIT study that identified cardiology or nephrology as a specialty. Proportions with CKD, for example, were greater in Australia and North America because these two regions had a greater proportion of participants recruited from nephology centres. Likewise, the higher proportions of current smokers at hypertension and cardiology sites likely reflects the greater proportions of these sites in Europe, Asia and South America where smoking rates are higher. This in turn reflects the changing pattern of management for TRH in some regions, where TRH is no longer the preserve of specialist hypertension centres.

As would be anticipated for a study done in centres specializing in the management of TRH, the SPIRIT study participants were generally prescribed multiple BP lowering agents as well as other therapies for cardiovascular disease prevention, such as lipid lowering and antithrombotic agents. While many different combinations of antihypertensive therapies were used, the prescribing patterns across specialties and across regions were far more similar

than dissimilar to each other, following national guidelines. Differences in prescribing practices between specialties likely reflect the varying prevalence of different comorbidities in their patient populations[12, 18-21] for which some specific antihypertensive drug classes are indicated. Higher use of CCBs amongst TRH individuals managed at cardiology centres may, for example, reflect the anti-anginal effects of this therapeutic class. The high prevalence of cardiology centres in the SPIRIT study is also the likely explanation for the high rates of use of the RAS inhibitors, CCBs, diuretics and beta blockers in combination. This is consistent with other studies carried out in populations with a high percentage of cardiac patients.[20, 22]

The American Heart Association's (AHA) 2018 scientific statement on the detection, evaluation and management of TRH[6] s and the European Society of Cardiology/European Society of Hypertension guidelines[5] specifically recommended the 3 drug antihypertensive combination of RAS blockade (ACE or ARB) with calcium antagonist therapy and a diuretic and there have been reports of increased uptake of this regimen[23] which are confirmed in the SPIRIT study (Supplementary Table 3). In contrast, the parallel recommendation for the use of aldosterone antagonists in fourth line has not been implemented to the same extent in clinical practice[20, 23] and their use in SPIRIT remains low, particularly amongst patients managed at cardiology centres. While the addition of an aldosterone antagonist may result in significant additional BP lowering,[20, 23] widespread use may have been tempered by the risk of hyperkaelemia, especially in patients with CKD. Other adverse effects, including erectile dysfunction, gynecomastia, and breast tenderness,[24] may have previously occurred in patients included in the survey, explaining also in part the low prescription rate of aldosterone antagonists. The definition of TRH requires that patients be prescribed a diuretic, but only 95% of SPIRIT study participants were actually treated with a diuretic, which likely

reflects discontinuation of the class due to intolerance after the initial diagnosis of TRH was made.

The marked variation in mean BP levels across specialties (e.g., AOBPM mean 132/78 mm Hg for cardiology versus 149/76 mm Hg for nephrology) likely reflects the different comorbidities of the patients recruited, as these differences in mean values are comparable across regions. The extensive use of AOBPM in the SPIRIT study reflects a more recent increase in the use of this modality for diagnosis of hypertension. While AOBPM can reduce white coat hypertension and is more accessible to patients and providers, ABPM is needed to assess BP variability and diurnal and nocturnal patterns, in order to diagnose TRH as recommended by guidelines.[3-6]

The estimated prevalence of TRH in the SPIRIT study (23.9/100,000 or 0.024%) is far below the prevalence reported in recent systematic reviews of TRH (11 to 16%).[9],[25, 26] The reasons for this are likely multiple, but the primary difference is the denominator used to make the prevalence estimates. In the SPIRIT study the denominator is the entire population from which the included centres drew TRH cases, whereas for most studies included in prior reviews[9] the denominator is the hypertensive patients managed at the specialist centres that participated. The populations included in the prior reviews is hugely enriched for TRH cases and the SPIRIT study findings for prevalence must be interpreted in this light. Taking the SPIRIT estimate for North America (0.028%) for example, and using data available for the United States from the AHA,[27] we can use a series of approximations to reconcile the two sets of data. Specifically, only 77% of the US general population are adults, only 34% of adults have hypertension, only 75% of adults with hypertension are treated and only a few are referred and managed at specialist hypertension centres. If it is assumed that one in 25 of US hypertensives attends a specialist centre and is diagnosed with TRH then the SPIRIT prevalence estimate of 0.028 % for TRH amongst the general population would equate to a

prevalence estimate for TRH in the US of about 3.5% among the population treated at specialist centres. A figure much closer to the prevalence estimates of 11 to 16%[9, 25, 26] reported by other studies. [9, 25, 26] The same broad issue applies for the comparison of the incidence estimates, which were 5.8/100,000/year (0.0058%) for the SPIRIT study versus 1.9% in the prior overview.[25]

The SPIRIT study benefits from the large size, diverse types of centres and multiple geographic regions included, as well as the standardised approach to the collection and analysis of the data. The data are highly contemporary and should provide a good indication of the characteristics of patients with TRH at the present time.

There are, however, limitations to the study design. Selection of countries, sites and participants was not done at random and while the characteristics of the patients included are consistent with those of prior studies they may have been biased by the non-random selection process. Likewise the observed commonalities and differences in patient characteristics and treatment patterns between regions and specialties may have been influenced by the same selection processes. SPIRIT did not have any African centres and there are no data on TRH patient characteristics and prevalence for that region.

The estimates of prevalence and incidence are prone to systematic and random error because it is not possible to be sure that all TRH cases were captured or that all TRH cases included fully met accepted definitions.[28, 29] In particular, because the study was based on a review of chart data without additional patient consultation or further investigation, it is possible that masked hypertension or secondary causes of hypertension may have been missed as there were no fixed criteria in the protocol to exclude such causes. Further, non-adherence to prescribed treatment is a frequent cause for the misdiagnosis of TRH and it was not possible to quantify adherence for most cases included. There are also likely to have been errors in

the estimates of the underlying catchment populations from which the TRH cases managed by the participating centres derived because these were based solely on estimates made by the centre investigators, without independent verification. Lastly, the SPIRIT study was conducted in 2016 using previous hypertension guidelines. This could mean the estimates of prevalence and incidence may be higher now using the newly recommended control target in the American guidelines [3] but not the European guidelines [5] where the control target is unchanged.

In conclusion, treatment resistant hypertension increases the risk for cardiovascular events. In this retrospective medical record review of specialist clinical centres, we determined that regardless of specialty or region, there was poor control of BP despite being on ≥ 4 anti-hypertensive drug classes. These data suggest the need for optimization of treatment and the development of more effective therapeutic strategies.

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Figure Legends

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Table 1. Treatment resistant hypertension patient characteristics by specialty and overall

Characteristics	Hypertension (N=862)	Cardiology (N=174)	Nephrology (N=298)	Other (N=221)	Overall (N=1555)
Age					
Mean (SD)	62.3 (12.6)	62.6 (13.6)	67.5 (11.9)	66.6 (12.4)	63.9 (12.7)
70+ years	30.7	37.4	47.7	44.8	36.7
Male sex	62.6	64.4	56.4	48.4	59.6
Ethnicity					
Asian	17.8	71.3	2.3	1.8	18.5
Black or African American	7.0	0.0	20.5	25.8	11.5
Caucasian	67.5	27.6	74.8	50.2	61.9
Other	7.8	1.1	2.3	22.2	7.8
Weight (kg)	91.2 (22.6)	79.3 (18.7)	94.2 (23.8)	98.2 (25.7)	91.5 (23.4)
Body mass index (kg/m2)	31.2 (6.1)	28.2 (4.9)	32.5 (6.9)	34.5 (8.0)	31.5 (6.6)
Current smoker	14.0	19.5	7.7	3.6	186 12.0
Medical history					
Obstructive sleep apnea	17.5	2.9	28.9	29.4	19.7
Treated obstructive sleep apnea	57.0	0.0	60.5	76.9	12.1
Hypertensive retinopathy	12.1	9.2	1.7	0.9	8.2
Myocardial infarction	9.2	4.6	10.4	6.3	8.5
Unstable angina	3.6	5.2	3.0	1.8	3.4
Heart failure	8.9	12.1	8.7	9.0	9.3
Atrial fibrillation	9.6	6.9	10.7	12.2	9.9
Stroke	10.8	13.8	7.7	7.2	10
Abdominal aortic aneurysm	1.4	1.1	1.3	2.3	1.5
Chronic kidney disease	18.0	5.2	50.3	36.2	25.3
Type 2 Diabetes	41.3	20.7	49.7	42.1	40.7
Dyslipidaemia	70.1	53.4	62.8	67.4	66.4
Laboratory assessment					
Creatinine (µmol/L)	92.3 (26.6)	86.5 (22.4)	110.8 (33.9)	99.4 (29.1)	96.2 (29.2)
Potassium (mmol/L)	4.1 (0.4)	4.1 (0.4)	4.2 (0.5)	4.2 (0.5)	4.2 (0.5)
eGFR (mL/min/1.73m2)	71.7 (24.2)	79.9 (25.4)	55.9 (20.82)	61.1 (20.8)	67.9 (24.5)
>=90	22.7	31.1	8.7	10.0	19.1
60-<90	49.0	47.3	34.1	41.2	44.5
<60	28.3	21.6	57.1	48.8	30.8

Data is expressed as a proportion and mean (SD) Other specialty category includes primary care, neurology, endocrinology, internal medicine, surgery.

Table 2. Blood pressure levels by different measurement methods overall and by specialty and overall

	Hypertension (N=862)	Cardiology (N=174)	Nephrology (N=298)	Other (N=221)	Overall (N=1555)
Daytime ABPM					
% with measures	47.7	78.7	49.3	9.0	46.0
Systolic Blood Pressure (mm Hg)	144.5 (18.9)	138.4 (17.6)	148.3 (20.2)	151.9 (19.8)	144.3 (19.2)
Diastolic Blood Pressure (mm Hg)	83.2 (13.3)	81.0 (14.2)	76.7 (13.9)	80.0 (11.5)	81.4 (13.8)
Night time ABPM					
% with measures	42.9	44.3	33.2	8.1	36.3
Systolic Blood Pressure (mm Hg)	132.6 (18.4)	130.9 (19.4)	132.2 (24.3)	137.2 (23.2)	132.4 (19.8)
Diastolic Blood Pressure (mm Hg)	74.4 (13.5)	76.8 (15.6)	67.2 (13.8)	71.4 (13.0)	73.4 (14.1)
24hr ABPM					
% with measures	41.5	44.3	36.6	8.1	36.1
Systolic Blood Pressure (mm Hg)	141.1 (17.7)	136.4 (17.1)	143.1 (19.1)	147.6 (19.7)	141.1 (18.0)
Diastolic Blood Pressure (mm Hg)	80.3 (13.1)	79.9 (16.4)	74.8 (13.1)	77.8 (10.4)	79.1 (13.7)
AOBPM					
% with measures	63.7	17.2	72.8	99.1	65.3
Systolic Blood Pressure (mm Hg)	143.8 (23.4)	132.0 (17.5)	148.9 (19.9)	144.0 (19.9)	144.6 (22.0)
Diastolic Blood Pressure (mm Hg)	80.5 (14.9)	77.9 (11.3)	75.9 (14.3)	79.4 (13.1)	79.2 (14.4)
HBPM					
% with measures	16.4	33.9	14.8	5.4	16.5
Systolic Blood Pressure (mm Hg)	145.6 (22.8)	143.6 (15.0)	150.9 (17.9)	146.1 (22.8)	146.1 (20.4)
Diastolic Blood Pressure (mm Hg)	81.8 (13.8)	81.2 (10.8)	78.0 (12.8)	75.8 (15.1)	80.7 (13.1)

Data is expressed as a proportion and mean (SD). ABPM - Ambulatory blood pressure measurement, AOBPM -automated office blood pressure measurement, HBPM - Home blood pressure measurement. Other specialty category includes primary care, neurology, endocrinology, internal medicine, surgery.

Table 3. Blood pressure lowering medication and other preventative therapies prescribed, by specialty and overall

	Hypertension (N=862)	Cardiology (N=174)	Nephrology (N=298)	Other (N=221)	Overall (N= 1555)
Renin-angiotensin systemic inhibitors	95.8	98.9	85.6	86.4	92.9
Angiotensin converting enzyme inhibitor	37.9	21.8	24.5	33.9	33.0
Angiotensin receptor blocker	59.2	78.7	61.7	53.8	61.1
Direct renin inhibitor	0.5	0.0	0.0	0.0	0.3
Calcium channel blockers	87.4	95.4	80.5	76.9	85.5
Dihydropyridine calcium channel blockers	81.3	93.1	72.8	66.1	78.8
Non-dihydropyridine calcium channel blockers	8.2	2.9	9.1	12.7	8.4
Beta Blockers	73.8	77.0	76.8	66.1	73.6
Alpha adrenergic receptor blockers	26.7	16.1	22.5	28.5	25.0
Diuretics	95.4	96.0	96.6	91.9	95.2
Loop diuretic	23.1	16.1	35.2	28.5	25.4
Thiazide	78.9	81.0	67.1	68.3	75.4
Potassium sparing diuretic	9.7	5.2	12.8	9.5	9.8
Aldosterone antagonists	41.3	19.5	35.2	26.7	35.6
Central adrenergic agonists	16.4	3.4	25.8	13.1	16.3
Vasodilators	6.8	8.6	24.5	17.6	12.0
Other antihypertensive drugs	(2.2)	0.0	1.3	6.8	2.4
NSAIDS	4.8	4.0	4.4	12.2	5.7
Glitazone	1.0	0.0	1.7	1.8	1.2
Aspirin	45.0	36.8	58.4	49.8	47.3
Anticoagulant	11.0	12.1	16.1	12.7	12.3
Antidepressant	8.8	6.9	9.7	16.7	9.9

Data is expressed as a proportion. All values recorded are in percentages. NSAIDS- Non- steroidal anti-inflammatory drugs. Other specialty category includes primary care, neurology, endocrinology, internal medicine, surgery.

Table 4. Estimated prevalence and incidence of treatment resistant hypertension by region and overall

Region	Number of sites contributing data	New incident patients diagnosed in a year	Prevalent patients managed in a year		Catchment population	Estimated prevalence /100,000^	Estimated incidence /100,000@
			Uncontrolled BP*	Controlled BP#			
Western Europe	19	2,323	5,125	4115	29,150,000	31.7 (31.1 - 32.4)	7.9 (7.7 - 8.3)
Eastern Europe	14	1,590	4,285	5,955	11,320,000	90.5 (88.7 - 92.2)	14.0 (13.4 - 14.8)
North America	19	2,945	4,065	4,323	30,312,000	27.7 (27.1 - 28.3)	9.7 (9.4 - 10.1)
South America	3	120	1,012	675	2,200,000	76.7 (73.1 - 80.4)	5.5 (4.6 - 6.5)
Australia	9	478	1585	1058	4,330,000	61.0 (58.8 - 63.4)	11.0 (10.1 - 12.1)
Asia	12	1,942	2,865	3600	84,700,000	7.6 (7.4 - 7.8)	2.3 (2.2 - 2.4)
All regions	76	9,398	18,937	19,726	162,012,000	23.9 (23.6 - 24.1)	5.8 (5.7 - 5.9)

This table only includes sites that have non-missing data for new patients, current patients and catchment population.

*Patients with uncontrolled hypertension on adequate doses of three or more agents, including a diuretic managed by the centre each year

#Patients with blood pressure controlled using 4 or more anti-hypertensive medications managed by the centre each year

^Estimated prevalence data is available for both patients with uncontrolled hypertension on adequate doses of three or more agents, including a diuretic and patients with blood pressure controlled using 4 or more anti-hypertensive medications managed by the centre each year

@Estimated incidence data are available only for patients with uncontrolled hypertension on adequate doses of three or more agents, including a diuretic managed by the centre each year