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Rationale and design of a large registry on renal denervation: the Global SYMPLICITY registry

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KEYWORDS

- cardiovascular interventions
- hypertension
- renal denervation
- resistant hypertension
- sympathetic nervous system

Abstract

Aims: Hypertension is a global healthcare concern associated with a wide range of comorbidities. The recognition that elevated sympathetic drive plays an important role in the pathogenesis of hypertension led to the use of renal artery denervation to interrupt the efferent and afferent sympathetic nerves between the brain and kidneys to lower blood pressure. Clinical trials of the Symplicity™ renal denervation system have demonstrated that radiofrequency ablation of renal artery nerves is safe and significantly lowers blood pressure in patients with severe resistant (systolic BP >160 mmHg) hypertension. Smaller ancillary studies in hypertensive patients suggest a benefit from renal denervation in a variety of conditions such as chronic kidney disease, glucose intolerance, sleep apnoea and heart failure.

Methods and results: The Global SYMPLICITY registry, which incorporates the GREAT SYMPLICITY registry initiated in Germany, is being conducted worldwide to evaluate the safety and efficacy of treatment with the Symplicity renal denervation system in real-world uncontrolled hypertensive patients, looking first at subjects with severe resistant hypertension to confirm the results of prior clinical trials, but then also subjects with a wider range of baseline blood pressure and coexisting comorbidities.

Conclusions: The rationale, design and first baseline data from the Global SYMPLICITY registry are presented.

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Abbreviations

EQ-5D European quality of life - 5 dimensions
HTN hypertension
SBP systolic blood pressure

Introduction

Hypertension represents a global healthcare problem[1] with a major impact on cardiovascular morbidity and mortality[2,3] that imposes a large economic burden on healthcare systems[4]. It accounts for 40% of deaths from ischaemic heart disease and 51% of all stroke deaths worldwide[2,4]. Hypertension is associated with additional morbidities such as congestive heart failure, chronic kidney disease, atrial fibrillation, and peripheral arterial disease[5,6]. Resistant hypertension is a condition in which, despite treatment with at least three drugs (one being a diuretic) at appropriate doses and sufficient medical adherence, blood pressure goals are not achieved (<140/90 mmHg)[5-8] and ambulatory blood pressure remains elevated[9]. Patients with resistant hypertension are at especially high risk for cardiovascular events, and other comorbidities such as sleep apnoea, diabetes mellitus and psychosocial disorders are more frequent in these patients[10,11].

It is widely accepted that sympathetic hyperactivity plays an important role in the development and maintenance of hypertension[12-14], and it has been increasingly implicated in treatment resistance[15,16]. The kidneys provide afferent signals to the central nervous system, with a reflex sympathetic activation, a generalised vasoconstriction and a pronounced increase in blood pressure[17,18]. Renal afferent denervation prevents or delays hypertension in experimental animal models[18] and in the kidneys sympathetic efferent outflow increases markedly, via alpha-1 and beta-1 receptors, vascular resistance, renin release from the juxtaglomerular cells and tubular sodium reabsorption[19-21]. Therefore, it appears plausible that interrupting the interaction between the brain and the kidneys to inhibit sympathetic stimulation could reduce blood pressure and related adverse outcomes[15,22].

Recently, an interventional technique became available aimed at interrupting afferent and efferent signals from sympathetic nerves located in the adventitia of the renal arteries[22]. The Symplicity HTN trial programme was started to test the hypothesis that application of radio-frequency energy in the renal arteries can reduce blood pressure in patients with resistant hypertension. The proof-of-concept study was the Symplicity HTN-1 trial, showing a significant and sustained blood pressure reduction[23], as confirmed by long-term follow-up studies up to 24 months[24]. Symplicity HTN-2 was a randomised parallel group trial in patients with severe resistant hypertension (systolic BP >160 mmHg), showing systolic blood pressure reduction of 32 mmHg at six months after treatment but no change in the control group[25]. After 12 months, the blood pressure reduction was similar to that observed after one month with similar responses in the crossover (former control) group[26]. The ongoing Symplicity HTN-3 trial will include 530 patients in the USA, with a sham procedure applied in the control group[27].

Ancillary studies have shown that, in patients with metabolic syndrome and resistant hypertension, glucose tolerance is improved due to a favourable impact on insulin resistance[28]. Renal denervation also reduces resistive indices in the kidneys and is able to improve urinary albumin excretion[29]. After renal denervation, a reduction of pulse wave reflection, pulse pressure and central as well as peripheral blood pressure has been observed[30]. In the heart, blood pressure reduction by renal sympathetic denervation was associated with a reduction of LV mass and an improvement in diastolic function[31]. While a reduction in heart rate has been observed[32], the chronotropic response to exercise was maintained[33]. Finally, the procedure might be useful in other conditions commonly associated with increased sympathetic activation such as polycystic ovary syndrome[34], renal failure[35], sleep apnoea[36,37], and electrical storm[38].

While the limited number of patients included in the Symplicity HTN studies[23-25] might provide evidence for efficacy, clearly larger populations are required to evaluate the safety and efficacy of the procedure more comprehensively. Furthermore, since renal denervation is an interventional technology, which can potentially cause harm and is costly, a large database is necessary to study safety and efficacy in specific subgroups.

Given that an increasing number of patients are treated in clinical practice with renal denervation, the GREAT SYMPLICITY registry was initiated in Germany and is now embedded in the larger Global SYMPLICITY registry being conducted worldwide in order to provide more in-depth information on this treatment. Herein, we report the rationale, design and first baseline data of these combined international registries on renal denervation.

Methods

OBJECTIVE

The Global SYMPLICITY registry aims to document the long-term safety and effectiveness of renal denervation in a real-world population of patients with hypertension and other diseases characterised by elevated sympathetic drive. Due to the early start and distribution of the procedure with the commercially available Symplicity™ renal denervation system (Medtronic, Santa Rosa, CA, USA) in Germany, the GREAT registry was initiated first with more focus on the needs within Germany, including detailed description of hypertension medications. Data from the GREAT registry are now incorporated into the Global SYMPLICITY registry. The primary objective of the registry is to assess the acute procedural and long-term safety and effectiveness of renal denervation in real-world patients with hypertension. In addition, the registry is designed to evaluate the effectiveness of renal denervation with regard to individual disease states characterised by elevated sympathetic drive (e.g., diabetes mellitus, heart failure, chronic kidney disease, cardiac arrhythmias and sleep apnoea). The registry will establish procedural benchmarking and practice patterns (e.g., evaluation of renal anatomy in clinical practice, procedural data such as number of ablations per artery, procedure and hospitalisation time and periprocedural safety events), assess the effect of geographical variation in subjects and procedural characteristics on clinical outcomes, and collect quality of life data related to the renal denervation procedure and to the disease state of subjects. Publication of the Global SYMPLICITY registry outcome will

include the patients enrolled in the GREAT registry. After primary publication of the results, investigators may be allowed to publish regional data on request and with the approval of the GSR publication committee.

The Global SYMPLICITY and GREAT registries are sponsored and funded by Medtronic, Inc. Medtronic personnel are responsible for site activation, required reporting functions, and monitoring.

DESIGN

The Global SYMPLICITY registry is a prospective, open-label, multicentre single-arm registry. The registry will collect data from a minimum of 5,000 patients who receive renal denervation (among whom at least 1,000 subjects will be from the GREAT registry). Treatment decisions are left to the discretion of the physician and will be performed according to best available hospital practice and in accordance with the product instructions for use. Consecutively treated subjects at participating hospitals who are undergoing renal denervation with the Symplicity™ renal denervation system are considered for enrolment in the registry. Registry enrolment is ongoing.

The registry recommends follow-up for subjects at 3, 6 and 12 months (±30 days) and then annually through at least three years, but ideally up to five years (±60 days). The Global SYMPLICITY registry will be conducted for a minimum of three years from enrolment to the final subject and has the possibility to increase follow-up to five years or until the registry has been formally terminated. The GREAT registry will follow patients for five years.

ETHICS AND PATIENT CONFIDENTIALITY

Confidentiality of all patients is protected. The protocol (including any possible amendments), informed consent forms, patient information sheets and safety reporting procedures were approved by each participating country, region or university authority as well as by the appropriate independent ethics committee or review board.

INCLUSION AND EXCLUSION CRITERIA

The registries aim to include a patient population that reflects current clinical practice in participating countries. Included patients must be age >18 years or as required by local regulations and be suitable candidates for renal denervation as determined by the enrolling physician. Signed informed consent regarding the nature of the registry and authorisation of data collection by the patient or legal representative, as defined by local regulations, is required for all patients enrolled in the registries in accordance with the Declaration of Helsinki.

All consecutive patients evaluated by an investigator and determined to be eligible candidates for the renal denervation procedure should be informed about the Global or GREAT SYMPLICITY registry and enrolled if inclusion criteria are met.

RENAL DENERVATION TREATMENT AND FOLLOW-UP ASSESSMENTS

The renal denervation procedure will be performed according to the standards in the respective hospital and the instructions for use of the Symplicity™ renal denervation system. Prior to the renal denervation procedure and at each follow-up visit, registry investigators should reconfirm medication usage and document any medication changes. Rarely, treatment failure can occur when no energy is delivered in the intended location by the Symplicity renal denervation system despite multiple attempts. Treatment failures are recorded in the electronic case report form and these patients are followed up for three months for safety purposes, after which they exit the registry.

Suggested follow-up of each patient is at 3, 6 and 12 months post procedure and then annually for a minimum of three years and up to five years. Registry exit forms should be completed in the following cases: withdrawal of consent by patient or investigator, treatment failure, patient death, loss of follow-up.

All tests and procedures fall inside the standard of care for a given hospital and are not specified by the registry. The items listed in **Table 1** represent a suggested sample of the standard of care data that will be collected in the electronic data capture system. At each office visit three office blood pressure measurements will be taken one minute apart using an automatic blood pressure monitor. When ambulatory blood pressure measurements are performed, compliance with published guidelines[6] is suggested (every 15 to 30 minutes during the day and every 30 to 60 minutes at night).

Similarly to the Symplicity HTN trial programme, renal imaging is recommended for patients enrolled into the registry. The registry will investigate the techniques used to detect renal artery abnormalities with angiography, magnetic resonance angiography, computerised tomography or duplex scan. Electrocardiography, left ventricular imaging and blood testing may be performed as clinically indicated. Advanced testing for metabolic disorders by the glucose tolerance test and urine testing to screen for microalbuminuria or undetected kidney disease will also be performed as clinically indicated for selected patients. **Table 1** includes a detailed list of diagnostic procedures that may be done at the discretion of the investigators and will also be captured.

QUALITY OF LIFE ASSESSMENT PROCEDURE

The EuroQOL-5 dimensions (EQ-5D) questionnaire is a standard instrument for use as a measure for health outcome and includes a visual analogue scale and a descriptive system[39]. The EQ-5D questionnaire will be provided in the local language and will be collected pre- and post-procedure, and at every follow-up.

DATA HANDLING AND STATISTIC EVALUATION

All data will be entered into an electronic data capture form using the Oracle™ Clinical Database Management System (Oracle, Redwood Shores, CA, USA). An independent contract research organisation (Institut für Herzinfarktforschung [IHF] Ludwigshafen, Germany) is responsible for data analysis. The enrolment period for the registry is approximately four years and recommended follow-up is for a minimum of three years and up to five years. All analyses will be performed based on all patients who passed the point of enrolment according to the intention-to-treat principle, provided consent/data release was obtained from the patient. Since the registries do not have a statistically powered hypothesis, there are no sample size calculations.

Table 1. Standard of care and additional parameters captured for registry patients.

Examination	Parameters
Patient characteristics	Age
	Gender
	Height, weight, waist circumference
	Medical health history/comorbid conditions
	Medication regimen
Office measurements	Blood pressure (average of 3 readings)
	Heart rate
Renal artery imaging	Duplex Doppler sonography
	Contrast-enhanced MRI
	Contrast-enhanced CT
	Angiogram
ABPM	Programmed number of readings (night, day)
	Number of successful readings (night, day)
	Overall average BP
	Daytime average BP
	Night-time average BP
	Max and min SBP, DBP
	Overall heart rate
ECG	QT interval
	Heart rate
LV imaging	Type of imaging
	LVEDVi
	LVESVi
	Ejection fraction
	LV mass
	E/E' ratio
Blood test	HbA1c
	Glucose
	Insulin
	Serum creatinine
	C-peptide
	Cystatin C
	BNP
	NT-proBNP
Urine test	Creatinine
	Albumin
	Albumin/creatinine ratio (UACR)
	Norepinephrine
Oral glucose tolerance test	Dose
	Glucose (0, 60, 120 min values)
	Insulin (0, 60, 120 min values)

ABPM: ambulatory blood pressure monitoring; BNP: brain natriuretic peptide; HbA1c: haemaglobin A1c; LVEDVi: left ventricular end diastolic volume index; LVESVi: left ventricular end systolic volume index; NT-proBNP: N-terminal pro-brain natriuretic peptide

The minimum number of enrolled patients is predefined and descriptive statistics for the clinical data will be provided. Categorical variables will be reported using counts and percentages. Continuous variables will be reported by giving the number of known values, the mean, standard deviation, and minimum and maximum values. All patients with available data will be included in the analyses. The registry will be conducted in such a way as to minimise the incidence of missing data. Analyses will be carried out for subgroups to assess consistency of results between subgroups. Imputation of missing data will not be performed.

SITE SELECTION, TRAINING AND MONITORING

Site selection will be performed based upon screening against a list of selection criteria, including qualification by training and expertise to conduct the procedure and the registry, investigator and staff experience in performing studies and registries, complying with protocol and regulatory requirements, adequate volume of patients meeting eligibility criteria, and experience of centres and physicians with an adequate laboratory set up for procedure and pre- and post-procedural management and monitoring. Investigators will be trained with respect to the protocol, timeframes, eligibility, consenting data collection and safety event reporting as well as source document requirements and regulatory requirements and compliance. In order to ensure high quality data collection, monitoring visits will be performed at least once in every centre. The aim is to monitor 10% of source data collected in the registries.

SAFETY MONITORING AND ADJUDICATION OF EVENTS

An independent clinical events committee (CEC) will adjudicate all protocol-defined safety events potentially related to renal denervation. These events include vascular complications such as haematomas, arterial bleeding, pseudoaneurysm or bleeding, renal artery perforation or dissection, renal artery reintervention post index procedure, new renal artery stenosis >70% within six months post procedure, contrast nephropathy (acute GFR drop of >25%) or new renal failure, new need for dialysis and new-onset end-stage renal disease. Additionally, hypertensive crisis unrelated to confirmed medication non-adherence requiring hospitalisation, any significant embolic event resulting in end-organ damage, stroke, acute myocardial infarction, atrial fibrillation or new-onset heart failure requiring hospitalisation more than 24 hours, and all-cause and cardiovascular death will be adjudicated by the CEC.

PRELIMINARY BASELINE CHARACTERISTICS

Over the period from February 2012 to January 2013 a total of 70 sites in 20 countries all over the world recruited 772 patients undergoing renal denervation for uncontrolled hypertension. Preliminary baseline characteristics are shown in **Table 2**. The Global and GREAT SYMPLICITY registries enrolled 63% and 61% male patients with an average age of 59.2 and 61.5 years, respectively. Patients in the GREAT SYMPLICITY were slightly older than those enrolled in the rest of the world.

BLOOD PRESSURE

Baseline office-based systolic blood pressure (SBP) in the overall registry population was 164.3±23.5 mmHg. There were some differences according to the distribution between blood pressure groups from <140 mmHg SBP to >180 mmHg SBP **(Table 3)**. The majority

Table 2. Baseline characteristics.

	All GSR patients (n=772)	GREAT only (n=389)	GSR excluding GREAT (n=383)
% male	62.2% (479/770)	61.0% (236/387)	63.4% (243/383)
Average age	60.4±12.3	61.5±11.5	59.2±13.0
Hypertension	99.3% (761/766)	100.0% (387/387)	98.7% (374/379)
Sleep apnoea	15.7% (113/720)	18.0% (65/362)	13.4% (48/358)
Diabetes	41.3% (316/766)	41.1% (159/387)	41.4% (157/379)
Chronic kidney disease	28.8% (220/765)	33.2% (128/386)	24.3% (92/379)
Atrial fibrillation	12.4% (95/765)	12.7% (49/387)	12.2% (46/378)
Heart failure	9.3% (71/763)	9.4% (36/384)	9.2% (35/379)
1 comorbidity	34.6% (266/768)	32.6% (126/387)	36.7% (140/381)
2 comorbidities	35.4% (272/768)	33.6% (130/387)	37.3% (142/381)
3+ comorbidities	29.7% (228/768)	33.9% (131/387)	25.5% (97/381)
Number of renal arteries	2.2±0.6	2.2±0.5	2.1±0.6

Values are n/N (%) or mean±standard deviation; GSR: Global SYMPLICITY registry

Table 3. Baseline blood pressure data.

	All GSR patients	GREAT only	GSR excluding GREAT
Mean office-based SBP±SD	164.3±23.51	160.6±23.65	168.3±22.74
<140 mmHg SBP	13.3% (99/743)	18.2% (69/379)	8.2% (30/364)
140-159 mmHg SBP	27.3% (203/743)	31.7% (120/379)	22.8% (83/364)
160-179 mmHg SBP	34.6% (257/743)	28.0% (106/379)	41.5% (151/364)
>180 mmHg SBP	24.8% (184/743)	22.2% (84/379)	27.5% (100/364)
Mean ambulatory SBP±SD	153.5±17.85	152.2±16.53	155.3±19.43

GSR: Global SYMPLICITY registry; SBP: systolic blood pressure

of patients had blood pressure values between 140 and 179 mmHg. Blood pressure values were slightly lower in the GREAT registry with 18.2% of patients presenting with SBP values <140 mmHg and 50.2% with values >160 mmHg at baseline. Among the patients in the Global SYMPLICITY registry (GSR) excluding the GREAT, 69.0% were ≥160 mmHg at baseline. Baseline ambulatory blood pressures are shown in **Table 3**.

COMORBIDITIES AND DIAGNOSTIC PROCEDURES

After careful evaluation by the investigators, patients were screened for comorbidities. Overall in this hypertensive population 16% of patients have sleep apnoea, 41.0% have diabetes mellitus, 29% have chronic kidney disease, 12% have atrial fibrillation and 9% have evidence of heart failure **(Table 2)**. The distribution of comorbidities according to baseline SBP is given in **Table 4**. Preliminary data suggest no clear association between number or type of comorbidity and baseline blood pressure.

Renal imaging before the denervation procedure was predominantly done by renal angiogram (66.4% overall, 54.5% GREAT, 78.4% other sites). Duplex ultrasound was also commonly used in the GREAT population (32.9%) but rarely by the GSR sites excluding GREAT (1.2%). MRI and CT were occasionally used by all sites (MRI 7.1%; CT 9.5% overall).

DRUG THERAPY

Table 5A summarises prescribed drug treatment. All patients were on high levels of concomitant treatments for hypertension (mean 4.3±1.3 drugs). However, the patients enrolled in GREAT were receiving a higher mean number of antihypertensive medications than patients from other sites. Concerning the distribution of different drug classes, there appears to be a greater usage of direct renin inhibitors, centrally-acting sympatholytics, direct-acting vasodilators and alpha-adrenergic blockers for patients enrolled in Germany versus other global sites outside Germany. The intensity of treatment does not appear to be related to the height of baseline blood pressure **(Table 5B)**. Patients with concomitant comorbidities had higher numbers of medications at presentation, particularly patients with chronic kidney disease or sleep apnoea **(Table 5C)**.

Table 4. Comorbidities per blood pressure group.

# of patients	All	<140 mmHg SBP	140-159 mmHg SBP	160-179 mmHg SBP	>180 mmHg SBP
Total	772	99 (12.8%)	203 (26.3%)	257 (33.3%)	184 (23.8%)
Male	62.2% (479/770)	57.6% (57/99)	60.9% (123/202)	71.1% (182/256)	53.8% (99/184)
Hypertension	99.3% (761/766)	96.0% (95/99)	99.5% (201/202)	100.0% (256/256)	100.0% (182/182)
Sleep apnoea	15.7% (113/720)	18.5% (17/92)	16.4% (31/189)	14.8% (36/244)	16.5% (28/170)
Diabetes	41.3% (316/766)	31.3% (31/99)	45.5% (92/202)	38.9% (100/257)	43.1% (78/181)
Chronic kidney disease	28.8% (220/765)	37.4% (37/99)	27.2% (55/202)	24.5% (63/257)	32.2% (58/180)
Atrial fibrillation	12.4% (95/765)	17.2% (17/99)	11.8% (24/203)	12.1% (31/257)	11.1% (20/180)
Heart failure	9.3% (71/763)	15.3% (15/98)	8.9% (18/202)	6.2% (16/257)	10.1% (18/179)
1 comorbidity	34.6% (266/768)	34.3% (34/99)	31.5% (64/203)	38.1% (98/257)	33.0% (60/182)
2 comorbidities	35.4% (272/768)	28.3% (28/99)	36.9% (75/203)	37.4% (96/257)	35.7% (65/182)
3+ comorbidities	29.7% (228/768)	37.4% (37/99)	31.0% (63/203)	24.1% (62/257)	31.3% (57/182)
Systolic BP, mean (mmHg)	164.3±23.5	127.6±10.4	150.4±5.7	167.3±5.6	195.4±13.3

SBP: systolic blood pressure

Table 5A. Baseline antihypertensive medication use.

		All GSR patients	GREAT only	GSR (excluding GREAT)
Mean # antihypertensive medications		4.3±1.3	4.6±1.3	4.1±1.3
Drug classes	Beta-blockers	78.0% (579/742)	79.0% (293/371)	77.1% (286/371)
	ACE inhibitors	33.2% (246/742)	37.5% (139/371)	28.8% (107/371)
	ARB	66.7% (495/742)	63.1% (234/371)	70.4% (261/371)
	CCB	74.4% (552/742)	73.6% (273/371)	75.2% (279/371)
	Diuretic	75.5% (560/742)	81.1% (301/371)	69.8% (259/371)
	Aldosterone antagonists	20.2% (150/742)	17.8% (66/371)	22.6% (84/371)
	Spironolactone	17.7% (131/742)	17.0% (63/371)	18.3% (68/371)
	Alpha-adrenergic blocker	34.5% (256/742)	41.0% (152/371)	28.0% (104/371)
	Direct-acting vasodilator	15.1% (112/742)	20.2% (75/371)	10.0% (37/371)
	Centrally-acting sympatholytics	28.4% (211/742)	35.8% (133/371)	21.0% (78/371)
	Direct renin inhibitor	8.2% (61/742)	13.5% (50/371)	3.0% (11/371)

ACE inhibitors: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; GSR: Global SYMPLICITY registry

Table 5B. Baseline antihypertensive medication use by systolic blood pressure.

		<140 mmHg SBP	140-159 mmHg SBP	160-179 mmHg SBP	≥180 mmHg SBP
Mean # antihypertensive medications		4.3±1.3	4.5±1.4	4.3±1.3	4.3±1.3
Drug classes	Beta-blocker	79.2% (76/96)	75.5% (148/196)	77.7% (195/251)	81.5% (145/178)
	ACE inhibitor	42.7% (41/96)	29.1% (57/196)	29.9% (75/251)	36.5% (65/178)
	ARB	53.1% (51/96)	69.4% (136/196)	70.9% (178/251)	66.9% (119/178)
	CCB	71.9% (69/96)	76.0% (149/196)	76.5% (192/251)	71.3% (127/178)
	Diuretic	75.0% (72/96)	79.1% (155/196)	74.9% (188/251)	71.9% (128/178)
	Aldosterone antagonist	27.1% (26/96)	21.4% (42/196)	16.7% (42/251)	20.2% (36/178)
	Spironolactone	26.0% (25/96)	19.9% (39/196)	14.7% (37/251)	15.2% (27/178)
	Alpha-adrenergic blocker	35.4% (34/96)	34.2% (67/196)	33.5% (84/251)	36.5% (65/178)
	Direct-acting vasodilator	20.8% (20/96)	10.2% (20/196)	13.1% (33/251)	18.5% (33/178)
	Centrally-acting sympatholytics	36.5% (35/96)	30.1% (59/196)	23.9% (60/251)	25.8% (46/178)
	Direct renin inhibitor	7.3% (7/96)	7.7% (15/196)	8.8% (22/251)	8.4% (15/178)

ACE inhibitors: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; SBP: systolic blood pressure

Table 5C. Baseline antihypertensive medication use by comorbidity.

		Sleep apnoea	Diabetes	Renal disease	Atrial fibrillation
Mean # antihypertensive medications		4.8±1.5	4.5±1.3	4.8±1.3	4.4±1.2
Drug classes	Beta-blockers	67.3% (74/110)	79.9% (243/304)	81.0% (170/210)	71.0% (66/93)
	ACE inhibitors	37.3% (41/110)	35.2% (107/304)	38.1% (80/210)	37.6% (35/93)
	ARB	70.0% (77/110)	67.1% (204/304)	64.3% (135/210)	64.5% (60/93)
	CCB	80.0% (88/110)	76.3% (232/304)	79.5% (167/210)	66.7% (62/93)
	Diuretic	78.2% (86/110)	78.9% (240/304)	80.0% (168/210)	81.7% (76/93)
	Aldosterone antagonists	30.0% (33/110)	19.7% (60/304)	20.0% (42/210)	19.4% (18/93)
	Spironolactone	27.3% (30/110)	17.4% (53/304)	18.6% (39/210)	16.1% (15/93)
	Alpha-adrenergic blocker	42.7% (47/110)	35.9% (109/304)	46.2% (97/210)	41.9% (39/93)
	Direct-acting vasodilator	24.5% (27/110)	18.1% (55/304)	22.4% (47/210)	16.1% (15/93)
	Centrally-acting sympatholytics	35.5% (39/110)	29.6% (90/304)	35.7% (75/210)	32.3% (30/93)
	Direct renin inhibitor	15.5% (17/110)	5.6% (17/304)	9.0% (19/210)	4.3% (4/93)

ACE inhibitors: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker; CCB: calcium channel blocker

Discussion

Resistant hypertension is associated with a particularly high rate of complications[11], and therefore requires intensive treatment[5-7,10]. Medical treatment usually consists of three or more drugs at maximally tolerated doses, one being a diuretic[5,6]. Many patients do not tolerate these drugs or do not achieve guideline recommended targets for blood pressure values despite intensive drug treatment. Recently, a new catheter-based technique of renal artery denervation[22] has gained a lot of interest not only in the scientific community but also in the public domain, in particular amongst the affected patients[40,41]. In fact, an expert panel from the European Society of Cardiology has recently published an overview of catheter-based renal denervation that provides guidance for the appropriate use of this novel therapy and highlights future potential applications for renal denervation[42]. The Symplicity HTN clinical development programme started with a proof-of-concept study in which a blood pressure reduction was proven by applying this procedure in treatment-resistant patients[23,24].

The sustained reductions of blood pressure, even in patients already receiving intensive medical treatment (in the trials more than five drug classes on average), have led many physicians to use the renal denervation technique in countries where the device is available. Although the number of patients in randomised trials is very limited there has been widespread use of the technique[40]. The low number of patients included in the trials precludes evaluation of safety in a large population treated under real-world conditions[41]. Furthermore, inclusion criteria in the studies were narrowed such that the applicability of the data to a broader population cannot be answered by the current SYMPLICITY clinical trials. The broader application, as shown herein, namely the treatment of patients with blood pressure levels lower than in those patients enrolled in the clinical trials, means that patients are included in the registry for whom no evidence of effectiveness is presently available. This will provide valuable data to guide real-world selection of hypertensive patients. Additionally, limited evidence is available concerning the renal denervation technique when comorbidities are prevalent, e.g., diabetes mellitus or chronic renal disease, where only circumstantial evidence for effectiveness is available. In order to understand further and to develop this treatment appropriately, these combined registries include broad patient populations that will provide information on real-life practice for a wide variety of comorbid conditions associated with activation of the sympathetic nervous system.

The Global SYMPLICITY registry aims to investigate 5,000 patients with a follow-up of at least three years and up to five years. After complete follow-up in the large patient population, the generated databases will allow investigators to answer questions as to whether the technique of renal denervation is applicable in a broad population or whether it is influenced by the site where treatment is performed, by limitations of safety or by the influence of comorbidities on treatment success. These registries aim to develop future research questions for renal denervation and improve the way to treat hypertension and in particular resistant hypertension, which is still unresolved with regard to the optimal method to improve cardiovascular morbidity and mortality.

The adverse event rate is quite low in patients in clinical trials. However, trial centres are selected and staff/clinicians have been extensively trained by proctors who introduced the techniques. It is important to establish the safety of renal denervation across broad patient populations treated in real-world settings and with less experience than those traditionally engaged in formal clinical trials. Therefore, the Global SYMPLICITY registry is specifically designed to evaluate the effect of treatment with the Symplicity renal denervation system in hypertensive patients with a wider range of baseline blood pressures and different levels of coexisting comorbidities. According to the first baseline data presented herein, it is apparent that a large number of patients were treated with lower blood pressure values than those randomised into formal clinical trials. Furthermore, there are centres involved in the registries with different backgrounds and clinical specialities. Some treatments are undertaken by vascular radiologists, but most by interventional cardiologists. It will be interesting to determine whether different comorbidity treatment modalities or clinical disciplines involved in the treatment of these patients provide evidence of differential effectiveness and real-world safety. The Global SYMPLICITY registry also has the goal to develop the technique and evaluate the results in a broad population involving different countries with differences in socioeconomic status.

In conclusion, the Global SYMPLICITY registry, including the patients from the GREAT registry, will provide a large database on renal denervation under real-world conditions with a primary goal to evaluate the observed safety and effectiveness of the Symplicity renal denervation system in treating resistant hypertension. The information might be of particular value to develop hypotheses further and power estimates for future controlled clinical trials and to identify appropriate target populations for future studies of interventional renal artery denervation.

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Conflict of interest statement

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