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【 ORIGINAL ARTICLE 】

The Prevalence of Japanese Outpatients with Hypertension Who Meet the Definition of Treatment Resistant Hypertension and Are Eligible for Enrolment in Clinical Trials of Endovascular Ultrasound Renal Denervation

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Abstract:

Objective A clinical trial (REQUIRE) was started to investigate the use of an ultrasound renal denervation system in the treatment of resistant hypertension (RHT). We analyzed the prevalence of patients who were eligible for inclusion in this cross-sectional study at the time of screening.

Methods Nine-hundred ninety-nine consecutive hypertension (HT) patients who were treated in our hospital as outpatients were classified into the following categories: patients treated with at least 3 types of antihypertensive drugs including diuretic agents who were eligible for enrolment in SYMPLICITY HTN-Japan (SH-J) with an office systolic blood pressure (SBP) of ≥160 mmHg, who were ≤80 years of age, and an estimated glomerular filtration rate (eGFR) of ≥45 mL/min/1.73 m^2 (RHT-S); and patients who were treated similar medications and who were eligible for enrolment in REQUIRE, with an SBP of ≥150 mmHg, ≤75 years of age, and an eGFR of ≥40 mL/min/1.73 m^2 (RHT-R). We investigated the proportion of patients in each category. We also investigated HT patients (1,423 cases) who were enrolled in the Chikushi Anti-Hypertension Trial (CHAT), a research network that includes general practitioners.

Results Eleven patients (1.1%) with RHT-S and 18 patients (1.8%) with RHT-R were identified. After the exclusion of patients with secondary HT and a diastolic blood pressure (DBP) of <90 mmHg (applied in REQUIRE), 5 patients (0.5%) with RHT-S and 4 patients (0.4%) with RHT-R remained. In the analysis of the CHAT study, only 2 (0.1%) patients with RHT-R remained.

Conclusion The number of eligible patients in the REQUIRE trial was decreased, largely due to the strict age restriction and the new DBP limitation. The prevalence of eligible patients in REQUIRE was estimated to be approximately 0.5 to 0.8 times that in SH-J. Since patient enrollment will be difficult, drastic measures may be required to recruit eligible patients.

Key words: resistant hypertension, catheter-based renal sympathetic denervation, humans, Asia, endovascular ultrasound renal denervation clinical trial, blood pressure

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Introduction

Hypertension (HT) accounts for a large percentage of lifestyle-related disease; it is estimated that there are approximately 43 million patients with HT in Japan (1). Some patients with resistant HT (RHT), in which neither the office blood pressure (BP) nor the home BP can be controlled despite treatment with 5 to 6 types of antihypertensive drugs. These patients have a poor prognosis and are extremely difficult to manage.

Catheter-based renal sympathetic denervation (RDN) has

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been reported to be effective for RHT in Australia and Europe (2-4). However, in the blinded SYMPLICITY HTN-3 (SH-3) trial, RDN did not achieve a significant decrease in BP in comparison to sham controls (5). There have been various discussions on the factors that influenced this result (6). The SYMPLICITY HTN-Japan (SH-J) trial was conducted in Japan (7). There was no sham catheter group in this study, the number of patients enrolled was small (n=41) and the analysis of the primary endpoint was underpowered. When the SH-3 and SH-J trials were analyzed in detail, the conclusion was that RDN had some efficacy and that a treatment effect could be expected. The following reasons for this efficacy were suggested (6, 7): 1) the operator's proficiency level was associated with the results because there was no method to objectively confirm that RDN had been sufficient; 2) in the sham group, adherence to oral antihypertensive treatment and diet therapy were improved after invasive inguinal artery puncture; 3) although adherence to medication is poor in most RHT patients (8), there is no method for confirming adherence; 4) the pre-control period in which the oral drug stabilized was short (2 weeks); 5) a large number of antihypertensive drugs were added; and 6) due to the nature of the device, cauterization may not have reached the nerve depth and circumference. As shown above, the results of the SH-3 trial were considered to be due to the catheter that was used in the study and the protocol failure and does not indicate the failure of RDN therapy. Future verification will become an important clinical issue.

The Paradise Ultrasound Renal Denervation System (PRDS)-001 uses ultrasound and improves on the faults of the previous-generation RDN system. The PRDS is expected to be highly effective because it can ablate deep renal nerves using ultrasound, and the ablation method uses a cooling balloon, which reduces the risk of overheating the arterial wall and prevents tissue damage (9). A study using a porcine model demonstrated that circumferential nerve cauterization was successful and that the technique was safe (10). The safety and efficacy use in the treatment of RHT in humans were confirmed in a prospective, single-group, open label study (11, 12).

A clinical trial (REQUIRE), in which this ultrasound renal denervation system was used to treat RHT, was started in Japan and Korea (ClinicalTrials.gov Identifier: NCT 02918305). The points in which REQUIRE shows improvement in comparison to SH-3 are as follows: 1) the control period in which drugs are not changed was extended to 1 month; 2) the study is mainly in Japan, where adherence to oral treatment is favorable (7); 3) the addition of oral drugs is strictly prohibited; 4) ablation will be conducted to a sufficient depth and circumference; and 5) methods that do not depend on the operator's skill and proficiency will be used. In addition, since it was reported that the sensitivity of Asians to β- blockers is superior in comparison to Caucasians (13), it is possible that REQUIRE will be more effective in Japanese patients. However, after the publication of the results of SH-3, the evaluation of RDN as an antihypertensive therapy generally became negative. It is not an exaggeration to say that the REQUIRE study provides the last chance for RDN to become established as an antihypertensive therapy. The transmission of new evidence from Japan with revised methods is important for determining the worldwide direction of RDN.

A new criterion for study patients was established in the REQUIRE study. The criterion requiring the use of at least 3 types of antihypertensive drugs (including diuretics) has not changed. The following criteria were added or changed: 1) an office systolic blood pressure (SBP) of ≥160 mmHg was changed to ≥150 mmHg; office diastolic blood pressure of ≥90 mmHg was added, the estimated glomerular filtration rate (eGFR) was changed from ≥45 mL/min/1.73 m^2 to ≥40 mL/min/1.73 m^2, and the age limit was changed from ≤80 years of age to ≤75 years of age. Furthermore, the SBP from 24-hour ambulatory blood pressure monitoring (ABPM) was increased from 135 mmHg to ≥140 mmHg. Only 41 patients were enrolled in the SH-J trial, which shows the difficulties associated with recruiting patients. We previously reported that there were very few patients with RHT whose SBP was ≥160 mmHg despite treatment with 3 or more oral antihypertensive drugs (including 1 diuretic) among consecutive outpatients with HT (14). Moreover, due to the inclusion of the sham catheter group and the fact that a number of treatment resistant patients have already been enrolled in SH-J, it is expected that patient enrollment will be difficult. Based on the situation regarding RDN so far, a sufficient number of patients must be analyzed in this clinical trial and new evidence must be established in order to avoid the disappearance of RDN from antihypertensive therapy. We therefore investigated the proportion of patients with RHT and the prevalence of patients who were eligible for the SH-J and REQUIRE clinical trials in a cross-sectional observational study based on the cohort of HT patients established in the base hospital and general medical institutions.

Materials and Methods

The definition of RHT was classified into 3 types, as follows.

The definition of RHT in the present study (Table 1)

1) RHT in the guidelines (RHT-G)

In the guidelines of the European Society of Cardiology and American Heart Association, RHT is defined as an SBP of ≥140/90 mmHg despite lifestyle improvement and oral treatment with at least 3 types of antihypertensive drugs at a usual dose or higher, including diuretics (15, 16). In the present study, patients with an office SBP of ≥140 mmHg, despite oral treatment with at least 3 types of antihypertensive drugs, including diuretics, was classified into the RHT-G group.

2) RHT in SYMPLICITY (RHT-S)

In the SH-3 and SH-J studies, RDN was indicated for

Table 1. Definitions of RHT.

	Unit	RHT of Guideline (RHT-G)	RHT for SYMPLICITY (RHT-S)	RHT for REQUIRE (RHT-R)
SBP Lower Limit	mmHg	≥140	≥160 (≥150 DM patient)	≥150
Renal Function Lower Limit (eGFR)	mL/min/1.73 m^2	No setting	≥45	≥40
Age Upper Limit	years	No setting	≤80	≤75

RHT: resistant HT, SBP: systolic blood pressure, eGFR: estimated glomerular filtration rate

RHT patients with an office SBP of ≥160 mmHg, despite oral treatment with at least 3 types of antihypertensive drugs, including diuretics (the indication for type 2 diabetes patients was an office SBP of ≥150 mmHg) (5). In the present study, patients who met these criteria, who were ≤80 years of age, and who had an eGFR of ≥45 mL/min/1.73 m^2 (in accordance with the SH-3 study protocol) were classified into the RHT-S group (17).

3) RHT in REQUIRE (RHT-R)

In the REQUIRE study, RDN was indicated for patients with RHT with wan office SBP of ≥150 mmHg and a diastolic BP (DBP) of ≥90 mmHg, despite oral treatment with at least 3 types of antihypertensive drugs, including diuretics. In the present study, patients with an SBP of ≥150 mmHg despite oral treatment with at least 3 types of antihypertensive drugs, including diuretics, who were ≤75 years of age, and who had an eGFR of ≥40 mL/min/1.73 m^2 were classified into the RHT-R group.

For antihypertensive drugs, it is recommended that diuretics are combined with calcium channel blockers (CCBs) or renin-angiotensin system inhibitors (RAS-Is), such as angiotensin II receptor blocker (ARB) and angiotensin converting enzyme inhibitor (ACE-I) (Guidelines for Management of Hypertension 2014). Furthermore, as seen from the results of the Anglo-Scandinavian cardiac outcomes trial (ASCOT) and LIFE studies (18, 19), RAS-Is (including ARB and ACE-I), CCBs, and thiazide diuretics are used as general antihypertensive therapy. We included RAS-Is, CCBs, and diuretics in the criteria for 3 or more antihypertensive drugs that were applied in the present study. In consideration of the fact that the combined use of ARB and ACE-I is not recommended based on the results of the ONTARGET study (20), the combination of ARB and ACE-I was counted as 1 antihypertensive drug.

Although a previous database was used, each study protocol was approved by the Institutional Review Board at Fukuoka University Chikushi Hospital. (R07-005, Chikushi Anti-Hypertension Trial (CHAT)-A:R09-001, CHAT-ANA:R 12-016, CHAT-AZIL:R12-027, CHAT-BP:R08-026, CHAT-C:R08-027, CHAT-E:R09-015, CHAT-J:09-021, CHAT-LIO: R13-006, CHAT-M:R10-028, CHAT-N:R11-013, CHAT-P:R 07-009, CHAT-Ras:R10-026, CHAT-REZh:R12-049, CHAT-T:R13-017). Written informed consent was obtained from all of the study participants in all of the studies.

Patients

Study population

1) Group-Hospital: Consecutive HT outpatients (April 2006 - March 2013, n=999) who were treated in Fukuoka University Chikushi Hospital were recruited. We consider that this reflects the outpatient population in acute care/base hospitals with a catheterization facility.

2) Group-CHAT: We investigated the HT patients (1,423 cases) enrolled in the research network, which included general practitioners, using this hospital as the base hospital (CHikushi Anti-Hypertension Trial; CHAT) (21, 22). The members of the CHAT network included 263 physicians who were based around the hospital. Outpatients with essential HT who were currently being treated at the hospitals/clinics that participated in the network, for whom the final report was submitted by April 1, 2016, were the subjects of this investigation. We consider that this reflects the outpatient population treated at general hospitals or by general practitioners.

In Group-Hospital, the BP was measured with a standard sphygmomanometer HEM-907 (OMRON Corporation, Tokyo, Japan) in a sitting position at the outpatient office. In Group-CHAT, BP was measured using the sphygmomanometer at each institution. A routine physical examination was performed.

Blood tests and urinalysis

General routine laboratory tests, including a blood cell count were performed. The eGFR value was calculated using a predictive equation (23). In Group-Hospital patients, the blood for the endocrine examination was sampled from the cubital vein after resting for 30 minutes in the prone position in order to exclude secondary HT. Endocrine examinations included measurements of the plasma renin activity (PRA), plasma aldosterone concentration (PAC), plasma adrenaline, plasma noradrenalin, plasma dopamine, serum cortisol, serum thyroid stimulating hormone (TSH), and serum free thyroxine 4 (FT4). In the urinalysis of Group-Hospital patients, spot urinary albumin (U-alb), spot urinary sodium (U-Na), spot urinary uric acid (U-UA), and spot urinary creatinine (U-cre) were assayed. In Group-CHAT, the routine blood sampling method that was used in each institution was applied.

Statistical analysis

The background information of the patient in Group-Hospital and Group-CHAT were classified and compared.

Then, the proportion of RHT in the two groups were investigated and analyzed in detail, to determine whether the patients were indicated for RDN. All of the statistical analyses were performed at Fukuoka University using the IBM SPSS Statistics 23 software program. Categorical and continuous variables were compared between Group-Hospital and Group-CHAT. In the case of normally distributed variables, Levene's test was conducted followed by a *t*-test (for equal variance) or Welch's test (for unequal variance). Wilcoxon's signed-rank test was used for items that were not normally distributed. The data are shown as the mean, standard deviation (SD) or the median, interquartile range (IQR). p values of <0.05 were considered to indicate statistical significance.

Results

The background information of the patients in Group-Hospital and Group-CHAT is shown in Table 2-1 and Table 2-2, respectively, and is compared in Table 3. In Group-Hospital, the number of patients with coronary heart disease (CHD) was larger and the frequency of oral ACE-I treatment was higher (Table 3), while the proportions of smokers, patients with diabetes, and patients receiving oral ARB treatment were higher in Group-CHAT (Table 3). Moreover, the SBP, DBP, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol values were higher in Group-Hospital (Table 3), while the body mass index, heart rate, albumin, uric acid, hemoglobin A1c, γ-glutamyl transpeptidase, and triglyceride values were higher in Group-CHAT (Table 3).

The prevalence of RHT in Group-Hospital is shown in Table 4-1 and Fig. 1. The screening results of 999 consecutive HT outpatients in Group-Hospital showed that among the patients who were orally treated with 3 types of antihypertensive drugs, 65 (6.5%) had an SBP of ≥140 mmHg (equivalent to RHT-G), 45 (4.5%) had an SBP of ≥150 mmHg, and 27 (2.7%) had an SBP of ≥160 mmHg (≥150 mmHg in patients with diabetes). Among these patients, 8 (31%) patients in the RHT-S group and 9 (20%) patients in the RHT-R were excluded based on the eGFR criteria, and 11 (41%) patients in the RHT-S group and 24 (53%) patients in the RHT-R group were excluded based on the age criteria. In the RHT-S group, there was only 1 patient with diabetes who had an SBP 150-160 mmHg who was excluded due to the age criteria. Eleven patients (1.1%) in the RHT-S group and 18 (1.8%) patients in the RHT-R group met both the eGFR and age criteria.

It is necessary to differentiate secondary HT, which includes renovascular HT, primary aldosteroinism (PA), Cushing's syndrome, pheochromocytoma, endocrine diseases such as hyperthyroidism, sleep apnea syndrome (SAS), and drug-induced HT (16). Generally, a PAC pg/mL to PRA ng/mL/h ratio (ARR) of >200 is used to screen for PA (24, 25). Patients with ARR >200 were excluded from the analysis because the further differentiation of PA was needed (RHT-S, n=2; RHT-R, n=2). Patients with suspected renovascular HT with extremely high renin values and in whom renal artery stenosis was confirmed (RHT-S, n=1; RHT-R, n=1) were also excluded. Since the blood pressure increases with a high salt intake, lifestyle improvements such as a low salt diet before RDN may reduce blood pressure. The salt intake was assessed based on the U-Na and U-cre values (26, 27), and patients with a salt intake of ≥12 g/day (RHT-S, n=3; RHT-R, n=6) were excluded. After applying these exclusion criteria, 5 (0.5%) patients remained in the RHT-S group. The REQUIRE trial also included a DBP criterion (DBP ≤ 90 mmHg); thus, after applying the exclusion criteria, 4 (0.4%) patients remained in the RHT-R group. There were no patients with suspected pheochromocytoma and no patients with drug-induced HT (such as pseudoaldosteronism). Similar to the SH-3 and SH-J study protocols, patients with SAS were not excluded.

The prevalence of RHT in Group-CHAT is shown in Table 4-2 and Fig. 2. Among the 1,423 patients in Group-CHAT, 80 (5.6%) patients were orally treated with 3 types of antihypertensive drug and had an SBP of ≥140 mmHg (equivalent to RHT-G), 38 (2.7%) had an SBP of ≥150 mmHg, and 13 (0.9%) had an SBP of ≥160 mmHg. Among the 13 RHT-S (SBP ≥160 mmHg) and 38 RHT-R (SBP ≥ 150 mmHg) 8 (62%) patients and 19 (50%) patients, respectively, were excluded based on the eGFR criteria, and 4 (31%) patients and 20 (53%) patients were excluded based on the age criteria. Thus, four (0.3%) patients in the RHT-S group and 10 (0.7%) patients in the RHT-R group met both criteria. Only 2 the 10 (0.1%) patients with RHT-R remained after the exclusion of 8 patients with a DBP of ≤90 mmHg. There were no reports of secondary HT in Group-CHAT.

Discussion

With regard to the patient background in Group-Hospital, the hospital is a cardiac catheter institution, and treats a larger number of patients with CHD and advanced arteriosclerosis; thus the patient population included a greater number of hypertensive patients and the frequency of ACE-I and β blocker use was higher. In Group-CHAT, the prevalence of patients with obesity, a smoking habit, hyperuricemia, and diabetes was higher, which indicates that the population included a larger number of patients with poor lifestyle control. The higher percentage of ARB use also corresponds to the widespread use of ARB in Japanese clinical practice.

The major findings of the present study were as follows:

1) In Group-Hospital, 1.1% of the RHT-S patients and 1.8% of the RHT-R met the age and eGFR criteria. After excluding patients with secondary HT and those with a high salt intake, 0.5% of RHT-S patients remained and 0.4% of the RHT-R remained after adding the limitation of DBP.

2) In Group-CHAT, 0.3% of the RHT-S patients and 0.7% of the RHT-R patients met the age and eGFR criteria. After adding the limitation of DBP, only 0.1% remained in the

Table 2. Patient Background in the 2 Groups.

Table 2-1. Patient Background: Group-Hospital.

	N	ratio (%)
Gender (Male)	525	53
Smoking	157	16
DM	119	12
DL	522	52
CHD (AP)	110	11
CHD (MI)	50	5
Aneurysm	6	0.6
ARB	555	56
ACE-I	86	8.6
CCB	492	49
Diuretic	203	20
Sympathetic	110	11
Vasodilator	130	13
Spironolactone	74	7.4
	Mean (SD), Median (IQR)	
Age, years	68 (59-76)	
BMI, kg/m^2	23.1 (21.3-25.5)	
SBP, mmHg	139.7 (23.6)	
DBP, mmHg	77.6 (14.3)	
HR, bpm	72.7 (13.5)	
WBC, 10^3/μL	5.5 (1.8)	
Hb, g/dL	13.3 (1.7)	
PLT, 10^4/μL	20.1 (5.5)	
Alb, g/dL	4.2 (0.5)	
γ-GTP, U/L	40.0 (71.0)	
HbA1c, %	5.6 (0.8)	
eGFR, mL/min/1.73m^2	65.9 (19.3)	
UA, mg/dL	5.4 (1.4)	
HDL-C, mg/dL	59.8 (14.6)	
LDL-C, mg/dL	112.4 (28.0)	
TG, mg/dL	100 (74-139)	
CRP, mg/dL	0.30 (1.21)	
BNP, pg/mL	19.0 (9.4-40.0)	
baPWV, cm/sec	1,694 (1,459-2,050)	
LVDd, mm	47.9 (4.8)	
IVST, mm	8.5 (3.4)	
EF, %	66.6 (8.4)	
SpotU-alb / U-cre ratio	86.3 (450.9)	
SpotU-UA / U-cre ratio	0.53 (0.20)	
SpotU-Na / U-cre ratio	1.63 (1.30)	
PRA, ng/mL/h	1.7 (5.1)	
PAC, pg/mL	68.9 (60.3)	
Adrenaline, pg/mL	37.3 (29.3)	
Noradrenaline, pg/mL	390.7 (207.4)	
Dopamine, pg/mL	15.8 (48.0)	
Cortisol, μg/dL	10.0 (4.9)	
TSH, μIU/mL	3.66 (25.50)	
FT4, ng/dL	1.43 (4.48)	

Table 2-2. Patient Background: Group-CHAT.

	N	ratio (%)
Gender (Male)	781	55
Smoking	295	21
Past Smoking	225	16
DM	501	35
DL	684	48
CHD	167	12
ARB	1,179	83
ACE-I	26	2
CCB	710	50
Diuretic	290	20
	Mean (SD), Median (IQR)	
Age, years	68 (66-76)	
BMI, kg/m^2	24.1 (22.1-26.7)	
SBP, mmHg	131.0 (14.7)	
DBP, mmHg	74.6 (11.2)	
HR, bpm	74.0 (11.0)	
WBC, 10^3/μL	6.1 (1.7)	
Hb, g/dL	13.5 (1.6)	
PLT, 10^4/μL	22.1 (5.8)	
Alb, g/dL	4.4 (2.1)	
γ-GTP, U/L	46.9 (59.3)	
HbA1c, %	6.2 (2.9)	
eGFR, mL/min/1.73m^2	66.5 (18.8)	
UA, mg/dL	5.7 (1.6)	
HDL-C, mg/dL	57.6 (15.6)	
LDL-C, mg/dL	108.5 (27.3)	
TG, mg/dL	120 (85-178)	
BUN, mg/dL	16.8 (6.2)	

CHAT: Chikushi Anti-Hypertension Trial, N: number, DM: diabetes mellitus, DL: dyslipidemia, CHD: coronary heart disease, AP: angina pectoris, MI: myocardial infarction, ARB: angiotensin II receptor blocker, ACE-I: angiotensin converting enzyme inhibitor, CCB: calcium channel blocker, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, bpm: beats per minute, WBC: white blood cells, Hb: hemoglobin, PLT: platelet count, Alb: albumin, γ-GTP: γ-glutamyl transpeptidase, HbA1c: hemoglobin A1c, eGFR: estimated glomerular filtration rate, UA: uric acid, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglycerides, CRP: C-reactive protein, BNP: brain natriuretic peptide, baPWV: brachial-ankle pulse wave velocity, LVDd: left ventricular end-diastolic diameter, IVST: interventricular septal thickness, EF: ejection fraction, U: urinary, cre: creatinine, Na: sodium, PRA: plasma renin activity, PAC: plasma aldosterone concentration, TSH: thyroid stimulating hormone, FT4: free thyroxine, SD: standard deviation, IQR: interquartile range

RHT-R group. In Group-Hospital and Group-Chat, the proportions of patients who remained in the RHT-S and RHT-R groups were extremely low (<1%).

In the REQUIRE trial, although it the prevalence of eligible patients might be expected to increase in comparison to the SH-J (based on the change of the SBP limit), it will actually decrease, largely due to the strict age restriction and the introduction of the DBP limit.

It was reported that 8.9% of adult HT patients have RHT, and that 12.8% of patients who are orally treated with anti-

Table 3. Comparison of Patient Background between Group-Hospital and Group-CHAT.

	Group-Hospital	Group-CHAT	
	ratio (%)	ratio (%)	p value
Gender (Male)	53	55	NS
Smoking	16	21	<0.001
DM	12	35	<0.001
DL	52	48	0.06
CHD	16	12	<0.05
ARB	56	83	<0.001
ACE-I	8.6	2	<0.001
CCB	49	50	NS
Diuretic	20	20	NS
	Mean (SD), Median (IQR)	Mean (SD), Median (IQR)	p value
Age, years	68 (59-76)	68 (66-76)	NS
BMI, kg/m^2	23.1 (21.3-25.5)	24.1 (22.1-26.7)	<0.001
SBP, mmHg	139.7 (23.6)	131.0 (14.7)	<0.001
DBP, mmHg	77.6 (14.3)	74.6 (11.2)	<0.001
HR, bpm	72.7 (13.5)	74.0 (11.0)	<0.05
Hb, g/dL	13.3 (1.7)	13.5 (1.6)	NS
Alb, g/dL	4.2 (0.5)	4.4 (2.1)	<0.05
UA, mg/dL	5.4 (1.4)	5.7 (1.6)	<0.005
HbA1c, %	5.6 (0.8)	6.2 (2.9)	<0.001
γ-GTP, U/L	40.0 (71.0)	46.9 (59.3)	<0.05
eGFR, mL/min/1.73m^2	65.9 (19.3)	66.5 (18.8)	NS
HDL-C, mg/dL	59.8 (14.6)	57.6 (15.6)	<0.005
LDL-C, mg/dL	112.4 (28.0)	108.5 (27.3)	<0.005
TG, mg/dL	100 (74-139)	120 (85-178)	<0.001

Parameters were analyzed using t-test between the 2 groups.

NS: not significant, CHAT: Chikushi Anti-Hypertension Trial, DM: diabetes mellitus, DL: dyslipidemia, CHD: coronary heart disease, ARB: angiotensin II receptor blocker, ACE-I: angiotensin converting enzyme inhibitor, CCB: calcium channel blocker, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, Hb: hemoglobin, Alb: albumin, UA: uric acid, HbA1c: hemoglobin A1c, γ-GTP: γ-glutamyl transpeptidase, eGFR: estimated glomerular filtration rate, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglycerides

Table 4. Prevalence of RHT in the 2 Groups.

Table 4-1. Group-Hospital.

Group-Hosptal (n=999)		RHT of Guideline (RHT-G)	RHT for SYMPLICITY (RHT-S)	RHT for REQUIRE (RHT-R)
With in SBP Limit		65 (6.5%)	27 (2.7%)	45 (4.5%)
	With in Renal Function Limit (eGFR)	No setting	18 (1.8%)	36 (3.6%)
	With in Age Upper Limit	No setting	16 (1.6%)	21 (2.1%)
	With in Renal Function and Age upper Limits	No setting	11 (1.1%)	18 (1.8%)

Table 4-2. Group-CHAT.

Group-CHAT (n=1,423)		RHT of Guideline (RHT-G)	RHT for SYMPLICITY (RHT-S)	RHT for REQUIRE (RHT-R)
With in SBP Limit		80 (5.6%)	13 (0.9%)	38 (2.7%)
	With in Renal Function Limit (eGFR)	No setting	5 (0.4%)	19 (1.3%)
	With in Age Upper Limit	No setting	9 (0.6%)	18 (1.3%)
	With in Renal Function and Age upper Limits	No setting	4 (0.3%)	10 (0.7%)

RHT: resistant HT, SBP: systolic blood pressure, eGFR: estimated glomerular filtration rate, CHAT: Chikushi Anti-Hypertension Trial

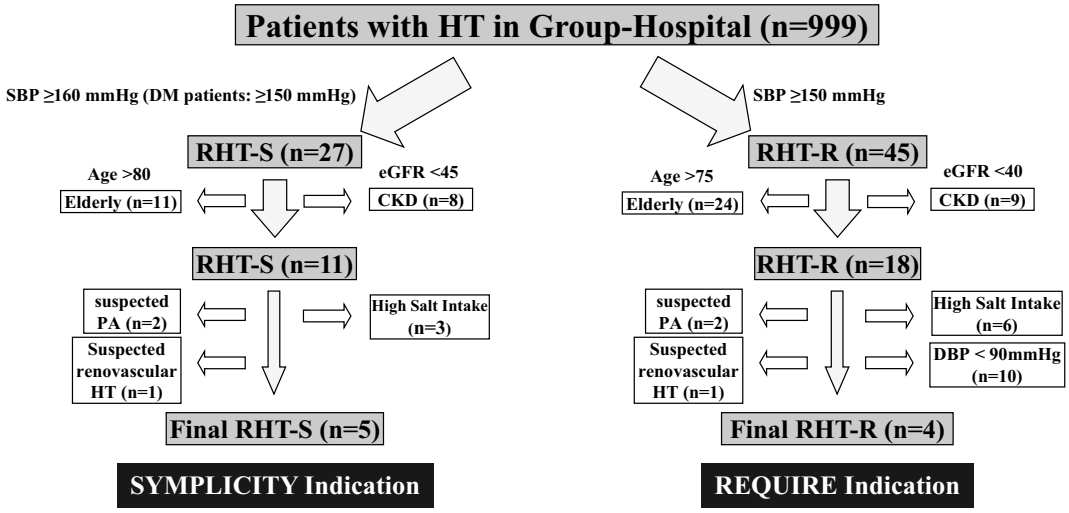

Figure 1. **The prevalence of RHT in Group-Hospital. The screening results of 999 consecutive HT outpatients in Group-Hospital showed that 27 (2.7%) with an SBP ≥160 mmHg (≥150 mmHg in diabetes patients) and 45 (4.5%) patients with an SBP of ≥150 mmHg were orally treated with 3 types of antihypertensive drugs. Eleven (1.1%) patients in the RHT-S group and 18 (1.8%) patients in the RHT-R group met both the eGFR and age criteria. After excluding the patients with secondary HT and a high salt intake, 5 (0.5%) patients remained in the RHT-S group. In REQUIRE, the criteria for DBP was set in addition to the above criteria. After excluding 10 patients with a DBP of <90 mmHg, 4 (0.4%) patients remained in the RHT-R group.**

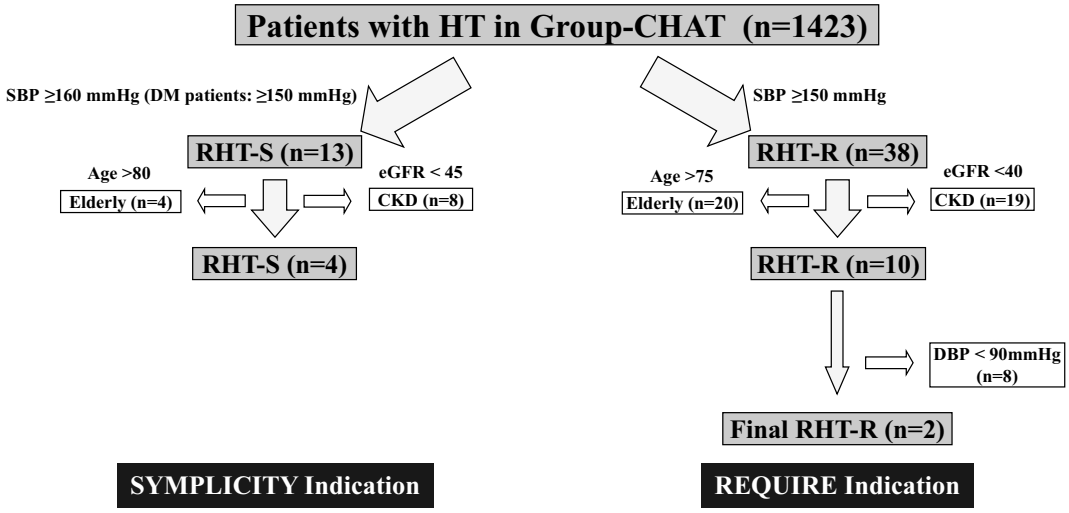

Figure 2. **The prevalence of RHT in Group-CHAT. Among the 1,423 patients in Group-CHAT, 13 (0.9%) patients with an SBP of ≥160 mmHg, and 38 (2.7%) patients with an SBP of ≥150 mmHg were orally treated with 3 types of antihypertensive drug. Four (0.3%) patients in the RHT-S group and 10 (0.7%) patients in the RHT-R group met both the eGFR and age criteria. Among the 10 patients in the RHT-R group, 8 patients had a DBP of <90 mmHg; thus, only 2 (0.1%) patients remained after the exclusion of these patients.**

hypertensive drugs have RHT (28). The prevalence of RHT-G in the present study (6.5%) was slightly lower than that reported in studies from the U.S. Since it the salt intake is reported to be higher in Japan (29), the effect of diuretics may be stronger in Japanese HT patients; this may be responsible for the lower prevalence of RHT (14).

Although the prevalence RHT, when evaluated by ABPM, is reported to be approximately 4.1% (30), the prevalence might differ slightly due to the different methods of investigation. In Group-Hospital, the final RHT-R /final RHT-S ratio was 4/5 (0.8). In Group-CHAT, the final RHT-R /final RHT-S ratio was 2/4 (0.5). Under similar conditions, it is estimated that the prevalence of patients eligible for enrolment in REQUIRE is 0.5 to 0.8 times that of SH-J. Thus, simple arithmetic suggests that only 21-33 patients will be enrolled if the patient enrollment status is similar to the SH-

J trial. Moreover, since the anatomical structure of the renal artery was not analyzed to confirm whether it met the RDN criteria, the structure of the bilateral renal artery must be carefully examined by renal artery angiography, computed tomography, or ultrasound. It was reported that unenhanced renal artery magnetic resonance angiography is effective in screening for renal artery stenosis (RAS) (31), and RAS was also found in a high percentage (23%) of RHT patients who were treated at our hospital (unpublished data). Since patients will be excluded from RDN clinical trials due to the structure of the renal blood vessels, the abovementioned number of enrolled patients will definitely decrease. In addition, it is unknown whether patients will provide their consent for the performance of RDN, and patients may be excluded as a result of ABPM.

Moreover, in REQUIRE, due to the inclusion of the group with a sham catheter from the femoral artery (which the SH-J trial did not include), and the fact that a number of treatment resistant patients had already been enrolled in the SH-J trial, patient enrollment is expected to be difficult; thus, the target population of 140 patients (study group, n=70; control group, n=70) may not be attained.

The highly limited indication for RDN treatment is one reason for the extremely small number of eligible patients (4, 32). We previously reported that the patients in whom RDN was indicated often had chronic kidney disease, cardiomegaly and arteriosclerosis (14). Generally, patients requiring 3 types of antihypertensive drugs have advanced nephrosclerosis and are frequently complicated with renal dysfunction. This group also includes a high percentage of elderly patients. Thus, elderly patients and renal dysfunction are large limiting factors for enrollment in studies on RDN.

After setting the criterion of a DBP of ≥90 mmHg in REQUIRE, approximately one half of the patients (n=10) were excluded from RHT-R. This additional criterion reduced the number of patients who were eligible for REQUIRE. The DBP limit was set because RDN is reported to be effective for patients with a higher DBP (33). When an *ad hoc* comparison was made of the backgrounds of patients with a DBP of <90 mmHg and those with a DBP of ≥90 mmHg, the patients in the latter group were found to be younger and to have a significantly higher pulse rate (Table 5), similarly to a previous report (33). It has been reported that RDN is more effective in younger patients (5), and there is a possibility that the effect of RDN in REQUIRE was greater in patients with a DBP value of ≥90 mmHg due to sympathetic nerve hyperactivity. This limit of DBP ≥90 mmHg may reduce the number of eligible patients, but is likely to identify patients in whom treatment will be effective.

With regard to the method of asking general practitioners to make patient referrals, in Group-CHAT, 0.3% of the patients were eligible for SH-J and 0.1% were eligible for REQUIRE; thus the prevalence of eligible patients who were treated by general practitioners was lower in comparison to those treated in the hospital outpatient clinic. In the CHAT study, although general practitioners and patients agreed to participate in the study and were considered to be cooperative, the prevalence of eligible patients was low. It is also considered that general practitioners were not enthusiastic about referring their chronic HT patients to base hospitals; thus, asking them to make patient referrals may not be particularly effective. Previously, when research volunteers were recruited through a newspaper, we were surprised that the number of general citizens who read the article was larger than expected. We consider that a direct enrollment approach in which HT patients who are orally treated with 3 types of drugs are recruited through newspapers, television, or a lecture that is open to the public, may be effective. Although the creation of a large-scale clinical HT cohort at an HT center, or similar facility-in which HT treatment could be managed collectively-might be effective in other countries, this is not realistic in Japan. Japan has few special institutions for HT, and patients are assigned to a medical department according to the treatment. For example, the Department of Hypertension conducts HT cohort studies, the Endocrinology Department diagnoses endocrine HT, the Radiology Department performs adrenal sampling, and the Department of Cardiovascular Medicine conducts percutaneous transluminal renal angioplasty. Since the specialization of HT treatment may be one of the reasons for the difficulty in enrolling RHT patients, cooperation between departments is an important issue.

Although enrollment in RDN studies is reported to face major obstacles, due to the highly invasive nature of RDN treatment, the major complications of RDN that have been reported are mostly due to the access site of the inguinal artery. It is expected that a radial artery approach will become an option for noninvasive PRDS in the future (12). Hemodialysis patients with uncontrolled HT (34), patients with PA who have poor BP control, and patients with indwelling renal artery stents with poor BP control (35) should be considered for RDN.

In the REDUCE HTN REINFORCE study using the Vessix system, an off-medication trial is being conducted in HT patients with an office SBP of 150-180 mmHg who have discontinued treatment with antihypertensive drugs (ClinicalTrials.gov Identifier: NCT02392351). SPYRAL HTN OFF-MED (36), a study using the Symplicity Spyral multielectrode renal denervation catheter in HT patients who are not treated with oral antihypertensive drugs, has also been started. There is a report that RDN is more effective in patients with higher blood pressure before its introduction (37), and we await the results with high expectations because the studies have enrolled large numbers of patients and it is clinically significant that RDN is indicated for patients who are unwilling to continue the use of antihypertensive drugs.

Even while off medication, PRDS will be less invasive if it can be performed from the radial artery, and it will be easier to conduct a clinical trial with a sham group. If RDN is effective for patients with milder HT, drug expenses will

Table 5. Patient Background of 18 Patients with RHT Indicated for REQUIRE, Analyzed Using t-test between 2 Groups with DBP 90mmHg or Higher and DBP Less than 90mmHg.

	DBP≥90mmHg (n=8)	DBP<90mmHg (n=10)	
	ratio (%)	ratio (%)	p
Gender (Male)	67 (52)	50 (53)	NS
Smoking	17 (41)	0	NS
DM	33 (52)	20 (42)	NS
DL	67 (52)	60 (52)	NS
CHD (AP)	0	10 (32)	NS
ARB	83 (41)	90 (32)	NS
ACE-I	50 (55)	30 (48)	NS
CCB	100	100	NS
Diuretic	100	100	NS
	Mean (SD), Median (IQR)	Mean (SD), Median (IQR)	
Age, years	64 (54-68)	74 (68-74)	<0.05
BMI, kg/m^2	24.6 (23.7-24.8)	24.0 (22.4-26.7)	NS
SBP, mmHg	160.7 (6.3)	166.7 (10.2)	NS
DBP, mmHg	99.8 (6.6)	77.2 (8.4)	<0.0001
HR, bpm	88.7 (11.5)	69.9 (10.2)	<0.01
WBC, 10^3/μL	6.0 (2.8)	5.7 (1.3)	NS
Hb, g/dL	14.5 (1.5)	13.4 (1.5)	NS
PLT, 10^4/μL	21.4 (5.3)	18.3 (4.9)	NS
Alb, g/dL	4.4 (0.4)	4.3 (0.4)	NS
γ-GTP, U/L	29.3 (15.2)	39.8 (26.0)	NS
HbA1c, %	5.5 (0.5)	5.7 (1.0)	NS
eGFR, mL/min/1.73m^2	66.9 (8.5)	69.3 (19.3)	NS
UA, mg/dL	5.5 (1.7)	5.7 (1.9)	NS
HDL-C, mg/dL	69.2 (19.4)	73.4 (24.0)	NS
LDL-C, mg/dL	115.7 (18.9)	108.5 (25.3)	NS
TG, mg/dL	74 (56-102)	86 (74-161)	NS
CRP, mg/dL	0.1 (0.1)	0.1 (0.0)	NS
BNP, pg/mL	12.2 (6.9-16.2)	24.7 (19.1-39.5)	<0.05
baPWV, cm/sec	1,622.5 (461.2)	2,122.3 (570.9)	NS
LVDd, mm	47.3 (3.1)	50.6 (6.9)	NS
IVST, mm	9.1 (0.8)	9.0 (1.4)	NS
EF, %	66.6 (6.0)	69.2 (2.4)	NS
SpotU-alb / U-cre ratio	41.4 (33.4)	30.3 (39.9)	NS
SpotU-UA / U-cre ratio	0.5 (0.1)	0.6 (0.3)	NS
SpotU-Na / U-cre ratio	1.4 (0.8-2.5)	2.0 (1.3-2.5)	NS

DM: diabetes mellitus, DL: dyslipidemia, CHD: coronary heart disease, AP: angina pectoris, ARB: angiotensin II receptor blocker, ACE-I: angiotensin converting enzyme inhibitor, CCB: calcium channel blocker, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, bpm: beats per minute, WBC: white blood cells, Hb: hemoglobin, Plt: platelet count, Alb: albumin, γ-GTP: γ-glutamyl transpeptidase, HbA1c: hemoglobin A1c, eGFR: estimated glomerular filtration rate, UA: uric acid, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglycerides, CRP: C-reactive protein, BNP: brain natriuretic peptide, baPWV: brachial-ankle pulse wave velocity, LVDd: left ventricular end-diastolic diameter, IVST: interventricular septal thickness, EF: ejection fraction, U: urinary, cre: creatinine, Na: sodium

be reduced and the development of cardiovascular diseases will be inhibited, which will reduce medical expenses. However, depending on the results of REQUIRE, it is possible that new off-medication clinical studies will not be conducted.

It is notable that secondary HT is frequently found during RDN screening. If effective HT treatment can be started from screening, and the impact of RDN on the prognosis of cardiovascular disease and the improvement of the life prognosis are demonstrated, it will be considered a cost-effective intervention for HT.

It is estimated that there are approximately 43 million HT patients in Japan (1). If the cohort in this study represents the nationwide HT patient population, simple arithmetic sug-

gests that approximately 2.8 million Japanese patients meet the definition of RHT-G. Since 0.5% of the patients remained in the final RHT-S group, it is anticipated that approximately 220,000 Japanese patients would be eligible for SH-J. In a similar study of 1,756 patients with HT, only 14 patients (0.8%) were eligible for SH-J (38), which was similar to this study. Since 0.4% of the patients remained in the final RHT-R group, it is estimated that approximately 170,000 Japanese patients would be eligible for enrolment in REQUIRE. If RDN had beneficial results in 170,000 RHT patients, medical expenses could be reduced as these patients would have been at high risk for cardiovascular disease in the near future. Since RDN is reported to have favorable effects on arrhythmia, including atrial fibrillation, urinary protein, diabetes, SAS, congestive heart failure, arteriosclerosis, left ventricular remodeling, depression, and quality of life (39-46), the introduction of RDN in HT treatment may change the present passive HT treatment to a more positive approach with the potential to improve the life prognosis associated with HT in patients throughout the country.

Conclusion

Although the number of eligible patients was increased in the REQUIRE trial was increased in comparison to the SH-J trial by the change systolic blood pressure limit, the proportion of eligible patients is not expected to increase due to the strict age restriction and introduction of the DBP limit. The prevalence of patients who are eligible for REQUIRE is estimated to be approximately 0.5 to 0.8 times that of SH-J. In addition, since fewer general practitioner-treated HT patients were indicated for RDN, we cannot expect general practitioners to introduce large numbers of eligible patients. Due to the inclusion of the sham catheter group in REQUIRE and the fact that a number of treatment resistant patients have already been enrolled in SH-J (which was conducted immediately before REQUIRE), it is expected that it will be difficult to enroll patients and obtain consent. However, since it is estimated that there are approximately 43 million HT patients in Japan, and a relatively high number of potentially eligible patients, drastic measures to promote patient enrollment are desirable, and the patient registration system should be further improved. The REQUIRE study is a very important clinical trial for the future of RDN therapy, and under the current circumstances, the failure of this clinical trial will mean the disappearance of RDN therapy. The success of this clinical trial is necessary for the progress of HT therapy, and we wish to draw the attention of the Japanese healthcare professionals who are involved in this clinical trial to the urgent crisis regarding the difficulties associated with patient enrollment.

Study limitations

Since the present study was observational and cross-sectional in nature, it is not conclusive. Although ABPM data is desirable, this requires wide screening including general practitioners; thus, the office BP was used instead. We did not analyze antihypertensive drug adherence or the doses of antihypertensive drugs; thus, a detailed evaluation of the patients' drug intake is needed. The prevalence of eligible patients may change according to the locality or the status of regional health care services that are provided by health insurance. Recently, the limitation of office BP in REQUIRE has been revised. We would like to report on changes in the frequency of cases in future.

Author's disclosure of potential Conflicts of Interest (COI).
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