Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension: data from SYMPLICITY HTN-3 and the Global SYMPLICITY Registry

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Aims	Catheter-based renal artery denervation (RDN) has been shown to lower blood pressure (BP) in certain patients with uncontrolled hypertension. Isolated systolic hypertension (ISH) (systolic BP [SBP] $\geq$140 mmHg and diastolic BP $<$90 mmHg), characterized by increased vascular stiffness, is the predominant hypertensive phenotype in elderly patients. This study compared baseline characteristics and SBP change at 6 months between patients with ISH and combined systolic−diastolic hypertension (CH).
Methods and results	This study pooled data from 1103 patients from SYMPLICITY HTN-3 and the Global SYMPLICITY Registry. A total of 429 patients had ISH, and 674 had CH. Patients with ISH were significantly older than those with CH (66 vs. 55 years), had more type 2 diabetes mellitus (52.9 vs. 34.6%), and a lower estimated glomerular filtration rate (71.8 vs. 78.6 mL/min/1.73 m^2); all $P < 0.001$. At 6 months, the SBP drop for CH patients was −18.7 ± 23.7 mmHg compared with a reduction of −10.9 ± 21.7 mmHg for ISH patients −7.8 mmHg, 95% confidence interval, CI, −10.5, −5.1, $P < 0.001$). The change in 24-h SBP at 6 months was −8.8 ± 16.2 mmHg in patients with CH vs. −5.8 ± 15.4 mmHg in ISH (−3.0 mmHg, 95% CI −5.4, −0.6, $P = 0.015$). Presence of ISH at baseline but not age was associated with less pronounced BP changes following the procedure. The strongest predictor of office SBP reduction at 6 months was CH, followed by aldosterone antagonist use and non-use of vasodilators.
Conclusion	The reduction in BP among patients with ISH following RDN was less pronounced than the reduction in patients with CH.
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Keywords	Renal denervation • Resistant hypertension • Sympathetic nervous system • Clinical trials

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Introduction

Despite the wide variety of pharmacologic treatment options, hypertension remains uncontrolled in a substantial number of patients.[1] The role of the sympathetic nervous system in the pathophysiology of hypertension is well established and has led to the development of alternate interventional approaches for the treatment of uncontrolled hypertension.[2−4] Catheter-based radiofrequency renal artery denervation (RDN) has been shown to significantly lower blood pressure (BP) in some patients with uncontrolled hypertension,[5−8] but with quite some variability in treatment effects.[9] Identification of specific subsets of patients who could potentially benefit from RDN or baseline characteristics that may help to predict outcomes following the procedure remain mostly unknown.[9,10] However, a difference in response based on patient age has been suggested by results from the SYMPLICITY HTN-3 trial, which found a numerically greater, although not significantly different, response to RDN in patients under age 65 years compared with older patients.[11,12] The main phenotype of hypertension in older patients is isolated systolic hypertension (ISH),[13,14] defined as office systolic BP (SBP) $\geq$140 mmHg and diastolic BP (DBP) <90 mmHg,[15] which is associated with increased vascular stiffness, increased pulse pressure (PP), and high risk for stroke and cardiovascular events.[16−18] These patients may benefit from pharmacologic therapy as outlined in the ESH/ESC Guidelines for the management of hypertension[15] but some will continue to have uncontrolled hypertension as evidenced by their enrolment in RDN trials. Preliminary data suggest significantly less pronounced reductions following RDN in patients with ISH when compared with those who have combined systolic−diastolic hypertension (CH).[19] However, these findings are limited by the lack of a control group or sham procedure and a relatively small sample size. The current analysis of patient-level pooled data from 2 large studies, the prospective, randomized, single-blind SYMPLICITY HTN-3 (ClinicalTrials.gov, NCT01418261) and the prospective, international Global SYMPLICITY Registry (GSR; ClinicalTrials.gov, NCT01534299), aims to assess the BP-lowering effect of RDN in patients with ISH compared with CH.

Methods

Patient-level data from SYMPLICITY HTN-3 and the GSR were pooled for this *post hoc* analysis of patients with ISH. Articles detailing the design and methodology of these studies have been published elsewhere.[20,21] Both studies were approved by the required national regulatory bodies and ethics committees, and all patients provided written informed consent for participation.

SYMPLICITY HTN-3

SYMPLICITY HTN-3 randomized patients in a 2:1 ratio to RDN or a sham procedure. Patients had a baseline SBP $\geq$160 mmHg and were prescribed three or more antihypertensive medications, including a diuretic, at maximally tolerated doses. The protocol provided escape criteria to allow changes in antihypertensive medication during the 2-week period between screening visits. Subjects were also required to have a 24-hour ambulatory SBP >135 mmHg before randomization. Additional clinical exclusion criteria included known secondary causes of hypertension or >1 hospitalization for hypertensive emergency in the previous year. Anatomic exclusion criteria included >50% renal artery stenosis, renal artery aneurysm, prior renal artery intervention, multiple renal arteries, renal artery diameter of <4 mm, or treatable segment of <20 mm in length. All office BP measurements were taken with an automatic BP monitor and printer (Omron Healthcare, Inc., Bannockburn, IL, USA). At the first screening visit, the appropriate arm for study measures was selected and then used for all subsequent follow-up visits. Patients were requested to take all antihypertensive medications at least 1 h prior to the BP measurements. At least three seated BP measurements taken at least 10 min apart were obtained. All 24-h ambulatory BP monitoring (ABPM) measurements were taken with a Spacelabs 24-h ABPM device (Spacelabs Medical, Issaquah, WA, USA), for consistency. The ABPM parameters were set for every 30 min throughout the day (7:00 am−9:59 pm) and for every 30 min at night (10:00 pm−6:59 am). Patients were asked to keep a diary of key activities (going to bed and getting up, taking medications, and other significant events). A 24-hour ABPM was considered adequate if the number of successful daytime readings captured was $\geq$21 and the number of successful nighttime readings captured was $\geq$12.

Global SYMPLICITY registry

The GSR is a prospective, single-arm, open-label, multicentre, observational study of RDN in patients with uncontrolled hypertension that aims to document current clinical practice with this new technology. The only inclusion criteria are age $\geq$18 years and eligibility for RDN as defined by local regulations with use of the Symplicity RDN system (Medtronic, Santa Rosa, CA, USA). The results of the first 998 patients were recently published.[22] The current analysis includes all patients from the GSR with an office SBP $\geq$140 mmHg while receiving at least three antihypertensive medications of different classes. Patients with a 24-h SBP <130 mmHg or daytime SBP <135 mmHg were excluded. Before treatment and at every follow-up visit, investigators confirmed hypertension medication intake by direct questioning and documented any medication changes. The GSR recommended that three BP measurements be taken according to standard practice at each office visit and 24-h ambulatory BP be measured in compliance with published guidelines. Before the RDN procedure, the most recently available office and ambulatory BP measurements were taken as baseline BP values and reported in the case report forms.

Isolated systolic hypertension

All patients with a baseline office SBP $\geq$140 mmHg and office DBP <90 mmHg were included in the ISH group, and patients with a baseline office SBP $\geq$140 mmHg and office DBP $\geq$90 mmHg were defined as the CH group. Office BP at baseline and 6-month follow-up after RDN were analysed, and the change in SBP and DBP at each time was compared between the ISH and CH groups. Ambulatory BP measurements at 6 months and BP changes between the groups were similarly compared. Changes in 6-month office and 24-h ambulatory BP were also compared for the ISH and CH patients in the RDN and sham control arms of the SYMPLICITY HTN-3 trial and in the GSR patients alone. To further explore the impact of age on the effect of RDN, the data were stratified according to baseline patient age ($\geq$65 vs. <65 years).

Renal denervation procedure

Catheter-based RDN was performed according to the Instructions for Use of the Symplicity™ RDN system following renal angiography to confirm suitable anatomy.

Statistical analyses

For between-group comparisons, the *t*-test was used for continuous variables, and the χ^2 or Fisher exact test was used for categorical

variables where appropriate. Changes between baseline and follow-up BP measurements were analysed using paired *t*-tests. All analyses were done using the SAS statistical package (version 9.3, Cary, NC, USA). Multivariable predictors of the office SBP change at 6 months were determined by multiple linear regression. The following covariates were considered for each model: ISH vs. CH, baseline office SBP, age, male sex, body mass index, number of medication classes at baseline, history of type 2 diabetes mellitus, history of coronary artery disease, obstructive sleep apnoea, history of stroke, estimated glomerular filtration rate (eGFR) at baseline, and heart rate at baseline. A stepwise selection algorithm was used to select significant covariates with entry/stay significance levels of 0.1/0.1, respectively. Data are shown as the mean with the standard deviation or 95% confidence interval (CI).

Results

SYMPLICITY HTN-3

Of the patients randomized to RDN, 225 patients had CH and 125 patients had ISH; 121 sham patients had CH and 48 had ISH. Baseline characteristics between the RDN and sham ISH patients were similar, and only obstructive sleep apnoea differed between RDN and sham CH patients (see Supplementary material online, *Table S1*). Patients with ISH were significantly older than patients with CH in both groups, and ISH patients also had a lower eGFR and heart rate ($P = 0.014$ for eGFR sham CH vs. sham ISH; $P < 0.001$ for all other comparisons). The 6-month office SBP change from baseline was significantly greater for the CH patients than the ISH patients in the RDN group (-7.2 mmHg, 95% CI -12.4, -2.0, $P = 0.007$), but there was no significant difference in SBP change between ISH and CH patients in the sham group (-2.9 mmHg, 95% CI -11.8, 6.0, $P = 0.519$) (*Figure 1*). The same pattern was observed for 24-h ambulatory SBP change at 6 months, which was significantly different for CH and ISH patients in the RDN group (-4.3 mmHg, 95% CI

-7.4, -1.1, $P = 0.008$) but not for patients in the sham group (-2.9 mmHg, 95% CI -8.0, 2.1, $P = 0.254$) (*Figure 2*). The change in office SBP in patients with CH was significantly greater in RDN group than the sham group (-17.9 ± 24.3 vs. -12.1 ± 27.2, $P = 0.043$). The *P*-value for interaction between treatment (RDN or sham) and CH/ISH was not significant at 0.393, indicating that the treatment effect is similar for the CH and ISH groups. The change in 24-h ambulatory SBP was -8.3 ± 16.3 in the RDN group and -5.7 ± 18.9 in the sham group ($P = 0.195$) for the patients with CH. The interaction *P*-value is 0.678.

Global SYMPLICITY registry

A total of 373 patients in the GSR population had CH and 288 had ISH. Similarly to the patients from SYMPLICITY HTN-3, the patients with ISH were significantly older (66 vs. 56 years) and had significantly lower eGFR (74.2 ± 25.5 vs. 81.5 ± 24.5 mL/min/1.73 m^2) and heart rate (66 vs. 73 bpm) ($P < 0.001$ for all). The ISH patients also had a greater prevalence of type 2 diabetes (47.9 vs. 31.7%, $P < 0.001$) (see Supplementary material online, *Table S2*). All patients had baseline and 6-month office BP data available. The patients from GSR showed a significantly greater 6-month office SBP drop in the CH vs. the ISH patients (-8.3 mmHg, 95% CI -11.8, -4.8; $P < 0.001$) (*Figure 1*). In the subgroup of patient with ABPM measurements ($n = 305$), the change in 24-h ambulatory SBP in ISH patients is numerically lower than that in CH patients, but the difference did not reach statistical significance (-1.9 mmHg, 95% CI -5.8, 2.0, $P = 0.337$) (*Figure 2*).

Pooled renal artery denervation population

A total of 1103 patients, 674 with CH and 429 with ISH, were included in this pooled analysis. The pooled population includes
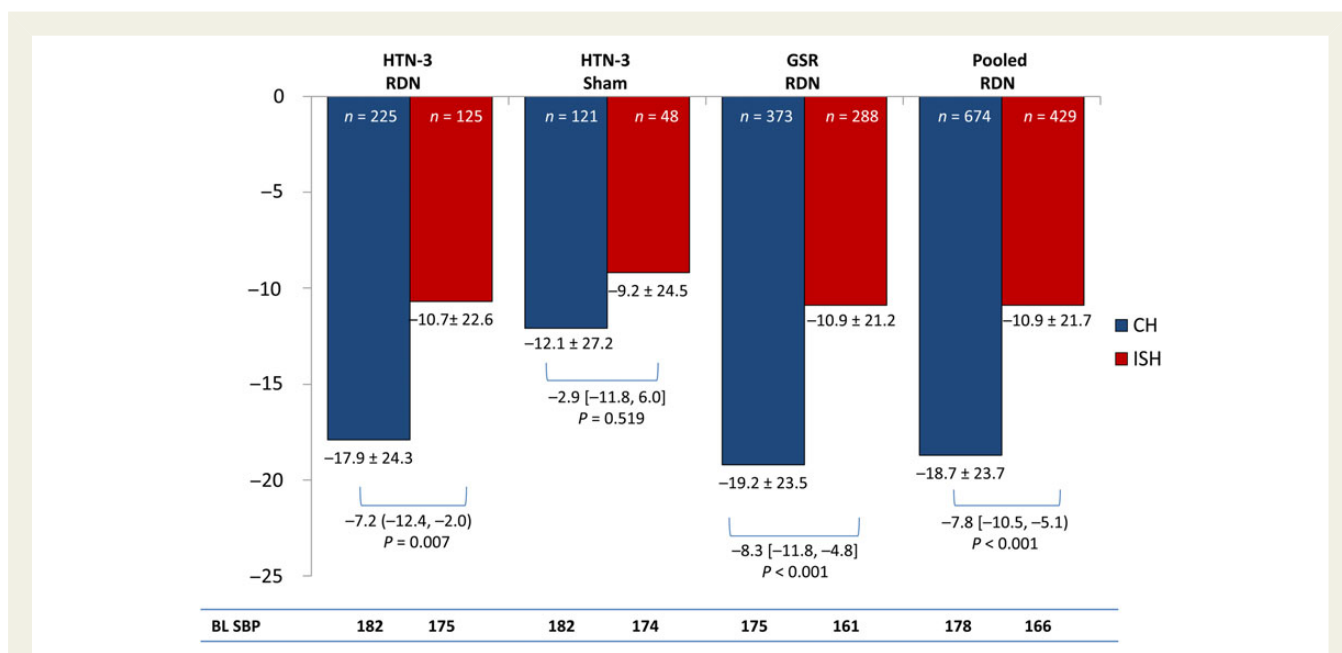

Figure 1 Office systolic blood pressure change at 6 months. BL, baseline; CH, combined (systolic–diastolic) hypertension; GSR, Global SYMPLICITY Registry; HTN-3, SYMPLICITY HTN-3 trial; ISH, isolated systolic hypertension; RDN, catheter-based renal denervation.
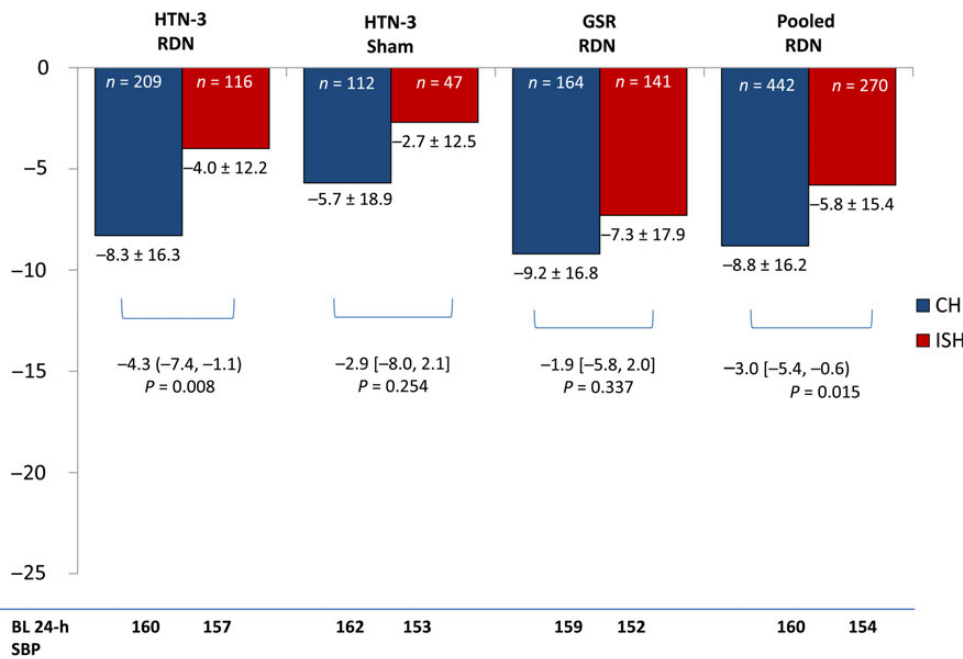
Figure 2 24-h ambulatory systolic blood pressure change at 6 months. BL, baseline; CH, combined (systolic−diastolic) hypertension; GSR, Global SYMPLICITY Registry; HTN-3, SYMPLICITY HTN-3 trial; ISH, isolated systolic hypertension; RDN, catheter-based renal denervation.

Table 1 Baseline characteristics of the pooled population

Characteristics	CH (N = 674)	ISH (N = 429)	P-value
Age (year)	55.1 ± 10.7	65.6 ± 9.4	<0.001
Male sex	63.9	59.7	0.161
BMI (kg/m^2)	31.9 ± 6.5	31.4 ± 6.3	0.222
Type 2 diabetes	34.6	52.9	<0.001
Hypercholesterolaemia	48.2	57.3	0.004
Peripheral artery disease	2.2	6.3	0.001
Coronary artery disease	12.5	14.7	0.318
Obstructive sleep apnoea	21.3	14.9	0.010
Stroke	10.7	9.8	0.685
eGFR (mL/min/1.73 m^2)	78.6 ± 21.3	71.8 ± 22.6	<0.001
Heart rate (bpm)	73.2 ± 14.4	64.7 ± 11.1	<0.001
Office SBP (mmHg)	178.4 ± 19.4	165.9 ± 15.4	<0.001
Office DBP (mmHg)	103.9 ± 11.3	78.1 ± 8.3	<0.001
Pulse pressure (mmHg)	74.5 ± 17.5	87.9 ± 16.4	<0.001
24-h SBP (mmHg)	160.5 ± 16.0	154.0 ± 13.9	<0.001
24-h DBP (mmHg)	94.9 ± 11.8	78.0 ± 9.8	<0.001

Values are mean ± SD or %.

patients who crossed over to receive RDN after unblinding of SYM-PLICITY HTN-3. Baseline characteristics are given in *Table 1*. Antihypertensive medication use was similar between the two groups except for direct renin inhibitors, which were significantly greater for patients with CH, and α-adrenergic blockers, which were more commonly prescribed in the patients with ISH (*Table 2*). Overall, patients with CH had significantly greater reductions in office and 24-h SBP than patients with ISH at 6 months after RDN (*Figures 1* and *2*). At 6 months, the SBP drop in the CH group was −18.7 ± 23.7 mmHg compared with a reduction of −10.9 ± 21.7 mmHg for ISH patients (−7.8 mmHg, 95% CI −10.5, −5.1, P < 0.001). The change in 24-h SBP at 6 months was −8.8 ± 16.2 mmHg in patients with CH vs. −5.8 ± 15.4 mmHg in ISH patients (−3.0 mmHg, 95% CI −5.4, −0.6, P = 0.015). Multivariate predictors of 6-month change in office SBP for the pooled population were baseline office SBP, baseline PP, total number of ablation attempts, baseline aldosterone antagonists use, lack of vasodilator use at baseline, and presence of CH (*Table 3*). There was no difference in 6-month change from baseline between patients with combined hypertension according to diabetes or no diabetes.

Isolated systolic hypertension vs. CH stratified by age

Office SBP change was significantly greater for CH patients compared with ISH patients regardless of age (−6.2 mmHg, 95% CI −10.2, −2.3, P = 0.002 for age <65 years and −12.7 mmHg, 95% CI −17.4, −7.9, P < 0.001 for age ≥65 years). There was no significant difference at 6 months in 24-h SBP change for ISH or CH patients <65 years old vs. patients ≥65 years old (P = 0.542 for ISH and P = 0.532 for CH; *Figure 3*). There was also no difference between younger and older patients with ISH based on office SBP (P = 0.672). Interestingly, older patients with CH had a significantly greater 6-month office SBP drop than younger CH

Table 2 Antihypertensive medication class prescription at baseline for the pooled population

Medication class	CH (N = 674)	ISH (N = 429)	P-value
Number of antihypertensive medication classes	4.6 ± 1.3	4.7 ± 1.2	0.316
ACE inhibitors	38.1	40.2	0.486
Angiotensin receptor blockers	60.6	64.0	0.278
Calcium channel blockers	75.0	76.2	0.667
Diuretics	87.3	88.8	0.507
Aldosterone antagonists	22.8	18.5	0.095
Alpha-2 agonists	39.3	40.9	0.613
Direct renin inhibitors	9.3	5.1	0.014
Beta blockers	80.7	81.1	0.875
Alpha-adrenergic blockers	20.8	29.7	0.001
Direct-acting vasodilators	24.9	2.7	0.244

Values are mean ± SD or %.
ACE, angiotensin-converting enzyme.

Table 3 Multivariate predictors of systolic blood pressure change at 6 months after renal denervation

Covariate	Estimate (95% CI)	P-value
Combined systolic−diastolic hypertension	−6.11 (−10.92, −1.30)	0.013
Baseline pulse pressure	−0.25 (−0.41, −0.10)	0.002
Baseline office SBP	−0.32 (−0.47, −0.17)	<0.001
Total number of ablation attempts	−0.53 (−0.93, −0.13)	0.010
Aldosterone antagonist use at baseline	−3.43 (−7.19, 0.33)	0.075
Vasodilator use at baseline	4.00 (0.60, 7.40)	0.021

patients (−23.2 ± 23.4 vs. −17.7 ± 23.6 mmHg, P = 0.018). However, the younger CH patients had a significantly greater 24-h SBP drop at 6 months compared with the younger ISH patients (−9.0 ± 16.8 vs. −5.1 ± 18.1 mmHg, P = 0.038).

Discussion

In this cohort of 1103 patients with uncontrolled hypertension, the documented BP-lowering effect of RDN was significantly less pronounced in patients with ISH than in patients with CH. Patients from SYMPLICITY HTN-3 treated with RDN and CH had a significantly greater office BP response to treatment than the ISH patients, but there was no significant difference between patients with CH and ISH in the sham group. A similar pattern was observed when the 24-h SBP change at 6 months was compared. Multivariable regression analysis of the SYMPLICTY HTN-3 and GSR pooled data set identified the presence of CH as a strong predictor of response

to RDN at 6 months. Interestingly, the presence of ISH, but not age above or below 65 years, was associated with less pronounced BP changes following the procedure.

Identification of specific subsets of patients who could potentially benefit from RDN or of baseline characteristics that may help to predict outcomes following the procedure remain mostly unknown.[10,22,23] In SYMPLICITY HTN-3 patients aged <65 years of age appeared to respond better to RDN than older patients (−5.73 mmHg, 95% CI −11.06, −0.40, P = 0.04).[11,12] The prevalence of ISH is greatest among the elderly, who typically have stiffer arteries with increasing age, which leads to a relatively lower DBP and a steeper increase in PP.[24] Available evidence suggests that patients with ISH are at higher risk for stroke or myocardial infarction and are more likely to develop cardiac complications such as heart failure, left ventricular hypertrophy, or atrial fibrillation when compared with patients with CH.[14,25,26] Pharmacologic treatment of older patients with ISH is challenged by the increased arterial stiffness characteristic of these patients and observations of a disproportionately lower reduction in DBP.[27] Long-term follow-up of older ISH patients randomized to treatment vs. placebo has confirmed the cardiovascular benefits associated with antihypertensive treatment in this population.[28,29] A recent comparison of pooled RDN data from 10 European centres (n = 109) with data from ISH patients receiving pharmacotherapy or placebo on the Systolic Hypertension in Europe (Syst-Eur) Trial[29] reported wide variability in responses across all groups. The decreases in the 24-h and nighttime SBP were larger in actively treated Syst-Eur patients than in RDN patients (P ≤ 0.013), whereas changes in daytime SBP and in the white-coat effect were similar (P ≥ 0.22). Both RDN and treated Syst-Eur patients had significantly greater office SBP reductions than the placebo group.[30]

Evidence indicates that the sympathetic nervous system is less active in older than in younger hypertensive patients.[31,32] In this pooled analysis, RDN reduced BP in both groups; however, the changes in office and ambulatory BPs were less pronounced in ISH patients than in CH patients across all groups. Herein patients in both CH age groups (<65 and ≥65 years) experienced a significantly larger reduction in office BP when compared with same aged ISH patients. However, among patients with ISH, the response to RDN of older patients was equal to the response of younger patients. Although patients with ISH consistently have a smaller reduction in office and 24-h SBPs compared with patients with CH, these data suggest that the mechanisms of BP lowering following RDN are not impaired by the physiological changes that occur with aging but rather by arterial stiffness, with ISH being a surrogate of the latter. Interestingly, only in the RDN group but not in the sham group of the SYMPLICITY HTN-3 trial significantly different changes in BP between ISH and CH patients have been observed. It is possible that inclusion of 33% ISH patients in the SYMPLICITY HTN-3 study is another factor that might have contributed to the neutral results of the trial; indeed, after exclusion of ISH patients, the changes in office SBP between the RDN and sham patients appear different (−17.9 ± 24.3 vs. −12.1 ± 27.2 mmHg, P = 0.043). These outcomes are supported by a recently published study that compared the effect of RDN in patients with CH vs. ISH. Office and ambulatory BPs were reduced after RDN in all patients, but the magnitude was significantly less pronounced in patients with ISH.[19] The findings
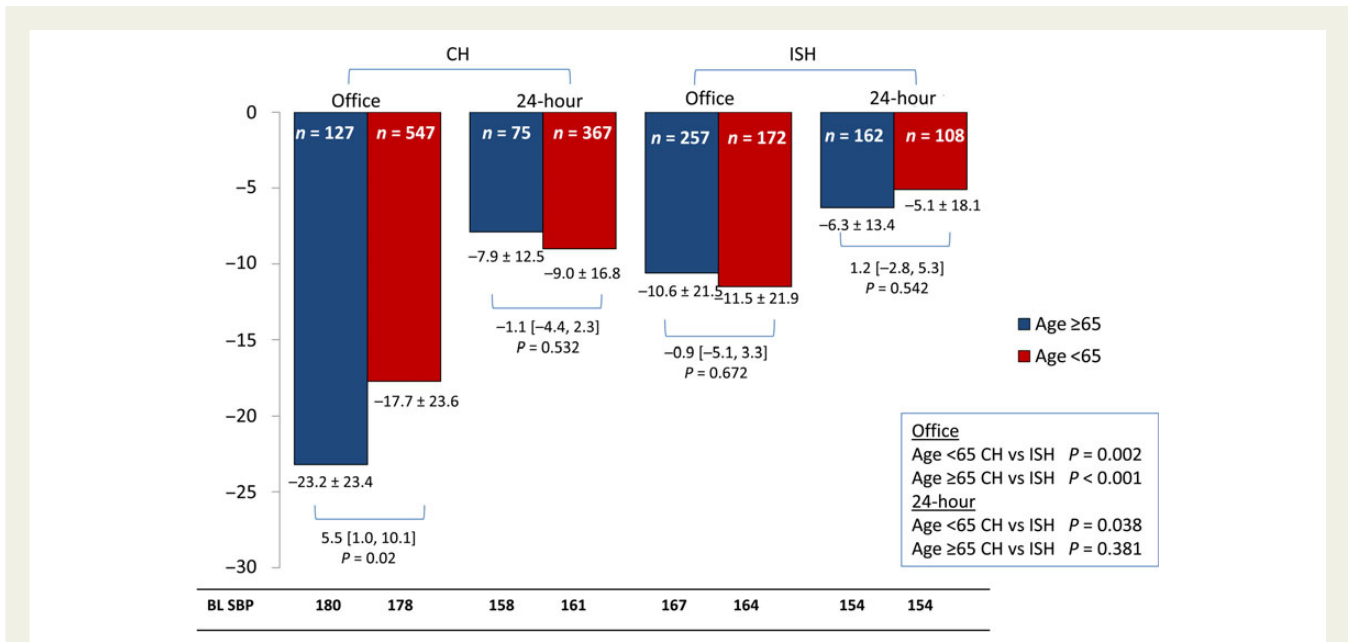
Figure 3 Pooled dataset: change in systolic blood pressure for age ≥65 vs. <65 years at 6 months for patients with combined systolic−diastolic hypertension or isolated systolic hypertension. BL, baseline.

were limited by the lack of a control group or sham procedure and the relatively small sample size. Experience in a relatively small number of patients from two centres in the United Kingdom is also consistent with our observation of a reduced response to RDN in patients with ISH.[33] Another study identified central PP, also a surrogate marker of vascular stiffness, to predict outcomes following RDN.[34] In patients with central PP below the median, the office and ambulatory BP changes after RDN were significantly higher. These data suggest that in cases where hypertension has established vascular damage to such an extent that ISH is present or central PP is increased, the vascular re-remodelling induced by RDN is precluded, and consequently less pronounced BP changes are observed following the procedure.

Identification of the appropriate patient population for RDN remains challenging. Attempts to use cardiac baroreflex sensitivity or norepinephrine renal or blood levels to identify RDN responders have not proved to be helpful.[35−37] Clinically easy achievable characteristics to identify patients with higher likelihood of response to RDN appear, indeed, more applicable than sophisticated measures of autonomic tone. In SYMPLICITY HTN-3, predictors of office SBP reduction at 6 months were baseline office SBP ≥ 180 mmHg, aldosterone antagonist use, and non-use of vasodilators. Herein the strongest predictor of office SBP reduction at 6 months was CH, followed by aldosterone antagonist use and non-use of vasodilators. Although a greater drop in BP is expected with increasing baseline SBP, multivariate analysis to adjust for this difference in baseline office SBP confirmed a significant difference in BP change between the CH and ISH patients.

Limitations

This study pooled RDN-treated patients from a randomized controlled trial with strict inclusion and exclusion criteria and a large all-comers registry, which allowed patient enrolment at the investigators' discretion. However, all patients included in this analysis met the definitions for office CH or ISH, and all were treated with the same RDN device. Although SYMPLICITY HTN-3 did not meet its primary endpoint, a number of confounding factors have been identified that may account for this result.[12] Differences in prescribed antihypertensive medications between CH and ISH patients at baseline as well as medication changes throughout the study could have affected the difference in BP change. Patients with CH had a substantially higher baseline SBP than those with ISH which may partially explain the greater reduction in SBP in these patients. The multivariable model may not completely compensate for this difference.

Conclusion

In the hitherto largest analysed population of patients with uncontrolled hypertension considered for RDN therapy, patients with ISH and CH appear to exhibit a reduction in SBP after RDN. However, patients with ISH who underwent RDN in SYMPLICITY HTN-3 and GSR had a significantly smaller reduction in office and ambulatory BPs after RDN than patients with CH. There was no difference in response to RDN between the patients with ISH who were younger than or older than 65 years of age. Patients with CH may represent good candidates for testing this procedure. This analysis should be considered hypothesis generating to inform the design of future trials in RDN.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

Funding

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