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

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation

Published Version
doi:10.1093/eurheartj/ehw325

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:32630575

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
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

Felix Mahfoud1*, George Bakris2, Deepak L. Bhatt3, Murray Esler4, Sebastian Ewen1, Martin Fahy5, David Kandzari6, Kazuomi Kario7, Giuseppe Mancia8, Michael Weber9, and Michael Böhm1

1Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Saarland University Hospital, Kirrberger Str., Geb. 40, Homburg/Saar 66421, Germany; 2University of Chicago Medicine, Chicago, IL, USA; 3Brigham and Women’s Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA, USA; 4Baker IDI Heart and Diabeties Institute, Melbourne, Australia; 5Medtronic, Santa Rosa, CA, USA; 6Piedmont Heart Institute, Atlanta, GA, USA; 7Jichi Medical University School of Medicine, Tochigi, Japan; 8University of Milano-Bicocca and Istituto Auxologico Italiano, Milan, Italy; and 9SUNY Downstate Medical Center, Brooklyn, NY, USA

Received 31 January 2016; revised 27 April 2016; accepted 29 June 2016; online publish-ahead-of-print 28 July 2016

See page 101 for the editorial comment on this article (doi:10.1093/eurheartj/ehw460)

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] ≥ 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 m2); all P < 0.001. At 6 months, the SBP drop for CH patients was −210.9 + 23.7 mmHg compared with a reduction of −210.9 + 23.7 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.

Clinical.Trials.gov identifiers
NCT01534299 and NCT01418261.

Keywords
Renal denervation • Resistant hypertension • Sympathetic nervous system • Clinical trials

* Corresponding author. Tel: +49 6841 16 15911, Fax: +49 6841 16 15910, Email: felix.mahfoud@uniklinikum-saarland.de
© The Author 2016. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Introduction

Despite the wide variety of pharmacologic treatment options, hypertension remains uncontrolled in a substantial number of patients. 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. Catheter-based radiofrequency renal artery denervation (RDN) has been shown to significantly lower blood pressure (BP) in some patients with uncontrolled hypertension, but with quite some variability in treatment effects. 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. However, a difference in response based on patient age has been suggested by results from the SYMPLECTIC 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. The main phenotype of hypertension in older patients is isolated systolic hypertension (ISH), defined as office systolic BP (SBP) ≥ 140 mmHg and diastolic BP (DBP) < 90 mmHg, which is associated with increased vascular stiffness, increased pulse pressure (PP), and high risk for stroke and cardiovascular events. These patients may benefit from pharmacologic therapy as outlined in the ESH/ESC Guidelines for the management of hypertension, 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). 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 SYMPLECTIC HTN-3 (ClinicalTrials.gov, NCT01418261) and the prospective, international Global SYMPLECTIC 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 SYMPLECTIC 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. Both studies were approved by the required national regulatory bodies and ethics committees, and all patients provided written informed consent for participation.

SYMPLECTIC HTN-3

SYMPLECTIC HTN-3 randomized patients in a 2:1 ratio to RDN or a sham procedure. Patients had a baseline SBP ≥ 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 ≥ 21 and the number of successful nighttime readings captured was ≥ 12.

Global SYMPLECTIC 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 ≥ 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. The current analysis includes all patients from the GSR with an office SBP ≥ 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 24-h 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 ≥ 140 mmHg and office DBP < 90 mmHg were included in the ISH group, and patients with a baseline office SBP ≥ 140 mmHg and office DBP ≥ 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 SYMPLECTIC 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 (≥ 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 χ² 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 ($-7.2 \text{mmHg}, 95\% \text{CI} -12.4, -2.0, P = 0.007$), but there was no significant difference in SBP change between ISH and CH patients in the sham group ($-2.9 \text{mmHg}, 95\% \text{CI} -11.8, 6.0, P = 0.519$) (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 ($-4.3 \text{mmHg}, 95\% \text{CI} -7.4, -1.1, P = 0.008$) but not for patients in the sham group ($-2.9 \text{mmHg}, 95\% \text{CI} -8.0, 2.1, P = 0.254$) (Figure 2). The change in office SBP in patients with CH was significantly greater in RDN group than the sham group ($-17.9 \pm 24.3 \text{mmHg}, 95\% \text{CI} -27.2, 1.1, P = 0.043$). 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 $-8.3 \pm 16.3$ in the RDN group and $-5.7 \pm 18.9$ 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$^3$) 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 ($-8.3 \text{mmHg}, 95\% \text{CI} -11.8, -4.8, P < 0.001$) (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 ($-1.9 \text{mmHg}, 95\% \text{CI} -5.8, 2.0, P = 0.337$) (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](image-url)
patients who crossed over to receive RDN after unblinding of SYMPLICITY 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 β-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 $-18.7 \pm 23.7$ mmHg compared with a reduction of $-10.9 \pm 21.7$ 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 $-8.8 \pm 16.2$ mmHg in patients with CH vs. $-5.8 \pm 15.4$ 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>
<thead>
<tr>
<th>Table 1 Baseline characteristics of the pooled population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Age (year)</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
</tr>
<tr>
<td>24-h SBP (mmHg)</td>
</tr>
<tr>
<td>24-h DBP (mmHg)</td>
</tr>
</tbody>
</table>

Values are mean ± SD or %.

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.
Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension

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

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

Values are mean ± SD or %.

ACE, angiotensin-converting enzyme.

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

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

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 SYMPHONY 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 SYMPHONY 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. In SYMPHONY 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). 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. 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. 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. 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. 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 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 < 0.01), whereas changes in daytime SBP and in the white-coat effect were similar (P ≥ 0.2). Both RDN and treated Syst-Eur patients had significantly greater office SBP reductions than the placebo group.

Evidence indicates that the sympathetic nervous system is less active in older than in younger hypertensive patients. 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 SYMPHONY 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 SYMPHONY 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. The findings
were limited by the lack of a control group or sham procedure and
the relatively small sample size. Experience in a relatively small num-
ber of patients from two centres in the United Kingdom is also con-
sistent with our observation of a reduced response to RDN in
patients with ISH. Another study identified central PP, also a sur-
rogate marker of vascular stiffness, to predict outcomes following
RDN. 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 pre-
cluded, and consequently less pronounced BP changes are observed
following the procedure.

Identification of the appropriate patient population for RDN re-
 mains challenging. Attempts to use cardiac baroreflex sensitivity or
norepinephrine renal or blood levels to identify RDN responders
have not proved to be helpful. Clinically easy achievable char-
acteristics 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, aldos-
terone antagonist use, and non-use of vasodilators. Herein the
strongest predictor of office SBP reduction at 6 months was CH, fol-
lowed 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 of-
lice SBP confirmed a significant difference in BP change between the
CH and ISH patients.

Limitations
This study pooled RDN-treated patients from a randomized con-
trolled trial with strict inclusion and exclusion criteria and a large all-
comers registry, which allowed patient enrolment at the investiga-
tors’ 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. Differences in pre-
scribed 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 uncon-
trolled hypertension considered for RDN therapy, patients with
ISH and CH appear to exhibit a reduction in SBP after RDN. How-
ever, 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 dif-
ference 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.
Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension

Authors’ contributions

Funding
The SYMPLICITY HTN-3 Trial and the Global Symplicity Registry are supported by Medtronic.

Conflict of interest: F.M. reports grants and personal fees from Medtronic during the conduct of the study; grants and personal fees from St. Jude Medical outside the submitted work; and support from Deutsche Hockdruckliga and Deutsche Gesellschaft für Kardiologie. G.B. reports personal fees from Medtronic during the conduct of the study; personal fees from Takeda, AbbVie, Janssen, Bayer, Relypsa, Merck, GSK outside the submitted work; and that he is the editor of the American Journal of Nephrology, Hypertension section editor of Up-to-Date, and an associate editor of Diabetes Care. D.L.B. reports grants from Medtronic during the conduct of the study; grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Pfizer, Roche, Sanofi-Aventis, and The Medicines Company outside the submitted work; and personal fees from Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences. D.L.B. reports that he serves on the Board of Directors of the Boston VA Research Institute and the Society of Cardiovascular Patient Care is chair of the American Heart Association Get with the Guidelines Steering Committee; and serves on the Data Monitoring Committees of Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and the Population Health Research Institute. His reports receiving honoraria from the American College of Cardiology (Senior Associate Editor, Clinical Trials and News, AC-C.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), WebMD (CMC steering committees), and Clinical Cardiology (Deputy Editor). D.L.B. is a site coinvestigator for Biotrinik and St. Jude Medical and a trustee of the American College of Cardiology. He conducts unfunded research with FlowCo, PLx Pharma, and Takeda. M.E. reports grants and personal fees from Medtronic during the conduct of the study. M.F. is a Medtronic employee. D.K. reports personal fees from Medtronic during the conduct of the study and personal fees from Bayer AG, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Ferrer, Merck, Menarini, Novartis, Recordati, Sanofi, Servier, and Takeda outside the submitted work. M.W. reports personal fees from Medtronic during the conduct of the study and personal fees from Boston Scientific, Novartis, Recor, and Arbor outside the submitted work. M.B. reports grants and personal fees from Medtronic during the conduct of the study; grants and personal fees from AstraZeneca, Bayer AG, Boehringer Ingelheim, Novartis, Pfizer, Sanofi-Aventis, and Servier outside the submitted work; and personal fees from Daiichi Sankyo, MSD, Berlin-Chemie, and St. Jude Medical outside the submitted work.

References


34. Ott C, Schmieder RE, Mahfoud F. Reduced effect of percutaneous renal denervation on blood pressure in patients who were not treated in trials of isolated systolic hypertension. J Hypertens 2015;33:193–199.

