Renal denervation: time to open Pandora’s box

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Summary

Depending on the populations studied and the definitions applied, the prevalence of treatment-resistant hypertension varies from 10% to 15%, but is higher in conditions associated with increased sympathetic drive, such as obesity, obstructive sleep apnoea, diabetes or renal dysfunction. The SYMPLICITY studies recently demonstrated that reducing sympathetic tone by intravascular renal denervation is feasible in treatment-resistant hypertension, but failed to provide conclusive evidence on the size and durability of the antihypertensive, renal and sympatholytic effects, long-term safety, quality of life, the possibility to relax antihypertensive drug treatment, cost-effectiveness, and long-term hard cardiovascular-renal outcomes. Renal denervation should therefore only be offered within a clinical research context at highly skilled tertiary referral centres that participate in international registries constructed independent of the manufacturers.

Key words: sympathetic nervous system; renal denervation; treatment-resistant hypertension

Introduction

Hypertension affects an estimated 20% to 30% of the world’s adult population [1]. Despite the availability of numerous safe and effective antihypertensive drugs, the percentage of patients achieving adequate blood pressure control meeting guideline targets remains low [1, 2]. Resistant hypertension is a blood pressure that stays above goal in spite of the concomitant use of antihypertensive medications from more than 3 drug classes [3]. Patients who require more than four drug classes to have their blood pressure controlled are also considered to have resistant hypertension. Preferably, the regimen should include a diuretic and all doses should be optimal [3]. Unfortunately, current guidelines for treatment resistant hypertension do not address non-adherence or the white-coat effect as possible underlying causes of so-called treatment resistance. Renal sympathetic nerves contribute to development and perpetuation of hypertension [4]. The efferent sympathetic nervous outflow to the kidney stimulates renin release, enhances tubular reabsorption of sodium and water, and reduces renal blood flow [4]. Afferent signals from the kidney modulate central sympathetic outflow and thereby contribute to the neurogenic elevation of blood pressure [4]. Excessive activation of the sympathetic nervous system probably contributes to the high blood pressure in treatment-resistant hypertension [5]. Currently, techniques that modulate sympathetic nervous activity via renal denervation [6, 7] possibly offer new avenues for the management of treatment-resistant hypertension. Moreover, other studies, most of them non-randomised [8, 9], suggested that renal denervation cannot only decrease blood pressure in resistant hypertension, but that this procedure might also have indications in the management of glucose intolerance [8], sleep apnoea [8], the polycystic ovary syndrome [10], left ventricular hypertrophy [10], or cardiac diastolic dysfunction [9]. These studies are opening a rapidly expanding area of exciting new research perspectives.

The SYMPLICITY studies

In 2009, Krum and colleagues reported a non-randomised proof-of-concept study (NCT 00483808 and NCT 00664638). The SYMPLICITY HTN-1 study showed that percutaneous radiofrequency catheter-based renal sympathetic denervation was feasible [11]. After the proof-of-concept study [11], the SYMPLICITY HTN-2 investigators published a small randomised clinical trial [12], in which 106 (55.8%) patients were randomly allocated to undergo renal denervation plus previous treatment (n = 52) or to maintain previous treatment alone (control group; n = 54) [12]. The primary endpoint was the office blood pressure at 6 months of follow-up. In the renal denervation group, office blood pressure decreased by 32/12 mm Hg (P <0.0001) from the baseline value of 178/96 mm Hg, whereas the corresponding 1/0-mm Hg change from 178/97 to 179/97 mm Hg in the control group was not significant (P ≥0.77) [12].

Subsequently, the SYMPLICITY HTN-1 investigators applied renal sympathetic denervation to 153 patients [13], including the 45 patients from SYMPLICITY HTN-1 study [11]. At 1, 3, 6, 12, 18, and 24 months, the percentage
of patients followed up for blood pressure amounted to 90.2, 88.2, 56.2, 41.8, 23.5 and 11.8, respectively [13]. At these time points, the blood pressure reductions averaged 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg [13]. During the first year of follow-up, eGFR remained stable, with a change at 1, 3, 6, and 12 months of +0.1, −1.6, −0.1, and −2.9 mL/min per 1.73 m², when the percentage of patients remaining in follow-up for renal function was 73.2, 66.7, 56.9, and 41.8 [13]. Only 10 patients (6.5%), had eGFR measured at 2 years. eGFR fell by 16.0 mL/min/1.73 m² in all patients (table 1) and by 7.8 and 24.2 mL/min/1.73 m² in patients who did not have (n = 5) or did have (n = 5) a diuretic added to their treatment [13].

**Clinical appraisal of the evidence**

**Duration and completeness of follow-up**
The SYMPLICITY HTN-1 [11] and SYMPLICITY HTN-2 [12] studies covered only 6 months. The proportion of patients in the SYMPLICITY HTN-1 registry [13] with a follow-up of 1 and 2 years was 41.8% and 11.7% for blood pressure and 41.8% and 6.5% for eGFR (table 1).

**Definition and management of resistant hypertension**
The definition of treatment-resistant hypertension in the SYMPLICITY reports, although in line with guidelines for the management of hypertension [3, 14, 15] was loose. In SYMPLICITY HTN-1 [11], treatment resistance included intolerance to blood pressure lowering drugs, which often occurs in non-adherent patients. At screening for SYMPLICITY HTN-2 [12], patients recorded the intake of medications for 2 weeks, but the number of patients excluded because of non-adherence was not reported. Moreover, the management of hypertension was suboptimal. The SYMPLICITY researchers did not report how lifestyle measures were reinforced and followed up, for instance by measurement of body mass index or the 24-h urinary sodium excretion [15]. At inclusion, 11% and 5% of the patients enrolled in SYMPLICITY HTN-2 [12] and the SYMPLICITY HTN-1 registry [13] were not taking diuretics, and only 17% and 22% were taking aldosterone antagonists, a drug class strongly recommend in treatment-resistant patients [16], particularly if plasma renin activity is low [17].

**Diagnosis of secondary hypertension**
In both SYMPLICITY HTN studies [11–12], screening for secondary hypertension was not mandatory and the procedures for a diagnostic workup were not standardised. In SYMPLICITY HTN-1 [11], known secondary hypertension was an exclusion criterion, while secondary hypertension was not even mentioned among the SYMPLICITY HTN-2 eligibility criteria [12].

**Assessment of adherence**
Poor medication-taking behaviour is a major problem among patients with hypertension, and is one of the main causes of failure to achieve blood pressure control [3]. SYMPLICITY HTN-1 did not address adherence at all [11]. In SYMPLICITY HTN-2 [12], eligible patients had to comply with at least three drugs, including a diuretic. However, this definition was lax, as neither at randomisation nor during follow-up was any attempt made to assess adherence in a systematic manner, for instance by measuring biomarkers of drug intake, drug metabolites or by means of electronic pill boxes [18, 19].

**Blood pressure measurement**
Notwithstanding the overwhelming evidence in favour of the superiority of out-of-office blood pressure measurement [20–23], in particular, in treatment-resistant patients [24], in both SYMPLICITY trials [11, 12] and even in the ongoing SYMPLICITY HTN-3 trial (http://clinicaltrials.gov/ct2/show/NCT01418261), the primary endpoint rested on office blood pressure. In SYMPLICITY HTN-1 [11], only 12 of 45 patients (27%) had adequate ambulatory blood-pressure monitoring at

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**Table 1: Effects of renal denervation on blood pressure and renal function in the Symplicity Registry.**

<table>
<thead>
<tr>
<th>Timeline in months</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with measurements</td>
<td>138 (90.2%)</td>
<td>135 (88.2%)</td>
<td>86 (56.2%)</td>
<td>64 (41.8%)</td>
<td>36 (23.5%)</td>
<td>18 (11.7%)</td>
</tr>
<tr>
<td>Mean systolic blood pressure changes (mm Hg)</td>
<td>−20</td>
<td>−24</td>
<td>−25</td>
<td>−23</td>
<td>−26</td>
<td>−32</td>
</tr>
<tr>
<td>Mean diastolic blood pressure changes (mm Hg)</td>
<td>−10</td>
<td>−11</td>
<td>−11</td>
<td>−11</td>
<td>−14</td>
<td>−14</td>
</tr>
<tr>
<td><strong>Renal function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with measurements</td>
<td>112 (73.2%)</td>
<td>102 (66.7%)</td>
<td>87 (56.9%)</td>
<td>64 (41.8%)</td>
<td>...</td>
<td>10 (6.5%)</td>
</tr>
<tr>
<td>Mean estimated glomerular filtration rate (eGFR) (mL/min/1.73m²)</td>
<td>+0.1</td>
<td>−1.6</td>
<td>−0.1</td>
<td>−2.9</td>
<td>...</td>
<td>−16.0</td>
</tr>
</tbody>
</table>

Data appear in reference 8. Numbers in parentheses (%) indicate the percentage of patients with follow-up measurements. An ellipsis indicates that the information is unavailable.
baseline and more than 30 days after denervation. The 24-h systolic blood pressure decreased by 11 mm Hg in 9 responders (according to office systolic blood pressure) and by 10 mm Hg in 3 non-responders. In SYMPLICITY HTN-2 [12], all eligible patients received an Omron HEM-705 monitor to record seated blood pressure daily for 2 weeks, 3 times in the morning and 3 times in the evening. The home blood pressure fell by 20/12 mm Hg in 32 patients in the renal denervation group, compared with a rise of 2.0 mm Hg in 40 controls, resulting in a between-group difference of 22/12 mm Hg (P <0.0001) [12]. At 6 months, the 24-h blood pressure decreased by 11/7 mm Hg in 20 patients randomised to renal denervation and did not change (−3/−1 mm Hg) in 25 control patients resulting in a between-group difference of 14/8 mm Hg (P ≤0.02) [12]. The SYMPLICITY HTN-2 investigators did not report the baseline values of the ambulatory or self-measured blood pressures, so that the prevalence of white-coat hypertension cannot be assessed. In summary, in the SYMPLICITY studies [11, 12], out-of-office blood pressure was not documented at recruitment, white-coat hypertension was not an exclusion criterion, and results based on the 24-h ambulatory blood pressure were available in less than half of the patients.

Safety
Animal studies on the safety of the SYMPLICITY™ Catheter System are scarce. Only in 2011, after publication of SYMPLICITY HTN-2 [12] and after the catheter had obtained a CE label in Europe, Rippy and coworkers [25] published results obtained 4 years earlier in 7 swine. In animals sacrificed 6 months after the procedure, the renal arteries showed fibrosis of 10–25% of the total media and underlying adventitia, with mild disruption of the external elastic lamina. In the SYMPLICITY studies [11, 12], imaging of the renal arteries was neither standardised in terms of the technique used at baseline and follow-up nor in terms of the operators, an issue that might be most relevant for duplex imaging.

Questions to be addressed
Future trials of renal denervation in the management of treatment-resistant hypertension should address the following issues:
1. Studies should be randomised with blinded assessment of the primary and secondary endpoints.
2. Renal denervation should be only offered to carefully selected patients. Secondary hypertension and non-adherence should be ruled out. Hypertension should be confirmed by out-of-office measurement.
3. Treatment should not only include diuretics, but also aldosterone antagonists.
4. As highlighted by the SYMPLICITY HTN-1 investigators [13], an outstanding question with regard to renal denervation in general and the radio-frequency approach taken in particular is the durability of the blood pressure lowering effect. Efferent nerves can regrow over a period of months to years [6, 26].
5. In view of decline of renal function at 2 years, as reported by the SYMPLICITY HTN-1 investigators [13], long term follow-up of renal function and the integrity of the renal arteries is of major importance.
6. The evidence available from the SYMPLICITY studies [11–13] was obtained with the first-generation 8 French compatible Ardian® catheter, which had a design different from the currently marketed 6 French devices. Newer ablation systems are being tested and will soon be released to the market. Trials comparing different denervation systems should focus on safety and the measurement of the activity of the sympathetic nervous system.

Conclusions
Renal denervation seems to be a procedure promoted by marketers without conclusive supporting evidence from long-term randomised clinical trials. A similar situation occurred with devices used for closure of a patent foramen ovale. Several devices not approved by the Food and Drug Administration were available for the prevention of recurrent stroke [27]. Evidence in support of the use for stroke prevention had only been provided by small and poorly controlled observational studies [28]. The CLOSURE I trial [29] was a large-scale, randomised study comparing device closure with the best medical therapy in patients with a patent foramen ovale, who have sustained a previous stroke or a transient ischaemic attack (TIA). The investigators reported that the 2 treatment groups did not differ in terms of the reduction in the risk of stroke, TIA or death [29]. Moreover, closure of the patent foramen ovale increased the risks of major vascular events and of atrial fibrillation [29]. For now, renal denervation should remain the last resort therapy in adherent and truly resistant patients with severe hypertension, in whom all other efforts to reduce blood pressure have failed. The intervention should only be offered to patients within a context of clinical research in highly skilled tertiary referral centres that participate in international registries constructed independent of the manufacturers. Consensus along these lines is rapidly growing in several European countries [30] as well as elsewhere [23, 31].

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References


Figure 1
Effect of sympathetic afferent and efferent nerves. Solid and dashed lines represent afferent and efferent nerve traffic, respectively.
Abbreviations: LV, left ventricular; GFR, glomerular filtration rate.