Renal denervation in treatment-resistant hypertension: a reappraisal
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The Symplicity HTN-1 and 2 studies proposed renal denervation (RDN) as an effective and safe approach to treat patients with resistant hypertension, and were followed by an unprecedented wave of enthusiasm. The announcement that Symplicity HTN-3 failed to meet its primary efficacy endpoint put an abrupt stop to these overoptimistic expectations. The use of a sound methodology was enough to see the typical 25–30 mmHg systolic blood pressure decrease observed after RDN melt down to <3 mmHg. RDN certainly deserves further investigation but is not ready for wide clinical application. For the time being, physicians should focus on improvement of drug adherence and skilful drug treatment adjustment, which allow reaching blood pressure target in the large majority of hypertensive patients.

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Renal denervation before Symplicity HTN-3
In 2009, Krum and colleagues [1] published a nonrandomised proof-of-concept study, testing percutaneous radiofrequency catheter-based renal sympathetic denervation (RDN) as a novel treatment of resistant hypertension in a cohort of 45 patients. RDN proved feasible, effective (blood pressure decrease: −27/17 mmHg at 12 months) and safe. One year later, the Symplicity HTN-2 investigators confirmed these impressive results in an open-label randomized trial including 106 patients with resistant hypertension. One hundred patients were assessed for the primary endpoint at 6 months: in the RDN group (n = 49), office blood pressure decreased by 32/12 mmHg (P < 0.0001), whereas blood pressure (BP) remained unchanged in the control group (n = 51) (+1/0 mmHg, P ≥ 0.77). Accordingly, at 6 months the between-group difference in office blood pressure averaged 33/11 mmHg (P < 0.0001) [2]. There were no serious procedure-related or device-related complications and occurrence of adverse events did not differ between groups [2]. Similar blood pressure decreases were documented in the Symplicity HTN-1 registry [3] (−25/11 mmHg).

Publication of the Symplicity studies [1–3] was followed by an unprecedented wave of enthusiasm. Medtronic Inc\textsuperscript{8} (Minneapolis, Minnesota, USA) paid $800 million up front to purchase Aridian\textsuperscript{8} (Mountain View, California, USA), the company that had developed the technology [4]. More than ten companies developed their own RDN system, five of which obtained the CE mark. While RDN remained an investigational procedure in the US, 8000, possibly 15 000–20 000 procedures were performed in Europe in less than 4 years [5], most of them using the mono-electrode Aridian-Medtronic\textsuperscript{8} catheter. Campaigns (www.poweroverpressure.com) and editorials [6] emphasising the high prevalence and major cardiovascular burden associated with resistant hypertension, and the urgent need for alternative, non-drug approaches flourished. New papers devoted to RDN were published every week, and all top-ranking journals were keen to publish studies and reviews addressing this novel approach [4]. In the meantime, dissenting and cautionary advice [7,8] and predictions [9\textsuperscript{**}] remained almost unheard.

Symplicity HTN-3
Symplicity HTN-3 [10\textsuperscript{**}] — a US randomized controlled trial including 535 patients assigned in a 2:1 ratio to RDN or a sham procedure put a stop to overoptimistic expectations. In contrast with Symplicity HTN-2 [2], in Symplicity HTN-3 [10\textsuperscript{**}], the mean decrease in office systolic blood pressure at 6 months was only 14.1 mm Hg in the
RDN group, as compared with 11.7 mmHg decrease in the sham group. In terms of baseline-adjusted between group difference, these numbers translate into a modest 2.4 mmHg advantage in favour of the technique, lower than the preset superiority margin of 5 mmHg [10**]. Similarly, while in Symplicity HTN-2, the systolic 24-h ambulatory blood pressure decrease was 11 mmHg in 20 patients treated with RDN (P = 0.006) compared to a non-significant (P = 0.51) decrease of 3 mmHg in 25 patients from the control group [2], in Symplicity HTN-3, the 24-h ambulatory blood pressure decrease was modest and of the same order of magnitude in both groups (−6.8 and −4.8 mmHg, respectively; P < 0.001 for both) [10**] (Table 1).

Proponents of RDN attributed the disappointing results of Symplicity HTN-3 to the lack of experience of most US operators with the procedure, insufficient proctoring and low average number of procedures per centre (~3) [11–13]. Retrospective analyses of stored angiographic and procedural records support these claims. They showed that in 74% of patients not even one fully circumferential renal artery application was achieved and that energy delivery was preferentially applied to the proximal artery, while renal nerves are closer to the distal artery [13]. Notably also, the number of ablations delivered was significantly correlated with office blood pressure decrease after RDN [14]. Still, this correlation did not reach statistical significance for ambulatory blood pressure [14]. Furthermore, it should be reminded that these analyses are all post hoc and thus are no more than hypothesis-generating [14]. Finally, technical reasons alone cannot account for the most striking difference between Symplicity HTN-2 [2] and Symplicity HTN-3 [10**]: while in Symplicity HTN-2, blood pressure remained unchanged in the placebo arm, in Symplicity HTN-3 it decreased to almost the same extent as in the RDN arm.

The most credible explanation is that Symplicity HTN-3 [10**] was blinded, while other studies were randomized but un-blinded (Symplicity HTN-2) [2] or purely observational. By contrast with Symplicity HTN-3, open-label studies such as Symplicity HTN-2 are subject to expectation, performance and evaluation biases [8]. In other words, knowing to which treatment group participants are allocated may have affected both physicians’ and patients’ behaviour, particularly if they felt that RDN was the last option available — as implied by the concept of resistant hypertension — or strongly believed in the efficacy of the technique. Symplicity HTN-2 investigators may have been inclined to measure blood pressure differently in the two groups: for example, the resting period before office BP measurements and the number of BP measurements taken may not have been the same in the RDN and control arms [8]. On the other side, being in the RDN group, and as such benefitting from increased attention from the caring physician may have improved adherence to drug treatment [7,8,9**]. Conversely, patients from the control arm may have been tempted not to take properly their medications in order to benefit

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td>Characteristics and results of 3 prospective and randomized studies of blood pressure lowering effects of RDN with Symplicity catheters</td>
</tr>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>No. of patients RDN Control</td>
</tr>
<tr>
<td>No. of drugs Intervention</td>
</tr>
<tr>
<td>No. of drugs Intervention RDN No active</td>
</tr>
<tr>
<td>Office SBP Baseline, mmHg</td>
</tr>
<tr>
<td>ΔFU – 6 month, mmHg</td>
</tr>
<tr>
<td>ΔRDN – control, mmHg</td>
</tr>
<tr>
<td>Ambulatory SBP Baseline, mmHg</td>
</tr>
<tr>
<td>ΔFU – 6 month, mmHg</td>
</tr>
<tr>
<td>ΔRDN – control, mmHg</td>
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</tbody>
</table>

Adapted from Ref. [27]

SBP, systolic blood pressure; RDN, renal denervation; 6 month, 6-month follow-up; ΔRDN-control in favour of renal denervation group; ΔFU in favour of control group. ?*, baseline ambulatory BPs values were not given in this study. −8** results is given just for the difference between 20 patients in renal denervation group and 25 patients in control group.
from RDN after assessment of the primary endpoint at six months [7,8]. In contrast, in a blinded study as Symplicity HTN-3 [10**], such biases are minimized. In particular, improved adherence to drug treatment due to inclusion of patients in a trial and massive attention devoted to them (Hawthorne effect) is likely to have occurred irrespective of the treatment arm, accounting for part of the substantial blood pressure decrease in the control group [15]. This phenomenon may have been particularly important, albeit not limited to the subgroup of 25% African-American patients [13,14].

The key message of Symplicity HTN-3 [10**] is simple: in patients meeting the entry criteria of the study (and probably those of Symplicity HTN-1 and 2 as well), the true overall benefit of RDN on systolic blood pressure is modest, <3 mmHg, without evidence of a favourable impact on morbidity-mortality so far. The results of three other recent rigorously executed randomized controlled trials using the same catheter, Oslo RDN [5] (Table 1), PRAGUE-15 [16] (Table 1) and DENER-HTN [17] including a lower number of well-trained operators are in line with those of Symplicity HTN-3 [10**], and confirm that the failure of RDN to achieve superiority over medical treatment cannot be entirely explained by inclusion of a high proportion of African Americans or insufficient degree of renal nerve ablation. Notably, in these studies [5,16,17], the absence of sham control group is compensated by the use of ambulatory blood pressure measurement both for patients’ selection and evaluation of efficacy, associated with evaluation of adherence using witnessed drug intake (OSLO-RDN) [5], or measurement of drugs in the urine (DENER-HTN and PRAGUE-15) [16,17]. This nice design allows controlling largely for both white coat and Hawthorne effects, while avoiding exposure of patients to unnecessary procedures. In the same line, a fourth randomized sham-controlled study performed in mild resistant hypertension (daytime systolic blood pressure between 135 and 149 mmHg and/ or daytime diastolic blood pressure between 90 and 94 mmHg on ≥3 drugs classes including a diuretic), Symplicity Flex [18], failed to show any advantage of RDN compared to drug treatment alone.

**Symplicity HTN-3 aftermath**
Most expert centres have witnessed a substantial blood pressure decrease after RDN in a minority of patients [5,19]. However, the current inability to identify those few responders, the modest overall benefits, and the high cost of the intervention should be balanced with its potential risks. In particular, more than 20 cases of de novo renal artery stenosis have been reported after RDN; most of them after the announcement that Symplicity HTN-3 failed to meet its primary endpoint [20–22] (Table 2). In view of these results, previous pharmacoeconomic [23–25] analyses became irrelevant, because they were based on weak assumptions. RDN deserves further investigation but is not ready for clinical use and should be restricted to research protocols [26]. According to [26], in Germany, the insurance companies which were the first in Europe to reimburse the procedure have terminated their coverage [27] and even well-known proponents of the technique acknowledge that RDN ‘should be returned back to the academic arena’ [28] before further clinical deployment. Lessons learnt from RDN should also be applied for other new treatment approaches of resistant hypertension such as electrical stimulation of baroreceptors [29] or creation of arteriovenous anastomosis [30]. Rather than wasting energy and money in numerous observational studies, such therapies should be evaluated in properly designed randomized controlled trials using a rigorous methodology. Furthermore, especially in the initial phase, these techniques should be reserved to truly resistant hypertensive patients, after careful exclusion of patients with secondary or white-coat resistant hypertension, and poorly adherent patients.

Are this news really bad news? Not really. After publication of Symplicity HTN-2, physicians and the lay public were too often swamped by an aggressive marketing emphasising not only the safety and efficacy of RDN, but also the alleged huge unmet need in the management of resistant hypertension and urgency of novel, non-drug treatment approaches. Critical analyses of the literature and recent studies show that these claims were largely exaggerated. The estimated 20–30% prevalence

<table>
<thead>
<tr>
<th>RDN system</th>
<th>No. of cases</th>
<th>Pre-existing stenosis (No.)</th>
<th>Time after RDN (months)</th>
<th>Bilateral/multiple stenosis (No.)</th>
<th>PTA/stenting (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symplicity (Ardian-Medtronic)</td>
<td>19</td>
<td>5</td>
<td>6 (median)</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Vessx-Boston</td>
<td>5</td>
<td>3</td>
<td>3–12</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>EnligHTN (Saint-Jude)</td>
<td>4</td>
<td>2</td>
<td>3–9</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Paradise (Recor, 1st generation)</td>
<td>2</td>
<td>No</td>
<td>6</td>
<td>NR</td>
<td>1</td>
</tr>
<tr>
<td>One Shot (Maya Covidiern)</td>
<td>1</td>
<td>NR</td>
<td>6</td>
<td>NR</td>
<td>–</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>31</strong></td>
<td><strong>10</strong></td>
<td><strong>3–12</strong></td>
<td><strong>6</strong></td>
<td><strong>18</strong></td>
</tr>
</tbody>
</table>

Updated from Ref. [20]
NR: not reported; PTA: percutaneous angioplasty; RDN: renal denervation.
of resistant hypertension reported in large clinical outcome trials [31] may be grossly overinflated due to inclusion of a substantial proportion of patients in whom drug treatment was not properly uptitrated [32]. Apparent treatment-resistant hypertension — that is uncontrolled office blood pressure on 3 or more antihypertensive drugs including a diuretic or blood pressure controlled on 4 drugs or more — accounts for 8.9% of the US adult hypertensive population and 12.9% in the subset receiving antihypertensive drugs [33]. However, this subset also includes an unknown proportion of patients with secondary and white coat hypertension and poorly adherent patients. In the 2010–2011 database of a large Israeli healthcare organisation [34*], resistant hypertensive patients defined as uncontrolled patients despite adherence to a drug regimen including a diuretic and at least 2 other antihypertensive drug classes at their maximal recommended dose accounted for only 2.2% of uncontrolled hypertensive patients and <1% of the total study population. This proportion may still be an overestimate, as screening for secondary or white coat resistant hypertension was performed only in a small minority of patients [34*]. Along the same lines, in a single centre retrospective chart review, the proportion of patients with resistant hypertension decreased from 30.9% to 3.4% when triple therapy had to include maximally dosed medications including a diuretic [35**]. Finally, drug dosages in urine or plasma of patients with resistant and difficult-to-treat hypertension documented poor or non-adherence in 23.5–65.5% of patients [36,37**,38,39].

In conclusion, patients with uncontrolled office blood pressure despite a triple therapy at maximal dose including a diuretic probably represent less than 5% of hypertensive patients. The prevalence of truly resistant hypertension, after exclusion of white coat and secondary hypertension, and apparently resistant hypertension due to low drug adherence may still be one order of magnitude lower. Even in this limited subset, blood pressure control may be achieved in a substantial proportion of patients by skilful drug treatment adjustment in expert centres [5,40]. While RDN deserves more in depth research, in the present state of knowledge, initiatives aiming at diagnosing and improving poor drug adherence [5] and optimisation of drug treatment [5,38] may prove much more cost-effective, both at the individual and public health policy level.

Conflict of interest statement
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References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


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In a large Israeli database the proportion of patient with uncontrolled office blood pressure despite adherence to a triple antihypertensive therapy was <2.5%. This figure may still be an overestimate, as only a small minority of patients were screened for secondary or white coat resistant hypertension.


In this single centre retrospective chart review, the proportion of patients with resistant hypertension defined as uncontrolled office blood pressure despite prescription of three antihypertensive drugs at maximal dosages including a diuretic was <3.5%.


Drug dosages in the urine show that up to 50% of patients with apparently resistant hypertension do not take or take only a few of the drugs prescribed. Changes in drug adherence may have a major impact on the apparent benefits of renal denervation, especially in observational and open randomized trials.

