BACKGROUND: The DENERHTN trial (Renal Denervation for Hypertension) confirmed the blood pressure-lowering efficacy of renal denervation added to a standardized stepped-care antihypertensive treatment for resistant hypertension at 6 months. We report the influence of adherence to antihypertensive treatment on blood pressure control.

METHODS: One hundred six patients with hypertension resistant to 4 weeks of treatment with indapamide 1.5 mg/d, ramipril 10 mg/d (or irbesartan 300 mg/d), and amlodipine 10 mg/d were randomly assigned to renal denervation plus standardized stepped-care antihypertensive treatment, or the same antihypertensive treatment alone. For standardized stepped-care antihypertensive treatment, spironolactone 25 mg/d, bisoprolol 10 mg/d, prazosin 5 mg/d, and rilmenidine 1 mg/d were sequentially added at monthly visits if home blood pressure was \( \geq 135/85 \) mm Hg after randomization. We assessed adherence to antihypertensive treatment at 6 months by drug screening in urine/plasma samples from 85 patients.

RESULTS: The numbers of fully adherent (20/40 versus 21/45), partially nonadherent (13/40 versus 20/45), or completely nonadherent patients (7/40 versus 4/45) to antihypertensive treatment were not different in the renal denervation and the control groups, respectively (\( P = 0.3605 \)). The difference in the change in daytime ambulatory systolic blood pressure from baseline to 6 months was \(-6.7\) mm Hg (\( P = 0.0461 \)) in fully adherent and \(-7.8\) mm Hg (\( P = 0.0996 \)) in nonadherent (partially nonadherent plus completely nonadherent) patients. The between-patient variability of daytime ambulatory systolic blood pressure was greater for nonadherent than for fully adherent patients.

CONCLUSIONS: In the DENERHTN trial, the prevalence of nonadherence to antihypertensive drugs at 6 months was high (\( \approx 50\% \)) but not different in the renal denervation and control groups. Regardless of adherence to treatment, renal denervation plus standardized stepped-care antihypertensive treatment resulted in a greater decrease in blood pressure than standardized stepped-care antihypertensive treatment alone.

The DENERHTN trial (Renal Denervation for Hypertension) was designed to assess the efficacy of renal denervation with the Symplicity flex catheter on ambulatory blood pressure (BP) and its safety. Renal denervation was added to a standardized stepped antihypertensive treatment (SSAHT) and was compared with the same SSAHT alone in patients with well-defined essential resistant hypertension that was further confirmed after a 4-week standardized triple therapy, using ambulatory BP monitoring. We previously showed that, at 6 months follow-up, renal denervation combined with a median number of 5 drugs of the SSAHT significantly reduces daytime systolic blood pressure, by ≈6 mm Hg more than the same SSAHT alone, in patients with resistant hypertension.

We report here the influence of adherence to SSAHT on blood pressure control, by determining urine N-acetyl-seryl-aspartyl-lysyl-proline/creatinine ratio and using ultrahigh performance liquid chromatography tandem mass spectrometry to detect the drugs in urine or plasma samples at 6 months.

### What Are the Clinical Implications?

- There was a high nonadherence rate to SSAHT (≈50%), but this rate was not different in the renal denervation and control groups, even though patients and healthcare providers were not blind to treatment.
- Regardless of adherence to SSAHT, renal denervation plus SSAHT decreased blood pressure more than SSAHT alone.
- These findings support the initial results of the DENERHTN trial and the evaluation of the blood pressure–lowering effects of future renal denervation trials including standardization of antihypertensive treatment regimens and monitoring of adherence.
- The high rate of nonadherence in patients with resistant hypertension provides a strong argument for its systematic detection by antihypertensive drug screening.

However, the MMAS-8 questionnaire has known limitations and does not have a high predictive value for medication adherence. Because adherence to antihypertensive drugs is a major potential confounder of treatment effect in blinded and nonblinded, randomized trials on renal denervation, we also assessed adherence to SSAHT using measurement of urine N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP)/creatinine ratio and ultrahigh performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) to detect the drugs or their corresponding metabolites in urine or plasma samples and therefore to confirm actual exposure to SSAHT.

The objectives of this prespecified analysis were to investigate: (1) whether adherence to SSAHT at 6 months assessed by urine AcSDKP/creatinine ratio and UPLC-MS/MS differed between the renal denervation and control groups, and (2) whether taking exposure to SSAHT into account modified the conclusions of the intent-to-treat analysis of the DENERHTN trial in terms of the BP-lowering effects of renal denervation.

### METHODS

#### Study Design

The DENERHTN study was a multicenter, prospective, randomized, open-label blinded end point evaluation controlled trial, conducted in 15 French tertiary care centers between May 22, 2012 and October 14, 2013. This trial was approved by the Comité de Protection des Personnes Ile de France VII. All participants provided written informed consent to participate in the study, including urine or plasma sample collection for antihypertensive drug screening.

#### Participants

All eligible patients received standardized triple antihypertensive therapy for 4 weeks, to confirm resistant hypertension by ambulatory BP monitoring; this comprised sustained-release indapamide 1.5 mg/d, ramipril 10 mg/d (or irbesartan 300 mg/d in the event of cough), and amlodipine 10 mg/d (or 5 mg/d in the event of leg edema). Patients with mean daytime ambulatory SBP of 135 mm Hg or higher or diastolic BP of 85 mm Hg or higher were randomly assigned in a 1:1 ratio to renal denervation plus SSAHT (renal denervation group) or to SSAHT alone (control group), using dedicated Web-based software.

We performed a median of 11 renal nerve ablations per patient (interquartile range, 10–12) using a single-electrode radiofrequency Symplicity catheter (Medtronic), 2 to 4 weeks after randomization, as described previously.

After randomization, 4 further drugs were added sequentially to the standard triple therapy at each monthly visit from months 2 to 5, if home SBP was 135 mm Hg or higher or diastolic BP was 85 mm Hg or higher: spironolactone 25 mg/d, bisoprolol 10 mg/d, sustained-release prazosin 5 mg/d, and rilmenidine 1 mg/d. No other antihypertensive drug was allowed during the 6-month follow-up after randomization.

Supine office BP, 7-day seated home BP, and ambulatory BP were measured as previously described.
Drug Screening in Urine or Plasma

Six months after randomization, urine or blood samples were collected between 8:00 and 10:00 AM, before ingestion of any antihypertensive medication (ie, at trough), office BP measurement or 24-hour ambulatory BP monitoring.

To assess adherence to ramipril, we measured spot urine AcSDKP/creatinine ratio; a threshold of 4 nmol/mmol was used to discriminate between patients with low and high adherence, as reported previously. AcSDKP was measured using a commercially available kit (SpiBio, CEA).

The other antihypertensive drugs or their metabolites were measured in urine (n=60) or plasma (n=25) samples by UPLC-MS/MS (online-only Data Supplement).

All samples were analyzed blind to the randomization and the prescribed antihypertensive treatment.

Study End Points

Full adherence to the SSAHT at 6 months was defined as the presence of all prescribed drugs in the samples and a urine AcSDKP/creatinine ratio of ≥4 nmol/mmol in patients treated with ramipril. Complete nonadherence was defined as the absence of all prescribed drugs in the samples and a urine AcSDKP/creatinine ratio of <4 nmol/mmol in patients treated with ramipril. Partial nonadherence was defined as all other combinations of results: the absence of at least one of the prescribed drugs using UPLC-MS/MS analysis or urine AcSDKP/creatinine measurement. Overall nonadherence was defined as partial plus complete nonadherence.

The primary efficacy end point of mean change in daytime ambulatory SBP from baseline to 6 months was assessed across the subgroups of patients who were fully adherent or nonadherent to SSAHT at 6 months. Other end points included changes from baseline to 6 months in all other BP parameters, and number of antihypertensive drugs prescribed and detected in urine or plasma at 6 months.

Statistical Analysis

Among the 1416 patients screened for eligibility, 106 were randomly assigned to treatment (53 patients in each group, intention-to-treat population). For the prespecified analysis on the influence of adherence to SSAHT on BP control, we did the statistical analysis on the per-protocol population, defined by the availability of both ambulatory BP-monitoring measurements and drug-screening data at 6 months.

We compared treatment groups by using the unpaired t test or Wilcoxon rank sum test for continuous variables, and the χ² test or Fisher exact test for categorical variables. We assessed treatment effect on BP parameters by analysis of covariance, including the baseline value as a covariable, as described previously. Data are presented as mean±standard deviation, or median (interquartile range). Mean differences for BP data are reported with their 95% confidence intervals (CIs). We used the SAS version 9.4 software (SAS Institute Inc). A P value <0.05 was considered significant. This trial is registered with ClinicalTrials.gov, Unique Identifier NCT01570777.

Independent Data Access and Analysis

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The trial was conducted under the guidance of an independent data and safety-monitoring board convened by the sponsor. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Of the 106 patients randomly assigned in the DENERHTN study, 85 were included in the adherence substudy: 40 of 53 in the renal denervation group and 45 of 53 in the control group. Baseline characteristics were not different between the 2 groups (online-only Data Supplement Table I) and were similar to those previously reported for the DENERHTN study.

The mean decrease in daytime ambulatory SBP from baseline to 6 months was significantly greater in the renal denervation group (–16.6 mm Hg; 95% CI, –20.8 to –12.5) than in the control group (–9.0 mm Hg; 95% CI, –13.0 to –5.1), with a mean baseline-adjusted difference between the 2 groups of –7.6 mm Hg (95% CI, –13.3 to –1.8, P=0.0104; Figure 1A), as reported in the main study.

Evaluation of Adherence to Treatment

The number of antihypertensive drugs actually detected in urine or plasma was not different between the 2 groups (P=0.5695; Figure 1B) but was lower than the number of drugs prescribed: the mean ratio of detected drugs to prescribed drugs was 75.0% in both groups (P=0.7637; Figure 1C).

The number of patients who were fully adherent, partially nonadherent, or completely nonadherent to the SSAHT at 6 months was not different in the renal denervation and control groups (fully adherent: 20 [50.0%] versus 21 [46.7%]; partially nonadherent: 13 [32.5%] versus 20 [44.4%]; completely nonadherent: 7 [17.5%] versus 4 [8.9%]; P=0.3605; Figure 1D). Overall, 44 of the 85 patients included in the adherence substudy (51.8%) were nonadherent to SSAHT at 6 months, including 11 patients (13.0%) who were completely nonadherent.

The number of antihypertensive drugs prescribed and the number actually detected did not differ significantly between the renal denervation and the control groups for fully adherent or nonadherent (partially plus completely nonadherent) patients (Table 1). The online-only Data Supplement Table II shows the number of antihypertensive drugs prescribed and the number actually detected within each nonadherence category (partial nonadherence or complete nonadherence). Overall, the level of adherence decreased as more antihypertensive drugs were prescribed (ie, fewer drugs detected in plasma/urine samples; online-only Data Supplement Table II).
BP changes in Patients Who Were Fully Adherent or Nonadherent to SSAHT

Baseline ambulatory BP was higher in patients who were nonadherent (partially plus completely nonadherent) than in those who were fully adherent to the SSAHT at 6 months; however, there were no significant differences between the renal denervation and control groups within each category of adherence (Table 2). For all levels of adherence, daytime and 24-hour ambulatory SBP at 6 months had decreased more in the renal denervation group than in the control group (Table 2). The baseline-adjusted difference in the change in daytime ambulatory SBP from baseline to 6 months between the 2 groups was −6.7 mm Hg (95% CI, −13.3 to −0.1; P = 0.0461) in fully adherent and −7.8 mm Hg (−17.1 to 1.5, P = 0.0996) in nonadherent patients (Table 2). The coefficients of variation (% = standard deviation/mean ratio) of daytime ambulatory SBP at 6 months were greater in the nonadherent group (renal denervation group, 13.6% and control group, 13.6%) than in the fully adherent group (renal denervation group, 9.7% and control group, 10.0%). Changes from baseline in daytime ambulatory SBP, the primary end point of the study, are shown in Figure 2.

The BP changes in patients who were partially or completely nonadherent are reported in the online-only Data Supplement Table III and Figure I. The baseline-adjusted difference in the change in daytime ambulatory SBP from baseline to 6 months between the renal denervation group and the control group was −11.0 mm Hg (−21.7 to −0.4, P = 0.0430) in partially nonadherent, and −9.3 mm Hg (−26.3 to 7.7, P = 0.2424) in completely nonadherent patients (online-only Data Supplemental Table III).

Finally, all other BP parameters tended to show greater decreases from baseline to 6 months in the renal denervation group than in the control group for all categories of adherence, but the differences between the
2 treatment groups were not significant (online-only Data Supplement Tables IV and V).

DISCUSSION

This is the first randomized controlled trial of renal denervation to report medication adherence assessed by UPLC-MS/MS analysis of urine or plasma samples and urine AcSDKP/creatinine ratio. Our results show that the patients with resistant hypertension selected for the DENERHTN trial who were closely monitored for >6 months and had given consent for the collection of urine and blood samples for antihypertensive drug screening, nevertheless had a high nonadherence rate at ≈50%, with 13% of the patients completely nonadherent to the antihypertensive drugs prescribed sequentially during the course of the trial. We also found that patients’ adherence to the SSAHT were not different between the 2 groups, and patients within each adherence category were exposed to approximately the same number of antihypertensive drugs. Overall, only 50.0% of the patients in the renal denervation group and 46.7% in the control group were fully adherent to the SSAHT at 6 months.

The analysis of the BP-lowering effects of renal denervation, taking exposure to the SSAHT into account, showed that the decrease in ambulatory BP was not confounded by improvements in adherence following the procedure in the renal denervation group or, conversely, by worsening adherence in the control group. Indeed, regardless of the adherence to the SSAHT at 6 months, ambulatory SBP decreased more when renal denervation was combined with SSAHT, both in patients who were fully adherent (mean additional BP reduction of ≈7 mm Hg) and in those nonadherent to SSAHT (mean additional BP reduction of ≈8 mm Hg). Even though the mean additional BP reduction after renal denervation was of similar magnitude regardless of the adherence to SSAHT, it did not reach statistical significance in patients who were nonadherent (P=0.0996) because of larger between-patient variability in daytime ambulatory SBP at 6 months in these patients than in those who were fully adherent (coefficient of variation, 13.6% versus ≈10%, respectively). With this larger between-patient variability, we calculated that we would need to randomly assign 60 patients to each group to detect
a difference in daytime ambulatory SBP change from baseline to 6 months of \(\approx -8\) mm Hg between renal denervation plus SSAHT and SSAHT alone (80% power, 5% type I error). Therefore, our results also suggest that poor adherence to SSAHT contributes to greater between-patient variability in the BP response, and is most likely one of several factors influencing variability that have been reported previously for renal denervation.9,10

Finally, in an exploratory analysis of the BP response to renal denervation in the subgroup of patients who were completely nonadherent, we observed that daytime ambulatory SBP decreased in 5 of 7 patients (range, \(-16\) to \(-4\) mm Hg) and in 2 of 4 patients in the control group (\(-6\) and \(-5\) mm Hg), but the difference was not statistically significant because of the small number of patients left in this subgroup (see online only Data Supplement). Further studies will be needed to confirm the efficacy of renal denervation in patients who are completely nonadherent to their antihypertensive treatment.

The ongoing debate about the clinical usefulness of the addition of renal denervation to optimal medical treatment in patients with resistant hypertension reflects the heterogeneity of BP results in the randomized, controlled trials reported to date.1,11–15 The reasons for these discordant results have been discussed extensively.16–19 None of the trials, with the exception of the DENERHTN trial, used standardized care, follow-up, BP measurements, or antihypertensive treatment strategy in the renal denervation and control groups, and systematically assessed adherence to the antihypertensive treatment, in particular, using UPLC-MS/MS.

Because the DENERHTN study was a prospective, randomized, open-label blinded end point evaluation trial using a medical device, it may have been prone to the Hawthorne effect, as in any other blinded studies, and open-label studies in particular,20 by which participants and healthcare providers may have consciously or subconsciously changed their behavior after treatment allocation, thus affecting the outcomes. The expected benefit of renal denervation, and the disappointment at not being offered “the new intervention” on the part of patients, families, and care providers may have increased or decreased medication adherence in unpredictable and uncontrolled ways. Consequent changes in adherence to the SSAHT may have been missed by the MMAS-8, which is known not to be sufficiently specific to

### Table 2. Ambulatory Systolic Blood Pressure at Randomization and After 6 Months Follow-up in Patients Who Were Fully Adherent or Nonadherent (Partially Nonadherent Plus Completely Nonadherent) to Standardized Stepped-Care Antihypertensive Treatment

<table>
<thead>
<tr>
<th>Renal Denervation Group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fully adherent patients</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ASBP, mmHg</strong></td>
<td>Mean Baseline-Adjusted Difference (95% CI)</td>
</tr>
<tr>
<td><strong>Randomization (Mean±SD)</strong></td>
<td>6 mo (Mean±SD)</td>
</tr>
<tr>
<td><strong>Daytime</strong></td>
<td>149.6±12.8</td>
</tr>
<tr>
<td><strong>Nighttime</strong></td>
<td>136.7±13.6</td>
</tr>
<tr>
<td><strong>24-h</strong></td>
<td>146.3±12.3</td>
</tr>
<tr>
<td><strong>Nonadherent patients</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ASBP, mmHg</strong></td>
<td>Mean Baseline-Adjusted Difference (95% CI)</td>
</tr>
<tr>
<td><strong>Randomization (Mean±SD)</strong></td>
<td>6 mo (Mean±SD)</td>
</tr>
<tr>
<td><strong>Daytime</strong></td>
<td>161.6±16.4</td>
</tr>
<tr>
<td><strong>Nighttime</strong></td>
<td>148.4±19.5</td>
</tr>
<tr>
<td><strong>24-h</strong></td>
<td>157.8±17.9</td>
</tr>
</tbody>
</table>

ASBP indicates ambulatory systolic blood pressure; CI, confidence interval; and SD, standard deviation.

*Renal denervation group versus control group.
ascertain medication adherence.\textsuperscript{3,4} However, our results show that overall exposure to the SSAHT drugs after 6 months follow-up was not different in the 2 treatment groups, excluding differences in patient behavior as the source of the difference in BP reduction. The results also suggest that healthcare providers likely behaved similarly in the 2 groups in terms of compliance with the medication titration and patient counseling protocol. Nevertheless, exposure to the SSAHT drugs was lower than expected in the patients with resistant hypertension who took part in this trial: the ratio of drugs detected to drugs prescribed was 75.0±39\% in the renal denervation group and 75.0±32\% in the control group. Indeed, 50.0\% of the patients in the renal denervation group and 53.3\% in the control group were either partially or completely nonadherent to SSAHT at 6 months. The true level of adherence to SSAHT could be even lower, because patients were fully informed that medication adherence was monitored throughout the trial, and this may have given rise to a toothbrush effect or white coat adherence phenomenon.\textsuperscript{3} However, our assays enabled us to determine partial or complete nonadherence to the SSAHT with high specificity, because the drugs were long acting: nondetection of any SSAHT drug in the urine or plasma samples collected at trough indicates that the nondetected drug(s) had not been ingested by the patient for a duration that exceeded at least 5 plasma half-lives of that given drug.

The high rate of nonadherence to SSAHT is consistent with previous reports by our group\textsuperscript{21} and others\textsuperscript{4–7,22} in other settings. Nonadherence was observed in the DENERHTN study despite every effort to maximize adherence by using all the approaches recommended by international guidelines.\textsuperscript{23} We provided the SSAHT drugs at no cost to the patients; we used long-acting antihypertensive treatments that are more forgiving in case a single day’s dose is omitted; we instructed patients to monitor their BP at home and provided devices for this purpose; we provided monthly visits with the same dedicated healthcare team, at no cost to the patient; and we avoided clinical inertia by using a protocol-driven therapeutic strategy based on home BP monitoring.\textsuperscript{24}

Figure 2. Spaghetti plots of individual changes in daytime ambulatory systolic blood pressure (SBP) between baseline and 6 months in the renal denervation group (red lines) and control group (blue lines) in patients who were fully adherent and nonadherent (partially nonadherent plus completely nonadherent) to SSAHT. SSAHT indicates standardized stepped antihypertensive treatment.
Data on adherence to treatment at baseline in patients referred for renal denervation, or included in the different renal denervation trials, are scarce.\textsuperscript{13,14,25} Adherence to antihypertensive medication was checked before randomization in the Prague-15\textsuperscript{13} and Oslo\textsuperscript{25} studies, by determinations of plasma drug concentration and by witnessing drug intake, respectively. Study design differed between these 2 trials and the DENERHTN trial. In the Prague-15 trial,\textsuperscript{13} renal denervation decreased 24-hour ambulatory SBP at 6 months (–8.6 mm Hg) to the same extent as antihypertensive treatment intensification including spironolactone (–8.1 mm Hg). In the Oslo trial,\textsuperscript{25} the daytime ambulatory SBP decrease in the renal denervation group with maintained antihypertensive treatment (unadjusted change, –10±12 mm Hg) was less marked than that in the group undergoing drug treatment intensification based on noninvasive hemodynamic measurements (unadjusted change, –19±12 mm Hg) at 6 months but not at 9 months; however the number of patients included was small. The BP-lowering effect observed in the denervation groups of the Prague-15 and Oslo trials may thus reflect more the effect of renal nerve ablation per se because only adherent patients were included in these 2 trials and their antihypertensive treatment was maintained unchanged for 6 months. However, adherence to antihypertensive treatment was not assessed at the time of primary end point assessment at 6 months in either of these 2 trials. Two additional single-arm, open-label studies have reported follow-up adherence data assessed by LC-MS/MS.\textsuperscript{26,27} The nonadherence rate had increased 6 months after renal denervation despite a decrease in the antihypertensive pill burden in 1 study,\textsuperscript{26} whereas, in the other, the adherence pattern did not change significantly after renal denervation and had no impact on the overall BP changes observed.\textsuperscript{27} We did not initially exclude patients enrolled in the DENERHTN trial on the basis of their adherence profile at randomization as in other studies,\textsuperscript{13,14,25} because: (1) the number of nonadherent patients was expected to be equally balanced in the 2 groups after randomization (which was found to be the case); (2) UPLC-MS/MS for the detection of antihypertensive drugs was not yet available when the trial started in May 2012 (and it was later shown that ≈25% of patients referred for renal denervation were in fact nonadherent to prescribed antihypertensive treatment); and (3) we planned to assess the effects of renal denervation on BP taking adherence to the SSAHT into account.

**Study Limitations**

The limitations of the DENERHTN trial have been discussed elsewhere.\textsuperscript{17,28} The limitations of this analysis include (1) the possibility of white coat adherence (see above); (2) the fact that drug dosages in body fluids were only semiquantitative and that all drugs were considered to have the same weight in the evaluation of adherence, whereas their impact on BP control may be different; (3) the fact that drug dosages were performed at 6 months after randomization and only reflect the level of drug adherence at the time of assessment of the primary end point; and (4) the fact that we cannot fully exclude a Hawthorne effect, because there was no sham group.\textsuperscript{1} Despite these limitations, our analysis suggests that potential intentional or unintentional biases attributable to adherence to the treatment protocol by physicians and patients are likely to have had minimal consequences for the results of the DENERHTN study, because the level of exposure to the SSAHT medications after 6 months follow-up was not different in the 2 treatment groups.

**CONCLUSION**

This analysis of the DENERHTN trial, taking into account adherence to SSAHT, as assessed by UPLC-MS/MS analysis and urine AcSDKP/creatinine ratio, reinforces the initial results of the trial by showing that the BP-lowering effects of renal denervation were not biased by differential adherence to SSAHT in the 2 groups. This finding contrasts with those of other studies reporting the impact of nonadherence on the BP response to antihypertensive drugs alone.\textsuperscript{21} We confirm here that the additional ≈6 to 10 mm Hg reduction in ambulatory BP that is achieved when renal denervation is added to SSAHT is a reasonable and plausible estimate of the BP response that can be expected with this procedure, regardless of adherence profile. This difference is clinically meaningful and may contribute to a reduction in cardiovascular morbidity\textsuperscript{29} if maintained in the long term after renal denervation.\textsuperscript{30,31}

Nonadherence to antihypertensive drugs will always impede the precise assessment of the BP-lowering effects of renal denervation in patients with resistant hypertension. Because renal denervation appears to be associated with a limited risk of adverse events,\textsuperscript{15,32} evaluation of the BP-lowering efficacy of new catheters using different technologies remains warranted in patients with resistant hypertension in whom antihypertensive treatment regimens should be standardized and adherence strictly monitored, but also in those with milder forms of hypertension in whom antihypertensive drugs could be stopped for a limited period.\textsuperscript{32} There are currently 6 randomized sham-controlled trials testing the ambulatory BP-lowering efficacy and the safety of renal denervation with various radiofrequency- or ultrasound-based denervation catheters or externally delivered ultrasound technology; their primary results are expected in 2017.\textsuperscript{33}

Meanwhile, physicians should take into account the high prevalence of nonadherence to antihypertensive treatment in patients with resistant hypertension, as shown even in the highly controlled setting of a randomized controlled trial with very close monitoring.
This nonadherence provides a strong argument for the systematic evaluation of adherence by antihypertensive drug screening with UPLC-MSMS and urine AcSDKP/creatinine measurements, as an integral part of the routine assessment of patient s with resistant hypertension.\textsuperscript{34}

**APPENDIX**


**ACKNOWLEDGMENTS**

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**DISCLOSURES**

Dr Azizi has received honoraria for advisory board meetings from Vessix, Boston Scientific Corporation, Cordis, Actelion, has received speakers’ honoraria from Cordis, CVRx, Servier; was involved as investigator in Symplicity HTN-2 (Ardisian/Medtronic) and Reduce-HTN (Vessix/Boston Scientific Corporation) trials; and has received a research grant from Servier. Drs Pereira and Hamdiddouche have no conflicts of interest. Dr Gosse has received fees for lectures from Servier, Novartis, Resmed; has received travel support to meetings from Resmed, Daichi-Sankyo; and was involved as investigator in trials from Novartis, Servier, Resmed, GSK, Lilly, BMS, Daichi Sankyo. Dr Monge has no conflict of interest. Dr Bobrie has received consulting fees or honoraria from Sanofi-Aventis, Gami bro, Fresenius; has received travel support to meetings from Novartis; has received fees for participation in review activities such as data-monitoring boards from Fresenius; has served as Board member for Fresenius; has received fees for writing or reviewing manuscripts for Sanofi-Aventis; and was involved as investigator in Symplicity HTN-2 (Ardisian/Medtronic) and Reduce-HTN (Vessix/Boston Scientific Corporation) trials. Dr Delsart has received travel support to meetings from Boucha ra, Daichi-Sankyo. Dr Mounier-Véhier has received consulting fees or honoraria from Abvivie, Ardia thermal-Ethérapie, Daichi Sankyo, Novartis, Bouchara Recordati, Pierre Fabre, Menarini, Boeringer-Inghelheim; has received travel support to meetings from Daichi Sankyo, Novartis, Bouchara recordati; Board membership: BTP-pro-BTP-Bayer Pharma, Daichi-Sankyo, Astra-Zeneca, Ardis-Thermal-Ethérapie; and has received research grants from Servier. Dr Courand has received travel support to meetings from Menarini, Bouchara-Recordati, Medtronic, Servier; and has received speaker’s honorarium from Servier. Dr Lanteime has received travel support to meetings from Medtronic, St Jude; and has received speaker’s honorarium from Medtronic, St Jude. Dr Denolle has received honoraria for advisory board meetings and speaker’s honoraria from Ardia, Menarini, Servier, Bayer, St Jude, Daichi-Sankyo, Medtronic, Bouchara Recordati; has received travel support to meetings from Servier, Daichi-Sankyo, St Jude, Res Med. Caroline Dour map-Collas has received consulting fees or honoraria from Boston Scientific, Cordis; has received honoraria for advisory board meetings from Novartis; and has received travel support to meetings from Servier. Dr Gierard reports personal fees from Bouchara-Recordati, Novartis, Astra-Zeneca, Daichi-Sankyo, ReCor, Bayer, outside the submitted work. Dr Zannad reports grants from French ministry of health during the conduct of the study; and personal fees from Boston Scientific, CVRx, outside the submitted work. Drs Ormezzano and Vaisse have no conflicts of interest. Dr Herpin reports personal fees from Bouchara-Recordati, Novartis, Astra-Zeneca, Daichi-Sankyo; and was involved as investigator in Symplicity HTN-2 (Ardisian/Medtronic) and Reduce-HTN (Vessix/Boston Scientific Corporation) trials; and has received a research grant from Servier. Drs Plouin and Ferrari have no conflicts of interest. Dr Plouin has received consulting fees or honoraria from Servier, Novartis, Menarini; has received personal fees from Bard, Resmed, Daiichi-Sankyo; and was involved as investigator in trials from Novartis, Servier, Resmed, GSK, Lilly, BMS, Daichi Sankyo. Dr Monge has no conflict of interest. Dr Bobrie has received consulting fees or honoraria from Sanofi-Aventis, Gami bro, Fresenius; has received travel support to meetings from Novartis; has received fees for participation in review activities such as data-monitoring boards from Fresenius; has served as Board member for Fresenius; has received fees for writing or reviewing manuscripts for Sanofi-Aventis; and was involved as investigator in Symplicity HTN-2 (Ardisian/Medtronic) and Reduce-HTN (Vessix/Boston Scientific Corporation) trials. Dr Delsart has received travel support to meetings from Bouchara, Daichi-Sankyo. 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FOOTNOTES
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