Adjusted Drug Treatment Is Superior to Renal Sympathetic Denervation in Patients With True Treatment-Resistant Hypertension

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Abstract—We aimed to investigate for the first time the blood pressure (BP)–lowering effect of renal sympathetic denervation (RDN) versus clinically adjusted drug treatment in true treatment-resistant hypertension (TRH) after excluding patients with confounding poor drug adherence. Patients with apparent TRH (n=65) were referred for RDN, and those with secondary and spurious hypertension (n=26) were excluded. TRH was defined as office systolic BP (SBP) >140 mm Hg, despite maximally tolerated doses of ≥3 antihypertensive drugs including a diuretic. In addition, ambulatory daytime SBP >135 mm Hg after witnessed intake of antihypertensive drugs was required, after which 20 patients had normalized BP and were excluded. Patients with true TRH were randomized and underwent RDN (n=9) performed with Symplicity Catheter System versus clinically adjusted drug treatment (n=10). The study was stopped early for ethical reasons because RDN had uncertain BP-lowering effect. Office SBP and diastolic BP in the drug-adjusted group changed from 160±14/88±13 mm Hg (±SD) at baseline to 132±10/77±8 mm Hg at 6 months (P<0.0005 and P=0.02, SBP and diastolic BP, respectively) and in the RDN group from 156±13/91±15 to 148±7/89±8 mm Hg (P=0.42 and P=0.48, SBP and diastolic BP, respectively). SBP and diastolic BP were significantly lower in the drug-adjusted group at 6 months (P=0.002 and P=0.004, respectively), and absolute changes in SBP were larger in the drug-adjusted group (P=0.008). Ambulatory BPs changed in parallel to office BPs. Our data suggest that adjusted drug treatment has superior BP lowering effects compared with RDN in patients with true TRH.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01673516

Key Words: blood pressure ■ drug therapy ■ hypertension

Approximately 12% of patients treated for hypertension remain with uncontrolled high blood pressure (BP), despite prescription of antihypertensive drugs.1 The fraction is reduced to ≥7.5% with use of ambulatory BP,1 comprising also patients prescribed ≥3 antihypertensive drugs in full doses including a diuretic, a condition defined as treatment-resistant hypertension (TRH). Renal sympathetic denervation (RDN) has been introduced as a new treatment of TRH.2 However, it has been known for decades that poor drug adherence is a major problem among patients with apparent TRH.3 The evidence, that is, data derived from prospective, randomized, and controlled research, that RDN lowers BP is limited.2 There is only 1 single controlled study in which 52 patients underwent the procedure, with insufficient documentation of ambulatory BP or adequate drug compliance.2 Thus, it is de facto unknown to what degree the decline in BP after RDN2 is caused by denervation itself. Improved drug adherence would be expected during an intervention because of increased attention to measurements and management.2 Neither placebo effect nor merely a chance finding possibly related to publication bias can be excluded.2 Because thousands of patients worldwide have undergone RDN, a costly invasive procedure with potential damage to the renal arteries,6 and with BP-lowering effect documented in only 1 randomized study;2 we aimed to investigate whether RDN truly lowers BP.

Recently, we reported that RDN had no effect on office and daytime ambulatory BP at 3 and 6 months in an open study of carefully selected patients with true TRH based on qualifying elevated ambulatory BP immediately after witnessed intake of the antihypertensive drugs.7 In the present study, we aimed...
for the first time to investigate the BP-lowering effect of RDN versus clinically adjusted drug therapy in patients with true TRH in a randomized prospectively study in a design that excluded the important confounding factor of drug adherence in addition to both secondary or spurious hypertension.

Methods

Study Design and Patients

After publication of the Symplicity HTN-2 study and subsequent local and national medical meeting activities, patients referred specifically for RDN from hospitals and specialist practices in Norway (n=65) were thoroughly worked-up in the nephrology outpatient clinic at Oslo University Hospital, Ulleval, in the time period from August 2012 to June 2013 by experienced physicians (F.M.F., A.C.L., A.H.). Patients with secondary and spurious hypertension, and some patients with high serum aldosterone levels (primary hyperaldosteronism without tumor or with high aldosterone/renin activity ratio) who responded to treatment with spironolactone, were identified and excluded. Spironolactone was not given routinely to all patients because this is not considered to be evidence based medicine by European hypertension guidelines. TRH was defined as uncontrolled hypertension (office systolic BP >140 mm Hg immediately after in the hospital area and every 30 minutes during nighttime. Ambulatory BP was measured every 20 minutes during daytime (15 hours of measurement) and documented in writing the outcome of the randomization. The study was approved by The National Committee for Research Ethics in Norway and by the institutional research committee at Oslo University Hospital. All patients gave written informed consent for participation in the study and publication of results. All patients who qualified for the procedure within the 11-month time period were included. All expenses were covered by the hospital (public) and patients were not paid.

Procedures

The drug-adjusted group had their antihypertensive medication adjusted at baseline, 1 month, and at 3 months by one of the investigators (F.M.F.) according to 2007 European Society of Hypertension/European Society of Cardiology hypertension guidelines and guided by using a noninvasive integrated hemodynamic measurements of impedance cardiography with the HOTMAN System (Hemo Sapiens Inc, Sedona, AZ) as previously described and validated. In short, this procedure aimed at tailoring the antihypertensive treatment to the underlying hemodynamic aberration such as further increasing the dose of diuretic in volume-overloaded patients or prescribing, or increasing the dose of vasodilatory medicines in patients with high peripheral resistance, or reducing the dose of drugs that cause negative inotropy in patients with reduced cardiac inotropy.

Meditation was aimed at being maintained unchanged in the RDN group. Renal denervation was performed using Symplicity Catheter System (Ardian, Mountain View, CA) by experienced and appropriately trained invasive radiologist (F.H., M.B.) as described by others and previously detailed by us and in the online-only Data Supplement. Patients were hospitalized overnight and followed with office BP measurements at 1, 3, and 6 months and ambulatory BP measurements at 2 weeks, and no change in medication was preplanned for the following 6 months. Patients could be 18 to 80 years of age with normal renal arteries at computed tomography or MRI examination within 2 years before participation. Patients with estimated glomerular filtration rate <60 mL/min per 1.73 m² (MDRD formula), urine albumin/creatinine ratio >50 mg/mmol or type 1 diabetes mellitus could not be included in line with the hitherto single published randomized study of BP-lowering effects of RDN. Patients were randomized (Figure 1) using a permuted block randomization list through a telephone call to a hospital employee who was not involved in the study, who was uninformed about the nature of the study, and who opened a sealed envelope arranged in a fixed order and documented in writing the outcome of the randomization.

The study was approved by The National Committee for Research Ethics in Norway and by the institutional research committee at Oslo University Hospital. All patients were paid, and included. All expenses were covered by the hospital (public) and patients were not paid.

Patients

Sixty-five patients were referred for RDN mostly from primary or secondary hospitals or specialist practices to the main university hospital in Oslo, Norway. Forty-five patients were excluded before randomization because of reasons summarized in the flow diagram in Figure 2. A total of 25 patients were excluded because they had secondary or spurious hypertension, and some patients with high serum aldosterone levels (primary hyperaldosteronism without tumor or with high aldosterone/renin activity ratio) who responded to treatment with spironolactone, were identified and excluded. Spironolactone was not given routinely to all patients because this is not considered to be evidence based medicine by European hypertension guidelines. TRH was defined as uncontrolled hypertension (office systolic BP >140 mm Hg immediately after in the hospital area and every 30 minutes during nighttime. Ambulatory BP was measured every 20 minutes during daytime (15 hours of measurement) and documented in writing the outcome of the randomization. The study was approved by The National Committee for Research Ethics in Norway and by the institutional research committee at Oslo University Hospital. All patients gave written informed consent for participation in the study and publication of results. All patients who qualified for the procedure within the 11-month time period were included. All expenses were covered by the hospital (public) and patients were not paid.

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hypertension (including 5 patients who normalized their BP when their diuretic treatment was further adjusted, 1 patient who normalized BP when given β-blocker, and 4 patients with primary hyperaldosteronism without tumor who normalized BP on spironolactone). Nineteen patients were excluded because they had normal ambulatory BP after witnessed intake of their BP medication just before the qualifying measurement. Thirteen of them were considered to have poor drug adherence because they had high ambulatory BPs taken by the referring physicians (average BP changed from 160±20/99±16 to 130±5/81±5 mm Hg). Six of them did not have previous ambulatory BPs, and we could not discriminate between poor drug compliance and white coat hypertension. One additional patient had severe symptomatic hypotension after witnessed intake of drugs and before mounting of ambulatory BP.

We randomized 20 patients but excluded 1 patient postrandomization because Conn’s disease was diagnosed at this stage; this patient did not go through RDN. The baseline characteristics of the patients allocated to RDN (n=9) and the patients allocated to the drug-adjusted group (n=10) are compared in the Table, and the 2 groups were comparable on BPs, demographic characteristics, disease history, and number of prior antihypertensive drugs. No comparison reached statistical significance.

Patients included in the randomized study (n=19) were 17 men and 2 women from 37 to 70 years, and their body mass index ranged between 23 and 39 kg/m² (Table). They used maximally tolerated doses of 3 to 8 antihypertensive drugs. Medication was changed according to hemodynamic status in the drug-adjusted group mainly as up- or down-titration of doses of drugs already prescribed; 4 patients had 1 more drug added: calcium channel blocker (n=1), α-blocker (n=2), and amiloride (n=1); and 1 patient had 2 more drugs added: minoxidil and amiloride. One patient in the RDN group stopped taking 2 drugs (moxonidine and hydrochlorothiazide) because of 2 episodes with postural hypotension 2 months after RDN. Otherwise no change in medication was done in the other patients in the RDN group.

Office BPs in the 2 Groups

In the drug-adjusted group, office SBP and diastolic BP changed from 160±14/88±13 mm Hg at baseline to 140±18/81±10 mm Hg at 3 months (P=0.01 and P=0.18 for SBP and diastolic BP, respectively) and to 132±10/77±8 mm Hg at 6 months (P<0.0005 and P=0.02 for SBP and diastolic BP, respectively). Comparing the 2 groups (Figure 3), office SBP and diastolic BP were significantly lower in the drug-adjusted group at 6 months (P=0.002 and P=0.004, respectively).

The graph on individual office SBP (Figure 4) shows how the groups split in favor of adjusted drug treatment.
Only 2 of the patients in the drug-adjusted group remained with clearly elevated office SBP >140 mm Hg at 6 months, whereas none of the RDN patients showed optimal BP control. All patients in the drug-adjusted group and only 3 patients in the RDN group had a reduction in office SBP of ≥10 mm Hg.
The reduction in office SBP at 6 months was 28±13 mm Hg (P<0.0005) in the drug-adjusted group and 8±15 mm Hg (P=0.12) in the RDN group. Thus, there was a 20-mm Hg larger reduction in the drug-adjusted group compared with the RDN group. Comparing the 2 groups, absolute changes in office SBP were significantly larger in the drug-adjusted group (P=0.008; Figure 5).

Ambulatory BPs in the 2 Groups

In the drug-adjusted group, daytime ambulatory SBP and diastolic BP changed from 152±12/88±8 mm Hg at baseline to 133±13/77±8 mm Hg at 3 months and to 133±11/77±8 mm Hg at 6 months. All these changes were statistically highly significant (<0.005). In the RDN group, daytime ambulatory SBP and diastolic BP changed from 152±10/93±8 mm Hg at baseline to 145±11/87±5 mm Hg at 3 months and to 142±9/86±6 mm Hg at 6 months. All changes were significant (P<0.05) except for the change in SBP from baseline to 3 months (P=0.06). Comparing the 2 groups, daytime ambulatory SBP and diastolic BP were significantly lower in the drug-adjusted group at 3 months (P=0.04 and P=0.009, respectively) and so was diastolic BP at 6 months (P=0.02), whereas the difference in SBP at 6 months was borderline significant (P=0.08, 2-tailed; Figure 6).

The reduction in daytime ambulatory SBP at 3 months was 19±12 mm Hg in the drug-adjusted group and 7±10 mm Hg in the RDN group. There was a significantly larger reduction in daytime ambulatory SBP of 12 mm Hg in favor of adjusted drug treatment compared with RDN at 3 months (P=0.03). The reduction in daytime ambulatory SBP at 6 months was 19±12 mm Hg in the drug-adjusted group and 10±12 mm Hg in the RDN group. The reduction in daytime ambulatory SBP of 9 mm Hg in favor of adjusted drug therapy compared with RDN at 6 months did not reach statistical significance (Figure 8).

Heart Rates in the 2 Groups

In the drug-adjusted group, office heart rate averaged 57±13 bpm at baseline and 58±15 bpm at 6 months (P=0.61). In the RDN group, office heart rate averaged 67±16 bpm at baseline and 63±14 bpm at 6 months (P=0.06). The changes between the 2 groups did not reach significance (P=0.07). Average daytime heart rates did not change from baseline to 3 or 6 months in either group, and changes were not significant between the groups (P=0.14).

Safety

One patient in the RDN group had a myocardial infarction 5 months after the procedure. Four patients had mild-to-moderate hematomas at the femoral access site for RDN. One patient had bradycardia and received atropin injection during RDN. Four patients in the drug-adjusted group and 1 patient in the RDN group had symptomatic hypotension. Two patients experience sexual dysfunction after increasing the dosage of spironolactone in the drug-adjusted group. No patient had detectable change in renal function.
Discussion

Careful exclusion of secondary and spurious hypertension and witnessed drug intake reduced the number of patients with apparent TRH to less than one third, based on qualifying ambulatory BP measurements. The latter true treatment-resistant patients with hypertension were randomized to RDN using the Symplicity Catheter System or clinically adjusted drug treatment guided by noninvasive hemodynamic measurements. The patients who had their antihypertensive medication adjusted had superior BP control compared with the patients who underwent RDN and who had almost unchanged BP. Therefore, we considered it unethical to continue the study after a risk–benefit evaluation of RDN that was without convincing effect on BP in these patients with uncontrolled ambulatory BP and thus high cardiovascular risk. The office BPs of our patients were slightly lower than in the Symplicity HTN-2, the first prospective randomized study, to a large extent because we excluded many patients with high office BP and poor drug adherence. However, we further ensured elevated 24-hour ambulatory BPs in our patients, and therefore, we have shown in the first randomized study ever of patients with elevated ambulatory BP that RDN hardly lowers BP. However, as a consequence thereof, we have not excluded that RDN lowers BP in patients with isolated office hypertension.

When looking at the individual data, the 2 treatment groups clearly split after 3-month and 6-month follow-up. Possibly 2 patients undergoing RDN could be characterized as responders, whereas only 3 patients in the drug-adjusted group remained with elevated BP at 6 months. Thus, we cannot exclude that among true treatment-resistant patients with hypertension there may be a few that respond to RDN. However, our data also suggest that the number of patients with true treatment resistance to drug treatment (true drug resistance) after all is low.

The drug-adjusted group had their antihypertensive medication adjusted according to 2007 European School of Hypertension/European Society of Cardiology hypertension guidelines and guided by impedance cardiography. Impedance cardiography has demonstrated its usefulness and reproducibility during the past years in various populations, including patients with hypertension and coronary artery disease. When the pharmacological class of antihypertensive agent does not correspond to the hemodynamic state, BP reduction is limited, BP fall is delayed, and side effects may occur more frequently. By contrast, when the pharmacological class of antihypertensive treatment is adapted to the hemodynamic state, BP reduction occurs more rapidly and to a greater extent as demonstrated in patients with resistant hypertension and in patients with mild-to-moderate hypertension.

Figure 6. Graph shows ambulatory daytime systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 3-month and 6-month follow-up for renal sympathetic denervation (RDN) and drug-adjusted groups (*P=0.04, ‡P=0.009, ‡‡P=0.02, †P=0.08 between groups).

Figure 7. Graph shows individual ambulatory systolic blood pressures at 3 month and 6 month for renal sympathetic denervation (RDN) and drug-adjusted groups. BP indicates blood pressure.
The Symplicity HTN-2 study comprised 106 patients who were randomized to RDN or control, and office BPs were reduced by 32/12 mm Hg in the intervention group at 6 months and remained unchanged in the control group. However, the Symplicity HTN-2 study put little emphasis on drug adherence, which was investigated by drug diary with no witnessed intake or measured plasma concentrations of the antihypertensive drugs. In another study of 84 patients taking on average 5 antihypertensive drugs, drugs were not detectable in the blood in one third of the patients and close to two third fulfilled the criteria of nonadherence. Patients with poor drug adherence who undergo RDN might be positively influenced by the attention which they get at follow-up and to such an extent that drug adherence may gradually improve and thereby partly explain the BP-lowering effects. This phenomenon, a potential placebo effect, is not controlled for in the randomized design of Symplicity HTN-2 and is the rationale why an ongoing follow-up study in the United States included sham operation. In a press release from Medtronic in the United States, the sponsor of the Symplicity studies, it is stated that HTN-3 did not reach its primary objective at 6 months. The press release is dated on January 9, 2014, whereas our manuscript submission is dated on December 22, 2013. The 2 studies seem to agree that RDN is ineffective in BP lowering. The Symplicity HTN-2 study further put little emphasis on ambulatory BP measurements and a possible white coat effect, which together with a possible placebo effect may contribute to the difference in BP between their study groups. In a large study in 10 European centers, the effect of RDN on lowering office BP and ambulatory BP was less efficient than active drug treatment but better than placebo imputed from a previous trial. The placebo effect can never be dismissed in hypertension research.

Symplicity HTN-2 is a remarkable study in this respect inasmuch as there is apparently no placebo effect in the control group. One single publication of randomized data in support of RDN also opens for chance finding. The data were monitored, collected, and managed by a sponsor with commercial interests, which could possibly be associated with publication bias. Attempts have also been made to artificially inflate the number of patients investigated in other randomized protocols, but this has been criticized. The widespread use of RDN in the clinical routine work of apparent patients with TRH in certain places in Europe is not based on sound evidence, and a leading center on TRH in Germany cannot find BP-lowering effect of RDN. The use of RDN is promoted actively and partly driven by the industry, which includes 6 companies with European CE marking of their catheters and several other companies with development of new devices in the pipeline.

Furthermore, it is well-known that participating in a study and coming to regular controls will improve prognosis, at least partly explained by improved drug adherence. The fact that only a minority of patients with apparent TRH are eligible for RDN has consistently been reported also by other investigators. Suboptimal drug treatment is common in patients apparently resistant to drug treatment. This has recently been investigated thoroughly in the United States and in Europe. Thus, important questions that emerge are when and how should final drug adaptation be performed before patients proceed to RDN? In the present study, we received 65 specialist referrals for RDN, but when further investigated, we excluded as many as 46 patients from eligibility to RDN, partly because they normalized BP after initial improvements of drug therapy or after witnessed intake of medication. Because we were able to improve BP control in almost all the patients who were further randomized to the drug-adjusted group, we may ask whether true resistance to drug treatment really exists in hypertension and whether this undermines the concept of drug resistance in hypertension and indications for invasive procedures including RDN.

The reproducibility of 24-hour BP in patients with hypertension is reasonably high. Based on our previous and current findings with ambulatory BPs for 3 to 6 months after RDN, we think that spurious hypertension or poor drug compliance may be excluded in our patient group. Furthermore, we consider the likelihood of our negative findings being by chance to be negligible. In addition, the possibility of chance finding must be balanced up against the fact that RDN now is performed in many countries on a loose ground. Our results may contribute to guiding further research in this area so that RDN in the future will be performed in people with true TRH who are properly identified. In this way, it will be possible to identify the true responder rate, if any, in future larger and ongoing studies.

Because SBP only changed from 152 to 145 and 142 mm Hg in the RDN group at 3 and 6 months, we found this to be sustained elevated ambulatory SBP with high risk of cardiovascular complications, and we decided to stop enrollment for ethical reasons. We came to this conclusion because we first did an open study and found no effect of RDN on ambulatory SBP through 6 months in patients who qualified by elevated ambulatory SBP after witnessed intake of their medication. Now, we had similar findings in the randomized study with same type of true treatment-resistant patients, which means that overall ambulatory SBP remained clearly elevated 6 months after RDN. In addition, the patients had previous cardiovascular disease and target organ damage as...
indicated in the Table, which also escalated their high risk. The multinational study by Persu et al.,19 which included our first subset of patients,7 suggests that responses to RDN are extremely variable and unpredictable. We now think that when limiting RDN to true treatment-resistant hypertensive people like we did in the our first study7 and in the present study, the responses to RDN become more easy to predict, small, and compatible with placebo.

The strength of our study is the careful identification of patients with TRH. The modest number of patients may be considered as a limitation. However, comparing with Symplicity HTN-2, we have a study size corresponding to ≥20% of all published randomized patients investigating RDN and the patients in our previous7 and present study undergoing RDN show consistent results when applying more thorough methods for patient selection than in the Symplicity HTN-1 and -2 studies.2,35

RDN in patients with hypertension is also hampered by multiple other insufficiencies.6,36–38 but we limit our conclusion to question whether there is a BP-lowering effect beyond the extended placebo effect of this new invasive procedure. Our attitudes, after the randomized evidence, have changed from being positive39 to becoming skeptical40,41 and even critical42 in <2 years. Also European and international recommendations have realized the problems with RDN.43–45 The patients with severe hypertension have multiple worries,46 but they cannot easily be cured by an invasive approach, despite multiple reports on the same cohort.47 With the multiple flaws in the designs of the Symplicity HTN-1 and -2 studies,2,35 as discussed above, we find it likely that sustained differences in BP47 are explained by the same flaws of whom missing control of drug adherence seems to be the most important one.44 In our study, adjusted drug treatment lowers BP through 6 months and at least has the potential for more long-lasting effects.

Perspectives
We did the first ever prospective and randomized comparison of RDN versus clinical drug adjustment in patients with true TRH who qualified by having elevated ambulatory BP after witnessed intake of BP medication. BP control through 6 months was superior by drug adjustment compared with renal denervation. RDN did not cause a meaningful decrease of BP in patients with true TRH and it is in our opinion currently not indicated in routine clinical use.

Disclosures
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References
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Adjusted Drug Treatment is Superior to Renal Sympathetic Denervation in Patients with True Treatment Resistant Hypertension: Expanded Methods

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Short title: Drugs vs. RDN in treatment resistant hypertension

The study is registered with ClinicalTrials.gov with trial identifier NCT01673516.

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Expanded Methods

Procedure for witnessed intake of antihypertensive drugs and subsequent ambulatory BP in order to qualify for the study

Patients were asked to bring their prescribed medication in original packaging to the clinical visit with one of the investigators (F.M.F., A.C.L.). Medication was documented and administered by the investigator and swallowed by the patient under continuous observation, in order to secure the intake of prescribed medication in prescribed doses. Patients were then under the observation by the investigator in order to prohibit throwing up the pills until 24-hour ambulatory BP device had been mounted and tested and clinical examinations had been carried out. Patients stayed in the hospital for 2 hours in order to capture those with potential symptomatic hypotension caused by full intake of medication. Visits with subsequent ambulatory BP measurements were done in the morning and further observation of patients in the hospital was done during daytime working hours.

Procedure for renal denervation

Renal denervation was performed using Symplicity™ Catheter System (Ardian, Mountain View, CA, U.S.A.) by experienced and appropriately trained invasive radiologist (P.H., M.B.). In summary, all procedures were performed by trans-femoral access, using 6 French guide catheters. Prior to ablation, heparin was administered and activated clotting time was kept above 250 s during the procedure. On average 8 (range 6-11) radiofrequency ablations were applied per renal artery. Pain was treated with intravenous analgetics and anxiolytics as needed. All procedures took between 40 and 50 min and were considered successful by interventionists.

Statistical power and study termination

We postulated that the difference between the RDN group and the drug adjustment group would be at least 20 mmHg in office systolic BP favoring the RDN group based on the Symplicity HTN-2 study (2) in which 6-month data showed that office BP in the RDN group dropped by 32/12 mmHg. Twenty seven patients per group would be required to demonstrate a difference of 20 mmHg at an alpha risk of 5% and a beta risk of 20% in a 2-sided t-test, assuming a SD of 13 mmHg. To end up with 27 subjects per group for per protocol analysis we aimed to enroll 60 patients and randomize 30 patients to each group (http://www.clinicaltrials.gov). However, after protocol approval and because we did not see BP lowering effect in our first study of patients who had RDN in an uncontrolled design, we decided to do one interim analysis. In early October 2013 the lead investigator (F.M.F.) had a clinical suspicion of inferior BP lowering effects of RDN, and on October 14, 2013 two of the investigators (F.M.F., S.E.K.) did a data inspection that led to the decision of performing the interim analysis. The decision was immediately reported on clinicaltrials.gov and in a notification to The National Committee for Research Ethics in Norway. On October 22, 2013 the investigators decided to stop inclusion because RDN showed inferior BP lowering effect compared to adjusted drug treatment, and it was considered unethical to continue doing RDN in hypertensive patients with uncontrolled ambulatory BP and previous cardiovascular disease and/or target organ damage. The last 6-months visit was done on December 12, 2013.