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Original research article

Catheter-based renal denervation versus intensified medical treatment in patients with resistant hypertension: Rationale and design of a multicenter randomized study—PRAGUE-15

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ABSTRACT

Catheter-based renal denervation (RDN) was considered as a promising method for treatment of resistant hypertension and was increasingly being used worldwide. However, there are equivocal results from only two randomized trials studying the effect of such intervention. Thus, additional data from properly designed long-term comparative trials are needed. The PRAGUE-15 trial is designed as an open, prospective, randomized multicenter trial comparing RDN versus intensified medical treatment in patients with resistant hypertension. Patients randomized to the medical treatment group will receive spironolactone in the absence of contraindications. The primary endpoint will be changes in systolic and diastolic pressure during ambulatory blood pressure monitoring (ABPM) from baseline to 6 months. Herein, we describe the trial design and methodology. The strengths of the trial include ABPM (as the objective endpoint), independent outcomes assessment, and therapeutic use of spironolactone.

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Introduction

Hypertension is highly prevalent and is the most important risk factor for development of cardiovascular disease and mortality [1,2]. The risk of development of cardiovascular disease is linearly related to both systolic and diastolic blood pressure (BP) [3]. Despite pharmacological advances in the area, effective control of BP remains poor [4,5]. Several factors contribute to this problem. Apart from prescription of inappropriate drugs, inadequate dosing, and non-adherence to treatment, approximately 10–15% of patients are resistant to three or more antihypertensive drugs including diuretics [6]. Recently, catheter-based renal denervation (RDN) has been considered to be a promising method for treatment of patients with resistant hypertension [7]. However, the rapid adoption of the procedure worldwide has been based on the outcome of one small randomized SYMPLICITY HTN-2 trial comparing RDN with antihypertensive treatment [8]. Nevertheless, recently published SYMPLICITY HTN-3 trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after RDN as compared with a sham control [9]. Thus, additional data from properly designed long-term comparative trials can help to establish the role of RDN in comparison to that of optimal drug treatment [6,10]. In the latter context, spironolactone has recently been shown to effectively lower BP in patients with resistant hypertension [11].

Therefore, we designed a multicenter randomized trial comparing the effect of catheter-based RDN versus intensified antihypertensive treatment (including use of antagonists of mineralocorticoid receptors) in patients with confirmed resistant hypertension.

PRAGUE-15 study design

The PRAGUE-15 study was designed as an academic, investigator-initiated, open, prospective, multicenter randomized trial (clinicaltrial.gov identifier: NCT 01560312). Patients with resistant hypertension were randomized (in a 1:1 ratio) to either catheter-based RDN plus optimal antihypertensive treatment (unchanged after randomization and without treatment with spironolactone) or optimal antihypertensive treatment (including spironolactone in all patients if not contraindicated after randomization). Three centers in the Czech Republic anticipated to enroll 120 patients. The study has been approved by a multicenter ethics committee and by all three local institutional ethics committees.

The inclusion and exclusion criteria are shown in Table 1. During screening, resistant hypertension had to be confirmed both by office BP measurement and 24-h ABPM. All patients were examined in a hypertension center to exclude most common forms of secondary hypertension (e.g., primary aldosteronism, pheochromocytoma, Cushing's syndrome, renal parenchymal disease, renovascular hypertension, drug-induced hypertension, and other conditions). Primary aldosteronism was diagnosed on the basis of an elevated serum aldosterone:renin ratio and failure to suppress aldosterone secretion after saline infusion, in line with accepted guidelines for diagnosis and treatment of primary aldosteronism [12]. For patients previously treated with spironolactone, randomization was performed 3–4 weeks after spironolactone withdrawal if all other criteria are met. Patients with known clear contraindications to spironolactone treatment during the screening period did not enter the study. Adherence to treatment was tested in all patients by unannounced quantitative measurements of plasma drug levels during the screening period before the randomization. Absence of at least one prescribed antihypertensive agent indicated that a patient was non-compliant, and that patient was then excluded from the study. Sampling was conducted at least 3 h after planned drug intake, during the expected half-life of the drug [13]. Liquid chromatography–dual mass spectrometry (LC/MS/MS) [14] was performed using a 3200 Q-trap triple quadrupole/linear ion trap mass spectrometer fitted with a TurboIonSpray source (MDS Sciex, Ontario, Canada). A rapid and sensitive LC/MS/MS method for simultaneous determination of doxazosine and verapamil in human serum has been developed in our toxicology laboratory [15]. Renal anatomy was evaluated during screening using CT or MR angiography.

Table 1 – Inclusion and exclusion criteria.

Inclusion criteria
- Resistant hypertension with office systolic blood pressure of >140 mmHg
- Systolic blood pressure of >130 mmHg during 24-h ambulatory blood pressure monitoring
- Treatment with at least three antihypertensive medications, including diuretics, at optimal doses
- Age of >18 years
- Signed informed consent

Exclusion criteria
- Any secondary form of hypertension
- Non-compliance with medical treatment
- Presence of any chronic renal disease (serum creatinine level of >200 μmol/l)
- Pregnancy
- History of myocardial infarction or stroke in the previous 6 months
- Presence of severe valvular stenotic disease
- Anatomical abnormality or a variant structure of either renal artery, including aneurysm, stenosis, a reference diameter of <4 mm, and a length of <20 mm
- An increased bleeding risk (thrombocytopenia of <50,000 platelets/μl of blood and an INR of >1.5)

The differences in systolic and diastolic BP recorded by 24-h ABPM between baseline and 6 months post-randomization is the primary endpoint of the study. Secondary endpoints include differences in systolic and diastolic BP recoded by ABPM and in the office between baseline and 1 year, 2 years, and 3 years post-randomization, as well as changes in standard clinical and laboratory parameters including renal function and post-denervation renal anatomy analyzed using CT or MR angiography 1 year after trial commencement. Another secondary endpoint is the effect of RDN on the medically treated group and the effect of spironolactone in the RDN group 1 year after randomization of patients exhibiting poor BP control.

Renal denervation procedures were performed using the Symplicity Renal Denervation System (Medtronic Inc., Mountain View, CA). Treatment involved at least four applications of

low-power (8-W) radiofrequency energy to each renal artery. Each treatment was delivered in a helical fashion within the artery via rotation of the catheter, and the pullback between ablations was approximately 5 mm.

After randomization, patients selected for RDN are maintaining on baseline medical therapy for 1 year. Patients selected for intensified medical treatment receive baseline medical therapy and spironolactone (25 mg daily) if no contraindication is evident. One year after randomization, patients in the medical treatment group may elect to undergo the RDN procedure after consultation with physicians and formation of informed preferences based on BP level. Similarly, spironolactone treatment may be commenced after 1 year in the RDN group if BP does not attain target levels. The precise design of the study is shown in Fig. 1. Changes in baseline pharmacological therapy were allowed only for important clinical reasons.

For power calculation of the final sample size of the study, the treatment response in each group was defined as a >5-mmHg decrease in the systolic and diastolic BP during 24-h ABPM between baseline and 6 months post-randomization (both BP compounds must be decreased to assign responders). We assumed 60% responders in the RDN group and 30% responders in the group with intensified medical treatment based on existing data [11,16,17]. A total of 112 patients (56 patients in each group) were thus needed to attain 90% power to demonstrate differences between groups at a two-sided alpha level of 0.05. If anticipated that approximately 5% of patients will prematurely withdraw from the study or become lost to follow-up, a total of 120 patients were needed to be randomized.

Nevertheless, the study was prematurely terminated on February 10, 2014. After the announcement that SYMPLICITY HTN-3 failed to meet its primary efficacy endpoint, we firstly suspended the study on January 10, 2014 and we subsequently performed the analysis of actual data of 106 enrolled patients. Based on the results of this analysis, we decided definitely to terminate the study.

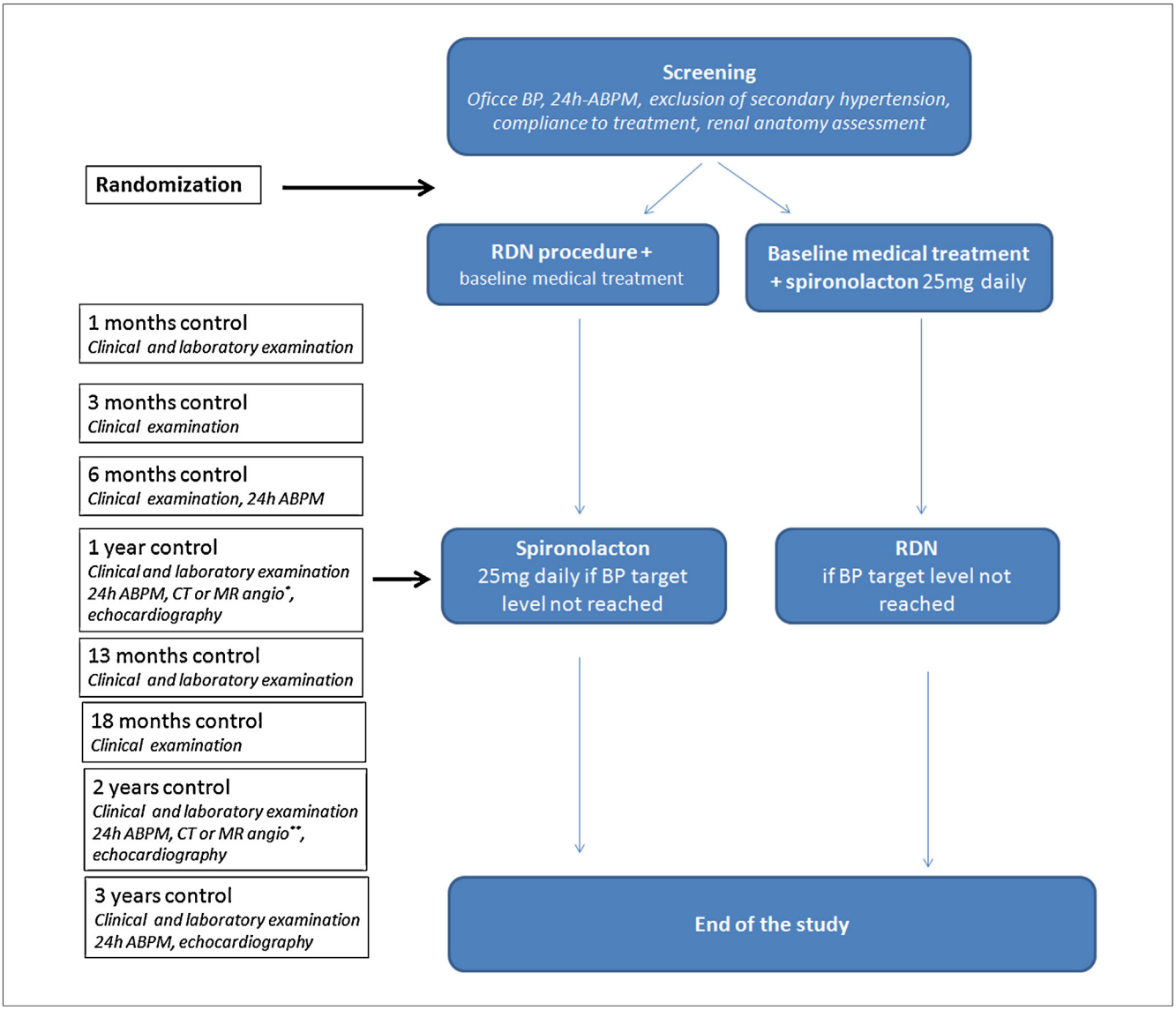

Fig. 1 – Design of the PRAGUE-15 study.

Discussion

The study was developed to assess the utility of catheter-based RDN in a setting of ''truly'' resistant hypertension when intensified combination antihypertensive therapy is used. Several differences are evident between the methodology of the present trial and those of previous trials that studied the utility of RDN in treatment of resistant hypertension [8,18–20].

First, 24-h ABPM data were required for diagnosis of resistant hypertension and for evaluation of the primary endpoint. To date, information on lowering BP after performance of the RDN procedure in published trials have been mainly based on office BP measurements. However, available data from the ABPM show remarkably lower effect on BP reduction [16,21,22]. Further, ABPM is, in general, a more sensitive predictor of the risk of adverse clinical cardiovascular outcomes than is office BP [6]. SYMPLICITY HTN-3 trial assessed the comparison of mean systolic 24-h ABPM change from baseline to 6 months in RDN and control arm as powered secondary effectiveness endpoint [9]. In our study, the primary endpoint is the differences in both systolic and diastolic BP recorded by 24-h ABPM between baseline and 6 months post-randomization.

Second, evaluation of adherence to treatment is an important feature of our study. Plasma drug levels were measured. This was not performed in any prior study evaluating the effect of RDN on resistant hypertension. Changes in treatment compliance before and after RDN may have a considerable effect on BP.

Third, it has recently been shown that spironolactone safely and effectively reduces BP in truly resistant hypertensive patients [11,17]. The drug is now often prescribed by specialists when the target BP cannot be achieved using combinations of three or four antihypertensive drugs. Therefore, we decided to add spironolactone as a baseline antihypertensive treatment for patients randomized to the medical treatment group. Further, the effect of spironolactone in those who do not respond to RDN was evaluated 1 year after randomization as will the effect of RDN on those receiving drugs including spironolactone.

A limitation of the study was that the power calculation was based on limited data regarding changes in 24-h ABMP [11,16,17]. Furthermore, the calculation of the efficacy of the primary endpoint was based on BP changes in individuals in contrast with the average BP changes used in power calculation in the SYMPLICITY HTN-3 trial [23]. We are also defining a treatment response as a decrease in both systolic and diastolic BP because cardiovascular events are linearly related to both systolic and diastolic BP [3,24]. Even though the study was prematurely terminated, the number of enrolled patients almost reached the planned study size and is thus the second-third largest randomized study on renal denervation - the patients number is (just by chance) exactly the same as in SYMPLICITY HTN-2 trial.

Conflict of interest

All authors declare that they have no conflict of interest to disclose.

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Ethical statement

Hereby we state, that the research was done according to ethical standards.

Informed consent

Hereby we state that patients enrolled to the study agreed to participate in the research and signed the informed consent allowed by ethical committees.

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