Resistant Hypertension: consequences and treatment options

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Resistant Hypertension: consequences and treatment options

Resistente hypertensie: gevolgen en behandelingsmogelijkheden

(met een samenvatting in het Nederlands)

Proefschrift

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CHAPTER 1

Introduction

Background

Sympathethic nerve activity and hypertension

Pathophysiology

In the adventitia of the renal arteries, sympathetic nerve fibers run from the spinal cord to the kidneys. Efferent fibers have been shown to innervate the afferent and efferent glomerular arterioles, proximal and distal renal tubules, thick ascending limb of Henle's loop and juxtaglomerular apparatus.(1) These fibers use norepinephrine as their neurotransmitter. The effect of these efferent fibers depends on the level of activity. At the lowest level, renal renin secretion is increased by activation of β1-adrenergic receptors in the juxtaglomerular granular cells. With increase of nerve activity, urinary sodium excretion is decreased by a stimulating effect on sodium reabsorption by tubular epithelial cells through α1B-adrenergic receptors located there. At a higher level, renal blood flow is decreased by a vasoconstrictive response to stimulation of α1A-receptors in the intrarenal vasculature. At this point, glomerular filtration rate decreases in parallel.(2) All of these responses increase blood pressure both through volume expansion and activation of the renin-angiotensin-aldosterone system (RAAS). Afferent nerve fibers include mechanosensory fibers located in the renal pelvic wall responding to stretch when pelvic pressure is increased, and chemoreceptor fibers responding to various stimuli, for example decrease in nitric oxide due to reduced nitric oxide synthase activity or kidney ischemia. Whereas the former have an inhibitory effect on efferent sympathetic activity, the latter were shown to increase the cerebral sympathetic output.(3-5) Substance P and calcitonin gene related peptide are the neurotransmitters of the afferent sympathetic fibers. Evidence suggests that in hypertension, inhibitory afferent activity is suppressed and excitatory afferent activity increased. Diseased (ischemic) kidneys are an important source of increased activating afferent activity.(6) Efferent sympathetic activity also increases blood pressure through vasoconstriction and increase of cardiac contractility and rate.(7) Figure 1 summarizes the pathways connecting sympathetic activity and hypertension.(8)

Measurement

The activity of the sympathetic nervous system cannot be measured easily in humans. Several methods have been developed in the past but each have their drawbacks.(9) Measurement of plasma norepinephrine (NE) has limited reproducibility (even with multiple samples taken) and sensitivity.(10) Plasma norephinephrine is a measure of the neurotransmitter secreted by the sympathetic

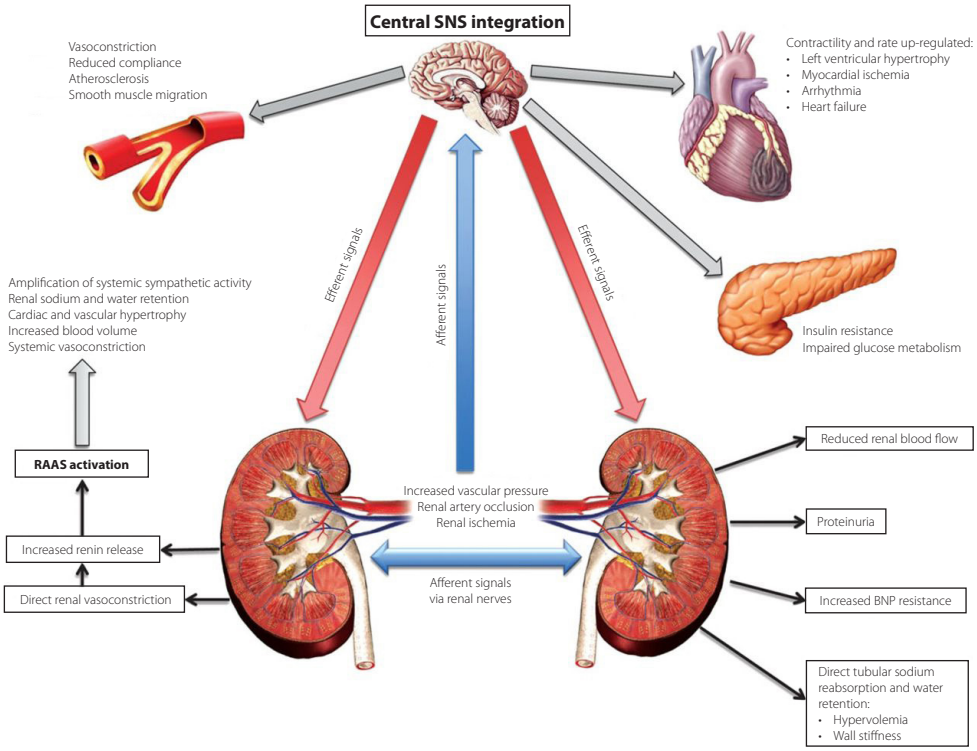

Figure 1 Sympathetic activity and hypertension
Abbreviations: SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system.
Reprinted with permission from Myat et al.(8)

neurons but represents only a small fraction (5-10%) of secreted NE and is also dependent on tissue clearance and reuptake processes.(11)

Microneurography can be used to directly record efferent post-ganglionic sympathetic nerve activity to the skeletal muscle circulation (MSNA). A microelectrode is inserted in a peripheral nerve (peroneal or brachial) and spontaneous bursts are recorded as bursts over time and bursts corrected for heart rate. It provides a dynamic assessment as responses to stimuli are instantaneously seen. Reproducibility is excellent both when measuring different nerve sites and when repeating measurements over time. A major drawback is that this method is strictly laboratory-bound, invasive and complex and it measures only sympathetic activity in the muscle or skin microcirculation. Whereas the microneurography used commonly measures multi-fiber discharge, measuring single-fiber discharge is also possible.(12) With the disadvantage of being even more complicated, the main advantage is that selecting a fiber with vasoconstrictive properties is possible.

Spillover techniques measure the NE appearance rate in plasma and can be applied both in the whole body and in a specific organ (regional NE spill over). With this isotope dilution technique, radiolabeled NE is infused and the regional extraction determined. The difference of regional venous and arterial plasma NE (obtained by regional catheterization) can then be corrected for the amount of NE that is extracted by the organ thus providing the local secretion of NE. MSNA relates closely to cardiac and renal NE spillover in healthy subjects.(9) However, norepinephrine spillover measurement has very limited availability and neither the spillover technique or MSNA is applicable in the clinical setting.

Evidence for sympathetic hyperactivity in hypertension and chronic kidney disease

Early studies on the role of sympathetic hyperactivity in the pathogenesis of hypertension used measurement of plasma catecholamines. Although plasma norephinephrine was higher in hypertensives than in normotensive subjects in the majority of studies (especially in younger subjects), a significant difference was found in only 39%, due to a small between group difference in combination with a large standard deviation.(13) In the 1990s, the role of sympathetic hyperactivity was proven by studies using better methods for measuring sympathetic activity. Sympathetic hyperactivity was shown to occur in hypertensives as shown by an increased total body and regional NE spillover (14;15) and by using MSNA in borderline and mild young hypertensives.(16-18) MSNA was also shown to increase in successive stages of hypertension and to be low in secondary hypertension. (19) MSNA increases with age and is higher in hypertensives versus normotensives in all age groups.(20) In NE spillover studies in hypertension, sympathetic activity in the heart, kidney and muscle is increased in hypertensives whereas the skin activity is not.(14;21) MSNA is higher in white coat hypertension as compared with normotension, and in absence of nocturnal decrease in blood pressure (non-dipping pattern).(22)

The role of the sympathetic system has also been investigated in hypertension in chronic kidney disease patients. Sympathetic activity measured by MSNA is increased in hemodialysis patients.(23;24) Even if kidney function greatly improves after kidney transplantation, sympathetic activity does not decline as long as the diseased native kidneys are in situ.(24) Correspondingly, nephrectomy decreases sympathetic hyperactivity in hemodialysis patients.(23) In hypertensive patients with less severe chronic kidney disease sympathetic activity is increased as well. MSNA was shown to be related to mean arterial pressure in CKD patients.(25) In hypertensive CKD patients, decrease of the estimated glomerular filtration rate

(eGFR) relates to progressive increase in MSNA.(26) Comparison of the response of the sympathetic nervous system to changes in extracellular volume in CKD patients versus healthy controls showed a parallel response at a higher level of MSNA.(27)

Effects of conventional therapy

Several pharmacological and lifestyle interventions affect sympathetic activity. In general, renin-angiotensin-aldosterone system (RAAS) inhibitors decrease sympathetic activity, shown in CKD, (28-30) in obese patients with hypertension,(31) and in heart failure.(32-37) In patients with essential hypertension evidence for a sympathetic activity lowering effect of ARBs has been more equivocal.(38;39) Both direct and indirect interactions between the RAAS and the sympathetic nerve system exist. In the kidneys, angiotensin facilitates the release of norepinephrine from the efferent sympathetic fibers resulting in a greater effect of sympathetic hyperactivity in the presence of angiotensin in rodent models. However, this effect has not been shown in conscious dogs nor humans. In the brain, angiotensin receptors are present in regions in the forebrain and brainstem involved in the regulation of efferent sympathetic nerve activity. Via those receptors, chronically increased angiotensin increases peripheral sympathetic activity.(40) On average, chronic treatment with RAAS inhibitors lowers but does not normalize sympathetic activity in CKD patients.(29) Normalization occurred when moxonidine was added to ARB treatment.(41) The effect of beta blockade on sympathetic outflow as measured with MSNA is more complex since long term treatment decreases the bursts/min whereas bursts/100 heartbeats remain stable in parallel with the decreased heart rate on beta blockade treatment.(42;43) Non selective betablockage with carvedilol has been shown to reduce both total body and cardiac NE spillover.(44) Calcium channel blockers (CCBs) increase sympathetic activity in most studies.(28;45;46) Sustained use of amlodipine has been shown to increase sympathetic activity in CKD patients.(28;47) Differences in sympathetic activation may exist between CCBs.(48) Dietary salt restriction, although having a beneficial effect on blood pressure, has been shown to increase MSNA.(49;50) Similarly, the thiazide diuretic chlorthalidone has been shown to increase sympathetic activity, whereas the aldosterone antagonist spironolactone had no effect on MSNA in the same study, despite a similar reduction of blood pressure.(51) A subsequent study showed that addition of spironolactone to chlorthalidone neutralizes the chlorthalidone induced increase in MSNA.(52) Another major lifestyle intervention in hypertension, weight reduction, has been shown to reduce MSNA in obese patients.(53;54) Regular exercise, which has an important blood pressure lowering effect,(55) has been shown to decrease sympathetic activity as well.(56;57)

In summary, while moxonidine, RAAS inhibitors and beta blockade reduce sympathetic hyperactivity, calcium antagonists and thiazide diuretics seem to increase sympathetic drive. Salt restriction increases, whereas weight reduction and regular exercise decrease sympathetic activity.

Renal denervation the procedure

Patient selection: resistant hypertension

In the Utrecht University Medical Center, patients with apparent resistant hypertension, that is an office blood pressure ≥140/90 mm Hg while being prescribed three or more antihypertensive drugs from different drug classes, including a diuretic, undergo systematic screening when renal denervation is considered. As perceived side effects are a frequent cause of insufficient treatment of hypertension, patients can also be considered if blood pressure fulfils the criteria but treatment is with less than three drugs because of intolerance to at least two of the four major antihypertensive drug classes (ACEi/ARB, diuretics, beta blockade, calcium channel blockade). If considered safe, antihypertensive drugs are temporarily stopped to obtain renin activity, aldosterone and metanephrine results without infering by these drugs. If clinically necessary, rescue medication is prescribed. Hyperaldosteronism and pheochromocytoma as a cause of resistant hypertension are thus excluded, and white coat (office only) hypertension is excluded by ambulatory blood pressure measurement. Next, CT or MRI scanning is performed to confirm accessibility of the renal arteries for the intervention and to exclude significant renal artery stenosis as a cause of the resistant hypertension. All patients are discussed in a multidisciplinary team meeting, attended by nephrologists, vascular medicine specialists, an interventional radiologist and an interventional cardiologist. If renal denervation is deemed indicated, the intervention is planned and informed consent asked for participation in one of the renal denervation studies. As described earlier, many patients are advised against renal denervation based on results from this work-up, mainly because of not fulfilling the blood pressure criteria or for finding a form of secondary hypertension indicating a different treatment.(58)

Percutaneous renal denervation

The renal denervation procedure is performed by an interventionalist, either a radiologist or a cardiologist, experienced in angiographic procedures. The femoral artery is accessed and a guiding wire is introduced into the renal arteries.

Unfractionated heparin is administered and renal artery anatomy confirmed by angiography. Then, the treatment catheter is inserted and renal denervation performed in each renal artery complying with the instructions of the manufacturer. For the Symplicity Flex catheter, used in most cases in SYMPATHY, the tip of the catheter is positioned against the renal artery wall in the distal and proximal artery and in all four quadrants of the circumference of the artery, followed by radiofrequency ablation through energy (8W) controlled by the generator. Figure 2 shows a catheter in place for the procedure. Pain and discomfort are managed by analgesics and sedatives administered intravenously during the procedure by a nurse anesthesist. Newer designs of renal denervation catheters can apply energy on several, circumferentially placed, electrodes simultaneously, as shown in figure 2 for the Symplicity Spyral catheter. After the target number of ablations

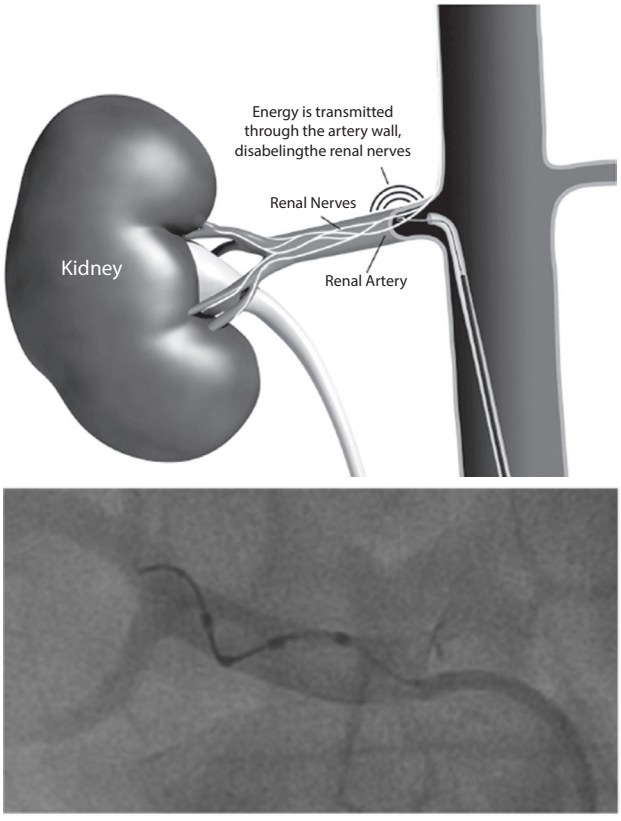

Figure 2 Renal denervation catheter in place.
Reprinted from: Schlaich et al.(64) (upper) and Kandzari et al.(65) (lower).

(preferably ≥6 ablations per side) is reached and the whole length of the artery treated, the catheter is removed and routine care of the groin after angiography applied. Patients stay in the hospital overnight and if no complications arise, are discharged the next morning.

Effects on sympathetic activity

The original proof-of-concept case report on percutaneous renal denervation for resistant hypertension contained a description of reduced renal and whole body norepinephrine spill over and reduced MSNA after the procedure.(59) The clinical studies thereafter however, did only seldomly include such direct proof of reduction of sympathetic drive, probably due to the complicated methods needed. For norepinephrine spill over, small human cohort studies have confirmed reduction by RDN, although with a great variability in the magnitude of the decrease achieved.(60) For MSNA, reports have been more diverse, with the largest being equally positive in showing reduction after RDN (61;62) but a small series in Utrecht not confirming these results.(63) To note: MSNA will only be affected by reduction of (the activity of) afferent nerve fibers along the renal arteries as it does not, like NE spillover techniques, measure efferent activity to the kidneys.

Research questions

At the beginning of the PhD project, the existence of the group of patients with resistant hypertension had just been rediscovered and the definition used was new. Little was known on the magnitude and risks of the phenomenon. We therefore started with investigating prevalence, clinical characteristics and associated risks in well-defined study populations of patients with CKD and those with a history of cardiovascular disease. Furthermore, promising results had been published on the effect of renal denervation on blood pressure in patients with resistant hypertension, but only a small randomized controlled trial had been reported. Although several antihypertensive drugs and lifestyle changes recommended in hypertension can lower sympathetic activity, an intervention directly aimed at this part of the pathophysiology of hypertension could be an important addition to the therapeutic options in hypertension. The SYMPATHY Dutch multi-center study was designed to answer many questions on the usefulness of RDN for treatment of hypertension. Special emphasis was on the effect of RDN in patients with CKD. The evidence from animal studies and pathophysiological background behind the hypothesis that patients with CKD might be a group with greater benefit of RDN was reviewed. Lastly, the finding that the renal denervation procedure evokes significant

pain during the ablations, necessitating use of intravenously administered opioid analgesics, lead to the hypothesis that RDN might be beneficial for patients with kidney-related pain.

Outline of the thesis

In the first part of this thesis, resistant hypertension is investigated in patients with chronic kidney disease in **chapter 2** and in those with a history of cardiovascular disease in **chapters 3 and 4**. Prevalence and clinical characteristics of these patients are studied, and associated cardiovascular and renal risks assessed. The second part focusses on renal denervation as a treatment option in resistant hypertension and in kidney related pain. In the first subsection, **chapter 5** reviews the reasons for special interest in renal denervation for nephrologists treating patients with chronic kidney disease. **Chapter 6** contains the rationale and design of the SYMPATHY trial on renal denervation for resistant hypertension, and **chapter 7** its main results. **Chapter 8** is on the effect of dietary sodium intake on the effect of RDN, and contains an exploratory analysis on changes in salt sensitivity after RDN. In the second subsection of part two, renal denervation is explored as a treatment option for kidney related pain. **Chapter 9** is an editorial that accompanied an early case report on RDN for pain in loin pain hematuria syndrome. A series of patients with either loin pain hematuria syndrome or polycystic kidney disease treated for pain is described in **chapter 10**. General discussion and summary of the findings are in **chapters 11 and 12**.

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CHAPTER 2

Prevalence of apparent therapy-resistant hypertension and its effect on outcome in patients with chronic kidney disease

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Abstract

New options recently became available for treatment of uncontrolled blood pressure. Information on the prevalence of therapy-resistant hypertension (TRH) in patients with chronic kidney disease and its consequences is relevant to balance risks and benefits of potential new therapies. Data of 788 patients with chronic kidney disease came from a multicenter study investigating the effect on outcome of an integrated multifactorial approach delivered by nurse practitioners added to usual care versus usual care alone. Blood pressure was measured at the office and during 30 minutes using an automated oscillometric device. Apparent therapy-resistant hypertension (aTRH) was defined as a blood pressure ≥ 130/80 mm Hg despite treatment with ≥3 antihypertensive drugs including a diuretic or treatment with ≥4 antihypertensive drugs. Participants were followed up for the occurrence of myocardial infarction, stroke or cardiovascular mortality (composite cardiovascular end point), and end-stage renal disease.

aTRH was present in 34% (office blood pressure) and in 32% (automated measurements). During 5.3 years of follow-up, 17% of patients with aTRH reached a cardiovascular end point and 27% reached end-stage renal disease. aTRH lead to a 1.5-fold higher risk (95% confidence interval 0.8-3.0) of a cardiovascular end point compared with controlled hypertensives in multivariable-adjusted analysis. aTRH increased end stage renal disease risk 2.3-fold (95% confidence interval 1.4-3.7). During 4 years of follow-up, the prevalence of aTRH did not decline in either treatment group. The prevalence of aTRH is high in patients with chronic kidney disease even after optimization of nephrologist care. The presence of aTRH is related to a substantially increased risk of renal and cardiovascular outcomes.

Hypertension is present in a vast majority of patients with chronic kidney disease (CKD) and is related to both cardiovascular disease (CVD) and progression of kidney failure. Awareness of the presence of hypertension is high in patients with CKD and guidelines emphasize the importance of blood pressure (BP) control.(1-3) In the past years, the concept of therapy-resistant hypertension (TRH), defined as uncontrolled high BP while using ≥3 antihypertensive drugs preferably including a diuretic or treatment with ≥4 antihypertensive drugs, has emerged with a prevalence of ~10% in the general hypertensive population.(4) One would expect a higher prevalence in the CKD patient group. To date, little is known on this topic.(5;6) Moreover, new therapeutic options have emerged (renal sympathetic denervation and carotid barostimulation) for those difficult to treat. We aimed to study the prevalence of TRH in patients with CKD. Secondly, we set out to assess the relationship with cardiovascular- and kidney-related outcomes. This may be of importance for balancing risk and benefit when thinking of using new therapies. Finally, so-called therapy-resistant hypertension sometimes merely is regarded as "undertreated hypertension".(7;8) Therefore, we studied whether the prevalence of TRH declines after several years of close follow-up.

Methods

Study design

MASTERPLAN (Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners) was a randomized controlled trial performed at the nephrology departments of 9 hospitals in the Netherlands from 2004 to 2010. Participating hospitals were teaching hospitals delivering the full range of nephrology treatment including hemodialysis and peritoneal dialysis. Three hospitals were tertiary care university hospitals running kidney transplantation programs. Design, rationale and main findings of the study have been described in detail previously.(9-11) In short, CKD patients with an estimated creatinine clearance of 20 to 70 ml/min per 1.73m^2 aged ≥18 years were included. Patients were randomized to a multifactorial approach for risk factor management by a nurse practitioner added to nephrologist care or to usual care by a nephrologist alone. In both groups, treatment goals were according to prevailing guidelines on cardiovascular risk management in CKD.(3;12) For blood pressure, the treatment goal was ≤130/85 mm Hg or ≤125/75 mm Hg in patients with proteinuria of ≥1 g per day. The multifactorial approach by the nurse

practitioners consisted of motivational interviewing for lifestyle changes (physical activity, smoking cessation and dietary advice including salt restriction and weight reduction), medication adjustments aimed at the target values in the guidelines and prescription of standard cardioprotective medication (statin, low dose aspirin and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker). The nurse practitioners were supervised by the nephrologist. In the reference group, usual care was delivered by the nephrologist.(9)

At baseline, information on medical history, lifestyle factors and medication use was obtained by questionnaire. Blood and urine samples were obtained including 24-hour urine collection in which proteinuria or albuminuria was measured depending on the presence of overt proteinuria in a spot urine sample. Albuminuria was converted to a value for proteinuria using the approach applied by the Chronic Kidney Disease Prognosis Consortium (ie, by multiplying albuminuria by 1.5).(13) Proteinuria was measured in 587 patients; reported proteinuria was based on albuminuria measurement in 207 patients (159 with only albuminuria available and 48 in which the converted value was higher than measured proteinuria). Blood pressure was measured in the office (BP was recorded twice after 5 minutes of rest with at least 15 s between measurements with the mean taken as the office BP unless a difference of >5 mm Hg was found, in which case remeasurement was done) and during 30 minutes in the supine position using a noninvasive automated oscillometric device (BP was recorded every 3 minutes, the mean of the last 5 measurements was taken). For details on the devices used we refer to a previous publication of the MASTERPLAN study group.(14) Patients were followed up for 5 years. In the intervention group, visits were at least once every 3 months and more often if considered indicated by the nurse practitioners. In the reference group, a more extensive follow-up visit was scheduled yearly and the frequency of outpatient follow-up was to the discretion of the nephrologist, thus representing usual care. During follow-up, information on medication use, office BP and laboratory values was collected in both groups.

For the present analyses, we used baseline office and automated device BP measurements and antihypertensive medication use for determination of the prevalence of apparent therapy-resistant hypertension (aTRH). The current treatment goal for hypertension in patients with CKD was used for defining uncontrolled BP (1). Definition of aTRH was systolic BP ≥ 130 mm Hg or diastolic BP ≥ 80 mm Hg despite prescription of ≥3 antihypertensive agents, including a diuretic or treatment with ≥4 antihypertensive drugs. Uncontrolled BP was defined as systolic BP ≥ 130 mm Hg or diastolic BP ≥ 80 mm Hg while using <3 antihypertensive drugs or 3 drugs not including a diuretic. Controlled BP

was defined as an office systolic BP <130 mm Hg and diastolic BP <80 mm Hg, while using <4 antihypertensive drugs. Kidney transplant recipients were also evaluated separately for the prevalence of aTRH. Thereafter, the prevalence of aTRH was determined in the intervention and reference groups after 2 and 4 years of follow-up. These prevalences were based on office BP measurements. As additional information, a less stringent definition of aTRH at BP ≥140/90 mm Hg while using ≥3 antihypertensive drugs was investigated (data supplement).

Endpoints

The primary outcome was a composite of myocardial infarction, ischemic stroke and cardiovascular disease mortality as described previously.(10) In short, during the follow-up in the study, all events were adjudicated by an independent committee. Myocardial infarction was defined as acute chest pain or tightness, accompanied by evident and lasting new ischemic changes on an ECG or an established rise and fall pattern of cardiac enzymes. Ischemic stroke was defined as characteristic clinical symptoms and evidence of recent cerebral ischemia on imaging (computed tomography or magnetic resonance imaging). Cardiovascular mortality was defined as death caused by myocardial infarction, stroke, ruptured abdominal aneurysm, terminal heart failure or sudden death. Regular trial follow-up ended July 2010. After completion of the trial an extension of the study was started. Follow-up in this study ended August 2011. These events were registered in routine patient care and were not evaluated by the event adjudication committee. Kidney replacement therapy defined as initiation of chronic dialysis or kidney transplantation was a secondary end point in the original study. In a previous secondary analysis, a composite renal end point of death, end-stage renal disease (ESRD), and 50% increase of serum creatinine was used.(11)

Statistical analyses

Backward stepwise logistic regression was used to identify factors associated with the presence of aTRH at baseline (p <0.15). Cox proportional hazards models were used to estimate hazards ratios (HRs) and corresponding 95% confidence intervals (CIs) for aTRH and uncontrolled hypertension at baseline when compared with controlled hypertension for the composite cardiovascular end point, the composite renal end point, ESRD, and all-cause mortality. Adjustments for confounders were made in various models.

Differences in prevalence of aTRH between the 2 treatment arms during the follow-up period were estimated with the use of linear mixed models (generalized estimating equations). The main assumption of the generalized estimating equation approach is that measurements are dependent within subjects and independent

between subjects. The correlation matrix that represented the within-subject dependencies was estimated using an autoregressive relationship (ie, correlation between variables within subjects is assumed to decline with time between the measurements). The link function used was logit. For the current analysis, the interest was in the mean difference over time in prevalence of aTRH between treatment arms. Generalized estimating equation analyses were performed using the on trial measurements with adjustments for baseline measurements, including systolic BP. All *p* values were two-sided, and *p* values ≤0.05 were considered to indicate statistical significance. No adjustment for multiple statistical testing was made.(15;16)

Results

Prevalence

BP was uncontrolled, which is ≥130/80 mm Hg at office measurement, in 76% of the 788 patients with CKD included. Almost half (45%) of these patients met the definition of aTRH (34% of the study population). With automated BP measurement, 32% of the patients had aTRH whereas 66% had uncontrolled BP (≥130 mm Hg systolic and/or ≥80 mm Hg diastolic). Patients with uncontrolled BP or aTRH were more likely to be men, more often had a history of vascular disease or diabetes mellitus, and were older than subjects with controlled BP (table 1). Below 45 years of age, prevalence of aTRH was 20% in men and 24% in women. In those aged 45 to 59 years and 60 to 74 years, the prevalence was 32% and 40%, respectively (table 2). Mean estimated glomerular filtration rate (eGFR) was 38 ± 15 ml/min per 1.73m^2 for the whole group. eGFR was comparable in the different BP groups (table 1). The use of antihypertensive medication according to control of hypertension is shown in table 3. Kidney transplant recipients (n=110) had similar control of BP: 74% had uncontrolled BP and 31% had aTRH based on office measurements. For automated measurements, the corresponding values were 62% for uncontrolled BP and 28% for aTRH.

Table 1 Patient characteristics in blood pressure control groups

		Controlled blood pressure	Uncontrolled blood pressure	Therapy-resistant hypertension
Clinical data		n=156 (20%)	n=363 (46%)	n=269 (34%)
Patient characteristics				
Sex (male)		90 (58%)	258 (71%)	187 (70%)
Age (years)		54 ± 16	60 ± 12	61 ± 12
Race (white)		148 (95%)	332 (92%)	245 (91%)
Kidney transplant		27 (17%)	49 (14%)	34 (13%)
Diabetes mellitus		25 (16%)	75 (21%)	93 (35%)
History of vascular disease		31 (20%)	97 (27%)	104 (39%)
BMI		26 ± 5	27 ± 4	28 ± 5
Current smoking		35 (23%)	66 (18%)	65 (25%)
Adherence to guidelines for physical exercise (yes)		70 (46%)	214 (60%)	167 (64%)
History of smoking (pack years)*		5 (0-11)	6 (0-13)	6 (0-13)
Blood pressure				
Office SBP (mm Hg)		115 ± 10	143 ± 17	146 ± 22
Office DBP (mm Hg)		69 ± 7	83 ± 10	82 ± 12
Pulse pressure		46 ± 9	59 ± 18	64 ± 19
Automated measurement SBP (mm Hg)		116 ± 11	138 ± 18	143 ± 21
Automated measurement DBP (mm Hg)		70 ± 8	81 ± 10	79 ± 11
Laboratory results				
eGFR (ml/min per 1.73m^2)		38 ± 15	40 ± 15	36 ± 14
eGFR category (ml/min per 1.73m^2)	< 15	2 (1%)	8 (2%)	12 (5%)
	15-30	46 (30%)	104 (29%)	88 (33%)
	30-45	67 (43%)	128 (35%)	98 (36%)
	45-60	29 (19%)	82 (23%)	55 (20%)
	60-75	9 (6%)	34 (9%)	15 (6%)
	>75	3 (2%)	7 (2%)	1 (0%)
Urinary protein excretion (g/24h)*		0.2 (0.1-0.6)	0.2 (0.1-0.8)	0.3 (0.1-0.8)
Urinary sodium excretion (mmol/24h)*		140 (103-170)	150 (117-191)	157 (117-199)
Events				
Composite cardiovascular end point		12 (7.7%)	39 (10.7%)	45 (16.7%)
Composite renal end point		63 (40.4%)	178 (49.0%)	147 (54.6%)
ESRD		27 (17.3%)	67 (18.5%)	72 (26.8%)
All-cause mortality		15 (9.6%)	65 (17.9%)	63 (23.4%)

Numbers are expressed as means with standard deviations or proportions as appropriate.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; DBP, diastolic blood pressure ; ESRD, end-stage renal disease; SBP, systolic blood pressure
*Variables that lack normality are expressed as medians with 25-75% range.
Controlled blood pressure: <130/80 mm Hg <4 antihypertensives
Uncontrolled blood pressure: >130/80 mm Hg; <3 antihypertensives or <4 antihypertensives without diuretic
Therapy-resistant hypertension: >130/80 mm Hg ≥3 antihypertensives including diuretic or ≥4 antihypertensives

Table 2 Sex-specific prevalence of therapy resistant hypertension in different age groups

Age	<45 years			45-59 years			60-74 years			>75 years		
	n	TRH	95% CI	n	TRH	95% CI	n	TRH	95% CI	n	TRH	95% CI
Sex												
Male	58	24.1%	14.9-36.6%	175	32.6%	26.1-39.8%	259	41.3%	35.5-47.4%	43	20.9%	11.2-35.4%
Female	55	20.0%	11.4-32.5%	91	30.8%	22.2-40.9%	87	36.8%	27.4-47.3%	20	55.0%	34.2-74.2%

CI indicates confidence interval; and TRH therapy-resistant hypertension

Table 3 Use of antihypertensive drugs in blood pressure control groups

	Controlled bloodpressure	Uncontrolled bloodpressure	Therapy-resistant hypertension
Antihypertensive treatment	n=156 (20%)	n=363 (46%)	n=269 (34%)
Mean no. of antihypertensive drugs (SD)	1.8 ± 1.0	1.6 ± 0.8	3.8 ± 0.8
No. of antihypertensive drugs ≥ 3	49 (31%)	44 (12%)	269 (100%)
No. of antihypertensive drugs ≥ 4	0 (0%)	0 (0%)	158 (58%)
ACE inhibitor	85 (55%)	156 (43%)	159 (59%)
ARB	50 (32%)	106 (29%)	129 (48%)
Beta blockade	54 (35%)	131 (36%)	207 (77%)
Calcium channel blockade	21 (14%)	91 (25%)	164 (61%)
Alpha blockade	2 (1%)	13 (4%)	56 (21%)
Loop diuretic	29 (19%)	29 (8%)	109 (41%)
Thiazide diuretic	34 (22%)	58 (16%)	148 (55%)
Potassium sparing diuretic	6 (4%)	2 (1%)	20 (7%)
Aldosterone antagonist	2 (1%)	3 (1%)	21 (8%)
Centrally acting sympathicolytic agent	0 (0%)	0 (0%)	1 (0%)
Direct acting vasodilatator	0 (0%)	2 (1%)	5 (2%)

ACE indicates angiotensin converting enzyme; and ARB angiotensin receptor blocker.
Controlled BP: <130/80; <4 antihypertensives
Uncontrolled BP: >130/80; < 3 antihypertensives or <4 antihypertensives without diuretic
Therapy-resistant hypertension: >130/80; ≥3 antihypertensives including diuretic or ≥4 antihypertensives

Relationship with outcome

During follow-up (5.3 ± 1.5 years for the composite end point) 17% of the patients with aTRH reached the composite end point of myocardial infarction, stroke or cardiovascular death and 27% reached ESRD. The presence of aTRH was related to a 1.7-fold higher risk (95% CI, 1.0-3.0) for the composite end point compared with controlled hypertension, when adjusted for age and sex. After adjustment for the other potential confounders (age, sex, history of diabetes mellitus, history of vascular disease, body mass index, eGFR, current smoking and adherence to guidelines for physical exercise), the hazard ratio was attenuated to 1.5 (95%CI, 0.8-3.0). Uncontrolled hypertension (<3 BP-lowering drugs or 3 drugs not including a diuretic) when compared with controlled hypertension was not related to the risk of a cardiovascular end point (table 4).

Table 4 Risks of therapy-resistant hypertension: cox proportional hazards analyses

End points	No. of events	Years of follow-up for the event (mean, SD)	Incidence rate (number/personyears)	Model 1		Model 2		Model 3	
				HR	95%CI	HR	95%CI	HR	95%CI
Composite cardiovascular endpoint*	96	5.3 (1.5)	23/1000						
Controlled BP				1.0 (ref)		1.0 (ref)		1.0 (ref)	
Uncontrolled BP				1.32	0.78-2.21	1.24	0.74-2.10	1.21	0.62-2.36
aTRH				1.87	1.11-3.18	1.75	1.03-2.96	1.53	0.79-2.97
ESRD	166	5.2 (1.6)	41/1000						
Controlled BP				1.0 (ref)		1.0 (ref)		1.0 (ref)	
Uncontrolled BP				1.09	0.70-1.71	1.26	0.80-1.99	1.59	0.99-2.56
aTRH				1.82	1.17-2.84	2.22	1.41-3.50	2.27	1.39-3.70
Composite renal endpoint**	388	4.5 (2.0)	108/1000						
Controlled BP				1.0 (ref)		1.0 (ref)		1.0 (ref)	
Uncontrolled BP				1.11	0.85-1.45	1.12	0.86-1.47	1.46	1.08-1.97
aTRH				1.38	1.04-1.82	1.40	1.06-1.86	1.53	1.11-2.09
All cause mortality	143	5.4 (1.3)	33/1000						
Controlled BP				1.0 (ref)		1.0 (ref)		1.0 (ref)	
Uncontrolled BP				1.10	0.72-1.71	1.01	0.65-1.57	1.73	0.96-3.13
aTRH				2.15	1.38-3.33	1.95	1.25-3.03	1.86	1.02-3.41

Model 1: crude
Model 2: adjusted for age and sex
Model 3: adjusted for age, sex, history of diabetes mellitus, history of vascular disease, BMI, eGFR, current smoking, adherence to guidelines for physical exercise
aTRH indicates apparent therapy-resistant hypertension; BP, blood pressure; CI, confidence interval; ESRD, end-stage renal disease; and HR, hazard ratio
* Composite of myocardial infarction, cerebral infarction and cardiovascular death
† Composite of death, ESRD (initiation of dialysis or kidney transplantation) or 50% increase in serum creatinine

aTRH was associated with a 2.2-fold increased risk of reaching ESRD (95% CI, 1.4-3.5) after adjustment for age and sex. After full adjustment, including eGFR at baseline, the HR for ESRD was 2.3 (95% CI, 1.4-3.7). Uncontrolled hypertension was related to an increased risk of ESRD of borderline statistical significance (HR, 1.3; 95% CI, 0.8-2.0 adjusted for age and sex and HR, 1.6; 95% CI, 1.0-2.6 after full adjustment).

The presence of aTRH increased all-cause mortality risk with an HR of 1.9 (95% CI, 1.0-3.4) in multivariable-adjusted analysis as did uncontrolled hypertension (HR, 1.7 95% CI, 1.0-3.1) compared with controlled BP.

The combined renal end point (death, ESRD, or 50% increase of serum creatinine) was reached by 55% of the patients with aTRH. The risk for the renal outcome increased 1.4-fold when adjusted for age and sex (95% CI, 1.1-1.9), and 1.5-fold after full adjustment (95% CI, 1.1-2.0). For uncontrolled hypertension, these risks were comparable (HR, 1.4; 95% CI, 1.1-2.0 in the multivariable-adjusted model). The 5-year event-free survival for aTRH was 82% (95% CI, 73-90) for the cardiovascular end point for women and 85% (95%CI, 80-91) for men. For ESRD the 5-year event-free survival was 85% (95% CI, 77-93) for women and 74% (95%CI, 67-81) for men.

Change in time

At baseline, the prevalence of aTRH was lower in the intervention group (guided by the nurse practitioners added to usual care): 31% versus 37% in the reference group (seen by the nephrologist). During follow-up, the prevalence of aTRH did not differ between groups with prevalences of 39% and 39% respectively at 2 years and 37% and 36% at 4 years. Among participants still in follow-up, the percentage of patients with uncontrolled but not resistant hypertension declined slightly during follow-up whereas the percentage of patients with controlled BP with <4 drugs increased (figure 1). These changes were more pronounced in the intervention group (data not shown). Time in follow-up and treatment group were not related to significant change in the presence of aTRH in the generalized estimating equation analyses in any of the models. The prevalences and risks of aTRH defined as BP ≥ 140/90 mm Hg despite use of ≥3 antihypertensives are described in the data supplement.

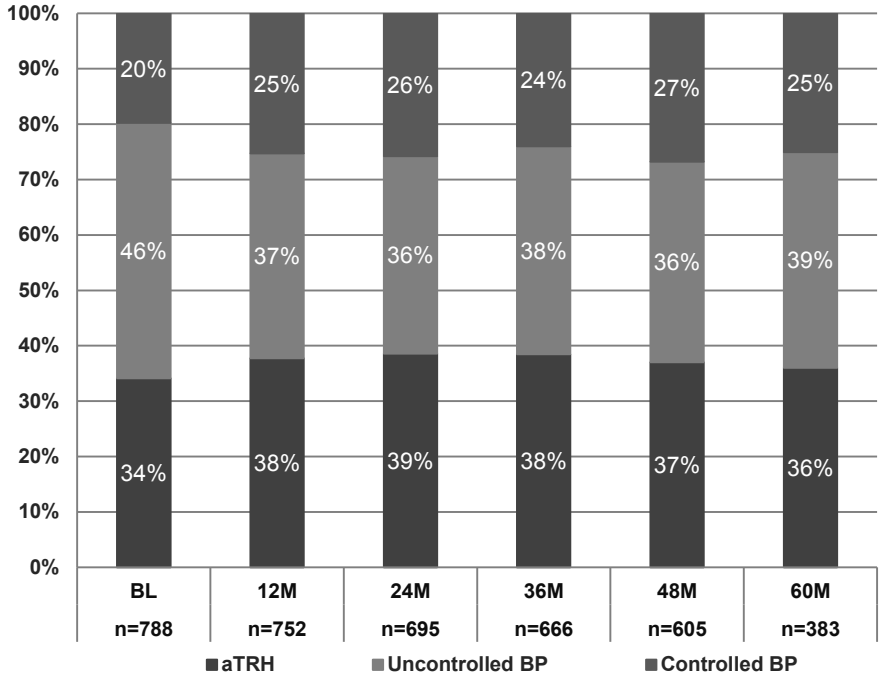

Figure 1 Hypertension control during follow-up

Discussion

In the MASTERPLAN cohort of patients with CKD, the prevalence of aTRH was high (32% -34%). The associated risks were considerable. Even intensive guidance by the nurse practitioners did not reduce the prevalence of aTRH.

Prevalence

Few studies have been able to investigate the prevalence of TRH because information on drug use is often lacking in large observational studies on BP control (4;17). A prevalence of 9% was found in a US primary care study. In the National Health and Nutrition Examination Survey (NHANES) cohort and in a Spanish hypertensive cohort studies, 12% of the hypertensive population fulfilled the criteria of TRH.(18;19) Even less is known about the prevalence of TRH in the CKD population, known for its increased cardiovascular risk and hypertension rate. In the population-based Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, aTRH was found in 25% of hypertensive patients with

an eGFR of 45 to 60 ml/min and in 33% of those with an eGFR <45 ml/min.(5) In the Chronic Renal Insufficiency Cohort (CRIC) study, hypertension was studied in patients with CKD without determining the prevalence of therapy-resistance, but in the groups using 3 or 4 antihypertensive drugs, BP was uncontrolled (≥140/90 mm Hg) in 31% and 39% respectively with almost 60% of patients with CKD using ≥3 antihypertensive drugs.(2) In the MASTERPLAN study, only patients with CKD under nephrologist care were included, thus adding that even in secondary care, prevalence of aTRH is high. Only a smaller Italian study investigated patients with CKD under nephrologist care (using the lower 130/80 mm Hg threshold) and found 23% of patients to be therapy-resistant.(6) As the age and sex distribution differ between the studies, and because these are main drivers of the prevalence, a direct comparison of the findings is not possible, apart from the statement that (a) TRH is a fairly common phenomenon in clinical practice.

In accordance with previous studies(5;6), aTRH patients with CKD were shown to have a different clinical profile with more often a history of cardiovascular disease and diabetes mellitus compared with patients with controlled BP. This has also been found in the general hypertensive population.(20;21) In contrast to the population-based studies (5;20;21), in our CKD cohort eGFR was similar in the different BP groups (table 1).

Relationship with outcome

Risks associated with aTRH have not been extensively studied, not even in the general hypertensive population. In a large cohort of 2521 incident therapy-resistant hypertensives, followed up from the first start of antihypertensive treatment and free from previous cardiovascular disease, an increased risk of 47% (95% CI, 1.33-1.62) on a composite cardiovascular end point was found when compared with patients treated with 3 antihypertensive drugs and controlled BP. However, the majority of events (77%) was the development of CKD defined as an eGFR<60 ml/min.(22) Another study conducted in 556 patients found the presence of 24-hour ambulatory BP measurement (ABPM) confirmed TRH to double the risk on a composite cardiovascular end point including ESRD after multivariable adjustment for other CVD risk factors (4.8 years of follow-up).(23) A recent study among 1920 patients reports a 2.2-fold increased risk for persistent aTRH on a cardiovascular composite end point in hypertensives free from previous cardiovascular disease, compared with nonresistant hypertension.(21) Persistent aTRH was defined as fulfilling the criteria for aTRH both at baseline and at follow-up after a few years of hypertension clinic care. The observational cohort REGARDS study found a 1.7-fold increased risk for coronary heart disease (95% CI, 1.3-2.2) for aTRH in multivariable

adjusted analysis when compared with no aTRH in 14.522 hypertensive patients free from previous coronary disease in 4.4 years of follow-up. The HRs for stroke and all-cause mortality were 1.3 (95% CI, 0.9-1.7) and 1.3 (95% CI, 1.1-1.5).(24) In the CKD population, HRs of ~2 and 2.7 have been found for cardiovascular and renal end points, respectively, for true TRH compared with controlled BP.(6) In the REGARDS study, even higher relative risks for ESRD were reported.(5) This study adds to the evidence on the increased risks associated with aTRH in patients with CKD under high-quality nephrologist care.

Change in time

The percentage of patients fulfilling the definition of aTRH did not decrease during follow-up (figure 1). This points to aTRH being a refractory problem as even intensified care as applied in MASTERPLAN does not address it effectively. A similar result was found in a non-CKD hypertensive cohort in which 66% of the patients with aTRH remained therapy-resistant after 4 years of follow-up in a hypertension clinic.(21) Also in the renal denervation studies (including patients with aTRH only), BP control figures were modest despite large decreases in office BP in some, with <50% of patients reaching controlled BP (25-27). In the Symplicity HTN-3 study, no control rates were mentioned but mean office BP remained well >140/90 mm Hg in both the renal denervation and sham control group, despite large decreases in BP that should probably at least partly be attributed to better compliance with drug treatment.(28) Although increase in antihypertensive drug treatment remains the main option for patients with aTRH,(29) for example, by increasing the use of aldosterone antagonists,(30) other options, such as baroreceptor therapy and percutaneous renal denervation need to be considered when BP remains high. A stepwise standardized increase of antihypertensive treatment combined with renal denervation as used by Azizi et al. could be an attractive approach.(27)

Strengths and limitations

Strength of this study is the setting of a trial studying routine nephrologist care when compared with increased effort by the nurse practitioners added to nephrologist care, thus representing antihypertensive treatment in a regular but optimized care setting. Therefore, the results are most likely an underestimation of the real life situation. BP control in this cohort is comparable with other CKD cohorts.(31) Because of the use of a cohort from a randomized controlled trial, medication use and end point registration were possibly superior to the previous studies investigating aTRH in CKD.

In the evaluation of aTRH, exclusion of a white coat effect is important. In the Spanish hypertensive cohort study, one third of the patients with aTRH were shown

to have well controlled BP when using ABPM.(19) Similarly, in the Italian CKD cohort study, 24% of the patients with office BP-based resistant hypertension were controlled at ABPM.(6) No ABPM measurements were available in MASTERPLAN. A white coat effect was diminished by using prolonged (30 minutes) automated measurement (in a quiet hospital environment). The estimated prevalence of TRH remained high using this approach. Although 24-hour ABPM is recognized as the preferred method to exclude white coat hypertension,(32) such automated measurements have been shown to have a significantly stronger correlation with ABPM readings than office BP.(33;34) Avoidance of office-induced BP increase by automated measurements is also still mentioned in the European Society of Hypertension guideline on ABPM.(35) Moreover, the fact that increased risks were associated with aTRH as defined in this study points to reliability of the results. Nonetheless, remaining white coat effects may have led to a -presumably slight- overestimation of the prevalence of aTRH.

Exclusion of secondary causes of hypertension, suboptimal dosing of anti-hypertensive drugs and nonadherence to treatment is important when studying aTRH. In this study, no data are available on these factors. However, because the study was designed to increase treatment effort in the nurse practitioner group, the last 2 issues were implicitly addressed (eg, dosage was increased according to a flowchart when BP goals were not reached).

Perspectives

As much as one-third of patients with CKD under nephrologist care was found to have aTRH in this study. Intense efforts to improve BP control with the use of lifestyle changes and optimization of antihypertensive drug treatment did not result in decline of aTRH prevalence. The presence of aTRH was related to a substantially increased risk on renal and cardiovascular outcomes. Continuation of research on both drug- and nondrug treatment for this patient group is needed. Measures resulting in a decrease of BP in this patient group will probably diminish the high risks related to aTRH but to date no prospective data are available. These data will be needed to be able to truly balance risks and benefits of new therapies for these high-risk patients.

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Supplement

Table S1 Patient characteristics in blood pressure control groups

		Controlled blood pressure	Uncontrolled blood pressure	Therapy-resistant hypertension
Clinical data		n=402 (51%)	n=183 (23%)	n=203 (26%)
Patient characteristics				
Gender (male)		248 (62%)	143 (78%)	144 (71%)
Age		56 ± 14	63 ± 11	62 ± 11
Race (Caucasian)		374 (93%)	166 (91%)	185 (91%)
Kidney transplant		61 (15%)	22 (12%)	27 (13%)
Diabetes mellitus		69 (17%)	47 (26%)	77 (38%)
History of vascular disease		92 (23%)	59 (32%)	81 (40%)
BMI		27 ± 5	27 ± 5	28 ± 5
Waist-hip ratio		0.94 ± 0.08	0.97 ± 0.08	0.98 ± 0.08
Current smoking		79 (20%)	34 (19%)	53 (27%)
History of smoking (pack years)*		4 (0-10)	7 (3-13)	8 (2-22)
Adherence to guidelines for physical exercise (yes)		215 (54%)	115 (65%)	121 (62%)
Statin use		260 (65%)	115 (63%)	138 (68%)
Blood pressure				
Office SBP (mm Hg)		123 ± 11	152 ± 14	158 ± 18
Office DBP (mm Hg)		75 ± 9	85 ± 11	86 ± 12
Pulse pressure		48 ± 10	66 ± 17	72 ± 18
Automated measurement SBP (mm Hg)		123 ± 12	145 ± 16	153 ± 20
Laboratory results				
eGFR (ml/min/1.73m2)		38 ± 15	40 ±15	36 ± 14
MDRD level	< 15	10 (3%)	4 (2%)	8 (4%)
	15-30	117 (29%)	54 (30%)	67 (33%)
	30-45	156 (39%)	62 (34%)	75 (37%)
	45-60	81 (20%)	46 (25%)	39 (19%)
	60-75	32 (8%)	14 (8%)	12 (6%)
	>75	6 (1%)	3 (2%)	2 (1%)
Urinary protein excretion (g/24h)*		0.2 (0.1-0.6)	0.3 (0.1-0.8)	0.3 (0.1-0.9)
Urinary sodium excretion (mmol/24h)*		147 (110-188)	154 (113-193)	156 (120-199)
Triglycerides*		1.6 (1.1-2.2)	1.5 (1.1-2.1)	1.8 (1.2-2.6)
Events				
Composite cardiovascular endpoint		38 (9.5%)	19 (10.4%)	39 (19.2%)
Composite renal endpoint		175 (43.5%)	94 (51.4%)	119 (58.6%)
ESRD		75 (18.7%)	34 (18.6%)	57 (28.1%)
All cause mortality		47 (11.7%)	38 (20.8%)	58 (28.6%)

Numbers are expressed as means with standard deviations or proportions as appropriate. Variables that lack normality are expressed as medians with 25-75% range (*).
Controlled blood pressure is defined as ≤ 140/90, uncontrolled blood pressure is defined as ≥140/90; <3 antihypertensives, therapy-resistant hypertension is defined as ≥140/90; ≥3 antihypertensives.
Abbreviations: BMI body mass index, ABPM ambulatory blood pressure measurement, ESRD end stage renal disease, eGFR estimated glomerular filtration rate. SBP systolic blood pressure, DBP diastolic blood pressure

Table S2 Gender specific prevalence of therapy resistant hypertension in different age groups

Age	<45 years			45-59 years			60-74 years			≥75 years		
	n	aTRH	95%CI	n	aTRH	95%CI	n	aTRH	95%CI	n	aTRH	95%CI
Sex												
Male	58	12.1%	3.4-20.7%	175	24.0%	17.6-30.4%	259	34.0%	28.2-39.8%	43	16.3%	4.8-27.8%
Female	55	12.7%	3.6-21.8%	91	20.9%	12.4-29.4%	87	29.9%	20.1-39.7%	20	35.0%	12.1-57.9%

Apparent therapy resistant hypertension is defined as blood pressure ≥ 140/90 mm Hg despite use of ≥ 3 antihypertensive drugs

Table S3 Use of antihypertensive drugs in blood pressure control groups

	Controlled BP	Uncontrolled BP	Therapy- resistant hypertension
Antihypertensive treatment	n=402 (51%)	n=183 (23%)	n=203 (26%)
Mean number of antihypertensive drugs (SD)	2.2 (1.3)	1.5 (0.7)	3.6 (0.8)
Number of antihypertensive drugs ≥3	159 (39.6%)	0 (0%)	203 (100%)
ACE inhibitor	55%	34%	58%
ARB	34%	33%	43%
Beta blockade	44%	32%	78%
Calcium channel blockade	24%	20%	70%
Alpha blockade	6%	0%	23%
Loop diuretic	21%	8%	33%
Thiazide diuretic	28%	18%	47%
Potassium sparing diuretic	4%	1%	4%
Aldosterone antagonist	4%	1%	4%
Centrally acting sympathicolytic agent	0%	0%	1%
Direct acting vasodilatator	0%	1%	3%

Abbreviations: ACE angiotensin converting enzyme, ARB angiotensin receptor blocker
Controlled BP is defined as <140/90 mm Hg, Uncontrolled BP is defined as ≥140/90 mm Hg; < 3 antihypertensives, Therapy-resistant hypertension is defined as ≥140/90 mm Hg; ≥3 antihypertensives

Table S4 Risks of apparent therapy-resistant hypertension: cox proportional hazards analyses

Endpoint	Number of events	Years of follow-up	Incidence rate	Model 1		Model 2		Model 3	
		(mean, SD)	(number/ person-years)	HR	95%CI	HR	95%CI	HR	95%CI
Composite cardiovascular endpoint*	96	5.3 (1.5)	23/1000						
Controlled BP				1.0 (ref)		1.0 (ref)		1.0 (ref)	
Uncontrolled BP				1.11	0.64-1.93	0.89	0.50-1.55	0.89	0.50-1.59
aTRH				2.32	1.48-3.62	1.92	1.22-3.03	1.39	0.86-2.25
ESRD	166	4.4 (1.3)	41/1000						
Controlled BP				1.0 (ref)		1.0 (ref)		1.0 (ref)	
Uncontrolled BP				1.02	0.68-1.53	1.23	0.81-1.87	1.08	0.69-1.68
aTRH				1.78	1.26-2.52	2.15	1.50-3.08	1.74	1.18-2.56
Composite renal endpoint**	388	4.5 (2.0)	108/1000						
Controlled BP				1.0 (ref)		1.0 (ref)		1.0 (ref)	
Uncontrolled BP				1.25	0.97-1.60	1.31	1.01-1.70	1.29	0.99-1.69
aTRH				1.59	1.26-2.01	1.67	1.31-2.11	1.34	1.04-1.73
All-cause mortality	143	5.4 (1.3)	33/1000						
Controlled BP				1.0 (ref)		1.0 (ref)		1.0 (ref)	
Uncontrolled BP				1.82	1.18-2.78	1.39	0.90-2.16	1.52	0.96-2.39
aTRH				2.87	1.95-4.22	2.26	1.53-3.34	1.64	1.08-2.51

Apparent therapy resistant hypertension is defined as blood pressure ≥ 140/90 mm Hg despite use of ≥ 3 antihypertensive drugs
Model 1: crude
Model 2: adjusted for age and sex
Model 3: adjusted for age, sex, history of diabetes mellitus, history of vascular disease, waist-hip ratio, eGFR, proteinuria, current smoking, adherence to guidelines for physical exercise, statin use and triglycerides
* Composite of myocardial infarction, cerebral infarction and cardiovascular death
** Composite of death, ESRD (initiation of dialysis or kidney transplantation) or 50% increase in serum creatinine

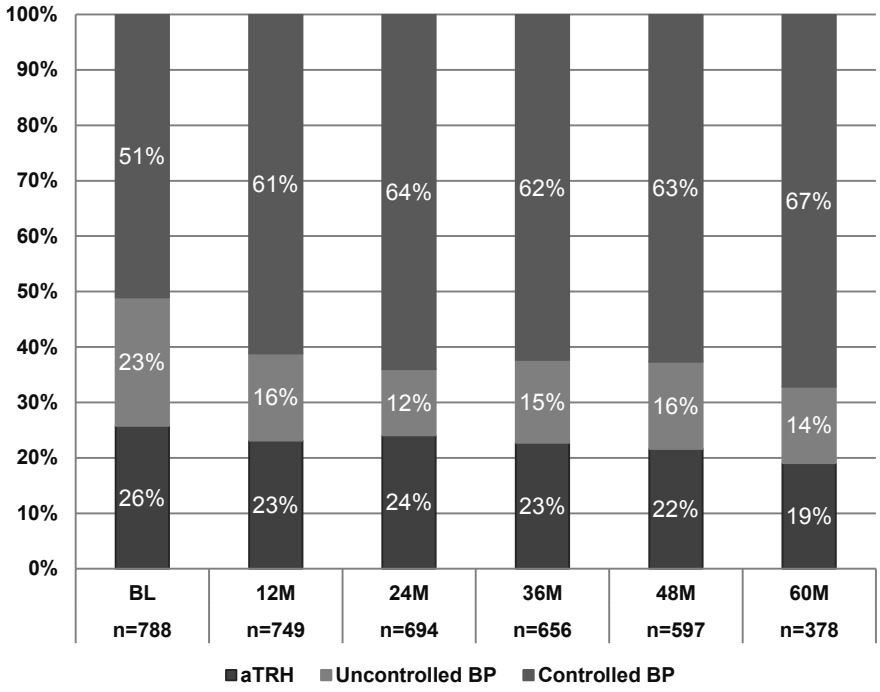

Figure S1 Hypertension control during follow-up

CHAPTER 3

Prevalence and clinical characteristics of apparent therapy-resistant hypertension in patients with cardiovascular disease: a cross-sectional cohort study in secondary care

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Abstract

Objectives

Our aim was to investigate the prevalence of apparent therapy-resistant hypertension (aTRH) in patients with clinical manifest cardiovascular disease (CVD), and to study clinical characteristics related to aTRH in this population.

Setting

The SMART study is a large, single center cohort study in secondary care.

Methods

Office blood pressure (BP) at inclusion was used to evaluate BP control in 6191 hypertensive patients with clinical manifest (cardio)vascular disease. Therapy-resistant hypertension was defined as blood pressure (BP) ≥140/90 mm Hg despite use of antihypertensive drugs from ≥3 drug classes including a diuretic or use of ≥4 antihypertensive drugs irrespective of BP. Logistic regression analysis was used to explore the relation between clinical characteristics measured at baseline and presence of aTRH.

Results

The prevalence of aTRH was 9.1% (95% CI 8.4-9.8). Prevalence increased with age and when albuminuria was present and was higher in patients with lower glomerular filtration rate (eGFR). Presence of aTRH was related to diabetes, female sex, duration and multiple locations of vascular disease, body mass index and waist circumference. Carotid intima-media thickness was higher (0.99 ± 0.28 vs. 0.93 ± 0.28) and ankle-brachial index lower (1.07 ± 0.20 vs. 1.10 ± 0.19) in aTRH patients compared to patients without aTRH.

Conclusions

aTRH is prevalent in patients with clinical manifest cardiovascular disease and is related to clinical factors known to be related with increased vascular risk, and with lower eGFR.

Introduction

Elevated blood pressure is strongly related to the occurrence of cardiovascular disease.(1;2) In patients with clinical manifest cardiovascular disease, the risk of a recurrent cardiovascular event is very high.(3) Hypertension has been shown to increase risk of recurrent cardiovascular events(4) and blood pressure-lowering drugs decrease the risk.(5;6) Therefore blood pressure control is strongly advised in these patients.(7) Although awareness and control of hypertension have improved in the last decade, the proportion of patients meeting blood pressure targets remains low.(8) Also for secondary prevention, control rate is only slightly over 50%, and antihypertensive medication is still underused, even in very high-risk patients.(9;10) With the emergence of new device based blood pressure-lowering therapies, such as percutaneous renal denervation(11-13) and implantable devices for barostimulation,(14) the concept of (apparent) therapy-resistant hypertension (aTRH) has regained attention.(15;16) Yet, detailed information on the prevalence and determinants of therapy resistant hypertension is limited, in particular among patients with a history of a cardiovascular event. Such information creates more awareness among clinicians and potentially leads to investigations into modifiable causes. We therefore set out to investigate the age- and sex-specific prevalence of therapy resistant hypertension in patients with clinically manifestcardiovascular disease. Secondly, we investigated clinical characteristics associated with aTRH in these patients.

Methods

Study design

The Second Manifestations of ARTerial disease (SMART) study is an ongoing prospective cohort study including 18-79 year old patients referred to the University Medical Center Utrecht with atherosclerotic cardiovascular disease or for treatment of cardiovascular risk factors. Design and rationale of the SMART study have been described in detail previously.(17) For this study, we selected patients referred for treatment of symptomatic cardiovascular disease (CVD) or for treatment of CVD risk factors with a history of manifest vascular disease. These patients were referred for coronary heart disease, cerebral vascular disease, peripheral artery disease, abdominal aortic aneurysm (AAA) or for CVD risk factor management with a history of CVD. Coronary artery disease was defined as myocardial infarction, angina pectoris or coronary revascularization. Patients with cerebrovascular disease had experienced a transient ischemic attack, ischemic stroke, amaurosis fugax, retinal

infarction, or a history of carotid surgery. Peripheral artery disease was defined as a symptomatic and documented obstruction of distal arteries of the leg or interventions (Fontaine classification II-IV confirmed with ankle brachial index (ABI) ≤0.90 in rest or decrease of ABI >20% after exercise, percutaneous transluminal angioplasty, bypass, or amputation). Patients with AAA had a suprarenal or infrarenal aneurysm of the aorta or a history of AAA surgery. Diabetes mellitus was defined as fasting serum glucose ≥7.0 mmol/l, self-reported diabetes and/or the use of oral antihyperglycemic agents or insulin.

Participants are subjected to an extensive vascular disease screening including a questionnaire on history and symptoms of CVD and risk factors for CVD, measurement of office blood pressure and anthropometrical characteristics, and laboratory tests including serum lipids, glucose and creatinine and urinary albumin and creatinine excretion. Blood pressure was measured on a single occasion in the office: with a semiautomatic oscillometric device during 25 minutes in supine position with measurement every 4 minutes and the mean taken as the blood pressure until 1999 and, thereafter, in sitting position, three times at both upper arms with the highest mean of the last two measurements on one arm taken as the blood pressure. Height and weight were measured without shoes and in light clothing. Waist and hip circumferences are measured in duplicate. Laboratory values are measured in venous blood using commercial enzymatic chemistry kits. For albuminuria, albumin/creatinine ratios (ACR) were calculated in a random urine sample. Normoalbuminuria is defined as an ACR <3 mg/mmol, 3-29 mg/mmol is classified as microalbuminuria and an ACR ≥30 mg/mmol as macroalbuminuria. Glomerular filtration rate was estimated from the measured serum creatinine by the CKDepi formula.(18) Ankle-brachial index was calculated from the highest systolic blood pressure measured at the posterior tibial and dorsal pedal arteries by Doppler and at both brachial arteries by a semi-automatic oscillometric device in supine position. Carotid intima-media thickness was measured three times at the left and right common carotid artery with the mean of all measurements being reported. Physical activity was quantified using a questionnaire on the usual pattern of leisure time physical activity in a week and expressed as METs/week (one MET is the rate of energy expenditure for an individual at rest, activities are assigned a MET intensity, weekly energy expenditure is calculated by multiplying hours spent on an activity by the activities' MET intensity). Details on these measurements can be found in previous publications.(17;19) Medication use was recorded at the baseline visit using a questionnaire. Use of antihypertensive drugs was recorded as use of angiotensin converting enzyme inhibitor (ACE inhibitor), angiotensin

receptor blocker (ARB), beta blocker, calcium channel blockade, diuretics including subclasses, aldosterone antagonist, alpha blocker, central acting antihypertensive or direct acting vasodilator. For this study, these cross-sectional data were used to define blood pressure (BP) control as no hypertension (that is below 140/90 mm Hg not using any antihypertensive drugs), controlled hypertension (that is below 140/90 mm Hg while using less than 4 antihypertensive drugs), uncontrolled but not therapy-resistant hypertension (that is ≥140/90 mm Hg while using less than 3 antihypertensive drugs or less than 4 drugs not including a diuretic), or apparent therapy-resistant hypertension. Apparent therapy-resistant hypertension was defined as BP ≥140/90 mm Hg while using ≥3 antihypertensive drugs including a diuretic or use of ≥4 antihypertensive drugs regardless of BP. For this study, we used data of all 7223 patients with cardiovascular disease included from September 1996 to February 2014. The SMART study was approved by the Medical Ethics Committee of the Utrecht University Medical Center and written informed consent was obtained from all patients.

Data analyses

Patient characteristics were evaluated according to blood pressure control group with means with standard deviations reported, median with 25-75% range for non-normally distributed data and as proportions for categorical data. Prevalence of apparent therapy resistant hypertension was reported in age and sex groups and in strata of eGFR and albuminuria as a proportion with corresponding 95% confidence intervals. Prevalence of aTRH according to eGFR and albuminuria was adjusted for age and sex using uni-anova analyses (estimated marginal means). Clinical factors possibly related to presence of aTRH were entered in an univariate logistic regression model first, secondly in an age and sex adjusted model and finally in a multivariable model containing all variables. Measurements of signs of vascular disease (carotid intima-media thickness, albuminuria and ankle-brachialis index) were related to presence of aTRH. For direct comparison of the magnitude of the relationships with aTRH, odds ratios (ORs) for one standard deviation change in the continuous clinical factors were analyzed. These results are presented as supplementary online material. Change of the prevalence of aTRH depending on the year of inclusion was investigated in a separate logistic regression analysis. Because of significant loss of participants due to missing data, imputation was used for the logistic regression analyses. Imputation was performed using bootstrapping and predictive mean matching (aregimpute in R, Hmisc package), assuming that these values were missing at random. Imputed variables included systolic and diastolic BP (0.6%), BMI (0.7%), waist circumference (4.0%), glucose (1.1%), hsCRP

(0.8%), lipid levels (1.0%), albuminuria (7.2%) and eGFR (1.0%), pack-years (1.1%) and alcohol use (1.2%), and carotid intima media thickness (3.5%). Analyses were performed in SPSS version 21 (SPSS, Chicago, IL). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

Study population

Of 7223 patients with clinically manifest vascular disease, 985 did not have hypertension and were excluded (14%). In the remaining 6191 patients, mean age was 61 ± 10 years and 75% was male. The first manifestation of vascular disease occurred less than 1 year earlier in 57%, between 1 and 5 years ago in 19%, between 6 and 15 years in 15%, and over 15 years ago in 9%. Locations of vascular disease were coronary artery disease in 66%, cerebral vascular disease in 27%, peripheral arterial disease in 17% and aneurysm of the abdominal aorta in 9%. More than one of these sites was clinically effected in 16% of patients. The majority was referred for CVD, with 10% of patients referred for treatment of cardiovascular risk factors only with vascular disease in the medical history.

Prevalence of aTRH

Blood pressure was controlled on less than 4 drugs in 41% of patients. Apparent therapy-resistant hypertension was present in 9.1% (95%CI 8.4-9.8%) of all patients. BP was uncontrolled but not therapy-resistant in 50% of patients. Patient characteristics according to BP control are shown in table 1.

The prevalence of aTRH increased with age in both sexes (figure 1). aTRH prevalence increased with decrease in eGFR: in patients with an eGFR above 90 ml/min/1.73m^2 aTRH was present in 6.0% of patients and in patients with an eGFR between 75 and 90 ml/min/1.73m^2 this was 6.2%. At an eGFR between 60 and 74 ml/min/1.73m^2 8.2% had aTRH. Between 45 and 60 ml/min/1.73m^2 15.1% and below 45 ml/min/1.73m^2, 26.8% of the patients fulfilled the criteria of aTRH. Albuminuria was related to aTRH: in patients without albuminuria, 8.0% had aTRH and in patients with microalbuminuria this was 14.8% and in patients with macroalbuminuria this was 15.5%. The age and sex adjusted prevalence estimates are presented in figure 2.

Table 1 Patient characteristics in blood pressure control groups

	Controlled hypertension N=2564	Uncontrolled hypertension N=3063	Resistant hypertension N=564
Sex (male)	77%	74%	69%
Age (years)	59 (10)	62 (10)	64 (9)
Diabetes mellitus (yes)	15%	19%	33%
History of cardiac vascular disease	81%	54%	71%
History of cerebral vascular disease	18%	33%	29%
History of peripheral arterial disease	10%	23%	18%
History of abdominal aortic aneurysm	7%	10%	12%
Duration of vascular disease (years)	0 (0-4)	0 (0-4)	1 (0-10)
Body mass index (kg/m^2)	27.0 (3.9)	26.9 (3.9)	28.3 (4.4)
Waist circumference (cm)	96 (12)	96 (12)	100 (13)
Office systolic BP (mm Hg)	124 (10)	156 (16)	152 (23)
Office diastolic BP (mm Hg)	75 (8)	88 (11)	85 (13)
Pulse pressure (mm Hg)	50 (9)	68 (16)	67 (18)
Fasting blood glucose (mmol/l)	6.1 (1.6)	6.4 (1.8)	6.8 (2.1)
HbA1c (%)	5.9 (0.9)	6.1 (1.0)	6.2 (1.0)
Total cholesterol (mmol/l)	4.6 (1.1)	5.0 (1.3)	4.7 (1.1)
LDL cholesterol (mmol/l)	2.7 (0.9)	3.0 (1.1)	2.7 (1.0)
HDL cholesterol (mmol/l)	1.2 (0.3)	1.3 (0.4)	1.2 (0.4)
Triglycerides (mmol/l)	1.4 (1.0-2.0)	1.4 (1.0-2.0)	1.5 (1.1-2.3)
HsCRP (mg/l)	1.9 (0.9-4.0)	2.2 (1.0-4.6)	2.3 (1.1-4.8)
eGFR (ml/min/1.73m^2)	77 (17)	75 (18)	66 (20)
eGFR category (ml/min/1.73m^2)			
<45	4%	6%	17%
45-60	11%	14%	22%
60-75	27%	31%	26%
75-90	35%	29%	21%
> 90	23%	21%	14%
Albuminuria			
None	91%	82%	75%
Micro	8%	16%	21%
Macro	1%	3%	4%
Pack-years	14 (3-31)	16 (3-33)	16 (0-35)
Alcohol use (any)	84%	81%	78%
Physical exercise score (METs*h/wk)	36 (16-63)	32 (14-60)	31 (14-55)
Carotid intima media thickness (mm)	0.89 (0.26)	0.97 (0.29)	0.99 (0.28)
Ankle-brachial index	1.13 (0.17)	1.07 (0.20)	1.07 (0.20)

Data are expressed as a proportion, mean with corresponding standard deviation (SD) or median with interquartile range if not normally distributed.
Controlled hypertension: BP<140/90 mm Hg while using 1-3 antihypertensive drugs
Uncontrolled non-resistant hypertension: ≥140/90 mm Hg while using <3 antihypertensive drugs or <4 antihypertensive drugs not including a diuretic
Apparent therapy-resistant hypertension: BP≥140/90 mm Hg while using ≥3 antihypertensive drugs including a diuretic or using ≥4 antihypertensive drugs regardless of BP.
Albuminuria is absent if ACR is <3 mg/mmol, microalbuminuria is defined as ACR 3-29 mg/mmol, macroalbuminuria is defined as ACR ≥30 mg/mmol, eGFR (ml/min/1.73m^2) was calculated using the CKD-epi formula

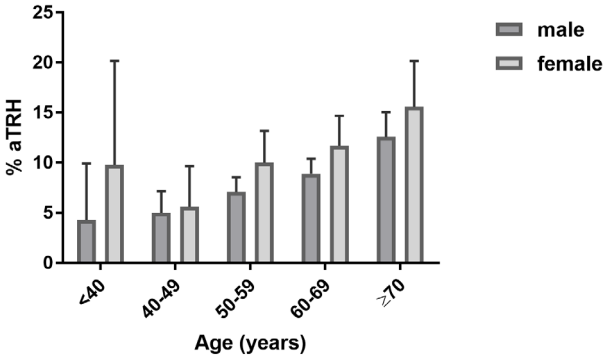

Figure 1 Prevalence of aTRH according to age and sex
Whiskers indicate 95% confidence intervals

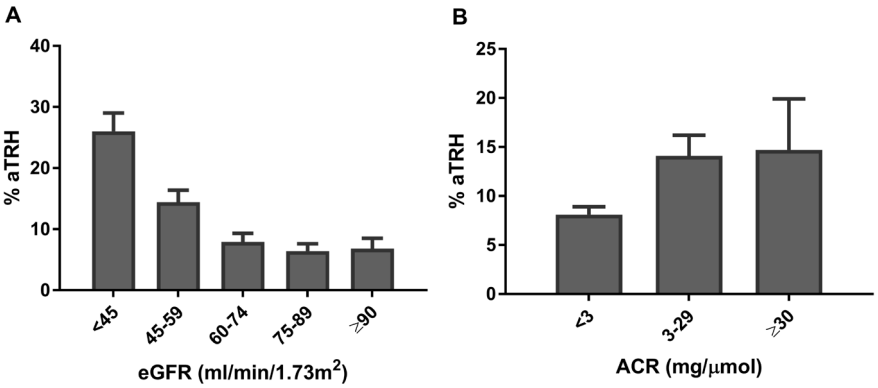

Figure 2 Prevalence of aTRH according to eGFR and albuminuria
Prevalences adjusted for age and sex, whiskers indicate 95% confidence intervals; eGFR estimated glomerular filtration rate using the CKDepi formula; ACR albumin-creatinin ratio

Determinants of aTRH

Antihypertensive drug use in the blood pressure groups is shown in table 2. In the aTRH group, use of renin-angiotensin-aldosterone system (RAAS) inhibitors was virtually universal just as use of diuretics (the latter being part of the aTRH definition). Beta blockade was used by a majority of aTRH patients (84%). Use of calcium channel blockers was much lower (54%). Aldosterone antagonists were used by 15% of the aTRH group patients.

Table 2 Use of antihypertensive drugs in blood pressure control groups

	Controlled hypertension n=2564	Uncontrolled hypertension n=3063	Resistant hypertension n=564
No. of classes antihypertensive drugs	1.7 ± 0.7	1.1 ± 0.9	3.6 ± 0.7
Number of antihypertensives ≥3	17%	6%	100%
Number of antihypertensives ≥4	0%	0%	51%
ACE inhibitor	38%	26%	66%
ARB	11%	9%	34%
Beta blockade	77%	45%	84%
Calcium channel blockade	24%	19%	54%
Alpha blockade	0.3%	1%	5%
Diuretic	20%	11%	98%
Thiazid diuretic	11%	7%	55%
Loop diuretic	9%	3%	43%
Potassium sparing diuretic	2%	2%	6%
Aldosterone antagonist	2%	1%	15%
Centrally acting antihypertensive	0.1%	0.2%	0.9%
Direct acting vasodilator	0%	0%	0.4%

ACE angiotensin converting enzyme, ARB angiotensin receptor blockade

Age- and sex-adjusted analyses showed that female sex, higher age, diabetes mellitus, duration and multiple locations of vascular disease, BMI and waist circumference, eGFR and albuminuria were related to aTRH as were lower total, HDL- and LDL-cholesterol and higher triglycerides (table 3). To facilitate comparison of the ORs of the different factors, these are expressed for one standard deviation change instead of one unit change in the supplementary table 1. Important relationships were for higher age (OR 1.38 per 10 years, 95%CI 1.25-1.51), diabetes mellitus (OR 2.31, 95%CI 1.92-2.80), BMI (OR 1.09 95%CI 1.07-1.12 per kg/m^2), eGFR (OR 0.77 for 10 ml/min/1.73m^2 higher eGFR, 95%CI 0.73-0.81) and albuminuria (OR 1.78, 95%CI 1.43-2.22 for microalbuminuria and OR 1.75, 95%CI 1.07-2.85 for macroalbuminuria, both compared with no albuminuria). Carotid intima-media thickness was significantly higher (0.99 ± 0.28 vs. 0.93 ± 0.28) and ankle-brachial index lower (1.07 ± 0.20 vs. 1.10 ± 0.19) in aTRH patients compared to patients without aTRH. Results from the full multivariable model are shown in table 3.

The prevalence of aTRH increased with 9% for every year later a participant was included in the study (logistic regression analysis), from 4.8% in those included before 2000 (n=1300) to 13.9% in those included in 2010 or thereafter (n=891).

Table 3 Factors related to presence of aTRH

	Univariate analysis		Age & sex adjusted analysis		Multivariable adjusted analysis	
	OR	95% CI	OR	95% CI	OR	95% CI
Sex (female)	**1.33**	**1.11-1.61**	**1.34**	**1.11-1.62**	**1.53**	**1.18-1.99**
Age (years)	**1.03**	**1.02-1.04**	**1.03**	**1.02-1.04**	1.01	0.99-1.02
Diabetes mellitus	**2.42**	**2.00-2.92**	**2.31**	**1.92-2.80**	**1.66**	**1.28-2.16**
History of cardiac vascular disease	**1.26**	**1.04-1.52**	**1.34**	**1.10-1.62**	0.98	0.54-1.78
History of cerebral vascular disease	1.18	0.98-1.43	1.13	0.93-1.37	0.97	0.53-1.77
History of peripheral vascular disease	1.13	0.90-1.40	1.08	0.86-1.35	0.77	0.42-1.41
History of abdominal aneurysmatic disease	**1.60**	**1.23-2.09**	**1.44**	**1.10-1.89**	1.09	0.59-2.01
Multiple locations of vascular disease	**2.12**	**1.74-2.59**	**1.99**	**1.63-2.44**	1.53	0.77-3.01
Duration of vascular disease (years)	**1.03**	**1.02-1.04**	**1.03**	**1.02-1.04**	1.01	1.00-1.02
Body mass index (kg/m^2)	**1.08**	**1.06-1.10**	**1.09**	**1.07-1.12**	**1.04**	**1.00-1.08**
Waist circumference (cm)	**1.03**	**1.02-1.03**	**1.03**	**1.03-1.04**	**1.01**	**1.00-1.03**
Total cholesterol (mmol/l)	**0.92**	**0.86-0.99**	**0.91**	**0.84-0.98**	0.95	0.87-1.04
LDL cholesterol (mmol/l)	**0.83**	**0.76-0.91**	**0.83**	**0.76-0.91**	**0.88**	**0.79-0.97**
HDL cholesterol (mmol/l)	0.83	0.65-1.06	**0.64**	**0.49-0.84**	1.04	0.77-1.40
Triglycerides (mmol/l)	**1.09**	**1.04-1.15**	**1.13**	**1.07-1.19**	**1.07**	**1.02-1.13**
Fasting glucose (mmol/l)	**1.15**	**1.10-1.19**	**1.15**	**1.10-1.19**	1.02	0.96-1.08
hsCRP (mg/l)	1.00	0.99-1.01	1.00	0.99-1.01	0.99	0.98-1.00
eGFR (ml/min/1.73m^2)	**0.97**	**0.97-0.98**	**0.97**	**0.97-0.98**	**0.98**	**0.97-0.98**
Albuminuria (no)	Ref		Ref		Ref	
Microalbuminuria	**1.97**	**1.59-2.45**	**1.78**	**1.43-2.22**	1.27	0.99-1.63
Macroalbuminuria	**1.91**	**1.18-3.10**	**1.75**	**1.07-2.85**	1.03	0.59-1.81
Pack-years	1.00	1.00-1.01	1.00	1.00-1.01	1.00	1.00-1.01
Alcohol use (any)	**0.76**	**0.61-0.94**	0.85	0.68-1.06	0.99	0.78-1.27
Physical exercise score (METs*h/wk)	1.00	1.00-1.00	1.00	1.00-1.00	1.00	1.00-1.00
Carotid intima-media thickness (mm)	**1.84**	**1.41-2.40**	**1.49**	**1.11-2.00**	1.20	0.85-1.68
Ankle-brachialis index	**0.42**	**0.28-0.65**	**0.54**	**0.35-0.84**	**0.54**	**0.31-0.96**

In the second model, age was adjusted only for sex, sex was adjusted only for age. In the multivariate analysis, total cholesterol was used for the other factors, HDL, LDL cholesterol and triglycerides were entered separately.

Adjustment for the location of the vascular disease the participant had suffered from (cardiac, cerebral, peripheral or aneurysmatic vascular disease) did not change the result. When all variables in the multivariable analysis where adjusted for, the increase per year was 11.6%.

Discussion

Therapy-resistant hypertension was present in 9.1% of hypertensive patients with clinically manifest vascular disease and 49.5% had uncontrolled but non-resistant hypertension. Clinical characteristics related to aTRH were higher age, female sex, BMI and waist circumference, diabetes mellitus and duration and multiple locations of vascular disease, lower eGFR and albuminuria. Patients with aTRH had a greater carotid intima-media thickness and lower ankle-brachial index representing greater burden of subclinical vascular damage.

The prevalence of aTRH has been reported to be 9-13% in the general hypertensive population.(20-22) In patients with chronic kidney disease, known for their high cardiovascular risk, a much higher prevalence of ~25-35% has been found, often using a more stringent blood pressure definition of <130/80 mm Hg.(23-25) Although several reports have shown a higher prevalence of vascular disease in those with aTRH in hypertensive populations.(21;22;26-28) the exact aTRH prevalence in patients with clinical manifest vascular disease has not been established. In the REGARDS study, 26% of 1694 hypertensive stroke and transient ischemic attack patients were assigned the label of aTRH, with a definition not including diuretic use (and only 59% using one).(29) The smaller (n=927) WISE study in women suspected of coronary artery disease, with less than halve having obstructive coronary artery disease confirmed, found a much lower prevalence of 10.4%. Information on patients with coronary artery disease was also reported from the INVEST and TNT trials with a prevalence of aTRH of 37.8% and 11.1% found, respectively.(30;31) However, the prevalence of aTRH might well be very different in patients participating in a trial compared to that in daily practice. Evidence comparable with this study comes from the REACH registry, mainly including patients with established (cardiac, cerebral and peripheral) arterial vascular disease (80%), that reported aprevalence of aTRH of 11.8%. Adding controlled BP while using ≥4 antihypertensive drugs led to an increase in aTRH to 21.6%.(32) The current study adjusts the estimate downwards, at least for patients with clinically manifest vascular disease of European descent. Black race has been found to be related to aTRH,(29;33) and apart from REACH, which is a worldwide study, all previous

estimates were from US studies naturally including more black participants, or even deliberately oversampling them (REGARDS). In this study, most (57%) patients had their first CVD event within one year prior to inclusion. In the subgroup of patients with a duration of vascular disease longer than 1 year the prevalence of aTRH was higher at 12% (95%CI 11-14%). Also important is that the prevalence of aTRH was 15% (95%CI 13-18%) in patients with more than one manifestation of vascular disease. The prevalence of aTRH can now be concluded to be 10-20% in patients with clinically manifest cardiovascular disease, with a strong influence of characteristics like race, age and sex. In this study, we add detailed age and sex specific prevalence data to the literature. During the study the prevalence of aTRH increased in participants newly included in the cohort. Adjustment for the clinical characteristics found to be related to aTRH and for location of vascular disease did not change this. A true increase in the prevalence of aTRH therefore exists. This confirms findings from NHANES (34) in a well-defined and carefully investigated cohort of patients with clinically manifest vascular disease.

aTRH patients were found to have a worse cardiovascular risk profile with a higher prevalence of diabetes mellitus and albuminuria, higher age and BMI and lower eGFR as compared to patients with prior cardiovascular disease with controlled or non-resistant uncontrolled BP. aTRH patients also had a longer duration of vascular disease and multiple locations of vascular disease more often. The clinical factors related to the presence of aTRH have been very consistent and similar in the previous studies in hypertensive populations. Higher age, higher BMI and/or waist circumference, presence of diabetes and prior vascular disease have been reported to be related to aTRH in most studies.(21;26-28;33;35) Two cohorts with an ethnically diverse population found black race to be related to aTRH.(29;33) Longer duration of hypertension has also been shown to be related to presence of resistant hypertension both in general hypertensive populations and in the REGARDS cerebrovascular disease patients.(26;29;35) Information on the duration of hypertension was not available in the SMART cohort. Sex differences have been less clear, with some studies reporting female predominance (27;31;32) just as in the present study, some finding no difference,(26; 28) and others a higher prevalence in men.(21;33) In conclusion, the clinical picture of patients with aTRH is no different in patients with prior vascular disease than in those without.

Impaired kidney function and albuminuria were strongly related to resistant hypertension in patients with cardiovascular disease. This is in accordance with the previous studies in the general hypertensive population (21;26-28;33;35) and also with the much higher prevalence of resistant hypertension found in chronic kidney disease patients. In the MASTERPLAN cohort investigating CKD patients under

nephrologist care we found 34% to have resistant hypertension using a more stringent CKD adjusted target BP of <130/80 mm Hg, and around one-quarter when using 140/90 mm Hg as target BP.(23) Similarly high prevalence was reported in a recent review summarizing the state of knowledge on resistant hypertension in CKD.(25) Analyses from the Chronic Renal Insufficiency Cohort (CRIC) disclosed an even higher prevalence of 40% using a slightly different definition of aTRH.(36) Clinical characteristics related to resistant hypertension were reported to be similar to the general hypertensive population in CKD.(24;36) The stroke/TIA patients with aTRH studied in REGARDS also had a greater chance of having aTRH if microalbuminuria or eGFR <60 ml/min/1.73m^2 were present, and in REACH an eGFR <60 ml/min/1.73m^2 was more frequent in aTRH.(29;32) This study adds detailed age and sex adjusted prevalence data according to eGFR and albuminuria. We feel this is an important aspect of aTRH especially for patients with prior cardiovascular disease like we studied. As CKD is an independent risk factor for cardiovascular disease, clustering with resistant hypertension can be expected to add up to a greatly increased CVD risk. For the patients we studied who have already suffered from CVD, the associated vascular risk may even be greater as well as the risk for end stage kidney disease.(22;23;36;37) Hypertension/vascular nephropathy is one of the commonest causes of ESRD.(38)

Apparent therapy-resistant hypertension has also been shown to increase risk for cardiovascular disease in both the general hypertensive population (22;35;39-41) and in patients with CKD (23;24;36;42) by 25-90% after adjustment for other cardiovascular risk factors. The REACH investigators reported a 20% increase in risk for a composite endpoint of cardiovascular death, myocardial infarction or stroke in patients with a history of vascular disease and aTRH in four years of follow-up.(32) Patients with aTRH, whether CKD, hypertensive only or with a history of cardiovascular disease, should be followed closely and every effort to increase blood pressure control should be made. Awareness of a high prevalence of aTRH in certain patient groups and clinical factors related to it might help improve vascular and renal outcomes.

Strengths of this study are the large, well defined population studied without restriction to one location of vascular disease, providing information for all physicians involved in CVD care. As the SMART study has been running for over 20 years now, change in the aTRH prevalence could also be studied. Risk factors were screened for with use of a standardized protocol. Office BP was calculated from the mean of several measurements. The most important limitation of the study, apart from the limitations inherent to the cross-sectional design with BP and medication use recorded at a single time-point, is that ambulatory blood pressure measurement

was not part of the protocol. White coat hypertension and masked hypertension leading to over- and underestimation of the prevalence of resistant hypertension, respectively, were therefore not excluded. As patients were often included shortly after the time of referral, the effect of adjustments made in antihypertensive drug treatment on the prevalence of aTRH was not assessed. For example, increase in the relatively low use of aldosterone-antagonists detected in the study could have decreased aTRH. The effect on the prevalence of aTRH however is unsure: reduction of under-treatment would decrease blood pressure decreasing aTRH, but increase in number of antihypertensive drugs would also increase aTRH based on the criterion of ≥4 drugs regardless of BP. Also, although use of antihypertensive drugs was carefully recorded, prescription refill data confirming adherence were not collected. Non-adherence has been shown to be an important cause of aTRH.(43) In conclusion, one of every 11 patients in a hospital-based population of patients with clinical manifest cardiovascular disease has apparent therapy-resistant hypertension. Risk factors are higher age, female sex, diabetes mellitus, duration and multiple locations of vascular disease, higher body mass index and waist circumference, lower eGFR, and albuminuria. Patients with aTRH deserve optimal treatment of cardiovascular risk factors in order to lower cardiovascular risk as well as the risk for end stage renal disease. Increased attention to aTRH could be an important effect of the new device-based hypertension therapies introduced the last decade.

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Table S1 Factors associated with aTRH standardized ORs

		Univariate analysis		Age & sex adjusted		Multivariate analysis	
	SD	OR	95% CI	OR	95% CI	OR	95% CI
Sex (female)						**1.53**	**1.18-1.99**
Age (years)	9.9	**1.37**	**1.25-1.50**	**1.37**	**1.25-1.50**	1.06	0.94-1.19
Diabetes mellitus						**1.66**	**1.28-2.16**
History of cardiac vascular disease						0.98	0.54-1.78
History of cerebral vascular disease						0.97	0.53-1.77
History of peripheral vascular disease						0.77	0.42-1.41
History of abdominal aneurysmatic disease						1.09	0.59-2.01
Multiple locations of vascular disease						1.53	0.77-3.01
Duration of vascular disease (years)	7.1	**1.26**	**1.18-1.35**	**1.22**	**1.13-1.31**	1.09	0.99-1.19
Body mass index (kg/m^2)	4.0	**1.36**	**1.26-1.47**	**1.43**	**1.31-1.55**	**1.18**	**1.01-1.38**
Waist circumference (cm)	11.8	**1.37**	**1.26-1.50**	**1.48**	**1.35-1.62**	**1.19**	**1.01-1.41**
Total cholesterol (mmol/l)	1.2	**0.91**	**0.83-0.99**	**0.89**	**0.82-0.98**	0.94	0.85-1.04
LDL cholesterol (mmol/l)	1.0	**0.83**	**0.76-0.91**	**0.83**	**0.75-0.91**	**0.87**	**0.79-0.97**
HDL cholesterol (mmol/l)	0.4	0.93	0.85-1.02	**0.85**	**0.77-0.94**	1.02	0.91-1.13
Triglycerides (mmol/l)	1.4	**1.13**	**1.05-1.22**	**1.18**	**1.09-1.28**	1.10	0.92-1.13
Fasting glucose (mmol/l)	1.7	**1.27**	**1.19-1.36**	**1.27**	**1.18-1.35**	1.03	0.93-1.15
hsCRP (mg/l)	9.1	1.03	0.95-1.11	1.00	0.92-1.09	0.90	0.80-1.02
eGFR (ml/min/1.73m^2)	18.0	**0.60**	**0.55-0.65**	**0.62**	**0.57-0.68**	**0.66**	**0.59-0.73**
Albuminuria (no)							
Microalbuminuria						1.27	0.99-1.63
Macroalbuminuria						1.03	0.59-1.81
Pack-years	20.1	1.06	0.98-1.16	1.08	1.00-1.18	1.02	0.92-1.12
Alcohol use						0.99	0.78-1.27
Physical exercise score	41.4	0.97	0.89-1.06	0.98	0.90-1.07	1.04	0.95-1.15
Carotid intima-media thickness (mm)	0.3	**1.18**	**1.10-1.28**	**1.12**	**1.03-1.21**	1.05	0.96-1.16
Ankle-brachialis index	0.2	**0.85**	**0.78-0.92**	**0.89**	**0.82-0.97**	**0.89**	**0.80-0.99**

In the multivariate analysis, total cholesterol was used for the other factors, HDL, LDL cholesterol and triglycerides were entered separately.

CHAPTER 4

Apparent resistant hypertension and the risk of vascular events and mortality in patients with manifest vascular disease

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Submitted

Abstract

Objectives

Patients with apparent resistant hypertension (aRH) are at increased risk for developing cardiovascular disease. It is unknown if this condition is related to increased cardiovascular risk in patients with clinically manifest vascular disease.

Methods

In 6191 hypertensive patients with clinically manifest vascular disease we evaluated the risk of subsequent vascular events and mortality between patients with controlled hypertension, uncontrolled hypertension, controlled aRH and uncontrolled aRH. Controlled aRH was defined as office blood pressure <140/90 mm Hg while using ≥4 antihypertensive drugs. Uncontrolled aRH was defined as office blood pressure ≥140/90 mm Hg while using 3 antihypertensive drugs including a diuretic, or ≥4 antihypertensive drugs. Outcomes of interest were myocardial infarction, stroke, cardiovascular mortality, the composite outcome of cardiovascular events and all-cause mortality.

Results

In total 2564 patients (41%) had controlled hypertension, 3063 patients (49%) had uncontrolled hypertension, 123 patients (2%) had controlled aRH, and 411 patients (7%) had uncontrolled aRH. During 7.1 years of follow-up patients with controlled aRH were at a higher risk of cardiovascular mortality (HR 1.86; 95%CI 1.10-3.15), and all-cause mortality (HR 1.64; 95%CI 1.07-2.52) compared with patients with controlled hypertension. Patients with uncontrolled aRH were at a higher risk of cardiovascular mortality (HR 1.36; 95%CI 1.01-1.83), and higher risk of all-cause mortality (HR 1.27; 95%CI 1.01-1.60) compared with patients with controlled hypertension.

Conclusions

In hypertensive patients with clinically manifest vascular disease, presence of controlled and uncontrolled aRH is related to an increased risk of cardiovascular mortality and all-cause mortality.

Introduction

Hypertension is a major modifiable risk factor for the development of cardiovascular disease, but also for subsequent cardiovascular events in patients with established cardiovascular disease.(1;2) Blood pressure lowering is needed to reduce cardiovascular risk but despite the availability of different classes of antihypertensive drugs, blood pressure goals are frequently not met.(3) A subgroup of patients with hypertension is considered to have apparent resistant hypertension, which is defined as uncontrolled blood pressure despite being treated with three or more antihypertensive medications or the use of four antihypertensive medications irrespective of blood pressure levels.(4) Apparent resistant hypertension has been reported in approximately 8-13% of the hypertensive population.(5;6) Patients with apparent resistant hypertension are at 1.5 times higher risk (95%CI 1.33-1.62) for developing cardiovascular disease compared with patients with non-resistant hypertension.(7) This might be caused by higher blood pressure levels and clustering of comorbidities that are related to both resistant hypertension and atherosclerosis. Comorbidities related to apparent resistant hypertension include obesity, diabetes and chronic kidney disease.(8;9) In hypertensive patients with manifest vascular disease there is a high prevalence of these risk factors which all contribute to the risk of subsequent events. Apparent resistant hypertension in patients with a history of vascular disease will most likely increase the risk of subsequent vascular events. However, whether apparent resistant hypertension confers an increased vascular risk beyond different levels of blood pressure remains to be clarified. For this purpose a distinction can be made between patients with controlled apparent resistant hypertension and uncontrolled apparent resistant hypertension. Therefore, we aimed to compare the risk for subsequent cardiovascular events and all-cause mortality between controlled apparent resistant hypertension, uncontrolled apparent resistant hypertension, uncontrolled hypertension and controlled hypertension in patients with clinically manifest vascular disease.

Methods

Subjects

The study population consisted of patients enrolled in the SMART study, an ongoing prospective single-center cohort study at the University Medical Center Utrecht. The study started in September 1996 and inclusion criteria were clinically manifest arterial disease (cerebrovascular disease, coronary heart disease, peripheral artery disease or abdominal aortic aneurysm) or an increased risk for atherosclerotic

vascular disease (hypertension, diabetes, hyperlipidemia). Cerebrovascular disease was defined as transient ischemic attack, cerebral infarction, (a)symptomatic carotid stenosis, amaurosis fugax or retinal infarction. Coronary artery disease was defined as angina pectoris, myocardial infarction, admission for percutaneous transluminal coronary angioplasty or coronary artery bypass graft. Peripheral arterial disease was defined as claudication of the legs, symptomatic and confirmed by resting ankle-brachial pressure index <0.9 in at least one leg, percutaneous transluminal angioplasty or leg amputation. Abdominal aortic aneurysm was defined as an aneurysm ≥3 centimeters (cm) or aneurysm surgery. Exclusion criteria were pregnancy, terminal malignant disease, not being independent in daily activities or insufficiently fluent in Dutch language. All study patients gave their written informed consent. The SMART study was approved by the ethics committee at the University Medical Center Utrecht. Detailed information on the rationale and design has been described elsewhere.(10)

For the present study, patients from this cohort with clinical manifest vascular disease and hypertension were eligible. Exclusion criterion was missing data on blood pressure or antihypertensive drug use (n=47), leaving 6191 patients for the analysis on cardiovascular events and all-cause mortality.

Measurements

Patients were asked to fill in a questionnaire regarding medical history. Physical examination was performed and fasting blood and urine samples were taken. From September 1998 on, a protocolized 12-lead 10 seconds electrocardiogram was made after 5 minutes rest with the patient in supine position. Carotid intima media thickness was measured in the anterolateral, posterolateral and mediolateral directions with an ATL Ultramark 9 (Advanced Technology Laboratories, Bothell, WA, USA) equipped with a 10-MHz linear array transducer. Carotid intima media thickness was defined as the mean of the left and right common carotid artery measurements. Between 1996 and 1999, office blood pressure was measured with a semiautomatic oscillometric device every 4 minutes at the right brachial arm in supine position during a total of 25 minutes. After 1999 blood pressure was measured with a non-random sphygmomanometer three times simultaneously at the right and left upper arm in upright position with an interval of 30 seconds. Before 1999 the mean blood pressure of all measurements was taken, after 1999 the mean of the last two blood pressure measurements from the highest arm was taken.

Definitions

Hypertension was defined as prescription of antihypertensive medication and/or measured office systolic blood pressure ≥140 or diastolic blood pressure ≥90 mm Hg. Medications were grouped based on drug class (angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, beta blockers, alpha blockers, calcium antagonists, diuretics, aldosterone antagonists, central acting antihypertensives, direct vasodilators). Patients were classified according to blood pressure control and use of antihypertensive medication; 1) controlled hypertension (blood pressure <140/90 mm Hg while using ≤3 antihypertensive drugs), 2) uncontrolled hypertension (blood pressure ≥140/90 mm Hg while using ≤2 antihypertensive drugs, or using 3 antihypertensive drugs not including a diuretic), 3) controlled apparent resistant hypertension (blood pressure <140/90 mm Hg while using ≥4 antihypertensive drugs), 4) and uncontrolled resistant hypertension (blood pressure ≥140/90 mm Hg while using 3 antihypertensive drugs including a diuretic, or ≥4 antihypertensive drugs). Diabetes was defined as fasting serum glucose ≥7.0 mmol/l, self-reported diabetes and/or use of insulin or oral hypoglycemic drugs. Body mass index was calculated by dividing weight in kilograms by the square of height in meters. Smoking was categorized as current smokers versus past/never smokers. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 creatinine equation.(11) Albuminuria was defined by an albumin/creatinine ratio ≥3 mg/mmol. Left ventricular hypertrophy on electrocardiography was defined according to the Sokolow-Lyon criterion when the voltage amplitude sum of either SV1+RV5 or SV1+RV6 was equal to or above 3.5 mV.(12)

Follow up and outcome evaluation

Patients were biannually asked to complete a questionnaire regarding hospital admissions and newly diagnosed diseases. Of each reported event, complete information was gathered by collecting hospital discharge letters, laboratory and radiology examinations. Death was reported by the medical specialist, general practitioner or relatives of the participant. Three members of the endpoint committee of physicians from different medical departments reviewed each event independently. The outcome events of interest for the present study included myocardial infarction, stroke, cardiovascular mortality, the composite of previous mentioned cardiovascular outcomes, and all-cause mortality (supplemental table 1). In total 310 patients (6.0%) were lost to follow up.

Data analyses

The relation between hypertension groups and cardiovascular events and all-cause mortality was evaluated by Cox proportional hazard models. Patients with controlled hypertension were chosen as the reference group. The results were adjusted for potential confounders based on literature including age, sex, smoking, body mass index, history of coronary artery disease, history of cerebrovascular disease, history of peripheral artery disease, history of abdominal aortic aneurysm, presence of diabetes mellitus, eGFR and albuminuria.(4;9;13) Three models were made. The first model included age and sex. The second model included age, sex, smoking, body mass index, type of vascular disease and diabetes. The third model included the before mentioned confounders and addition of albuminuria and eGFR. Sensitivity analyses were performed to determine the influence of patients with uncontrolled hypertension who are not treated with antihypertensive medication. Sensitivity analyses were also performed to determine whether the risk for cardiovascular disease and mortality were independent of differences in markers of end-organ damage by including left ventricular hypertrophy and carotid intima media thickness in the model. Results are presented as hazard ratios (HR) with 95% confidence intervals (95%CI). Proportional hazard assumptions were evaluated using Schoenfeld residuals, no violation was observed. There was no multicollinearity observed among variables in the models. Missing data were imputed using bootstrapping and predictive mean matching (aregImpute-algorithm in R, Hmisc-package), assuming that these values were missing at random.(14) Imputed variables included smoking (0.6%), body mass index (0.1%), eGFR (0.4%) and albuminuria (6.7%). Probability values less than 0.05 were considered significant. Analysis were performed with R statistical software version 3.0.3 (http://R-project.org).

Results

Baseline characteristics

In total 2564 patients (41%) had controlled hypertension, 3063 patients (49%) had uncontrolled hypertension, 123 patients (2%) had controlled apparent resistant hypertension, and 411 patients (7%) had uncontrolled apparent resistant hypertension (figure 1). In the uncontrolled hypertensive group 885 patients (29%) had high blood pressure (≥140/90 mm Hg) but did not use antihypertensive medication. Compared with patients with controlled hypertension, uncontrolled hypertension, or controlled apparent resistant hypertension, patients with uncontrolled apparent resistant hypertension had a higher mean age (64±9

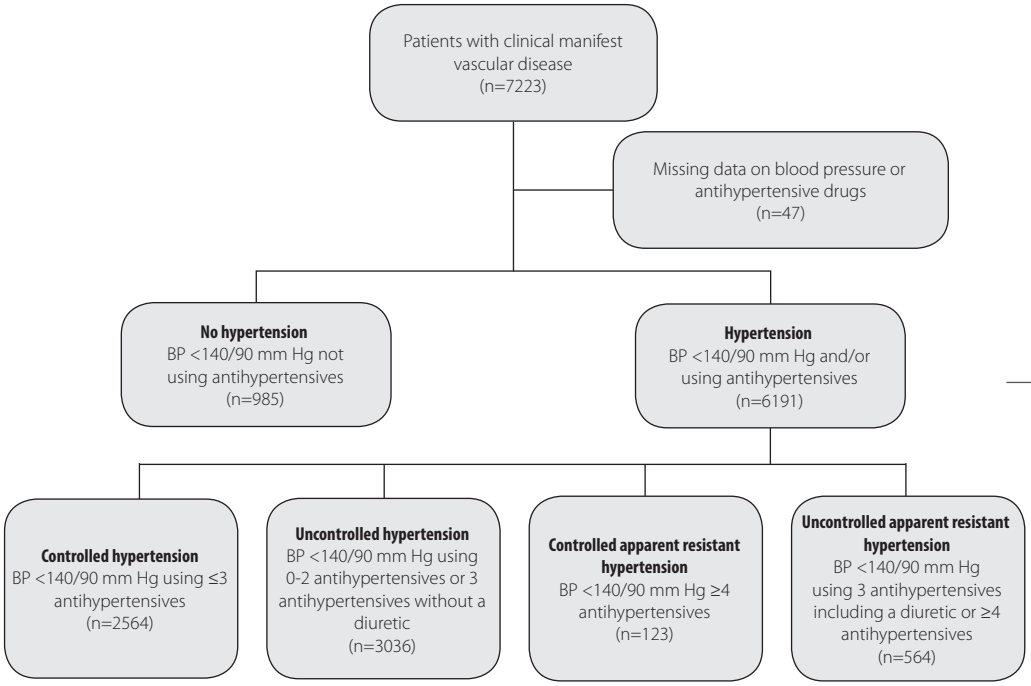

Figure 1 Flowchart of the study population

years), and were more likely to have diabetes and albuminuria (table 1). Mean number of prescribed antihypertensive drugs was 1.7 (standard deviation (SD) 0.8) in patients with controlled hypertension, 1.1 (SD 0.9) in patients with uncontrolled hypertension, 4.1 (SD 0.4) in patients with controlled apparent resistant hypertension, and 3.5 (SD 0.7) in patients with uncontrolled apparent resistant hypertension (table 2).

Risk of cardiovascular events and all-cause mortality

During the median follow up of 7.1 years (interquartile range 3.8-10.7) 749 patients experienced a myocardial infarction and 397 patients experienced a stroke. A total of 1556 patients died of any cause of whom 787 due to a cardiovascular cause. The composite outcome of cardiovascular events occurred in 1077 patients. Patients with uncontrolled hypertension had higher crude events rates for all outcomes compared with patients with controlled hypertension (table 3). Patients with uncontrolled apparent resistant hypertension had the highest crude event rates per 1000 person-years for the combined

Table 1 Baseline characteristics of all participants by hypertension groups

	Controlled hypertension (n = 2564)	Uncontrolled hypertension (n = 3063)	Controlled apparent resistant hypertension (n = 123)	Uncontrolled apparent resistant hypertension (n = 441)
Age (years)	59 (10)	62 (10)	62 (9)	64 (9)
Male	1966 (77%)	2272 (74%)	87 (71%)	304 (69%)
History of vascular disease				
Cerebrovascular disease	473 (18%)	1009 (33%)	35 (28%)	133 (30%)
Coronary heart disease	2063 (80%)	1642 (54%)	95 (77%)	305 (69%)
Abdominal aortic aneurysm	169 (7%)	293 (10%)	18 (15%)	52 (12%)
Peripheral arterial disease	250 (10%)	697 (23%)	19 (15%)	85 (19%)
Duration of vascular disease (years)	0 [0-4]	0 [0-4]	1 [0-9]	2 [0-10]
Current smoking	768 (30%)	919 (30%)	21 (17%)	106 (24%)
Diabetes mellitus	383 (15%)	586 (19%)	40 (33%)	148 (34%)
Body mass index (kg/m^2)	27 (4)	27 (4)	29 (5)	28 (4)
Systolic blood pressure (mm Hg)	124 (10)	156 (16)	123 (12)	160 (18)
Diastolic blood pressure (mm Hg)	75 (8)	88 (11)	74 (8)	88 (12)
Carotid intima media thickness (mm)	0.89 (0.26)	0.97 (0.29)	0.96 (0.32)	0.99 (0.27)
Left ventricular hypertrophy	100 (4.2%)	236 (8.7%)	4 (3.5%)	41 (9.8%)
Total cholesterol (mmol/L)	4.6 (1.1)	5.0 (1.3)	4.6 (1.0)	4.8 (1.2)
LDL-cholesterol (mmol/L)	2.7 (0.9)	3.0 (1.1)	2.6 (0.9)	2.7 (1.0)
HDL-cholesterol (mmol/L)	1.2 (0.3)	1.3 (0.4)	1.1 (0.3)	1.2 (0.4)
Creatinine (µmol/L)	92 (33)	95 (45)	109 (36)	104 (37)
eGFR (mL/min/1.73m^2)	77 (17)	75 (18)	64 (20)	66 (20)
Albuminuria	218 (9%)	519 (18%)	17 (15%)	112 (28%)
HbA1c (%)	5.9 (0.9)	6.1 (1.0)	6.1 (0.8)	6.3 (1.0)
Use of lipid-lowering-drugs	2039 (80%)	1895 (62%)	98 (80%)	342 (78%)
Use of antiplatelet-drugs	2210 (86%)	2227 (73%)	95 (77%)	339 (77%)

Values are presented as mean (standard deviation), median [interquartile range] or count (percentage)
Controlled hypertension: blood pressure <140/90mmHg and using ≤3 antihypertensives
Uncontrolled hypertension: blood pressure ≥140/90mmHg and using ≤2 antihypertensives or 3 antihypertensives without a diuretic
Controlled apparent resistant hypertension: blood pressure <140/90mmHg and using ≥4 antihypertensives
Uncontrolled apparent resistant hypertension: blood pressure ≥140/90mmHg and using 3 antihypertensives including a diuretic or using ≥4 antihypertensives

Table 2 Antihypertensive drugs use of all participants by hypertension classification

	Controlled hypertension	Uncontrolled hypertension	Controlled apparent resistant hypertension	Uncontrolled apparent resistant hypertension
	(n = 2564)	(n = 3063)	(n = 123)	(n = 441)
No. of antihypertensive drugs	1.7 (0.8)	1.1 (0.9)	4.1 (0.4)	3.5 (0.7)
ACE-inhibitors	965 (38%)	799 (26%)	91 (74%)	286 (65%)
Angiotensin II receptor blockers	274 (11%)	289 (9%)	39 (32%)	153 (35%)
Calcium antagonists	611 (24%)	568 (19%)	83 (67%)	221 (50%)
Loop diuretic	234 (9%)	105 (3%)	65 (53%)	176 (40%)
Thiazide diuretic	277 (11%)	223 (7%)	54 (44%)	255 (58%)
Potassium sparing diuretic	50 (2%)	63 (2%)	5 (4%)	30 (7%)
Aldosterone antagonists	56 (2%)	18 (1%)	49 (40%)	38 (9%)
Alpha blockers	8 (0.3%)	26 (1%)	5 (4%)	24 (5%)
Beta blockers	1965 (77%)	1379 (45%)	115 (94%)	357 (81%)
Central acting antihypertensives	2 (0.1%)	5 (0.2%)	2 (2%)	3 (1%)
Direct vasodilators	0 (0%)	0 (0%)	1 (0.8%)	1 (0.2%)

Values are presented as mean (standard deviation) or count (percentage)
Controlled hypertension: blood pressure <140/90mmHg and using ≤3 antihypertensives
Uncontrolled hypertension: blood pressure ≥140/90mmHg and using ≤2 antihypertensives or 3 antihypertensives without a diuretic
Controlled apparent resistant hypertension: blood pressure <140/90mmHg and using ≥4 antihypertensives
Uncontrolled apparent resistant hypertension: blood pressure ≥140/90mmHg and using 3 antihypertensives including a diuretic or using ≥4 antihypertensives

Table 3 Crude event rates for cardiovascular and mortality outcomes according to hypertension groups

	Controlled hypertension	Uncontrolled hypertension	Controlled Apparent resistant hypertension	Uncontrolled apparent resistant hypertension
	(n = 2564)	(n = 3063)	(n = 123)	(n = 441)
	Events per 1000 py	Events per 1000 py	Events per 1000 py	Events per 1000 py
Myocardial infarction	12.2	13.3	15.8	17.1
Stroke	4.6	7.8	8.8	10.7
Cardiovascular mortality	9.0	16.7	28.0	25.8
Cardiovascular events	19.0	26.0	36.8	38.5
All-cause mortality	17.6	31.0	40.3	41.7

Abbreviations: py; person-years
Controlled hypertension: blood pressure <140/90mmHg and using ≤3 antihypertensives
Uncontrolled hypertension: blood pressure ≥140/90mmHg and using ≤2 antihypertensives or 3 antihypertensives without a diuretic
Controlled apparent resistant hypertension: blood pressure <140/90mmHg and using ≥4 antihypertensives
Uncontrolled apparent resistant hypertension: blood pressure ≥140/90mmHg and using 3 antihypertensives including a diuretic or using ≥4 antihypertensives

outcome of cardiovascular events (38.5), and for all-cause mortality (41.7). Compared with controlled hypertension, presence of controlled apparent resistant hypertension was related to a higher risk of cardiovascular mortality (HR 1.86; 95%CI 1.10-3.15), and all-cause mortality (HR 1.64; 95%CI 1.07-2.52) (table 4, model III). Presence of uncontrolled apparent resistant hypertension was related to a higher risk of cardiovascular mortality (HR 1.36; 95%CI 1.01-1.83), and higher risk of all-cause mortality (HR 1.27; 95%CI 1.01-1.60) compared with controlled hypertension. Patients with uncontrolled hypertension were are at higher risk of stroke (HR 1.50; 95%CI 1.15-1.96), cardiovascular mortality (HR 1.134; 95%CI 1.11-1.62), and the composite outcome of cardiovascular events (HR 1.17; 95%CI 1.03 -1.34), compared with patients with controlled hypertension (table 4, model I). However, patients were no longer at higher risk for adverse events when additional adjustments were made for other potential confounders (table 4, model III). Sensitivity analyses were performed to determine whether the results for the uncontrolled hypertension group were influenced by the proportion of untreated patients with uncontrolled blood pressure (≥140/90 mm Hg). Exclusion of these patients (n=885) did not change the results (supplemental table 2). Lastly, in sensitivity analyses additional adjustments were made for markers of end-organ damage, including left ventricular hypertrophy and carotid intima media thickness (supplemental table 3). Addition of these markers did not substantially change the results.

Table 4 Relation between hypertension groups and cardiovascular events and mortality

	Controlled hypertension (n=2564)		Uncontrolled hypertension (n=3063)		Controlled apparent resistant hypertension (n=123)		Uncontrolled apparent resistant hypertension (n=441)	
	Event no.	HR (95%CI)	Event no.	HR (95%CI)	Event no.	HR (95%CI)	Event no.	HR (95%CI)
Myocardial infarction	219		315		9		43	
Model I		reference		1.00 (0.83 - 1.19)		1.24 (0.64 - 2.43)		1.28 (0.92 - 1.78)
Model II		reference		0.98 (0.81 - 1.18)		1.08 (0.55 - 2.13)		1.12 (0.80 - 1.57)
Model III		reference		0.99 (0.82 - 1.18)		0.99 (0.50 - 1.94)		1.04 (0.74 - 1.46)
Stroke	82		185		5		27	
Model I		reference		1.50 (1.15 - 1.96)		1.63 (0.66 - 4.04)		1.92 (1.23 - 2.98)
Model II		reference		1.13 (0.86 - 1.50)		1.52 (0.61 - 3.79)		1.59 (1.01 - 2.49)
Model III		reference		1.12 (0.85 - 1.47)		1.37 (0.55 - 3.42)		1.40 (0.89 - 2.19)
Cardiovascular mortality	161		397		16		65	
Model I		reference		1.34 (1.11 - 1.62)		2.82 (1.68 - 4.72)		2.05 (1.53 - 2.74)
Model II		reference		1.08 (0.89 - 1.31)		2.10 (1.24 - 3.55)		1.53 (1.14 - 2.06)
Model III		reference		1.09 (0.90 - 1.32)		1.86 (1.10 - 3.15)		1.36 (1.01 - 1.83)
Cardiovascular events	341		618		21		97	
Model I		reference		1.17 (1.03 - 1.34)		1.72 (1.10 - 2.67)		1.68 (1.34 - 2.12)
Model II		reference		1.04 (0.90 - 1.19)		1.42 (0.91 - 2.22)		1.40 (1.11 - 1.76)
Model III		reference		1.04 (0.90 - 1.20)		1.28 (0.82 - 2.00)		1.25 (0.99 - 1.58)
All-cause mortality	316		737		23		105	
Model I		reference		1.03 (0.89 - 1.19)		2.15 (1.41 - 3.29)		1.73 (1.38 - 2.17)
Model II		reference		1.27 (1.11 - 1.46)		1.79 (1.16 - 2.75)		1.40 (1.11 - 1.75)
Model III		reference		1.03 (0.90 - 1.19)		1.64 (1.07 - 2.52)		1.27 (1.01 - 1.60)

Model I was adjusted for age and sex
Model II was adjusted for age, sex, smoking, BMI, diabetes, and location of vascular disease
Model III was adjusted for age, sex, smoking, BMI, diabetes, location of vascular disease, eGFR and albuminuria
Controlled hypertension: blood pressure <140/90mmHg and using ≤3 antihypertensives
Uncontrolled hypertension: blood pressure ≥140/90mmHg and using ≤2 antihypertensives or 3 antihypertensives without a diuretic
Controlled apparent resistant hypertension: blood pressure <140/90mmHg and using ≥4 antihypertensives
Uncontrolled apparent resistant hypertension: blood pressure ≥140/90mmHg and using 3 antihypertensives including a diuretic or using ≥4 antihypertensives

Discussion

In the present study in hypertensive patients with clinically manifest vascular disease, the presence of controlled and uncontrolled apparent resistant hypertension is related to a higher risk of cardiovascular mortality and all-cause mortality, compared with patients with controlled hypertension. Patients with uncontrolled hypertension are not at increased risk of cardiovascular events, after correction for confounding factors, compared with patients with controlled hypertension.

Previous studies demonstrated that patients with resistant hypertension are at higher risk of development of cardiovascular disease compared with non-resistant hypertensive patients.(7; 15; 16) This study adds that apparent resistant hypertension also confers an increased risk of subsequent cardiovascular events. This finding is supported by previous studies in high-risk populations including patients with a history of cardiovascular disease and patients with vascular risk factors. The REACH study reported that resistant hypertension was related to a 10% higher risk for cardiovascular events in a mixed population of patients with subclinical and established vascular disease.(17) In patients with coronary heart disease presence of resistant hypertension was related to 64% higher risk of a major cardiovascular events.(18) In this study diuretic drug use was not a requirement for the definition of resistant hypertension, limiting direct comparison with our results.

The increased risk of cardiovascular mortality in patients with apparent resistant hypertension was also present in patients with controlled apparent resistant hypertension. Conflicting results have been reported regarding this topic. A population based cohort study reported that patients with controlled resistant hypertension were at 21% higher risk for ischemic heart events (95%CI 16% - 26%) and 5% higher risk for mortality (95%CI 2% - 9%) compared with patients with non-resistant hypertension.(15) In the REGARDS study there was no increased cardiovascular risk observed for patients with resistant hypertension and controlled blood pressure compared with non-resistant hypertensive patients.(16) This might in part be attributable to the relatively small number of cardiovascular events observed (23 strokes and 17 coronary heart diseases) in patients with controlled resistant hypertension.

Increased mortality risk in patients with apparent resistant hypertension could result from a longstanding history of poorly controlled blood pressure.(4) Although duration of hypertension was unknown, patients with controlled and uncontrolled apparent resistant hypertension did suffer from a slightly longer history of vascular disease compared with patients with controlled hypertension and uncontrolled

hypertension. Prolonged exposure to high blood pressure can lead to hypertensive end-organ damage, such as left ventricular hypertrophy, which in turn is related to increased cardiovascular risk.(19) However, additional adjustment for markers of end-organ damage (i.e. left ventricular hypertrophy and carotid intima media thickness) did not substantially change the magnitude or direction of the effect estimates. Yet, this observation does not exclude the possibility that end-organ damage may attribute to increased cardiovascular mortality risk for patients with apparent resistant hypertension. For example, presence of end-organ damage at other locations (i.e. retinopathy) was not assessed.

Patients with uncontrolled blood pressure were not at increased risk of cardiovascular events and mortality compared with patients with controlled hypertension, after correction for confounding factors. This observation suggests that the higher risk in these patients is more likely driven by other vascular risk factors rather than elevated blood pressure. It is also possible that misclassification of patients with white coat hypertension may have occurred because blood pressure was measured using office measurements. Patients with white coat hypertension could have been labelled as having uncontrolled hypertension or uncontrolled apparent resistant hypertension (depending on the number of prescribed antihypertensive drugs).

The global prevalence of hypertension is predicted to rise by 9% in men and 13% in women between 2000 and 2025.(20) This will most likely be accompanied by a rise in apparent resistant hypertension. Blood pressure targets (<140/90 mm Hg) were reached in 123 patients with apparent resistant hypertension, whereas 441 patients had uncontrolled apparent resistant hypertension. This shows that the majority of apparent resistant hypertensive patients fail to achieve blood pressure goals despite being prescribed a triple drug regimen. This observation highlights the importance to continue with the development of alternative treatments, such as device-based therapies, to meet blood pressure goals in patients with uncontrolled apparent resistant hypertension. In patients with controlled apparent resistant hypertension it is important to attain to all recommended treatment targets for secondary prevention in order to reduce the risk of subsequent vascular events.

The major strength of the SMART study is the prospective cohort study design with sufficient follow up time and a large number of clinical relevant outcomes. Blood pressure was measured according to a highly standardized protocol. Some limitations need to be considered. We adjusted for potential confounders in the analyses but confounding by indication cannot be ruled out. Clinicians

may have identified patients with apparent resistant hypertension as having a high cardiovascular risk and therefore prescribed three or more antihypertensive drugs. On the other hand, all patients with clinically manifest vascular disease are considered high-risk patients for whom intensive cardiovascular risk reducing measures are indicated.(21) Furthermore, no information regarding medication adherence was available. Antihypertensive drug use was assessed by self-report and was checked with the electronic health record for the most up to date medication use, which is the most useful method in a clinical setting.(22) Lastly, blood pressure and use of antihypertensive drugs were measured at baseline but may have changed during follow-up. Previous studies in resistant hypertensive patients demonstrated that a large proportion of these patients still fulfilled the criteria of resistant hypertension during follow-up.(23, 24)

In conclusion, in hypertensive patients with clinically manifest vascular disease, presence of controlled and uncontrolled apparent resistant hypertension is related to an increased risk of cardiovascular mortality and all-cause mortality. Recognizing apparent resistant hypertension, particularly in patients already at high vascular risk, may alert clinicians to monitor for end-organ damage and to attain to treatment targets beyond blood pressure control.

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Supplement

Table S1 Definitions of vascular events and mortality

Myocardial infarction	At least two of the following criteria: 1. chest pain for at least 20 minutes, not disappearing after administration of nitrates; 2. ST-elevation > 1mm in two following leads or a left bundle branch block of the electrocardiogram; 3. Creatine kinase (CK) elevation of at least two times the normal value of CK and a myocardial fraction >5% of total CK
Stroke	Definite: relevant clinical features causing an increase in impairment of at least one grade on the modified Rankrin scale, accompanied by an infarction of hemorrhage on a repeat CT-scan Probable: clinical deficits causing an increase in impairment of at least one grade in the modified Rankin scale, without CT documentation
Cardiovascular mortality	Death from myocardial infarction, stroke, congestive heart failure, or rupture of abdominal aortic aneurysm. Sudden death (unexpected cardiac death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence)
Cardiovascular event	Composite of myocardial infarction, stroke, retinal infarction, and cardiovascular mortality
All-cause mortality	Death from any cause

Table S2 Relation between hypertension groups and cardiovascular events and mortality, excluding 885 patients with uncontrolled hypertension not using antihypertensive drugs

	Controlled hypertension (n=2564)		**Uncontrolled hypertension** (n=2178)		**Controlled apparent resistant hypertension** (n=123)		**Uncontrolled apparent resistant hypertension** (n=441)	
	Event no.	HR (95%CI)	Event no.	HR (95%CI)	Event no.	HR (95%CI)	Event no.	HR (95%CI)
Myocardial infarction	219		215		9		43	
Model I		reference		0.97 (0.80 - 1.17)		1.26 (0.64 - 2.45)		1.30 (0.93 - 1.81)
Model II		reference		0.95 (0.78 - 1.16)		1.10 (0.56 - 2.15)		1.14 (0.81 - 1.60)
Model III		reference		0.95 (0.78 - 1.15)		0.98 (0.50 - 1.92)		1.05 (0.74 - 1.47)
Stroke	82		131		5		27	
Model I		reference		1.51 (1.14 - 2.01)		1.64 (0.66 - 4.04)		1.94 (1.24 - 3.02)
Model II		reference		1.25 (0.94 - 1.67)		1.60 (0.64 - 3.98)		1.64 (1.05 - 2.58)
Model III		reference		1.21 (0.90 - 1.61)		1.43 (0.57 - 3.59)		1.45 (0.92 - 2.28)
Cardiovascular mortality	161		278		16		65	
Model I		reference		1.32 (1.09 - 1.62)		2.81 (1.68 - 4.71)		2.05 (1.53 - 2.75)
Model II		reference		1.14 (0.93 - 1.39)		2.15 (1.27 - 3.64)		1.54 (1.15 - 2.08)
Model III		reference		1.13 (0.92 - 1.38)		1.84 (1.09 - 3.13)		1.36 (1.01 - 1.83)
Cardiovascular events	341		433		21		97	
Model I		reference		1.16 (1.01 - 1.35)		1.72 (1.11 - 2.68)		1.70 (1.35 - 2.14)
Model II		reference		1.06 (0.91 - 1.23)		1.45 (0.92 - 2.27)		1.41 (1.12 - 1.79)
Model III		reference		1.05 (0.90 - 1.22)		1.28 (0.82 - 2.01)		1.26 (1.00 - 1.59)
All-cause mortality	316		487		23		105	
Model I		reference		1.05 (0.90 - 1.22)		2.13 (1.40 - 3.27)		1.73 (1.38 - 2.17)
Model II		reference		1.19 (1.03 - 1.38)		1.79 (1.16 - 2.75)		1.40 (1.12 - 1.77)
Model III		reference		1.04 (0.90 - 1.21)		1.60 (1.03 - 2.46)		1.27 (1.01 - 1.60)

Model I was adjusted for age and sex;
Model II was adjusted for age, sex, smoking, BMI, diabetes and location of vascular disease
Model III was adjusted for age, sex, smoking, BMI, diabetes, location of vascular disease, eGFR and albuminuria;
Controlled hypertension: blood pressure <140/90mmHg and using ≤3 antihypertensives
Uncontrolled hypertension: blood pressure ≥140/90mmHg and using ≤2 antihypertensives or 3 antihypertensives without a diuretic
Controlled apparent resistant hypertension: blood pressure <140/90mmHg and using ≥4 antihypertensives
Uncontrolled apparent resistant hypertension: blood pressure ≥140/90mmHg and using 3 antihypertensives including a diuretic or using ≥4 antihypertensives

Table S3 Relation between hypertension groups and cardiovascular events and mortality

	Controlled hypertension (n=2564)		Uncontrolled hypertension (n=3063)		Controlled apparent resistant hypertension (n=123)		Uncontrolled apparent resistant hypertension (n=441)	
	Event no.	HR (95%CI)	Event no.	HR (95%CI)	Event no.	HR (95%CI)	Event no.	HR (95%CI)
Myocardial infarction	219		315		9		43	
Model I		reference		1.00 (0.81 - 1.22)		0.88 (0.41 - 1.89)		1.03 (0.72 - 1.48)
Stroke	82		185		5		27	
Model I		reference		1.10 (0.81 - 1.49)		1.44 (0.52 - 3.99)		1.55 (0.97 - 2.45)
Cardiovascular mortality	161		397		16		65	
Model I		reference		1.18 (0.95 - 1.46)		1.96 (1.07 - 3.58)		1.44 (1.04 - 2.00)
Cardiovascular events	341		618		21		97	
Model I		reference		1.03 (0.88 - 1.20)		1.26 (0.77 - 2.07)		1.25 (0.98 - 1.61)
All-cause mortality	316		737		23		105	
Model I		reference		1.06 (0.90 - 1.23)		1.78 (1.11 - 2.85)		1.27 (0.99 - 1.63)

Model I was adjusted for age, sex, smoking, BMI, diabetes, location of vascular disease, eGFR, albuminuria, left ventricular hypertrophy and carotid intima media thickness

Controlled hypertension: blood pressure <140/90mmHg and using ≤3 antihypertensives

Uncontrolled hypertension: blood pressure ≥140/90mmHg and using ≤2 antihypertensives or 3 antihypertensives without a diuretic

Controlled apparent resistant hypertension: blood pressure <140/90mmHg and using ≥4 antihypertensives

Uncontrolled apparent resistant hypertension: blood pressure ≥140/90mmHg and using 3 antihypertensives including a diuretic or using ≥4 antihypertensives

CHAPTER 5

Sympathetic activation secondary to chronic kidney disease: therapeutic target for renal denervation?

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Abstract

Percutaneous ablation of the renal nerves (renal denervation, RDN) has recently become available for treatment of (therapy-resistant) hypertension. In this review, the potential importance of RDN for patients with chronic kidney disease (CKD) is discussed. An overview of the role of the renal nerves is given, and the role of the kidneys as both generators and recipients of sympathetic hyperactivity is described. The clinical relevance of increased sympathetic nervous system activity in CKD is reviewed, and the effects of conventional treatment on sympathetic hyperactivity are summarized. Next, we present the current knowledge on the effect of RDN in CKD from both experimental and clinical studies. Finally, we discuss how this knowledge may help us in predicting the effect of RDN in hypertensive patients and ways to monitor the effect of the procedure itself.

Introduction

Increased activity of the sympathetic nervous system (SNS) can contribute to the pathogenesis of hypertension, cardiovascular morbidity and mortality and possibly kidney failure progression.(1;2) Recently, catheter based renal denervation (RDN) has become available for the treatment of hypertension. Many centers all over the world have started with this therapy or are considering doing so. RDN is aimed to reduce (or even eliminate) the activity of renal afferent and efferent nerves. It seems attractive to hypothesize that this intervention is especially effective in disease conditions where these nerves are particularly active.

In this review, we will first briefly summarize the role of renal nerves and the fact that kidneys are likely to be both generators and recipients of sympathetic hyperactivity. Next, we will discuss conventional treatment options. We then briefly review evidence on the clinical relevance of increased SNS activity in chronic kidney disease (CKD) and on the effect of RDN in CKD from both experimental and clinical studies. Finally, we discuss how this knowledge could help us in positioning RDN within our therapeutic arsenal.

Pathogenesis

There is convincing evidence that the kidneys can be both generators and recipients of increased SNS activity. To explain this, we briefly outline the function of the renal nerves and their possible role in disease conditions such as hypertension and CKD. The subject has been reviewed extensively in the past.(3-10)

The kidneys have both afferent and efferent nerve fibers. These are located in the adventitia around the renal artery.(11) Nerve activity is difficult to measure but studies applying nerve stimulation have revealed various effects of these nerves. Graded stimulation of efferent activity induces renin release (renin-angiotensin-aldosterone system, RAAS activation) followed by an increase in sodium reabsorption and a decrease in renal blood flow at higher levels of stimulation (figure 1).(9) There is clear evidence that increased afferent activity can cause hypertension.(12;13) Kidney injury or kidney ischemia plays a central role in this respect. The precise mechanism of afferent activation in kidney injury is complex. Various processes and substances may be involved, including ischemia, increased activity of RAAS, adenosine and chemoreflex activation, decreased nitric oxide availability and possibly reduced renalase availability.(3;7;14) Campese et al. showed in subtotally nephrectomized rats that blood pressure rapidly increases

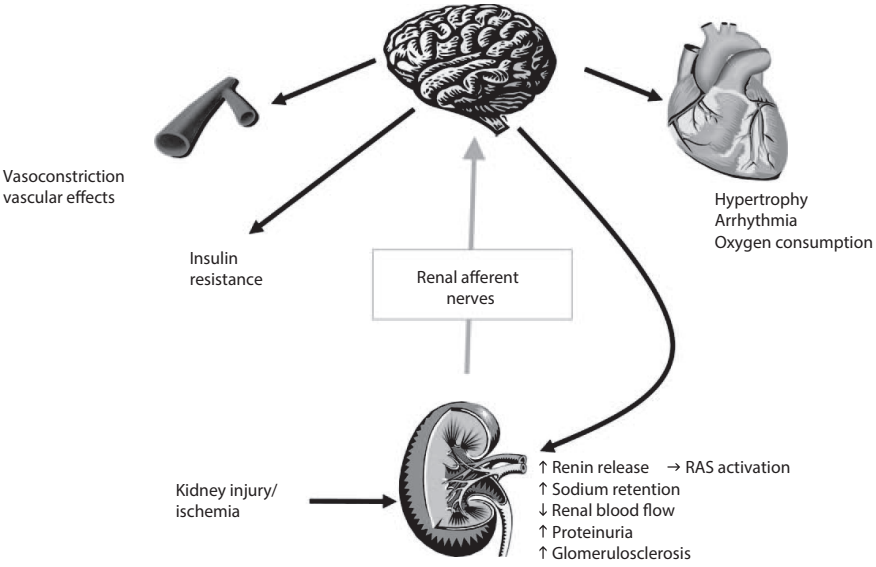

Figure 1 Schematic representation of the kidney involvement in the pathogenesis of sympathetic hyperactivity. Minimal kidney damage, not necessarily affecting kidney function, results in area(s) of ischemia. This results in increased afferent nerve activity and increased activation of the renin-angiotensin system (RAS) and central nervous system (CNS). Increased central sympathetic outflow affects many organs also including the cardiovascular system. In addition, RAS activation may enhance sympathetic activity on the peripheral level.

after surgery, which was abolished by afferent denervation.(15) Importantly, in a later study in rats they showed that applying a small lesion in one kidney by an intrarenal phenol injection, not affecting kidney function, increases sympathetic activity and leads to a long term increase in noradrenaline secretion and hypertension.(16) These effects are also abolished by afferent denervation. Afferent activity from the kidneys also increases when mechanosensory fibers located in the pelvic wall are stimulated by stretch when pelvic pressure is increased. Increased afferent activity from the kidneys in this situation has an *inhibitory* effect with a decrease in efferent activity to the kidneys and resultant natriuresis from the contralateral kidney (an inhibitory renorenal reflex response).(10;17) Other renal receptors (e.g renal vein mechanoreceptors) have also been shown to be involved in inhibitory reflex responses.(10) The pelvic pressure dependent inhibitory afferent activity is increased in high salt diet and with increased renal efferent activity.(17) However, in rats with heart failure or hypertension, this inhibitory afferent activity was suppressed because of a suppressive effect of intrarenal angiotensin.(19;20)

It might be that in situations of kidney injury, this inhibitory function is suppressed in a similar way or overruled by the excitatory afferent activity as described above.

In clinical research, Kim et al.(21) were among the first to describe that the presence of diseased kidneys can lead to hypertension characterized by high peripheral vascular resistance. They reported that bilateral nephrectomy resulted in a substantial drop in blood pressure, which was caused by a decrease in peripheral vascular resistance. Converse et al.(22) were the first to show that muscle sympathetic nerve activity (MSNA) is increased in dialysis patients whereas it is comparable with normal individuals in bilateral nephrectomized dialysis patients. These data provide very convincing evidence that the diseased kidneys are critically involved in the pathogenesis of increased MSNA, which is a reliable measurement of central sympathetic activity, as illustrated in figure 1. In subsequent studies, we and others showed that MSNA is increased not only in dialysis patients but already in patients with CKD not on dialysis yet.(23-33) In a study in polycystic kidney disease patients we showed that MSNA was increased in hypertensive patients with normal kidney function, (25) suggesting that it is parenchymal injury and not decreased estimated glomerular filtration rate (eGFR) per se that drives the MSNA. Supporting this statement, we found that unilateral nephrectomy for living kidney donation (resulting in decreased renal mass in absence of parenchymal disease) did not affect MSNA measured several months after donation.(26) We also found parallel shifts of renin activity and MSNA along with changes in volume status in CKD patients.(26) This clearly underscores the interrelationship between the RAAS and the sympathetic system, and can be best explained by a cause and effect relation or a common origin. This is discussed in great detail elsewhere.(3;4;34) Finally, an interaction with the nitric oxide system was found.(35)

Taken together, the available data seem to indicate that kidney injury/failure is associated with increased sympathetic activity, quantified by MSNA. In this pathophysiological model the afferent renal nerves are of crucial importance. Kidney ischemia could be a central mechanism.

Relevance

Sympathetic hyperactivity, blood pressure and outcome in chronic kidney disease

Hypertension is highly prevalent in patients with CKD. Recent analyses show that insufficiently controlled blood pressure is often present.(36-38) In hypertensive CKD patients, MSNA increases in successive stages of CKD.(23) There is some evidence indicating that the level of MSNA is related to the mean arterial pressure in patients

with CKD.(4) Moreover, lowering of sympathetic drive by antihypertensive treatment causes a parallel decrease in MSNA and blood pressure.(24;27;39;40) Although a detrimental effect on clinical outcome of sympathetic hyperactivity can be inferred from its connection with hypertension, direct evidence for this is scarce in CKD. This is in contrast to heart failure, in which sympathetic hyperactivity has been shown to predict mortality in many studies.(41-44) Some evidence however does exist. In hemodialysis patients, an increase in plasma noradrenaline has been shown to predict mortality and cardiovascular events.(45) In hemodialysis patients with heart failure carvedilol has been shown to decrease mortality(46) which could be related to its sympathicolytic effect.(47) A study in CKD patients (stage 3-4) found MSNA to be associated with a composite endpoint of mortality and cardiovascular events in 6 years of follow-up (in multivariate analysis including blood pressure and age).(48) We found an increase in left ventricular mass with higher MSNA in CKD patients.(30) As all other studies measuring MSNA in CKD were cross-sectional, it is currently unknown whether sympathetic hyperactivity is involved in the rate of progression of CKD rather than (only) being a consequence of decline in GFR. Animal studies however, have shown beneficial effects of lowering of sympathetic drive on renal injury and proteinuria, whether by medication as previously reviewed(14) or by RDN (described below). In patients with advanced CKD (GFR <30 ml/min) the sympathicolytic agent moxonidine has been shown to decrease kidney function decline in a short (6 months) follow-up period.(49) The possible role of sympathetic activity on outcome in CKD patients is discussed in more detail elsewhere.(3;4;34)

Effects of conventional (non)medical therapy

Several pharmacological and lifestyle interventions affect sympathetic activity. Most of the studies were done in various forms of hypertension and heart failure. Only a few were specifically done in CKD. In general, RAAS inhibitors decrease sympathetic activity. Indeed, we have documented that chronic treatment with an angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB) and aliskiren lowers MSNA in CKD patients.(24;27;29) In patients with essential hypertension evidence for a sympathetic activity lowering effect of ARBs has been more equivocal.(50;51) In heart failure patients, both ACE inhibition and ARB treatment have been shown to reduce cardiac sympathetic activity using ^{123}I-metaiodobenzyl-guanidine (^{123}I-MIBG).(52-57) Although a head-to-head comparison was not done, the effect of the various compounds seems comparable. The precise mechanism of this effect is unknown. It seems attractive to hypothesize that intrarenal effects of these agents (for instance increase in renal perfusion and therefore decrease in ischemia) could be of relevance. Effects within the central

nervous system cannot be ruled out. An old study suggests some blood pressure lowering effect of an ACEi in bilaterally nephrectomized patients.(58) On average, chronic treatment with RAAS inhibitors lowers but does not normalize sympathetic activity in CKD patients. (27) Normalization occurred when moxonidine was added to ARB treatment (40). The effect of beta-blockade on sympathetic outflow as measured with MSNA is more complex as long-term treatment decreases the bursts per minute, whereas bursts per 100 heartbeats remain stable in parallel with the decreased heart rate on beta-blockade treatment. (59;60) In patients with heart failure MSNA decreased on chronic beta-blockade treatment in several studies.(61;62) No data are available on the effect of beta blockade on sympathetic overdrive in CKD patients. Calcium-channel blockers increase sympathetic activity in most studies.(24;63;64) Sustained use of amlodipine has been shown to increase sympathetic activity in CKD patients.(24;65) Differences in sympathetic activation may exist between calcium-channel blockers.(66) Dietary salt restriction, although having a beneficial effect on blood pressure, has been shown to increase MSNA. (67;68) Similarly, the thiazide diuretic chlorthalidone has been shown to increase sympathetic activity, whereas the aldosterone antagonist spironolactone had no effect on MSNA in the same study, despite a similar reduction of blood pressure. (69) A subsequent study showed that addition of spironolactone to chlorthalidone neutralizes the chlorthalidone-induced increase in MSNA.(70) Again, no studies are available on the effects of spironolactone on sympathetic activity in CKD. The other major lifestyle intervention in hypertension, weight reduction, has been shown to reduce MSNA in obese patients.(71;72) In obese patients with normal kidney function, weight reduction has been shown to decrease microalbuminuria in parallel with a decrease in MSNA and blood pressure.(73)

In summary, while moxonidine and RAAS inhibitors reduce sympathetic hyperactivity in CKD, the effect of beta-blockade is uncertain and calcium antagonists and thiazide diuretics seem to increase sympathetic drive. Salt restriction increases, whereas weight reduction decreases MSNA.

New treatment option: renal denervation

Given the pathophysiological evidence outlined above, it is attractive to hypothesize that RDN could be especially effective in patients with kidney disease or injury. What experimental evidence is available for this? What is already known about the effect of RDN in CKD patients?

Evidence from experimental studies on renal denervation in different models of chronic kidney disease

Disruption of the renal nerves can be achieved in rodents by chemical sympathectomy with guanethidine, bilateral dorsal rhizotomy, or direct RDN by stripping the renal artery mechanically followed by application of phenol in alcohol directly on the renal artery. These approaches have been applied in numerous experimental settings. Studies relevant for CKD are listed in table 1. The studies have provided us with important information on the antihypertensive and renoprotective effects of RDN.

Etiologically, it is clear that disturbing renal sympathetic activity ameliorates the development of hypertension and subsequent renal injury in nitric oxide synthase inhibition(74;75) and in the unilateral nephrectomized Dahl salt-sensitive rat when RDN precedes exposure to 8% salt.(76) Very relevant to the clinic, is whether denervation subsequent to renal ablation can lower blood pressure and provide kidney protection. This appears to be the case for dorsal rhizotomy.(77;78) In fact, bilateral dorsal rhizotomy lowers blood pressure, proteinuria and activation of the brain renin- angiotensin system in unilateral nephrectomized spontaneously hypertensive rat (SHR), strongly suggesting that renal afferent activity is also important for maintenance of the central generation of hypertension in this model.(79) Similarly in rats with subtotal nephrectomy, bilateral dorsal rhizotomy prevents in large part the development of hypertension, the increase in serum creatinine and the increase in noradrenaline turnover rate in hypothalamic nuclei and adjacent structures.(15;80) Furthermore, some studies combined dorsal rhizotomy or RDN with the second operation in two-stage renal ablation.(15;80;81) However, in such protocols, RDN is a preventive rather than rescue intervention as glomerulosclerosis only occurs after the second stage of ablation.

In an recent study of the cardiorenal syndrome, in which aortic regurgitation was induced in uninephrectomized rats, prior RDN provided marked and long-term (6 month) reduction of glomerular injury and albuminuria with no effect on blood pressure (already reduced by aortic regurgitation) and only a minor effect on GFR.(82) Interestingly this study also found persistent absence of renal noradrenaline and reduction of renal angiotensinogen, angiotensin II and the angiotensin type 1 receptor after 6 months suggesting that in this model recovery of renal innervation was much slower than in most other studies.

RDN in Dahl salt-sensitive rats, in which they removed the right kidney and denervated the left renal artery, showed a protective effect against glomerulosclerosis, albuminuria and podocyte injury, compared with no denervation (sham surgery).(76) Furthermore, when Anti–Thy-1.1 glomerulonephritis was induced in

Table 1 Effects of renal denervation, dorsal rhizotomy or neonatal sympathectomy on blood pressure, renal function, renal injury and the renin angiotensin system in different models of CKD

Model	Treatment	Study Length	Blood Pressure	Glomerular Filtration Rate	UalbV UproV	Glomerular Injury	Tubulo-int. Injury	Renin Angiotensin System	Ref.
UNX + Aortic regurgitation	Renal denervation	26 wk	SBP ↔ DBP ↓	↔/↑ (P=0.06)	↓↓	↓	N/Az	Plasma AII, renal AII, urine angiotensinogen↓	(82)
5/6 NX excision	Dorsal rhizotomy	16 wk	↓	↑	↓	↓	↓	N/A	(77)
5/6 NX excision	Renal denervation	12 wk	↔	↔	↓	↓	↓	N/A	(81)
UNX + SHR	Dorsal rhizotomy	12 wk	↓	N/A	↓	N/A	N/A	Brain RAS ↓	(79)
5/6 NX infarction	Dorsal rhizotomy	6 wk	↓	↑	N/A	↑	N/A	N/A	(15)
5/6 NX infarction	Dorsal rhizotomy	6 wk	↓	↑	N/A	N/A	N/A	N/A	(80)
5/6 NX infarction	Neonatal sympathectomy (guanethidine)	6 wk	↓	↔	↓	↔	N/A	N/A	(11)
UNX + Dahl salt-sensitive	Renal denervation	6 wk	SBP ↔	↑	↓	↓	N/A	Renal renin activity ↓	(76)
NO synthase inhibition	Renal denervation	4 wk	↓	N/A	↓	N/A	N/A	N/A	(74)
NO synthase inhibition	Renal denervation	4 wk	N/A	N/A	↓	↓↓	↓	N/A	(75)
ADPKD	Renal denervation	4 wk	↓	↑	N/A	N/A	N/A	N/A	(78)
Dahl salt-sensitive + amlodipine	Renal denervation	3 wk	↔	↔	↓	↓	N/A	N/A	(139)
UNX + Cyclosporine A	Renal denervation	3 wk	SBP ↔	↔	↔	N/A	↔	N/A	(84)
UUO (mice)	Renal denervation	10 d	N/A	N/A	N/A	N/A	↓	N/A	(85)
Anti–Thy-1.1 nephritis	Renal denervation	5 d	N/A	N/A	↓	↓	N/A	N/A	(83)

Abbreviations: UalbV, albuminuria; UproV, proteinuria; tubulo-int., tubulointerstitial; UNX, uninephrectomy; SBP, systolic blood pressure; DBP, diastolic blood pressure; N/A, not available; AII, angiotensin II; NX, nephrectomy; SHR, spontaneously hypertensive rat; RAS, Renin Angiotensin System; NO, nitric oxide; ADPKD, autosomal dominant polycystic kidney disease; UUO, unilateral ureteral obstruction; ↑, increased; ↓, decreased; ↔, unchanged (all in comparison to levels found in the non-denervated model).

rats, 2 days after RDN was performed, there was less albuminuria, mesangiolysis and renal inflammation.(83) However, RDN could not prevent renal injury induced by cyclosporine A.(84) Finally, renal nerves even appear to be involved in unilateral ureter obstruction, a nonhemodynamic model of renal injury,(85) suggesting that local nerve-derived signalling molecules can play an important role in tubulointerstitial fibrosis.

The studies shown in the table are listed according to their duration after denervation (study length). What is clearly apparent is that the SPB-lowering effect of direct RDN in rats does not exceed 4 weeks. Indeed, a recent study using neuropeptide Y immunoreactivity shows that 4 days after RDN most nerve fibers have disappeared, but within 4 weeks after RDN approximately 50% of both afferent (sensory) and efferent fibers become visible, and by 12 weeks practically all fibers have recovered.(86) After completely severing all connections by renal transplantation recovery of innervation in rats takes longer, but by 9 months noradrenaline levels in the transplant are normal.(87) Longer lasting interruption of renal afferent sympathetic activity can be achieved by bilateral dorsal rhizotomy, that is, by destroying the ganglia.(88;89) Not surprisingly, this appears to be irreversible(90), although this has not specifically been studied in the kidney. Chemical sympathectomy seems to be irreversible in rats pups(91) and renal ablation by 5/6 nephrectomy in 9-week-old rats, which had been chemically sympathectomized as pups, resulted in less severe hypertension and proteinuria. (11) Whether chemical sympathectomy can lower blood pressure and reduce renal injury after renal ablation is unknown.

Note that in longer CKD studies, RDN, although presumably only leading to transient period of reduced sympathetic activity, can lead to a long-term reduction in proteinuria and renal injury.(81) This emphasizes the central role of the kidney in the pathogenesis of sympathetic hyperactivity.

So all together, there is experimental evidence that RDN may not only reduce blood pressure, but also has beneficial effects on various variables associated with CKD progression. Available evidence on the role of afferent and efferent nerves in CKD, together with the experimental evidence on RDN in various experimental models of kidney injury, logically leads to the question whether there could be a role for RDN in the treatment of CKD patients.

Early clinical evidence

Prior to the availability of effective medical treatment for hypertension, surgical sympathectomy, most commonly by thoracolumbar splanchnicectomy, was performed in patients with severe hypertension and associated organ damage.

(92;93) A large beneficial effect on 5-year mortality was found in a large series by Smithwick and Thompson(92) in comparison with patients managed conservatively despite a blood pressure decrease in only half of the patients. These procedures had significant perioperative mortality risk and numerous side-effects and were abandoned when medical treatment became feasible, but still they are an important proof of principle for the possibility of lowering blood pressure by denervation of the sympathetic nerves in humans.

Current evidence with renal denervation

In 2009, the first results on the effects of RDN on blood pressure became available. First but also subsequent results suggest a substantial blood pressure-lowering effect in so-called resistant hypertension patients, which is usually defined as sustained high blood pressure despite the use of three or more antihypertensive agents. The effect has been shown to be sustained for 2-3 years of follow-up.(94-97)

Evidence of an effect on sympathetic activity

Direct measurements of the inhibitory effect of RDN on the sympathetic activity are scarce. The first article by Schlaich et al. (98) reports a decrease in noradrenaline spillover of 48 and 75% in the kidneys of their patient accompanied by a reduction in total body noradrenaline spillover of 42%, halving of renin activity, and a great reduction in MSNA after RDN. Symplicity-1 reported a similar decrease in renal noradrenaline spillover of 47% in 10 patients.(99) Studies using MSNA showed mixed results. The largest report including 25 patients found a modest decrease in multiunit MSNA 3 months after RDN and a significant decrease in MSNA measured with the single unit technique.(100) Several other reports however did not find a decline in MSNA after RDN(101;102) although both had more patients not responding with a blood pressure decline. None of these studies found response in MSNA and blood pressure response to be related. One report on two patients with end-stage renal disease (ESRD) found a modest decrease in noradrenaline spillover and a significant decrease in MSNA.(103)

Evidence in chronic kidney disease

In the Symplicity trials, an eGFR lower than 45 ml/min per 1.73m^2 was arbitrarily chosen as a contraindication for RDN. As a consequence, little evidence exists on the effect of RDN in moderate-to-severe CKD. One small study found a similar effect on office blood pressure in 15 stage 3-4 CKD patients without significant changes in eGFR or microalbuminuria in 3-6 months of follow-up.(104) Analysis of kidney function 6 months after RDN in 88 eGFR higher than 45 ml/min/1.73m^2 patients showed a non-significant decrease in GFR of 4 ml/min per 1.73m^2 (despite a major

decrease in blood pressure), a nonsignificant decrease in mean albuminuria, and a significant shift in the distribution of albuminuria towards normoalbuminuria.(105) A few other case series with 6 months of follow-up after RDN included approximately 35% CKD patients and found a similar blood pressure lowering effect and no change in eGFR or albuminuria.(106;107) Thus, a significant blood pressure lowering effect is likely in CKD patients and RDN appears to be well tolerated in this patient group, at least for the duration of these studies. Although beneficial effects on progression of CKD and albuminuria are to be expected from the blood pressure lowering effect and might be even greater than expected owing to a direct beneficial effect of less sympathetic activity, this remains unproven at present. In patients on hemodialyse, only case reports and a small series have been published reporting safety and significant blood pressure decrease after RDN, although in the series only SBP, not DBP decreased.(103;108-110) In hemodialyse patients, suitability of the renal arteries (of the atrophic kidneys) for RDN is a concern. In conclusion, very little evidence exists on the effects of RDN in CKD.

Where do we go from here?

Which patients groups are likely to benefit most from renal denervation?

The reason for choosing resistant hypertension patients in the first trials on RDN was obvious. At the time of introduction there were no data on efficacy and safety. With that in mind, it was perfectly understandable and may have even been very wise to obtain the first results with this therapy in patients who were otherwise untreatable. However, the choice for this group of patients is not supported by any specific knowledge of the pathophysiology suggesting that these patients are especially likely to benefit. On the contrary, in a recent analysis we found that in a group of patients referred because of resistant hypertension, approximately half of the patients did not meet the blood pressure criteria, or could be adequately treated with simple adjustments of dosages or had a secondary form of hypertension.(111) The fact that resistant hypertension patients represent a mixed group of diagnoses was also seen in other studies.

It is important to realize that RDN is meant to produce a very localized effect, that is, disrupting renal nerves located within the renal artery wall. This concept is essentially different from pharmacological therapy wherein the intervention is 'offered' to the whole body. Therefore, it is especially important to address the question which patients are likely to benefit. In that respect it seems attractive to hypothesize that RDN is effective in disease conditions characterized by increased activity of afferent and/or efferent renal nerve activity. This is important for yet

another reason. The currently available data show a substantial variability of the blood pressure-lowering capacity of RDN.(112) At present, there are no clinical characteristics that can predict response to RDN other than the level of the office SBP.(112;113) There are several explanations for variability in response. One of them is that there may be (considerable) differences between patients in the level of activity of the renal nerves. As mentioned above, it seems likely that RDN is especially effective in patients with (pathologically) active renal nerves and not effective in patients in whom nerves are not active.

Given these considerations, the question arises in which patients renal afferent and efferent fibers are especially active (figure 1). These nerve activities cannot be measured directly in humans. Whether increased efferent activity exists in humans as a primary abnormality, that is, because of a primary abnormality in the central nervous system, is unknown. One could think, for instance, of genetic factors. There is convincing evidence that increased afferent activity results in hypertension in experimental conditions as well as in humans. The primary abnormality seems to be kidney injury and/or failure. There is convincing evidence that this includes CKD over the whole range of kidney function. In these studies (see Pathogenesis), patients with variable kidney diagnoses were included. Is there reason to believe that there are differences between kidney diseases in the degree of kidney ischemia? This question has not been addressed before and also seems to be difficult to study. Renal artery stenosis or, in general, patients with atherosclerotic disease also have high MSNA.(114) Polycystic disease patients with preserved kidney function, but likely to have ischemic areas in their kidneys, already have high MSNA.(25) It has been extensively documented that ESRD patients show increased MSNA.(22;115;116) So, dialysis patients and transplant patients with their native kidneys still present could be likely candidates for RDN. Also, heart failure patients, who often have some degree of kidney failure as well, are likely to have kidney ischemia. Indeed, numerous studies have shown high MSNA levels in heart failure patients.(116;117)

If we accept the considerations mentioned above, it seems attractive to hypothesize that there could be an inverse relation between kidney function and possible antihypertensive effect of RDN. In a recent analysis of a large group of patients this was not found.(112) In contrast, we analyzed patients shortly before RDN, without their antihypertensive medication, because many agents influence GFR. Indeed, we found this inverse relation (submitted). A recent analysis of the combined datasets of Symplicity 1 and Symplicity 2 also suggested a trend toward an association between lower eGFR and greater blood pressure-lowering effect (abstract SA-OR036, ASN renal week 2013).

Diagnostic tests to select patients for renal denervation

So, taking this one step further, what kind of diagnostic tests could be helpful to select patients with kidney failure that are likely to benefit from RDN? It is important to confirm the predictive value of GFR in larger studies. Given the close relationship between the RAAS and sympathetic hyperactivity (see Pathogenesis), activity of the RAAS as measured by plasma renin and aldosterone levels or quantified functionally as the blood pressure drop after captopril is of interest to evaluate.(118;119) Higher RAAS activity might be predictive of a greater response to RDN. Measurement of increase in renin activity after captopril could also be useful, as it has been shown to predict blood pressure response to nephrectomy of the native kidneys after kidney transplantation.(120) However, RAAS activity is influenced by factors other than sympathetic activity and cannot be measured reliably under antihypertensive treatment. Furthermore, variables directly or indirectly related to the SNS should be studied, including plasma level and urine excretion of catecholamines and absence of nocturnal dipping.(121) In the one study evaluating dipping status and effect of RDN, such a predictive value was not found.(112) Increased renal and/or systemic vascular resistance might also be a marker of sympathetic efferent hyperactivity (see Pathogenesis). In recent years, there has been much interest in finding biomarkers predicting progression of CKD.(122) Most promising perhaps is neutrophil gelatinase-associated lipocalin, a protein released from the tubules after ischemic damage that increases in successive stages of CKD (measured in both serum and urine). This protein is believed to represent the tubuleinterstitial hypoxia, atrophy and fibrosis associated with CKD and was found to be predictive of further decline in GFR.(123-125) Other markers representative of oxidative stress (that might play an important role in sympathetic activation) or endothelial dysfunction might also be useful in selecting CKD patients for RDN: for example symmetric dimethylarginine, which is bound to HDL, inhibits nitric oxide synthase in CKD and increases with decline of GFR.(126;127)

A different approach would be to detect kidney ischemia with use of advanced radiological techniques. Renal blood oxygen level-dependent (BOLD) MRI, which displays the deoxy/oxy hemoglobin ratio in tissue, can be used to estimate the oxygen level in the kidneys of CKD patients.(128) However, a large study found no decline in kidney oxygen level measured by BOLD MRI in successive stages of CKD.(129) The precise role of this technique needs to be established. For an overview of potential strategies for predicting a beneficial effect of RDN in CKD patients, see table 2.

Table 2 Possible predictive variables for the effect of renal denervation

Technique	Rationale
Functional tests	
eGFR	Low GFR associates with high sympathetic activity
Plasma renin and aldosterone	High RAAS activity associates with high sympathetic activity
Captopril test	High RAAS activity associates with high sympathetic activity
Plasma and/or urinary catecholamines	Catecholamines represent efferent sympathetic activity
ABPM dipping pattern	Absence of nocturnal dipping associates with high sympathetic activity
Imaging	
Renal vascular resistance (duplex ultrasound, MRI with arterial spin labeling)	High RVR possibly relates to high renal efferent sympathetic activity
Systemic vascular resistance (measuring cardiac output by ultrasound or MRI and MAP)	High PVR possibly relates to high systemic efferent sympathetic activity
BOLD MRI	Presence of (areas of) kidney ischaemia may predict greater kidney afferent sympathetic activity
Markers	
NGAL	Represents interstitial hypoxia that may associate with high kidney afferent sympathetic activity
Markers of oxidative stress and/or endothelial dysfunction	Variables of oxidative stress and endothelial dysfunction may be associated with increased sympathetic activity

Abbreviations: ABPM, ambulatory blood pressure measurement; BOLD MRI, blood oxygen level dependent magnetic resonance imaging; NGAL, neutrophil gelatinase-associated lipocalin

How to monitor the intervention itself?

As mentioned above, currently available data show variability in antihypertensive effect of RDN. This can also be explained by variability in the efficacy of the intervention itself. So there is great need for a tool or variable to monitor efficacy of the intervention during the procedure. Such a method should enable the interventionalist to obtain information on the completeness of the procedure, preferably within the intervention unit.

One of the direct effects of disrupting afferent nerves could be that stimulation of renal nerves no longer causes a rise in blood pressure. During the RDN procedure, with the use of a catheter that applies nerve stimulation in the renal arteries, a subsequent increase in blood pressure can be monitored. Lack of response after the RDN procedure could then confirm adequate ablation of the afferent sympathetic

nerves. Indeed this concept has been tested in a recent experimental study. (130;131) One study in humans also reports such a procedure, although details are not mentioned.(132) As would be expected from a decline in sympathetic activity, RDN has been shown to reduce vascular resistance in the renal vessels with use of intra-procedural measurement in swine.(133) In humans, the resistance index measured by duplex ultrasound (105) or MRI (134) has been shown to decrease after RDN as well. Intraprocedural measurement of renal vascular resistance (with or without nerve stimulation) might therefore be a way to confirm effective ablation of the sympathetic nerves. Such a strategy would allow an immediate repeated attempt at RDN when effective ablation is not confirmed.

For approximately 15 years, cardiac electrophysiologists make use of mapping catheters to localize electrical activity within the cardiac cavity. In principle such an electroanatomic mapping system consists of three parts: 1] (nonfluoroscopic) catheter localization, 2] three-dimensional display of electrical activity and voltage, and 3] 3D display of the anatomy of the heart chamber. Recent advances allow display of catheter position and stored electrograms jointly with anatomic information of the target cardiac chamber generated through other imaging techniques such as CT or MRI. This concept seems extremely interesting in the field of RDN and worth exploration. One could think of several types of applications, including localization of nerve activity prior to the intervention, but also localizing residual autonomic nerve activity after the procedure. Admittedly, many challenges lie ahead. Most likely electrical activity within the renal artery wall is much lower than within the heart; possibly there is much 'background noise' of nerves and ganglia in the area. Furthermore, the renal artery is a much smaller cavity than the cardiac chambers. In order to advance in this field we need to collaborate intensely with cardiac electrophysiologists.

Apart from these functional tests, also advanced (intra-vascular) imaging techniques could be of use to locate the perivascular nerves and analyze the effect of an intervention.

Giving the abovementioned considerations, it also becomes increasingly clear how little we know about the normal anatomy of the renal nerves. Available data seem to indicate that the majority of nerves are located within 3 mm of the arterial lumen, but that some may be more distant.(11;135) Little is known on the type of nerves (efferent and afferent) and whether there are differences between the various disease conditions. It would be interesting to address the hypothesis that the number and/or types of nerves differ in various disease conditions, for instance afferent nerves are (much) more prevalent in CKD patients than in normal individuals. This type of research can be done in tissues obtained at autopsy or

operation. Secondly, we basically do not know what an 'adequate' denervation procedure really means. Is total destruction of all nerves really necessary, or is a partial effect enough? Are there differences in that respect between devices? Whether the differences in design between the various devices are of any clinical relevance, in terms of efficacy and safety, is at present totally unknown. To advance in this field, research in large animals that can accommodate a denervation catheter in their renal arteries is needed. Readouts of a RDN procedure could be the percentage and degree of nerve damage, but also a downstream effect such as noradrenaline content of kidney tissue.

Future developments

Given the above-mentioned information, we submit that the concept of RDN is of great interest and potential relevance, not for all hypertensive patients, but for carefully selected subgroups. At the time of preparing the revised version of this article (January 2014), we were aware of the press release of Medtronic concerning Symplicity 3. Details were not available at this time. When full details on Symplicity 3 are available, we submit that discussion on the reasons of failure to reach the primary efficacy endpoint should be focused on patient selection and procedure and device characteristics.

Up to now, RDN has mainly been applied in patients with so-called resistant hypertension and has demonstrated a rather variable effect on blood pressure. We hypothesize that the most important reasons for this variability are: variability of the contribution of the renal nerves to hypertension and variability of denervation procedure itself. So, research addressing these possibilities is greatly needed. Furthermore, based on experimental and human data outlined earlier, we again submit the hypothesis that CKD patients are especially likely to benefit from RDN.(1;5;14;136-138) Present-day standard therapy in CKD patients includes RAAS inhibitors, which reduce but do not normalize sympathetic activity.(32) Also blood pressure is often not adequately controlled in CKD.(36-38) Beneficial effects of RDN may include not only reduction in cardiovascular morbidity and mortality, but also reduction in progression of CKD. Given the financial burden to society of the ESRD programs, any reduction of CKD progression could be very cost-effective. It would be worth performing a clinical trial on the hypothesis that RDN, when added to currently accepted standard antihypertensive therapy, results in a reduction of important kidney and cardiovascular endpoints without relevant long-term side-effects. If such (an) effect(s) would be found, then RDN most likely would be a (highly) cost-effective addition to present day treatment options for this patient group.

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CHAPTER 6

The effect of renal denervation added to standard pharmacologic treatment versus standard pharmacologic treatment alone in patients with resistant hypertension: Rationale and design of the SYMPATHY trial

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Abstract

The first studies on renal denervation (RDN), suggest that this treatment is feasible, effective and safe in the short-term. Presently available data are promising but important uncertainties exist; therefore, SYMPATHY has been initiated. SYMPATHY is a multicenter, randomized, controlled trial in patients randomized to RDN in addition to usual care (intervention group) or to continued usual care (control group). Randomization will take place in a ratio of 2 to 1. At least 300 participants will be included to answer the primary objective. Sample size may be extended to a maximum of 570 to address key secondary objectives. The primary objective is to assess whether RDN added to usual care compared with usual care alone reduces blood pressure (BP) (ambulatory daytime systolic BP) in subjects with an average daytime systolic BP ≥135 mm Hg, despite use of ≥3 BP-lowering agents, 6 months after RDN. Key secondary objectives are evaluated at 6 months and at regular intervals during continued follow-up, and include: the effect of RDN on the use of BP-lowering agents, in different subgroups (across strata of estimated glomerular filtration rate and of baseline BP), and on office BP, quality of life and cost-effectiveness.

Hypertension is a global public health concern. It is estimated that 30 to 40% of the adult population in the developed world suffers from this condition. Despite availability of numerous safe and effective pharmacological therapies, only approximately one-third of patients achieve an adequate controlled blood pressure (BP).(1) A subgroup of these patients have resistant hypertension, defined by the American Heart Association as a BP that remains above treatment goals despite concurrent use of medication from 3 different antihypertensive classes at appropriate doses, one ideally being a diuretic.(2) Increased activation of the sympathetic nervous system is identified as an important factor in the development and progression of hypertension.(3) In this context, a catheter-based approach has been developed to disrupt the renal sympathetic nerves, using radiofrequency energy.(4) After a proof-of-principle study (5), the first randomized controlled trial (RCT), the Symplicity HTN-2 trial, showed in a relatively small number of patients (n=106, randomization ratio 1:1) that renal denervation (RDN) is efficacious. (6) Office systolic blood pressure (SBP)/ diastolic BP values decreased with -32/-12mmHg in patients treated with RDN, after 6 months of follow-up, whereas BP did not change in the control-group.(6)

Remaining questions

Presently available data are promising, but important uncertainties exist. Firstly, in previous studies,(5;6) and also in the ongoing Symplicity HTN-3 trial, inclusion and quantification of effect were based on office BP, without exclusion of white coat hypertension or confirmation of hypertension by more precise ambulatory BP monitoring (ABPM). The second issue concerns safety: delivery of radiofrequent energy can potentially result in focal alterations of media and adventitia.(7) In the HTN-1 and HTN-2 trials,(5;6) only one case of aggravation of a preexisting renal artery stenosis was described, but case-reports of stenosis after RDN have recently been published. (8;9) Furthermore, patients with impaired renal function (estimated glomerular filtration rate (eGFR) <45 ml/min per 1.73m^2) were excluded in previous studies. We hypothesize that RDN is especially beneficial for these patients because impaired kidney function is a disease state characterized by sympathetic activation.(10) A recent pilot study suggests that RDN has a favorable short-term safety profile and a beneficial effect on BP in patients with resistant hypertension and concomitant chronic kidney disease (CKD; stages 3-4).(11) Likewise, efficacy and safety of RDN in patients with milder forms of hypertension (office SBP 140-160 mm Hg despite use of ≥3 antihypertensive drugs) are not well known. A recent pilot study suggests that RDN is safe and efficious for these patients.(12)

In Symplicity HTN-2, a broad range of effect was observed, evidenced by a standard deviation of 23/11mm Hg. Moreover, in 10% of patients, SBP did not decrease, being classified as nonresponders.(6) Evidence on factors determining the BP-lowering effect after RDN is limited.(5) We observed that approximately 35% of the patients referred for treatment with RDN have an additional renal artery. According to exclusion criteria used in previous trials, these patients would have been excluded from treatment with RDN. We have decided not to primarily exclude these patients because of the high prevalence and lack of data. RDN is a costly and invasive procedure. However, when the effects of RDN on BP are extrapolated to a reduction in cardiovascular events, with associated health gains and cost reductions, RDN can be a cost-effective treatment in the long run. RDN also has potential to reduce lifetime multiple drug use, with associated savings and implications for quality of life. Currently, only one modeling study on cost-effectiveness of RDN is published suggesting that RDN could be cost-effective in the long run.(13) However, widespread implementation of RDN should be based on empirical data on effectiveness and cost-effectiveness, not only on modeling studies.

Study objectives

The SYMPATHY trial is registered in clinicaltrial.gov: NCT01850901. The primary objective is to assess whether RDN added to usual care compared with usual care alone will lower BP in patients with resistant hypertension. The primary objective is to assess whether RDN added to usual care compared to usual care alone reduces BP (average ambulatory daytime SBP determined using ABPM) after 6 months in subjects with an average mean daytime SBP ≥135 mm Hg determined using ABPM, despite use of ≥3 BP-lowering agents. The following key secondary objectives are evaluated at 6 months and at regular intervals during continued follow-up (12, 18, and 24 months):

1. To assess the effect of RDN on the use of BP-lowering agents (defined as defined daily dose (DDD) of all prescribed drugs).
2. To explore the effect of RDN in different subgroups: across strata of eGFR (eGFR 20-60 ml/min per 1.73m^2 and eGFR >60 ml/min per 1.73m^2) and of baseline BP (office SBP 140-160 mm Hg and office SBP >160 mm Hg).
3. To assess the effect of RDN on office BP.

Furthermore, information will be collected concerning:

- The effect of RDN on eGFR and incidence of periprocedural complications (definition: appendix A).
- The long-term effect of RDN on fatal- and nonfatal cardiovascular events (definition: appendix A).
- The cost-effectiveness of RDN.
- The impact of RDN on quality of life.
- The budget impact of introducing RDN in health care.
- The determinants and mechanisms of the BP-lowering effect.

Study design

SYMPATHY is a multicenter RCT in approximately 26 centers in the Netherlands (appendix B). Randomization is in 2:1 ratio to addition of RDN to usual care or to continued usual care and in randomized blocks per stratum, with strata defined by hospital and eGFR, using a Web-based computerized approach. We have chosen for a 2:1 rate because in the Netherlands, patients with resistant hypertension can be treated with RDN outside the context of a trial. Therefore, potential eligible participants might think that RDN is the solution for their longstanding hypertension and might favor treatment than opt for participation in a RCT. Therefore, we believe that the 2:1 randomization is favorable for recruitment and does not affect internal validity of the trial.

Study population

The study population consists of adults with resistant hypertension, (average ambulatory daytime SBP ≥135 mm Hg, despite use ≥3 BP-lowering agents). To determine eligibility for study participation, patients are screened. The 'inclusion criterion' for screening is an office SBP ≥140 mm Hg. The first aim of screening is to confirm diagnosis of hypertension because several studies have indicated that a substantial proportion (up to one-third) suspected of resistant hypertension based on office measurements, in fact, has white coat hypertension when ABPM is applied.(14;15) This strategy complies with the European Society of Hypertension (ESH) position statement.(16) During the screening period, also secondary causes of hypertension are excluded according to current guidelines, and noninvasive imaging of the renal arteries and kidneys is made. Furthermore, special attention is devoted to determine compliance. During the screening period, medication use and compliance are carefully verified using methods available in every day clinical practice: evaluation of the heart rate (beta blocker use), determination of angiotensin-converting enzyme in plasma (angiotensin-converting enzyme (ACE)

inhibitor use), and the 'medication adherence scale' by Morisky et al.(17) After the screening period, all patients are discussed in a multidisciplinary meeting to decide whether a patient is eligible for inclusion. Inclusion and exclusion criteria are shown in the table.

Table Inclusion and exclusion criteria

Inclusion criteria

1. Individual has a mean day-time SBP ≥ 135 mm Hg, determined using ABPM, while the patient uses ≥ 3 antihypertensive agents for ≥ 3 months prior to inclusion.
2. Individual is ≥18 years of age.

Exclusion criteria

3. Individual is unable or unwilling to sign informed consent.
4. Individual has a treatable secondary cause of hypertension
5. Individual has an eGFR <20 mL/min/1.73m2 using the MDRD calculation.
6. Individual has renal artery anatomy that is ineligible for treatment
7. Individual has any serious medical condition, which in the opinion of the investigator, may adversely affect the safety and/or effectiveness of the participant or the study.
8. Individual is pregnant, nursing or planning to be pregnant.
9. Individual has a known, unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or would be unlikely or unable to comply with study follow-up requirements.
10. Individual is currently enrolled in another investigational drug or device trial.

Abbreviations: SBP, systolic blood pressure; ABPM, ambulatory blood pressure measurement; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease

Study end points

The primary effectiveness end point is change in BP (average ambulatory daytime SBP) after 6 months of follow-up in the intervention group compared with the control group. Key secondary end points are:

- Change in amount of antihypertensive medication defined as DDD of all prescribed drugs 6 months after the intervention (intervention group) or 6 months after the baseline visit (control group).
- The effect of RDN in different subgroups: across strata of eGFR and of baseline BP.
- Change in office BP 6 months after the intervention (intervention group) or 6 months after the baseline visit (control group).

Other study parameters concern:

- Safety during short- and long-term follow-up:
  - Change in eGFR 6 months after the intervention (intervention group) or 6 months after the baseline visit (control group) and during long-term follow-up (12, 18, 24 months after randomization).
  - Incidence of periprocedural complications.
  - Incidence of serious adverse events (SAEs; definition: appendix C).
- The cost-effectiveness of RDN.
- The impact of RDN on quality of life.
- The budget impact of introducing RDN in health care.

Study interventions

Usual care

Both the intervention and the control group are treated with usual care. In the intervention group, RDN is added. Therapy in line with national cardiovascular disease prevention guidelines based on, for example, NICE guidelines (18) or European Society of Hypertension/ European Society of Cardiology (19) for both groups.

Investigational treatment: RDN

Renal denervation is performed by a certified interventional radiologist/cardiologist in the angiography suite. Based on advice of the Health Care Insurance Board of the Netherlands (College Voor Zorgverzekeringen: http://www.cvz.nl/en/home), the Minister of Health has decided to allow 'conditional' reimbursement of RDN by the health care system starting January 1, 2013, for a period of 4 years. The main condition of this 'conditional' reimbursement was that the medical community would collect data on efficacy and safety of the procedure. The present study was aimed to comply with these conditons. At the time of writing (June 2013), reimbursement was only made available for the Medtronic Symplicity device because, at that time, published data on safety and efficacy of this device were available. Therefore, this device will be used in the current study. However, periodic re-evaluation of this position of the authorities is already scheduled.

Because the RDN catheters are included in the reimbursement, these catheters are paid by the health insurance companies. In case other devices are allowed in context of the conditional reimbursement, the use of these devices is allowed in the current trial. One can speculate about consequences of using different devices. Only when a certain device is selectively used in a certain patient group with a high

(or low) baseline probability of success of RDN and when that certain device would indeed result in a greater (or lesser) magnitude of the BP-lowering effect, this may result in potential bias. Evidence to substantiate both notions is at present lacking. The SYMPATHY trial is to some extent protected against occurrence of such bias as randomization occurs in strata of centers. Furthermore, participating physicians are recommended to use only one device during certain periods. The type of device will be registered and evaluated after the trial has ended.

Using local anesthetics, cannulation of the femoral artery is performed. A sheath is introduced, and unfractionated heparin will be given. Renal angiograms are performed to confirm anatomical eligibility. Hereafter, the treatment catheter is introduced into each renal artery. Bilateral treatment of the renal arteries is performed using series of radiofrequent energy deliveries along each artery, aiming up to ≥4-6 treatment points per artery (approximately 8W per treatment point). Intraprocedural visceral pain is managed with intravenous analgetics and sedatives. A control angiography is performed after the procedure. Catheter tip impedance and temperature are constantly monitored during energy delivery. Patients with an increased risk for contrast nephropathy will be treated with prehydration and posthydration according to guidelines.

Guidelines for adjustments in antihypertensive medication

Baseline antihypertensive medication is intended to be unchanged in both treatment and control groups for at least 6 months to evaluate the primary endpoint. However, in case changes in antihypertensive treatment are considered medically necessary (ie, significant BP changes or adverse events directly related to BP or antihypertensive drugs), medications and/or doses may be adjusted according to predefined protocol (appendix D). Changes in medication will be well documented.

Study procedures

At the moment of the baseline visit, the informed consent is signed, and the participant is randomized. Renal denervation is planned shortly after the baseline visit. Patients will visit the hospital at 1, 3, 6, 12, 18 and 24 months after RDN (intervention group) or after the baseline visit (control group). Appendix E shows an overview of study procedures.

Study measurements

Set of BP measurements

- Office BP is taken using an automatic device, in sitting position after 10 minutes of rest, twice at both arms using an appropriate cuff-size. The mean value of these measurements is used as 'office BP'.

- Orthostatic BP changes: BP is taken at the arm with highest BP after ≥5 minutes in supine position using an automatic device. Afterwards, BP is taken after, respectively, 1 and 3 minutes in standing position. Complaints of orthostatic hypotension are noted.
- Noninvasive semicontinuous BP measurement will be taken in sitting position, every 5 minutes using an automatic device during a 1-hour resting period.
- Ambulatory BP monitoring will be taken noninvasively, with readings taken every 30 minutes during daytime and every 60 minutes during nighttime. A measurement is considered to be valid when ≥70% of the recordings has been successful.
- Home BP measurements: After RDN (intervention group) or after the baseline procedures (control group), patients receive a home BP device (this is optional for centers, only when devices are available). They will measure their BP one week (twice in the morning and twice in the evening) per month according to the ESH guideline, during 12 months after randomization.

Laboratory measurements

- Blood sampling in a fasting state: creatinine (µmol/l), potassium (mmol/l), glucose (mmol/l), cholesterol (mmol/l), triglycerides (mmol/l), high density lipoprotein cholesterol (mmol/l), low density lipoprotein cholesterol (mmol/l), high-sensitivity C-reactive protein (mg/l) and insulin (mIU/l) will be determined.
- Collecting urine for 24 hours: sodium (mmol/24 h), creatinine (mmol/24 h), proteins (g/24 h), and albumin (mg/24 h) will be determined. In selected centers, catecholamines are determined.

Questionnaires

- Quality of life is monitored using 2 questionnaires: Short-Form 36 (20) and EuroQol 5 Dimensions.(21)
- Absence from work: data on absence from work are retrieved using parts of the Short-Form Health and Labour Questionnaire.(22)
- Other questionnaires and diaries: a patient diary is used to collect data on health care resources use, such as length of hospital stay, duration of interventions, additional treatments for complications (if any), and number of general practitioner visits.

Sample size considerations

Based on results of the Simplicity HTN-2 trial (no change in BP in the reference group at 6 months) and observational results from Mahfoud et al. (mean difference of 10 mm Hg in daytime systolic ABPM among 346 patients, 6 months after RDN), we anticipate a mean difference in daytime systolic ABPM of 10 mm Hg in our

study. The SD is difficult to estimate from published literature, as these data are rarely presented. From a figure in the publication of Mahfoud et al, the SD could be estimated as being around 15 mm Hg. Pilot data from our center (17 patients) show an SD around the mean difference in systolic ABPM of 22 mm Hg. Therefore, we assumed an SD around the mean difference of 20 mm Hg.

To detect a difference of 10 mm Hg (assuming an SD of 20 mm Hg and a simple t test between groups), 195 participants have to be evaluated to have 90% power at a 2-sided α of 5% (randomization ratio 2:1, 130 in the intervention group and 65 in the control group). To conclude on the key secondary outcomes, that is, change in medication (defined as DDD) at 6 months, a larger sample size is considered necessary. Little experimental data on the anticipated effect of RDN are available. A sample size of 300 would be sufficient to detect a relative effect size of 0.35 with a power of 80% and a relative effect size of 0.4 with a power of 90%, both of which are considered a moderate effect. Therefore, it is concluded that 300 patients in total are the target sample size to demonstrate both a clinically relevant effect on BP and a moderate effect on medication use.

Primary analysis will be based on a linear model including at least treatment arm and baseline SBP as covariates. If the correlation between baseline SBP and SBP at 6 months follow-up is ≥0.3, which is not unreasonable, statistical evaluation is approximately at least $(0.3)^2$ more efficient than a simple t-test, so 9% less patients would be required. On the other hand, drop-out up to 6 months is anticipated, of the same order of magnitude. Taking drop-out into account, total sample size is 300. In addition, subgroup analyses are considered of substantial importance. Thus, sample size can be extended after analysis of the first 300 participants, to detect smaller differences between treatment groups. If the interaction effect is assumed to be approximately 50% of the main effect, 570 patients in total (in 2:1 ratio) are required to achieve 80% power at a significance level of 5%, with the same assumed SD. This is the maximum sample size proposed. The data safety and monitoring board (DSMB) will decide on actual sample size based on results of the first 300 patients. This decision is based on the estimated SD of the defined primary BP outcome (appendix F), and considerations of clinical relevance.

Data analysis

Primary outcome

Primary efficacy analysis is based on the (modified) intention-to-treat population including all patients randomized with available BP data ≥1 follow-up visit. The analysis model is an analysis of covariance, including at least baseline SBP as

covariate and treatment group as factor. Inclusion of hospital as factor will be considered, if feasible considering number of hospitals and patients per hospital. Unless otherwise specified, a 2-sided 0.05 level of significance is used.

Key secondary end points

To evaluate the effect of RDN in strata of eGFR, the same analysis is applied including eGFR strata as factors, and an interaction term of treatment by eGFR. In case of significant interaction at 5% level, treatment effects will be estimated per stratum and confidence intervals provided. Other subgroup analyses are performed in a similar fashion. The primary time point for comparison is at 6 months. The final subgroup analyses will be based on the complete sample, after potential increase in sample size. Primary analysis is performed when 6 months follow-up data of all patients are available. With extended follow-up up to 2 years, repeated measurements of SBP are available. These will be further analyzed using a mixed model for repeated measurements, including subject as random factor, baseline as covariate and time point, and treatment group and interaction between time point and treatment group as fixed factors. An unstructured covariance matrix will be assumed.

Other end points

Event rates of the composite cardiovascular end point will be compared between groups in an explorative fashion, according to the intention-to-treat principle, when 6-month follow-up data of all patients are available. After completing full follow-up of all patients, event rates will be compared again during prolonged follow-up. It is expected that during the longer period of follow-up, a nonnegligible number of patients assigned to usual care may have switched to RDN. To avoid bias, event data are also analyzed in an 'as treated' analysis, in which longitudinal course of treatment is taken into account (marginal structural model).(23-25) Incidences of key SAEs and adverse events, specifically cardiovascular events, will be presented per group. For economic evaluation, a cost-utility analysis will be performed. In a cost-utility analysis, efficiency is measured in terms of costs per quality-adjusted life-year. Incremental costs and incremental effects of the intervention over the control arm of the trial are compared, using a time horizon of both 6 months and 2 years, following main analysis of effectiveness. Incremental cost effectiveness ratios, that is, difference in costs between treatments divided by differences in effect, are estimated. Probabilistic sensitivity analysis, using bootstrapping techniques, is used to estimate uncertainty in model outcomes. Results are presented in a cost-effectiveness plane and a cost-effectiveness acceptability curve, the latter presenting the probability that implementing RDN is cost-effective compared

with usual care, given different willingness to pay for a quality-adjusted life-year thresholds. Costs and effects are discounted according to Dutch standards for discounting in health economic evaluation.(23) To study cost-effectiveness in the long run (10 and 20 years, lifetime) a Markov-type model will be developed, distinguishing the most relevant health outcomes associated with hypertension. Secondary data from existing meta-analyses for associations between (decreased) hypertension and (decreased) mortality and morbidity from these diseases will be used. In addition, annual cost and quality of life consequences associated with long-term sequelae of hypertension are used from secondary sources. All analyses are performed from societal perspective. Direct health care costs are calculated by multiplying the volume of (health care) consumption as registered within the follow-up period by its cost. Standard reference cost pricing, as available from Dutch guidelines for costing research within economic evaluations, is used.(26) Both direct health care costs and direct and indirect non-health care costs are included, to measure costs from a societal perspective. The friction cost method is used to estimate indirect non-health care costs. The incremental RDN treatment costs are calculated as the difference in total direct and indirect cost between both study arms.

The budget impact analysis (BIA) studies different scenarios of either or not introducing RDN in the treatment of resistant hypertension. The aim is to study costs of different scenarios for nationwide introduction of RDN in clinical care for hypertensive patients. The BIA is performed with a time-horizon of 10 years and split in results for all 10 years to demonstrate whether the return on investments improve over time. The BIA is performed from different perspectives: societal perspective, perspective from the health care budgetary framework, and, finally, the perspective of health care insurance companies, including all reimbursed health care.

Ethical considerations

SYMPATHY is conducted according to the principles of the Declaration of Helsinki (59th amendment, Seoul 2008) and in accordance with the Medical Research Involving Human Subjects Act (Wet medisch-wetenschappelijk onderzoek). SYMPATHY is approved by the Medical Research Ethics Committee of the University Medical Center Utrecht.

Data management

Handling of personal data complies with the Dutch Personal Data Protection Act. This study uses Web-based case record forms, developed by data management of the Julius Center.

Event adjudication committee

The definition of cardiovascular events is stated in appendix A. From all reported events documentation is requested for the investigators. All events, including death, are formally evaluated by an independent event adjudication committee (blinded for the intervention allocation), consisting of physicians with different specializations. Events are coded as fatal and nonfatal.

Data safety and monitoring board

An independent DSMB is installed to monitor the study according to present best practice as described in the DAMOCLES study.(27) The DSMB consists of a biostatistician (chair), and two nephrologists. The study team ensures that the DSMB is provided with regular reports on study progress and intermediate safety reports (including adjudicated events), including primary outcomes in case relevant. The DSMB primarily monitors safety and scientific integrity and merit of the trial and advises on sample size extension. No interim stopping is foreseen for reasons of efficacy.

Sponsoring

SYMPATHY is an investigator-driven trial and received unrestricted grants from The Netherlands Organisation for Health Research and Development (ZonMw, http://www.zonmw.nl/en) and Medtronic. Publications are not restricted by ZonMw and Medtronic; they will only be informed of publications.

Summary

SYMPATHY will give insight in the effect of RDN on ABPM in patients with an office SBP ≥140 mm Hg despite the use of ≥3 antihypertensive drugs, the effect in subgroups (across strata of eGFR and of baseline BP), safety, cost-effectiveness, the budget impact of introducing RDN in health care, and the impact on quality of life.

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Appendix A

Definition of cardiovascular events and periprocedural complications

Cardiovascular events are defined as death from cardiovascular causes and nonfatal cardiovascular events:

- Acute coronary syndrome:
- Myocardial infarction (STEMI/NSTEMI)
- Instable angina pectoris
- Congestive heart failure
- Coronary artery bypass graft
- Percutaneous transluminal coronary angioplasty and/ or stenting
- Transient ischemic attack
- Cerebral vascular accident
- Therapeutic carotid procedure (endarterectomy and/or stenting)
- Vascular intervention of peripheral arterial ischemia (revascularization, percutaneous transluminal angioplasty, and/or stenting)
- Kidney failure (requiring dialysis and not requiring dialysis)

Periprocedural complications are defined as:

- Vascular complication: pseudoaneurysm, perforation or obstruction of the femoral artery, AV fistula
- Hematoma
- Infection
- Anaphylaxis
- Mild allergic reaction
- Cardiac arrhythmias
- Kidney failure: an increase in creatinine of ≥50 µmol/l per day with a baseline value <300 µmol/l, independent of urine production
- Bleeding:
    - *Class I hemorrhage:* ≤15% loss of blood volume. No change in vital signs and fluid resuscitation is not necessary.
    - *Class II hemorrhage:* 15% to 30% loss of total blood volume. Presence of tachycardia, decreased blood pressure. Volume resuscitation is required.
    - *Class III hemorrhage:* 30% to 40% loss of blood volume. Decreased blood pressure, increased heart rate. Fluid resuscitation and blood transfusion necessary.
    - *Class IV hemorrhage:* loss of >40% of blood volume. Aggressive resuscitation is required to prevent death.
- Death
- Other

Appendix B
SYMPATHY study organization

Participating centers:

- University Medical Center Utrecht, Utrecht, The Netherlands (participating).
- Maasstad Hospital, Rotterdam, The Netherlands (participating).
- Leiden University Medical Center, Leiden, The Netherlands (participating).
- Medical Center Alkmaar, Alkmaar, The Netherlands (participating).
- Catharina Hospital, Eindhoven, The Netherlands (participating).
- Canisius Wilhelmina Hospital Nijmegen, The Netherlands (participating).
- Medical Center Haaglanden, The Hague, The Netherlands (participating).
- Isala Clinics, Zwolle, The Netherlands (participating).
- Ziekenhuisgroep Twente, Almelo, The Netherlands (participating).
- Martini Hospital, Groningen, The Netherlands (participating).
- Albert Schweizer Hospital, Dordrecht, The Netherlands (participating).
- Medical Center Leeuwarden, Leeuwarden, The Netherlands (participating).
- Antonius Hospital Nieuwegein, The Netherlands (participating).
- Amphia, Breda, The Netherlands (participating).
- Academic Medical Center Amsterdam, Amsterdam, The Netherlands (participating).
- University Hospital Maastricht, Maastricht, The Netherlands (participating).
- Scheper Hospital, Emmen, The Netherlands (participating).
- Rijnstate Hospital, Arnhem, The Netherlands (provisionally agreed).
- Vrije Universiteit Medical Center, Amsterdam, The Netherlands (provisionally agreed).
- Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands (provisionally agreed).
- TweeSteden Hospital, Tilburg, The Netherlands (provisionally agreed).
- Jeroen Bosch Hospital, Den Bosch, The Netherlands (provisionally agreed).
- Ijsselland Hospital, Capelle aan de Ijssel, The Netherlands (provisionally agreed).
- Haga Hospital, The Hague, The Netherlands (provisionally agreed).
- ZorgSaam, Terneuzen, The Netherlands (provisionally agreed).
- University Medical Center Groningen, Groningen, The Netherlands (provisionally agreed).

Appendix C
Definition of adverse events and SAEs

Adverse events are defined as any undesirable medical experience occurring to a subject during a clinical trial that is spontaneously reported by the participant, whether considered related to the investigational treatment. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded and entered in the electronic CRF.

Any SAE is any untoward medical occurrence or effect that at any dose:

- results in death
- is life threatening (at the time of the event)
- requires hospitalization or prolongation of existing inpatients' hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, major safety finding from a newly completed animal study, etc.

Appendix D
Guidelines for antihypertensive medication adjustments

Adjustments in antihypertensive medication can be classified either as a 'low BP action' or as a 'high BP action'. The first action is defined as adjustment of medication for patients whose SBP is reduced to <120 mm Hg (or <110 mm Hg for diabetics) and have signs and symptoms of hypotension or reduced organ perfusion. These patients will have doses and/or classes of medications reduced. If at an office visit, SBP is <120 mm Hg (or <110 mm Hg for diabetics) without symptoms, a repeat visit for BP measurement is scheduled 7 to 14 days later. If SBP remains <120 mm Hg (or <110 mm Hg for diabetics), doses and/or classes of medications will be reduced. A high BP action is a clinical intervention, which is required for patients whose SBP rises >15 mm Hg above their baseline BP and have documented clinical adverse events possibly related to persistent or elevated hypertension. These patients may have either doses of medications increased or additional medications prescribed. If at an office visit, BP is >15 mm Hg higher than baseline without symptoms, a repeat visit for BP measurement is to be scheduled 7 to 14 days later. If the SBP remains >15 mm Hg above baseline, either doses of medications will be increased or additional medications will be prescribed.

Appendix E Overview of study procedures

	V1	V2	V3 Telephone	V4	V5	V6	V7-V9
	Baseline	Renal Denervation	1 wk	1 m	3 m	6 m	12, 18, 24 m
Time window:							
Intervention group	≤2 wk after	only in	± 3 d	± 7 d	± 7 d	± 14 d	± 14 d
Control group	randomization*	inter-vention group	-	± 7 d	± 7 d	± 14 d	± 14 d
Intervention group	x	x	x	x	x	x	x
Control group	x			x	x	x	x
Record demographic information and medical history	x						
Documentation of adverse events			x	x	x	x	x
Documentation of healthcare use				x	x	x	x
Medication review	x		x	x	x	x	x
Physical examination	x			x	x	x	x
1-h non-invasive BP measurement	x					x	(visit 7 and 9)
ABPM	x					x	(visit 7 and 9)
Laboratory tests							
plasma tests	x		x†			x	x
24h urine	x					x	(visit 7 and 9)
Questionnaires							
SF-36	x			x	x	x	x
EQ-5D	x			x	x	x	x

*Intervention group: 3 weeks before the RDN
†Plasma Creatinine is only determined in the intervention group. Subject can go to a laboratory close to home
Abbreviations: ABPM, ambulatory blood pressure monitoring

Appendix F Guidance for total sample size

Interaction effect (mm Hg)	Standard Deviation (assumption)	Sample size (total)	Power
2.5	8	570	94%
		480	90%
		390	83%
	9	570	88%
		480	82%
		390	73%
	10	570	80%
		480	73%
		390	64%

CHAPTER 7

Impact of medication adherence on the effect of renal denervation The SYMPATHY trial

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Abstract

Randomized trials of catheter-based renal denervation (RDN) as therapy for resistant hypertension showed conflicting results in blood pressure (BP) lowering effect. Adherence to medication is modest in this patient group and may importantly drive these conflicting results. SYMPATHY is a prospective open label multicenter trial in Dutch patients with resistant hypertension. Primary outcome was change in daytime systolic ambulatory BP at 6 months. Patients were randomly assigned to RDN on top of usual care. Adherence to BP lowering drugs was assessed at baseline and follow-up, using blood samples drawn synchronously with BP measurements. Patients and physicians were unaware of the adherence assessment. Primary analyses showed a mean difference between RDN (n=95) and control (n=44) in changes in daytime systolic ambulatory BP after 6 months of 2.0 mm Hg (95% confidence interval, -6.1 to 10.2 mm Hg) in favor of control. In 80% of patients, fewer medications were detected than prescribed and adherence changed during follow-up in 31%. In those with stable adherence during follow-up, mean difference between RDN and control for daytime systolic ambulatory BP was -3.3 mm Hg (-13.7 to 7.2 mm Hg) in favor of RDN. RDN as therapy for resistant hypertension was not superior to usual care. Objective assessment of medication use shows that medication adherence is extremely poor, when patients are unaware of monitoring. Changes over time in adherence are common and affect treatment estimates considerably. Objective measurement of medication adherence during follow-up is strongly recommended in randomized trials.

Introduction

The effects of percutaneous catheter-based renal denervation (RDN) as new therapy for resistant hypertension have been evaluated several times in the past years.(1-8) First studies suggested large effects on blood pressure (BP). However, in the first sham-controlled randomized trial, no difference in treated versus controlled participants was found.(2) Subgroup analyses of RDN studies have identified different factors of relevance in determining the overall effect of the intervention on BP.(9-11) Of particular interest is medication adherence. To quantify the effect of the addition of RDN to medical treatment, it is imperative that antihypertensive medical treatment remains unchanged. Recent small studies, using urine or blood samples to detect medication, suggested that adherence is particularly poor in presumed resistant hypertensive participants.(12-14)

The present randomized controlled trial (RCT) was designed to assess the efficacy of RDN in resistant hypertension participants, the primary end point being daytime systolic ambulatory blood pressure (ABPM) at 6 months after RDN. In addition, we explored the effect of adherence on the study outcomes.

Methods

Study design and population

The rationale and design of SYMPATHY have been described previously.(15) Briefly, SYMPATHY is a multicenter RCT in 14 centers in the Netherlands. For this trial a system of conditional reimbursement was available for 4 years (2013-2016), indicating that the intervention was covered by the healthcare insurance, only when patients participated in SYMPATHY. The consequence was that SYMPATHY findings were used by National Health Care Institute to advise the government at the end of 2016 whether RDN should be part of the standard reimbursement package of the Dutch healthcare insurances (https://english.zorginstituutnederland.nl/publications/reports/2012/04/06/conditional-reimbursement-of-health-care). Because we had to deliver the report on the SYMPATHY findings to the National Health Care Institute no later than August 1, 2016, participants had to be included before January 1, 2016. In SYMPATHY adults were included with resistant hypertension, defined as an average daytime systolic ABPM measurement ≥135 mm Hg, despite use ≥3 BP lowering-agents or with documented intolerance for ≥2 BP lowering agents. Participating physicians were advised to exclude white coat hypertension, secondary causes of hypertension and anatomical abnormalities that would make RDN nonfeasible, using a standardized protocol.(16) Randomization was performed

in a 2:1 ratio to receive either RDN on top of usual care or usual care alone using a web-based computerized approach, with stratification by hospital and estimated glomerular filtration rate (20-60 and >60 ml/min/1.73m^2).(15) Ethics approval was obtained at the University Medical Center Utrecht (No. 12/540). All subjects gave informed consent. The trial was performed in accordance with the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001.

Outcome assessment

The primary outcome was change in daytime systolic ABPM 6 months after RDN or inclusion into the study (control group). Secondary outcomes were change in office systolic blood pressure (SBP), prescribed BP lowering drugs and change in kidney function. Other outcomes were periprocedural complications. ABPM monitoring was performed noninvasively, with readings every 30 minutes during day-time and every 60 minutes during nighttime, and was considered valid when ≥70% of the recordings were successful. Office BP was taken using an automatic device, in sitting position after 10 minutes of rest, twice at both arms using an appropriate cuff size. The mean was used as office BP. Both ABPM and office BP were measured with recommended devices according to the European Society of Hypertension/ European Society of Cardiology guidelines.(17) Blood was sampled on the same day as BP was assessed. At study visits the use of all medication was queried. BP lowering agents were classified according to the Anatomical Therapeutic Chemical classification system of the World Health Organization Collaborating Centre for Drug Statistics. We calculated the defined daily dose of BP lowering agents per participant per visit. The intention was to unchange baseline BP lowering medication till the 6-months visit (primary end point). In case adjustments in medication were necessary, these were made according to a predefined protocol (supplement).(15)

Important adjustments during the course of the trial

In January 2014, we added participants with documented intolerance to ≥ 2 BP lowering agents. These participants represent a sizable group of difficult to treat hypertensive patients, for whom RDN could be beneficial as well. Second, from October 2014, National Health Care Institute allowed conditional reimbursement when participants were treated with the EnligHTN Ablation catheter (St Jude Medical, St Paul, MN, USA).(15;18) Choice of catheter was made by the interventionist. During the course of the trial, it became increasingly clear that

objective assessment of medication adherence is of utmost importance based on reports suggesting poor adherence in this class of participants.(12-14) We decided to use stored samples for drug level measurements. Of relevance, participants and attending physicians were unaware of the adherence assessments.

The original sample size estimation was set at 300 randomized participants. However, after Symplicity HTN-3 inclusion slowed dramatically. DENERHTN provided data to assume that a study size of 100 to 150 participants could be sufficient.(1) We estimated that such a number could be feasible by January 1, 2016. We expected a difference of 5 mm Hg in SBP (with standard deviation of 10 mm Hg) between the RDN and control group. Our power would be between 80 and 90% with a 2-side α of 0.05. After consultation with the data safety monitoring board, we decided to continue the study. All described adjustments were approved by the Ethical Committee of University Medical Center Utrecht.

Adherence measurements

Liquid chromatography, combined with tandem mass spectrometry was used to screen BP lowering drugs. This technique has proved to be reliable, accurate and precise.(19) The acquired mass spectra were compared with an in-house library (compound library and tandem mass spectometry mass spectral library) built with automated screening software (TOD ID, Thermo Fisher Scientific) which contained the mass/charge of the precursor ion, retention time, product ions, and the entire tandem mass spectrometry spectra of 40 compounds including metabolites covering over 95% of all BP lowering drugs registered in The Netherlands. Identification was achieved by comparing full tandem mass spectrometry spectra and mass/charge of precursor ion with the confirmation by the second selected reaction monitoring transitions. Using the developed method, the identification results from spiked serum samples within therapeutic concentration ranges indicated 95% sensitivity and 91% specificity. Participants were categorized into adherent (81%-100% match prescribed versus measured), poorly adherent (1%-80% match prescribed versus measured) and completely non-adherent (0% match prescribed versus measured).(20)

Intervention

Usual care was based on the guidelines of the European Society Hypertension/ European Society of Cardiology.(17) The RDN procedure was performed by an interventional radiologist or cardiologist.

Data analyses

Primary efficacy analysis was based on the (modified) intention to treat population including all participants randomized with available BP data ≥ 1 follow-up visit. The primary analysis, that is, mean of change in daytime systolic ABPM between treatment arms was based on t-test. All other analyses were performed using either t-tests (continuous variables (mean of change)) or chi-square test for dichotomous variables. Linear regression models were used to study whether treatment effects differed across predefined subgroups, using multiplicative interaction terms (treatment group*subgroup). Linear regression models with adjustments for lifestyle changes and for changes in prescribed and detected medication were run to study the effects of these factors on the observed change in the daytime ABPM and in office systolic pressure. A 2-sided 0.05 level of significance is used. Statistical analyses were done using SPSS version 22 (IBM Corp, Armonk, NY, USA).

Meta-analysis

To place the SYMPATHY results in perspective of other RDN RCT results, we performed a systematic meta-analysis (supplement).

Results

From May 23, 2013 until January 1, 2016, 139 participants were randomized, 95 to RDN and 44 to usual care. After randomization, 4 participants declined RDN. One participant, randomized to the usual care group, received RDN within the first 6 months. Before the first 6-months visit, 8 participants (5 RDN) withdrew their participation for follow-up measurements (figure 1). Baseline characteristics are shown in table 1. Mean daytime systolic ABPM was 160 mm Hg (SD 17 mm Hg) and daytime diastolic ABPM was 93 mm Hg (15 mm Hg). Mean office BP was 169 (25)/96 (16) mm Hg. In 60 participants the Symplicity catheter was used and in 31 the EnligHTN Ablation catheter. Mean number of ablations was 15.(7)

Effect of renal denervation on blood pressure

Six month data on daytime ABPM were available for 124 participants (figure 1). Overall, BP levels declined significantly (table 2). Mean differences between groups in changes in daytime systolic ABPM after 6 months were 2.0 mm Hg (-6.1 to 10.2 mm Hg), in 24-hour systolic ABPM 1.0 mm Hg (-7.1 to 9.1 mm Hg), and in office SBP -8.2 mm Hg (-17.1 to 0.7 mm Hg). The findings were the same when using a complete case analysis approach (table S1 in the Supplement) or sensitivity analysis for patients with true resistant hypertension, defined as the use of ≥3 classes of BP lowering drugs (data not shown). Our meta-analysis (including 984 subjects from 7

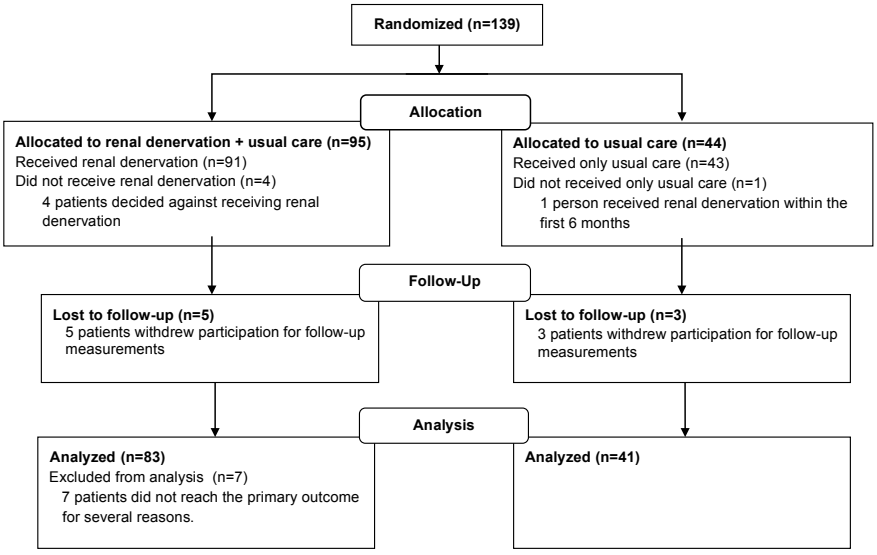

Figure 1 Flow-diagram of the SYMPATHY trial

studies) showed no significant benefit of RDN compared with usual care alone for daytime systolic ABPM (-1.60 mm Hg (-4.32 to 1.11 mm Hg)).

Adverse events

We observed 17 periprocedural complications, including 4 vascular, 8 bleeding and 5 other (mild) complications (table S2). All participants recovered without sequelae. Kidney function declined by 1.5 (-3.1 to 0.1) ml/min/1.73m^2 at 6 months, with no difference between groups. During 6-month follow-up, 36 self-reported, unadjudicated serious adverse events were registered: 24 (26%) in the intervention group and 12 (27%) in the usual care group (table S3).

Subgroup analyses

Predefined subgroup analysis showed no statistically significant interaction between kidney function or baseline BP and RDN effects on BP. None of several post hoc subgroup analyses (sex, body mass index, previous cardiovascular disease, smoking, urinary sodium excretion, size of the hospital (large centers/small centers), baseline use of spironolactone, and catheter type) reached statistical significance.

Medication adherence at baseline and follow-up

Prescribed medication did not differ significantly between treatment groups at 6 months and increased in both groups over time (table 3; table S4). Information on adherence was available for 98 and 83 participants at baseline and at follow-

Table 1 Baseline characteristics of the intention-to-treat population

Characteristics	Renal denervation group (n=95)	Control group (n=44)
Age (years)	62 (12)	60 (10)
Male*	40 (42.1)	13 (29.5)
White*	92 (96.8)	42 (95.5)
History of cardiovascular disease*	41 (43.2)	19 (43.2)
Current smoking*	22 (23.2)	10 (22.7)
Diabetes mellitus*	26 (27.4)	14 (31.8)
BMI (kg/m^2)	28.6 (4.8)	29.4 (4.6)
Plasma creatinine (µmol/l)	87 (36)	88 (27)
eGFR estimated with CKD-epi (ml/min/1.73m^2)	77 (19)	80 (21)
LDL (mmol/l)	3.1 (1.1)	2.8 (1.0)
Office SBP (mm Hg)	170.3 (25.9)	164.7 (22.0)
Office DBP (mm Hg)	96.1 (17.7)	94.4 (12.5)
24-h systolic ABPM (mm Hg)	157.3 (15.6)	155.8 (17.4)
24-h diastolic ABPM (mm Hg)	90.1 (14.3)	91.4 (12.6)
Daytime systolic ABPM (mm Hg)	160.8 (16.0)	159.5 (18.2)
Daytime diastolic ABPM (mm Hg)	92.4 (15.0)	94.5 (13.5)
Night time systolic ABPM (mm Hg)	146.0 (16.7)	144.8 (16.7)
Night time diastolic ABPM (mm Hg)	81.7 (12.5)	82.7 (12.1)
Number of BP lowering drugs	3.7 (1.5)	3.4 (1.5)
Number BP lowering classes	3.5 (1.3)	3.2 (1.3)
Daily Dose Used of BP lowering drugs	5.5 (4.0)	5.3 (3.4)
Diuretics*¥	69 (72.6)	26 (59.1)
Beta blocker*	60 (63.2)	26 (59.1)
ACE inhibitor*	25 (26.3)	15 (34.1)
Angiotensin receptor blocker*	57 (60)	26 (59.1)
Renin inhibitor*	3 (3.2)	0 (0)
Calcium antagonist*	60 (63.2)	27 (61.4)
Spironolactone*	23 (24.2)	10 (22.7)
Aldosterone antagonist*	5 (5.3)	3 (6.8)
Alpha blocker*	30 (31.6)	11 (25.0)
Centrally acting antihypertensive drug*	9 (9.5)	3 (6.8)
Other*	4 (4.2)	0 (0)

Data are expressed as mean±SD unless stated otherwise.
*Data are expressed as n(%).
¥Diuretics without spironolactone and other aldosterone antagonists.
Abbreviations: BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate; LDL, Low Density Lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABPM, ambulatory blood pressure measurement; BP, blood pressure; ACE, Angiotensin Converting Enzyme

Table 2 Blood pressure levels at baseline, follow-up, and the mean difference in the SYMPATHY trial of all participants

	Renal denervation group			Control group			Mean difference between groups (95%CI)	P value
	Baseline	6 months	Mean difference (95%CI)	Baseline	6 months	Mean difference (95%CI)		
ABPM	N=95	N=83		N=44	N=41			
Daytime systolic ABPM	160.8 ±16.0	155.2 ±23.9	-6.0 (-10.7 to -1.2)	159.5 ±18.2	152.4 ±20.1	-7.9 (-14.7 to -1.3)	2.0 (-6.1 to 10.2)	0.625
Daytime diastolic ABPM	92.4 ±15.0	90.3 ±16.2	-3.5 (-6.4 to -0.7)	94.5 ±13.5	89.4 ±13.3	-4.7 (-8.3 to -1.1)	1.2 (-3.5 to 5.9)	0.615
Night systolic ABPM	146.0 ±16.7	141.9 ± 21.5	-3.8 (-8.7 to 1.1)	144.8 ±16.7	139.4 ±23.3	-7.9 (-15.0 to -0.8)	4.1 (-4.4 to 12.6)	0.340
Night diastolic ABPM	81.7 ±12.5	80.2 ±13.3	-2.6 (-5.6 to 0.4)	82.7 ±12.1	80.6 ±13.9	-3.3 (-7.8 to 1.2)	0.7 (-4.5 to 5.9)	0.780
24-h systolic ABPM	157.3 ±15.6	152.0 ±23.5	-5.6 (-10.2 to -0.9)	155.8 ±17.4	150.2 ±22.2	-6.6 (-13.3 to -0.2)	1.0 (-7.1 to 9.1)	0.805
24-h diastolic ABPM	90.0 ±14.2	87.8 ±15.4	-3.5 (-6.3 to -0.8)	91.4 ±12.6	87.2 ±12.8	-3.9 (-7.7 to -0.1)	0.4 (-4.3 to 5.1)	0.871
Office BP	N=95	N=94		N=44	N=44			
Office SBP	170.3±25.9	162.7 ±26.7	-7.5 (-12.5 to -2.5)	164.7 ±22.0	165.4 ±25.4	0.7 (-6.9 to 8.3)	-8.2 (-17.1 to 0.7)	0.069
Office DBP	96.1 ±17.7	91.6 ±18.4	-4.4 (-7.4 to -1.4)	94.4 ±12.5	95.4 ±16.6	0.9 (-3.7 to 5.6)	-5.3 (-10.7 to 0.1)	0.053

Data are expressed as mean±SD unless stated otherwise.
P-value presented for the mean difference in effect between the intervention group and control group.
Abbreviations: ABPM, ambulatory blood pressure measurement; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3 Prescribed versus measured blood pressure lowering drugs and change in adherence (n=78)

Determinants of BP lowering drugs	Renal denervation group			Control group			Mean difference between groups†
	Baseline (n=63)	6 months (n=51)	Mean Change*	Baseline (n=35)	6 months (n=32)	Mean Change*	
No. of BP lowering drugs prescribed	3.7 ±1.5	4.0 ±1.7	0.3 ±0.1	3.4 ±1.5	3.9 ±1.2	0.4 ±0.2	-0.1 (-0.4 to 0.1)
No. of BP lowering drugs detected	1.8 ±1.4	2.0 ±1.5	0.2 ±0.2	1.7 ±1.3	2.0 ±1.0	0.4 ±0.2	-0.2 (-0.7 to 0.4)
Mean difference between prescribed and measured	1.8 (1.3 to 2.2)	1.9 (1.5 to 2.4)	0.1 ±0.2	1.8 (1.3 to 2.4)	1.8 (1.3 to 2.3)	-0.1 ±0.2	0.2 (-0.4 to 0.8)
P value	<0.001	<0.001	0.705	<0.001	<0.001	0.474	

Data are expressed as mean ±SD, unless stated otherwise. P-value presented for the mean difference between number of prescribed blood pressure lowering drugs and number of measured blood pressure lowering drugs in blood.
*mean change expressed as mean (±SE).
†mean difference between renal denervation and control group for changes six months after renal denervation.
Abbreviations: No., number; BP, blood pressure.

up, respectively (78 pairs). At both study time points, adherence was poor: 80% were either poorly adherent or completely non-adherent. In 54 (29 in RDN group) participants adherence remained stable. The adherence category changed (eg, from poorly adherent to completely nonadherent) in 31% of the participants (n=24). There was no significant difference in change in adherence between treatment arms (table 3).

Medication adherence and blood pressure

Baseline and 6-month daytime systolic ABPM were the highest in participants completely nonadherent in an analysis restricted to the 78 participants with adherence measurements at baseline and at follow-up (table S5). When medication adherence was the same at baseline and follow-up, daytime systolic ABPM was 3.3 mm Hg (-13.7 to 7.2 mm Hg) lower in favor of the RDN group (figure 2). The same trend was seen for 24-hour systolic ABPM (-4.7 mm Hg (-15.3 to 5.8 mm Hg)) and office SBP (-14.0 mm Hg (-25.7 to -2.4 mm Hg); P=0.422 for the interaction term). Baseline characteristics did not differ significantly between the intervention and control group in this selected population (table S6). In particular, no difference was found in factors that potentially drive a larger RDN effect.

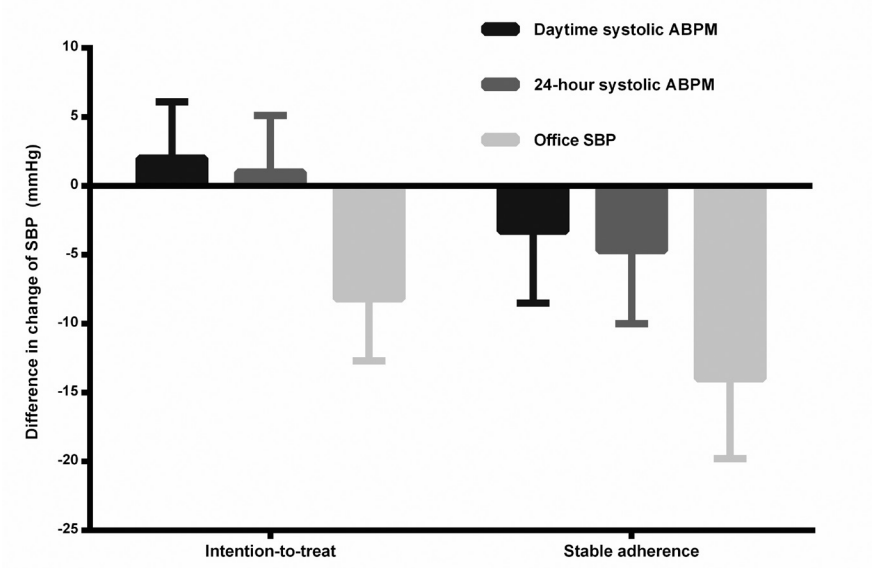

Figure 2 Mean difference (±SE) between control group and renal denervation group for change in systolic blood pressure after six months, presented for intention-to-treat population (n=139) and population with stable medication adherence (n=54).
Abbreviations: ABPM, ambulatory blood pressure measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Discussion

This is the second largest RCT studying the effect of RDN on BP in participants defined as treatment-resistant hypertensives. Six months after RDN, no significant reduction in day-time or 24-hour systolic ABPM was observed compared with usual care alone. Effect of RDN on office SBP was of borderline significance. Results are in line with most of the other trials.(1-3;5;6;8) Our systematic review showed that the pooled effect of RDN on BP is most pronounced for office SBP (-5.4 mm Hg, figure S2), yet, not statistically significant (P=0.27).

The possible reasons of the variability in the effects on BP between participants and between studies have been extensively discussed over recent years.(9;11;21) Relevant factors could be related to the device, the procedure itself, and participant characteristics. In this respect, medication adherence is of particular relevance because recent studies suggested poor adherence in this type of participants.(12-14;22-24) To our knowledge, we are the first trial on RDN to objectively assess medication adherence changes during the study. Strong features of our study are that blood samples were taken on the day of the ABPM and the fact that both participants and treating physicians were unaware of the assessments, resulting in an accurate representation of the every-day reality. Questionnaires used in trials on RDN are likely to overestimate adherence.(1;2;4;6) With a direct adherence assessment we confirm that BP medication adherence is very low at baseline and at follow-up. This finding is in line with the single direct adherence measurements in the PRAGUE trial (at screening) and DENERHTN trial (at 6-month follow-up).(7;22) In addition, BP was higher in participants with poor adherence (table S5). Therefore, our data support the notion that poor medication adherence contributes to the condition of apparent resistant hypertension.

A second important aspect is that in about one third of the participants adherence to BP lowering drugs either increased or decreased during follow-up. There was a trend toward more detected BP lowering pills at follow-up, more pronounced in the control group than in the RDN group. This may be because of the more intensive follow-up during the trial and the absence of blinding for the intervention (no sham procedure). The large percentage of change, with either decrease or increase in medication use, makes it virtually impossible to quantify the effect of the addition of RDN to medical treatment. This is especially the case when, as in our study, changes occur without the treating physicians knowing it. In those patients with the same number of medication at baseline and at follow-up, all BP measurements suggested a greater, albeit not statistically significant, decrease in the RDN arm. Figure 2 clearly suggests that the overall direction of the effect on BP

considerably changed when taking medication adherence into account. In none of the previous RCTs in the RDN field, was adherence quantified in both arms at both baseline and follow-up. It could be that in the other trials, adherence was better than in this study, but it seems appropriate to conclude that poor adherence and changes in adherence were probably major factors of concern.

Our results may have considerable societal impact. These patients use healthcare facilities by (frequently) visiting physicians, by collecting medication from the pharmacy, without using it, meanwhile staying at increased cardiovascular risk. Although the relationship between hypertension and increased cardiovascular risk is well established, some participants feel great resistance for prolonged pharmacological therapy. The reasons are likely complex and include the fact that hypertension is usually free of symptoms and that participants experience side effects of medication. This triggers 2 lines of thinking. First, there is great need to more extensively focus on interventions that potentially improve medication adherence. Indeed, in DENERHTN, in which specific efforts were undertaken to improve medication use, full adherence was found in half of the study population,(22) which is much better than the 20% found in this study, but still far from perfect. Alternatively, society could accept that a certain percentage of hypertensive participants are not able or willing to use medical treatment for whatever (set of) reason(s). For such participants, alternative approaches, including device-related treatment strategies, could be considered as options worth exploration.

An important limitation of our trial is probably that participants were not blinded to the intervention (no sham procedure). We tried to offset this by blinded assessment of the primary outcome, assessment of lifestyle changes that may affect BP for adjustment (salt intake, and weight change), and objective measurements of (change in) medication adherence for use in the statistical analyses of the results. Second, although we had a mix of patients (resistant, and intolerant), it is unlikely that this affects our findings, because our sensitivity analysis revealed no difference in effect when taken the resistant group separately. Another potential limitation might be the use of 2 different devices. This is only an issue when the 2 devices differ in their BP lowering effect, of which no evidence is available, yet. Further, not all patients were on diuretics, which is presently (more or less) accepted as mandatory to meet the definition of resistant hypertension. At the time we designed our study that was not yet so clearly the case. Indeed, it is possible that the lack of diuretic use has influenced our results. Finally, the drug level measurements provided qualitative results: the drug is either detectable or not detectable. Therefore, we might have underestimated the number of changes, because dosage and class changes were not detected.

Perspectives

This study shows in primary analysis that RDN is not superior to usual care in reducing BP in participants with resistant hypertension. Medication adherence seems to be very low when participants are unaware of monitoring. Our data suggest that poor adherence (partially) explains the condition of resistant hypertension. Second, and importantly, our data suggest that the direction and the magnitude of the treatment effect considerably change when medication adherence is taken into account. This factor could also have been of relevance in earlier RDN studies. It can only be overcome in future trials by studying unmedicated participants or by detailed monitoring of prescribed and actually used medication.

Novelty and Significance

What is New?

This is the first randomized controlled trial on the effect of renal denervation on blood pressure that included a baseline and end-of-study objective measurement of adherence to antihypertensive medication.

What is relevant?

In primairy analysis renal denervation was not superior to usual care alone in patients with resistant hypertension.

Medication adherence was very low in resistant hypertensive patients participating in a trial.

In patients with proven stable adherence during the study, the direction and magnitude of the effect on BP differed from the primary analysis.

Summary

Medication adherence is very low in resistant hypertension patients and changes over time, which has considerable effect on the overall interpretation of the results. Objective assessment of medication adherence is mandatory in future trials in (resistant) hypertensive patients.

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Table S1 Blood pressure levels at baseline, follow-up and the mean difference in the SYMPATHY trial. Only in participants with blood pressure data on both baseline and 6 months follow-up

	Renal denervation group			Control group		
Blood pressure	Baseline	6 months	Mean difference (95%CI)	Baseline	6 months	Mean difference (95%CI)
ABPM	N=83	N=83		N=41	N=41	
Daytime systolic ABPM	161.2 ±16.1	155.2 ±23.9	-6.0 (-10.7 to -1.2)	160.4 ±18.5	152.4 ±20.8	-8.0 (-14.6 to -1.3)
Daytime diastolic ABPM	93.9 ±14.6	90.3 ±16.2	-3.5 (-6.4 to -0.7)	94.2 ±13.9	89.4 ±13.3	-4.7 (-8.3 to -1.1)
Night systolic ABPM	145.2±16.5	141.5 ±21.3	-3.8 (-8.7 to 1.1)	146.3 ±16.8	138.4 ±22.8	-7.9 (-15.0 to -0.8)
Night diastolic ABPM	82.5 ±12.1	80.0 ±13.3	-2.6 (-5.6 to 0.4)	83.4 ±11.4	80.1 ±13.7	-3.3 (-7.8 to 1.2)
24h systolic ABPM	157.5 ±16.1	151.3 ±22.0	-6.2 (-10.7 to -1.7)	156.7 ±17.5	150.1 ±22.2	-6.6 (-13.3 to 0.2)
24h diastolic ABPM	91.5 ±14.0	87.4 ±15.2	-4.1 (-6.8 to -1.4)	91.1 ±12.9	87.2 ±12.8	-3.9 (-7.7 to -0.1)
Office BP	N=79	N=79		N=40	N=40	
Office SBP	170.7±25.0	162.0 ±28.1	-8.7 (-14.0 to -3.2)	165.5 ±22.3	165.4 ±25.4	-1.3 (-8.1 to 5.6)
Office DBP	97.7 ±17.3	92.7 ±18.3	-5.0 (-8.4 to -1.6)	94.0 ±12.7	93.1 ±14.3	-0.8 (-4.9 to 3.4)

Data analysed with paired samples T-test.
Data are expressed as mean ±SD unless stated otherwise.
Abbreviations: ABPM, ambulatory blood pressure measurements; 24h, 24hour; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table S2 Peri-procedural complications in renal denervation group

Complications	No. of participants (%)
Vascular complications	4 (4.4)
Aneurysm spurium	2
Arrhythmia	1
Other	1
Bleeding complications	8 (8.8)
Hematoma	6
Other	2
Total no. of complications	12 (13.2)
Other complaints	5 (5.5)
Back pain	3
Groin pain	1
Hypotension	1
Prolonged admission	4 (4.4)

Data are expressed as number (percentage of denervated participants, n=91)
Abbrevations: No., number.
Definitions:
Vascular complications: pseudo aneurysm, perforation or obstruction of the femoral artery, artrio-venous-fistula, haematoma, infection, anaphylaxis, mild allergic reaction, cardiac arrhythmias, death.
Kidney failure: decline of 30% of eGFR compared to baseline value.

Table S3 Serious adverse events

Serious adverse events	RDN group (n=91)	Control group (n=44)
Ablation retinae	1	
Arrhythmia	4	1
Carcinoma	1	
Cerebra Vascular Accident	2	
Collapse		1
Collapse and weight loss		2
Decompensation cordis	1	
Diarrhea	1	
Dyspnea with fever	1	
Elective coronary angiography		1
Elective Coronary Artery Bypass Grafting		1
Elective hospitalization to adjust antihypertensive medication	2	1
Elective surgery	4	4
Epileptic insult	2	
Intoxication	1	
Microcytic anemia		1
Pericarditis	1	
Readmission due slow bleeding complication leg	1	
Recanalization occluded stent	2	
Trauma	1	
Total number serious adverse events	24	12

Serious adverse events were self-reported and not adjudicated.

Table S4 Mean change in prescribed medication between baseline and 6 months

Determinants of prescribed BP lowering drugs	Renal denervation group (n=95)	Control group (n=44)	Mean difference (95%CI)	P-value
No. of classes of BP lowering drugs	0.2 ±0.1	0.3 ±0.1	-0.1 (-0.3 to 0.1)	0.433
Number of BP lowering drugs	0.3 ±0.1	0.4 ±0.2	-0.1 (-0.4 to 0.1)	0.331
Daily defined use of BP lowering drugs	-0.1 ±0.1	0.1 ±0.3	-0.1 (-0.6 to 0.4)	0.680

Data presented as mean change ±SE, unless stated otherwise.
Abbrevations: No., number; BP, blood pressure.

Table S5 Daytime systolic ambulatory blood pressure at baseline and 6 months by adherence category

Daytime systolic ABPM	Non-adherent	Poorly-adherent	Adherent
Baseline	(n=18)	(n=56)	(n=24)
	166.3 (16.9)	157.8 (15.5)	161.9 (19.8)
6 months	(n=10)	(n=60)	(n=13)
	173.2 (23.5)	148.6 (17.1)	147.6 (28.0)

Data are expressed as mean ±SD, unless stated otherwise.

Table S6 Baseline characteristics of study population with stable medication adherence

Characteristics	Renal denervation group	Control group
	(n=29)	(n=25)
Age (years)	63 (10)	62 (10)
Male *	14 (48.3)	8 (32.0)
Caucasian *	28 (96.6)	23 (92.0)
History of cardiovascular disease *	15 (51.7)	11 (44.0)
Current smoking *	6 (20.7)	6 (24.0)
Diabetes mellitus *	7 (24.1)	8 (32.0)
BMI (kg/m^2)	28.6 (4.7)	29.5 (4.9)
Plasma creatinine (µmol/l)	86 (22)	94 (26)
eGFR estimated with CKD-epi (ml/min/1.73m^2)	75 (18)	73 (19)
LDL (mmol/l)	3.5 (1.2)	2.9 (1.1)
Office SBP (mm Hg)	163.1 (18.2)	160.3 (23.3)
Office DBP (mm Hg)	91.1 (12.6)	89.6 (11.5)
24-h systolic ABPM (mm Hg)	155.3 (12.4)	154.0 (19.3)
24-h diastolic ABPM (mm Hg)	89.4 (13.3)	89.0 (15.2)
Daytime systolic ABPM (mm Hg)	158.7 (12.5)	157.6 (19.8)
Daytime diastolic ABPM (mm Hg)	90.9 (13.7)	91.8 (15.9)
Nighttime systolic ABPM (mm Hg)	144.2 (16.4)	142.4 (16.6)
Nighttime diastolic ABPM (mm Hg)	81.9 (13.8)	79.9 (13.6)

Data are expressed as mean±SD unless stated otherwise.
* Data are expressed as n(%).
Abbreviations: BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate; LDL, Low Density Lipoprotein. SBP, systolic blood pressure; DBP, diastolic blood pressure; 24-h, 24-hour; ABPM, ambulatory blood pressure measurements.

Meta-analysis

Methods

PubMed, Embase and Cochrane databases were searched. We chose "resistant hypertension" and "renal denervation" and their synonyms (table S7) as search terms for titles and abstracts. Eligible for inclusion were reports of RCTs comparing RDN with care as usual in resistant hypertension. SBP had to be measured by ABPM monitoring at baseline and at six months. We used the GRADE-approach (Grading of Recommendations, Assessment, Development and Evaluations) to critically assess study design, generalizability and quality of the study of the remaining RCTs and to give a final score for the available evidence in a summary of findings table (http://clinicalevidence.bmj.com/x/set/static/ ebm/learn/665072.html). We extracted the change in daytime systolic ABPM between baseline and six-month follow-up for both RDN and control groups. The pooled effect size and its confidence interval were estimated using Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). As we assumed that the true effect size differed among studies, we used a random-effects model.

Results

Our systematic review included seventeen relevant studies (figure S1). One study was excluded, as treatment in the control group could not be considered care as usual. Eight other excluded studies did not provide data on six months. Finally, we included eight studies.(1-8) Three studies were sham controlled, including the largest trial, HTN-3 (tables S8, S9). In our meta-analysis, including the SYMPATHY results, pooled effect on daytime systolic ABPM and office BP showed no significant decline in favour of RDN (P=0.25 and P=0.27, respectively). The decline in systolic ABPM was significant in favor of the denervated population, with a mean difference of -2.8 (-5.4 to -0.1) mm Hg (figure S2, table S10).

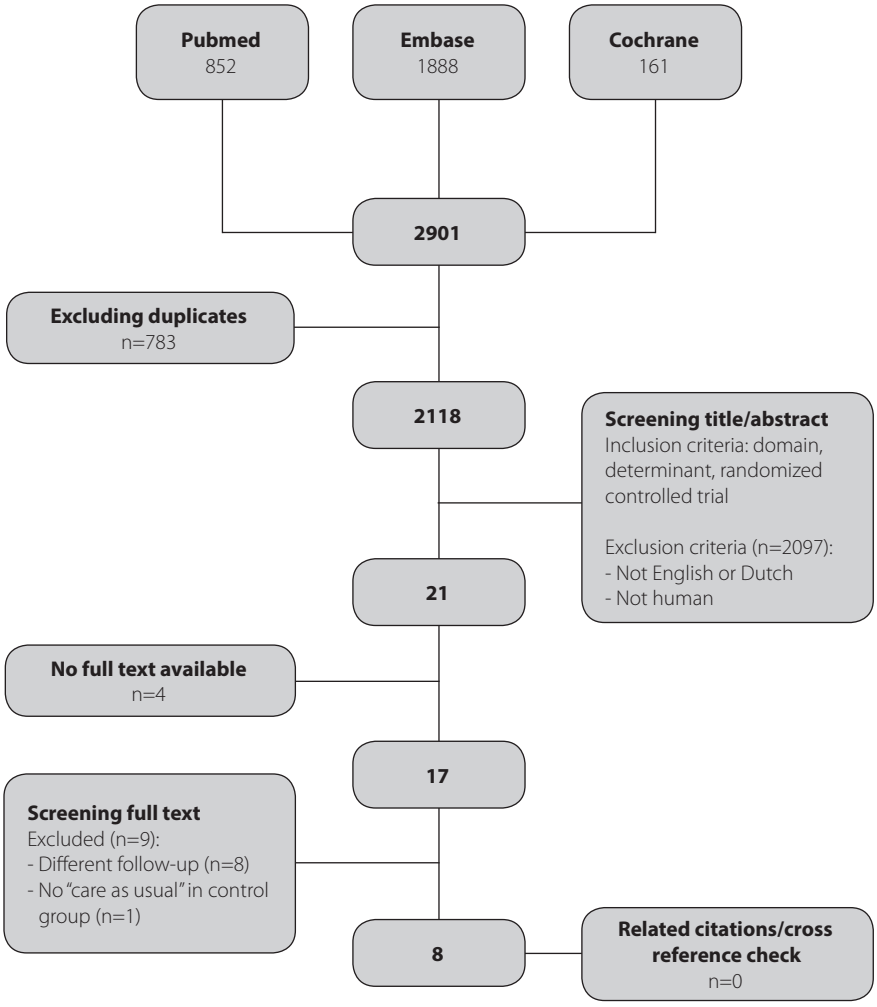


Figure S1 Systematic search of the literature

Search performed 11th july 2016

Table S7 Search strategy

Search items	Pubmed
Domain	(((((((high BP*[Title/Abstract]) OR elevated BP*[Title/Abstract]) OR hypertens*[Title/Abstract]) OR raised BP*[Title/Abstract]) OR hypertension [MeSH Terms])) AND (((resistant[Title/Abstract]) OR uncontrolled[Title/Abstract]) OR refractory[Title/Abstract]))
AND	
Determinant	((((((renal[Title/Abstract]) OR kidney[Title/Abstract]) OR kidney [MeSH Terms]) OR renal artery[MeSH Terms])) AND (((((denervation[Title/Abstract]) OR sympathectomy[Title/Abstract]) OR radio frequency ablation[Title/Abstract]) OR sympathectomy[MeSH Terms]) OR denervation[MeSH Terms]))
Outcome	x
Results	852 hits

Table S8. Study characteristics(1-8)

Characteristics	HTN-2 2010	HTN-3 2014	Oslo 2014	PRAGUE 2015
Location	Europe, Australia, New Zealand	USA	Norway	Czech Republic
Center	Multiple	Multiple	Single	Multiple
Primary BP endpoint	Office systolic	Office systolic	Office systolic	24 hour systolic
ABPM entry criteria (mm Hg)	-	24 hour ≥160/-	Daytime >135/-	24 hour >130/-
eGFR criteria (ml/min/1.73m^2)	≥45	≥45	≥45	-
No. of participants randomized (No. RDN/CON)	106 (52/54)	535 (364/171)	20 (10/10)	106 (52/54)
Treatment in control group	Drug treatment	Sham plus maintained drug treatment	Drugs adjusted to hemodynamic condition	Intensified drug treatment plus spironolactone
Women %RDN/%CON	35/50	36/41	0/22	23/37
Mean age (years)	58/58	58/56	57/63	56/59
White ethnicity %RDN/%CON	98/96	73/70	100/100	100/100
No. of BP lowering drugs	5.2/5.3	5.1/5.2	5.1/5.0	5.4/5.4
Drug adherence assessment	Diary	Diary	Witnessed intake	Plasma drug concentrations at baseline

Abbreviations: BP, blood pressure; ABPM, ambulatory blood pressure measurement; eGFR, estimated glomerular filtration rate; RDN, renal denervation; CON, control.

Embase	Cochrane
hypertens*:ab,ti OR 'high BP':ab,ti OR 'elevated BP':ab,ti OR 'raised BP':ab,ti AND (resistant:ab,ti OR uncontrolled:ab,ti OR refractory:ab,ti) OR 'resistant hypertension'/exp	((hypertens*:ti,ab OR "high BP":ti,ab OR "elevated BP":ti,ab OR "raised BP":ti,ab OR hypertension [MeSH]) AND (resistant:ti,ab OR uncontrolled:ti,ab OR refractory:ti,ab))
renal:ab,ti OR kidney:ab,ti OR 'kidney'/exp AND (denervation:ab,ti OR sympathectomy:ab,ti OR 'radio frequency ablation':ab,ti) OR 'kidney denervation'/exp	((renal:ti,ab OR kidney:ti,ab OR kidney [MeSH] OR "renal artery" [MeSH]) AND denervation:ti,ab OR sympathectomy:ti,ab OR "radio frequency ablation":ti,ab OR denervation [MeSH] OR sympathectomy [MeSH]))
x	x
1888 hits	161 hits

DENERHTN 2015	Symplicity-F 2015	Symplicity-J 2015	ReSET 2016	SYMPATHY 2016
France	Germany	Japan	Denmark	Netherlands
Multiple	Single	Multiple	Single	Multiple
Daytime systolic	24 hour systolic	Office systolic	Daytime systolic	Daytime systolic
Daytime ≥135/≥85	Daytime 135-149/90-94	24 hour ≥135/-	Daytime ≥145/-	Daytime ≥135/-
≥40	≥45	≥45	>30	≥20
106 (53/53)	71 (35/36)	41 (22/19)	99 (36/33)	139 (95/44)
Standardized drug treatment guided by home BP	Sham plus maintained drug treatment	Drug treatment	Sham plus maintained drug treatment	Drug treatment
40/36	31/23	32/16	25/27	58/71
55/55	65/57	60/56	54/57	62/60
79/77	100/100	0/0	97/97	97/96
3.0/3.0	4.4/4.3	4.9/4.9	4.1/4.2	3.8/3.4
Diary	Interview	Diary	-	Plasma drug concentrations at baseline and follow-up

Table S9 Quality assessment table for GRADE approach per study

Study	HTN-2	HTN-3	OSLO	PRAGUE	DENERHTN	Symplicity-J	Symplicity-F	ReSET	SYMPATHY
	2010	2014	2014	2015	2015	2015	2015	2016	2016
General									
Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Sample size	106	535	20	106	106	41	71	68	139
Generalizability									
Population of interest (a)	+	+	+	+	+	+	+	+	+
Intervention (b)	+	+	+	+	+	+	+	+	+
Control (c)	+	+	+	+	+	+	+	+	+
Outcome (d)	+	+	+	+	+	+	+	+	+
Daytime systolic ABPM	3	2	2	2	1	3	2	1	1
24-hour systolic ABPM	2	2	2	1	2	2	1	2	2
Office SBP	1	1	1	2	2	1	3	2	2
Quality									
No selective inclusion of participants (e)	+	+	+	+	+	+	+	+	+
Random sequence generation (f)	+/-	+	+	-	+	+	+	+	+
Concealment of allocation (g)	-	+	+	-	+	-	+	+	+
Blinding Participant (h)	-	+	-	-	-	-	+	+	-
Outcome	-	+	-	-	+	-	+	+	+
Trial ended as scheduled (i)	+	+	-	-	+	+	+	+	+
Loss to follow-up (j)	+	+	+	+	+	+	+	+	+
Intention-to-treat analysis (k)	+	+	+	+	-	+	-	+	+
No selective outcome reporting (l)	+	+	+	+	+	+	+	+	+
No suspected conflict of interest	-*	+	+	+	+	+	+	+	+

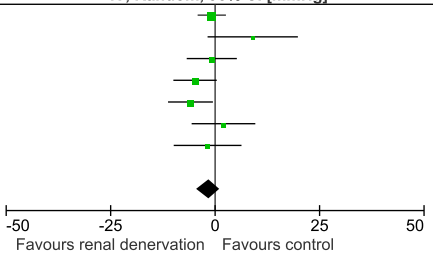
(a) participants with uncontrolled hypertension; (b) renal denervation; (c) usual care; (d) 1: primary outcome 2: secondary outcome 3: not available; (e) +: no selective inclusion, -: selective inclusion; (f) +: random sequence generation, +/-: predetermined sequence / small blocks, -: no random sequence generation reported; (g) +:concealed allocation, -: -no concealed allocation or unclear method reported; (h) +: sham-procedure, -: open label; (i) +: ended as scheduled, -: trial ended preliminary; (j) + ≤ 20% loss to follow-up, non-selective; -: ≥ 20% loss to follow-up, non-selective; (k) +: intention to treat analysis, -: modified intention to treat analysis or per-protocol analysis; (l) +: non-selective outcome reporting, -: selective outcome reporting

* The sponsor designed the study in collaboration with the study investigators and was responsible for data collection and analysis

A

Study or Subgroup	Renal denervation Mean [mmHg]	SD [mmHg]	Total	Control Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]	Year
HTN-3 2014	-7.2	16.2	325	-6.4	18.6	159	27.3%	-0.80 [-4.19, 2.59]	2014
OSLO 2014	-10	12	9	-19	12	10	5.6%	9.00 [-1.81, 19.81]	2014
PRAGUE 2015	-9	15.8	52	-8.2	15.7	54	14.3%	-0.80 [-6.80, 5.20]	2015
Symplicity-Flex 2015	-8.5	11.3	32	-3.7	10.3	35	17.3%	-4.80 [-9.99, 0.39]	2015
DenerHTN 2015	-15.8	13.8	48	-9.9	13.7	53	16.6%	-5.90 [-11.27, -0.53]	2015
Sympathy 2016	-6	21.8	95	-8	21.1	44	10.0%	2.00 [-5.62, 9.62]	2016
ReSET 2016	-6.1	18.9	35	-4.3	15.1	33	9.0%	-1.80 [-9.91, 6.31]	2016
Total (95% CI)			**596**			**388**	**100.0%**	**-1.60 [-4.32, 1.11]**	

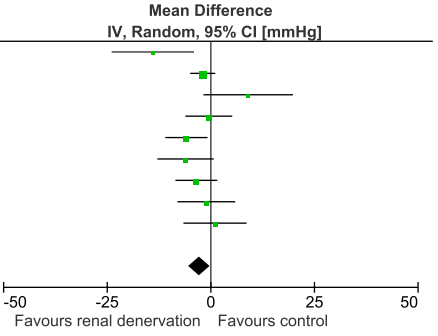
Heterogeneity: Tau² = 4.04; Chi² = 8.75, df = 6 (P = 0.19); I² = 31%
Test for overall effect: Z = 1.16 (P = 0.25)



B

Study or Subgroup	Renal denervation Mean [mmHg]	SD [mmHg]	Total	Control Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]	Year
HTN-2 2010	-11	15	20	3	19	25	5.7%	-14.00 [-23.93, -4.07]	2010
HTN-3 2014	-6.75	15.11	353	-4.79	17.25	171	20.7%	-1.96 [-4.99, 1.07]	2014
OSLO 2014	-10	12	9	-19	12	10	5.0%	9.00 [-1.81, 19.81]	2014
PRAGUE 2015	-8.6	12.14	52	-8.1	17.25	54	12.4%	-0.50 [-6.16, 5.16]	2015
DenerHTN 2015	-15.4	13.08	48	-9.5	13	53	13.9%	-5.90 [-10.99, -0.81]	2015
Symplicity-Japan 2015	-7.5	12	22	-1.4	10.2	19	10.0%	-6.10 [-12.90, 0.70]	2015
Symplicity-Flex 2015	-7	11	32	-3.5	10	35	14.0%	-3.50 [-8.55, 1.55]	2015
ReSET 2016	-3.7	16.4	35	-2.6	12.8	33	9.6%	-1.10 [-8.07, 5.87]	2016
Sympathy 2016	-5.6	21.4	95	-6.6	21.3	44	8.5%	1.00 [-6.62, 8.62]	2016
Total (95% CI)			**666**			**444**	**100.0%**	**-2.76 [-5.43, -0.10]**	

Heterogeneity: Tau² = 6.53; Chi² = 13.96, df = 8 (P = 0.08); I² = 43%
Test for overall effect: Z = 2.03 (P = 0.04)



C

Study or Subgroup	Renal denervation Mean [mmHg]	SD [mmHg]	Total	Control Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]	Year
HTN-2 2010	-32	23	49	1	21	51	14.4%	-33.00 [-41.64, -24.36]	2010
HTN-3 2014	-14.13	23.93	353	-11.74	25.94	171	15.7%	-2.39 [-7.01, 2.23]	2014
OSLO 2014	-8	15	9	-28	13	10	12.7%	20.00 [7.31, 32.69]	2014
DenerHTN 2015	-15.1	19.4	48	-9.5	19.3	53	14.8%	-5.60 [-13.16, 1.96]	2015
PRAGUE 2015	-12.4	16.9	52	-14.3	20.2	54	15.0%	1.90 [-5.18, 8.98]	2015
Symplicity-Japan 2015	-16.6	19	22	-7.9	21	19	12.9%	-8.70 [-21.04, 3.64]	2015
Sympathy 2016	-7.5	24.3	95	0.7	25	44	14.4%	-8.20 [-17.06, 0.66]	2016
Total (95% CI)			**628**			**402**	**100.0%**	**-5.44 [-15.09, 4.22]**	

Heterogeneity: Tau² = 148.60; Chi² = 60.95, df = 6 (P < 0.00001); I² = 90%
Test for overall effect: Z = 1.10 (P = 0.27)

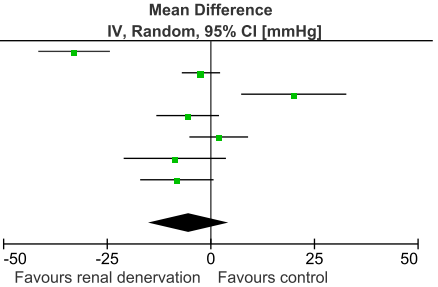


Figure S2 Forest plots of comparison renal denervation vs. control for change in daytime systolic ambulatory blood pressure (A), 24-hour systolic ambulatory blood pressure (B) and office systolic blood pressure (C) 6 months after inclusion.(1-8)

Renal sympathetic denervation as a new treatment for therapy resistant hypertension
Study population: resistant hypertension
Setting: secondary / third line centers
Intervention: renal denervation
Comparison: usual care

Table S10 Summary of findings table (meta-analysis)

Outcomes	Mean difference (95% CI) mm Hg	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Daytime systolic ABPM (follow-up 6 months)	-1.60 (-4.32 to 1.11)	984 (7)	Moderate	High score on: RCT's, generalizable to our population. Low score on: (sham and open label studies), inconsistent results.
24-hour systolic ABPM (follow-up 6 months)	-2.76 (-5.43 to -0.10)	1110 (9)	Moderate	High score on: RCT's, generalizable to our population, large number of studies. Low score on: sham and open label studies, inconsistent results.
Office SBP (follow-up 6 months)	-5.44 (-15.09 to 4.22)	1030 (7)	Moderate	High score on: RCT's, generalizable to our population. Low score on: sham and open label studies, inconsistent results, concealment of allocation in some studies unclear.

GRADE: Grading of Recommendations, Assessment, Development and Evaluations, score based on BMJ Clinical Evidence(1).
Abbreviations: No., numbers; RCTs, Randomized Controlled Trials; ABPM ambulatory blood pressure measurement; SBP, systolic blood pressure.

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CHAPTER 8

Salt intake and blood pressure response to percutaneous renal denervation in resistant hypertension

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Journal of Clinical Hypertension, in press

Abstract

The effect of lowering sympathetic nerve activity by renal denervation (RDN) is highly variable. With the exception of office systolic blood pressure (BP), predictors of the BP lowering effect have not been identified. As dietary sodium intake influences sympathetic drive, and, conversely, sympathetic activity influences salt sensitivity in hypertension, we investigated 24h urinary sodium excretion in participants of the SYMPATHY trial. SYMPATHY investigated RDN in patients with resistant hypertension. Both 24-hour ambulatory and office BP measurements were endpoints. No relationship was found for baseline sodium excretion and change in BP 6 months after RDN in multivariable adjusted regression analysis. Change in the salt intake-measured BP relationships at 6 months versus baseline was used as a measure for salt sensitivity. BP was 8 mm Hg lower with similar salt intake after RDN, suggesting a decrease in salt sensitivity. However, the change was similar in the control group, and thus not attributable to RDN.

Introduction

Since the introduction of percutaneous renal denervation (RDN) for treatment of so-called resistant hypertension in 2009, the appreciation of the technique has changed from worldwide enthusiasm to widespread disappointment. Several studies and systemic reviews(1-6) have adjusted the expectations from the solution to hypertension in general to a possibly useful addition in antihypertensive treatment after further improvement of the procedure.(7) Patient selection has been one of the explanations for the large variability in the blood pressure (BP) effect, since the contribution of sympathetic hyperactivity to hypertension may differ significantly between subjects.(8;9)

Dietary sodium intake is known to be related to sympathetic activity, with lower intake associated with higher sympathetic drive.(10) Conversely, since efferent sympathetic activity directly increases tubular sodium absorption,(11) lowering sympathetic output to the kidneys may be beneficial especially in patients with high salt intake as an important contributor to their hypertension. Renal denervation, aimed at lowering sympathetic hyperactivity, might improve salt sensitivity.(12) Our hypothesis was that dietary salt intake is related to the blood pressure lowering effect of RDN. Measurement of salt excretion would then be helpful to select patients likely to benefit from the procedure. We therefore set out to investigate the relationship of dietary salt intake with the blood pressure lowering effect of RDN and change in salt sensitivity after RDN.

Methods

Study population

SYMPATHY is a multicenter randomized controlled trial conducted in the Netherlands from 2013 to 2016. Design and rationale have been published previously.(13) In short, participants were eligible for inclusion if they had resistant hypertension, defined as an average daytime systolic blood pressure ≥135 mm Hg despite use of three or more BP lowering drugs, or with use of less antihypertensive drugs due to intolerance to at least two of the major antihypertensive drug classes. Major exclusion criteria were severe renal insufficiency (estimated glomerular filtration rate (eGFR) below 20 ml/min/1.73m^2) and renal artery anatomy ineligible for treatment. A standardized protocol was provided to exclude secondary and white coat hypertension before inclusion. Adherence to antihypertensive drug treatment and dietary sodium restriction were discussed as part of usual care before inclusion. No dietary manipulations were done in SYMPATHY. Randomization was

in a 2:1 ratio to RDN added to the usual antihypertensive drug regime versus usual antihypertensive drug therapy alone. The antihypertensive medication was to remain stable during follow-up unless clinical reasons (for example symptomatic hypotension or cardiovascular events) made adjustments necessary. The primary endpoint was assessed at 6 months. Patients and physicians were blinded for the primary outcome of daytime systolic blood pressure. The University Medical Center Utrecht ethical review committee approved the protocol and all participants gave signed informed consent.

Measurements

After three months of stable antihypertensive drug treatment, patients could be included in the study and a baseline visit was planned. At baseline, 24h ambulatory BP measurement was performed. Blood pressure was measured every 30 minutes during daytime and every 60 minutes during the night. The measurement was considered to be valid when ≥70% of the recordings had been successful. Office BP was taken using an automated device, in sitting position after 10 minutes of rest, twice at both arms. The mean value was taken as office BP. Blood was drawn after an overnight fast in the morning after the ambulatory blood pressure measurement. Participants returned urine collected in the 24 hours before the baseline visit. Detailed written instructions were provided to increase completeness of the collection. In the urine sodium, potassium, creatinine and protein excretion were measured. At 6 months after the baseline visit, both ambulatory blood pressure and office blood pressure were measured again, and a blood and 24h urine sample collected. At both time points, 24h urine collection and blood pressure measurements were thus performed simultaneously. As antihypertensive medication had to be stable 3 months before the baseline visit and was to remain stable during the study (unless change was necessary for clinical reasons as described in the protocol), participants could be concluded to be in a steady state, with 24h urinary sodium excretion representing dietary sodium intake and adherence to the salt restriction advice. Weight was measured at both time points without shoes in light clothing. Height was measured without shoes at baseline. Participants were asked to bring all medication used to the visits. Frequency and dose of antihypertensive drugs used were recorded and checked with the patient. Combination preparations were recorded as their separate components. To include both data on number of antihypertensive drugs used and dosage, defined daily dosages were calculated for classes of antihypertensive drugs. The defined daily dosage methodology was developed by the WHO to facilitate use of drug consumption data in studies. Drugs with an ATC code were assigned a defined daily dosage (DDD), a unit of

measurement, defined as the assumed average maintenance dose per day for a drug used for its main indication.(14) For this study, DDDs of antihypertensive drugs from different classes were added to a total number of antihypertensive DDDs used.

Intervention

Usual care was based on the guidelines of the European Society of Hypertension/ European Society of Cardiology.(15) In the intervention group, renal denervation was performed by an interventional radiologist or cardiologist according to the manufacturers' instructions, within one month after the baseline visit. The Symplicity Flex Catheter (Medtronic, Santa Rosa, California, USA) was used in the majority of patients. After conditional reimbursement was expanded to the EnligHTN Catheter (St. Jude Medical, St. Paul, Minnesota, USA), this catheter could be used in the study as well.

Urine sample analyses

For the first part of this study, the relationship of dietary sodium intake with the blood pressure lowering effect of RDN, interest was in the intervention group only in which RDN had to be performed within 1 month after the baseline visit (crossover was allowed for patients in the control group after 6 months). Patients randomized to RDN who did not have the procedure were excluded (per protocol analysis). Subsequently, participants who did not hand in a baseline 24h urine sample were excluded. The accuracy of collection of the 24h urine sample was determined based on the amount of creatinine in the sample. Urinary creatinine excretion in 24h depends on muscle mass when in a steady state. Formulas to estimate 24h creatinine excretion from gender, age and weight, representing main determinants of muscle mass, have been developed in several populations.(16) Expected creatinine excretion based on gender, age and weight was calculated and compared with the measured value. For this study, the formula proposed by Forni and Ogna was used.(17) This formula was developed and validated in a Swiss study on adult participants with preserved kidney function and of Caucasian race, representative of the general European population. As creatinine excretion is normally distributed in the population, the range between the 5% and 95% percentile can also be determined as described by these authors (similar to growth charts, an individual can have a low or high creatinine excretion for his/her age, sex and weight). The measured creatinine excretion is then compared with the estimated value. A large difference between the two raises suspicion of inadequate collection of the 24h urine sample. In this study, a 24h urine sample was considered

valid when measured creatinine excretion was between the 5th and 95th percentile of the estimated creatinine excretion. Measured sodium excretion in 24 hours was then used in the analysis. In an additional analysis, done to be able to use all urine samples regardless of the accuracy of collection, sodium/creatinine ratios from the samples were used to estimate 24h sodium excretion using the formula developed by Tanaka for spot urine samples.(18) Both formulas can be found in the supplementary file.

Salt sensitivity assessment

As no dietary manipulations were done in Sympathy, salt sensitivity could not be investigated with the standard method of changing sodium intake with comparison of BP at low versus high salt diet. As a proxy, the relationship of sodium excretion (assumed to equal sodium intake since participants were stably on their regular diet) with systolic blood pressure measured in the same 24 hours was compared at baseline and at 6 months after RDN. Initial analysis again was on a selection of urine samples deemed to have been well collected, based on the measured creatinine excretion between p5-p95 of the estimated value criterion described above, both at baseline and at six months. Moreover, samples were excluded if 24h creatinine excretion was more than 30% different at six months compared to baseline (representing remaining suspicion of collection errors). As for the primary analysis, an additional analysis was done using estimated 24h sodium excretion based on the Tanaka formula for spot urine samples. Change in salt sensitivity during follow-up was analysed by the same method in the control group, representative of change not attributable to the RDN procedure.

Statistical analysis

Baseline characteristics are described as mean with standard deviation or proportions as appropriate. Change in 24h systolic BP and office systolic BP between baseline and six months after RDN was investigated using a paired samples T-test. Multivariable adjusted linear regression analyses were used to investigate a relationship of baseline dietary sodium intake (represented by 24h urinary sodium excretion) with the change in blood pressure 6 months after RDN (primary analysis). First, urine samples suspect for inaccurate collection were excluded. Hereafter, the regression analysis was repeated using estimated 24h sodium excretion based on the Tanaka formula, including all samples. Antihypertensive drug use, measured as total amount of defined daily dosages used, was adjusted for in the last model. In the second part of the study, linear regression was used with urinary sodium excretion as the independent and measured systolic blood pressure as the

dependent, both at baseline and at 6 months. In these analyses, antihypertensive drug use was adjusted for as several of these potentially influence salt sensitivity (again using defined daily dosages). These analyses were repeated in the control group, to determine whether a change in salt sensitivity during follow-up was due to the RDN procedure or by other factors. SPSS version 21 (Chicago, IL) was used for all analyses.

Results

Study population and change in BP after RDN

Of 95 participants randomized to RDN, 4 decided against receiving renal denervation and were excluded. Baseline and follow-up blood pressure and baseline 24h urinary sodium excretion were available for 76 participants. Figure 1 shows the number of participants in the different analyses and reasons for exclusion. Baseline characteristics are shown in table 1, and antihypertensive drug use in table 2. Mean dietary sodium intake was 154 mmol per day (±SD 65) and mean 24h BP 159 ± 15/90 ± 14 mm Hg. One third of the participants was diabetic, almost halve had a history of cardiovascular disease and kidney function was well preserved (mean eGFR 78 ± 18 ml/min/1.73m^2). Five urine samples were excluded for incomplete collection (below the p5) and six for over collection (ending the collection period to late, measured creatinine excretion above the p95). Six months after RDN, 24h systolic BP had decreased with 7.5 mm Hg (standard error (SE) 2.7 mm Hg, p=0.007) and 24h diastolic BP with 4.5 mm Hg (SE 1.6 mm Hg, p=0.007). Change in office BP was -8.1 mm Hg (SE 2.8, p=0.005) for systolic BP and -4.1 mm Hg (SE 1.7, p=0.014) for diastolic BP. Mean sodium intake was only marginally lower at six months (mean difference 16 mmol/d, SE 9, p=0.08).

Dietary sodium intake and blood pressure after RDN

Dietary sodium intake at baseline was not related to the change in BP after RDN (table 3a) in the different models. Analyses were performed for every 10 mmol increase in sodium excretion per day (comparable with 0.58 grams dietary salt (sodium chloride) intake) and for quartiles of sodium intake, and adjusted for baseline systolic BP, age, gender, BMI, race, kidney function and antihypertensive drug use. Neither change in 24h systolic BP or change in office systolic BP were related to dietary sodium intake. For example, in the age, sex and baseline systolic BP adjusted model, 10 mmol higher sodium excretion at baseline was related to a 0.5 mm Hg greater decline (-0.5 mm Hg) in ambulatory systolic BP at six months, with a 95% confidence interval of -1.5 to +0.5 mm Hg. The change in BP according

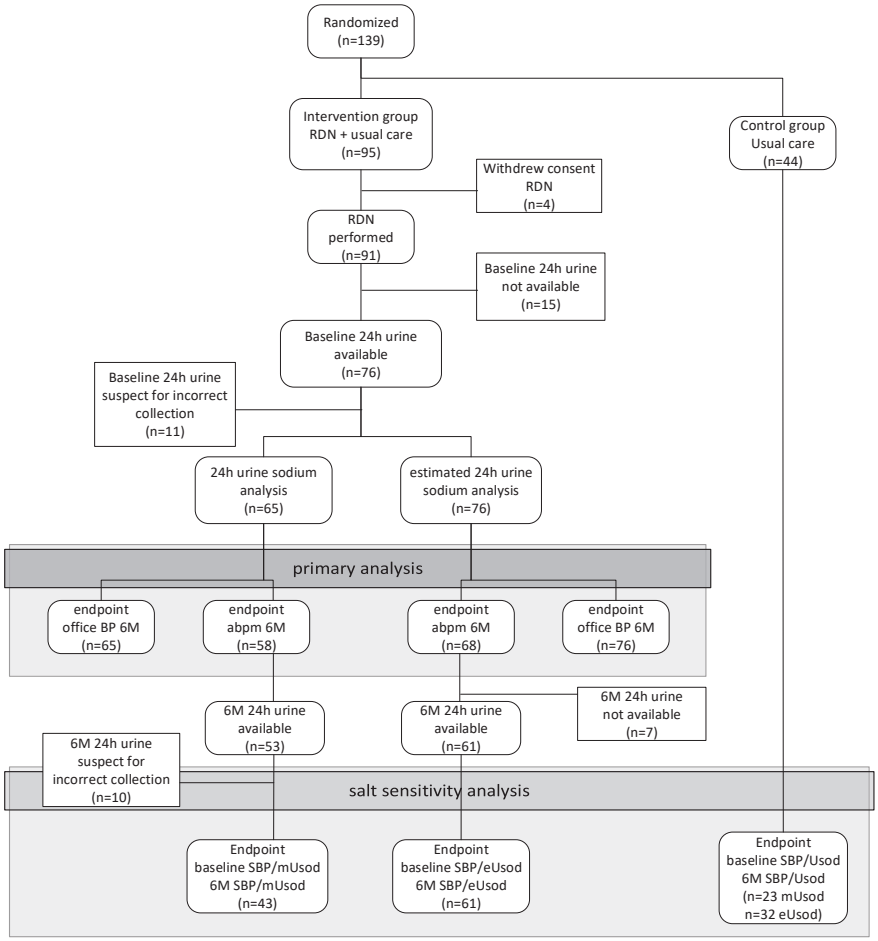

Figure 1 Flowchart of the study
Abbreviations: RDN, renal denervation; BP, blood pressure; abpm, ambulatory blood pressure measurement; SBP, systolic BP; mUsod, measured urinary sodium excretion; eUsod, estimated urinary sodium excretion

Table 1 Baseline characteristics		
Sex (male)	53%	
Age at renal denervation (years)	62	12
Race (caucasian)	96%	
Diabetes mellitus	33%	
History of cardiovascular disease	47%	
Body mass index (kg/m2)	28.5	5.0
Current smoking	21%	
Alcohol intake ≥1 unit/day	65%	
eGFR (ml/min/1.73m^2)	78	18
Urinary sodium excretion (mmol/d)	154	65
Estimated sodium excretion (mmol/d)	167	30
24h mean systolic blood pressure (mm Hg)	159	15
24h mean diastolic blood pressure (mm Hg)	90	14
24h mean daytime systolic blood pressure (mm Hg)	162	16
24h mean daytime diastolic blood pressure (mm Hg)	116	147
Office systolic pressure (mm Hg)	170	25
Office diastolic pressure (mm Hg)	94	16
Office pulse pressure (mm Hg)	76	19
Change in mean 24h systolic BP at 6 months (mm Hg)	-7.5	-12.9 to -2.1
Change in mean 24h diastolic BP at 6 months (mm Hg)	-4.5	-7.7 to -1.3
Change in office systolic BP at 6 months (mm Hg)	-8.1	-13.7 to -2.5
Change in office diastolic BP at 6 months (mm Hg)	-4.1	-7.4 to -0.9

Data are expressed as proportions, mean with standard deviation and difference with 95% confidence interval as appropriate.
Abbreviations: eGFR, estimated glomerular filtration rate; BP, blood pressure

Table 2 Antihypertensive drug use at baseline	
Alpha blockade	28.0
ACE inhibitor	25.3
ARB	64.0
Renin inhibitor	4.0
Aldosterone antagonist	32.0
Beta blockade	69.3
Calcium channel blockade	68.0
Diuretic	78.7
Centrally acting sympathicolytic agent	5.3
Direct acting vasodilatator	5.3
No. of antihypertensive drugs	3.8 ± 1.4
Total defined daily dosage use	5.6 ± 4.3

Expressed in proportion for different drug classes and mean with standard deviation for antihypertensive drugs and defined daily dosages per participant

Table 3a Baseline salt excretion and change in BP at 6 months

	Change in 6 months office systolic BP				Change in 6 months 24h ambulatory systolic BP			
	B	95%CI		p	B	95%CI		p
Model 1								
Baseline Na urine (10mmol/24h)	-0.20	-1.11	0.71	0.67	-0.56	-1.58	0.47	0.28
Baseline salt excretion quartile	-0.75	-5.83	4.34	0.77	-0.83	-6.52	4.86	0.77
Model 2								
Baseline Na urine (10mmol/24h)	-0.43	-1.28	0.41	0.31	-0.50	-1.54	0.54	0.34
Baseline salt excretion quartile	-1.46	-6.16	3.23	0.54	-0.68	-6.40	5.04	0.81
Model 3								
Baseline Na urine (10mmol/24h)	-0.53	-1.55	0.48	0.30	-0.20	-1.43	1.03	0.75
Baseline salt excretion quartile	-1.85	-7.23	3.52	0.49	1.17	-5.24	7.59	0.72
Model 4								
Baseline Na urine (10mmol/24h)	-0.53	-1.55	0.49	0.30	-0.20	-1.44	1.04	0.75
Baseline salt excretion quartile	-1.85	-7.26	3.57	0.50	1.17	-5.30	7.65	0.72
Model 5								
Baseline Na urine (10mmol/24h)	-0.58	-1.60	0.45	0.26	-0.33	-1.60	0.94	0.60
Baseline salt excretion quartile	-2.36	-7.86	3.14	0.39	0.32	-6.47	7.11	0.93
Model 6								
Baseline Na urine (10mmol/24h)	-0.60	-1.64	0.45	0.26	-0.39	-1.70	0.91	0.55
Baseline salt excretion quartile	-2.35	-7.92	3.21	0.40	0.20	-6.70	7.09	0.95
Model 7								
Baseline Na urine (10mmol/24h)	-0.59	-1.65	0.46	0.26	-0.39	-1.69	0.92	0.55
Baseline salt excretion quartile	-2.64	-8.12	2.84	0.34	0.13	-6.53	6.80	0.97

Model 1: crude; **Model 2**: adjusted for baseline systolic BP; **Model 3**: adjusted for baseline systolic BP, age and gender; **Model 4**: adjusted for baseline systolic BP, age, gender and race; **Model 5**: adjusted for baseline systolic BP, age, gender, race and BMI; **Model 6**: adjusted for baseline systolic BP, age, gender, race, BMI and baseline eGFR; **Model 7**: adjusted for baseline systolic BP, age, gender, race, BMI, baseline eGFR and baseline antihypertensive drug use

Table 3b Baseline salt excretion and change in BP at 6 months

	Change in 6 months office systolic BP				Change in 6 months 24h ambulatory systolic BP			
	B	95%CI		p	B	95%CI		p
Model 1								
Estimated 24h sodium excretion Tanaka (10 mmol/24h)	-0.25	-2.15	1.64	0.79	-0.004	-1.80	1.79	1.00
Salt excretion quartile based on Tanaka estimation	-1.90	-6.90	3.09	0.45	1.21	-3.68	6.10	0.62
Model 2								
Estimated 24h sodium excretion Tanaka (10 mmol/24h)	-0.80	-2.57	0.97	0.37	0.13	-1.70	1.97	0.89
Salt excretion quartile based on Tanaka estimation	-3.02	-7.65	1.62	0.20	1.61	-3.38	6.60	0.52
Model 3								
Estimated 24h sodium excretion Tanaka (10 mmol/24h)	-0.67	-2.48	1.15	0.46	0.42	-1.46	2.29	0.66
Salt excretion quartile based on Tanaka estimation	-2.71	-7.37	1.96	0.25	2.08	-2.94	7.09	0.41
Model 4								
Estimated 24h sodium excretion Tanaka (10 mmol/24h)	-0.67	-2.50	1.16	0.47	0.42	-1.47	2.31	0.66
Salt excretion quartile based on Tanaka estimation	-2.73	-7.45	2.00	0.25	2.05	-3.03	7.12	0.42
Model 5								
Estimated 24h sodium excretion Tanaka (10 mmol/24h)	-0.82	-2.70	1.06	0.39	0.11	-1.86	2.09	0.91
Salt excretion quartile based on Tanaka estimation	-3.18	-8.03	1.67	0.20	1.19	-4.24	6.61	0.66
Model 6								
Estimated 24h sodium excretion Tanaka (10 mmol/24h)	-0.83	-2.73	1.06	0.38	0.05	-1.97	2.06	0.96
Salt excretion quartile based on Tanaka estimation	-3.19	-8.07	1.70	0.20	1.07	-4.43	6.57	0.70
Model 7								
Estimated 24h sodium excretion Tanaka (10 mmol/24h)	-0.61	-2.57	1.35	0.54	0.04	-2.05	2.12	0.97
Salt excretion quartile based on Tanaka estimation	-2.71	-7.74	2.32	0.29	0.88	-4.75	6.52	0.75

Model 1: crude; **Model 2**: adjusted for baseline systolic BP; **Model 3**: adjusted for baseline systolic BP, age and gender; **Model 4**: adjusted for baseline systolic BP, age, gender and race; **Model 5**: adjusted for baseline systolic BP, age, gender, race and BMI; **Model 6**: adjusted for baseline systolic BP, age, gender, race, BMI and baseline eGFR; **Model 7**: adjusted for baseline systolic BP, age, gender, race, BMI, baseline eGFR and baseline antihypertensive drug use

to quartile of sodium intake is shown in figure 2. As table 3b shows results were similar in the analysis using the estimated sodium excretion with no significant relationship found for baseline sodium excretion with change in BP at 6 months after RDN.

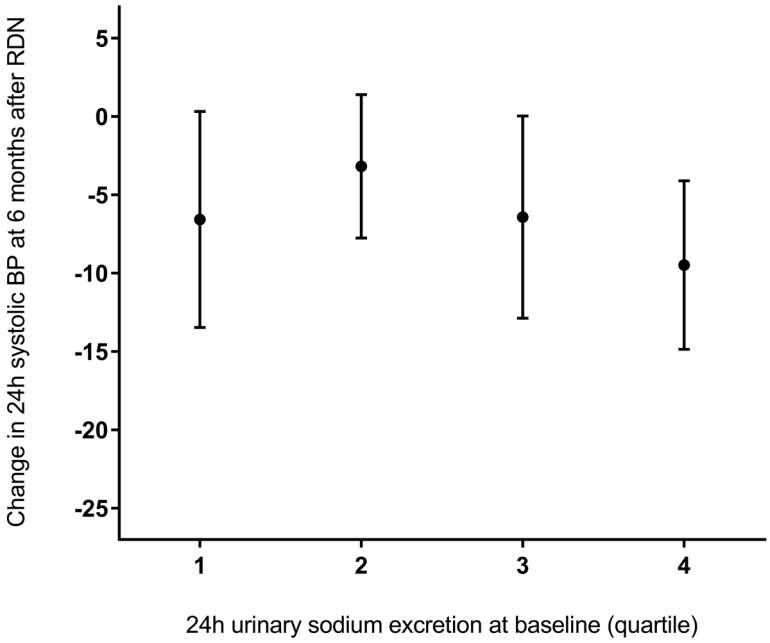

Figure 2 Baseline sodium excretion and change in blood pressure after renal denervation.
Mean change with whiskers indicating standard errors.
Quartiles of sodium excretion are 1 = ≤107 mmol/d, 2= 108-145 mmol/d, 3=146-193 mmol/d, 4= ≥194 mmol/d.

Changes in salt sensitivity

Daily sodium excretion was not related to ambulatory systolic blood pressure either at baseline nor at six months after RDN (supplementary figures 1 and 2). The crude regression analysis showed a decrease of 0.06 mm Hg in 24h systolic BP for every 10 mmol higher sodium intake (95%CI -0.98 to +0.85) at baseline, and of 0.06 mm Hg (95%CI -1.08 to +0.95) at six months after RDN. The intercept of the regression line was 8 mm Hg lower at six months (149 mm Hg versus 157 mm Hg at baseline) representing a shift of the sodium intake – blood pressure relationship to a lower level after RDN. Thus, at a given level of sodium intake, blood pressure was lower after RDN indicating a decrease in salt sensitivity. Adjustment for antihypertensive

drug use did not change the results. The analysis using the estimation of sodium excretion by the TANAKA formula showed a similar result, with a decrease in the intercept of 13 mm Hg (164 versus 177 mm Hg at baseline). In the control group, however, a similar shift of the sodium intake – blood pressure relationship was found to an even 19 mm Hg lower level at 6 months, both in the patients with well collected urine samples (n=23) and in the estimated sodium excretion analyses (n=32). Thus, although salt sensitivity decreased during follow-up, the decrease was caused by other factors than the RDN procedure.

Discussion

Dietary sodium intake was not related to the blood pressure lowering effect of renal denervation in this study. Salt sensitivity decreased after RDN, but a similar decrease was found in the control group during follow-up.

Dietary sodium intake and blood pressure after RDN

Dietary sodium restriction is routinely advised in hypertension, and leads to an important lowering of BP also in so-called resistant hypertension.(19-21) Sympathetic activity however increases when sodium intake is decreased, similar to the effect of (thiazide) diuretics and representing a feedback mechanism.(10;22;23) Efferent sympathetic activity to the kidneys leads to direct stimulation of tubular sodium reabsorption, aside from stimulating renin secretion and decreasing renal blood flow.(11) Measurement of sodium excretion, representing dietary sodium intake, was therefore hypothesized to be useful to predict the blood pressure lowering effect of RDN. No such relationship was found in the current study. One explanation could be that both a low and high sodium intake are related to a beneficial effect of RDN. Since the participants in this study with low sodium intake were still severely hypertensive, the contribution of both the renin-angiotensin-aldosterone system (RAAS) and sympathetic hyperactivity to the hypertension is assumed to have been high in these patients. Renal denervation is expected to lower both as these systems are highly connected.(24) In participants on a high sodium diet, volume expansion can be hypothesized to be important in the pathophysiology of hypertension, and renal denervation leading to increased sodium excretion expected to lead to decrease in BP. Relationships of sodium intake and BP lowering effect of RDN have only been studied by few. In studies investigating clinical factors predictive of the BP response after RDN, sodium intake was seldomly included as a possibility.(25; 26) Pöss et al. investigated relationships of 24h urinary sodium excretion as estimated from urine samples by the Kawasaki

formula with the BP change after RDN. As in this study, no prediction of the change in BP after RDN was found.(27) As the effectiveness of the RDN procedure probably differs between subjects, future studies using improved catheter systems or procedures (for example more distal ablation and intra-procedural assessment of the effect) might find different results. At this time, measurement of urinary sodium excretion cannot be used to select patients with (resistant) hypertension likely to benefit from RDN.

Changes in salt sensitivity

Large, worldwide population studies have shown an increase of blood pressure with higher sodium intake, with a steeper increase at higher levels (>3 g/d).(28) Salt sensitivity, that is change in blood pressure in response to change in salt intake, is normally distributed in the population, as opposed to present or absent in an individual.(29; 30) Salt sensitivity is higher in higher age and in presence of hypertension.(28; 31) In animal models of salt sensitive hypertension, development of hypertension on high salt diet is attenuated by renal denervation, leading to the hypothesis that sympathetic activity is an important contributor to the development of salt sensitive hypertension.(12; 31) Increased sympathetic activity counteracts pressure natriuresis, and a higher blood pressure is needed to excrete sodium when sympathetic nerve activity is high.(12; 30; 32) In the GenSalt study increased sympathetic reactivity, measured as increase in BP in a cold pressor test, has been shown to be related to salt sensitivity in humans.(33) From this background, an effect of lowering sympathetic activity by RDN on salt sensitivity is expected. In this study, a shift was indeed found in the sodium intake – blood pressure relationship in the whole study population in accordance with such an effect. However, a similar shift was found in the control group. The decrease in salt sensitivity therefore is not attributable to the RDN procedure.

Salt sensitivity has not been investigated in RDN studies before. Pöss et al. relate a higher 24h urinary sodium excretion after RDN to a beneficial effect of RDN. As the amount of sodium excreted in the urine depends on what is ingested in the diet (if in a steady state, as assumed in both studies), this can't be seen as proof for an increase in salt excretion due to a beneficial effect of the RDN procedure. As mean BP decreased after RDN in their study, it does show that the increase in sodium intake did not lead to an increase in BP as would be expected.

Strengths and limitations

Strengths of this study are that blood pressure and sodium excretion were measured carefully by 24h ambulatory blood pressure measurement and collection of 24h urine samples both at baseline and 6 months after RDN. Participants were closely

followed in the setting of a randomized clinical trial. Appropriateness of collection of 24h urine samples was assessed and antihypertensive drug use and several clinical factors could be adjusted for in the analyses. However, the study also has important limitations. The main analysis of the BP lowering effect of RDN in SYMPATHY was neutral suggesting insufficient effectiveness of the renal denervation procedure at least in part of the participants.(34) Size is another limitation, especially for the salt sensitivity analysis, partly due to exclusions for suspected 24h urine collection errors. No dietary interventions were done in this study, and salt sensitivity therefore could not be investigated in the appropriate way. No measurements of activity of the RAAS were available. We therefore could not investigate whether a combination of sodium intake and RAAS activity would better predict the BP lowering effect of RDN. However, adjustment for antihypertensive drug use, including RAAS inhibition, did not change the results. Lastly, from the main analysis of the SYMPATHY trial we now know that non-adherence to antihypertensive drug treatment is very prevalent in these patients. This could have introduced bias in the current study as well.

Conclusions

Dietary sodium intake was not related to change in BP after RDN. Salt sensitivity decreased during follow-up, but the change was not attributable to the RDN procedure. Dietary sodium intake cannot be used to identify patients that benefit from RDN. Dietary intervention studies might conclude differently on an effect on salt sensitivity of RDN.

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Supplement

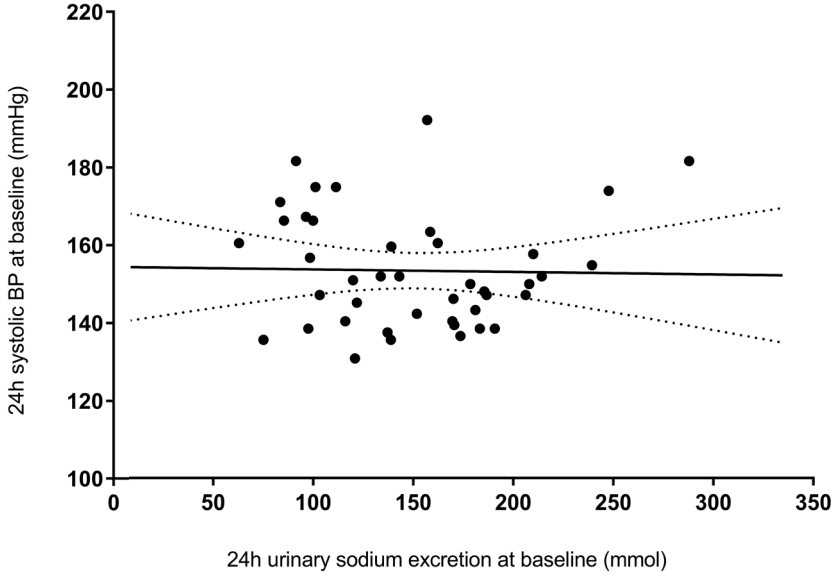

Figure S1 24h urinary sodium excretion and mean 24h systolic blood pressure levels at baseline

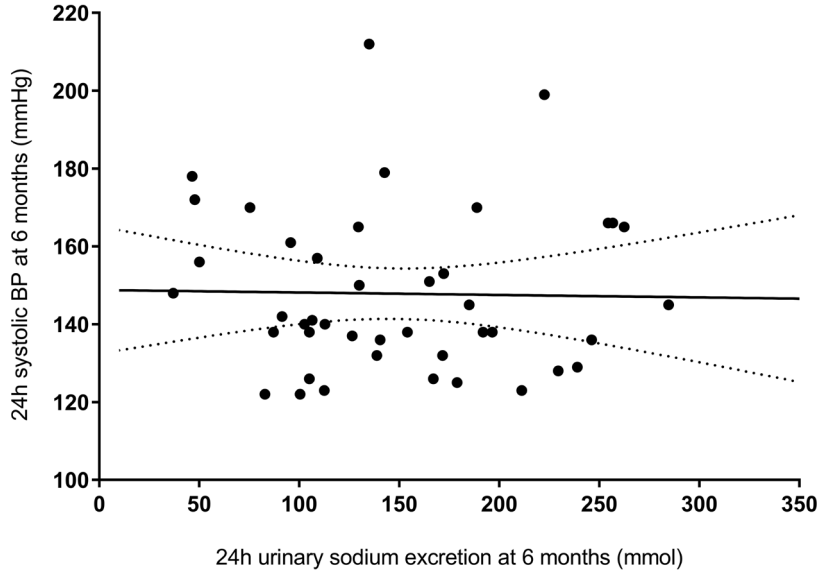

Figure S2 24h urinary sodium excretion and mean 24h systolic blood pressure levels six months after RDN

CHAPTER 9

Catheter-based renal denervation as a novel treatment for loin pain hematuria syndrome

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Renal denervation using a catheter delivering radiofrequency energy to the renal artery vessel wall has recently emerged as a promising new treatment for difficult-to-treat hypertension. The beneficial effect of this intervention, attributable to sympathetic nerves interruption, has been coherently demonstrated in both an observational study(1;2) and a controlled trial.(3;4) Of note, according to the available follow-up studies, the hypotensive effect of renal denervation has been shown to last for up to 2-3 years. The European Society of Hypertension has published a position paper with recommendations for the application of this new technique including the eligibility criteria and issues that need to be addressed in further trials.(5) Several other conditions associated with sympathetic overactivity as diverse as heart failure, atrial fibrillation, insulin resistance,(6) sleep apnoea(7) and polycystic ovary syndrome(8) have been described as being responsive to renal denervation and/or are being subjected to further study. Renal denervation has become a hot topic as illustrated by the large number of ongoing and planned trials of the technique.(9) In this issue, Gambaro et al. describe the use of catheter-based renal denervation for yet another indication, namely pain control in loin pain hematuria syndrome (LPHS).

LPHS is a rare condition of uncertain aetiology and definition. Over 100 papers on LPHS have been cited in PubMed (accessed on 18 March, 2013) so far, but many nephrologists agree that the actual number of cases is probably far larger. First described in 1967, LPHS is still a poorly understood condition consisting of recurrent flank pain often accompanied by non-visible or visible hematuria. Women are more often affected (about three-fourths of cases described so far) than men and patients are typically young at onset. The pain is often unilateral, but recurrences on the contralateral side after invasive treatment are the rule rather than the exception. Pain exacerbations may be accompanied by low-grade fever and sometimes urinary symptoms mimicking urinary tract infection.(10) Episodes of (particularly) visible or non-visible hematuria very often accompany exacerbation of loin/flank pain. The duration of such episodes is variable but in some cases symptoms persist for months and cause serious disability. Pain may be severe and associated with nausea and vomiting, mimicking renal colic. Often, opioid analgesics are eventually prescribed in the most severe cases. Kidney function remains normal and development of hypertension is not associated with the syndrome. Although spontaneous disappearance of symptoms can occur after years, many patients remain symptomatic long-term.(11) A diagnosis of LPHS can only be made after a thorough evaluation for, and exclusion of other causes of loin pain and/or hematuria. Interestingly, many patients report a history of nephrolithiasis.(12) A kidney biopsy shows no glomerular abnormalities, but intra-

tubular erythrocytes are seen more often than in healthy controls (7.2 versus 1.6%) suggesting a glomerular origin of hematuria.(12) Disparate structural abnormalities of the glomerular basement membrane, from excessive thickening to excessive thinning, may be the explanation.(12) Several other hypotheses for the cause of LPHS have been proposed including microvascular abnormalities, abnormal platelet function, intra-tubular microcrystal formation and complement activation.(10;13) The complexity of this disorder is underscored by the fact that many patients meet the criteria for somatoform disorder on the basis of other physical complaints preceding the onset of LPHS.(14)

LPHS, although rare, is a condition that challenges the urologists and nephrologists to whom these patients are referred since treatment is difficult. Pain is often severe, necessitating high dose analgesics including opioids. Clinical experience suggests that ~5 days treatment with an intravenous opioid is usually successful in terminating a painful episode, though patient-controlled analgesia protocols are sometimes needed. Management by multidisciplinary teams including a psychiatrist/psychologist and pain specialist is advisable, yet results are often disappointing with more than half of the patients experiencing no improvement of pain.(14) Several invasive strategies have therefore been explored in the past for very severe cases. Intra-ureteric capsaicin administration to interrupt nociceptive fibers was reported to produce short-term pain relief, but was abandoned because it was found to be associated with irreversible renal damage.(15) The fact that regional nerve blocks can give temporary relief has led to the application of neuromodulation with implantable electrodes and intrathecal pumps delivering opioids.(16;17) Permanent denervation of the kidney by either surgical neurectomy (often combined with capsulotomy) or even autotransplantation of a kidney has been performed for LPHS. One report comparing these techniques found renal neurectomy to be less successful than autotransplantation with 33% versus 76% of patients being pain-free in long-term follow-up (mean 8 years).(18) Comparable success rates for surgical denervation were found in other studies.(19;20) Chin et al.(21) reported similar long-term success of autotransplantation with 69% of 26 procedures leading to the absence of pain at a mean follow-up of 7 years. However, recurrences in the transplanted kidney and/or in the contralateral kidney are not unusual, and all authors reported graft loss from perioperative complications (due to ischaemia or thrombosis).(18;21;22) Thus, LPHS remains a very challenging clinical condition to treat and as such, it qualifies as a disorder for which it is appropriate to investigate novel, innovative approaches to alleviate the suffering and disability of patients with its most severe forms.

In their case report in this issue, Gambaro et al. describe a patient with a typical LPHS also suffering from hypertension successfully treated for both pain and hypertension with catheter-based renal denervation. At 6 months, the patient has remained pain-free and normotensive without antihypertensive treatment. Since catheter-based renal denervation has been shown to be a safe procedure in the trials reported so far, this treatment could be the long-sought less invasive treatment for LPHS.

However, many questions remain. The first is whether pain fibers can be interrupted by the denervation procedure. The afferent sensory innervation of the kidney consists of unmyelinated fibers using substance P and calcitonin gene-related peptide as primary neurotransmitters. In contrast to the efferent innervation that is distributed to all segments of the renal vasculature and tubules, the sensory nerve endings are primarily located in the renal pelvic wall. The cell bodies of these nerves are predominantly located in the T12-L3 dorsal root ganglia.(23) Most fibers seem to travel to the spinal cord alongside the renal artery in close proximity to the lumen.(24) The afferent nerves must also be involved in the perception of pain, but the population of fibers involved is unknown.(25) During catheter-based renal denervation, significant pain is evoked,(1) thus supporting an effect on pain perception fibers with the procedure. A second issue is the possibility of re-innervation after the procedure. The difference in success rate of the two surgical procedures (neurectomy versus autotransplantation) has been attributed to more frequent re-innervation with the former or, alternatively, less complete denervation with the neurectomy procedure.(18) Renal allografts have been shown to be not completely denervated but to have structurally abnormal innervation in the renal hilum and parenchyma with evidence of regeneration after transplantation.(26) However, nephrolithiasis in grafts does not typically cause pain, suggesting absence of functional nociceptive fibers.(27) In rats, re-innervation with both sensory and efferent fibers has been shown to occur after surgical denervation.(28) However, in the trials of renal denervation for hypertension, a sustained decrease in blood pressure is found, with no evidence of functional re-innervation. This issue will probably become clearer over the coming years. In theory, renal denervation can be repeated in cases with evidence of re-innervation.

Another puzzling point in the case report by Gambaro is the remarkable hypotensive effect of unilateral renal denervation. One would expect the remaining sympathetic innervation to and from the left kidney to keep blood pressure high. A possible explanation is that the right kidney, being smaller and painful, was diseased and generated increased sympathetic drive on its own. In this regard, a

recent report by Shetty et al. of a patient whose renal pain secondary to polycystic renal disease disappeared after catheter-based renal denervation for treatment of hypertension is of obvious interest. This patient had immediate resolution of pain but decrease of systolic blood pressure did not occur till 3 months later.(29) This might suggest a different effect of catheter-based renal denervation on afferent sympathetic and nociceptive fibers. Furthermore, these authors suggest that renal denervation for pain management could also have a role in polycystic kidney disease patients, in whom pain can also be a difficult-to-treat problem sometimes necessitating operative measures.

Thus, whereas the observations by Gambaro are hypothesis generating, solid evidence is needed before recommending renal denervation for treatment of LPHS and other painful renal diseases. In light of the modest results of surgical denervation, the danger of publication bias (with only positive results being reported) and the possibility of a large placebo effect in this poorly understood syndrome, a clinical trial should be performed. We envisage a pan-European, investigator-initiated, industry-independent trial in patients with LPHS and inadequate response to conservative treatment referred to national centers with expertise in renal denervation. These patients could be randomized to catheter-based denervation or a control intervention with pain control as the primary outcome. Well-validated pain scoring methods would be used. Given the rareness of this disorder, participation of centers across Europe would be necessary. With inclusion of one to two patients per center, enrolling up to 40 patients should be possible. The design could allow crossover after 6 months. Such a trial would also include long-term follow up and would clarify whether catheter-based renal denervation is the answer to the unmet need in a category of patients affected by this rare condition.

In conclusion, LPHS remains an enigmatic syndrome that can cause debilitating pain which often responds poorly to conservative care. Instead of the drastic surgical measures taken in the past, a safe, less-invasive, treatment may now be available. Application of catheter-based renal denervation should be subjected to a properly conducted clinical trial in order to provide definitive evidence for its effectiveness, or otherwise, in LPHS.

(See related article by Gambaro et al. Percutaneous renal sympathetic nerve ablation for loin pain hematuria syndrome. Nephrol Dial Transplant 2013; 28: 2393–2395.)

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CHAPTER 10

Catheter-based renal denervation as therapy for chronic severe kidney-related pain

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Abstract

Background

Loin pain hematuria syndrome (LPHS) and autosomal dominant polycystic kidney disease (ADPKD) are the most important non-urological conditions to cause chronic severe kidney-related pain. Multidisciplinary programs and surgical methods have shown inconsistent results with respect to pain reduction. Percutaneous catheter-based renal denervation (RDN) could be a less invasive treatment option for these patients.

Methods

Our aim was to explore the change in perceived pain and use of analgesic medication from baseline to three, six and 12 months after RDN. Patients with LPHS or ADPKD, who experienced kidney-related pain ≥3 months with a visual analog scale (VAS)-score of ≥50/100, could be included. Percutaneous RDN was performed with a single electrode radio-frequency ablation catheter.

Results

In eleven patients (six with LPHS and five with ADPKD) RDN was performed. Perceived pain declined in the whole group with 23 mm (p=0.012 for the total group). In patients with LPHS and ADPKD, the median daily defined dosage of analgesic medication, decreased from 1.6 [interquartile range 0.7-2.3] and 1.4 [0.0-7.4] at baseline to 0.3 ([0.0-1.9], P=0.138) and 0.0 ([0.0-0.8], P=0.285) at 12 months, respectively. Mean eGFR decreased in the whole group with 5.4 ml/min/1.72m^2 at six months compared to baseline (P=0.163).

Conclusions

These results suggest that percutaneous catheter-based RDN reduces pain complaints and use of analgesic medication in patients with LPHS or ADPKD. The present results can serve as the rationale for a larger, preferably randomized (sham) controlled study.

Introduction

Loin pain hematuria syndrome (LPHS) and autosomal dominant polycystic kidney disease (ADPKD) are the most important non-urological conditions to cause kidney-related pain. LPHS is a rare disease and a diagnosis per exclusionem. Patients often experience intense, sometimes invalidating unilateral or bilateral flank pain longer than six months and hematuria (with or without dysmorphic erythrocytes). This disease can be associated with glomerulonephritis, usually IgA nephropathy.(1) Pain in LPHS is thought to be caused by tubular obstruction due to erythrocytes and/or microcrystals, which leads to capsular distension and, eventually, visceral pain.(2;3) LPHS is usually not associated with deterioration in kidney function, infection or hypertension.(3;4)

ADPKD is the leading cause of end-stage renal disease in Europe.(5) Patients with ADPKD can experience invalidating pain, which is thought to be caused by stretching of the renal capsule by expansion of renal cysts, which causes visceral pain.(6) Chronic pain in LPHS and ADPKD is difficult to treat. Often analgesic medication is necessary to control the pain, in many cases also including opioids.(7) Surgical procedures, such as nephrectomy, renal auto-transplantation or laparoscopic renal denervation (RDN) have proven to be effective in pain relief.(3;8) However, these procedures are invasive and nephrectomy of a still functioning kidney will bring the patient at greater risk for end-stage kidney disease, especially in ADPKD.

Catheter-based RDN was introduced as a possible treatment of apparent resistant hypertension.(9) It aims to disrupt the renal sympathetic nerves by using variable methodologies within the renal arteries including radiofrequency, intravascular ultrasound and local application of neurotoxic agents, such as ethanol.(10-14) Conceptually, catheter-based RDN may be an attractive option for treating kidney-related pain as the majority of pain-conducting nerve fibers are located circumferentially around the renal artery and the hilum.(4;15) At present, there are some case reports that suggest a beneficial effect of catheter-based RDN in LPHS.(16-19) In addition, we published a case report on the effects of catheter-based RDN in a patient with ADPKD on both sides with a tremendous drop in perceived pain.(16)

Our aim was to study the effect of catheter-based RDN on perceived pain and the use of analgesic medication in patients with LPHS or ADPKD with kidney-related pain in a larger group of patients to guide further research. Secondly, we summarized available evidence in the literature.

Subjects and Methods

This pilot study was designed as a prospective cohort. Patients were referred to our department by colleagues of our own hospital and from other centers across the Netherlands between May 2013 and April 2015. Patients had either kidney-related pain due to LPHS or to ADPKD. All LPHS patients had a history of urological and nephrological analysis to rule out other treatable causes of their complaints, as well as consultation of a pain specialist and/or psychologist. Patients with ADPKD were thoroughly screened for other causes of pain, as they participated in a study that investigated a stepwise program with sequential percutaneous celiac nerve blockade to treat chronic invalidating pain.(20) In case there was no pain relief after the nerve blockade, we assumed that the pain stimuli travelled via the aortico-renal plexus and RDN could be an option. All patients were discussed in a multidisciplinary setting.(21) They were considered eligible for RDN when they were ≥18 years old, had invalidating kidney-related pain (≥ 3 months pain duration, ≥50/100 on Visual Analogue Scale (VAS) and insufficient response to previous analgesic therapies) and when a computer tomography angiogram or magnetic resonance angiogram showed a diameter > 4 mm and a length of > 20 mm of the renal artery at the side of the pain. All patients gave their permission to be part of this study, in accordance with the declaration of Helsinki.

Pain assessment

Perceived pain was assessed with a validated Dutch questionnaire (MPQ-DV), which is based on the McGill pain questionnaire (MPQ).(22;23) In this questionnaire patients were asked to fill out their maximal visual analogue scale (VAS)-score. The VAS-score is the maximum pain a patient has experienced in the last two weeks on a scale from 0 (no pain at all) to 100 mm (maximum of pain possible). Patients were asked to fill out the questionnaire at baseline (pre-RDN), three, six and 12 months post-RDN.

Analgesic use assessment

Medication was screened for analgesic medication, according to the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization Collaborating Centre for Drug Statistics (http://www.whocc.no/atc_ddd_index/) at baseline, three, six and 12 months. We registered the number of different classes of analgesics and we calculated the total daily defined use (DDD) of analgesic medication per patient per visit.

Kidney function and blood pressure assessment

At baseline and six months, the estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.(24) Office blood pressure measurements were collected at baseline and at six months and calculated as the average of three measurements on each arm. All blood pressure measurements were done with methods and devices in accordance with the latest recommendations of the European Hypertension Consensus.(25)

Renal denervation

The UMC Utrecht is an European Society of Hypertension center of excellence and participated in a number of RDN trials for hypertension. Detailed information on the procedure is published elsewhere(26;27) The procedure was performed by an experienced interventionist using the radiofrequency ablation Symplicity™ catheter (Medtronic Inc., Santa Rosa, California), only in the renal arteries located on the side where the patient experienced pain. The interventionist decided on the number of ablations and if all (accessory) arteries could be treated on that particular side. When the patient experienced pain on both sides, the side with the highest VAS-score would be treated first and three months later the other side, if no procedural complications had occurred the first time. Adverse events were collected at follow-up.

Statistical analysis

Normally distributed variables are expressed as mean ± SD, whereas non-normally distributed variables are reported as median [Interquartile range]. Changes in VAS score, analgesics used and DDD between baseline and follow-up were analyzed with the Wilcoxon signed-rank test. Changes were analyzed for the whole group, as well as stratified for ADPKD and LPHS. Paired T-test analysis was used to analyze changes in blood pressure and eGFR between baseline and six months. A two-tailed p-value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA).

Pooling data of other published case-reports

PubMed and Embase were searched for case reports assessing RDN and the effect on pain relief in patients with LPHS and ADPKD. The following broad search terms were used to cover all the aspects, as we hypothesized that there would only be small series and case-reports available: kidney pain, renal denervation, autosomal

dominant polycystic kidney disease, ADPKD, loin pain hematuria syndrome, LPHS. Eligible for inclusion were reports of kidney-related pain and percutaneous catheter-based RDN. We extracted, if possible, data on change in perceived pain and in analgesic medication between baseline and six and 12 months follow-up.

Results

Baseline characteristics

Eleven patients with kidney-related pain were included: six patients with LPHS and five patients with ADPKD (table 1). Mean age was 40±9 years and nine of the 11 patients were female. All patients with ADPKD and one LPHS patient used antihypertensive medication. Kidney function was impaired in the ADPKD group as compared to the LPHS group (eGFR 51±31 vs. 117±15 ml/min/1.73m^2). Median duration of chronic pain was longer in the ADPKD group with 4.0 [2.4-19.5] years, as compared with 1.5 [0.5-6.5] years in the LPHS group. Fifty-five percent of all patients experienced pain at the right side. The LPHS group noted the highest pain experience, with a median VAS-score of 84 [77-94] mm compared to a VAS-score of 76 [64-86] mm in the ADPKD group. In addition, patients in the LPHS group used, on average, one class of analgesic medication more than patients in the ADPKD group (3.0 versus 2.0 pills). Fifty-five percent of the patients (n=6) used some type of opioid as treatment for their pain.

Change in perceived pain after renal denervation

RDN was performed on both sides in two patients and unilaterally in nine. Mean number of ablations per kidney was 7(±1). There were no serious adverse events reported after the procedure. Figure S1 represents the individual data of the VAS-score, per patient group (LPHS and ADPKD). Perceived pain declined in the overall population from 82 [70-92] mm to 68 [55-79] mm (P=0.036) and 59 [0-71] mm (P=0.012) at three and 12 months after RDN, respectively. The decrease was consistent in both groups (table 2).

Change in use of analgesic medication after renal denervation

In the whole group the median number of classes of analgesic medication decreased significantly from 2.0 [2.0-3.0] at baseline to 1.5 [0.8 - 2.3] at three months (P=0.033) and decreased slightly further at 12 months to 1.0 [0.0 - 2.0] (P=0.011) (table 2). Figure S2 represents the individual data of the DDD of analgesic medication. Overall, a reduction in DDD was seen from 1.4 [0.4 - 2.1] at baseline to 0.6 [0.3 -1.4] and 0.0 [0.0-1.6] at three and 12 months (P=0.018 and 0.068, respectively). In the LPHS group the DDD was reduced from 1.6 [0.7-2.3] at baseline to 0.6 [0.5 - 1.4]

Table 1 Baseline characteristics

	All	Loin pain hematuria syndrome	Autosomal-Dominant Polycystic Kidney Disease
	(n=11)	(n=6)	(n=5)
Age (years)	40 (9)	37 (10)	45 (7)
Male *	2 (18)	1 (17)	1 (20)
Caucasian*	11 (100)	6 (100)	5 (100)
Hypertension *	5 (45)	1 (17)	5 (100)
Dyslipidemia*	0 (0)	0 (0)	0 (0)
Diabetes mellitus type 2*	2 (18)	1 (17)	1 (20)
(Cardio)vascular diseases*	1 (9)	1 (17)	0 (0)
Pain duration (years)	2.5 [0.75-6.0]	1.5 [0.5-6.5]	4.0 [2.4-19.5]
Visual Analog Score (mm)	82 [70-92]	84 [77-94]	76 [64-86]
Pain side			
Right	6 (55)	4 (67)	2 (40)
Left	3 (27)	2 (33)	1 (20)
Both	2 (18)	0 (0)	2 (40)
Classes pain medication	2.0 [2.0-3.0]	2.5 [2.0-3.0]	2.0 [0.5-3.5]
Use of opioids*	6 (55)	4 (67)	2 (40)
DDD pain medication	1.4 [0.4-2.1]	1.6 [0.7-2.3]	1.4 [0.0-7.4]
Body mass index (kg/m^2)	27.2 (4.7)	25.8 (2.5)	28.9 (6.4)
Office blood pressure			
Systolic mm Hg	130 (21)	118 (16)	144 (17)
Diastolic mm Hg	80 (13)	72 (8)	91 (9)
Heart rate bpm	77 (11)	78 (12)	74 (9)
Classes antihypertensive medication	1.0 [0.0-3.0]	0.0 [0.0-1.0]	3.0 [1.0-3.5]
eGFR, CKD epi ml/min/1.73m^2	90 (37)	115 (14)	60 (33)
eGFR < 60 ml/min/1.73m^2	2 (18)	0 (0)	2 (40)

Continuous values are expressed as mean (±SD) or as median [interquartile] when applicable.
* Values represent number of patients (%).
Abbreviations: No., number; eGFR, estimated glomerular filtration rate; bpm, beats per minute; DDD, daily defined dose.

Table 2a Change in perceived pain and use of pain medication in the whole group

	Baseline	3 months (n=11)	P-value	6 months (n=11)	P-value	12 months (n=11)	P-value
Visual Analog Score (mm)	82 [70-92]	68 [55-79]	0.036	61 [34-66]	0.028	59 [0-71]	0.012
No. of classes of pain medication	2.0 [2.0-3.0]	1.5 [0.8-2.3]	0.033	2.0 [0.0-2.0]	0.084	1.0 [0.0-2.0]	0.011
Daily defined use of pain medication	1.4 [0.4-2.1]	0.6 [0.3-1.4]	0.018	0.4 [0.0-0.9]	0.214	0.0 [0.0-1.6]	0.068

Table 2b Change in perceived pain and use of pain medication in Loin Pain Hematuria Syndrome

	Baseline	3 months (n=6)	P-value	6 months (n=6)	P-value	12 months (n=6)	P-value
Visual Analog Score (mm)	84 [77-94]	73 [34-88]	0.144	64 [47-70]	0.180	69 [15-94]	0.109
No. of classes of pain medication	2.5 [2.0-3.0]	1.5 [1.0-2.0]	0.034	2.0 [2.0-2.3]	0.157	1.5 [0.0-2.0]	0.039
Daily defined use of pain medication	1.6 [0.7-2.3]	0.6 [0.5-1.4]	0.042	0.4 [0.4-1.8]	0.345	0.3 [0.0-1.9]	0.138

Table 2c Change in perceived pain and use of pain medication in Autosomal-Dominant Polycystic Kidney Disease

	Baseline	3 months (n=5)	P-value	6 months (n=5)	P-value	12 months (n=5)	P-value
Visual Analog Score (mm)	76 [64-86]	64 [55-73]	0.068	52 [11-65]	0.068	45 [0-62]	0.043
No. of classes of pain medication	2.0 [0.5-3.5]	1.5 [0.0-3.8]	0.414	0.0 [0.0-2.5]	0.197	0.5 [0.0-2.0]	0.109
Daily defined use of pain medication	1.4 [0.0-7.4]	0.7 [0.0-10.4]	0.180	0.0 [0.0-1.2]	0.465	0.0 [0.0-0.8]	0.285

Data are expressed as median [interquartile] compared to baseline. N represents the number of patients with information on the variable of interest at baseline and at follow-up. Abbreviations: MM, millimeters; No., number; P-value represents the mean difference from baseline to three, six and 12 months follow-up.

and 0.3 [0.0 - 1.9] at three and 12 months (P=0.042 and P=0.138, respectively). This was similar for the ADPKD group, where at three months and 12 months the DDD decreased to, respectively, 0.7 ([0.0 -10.4], P=0.180) and 0.0 ([0.0-0.8], P=0.285).

Kidney function and blood pressure

Figure S3 shows the available data on eGFR in each individual patient (n=11). Overall, eGFR decreased (87±41 versus 82±41 ml/min/1.73m^2) (table S1). The change seems to be mainly caused by one LPHS patient (figure S3). In the ADPKD group office systolic blood pressure declined at six months with a mean of 5±6 mm Hg compared to baseline, accompanied with a median reduction in the use of blood pressure lowering drugs of 1.5 pills. The mean blood pressure increased in the LPHS group (109±13/70±9 versus 116±6/71±5 mm Hg). Still, the only patient with hypertensive medication in this group could stop with this medication, due to better regulation of his blood pressure (table S1).

Pooled data of other published case-reports

One-hundred-thirty-six studies were found to be eligible to our research question (49 in PubMed). We subtracted 32 duplicates. After screening of title and abstract, we found one case series with four patients and one case-report exploring the effect of RDN on kidney-related pain in LPHS (table S2 and S3). Data about use of analgesic medication could be extracted.(17;18) However, in the case series, the VAS was based on a quality of life assessment scale (EQ-5D) and for our research question not eligible to assess perceived pain(18) The other case-report was of Gambaro et al., in which no baseline VAS was published.(17) We found two case-reports about RDN in ADPKD, of which one was from our center (table S2 and S3).(16;19) The second report was published by Shetty et al, and which VAS and number of classes of analgesic medication could be extracted.(19) Follow-up data on kidney function were lacking in all case-reports. The pooled effect of RDN on decline in number of classes of analgesic medication at six months in patients with LPHS and ADPKD was more pronounced with a median decline of -1.0 [-2.0 - 0.0] pills (p=0.010) and -2.0 [-2.5 - -0.5] pills (p=0.066) (table S4).

Discussion

This pilot study reports on the largest dataset of results of percutaneous catheter-based RDN for the treatment of kidney-related pain in patients with LPHS and ADPKD. The results suggest that a reduction of pain occurred despite of the fact that also the use of analgesic medication decreased. Our data also suggests that this effect is sustained, at least for 12 months.

There are only a few case reports that describe RDN may result in pain relief and reduction in the use of analgesics in patients with kidney-related pain.(16-19) Our results are in line with those reports. However, comparison of the various reports is difficult because of the lack of standardization in pain assessment. A difference in VAS of ≥ 11 mm is considered to be of clinically significant importance,(28) which was the case in both the LPHS and ADPKD group. The reduction in analgesic drug use is also of interest and of particular relevance in ADPKD. Acetaminophen (paracetamol) is often insufficient, non-steroidal anti-inflammatory agents are contra-indicated in patients with CKD and opioids are associated with relevant side effects.(7) Indeed, six of the 11 patients were on opioids. Some patients reported difficulties in reducing and stopping opioids because of physical and mental dependency, and needed professional guidance and support for that. We believe that the sustained effect (up to 12 months), the reduction in medication use and the reported difficulties in stopping opioids, do give support to the idea that the effect of RDN on pain is real. Obviously, we cannot rule out a placebo-effect since a sham-control arm was missing.

LPHS often is a difficult to treat medical condition. The precise pathogenesis is uncertain. Psychological evaluation is also recommended. Taba et al. recently reviewed possible therapies for kidney-related pain in patients with LPHS. Minimal invasive therapies like bivacaine infusion and celiac plexus blockade gave inconclusive results on efficacy and safety. More invasive methods as surgical RDN and kidney auto-transplantation were reported to have higher success rates, but can be associated with relevant complications. Further, recurrence of pain after surgical RDN can be up to 75% after 12 months,(3) which is in contrast to our study. Moreover, percutaneous RDN would be much easier and safe to repeat for recurrence of pain.

For ADPKD, several approaches have been studied to reduce perceived pain. Tolvaptan, a vasopressin V2 receptor antagonist, which reduces cysts growth, may be helpful to reduce pain.(29) More invasive procedures include percutaneous nerve blockade, transcatheter arterial embolization (TAE) and finally nephrectomy.(8) Percutaneous catheter-based RDN may therefore be an alternative in both disease conditions, as it is less invasive with low complication rate. However, it is important to emphasize that our ADPKD population was highly selected and only found eligible, when celiac blockade did not reduce the pain.(30)

Presently, RDN is mainly applied in patients with so called resistant hypertension. There is no specific pathophysiologic argument for that.(31) Earlier, we hypothesized that patients with kidney injury were more likely to have increased

activity of the renal nerves and therefore could benefit of RDN.(32-34) Indeed, all ADPKD patients were on antihypertensive drugs and showed a decrease in blood pressure and in number of antihypertensive drugs after RDN, despite the fact that most of these patients were only treated unilaterally. However, the decline in blood pressure could also be, partially, due to better pain control. There was a small overall reduction in renal function six months after RDN, assessed as eGFR. This seems to be mainly explained by one LPHS patient. Unfortunately no repeat measurements are available in this patient. In our study, patients with reduced renal function at baseline were pre- and post-hydrated according to our hospital protocol for preventing contrast nephropathy. Possible other explanations for the decline in renal function can be: lower perfusion of the kidney due to a decline in blood pressure, normal variation overtime or progression of the underlying kidney disease. Obviously, in future studies eGFR should to be closely monitored.

Some limitations of the study need to be discussed. First, this study should be considered as a pilot study. It lacks a control group and has a small sample size. Secondly, the effect on pain showed a great variability, i.e. in some patients there was little or no effect, while in others a substantial effect was found. All procedures were done with the Medtronic Symplicity device. It is now clear that, with this device, a highly variable degree of denervation is obtained.(35;36) Also the location in the renal artery of application and the number of ablation points seem to be of critical importance.(36;37) So, it is possible that the variability in the observed effect is partially explained by a variable degree of completeness of denervation. Further, our data seem to suggest that the effect on pain increases over time. Thirdly, there could have occurred regression to the mean, but patients had experienced pain with a median duration of 1.5 years, which was at least three months stable. In addition, serious adverse events related to the RDN procedure were not reported.

In conclusion, the present data suggest that catheter-based RDN can have a beneficial effect on kidney-related pain and the use of analgesic medication in patients with LPHS and ADPKD. This needs further exploration, because alternative strategies in these disease conditions are insufficient, associated with side effects and/or (much) more invasive. A next study on this subject should be a randomized, preferably sham-controlled clinical study in order to determine whether catheter-based RDN is a meaningful addition to the treatment options in these often difficult-to-treat patients.

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Supplement

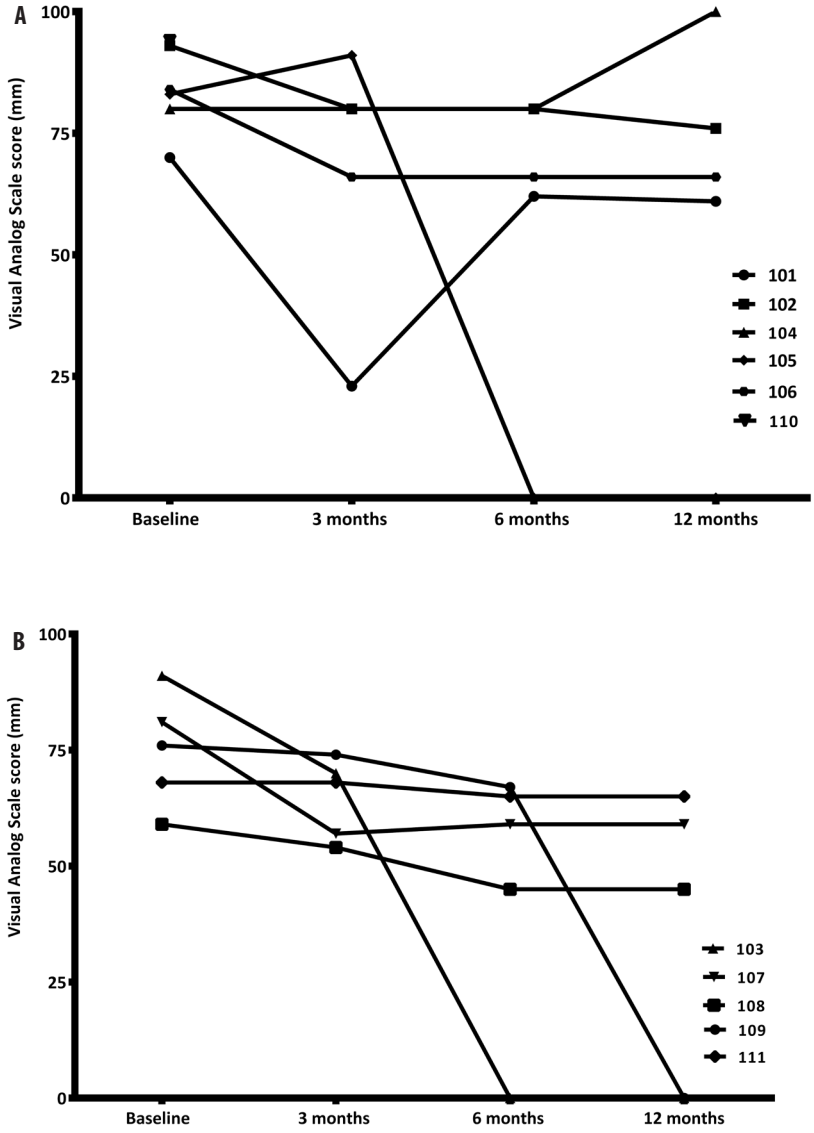

Figure S1 Individual data for baseline and follow-up
Presented for the score on the visual analogue scale and assigned by loin pain hematuria syndrome (A) or autosomal polycystic kidney disease (B).

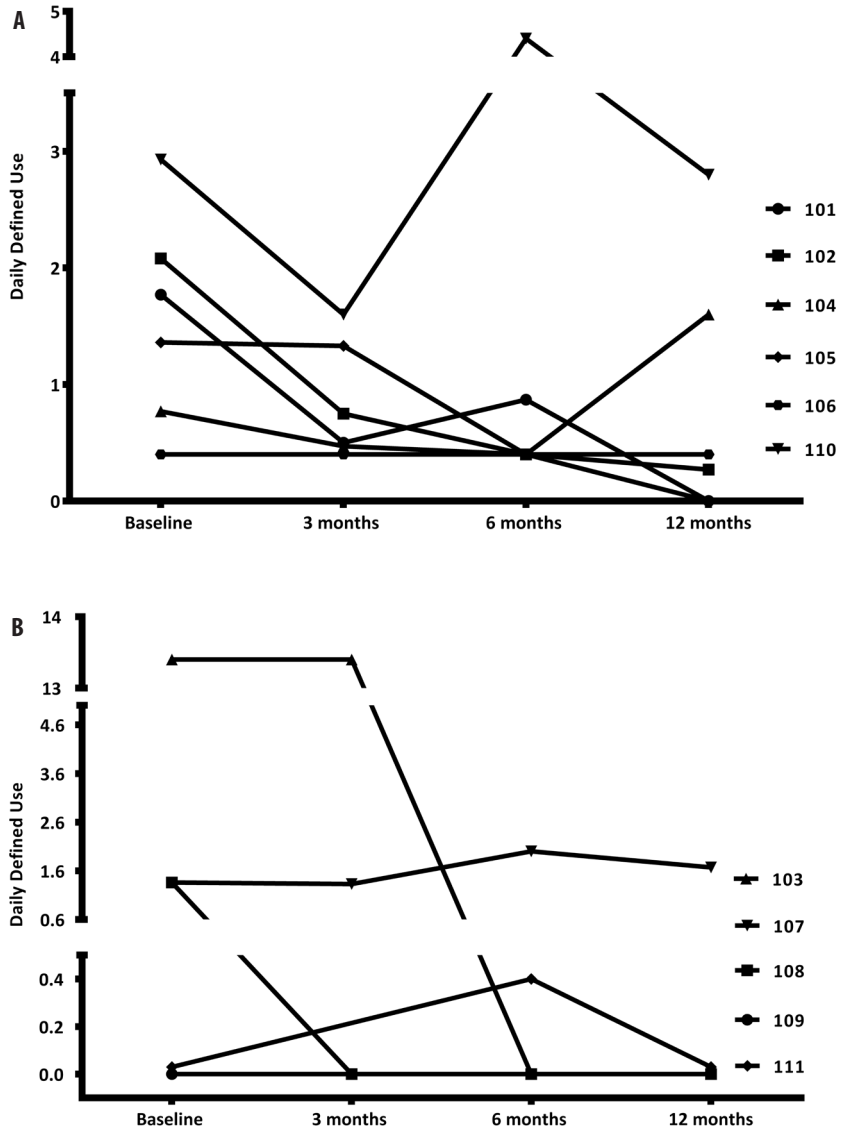

Figure S2 Individual data for baseline and follow-up
Presented for daily defined use and assigned by loin pain hematuria syndrome (A) or autosomal polycystic kidney disease (B).

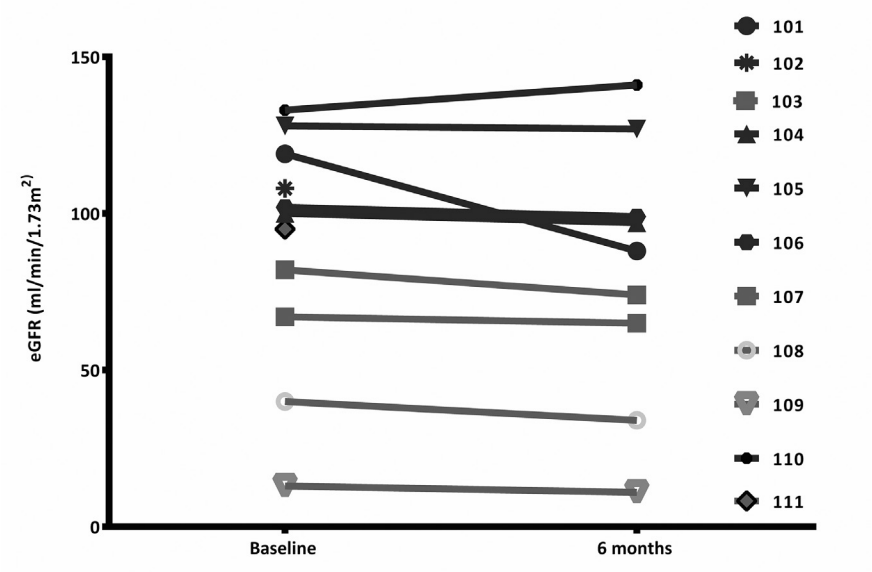

Figure S3 Individual data for baseline and six months
Presented for estimated glomerular filtration rate (eGFR).
Autosomal Dominant Kidney Disease Loin Pain Hematuria Syndrome

Table S1 Change in kidney function and blood pressure 6 months after renal denervation

	Baseline	6 months	P-value
Total group			
eGFR, CKD epi ml/min/1.73m^2 (n=11)	87(41)	82(41)	0.163
Office blood pressure mm Hg (n=7)	125(18)/81(13)	125(11)/81(13)	0.972/0.847
No. of classes of antihypertensive medication (n=7)	1.0 [0.0-3.0]	0.0 [0.0-1.3]	0.066
Loin pain hematuria syndrome			
eGFR, CKD epi ml/min/1.73m^2 (n=6)	117 (15)	110 (22)	0.400
Office blood pressure mm Hg (n=3)	109(13)/70 (9)	116(6)/71(5)	0.385/0.911
No. of classes of antihypertensive medication (n=3)	0.0 [0.0-1.0]	0.0 [0.0-0.0]	0.157
Autosomal-Dominant Polycystic Kidney Disease			
eGFR, CKD epi ml/min/1.73m^2 (n=5)	51 (31)	46 (29)	0.073
Office blood pressure mm Hg (n=4)	137(10)/89(8)	132(7)/89(5)	0.180/0.895
No. of classes of antihypertensive medication (n=4)	3.0 [1.0-3.5]	1.5 [0.3-2.8]	0.180

Data are expressed as mean (±SD) or median [interquartile], if applicable. N represents the number of patients with information on the variable of interest at baseline and at follow-up. P-value represents the difference in mean blood pressure from baseline to six months follow-up.
Abbreviations: eGFR, estimated glomerular filtration rate; No., number.

Table S2 Study characteristics of the included studies

	Current study	Prasad et al.	Gambaro et al.	Shetty et al.
Journal	N/A	Am J Kidney Dis	Nephrol Dial Transplant	Int J Cariol
Publication year	N/A	2016	2013	2013
PMID	N/A	27528372	23658250	22721643
Country	Netherlands	Canada	Italy	Australia
Study design	Cohort	Cohort	Single case	Single case
Study population	ADPKD (n=5) LPHS (n=6)	LPHS (n=4)	LPHS (n=1)	ADPKD (n=1)
Follow-up	6 months	6 months	6 months	12 months
Pain assessment tool	McGill pain questionnaire	EQ-5D VAS*	Unknown	Comparative Pain Scale
Device used	Symplicity	Vessex	Symplicity	Symplicity

*not suitable for pain assessment, as it is designed for quality of life assessment.
Abbreviations: PMID, PubMed Identification number; N/A, not applicable; ADPKD, autosomal-dominant polycystic kidney disease; LPHS, loin pain hematuria syndrome;

Table S3 Baseline characteristics of all included studies in meta-analysis

	All (n=17)	Loin pain hematuria syndrome (n=11)	Autosomal-Dominant Polycystic Kidney Disease (n=6)
Age (years)	41(11)	37(12)	49(8)
Sexe male*	2(12)	1(9)	1(17)
Caucasian*	17(100)	11(100)	6(100)
Hypertension *	7(41)	1(14)	6(100)
Pain duration (years)	4.0 [1.1-6.0]	1.5 [0.5-6.5]	4.0 [2.4-19.5]
Visual Analog Score (mm)	80 [70-92]	84 [77-94]	76 [64-86]
Pain side			
Right	11(65)	8(27)	3(50)
Left	4(23)	3(73)	1(17)
Both	2(12)	0(0)	2(33)
No. of classes pain medication	2.0 [2.0-3.0]	2.5 [2.0-3.0]	2.0 [0.5-3.5]
Daily defined use of pain medication	1.1 [0.2-1.6]	1.1 [0.7-1.8]	1.4 [0.0-7.4]
Office blood pressure (mm Hg)	133(23) / 83(15)	118(16) / 72(8)	148(19) / 94(10)
24-hour ABPM (mm Hg)	140(18) / 88(6)	N/A	140(18) / 88(6)
No. of classes antihypertensive medication	1.0 [0.0-3.0]	0.0 [0.0-1.0]	3.0 [1.0-3.5]
eGFR, CKD epi (ml/min/1.73m^2)	89(31)	102(21)	66(34)
Device used			
Symplicity	13(77)	7(64)	6(100)
Boston	4(23)	4(36)	0(0)

Continuous values are expressed as mean (±SD) or as median [interquartile] when applicable.
* Value represents number of patients (%)
Abbreviations: No., number; ABPM, ambulatory blood pressure measurement; eGFR, estimated glomerular filtration rate; bpm, beats per minute.

Table S4a Results of the pooled data: change in perceived pain and use of pain medication in patients with kidney related pain (all)

	Baseline	**6 months** (n=16)	**P-value**
Visual Analog Score (mm)	80 [70-92]	59 [0-66]	0.028
No. of classes of pain medication	2.0 [2.0-3.0]	1.0 [0.0-2.0]	0.002
Daily defined use of pain medication	1.1 [0.2-1.6]	0.0 [0.0-0.4]	0.034

Table S4b Results of the pooled data: change in perceived pain and use of pain medication in Loin Pain Hematuria Syndrome

	Baseline	**6 months** (n=11)	**P-value**
Visual Analog Score (mm)*	84 [77-94]	64 [47-70]	0.180
No. of classes of pain medication	2.5 [2.0-3.0]	1.0 [1.0-2.0]	0.010
Daily defined use of pain medication	1.1 [0.7-1.8]	0.3 [0.0-0.4]	0.086

Table S4c Results of the pooled data: change in perceived pain and use of pain medication in Autosomal-Dominant Polycystic Kidney Disease

	Baseline	6 months (n=5)	P-value
Visual Analog Score (mm)	76 [64-86]	45 [0-63]	0.068
No. of classes of pain medication	2.0 [0.5-3.5]	0.0 [0.0-1.5]	0.066
Daily defined use of pain medication¥	1.4 [0.0-7.4]	0.0 [0.0-1.0]	0.285

Data are expressed as median [interquartile] compared to baseline. N represents the number of patients with information on the variable of interest at baseline and at follow-up.
¥Data could only be obtained of the original study (n=4)
Abbreviations: MM, millimeters; No., number; P-value represents the mean difference from baseline to six months follow-up.

CHAPTER 11

General discussion

Resistant hypertension as a disease entity

In the first three chapters of this thesis, presence of resistant hypertension was shown to be related to clinical factors known to lead to increased risk for (subsequent) cardiovascular disease. The label 'resistant hypertension' also was associated with independently increased vascular risks. This label can therefore increase awareness in both patients and physicians and possibly lead to more effort to decrease blood pressure (BP). However, using the label of resistant hypertension has several drawbacks. First, there is variability in the blood pressure level used for cut-off, for example 130/80 mm Hg in diabetics and in those with chronic kidney disease and 140/90 mm Hg in others in some, but not all studies.(1-4) Moreover, use of a diuretic is inconsistently required for a label of resistant hypertension.(4-7) A far more important problem is the issue of 'apparent' and 'true' resistant hypertension. The term apparent resistant hypertension is used in our studies because of dependence on (duplicate or triplicate) office blood pressure measurements. An important subgroup of the resistant hypertensive patients based on office blood pressure measurements in the outpatient clinic will probably have normal blood pressure at 24h ambulatory or at home blood pressure measurement. This 'white coat hypertension' has been shown to be associated with increased risk for development of (continuous) hypertension but does not have the increased cardiovascular risk of confirmed hypertension.(8;9) Another important issue is that SYMPATHY has confirmed previous reports on a very high prevalence of non-adherence to antihypertensive drug treatment in a population fulfilling the definition of resistant hypertension.(10) Although their hypertension is indeed difficult to control, the implication of resistance to all commonly used antihypertensive drugs clearly does not hold true in these patients. Another problem with the definition is that secondary hypertension in the common opinion has to have been excluded before deciding on the resistance of hypertension. For hyperaldosteronism, for example, this implicit assumption is easy to understand and comply with. For causes like obstructive sleep apnoea and obesity however, the effort required for investigating and treating these factors before a diagnosis of resistant hypertension can be made is much less well defined. Finally, the division of uncontrolled elevated blood pressure in subgroups of non-resistant and resistant hypertension for assessing cardiovascular risk is not very useful for individual patients. For example, a patient with a blood pressure level of 180/95 mm Hg on two drugs (uncontrolled non-resistant hypertension) starting a third (a diuretic) and reaching a blood pressure of 142/90 mm Hg (resistant hypertension) can hardly be expected to have *increased* his (her) cardiovascular

risk as the definition of resistant hypertension implies. With these difficulties in defining 'resistant' hypertension, it seems inappropriate to develop and test invasive treatment options (renal denervation (RDN), carotid stenting, baroreflex stimulation) for the indication of 'resistant' hypertension.

In conclusion, the emergence of the label of resistant hypertension with the introduction of device-based therapies for hypertension has been very useful to draw attention to an important subgroup of hypertensive patients. At present we should leave this definition and shift towards 'uncontrolled elevated blood pressure despite prescription of ≥3 antihypertensive drugs'. These patients, less rare than previously thought, are at high cardiovascular risk and labelled like this for a significant part due to non-adherence to lifelong drug therapy. The search for ways to decrease the cardiovascular risk patients with uncontrolled hypertension are subject to should continue.

"Resistant hypertension: resistance to treatment or resistance to taking treatment?"(11)

The future of renal denervation

The history of renal denervation dates back to the fifties of the last century, when surgical renal denervation was the only treatment option for severely hypertensive patients. Although abandoned since antihypertensive drug treatment, with much less side effects, became available, the principle of lowering blood pressure by intervening with the sympathetic nerve fibers to and from the kidneys was demonstrated without doubt.(12) The recent history of percutaneous renal denervation unfortunately is much less straightforward. A single small randomized controlled trial reporting a result now judged to be too good to be true led to limitless introduction of the new procedure for treatment of the rediscovered entity of resistant hypertension.(13) Thousands of patients were treated outside study context or within cohorts reporting similar extremely positive results, mainly based on changes in office blood pressure.(14-18) Several years later, the presentation of the Symplicity HTN-3 study reporting no difference in change in either office or 24-hour ambulatory blood pressure after RDN as compared with controls subjected to a sham procedure(19) made the common opinion take a hairpin bend from overly enthusiastic to downright pessimistic. In the three years since, several randomized controlled trials have been added to the clinical evidence.(20-25) With the addition of SYMPATHY in November 2016, systematic review of the evidence is on about thousand patients with resistant hypertension. With a non-significant decrease in daytime systolic BP and a significant but modest decrease in 24h systolic BP of

2.8 mm Hg as compared with control, percutaneous renal denervation cannot be recommended for treatment of (resistant) hypertension at this time.

However, even after this result, renal denervation should not be completely abandoned. There is a number of arguments.

Improvement of the renal denervation procedure

The technique for percutaneous denervation used in studies that have been published so far can probably be improved. The anatomy of the sympathetic nerve fibers alongside the renal arteries was incompletely known when RDN was developed. With the introduction of the technique this naturally was given more attention and detailed information on the density, type (efferent versus afferent) and distance from the artery lumen of renal nerve fibers is now available.(26) The report shows that although less nerve fibers are present more distally alongside the artery, these fibers are more close to the lumen than the proximal ones and thus more easily reached by an intervention applied by an intra-arterial catheter. In a porcine model, higher efficiency of the RDN procedure has indeed been shown when the distal artery and branches are targeted.(27) Effectiveness of denervation was detected by measuring renal norepinephrine concentration and renal cortical axon density in this study. Distal denervation was not specifically aimed for in the current human trials, and since concerns were on causing stenosis in treated arteries in the past, more proximal denervation is more likely to have been performed. In Symplicity HTN-3, only about a quarter of the RDN group participants received a four-quadrant ablation in at least one renal artery, and a post-hoc analysis showed a non-significant increase in treatment effect with such circumferential denervation.(28) Similarly, the number of ablation attempts was predictive of the treatment effect. Importantly, no safety issues have been reported so far precluding further development of the technique. Aside from the location and quantity of ablation attempts, the technique might also be improved by changing the device. Multi-electrode catheters and newer strategies such as locally injected toxins resulting in more extensive and more predictable damage to sympathetic nerve fibers have been developed. Admittedly, these have not proven their superiority yet. Consensus exists that evidence on effective denervation in animal models should be presented before starting clinical trials with new devices, as opposed to the reverse order in the Symplicity studies.(29) Although a safety margin apparently exists given the reassuring reports so far, more effective renal denervation devices might also carry a greater risk for causing renal artery stenosis, and safety should also be proven for improved techniques.

Improvement of trial design

The impressively low adherence to antihypertensive drug treatment, although equally low before and after RDN in studies investigating this (using the only reliable method of direct measurement of drugs in blood or urine),(30;31) has the potential to produce significant bias especially in trials investigating the 'resistant hypertension' group of patients. Participating in a study is likely to influence adherence behaviour (Hawthorne effect), at the least obscuring the blood pressure lowering effect of the intervention. At this time, it is uncertain whether adherence changes in a different direction in an intervention group versus control, especially if no sham procedure is applied. Newer studies have to be designed in ways tackling this problem, either by including patients not on antihypertensive drugs or by measuring adherence using direct techniques on several time-points during the trial. Both European and American consensus groups have emphasized the need for more rigorous design of future RDN trials.(32;33) Aside from the adherence issue, a standardized antihypertensive drug treatment protocol as used in the DENERHTN trial on RDN, is advised. In Symplicity HTN-3, almost 40% of the participants had either decrease or increase in antihypertensive drugs prescribed during the trial potentially obscuring the RDN blood pressure effect. Moreover, antihypertensive drugs have varying effects on sympathetic activity. Drug regime differences between intervention and control groups therefore add difficulty in the assessment of the blood pressure lowering effect of the intervention.(28) Also, a placebo effect of the invasive treatment can be excluded by applying a sham procedure in the control group in future trials. As renal angiography does have risks, exposure of the control group to a sham procedure is still controversial, with different advice given by the two expert consensus groups.(32;33) As acceptance of a sham procedure has increased following the difficulties in RDN trials, and since both a placebo and an adherence effect might play a role in the invasive RDN procedure, application of sham in future trials should be strongly considered. Although likewise not uniformly supported,(33) most investigators feel 24h ambulatory blood pressure measurement should be used both for inclusion (exclusion of 'white coat' hypertension) and for assessment of the effect (more reliable than office BP and easy blinding of participant and investigator).

Assessment of the effectiveness of denervation

The renal denervation procedure still is a 'black box' intervention since no methods are clinically available to confirm adequate ablation during and after the procedure. Small studies have shown that intra-interventional measurement of the effectiveness of the procedure is no longer impossible. Increase in renal blood flow

directly after RDN measured by an intra-arterial catheter has been demonstrated in pig models and is a potential measure of the effectiveness of the ablations.(34;35) A small human study compared the blood pressure increase induced by intra-arterial renal nerve stimulation before and after the RDN procedure. The difference in BP increase on stimulation was positively related to the BP decrease three and six months after RDN.(36) Classic methods to measure sympathetic activity, muscle sympathetic nerve activity and renal norepinephrine spill-over, are laborious and have limited availability making them unsuitable for clinical use. Biomarkers such as neuropeptide Y, co-released with norepinephrine by sympathetic nerve fibers, and renal veno-arterial norepinephrine gradient changes have been shown to correlate with the BP lowering effect of RDN.(37;38) Another possibility is measurement of a nerve damage biomarker, released into the circulation after radiofrequent ablation, to assess the impact of the ablations performed. Such biomarkers could potentially be measured during the procedure and used for guiding the operator. A proof of principle has also been reported for measurement of plasma levels of asymmetric or symmetric dimethylarginine (ADMA/SDMA) before and after RDN, with plasma levels of these influencers of endothelial function (decrease in nitric oxide synthase for ADMA) being related to sympathetic activity measured by MSNA after RDN. (39) Although interesting, these methods need further development and proof of usefulness in clinical practice.

Improved patient selection

The renal denervation trials in hypertension published so far mostly included participants with resistant hypertension. No pathophysiological background exists for this choice. The large cardiovascular risks and the insufficiency of antihypertensive drug treatment in this subgroup were probably the main consideration, especially with the unknown safety profile of renal denervation at that time. This highly selected subgroup of hypertensive patients might not have been the best to prove the effectiveness of renal denervation in, both due to the complex and unstable antihypertensive drug regime used (including varying adherence) and possibly also due to irreversible vascular damage leading to sustained hypertension despite decreased sympathetic activity.(29) Unfortunately, the RDN trials have not revealed patient-related factors predictive of a beneficial effect of RDN. The only factor consistently found is a higher level of systolic BP before the intervention. (22;28;40) Isolated systolic hypertension however has been shown to be related to diminished response when compared with combined (both systolic and diastolic) hypertension.(41) This might also be related to stiffness of the vasculature causing a lesser BP-lowering effect of a similar decrease in sympathetic activity. Younger

hypertensive patients, not on antihypertensive medication yet, might respond to RDN more easily. Selection of patients suspected of a greater contribution of sympathetic activity in the pathophysiology of their hypertension is an attractive approach, too. As argued in chapter 5, patients with chronic kidney disease would be a natural target. However, reports so far have reported conflicting results,(28;42) and SYMPATHY was underpowered for studying a differential effect of RDN in strata of estimated glomerular filtration rate. Possibly, a future study could also be designed to test the effect of sympatholytic drug use on blood pressure in a run-in phase and selectively include participants experiencing a beneficial effect.

Indications other than hypertension

An effective renal denervation procedure has the potential to have beneficial effects in other disease states associated with increased sympathetic activity, such as heart failure, metabolic syndrome, sleep apnoea and cardiac arrhythmias.(43-46) Beneficial effects have been reported but the evidence is mainly from cohort studies suffering from the same potential biases that distorted the initial studies on RDN for hypertension. Many randomized controlled trials are investigating the role of RDN in these other diseases.(47) As described in chapters 9 and 10, renal denervation holds promise as a valuable addition to the therapeutic possibilities for kidney-related pain in both autosomal dominant polycystic kidney disease and the loin pain hematuria syndrome. A randomized sham-controlled trial is needed before RDN can be accepted as a therapeutic option with proven benefit for kidney-related pain.

Conclusion

Naturally, any improvement will have to prove its usefulness in experimental and clinical trials before re-introduction of renal denervation in clinical practice can be considered. It should not be overlooked that a blood pressure lowering treatment independent of adherence for the rest of one's lifetime would be extremely welcome. Expectations, however, should probably be more modest than in the past. RDN will not end the need for lifelong antihypertensive drug treatment but at best be an addition to the therapeutic possibilities. Hopefully one day, patients selected for sympathetic hyperactivity as the most important (remaining) cause of hypertension, can be helped with a good RDN procedure, with decreasing numbers of myocardial infarctions and strokes as a result.

"The failure of Symplicity-HTN3 to meet its efficacy endpoint is more of a speedbump than a 'road closed' sign for renal denervation."(48)

Intervening in non-adherence in resistant hypertension

Non-adherence in (resistant) hypertension

Hypertension has long been known to be related to increased risk for cardiovascular diseases.(49) The studies in this thesis show that this is even more true for the subgroup of patients labelled as 'therapy-resistant'. Although over 55 drugs in 13 drug classes and in multiple combined medication preparations are registered for the treatment of hypertension,(50) reaching a target blood pressure level is very difficult in a substantial number of patients.(51) Non-adherence to antihypertensive drug use has long been a major concern in this respect. Adherence is defined by the WHO as the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.(52) Studies in patients newly started on antihypertensive drugs using pharmacy prescription refill data show that only 50-60% of patients have good or intermediate (>80% and 40-79% of days covered) adherence in the first year.(53) Long-term adherence is similarly low.(54-56) Comorbidity like diabetes mellitus and history of vascular disease (antihypertensive drug use for secondary prevention) are clinical factors related to higher adherence.(53;54;56) Younger age and female sex are related to lower adherence in most studies.(55;56) From SYMPATHY and other studies on renal denervation we now know that adherence, although somewhat higher than described above, is strikingly low in the resistant hypertension patients as well (fully adherent 48%-56% and even lower in SYMPATHY).(30;31;57) Since these measurements were all done in patients included in a trial, non-adherence might be even more frequent in clinical practice. Patient characteristics related to (non) adherence have not yet been studied in resistant hypertension. The adverse effect of non-adherence on cardiovascular outcomes was shown in several, naturally only observational studies, with a 20-30% lower risk in adherent patients after adjustment for comorbidity.(56;58;59) The World Health Organisation published an extensive report on adherence to medication for chronic illnesses with a call to action already in 2003.(52) With this background in mind, surprisingly little attention was given to non-adherence in the literature on resistant hypertension of the past few years. Non-adherence was merely to be excluded before deciding blood pressure was resistant.

Measuring adherence

This simple advice however is not easy to follow, since measuring adherence is difficult in clinical practice. Self-report by a questionnaire, most commonly the

8-factor Morisky Medication Adherence Scale (MMAS-8), is the easiest method. The large difference in the estimate of full adherence in the DENERHTN trial by the MMAS-8 and by direct measurement of medication (metabolites) in urine or plasma (75 versus 50%) illustrates the limitations of self-report in adherence studies.(22;30) Inaccurate patient recall and social desirability will have a role in underestimation by questionnaires. Using pharmacy prescription refill data or electronic devices recording drug package opening are more reliable but also more time-consuming, costly and still indirect methods.(60;61) Measuring of compounds or their metabolites in the plasma or urine has become available for antihypertensive drugs only recently.(10) If the liquid chromatography with tandem mass spectrometry (LC-MS/MS) method used in SYMPATHY comes available in clinical practice (and in studies as well), this will likely be an important step towards tackling non-adherence. However, even this direct method has limitations. Most importantly, the pharmacokinetics of a drug will influence the ability of the test to detect non-adherence. The test as currently used is quantitative only, and missing of a few doses will possibly go unnoticed if the halve life of the compound is long. Also, the term white-coat adherence or a tooth brush effect has already been introduced with adherence being higher only at the times of the test.(60)

Interventions for enhancing adherence

Many studies and several reviews have investigated interventions aimed at improving adherence in the past 15 years. Two Cochrane reviews have been published, the first on interventions in hypertension only and a recent one on adherence in chronic disease in general. Both conclude that interventions aimed at improving adherence can have significant but modest effects on both adherence and clinical outcome (most often, blood pressure).(62;63) Such modest effects, lowering BP with ~3 mm Hg on average, would still lead to an important lowering of cardiovascular disease risk as is known for decrease in BP by antihypertensive drugs.(64)

Adherence is a very complex issue: health system factors (patient-provider relationship, reimbursement, time dedicated to promoting adherence, (in)ability to increase self-management capacity), social/economic factors (socioeconomic status, low level of education, lack of effective social support), condition-related factors (severity of symptoms, rate of progression, severity of the disease influencing the risk perception of patients), therapy-related factors (complexity of the regimen, duration of treatment, time to beneficial effects, side-effects) and patient-related factors (knowledge, attitudes, beliefs, perceptions) all play a role.(52) Importantly, a distinction can be made between unintentional and intentional non-adherence,

with the former representing execution errors and being addressed by many adherence interventions (for example reminders or pill boxes), and the latter representing non-persistence, that is a decision to stop the treatment after some time. A study on electronic monitoring in patients in phase IV antihypertensive drug trials showed that intentional non-adherence explains a far greater part of the omission of prescribed medication than the unintentional counterpart.(65) Patients' views on the causes of hypertension and perspectives on drug taking can be very different from the medical standpoint influencing adherence behaviour.(66) A framework called the common sense model of self-regulation of health and illness describes how individuals evaluate somatic stimuli, leading to hypotheses about the meaning of symptoms affecting the emotional state and resulting in (non) behaviour (selection of a coping strategy).(67) For example, high blood pressure is attributed to stress instead of seen as a medical condition, and disappearance of symptoms like headache and dizziness is interpreted as proof that hypertension has gone, making continuous use of antihypertensive drugs unnecessary.

Quite diverse interventions have been studied, from simplification of dosing regimens, patient education, motivation and support, to reminders, combinations of these and more. The Cochrane review on adherence in hypertension divides the interventions studied in groups and concludes that patient education alone is ineffective, whereas simplification of dosing regimens increased adherence in most studies, and results for motivational and complex interventions were inconclusive.(62) A recent systematic review on interventions to increase adherence in hypertension reported on features of interventions predictive of an effect. Interventions aimed at treating physicians were less effective than those aimed at patients. Whether the intervention was done by a physician or a pharmacist, or by face-to-face contact versus by telephone or mail made no difference. Contra-intuitively, theory-based interventions were no better than those not founded in behaviour science models.(68) Specific intervention content, for example addressing barriers in adherence, decisional balance activity, motivational interviewing, social support and self-monitoring of blood pressure, were also not shown to have a superior effect. Interventions with multiple components, however, were more effective than single component ones, as was concluded in the recent Cochrane review.(63;68) In conclusion, although evidence exists that interventions can be effective, identifying successful components for future composite interventions is a challenge.

Following the finding that unintentional non-adherence, at which many 'simple' interventions like reminders and simplifying the drug regimen (such as once a day or combined preparation dosing) aim at, is of much smaller magnitude than intentional non-adherence, interventions aimed at changing the decision-making

process and resulting non-adherence behaviour are likely to be the way forward. Unfortunately, intervention studies often lack reference to an underlying theory for behavioural change, although implicitly using such theories to remove barriers for adherence. Recently, effort has been made to dissect what makes adherence interventions successful. The Theoretical Domains Framework, composed of 14 domains (table) representing theory of behavioural change was developed and validated.(69) A new Cochrane review on adherence interventions for hypertension used this system.(70;71) The upside is that a modest (-3 mm Hg) but highly significant and clinically relevant effect of interventions was confirmed, and that a significant effect was found for several domains. The downside is that no discriminative effect was found for the number of different behavioral change domains addressed in studies nor for the intensity of intervening within the domains. The reviewers report difficulty in coding domains because of insufficient detail reported for intervention and control groups, large heterogeneity and risk of bias.(71)

Conclusion

The issue of non-adherence is complex and of impressive magnitude in resistant hypertension. Measurement is difficult but will likely improve in the near future if the direct liquid chromatography with tandem mass spectrometry method comes more widely available. Interventions have so far had modest but clinically relevant and significant results. Finding effective multicomponent interventions addressing unintentional and particularly intentional non-adherence is a great challenge. Systematic report and analysis of the behavioral theory components used by interventions will increase our understanding and hopefully lead to effective multifactorial approaches in the future.

"Drugs don't work in patients who don't take them."(72)

Table 1 Theoretical frames network domains with definitions

Domain	Definition
Knowledge	An awareness of the existence of something
Skills	An ability or proficiency acquired through practice
Social/ professional role and identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use
Optimism	The confidence that things will happen for the best or that desired goals will be attained
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way
Goals	Mental representations of outcomes or end states that an individual wants to achieve
Memory, attention and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour
Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours
Emotion	A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event
Behavioural regulation	Anything aimed at managing or changing objectively observed or measured actions

Reprinted from Cane et al.(69)

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CHAPTER 12

Summary

The importance of hypertension for the risk of cardiovascular disease cannot be emphasized enough. Large studies in the general population, in patients with previous vascular disease and in those with chronic kidney disease invariably show increased risk of (subsequent) cardiovascular events in hypertensive patients.(1-3) Despite the availability of numerous blood pressure lowering drugs and general access to high-quality health care, the control of hypertension remains disappointedly low.(4;5) With the emergence of device-based therapy for hypertension, consisting of baroreceptor stimulation and percutaneous renal denervation (RDN), a group of patients within those with uncontrolled blood pressure has regained attention. These patients, labelled as resistant to treatment with antihypertensive drugs, are at the highest end of uncontrolled blood pressure and generally have a long history of unsuccessful treatment attempts.

In **chapter 2**, we show that in patients with chronic kidney disease, including kidney transplant recipients, resistant hypertension is very prevalent even in a randomized controlled trial setting where usual care was compared with intensive guidance by nurse practitioners added to usual care. Resistant hypertension, present in 1/3 of patients, was shown to be related to a 1.5-fold higher risk for the composite cardiovascular outcome and 2.3-fold increased risk for reaching end stage kidney disease.

In **chapter 3**, the prevalence of resistant hypertension is investigated in over 6000 hypertensive recipients with a history of cardiovascular disease. In this population, a higher blood pressure cut-off of 140/90 mm Hg was used in the definition of resistant hypertension. One of every eleven patients was found to have resistant hypertension. Clinical factors related to presence of resistant hypertension were diabetes mellitus, female sex, duration and multiple locations of vascular disease, body mass index and waist circumference. Resistant hypertension was found to be strongly related to increasing age, diminished kidney function and presence of albuminuria. Other signs of subclinical vascular disease, increased carotid intima-media thickness and decreased ankle-brachial index, were also related to resistant hypertension.

Increased risk for subsequent cardiovascular events was shown to be present in these patients with a history of cardiovascular disease in **chapter 4**. A 44% increase in risk for cardiovascular death and a 25% higher risk for a composite endpoint of myocardial infarction, cerebral vascular disease including retinal infarction and cardiovascular mortality were found as compared with patients with controlled hypertension and a history of cardiovascular disease. These increased risks applied also for patients with controlled resistant hypertension, labelled as resistant hypertensive based on use of ≥4 antihypertensive drugs.

In the pathophysiology of hypertension, increased activity of the renin-angiotensin-aldosterone system (RAAS), renal sodium retention and hyperactivity of the sympathetic nerve system are important and connected players. Increased sympathetic activity increases blood pressure by increasing cardiac contractility and heart rate, by increasing peripheral vascular resistance due to vasoconstriction and by increasing renin production in the kidneys, directly stimulating tubular sodium reabsorption and by a reduction of renal blood flow.(6;7) Stimulation of the RAAS on its turn leads to vasoconstriction, renal sodium retention and increases the effect of sympathetic activity in the kidneys. The kidneys are not only an important target for sympathetic nerve fibers but also a source of sympathetic activity. The knowledge from animal and clinical studies on sympathetic hyperactivity in chronic kidney disease is reviewed in **chapter 5**. Experimental renal denervation can prevent the development of hypertension in animals put at high risk, for example by subtotal nephrectomy. Moreover, dorsal rhizotomy, surgery that only affects afferent sympathetic activity, was shown to decrease blood pressure in hypertensive rats with kidney disease. Renal denervation has kidney protective effects in these animals. Human studies have shown increased sympathetic activity when measured by MSNA, a method that measures efferent sympathetic activity to the skeletal muscles, in patients with kidney disease with a graded increase with deterioration of glomerular filtration. These patients might therefore benefit most from a new antihypertensive treatment aimed at decreasing sympathetic activity. Antihypertensive drugs have a variable effect on sympathetic activity, with diuretics and calcium channel blockers having a stimulating effect, whereas RAAS inhibitors, beta blockers and centrally acting drugs have an inhibitory effect.

In **chapter 6**, the design and rationale of the SYMPATHY trial are described. Apart from the aim to confirm the beneficial results of renal denervation on blood pressure in patients with resistant hypertension reported at that time,(8-10) an important second goal was to find out whether renal denervation has better results in patients with diminished kidney function based on the pathophysiology described in chapter 5.

Chapter 7 contains a picture on how the medical opinion on renal denervation for resistant hypertension changed in the years it was investigated in the Netherlands as a new promising treatment under conditional reimbursement. At the start, although only one small trial had shown a beneficial effect, renal denervation had already found broad application in usual care based on several large cohort studies with the endpoint of change in office BP. During the trial, the opposite result from the large sham-controlled Symplicity HTN-3 study changed the common opinion into downright pessimism and for SYMPATHY and other studies, enrolment became

a very difficult task. As a consequence, too little power remained for the important subanalysis of stratification by level of estimated glomerular filtration rate (eGFR). An interaction term however, showed no differential effect with a lower eGFR. Moreover, the overall result of the trial was negative, with decreases of daytime systolic blood pressure of 6.0 mm Hg (95%CI -10.7 to -1.2) and 7.9 mm Hg (95%CI -14.7 to -1.3) in the intervention and control groups respectively. An important issue in the renal denervation for resistant hypertension studies is the non-adherence. Only slightly more than half of the prescribed drugs were detected in SYMPATHY, and only ~20% of these multi-drug treated patients were fully adherent. Similar results came from other studies.(11-13) Although the difference in adherence at baseline and at the time of the primary endpoint was not significant, and no significant difference in adherence rate between control and intervention group was found, a secondary analysis in the group with stable (non)adherence found a difference in daytime systolic BP between intervention and control of -3.3 mm Hg (95%CI -13.7 to 7.2) in only 54 patients.

In **chapter 8**, dietary sodium intake is not found to be predictive of the blood pressure lowering effect of RDN. Salt sensitivity decreased during follow-up after RDN, but a similar change was found in the control group. Therefore, the decrease in salt sensitivity was not attributable to the RDN procedure.

Since the renal denervation procedure evokes significant pain, RDN can be expected to also be beneficial for patients with kidney-related pain, since this suggests that pain fibers can be interrupted. **Chapter 9** describes the potential benefit for patients with loin pain hematuria syndrome. In **chapter 10**, a beneficial effect of RDN is found on perceived pain in patients with either loin pain hematuria syndrome or autosomal dominant polycystic kidney disease with kidney-related pain.

In **chapter 11**, the results of the studies are placed in a broader context, and perspectives discussed.

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CHAPTER 13

Samenvatting in het Nederlands

Het is al lang bekend dat het hebben van een hoge bloeddruk het risico op hart- en vaatziekten sterk verhoogt. Dit geldt voor alle populaties waarin het is onderzocht, onder meer de algemene bevolking en mensen met eerder vaatlijden of een gestoorde nierfunctie. Hoewel er veel verschillende medicijnen tegen hoge bloeddruk zijn en de gezondheidszorg (in Nederland) goed toegankelijk en van hoge kwaliteit is, blijft de bloeddruk bij een aanzienlijk deel van de patiënten te hoog. In **hoofdstuk 1** wordt een inleiding gegeven waarin wordt beschreven dat er de laatste jaren nieuwe mogelijkheden voor het behandelen van hoge bloeddruk bijgekomen zijn, namelijk door middel van een procedure in plaats van door middel van een medicijn. In dit proefschrift wordt renale denervatie onderzocht, waarbij met behulp van een katheter die via de lies in de slagaders van de nieren wordt gebracht de zenuwvezels van het sympathische zenuwstelsel die rond die bloedvaten lopen door middel van radiofrequente energie (deels) uitgeschakeld worden. De activiteit van deze zenuwvezels verhoogt de bloeddruk, enerzijds door vezels die naar de nieren toe lopen, waarvan de activiteit zorgt voor vasthouden van zout door de nier, verhoogde productie van renine (een hormoon dat de bloeddruk verhoogt) door de nier en vernauwing van de bloedvaten in de nier. Al deze effecten zorgen voor een verhoging van de bloeddruk. Anderzijds zijn er vezels vanuit de nieren naar de hersenen, waarvan de activiteit de bloeddruk verhoogt doordat als gevolg daarvan vanuit de hersenen zenuwsignalen aan de bloedvaten in het lichaam ontstaan die voor vernauwing zorgen, en naar het hart waar ze de contractiekracht doen toenemen. De druk in de bloedvaten neemt door beide effecten verder toe. Via de hersenen neemt ook het bloeddrukverhogende zenuwsignaal naar de nieren toe (zie figuur 1 in hoofdstuk 1). Onderbreken van deze zenuwsignalen met behulp van de katheter zou daarom de bloeddruk moeten kunnen verlagen. In de onderzoeken naar deze methode zijn patiënten onderzocht die zogenaamde resistente hypertensie hebben, dat wil zeggen een te hoge bloeddruk ondanks behandeling met drie of meer bloeddrukverlagende medicijnen uit verschillende groepen waaronder een plastablet, of gebruik van vier of meer bloeddrukverlagende medicijnen. Zulke patiënten hebben vaak een lange voorgeschiedenis van niet succesvolle pogingen de bloeddruk met medicatie omlaag te krijgen en een ernstig verhoogde bloeddruk. Door het onderzoeken van de renale denervatie procedure is er meer aandacht gekomen voor deze groep.

Dit proefschrift begint, na de inleiding, met een aantal onderzoeken naar het voorkomen van resistente hypertensie. In **hoofdstuk 2** wordt beschreven dat in een studie bij patiënten met chronisch nierfalen, 1/3 van de patiënten resistente hypertensie heeft. Ook werd aangetoond dat deze resistente hypertensie een 1,5

keer verhoogd risico op vaatziekten geeft, en zelfs een 2,3 keer verhoogd risico op eindstadium nierfalen. In **hoofdstuk 3** wordt het voorkomen van resistente hypertensie onderzocht bij 6200 patiënten met een voorgeschiedenis van hart- en vaatziekte. Bij deze patiënten werd een hogere afkapwaarde voor een te hoge bloeddruk gebruikt, namelijk 140/90 mm Hg. Eén op de elf patiënten bleek resistente hypertensie te hebben. Kenmerken die samenhangen met het hebben van resistente hypertensie waren diabetes mellitus, vrouwelijk geslacht, hoger gewicht (body mass index en middelomtrek) en langere duur van vaatlijden en vaatlijden op meerdere plaatsen in het lichaam. Resistente hypertensie kwam vaker voor bij stijgen van de leeftijd en hing sterk samen met gestoorde nierfunctie en albuminurie (eiwitverlies in de urine). Andere tekenen van niet klinisch manifest vaatlijden, namelijk toegenomen vaatwanddikte in de halsvaten en verlaagde enkel-arm index (ratio van de systolische bloeddruk aan arm en been), waren ook vaker aanwezig bij patiënten met resistente hypertensie. In **hoofdstuk 4** werd aangetoond dat ook in deze groep patiënten met vaatlijden en resistente hypertensie het risico op een volgende uiting van vaatlijden 25% hoger is, en het risico op overlijden aan hart- en vaatziekten 44% hoger in vergelijking met patiënten met een voorgeschiedenis van vaatlijden met een goed gereguleerde bloeddruk. Deze verhoogde risico's gelden ook voor patiënten met resistente hypertensie en een goed gereguleerde bloeddruk (de groep die op grond van gebruik van ≥4 bloeddrukverlagende medicijnen het label resistente hypertensie krijgt).

In **hoofdstuk 5** wordt de kennis over verhoogde activiteit van het sympathisch zenuwstelsel bij chronische nierinsufficiëntie (verminderde nierfunctie) samengevat. Bij proefdieren zijn verschillende studies met renale denervatie gedaan, waarbij werd aangetoond dat beschadigen van de zenuwvezels rondom de niervaten het ontwikkelen van hoge bloeddruk kan voorkomen. Ook werd aangetoond dat selectief voorkomen van het sympathische signaal vanuit de nieren naar de hersenen de bloeddruk bij ratten met een gestoorde nierfunctie kan verlagen. In deze dierstudies had het onderbreken van de zenuwactiviteit een beschermend effect op de nieren (betere functie en minder albuminurie). Bij mensen is aangetoond dat bij verminderde nierfunctie de sympathische zenuwactiviteit naar de spieren verhoogd is. Ook werd gevonden dat de sympathische activiteit bij slechtere nierfunctie steeds hoger wordt. Patiënten met nierinsufficiëntie zouden daarom baat kunnen hebben bij een nieuwe bloeddrukbehandeling die gericht is op het verminderen van sympathische zenuwactiviteit. Bloeddrukverlagende medicijnen hebben een wisselend effect op de sympathische zenuwactiviteit:

plastabletten en calciumkanaal blokkers verhogen de sympathische activiteit terwijl renine-angiotensine-aldosteron systeem remmers, betablokkers en centraal werkende middelen een remmend effect erop hebben.

In **hoofdstuk 6** wordt de opzet van de SYMPATHY studie beschreven. Deze gerandomiseerde studie had als doel de goede resultaten van renale denervatie op de bloeddruk bij patiënten met resistente hypertensie die in eerdere studies gevonden waren te bevestigen. Een belangrijk tweede doel was om te onderzoeken of renale denervatie meer bloeddrukverlaging geeft bij patiënten met een verminderde nierfunctie, gebaseerd op de pathofysiologie beschreven in hoofdstuk 5.

Hoofdstuk 7 beschrijft hoe de opinie over renale denervatie voor de behandeling van resistente hypertensie is veranderd in de jaren dat het in Nederland werd onderzocht als een nieuwe, veelbelovende behandeling tijdens voorwaardelijke toelating tot het basispakket van de zorgverzekering. In het begin had één enkele kleine gerandomiseerde studie een gunstig effect laten zien. Desondanks werd renale denervatie al op grote schaal toegepast in de patiëntenzorg gebaseerd op verschillende grote cohort studies die de verandering in office systolische bloeddruk (bovendruk gemeten in de spreekkamer) als eindpunt hadden. Gedurende de SYMPATHY trial werd het tegengestelde resultaat van de Symplicity HTN-3 studie bekend. In deze grote Amerikaanse studie ondergingen de patiënten in de controlegroep angiografie zonder denervatie (sham procedure). De bloeddrukdaling was in de renale denervatiegroep niet groter dan in de controlegroep. Na presentatie van deze uitkomst veranderde het algemene oordeel over renale denervatie naar ronduit pessimistisch en werd de inclusie in SYMPATHY en andere lopende studies heel moeizaam. Als gevolg hiervan had de SYMPATHY studie uiteindelijk te weinig power voor de belangrijke subanalyse van het effect van renale denervatie bij een verminderde versus een normale nierfunctie, waarvoor gestratificeerd was. Een interactieterm liet geen ander effect zien bij een slechtere nierfunctie. De uitkomst van de studie is dat er geen verschil in bloeddrukdaling was tussen de interventie- en controlegroep, met een daling van de systolische bloeddruk tijdens het daginterval van 6,0 mm Hg (95% betrouwbaarheidsinterval -10,7 tot -1,2 mm Hg) in de interventiegroep en van 7,9 mm Hg (95% betrouwbaarheidsinterval -14,7 tot -1,3 mm Hg) in de controlegroep. Verder blijkt therapietrouw, het volgens de adviezen van de zorgverlener innemen van de medicatie, een belangrijk probleem te zijn bij patiënten met resistente hypertensie. In SYMPATHY kon slechts de helft van de voorgeschreven bloeddrukverlagende medicijnen worden teruggevonden in het bloed van de

patiënten. Ook was slechts ongeveer 20% van de deelnemers therapietrouw voor alle voorgeschreven bloeddrukverlagende medicijnen. Andere studies bij patiënten met resistente hypertensie hebben vergelijkbare resultaten laten zien. In SYMPATHY was er geen significant verschil in therapietrouw tussen de beginmeting en de eindpuntmeting na 6 maanden. De therapietrouw in de interventie- en de controlegroep was vergelijkbaar. Een aanvullende analyse in alleen de groep deelnemers met stabiele therapietrouw liet een verschil in de systolische bloeddruk tijdens het daginterval zien van 3,3 mm Hg (95% betrouwbaarheidsinterval -13,7 tot 7,2 mm Hg) in het voordeel van de renale denervatiegroep. Deze groep bestond uit slechts 54 patiënten.

In **hoofdstuk 8** werd onderzocht of de hoeveelheid zout in de voeding het effect van renale denervatie op de bloeddruk kan voorspellen. Zo'n verband werd niet gevonden. Wel leek de gevoeligheid voor zout, dat wil zeggen de mate waarin de bloeddruk stijgt bij een hogere zoutinname, kleiner te worden in de loop van de studie. Echter, in de controlegroep werd een vergelijkbare afname van de zoutgevoeligheid gevonden. De daling kan daarom niet worden toegeschreven aan de renale denervatie procedure.

Omdat patiënten tijdens de renale denervatie procedure aanzienlijke pijn hebben als hiervoor geen intraveneuze pijnstilling wordt gegeven, is te verwachten dat ook pijnvezels beschadigd raken door de denervatie. De behandeling zou daarom ook voor patiënten met pijn aan de nieren gunstig kunnen zijn. **Hoofdstuk 9** beschrijft het mogelijke voordeel bij patiënten met het zogenaamde loin pain hematuria syndroom, een niergerelateerd pijnsyndroom. In **hoofdstuk 10** wordt een gunstig effect van renale denervatie gevonden op de gerapporteerde pijn bij patiënten met loin pain hematuria syndrome of autosomaal dominante polycysteuze nierziekte en niergerelateerde pijn.

In **hoofdstuk 11** worden de uitkomsten van de studies in een bredere context geplaatst en toekomstperspectieven besproken.

APPENDICES

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Dankwoord

Het dankwoord is een mooi hoofdstuk in een proefschrift. Wat ben ik blij dat ik er één mag schrijven en wat zijn er veel mensen te bedanken.

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En dat geeft niet!

Esther

Curriculum vitae

Esther de Beus was born on April 29, 1978 in Tilburg. After graduating at the atheneum at the Cobbenhagen College (cum laude), she moved to Maastricht for studying medicine in 1996. Here, she worked as a student-assistant in the department of Anatomy and Embryology, where she trained fellow students. She obtained her medical degree (cum laude) in 2002 and returned to Brabant to start as a resident internal medicine not in training at the St. Elisabeth Hospital in Tilburg. After a few months, the opportunity came to start the specialist training for internal medicine. Four years later, she was accepted for a fellowship nephrology at the Radboud University Medical Center in Nijmegen, and went to the Jeroen Bosch Hospital in 's Hertogenbosch for the first 14 months of the programme. Then, she moved from Tilburg to Nijmegen to finish her education and became internist and nephrologist in 2009.

From Nijmegen, she worked as a nephrologist to replace absent staff in the Canisius-Wilhelmina Hospital in Nijmegen and in the Rijnstate Hospital in Arnhem in 2009 and 2010. In 2011, she started as a staff member in the Nephrology department of the University Medical Center Utrecht, and moved to Utrecht. There, she expanded her skills in kidney transplantation, being a member of the (pre) transplantation team. In 2013, she was accepted for a PhD position in the renal denervation research programme headed by Dr. Peter Blankestijn, and combined research with transplantation care. In 2017, when the temporary (PhD) commission ended, a short period of bridging a pregnancy leave in the Haga Hospital in The Hague followed. Thereafter, she went to the Erasmus Medical Center in Rotterdam, where dialysis care is at the heart of her work.