

Evaluation of Renal Denervation by 24-Hour Ambulatory Blood Pressure and Quantified Antihypertensive Medication

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Abstract

Background: Previous studies of renal denervation (RDN) have mainly focused on the effect on office blood pressure (BP) and number of antihypertensive drugs although these are known as sub-optimal endpoints.

Aim: The aim of this study was to evaluate the effect of RDN by combining 24-hour ambulatory blood pressure (ABP) measurements and quantified antihypertensive medication at 12 months after RDN.

Methods: Fifty-one patients (71% men, mean age 56 years) with resistant hypertension were treated with RDN. Office BP and ABP were measured at baseline and 6 and 12 months after RDN. Concomitantly the administration of antihypertensive drugs was assessed by their total defined daily dose (DDD). Results are presented as mean values (\pm SD).

Results: The change in daytime systolic ABP at 6 and 12 months was -8.6 (22.5) (P=0.01) and -4.2 (22.3) mmHg (P=NS). Quantified antihypertensive medication was assessed, and at 12 months after RDN there was no change in antihypertensive medication in 33% of patients using the DDD method versus 53% of patients using counts of number of antihypertensive drugs (NS). At 12 months after RDN a ≥ 5 mmHg reduction in MAP (24-hour ABP) was found in 36% of the patients in addition to an unchanged or reduced DDD, whereas this was seen in 42% of patients when number of antihypertensive drugs were used (NS).

Conclusions: There was no effect of RDN on ABP after 12 months. We have presented a method that embraces both ABP and quantitative assessment of antihypertensive medication to evaluate RDN by combined Δ DDD/24-hour Δ MAP.

Keywords: Resistant hypertension; Renal denervation; Antihypertensive medication; 24-hour ambulatory blood pressure measurement

Introduction

Percutaneous catheter-based renal denervation (RDN) was introduced as a treatment option for patients with therapy resistant hypertension, initially with promising results [1,2]. A large sham-controlled trial, however, has questioned the benefit of RDN [3]. In a previous study, we observed that 41% of patients referred for RDN had a history of intolerance to antihypertensive agents or compliance problems and that only approximately 50% of those referred were actually eligible for the treatment [4]. A high baseline blood pressure (BP) has been shown to be a predictor of successful response to RDN [5-7]. The influence of renal function for RDN response has not been clarified. In one study lower estimated glomerular filtration rate (eGFR) was associated with poor response to RDN [8], whereas another study has shown that RDN in CKD stages 3-4 (eGFR from 15 to 60 ml/min/1.73 m²) halts the decline in renal function [9]. Still there is much to learn about the effect of RDN and the role of patient selection.

Counting the number of BP lowering drugs has been the standard method to quantify the amount of antihypertensive medication [1-3]. Many studies have aimed - if possible - not to adjust antihypertensive medication during the follow up period³. This approach, however, has in reality proven difficult. This is both due to changes in BP after RDN as well as patients desire to reduce or discontinue medication. Therefore, a single score quantifying antihypertensive medication and detecting all adjustments in medication would be beneficial. By adding the *Defined Daily Dose* (DDD) stated by WHO [10] for each prescribed antihypertensive drug a single score value can describe the total load of antihypertensive medication per day.

The primary endpoint in most studies evaluating the effect of RDN has been reductions in office BP [1-3]. Twenty-four hour ambulatory blood pressure (ABP) has a consistently stronger association with both mortality and long-term complications of hypertension than both office BP [11] and home BP [12], and thus greater attention should be paid to this variable when evaluating treatment of hypertension.

One of the challenges is to differentiate the BP lowering effects of RDN from changes induced by changes in antihypertensive medication during the follow-up. The aim of this study was to describe RDN evaluation by combining 24-hour APB and quantified antihypertensive medication at 12 months after RDN in 51 consecutively treated patients. Furthermore, assess the effect of RDN on day- and nighttime BP was evaluated from the ABP analyses.

Material and Methods

Patients

We prospectively evaluated the first 51 patients having RDN

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performed at Rigshospitalet, Copenhagen University Hospital, Denmark from April 2011 to April 2013. Patient selection and clinical work up has previously been described [4]. We accepted patients for RDN who fulfilled the criteria from the European Society of Hypertensions position paper on RDN [13] as well as those who did not achieve a target BP on < 3 antihypertensive drugs due to intolerance or side effects. No ethical approval was required, because the patients in this study were referred for routine treatment and follow-up.

Procedure

Patients had a RDN procedure performed with the use of radiofrequency energy delivered by either the Symplicity renal denervation catheter (Medtronic) or the EnligHTN renal denervation catheter (St. Jude Medical). The same two operators, one interventional cardiologist and one invasive electrophysiologist, both highly experienced, performed all RDN procedures in collaboration. None of the operators had performed RDN prior to the 51 patients included in this study and initial procedures were performed with a proctor present. During each procedure the same two operators participated during the whole procedure and each operator performed RDN on one renal artery in each patient (random which artery was treated by whom). This strategy was decided to increase the operator experience for this new treatment.

Blood pressure measurements

Office BP as well as ABP were measured prior to RDN, and during follow-up at 6 and 12 months after RDN.

Office BP measurement was achieved with a semi automated device (UA-852 device, A&D Company Limited, Higashi-Ikebukuro, Japan) after five minutes of rest in the sitting position with a fitted cuff at both arms to exclude any difference. Three measurements were performed, and the average of the latter two was registered.

ABP was done with an electronic device (Spacelab 90202 or 90207 device, Spacelabs Inc. Redmonds, Wash., USA) with a fitted cuff on the upper arm with the highest office BP measuring BP every 15 minutes during daytime (7AM to 11PM), and every half hour during night time (11PM to 7AM). At least 70% successful readings during both day and night were considered sufficient [14] with a minimum of 21 readings in total and at least 7 readings during nighttime. Patients were instructed to engage in normal activities while being monitored, but to avoid strenuous exercise, and during measuring keep the arm still and the cuff at heart level [14]. Nightly BP dipping was defined as a > 10% drop in both systolic and diastolic BP during night-time compared to daytime, equal to a night/day ratio of <0.9 [14,15].

Quantification of antihypertensive agents

The DDD is stated by the World Health Organisation [16,17] to be the assumed average maintenance dose per day of a drug used for its main indication in adults. From the patient's list of medication all antihypertensive agents were converted to a DDD-value for each medication, and combination therapies were calculated for each agent. Finally all DDD were added to give a single score value. Total DDD calculation was performed prior to RDN, and at 6 and 12 months after the treatment. Changes to antihypertensive medication during follow-up were limited in line with the protocol of SymplicityHTN-3.

Example on calculating the total DDD for a patient:

- Hydrochlorothiazide; dosage 25 mg/day (DDD: 25 mg) = 1 DDD

- ACE inhibitor (Enalapril): dosage 20 mg/day (DDD: 10 mg) = 2

DDD

- Calcium channel blocker (Amlodipine): dosage 10 mg/day (DDD: 5 mg) = 2 DDD

In total
= 5 DDD

Responders: In the present study, a responder was defined as:

- a patient who had a reduction in MAP of ≥ 5 mmHg, as assessed by 24-hour ABP, and an unchanged or reduced DDD of antihypertensive medication.

Whereas previous RDN studies have definitions such as:

- a ≥ 10 mmHg reduction in systolic office BP², or

- a ≥ 5 mmHg reduction in average systolic ABP [16].

Statistics

Variables were expressed as percentages or by their mean values and standard deviations (\pm SD). Changes in BP and DDD antihypertensive medication from baseline to follow up were assessed by the parametric Student's t-test for paired samples. Changes in number of antihypertensive agents were assessed with the non-parametric Wilcoxon test. Difference in proportion of patients with unchanged DDD or unchanged as well as difference in proportion of responders between Δ DDD/ Δ MAP and Δ number of antihypertensive agents/ Δ MAP was assessed with χ^2 test. P values ≤ 0.05 were considered significant. Statistical analysis was performed using R (<http://www.r-project.org/>).

Result

Demographics and clinical characteristics

Baseline demographic data and clinical characteristics are listed in Table 1.

Forty-one patients fulfilled the criteria from the European Society of Hypertensions position paper on RDN [13], and 10 patients with severe hypertension were treated due to unacceptable side effects to antihypertensive medication (5 patients received 1 drug/day and 5 patients received 2 drugs/day).

Follow-up

At 12 months 6 patients were lost for follow-up. Three patients had their follow-up visit at a local hospital (insufficient 24-hour ABP data), 2 patients had an extensive delay in their 12 months visit, and finally, one patient (who was well controlled in ABP in 6 months) had a non-fatal cerebral hemorrhage and did not have the 24-hour ABP performed.

Procedure

Forty-one out of 51 patients (80%) had RDN performed with the Symplicity Renal Denervation System (Medtronic) and in 10 patients (20%) the EnligHTN renal denervation system (St. Jude Medical, Inc.) was used. Patients received in average 12 (3) ablations in total, equally distributed in right and left renal arteries. There were no difference in either Δ ABP (24-hour average MAP) (P=0.425) or Δ DDD (P=0.094) at 12 months vs. baseline between patients who had RDN performed with the two catheter systems (unpaired t-test).

Combined changes in BP and antihypertensive therapy

Changes in 24-hour average MAP and antihypertensive medication,

and their relation are illustrated in Figure 1. Figure 1A exhibits the correlation between Δ DDD vs. Δ MAP at 12 month minus baseline after RDN. 16 of 45 (36%) patients had a ≥ 5 mmHg Δ MAP and an unchanged or reduced DDD. Figure 1B exhibits the correlation between Δ number of antihypertensive drugs vs. Δ MAP at 12 month minus baseline after RDN. Nineteen out of forty-five (42%) patients had a ≥ 5 mmHg Δ MAP and an unchanged or reduced number of antihypertensive drugs. There was no statistical difference between the two approaches to assessing antihypertensive medication in combination with Δ MAP ($p=0.52$, NS). When comparing rates of change in medication by DDD or the number of antihypertensive drugs, no change in medication was recorded in 33% (15/45) vs. 53% (24/45) of the patients at 12 months ($P=0.056$, NS).

Additional blood pressure results

Results for office BP as well as ABP are summarized in Table 2, and graphic illustration of office BP and ABP changes are given in Figure 2.

The cut-off value of BP reduction defining a responder could obviously influence the number of responders. If the definitions of a responder in the present study, had been ≥ 10 mmHg reduction in systolic office BP combined with unchanged or decreased DDD at 12 months after RDN 44% ($n=20$) of patients would have been responders, whereas a ≥ 5 mmHg systolic ABP reduction combined with unchanged or decreased DDD was seen in 47% ($n=21$) of the patients.

At baseline, and at 6 and 12 months, the rate of nightly dipping was 9/51 (18%), 5/47 (11%) and 0/45 (0%), respectively.

Heart rate did not differ between baseline, 6 and 12 months neither in 24-hour average, day or night-time.

Antihypertensive medication

The monitoring of antihypertensive medication is summarized in Table 3 including an overview of class of antihypertensive medications. Figure 3 shows the correlation between number of antihypertensive drugs and DDD at baseline. The graphs for both 6 and 12 months are similar, and they clearly illustrates that antihypertensive medication

is predominantly given in supra-DDD-value dosage, a tendency that increases with increasing number of drugs administered.

Other parameters

Blood-hemoglobin concentration and plasma-creatinine levels did not change during 6-month follow-up. Plasma-creatinine, however, increased within the normal range from 86 (26) μ mol/L at baseline to 92 (33) μ mol/L at 12-month follow-up ($P \leq 0.01$).

Discussion

ABP, MAP and DDD

In the present study there was no overall significant change in ABP 12 months after RDN. When evaluating RDN results by combining 24-hour MAP and the total load of antihypertensive medication by DDD we have reduced some of the uncertainties with medication changes during follow-up. The ≥ 5 mmHg reduction of 24-hour MAP as part of the responder definition was chosen as it reflects a clinical meaningful reduction in an overall measurement of BP. More patients tended to be incorrectly categorized as having no change in medication when the number of antihypertensive drugs is counted (53%) is compared to the DDD-method (33%). This difference was only nearly significant, $P=0.056$, but still illustrates how changes in antihypertensive medication can be made without affecting the number of antihypertensive agents. Therefore, we believe that using DDD combined with 24-hour MAP is more accurate than using the number of antihypertensive drugs combined with 24-hour MAP, although it is not significant. This approach might be helpful to obtain an accurate knowledge of the interactions of various contributors to BP reductions after RDN and the inevitably change in medication. Used in a larger scale this method may be helpful to identify what characterizes the responders vs. non-responders after treatment with RDN.

Antihypertensive medication

In the Symplicity HTN-3 trial almost 40% of the patients in both groups had a change in antihypertensive medication during the follow-up period, equally distributed in the actively treated and the sham group [3]. Interestingly, it is stated in the Symplicity HTN-3 protocol that a full dose of an antihypertensive drug “may differ among patients depending on co-morbidities and concomitant medications”, which is basically the problem with counting the number of antihypertensive drugs. A change in medication can be a reduction in a drug before complete discontinuation, and many multi-drug regimens are based on sub-maximal levels to limit the discomfort of side effects. The number of antihypertensive medications used as a part of the evaluation of the RDN effect is very vulnerable tool, since a reduction in the dose of one drug – primarily considered as a success – may camouflage an increase in dose of the remaining antihypertensive drugs. On the other hand a total DDD per day the amount of antihypertensive treatment is included across medication classes and doses. By using DDD we exclude this problem and get a single score that is unaffected of doses, and yet very sensitive to even small changes in antihypertensive medication.

Office BP and ABP

The most pronounced BP lowering effect of RDN is recorded during daytime, which could be ascribed to a higher level of sympathetic nervous activity compared with the level at night-time [18]. The proportion of nightly ‘dippers’ was reduced from 18% at baseline to 0% at 12 months after RDN, which partly may be explained by the concept, that RDN has the greatest influence on BP affected by the sympathetic nervous system.

Male gender (%)	71
Age, years (SD)	56 (13)
BMI, kg/m ² (SD)	29 (5)
Office BP, systolic/diastolic, mmHg (SD)	171(28)/99(16)
24-hour BP, systolic/diastolic, mmHg (SD)	157(22)/90(14)
Daytime	161(22)/95(17)
Nighttime	147(23)/81(14)
Duration of hypertension history, years (SD)	14 (10)
⁵¹ Cr-EDTA clearance ml/min*1.73m ² (SD)	80 (18)
Plasma creatinine, μ mol/L (SD)	88 (45)
Diabetes, % (n)	20 (10)
AMI, % (n)	8 (4)
CABG/PCI, % (n)	10 (5)
Stroke, % (n)	18 (9)
TIA, % (n)	4 (2)

Table 1: Demographics and Clinical Characteristics (N=51).

Overview of the baseline demographics and clinical data of the first 51 patients having RDN performed from April 2011 to April 2013 at our institution.

BMI: Body Mass Index. BP: Blood Pressure. Cr-EDTA: Chromium ethylenediaminetetraacetate.

AMI: Acute Myocardial Infarction. CABG: Coronary Artery Bypass Graft. PCI: Percutaneous

Coronary Intervention. TIA: Transient Ischemic Attack.

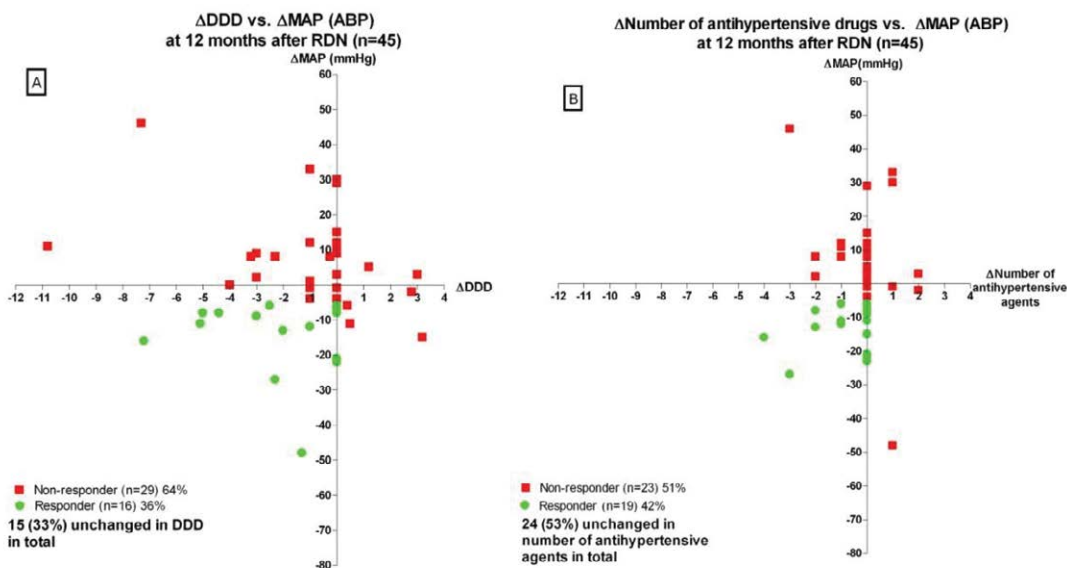


Figure 1: ΔDDD and Δ number of Antihypertensive Drugs Compared to Δ map
A: Illustrates the correlation between ΔDDD vs. ΔMAP at 12 month minus baseline after RDN. **B:** Illustrates the correlation between Δ number of antihypertensive drugs vs. ΔMAP at 12 month minus baseline after RDN.

A and B: Green color indicates a responder (defined as a ≥ 5 mmHg reduction in 24-hour MAP combined with unchanged or reduced DDD) and red color indicates a non-responder to the treatment. The ≥ 5 mmHg reduction in MAP is an arbitrary cut-off value chosen as it reflects a clinically relevant reduction in an overall measurement of blood pressure.

DDD: Defined Daily Dose.

MAP: Mean Arterial Pressure.

ABP: Ambulatory Blood Pressure.

Keeping in mind that reproducibility of the dipping pattern is low [19], non-dipping in patients with resistant HTN is related to several factors such as endothelial dysfunction [20] and timing of antihypertensive drug administration [21]. The Symplicity HTN-3 has - in a separate publication [22] - split their ABP data up into day and night, and found a BP lowering effect in both day and night-time. Our data suggest that RDN has a more pronounced effect on daytime than nighttime ABP which is supported by Völz et al. [23]. Daytime ABP could therefore be a more appropriate endpoint. Although guidelines from the European Society of Hypertension [14] state (mostly due to vast availability), they do acknowledge superiority of the accuracy of ABP. When introducing a new treatment for hypertension, like RDN, we suggest ABP as the proper measure of changes in BP. The discrepancy between reductions in office BP and ABP - with effect on office BP being more pronounced than ABP - is a phenomenon also seen in pharmacological studies of severe hypertension [24,25].

Patient selection

We included 10 patients with verified intolerance to a spectrum of antihypertensive drugs in our analysis, patients that would have been excluded from other studies. A definitive decision on RDN based current studies cannot be made of either the BP lowering effect or the possible additional effects. RDN treatment may have a future in appropriately selected patients with resistant hypertension using suitable and effective catheters by experienced operators. While awaiting the results of future

studies in this field, the RDN procedure should, nevertheless, be at least considered for patients with verified intolerance of antihypertensive drugs to reduce their risk of stroke and other cardiovascular disease. Measurement of the muscular sympathetic nerve activity is at present time an extremely difficult test to use as a screening tool, but could be a valuable option to guide patient selection for RDN, especially if it could be refined and less time consuming.

Strengths and limitations

Limitations of this study are the relatively small number of patients, its observational nature, the use two different RDN systems and unverified adherence to antihypertensive medication. It would have been ideal to have a more accurate evaluation on compliance, such as pill counting, urine or plasma analysis of concentrations of antihypertensive medication or their metabolites. Regression towards the mean could also explain the relative small reductions in BP.

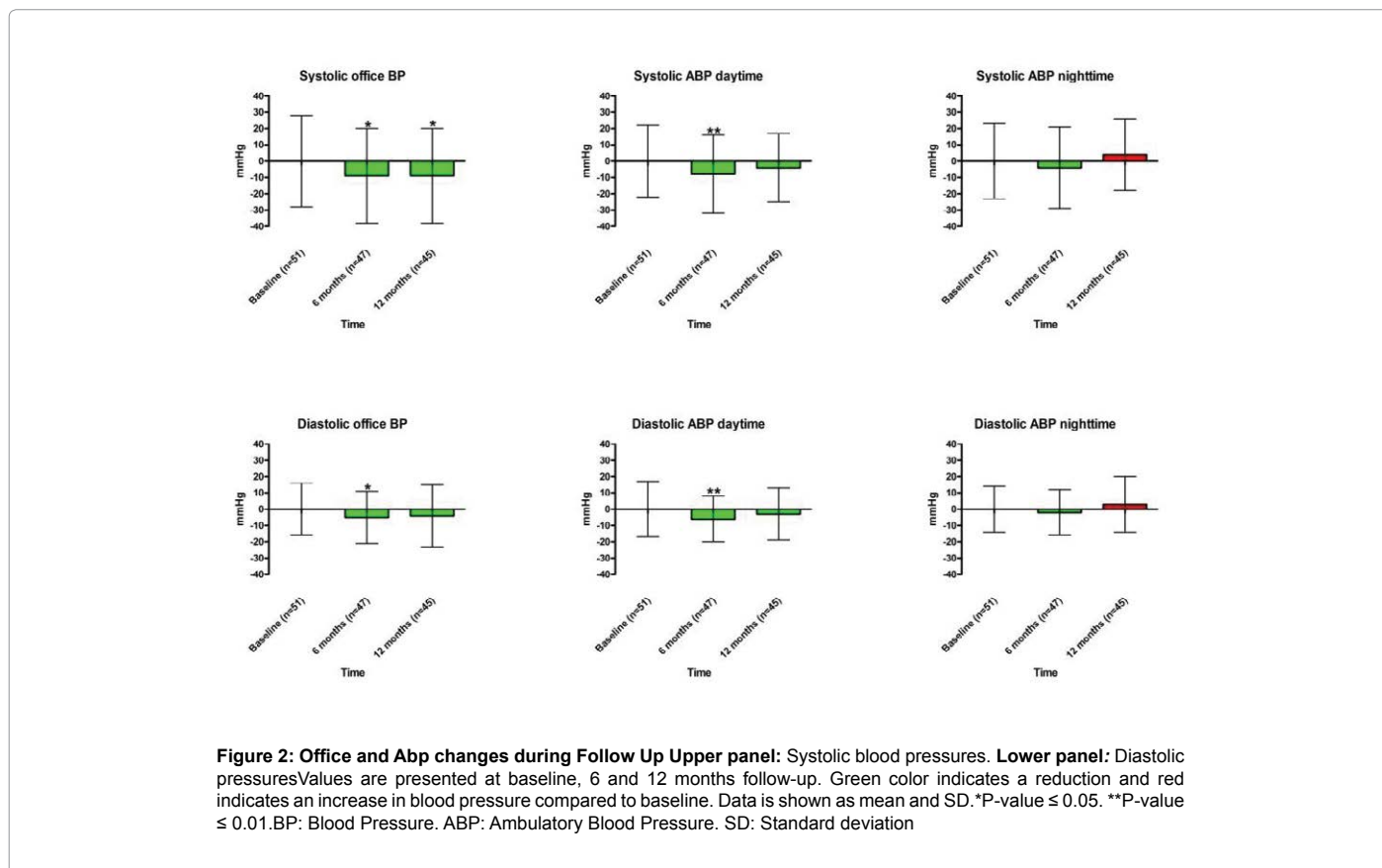
The strengths of the study are that all patients went through a thorough clinical work up to exclude secondary causes of hypertension, the same two operators performed all RDN procedures, and there was a close follow-up of each patient.

Conclusion

In a consecutive cohort of patients with resistant hypertension we did not see the previously described consistent BP reduction from RDN in office BP and ABP. Using the ΔDDD/24-hour ΔMAP method,

	Baseline n=51 (SD)	6 months follow up n=47 (SD)	12 months follow up n=45 (SD)	Change between baseline and 6 months Mean (95% CI)	P-value	Change between baseline and 12 months Mean (95% CI)	P-value
Office blood pressure (mmHg)							
Systolic	171 (28)	163 (29)	162 (29)	-8.3 (-16.4 to -0.1)	0.05	-11.0 (-20.3 to -1.8)	0.02
Diastolic	99 (16)	94 (16)	95 (19)	-4.46 (-8.9 to -0.1)	0.05	-5.04 (-10.5 to 0.4)	0.06
24-hour ambulatory blood pressure (mmHg)							
24-hour							
Systolic	157 (22)	151 (24)	155 (21)	-6.9 (-13.3 to -0.4)	0.04	-2.6 (-8.8 to 3.5)	0.39
Diastolic	90 (14)	86 (14)	90 (16)	-3.5 (-7.4 to 0.5)	0.08	0.3 (-4.0 to 4.5)	0.91
MAP	112 (15)	107 (15)	111 (16)	-4.9 (-9.6 to -0.2)	0.04	-0.9 (-5.9 to 4.1)	0.71
Daytime							
Systolic	161 (22)	153 (24)	158 (21)	-8.6 (-15.2 to -2.0)	0.01	-4.2 (-10.9 to 2.5)	0.21
Diastolic	95 (17)	89 (14)	92 (16)	-6.3 (-11.1 to -1.5)	0.01	-3.2 (-8.9 to 2.5)	0.27
MAP	117 (16)	110 (15)	113 (16)	-7.3 (-12.2 to -2.4)	0.004	-4.1 (-9.5 to 1.3)	0.13
Night time							
Systolic	147 (23)	143 (25)	150 (22)	-5.1 (-11.8 to 1.6)	0.13	2.9 (-3.5 to 9.3)	0.36
Diastolic	81 (14)	80 (14)	84 (17)	-1.9 (-6.4 to 2.6)	0.40	2.8 (-1.9 to 7.4)	0.24
MAP	103 (15)	101 (16)	106 (17)	-3.1 (-8.1 to 1.8)	0.21	2.6 (-2.4 to 7.5)	0.31

Table 2: The Effect of RDN on Blood Pressure P-values of 0.05 or less were considered significant. MAP: Mean Arterial Pressure. CI: Confidence interval. SD: ± Standard deviation



	Baseline (n=51)	6 months follow-up (n=47)	12 months follow-up (n=45)	Change between baseline and 6 months Mean (95% CI)	P-value	Change between baseline and 12 months Mean (95% CI)	P-value
Number of antihypertensive drugs (SD)	3.9 (1.7)	3.7 (1.9)	3.4 (1.7)	-1.0 (-1.5 to 0.5)	0.16	-1.0 (-1.5 to -1.1)	0.02
DDD per day (SD)	6.8 (4.0)	6.3 (3.6)	5.6 (3.3)	-0.6 (-1.3 to 0.1)	0.09	-1.2 (-1.9 to -0.4)	0.04

Table 3a: Antihypertensive drugs I Antihypertensive medication by number of antihypertensive agents and DDD (daily defined dose). P values of 0.05 or less were considered significant. CI: Confidence interval. SD: ± Standard deviation.

	Baseline (n=51)	6 months follow up (n=47)	12 months follow up (n=45)
Diuretics	38 (75%)	34 (72%)	32 (71%)
Aldosterone antagonist	14 (27%)	13 (28%)	12 (27%)
Angiotensin-receptor blocker	27 (53%)	26 (55%)	26 (58%)
ACE inhibitor	21 (41%)	18 (38%)	14 (31%)
Direct renin inhibitor	5 (10%)	3 (6%)	0 (0%)
Calcium-channel blocker	39 (76%)	33 (70%)	29 (64%)
β blocker	19 (37%)	16 (34%)	14 (31%)
α and β blocker	8 (16%)	8 (17%)	9 (20%)
α blocker	7 (14%)	5 (11%)	4 (9%)
Centrally acting sympatholytic (eg. moxonidine)	6 (12%)	6 (13%)	5 (11%)
Minoxidil	7 (14%)	5 (11%)	4 (9%)

Table 3b: Antihypertensive Drugs II Antihypertensive medication by drug classes. ACE: Angiotensin Converting Enzyme.

Number of antihypertensive drugs vs. DDD at baseline (n=51)

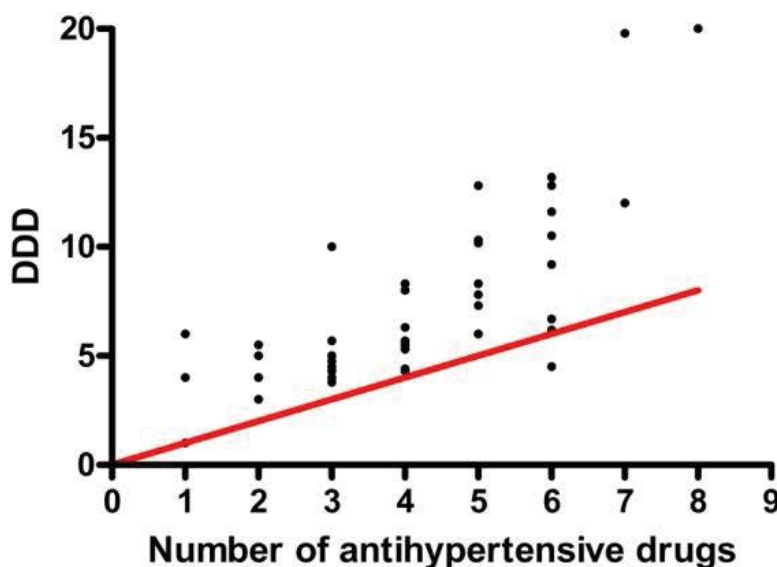


Figure 3: Correlation between DDD and number of Anti hypertensive drugs

Figure 3 illustrates the correlations between number of antihypertensive agents and DDD given at baseline, and is comparable to both 6 and 12 months (not shown). The red line indicates the line corresponding to antihypertensive drugs given at their maximal dosages equal to their DDD value.

however, it is possible to identify responders and non-responders using a combination of ABP and quantified antihypertensive medication. When evaluating non-pharmacological therapy pharmacological antihypertensive treatment must be quantified to untangle the BP lowering effect from the pharmacological induced due to changes in medication.

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Conflicts of Interest

All authors declare that (1) None of the authors have received any support from any company for the submitted work; (2) JHS have declared a consultancy affiliation within the previous 3 years with Medtronic that as a company might have an interest in the submitted work; (3) All authors have no non-financial interests that may be relevant to the submitted work. All authors included on this paper fulfill the criteria of authorship, and have contributed to conception and design, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published.

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