

# The effect of renal denervation on central blood pressure and arterial stiffness in treatment resistant essential hypertension: a substudy of a randomized sham-controlled double-blinded trial (the ReSET trial)

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Disclosures: None



# Background & aim

- A recent Danish sham-controlled trial (ReSET)<sup>1</sup> showed no sustained effect of renal denervation (RDN) on 24-hour ambulatory blood pressure (BP) measurements (24h ABPM) in patients with treatment resistant hypertension
- Findings were similar to the neutral outcome of the SYMPPLICITY HTN-3 trial<sup>2</sup> + German trial (Desch *et al.*<sup>3</sup>)
- The aim of this substudy was to determine whether RDN affects central blood pressure (C-BP) and arterial stiffness

1) Mathiassen *et al.* J Hypertens 2016 Aug;34(8):1639-47.

2) Bhatt *et al.* N Engl J Med. 2014 Apr 10;370(15):1393-401.

3) Desch *et al.* Hypertension. 2015 Jun;65(6):1202-8.

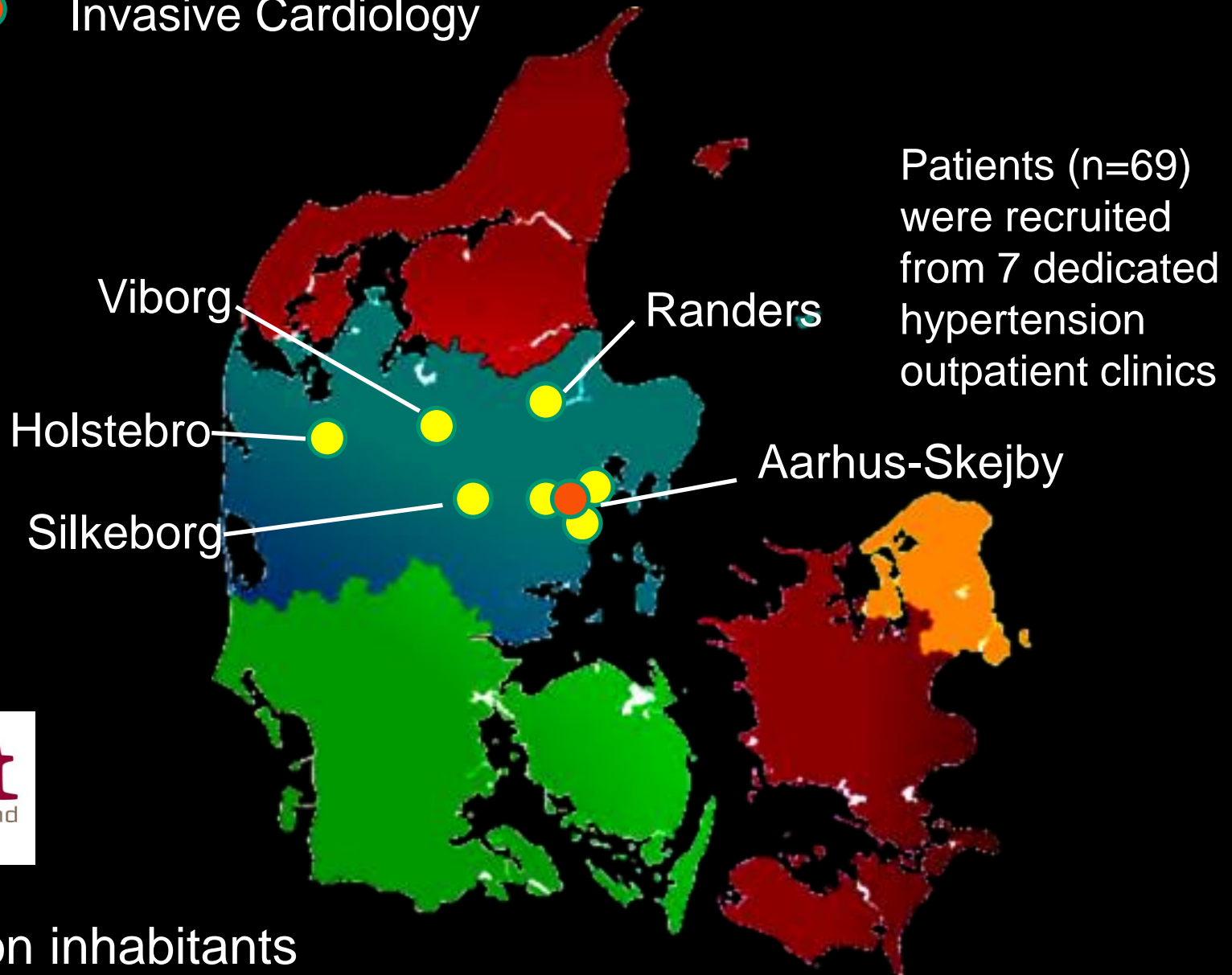
# ReSET = Renal Sympathectomy in Treatment Resistant Essential Hypertension, a Sham Controlled Randomized Trial

- Danish collaborative study initiated before the HTN-3 trial (Sept. 2011-February 2015)
- Investigator initiated and driven
- No company support
- Hypothesis: RDN reduces daytime systolic BP by 10 mmHg compared to SHAM in a double blinded RCT design
- Power calculation:  $n = 70$  (2 x 35)

ClinicalTrials.gov NCT01459900

Mathiassen *et al.* J Hypertens 2016 Aug;34(8):1639-47.

- Outpatient clinics for complicated hypertension
- Invasive Cardiology



# ReSET study criteria

## Inclusion

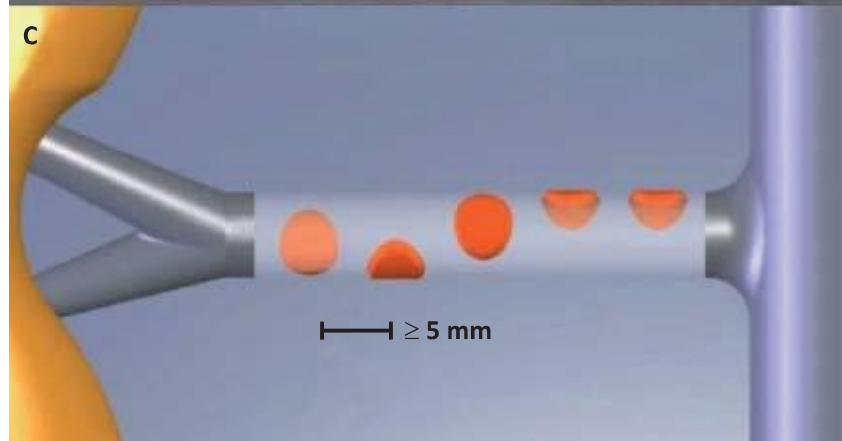
- Age [30 – 70] year
- 1 month of stable antihypertensive treatment with at least 3 antihypertensive agents including a diuretic (or in case of diuretics intolerance a minimum of 3 non-diuretic drugs)
- Daytime ABPM systolic blood pressure  $\geq 145$  mmHg, preceded by 14 days of scheduled drug intake showing at least 85% adherence

## Exclusion

- Chronic renal failure (eGFR  $<30$  ml/min per  $1.73$  m<sup>2</sup>)
- Secondary hypertension
- Coronary artery disease
- Permanent atrial fibrillation
- LV ejection fraction  $<50\%$
- Renal artery disease
- Multiple renal arteries
- Renal artery diameter  $< 4$  mm
- Renal artery length  $<20$  mm

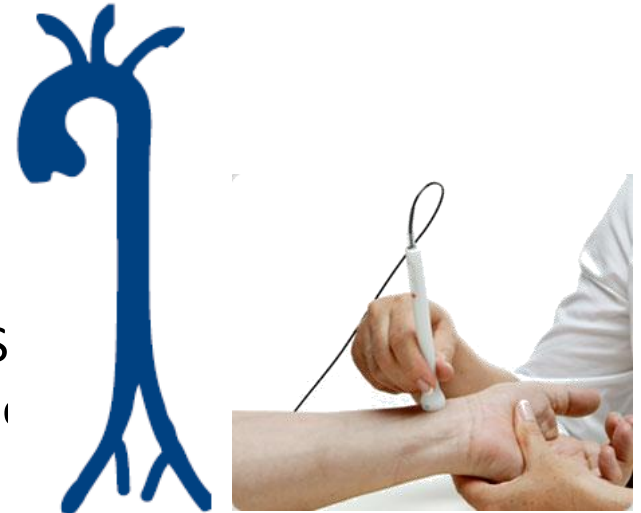
# Intervention

- Catheter-based RDN or a SHAM procedure (1:1 ratio) using the unipolar Medtronic Flex catheter
- Sedative drugs were administered (fentanyl and midazolam) prior to randomization
- RDN was performed by a single experienced invasive cardiologist qualified by 9 pre-trial RDN<sup>1</sup>
- For the SHAM procedure the catheter was kept in situ and dummy radiograph scans were performed for 10 – 15 min
- Patients and caretaking physicians were blinded during the 6-month follow-up period



# Methods

- Central BP and carotid-femoral pulse wave velocity (PWV) was obtained with the SphygmoCor device using brachial systolic and diastolic BP for calibration
- Aortic length was approximated by subtracting the distance between the suprasternal notch (S) and the carotid artery from the distance between the SN and the femoral artery
- PWV were converted to direct distance (carotid artery–femoral artery  $\times 0.8$ ) using the equation developed by Vermeersch *et al.*
- All 24-h ABPM was done using either the SpaceLabs 90207 or 90217 ABPM monitor with BP readings every 20 min.



Van Bortel *et al.* J Hypertens 2012; 30: 445–448.

Vermeersch *et al.* J Hypertens 2009; 27: 2377–2385.

# Results

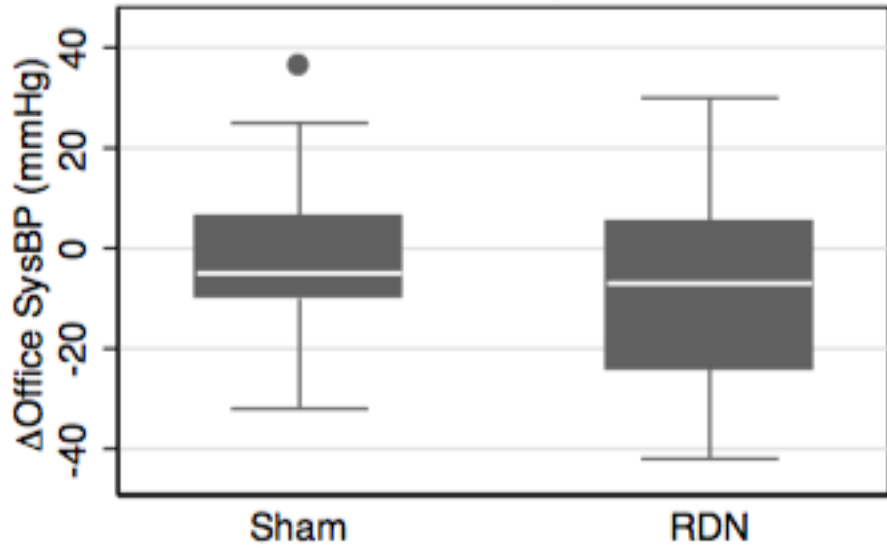
53 patients (77% of the ReSET cohort) were included in this substudy

<b>Baseline demographics</b>	<b>SHAM (n=27)</b>	<b>RDN (n=26)</b>	<b><i>P</i></b>
<b>Age (years)</b>	59±9	54±8	0.04
<b>Males (%)</b>	78%	65%	0.32
<b>BMI (kg/m<sup>2</sup>)</b>	30±3	28±5	0.15
<b>Type 2 DM</b>	27%	27%	0.99
<b>eGFR (ml/min/1.73 m<sup>2</sup>)</b>	77±17	82±13	0.23
<b>Antihypertensive drugs (n)</b>	4.2	4.4	0.48
<b>Antihypertensive drugs (DDD)</b>	7±2	7±3	0.97
<b>Office systolic BP (mmHg)</b>	165±19	160±19	0.37
<b>Office diastolic BP (mmHg)</b>	92±17	99±11	0.06
<b>24h ABPM systolic (mmHg)</b>	153±14	151±13	0.72
<b>24h ABPM diastolic (mmHg)</b>	88±11	92±9	0.14
<b>Central systolic BP (mmHg)</b>	146±20	143±17	0.55
<b>Central diastolic BP (mmHg)</b>	92±14	95±10	0.48
<b>Aix (%)</b>	26±9	28±13	0.66
<b>PWV (direct distance) (m/s)</b>	10.7±2.1	10.1±2.2	0.28

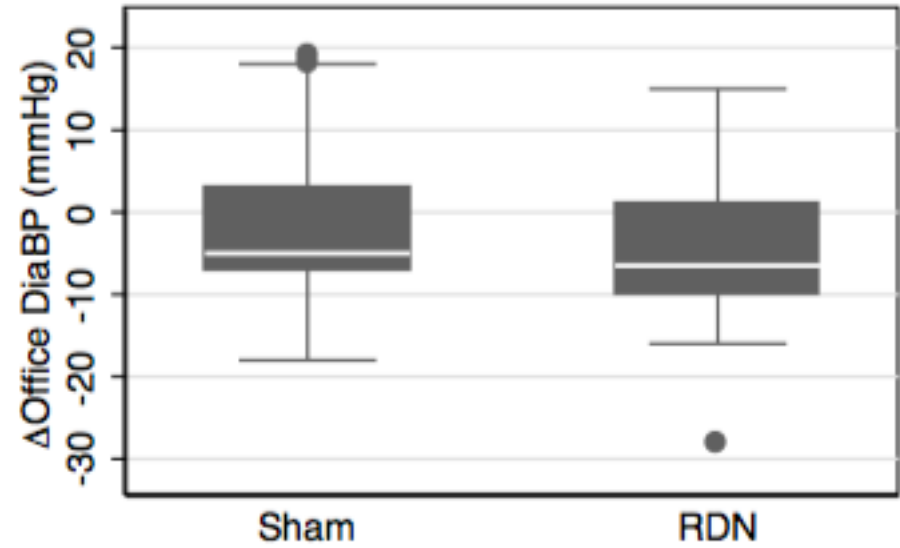


$\Delta$ =Mean difference (6 months-baseline)

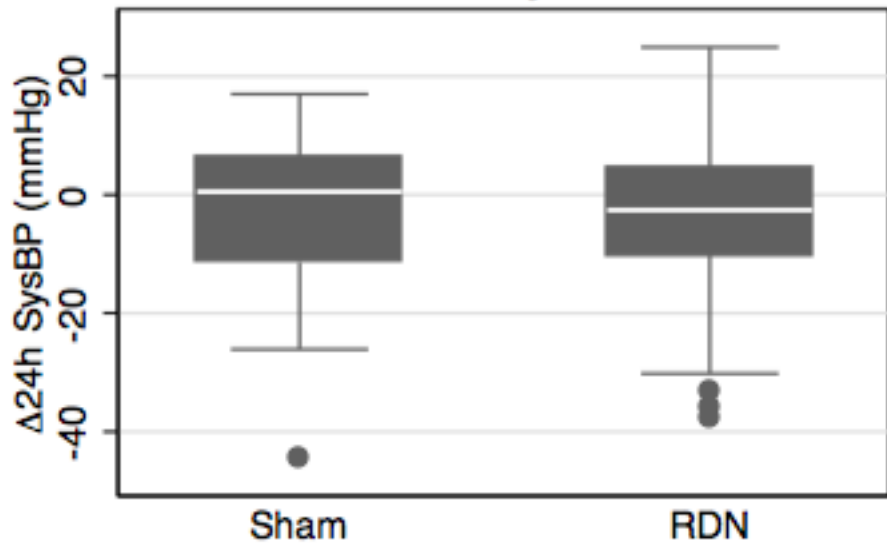
$\Delta$ Office SysBP



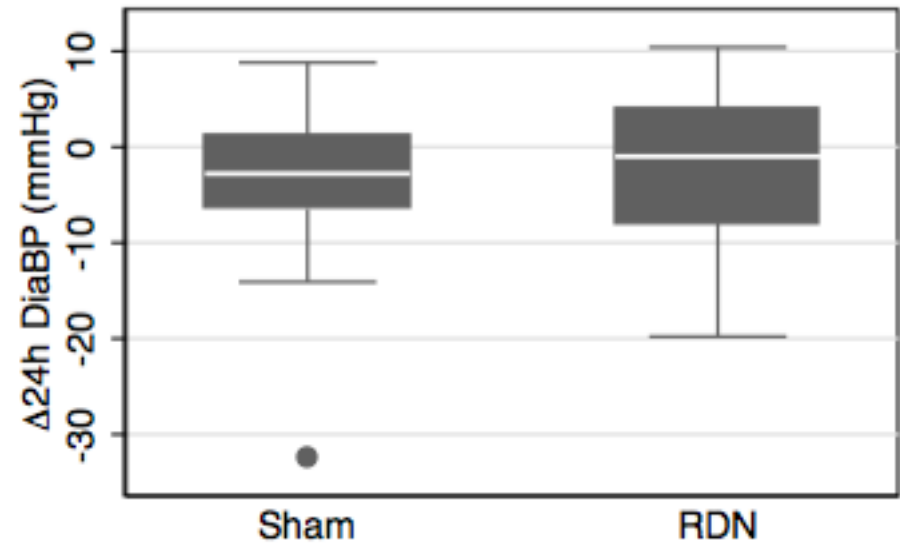
$\Delta$ Office DiaBP



$\Delta$ 24h SysBP

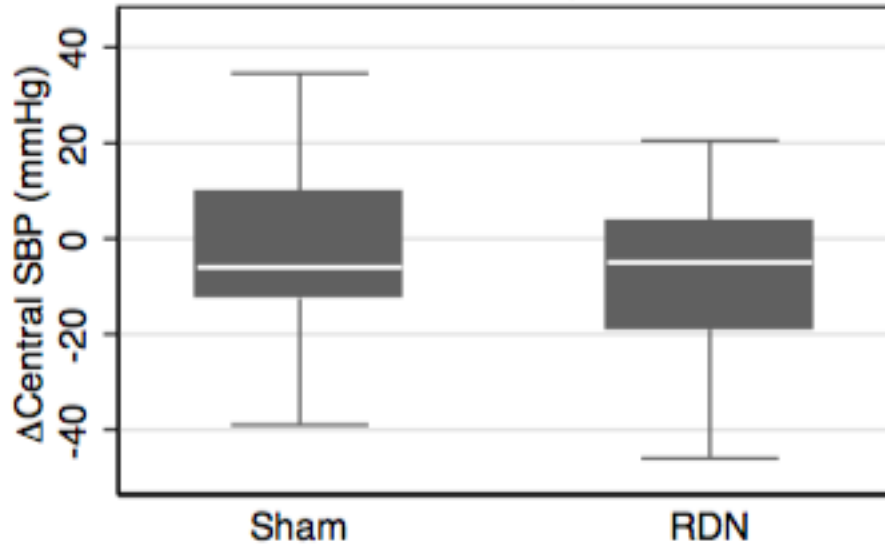


$\Delta$ 24h DiaBP

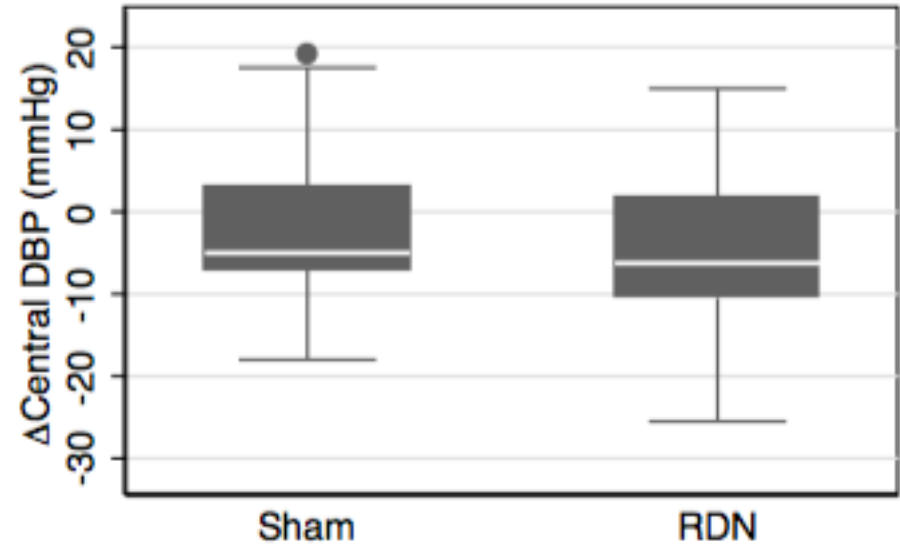


$\Delta$ =Mean difference (6 months-baseline)

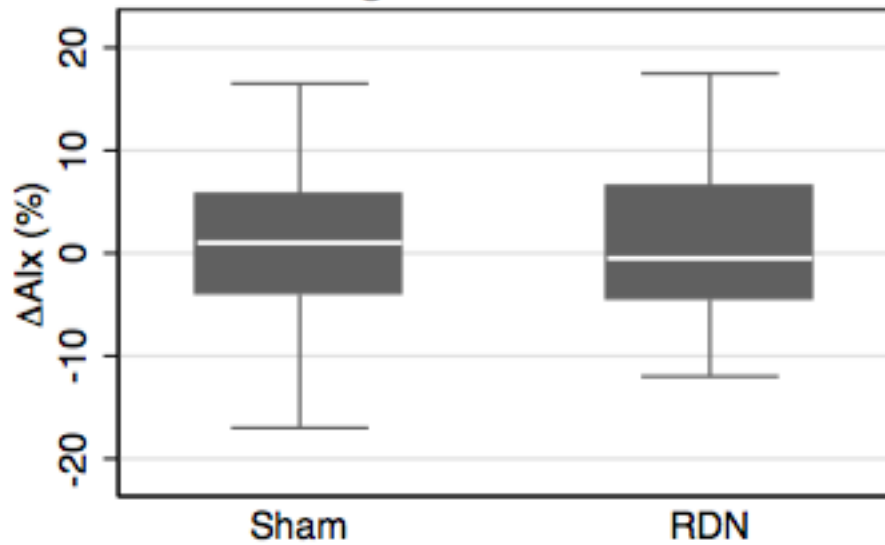
$\Delta$ Central SysBP



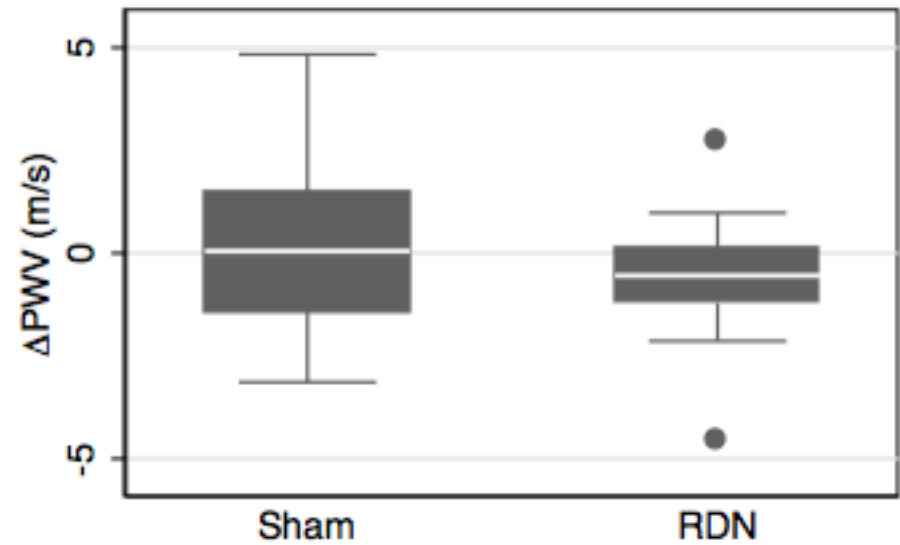
$\Delta$ Central DiaBP



$\Delta$ Augmentation index



$\Delta$ PWV



# Within and between group comparison (SHAM vs. RDN)

Within & between group changes	$\Delta$ SHAM		$\Delta$ RDN		$\Delta$ SHAM vs. $\Delta$ RDN	
	Mean (95% CI)	<i>P</i>	Mean (95% CI)	<i>P</i>	Mean (95% CI)	<i>P</i>
Office SysBP (mmHg)	-2 (-8; 5)	0.59	-8 (-15; -1)	<b>0.03</b>	6 (-3; 15)	0.19
Office DiaBP (mmHg)	-2 (-6; 2)	0.27	-5 (-9; -1)	<b>0.01</b>	3 (-2; 8)	0.25
24h Sys (mmHg)	-4 (-9; 1)	0.12	-5 (-12; 2)	0.18	1 (-8; 9)	0.84
24h Dia (mmHg)	-3 (-6; 0)	<b>0.04</b>	-3 (-6; 1)	0.11	-1 (-5; 4)	0.76
Central SysBP (mmHg)	-2 (-9; 4)	0.51	-8 (-14; -1)	<b>0.02</b>	5 (-3; 14)	0.22
Central DiaBP (mmHg)	-2 (-6; 2)	0.24	-5 (-8; -1)	<b>0.01</b>	3 (-2; 8)	0.29
Aix (%)	1 (-2; 3)	0.59	1 (-2; 4)	0.50	0 (-4; 4)	0.90
Aix@hr75 (%)	1 (-2; 3)	0.63	1 (-1; 3)	0.41	0 (-4; 3)	0.85
Time to reflection (ms)	-2 (-6; 2)	0.28	1 (-2; 5)	0.52	-3 (-8; 2)	0.21
SEVR (Buckberg ratio)	-4 (-11; 4)	0.32	-1 (-11; 10)	0.91	-3 (-16; 10)	0.62
PWV (m/s)	0.1 (-0.7; 0.9)	0.81	-0.6 (-1.1; -0.1)	<b>0.03</b>	-0.7 (-1.6; 0.2)	0.13

$\Delta$ =Mean difference (6 months-baseline)

# Conclusion

- In agreement with other sham-controlled studies no significant effect of RDN on BP (office BP & 24h AMBP)
- In a sham-controlled setting, there were no significant effects of RDN on central BP or arterial stiffness

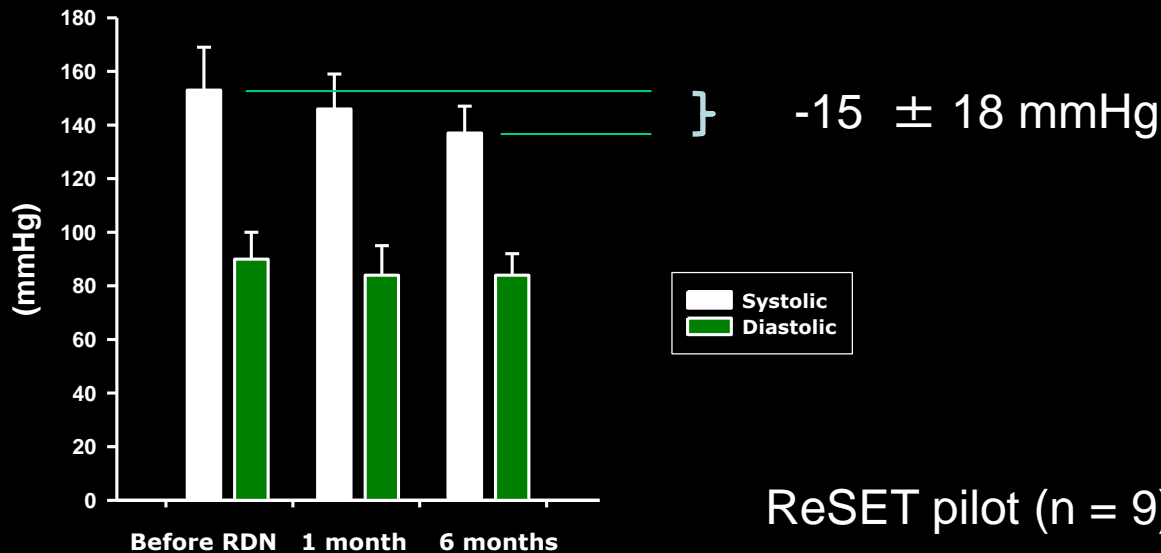
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# ReSET Study Hypothesis

RDN reduces systolic daytime BP by 10 mmHg compared to SHAM in a double blinded randomized trial design.

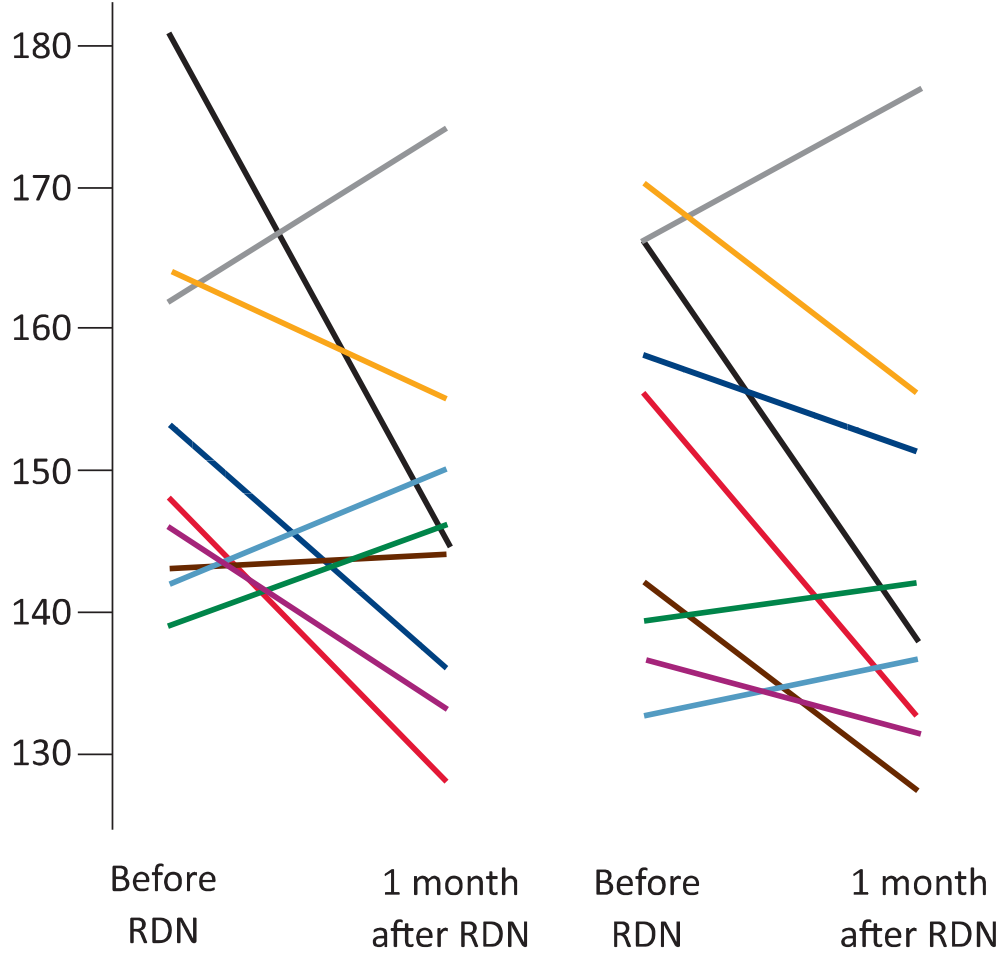
Power calculation:  $n = 70$  (2 x 35)



ReSET pilot ( $n = 9$ ).

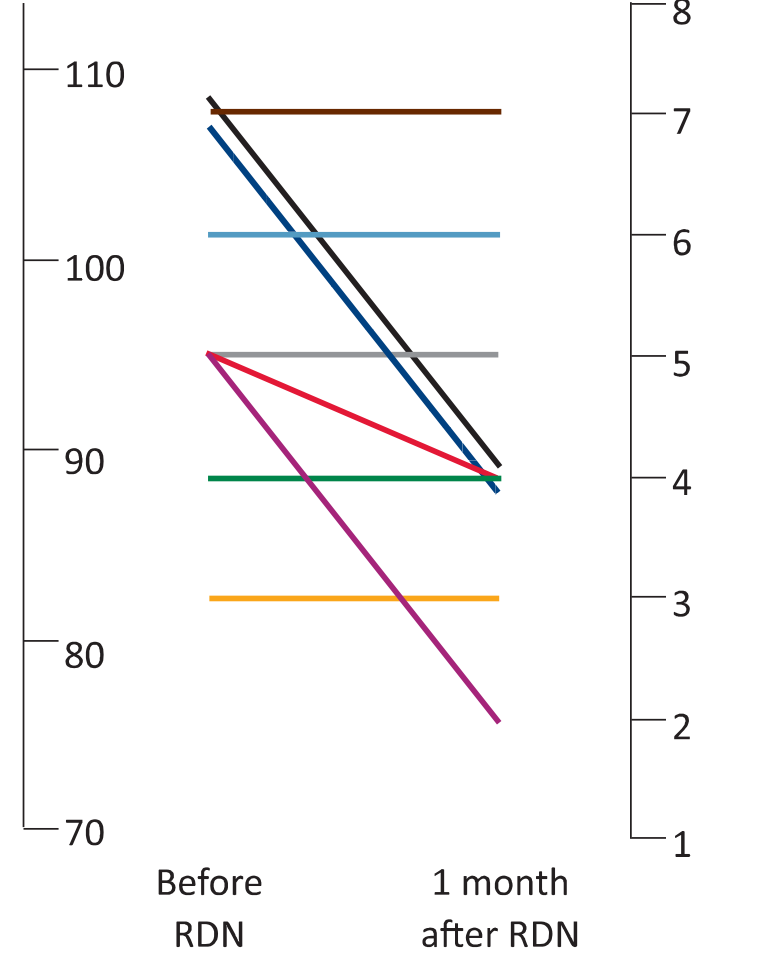
### Systolic blood pressure

mmHg

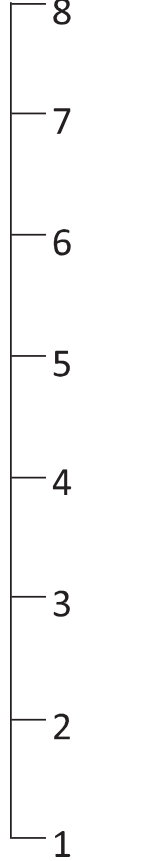


### Diastolic blood pressure

mmHg



Drugs, n



- Patient 1      — Patient 3      — Patient 5      — Patient 7      — Patient 9
- Patient 2      — Patient 4      — Patient 6      — Patient 8

24-hour ambulatory daytime blood pressure and number of anti-hypertensive drugs before and after the catheter-based renal denervation (RDN).

# ReSET daytime (9-21) ABPM changes (mmHg $\pm$ SD)

		RDN	SHAM
1 month	Systolic	-6,0 $\pm$ 11,0*	0,0 $\pm$ 15,0*
	Diastolic	-4,2 $\pm$ 6,6**	0,2 $\pm$ 8,4**
3 month	Systolic	-6,2 $\pm$ 18,8	-6,0 $\pm$ 13,5
	Diastolic	-2,4 $\pm$ 10,3	-3,2 $\pm$ 6,2
6 month	Systolic	-6,1 $\pm$ 18,9	-3,2 $\pm$ 10,8
	Diastolic	-4,3 $\pm$ 15,1	-3,6 $\pm$ 8,3

\*  $p = 0,08$

\*\*  $p = 0,02$



# ReSET RDN procedure data

	ReSET	HTN 3
Duration (min):	42 ± 11	92 ± 38
Contrast (ml):	85 ± 25	77 ± 77
Ablations:	10,9 ± 1,1 (5.4 ± 1.0 sin) (5.5 ± 0.9 dx)	9,2 ± 1,0

# ReSET Blinding

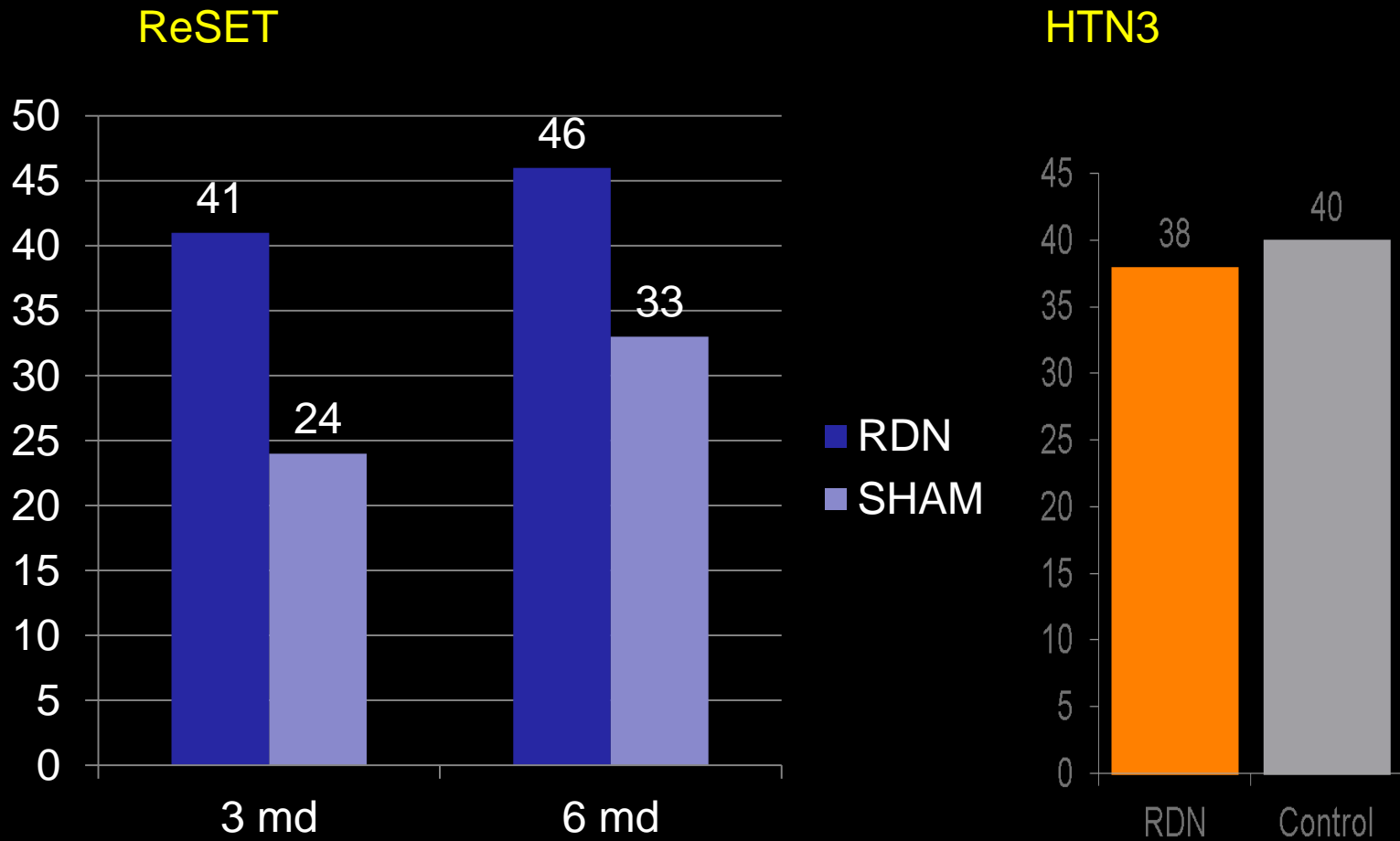
Blinding index at discharge: 0,83

Index value:

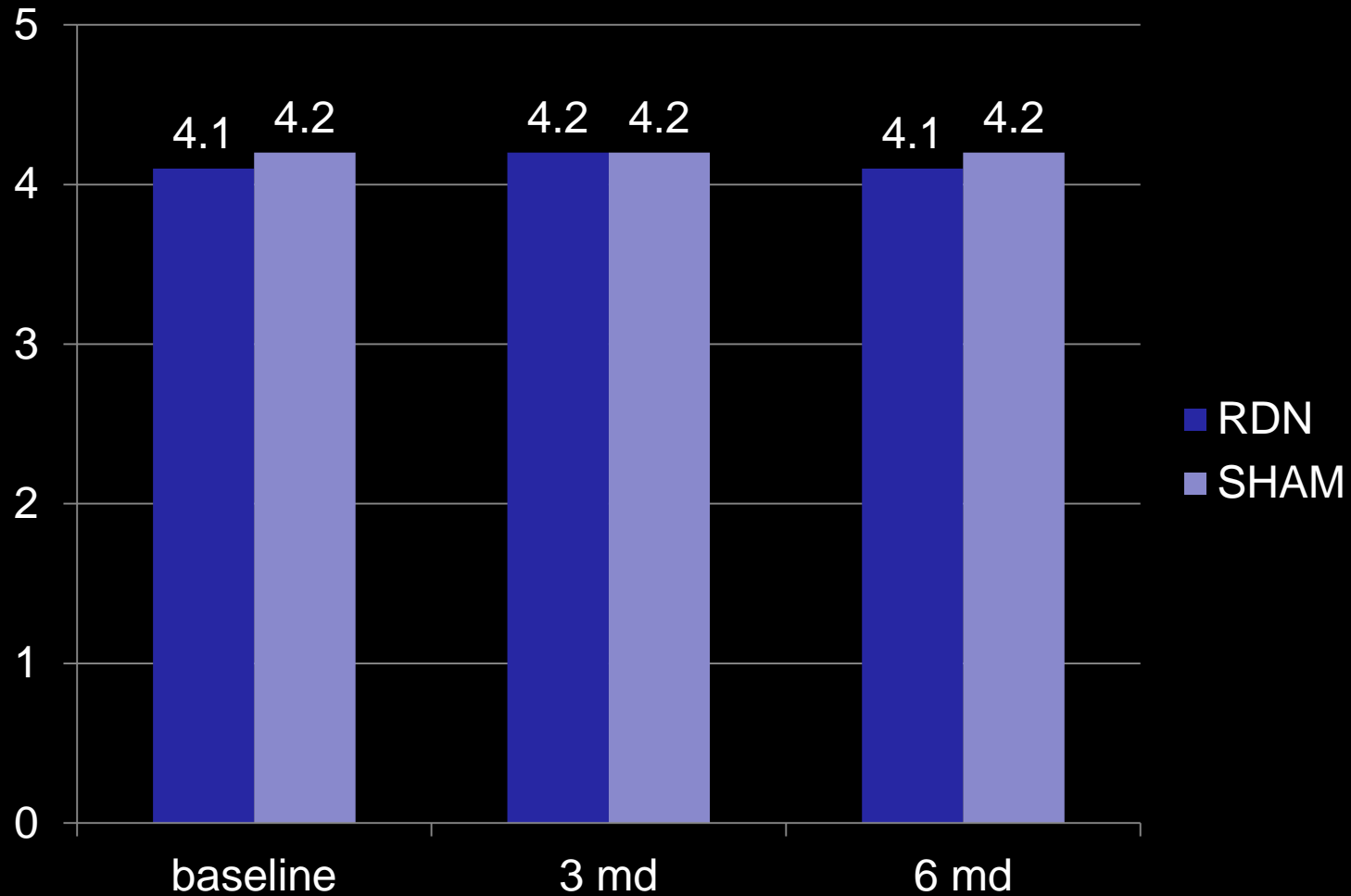
1 indicates perfect blinding

< 0.5 indicates insufficient blinding

# ReSET patients with changes in antihypertensives (%)



# ReSET Antihypertensiva (numbers)



# ReSET Antihypertensiva DDD

