Renal denervation: promising treatment for resistant hypertension ?

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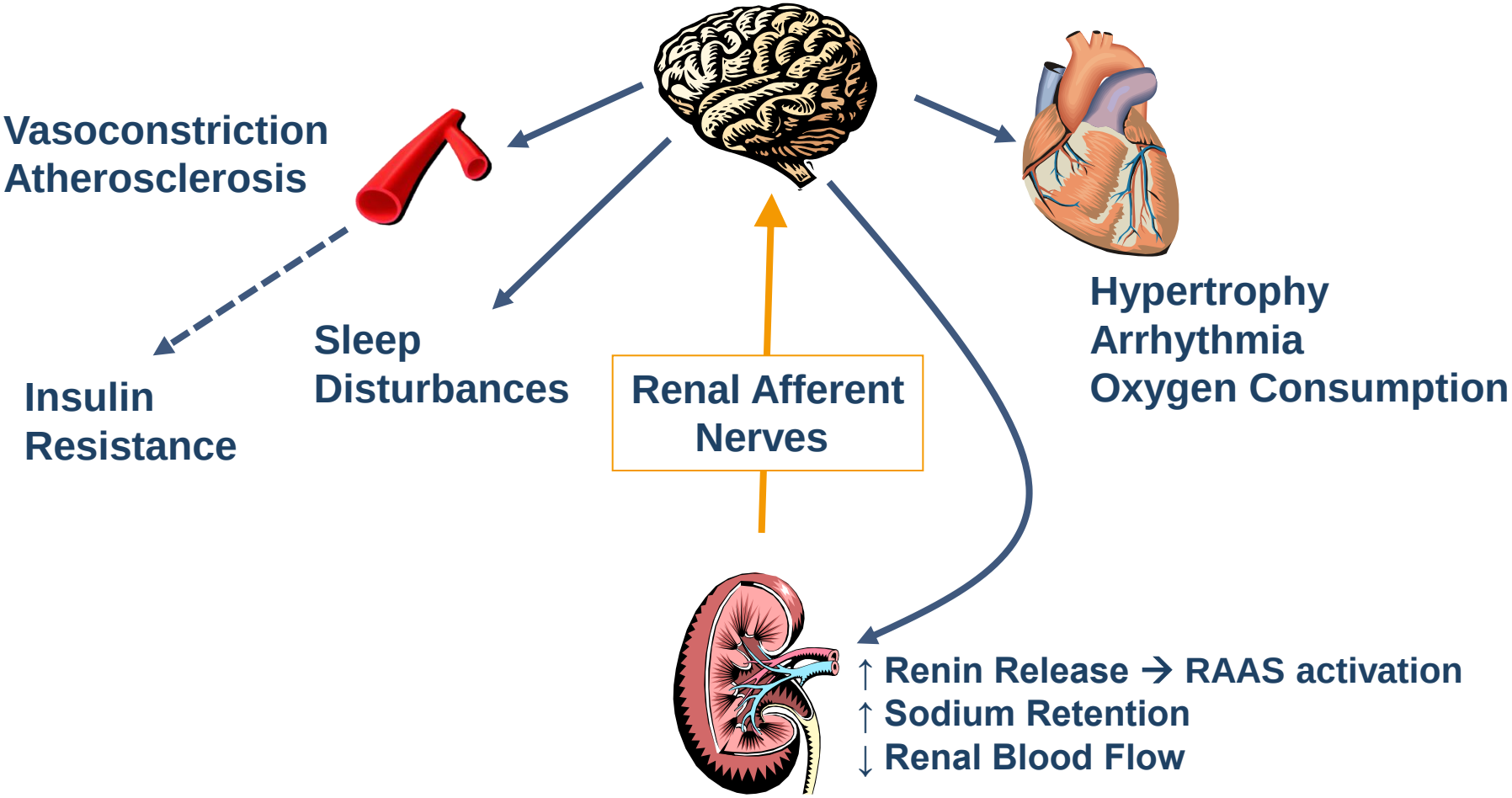
Renal Sympathetic Afferent Nerves:

Kidney as Origin of Central Sympathetic Drive

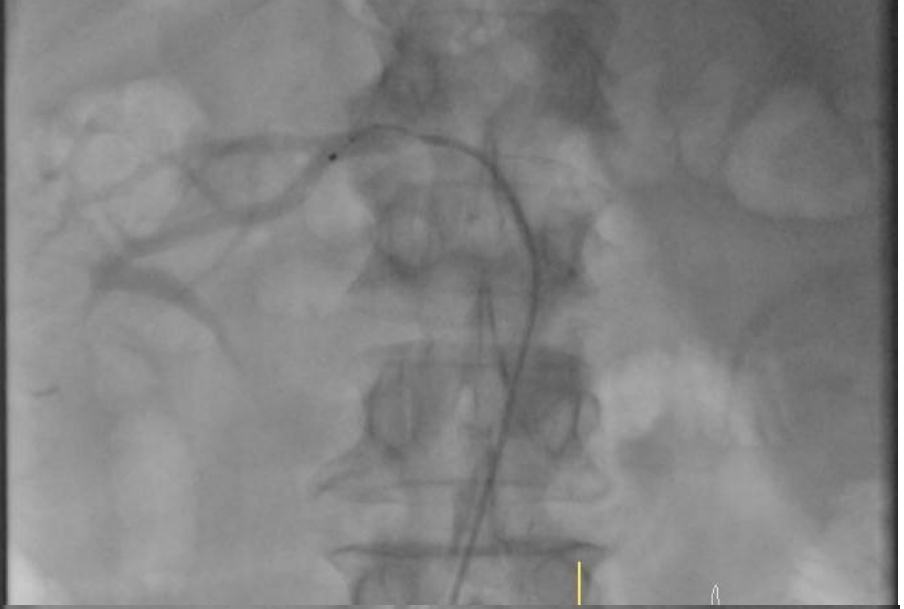
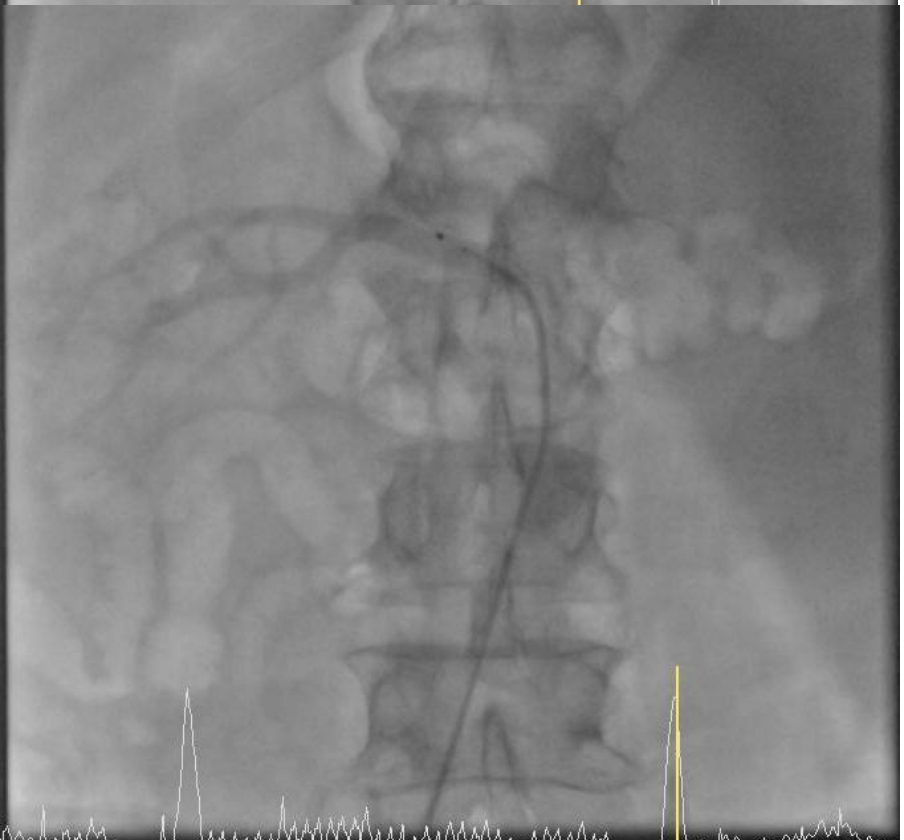
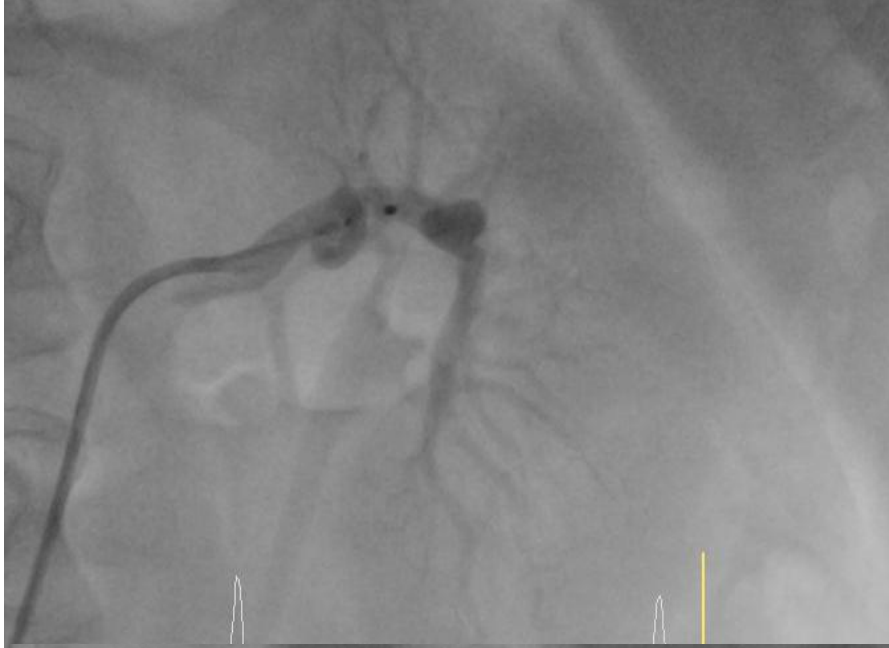
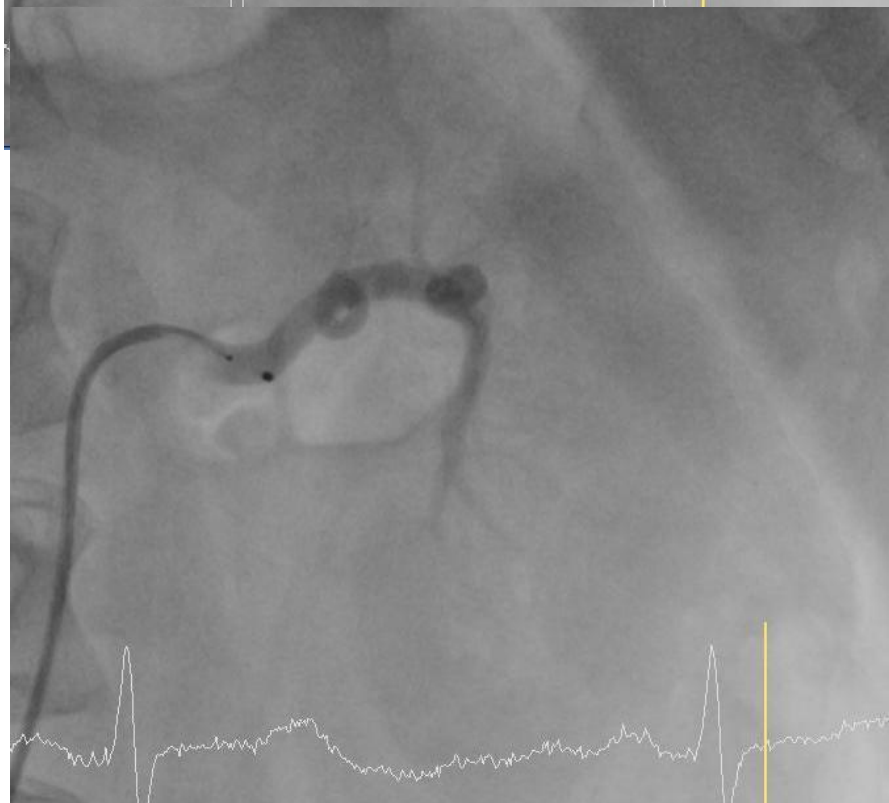


Introductory case

Male, 64-years, in early pension for severe hypertension lasting >30 years

- Father + 73 years due to acute stroke, mother was hypertensive diabetic, + 53 years due to sepsis.
- 1979 diagnosis of hypertension (follow-up in hypertension center, blood pressure could not be normalized)
- Obesity (173 cm / 95 kg)
- 1998 diabetes type II, since 2002 on insulin
- 2004 UAP - PCI on LAD + RCA , 2005 CABG on LAD + RCA
- Hyperlipoproteinemia on statin therapy
- Hypothyreosis on hormonal substitution
- Ex-smoker (smoked till 2004)

- drugs: Prestance 10/10 mg 1-0-0, Concor 5 mg 1-0-0, Rasilez HCT 150/12,5 mg 1-0-0, Zoxon 2 mg 1-0-1, Siofor 1000 1-1-1, Januvia 100 1-0-0, Anopyrin 100 1-0-0, Simgal 20 mg 0-0-1, Euthyrox 125 ug 1-0-0, Humalog 6-6-6, Lantus 0-0-0-18

Renal denervation (catheter ablation of perirenal sympaticus).

- Date: 4.11.2011 Duration: 52 minutes
- Operators: Widimský, Toušek. Analgosedation: Bednář
- Drugs: Heparin 10 000 U, ketamin, midazolam and propofol as per anesthesiology protocol, contrast Omnipaque 350 (80 ml).
- Initial BP 157 / 77 mmHg, final BP 110 / 60 mmHg
- Procedure smooth, no complications.

Max. temperature (degrees C) / impedance decrease (%)

	1.ablace	2.ablace	3.ablace	4.ablace	5.ablace	6.ablace
A.renalis sin.	50° / 12%	56° / 18%	66° / 16% (jen 30 s.)	67° / 18% (jen 40 s.)	60° / 23%	60° / 18%
A.renalis dx.	66° / 23% (jen 60 s.)	63° / 23%	48° / 6%	68° / 20% (jen 37 s.)		

BP before RDN and after 3 months

Before randomization:

- **BP (ambulance): 216/106 mmHg**
- **BP (mean 24-h ABPM): 152/84 mmHg**

6 months after RDN:

- **BP (ambulance): 145/85 mmHg**
- **BP (mean 24-h ABPM): 132/74 mmHg**

Renal denervation: hope for patients with severe resistant hypertension ?

Randomized study „PRAGUE-15“

P. Widimský, M. Táborský, M. Branny, J. Widimský jr.

Pavel Osmančík, Petr Toušek, Karol Čurila, Ondřej Petrák, Ján Rosa, František Bednář, Jan Václavík, Eva Kocianová, David Richter, Tomáš Skála, Aleš Smékal, Igor Nykl, Ota Jiravský

Inclusion criteria	Exclusion criteria
Syst. BP (ambulance) ≥ 140/90 mmHg*	Secondary hypertension
ABPM 24-h mean ≥130/80 mmHg*	Renal failure with creatinin >200 umol/l
Above BP levels measured while on ≥3 antihypertensive drugs and compliance confirmed	Gravidity incl. potential
Age ≥18 years	Acute MI or acute stroke during last 6 months
Signed informed consent	Valvular stenosis
	Unfavourable anatomy of renal arteries
	Serious coagulation disorders (trombo < 50, INR > 1,5)

Unique features of the PRAGUE-15 study

- **24-h ABPM as primary evaluation method**
- **Lab exams for drug compliance before entering the study**
- **RDN effect can be compared with spironolactone effect**
- **Independent results analysis (treatment effect assessed in other hospital)**

Is it possible to assess RDN effect during/immediately after the procedure ?

- **NO !**

- Parameters of ***technically*** successfull procedure:
- Number of ablation sites ?
- Temperature increase ?
- Impedance decrease ?
- Tiny luminal irregularities ?

…….. and of course absence of complications !

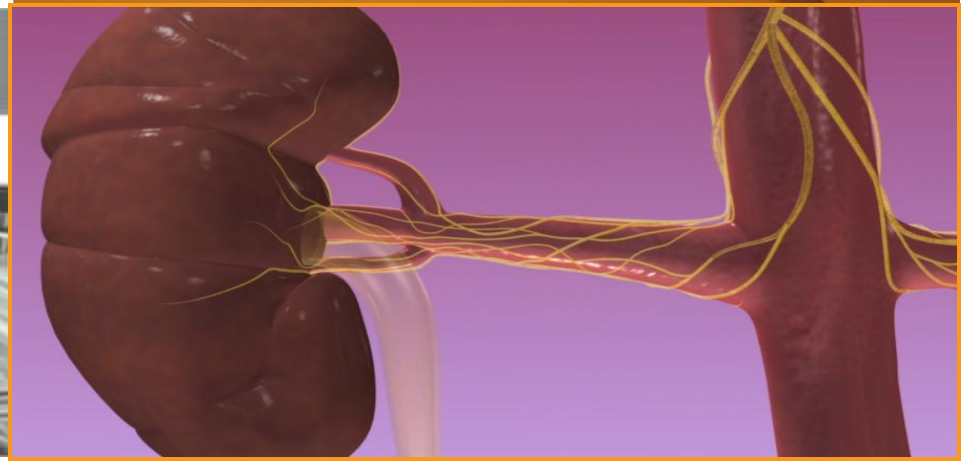
Initial 40 RDN procedures

- 1x renal artery dissection requiring stent implantation
- 2x arterial spasm (resolving after nitrates)
- 1x laryngospasm during analgosedation
- 3x incomplete procedure (anatomy)
- Mean nr. of ablations: 4.8 per artery
- Mean impedance fall: -13,8 Ω
- Mean achieved temperature: 52,4 °C

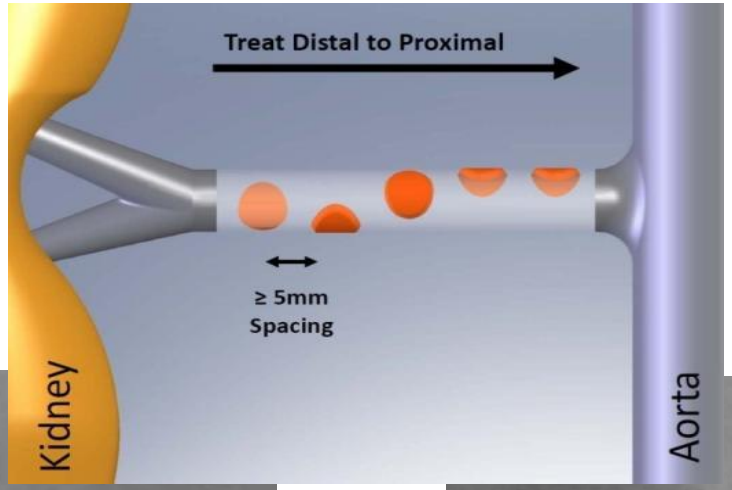
Summary of our initial experience

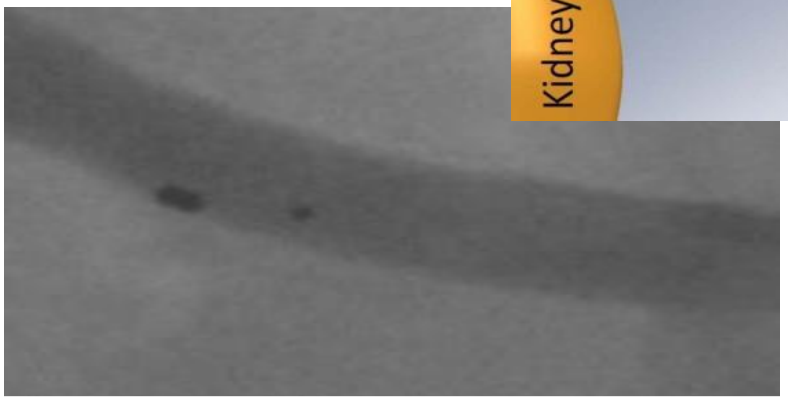
- **Method is technically simple**
- **Complication rate is low**
- **We cannot yet assess RDN effectivity**

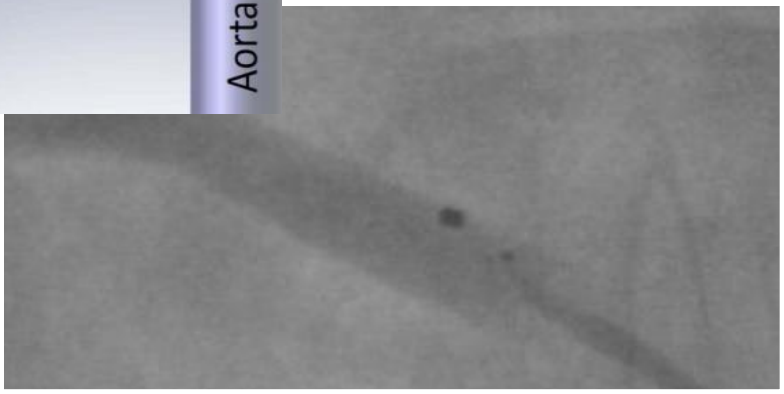
Medtronic Symplicity RF system

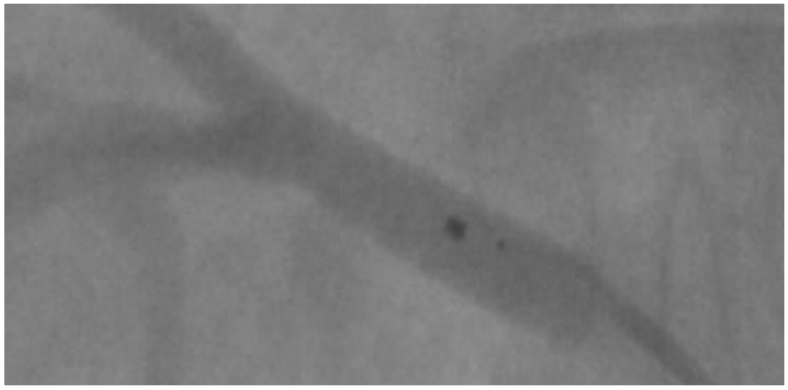


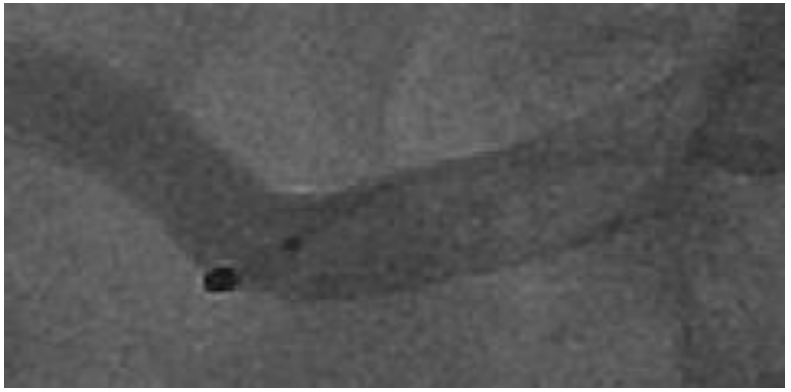
Vessel wall contact



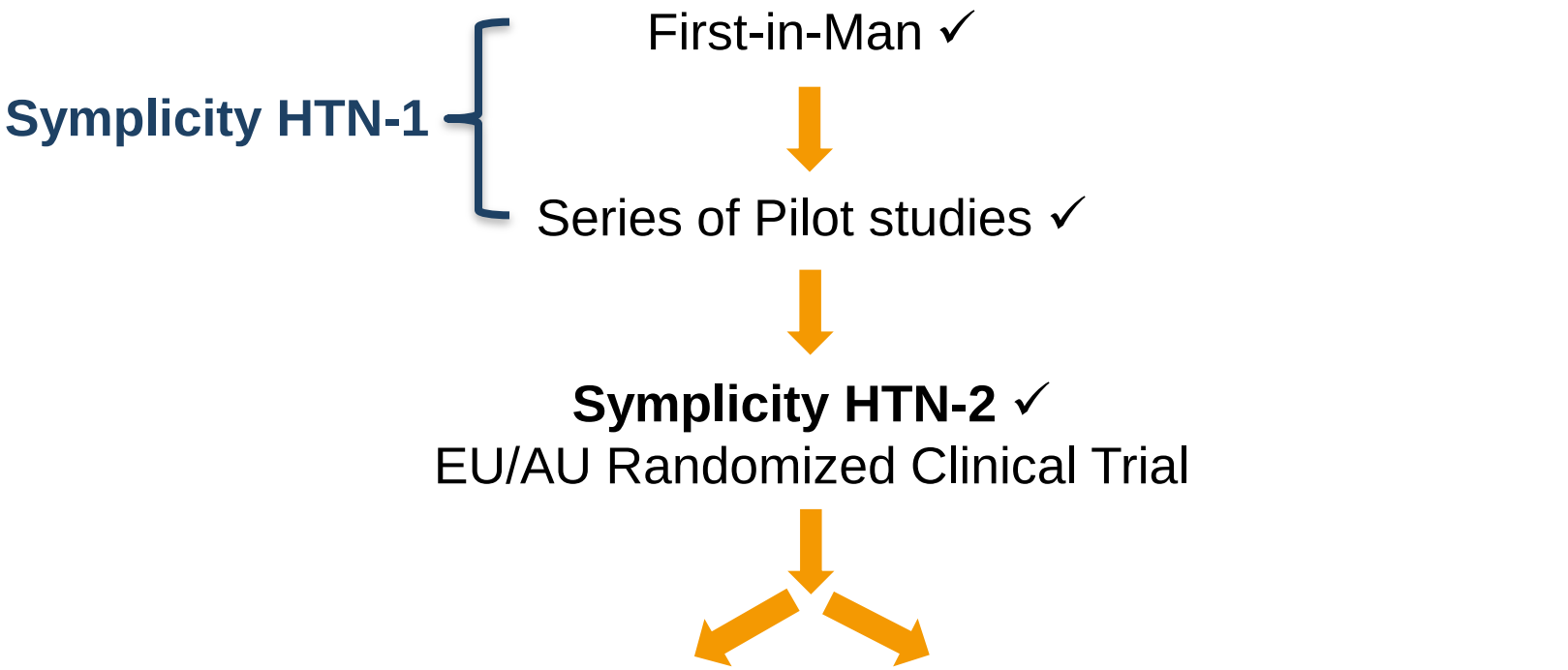








Staged Clinical Evaluation



Symplicity HTN-1


THE LANCET

Volume 373 · Number 9671 · Pages 1223-1310 · April 11-17, 2009 www.thelancet.com

Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobotka, Jerzy Sadowski, Krzysztof Bartus, Boguslaw Kapelak, Anthony Walton, Horst Sievert, Suku Thambar, William T Abraham, Murray Esler

Lancet. 2009;373:1275-1281

Initial Cohort – Reported in the *Lancet*, 2009:

-First-in-man, non-randomized

-Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)

- 12-month data

\

Expanded Cohort – This Report (Symplicity HTN-1):

-Expanded cohort of patients (n=153)

-24-month follow-up

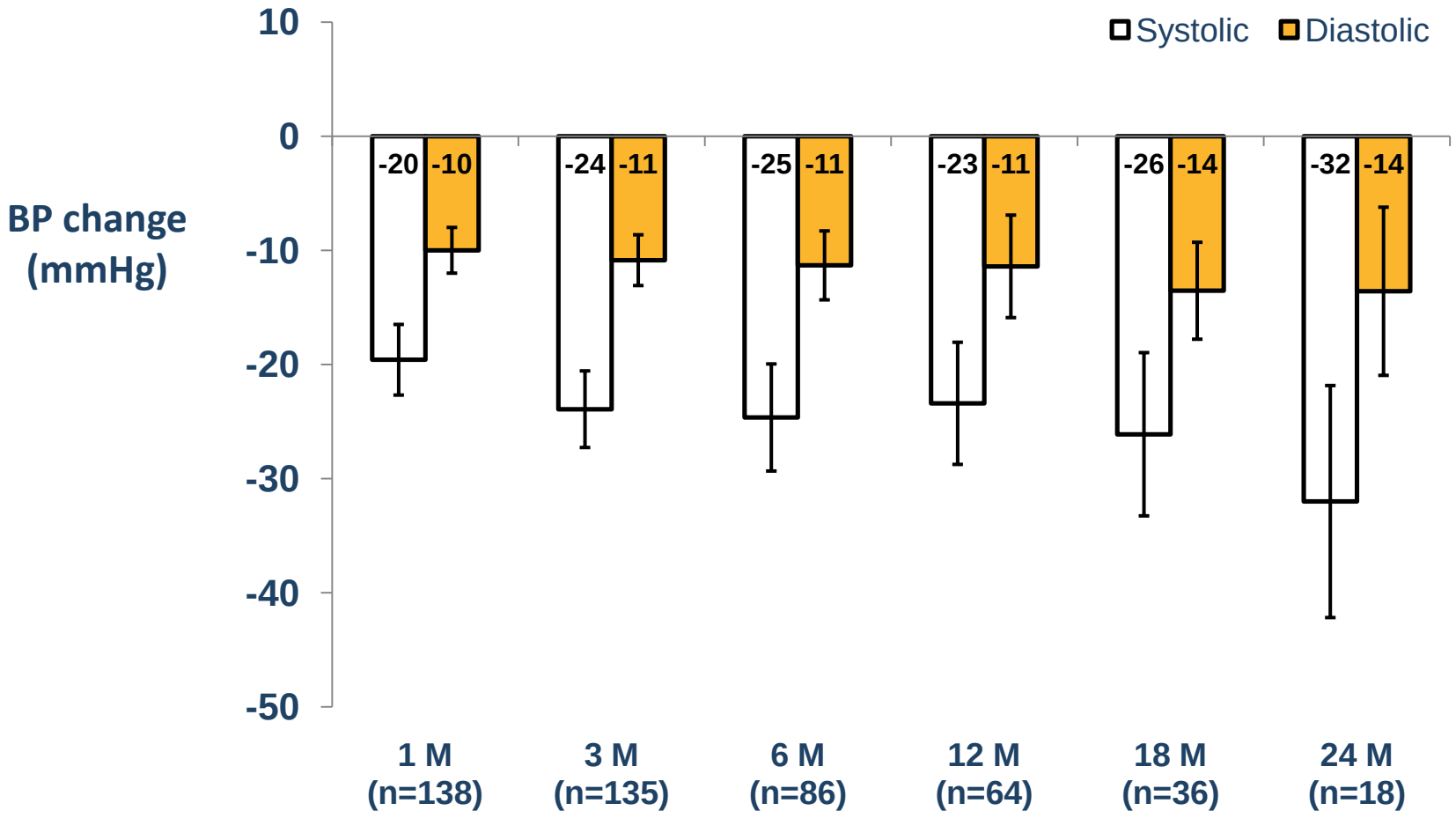
Sievert et al. European Society of Cardiology. 2010.

Baseline Patient Characteristics

Demographics	Age (years)	57 ± 11
	Gender (% female)	39%
	Race (% non-Caucasian)	5%
Co-morbidities	Diabetes Mellitus II (%)	31%
	CAD (%)	22%
	Hyperlipidemia (%)	68%
	eGFR (mL/min/1.73m^2)	83 ± 20
Blood Pressure	**Baseline BP (mmHg)**	**176/98 ± 17/15**
	Number of anti-HTN meds (mean)	**5.0 ± 1.4**
	ACE/ARB (%)	90%
	Beta-blocker (%)	82%
	Calcium channel blocker (%)	75%
	Vasodilator (%)	19%
	Diuretic (%)	95%
	Spironolactone (%)	21%

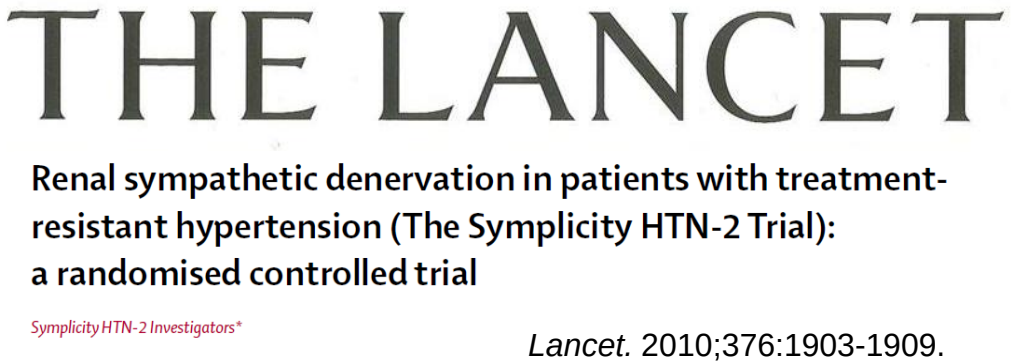
Sievert et al. European Society of Cardiology. 2010.

Significant, Sustained BP Reduction



Sievert et al. European Society of Cardiology. 2010.

Symplicity HTN-2


THE LANCET

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

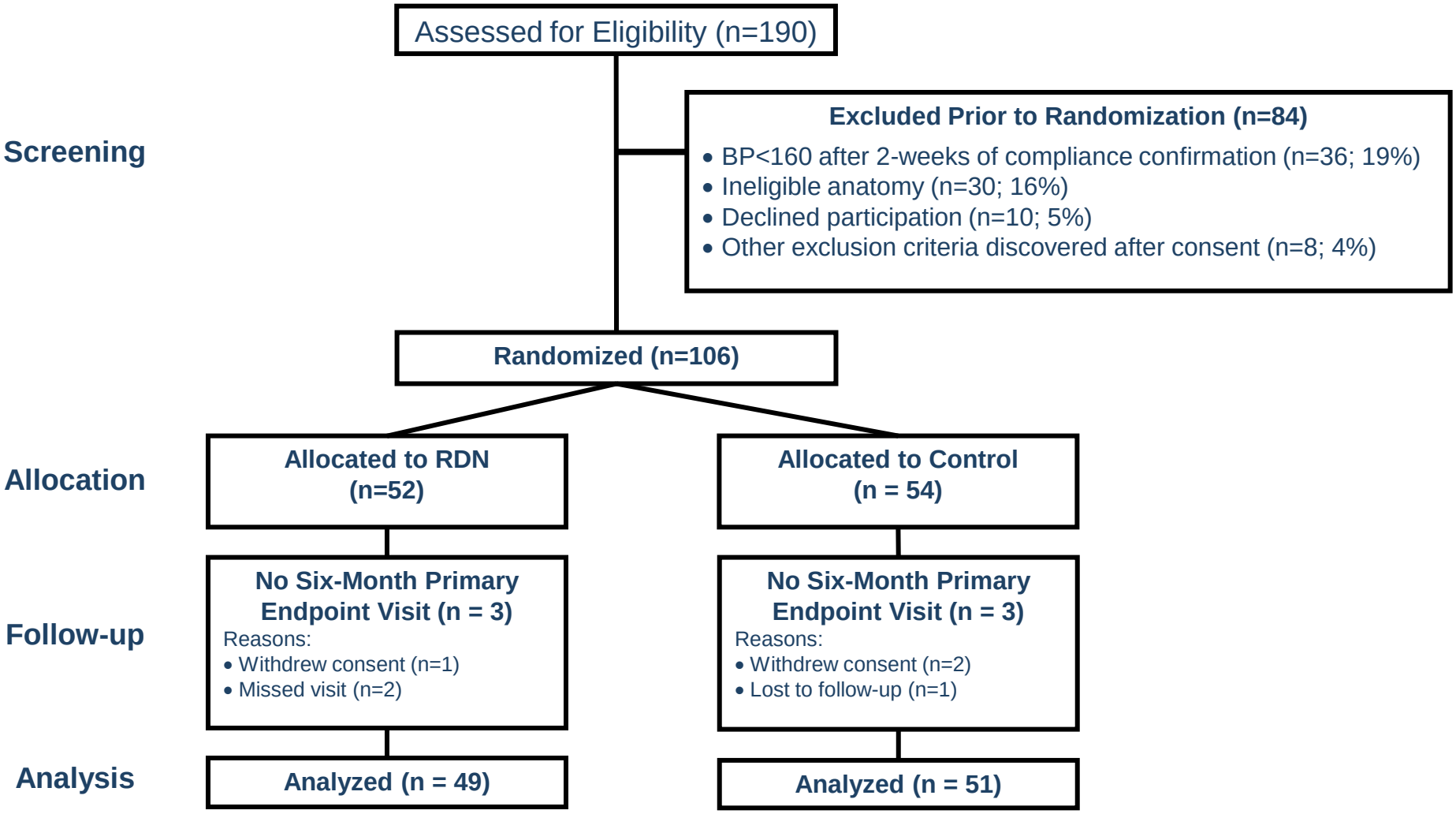
*Symplicity HTN-2 Investigators**

Lancet. 2010;376:1903-1909.

- **Purpose:** To demonstrate the effectiveness of catheter-based renal denervation for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial
- **Patients:** 106 patients randomized 1:1 to treatment with renal denervation vs. control
- **Clinical Sites:** 24 centers in Europe, Australia, & New Zealand (67% were designated hypertension centers of excellence)

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Patient Disposition



Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Baseline Characteristics

	RDN (n=52)	Control (n=54)	p-value
Baseline Systolic BP (mmHg)	178 ± 18	178 ± 16	0.97
Baseline Diastolic BP (mmHg)	97 ± 16	98 ± 17	0.80
Age	58 ± 12	58 ± 12	0.97
Gender (% female)	35%	50%	0.12
Race (% Caucasian)	98%	96%	>0.99
BMI (kg/m^2)	31 ± 5	31 ± 5	0.77
Type 2 diabetes	40%	28%	0.22
Coronary Artery Disease	19%	7%	0.09
Hypercholesterolemia	52%	52%	>0.99
eGFR (MDRD, $ml/min/1.73m^2$)	77 ± 19	86 ± 20	0.013
eGFR 45-60 (% patients)	21%	11%	0.19
Serum Creatinine (mg/dL)	1.0 ± 0.3	0.9 ± 0.2	0.003
Urine Alb/Creat Ratio (mg/g)†	128 ± 363	109 ± 254	0.64
Cystatin C (mg/L)††	0.9 ± 0.2	0.8 ± 0.2	0.16
Heart rate (bpm)	75 ± 15	71 ± 15	0.23

† n=42 for RDN and n=43 for Control, Wilcoxon rank-sum test for two independent samples used for between-group comparisons of UACR
†† n=39 for RDN and n=42 for Control

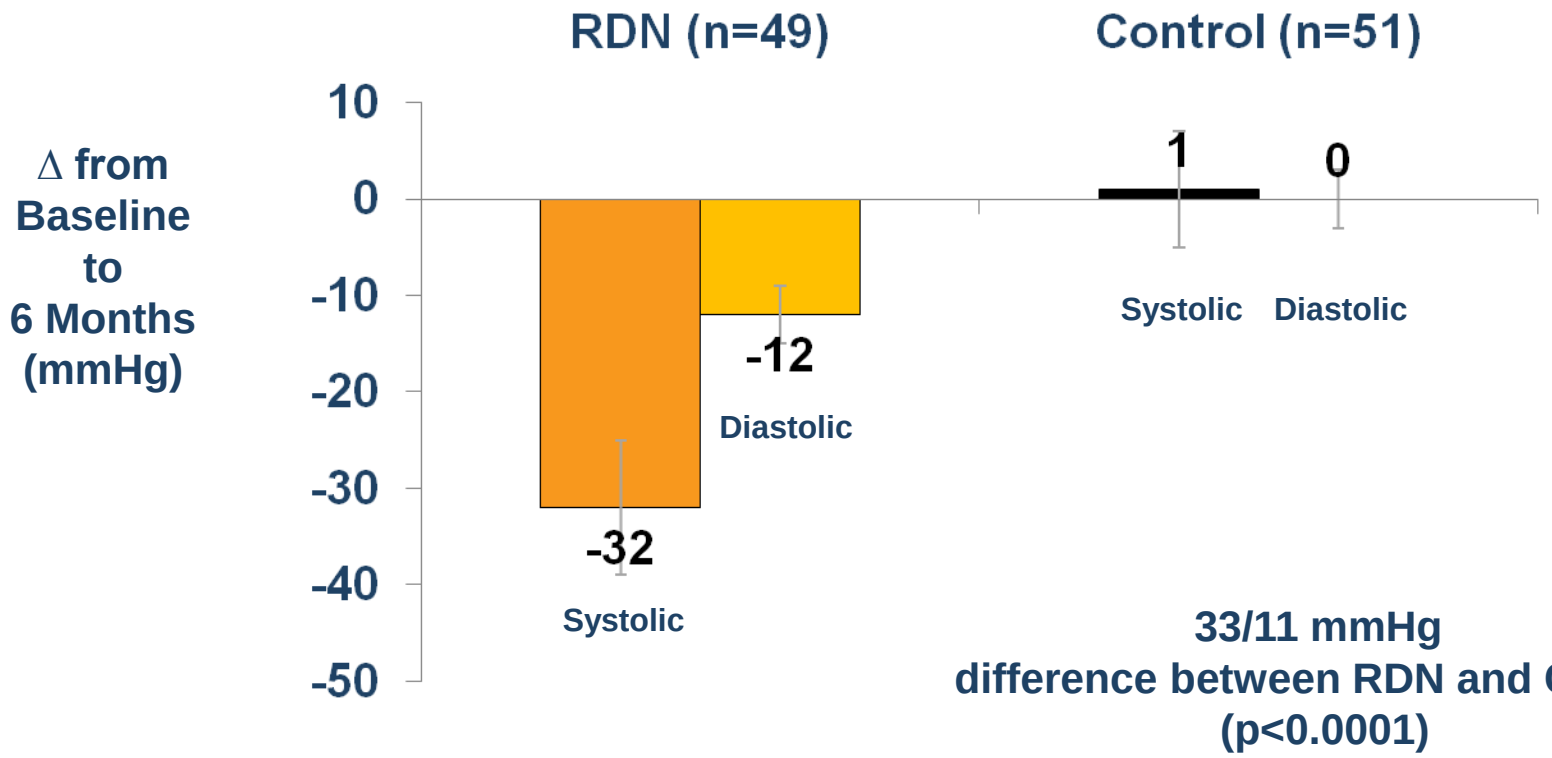
Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Baseline Medications

	RDN (n=52)	Control (n=54)	p-value
Number Anti-HTN medications	5.2 ± 1.5	5.3 ± 1.8	0.75
% patients on HTN meds >5 years	71%	78%	0.51
% percent patients on ≥5 medications	67%	57%	0.32
% patients on drug class:			
ACEi/ARB	96%	94%	>0.99
Direct renin inhibitor	15%	19%	0.80
Beta-adrenergic blocker	83%	69%	0.12
Calcium channel blocker	79%	83%	0.62
Diuretic	89%	91%	0.76
Aldosterone antagonist	17%	17%	>0.99
Vasodilator	15%	17%	>0.99
Alpha-1 adrenergic blocker	33%	19%	0.12
Centrally acting sympatholytic	52%	52%	>0.99

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

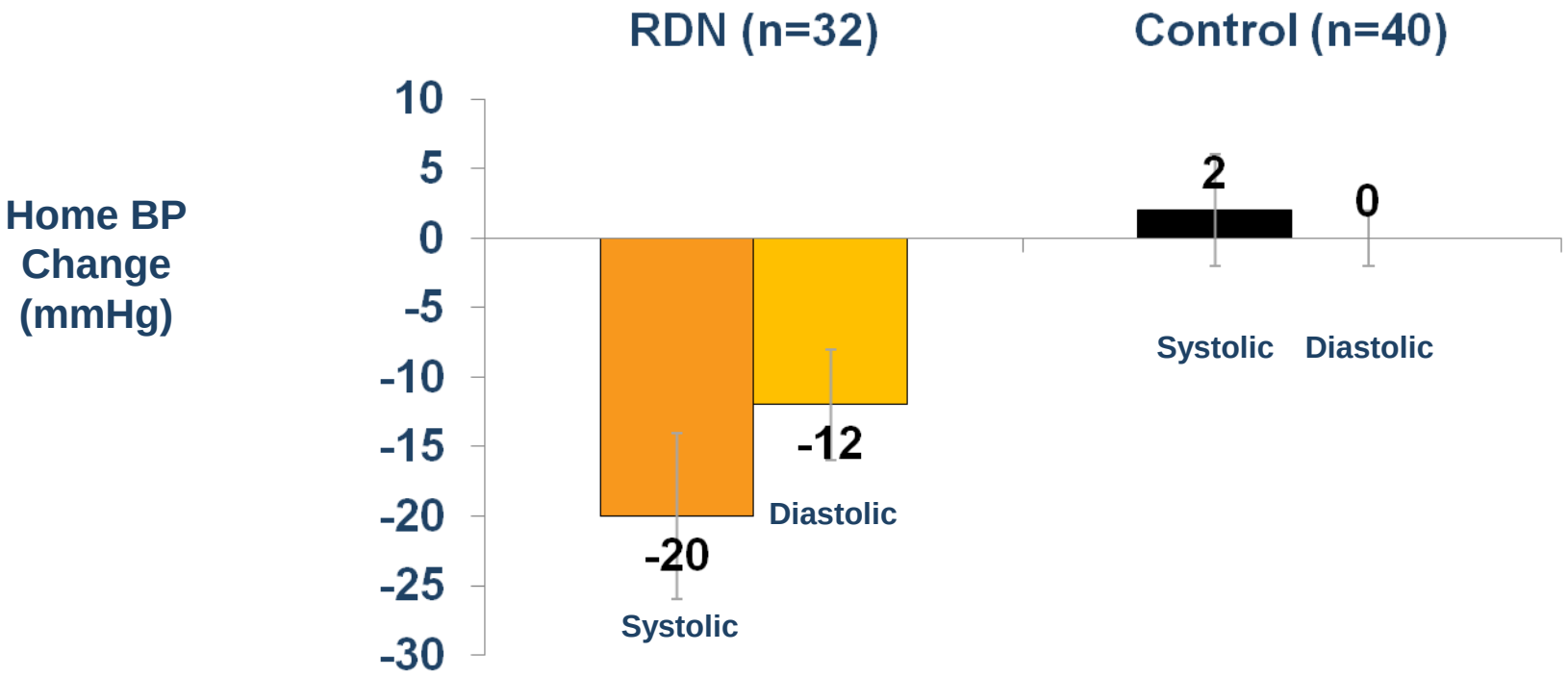
Primary Endpoint: 6-Month Office BP



- 84% of RDN patients had ≥ 10 mmHg reduction in SBP
- 10% of RDN patients had no reduction in SBP

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Home & 24 Hour Ambulatory BP

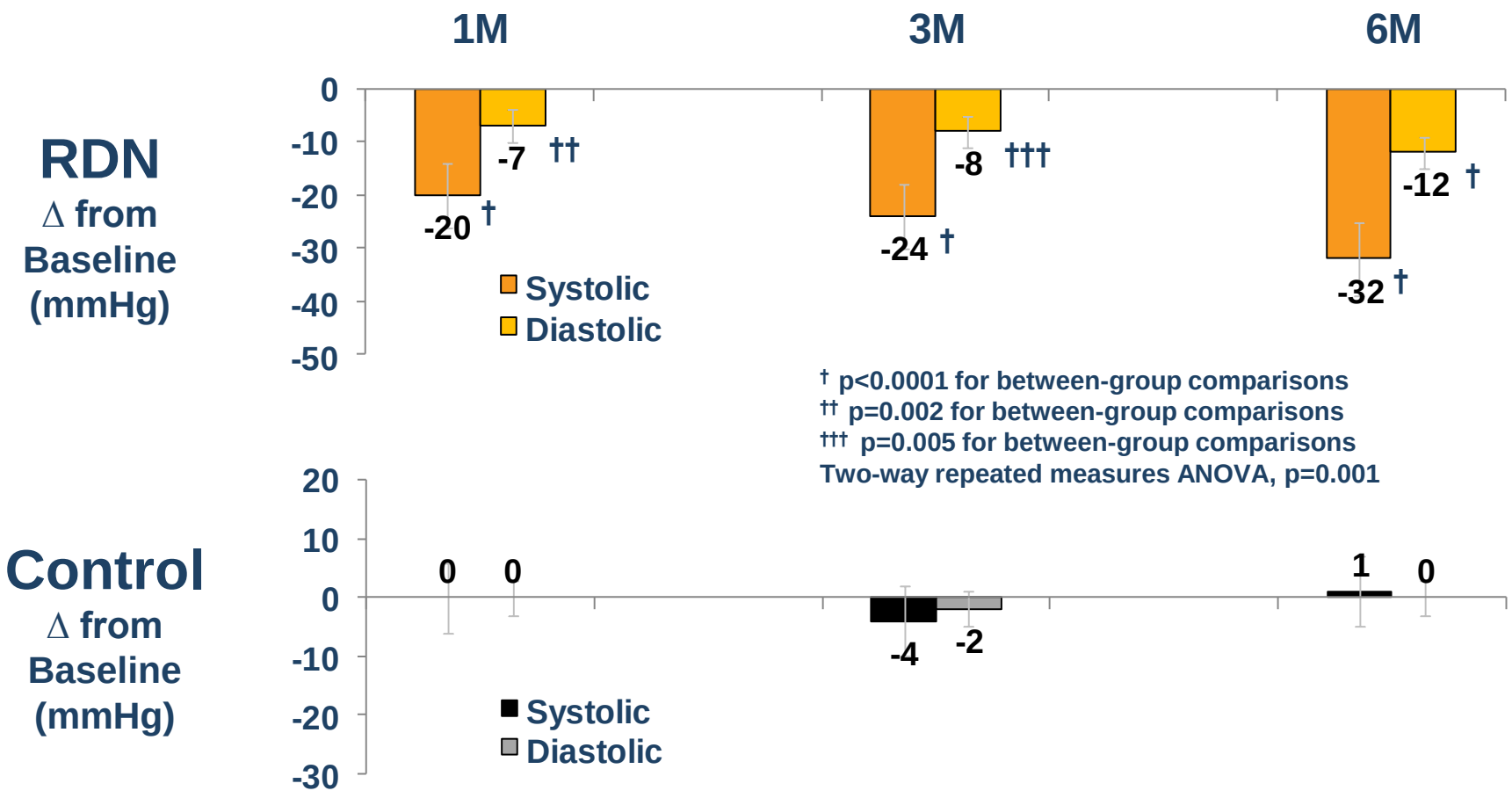


24-h ABPM:

- Analysis on technically sufficient (>70% of readings) paired baseline and 6-month
- RDN (n=20): -11/-7 mmHg (SD 15/11; p=0.006 SBP change, p=0.014 for DBP change)
- Control (n=25): -3/ -1 mmHg (SD 19/12; p=0.51 for systolic, p=0.75 for diastolic)

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Time Course of Office BP Change



Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Procedural Safety

- No serious device or procedure related adverse events (n=52)
- Minor adverse events
  - 1 femoral artery pseudoaneurysm treated with manual compression
  - 1 post-procedural drop in BP resulting in a reduction in medication
  - 1 urinary tract infection
  - 1 prolonged hospitalization for evaluation of paraesthesias
  - 1 back pain treated with pain medications & resolved after one month
- 6-month renal imaging (n=43)
  - No vascular abnormality at any RF treatment site
  - 1 MRA indicates possible progression of a pre-existing stenosis unrelated to RF treatment (no further therapy warranted)

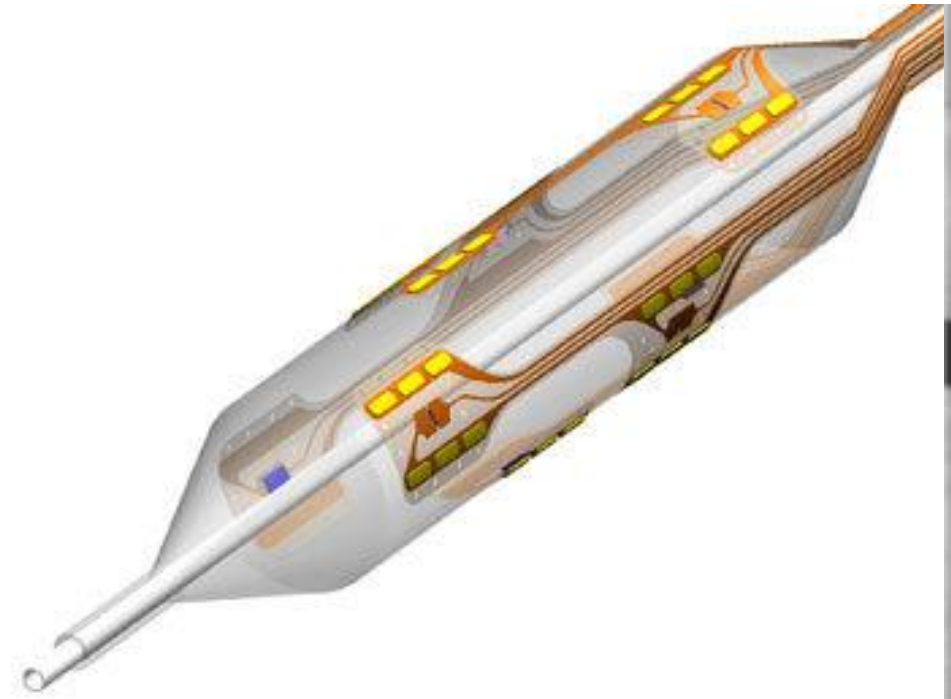
Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

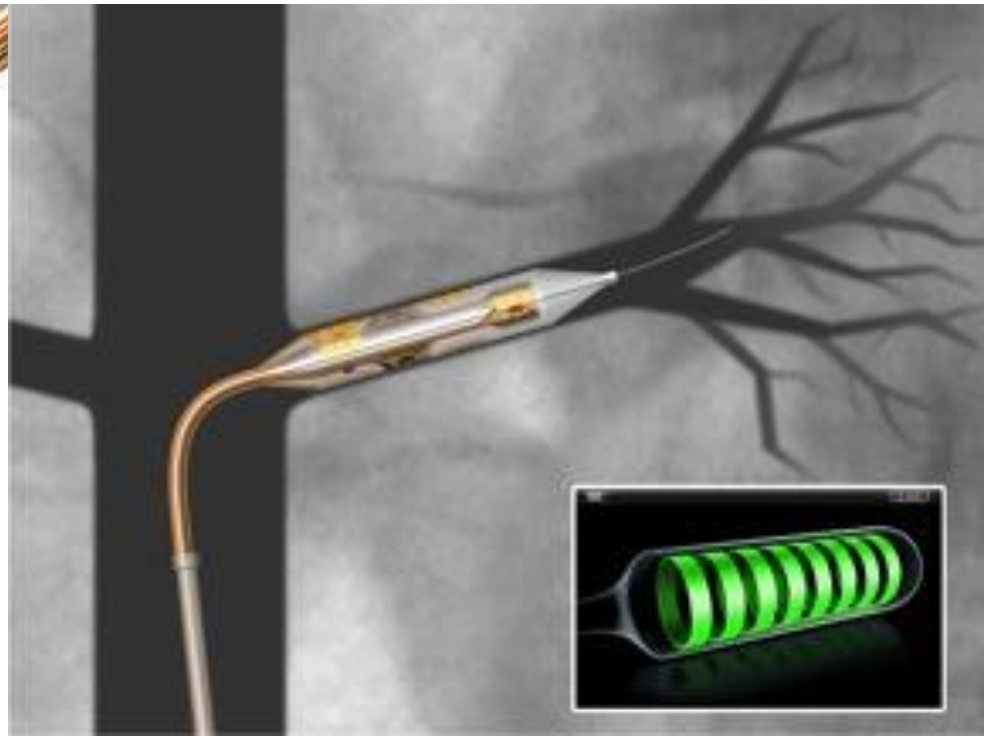
Lancet Conclusions

- Catheter-based renal denervation, done in a multicentre, randomised trial in patients with treatment-resistant essential hypertension, resulted in significant reductions in BP.
- The magnitude of BP reduction can be predicted to affect the development of hypertension-related diseases and mortality
- The technique was applied without major complications.
- This therapeutic innovation, based on the described neural pathophysiology of essential hypertension, affirms the crucial relevance of renal nerves in the maintenance of BP in patients with hypertension.
- Catheter-based renal denervation is beneficial for patients with treatment-resistant essential hypertension.

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Other technical approches to renal denervation.
CE-marked systems



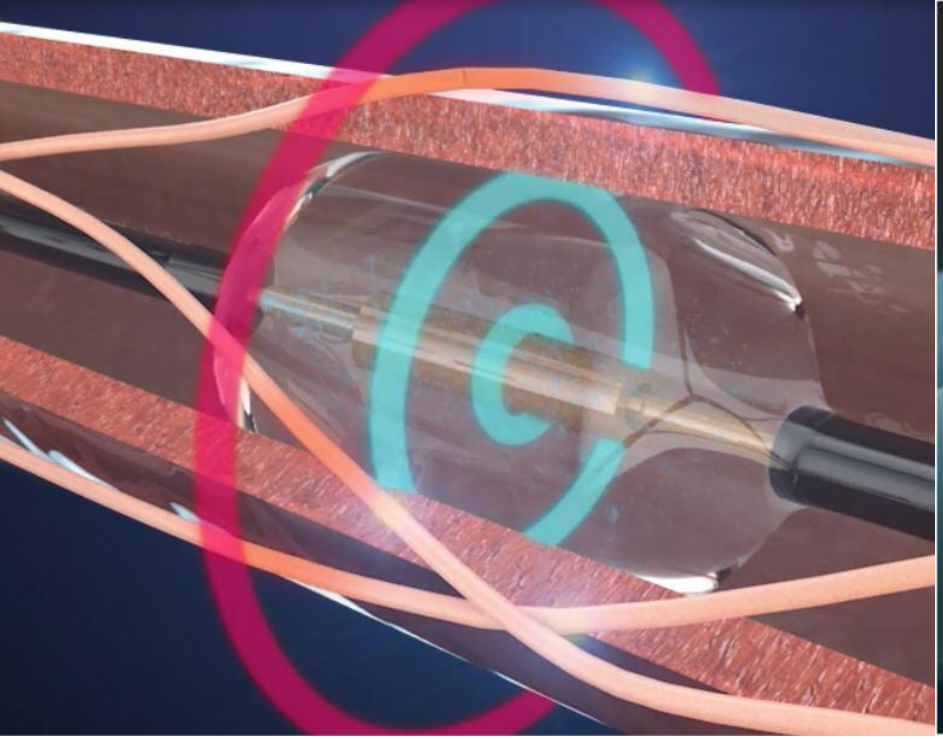


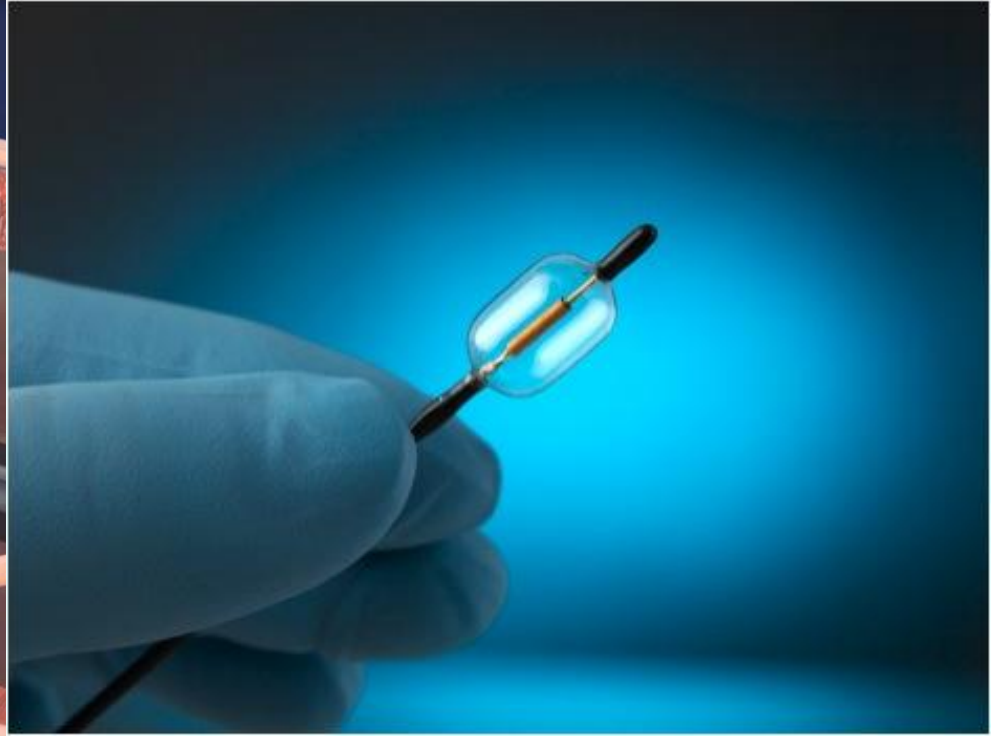
Boston Scientific Vessix Renal Denervation System™

over-the-wire balloon catheter
array of radiofrequency electrodes
proprietary bipolar radiofrequency generator
balloon occludes blood flow 30 seconds during RF delivery
V2 is significantly faster then Symplicity.

St. Jude Medical EnligHTN™

Covidien's RHAS (Renal Hypertension Ablation System)
Covidien OneShot™





ReCor Medical PARADISE™
(Percutaneous Renal Denervation System)

F Mahfoud, SE Kjeldsen: Catheter-based renal denervation: a word of caution.

EuroIntervention 2013 Jan 22;8(9).

- The largest –albeit in patient numbers still limited– clinical experience with the longest follow-up has been obtained with the Symplicity catheter system.
- Device selection: 1) Advantages and disadvantages of the available CE-marked devices for catheter-based renal denervation ? 2) Interventional features (duration, radiation, sheath diameter 6-9F) of different technologies ? 3) Differences in clinical outcomes ? 4) Effectivity vs. complication rates ?

- In the light of the huge market for renal denervation systems, a word of caution is required. All devices have to show favourable safety and efficacy profiles in a larger cohort of patients with subsequent follow-up before general use can be recommended.
- Recently, concerns have been raised that renal denervation might induce renal artery stenosis (Kaltenbach B et al. JACC 2012 Oct 24 Epub ahead of print).
- **Therefore, clinical data on the long-term vascular safety in a large cohort of patients –for each of the devices– is needed in order definitely to determine the role of renal denervation in antihypertensive therapy.**

Mulder J et al. **Renal Sensory and Sympathetic Nerves Reinnervate the Kidney in a Similar Time Dependent Fashion Following Renal Denervation in Rats.**

Karolinska Institut, Stockholm, Sweden.

Am J Physiol Regul Integr Comp Physiol 2013 Feb 13. [Epub ahead of print]

- **Conclusion: in normotensive rats, reinnervation of the renal sensory nerves occurs over the same time course as reinnervation of the renal sympathetic nerves, both being complete at 9 to 12 weeks following renal denervation.**

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Expert consensus statement

Expert consensus statement of the Czech Society of Cardiology and the Czech Society of Hypertension on catheter-based sympathetic renal denervation procedures (RDN) in the Czech Republic

P. Widimský[a,*], J. Filipovský[b], J. Widimský Jr.[b], M. Branny[a], V. Monhart[b], M. Táborský[a]

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ABSTRACT

The Czech Society of Cardiology and the Czech Society for Hypertension provide an expert consensus statement on the implementation of catheter based renal denervation in the Czech Republic. Conclusion: until additional and/or larger randomized clinical trials confirm (or not) the promising results of initial studies, renal denervation can be performed exclusively as part of specific research protocols, approved by ethical committees. Renal denervation should be performed only in tertiary centers with ongoing research and publication activity to guarantee, that the results will be objectively and critically evaluated. It is unethical to promote this method already today (early 2012) for routine hypertensive patients as a standard (proven) part of their treatment. Each patient must be informed, that renal denervation still is in the phase of clinical research.