What can we do when other therapies fail?: The HTN Guidelines

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BAROSTIM THERAPY SUMMIT
September 30th, 2017 • Radisson Blu, Berlin, Germany

CHARITE – UNIVERSITÄTSMEDIZIN BERLIN
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Agenda

- Hypertension Treatment Overview
- Therapeutic Options

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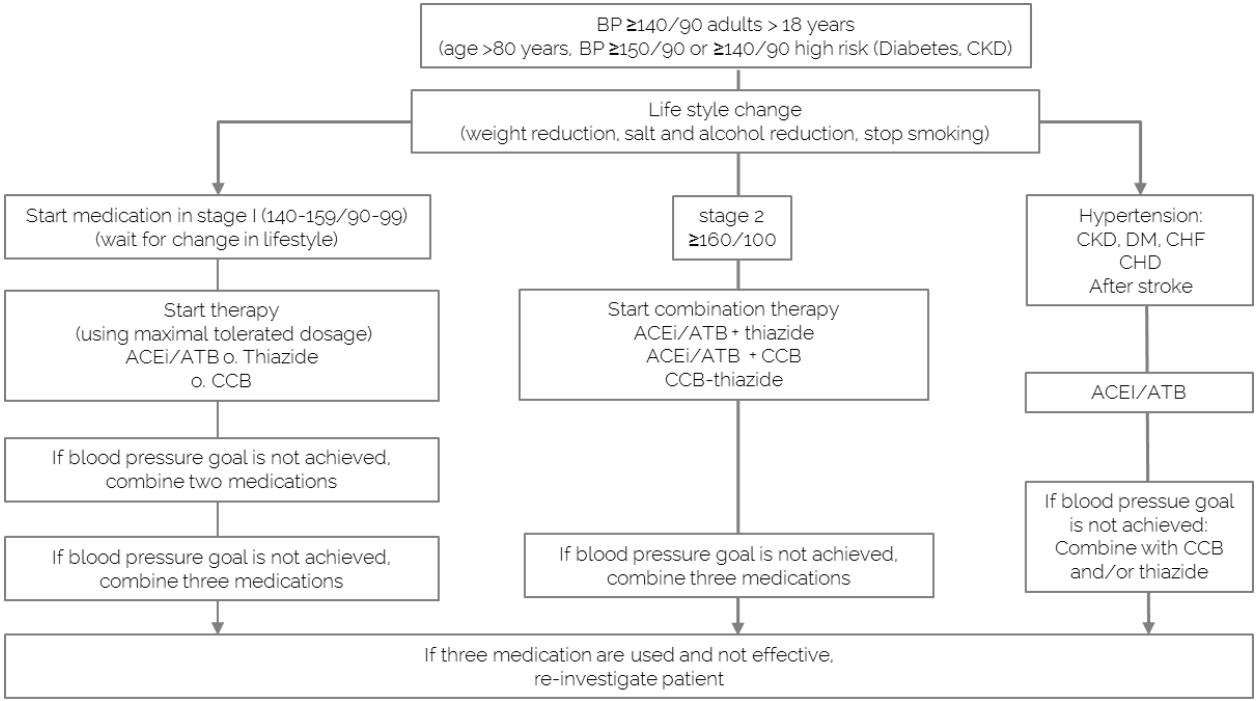
Hypertension Treatment Algorithm



van der Giet, Der Nephrologe, 2014

The definition of “therapy-resistant hypertension“ is difficult-to-treat hypertension

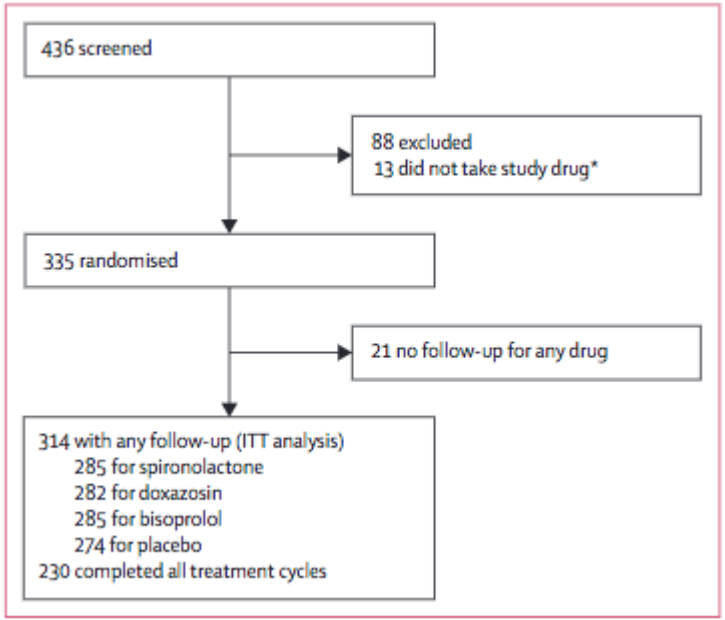
- Blood pressure above treatment goals using triple medication including thiazide in maximum tolerated dosage

Reevaluation of patient

1. Compliance? (e.g. check medication in urine)
2. Any signs of secondary hypertension (including OSAS, Hyperaldosteronism, interacting medication etc.)
3. Optimisation of life style (reducing salt consumption etc.)

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2)

A RANDOMIZED, DOUBLE-BLIND CROSSOVER TRIAL



Lancet 2015; 386: 2059-68

- Patienten hatten max. toleriert ACD und bekamen für jeweils 12 Wochen (nach 6 Wochen Dosiseskalation) jeweils nach einem rollierenden Schema die vier zusätzlichen Medikamente

- Patienten (sitzend) mit Blutdruck von >140 mmHg syst. bzw. >135 mmHg syst. (Diabetes)

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2)

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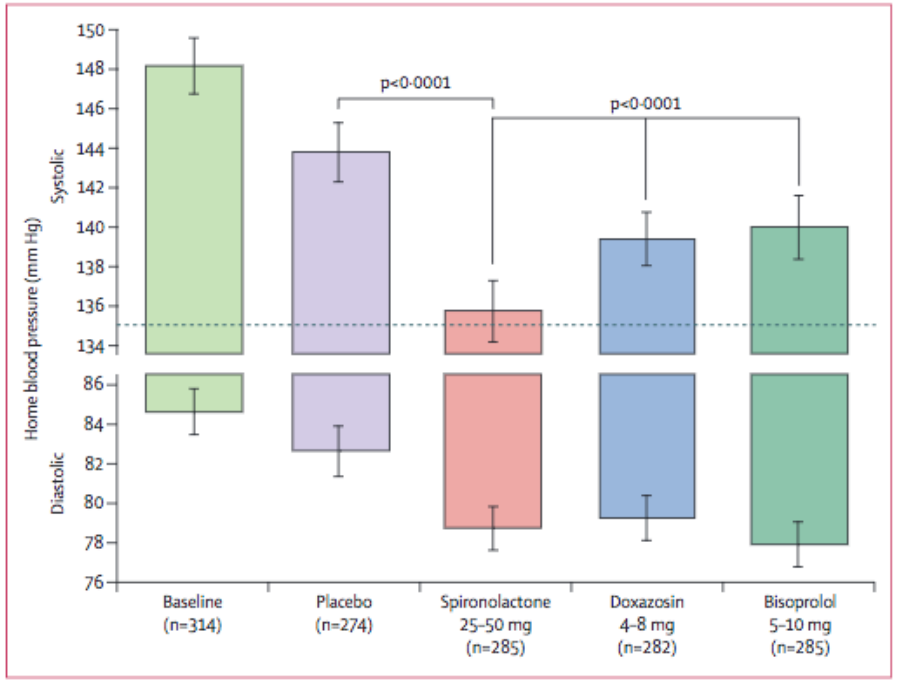


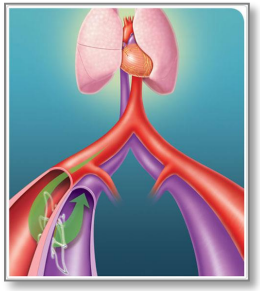
Lancet 2015; 386: 2059-68

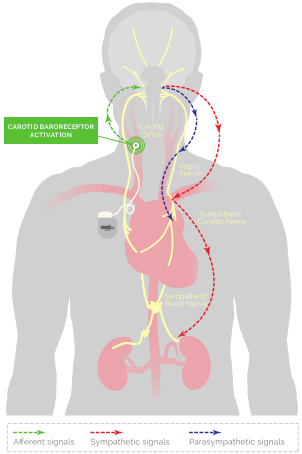
What next?

- Clonidin
- Moxonidin
- Minoxidil
- etc.

Device-based therapies to treat hypertension

- Electric renal denervation
- Ethanol renal denervation (under development)
- Ultrasound renal denervation
- ROX-Coupler
- Passive baroreceptor stimulation
- Electric baroreceptor stimulation





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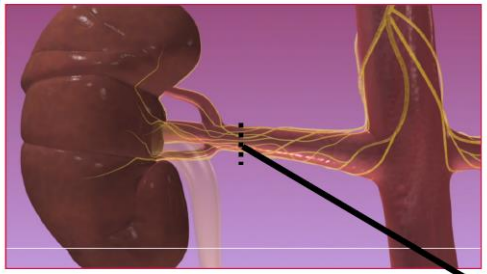
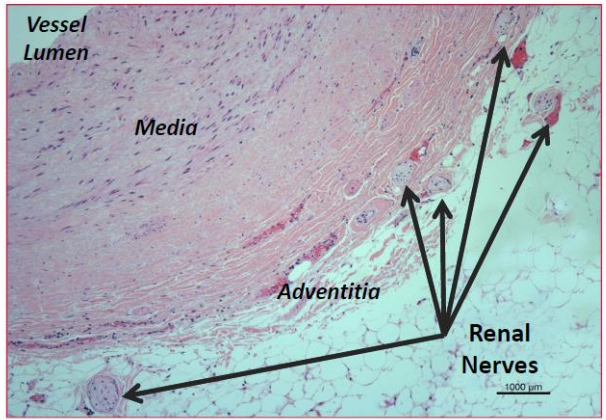
Renal Denervation
ELECTRIC

Renal Anatomy Allows a Catheter-Based Approach

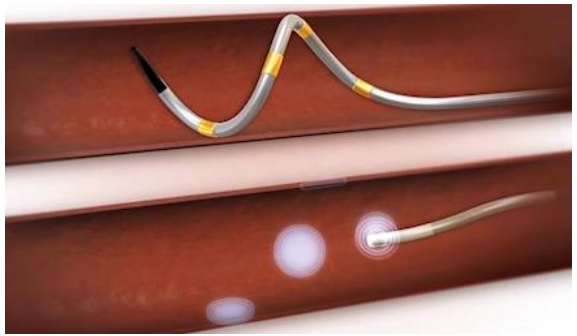


- Arise from T10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia
- The only location that renal efferent & afferent nerves travel together

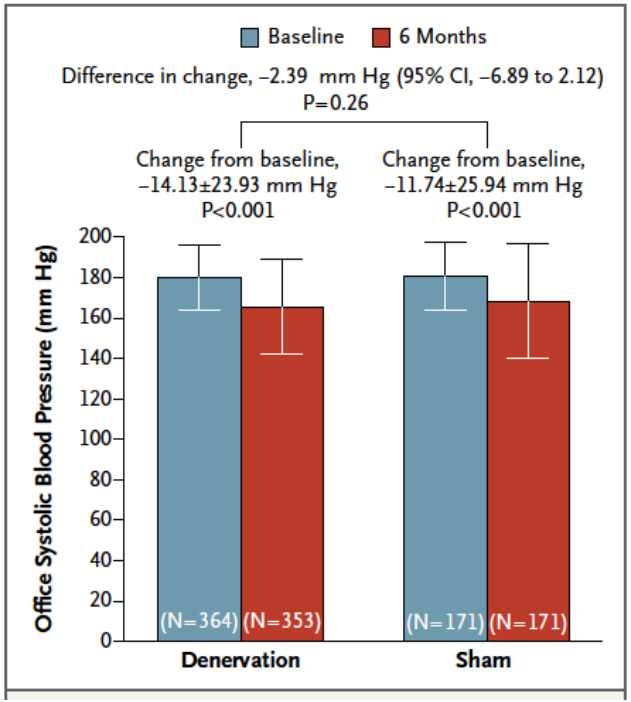


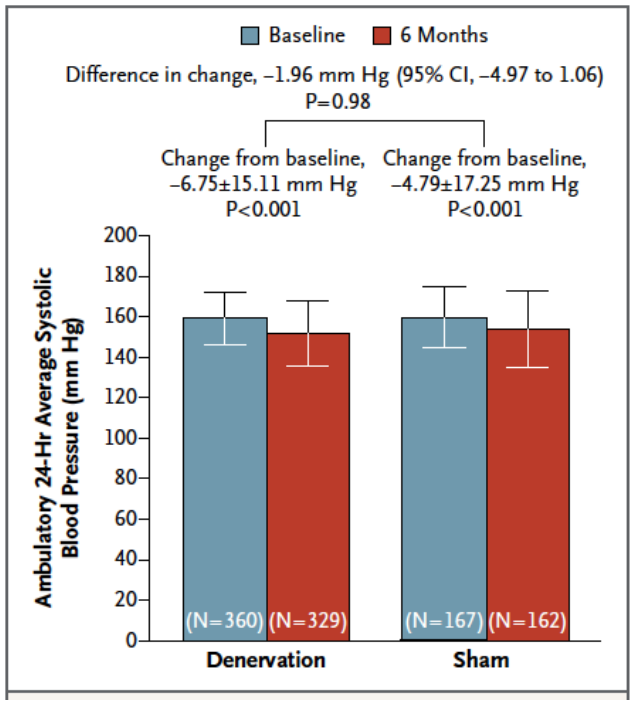
Schlaich, ESH 2010

One-point (old model) or Multi-point-Ablation (Spyral)



A Controlled Trial of Renal Denervation for Resistant Hypertension

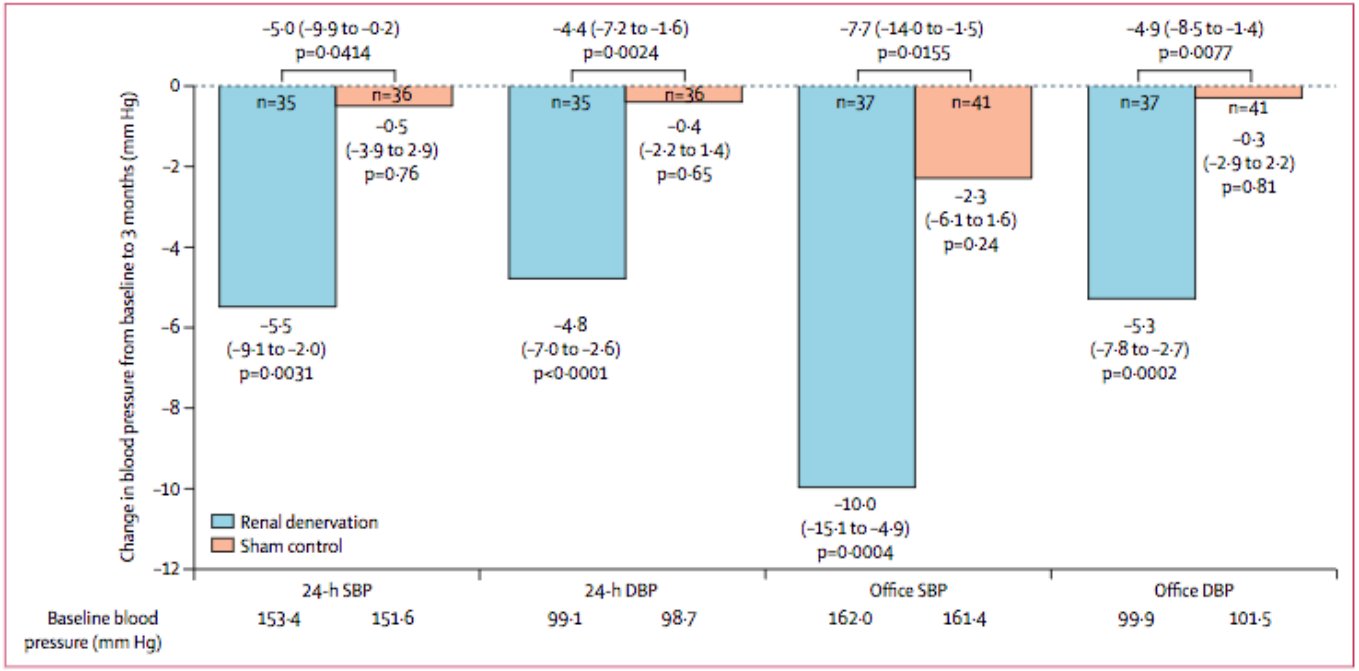




N Engl J Med 2014;370:1393-401.

Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED)

A RANDOMISED, SHAM-CONTROLLED, PROOF OF CONCEPT TRIAL



www.thelancet.com **Published online August 28, 2017**

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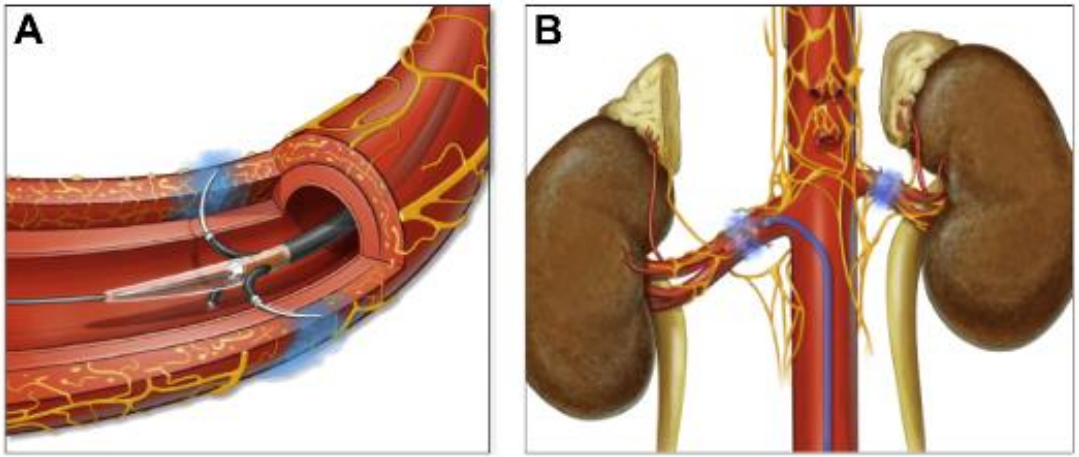
- Therapeutic Options:
  - Electric renal denervation
  - **Ethanol renal denervation**
  - Ultrasound renal denervation
  - ROX-Coupler
  - Passive baroreceptor stimulation
  - Electric baroreceptor stimulation

BAROSTIM THERAPY™

Transcatheter Alcohol-mediated Perivascular Renal Denervation with Peregrine System

FIRST-IN-HUMAN EXPERIENCE



JACC: CARDIOVASCULAR INTERVENTIONS VOL. 9, NO. 6, 2016

Tim A. Fischell, MD,[a,b] Adrian Ebner, MD,[c] Santiago Gallo, MD,[c] Fumiaki Ikeno, MD,[d] Laura Minarsch, RT,[e] Félix Vega, VMD,[f] Nicole Haratani, RN, BSN,[b] Vartan E. Ghazarossian, PhD[b]

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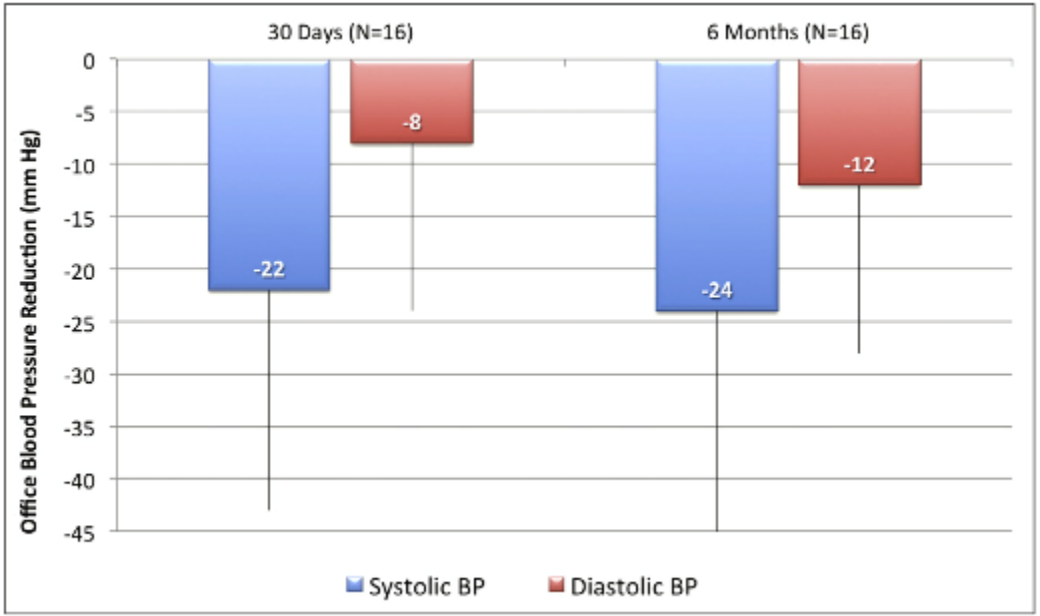

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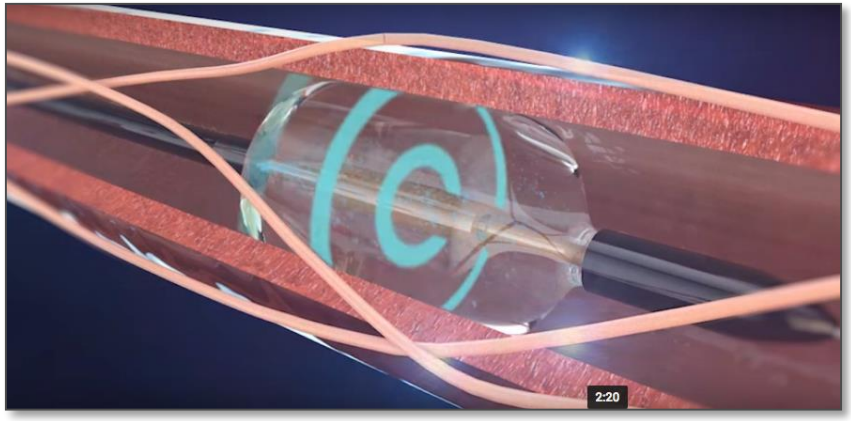
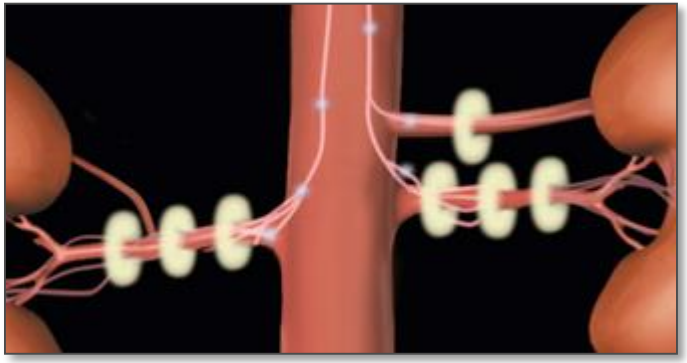
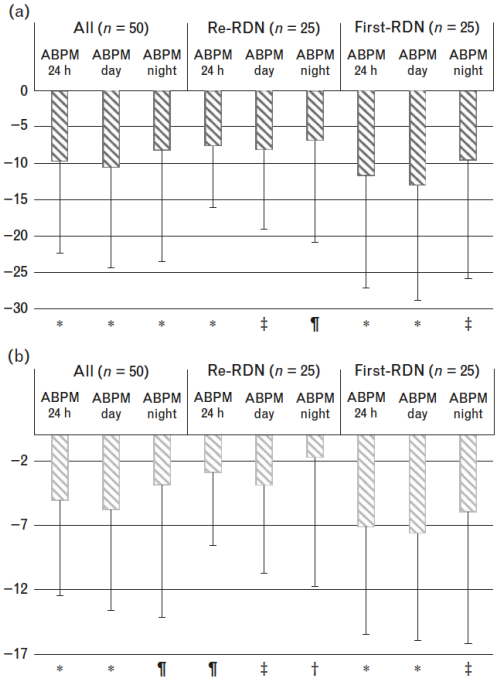
Paradise Renal Denervation Catheter





Ultrasound-based renal sympathetic denervation for the treatment of therapy-resistant hypertension

A SINGLE-CENTER EXPERIENCE



	Nonresponder, $n = 19$	Responder, $n = 31$	P value
Office blood pressure			
SBP (mmHg)	169.4 ± 16.0	174.1 ± 26.5	0.54
DBP (mmHg)	83.5 ± 18.0	95.0 ± 17.0	0.051
Ambulatory blood pressure			
SBP			
General (mmHg)	149.1 ± 9.1	155.6 ± 13.6	0.074
Daytime (mmHg)	151.4 ± 8.3	158.2 ± 13.1	0.054
Night-time (mmHg)	142.4 ± 14.0	148.9 ± 19.2	0.214
DBP			
General (mmHg)	79.7 ± 11.9	87.3 ± 11.6	0.034
Daytime (mmHg)	81.8 ± 11.8	89.3 ± 11.8	0.039
Night-time (mmHg)	73.2 ± 13.5	82.1 ± 12.6	0.025
Isolated systolic hypertension (%)	14 (74)	19 (61)	0.37

J Hypertens 35:1310–1317 Copyright © 2017

Karl Fengler[a], Robert Höllriegel[a], Thomas Okon[a], Thomas Stiermaier[b], Karl-Philipp Rommel[a], Stephan Blazek[a], Christian Besler[a], Max von Roeder[a], Martin Petzold[a], Gerhard Schuler[a], and Philipp Lurz[a]

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  - Passive baroreceptor stimulation
  - Electric baroreceptor stimulation

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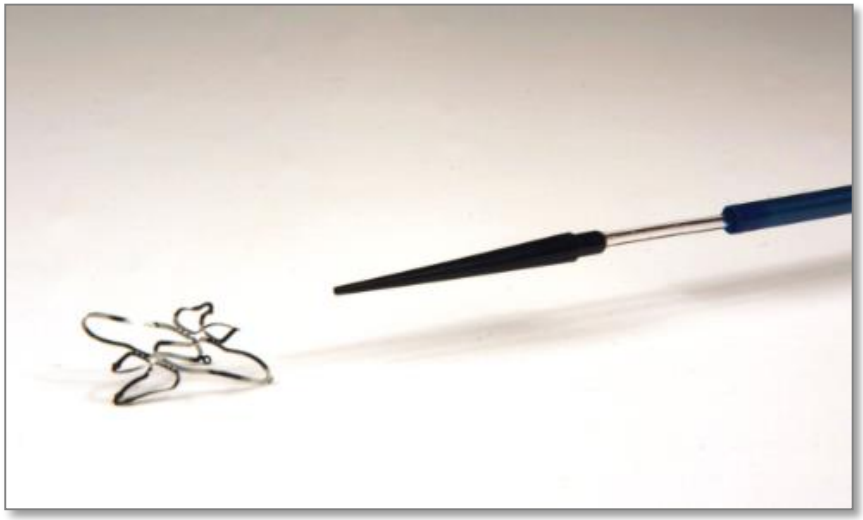
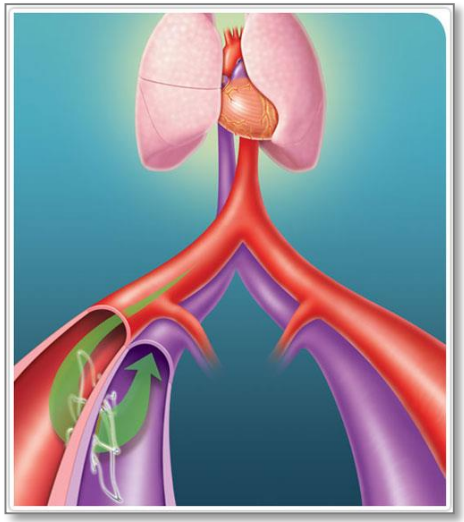
Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study)

A RANDOMISED CONTROLLED TRIAL





Lancet 2015; 385: 1634–41

*Melvin D Lobo, Paul A Sobotka, Alice Stanton, John R Cockcroft, Neil Sulke, Eamon Dolan, Markus van der Giet, Joachim Hoyer, Stephen S Furniss, John P Foran, Adam Witkowski, Andrzej Januszewicz, Danny Schoors, Konstantinos Tsioufis, Benno J Rensing, Benjamin Scott, G André Ng, Christian Ott, Roland E Schmieder, for the ROX CONTROL HTN Investigators**

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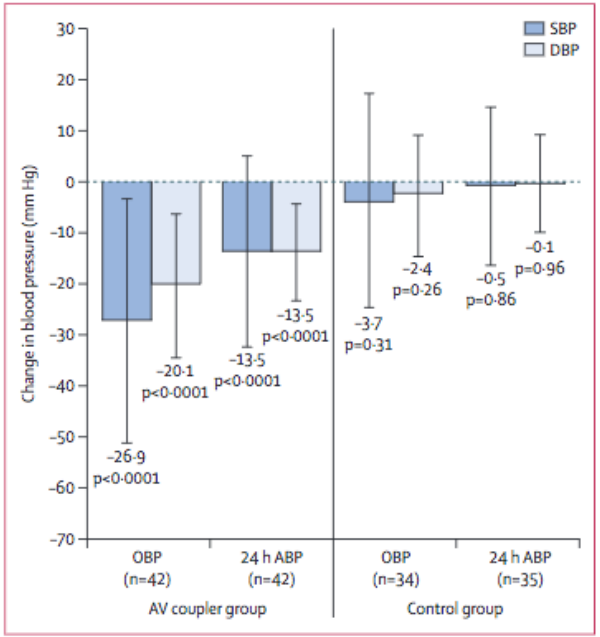

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  - Electric baroreceptor stimulation

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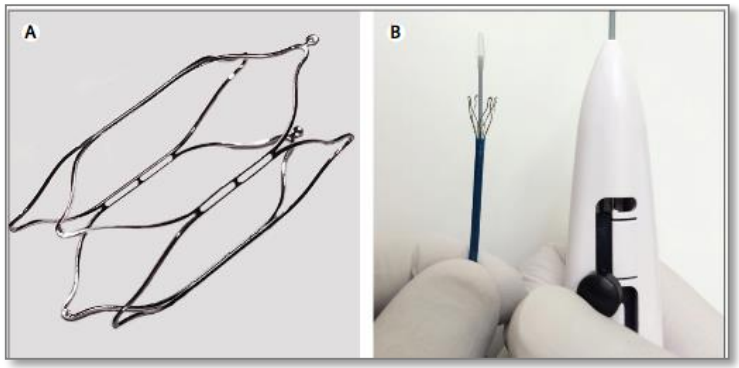
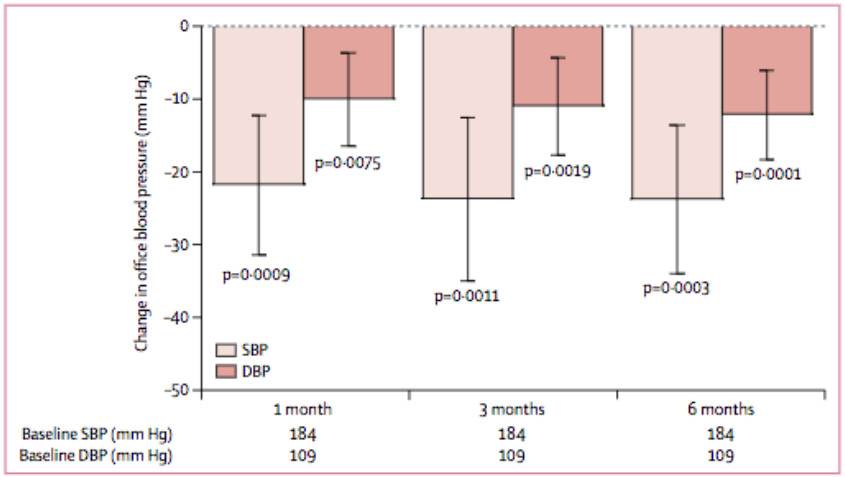
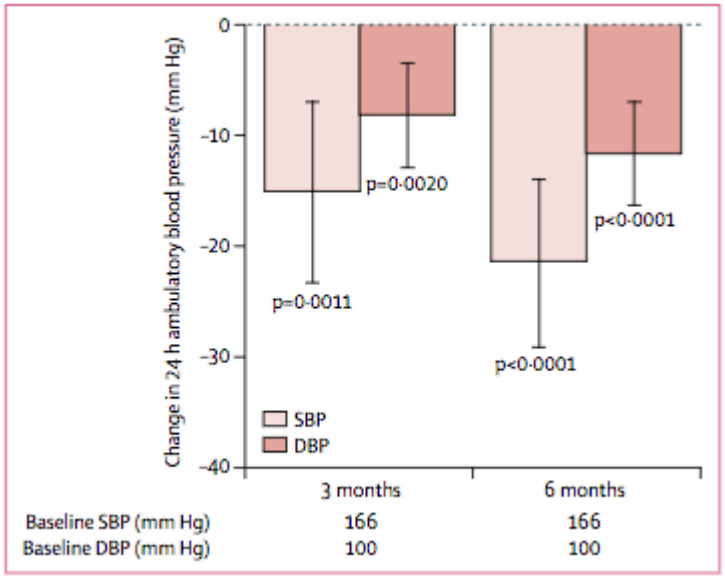
Mobius HD



Endovascular baroreflex amplification for resistant hypertension

A SAFETY AND PROOF-OF-PRINCIPLE CLINICAL STUDY





n=30 patients

www.thelancet.com **Published online September 1, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32337-1**

*Wilko Spiering, Bryan Williams, Jan Van der Heyden, Monique van Kleef, Rob Lo, Jorie Versmissen, Adriaan Moelker, Abraham Kroon, Hannes Reuter, Gary Ansel, Gregg W Stone, Mark Bates, for the CALM-FIM_EUR investigators**

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  - **Electric baroreceptor stimulation**

BAROSTIM THERAPY™

BAROSTIM THERAPY is one of the few device-based therapies mentioned in the 2013 HTN guidelines

European Heart Journal
doi:10.1093/eurheartj/eht151

ESH AND ESC GUIDELINES

2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

Authors/Task Force Members: Giuseppe Mancia (Chairperson) (Italy)*, Robert Fagard (Chairperson) (Belgium)*, Krzysztof Narkiewicz (Section co-ordinator) (Poland), Josep Redon (Section co-ordinator) (Spain), Alberto Zanchetti (Section co-ordinator) (Italy), Michael Böhm (Germany), Thierry Christiaens (Belgium), Renata Cifkova (Czech Republic), Guy De Backer (Belgium), Anna Dominiczak (UK), Maurizio Galderisi (Italy), Diederick E. Grobbee (Netherlands), Tiny Jaarsma (Sweden), Paulus Kirchhof (Germany/UK), Sverre E. Kjeldsen (Norway), Stéphane Laurent (France), Athanasios J. Manolis (Greece), Peter M. Nilsson (Sweden), Luis Miguel Ruilope (Spain), Roland E. Schmieder (Germany), Per Anton Sirnes (Norway), Peter Sleight (UK), Margus Viigimaa (Estonia), Bernard Waeber (Switzerland), Faiez Zannad (France)

Therapeutic strategies in patients with resistant hypertension

Recommendations	Class [a]	Level [b]	Ref. [c]
In resistant hypertensive patients it is recommended that physicians check whether the drugs included in the existing multiple drug regimen have any BP lowering effect, and withdraw them if their effect is absent or minimal.	I	C	-
Mineralocorticoid receptor antagonists, amiloride, and the alpha-1-blocker doxazosin should be considered, if no contraindication exists.	IIa	B	604, 606, 607, 608
In case of ineffectiveness of drug treatment invasive procedures such as renal denervation and baroreceptor stimulation may be considered.	IIb	C	-
Until more evidence is available on the long-term efficacy and safety of renal denervation and baroreceptor stimulation, it is recommended that these procedures remain in the hands of experienced operators and diagnosis and follow-up restricted to hypertension centers.	I	C	-
It is recommended that the invasive approaches are considered only for truly resistant hypertensive patients, with clinic values ≥160 mmHg SBP or ≥110 mmHg DBP and with BP elevation confirmed by ABPM.	I	C	-

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

BAROSTIM THERAPY mechanism of action

3. Brain

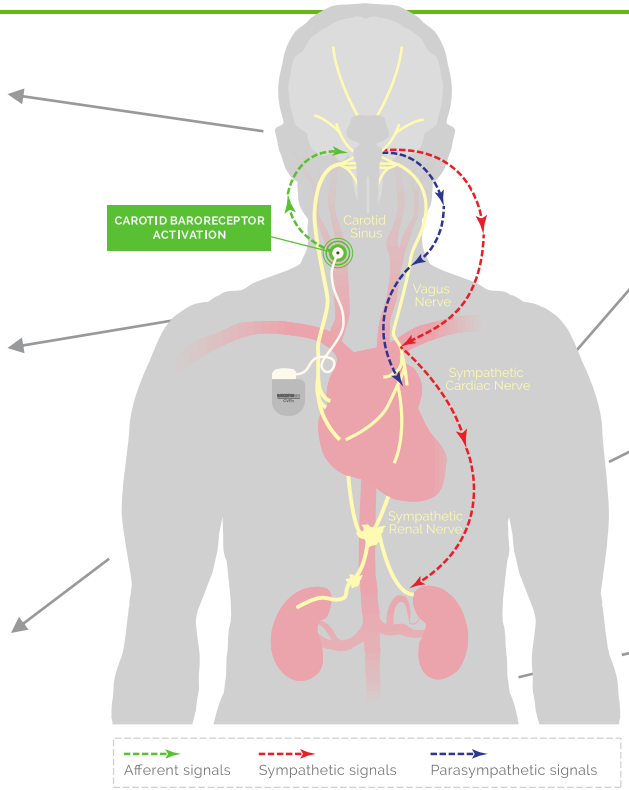
- Achieves autonomic balance by reducing sympathetic activity while increasing parasympathetic activity.

2. Baroreceptors

- Sensors that provide information to the central nervous system, which are used in autonomic reflexes and act as part of the baroreflex.
- Are stimulated by BAROSTIM THERAPY™.

1. BAROSTIM NEO™

- A single electrode, powered by one of the most powerful implantable batteries in the world.
- Activates the baroreflex.



In resistant hypertension:

4. Heart

↓ HR ↓Remodeling

- Reduces myocardial work
- Reduces LV hypertrophy

5. Blood Vessels

↑Vasodilation ↑ Venous capacitance

- Reduces arterial pressure
- Reduces pulse pressure

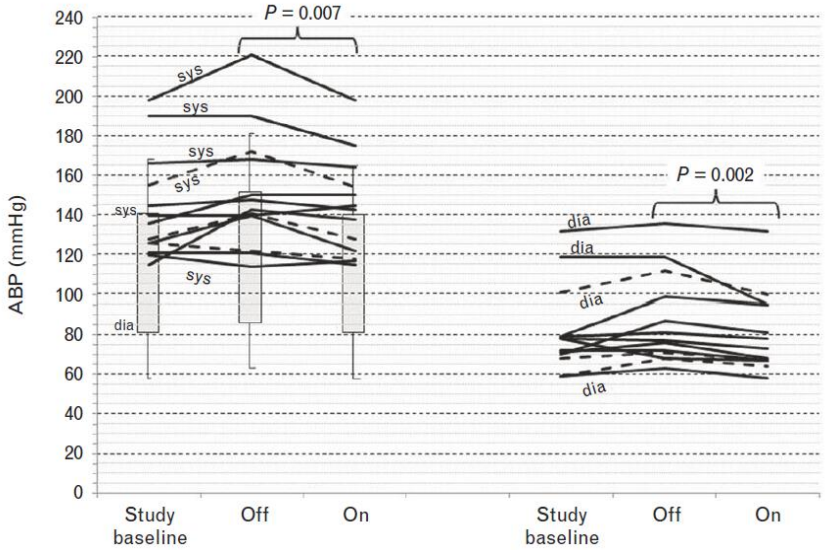
6. Kidneys

↑ Diuresis ↓ Renin secretion

- Reduces arterial pressure
- Reduces pulse pressure

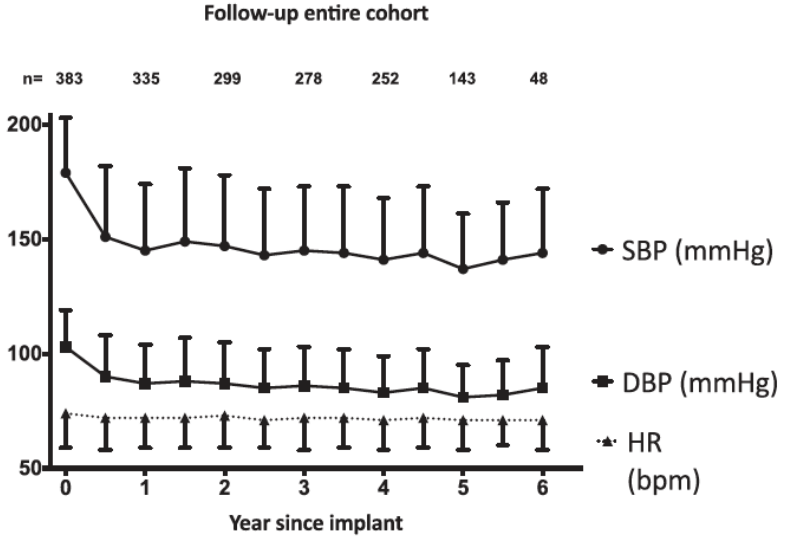
Latest clinical results

A randomised, double-blind study has shown a 10mmHg SBP reduction in ABPM (n=16)



Beige J et al, J Hypertens 2017

A meta-analysis has shown a sustained blood pressure reduction (n=383)



de Leeuw et al, Hypertension 2017

What are the current challenges with device-based therapies?

- We do not know which patients benefit most
- Failure rates vary between 25 – 50%
- "Placebo" or "sham" controlled studies are missing
- Effect of electric renal denervation on blood pressure is documented, but much lower than expected
- Intervention trials have relatively low numbers of patients as compared to pharma trials
- Currently a paradigm shift is observed (and neccessary) – treatment of stage II and III hypertensives is favored for interventional trials
- Most current devices are under development and can only be used in trials

- **BAROSTIM THERAPY remains an exception today as it is reimbursed in several countries and is the subject of a consensus in Germany and the Netherlands**

Thank you.