20ο Πανελλήνιο Συνέδριο Νεφρολογίας

Ελληνική Νεφρολογική Εταιρεία

3-6 Μαΐου 2018

Μέγαρο Διεθνές Συνεδριακό Κέντρο Αθηνών, **Αθήνα**

Ο ρόλος της νεφρικής απονεύρωσης

Κώστας Τσιούφης

Αν. Καθηγητής Καρδιολογίας, ΕΚΠΑ

Πρόεδρος Ελληνικής Καρδιολογικής Εταιρείας

President of European Society of Hypertension (ESH)

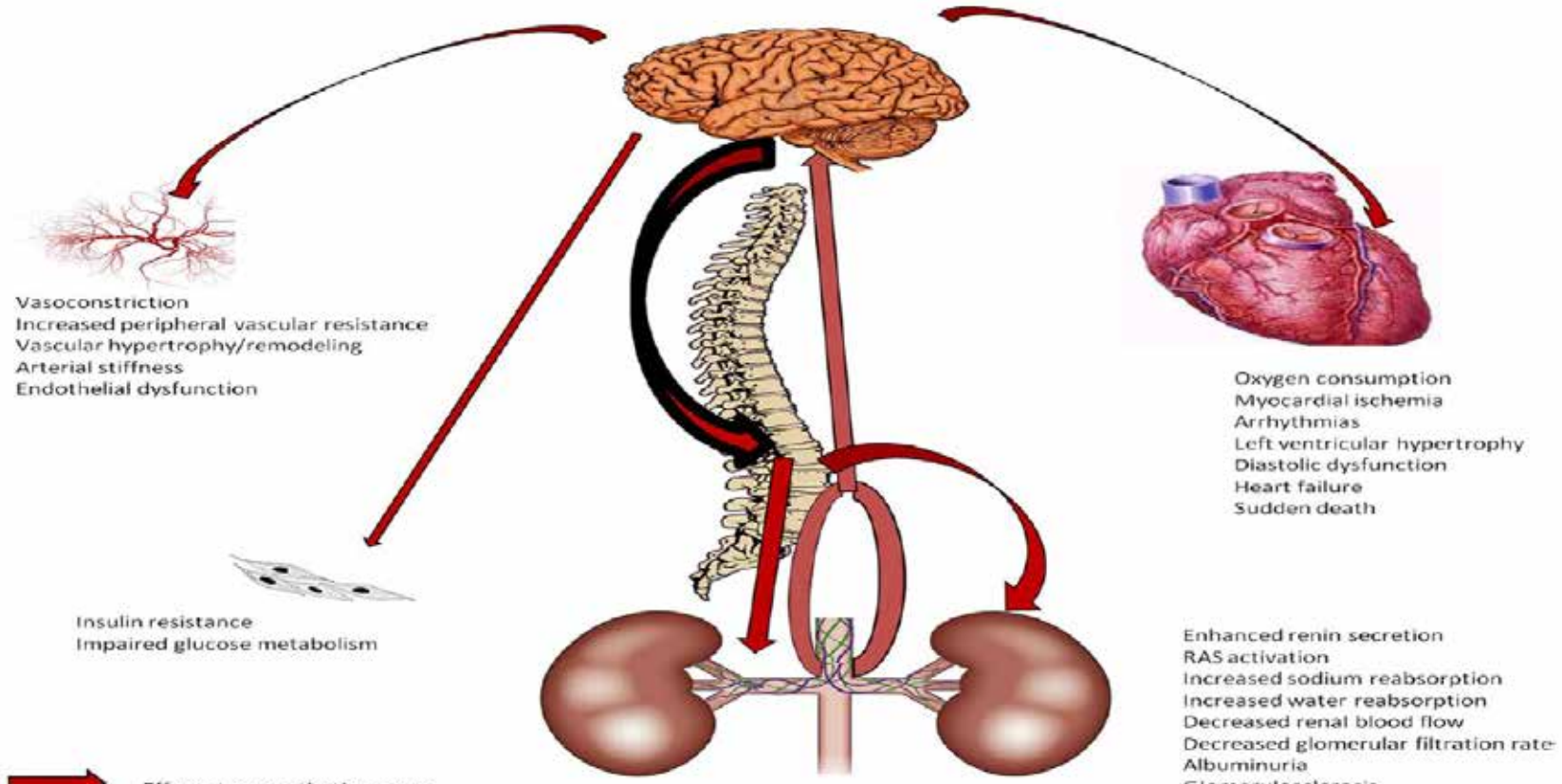
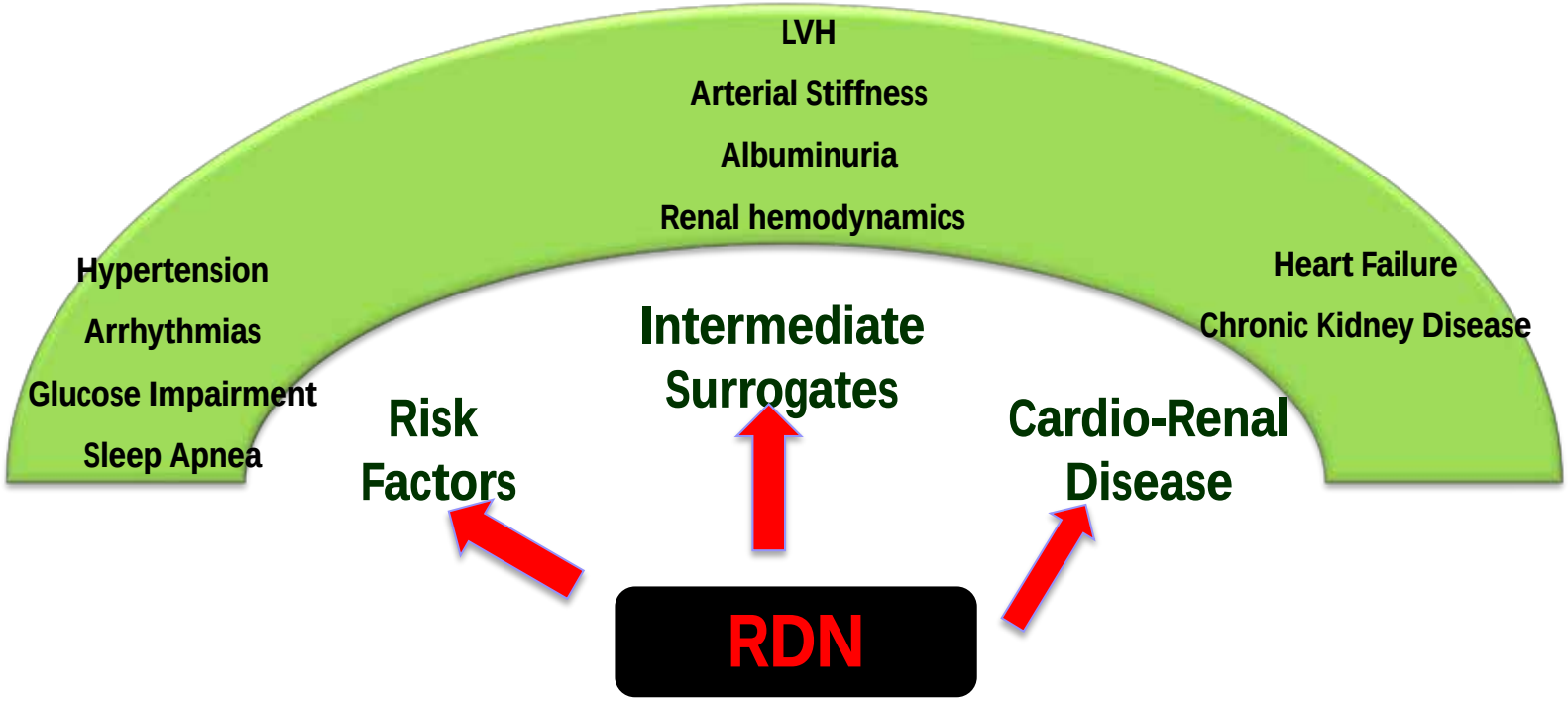


Figure 2. Diagram depicting the influence of efferent and afferent sympathetic fibers in modulating sympathetic responses of the kidney, the heart, the vasculature, and other target organs.

Papademetriou V, Tsioufis C, Doumas M. Circulation 2014

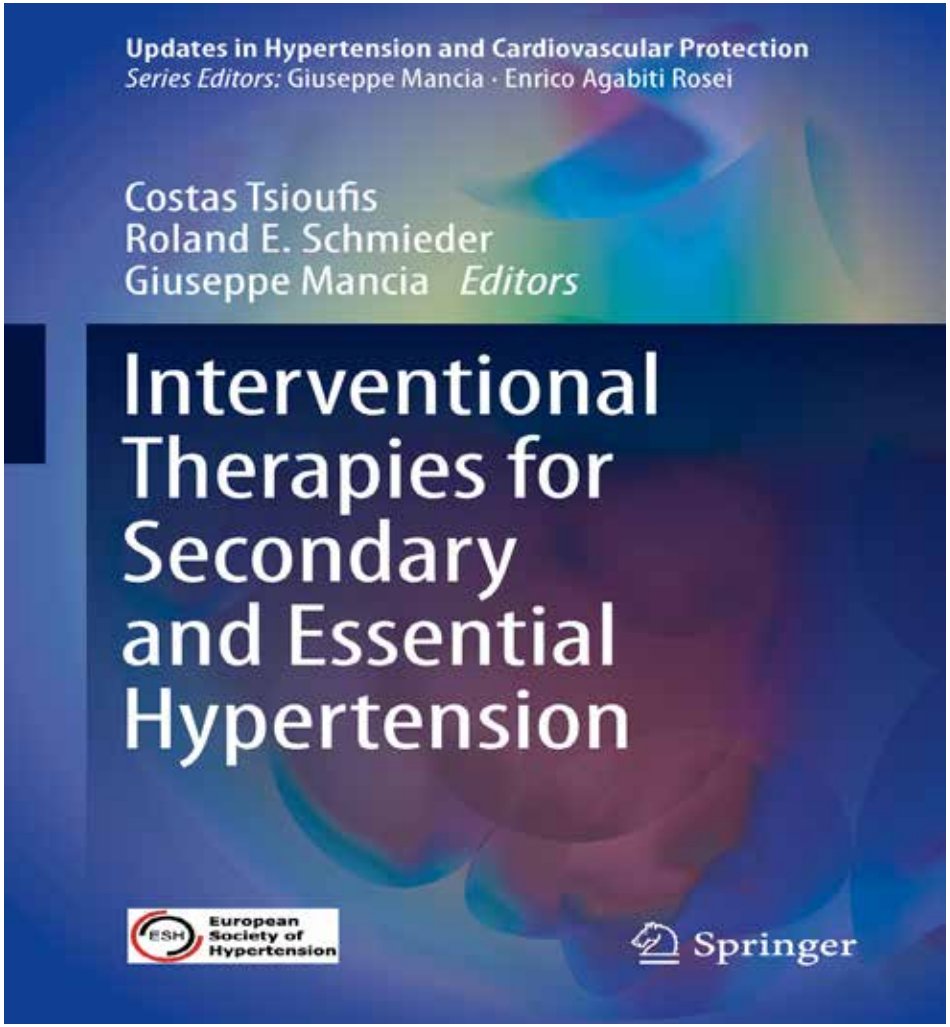
Favorable effects of RDN on intermediate end points



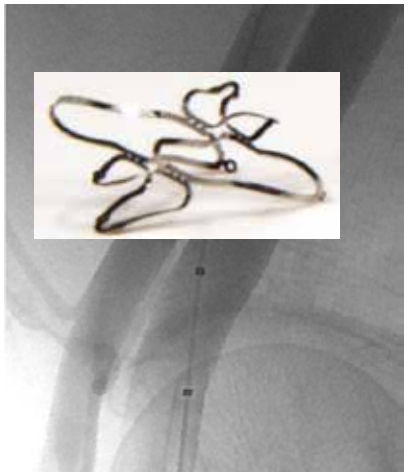
Ukena C, et al. Int J Cardiol 2013
Brandt MC, et al. J Am Coll Cardiol. 2012; 59:901-909
Mahfoud F, et al. Circulation. 2011; 123:1940-1946
Mahfoud F, et al. Hypertension. 2012; 60:419-424.
Mahfoud F, et al. Eur Heart J 2014
Tsioufis C, et al, JHH 2014
Tsioufis et al, JH 2014

Interventional therapy for Resistant Hypertension

30's-50's
Surgical sympathectomy



Iliac A-V anastomosis

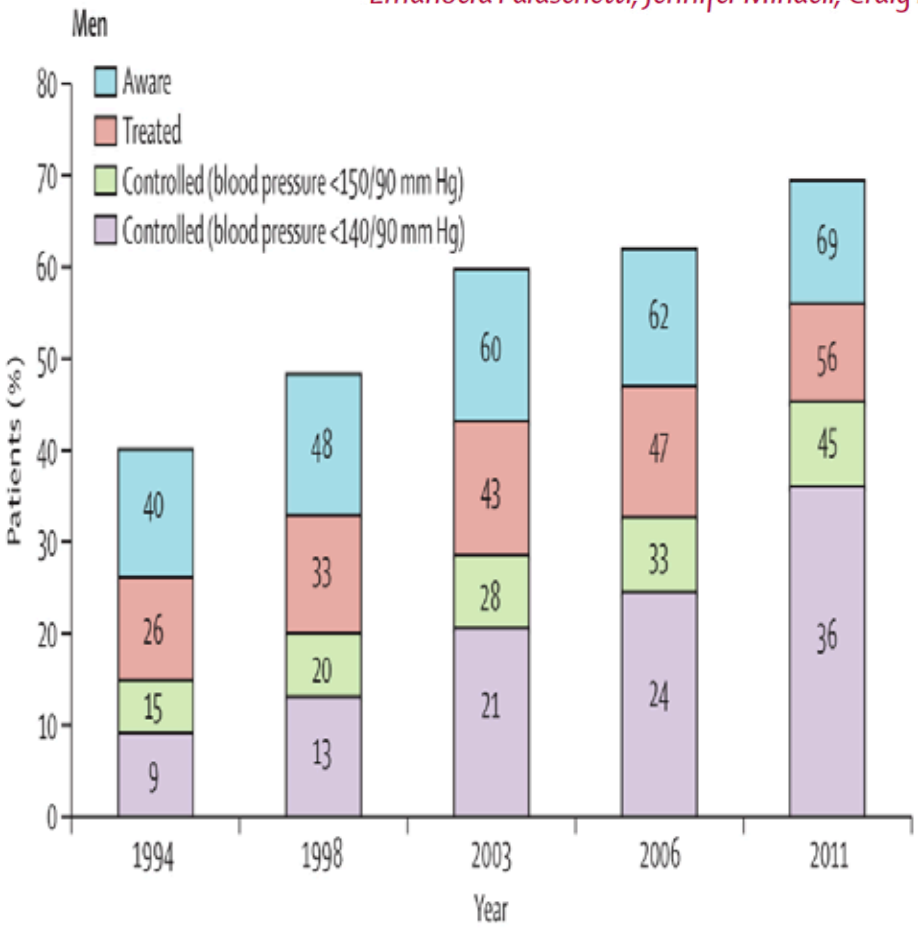


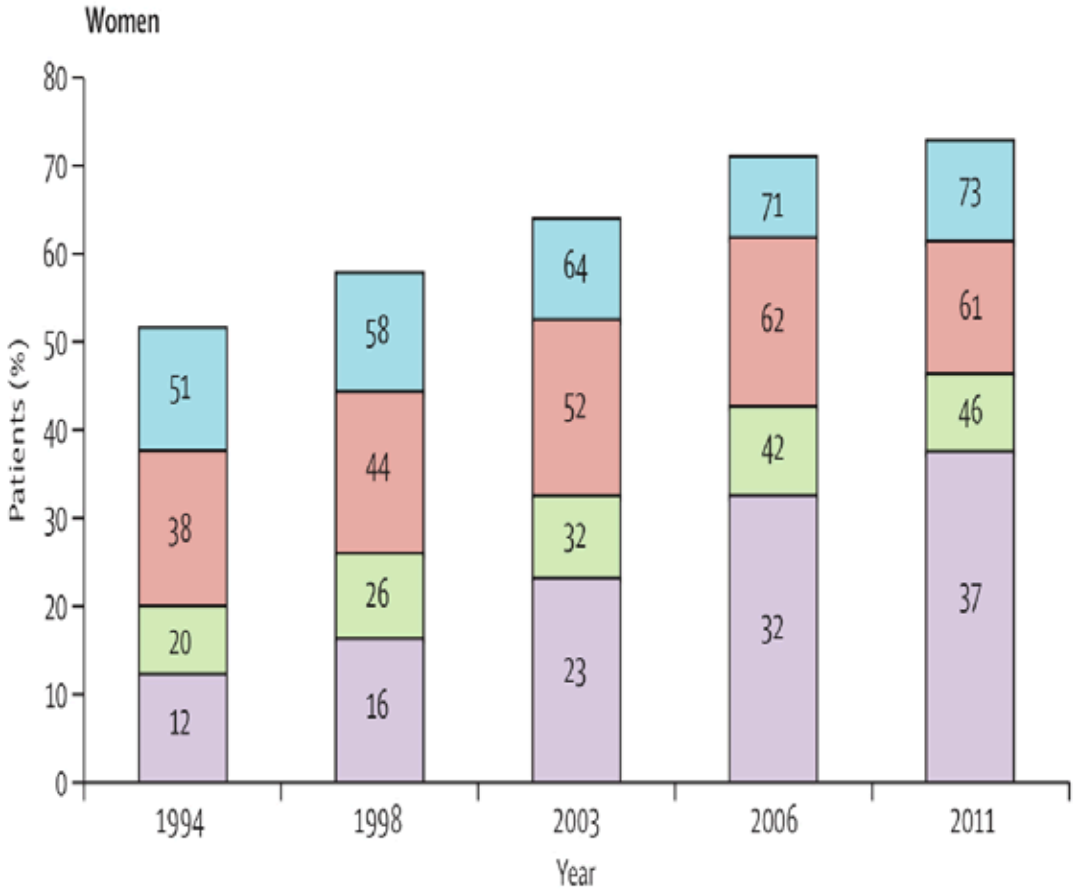
There are some reasons to discuss for RDN in 2018

Are we happy with the control of HTN in 2018?

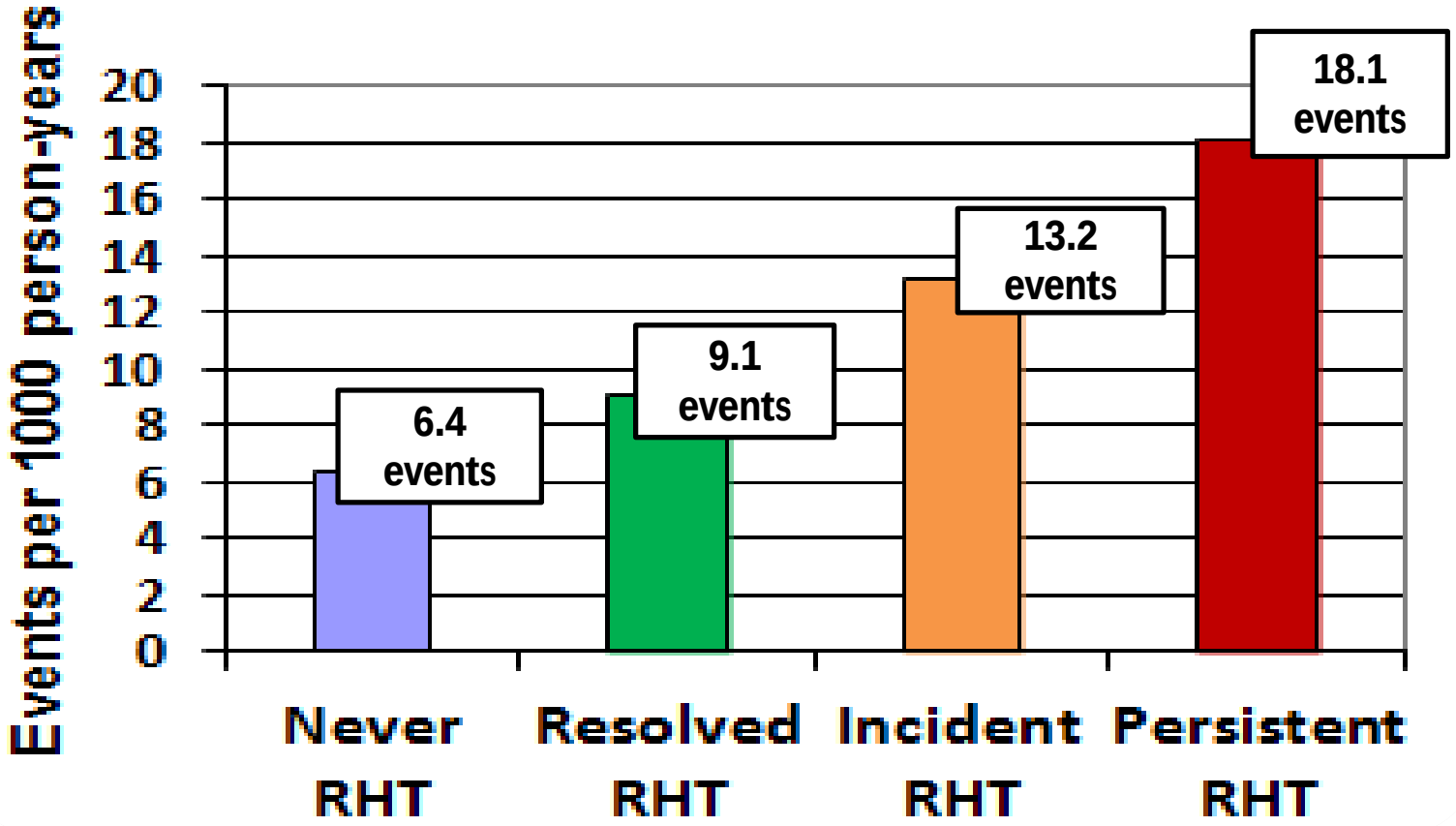
Hypertension management in England: a serial cross-sectional study from 1994 to 2011

Emanuela Falaschetti, Jennifer Mindell, Craig Knott, Neil Poulter





CV end points and patterns of RHTN

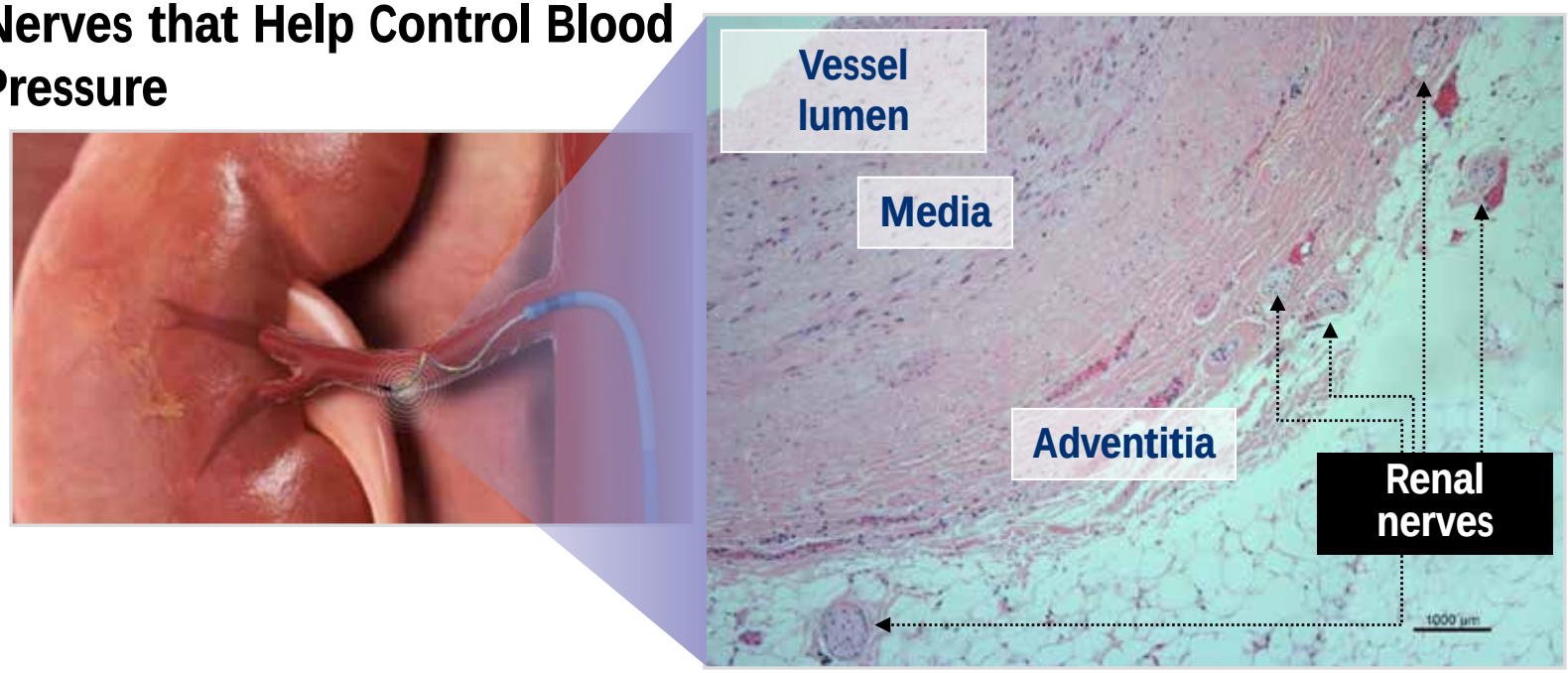


Tsioufis C, et al, J Hypertens. Feb 2014

Renal Anatomy Allows a Catheter-Based Approach

RENAL DENERVATION

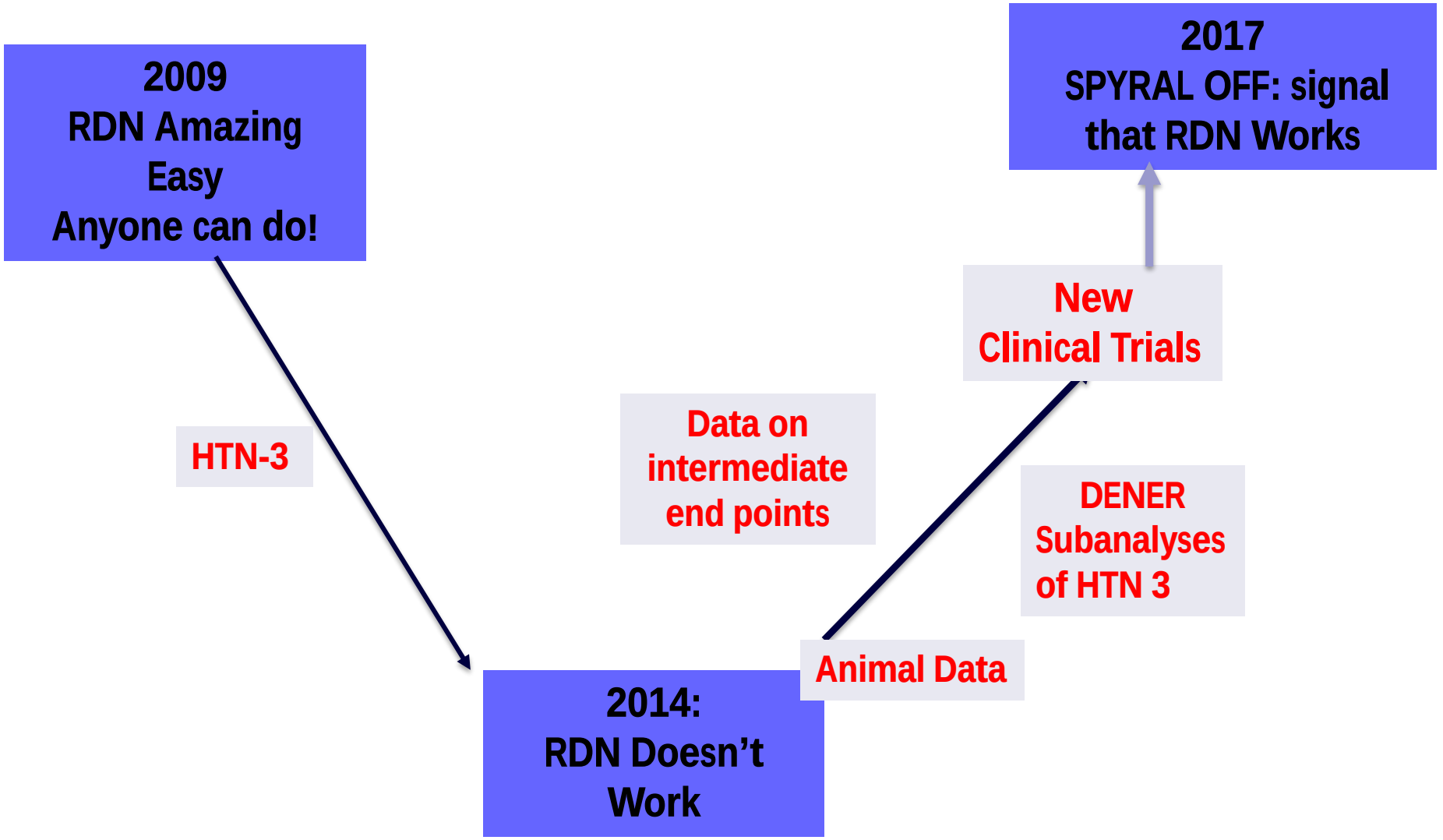
Deliver Energy to the Renal Nerves that Help Control Blood Pressure



RDN trials: Safety profile

	Symplicity HTN-1	Symplicity HTN-2	Symplicity HTN-3	EnligHTN 1	Reduce-HTN	Global Symplicity Registry
Hypotension, n	3	2	-	1	0	-
Hypertensive emergency, n	13	14	9	1	1	5
Renal artery stenosis >70% or in need of stent, n	2	0	1	1	2	1
Significant worsening of renal function , n	1	2	5	1	15	5
eGFR at baseline, ml/min/1.73m^2	83.6±19.7	77±19	72.8±15.7	84.7±18	83.9±24.1	76.2 (60-92)
eGFR at follow-up, ml/min/1.73m^2	74.3±28.0	77±18	70.6±17.4	76.4±25.3	82.9±23.7	74.4 (57-89)

RDN: Efficacy to lower BP



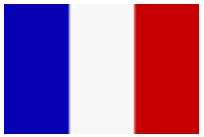
A Controlled Trial of Renal Denervation for Resistant Hypertension

Bhatt DL, NEJ 2014

Primary safety endpoint was met

Primary efficacy endpoint was not met

Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial



Azazi M, Lancet 2015

Primary efficacy endpoint was met

I. Medication

- Obtain data in off medication patients
- Standardize medication
- Measure adherence
  - Toxicological analyses

II. Patient selection

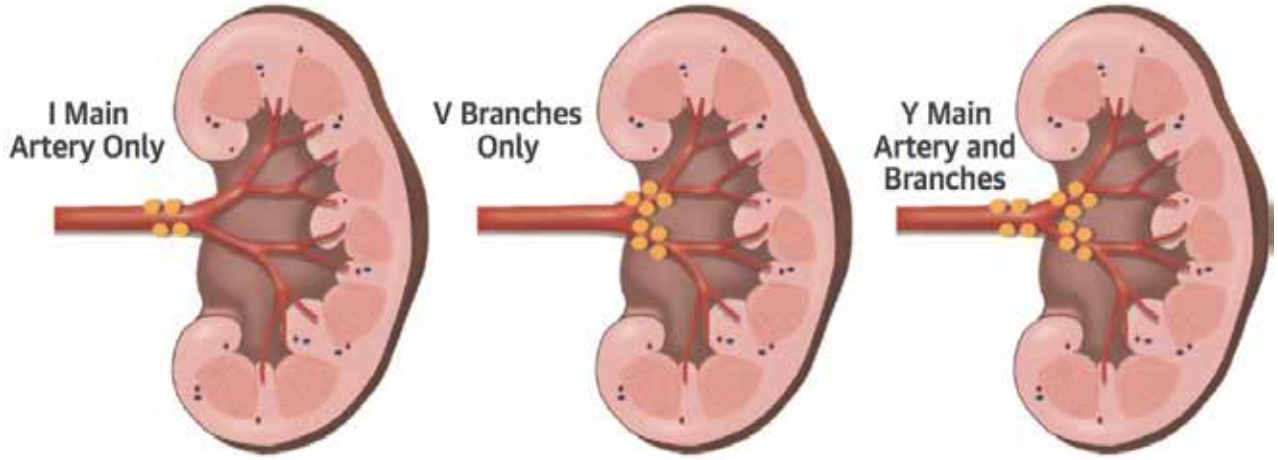
- Exclude isolated systolic hypertensive patients
- Moderate hypertension, no severe resistant hypertension

III. Procedural aspects

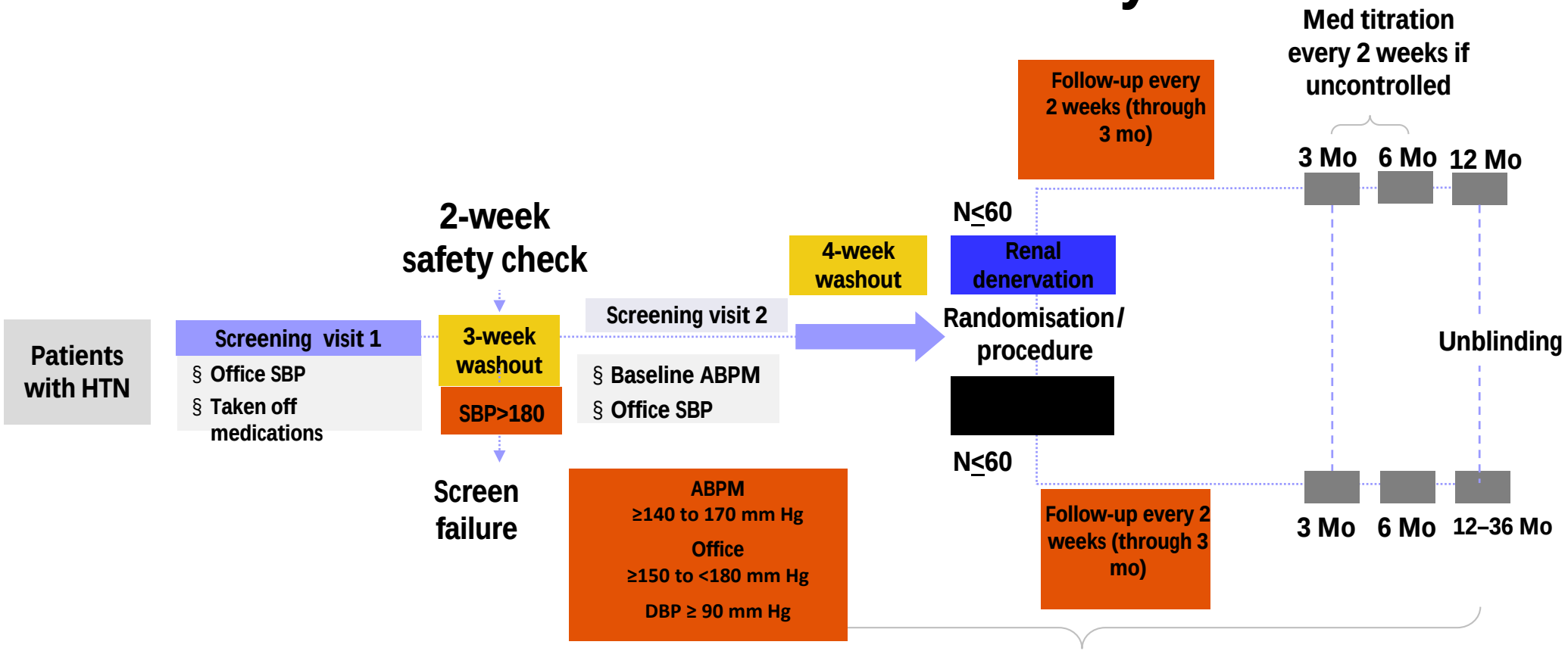
- Active (!) treatment

- Distally focused ablation

- Standardize procedural instructions



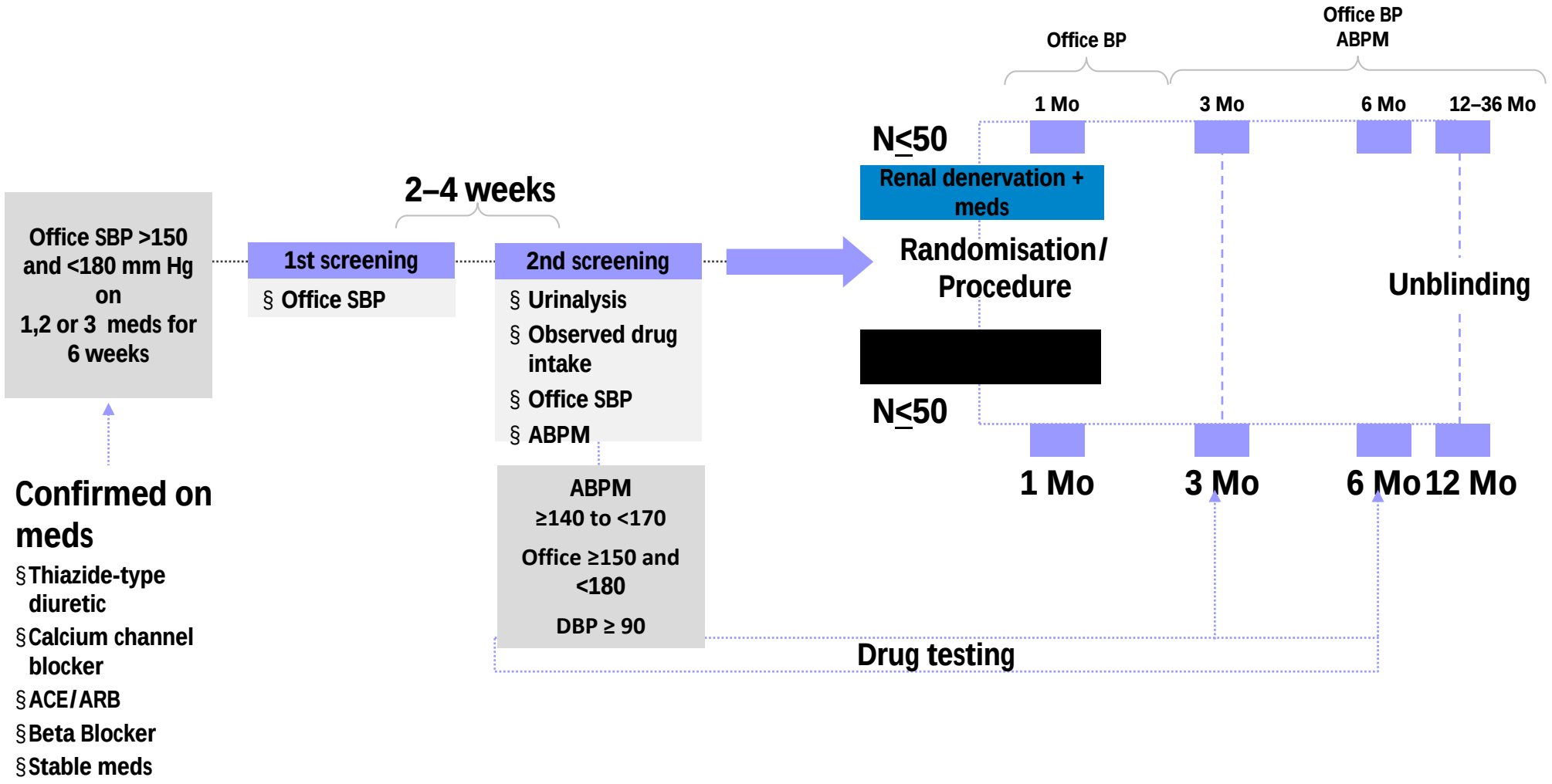
SPYRAL HTN–OFF MED Study



■ Represents study safety measures

Drug testing to confirm washout at Screening visit 2 and 3 mo; drug testing at 6 mo and 12 mo

SPYRAL HTN–ON MED Study



SPYRAL HTN – OFF MED

THE LANCET

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

*Raymond R Townsend, Felix Mahfoud, David E Kandzari, Kazuomi Kario, Stuart Pocock, Michael A Weber, Sebastian Ewen, Konstantinos Tsioufis, Dimitrios Tousoulis, Andrew S P Sharp, Anthony F Watkinson, Roland E Schmieder, Axel Schmid, James W Choi, Cara East, Anthony Walton, Ingrid Hopper, Debbie L Cohen, Robert Wilensky, David P Lee, Adrian Ma, Chandan M Devireddy, Janice P Lea, Philipp C Lurz, Karl Fengler, Justin Davies, Neil Chapman, Sidney A Cohen, Vanessa DeBruin, Martin Fahy, Denise E Jones, Martin Rothman, Michael Böhm, on behalf of the SPYRAL HTN-OFF MED trial investigators**

Townsend et al, *Lancet*. Published online 28 Aug 2017

SPYRAL HTN
Global Trial Center Locations

21 Recruiting Sites in:

- USA
- Europe
- Japan
- Australia

SPYRAL HTN – OFF MED

n Key Patient Eligibility Criteria

Inclusion

1. Patient is either:
   A. Not on antihypertensive medications, OR
   B. Permitting discontinuation of drug therapy
2. Office SBP ≥ 150 and < 180 mm Hg
3. Office DBP ≥ 90 mm Hg
4. Systolic 24-hour mean ABPM ≥ 140 and < 170 mm Hg

Exclusion

1. Ineligible renal artery anatomy (accessory arteries allowed)
2. eGFR < 45 mL/min/1.73m^2
3. Type 1 diabetes mellitus or type 2 diabetes mellitus with HbA1C > 8.0%
4. Secondary causes of hypertension

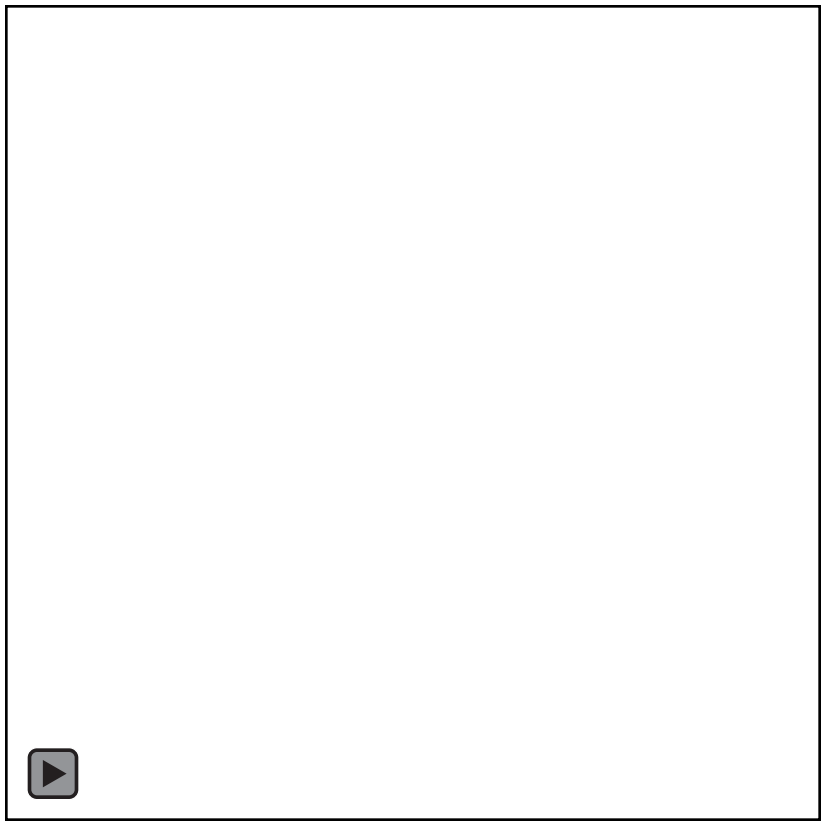
SPYRAL HTN – OFF MED

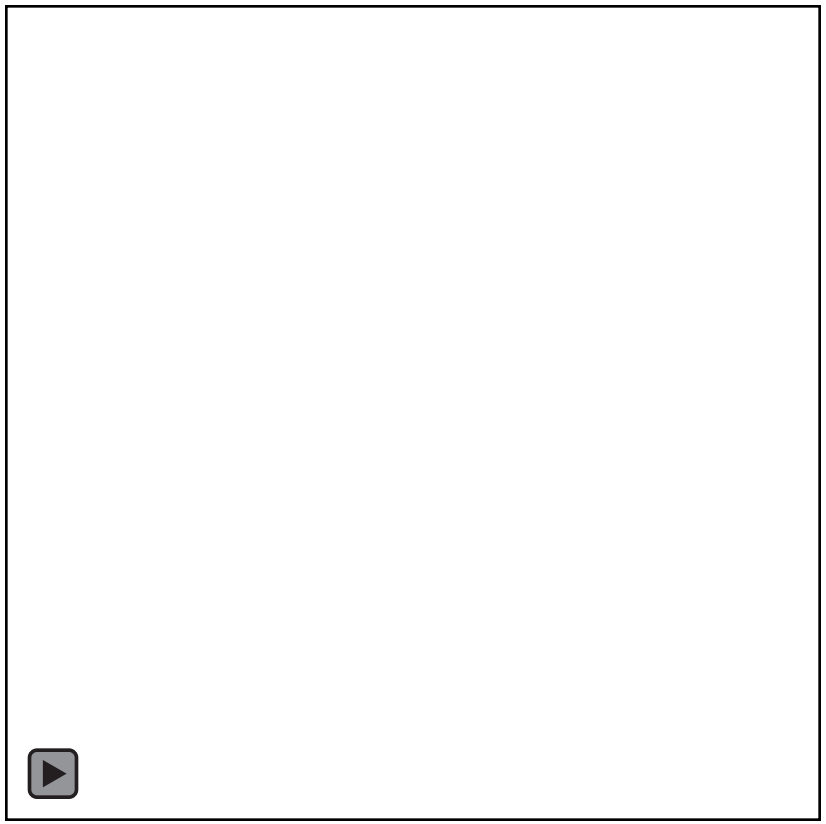
Baseline Blood Pressure

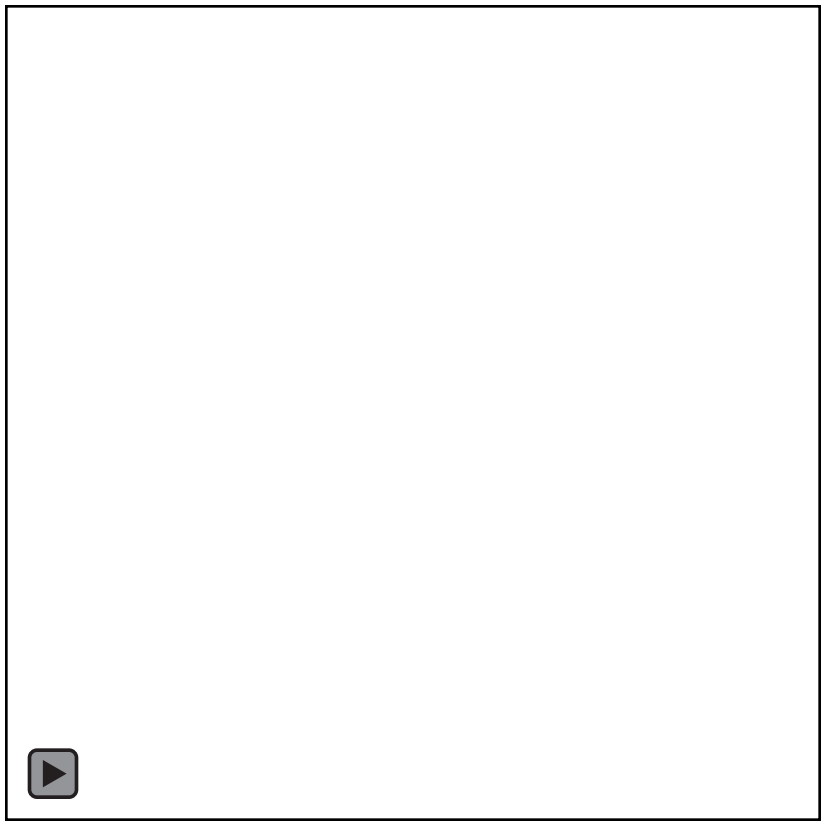
Mean ± SD	RDN	Sham Control	
Office measurements	**N = 38**	**N = 42**	
Office SBP (mm Hg)	162.0 ± 7.6	161.4 ± 6.4	
Office DBP (mm Hg)	99.9 ± 6.8	101.5 ± 7.5	!
Office heart rate (bpm)	71.1 ± 11.0	73.4 ± 9.8	
24-hour measurements	**N = 37**	**N = 42**	
Mean 24-hour SBP (mm Hg)	153.4 ± 9.0	151.6 ± 7.4	
Mean 24-hour DBP (mm Hg)	99.1 ± 7.7	98.7 ± 8.2	!
Mean 24-hour heart rate (bpm)	72.3 ± 10.9	75.5 ± 11.5	

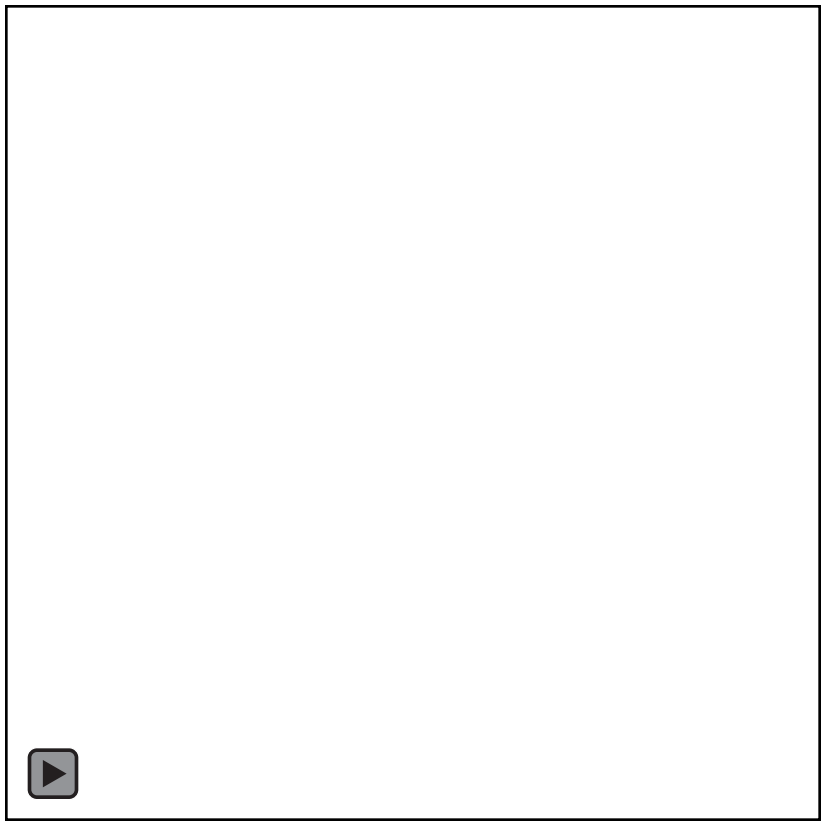
n*P* = NS for differences in all baseline characteristics

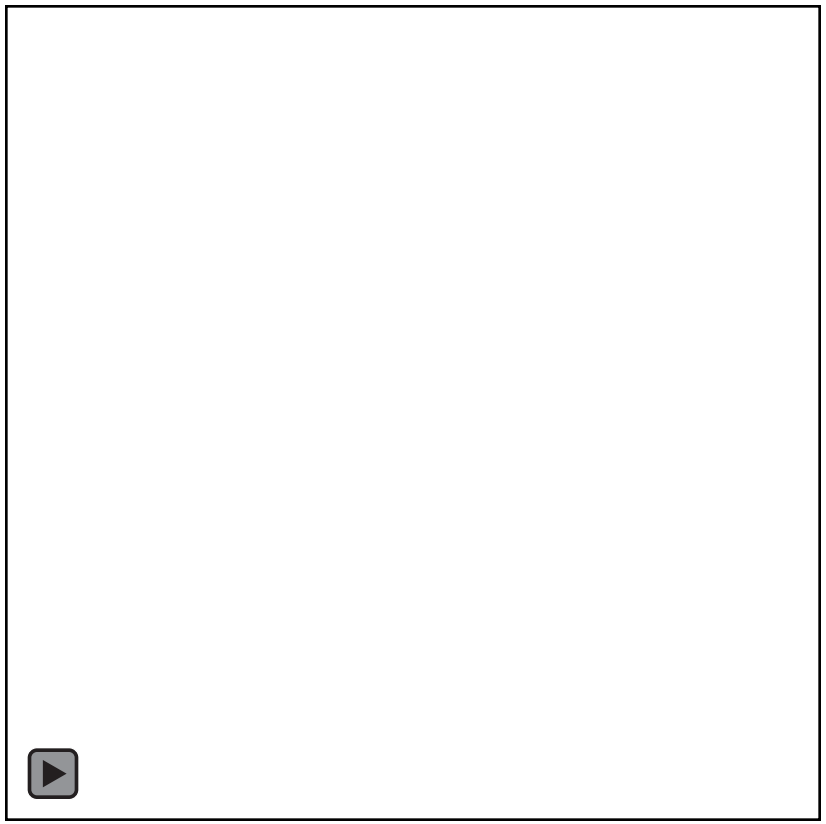
R. Townsend..... C. Tsioufis, ...M. Bohm, Lancet 2017











SPYRAL HTN – OFF MED

Laboratory Values at Baseline and 3 Months

Mean ± SD	Baseline		Change at 3 months	
	RDN	Sham	RDN	Sham
Plasma Renin Activity (ng/mL/h)	0.93 ± 0.74	1.15 ± 1.36	-0.24 ± 0.71	-0.02 ± 0.80
Aldosterone (ng/dL)	7.54 ± 3.75	8.87 ± 6.79	-2.00 ± 3.86	-1.22 ± 6.24
Serum Creatinine (mg/dL)	0.93 ± 0.19	0.89 ± 0.19	-0.03 ± 0.10	-0.01 ± 0.09
eGFR (ml/min/1·73 m^2)	80.86 ± 16.69	88.25 ± 20.52	2.19 ± 11.13	1.11 ± 13.42
Glucose (mmol/L)	5.50 ± 1.58	5.10 ± 1.11	-0.36 ± 1.54	0.10 ± 1.34
Potassium (mmol/L)	4.17 ± 0.38	4.17 ± 0.33	0.00 ± 0.34	-0.01 ± 0.44
Sodium (mmol/L)	139.76 ± 2.56	139.50 ± 2.51	0.11 ± 2.34	0.10 ± 2.70

R. Townsend..... C. Tsioufis, ...M. Bohm, Lancet 2017

SPYRAL HTN – OFF MED

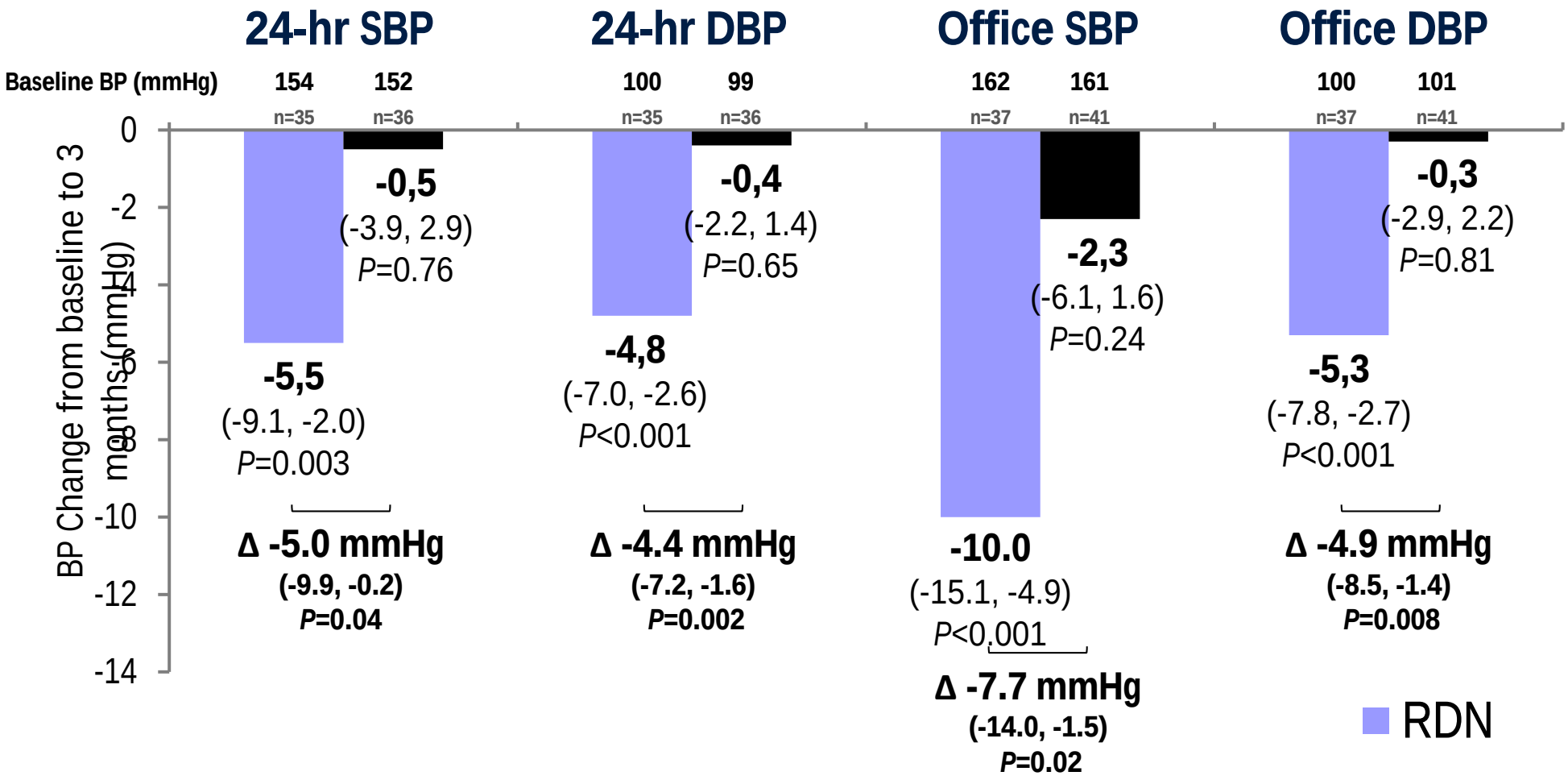
Procedural Details

Mean ± SD	RDN (N = 38)	Sham Control (N = 42)
Number of main renal arteries treated per patient	2.2 ± 0.5	NA
Number of branches treated per patient	5.2 ± 2.5	NA
Total number of ablations per patient	43.8 ± 13.1	NA
Main artery ablations	17.9 ± 10.5	NA
Branch ablations	25.9 ± 12.8	NA
Treatment time (min)	57.1 ± 19.7	NA
Contrast volume used (cc)	251.0 ± 99.4	83.3 ± 38.5

R. Townsend..... C. Tsioufis,.....M. Bohm, Lancet 2017

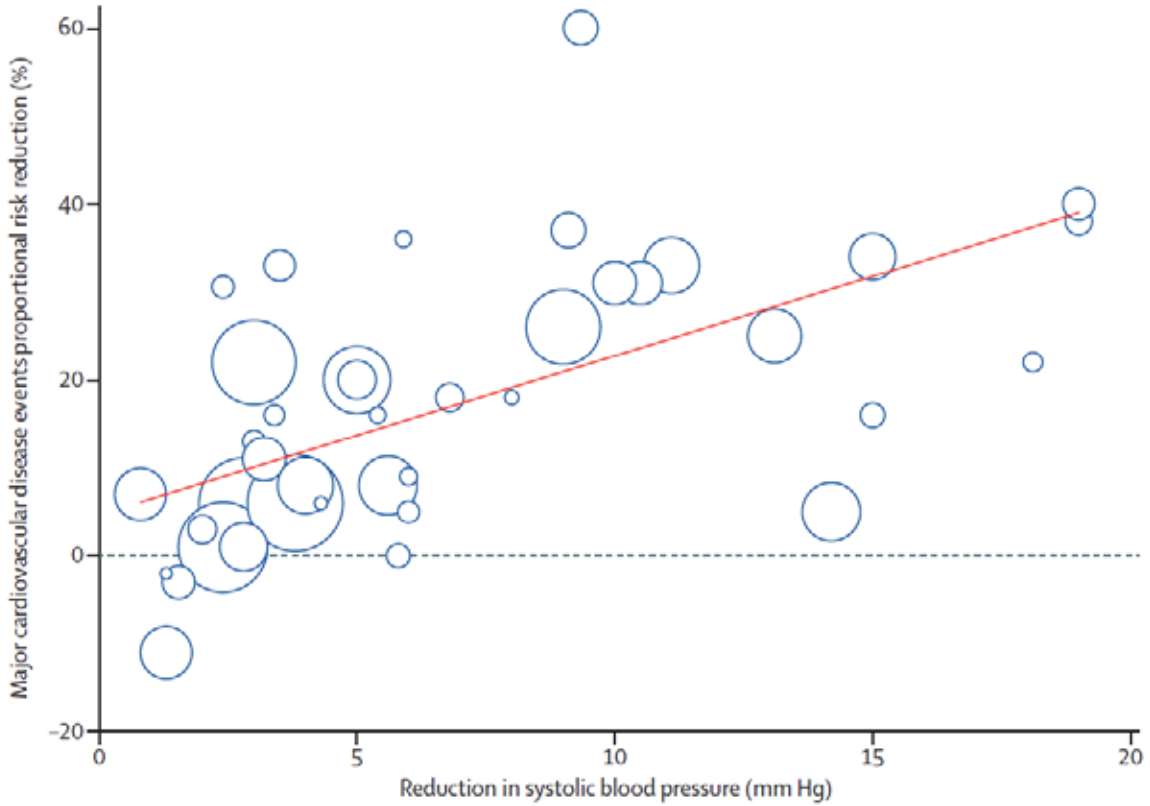
SPYRAL HTN – OFF MED

Blood Pressure Change at 3 Months



R. Townsend..... C. Tsioufis, D. Tousoulis.....M. Bohm, Lancet 2017

SPYRAL HTN – OFF MED
What do the results mean?
Perspective: Extrapolated Risk Reduction



- **≈ 20% reduction in relative risk for cardiovascular events with the presently observed OSBP 7.7 mm Hg difference between treatment groups**

Ettehad D, Emdin CA, Kiran A, et al. Lancet. 2016; 387: 957-67.

SPYRAL HTN – OFF MED
Conclusions

- **Biologic proof of principle** for the efficacy of renal denervation, not powered for statistical significance
- **Clinically significant blood pressure reductions** at 3 months
  - In mild to moderate hypertensive patients treated with RDN
  - In the absence of anti-hypertensive medications compared to sham control
- **No major safety events**
  - Despite a more complete denervation procedure that extended into renal artery branch vessels
- **The results of this feasibility study will inform the design of a larger pivotal trial**

R. Townsend….. C. Tsioufis,……M. Bohm, Lancet 2017

Blood Pressure

ISSN: 0803-7051 (Print) 1651-1999 (Online) Journal homepage: http://www.tandfonline.com/loi/iblo20

Renal denervation in hypertension: is it the end or the beginning of a SPYRAL?

Michel Burnier, Krzysztof Narkiewicz, Sverre E. Kjeldsen & Suzanne Oparil

SPYRAL HTN-OFF MED study: Renal denervation in the spiral orbits of current results and future studies

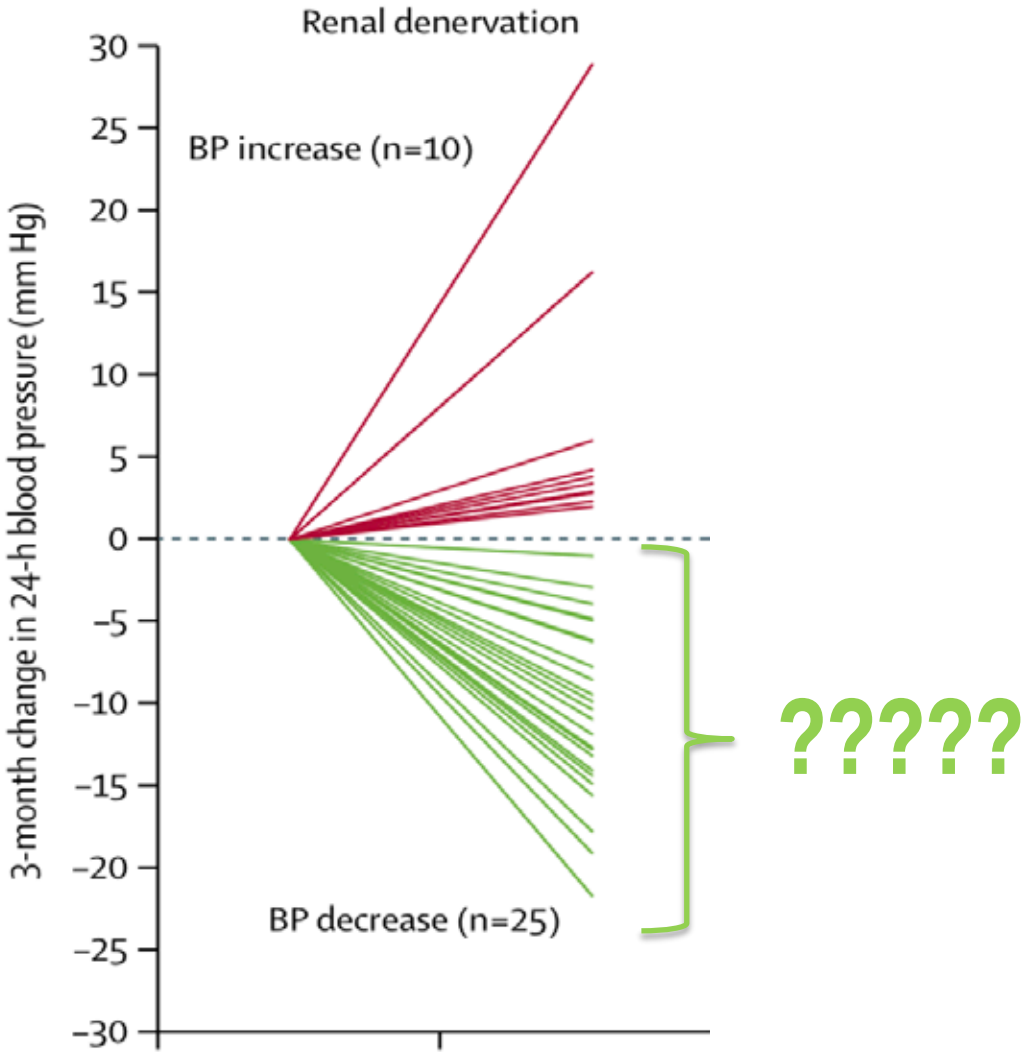
Costas Tsioufis, Kyriakos Dimitriadis, Vasilios Papademetriou, Dimitrios Tousoulis

2018 euroPCR

SPYRAL ON MEDICATION RESULTS

Unmet needs

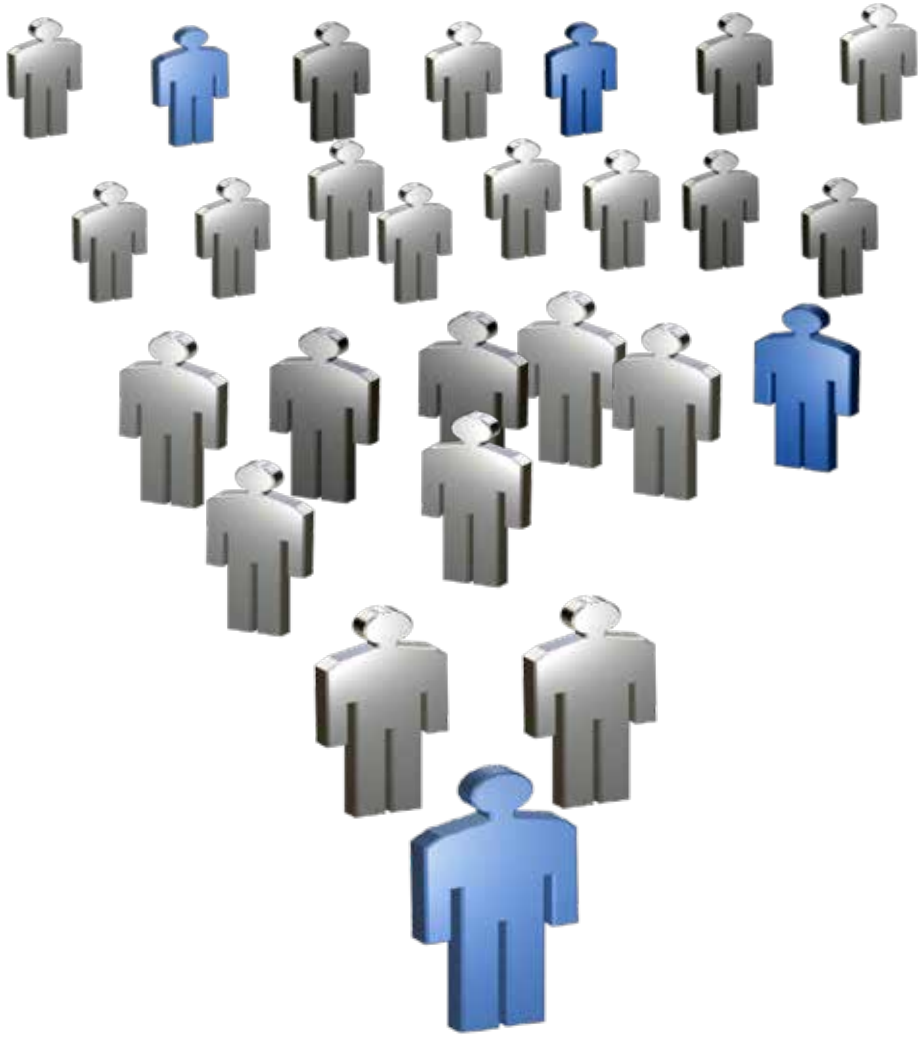
I. Identification of responders NEE



Townsend RR, Lancet 2017

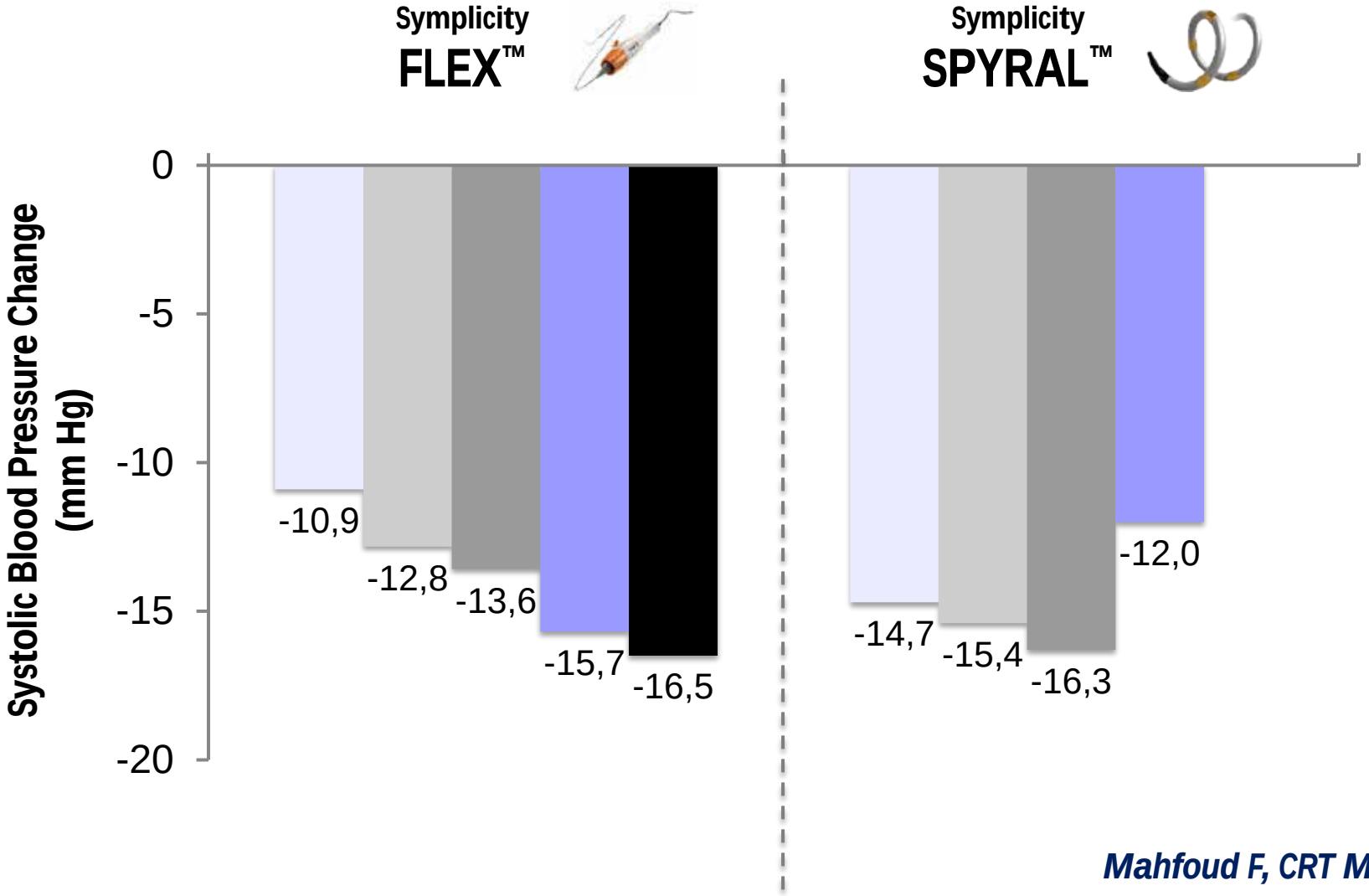
The challenge is to identify the ideal hypertensive patient for RDN.....

Not all patients with hypertension may be suitable for renal denervation....



Unmet needs

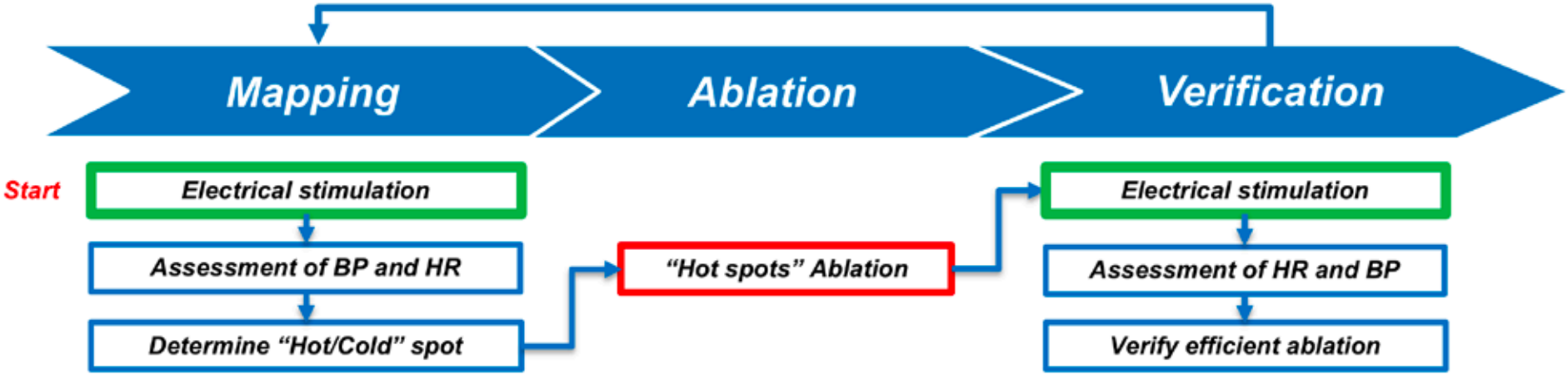
II. Sustained efficacy?

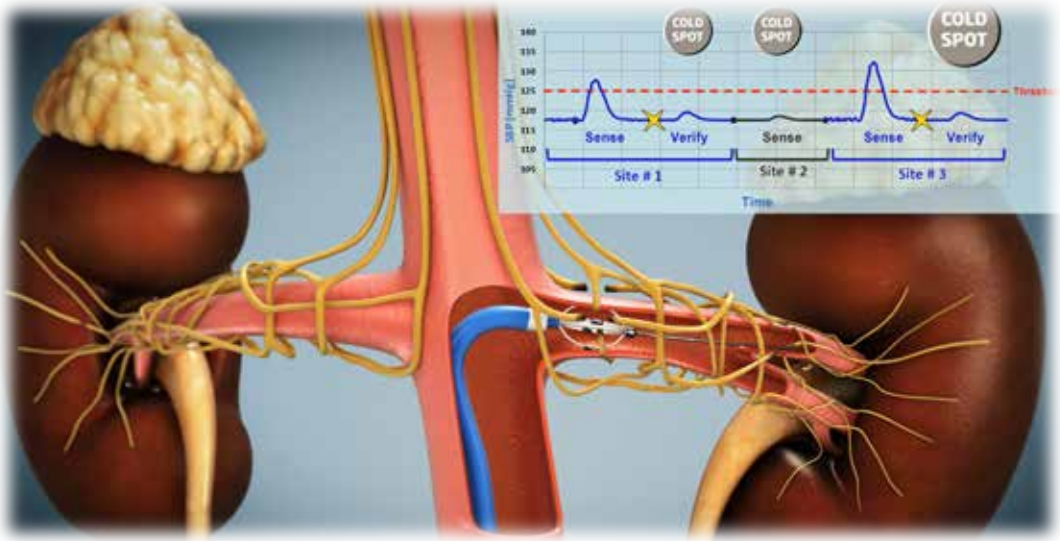


Mahfoud F, CRT Meeting 2018

Unmet needs

III. Real time feedback

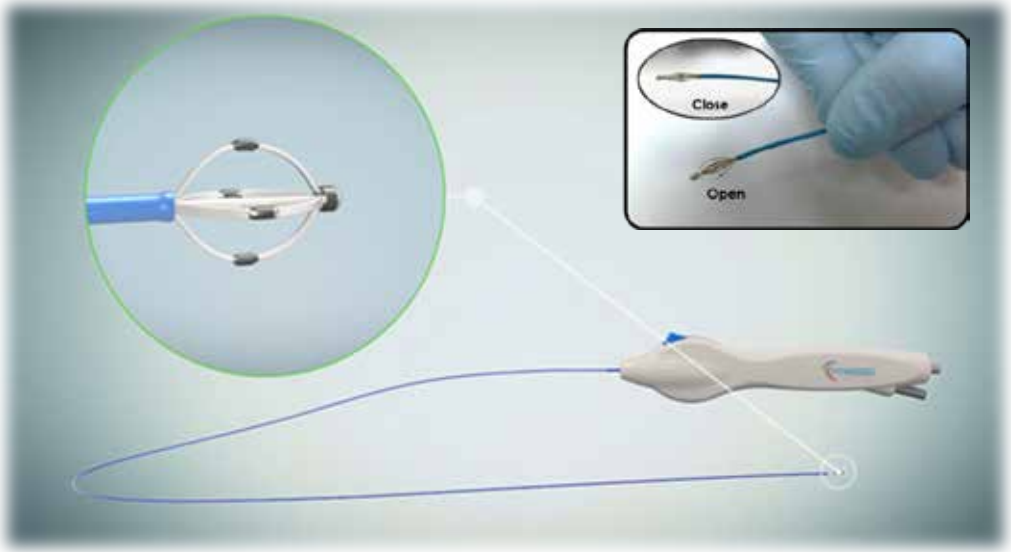




Mahfoud F, EuroPCR 2017

ConfidenHT™

System



Catheter

- Multi-electrode
- Flexible design
- Adjustable basket size
- 8F GC/ 0.014” GW compatible
- Femoral access approach

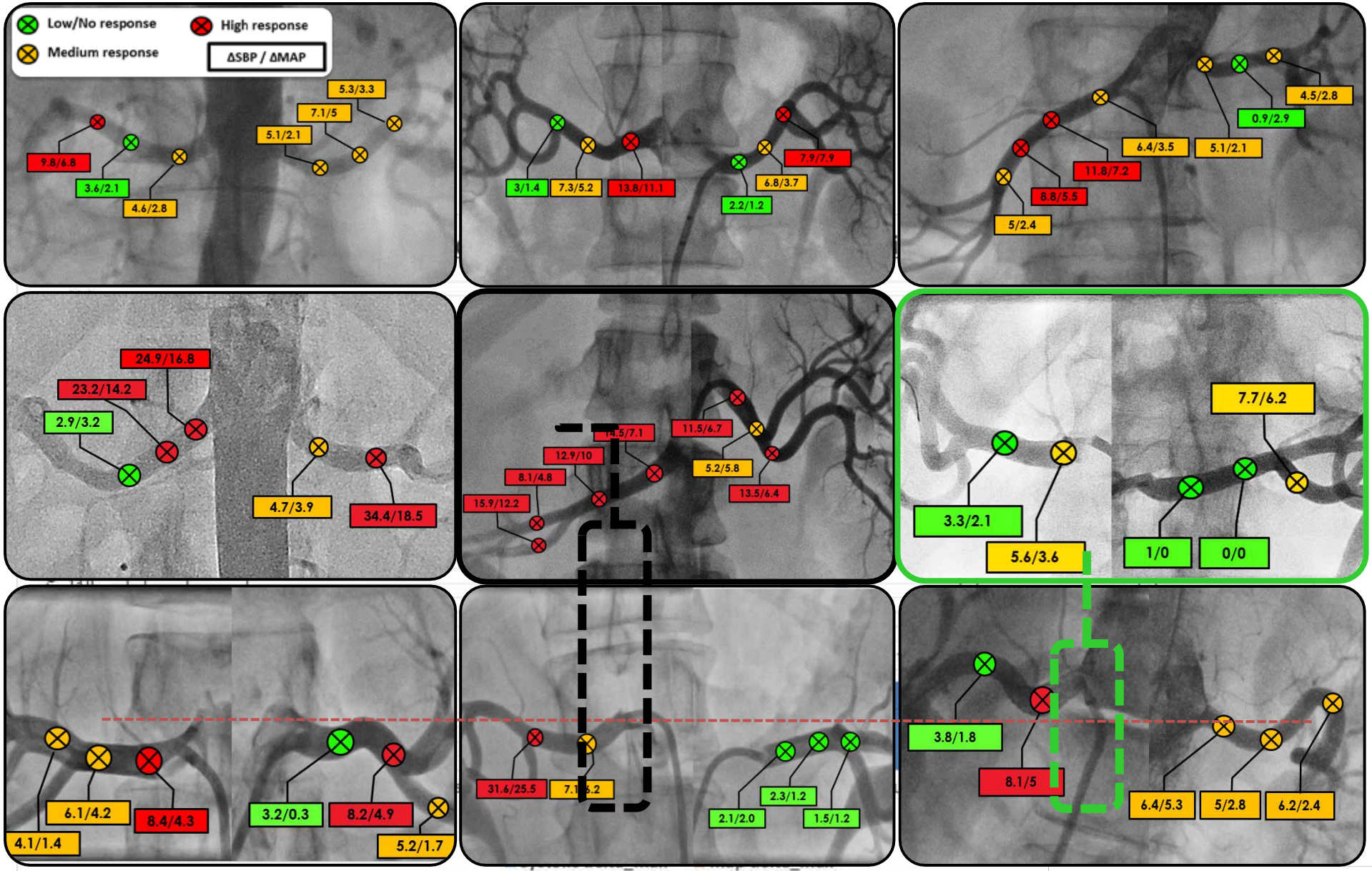
Console

- Multi channel generator
- Real time physiological signals’ analysis using a proprietary algorithm
- Configurable outputs

Tsioufis et al. Euro PCR 2017

PYTHAGORAS MEDICAL

Large variation in response per patient and per location



Tsioufis et al. Euro PCR 2017

Unmet needs

III. Effects of RDN on Heart failure, CKD

RDN and HF

Animal Data

- Long-term RDN in rats after MI improved LV function and restored natriuresis

Nozawa et al, Heart Vessels. 2002;16:51–6.

Souza et al, Braz J Med Biol Res. 2004;37:285–93.

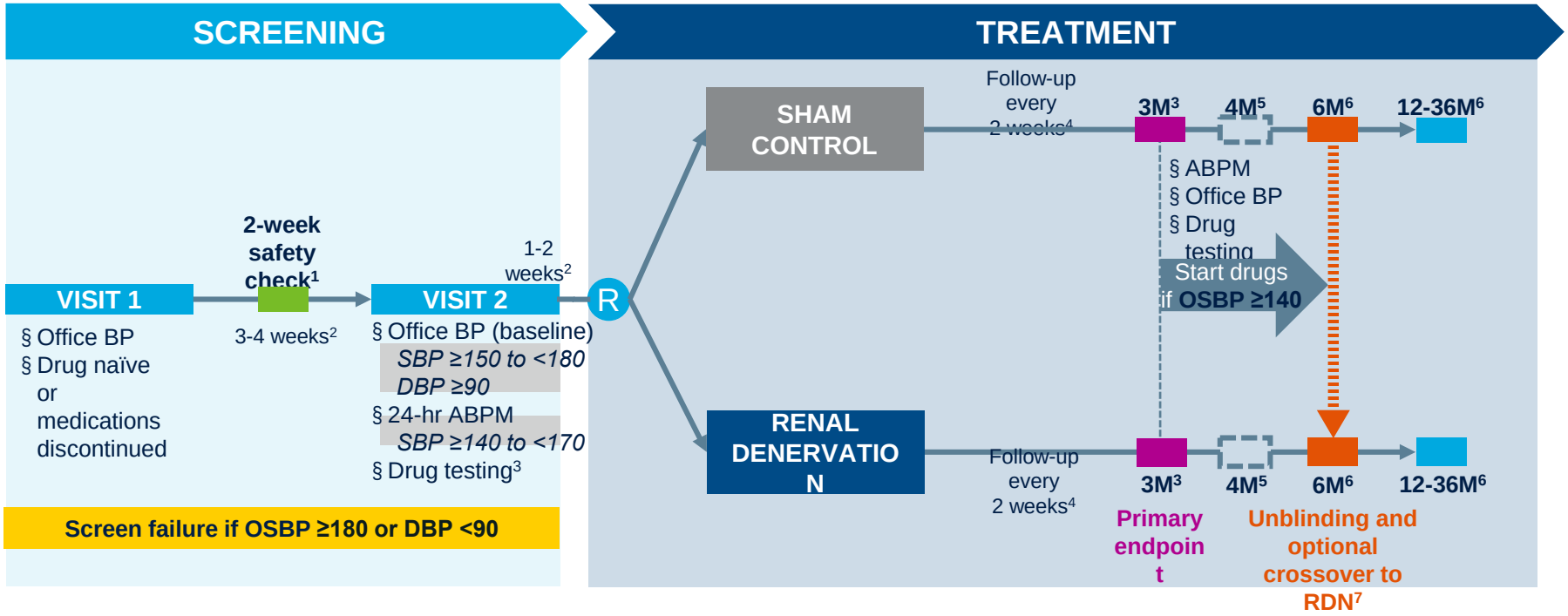
- RDN restores diuresis and natriuresis in response to exogenously administered ANP in rats with heart failure induced by coronary ligation

Pettersson et al, Acta Physiol Scand. 1989;135:487–92.

HF: Renal Denervation trials

Trial	Number of pts (n)	Type of HF population	Design of study	Duration of follow up	Main findings – Efficacy	Main findings - Safety	Current status of study
REACH - Pilot	7	NYHA class III or IV	Open-label, non-randomized FIM trial evaluation of the safety of RDN	6 months	Significant increase in 6-minute walk distance A self-reported improvement of symptoms	A non-significant trend to reduction in BP No statistically significant change in HR No deterioration of renal function	Completed
Olomouc I Pilot	51	NYHA III, LVEF ≤ 35%. on OMT	Single center, randomized (1:1) control trial, RDN + OMT VS OMT	12 months	(preliminary data) Significant increase in LVEF LVESEV & LVEDV decreased NT-proBNP significantly decreased	No significant BP decrease - 1 hypotension event RDN did not change renal function	ON GOING
REACH-HF	216	HFrEF, LVEF ≤ 45%, on OMT,	Single center, randomized (1:1) control trial, RDN + OMT VS OMT	12 months			ON GOING
DIASTOLE	60	LVEF > 50 %, LV diastolic dysfunction, hypertensive	Randomized (1:1) control trial, RDN + OMT VS OMT				Currently recruiting participants

SPYRAL HTN PIVOTAL
Randomized, sham-controlled trial



[1]Only for patients discontinuing anti-hypertensive medications. [2]According to scheduling. [3]Drug testing to ensure no medications are present. [4]Optional follow up at weeks 6 and/or 10 if the patient is not controlled. [5]Only for patients with BP ≥140 mmHg at 3M. [6]Drug testing to ensure prescribed medications are present (if on drug). [7]6 and 12 month renal imaging.

Courtesy of Medtronic