Transcatheter Renal Denervation

AMC Experience SYMPLICITY Registry

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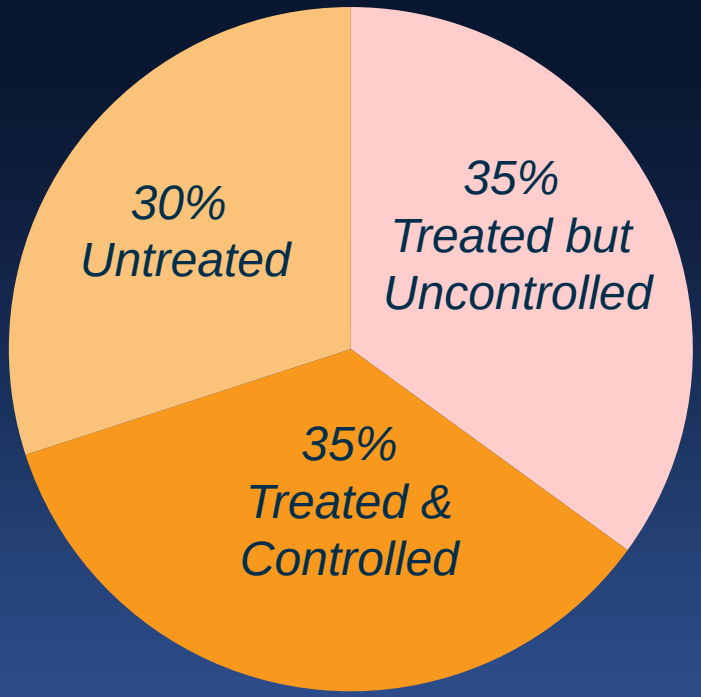
Hypertension Epidemiology



- Single largest contributor to death worldwide
- Every 20/10 mmHg increase in BP correlates with a doubling of 10-year cardiovascular mortality
- Dramatically increases risk of stroke, heart attack, heart failure, & kidney failure
- Only half of all treated hypertensive patients are controlled to established BP targets
- High prevalence:
  - Affects 1 in 3 adults
  - 1B people worldwide → 1.6 B by 2025
- **Resistant HTN : 5-30%**

Chobanian et al. Hypertension. 2003;42(6):1206–1252.

Effects of Increased Sympathetic Tone

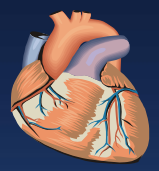
Causes of increased afferent signaling from the kidney to central integrative structures

Consequences of increased efferent sympathetic outflow to the kidney and other organs

Factors that might contribute to increased renal afferent signaling:

- Adenosine
- Acidosis
- Oxidative stress
- Inflammation
- Endothelial factors
- Angiotensin II
- ischemia

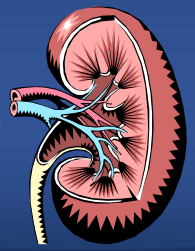
Renal denervation



Remodeling
Hypertrophy
Arrhythmias
Ischemia
Apoptosis

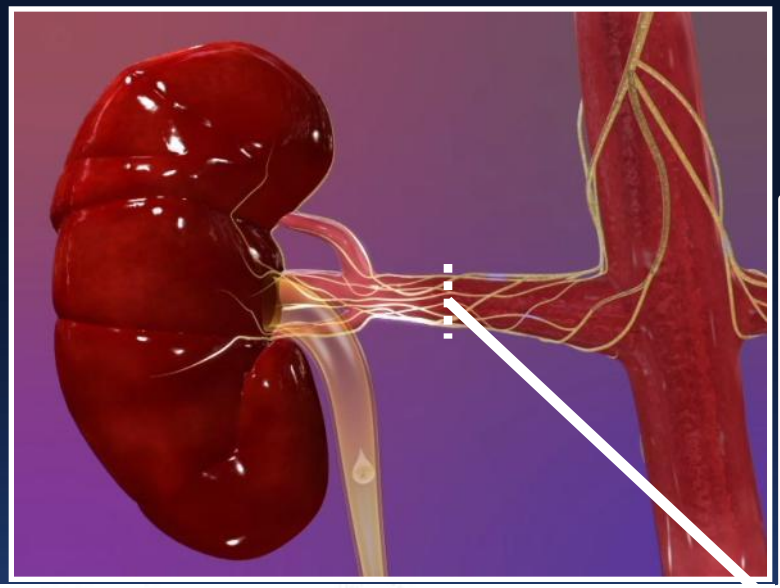
Medial hyperplasia
Arterial compliance ↓
Endothelial dysfunction

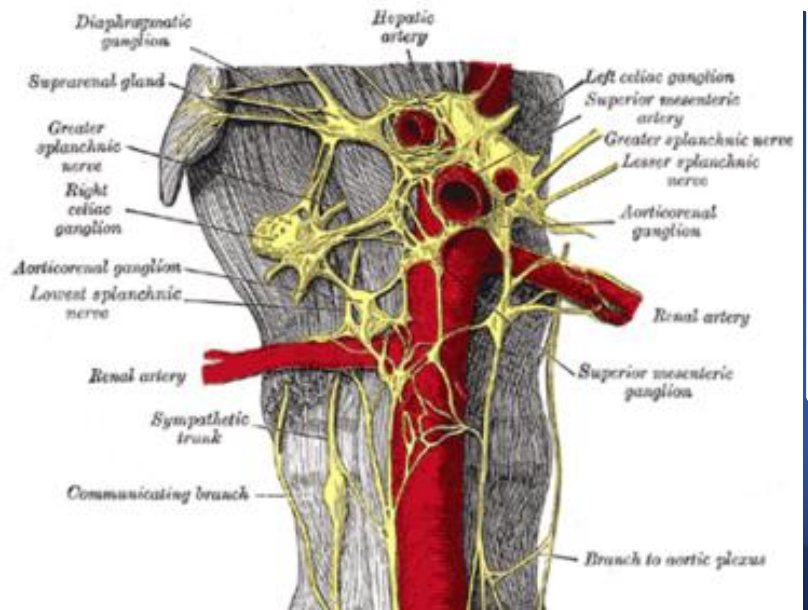
Renal injury / Renal ischemia



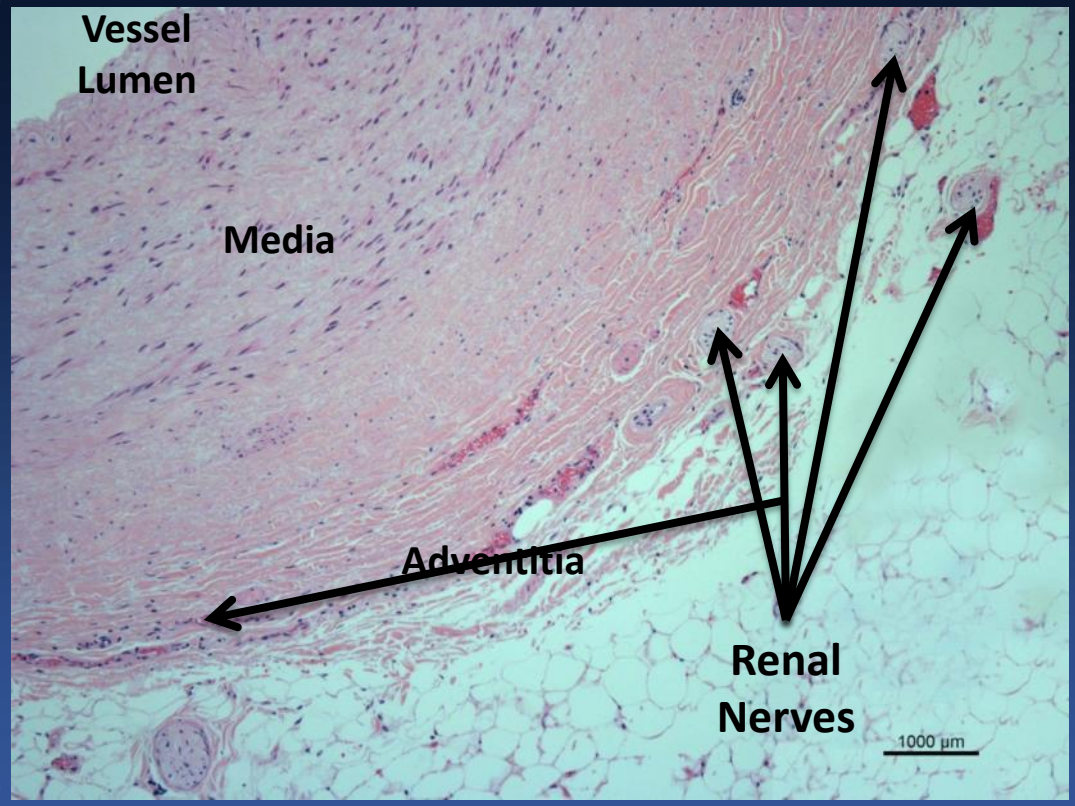
Na^+ / H_2O retention
Reduced renal blood flow
Activation of the RAAS
Proteinuria
Glomerulosclerosis

Renal Nerves as a Therapeutic Target





- Arise from ~ T10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia

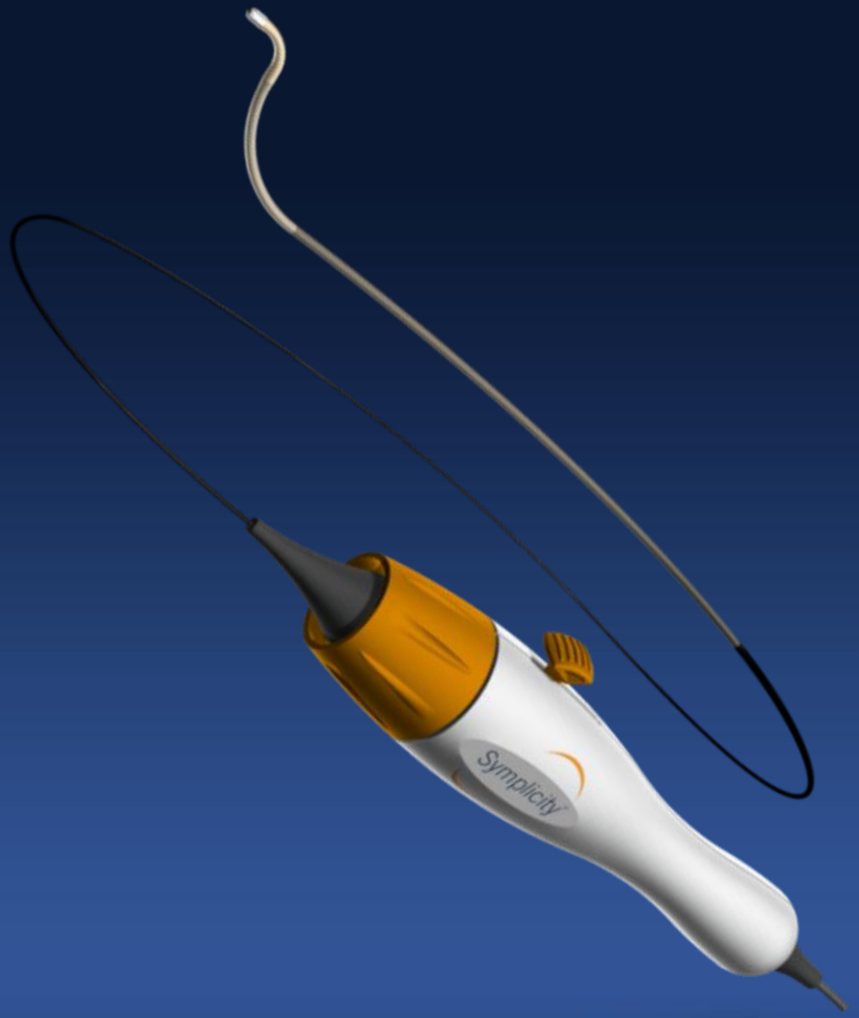


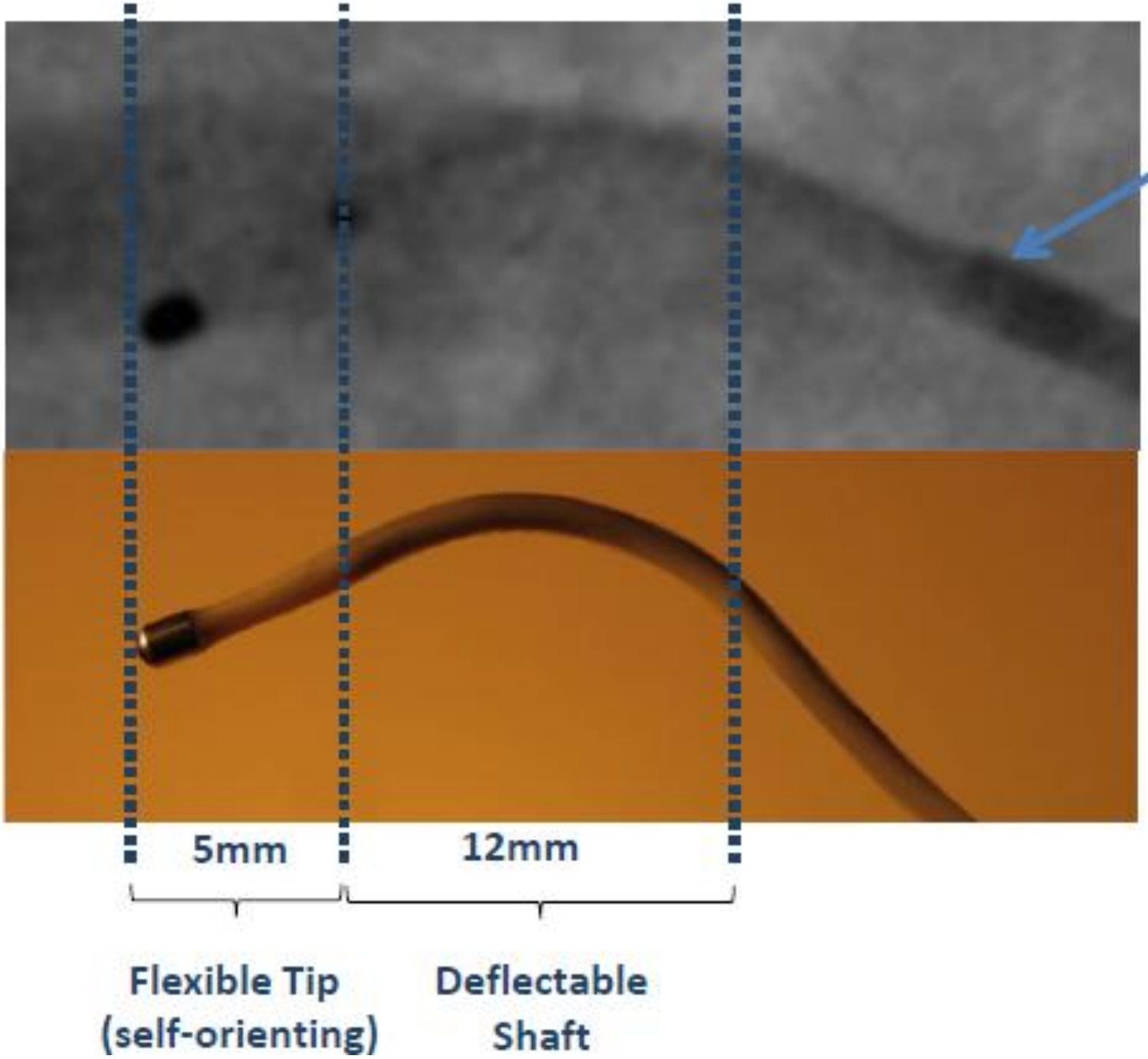
Generator

- Energy maximum 8 Watt
- It automatically switches off if
  - temperature increases too fast or too slowly
  - temperature is higher than 75 ˚C
  - Impedance does not decrease sufficiently

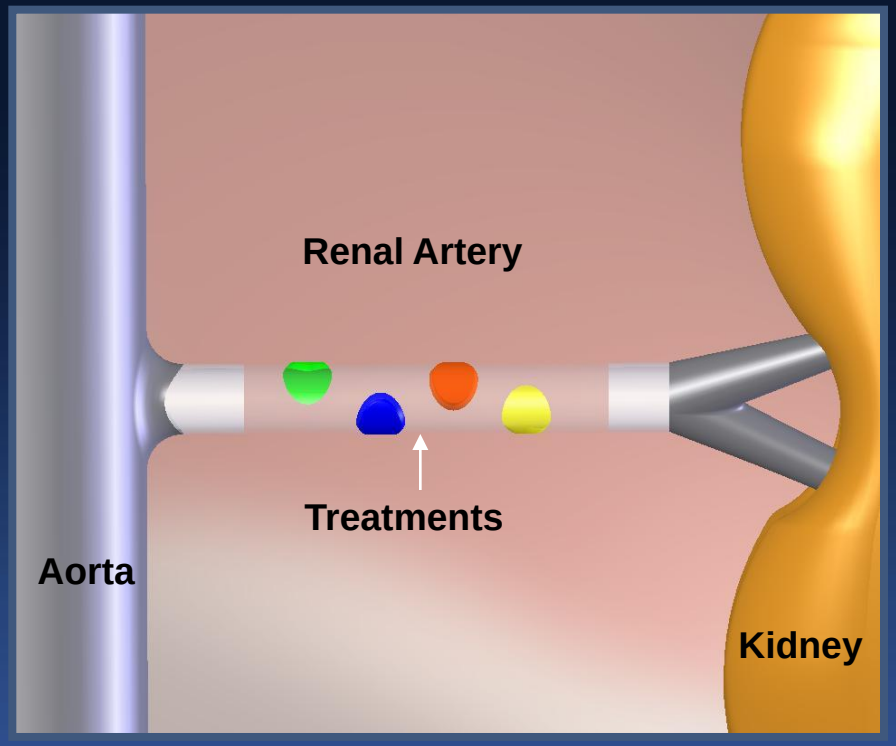
Simplicity™ Catheter

- Radiofrequency electrode tip
- Handle allows bending of the tip and rotation
- Compatible with a 6 F guiding catheter



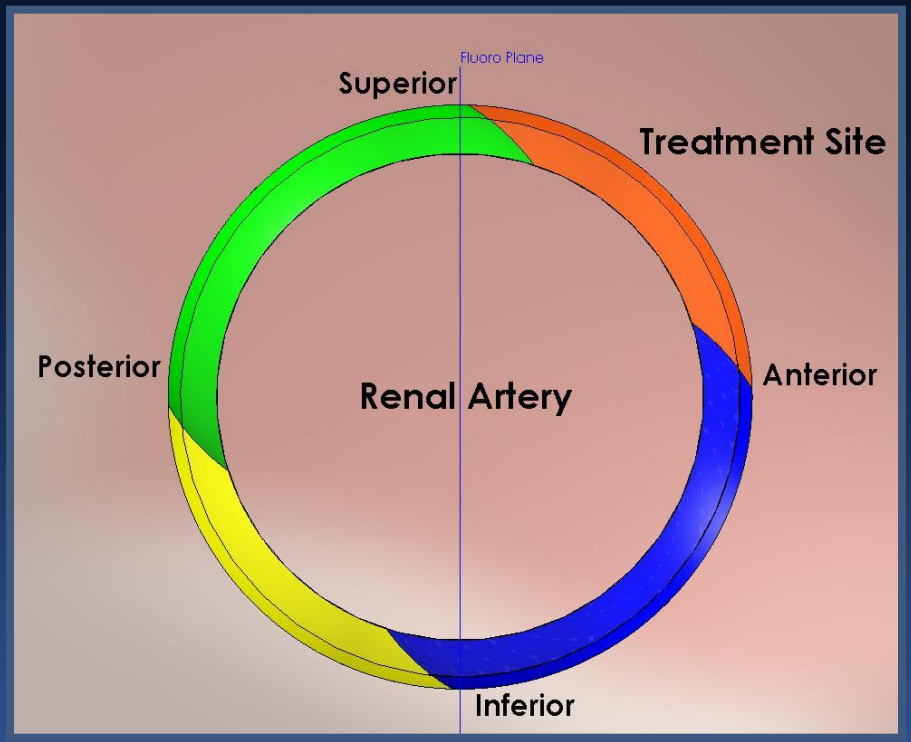

Tip of Guiding catheter
5mm
12mm
Flexible Tip (self-orienting)
Deflectable Shaft

Treatment Strategy



Focal ablations

spaced along vessel



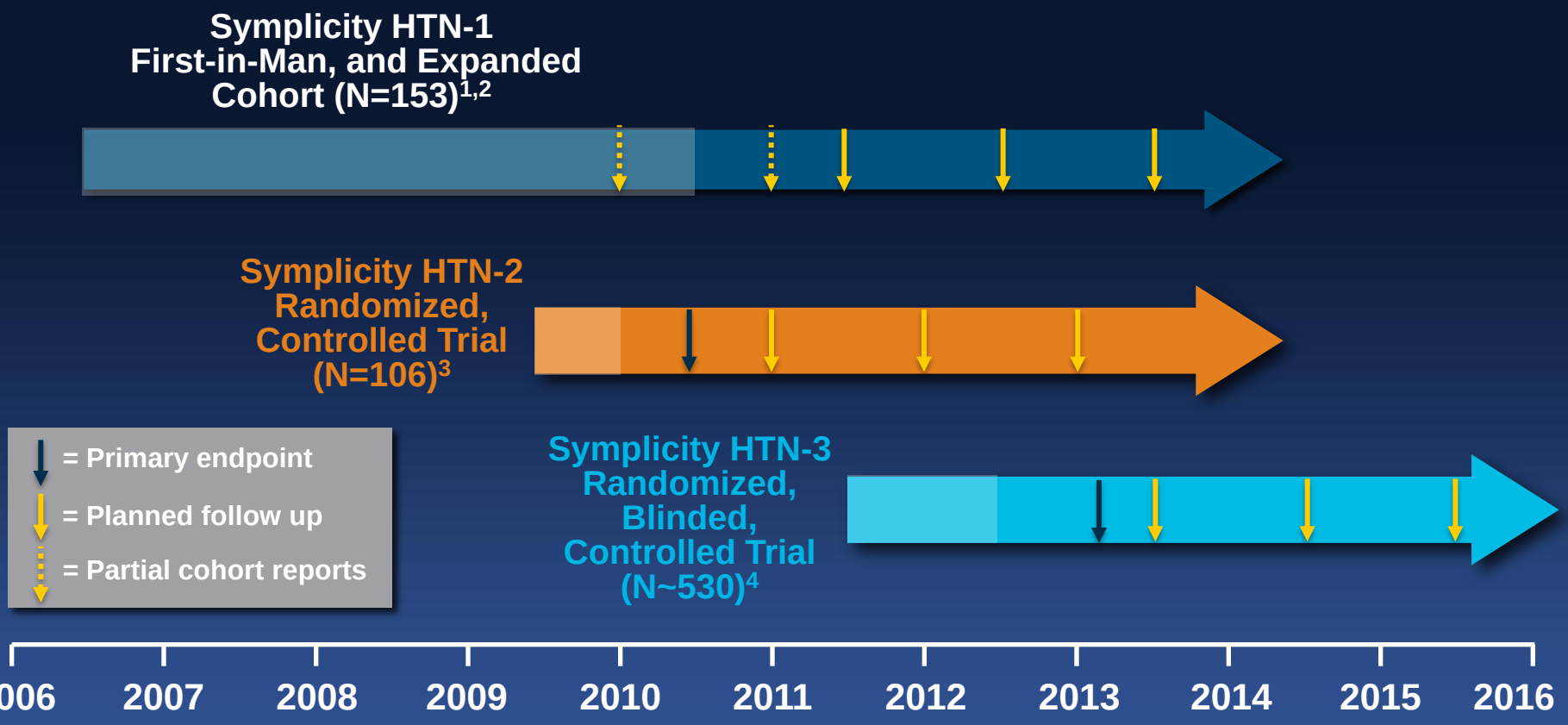
Multiple focal ablations

↑ circumferential coverage

Procedural details

- Premedication
  - Aspirin 100 mg/day (to be continued for 1 week)
  - 10-20 mg morphin + sedatives
  - 5,000 U heparin
  - Nitro i.a.
- 6 F femoral sheath
- 6 F renal guiding catheter
- Angiography of all renal arteries
- Introduce radiofrequency catheter
- 4-8 ablations, 2 min each

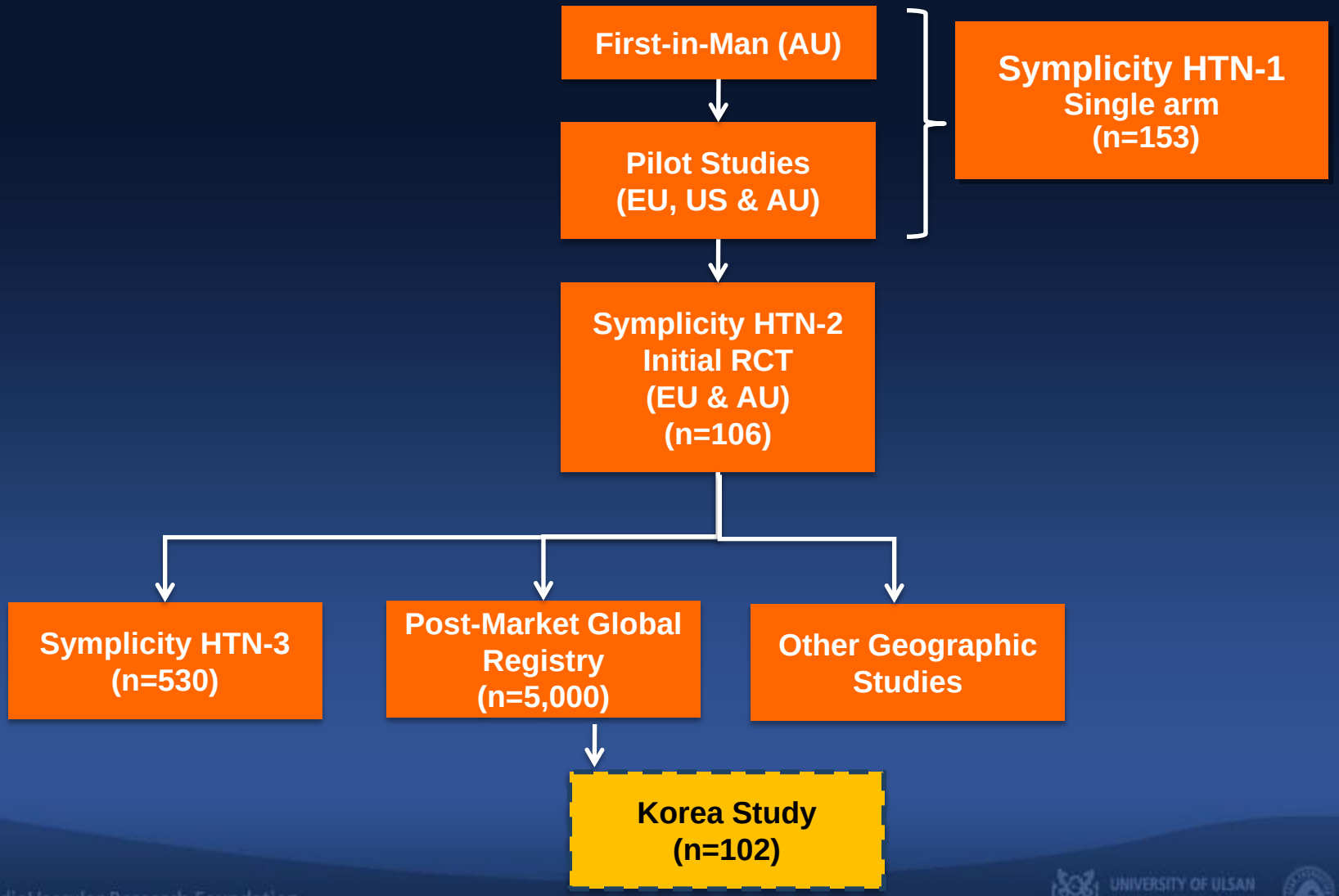
The Symplicity HTN Clinical Trial Program



Shading on bars indicates clinical trial enrollment periods.
Enrollment period for HTN-3 is estimated.

1. Krum H, et al. *Lancet*. 2009;373:1275-1281.
2. Symplicity HTN-1 Investigators. *Hypertension*. 2011;57:911-917.
3. Esler et al. *Lancet*. 2010;376:1903-1909.
4. Data on file, Medtronic.

Global Program for Uncontrolled Hypertension



SYMPLICITY Korea study

Patients & Centers

Study Population

- Approximately 5000 patients will be enrolled in Global SYMPLICITY Registry
- All consecutive patients who undergo the renal denervation procedure are candidates to be enrolled
- Patients should be treated according to routine hospital care

Centers

- Approximately 200 centers world-wide

Korea Patients and Centers

Study Population

- Approximately 200 patients will be enrolled in the Global SYMPLICITY Registry in Korea
- Focus in Korea is on resistant hypertension patient population for purposes of Health Technology Assessment submission

Centers

- Approximately 10 centers in Korea

Korea Centers and Principal Investigators

Site	Principal Investigator
Asan Medical Center	Seung-Jung Park
Gachon University Gill Hospital	Tae-Hoon Ahn
Gangnam Severance Hospital	Hyuck-Moon Kwon
Korea University Guro Hospital	Chang-Gyu Park
Kyung Hee University Hospital	Chong-Jin Kim
Samsung Medical Center	Hyeon-Cheol Gwon
Seoul National University Bundang Hospital	Dong-Ju Choi
Seoul National University Hospital	Hyo-Soo Kim
Seoul Saint Mary's Hospital	Ki-Bae Seung
Severance Hospital	Yang-Soo Jang

Key Inclusion Criteria

- Age ≥ 18 years
- Systolic blood pressure **≥ 160 mmHg** (≥ 150 mmHg for type 2 diabetics) based on an average of 3 office blood pressure readings.
- Patient is adhering to a stable drug regimen including **3 or more** antihypertensive medications (with no changes for a minimum of 2 weeks prior to enrollment)

Key Exclusion Criteria

- Ineligible anatomy:
  - Main renal arteries < 4 mm in diameter
  - Main renal arteries < 20 mm length
  - Renal artery abnormality or stenosis
- History of prior renal artery intervention
- eGFR of < 45mL/min/1.73m^2

Clinical Data Measures

- Key measures:

Patient demographics
Medical health history
Office Blood Pressure
Heart rate
Renal artery imaging (prior to procedure)
Medications Log
EQ5D Quality of Life

Study Design

Recommended Follow-up assessments will be performed at:

- 3 months ± 30 days
- 6 months ± 30 days
- 1 year ± 60 days
- 2 year ± 60 days
- 3 year ± 60 days
- Possibly 4 year ± 60 days
- Possibly 5 year ± 60 days

Baseline Characteristics

	Symplicity HTN-2 (n=52)	AMC (n=13)
Baseline Systolic BP (mmHg)	178 ± 18	179.9 ± 16.6
Baseline Diastolic BP (mmHg)	97 ± 16	100.3 ± 15.9
Age	58 ± 12	54 ± 13.5
Gender (% female)	35%	23.1%
BMI (kg/m^2)	31 ± 5	26.4 ± 3.7
Type 2 diabetes	40%	28%
Coronary Artery Disease	19%	46.2%
Hypercholesterolemia	52%	100%
eGFR (MDRD, ml/min/1.73m^2)	77 ± 19	68.2 ± 13.2
Serum Creatinine (mg/dL)	1.0 ± 0.3	0.97 ± 0.3
Urine Alb/Creat Ratio (mg/g)†	128 ± 363	1125.9 ± 1173.9
Heart rate (bpm)	75 ± 15	73.8 ± 7.2

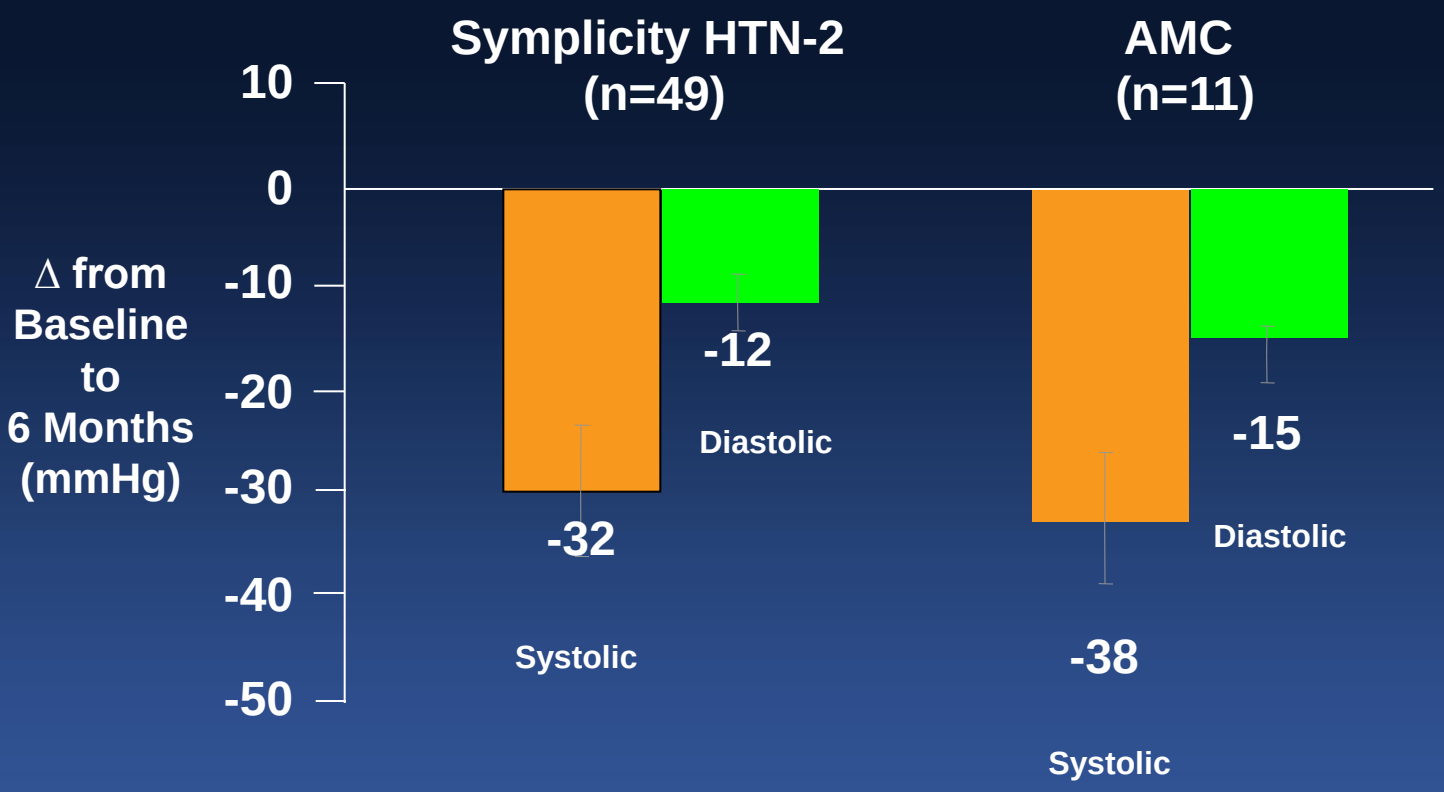
Esler et al. *Lancet*. 2010;376:1903-9.

Baseline Medications

	Symplicity HTN-2 (n=52)	AMC (n=13)
Number Anti-HTN medications	5.2 ± 1.5	3.8 ± 1.1
% patients on HTN meds >5 years	71%	72.7%
% percent patients on ≥5 medications	67%	15.4%
% patients on drug class:		
ACEI/ARB	96%	92.3%
Direct renin inhibitor	15%	-
Beta-adrenergic blocker	83%	92.3%
Calcium channel blocker	79%	66.7%
Diuretic	89%	81.8%
Aldosterone antagonist	17%	9.1%
Vasodilator	15%	7.7%
Alpha-1 adrenergic blocker	33%	27.3%
Centrally acting sympatholytic	52%	-

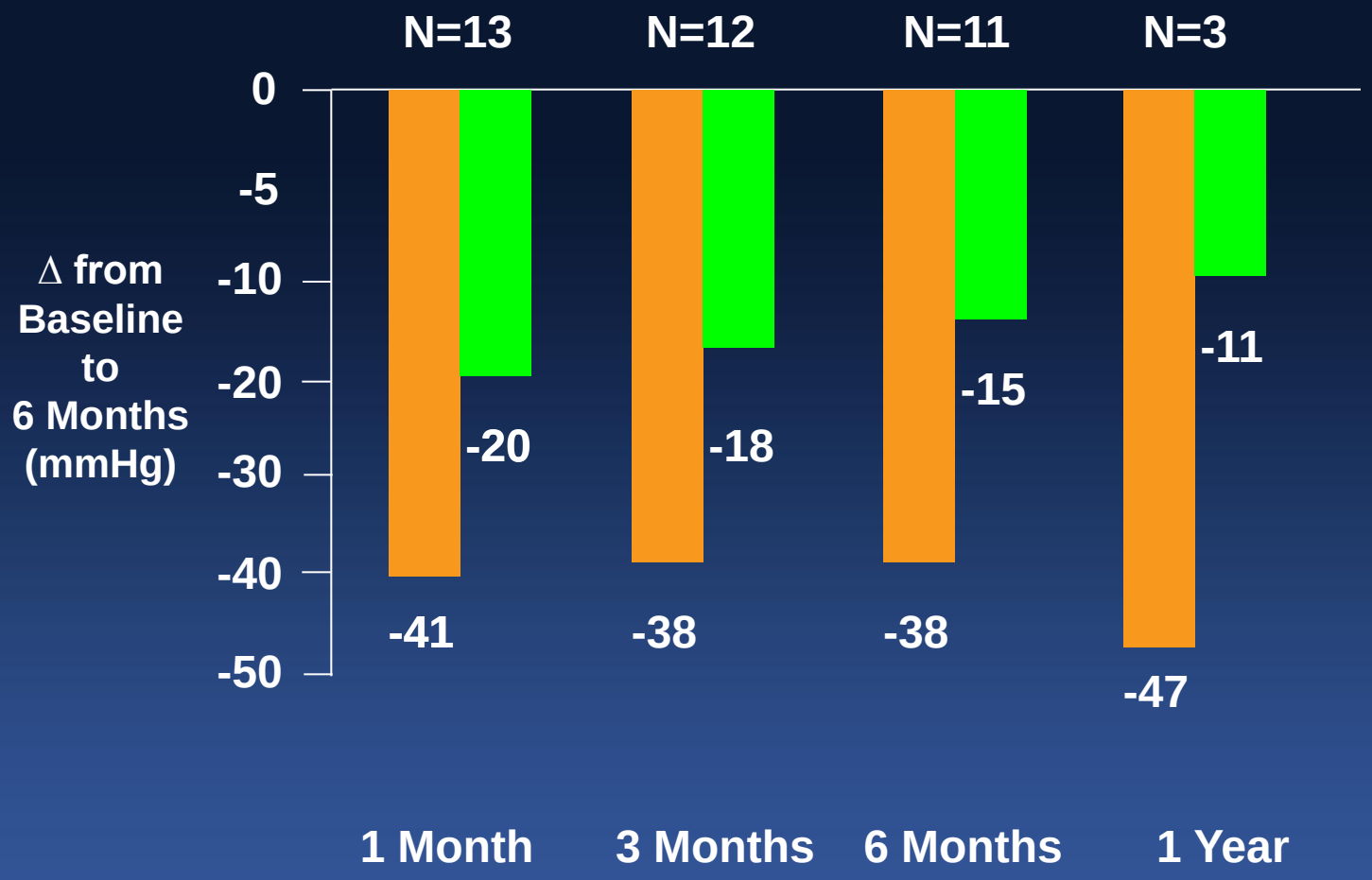
Esler et al. *Lancet*. 2010;376:1903-9.

Primary Endpoint: 6-Month Office BP



Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-9.

Change in Office BP : AMC



AMC Data

Procedural Safety

- Procedure time : 81 ± 4.5 minutes
- Amount of Contrast Medium : 63.9 ± 6.8 cc

  - 1 patient : Cr 0.90 -> 1yr later : 1.21 DM with Nephropathy
- Ablation Points

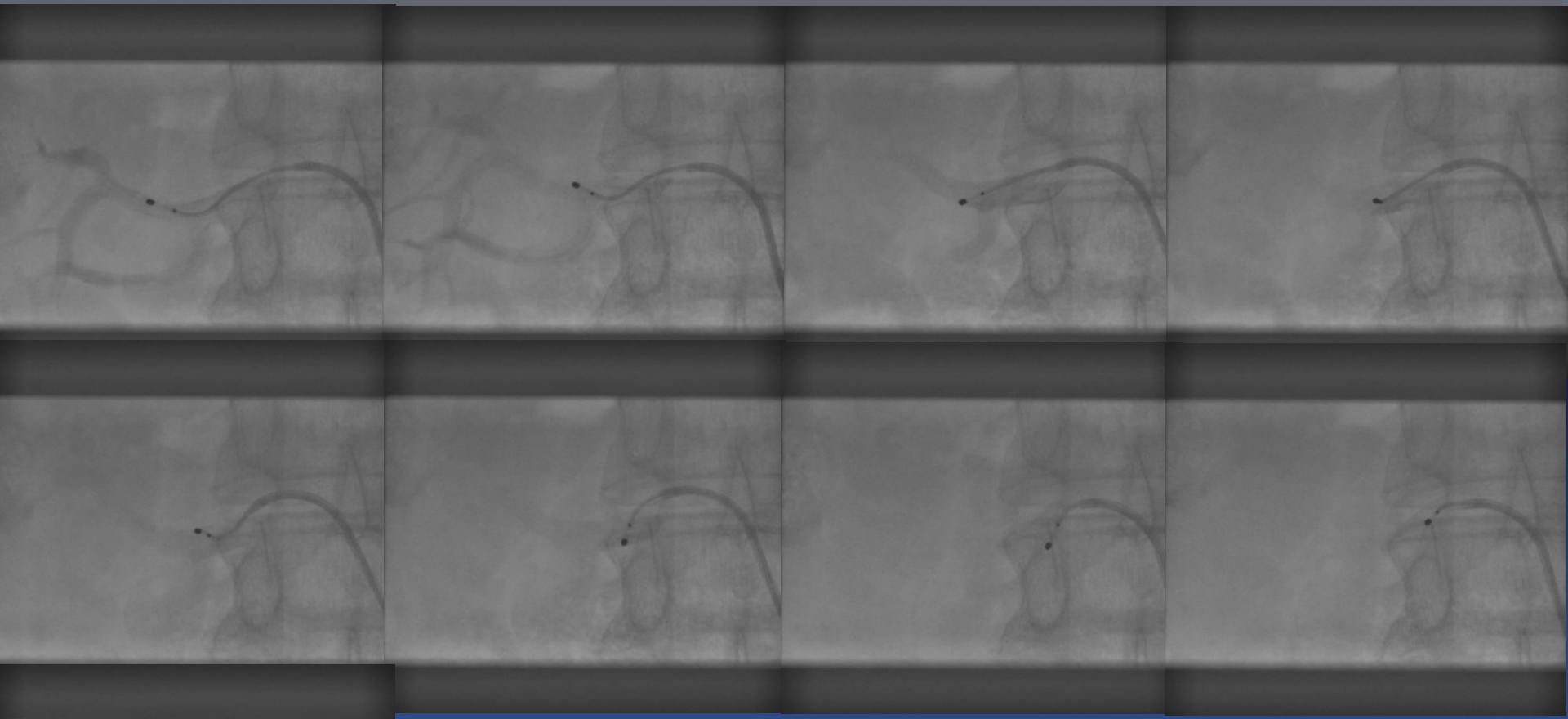
  - Right : 11.5 ± 3.8

  - Left : 13.1 ± 4.5
- Intravenous narcotics & sedatives used to manage pain during delivery of RF energy
- No catheter or generator malfunctions
- No major complications
- No Minor complications

AMC Cases - RAS

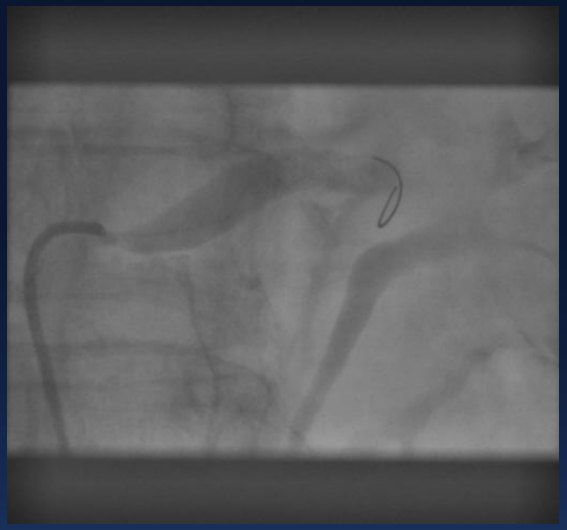
- 65/ M, 170cm, 68kg
- HTN, variant angina
- Exforge 5/160mg, dilatrend 25mg, atacand plus 1T qd.
- Initial BP: 178/122, HR 87/min
- Cr 0.9
- Procedure time; 120 min
- Contrast medium ; Visipaque, 90 cc

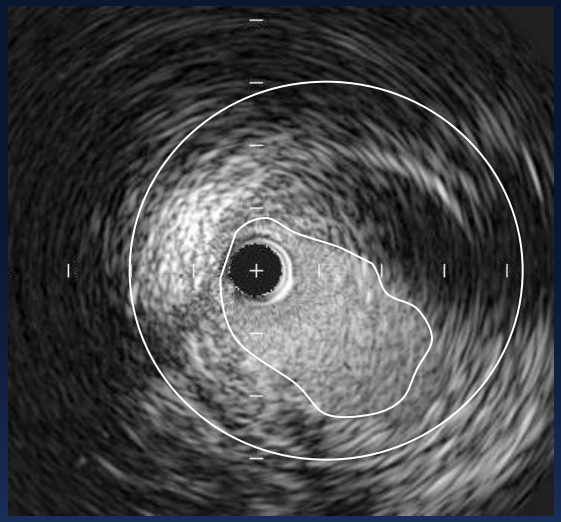
Successful Ablation in Right Renal Aretery

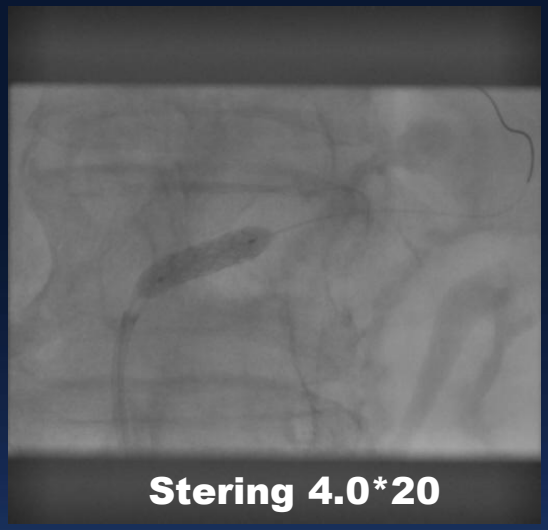


Totally, 14 ablations were done in Right Renal Artery

And Then, Left Renal Artery….







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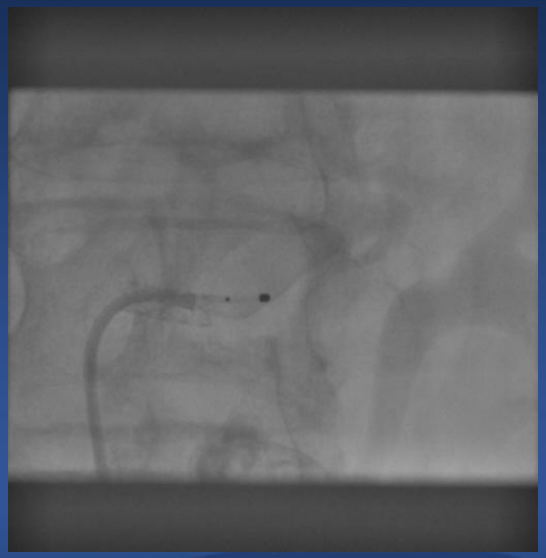


Additionally, 14 ablations were done in Left Renal Artery

Follow Up

- No procedure related complication
- Discharge 1 day later
- 1 month follow up : 140/80 mmHg, HR 70
- 3 months : 139/89 mmHg, HR68

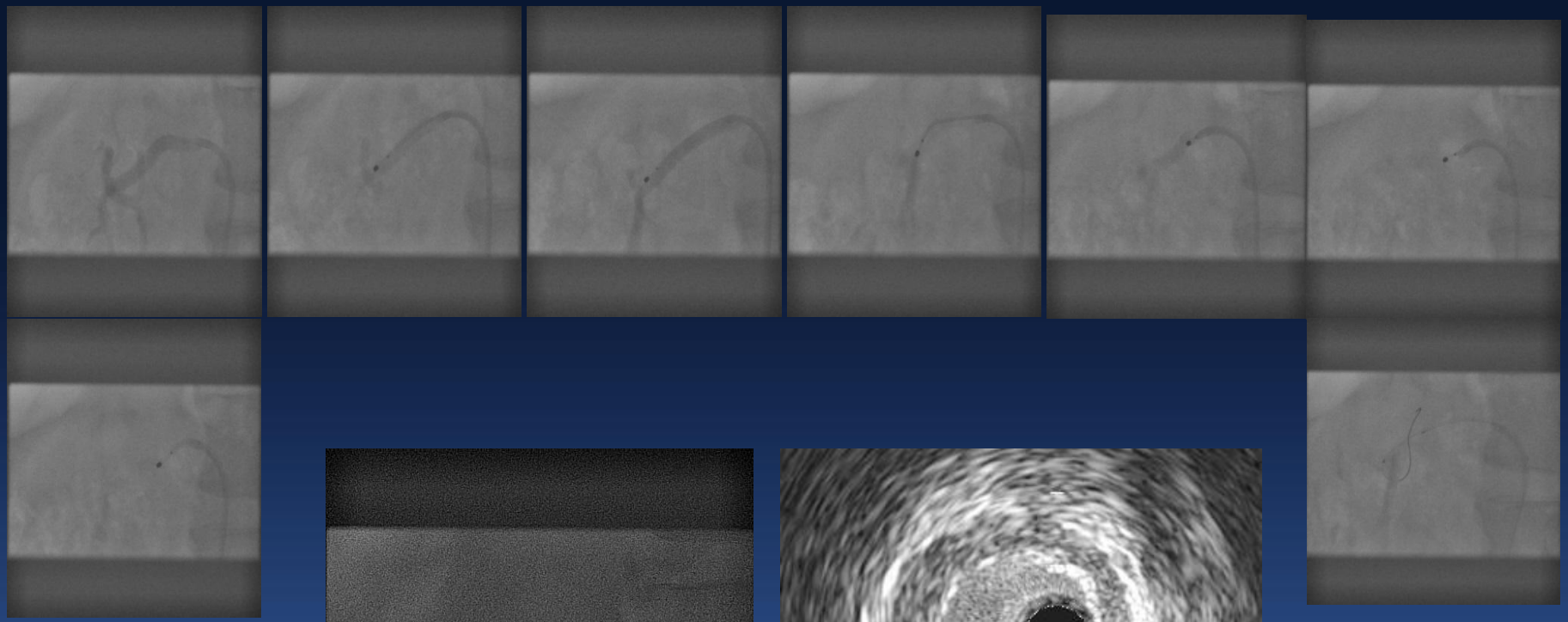
AMC Cases

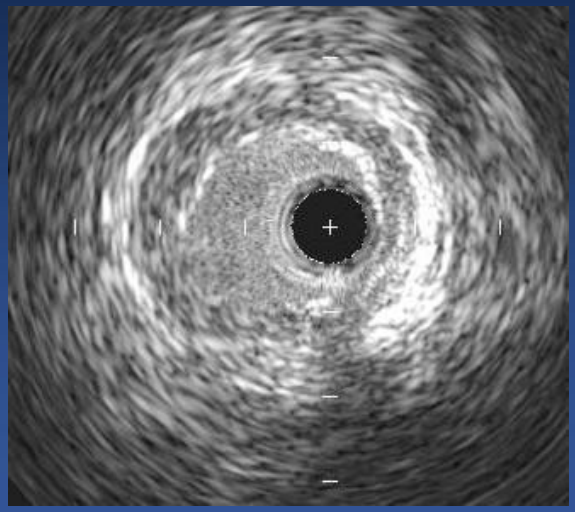
- 53/ M, 171cm, 78kg
- HTN, DM
- Caduet 5/20mg, cadura XL 1T, dichlozid 25mg, exforge 5/160mg, tenormin 50mg qd
- Initial BP: 167/88
- Cr 0.97
- Procedure time; 80min
- Contrast medium ; Visipaque, 70 cc

Successful Ablation in Left Renal Aretery

Totally, 14 ablations were done in Left Renal Artery

And Then, Right Renal Artery….





Additionally, 14 ablations were done in Right Renal Artery

Follow Up

- No procedure related complication
- Discharge 1 day later
- 1 month follow up : 155/85 mmHg, HR 78
- 3 months : 145/85 mmHg, HR 77
- 6 months : 135/78 mmHb, HR 65

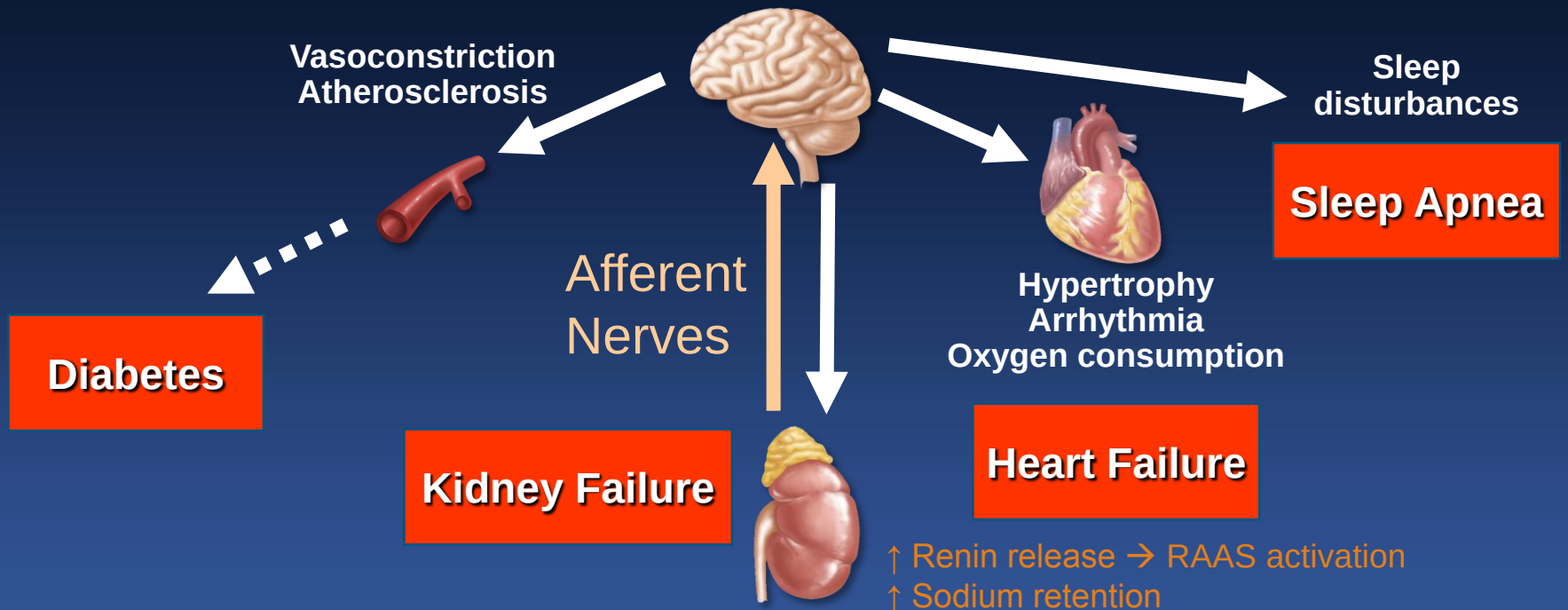
Unmet Needs in RND?

- No Sham Control Group – Symplicity HTN-3
- 24 ABPM was available in a small portion
- Long term effect during nerve regeneration
- Exclusion : dual renal artery, accessory artery, no data on unilateral RND
- Lack of preprocedural marker
- No clinical applicable technique
- No data ; less severe HTN, hard end points
- Cost-benefit studies
- Standardized certification of RND centers

Schmieder RE, et al. J Htn 2012;30:837-41

Future Directions for Research

- Chronic activation of renal nerves is common in multiple conditions/disease states[1,2]
- Future research may be warranted in disease states characterized by hyperactive afferent and efferent renal nerves



RAAS = renin-angiotensin-aldosterone system.

1. Adapted from Schlaich MP, et al. *Hypertension*. 2009;54:1195-1201.
2. Blankestijn PJ, et al. *Nephrol Dial Transplant*. 2011;26:2732-2734.

Conclusions

- Transcatheter Renal Denervation results in significant reductions in BP
- The procedure seems to be very safe
- The effect is sustained up to 1 year
- It may also be beneficial in patients with diabetes, sleep apnea, heart failure and other diseases
- However, we still need to be under the strict indication, such as true resistant hypertension