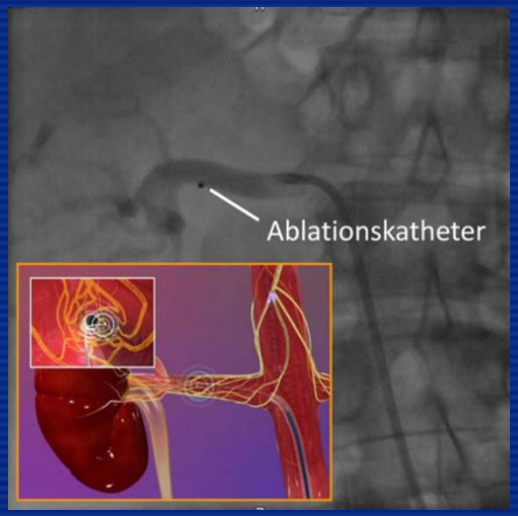
SAMSUNG
삼성서울병원

JCR 2013

Real World Experience with Renal Denervation Therapy

Seung-Hyuk Choi
Division of Cardiology
Samsung Medical Center
Seoul, Korea



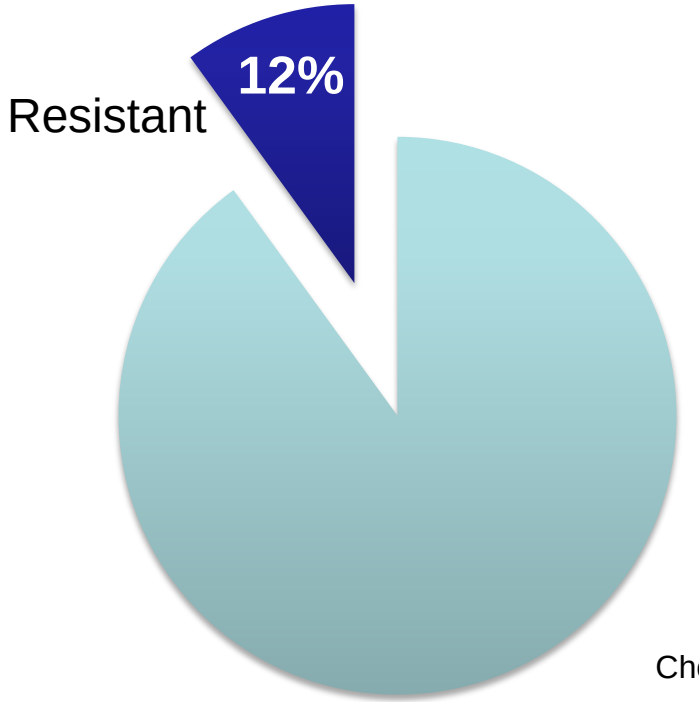
Hypertension

A Major Public Health Burden

- **Astonishing prevalence**
  - **1 in 3 adults**
  - **1 billion people worldwide → 1.6 billion by 2025**
- **Single largest contributor to death**
- **Dramatically increases risk of heart attack, stroke, heart failure, kidney failure & insulin resistance**

Resistant hypertension

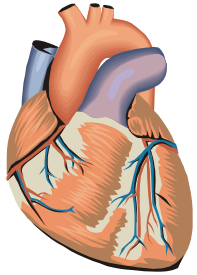
- **Failure to achieve target blood pressure (<140mmHg) values despite triple drug regimen (including a diuretic)**



Chobanian AV. Hypertension 2003; 42:1206-52.
Calhoun DA. Circulation 2008; 117:e510-26.

Renal Sympathetic Nerve Activity:
RDN Disrupts Renal Nerves, Lowering SNS Activity

- Vasoconstriction
- Atherosclerosis



- ↑ Contractility
- ↑ Heart rate
- Hypertrophy
- Arrhythmia
- Heart Failure

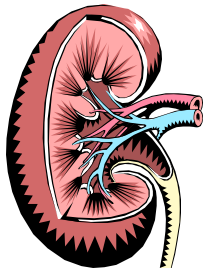
Efferent Nerves

-- *Renal Denervation (RDN)* --

Afferent Nerves

Blood Pressure

+ Increase co-morbidities

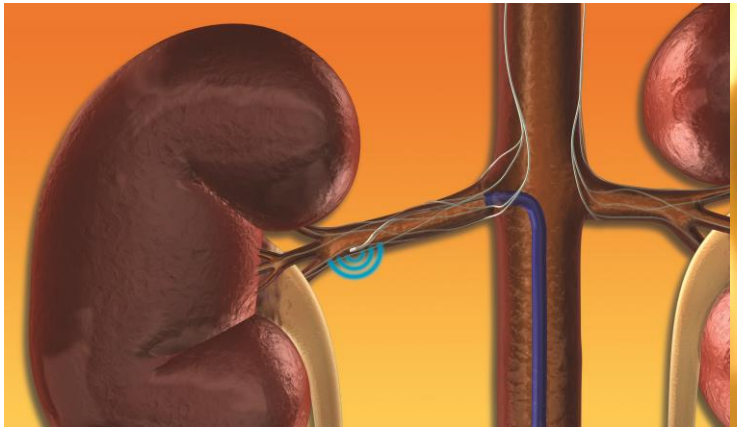


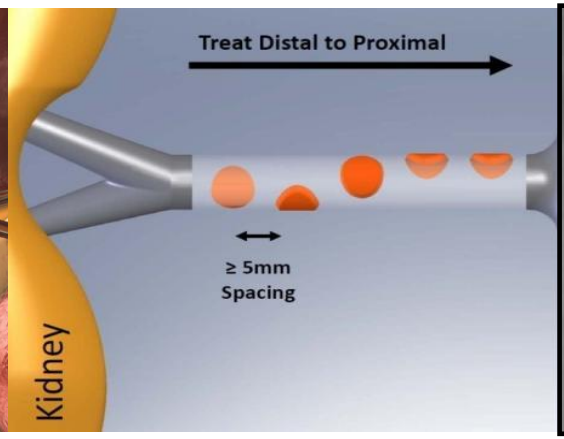
- ↑ Renin Release → RAAS activation
- ↑ Sodium Retention
- ↓ Renal Blood Flow
- ↓ Kidney function

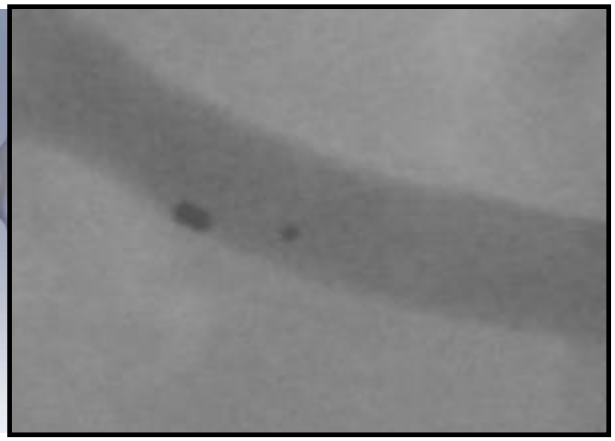
Schlaich et al. Hypertension. 2009;54(6):1195-1201.

Schlaich et al. Hypertension. 2009;54(6):1195-1201.

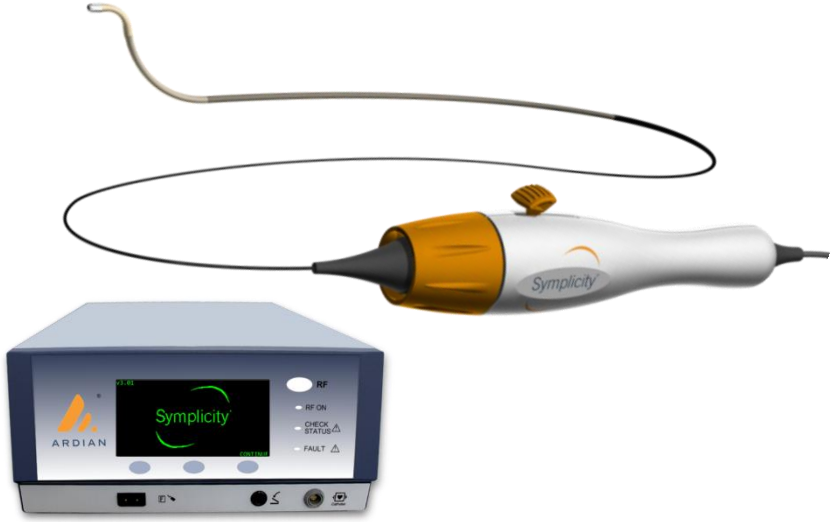
Ardian Symplicity Catheter System







- Standard interventional technique: 6,8F
- 4-6 two-minute treatments per artery
- Proprietary RF Generator
  - Automated
  - Low-power (8W)
  - Built-in safety algorithms



Staged Clinical Evaluation

Symplicity HTN-1

First-in-Man ✓

Series of Pilot studies ✓

Symplicity HTN-2 ✓
EU/AU Randomized Clinical Trial

USA

Symplicity HTN-3
US Randomized Clinical Trial
(upcoming)

EU/AU

Other Areas of Research:
Insulin Resistance, HF/Cardiorenal,
Sleep Apnea, More

The Symplicity HTN-1 & 2 Trials

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

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

*Symplicity HTN-2 Investigators**

Lancet. 2010;376:1903-9

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Renal Sympathetic Denervation for Treatment of Drug-Resistant Hypertension : One-Year Results From the Symplicity HTN-2 Randomized, Controlled Trial

Murray D. Esler, Henry Krum, Markus Schlaich, Roland E. Schmieder, Michael Böhm and Paul A. Sobotka
for the Symplicity HTN-2 Investigators

Circulation 2012;126:2976

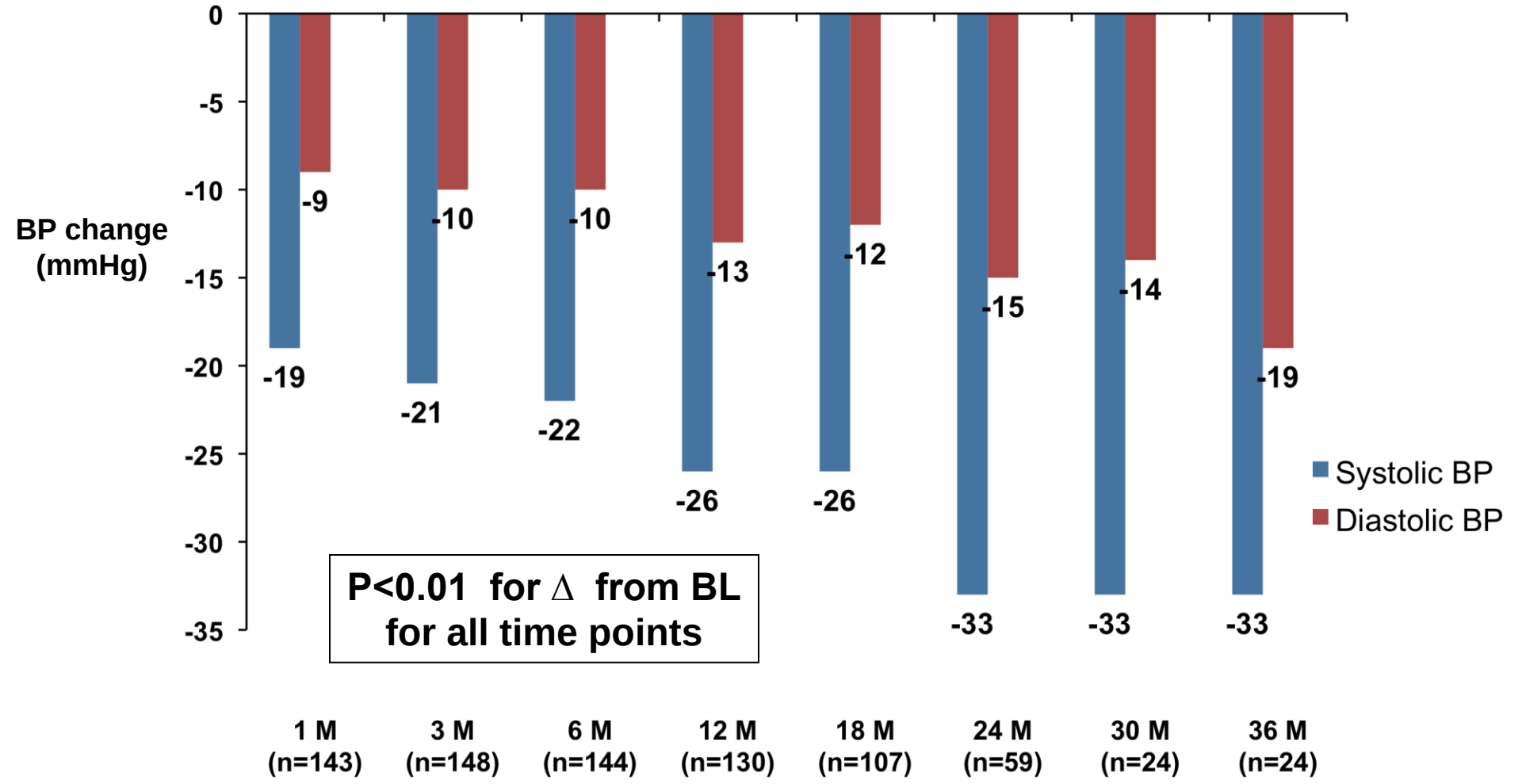
Inclusion and exclusion criteria

- **Key inclusion criteria**
  - **Office blood pressure *≥160 mmHg (≥150 mmHg for diabetics)* despite ≥3 anti-hypertensive medications**
  - **eGFR (MDRD) ≥45 mL/min/1.73m^2**

- **Key exclusion criteria**
  - **known secondary cause of hypertension**
  - **Type I diabetes mellitus**
  - **renovascular abnormalities: significant renal artery stenosis, prior renal stenting or angioplasty, dual renal arteries**

The Symplicity HTN-1 Trial

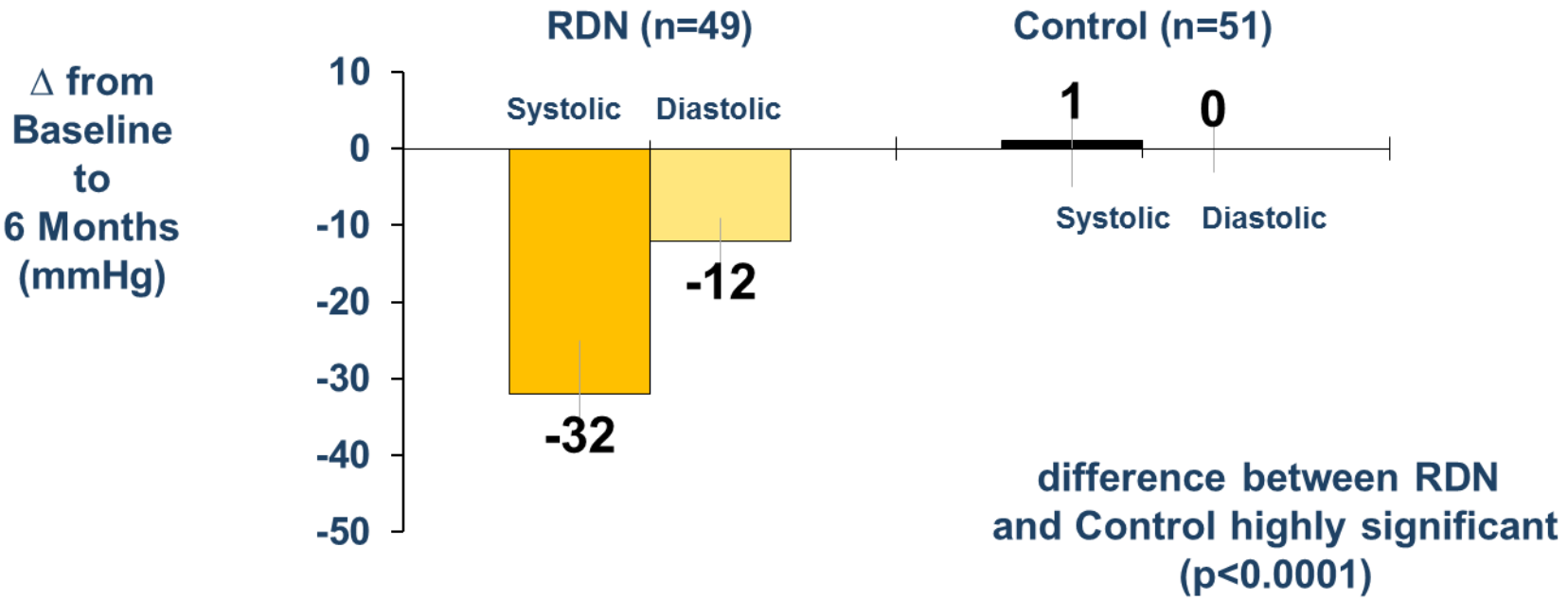
36 month F/U data



Sobotka et al. ACC 2012

The Symplicity HTN-2 Trial

Primary endpoint : Change in office systolic BP



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

Lancet 2010;376:1903-09

SYMPLICITY RDN Global Clinical Program

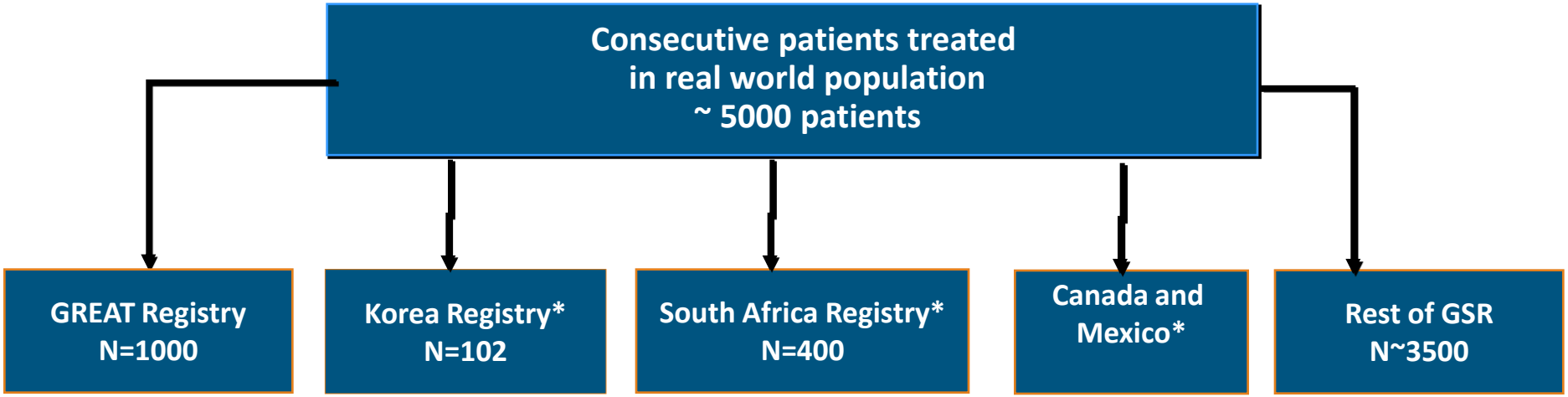
Enrollment Complete / In Follow Up

Symplicity HTN-1	Series of non-randomized pilot studies (n =153)	3 yr
Symplicity HTN-2	1:1 Randomization Symplicity Catheter System vs control (n = 106)	2 yr
SYMPLICITY HTN-3	Randomized Controlled Trial (2:1), (530 randomized)	Enroll complete

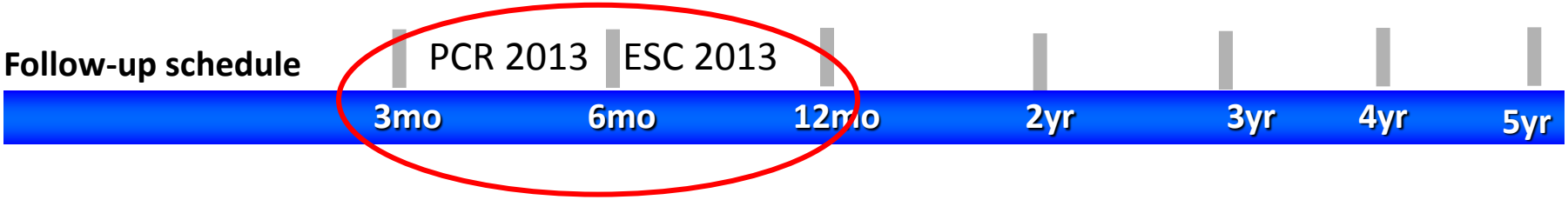
Planning / Enrolling

SYMPLICITY-HF	Feasibility Study, 40 subjects	Enroll
Global SYMPLICITY Registry	Prospective, non-interventional Registry, ~5,000 subjects	Enroll
SYMPLICITY HTN-Japan	Randomized Controlled Trial (1:1) n=100	Enroll
SYMPLICITY HTN-4	Randomized Controlled Trial	Plan
Symplicity HTN-India	Single-arm Study	Plan

Global SYMPLICITY Registry



~ 200 sites International
Min. 10% randomly assigned to 100% monitoring
30% monitoring to date

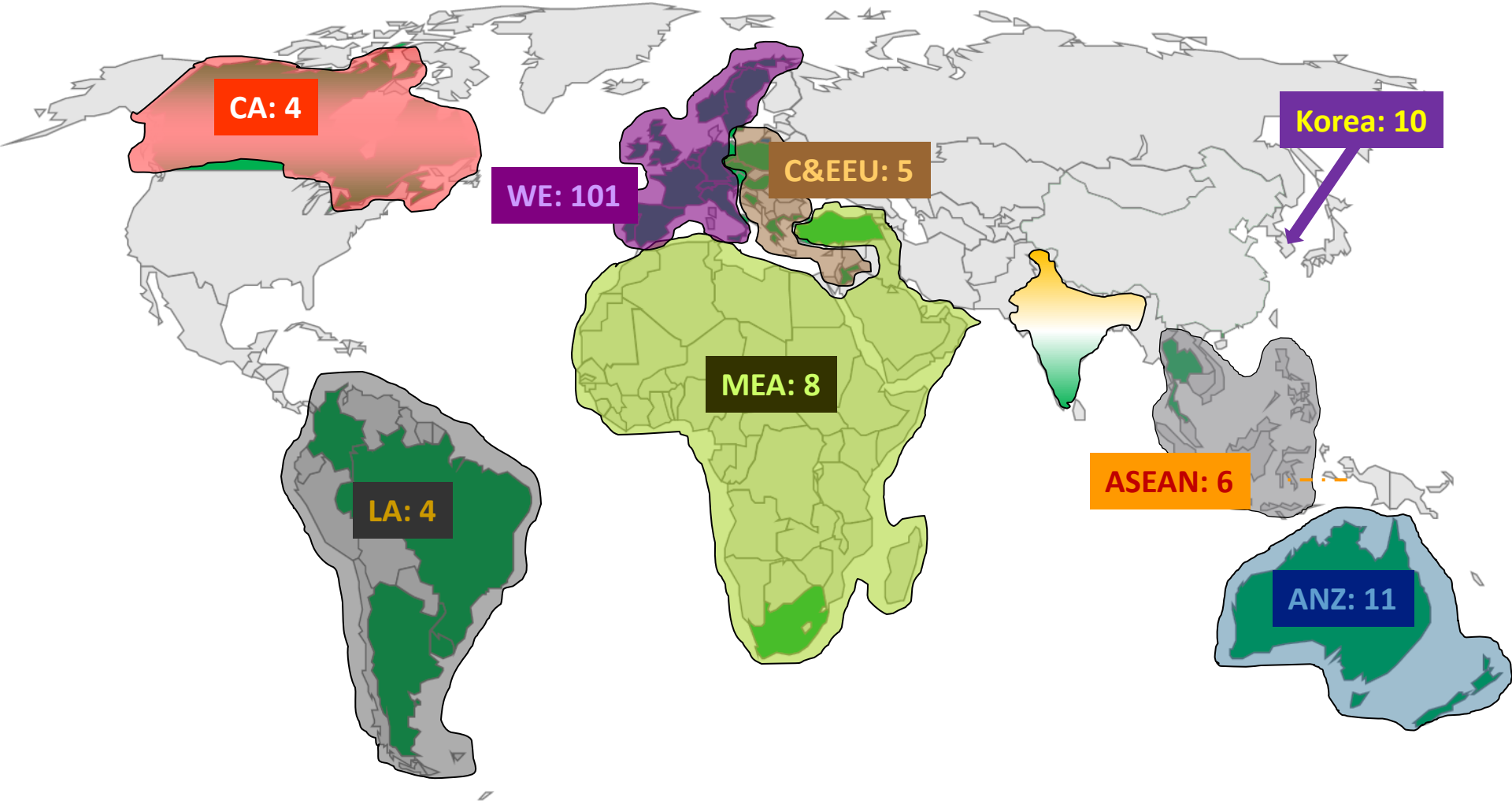


To document the **long-term safety and effectiveness** of renal denervation in a **real world** patient population

***: limited to resistant hypertension only**

Global SYMPLICITY Registry – Activated Site Locations

149 sites



Inclusion/Exclusion Criteria

Key Inclusion Criteria

- ≥ 18 years
- Systolic BP≥160 mm Hg, ≥150 mm Hg in type II diabetes
- Stable drug regimen of 3 or more medications

Key Exclusion Criteria

- Renal artery anatomy that is ineligible for treatment
  - Hemodynamically or significant renal artery abnormality
  - Renal diameter <4 mm or <20 mm treatable length
- eGFR <45 mL/min/1.73m^2
- Type 1 diabetes mellitus

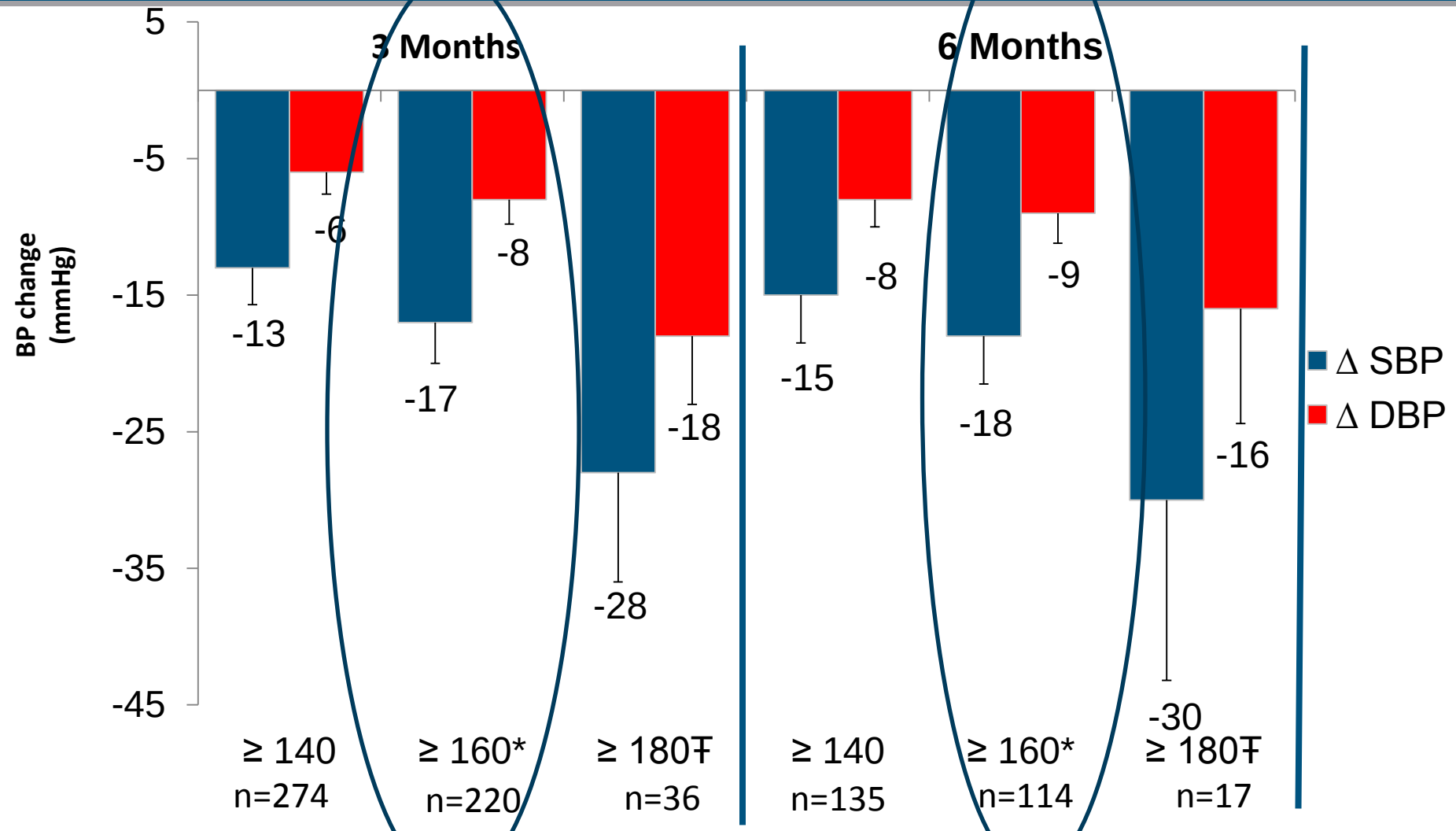
Baseline Patient Characteristics
All GSR Patients N=1158

Demographics	Age (years)	60 ± 12
	Gender (% male)	60%
	Race (% African Dissent)	1.3%
	BMI (kg/m^2)	31 ± 5.7
	History of Renal Insufficiency (eGFR<60)	21%
	eGFR (ml/min/1.73 m^2) n=1061	79 ± 44
	eGFR > 45 mL/min/1.73 m^2	90%
	Serum Creatinine (mg/dl) n=896	1.09 ± 0.79

Baseline Patient Characteristics
All GSR Patients N=1158

Baseline BP (mm Hg)	**164/89 ± 24/16**
Number of classes anti-HTN meds (mean)	4.39 ± 1.33
Diuretic (%)	76%
Aldosterone blocker (%)	20%
ACE (%)	35%
ARB (%)	65%
Beta-Blocker (%)	78%
Calcium Channel Blocker (%)	75%
Alpha adrenergic Blocker(%)	34%
Vasodilator (%)	14%
Direct Renin Inhibitor (%)	7%

Change in Office BP For overall GSR Population



P<.0001 for all values compared to baseline except: p=0.0002 (SBP≥180 mm Hg, 6 mo) p=0.0008 (DBP ≥180 mm Hg, 6 mo)

*≥ 150 mm Hg in Diabetics

Ŧ ≥ 100 mm Hg DBP

Mahfoud PCR 2013

Possible extended indication

Effect of renal denervation for moderate treatment resistant hypertension ?

Moderate treatment resistant hypertension
: 140mmHg <systolic BP <160mmHg

SMC registry

- **Key inclusion criteria**
  - **Office blood pressure ≥140 mmHg despite ≥3 anti-hypertensive medications**
  - **eGFR (MDRD) ≥45 mL/min/1.73m^2**

- **Key exclusion criteria**
  - **known secondary cause of hypertension**
  - **Type I diabetes mellitus**
  - **renovascular abnormalities: significant renal artery stenosis, prior renal stenting or angioplasty**

SMC registry (n=29)

Demographics	Age (years)	52 ± 14
	Gender (% female)	17.2%
Co-morbidities	Diabetes Mellitus II (%)	25.0%
	CAD (%)	17.2%
	Hyperlipidemia (%)	55.3%
	eGFR (mL/min/1.73m^2)	78.6 ± 16.3
Blood Pressure	**Baseline BP (mmHg)**	**166/102 ± 18/21**
	Number of anti-HTN meds (mean)	**3.6 ± 0.9**
	ACE/ARB (%)	89.7%
	Beta-blocker (%)	72.4%
	Calcium channel blocker (%)	82.8%
	Vasodilator (%)	3.4%
	Diuretic (%)	86.2%
	Spironolactone (%)	13.8%
	Alpha-blocker(%)	3.4%

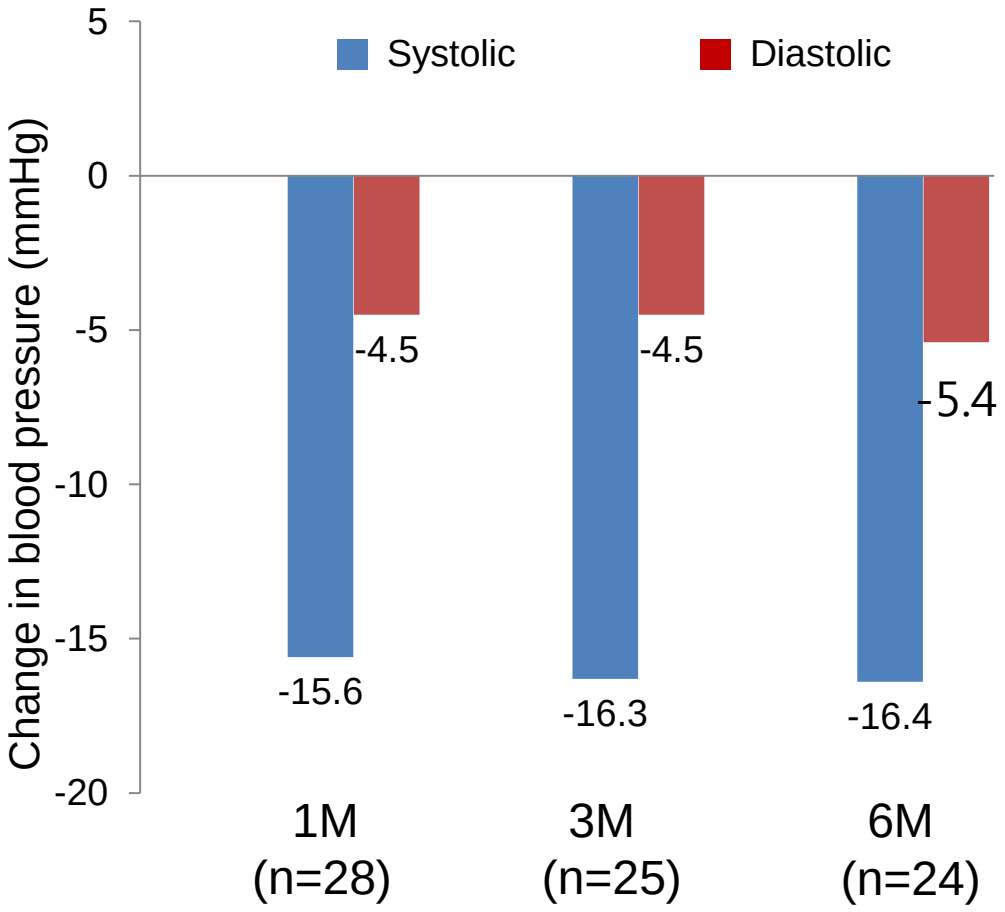
Procedural data

Total 38 case

	Right	Left
Number of denervation	5.9 (5-11)	5.3 (3-8)
RDC 1	26 (72%)	25 (69%)
IMA	10	11
Accessory vessel denervation	2	1
Wire guided procedure	6	7

- Mean procedure time : 56 minutes
- Contrast media : around 50 cc

Office BP change (n=29)



6 Month Non-responder : 9/24 (37.5%)
: defined as a SBP reduction of < 10mmHg

Case 1

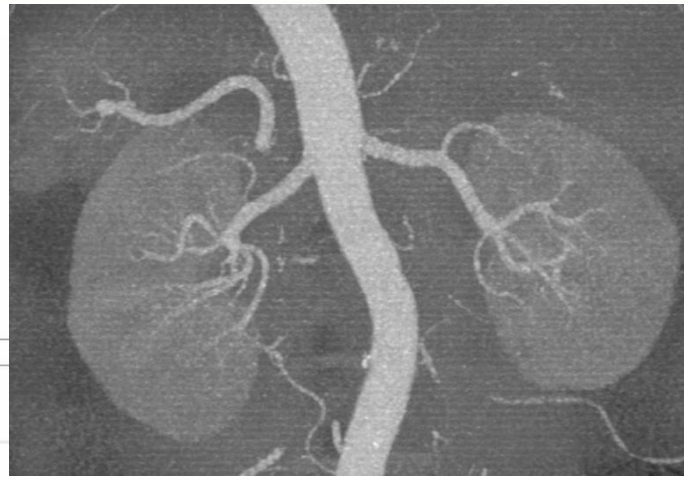
- **M/45**
- **Office BP : 170/115 mmHg HR: 88/min**
- **171cm, 94 kg, policeman**
- **Hypertension for 5 year**
- **No secondary hypertension**
- **Medication Chart**

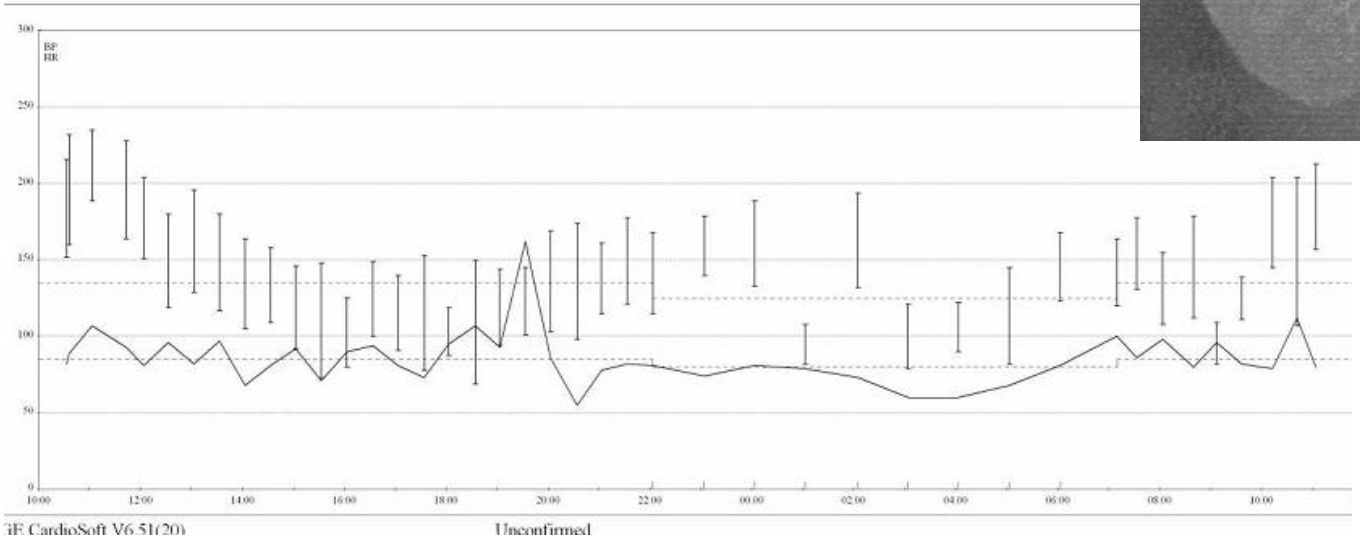
Office BP	170/115mmHg
Felodipine	5 mg
Carvedilol	50mg
Valsartan	320mg
Hydrochlorothizide	12.5mg

Case

24hr Average BP : 167 / 113 mmHg

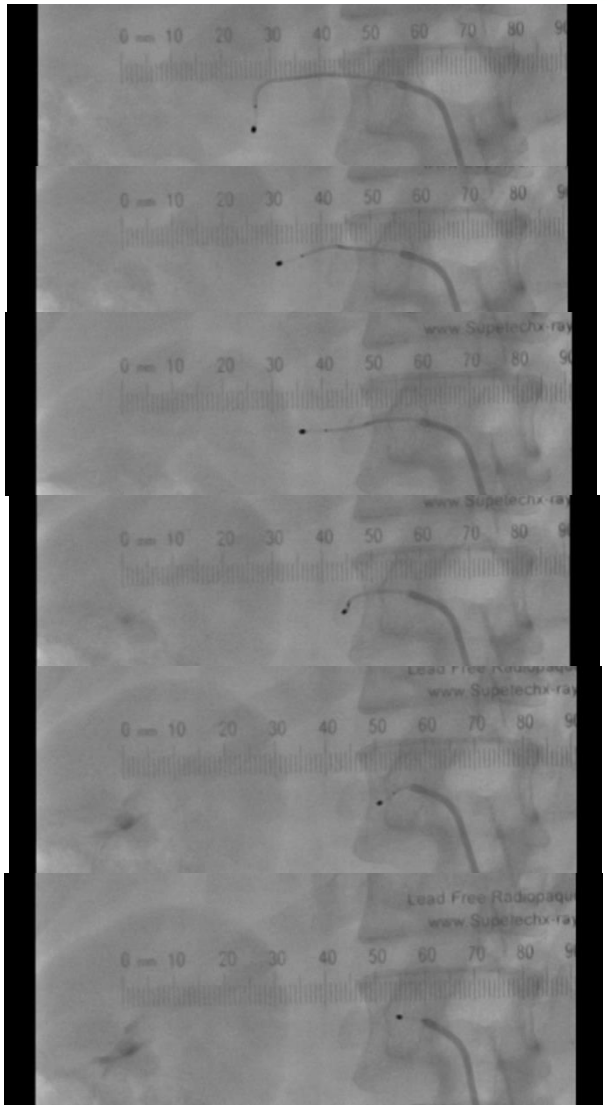
AVERAGE AWAKE BP : 171 / 114 mmHg
AVERAGE ASLEEP BP : 155 / 108 mmHg

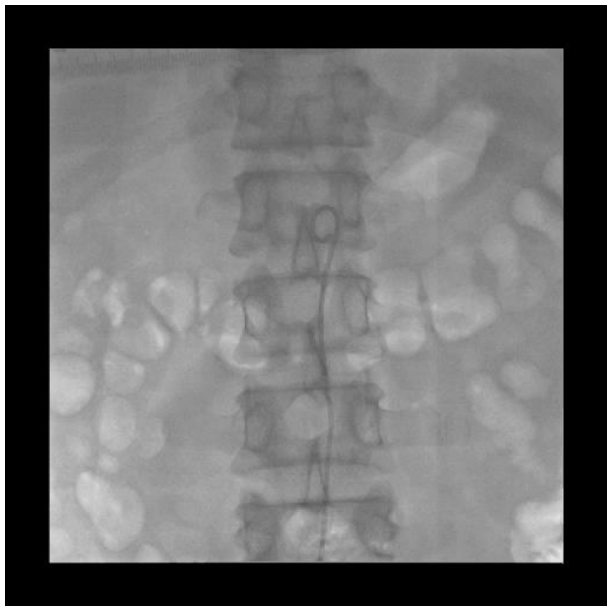


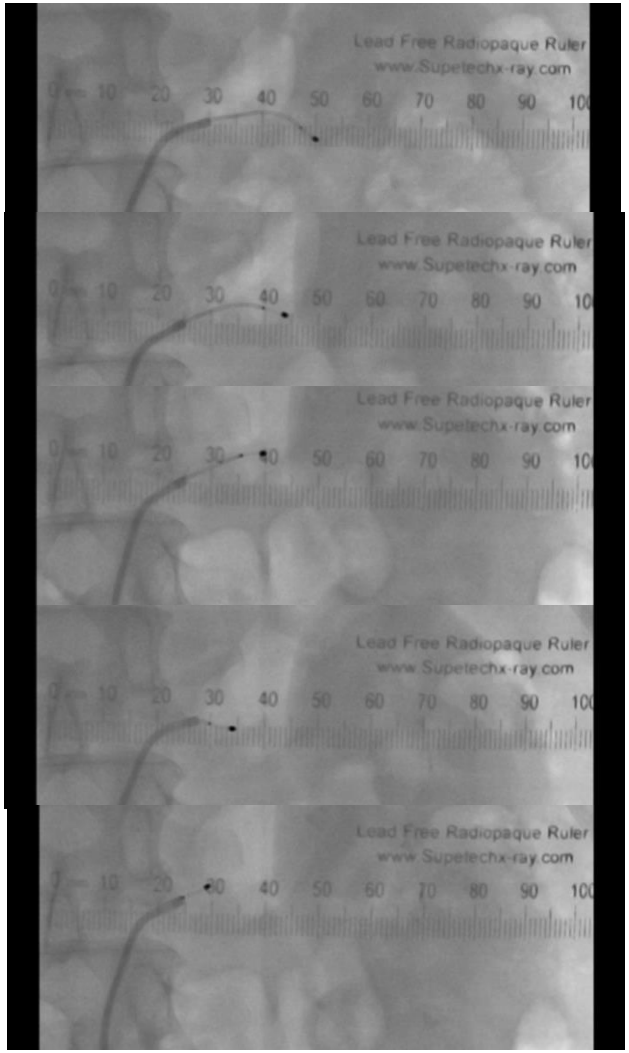


Additional treatment option : renal artery denervation in 19th, March, 2012

Case : Renal denervation







Blood Pressure F/U

Weight gain : 5 kg **Hyper-responder**

Months	Initial (3/12/12)	1	6	9	12 (4/1/13)
BP mmHg	**170/115**	**144/90**	**130/85**	**110/75**	**105/70**

Medication

Felodipine 5mg
Carvedilol 50mg
Valsartan 320mg
Hydrothiazide 12.5mg

dizziness

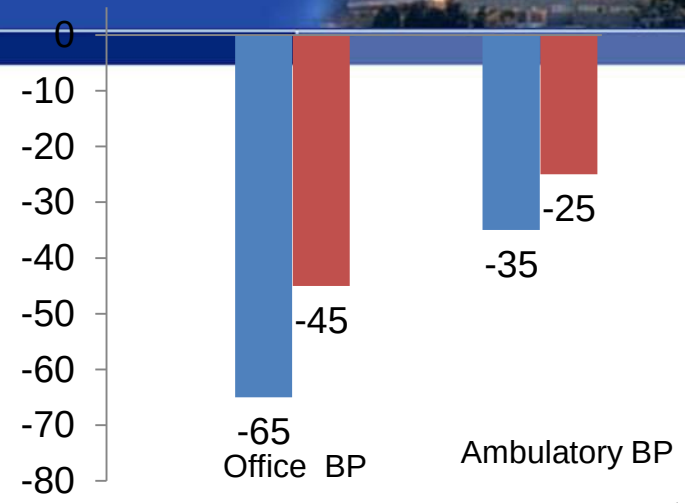
160mg↓

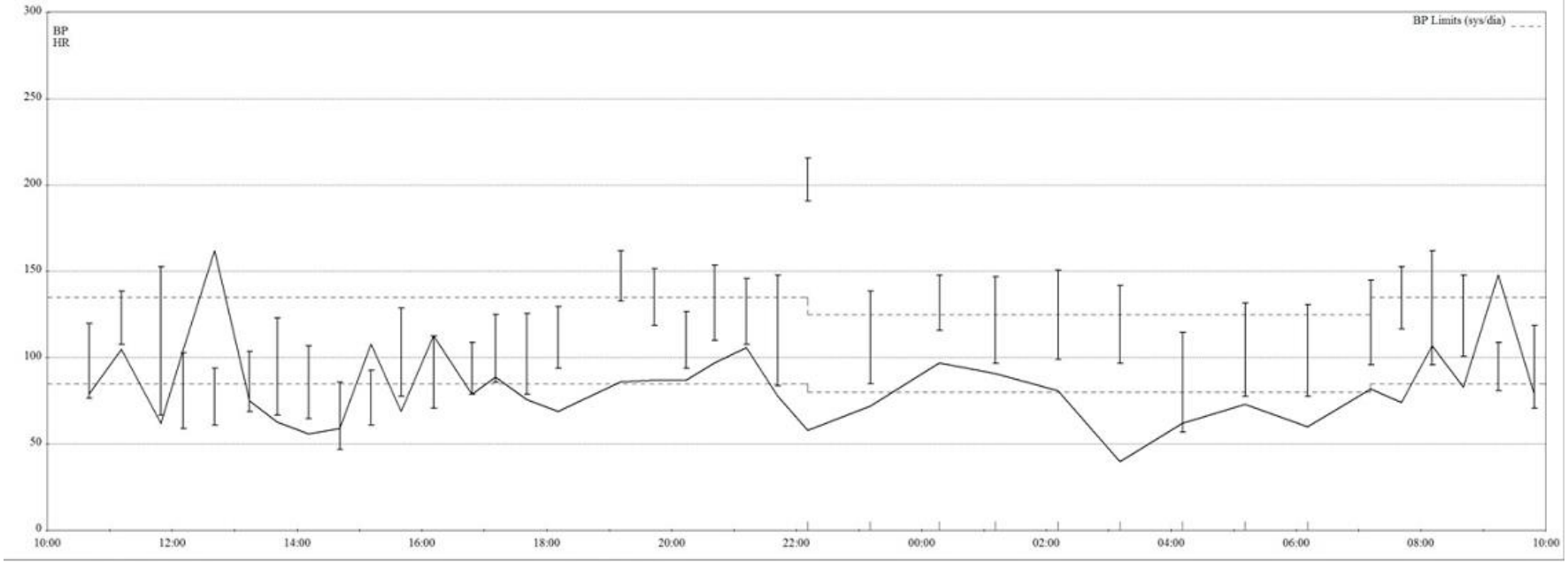
Felodipine D/C

12 month F/U

24hr Average BP : 132 / 88 mmHg

AVERAGE AWAKE BP : 123 / 85 mmHg
AVERAGE ASLEEP BP : 146 / 99 mmHg

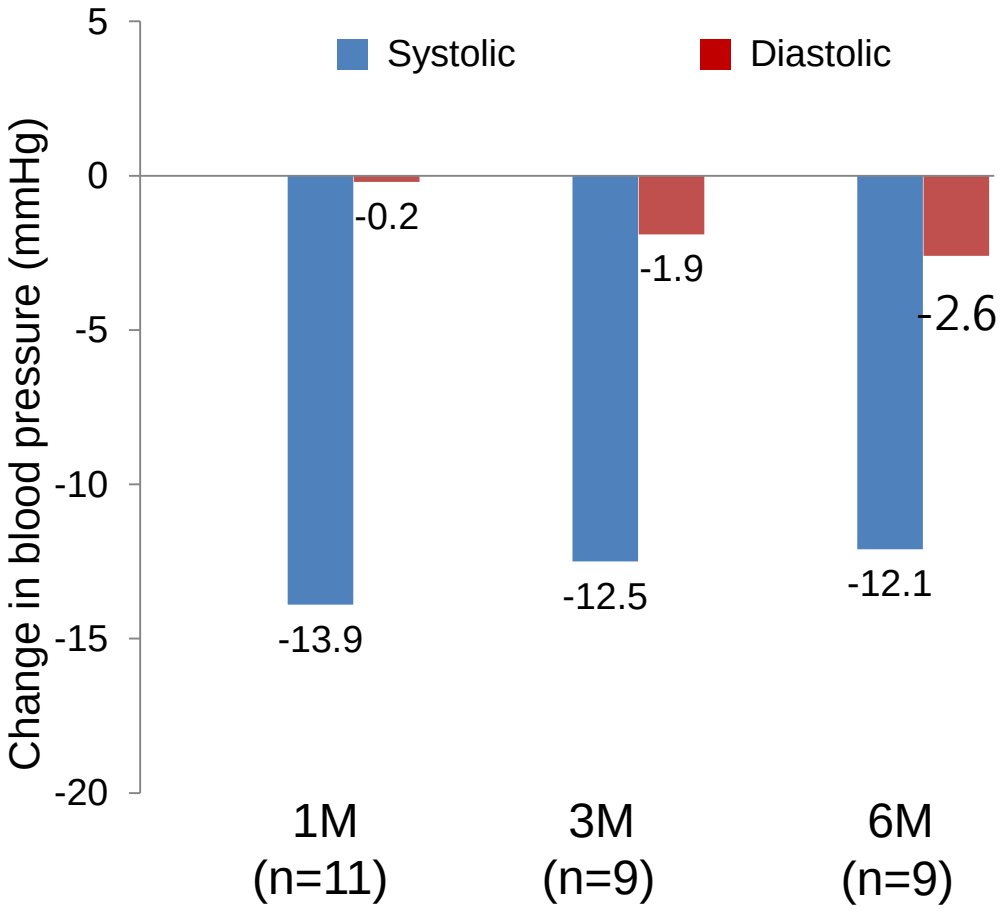




Moderate resistant hypertension
140 mmHg < Baseline systolic BP <160mmHg (n=11)

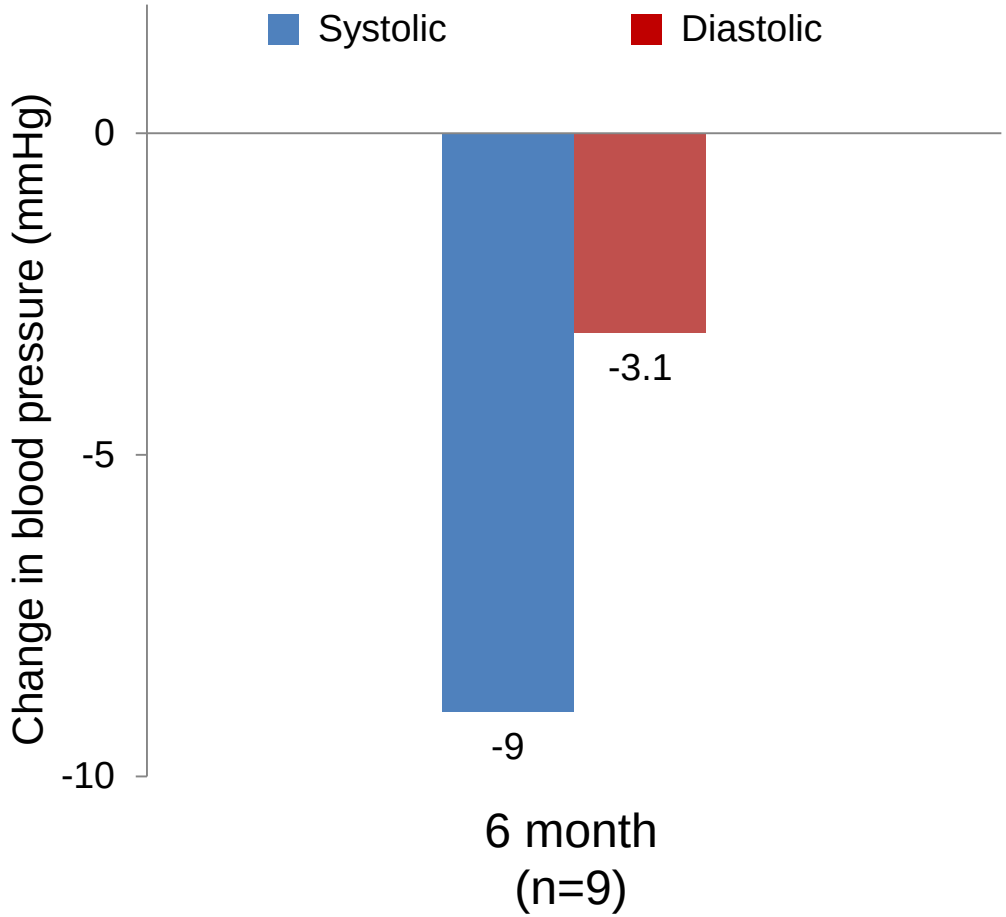
Demographics	Age (years)	53.7 ± 14
	Gender (% female)	9.1%
Co-morbidities	Diabetes Mellitus II (%)	27.3%
	CAD (%)	18.2%
	Hyperlipidemia (%)	63.6%
	eGFR (mL/min/1.73m^2)	80.9 ± 23.1
Blood Pressure	**Baseline BP (mmHg)**	**154/92 ± 5/12**
	Number of anti-HTN meds (mean)	**3.6 ± 1.2**
	ACE/ARB (%)	81.8%
	Beta-blocker (%)	72.7%
	Calcium channel blocker (%)	90.9%
	Vasodilator (%)	9.1%
	Diuretic (%)	90.9%
	Spironolactone (%)	9.1%
	Alpha-blocker(%)	9.1%

Office BP change (n=11)



6 Month Non-responder : 5/9 (55.6%)
: defined as a SBP reduction of < 10mmHg

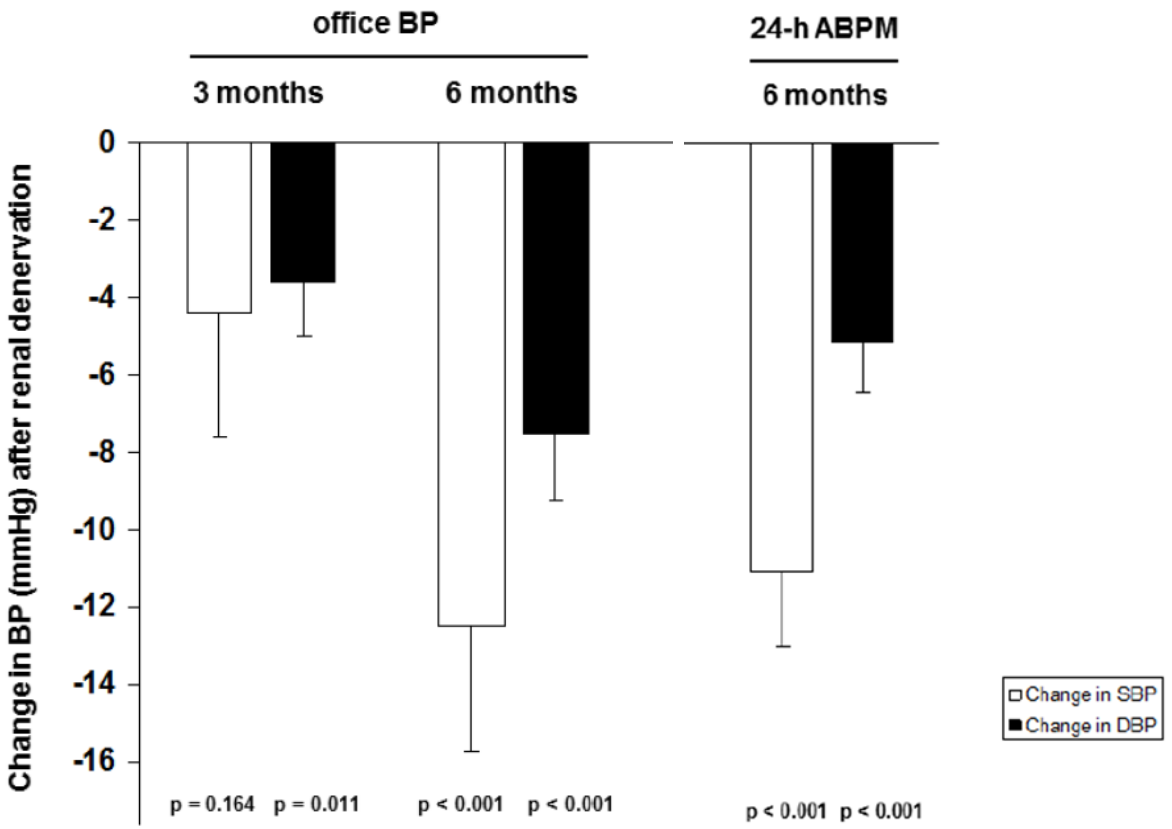
24 hr Ambulatory BP change (n=11)



Efficacy of RDN for moderate resistant hypertension

N=54 patients with moderate r-hypertension
& 24-h ABPM > 130/80mmHg

Baseline systolic BP 151 mmHg
diastolic BP 82 mmHg
No of medications : 5.1



Office BP reduction : -13/7 mmHg

Ott C, Mahfoud F, et al. JACC 2013 in press

Possible extended indication

Still lack of evidence for the efficacy of RDN for moderate resistant hypertension

We need more data to prove it

Moderate treatment resistant hypertension
: 140mmHg <systolic BP <160mmHg


SAFETY
FIRST

The Symplicity HTN-1 & 2 Trial

- Procedure complication rate 3% (4/153 pts)
  - Renal artery dissection : 1
  - Pseudoaneurysm/hematoma : 3
- Short-term renal angiography (n=20)
  - no stenosis
- 6 months imaging study (MRA, CTA, Duplex)(n=81)
  - no stenosis
- Renal function
  - no class IV CKD, no dialysis required
  - no Cr double
- Death : 2 patients (MI, Sudden cardiac death)

Hypertension 2011;57:911-17

	Renal denervation group		Control group		Difference in mean change (95% CI)	p value
	Patients (n)	Mean change (SD)	Patients (n)	Mean change (SD)		
eGFR* (mL/min per 1·73 m²)	49	0·2 (11)	51	0·9 (12)	−0·7 (−5·4 to 3·9)	0·76
Serum creatinine (μmol/L)	49	0·2 (17·6)	51	−1·1 (10·3)	1·3 (−4·5 to 7·0)	0·67
Cystatin C (mg/L)	37	0·1 (0·2)	40	0·0 (0·1)	0·0 (0·0 to 0·1)	0·31

eGFR=estimated glomerular filtration rate. *Calculated on the basis of Modification of Diet in Renal Disease Study criteria.[12]

Table 2: **Baseline, change from baseline to 6 months, and difference in change in measured concentrations of eGFR, serum creatinine, and cystatin C for renal denervation and control groups**

Lancet 2010;376:1903-09

Safety profile – data from SMC

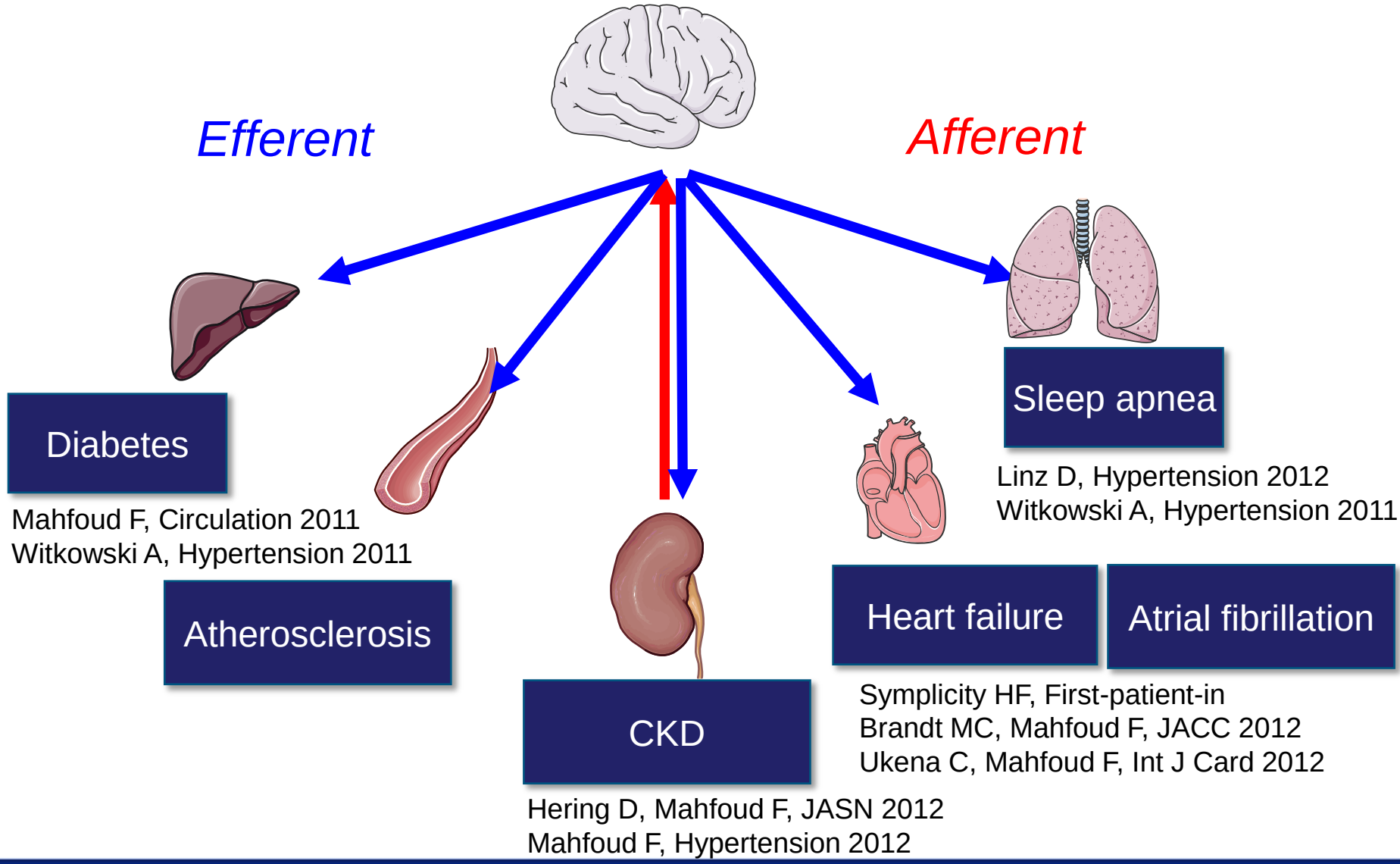
- **procedure related complications (n=29)**
  - **No access site complications**
  - **No renal artery complications including dissection**
  - **3 spasm**
  - **1 junctional bradycardia**

- **Long term complications**
  - **No renal artery stenosis at 6 month duplex (n= 27)**

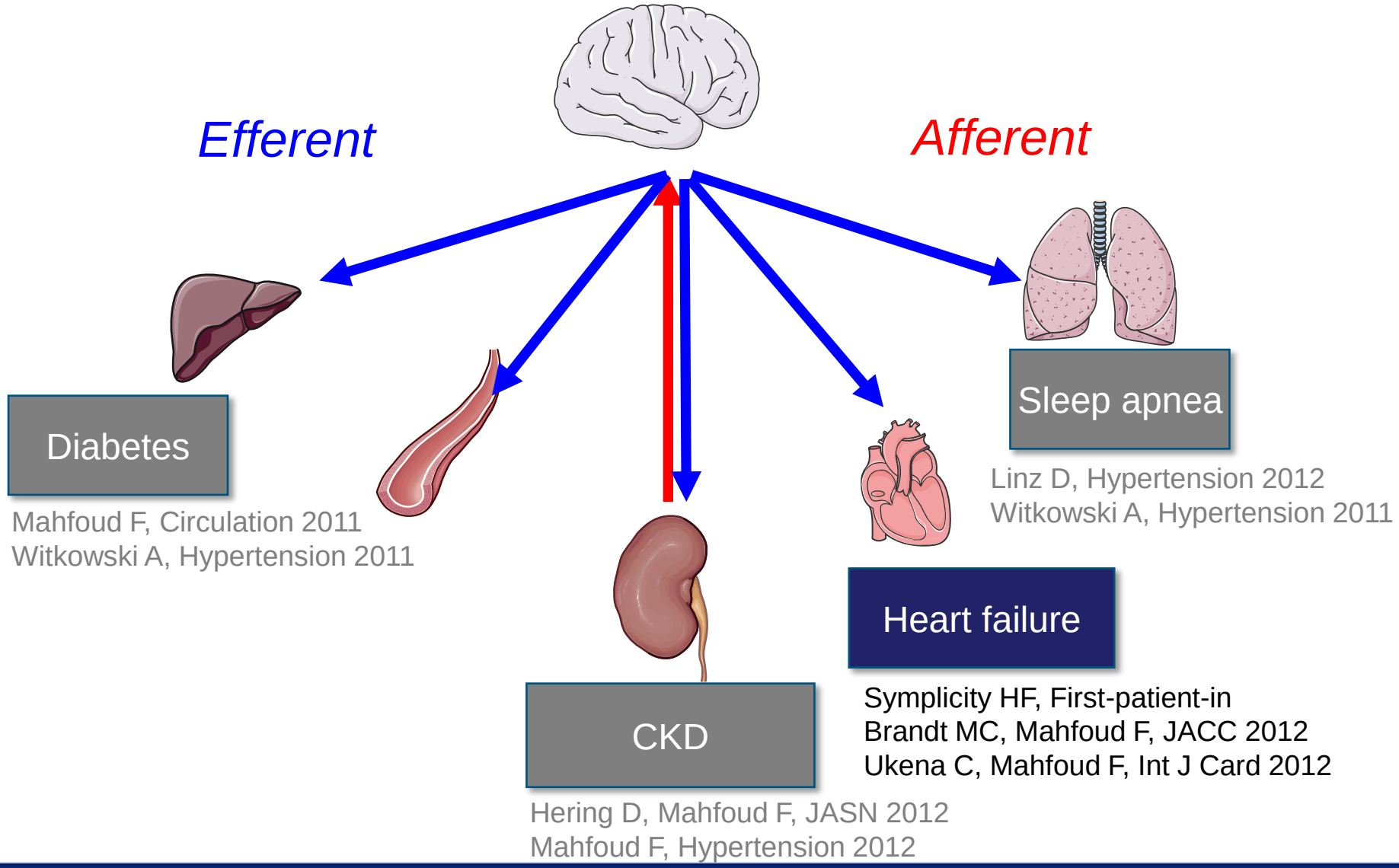
Table. Renal function at Baseline and 6 months

n=27	Baseline	6 months	changes at 6 months
eGFR, mL/min per 1.73 m²	76.0±17.0	73.2±12.2	4.7±14.8
Serum creatine (mg/dL)	1.0±0.2	1.1±0.2	0.1±0.3

The effects of renal denervation beyond resistant hypertension

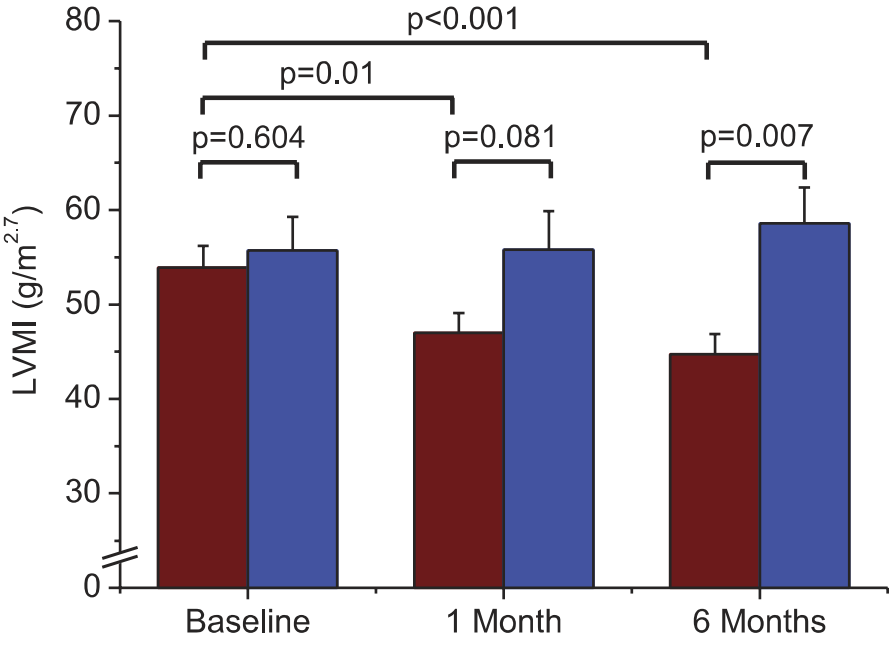


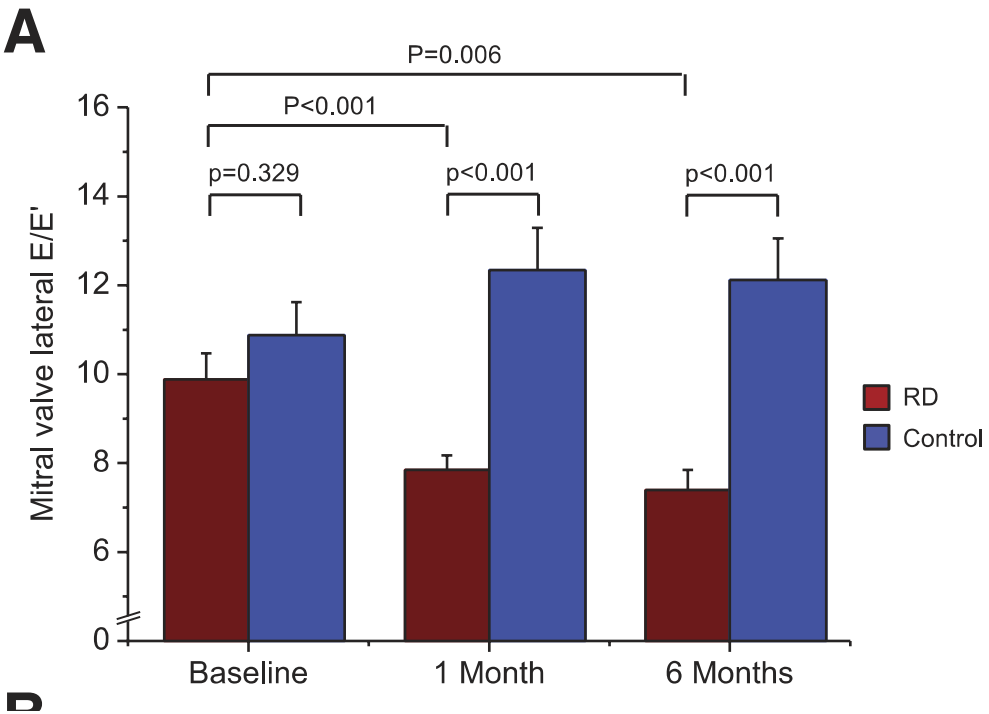
The effects of renal denervation beyond resistant hypertension



Renal Sympathetic Denervation Reduces Left Ventricular Hypertrophy and Improves Cardiac Function in Patients With Resistant Hypertension

Mathias C. Brandt, MD,*† Felix Mahfoud, MD,§ Sara Reda, MD,*†
Stephan H. Schirmer, MD, PHD,§ Erland Erdmann, MD,† Michael Böhm, MD,§
Uta C. Hoppe, MD*†‡





N=64,
46 patients underwnt RDN

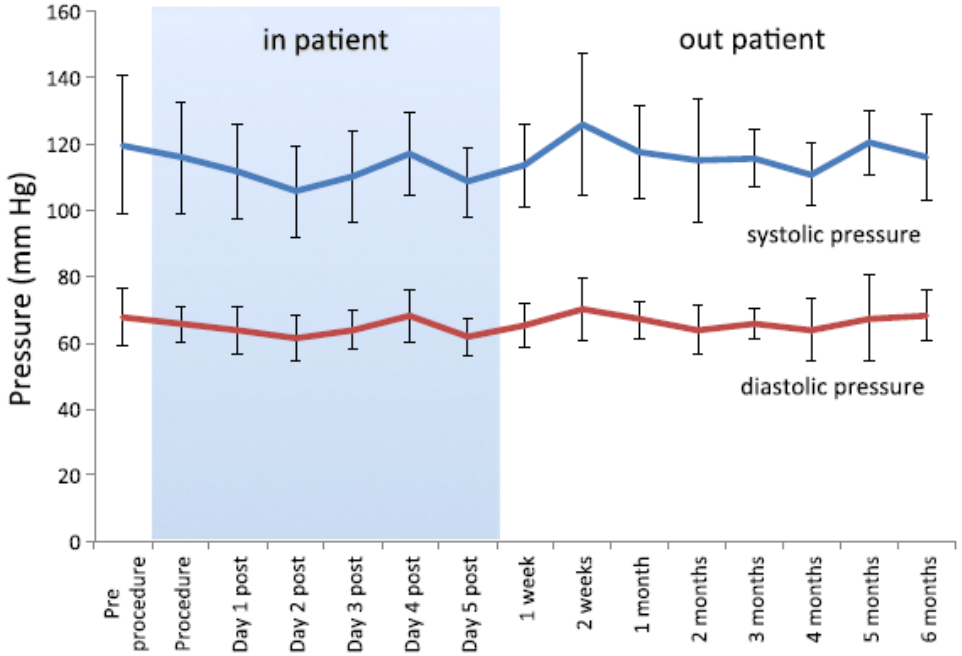
Brandt MC, Mahfoud F, JACC 2012

First-in-man safety evaluation of renal denervation for chronic systolic heart failure: Primary outcome from REACH-Pilot study

Justin E. Davies [a,*], Charlotte H. Manisty [a], Ricardo Petraco [a], Anthony J. Barron [a], Beth Unsworth [a], Jamil Mayet [a], Mohamad Hamady [a], Alun D. Hughes [a], Peter S. Sever [a], Paul A. Sobotka [b], Darrel P. Francis [a]

[a] National Heart and Lung Institute, International Centre for Circulatory Health, Imperial College London & Imperial College Healthcare NHS Trust, London, UK
[b] The Ohio State University, Columbus, OH, USA

7 patients
Mean BP 112/65mmHg
EF : 43±15%



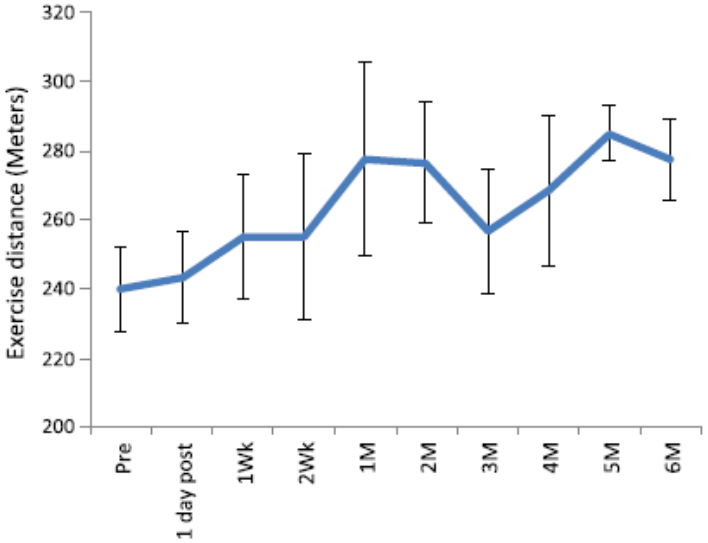


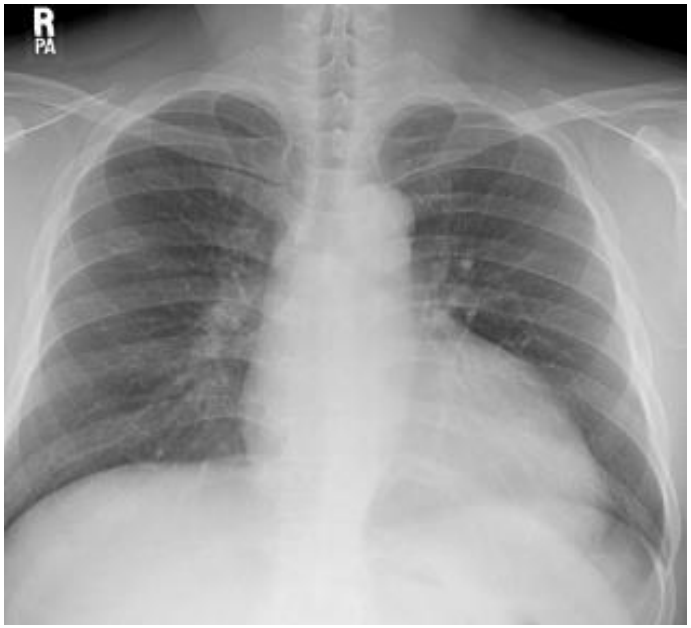
Fig. 2. Increase in 6 minute walk test over 6 months following renal denervation. The 6 minute walk test was performed before denervation, and then at each follow-up visit. Each patient individually had a numerical increase.

Davies JE et al, Int J Cardiol 2013;162:189-92

Case 2

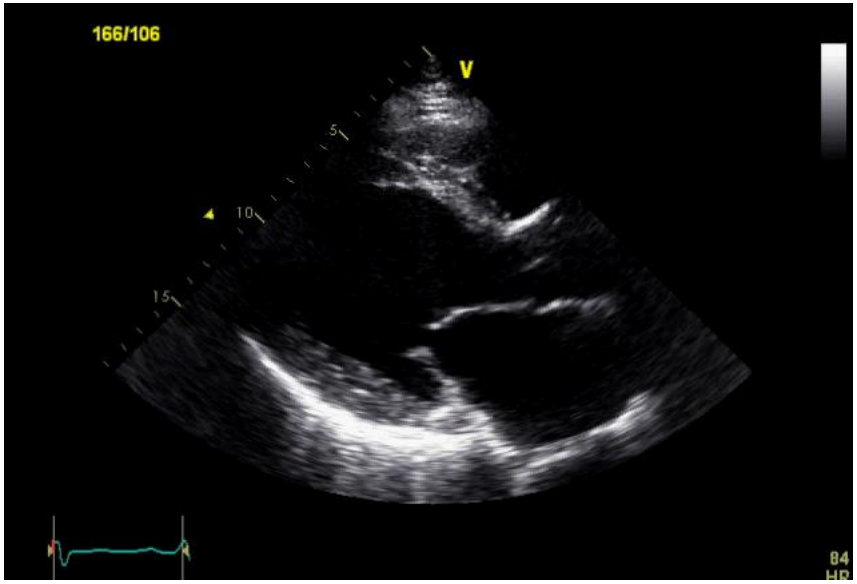
- **M/42**
- **Office BP : 158/120 mmHg HR: 83/min**
- **177cm, 104 kg**
- **Hypertension for 2 year**
- **Medication Chart**

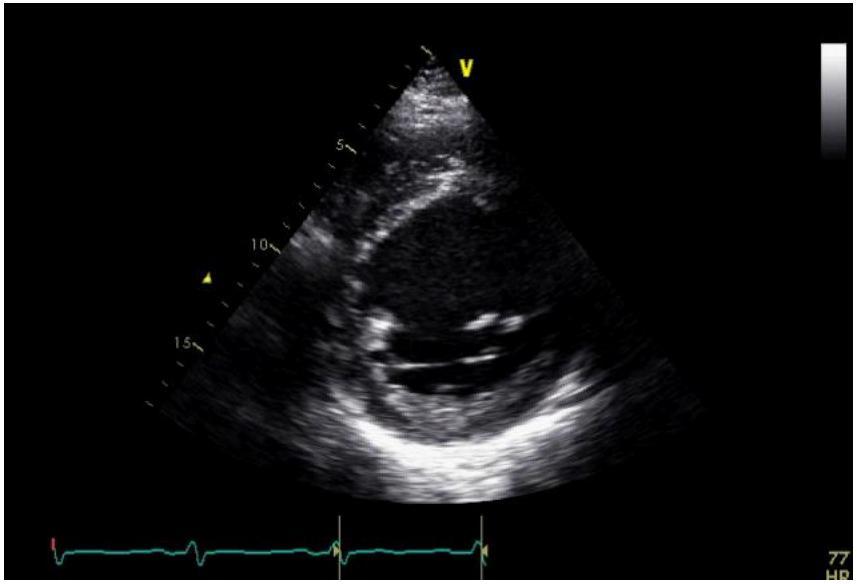
Office BP	158/120 mmHg
Amlodipine	5 mg
Bisoprolol	10 mg
Losartan	100 mg
Hydrochlorothizide	12.5 mg



Echocardiography

Baseline echo





Blood Pressure F/U

After the successful renal denervation

Months	Initial (4/6/12)	1	6	9	12 (4/22/13)
BP mmHg	**158/120**	**150/105**	**151/98**	**150/115**	**150/110**

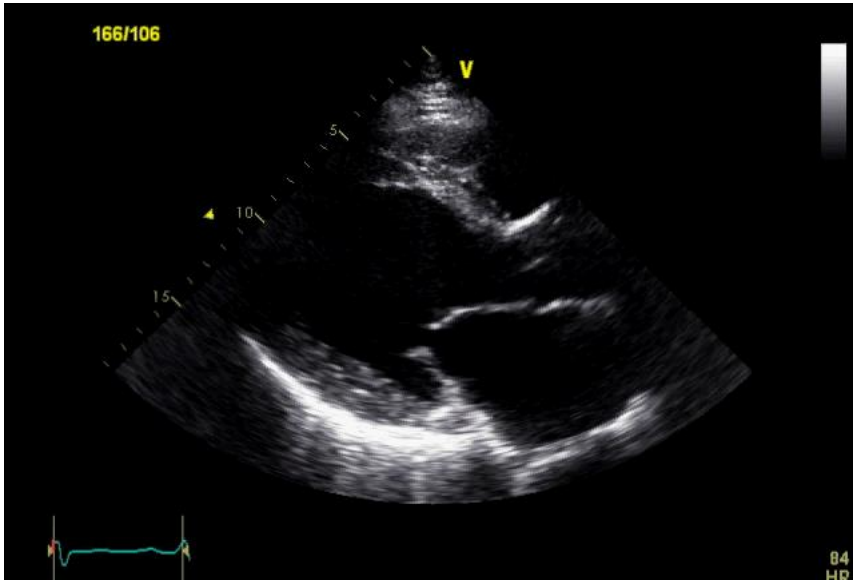
- 8/10 mmHg

Medication

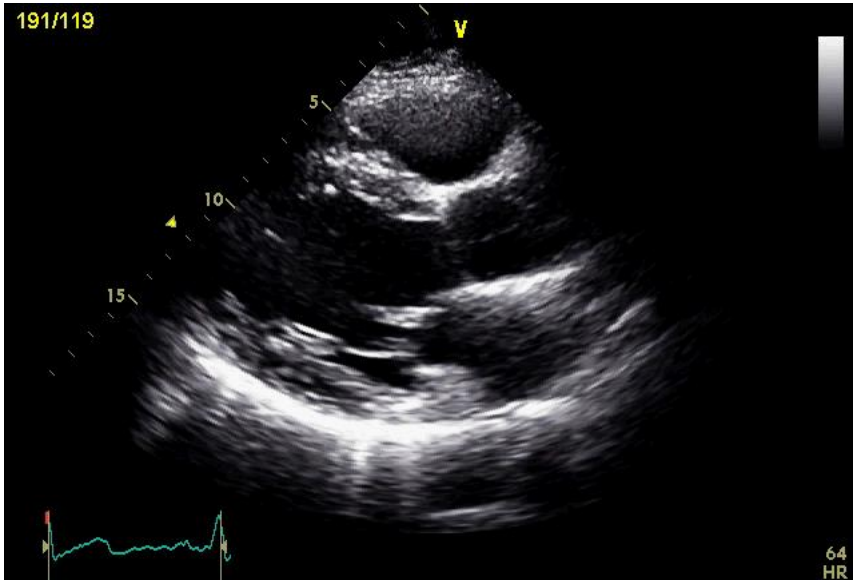
Amlodipine 5 mg
Bisoprolol 10 mg
losartan 100 mg
Hydrothiazide 12.5mg

Echocardiography

preRDN-Echo

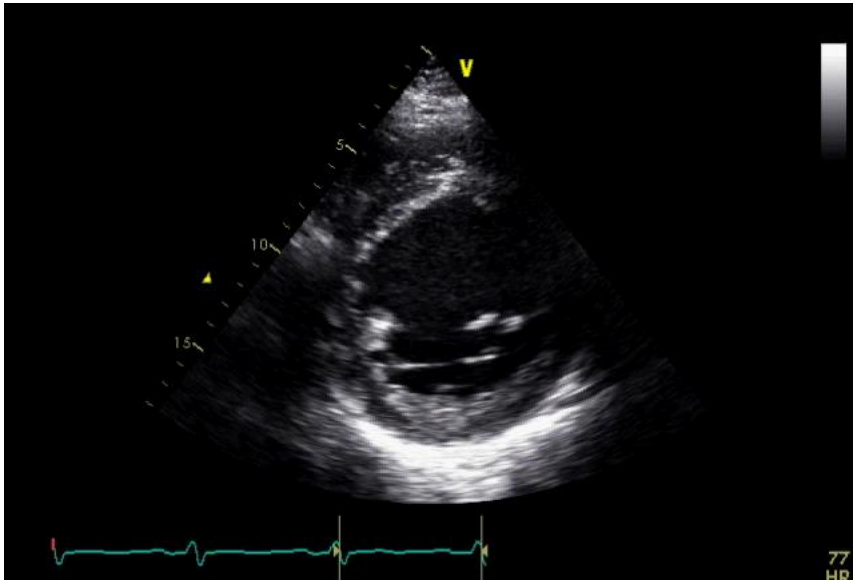


6 months later-echo

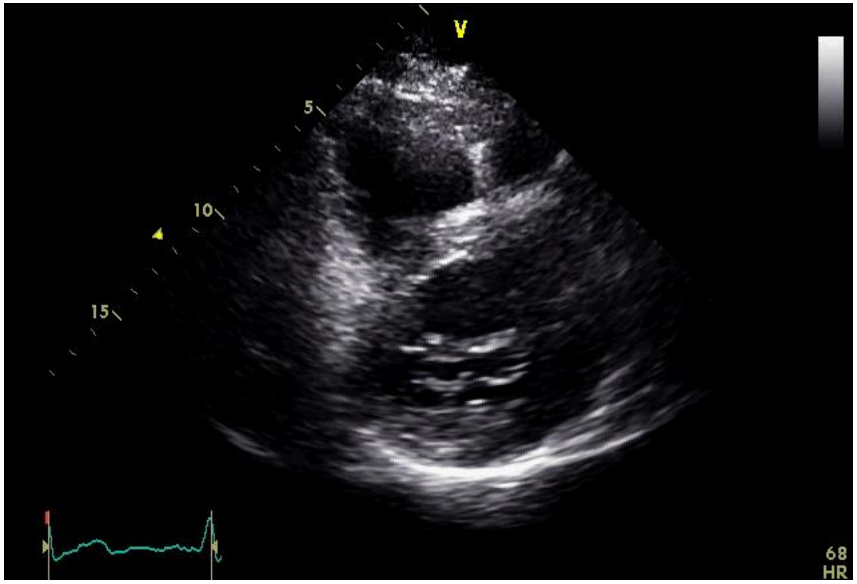


Echocardiography

preRDN-Echo

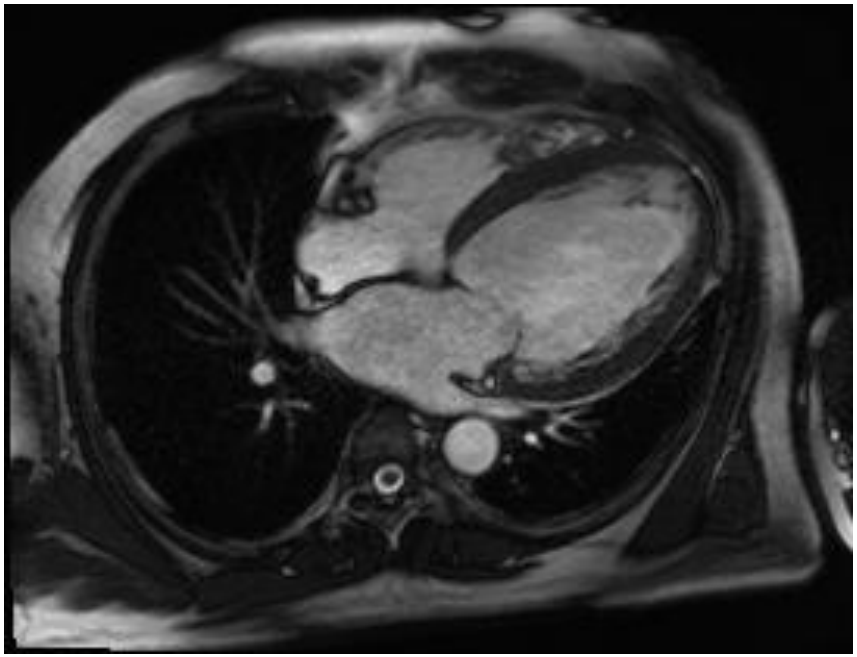


6 months later-echo

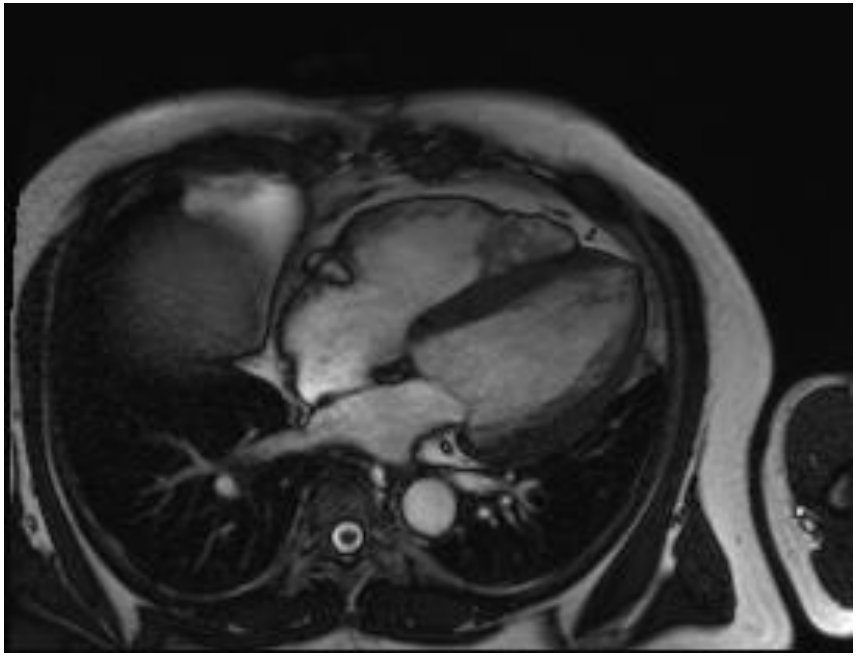


Heart MRI

preRDN-CMR 4ch Cine



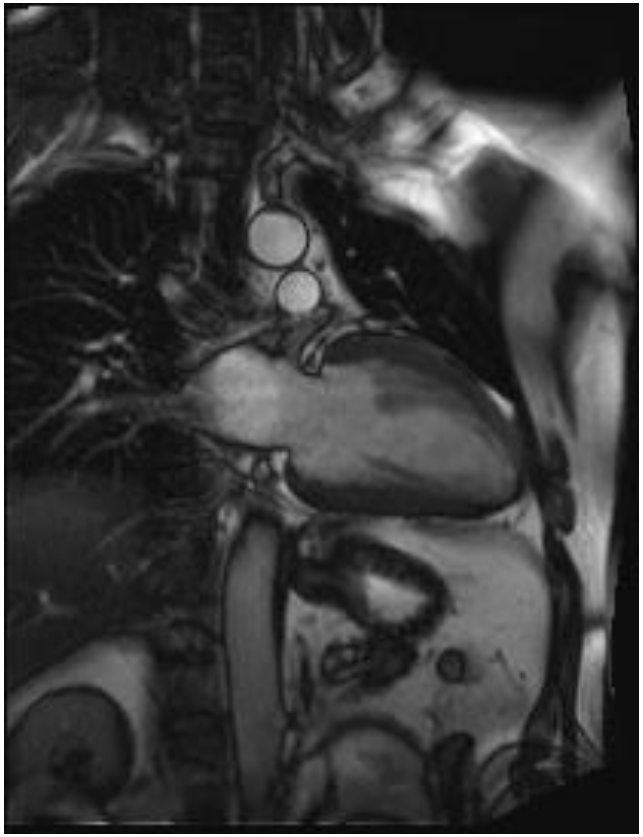
12 months later-CMR 4ch Cine



Heart MRI

preRDN-CMR 2ch Cine

12 months later-CMR 2ch Cine



Changes of echo and MRI parameter after RDN

Echocardiography	Baseline	6 months later	Cadiac MR	Baseline	12 months later
			LV analysis		
LV end diastoic volume (ml)	444.3	179.8	LV end diastoic volume (ml)	498.2	205.0
LV end systoic volume (ml)	340.2	107.6	LV end systoic volume (ml)	366.6	69.8
LA diameter (mm)	60	55	LV wall mass (g)	353.1	221.5
LAVI (ml/ml)	76.1	45.4	Stroke volume (ml)	131.6	135.2
E decel time (msec)	170	240	Cardiac output (l/min)	12.1	8.9
E'(m/s)	0.05	0.057	EF% (by calculated)	26·4	65·9
A'(m/s)	0.05	0.072	***RV analysis***		
E/E'	21.2	12.3	RV diastoic volume (ml)	221.4	202.4
EF% (by Simpson's method)	23.4	40.0	RV systolic volume (ml)	112.9	89.3
			EF% (by calculated)	49	55

EF ; ejection fraction, LAVI ; left atrium volume index, LV ; left ventricle, LVOT ; left ventricle out tract, MV ; mitral valve,

MR ; magnetic resonance, RDN ; renal sympathetic denervation, VTI ; velocity time integral

SYMPLICITY-HF

Renal Denervation in Patients with Chronic Heart Failure & Renal Impairment

Inclusion criteria

- **50 patient with CHF in NYHA class II-III**
- **LV-EF <40%**
- **eGFR 30-75 ml/min/1.73m^2**
- **Optimal and stable medical therapy**

First patients enrolled in April 2012

Additional Effects of RDN

Effect of renal denervation for treatment of *heart failure*

Summary

- Renal denervation is an effective and safe treatment modality for patients with resistant hypertension.
- Preliminary data of Global registry demonstrates excellent procedural and clinical safety profile of renal denervation in a real world population.
- Renal denervation may be a safe and effective treatment for patients with moderate resistant hypertension.
- Renal denervation may be applicable to the various disease beyond resistant hypertension.
- We need more real world data to prove the long-term efficacy and safety of renal denervation therapy.

Renal denervation