Is It the Beginning of the end, or the end of the beginning?

Reflections on renal denervation

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Conflict of Interest

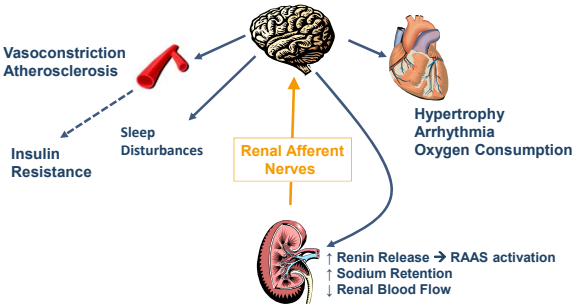
None

Presentation Outlines

- Symplicity HTN-1 and -2
- Symplicity HTN-3
- Key questions to be answered
  - ❖Readout of the completion of the procedure:
    - ❖Signals during the procedure
    - ❖High frequency voltage stimulation?
  - ❖Patient selection:
    - ❖Novel biomarkers?
- F/U data of Symplicity HTN-3

Renal Sympathetic Activation: Afferent Nerves

Kidney as Origin of Central Sympathetic Drive



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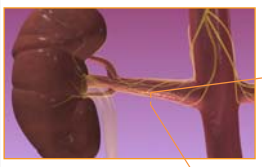
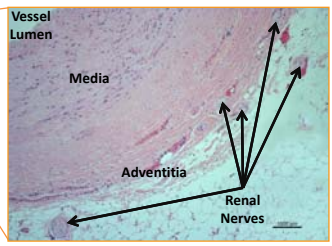
Renal Nerve Anatomy



- Nerves arise from T10-L2
- The nerves arborize around the artery and primarily lie within the adventitia



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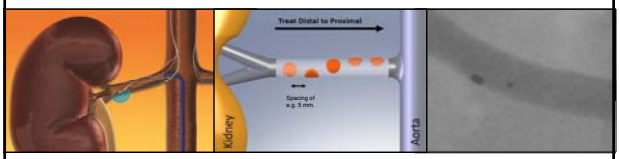
Renal Nerve Anatomy Allows a Catheter-Based Approach



- Renal artery access via standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF generator
  - Automated
  - Low power
  - Built-in safety algorithms

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Symplicity HTN-1

THE LANCET

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

Lancet. 2009;373:1275-1281

Hypertension

Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension

Durability of Blood Pressure Reduction Out to 24 Months

Symplicity HTN-1 Investigators*

Hypertension. 2011;57:911-917.

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)

-36-month follow-up

* Lancet 2014;**383**(9917):622-9.

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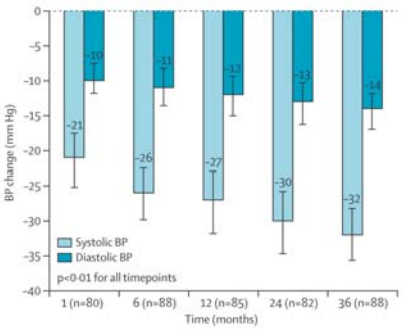
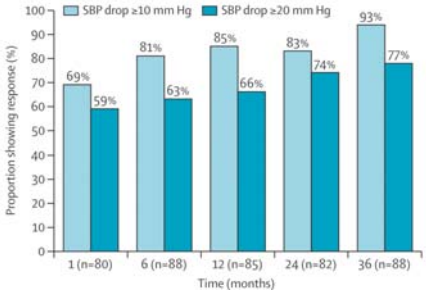
Symplicity HTN-1: BP Reductions through 3 years



Lancet 2014;383(9917):622-9.

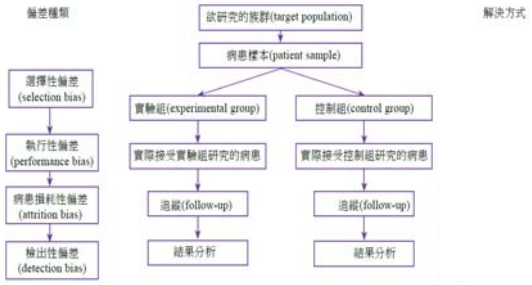
Symplicity HTN-1: Percentage Responders Over Time

Response defined as an office SBP reduction ≥ 10 and 20mmHg



Lancet 2014;**383**(9917):622-9.

Bias and "Bias-proof" Solutions



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Validity Checkup

1. 病患的治療分派是隨機的嗎?
2. 隨機分派過程是否隱匿?
3. 對照組與實驗組病患在進入試驗時是否相似?
4. 病患的追蹤是否夠久、夠完整?
5. 所有的病患都被放到原先分派的組別做分析?
6. 病患、醫師、評估者是否對治療分派不知情?
7. 對照組與實驗組病患是否被同等對待?

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Symplicity HTN-2

THE LANCET

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

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.

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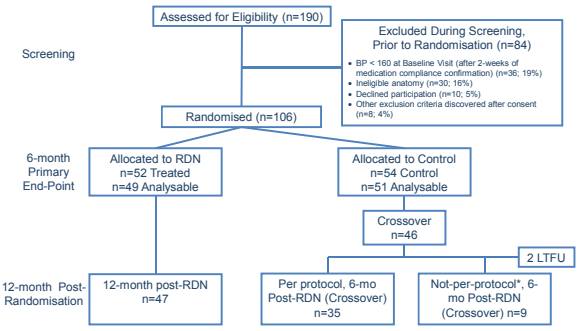
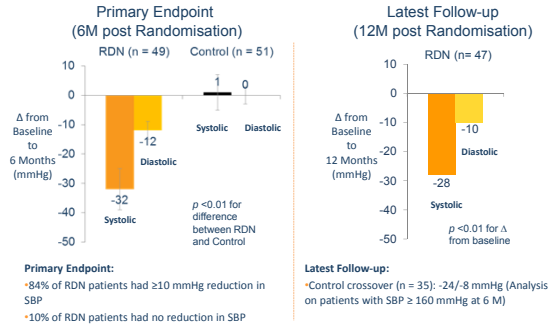
Symplicity HTN-2: Patient disposition



* Crossed-over with ineligible BP (<160 mmHg)

Symplicity HTN-2: Primary Endpoint and Latest Follow-up



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

Latest Follow-up:
- Control crossover (n = 35): -24/-8 mmHg (Analysis on patients with SBP ≥ 160 mmHg at 6 M)

Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Esler, M.)

Symplicity HTN-2: Renal Function Results

RDN
N=47

Treated at Randomisation

	Baseline	6 month	12 months
eGFR (ml/min/1.73m²)	76.9 ±19.3 (n= 49)	77.1±18.8 (n=49)	78.2±17.4 (n=45)
Cystatin C (mg/L)	0.91±0.25 (n=38)	0.98±0.36 (n=40)	0.98±0.30 (n=38)

Crossover
N=35

Treated after 6-mo follow-up

	Baseline	6 month	12 months
eGFR (ml/min/1.73m²)	88.8 ± 20.7 (n = 35)	89.3±19.5 (n = 35)	85.2±18.3 (n = 35)
Cystatin C (mg/L)	0.78 ± 0.17 (n=27)	0.82±0.16 (n=26)	0.89±0.20 (n=26)

Symplicity HTN-2 Investigators. *The Lancet*. 2010.

Renal Denervation in Patients with Uncontrolled Hypertension: Results of the SYMPLICITY HTN 3 Trial

The SYMPLICITY HTN-3 Investigators

Background

- Due to aging of the population and greater trends towards obesity, hypertension is growing in prevalence worldwide.
- Approximately 10% of patients with diagnosed hypertension have “resistant” hypertension.
- The sympathetic nervous system appears to play an important role in resistant hypertension.
- Prior non-blinded studies have suggested that catheter-based renal artery denervation reduces blood pressure in resistant hypertension.

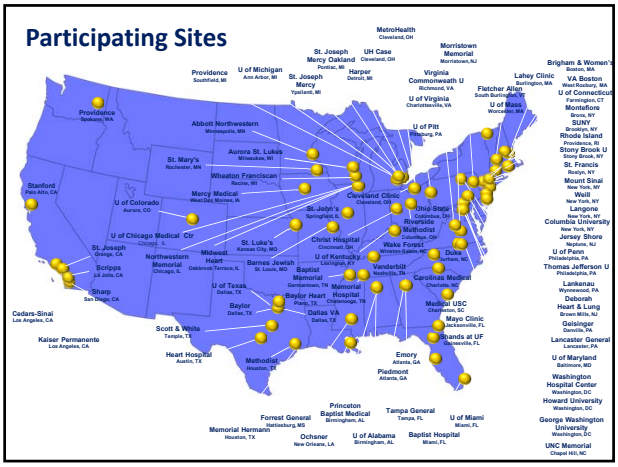
Bhatt DL, Kandzari DE, O’Neill WW, et al...Bakris GL. N Engl J Med 2014

Trial Objectives

- **SYMPLICITY HTN-3** is the first prospective, multi-center, randomized, blinded, sham controlled study to evaluate both the safety and efficacy of percutaneous renal artery denervation in patients with severe treatment-resistant hypertension.
- The trial included 535 patients enrolled by 88 participating US centers.

Bhatt DL, Kandzari DE, O’Neill WW, et al...Bakris GL. N Engl J Med 2014

Participating Sites



SYMPLICITY HTN-3 Committees

Steering Committee

Co-PIs: Deepak L. Bhatt, MD, MPH, and George L. Bakris, MD

Chair: William O'Neill, MD

Members: Sidney A. Cohen, MD, PhD; Ralph D'Agostino, PhD; Murray Esler, MBBS, PhD; John Flack, MD, MPH; David Kandzari, MD; Barry Katzen, MD; Martin Leon, MD; Laura Mauri, MD, MSc; Manuela Negoita, MD; Suzanne Oparil, MD; Krishna Rocha-Singh, MD; Ray Townsend, MD; Paul Sobotka, MD

Independent Data & Safety Monitoring Board

Chair: Bernard J. Gersh, MB, ChB, D.Phil

Members: John A. Ambrose, MD; Phyllis August, MD, MPH; Glenn M. Chertow, MD; Stuart Pocock, BSc, MSc, PhD

Non-voting member: Joseph Massaro, PhD

Independent Statistical Analysis Validation

Harvard Clinical Research Institute

Independent Clinical Events Committee

Chair: Clive Rosendorff, MD, PhD, DSc Med

Members: Ladan Golestaneh, MD; Steven Marx, MD; Michele H. Mokrzycki, MD; Joel Neugarten, MD

Non-voting members: Sorin Brener, MD; Roxana Mehran, MD

Renal Artery Duplex Core Laboratory

Michael Jaff, DO, VasCore

Angiographic Core Laboratory

Jeffrey J. Popma, MD

Beth Israel Deaconess Medical Center

MRA Core Laboratory

Milind Y. Desai, MD, C5 Research

Blood Core Laboratory

Tania Cochran, Sr. Project Manager

ACM Global Laboratory

Sponsor

Medtronic, Inc.

Key Inclusion Criteria

- Age ≥18 and ≤80 years at time of randomization
- Stable medication regimen including **full tolerated doses of 3 or more antihypertensive medications of different classes**, including a diuretic (with no changes for a minimum of 2 weeks prior to screening) and no expected changes for at least 6 months
- Office SBP ≥160 mm Hg based on an average of 3 blood pressure readings measured at both an initial and a confirmatory screening visit
- Written informed consent

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

Key Exclusion Criteria

- ABPM 24 hour average SBP <135 mm Hg
- eGFR of <45 mL/min/1.73 m^2
- Main renal arteries <4 mm diameter or <20 mm treatable length
- Multiple renal arteries where the main renal artery is estimated to supply <75% of the kidney
- Renal artery stenosis >50% or aneurysm in either renal artery
- History of prior renal artery intervention

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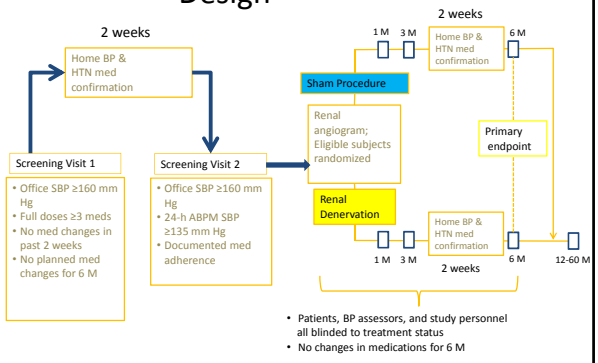
SYMPLICITY HTN-3 Trial Design



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Primary Safety Endpoint

- The rate of Major Adverse Events (MAE) in the treatment group compared with an Objective Performance Criterion (OPC)
- OPC = 9.8% (derived from historical data)
- MAE was defined as all-cause mortality, end-stage renal disease, embolic event resulting in end-organ damage, renal artery or other vascular complication, hypertensive crisis through 30 days, or new renal artery stenosis within six months

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

Efficacy Endpoints

Primary Effectiveness Endpoint:

- Comparison of office SBP change from baseline to 6 months in RDN arm compared with change from baseline to 6 months in control arm

$$\text{Endpoint} = (SBP_{RDN\ 6\ month} - SBP_{RDN\ Baseline}) - (SBP_{CTL\ 6\ month} - SBP_{CTL\ Baseline})$$

- *Superiority margin of 5 mm Hg*

Powered Secondary Effectiveness Endpoint:

- Comparison of mean 24-hour ambulatory (ABPM) SBP change from baseline to 6 months in RDN arm compared with change from baseline to 6 months in control arm
- *Superiority margin of 2 mm Hg*

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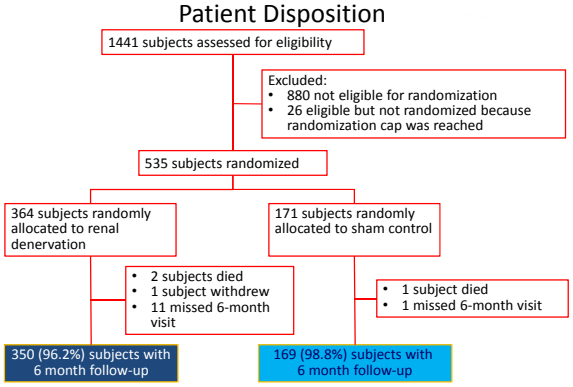
Patient Disposition



Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

Results: Population Demographics

	Renal Denervation (N=364)	Sham Procedure (N=171)	P
Age (years)	57.9 ± 10.4	56.2 ± 11.2	0.09
Male sex (%)	59.1	64.3	0.26
Office systolic blood pressure (mm Hg)	180±16	180±17	0.77
24 hour mean systolic ABPM (mm Hg)	159±13	160±15	0.83
BMI (kg/m^2)	34.2 ± 6.5	33.9 ±6.4	0.56
Race* (%)			0.57
African American	24.8	29.2	
White	73.0	69.6	
Medical history (%)			
Renal insufficiency (eGFR<60 ml/min/1.73m^2)	9.3	9.9	0.88
Renal artery stenosis	1.4	2.3	0.48
Obstructive sleep apnea	25.8	31.6	0.18
Stroke	8.0	11.1	0.26
Type 2 diabetes	47.0	40.9	0.19
Hospitalization for hypertensive crisis	22.8	22.2	0.91
Hyperlipidemia	69.2	64.9	0.32
Current smoking	9.9	12.3	0.45

*Race also includes Asian, Native American, or other

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Baseline Hypertensive Therapy

Characteristic	Renal Denervation (N=364)	Sham Procedure (N=171)
No. of antihypertensive medications	5.1 ± 1.4	5.2 ± 1.4
Angiotensin-converting enzyme inhibitors	49.2	41.5
% at max tolerated dose	45.9	37.4
Angiotensin receptor blockers	50.0	53.2
% at max tolerated dose	49.5	51.5
Aldosterone antagonists	22.5	28.7
Alpha-adrenergic blockers	11.0	13.5
Beta blockers	85.2	86.0
Calcium channel blockers	69.8	73.1
% at max tolerated dose	57.1	63.7
Centrally-acting sympatholytics	49.2	43.9
Diuretics	99.7	100
% at max tolerated dose	96.4	97.7
Direct renin inhibitors	7.1	7.0
Direct-acting vasodilators	36.8	45.0

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Blinding Efficacy

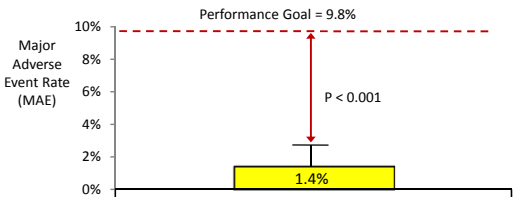
- Blinding Procedure:
- All patients underwent renal angiography
- Conscious sedation
- Sensory isolation (e.g., blindfold and music)
- Lack of familiarity with procedural details and expected duration
- Assessed by questionnaire at discharge and 6 months (before unblinding)

Time	Blinding Index*	95% CI
Discharge	0.68	(0.64, 0.72)
6 Months	0.77	(0.74, 0.81)

*The lower boundaries of the confidence intervals of the blinding index are both > 0.5, indicating sufficient evidence of blinding.

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

Primary Safety Endpoint



	Renal Denervation (N=364)	Sham Procedure (N=171)	Difference [95% CI]	P*
MAE	1.4% (5/361)	0.6% (1/171)	0.8% [-0.9%, 2.5%]	0.67

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Safety Event Rate

Safety Measures (%)	Renal Denervation (N=364)	Sham Procedure (N=171)	Difference (95% CI)	P
Major Adverse Events	1.4	0.6	0.8 (-0.9, 2.5)	0.67
To 6 Months				
6-Month Composite Safety	4.0	5.8	-1.9 (-6.0, 2.2)	0.37
Death	0.6	0.6	0.0 (-1.4, 1.4)	1.00
Myocardial infarction	1.7	1.8	0.0 (-2.4, 2.3)	1.00
New onset ESRD	0	0	-	-
Serum creatinine elevation >50%	1.4	0.6	0.8 (-0.8, 2.5)	0.67
Embolic event resulting in end-organ damage	0.3	0	0.3 (-0.3, 0.8)	1.00
Renal artery intervention	0	0	-	-
Vascular complication requiring treatment	0.3	0	0.3 (-0.3, 0.8)	1.00
Hypertensive crisis/emergency	2.6	5.3	-2.7 (-6.4, 1.0)	0.13
Stroke	1.1	1.2	0.0 (-2.0, 1.9)	1.00
Hospitalization for new onset heart failure	2.6	1.8	0.8 (-1.8, 3.4)	0.76
Hospitalization for atrial fibrillation	1.4	0.6	0.8 (-0.8, 2.5)	0.67
New renal artery stenosis >70%	0.3	0	0.3 (-0.3, 0.9)	1.00

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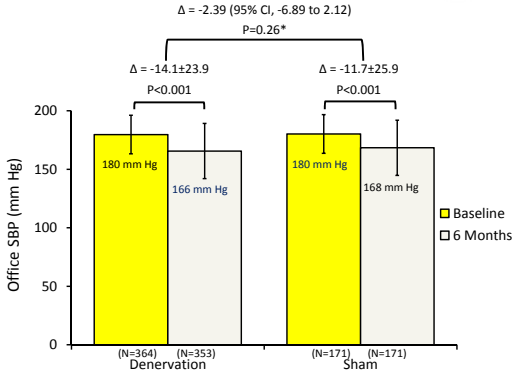
Primary Efficacy Endpoint



*P value for superiority with a 5 mm Hg margin; bars denote standard deviations

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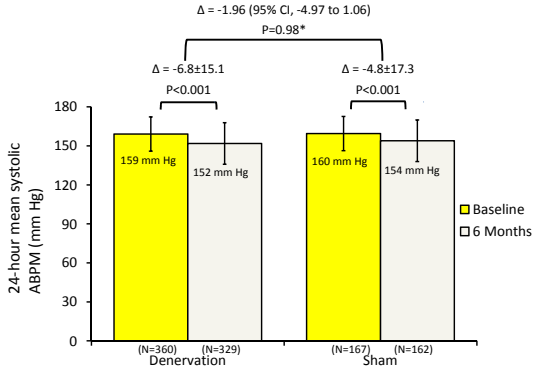
Powered Secondary Efficacy Endpoint



*P value for superiority with a 2 mm Hg margin; bars denote standard deviations

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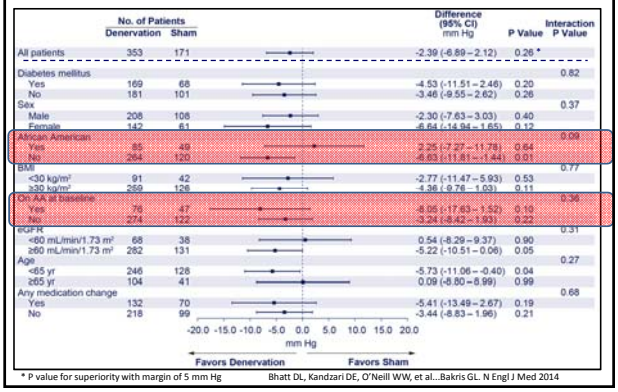
Results: Pre-specified Subgroup Analyses



* P value for superiority with margin of 5 mm Hg

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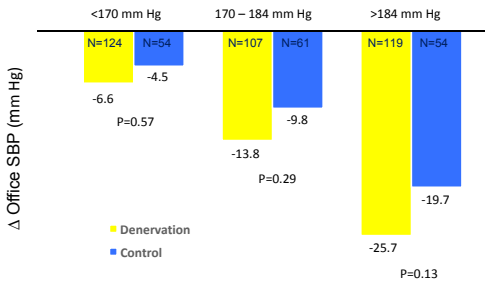
Change in Office SBP by Tertile of Baseline Office SBP



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Potential Limitations

- Drug adherence not measured by blood levels, but adherence was measured by patient diaries at baseline and 6 months.
- Medication changes did occur, but results unchanged even when these patients were censored.
- Duration of primary endpoint may have been too short, but prior studies had found benefit by 6 months.
- Operator learning curve is always a possibility, but we found no relationship with procedural volume in the trial.
- Biological confirmation of denervation did not occur, as there is no accepted measure, but appropriate energy delivery was confirmed.

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

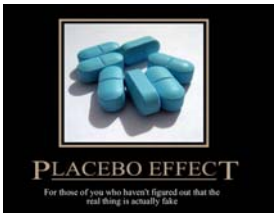
Conclusions

- In a prospective, multicenter, randomized, blinded, sham controlled trial of patients with uncontrolled resistant hypertension, percutaneous renal denervation was safe but not associated with significant additional reductions in office or ambulatory blood pressure.
- These results underscore the importance of blinding and sham controls in evaluations of new devices.
- Further study in rigorously designed clinical trials will be necessary to confirm previously reported benefits of renal denervation in patients with resistant hypertension or to validate alternate methods of renal denervation.

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

Explanations to this disappointing negative trial

- **A mere placebo effect?**



What went wrong?

Is it the end of RDN?

Comparison of HTN-2 and HTN-3 Trial Designs

	HTN-2 (N = 106)	HTN-3 (N = 535)
Randomized	✓	✓
Patient blinded	✗	✓
F/U assessor blinded	✗	✓
ABPM SBP ≥135 mm Hg required?	✗	✓
Stable 3+ drug regimen with no changes ≥2 weeks prior to enrollment	✓	✓
Omron BP machine with printer	✓	✓
Maximum tolerated doses	✗	✓
2 office visits prior to randomization	✓	✓
New investigators	✓/✗	✓
Homogeneous patient population	✓	✗

Major differences of Symplicity HTN-3 from Symplicity HTN-2

- **A sham control:**
  - The study was powered to look at a 5 mm Hg difference (advantage, if you will) for renal denervation and a 2 mm Hg advantage in the ambulatory blood pressure monitoring (ABPM) level, a pre-specified secondary endpoint.
- **Everyone have an ABPM reading to qualify for the study:**
  - a 6-month 24-hour ABPM reading to see how that correlates with office blood pressure.
  - home blood pressures were also measured, in part to assess adherence and also for corroboration with ABPM, because there is a good correlation already established in the literature between ABPM and home BP.
- **Everyone should be on maximally tolerated doses of antihypertensive medications, as recommended:**
  - **Thiazide or thiazide-like diuretic,**
  - **Renin-angiotensin system (RAS) blocker** ([ACE] inhibitor or [ARB])
  - **Calcium channel blocker.**
  - After that, spironolactone can be added,
  - Any other medication after above deemed acceptable

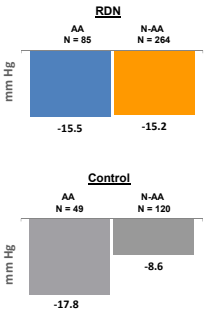
Explanations to this disappointing negative trial

- **Possibility 1: sham treatment-> improved compliance, taking drugs they didn't take before**
  - everybody in the placebo or sham group decided to take all their medicines when they weren't taking them before.
  - Did they seek other medical help with differential patterns?
- **Possibility 2: blind to interventionalist? effective procedure done?**
  - did everyone do proper denervation?
- **Possibility 3: no additive or synergistic effect, progressive less -> In trials, patients were on maximal doses->RDN effect is less than expected**
  - To be in the trial, patients had to have a systolic blood pressure higher than 160 mm Hg and had to be on 3 drugs, all at maximal doses, and 1 of them had to be a diuretic.
  - Everybody got the drugs they were supposed to get. Then when you add RDN on, maybe you don't get that much more

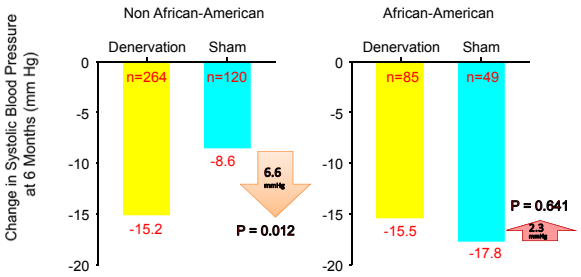
Demographics and Control Group Impact

	African American Control (N = 50)	Non–African American Control (N = 121)
OBP at baseline	183.9 ± 19.8	178.6 ± 10.7
Age	52.4 ± 10.7	57.8 ± 11.1
Male	54.0%	68.6%
Smoking	30.0%	47.1%
Type 2 diabetes	34.0%	43.8%
Hypercholesterolemia	56.0%	68.6%
History of sleep apnea	26.0%	33.9%
No. of antihypertensive medications	5.5 ± 1.6	5.1 ± 1.3
Vasodilator usage at baseline	56.0%	40.5%

Vasodilators are dosed up to 4x daily, making compliance a challenge

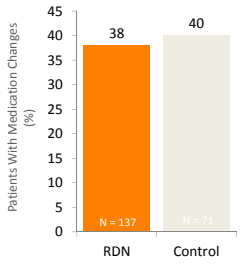


What were the BP changes in African Americans vs. Non African Americans?



HTN-3: Challenge of Limiting Medication Changes in Uncontrolled Hypertension Population

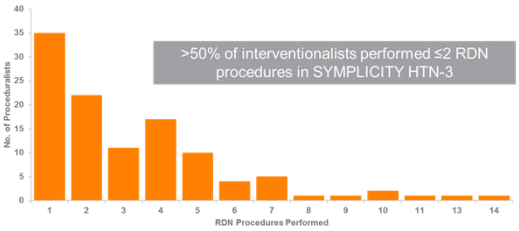
- **Protocol mandated maximum doses and *no* medication changes**
- **~40% of patients(n = 211) in the trial required medication changes**
  - **69%** of first medication changes were medically necessary



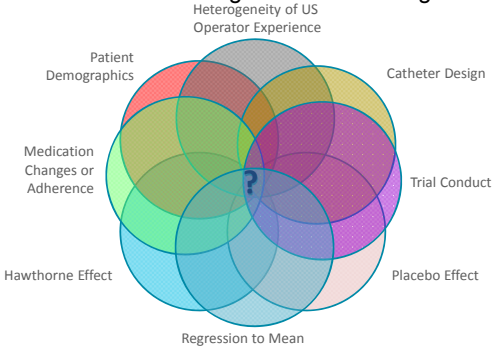
HTN-3: Procedural Experience

	HTN-1	HTN-3
No. of operators	20	112
No. of procedures per operator	6.0	3.3
No. of procedures per site	8.6	4.7

a) 5X more operators vs HTN-1
b) Greater heterogeneity of operator experience vs. HTN-1 and HTN-2
c) Case proctoring was different and not comparable



HTN-3: Continuing Areas of Investigation



Key questions to be answered

- Readout of the completion of the procedure:
  - Ongoing animal studies
  - ECG for monitoring autonomic function
  - High frequency voltage stimulation
- Patient selection:
  - Novel biomarkers
  - MicroRNA?

Resistant hypertension? Assessment of adherence by toxicological urine analysis

Oliver Jung[a], Janis L. Gechter[a], Cora Wunder[b], Alexander Paulke[b], Christine Bartel[a], Helmut Geiger[a], and Stefan W. Toennes[b]

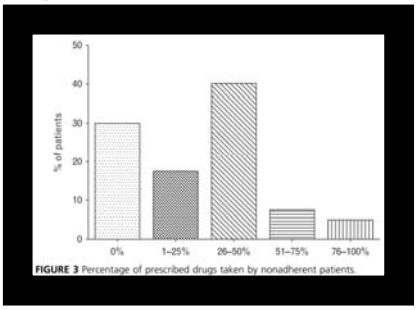


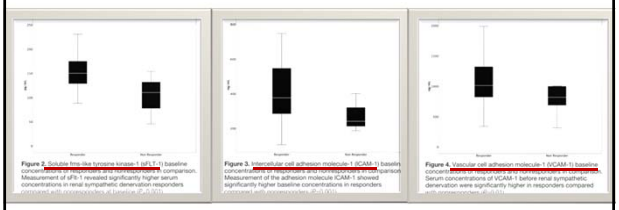
FIGURE 3 Percentage of prescribed drugs taken by nonadherent patients.

J Hypertens 2013;**31**(4):766-74.

Renal Denervation

Soluble fms-Like Tyrosine Kinase-1 and Endothelial Adhesion Molecules (Intercellular Cell Adhesion Molecule-1 and Vascular Cell Adhesion Molecule-1) as Predictive Markers for Blood Pressure Reduction After Renal Sympathetic Denervation

Oliver Dörr, Christoph Liebetrau, Helge Möllmann, Luise Gaede, Christian Troidl, Johannes Rixe, Christian Hamm, Holger Nef



Hypertension 2014;**63**(5):984-90.

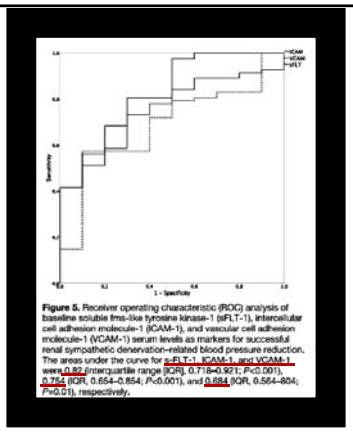
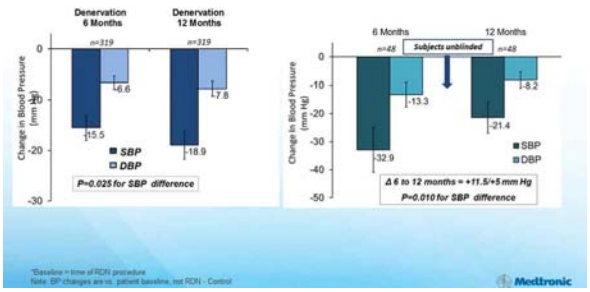


Figure 5. Receiver operating characteristic (ROC) analysis of baseline soluble fms-like tyrosine kinase-1 (sFLT-1), intercellular cell adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) serum levels as markers for successful renal sympathetic denervation–related blood pressure reduction. The areas under the curve for sFLT-1, ICAM-1, and VCAM-1 were 0.82 (interquartile range [IQR], 0.71–0.921; *P*<0.001), 0.754 (IQR, 0.654–0.854; *P*<0.001), and 0.684 (IQR, 0.564–804; *P*=0.01), respectively.

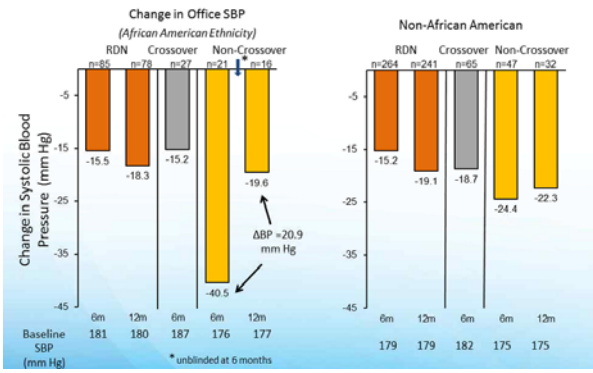
Hypertension 2014;**63**(5):984-90.

Follow-up data of Symplicity HTN-3 study

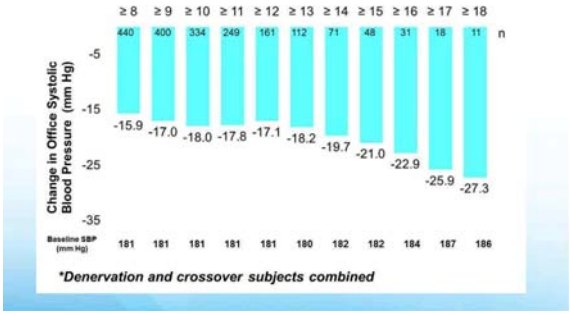
Between the 6 Month to 12 Month follow up:
- ***The original RDN group saw a significant reduction in office BP***
- ***The non-treatment / non-crossover group saw a significant increase in office BP***



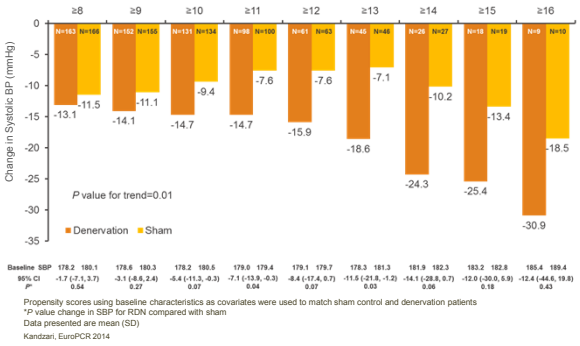
The changes in Office SBP from 6 to 12 Months were even more pronounced in patients of African American ethnicity who did not receive treatment



The positive correlation of the total number of ablations and the circumferential pattern of ablations on systolic BP drop is maintained and enhanced when the 6-month data from the crossover subjects

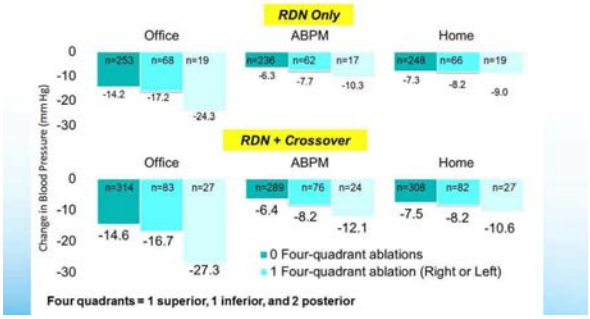


SYMPLICITY HTN-3: Impact of Number of Ablation Attempts on Change in Office Systolic Blood Pressure: Matched Cohort Analysis



Propensity scores using baseline characteristics as covariates were used to match sham control and denervation patients
*P value change in SBP for RDN compared with sham
Data presented are mean (SD)
Kandzari, EuroPCR 2014

The positive correlation of the total number of ablations and the circumferential pattern of ablations on systolic BP drop is maintained and enhanced when the 6-month data from the crossover subjects



Four quadrants = 1 superior, 1 inferior, and 2 posterior

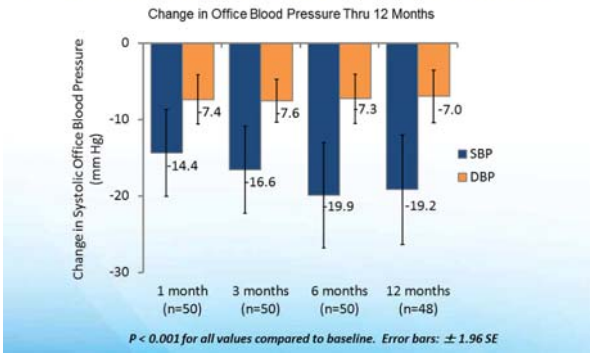
Symplicity Spyral Feasibility Study Objective

- Purpose: To assess performance of the multi-electrode catheter
- Primary goal: Acute procedural safety assessment

Note: Given the focus on safety, we only allowed 1 treatment per artery *(Number of full 60-Second Ablations: 6.5 ± 1.5)*

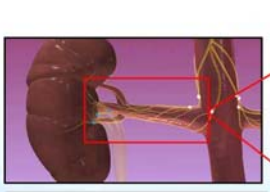
Participating Centers

Significant reduction in office blood pressure compared to baseline demonstrated out to 12 months, despite only 1 set of treatments per artery

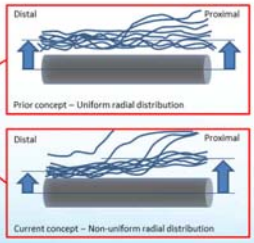


P < 0.001 for all values compared to baseline. Error bars: ± 1.96 SE

Our view of renal nerve distribution has changed!

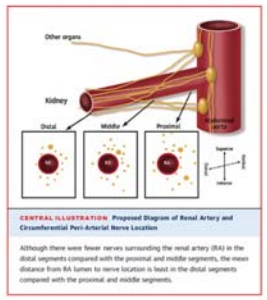


Renal nerves may have a positional bias on radial distance from the arterial lumen: distal nerves are closer



New Insights on Renal Nerve Anatomy

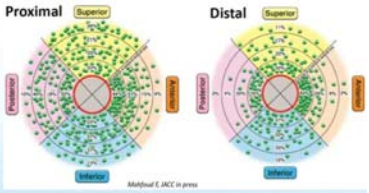
- Recently released paper details renal nerve anatomic location
- Bilateral renal arteries were collected from human autopsy subjects
- Reduced distance from lumen as you move distal versus proximal



J Am Coll Cardiol 2014;64:635-643

Can we do better with new methodological approaches to denervation with the existing technology?

- Histological analysis by Renu Virmani and others suggest that a more distal approach could increase the frequency of successful ablations
- Distal ablation strategies can be executed with the existing catheters
- **Human Main Renal Artery**
  - **5.18 + 0.71mm Dia.**
- **Human Branch Renal Artery**
  - **4.05+0.90mm Dia. Superior**
  - **3.81+0.80mm Dia. Inferior**



2 mm radial intervals per ring

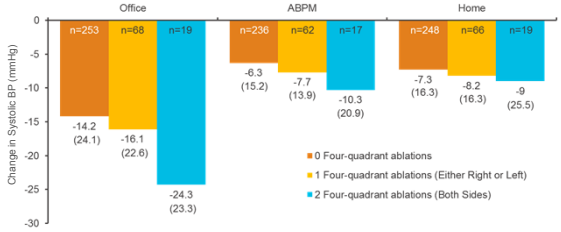
Procedural Variability

Correlation with number of ablations
Correlation with 4-quadrant ablation pattern

4 quadrant ablation pattern

Kandzari, EuroPCR 2014

SYMPLICITY HTN-3: Systolic Blood Pressure Change at 6 Months According to Ablation Pattern



Baseline SBP Measurements (mm Hg)			
0 four-quadrant tx	179.6	158.7	168.5
1 Four-quadrant tx	178.8	161.2	171.3
2 Four-quadrant tx	186.9	159.9	170.4

Four quadrants = 1 superior, 1 inferior, and 2 posterior/anterior

Kandzari, EuroPCR 2014

Great minds discuss ideas;
Average minds discuss events;
Small minds discuss people.

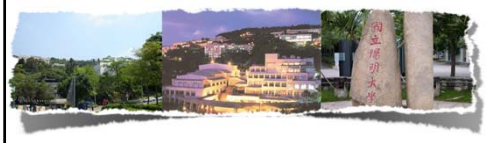
- Eleanor Roosevelt

More patience is needed!

Thanks for Your Attention!

Questions and Comments?

追求學術卓越、邁向國際一流

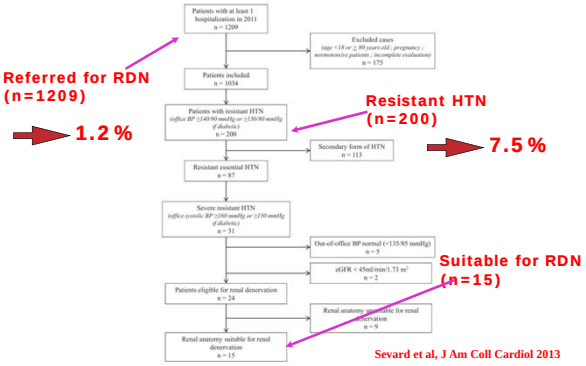


Renal Sympathetic Denervation for Resistant Hypertension-

Preliminary Experiences of Taipei Veterans General Hospital

Hao-min Cheng, M.D., Ph.D; Shih-Hsien Sung, M.D.
Taipei Veteran General Hospital
National Yang-Ming University

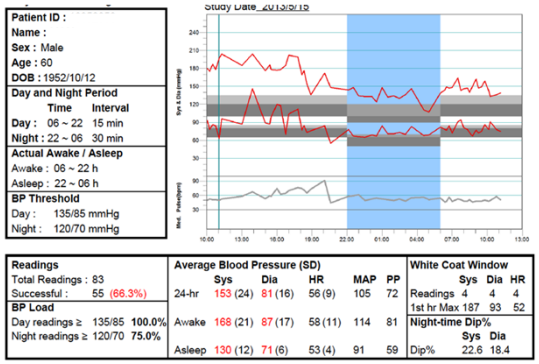
Eligibility for RDN Among "Refractory" Hypertensives



Case 1

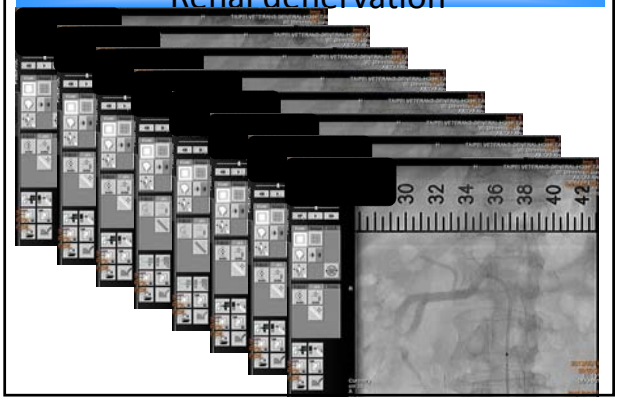
- Mr. Huang, 61 year-old man
- Medical History:
  - Hypertension
- Medications
  - Irbesartan 150mg, Carvedilol 25mg BID, Nifedipine 30mg, Dichlotride 12.5mg, Aldactone 25mg
- Office BP
  - 2013/05/07: 169/80p81
- Estimated GFR
  47.3cc/min

ABPM before Procedure

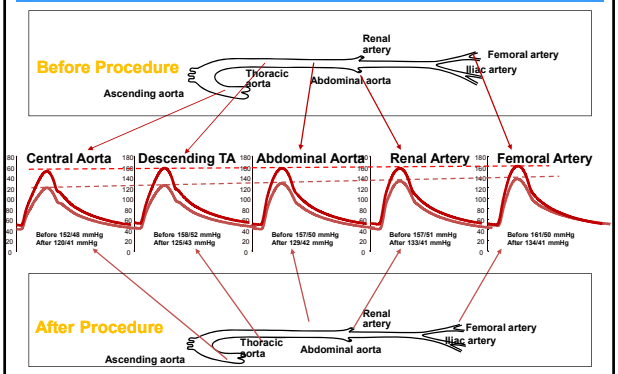


Renal MRI

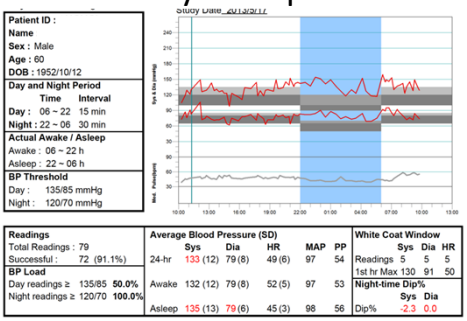
Renal denervation



Pressure waveform Changes during Procedure



ABPM 1 day after procedure



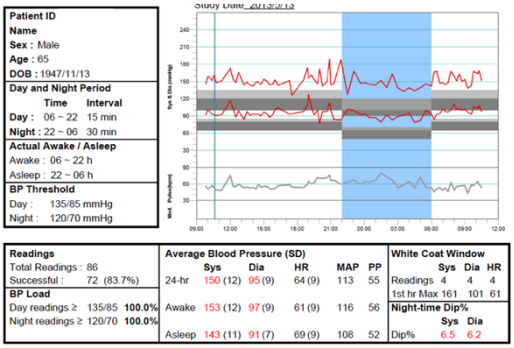
2013/5/29: Office BP 142/69p60
2013/6/25: Office BP 129/62p58
2013/9/1: eGFR 49.8mmHg

Case 2

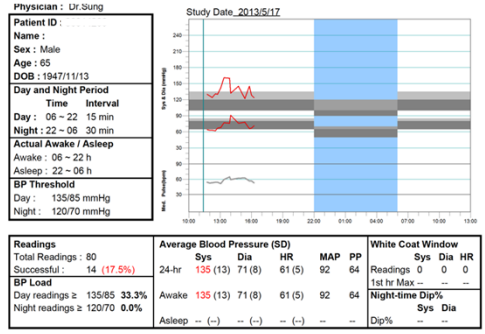
- Mr. Liu, 66 year-old retired air force officer
- Medical History:
  - Hypertension
  - CAD (LAD-D2 60% stenosis)
- Medications
  - Telmisartan 80mg, Bisoprolol 5mg, Amlodipine 10mg, Natrilix 1.5mg, Aldactone 25mg
  - Fenofibrate 200mg
- Office BP
  - 2013/05/08: 148/97p59
- Estimated GFR

  92cc/min

ABPM before Procedure

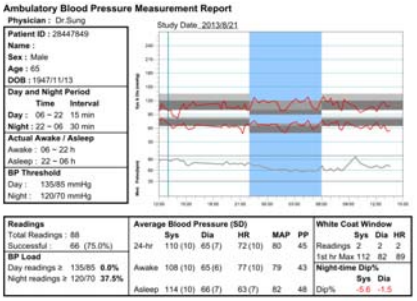


ABPM 1 day after procedure



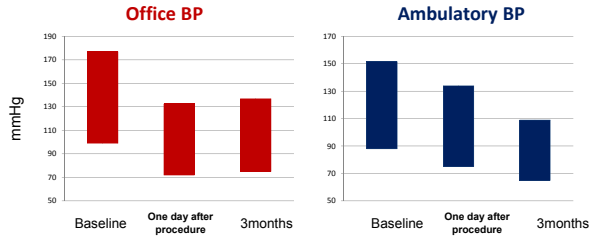
2013/5/29: Office BP 123/75p60

ABPM 3 months after procedure



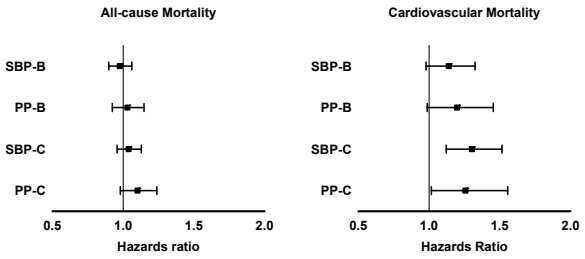
2013/8/21: eGFR 93cc/min

Summarized Results of RDN -SBP/DBP



Predictors for Mortality: Kinmen Study

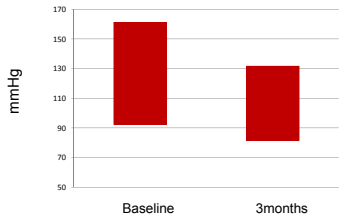
Multi-variate Analysis



All adjusted for age, sex, heart rate, BMI, current smoker, fasting plasma glucose, cholesterol/HDL, PWV, LVM, IMT, and eGFR

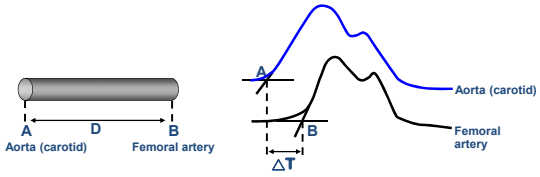
Wang KL, Cheng HM, Chuang SY, Spurgeon HA, Ting CT, Lakatta EG, Yin FCP, Chou P, Chen CH. Central or peripheral systolic or pulse pressure: Which best relates to target organs and future mortality? *J. Hypertens.* 2009;27:461-467

Summarized Results of RDN- Central BP



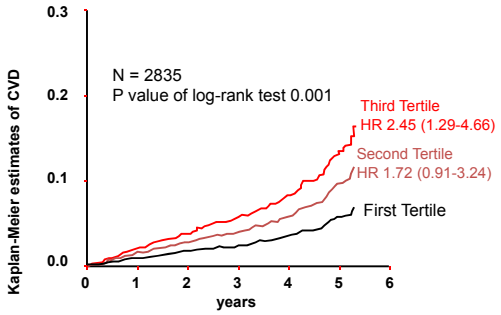
Arterial Stiffness

A Major Determinant of Central BP



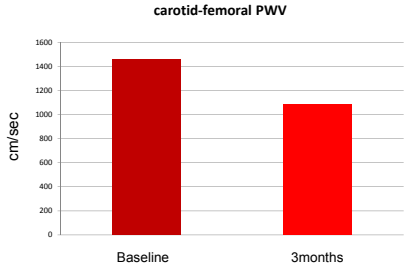
PWV = Distance (D) / Time delay (ΔT) m/sec

PWV is Predictive of CVD Events in Apparently Healthy Subjects

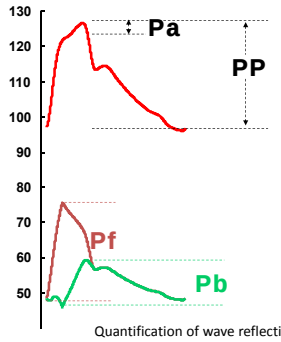


Circulation 2006;113:657-663

Summarized Results -Arterial Stiffness



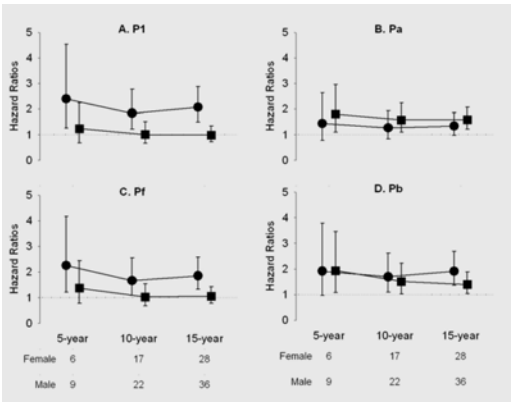
Wave Reflection
A Major Determinant of Central BP



AIx = Pa/PP = 0.31

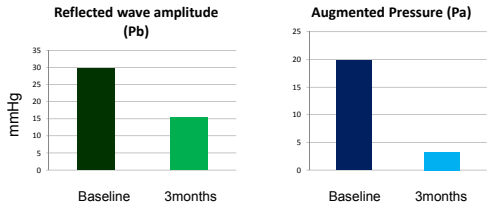
Pf = forward = 27 mmHg
Pb = reflected = 11 mmHg
RI = Pb/(Pf + Pb) = 0.29

Quantification of wave reflection in the human aorta from pressure alone: a proof of principle. Hypertension. 2006;48:595-601.



Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: A community-based study. *Hypertension*. 2010;55:799-805

Summarized Results of RDN
-Wave Reflection



Short-Term Blood Pressure Variability Predicts Mortality and Is Independently Determined by Arterial Wave Reflections

Hazard ratios and 95% confidence intervals per 1 standard deviation increment of each variable for all-cause and cardiovascular mortalities (n=836)

Variable	All-cause mortality	Cardiovascular mortality
Adjusted for 24-h SBP, cf-PWV, Pb, and other variables*		
wSD (3.5 mmHg)	1.38 (1.14-1.67)	1.82 (1.32-2.52)
ARV (2.9 mmHg)	1.34 (1.07-1.12)	1.81 (1.34-2.45)
Daytime SD (4.0 mmHg)	1.33 (1.11-1.61)	1.73 (1.27-2.35)
Nighttime SD (4.3 mmHg)	1.23 (1.02-1.49)	1.42 (1.04-1.93)

*other variables included age, sex, waist circumference, heart rate, heart rate variability, creatinine, fasting glucose, smoking, and cholesterol.

JACC 2013, in revision

Effects of Hemodynamic Parameters on BP Variability

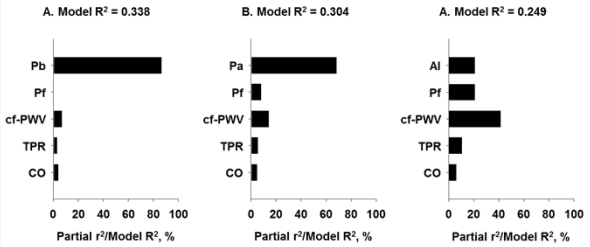
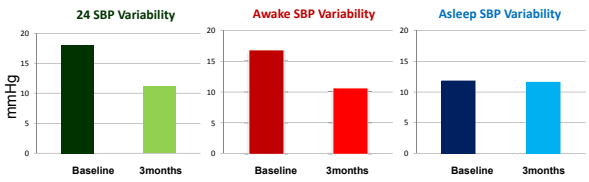


Figure 2. Relative contributions of the hemodynamic parameters to the variance of wSD. Panel A, Pb as the measure of wave reflections; B. Pa as the measure of wave reflections; C. AI as the measure of wave reflections.

JACC 2013, in revision

Summarized Results of RDN-
BP Variability



Demonstrated Versatility in Broad Range of Anatomies with Remarkable Safety Profile

Varied Patient Anatomies

•98% anatomically eligible
•Average number renal arteries: 2.16
•Mean length of renal artery: 43 +/- 14 mm
•Mean diameter of artery: 5.7 +/- 1.2 mm

Procedure (n=617)

•9% incidence of spasm
•2 patients with vascular complications
•Pseudoaneurysm/hematoma
•No serious adverse events related to delivering RF to the renal artery with the Symplicity Flex™ catheter

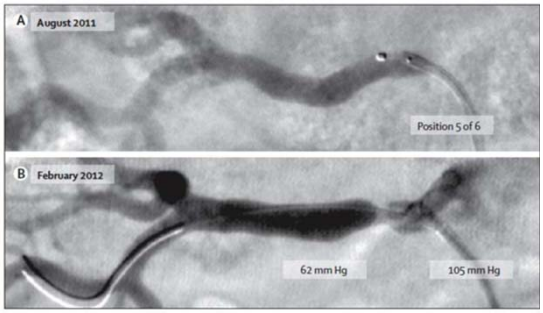
Post-Procedure through 6M*

•No new vascular abnormalities
•2 hypertensive crises
•1 death deemed unrelated to device or procedure
•1 new onset of end-stage renal disease
•2 MI

*Data collected on all patients who reached either 3 or 6M F/U

91 **EuroPCR 2013 annual meeting**

Secondary Rise in BP after RDN



Lancet 2012; 380: 778

Therapeutic strategies in patients with resistant hypertension

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

93 **2013 ESC guideline of Arterial Hypertension**

Summaries

- Renal sympathetic denervation seems a feasible procedure for the management of patients with resistant hypertension
- Suggested by the improved surrogate prognostic hemodynamic indices, it is anticipated that future cardiovascular events of patients receiving RDN could be reduced considerably.

受試者招募

- Populations:
  - Study associated with RDN in patients with resistant HTN
- Objects:
  - The associations of cardiocerebral interactions beyond BP reductions
- Fee:
  - Free of Symplicity catheter (but <20000 procedure fee charged by the hospital)
  - Free of ABPM study, Brain MRI, Sleep study
- PI: 陳震寰教授、鄭浩民醫師、宋思賢醫師
- However, patients have to follow the study protocol for clinical follow-up including Home BP and ABPM.

Thanks for Your Listening!

Renal Sympathetic Denervation for Resistant Hypertension-

Preliminary Experiences of Taipei Veterans General Hospital

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