Renal denervation for treatment of resistant hypertension

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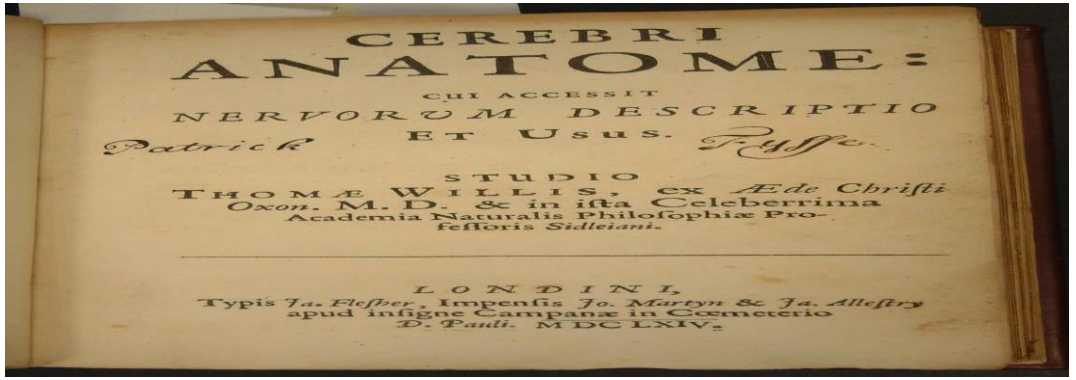
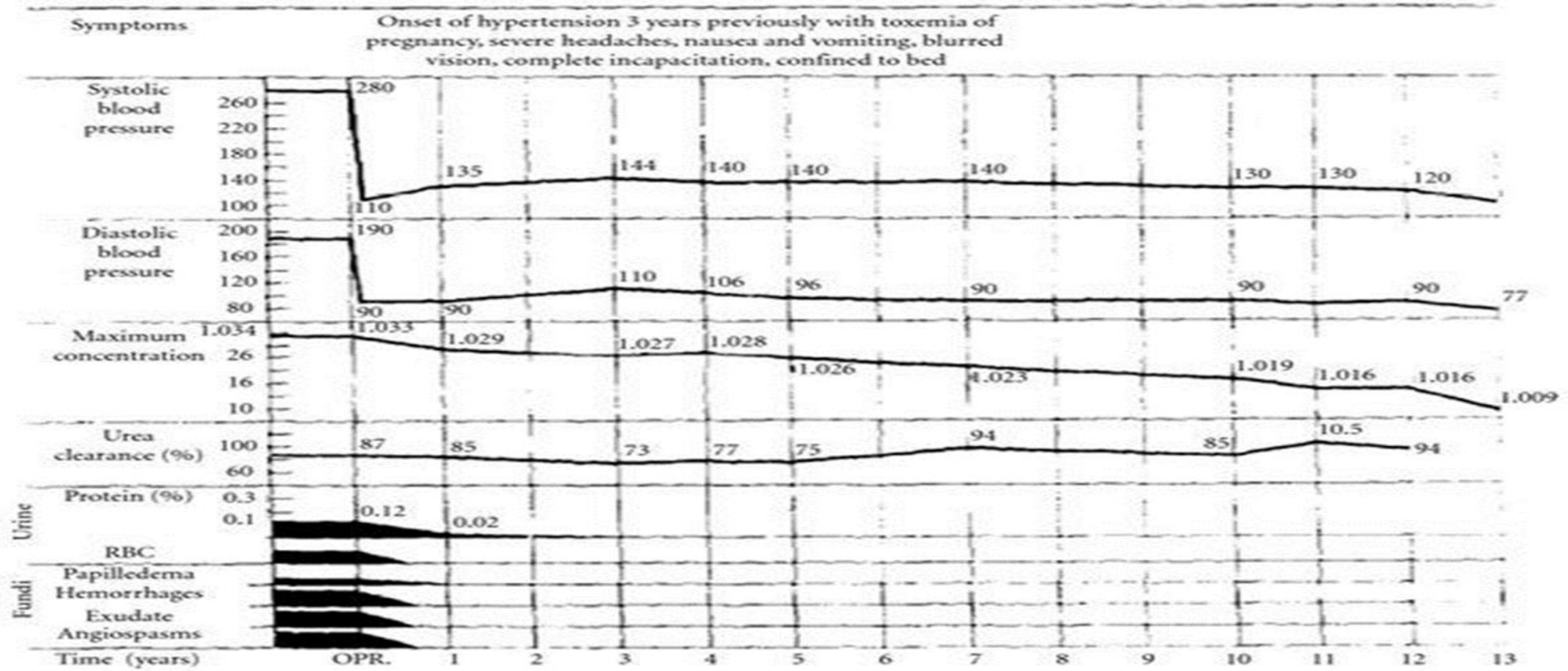
Thomas Willis: 1621-1675

Discoveries:

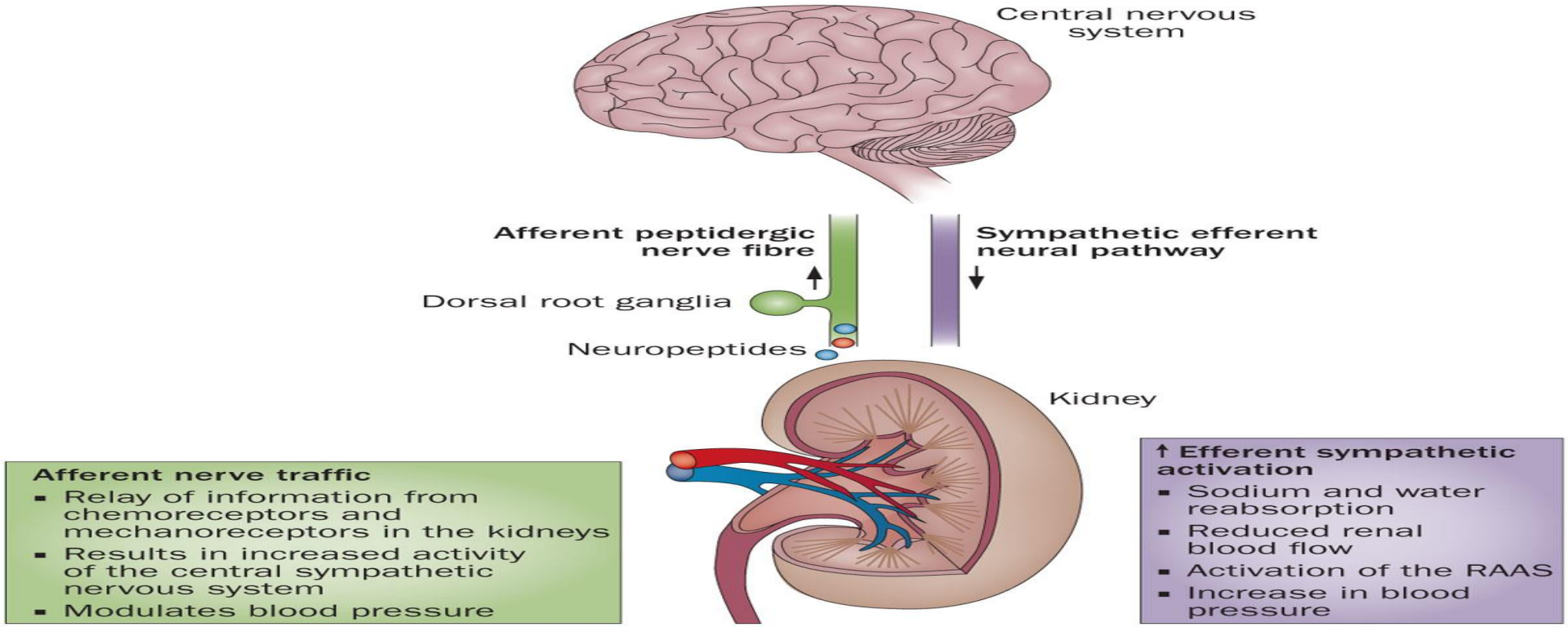
- Circle of Willis
- *1664 (anatomy of brain and nerves)*
- Neurologist- treatment epilepsy


CEREBRI
ANATOME:
CUI ACCESSIT
NERVORUM DESCRIPTIO
ET USUS.
STUDIO
THOMÆ WILLIS, ex Ædæ Christi
Oxon. M. D. &c in ista Celeberrima
Academia Naturalis Philosophiæ Pro-
fessoris Sidleiani.
LONDINI,
Typis Ja. Flesher, Impensis Jo. Martyn & Ja. Allestry
apud insigne Campanæ in Cœmeterio
D. Pauli. MDCLXIV.

Surgical sympathectomy (splanchnicectomy)

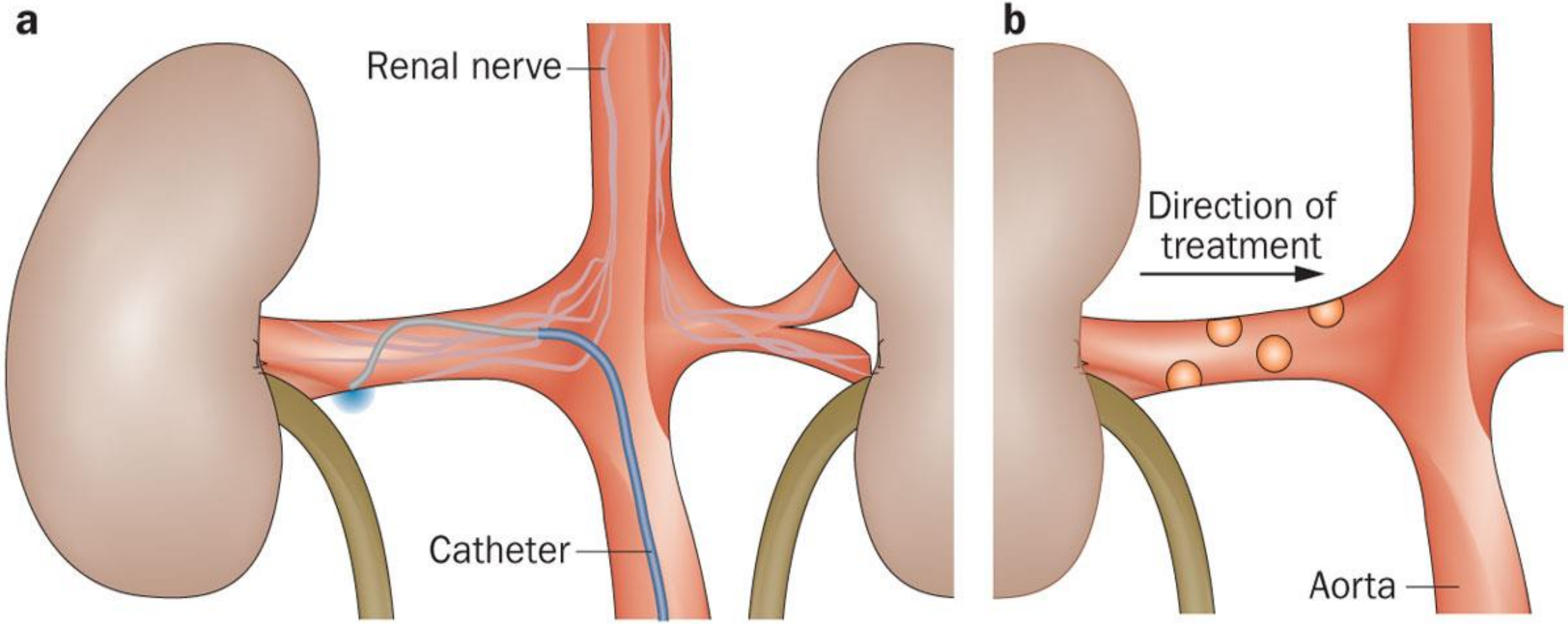


Sympathomodulation of the efferent sympathetic nervous system



Veelken R and Schmieder R. Renal denervation—implications for chronic kidney disease
Nat Rev Nephrol 2014; 10: 305-313

Renal sympathetic denervation (RDN)



Veelken and Schmieder. Renal denervation- implications for chronic kidney disease. *Nat. Rev. Nephrol 2014; 10: 305-313.*

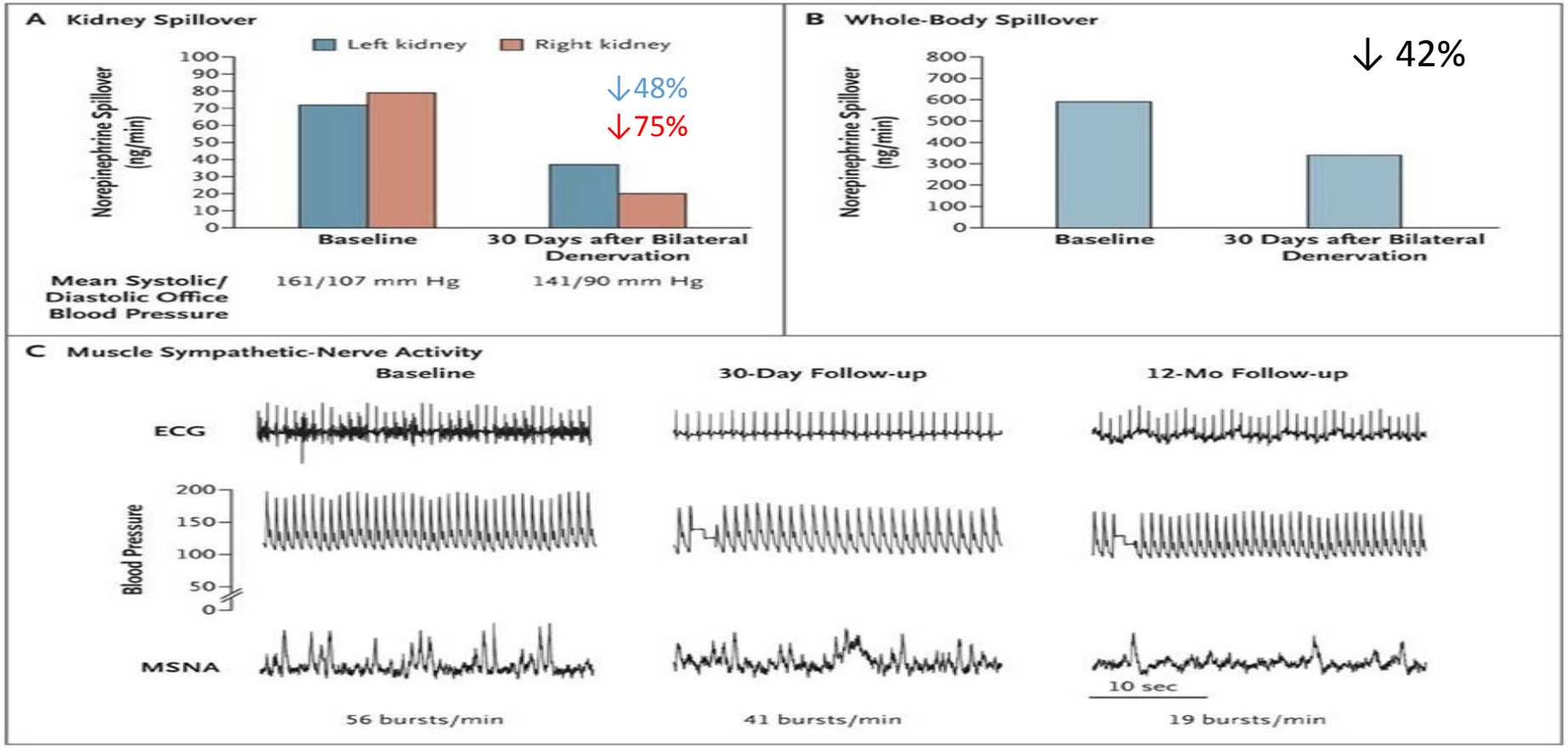
Response Assessment

- Renal afferent and efferent nerve activity cannot be quantified directly
- Plasma and urinary norepinephrine concentrations- result of removal rates and not selectively release rates

- **Renal vein norepinephrine spillover**:
  - Displays the rate at which norepinephrine is released from the sympathetic nerves into the circulation
  - Involves infusion of radioactive tritium- labelled *d,l* norepinephrine
  - Requires renal catheterization and results not immediate
- **Muscle Sympathetic Nerve Activity (MSNA)**
  - Intraneural recording using tungsten microelectrode, with tip in peripheral nerve (peroneal nerve)
  - Correlates with whole body, renal and cardiac norepinephrine spillover levels
  - Inhibition of afferent renal nerve activity may contribute to reduction in central sympathetic tone
  - Time consuming, invasive, requires trained operator

Norepinephrine and MSNA- gold standard methods to quantify sympathetic activity in human investigation

Norepinephrine Renal and Whole-body Spillover and Results of Microneurography before and after Renal Nerve- Ablation



- Renin activity halved (0.3 to 0.15 µg/l/hr
- Renal plasma flow increase (719 to 1126 ml/min

Schlaich *et al. N Eng J Med* 2009; 361: 932-934

RDN is a ‘BLIND’ Procedure

- In most clinical trials of catheter-based RDN, objective evidence that renal denervation has been achieved is lacking
- Symplicity HTN-1 Trial:

  Krum *et al*. Cather-based renal sympathetic denervation for resistant hypertension: multicentre safety and proof-of-principle cohort study. *Lancet* 2009; 373: 1275-81.

  - Assessment of whether the radiofrequency procedure results in successful efferent renal sympathetic nerve denervation only done in 10 of 50 patients (norepinephrine spillover test)
  - Degree of denervation: mean 45% (95% CI 28-65%) at 1 month post denervation (less than expected 90-95%)
  - But as hypertensive response was adequate (↓ mean 6-month BP of 22/12 mm Hg)- investigators were satisfied

RDN is a ‘BLIND’ Procedure

- **Subsequent trials: almost universal failure to apply a confirmatory test for achieved renal denervation**

- Current clinical practise, assessment of quality of renal denervation:

➢Documentation of impedance drop and energy delivery from generator

➢Visualization of arterial notches (due to oedema) following ablation procedure

Positive clinical trials: Shortfall

- Non randomized trials comparing treatment results with baseline observations, rather than with results in a control group

  Krum et al 2009. The SYMPLICITY HTN-1 Trial

  Both systolic and diastolic BP significantly lower after procedure than those before procedure (p = 0.026 and 0.027 respectively)

- Randomised with control group but no blinding of patients or assessors

  Esler *et al*. 2010. The SYMPLICITY HTN-2 Trial

- Small sample size

  Mahfoud *et al,* 2011. Prospectively assigned 37 patients to RDN and 13 controls.

- Poor study design

  Mahfoud et al, 2012. Consecutive patients, 88 RDN and 12 controls

- Absence of a placebo-like procedure as a control: All trials

RDN: Next big innovation

- Multiple publications
- 2013: 294 papers dealing with renal denervation

American Heart Association®
Learn and Live

Radio waves to kidneys lower persistent high blood pressure
December 17, 2012

- Talk of using RDN to treat moderate hypertension and in patients ‘fed up’ of taking their antihypertensive medications

Bloomberg

Medtronic to Buy Ardian for $800 Million to Gain Novel Hypertension Device

By David Olmos Nov 23, 2010

How do editors decide to publish/ reject manuscript?

- "**New, true, relevant**"

New: first RDN use in humans 21st century

- First-in man study

-Schlaich *et al*. Renal sympathetic-nerve ablation for uncontrolled hypertension. *N Eng J Med* 2009; 361:932-34.

-Successful denervation with Symplicity catheter system- reduction in norepinephrine spillover in both kidneys (48% and 75%), reduced MSNA; was associated with reduced renin activity, improved renal plasma flow and sustained BP reductions (141/90 at 1 month; 127/81 at 1 year).

True- evidence of antihypertensive effect of RDN has been confirmed in four mammalian species (rats, dogs, rabbits, pigs)

Relevant:

- 0ne billion people in the world have hypertension, incidence predicted to increase by 60% in 2025
- Prevalence of true resistant hypertension: 12.8% (National Health and Nutrition Survey, USA)
- 10 mm Hg ↓ in usual SBP or 5 mm Hg ↓ in usual DBP → 40 % lower risk of stroke death, 30% lower risk of IHD/ vascular death

How do editors decide to publish/ reject manuscript?

- To be the first to publish original information
- Confirmatory data less appealing

A new procedure, particularly one with promising early results, will most likely receive an extra boost when assigning priority for acceptance

How do editors decide to publish/ reject manuscript?

- **Impact factor**

- Measure reflecting the average number of citations to recent articles published in the journal
- Frequently used as proxy for the relative importance of a journal within its field

A novel, rapidly emerging technology will stimulate great deal of research, resulting in multiple publications and citations

Selected negative clinical trials of renal denervation

Author	Year	Study type	N	Primary Outcome	Conclusion
Elmula *et al*	2014	Randomized	Adjusted medical therapy (n=10) vs RDN (n=9)	Systolic BP and diastolic BP significantly lower in drug adjusted group (p=0.002 and p=0.004). RDN had uncertain BP lowering effect	Adjusted drug treatment has superior BP lowering effects compared to RDN in patients with true resistant hypertension
Elmula *et al*	2013	Observational	RDN (n=6)	Mean office and ambulatory BP remained unchanged at 1, 3, 6 months	RDN had no effect on office and ambulatory BP
Brinkman et al	2012	Case control series	12	Office BP change 157/85±7/4 vs 157/85±6/4 mm Hg	Office BP not significantly different 6 months post-procedure

Evidence based practice

Making conscientious effort to base clinical decisions on research that is **most** likely to be free from bias, and using interventions most likely to improve how long or well patients live.

Original Article

A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O'Neill, M.D., Ralph D'Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., George L. Bakris, M.D., for the SYMPLICITY HTN-3 Investigators

N Engl J Med
Volume 370(15):1393-1401
April 10, 2014

The NEW ENGLAND JOURNAL of MEDICINE

Randomized SYMPLICITY Hypertension (HTN)- 3 Clinical Trial

- First prospective, multicentre, randomized, blinded, sham-controlled study
- 535 patients
- Aim: To evaluate both the safety and efficacy of percutaneous renal artery denervation in patients with severe treatment-resistant HTN
- Trial sponsor: Medtronic
- Independent Validation: Harvard Clinical Research Institute

Inclusion Criteria

- Age 18-80 years
- Resistant hypertension:
    - office systolic blood pressure (SBP) ≥ 160 mm Hg (average of 3 BP readings)
    - measured at initial ***and*** confirmatory screening visit
    - automated 24-hour ambulatory blood pressure (ABPM) ≥ 135 mm Hg
- Stable medication regimen:
    - full tolerated doses of ≥ 3 antihypertensive drugs of different classes, including a diuretic
    - no changes for a minimum of 2 weeks before screening and no expected changes for at least 6 months
- Written informed consent

Methods

- Randomly assigned in a 2:1 ratio
- All patients underwent renal angiography
- Conscious sedation
- Sensory isolation
- Treatment group: renal denervation using radiofrequency energy (Simplicity renal denervation catheter)
- Sham group: renal angiogram only
- Both patients and blood pressure assessors were unaware of study-group assignments

Outcome variables

- **<u>Primary efficacy end point</u>**:

Mean change in office SBP from baseline to 6 months in the denervation group compared with mean change in sham group

$$(SBP_{RDN\ 6\ month} - SBP_{RDN\ baseline}) - (SBP_{CTL\ 6\ month} - SBP_{CTL\ baseline})$$

Superiority margin = 5 mmHg

- **<u>Secondary end point</u>**:

Comparison of mean 24-hour ABPM from baseline in RDN group compared with change from baseline to 6 months in control group

Pre-specified difference of 2 mm Hg

Table 1. Baseline Characteristics of the Study Population.*

Characteristic	Renal-Denervation Group (N=364)	Sham-Procedure Group (N=171)
Age — yr	57.9±10.4	56.2±11.2
Male sex — no. (%)	215 (59.1)	110 (64.3)
Body-mass index†	34.2±6.5	33.9±6.4
Race — no./total no. (%)‡		
Black	90/363 (24.8)	50/171 (29.2)
White	265/363 (73.0)	119/171 (69.6)
Asian	2/363 (0.6)	0/171
Other	6/363 (1.7)	2/171 (1.2)
Medical history — no. (%)		
Renal insufficiency§	34 (9.3)	17 (9.9)
Renal-artery stenosis	5 (1.4)	4 (2.3)
Obstructive sleep apnea	94 (25.8)	54 (31.6)
Stroke	29 (8.0)	19 (11.1)
Transient ischemic attack	28 (7.7)	13 (7.6)
Peripheral artery disease	19 (5.2)	5 (2.9)
Cardiac disease		
Coronary artery disease	101 (27.7)	43 (25.1)
Myocardial infarction	32 (8.8)	11 (6.4)
Diabetes		
Type 1	0	0
Type 2	171 (47.0)	70 (40.9)
Hyperlipidemia — no. (%)	252 (69.2)	111 (64.9)
Current smoker — no. (%)	36 (9.9)	21 (12.3)
Family history of hypertension — no./total no. (%)	305/361 (84.5)	140/170 (82.4)
Hypertension history — no. (%)		
Hospitalization for hypertensive crisis	83 (22.8)	38 (22.2)
Hospitalization for hypotension	8 (2.2)	4 (2.3)
No. of antihypertensive medications	5.1±1.4	5.2±1.4
Type of antihypertensive medication — no. (%)		
ACE inhibitor		
Patients taking medication	179 (49.2)	71 (41.5)
Patients taking maximally tolerated dose	167 (45.9)	64 (37.4)
Angiotensin-receptor blocker		
Patients taking medication	182 (50.0)	91 (53.2)
Patients taking maximally tolerated dose	180 (49.5)	88 (51.5)
Aldosterone antagonist	82 (22.5)	49 (28.7)
Alpha-adrenergic blocker	40 (11.0)	23 (13.5)
Beta-blocker	310 (85.2)	147 (86.0)
Calcium-channel blocker		
Patients taking medication	254 (69.8)	125 (73.1)
Patients taking maximally tolerated dose	208 (57.1)	109 (63.7)
Centrally acting sympatholytic agent	179 (49.2)	75 (43.9)
Direct-acting renin inhibitor	26 (7.1)	12 (7.0)
Direct-acting vasodilator	134 (36.8)	77 (45.0)
Diuretic		
Patients taking medication	363 (99.7)	171 (100)
Patients taking maximally tolerated dose	351 (96.4)	167 (97.7)

* Plus–minus values are means ±SD. All differences in characteristics between groups were nonsignificant. ACE denotes angiotensin-converting enzyme.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was determined by self-report.
§ Renal insufficiency was defined as an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area.

Bhatt *et al*. N Eng J Med 2014; 370: 1393-1401

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- '*Primum non nocere*'
- The Hippocratic Oath: includes the promise 'to abstain from doing harm'

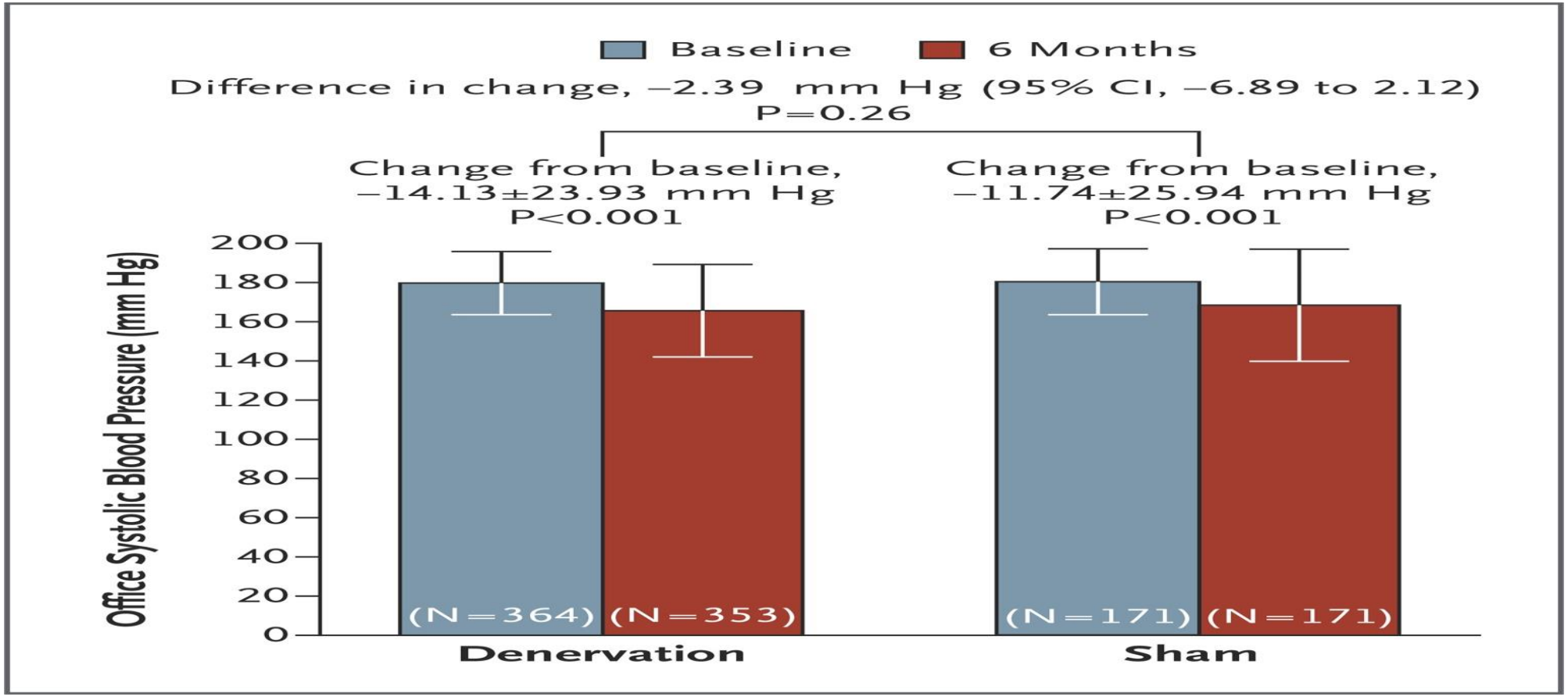
Bhatt *et al*. *N Eng J Med* 2014; 370: 1393-1401

Table 2. Safety End Points.*

End point	Renal-Denervation Group	Sham-Procedure Group	Percentage-Point Difference (95% CI)
	no. of patients/total no. (%)		P=0.67
Major adverse event†	5/361 (1.4)	1/171 (0.6)	0.8 (–0.9 to 2.5)
Composite safety end point at 6 mo‡	14/354 (4.0)	10/171 (5.8)	–1.9 (–6.0 to 2.2)
Specific event within 6 mo			
Death	2/352 (0.6)	1/171 (0.6)	0.0 (–1.4 to 1.4)
Myocardial infarction	6/352 (1.7)	3/171 (1.8)	0.0 (–2.4 to 2.3)
New-onset end-stage renal disease	0/352	0/171	—
Increase in serum creatinine of >50% from baseline	5/352 (1.4)	1/171 (0.6)	0.8 (–0.8 to 2.5)
Embolic event resulting in end-organ damage	1/352 (0.3)	0/171	0.3 (–0.3 to 0.8)
Renal-artery intervention	0/352	0/171	—
Vascular complication requiring treatment	1/352 (0.3)	0/171	0.3 (–0.3 to 0.8)
Hypertensive crisis or emergency	9/352 (2.6)	9/171 (5.3)	–2.7 (–6.4 to 1.0)
Stroke	4/352 (1.1)	2/171 (1.2)	0.0 (–2.0 to 1.9)
Hospitalization for new-onset heart failure	9/352 (2.6)	3/171 (1.8)	0.8 (–1.8 to 3.4)
Hospitalization for atrial fibrillation	5/352 (1.4)	1/171 (0.6)	0.8 (–0.8 to 2.5)
New renal-artery stenosis of >70%	1/332 (0.3)	0/165	0.3 (–0.3 to 0.9)

* CI denotes confidence interval.
† The primary safety end point was a composite of major adverse events, defined as death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, or hypertensive crisis within 30 days or new renal-artery stenosis of more than 70% within 6 months. The objective performance criterion for the primary safety end point was a rate of major adverse events of 9.8%, which was derived from historical data. The rate in the renal-denervation group was 1.4% with an upper boundary of the one-sided 95% CI of 2.9%; therefore, the performance criterion was met with a P value of <0.001.
‡ This end point was a composite of death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, hypertensive crisis, or new renal-artery stenosis of more than 70% within 6 months.

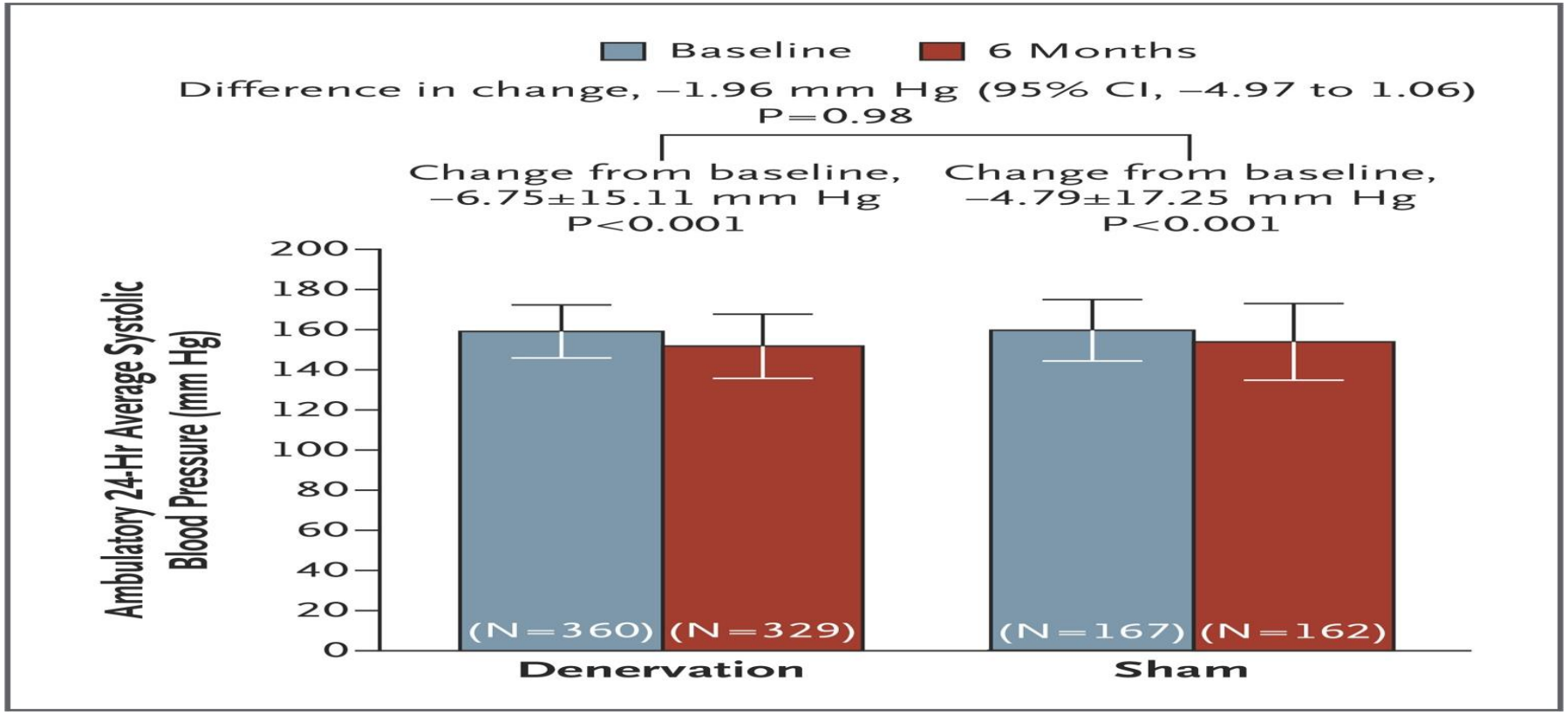
Primary efficacy end point



Superiority margin 5 mm Hg

Bhatt *et al*. *N Eng J Med* 2014; 370: 1393-1401

Secondary efficacy end point



Superiority margin 2 mm Hg

Bhatt *et al*. *N Eng J Med* 2014; 370: 1393-1401

Conclusion: SYMPLICITY HTN-3

- This randomized, sham-controlled, blinded trial **did not** show a benefit of renal-artery denervation with respect to either a reduction in office or ambulatory systolic blood pressure at 6 months.

Limitations

- “It is reasonable to have perfection in our eye that we may always advance toward it, though we know it can never be reached”

  Samuel Johnson

- 88 centres
- > 100 operators
- No hands-on experience prior to trial (expert interventional cardiologists involved)
- Energy delivery

Conclusion

- Randomized controlled trial, with blinding and sham controls (controversial) is **essential** in the evaluation of new medical devices before their adoption for clinical use.
- Renal denervation **cannot** be recommended for use in clinical practise for the management of resistant hypertension

Recommendation

Use of RDN in clinical trials and research laboratories

- Mandatory testing for achieved renal denervation

-Norepinephrine spillover test– limited availability and cumbersome

-University of the Witwatersrand, Department of Nuclear Medicine:

Not available

Recommendation

Update: New areas of research

- Testing for end- products of sympathetic nerve protein degradation

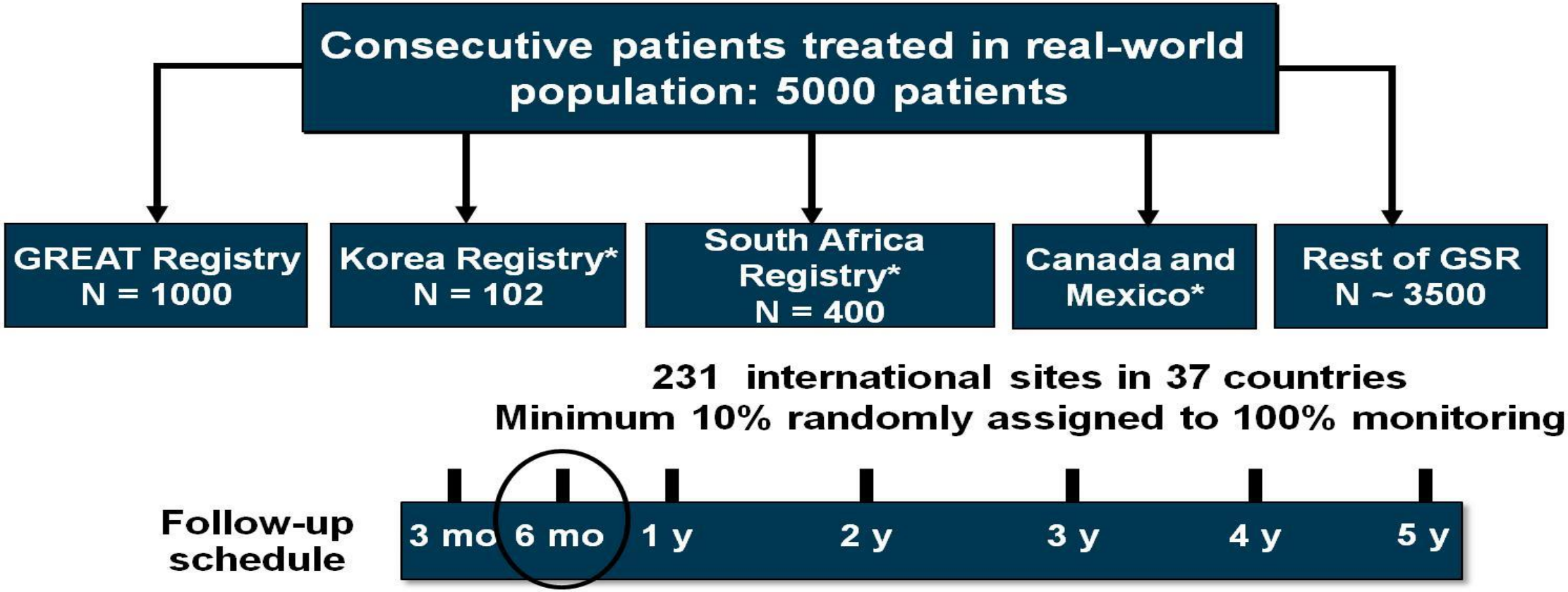
  e.g. tyrosine hydroxylase fragments in urine

- Adenosine infusion into renal artery:

➢Normally increases SNS activity and BP

➢Can be given before and after denervation procedure- a reduction in the blood pressure response (post procedure) indicative of afferent nerve ablation

Global SYMPLICITY Registry



*Limited to resistant HTN only

Böhm M, et al. ACC 2014.[1]

Thank you

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