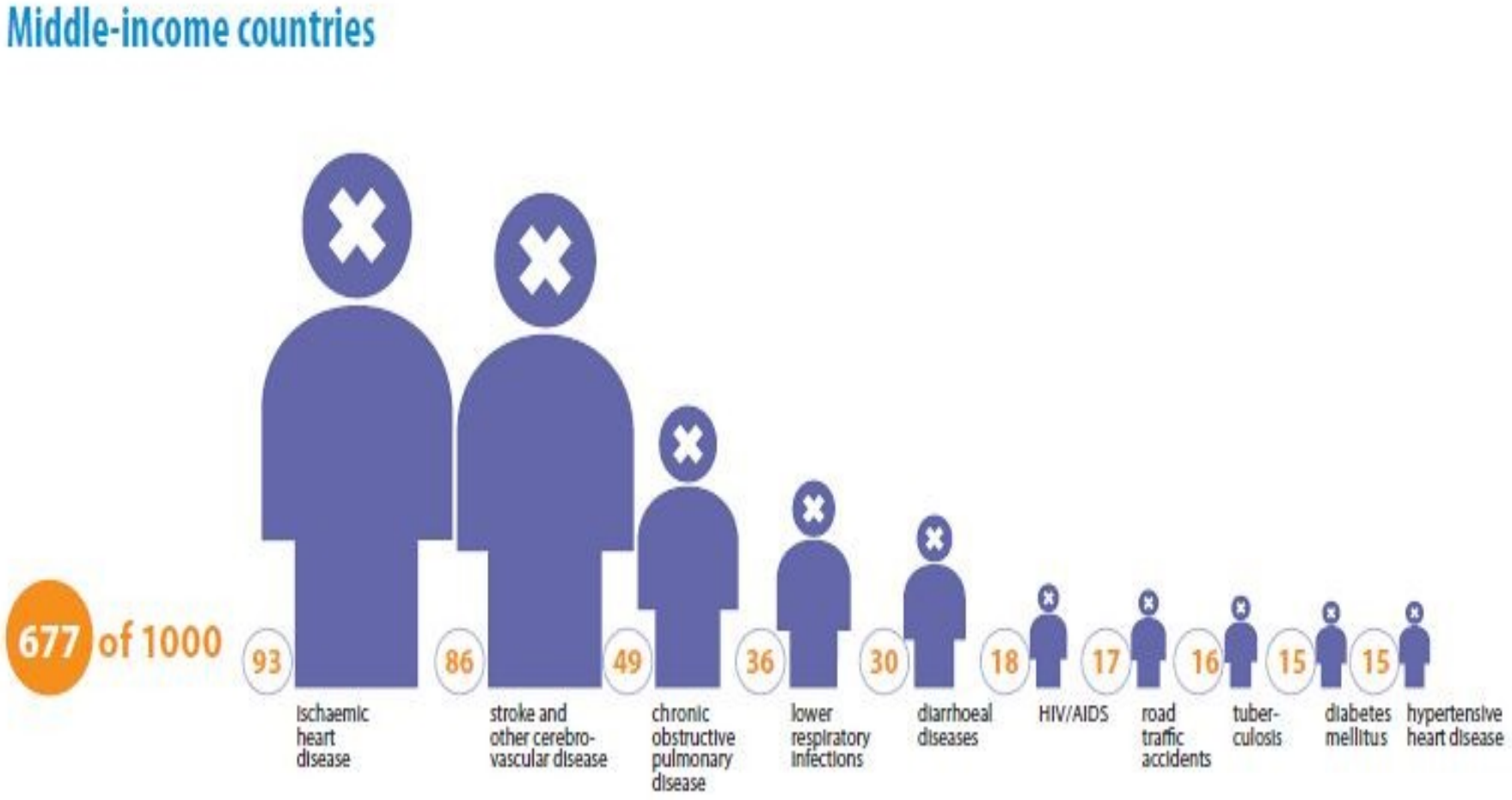
renal denervation and baroreceptor stimulation in the treatment of resistant hypertension

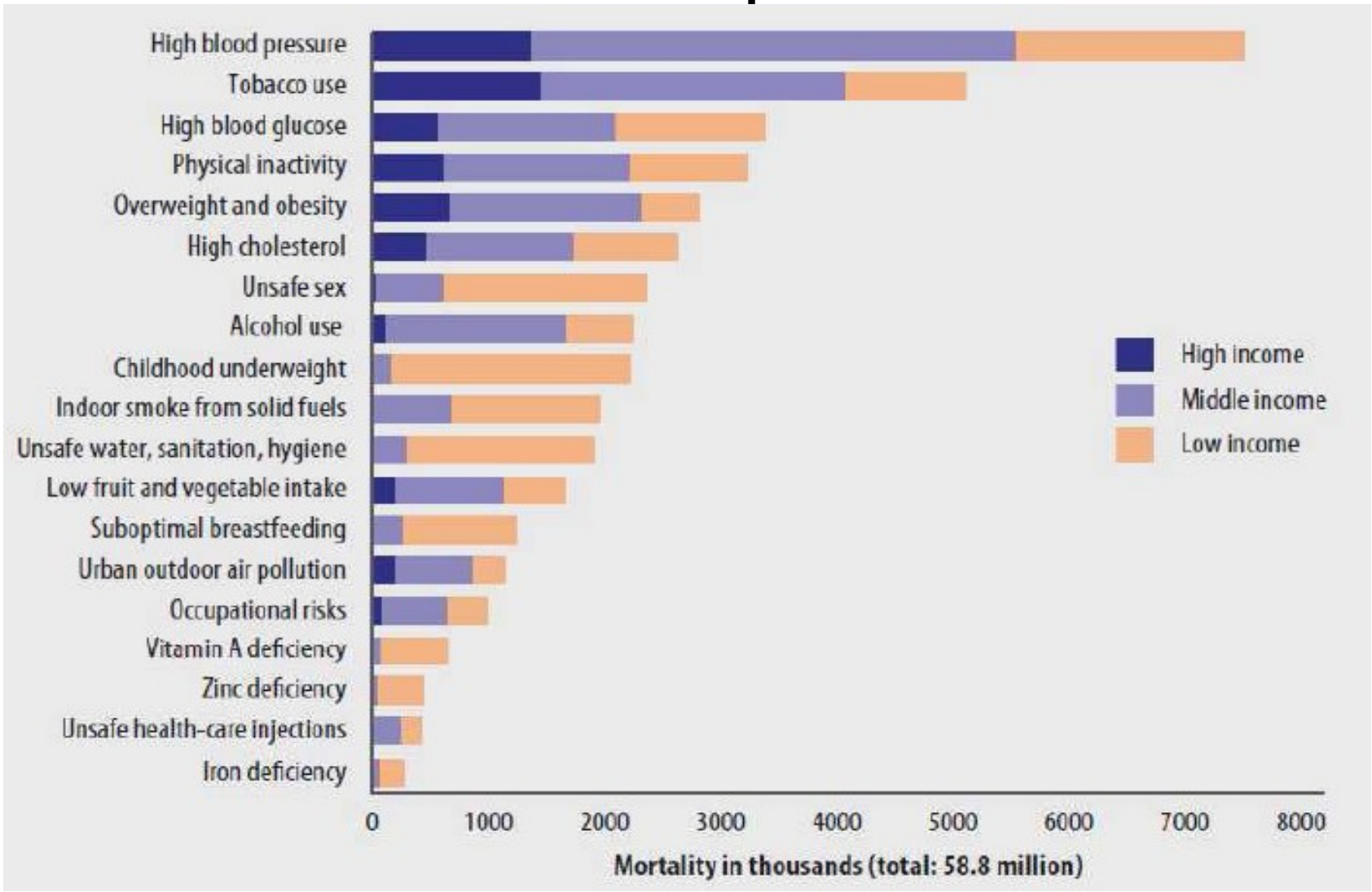
Kostadin Kichukov, MD, PhD
Department of cardiology, angiology and invasive electrophysiology
City Clinic - Sofia

Cardiovascular and cerebrovascular disease:



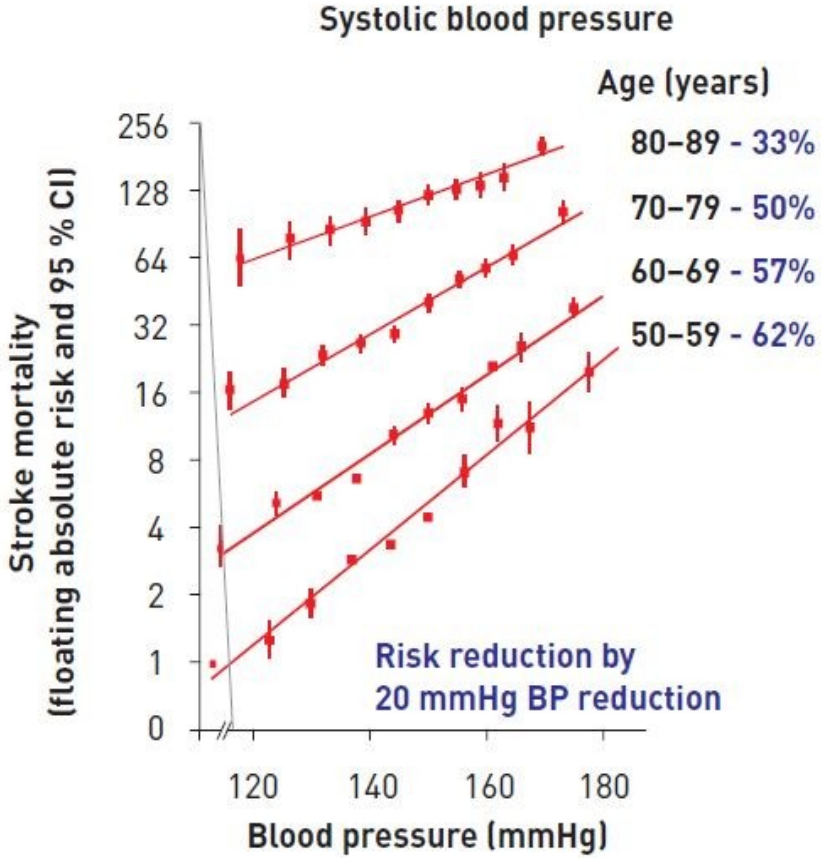
Global Burden of disease – WHO 2012

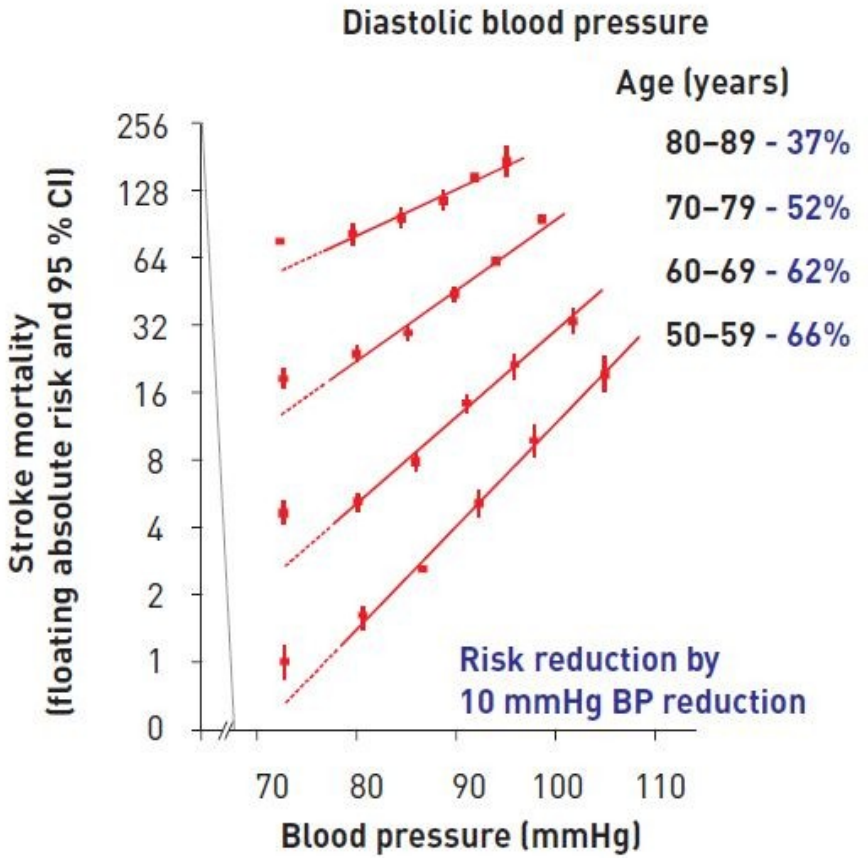
Treatment of Hypertension – unmet



Global Burden of disease – WHO 2012

Pure statistics and lemmas about benefits of BP lowering





The PCR-EAPCI Textbook 2012, p 489

Resistant hypertension (RH) Definition and scope of the problem

- **Resistant hypertension** is a blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes
- One of the 3 agents should be a (thiazide) diuretic and all agents should be prescribed at optimal dose amounts
- **Treatment-resistant hypertension**
  - BP remains above goal on more than 3 medications

Calhoun Circulation 2008; 117:e510-e526
Mancia G Eur H J 2007; 28:1462-1563

Before considering RH
What to look for?

- White coat hypertension – Don't underestimate ABPM
- Secondary hypertension – Multidisciplinary approach
- Inaccurate measurement – Follow GL
- Inappropriate drug combinations – Follow GL
- Interfering substances – Somewhere next
- Sleep apnoea – Curable condition

Real life data – Utrecht registry. Referral for RDN – 66% dropouts.

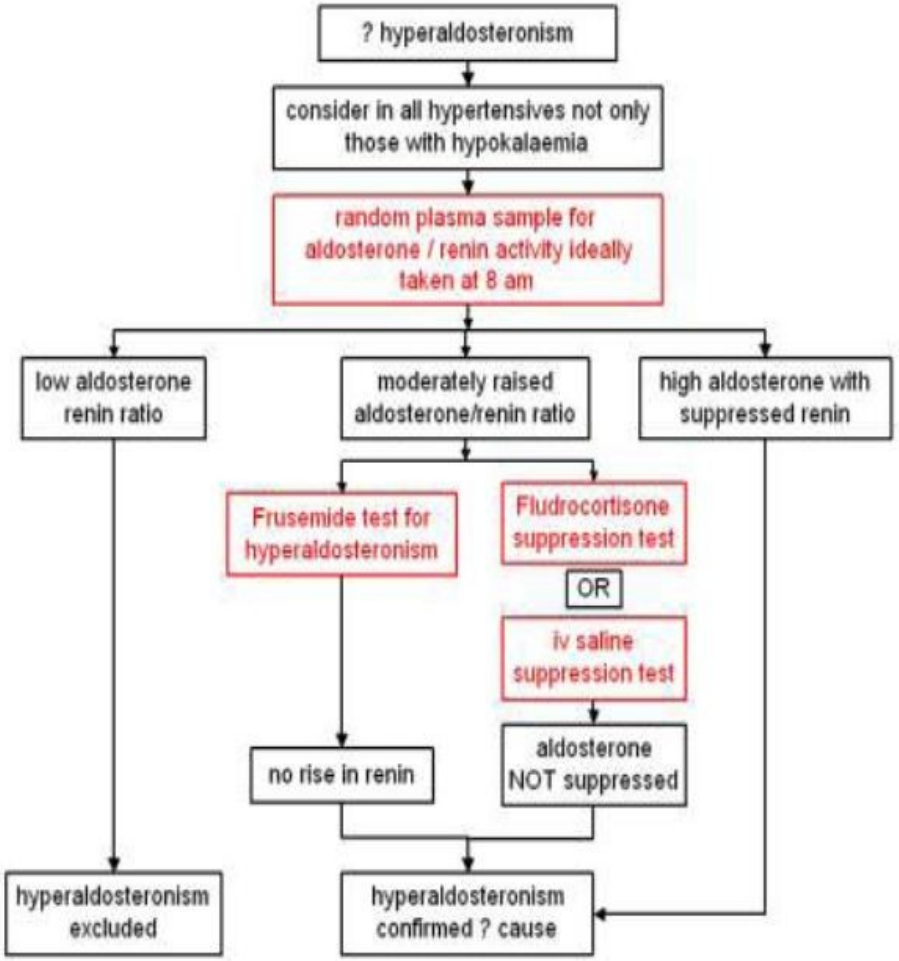
RHC 2013

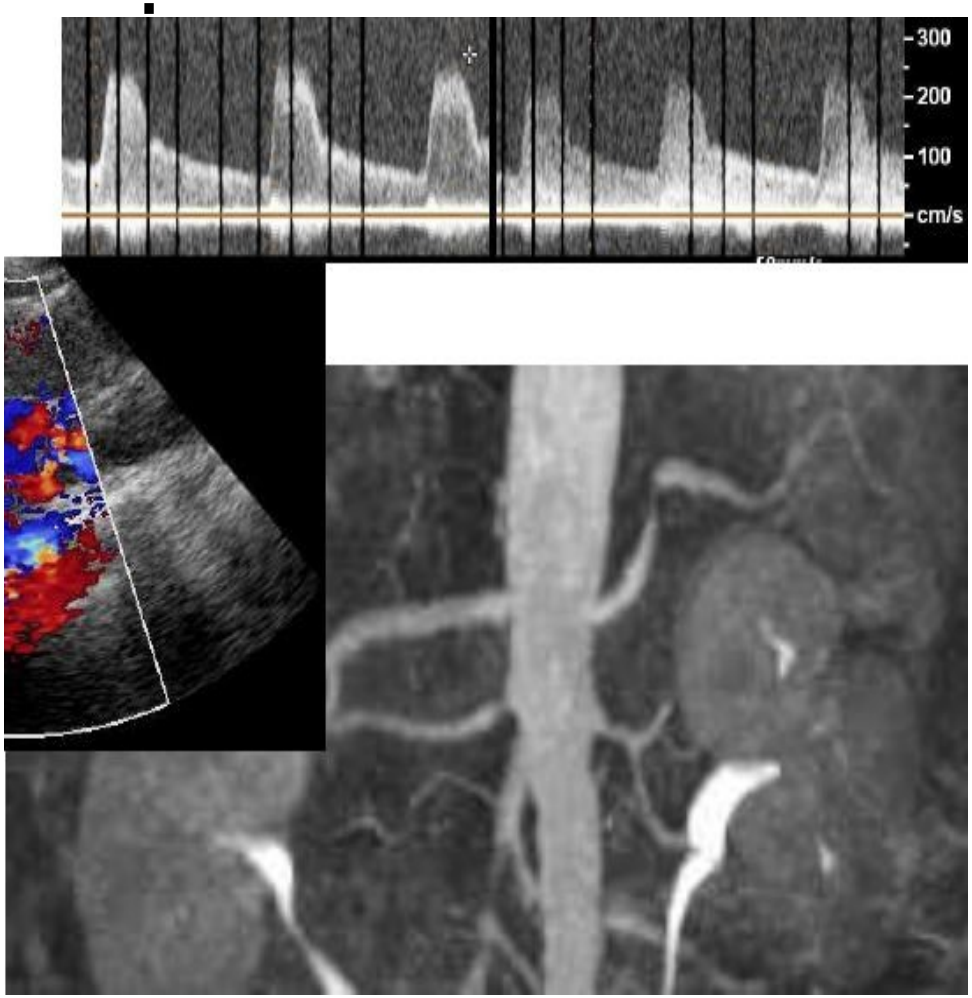
Results: Excluded patients (n=121)

Blood Pressure	**49 (41%)**
- Office SBP<160 mmHg	23 (19%)
- Mean 24-h ABPM < threshold	26 (22%)
Secondary cause of hypertension	**14 (12%)**
- Primary hyperaldosteronism	11 (9%)
- Primary hyperparathyroidism	1 (1.3%)
- Pseudo-hyperaldosteronism	1 (1.3%)
- Coarctatio aortae	1 (1.3%)
Ineligible renal artery anatomy	**9 (7%)**
- Renal artery stent	3 (4%)
- Renal artery stenosis	6 (5%)
Co-morbidity	**10 (8%)**
Options for pharmacological treatment	**15 (12%)**
Other reasons	**24 (20%)**

Blankestijn, P. J. RHC 2013

Secondary Hypertension
Hyperaldosteronism / Renal artery



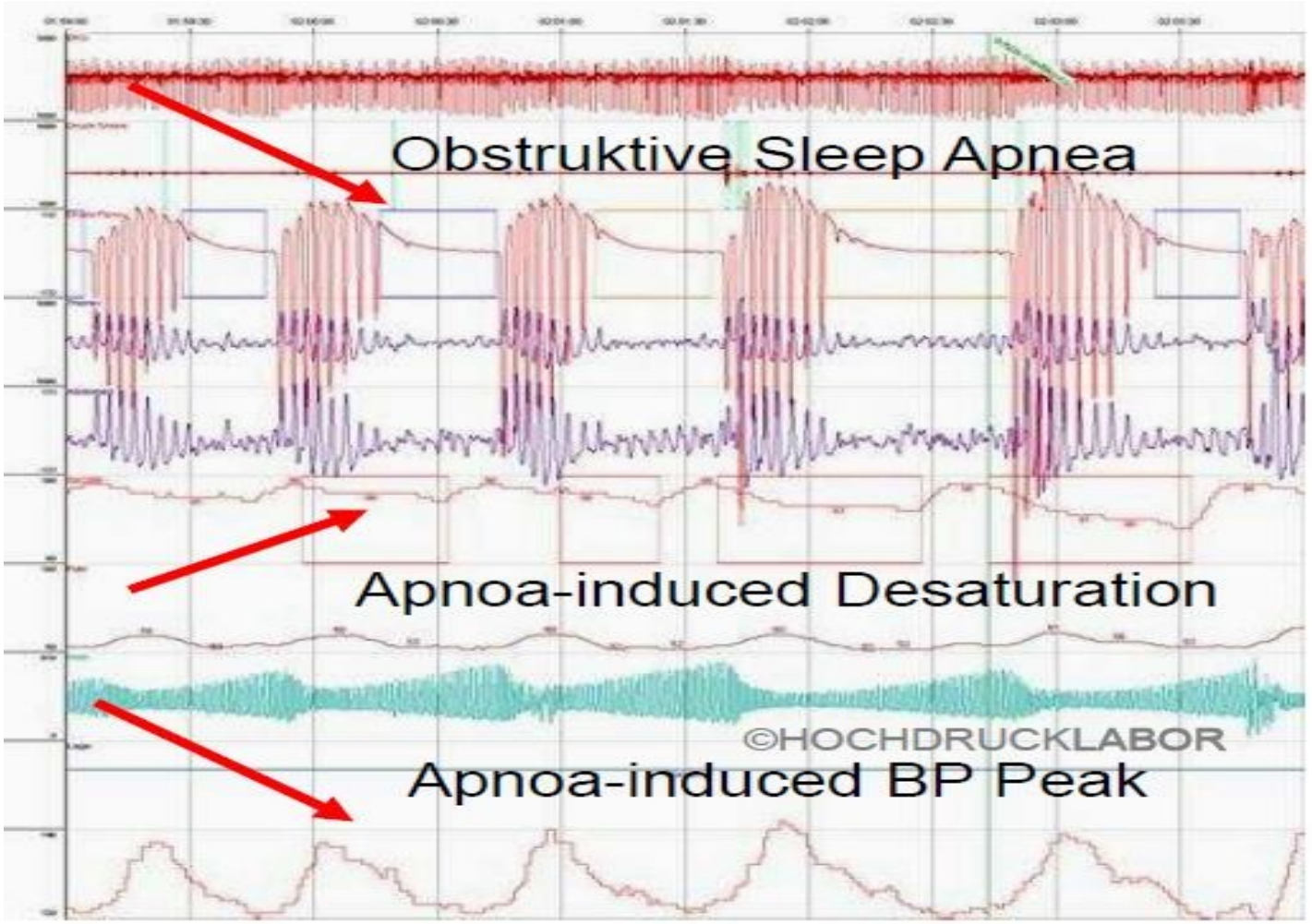


Prof Klaus Weber, Doz. Jan Borgel, RHC

Interfering substances
Inappropriate drug usage

Medication that can interfere with blood pressure control (Calhoun et al Hypertension 2008)	
Nonnarcotic analgesics	- Non-steroidal anti-inflammatory agents, including aspirin - Selective COX-2 inhibitors
Sympathomimetic agents	Decongestants, diet pills, cocaine
Stimulants	Methylphenidate, dexmethylphenidate, dextro-amphetamine, amphetamine, methamphetamine, modafinil
Alcohol	
Oral contraceptives	
Cyclosporine	
Erythropoietin	
Natural licorice	
Herbal compounds	Ephedra or Ma Huang

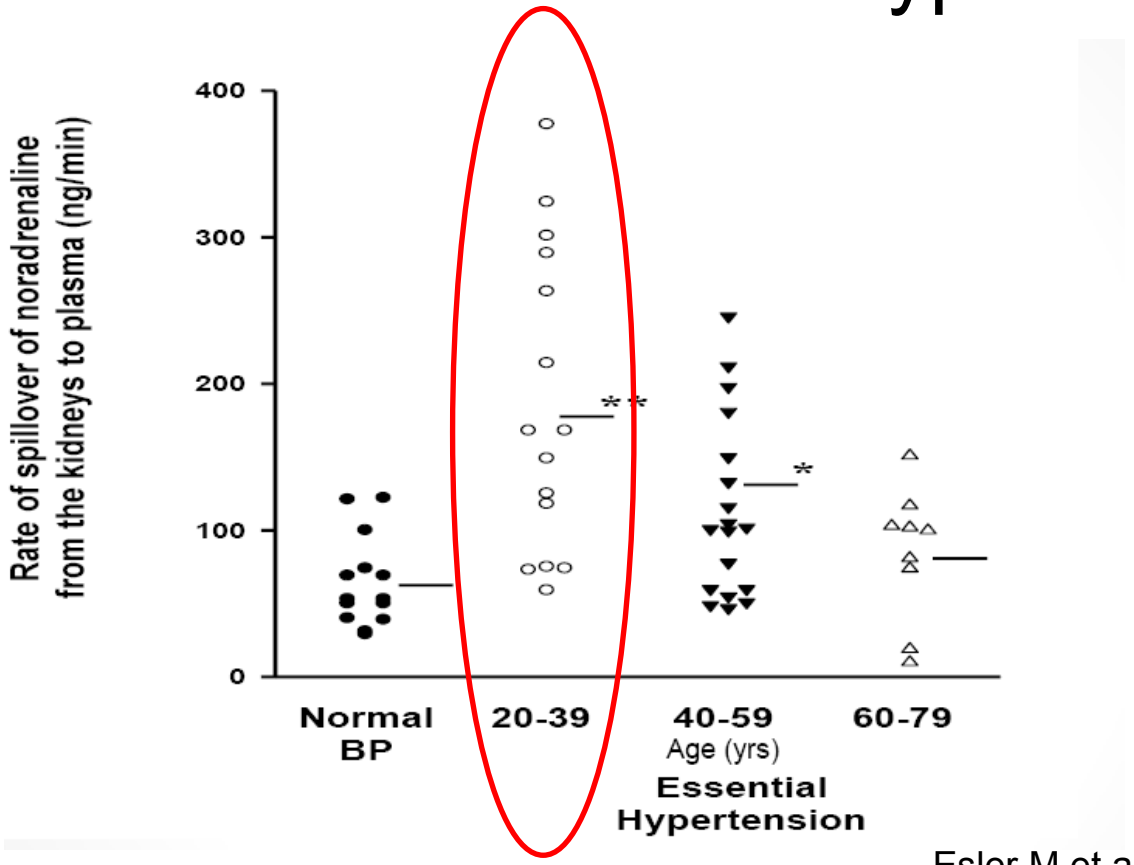
Obstructive sleep apnoea
Underestimated in Hypertension



Prof Klaus Weber, Doz. Jan Borgel, RHC 2013

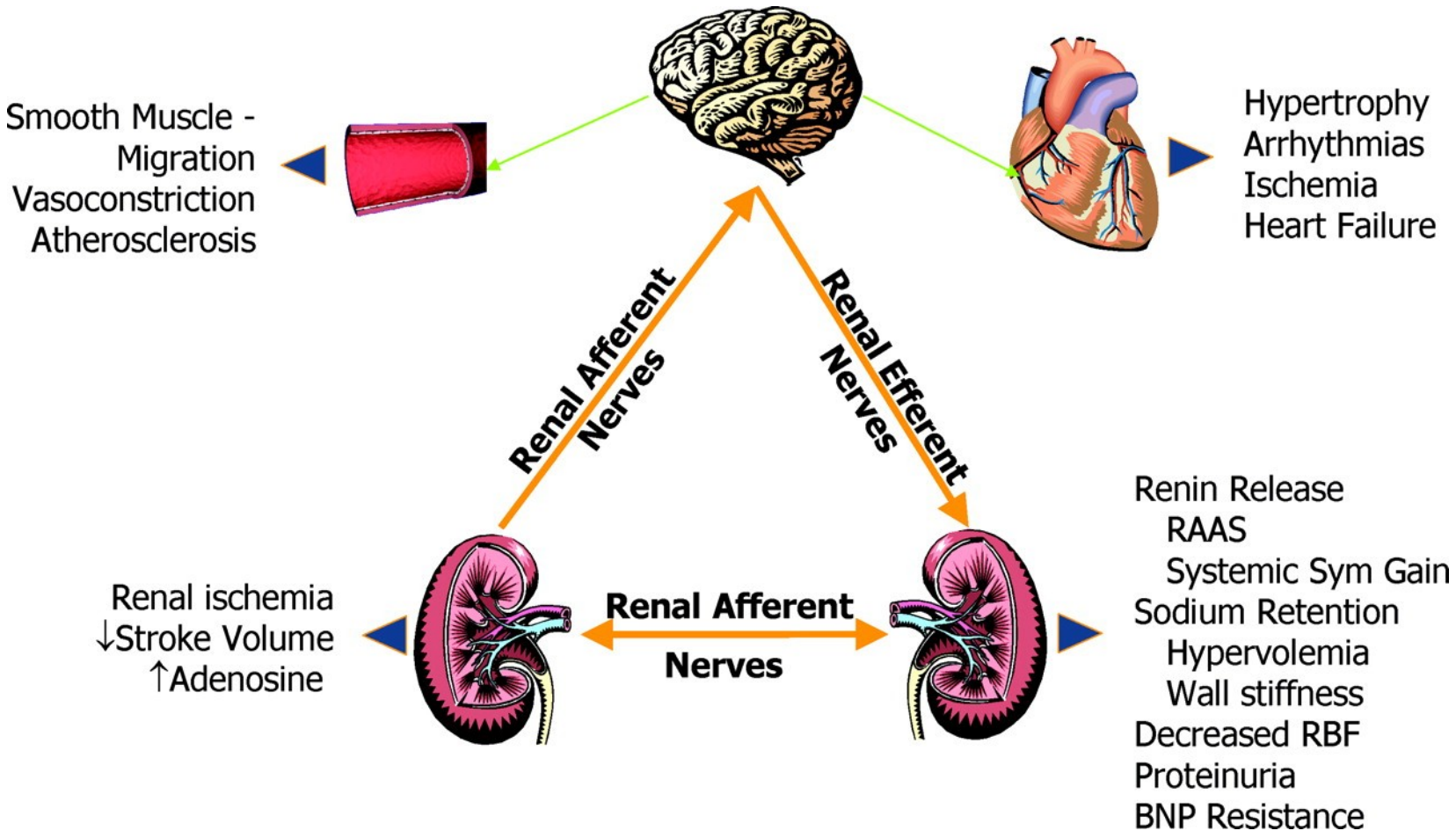
Renal sympathetic denervation Physiological background

- Activation of renal sympathetic nerves in patients with essential hypertension



Esler M et al J.Hypertension 1990; 8: S53-

Physiological and pathophysiological actions of renal sympathetic afferent and efferent nerves.



Krum H et al. Circulation 2011;123:209-215

American Heart Association
Learn and Live

From theory to practice

(12) **United States Patent**
Levin et al.

(54) **RENAL NERVE STIMULATION METHOD AND APPARATUS FOR TREATMENT OF PATIENTS**

(75) Inventors: **Howard R. Levin**, Teaneck, NJ (US); **Mark Gelfand**, New York, NY (US)

(73) Assignee: **Ardian, Inc.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 627 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/408,665**

(22) Filed: **Apr. 8, 2003**

(65) **Prior Publication Data**

US 2003/0216792 A1 Nov. 20, 2003

(10) **Patent No.: US 7,162,303 B2**

(45) **Date of Patent: *Jan. 9, 2007**

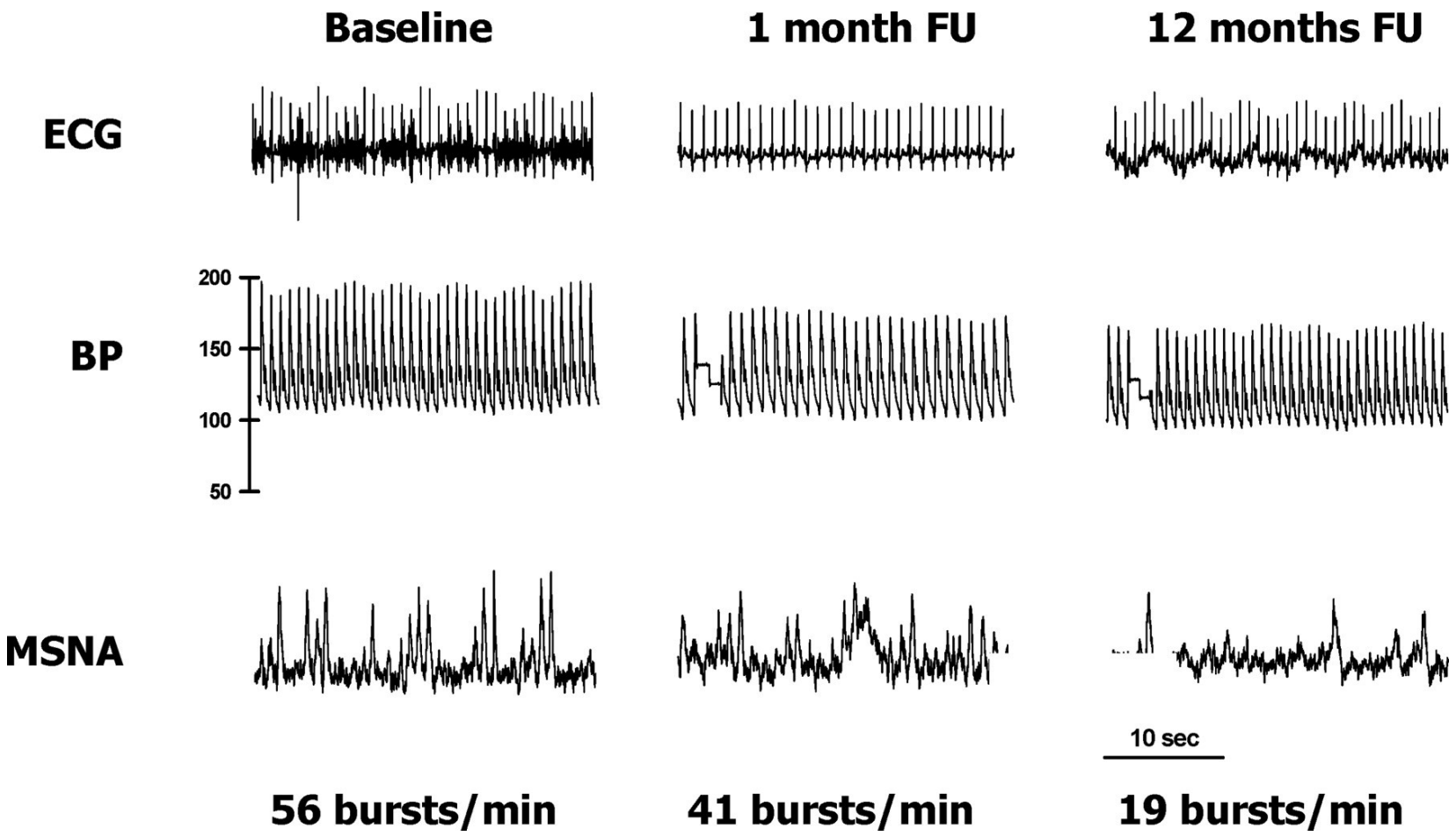
Related U.S. Application Data

(60) Provisional application No. 60/370,190, filed on Apr. 8, 2002, provisional application No. 60/415,575, filed on Oct. 3, 2002, provisional application No. 60/442,970, filed on Jan. 29, 2003.

ABSTRACT

A method and apparatus for treatment of heart failure, hypertension and renal failure by stimulating the renal nerve. The goal of therapy is to reduce sympathetic activity of the renal nerve. Therapy is accomplished by at least partially blocking the nerve with drug infusion or electrostimulation. Apparatus can be permanently implanted or catheter based.

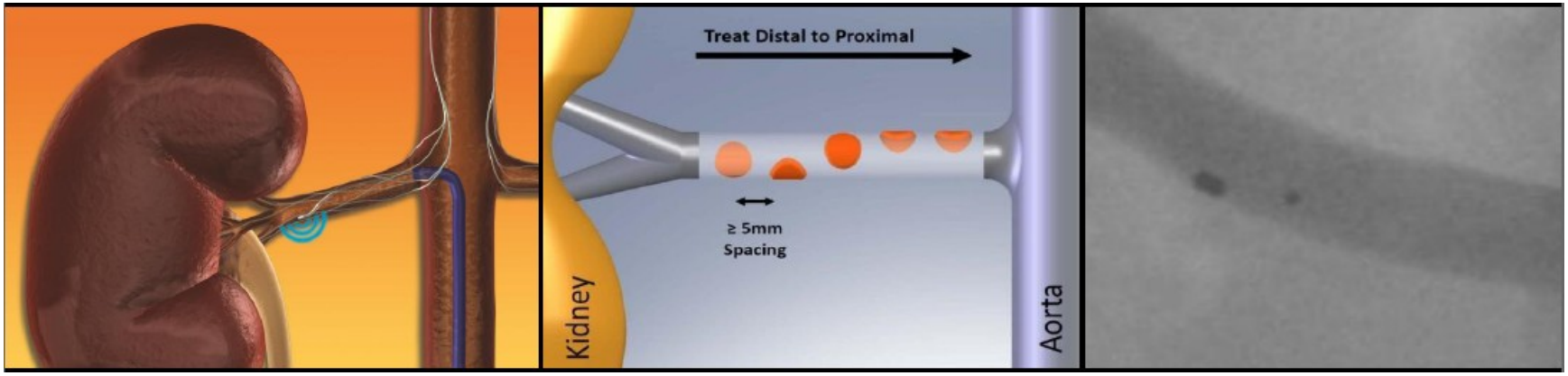
Effect of renal sympathetic denervation on muscle sympathetic nerve activity (MSNA) over 12 months of follow-up (FU).



Krum H et al. Circulation 2011;123:209-215

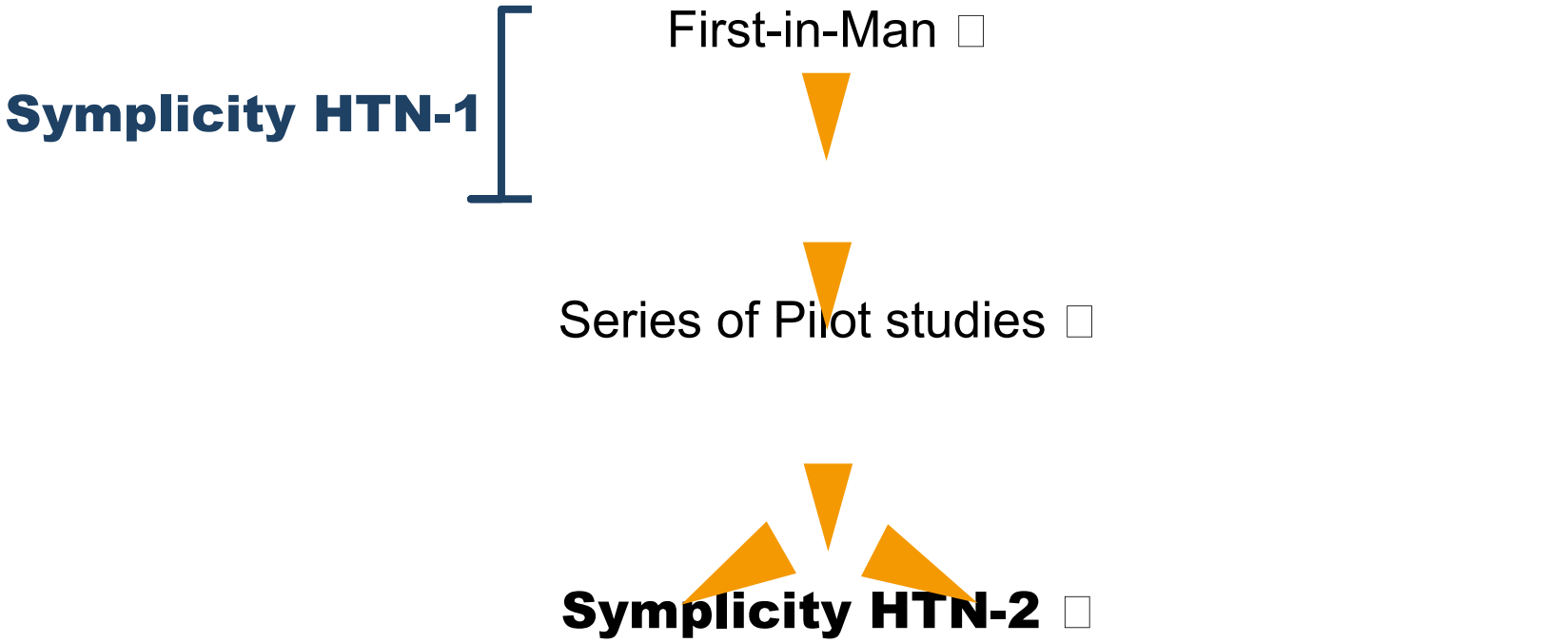
Catheter based RF renal nerve ablation Symplicity catheter

- Interventional technique (Medtronic)
- 6F Femoral artery approach
- Single electrode catheter with deflectable tip
- 4-6 two minute treatments per artery
- RF generator



Symplicity HTN Studies

Staged Clinical Evaluation



Symplicity HTN-3
US Randomized Clinical Trial
(upcoming)

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

Symplicity HTN-1+2 Study Population

Inclusion Criteria:

- **Office SBP ≥ 160 mmHg (≥ 150 mmHg with type II diabetes mellitus)**
- Stable drug regimen **of 3+ more anti-HTN medications**
- Age 18-85 years
- Solitary renal vessels - Length>20mm, Diameter>4mm.

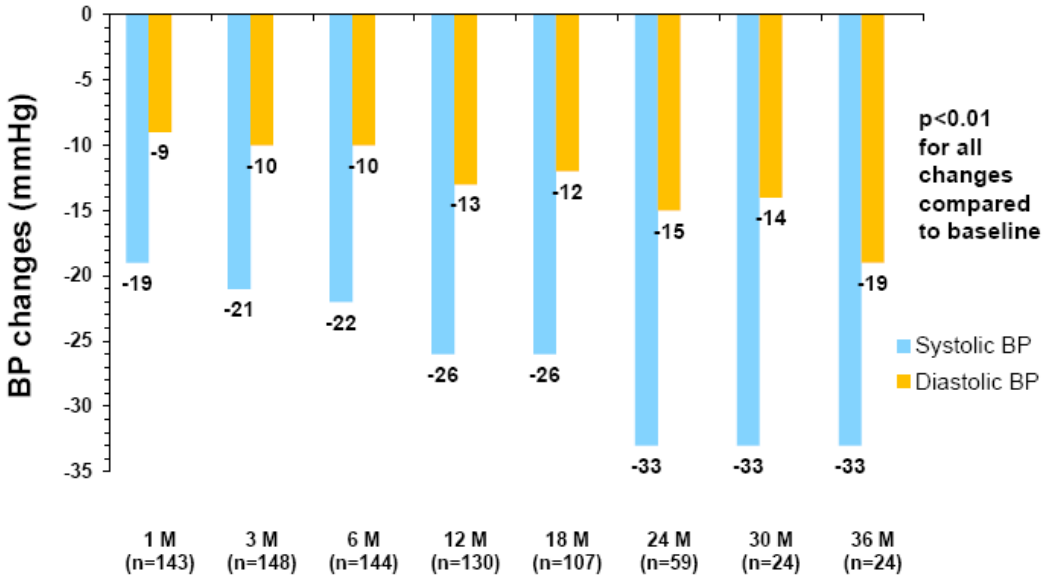
Exclusion Criteria:

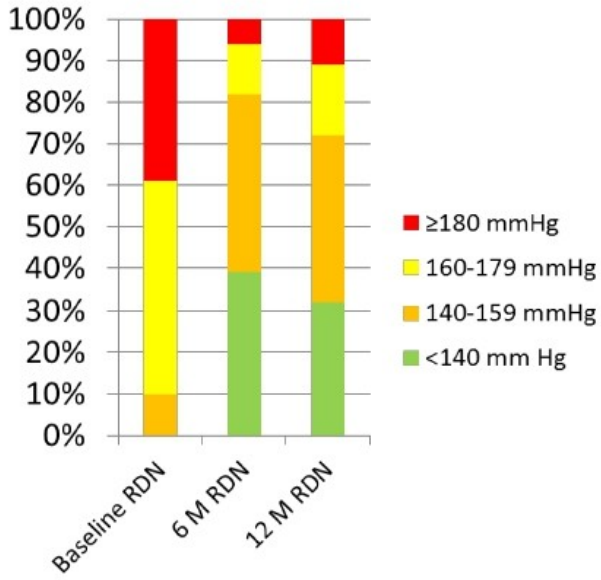
- Hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention

Symplicity HTN-2 Investigators. The Lancet. 2010

Efficacy data
Symplicity HTN-1

- Blood pressure reduction sustained over 3Y

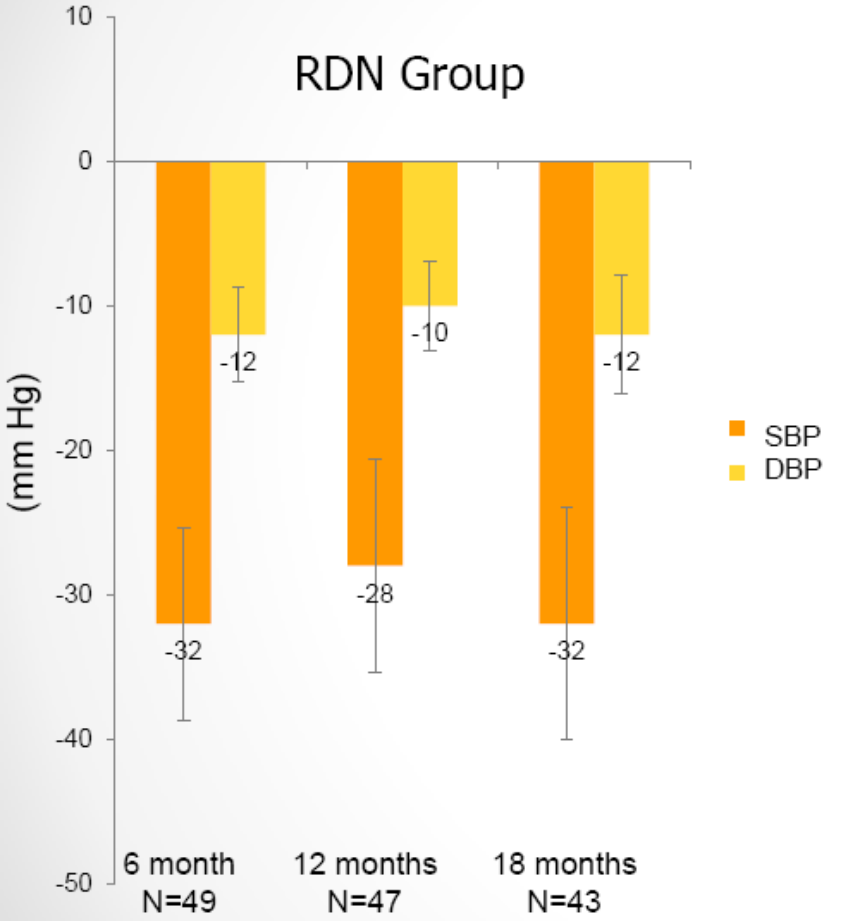


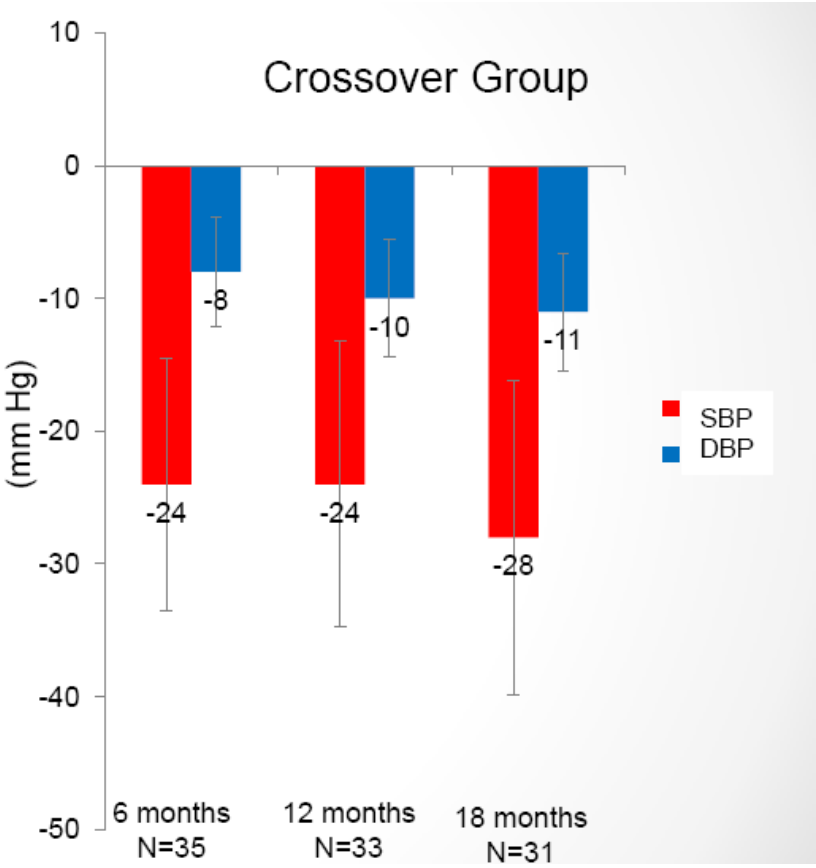


Baseline BP (mmHg)
-176/98±17/15
Number of anti-HTN meds -
5,0±1,4

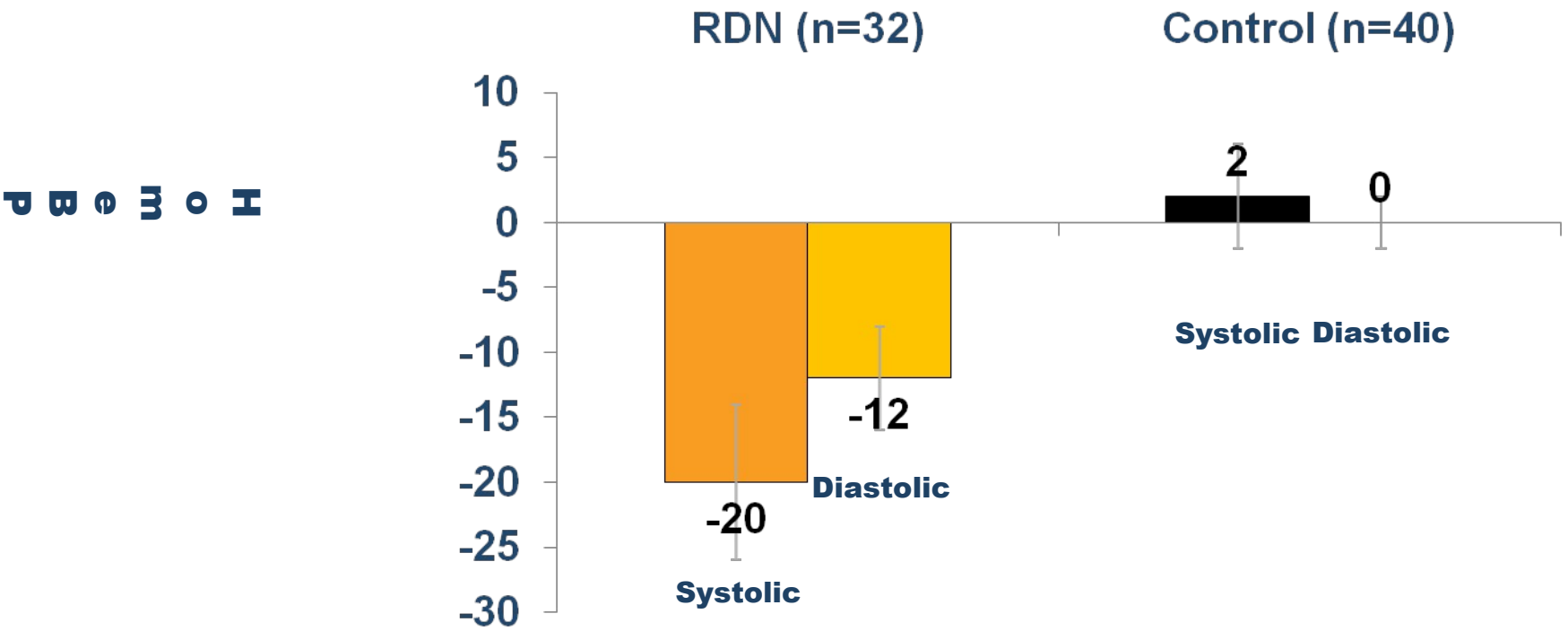
Sobotka PA, Oral presentation, ACC 2012

Efficacy data
Simplicity HTN-2





Symplicity HTN 2
Home & 24 Hour Ambulatory BP



24-h ABPM:

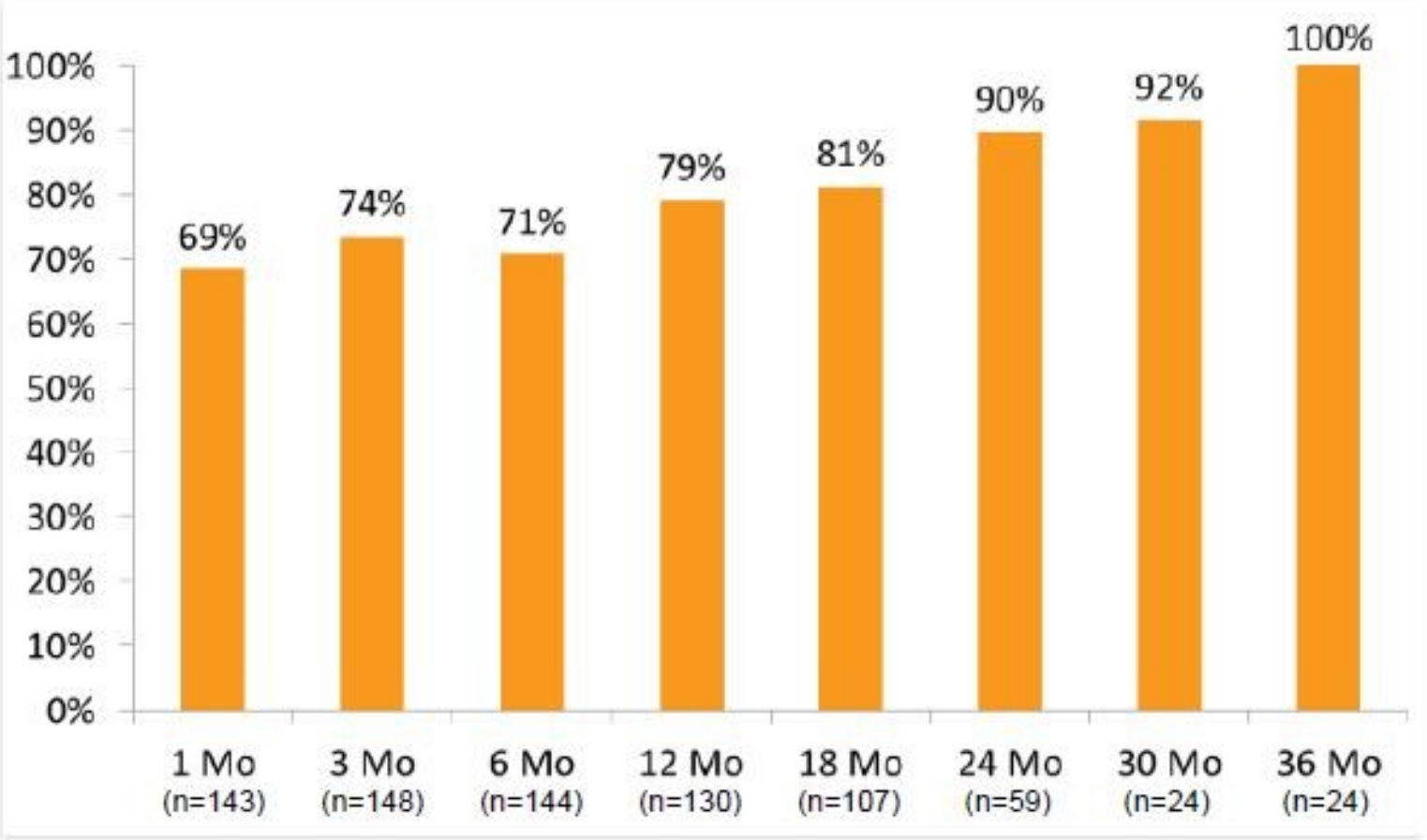
· Analysis on technically sufficient (>70% of readings) paired baseline and 6-month

· RDN (n=20): -11/-7 mmHg (SD 15/11; p=0.006 SBP change, p=0.014 for DBP change)

· Control (n=25): -3/ -1 mmHg (SD 19/12; p=0.51 for systolic, p=0.75 for diastolic)

Symplicity HTN-2 Investigators. The Lancet. 2010.

Symplicity HTN-1 Response



Symplicity HTN-1Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Krum, H.)

Symplicity HTN - 1+2 safety

- No change from pre-procedure eGFR values
- No orthostatic events
- No electrolyte disturbances
- 3 hypertensive events
- 1 hypotensive event
- 1 mild transient renal failure, managed medically

Target organ protection and additional benefits

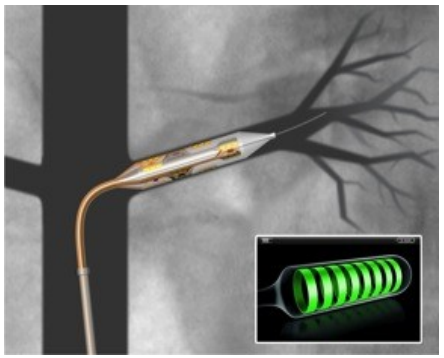
- Optimized cardio-respiratory response to exercise
- Reduction in LV mass
- Improvement in diastolic function
- Improvement in glucose tolerance
- Improvement in subjective assessment of physical state, mental state and QoL parameters, improved response to stress, reduced anxiety and depression scores
- Cost effectiveness

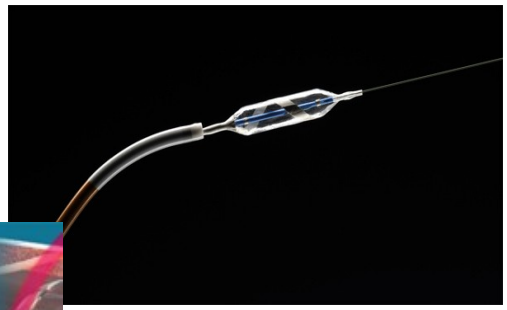
Ukena et al J Am Coll Cardiol. 2011;58(11):1176-1182. doi:10.1016/j.jacc.2011.05.036
Brandt et al, J Am Coll Cardiol 2012
Mahfoud F et al, Circulation 2011; 123 1940-1946
Fischer et al European Heart Journal (2012) 33 (Abstract Supplement), 182-183

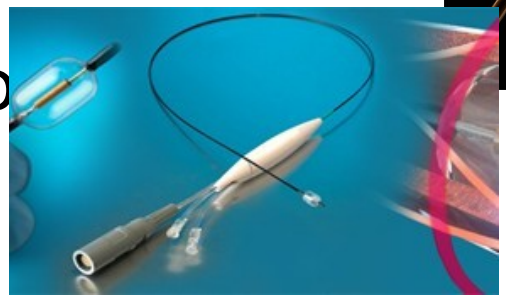
A boom of interventional treatment for RH

Uncoming device

- Catheters utilizing RF energy
  - St Jude EnligHTN
  - Vessix V2 RF balloon
  - Covidien One Shot balloon
- Other treatment modalities
  - Ultrasound
  - Chemical denervatio







SJM's EnligHTN

- **multi-electrode (4) renal artery ablation catheter**
- **Two basket sizes:**
  - Small: 16 mm length
  - Large: 18 mm length
- **8 F compatible**
- **deflectable tip**

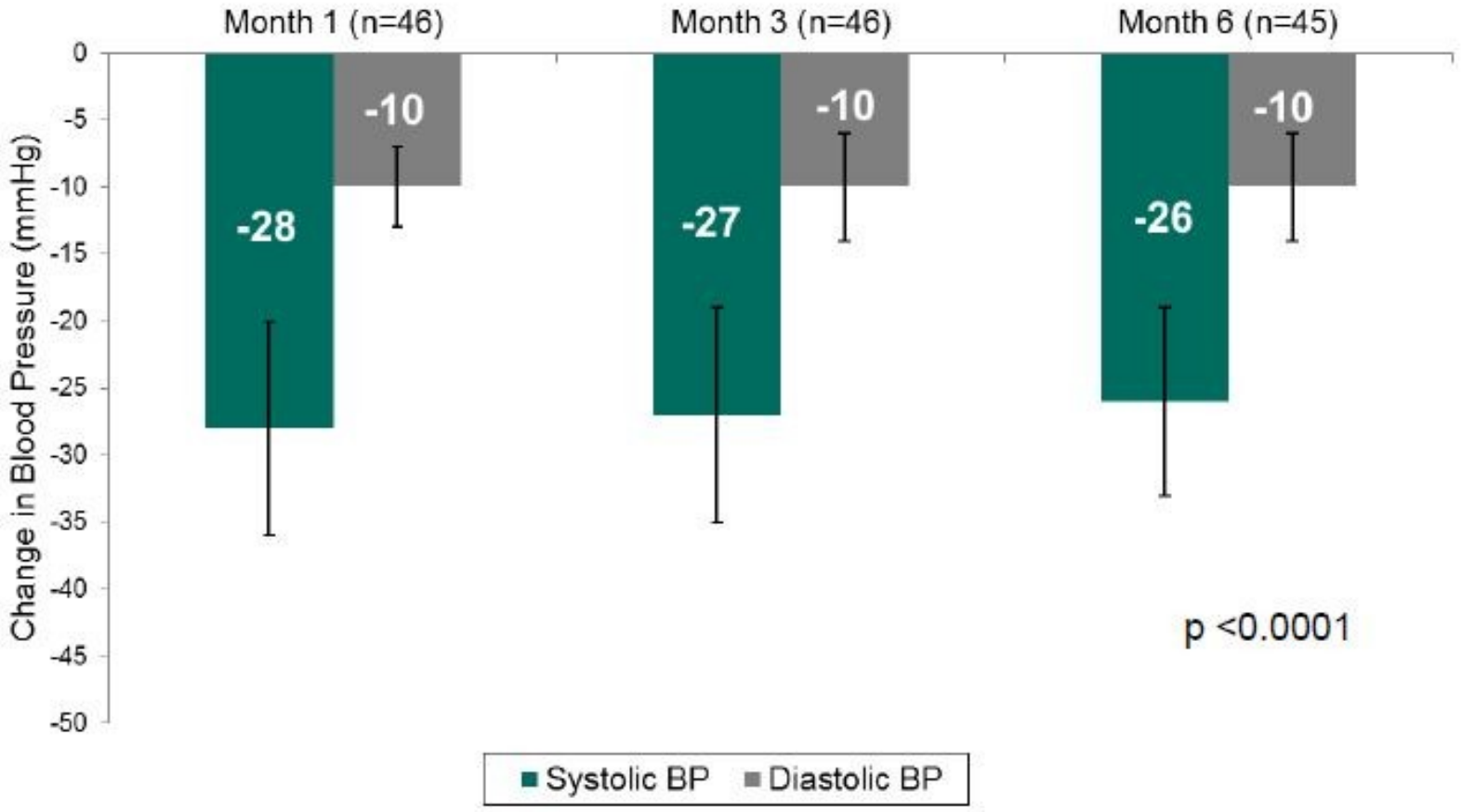
Advantages:

- **Minimal catheter manipulations**
- **Short ablation time**

EnligHTN 1 study - Criteria

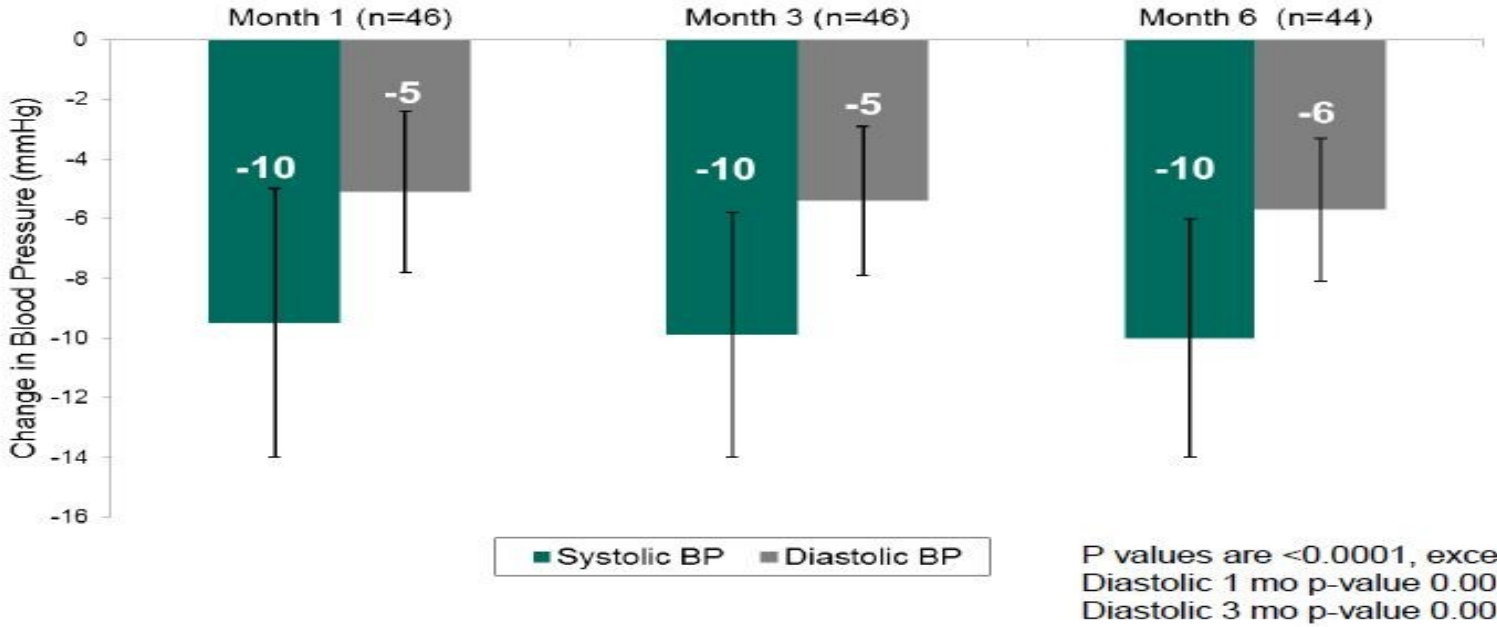
- Inclusion Criteria
  - Office SBP ≥160 mmHg (≥150 mmHg for patient with type 2 diabetes).
  - Use of ≥3 antihypertensive medications at maximally tolerated doses (one diuretic).
  - ≥18 and ≤80 years old
- Exclusion criteria
  - Prior renal artery intervention
  - Renal artery atherosclerosis (>30%)
  - Multiple main renal arteries
  - Diameter <4 mm or length <20 mm
  - eGFR of <45 mL/min/1.73m2

EnligHTN 1 study – Proof of benefit



Papademetriou V, AHA Hotline Session, Los Angeles 2012

EnligHTN 1 study – Proof of benefit



P values are <0.0001, except
Diastolic 1 mo p-value 0.0003
Diastolic 3 mo p-value 0.0002

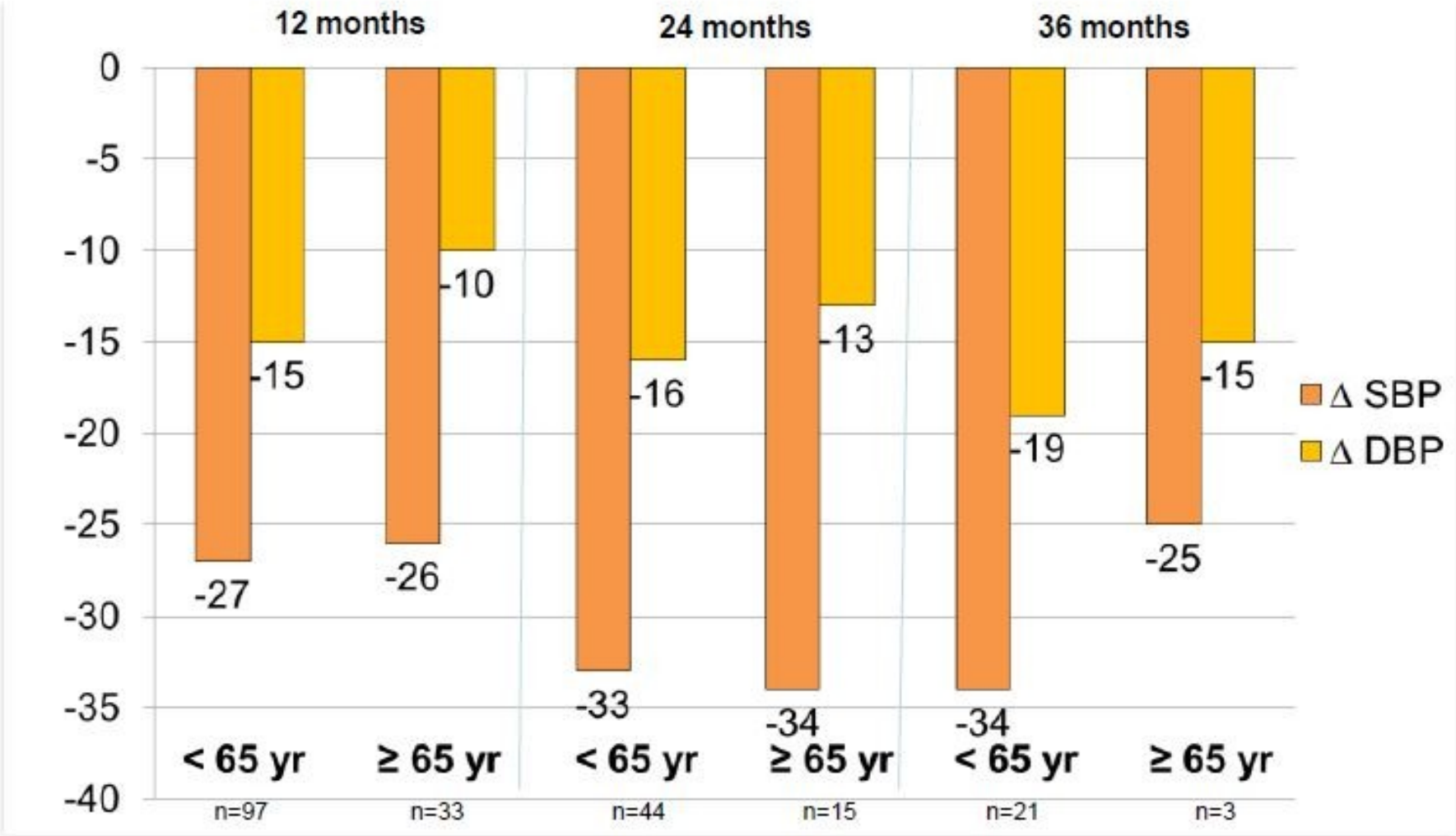
Papademetriou V, AHA Hotline Session, Los Angeles 2012

	Baseline (n=46)	Month 1 (n=46)	Month 3 (n=46)	Month 6 (n=45)
eGFR (mL/min/1.73m^2)	87 (±19)	85 (±20)	84 (±22)	82 (±20)
Cystatin C (mg/L)	1.14 (±0.29)	1.00 (±0.25)	0.97 (±0.20)	1.00 (±0.23)

How to perform RDN?

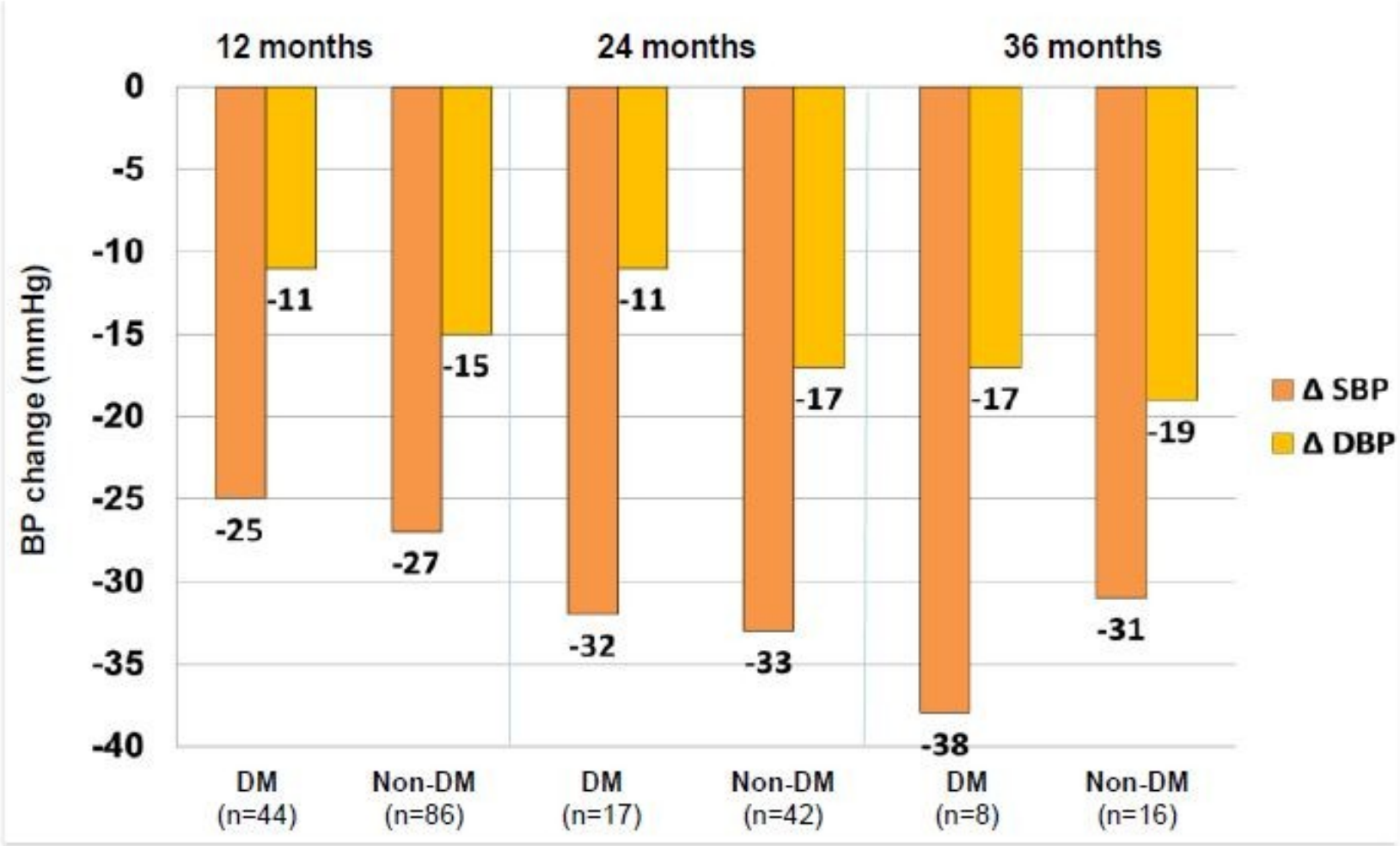
- Easy when on film.

Predictors of response to RDN.



Sobotka P, ACC 2012

Predictors of response to RDN. Diabetes?

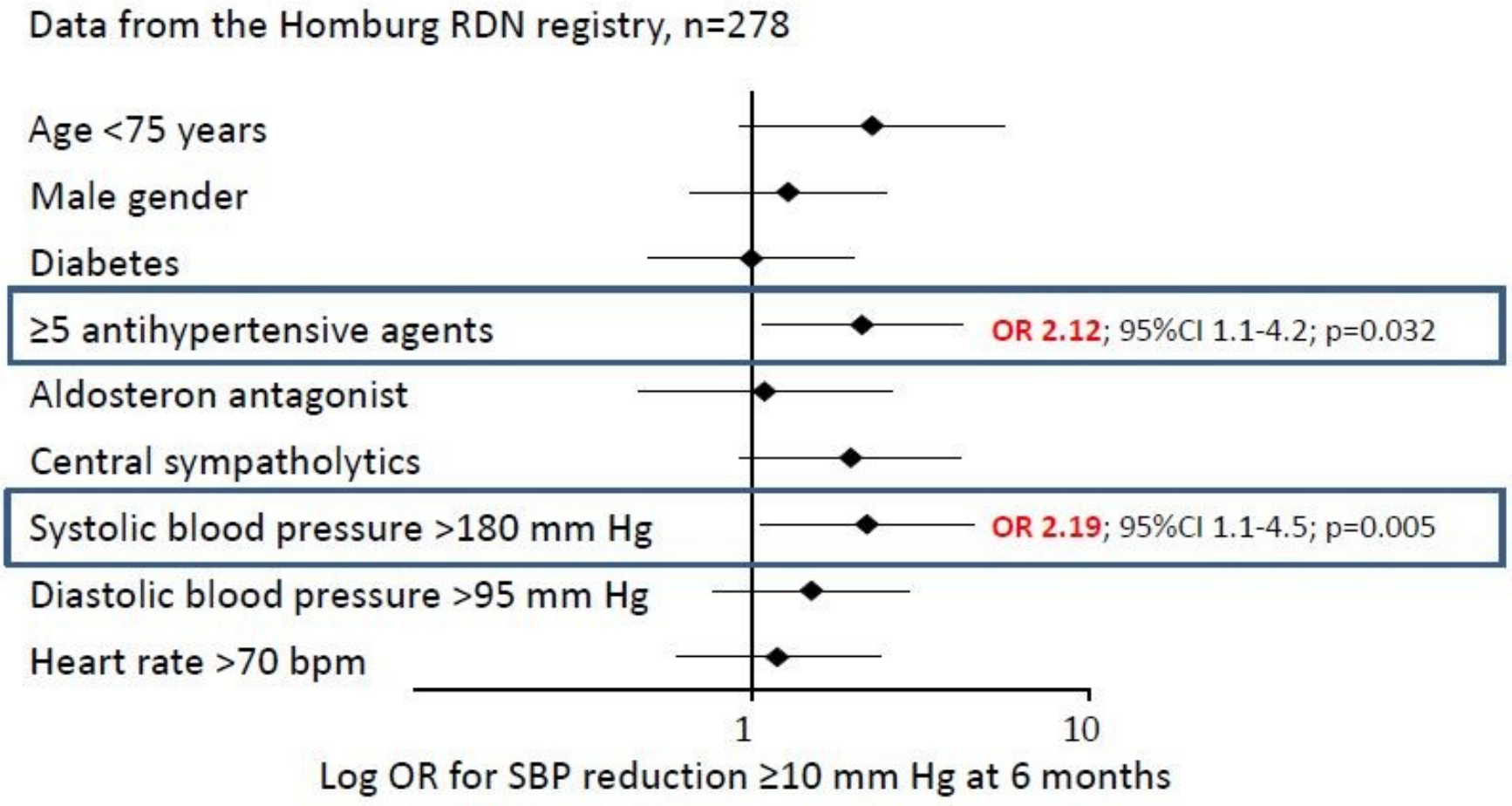


Sobotka P, ACC 2012

Predictors of response to RDN. Renal function?

Sobotka P, ACC 2012

Predictors of response to RDN. Data from Homburg/Saar



Christrian Ukena, RHC 2013

Predictors of response to RDN. Type of device?

EnligHTN (St. Jude Medical)

EnligHTN-1: (n =46)

ΔoSBP at 6 month: -26mmHg

Response Rate: 76%

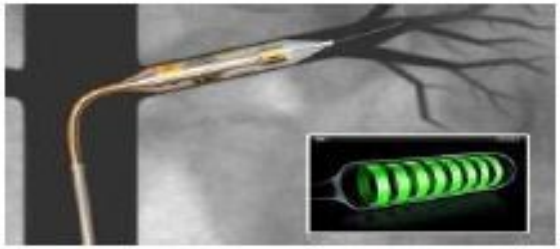
OneShot (Covidien)

RHAS: (n = 8)

ΔoSBP at 6 month: -42mmHg

ΔoDBP at 6 month: -15mmHg

Vessix V2 (Boston Scientific)



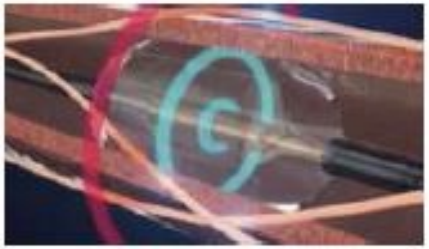
ReduceHTN: (n = 7)

ΔoSBP at 1 month: -30mmHg

ΔoDBP at 1 month: -11mmHg

Response Rate: 100% at 1 month

Paradise (ReCor)



REALISE: (n = 15)

ΔoSBP at 3 month: -32mmHg

ΔoDBP at 3 month: -16mmHg

Prof Erwin Blessing, RHC

A “Non-responding” patient. Why?

Hypothesis 1 for Non-Response “The Patient”

You did a *good technical but clinically ineffective job because* in some patients:

- Overactivation of sympathetic system trough the kidneys is not involved in the pathophysiology of resistant

A “Non-responding” patient. Why?

Hypothesis 2 for Non-Response “The Technique”

You did an *ineffective job because you don’t know the* temperature at the adventitia/nerves level and in some patients :

- Atheromatous disease and renal artery thickness are limiting temperature rise/transduction
- A significant proportion of nerves are at more than 4 mm from the intima which distance may be out of the efficacy

A “Non-responding” patient. Why?

Hypothesis 3 for Non-Response “The Doctor”

You did an *ineffective job because you don’t follow current* recommendations of use of the device :

- Diameter/lenght of the target vessels
- Inappropriate value of impedance (tissue contact)
- To limited number of ablations (< 4) per artery or unilateral procedure
- Inappropriate duration of ablation

Open questions: FU?

- Not mentioned in the ESH position paper1
- NICE states that '*reported outcome measures*
- *should include adverse events and the long-term effect of the procedure on BP"*2
- Long-term FU and participation in registries recommended in the German consensus3
- FU described in detail in the French consensus4

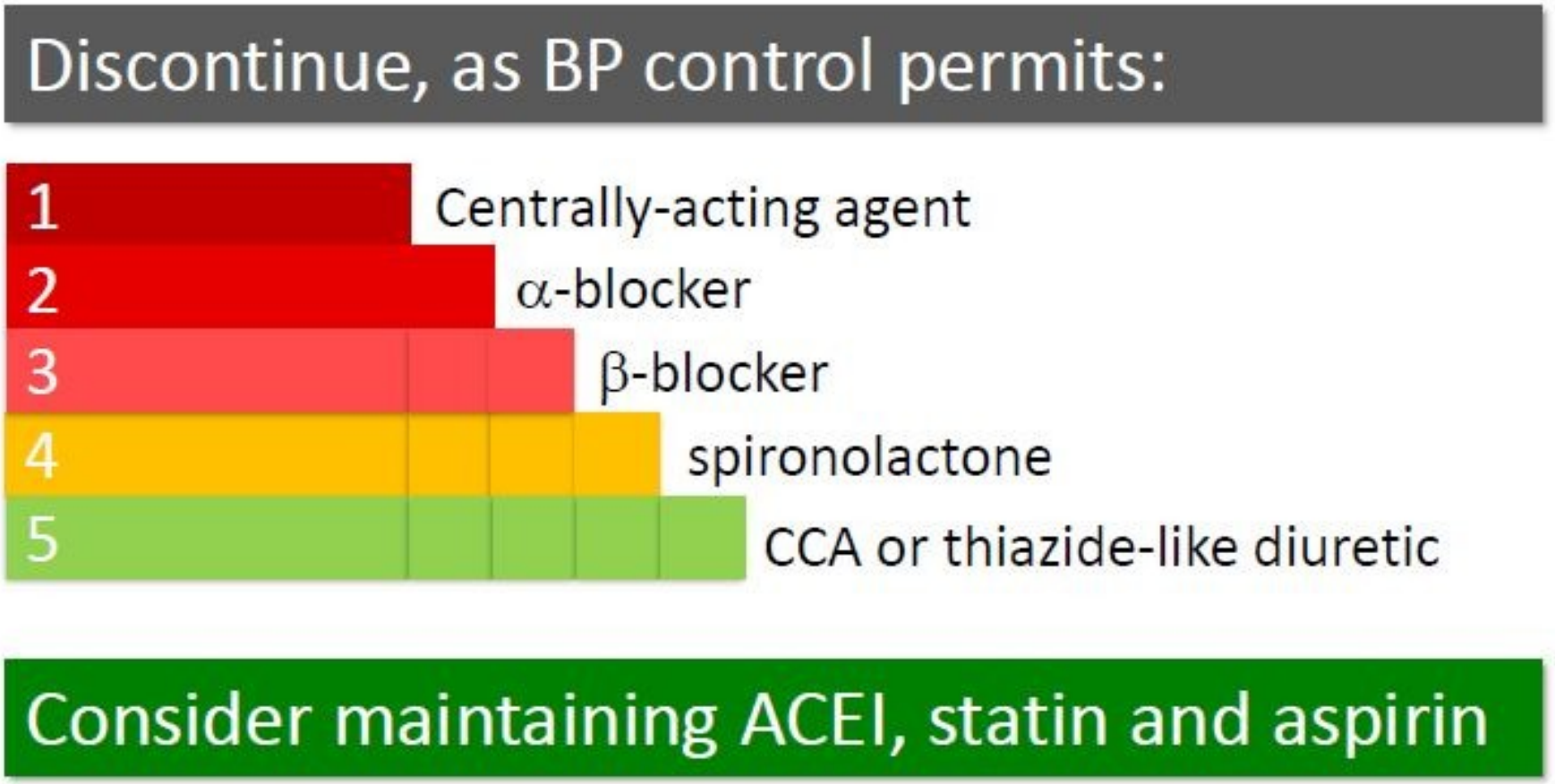
1 Schmieder RE et al, J Hypertens 2012
2 www.nice.org.uk/ipg418
3 Mahfoud F et al, 2012
4 Pathak A et al, Diagn Interv Radiol 2012

Open questions: Post-procedure FU?

- **BP** - 1 hour in the post-procedure monitoring room before returning to the room and a hospital stay of 24 h
- **ABPM** - 6, 12, 24 and 36 M after RDN
- **Kidney** - eGFR (plus proteinuria if initial proteinuria) after 6, 12, 24 and 36 M
- **Anatomy** - Angio-CT after 12 and 36 M

Pathak A et al, Diagn Interv Radiol 2012
Plouin, RHC 2013

Advice – Change therapy at Mo 3



Plouin, RHC 2013

Other areas of clinical development

Heart failure

LV Hypertrophy

Sleep apnoea

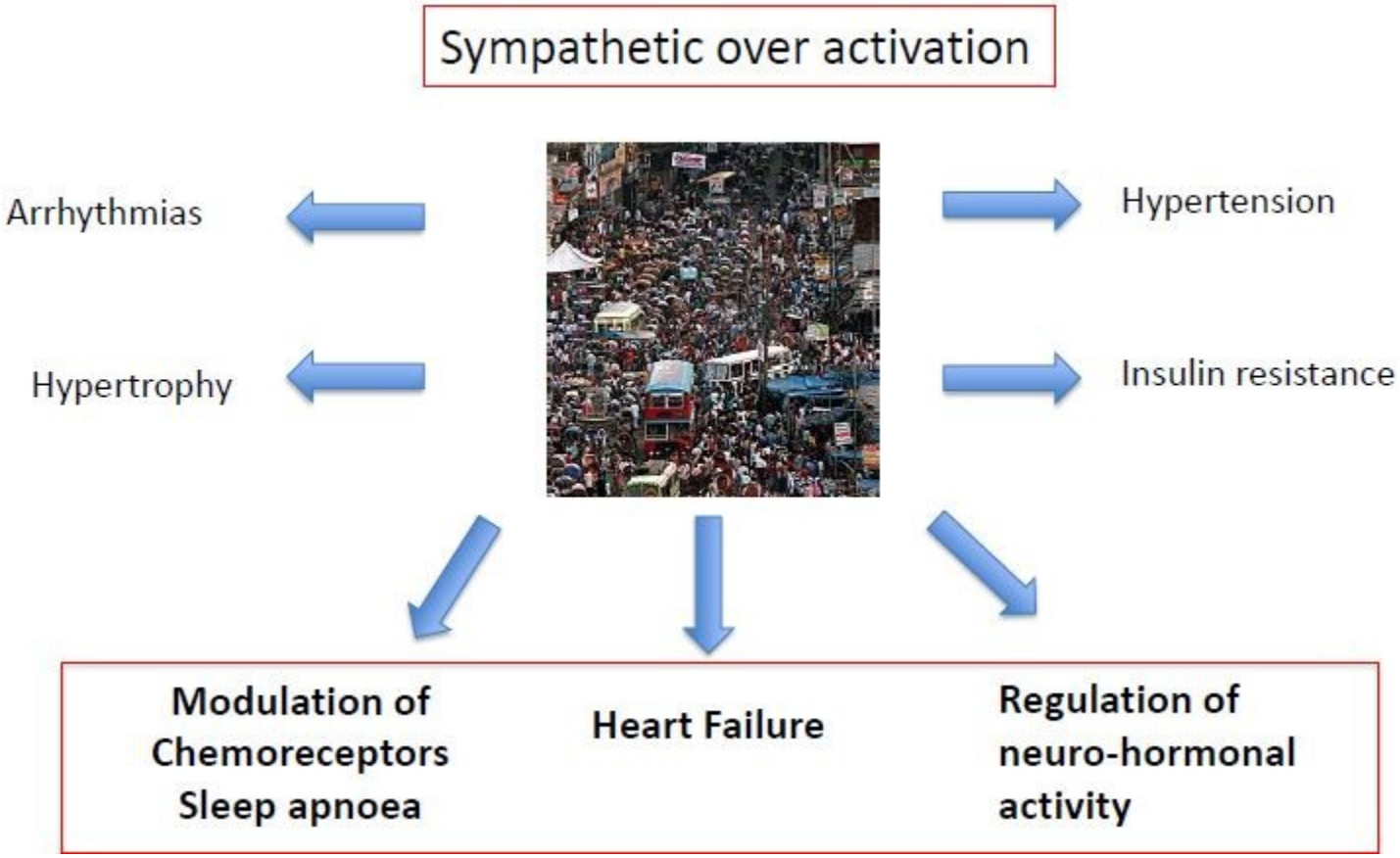
Insulin resistance

Chronic kidney disease

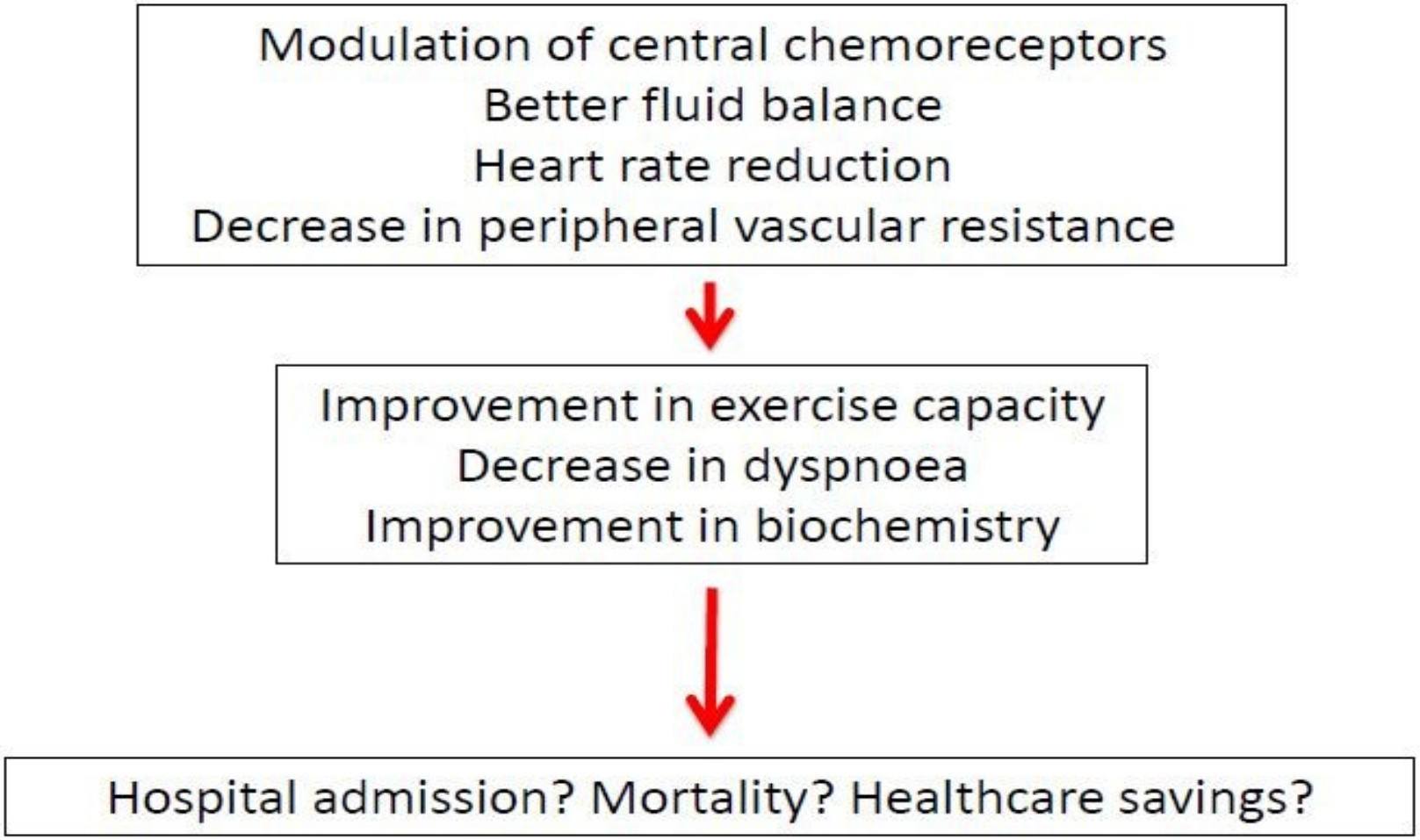
Atrial fibrilation

New Indications for Transcatheter Renal Denervation

Chronic Heart Failure



Potential Benefits of RND in CHF



Studies reporting safety of RND

REACH-Pilot[1]

Design
- 7 patient safety study
- Chronic mod-severe heart failure
- In-patient follow-up 5 day admission
- Bilateral renal denervation

Aims
- Safety of renal denervation
- Follow-up for 6 months

Results
- No procedural complications
- No acute/medium term complication
- Improvement in 6 min walk

OLOMOUC 1 [2]

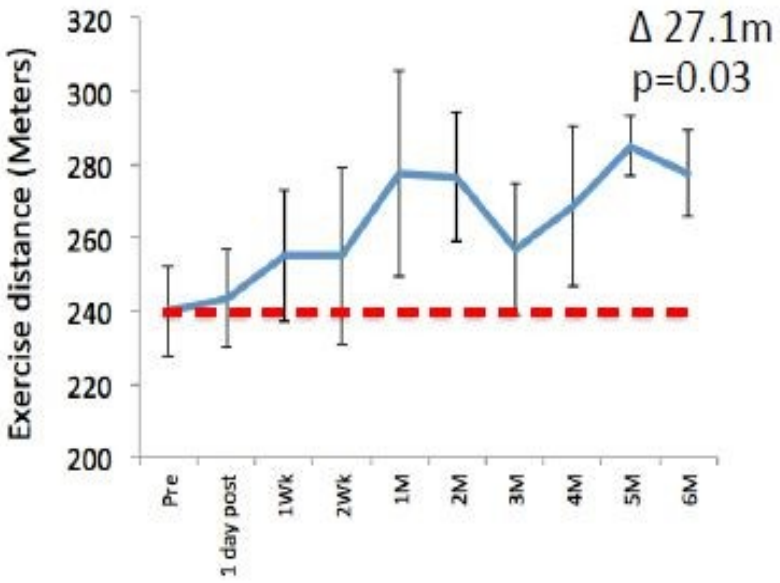
Design
- 51 Randomised (OMT vs RDN)
- NYHA III or IV
- Bilateral renal denervation
- Heart rate >70

Aims
- Safety of renal denervation
- Change in LV function

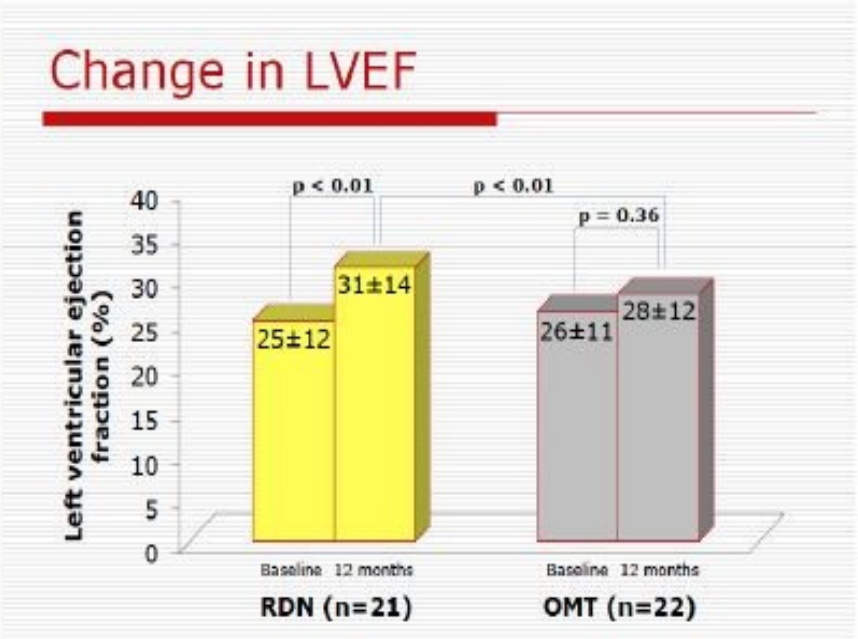
Results
- No procedural complications
- No acute/medium complication
- Improvement in EF

1. REACH-Pilot, Davies JE, Francis DP et al. International Journal of Cardiology (ePub, October 2012)
2. OLOMOUC I study, ESC Munich 2012

Improvement in exercise capacity
REACH-Pilot

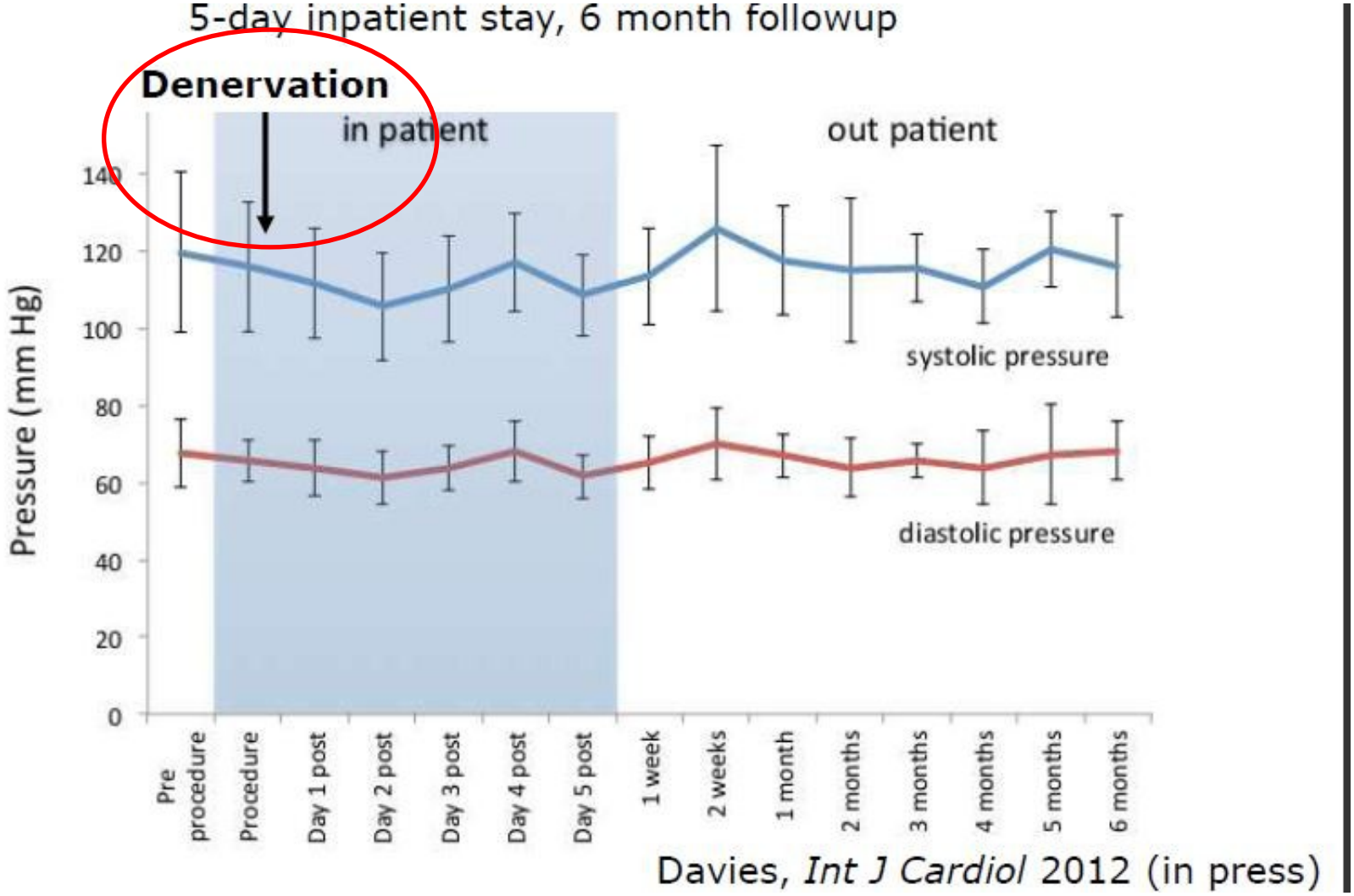


Improvement in ejection fraction
OLOMOUC I Study

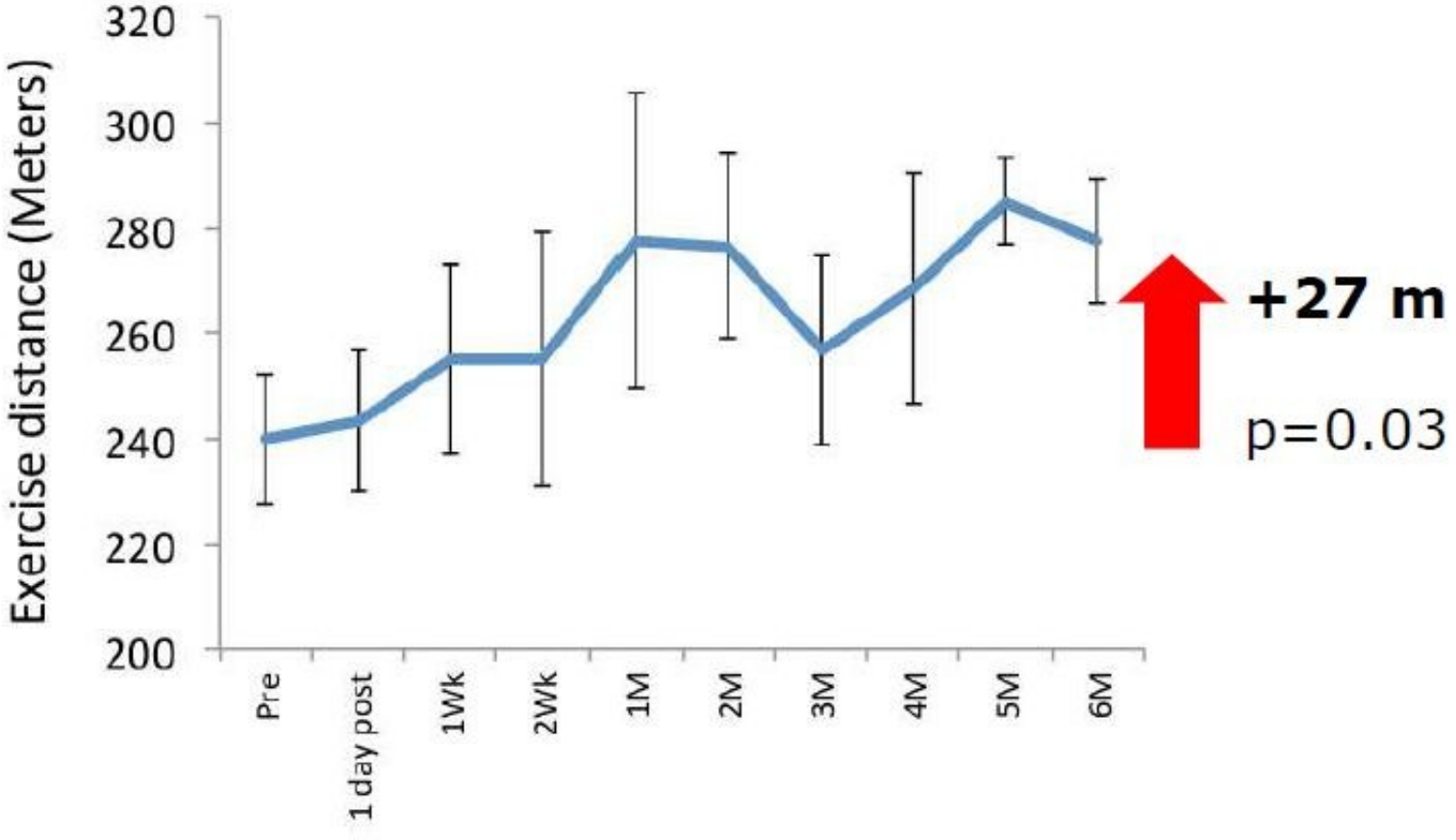


REACH-Pilot, Davies JE, Francis DP et al. International Journal of Cardiology (epub online)
OLOMOUC I Study, ESC 2012

BP remains stable in CHF post-

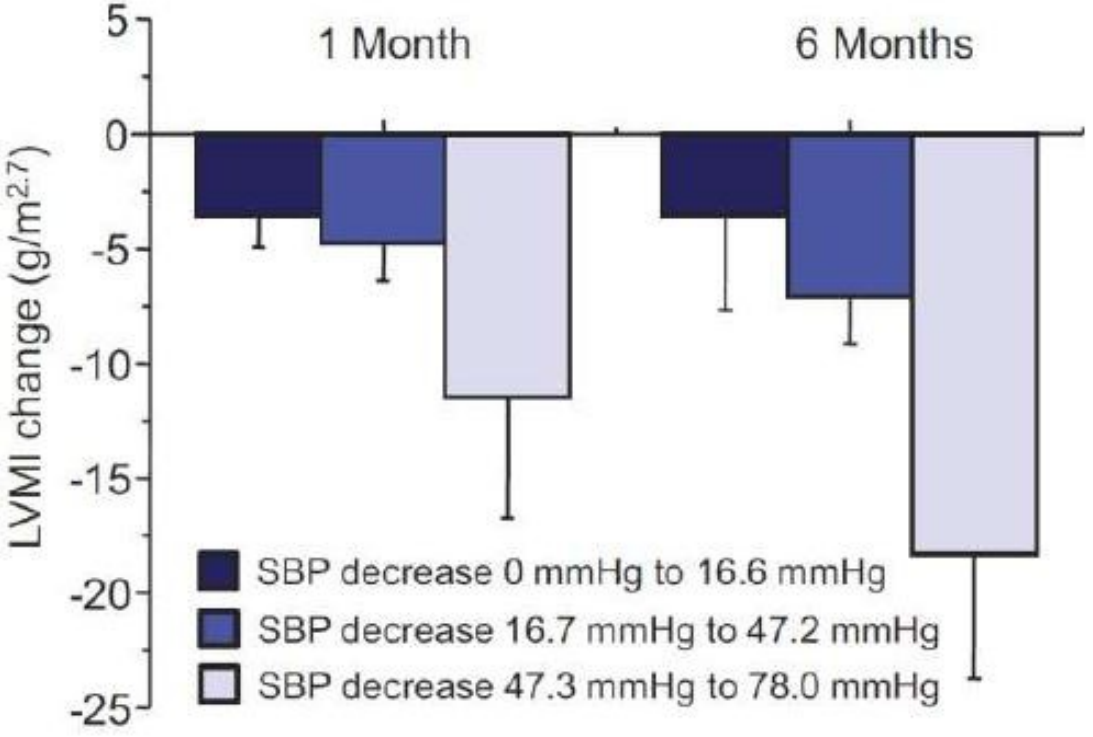


Safety evaluation of renal denervation in CHF



Davies, *Int J Cardiol* 2012 (in press)

Denervation is reported to reduce LVH in Hypertension



"LV mass regression occurred also in 5 of 6 RD 'nonresponders', supporting the notion of BP-independent effects of RD on LVH"

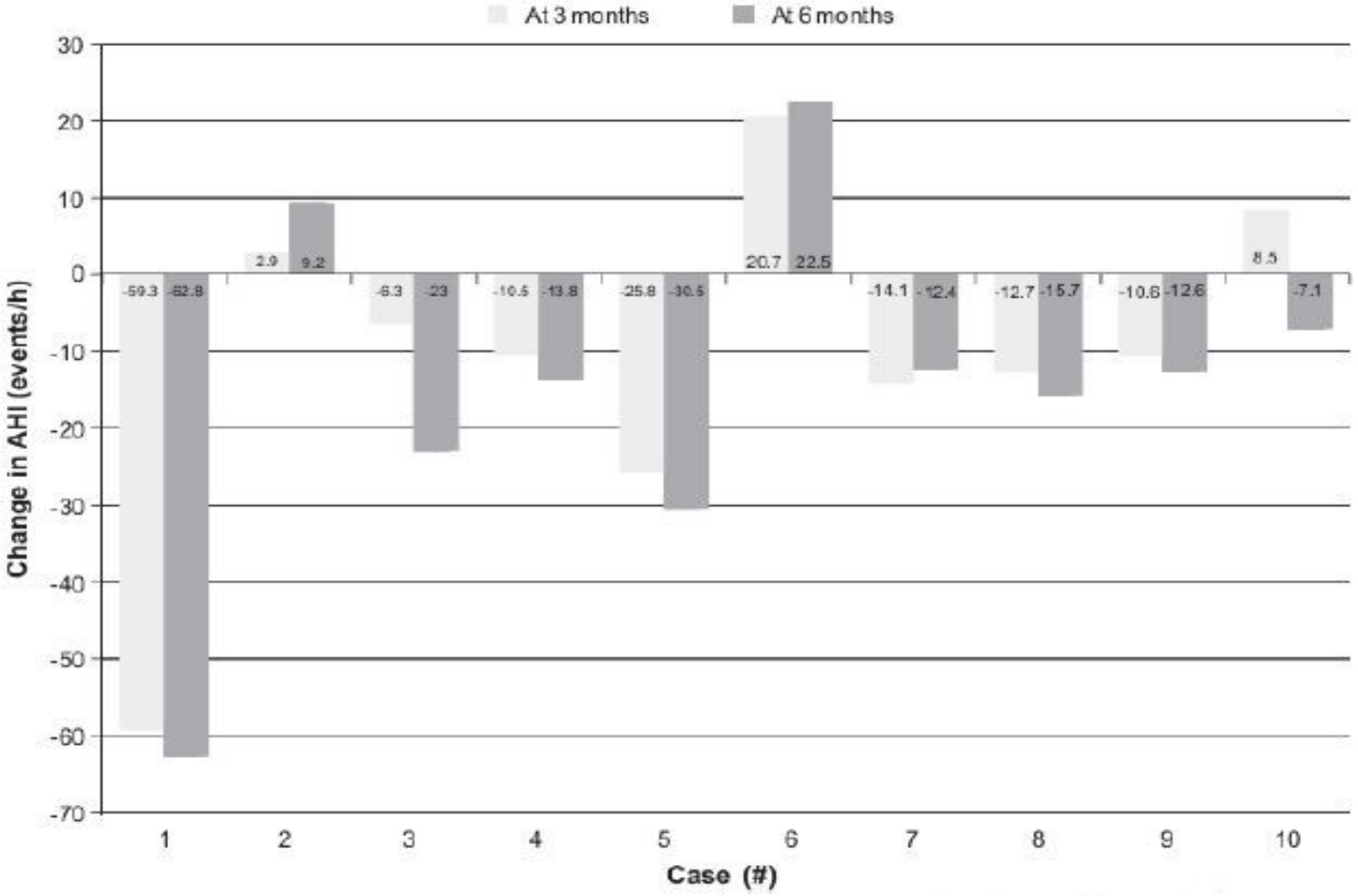
Brandt et al. *J Am Coll Cardiol*. 2012;59:901–9

Obstructive Sleep Apnea

- Mechanisms linking OSA and Resistant Hypertension
  - Volume excess
    - Redistribution of fluid from legs to neck and chest in recumbent position, leading to increased peripharyngeal edema and upper airway resistance
      - Friedman O., et. al. Hypertension 2010;56:1077-1082
    - Removal of fluid reduces AHI
      - Elias RM., et. al. Nephrol Dial Transplant 2012;27(4):1569-73
  - Aldosterone
    - Excess aldosterone is associated with OSA
      - Dudenbostel T, Calhoun DA. J Hum Hypertens 2012;26(5):281-7
  - Sympathetic nervous system overactivation
    - MSNA is elevated in OSA
      - Grassi G., et. al. Hypertension 2005;46:321-325
    - Deactivation of chemoreceptors reduces MSNA and OSA
      - Narkiewicz K., et. al. Circulation 1999;100:2332-2335
    - Renal Denervation reduces MSNA and OSA
      - Witkowski A. et. al. Hypertension 2011; 58:559-565

Sobotka
Curr Cardiol Rep 2012

RND in Hypertension Seems to Reduces OSA



Witkowski, Hypertension 2011

Effect of Renal Sympathetic Denervation on Glucose Metabolism in Patients With RH

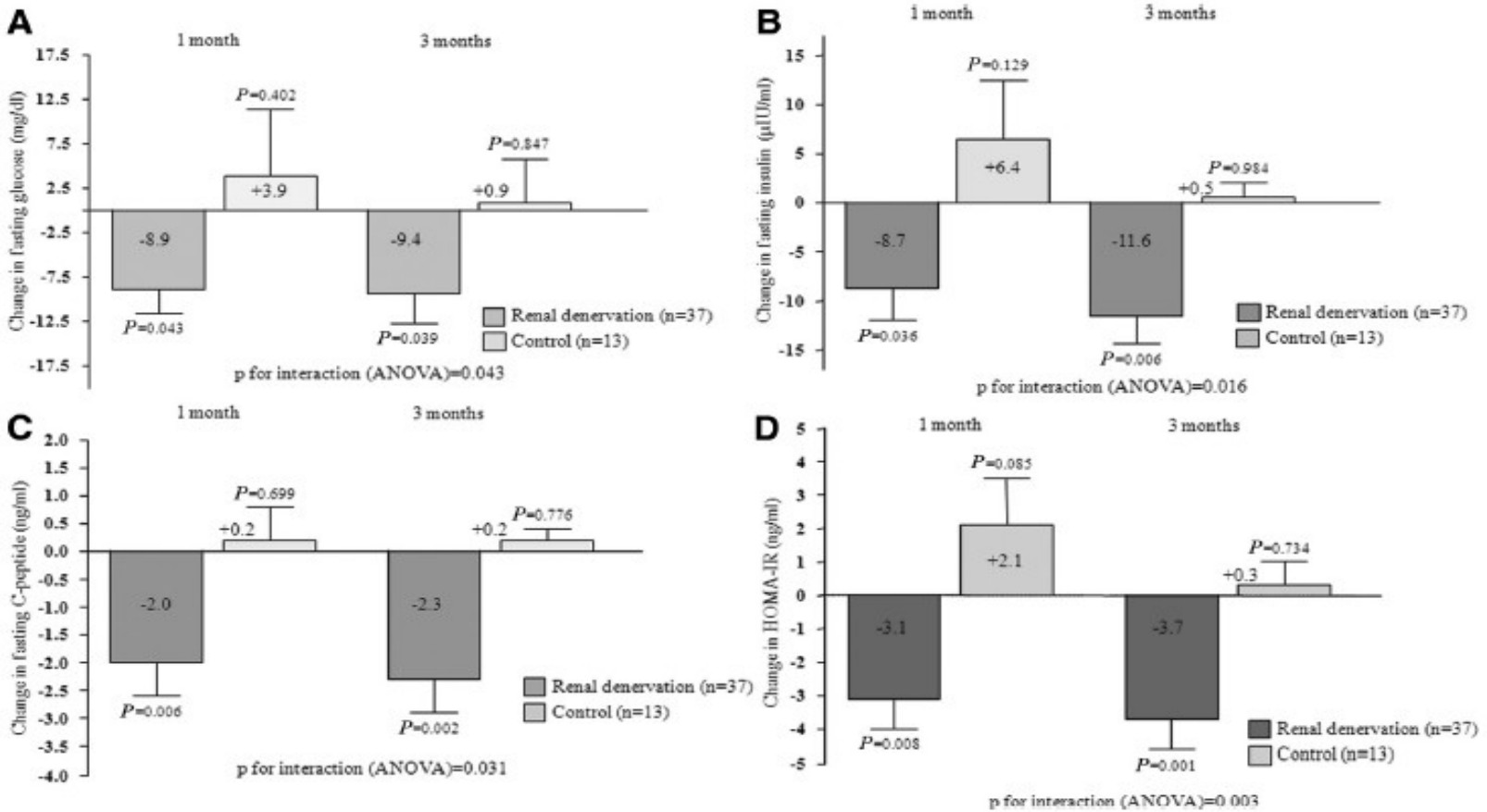


Figure 2. Change (SEM) in fasting glucose (**A**), fasting insulin (**B**), C-peptide (**C**), and homeostasis model assessment–insulin resistance (HOMA-IR; **D**) at 1 and 3 months compared with baseline. *P* values refer to change compared with baseline. Between-group effects, measured by 2-way repeated measures ANOVA, are given as *P* for interaction.

Mahfoud et al. Circulation. 2011;123:1940-1946;

RDN+RH+CKD=?

CLINICAL RESEARCH www.jasn.org

Renal Denervation in Moderate to Severe CKD

Dagmara Hering,*† Felix Mahfoud,‡ Antony S. Walton,§ Henry Krum,§ Gavin W. Lambert,* Elisabeth A. Lambert,* Paul A. Sobotka,‖¶ Michael Böhm,‡ Bodo Cremers,‡ Murray D. Esler,*§ and Markus P. Schlaich*§

*Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Australia; †Department of Hypertension and Diabetology, Medical University of Gdansk, Poland; ‡Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; §Heart Centre Alfred Hospital, Melbourne, Australia; ‖Department of Medicine and Cardiology, Hennepin County Medical Center, University of Minnesota, Minneapolis, Minnesota; and ¶Medtronic ARDIAN Inc., Mountain View, California

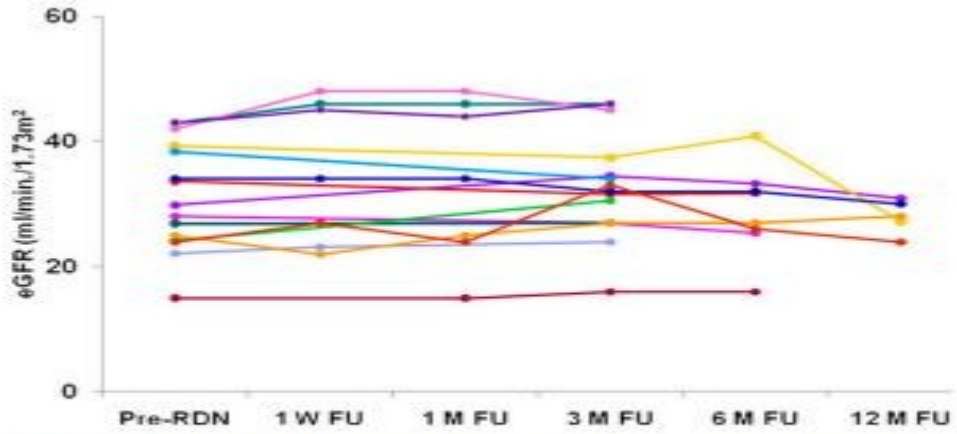


Figure 1. Individual changes in creatinine-based estimated GFR before renal denervation (pre-RDN); at 1 week (W); and at 1-, 3-, 6-, and 12-month (M) follow-up (FU).

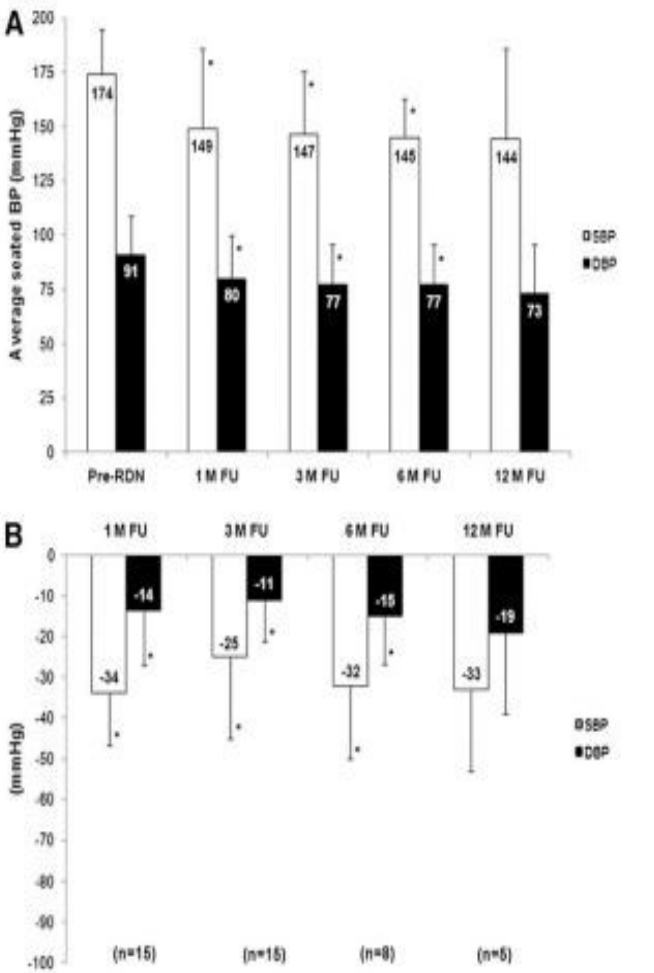


Figure 2. Office BP values at follow-up. Changes in average office BP (A) and mean decrease in office BP (B) at follow-up. Error bars represent SDs. *$P<0.001$ versus baseline (before the procedure). FU, follow-up; M, month; pre-RDN, prerenal denervation.

RDN effect on Atrial fibrillation

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Volume 60, Issue 13, September 2012 >

Clinical Research | September 2012

A Randomized Comparison of Pulmonary Vein Isolation With Versus Without Concomitant Renal Artery Denervation in Patients With Refractory Symptomatic Atrial Fibrillation and Resistant Hypertension

Evgeny Pokushalov, MD, PhD; Alexander Romanov, MD; Giorgio Corbucci, PhD; Sergey Artyomenko, MD; Vera Baranova, MD; Alex Turov, MD; Natalya Shirokova, MD; Alexander Karaskov, MD, PhD; Suneet Mittal, MD; Jonathan S. Steinberg, MD

Clin Res Cardiol. 2012 Jan;101(1):63-7. doi: 10.1007/s00392-011-0365-5. Epub 2011 Sep 29.

Renal sympathetic denervation for treatment of electrical storm: first-in-man experience.

Ukena C, Bauer A, Mahfoud F, Schreieck J, Neuberger HR, Eick C, Sobotka PA, Gawaz M, Böhm M.

Klinik für Innere Medizin III (Kardiologie, Angiologie und Internistische Intensivmedizin), Universitätsklinikum des Saarlandes, Kirrberger Str. 1, 66421 Homburg/Saar, Germany. Christian.Ukena@uks.eu

Abstract

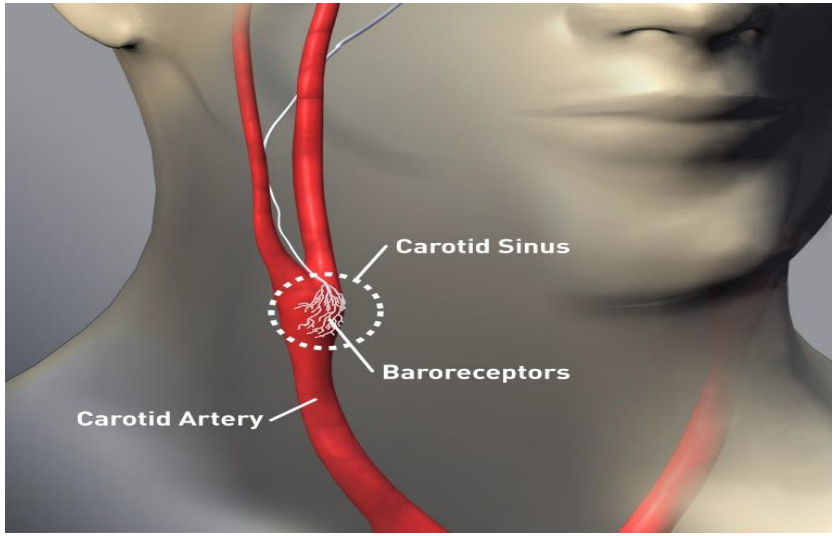
INTRODUCTION: Sympathetic activity plays an important role in the pathogenesis of ventricular tachyarrhythmia. Catheter-based renal sympathetic denervation (RDN) is a novel treatment option for patients with resistant hypertension, proved to reduce local and whole-body sympathetic activity.

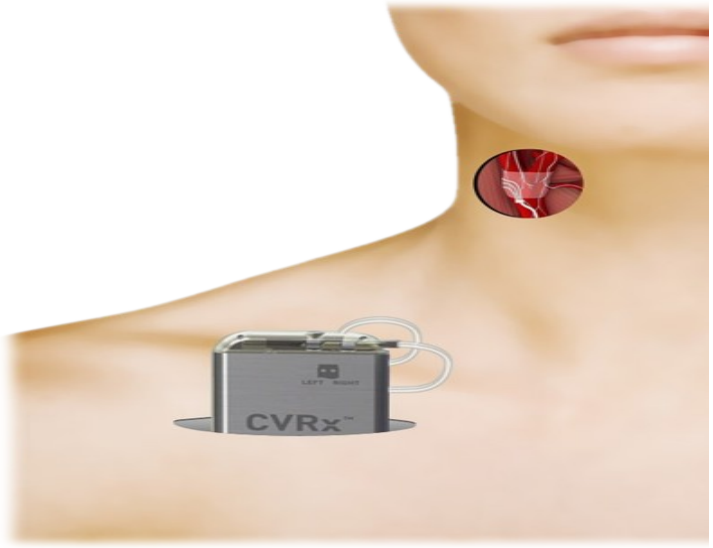
METHODS: Two patients with chronic heart failure (CHF) (non-obstructive hypertrophic and dilated cardiomyopathy, NYHA III) suffering from therapy resistant electrical storm underwent therapeutic renal denervation. In both patients, RDN was conducted with agreement of the local ethics committee and after obtaining informed consent.

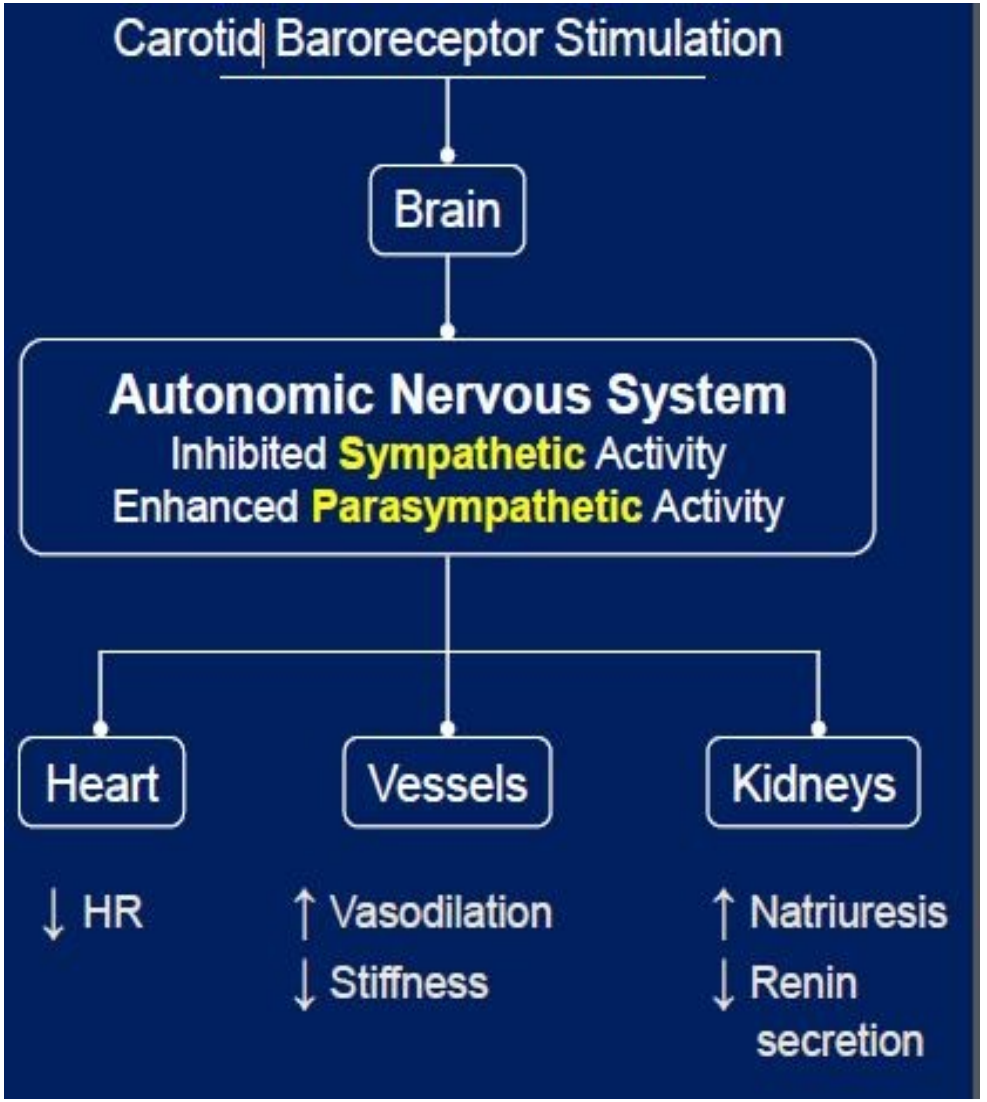
RESULTS: The patient with hypertrophic cardiomyopathy had recurrent monomorphic ventricular tachycardia despite extensive antiarrhythmic therapy, following repeated endocardial and epicardial electrophysiological ablation attempts to destroy an arrhythmogenic intramural focus in the left ventricle. The second patient, with dilated nonischemic cardiomyopathy, suffered from recurrent episodes of polymorphic ventricular tachycardia and ventricular fibrillation. The patient declined catheter ablation of these tachycardias. In both patients, RDN was performed without procedure-related complications. Following RDN, ventricular tachyarrhythmias were significantly reduced in both patients. Blood pressure and clinical status remained stable during the procedure and follow-up in these patients with CHF.

CONCLUSION: Our findings suggest that RDN is feasible even in cardiac unstable patients. Randomized controlled trials are urgently needed to study the effects of RD in patients with electrical storm and CHF.

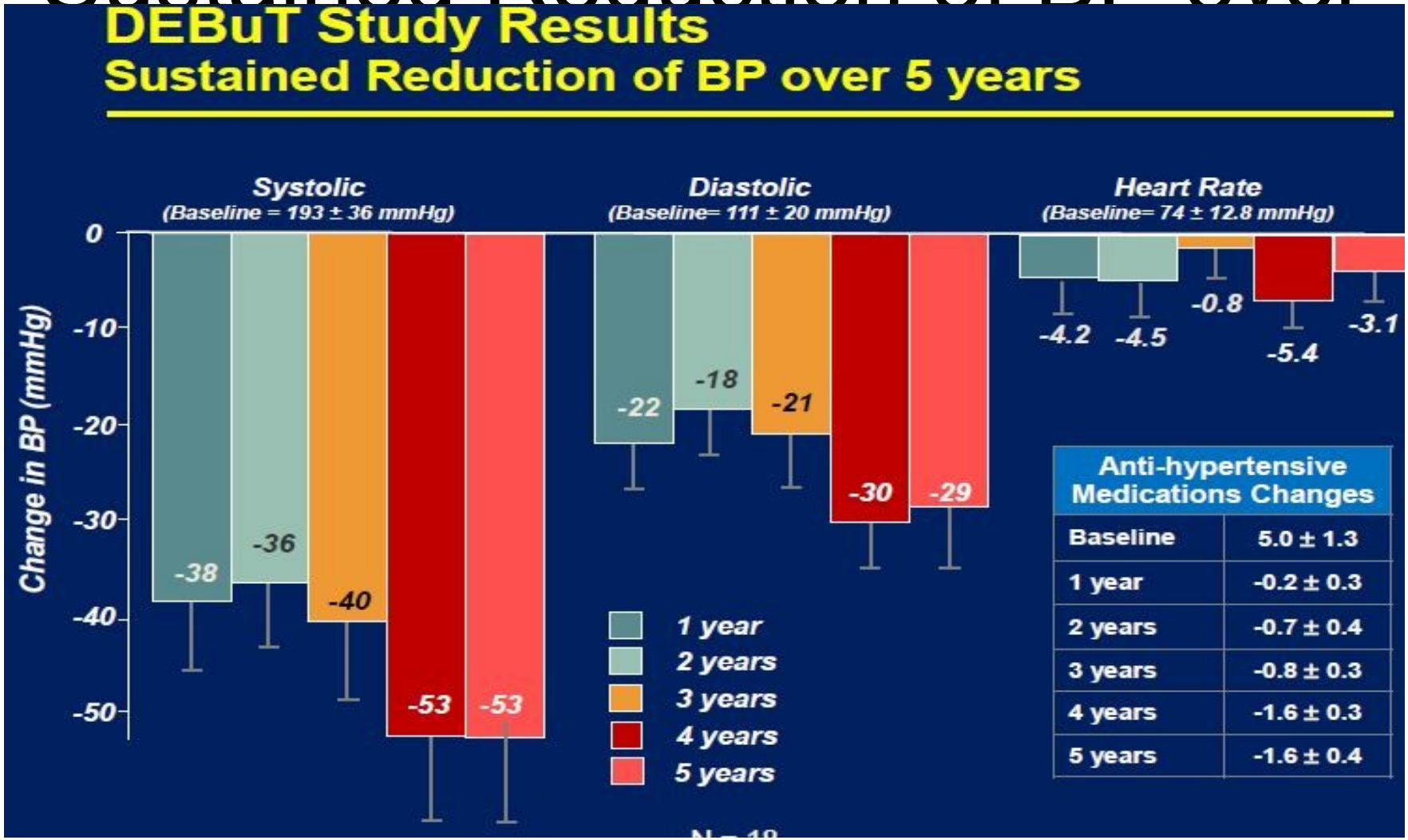
Baroreflex Activation Therapy (BAT)



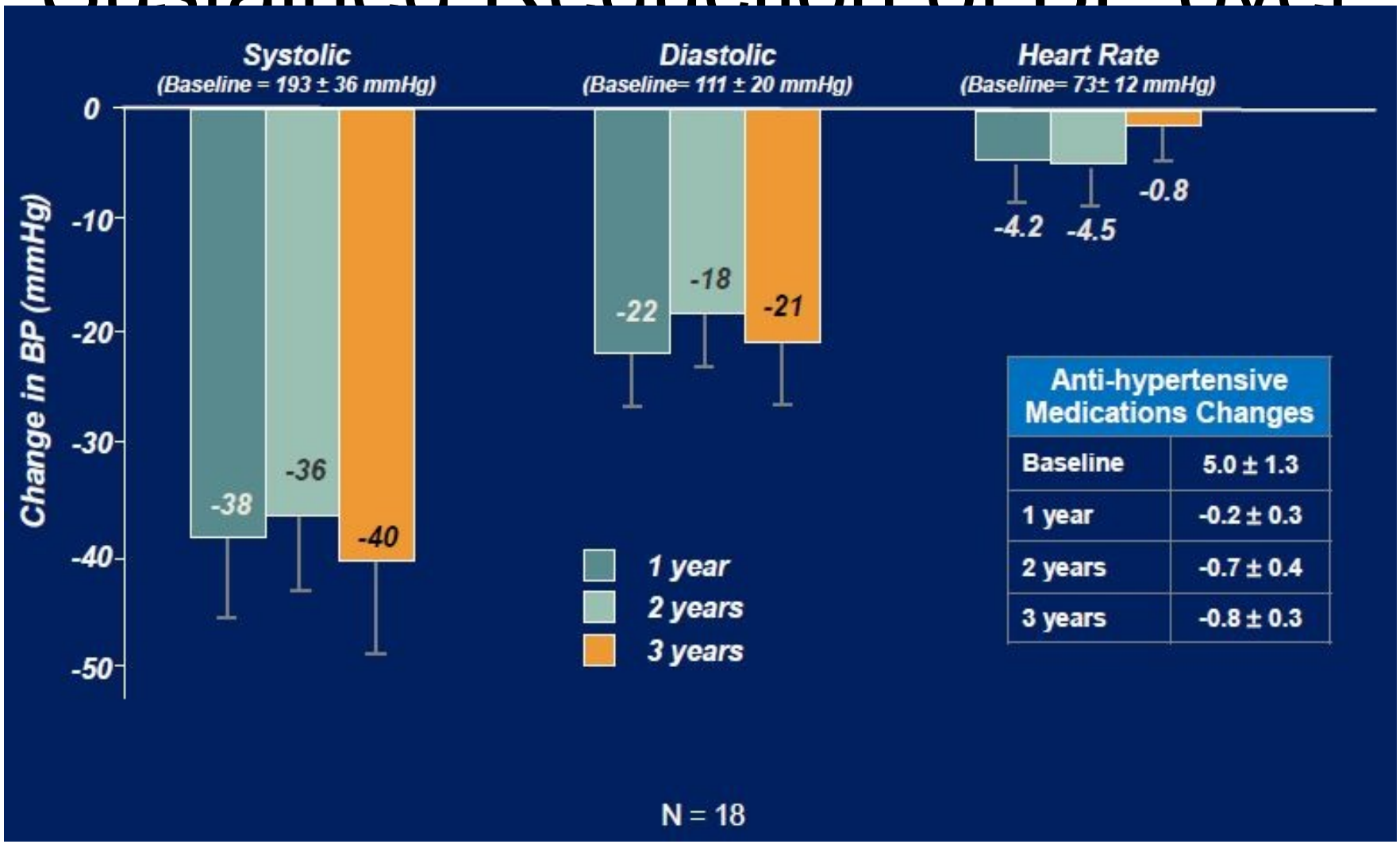




DEBuT Study Results
Sustained Reduction of BP over

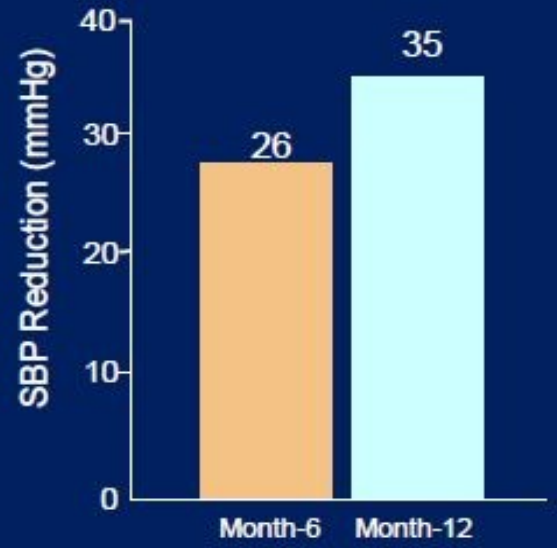


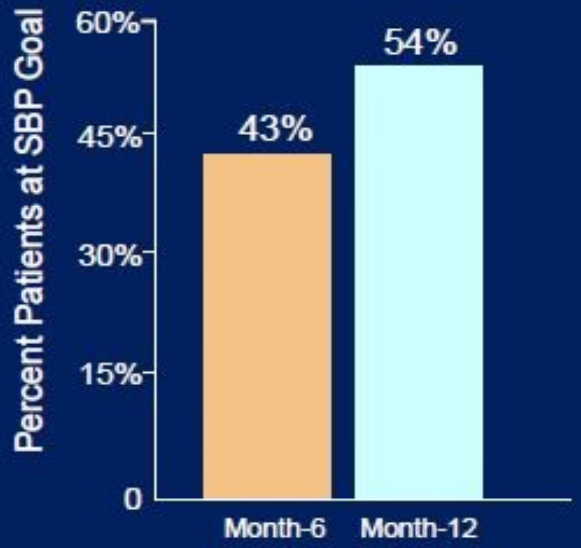
DEBuT Study Results
Sustained Reduction of BP over



Rheos Pivotal Trial Results at 12 Months - Post-Hoc

- 81% of patients were responders (SBP ≥ 10 mmHg relative to pre-implant)
- Therapeutic efficacy continued to improve over time:

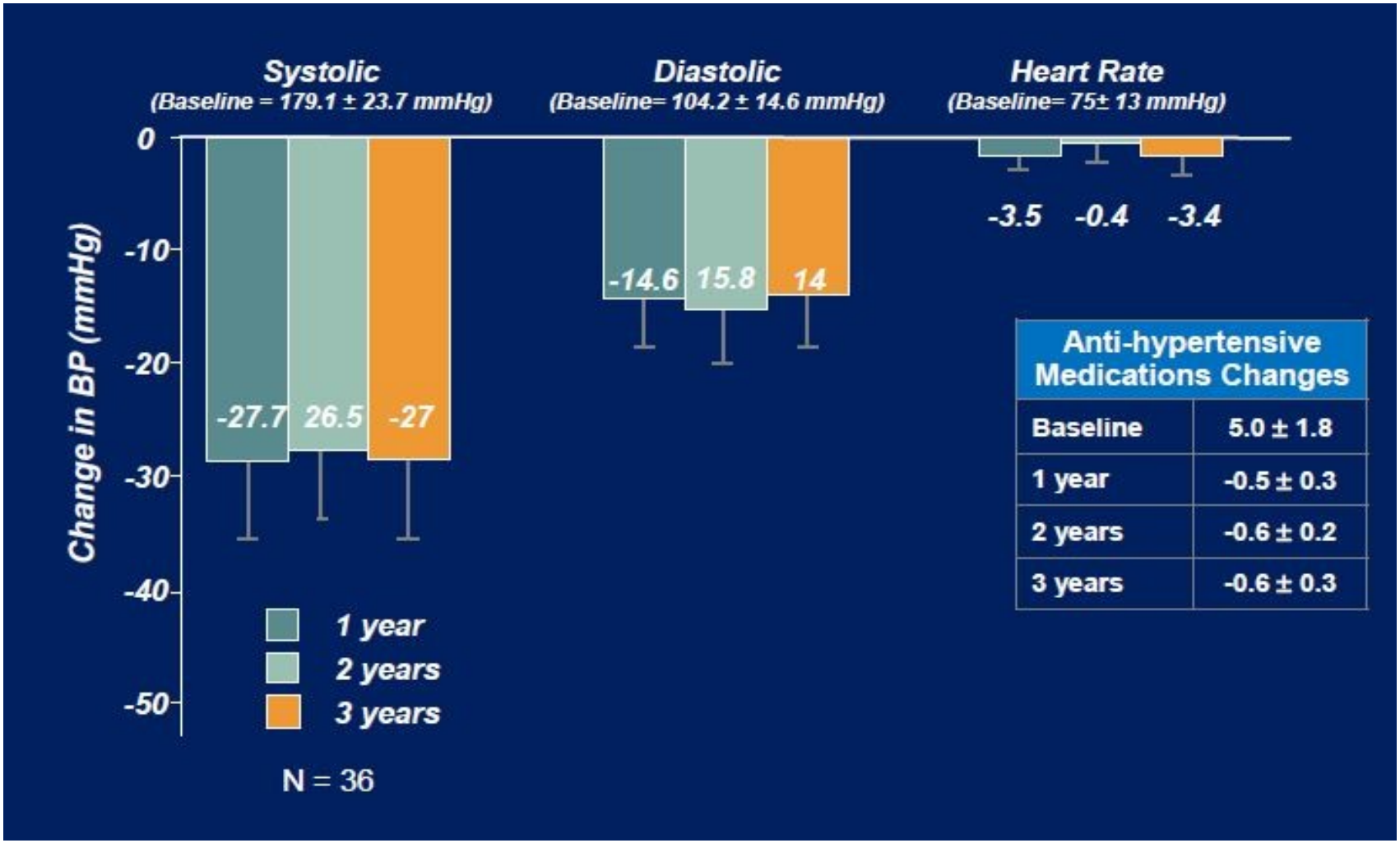




Bisognano et al, HTN 2011

Bisognano, JACC 2011, 58 (7): 765-73

Rheos - Pivotal Trial Results Sustained Reduction of BP over



Bisognano, JACC 2011, 58 (7): 765-73

Aknowledgements

I wish to thank the following persons for making this presentation possible:
Ass. Prof. Ivo Petrov, MD, PhD
Stanislav Kernov, MD
Christo Dimitrov, MD
Lora Nikolova, MD
Elena Bolyukova
Ivo Andreev

Thank you for your attention!