19th CardioVascular Summit-TCTAP 2014
Seoul, Korea, April 22-25, 2014

Clinical Data and Guidelines Update; From Clinical Trials to Real-world Registries

Horst Sievert,
Sameer Gafoor, Stefan Bertog,
Ilona Hofmann, Laura Vaskelyte,
Predrag Matić, Markus Reinartz
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Frankfurt, Germany

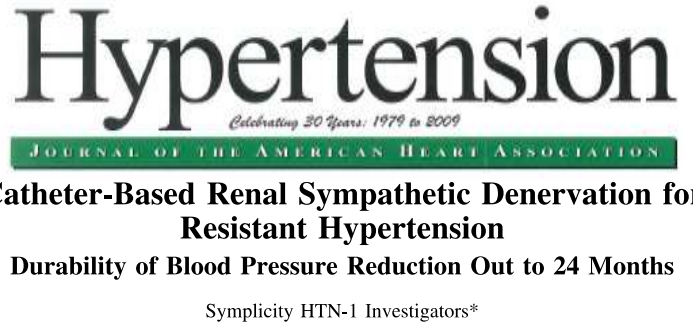
Symplicity HTN-1


THE LANCET

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, Bogusław Kapelak, Anthony Walton, Horst Sievert, Suku Thambar, William T Abraham, Murray Esler

Lancet. 2009;373:1275-1281


Hypertension

Celebrating 30 Years: 1979 to 2009

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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)

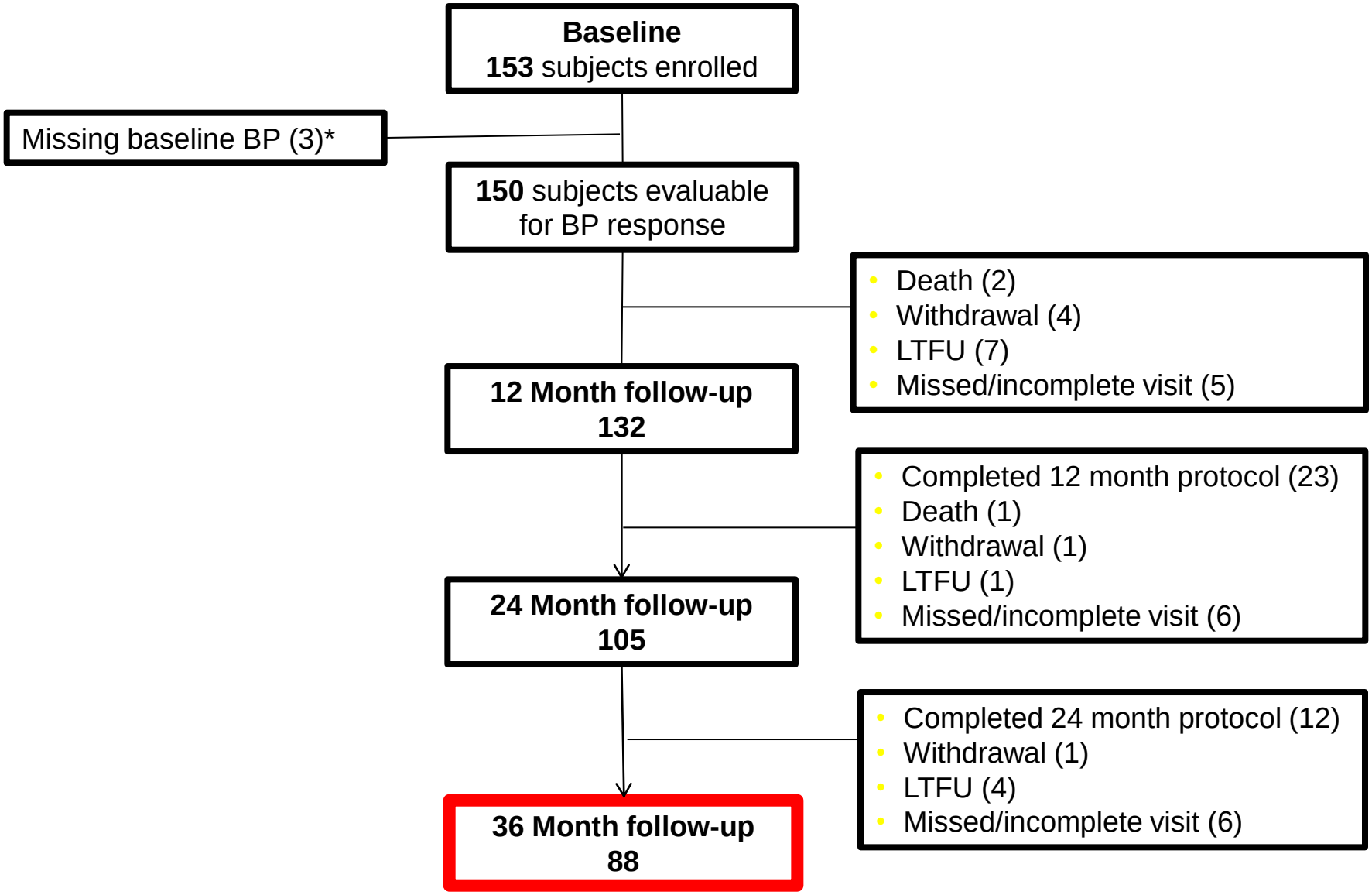
\

Expanded Cohort – initially reported in Hypertension, 2011, updated

-n=153

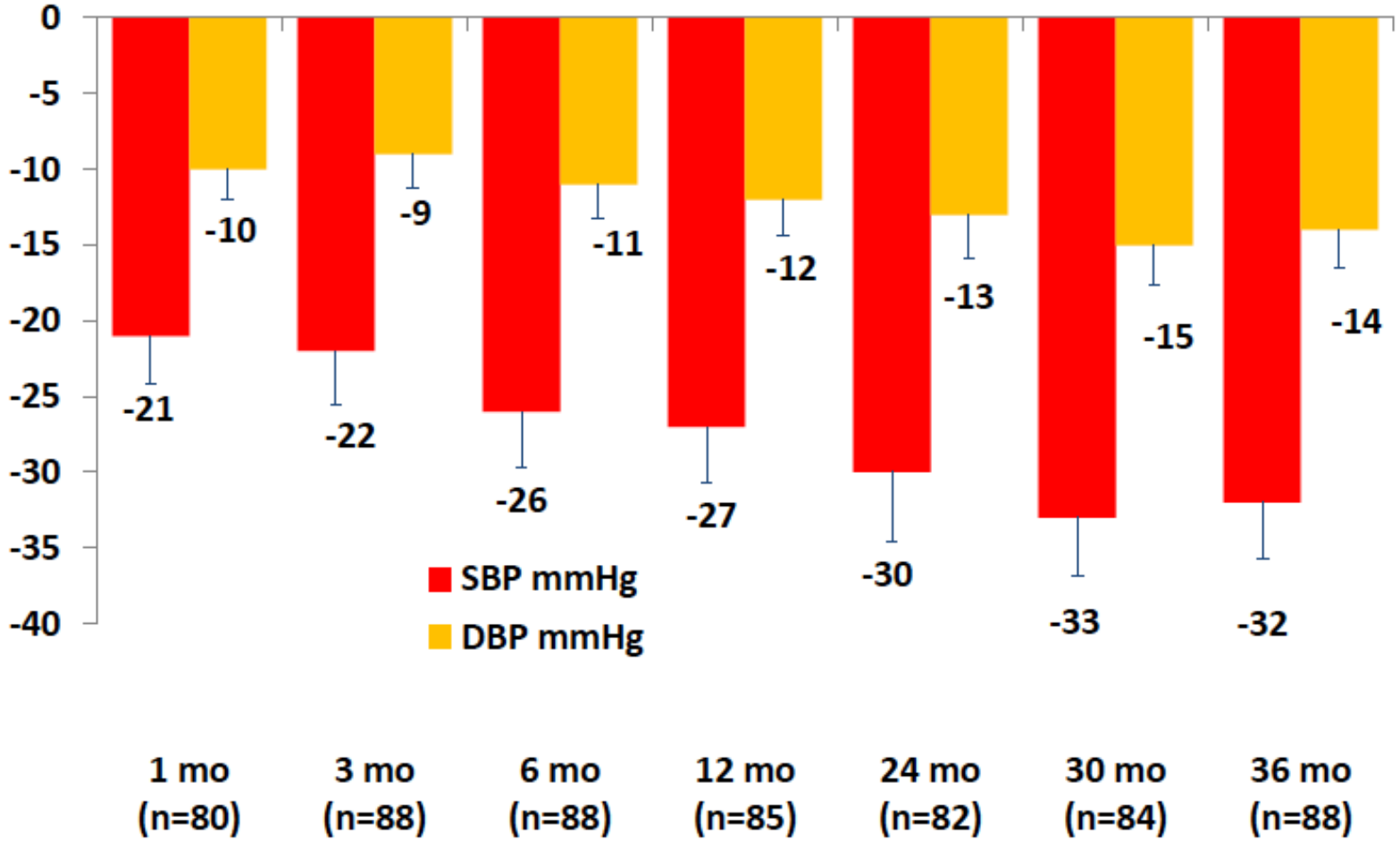
- 36 -month follow-up

Symplicity HTN 3: Patient Disposition 2013



Krum H, ESC 2013

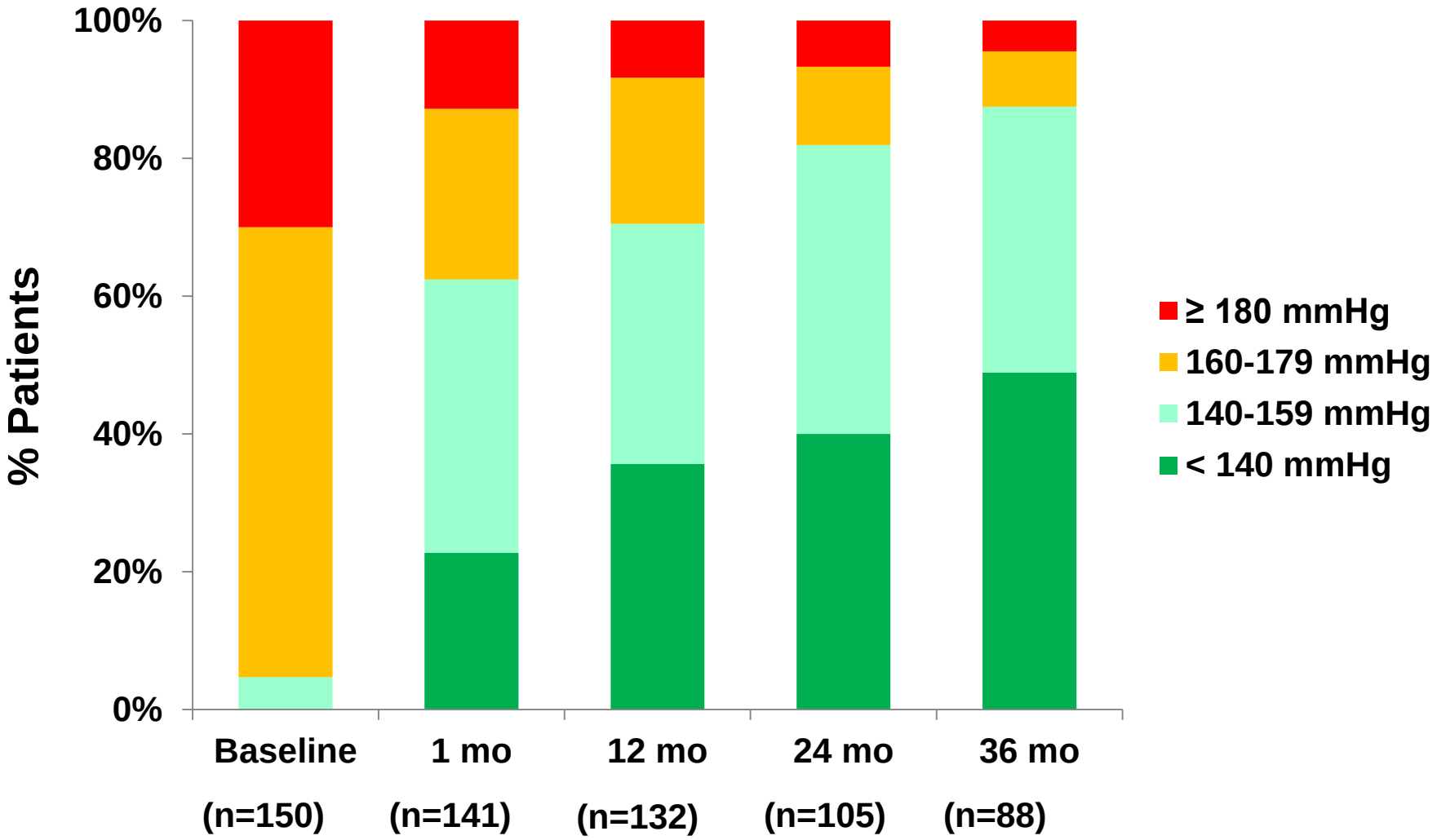
SYMPLICITY HTN-1
Shows Long-Lasting Changes in Office Blood Pressure
Mean BP decrease in 88 patients seen until 30 months



Krum H, ESC 2013

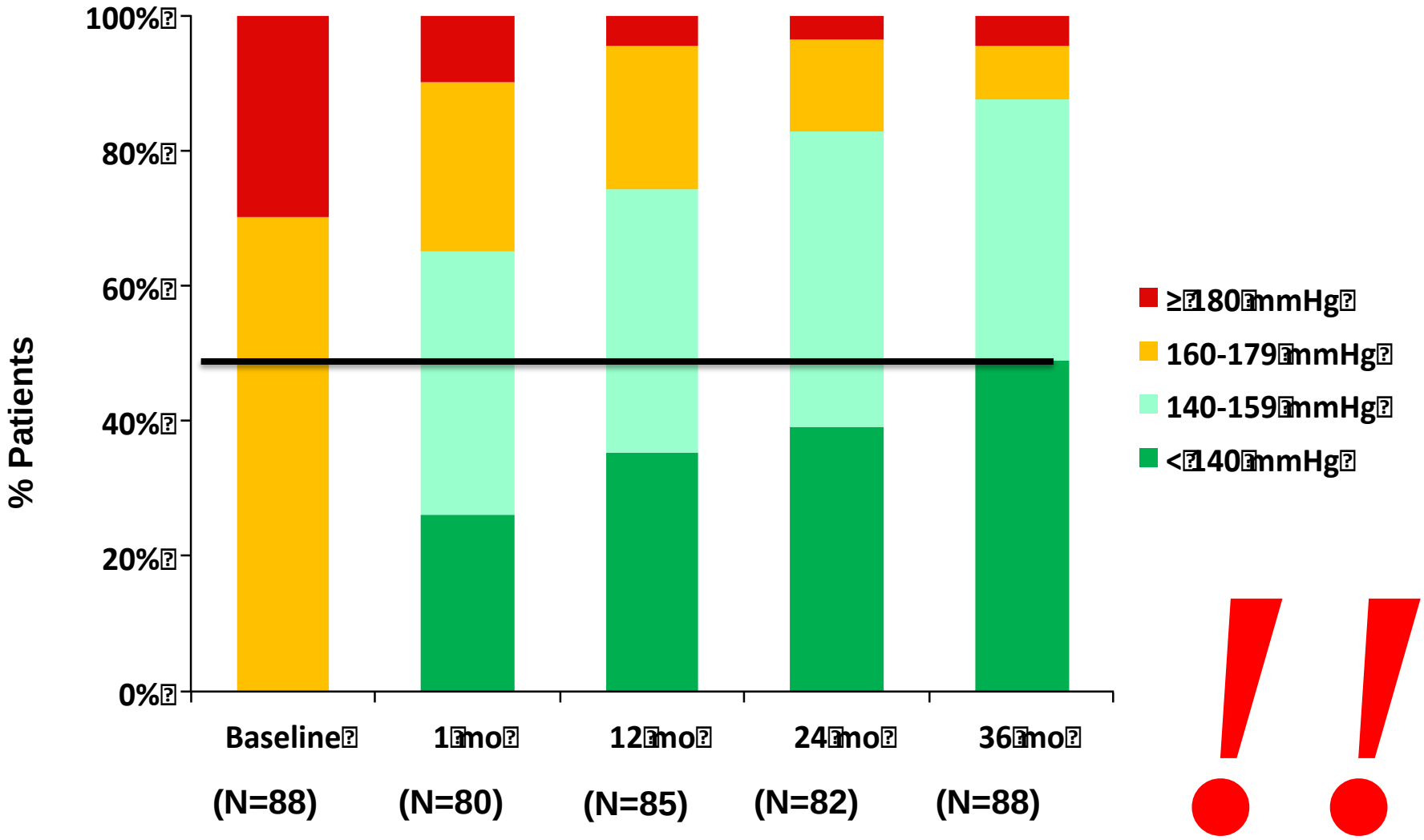
Krum ESC 2013

Achievement of BP Goals (All Patients)



Krum H, ESC 2013

Achievement of BP Goals (n=88)



Krum H, ESC 2013

Laboratory Results to 36-Months

Mean ± SD	Na+ (mmol/L)	K+ (mmol/L)	SCr (µmol/L)	eGFR (mL/min/1.73m²)
Baseline	140.4 ± 3.9 (143)	4.1 ± 0.6 (145)	83.8 ± 20.1 (143)	83.6 ±19.7 (145)
3 Months	140.4 ± 3.1 (125)	4.1 ± 0.5 (125)	85.8 ± 22.6 (132)	82.6 ±21.0 (132)
6 Months	140.5 ± 3.2 (136)	4.1 ± 0.4 (136)	85.2 ± 20.1 (142)	82.6 ± 20.9 (142)
12 Months	140.1 ± 3.3 (130)	4.0 ± 0.4 (129)	85.4 ± 19.8 (130)	81.8 ± 19.5 (130)
24 Months	139.9 ± 3.0 (43)	4.1 ± 0.4 (43)	92.9 ± 29.8 (43)	76.8 ± 22.8 (43)
36 Months	139.7 ± 243 (29)	4.2 ± 0.9 (29)	92.0± 32.5 (28)	74.3 ± 28.0 (29)

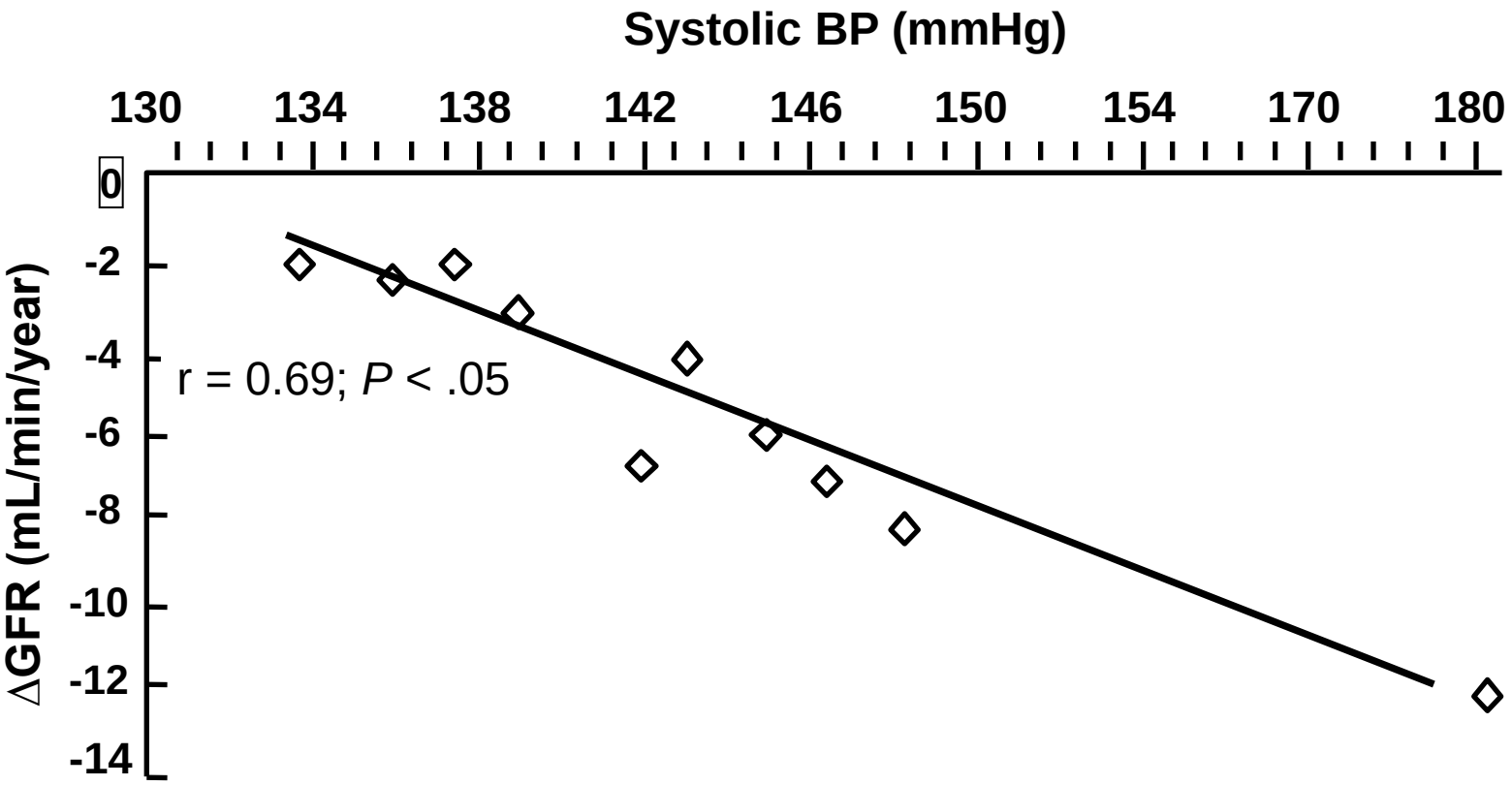
P<0.05

N=29

Needs to be further analyzed

Krum H, ESC 2013

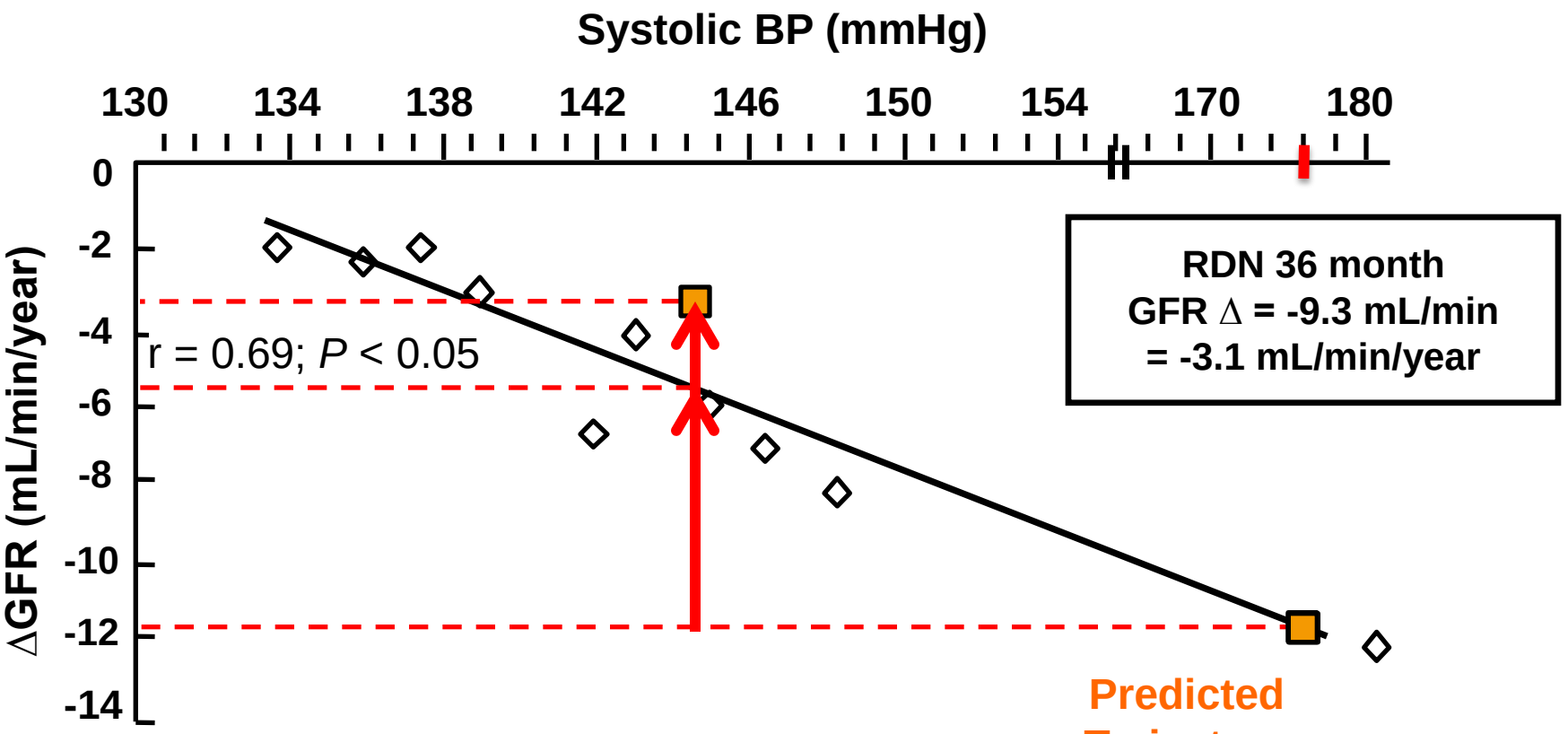
Expected Decrease of GFR in Hypertension



Parving HH, et al. Br Med J. 1989.
Viberti GC, et al. JAMA. 1993.
Klahr S, et al. N Eng J Med. 1994.
Hebert L, et al. Kidney Int. 1994.
Lebovitz H, et al. Kidney Int. 1994.
Moschio G, et al. N Engl J Med. 1996.
Bakris GL, et al. Kidney Int. 1996.
Bakris GL. Hypertension. 1997.
The GISEN Group. Lancet. 1997.

Bakris et al. Am J Kidney Dis. 2000;36(3):646-661

GFR expected vs observed



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Possible renal artery stenosis out to 36-Months

	0-6 Months	> 6-18 Months	> 18-36 Months
Hemodynamically stable, no intervention required	**1**	**1**	**-**
Stented without sequelae	**-**	**-**	**1**
Non-significant, no intervention required	**-**	**1**	**-**

Krum H, ESC 2013

Adverse events out to 36-Months

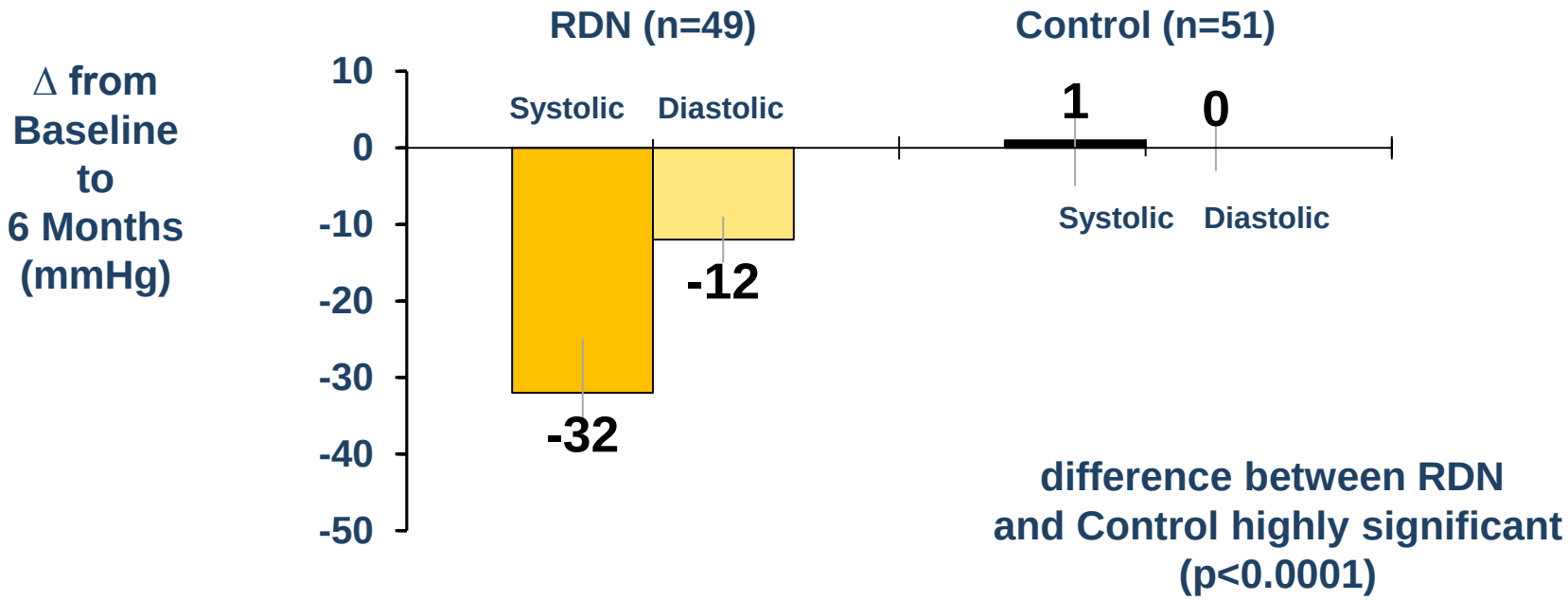
- 1 patient with Hypotension and Renal Failure (18 m)
  - Due to sepsis; successfully treated; Renal failure resolved
- 1 patient with Hypotension and Renal Failure (24 m)
  - Post-operative hypovolemia with continuation of antihypertensive medications leading to acute tubular necrosis (ATN)
  - Responded to treatment and ATN resolved
- Hypotension Episode
  - Associated with severe diarrhoea and dehydration
  - Resolved without further incident
- Two episodes Orthostatic Hypotension in 1 patient (Both resolved)
- Hypertensive episodes
  - 13 subjects requiring hospitalization
- Death
  - Myocardial infarction, after 3rd day
  - Sudden cardiac death, after 6 months
  - Cardio-respiratory arrest, after 18 months

Krum H, ESC 2013

SYMPLICITY HTN-2

- Multicenter Phase II feasibility study June 2009 - January 2010
  - 24 centers
- Primary efficacy endpoint
  - 6 month office based BP
- 190 patients eligible, 106 randomized
  - 49 treated, 51 controls

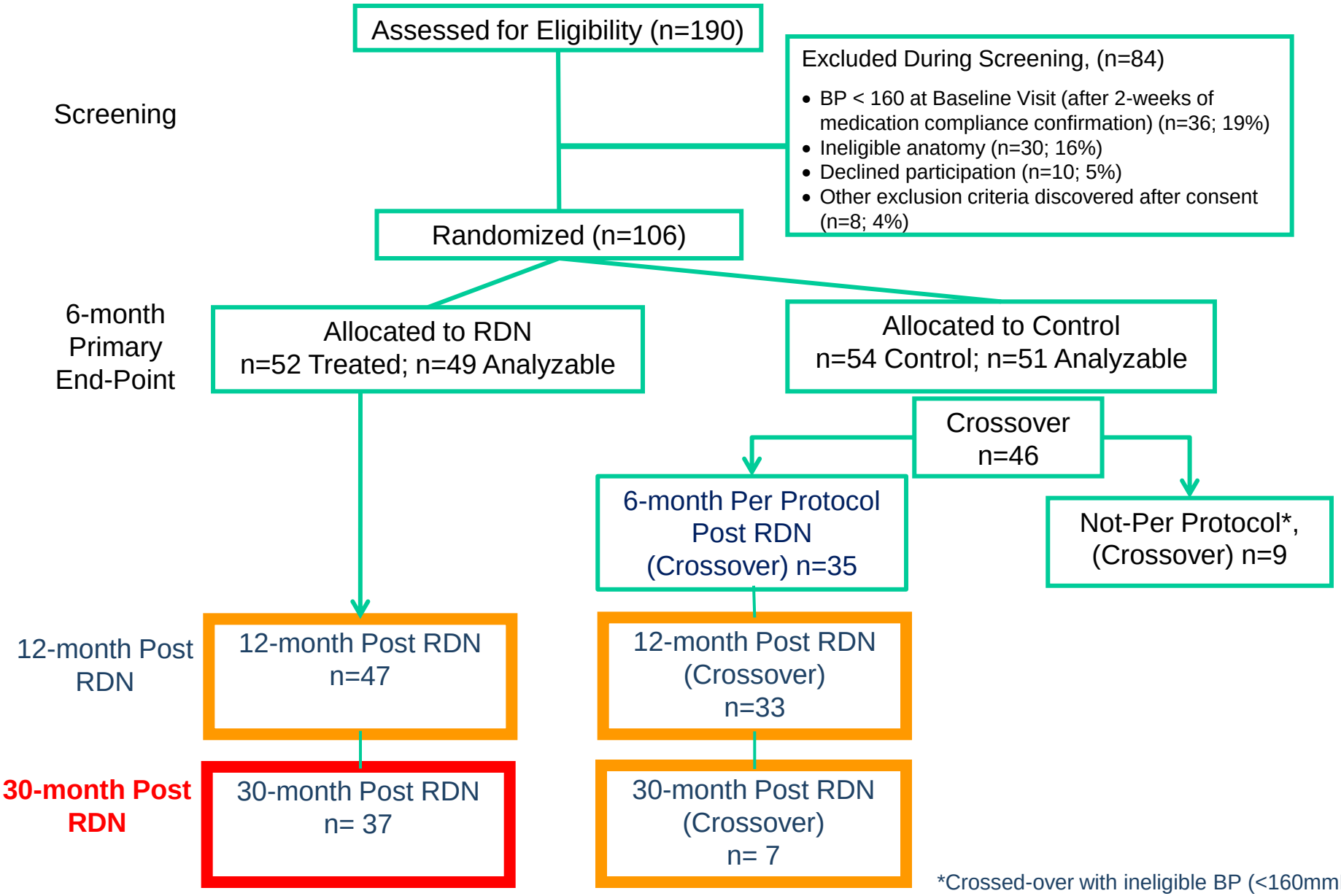
Primary Endpoint: 6-Month Office BP



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

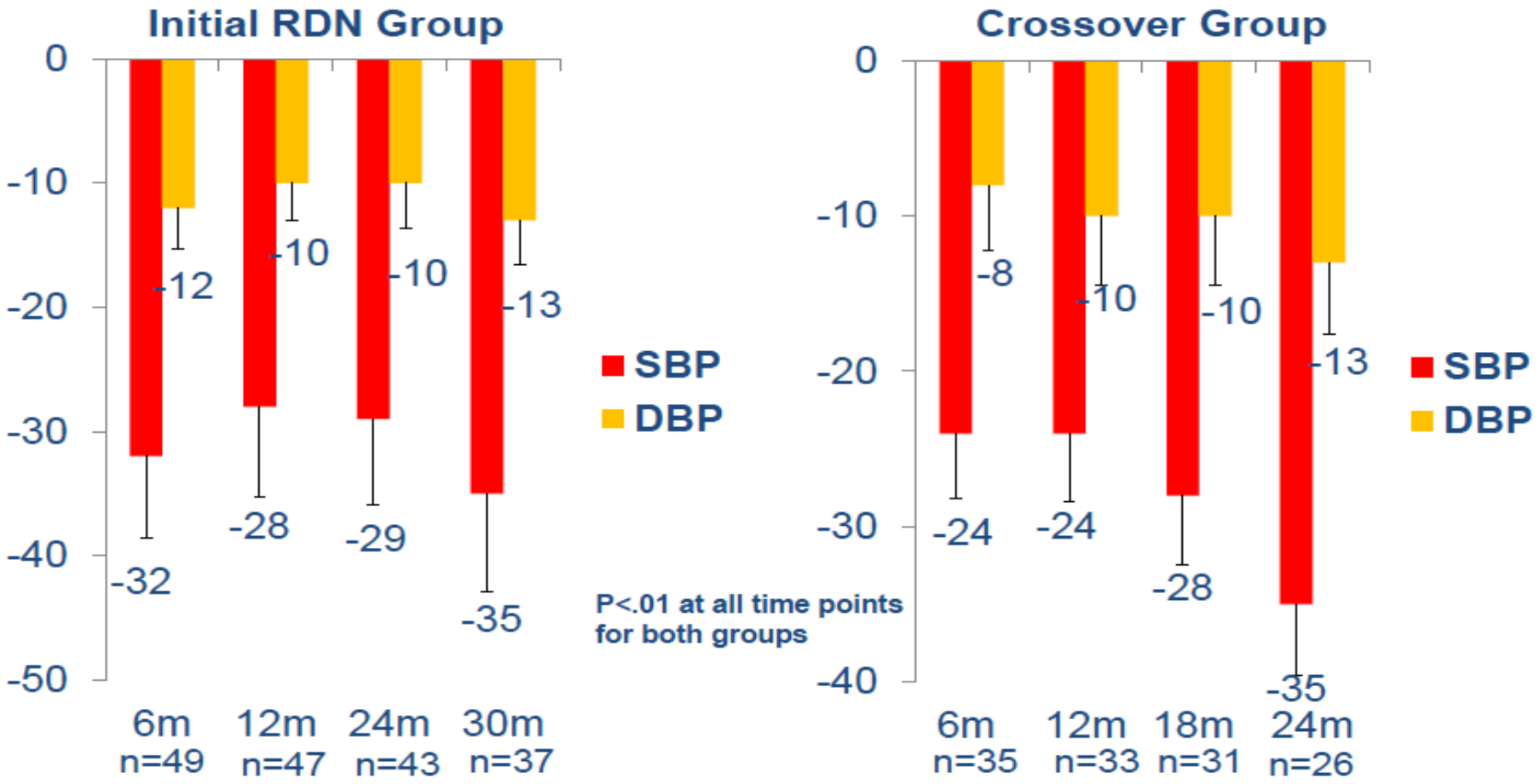
Symplicity HTN-2 Investigators. *Lancet.* 2010;376:1903-1909

Patient Disposition



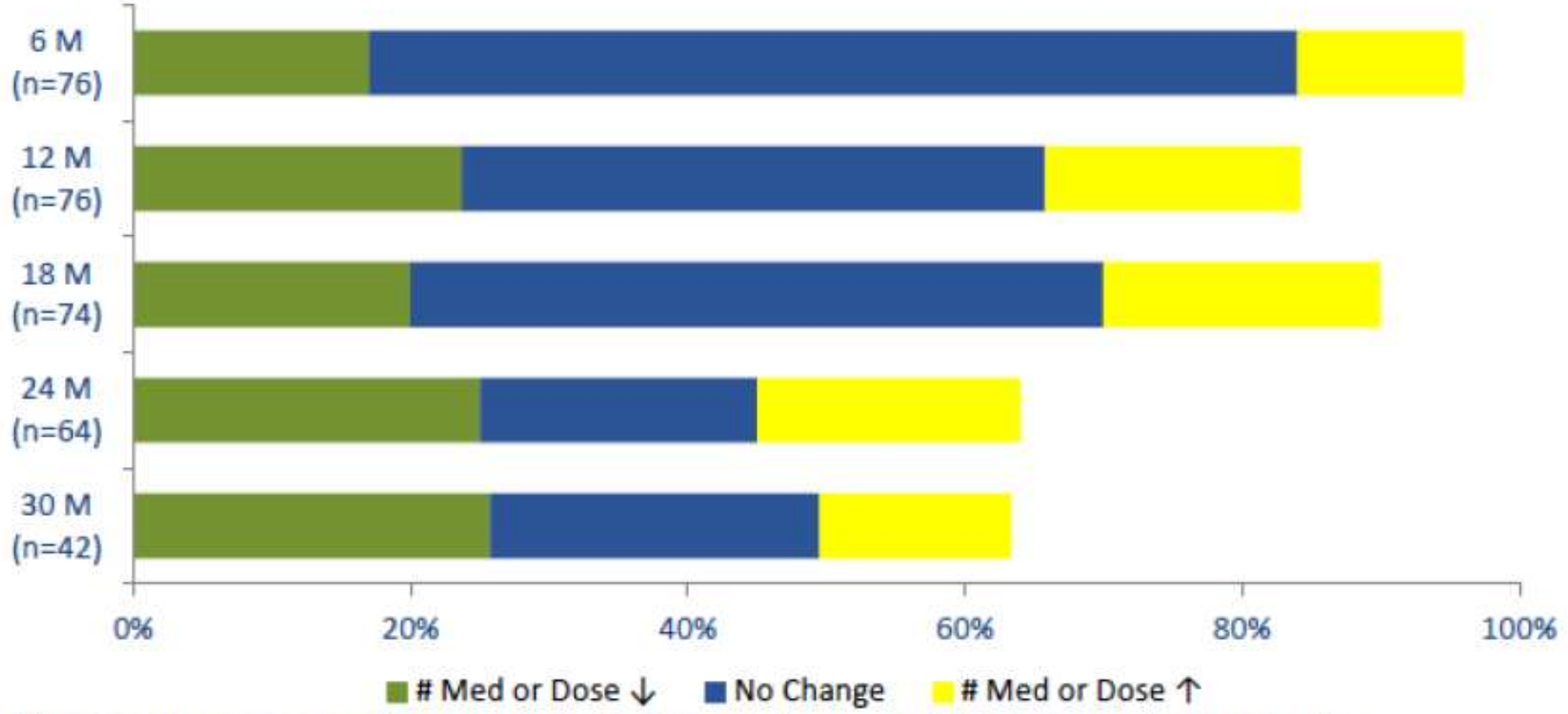
Esler M, ASH 2013

SYMPLICITY HTN-2 Shows Decrease in Office BP at 30 Months



Esler M, ASH 2013

SYMPLICITY HTN-2 Shows no Change or Decrease in Overall Medications After Procedure



Physicians were encouraged to maintain medications and dosages up to the 6-month primary endpoint.

Increase: if any or both meds and/or dose increase, Decrease: if any or both meds and/or dose decrease.
Values may not total to 100% due to indeterminate modifications, e.g., combination of med/dose increase and decrease.

Esler M, ASH 2013

SYMPLICITY HTN-2 shows few adverse events through 30m

- Procedural
  - 1 hematoma, 1 dissection
- 0-12 months
  - 9 hypertensive events needing hospitalization
  - 2 hypotensive events needing hospitalization
- 12-30 months
  - 3 hypertensive events requiring hospitalization
  - 1 mild transient acute renal failure
  - 2 deaths unrelated to device or therapy
- No Change in GFR, No Renal Artery Stenosis

Esler M, ASH 2013

Symplicity HTN 3

- Multi-center, randomized, blinded, sham controlled
- 535 patients
- 88 centers
- Main inclusion criteria
  - Age ≥18 and ≤80 years
  - 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
  - Office Systolic BP ≥160 mm Hg
- Main exclusion criteria
  - ABPM 24 hour average Systolic BP <135 mm Hg
  - eGFR of <45 mL/min/1.73 m^2
  - Anatomical criteria

HTN-3: Primary Endpoints

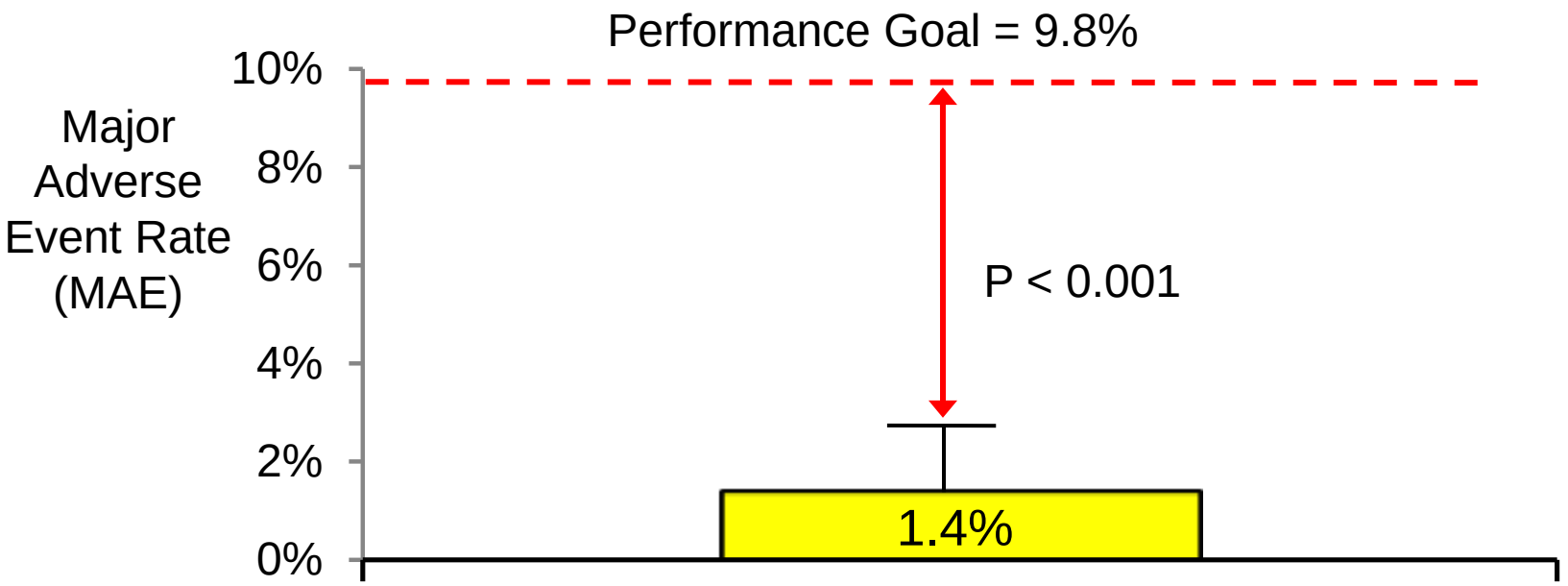
- Safety endpoint
  - Major Adverse Events (MAE) in the treatment group compared with an Objective Performance Criterion (OPC = 9.8% - derived from historical data)
- Efficacy endpoint
  - Comparison of office SBP change from baseline to 6 months in RDN arm compared with change from baseline to 6 months in control arm
    - Endpoint = $(SBP_{RDN\ 6\ month} - SBP_{RDN\ Baseline}) - (SBP_{CTL\ 6\ month} - SBP_{CTL\ Baseline})$
  - *Superiority margin of 5 mm Hg*

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

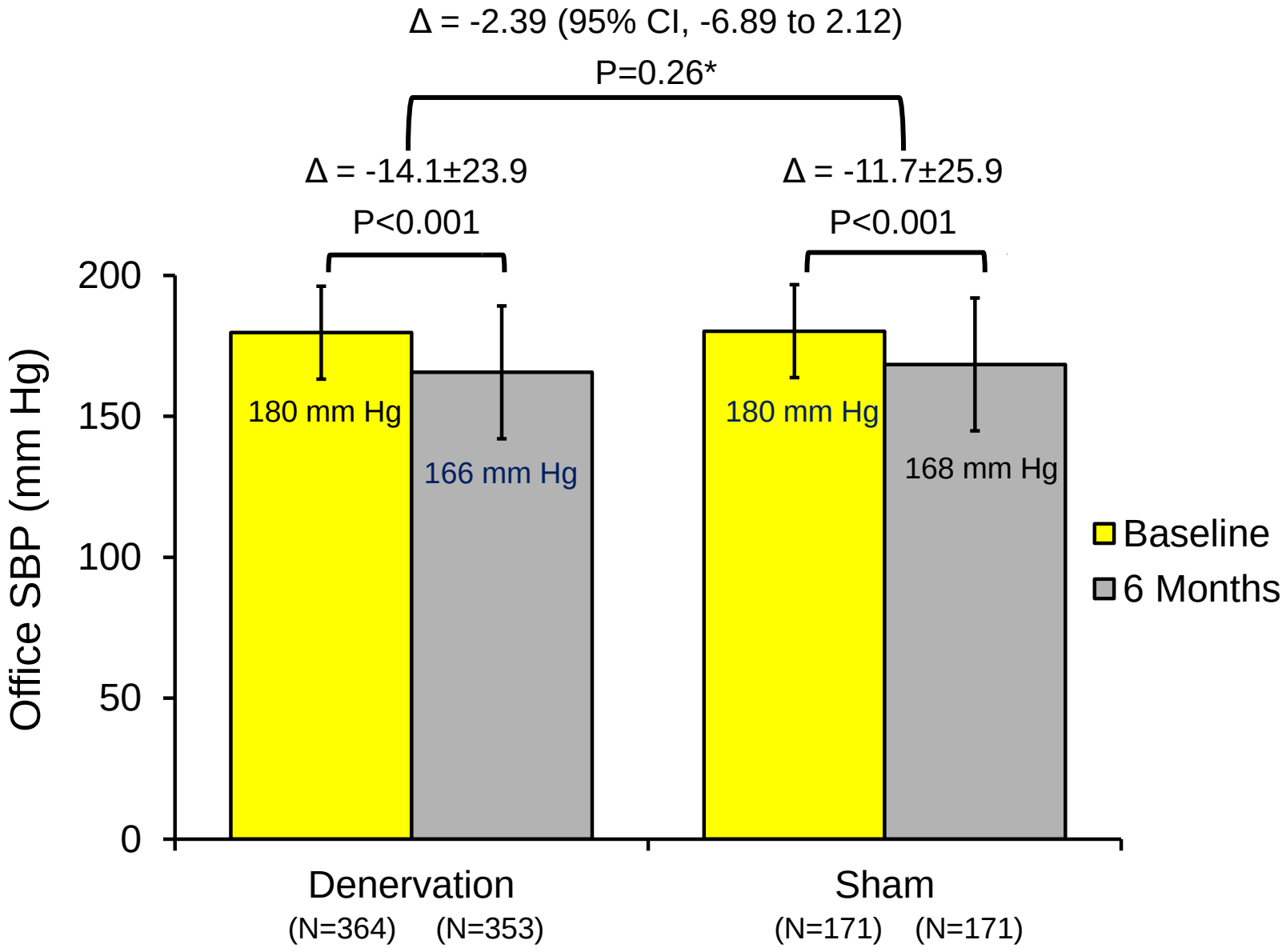
*Race also includes Asian, Native American, or other

HTN-3 Primary Safety Endpoint



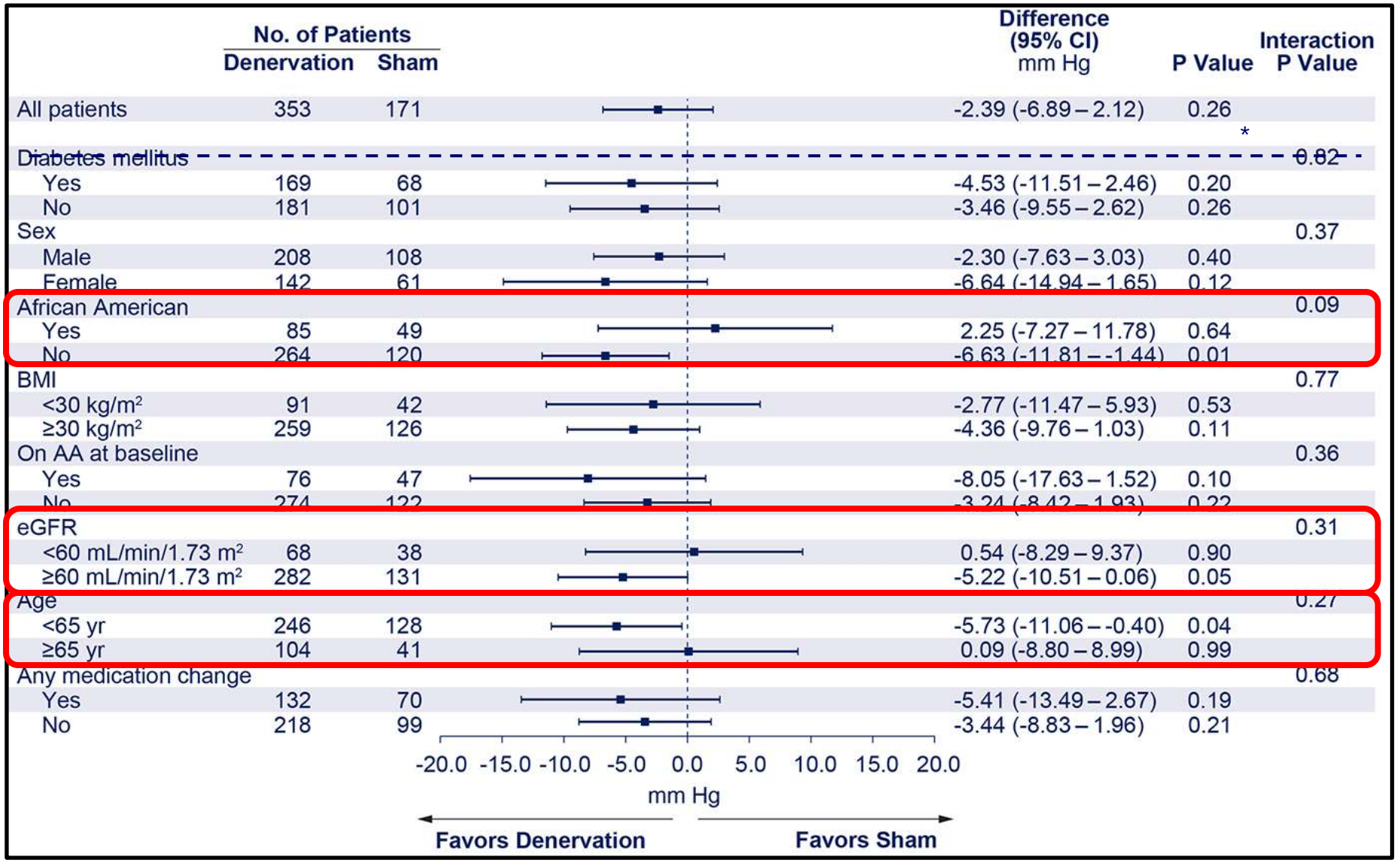
	Renal Denervation (N=364)	Sham Procedure (N=171)	Difference [95% CI]	P*
MAE	1.4% (5/361)	0.6% (1/171)	0.8% [-0.9%, 2.5%]	0.67

Primary Efficacy Endpoint



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

HTN-3 Prespecified Subgroup Analyses



* P value for superiority with margin of 5 mm Hg

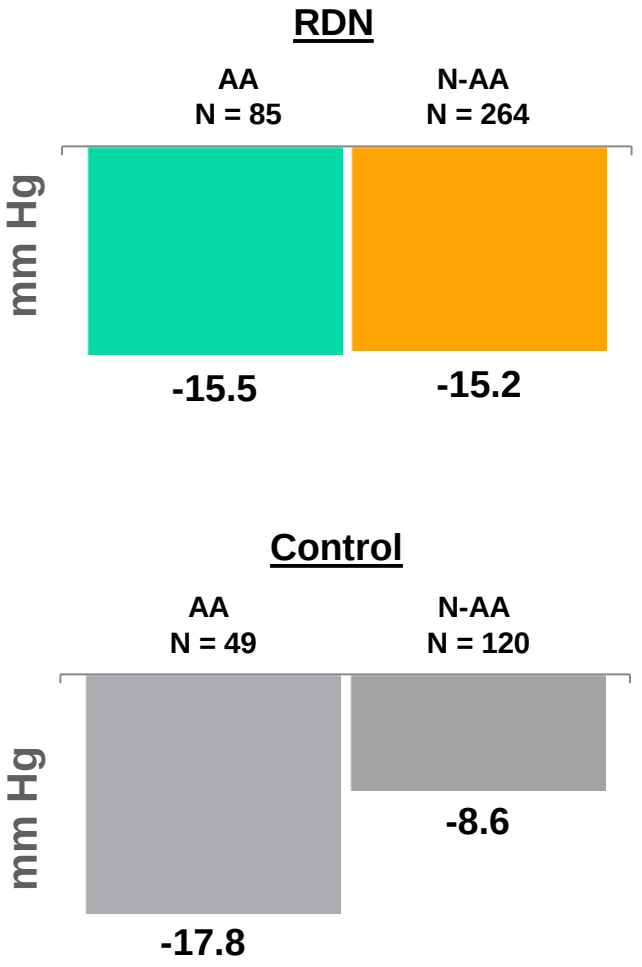
Why did HTN-3 fail?

Multiple potential reasons

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%

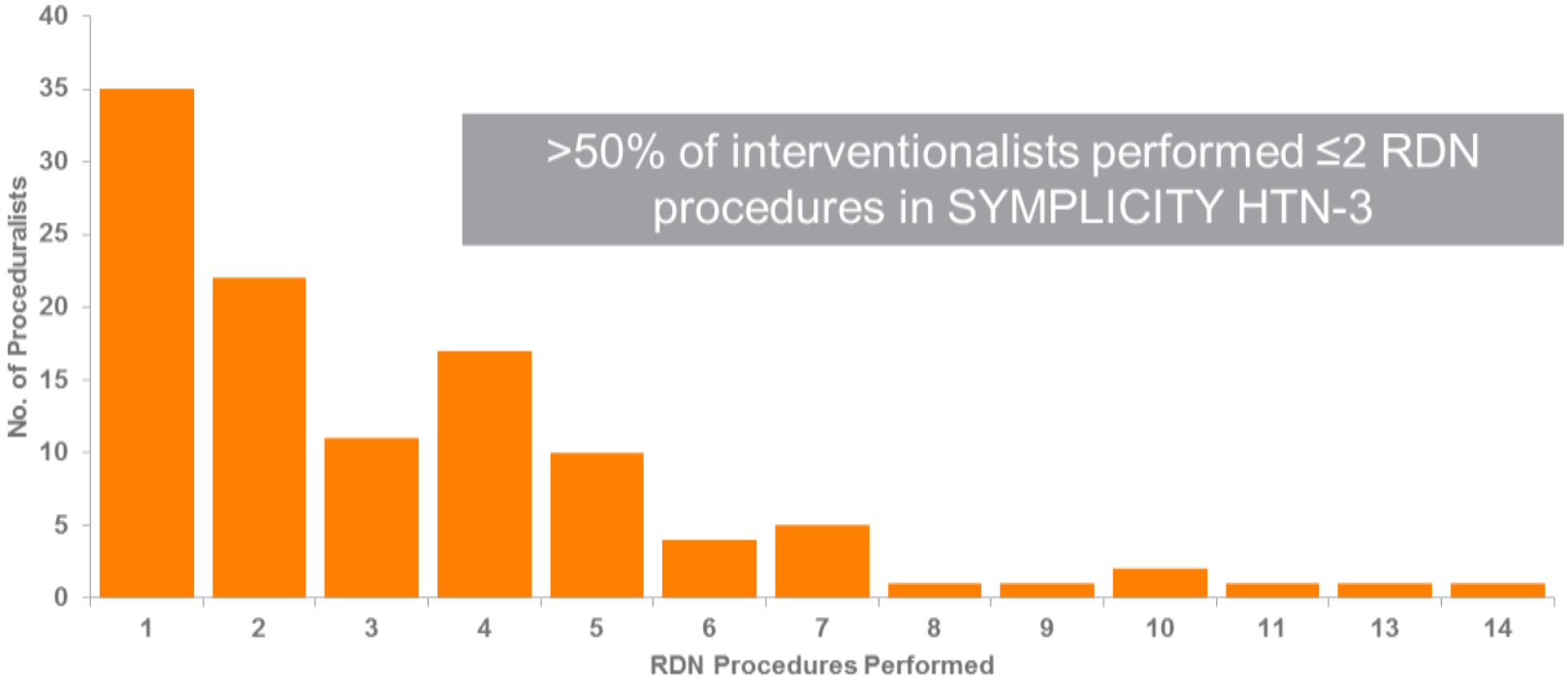
Vasodilators are dosed up to 4x daily, making compliance a challenge



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

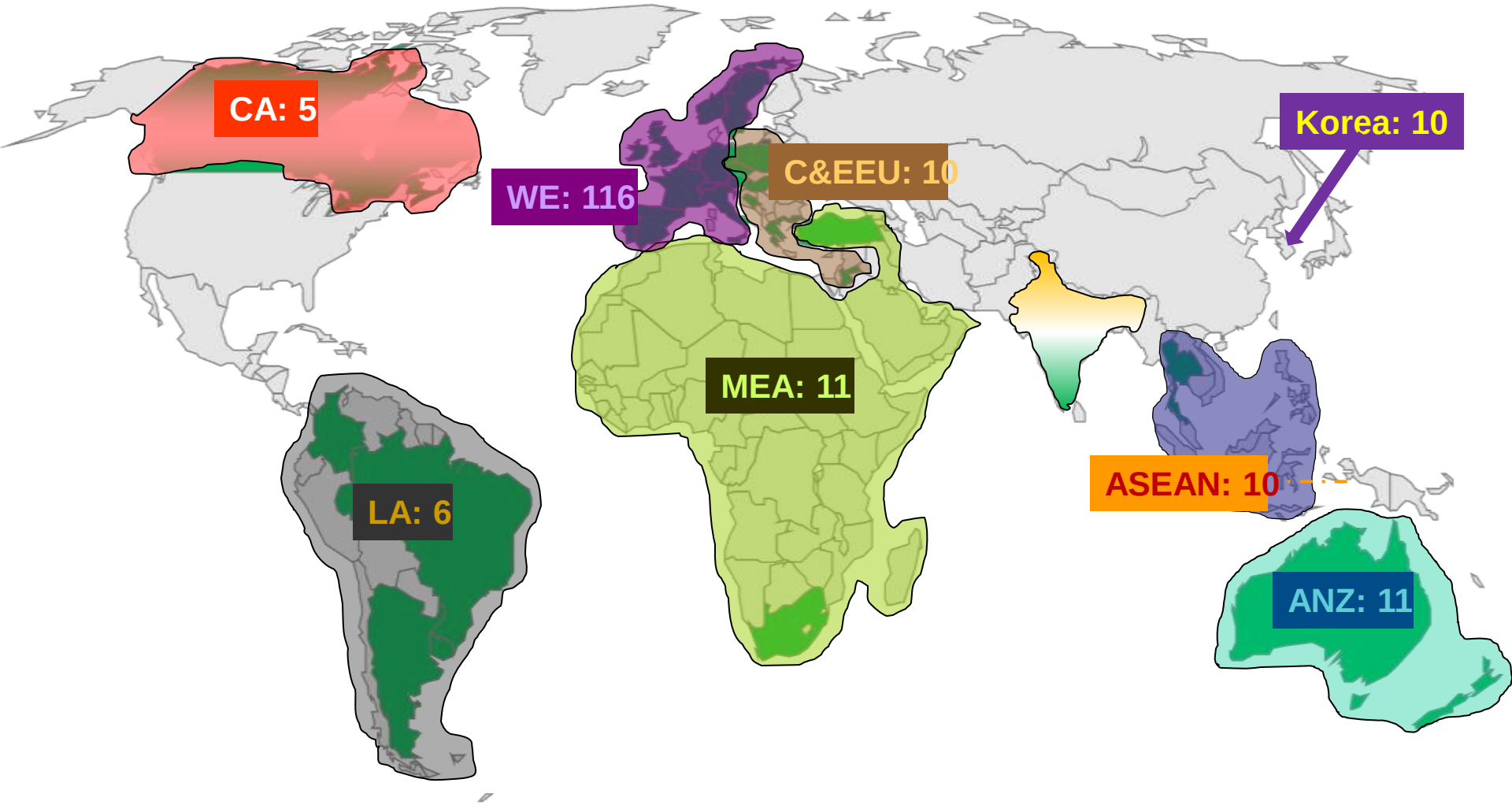
a) 5X more operators vs HTN-1
b) Greater heterogeneity of operator experience vs. HTN-1 and HTN-2
c) Case proctoring was different and not comparable



Global SYMPLICITY Registry

- Prospective, open label, multi-center, international registry
- Up to 5000 real world patients with uncontrolled hypertension and some with conditions associated with sympathetic nervous system activation
- Key Inclusion:
  - Older than 18 years
  - Clinical candidates for renal denervation

Study Centers

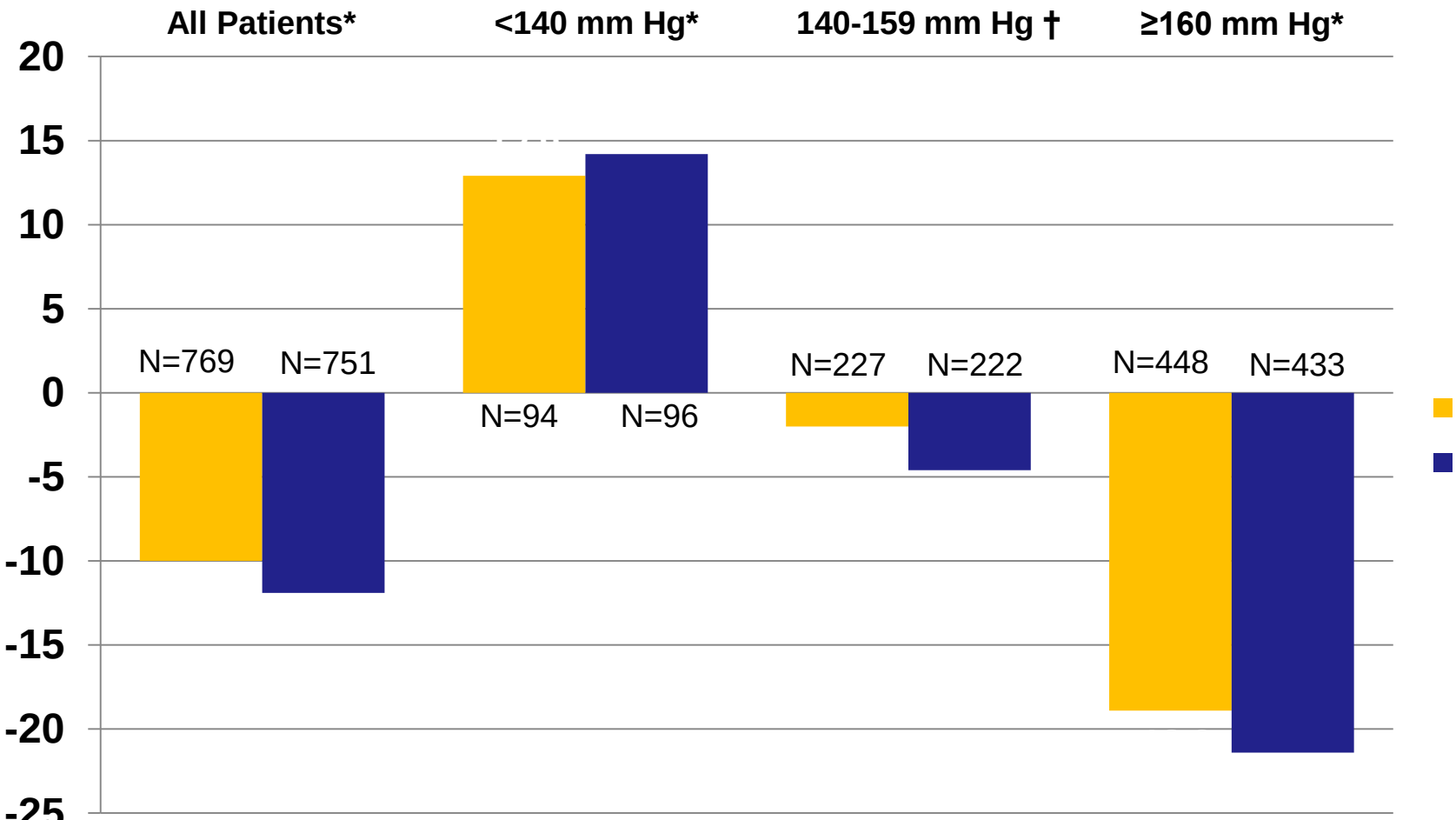


Safety in HTN-3 and GSR

	HTN-3 RDN arm (N=364)	GSR All Patients (N=1000)	GSR OSBP≥160 and ABPM≥135* (N=327)
MAE	1.4%	0.8%	1.3%
At 6 month			
Death	0.6%	0.4%	0.3%
New onset end stage renal disease	0.0%	0.2%	0.3%
Significant embolic event resulting in end-organ damage	0.3%	0.0%	0.0%
Renal artery re-intervention	0.0%	0.2%	0.0%
Vascular complication	0.3%	0.4%	0.7%
Hypertensive crisis/emergency	2.6%	1.0%	1.7%
New renal artery stenosis > 70%	0.3%	0.0%	0.0%

M. Böhm, ACC 2014

Change in Office Systolic BP for All Patients and Subgroups



*P<0.0001 for both 3 and 6 month change from baseline

†P=0.14 at 3 months and P=0.0006 at 6 months

M. Böhm, ACC 2014

… and Guidelines?

- Almost all guidelines at least consider renal denervation as an option in resistant hypertension
- Recommendations usually follow the study protocols of HTN-1 and HTN-2
- Most guidelines recommend to exclude patients with renal insufficiency

And guidelines after HTN-3 ?

- They did not change yet
- Most scientific societies did not react yet or reacted but did not say more than “data should be analyzed carefully”
- Which means you can continue to do renal denervation if you believe it is indicated in your patients

The Joint UK Society's Working Group on Renal Denervation.
Our initial response to the Medtronic Symplicity HTN3 announcement.

Mark Caulfield[1] (Chair), Mark de Belder[2], Trevor Cleveland[3], David Collier[1], Indranil Dasgupta, John Deanfield[4], Charles Knight[5], Melvin Lobo[1], Matthew Matson[3], Jon Moss[3], Neil Poulter[1], Iain Simpson[5], Bryan Williams[1].

On behalf of the British Hypertension Society[1], the British Cardiovascular Intervention Society[2], the British Society for Interventional Radiology[3], National Institute for Clinical Outcomes Research[4], the British Cardiovascular Society[5], and the Renal Association[6].

- While we await the data from Symplicity HTN3, we recommend a temporary moratorium on renal denervation procedures for all cases as part of routine care in the NHS and private practice in the UK.

- Our proposed temporary moratorium should not apply to clinical trials as there are many other technologies that are in development for renal denervation (including by Medtronic).

Cardiovascular and Interventional Radiological Society of Europe

CIRSE

Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Brief Statement on RDN Study Cessations

Authored by the CIRSE Renal Denervation Task Force: Jon Moss[1] (Chairman), Dierk Vorwerk[2], Anna Maria Belli[3], Jan Peregrin[4], Mick Lee[5], Jim Reekers[6].

- An analysis of the Symplicity HTN-3 data is needed before an informed opinion can be reached.

From: **Eshonline.org** info@eshonline.org
Subject: European Society of Hypertension - STATEMENT ON SYMPLICITY HTN-3 RESULTS
Date: 11 Apr 2014 11:06
To: horstsievertmd@aol.com

European Society of Hypertension

www.eshonline.org

ESH E-NEWSLETTER

ESH STATEMENT ON SYMPLICITY HTN-3 RESULTS

The negative results of the Symplicity HTN-3 study (1) raises the question whether, as it has been said in the accompanying Editorial (2), the "renal denervation train" has been brought to a "grinding halt" (2) as far as its use for the treatment of resistant hypertension is concerned. The European Society of Hypertension believes that although in the Symplicity HTN-3 study use of an appropriate control group makes the results less open to confounders than those of previous studies, the conclusion that renal denervation is ineffective is not justified.

In Summary

- Lots of evidence
  - but in both directions
- Lots of confusion
  - As always: more trials → more questions
- Still some freedom for individual decisions
  - Don’t know for how long

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Renal Denervation
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Thank you!