Beyond SYMPLICITY HTN 3: What's Next

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Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below

Affiliation/Financial Relationship	Company
Grant/Research Support	Abbott Vascular,Boston Scientific Corporation, Medtronic CardioVascular
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Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

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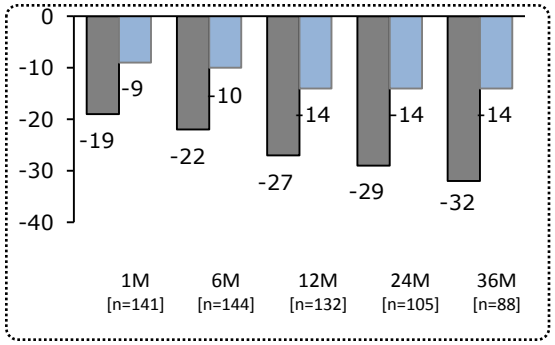
Consistent and Significant Reductions in Blood Pressure Among Early Phase RDN Trials for Refractory Stage II HTN

Blood pressure (BP) reduction in mmHg

Systolic BP
Diastolic BP

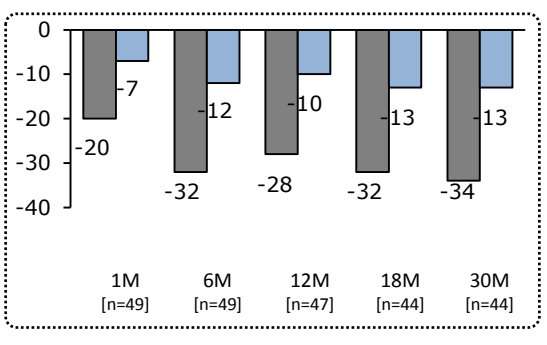
Study details
- Start: 04/2008
- Patient group: Refractory stage II hypertension
- # of pts (target enrollment): 45 [expanded: 153]
- Main endpoint: Safety of RSD treatment
- MAE: None[1]

Symplicity HTN-1[1]



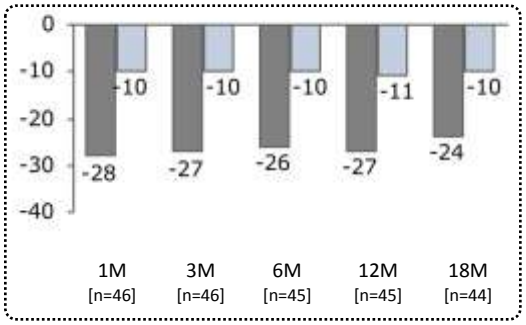
Study details
- Start: 06/2009
- Patient group: Refractory stage II hypertension
- # of pts (target enrollment): 106 [randomized 1:1]
- Main endpoint: Blood pressure reduction
- MAE: 2[5]

Symplicity HTN-2[2]



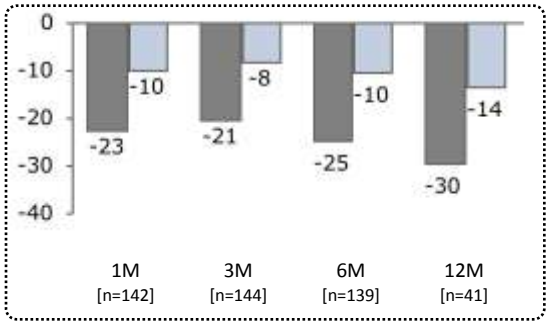
Study details
- Start: 10/2011
- Patient group: Refractory stage II hypertension
- # of pts (target enrollment): 47
- Main endpoint: Office blood pressure
- MAE: [0/4][6]

EnligHTN-I[3]



Study details
- Start: 02/2012
- Patient group: Refractory stage II hypertension
- # of pts (target enrollment): 18 [expanded: 146]
- Main endpoint: Change in SBP and DBP
- MAE: 8[7]

REDUCE-HTN[4]



1 As per 09/10/2013 2 As per 05/23/2013 3 As per 10/31/2013 4 As per 10/31/2013

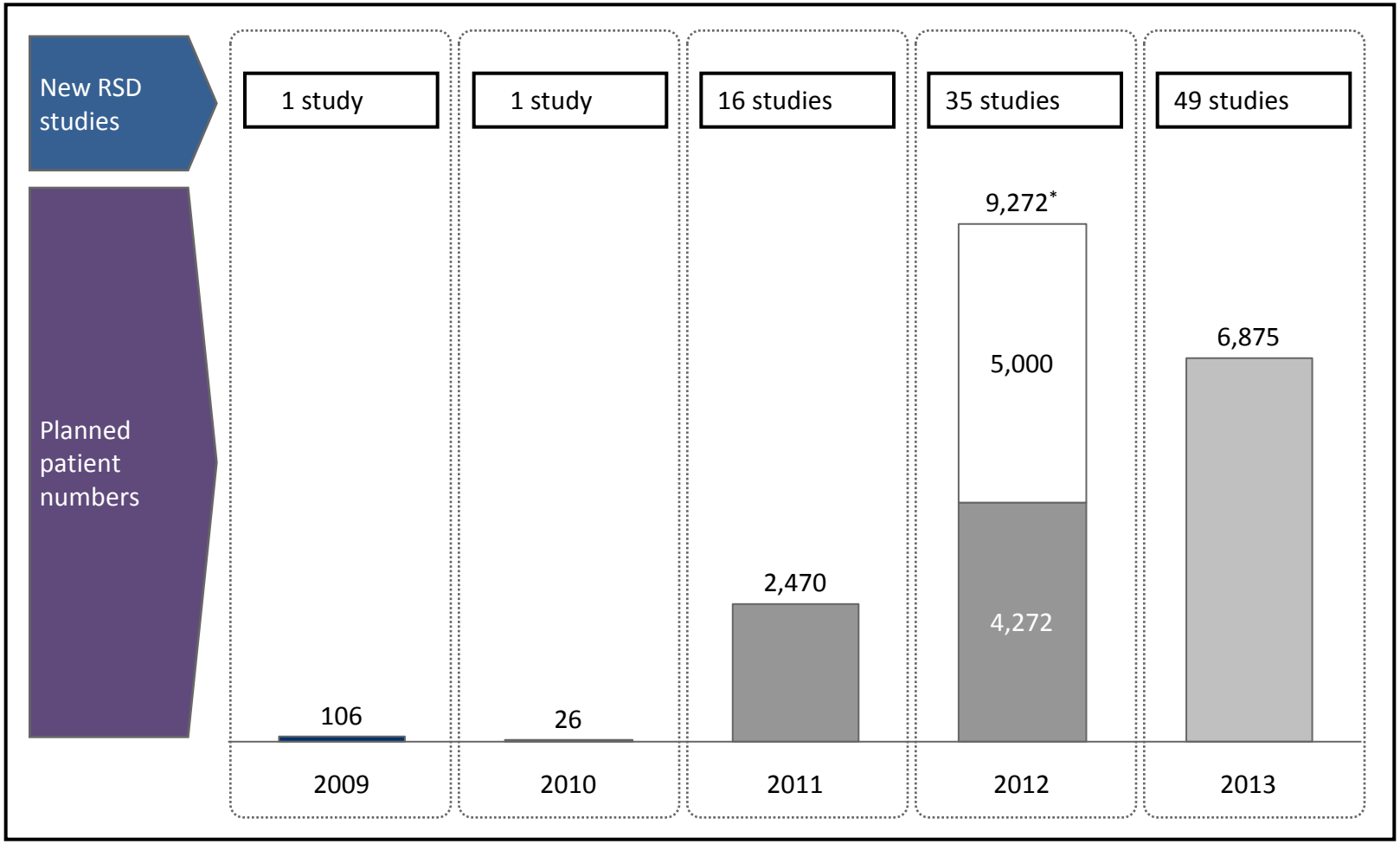
5 MAE's: a) One renal artery dissection from injection of contrast into renal artery wall during dye angiography. Lesion was stented without further consequence. b) One hospitalization prolonged in a crossover patient due to hypotension following RDN. IV fluids administered, anti-hypertensive medication decreased and patient discharged without further incident.

6 No serious peri-procedural events; 4 MAE's through 18M: a) Worsening of pre-existing proteinuria b) Symptomatic hypotension c) Worsening of pre-existing renal artery stenosis d) New stenotic lesion

7 MAE: a) Bilateral flank pain: Extended hospital stay for observation, add. testing was negative b) Renal artery stenosis: Baseline stenosis was 17% based on core lab assessment of angiogram; stenosis at 6M FU; patient received PTA/stent; continues to be monitored c) Access site infection (2 pts.) d) Vomiting e) Hematoma f) Pseudoaneurysm at access site g) Femoral artery thrombus

Source: Clinicaltrials.gov; Press releases; Congress presentations; Medical papers

Annualized Increase in Number and Size of RDN Clinical Trials



* Includes MDT Global Symplicity RSD study with 5,000 planned patients

Source: Clinicaltrials.gov (search terms: “Renal denervation”, “Renal sympathetic denervation”, “RDN”, “RSD”)

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PRESS RELEASE | January 9, 2014, 7:01 a.m. ET

Medtronic Announces U.S. Renal Denervation Pivotal Trial Fails to Meet Primary Efficacy Endpoint While Meeting Primary Safety

Renal denervation: the need for more analysis

January 24, 2014 by admin | Leave a Comment

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Importantly, the guidelines stipulated that before resistant hypertension could be Pic: Hemera Technologies/Getty Images diagnosed, white coat hypertension had to be excluded using ambulatory blood pressure monitoring

Scientific method has overcome fiscal hype over
catheter which could ablate the sympathetic nerv
renal arteries, thereby reportedly reducing blood
pressure where treatment with drugs had failed,
Prof Eoin O'Brien.

A remarkable story of the battle between financial
and scientific reasoning began in January 2011
Medtronic Inc acquired a privately-held company
Inc for $800 million (€585 million), with additional
payments to be related to profit over four years.

Bloomberg
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Medtronic Nerve-Burning Failure Stymies Industry Progress

Heartwire

SYMPLICITY HTN-3 Complicates Renal-D
Field, Say Experts

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Boston Scientific stands fast on renal denervation

(Not So Simple) SYMPLICITY HTN 3
Proposed Mechanisms of Failure to Meet Efficacy Endpoint

- Ineffective Procedure
- Patient Population
- Study Design
- Observer Bias and Regression to the Mean
- Patient Bias and Behavior

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Renal Denervation for Treatment Resistant HTN
Why Might RDN Not Show Benefit?

- Ineffective Procedure
  - Differing methods of RF delivery, differing energy modes
  - Limited predictability of treatment effect
    - Degree of HTN, number of treatments, unilateral vs bilateral
  - No biomarker/surrogate of procedural efficacy
    - What is an acceptable reduction in hypersympathetic activity?
  - Limited understanding of interaction between RDN and physiology

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Is the Reduction in Afferent Activity Following RDN Sustained?

Parameter	Baseline	3 Months	6 Months	12 Months	*P* value
SBP, mm Hg	166 ± 22	154 ± 24	150 ± 27	144 ± 24	<0.001
DBP, mm HG	88 ± 19	82 ± 17	79 ± 16	77 ± 13	<0.001
HR, bpm	66 ± 14	66 ± 14	65 ± 14	67 ± 13	0.66
MSNA, bursts/min	51 ± 11	43 ± 14	45 ± 13	45 ± 15	0.001
MSNA, bursts/100 heartbeats	80 ± 16	69 ± 17	70 ± 16	69 ± 18	<0.001

Hering, Esler, Schlaich et al. Hypertension 2014 *In press*

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Renal Denervation for Treatment Resistant HTN
Why Might RDN Not Show Benefit?

- Ineffective Procedure
- Patient Population
  - Expansion to broader, less selected population suggests less robust but still meaningful treatment effect
  - No clear insights to subgroups of particular interest: diabetes, CKD, non-Caucasian

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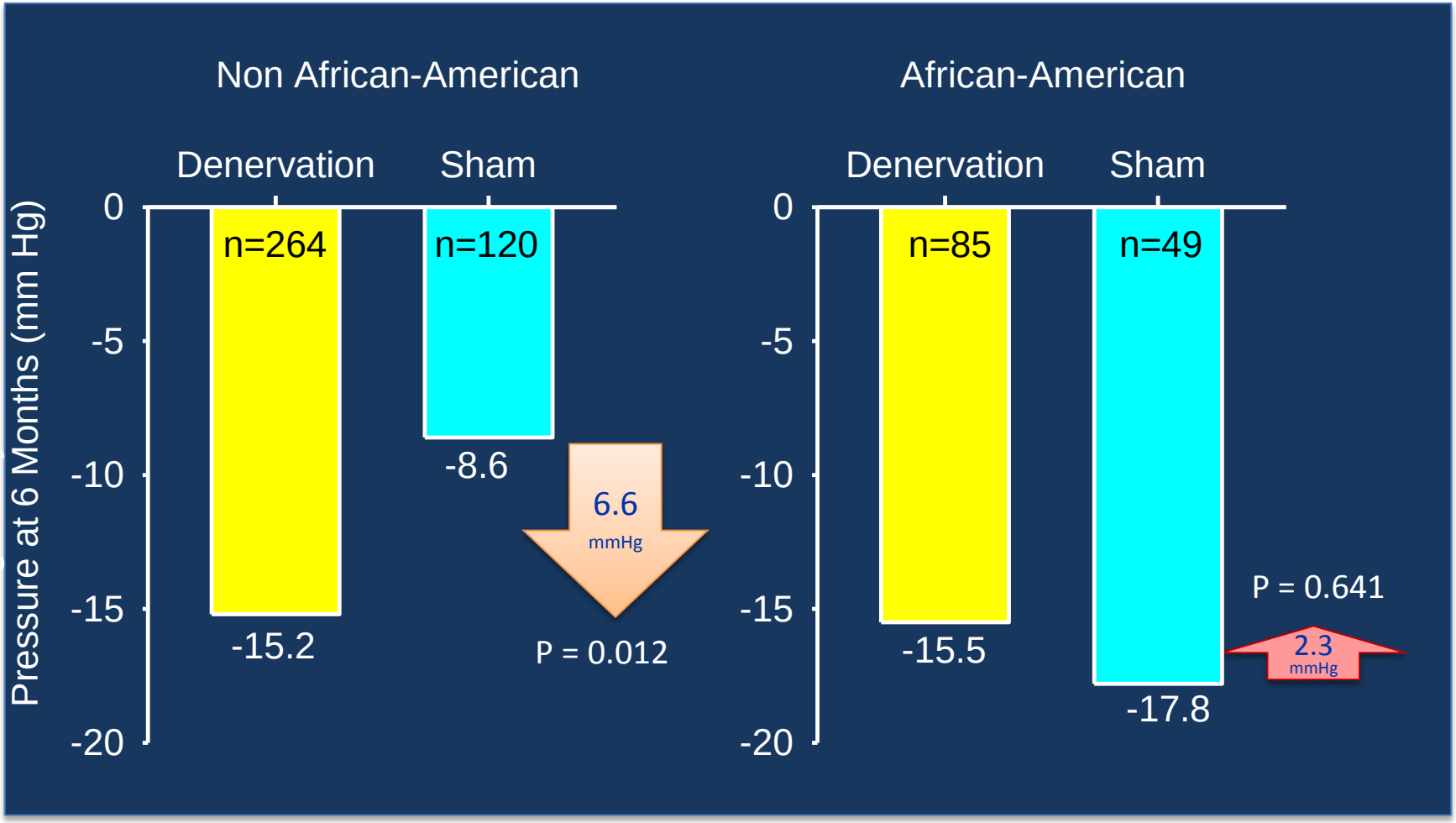
Blood Pressure Changes Among Pre-specified Subgroups in SYMPLICITY HTN 3



Medtronic Data on File

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Renal Denervation for Treatment Resistant HTN
Why Might RDN Not Show Benefit?

- Ineffective Procedure
- Patient Population
  - Expansion to broader, less selected population suggests less robust but still meaningful treatment effect
  - No clear insights to subgroups of particular interest: diabetes, CKD, non-Caucasian
  - Impact of medications, medication changes and compliance

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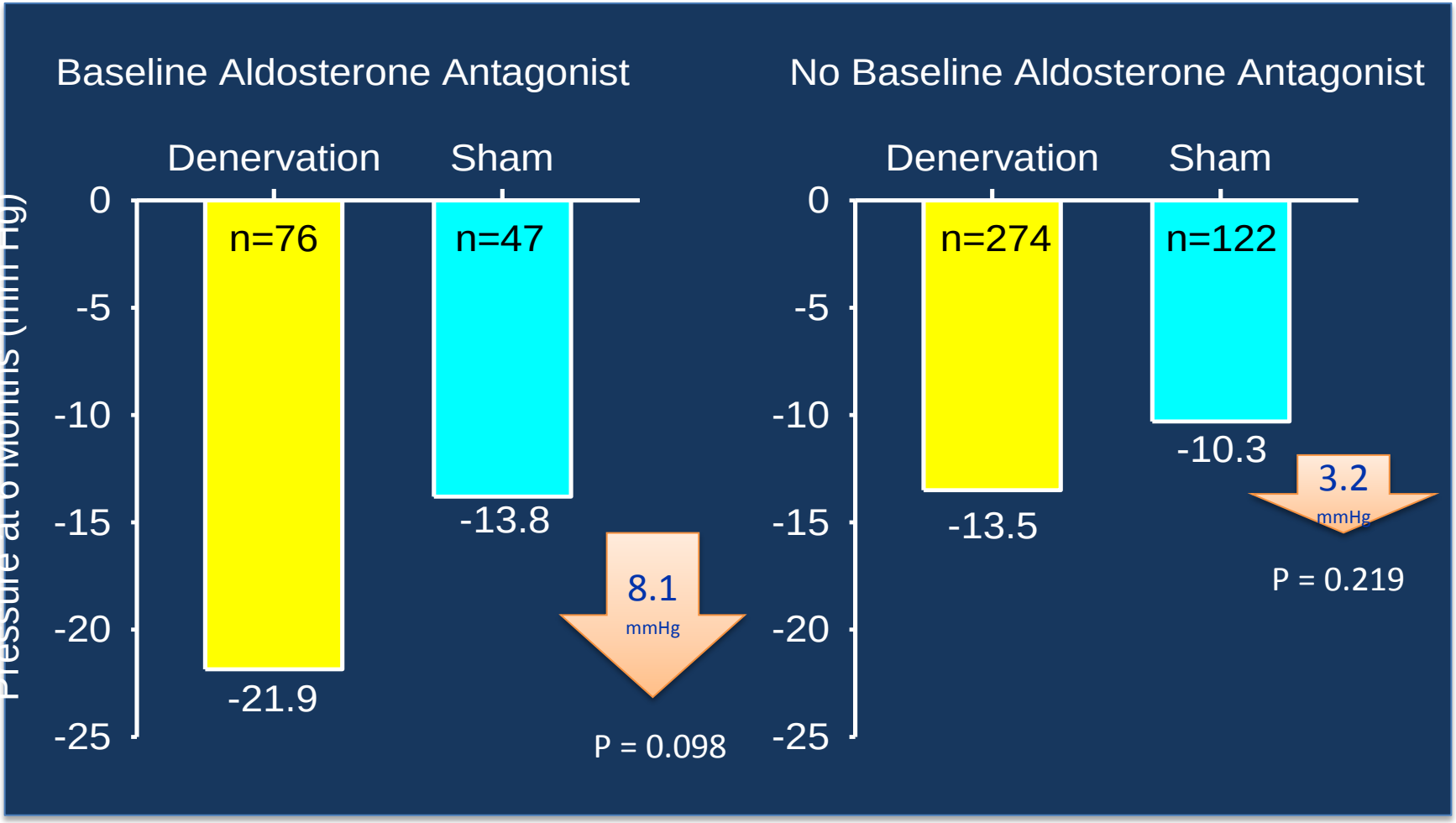
Blood Pressure Changes Among Pre-specified Subgroups in SYMPLICITY HTN 3



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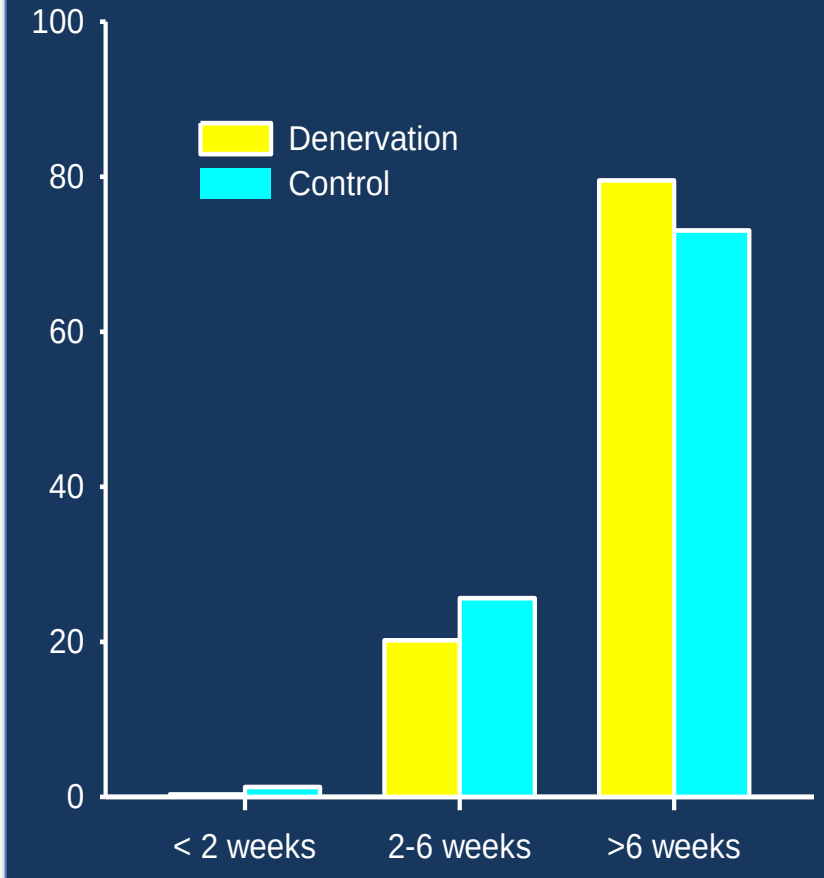
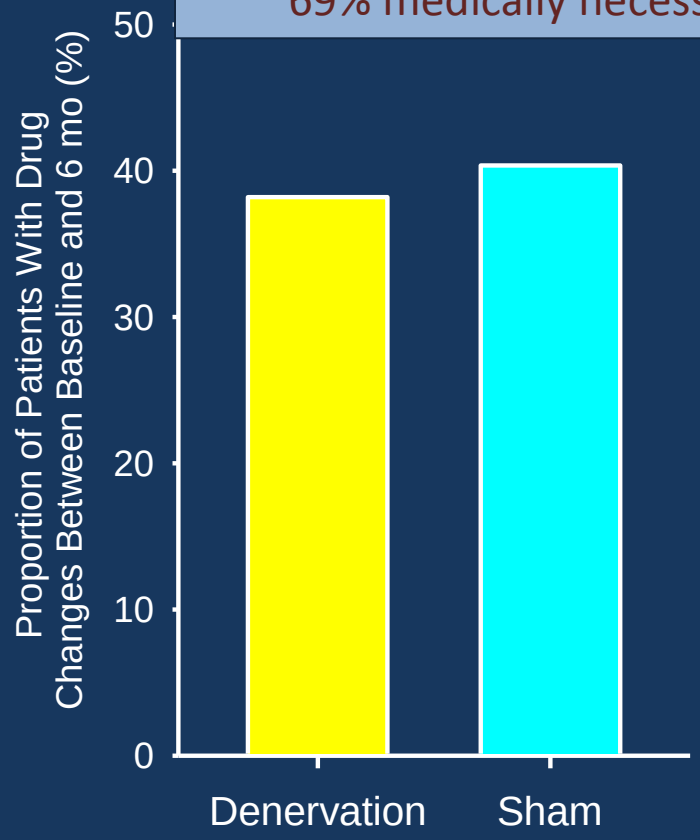
Medication Changes Pre- and Post Randomization in HTN 3

~ 80% on stable regimen 6 weeks prior to randomization



~ 40% required med changes before 6 month endpoint
69% medically necessary



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Renal Denervation for Treatment Resistant HTN
Why Might RDN Not Show Benefit?

- Ineffective Procedure
- Patient Population
- Study Design

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Comparison of HTN-2 and HTN-3 Trial Designs

	HTN 2 N=106	HTN 3 N=530
Randomized	✓	✓
Patient Blinded	✗	✓
F/U Assessor Blinded	✗	✓
ABPM SBP ≥ 135 mm Hg required?	✗	✓
Stable drug 3+ regimen with no changes ≥2 weeks prior to enrollment	✓	✓
Omron BP machine with printer	✓	✓
Randomize after angiogram	✓	✓
Escape medications	✓	✓
2 office visits prior to randomization	✓	✓
New investigators	✓ / ✗	✓

Renal Denervation for Treatment Resistant HTN
Why Might RDN Not Show Benefit?

- Ineffective Procedure
- Patient Population
- Study Design
- Observer Bias and Regression to the Mean

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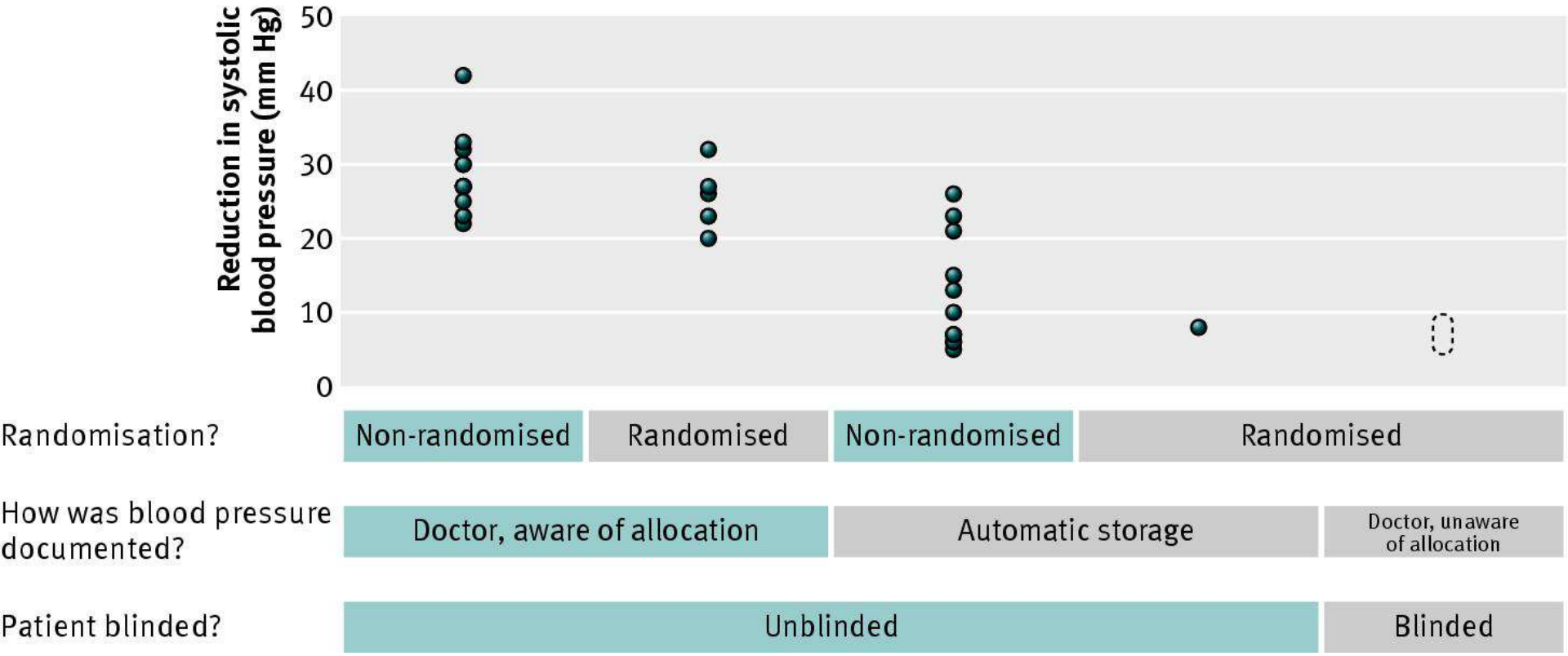
Removing the hype from hypertension

Symplicity HTN-3 illustrates the importance of randomisation and blinding for exciting new treatments

Matthew J Shun-Shin *academic clinical fellow in cardiology*, James P Howard *academic clinical fellow in cardiology*, Darrel P Francis *professor of cardiology*



Shun-Shin, Howard, Francis. BMJ 2014

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Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Unintentional overestimation of an expected antihypertensive effect in drug and device trials: Mechanisms and solutions

James P. Howard [a,*], Graham D. Cole [a], Horst Sievert [b], Deepak L. Bhatt [c], Vasilios Papademetriou [d], David E. Kandzari [e], Justin E. Davies [a], Darrel P. Francis [a]

- Office pressure drops may be artifactually larger than ambulatory drops in renal denervation trials because of either overestimation of baseline office pressures, or underestimation
  - Overestimate: patients are selected on the basis of exceeding a threshold on any marker that naturally fluctuates with time ('regression to the mean')
  - Underestimation of final office pressures may be explained by observer bias ('check once more')
  - Patient knowledge of treatment status may impact compliance

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Catheter-Based Renal Denervation for Treatment Resistant HTN
Why Might RDN Not Show Benefit?

- Ineffective Procedure
- Patient Population
- Study Design
- Observer Bias and Regression to the Mean
- Patient Bias and Behavior

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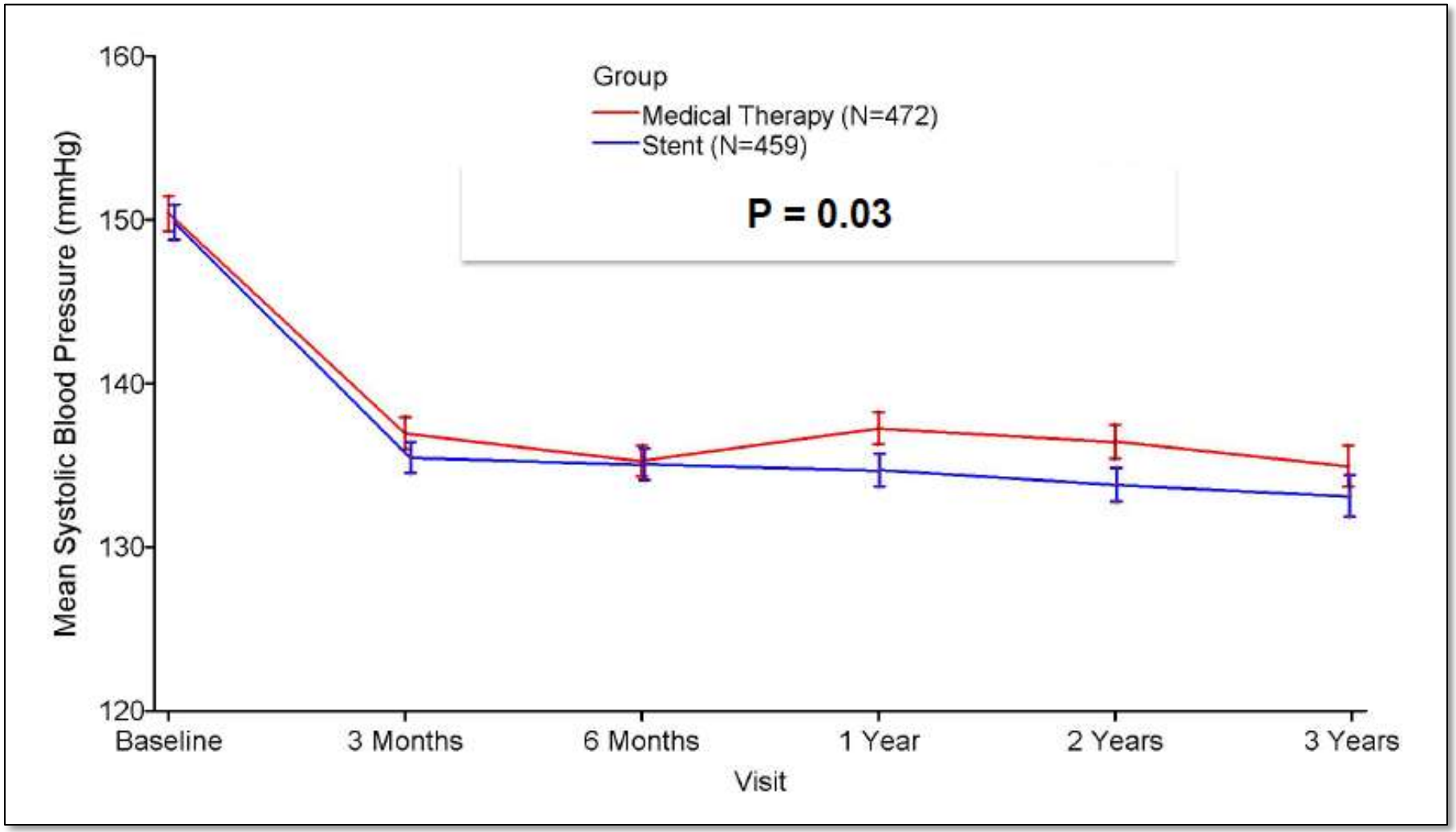
CORAL Trial
Differentiating “Sham” vs “Placebo” Effect



Cooper et al. NEJM 2013

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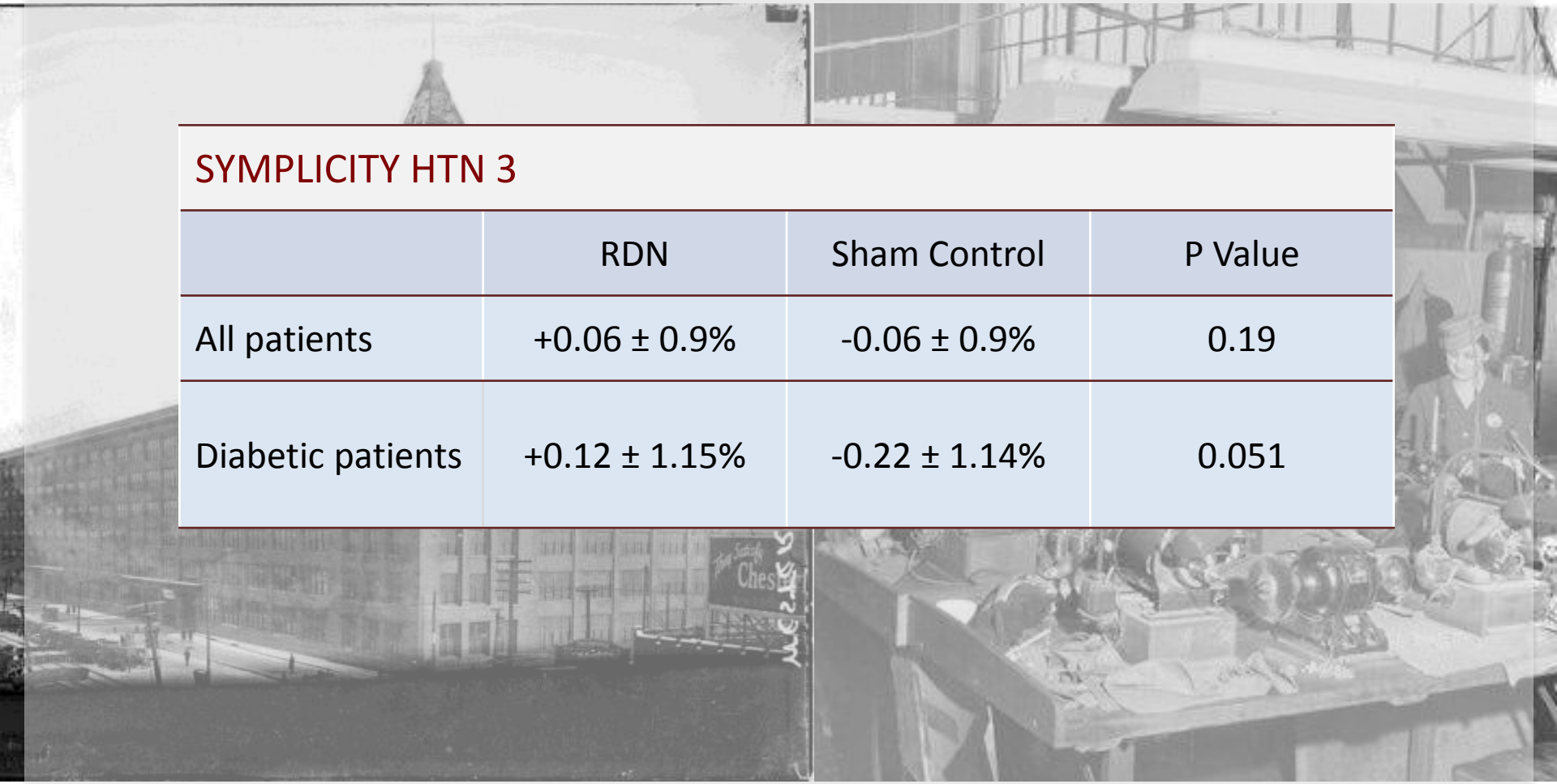
Impact of Clinical Trial Participation on Patient Behavior and Outcomes
Hawthorne Effect



SYMPLICITY HTN 3

	RDN	Sham Control	P Value
All patients	+0.06 ± 0.9%	-0.06 ± 0.9%	0.19
Diabetic patients	+0.12 ± 1.15%	-0.22 ± 1.14%	0.051

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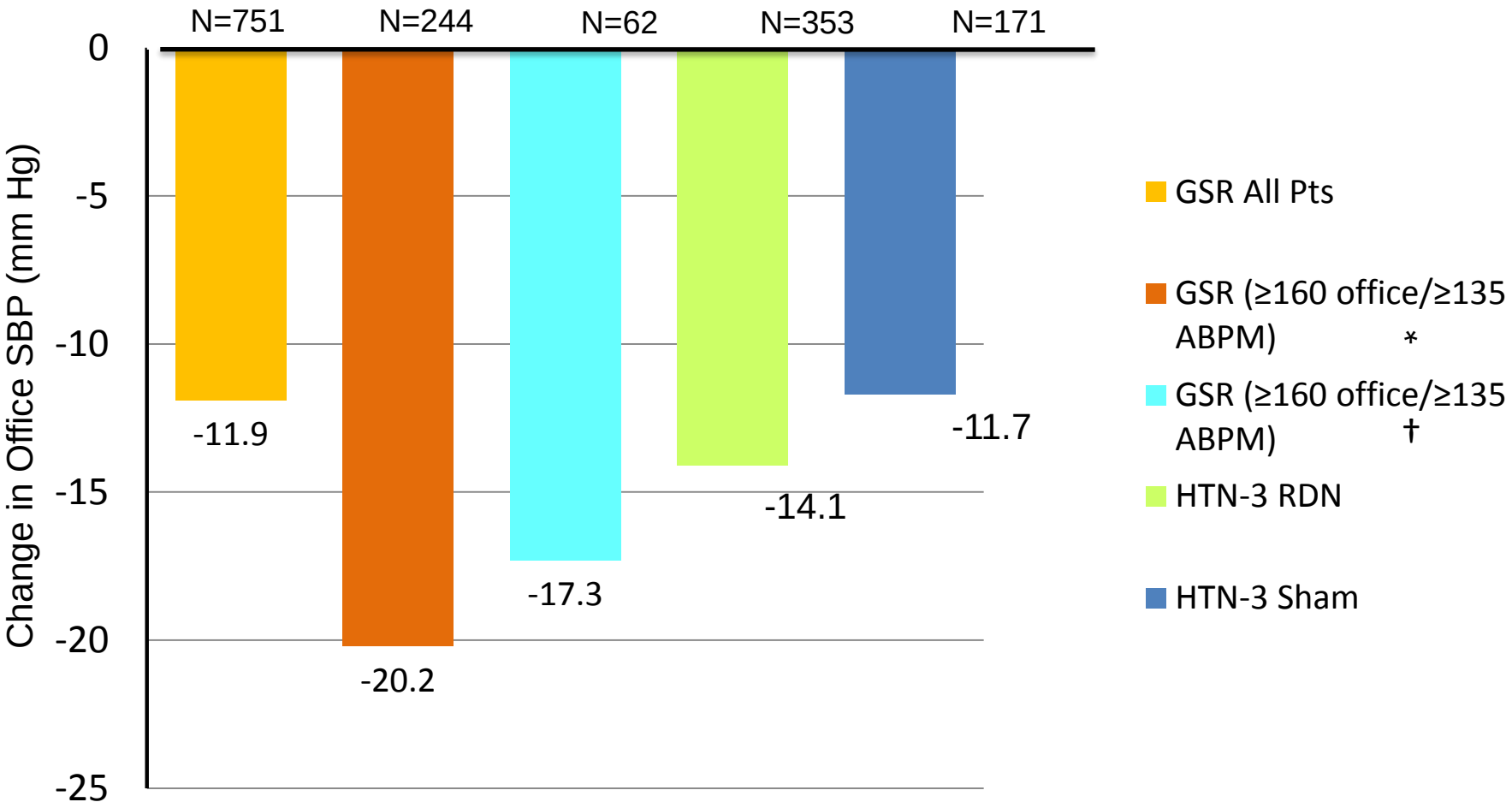
Change in Office SBP at 6 Months in GSR and SYMPLICITY HTN 3



*with ≥3 antihypertensive medication classes
† with ≥3 antihypertensive meds at maximum tolerated dose

Bhatt et al. NEJM 2014; Bohm ACC 2014

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Predictors of Blood Pressure Response in GSR and HTN 3 Trials

SYMPLICITY HTN-3 RDN Arm - Multivariate Predictors of Office SBP Change at 6-Months

318 Subjects Included in Analysis

Covariate	Estimate	Standard Error	P Value
Baseline Office SBP at >= 180	**-14.31089**	**2.51207**	**<0.0001**
Total Number of Attempts	**-0.93574**	**0.45352**	**0.0399**
Aldosterone Antagonist	**-9.77411**	**3.08819**	**0.0017**
Vasodilator	**7.55107**	**2.6362**	**0.0045**

GSR Severe Resistant HTN Subset* - Multivariate Predictors of Office SBP Change at 6-Months

220 Subjects Included in Analysis

Covariate	Estimate	Standard Error	P Value
Baseline OSBP ≥ 180	**-17.17156**	**2.76427**	**<0.0001**
Male gender	**-5.15111**	**2.76947**	**0.0643**
Age < 65	**-5.89746**	**2.65917**	**0.0276**
Total Number Attempts	**-0.77441**	**0.32516**	**0.0181**
Calcium Channel Blocker use	**5.39727**	**3.19859**	**0.0930**
Vasodilator use	**7.11995**	**3.51914**	**0.0443**

** OSBP ≥ 160, ABPM ≥ 135, # Medication Classes ≥ 3*

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Catheter-Based Renal Denervation
Future Perspectives

- Effectiveness of RDN cannot be measured by a singular trial and may not be extrapolated to other denervation methods
  - Oversimplification to assume a singular therapy to uniformly treat a heterogeneous disease condition
- Need to revisit physiology and identify practical measures of effective sympathetic interruption
- Forthcoming evaluation of RDN for treatment resistant HTN will require careful trial design that:
  - Demonstrates biologic efficacy, and
  - Differentiates potential confounders of observer and patient bias
  - Focus on less variable and more independent endpoints (*eg*, ABPM)
- RDN in clinical practice should be applied judiciously and in context of dedicated follow-up of outcomes
- Studies examining pleitropic effects of reducing sympathetic signature must and will be held to same standard and ideally be supported independent of BP lowering

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