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Renal Denervation and Treatment of Hypertension: Clinical Update

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Disclosures

Physician name	Company	Relationship
Horst Sievert	Abbott, Access Closure, AGA, Angiomed, Aptus, Atrium, Avinger, Bard, Boston Scientific, Bridgepoint, Cardiac Dimensions, CardioKinetix, CardioMEMS, Coherex, Contego, Covidien, CSI, CVRx, EndoCross, ev3, FlowCardia, Gardia, Gore, Guided Delivery Systems, InSeal Medical, Lumen Biomedical, HLT, Lifetech, Lutonix, Maya Medical, Medtronic, NDC, Occlutech, Osprey, Ostial, PendraCare, pfm Medical, Recor, ResMed, Rox Medical, SentreHeart, Spectranetics, SquareOne, Trireme, Trivascular, Venus Medical, Veryan, Vessix	Consulting fees, Travel expenses, Study honoraria
	Cardiokinetix, Access Closure, Lumen Biomedical, Coherex, SMT	Stock options, Stocks
	Cook, St. Jude Medical	Grant Research Support

At the time
when this session
was planned:

Renal denervation
was one of the most promising
new treatment options

Renal denervation

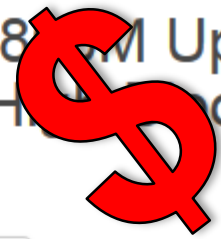
- Had shown very impressive acute and long-term results in resistant hypertension
- It had shown promising initial results in many other diseases
 - Heart failure
 - Diabetes
 - Sleep apnea
 - Arrhythmias
 -

Even before these results became available,

The deal involves payments based on milestones. The deal includes milestone-based payments equal to annual revenue growth over the next four and a half years, the statement said.

1.4 billion

Medtronic Buys Ardian for \$800M Upfront, Grabs Novel Treatment for High Blood Pressure



Luke Timmerman | 11/23/10 | Follow @luke_timmerman

It didn't take **Ardian** long to cash in. It showed the world what it really has come up with for the treatment of high blood pressure.

Medical device giant **Medtronic** (NYSE: **MDT**) said it has agreed to pay \$800 million upfront, plus commercial milestone payments through 2014 to acquire Mountain View, CA-based Ardian. Medtronic had previously built up an 11 percent ownership stake in Ardian, when it invested with its venture backers, which include Morgenthaler Ventures, Advanced Technology Ventures, Split Rock Partners, and Emergent Medical Partners.

Ardian's windfall comes about one week after it presented some eye-opening clinical trial results in *The Lancet*, and at the American Heart



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Millions of people
all over the world

... including myself ...

... had been very sad
that they did not have
Ardian stocks

At the time
when I received the
assignment for this lecture:

A surprising press release had
caused a little earthquake:



Medtronic

NEWS RELEASE

Everybody involved in renal denervation will remember forever where he was when this message did come out

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FOR IMMEDIATE RELEASE

**MEDTRONIC ANNOUNCES U.S. RENAL DENERVATION
PIVOTAL TRIAL FAILS TO MEET PRIMARY EFFICACY ENDPOINT
WHILE MEETING PRIMARY SAFETY ENDPOINT**

MINNEAPOLIS – January 9, 2014 – Medtronic, Inc. (NYSE: MDT) today announced that its U.S. pivotal trial in renal denervation for treatment-resistant hypertension, SYMPPLICITY HTN-3, failed to meet its primary efficacy endpoint. The trial met its primary safety endpoint, and the trial’s Data Safety Monitoring Board (DSMB) concluded that there were no safety concerns in the study.

Millions of people
all over the world

... including myself ...

... had been very happy that
they did not have
Medtronic stocks

And everybody....

... including those who had been
against renal denervation from the
beginning...

... asked:

“How could this happen?”

Renal nerves and renal denervation did not come out of the Blue

- Histology findings
- Animal data
- Surgical experience
- Clinical experience
- Results from prospective controlled clinical trials

So there is little doubt
that renal denervation as
a concept is working

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

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D.,
William W. O'Neill, M.D.,
M. Flack, M.D., M.P.H., B
Leon, M.D., Minglei Liu, F
Manuela Negoita, M.D.,
Suzanne Oparil, M.D.,
Raymond R. Townsend,
for the SYMPLIC

The NEW ENGLAND JOURNAL of MEDICINE

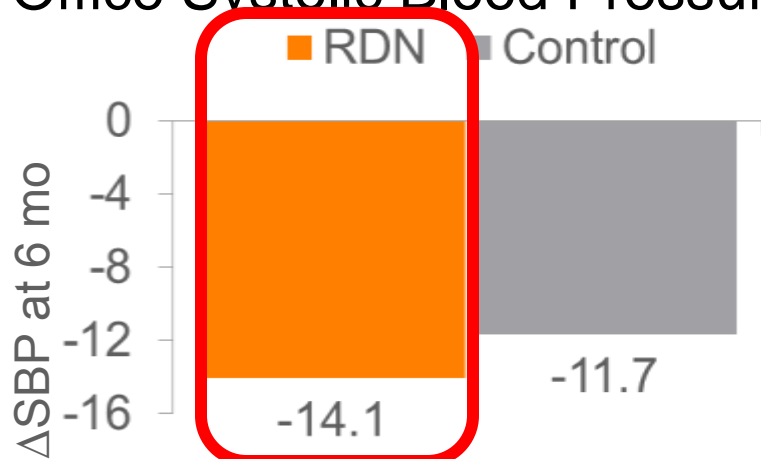
ORIGINAL ARTICLE

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., and George L. Bakris, M.D.,
for the SYMPLICITY HTN-3 Investigators*

Primary Efficacy Endpoint

Office Systolic Blood Pressure at 6 Months, 5 mm Superiority Margin



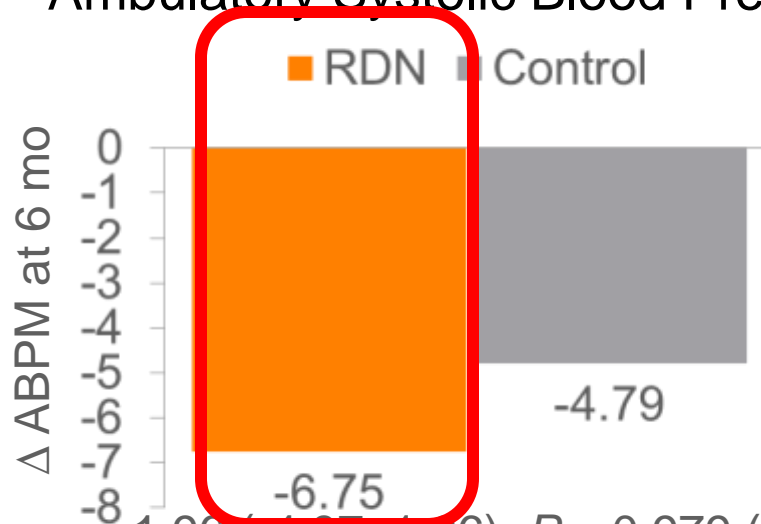
	RDN	Control	P value
Baseline SBP	179.7	180.2	0.765
6 mo SBP	165.6	168.4	0.260

Change -14.1 -11.7 0.255¹
 P < 0.001 P < 0.001

-2.39 (-6.89, 2.12), P = 0.255 (Primary analysis with 5 mm Hg superiority margin)

Secondary Efficacy Endpoint

Ambulatory Systolic Blood Pressure at 6 Months, 2 mm Superiority Margin



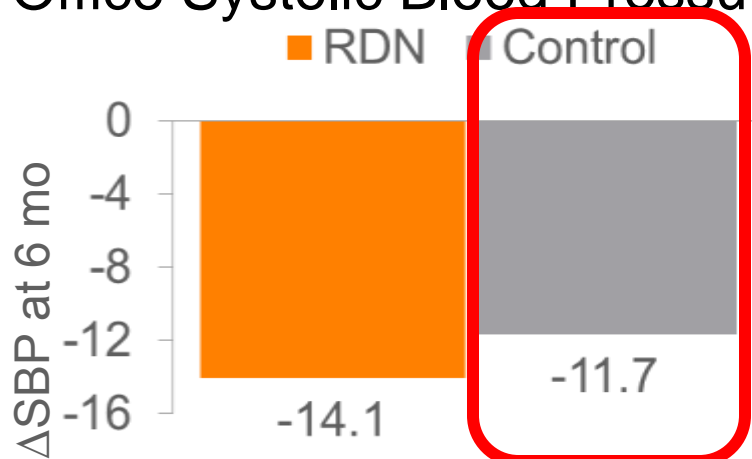
	RDN	Control	P value
Baseline SBP	158.55	158.85	0.828
6 mo SBP	151.80	154.05	0.201

Change -6.75 -4.79 0.979
 P < 0.001 P < 0.001

-1.96 (-4.97, 1.06), P = 0.979 (ITT analysis with 2 mm Hg superiority margin)

Primary Efficacy Endpoint

Office Systolic Blood Pressure at 6 Months, 5 mm Superiority Margin



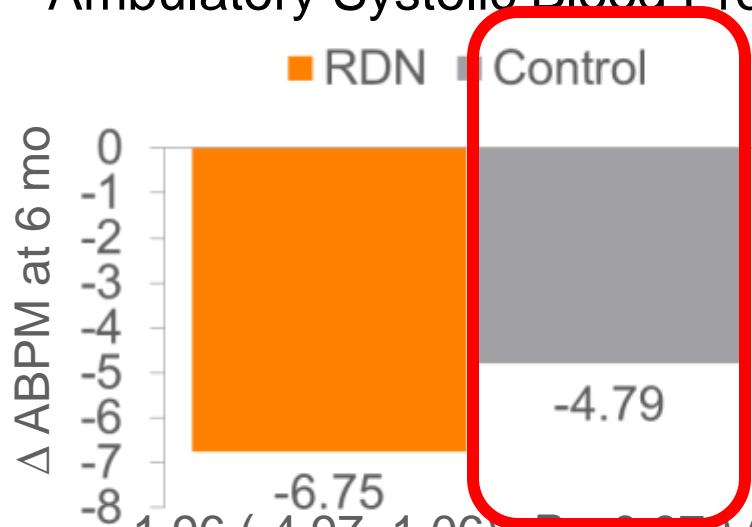
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Why did BP go down in the control group?

- Placebo?
 - Possible but not very likely!
 - There is no placebo effect on ABPM
 - There was no placebo effect on BP in renal stenting studies
- What else?
 - Stable meds period before randomization too short
 - Compliance issues with antihypertensive meds
 - Life style changes during the trial
 - Patients did not have resistant hypertension

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HTN 3 Patient Selection

Catheter-Based Renal Denervation for Resistant Hypertension: Rationale and Design of the SYMPPLICITY HTN-3 Trial

David E. Kandzari, MD; Deepak L. Bhatt, MD, MPH; Paul A. Sobotka, MD; William W. O'Neill, MD; Murray Esler, MBBS, PhD; John M. Flack, MD, MPH; Barry T. Katzen, MD; Martin B. Leon, MD; Joseph M. Massaro, PhD; Manuela Negoita, MD; Suzanne Oparil, MD; Krishna Rocha-Singh, MD; Craig Straley; Raymond R. Townsend, MD; George Bakris, MD

..... individuals (1) with an average office SBP ≥ 160 mm Hg, and (2) receiving a **stable** antihypertensive treatment regimen (ie, without change in dose or medication) for at **least 2 weeks** prior to enrollment.

“stable and optimized”

- i.e. medication changes could (and did) occur until 2 weeks before randomisation
- Until then, medication was “optimized”
- However, antihypertensive drugs result in a stable BP only after 2 months
 - Patients (in both treatment groups) had been on a decline of there blood pressure
 - This may have overshadowed any treatment effect of renal denervation

Daily life example

- There is no question that rain does make people wet
- There is also no question that umbrellas protect people against becoming wet
- So if it rains and one study participant does have an umbrella and the other one not, #1 will stay dry and #2 will become wet
- But if both are standing under a roof, both will stay dry and we will not see any effect of the umbrella

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 - **Compliance issues with antihypertensive meds**
 - Life style changes during the trial
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Compliance issues

Enrolment into HTN 3 was difficult

- Difficult for centers to find enough patients
- Many patients wanted to participate because they wanted to get away from their meds
- Difficult for patients to fulfill the entrance criteria
 - During the screening period, patients may have reduced their meds in order to become eligible
 - During the study (and again 2 weeks before the end of the study) patients were enforced to take their meds
- Many patients participated in the study, because they wanted to reduce meds
 - If there was a treatment effect patients could have reduced their meds without telling

Daily life example

- Initially, study participants did not stay below the roof
 - and got wet
- Later, they went under the roof
 - Therefore, there was no additional benefit of using an umbrella

Why did BP go down in the control group?

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Hawthorne effect

Patients may change
their behavior
if they feel being
observed in a trial

Daily life example

- Study participants stayed at home
- No need for (and no expected benefit from) an umbrella or a roof

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Otherwise BP would not have decreased in the control group

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- A full dose of antihypertensive medication must be documented as
- the highest dose per product labeling or treatment guidelines,
 - or highest tolerated
 - or appropriate dose per the investigator's best judgment.

This allowed to enrol patients who in fact had not resistant hypertension

Daily life example

- It did not rain

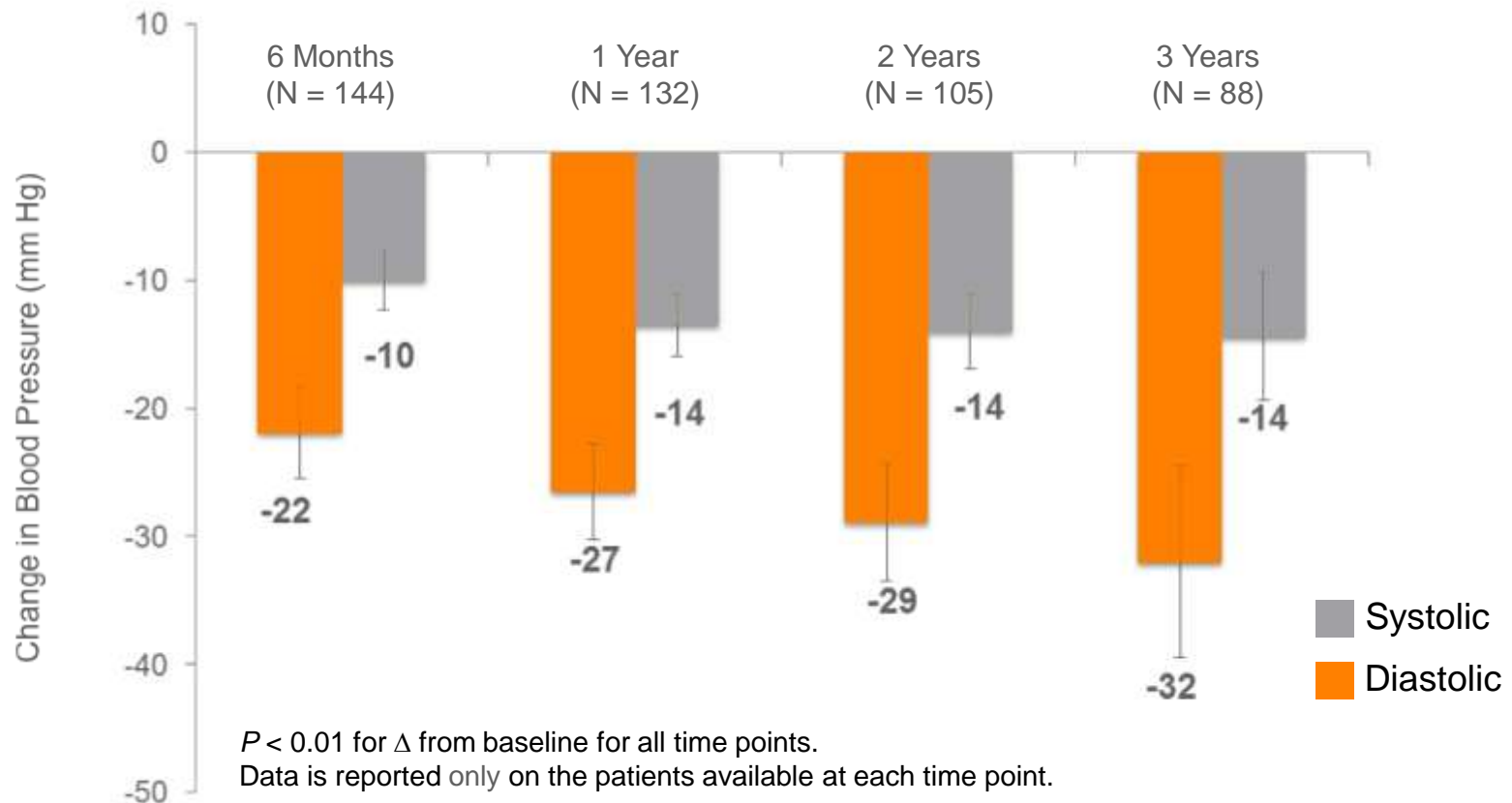
Other potential reasons why HTN 3 failed

- Follow-up too short?
 - We know from other trials that there had been many “late-responders” beyond 6 months
- Patient selection?
 - Are North-Americans different?
 - Or their lifestyle?
- Question of technique?
 - Is the Symplicity catheter not good enough?
 - Is there a learning curve?

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SYMPPLICITY HTN-1: Significant, Sustained BP Reduction to 3 Years



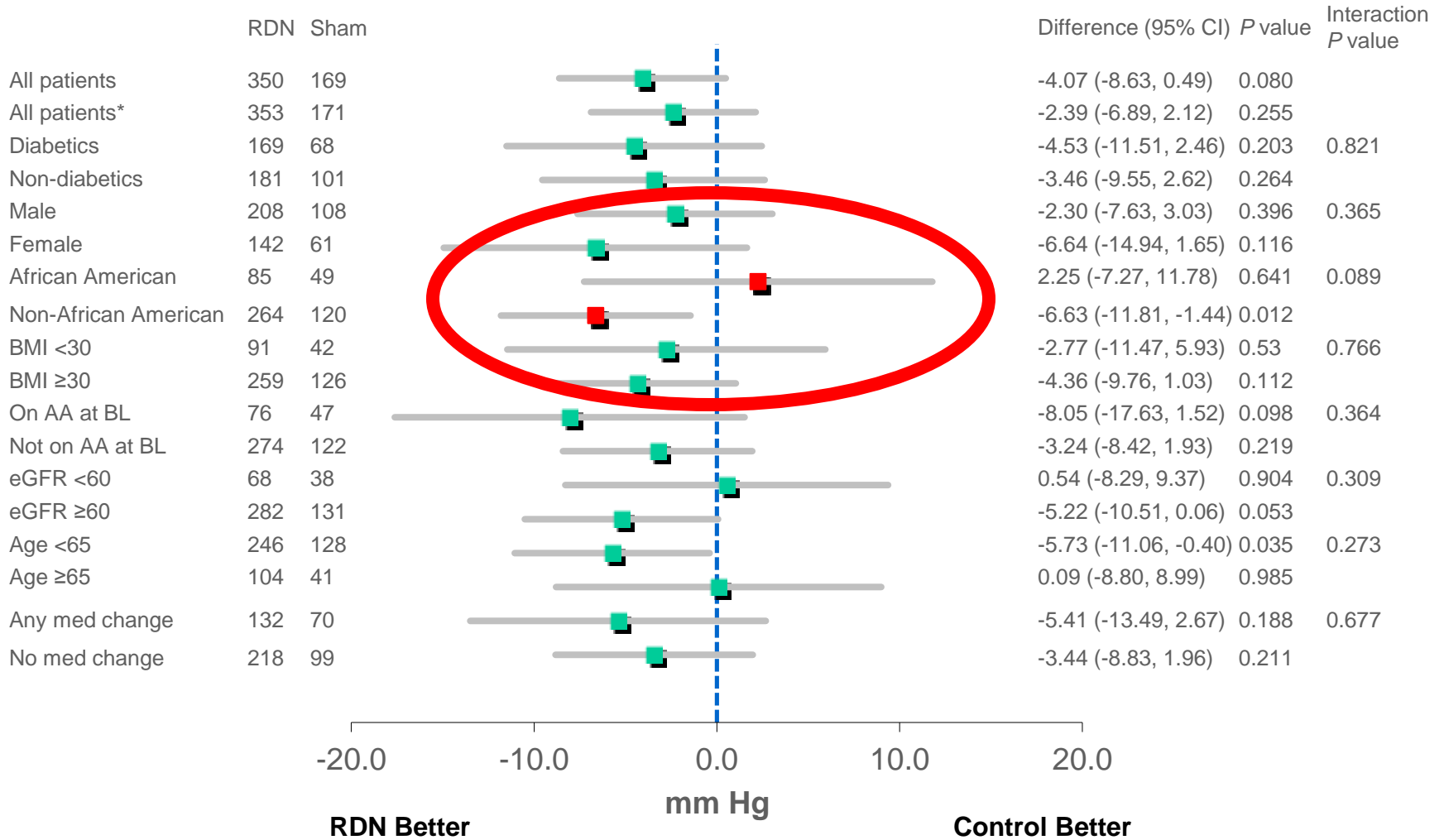
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HTN 3 Demographics

Characteristic (Mean ± SD or %)	Renal Denervation (N = 364)	Sham Procedure (N = 171)	<i>P</i>
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-h 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/1.73 m 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

Pre-Specified Subgroup Analysis

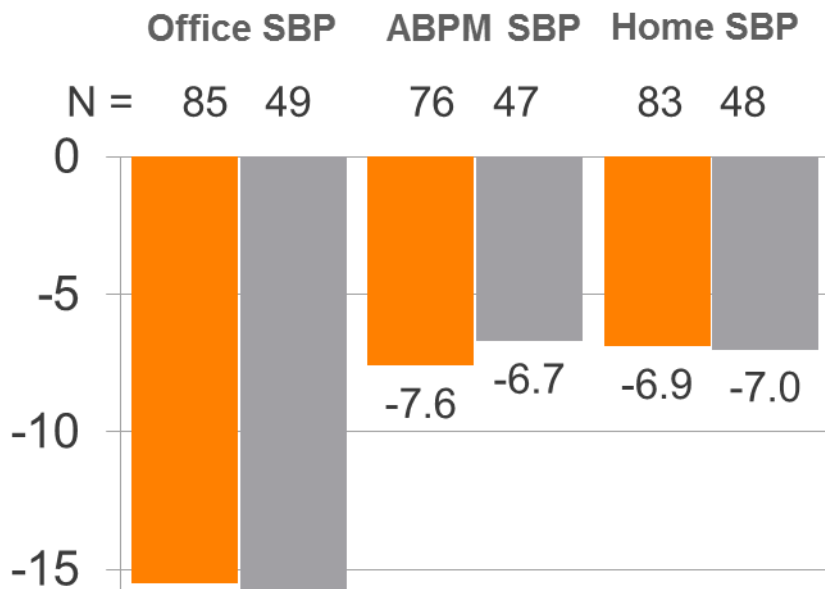


* ITT population, 5 mm Hg superiority margin test .

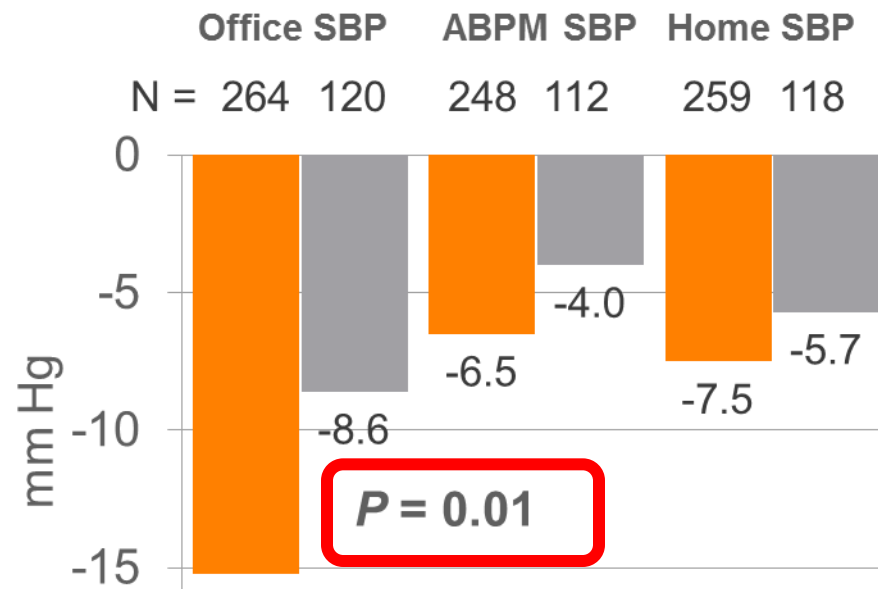
HTN-3:

Different Control Response in African American Population

African Americans



Non-African Americans



**Including non-African Americans
only could have made
a positive trial !!**

Other potential reasons why HTN 3 failed

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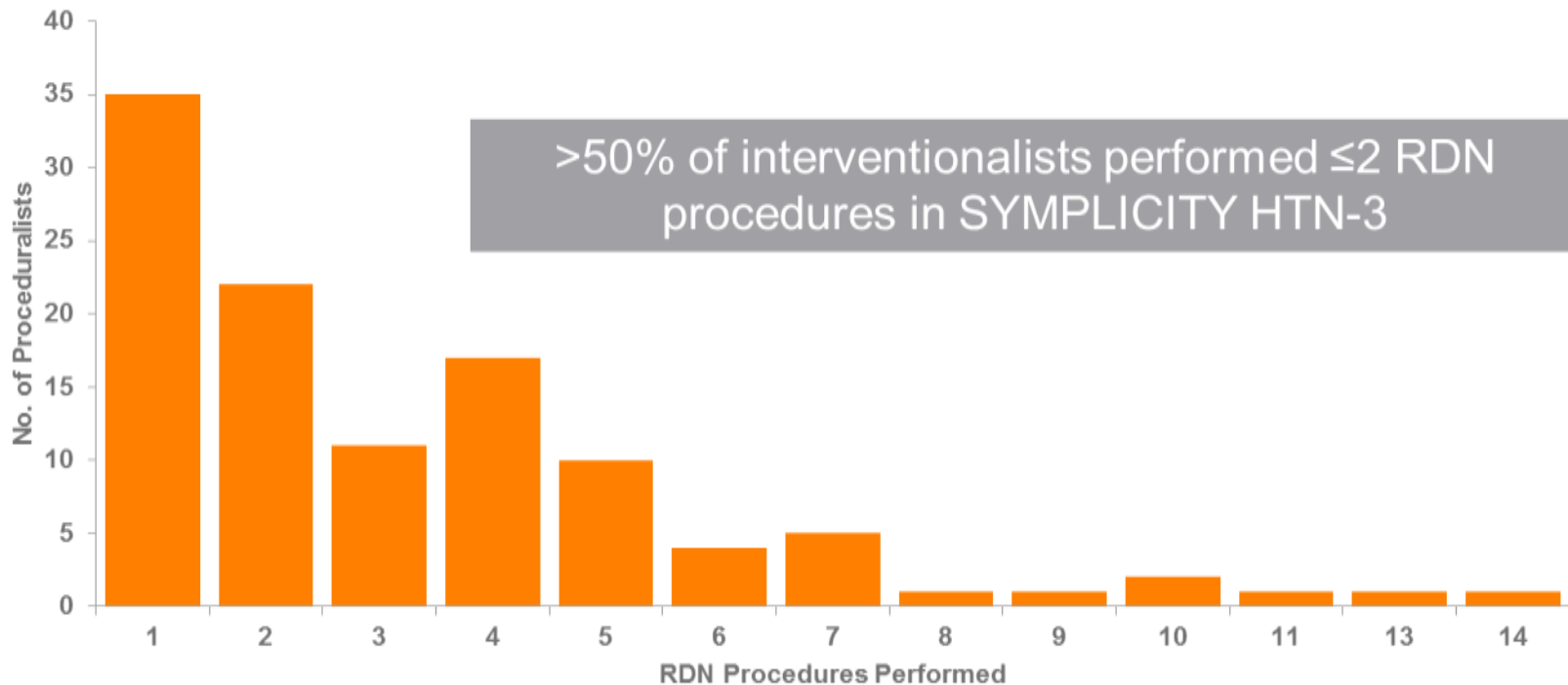
Potential device issues

- Differences between the 1st gen device (Arch) and the 2nd gen device (Flex)?
- Other devices may deliver the energy
 - deeper into the vessel wall
 - more consistently

Heterogeneity of US Operator 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



So what was fake?

Renal Denervation or HTN 3?

- We do not know yet
- HTN 3 has to be further analysed
- At the end the take home message could be that randomized sham controlled trials are very important in order to discover the truth
- But it could also be that they may be very misleading
 - because randomization and sham alone does not guarantee a meaningful study

Thank you!

TRENDS 2015

FEBRUARY 6–7, 2015 | FRANKFURT, GERMANY



Baro- and Chemoreceptor Manipulation
Renal Denervation
Device Based Treatment of Hypertension
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