A Tale of Two Studies: Symplicity HTN-2 and 3.

Is it the Best of Times or the Worst of Times?

TCTAP Seoul April 24, 2014

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A Tale of Two Cities

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Renal Denervation for Resistant Hypertension

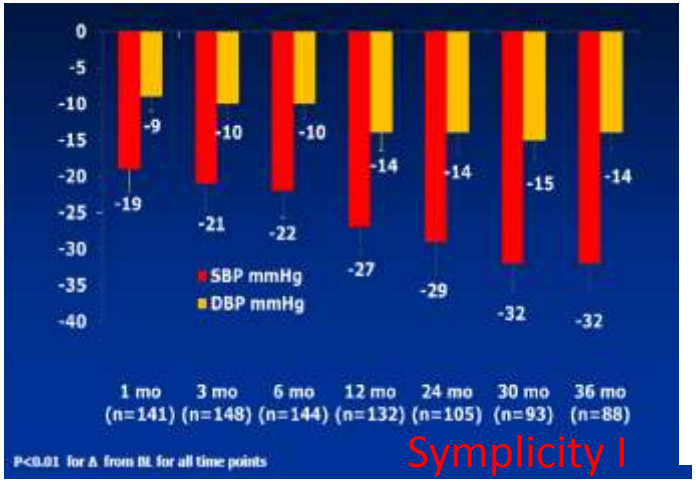
Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O'Neill, M.D., Ralph D'Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna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

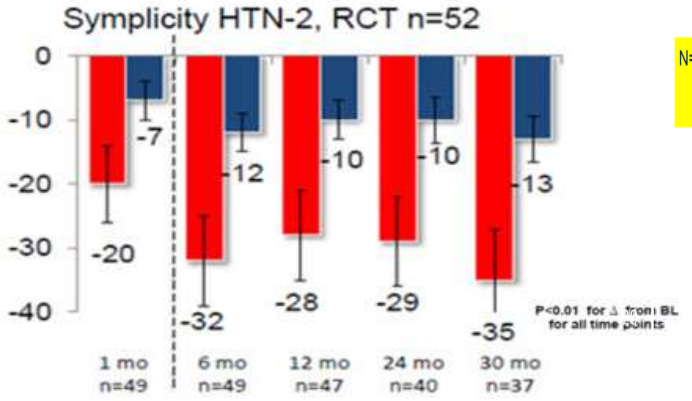
Best of Times

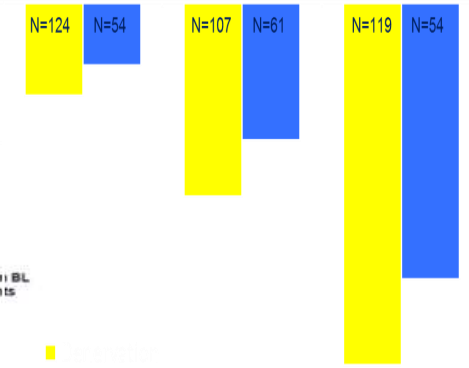
- Symplicity HTN-1 shows better than expected results.
- Symplicity HTN-2 is positive with a p value < .0001
- Studies from a host of early stage companies using various renal denervation techniques are all able to replicate Symplicity data.

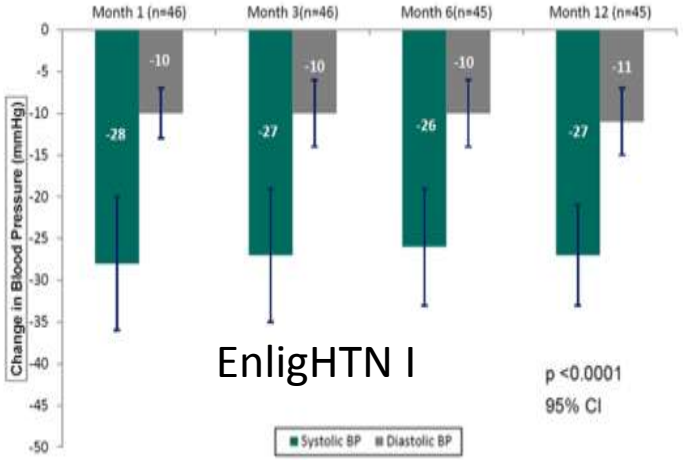
Worst of Times

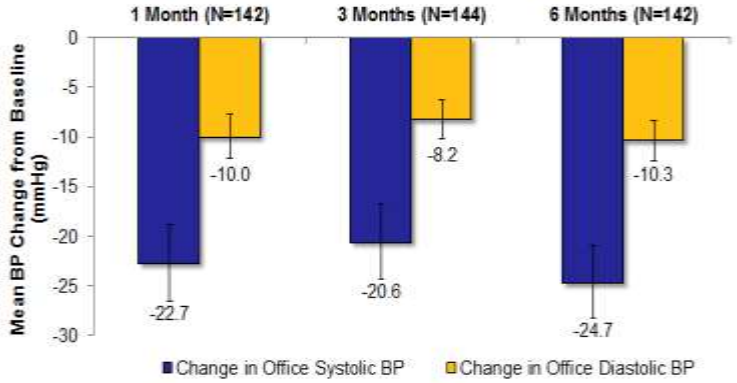
- Symplicity HTN-3 fails to meet primary endpoint.
- Presentation at ACC14 is widely applauded.
- Study results are accepted without question despite the fact that they run contrary to results of all other studies to date.
- Study design is heralded as the template for all future renal denervation studies and possibly studies of all future medical devices.





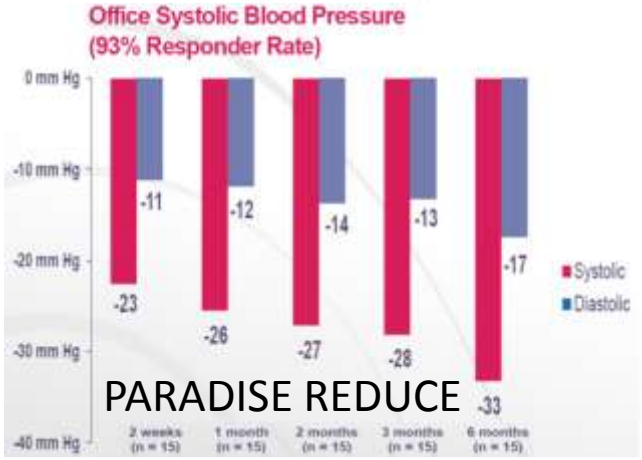


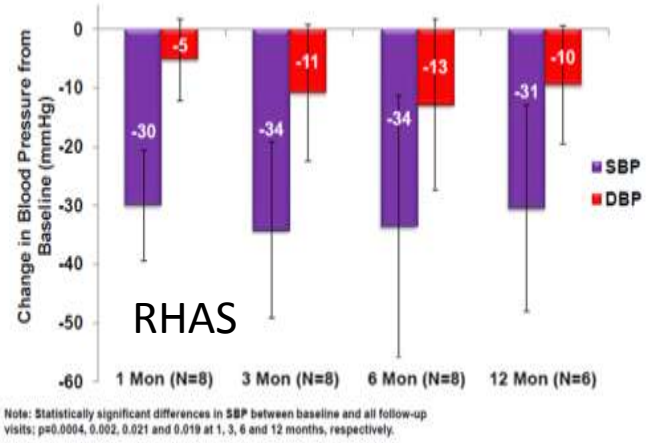




P<.0001 for each timepoint vs baseline.
Error bars represent 95% confidence bounds.

REDUCE HTN





Note: Statistically significant differences in SBP between baseline and all follow-up visits: p≤0.0004, 0.002, 0.021 and 0.019 at 1, 3, 6 and 12 months, respectively.

Symplicity HTN-2


THE LANCET

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

Symplicity HTN-2 Investigators*

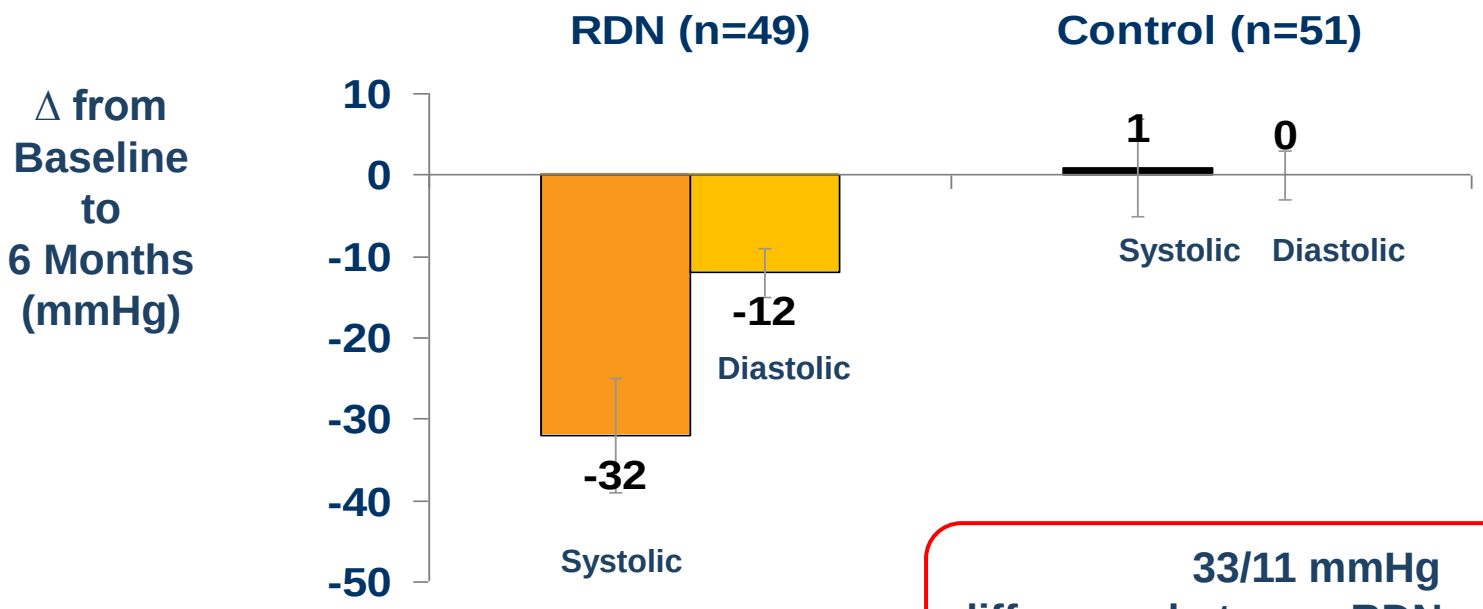
Lancet. 2010;376:1903-1909

- **Study design:** randomized, controlled, clinical trial
- **Patients:** 106 patients randomized 1:1 to treatment with renal denervation vs. control
- **Clinical Sites:** 24 centers in Europe, Australia, & New Zealand

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

Symplicity HTN-2

Primary Endpoint: 6-Month Office BP

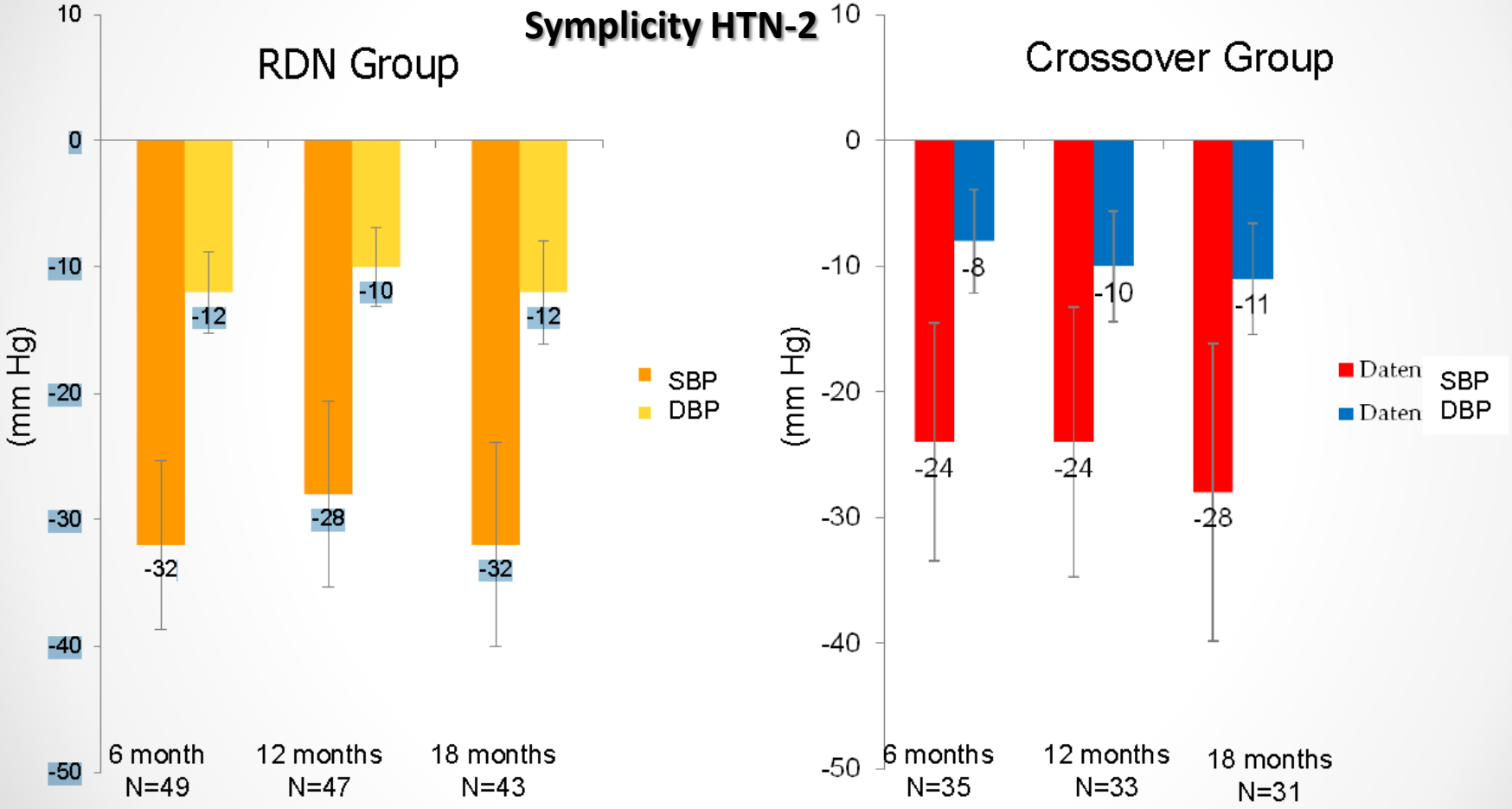


33/11 mmHg difference between RDN and Control (p<0.0001)

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

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

Change in Office Blood Pressure Through 18 Months*



P-values < 0.01 at each time point
compared to pre procedure values for each group

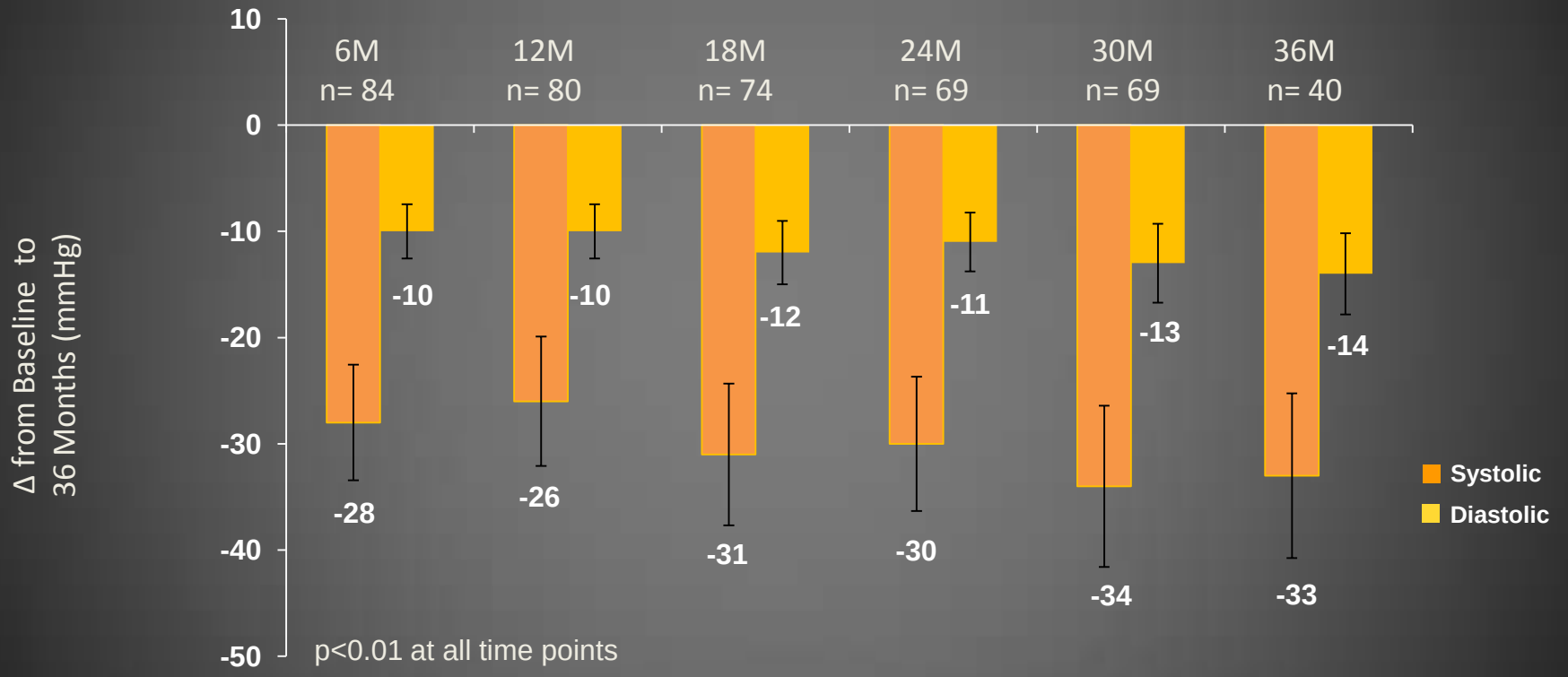
*Post Procedure follow up

From presentation by Michael Böhm

Vessix™
Renal Denervation System

Symplicity HTN-2: BP Reductions Sustained to 3 Years*

Sustained Reductions in the Pooled (RDN and Crossover) Group**



* Reference: Symplicity HTN-2 Investigators. Renal sympathetic denervation in patients with treatment-resistant hypertension. *The Lancet*. 2010; 376: 1903–1909. Expanded results presented at the Transcatheter Cardiovascular Therapies annual meeting 2013

** Only patients in the RDN group reached the 36 month follow up visit

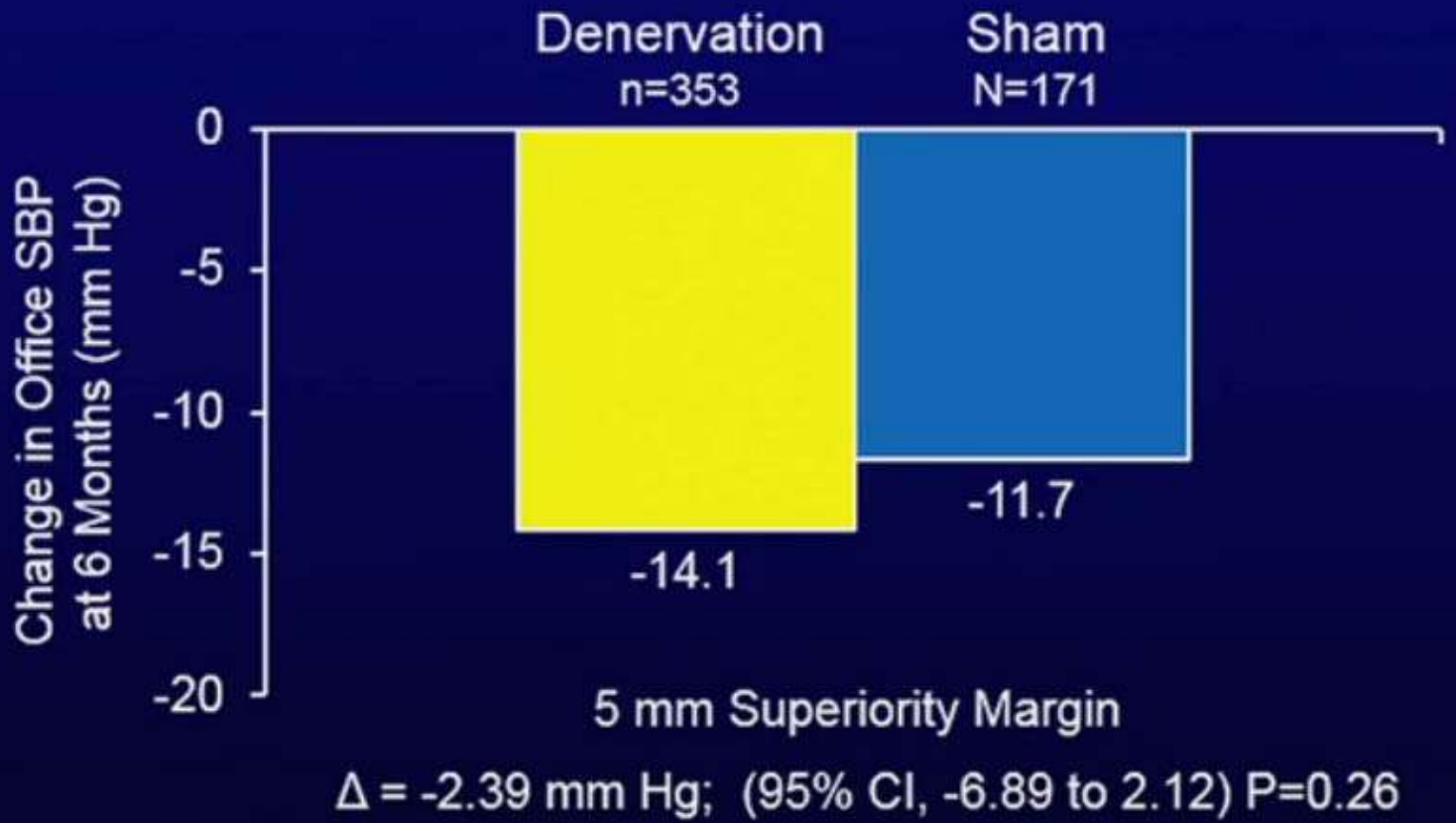
Relatively small well designed studies but most were not randomized and none were blinded or sham controlled. We designed rigorous and in fact largest trial of renal denervation to date.

Symplicity HTN - 3

- 89 Centers
- Inclusion/Exclusion criteria similar to HTN - 2
- 535 patients randomized 2:1 to RDN vs. sham procedure.
- Followed six months.
- Allowed to adjust medicines during follow-up, if BP too high or too low.

No Significant difference at six months.

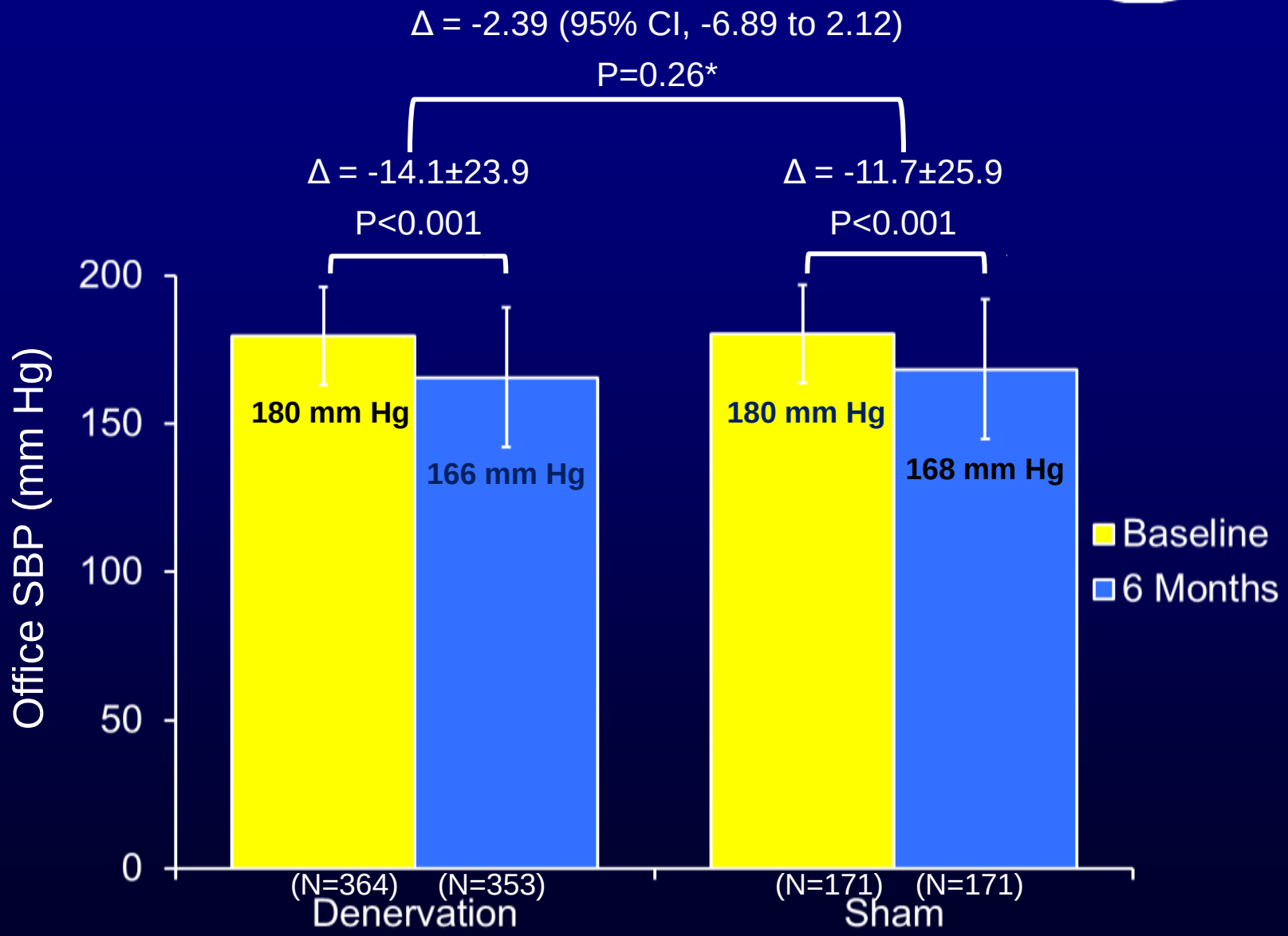
Primary Efficacy Endpoint
Change in Office SBP



Δ = -2.39 mm Hg; (95% CI, -6.89 to 2.12) P=0.26

Primary Efficacy Endpoint

Symplicity HTN - 3 Clinical Study

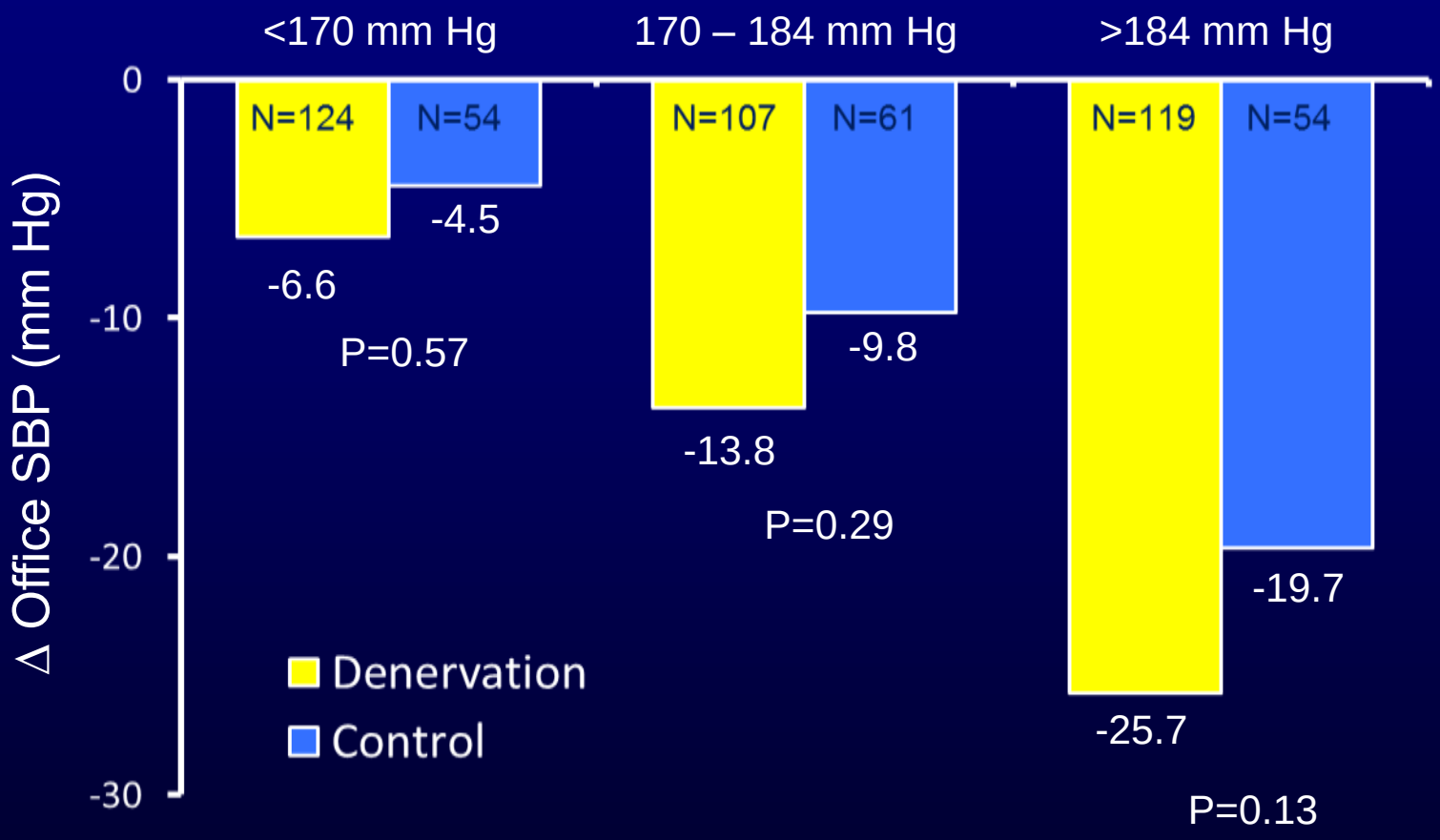


**P value for superiority with a 5 mm Hg margin; bars denote standard deviations*

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

Change in Office SBP by Tertile of Baseline Office SBP

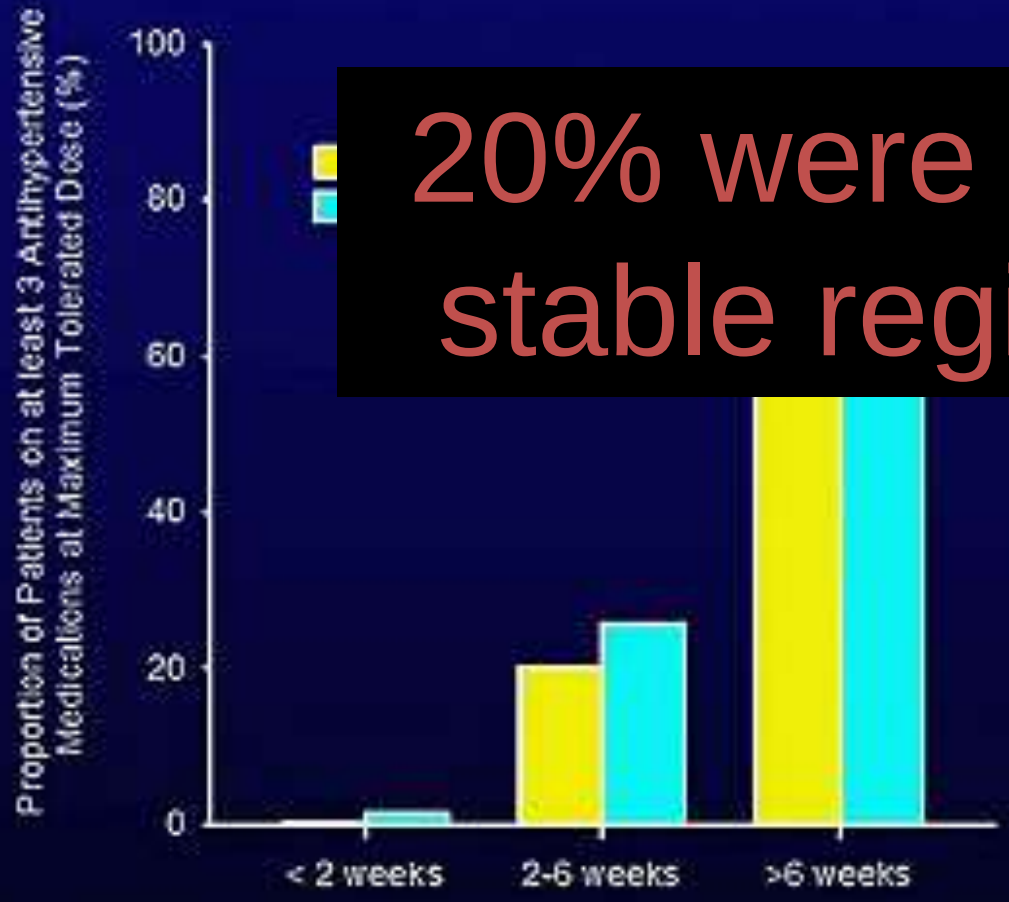
Symplicity HTN - 3 Clinical Study



Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

Did many patients change antihypertensive drug regimens shortly before qualifying?

Symplicity HTN - 3 Clinical Study



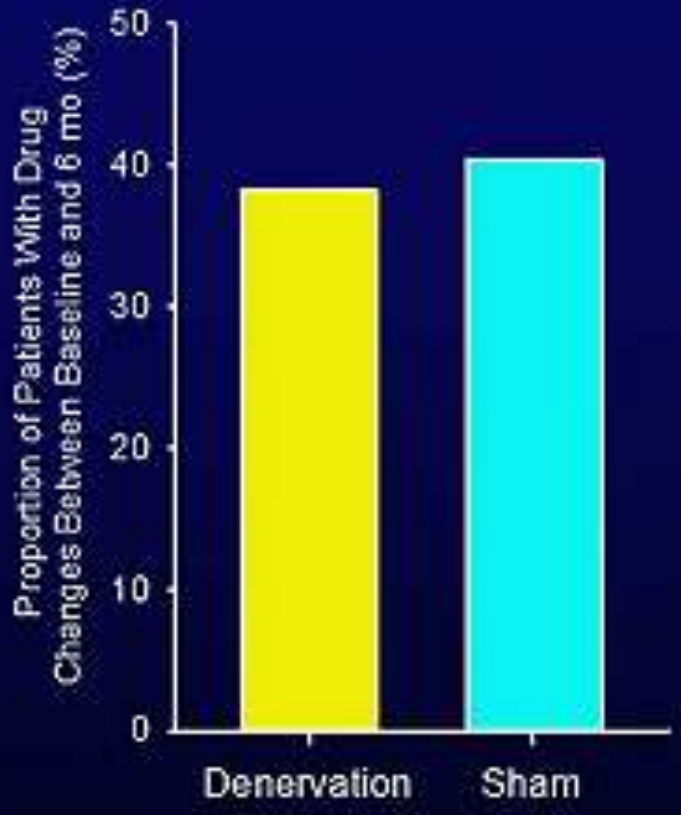
20% were not on stable regimens

atients
stable
regimes
for at least 6w prior to inclusion

Medtronic Data on File

Were there frequent drug changes between baseline and 6 months of follow up?

Symplicity HTN - 3 Clinical Study



Protocol mandated:

Maximum **doses and**

No **medication changes**

~40% of patients required medication changes*

69% of first medication changes were medically necessary

*Changes included class or dose

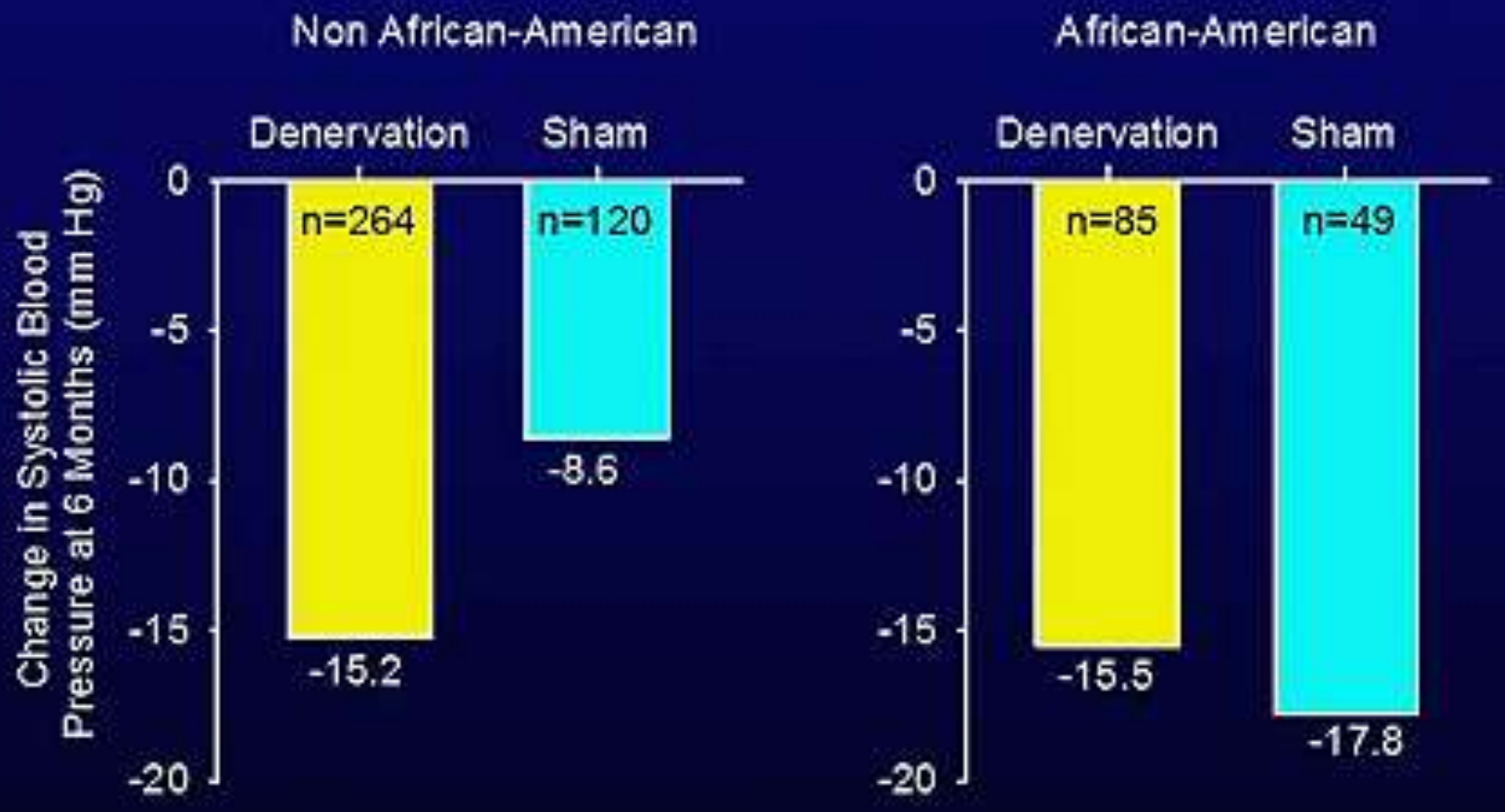
Medtronic Data on File

Afro-Americans

- Afro- Americans comprised 26% of study patients, but 29% of sham patients and 24% of treated patients.
- Blood pressure decreases in treated Afro-Americans and non-Afro-Americans were almost identical.
- However, the blood pressure drop in sham Afro-Americans was greater than that seen in treated patients, and several-fold higher than that seen anywhere else.
- Re-calculating the primary endpoint excluding the Afro-American cohort gives a superiority margin of 6.6% and a $p<0.012$.
- The only plausible explanation for these data is that the patients in question were non-compliant with medication prior to the study, and became compliant during the study.

What were the BP changes in African Americans vs. Non African Americans?

Symplicity HTN - 3 Clinical Study



Medtronic Data on File

Subgroup findings are at best hypothesis generating

Reasons for Differences in Results?

HTN-2

- Patients referred from hypertension clinics where medical regimen had been optimized prior to entrance into study. These were truly refractory patients.
- Denervation performed by experienced operators.
- Meds were rarely changed during follow-up period.

HTN-3

- Patients referred from primary care doctors or from investigators' own practice. Medical regimen was not uniformly optimized until after patient was first evaluated.
- Operators had no previous experience with denervation technique.
- 40% of patients had change of meds during follow-up period.

What Did HTN-2 Demonstrate?

- In a cohortof patients with refractory hypertension, the blood pressure does not change over a six-month observation period during which medicines are unchanged.
- In a comparable cohort followed for the same six months, there is a striking reduction of BP following renal denervation.
- Comparison of blood pressure reduction in the treated vs control groups was positive for treatment at $p<.0001$.
- When the control group was then treated, they experienced similar drops in BP.

What Did HTN-3 Demonstrate?

- If one designs a sufficiently complex study, and administers it poorly, even the most obvious difference can be obscured.
- In a cohort of patients with “refractory” hypertension, changing medicine during a six month period of observation can result in a significant BP drop.
- Renal denervation is not superior to medical management in a cohort responsive to better compliance and/or introduction of new medicines.

We All Love Statistics, but We All Hate Statistics

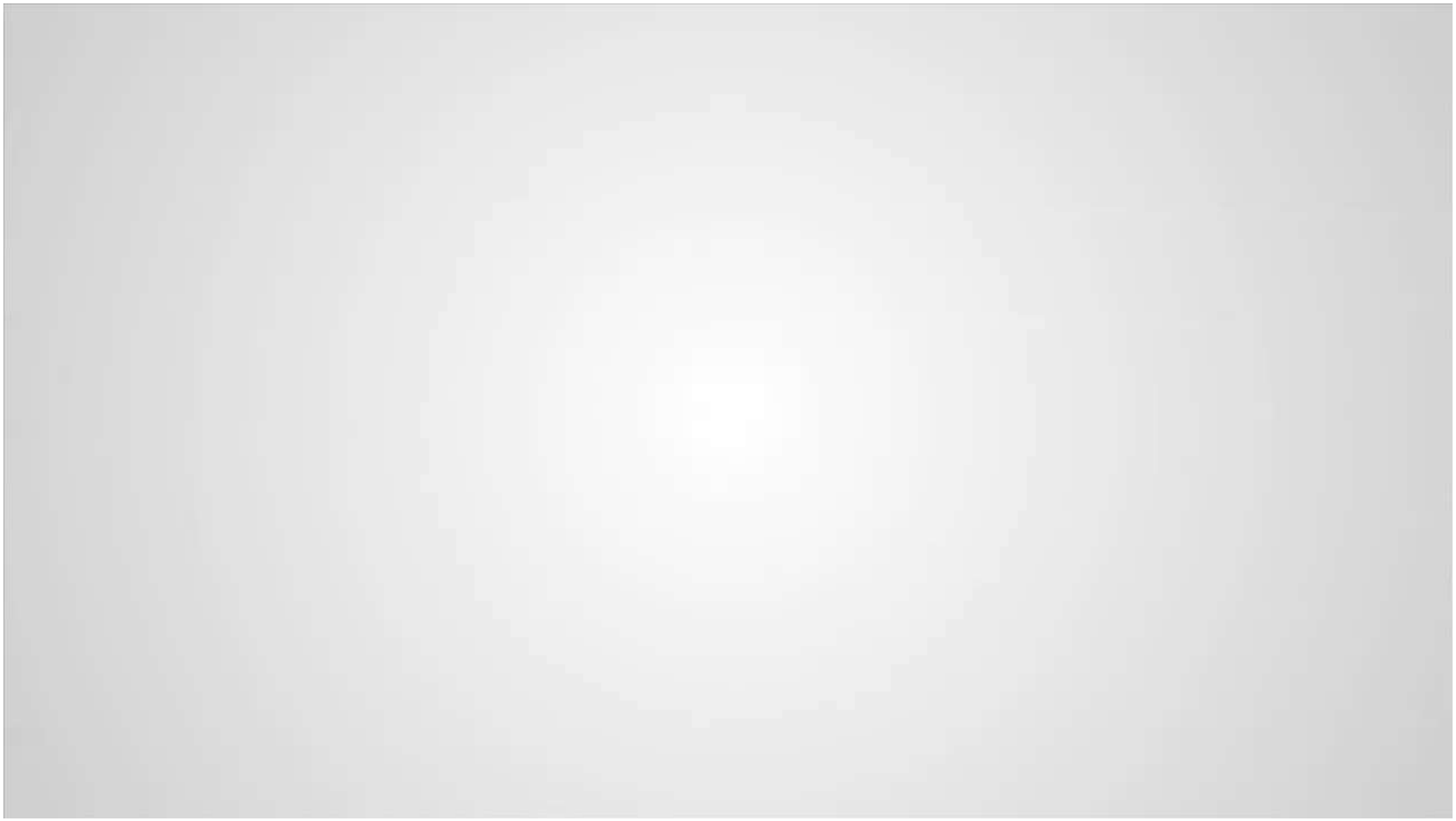
- In general, we love that p<.05 means there is a "significant" difference, and that p>.05 means that there is no statistically significant difference. That is easy. We don't have to think.
- What we hate is to think about is what P>.05 really means.
- What p>.05 really means is that we have failed to disprove the null hypothesis.
- We haven't **proven** anything.

What Did HTN-3 Prove?

- In HTN-3, 10s of millions of $ (that's 10s of billions of won) were spent to prove nothing.
- Specifically, they did not prove that renal denervation works, nor did they prove that it does not work.
- All they proved was that if one designs a complicated enough study, and administers it poorly enough, it is possible to fail to prove that the sun rises in the East and sets in the West.

What did HTN-3 Prove?
Absolutely Nothing!

Definitive Gold standard Randomized Blinded sham controlled study and that’s the truth. Largest and most rigorous clinical trial



Definitive Gold standard Randomized Blinded sham controlled study and we found the truth.

Slogans, Themes and Mantra

- If you say the same thing over and over again, people start to believe it, whether or not it is true.
- This technique is used in advertising (“breakfast of champions”), politics (“time for change;” “I like Ike”), religion (“Jesus saves”) and the practice of law.
- In advertising and politics they are called slogans. Lawyers call them themes.
- When used by zealots, they are called mantra (“allāhu 'ákbar, God is great;” “hare krishna, hare krishna;”)

Gold Standard?

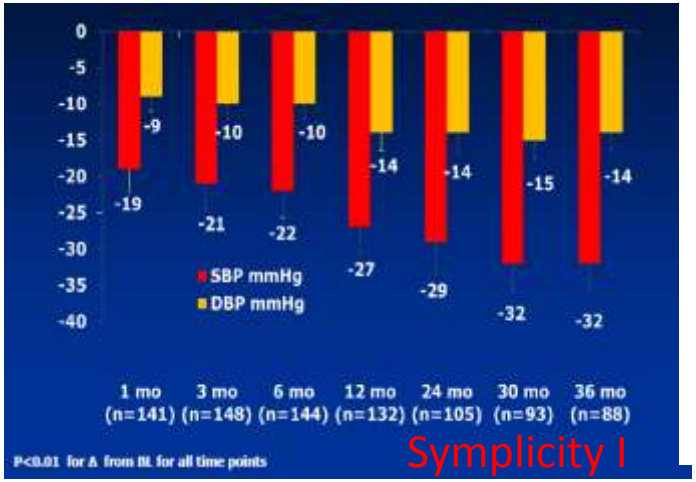
- Whether slogans, themes or mantra, the HTN-3 investigators are using these techniques to beatify their study design, justify their findings and propagate a big mistake.
- What makes a “randomized blinded sham controlled study,” the “largest and most rigorous clinical trial,” a “definitive gold standard?”
- This is a failed study. How can it be a model for the future?

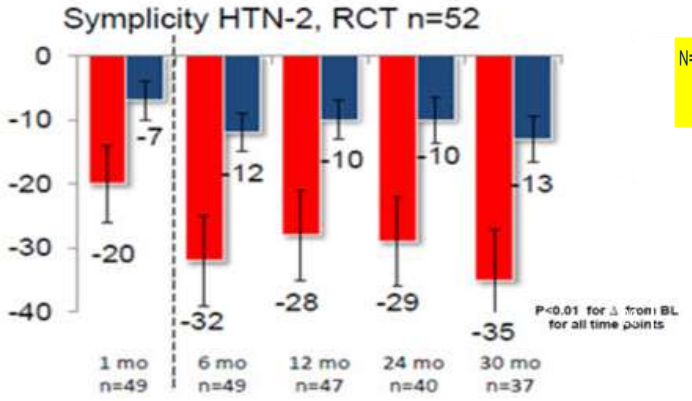
Consequences: Bandwagon effect

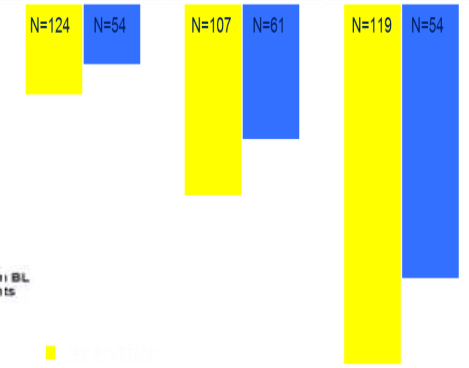
Since 2010, people getting a procedure that may not be effective.

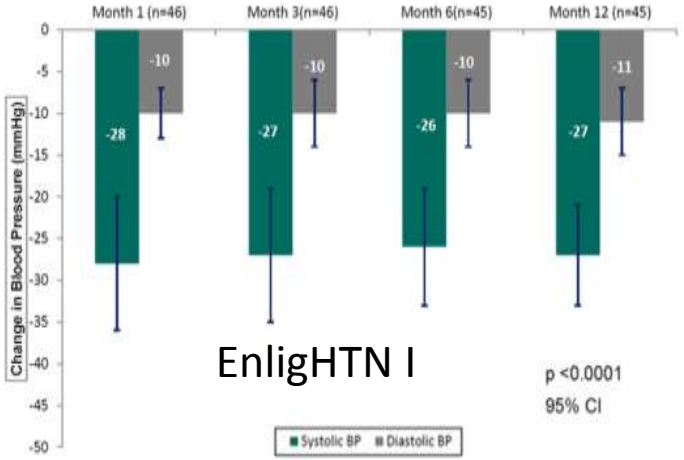
Symplicity HTN–3: Is This the End of Renal Denervation?

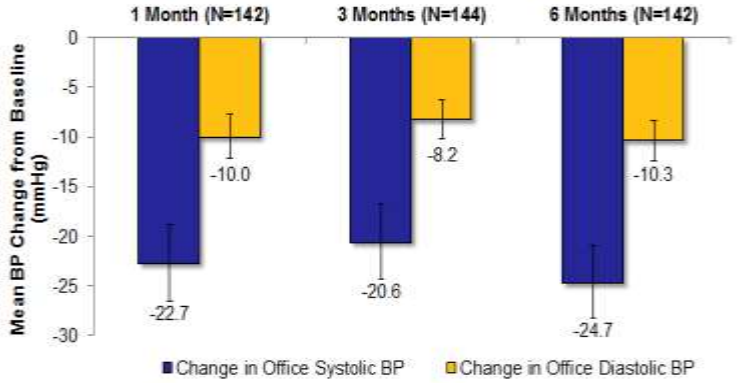
Is this the end of renal denervation?











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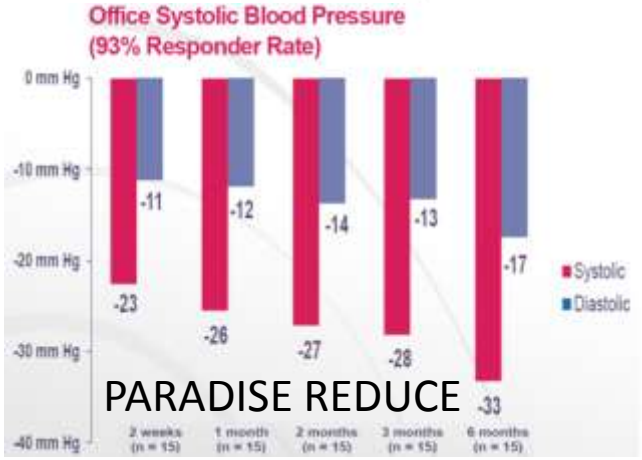
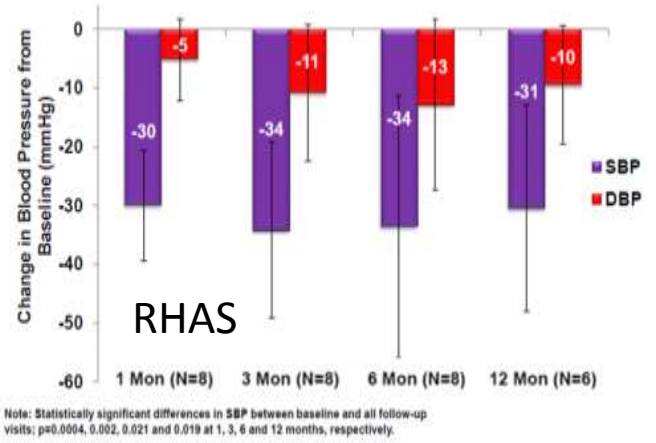
REDUCE HTN





Note: Statistically significant differences in SBP between baseline and all follow-up visits: p≤0.0004, 0.002, 0.021 and 0.019 at 1, 3, 6 and 12 months, respectively.

What is Next?

- We have enough data from enough studies from enough companies and medical centers with enough geographical diversity to know that renal denervation works.
- HTN-3 reinforced the procedure's safety.
- Let's design a simple study (like HTN–2) with a properly chosen and controllable patient cohort in order to prove once and for all the efficacy of this disruptive technology.
- And for heavens sake, please let us not adopt the HTN-3 model for evaluation of future devices.

What About Rigorous, Blinded, Sham Control?

- If any of you believe that performing renal angiography can lower BP 12 mmHg via placebo effect or some other mechanism,
- Do a randomized study of renal angiography vs. optimal medical therapy to prove it.
- If you are correct, I will personally submit your name(s) to the Nobel committee.