Renal Denervation Works! Why Can't We Prove it? TCTAP Seoul – April 28, 2019 James R. Margolis, MD - Miami, Florida USA

No Conflicts

- This is not a scientific talk.
- This is an editorial.
- Sometimes it is necessary for common sense to take the place of pedantry in order that we not lose the forest for the trees.

Hypertension leads to an increased risk of death from stroke and heart disease



CV mortality risk doubles for every 20 mmHg increase in systolic blood pressure.^{1,2}

¹Chobanian et al. Hypertension 2003;42:1206-1252 ²Lancet 2002;360:1903-1913

Sometimes, there are simple solutions to complex problems...



Some people make difficult tasks look easy



Roger Federer

Others make easy jobs look difficult



Introduction

- Early experiments with renal denervation in animals and later in man demonstrated extraordinary effectiveness in lowering both systolic and diastolic BP in patients with refractory hypertension.
- Results were similar no matter how denervation was accomplished.
- There were no safety issues.

Blood pressure-lowering effects of renal sympathetic denervation.









Symplicity III



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 treatmentresistant 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

Primary Endpoint: 6-Month Office BP



- 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

Symplicity HTN-2: First Randomized Renal Denervation Trial

Primary endpoint: Change in Systolic and Diastolic BP post Renal Denervation Treatment



Treatment Cohort

Control Cohort

6 M Post Randomization No Renal Denervation Treatment (Baseline) 12 M Post Randomization TREATED POST 6M



Symplicity 2 - summary

- An <u>elegant</u> study:
 - Quick
 - Low cost
 - Easy to perform
 - Easy to control
 - Easy to understand



 Clear cut finding: supported the superiority of renal denervation with a p value <.0001 – i.e., a less than one chance in 10,000 that the findings were by serendipity.

Then, it was time for pivotal study - choices

- Repeat Symplicity 2
 - Different venues
 - Different Patients
 - Different operators
 - Same attention to detail
- Reinvent the wheel

It was decided to reinvent the wheel

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.



Reinventing the Wheel Symplicity 2

- 24 centers
- 106 patients
- 1:1 randomization
- No sham control
- Patients recruited from hypertension clinics
- Not allowed to adjust medicines during follow-up
- Only rare exceptions to above.
- Procedures performed by experienced operators
- Study carefully controlled throughout
- Positive at p<.0001
- At six months, 35 control patients were treated wit RF. Response of these patients same as that of those in control group.

- 88 centers
- 535 patients
- 2:1 randomization
- Sham control
- Patients recruited from local practices
- Allowed to adjust medicines during follow-up, if BP too high or too low.

Symplicity 3

- 40% of patients adjusted meds during follow-up
- Procedures performed by inexperienced operators
- Study poorly controlled
- Did not meet primary endpoint
- Control patients never treated

Criticisms and Answers

- Criticisms
 - Not blinded
 - Office blood pressures
 - Small study
- Answers
 - It is really stretching to suggest that placebo effect can persist for three years and longer.
 - Office blood pressures are the prognostic gold standard.
 - Framingham data was obtained with same technique used in Symplicity 2
 - ABPMs are uncomfortable for patients and impractical for doctors
 - Raise your hand if you use ABPM in your routine practice.
 - Study strongly positive with 106 patients

Office BP vs ABPM

- Office blood pressures are the prognostic gold standard.
- ABPMs are uncomfortable for patients and impractical for doctors
- Framingham data was obtained with same technique used in Symplicity 2
- Raise your hand if you use ABPM in your routine practice.

Comments and Conclusions

- Symplicity 2 was an elegant study Renal denervation works
 - Positive despite small sample size.
 - Crossover results seal the deal.
- Only thing left to do is to repeat the study with a slightly larger cohort, but with the same attention to detail as in Symplicity 2.
 - All patients under control of hypertension doctors
 - Small cohort whose compliance can be controlled
 - Experienced operators

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 \$ were spent to prove nothing.
- Specifically, they did not prove that renable pervation 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 cast ant et: in the vest in the set of the set of the set of the set.

Final thought

• Even in America, bigger is not always better.

First Angioplasty Patient 40 Years Later What If he had been randomized to a sham procedure?

