The Limits of Sham-Control in Device Trials of Hypertension

Evolving Understanding based on Available Clinical Trial Experience

Clinical Development of RCT in HTN Device Therapy
Evolution of Evidence

RCT (sham)	N
Symplicity HTN 3	535
SPYRAL HTN-OFF MED	80
SPYRAL HTN-ON MED	80
RADIANCE HTN-SOLO	146
WAVE IV	81
Flex	71
ReSET	69
total	1062

RCT (no -sham)	N
Symplicity HTN 2	106
DENER HTN	106
HTN Japan	41
INSPIReD	15
RDN OSA	60
SYMPATHY	139
PRAGUE 15	106
DENERV HTA	27
RDN OSLO	19
total	619

Non-Randomized	N
GLOBAL SYMPLICITY REGISTRY	2583
SYMPLICITY HTN 1	50
UK Registry	253
Portugal Registry	31
TREND Registry	191
Kazakhstan Registry	63
Heidelberg Registry	63
EncoreD	109
RAPID	50
EnligHTN 1	46
EnligHTN 2	133
EnligHTN 3	39
SPYRAL FIM	50
Reduce HTN	146
Swedish Registry	252
Irish Registry	31
ACHIEVE	100
total	4190

Total: N=5,871

Placebo Effect in HTN Device BP Trials

5861 Subjects with Sham, without sham and registry

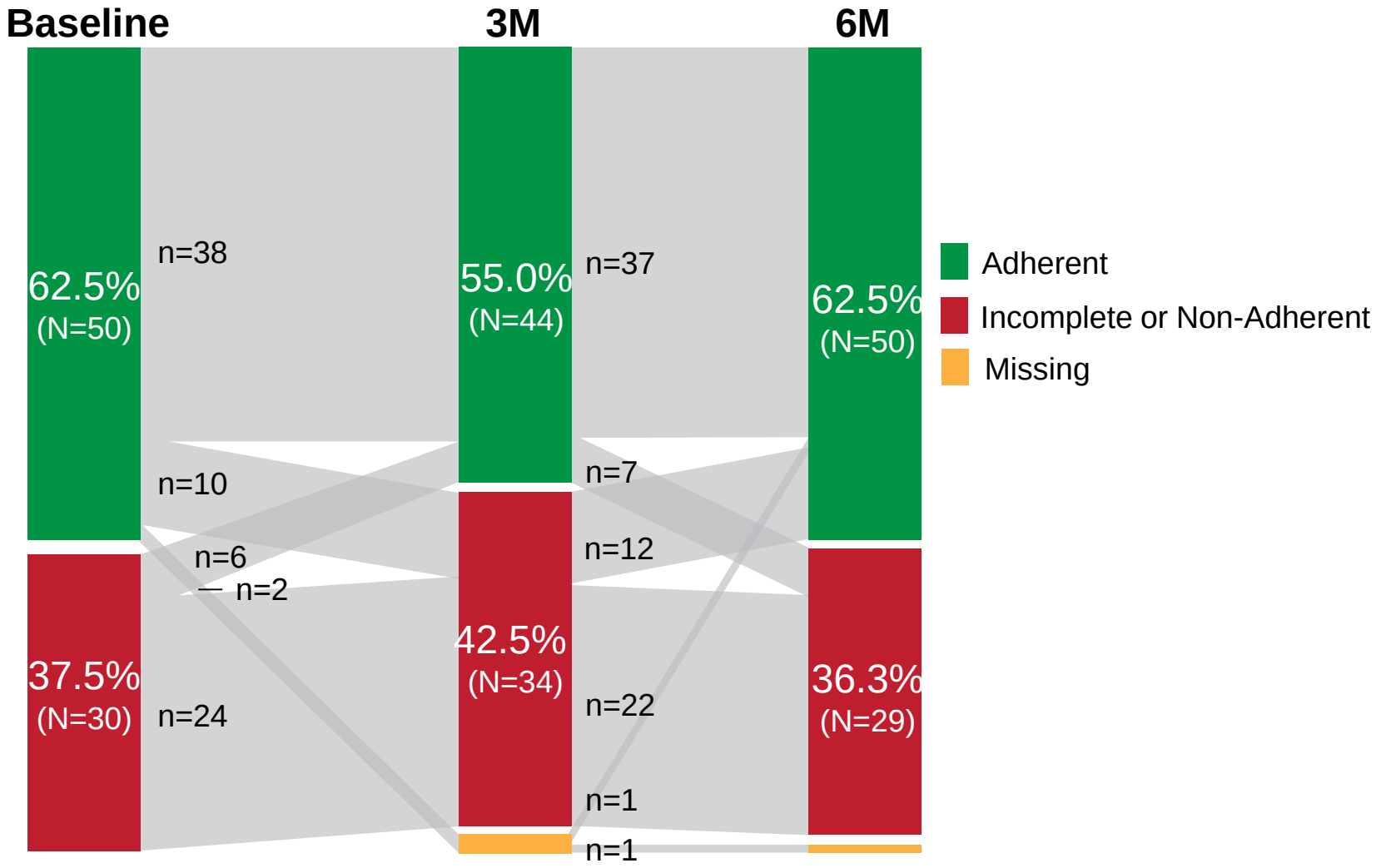
- Despite few precedents among medical devices, sham controlled trials have evolved as an expected standard for US regulatory approval of novel device therapy for hypertension
- Sham control may not prevent (and may amplify) biased behavior among randomized groups or investigators
- Blood pressure reductions in randomized sham controlled trials appear generally similar to randomized controlled trials and most registries

David Kandzari, TCT 2018

Unique reasons Sham may NOT elucidate placebo effect in HTN RCT

- Availability of a trial endpoint, BP, to subjects and blinded trial observers
  - Does a subject's or blinded trial investigator's knowledge about BP change their relation to diet, exercise and medications and reporting drug Adverse Events
- Opportunity to self medicate
  - Trial participation increases awareness of the hazards of excess BP
  - HTN patients have large reservoirs of approved medications to treat BP, many have been trained in self medication
  - Subjects may self select to participate in trials with an underlying desire to reduce, eliminate or prevent acceleration of medications (Roland Schmieder, TCT 2018)
  - Axiomatic: medication effects on bp > placebo effect
- Blinding may not be technically possible

Only 34% Subjects are Persistent at all measures



Sphral On MED

Kandzari D, et al, *Lancet*. 2018;391:2346-2355

Off Protocol Medication changes not equal in sham vs treatment

Azizi et al. Endovascular Ultrasound Renal Denervation to Treat Hypertension
: The RADIANCE-HTN SOLO Randomized Trial

Table S5. Patients Receiving Antihypertensive Medication During the Study

Circumstances and Timing of Antihypertensive Medication Restart

Renal Denervation (n=74)	**Sham Procedure (n=72)**	**P Value**
Total patients receiving antihypertensive medications prior to 2-month ambulatory blood pressure measurement		
• 5 (6·8%) *	13 (18·1%)	0·04
Protocol defined criteria		
• 1 (1·4%)	3 (4·2%)	0·36
Physician decision or patient preference		
• 4 (5·4%)	10 (13·9%)	0·10

* 3/5 did not receive the RDN procedure

Self BP Measurement and medication titration mask placebo effect

- Medication persistence is unequal in sham and treatment placebo effect is obscured

- The presumption that sham reveals placebo effect is wrong if patients use off label drugs differently in treatment and sham arms
  - Highly successful intervention reducing BP may cause reduction of adherence/persistence- masking treatment effect
  - Failed interventions or sham allocation, with little effect on BP, may cause increase in adherence/persistence or addition of medications

- **Awareness of BP and opportunity to self medicate inherently reduce the value of a sham to measure placebo effect**

ROX- significant change in BP cause changes in medication use

Events related to *improvement* in BP	ROX Coupler (n = 42)		Control Group (n = 39)		*p*-value
Non-serious events:	Events	Patients	Events	Patients	
Hypotensive symptoms permitting reduction in antihypertensive meds	8	8 (19.0%)	0	0 (0%)	0.0056
Events related to *worsening* in BP					
Serious events:	Events	Patients	Events	Patients	
Hypertensive crisis	0	0 (0%)	~~5~~ 6*	4 (10.3%)	0.0101
Non-serious events:					
Worsening BP requiring increase in medication	1	1 (2.4%)	4	4 (10.3%)	
TOTAL	1	1 (2.4%)	10	8 (20.5%)	0.0027

Desired medication reduction

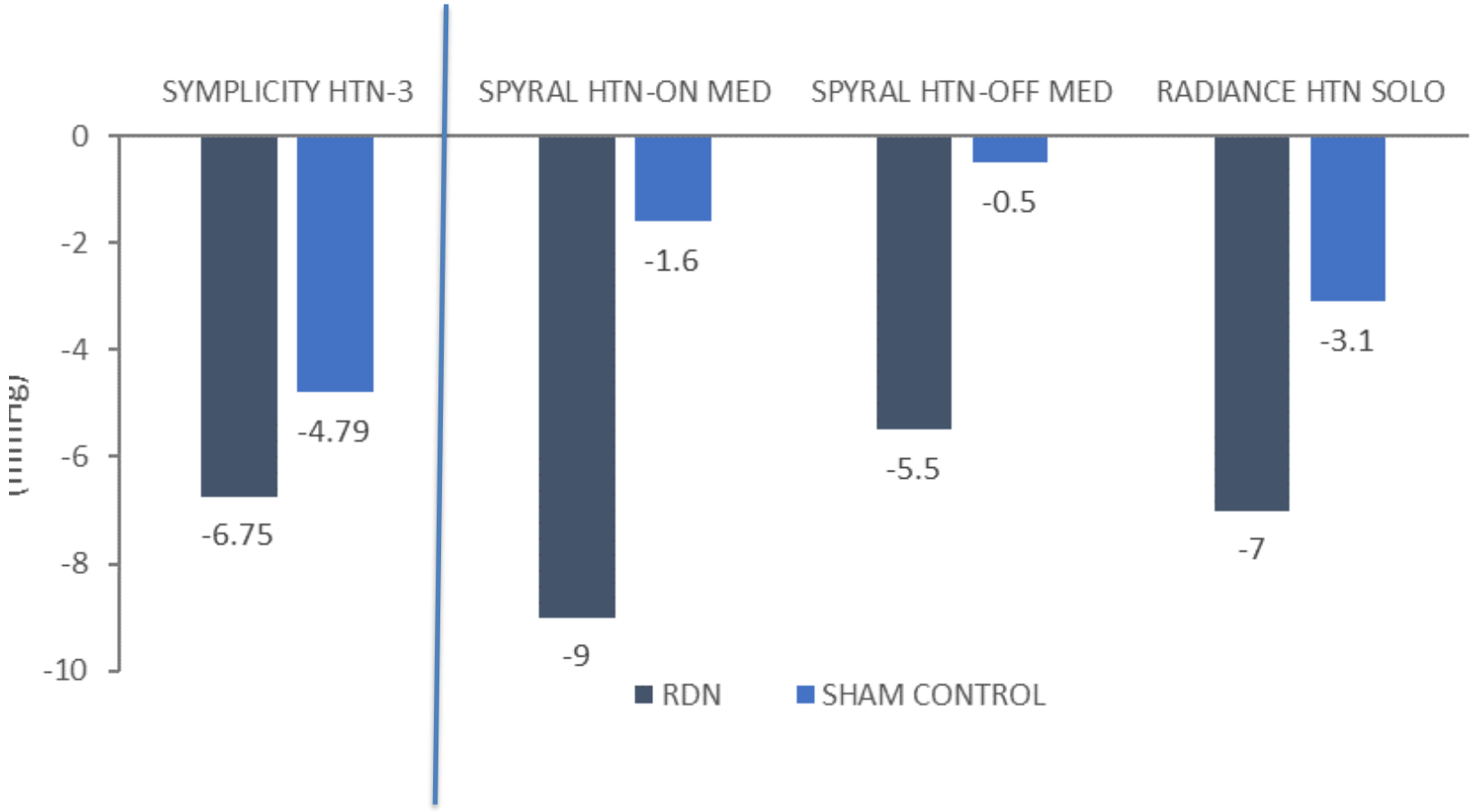
Reoccurring events and far worse than venous stenosis

* Average hospital stay 5 days; range 2-10 days

Not included above, one Control group death related to hypertension at month 8

Lobo, et al. Lancet 2015

Head to Head Comparison of randomized *sham*-controlled trials of renal denervation



Sham cannot identify placebo effect in device trials of HTN

- Placebo effect on oBP is unknowable
  - Data do not support the assumption placebo-control and treatment act similarly
- Placebo effect on blinded ABP is likely small, possibly indistinguishable from ZERO
  - Placebo effect is likely smaller than the commonly used anti hypertensive agents
- Patients who participate in HTN device trials exhibit high rates of non persistence
  - This variable behavior is evident even when subjects know they are being monitored

Blinding is not always possible

1. Treatment effect is large and temporally related to the procedure
2. Specific signs or symptoms are relatable to the device

   ROX:

   Groin thrill

   Groin bruit

   Development of venous stenosis

   Baro Stim: neck twitch

- Subjects in the treatment group and blinded team have reason to suspect treatment allocation
- Subjects in control arm and blinded team may infer the allocation

Sham trial design in HTN trials may not add information yet add subject risk and trial cost

- Placebo effect on blinded ABP at 3 or 6 months is small
- When the placebo effect is less than the impact of self medication by subjects- placebo effect is obscured
- When blinding is futile, presumptions of sham arm revealing placebo effect are incorrect