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FDA Presentation

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Section 2: Hypertension Background

Section 3: Overview of Device Anatomical Targets

Section 4: Evolution of Clinical Evidence

Section 5: Clinical Study Design Elements

Section 6: Safety Endpoints

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Panel Purpose

- FDA is requesting panel recommendations on:
  - Indications for use
  - Critical clinical study design elements
  - Safety endpoints
  - Effectiveness endpoints
  - Device and population based benefit and risk balance
  - Pre/Post market balance

Overview of Discussion

- We will discuss:
  - Current treatment of hypertension
  - Anatomical targets of device based therapies
  - Clinical evidence supporting device therapies
  - Clinical study design elements

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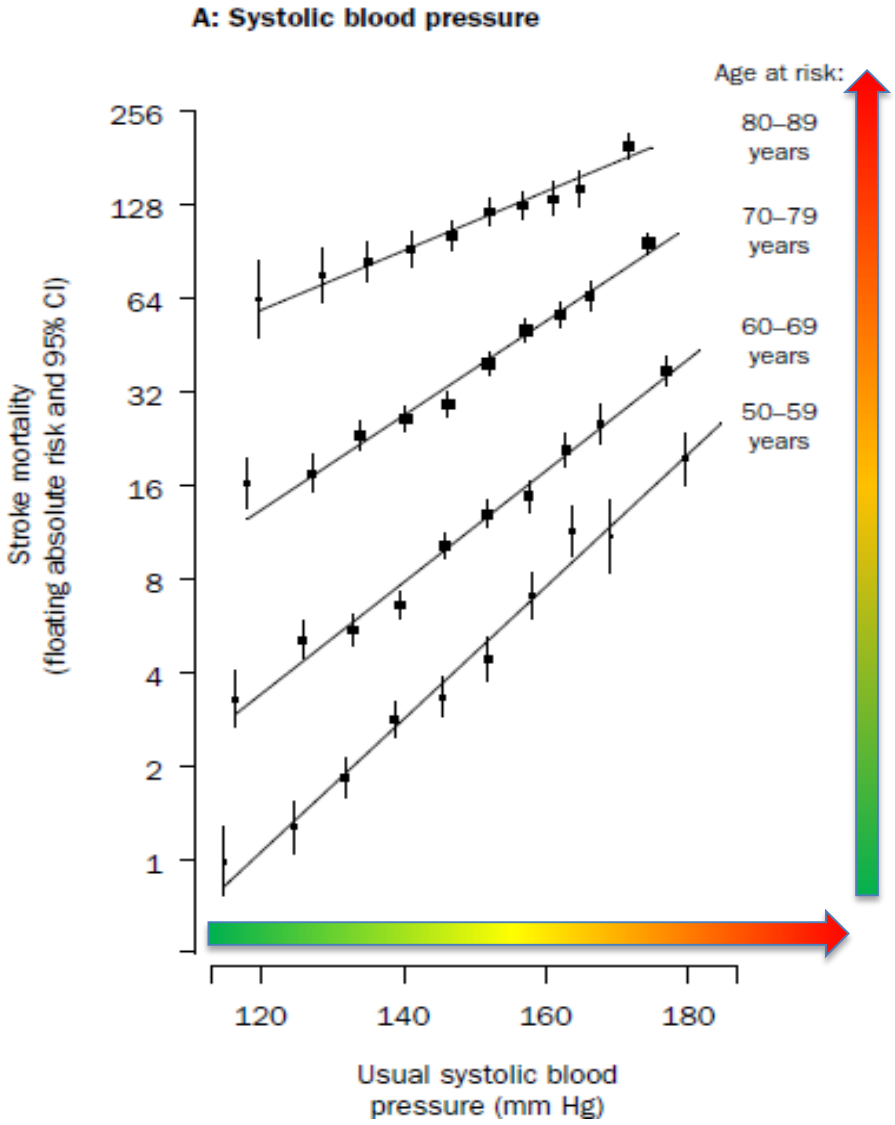
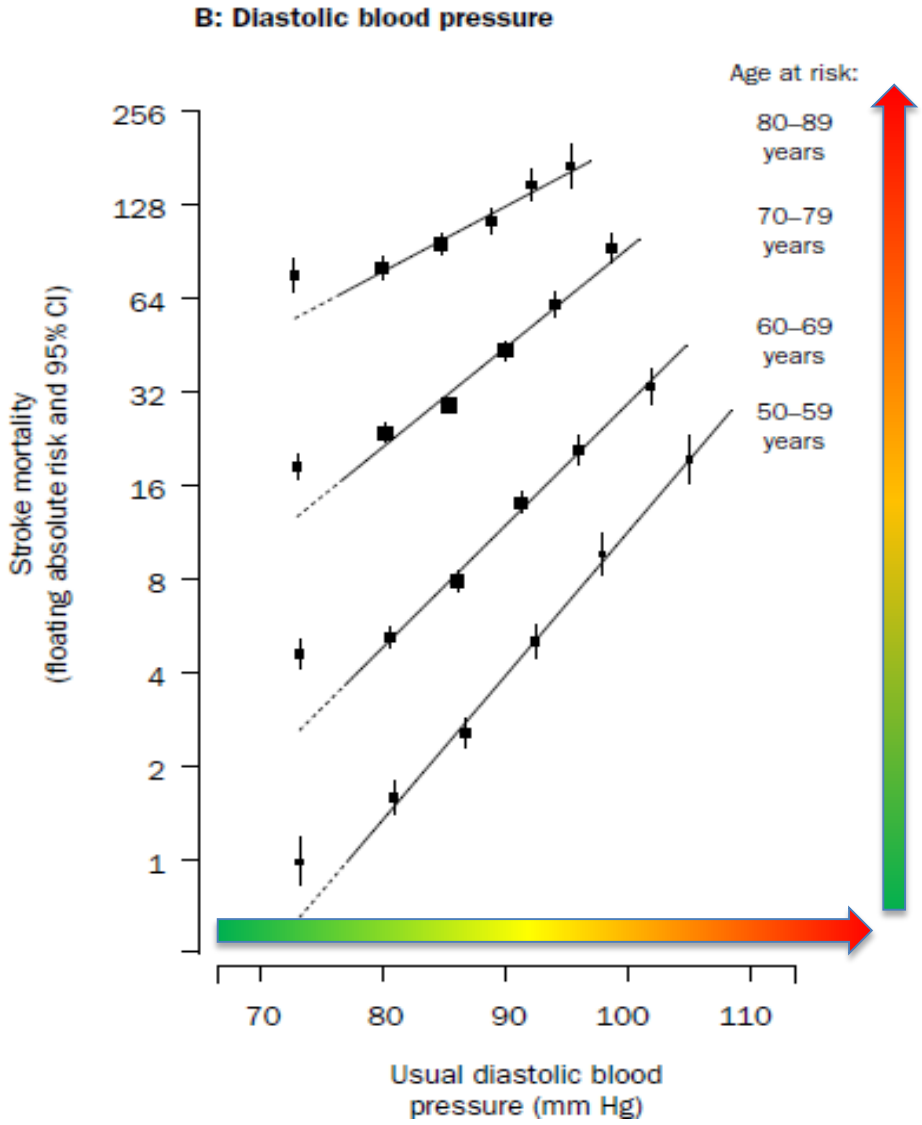
Current Guidelines: Hypertension

	Office Blood Pressure (mmHg)		
2003 JNC 7 / 2014 JNC 8	**SBP**		**DBP**
Stage 1	140-159	OR	90-99
Stage 2	≥ 160	OR	≥ 100
2017 ACC/AHA	**SBP**		**DBP**
Stage 1	130-139	OR	80-89
Stage 2	≥ 140	OR	≥ 90
2018 AAFP/ACP	**SBP**		**DBP**
JNC 8 & Initiate treatment ≥ 60 y.o. if SBP ≥150 mmHg			

Whelton PK, et al. Circulation. 2018;138(17):e484-e594
Qaseem A, et al. Ann Intern Med. 2017;166(6):430-7

BP Link to CV Outcomes





Lewington S, et al. Lancet. 2002;360(9349):1903-13

Hypertension Treatment Guidelines

Elevated Blood Pressure 120-129 / <80 mmHg	**Lifestyle Changes (e.g. weight loss, healthy diet, physical activity) & Periodic Reassessment (i.e. 3- 6 months)**		
Stage 1 Hypertension 130-139/80-89 mmHg	**Lifestyle Changes & Periodic Reassessment**	10 yr Cardiovascular risk ≥ 10% **OR** Cardiovascular disease, diabetes mellitus, chronic kidney disease	→ Antihypertensive Medication Therapy
Stage 2 Hypertension ≥ 140/90 mmHg		→	Antihypertensive Medication Therapy 2 Agents Different Classes

Whelton PK, et al. Circulation. 2018;138(17):e484-e594

Pharmacotherapy Treatment

- Relative risk of total major cardiovascular events are reduced by the antihypertensive medication regimens, with no significant differences in events between drug classes as determined by large clinical trials (e.g. ALLHAT)
- Pharmaceuticals are indicated for treatment of hypertension as sole agents and/or in combination with other antihypertensive drugs for more severe forms of hypertension
- Role for devices with or without drug therapy remains unclear

J Hypertens. 1998;16(2):127-37
Jama. 2002;288(23):2981-97

Pharmacotherapy Treatment (cont.)

- Treatment strategy depends on a variety of factors (e.g. age, comorbidities, drug interactions, etc.)
- Poor medication adherence
  - Failure to fill (28%)
  - Omission of Dose (10%)
  - Discontinuation of treatment w/in first year (40%)
- Medication adherence may impact evaluation of device effectiveness

Vrijens B, et. al. Front Pharmacol. 2017;8:100

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Devices Target Mechanisms of BP Regulation

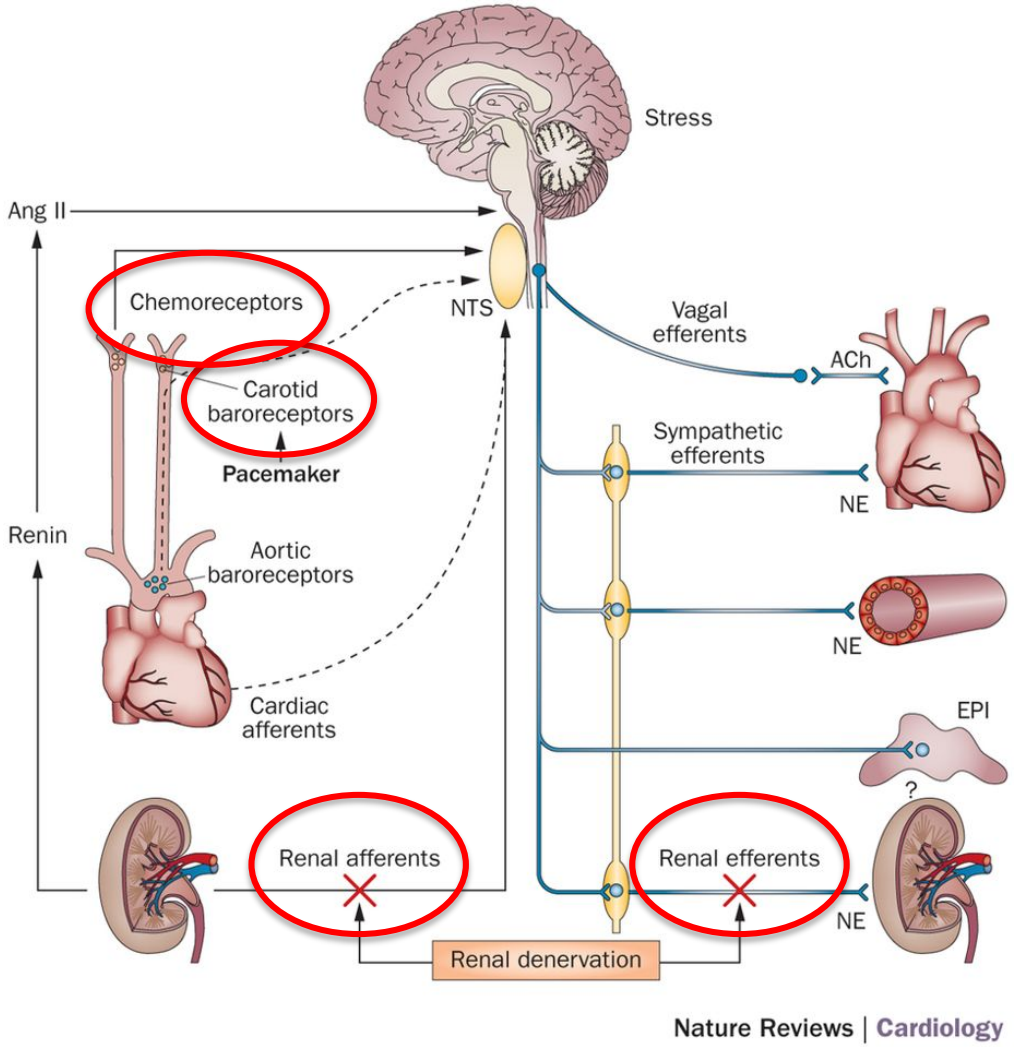

FIGURE: Victor RG. Nat Rev Cardiol. 2015;12(8):451-63

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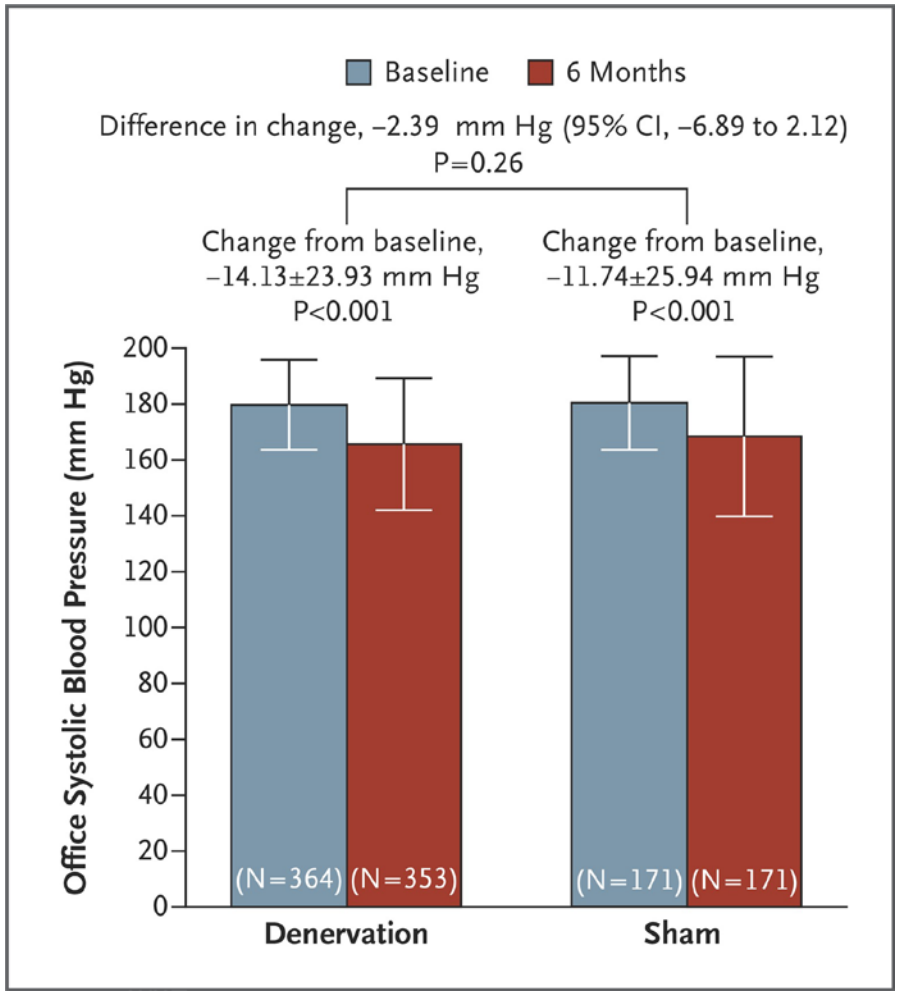
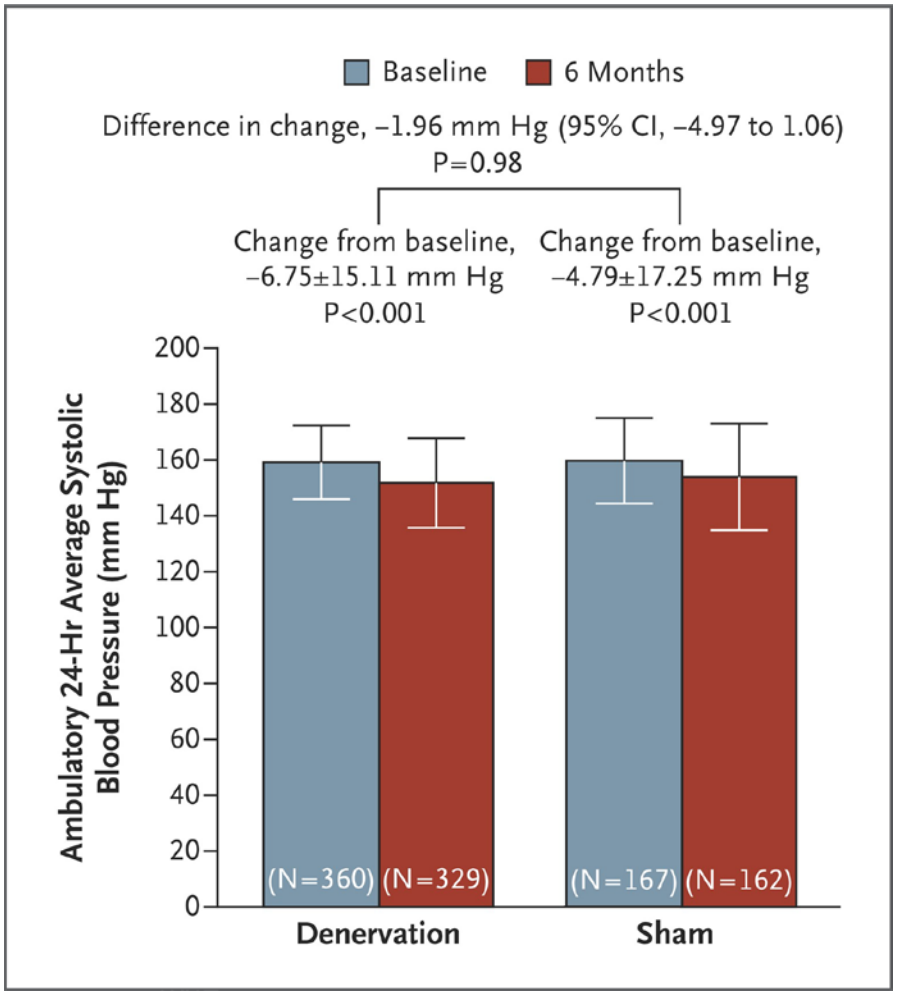
First Sham Controlled RCT Renal Denervation

- Early RCT studies were positive, but the results had some limitations
- HTN-3 Study Design Features:
  - Randomized, **sham** controlled
  - Subjects with drug-resistant hypertension
  - Office SBP & ABPM collected
  - Primary Effectiveness Endpoint: Δ Office SBP at 6 months (5 mmHg superiority margin)

Symplicity HTN-3 Results



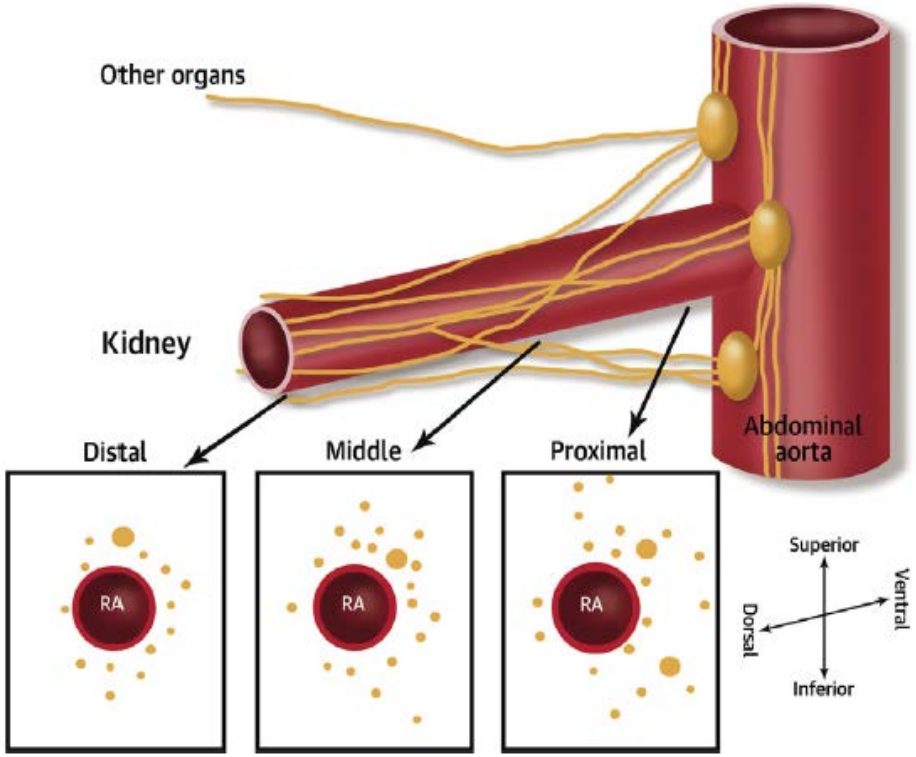


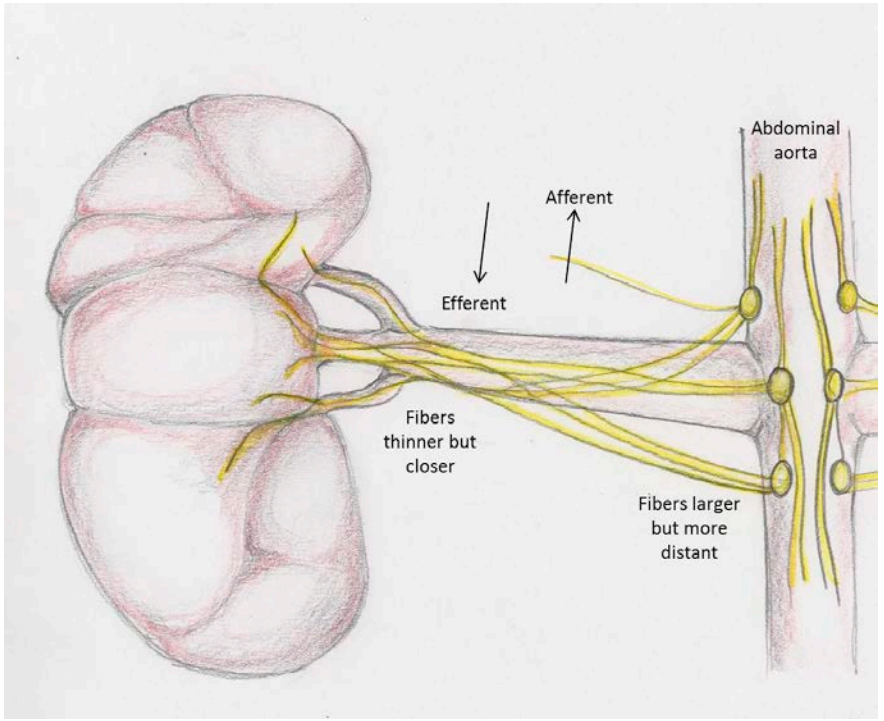
Bhatt DL, et al. N Engl J Med. 2014;370(15):1393-401

Potential Confounders

- Medication adherence
- Procedural technique variations for complete denervation
- Ethnic subgroups
- Regression to the mean

RDN: Shift to a Distal Target



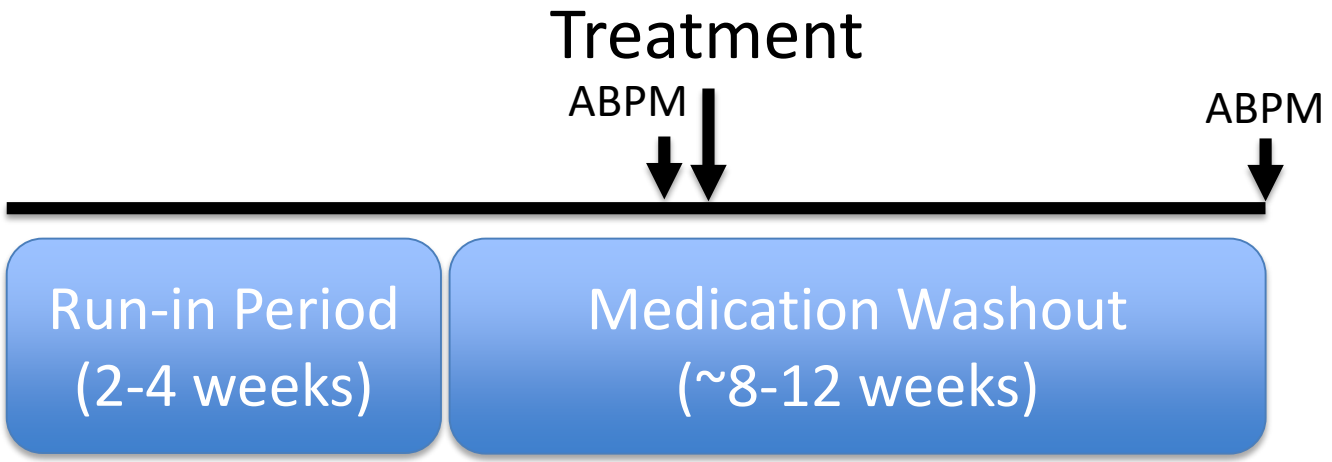


Sakakura K, et al. J Am Coll Cardiol. 2014;64(7):635-43

FIGURE: Silva JD, et al. J Am Soc Hypertens. 2016;10(8):656-70

2014 American Society of Hypertension (ASH) Recommendations

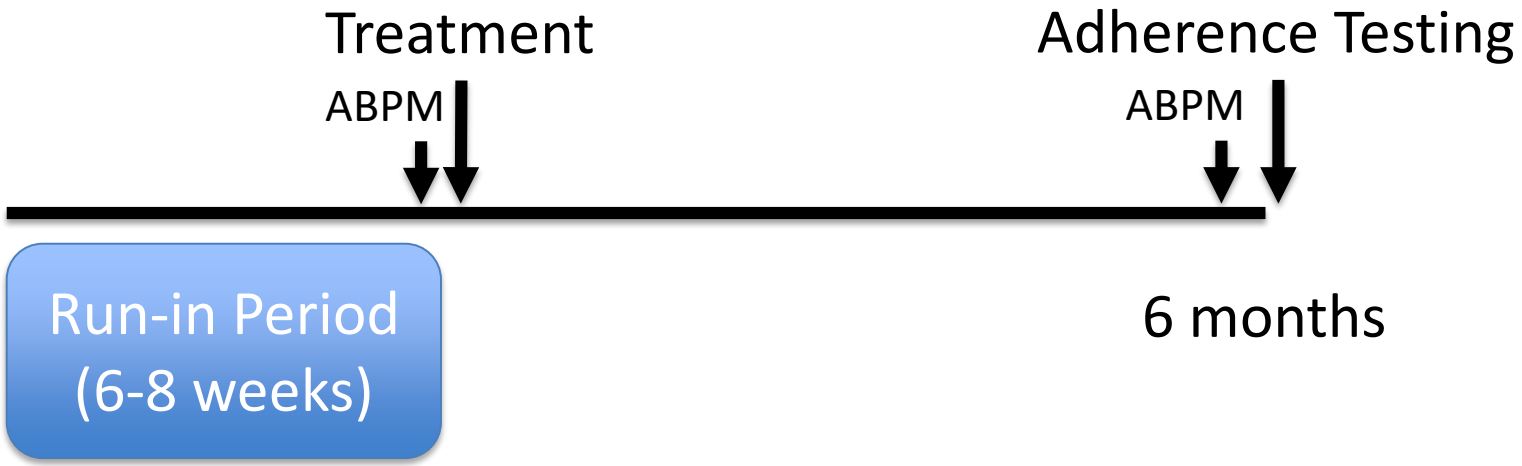
- Phase II Clinical Trial (Medication "OFF")
  - Obtain clear proof of principle
  - Demonstrate effectiveness in medication OFF population



White WB, et al. J Am Soc Hypertens. 2015;9(5):341-50

2014 ASH Recommendations (cont.)

- Phase III Clinical Trial (Medication "ON")
  - Demonstrate device effectiveness in presence of medications
  - Allows evaluation in real-world population



White WB, et al. J Am Soc Hypertens. 2015;9(5):341-50

Comparison of Current Studies

Commonalities

- Randomization
- Sham control
- Double blinding
- Measurement of Office and Ambulatory BP

Differences

- Severity of HTN
- Medication presence / absence
- Adherence evaluation method
- Endpoints
  - BP measurement type
  - Timing

Mahfoud F, et al. Eur Heart J. 2017;38(44):3272-81

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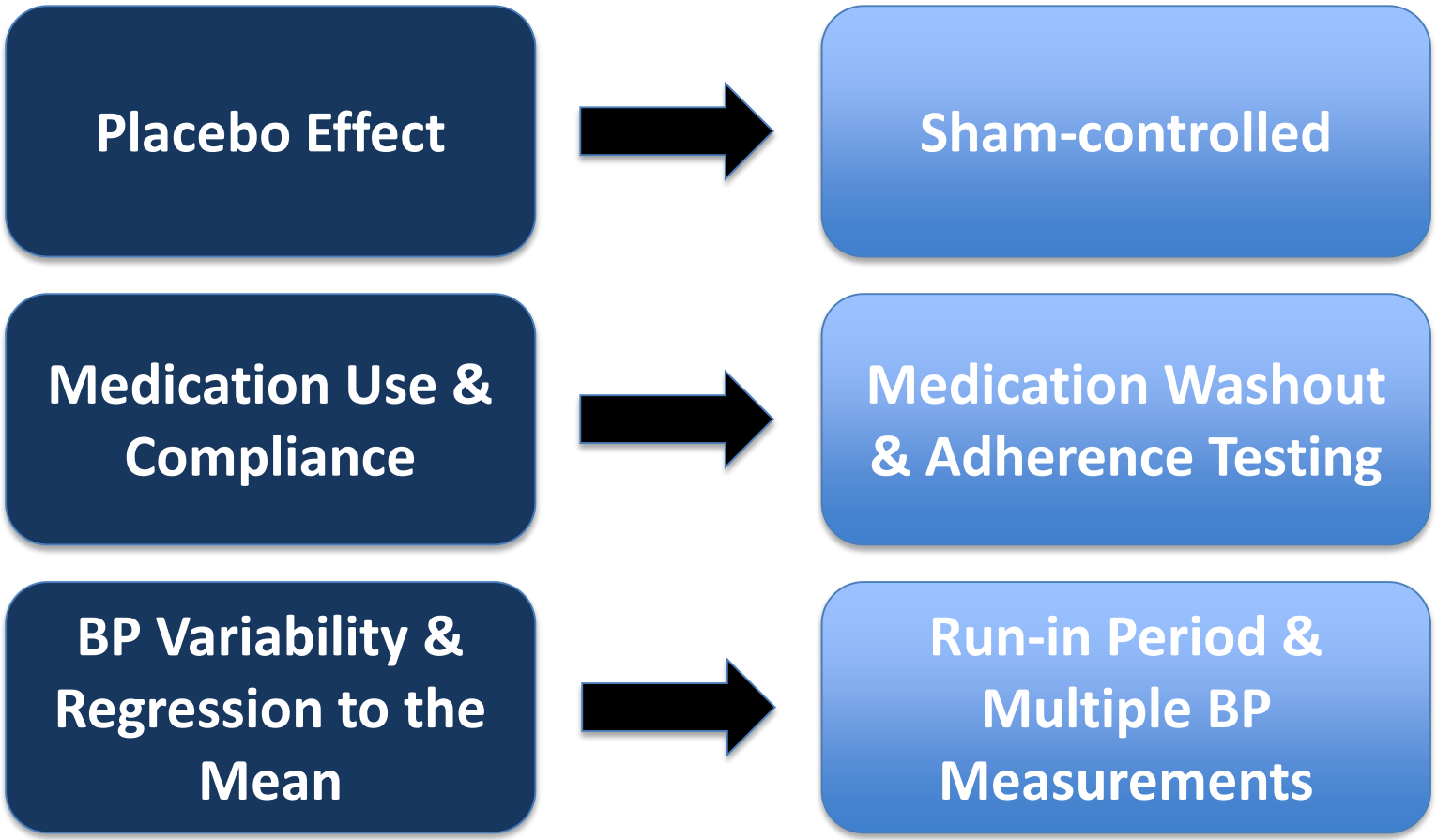
Categorizing the Patient Population

- The hypertensive population is complex, definitions for “hypertension” are continuously revised
- Unclear which patients may benefit from device based therapies
  - Severe Hypertension
  - Uncontrolled Resistant Hypertension
  - Controlled by Medications
  - Medication Naive

Minimization of Confounders



Considerations for Study Designs

Medication OFF

Value:

- Isolate device effect from medication confounders

Potential Confounding Factors:

- Safety concerns limit severity of hypertension studied
- Limited study of durability of device effect

Medication ON

Value:

- Evaluate device function with real world medication use

Potential Confounding Factors:

- Medication adherence
- Discerning device and medication effect

Additional Study Features

- Pre-specified Interim Analysis
  - May stop for futility, conclude early success, and/or conduct sample size re-estimation
  - Sufficient sample size needs to be ensured for safety evaluation when study is stopped early for effectiveness
- Patient Crossover
  - May help facilitate patient enrollment
  - Equipoise for study should be maintained
  - May limit dataset for long term comparisons of safety and effectiveness

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Analysis of Adverse Events

- Safety profile of a device is assessed by adverse events (AE)
- AE are impacted by:
  - Device design
  - Means required to evaluate subject suitability
  - Techniques used to achieve therapeutic benefit
  - Anatomic location of the treatment
  - Whether an implant is left behind

Safety Endpoints

- **Procedural Safety:** Captures serious procedure or system-related adverse events occurring within 30 days of treatment, expressed as the event free rate
- **Treatment Safety:** Captures adverse events related to therapy like drug reactions, hypertensive crisis and any therapy specific AE
- **Device Safety:** the event-free rate for all major hypertension-related and serious device-related adverse events occurring beyond 30 days post-treatment.

Methods of Safety Analysis

- **RCT:** Compare AE severity and rates between the control and experimental groups
- **Single arm study:** Performance goals (PG) need to be derived on safety data from comparable populations undergoing similar therapies.
- Establishing a meaningful PG and safety margin can be challenging when a device is truly novel

Example: Potential Risks of Carotid Devices

Potential Complications

- Cerebral angiography
- Distal emboli
- Vascular changes from altered geometry & flow
- Need to assess acute and chronic local and downstream effects: carotid duplex scan & brain imaging
- Not easily removable

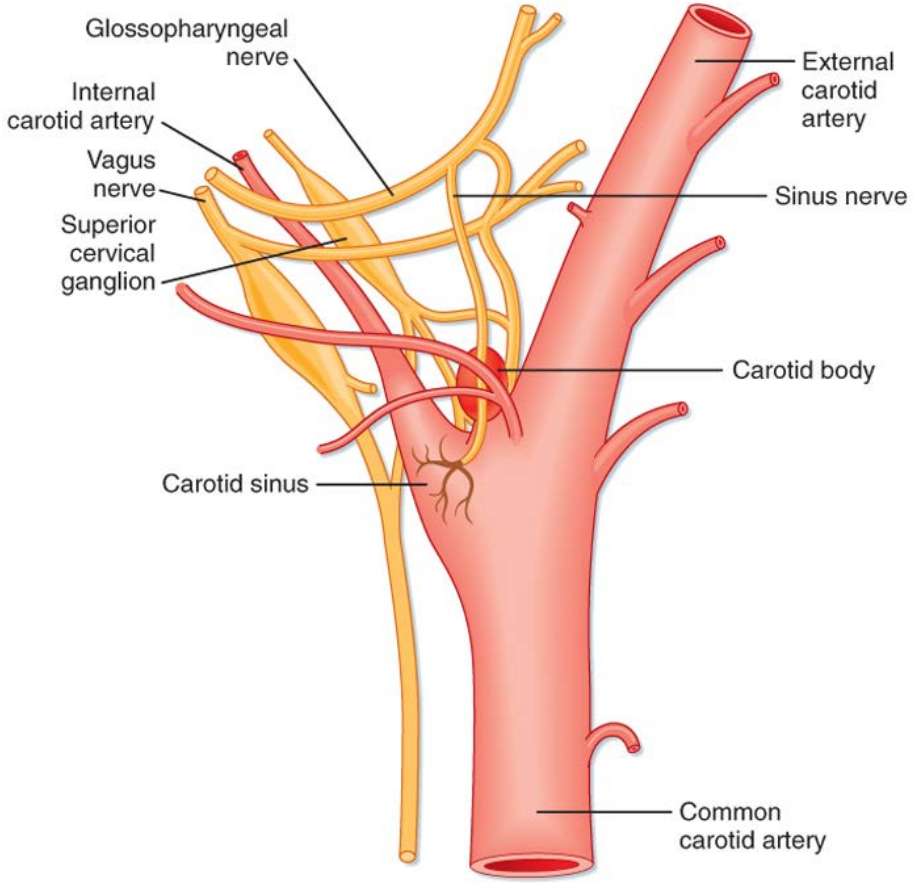

FIGURE: Koeppen & Stanton: Berne and Levy Physiology, 6th Edition. 2008

Example: Potential Risks of Peripheral AV Fistulas

Potential Complications

- Combined arterial and venous access
- Predicable venous stenosis known to develop in AVF
- Adverse hemodynamic effects of the AVF on the cardiopulmonary system
- Device not easily removable

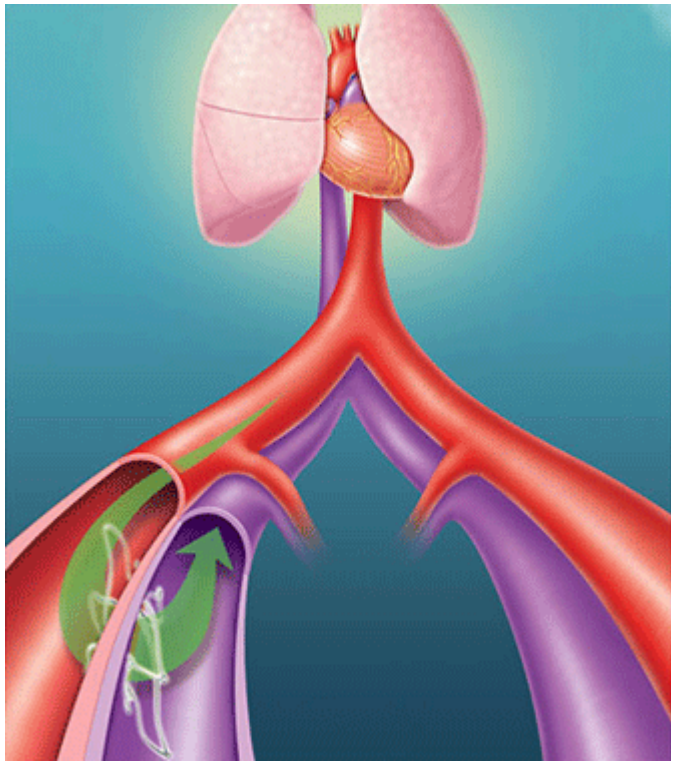

FIGURE: https://www.medgadget.com/2015/01/coupler-device-shows-promise-hypertension-control-video.html

Example: Risks of Renal Denervation

Potential Complications

- Vascular access site complications
- Renal artery injury:
  - Acute dissection
  - Late stenosis
- Impact on longer term glomerular filtration rate (GFR)

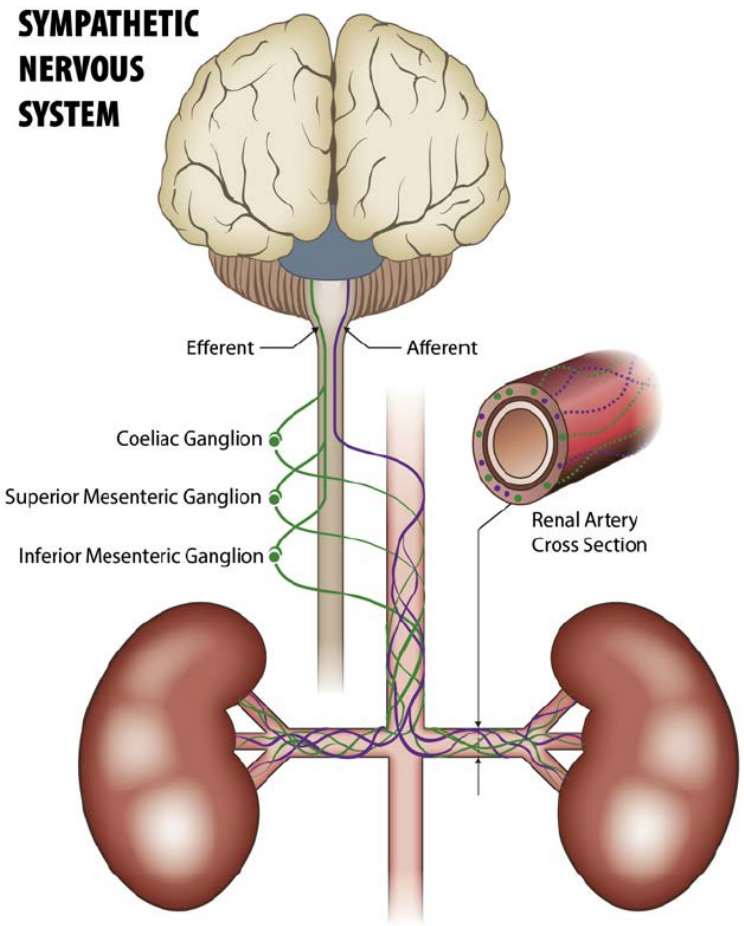

Figure 1. Functional anatomy of renal sympathetic innervation.

FIGURE: Froeschl, et al. Ca J of Cardiology. 2013;29:636-638

Catheter based RD Safety

STUDY	HTN-1	HTN-2	HTN-3	Enlig-HTN	Reduce-HTN
Subject Number	153	52	364	46	146
Final Safety Subject Number	88	70	364	46	146
Device	Symplicity	Symplicity	Symplicity	Enlighten	Vessix
Months of F/U	36	36	6	6	6
Imaging Modality	US or CT or MR	US or CT or MR	US or CT or MR	US	US
Access Site Complications	3	1	0	8	5
Acute Renal Artery Issues	1	1	0	12	1
Last RAS > 70% or stent	2	0	1	1	1
Worse renal function	1	2	5	1	2

Thomopoulos C, et al. Safety of Renal Denervation. In: Tsioufis C, Schmieder RE, Mancia G, eds. Interventional Therapies for Secondary and Essential Hypertension. Cham: Springer International Publishing; 2016:231-43.

Renal Artery Imaging

METHOD	ADVANTAGES	DISADVANTAGES
Duplex Scan	• Cost effective • No radiation	• Operator dependent • Distal visualization challenging • Poor grading of degree of stenosis
CT Angio	• High accuracy • Multiplanar resolution, even of branch vessels	• Higher cost • Exposure to radiation & iodinated contrast
MR Angio	• No radiation • Accurate in detecting proximal lesions	• Gadolinium exposure • Less accurate for branch vessels • Higher cost

Safety Evaluation of Devices

- To properly assess safety, trials of devices used to treat hypertension require:
  - Meaningful safety endpoints,
  - Appropriate imaging to be able to accurately capture all relevant events, and
  - Adequate study duration to assess the potential for device related adverse events
- Primary safety hypothesis remains important for device safety evaluation

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BP as a Surrogate Endpoint

- Framingham Heart Study: Elevated SBP is associated with increased risk of CV events, with greater risk with advancing age
- Medications: Relative risk of total major CV events reduced with treatment; no significant difference by drug class
- Surrogate endpoint of BP is appropriate if the reduction in BP is associated with morbidity and/or mortality outcomes
- Unclear whether BP lowering by devices will lead to same CV benefits as established by current medications

Kannel WB, et al. Am J Cardiol. 1971;27(4):335-46

Comparison of Methods of BP Measurement

Parameter	Office BP	Home Daytime BP	ABPM
Predicts CV outcomes	Poor-Moderate	Moderate	High
Detects nighttime dipping	Poor	Moderate	High
Captures 24 h activity	Poor	Depends on number of readings	High
Allows risk stratification	Poor	Moderate	High
Easy to perform	Yes	Depends on number of readings	No
Identifies WC or masked HTN	No	Maybe	Yes
Observer bias	High	Low	Low

Pickering TG, et al. Engl J Med. 2006;354: 2368–2374
Whelton PK, et al. Circulation. 2018;138(17):e484-e594.

Defining Clinically-Meaningful BP Reduction

The relationship between BP and risk for future CV events is well established, but the BP levels likely vary according to methodology of measurement:

- Lassere: Meta-analysis; BP measurement modality not defined or variable: Showed that the threshold for stroke was ≥7.1 mmHg SBP/2.4 DBP
- Verdecchia: Meta-analysis; BP measurement modality not defined or variable: Showed that the threshold for CV events was ≥4.6 mmHg SBP/2.2 DBP
- Stevens: Meta-analysis; BP measurement modality variable: Showed an increased risk for CV events with elevated BP

Lassere, et al. BMC Med Res Method. 2012;12:27
Verdechhia, et al. J Hypertens. 2010;28:1356
Stevens, et al. BMJ. 2016;354:i4098

Efficacy of Anti-Hypertensive Medications for BP Reduction

Medication	No of Trials	No. of Patients	SBP* Reduction	DBP* Reduction
ACE Inhibitors	36	1898	12.5±5.3	9.5±3.4
Alpha Blocker	15	1849	15.5±4.8	11.7±1.3
Beta Blocker	18	908	14.8±4.9	12.2±2.2
Calcium-channel Blocker	34	3727	15.3±5.0	10.5±2.8
Thiazides	18	1657	15.3±5.4	9.8±3.6
Loop Diuretics	17	366	15.8±7.8	8.2±4.7
Average	137	10405	14.8±1.1	10.5±1.0

***Sitting or supine BP**

Wu J, et al. Am J Hypertens. 2005;18(7):935-42

Measuring Durability of Effect

- Recent feasibility studies have established short-term effectiveness around 2-3 months for RDN.
- Short-term results may not predict long-term success.
- Relationship of BP reduction to reduced CV events is based on a sustained effect of the pharmacological intervention
- Concomitant medication use during the trial may confound treatment effect.

Rapsomaniki E, et al. Lancet. 2014;383(9932):1899-911

Methods for Statistical Comparison

- RCT: Comparison of primary effectiveness between control and treatment arms.
- Demonstration of an outcome driven difference in mean BP reduction:

Superiority	Device – Control > 0
Super Superiority	Device – Control > Clinically Meaningful Margin

- Non-inferiority may provide value after approval of device based therapies.

Additional Endpoints to Consider

- Patients preference information (PPI)
  - Weigh risk tolerance and benefits
  - Quality of Life (QoL) measurements
- Patient reported outcome measures may be considered for certain secondary safety endpoints
- Assessment of changes in medication burden
  - Type, dosage, frequency

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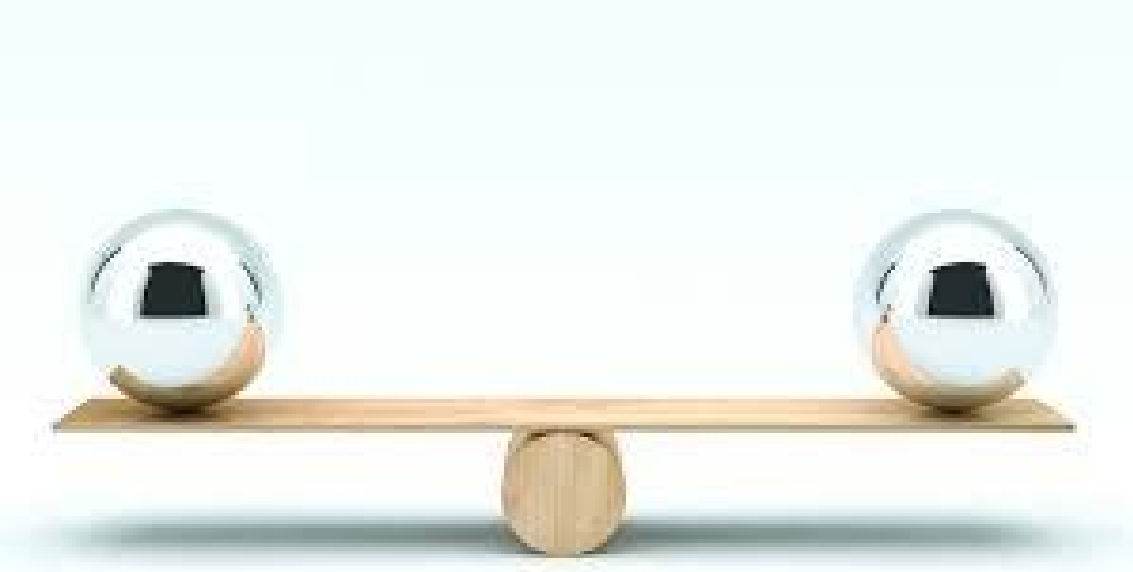
Pre / Post Market Balance



Premarket

Assurance of safety & effectiveness

Postmarket

Opportunities to gather additional clinical data and real-world evidence

Pre / Post Market Balance (cont.)

- Patient Population
  - Specific versus Generalizable
  - Identification of responders
- Identification of longer term safety concerns
- Evaluating the durability of the treatment effect with real world medication use

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Conclusions

- Device based therapies may be an important option for different hypertensive populations
- Establish reasonable benefit-risk profile and population
- Future clinical studies should answer key questions for safety and effectiveness

Recap of Panel Purpose

- FDA is requesting panel recommendations on:
  - Indications for use
  - Critical clinical study design elements
  - Safety endpoints
  - Effectiveness endpoints
  - Device and population based benefit and risk balance
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FDA U.S. FOOD & DRUG ADMINISTRATION

Thank you