Hypertension: Guidelines and Updates

Hypertension 2017: Where are We Now?
VuMedi Webinar, November 21, 2017

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Presenter Disclosure Information

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FINANCIAL DISCLOSURE:
Institutional Grant: Lilly
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I was a member of JNCs 7 & 8, but not the 2017 ACC/AHA HTN Guidelines

The content does not necessarily represent the official views of the SPRINT or ACCORD Steering Committees, the NIH, the VA, or the U.S. government

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/ APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

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Publication Information

This slide set is adapted from the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/ NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Published on November 13, 2017, available at: *Hypertension* and *Journal of the American College of Cardiology.*

The full-text guidelines are also available on the following websites: AHA (professional.heart.org) and ACC (www.acc.org)

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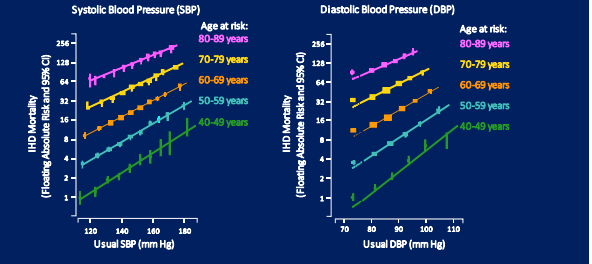
Blood Pressure (BP) and Cardiovascular Disease (CVD) Risk



Lewington et al. *Lancet.* 2002;360:1903-1913.

Diastolic BP Goal Trials

Several trials used DBP goal ~90 mm Hg and demonstrated consistent reduction of CVD events

1. **VA Cooperative Study**
   - Entry: DBP 90-129 mm Hg
   - Goal: DBP <90 mm Hg
2. **Hypertension Detection and Follow-up Program (HDFP)**
   - Entry: DBP ≥90 mm Hg
   - Goal: DBP ≤90 mm Hg and at least 10 mm Hg ↓
3. **Australian National Blood Pressure (ANBP) Trial**
   - Entry: DBP 95 to <110 mm Hg
   - Goal: DBP ≤90 mm Hg initially, then after 1 year, lowered to ≤80 mm Hg
4. **STOP-Hypertension Trial**
   - Entry: SBP 180-230 mm Hg + DBP ≥90 mm Hg, or DBP 105-120 mm Hg irrespective of SBP
   - Goal: BP <160/95 mm Hg

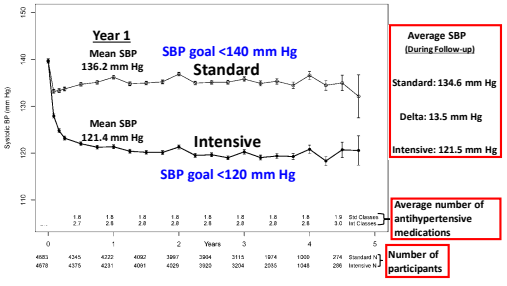
HOT Trial
- no further benefit (or harm) to DBP <85 or <80 mm Hg

Major Randomized Trials Testing SBP Goals in General (Older) Populations Prior to SPRINT

	SHEP	Syst-Eur	HYVET	JATOS	VALISH
Age	≥60	≥60	≥80	65-85	70-84
Number	4,736	4,695	3,845	4,418	3,260
Entry SBP	160-219	160-219	160-199	≥160	≥160
Goal SBP	<148	<150	<150	<140	<140
Achieved SBP	142	151	144	136	137
Stroke ↓	36%	42%	ns	ns	ns
CVD ↓	32%	31%	34%	ns	ns
Mortality ↓	ns	ns	21%	ns	ns

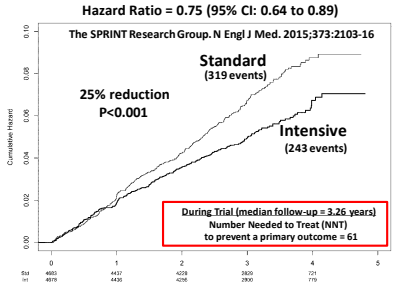
SBP = systolic blood pressure; CVD = cardiovascular disease

Systolic BP Intervention Trial (SPRINT)



SPRINT Primary Outcome (CVD)
Cumulative Hazard

Hazard Ratio = 0.75 (95% CI: 0.64 to 0.89)

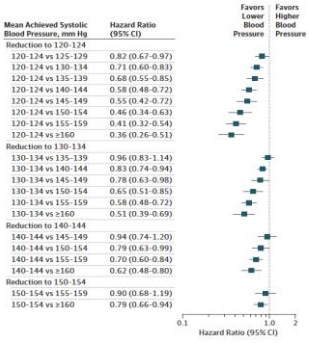


	Hazard Ratio	P value
Primary Outcome	0.75	<0.001
Components		
All MI	0.83	0.19
Non-MI ACS	1.00	0.99
All Stroke	0.89	0.50
All HF	0.62	0.002
CVD Death	0.57	0.005

Hazard ratios and 95%CIs for major CVD associated with more intensive reductions in SBP

42 trials, n=144,220
Most of the trials included significant numbers of participants with diabetes mellitus

Bundy JD, et al. JAMA Cardiol. 2017;2:775-81



Changes in BP Categories from JNC7 to the New Guideline

SBP		DBP	JNC7	2017 ACC/AHA
<120	and	<80	Normal BP	Normal BP
120–129	and	<80	Prehypertension	Elevated BP
130–139	or	80–89	Prehypertension	Stage 1 hypertension
140–159	or	90-99	Stage 1 hypertension	Stage 2 hypertension
≥160	or	≥100	Stage 2 hypertension	Stage 2 hypertension

The categorization of BP should be based on the average of ≥ 2 readings on ≥ 2 occasions following a standardized protocol.
Adults with SBP and DBP in two categories are designated into the higher category.

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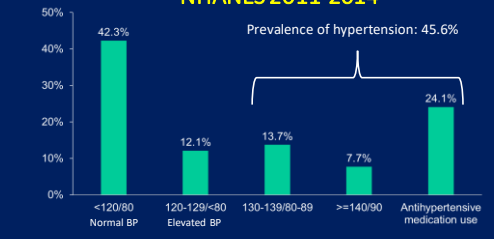
120–129	and	<80	Prehypertension	Elevated BP
130–139	or	80–89	Prehypertension	Stage 1 hypertension
140–159	or	90-99	Stage 1 hypertension	Stage 2 hypertension
≥160	or	≥100	Stage 2 hypertension	Stage 2 hypertension

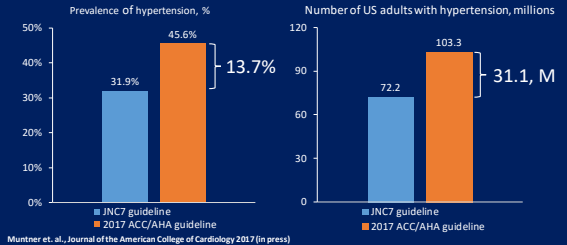
The 2017 ACC/AHA guideline definition of hypertension:
SBP ≥ 130 mm Hg or
DBP ≥ 80 mm Hg

Distribution of US adults into BP Categories – NHANES 2011-2014



Muntner et. al., Journal of the American College of Cardiology 2017 (in press)
Muntner, et. al., Circulation 2017 (in press)

Prevalence of Hypertension – 2017 ACC/AHA and JN7 Guidelines



Muntner et. al., Journal of the American College of Cardiology 2017 (in press)
Muntner, et. al., Circulation 2017 (in press)

BP Measurement Methodology in SPRINT

- Similar to what has been used in virtually all HTN outcome trials defining the recommended BP thresholds and goals in guidelines.
- Similar to what has been recommended for clinical practice by virtually all HTN guidelines around the world for decades, including all JNCs, ASH/ISH, VA/DoD, ESH/ESC, UK/NICE, Canadian/CHEP, Australian, ...

BP Measurement in SPRINT (Automated)

- Visit BP was the average of 3 seated office BP measurements obtained using an automated measurement device: Omron 907XL.
- Appropriate cuff size was determined by arm circumference.
- Participant was seated with back supported and arm bared and supported at heart level.
- Device was set to delay 5 minutes and then take/average 3 BP measurements, during which time participant refrained from talking.

Cushman, et al. Hypertension. 2016;67:263-5

Accurate Measurement of BP in the Office

COR	LOE	Recommendation for Accurate Measurement of BP in the Office
I	C-EO	For diagnosis and management of high BP, proper methods are recommended for accurate measurement and documentation of BP.

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Out-of-Office and Self-Monitoring of BP

COR	LOE	Recommendation for Out-of-Office and Self-Monitoring of BP
I	A^{SR}	Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions.

SR indicates systematic review.

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BP Treatment Threshold and the Use of CVD Risk Estimation to Guide Drug Treatment of Hypertension

COR	LOE	Recommendations for BP Treatment Threshold and Use of Risk Estimation* to Guide Drug Treatment of Hypertension
I	SBP: A DBP: C-EO	Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher, and for primary prevention in adults with an estimated 10-year ASCVD risk of 10% or higher and an average SBP 130 mm Hg or higher or an average DBP 80 mm Hg or higher.
I	C-LD	Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher.

*ACC/AHA Pooled Cohort Equations (http://tools.acc.org/ASCVD-Risk-Estimator/) to estimate 10-year risk of atherosclerotic CVD (ASCVD).

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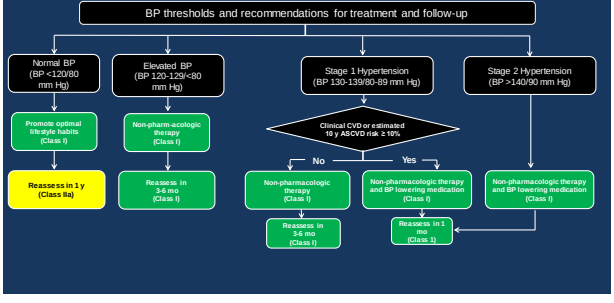
ACC/AHA POOLED COHORT EQUATIONS

To estimate the 10-year risk of atherosclerotic CVD

http://tools.acc.org/ASCVD-Risk-Estimator/

BP THRESHOLDS AND RECOMMENDATIONS FOR TREATMENT AND FOLLOW UP



Thank you!

Hypertension 2017: Where are we now?

BP Targets in Patients with and without Chronic Kidney Disease.

Clive Rosendorff, MD, PhD, DScMed, FACC, FAHA, FRCP.

Professor of Medicine (Cardiology), Icahn School of Medicine at Mount Sinai, New York, NY, USA
and
James J. Peters VA Medical Center, Bronx, NY, USA

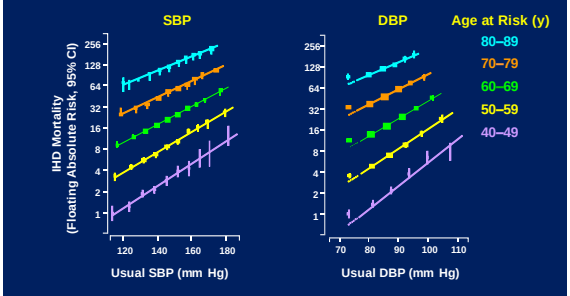
Disclosures

I was a member of the SPRINT Intervention Committee

I have no other disclosures relating to the subject matter of this presentation.

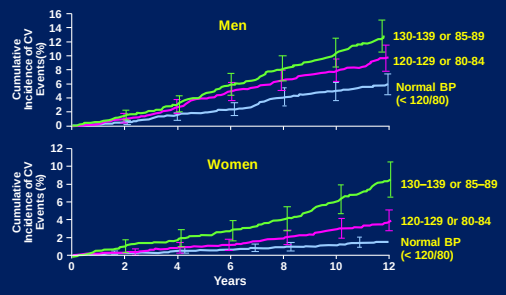
Lower Is Better:

12.7 million person years
IHD Rates by SBP, DBP, and Age



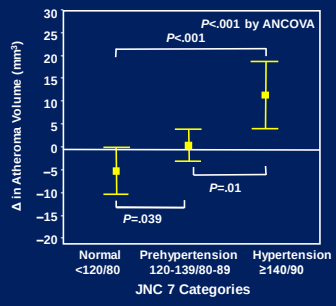
IHD = ischemic heart disease; CI = confidence interval.
Lewington et al. *Lancet.* 2002;360:1903-1913.

Impact of Pre-Hypertension on CV Risk
Lower Blood Pressure is Better

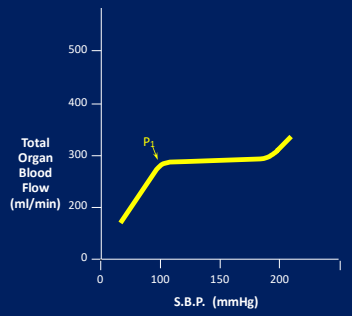


Normal BP: < 120/80 mm Hg; Pre-hypertension: 120–139 or 80–89 mm Hg.
Vasan RS et al. *N Engl J Med.* 2001;345:1291-1297.

Progression Rate of Coronary Artery Disease According to JNC 7 BP Categories

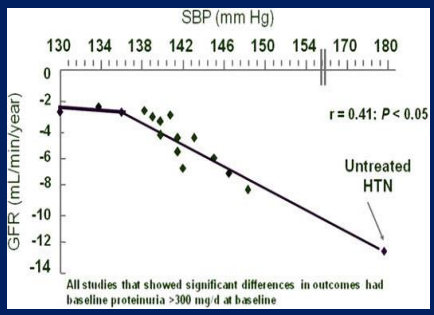


Sipahi I et al. *J Am Coll Cardiol.* 2006;48:833-838.

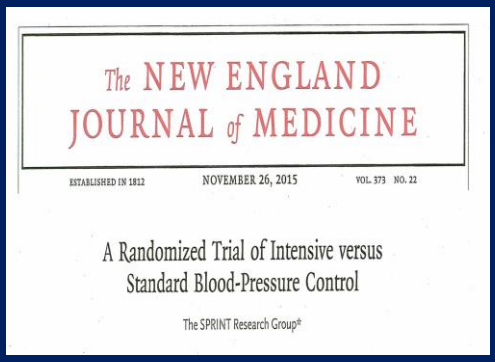


Rosendorff, In "Hypertension, A Companion to Braunwald's Heart Disease" Ed. Black & Elliott, Elsevier 2013; 253-261

Achieved B.P. and the Rate of Decline in Renal Function.



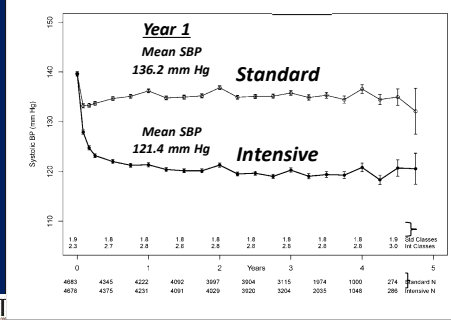
Khosla et al. Med Clin N Am 2009;93:697-715



Selected Baseline Characteristics of the SPRINT Population

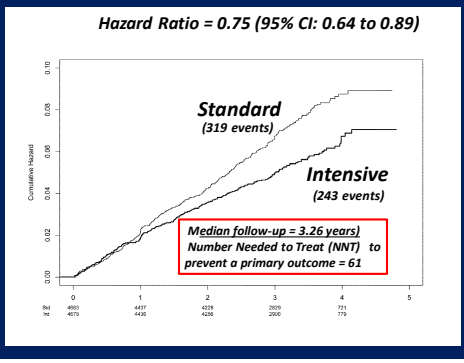
CHARACTERISTIC	INTENSIVE TREATMENT (N=4678)	STANDARD TREATMENT (N=4683)
Criterion for increased CV risk – no. (%)		
Age ≥75 yr	1317 (28.2)	1319 (28.2)
Chronic kidney disease	1330 (28.4)	1316 (28.1)
Cardiovascular disease	940 (20.1)	937 (20)
Framingham R.S.≥15%	2870 (61.4)	2867 (61.2)
Estimated GFR – ml/min/1.73m^2		
All	71.8±20.7	71.7±20.5
eGFR ≥60	81.3±15.5	81.1±15.5
eGFR <60	47.8±9.5	47.9±9.5

Systolic BP During Follow-up

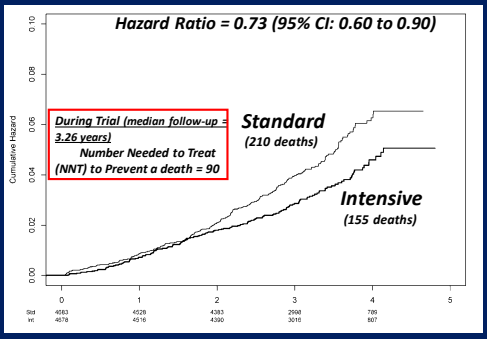


SPRINT Primary Outcome

MI, ACS, stroke, HF, CV death



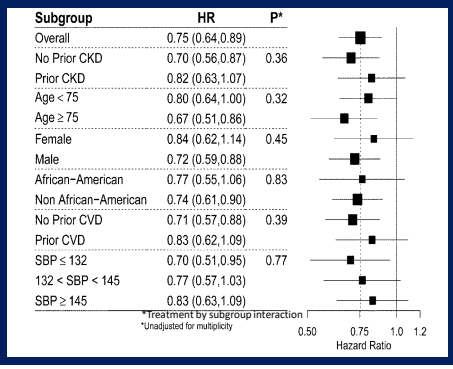
SPRINT - All-cause Mortality Cumulative Hazard



SPRINT Primary Outcome and its Components Event Rates and Hazard Ratios

	Intensive		Standard			
	No. of Events	Rate, %/year	No. of Events	Rate, %/year	HR (95% CI)	P value
Primary Outcome	243	1.65	319	2.19	0.75 (0.64, 0.89)	<0.001
All MI	97	0.65	116	0.78	0.83 (0.64, 1.09)	0.19
Non-MI ACS	40	0.27	40	0.27	1.00 (0.64, 1.55)	0.99
All Stroke	62	0.41	70	0.47	0.89 (0.63, 1.25)	0.50
All HF	62	0.41	100	0.67	0.62 (0.45, 0.84)	0.002
CVD Death	37	0.25	65	0.43	0.57 (0.38, 0.85)	0.005

Primary Outcome Experience in the Six Pre-specified Subgroups of Interest



It is a fool who is blown about with every wind of criticism

Samuel Johnson 1709-1784

CRITICISMS

1. Unacceptable incidence of adverse events
2. "I would not apply these findings to my elderly, frail patients"
3. The absolute risk reduction is small
4. No benefit in preventing stroke
5. We do not measure blood pressure with the same care as in SPRINT

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Adverse Events

1.Patients without CKD at Baseline: ≥30% reduction in eGFR:
Standard: 0.35%/y
Intensive: 1.21%/y P<0.001 (?RAS blockers)

2. Other

	Intensive %	Standard %	HR	P
Hypotension	2.4	1.4	1.67	0.001
Syncope	2.3	1.7	1.33	0.05
Hyponatremia	3.8	2.1	1.76	<0.001
Hypokalemia	2.4	1.6	1.50	0.006

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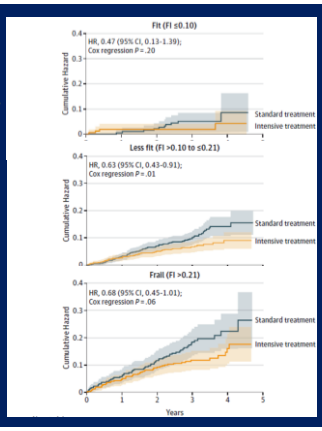
SPRINT
Primary Outcome
in Subjects >75 years,
by Baseline Frailty Status



Williamson et al.
JAMA 2016,
doi:10.1001/jama.2016.7050

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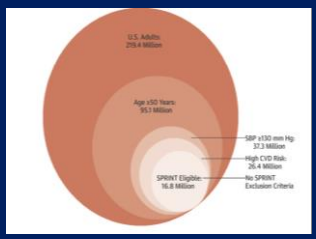
Generalizability of SPRINT Results to the U.S. Adult Population, and Potential Impact on Outcomes.



	CV Events %/y	Mortality %/y	Stroke %/y
Standard	2.19	1.40	0.47
Intensive	1.65	1.03	0.41
Difference	0.54	0.37	0.06
Fewer events p.a.	90,700	62,200	10,100

Bress et al. *J Am Coll Cardiol*. 2016;67(5):463-472.

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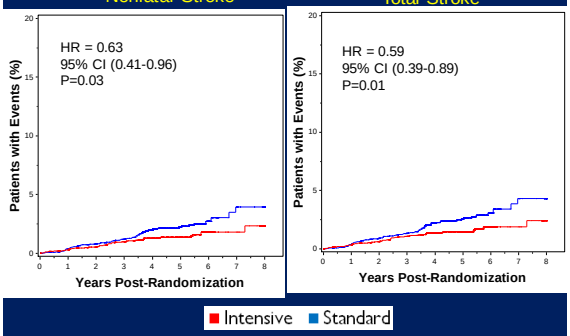
ACCORD - STROKE



Why were Stroke Outcomes in ACCORD and SPRINT Different?

An Hypotheses

ACCORD stroke K-M curves started to diverge at about 3.5 years. SPRINT was stopped before that (median follow-up 3.26 years). The SPRINT 11% RRR for stroke might have increased to significant levels with more time.

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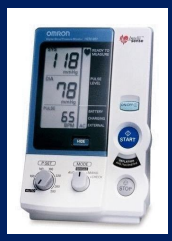
CRITICISMS

1. Unacceptable incidence of adverse events
2. "I would not apply these findings to my elderly, frail patients"
3. The absolute risk reduction is small
4. No benefit in preventing stroke
5. We do not usually measure blood pressure with the same care as in SPRINT.

"The doctor will now measure your blood pressure"



BP MEASUREMENT

1. Patient sits in a quiet room for 5 minutes.
2. Automated BP measurement system.
3. Mean of 3 measurements.

Categories of BP in Adults

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120-129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130-139 mm Hg	or	80-89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

Whelton PK et al. 2017 High Blood Pressure Clinical Practice Guideline

Summary

- The 130/80 mm Hg cutoff for the diagnosis of hypertension and for the goal of anti-hypertensive treatment is reasonable.
- However, physicians should be aware that a SBP target of <120 mm Hg has been shown to reduce cardiovascular events and mortality.
- BP is a continuous variable, so "lower is better", as long as patients are carefully monitored for symptoms or signs of intolerance.
- Management should, therefore, be individualized.

Non-Pharmacological Treatment of Hypertension

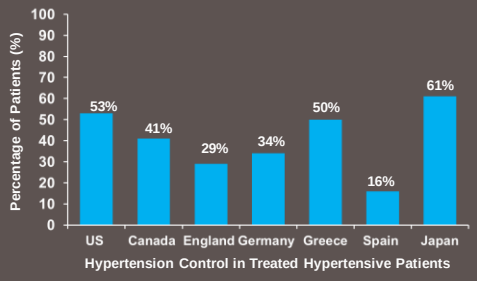
Marcos Rothstein, MD
Professor of Medicine
Department of Medicine ~ Division of Nephrology

Washington University in St. Louis
School of Medicine

"Haemastaticks"
(1733)
Stephen Hales
(1677-1761)

Medicine
Nephrology

Failure of Current Multidrug Approach to Successfully Treat Hypertension

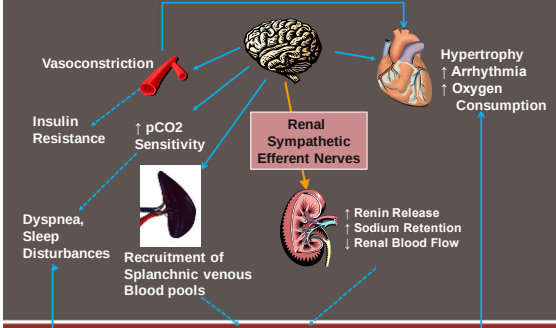


Kearney PM, et al. J *Hypertens*. 2004; 22:11-19.

Forms of Human HTN with Neurogenic Component

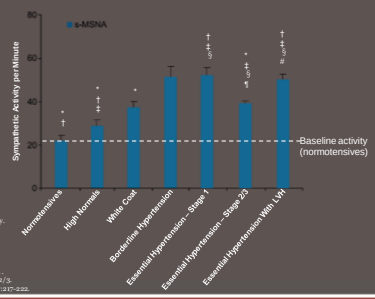
- Essential HTN
- Obesity-renal HTN
- Renal HTN
- HTN associated with obstructive sleep apnea
- Preeclampsia

Consequences of Chronic Elevated Central Sympathetic Drive



Central Sympathetic Drive in Hypertension

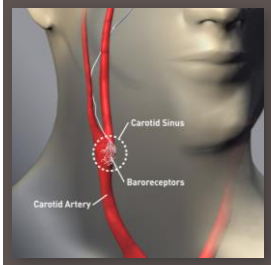
Sympathetic drive is elevated in multiple types of hypertension



s-MSNA=single-unite fferent sympathetic nerveactivity.
LVH=left ventricular hypertrophy.
*P<0.05 Compared with borderline hypertension.
†P<0.05 Compared with white coat hypertension.
‡P<0.05 Compared with normal pressure.
§P<0.05 Compared with high-normal pressure.
¶P<0.05 Compared with essential hypertension–stage 1.
#P<0.05 Compared with essential hypertension–stage 2/3.
Adapted from Smith P, et al. *Am J Hypertens.* 2004; 17:217-222.

Baroreflex Activation Therapy (BAT)

Continuously Modulates the Autonomic Nervous System



Carotid Baroreceptor Stimulation

↓

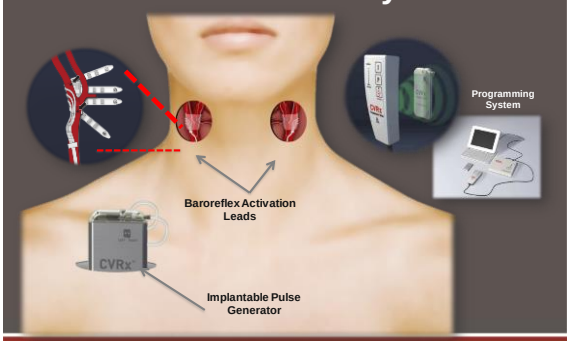
Brain

↓

Autonomic Nervous System
Inhibited **Sympathetic** Activity
Enhanced **Parasympathetic** Activity

Heart	Vessels	Kidneys
↓ HR	↑ Vasodilation ↓ Stiffness	↑ Diuresis ↓ Renin secretion

The CVRx Rheos System



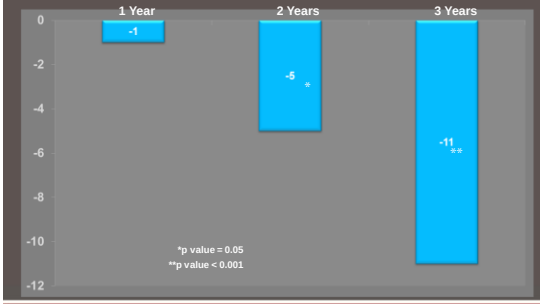
BP Pre/Post Implant

St. Louis Patient #2

	SBP	DBP	MAP	HR	Device RX
Pre	202 ± 21	108 ± 9	134 ± 11	79 ± 7	NA
6 Mths	153 ± 15	80 ± 13	101 ± 13	64 ± 8	Amps = 8 Freq = 30 pps Width = 480
8 Yrs*	130 ± 10	70 ± 6	90 ± 6	68 ± 5	Amps = 7 Freq = 50 pps Width = 120

*Drug Rx – Maxide 75/50 mgs QD

Change in Antihypertensive Therapeutic Index Over Time



Moving Forward:
Miniaturization to Reduce Procedure Invasiveness

Endovascular Prosthesis for Carotid Baroreceptor Amplification

(Mobius HD™, Vascular Dynamics Inc.)

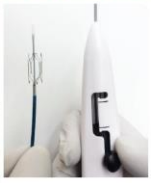
Current available sizes

- *Size A – 5.0-7.0 mm*
- *Size B – 6.25-9.00 mm*
- *Size C – 8.00-11.75 mm*

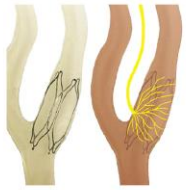
CAUTION: Investigational Device. Limited by Federal (United States) law to investigational use.

The Mobius HD® Implant

Question: Does this device provide a new, safe and effective treatment option for patients with Resistant Hypertension ?



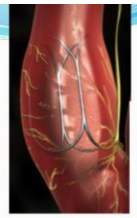
→ *Transfemoral artery sheath for insertion*

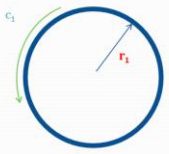


→ *implanted into the carotid bulb, increasing wall tension and sensitizing the baroreceptor*

Mechanism of Action

- Deployment of the device reshapes the artery
- The reshaped artery leads to an increased effective radius of curvature of the artery
- The increased effective radius amplifies the signals detected by the baroreceptors

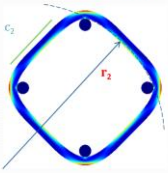




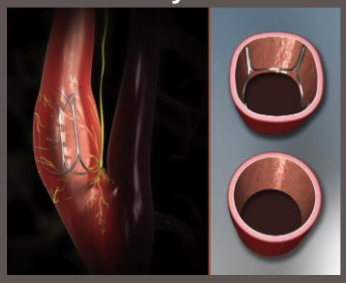
$$\uparrow\varepsilon = \frac{p \uparrow r}{t E}$$

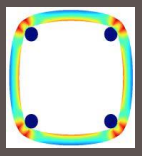
$r_2 > r_1$

- ε = wall strain
- p = pressure inside artery
- r = artery internal radius
- t = artery wall thickness
- E = Young's Modulus
- C = perimeter



Vascular Dynamics Mobius Device



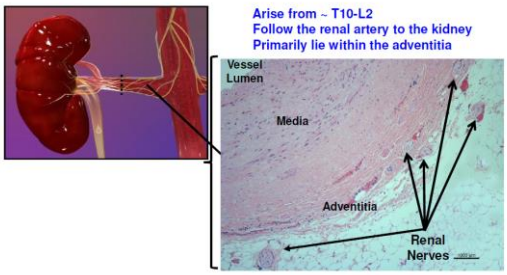


CALM-2 Study Exclusion criteria (3)

- **Procedural Considerations**
- Bleeding risk with dual anti-platelet therapy
- Current or planned use of chronic anticoagulation therapy
- Unsuitable for femoral access
- Prior carotid surgery or stent placement or therapeutic radiation to the neck
- Obstructive carotid disease, plaque, ulceration
- >150μm IMT* at implantation site and/or proximal to the carotid artery bulb and/or ≥50% disease distal to the carotid artery bulb, including the intracranial circulation
- Significant obstructive vascular disease, calcification or plaque of aortic arch and great vessels on ultrasound, CTA or MRA
- ICA lumen diameters <4.5 mm or >12.5 mm within the planned location of the implant placement (CTA or MRA) or landing zone restrictions, i.e. inadequate vessel length or tapering, and/or curvature, precluding safe implant placement

IMT intima-media thickness*

Renal Nerves as a Therapeutic Target



Techniques

RFA

US — Internal / Non-Invasive

Cryoblation

Pharmacological sympathetic blockade

Denervation Catheter Designs

Staged Clinical Evaluation

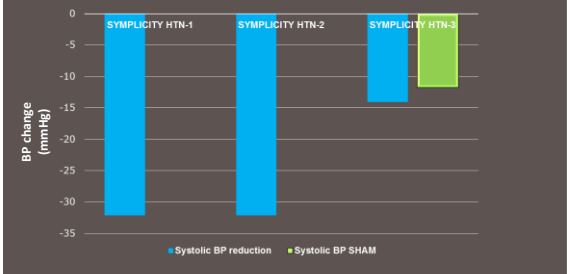
Symplicity HTN-1
- First-in-Man ✓
- Series of Pilot studies ✓

Symplicity HTN-2 ✓
EU/AU Randomized Clinical Trial

USA	EU/AU
Symplicity HTN-3 US Randomized Clinical Trial	Other Areas of Research: Insulin Resistance, HF/Cardiorenal, Sleep Apnea, More

Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

BP Lowering Effect of SYMPLICITY HTN trials



Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917; Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909 ; Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014;370:1393-1401

What Does This Mean?

- Renal Denervation does not work
- Wrong mouse trap
  - Next generation RF devices
  - Chemical
  - Ultrasound
- Wrong population of pt's
  - Too extreme

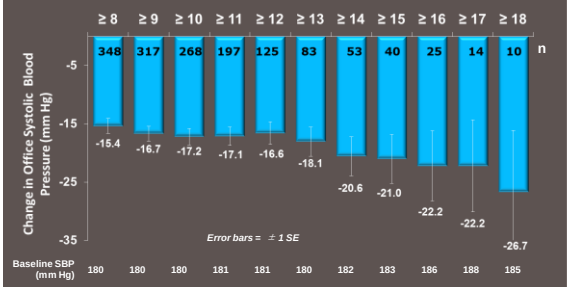
Simplicity HTN3: Exploring an Unexpected Result

- Inadequate operator technique
- Misunderstood renal nerve anatomy
- Suboptimal catheter design

Procedural Variability

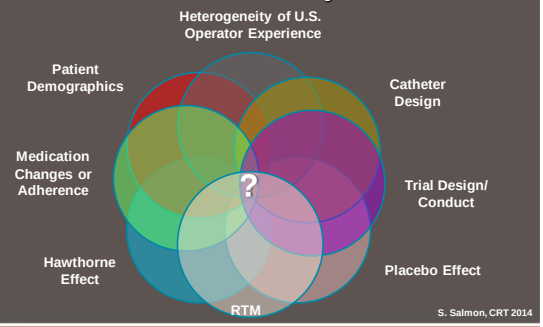
Correlation with # of ablations
Correlation with 4-quadrant ablation pattern

Relationship Between SBP Changes and Number of Ablations Attempted for Denervation Group at 6 Months



Number of ablations remains significant after adjustment for baseline blood pressure

Areas of Speculation on the Causes of the SYMPLICITY HTN-3 Efficacy Results..



S. Salmon, CRT 2014

Ongoing Studies Recruiting Patients

- SPYRAL HTN-ON MED Study
- SPYRAL HTN-OFF MED Study
- Renal Sympathetic Denervation in Metabolic Syndrome (Metabolic Syndrome Study)
- Renal Denervation Using the Vessix Renal Denervation System for the Treatment of Hypertension (REDUCE HTN:REINFORCE)
- TrAnsCatHeter Intravascular Ultrasound Energy deliVery for rEnal Denervation (ACHIEVE)

https://clinicaltrials.gov/ct2/results?term=renal+denervation&pg=2

Ongoing Studies Recruiting Patients

- Renal Denervation using the KONA External Ultrasound device
- Renal Denervation in Patients with Chronic Heart Failure and Resynchronization therapy
- Renal Denervation in Patients with Heart Failure Secondary to Chagas Disease
- Renal Denervation in Patients with Heart Failure and Severe Left Ventricular Dysfunction
- A Feasibility Study to Evaluate the Effect of Concomitant Renal Denervation and Cardiac Ablation on AF Recurrence
- Renal Denervation in Patients Undergoing VT Ablation: Combined Renal Denervation and VT Ablation vs Simply VT Ablation

https://clinicaltrials.gov/ct2/results?term=renal+denervation&pg=2

Medtronic Spyral Catheter

SPYRAL HTN Global Clinical Trial Program

First Phase Includes Two Parallel Trials

20 Sites Globally

SPYRAL HTN-OFF MED
- 100 patients
- Sham RCT (1:1)
- Main body and branch ablation
- No specific medication requirement
- Focus on ABPM change at 3 months
- **QOL data to be measured**

SPYRAL HTN-ON MED
- 100 patients
- Sham RCT (1:1)
- Main body and branch ablation
- No max tolerated dose
- Focus on ABPM change at 3 months
- QOL data to be measured

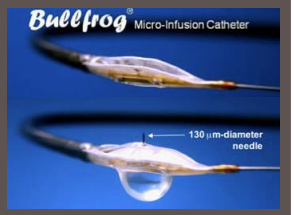
Second Phase

SPYRAL HTN Pivotal
- Based on OFF/ON trial results
- Cost Effectiveness Data/QOL to be measured

Adventitial Delivery Targets the Renal Sympathetic Nerves

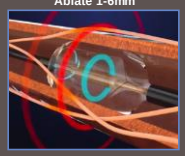
The Bullfrog Micro-Infusion Catheter

- Uses common balloon-inflation techniques (2 atm)
- Allows targeted deliver to renal sympathetic nerve sheath
- FDA 510(k)-cleared for delivery to the vessel wall and perivascular area



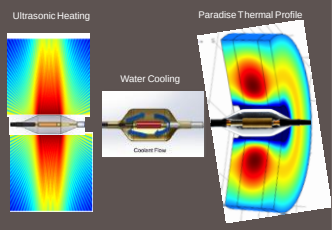
Paradise: Ultrasound Technology for Renal Denervation

Paradise RDN System Objective
Cool 0-1mm
Ablate 1-6mm



- Cool – to protect the renal artery – from the inside
- Heat – to ablate the renal nerves – on the outside

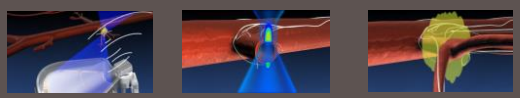
Paradise Technology Modeling



Paradise Thermal Profile Objective:
Protect Renal Arteries & Ablate Renal Nerves

Kona Medical *Surround Sound*® HTN Therapy Non-Invasive Renal Denervation

1. Imaging and therapy ultrasound positioned beneath patient
2. Ultrasound imaging used to identify renal artery

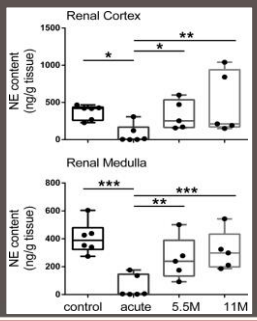


3. External ultrasound energy guided by ultrasound image and motion tracking
4. Focused ultrasound energy administered in treatment "pattern" to ablate nerves located outside of artery
5. Energy field surrounds artery, ablates renal nerves

Note: Kona Surround Sound Hypertension Therapy is investigational and not approved for sale

Reinnervation Following RDN?

NE content in sheep following RDN and at 5.5 and 11 months



Booth et al, Hypertension 2015

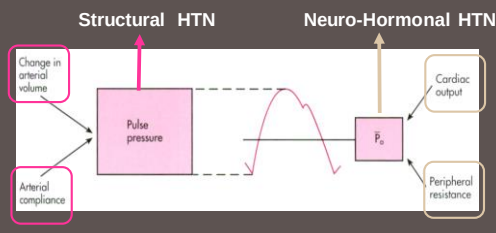
Indications for Renal Denervation Looking to the Future

Indication	Comment
1. Treatment-resistant hypertension (TRH)	• Poorly defined condition • TRUE TRH is rare • Inconsistent evidence that RDN is better than drugs • Improved RDN studies ongoing
2. Patients with poor drug compliance	• Improved in long-term BP control could justify RDN intervention
3. Systolic HTN in the elderly	• Sympathetic NS is a factor • Responds well to drugs • Question about ablation energy across atherosclerotic vessels

Indications for Renal Denervation Looking to the Future

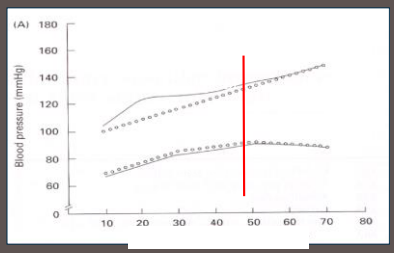
Indication	Comment
4. Hypertension in young adults	• High sympathetic NS is a hallmark • Early evidence for LVH, arterial stiffness, etc • RDN could potentially improve life-long natural history of HTN
5. Hypertension related to CKD	• Early evidence the RDN may reduce rate of decline
6. Atrial fibrillation and heart failure	• These are being studied independent of hypertension

Structural verses Neuro Hormonal Hypertension



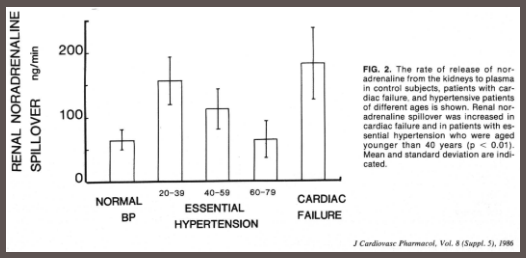
Adapted from *Physiology;* Berne & Levy

Elastic Fibers are Terminally Differentiated After the age of 50, HTN is principally Structural



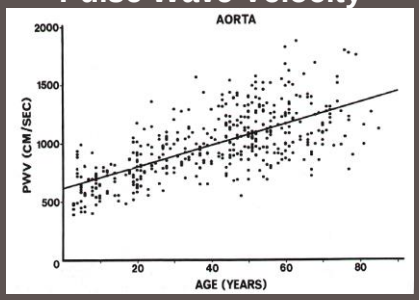
Burt. *Hypertension* 1995;25:313

Renal Sympathetic Activity Declines with Age



Esler et.al., J Cardiovasc Pharmacol, 1986

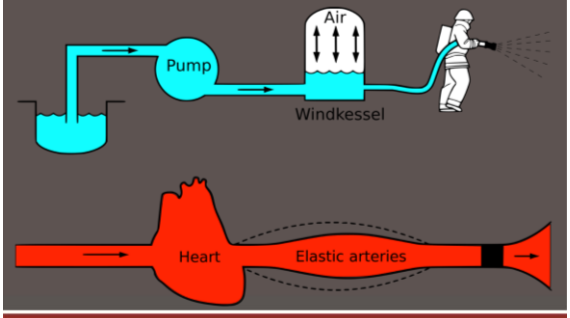
Loss of Aortic Elasticity Increases Pulse Wave Velocity



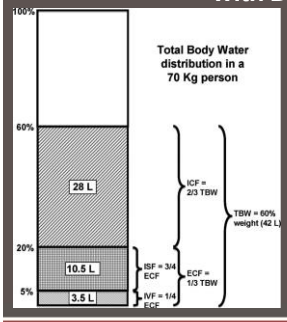
Avolio et al; *Circ*:1983

The aorta is meant to buffer each heart beat

The Windkessel Function of the Aorta



Reduction of Arterial Volume with Diuretics



2.4% of total body water is arterial (42l water in a 70kg adult);

To reduce effective arterial volume by 1 liter, a diuretic must remove 25% circulating volume;

Restoring Windkessel with diuretics inherently activates RAA and is associated with systemic AE.

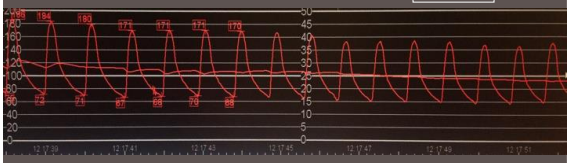
adapted by Cevasco M and Dunlap ME

Mechanical solutions for structural hypertension: Immediate BP reduction (-28/-15 mmHg)

186-180

Systolic BP
(mmHg)

150-153



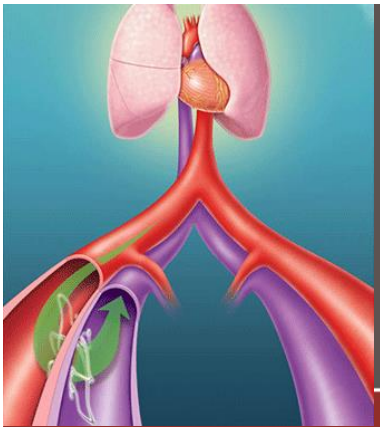
~72

Diastolic BP
(mmHg)

~60

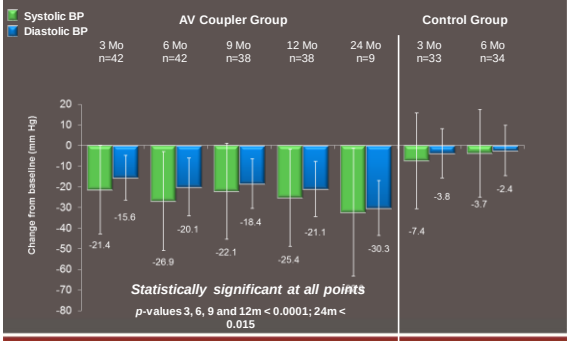
Eliminates the possibility of placebo, sham or Hawthorne effects

ROX Coupler Device

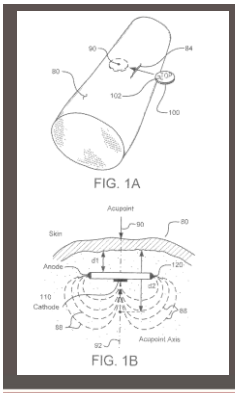


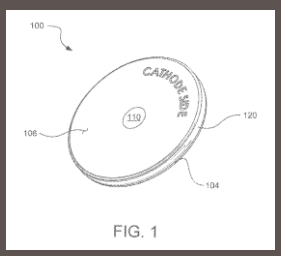
ROX Coupler Device

Randomized RH-02: Change in Office BP



Electroceutical (eCoin)





Valencia Technologies Patent US 8805512 B1

eCoin for the Rx of HTN

Median Nerve Stimulation

- Activates somatic afferent nerve fibers in the BP control centers of the brain:
  - Arcuate and periventricular nuclei of the hypothalamus
  - Ventrolateral periaqueductal gray in the midbrain
  - Nucleus tractus solitary
  - Caudal ventral lateral medulla

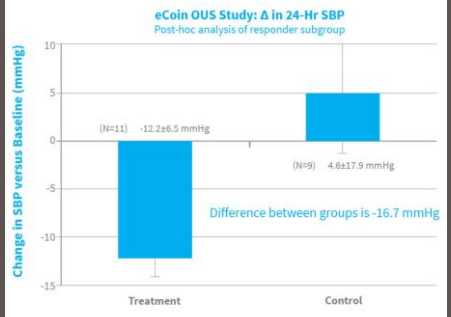
This stimulation will release opioids, GABA and cause sustained inhibition of sympathetic premotor neurons, responsible for vasoconstriction

Tjen-A-Looi SC, Li P, et al. AJP, 2007:293(6):H3627-H3635

Median Nerve Stimulation

- 30 minute stimulation will release prolonged transcriptional precursors such as mRNA preproenkephalin (PPE) for over 72 hrs.
- Long-term effects are seen between 4-8 wks
- Proposed scheme: 30 min sessions weekly at 5-10 pulses/sec.

Li M, Tjen-A-Looi SC, et al. Autonomic Neuroscience 2012:170(0):30-35



Summary

- **Resistant Hypertension is a "Rule-Out" Diagnosis**
- **Poor Drug and Diet Adherence and High Sodium Intake are most common causes**
- **Device Therapy is still evolving and moving forward**