Hypertension (HTN) & Cardiovascular Disease (CVD)

Plus: HTN management in 2024 and beyond

Florian Rader, M.D, M.Sc.
Medical Director, Hypertension Center of Excellence
Co-Director, Clinic for Hypertrophic Cardiomyopathy and Aortopathies
Associate Director, Non-invasive Laboratory

September 21, 2024 L.A. Care Quality Improvement Conference
Directly Provided CME/CE Activity by L.A. Care Health Plan
Hilton Woodland Hills, CA

Cedars Sinai

Disclosures

The following CME Planners do not have relevant financial relationships with ineligible companies in the past 24 months:

- Leilanie Mercurio, L.A. Care Provider Continuing Education (PCE) Program Manager, CME Planner.
- Donna Sutton, Senior Director, Stars Excellence, Quality Improvement, L.A. Care Health Plan, CME Planner.
- Bettsy Santana, MPH, Senior Manager of Initiatives, Quality Improvement, L.A. Care Health Plan, CME Planner.

The following ineligible companies have relevant financial relationships with CME Presenter Florian Rader, MD, MSc, Medical Director of the Hypertension Center of Excellence, Associate Director of Non-invasive Laboratory; and Co-Director, Clinic for Hypertrophic Cardiomyopathy and Aortopathies at Cedars-Sinai Smidt Heart Institute.

- Bristol Myers Squibb, Cytokinetics, Idorsia, Recor Medical, Medtronic, and Mineralys.

- Dr. Florian Rader is a Consultant for the ineligible companies listed here.

All relevant financial relationships of Dr. Florian Rader, CME Faculty, with ineligible companies have been mitigated.

An ineligible company is any entity whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Commercial support was not received for this CME/CE activity.

Learning Objectives

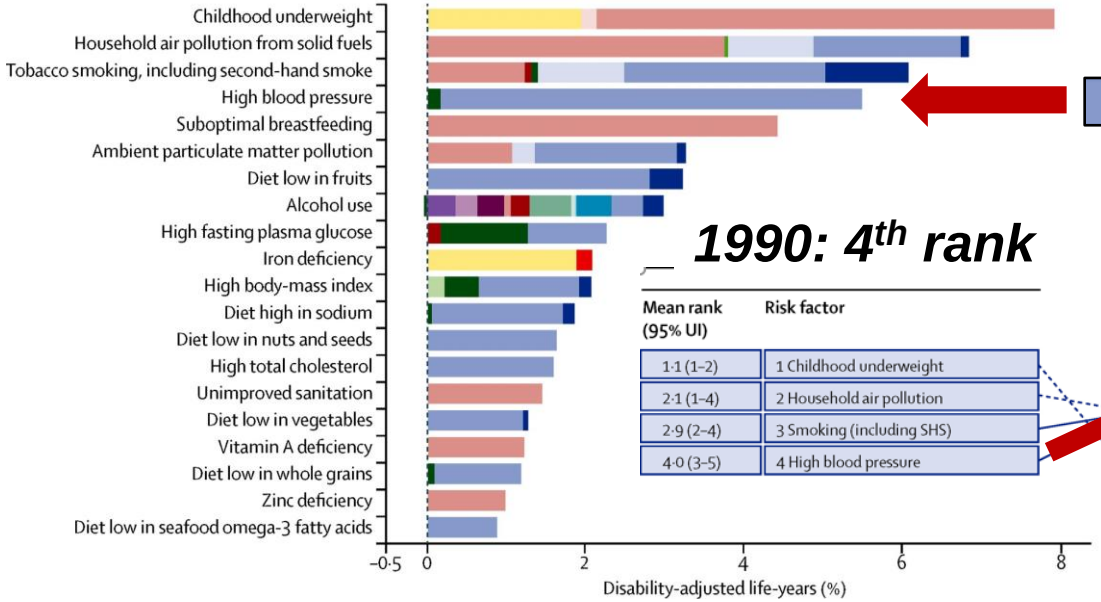
At the completion of the activity, learners can:

1. **Summarize differences in BP trajectories between women and men.**
2. **Identify hypertension as main modifiable cardiovascular risk factor.**
3. **Specify BP goals in essential hypertension.**
4. **List first line treatment options for hypertension.**
5. **Recognize main indications and contraindications of renal denervation.**

Overview

1. **Hypertension's global disease burden and some sex differences**
2. **The trajectory of HTN in women vs. men**
3. **Hypertension as it related to CV risk**
4. **The guideline debacle and BP treatment goals**
5. **Screening for secondary hypertension made easy**
6. **Hypertension treatment-my approach**
7. **New drugs and renal denervation**

Hypertension= global public enemy #1



Cardiovascular risk

1990: 4th rank

Mean rank (95% UI)	Risk factor
1·1 (1–2)	1 Childhood underweight
2·1 (1–4)	2 Household air pollution
2·9 (2–4)	3 Smoking (including SHS)
4·0 (3–5)	4 High blood pressure

2010: 1st rank

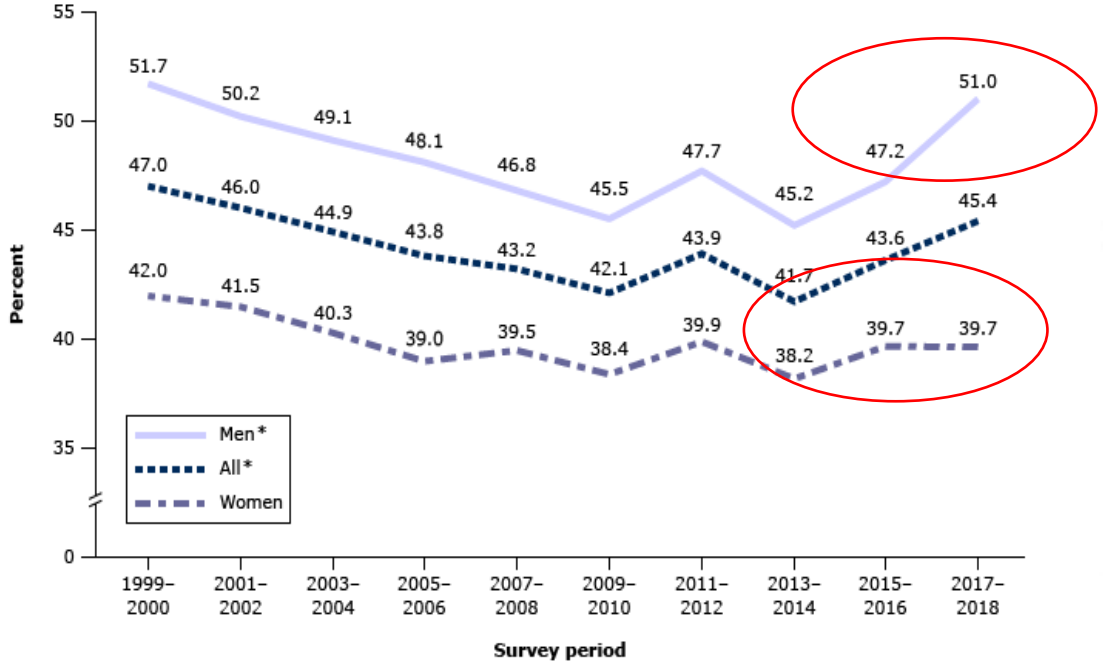
Risk factor	Mean rank (95% UI)	% change (95% UI)
1 High blood pressure	1·1 (1–2)	27% (19 to 34)
2 Smoking (including SHS)	1·9 (1–2)	3% (−5 to 11)
3 Household air pollution	4·6 (3–7)	−37% (−44 to −29)
4 Low fruit	5·0 (4–8)	29% (25 to 34)

World Health Organization

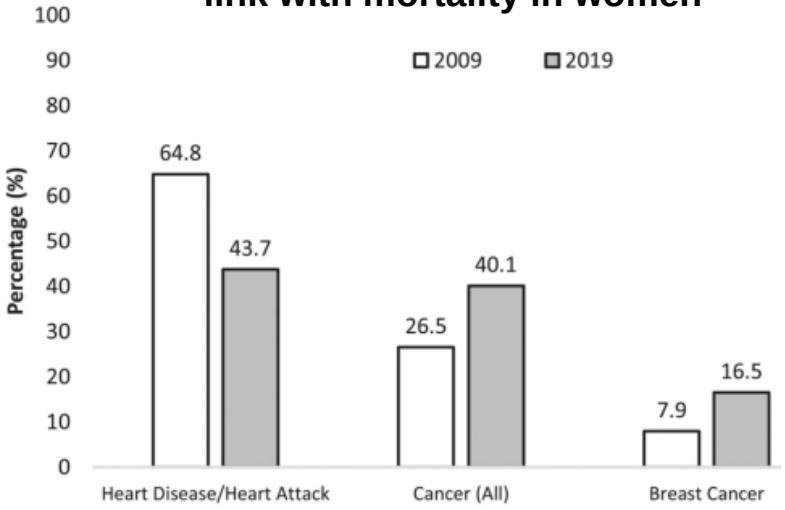
IMPACT: 1.3 billion hypertensives globally → most are uncontrolled

Lim et al. *The Lancet* 2012;380(9859):2224-2260

US Prevalence of Hypertension



Awareness of CV disease's link with mortality in women



Cedars Sinai

Ostchega Y, Fryar CD, Nwankwo T, Nguyen DT. NCHS Data Brief No. 364, 2020

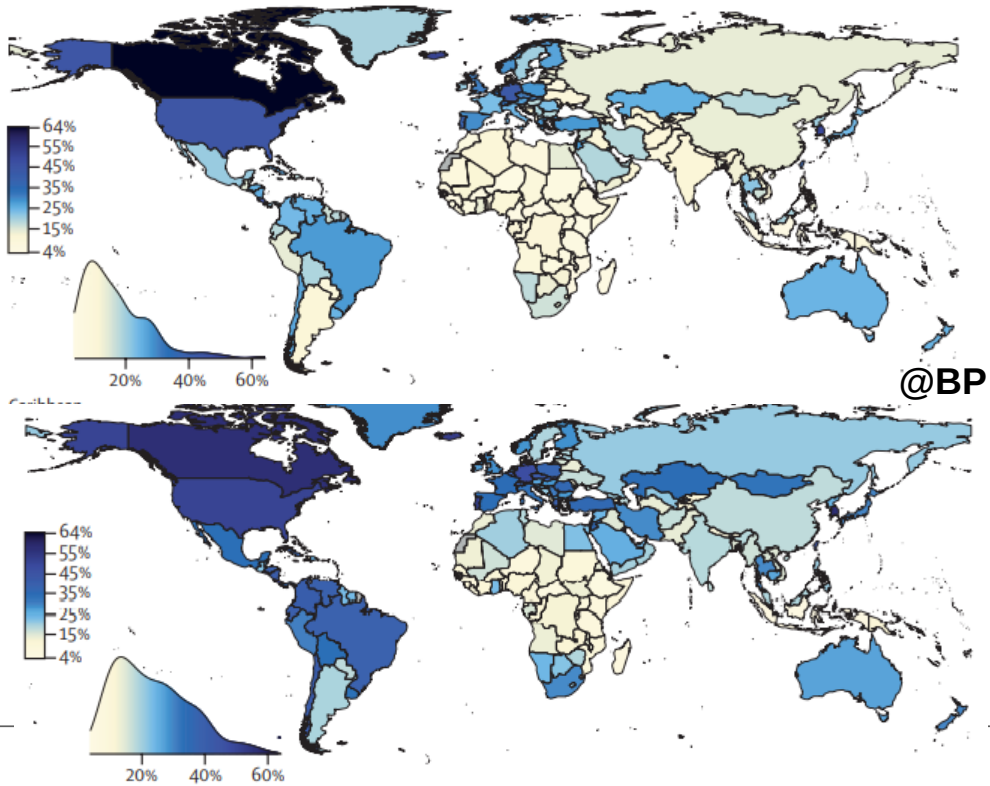
Cushman et al Circulation 2021

Global control rates: women are doing somewhat better

1.3 billion hypertensives and most are uncontrolled!

Men

Women

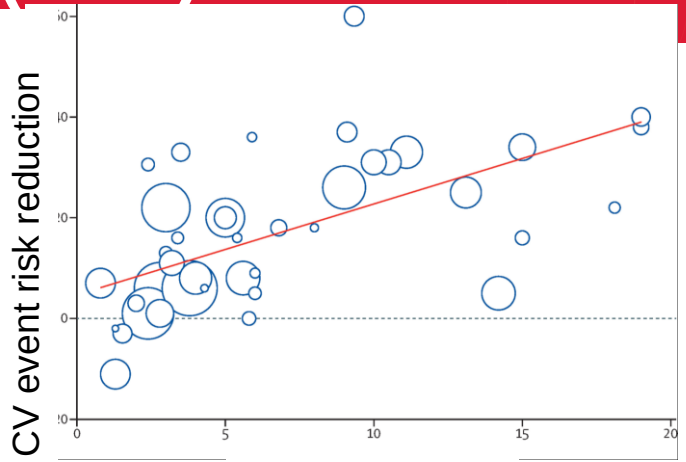


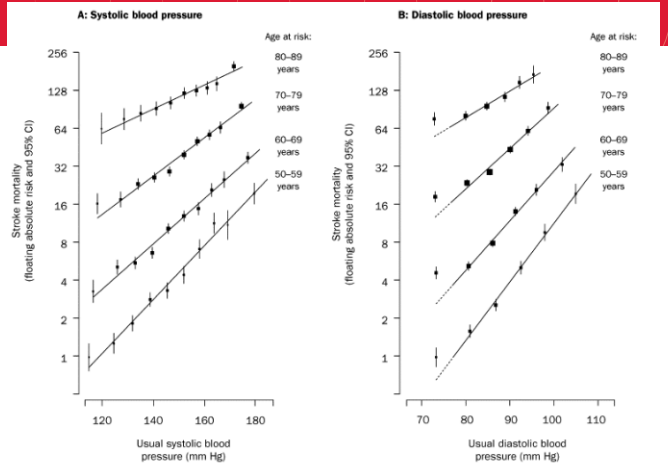
@BP goal ≤140/90 mmHg

Cedars Sinai

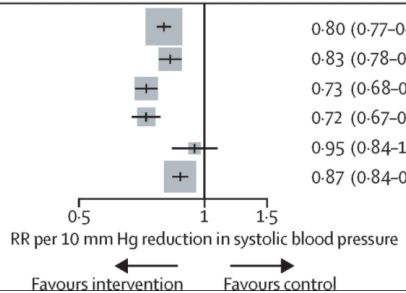
NCD Risk Factor Collaboration. The Lancet 2021 ttps://doi.org/10.1016/ S0140-6736(21)01330-1

Even small reduction in Systolic Blood Pressure (SBP) count!





		Intervention		Control		RR (95% CI) per 10 mm Hg reduction in systolic blood pressure	
		Events	Participants	Events	Participants		
Major cardiovascular events	55	13209	137319	14068	128259	0·80 (0·77–0·83)	-20%
Coronary heart disease	56	4862	136986	5301	128548	0·83 (0·78–0·88)	-17%
Stroke	54	4635	136682	5378	128641	0·73 (0·68–0·77)	-27%
Heart failure	43	3284	115411	3760	107440	0·72 (0·67–0·78)	-28%
Renal failure	16	890	39888	834	39043	0·95 (0·84–1·07)	
All-cause mortality	57	9775	138298	9998	129700	0·87 (0·84–0·91)	-17%



Cedars Sinai

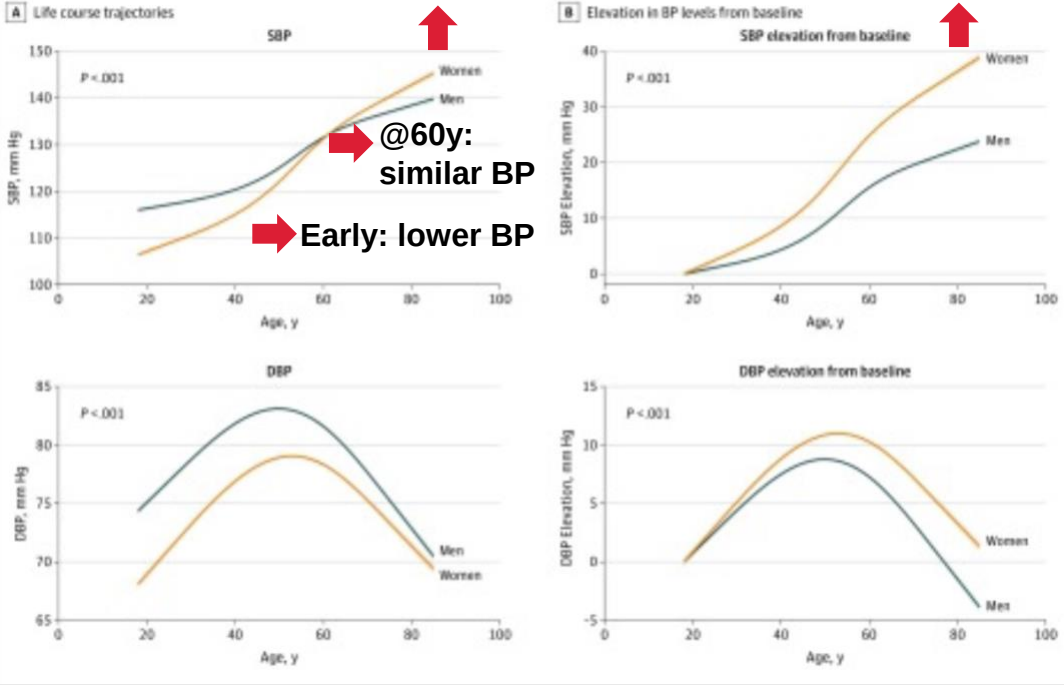
Ettehad D, et al. *Lancet*. 2016,387:957–967

Lewington etal. Lancet 2002; 360: 1903–13

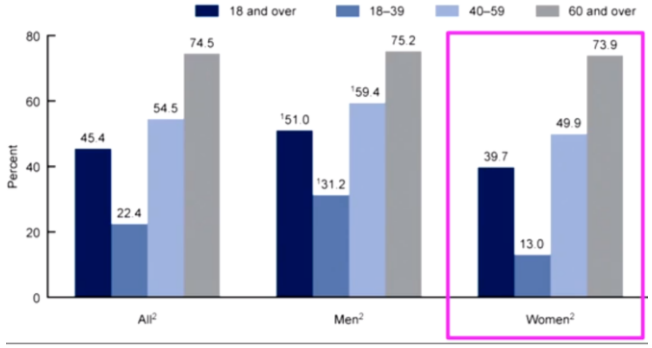
Lifetime Blood Pressure (BP) trajectories by sex

Elderly: worse BP

BP increase over a lifetime is greater in women

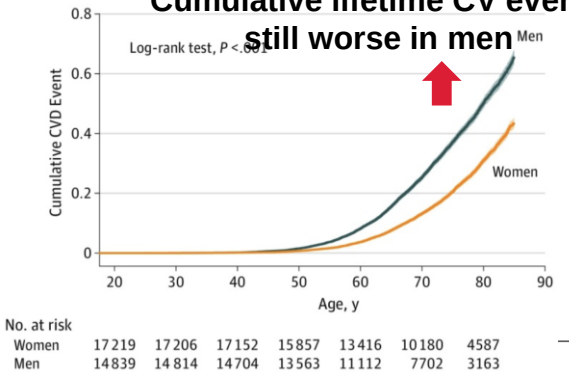


>60 years, prevalence same as men



/www.cdc.gov/nchs/products/databriefs/db364.htm

Cumulative lifetime CV events still worse in men



No. at risk

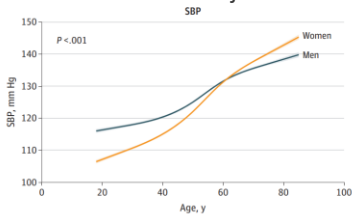
Women	17219	17206	17152	15857	13416	10180	4587
Men	14839	14814	14704	13563	11112	7702	3163

Cedars Sinai

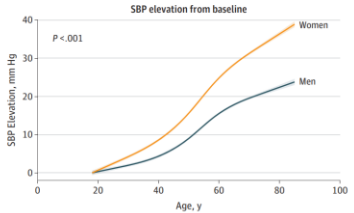
Hongwei J et al. JAMA Cardiol. 2020 Mar 1;5(3):19-26

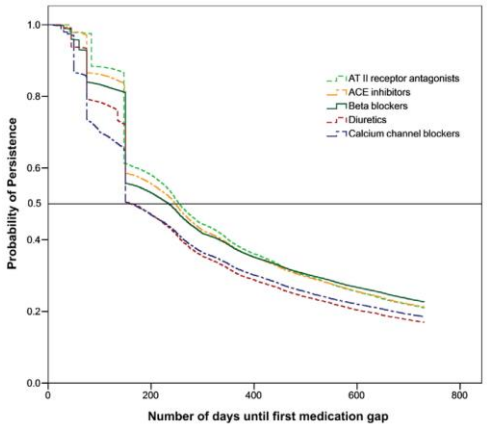
Lifetime BP trajectories in general

Life course trajectories[1]

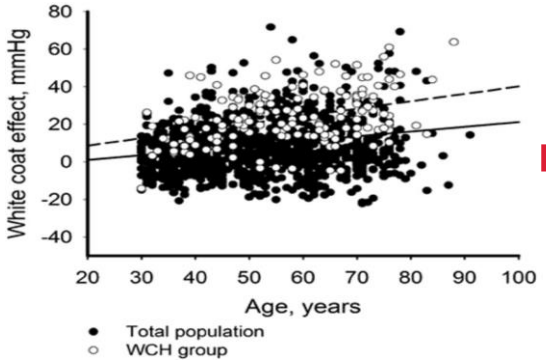


Elevation in BP levels from baseline[1]





Regressions of white coat effect on age[2]



White-coat effect increases by ~4 mmHg per decade

→ *out-of-office BP assessment crucial in older hypertensive patients*

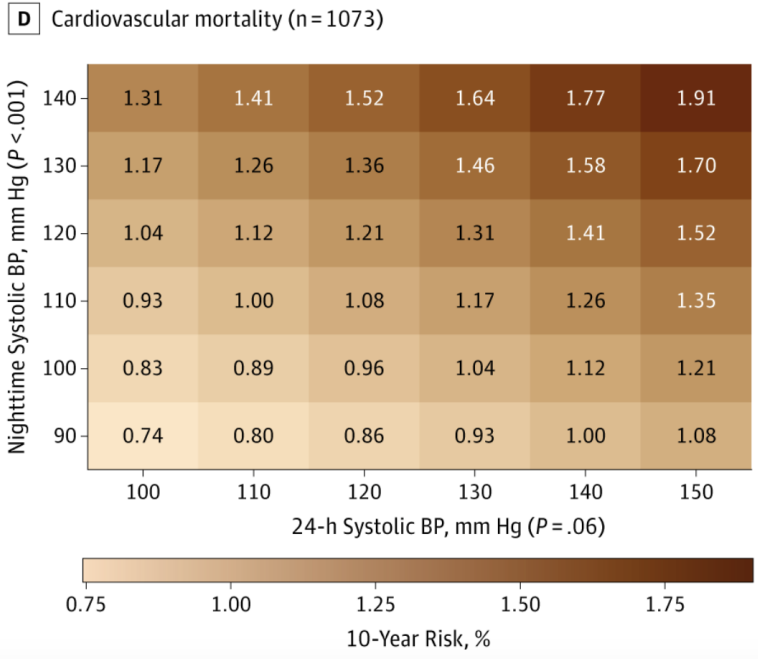
Lifetime BP and White-coat effect increase over time, while BP medication adherence decreases over time → thus, an increase of BP over time is expected thus medication adjustments (based on OOO BP) is necessary!

Cedars Sinai OOO BP– out of office blood pressure

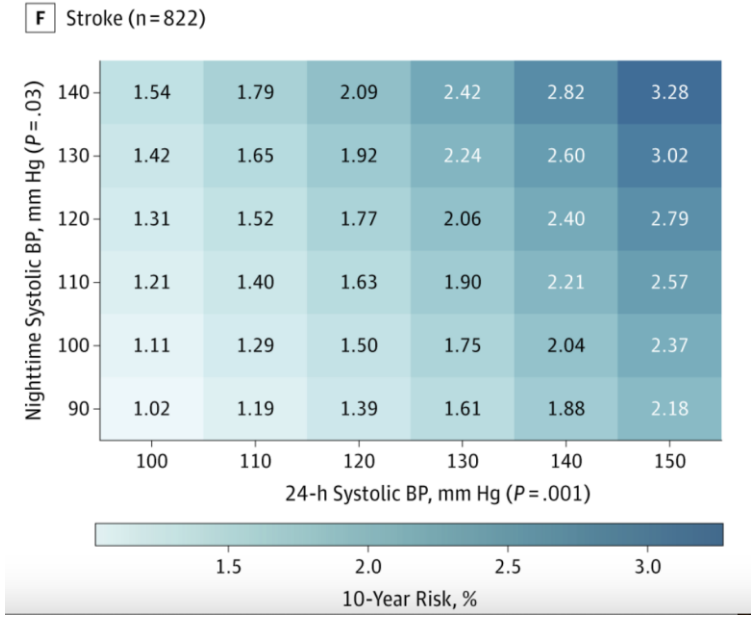
Hongwei J,… Cheng S JAMA Cardiol. 2020;5(3):255-262
Franklin et al. JACC. 2016;68;2033-2043
M. Schulz et al. International Journal of Cardiology 220 (2016) 668–676

Association of BP and Cardiovascular (CV)

11 135 adults with office and ambulatory BP data from Europe, South America, Asia



It is not only BP but also the interaction with nighttime BP!

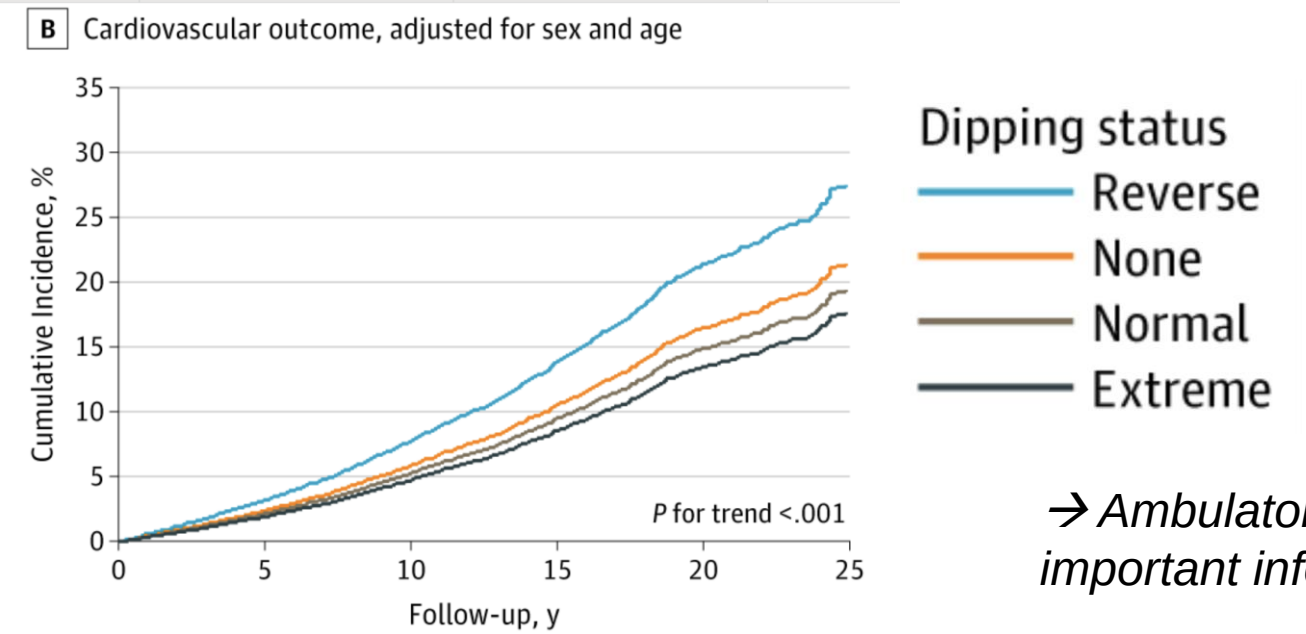


Cedars Sinai

Yang et al *JAMA.* 2019;322(5):409-420.

Association of BP and CV

11 135 adults with office and ambulatory BP data from Europe, South America, Asia



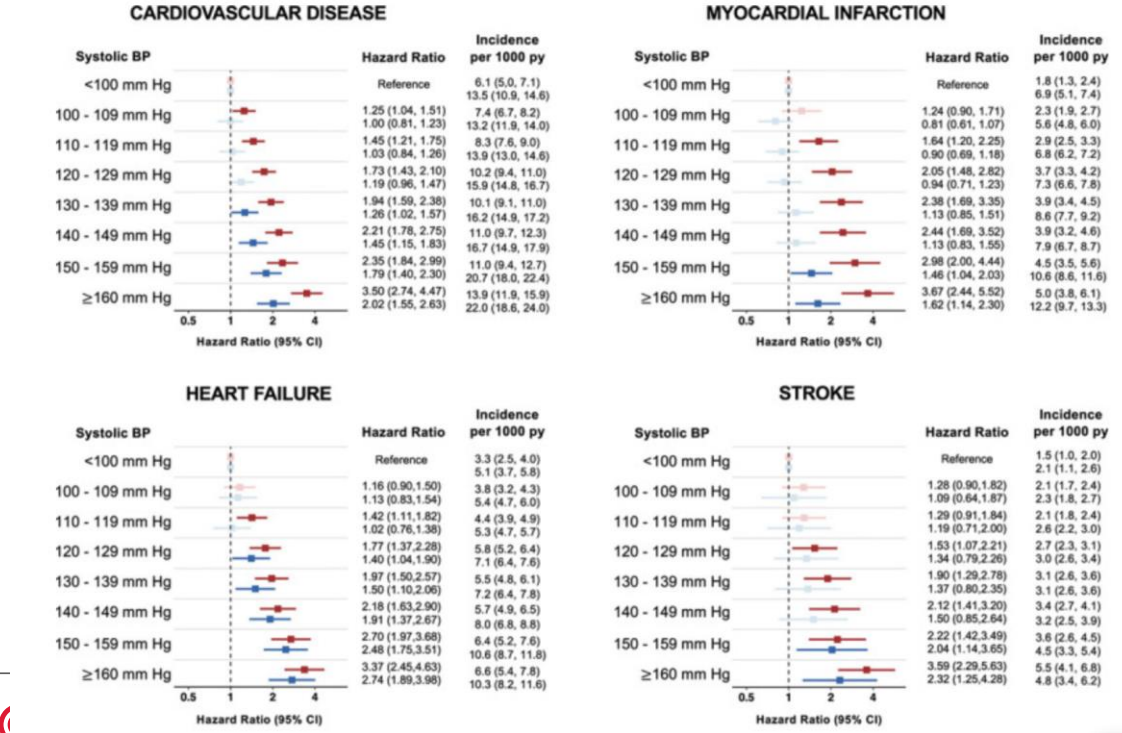
→ *Ambulatory BP monitoring provides important information on CV risk!*

Cedars Sinai

Yang et al *JAMA.* 2019;322(5):409-420.

Association of BP and CV risk by Sex

27,542 participants of Framingham Heart Study, Multi-Ethnic Study of Atherosclerosis, Atherosclerosis Risk in Communities Study, and Coronary Artery Risk Development in Young Adults Study



CV risk increases at much lower BP elevations in women compared to men

→ Do we need to aim for lower BP in women?

Hongwei J, …, Rader F, …, Cheng S Circulation. 2021 Feb 16; 143(7): 761–763

What is the scariest complication of Hypertension?

Ipsos Public Affairs online survey was conducted for the AMA and American Heart Association. It surveyed 1,000 U.S. adults with hypertension

55% of respondents with high blood pressure said they worry they'll have a heart attack and **56% say they worry they'll have a stroke**

In my experience it is a lot more than half of my patients whose main driver to lower BP is to avoid a stroke!

https://www.heart.org/en/news/2019/05/24/many-with-high-blood-pressure-arent-worried-should-they-be, last accessed 9-4-2024

Non-modifiable Risk Factors of Stroke

1. **Age: incidence doubles after age 55.**

2. **Gender: premenopausal women: pregnancy and OCP, older: men increased risk.**

3. **Genetics: CADASIL**, CARASIL, **Fabry's disease**, MELAS, homocystinuria, **sickle cell disease**, connective tissue/collagen vascular disorders; GWAS studies identified several loci associated with specific types of stroke mechanisms.

Park et al. J Neurol Sci. 2016 June 15; 365: 203–206

Non-modifiable Risk Factors of Stroke

Race/ethnicity: Black (Caribbean) race double the risk of ischemic and hemorrhagic stroke compared to age-matched Whites.

-One meta-analysis found 60% greater risk of recurrent stroke: surrogate for risk factors? Those risk factors were also much more prevalent (HTN, DM, smoking, prior stroke).

-In the Northern Manhattan Study, stroke was most common among Blacks (even after adjustment for socioeconomics): Blacks (13/1000 person-years), **Hispanics** (10/1000 person-years), and lowest in **Whites** (9/1000 person-years); **However after age 75; after that Hispanics had the highest incidence**

Park et al. J Neurol Sci. 2016 June 15; 365: 203–206
Gardner et al. Stroke. 2020 Apr; 51(4): 1064–1069.

Modifiable Risk Factors of Stroke

Up to 90% of strokes are preventable and attributable to modifiable risk factors!

Hypertension accounts for 1/3 of all strokes in developing countries and 2/3 in developed countries.

Lifestyle and Screening for presence of risk factors is key!

Diener HC and Hankey GJ. J Am Coll Cardiol 2020;75:1804–18)

Modifiable Risk Factors of Stroke

1. **Hypertension #1**, risk factor even below cut-offs for “normotension”, accounts for up to 70% of strokes, relative risk ~3.5 in younger adults and decreases with increasing risk (competing risks, e.g., AFIB).
2. **Diabetes Mellitus (DM):** doubles risk.
3. **Cardiac:** Atrial Fibrillation (AFib): 25% of strokes >80 years; AFib risk increases with age and correlates with HTN; also PFOs, myxomas, fibroelastomas, endocarditis.
4. **Smoking:** doubles the risk.
5. **Hyperlipidemia:** TC and LDL increase and HDL reduces ischemic stroke risk but lower TC is associated with increased hemorrhagic stroke risk. However, statins lower ischemic stroke risk and probably do not increase hemorrhagic stroke risk (debatable).
6. **Alcohol:** light/moderate use may lower risk but overall the correlation with stroke risk is linear.
7. **Inflammation:** modest association of CRP and stroke risk, influenza vaccination associated with lower stroke risk, COVID-19 shown to cause large vessel thrombosis and strokes.

Diener HC and Hankey GJ. J Am Coll Cardiol 2020;75:1804–18)

Treatment Options for Primary Prevention before a Stroke occurs

Lifestyle modifications

1. **Healthy diet (Mediterranean diet:** 3 randomized controlled trials (RCTs), 9,052 adults, 167 strokes; RR: 0.65; 95% CI: 0.39 to 1.11); **DASH diet: (HTN: -11 mmHg; Normotension: -3 mmHg); dietary potassium: (HTN: -4-5 mmHg; Normotension: -2 mmHg)**

2. **Weight loss (HTN: -5 mmHg, normotension: -2/3 mmHg)**

3. **Smoking cessation:** nearly disappears 2-4 years after quitting! **(HTN: -4 mmHg)**

4. **Physical activity (HTN: -5-6 mmHg; Normotension: 2-4 mmHg)**

5. **Cessation/reduction of alcohol (HTN: -4 mmHg; Normotension: -3 mmHg)**

Diener HC and Hankey GJ. J Am Coll Cardiol 2020;75:1804–18)
Arnett et al. Circulation 2019;140(11):e596-e646

Treatment Options for Primary Prevention before a Stroke occurs

Cholesterol lowering

1. Statins are more effective in lowering risk of Myocardial infarction (MI) and Cardiovascular (CV) death than that of stroke but they do work!

A meta-analysis of randomized controlled trials (RCTs) including 94,283 adults:

-reductions on nonfatal MI (RR: 0.62)

-CV mortality (RR: 0.80)

-nonfatal stroke (RR: 0.83)

2. Lowering LDL by 77 mg/dl with atorvastatin 40 mg for 5 years will prevent 5 strokes in 100 patients (5%), cause 0.5-1 new onset DM in 100 (1%), and 0.05 to 0.1 in 100 intracerebral hemorrhage (0.1%)-although in a large meta-analysis of 287,651 patients, there was **no statistically significant increase in ICH risk** (OR: 1.12; 95% CI: 0.98 to 1.28).

3. Proprotein Convertase Subtilisin / Kexin type 9 (PCSK-9) inhibitors: meta-analysis of 20 RCTs: OR 0.77; 95% CI: 0.67 to 0.89

Diener HC and Hankey GJ. J Am Coll Cardiol 2020;75:1804–18)

Treatment Options for Primary Prevention before a Stroke occurs

1. Aspirin

- Similar reduction of ischemic stroke (HR 0.81) as increase of hemorrhagic stroke (HR 1.34)

- Number-Needed-to-Treat (NNT) to prevent 1 stroke: 241

- NNT to cause major bleed: 210

2. Anticoagulation in AFib: ~64% risk reduction

3. Closure of Patent foramen ovale (PFO): not recommended in primary prevention (unless in divers) but effective for secondary prevention.

Diener HC and Hankey GJ. J Am Coll Cardiol 2020;75:1804–18)

Treatment Options for Primary Prevention before a Stroke occurs

Reduction in Blood Pressure

- A 10/5 mmHg reduction of BP leads to

41% reduction of stroke (95% Cardiac index CI: 33% to 48%)

22% reduction of Coronary Artery Disease (CAD) events (95% CI: 17% to 27%)

Law MR et al. BMJ 2009;338:b1665.
Diener HC and Hankey GJ. J Am Coll Cardiol 2020;75:1804–18)

Primary Prevention of Hemorrhagic Stroke

Reduction in BP leads to decreased risk for Intracerebral Hemorrhage (ICH)

1. PROGRESS (Perindopril Protection Against Recurrent Stroke Study).

Perindopril and indapamide reduced the risks of first and recurrent ICH (HR: 0.44 and 0.37, respectively).

2. SPS3 (Secondary Prevention of Small Subcortical Strokes).

Lowering (systolic blood pressure) SBP <130 mm Hg in patients with small vessel disease reduced the risk of ICH (HR: 0.37).

3. In AFIB DOACs reduce risk of ICH over warfarin by 50 to 80% and have a similar risk of ICH as seen with aspirin!

PROGRESS Arch Intern Med 2003;163:1069–75
Ruff et al. Lancet 2014;383:955–62.
Connolly et al N Engl J Med 2011;364:806–17.

BP goals
confusion (and clarification)

JAMA
The Journal of the American Medical Association

JAMA. doi:10.1001/jama.2013.284427
Published online December 18, 2013.

Special Communication

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD;

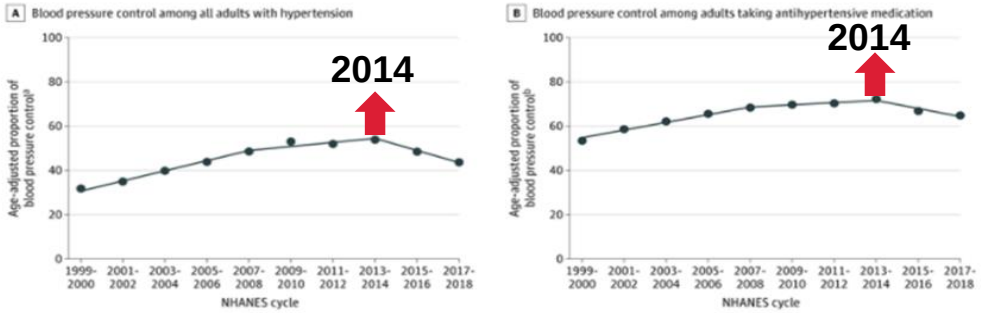
Relaxed Drug Rx Thresholds for Office BP

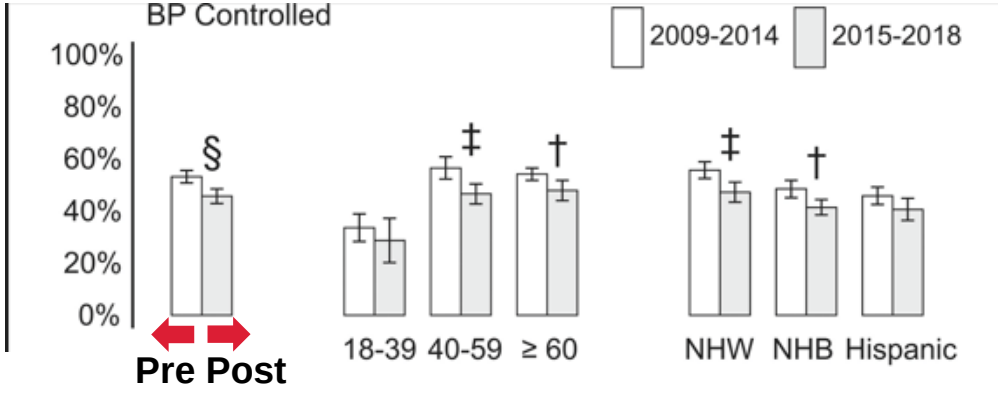
	Age ≥ 60	Age < 60	Diabetes, CKD
"JNC 8"* (2014)	150/90	140/90	140/90
JNC 7 (2003)	140/90		130/80

Cedars Sinai

***Not endorsed by NIH or any medical society**

Aftermath of 2014 guidelines: Hypertension control is worsening, even at 140/90 mmHg!





JNC 8 debacle

Worse control rates across the board but specifically in high-risk groups

- **Older hypertensives**
- **NH Black hypertensives**
- **Hispanic hypertensives**

Cedars Sinai

Muntner P et al. JAMA. 2020;324:1190
Egan BM et al. Hypertension. 2021;78:578–58

SPRINT STUDY: finally, things are making sense

Randomized 9361 participants age ≥50 (mean 68) with 10-year CV risk of 20%

- Excluded recent prior stroke, diabetics (previously studied)

- 2648 with CKD

- 2636 ≥75 years of age

- 1877 with Hx of CVD

→ Target office SBP: 120 superior to 140 mm Hg

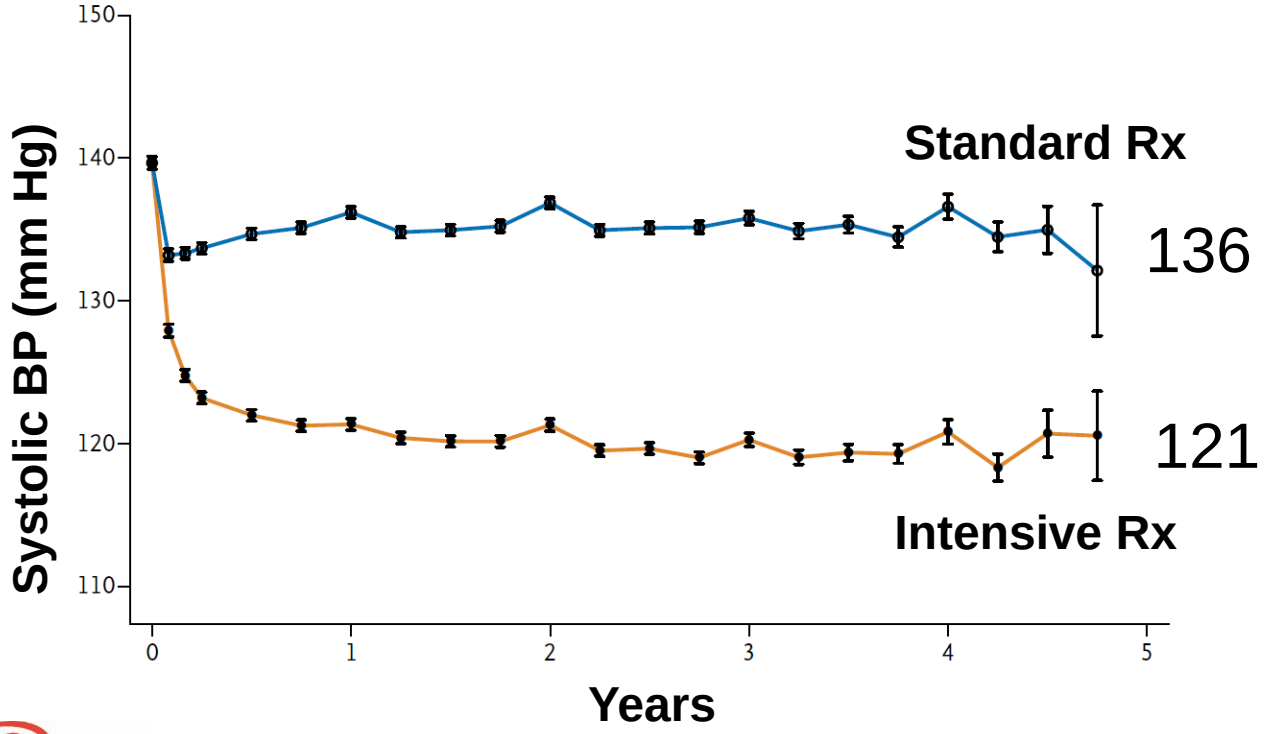
BP measurement: *3 unattended automated office BP readings → less white coat effect*

Cedars Sinai

SPRINT
Systolic Blood Pressure Intervention Trial

The SPRINT Research Group· N Engl J Med 2015; 373:2103-2116

SPRINT STUDY – achieved BP

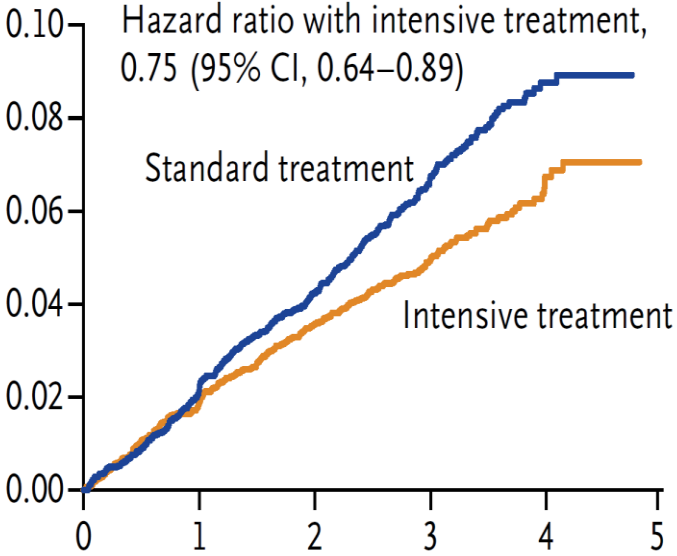


Cedar SPRINT
Systolic Blood Pressure Intervention Trial

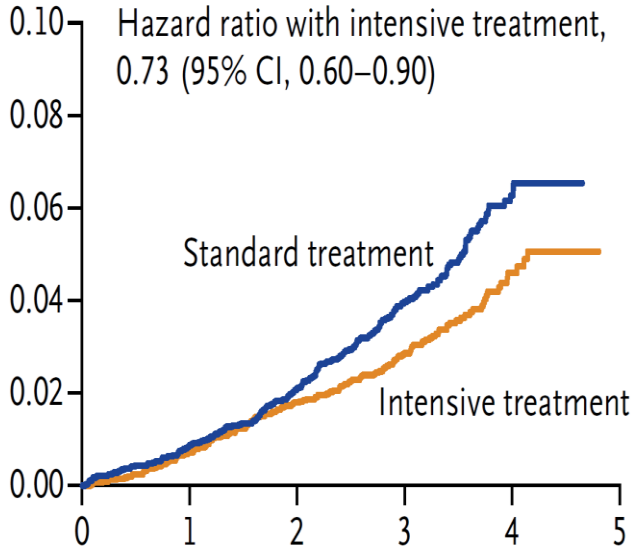
The SPRINT Research Group· N Engl J Med 2015; 373:2103-2116

SPRINT STUDY – Outcomes

CVD Event



Death*



Years of follow up

*Stopped early after mean follow up of 3.26 years.

SPRINT Result Components

	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

However, excess of emergency department visits for hypotension, syncope, electrolyte abnormalities, and acute kidney injury have occurred

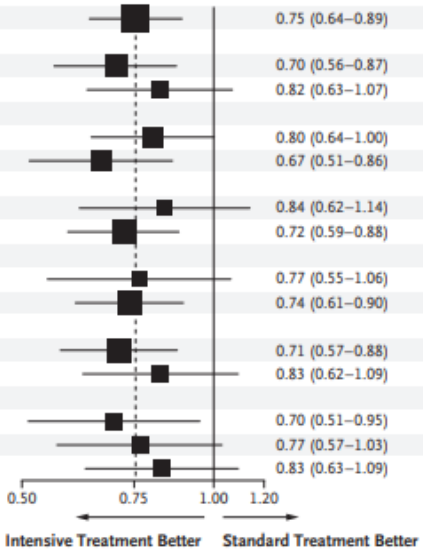
Cedars SPRINT Systolic Blood Pressure Intervention Trial

The SPRINT Research Group. N Engl J Med 2015; 373:2103-2116

Association of BP and CV risk by Sex

SPRINT trial (BP goal <120 vs. <140)

Subgroup	Intensive Treatment	Standard Treatment	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with primary outcome/total no. (%)			
Overall	243/4678 (5.2)	319/4683 (6.8)	0.75 (0.64–0.89)	
Previous CKD				0.36
No	135/3348 (4.0)	193/3367 (5.7)	0.70 (0.56–0.87)	
Yes	108/1330 (8.1)	126/1316 (9.6)	0.82 (0.63–1.07)	
Age				0.32
<75 yr	142/3361 (4.2)	175/3364 (5.2)	0.80 (0.64–1.00)	
≥75 yr	101/1317 (7.7)	144/1319 (10.9)	0.67 (0.51–0.86)	
Sex				0.45
Female	77/1684 (4.6)	89/1648 (5.4)	0.84 (0.62–1.14)	
Male	166/2994 (5.5)	230/3035 (7.6)	0.72 (0.59–0.88)	
Race				0.83
Black	62/1454 (4.3)	85/1493 (5.7)	0.77 (0.55–1.06)	
Nonblack	181/3224 (5.6)	234/3190 (7.3)	0.74 (0.61–0.90)	
Previous cardiovascular disease				0.39
No	149/3738 (4.0)	208/3746 (5.6)	0.71 (0.57–0.88)	
Yes	94/940 (10.0)	111/937 (11.8)	0.83 (0.62–1.09)	
Systolic blood pressure				0.77
≤132 mm Hg	71/1583 (4.5)	98/1553 (6.3)	0.70 (0.51–0.95)	
>132 to <145 mm Hg	77/1489 (5.2)	106/1549 (6.8)	0.77 (0.57–1.03)	
≥145 mm Hg	95/1606 (5.9)	115/1581 (7.3)	0.83 (0.63–1.09)	



Benefit of lower BP was similar (or slightly greater) in men

However: less women in trial, CV risk was lower so benefit less obvious

Cedars Sinai

The SPRINT Research Group· N Engl J Med 2015; 373:2103-2116

Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years

A Randomized Clinical Trial (n=2,636)

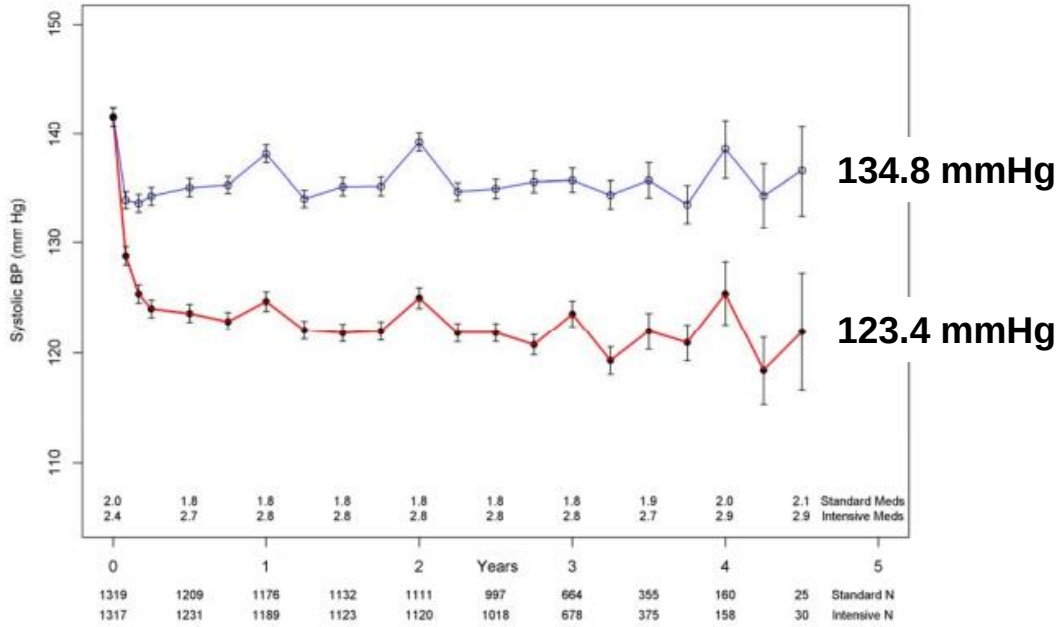
Jeff D. Williamson, MD, MHS; Mark A. Supiano, MD; William B. Applegate, MD, MPH; Dan R. Berlowitz, MD; Ruth C. Campbell, MD, MSPH;

Question: Do we need higher BP goals in frail elderly patients?

Williamson JD et al. JAMA. 2016;315(24):2673-2682

SPRINT Results: 75+

Ambulatory, 38% female, mean age 80y, 17% black, 16% CKD (GFR<45), 50% used statin



Cedars Sinai

SPRINT Systolic Blood Pressure Intervention Trial

Williamson JD et al. JAMA. 2016;315(24):2673-2682

SPRINT Results: 75+

Composite: *HR 0.66* (CI 0.51 - 0.85) - *HF and mortality driven*

All-cause mortality: *HR 0.67* (CI 049-0.91)

SAE: *HR 0.99* (CI 0.89-1.11)

+30% reduction in GFR: HR 3.14 (1.66-6.37)

+50% reduction in GFR: no difference

Hypotension, electrolyte abnormality all NS but numerically more common in intense group

Injurious falls and syncope: no difference

Williamson JD et al. JAMA. 2016;315(24):2673-2682

SPRINT Results: 75+

Fit: **group diff: -13.5 mmHg**

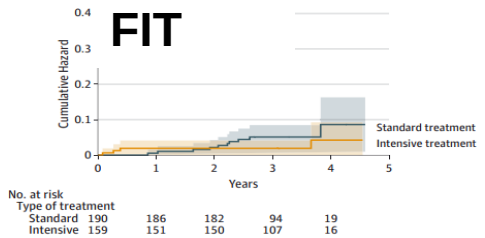
→HR 0.47 (CI 0.13 - 1.39)

Less fit: **group diff: -11.3 mmHg**

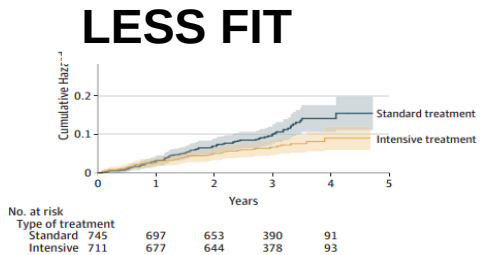
→HR 0.63 (CI 0.43 - 0.91)

Frail: **group diff: -10.8 mmHg**

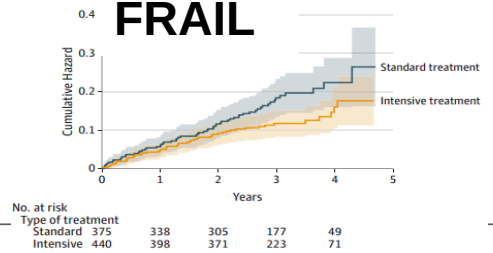
→HR 0.68 (CI 0.45 - 1.01)



p=0.2



p=0.01



p=0.06

Cedars-Sinai

SPRINT Systolic Blood Pressure Intervention Trial

Williamson JD et al. JAMA. 2016;315(24):2673-2682

How to translate SPRINT data into clinical practice?

- No patients with diabetes or prior CVA
- BP was assessed with AOBP → reduction of white coat effect

→ As long as you make sure you don't (over-)treat white-coat hypertension, these results apply to your patients!

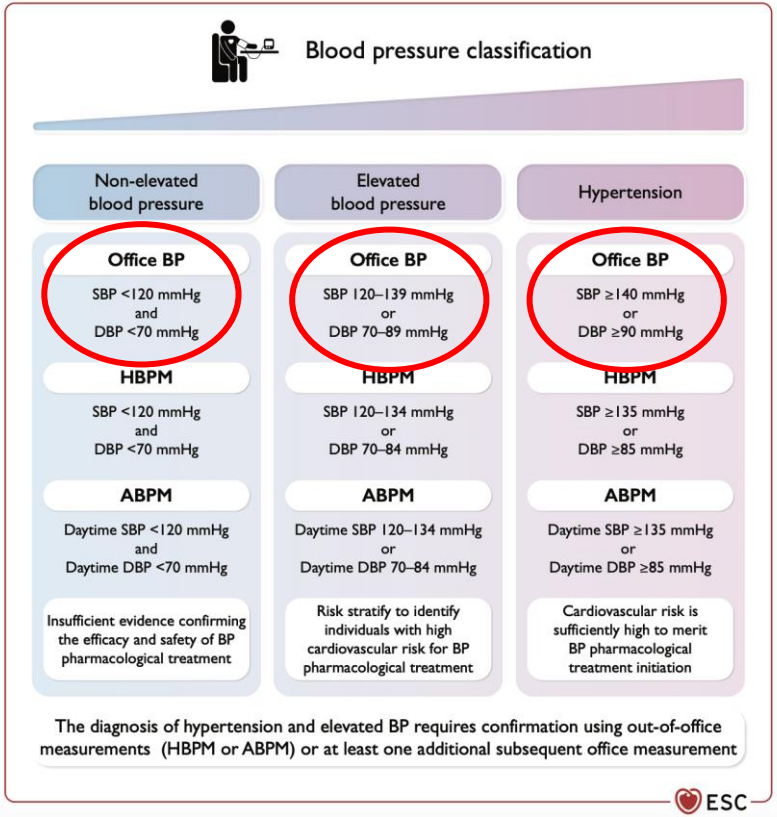
Hypertension burden in the US: bigger than ever!

SBP		DBP	JNC 7	2017
<120	and	<80	Normal BP	Normal BP
120-129	and	<80	Pre-HTN	Elevated BP
130-139	or	80-89	Pre-HTN	Stage 1 HTN
140-159	or	90-99	Stage 1 HTN	Stage 2 HTN
≥160	or	≥100	Stage 2 HTN	Stage 2 HTN
US Prevalence			**72 mio (32%)**	**103 mio (46%)**
US Control Rates			**53.4%**	**39.0%**

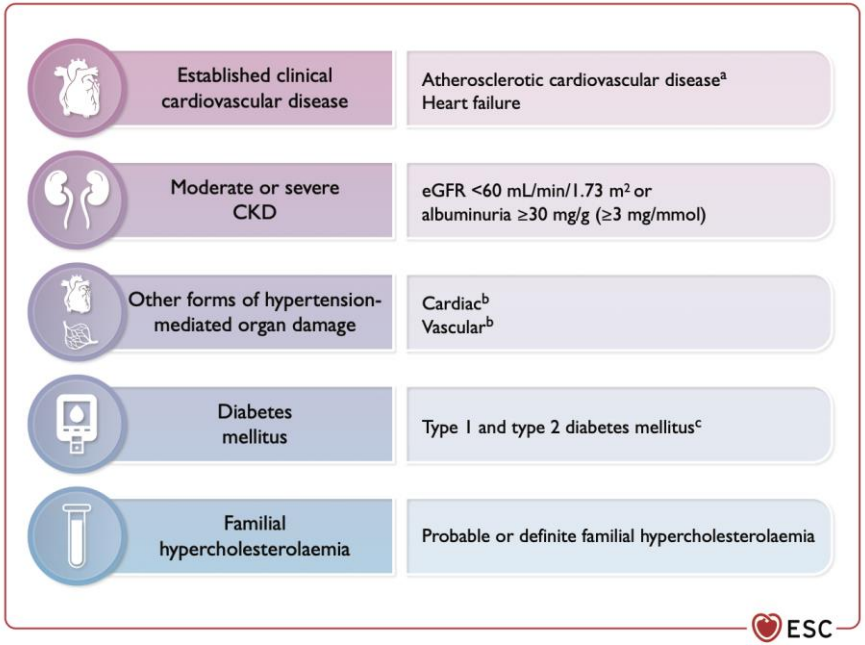
Cedars Sinai

Muntner P et al. Circulation. 2018 Jan 9;137(2):109-118
Whelton et al. Circulation. 2018 Oct 23;138(17):e426-e483

Hot off the press: 2024 ESC Hypertension guidelines



Hypertension still defined as ≥140/90 mmHg; however treatment to 120-129 now recommended for high risk patients



Cedars Sinai

McEvoy et al.European Heart Journal 2024.00, 1-107

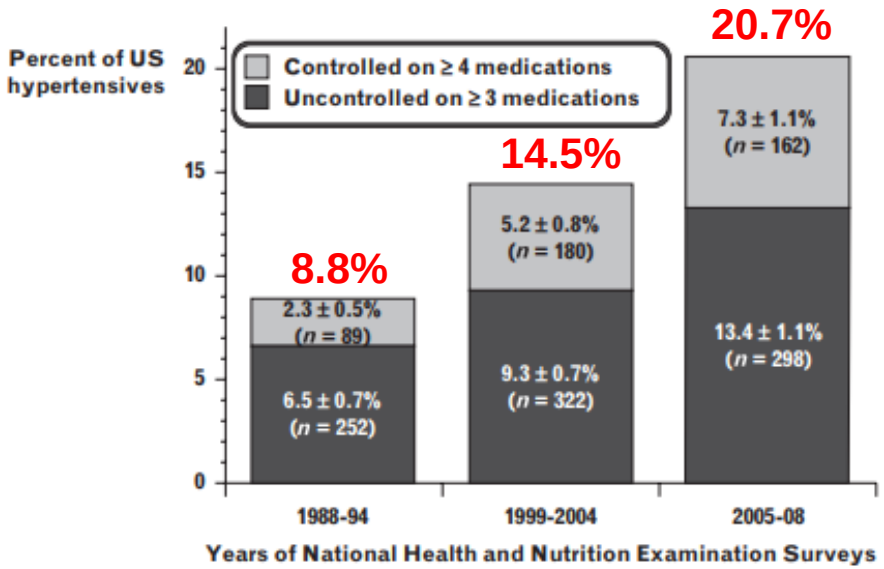
Barrier to control: Resistant Hypertension

- **BP ≥ 130/80 mmHg on 3 meds (1 diuretic) or 4 meds irrespective of BP**

- **Prevalence appears to be on the rise**
  - NHANES: estimate 1998-2008 8.9%

    estimate 2005-2008 20.7%

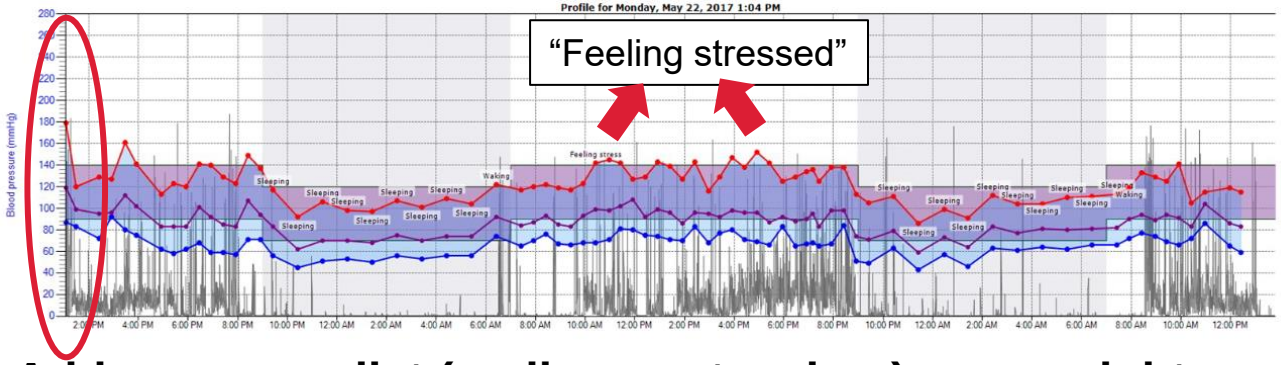
- **Predictors of Resistant HTN**
- Older age
- Obesity
- Chronic kidney disease
- Left ventricular hypertrophy



Curr Opin Cardiol. 2012;27: 386-91
Hypertension. 2008;51:1403-1419

But: Watch out for Imposters of (Pseudo-) Resistant Hypertension!

- **Inaccurate BP measurement (home and office): train your staff and patients!**
- **White-coat effect (also associated with older age): home and ambulatory BP assessment!**



- **Address poor diet (sodium, potassium), overweight, secondary causes, concomitant medications, …**
- **Non-adherence: assume 50-60% of patient do not take meds as prescribed**

Cedars Sinai

Curr Opin Cardiol. 2012;27: 386-91
Hypertension. 2008;51:1403-1419

Resistant Hypertension: *rule out secondary Hypertension*

- Obstructive sleep apnea

C-PAP not very effective in reducing BP, mostly nocturnal BP

- Primary aldosteronism

Prevalence 6-20%, adenoma, obesity-related: learn how to screen and collaborate with experts

- Pheochromocytoma

Plasma metanephrines 99% sensitive

- Cushing's Syndrome

Mineralcorticoid stimulation→mineralcorticoid antagonists effective (+specific medications, surgery!)

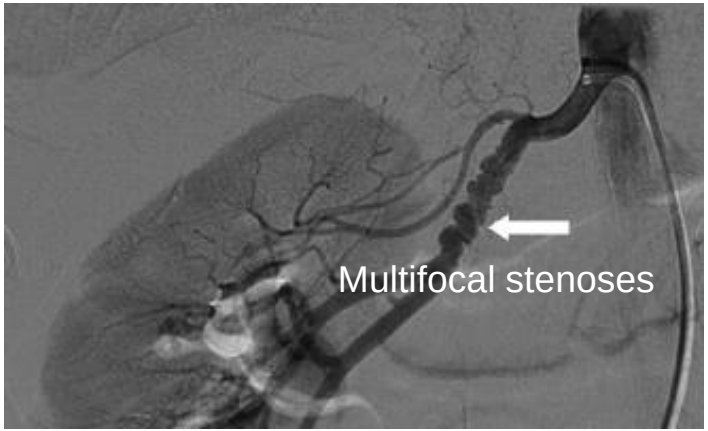
- CKD, ESRD: volume control!

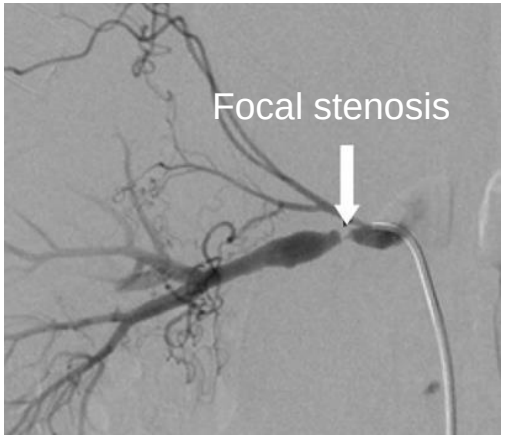
- Renal artery stenosis, Fibromuscular dysplasia: renal vascular ultrasound not always reliable

Iftikhar IH J Hypertens. 2014 Dec;32(12):2341-50; Muxfeldt ES Hypertension. 2015;65:736-742

Renovascular hypertension: Fibromuscular dysplasia

Affects *mostly women* but men may have it; typically seen in patients < 50 years





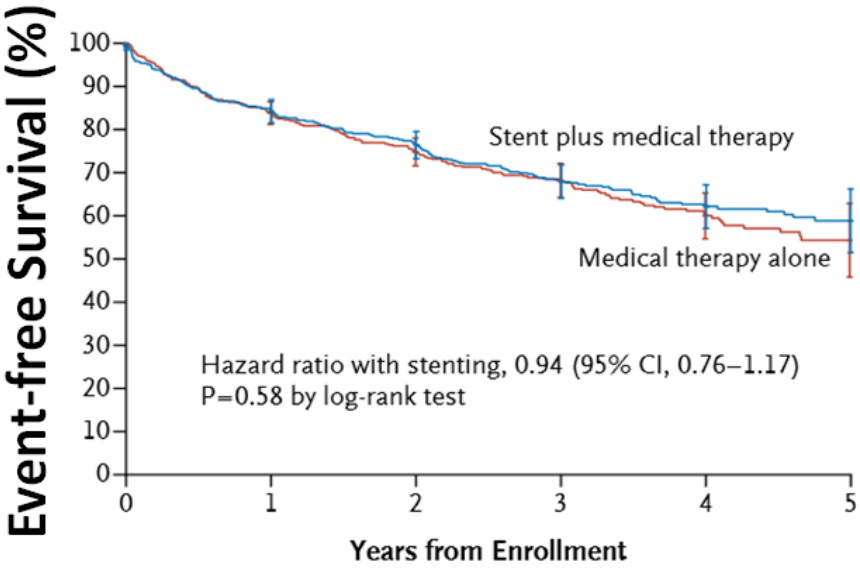
→ Cause is unknown but genetics (10% familial), smoking, estrogen play a role

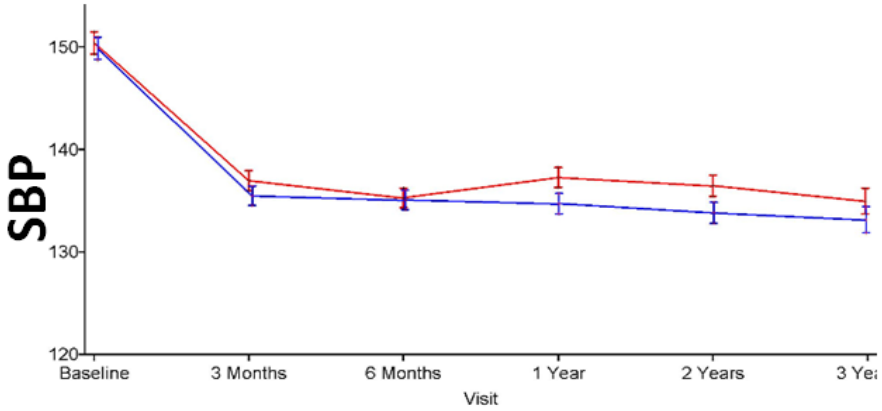
→ Flank bruit, hypertension, headache and stroke (can also affect Carotid arteries)

→ Treat with ARB (and ACEi) but angioplasty is also a treatment option

Poloskey SL et al Circulation. 2012;125:e636-e639

Renovascular HTN: CORAL trial





No difference in renal or CV events

No difference in BP reduction

Cooper CJ et al. N Engl J Med 2014;370:13-22

Renovascular HTN

→ ARAS indicates high CV risk (~peripheral artery disease)

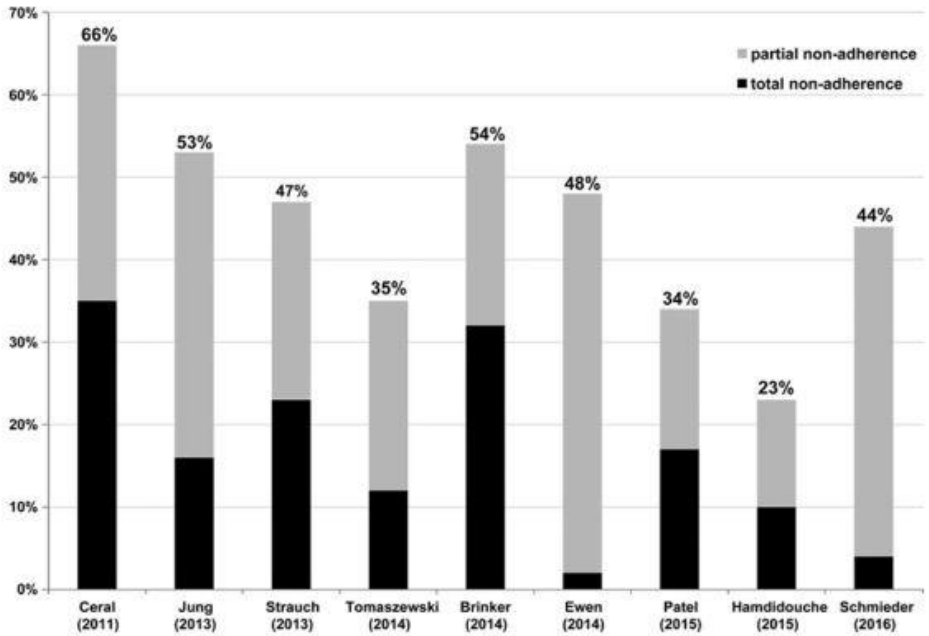
Aggressive medical therapy to prevent CV events is the primary goal:

- ASA
- Statin
- ARB (with close monitoring of renal functions)
- Cessation of smoking

Revascularization should be reserved for no option patients with bilateral disease and Pickering disease (flash pulmonary edema)

Nonadherence to antihypertensive medications

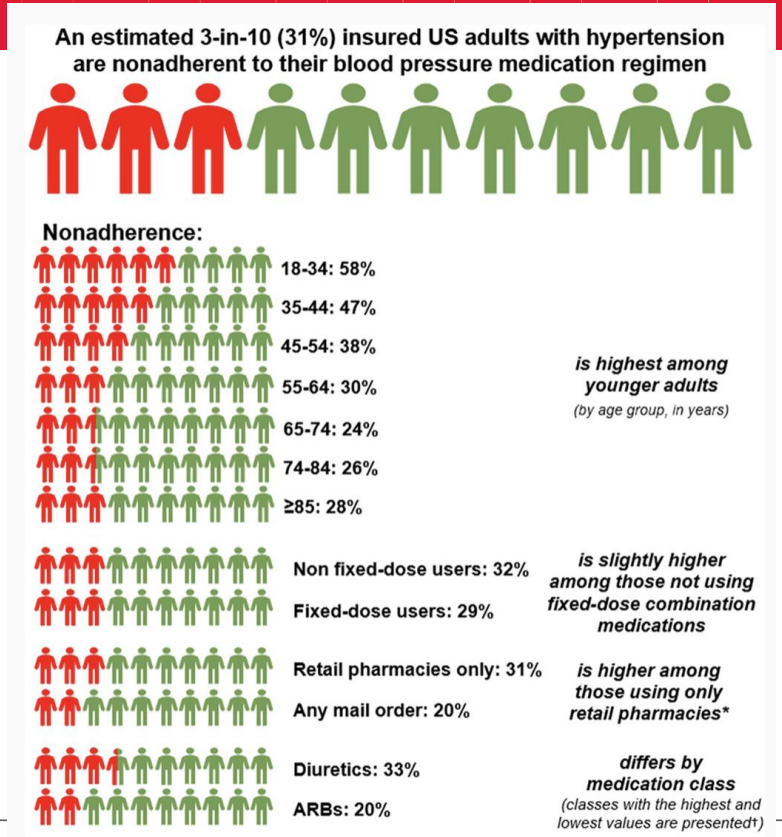
Proportion of poor or nonadherence according to drug monitoring in different cohorts of patients with apparently resistant hypertension.



Berra E et al. Hypertension. 2016;68:297-306

Nonadherence to antihypertensive medications

Data from several insurance claims databases in combination with National Health Interview Survey a total of 24 million hypertensives ≥18 years projecting national estimates of non-adherence to antihypertensive medications



Chang et al. Hypertension. 2019;74:1324–1332

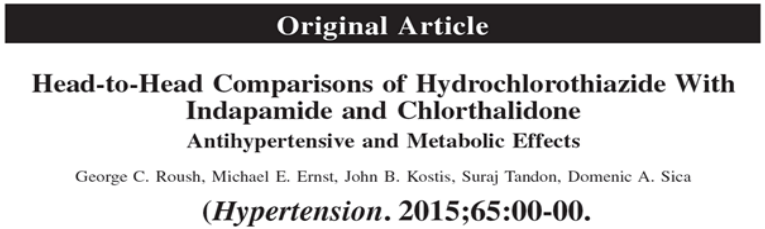
HTN Treatment-my approach

First line:

1. Angiotensin receptor blockers
2. Amlodipine (or nifedipine)

} Start together at low to medium dose if BP >20 mmHG above goal
Combination therapy is more effective with less side effects than maximizing the dose of a single medication

Second line: thiazide diuretic



Original Article

Head-to-Head Comparisons of Hydrochlorothiazide With Indapamide and Chlorthalidone

Antihypertensive and Metabolic Effects

George C. Roush, Michael E. Ernst, John B. Kostis, Suraj Tandon, Domenic A. Sica

(*Hypertension*. 2015;65:00-00.

BP reduction

1.25 mg indapamide
=25 mg chlorthalidone
= 60 mg HCTZ

} **Similar metabolic side-effects**

Watch for

- Hyponatremia
- Orthostatic hypotension
- Renal failure
- Erectile dysfunction
- Gout

→ ***Not first line in my practice***

HTN Treatment-my approach

Third line: mineralcorticoid receptor antagonists (MRAs)

Spironolactone

Eplerenone (twice daily dosing more effective)

} **Careful in CKD**
Close monitoring of K and Cr!
Some need dietary modifications (low potassium diet)

Fourth line:

Vasodilating beta blockers: carvedilol, bystolic: better tolerance and metabolic SE than selective BB

Alpha blockers, Guanfacine (fatigue)

Nitrates: lowers systolic BP and pulse pressure in isolated systolic hypertension

Franklin SS. Curr Hypertens Rep. 2000 Jun;2(3):253-9

Resistant HTN Treatment - my approach

Multi-drug regimens by definition → Compliance difficult

Avoid short-acting medications like

- Hydralazine
- Clonidine……THE WORST
- Labetalol
- Lisinopril

Use combination pills

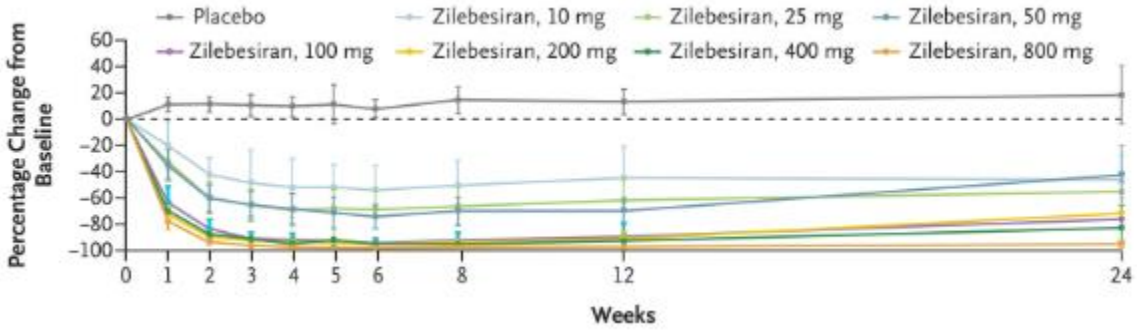
- Amlodipine, valsartan, HCTZ
- Amlodipine, olmesartan, HCTZ
- Azilsartan, chlorthalidone
- Telmisartan, amlodipine
- Spironolactone, HCTZ

New drugs on the horizon: Zilesbiran

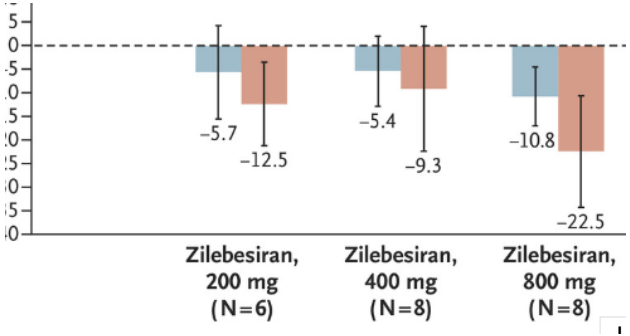
RNA interference agent to decrease angiotensinogen (precursor of angiotensin)

→ **Single subcutaneous injection >200 mg (up to 800 mg) led to decreased angiotensin levels and BP reductions, lessened with high salt diet, increased with irbesartan**

Lower angiotensin levels



BP reduction @24 weeks



→ **Adverse events: 9% injection site reaction, no hypotension, hyperkalemia or AKI, all other AEs more frequently in placebo group**

Desai AS et al N Engl J Med 2023;389:228-38

New drugs on the horizon: Zilesbiran

KARDIA 2 (unpublished) 1500 uncontrolled hypertensives were randomized to zilebesiran vs. placebo after a run-in period with indapamide 2.5 mg daily, or amlodipine 5 mg daily, or olmesartan 40 mg daily

Primary outcome: change from baseline to 3-month 24-hour mean ambulatory systolic blood pressure

-12.1 mmHg in the **indapamide group for zilebesiran** vs. placebo ($p < 0.001$)
-9.7 mmHg in the **amlodipine group for zilebesiran** vs. placebo ($p < 0.001$)
-4.0 mmHg in the **olmesartan group for zilebesiran** vs. placebo ($p = 0.036$)

→ These changes were sustained to 6 months
→ No deaths or no adverse events leading to study discontinuation

New drugs: Aprocitentan (FDA approved)

Once-daily, dual endothelin A and B receptor antagonist, with a half-life of 44 h

PRECISION phase III trial: Resistant HTN (n=730) on single triple pill, mean age 61 y; 25% CKD 3-4

Adverse events:

Edema (2-18%, 7 discontinued, some diuretic use)

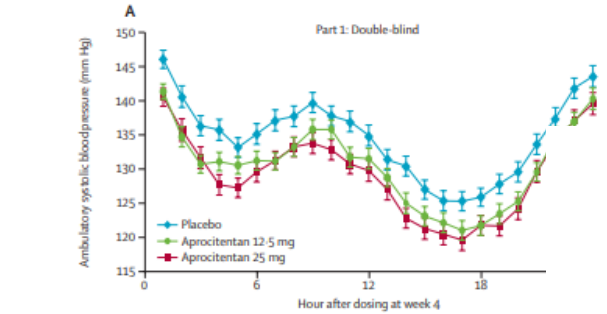
-Minimal change in GFR

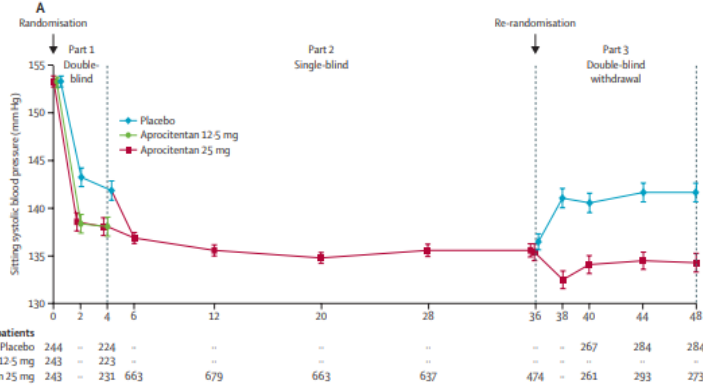
-Albuminuria improved

-No hyperkalemia

→ **Good option for patients with kidney disease!**

→ **Only 12.5 mg dose approved in the US (+25 mg in EU)**





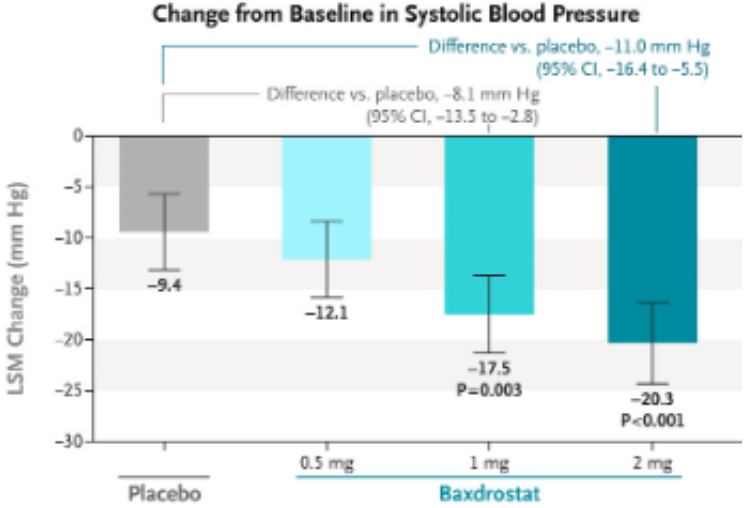
Cedars Sinai

Schlaich MP et al. Lancet 2022; 400: 1927–37

New drugs on the horizon: Aldosterone synthase inhibitors

Baxdrostat and Lorundrostat

e.g.: proof-concept study (n=275; placebo n=69, 0.5 mg n-69, 1mg n=69 2mg n= 67) for 12 weeks, GFR>45, DM 40%, all on diuretic, most on ACEi or ARB, 70% on CCB, 60% on BB



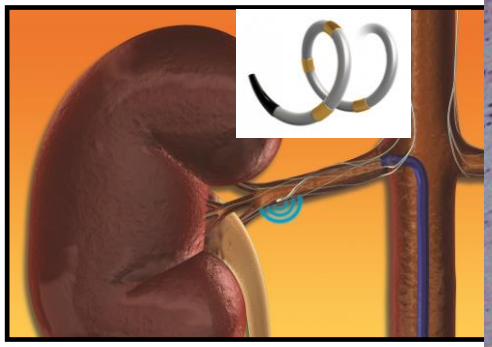
→ Pivotal phase 3 trials are ongoing

Adverse Events: hyponatremia, hyperkalemia (rare and reversible/manageable)

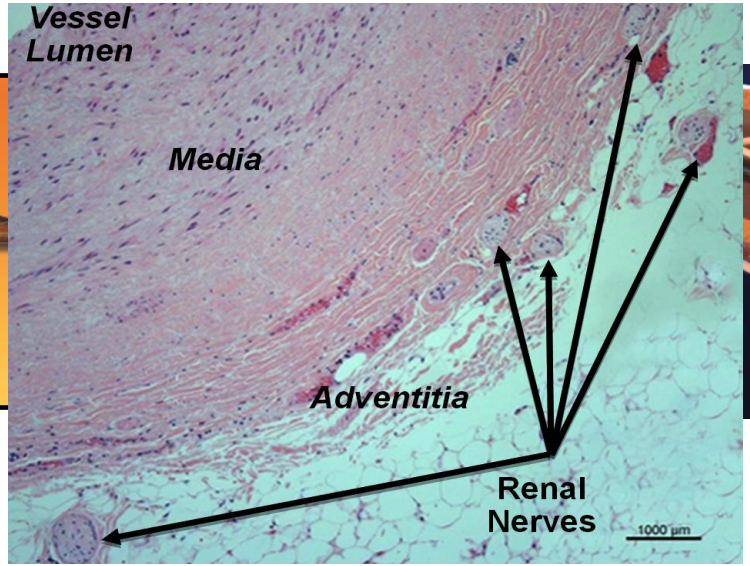
Cedars Sinai

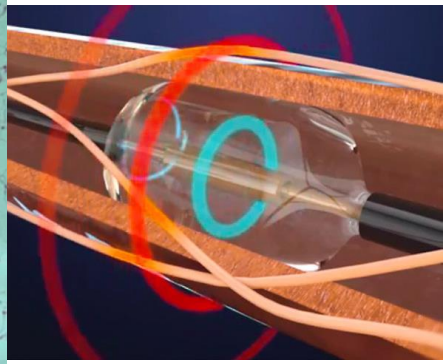
Freeman MW et al N Engl J Med 2023;388:395-405.

Renal Denervation - the next chapter



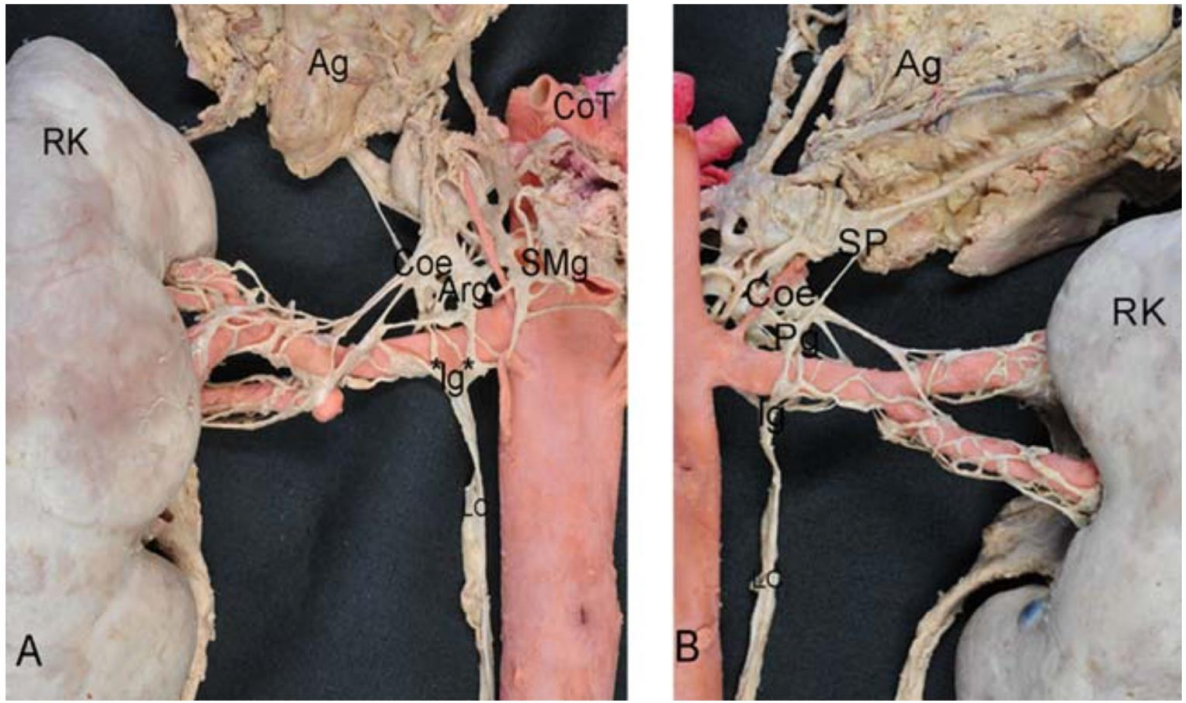
Intraarterial
Radiofrequency





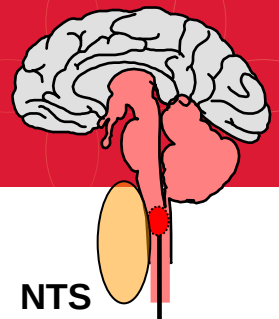
Intraarterial
Ultrasound

The renal sympathetic nerves



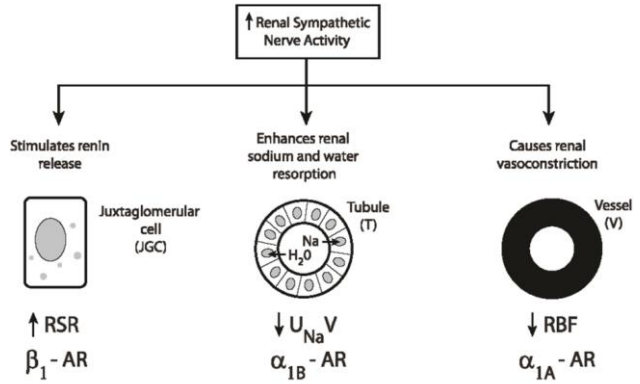
Cedars Sinai

Mompeo et al. *Clin Anat*. 2016 Jul;29(5):660-4



NTS

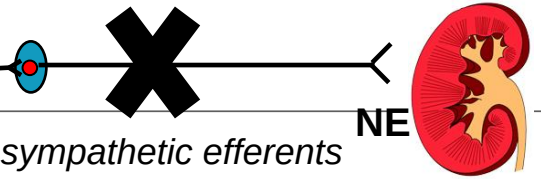
Renal efferent nerves>>Renal afferent nerves



Modified from Di Bona, G.F. Am J Physiol Rgul Integr Comp Physiol 289: R633-R641 2005.

Effects of RDN

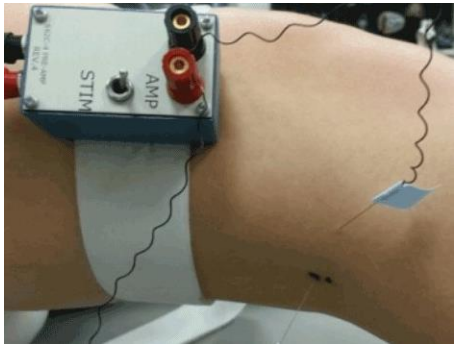
- Decrease of Renin release
- Less tubular Na and H2O resorption
- Increase of renal blood flow

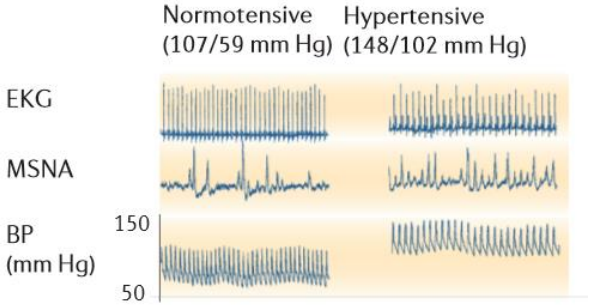


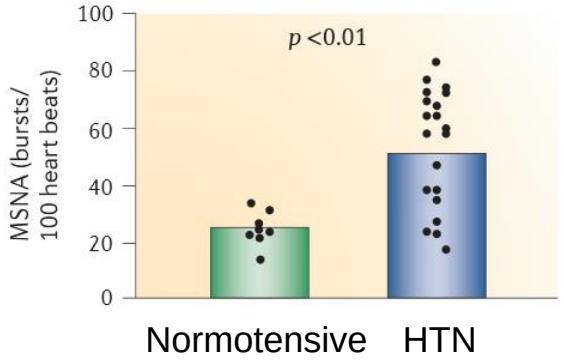
sympathetic efferents

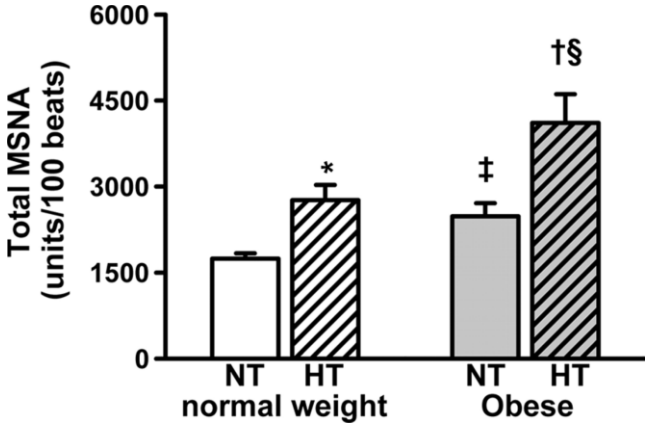
NE

Overactive Sympathetic nerve activity (SNA) in HTN









Increased SNA also in
-CKD
-OSA
-CHF
-Middle aged > old hypertensives?

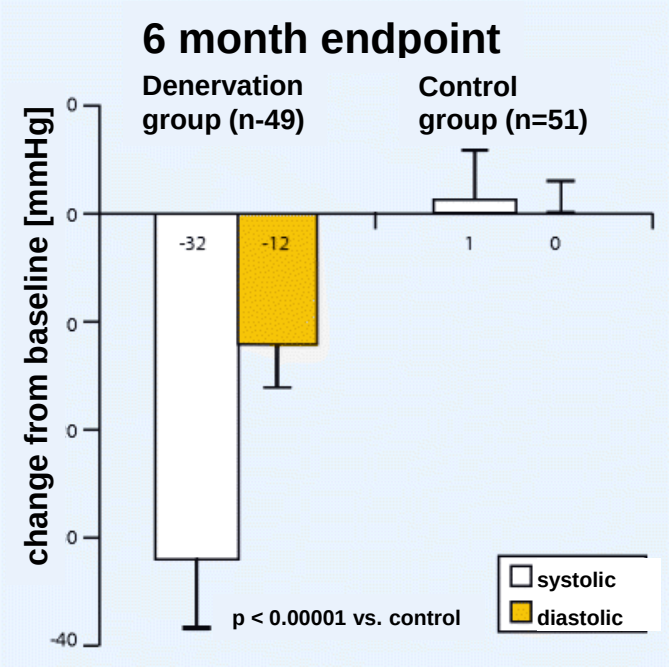
Cedars Sinai

PG Guyenet *Nature Reviews Neuroscience*, 2006
Lambert et al. *Hypertension* 2007 50:862

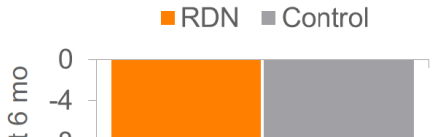
Initial Renal denervation (RDN) Data

Renal denervation (RDN) is a minimally invasive procedure to treat resistant hypertension.

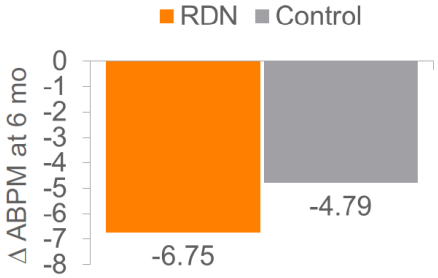
GREAT !



NOT SO GREAT !



	RDN	Control	*P* value
Baseline SBP	179.7	180.2	0.765
6 mo SBP	165.6	168.4	0.260
Change	*-14.1* *P < 0.001*	*-11.7* *P < 0.001*	*0.255*[1]



	RDN	Control	*P* value
Baseline SBP	158.55	158.85	0.828
6 mo SBP	151.80	154.05	0.201
Change	*-6.75* *P < 0.001*	*-4.79* *P < 0.001*	*0.979*

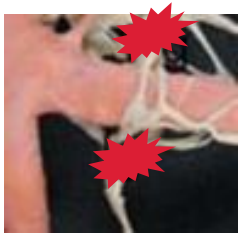
Cedars Sinai

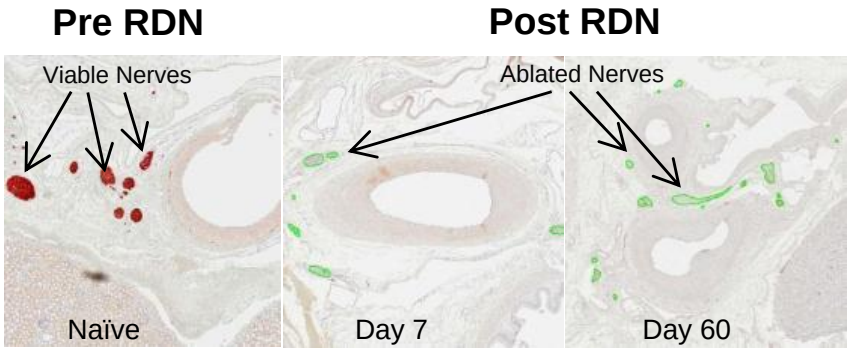
Symplicity HTN-2 Investigators. *Lancet* 2010; 376: 1903–09

Symplicity HTN-3 Investigators. NEJM 2014;370:1393-401

Pre Simplicity-HTN 3: ~50 RDN companies
Post Simplicity-HTN 3: 3 contenders (and a few…)

How to get from the renal arterial lumen to the periarterial renal nerves?





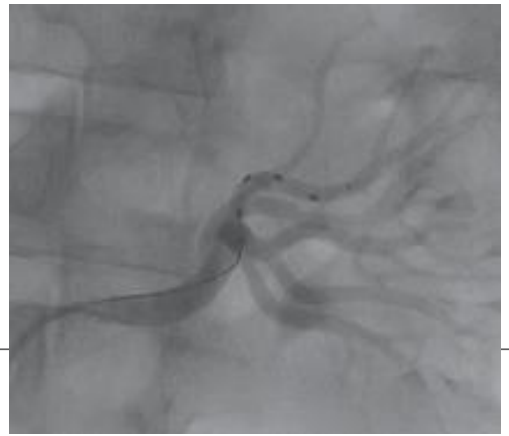
Intraarterial Ultrasound → **PARADISE system (FDA approved)**

Intraarterial Radiofrequency → **SPYRAL system (FDA approved)**

Pathak et al. EuroIntervention. 2015 Aug;11(4):477-84

SPYRAL Trials program

Then: Single electrode catheter

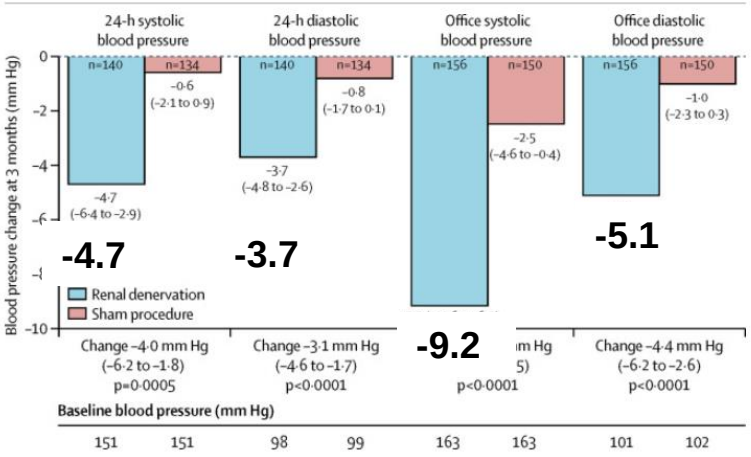


Now: Multi-electrode Catheter
-less manipulation for better circumferential ablation

SPYRAL Trials program: RDN without background BP medications

SPYRAL OFF Meds Pivotal

(n=331) @ 3 months



Cedars Sinai

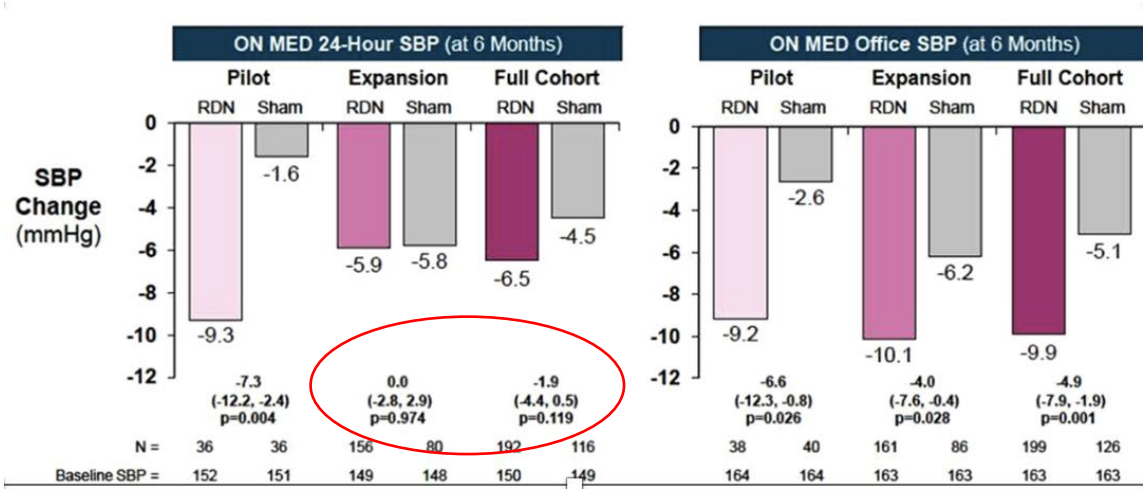
Boehm M et al. Lancet 2020

SPYRAL Trials program: RDN with background BP medications

SPYRAL ON Meds @ 6 months

Proof-of-concept (n=80)

Pivotal (n=80 + 257)

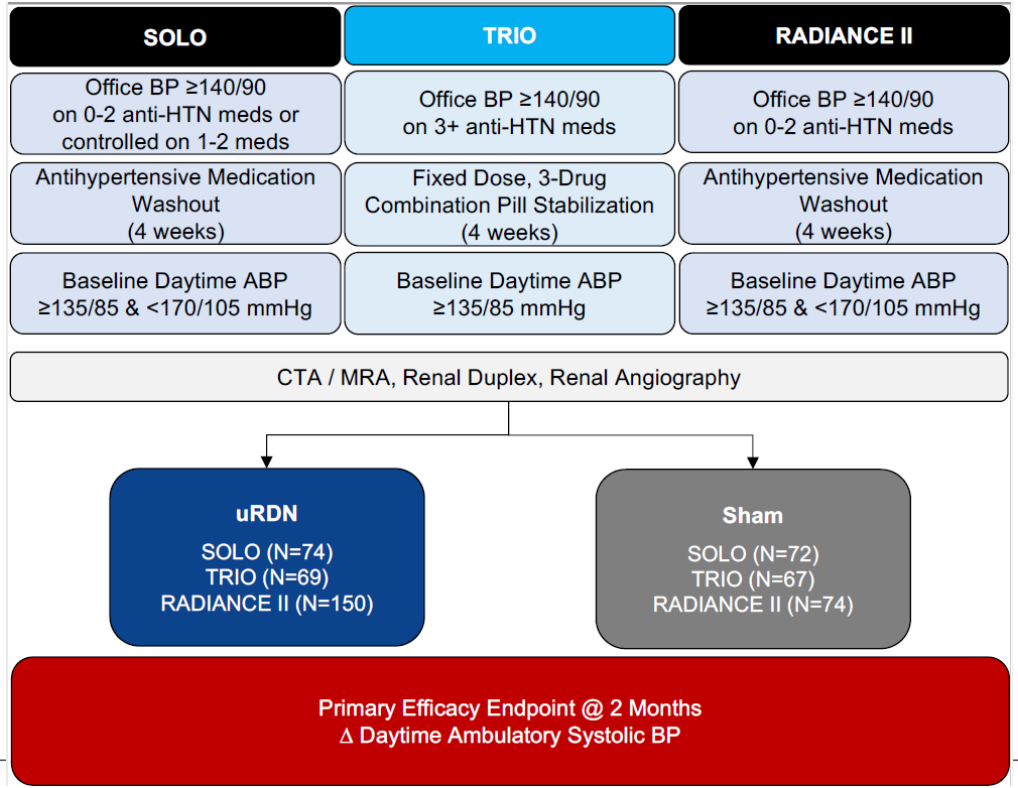


24-hour ASBP (primary outcome): -6.5 mmHg RDN vs. -4.5 mmHg sham (p = 0.12)
Office SBP: -9.9 mmHg RDN vs. -5.1 mmHg sham (p = 0.001)
Mean number of BP medications: 1.9 RDN vs. 2.1 sham (p = 0.01)
Medication burden: 2.9 RDN vs. 3.5 sham (p = 0.04)

Cedars Sinai

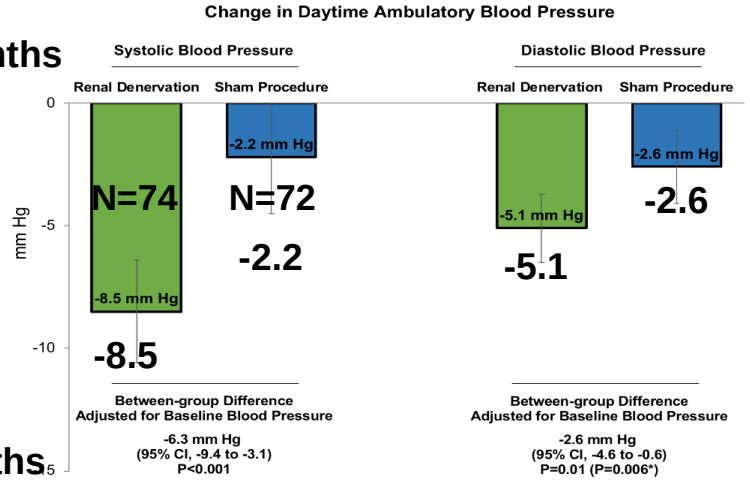
Kandzari DE et al. Lancet 2018
Kandzari et al ACC 2022 (unpublished)

RADIANCE Trial program

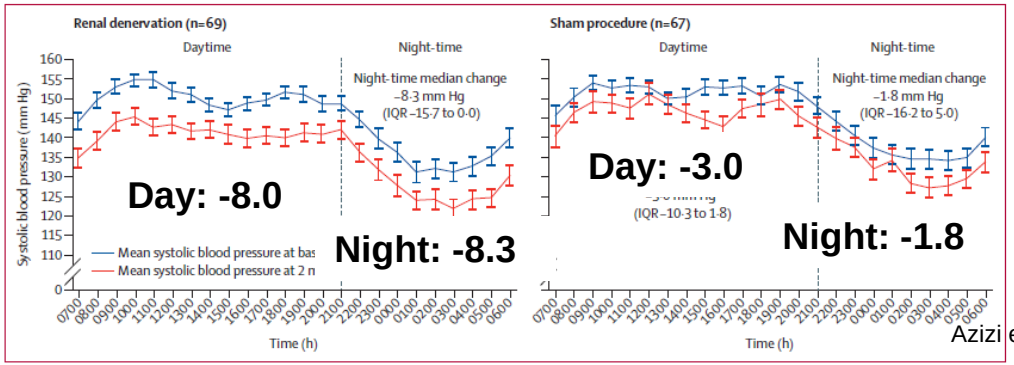


RADIANCE Trial program

SOLO (n=146) @ 2 months



TRIO (n=136) @ 2 months

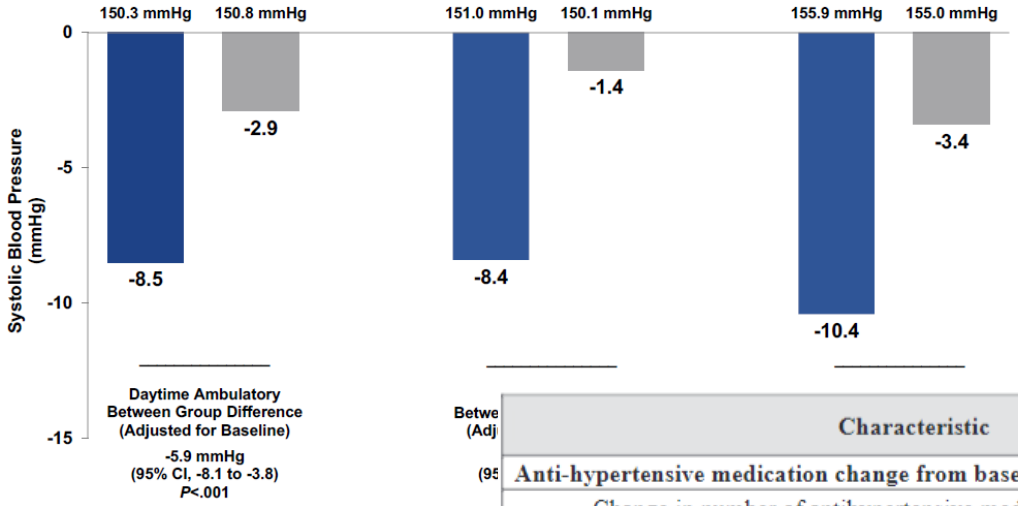


Cedars Sinai

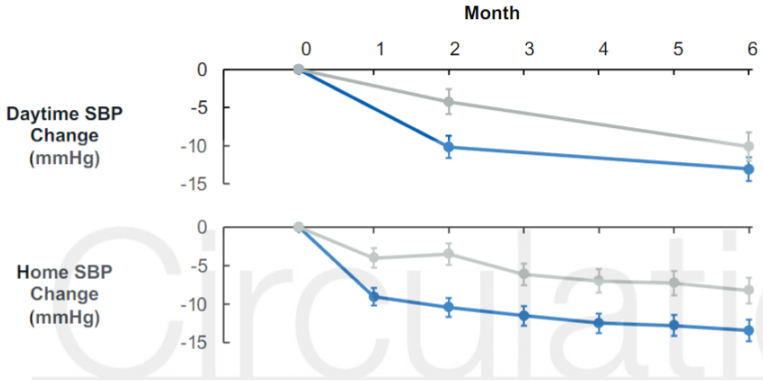
Azizi M, et al. *Lancet*. 2018
Azizi et al JAMA Cardiol. 2022 Dec 1;7(12):1244-1252
Azizi et al JAMA. 2023 Feb 28;329(8):651-661

RADIANCE Trial program

Pooled (uRDN: n=293, Sham: n=213) @ 2 months



Pooled (uRDN: n=285, Sham: n=204) @ 6 months



Characteristic	uRDN+AHT (n=285)	Sham + AHT (n=204)	P value*
Anti-hypertensive medication change from baseline to 6 months			
Change in number of antihypertensive medications, mean ± SD	1.1 ± 1.0	1.3 ± 1.0	0.001
Change in Defined Daily Dose, mean ± SD	1.3 ± 1.6	1.6 ± 1.6	0.001
Change in antihypertensive medication load index, mean ± SD	0.5 ± 0.6	0.6 ± 0.6	0.001

Cedars Sinai

Kirtane et al JAMA Cardiol. 2023 May 1;8(5):464-473
Azizi et al. Circulation 2023 Oct 26

Renal Denervation: who is and who is not a candidate

Indications for RDN

-Uncontrolled hypertension confirmed by out-of-office (ideally ambulatory) BP assessment
-Resistant hypertension, uncontrolled
-Hypertension, uncontrolled with elevated CV risk
-Hypertension, uncontrolled despite many (appropriate) attempts (HTN specialist endorsement)
-Hypertension, uncontrolled due to medication intolerance
-Hypertension, uncontrolled due to non-compliance
-RDN performed by an operator with renal artery engagement and intervention

Clinical reality: Patient chooses RDN instead of adding additional BP medications

Practitioners need to educate but the patient should have a say regarding their treatment *[Shared decision-making]*

Catheter Cardiovasc Interv. 2021;98:416–26

Renal Denervation: who is and who is not a candidate

(Current) Contraindications for RDN

- Treatable secondary causes of hypertension (especially hyperaldosteronism, sleep apnea may be an exception)
- Renal artery stenosis (>30%)
- Fibromuscular dysplasia
- GFR < 40
- Hemodialysis
- Kidney transplant
- Single functioning kidney

Catheter Cardiovasc Interv. 2021;98:416–26

Conclusions

- Hypertension is the main CV risk factor and thus has to be a primary focus in every preventative practice
- The trajectory of BP increases over a lifetime differs in women compared to men
- Aggressive treatment goals (<130/80) are likely beneficial for most patients, including elderly and frail patients. However, not all tolerate these goals and evaluation of orthostatic hypotension and other side effects are essential to **optimize outcomes AND quality of life.**
- Hypertension treatment is effective and tolerable for most with optimal medical therapy.
- New medication and device-based therapies will hopefully aid to improve HTN control rates
- Renal denervation is now clinical reality → HTN experts as well as payors still have to find its place in treatment algorithms. In Europe RDN has now a class 2B recommendation for resistant hypertension.

Frequently Asked Questions (FAQs):

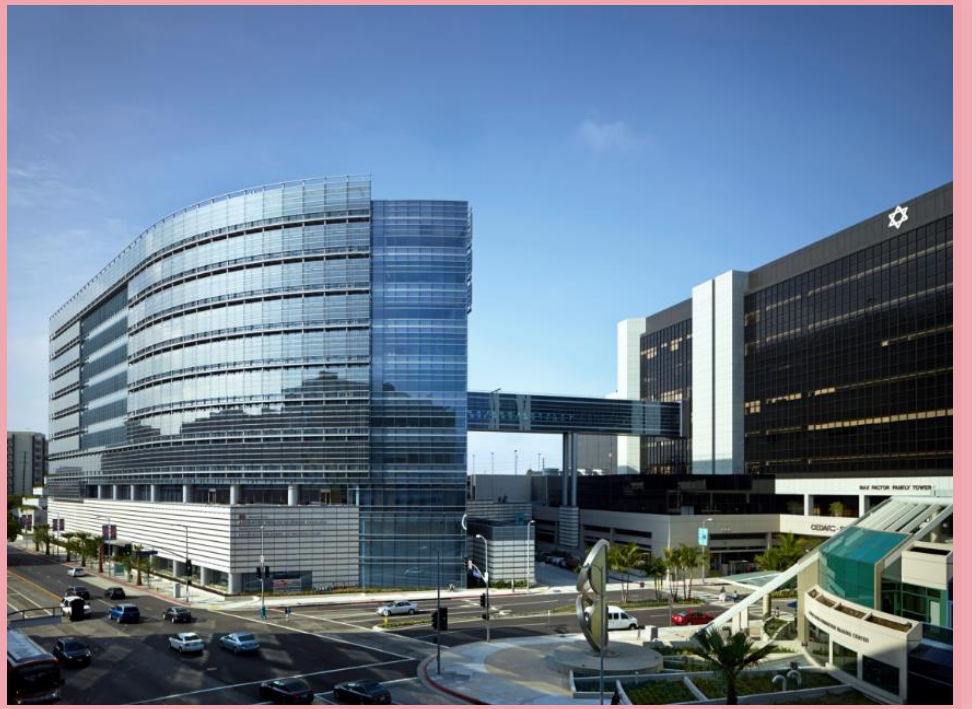
1. What are the optimal BP goals for elderly patients? BP goals must be individualized and although a BP goal of <130/80 is desirable, such goals are sometimes not tolerated, especially in the setting of orthostatic hypotension.

2. Is assessment of clinic or office BP enough? No, home BP and ambulatory BP monitoring are essential to optimize patients' hypertension treatment.

3. What are the best tolerated BP medications? Long-acting angiotensin receptor blockers and non-dihydropyridine calcium channel blockers have the highest continuation rates.

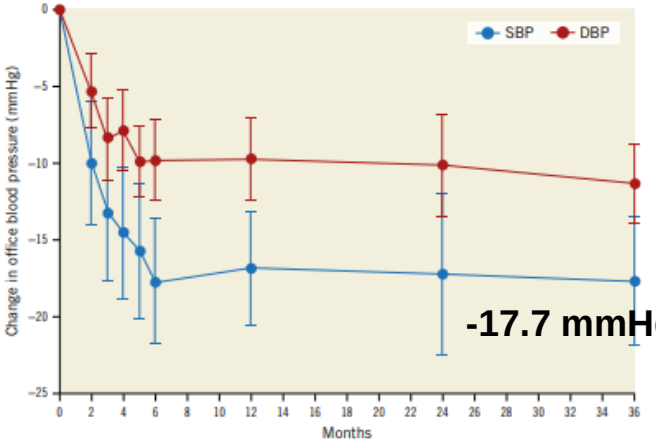
4. Does everyone with a BP of 130-139/80-89 have to be treated with medications. according the 2017 ACC/AHA hypertension guidelines? No. Lifestyle modifications first and only patients who have a calculated cardiovascular risk >10% should be started on antihypertensive medications.
   A conversation between the practitioner and the patient is crucial for these treatment decisions.

florian.rader@cshs.org

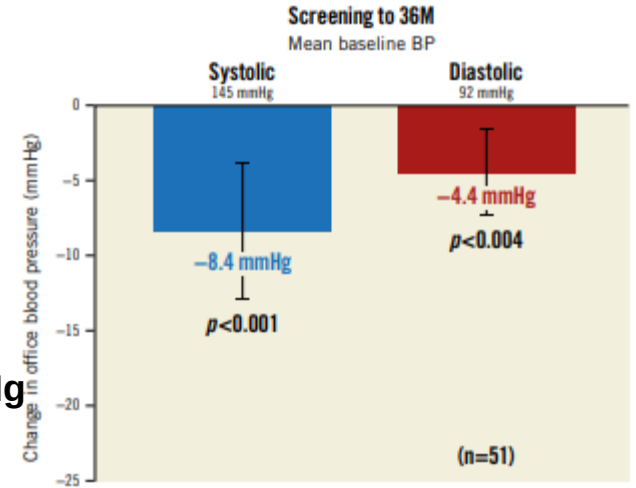


Durability: SOLO 36-month results

Clinical characteristics		n=51
Age, years		53.9±11.4
Female sex		33.3 (17/51)
Race	White	82.4 (42/51)
	Black	13.7 (7/51)
	Other	3.9 (2/51)
Body mass index, kg/m²		29.8±6.1
Abdominal obesity		52.9 (27/51)
eGFR – ml/min/1.73 m²		86.1±17.6
eGFR <60 ml/min/1.73 m²		0 (0/51)
Type 2 diabetes		0 (0/51)
Sleep apnoea		7.8 (4/51)
Screening blood pressure (before anti-HTN med washout)		
Office BP, mmHg		144.5/92.1±13.6/10.4
Baseline blood pressure (after anti-HTN med washout)		
Office BP, mmHg		153.9/99.1±12.7/7.8
Daytime ABP, mmHg		150.8/93.2±7.4/4.9
24-hour ABP, mmHg		142.7/87.2±7.8/5.0



Number of antihypertensive medications (mean)					
BL	2M	6M	12M	24M	36M
0.0	0.1	0.9	1.0	1.2	1.3



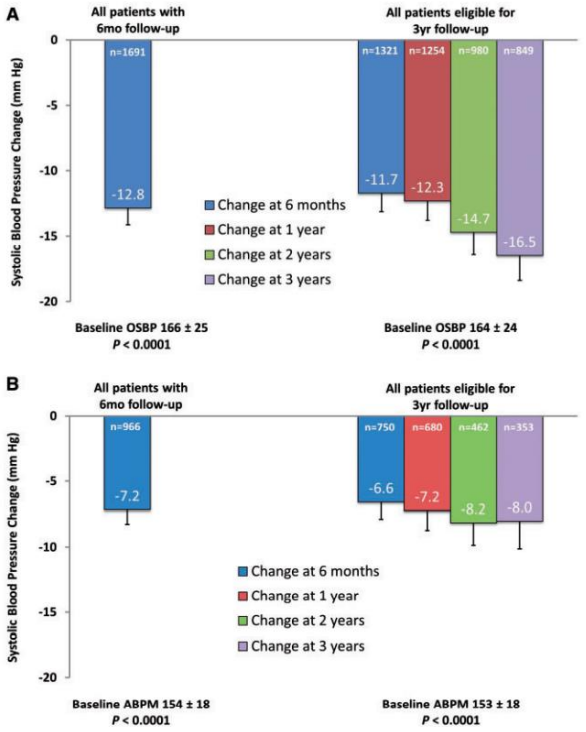
	Screening	36M	Δ screening to 36M	*p*-value
# of meds	1.2±0.7	1.3±0.8	0.1±1.0	*p*=0.461*

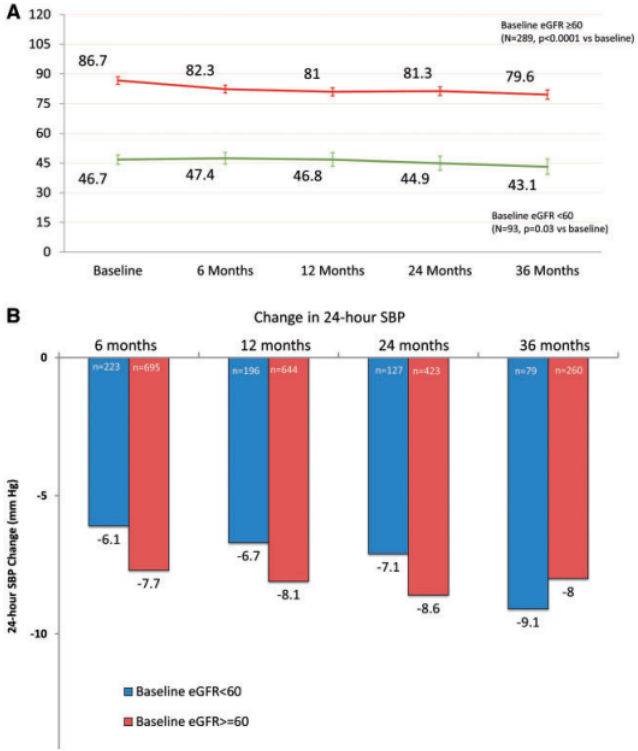
No new adverse events related to RDN; 1 TIA occurred 458 days after randomization

Cedars Sinai

Rader et al. EuroIntervention. 2022 Oct 7;18(8):e677-e685

SPYRAL Durability: Global Simplicity Registry
Up to 3 years





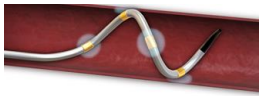
Cedars Sinai

Mahfoud et al. European Heart Journal (2019) 40, 3474–3482

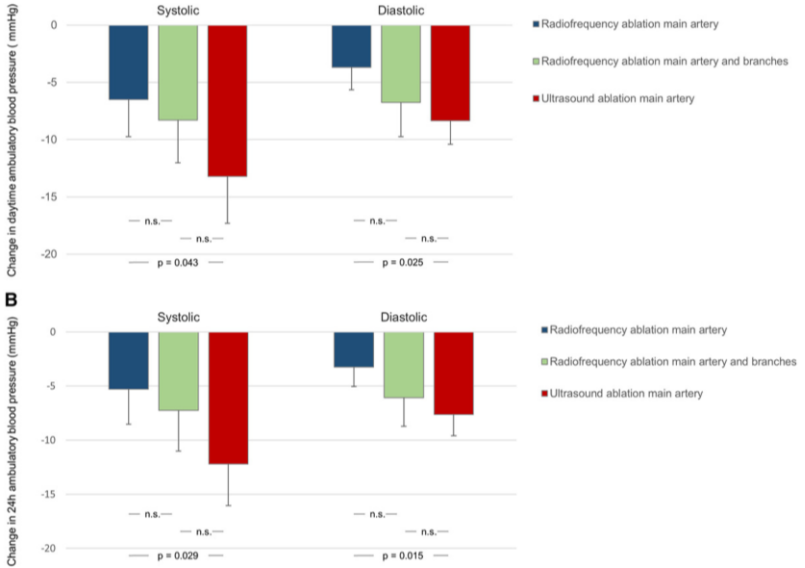
So, which is better? RF-RDN or US-RDN

Are all RDN technologies equal? RADIOSOUND-HTN

Characteristics	All (n=120)	RF Main Only (n=39)	RF Branches (n=39)	US (n=42)	*P* Value
Age	63.5±9.4	63.8±9.9	62.1±10.2	64.6±8.0	0.48*
Body mass index, kg/m^2	31.6±5.6	30.6±5.4	31.6±5.9	32.6±5.4	0.27*
Female, n (%)	37 (31)	13 (33)	15 (38)	10 (24)	0.36†
Serum creatinine, mg/dL	0.98±0.24	0.94±0.17	0.98±0.25	1.01±0.27	0.30*
eGFR, mL·min^{-1}·1.73m^{-2}	77.4±17.9	79.3±15.2	76.9±18.0	76.2±20.3	0.72*
Right renal artery diameter, mm	5.8±0.7	5.7±0.8	5.9±0.7	5.9±0.6	0.41*
Left renal artery diameter, mm	6.0±0.8	6.1±0.8	5.9±0.9	6.0±0.7	0.53*
Smoker, n (%)	55 (46)	17 (44)	20 (51)	18 (43)	0.75†
Diabetes mellitus, n (%)	55 (46)	15 (38)	18 (46)	22 (52)	0.59†
Peripheral artery disease, n (%)	11 (9)	3 (8)	4 (10)	4 (10)	0.92†
Coronary artery disease, n (%)	43 (36)	9 (23)	15 (38)	19 (45)	0.11†
Previous stroke, n (%)	6 (5)	2 (5)	2 (5)	2 (5)	0.99†
Previous myocardial infarction, n (%)	18 (15)	3 (8)	7 (18)	8 (19)	0.30†
Atrial fibrillation, n (%)	21 (18)	7 (18)	6 (15)	8 (19)	0.91†
Oral anticoagulation, n (%)	25 (21)	8 (21)	8 (21)	9 (21)	0.99†
Dyslipidemia, n (%)	101 (84)	35 (90)	33 (85)	33 (79)	0.39†



Contrast agent used, mL	110.6±62.2	90.8±54.8	143.1±66.6	98.7±52.9	<0.001*
Cincefluoroscopy time, min	11.2±7.8	8.9±5.6	16.8±8.0	8.1±6.5	<0.001*



→ RF ablation into branches appears to be equally potent as US-RDN but technically more difficult with greater contrast and fluoroscopy time

Cedars Sinai

Fengler K et al Circulation. 2019;139:590–600

Chronic Hypertension and Pregnancy (CHAP) trial

Open label trial of 2292 participants with mild HTN: labetalol (31%), nifedipine (18%), 50% SOC (no Rx unless HTN became severe, i.e. >1670/110)

Outcomes: preterm delivery, placental abruption, fetal death, small for gestational age newborns (secondary outcome)

Results: primary outcome occurred in 30.1% in the labetalol group; 31.2% in the nifedipine group; and 37% in the standard care group → *Earlier treatment led to better pregnancy outcomes with no apparent increase in fetal risk; no difference between labetalol and nifedipine*

Non-severe adverse events were more common in nifedipine than labetalol (headache, dizziness) – is nifedipine just more effective?

Tita et al. N Engl J Med 2022;386:1781-9

Chronic Hypertension and Pregnancy (CHAP) trial

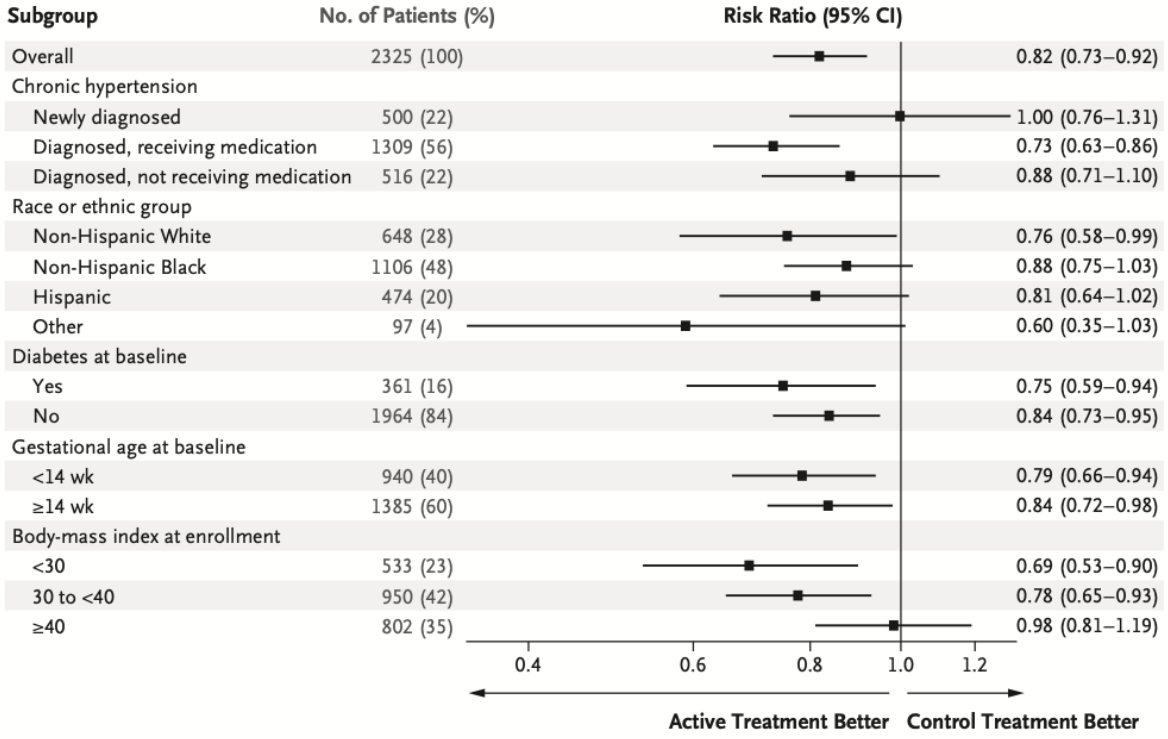
No HTN type, race or age subgroup differences seen

Open label trial of … **(no Rx unless HTN became severe, i.e**

Outcomes: preteri… (secondary outcome)

Results: primary o… …; and 37% in the standard care grou… *…rease in fetal risk; no difference betwee…*

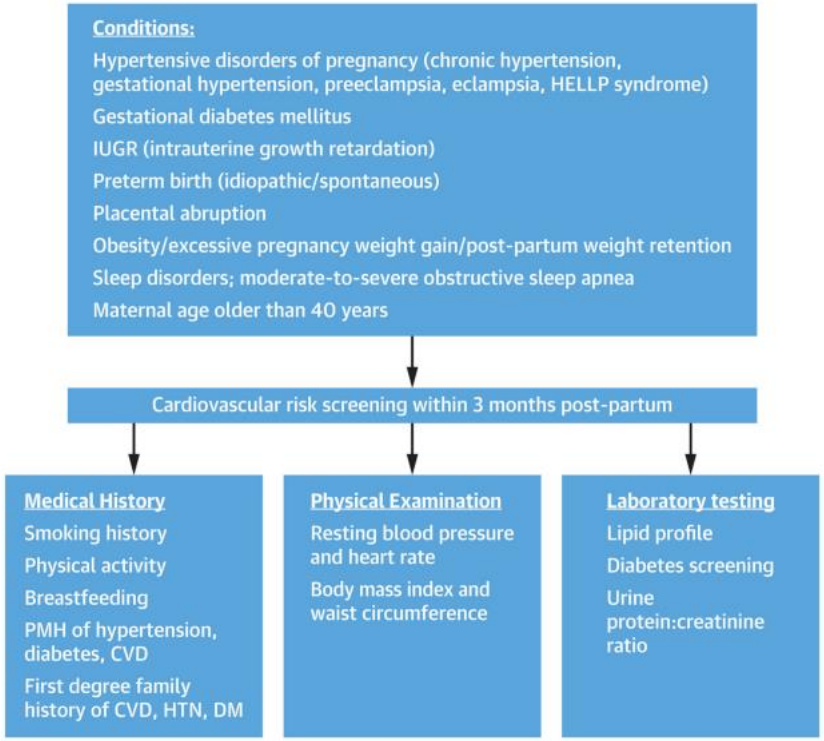
Non-severe adver… ***…ss) – is nifedipine just more effective?***



Cedars Sinai

Tita et al. N Engl J Med 2022;386:1781-9

CV risk increases with adverse pregnancy outcomes→ screen and follow up postpartum



Focus of Womens' Heart Centers

Cedars Sinai

Cho et al 2020. J Am Coll Cardiol. 2020 May 26; 75(20): 2602–2618.

Thank you!

florian.rader@cshs.org