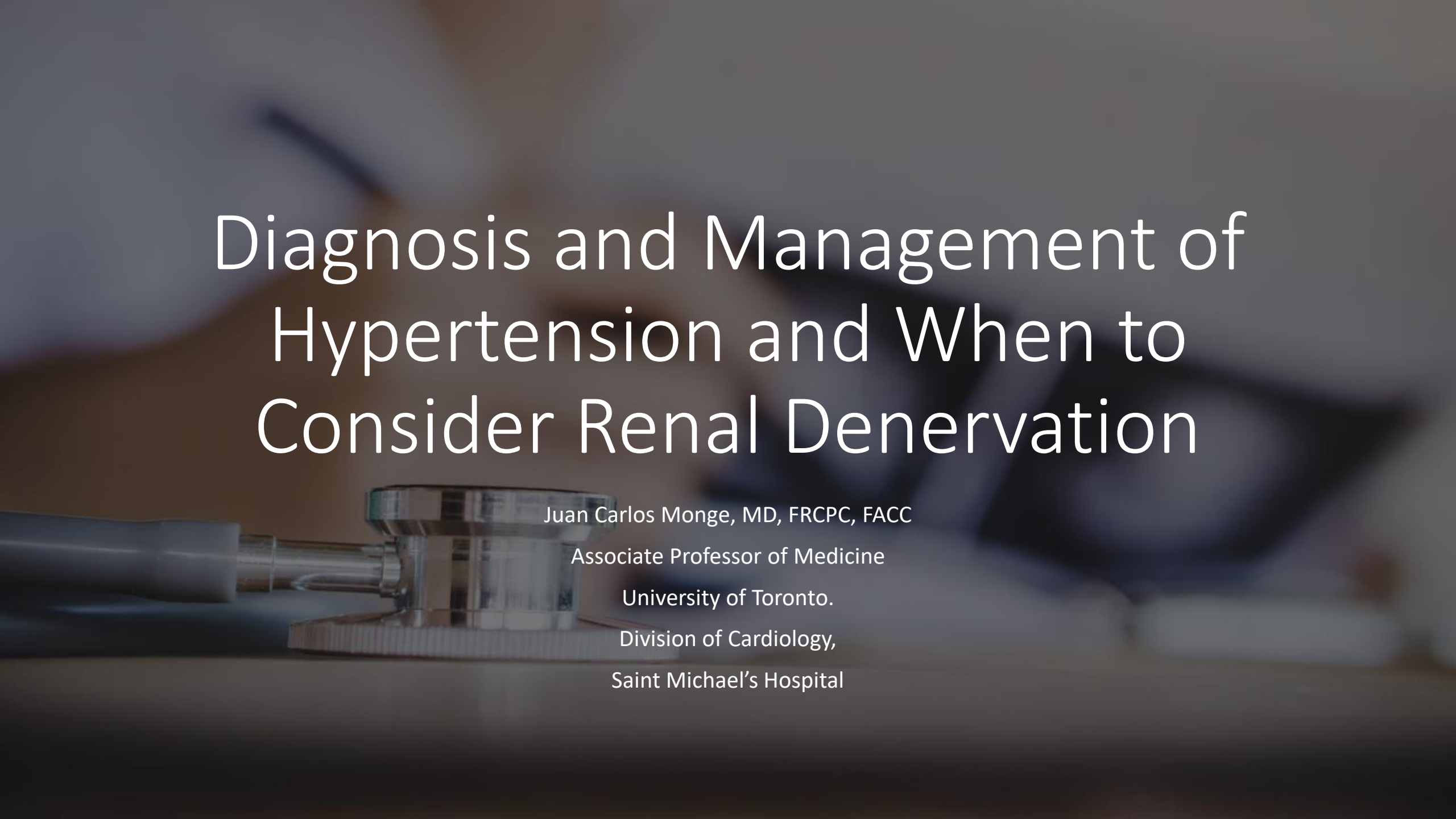
Diagnosis and Management of Hypertension and When to Consider Renal Denervation



Juan Carlos Monge, MD, FRCPC, FACC

Associate Professor of Medicine

University of Toronto.

Division of Cardiology,

Saint Michael's Hospital

ST. MICHAEL'S
UNITY HEALTH TORONTO

Presenter Disclosure

Dr. Juan Carlos Monge

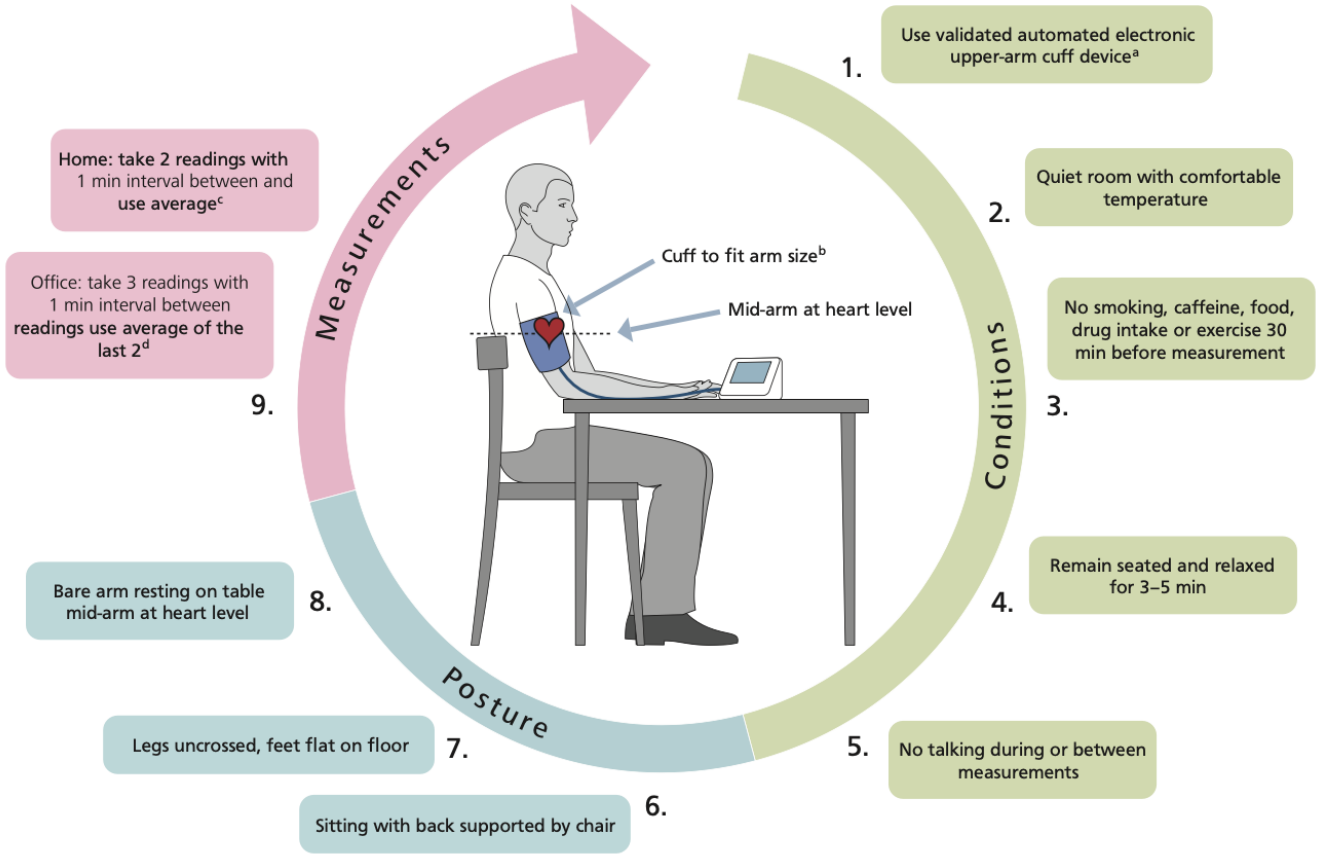
Diagnosis and management of hypertension and when to consider renal artery denervation

Relationships with financial sponsors:

- **Grants/Research Support:** N/A
- **Speakers Bureau/Honoraria:** CHRC
- **Consulting Fees:** N/A
- **Patents:** N/A
- **Other:** N/A

Diagnosis of Hypertension

- Proper measurements of office and home BP
- Increased use of ABPM



ESH Guidelines

2023 ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension

Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA)

Authors/Task Force Members: Giuseppe Mancia (Chairperson)[a,*], Reinhold Kreutz (Co-Chair)[b,*], Mattias Brunström[c], Michel Burnier[d], Guido Grassi[e], Andrzej Januszewicz[f], Maria Lorenza Muiesan[g], Konstantinos Tsioufis[h], Enrico Agabiti-Rosei[i], Engi Abd Elhady Algharably[b], Michel Azizi[j,k], Athanase Benetos[l], Claudio Borghi[m], Jana Brguljan Hitij[n], Renata Cifkova[o,p], Antonio Coca[q], Veronique Cornelissen[r], J. Kennedy Cruickshank[s], Pedro G. Cunha[t,u], A.H. Jan Danser[v], Rosa Maria de Pinho[w], Christian Delles[x], Anna F. Dominiczak[y], Maria Dorobantu[z], Michalis Doumas[aa], María S. Fernández-Alfonso[bb,cc], Jean-Michel Halimi[dd,ee,ff], Zoltán Járai[gg], Bojan Jelakovic[hh], Jens Jordan[ii,jj], Tatiana Kuznetsova[kk], Stephane Laurent[ll], Dragan Lovic[mm], Empar Lurbe[nn,oo,pp], Felix Mahfoud[qq,rr], Athanasios Manolis[ss], Marius Miglinas[tt,uu], Krzystof Narkiewicz[vv], Teemu Niiranen[ww,xx], Paolo Palatini[yy], Gianfranco Parati[zz,aaa], Atul Pathak[bbb], Alexandre Persu[ccc], Jorge Polonia[ddd], Josep Redon[oo,eee,fff], Pantelis Sarafidis[ggg], Roland Schmieder[hhh], Bart Spronck[iii], Stella Stabouli[jjj], George Stergiou[kkk], Stefano Taddei[lll], Costas Thomopoulos[mmm], Maciej Tomaszewski[nnn,ooo], Philippe Van de Borne[ppp], Christoph Wanner[qqq], Thomas Weber[rrr], Bryan Williams[sss], Zhen-Yu Zhang[ttt], and Sverre E. Kjeldsen[uuu]

Mancia, Giuseppe; Kreutz, Reinhold; Brunström, Mattias; et al. *Journal of Hypertension*. 41(12):1874-2071, December 2023.

Office BP thresholds for drug treatment initiation

Recommendations and statements	CoR	LoE
In patients 18 to 79 years, the recommended office threshold for initiation of drug treatment is 140 mmHg for SBP and/or 90 mmHg for DBP.	I	A
In patients ≥80 years, the recommended office SBP threshold for initiation of drug treatment is 160 mmHg.	I	B
However, in patients ≥80 years a lower SBP threshold in the range 140 – 159 mmHg may be considered.	II	C
The office SBP and DBP thresholds for initiation of drug treatment in frail patients should be individualized.	I	C
In adult patients with a history of CVD, predominantly CAD, drug treatment should be initiated in the high-normal BP range (SBP ≥130 or DBP ≥80 mmHg).	I	A

Office BP targets for drug treatment

Recommendations and statements	CoR	LoE
Patients 18 to 64 years old		
The goal is to lower office BP to <130/80mmHg.	I	A
Patients 65 to 79 years old		
The primary goal of treatment is to lower BP to <140/80mmHg.	I	A
However, lowering BP to below 130/80mmHg can be considered if treatment is well tolerated.	II	B
Patients 65 to 79 years old with ISH		
The primary goal of treatment is to lower SBP in the 140 to 150 mmHg range.	I	A
However, a reduction of office SBP in the 130 to 139 mmHg range should be considered if well tolerated, albeit cautiously if DBP is already below 70 mmHg.	I	B
Patients ≥80 years old		
Office SBP should be lowered to a SBP in the 140 to 150 mmHg range.	I	A
However, reduction of office SBP between 130 to 139 mmHg may be considered if well tolerated, albeit cautiously if DBP is already below 70 mmHg.	II	B

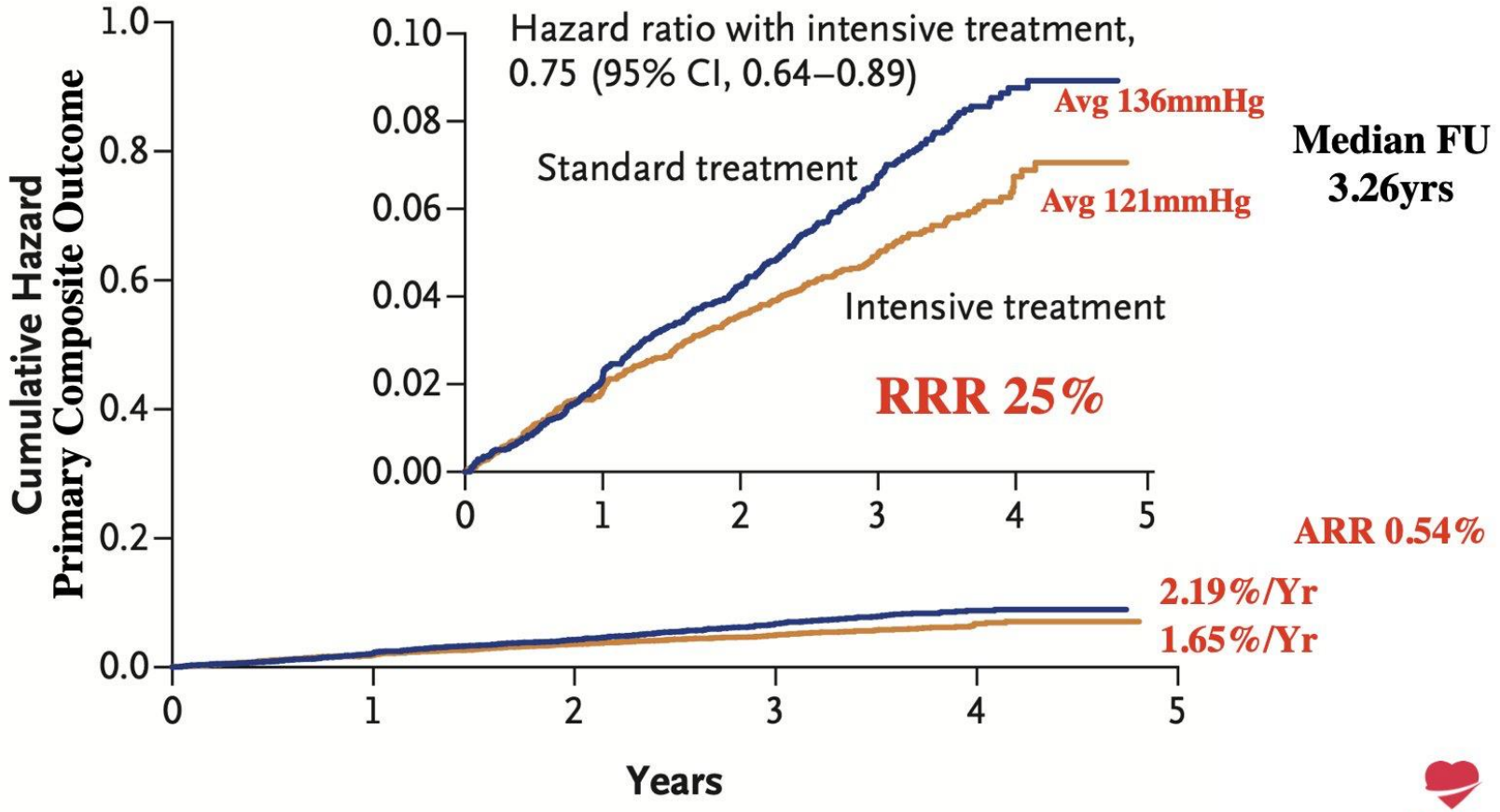
Age >50yrs + 1 CVD Risk - BP >130mmHg

SPRINT Trial

Target BP <120 mmHg Intervention Group

Target BP <140 mmHg Standard Group

Outcome: MI, Stroke, Heart Failure, CV Death



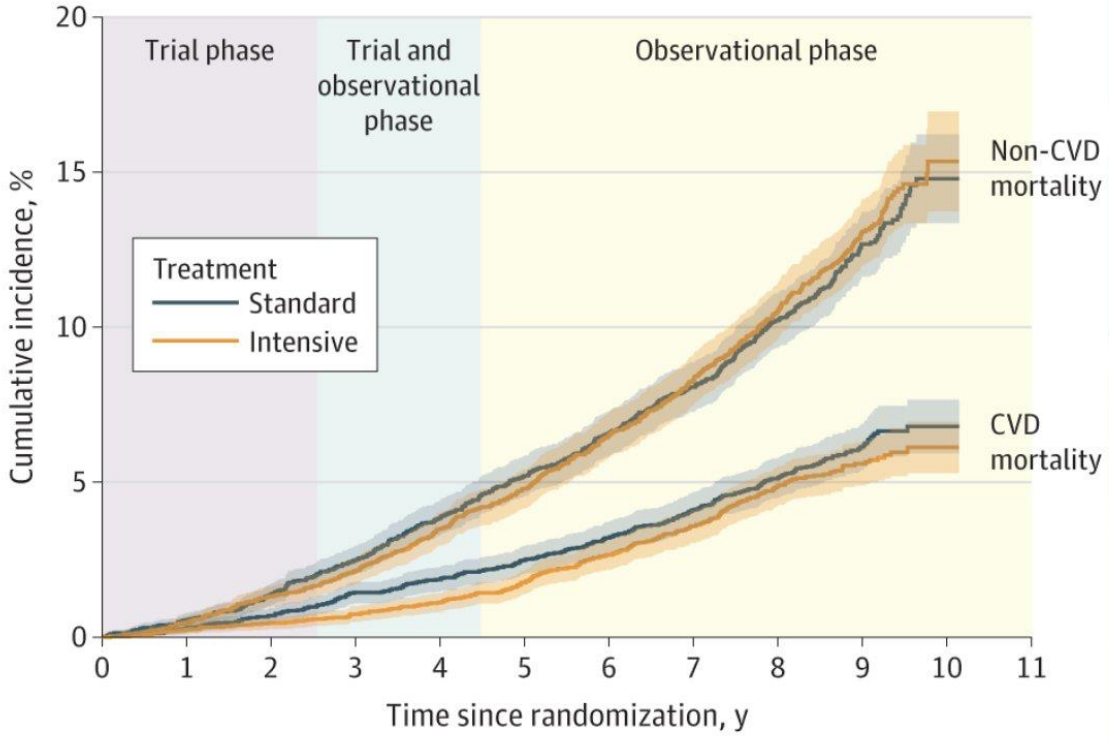
A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26;373(22):2103-16.

My HEART Health

SPRINT Trial - Extended Follow Up

Median FU 8.8 years

A Cumulative incidence of CVD and non-CVD mortality by treatment group



No CVD Mortality Benefit

No All Cause Mortality Benefit

Average Intensive Arm BP
Year 3 121mmHg
Year 5 132mmHg
Year 10 140mmHg

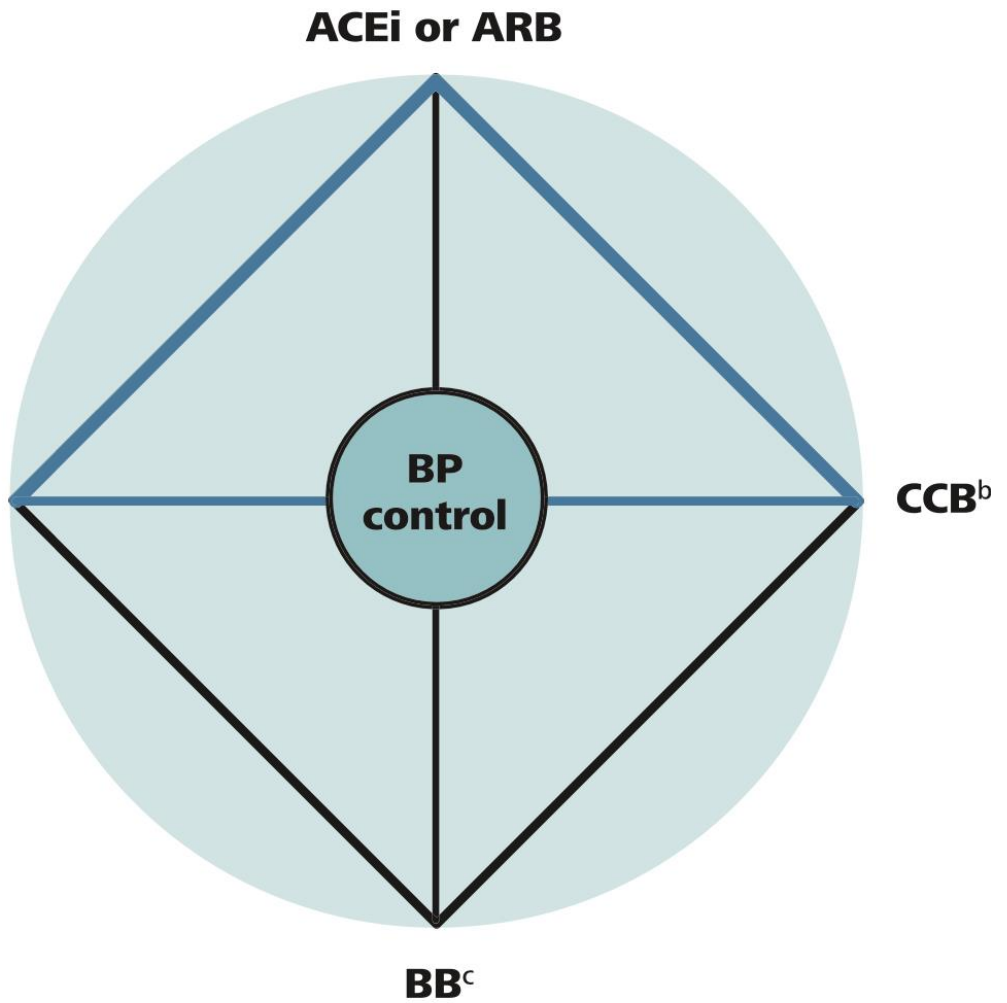
NB Lowering & Keeping Low BP

Longer-Term All-Cause and Cardiovascular Mortality With Intensive Blood Pressure Control: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol*. Published online October 12, 2022.

My HEART Health

Prescribing patterns:

- Start with dual combination therapy in most patients
- Uptitrate to maximum well tolerated doses and to triple therapy if needed
- **Once daily (preferred in the morning)**
- **Add further drugs if needed**
- **Preferred use of SPCs at any step**



Additional drug classes

General antihypertensive therapy:

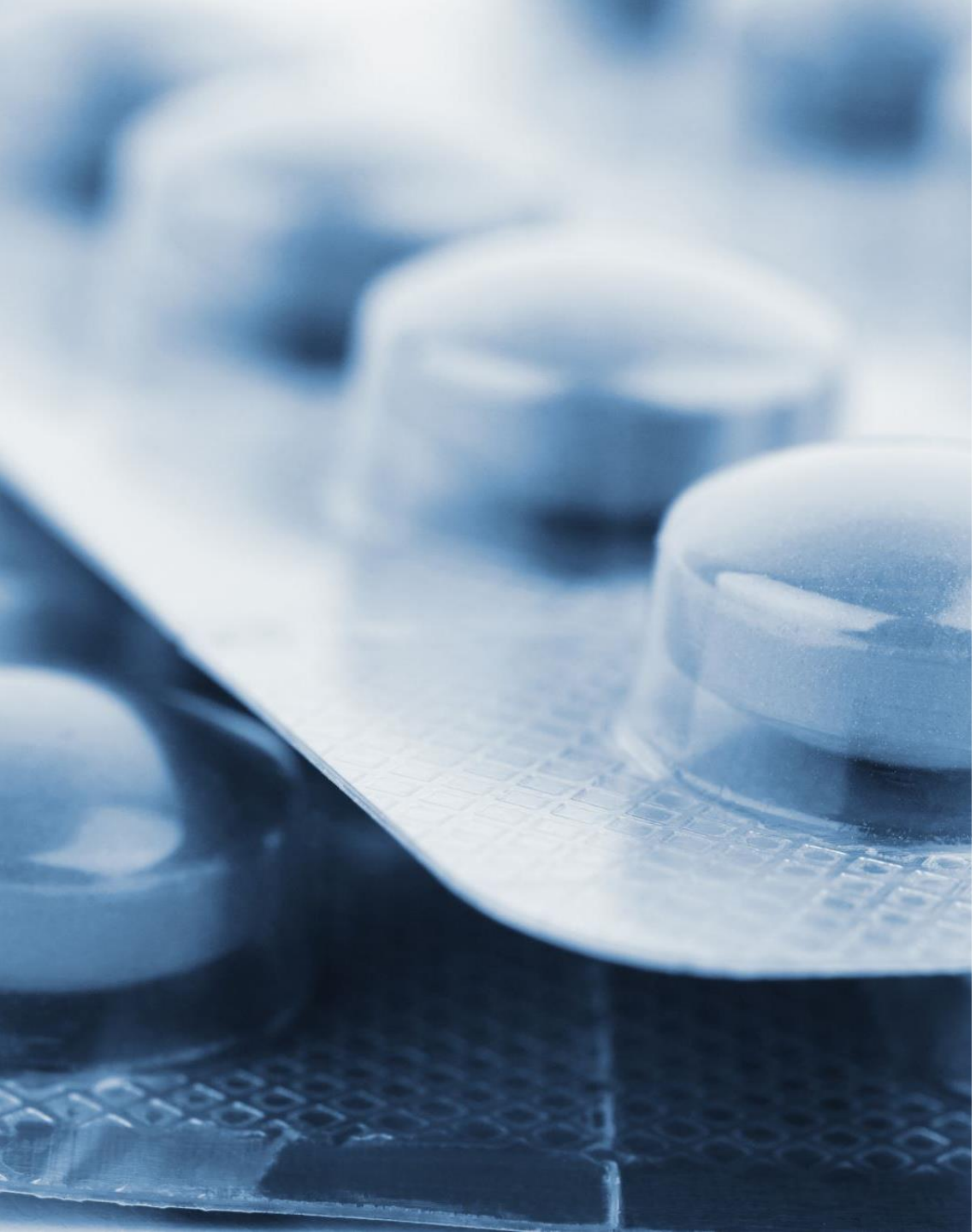
- Steroidal MRA
- Loop Diuretic
- Alpha-1 Blocker
- Centrally acting agent
- Vasodilator

Special comorbidities:

- ARNi
- SGLT2i
- Non-Steroidal MRA

General recommendations for antihypertensive drug treatment

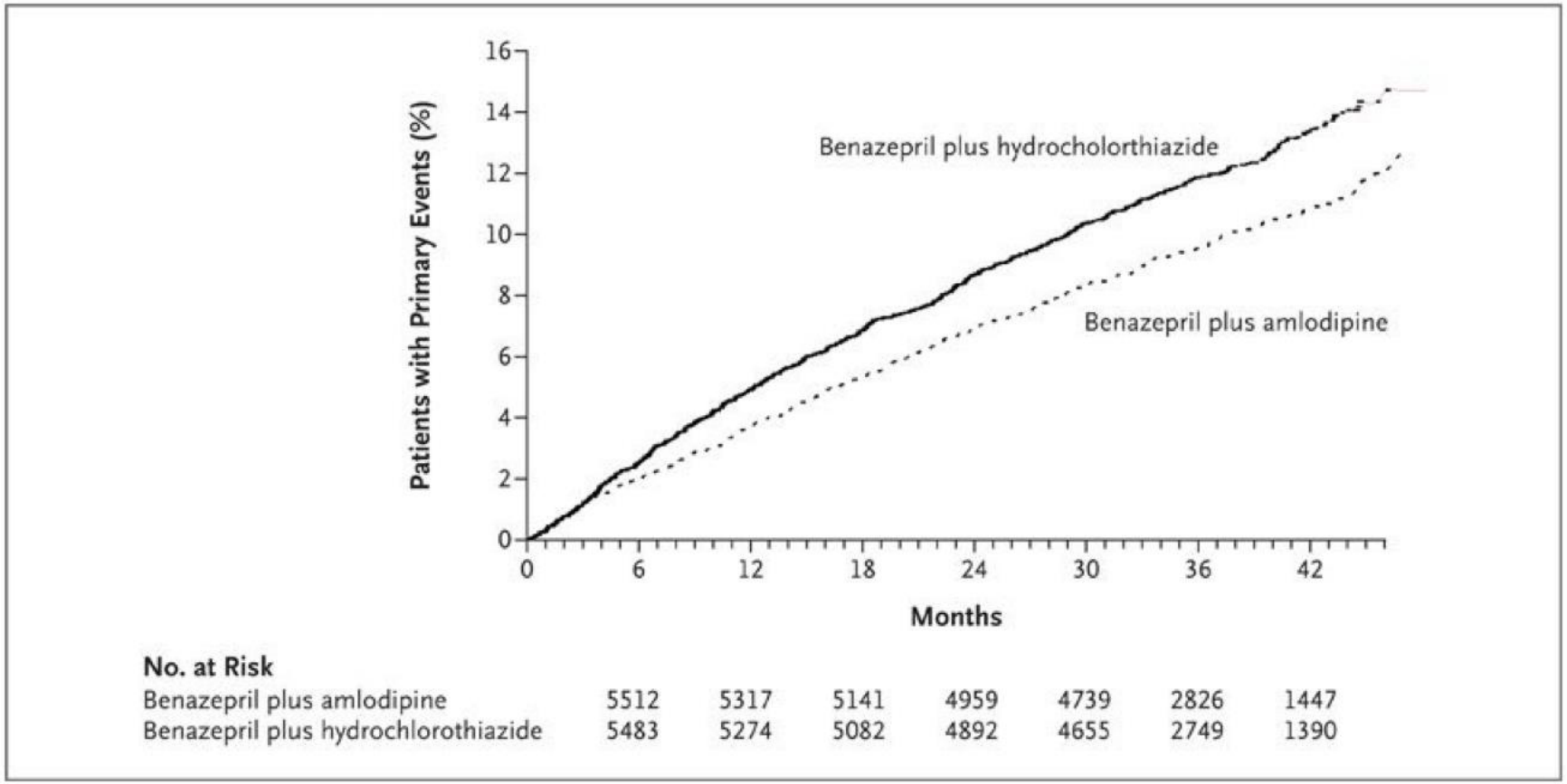
Recommendations and statements	CoR	LoE
BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction.	I	A
Five major drug classes including ACEis, ARBs, BBs, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced BP and CV events in RCTs. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies.	I	A
Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or Thiazide/Thiazide-like diuretic. Other combinations of the five major drug classes can be used.	I	A
Initiation with monotherapy should be considered in patients with: • grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) • high-normal BP and very high CV risk, • frailty and/or and advance age.	I	C



Rationale for initial single agent or initial combination

- ACE inhibitors and Angiotensin Receptor Blockers have extensive evidence of cardiovascular, cerebrovascular and renal protection in hypertension and in individuals at an increased risk of such outcomes: Start with one of these agents if there is no contraindication and mono-therapy is indicated
- What about the second agent, either as an add-on or when initiating therapy with a combination?

ACCOMPLISH Trial



RR= 19.6%

Jamerson, K et al. N Engl J Med 2008;359:2417-2428

And what if a third agent is needed?

Add a diuretic, but which one:

1) Hydrochlorotiazide
2) Indapamide
3) Chlorthalidone
4) Furosemide

DCP: The Diuretic Comparison Project

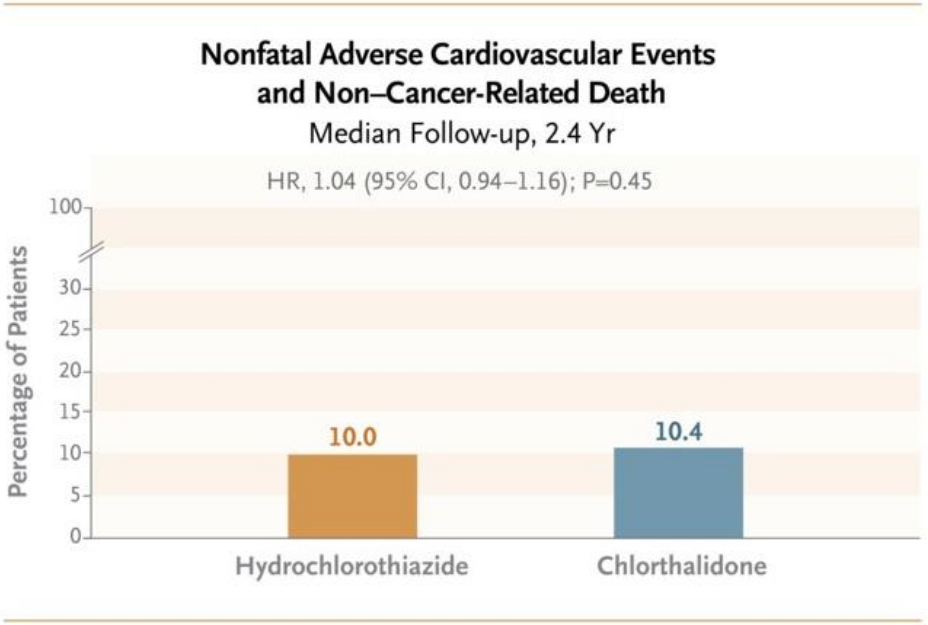
RESULTS

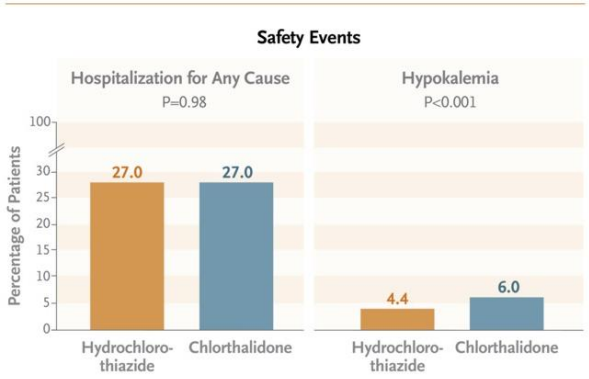
Efficacy: During a median follow-up of 2.4 years, the incidence of primary-outcome events did not differ significantly between the chlorthalidone and hydrochlorothiazide groups.

Safety: The incidence of hospitalization for any cause did not differ between the groups. Hypokalemia was more common in the chlorthalidone group than in the hydrochlorothiazide group.

LIMITATIONS AND REMAINING QUESTIONS

- More patients assigned to receive chlorthalidone switched back to hydrochlorothiazide, as compared with patients assigned to continue treatment with hydrochlorothiazide switching over to chlorthalidone — possibly owing to the open-label nature of the trial.
- Only 5% of participants were receiving a daily 50-mg dose of hydrochlorothiazide at baseline; thus, the trial primarily compared hydrochlorothiazide at a daily dose of 25 mg with chlorthalidone at a daily dose of 12.5 mg, and the results should not be extrapolated to other dosages.





CONCLUSIONS

In a large pragmatic trial among U.S. veterans with hypertension, patients who received chorthalidone did not have a lower occurrence of nonfatal cardiovascular events or non–cancer-related death than those who received hydrochlorothiazide.

Areef, I. et al. N Engl J Med 2022; 387:2401-2410

What About Patients with Resistant Hypertension

- Defined as not controlled on three drugs (or requiring more than three drugs for control)
- Several choices: Spironolactone (and other steroidal and non-steroidal MRAs), Hydralazine, Doxazosin, Prazosin, Clonidine, Alpha Methyl Dopa,
- Endothelin Receptor antagonists, Aldosterone Synthase inhibitors, and other drug classes undergoing research.

Which drug would you choose as a 4th agent in resistant hypertension?
-Patient already on ACE/ARB, CCB, and diuretic.

- 1) Hydralazine
- 2) Doxazosin
- 3) Beta-blocker
- 4) Spironolactone
- 5) Clonidine

Meta-analysis of Spironolactone Trials

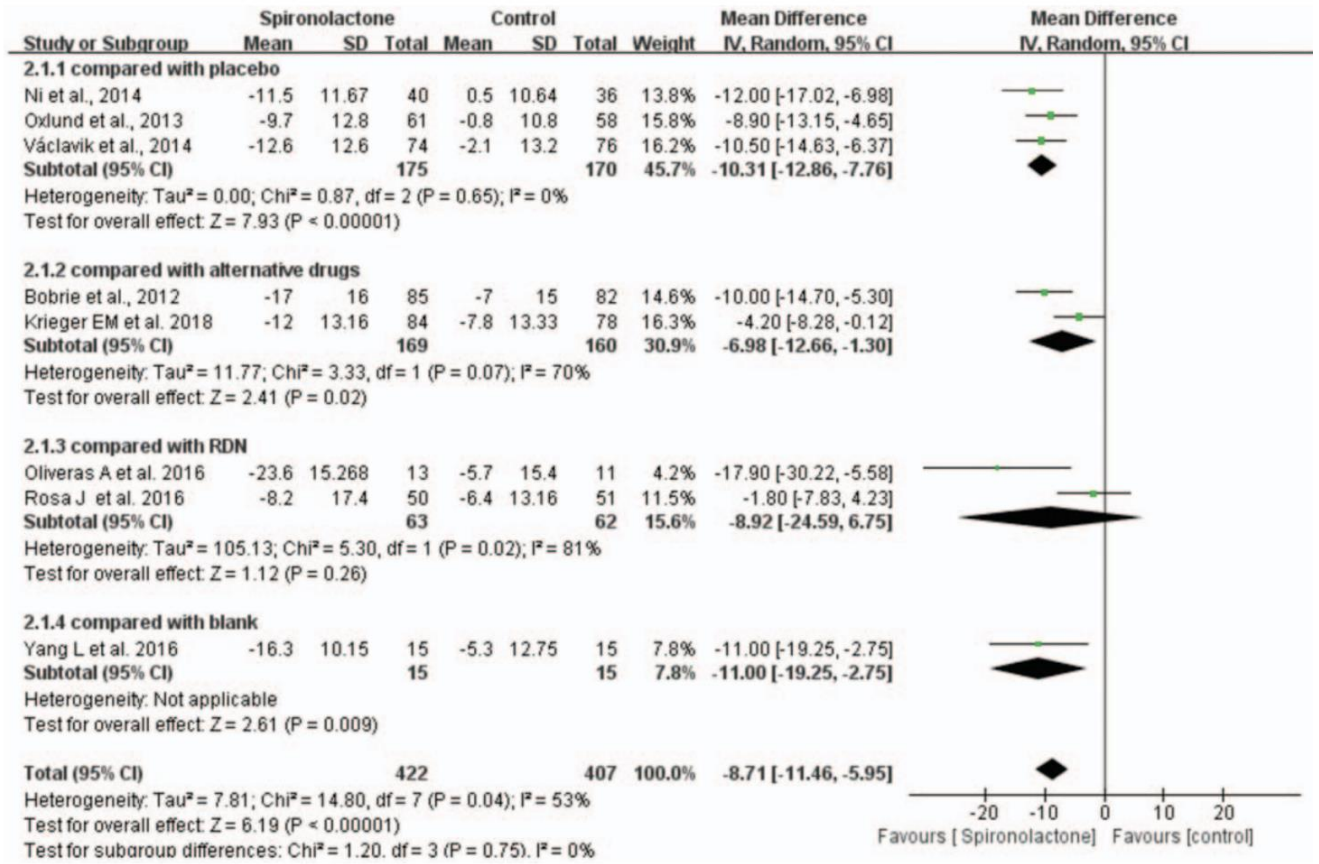


Figure 5. Forest plots comparing the 24-hour ambulatory SBP between the spironolactone group and other groups.

Chen C et al. Medicine (Baltimore). 2020, 99(34):e21694.

PATHWAY

Primary Outcome
HSBP at Final visit only

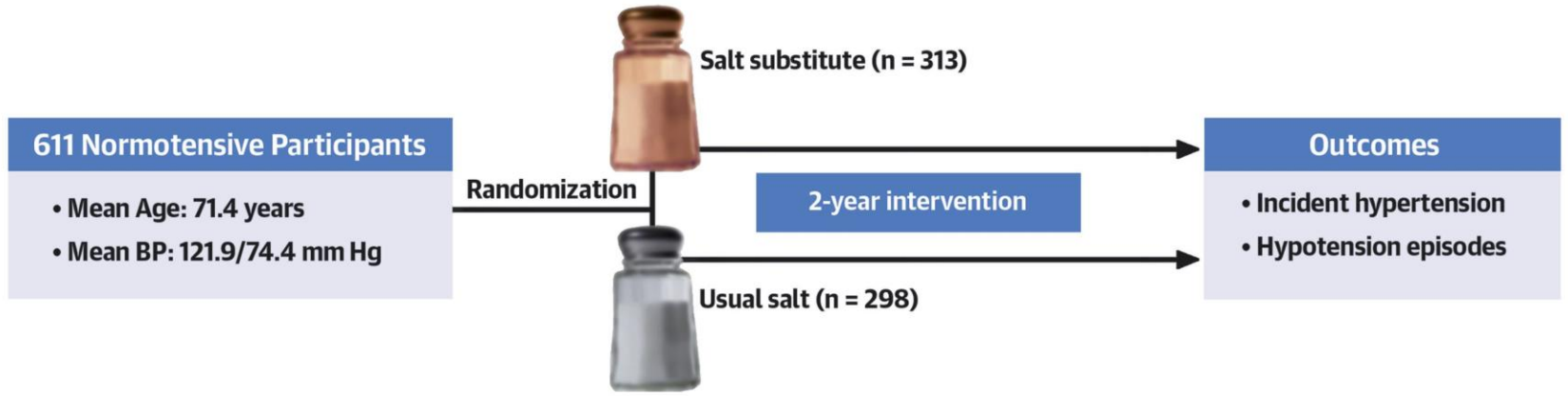
Final visit on each drug		Blood pressure (mmHg)	Change from baseline
Means	Spironolactone	133.4 (131.9,134.9)	-14.3 (-15.8,-12.8)
	Doxazosin	138.2 (136.7,139.6)	-9.5 (-11.0, -8.0)
	Bisoprolol	138.7 (137.2,140.2)	-9.0 (-10.4, -7.5)
	Placebo	143.2 (141.7,144.7)	-4.4 (-5.9, -2.9)
			p value
Mean differences	Spironolactone vs Placebo	-9.85 (-11.6,-8.12)	<0·001
	Spironolactone vs mean Bisoprolol/Doxazosin	-5.04 (-6.54,-3.55)	<0·001
	Spironolactone vs Doxazosin	-4.78 (-6.50,-3.06)	<0·001
	Spironolactone vs Bisoprolol	-5.31 (-7.03,-3.59)	<0·001

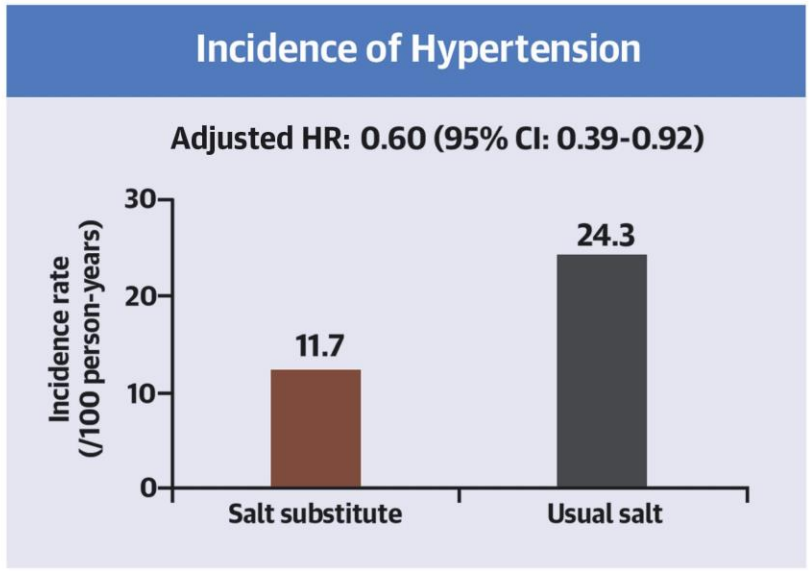
Williams, B et al. Lancet. 2015, 386(10008):2059-2068

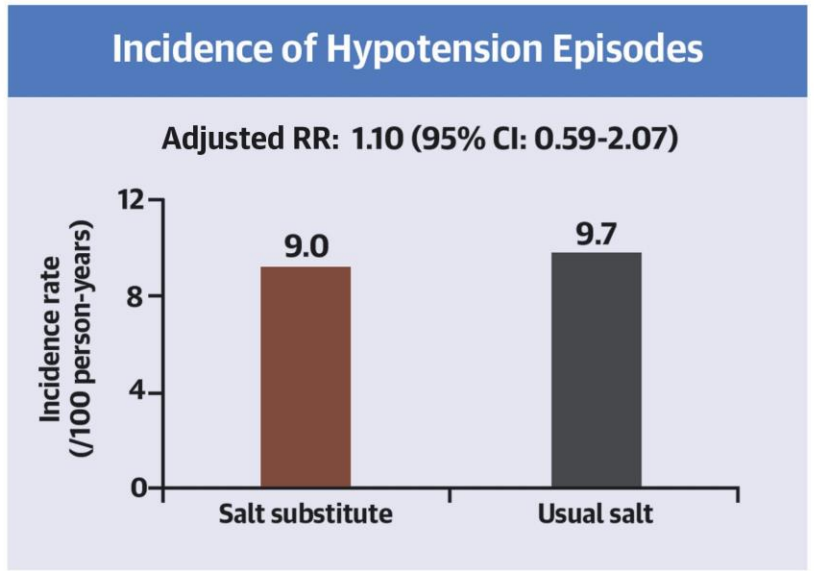
Is there a role for non-pharmacological interventions?

- Lifestyle changes should be implemented in all cases
- Weight management
- Treatment of sleep apnea
- Reduction of alcohol intake
- Dietary approaches: salt restriction, DASH diet
- Increase in physical activity
- Role of salt substitutes?

CENTRAL ILLUSTRATION: Salt Substitute Reduces the Incidence of Hypertension Without Increasing Hypotension







Zhang X, et al. J Am Coll Cardiol. 2024;83(7):711-722.

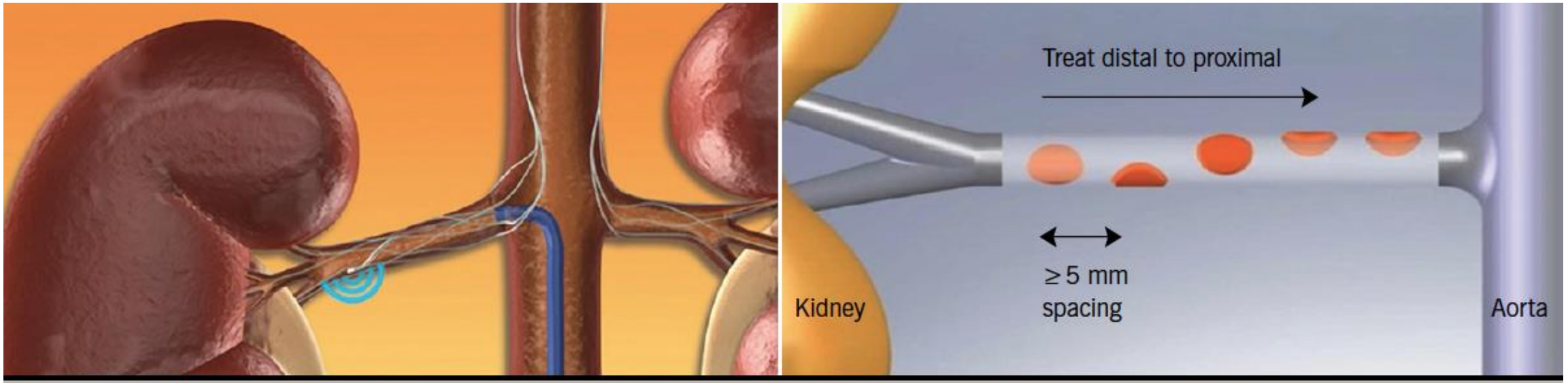
This study sought to assess the effects of a salt substitute (62.5% NaCl, 25% KCl, and 12.5% flavorings) on incidence of hypertension and hypotension among older adults with normal blood pressure.

Is there a role for non-pharmacological interventions?

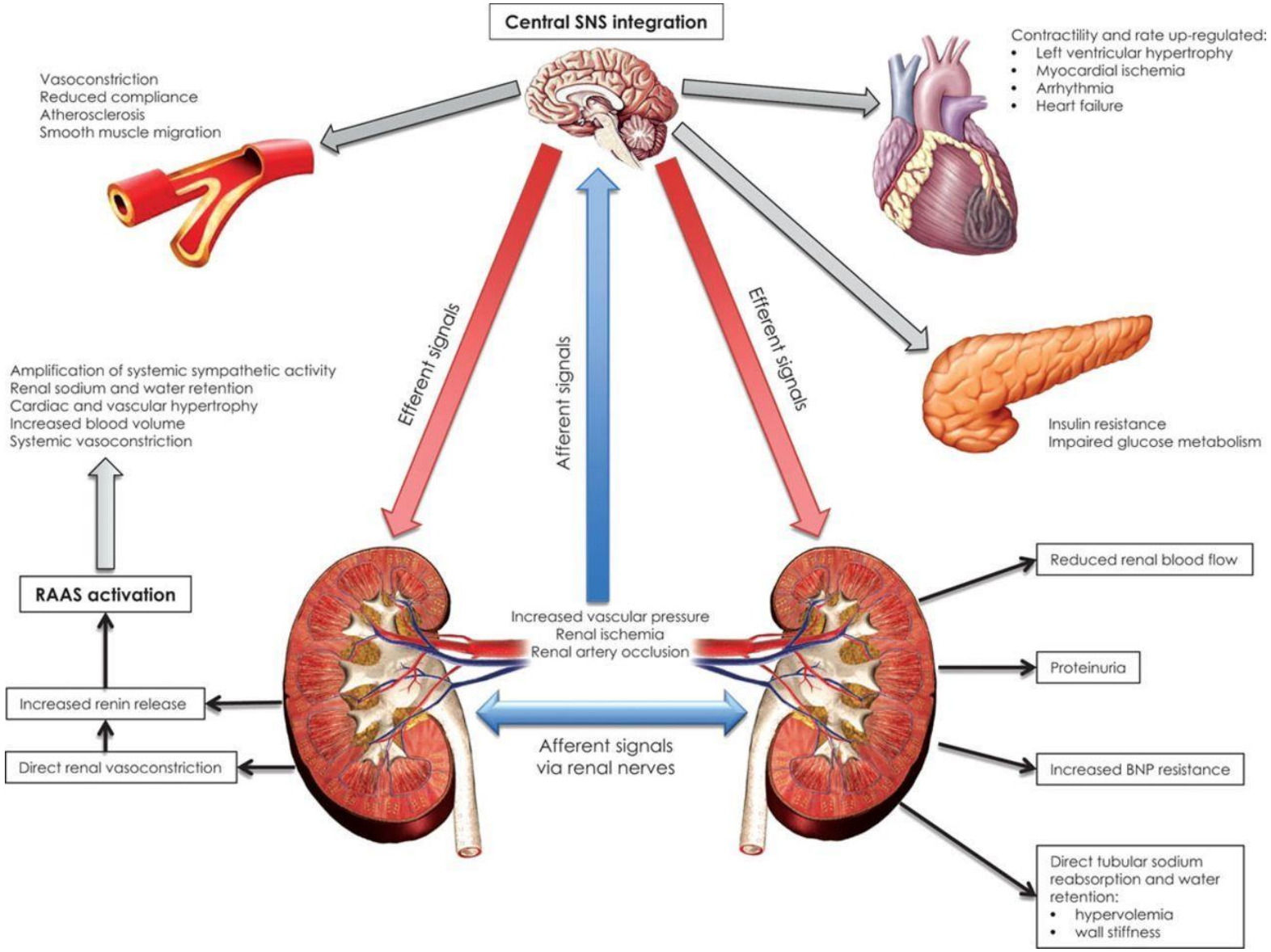
- *Lifestyle changes should be implemented in all cases*
- *Weight management*
- *Treatment of sleep apnea*
- *Reduction of alcohol intake*
- *Dietary approaches: salt restriction, DASH diet*
- *Role of salt substitutes?*
- **Device-based interventional approaches: Renal Denervation**

Renal Denervation

- Endovascular renal denervation with radiofrequency energy or high frequency unfocused ultrasound energy represents a treatment option, that is additive or alternative to increasing medication in patients with uncontrolled resistant hypertension confirmed by ABPM after excluding secondary causes of hypertension



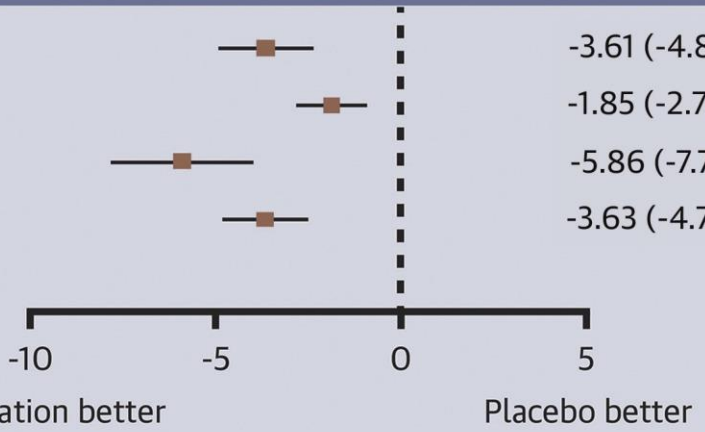
Images courtesy of Medtronic


Central SNS integration
Vasoconstriction
Reduced compliance
Atherosclerosis
Smooth muscle migration
Contractility and rate up-regulated:
• Left ventricular hypertrophy
• Myocardial ischemia
• Arrhythmia
• Heart failure
Efferent signals
Afferent signals
Efferent signals
Amplification of systemic sympathetic activity
Renal sodium and water retention
Cardiac and vascular hypertrophy
Increased blood volume
Systemic vasoconstriction
Insulin resistance
Impaired glucose metabolism
RAAS activation
Increased vascular pressure
Renal ischemia
Renal artery occlusion
Reduced renal blood flow
Proteinuria
Increased renin release
Direct renal vasoconstriction
Afferent signals
via renal nerves
Increased BNP resistance
Direct tubular sodium reabsorption and water retention:
• hypervolemia
• wall stiffness

Meta-analysis of Renal Denervation Trials

CENTRAL ILLUSTRATION: Renal Denervation Versus Placebo
Meta-Analysis (N = 1,368)

Endpoint	Heterogeneity (I^2)	Changes in mean difference in blood pressures (mm Hg)	Mean difference [95% CI]	*P* Value
Ambulatory systolic blood pressure	0		-3.61 (-4.89 to -2.33)	<0.0001
Ambulatory diastolic blood pressure	18.6		-1.85 (-2.78 to -0.92)	<0.0001
Office systolic blood pressure	0		-5.86 (-7.77 to -3.94)	<0.0001
Office diastolic blood pressure	0		-3.63 (-4.77 to -2.50)	<0.0001



Ahmad, Y. et al. J Am Coll Cardiol Intv. 2021;14(23):2614–2624.

When to Consider Renal Denervation

2023 ESH Guidelines

Use of renal denervation

Recommendations and statements	CoR	LoE
RDN can be considered as a treatment option in patients with an eGFR >40 ml/min/1.73m^2 who have uncontrolled BP despite the use of antihypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life.	**II**	**B**
RDN can be considered as an additional treatment option in patients with true resistant hypertension if eGFR is >40 ml/min/1.73m^2.	**II**	**B**