Renal Pharmacists Network Education Evening
Vancouver 2025

Resistant Hypertension

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Assistant Professor of Medicine, UBC

Objectives

- Define resistant hypertension and understand its diagnostic criteria.
- Recognize renal-specific contributors to resistant hypertension.
- Apply pharmacologic strategies with renal considerations.
- Identify pharmacist interventions to optimize blood pressure control.
- Highlight the pharmacist’s role in interdisciplinary care.

Canada

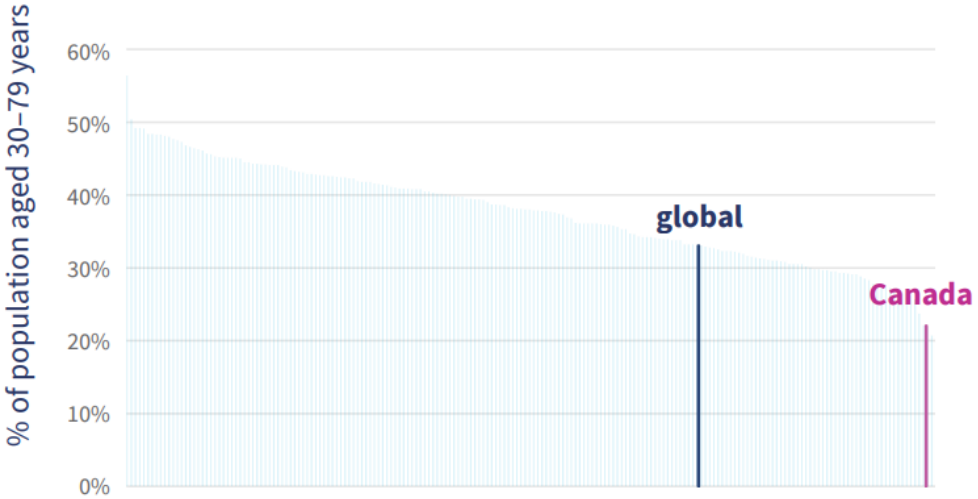
Hypertension profile

Total population (2019): 37 523 000

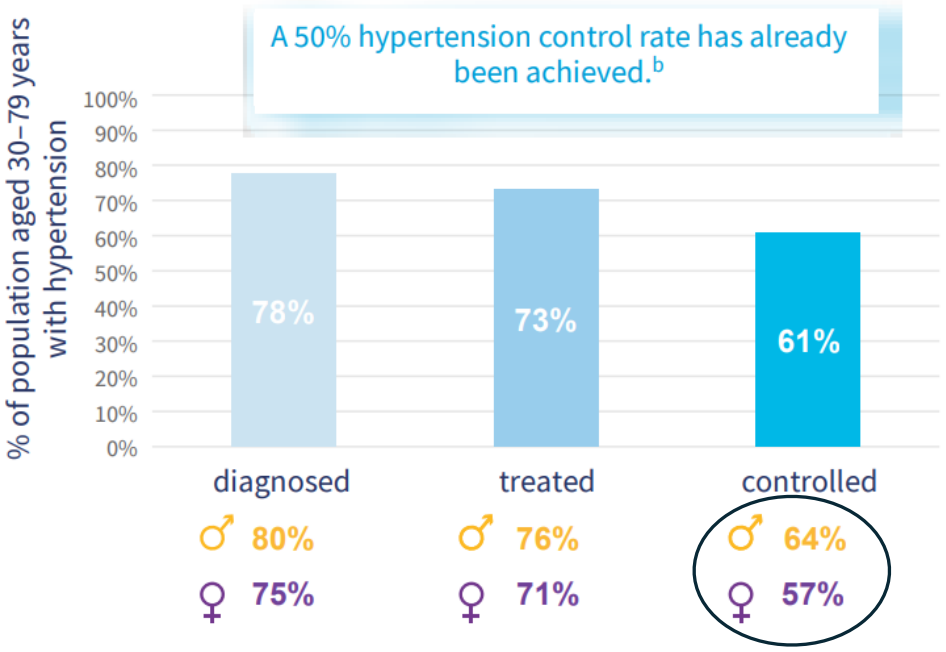
Total deaths (2019): 278 000

Age-standardized prevalence of hypertension among adults aged 30–79 years (2019)[a] ⚥ 22% ♂ 24% ♀ 20%

Prevalence of hypertension – global comparison (both sexes)[a]

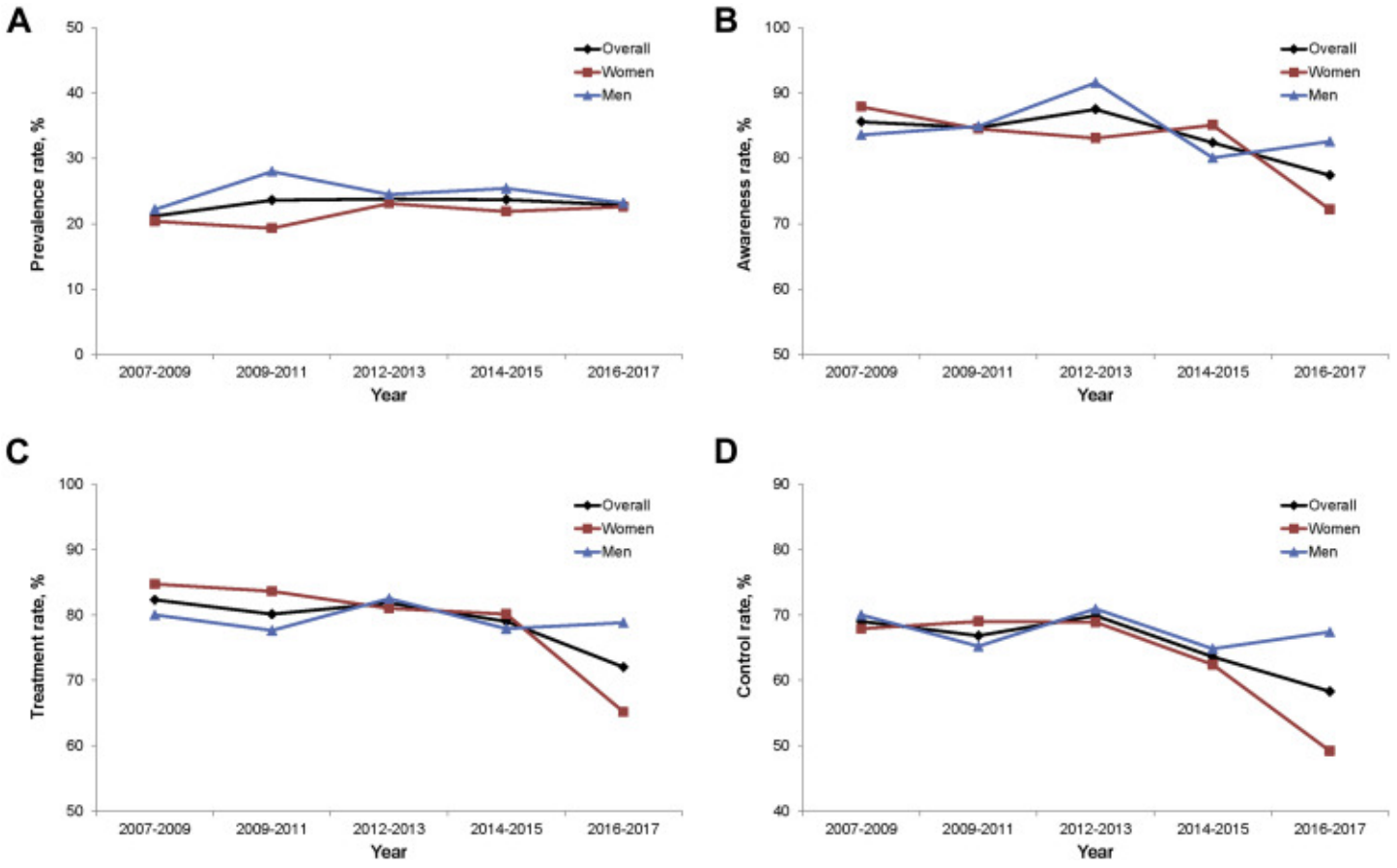


Of the **6.3 million** adults aged 30–79 years with hypertension:



World Health Organization – Hypertension profiles, 2023

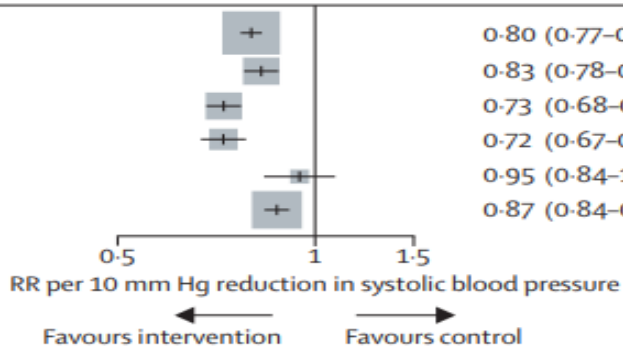
BP treatment and control rates are ***declining*** in Canada



Leung AA et al. Can J Cardiol 2020; 36: 732-739. doi:10.1016/j.cjca.2020.02.092

Better BP = lower mortality

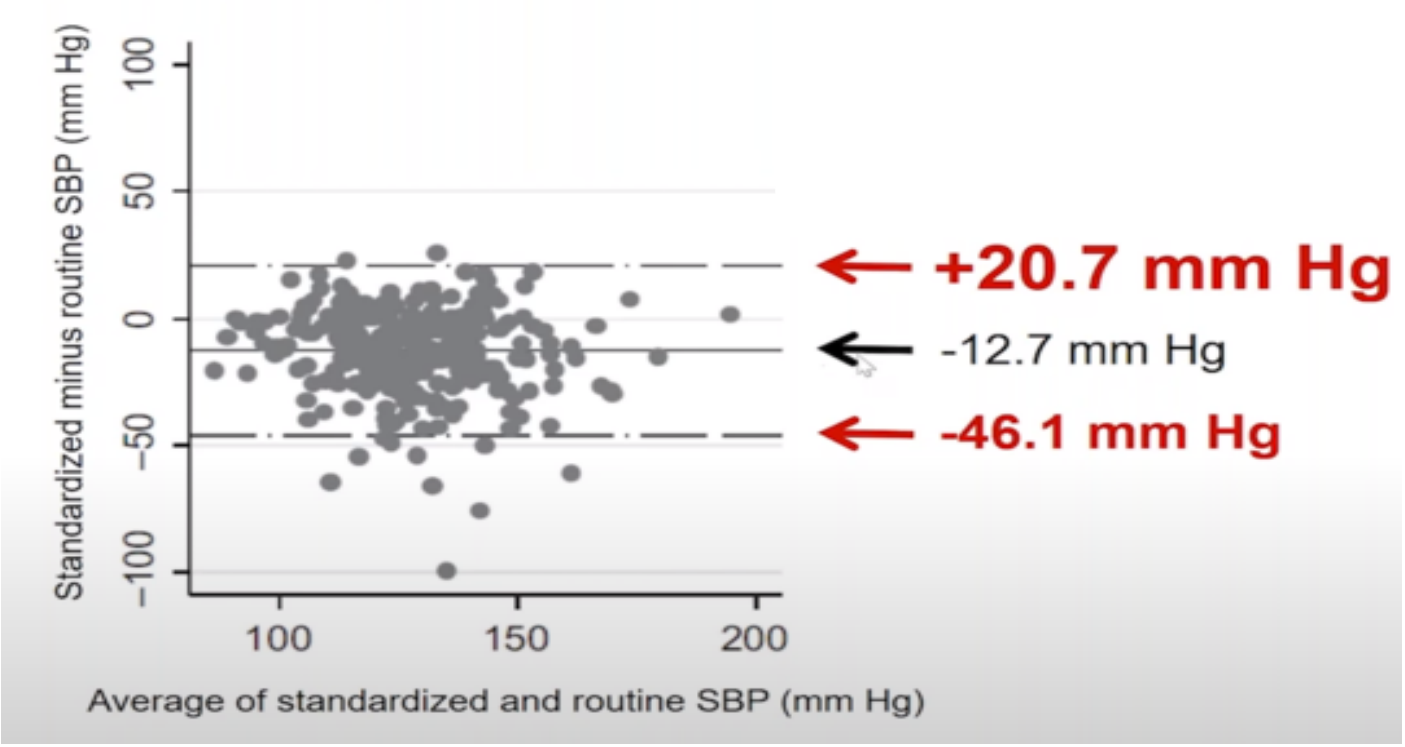
	Studies	Intervention		Control		RR (95% CI) per 10 mm Hg reduction in systolic blood pressure
		Events	Participants	Events	Participants	
Major cardiovascular events	55	13209	137319	14068	128259	0·80 (0·77–0·83)
Coronary heart disease	56	4862	136986	5301	128548	0·83 (0·78–0·88)
Stroke	54	4635	136682	5378	128641	0·73 (0·68–0·77)
Heart failure	43	3284	115411	3760	107440	0·72 (0·67–0·78)
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)



- 20% RRR in MACE
- ~30% RRR in CVA
- ~10% RRR in death

Ettehad et al. Lancet 2016

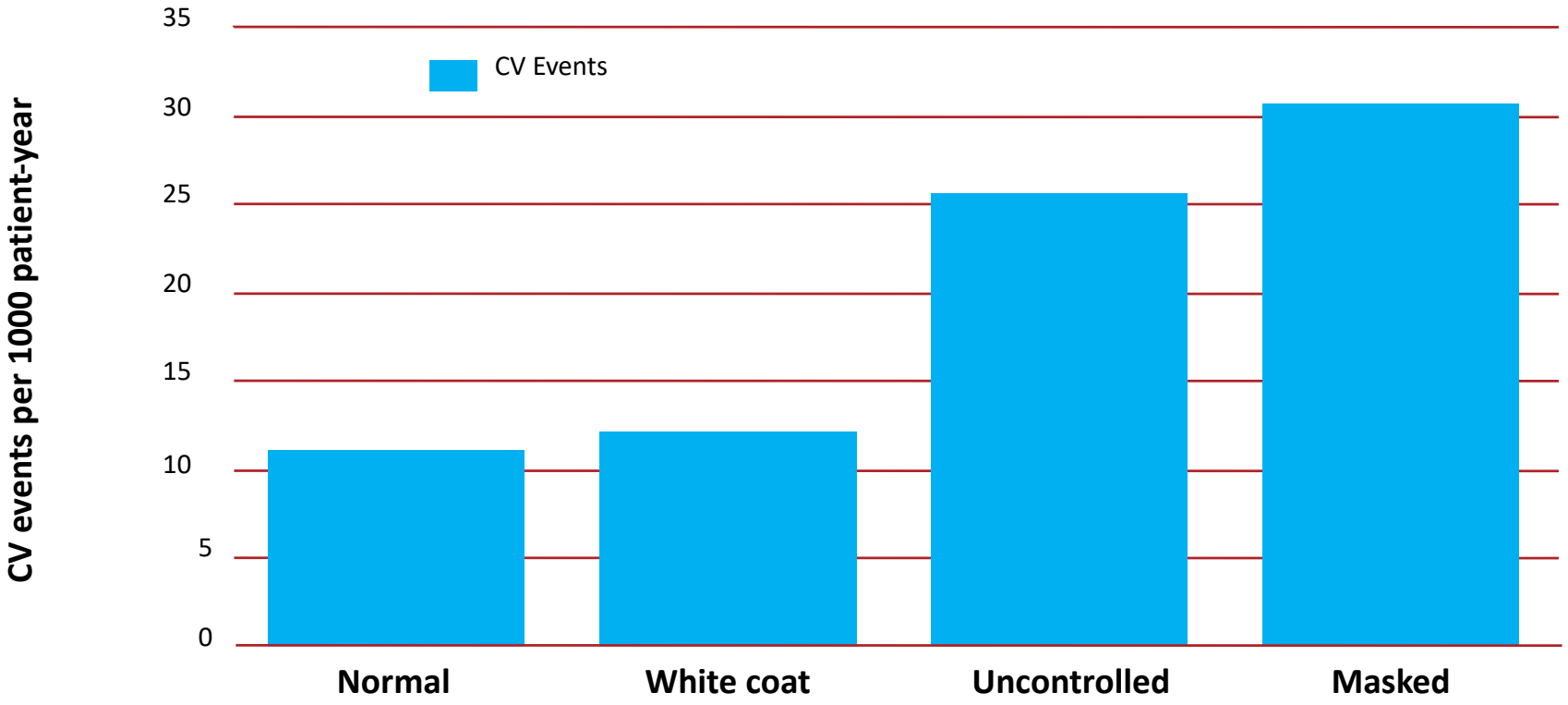
Poor correlation between “casual” and “standardized” office BP



- 275 CKD patients (mean eGFR 29)
- *Standardized* = SPRINT technique
- *Casual* = single reading, attended
- **SBP 12.7 mmHg lower with *standardized***
- **LARGE variation**

Agarwal et al. JAHA 2017

Worse prognosis for ***Masked HTN***



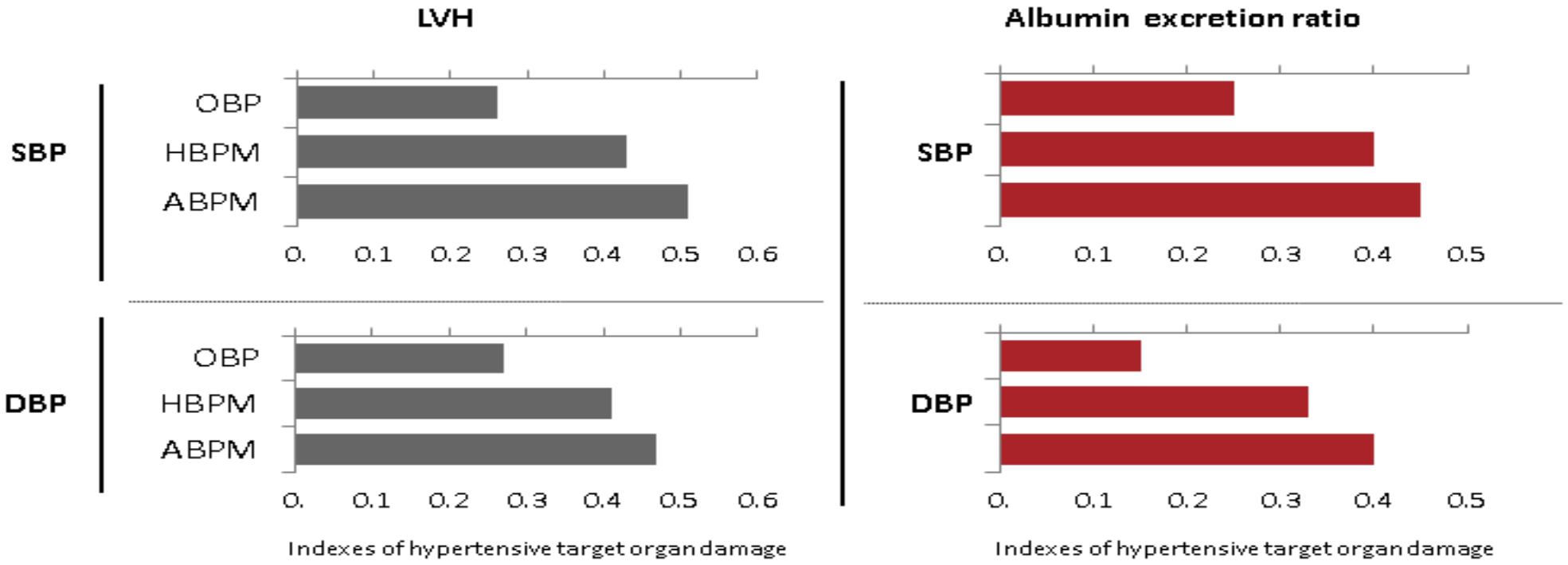
10% - 20% of CKD patients have White Coat HTN

10%-30% have masked HTN

Okhubo T, et al. *J Am Coll Cardiol* 2005;46;508-15

Hypertension Canada 2020 slide deck

Out-of-Office BP Measurements correlate with End Organ Damage



OBP = office BP measurement
HBPM = home BP measurement
ABPM = ambulatory BP measurement
SBP = systolic BP
DBP = diastolic BP

Mulè G, et al. *J Cardiovasc Risk* 2002;9:123-9.
Hypertension Canada 2020 slide deck

Hypertension Canada recommended BP devices

Recommended by
Recommandé par
Hypertension Canada
Gold | Or

Recommended by
Recommandé par
Hypertension Canada
Silver | Argent

https://hypertension.ca/bpdevices

OFFICE

Microlife
Watch BP Office
BP3SK1-3B

HOME

Omron
10 Series Upper Arm
BP7450CAN

LOWER BP TARGET trials

#NephJC

Shahin Mohammed, @shahsonride.bsky.social

	BPROAD	ACCORD	SPRINT	ESPRIT
N=	12821	4733	9261	11255
Age	>50	40-79 with CVD or 55-79 with subclinical CVD	>55	>50
Diabetes	100%	100%	Excluded	38.7%
Chronic Kidney Disease Exclusion Criteria	Excluded if eGFR <30 or creatinine >2 mg/dl	Excluded creatinine >1.5 mg/dl	Excluded if eGFR <20	Excluded eGFR < 45
	Exclude if • Proteinuria > 1 g/day • GN	Exclude if • Proteinuria > 1 g/day • Organ transplant	Exclude if • Proteinuria > 1 g/day • GN likely/needing IS • Organ transplant	Exclude if • Proteinuria ≥ 2+ in last 6 months • GN likely/needing IS • Organ transplant
Country	China	USA, Canada	USA	China
Mean Age	63.8	62.2	67.9	64.6
BP method	Automated (Omron)	Automated (Omron)	Automated (Omron) Mainly unattended	Automated (Omron)

Target SBP ~120 (vs 140) in **DMII** reduced CV events

#NephJC

	BPROAD	ACCORD	SPRINT	ESPRIT
Median follow-up	4.2 years	4.7 years	3.26 years	3.4 years
Mean achieved Systolic BP (SBP)	121.6 vs 133.2	119.3 vs 133.5	121.4 vs 136.2	119.1 vs 134.8
Mean achieved SBP difference	-11.6 at 1 year	-14.2 at 1 year	-14.8 at 1 year	-15.7
Composite CV Outcomes	IR 1.65 vs 2.09 HR 0.79 (0.69-0.90)	1.87 vs 2.89% /year HR 0.88 (0.73- 1.06)	1.65 vs 2.19% /year HR 0.75 (0.64-0.89)	7.4 vs 8.8% HR 0.88 (0.78-0.99)
All Cause Mortality	IR 0.69 vs 0.73 HR 0.95 (0.77-1.17)	1.28 vs 1.19 % /year HR 1.07 (0.85-1.35)	1.03 vs 1.4% /year HR 0.73 (0.60-0.90)	2.8 vs 3.6% HR 0.79 (0.64-0.97)
Stroke	IR 1.19 vs 1.5 HR 0.79 (0.67-0.92)	0.32 vs 0.53% /year HR 0.59 (0.39-0.89)	0.41 vs 0.47% /year HR 0.89 (0.63-1.25)	4.7 vs 5.4% HR 0.86 (0.73-1.02)
Heart Failure	IR 0.13 vs .19 HR 0.66 (0.41-1.04)	0.73 vs 0.78% /year HR 0.94 (0.70-1.26)	0.41 vs 0.67% /year HR 0.62 (0.45-0.84)	1 vs 1.4% HR 0.73 (0.52-1.03)
CV Death	IR 0.24 vs 0.32 HR 0.76 (0.55-1.06)	0.52 vs 0.49% /year HR 1.06 (0.74-1.52)	0.25 vs 0.43% /year HR 0.57 (0.38-0.85)	1.1 vs 1.7% HR 0.61 (0.44-0.84)

Canadian Journal of Cardiology
36(2020)591e592

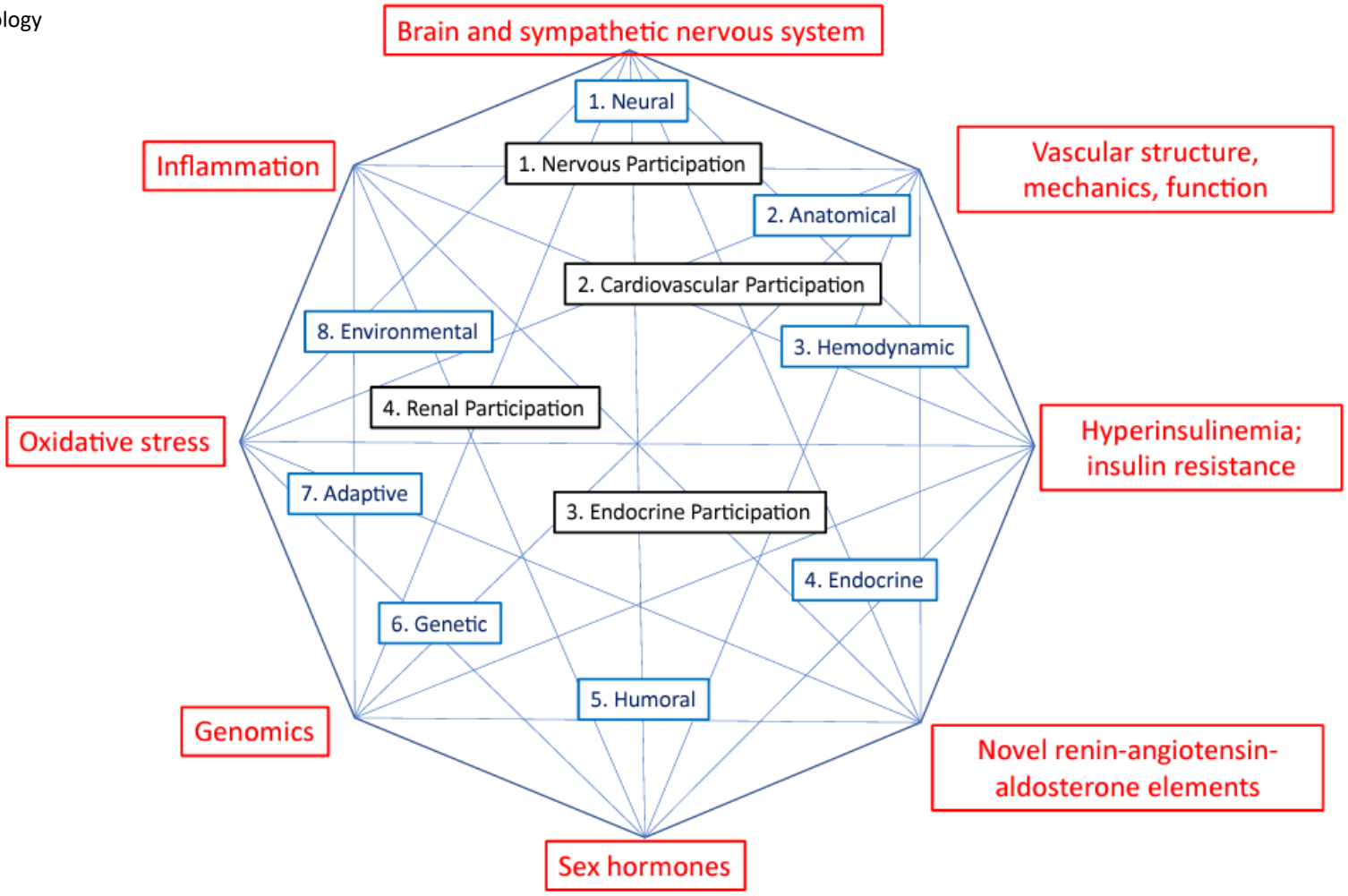
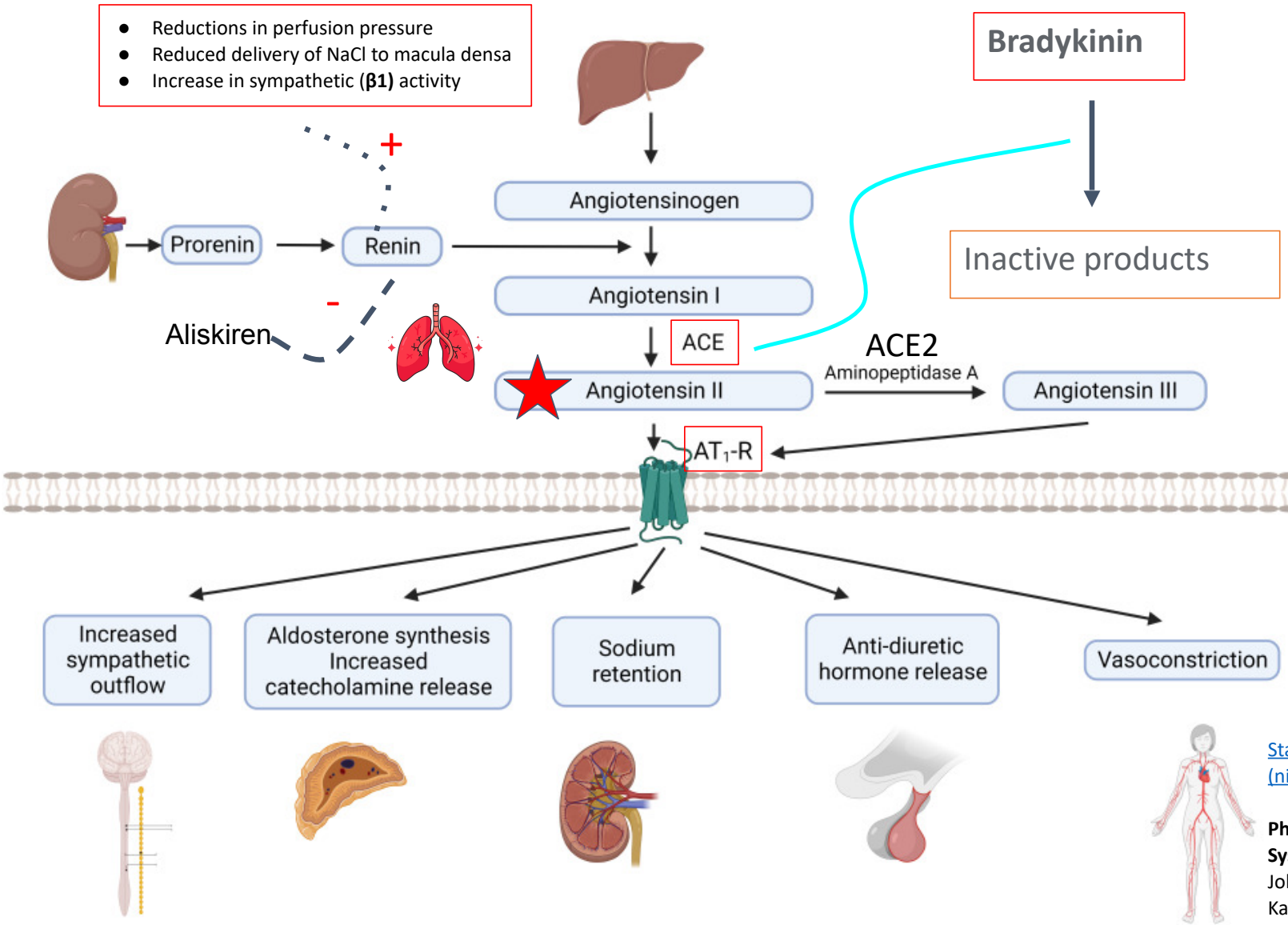


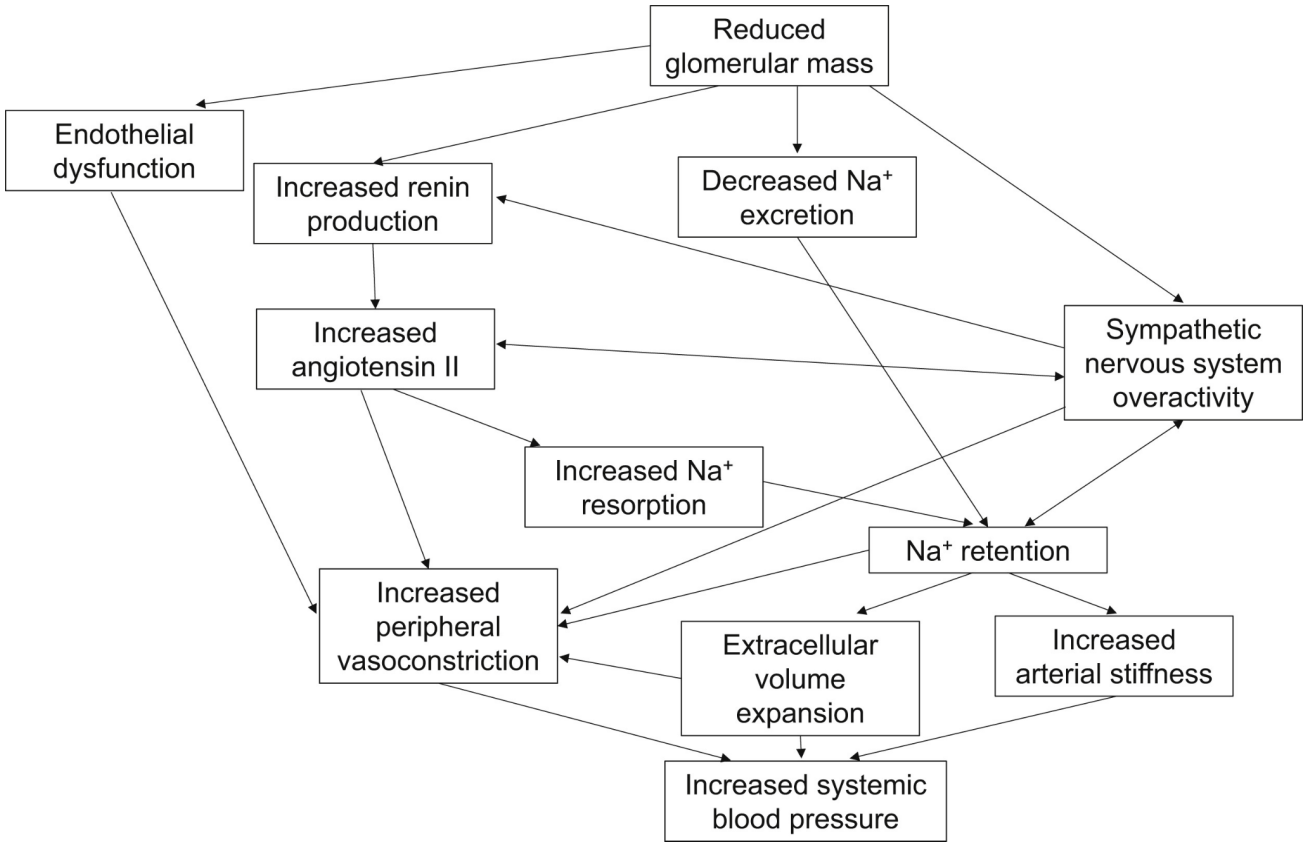
Figure 1. Different aspects of Irving Page's mosaic theory of hypertension revisited in this compendium. The 4 **black** elements are the principal components mentioned in the original 1949 paper.[1] The 8 blue components are enumerated in the subsequent, more extensive revisiting of the theme in 1982.[2] The 8 **red** components are themes dealt with by review papers in the current issue of the *Canadian Journal of Cardiology*.



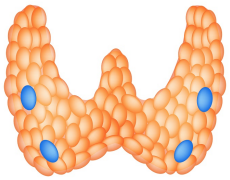
[StatPearls - NCBI Bookshelf (nih.gov)]

Physiology, Renin Angiotensin System
John H. Fountain; Jasleen Kaur; Sarah L. Lappin.

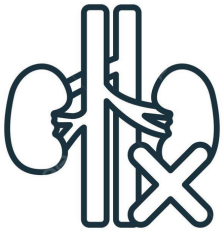
Mechanisms of HTN in CKD



ESA



HyperPTH



Uremia

Hypertension in CKD: Core Curriculum 2019 . AJKD

True Resistant Hypertension Definition

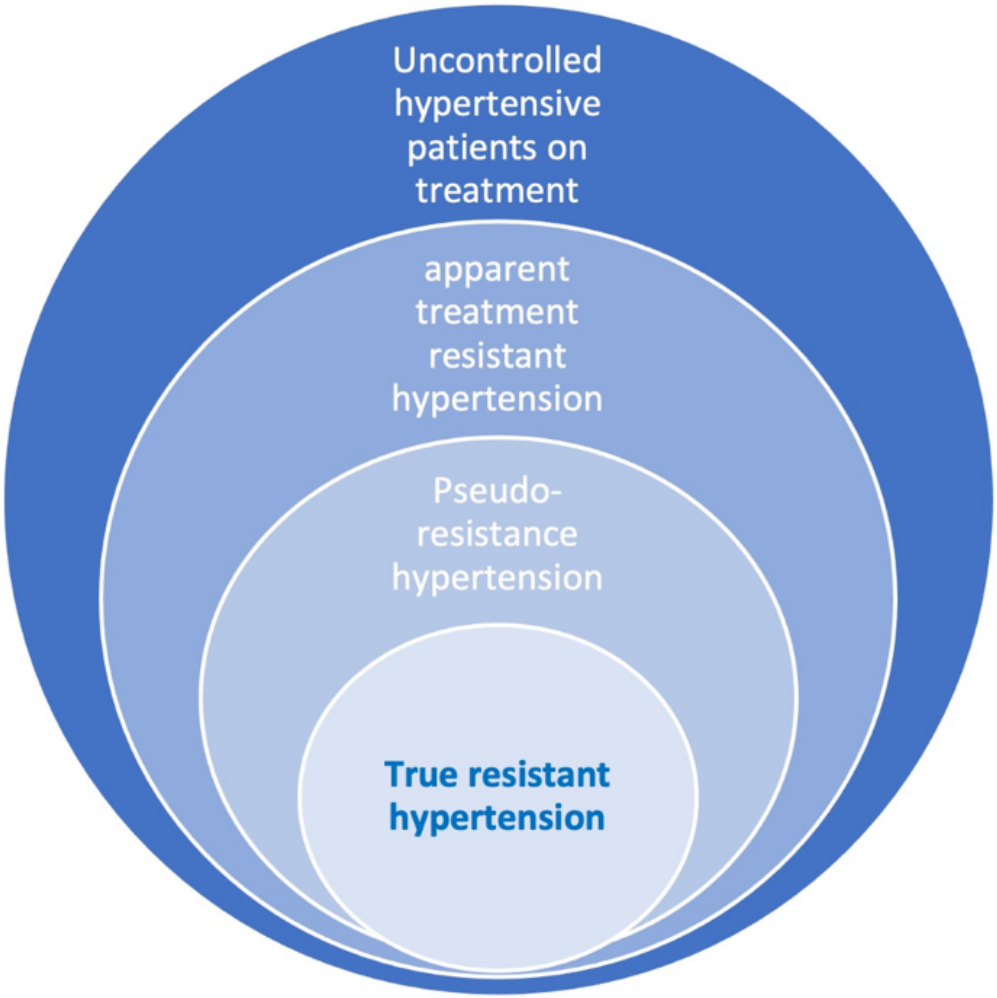
- Inadequately controlled blood pressure despite receiving three or more adequately dosed antihypertensive medications, of which at least one is a diuretic. (Carey R et al. AHA Scientific Statement 2018)

- Exclusion of:
  - Secondary causes –aldosteronism, OSA
  - Improper Measurement
  - White Coat Hypertension
  - Non-adherence -50%
  - Hypertension aggravators (e.g. NSAIDs etc)

Box 2: Medications and substances that can increase blood pressure[13]

- Alcohol
- Nonsteroidal anti-inflammatory drugs
- Oral contraceptives
- Antidepressants (monamine oxidase inhibitors, certain serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors)
- Stimulants (amphetamines and cocaine), sympathomimetics and decongestants
- Corticosteroids and anabolic steroids
- Erythropoetin and analogues
- Natural licorice
- Herbal products (e.g., ma huang [ephedra] and bitter orange)
- Chemotherapeutic agents (e.g., tyrosine kinase inhibitors and vascular endothelial growth factor inhibitors)

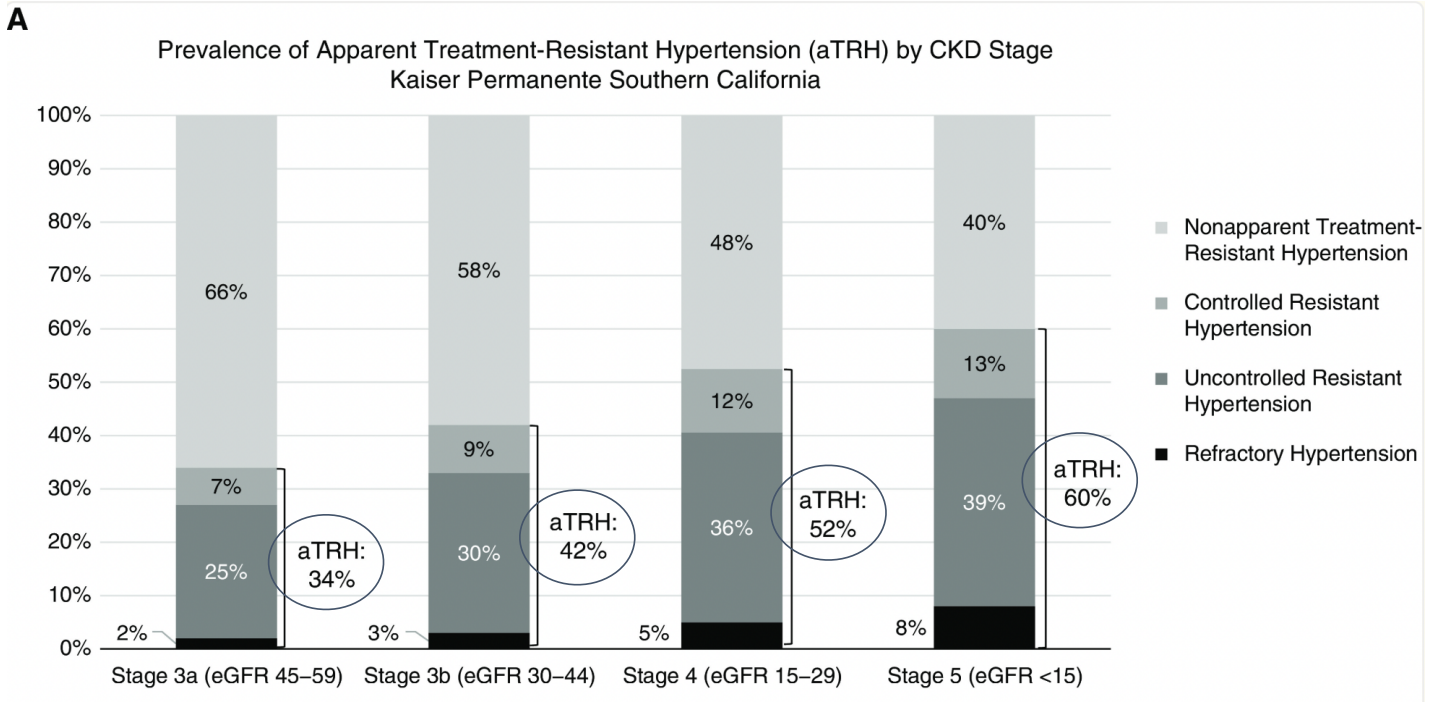
Padwal et al. CMAJ, 2014.



R. Alsharari et al. Journal of Human Hypertension (2022).

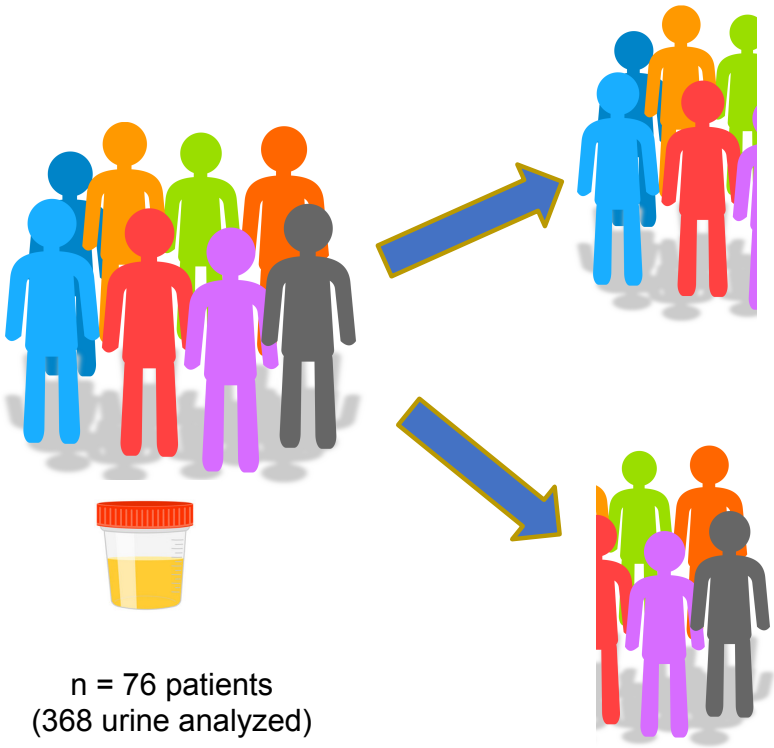
Resistant HTN in CKD

- 60-90% of those with CKD have hypertension
- **Apparent** resistant HTN (aTRH) around 48% - 55%; diuretic use lowered it to 23% - 31%
- Rates of aTRH increase with declining eGFR
- 35%–40% would require 4+ BP meds



Kurella, NJ et al. JASN 2022

Are patients actually taking their medications?



n = 76 patients
(368 urine analyzed)

40 (52.6%)
non-adherent

36 (47.4%)
adherent

12 (**30%**) complete nonadherence

7 (**17.5%**) < 25% adherence

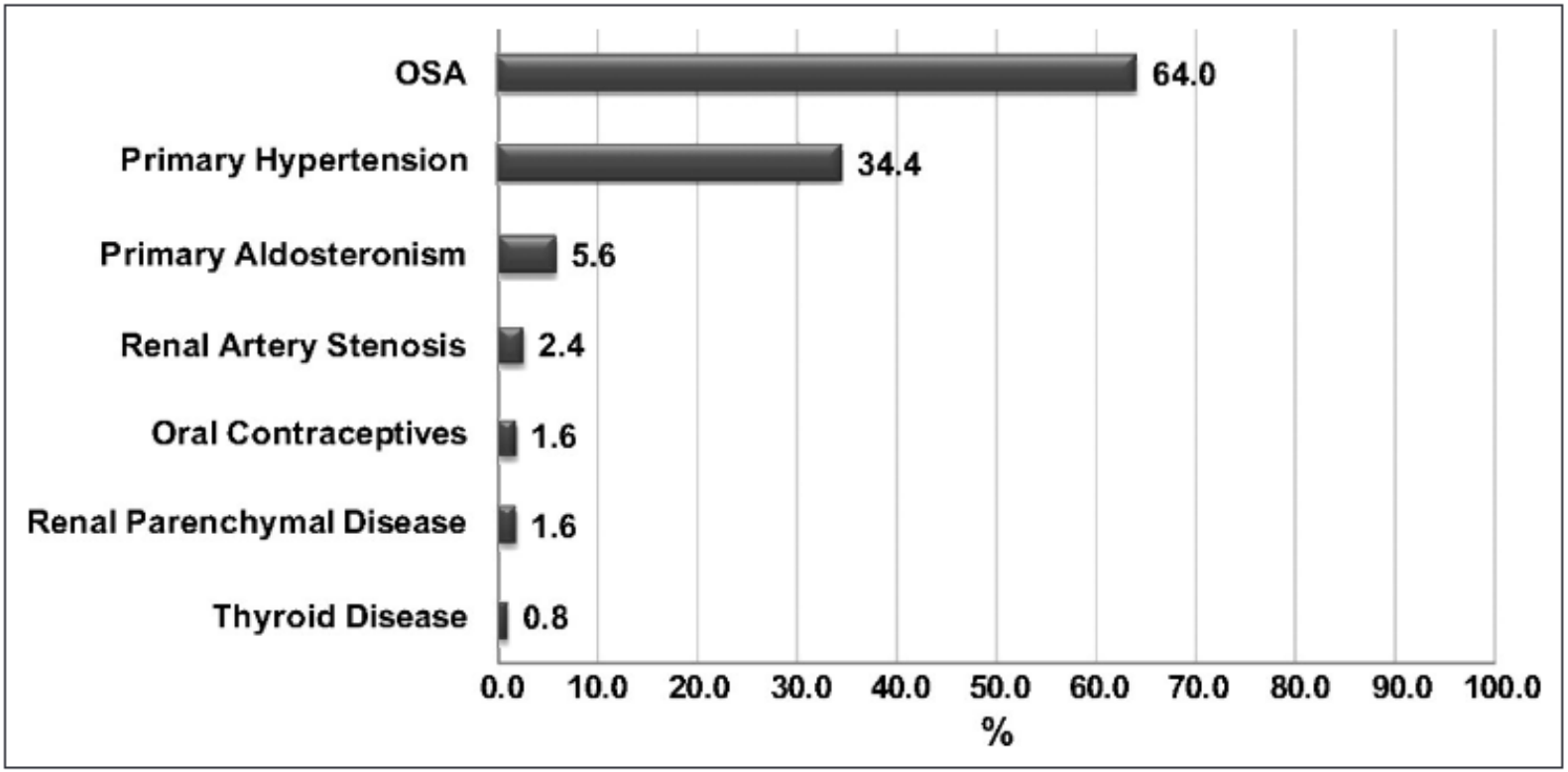
16 (**40%**) 26 - 50% adherence

3 (7.5%) 51 - 75% adherence

2 (5%) >75% adherence

Jung et al. Journal of Hypertension 2013, 31:766–774

OSA most common cause of “true” resistant hypertension



Lorenzi-Filho et al. Hypertension. 2011

Does replacing table salt with a salt substitute (NaCl + KCl) lower cardiovascular events and death? The Salt Substitute and Stroke Study

#NephJC

Study Population

Cluster-randomized trial

600 villages

Rural China

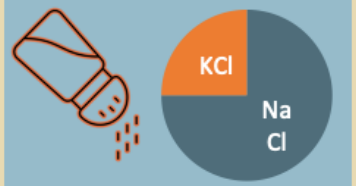
N=20,995

H/o stroke or Age ≥ 60 year with HTN

Intervention

Regular salt

Follow up 5 year



Salt substitute

	Stroke	Major CV Events	Death	Hyperkalemia
	Events per 1000 patient-years			
Regular salt	33.65	56.29	44.61	3.30
	rate ratio			
	0.86 [0.77-0.96] P=0.006	**0.87** [0.8-0.94] P<0.001	**0.88** [0.82-0.95] P<0.001	**1.04** [0.8-1.37] P=0.76
Salt substitute	29.14	49.09	39.28	3.35
	Events per 1000 patient-years			

Among patients with a history of stroke or those older than 60 years with high blood pressure, the rates of stroke, major cardiovascular events and death was lower with a potassium containing salt substitute than with regular salt.

Effect of Salt Substitution on Cardiovascular Events and Death B.Neal, Y.Wu, X.Feng et al. *N Engl J Med 2021;385:1067-1077*

Visual Abstract by @nefron1310

Factors Associated with Therapeutic Inertia

Patient Factors

- **Age**
- Male Sex
- Comorbidity especially psychiatric
- **BP close to target**
- Life expectancy

Physician/Care Provider Factors

- Knowledge gap
- Uncertainty about BP measurement
- Uncertainty about BP Target
- Concerns about safety
- Aversion to ambiguity

System Factors

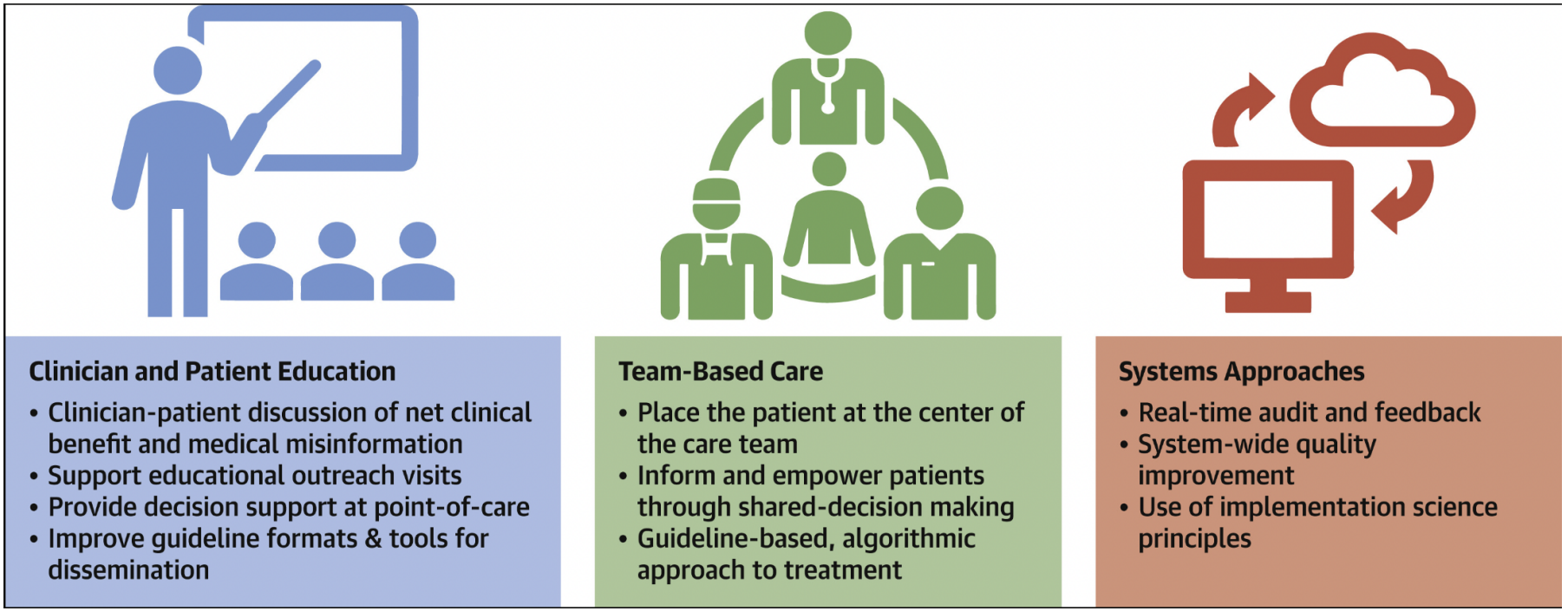
- Time Constraint
- Frequency of follow up
- High patient volumes

Redón J et al. *J Hypertens* 2010;28:1770-7
Howes F et al. *Aust Fam Physician* 2010;39:511-6
Milman T et al. *Medicine (Baltimore)* 2018;97:e11121
Usherwood T et a. Aust Prescr. 2024 Feb;47(1):15-19.

Interventions to Aid in Adherence

- Reminder packaging including with behavioural prompts such as electronic pill monitors, m-health apps.
- Home BP measurement
- Increased education/awareness
- More frequent follow ups (or check ins)
- Lowering economic barriers
- Combination pills
- **Multi disciplinary approach**

Multi-faceted Interventions to Reduce Therapeutic Inertia



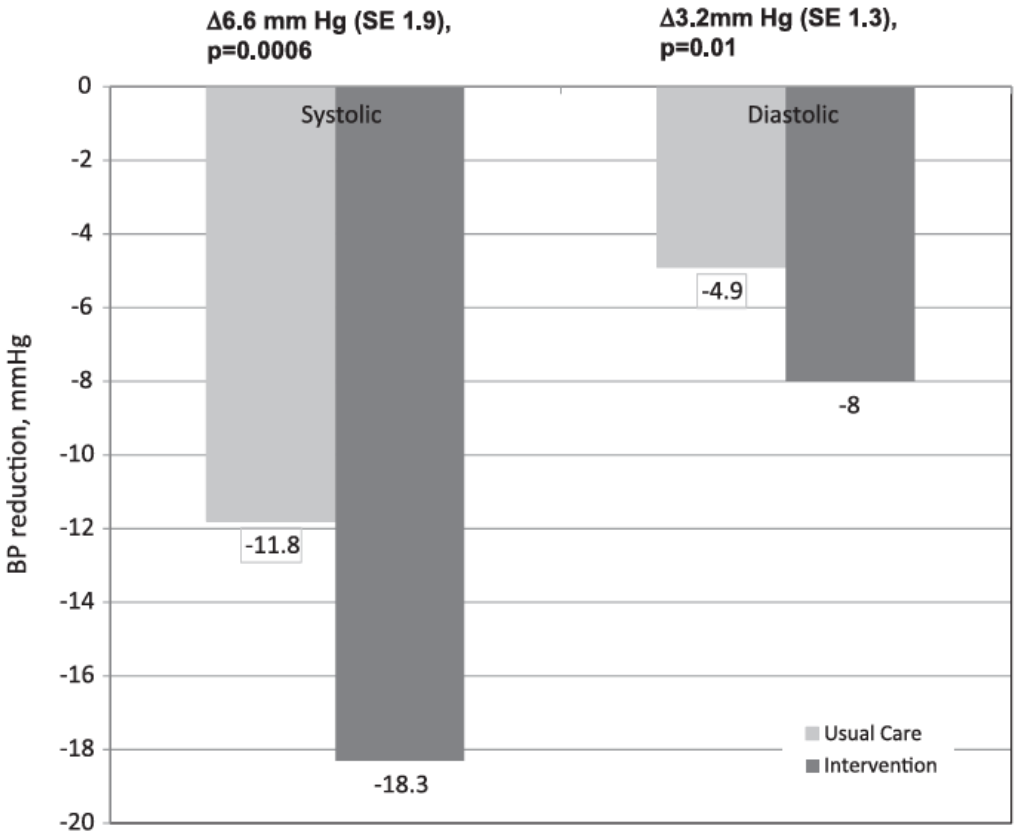
Powell RE, et al. *Diabetes Obes Metab* 2021;23:2137-54. 10.1111/dom.14455
Drakos A et al. Circ Cardiovasc Qual Outcomes 2024: 17(4)

The Alberta Clinical Trial in Optimizing Hypertension (RxACTION)

- RCT 340 patients with diagnosed hypertension
- Specially trained pharmacists who were able to independently prescribe antihypertensive therapy using the Hypertension Canada guidelines, in addition to counseling and reviewing medications compared vs. usual care.
- Patients continued to access their primary care physician and notified of any medication changes
- Pharmacists were responsible for follow-up and monitoring lab values

Tsuyuki RT, Houle SK, Charrois TL, et al. Randomized Trial of the Effect of Pharmacist Prescribing on Improving Blood Pressure in the Community: The Alberta Clinical Trial in Optimizing Hypertension (RxACTION). Circulation. 2015;132(2):93-100.

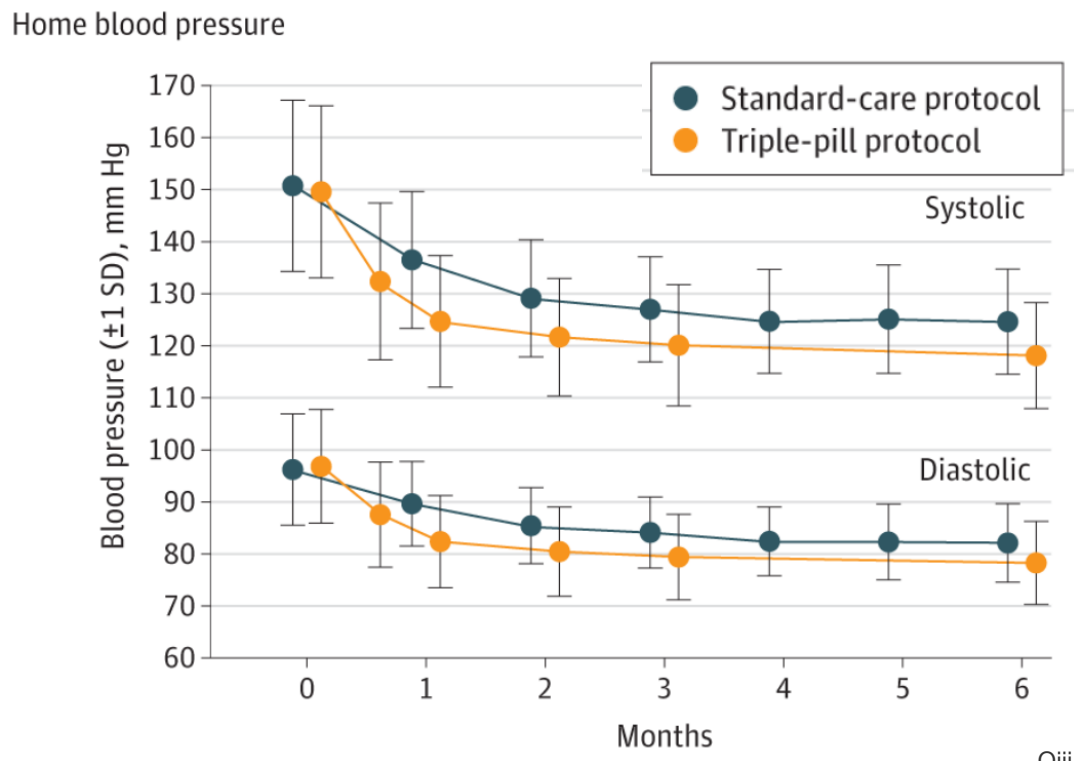
The Alberta Clinical Trial in Optimizing Hypertension (RxACTION)



At 6 months, pharmacist intervention reduced BP **6.5/3.1 mmHg** vs. usual care with similar mean number medications prescribed in both groups

Tsuyuki RT, Houle SK, Charrois TL, et al. Randomized Trial of the Effect of Pharmacist Prescribing on Improving Blood Pressure in the Community: The Alberta Clinical Trial in Optimizing Hypertension (RxACTION). Circulation. 2015;132(2):93-100.

Low-Dose Triple-Pill vs Standard-Care Protocols for HTN in Nigeria - A Randomized Clinical Trial

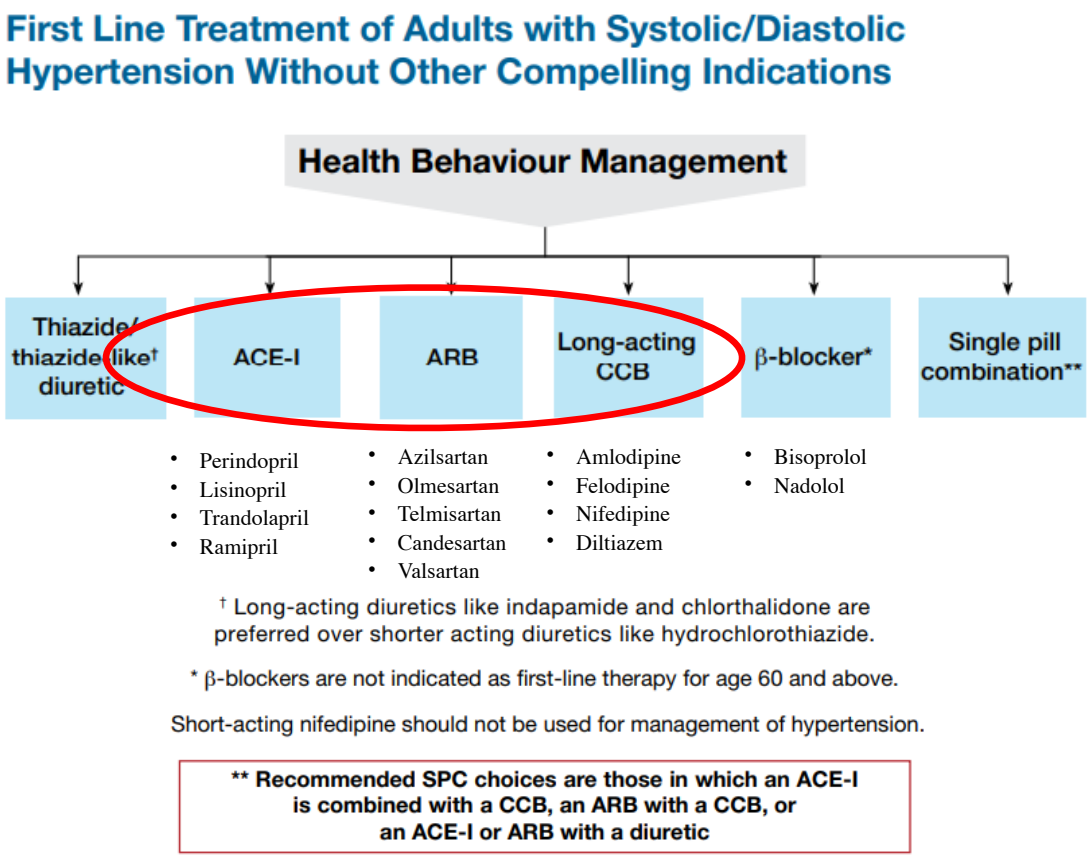


N=300 with uncontrolled HTN
Amlodipine +Telmisartan + Indapamide vs.
Amlodipine + standard titration
Primary Outcome: 6 month change in home BP

- **Reduction in home SBP by 5.8 mmHg in triple pill group**
- No increase in discontinuation due to adverse events
- At month 6, 62% in triple pill group had home BP < 130/80 mm Hg (vs 28% in standard)

Ojji DB, Salam A, Sani MU, et al. Low-Dose Triple-Pill vs Standard-Care Protocols for Hypertension Treatment in Nigeria: A Randomized Clinical Trial. *JAMA.* 2024.

Which medication(s) to use?



- **Use long-acting agents**
- **Use combination pills (*ADVANCE, HOPE-3, ACCOMPLISH*)**
- **Low doses of multiple drugs may be more effective**
- **ACEI + ARBs should not be used**
- **Consider white coat hypertension and non-adherence**
- **Repeat renal panel after initiation/changing ACEI, ARB and/or diuretics.**
- **Consider referral to a hypertension specialist if BP not controlled with 3 anti-HTN medications.**

Hypertension Canada website

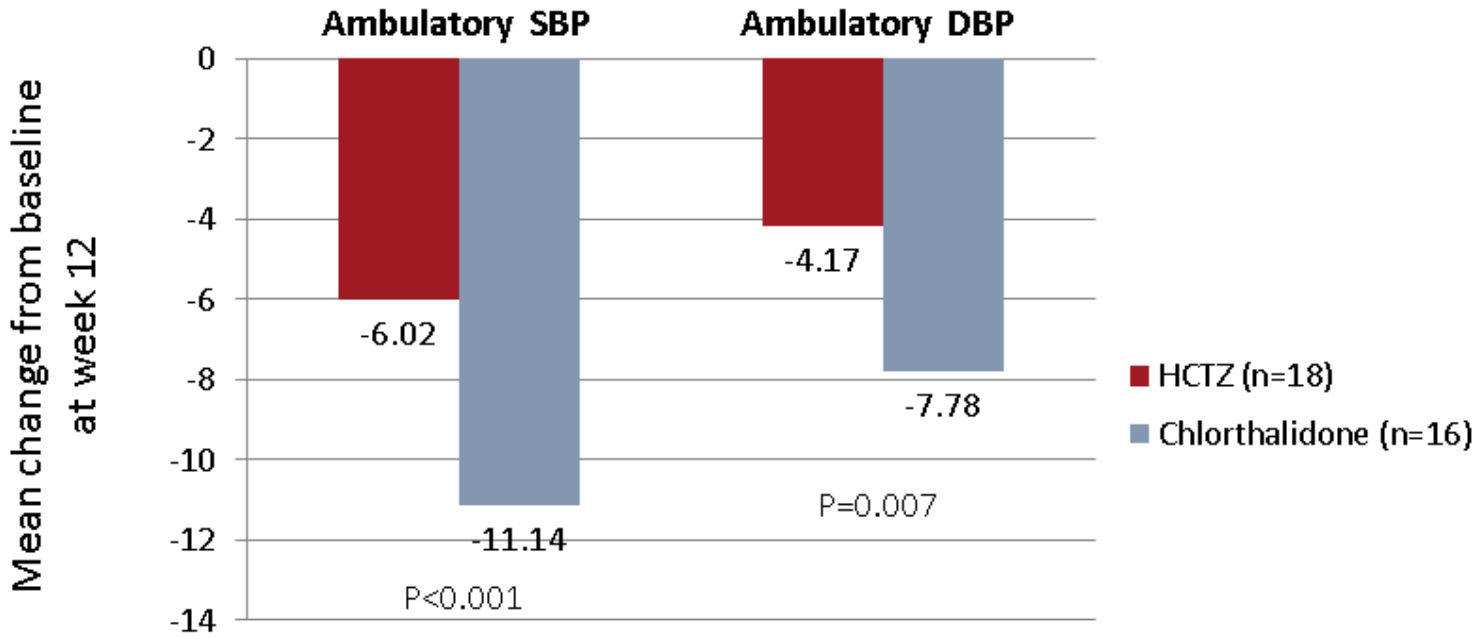
Foundational Therapies in CKD

- **ACE Inhibitors**
  - Shallow dose response curve: therefore lower doses likely need BID dosing
  - Most ACEIs are cleared renally, except for Trandolapril that is metabolized/cleared hepatically and renally so theoretically less hyperkalemia
  - Ramipril highest affinity to ACE
  - Perindopril longest acting

- **ARB**
  - side effect profile similar to placebo
  - most are dually metabolized/cleared hepatically and renally
  - lowest AT1 receptor binding affinity ARB is losartan
  - longest acting telmisartan, azilsartan

- **2nd line agent in CKD - up for discussion!**

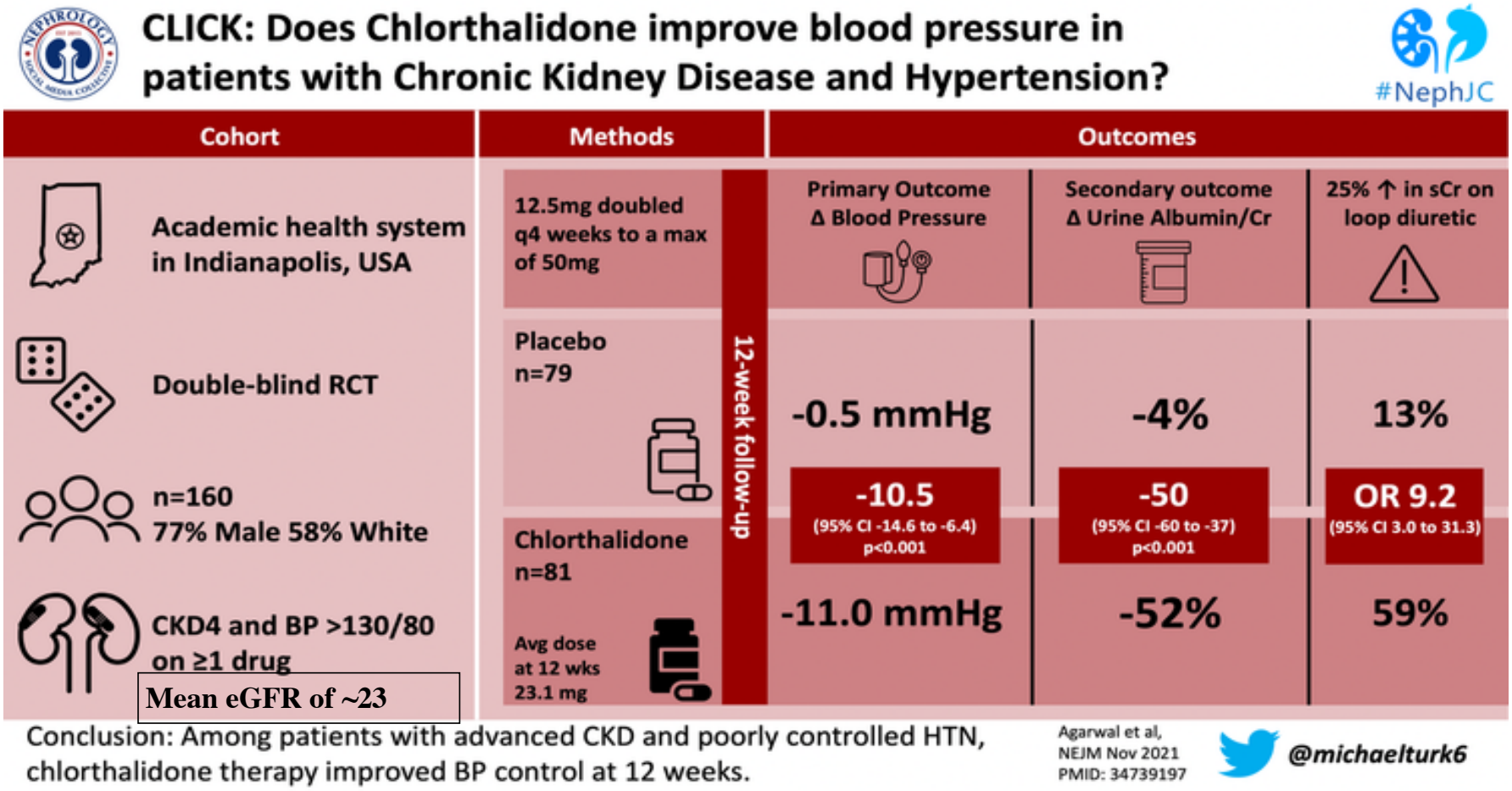
Chlorthalidone >>> HCTZ



- Half-life of HCTZ – 6 to 9 hours (duration 12 hours)
- Half-life of Chlorthalidone – **40 hours** (duration 24 - 48 hours)

Pareek AK, et al. *J Am Coll Cardiol* 2016;67(4):379-89
Carter et al. *Hypertension*. 2004

Chlorthalidone very effective in advanced CKD

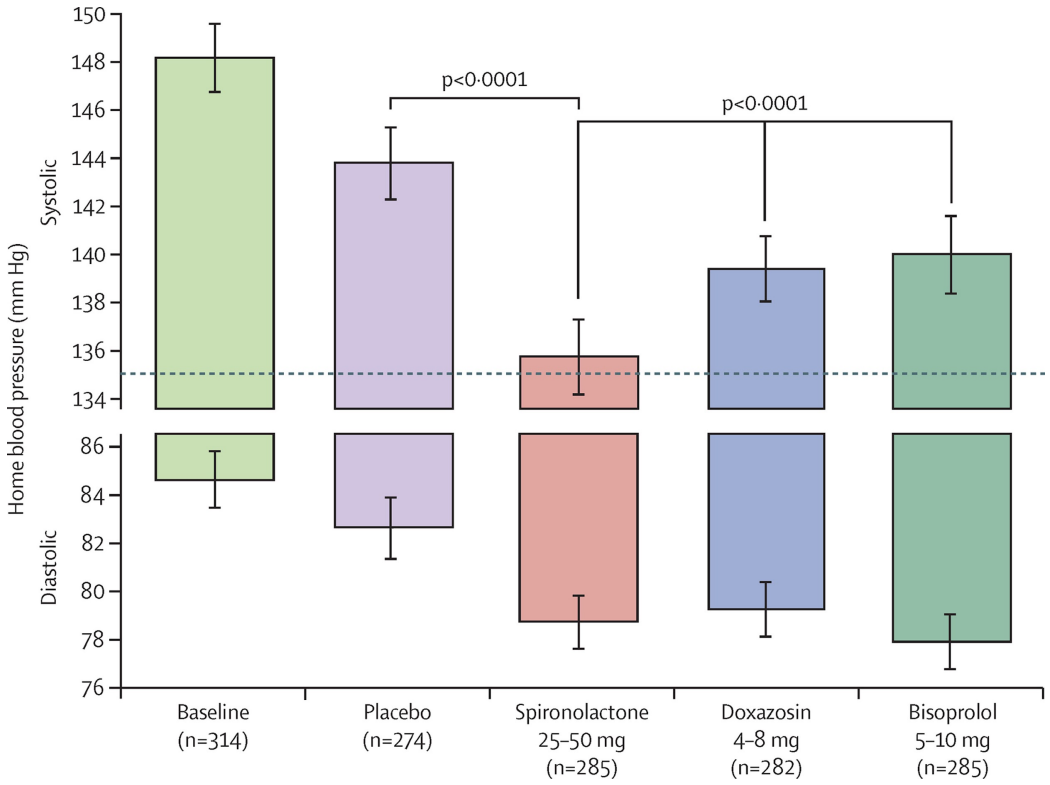


Conclusion: Among patients with advanced CKD and poorly controlled HTN, chlorthalidone therapy improved BP control at 12 weeks.

Agarwal et al,
NEJM Nov 2021
PMID: 34739197

@michaelturk6

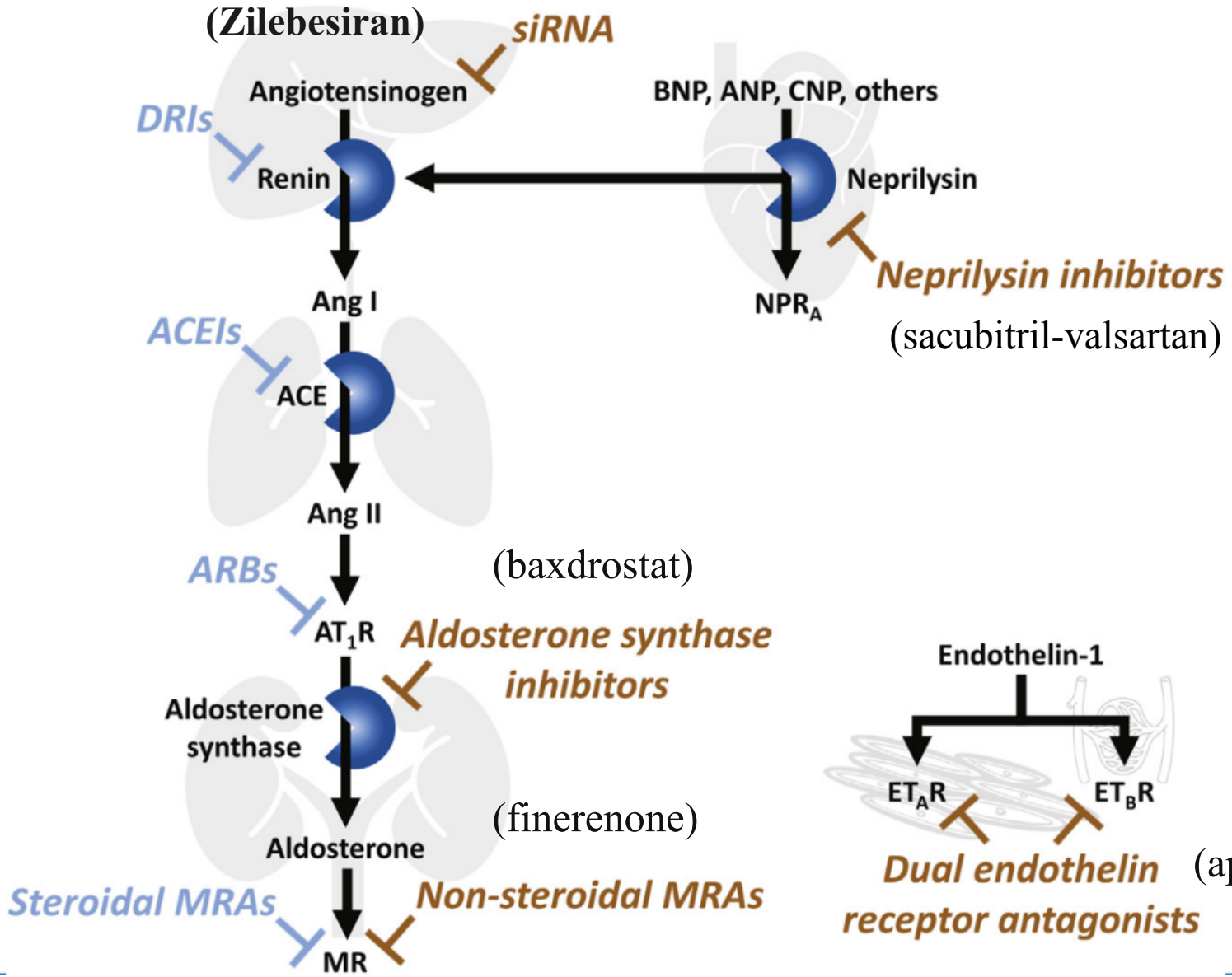
4th line agents (PATHWAY-2)



Spironolactone **<u>better</u>** than Doxazosin and Bisoprolol for resistant HTN

<u>Exclusion</u>: patients with eGFR <45 ml/min or abnormal *K+*

Williams et al. Lancet. 2015



Cohen and Bress. AJKD, 2023

Effect of **Dapagliflozin on SBP** in Patients With CKD, with or without T2D

Changes in SBP with DAPA versus PBO

	Overall (N=4304)	T2D (n=2906)	No T2D (n=1398)
SBP difference between DAPA and PBO (95% CI), mmHg			
Week 2	-3.6[a] (-4.4, -2.8)	-4.2 (-5.1, -3.2)	-2.5 (-3.9, -1.1)
Over the trial duration	**-2.9** (-3.6, -2.3)	**-3.2** (-4.0, -2.5)	**-2.3** (-3.4, -1.2)
Percent of primary outcome benefit with DAPA explained by SBP reduction at Week 2 (95% CI)	7.6% (1.8, 20.9)	8.6% (1.3, 33.0)	3.6% (-9.9, 31.7)

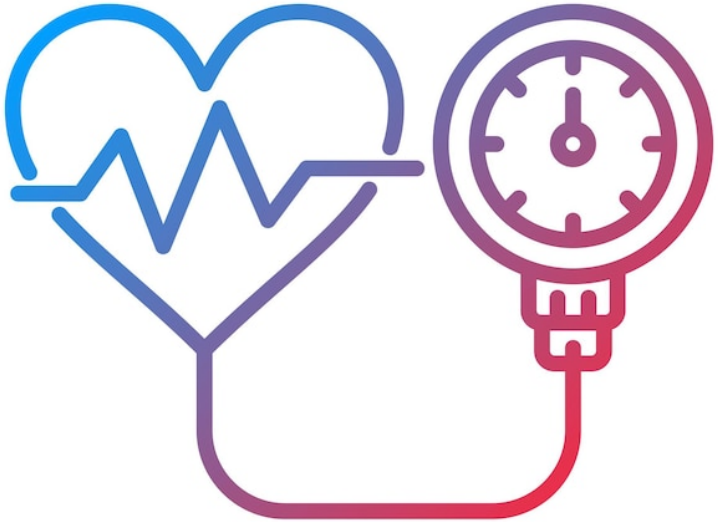
SBP reduction with DAPA did not explain the primary outcome benefit

[a]p<0.001

CKD = chronic kidney disease; DAPA = dapagliflozin; PBO = placebo; SBP = systolic blood pressure; T2D = type 2 diabetes.

Provenzano M et al. Poster presented at: Virtual WCN; February 24-27, 2022; Kuala Lumpur, Malaysia. *Kidney Int Rep.* 2022;7(2)(suppl):S112. Abs POS-255.

Empagliflozin for Patients With Presumed Resistant Hypertension: A Post Hoc Analysis of the EMPA-REG OUTCOME Trial



Resistant HTN

−4.5 (−5.9 to −3.1) mmHg SBP

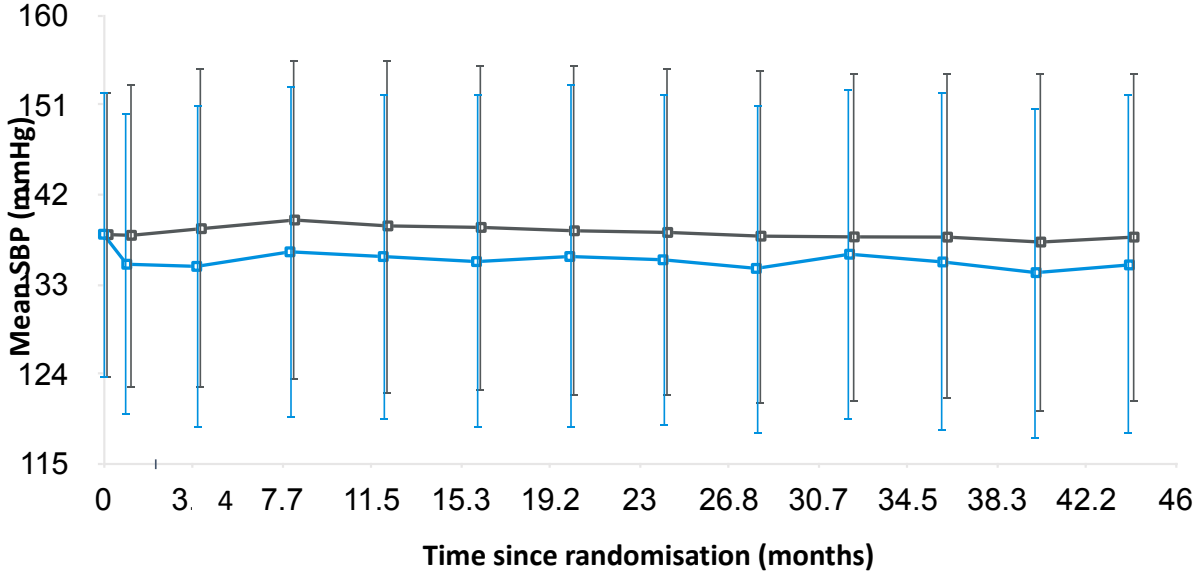
Non resistant HTN

−3.7 (−4.5 to −2.9) mmHg SBP

*at 12 weeks and sustained at 3-year f/u

Ferreira et al. American Journal of Hypertension 33(12) December 2020

Finerenone resulted in a modest and consistent reduction in **office SBP** (overall LS-mean difference of –2.71)



Mean SBP at baseline (mmHg):

Placebo: 137.98±14.42

Finerenone: 138.02±14.31

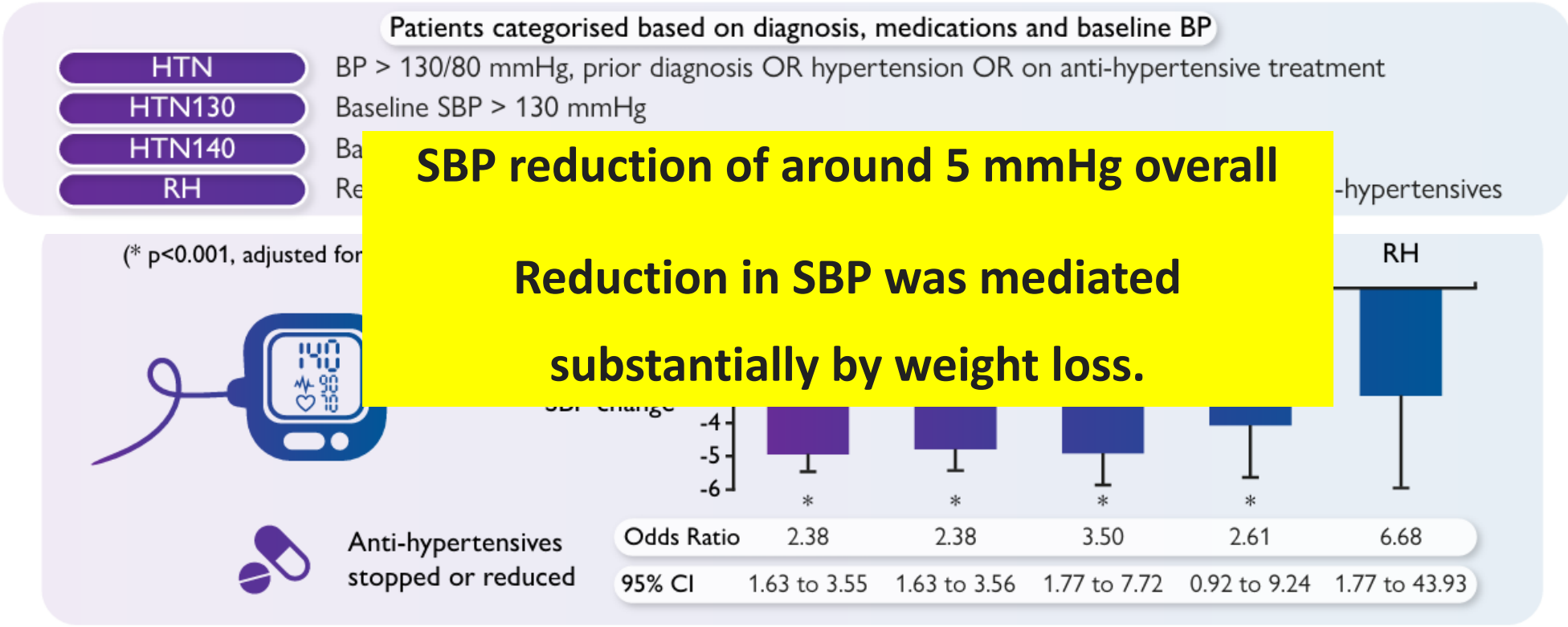
Overall LS-mean difference:
–2.71 (95% CI –3.29 to –2.12)

Number of patients						
Finerenone		2745	2628	1907	903	348
Placebo		2754	2640	1895	884	353
LS-mean change in SBP from baseline (mmHg)						
Finerenone	Ref	–3.20	–2.07	–1.61	–1.82	–2.01
Placebo	Ref	0.67	0.85	0.62	0.37	0.13

CI, confidence interval; LS, least-squares

Ruilope L. Hypertension. 2022;79:2685–2695. DOI: 10.1161/HYPERTENSIONAHA.122.19744

Semaglutide and blood pressure: an individual patient data meta-analysis



SBP reduction of around 5 mmHg overall

Reduction in SBP was mediated substantially by weight loss.

Kennedy et al. Eur Heart J. 2024 Oct 7;45(38):4124-4134

Is aprocitentan, a dual endothelin antagonist, effective in lowering blood pressure in resistant hypertension?

#NephJC

Multicenter – N. America, Europe, Asia, Australia

Systolic BP ≥ 140/90 on 3 antihypertensives (including diuretic)

Primary end point: Least square mean change in office SBP from baseline to week 4 and from withdrawal to week 40

730 patients

Part 1: 4 weeks Double blind

704

Part 2: 32 weeks

613

Part 3: 12 weeks withdrawal

577 patients

Placebo

Aprocitentan 12.5mg OD

–3·8 mm Hg (–6·8 to –0·8, p

Aprocitentan 25mg OD

–3·7 mm Hg (–6·7 to –0·8; p

4.36 mm Hg

–1.47 mm Hg

withdrawal

ocitentan: p<0·0001)

18%

HIGH risk population (DMII, CV, CKD), not on SGLT2i

Modest improvement in BP of -3.7 to -5.9 mmHg over a 4 week period (PATHWAY-2 was -8.7mmHg)

Fluid retention common side effect

Conclusion: The study showed that aprocitentan was effective in lowering blood pressure at week 4 with a sustained effect at week 40 in resistant hypertension

VA created by Sandhya Suresh @sandyrvsdav

Schlaich, et al. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. Lancet 2022 Nov 4:S0140-6736(22)02034-7

Is The Aldosterone Synthase Inhibitor- Baxdrostat Effective in Treatment-Resistant Hypertension?

NEPH MADNESS 2025

Multicenter, double blind RCT

BP>130/80 on at least 3 antihypertensives
N = 248

Baxdrostat
(0.5, 1 or 2 mg)
Once daily

VS

Placebo

eGFR > 45 mL/minute

At 12 weeks	Placebo LSM±SE (In mm Hg)	Baxdrostat 0.5 mg	Baxdrostat 1 mg	Baxdrostat 2 mg
Primary endpoint Change in SBP	-9.4	−12.1±1.9	−17.5±2.0 *P=0.003*	−20.3±2.1 *P<0.001*
Secondary endpoint Change in DBP	−9.5±1.89	−12.1±1.92	−17.5±1.97 *p=0.0034*	−18.4±2.01 *p=0.0012*

No deaths, serious adverse events were attributed to baxdrostat
No instances of adrenocortical insufficiency

SBP systolic blood pressure, DBP diastolic BP

Conclusion: Patients with treatment-resistant hypertension who received baxdrostat had dose-related reductions in blood pressure.

Reference: Freeman et al, Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension, NEJM, 2023

VA by @krithicism

KARDIA-1: How does RNA interference targeting angiotensinogen with zilebesiran impact blood pressure control in patients with mild to moderate hypertension?

NEPH MADNESS 2025

Phase 2, randomized, double-blind, dose-ranging study

394 adults with mild-to-moderate hypertension after antihypertensive washout

Daytime mean ambulatory systolic BP of 135-160 mmHg

25% Black, 44% women, mean age 57 years

Zilebesiran

Investigational RNA interference therapeutic, targeting hepatic angiotensinogen synthesis.

Subcutaneous injections, every 6 months

	Zilebesiran 150 mg	Zilebesiran 300 mg	Zilebesiran 600 mg	Placebo
Change in 24h Mean SBP at 3 Months (mmHg)	-7.3 (-10.3 to -4.4)	-10.0 (-12.0 to -7.9)	-8.9 (-11.9 to -6.0)	6.8 (3.6 to 9.9)
LSM Difference vs Placebo (mmHg)	-14.1 (-19.2 to -9.0)	-16.7 (-21.2 to -12.3)	-15.7 (-20.8 to -10.6)	
Adverse events (%)	60.9%			50.7%
Serious adverse events (%)	3.6%			6.7%

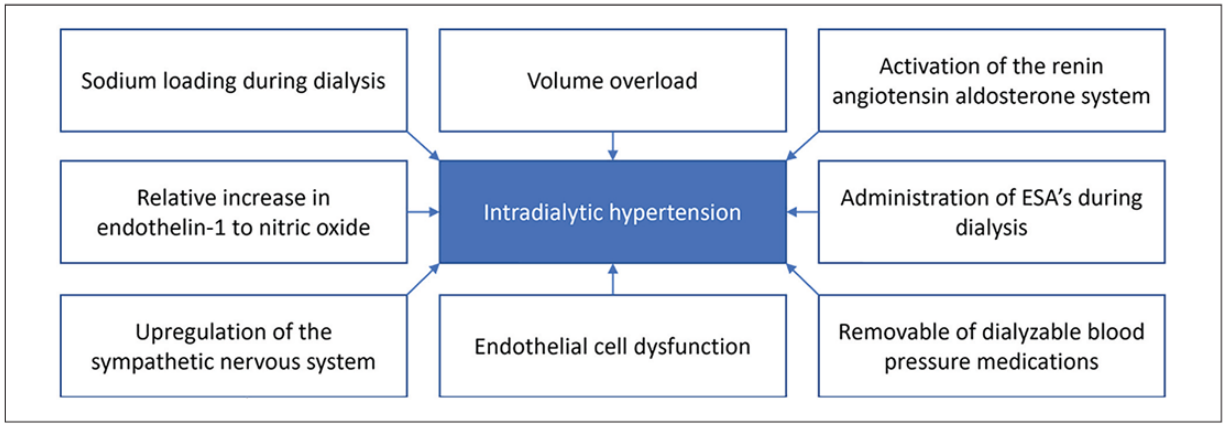
LMS- least-squares mean

Conclusion: In adults with mild to moderate hypertension, treatment with zilebesiran across a range of doses at 3-month or 6-month intervals significantly reduced 24-hour mean ambulatory SBP at month 3.

Reference: Bakris GL, et al. *RNA Interference With Zilebesiran for Mild to Moderate Hypertension: The KARDIA-1 Randomized Clinical Trial*. JAMA. 2024

VA by @nephroseeker.medsky.social

HTN in ESRD

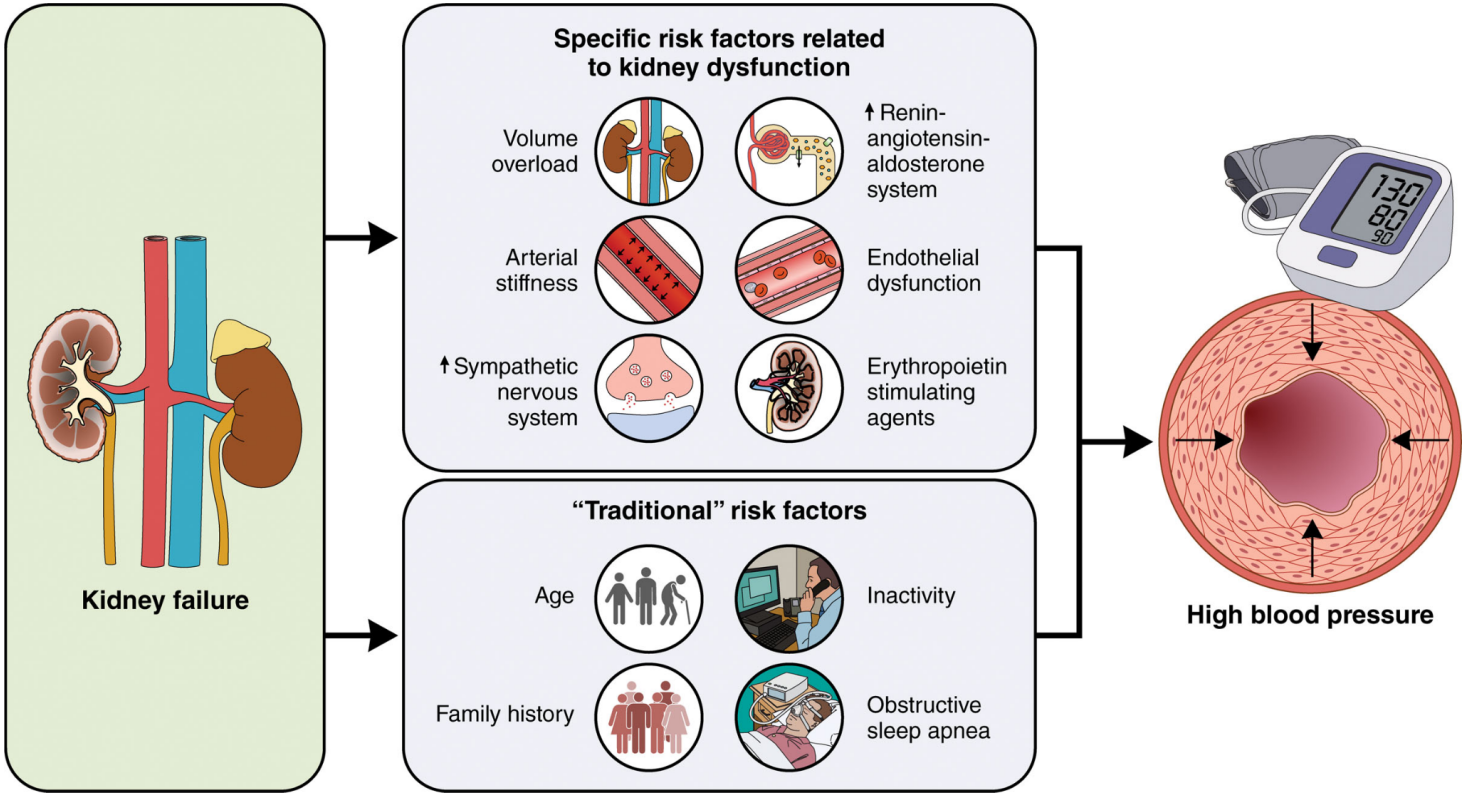


	HEMODIALYSIS	PERITONEAL DIALYSIS
Ambulatory blood pressure (BP) monitoring	≥130/80 (44 hours) during midweek dialysis-free interval	≥130/80 (24 hours)
Home BP	≥135/85 (a.m. and p.m. readings over 6 consecutive nondialysis days)	≥135/85 (a.m. and p.m. readings over 7 consecutive days)
Office BP	>140/90 (average of 3 appropriately measured readings on a midweek dialysis-free day)	>140/90

The National Kidney Foundation guidelines recommend aiming for pre-HD BP less than 140/90 mm Hg and post-HD BP less than 130/80 mm Hg.

Prasad et al. CJKD

Pathophysiology of HTN in HD



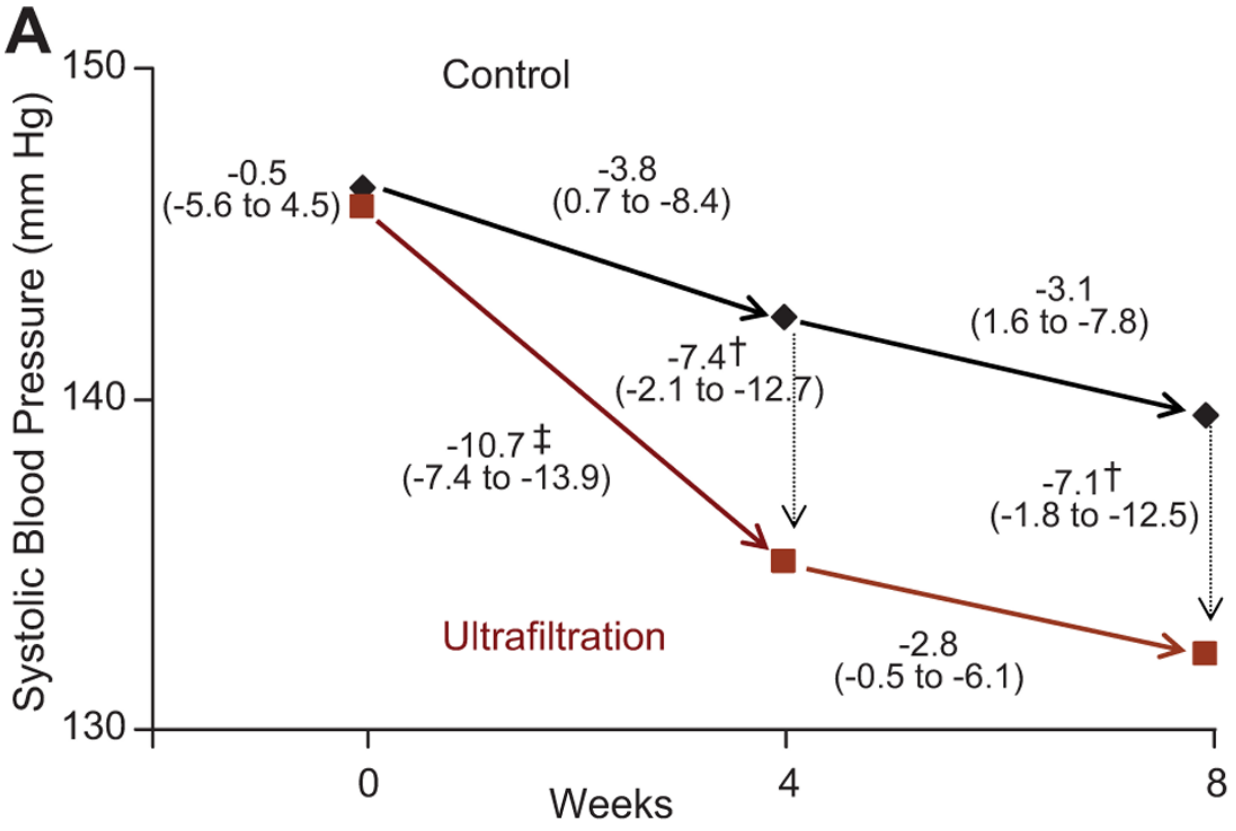
Bansal et al. Hypertension in Patients Treated With Hemodialysis. *Hypertension.* 2023.

NO standardized BP targets in dialysis patients

- The BID pilot study (Blood Pressure In Dialysis) - intensive BP lowering to pre-HD SBP goal of 110 - 140 mmHg did not yield a reduction in LV mass or lower the incidence of CV events compared with the standard arm (SBP goal, 155–165 mmHg)
- NKF KDOQI - pre-HD BP >140/90 mmHg or with post-HD BP >130/80 mmHg.
- Observational studies have shown **inconsistent findings** between dialysis BP readings and MACE outcomes (CVA, CV, and all-cause mortality)
- **44 hour interdialytic ABPM** (**gold standard)** has been shown to be a superior risk predictor for mortality
- Home BP has been shown to closely correlate with 44 hour interdialytic ABPM *(Bansal et al. 2021. AJKD)* and is a reasonable alternative

Bansal et al. Hypertension in Patients Treated With Hemodialysis. *Hypertension.* 2023.

Dry weight reduction improves BP in HD patient - **DRIP trial**



DW reduction of 1.0kg at **8 weeks** resulted in **-6.6 mmHg** improvement in SBP

More than half the patients in the intervention group had reduction in SBP by at least 10 mm Hg

Agarwal et al. Hypertension. 2010

Antihypertensive Medications in dialysis

- RAASi have **not** demonstrated consistent benefits on cardiovascular outcomes in patients treated with HD
- Some data supports the use of CCBs for cardiovascular risk reduction in patients on HD

Table 2. Dialyzability of Commonly Used Antihypertensive Drugs*

	RAAS inhibitors	CCBs	β-Blockers	Other
High dialyzability	Benazepril, captopril, enalapril, lisinopril, ~~ramipril~~	None	Atenolol, metoprolol, ~~propranolol~~	Minoxidil
Low dialyzability	Fosinopril, trandolapril, ARBs	Amlodipine, diltiazem, felodipine, verapamil	Carvedilol, labetalol	α-Blockers, hydralazine, clonidine

Jula K Inrig**. Antihypertensive Agents in Hemodialysis Patients: A Current Perspective.** Semin Dial. 2010

Bansal et al. Hypertension in Patients Treated With Hemodialysis. *Hypertension.* 2023.

The Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL)

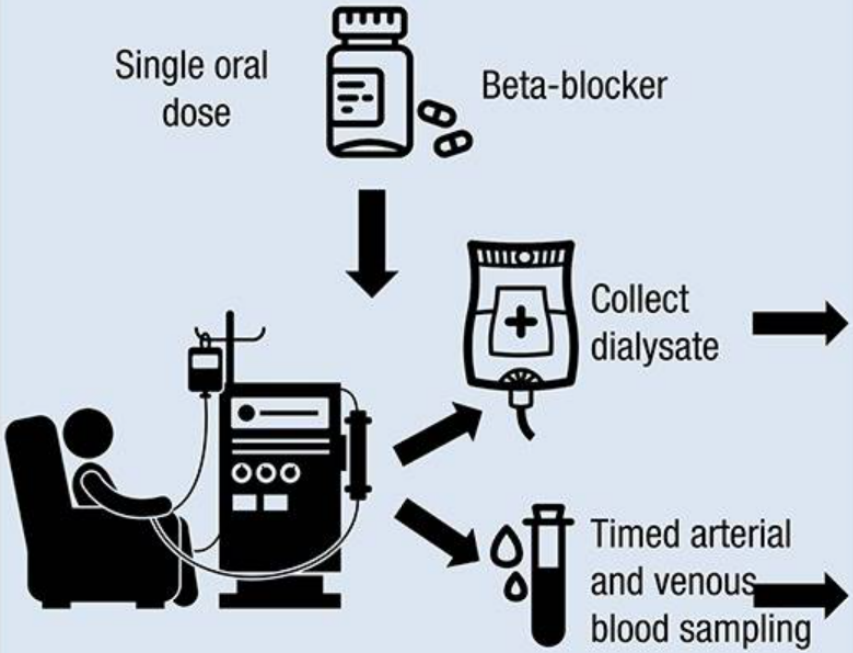
- Randomized single-center trial (Indianapolis, IN, USA) - 86% black patients. 2014
- Compared Lisinopril (n = 100) vs Atenolol (n = 100) 3x/week post-HD to see which one would cause greater LVH regression. BP
- **Terminated early → Lisinopril group: increase in all-cause serious adverse events, all-cause hospitalization rates, hypertension and hyperkalemia.**
- **Atenolol >> Lisinopril in lowering BP** (more fall and fractures with Atenolol). Home SBP target < 140 mm Hg seems safe.
- Similarly, Carvedilol (compared to placebo) - reduced in CV risk and all-cause mortality in dialysis patients with dilated cardiomyopathy *(Cice G et al. J Am Coll Cardiol. 2003)*

R. Agarwal et al. Nephrol Dial Transplant (2014) 29: 681–687

Beta-blocker Dialyzability in Chronic Hemodialysis Patients

CJASN
Clinical Journal of American Society of Nephrology

Methods: Open-label crossover study, N=8



Findings: Determined dialytic clearance two ways

Poorly dialyzed → Highly dialyzed

	Carvedilol	Bisoprolol	Metoprolol	Atenolol
Recovery clearance method (ml/min)	**0.2** +/- 0.6	**44** +/- 9	**87** +/- 28	**72** +/- 21
A-V difference method (ml/min)	**24** +/- 18	**96** +/- 17	**114** +/- 19	**167** +/- 23

Conclusions Atenolol, metoprolol, and bisoprolol are extensively cleared by hemodialysis as compared to the negligible dialytic clearance of carvedilol.

Alvin Tieu, Thomas Velenosi, Andrew Kucey, Matthew Weir and Bradley Urquhart. Beta-blocker Dialyzability in Chronic Hemodialysis Patients. doi:10.2215/CJN.07470717

Spironolactone in Hemodialysis

- **SPin-D trial -**
  - randomized to placebo vs spironolactone (12.5, 25, 50mg).
  - Small study (n = 129) - anuric maintenance HD. 30% ACEI/ARB usage, ~45% β blocker
  - Spironolactone appears safe with carefully monitoring at doses of 12.5 and 25mg

- **Randomized, double-blinded trial of 82 patients -** Spironolactone 25mg vs. placebo; China
  - Therapy was dosed after dialysis or in the morning on non-dialysis days
  - Mean baseline BP was approximately 152/91 mmHg.
  - After 12 weeks, the mean between-group **difference in morning BP was 17/8 mmHg lower in the spironolactone** (mean dose 42.5 mg daily) and **24-h ambulatory BP was 12.5/7 mmHg** in the spironolactone group ($p<0.05$).
  - Two patients in the spironolactone group stopped due to hyperkalemia (serum K > 5.5)

Charytan, David M et aSPin-D trial. Kidney Int. 2019
Ni X et al. J Clin Hypertens. 2014

Spironolactone in PD

- ➔ Used quite regularly for hypokalemia, blood pressure control and/or diuretics
- ➔ Rarely see issues with hyperkalemia
- ➔ Spironolactone 25mg daily - significant reduction in SBP from 151 +/- 17 to 124 +/- 23 mm Hg (p = 0.02) - *Ottawa group (Langote A et al. Spironolactone is effective in treating hypokalemia among peritoneal dialysis patients. PLoS ONE 2017)*

What is the effect of taking versus holding blood pressure medications on intradialytic hypotension? - The TAKE-HOLD study

Kidney360

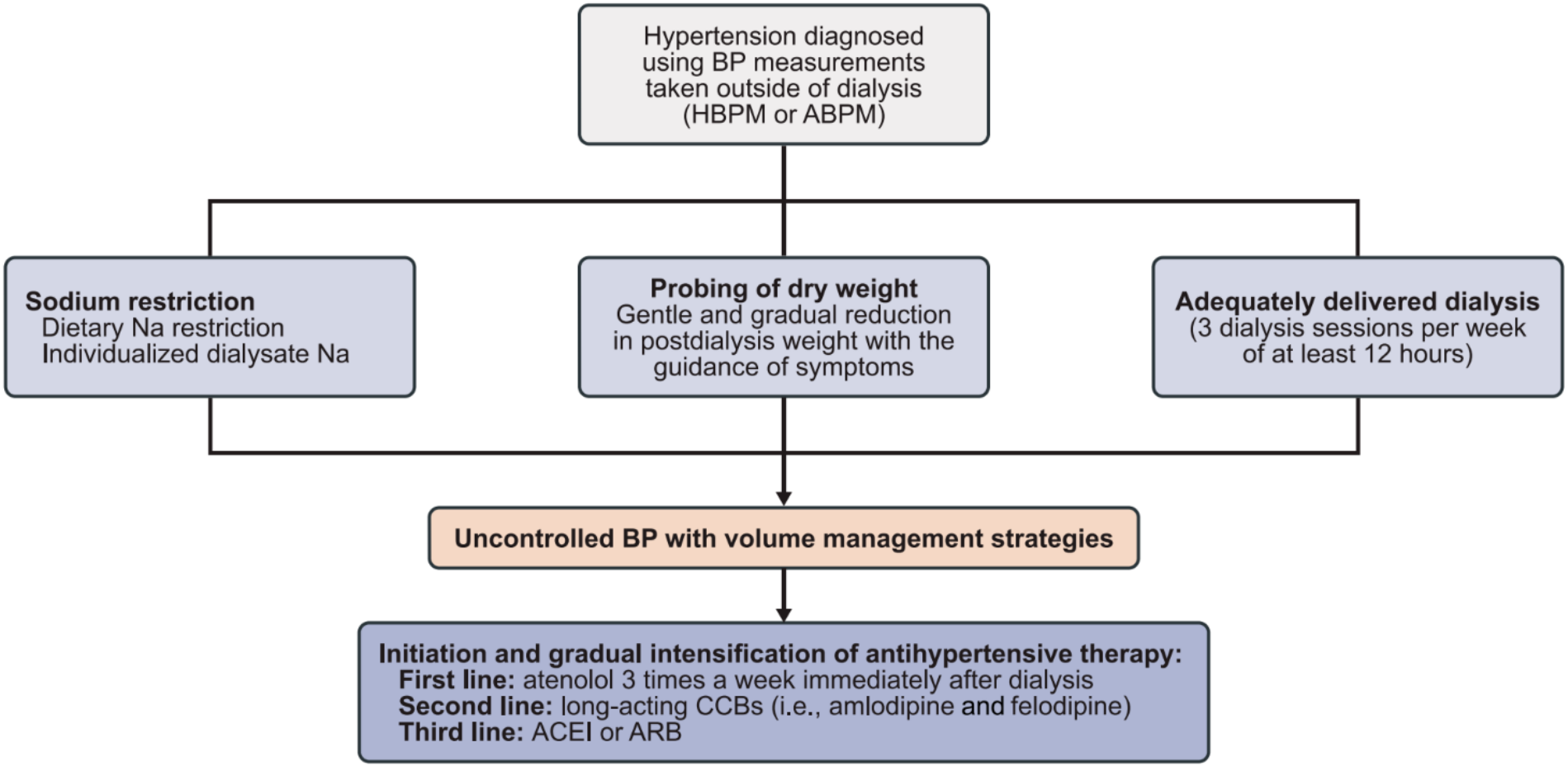
Ten dialysis units randomized in a 1:1 ratio to the TAKE or HOLD intervention

		Primary outcome	Secondary outcomes	
			Uncontrolled HTN	Failure to achieve DW
TAKE	65	18.5%	38.5%	67.7%
HOLD	64	16.6%	53.0%	77.3%
Mean difference		7.9% (-3.0 to 18.7)	-14.6% (-28.0 to -1.2)	-9.6% (-16.1 to -3.1)

Given the sparse data, dosing of BP medications in HD should be individualized

Conclusions a strategy of taking BP medications dosed more than once daily was not non-inferior to holding BP medications for the primary outcome of intradialytic hypotension, but did reduce the occurrence of uncontrolled hypertension.

Tara I. Chang, Emily Tamar Tatoian, Maria E. Montez-Rath, *et al.* ***Timing of Antihypertensive Medications on Key Outcomes in Hemodialysis (TAKE-HOLD): a Cluster Randomized Trial.*** *Kidney360.* DOI: 10.34067/KID.0001922021 **Visual Abstract by Pablo Garcia, MD**



Resistant Hypertension in Dialysis: Epidemiology, Diagnosis, and Management.
JASN 35: 505–514, April, 2024

SUMMARY

- BP management requires multidisciplinary and comprehensive care
- Ensure adherence as a cause of resistant HTN in CKD
- Single pill combo drugs work well and reduce pill burden (low doses of different classes)
- Pharmacist play a vital role in managing HTN in general population and CKD
- Spironolactone in CKD (non DM) works well
- CKD - Look out for upcoming trials (eg. **EASi-KIDNEY and BaxDUO)**
- HD - Uncontrolled HTN (>3 BP meds) is volume expanded, unless proven otherwise
- HD - importance of individualized targets and timing of medications. Atenolol 3x/week post-HD Amlodipine and then ACEIs/ARBs. Caution with Spironolactone.
- **NEW HYPERTENSION CANADA 2025 GUIDELINES TO BE RELEASED SOON**

THANK YOU!!