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RESISTANT ARTERIAL HYPERTENSION

OBJECTIVES

- Cases, cases, cases
- Resistant Hypertension
- Secondary Hypertension
- Good PC work-up for resistant hypertension/secondary HTN
- Spironolactone.. why we should use it more
- Circumstances for more individualized care (as opposed to guideline mediated)

CASE 1

- 55-year-old man with class 2 obesity and a long history of HTN returns for annual follow-up
- Meds:
  - nifedipine 90 qd
  - chlorthalidone 12.5 qd
  - lisinopril 20 bid
  - carvedilol 12.5 bid
  - clonidine 0.2 bid
  - hydralazine 20 tid
  - KCl 20 mEq bid
- BP 150/100 mmHg, BMI 38, HR 60
- Normal GFR
- Normal K^+

RESISTANT HYPERTENSION

- Blood pressure > goal in spite of concurrent use of 3 antihypertensive agents of different classes:
  - usually long-acting CCB, RAASi and a diuretic
  - prescribed at maximum or maximally tolerated daily doses
- Includes those with <u>controlled *BP on ≥ 4 medications*</u>
- Requires
  - Confirmation of medication adherence
  - Exclusion of white coat effect

Hypertension. 2018 ; 72:e53-e90

RESISTANT HYPERTENSION

- 12-15% of treated adults with hypertension
- In two large retrospective population studies those with RAH
  - 47% more likely to suffer combined outcomes of death, MI, HF, CVA or CKD over median 3.8 years follow-up.
  - Increased risk : ESRD (32%), ischemic cardiac event (24%), heart failure (46%), stroke (14%), death (6%).

Blood pressure, 2023, vol 30
Circulation, 2012, vol 125

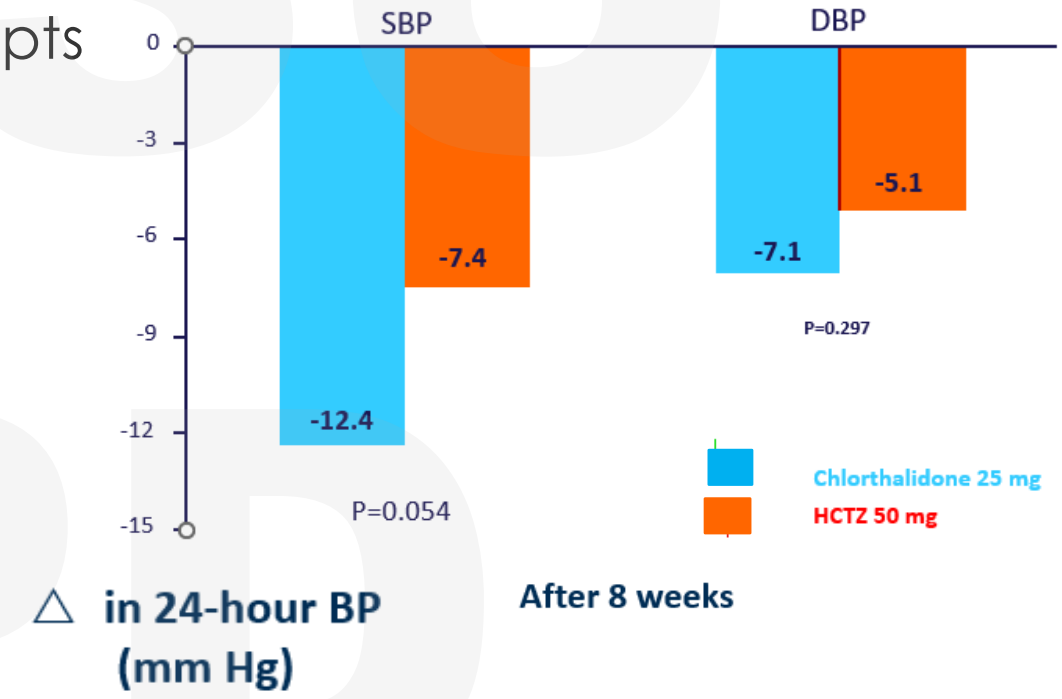
MANAGEMENT

- Exclude other causes
- Optimize lifestyle
- Ensure low sodium diet < 2-3 g/day

- Optimize 3 drug regimen
  - RAS blocker
  - CCB
  - diuretic dose *appropriate for kidney function*

VOLUME EXCESS IN RESISTANT HTN PATIENTS

- Evidence of volume overload in ~ 70% of pts
- How do find out?
  - Physical exam
- Use longer acting thiazide:
  - chlorthalidone, indapamide
- Adjust to GFR
  - Consider change thiazides to loop diuretic in advanced CKD with volume issues



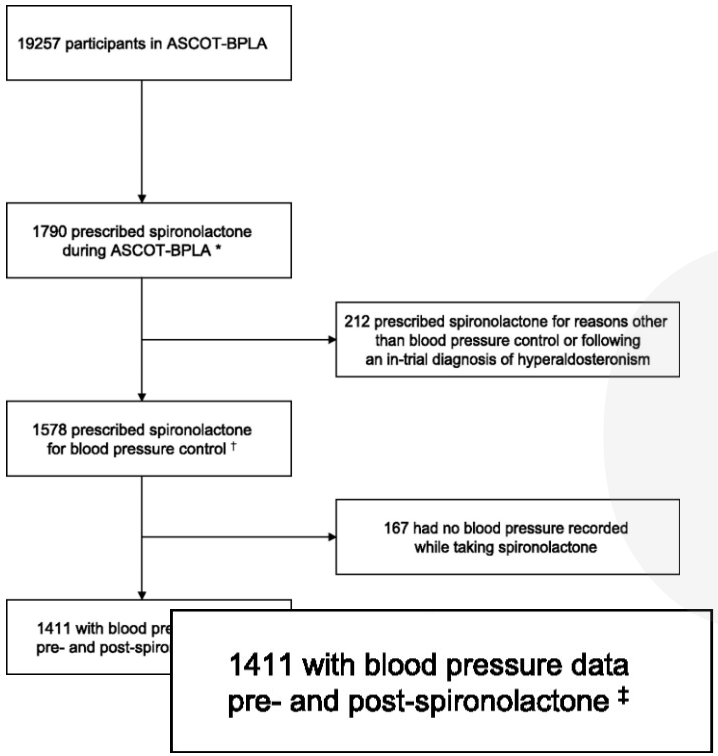
Ernst Hypertension 2006;47:352

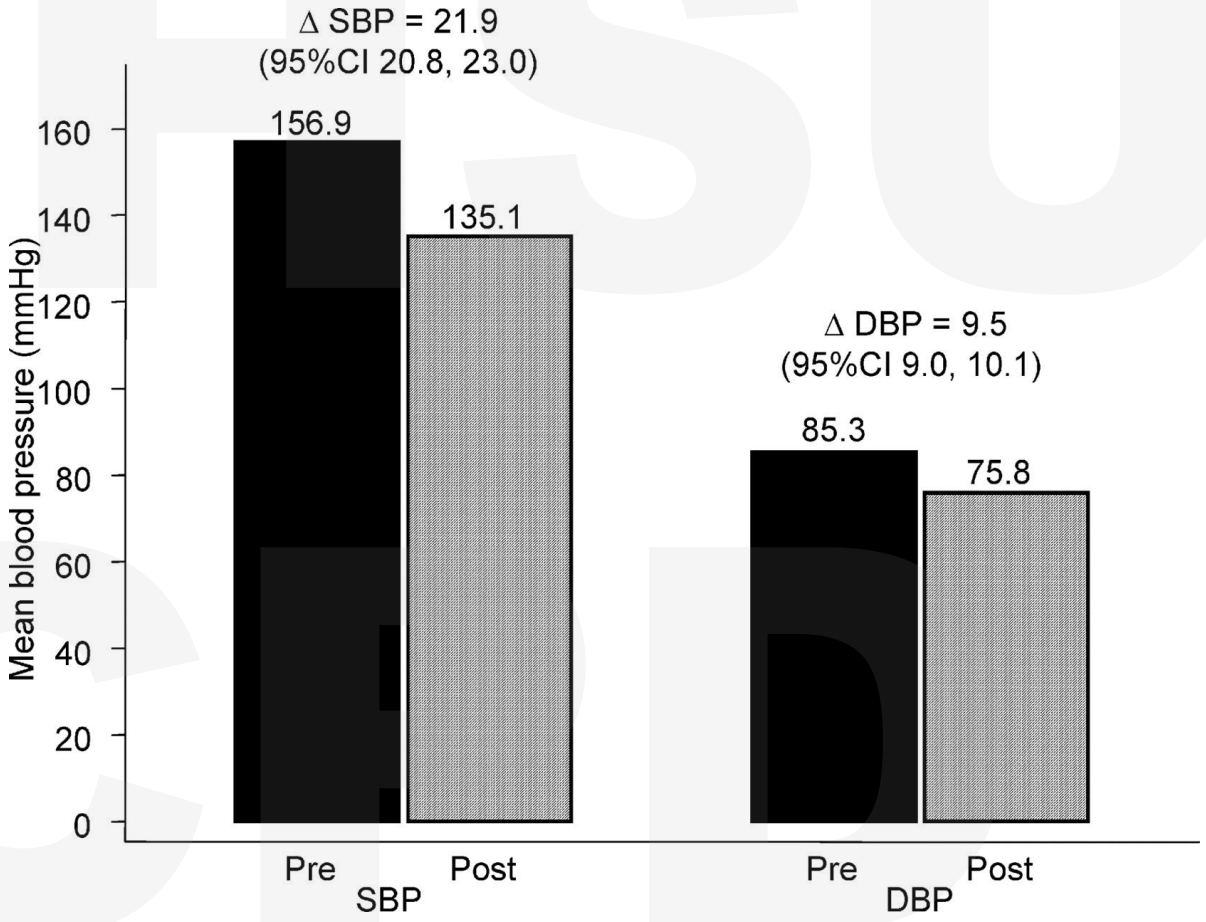
MANAGEMENT: CON'T

- Add Mineralocorticoid Blocker (MRA):
  - spironolactone or eplerenone
  - if intolerant consider amiloride

SPIRONOLACTONE IN RESISTANT HTN

The ASCOT Trial was designed to compare a calcium blocker vs a beta blocker





Hypertension. 2007 Apr;49;839-45.
http://hyper.ahajournals.org/cgi/content/full/49/4/839

CASE 1

- 55 year-old man with class 2 obesity and a long history of HTN returns for annual follow-up.
- Meds:
  - +spironolactone 12.5 qd (or eplerenone 25 mg BID)
  - nifedipine 90 XL QD (make sure it is extended release)
  - chlorthalidone increase to 25 mg qd (follow K closely)
  - lisinopril 20 bid → decrease to QD (combo with spiro increases risk of high K)
  - carvedilol 12.5 bid
  - clonidine 0.2 bid (consider weaning off in near future)
  - hydralazine 20 tid → hopefully stop soon as spironolactone titrated up
  - KCl 20 mEq bid → stop
- Chem panel ~ 2 wk after initiation and w/dose

WHEN YOU SHOULD BE SUSPICIOUS FOR SECONDARY HTN

- Younger patients (< 30 yo) with grade 2 HTN
- Sudden onset
- True resistant HTN
- Hypertensive Emergency
- Malignant HTN
- Clinical features of obstructive sleep apnea
- Severe HTN in pregnancy (> 160/110 mmHg)
- Clinical features suggestive of endocrine causes
- Clinical features suggestive of atherosclerotic renovascular disease or fibromuscular dysplasia
- Unprovoked or excessive hypokalemia

CAUSES OF SECONDARY HYPERTENSION WITH CLINICAL INDICATIONS

Common causes
Renal parenchymal disease
Renovascular disease
Primary aldosteronism
Obstructive sleep apnea
Drug or alcohol induced
Uncommon causes
Pheochromocytoma
Cushing's syndrome
Hypothyroidism
Hyperthyroidism
Aortic coarctation (undiagnosed or repaired)
Primary hyperparathyroidism
Congenital adrenal hyperplasia
Mineralocorticoid excess syndromes other than primary aldosteronism
Acromegaly

Journal of Hypertension 2023; 41

PRIMARY CARE WORK-UP FOR RESISTANT ARTERIAL HYPERTENSION (RAH) / SECONDARY HYPERTENSION

- UA+micro
  - Eval for hematuria/proteinuria →glomerulonephritis can present w HTN
- Renal Imaging with evaluation of renal arteries
  - Structural abnormalities → ADPKD
  - Renal artery stenosis (RAS)
- Aldosterone (PAC) and renin (PRA or PRC)
  - Morning blood sample
  - Also draw potassium, as $[K^+]$ needs to be > 3.5 mg/dL
- Thyroid testing
- Screening for OSA

CASE 2

- 30 year old man comes to clinic with BP 150/100 mmHg on 2 meds (CCB and ACEI)
- Creatinine normal, K 3.3 mEq/L

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- PRA : 0.4 ng/ml/hr

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- CT adrenal glands:
  - 1.6 cm mass on left side, HU < 10

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- CT adrenal glands:
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- Pt underwent left adrenalectomy
- Currently normotensive on no medications

AHA 2025 GUIDELINES

3.2.3.1. Primary Aldosteronism

Recommendations for Primary Aldosteronism		
COR	**LOE**	**Recommendations**
1	**C-EO**	1. In adults with hypertension, screening for primary aldosteronism is recommended in the presence of any of the following conditions to increase rates of detection, diagnosis, and specific targeted therapy: resistant hypertension (regardless of whether hypokalemia is present), hypokalemia (spontaneous or diuretic induced), OSA, incidentally discovered adrenal mass, family history of early-onset hypertension, or stroke at a young age (<40 years).
2b	**C-EO**	2. In adults with stage 2 hypertension, screening for primary aldosteronism may be considered to increase rates of detection, diagnosis, and specific targeted therapy.

We tend to do this

WEAK
Expert opinion

Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline

Gail K. Adler,[1] Michael Stowasser,[2] Ricardo R. Correa,[3] Nadia Khan,[4] Gregory Kline,[5] Michael J. McGowan,[6] Paolo Mulatero,[7] M. Hassan Murad,[8] Rhian M. Touyz,[9] Anand Vaidya,[1] Tracy A. Williams,[10] Jun Yang,[11,12] William F. Young,[8] Maria-Christina Zennaro,[13,14] and Juan P. Brito[8,15]

IN ALL INDIVIDUALS WITH HYPERTENSION, WE SUGGEST SCREENING FOR PRIMARY ALDOSTERONISM (PA) **NEW**

In individuals with primary aldosteronism (PA) receiving PA-specific medical therapy whose hypertension is not controlled and renin is suppressed, we suggest increasing PA-specific medical therapy to raise renin **NEW**

The Journal of Clinical Endocrinology & Metabolism, 2025, 00, 1–43
https://doi.org/10.1210/clinem/dgaf284
Advance access publication 14 July 2025

Clinical Practice Guideline

CAVEATS YOU SHOULD KNOW WHEN TESTING

Effect on renin or aldosterone	Medication
Lower renin	β-adrenergic blockers, central acting α_2-agonists (clonidine, α-methyldopa), NSAIDs Combined estrogen and progesterone-containing OCPs and HRT decrease DRC (impact on PRA described below)
Raise renin	MRAs, diuretics including ENaC inhibitors (amiloride, triamterene), ARBs, ACE inhibitors, SGLT2 inhibitors Combined estrogen and progesterone-containing OCPs and HRT increase PRA (impact on DRC described above) Drospirenone blocks the MR and thus increases PRA and DRC
Lower aldosterone	ARBs, ACE inhibitors, β-adrenergic blockers, central α_2-agonist (clonidine, α-methyldopa)
Raise aldosterone	Diuretics[a], MRAs Combined estrogen and progesterone-containing OCPs and HRT Drospirenone

CASE 3

- 54 year old man with 10 year history of HTN, CKD 3b and a history of hypokalemia
- Meds
  - HCTZ 25 mg daily
  - Lisinopril 40 mg daily
  - Felodipine 2.5 mg daily
  - KCl 20 mEq BID
- BP 159/92, HR 64
- eGFR 42, K^+ 3.1

CASE 3

- Aldosterone 28 ng/dl , renin activity < 0.5 ng/ml/hr, K^+ normal
- CT A/P with 3 x 1.5 cm adrenal nodule
- Adrenal vein sampling was consistent with bilateral adrenal hyperplasia
- Current meds:
  - Eplerenone 50 mg BID (renin unsuppressed)
  - Nifedipine 90 mg SA daily
  - Lisinopril 40 mg daily
  - Carvedilol 25 mg BID
- eGFR 18 mL/min, K^+ normal

<u>treatment goals:</u>

BP management

Normokalemia

and

non-suppressed renin (→)

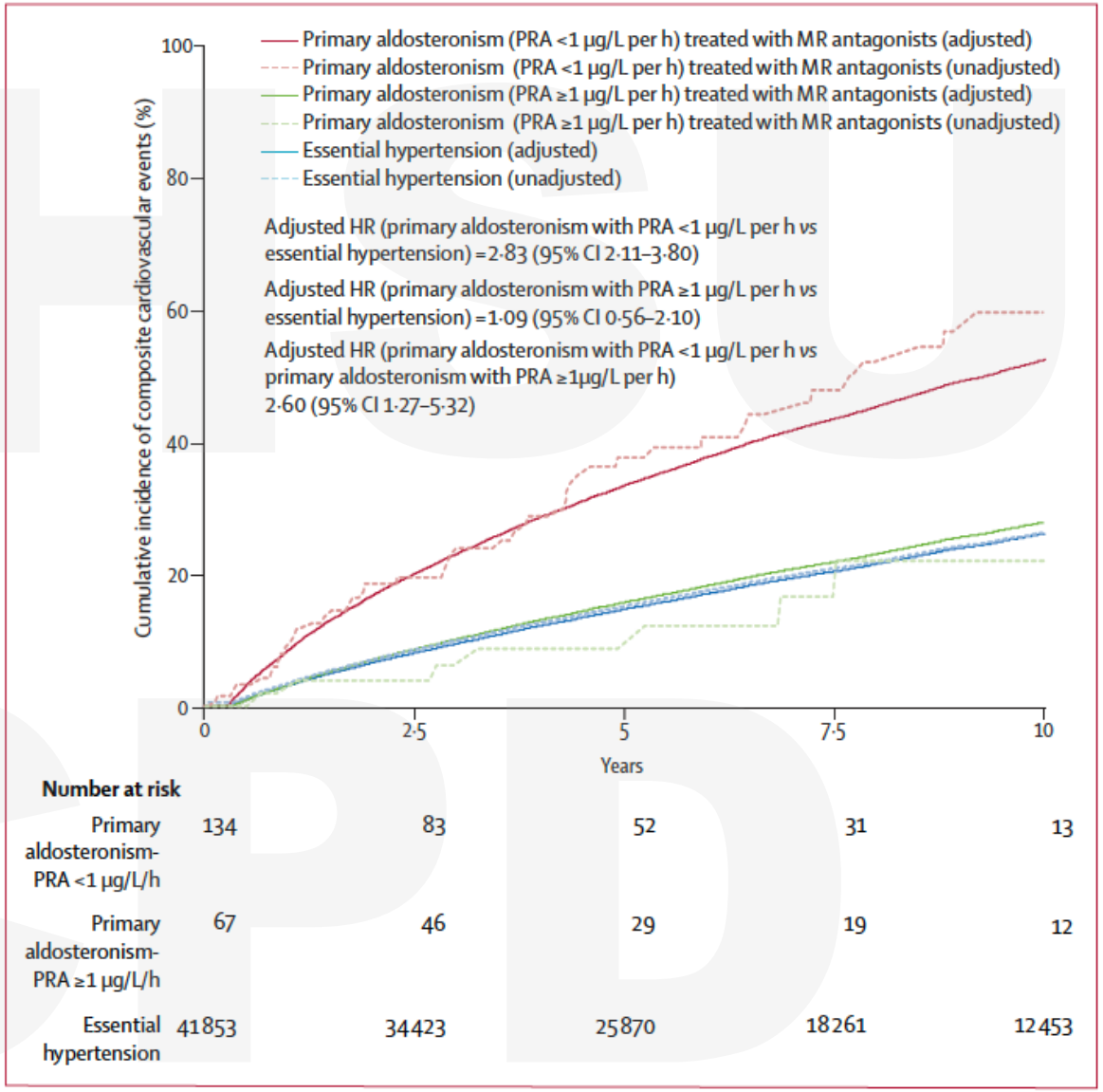


Figure 3: **Standardised cumulative incidence curve of composite cardiovascular outcomes stratified by plasma renin activity**

The current practice of MR antagonist therapy in primary aldosteronism is associated with significantly higher risk for incident cardiometabolic events and death, independent of blood pressure control, than for patients with essential hypertension. Titration of MR antagonist therapy to raise renin might mitigate this excess risk.

Hundemer *Lancet Diabetes Endocrinol* 6:51-9 2018

The Unrecognized Prevalence of Primary Aldosteronism

A Cross-sectional Study

Jenifer M. Brown, MD; Mohammed Siddiqui, MD; David A. Calhoun, MD; Robert M. Carey, MD; Paul N. Hopkins, MD, MSPH; Gordon H. Williams, MD; and Anand Vaidya, MD, MMSc

Background: Primary aldosteronism is a nonsuppressible renin-independent aldosterone production that causes hypertension and cardiovascular disease.

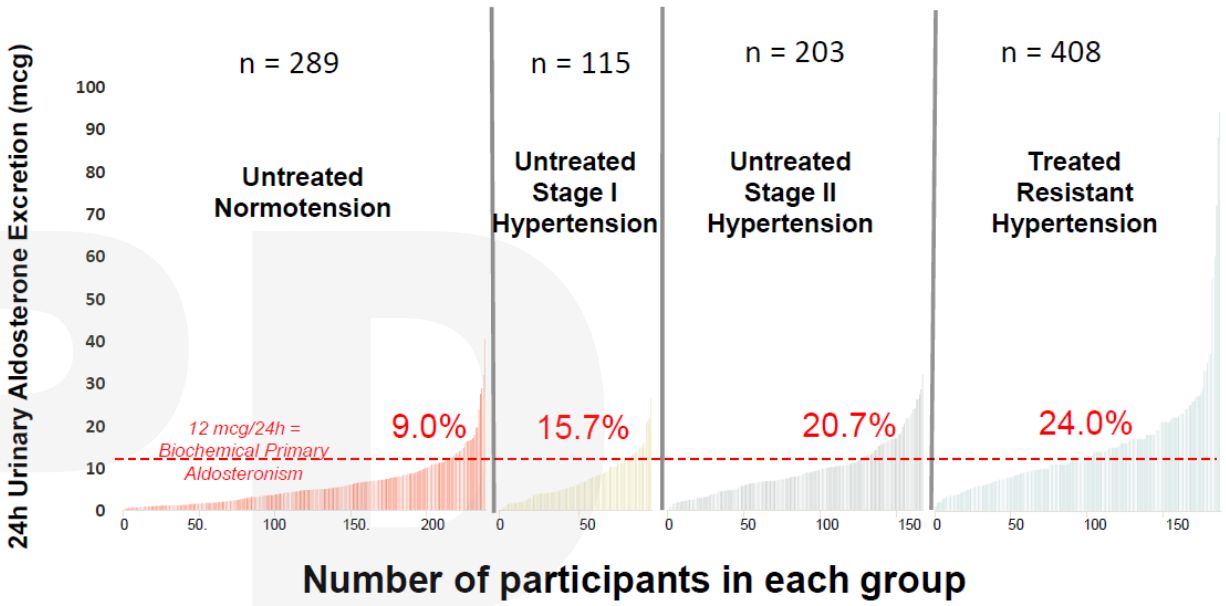
Objective: To characterize the prevalence of nonsuppressible renin-independent aldosterone production, as well as biochemically overt primary aldosteronism, in relation to blood pressure.

Design: Cross-sectional study.

Setting: 4 U.S. academic medical centers.

Participants: Participants with normotension (*n* = 289), stage 1 hypertension (*n* = 115), stage 2 hypertension (*n* = 203), and resistant hypertension (*n* = 408).

Prevalence of Primary Aldosteronism



Primary Funding Source: National Institutes of Health.

Ann Intern Med. 2020;173:10-20.

Brown JM, Siddiqui M, Calhoun DA, Carey RM, Hopkins PN, Williams GH, Vaidya A. The Unrecognized Prevalence of Primary Aldosteronism: A Cross-sectional Study. Ann Intern Med. 2020 Jul 7;173(1):10-20.

CASE 4

- 83 yo M w/ DM2, HTN, SSS s/p PPM, carotid artery stenosis, prior CVA, and new AKI.
- BP "going crazy" on:
  - Indapamide 2.5 mg daily
  - Irbesartan 300 mg daily
  - And… "as many lisinopril 20 mg as needed to get BP down" (old Rx)
- BP at home, reportedly 180/90s; BP in clinic 100/59
- Baseline Cr 1.0, Cr 1.4 in clinic

SO MUCH VASCULAR DISEASE… CONCERN FOR RENAL ARTERY STENOSIS

- Renal duplex US…

Aorta

	PS cm/s
Aorta prox	79

Mesenteric Arteries

	PS cm/s	ED cm/s	RI	Details
Celiac A prox	299	70	0.77	Deep insp: 148/33 cm/s
SMA prox	264	22	0.92	

Renal Vessels

Right Kidney Arteries:

	PS cm/s	ED cm/s	RI	EDR
Renal A prox	270	31		
Renal A mid	188	34		
Renal A distal	159	36		
Cortex upper	63	17	0.73	0.27
Cortex lower	74	19	0.74	0.26

RAR 3.4.

Left Kidney Arteries:

	PS cm/s	ED cm/s	RI	EDR
Renal A prox	222	34		
Renal A mid	221	40		
Renal A distal	120	25		
Cortex upper	74	20	0.73	0.27
Cortex lower	61	15	0.75	0.25

RAR 2.8.

Renal Veins:

	RIGHT	LEFT
	PV cm/s	PV cm/s
Renal vein	40	71

Kidney Measurements:

	RIGHT	LEFT
Kidney Size	L 10.6 cm	L 10.5 cm

KIDNEY ULTRASOUND WITH RENAL ARTERY DOPPLERS

Table 2: Direct and Indirect Doppler US Diagnostic Criteria for Renal Artery Stenosis

Diagnostic Criteria	Threshold Cutoff
Direct criteria	
Main renal artery PSV (cm/sec)	>200
Ratio of main renal artery PSV to prerenal abdominal aorta PSV	>3.5:1
Lack of Doppler US signal in cases of occlusion	NA
Doppler US artifacts caused by turbulence (aliasing)	NA
Indirect criteria	
Pulsus parvus et tardus waveform (blunted and delayed systolic upstroke)	NA
Acceleration index (cm/sec^2)	<300
Acceleration time (time to peak systole) (msec)	>70

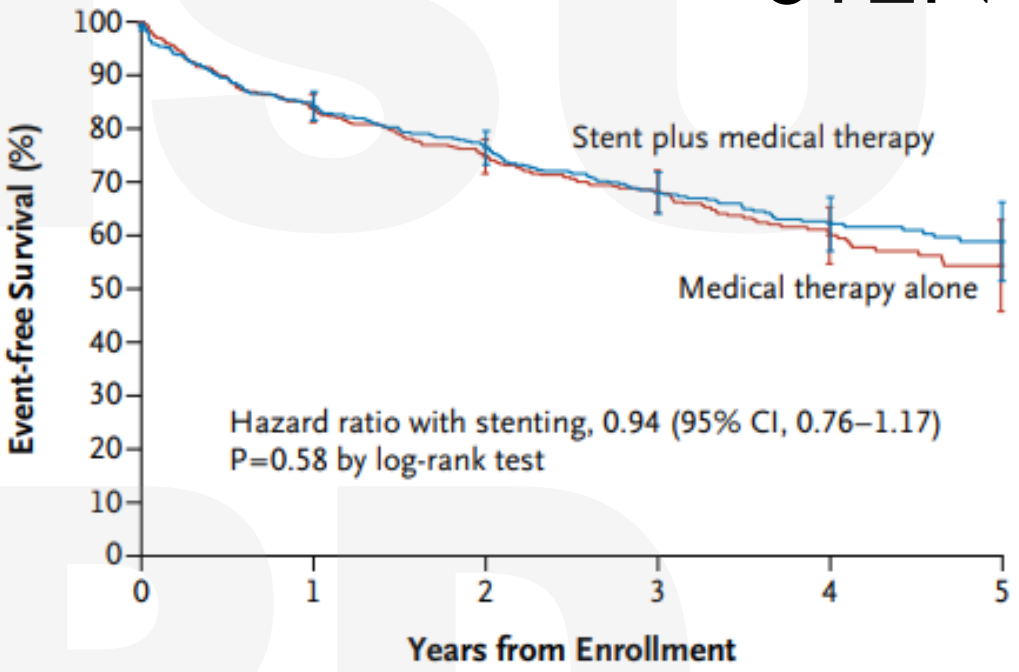
TREATMENT OF RENAL ARTERY STENOSIS

- Medical therapy is as good or better than PTA/stenting
  - BP control
    - ACEi or ARB if tolerated, avoid if bilateral RAS
  - Lipid control
  - Consider adding a low dose diuretic

Stent + Medical Therapy 35.1%, 3-years

Medical Therapy 35.8%, 3-years

No benefits by stenosis, BP, or gradients



No. at Risk

Medical therapy alone	472	371	314	214	115	40
Stent plus medical therapy	459	362	318	224	131	59

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

CORAL Primary Endpoint Composite of Clinical Events was Negative

WHEN TO INTERVENE IN RAS

- Solitary kidney with increasing creatinine
- Flash pulmonary edema
- Significant, high grade, bilateral disease with rapidly increasing creatinine
- Refractory hypertension
- +/- AKI with ACEi/ARB

INTERVENTION ON RAS IS NOT WITHOUT RISKS

- Atheroemboli
- Dissection of the renal artery
- Renal artery perforation or rupture
- Renal artery thrombosis or occlusion
- Segmental infarction
- Aortic dissection
- Contrast induced nephropathy
- Spinal paraplegia/paralysis
- Additional access related complications (femoral or brachial artery)

CASE 4- MANAGEMENT

- Indapamide, irbesartan and lisinopril all stopped
- Started on nifedipine 30 mg BID
- BP 134-152/55-62 on nifedipine 30 mg daily
- Repeat labs Cr 1.4→ 1.2
- Continue to monitor and hold on referral for intervention at this time

WHEN TO JUMP OFF THE GUIDELINES..

- Individualized care
- Not all our patients were represented in the studies used to create the guidelines
- Sometimes our patients have data that does not allow us to follow guidelines and manage all their medical needs appropriately/safely
- Always discuss risk/benefits with patient

CASE 5

- 82 year old man w DM2, HTN, CVA, PTSD, CKD 3a re-referred for poorly controlled HTN and worsening Cr.
- Medications
  - Amlodipine 10 mg
  - Prazosin 2 mg qhs (nightmares)
  - Previously on losartan – stopped for hyperkalemia
- BP 155-175/44-53, HR 54-65
- Cr 1.6, eGFR 43 mL/min summer 2025 → Cr 2.2, eGFR 28 mL/min 2026
- Overall feeling poorly

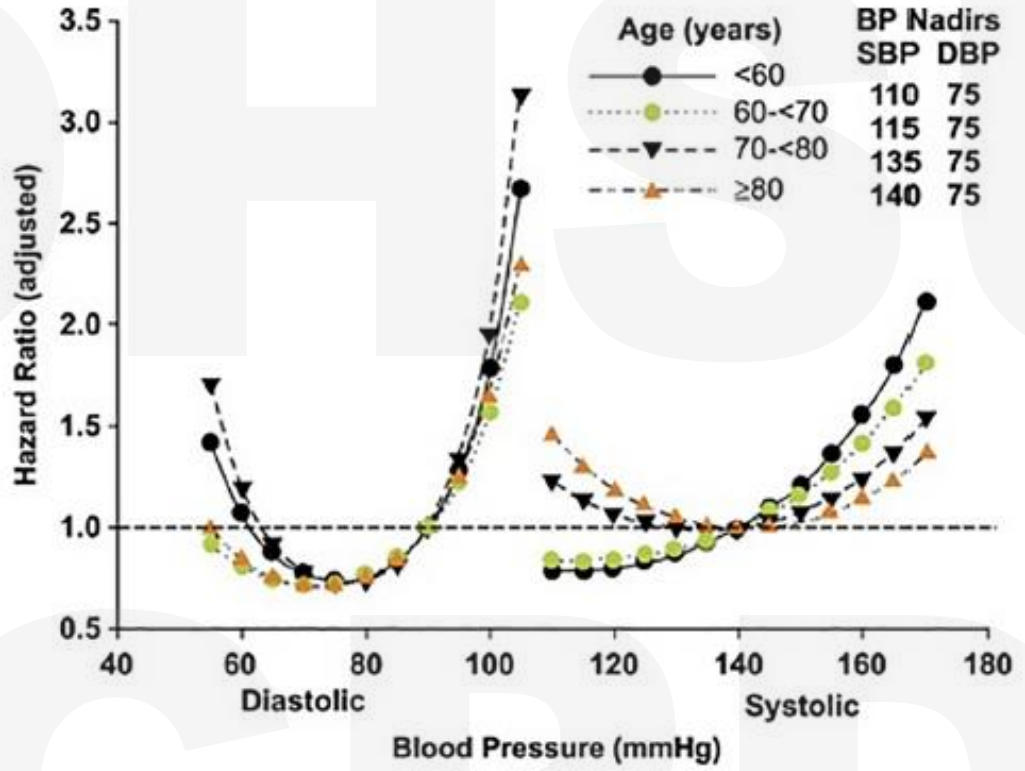
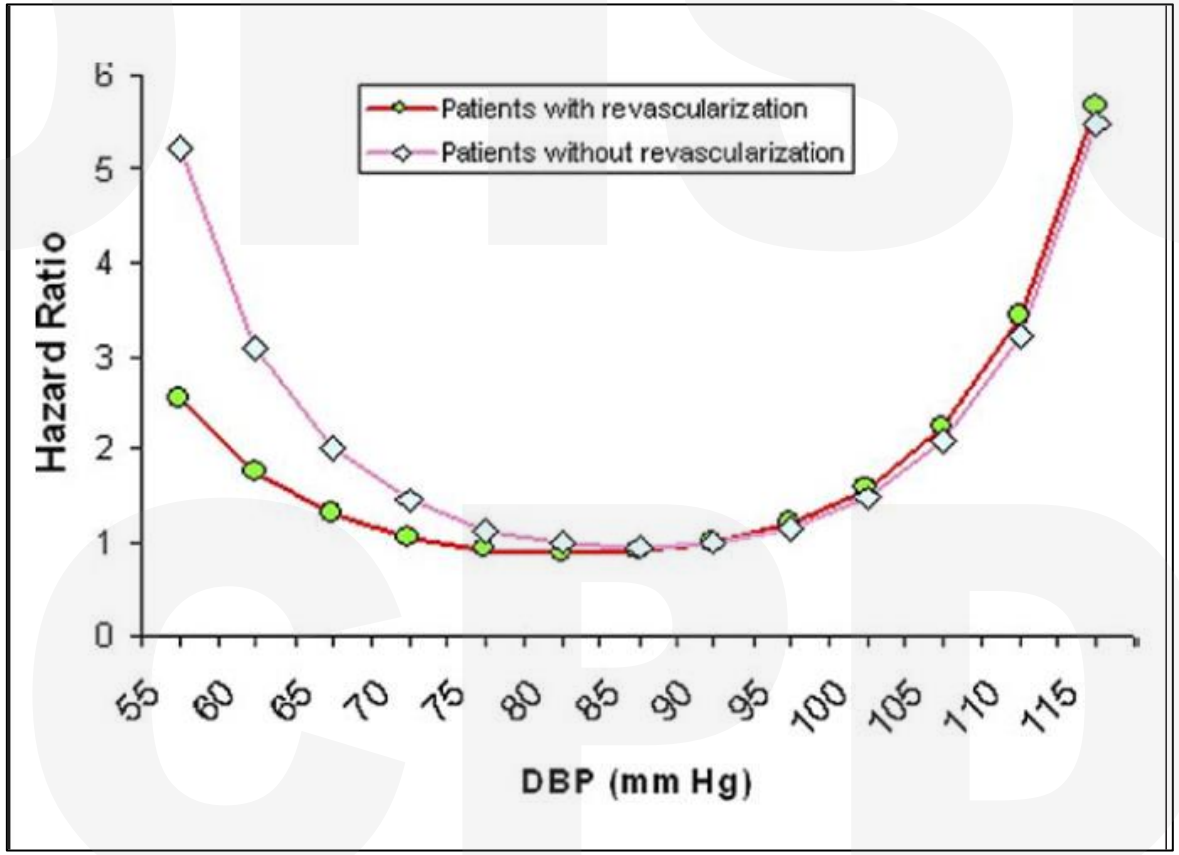


Fig. 1. The J-curve for diastolic blood pressure. From DeNardo et al. *AmJMed*, 2010;123: 719–726 with permission from Elsevier.

American Heart Journal Plus: Cardiology Research and Practice 12 (2021) 100065

PATIENTS WHO WERE REVASCULARIZED BETTER TOLERATE A LOWER DBP THAN THOSE WHO WERE NOT



The J-Curve Between Blood Pressure and Coronary Artery Disease or Essential Hypertension

JACC Vol. 54, No. 20, 2009
November 10, 2009:1827–34

CASE 5 - MANAGEMENT

- First line medications to consider
  - Dihydropyridine CCB
  - ? Thiazide
  - ACEi/ARB
- Consideration of adding a nitrate…
  - Risk of tachyphylaxis, but lowers systolic> diastolic
- Plan for a trial of ISMN 15 mg daily..

CASE 6

- 63 year old man DM2, HTN, CAD, OSA, h/o multifocal stroke
- Meds
  - Losartan 50 mg BID
  - Carvedilol 25 mg BID
  - Nifedipine 60 mg SA daily
  - Empagliflozin12.5 mg daily
- BP 140-150/80s, HR 60-70s

CTA Neck:

LEFT CAROTID: The left common carotid is nonopacified the level of the bifurcation with distal reconstitution. There is approximately 80% stenosis of the proximal left internal carotid artery with multifocal less than 80% stenoses.

RIGHT CAROTID: No aneurysm, dissection, traumatic vascular injury. Calcified atherosclerosis causes greater than 80% stenosis of the mid to distal common carotid artery with distal reconstitution. Calcified atherosclerosis causing this greater than 70% stenosis of the proximal internal carotid artery with normal distal opacification

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- Review risk benefits of HTN control and decrease cerebral perfusion
- Recrudescence of CVA symptoms with lower reading
- In this patient I made no changes
- Awaiting revascularization

CASE 7 - ORTHOSTATIC HYPOTENSION

- 76 year old man ESRD s/p DDKT, DM2, HTN, Afib, CAD s/p 2V CABG
- Medications
  - Amlodipine 10 mg daily
  - Carvedilol 6.25 mg BID
  - (hyperkalemia w ACEi/ARB)
- BP in clinic 94/58, HR 70
- Home BPs ranging 145-180/60-90s sitting and drop to 86-low 100s/50s with standing.. ? Syncopal episode

THERE IS NOT A CLEAR, EASY ANSWER..

- But you have to step off the guidelines
- First amlodipine was stopped, subsequently carvedilol halved to 3.125 mg BID
- Additional work-up pending with zio, TTE, tilt table, etc
- BP improved to > 100 systolic standing, remains intermittently elevated sitting but strict sodium restriction has also helped..

6 QUESTIONS TO ANSWER FOR RESISTANT HYPERTENSIVES

- Is it true?
- Is it a dietary sodium problem?
- Is volume status optimized?
- Are we missing a secondary cause?
- Are we using a Mineralocorticoid Receptor Antagonist (MRA)? If not, why not? if MRA is not an option, can Amiloride (Enac blocker) be used?
- Would the patient benefit from a referral to a HTN specialist?

IN SUMMARY

- Long-acting CCB, RAASi and a diuretic are the base of treatment
- Think about spironolactone more
  - Requires lab follow-up for potassium and Cr
  - Renin levels can be followed
- Stenting is not always the answer in RAS
- Don't forget the J-curve for diastolic BPs
- Know if your patient's CV disease is revascularized or not, it makes a difference
- Discuss thought process with patient if you think best to diverge from guidelines

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CASE 8

- 75 yo man comes to see you for LUTS.
- Meds: none
- BP 120/75, HR 80
- Do you start him on doxazosin for BPH?

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- 75 yo man comes to see you for LUTS.
- Meds: none
- BP 120/75, HR 80
- Do you start him on doxazosin for BPH?
- What if his BP is 160/75—is doxazosin a good first-line agent?

CASE 8

- No!!
- ALL-HAT trial
  - Doxazosin monotherapy arm terminated early due to excess CHF
  - Reflex tachycardia?
- Use tamsulosin for BPH when BP doesn't need lowering
  - esp elderly, fall risk
- Avoid use of a-blocker w/o concomitant b-blocker
  - unless pulse is already low

CASE 9

- 55 yo man with diabetes and HTN comes to you for annual follow-up.

- BP R 140/95, L 140/95, HR 70, BMI 31
- Meds: nifedipine 30 qd, atenolol 25 qd
- creatinine 0.9, microalbumin 10 mg/g

- What now?

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- What now?
- Is ACEi or ARB "mandatory"?

CASE 9

- Strongest data for ACEi or ARB is in those with heaviest proteinuria

- NO GOOD DATA to support ACEi or ARB over other agents to treat HTN
  - in diabetes w/ no albuminuria
  - in CKD w/ no proteinuria

5.3.1. Diabetes

Recommendations for Diabetes Referenced studies that support the recommendations are summarized in the Evidence Table.		
COR	**LOE**	**Recommendations**
1	A	1. In adults with T2D and hypertension, antihypertensive drug treatment should be initiated at an SBP of ≥130 mm Hg with a treatment goal of <130 mm Hg, with encouragement to achieve an SBP <120 mm Hg to reduce CVD morbidity and mortality.[1–5]
1	C-LD	2. In adults with T2D and hypertension, antihypertensive drug treatment should be initiated at a DBP of ≥80 mm Hg with a treatment goal of <80 mm Hg to reduce CVD morbidity and mortality.[6]
1	A	3. In adults with T2D and hypertension, all first-line classes of antihypertensive agents (ie, thiazide-type diuretics, long-acting CCB, ACEi, and ARB) are useful and effective for BP lowering.[1,7–9]
1	A	4. In adults with diabetes and hypertension, ACEi or ARB are recommended in the presence of CKD as identified by eGFR <60 mL/min/1.73 m^2 or albuminuria ≥30 mg/g and should be considered when mild albuminuria (<30 mg/g) is present to delay progression of diabetes-related kidney disease.[10–12]

AHA 2025 HTN Guidelines

ACE-I OR ARB IN DIABETES

- YES, if
  - Proteinuric (albuminuric)
    - > 30 mg albuminuria by albumin:creatinine ratio
    - or enough to show up on dipstick
  - Tolerated
    - < 30% increase in creatinine w/ initiation or titration
    - No hyperkalemia
    - Not hypotensive

- NO, if
  - Not hypertensive
  - Already on ACEi or ARB (do not combine)
  - On chronic NSAIDs
  - On spironolactone, eplerenone, aliskerin (*use caution*)
  - Hx significant AKI w/ ACEi or ARB
  - High risk for bladder outlet obstruction or volume depletion
  - Patient unreliable for f/u (ie, labs)

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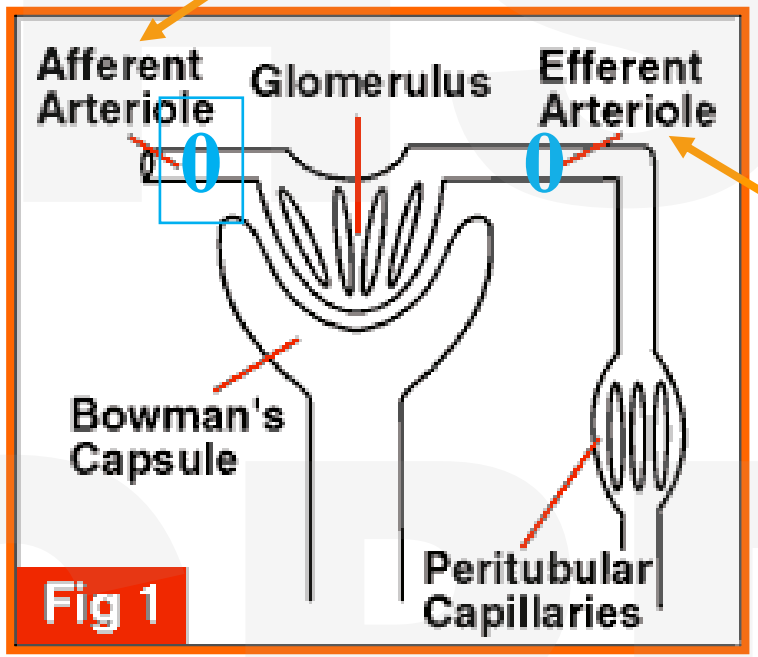
– On chronic NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs): cause *afferent arteriole* constriction, resulting in *decreased GFR*

BP



ACEi and ARBs dilate the *efferent arteriole* - - thus decreasing glomerular capillary pressure, and decreasing GFR

Proteinuric Disease eg Diabetes: dilated *afferent arteriole* allows transmission of high systemic pressure into glomerulus, resulting in *glomerular damage and proteinuria*

Kerendia

Finerenone

Prescription
Kerendia 10mg (30 tablets)

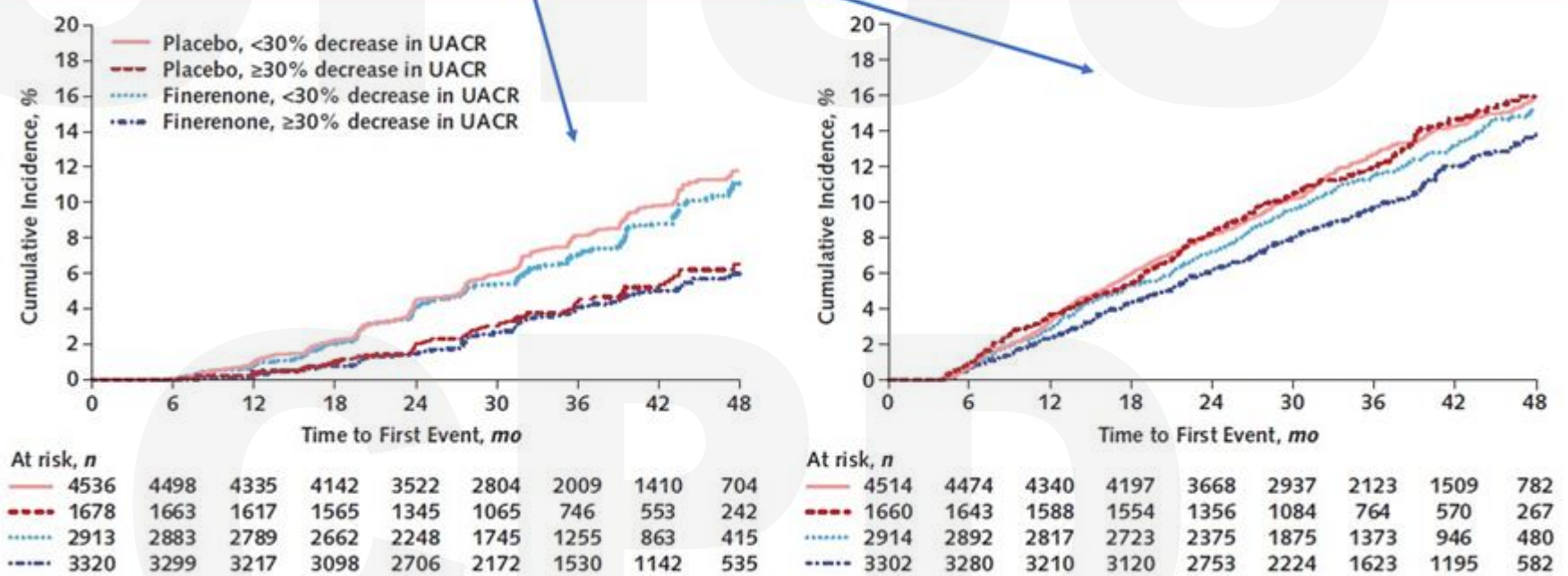
Pay as little as $660.08 for Kerendia with GoodRx Gold. Start free trial

Choose pharmacy — Portland, OR

Albertsons (Sav-on) — Pay online	$666.58 Special offers	
Safeway — Pay online	$666.58 Special offers	
Capsule Pharmacy	$676.66	
Fred Meyer Pharmacy — Pay online	$705.21	
QFC — Pay online	$705.21	
CVS Pharmacy	$728.85	
Target (CVS)	$728.85	
Walgreens	$730.27	
Walgreens Specialty Pharma...	$730.27	
Walmart	$745.90	

Finerenone in diabetic kidney disease (pooled FIGARO and FIDELIO data)

Figure 3. Cumulative incidences for the kidney and cardiovascular composite outcomes by treatment group and relative reduction in UACR at month 4.



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How do spiro and finerenone compare for albuminuria reduction/slowing progression of CKD?

Pharmacologic differences among spironolactone, eplerenone and finerenone

Characteristics	Spironolactone $	Eplerenone $$	Finerenone $$$
Structural properties	Steroidal	Steroidal	Non-steroidal
Absorption	100% bioavailable	69% bioavailable	44% bioavailable
MR affinity (nmol/l)	24.2 (high)	990 (low)	17.8 (high)
MR selectivity	Low	Medium	High
Tissue distribution	Kidney >> heart, >6-fold	Kidney > heart, ≈3-fold	Equivalent, 1:1
Metabolites	Hepatic, active metabolites	No active	No active
Half-life (hours)	>20	3–6	2–4
Hyperkalaemia	High	Moderate	Low
BP-lowering effect	Strong	Weak	Weak
Anti-fibrotic effect[a]	Moderate	Moderate	High

Kobayashi *NDT* 39:1063 2024