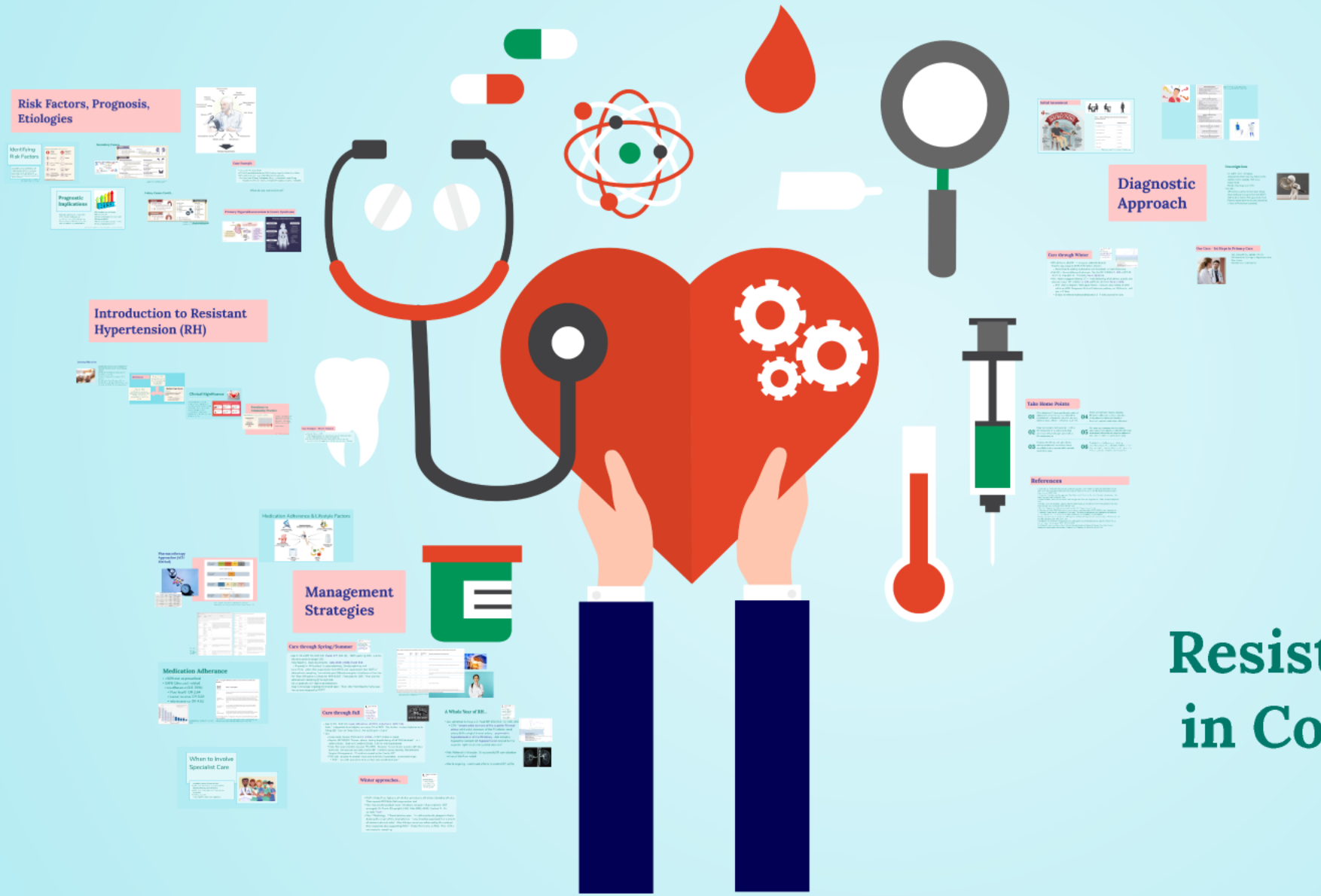


Resistant Hypertension in Community Practice

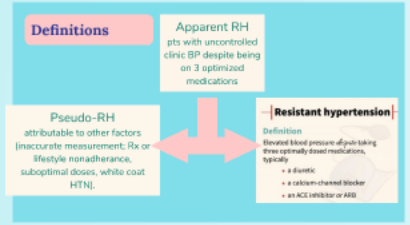
Caroline Correia

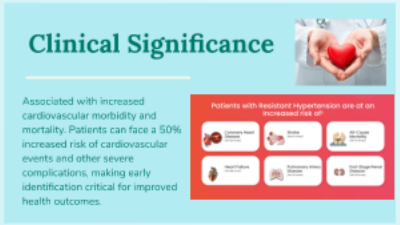
Apr 2025

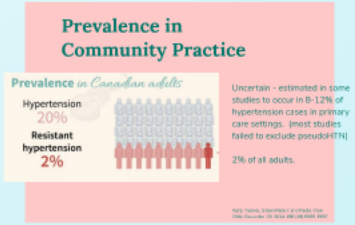
Introduction to Resistant Hypertension (RH)

Learning Objectives

- Describe the prevalence and risk factors for Resistant Hypertension (RH) in community practice
- List the clinical circumstances in which it should be suspected
- Develop a framework for approach to it's work up
- Describe when to involve specialist care
- Describe the challenges patients & providers face when multiple collaborating providers







Case Example - Mrs H. Tension

- 71F with HTN since 2009.
- PMHx: Hypercholesterolemia, DDD, Restless Legs Sx, White Coat Effect.
- BP control had been avg <140/<80 over the past 15y.
- Rx: Irbesartan 300mg, Amlodipine 10mg, hydrochlorothiazide 25mg.
  - Presents to office Jan 2024 with home BP readings recently ~160s/90s.

Learning Objectives

- Describe the prevalence and risk factors for Resistant Hypertension (RH) in community practice
- List the clinical circumstances in which it should be suspected
- Develop a framework for approach to it's work up
- Describe when to involve specialist care
- Describe the challenges patients & providers face when multiple collaborating providers

Definitions

Apparent RH

pts with uncontrolled clinic BP despite being on 3 optimized medications

Pseudo-RH

attributable to other factors (inaccurate measurement; Rx or lifestyle nonadherance, suboptimal doses, white coat HTN).

Resistant hypertension

Definition

Elevated blood pressure *despite* taking three optimally dosed medications, typically

- a diuretic
- a calcium-channel blocker
- an ACE inhibitor *or* ARB

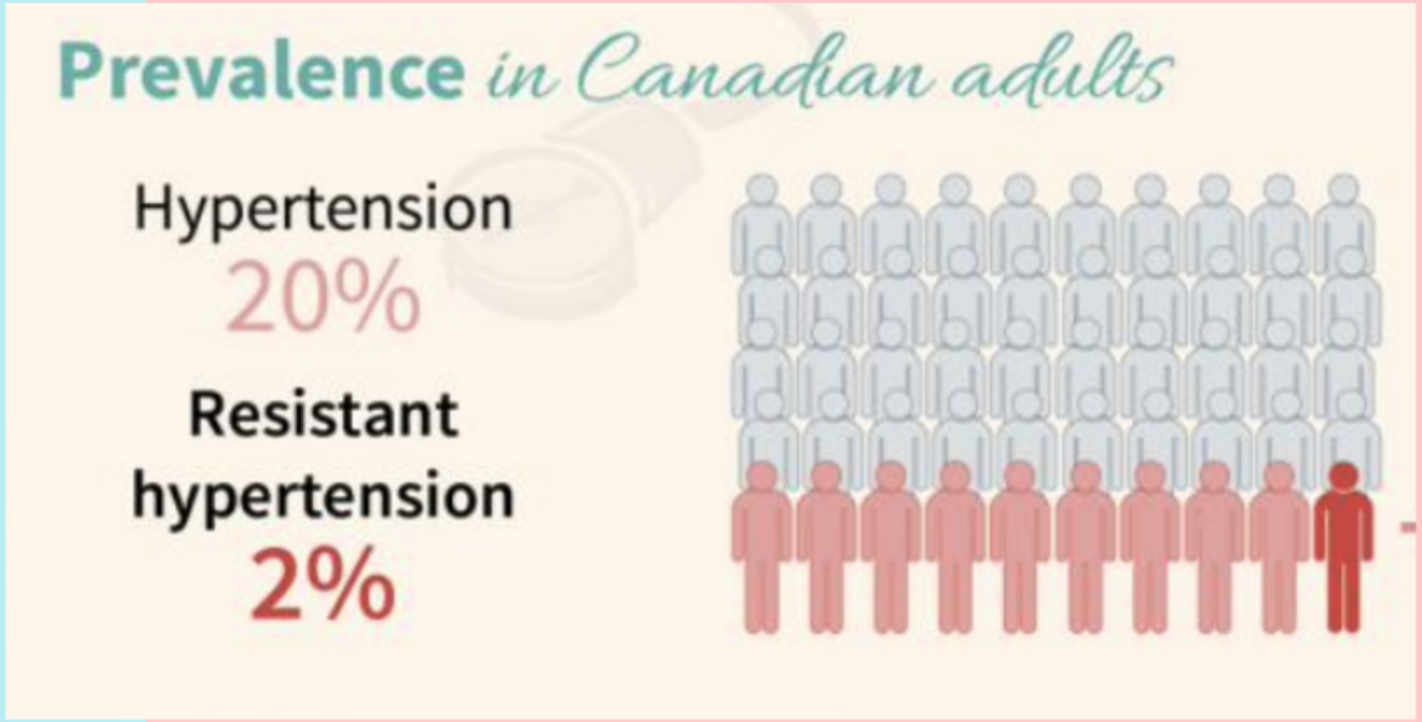
Clinical Significance

Associated with increased cardiovascular morbidity and mortality. Patients can face a 50% increased risk of cardiovascular events and other severe complications, making early identification critical for improved health outcomes.

Patients with Resistant Hypertension are at an Increased risk of[3]

- Coronary Heart Disease (HR:1.44 times)
- Stroke (HR:1.57 times)
- All-Cause Mortality (HR:1.30 times)
- Heart Failure (HR:1.88 times)
- Pulmonary Artery Disease (HR:1.23 times)
- End-Stage Renal Disease (HR:1.95 times)

Prevalence in Community Practice



Uncertain - estimated in some studies to occur in 8-12% of hypertension cases in primary care settings. (most studies failed to exclude pseudoHTN)

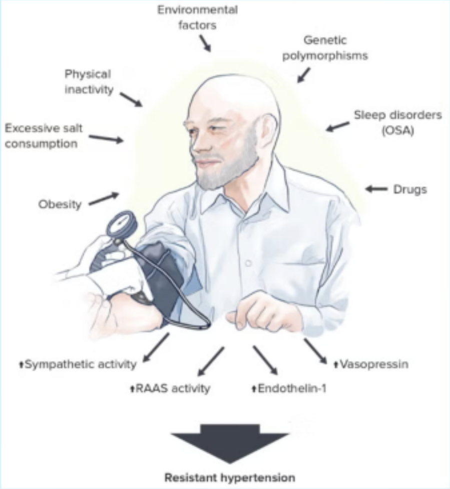
2% of all adults.

Raj S. Padwal, Simon Rabkin and Nadia Khan
CMAJ December 09, 2014 186 (18) E689-E697

Case Example - Mrs H. Tension

- 71F with HTN since 2009.
- PMHx: Hypercholesterolemia, DDD, Restless Legs Sx, White Coat Effect.
- BP control had been avg <140/<80 over the past 15y.
- Rx: Irbesartan 300mg, Amlodipine 10mg, hydrochlorothiazide 25mg.
    - Presents to office Jan 2024 with home BP readings recently ~160s/90s.

Risk Factors, Prognosis, Etiologies

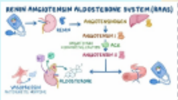


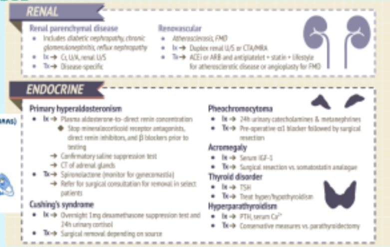
Identifying Risk Factors

Key risk factors for resistant hypertension include demographics such as age, gender, and African/Caribbean ancestry, as well as lifestyle factors like excessive alcohol and salt intake, obesity, and diabetes. Additionally, conditions like chronic kidney disease and poorly controlled hypertension elevate the risk profile significantly.

Raj S. Padwal, Simon Rabkin and Nadia Khan
CMAJ December 09, 2014 186 (18) E689-E697

Secondary Causes





The Intern at Work: https://www.theinternatwork.com/infographics-2/2020/9/20/resistant-hypertension

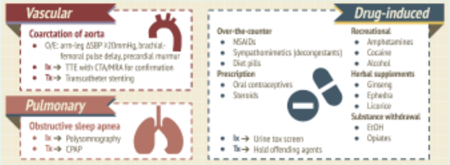
Prognostic Implications

Resistant hypertension is associated with increased cardiovascular morbidity and mortality. Highlighting the importance of identifying individuals early to support timely management.

50% Cardiovascular Events
46% risk of CHF
24% risk of Ischemic Cardiac Event
32% risk of ESRD
14% risk of Cerebrovascular Events
6% risk of premature death

Daugherty SL et al. Circulation 2012; Rimoldi SF et al Eur Heart J 2015; Sim JJ et al Kidney Int 2015

2ndary Causes Cont'd...



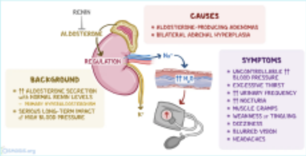
The Intern at Work: https://www.theinternatwork.com/infographics-2/2020/9/20/resistant-hypertension

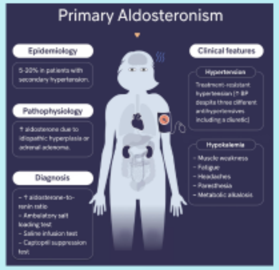
Case Example

- 71F with HTN since 2009.
- PMHx: Hypercholesterolemia, DDD, Restless Legs Sx, White Coat Effect.
- BP control had been avg <140/<80 over the past 15y.
- Rx: Irbesartan 300mg, Amlodipine 10mg, hydrochlorothiazide 25mg.
  - Presents to office Jan 2024 with home BP readings recently ~160s/90s.

What do you want to know?

Primary Hyperaldosteronism & Conn's Syndrome

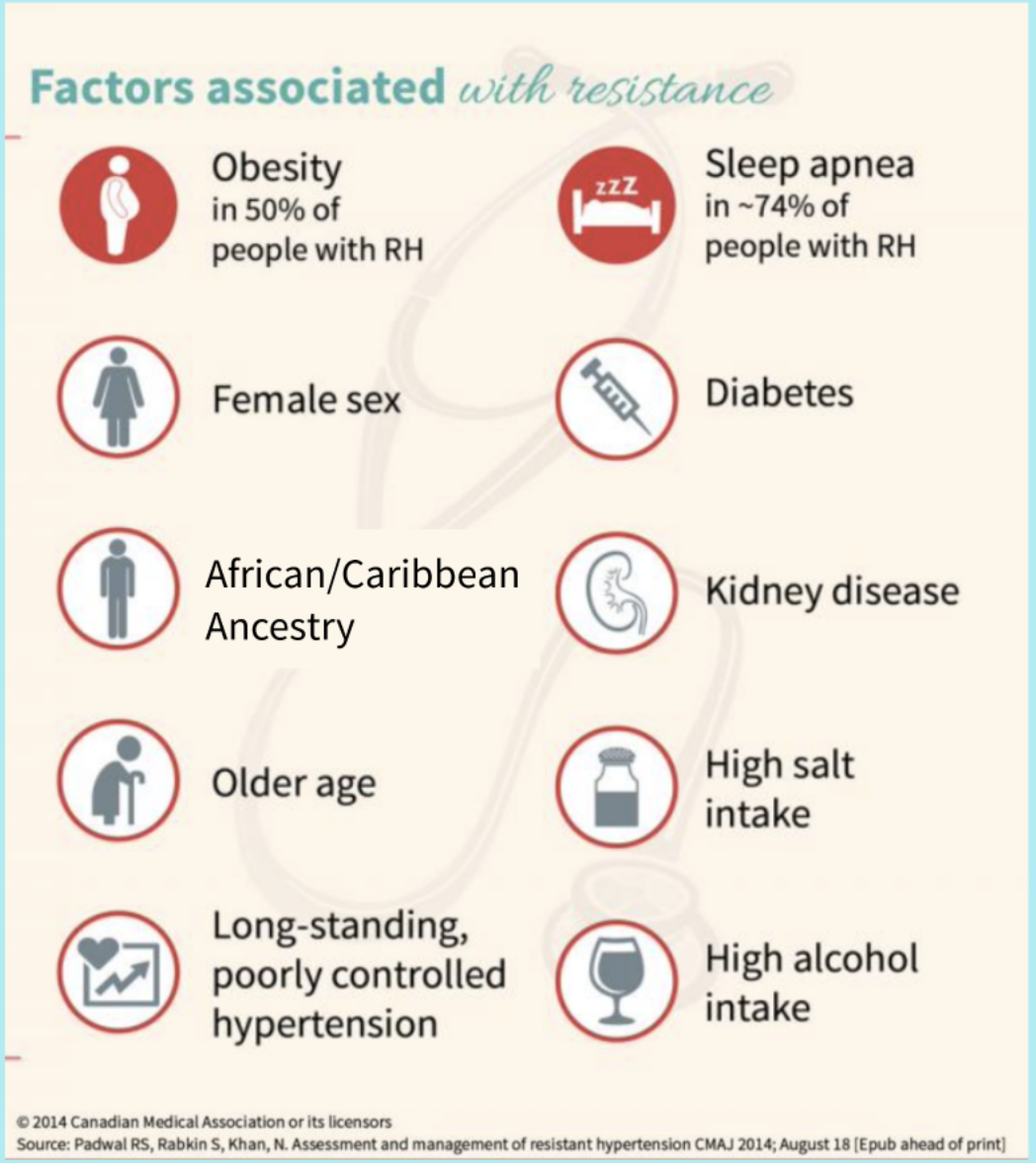




Identifying Risk Factors

Key risk factors for resistant hypertension include demographics such as age, gender, and African/ Caribbean ancestry, as well as lifestyle factors like excessive alcohol and salt intake, obesity, and diabetes. Additionally, conditions like chronic kidney disease and poorly controlled hypertension elevate the risk profile significantly.

Raj S. Padwal, Simon Rabkin and Nadia Khan
CMAJ December 09, 2014 186 (18) E689-E697



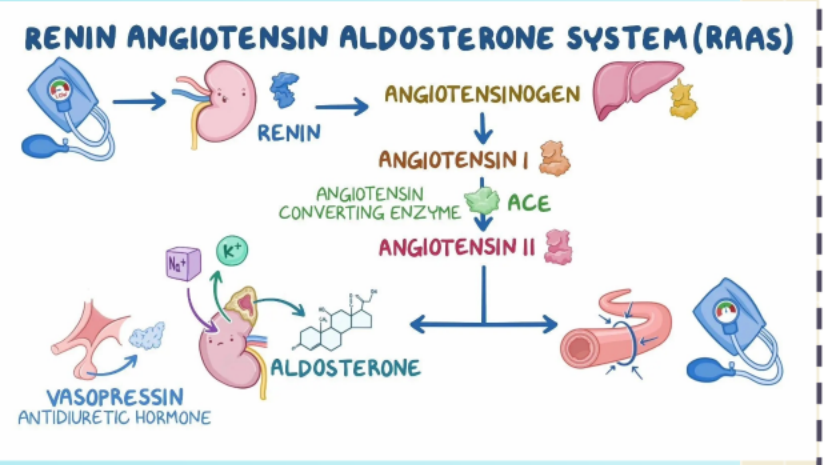
Prognostic Implications

Resistant hypertension is associated with increased cardiovascular morbidity and mortality. Highlighting the importance of identifing individuals early to support timely management.

50% Cardiovascular Events
46% risk of CHF
24% risk of Ischemic Cardiac Event
32% risk of ESRD
14% risk of Cerebrovascular Events
6% risk of premature death

Daugherty SL et al. Circulating 2012; Rimoldi SF et al Our Heart J 2015; Sim JJ et al Kidney Int 2015

Secondary Causes



RENAL

Renal parenchymal disease

- Includes *diabetic nephropathy, chronic glomerulonephritis, reflux nephropathy*
- Ix → Cr, U/A, renal U/S
- Tx → Disease-specific

Renovascular

- *Atherosclerosis, FMD*
- Ix → Duplex renal U/S or CTA/MRA
- Tx → ACEi or ARB and antiplatelet + statin + lifestyle for atherosclerotic disease or angioplasty for FMD

ENDOCRINE

Primary hyperaldosteronism

- Ix → Plasma aldosterone-to- direct renin concentration
  - ◆ Stop mineralocorticoid receptor antagonists, direct renin inhibitors, and β blockers prior to testing
  - → Confirmatory saline suppression test
  - → CT of adrenal glands
- Tx → Spironolactone (monitor for gynecomastia)
  - → Refer for surgical consultation for removal in select patients

Cushing's syndrome

- Ix → Overnight 1mg dexamethasone suppression test and 24h urinary cortisol
- Tx → Surgical removal depending on source

Pheochromocytoma

- Ix → 24h urinary catecholamines & metanephrines
- Tx → Pre-operative α1 blocker followed by surgical resection

Acromegaly

- Ix → Serum IGF-1
- Tx → Surgical resection vs. somatostatin analogue

Thyroid disorder

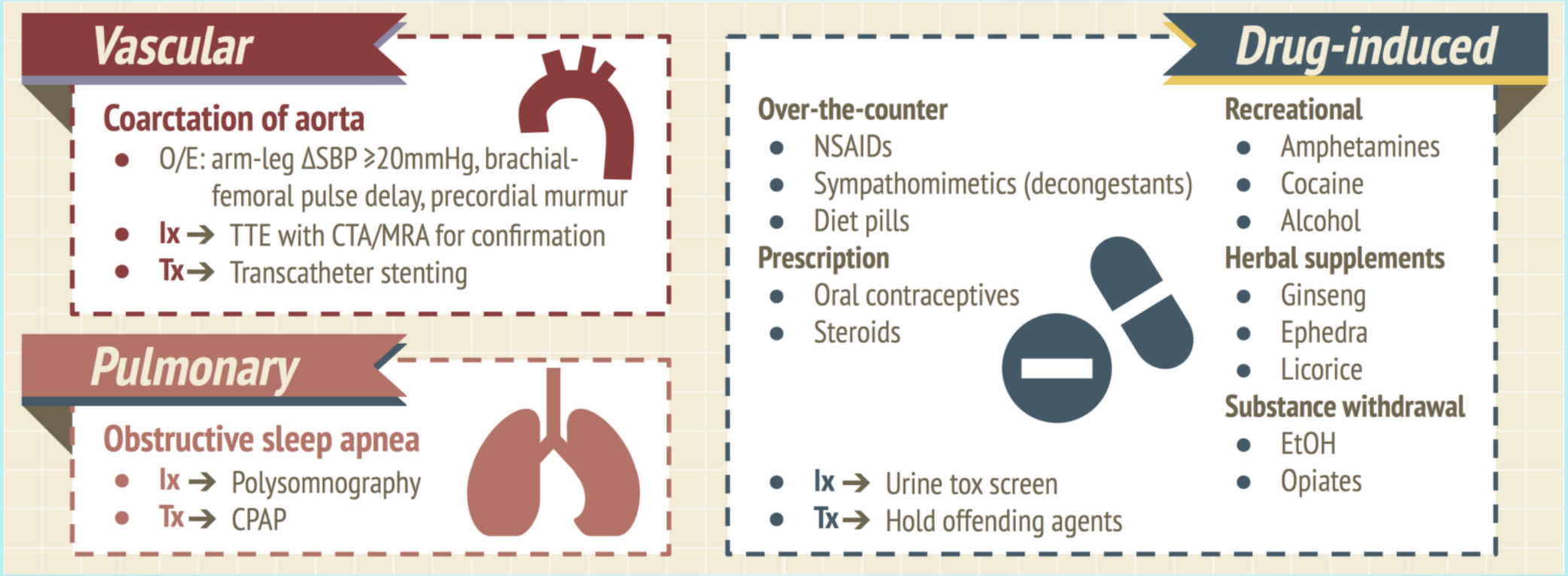
- Ix → TSH
- Tx → Treat hyper/hypothyroidism

Hyperparathyroidism

- Ix → PTH, serum Ca^{2+}
- Tx → Conservative measures vs. parathyroidectomy

The Intern at Work. https://www.theinternatwork.com/infographics-2/2020/9/20/resistant-hypertension

2ndary Causes Cont'd...



The Intern at Work. https://www.theinternatwork.com/infographics-2/2020/9/20/resistant-hypertension

Case Example

- 71F with HTN since 2009.
- PMHx: Hypercholesterolemia, DDD, Restless Legs Sx, White Coat Effect.
- BP control had been avg <140/<80 over the past 15y.
- Rx: Irbesartan 300mg, Amlodipine 10mg, hydrochlorothiazide 25mg.
    - Presents to office Jan 2024 with home BP readings recently ~160s/90s.

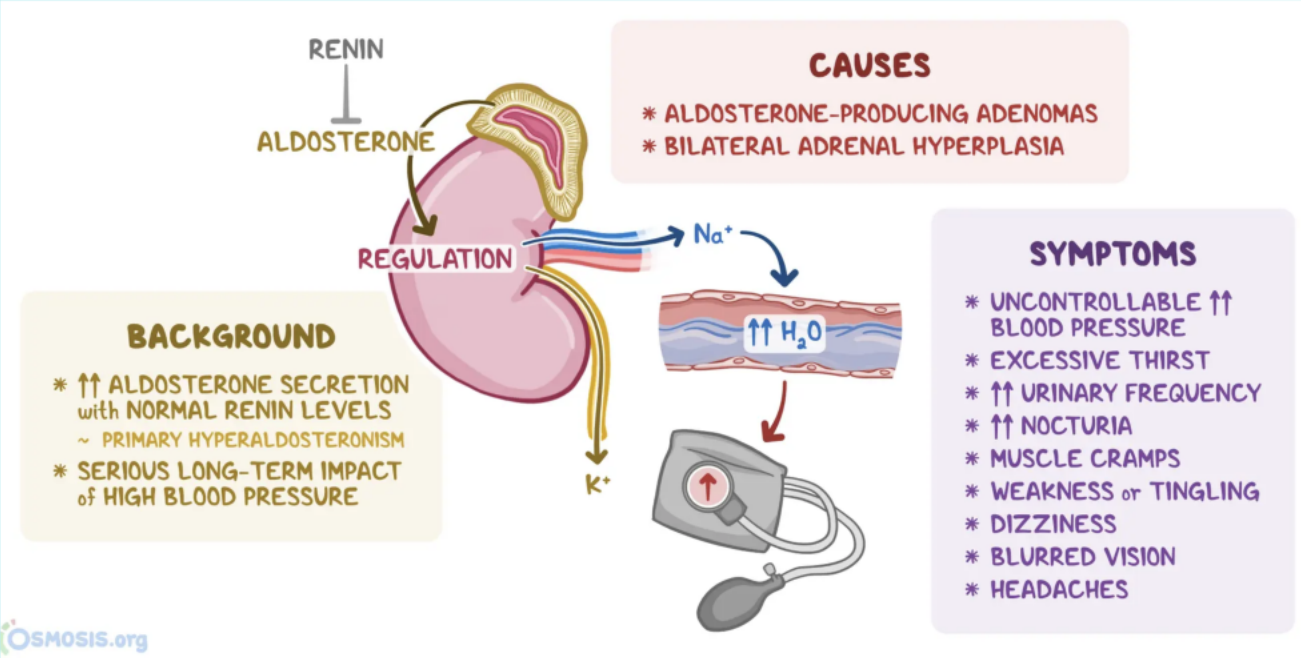
What do you want to know?

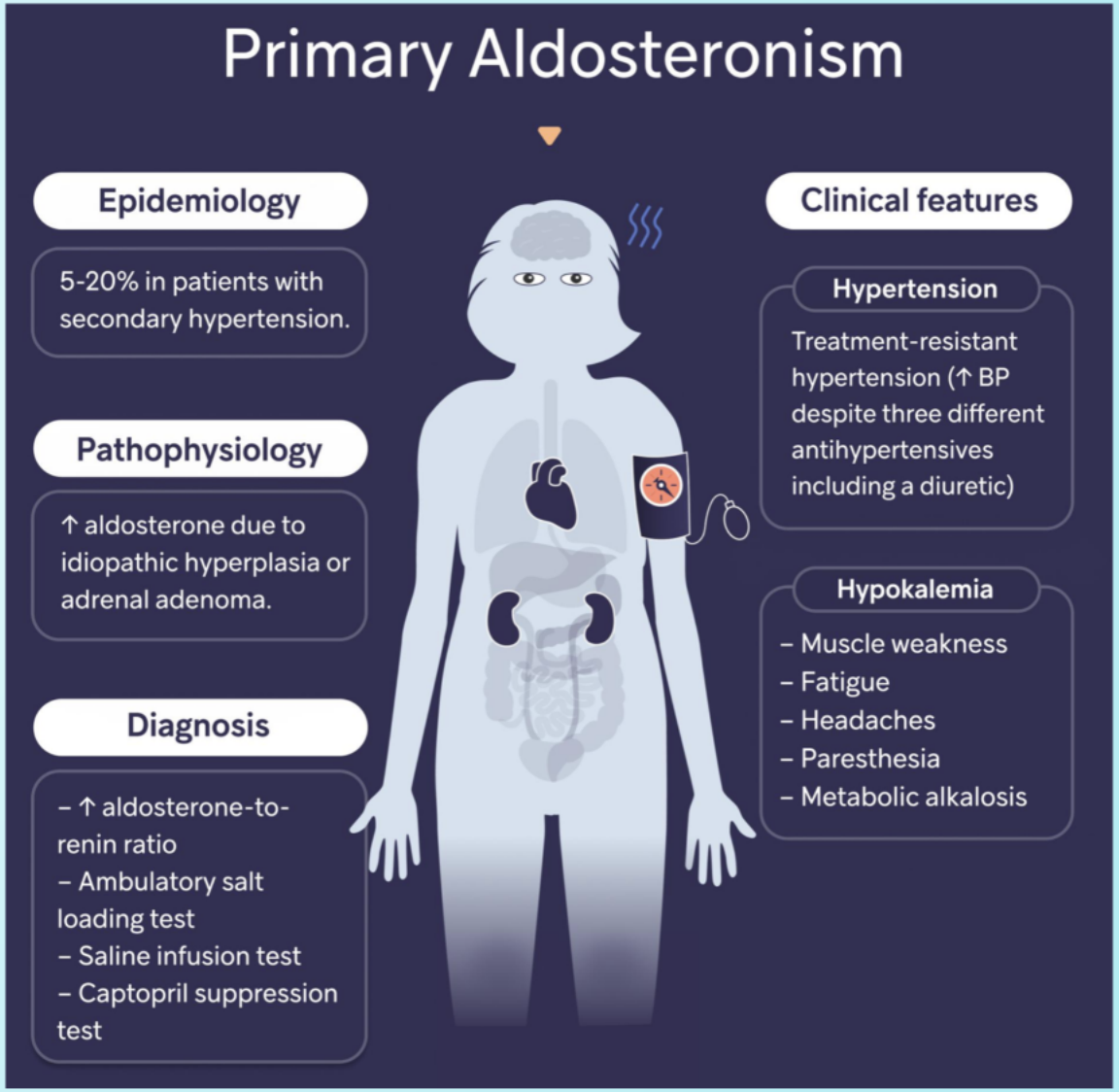
Case Example

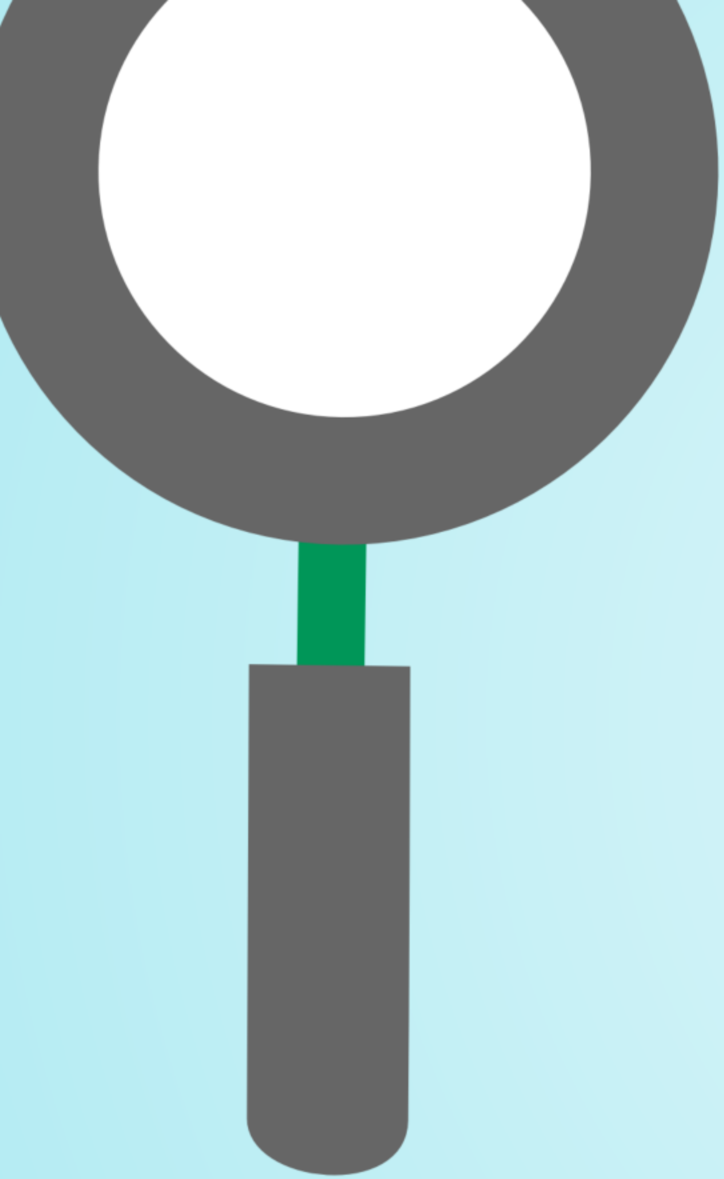
- 71F with HTN since 2009.
- PMHx: Hypercholesterolemia, DDD, Restless Legs Sx, White Coat Effect.
- BP control had been avg <140/<80 over the past 15y.
- Rx: Irbesartan 300mg, Amlodipine 10mg, hydrochlorothiazide 25mg.
    - Presents to office Jan 2024 with home BP readings recently ~160s/90s.

- Reports compliance with therapy, no NSAIDs, EtOH, Drug use
- Denies flushing/tachycardia/panic attacks/recurrent headaches
- No snoring/apnea, but poor sleep with restless legs.
- Reports: “daughter has been diagnosed with ?Conn syndrome”

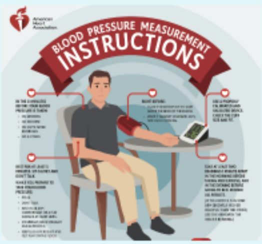
Primary Hyperaldosteronism & Conn's Syndrome

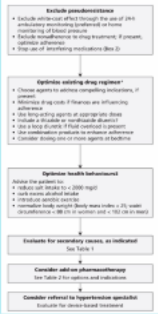






Initial Assessment





Diagnostic Approach

Investigations

- Cr, eGFR, ACR, Urinalysis, Aldosterone:Renin Activity Ratio (ARR) (before 10am, seated), TSH, Ca++
- Sleep Study
- Renal artery duplex or CTA

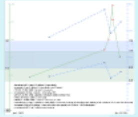
Consider:

- 24h urinary cortisol or low dose (1mg) dexamethasone suppression test (DST)
- Salt (oral) or Saline (IV) suppression test
- Plasma metanephrines & catecholamines (if s/sx of Pheochromocytoma)

Our Case - 1st Steps in Primary Care

O/E: Office BP Tru: 190/90 HR: 72
No features of Cushings or Hyperthyroidism.
Non-obese.
Normal neck circumference.

Care through Winter



- BPs @ home 181/94 --> terazocin added & titrated
- Nephrology requests 8AM ARR, defers pheo Ix
  - Recommends adding hydralazine (not tolerated), so Spironolactone.
- Feb US = Normal kidneys & adrenals. Rpt Ax: BP: 150/94. Cr 120. eGFR 39, ACR 1.6 Aldo 862 (N: 118-946). Renin 383.8 (H)
- Mar: Nephro suggest Adrenal CT = "mild thickening of b/l adrenal glands, w/o discrete mass." BP: 142/52. Cr 178. eGFR 24. ACR 4.4. Renin >1000.
  - PCP letter to Nephro: ?RAS given Renin. Concern about interp of ARR while on ARB. Response: Stick w/ Endocrine pathway re: PA/Conn's. will see in 2-3mo
  - Endocrine referral redirected/rejected x 3. Finally booked for June.

Initial Assessment

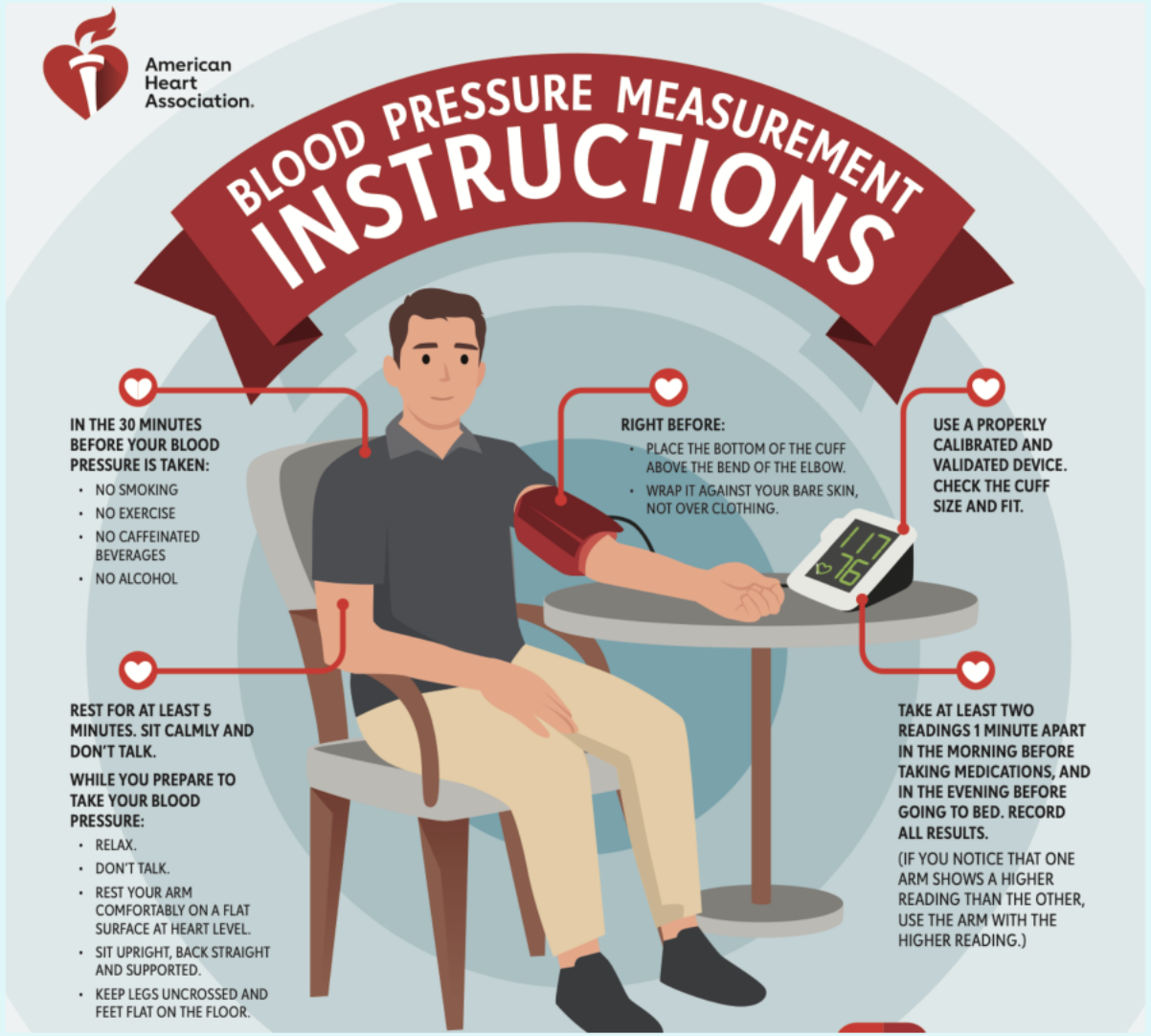


Table 2 Potential SBP Impacts for the Recommended Steps in Patient Preparation

Preparatory Step	Potential Impact on SBP
Empty bladder if needed	10 mm Hg
Place cuff on bare arm	5-50 mm Hg
Select proper cuff size	2-10 mm Hg
Arm supported with cuff at heart level	10 mm Hg
Back and feet supported	6 mm Hg
Legs uncrossed	2-8 mm Hg
Quiet space	10 mm Hg

Cluett, Jennifer L. et al. Evaluation and Management of Resistant Hypertension: Core Curriculum. American Journal of Kidney Diseases, 2024

Exclude pseudoresistance

- Exclude white-coat effect through the use of 24-h ambulatory monitoring (preferred) or home monitoring of blood pressure
- Exclude nonadherence to drug treatment; if present, optimize adherence
- Stop use of interfering medications (Box 2)

↓

Optimize existing drug regimen*

- Choose agents to address compelling indications, if present
- Minimize drug costs if finances are influencing adherence
- Use long-acting agents at appropriate doses
- Include a thiazide or nonthiazide diuretic†
- Use a loop diuretic if fluid overload is present
- Use combination products to enhance adherence
- Consider dosing one or more agents at bedtime

↓

Optimize health behaviours‡

Advise the patient to:

- reduce salt intake to < 2000 mg/d
- curb excess alcohol intake
- introduce aerobic exercise
- normalize body weight (body mass index < 25; waist circumference < 88 cm in women and < 102 cm in men)

↓

Evaluate for secondary causes, as indicated

See Table 1

↓

Consider add-on pharmacotherapy

See Table 2 for options and indications

↓

Consider referral to hypertension specialist

Evaluate for device-based treatment

Raj S. Padwal, Simon Rabkin and Nadia Khan
CMAJ December 09, 2014 186 (18) E689-E697

Exclude pseudoresistance

- Exclude white-coat effect through the use of 24-h ambulatory monitoring (preferred) or home monitoring of blood pressure
- Exclude nonadherence to drug treatment; if present, optimize adherence
- Stop use of interfering medications (Box 2)

↓

Optimize existing drug regimen*

- Choose agents to address compelling indications, if present
- Minimize drug costs if finances are influencing adherence
- Use long-acting agents at appropriate doses
- Include a thiazide or nonthiazide diuretic†
- Use a loop diuretic if fluid overload is present
- Use combination products to enhance adherence
- Consider dosing one or more agents at bedtime

↓

Optimize health behaviours‡

Advise the patient to:

- reduce salt intake to < 2000 mg/d
- curb excess alcohol intake
- introduce aerobic exercise
- normalize body weight (body mass index < 25; waist circumference < 88 cm in women and < 102 cm in men)

↓

Evaluate for secondary causes, as indicated

See Table 1

↓

Consider add-on pharmacotherapy

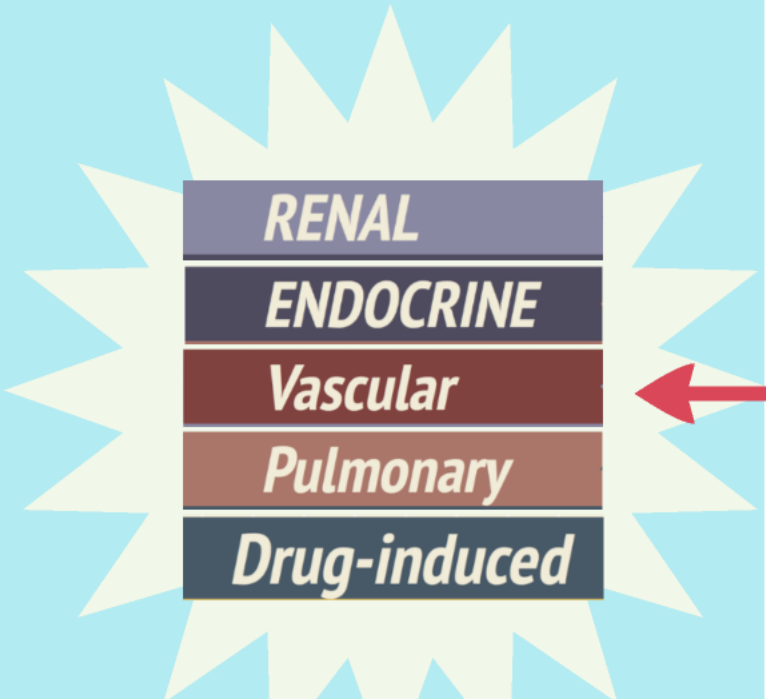
See Table 2 for options and indications

↓

Consider referral to hypertension specialist

Evaluate for device-based treatment

Raj S. Padwal, Simon Rabkin and Nadia Khan
CMAJ December 09, 2014 186 (18) E689-E697



Investigations

- Cr, eGFR, ACR, Urinalysis, Aldosterone:Renin Activity Ratio (ARR) (before 10am, seated), TSH, Ca++
- Sleep Study
- Renal artery duplex or CTA

Consider:

- 24h urinary cortisol or low dose (1mg) dexamethasone suppression test (DST)
- Salt (oral) or Saline (IV) suppression test
- Plasma metanephrines & catecholamines (if s/sx of Pheochromocytoma)

Our Case - 1st Steps in Primary Care

O/E: Office BP Tru: 190/90 HR: 72

No features of Cushings or Hyperthyroidism.

Non-obese.

Normal neck circumference.

Our Case - 1st Steps in Primary Care

O/E: Office BP Tru: 190/90 HR: 72
No features of Cushings or Hyperthyroidism.
Non-obese.
Normal neck circumference.

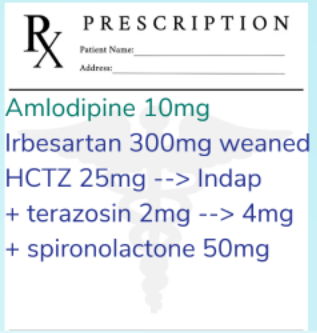
What would you recommend as initial steps?

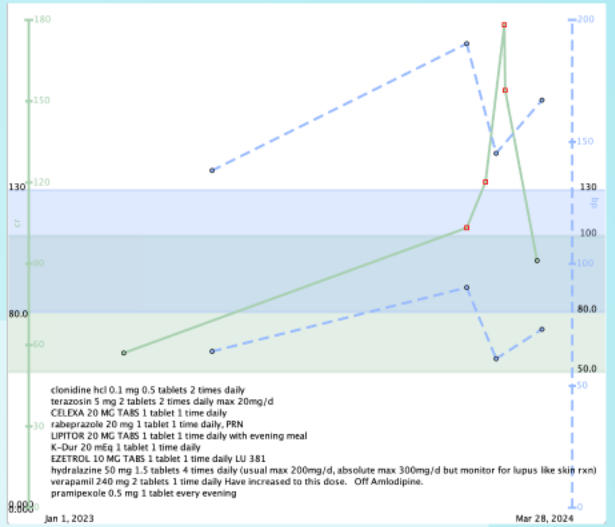
Our Case - 1st Steps in Primary Care

O/E: Office BP Tru: 190/90 HR: 72
No features of Cushings or Hyperthyroidism.
Non-obese.
Normal neck circumference.

1. Pt to monitor at home, if consistently >160/100 to call in & start hydralazine or terazosin.
2. Labs: Cr 103 (baseline <65), eGFR 47 (baseline >90). TSH nwl.
3. Refer for Renal US "w/ dopplers & assess adrenals"
4. Refer to Nephro
5. Refer for sleep study

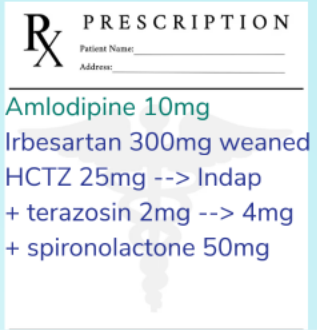
Care through Winter

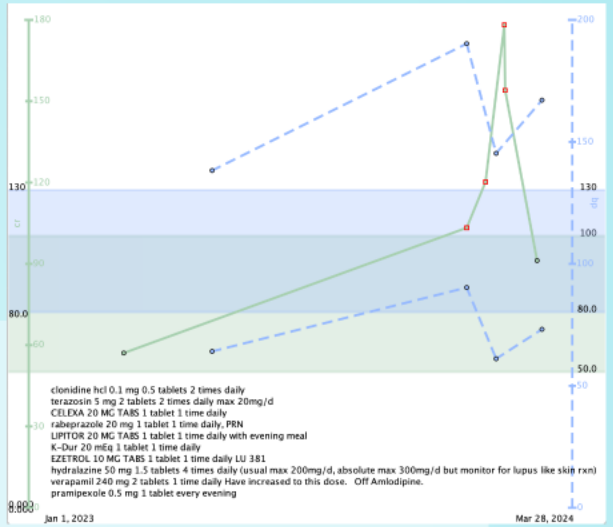




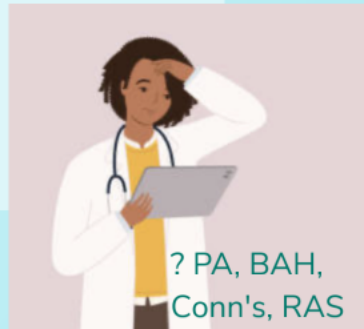
- BPs @ home 181/94 --> terazocin added & titrated
- Nephrology requests 8AM ARR, defers pheo Ix
  - Recommends adding hydralazine (not tolerated), so Spironolactone.
- Feb US = Normal kidneys & adrenals. Rpt Ax: BP: 150/94. Cr 120. eGFR 39, ACR 1.6 Aldo 862 (N: 118-946), Renin 383.8 (H)
- Mar: Nephro suggest Adrenal CT = "mild thickening of b/l adrenal glands, w/o discrete mass." BP: 142/52. Cr 178. eGFR 24. ACR 4.4. Renin >1000.
  - PCP letter to Nephro: ?RAS given Renin. Concern about interp of ARR while on ARB. Response: Stick w/ Endocrine pathway re: PA/Conn's. will see in 2-3mo
  - Endocrine referral redirected/rejected x 3. Finally booked for June.

Care through Winter



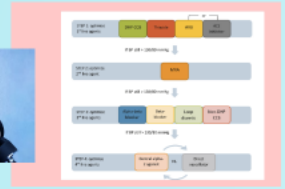


- BPs @ home 181/94 --> terazocin added & titrated
- Nephrology requests 8AM ARR, defers pheo Ix
  - Recommends adding hydralazine (not tolerated), so Spironolactone.
- Feb US = Normal kidneys & adrenals. Rpt Ax: BP: 150/94. Cr 120. eGFR 39, ACR 1.6 Aldo 862 (N: 118-946), Renin 383.8 (H)
- Mar: Nephro suggest Adrenal CT = "mild thickening of b/l adrenal glands, w/o discrete mass." BP: 142/52. Cr 178. eGFR 24. ACR 4.4. Renin >1000.
  - PCP letter to Nephro: ?RAS given Renin. Concern about interp of ARR while on ARB. Response: Stick w/ Endocrine pathway re: PA/Conn's. will see in 2-3mo
  - Endocrine referral redirected/rejected x 3. Finally booked for June.



Medication Adherence & Lifestyle Factors

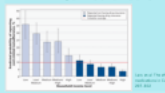
Pharmacotherapy Approaches (ACD Method)



Management Strategies

Medication Adherance

- >50% not as prescribed
- 9.6% Cdns cost-related nonadherance (3.6-35%)
  - Poor health OR 2.64
  - Lower income OR 3.29
  - w/o insurance OR 4.52



When to Involve Specialist Care

- secondary causes of hypertension
- patients exhibit resistance despite optimal pharmacotherapy and adherence.
- patients experiencing severe hypertension symptoms
- chal lenging cases
- those requiring advanced diagnostics

Care through Spring/Summer

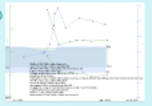
- Apr Cr 91 eGFR 55, ACR 3.8 Renin 177 (2.8-46). SBPs pushing 160 - plan to titrate terzosin to target 130.
- May: Nephro - med adjustments. Aldo 2040 (<946), Renin 316.
  - Expands Ix: AM cortisol, Ucatecholamines, Umetanephrines wnl.
- June: Endo - plans Dex suppression test (DST), salt suppression test (SST)+/- adrenal vein sampling. "cannot interpret Aldosterone given interference from her Rx" Plan: Off spirono x 8wks for ARR & SST. Then plan for DST. Then plan for adrenal vein sampling @ Sunnybrook.
- Jul: pt gradually self tapers spironlactone.
- Aug: I encourage ongoing monitored taper. Then letter from Nephro "why was her spirono stopped by PCP?!"

Care through Fall

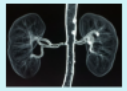
- Sep: Cr 87. ACR 3.8. Lytes, AM cortisol, ACTH N. Aldo, Renin, ARR 7 (N). Endo: "indapamide & amlodipine can cause FN w/ ARR. Rec further increase hydralazine to 75mg QID. Cont on Teraz 10 bid ; Amlod 10 qam + 5 qhs"
- Oct
  - Sleep study: Severe PMLS and mild OSA - CPAP titration initiated.
  - Nephro: BP 165/62. "Normal adrenal testing despite being off all RAS blockade" - will defer to Endo. Start on Clonidine 0.5 bid. SloK for mild hypokalemia.
  - Endo: Rec wean clonidine (causes FPs ARR). Restates "no conclusion possible d/t Indap & Amlod... not sure we can safely control BP in order to pursue testing. Recommend Surgical Management... Pt wishes to speak w/ her Family MD"
  - PCP visit - pt quite frustrated - back and forth b/w 2 specialists, inconsistent msgs
    - PCP: "liase with specialists to try to facilitate coordinated plan"

A Whole Year of RH...

- Jan: admitted to hosp x 2. Peak BP 251/110. Cr 100-160
  - CTA: "severe ostial stenosis of the superior Rt renal artery, mild ostial stenoses of the Rt inferior renal artery & the single Lt renal artery... asymmetric hypoattenuation of the Rt kidney... ddx includes hypoenhancement d/t hypoperfusion related to the superior right renal artery ostial stenosis"



- Feb: Referral to Vascular. Unsuccessful IR cannalization w/ very little flow noted.

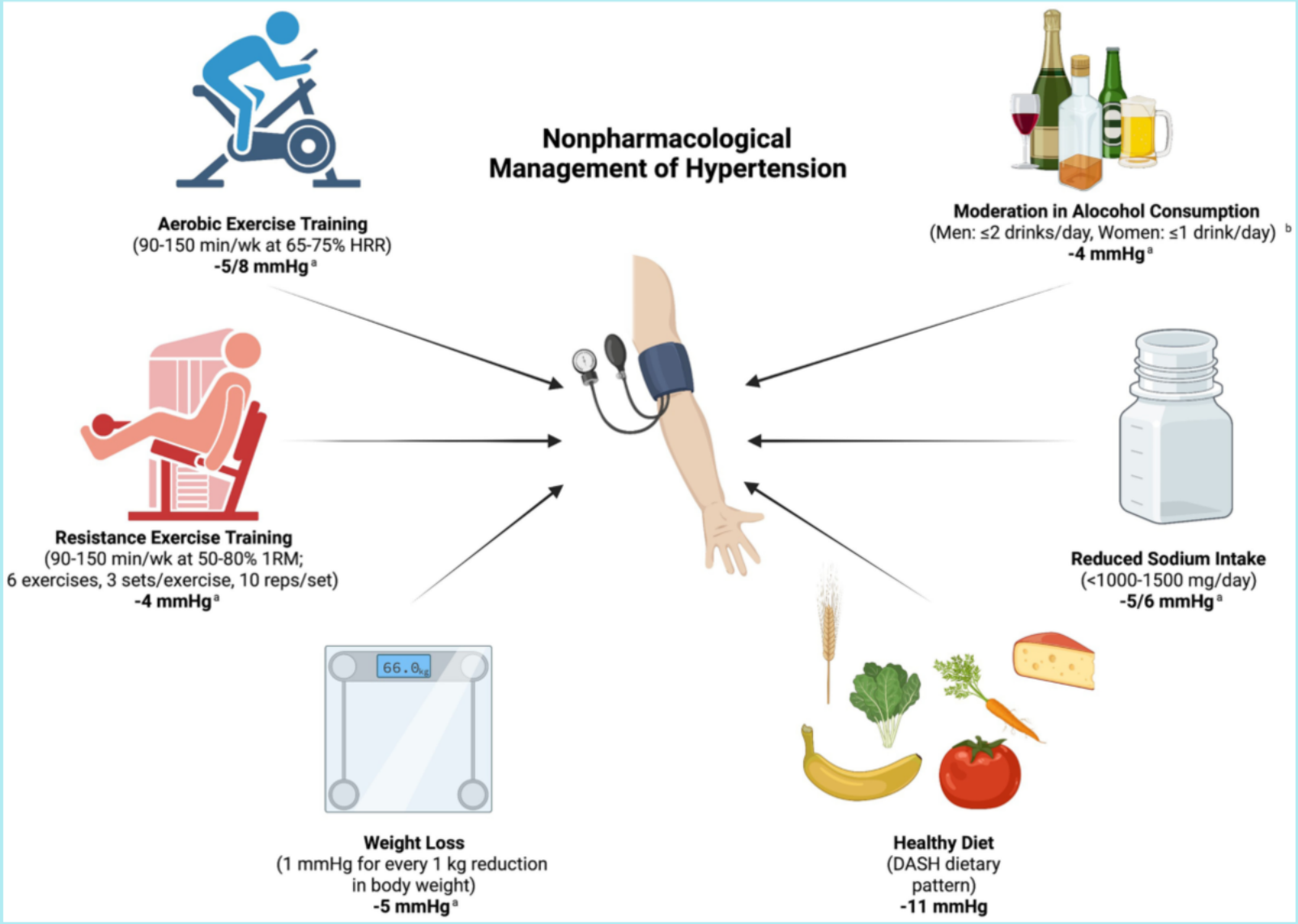


- Mar & ongoing - continued efforts to control BP w/ Rx

Winter approaches...

- PCP + Endo Plan: Spirono off x6-8w; amlodipine off x2wk; Clonidine off x2w. Then repeat ARR & do Salt suppression test
- Nov: Successful gradual wean. Introduce verapamil & pramipizole. SST arranged: 0h: Renin 85 upright (<46). Aldo 948 (<946). Cortisol N. 4h sample: "lost".
- Dec: ? Radiology - ? Renal arteries seen. "++ atherosclerotic plaque in Aorta & along the origin of the renal arteries - "would not be surprised if an element of stenosis at renal ostia". Also kidneys were less enhanced by the contrast than expected, also supporting RAS." Endo: Reninoma vs RAS. Plan: CTA + renovascular sampling.

Medication Adherence & Lifestyle Factors

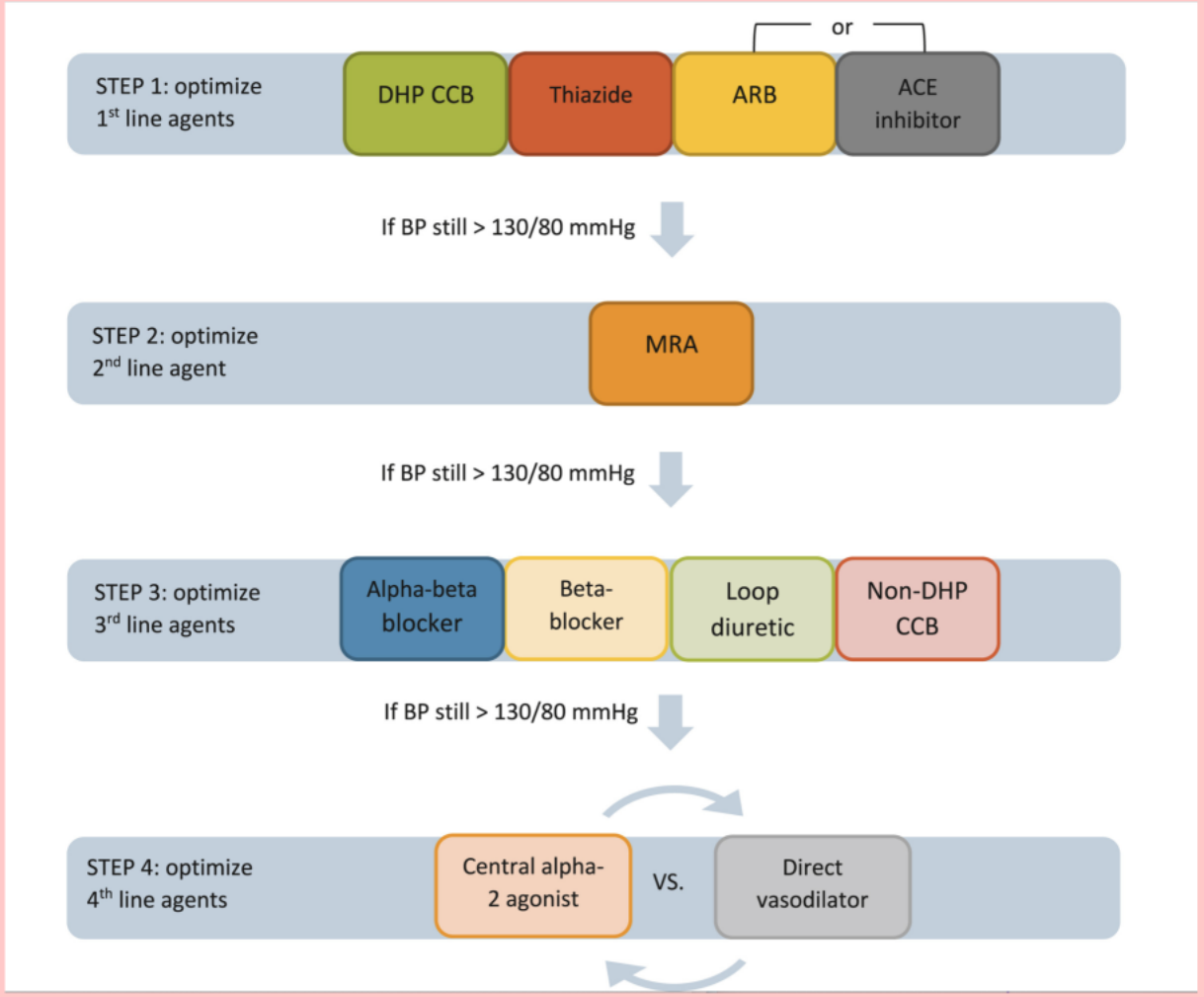


Pharmacotherapy Approaches (ACD Method)

Antihypertensive Drug Classes

	Classes	Drug Names	Examples	Mechanism of Action	Main Effect on BP
A	ACE Inhibitors	"pril"	Lisinopril Enalapril	Inhibit ACE	↓ SVR, SV
A	ARBs	"sartan"	Losartan Valsartan	Block Angiotensin II Receptors	↓ SVR, SV
A	Alpha Blockers	"osin"	Doxazosin Terazosin	Block Alpha Receptors	↓ SVR
B	Beta Blockers	"lol"	Metoprolol Labetalol	Block Beta Receptors	↓ HR, SV
C	Calcium Channel Blockers (CCBs)	"dipine"	Amlodipine Nicardipine	Block Calcium Channels	↓ SVR
D	Diuretics	"ide"	Furosemide Hydrochlorothiazide	Facilitate Diuresis	↓ SV

**Alpha blockers refer to selective alpha-1 blockers, and calcium channel blockers refer to dihydropyridines



Cluett, Jennifer L. et al. Evaluation and Management of Resistant Hypertension: Core Curriculum. American Journal of Kidney Diseases, 2024

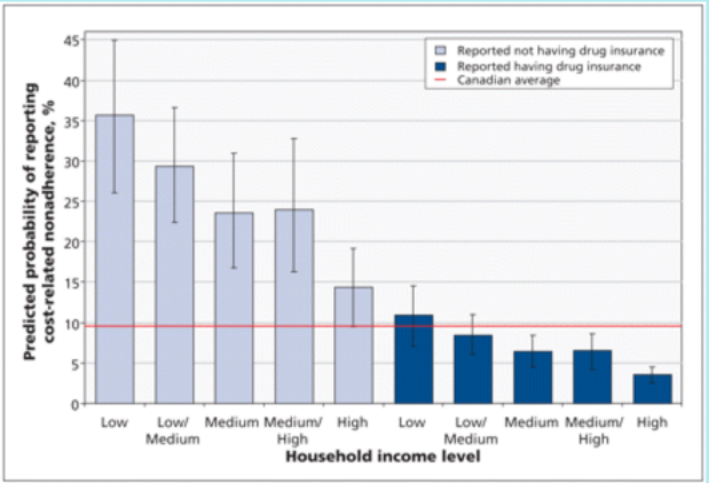
Medications to be considered for add-on therapy to standard base three-drug regimen* for the treatment of resistant hypertension

Drug class; agent	Typical dosage†	Half-life†	Comments
Antivolume (most useful if plasma renin activity < 0.65 ng/mL per hour)[28]			
Mineralocorticoid-receptor antagonist			
Eplerenone	50–100 mg once daily or in two divided doses	4–6 h	Reduced risk of cardiovascular-related hospital admission (RR 0.62, 95% CI 0.52–0.74) and total mortality (RR 0.79, 95% CI 0.66–0.95) among patients with heart failure and reduced ejection fraction (see Table 3).[29] Patients need to be monitored for hyperkalemia and prerenal failure. Spironolactone may cause painful gynecomastia, impotence, decreased libido or irregular menses, collectively occurring in 5%–30% of patients.
Spironolactone	25–50 mg once daily for primary resistant hypertension; 25–200 mg once daily for primary aldosteronism	80 min; 10–20 h for active metabolites	
Epithelial sodium-channel inhibitor			
Amiloride	5–10 mg once daily or in two divided doses	6–9 h	Most commonly used as second- or third-line treatment for primary aldosteronism. Patients need to be monitored for hyperkalemia and renal failure.
Loop diuretic			
Furosemide	40–120 mg daily in two or three divided doses	0.5–2 h	Useful in patients with fluid overload states such as renal or heart failure. Patients need to be monitored for electrolyte disturbances, ototoxicity and renal failure.
α-1 Adrenergic antagonist			
Doxazosin	2–16 mg once daily	22 h	Dose at bedtime. Useful if benign prostatic hypertrophy is present. May cause dizziness (5%–20%), orthostasis (2%), sedation (5%) or fluid retention (7%). Dizziness and orthostasis may be the most prominent adverse effects with the first dose.
Terazosin	1–20 mg once daily	12 h	
Anti-renin (most useful if plasma renin activity ≥ 0.65 ng/mL per hour)[28]			
β-Adrenergic antagonist‡			
Atenolol	25–100 mg once daily	6–7 h	See Table 3 for compelling indications. May cause bradycardia (3%), heart block, weight gain (< 1%) or diabetes (1%–3%). May aggravate acute heart failure, asthma and severe peripheral vascular disease. Pharmacologic differences exist that are of uncertain clinical significance: labetolol also blocks α-1 and β-2 receptors, and nebivolol has a vasodilatory, nitric oxide–potentiating action. Negative chronotropic action is synergistic with non-dihydropyridine calcium-channel blockers. Tachycardia may occur with abrupt withdrawal.
Bisoprolol	2.5–10 mg daily	9–12 h	
Labetolol	100–400 mg twice daily	6–8 h	
Metoprolol	50–200 mg daily in two divided doses	3–9 h	
Nebivolol	5–20 mg once daily	10–12 h	
Direct renin inhibitor			
Aliskiren	150–300 mg once daily	16–32 h	Patients need to be monitored for hyperkalemia. Do not use in combination with another renin–angiotensin system blocking agent in patients with diabetes because the risk of cardiovascular events and hyperkalemia is increased.[40]
Centrally acting α-2 agonist			
Clonidine	0.1–0.4 mg twice daily	12–16 h	May cause sedation (10%–30%), dry mouth and eyes (30%) or bradycardia (0.3%). Rebound hypertension occurs with abrupt discontinuation. Methyldopa can be used in pregnant patients, but it has mild efficacy and, in rare circumstances, can cause a lupus-like syndrome.
Methyldopa	250–1000 mg daily in two divided doses	2 h	
Vasodilator (neither antivolume nor anti-renin)			
Hydralazine	25–100 mg daily in two divided doses	2–8 h	Indicated for use in black patients with systolic heart failure (in combination with nitrates). Commonly used in pregnant patients because its safety has been established. May exacerbate angina and cause palpitations (5%), fluid retention (5%) or drug-induced lupus (5%–20%).
Minoxidil	2.5–80 mg once daily or in two divided doses	3–4 h	May cause tachycardia (80%), fluid retention (80%), hypertrichosis (80%), pericarditis or pericardial effusion (3%).

Raj S. Padwal, Simon Rabkin and Nadia Khan
CMAJ December 09, 2014 186 (18) E689-E697

Medication Adherance

- >50% not as prescribed
- 9.6% Cdns cost-related nonadherance (3.6-35%)
  - Poor health OR 2.64
  - Lower income OR 3.29
  - w/o insurance OR 4.52



Law, et al. The effect of cost on adherence to prescription medications in Canada. CMAJ February 21, 2012 184 (3) 297-302

Table 4 Strategies to Minimize or Address Common Barriers to Medication Adherence

Barriers to Medication Adherence	Strategies to Minimize/Address
Cost	•Choose low-cost generic medications where feasible•Reduce copays with combination tablets (if generic)
Complexity of regimen/too many pills	•Convert to once daily formulations where available•Convert to combination tablets to minimize pill burden•Use blister packs/pill boxes•Minimize trips to pharmacy for refills•Use 90-day refills instead of 30-day refills•Ensure all medications (not just BP medications) are eligible to be refilled at the same time•Use mail order if available/cost effective
Adverse effects of medications	•Use lowest effective doses of BP medications to minimize side effects•ARB/ACE inhibitors can counteract edema from CCBs•ARB/ACE inhibitors can counteract hypokalemia from thiazides
Patient motivation/insight	•Multidisciplinary team-based care•Patient education and motivational interviewing•Text messaging reminders•Home BP monitoring with ongoing feedback through electronic health record and ability to modify medications and doses

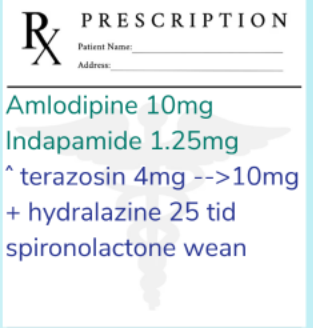
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker.

Cluett, Jennifer L. et al. Evaluation and Management of Resistant Hypertension: Core Curriculum. American Journal of Kidney Diseases, 2024; 84:3, 374 - 387

When to Involve Specialist Care

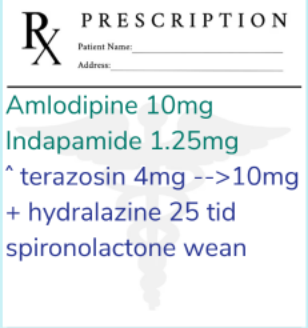
- secondary causes of hypertension
- patients exhibit resistance despite optimal pharmacotherapy and adherence.
- patients experiencing severe hypertension symptoms
- challenging cases
- those requiring advanced diagnostics

Care through Spring/Summer

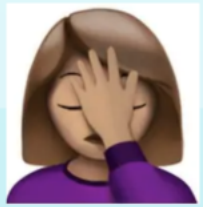


- Apr Cr 91 eGFR 55, ACR 3.8 Renin 177 (2.8-46). SBPs pushing 160 - plan to titrate terzosin to target 130.
- May: Nephro - med adjustments. Aldo 2040 (<946), Renin 316.
  - Expands Ix: AM cortisol, Ucatecholamines, Umetanephrines wnl.
- June: Endo - plans Dex suppression test (DST), salt suppression test (SST)+/- adrenal vein sampling. “cannot interpret Aldosterone given interference from her Rx" Plan: Off spirono x 8wks for ARR & SST. Then plan for DST. Then plan for adrenal vein sampling @ Sunnybrook.
- Jul: pt gradually self tapers spironlactone.
- Aug: I encourage ongoing monitored taper. Then letter from Nephro "why was her spirono stopped by PCP?"

Care through Spring/Summer



- Apr Cr 91 eGFR 55, ACR 3.8 Renin 177 (2.8-46). SBPs pushing 160 - plan to titrate terzosin to target 130.
- May: Nephro - med adjustments. Aldo 2040 (<946), Renin 316.
  - Expands Ix: AM cortisol, Ucatecholamines, Umetanephrines wnl.
- June: Endo - plans Dex suppression test (DST), salt suppression test (SST)+/- adrenal vein sampling. “cannot interpret Aldosterone given interference from her Rx" Plan: Off spirono x 8wks for ARR & SST. Then plan for DST. Then plan for adrenal vein sampling @ Sunnybrook.
- Jul: pt gradually self tapers spironlactone.
- Aug: I encourage ongoing monitored taper. Then letter from Nephro "why was her spirono stopped by PCP?"



Care through Fall

RX PRESCRIPTION
Patient Name:
Address:

^terazosin 20mg
^hydralazine 75mg qid
Amlodipine weaned
clonidine weaned
Indapamide weaned
+ verapamil 180-->240

- Sep: Cr 87. ACR 3.8. Lytes, AM cortisol, ACTH N. Aldo, Renin, ARR 7 (N).
  Endo: “indapamide & amlodipine can cause FN w/ ARR. Rec further increase hydralazine to 75mg QID. Cont on Teraz 10 bid ; Amlod 10 qam + 5 qho"
- Oct:
  - Sleep study: Severe PMLS and mild OSA - CPAP titration initiated.
  - Nephro: BP 165/62. “Normal adrenal testing despite being off all RAS blockade” - will defer to Endo. Start on Clonidine 0.5 bid. SloK for mild hypokalemia.
  - Endo: Rec wean clonidine (causes FPs ARR). Restates "no conclusion possible d/t Indap & Amlod... not sure we can safely control BP in order to pursue testing. Recommend Surgical Management... Pt wishes to speak w/ her Family MD”
  - PCP visit - pt quite frustrated - back and forth b/w 2 specialists, inconsistent msgs
    - PCP: "liase with specialists to try to facilitate coordinated plan"

Table 5 Effect of Antihypertensive Medication Classes on the Plasma Aldosterone Concentration to Plasma Renin Activity Ratio

Medication Class	Effect on PAC	Effect on PRA	Overall Effect on ARR	Interpretation of ARR if Medication Continued During Testing
β_1-Receptor antagonists	↓	↓↓	↑	Low PAC (<5 ng/dL) argues against PA even if renin activity is suppressed.
Central α_2-agonists	↓	↓↓	↑	
ACE inhibitors	↓	↑ ↔	↓	Low renin activity would be highly suggestive of PA. High renin activity would not rule out PA.
ARBs	↓	↑ ↔	↓	
Diuretics (loop and thiazide)	↔ ↑	↑↑	↓	Similar to ACE inhibitors/ARBs
MRA	↔ ↑	↑↑	↓	If renin not suppressed, MRA should be held for testing. Diagnosis of PA can be made if PAC is high and PRC is suppressed.
DHP calcium channel blockers	↔ ↓	↔ ↑	↓	Data are mixed, but may produce excess false-negative results.
α_1-Receptor antagonists	↔	↔	↔	Does not interfere with testing.
Direct arterial vasodilators	↔	↔	↔	
Non-DHP calcium channel blockers	↔	↔	↔	

Based on information in Jędrusik P, Symonides B, Lewandowski J, Gaciong Z. The effect of antihypertensive medications on testing for primary aldosteronism. *Front. Pharmacol.* 2021;12:684111. doi:10.3389/fphar.2021.684111. Abbreviations: ACE, angiotensin converting enzyme; ARR; aldosterone to renin ratio; ARB, angiotensin receptor blockers; DHP, dihydropyridine; MRA, mineralocorticoid receptor antagonists; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC, plasma renin concentration.

Jędrusik et al. The effect of antihypertensive medications on testing primary aldosteronism. Front. Pharmacol. 2021

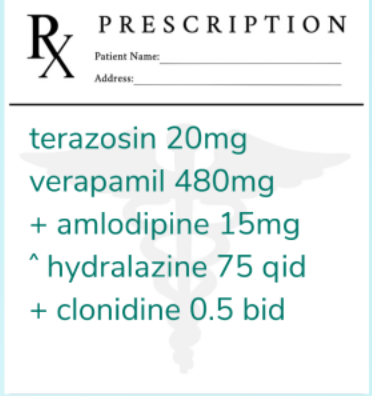
Table 5 Effect of Antihypertensive Medication Classes on the Plasma Aldosterone Concentration to Plasma Renin Activity Ratio

Medication Class	Effect on PAC	Effect on PRA	Overall Effect on ARR	Interpretation of ARR if Medication Continued During Testing
β_1-Receptor antagonists	↓	↓↓	↑	Low PAC (<5 ng/dL) argues against PA even if renin activity is suppressed.
Central α_2-agonists	↓	↓↓	↑	
ACE inhibitors	↓	↑ ↔	↓	Low renin activity would be highly suggestive of PA. High renin activity would not rule out PA.
ARBs	↓	↑ ↔	↓	
Diuretics (loop and thiazide)	↔ ↑	↑↑	↓	Similar to ACE inhibitors/ARBs
MRA	↔ ↑	↑↑	↓	If renin not suppressed, MRA should be held for testing. Diagnosis of PA can be made if PAC is high and PRC is suppressed.
DHP calcium channel blockers	↔ ↓	↔ ↑	↓	Data are mixed, but may produce excess false-negative results.
α_1-Receptor antagonists	↔	↔	↔	Does not interfere with testing.
Direct arterial vasodilators	↔	↔	↔	
Non-DHP calcium channel blockers	↔	↔	↔	

Based on information in Jędrusik P, Symonides B, Lewandowski J, Gaciong Z. The effect of antihypertensive medications on testing for primary aldosteronism. *Front. Pharmacol.* 2021;12:684111. doi:10.3389/fphar.2021.684111. Abbreviations: ACE, angiotensin converting enzyme; ARR; aldosterone to renin ratio; ARB, angiotensin receptor blockers; DHP, dihydropyridine; MRA, mineralocorticoid receptor antagonists; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC, plasma renin concentration.

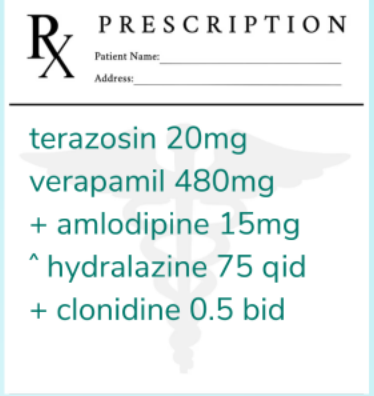
Jędrusik et al. The effect of antihypertensive medications on testing primary aldosteronism. Front. Pharmacol. 2021

Winter approaches...



- PCP + Endo Plan: Spirono off x6-8w; amlodipine off x2wk; Clonidine off x2w. Then repeat ARR & do Salt suppression test
- Nov: Successful gradual wean. Introduce verapamil & pramipizole. SST arranged: 0h: Renin 85 upright (<46). Aldo 948 (<946). Cortisol N. 4h sample: "lost".
- Dec: ? Radiology - ? Renal arteries seen. "++ atherosclerotic plaque in Aorta & along the origin of the renal arteries - “would not be surprised if an element of stenosis at renal ostia”. Also kidneys were less enhanced by the contrast than expected, also supporting RAS." Endo: Reninoma vs RAS. Plan: CTA + renovascular sampling.

Winter approaches...



- PCP + Endo Plan: Spirono off x6-8w; amlodipine off x2wk; Clonidine off x2w. Then repeat ARR & do Salt suppression test
- Nov: Successful gradual wean. Introduce verapamil & pramipizole. SST arranged: 0h: Renin 85 upright (<46). Aldo 948 (<946). Cortisol N. 4h sample: "lost".
- Dec: ? Radiology - ? Renal arteries seen. "++ atherosclerotic plaque in Aorta & along the origin of the renal arteries - “would not be surprised if an element of stenosis at renal ostia”. Also kidneys were less enhanced by the contrast than expected, also supporting RAS." Endo: Reninoma vs RAS. Plan: CTA + renovascular sampling.

A Whole Year of RH…

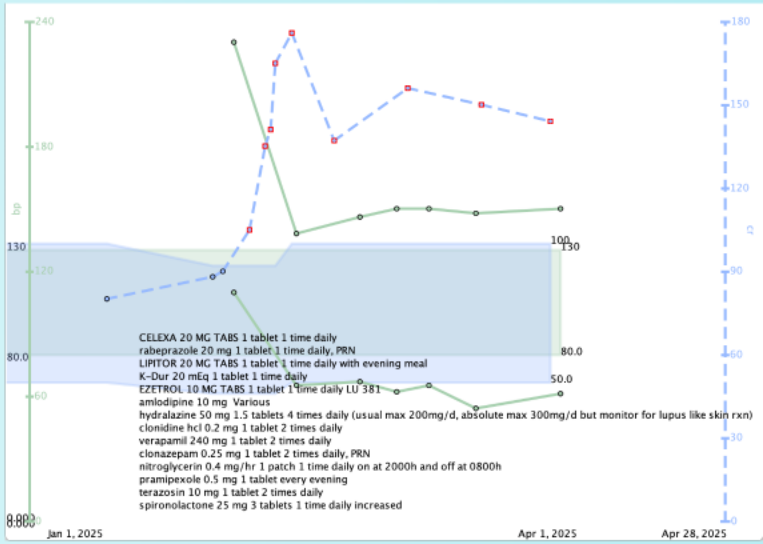
PRESCRIPTION

Patient Name:

Address:

terazosin 20mg
verapamil 480mg
amlodipine 15mg
hydralazine 75 qid
clonidine 0.2 bid
+ NTG 0.4mg/h
+Spironolactone 50-75/d

- Jan: admitted to hosp x 2. Peak BP 251/110. Cr 100-160
  - CTA: "severe ostial stenosis of the superior Rt renal artery, mild ostial stenoses of the Rt inferior renal artery & the single Lt renal artery… asymmetric hypoattenuation of the Rt kidney… ddx includes hypoenhancement d/t hypoperfusion related to the superior right renal artery ostial stenosis"



- Feb: Referral to Vascular. Unsuccessful IR cannalization w/ very little flow noted.

- Mar & ongoing - continued efforts to control BP w/ Rx

Take Home Points

01 RH is defined as BP above goal despite confirmed adherence to 3 first-line agents or when BP is controlled with ≥4 meds at maximal or maximally tolerated doses. Affects ~ 10% of adults w/ HTN.

02 Diagnosis requires both accurate in-office BP measurement as well as excluding white coat effects through out-of-office BP measurements

03 Patients with RH are at higher risk for adverse cardiovascular events and are more likely to have a potentially treatable secondary cause

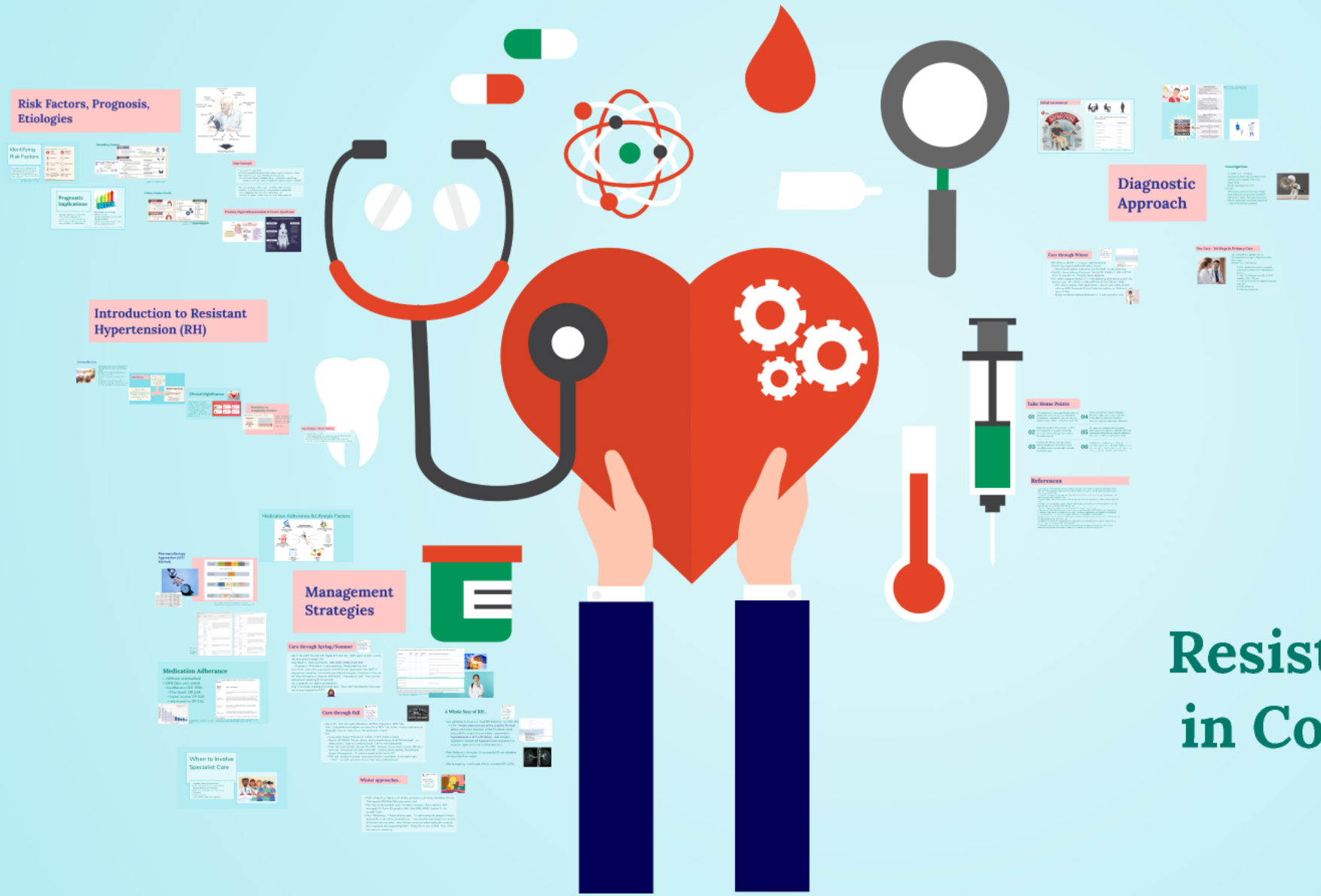
04 Effective treatment includes ongoing lifestyle modifications and collaboration with patients to detect and address barriers to optimal medication adherence.

05 Pharmacologic treatment should prioritize optimizing 1st-line (diuretic, ACEi/ARB, DHP CCB) medications followed by the stepwise addition of 2nd-, 3rd-, and 4th-line agents as tolerated.

06 Evaluate for and address any underlying secondary causes. A coordinated, multidisciplinary team approach including clinicians with experience in treating resistant hypertension is essential.

References

1. Calhoun et al. Resistant Hypertension: Diagnosis, Evaluation, and Treatment: A Scientific Statement From the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension. 2008; 51(6).
2. Viera et al. Evaluation and Management of the Patient with Difficult-to-Control or Resistant Hypertension. Am Fam Physician. 2009; 70(10): 860-869.
3. Padwal, Rabkin, and Khan. Assessment and Management of Resistant Hypertension. CMAJ. 2014;186(18):E689-E697.
4. Hiremath et al. Hypertension Canada's 2020 Evidence Review and Guidelines for the Management of Resistant Hypertension. Can J Cardiology. 2020; 36: 625-634.
5. Resistant Hypertension: New recommendations for 2020. Hypertension Canada
6. The Intern at Work. 2020. https://www.theinternatwork.com/infographics-2/2020/9/20/resistant-hypertension.
7. Jędrusik P, Symonides B, Lewandowski J, Gaciong Z. The effect of antihypertensive medications on testing for primary aldosteronism. Front. Pharmacol. 2021;12:684111. doi:10.3389/fphar.2021.684111.
8. Cluett, Jennifer L. et al. Evaluation and Management of Resistant Hypertension: Core Curriculum. American Journal of Kidney Diseases, 2024; 84:3, 374 - 387
9. Bergland et al. Detection of Nonadherence to Antihypertensive Treatment by Measurements of Serum Drug Concentrations. Hypertension. 2021; 78:3, 617-628.
10. Michael R. Law, Lucy Cheng, Irfan A. Dhalla, Deborah Heard and Steven G. Morgan. The effect of cost on adherence to prescription medications in Canada. CMAJ February 21, 2012 184 (3) 297-302



Resistant Hypertension in Community Practice

Caroline Correia

Apr 2025