Management of Uncontrolled Hypertension

Januvi Jegatheswaran, MD FRCPC
Nephrologist and Hypertension Specialist, The Ottawa Hospital
Assistant Professor, University of Ottawa

Disclosure of Speaker

- **Relationships with commercial interests:**
  - Grants/Research Support: Department of Medicine, The Ottawa Hospital
  - Speakers Bureau/Honoraria: Otsuka
- **Potential for conflict(s) of interest:** None
- **Mitigation of potential bias:** None

LEARNING OBJECTIVES

1. Identify common causes of uncontrolled hypertension
2. Recognize when to suspect and evaluate for secondary causes of hypertension
3. Explain the role of lifestyle modification, medication review, and out-of-office blood pressure monitoring in evaluating uncontrolled hypertension
4. Review an evidence-based, stepwise approach to reassessing and intensifying antihypertensive therapy.

Patient RM

- 56M, type 2 DM, overweight, BP never well controlled for years. He has no known vascular disease
- He admits to eating at fast food restaurants frequently.
- He works in construction, doesn't have time to exercise as he is usually tired after work.
- His partner says he 'snores loudly'
- Current medications:
  - Ramipril/HCTZ 10/25 mg od, amlodipine 10 mg od
  - Metformin 1 g bid, atorvastatin 20 mg od, ECASA 81 mg od

Patient RM

- On exam wt 108 kg, BMI 39
  - Casual BP 160/94
  - Resting BP 154/90
  - No abdominal bruits
  - Mild amount of pre-tibial edema
- K 4.1 mmol/L, Cr 86 µmol/L
- ECG normal

What should we call this? (POLL)

A. Uncontrolled hypertension
B. Refractory hypertension
C. Resistant hypertension

What should we call this?

A. Uncontrolled hypertension
B. Refractory hypertension
C. RESISTANT HYPERTENSION

   Blood pressure above target despite three antihypertensive agents at optimal doses, preferably including a diuretic

What should be the next step? (POLL: Choose all that apply)

A. Confirm medication adherence
B. Lifestyle Counselling
C. Do an ABPM to rule out white coat hypertension
D. Secondary Hypertension Workup
E. Intensify Pharmacotherapy

What should be the next step? (POLL Answer)

A. **Confirm medication adherence**
B. **Lifestyle Counselling**
C. **Do an ABPM to rule out white coat HT**
D. Secondary Hypertension Workup (not yet)
E. **Intensify Pharmacotherapy**

Stepwise Approach

1. Step 1
   - Exclude white coat hypertension and/or non-adherence
2. Step 2
   - Identify and address lifestyle factors and discontinue interfering substances
3. Step 3
   - Medication rationalization and intensification
4. Step 4
   - Investigate for secondary causes
   - Refer to Hypertension Specialist

Adapted from Calhoun et al. Circulation 2008

STEP 1

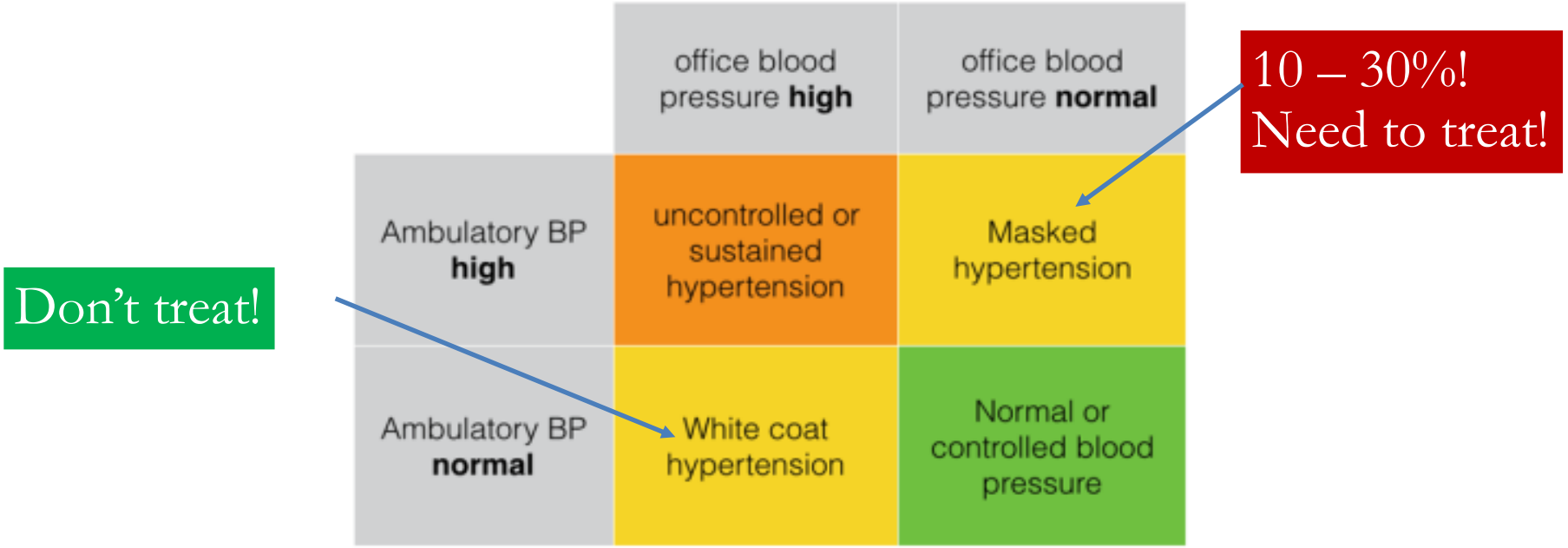
Exclude Pseudoresistance

- Is the patient adherent with prescribed regimen?
- Do out of Office BP measurement: eg home or ambulatory blood pressure measurements

Checking adherence

- Ask the patient in non-judgemental way
- Count pills in bottles/ review blister pack dates
- Call pharmacy for refill dates
- Look for clues – normal or high HR while on beta-blocker or low potassium on ACEi/ARB/MRA

Out of Office: Ambulatory Monitoring



The white coat effect?

- Increases with increasing age
- More common in women than men
- Detect using
    - 24-hour Ambulatory blood pressure monitoring
    - Alternatives (Home BP log)

How common is white coat hypertension?

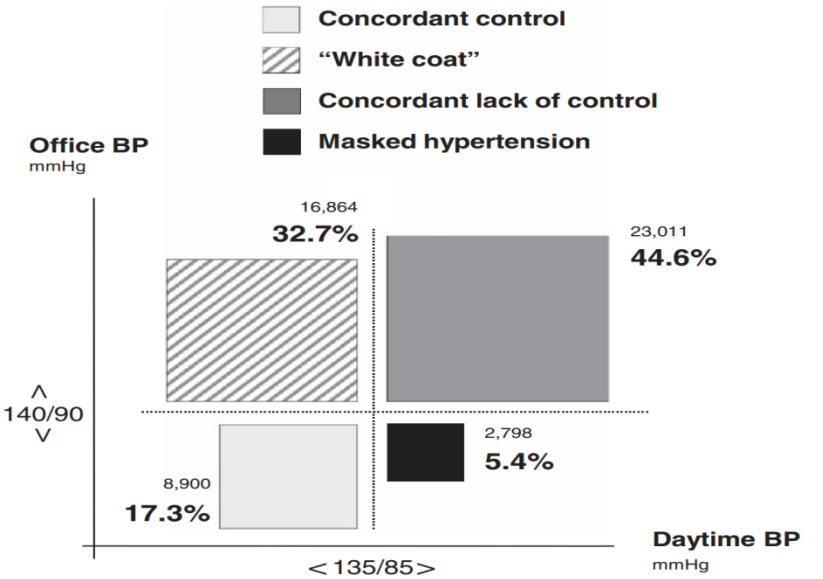
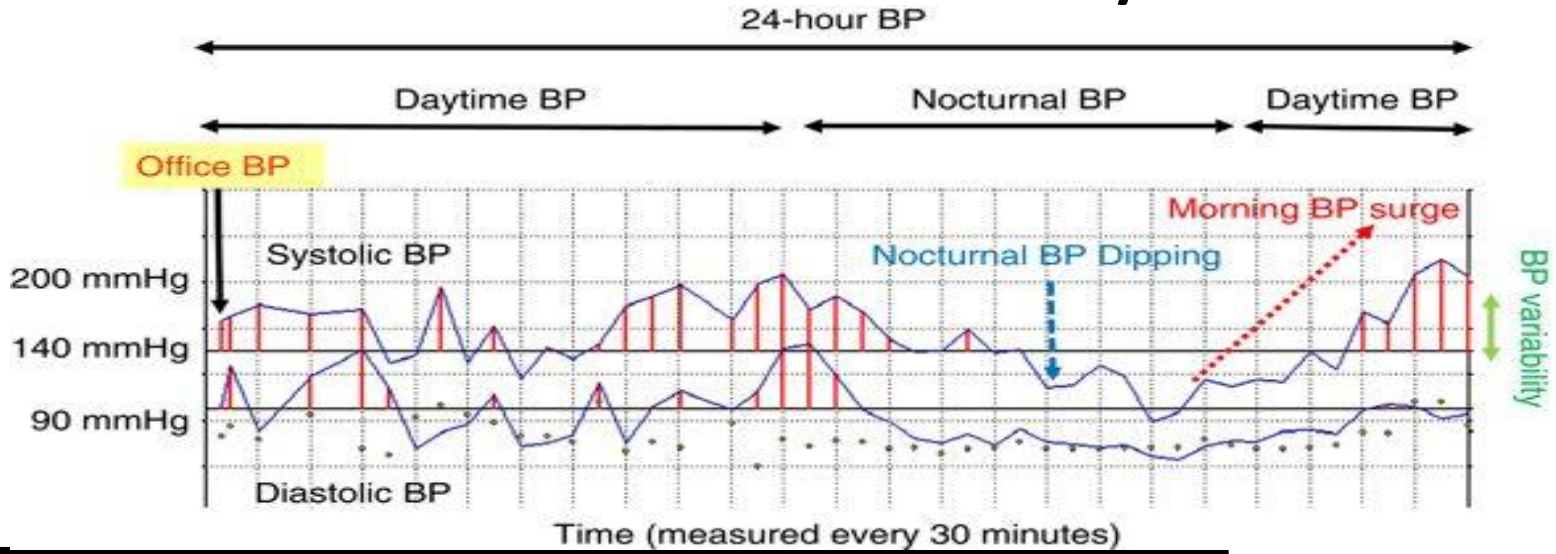


Figure 2 Distribution of 51 573 hypertensive patients from the Spanish Ambulatory Blood Pressure Monitoring Registry according to office and daytime ambulatory blood pressure criteria.

Overall white coat hypertension in registries varied from ~ 10% to 40% depending on population and definitions

Source: Gorostidi et al, HT Research 2015

Out of Office: Ambulatory Monitoring



Out of office assessment of BP
Overall blood pressure load
Does the blood pressure dip at night?
Variability: is there labile BP?
Are certain activities precipitating high/low BP?

STEP 1

Exclude Pseudoresistance

- Is the patient adherent with prescribed regimen?
- Do out of Office BP measurement: eg home or ambulatory blood pressure measurements

Return to Case about RM

- examination of pill bottles suggests patient is up to date on meds
- 24 hour ABPM does confirm poorly controlled BP with
  - daytime average 152/86,
  - nocturnal 145/84 (non dipper)

STEP 2

Identify and Reverse Contributing Lifestyle Factors

- Exercise (moderate intensity, > 30 minutes, > 4 times/week). The WHO advises at least 150–300 minutes per week.
- of moderate aerobic activity per week
- Weight Loss
- Diet: Decrease sodium intake to less than 2g per day; increase potassium intake to more than 3.5g per day; DASH diet
- Stress Reduction
- Limit Alcohol intake (≤ 2 drinks day; Per week ≤ 14 for men; 9 for women)

Other Interventions

Increase potassium to more than 3.5g per day	4-7 mm Hg	Feeding RCTs, K supplements
Exercise	4-10mm Hg	Short FU RCTs Not blinded Supervised moderate-high intensity exercise
Yoga/meditation	3-6 mm Hg	Low quality RCTs

Lifestyle modifications can work, but only for a motivated subset. Requires commitment and lifestyle change

Pragmatic Trial in NEJM

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

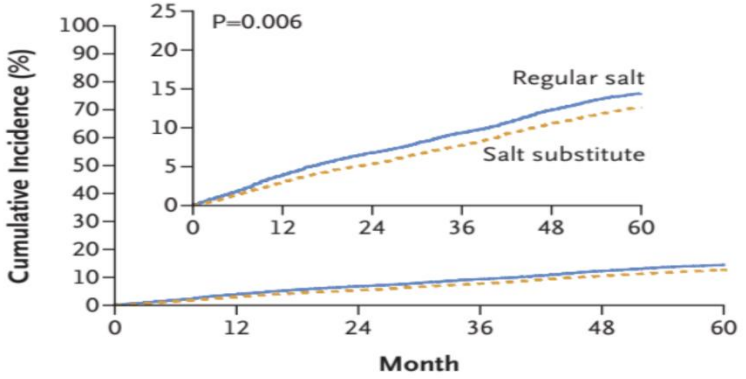
	Stroke	Major CV Events	Death	Hyperkalemia
	Events per 1000 patient-years			
Regular salt	33.65	56.29	44.61	3.30
	rate ratio			
	0.86 [0.77-0.96] P=0.006	**0.87** [0.8-0.94] P<0.001	**0.88** [0.82-0.95] P<0.001	**1.04** [0.8-1.37] P=0.76
Salt substitute	29.14	49.09	39.28	3.35
	Events per 1000 patient-years			

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*

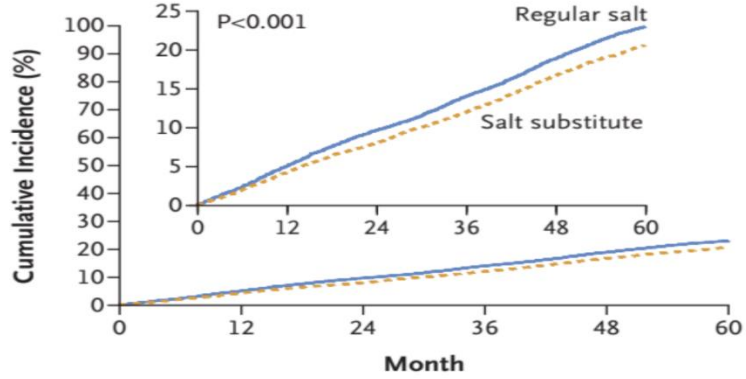
Visual Abstract by @nefron1310

A Stroke



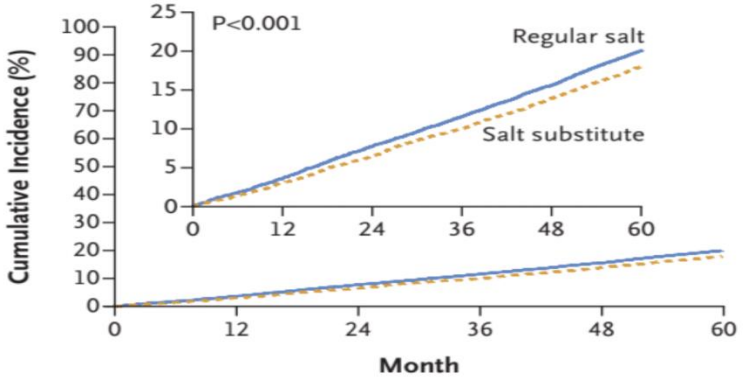
No. at Risk						
Regular salt	10,491	9870	9288	8752	8138	7580
Salt substitute	10,504	9992	9508	8997	8385	7846

B Major Adverse Cardiovascular Events



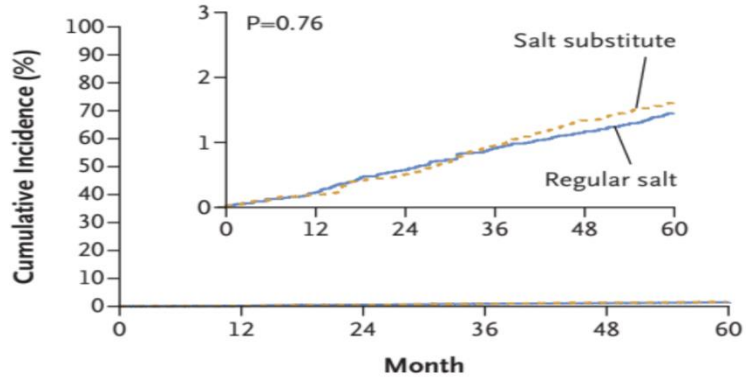
No. at Risk						
Regular salt	10,491	9860	9259	8658	8002	7412
Salt substitute	10,504	9976	9478	8922	8277	7716

C Death from Any Cause



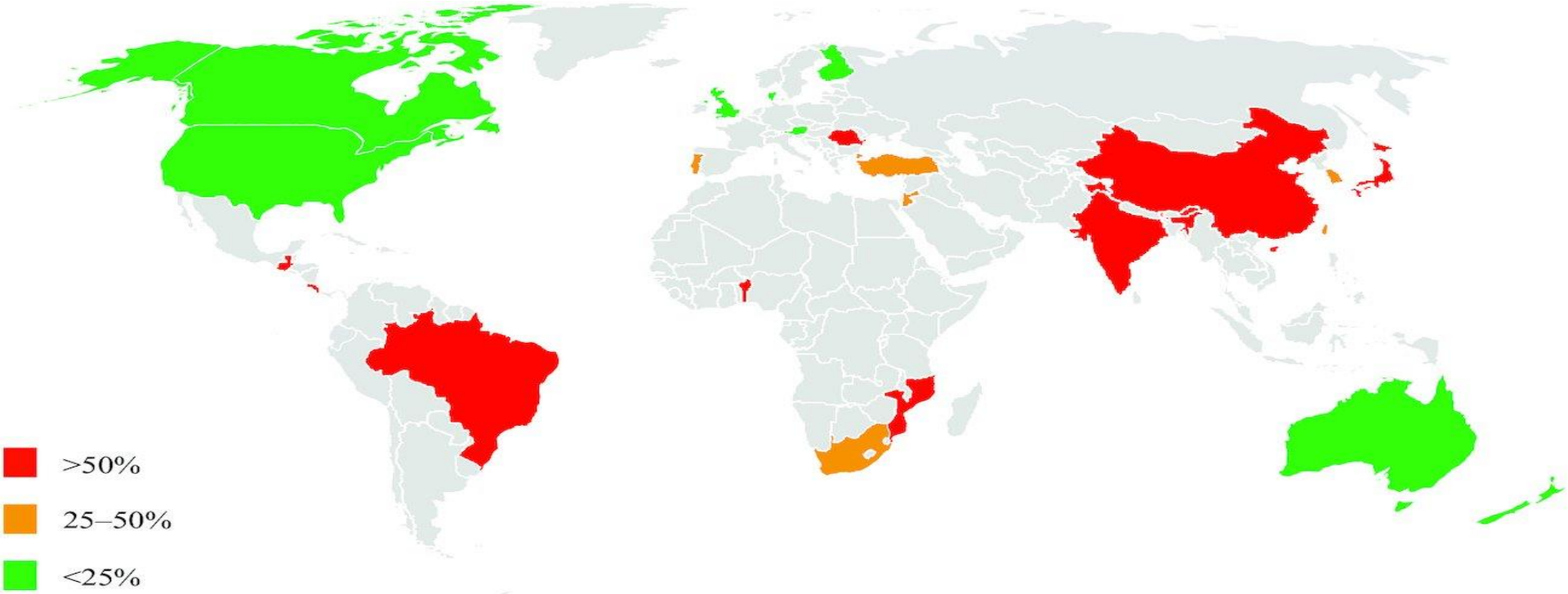
No. at Risk						
Regular salt	10,491	10,116	9681	9279	8859	8391
Salt substitute	10,504	10,189	9829	9452	9043	8617

D Hyperkalemia



No. at Risk						
Regular salt	10,491	10,113	9676	9274	8853	8385
Salt substitute	10,504	10,187	9827	9451	9038	8612

Source of sodium = salt added in household



In red countries = salt added in household, individual behaviour important
In green countries = food industry has to be targeted

Bhat S, et al., *Adv Nutr. 2020*

Exercise: Dynamic or Resistance?

For non-hypertensive individuals (to reduce the possibility of becoming hypertensive) or for hypertensive patients (to reduce their BP), prescribe the accumulation of **30-60 minutes** of moderate intensity dynamic exercise (e.g., walking, jogging, cycling, or swimming) **4-7 days per week** in addition to the routine activities of daily living (Grade D).

Higher intensities of exercise are not more effective (Grade D).

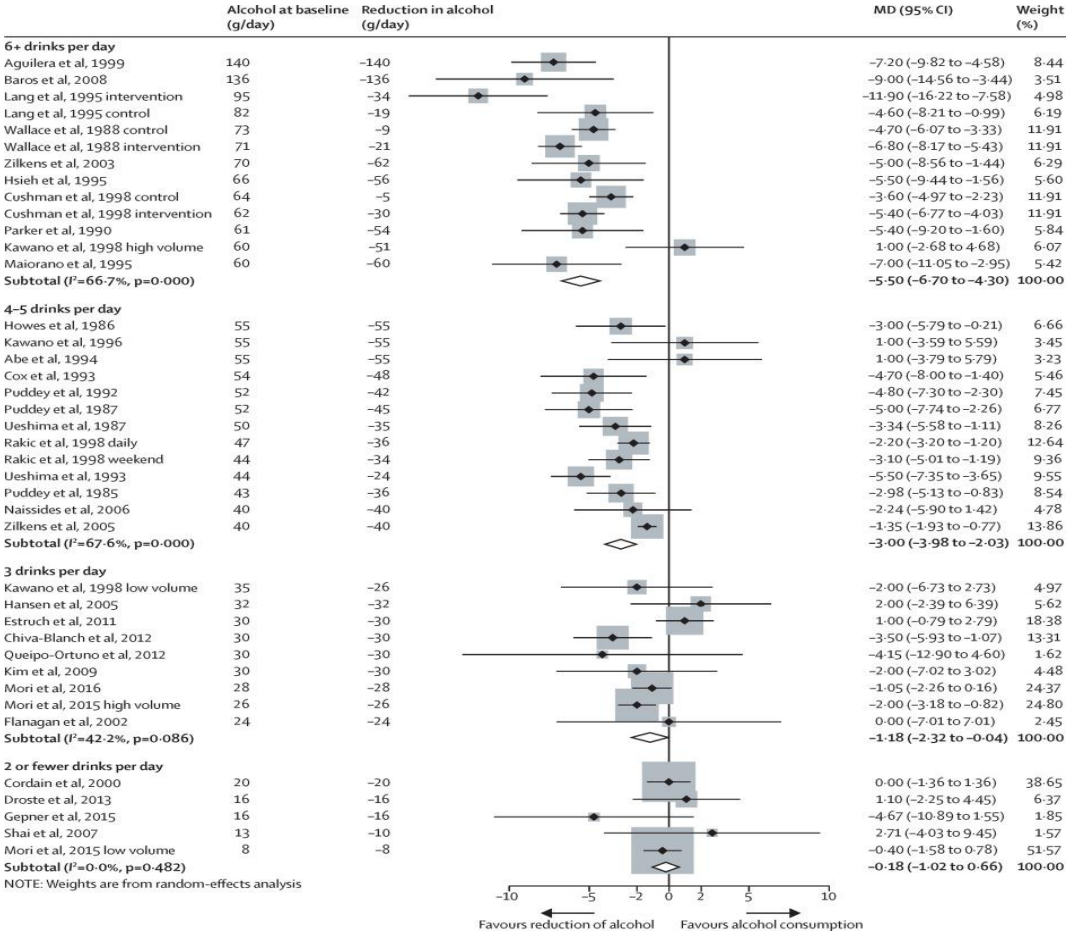
For non-hypertensive or stage 1 hypertensive individuals, the use of **resistance or weight training exercise** (such as free weight lifting, fixed weight lifting, or handgrip exercise) **does not** adversely influence BP (Grade D).

Hypertension CANADA

Alcohol?

Reducing alcohol intake reduces BP in a dose dependent manner

RCT data



Roerecke et al, Lancet Public Health 2017

STEP 2

Identify and Reverse Contributing Lifestyle Factors

- Exercise (moderate intensity, > 30 minutes, > 4 times/week
- Weight Loss
- Diet: Decrease sodium intake; increase potassium intake; DASH diet
- Stress Reduction
- Limit Alcohol intake (≤ 2 drinks day; Per week ≤ 14 for men; 9 for women)

Case RM

- BMI 39, inactive
- poor diet, high salt presumed
- alcohol not an issue

Implications

- Needs to lose weight and improve diet, but this will take time
- But more immediately…

STEP 3

Pharmacologic Treatment

Maximize therapy, including possibility of adding mineralocorticoid antagonist

Combine agents with different mechanism of action

STEP 3

Pharmacologic Treatment

Maximize diuretic therapy, including possibility of adding mineralocorticoid antagonist

Combine agents with different mechanism of action

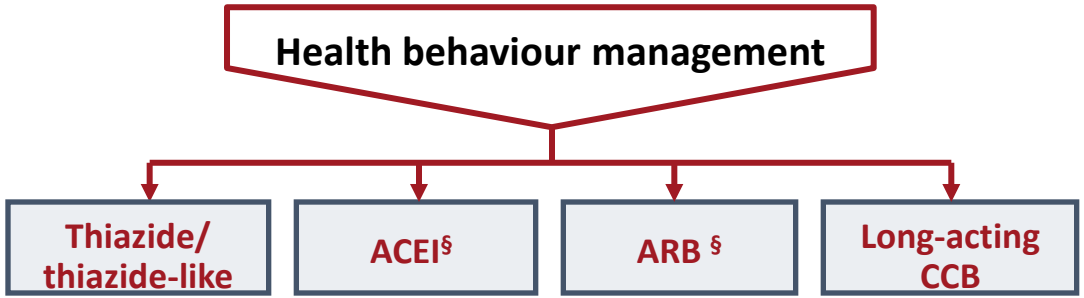
Case RM

- Can increase dose of diuretic (hctz 25 mg)
- short acting ACE-i (ramipril 10 mg)
- ?submaximal dose of amlodipine (for size)

First Line Treatment of Adults with Systolic/Diastolic Hypertension

TARGET <130/80 mmHg (automated measurement method)

INITIAL TREATMENT



§Renin angiotensin system (RAS) inhibitors are contraindicated in pregnancy and caution is required in prescribing to women of child bearing potential

****Recommended single-pill combination choices are those in which an ACE-I is combined with a CCB, an ARB with a CCB, or an ACE-I or ARB with a diuretic**

Management Case RM

- Change ramipril to perindopril 8mg. This comes in combination pills with indapamide, so switch HCTZ to 2.5mg of indapamide.
- Increase amlodipine to 20mg daily

- Returns in 8 weeks
  - Lytes, Cr stable
  - Home BPs average 138/80

Target for Diabetes: < 130/80; What now??

What will you do now? (POLL)

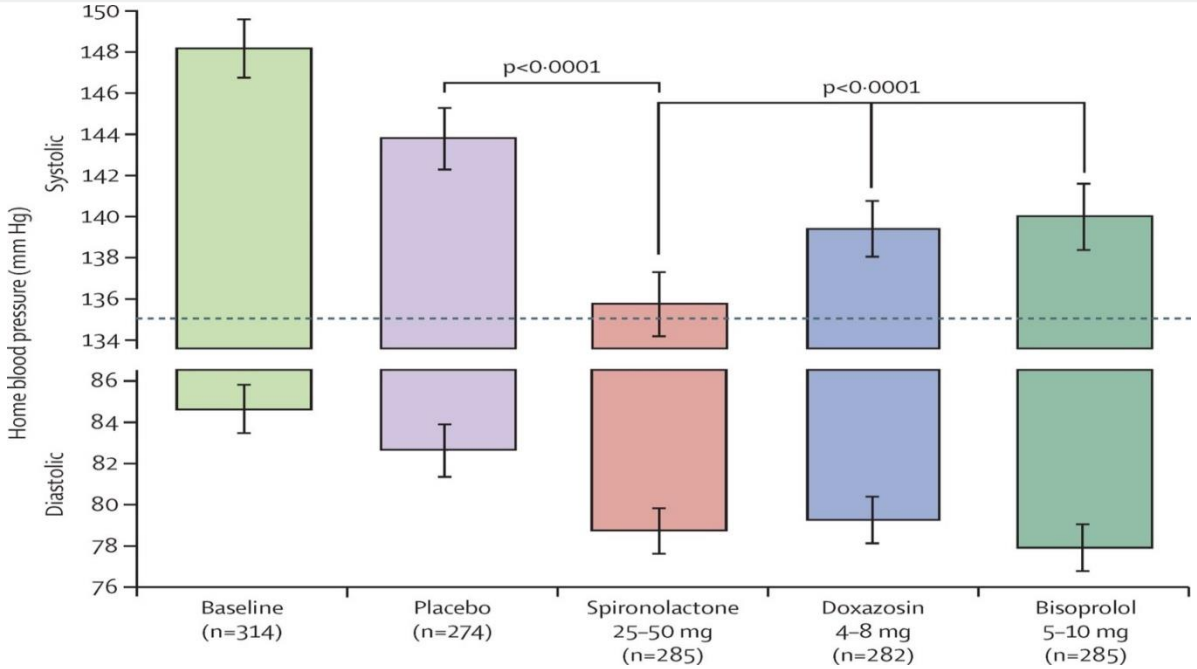
A. Add 4th drug: spironolactone
B. Check for renal artery stenosis
C. Add 4th drug: beta-blocker
D. Check 24 hour urine for metanephrines

What will you do now? (POLL)

A. **Add 4th drug: spironolactone**
B. Check for renal artery stenosis
C. Add 4th drug: beta-blocker
D. Check 24 hour urine for metanephrines

Fourth line Antihypertensive

If BP remains above target despite 3-drug combination therapy consisting of an ACEI or ARB; a thiazide or thiazide-like diuretic; and a long-acting dihydropyridine CCB at their maximally tolerated doses, the addition of spironolactone is suggested.	Conditional	Moderate



Source: PATHWAY-2; Lancet 2014

Tips on using Spironolactone

- Empiric Spironolactone or test for Primary aldosteronism?
- Spironolactone or Eplerenone
  - Side effect profile
  - Medication coverage
- Amiloride

STEP 4: Investigate for secondary causes

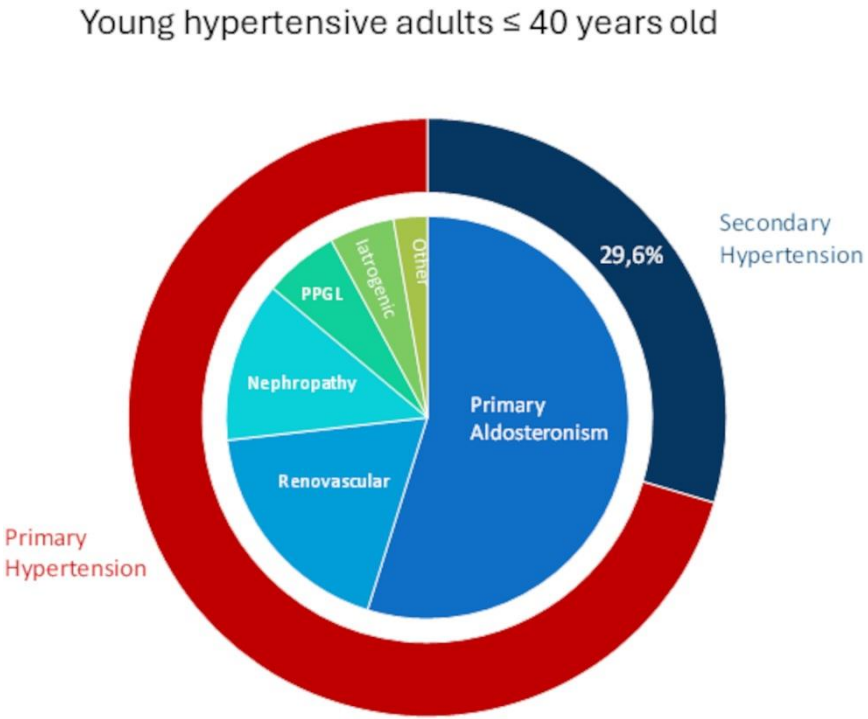
High frequency of secondary causes:

- 125 consecutive patients with resistant hypertension fully investigated for secondary causes

- 66% had one or more identifiable cause:
  - obstructive sleep apnea (64.0%)
  - primary aldosteronism (5.6%)
  - renal artery stenosis (2.4%)
  - renal parenchymal disease (1.6%)
  - oral contraceptives (1.6%)
  - thyroid disorders (0.8%).

Pedrosa et al. Hypertension 2011

Prevalence of Secondary Hypertension



Freminville, JB. Et al. (2024) Hypertension

Management Case RM

- Returns 2 weeks after initiation of spironolactone 25 mg
  - Home BPs average 124/75
  - Edema almost gone
  - Lytes, Cr stable
- Sleep Study ordered
  - Confirms obstructive sleep apnea
  - Awaiting recall for CPAP

Patient RM Summary

- BP above target despite 3 meds should raise a red flag
- Organized approach
  - Rule out pseudohypertension
  - Identify lifestyle factors
  - Intensify antihypertensive therapy
    - Add 4th line agent if still uncontrolled
  - Limited investigation for secondary causes
  - Referral if uncontrolled after 6 months or suspected secondary causes

Patient NA

- 37-year-old man, works in the IT sector on contract basis
- Diagnosed with HTN ~3 years ago
- Strong family history (both parents)
- No DM; BMI 27; no other co-morbidities
- GP retired 2 years ago, would fill in Rx at walk-in clinics
- BP was ‘good’ doesn’t remember values

Patient NA contd..

- Visit 1: BP 172/104
  - Taking 5 mg Amlodipine daily
  - Dose increased to 10 mg daily
- Visit 2: BP 168/102
  - Add Trandolapril 1 mg daily
- Visit 3: 2 weeks later, BP 156/90
  - Increased Trandolapril to 4 mg daily
- Visit 4: 2 months later: BP 164/98
  - Added chlorthalidone 25mg daily
- Visit 5: 2 months later: BP 167/95

Review: Stepwise Approach

- Step 1
  - Exclude white coat hypertension and/or non-adherence
- Step 2
  - Identify and address lifestyle factors and discontinue interfering substances
- Step 3
  - Medication rationalization and intensification
- Step 4
  - Investigate for secondary causes
  - Refer to Hypertension Specialist

Adapted from Calhoun et al. Circulation 2008

What should be your next step? (POLL)

A. Treat with watchful expectancy
B. Check for drug adherence
C. Investigate for secondary hypertension
D. Add fourth anti-hypertensive medication
E. You suspect white coat effect; order 24-hour ABPM

What should be your next step? (POLL)

A. Treat with watchful expectancy
B. **Check for drug adherence**
C. Investigate for secondary hypertension
D. Add fourth anti-hypertensive medication
E. You suspect white coat effect; order 24-hour ABPM

Pseudo-Hypertension

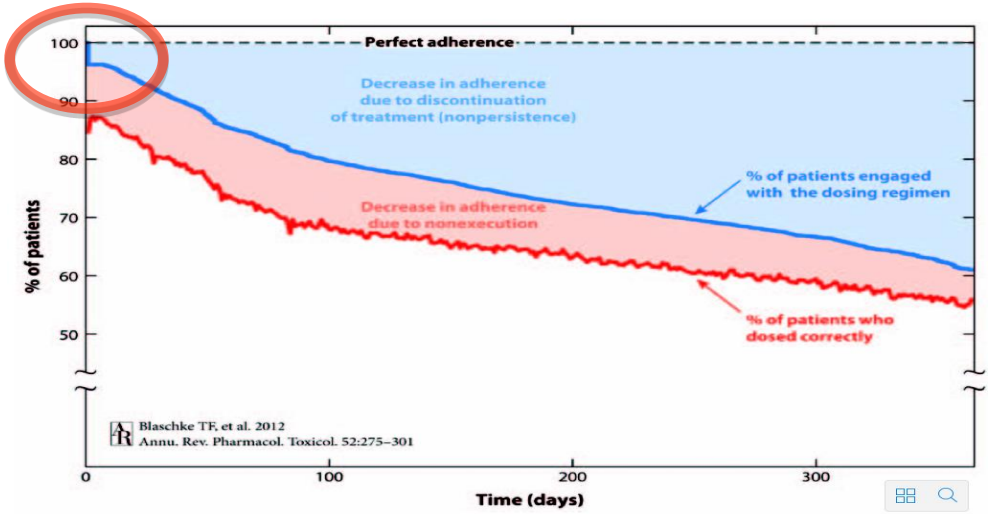
- Patient factors
  - White Coat effect
  - Poor patient ‘concordance’ with Rx:
    - Side effects
    - complicated dosing
    - inadequate pt education
    - memory/psychiatric/cognition issues
    - difficult relation with MD
    - Costs of drugs

Source: Myat et al, *BMJ 2012;345:e7473*

Non- adherence (non-compliance)

- ‘Adherence’: non-judgmental, statement of fact rather than of blame
- Quite common, ranges from 10 - 100 % in literature
- Increases with
    - long term/chronic therapy
    - increased pill burden (> 50% with > 4 meds/day) *[Osterberg et al; N Engl J Med 2005;353:487-97.]*

Adherence (Compliance)



~ 5% patients: do not fill prescription at all

Cost

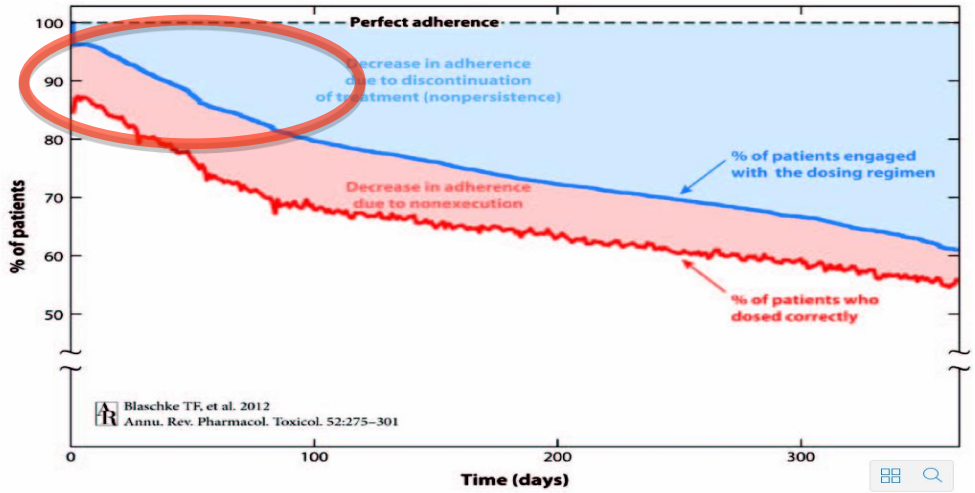
do not understand importance

Solution:

-Generics

-Earlier Follow-up (phone calls or visits)

Adherence (Compliance)

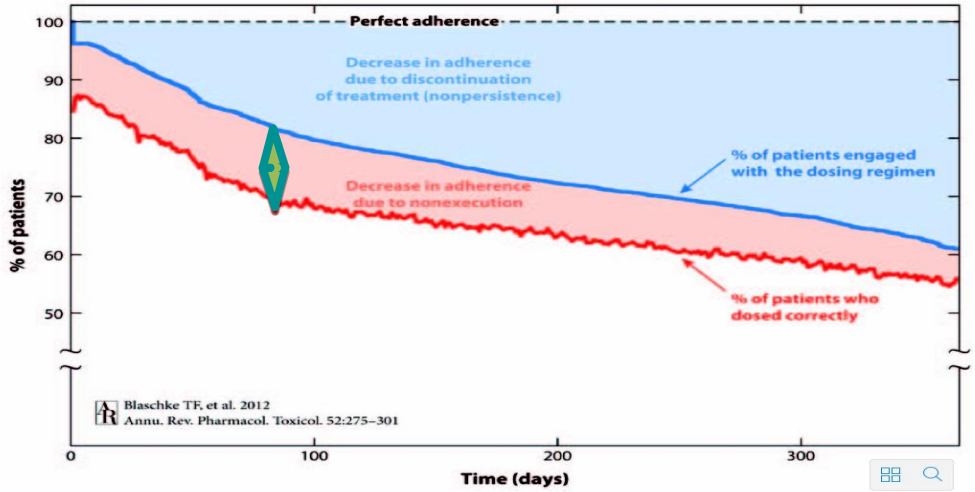


Gradual Fall off in early period

- Side effects
- Do not understand need (‘my BP is normal now’)

Solution
-Choice of meds
-Earlier Follow-up (phone calls or visits)

Adherence (Compliance)



~10% patients 'engaged' with taking pills, but forget on any given day

Solution
-Combination pills, taken once daily
-Use blister packs or dosettes

How do you diagnose non-adherence?

1. Indirect methods:
   - Ask the patient!
   - Count pills from pill bottle
   - Call pharmacy to check frequency of Rx fills
2. Direct Methods
   - Direct observed therapy
   - Measure serum/urinary drug levels

Back to our patient..

Admitted to occasionally forgetting pills

Checked with pharmacy:

last refill for 30 tablets of 5 mg Amlodipine 3 months ago;

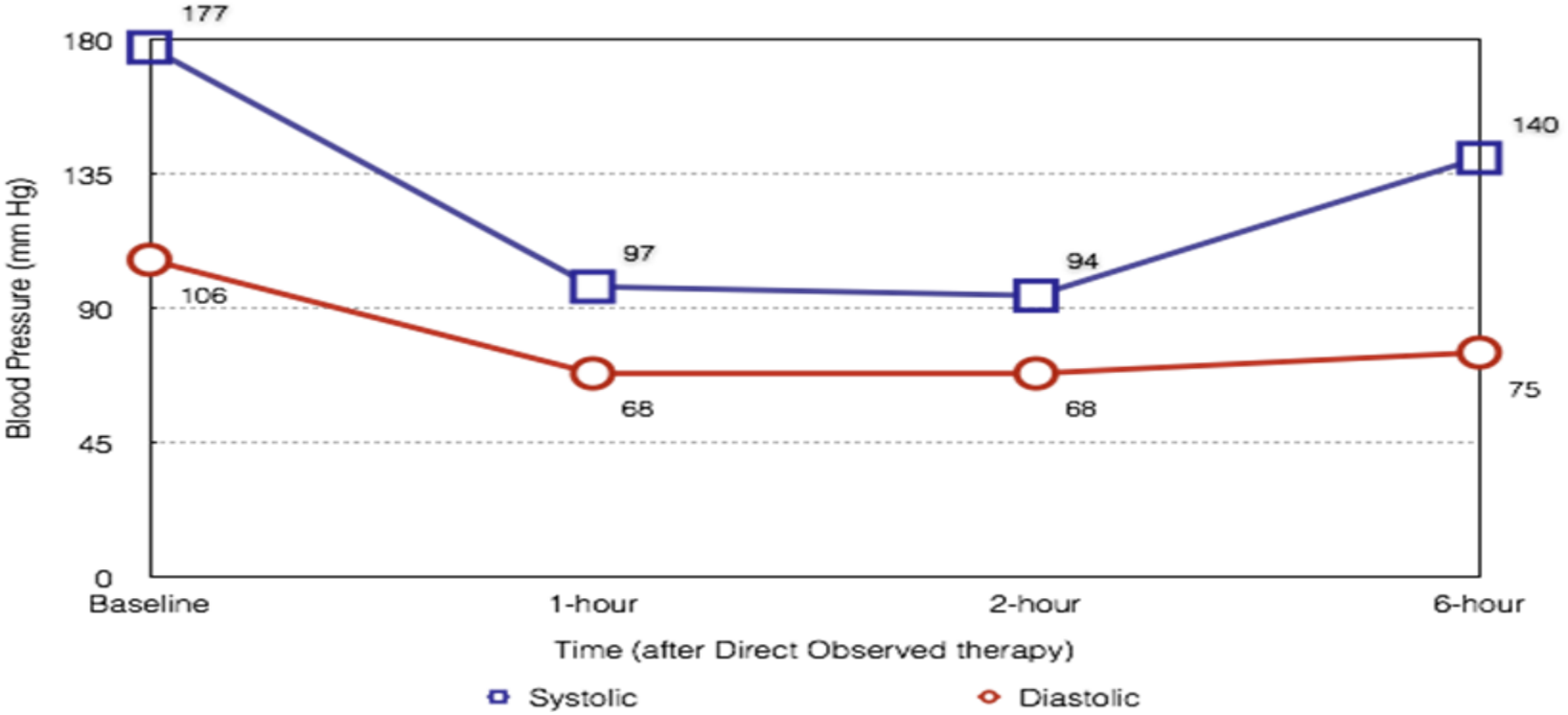
last refill for 30 tablets 1 mg Trandolapril 2 1/2 months ago

- Spent some time explaining impact of hypertension on health (Stroke, Vision, Kidney failure, Heart failure)
- Encouraged to refill prescriptions when he ran out
- Follow up (Nurse Visit) in 4 weeks
    - BP 136/78 on same meds;
- 6 months later (with monthly phone calls):
    - BP still controlled on same meds

An extreme case of non-adherence

Time of visit in relation to RDN	Casual	**10 minute resting**	Upright	ABPM average	Heart rate	Prescribed Medications
- 2 months	202/104	**199/102**	190/108	176/100	80	Olmesartan 40 mg od Metoprolol 75 mg bid Prazosin 5 mg od Furosemide 120 mg bid Metolazone 5 mg od Spironolactone 50 mg bid
+1 day	162/104	**164/106**	162/110		62	As above
+1 week	174/104	**159/101**	160/100		64	As above
+2 weeks	171/94	**182/96**	174/100		68	As above + clonidine 0.1 mg bid
+4 weeks	186/100	**180/91**	192/99		74	As above

An extreme case of non-adherence: Effect of Direct Observed Therapy

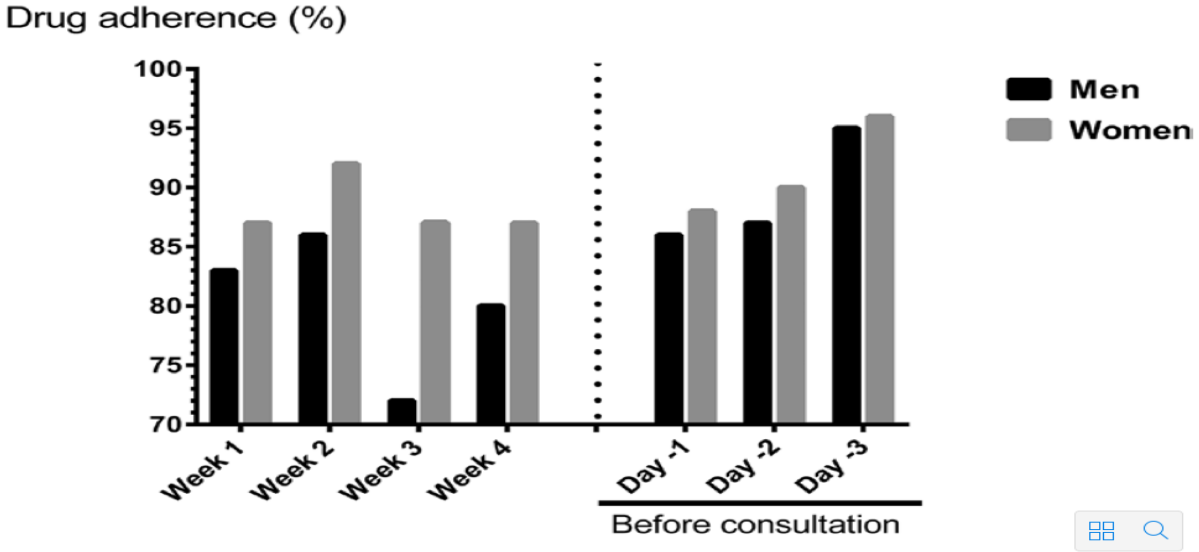


Alternative to DOT

- Urine chemical assays
  - Real-time data about what was taken close to time of testing only (snapshot), risk of white-coat adherence

“White coat” adherence

220 ***Hypertension*** **August 2013**



Increasing adherence in anticipation of MD visit

When should you screen for Secondary HT?

- Sudden worsening of HT in previously well controlled patient
- HT < 30 years age in non-obese, non-black patient with no family history
- Hypertensive Emergency (previously called Malignant or Accelerated HT)
- Severe or Resistant HT

Secondary Hypertension? Endocrine HTN

Screening for hyperaldosteronism should be considered for at least the following patients (Grade D):

- hypertensive patients with; spontaneous hypokalemia (K+ less than 3.5 mmol/L);
- hypertensive patients with marked diuretic-induced hypokalemia (K+ less than 3.0 mmol/L);
- patients with hypertension refractory to treatment with three or more drugs; and
- hypertensive patients found to have an incidental adrenal adenoma.

Pheochromocytomas are rare. If this is suspected, then the patient should be referred to endocrinology for further management.

Hypertension CANADA

Secondary Hypertension? Renovascular HTN Screening

Patients presenting with two or more of the following clinical clues listed below suggesting renovascular hypertension should be investigated (Grade D).

1. Sudden onset or worsening of hypertension and age older than 55 years or younger than 30 years;
2. the presence of an abdominal bruit;
3. hypertension resistant to three or more drugs;
4. a rise in serum creatinine level of ≥30% associated with use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist;
5. other atherosclerotic vascular disease, particularly in patients who smoke or have dyslipidemia;
6. recurrent pulmonary edema associated with hypertensive surges.

Hypertension CANADA

Secondary Hypertension? Renovascular HTN Treatment

- Patients with hypertension attributable to atherosclerotic RAS should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone (Grade B)
- Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant RAS could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema (Grade D)

Hypertension CANADA

Summary

- Non-adherence is very common, frequently under diagnosed
- Suspect in patients who have no response to appropriately escalating therapy
  - especially with physiological clues (eg elevated HR on Beta-blockers + clonidine)
- No magic bullet to fix: requires multi-modal approach:
  - education
  - frequent follow-up
  - medication reminder aids (dosettes, blister packs, electronic aids)

Stepwise Approach

1. Step 1
   - Exclude white coat hypertension and/or non-adherence
2. Step 2
   - Identify and address lifestyle factors and discontinue interfering substances
3. Step 3
   - Medication rationalization and intensification
4. Step 4
   - Investigate for secondary causes
   - Refer to Hypertension Specialist

Adapted from Calhoun et al. Circulation 2008


THANK YOU!