Hypertension and Hyperlipidemia Management in the Ambulatory Setting

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Objectives

- Compare and contract antihypertensive classes for resistant hypertension
- Compare and contrast antihypertensive classes for isolated systolic hypertension
- Describe the changes in statin groups and the impact on treatment of dyslipidemia
- Compare and contract second line medications for treatment of dyslipidemia

Hypertension

Leading risk factor for cardiovascular disease, stroke, disability and death

30% of people over the age of 20 in the United States have hypertension

Beckett NS. N Engl J Med. 2008;358(18):1887.
Carey RM. Hypertension. 2013;72:e53-e90.

Resistant Hypertension (RH)

Prevalence and Prognosis of RH

Prevalence of RH

- Apparent treatment RH → 12--15%
- True RH → 10.3%
- In patients with CKD → 22.9%

Prognosis of RH

- 47% more likely to suffer the combined outcomes of death, MI, HF, stroke, or CKD
- 32% increased risk of developing CKD
- 24% increased risk of ischemic heart disease
- 46% increased risk of heart failure
- 14% increased risk of stroke
- 6% increased risk of death

Carey RM. Hypertension. 2018;72:e53-e90.
Noubiap JJ. Heart. 2019;105:98-105.

Increased risk of RH

African American

Elderly

Male

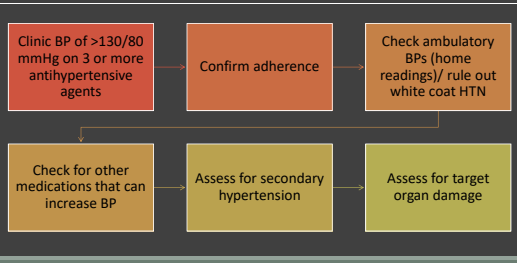
Comorbidities:

- Obesity
- Left ventricular hypertrophy
- Albuminuria
- Diabetes
- Obstructive sleep apnea

Genetics

Carey RM. Hypertension. 2018;72:e53-e90.

Diagnosing RH



Carey RM. Hypertension. 2018;72:e53-e90.

Primary Aldosteronism

- Aldosterone production is inappropriately high and independent of RAS system
- HTN → volume expansion and sympathetic nervous system activation, hypokalemia, metabolic alkalosis, and cardiovascular and renal disease
- Aldosterone → toxic
- Primary hyperaldosteronism is cause of RH is 20% of patients

Carey RM. Hypertension. 2018;72:e53-e90.

Renal Artery Stenosis

- HTN is accelerated or worsened by renal artery stenosis
- Optimizing antihypertensive therapy is the primary treatment
- Most will tolerate ACEi or ARB without renal effects
  - 10-20% will develop increase in serum creatinine
- A subset will develop progressive disease with worsening hypertension, renal insufficiency or circulatory congestion (flash pulmonary edema)
- Renal artery stenosis is cause of RH is 24% of older patients

Carey RM. Hypertension. 2018;72:e53-e90.

Clinical Inertia

Only 50% of patients with uncontrolled RH were prescribed optimal antihypertensive regimens

90% were prescribed a diuretic
- 42% were dosed at <50% of their maximally recommended dose

African American patients and patients with DM, CKD or CAD were more likely to be on optimal regimens

By standardizing BP measurements and using treatment algorithm, Kaiser Permanente showed an increase in BP control from 54% to 84%

Carey RM. Hypertension. 2018;72:e53-e90.

Lifestyle Interventions for RH

Carey RM. Hypertension. 2018;72:e53-e90.

Steps in Management of RH

Step 1	Exclude other causes Ensure low sodium diet Maximize lifestyle Ensure adherence
Step 2	Substitute optimally dose thiazide-like diuretic
Step 3	Add a mineralocorticoid receptor antagonist

Carey RM. Hypertension. 2018;72:e53-e90.

Steps in Management of RH

Step 4
Check heart rate
If greater than 70bpm, add a beta-blocker

Step 5
Add hydralazine and titrate to max dose
If patient has heart failure with reduced ejection fraction (HFrEF) use in combination with isosorbide mononitrate

Step 6
Substitute minoxidil for hydralazine
Must be used in combination with beta-blocker and loop diuretic

Carey RM. Hypertension. 2018;72:e53-e90.

Patient Case

Patient is a 70 year old African American male presenting to your clinic for elevated blood pressure. BP was 148/96 with HR of 78; and 146/96 on repeat. This is consistent with his BP readings from recent office visits. Patient has not been checking his BP at home.

Home medications include:

HCTZ 25mg daily
Lisinopril 40mg daily
Amlodipine 10mg daily
Atorvastatin 40mg daily
Metformin 1000mg BID

Labs include:

sCr: 0.9
BUN: 15
CrCl: 86ml/min
K+: 4.2
Na+: 140

Question 1

Based on patient's current medications, what changes do you recommend for his antihypertensive regimen?

1. START spironolactone 25mg daily
2. STOP HCTZ, and START chlorthalidone 50mg daily
3. STOP HCTZ, and START spironolactone 25mg daily
4. No changes and have patient monitor BP at home

Question 2

For a patient currently on amlodipine 10mg daily, chlorthalidone 50mg daily and losartan 100mg daily; which of the following drugs would be preferred in the treatment of resistant hypertension?

1. Spironolactone
2. Hydralazine
3. Clonidine
4. Carvedilol

Isolated Systolic HTN (ISH)

Prevalence and Prognosis

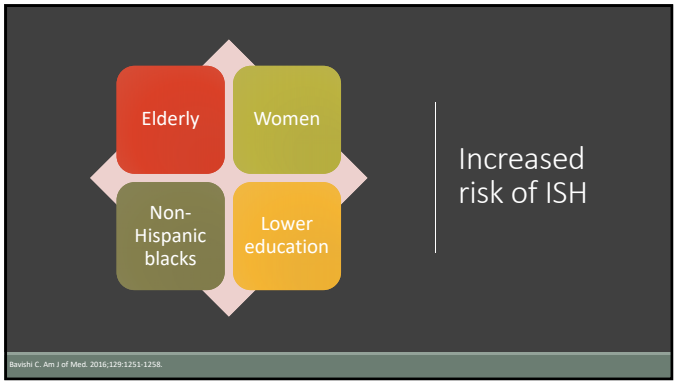
Prevalence of ISH:

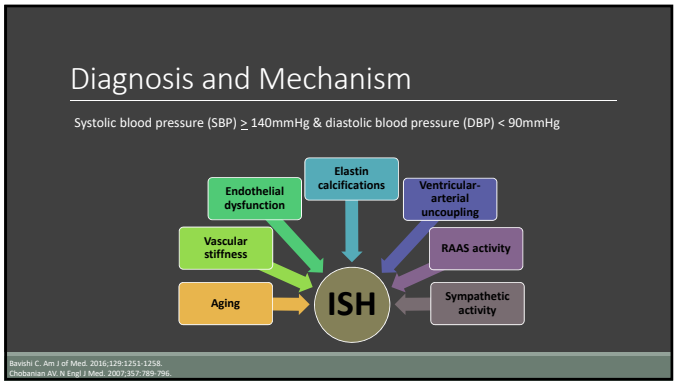
- Overall → 9.4%
- Elderly (age ≥ 60 years) → 29.4%
- Age 40-59 years → 6%
- Age 18-39 years → 1.8%

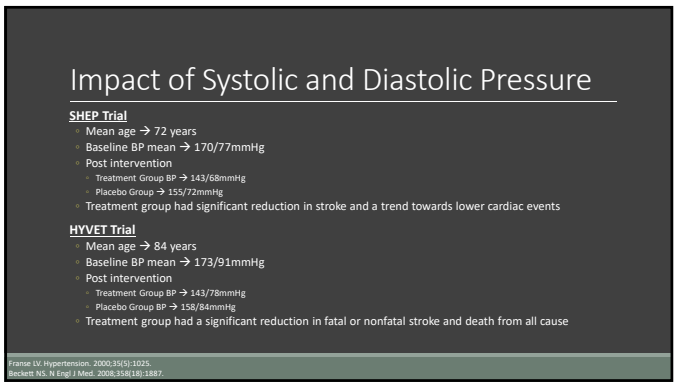
Prognosis of ISH:

- 2 to 4 fold increase risk of myocardial infarction, left ventricular hypertrophy, renal dysfunction, stroke, and cardiovascular mortality
- 34% increase in coronary artery disease, 33% increase in cerebrovascular disease, and 26% increase in heart failure
- Systolic and pulse pressure are directly related to cardiovascular risk
- Diastolic pressure is inversely related to cardiovascular risk

Ravishi C. Am J of Med. 2016;129:1251-1258.
Izzo JL Jr. Hypertension. 2000;35(5):1021.
Young JH. J Am Soc Nephrol. 202;13(11):2776.


Elderly
Women
Non-Hispanic blacks
Lower education
Increased risk of ISH
Bavishi C. Am J of Med. 2016;129:1251-1258.


Diagnosis and Mechanism
Systolic blood pressure (SBP) ≥ 140mmHg & diastolic blood pressure (DBP) < 90mmHg
Elastin calcifications
Endothelial dysfunction
Ventricular-arterial uncoupling
Vascular stiffness
RAAS activity
Aging
ISH
Sympathetic activity
Bavishi C. Am J of Med. 2016;129:1251-1258.
Chobanian AV. N Engl J Med. 2007;357:789-796.


Impact of Systolic and Diastolic Pressure
SHEP Trial
Mean age → 72 years
Baseline BP mean → 170/77mmHg
Post intervention
Treatment Group BP → 143/68mmHg
Placebo Group → 155/72mmHg
Treatment group had significant reduction in stroke and a trend towards lower cardiac events
HYVET Trial
Mean age → 84 years
Baseline BP mean → 173/91mmHg
Post intervention
Treatment Group BP → 143/78mmHg
Placebo Group BP → 158/84mmHg
Treatment group had a significant reduction in fatal or nonfatal stroke and death from all cause
Franse LV. Hypertension. 2000;35(5):1025.
Beckett NS. N Engl J Med. 2008;358(18):1887.

Treatment of ISH

First line → all showed reduced risk of stroke and other morbid events
- Thiazide-like diuretics
  - Chlorthalidone or indapamide
  - HCTZ does NOT decrease morbidity; mortality is similar
- Dihydropyridine calcium channel blockers
  - Amlodipine, nitrendipine, nifedipine

Second line → less efficacy in ISH compared to first line agents
- ACEi
- ARB
  - Still consider as first line for patients with compelling indications

Franse LV. Hypertension. 2000;35(5):1025.
Beckett NS. N Engl J Med. 2008;358(18):1887.

After triple therapy

Spironolactone or eplerenone

Doxazosin

Nebivolol

Bavishi C. Am J of Med. 2016;129:1251-1258.

Beta-Blockers

- Little efficacy for management of hypertension
- Impact on peripheral not central blood pressure
- LIFE-ISH trial showed atenolol was inferior to losartan for cardiovascular risk reduction
- STOP-2 trial showed highest events for stroke in diuretic + beta blockers vs. ACEi + CCB

Franse LV. Hypertension. 2000;35(5):1025.
Beckett NS. N Engl J Med. 2008;358(18):1887.

Question 1

Which classes of antihypertensive been shown to positively impact the morbidity and mortality associated with ISH?

1. Thiazide + Beta Blockers
2. Thiazide + CCB
3. CCB + ACEi
4. Thiazide + ACEi

Question 2

With which of the following comorbidities would ACEi or ARB therapy be consider as a first line therapy in a patient with ISH?

1. COPD
2. Heart Failure
3. Anemia
4. Hyperlipidemia

Lipid management

Cardiovascular Disease

Leading cause of morbidity and mortality in middle and high income countries worldwide

Direct link between LDL-C and cardiovascular events

First-line treatment → statin therapy

Treatment goals may not be met
- Despite maximal statin dose
- Statin intolerances

Grundy SM. JACC. 2019;73(24):e285-e350.
Hammersley D. Ther Adv Chronic Dis. 2017;8(1):4-11)

Clinical ASCVD

All patients:
- High intensity or maximally tolerated statin

Subsection: Very high risk ASCVD
- History of multiple major ASCVD events or 1 major event and multiple high risk conditions
  - If LDL-C is >70mg/dL, consider addition of nonstatin therapy

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High Risk for Future ASCVD Event

Major ASCVD Events	High risk Conditions
• Recent acute coronary syndrome • History of myocardial infarction • History of ischemic stroke • Symptomatic peripheral arterial disease	• Age ≥ 65 years • Heterozygous familial hypercholesterolemia • History of prior coronary artery bypass surgery or PCI • Diabetes mellitus • Hypertension • Chronic kidney disease (eGFR 15-59ml/min/1.73m^2) • Current smoker • Persistently elevated LDL-C ≥ 100mg/dL despite max statin and ezetimibe • History of congestive heart failure

Grundy SM. JACC. 2019;73(24):e285-e350.

Severe Primary Hypercholesterolemia

All patients 20-75 years with LDL-C ≥190mg/dL	• High intensity or maximally tolerated statin
Subsection: If LDL-C is >100mg/dL on statin	• Consider adding ezetimibe
Subsection: If LDL-C has not decreased by 50% and TG are <300mg/dL on statin and ezetimibe	• Consider addition of bile acid sequestrant
Further subsection: If LDL-C is >100mg/dL on statin and ezetimibe AND patient has multiple risk factors	• Consider adding PSCK9i

Grundy SM. JACC. 2019;73(24):e285-e350.

Diabetic patients

Age 40-75 years with LDL-C 70-189mg/dL

- Start moderate intensity statin
  - Aim for 30-50% reduction in LDL-C
- Do not need to calculate ASCVD risk score

Subsection: Patients age 50-75 years OR with multiple risk factors

- Reasonable to use high intensity statin
  - Aim for at least 50% reduction in LDL-C

Subsection: Patients age >75 years

- Clinical assessment and risk discussion

Grundy SM. JACC. 2019;73(24):e285-e350.

DM-Specific Risk Enhancers

Long duration
- ≥10 years for type 2 or ≥20 years for type 1)
- Albuminuria ≥30mg albumin/mg creatinine
- eGFR <60ml/mini/1.73m^2
- Retinopathy
- Neuropathy
- Ankle brachial index <0.9

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Non-diabetic Patients

Patients 40-75 years with LDL-C 70-189mg/dL and ASCVD 10 year risk score ≥7.5%

- Start moderate intensity statin

Subsection: If risk status is uncertain

- Consider coronary artery calcium

Subsection: If ASCVD 10 year risk is 5-7.5% with risk factors

- May favor statin therapy

Subsection: If ASCVD 10 year risk is ≥20%

- Start high intensity statin

Grundy SM. JACC. 2019;73(24):e285-e350.

Risk-Enhancing Factors

- Family history of premature ASCVD
- Persistently elevated LDL-C levels ≥160mg/dL
- Persistently elevated TG ≥175mg/dL
- Metabolic syndrome
- Chronic kidney disease
- History of preeclampsia
- Premature menopause
- Chronic inflammatory disorders
- High risk ethnic groups

Grundy SM. JACC. 2019;73(24):e285-e350.

Coronary Artery Calcium Scores

If CAC score = 0	If CAC score = 1-99	If CAC score ≥ 100

• Statin therapy may be withheld or delayed
• Unless patient is a:
  • Smoker
  • Has diabetes
  • Strong family history of premature ASCVD
	• Favors the use of statin therapy	• Statin therapy is indicated

Grundy SM. JACC. 2019;73(24):e285-e350.

Patients who may benefit from CAC

- Patients reluctant to start statin who wish to better understand their risk
- Patients concerned about re-trialing statin after discontinuation due to side effects
- Older patients (male 55-80 or women 60-80 year) with low risk and question their benefit from statins
- Middle aged adults (40-55 years) with 10 year risk score of 5-7.5% with risk factors

Grundy SM. JACC. 2019;73(24):e285-e350.

Monitoring

Check lipid panel 4-12 weeks after initiating therapy

Recheck lipid panel every 3-12 months as clinically indicated

Grundy SM. JACC. 2019;73(24):e285-e350.

Statins and Their Intensities

Low	Moderate	High
• Simvastatin 10mg • Pravastatin 10-20mg • Lovastatin 20mg • Fluvastatin 20-40mg	• Atorvastatin 10-20mg • Rosuvastatin 5-10mg • Simvastatin 20-40mg • Pravastatin 40-80mg • Lovastatin 40-80mg • Fluvastatin 40mg BID or XL 80mg daily • Pitavastatin 1-4mg daily	• Atorvastatin 40-80mg • Rosuvastatin 20-40mg

Grundy SM. JACC. 2019;73(24):e285-e350.

Ezetimibe

Mechanism of action
- Selective inhibits intestinal cholesterol absorption

Therapeutic effect
- Additional 12-19% LDL-C lowering when added to statin

IMPROVE-IT Trial
- Duration → 10 years
- Patient population → high risk patients with LDL-C <125mg/dL
- Assessed impact of ezetimibe therapy in conjunction with simvastatin vs. simvastatin monotherapy
- Results →
  - LDL-C → 53.7mg/dL vs 69.5mg/dL (p<0.001)
  - Cardiovascular event rate → 32.7% vs 34.7% (p=0.016)
  - No difference in adverse events

Cannon C. N Engl J Med. 2015;372:2387–2397

Bile Acid Sequestrants

Mechanism of action
- Binds to bile acids in the intestine and prevents them from being reabsorbed into the blood
- Body needs cholesterol to make bile → liver uses cholesterol from blood → reduces LDL-C in blood

Therapeutic effect
- Additional 15-30% LDL-C lowering when added to statin

Effects of Bile Acid Sequestrants
- Meta-analysis of randomized controlled trials
  - Cholestyramine and colesevelam
- Assess effect of bile acid sequestrants on cardiovascular risk
- Results →
  - Cholestyramine reduced LDL-C by 23.5mg/dL
  - Colesevalam reduced LDL-C by 22.7mg/dL
  - No significant reduction in cardiovascular risk

Ross S. Circ Cardiovasc Genet. 2015;8(4)L618-627.

PSCK9-inhibitors

Mechanism of action
- Blocking activity of PCSK9 reduces degradation of LDL receptors and increases clearance of LDL-C

Therapeutic effect
- Additional 12-19% LDL-C lowering when added to statin

FOURIER Trial
- Patient population → established CV disease on statin
- Assessed impact of evolocumab therapy in conjunction with statin vs. statin + placebo
- Results →
  - LDL-C → absolute reduction of PCSK9I of 56mg/dL (median LDL-C in with PCSK9i = 30mg/dL)
  - Cardiovascular event rate → 12.6% vs 14.6% (p<0.0001)
  - No difference in adverse events

Murphy SA. JAMA Cardiol. 2019

Patient Case

RJ is a 55 year old AA male who had an LDL of 210mg/dL at baseline. Three months ago, patient was started on rosuvastatin 40mg daily. One week ago, his lipid panel was repeated which showed: LDL = 110, HDL = 40, TG = 140.

Question 1

Is RJ currently meeting goal for his cholesterol management?

1. Yes

2. No

Question 2

According to the 2018 guidelines, what additional therapy would you consider for RJ?

1. Ezetimibe, patient's LDL is >100mg/dL on statin therapy

2. Bile acid sequestrant, patient's LDL is >100mg/dL on statin therapy

3. PCSK9i, patient's LDL is >100mg/dL on statin therapy

Drugs/Substances increasing BP

- NSAIDS
- Oral contraceptives
- Sympathomimetic
- Cyclosporine
- Tacrolimus
- Erythropoietin
- VEFF inhibitors
- Alcohol
- Cocaine
- Amphetamines
- Antidepressants
- Glucocorticoids
- Mineralocorticoids