Blood Pressure

Cholesterol Management

OPL Patient Profile CE Program – 2017
BLOOD PRESSURE:
Evidence Based Guideline to Simplify Clinical Management
LEARNING OBJECTIVES

- Review basic concepts related to hypertension (HTN)
- Understand the background data and development of the JNC-8 guidelines (Joint National Committee)
- Devise evidence-based treatment plans for managing hypertension and discuss the different medications used
- Highlight the limitations of the new guideline
IMPACT OF HYPERTENSION

- Leading risk factor for cardiovascular diseases (CVD) and mortality worldwide
- Over 1 billion individuals in the world!
- Over 7 million deaths per year
- Over 1/3 of the Lebanese population
- 75% of the Lebanese aged >65 years have hypertension
- Around 50% of hypertensive Lebanese patients are receiving medical therapy
- 54% have controlled hypertension on therapy
BLOOD PRESSURE DEFINITION

- **BP = CO** (cardiac output) $\times$ **PVR** (peripheral vascular resistance)

- Arterial blood pressure is necessary for organ perfusion

- Sympathetic Nervous System (SNS), Renin Angiotensin Aldosterone System (RAAS), and plasma volume affect the blood pressure

BP MEASUREMENT

- Right machine
- Well seated
- 5 minutes of rest
- No conversation
- Arm at heart level
- Avoid tobacco or caffeine before BP measurement
- Two seated readings
- Major role in ambulatory BP measurement

## BP ELEVATION

### 1º (Essential) HTN
- Age
- Obesity
- Family History
- Race
- High Sodium diet >3g
- Alcohol Consumption
- Physical Inactivity

### 2º HTN
- Chronic kidney disease
- Primary aldosteronism
- Obstructive sleep apnea
- Pheochromocytoma
- Cushing's syndrome
- Coarctation of the aorta
- Hyperthyroidism / Hyperparathyroidism
- Illicit drug use

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COMPLICATIONS OF HIGH BP

- Heart failure (HF)
- Myocardial infarction (MI)
- Ischemic stroke
- Intracerebral hemorrhage
- Renal dysfunction
- Ocular problems
- Cognitive decline?!
GUIDELINE DEVELOPMENT

Earliest Guidelines


JNC I JNC II JNC III JNC IV JNC V JNC VI JNC 7

8th Report

NHBPEP Starts

28 drugs DBP ≥105 Diuretics

34 drugs Diuretics

43 drugs Low dose diuretics, β-blockers Added

50 drugs ACEI, CCB

68 drugs Diuretics/β blockers

84 drugs 7 options

>125 drugs Diuretics (ALLHAT)
2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults
Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD;
Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH;
Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS;
Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD;
Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH
Evidence-based guideline
- RCT
- >2000 participants
- Multicentre trials since 1966

Three highest-ranked questions related to BP management:
- Does initiating antihypertensive therapy at a specific BP threshold improve outcomes? **THRESHOLD**
- Does treatment with antihypertensive therapy to a specific BP goal lead to improved outcomes? **GOAL**
- Do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific outcomes? **CHOICE**

Nine major recommendations
## RECOMMENDATIONS’ STRENGTH

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong Recommendation There is high certainty based on evidence that the net benefit is substantial.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate Recommendation There is moderate certainty based on evidence that the net benefit is moderate to substantial or there is high certainty that the net benefit is moderate.</td>
</tr>
<tr>
<td>C</td>
<td>Weak Recommendation There is at least moderate certainty based on evidence that there is a small net benefit.</td>
</tr>
<tr>
<td>D</td>
<td>Recommendation against There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.</td>
</tr>
<tr>
<td>E</td>
<td>Expert Opinion (“There is insufficient evidence or evidence is unclear or conflicting, but this is what the committee recommends.”) Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the committee thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.</td>
</tr>
<tr>
<td>N</td>
<td>No Recommendation for or against (“There is insufficient evidence or evidence is unclear or conflicting.”) Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the committee thought no recommendation should be made. Further research is recommended in this area.</td>
</tr>
</tbody>
</table>
LIFESTYLE RECOMMENDATIONS

- Moderate sodium reduction
- Regular exercise
- Weight loss
- Alcohol intake
- DASH diet
**RECOMMENDATION #1**

- **60 years** old patients and above → **Lower BP < 150/90 mmHg (A)**

- Lower BP with no adverse effects → Continue the treatment

- Conflict for high-risk patients
RECOMMENDATION # II

- **30-59 years old patients** → **DBP < 90 mmHg** *(A)*
- **18-29 years old patients** → **DBP < 90 mmHg** *(E)*

- Controlled DBP reduces CV events, HF, and M&M
- Caution for low DBP < 60 mmHg
RECOMMENDATION # III

- Patients < 60 years old $\rightarrow$ SBP < 140 mmHg (E)
RECOMMENDATION # IV

- Chronic Kidney Disease (CKD) patients (18-70 years) → BP < 140/90 mmHg (E)

- CKD means CrCl < 60 mL/min; or albuminuria defined as >30 mg of albumin/g of creatinine

- For patients > 70 years old → Individualize the treatment
Diabetic patients $\rightarrow$ BP $<$ 140/90 mmHg (E)

- Supported by the ACCORD trial, and the UKPDS study
- First 5 recommendations $\rightarrow$ Thresholds & goals
### SUMMARY: BP GOALS

<table>
<thead>
<tr>
<th>Category</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 YEARS OLD</td>
<td>&lt;150/90 mmHg</td>
</tr>
<tr>
<td>&lt; 60 YEARS OLD</td>
<td>&lt;140/90 mmHg</td>
</tr>
<tr>
<td>CKD</td>
<td>&lt;140/90 mmHg</td>
</tr>
<tr>
<td>DIABETES</td>
<td>&lt;140/90 mmHg</td>
</tr>
</tbody>
</table>
RECOMMENDATION # VI

- Any non-black patient with no diabetes nor CKD (B)
- Thiazides (chlorthalidone) showed benefits in HF
- Beta-blockers might increase stroke risk
- Alpha-blockers might increase HF risk
RECOMMENDATION # VII

- **Black patients** without diabetes (B), or with diabetes (C) → **Diuretics** or **CCB**

- Blacks on ACE Inhibitors vs. CCB had a higher stroke risk

- More studies for blacks with diabetes
**RECOMMENDATION #VIII**

- **CKD** patients >18 years → **ACE Inhibitor** or **ARB** (B)
- Treatment is a **priority** regardless of race or diabetes
- ACE Inh or ARB improve kidney outcome
- Monitor renal function and electrolytes

![Diagram showing C(CKD) → B(Black) → D(Diabetic)]
RECOMMENDATION # IX (E)

- Attain and maintain BP
- Two strategies if goal is not achieved within one month:
  - Increase the dose of the initial drug
  - Add a second drug
- Two drugs are not enough → add drug #3
- Refer to a HTN specialist
- Remarks:
  - Dual therapy to start when BP > 160/100 mmHg
  - Spironolactone role in resistant HTN
  - Compelling indications for beta blockers exist (CAD - HF - post MI)
TREATMENT REVIEW

GENERAL POPULATION
- THIAZIDES - CCB - ACE I - ARB

BLACKS
- THIAZIDES - CCB

CKD
- ACE I - ARB
MEDICATION REMARKS

- **THIAZIDES:**

  - Chlorthalidone/Indapamide might be superior
  - Avoid when CrCl < 30 mL/min (Loops)
  - Hyperuricemia and gout!
  - Monitor the electrolytes
  - Prescribe low to moderate doses
  - Doses:
    - Hydrochlorothiazide 12.5-25 mg
    - Chlorthalidone 12.5-25 mg
    - Indapamide 1.25-2.5 mg
MEDICATION REMARKS

- **ACE inhibitors / ARBs:**
  - Start with a low dose
  - Dry cough, angioedema
  - Avoid in pregnancy
  - Monitor creatinine, and potassium
  - Avoid in bilateral renal artery stenosis
  - Never to be prescribed together
# ACE Inh / ARB DOSES

<table>
<thead>
<tr>
<th>GENERIC ACE I</th>
<th>DOSE RANGE</th>
<th>GENERIC ARB</th>
<th>DOSE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>12.5-50 mg bid/tid</td>
<td>Losartan</td>
<td>25-100 mg</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10-40 mg</td>
<td>Candesartan</td>
<td>8-32 mg</td>
</tr>
<tr>
<td>Perindopril</td>
<td>4-16 mg</td>
<td>Valsartan</td>
<td>80-320 mg</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5-10 (20) mg</td>
<td>Irbesartan</td>
<td>150-300 mg</td>
</tr>
<tr>
<td>Quinapril</td>
<td>10-80 mg</td>
<td>Telmisartan</td>
<td>40-80 mg</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>2-8 mg</td>
<td>Olmesartan</td>
<td>20-40 mg</td>
</tr>
<tr>
<td>Enalapril</td>
<td>10-40 mg</td>
<td>Eprosartan</td>
<td>400-800 mg</td>
</tr>
</tbody>
</table>
MEDICATION REMARKS

- **CCBs:**
  - Amlodipine (Dihydropyridine:DHP) lacks negative inotopic/chronotropic effects
  - Verapamil and diltiazem (non-DHP) have significant negative inotropic and chronotropic effects
  - Non-DHPs have many drug interactions

- Pedal edema is a common side effect

- Commonly used drugs: Amlodipine/Felodipine (2.5-10 mg), Lercanidipine (10-20 mg) Nifedipine XL (30-90 mg), Diltiazem XL (120-180 mg bid), Verapamil SR (120-480 mg)
ALGORITHM

Adult aged ≥18 years with hypertension

Implement lifestyle interventions (continue throughout management).

Set blood pressure goal and initiate blood pressure lowering medication based on age, diabetes, and chronic kidney disease (CKD).

General population (no diabetes or CKD)

Diabetes or CKD present

All ages

Diabetes present

No CKD

Blood pressure goal
SBP < 150 mm Hg
DBP < 90 mm Hg

Blood pressure goal
SBP < 140 mm Hg
DBP < 90 mm Hg

Blood pressure goal
SBP < 140 mm Hg
DBP < 90 mm Hg

Blood pressure goal
SBP < 140 mm Hg
DBP < 90 mm Hg

All ages

CKD present with or without diabetes

Age ≥60 years

Age <60 years

Blood pressure goal
SBP < 140 mm Hg
DBP < 90 mm Hg

Nonblack

Black

Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination.

Initiate thiazide-type diuretic or CCB, alone or in combination.

Initiate ACEI or ARB, alone or in combination with other drug class.
## COMPARISON OF HTN GUIDELINES

<table>
<thead>
<tr>
<th>Blood Pressure (mm Hg)</th>
<th>NICE 2011</th>
<th>ESH/ESC 2013</th>
<th>AHA/ACC/CDC 2013</th>
<th>ASH/ISH 2014</th>
<th>JNC 8 2014</th>
<th>ACC/AHA/ASH IHD 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition of hypertension</strong></td>
<td>≥140/90 and daytime ABPM or home BP ≥135/85</td>
<td>≥140/90</td>
<td>≥140/90</td>
<td>≥140/90</td>
<td>Not addressed</td>
<td>Not addressed</td>
</tr>
<tr>
<td><strong>Drug therapy</strong></td>
<td>≥160/100 or daytime ABPM ≥150/95</td>
<td>≥140/90</td>
<td>≥140/90</td>
<td>≥140/90</td>
<td>&lt;60 yr ≥140/90 &lt;60 yr ≥150/90</td>
<td>≥140/90</td>
</tr>
<tr>
<td><strong>β-Blockers as first-line drug</strong></td>
<td>No (Step 4)</td>
<td>Yes</td>
<td>No (Step 3)</td>
<td>No (Step 4)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Diuretic</strong></td>
<td>Chlorthalidone Indapamide</td>
<td>Thiazides, Chlorthalidone, Indapamide</td>
<td>Thiazides</td>
<td>Thiazides, Chlorthalidone, Indapamide</td>
<td>Thiazides, Chlorthalidone, Indapamide</td>
<td>Thiazides, Chlorthalidone, Indapamide</td>
</tr>
<tr>
<td><strong>Initiate therapy with two drugs</strong></td>
<td>Not mentioned</td>
<td>In patients with markedly elevated BP</td>
<td>≥160/100</td>
<td>≥160/100</td>
<td>≥160/100</td>
<td>≥160/100</td>
</tr>
<tr>
<td><strong>BP targets</strong></td>
<td>&lt;140/90 80 yr &lt;150/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;60 yr &lt;140/90 &lt;60 yr &lt;150/90</td>
<td>&lt;140/90 130/80 if CAD, CAD risk equivalent, stroke, TIA, Framingham risk score ≥20%</td>
</tr>
<tr>
<td><strong>BP target in patients with diabetes mellitus</strong></td>
<td>Not addressed</td>
<td>&lt;140/85</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
</tr>
</tbody>
</table>
Key Takeaways

- JNC 8 is a high-quality evidence-based guideline

- Limitations exist:
  - Prior CVD patients are not addressed
  - High risk patients (60-80 yrs) might suffer from higher stroke rates
  - SPRINT, FEVER might impact the new guidelines to lower the BP threshold
  - No guidance for resistant HTN beyond referral to a specialist

- These recommendations are not a substitute for clinical judgment, and decisions must carefully consider each individual patient
CASE SCENARIOS
Rima is a 64 years old woman suffering from HTN, & dyslipidemia. She tolerates her medications well except for minor pedal edema since starting her anti-hypertensive medication. Current medications are amlodipine 5 mg/d and rosuvastatin 10 mg/d. On exam, the average of 2 BP readings is 158/88 mmHg which is consistent with measurements she has obtained at home.

Which of the following is the most appropriate next step in management?

A- Add lisinopril
B- Add metoprolol
C- Increase the dose of amlodipine to 10 mg/d
D- Add spironolactone
E- Continue current regimen
CASE 2

A 57 African man is evaluated for treatment of newly diagnosed HTN. History is notable for high cholesterol which is treated with simvastatin 40 mg/d. On exam, BP 152/94 mmHg, HR 72 bpm, BMI 28. Labs show Cr 1.0 mg/dL, fasting glucose 99 mg/dL, and K+ 4.4 meq/L.

In addition to recommending lifestyle modifications, which of the following drugs would you select?

A- Ramipril
B- Verapamil
C- Indapamide
D- Valsartan
E- Two of the above
Mazen is a 48 year old man visiting a clinic for newly diagnosed HTN confirmed by multiple measurements. On exam, BP 162/95 mmHg, HR 64 bpm. Labs show Cr 1.7 mg/dL, fasting glucose 141 mg/dL.

Which of the following is most likely to be effective in controlling Mazen’s hypertension?

A- Amlodipine  
B- Lisinopril  
C- Losartan  
D- Telmisartan and Amlodipine  
E- Losartan and Lisinopril
Thank you...
CHOLESTEROL MANAGEMENT: State of the Art

OPL Patient Profile CE Program – 2017
Learning Objectives

- Discuss the relation between cholesterol and atherosclerotic cardiovascular disease (ASCVD)
- Discuss the ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce ASCVD in Adults
- Assess the role of statins in management of cholesterol with regard to efficacy, safety, and concomitant drug use
- Describe data from the IMPROVE-IT trial on the use of ezetimibe
- Explain the role of PCSK9 inhibitors in treating patients with dyslipidemia
ASCVD Facts

- Largest killer of men and women in Lebanon (47%)
- The root cause is elevated cholesterol carried by circulating apo B-containing lipoproteins
- **non–HDL-C** and **LDL-C**, [atherogenic cholesterol]
- Men have a higher prevalence
- **ASCV:**
  - Acute coronary syndrome (ACS)
    - Myocardial Infarction (MI)
    - Unstable Angina (UA)
  - Stable Angina
  - Stroke
  - Transient Ischemic Attack (TIA)
  - Peripheral Artery Disease (PAD)
Atherosclerosis Timeline

- **Normal**

- **Fatty streak**

- **Foam cells**

- **Lipid-rich plaque**

- **Fibrous cap**

- **Thrombus**

- **Lipid core**
CHD and Cholesterol

Lifetime Coronary Heart Disease (CHD) Risk (%)

Total Cholesterol Levels (mg/dL)

<200
200 - 239
>239

Men
Women
**Guidelines Timeline**

- **ATP I** 1988
  - Strong support for resins & niacin

- **ATP II** 1993
  - Statins included but fibrates for mixed hyperlipidemia

- **ATP III** 2002
  - Statins as a priority
    - LDL-C goal < 100 mg/dL

- **ATP III update** 2004
  - High risk patients (increasing statins dose)
    - LDL-C goal < 70 mg/dL

**Adult Treatment Panel: ATP**
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce ASCVD in Adults
Expert Panel

- 5-year collaborative effort between a diverse set of expert reviewers

- Evidence collected and assessed from randomized controlled trials (RCT), systemic reviews, & meta-analysis (highest quality evidence)

- Authors submitted relationships with industry (RWI) disclosures
Scope of the Guideline

- Treatment of adults > 21 years of age
- Managed cholesterol and not dyslipidemia

Answered 3 critical questions:
  - Whom to treat?
  - With what we will treat?
  - How intensively we will treat?

Recommended the utilization of the new Pooled Cohort Equations for ASCVD risk assessment in a subset of patients
ASCVD Calculator


![ASCVD Risk Calculator Image](image-url)
Recommendations

- Encourage adherence to a healthy lifestyle

- "Treat to target" and "lower is best" strategies are no longer advocated
Recommendations (cont’d)

- Recommend statin therapy in 4 groups
- Reinforce on clinician – patient discussion before initiating statin therapy
- Select the appropriate statin intensity
- Regularly monitor patients for adherence to lifestyle and statin therapy
Gray Area

New York Heart Association (NYHA) class II-IV ischemic systemic heart failure

Hemodialysis patients

Elderly > 75 years, unless ASCVD is present
Four Statin Benefit Groups

1. **CLINICAL ASCVD PATIENTS**
   - LDL-C ≥ 190 mg/dL

2. **DIABETICS (40 – 75 yrs); with LDL-C 70 – 189 mg/dL**

3. **PATIENTS (40 – 75 yrs); with LDL-C 70 – 189 mg/dL & ASCVD RISK ≥ 7.5%**
Clinical ASCVD:
- ACS
- History of MI
- Stable or UA
- Coronary or other Arterial Revascularization
- Stroke – TIA
- PAD

Depends on patient age:
- Age ≤ 75 yrs ➔ High-intensity statin
- Age > 75 yrs ➔ Moderate-intensity statin
## Intensity of Statins

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease <strong>LDL-C ≥ 50%</strong></td>
<td>Decrease LDL-C by 30 - 50%</td>
<td>Decrease LDL-C &lt; 30%</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg</td>
<td>Fluvastatin 40 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4 mg</td>
<td></td>
</tr>
</tbody>
</table>
- Evaluate for secondary causes of hyperlipidemia
- Treat with **high-intensity statin**
- Achieve at least a 50% reduction in LDL-C
- Non-statin therapy may be considered for further reductions
Use the ASCVD risk calculator

- Diabetics (type 1 or 2) with an estimated 10-year (yr) ASCVD risk ≥ 7.5% ➔ **High-intensity statins**

- Diabetics (type 1 or 2) with an estimated 10-yr ASCVD risk < 7.5% ➔ **Moderate-intensity statins**
Use the ASCVD risk calculator

- Risk $\geq 7.5\% \rightarrow$ Moderate to high-intensity statin

- Risk 5.0 - 7.5% $\rightarrow$ Moderate intensity statin ?!
Factors to Consider (Risk 5 – 7.5 %)

- LDL-C $\geq 160$ mg/dL
- Evidence of genetic hyperlipidemias
- Family history of premature ASCVD
- C-Reactive Protein (CRP) $\geq 2$ mg/L
- Ankle-brachial index (ABI) $< 0.9$
- Coronary artery calcification $\geq 300$ Agatston units
Therapy Management

- Initial fasting lipid panel
- Baseline liver function tests (LFTs)
- Second panel within 4 – 12 weeks (continuous monitoring every 3 – 12 months)
- Decrease in statins’ dose may be considered when 2 consecutive values of LDL-C < 40 mg/dL
- Muscle symptoms ➔ Creatine Kinase (CK) measurement
Statins Mechanism of Action (1)

VLDL=very low-density lipoprotein
IDL=intermediate-density lipoprotein
Statins Mechanism of Action (2)
Statins Adverse Effects (5Ms)

- **Metabolic dysfunction**
  - New onset of diabetes (0.1-0.3 / 100 cases treated per yr)
  - Benefits outweigh the risks

- **Muscles**
  - Patient’s history
  - Monitor closely (CK >10 x normal limit, creatinine & signs/symptoms)
  - Evaluate for precipitating factors (Vitamin D deficiency, hypothyroidism, organ dysfunction, rheumatic conditions)
  - Manage accordingly (low doses, hydrophilic statins, coenzyme Q10, alternate dosing strategies)

- **Major organ effects**
  - Alanine transaminase (ALT) >3 times upper limit (Contraindication)
  - Renal dysfunction (rosuvastatin)

- **Maternal contraindication** (pregnancy category X)

- **Medication interactions**
  - Gemfibrozil, cyclosporine, amiodarone, macrolides, antifungal medications, digoxin, warfain, protease inhibitors, daptomycin, amlodipine
  - Least to interfere with CYP (pravastatin, fluvastatin)
Statin Safety Recommendations

- Moderate-Intensity statin therapy is used:
  - When high intensity is CI
  - In the presence of characteristics predisposing to S.E:
    - Multiple or serious comorbidities (impaired renal or hepatic function)
    - History of previous statin intolerance or muscle disorders
    - Unexplained ALT elevations >3 times ULN
    - Concomitant use of drugs affecting statin metabolism
    - >75 years of age
    - History of hemorrhagic stroke
    - Asian ancestry
When should a non-statin be used in a patient with hypercholesterolemia?
## Dyslipidemia Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td>↓ 18-55%</td>
<td>↑ 5-15%</td>
<td>↓ 7-30 %</td>
</tr>
<tr>
<td><strong>BAS</strong></td>
<td>↓ 15-30%</td>
<td>↑ 3-5%</td>
<td>↑ 0-10%</td>
</tr>
<tr>
<td><strong>Nicotinic acid</strong></td>
<td>↓ 5-25%</td>
<td>↑ 15-35%</td>
<td>↓ 20-50 %</td>
</tr>
<tr>
<td><strong>Fibric acids</strong></td>
<td>↓ 5-↑20%</td>
<td>↑ 10-20%</td>
<td>↓ 20-50 %</td>
</tr>
<tr>
<td><strong>Cholesterol absorption inhibitors</strong></td>
<td>↓ 13-20%</td>
<td>↑ 3-5%</td>
<td>↓ 5-11%</td>
</tr>
<tr>
<td><strong>Long-chain omega-3 fatty acid drugs</strong></td>
<td>↓ 6-↑25%</td>
<td>↓ 5-↑7 %</td>
<td>↓ 19-44%</td>
</tr>
<tr>
<td><strong>PCSK9 inhibitors</strong></td>
<td>↓ 40-72%</td>
<td>↑ 0-10%</td>
<td>↓ 0-17%</td>
</tr>
</tbody>
</table>

- **Primarily for hypertriglyceridemia**
- **For LDL-C lowering**

**BAS** = Bile acid sequestrants
**TG** = Triglycerides
Non-Statin Medications

POTENTIAL INDICATIONS

- In statin candidates but are completely statin intolerant
- Nonstatin only after maximally tolerated statin

FACTORS TO CONSIDER

- Monitor adherence to therapy and lifestyle
- Control other risk factors
- Evaluate percentage of LDL-C reduction

OPTIONAL INTERVENTIONS

- Ezetimibe as the first agent, BAS as a later option
- PCSK9 inhibitor with or in place of ezetimibe
- Niacin not recommended for use
- Mipomersen, lomitapide for patients with FH
2016 ACC Expert Consensus Decision Pathway: In Clinical ASCVD and co-morbidities

≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL in diabetes) on maximally tolerated statin

Yes

No

CLINICAN-PATIENT DISCUSSION REGARDING TREATMENT FACTORS

Decision for no additional medication

Optional nonstatin medications to consider

1. Consider ezetimibe first (consider bile acid sequestrant if ezetimibe intolerant and triglycerides <300 mg/dL)

2. Consider adding or replacing with PCSK9 inhibitor second

≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL in diabetes) on maximally tolerated statin

Yes

Continue to monitor adherence, treatment, LDL-C response
Ezetimibe

Inhibits intestinal cholesterol absorption

↓ intestinal delivery of cholesterol to liver

↑ expression of hepatic LDL-R

↓ cholesterol content of atherogenic particles

Liver Biosynthesis

Extrahepatic Tissues

Intestinal Absorption

Dietary Cholesterol

Biliary Excretion

Enterohepatic Circulation

Intestinal Absorption

Excretion

Intestinal Brush Border

Intestinal Lumen

Dose 10 mg daily
Ezetimibe

Double-blind randomized trial

IMPROVE-IT trial

18,144 patients with ACS

Simva vs ezetimibe

Age ≥50 years (LDL-C 50-125 mg/dL)

Rate at 7-years: 34.7% vs. 32.7% (p=0.016)

Hazard ratio, 0.936 (95% CI, 0.89–0.99)

P=0.016

Simvastatin monotherapy

Simvastatin–ezetimibe

Years since Randomization

Event Rate (%)

0 1 2 3 4 5 6 7

0 10 20 30 40 50 60 70 80 90 100
Ezetimibe

Results of IMPROVE-IT trial

- Lowering LDL reduces CVD events
  - MI, ischemic stroke, all cause CVD

- Even lower is even better
  - Achieved mean LDL-C 53 vs 70mg/dl at 1 year

- Confirms ezetimibe safety profile
  - No significant difference between-groups in LFT elevation, gallbladder or muscle related S.E. and cancer
Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) Inhibitors

Without PCSK9 inhibition

With PCSK9 inhibition

The mAb binds to PCSK9, inhibiting the binding of PCSK9 to LDLR.
## PCSK9 Inhibitors – Role in therapy

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA approval</strong></td>
<td>Adjunct to diet and maximally tolerated statin therapy who require additional lowering of LDL-C</td>
<td></td>
</tr>
<tr>
<td><strong>FDA indication</strong></td>
<td>• Clinical ASCVD &lt;br&gt;• Adults heterozygous FH</td>
<td>• Clinical ASCVD &lt;br&gt;• Adults heterozygous FH &lt;br&gt;• Adults homozygous FH</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>75 – 150 mg SC q 2 weeks</td>
<td>140 SC q 2 weeks or 420 mg SC once monthly in homozygous FH</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>• Use in statin intolerance is debated and evolving</td>
<td></td>
</tr>
</tbody>
</table>
PCSK9 Inhibitors – Efficacy and Safety

- LDL-C lowering effect

- Safety: No increase in serious and non serious S.E vs placebo

- Several pending large-scale outcome trials
## PCSK9 Inhibitors – Instructions and Counseling

<table>
<thead>
<tr>
<th>Injections</th>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Single-use, prefilled autoinjector or syringe</td>
<td>• Rotate injection sites</td>
<td>• The time required for injection is 15 sec</td>
</tr>
<tr>
<td>• Patient self-injects medicine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Storage</th>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Store unused syringes in refrigerator between 2 – 8°C</td>
<td>• Do not keep at room T° for &gt; than 24 hours</td>
<td>• May be stored at room T° if used within 30 days</td>
</tr>
<tr>
<td>• Protect from light</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Administration</th>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Do not shake</td>
<td>• Administer injection within 7 days after the missed dose</td>
<td></td>
</tr>
<tr>
<td>• Allow to warm to room T° for 30 – 40 mins</td>
<td>• Resume original schedule</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Missed a dose</th>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Administer injection within 7 days after the missed dose</td>
<td>• Resume original schedule</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comments</th>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Caution for allergic reactions (D/C and treat)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PCSK9 – Summary Points

**Advantages**

- Robust LDL-C reductions
- Best potential to significantly lower CV events, with statin therapy
- Well tolerated
- Preliminary outcomes data has positive trends
- Best option after statin therapy for FH

**Disadvantages**

- Outcomes data ongoing
- Injectable medication
- High cost
- Potential increase in insurance premiums
- Cost effectiveness studies are needed
- Reasonable to consider ezetimibe before PCSK9 inhibitor therapy
Key Takeaways

- ASCVD risk reduction is the overall goal
  - Aspirin
  - Blood pressure control & Body weight management
  - Cholesterol levels & Cigarette smoking cessation
  - Diet & Diabetes control
  - Exercise

- Lifestyle intervention is always the first step
- Moderate- or High-Intensity statin therapy approach
- Patient-Provider discussion to guide treatment
- Regular follow up to assess adherence

- Ezetimibe is the most proven nonstatin therapy in combination with statin to reduce ASCVD events
- PCSK9 inhibitors are potent and have a role (with statin therapy) in some patients with ASCVD and/or FH
SECOND OPINION

I'M NOT SURE HOW I FEEL ABOUT THE NEW CHOLESTEROL GUIDELINES...

STATINS
25¢
Case 1

- Rani is a 45-year old white man without any history of CV disease. His LDL-C is 194 mg/dL, and his 10-year risk for CV events is calculated to be 5%. According to the newest guideline, what is the best practice for this patient now?
  
  a. **Atorvastatin 10 mg/day**
  b. **Rosuvastatin 20 mg/day**
  c. **Pravastatin 20 mg/day**
  d. **No treatment is needed**
Case 2

- Which of the following has been reported to be associated with increased risk for muscle symptoms and rhabdomyolysis in patients on statin therapy?
  
  a. Gemfibrozil
  b. Fenofibrate
  c. Niacin
  d. Cholestyramine
Case 3

- Haifa is a 46 year old white woman with total cholesterol (TC) of 228 mg/dL, HDL 55 mg/dL and a SBP of 150 mmHg. We know that she is on amlodipine 5 mg/day but she is not diabetic nor a smoker.

- Her 10-year ASCVD risk is calculated to be 2%. The ideal treatment according to the guideline would be:
  a. **Atorvastatin 40 mg/day**
  b. **Fluvastatin XL 80 mg/day**
  c. **Simvastatin 20 mg/day**
  d. **No treatment is needed**
Case 4

- 59-year old woman admitted for acute MI
- PMH: hypercholesterolemia, chronic stable angina
- Treated: (States adherence)
  - Rosuvastatin 40 mg/day
  - Lifestyle modifications
  - AND other meds
- LDL-C has ↓ 40% from baseline, currently LDL-C 126 mg/dL

1. Which of the following do you recommend?
   a. Pt has achieved acceptable LDL-C reduction; no modifications to therapy are needed
   b. Pt had less-than-anticipated response on high-intensity statin; start ezetimibe
   c. Pt had less-than-anticipated response on high-intensity statin; try further increasing the dose prior to adding non-statin
   d. Pt is intolerant to statin therapy; stop rosvastatin
Case 4

- Based on your recommendations, the pt is now receiving Rosuvastatin 40 mg/day + Ezetimibe
- LDL-C has ↓ 45% from baseline

2. Which of the following do you recommend?
   a. Pt has achieved acceptable LDL-C reduction; no modifications to therapy are needed
   b. Pt should receive statin + niacin extended-release
   c. Pt should receive ezetimibe + a PCSK9 inhibitor
   d. Pt should receive statin + a PCSK9 inhibitor
Thank You