Blood Pressure

Cholesterol Management

OPL Patient Profile CE Program – 2017

BLOOD PRESSURE:

Evidence Based Guideline to Simplify Clinical Management

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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

Matar et al. J Clin Hypertens (Greenwich). 2015 May;17(5):381-8.

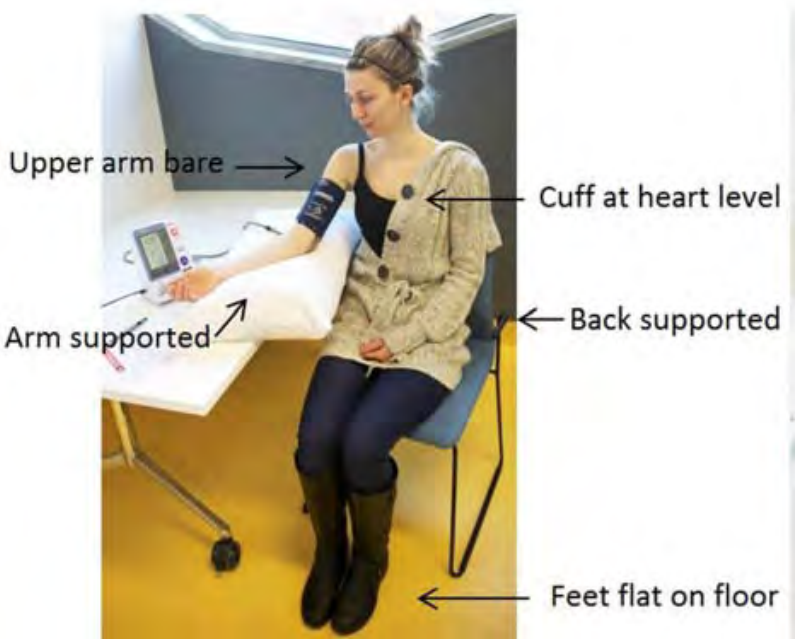
BLOOD PRESSURE DEFINITION

- **BP = CO** (cardiac output) **x 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

"Understanding blood pressure readings". American Heart Association. January 2011.

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



O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, et al. (2003). "European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement". *J. Hypertens.* **21** (5): 821–48.

BP ELEVATION

1º (Essential) HTN

- Age
- Obesity
- Family History
- Race
- High Sodium diet >3g
- Alcohol Consumption
- Physical Inactivity

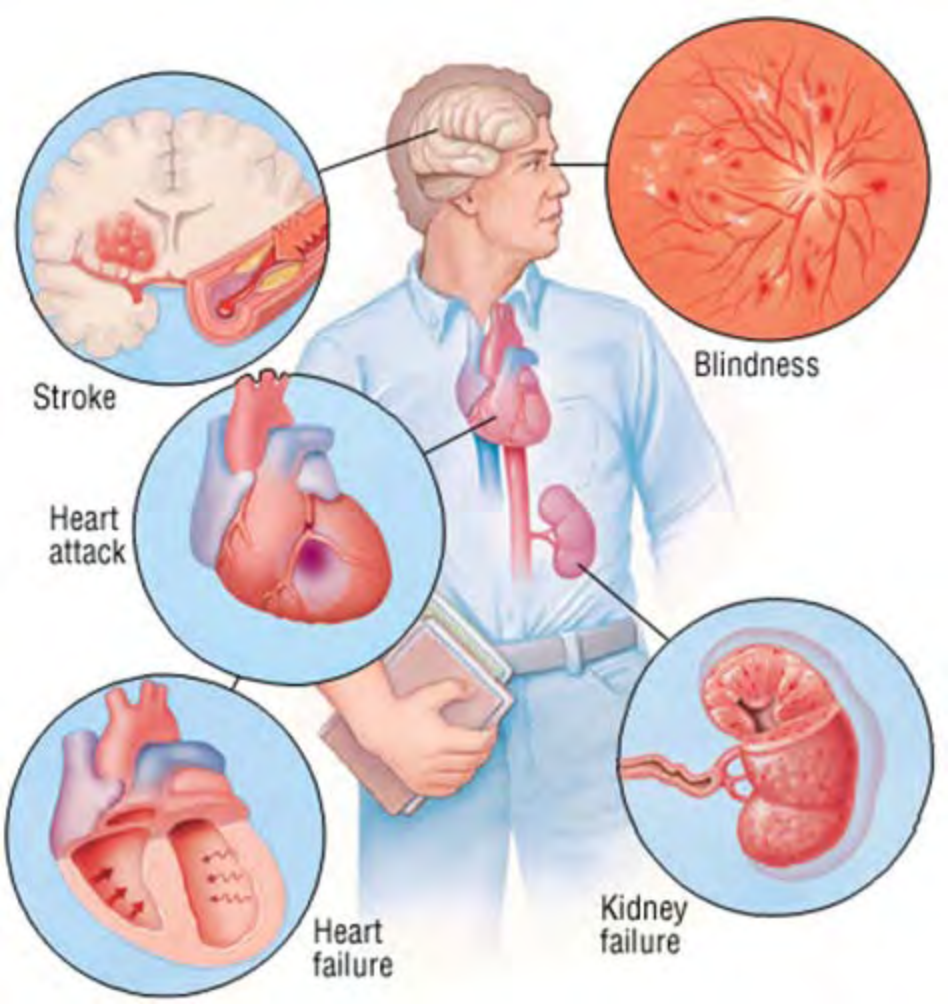
2º HTN

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

Poulter, NR; Prabhakaran, D; Caulfield, M (22 August 2015). "Hypertension.". Lancet (London, England). **386** (9995): 801–12.

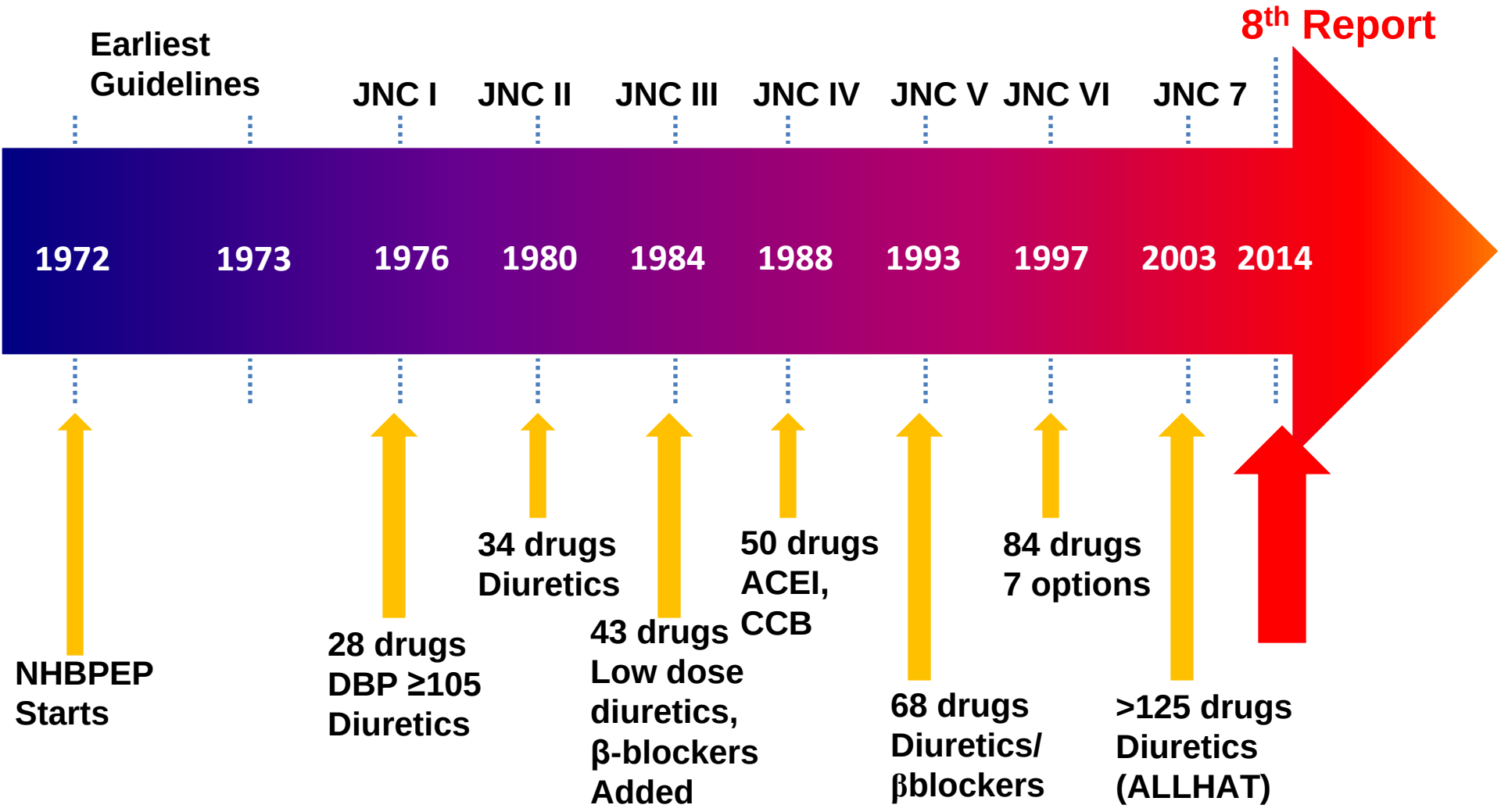
COMPLICATIONS OF HIGH BP

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



"Global health risks: mortality and burden of disease attributable to selected major risks" (PDF). World Health Organization. 2009.

GUIDELINE DEVELOPMENT



JNC-8

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

JAMA. 2014;311(5):507-520. doi:10.1001/jama.2013.284427

JNC-8 OVERVIEW

- 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

Grade	Strength of Recommendation
A	Strong Recommendation There is high certainty based on evidence that the net benefit is substantial.
B	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.
C	Weak Recommendation There is at least moderate certainty based on evidence that there is a small net benefit.
D	Recommendation against There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.
E	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.
N	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.

LIFESTYLE RECOMMENDATIONS

- Moderate sodium reduction
- Regular exercise
- Weight loss
- Alcohol intake
- DASH diet

RECOMMENDATION # I

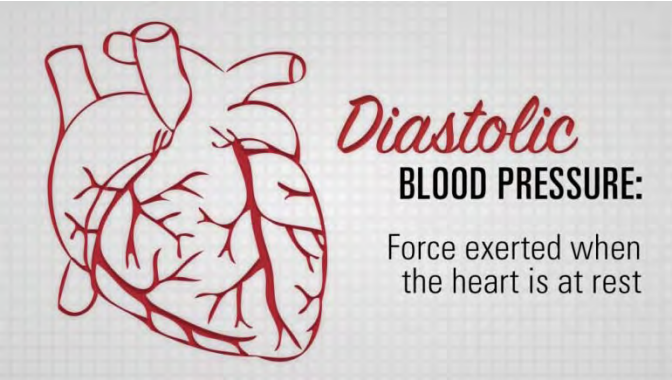
- **60 years** old patients and above → **Lower BP< 150/90 mmHg** (A)

- Lower BP with no adverse effects → Continue the treatment

- Conflict for high-risk patients

RECOMMENDATION # II

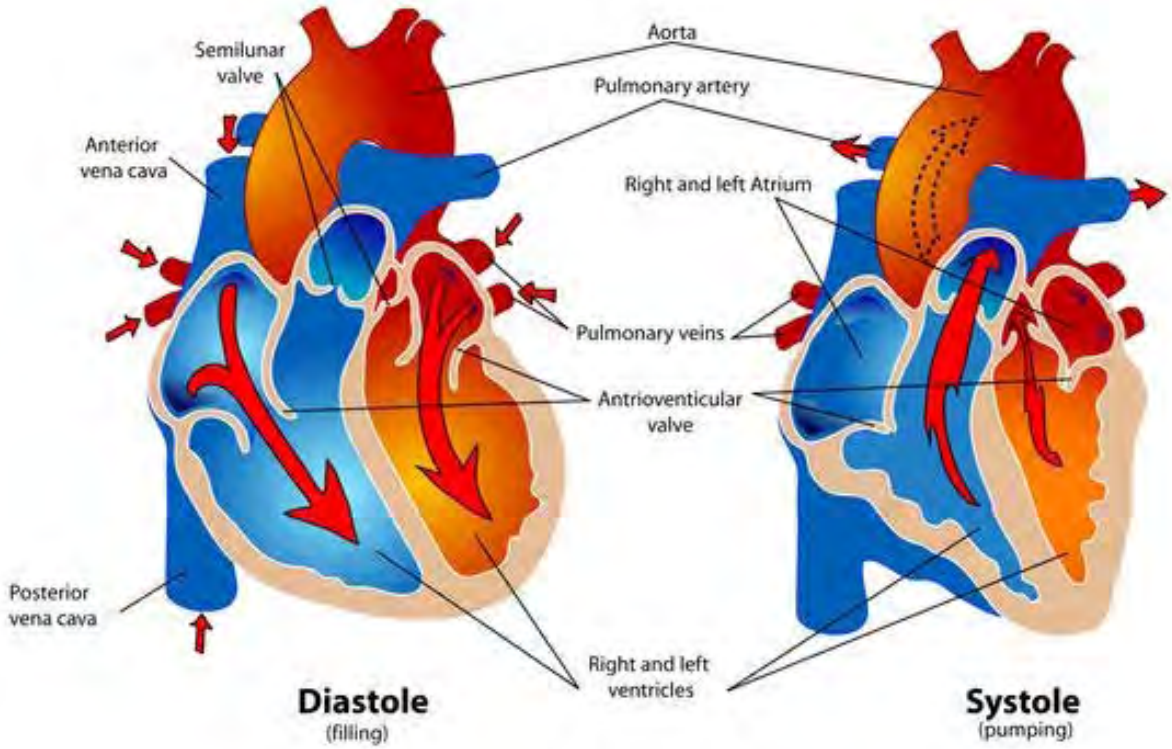
- **30-59** years old patients → **DBP < 90 mmHg** (A)
- **18-29** years old patients → **DBP < 90 mmHg** (E)



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

RECOMMENDATION # III

- Patients **< 60** years old → **SBP < 140 mmHg** (E)



RECOMMENDATION # IV

- Chronic Kidney Disease (**CKD**) patients (18-70years) →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

RECOMMENDATION # V

- **Diabetic** patients→ BP**< 140/90 mmHg** (E)

- Supported by the ACCORD trial, and the UKPDS study

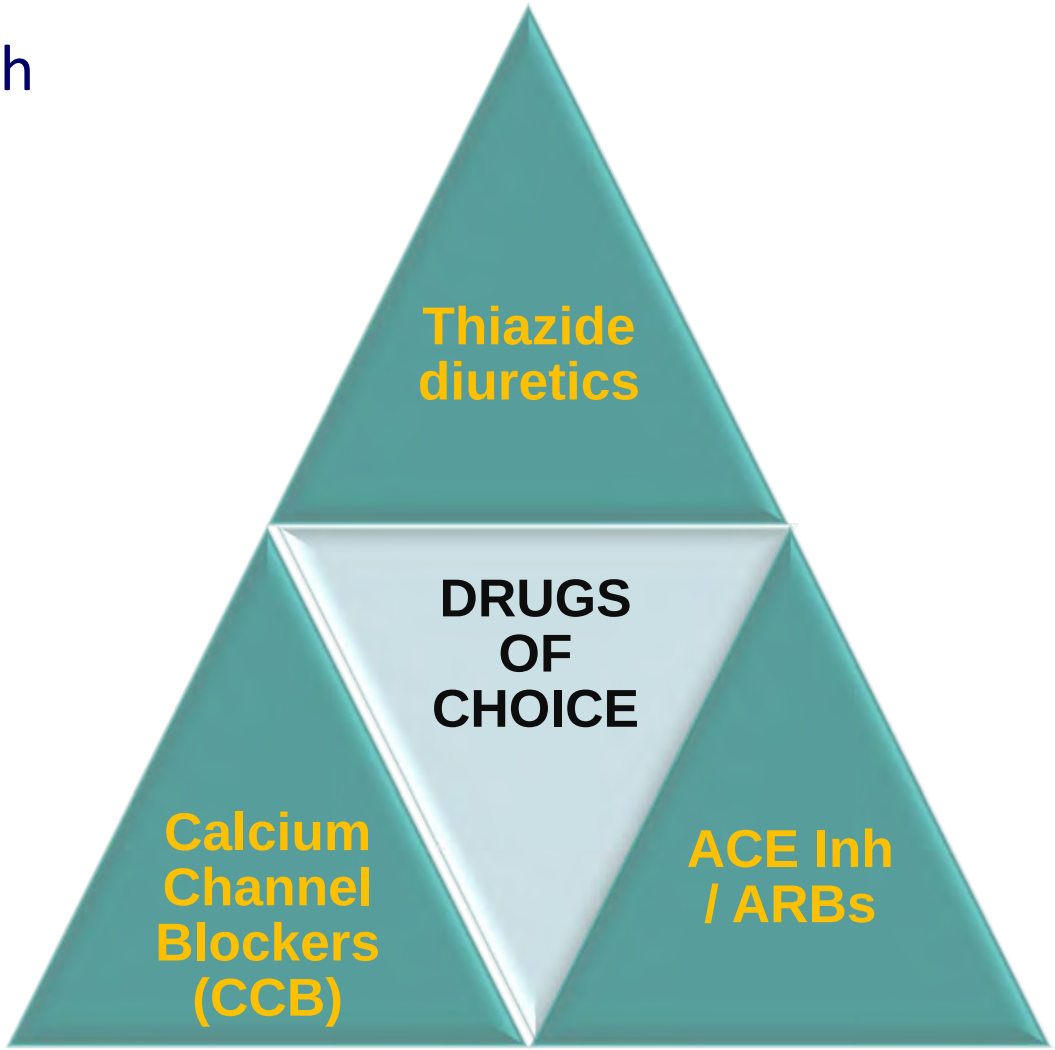
- First 5 recommendations → Thresholds & goals

SUMMARY: BP GOALS

> 60 YEARS OLD	•<150/90 mmHg
< 60 YEARS OLD	•<140/90 mmHg
CKD	•<140/90 mmHg
DIABETES	•<140/90 mmHg

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

C (CKD) → B (Black) → D (Diabetic)

RECOMMENDATION # IX (E)

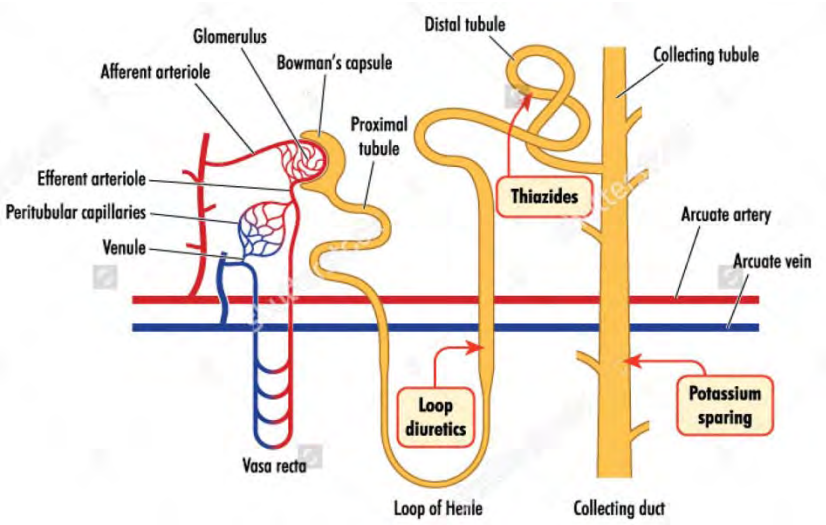
- Attain and maintain BP
- Two strategies if goal is not achieved within one month:
  - Increase the dose of the initial drug
  - **Add a second drug**
- Two drugs are not enough → add drug #3
- Refer to a HTN specialist
- Remarks:
  - Dual therapy to start when BP > 160/100 mmHg
  - Spironolactone role 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

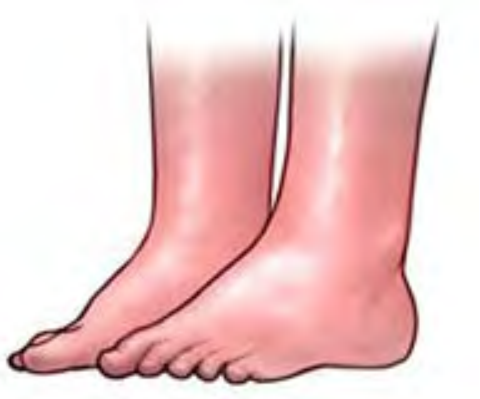
- **<u>ACE inhibitors / ARBs</u>:**
  - Start with a low dose
  - Dry cough, angioedema
  - Avoid in pregnancy
  - Monitor creatinine, and potassium
  - Avoid in bilateral renal artery stenosis
  - Never to be prescribed together

ACE Inh / ARB DOSES

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

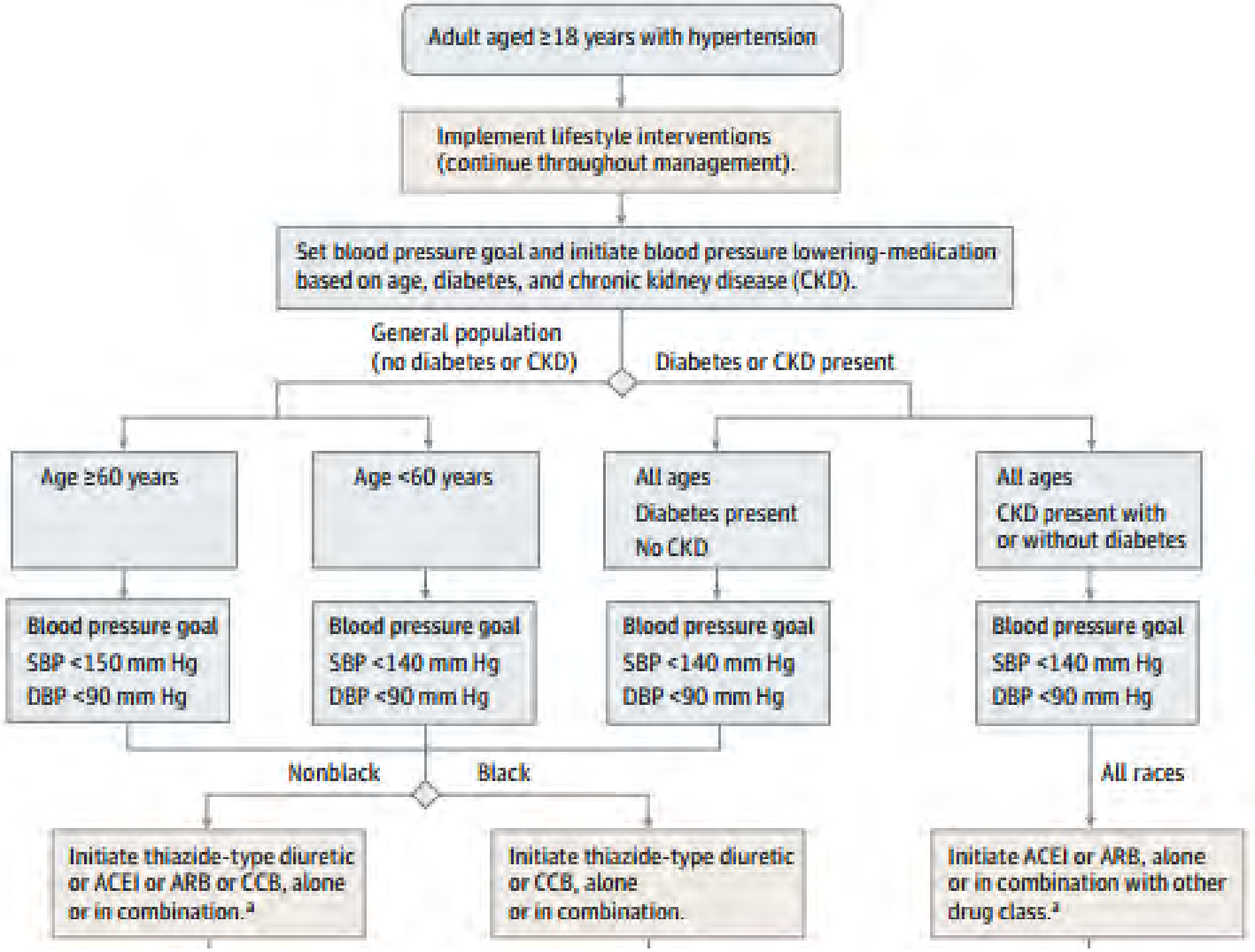
MEDICATION REMARKS

- **CCBs:**
  - Amlodipine (Dihydropyridine:DHP) lacks negative inotropic/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
Age ≥60 years
Age <60 years
All ages
Diabetes present
No CKD
All ages
CKD present with or without diabetes
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
Nonblack
Black
All races
Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination.[a]
Initiate thiazide-type diuretic or CCB, alone or in combination.
Initiate ACEI or ARB, alone or in combination with other drug class.[a]

COMPARISON OF HTN GUIDELINES

Blood Pressure (mm Hg)	NICE 2011	ESH/ESC 2013	AHA/ACC/CDC 2013	ASH/ISH 2014	JNC 8 2014	ACC/AHA/ASH IHD 2014
Definition of hypertension	≥140/90 and daytime ABPM or home BP ≥135/85	≥140/90	≥140/90	≥140/90	Not addressed	Not addressed
Drug therapy	≥160/100 or daytime ABPM ≥150/95	≥140/90	≥140/90	≥140/90	<60 yr ≥140/90 ≥60 yr ≥150/90	≥140/90
ß-Blockers as first-line drug	No (Step 4)	Yes	No (Step 3)	No (Step 4)	No	No Yes if CAD
Diuretic	Chlorthalidone Indapamide	Thiazides, Chlorthalidone, Indapamide	Thiazides	Thiazides, Chlorthalidone, Indapamide	Thiazides, Chlorthalidone, Indapamide	Thiazides, Chlorthalidone, Indapamide
Initiate therapy with two drugs	Not mentioned	In patients with markedly elevated BP	≥160/100	≥160/100	≥160/100	≥160/100
BP targets	<140/90 ≥80 yr <150/90	<140/90 elderly <80 yr; SBP 140-150; SBP <140 in fit patients; Elderly ≥80 yr; SBP 140-150	<140/90 Lower targets may be appropriate in some patients, including the elderly	<140/90 ≥80 yr <150/90	<60 yr <140/90 ≥60 yr <150/90	<140/90 <130/80 if CAD, CAD risk equivalent, stroke, TIA, Framingham risk score ≥20%
BP target in patients with diabetes mellitus	Not addressed	<140/85	<140/90 Lower targets may be considered	<140/90	<140/90	<140/90 Lower targets may be considered

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

CASE 1

- *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

CASE 3

- *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

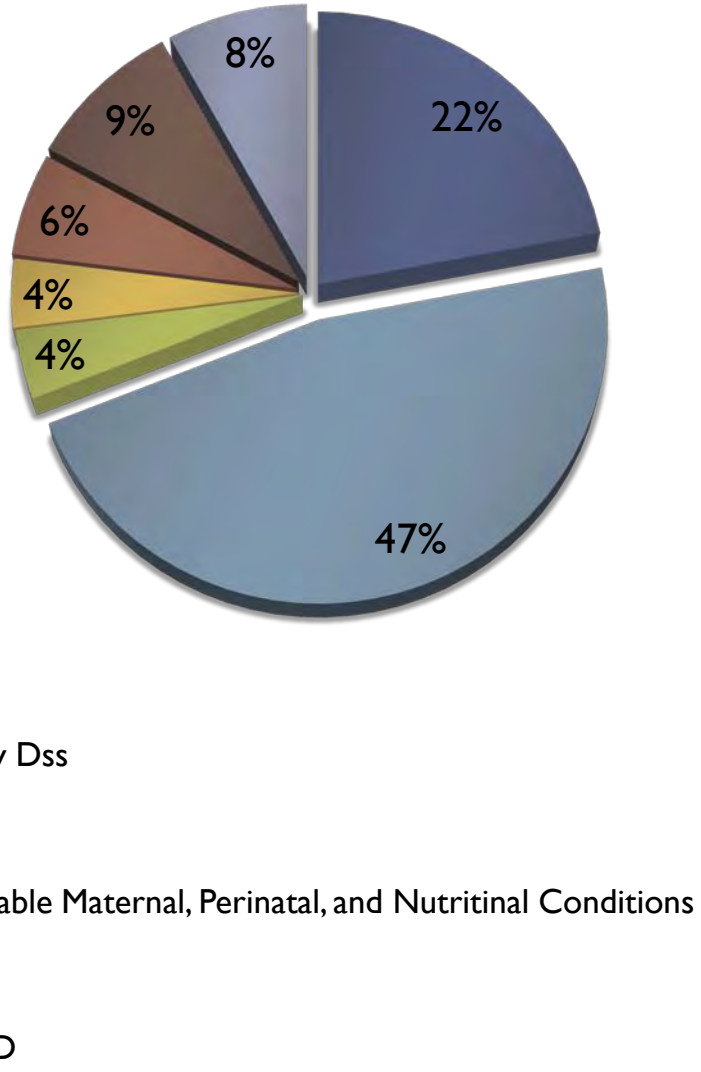
- Discuss the relation between cholesterol and atherosclerotic cardiovascular disease (ASCVD)
- Discuss the ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce ASCVD in Adults
- Assess the role of statins in management of cholesterol with regard to efficacy, safety, and concomitant drug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

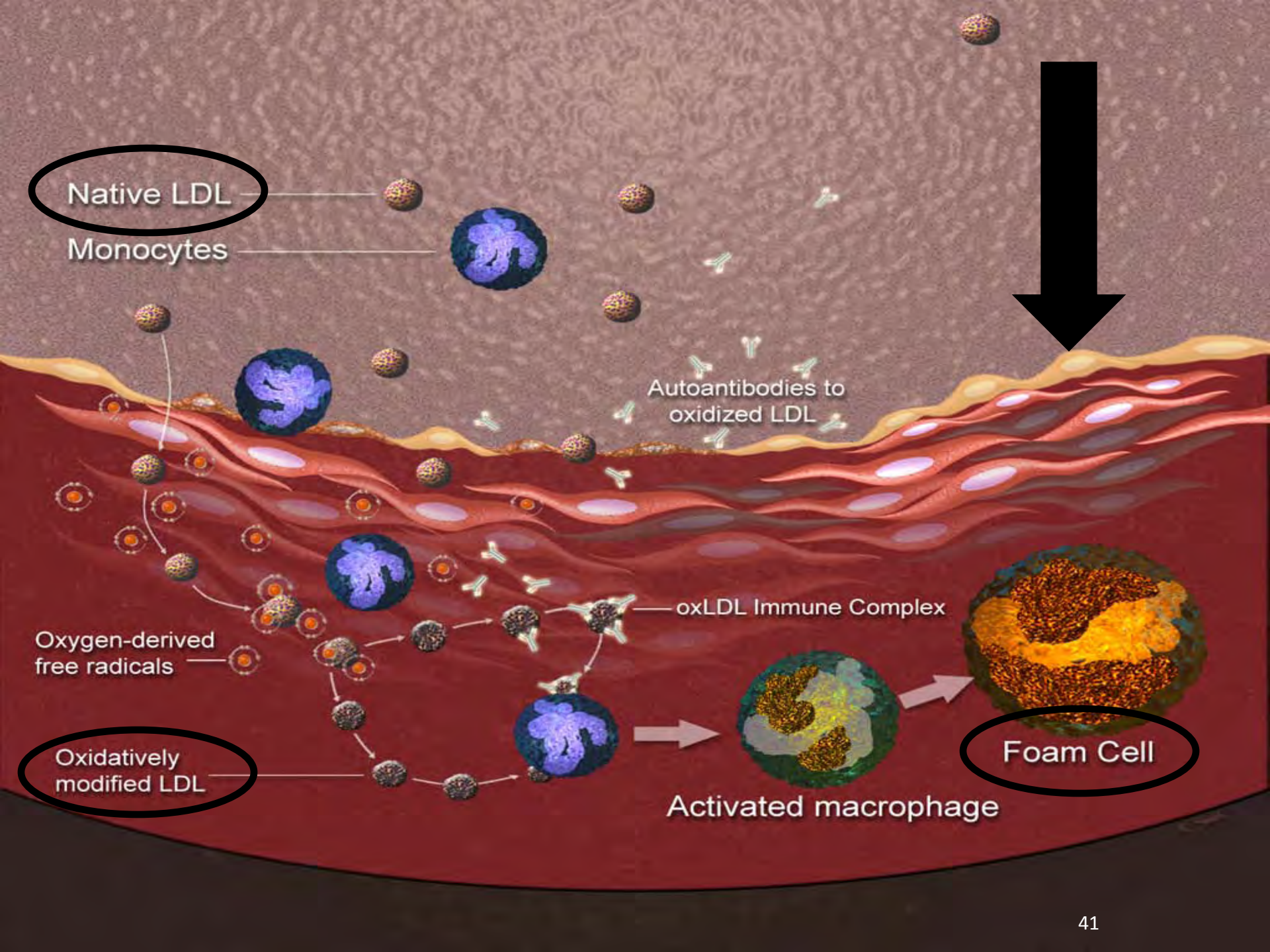
ASCVD Facts

- Largest killer of men and women in Lebanon (47%)
- The root cause is elevated cholesterol carried by circulating apo B-containing lipoproteins

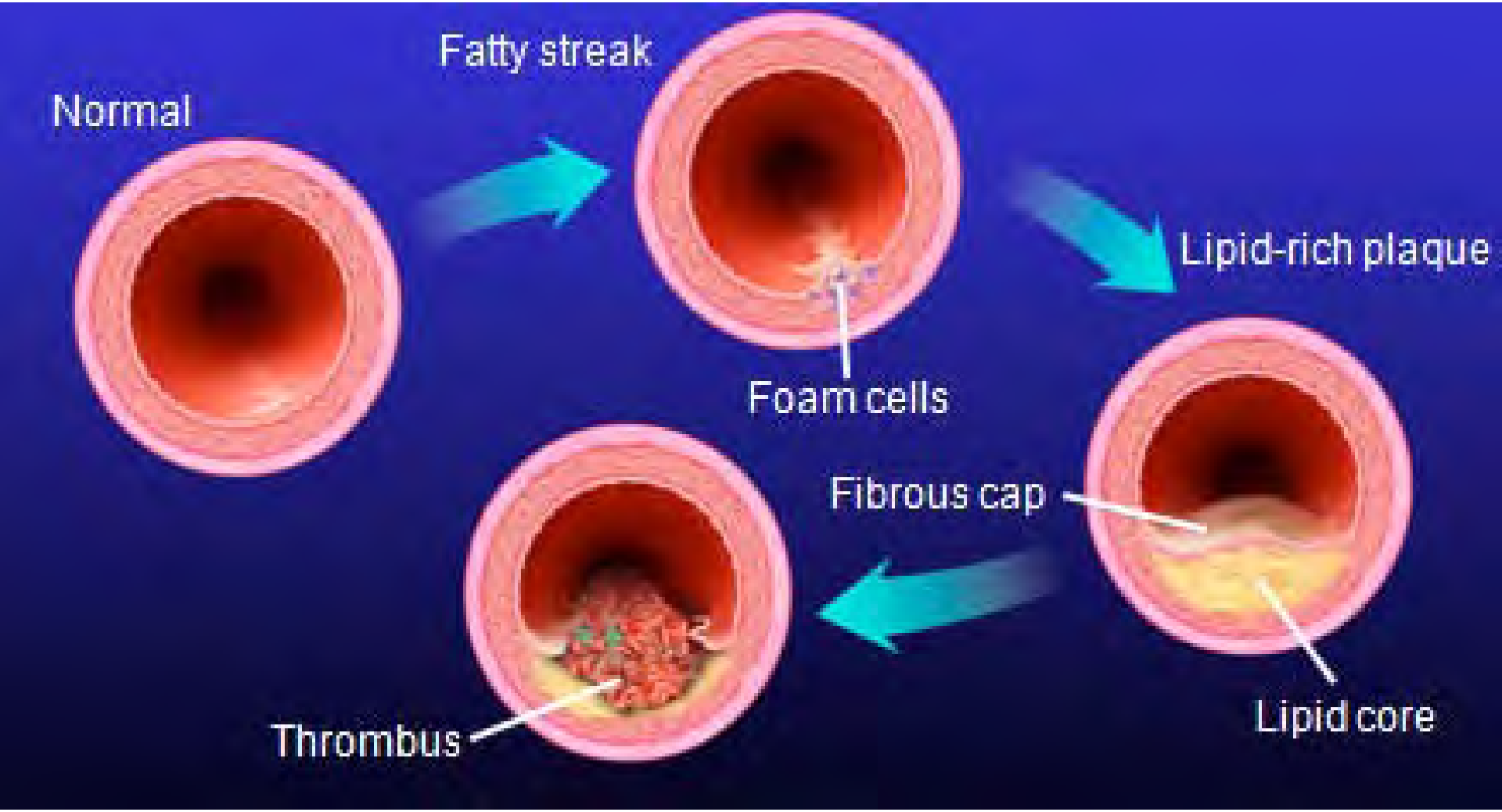
→ **non–HDL-C** and **LDL-C**, [*atherogenic cholesterol]*

- 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)

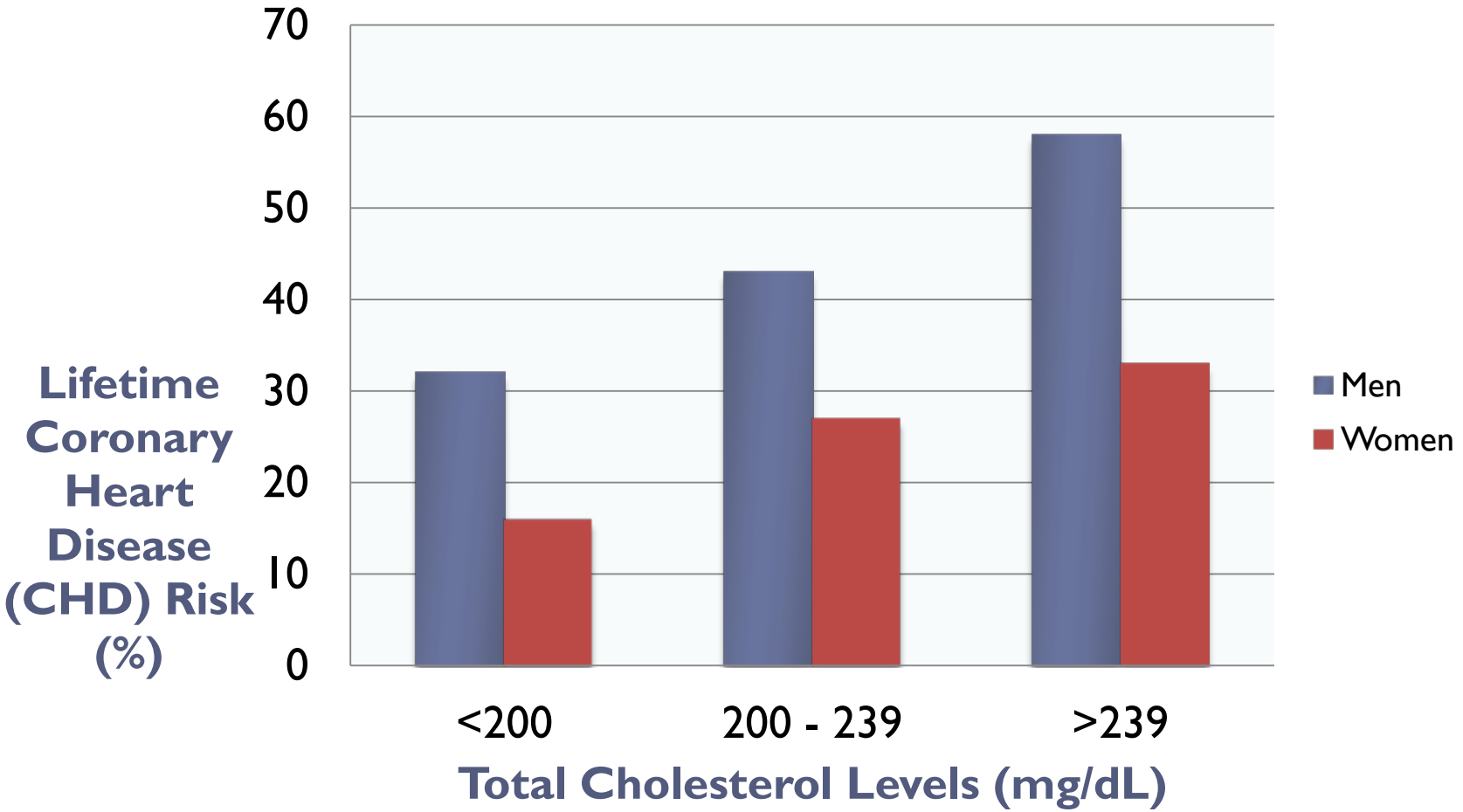



Native LDL
Monocytes
Autoantibodies to oxidized LDL
oxLDL Immune Complex
Oxygen-derived free radicals
Oxidatively modified LDL
Activated macrophage
Foam Cell

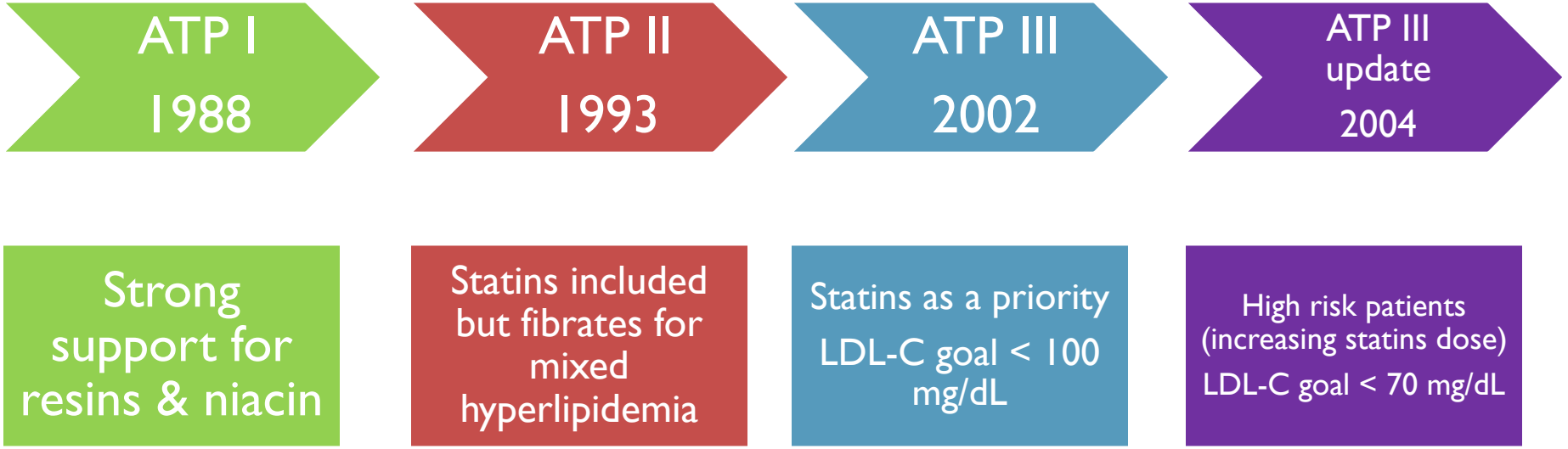
Atherosclerosis Timeline



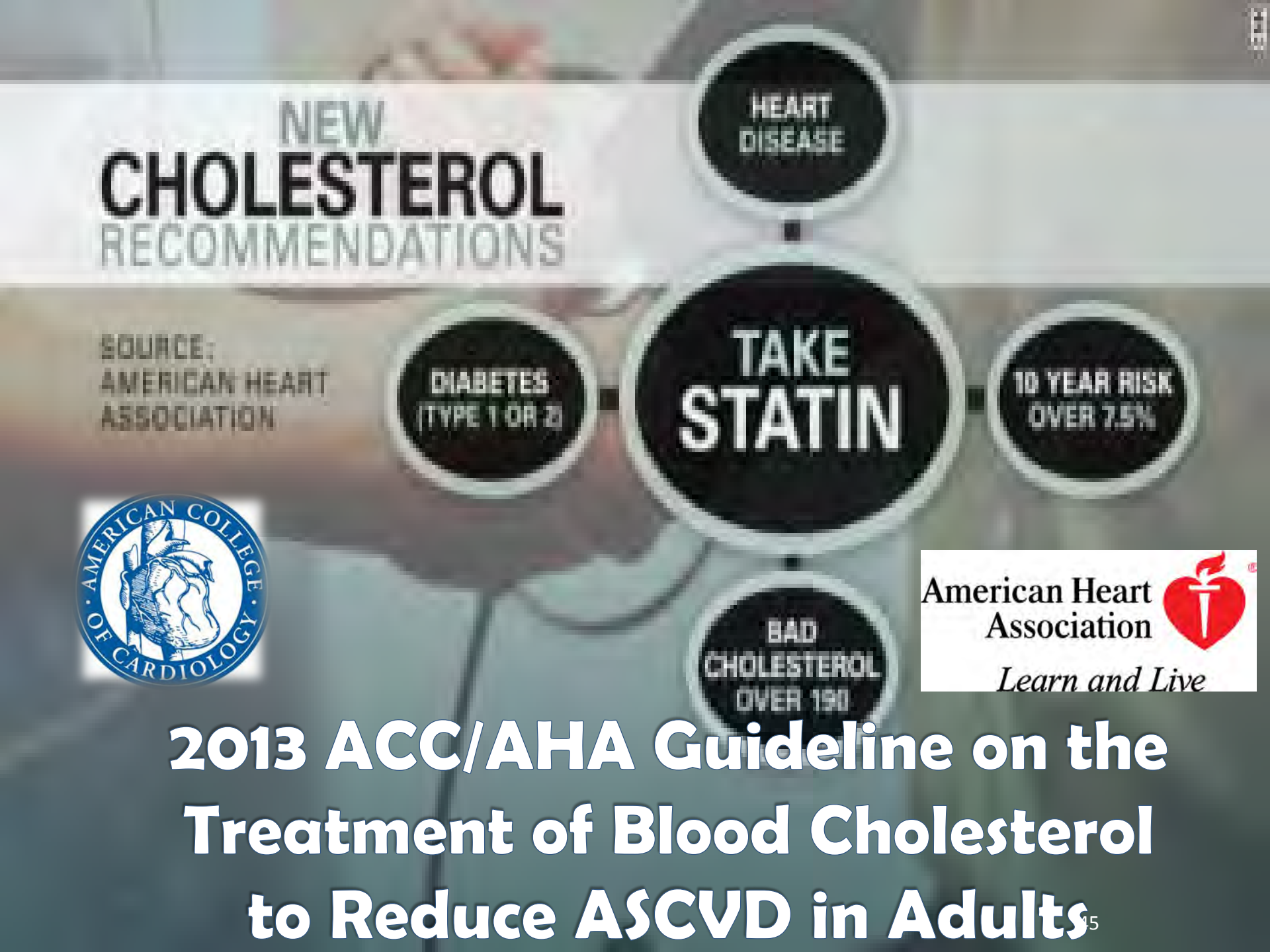
CHD and Cholesterol



Guidelines Timeline



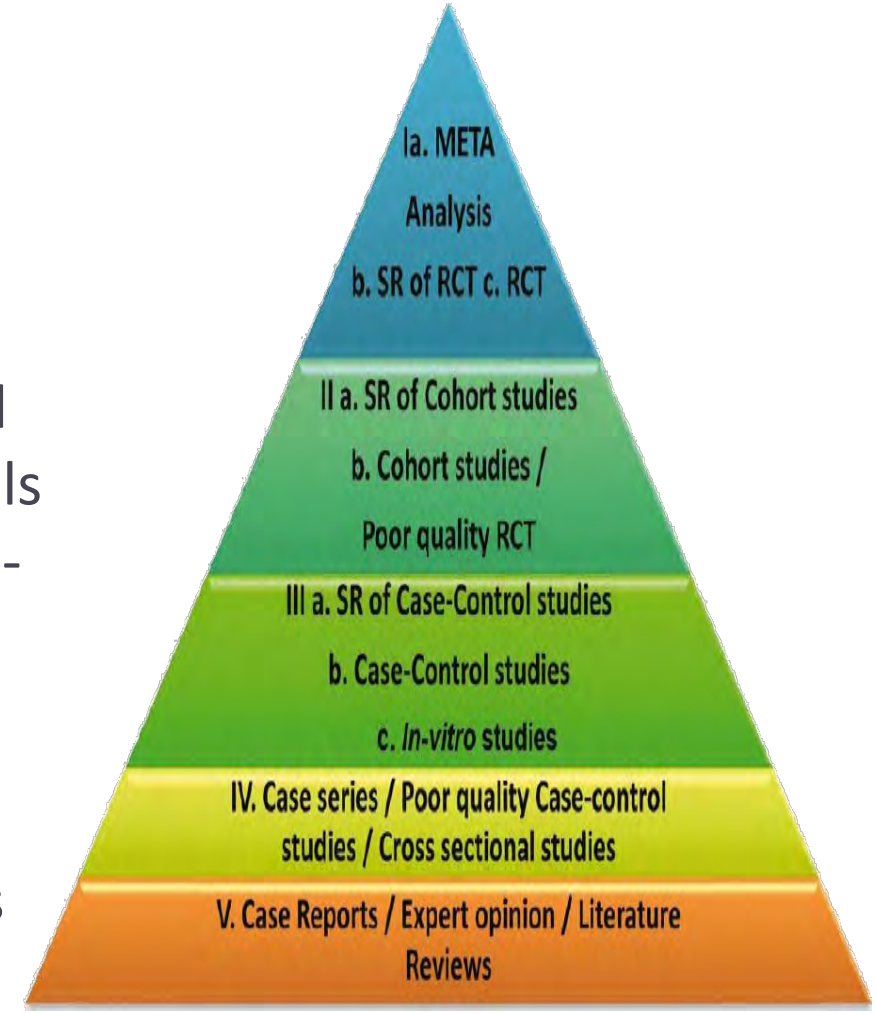
Adult Treatment Panel: ATP



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

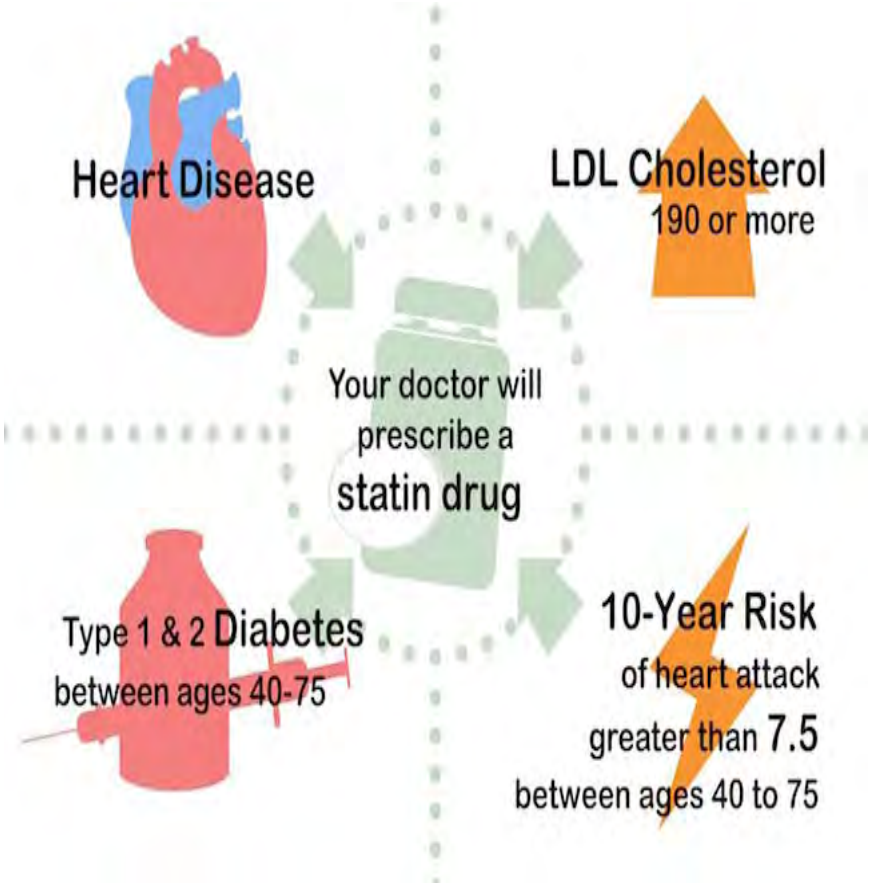
- http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx for risk equations).

Recommendations

- Encourage adherence to a healthy lifestyle
- "Tr[illegible]arget" and "lo[illegible]est" 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



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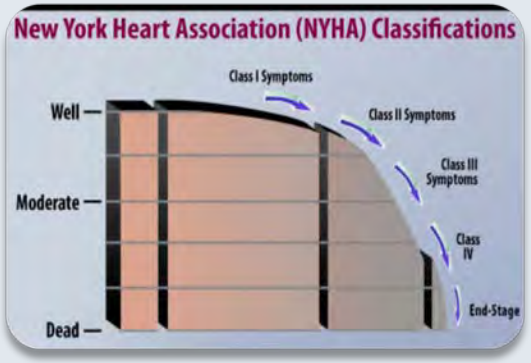
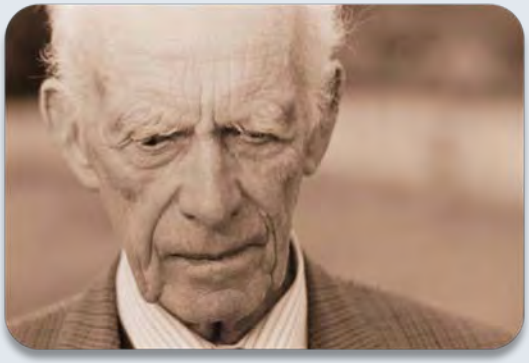




New York Heart Association (NYHA) class II-IV ischemic systemic heart failure

Hemodialysis patients

Elderly > 75 years, unless ASCVD is present

Four Statin Benefit Groups

CLINICAL ASCVD PATIENTS

LDL-C ≥ 190 mg/dL

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

PATIENTS (40 – 75 yrs); *with LDL-C 70 – 189 mg/dL & ASCVD RISK ≥ 7.5%*

CLINICAL ASCVD PATIENTS

- 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

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Decrease **LDL-C ≥ 50%**	Decrease LDL-C by 30 - 50%	Decrease LDL-C < 30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Fluvastatin XL 80 mg Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Fluvastatin 40 mg Pitavastatin 1 mg

LDL-C ≥ 190 mg/dL

- 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

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

- 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**

PATIENTS (40 – 75 yrs); *with LDL-C 70 – 189 mg/dL & ASCVD RISK ≥ 7.5%*

- Use the ASCVD risk calculator
- Risk ≥ 7.5% → **Moderate to high-intensity statin**
- Risk 5.0 -7.5 % → Moderate intensity statin ?!

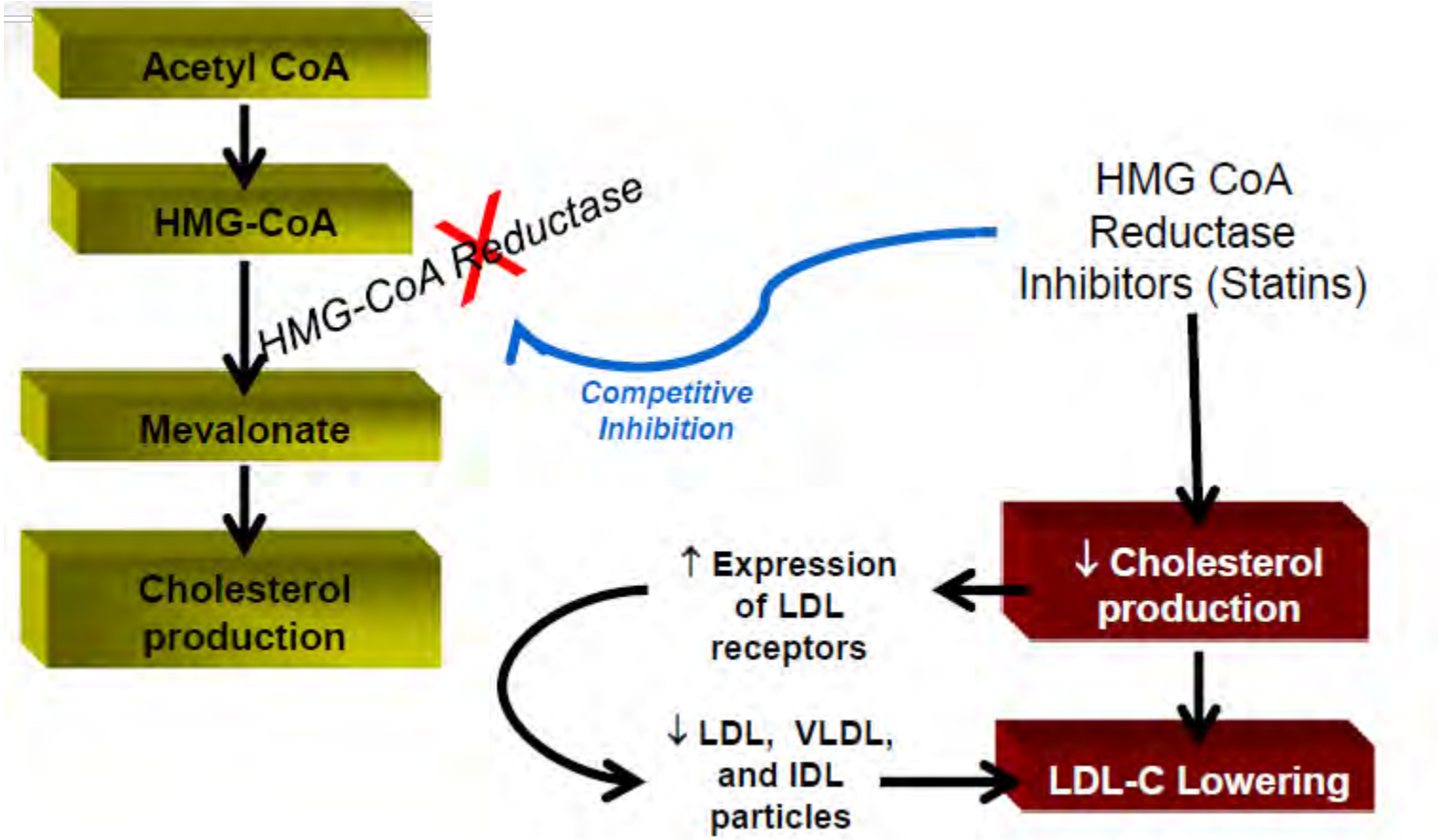
Factors to Consider (Risk 5 – 7.5 %)

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

Therapy Management

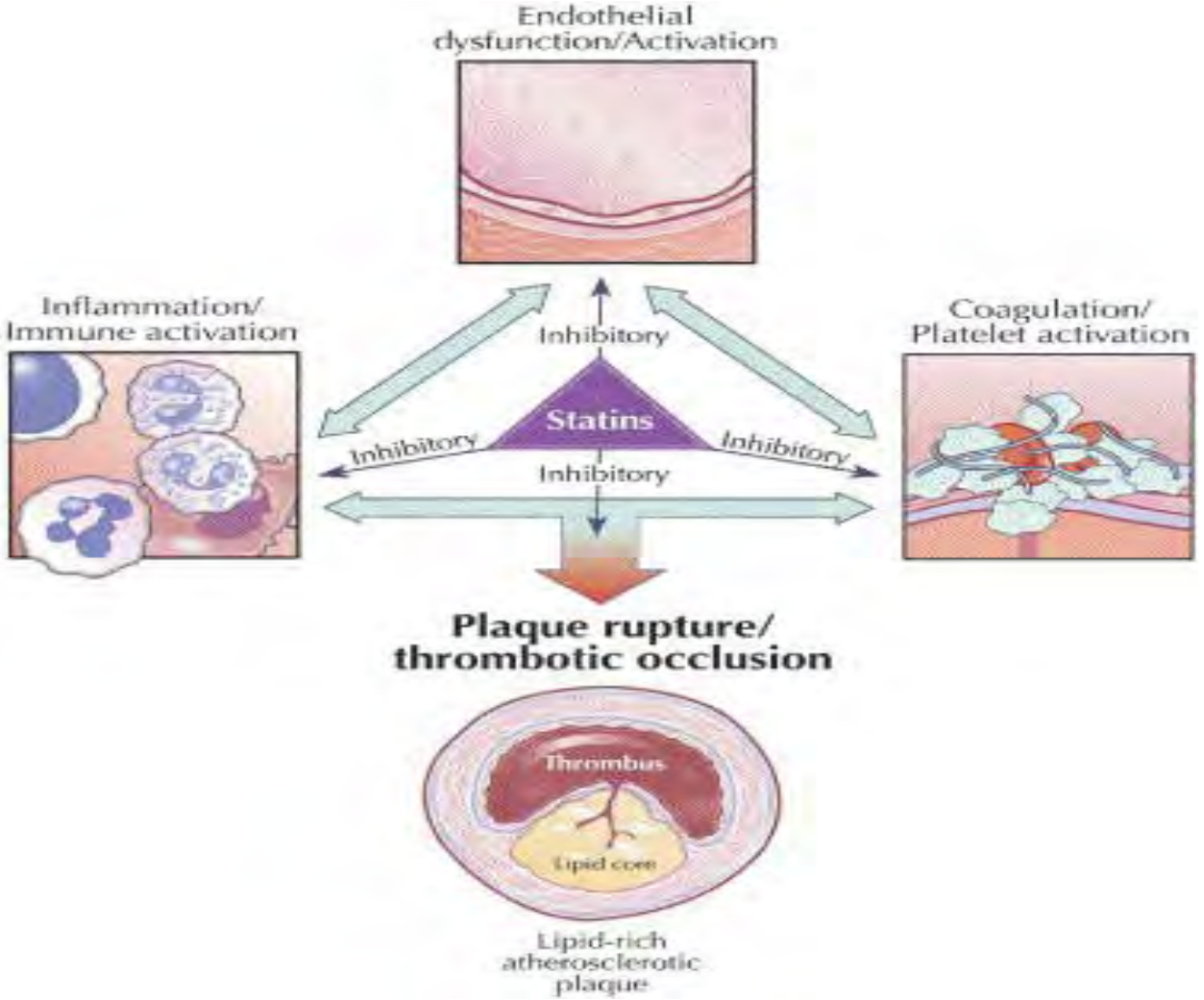
- Initial fasting lipid panel
- Baseline liver function tests (LFTs)
- Second panel within 4 – 12 weeks (continuous monitoring every 3 – 12 months)
- Decrease in statins' dose may be considered when 2 consecutive values of LDL-C < 40 mg/dL
- Muscle symptoms → Creatine Kinase (CK) measurement

Statins Mechanism of Action (1)



VLDL=very low-density lipoprotein
IDL=intermediate-density lipoprotein

Statins Mechanism of Action (2)



J Am Coll Cardiol. 2005;46(8):1425-1433. doi:10.1016/j.jacc.2005.05.086

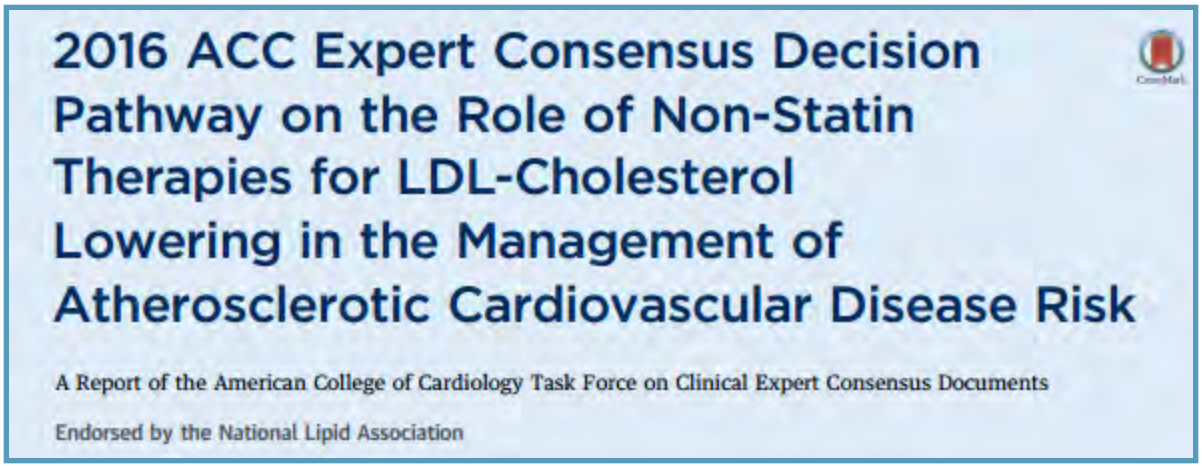
Statins Adverse Effects (5Ms)

- **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

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

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

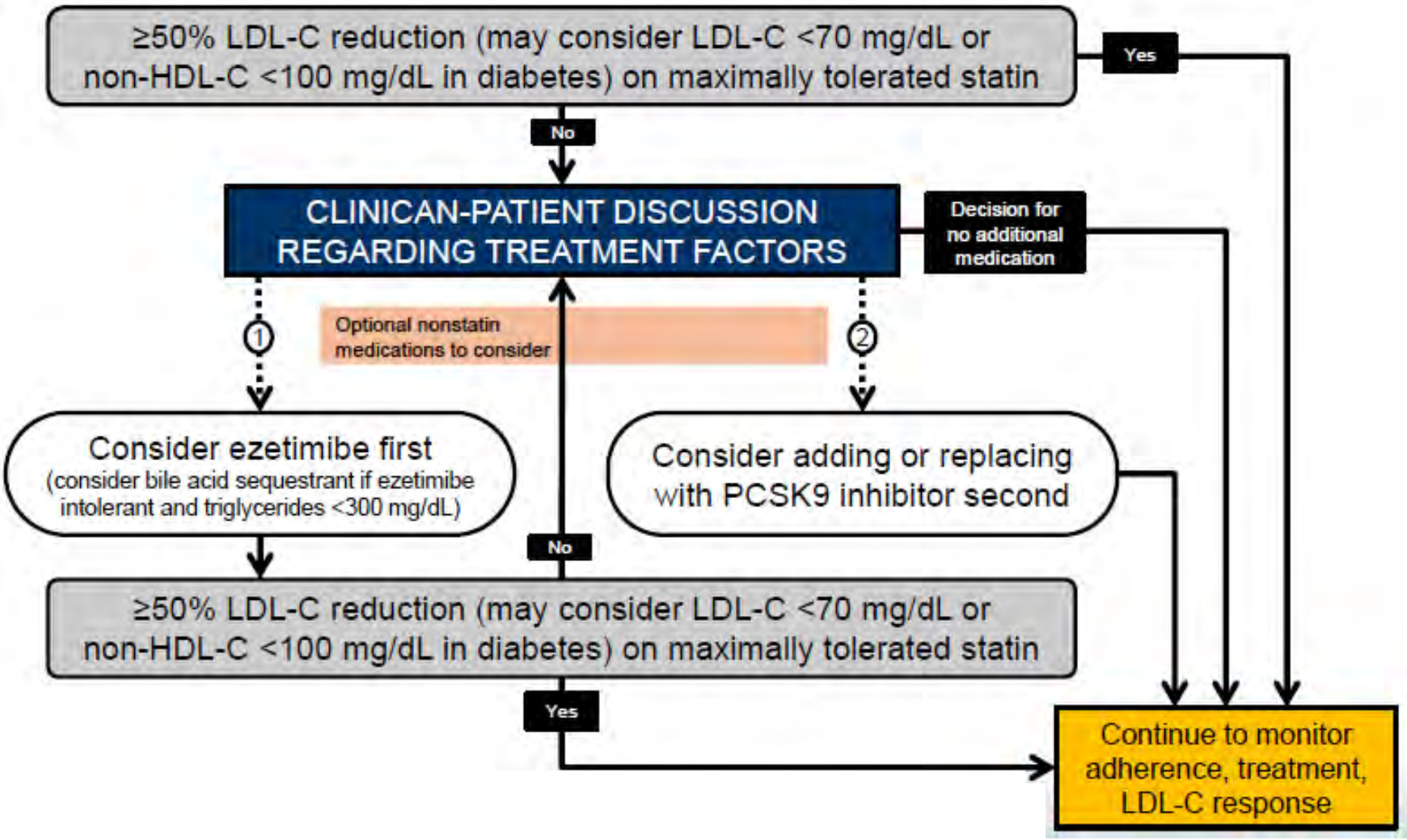
OPTIONAL INTERVENTIONS

- 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

FH: Familial Hypercholesterolemia

Lloyd-Jones D et al. *J Am Coll Cardiol. 2016. doi:10.1016/j.jacc.2016.03.519*

2016 ACC Expert Consensus Decision Pathway: In Clinical ASCVD and co-morbidities



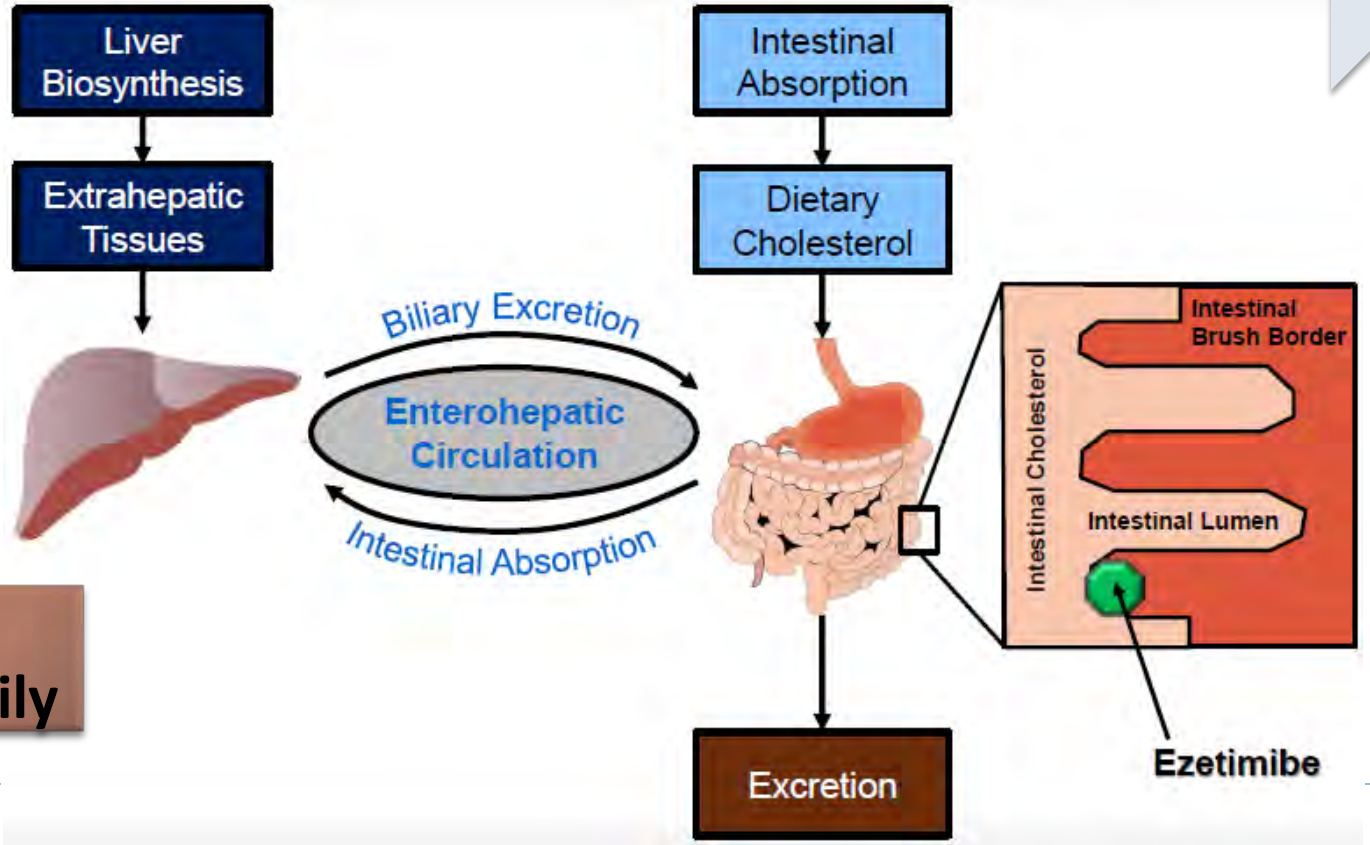
Ezetimibe

Inhibits intestinal cholesterol absorption

↓ intestinal delivery of cholesterol to liver

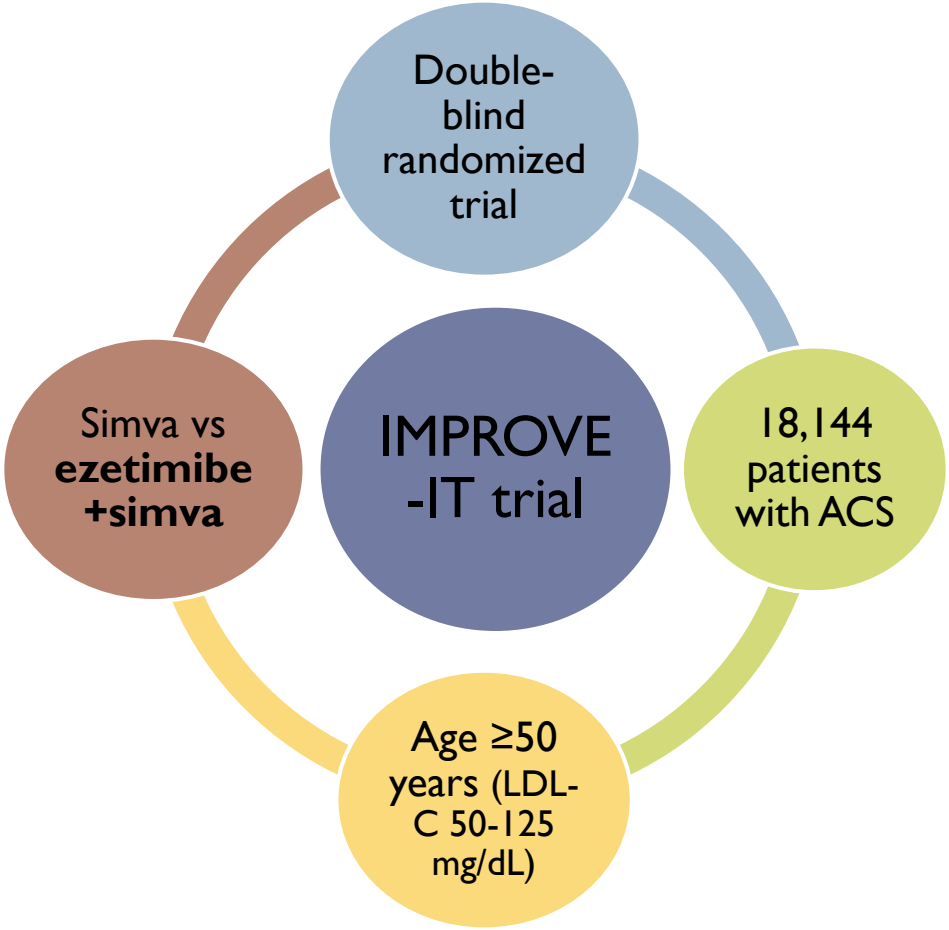
↑ expression of hepatic LDL-R

↓ cholesterol content of atherogenic particles

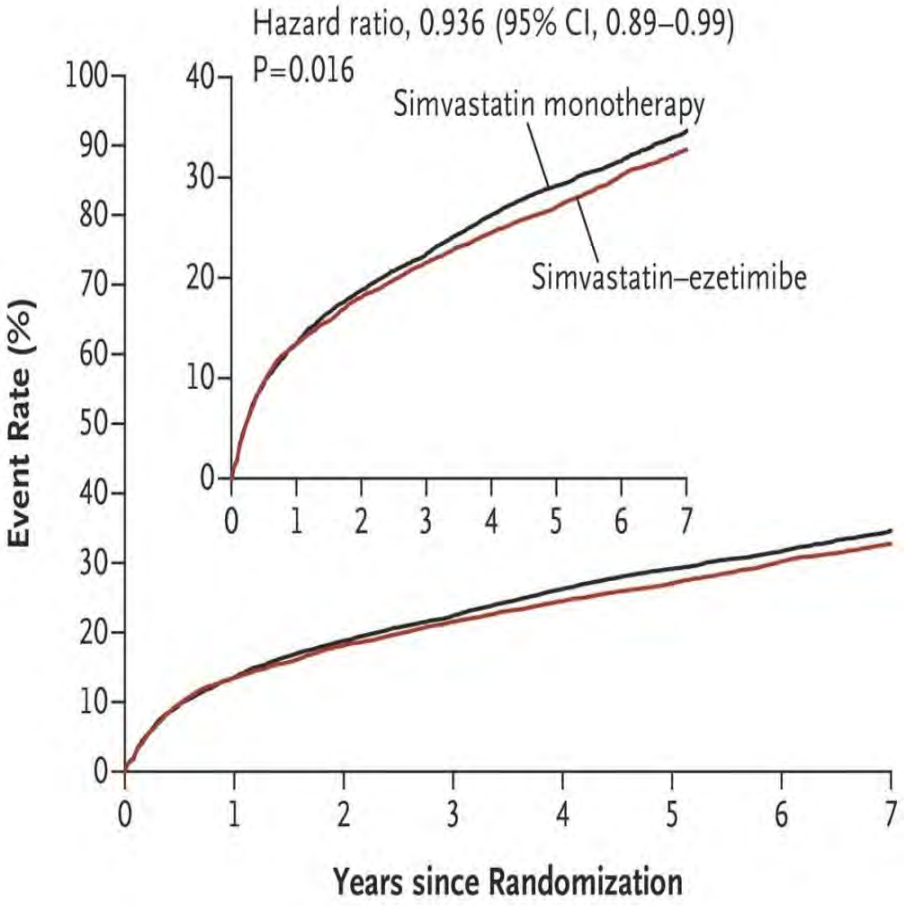


Dose
10 mg daily

Ezetimibe



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



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

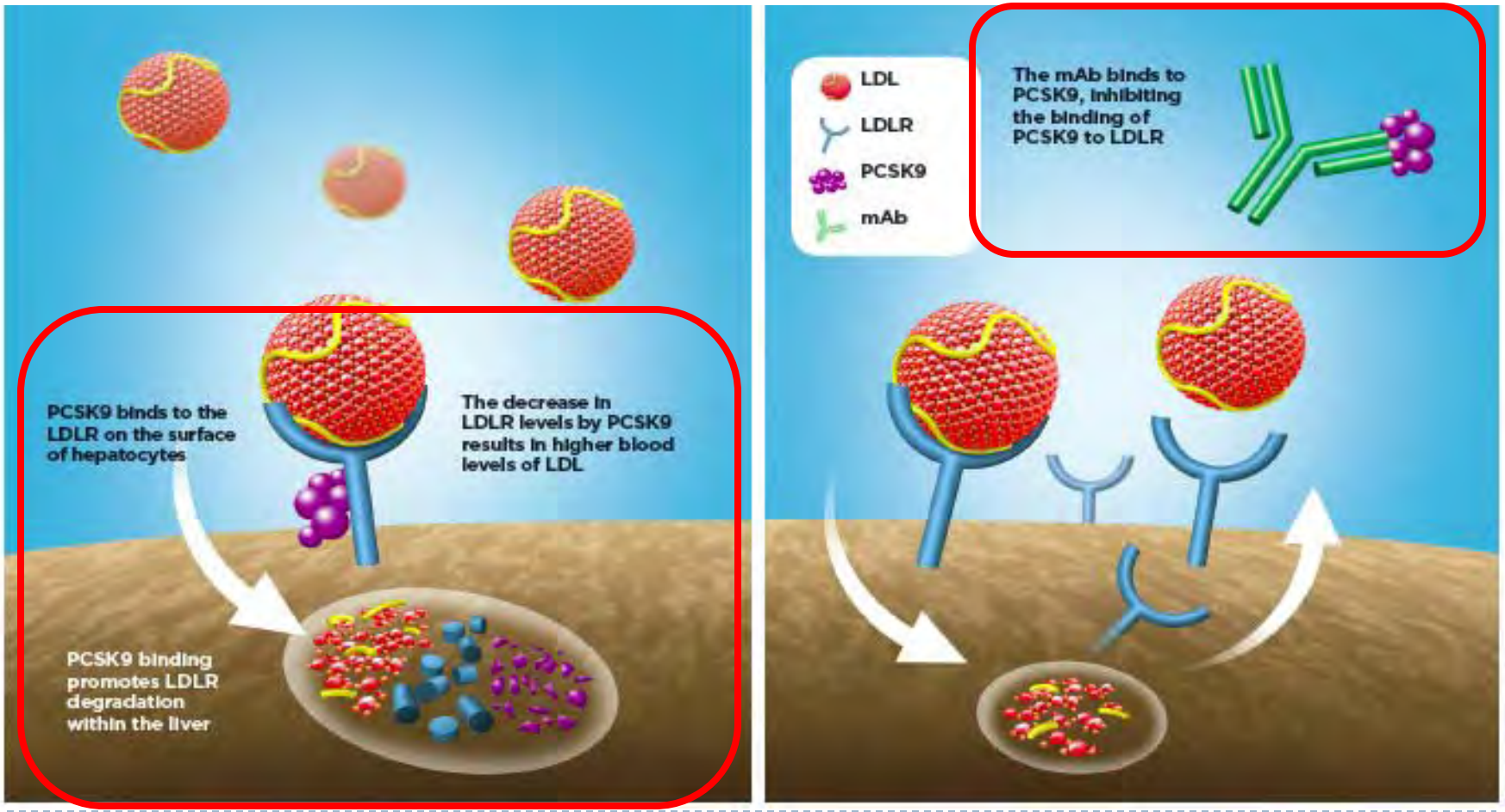
Confirms ezetimibe safety profile

- 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

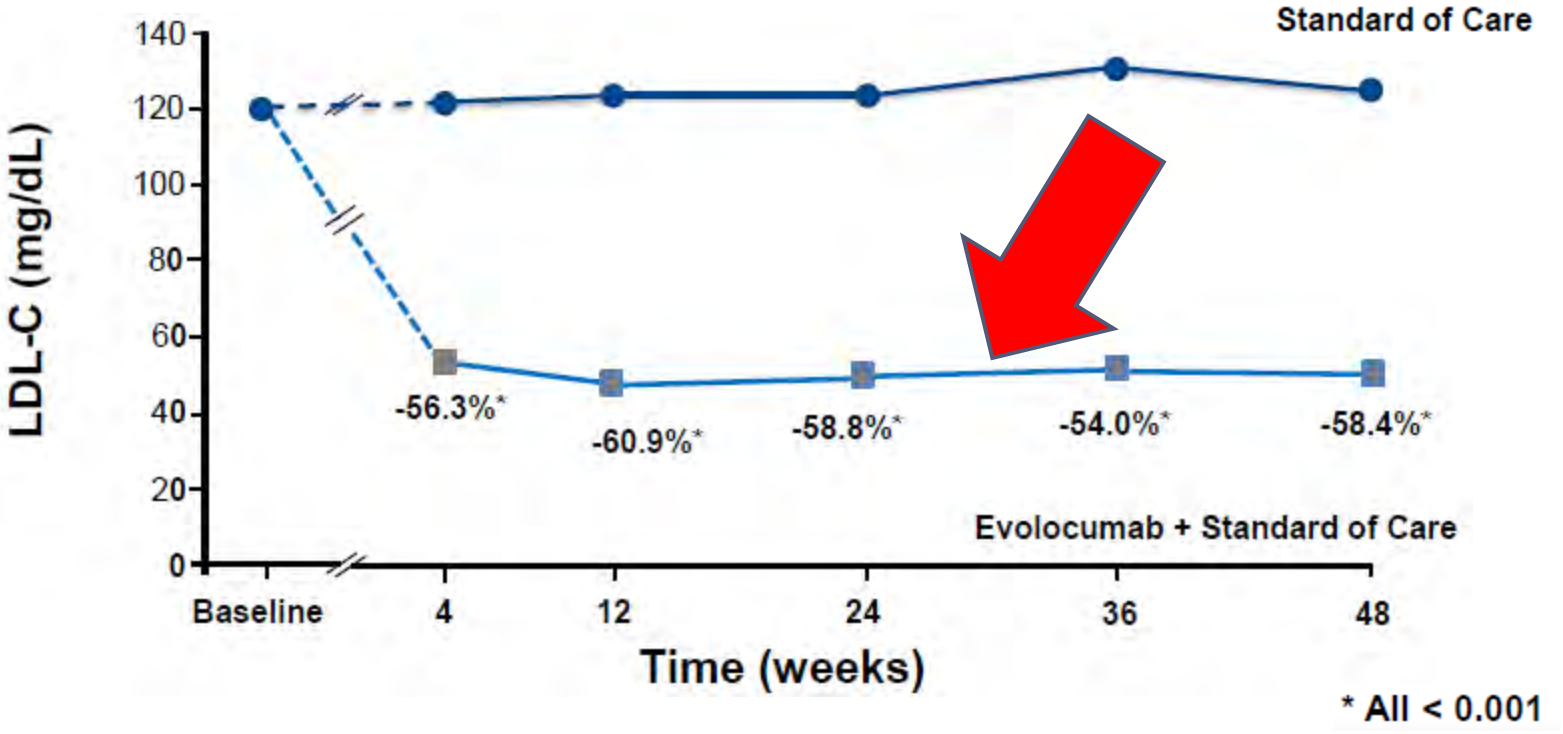


PCSK9 Inhibitors – Role in therapy

	Alirocumab	Evolocumab
FDA approval	Adjunct to diet and maximally tolerated statin therapy who require additional lowering of LDL-C	
FDA indication	• Clinical ASCVD • Adults heterozygous FH	• Clinical ASCVD • Adults heterozygous FH • Adults homozygous FH
Dosing	75 – 150 mg SC q 2 weeks	140 SC q 2 weeks or 420 mg SC once monthly in homozygous FH
Comments	• Use in statin intolerance is debated and evolving	

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

	Alirocumab	Evolocumab
Injections	• Single-use, prefilled autoinjector or syringe • Patient self-injects medicine • Rotate injection sites • The time required for injection is 15 sec	
Storage	• Store unused syringes in refrigerator between 2 – 8°C • Protect from light	
	Do not keep at room T° for > than 24 hours	May be stored at room T° if used within 30 days
Administration	• Do not shake • Allow to warm to room T° for 30 – 40 mins	
Missed a dose	• Administer injection within 7 days after the missed dose • Resume original schedule	
Comments	• Caution for allergic reactions (D/C and treat)	

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

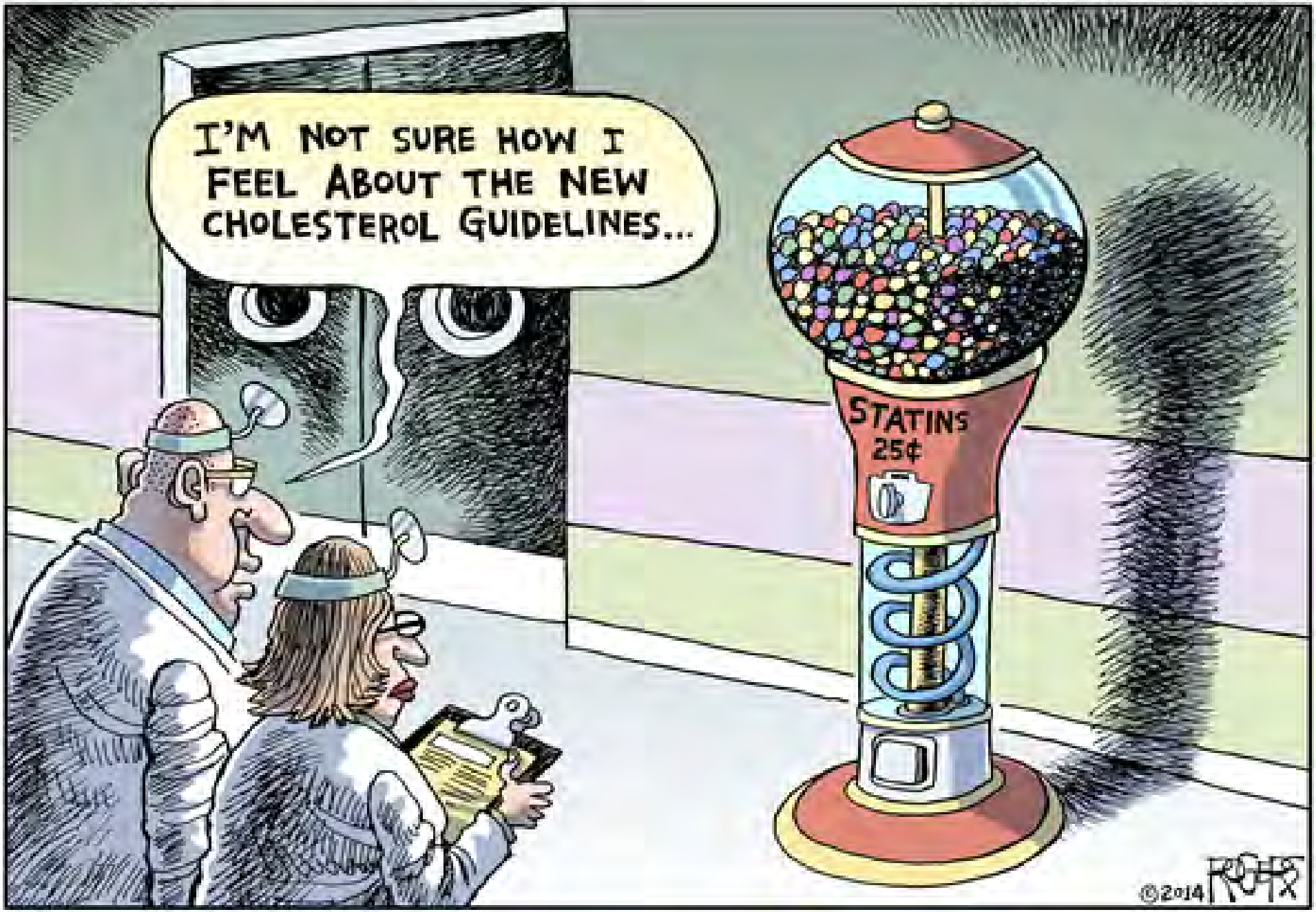
- ASCVD risk reduction is the overall goal
  - *Aspirin*
  - *Blood pressure control & Body weight management*
  - *Cholesterol levels & Cigarette smoking cessation*
  - *Diet & Diabetes control*
  - *Exercise*

- 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

BY ROB ROGERS



CASE SCENARIOS

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 rosuvastatin**

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