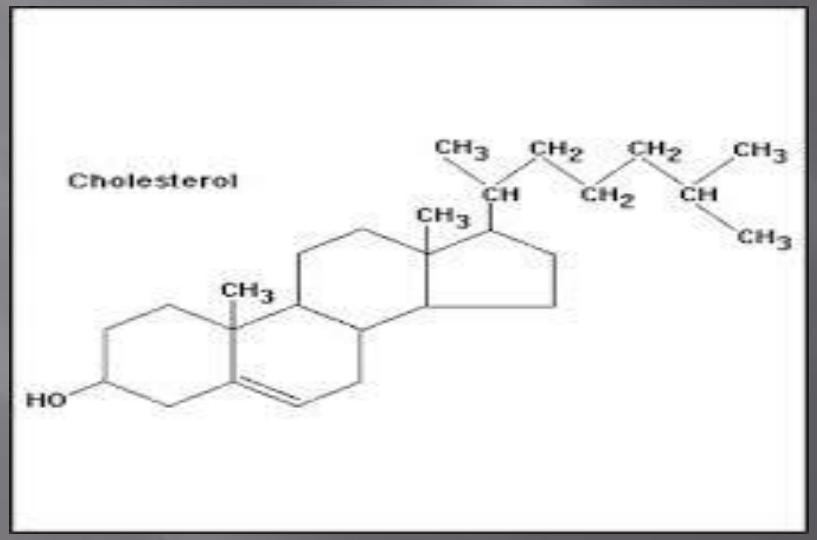
LMU MLS CONTINUING EDUCATION CONFERENCE NOVEMBER 2014

PACE SESSION # 304-115-14
THE LABORATORY'S ROLE IN THE NEW GUIDELINES FOR CHOLESTEROL TREATMENT



Joshua Shepherd PA-C, MMS, MT (ASCP)

Disclosures

- None

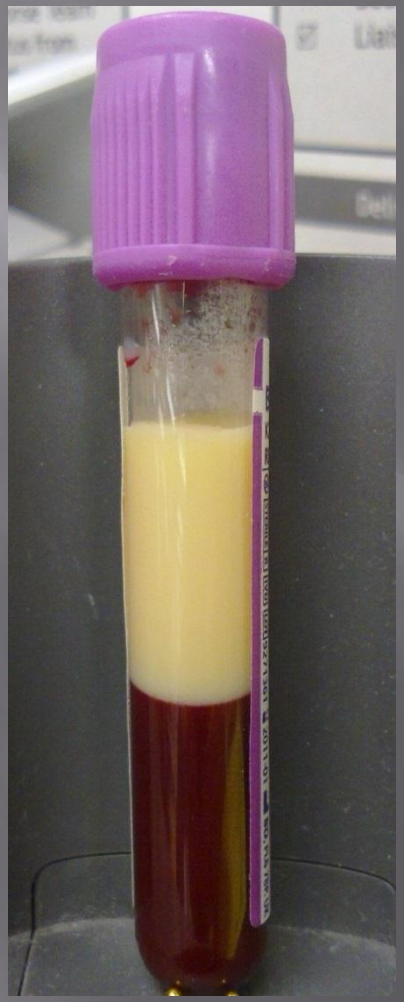
Objectives

- What is Cholesterol?
- Why cholesterol is it important?
- Review the National Cholesterol Education Programs guidelines (NCEP-ATPIII)
- Discuss New guidelines from the American Heart Association and American College of Cardiology
- Discuss treatment of Cholesterol
- Discuss the laboratories role concerning lipid management and new guidelines
- Discuss new research and treatment of lipid

What is Dyslipidemia ?

- Abnormal amount of lipids (e.g. cholesterol and/or fat) in the blood
- In developed countries, most dyslipidemias are hyperlipidemias; that is, an elevation of lipids in the blood
- This is often due to diet and lifestyle

Dyslipidemia



Dyslipidemia: Physical Findings

- Xanthomas
  - The most common dermatologic manifestation of dyslipidemia is xanthomas. These firm and nontender cutaneous deposits of cholesteryl ester-enriched foam cells are most commonly observed with high levels of LDL

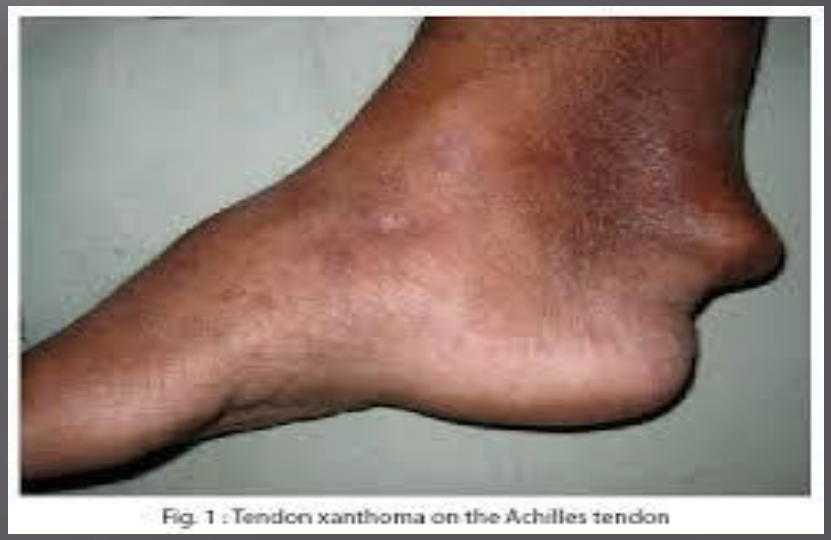


Fig. 1 : Tendon xanthoma on the Achilles tendon

Why Does Cholesterol Matter ?

- Cardiovascular disease remains the leading cause of death in the US
  - Coronary artery disease is the most common type
    - Causes approximately 380,000 deaths annually
    - Causes approximately 720,000 heart attacks annually
    - Cost estimated to be about 108.9 billion dollars per year
      - Factors in the health care cost, medications and lost of productivity.

Why Does Cholesterol Matter?

- Dyslipidemia is one of the major modifiable risk factors for cardiovascular disease
  - An estimated 71 million Americans have high cholesterol

ATP III Guidelines

Step 1

Determine lipoprotein levels–obtain complete lipoprotein profile after 9- to 12-hour fast.

ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol – Primary Target of Therapy	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

ATP III Guidelines

2

Step 2 Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):

- Clinical CHD
- Symptomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm.

3

Step 3 Determine presence of major risk factors (other than LDL):

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals
Cigarette smoking
Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
Low HDL cholesterol (<40 mg/dL)*
Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
Age (men ≥45 years; women ≥55 years)

** HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.*

- Note: in ATP III, diabetes is regarded as a CHD risk equivalent.

ATP III Guidelines

Step 4

If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalent, assess 10-year (short-term) CHD risk (see Framingham tables).
Three levels of 10-year risk:

- >20% — CHD risk equivalent
- 10-20%
- <10%

Step 5

Determine risk category:

- Establish LDL goal of therapy
- Determine need for therapeutic lifestyle changes (TLC)
- Determine level for drug consideration

LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* *Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.*

† *Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.*

ATP III Guidelines

Step 6

Initiate therapeutic lifestyle changes (TLC) if LDL is above goal.

TLC Features

- TLC Diet:
  - Saturated fat <7% of calories, cholesterol <200 mg/day
  - Consider increased viscous (soluble) fiber (10-25 g/day) and plant stanols/sterols (2g/day) as therapeutic options to enhance LDL lowering
- Weight management
- Increased physical activity.

ATP III Guidelines

- Considers risk along with laboratory values and has a laboratory value assigned as a goal
- When treatment is initiated a lipid panel will be needed to determine if goal as been reached.

Hypertriglyceridemia

- ATP III guidelines
  - When Triglycerides are >500 mg/dL the initial goal is to prevent pancreatitis by lowering the triglycerides with nonpharmacologic therapy and a triglyceride lowering drug such as a fibrate or niacin
- ACC/AHA Guidelines
  - When Triglycerides are >1000
  - There was no evidence found that triglyceride lowering medication for triglyceride levels between 500-1000 decreased the risk for hyperlipidemic pancreatitis
  - Suggested to rule out secondary cause first

New Guidelines

- Established by the American Academy of Cardiology and the American Heart Association in conjunction with the National Heart, Lung and Blood Institute
- All recommendations are based on meta-analysis of all research done to date on the treatment of cardiovascular disease

ACC/AHA Guidelines (New Guidelines)

- 4 Statin benefit groups were identified to concentrate the effort to reduce ASCVD events
- No specific LDL-C and /or no non-HDL-C treatment goals but instead identifies the intensity of statin therapy to implement
- Does not advocate for the use of any other class of medication other than statins to control cholesterol levels
- Uses a different risk calculator than Framingham risk score calculator

ACA/AHA Guidelines

- ASCVD risk score calculator
  - Gender
  - Age
  - Race*
  - Total cholesterol
  - HDL-C
  - Systolic blood pressure
  - Hypertension
  - Smoker
  - Diabetic
- Framingham Score Calculator not used
  - ATP III guidelines

Treatment groups

- Group 1
  - Individuals with clinical atherosclerotic cardiovascular disease
- Group 2
  - Individuals with a LDL-cholesterol 190mg/dL or greater
- Group 3
  - Individuals with diabetes aged 40-75 years old with LDL-cholesterol levels between 70 and 189 mg/dL and without evidence of atherosclerotic cardiovascular disease

Treatment Groups

- Group 4
  - Individuals w/o DM or cardiovascular disease, LDL levels between 70-189 and 10-year risk of atherosclerotic cardiovascular disease >7.5%

Treatment

- Group 1 and Group 2
  - Treat with high intensity statin therapy to achieve a decrease in LDL of at least 50%
  - If not tolerated use a moderate intensity statin to achieve a decrease in LDL of 30-49%
- Group 3
  - Treat with moderate intensity statin therapy that reduces LDL-C 30-49%
- Group 4
  - Treat with moderate to high intensity statin therapy

Treatment

Table 1. Statin Therapy

Intensity	Definition	Dosage
Low	Daily dose lowers LDL-C by <30%, on average	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg
Moderate	Daily dose lowers LDL-C by approximately 30% to <50%, on average	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2-4 mg
High	Daily dose lowers LDL-C by approximately ≥50%, on average	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg

C: cholesterol; XL: extended-release.
Source: Reference 1.

Treatment

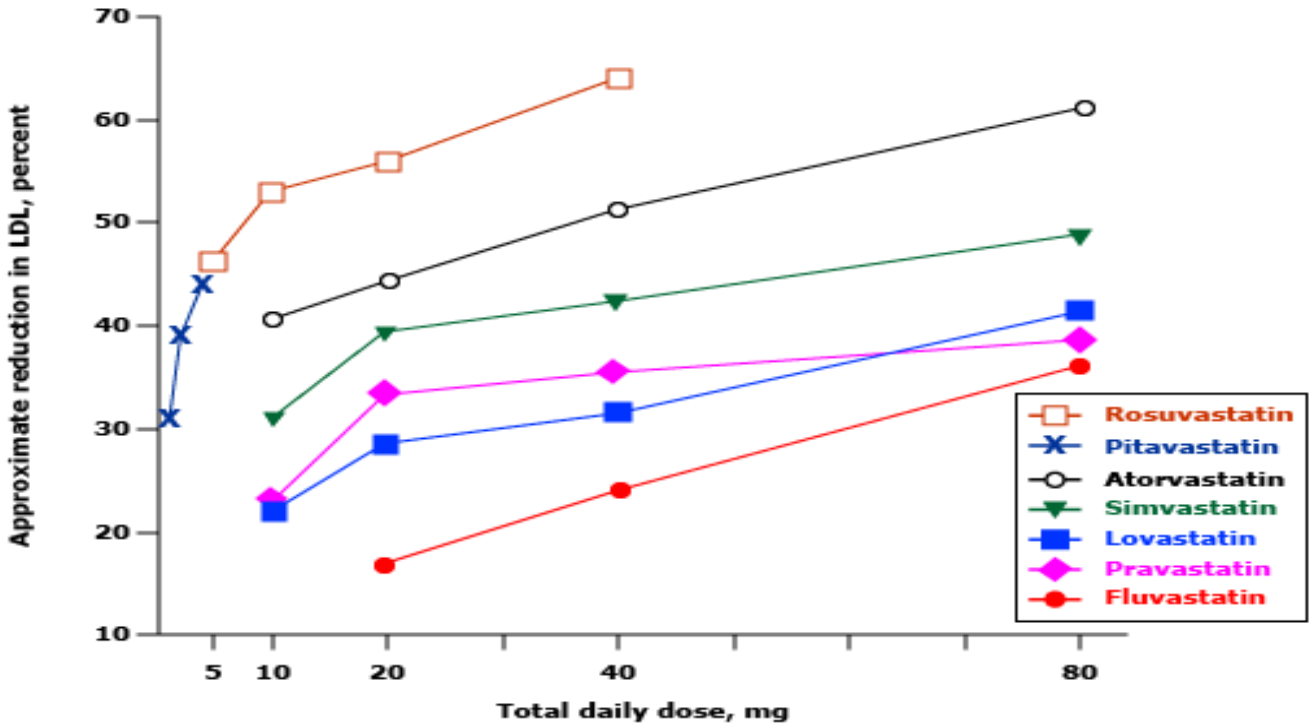
- Begin Treatment with a Statin drug
  - Mechanism of Action
    - The inhibition of HMG CoA reductase enzyme in the liver that is responsible for synthesizing cholesterol
- List of Statin Drug
  - Lipitor (Atorvastatin)
  - Crestor (Rouvastatin)
  - Pravachol (Pravastatin)
  - Livalo (Pitavastatin)
  - Altoprev (Lovastatin)
    - Red Rice Yeast
  - Zocor (Simvastatin)

Treatment

- Lipitor
- Simvastatin
- Crestor
  - Used the most because of the potential to lower LDL cholesterol

Comparison of Statin Drugs

Comparison of the efficacy of statin drugs



Comparison of the percent reduction in serum low density lipoprotein (LDL)-cholesterol with various statin drugs.

Treatment

- Always Prescribe a STATIN!!!
- If not tolerated well
  - Prescribe a different Statin
- When that's not tolerated
  - Prescribe a lower dose statin
- When that fails
  - Prescribe a longer acting statin every other day or 3 times per week
- STATIN STATIN STATIN!!!!!

Treatment

Treatment

- Lipitor (atorvastatin)
  - The most successful commercially advertised drug in history
  - Estimates conclude that by the year 2020 this drug will have profited over 1 trillion dollars

Treatment

- Drugs other than statins:
  - Zetia
  - Welchol
  - Questran
- Even though these medications reduce LDL-cholesterol studies have not shown that they reduce the likelihood of Cardiovascular events

Statin Therapy Benefit

- Justification for the Use of Statin Prevention: An Intervention Trial Evaluating Rosuvastatin
  - JUPITER Trial
    - 2003-2008
  - Study showed that statin therapy with Rosuvastatin showed a primary prevention in strokes and myocardial infarctions by approximately 50%

Laboratories role

- Lipid screening according to guidelines
  - High risk
    - Consider patients to be at higher risk if they have more than one risk factor (hypertension, smoking, family history) or a single risk factor that is severe
    - Screen for lipid abnormalities starting at age 25 in male patients and age 35 in female patients
  - Not high risk
    - Does not have more than 1 risk factor
    - Screen for lipid abnormalities starting at age 35 in male patients and age 45 in female patients

Laboratories role

- Before initiating statin therapy
  - CPK
  - Liver enzymes at baseline
- After statin initiating therapy
  - Recheck lipid panel
    - Compliance with medication
    - LDL reduction is adequate
      - Percentages goals
- Lipid panel concerning triglycerides

Laboratories role

- Ruling out secondary causes of hyperlipidemia
  - Nephrotic syndrome
    - Urinalysis
    - 24 hour urine
    - GFR
    - Creatinine
    - BUN
  - Thyroid disorders
    - TSH
    - Free T3 and T4
    - Thyroid antibodies (possibly)

Laboratories role

- Statin Therapy Adverse reactions
  - If unexplained severe muscle aches and/or fatigue occur the medication should be stopped immediately and laboratory studies ordered to rule out Rhabdomyolysis
    - CPK
    - Urinalysis- Myoglobinuria
    - Creatinine
  - Diabetes
    - Glucose
    - A1C (Every 3 months)
    - Microalbumin

Laboratory testing under the Affordable Care Act

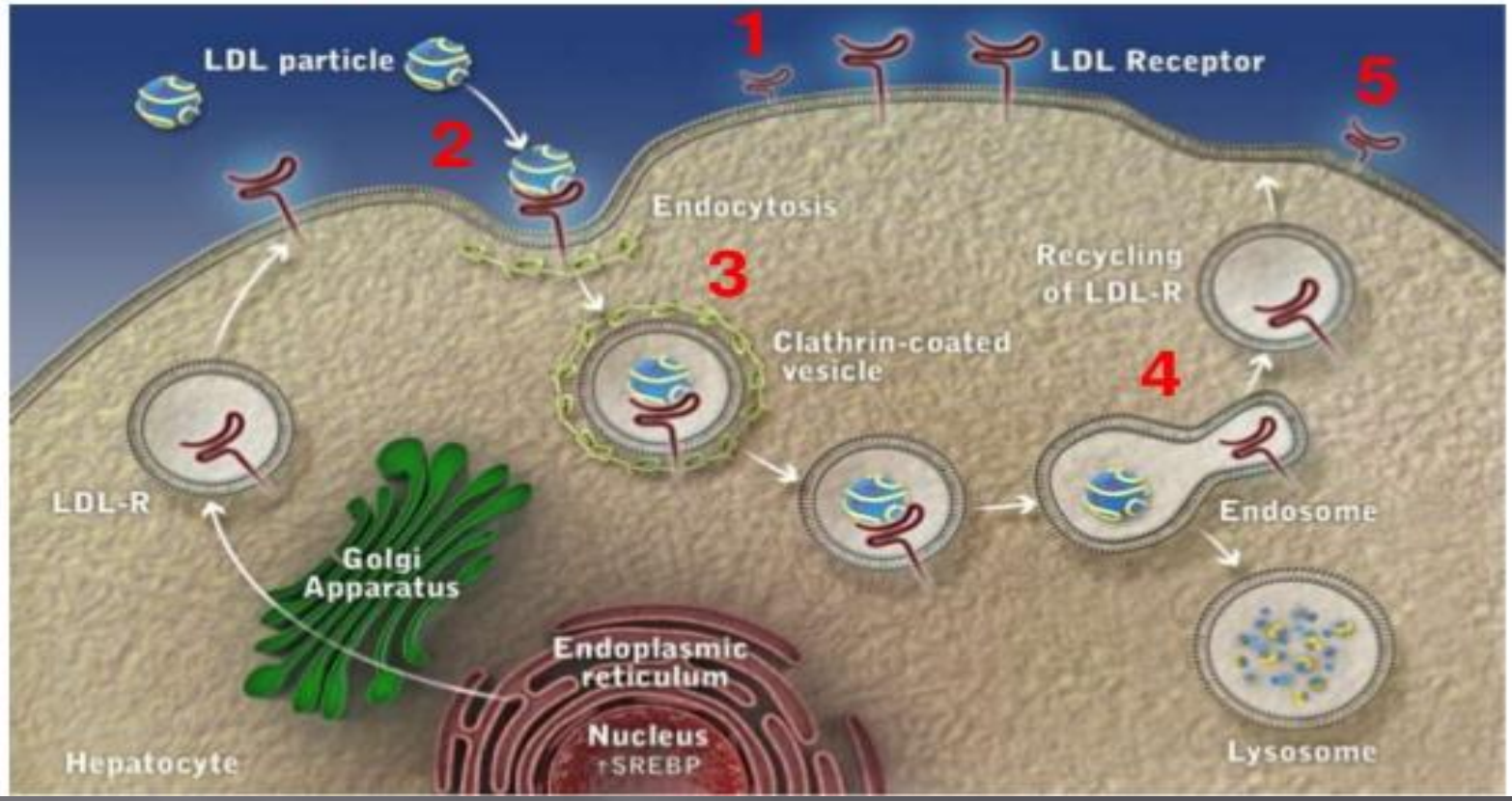
- If the screening recommendations by the USPSTF are a category A or B there is no shared cost to the patient
- Screening lipid panel
  - Men >35 years old and women >45 years old
  - Category A recommendation
  - Men 20-35 year old and women 20-45 years old at increased risk
  - Category B recommendation

New cholesterol research and treatment

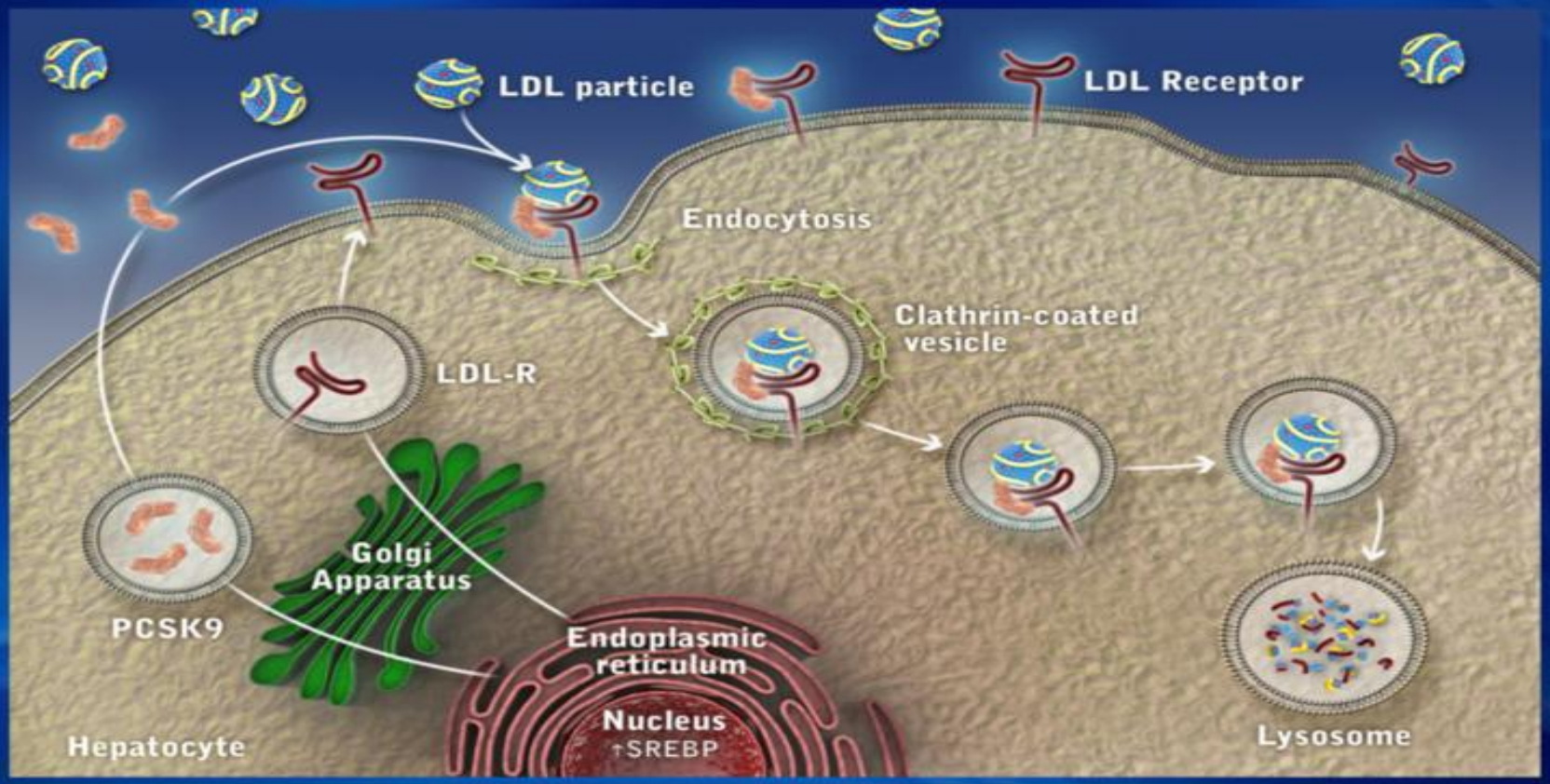
- Proprotein convertase subtilisin/kexin type 9
  - Also known as PCSK9
- Serine protease that reduces both hepatic and extrahepatic low-density lipoprotein (LDL) receptor (LDLR) levels and increases plasma LDL cholesterol

PCSK-9

LDL Receptor Function and Life Cycle



PCSK9


The Role of PCSK9 in the Regulation of LDL Receptor Expression
LDL particle
LDL Receptor
Endocytosis
Clathrin-coated vesicle
LDL-R
Golgi Apparatus
PCSK9
Endoplasmic reticulum
Nucleus
↑SREBP
Hepatocyte
Lysosome

16

PCSK9 Medications

VBWG

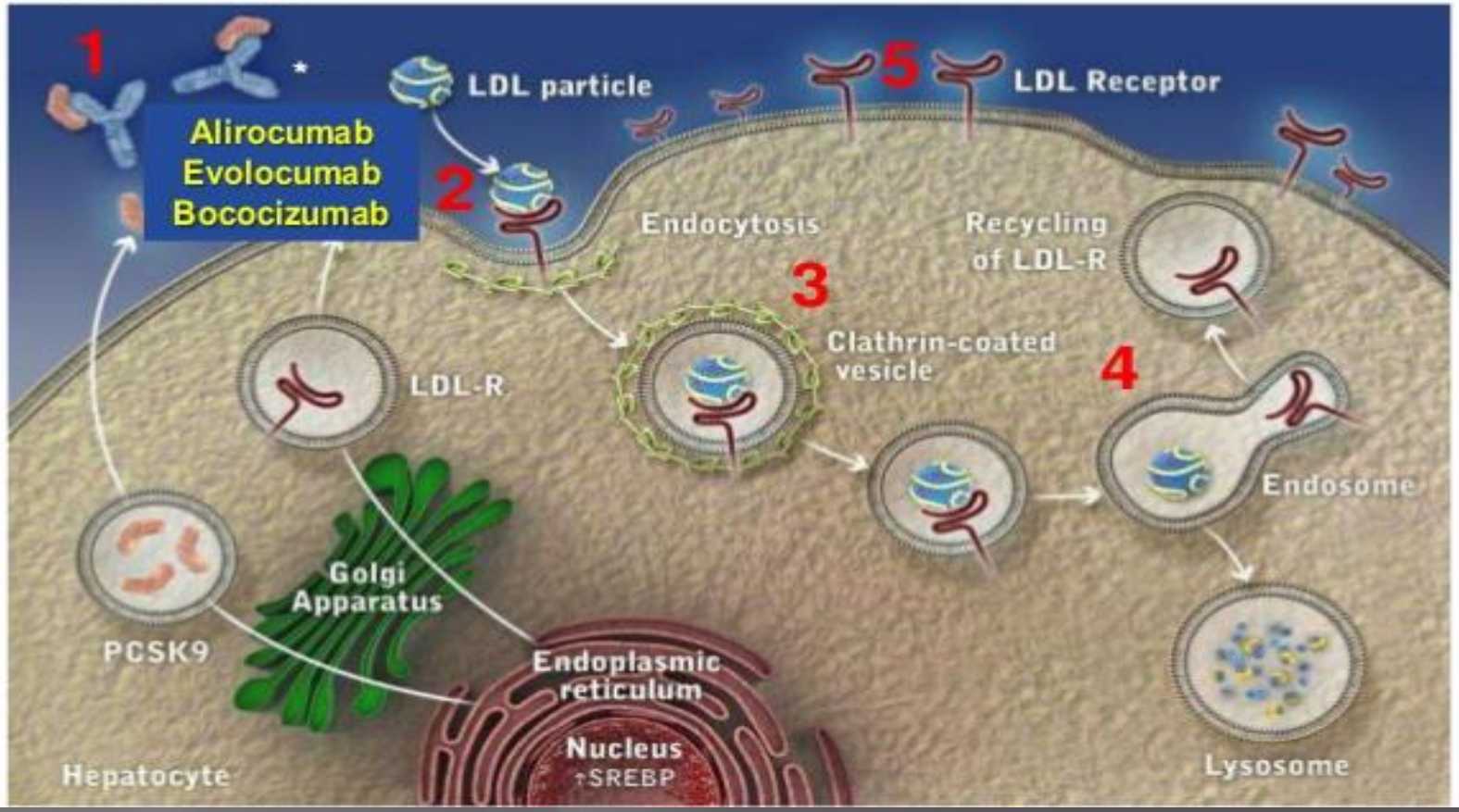
PCSK9 Inhibitors in Development

Molecule	Developer	Description	Clinical Stage
Alirocumab	Regeneron/Sanofi	Fully human IgG1 mAb	Phase 3
Evolocumab	Amgen	Fully human IgG1 mAb	Phase 3
Bococizumab	Pfizer	Humanized IgG1 mAb	Phase 3
RG-7652	Roche	mAb	Phase 3
LY3015014	Eli Lilly	mAb	Phase 2[a]
ALN-PCS02	Alnylam	RNA interference therapeutic	Phase 1

mAb = monoclonal antibody

Sheridan C. *Nature Biotechnology*. December 12, 2013; V31:1058.

PCSK9


Impact of PCSK9 monoclonal antibody on LDL receptor
1
Alirocumab
Evolocumab
Bococizumab
LDL particle
2
5
LDL Receptor
Endocytosis
Recycling
of LDL-R
3
Clathrin-coated
vesicle
LDL-R
4
Endosome
Golgi
Apparatus
PCSK9
Endoplasmic
reticulum
Nucleus
↑SREBP
Hepatocyte
Lysosome

PCSK9

- Requires genetic testing to make the diagnosis
  - Usually associated with familial hyperlipidemias
- Treatment with PCSK9 inhibitors could be an alternative to statin intolerant patients
- Several studies and clinical trials are being preformed in the US presently
  - University of Tennessee is currently participating in one of the trials

Final Thoughts

- Studies are now being conducted more thoroughly about lipids and their overall function
- There are still many questions that need to be answered about Statin drugs and their benefits
  - Statins work not only work to lower LDL but are suspected have a undefined mechanism at work that has not been discovered
    - Possible anti-inflammatory effect, helps to increase nitric oxide in the vasculature or immune modulating effects
  - Future studies will look at statins benefits against anti-inflammatory and immune modulating drugs, such as methotrexate

Final Thoughts

- There will still be a need for laboratory testing
  - Screening lipid panels
  - Periodic lipid panels to assess for compliance
  - Checking baseline labs for initiating treatment
- With new research genetic testing may become important in the diagnoses and treatment of lipid disorders

Question #1

- This 54 year old white male just started Simvastatin about 1 month ago. He is in the office today with fatigue and severe muscle cramps. He denies having any symptoms like this in the past. Which lab would be most appropriate to order?
- A TSH
- B CBC
- C CPK

Answer #1

- **Answer CPK**

- Elevations in CPK can indicate Rhabdomyolysis
- Also consider Creatinine and Urinalysis

Question #2

- This 50 year old white female comes to the office and has a 8 year history of diabetes and hypertension. She reports that both are well controlled. She is here for laboratory studies today.
- Labs:
- A1C 6.8%
- Total chol. 220
- HDL-C 40
- LDL-C 120
- Triglycerides 280
- Should patient be started on Statin therapy?

Answer #2

- Patient needs to treated with moderate intensity statin therapy
- Group 2 - Individuals with a LDL-cholesterol 190mg/dL or greater

Question #3

- A 45 year old male comes to the office for a general check up. Reports that he has not been to see a healthcare provider in years. Denies any medical problems and takes no medications regularly.
- Fasting Lipid Panel
  - HDL-C 35
  - Total Cholesterol 300
  - Triglycerides 350
  - LDL-C 195
- Does this Patient need treated?

Answer #3

- Patient needs to treated with moderate to high intensity statin therapy
- Group 3 - Individuals with diabetes aged 40-75 years old with LDL-cholesterol levels between 70 and 189 mg/dL and without evidence of atherosclerotic cardiovascular disease

References

- Lipid Disorders-Cholesterol presentation by Arlene Salmon PA-C; TAPA 2014
- Applying New Guidelines for Lipid Management presentation by Jim Yates MD; UT Conference 2014
- Evidenced based Evaluation and Management of Lipids and Cardiovascular risks presentation by Jay Crook MD; UT conferences 2013
- What is the Role of the Clinical Laboratory in the new ACC/AHA Guidelines for the Treatment of Blood Cholesterol in Adults by Ishwarlal Jialal MD; ASCP Article 2014

QUESTIONS???