



8-7-2015

# The Role and Management of Statins in Dyslipidemia and Addressing Patient Barriers to Use

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## Recommended Citation

O'Neal, Katherine S. and Johnson, Jeremy L., "The Role and Management of Statins in Dyslipidemia and Addressing Patient Barriers to Use" (2015). *Faculty Articles & Research*. 22.

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AUGUST 5 - 8, 2015  
NEW ORLEANS, LOUISIANA

**AADE** American Association  
of Diabetes Educators



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# The Role and Management of Statins in Dyslipidemia and Addressing Patient Barriers to Use

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# Objectives

- Define the role of statins for patients with diabetes
- Recommend appropriate statin therapy with evidence-based indications from recent guidelines
- Adjust statin therapy based on barriers encountered with myopathy and other health concerns
- Describe alternatives to statin therapy

# The US Diabetes “Epidemic”

- National prevalence of diabetes (2010)
  - Age  $\geq$  20 years: 11.3% (25.6 million)
  - Age  $\geq$  65 years: 26.9% (10.9 million)
- National prevalence of prediabetes (2010)
  - Age  $\geq$  20 years: 35% (estimated 79 million)
  - Age  $\geq$  65 years: 50%

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# Complications of Diabetes

**Macrovascular**

*Kidney Disease*

**Blindness** **Heart Attack**

**Loss of Feeling**

*Dialysis*

**Neuropathic**

**Stroke**

**Amputation**

**Microvascular**

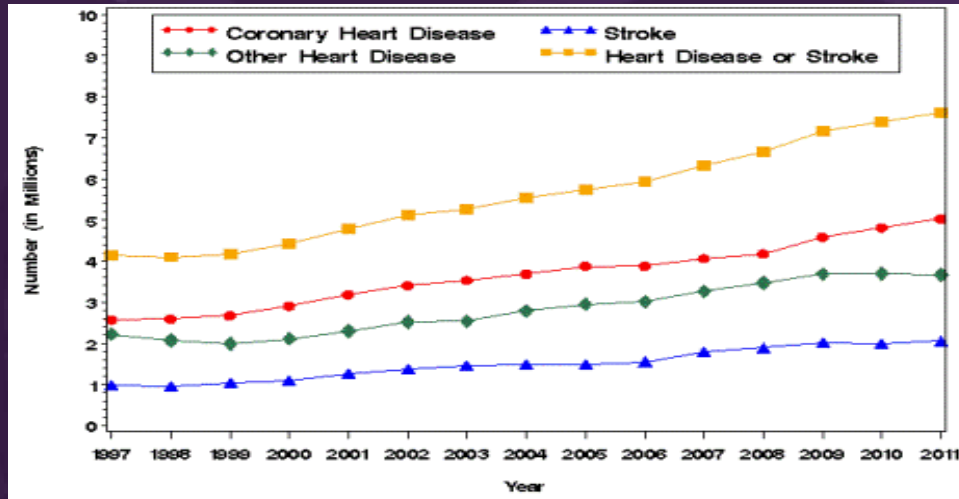
**Pain**

**Retinopathy**

# Macrovascular Complications

## Heart Disease and Stroke

Americans with Diabetes  $\geq 35$  yo (2011)



- 5 million with heart disease
- 3.7 million with other heart “condition”
- 2.1 million with reported stroke
- 7.6 million with heart disease or stroke

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# Heart Disease and Stroke

- Diabetes-related death certificates in people  $\geq 65$  yo (2004)
  - Heart disease noted in 68%
  - Stroke noted in 16%
- Risk
  - Heart disease death rates and risk of stroke are 2 - 4 times higher in adults with diabetes vs. those without diabetes

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# CHD and Diabetes

- CVD is the major cause of morbidity and mortality in patients with diabetes
- Dyslipidemia and hypertension are clear risk factors
  - Many studies have shown benefit in controlling these to prevent or slow CVD in diabetes

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# Why We Care About Statins

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# Lipid Guidelines

Review of NCEP ATP III

Highlights of the new 2013 ACC/AHA Blood Cholesterol Guidelines  
ADA Guidelines

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Detection 

Third Report of the  
National Cholesterol  
Education Program (NCEP)  
Expert Panel on

Detection,  
Evaluation,  
and Treatment  
of High Blood  
Cholesterol  
in Adults  
(Adult Treatment  
Panel III)

Evaluation 

Final Report

Treatment 



**NCEP ATP III**  
**Released: 2001**  
**Updated: 2004**

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# Goal Values or Targets

- TC < 200 mg/dL
- HDL > 40 mg/dL (>50mg/dL for women)
- TG < 150 mg/dL
- LDL goal must be determined based on risk

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# NCEP ATP III Guidelines

1

**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

*“LDL is the major atherogenic lipoprotein and has long been identified by NCEP as the primary target of cholesterol-lowering therapy”*

*“This focus on LDL has been strongly validated by recent clinical trials, which show the efficacy of LDL-lowering therapy for reducing risk for CHD”*

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# NCEP ATP III Guidelines

## Treatment of elevated triglycerides ( $\geq 150$ mg/dL)

- Primary aim of therapy is to reach LDL goal
- Intensify weight management
- Increase physical activity
- If triglycerides are  $\geq 200$  mg/dL after LDL goal is reached, set secondary goal for non-HDL cholesterol (total - HDL) 30 mg/dL higher than LDL goal.

## If triglycerides $\geq 500$ mg/dL, first lower triglycerides to prevent pancreatitis:

- very low-fat diet ( $\leq 15\%$  of calories from fat)
- weight management and physical activity
- fibrate or nicotinic acid
- when triglycerides  $< 500$  mg/dL, turn to LDL-lowering therapy.

# Three Categories of Risk that Modify LDL-Cholesterol Goals

## Risk Category

## LDL Goal (mg/dL)

CHD and CHD risk  
equivalents

<100

Multiple (2+) risk factors

<130

Zero to one risk factor

<160

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

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC) (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 (optional <70)	≥100	≥100 (<100: consider drug options)
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10–20%: ≥130 (100-129: consider drug options)
			10-year risk <10%: ≥160
0–1 Risk Factor	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

# Optional LDL Goal < 70 mg/dL

- Option for patients at “very high risk”
  - Must have established CVD plus any of:
    - Multiple major risk factors (especially diabetes)
    - Severe and poorly controlled risk factors (especially cigarette smoking)
    - Multiple risk factors of Metabolic Syndrome
      - High TG > 200 mg/dL plus
      - Non-HDL  $\geq$  130 mg/dL with low HDL < 40 mg/dL
    - History of acute coronary syndromes (ACS)

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# Not Good Enough?

- “Half of all myocardial infarctions and strokes occur despite apparently healthy men and women with LDL levels below currently recommended thresholds for treatment”
- “Even with adequate LDL lowering, many patients on statin therapy have significant CVD risk”

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# **2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults**

Released Mid-November 2013

Journal of the American College of Cardiology

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Stone NJ, et al.  
2013 ACC/AHA Blood Cholesterol Guideline

## 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

### **A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines**

*Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease*

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# 2013 ACC/AHA Blood Cholesterol Guidelines

- Expert panel for ATP 4
- Partnered with ACC/AHA
- Focus on ASCVD risk reduction, not comprehensive lipid management
- Only used RCT, systematic reviews, meta-analyses of RCT

# 3 Critical Questions

1. What is the evidence for LDL and non-HDL goals for the secondary prevention of ASCVD?
2. Same as #1, but primary prevention
3. For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific cholesterol-modifying drugs used for lipid management in general and in selected subgroups?

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# Findings

- “unable to find evidence to support titrating statins to a target LDL or non-HDL goal”
- “extensive evidence that appropriate statin intensity should be used to reduce ASCVD risk”
- “use of non-statins to additionally lower non-HDL once LDL goal achieved, DID NOT further reduce ASCVD outcomes”

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# Findings

- Non-statin therapies in general have not demonstrated significant ASCVD event reduction.
- Lifestyle modifications remain a critical component of health promotion and ASCVD risk reduction
- Identification of 4 statin benefit groups to focus on ASCVD risk reduction

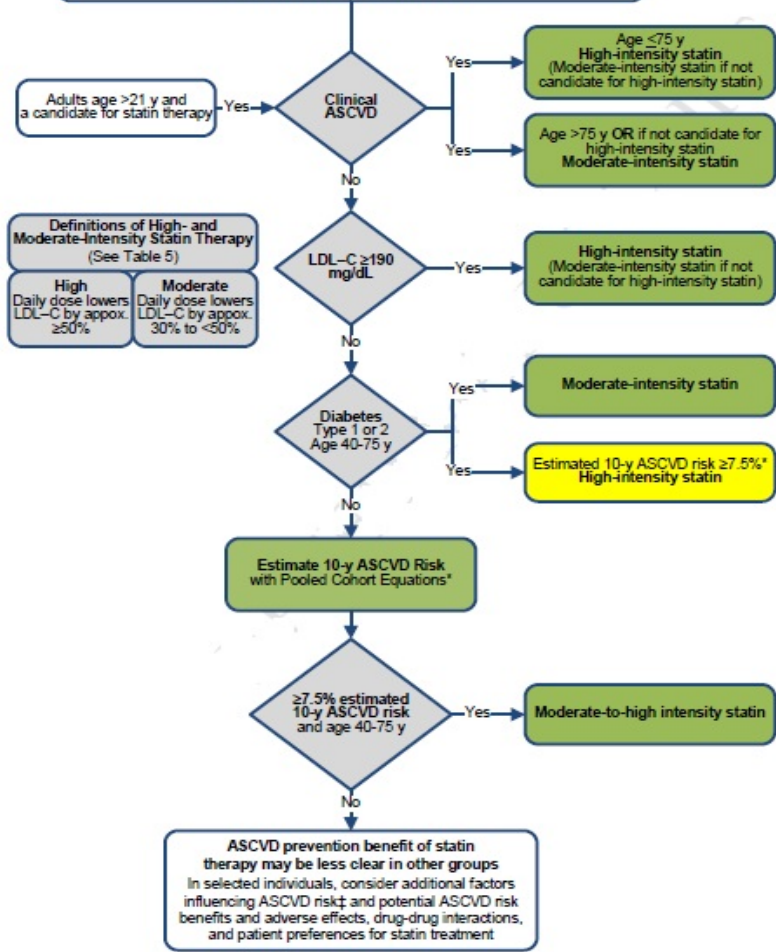
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# 4 Statin Benefit Groups

- Clinical ASCVD  $\leq$  75 yo (secondary prevention)
- Primary elevation of LDL  $\geq$  190 mg/dL
- 40-75 yo with Diabetes and LDL 70-189 mg/dL
- No clinical ASCVD or Diabetes, 40-75 yo and LDL 70-189 mg/dL and 10-year ASCVD risk of 7.5% or higher

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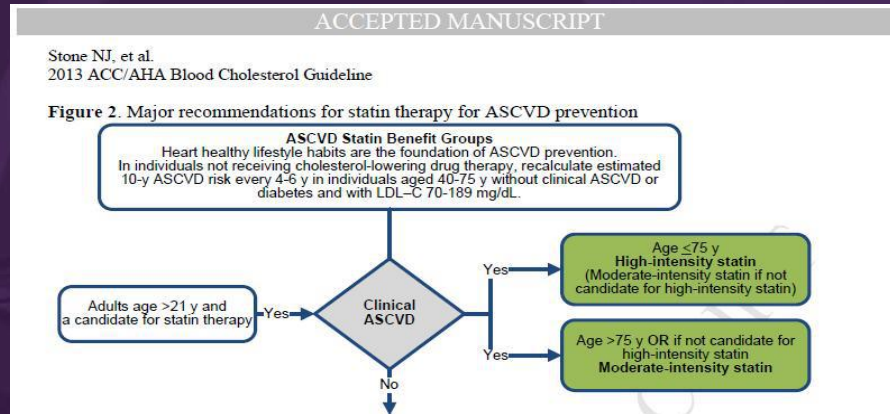
**ASCVD Statin Benefit Groups**  
 Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL-C 70-189 mg/dL.



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# Clinical ASCVD $\leq$ 75 years

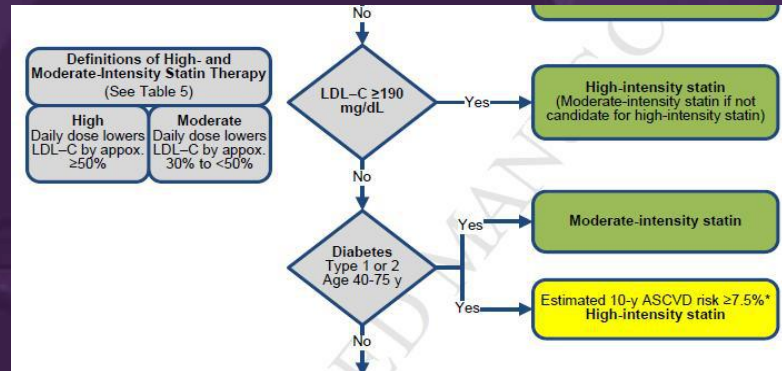
- High-intensity statin therapy (1<sup>st</sup> line)
- If not tolerated, use moderate-intensity
- If > 75 years, consider benefits vs risks and may use moderate- or high-intensity statin



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# LDL $\geq$ 190 mg/dL

- High-intensity statin therapy
- If not tolerated, use maximum tolerated intensity
- Once maximum intensity achieved, may consider addition of non-statins to further lower LDL (weak data—expert opinion)

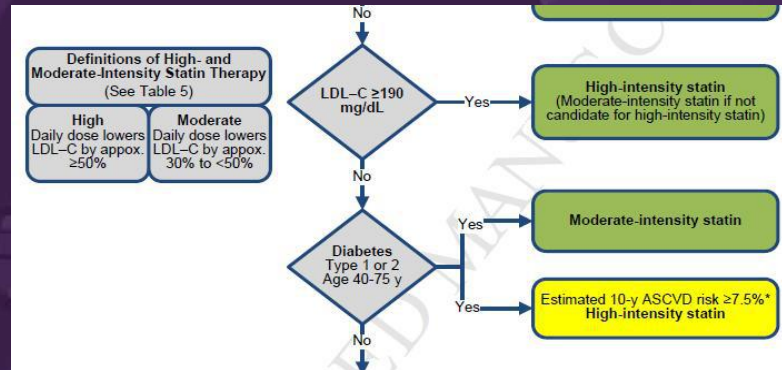


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# 40-75 years with Diabetes and LDL 70-189 mg/dL

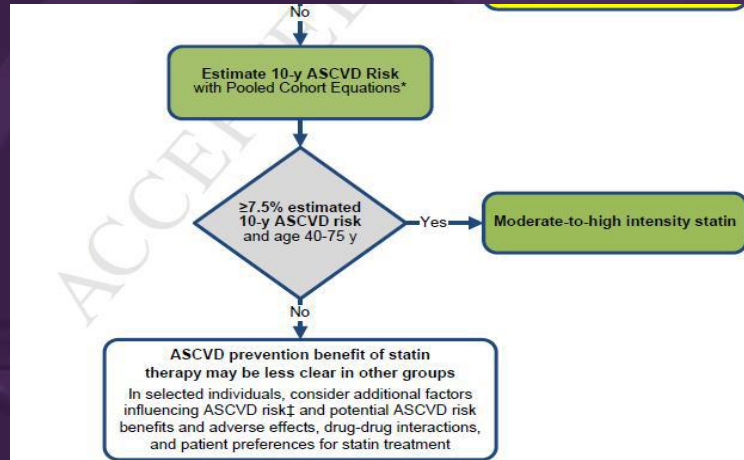
- Moderate-intensity statin therapy
- If ASCVD 10-year risk  $\geq 7.5\%$ , use high-intensity
- If  $< 40$  or  $> 75$  years, consider benefits vs risks and patient preferences



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# No Clinical ASCVD or Diabetes, 40-75 yo and LDL 70-189 mg/dL and 10-year ASCVD Risk of 7.5% or Higher

- Moderate- to High-intensity statin therapy



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# Adults with LDL <190 mg/dL not Fitting into a Statin Benefit Group

- Additional factors may be considered to inform treatment decision making
  - LDL  $\geq$  160 mg/dL
  - Genetic hyperlipidemia
  - Family history of premature ASCVD  $\text{♂}$  < 55 years or  $\text{♀}$  < 65 years
  - High C-reactive Protein (CRP) > 2 mg/L
  - Coronary artery calcium score  $\geq$  300 Agatston units or  $\geq$  75 percentile for age, sex, ethnicity
  - ABI < 0.9
  - Lifetime risk of ASCVD

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# Intensity of Statin Therapy

- Expected LDL-lowering:
  - High-intensity  $\geq 50\%$
  - Moderate-intensity 30 to  $< 50\%$
  - Low-intensity  $< 30\%$
- High-intensity reduces ASCVD risk more
- However, moderate- or low-intensity still provides protection, just not as much as high-intensity

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# Statin Intensity Categories and Drugs

High-intensity	Moderate-intensity	Low-intensity
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40 mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

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# Case Question 1

Patient is a 58 YO male with diabetes and an LDL of 198 mg/dL.  
Per the 2013 ACC/AHA guidelines, how should he be treated?

- A. Pravastatin 80 mg
- B. Rosuvastatin 20 mg
- C. Atorvastatin 20 mg
- D. Fluvastatin 40 mg

## Case Question 2

Patient is a 62 YO female with diabetes, an LDL of 82 (on no statin), and an ASCVD 10-year risk of 7.8%. Per 2013 ACC/AHA guidelines, how should she be treated?

- A. Atorvastatin 80 mg
- B. Pitavastatin 1 mg
- C. Lovastatin 20 mg
- D. Pravastatin 80 mg

# Calculation of ASCVD 10-year Risk (%)

- Pooled Cohorts Equations
  - Calculates risk of CHD death, fatal or non-fatal MI or stroke
  - Used for “white and black men and women” without clinical ASCVD
  - Controversial calculation
    - This places many more people in higher risk categories than the Framingham Risk tool

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All fields are required to compute ASCVD risk.

Gender

 Male Female

Age

Race

 White African American Other

HDL - Cholesterol (mg/dL)

Total Cholesterol (mg/dL)

Systolic Blood Pressure

Diabetes

 Yes No

Treatment for Hypertension

 Yes No

Smoker

 Yes No

\*Intended for use if there is not ASCVD and the LDL-cholesterol is <190 mg/dL

\*\*Optimal risk factors include: Total cholesterol of 170 mg/dL, HDL-cholesterol of 50 mg/dL, Systolic BP of 110 mm Hg, Not taking medications for hypertension, Not a diabetic, Not a smoker

# Statin Safety Recommendations

- Moderate-intensity statin should be used instead of high-intensity if high risk of statin-associated adverse effects
  - Impaired renal or hepatic function
  - Previous statin intolerances or muscle disorder
  - ALT > 3 times upper limit of normal (CI)
  - On drugs that affect statin metabolism
  - > 75 years of age
  - Possibly history of hemorrhagic stroke
  - Possibly Asian ancestry

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# Statin Safety Recommendations

- Monitor creatine kinase (CK or CPK)
  - Baseline and if myopathy symptoms
- Monitor ALT (liver function)
  - Baseline and if hepatotoxic symptoms
- Consider ↓ statin dose if 2 consecutive LDL < 40 mg/dL
- Avoid simvastatin 80 mg
- Evaluate for new onset diabetes

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# Monitoring Statin Therapy

- Initial fasting lipid panel (then start drug)
- Check fasting lipid panel 4-12 weeks (often 6-8 weeks); to check adherence, NOT to achieve a target or goal
- Then check fasting lipid panel 3-12 months

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# Monitoring Statin Therapy

- Insufficient response to statin dose
  - Reinforce adherence to medication and lifestyle
  - Exclude secondary causes
  - If higher-risk ASCVD patients on max statin dose, may consider adding non-statin
    - Clinical ASCVD < 75 years
    - Baseline LDL  $\geq$  190 mg/dL
    - 40-75 years old with diabetes

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# Summary of Lipid Guideline Differences

## ATP 3

- Focus on LDL goals
- Use statins or any lipid-lowering drugs to attain goal

## 2013 ACC/AHA

- Focus on statin intensity
- Use statins almost exclusively

# ADA 2014 Standards of Care

- Statin therapy if LDL > 100 mg/dL
- Statin therapy regardless of baseline lipid levels in DM:
  - With overt CVD
  - Without CVD, > 40 yoa,  $\geq 1$  CVD risk factor
- If LDL goal of < 100 mg/dL is not reached with optimal statin dosing, an LDL reduction of 30 - 40% from baseline is an alternative therapeutic goal
- “Combination drug therapy has been shown not to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended.”

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# ADA 2015 Standards of Care

- **High-intensity statin**
  - All ages with DM and overt CVD
  - 40-75 yo DM with additional CVD risk
- **Moderate- or High-intensity statin**
  - <40 yo DM with additional CVD risk
  - >75 yo DM with additional CVD risk
- **Moderate-intensity statin**
  - 40-75 yo DM without additional CVD risk
  - >75 yo DM without additional CVD risk
- Adjust statin intensity based on patient response (AE, LDL)
- Lipid panel for monitoring adherence
- “Combination therapy has not been shown to provide additional CVD benefit above statin therapy alone and is not generally recommended”

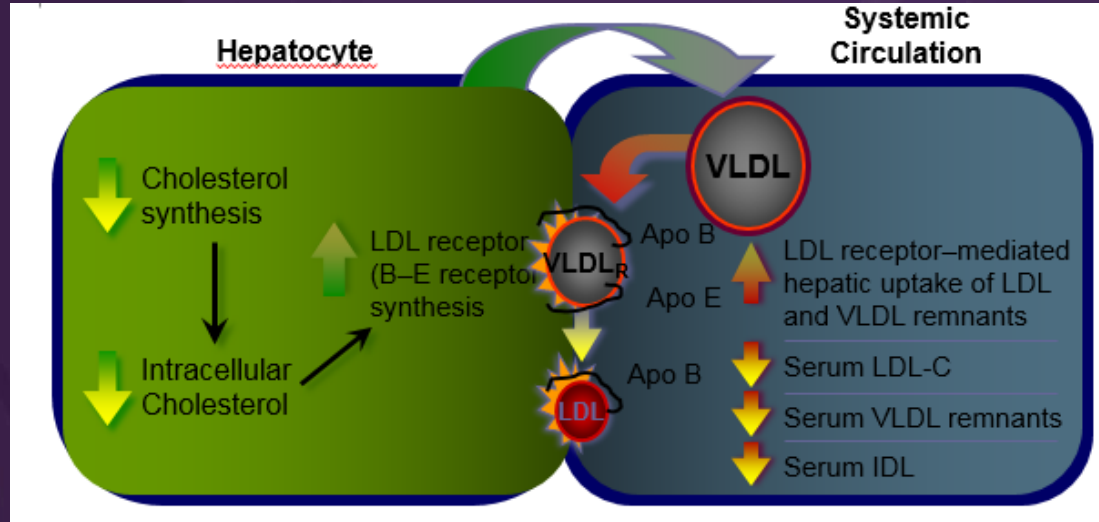
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# Statin Myopathy

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# Statin Mechanism of Action



Reduces hepatic cholesterol synthesis, lowering intracellular cholesterol, which stimulates upregulation of LDL receptors and increases the uptake of non-HDL particles from the systemic circulation

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# Definitions of Statin Myopathy

- **Myopathy**
  - Any muscle complaint related to statin use
- **Myalgia**
  - Muscle symptoms without elevated creatine kinase (CK)
- **Myositis**
  - Elevated serum CK with or without muscle symptoms
- **Rhabdomyolysis**
  - Severe muscle symptoms with CK elevated > 10 times the upper limit of normal (ULN)

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# Characteristics of Statin Myopathy

- **Localization**: Generalized (60%) or localized to large proximal muscle groups. Lower extremities more frequently (25%) affected than upper (8%)
- **Type**: Heaviness, stiffness, cramps
- **“Equivalent” of muscle pain**: Weakness, tendonitis
- **Frequency and duration**: Usually intermittent lasting several minutes to hours
- **Timing**: < 1 month to several years

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# Statin Myopathy – Randomized Controlled Trials (RCT)

- Rarely reported in RCTs
  - RCT reported 1-5% of patients experiencing myalgia
  - Patients are carefully selected for RCT
    - Patients with renal or hepatic insufficiency, poorly controlled diabetes, history of muscle complaints, and taking drugs with possible drug interactions usually excluded from trials
  - Most studies focus on reporting rhabdo vs. myalgia
  - Lack of consensus on definitions

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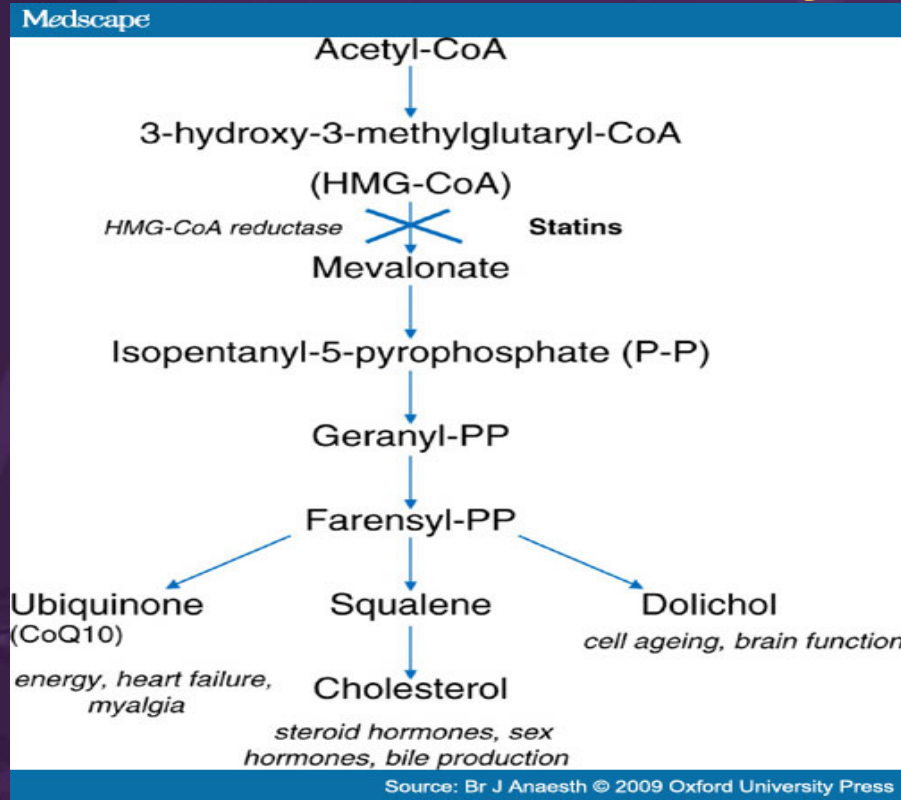
# Statin Myopathy – Observational Studies Outpatient

- Higher frequency of myopathy
  - 9-20%
- PRIMO Study
  - 10.5%

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Pasternak RC, et al. ACC/AHA/NHLBI Clinical advisory on the use and safety of statins. Journal of the American College of Cardiology, 2002. Bruckert E, et al. Mild to moderate muscular symptoms with dosage statin therapy, PRIMO. Cardiovascular Drugs and Therapy, 2006.

# What Causes Statin Myopathy



Carrier of  
SLCO1B1  
gene  
polymorphisms

Drug or food  
interactions  
(CYP3A4,  
CYP2C9, UGT,  
OAT1B1)

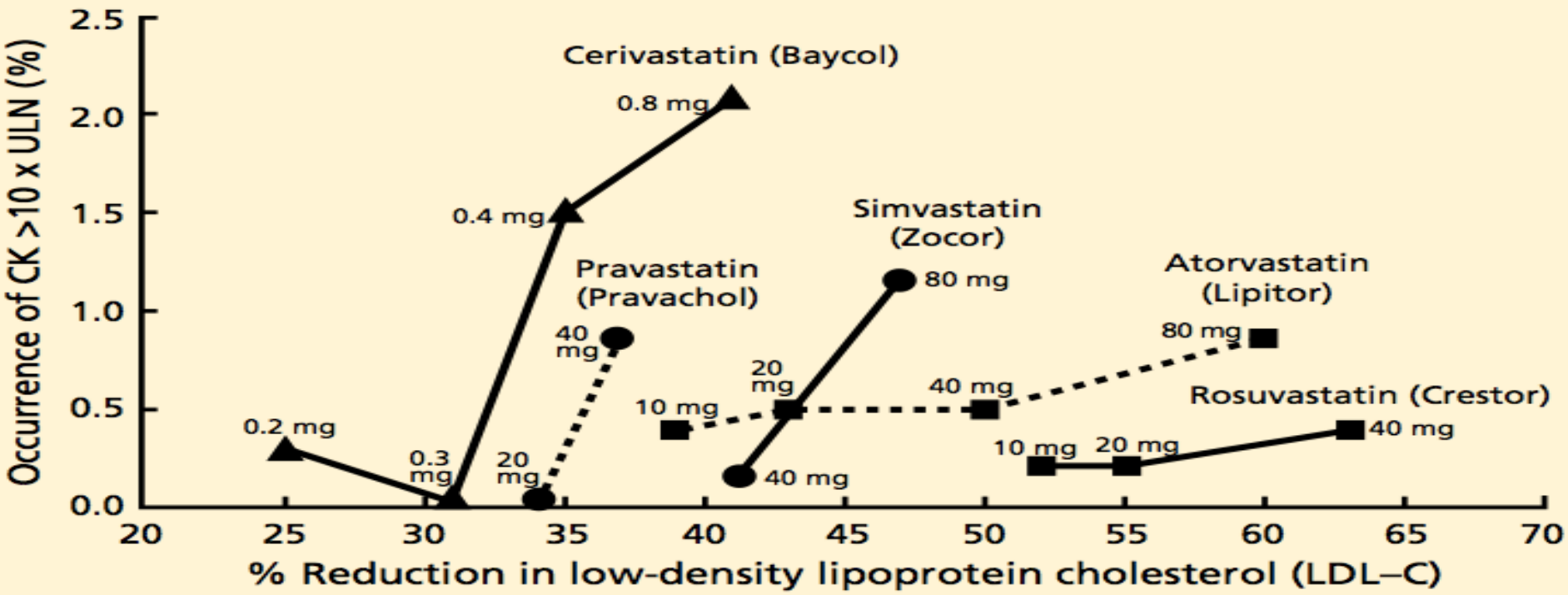
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# Pharmacotherapy Considerations

Medication	Lipophilicity	Metabolism	Half-life	Metabolites
Rosuvastatin	Hydrophilic	CYP2C9	~21	Minor active metabolite
Atorvastatin	Lipophilic	CYP3A4	~15-30	Active metabolite
Simvastatin	Lipophilic	CYP3A4	~2-3	Active metabolite
Pitavastatin	Lipophilic	CYP3A4	~12	No active metabolite
Lovastatin	Lipophilic	CYP3A4	~3	Active metabolite
Pravastatin	Hydrophilic	Sulfation	~1-3	No active metabolite
Fluvastatin	Lipophilic	CYP2C9	~5	No active metabolite



# LDL-C reduction and creatine kinase (CK) elevation



**FIGURE 1**

REPRINTED FROM BREWER HB JR. BENEFIT-RISK ASSESSMENT OF ROSUVASTATIN 10 TO 40 MILLIGRAMS. AM J CARDIOL 2003; 92(SUPPL):23K-29K, COPYRIGHT 2003, WITH PERMISSION FROM ELSEVIER; WWW.SCIENCEDIRECT.COM/SCIENCE/JOURNAL/ 00029149.

# Statin Toxicity

- Simvastatin 40-80mg – 18.2%
- Atorvastatin 40-80mg – 14.9%
- Pravastatin 40mg – 10.9%
- Fluvastatin XL 80mg – 5.1%



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# Risk Factors for Statin Myopathy

## Endogenous Risks

- Advanced age (>65)
- Low BMI and frailty
- Multisystem disease
- Hypothyroidism
- Hypertriglyceridemia
- Metabolic muscle disease
- Family history of muscular symptoms
- History of elevated CK or muscle symptoms

## Exogenous Risks

- Alcohol consumption
- Heavy exercise
- Surgery with severe metabolic demands
- >1 L grapefruit juice daily
- Drug interactions

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# Drugs Affecting CYP450 (3A4)

- Cyclosporine
- Nondihydropyridine Calcium Channel Blockers (i.e. verapamil, diltiazem)
- Amiodarone
- Azole antifungals (i.e. fluconazole)
- Colchicine
- Digoxin
- Protease inhibitors
- Warfarin
- Macrolide antibiotics (i.e. azithromycin)

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# Drugs Affecting CYP450 (2C9)

- Azole antifungals (i.e. fluconazole)
- H<sub>2</sub> receptor antagonists (i.e. ranitidine)
- Proton pump inhibitors (i.e. omeprazole)
- Warfarin
- NSAIDs
- Sulfonylureas (i.e. glipizide)
- ARBs
- Amiodarone

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# Gemfibrozil

- Inhibits glucuronidation of UGT
- Inhibits the OATP1B1 transporter
  - Increased levels of statin and increased risk of adverse effects

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# Simvastatin

- **SEARCH trial – 80mg vs. 20mg**
  - Major CV events 24.5% vs. 25.7%
  - Myopathy (CK>10x ULN + symptoms)
    - 52 patients on 80mg; 1 patient on 20mg
  - Rhabdomyolysis (CK>40x ULN + symptoms)
    - 22 patients on 80mg; 0 patients on 20mg
  - Risk declines from 5 to 2/1000 person years in the first 12 months, then from 1 to 0.4/1000 per years after 12 months
  - Risk of myopathy found to be 3x higher and risk of fatal rhabdomyolysis higher than with more potent LDL lowering drugs atorvastatin and rosuvastatin

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# Simvastatin Dosing Restrictions

- 80mg restricted to those taking it >12 months prior to 6/8/2011
- Maximum dose of simvastatin established when used concomitantly with other drugs:

Drug	Simvastatin Max Dose
Amiodarone	20mg
Amlodipine	20mg
Diltiazem	10mg
Verapamil	10mg

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Acetyl-CoA

3-hydroxy-3-methylglutaryl-CoA

(HMG-CoA)

*HMG-CoA reductase***Statins**

Mevalonate

Isopentanyl-5-pyrophosphate (P-P)

Geranyl-PP

Farnesyl-PP

Ubiquinone  
(CoQ10)*energy, heart failure,  
myalgia*

Squalene

Cholesterol

*steroid hormones, sex  
hormones, bile production*

Dolichol

*cell ageing, brain function*

Source: Br J Anaesth © 2009 Oxford University Press

# CoEnzyme Q10 Supplementation

- **Bookstaver and colleagues**
  - CoQ10 60mg twice daily
  - No more effective than placebo in decreasing muscle pain that was presumed to be statin induced
- **Kelly and colleagues**
  - CoQ10 100mg/day
  - Myopathic pain improved from baseline in treated patients
- **Ganesan and colleagues**
  - Relationship of GLUT4 protein levels, CoQ10, and statins

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# CoEnzyme Q10

- **Dose**: 100-300mg/day in divided doses
- **Adverse Effects**: (<1%) nausea/vomiting, diarrhea, elevated transaminases (rare)
- **Drug Interactions**: diminished effect of warfarin
- Rated as 'Likely Safe'

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# Management of Myopathy

- Muscle symptoms
  - Stop statin (2-6 week drug holiday)
  - Measure CK, serum creatinine and urinalysis
- Symptoms resolve
  - Restart original statin at same or lower dose
  - If recurrence, stop original statin
  - When symptoms resolve, start new statin at a lower dose
- If not resolved > 2 months, likely not statin; resume original dose
- If intolerant of statins, may use non-statin

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# Alternate Statin Dosing

- Use a lower toxicity statin
  - Fluvastatin XL 80mg (39% LDL lowering potential)
- Use a statin with less CYP450 dependence
  - Pravastatin
- Use alternate day or once/twice weekly dosing with longer acting statins (rosuvastatin, atorvastatin, pitavastatin)
  - 35% LDL lowering with rosuvastatin 5mg every other day
  - 26% LDL lowering with rosuvastatin 5-10mg twice weekly

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# Statin Discontinuation

- **Retrospective cohort study**: 107,835 patients over 9 years
- **Statin discontinued**: 57,292 (53%)
- **Statin-related events**: 18,778 (17.4%)
- **Findings**:
  - Of 11,124 who discontinued, 6579 were re-challenged with statin over next 12 months
  - 92.2% were still taking statin after 12 months
  - 2721 who were re-challenged with same statin, 1295 were still taking 12 months later

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# Bottom Line

- Most patient re-challenged can tolerate statins long-term
  - Statin-related events may have other causes, are tolerable or may be specific to individual statins rather than the entire drug class
- If patients develop muscle symptoms after start
  - Determine likelihood that muscle symptoms are due to the statin
  - Balance of expected statin therapy with the likelihood that muscle symptoms are due to statin

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# Case Question 3

- 45 YO Male with past medical history: hypertension, type 2 diabetes, obesity and smoker complaining of muscle pain
- Labs: ALT/AST WNL and CK 350
- ASCVD risk is 9%
- Medications: Metformin 500 mg 1 tablet twice daily, Lisinopril 40mg daily, HCTZ 25mg daily, amlodipine 10mg, and simvastatin 40mg once daily  
(History of being started on atorvastatin 80mg once daily but complained of muscle pain shortly after. PCP immediately switched to simvastatin 40mg.)

Which of the following is the best recommendation:

- A. Change statin therapy to bile acid sequestrant
- B. Decrease simvastatin to 20mg once daily
- C. Provide a 6-week statin drug holiday and re-challenge with atorvastatin 40mg
- D. Discontinue simvastatin and start rosuvastatin 20mg

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# Other Statin Concerns

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# Statin and Diabetes

- **JUPITER**

- N=17,802
- 27% increase in risk of diabetes (p=0.01)
- 39% reduction in primary endpoint (MI, stroke, CV deaths) for patients with diabetes risk factors and 52% reduction in those that with no risk factors
- 134 vascular deaths avoided for every 54 new cases of diabetes

- **Meta-analysis (PROVE IT-TIMI 22, TNT, IDEAL, A to Z, SEARCH)**

- High-dose statins (atorvastatin and simvastatin) increased risk of diabetes (OR 1.12)

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# Statins and Cognitive Impairment / Dementia

- **Meta-analysis evaluating 16 studies**: Without baseline cognitive dysfunction, no effect on cognition
  - Long-term data may support beneficial role for statins in prevention of dementia (HR 0.71, CI 0.61-0.82)
  - 5 studies showed 29% reduction in incidence of dementia
- **Prospective study of 6,600 patients**: Patients with normal cognitive function or mild cognitive impairment and statin use performed better on attention measures and had slower annual worsening of Clinical Dementia Rating Sum of Boxes ( $P < 0.006$ )
  - No difference in cognitive decline

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# Statins and Acute Kidney Injury

- Retrospective analysis of > 2 million patients on moderate to high intensity statins:
  - Rosuvastatin  $\geq$  10mg
  - Atorvastatin  $\geq$  20mg
  - Simvastatin  $\geq$  40mg
- 34% greater risk of hospitalization for acute kidney injury (AKI) in first 120 days of treatment with statin (CI 1.25-1.43)
  - NNH was 1700 for 1 AKI hospitalization within the 120 days
- Retrospective analysis of > 3 million patients on statin, no increase in AKI as a whole
  - simvastatin 40-80mg have increased risk of AKI

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# Bottom Line

- **Diabetes**: cardiovascular benefits outweigh the small absolute risks of developing diabetes
- **Dementia**: there is no increased risk of cognitive decline, and there may even be a protective role
- **Acute Kidney Injury**: cardiovascular benefits of statin therapy outweigh the proposed risk of acute kidney injury

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# Drug Therapy Options

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# Statin Considerations

## Adverse Effects

- Myopathy (rhabdomyolysis)
- Elevated liver transaminases (rare)

## Contraindications

- Pregnancy, active liver disease

## Monitor

- Fasting lipid profile (6 - 8 weeks)
- Baseline CPK (CK) and again if muscle pain
- Baseline LFT and again periodically

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# Statin Pearls

- Dose in evening unless long half-life (atorva-, rosuva-)
- Myopathy - rechallenge with lower dose or different statin
  - Less with prava- (maybe rosuva- and pitava-)
  - CoQ10, alternate dosing with long-half-life statins
- Drug interactions
  - Many (CYP 3A4, 2C9)
  - Less with pravastatin
- Recent label changes:
  - No more simvastatin 80 mg
  - Risk of diabetes, cognitive impairment, less liver monitoring, drug interactions

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# Non-Statin Therapy Options

- Fibrate
- Niacin
- Bile Acid Sequestrant
- Cholesterol absorption inhibitor
- Omega 3 fatty acid
- PCSK9 Monoclonal Antibodies (future)
- Complementary and Alternative Agents
  - Cholestoff: Contains plant stanols and sterols (15 - 20% LDL lowering)
  - Fish oil: 2000 - 4000 mg/day
  - Soluble fiber: 10 - 25 g/day
  - Red Yeast Rice: 1200 - 2400 mg contains lovastatin 2 - 6 mg equivalence (20 - 25% LDL lowering)
  - CoEnzyme Q10: 100 - 300 mg/day

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# Patient Education

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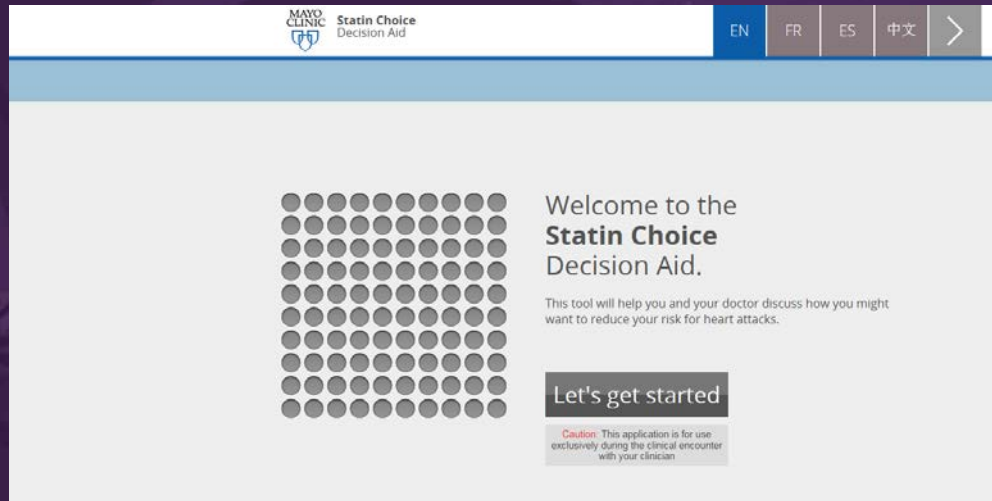
# Health Literacy Sensitive Approaches

- Explain the differences between statins and about medication itself
  - Patients also have fear of perceived adverse effects and have misunderstanding of the benefits
- Use an analogy that the patient can relate to
- Visual aids
- Plain language
- Relate to diabetes and have patient repeat back goals

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# Motivational Interviewing

- Identify what is important to them (e.g. family, grandkids)
- Involve patient with decision process (shared decision making)
  - Mayo Clinic shared decision making tools



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# Complex Case 1

- 60 YO Male complaining of general pain with past medication history type 2 diabetes, HTN, dyslipidemia, CAD, MI, CABG, left carotid endarterectomy

	Baseline	2 Weeks Later	6 weeks later
Statin	Pravastatin 40mg	None for 4 weeks	None for 10 weeks
CPK (units/L)	None	563	711
LDL (mg/dL)	96		122
Muscle Pain	Present	Not Resolved	Not resolved
Plan	Stop pravastatin	No drug therapy	?

Which of the following is the best recommendation:

- A. Re-challenge statin with rosuvastatin 5mg every other day with coenzyme Q10 supplementation
- B. Re-challenge with pravastatin XXmg
- C. Re-challenge with atorvastatin 40mg
- D. Start bile acid sequestrant

# Complex Case 2

- 51 YO Male with past medical history: Dyslipidemia, hypertension, obesity, hypothyroid, coronary artery disease, type 2 diabetes
- Current labs (2015): TC 395, HDL 46, LDL 320, TG 145, AST/ALT 22/38, CK WNL
- Medication intolerances: complaints of myalgias with ALL statins (history of hospital admission in 2013 with AST/ALT 1100/1200, CK 50,000 on atorvastatin 40mg), gemfibrozil, fenofibrate, niacin, ezetimibe
- Not currently on treatment for his dyslipidemia

Which of the following is the best recommendation:

- A. Re-challenge statin with rosuvastatin 5mg every other day with coenzyme Q10 supplementation
- B. Try CholestOff
- C. Try fish oil
- D. Start bile acid sequestrant

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# The Role and Management of Statins in Dyslipidemia and Addressing Patient Barriers to Use

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