Lipid Management in Primary Care

Justin Guthier, DO

August 2019

Financial Disclosures

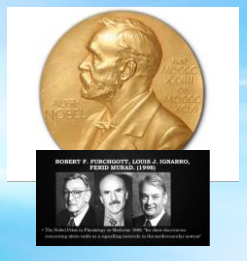
- None

Agenda

- Overview of Pathophysiology of Coronary Artery Disease
- Have the ACC Guidelines Changed the Goals?
  - Brief History of Cholesterol Guideline Development
  - Detailed Review of 4 statin benefit Groups
    - Brief discussion of statin use in the Elderly
    - Brief discussion of statin safety: New onset diabetes
    - Focus on personalized risk assessment and non statin therapies
  - Review of Top 10 Take Home Messages from 2018 Guideline Update

History of Atherosclerosis

- Culmination of two lines of investigation in the 1970s and 1980s forged in the field of vascular biology and two major discoveries
  - Nitric oxide was a physiological dilator of blood vessels, a discovery for which Furchgott, Ignarro, and Murad received the 1998 Nobel Prize in Physiology or Medicine
  - The observation that thrombotic occlusion of a ruptured or eroded atherosclerotic plaque led to acute myocardial infarction



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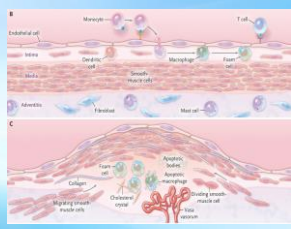
Atherosclerosis Pathogenesis

- Atherosclerosis is a chronic inflammation of arteries, which develops over decades in response to the biologic effects of risk factors
- Atherogenesis begins when endothelial cells affected by multiple factors change their permeability to promote the entry and retention of blood-borne monocytes and cholesterol-containing LDL particles
  - Oxidative
  - Hemodynamic
  - Biochemical stimuli (from smoking, hypertension, or dyslipidemia)
  - Inflammatory factors



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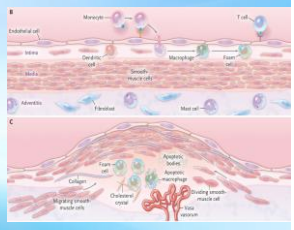
Atherosclerosis Pathogenesis

- Inflammation and biochemical modifications ensue, causing endothelial and smooth-muscle cells to proliferate, produce extracellular matrix molecules and form a fibrous cap over the developing atheromatous plaque.



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Atherosclerosis Pathogenesis

- Plaques lead to clinical symptoms by producing flow-limiting stenoses (causing stable angina) or by provoking thrombi that interrupt blood flow on either a temporary basis (causing unstable angina) or a permanent one (causing myocardial infarction).
- Physical disruption (rupture) of the plaque exposes procoagulant material within the core of the plaque to coagulation proteins and platelets, triggering thrombosis

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ATP III Guidelines

- Prior management had focused on cholesterol treatment targets
- Issued in 2013, the ACC/AHA guidelines challenged the established practice based on the 2004 NCEP ATP III Guidelines.
- The ATP III guidelines **placed a heavy emphasis on specific low density lipoprotein (LDL) cholesterol levels in deciding which patients should start statin therapy**.

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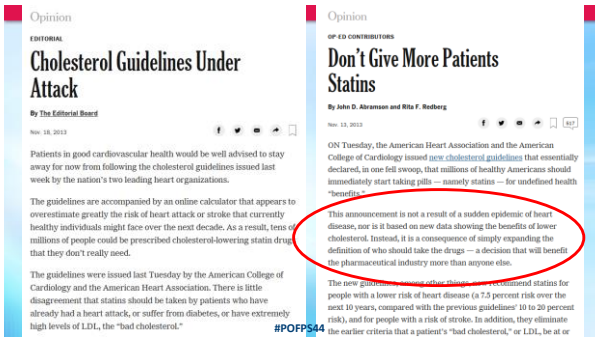

Opinion

EDITORIAL

Cholesterol Guidelines Under Attack

By The Editorial Board

Nov. 18, 2013

Patients in good cardiovascular health would be well advised to stay away for now from following the cholesterol guidelines issued last week by the nation's two leading heart organizations.

The guidelines are accompanied by an online calculator that appears to overestimate greatly the risk of heart attack or stroke that currently healthy individuals might face over the next decade. As a result, tens of millions of people could be prescribed cholesterol-lowering statin drugs that they don't really need.

The guidelines were issued last Tuesday by the American College of Cardiology and the American Heart Association. There is little disagreement that statins should be taken by patients who have already had a heart attack, or suffer from diabetes, or have extremely high levels of LDL, the "bad cholesterol."

Opinion

OP-ED CONTRIBUTORS

Don't Give More Patients Statins

By John D. Abramson and Rita F. Redberg

Nov. 13, 2013

ON Tuesday, the American Heart Association and the American College of Cardiology issued new cholesterol guidelines that essentially declared, in one fell swoop, that millions of healthy Americans should immediately start taking pills — namely statins — for undefined health "benefits."

This announcement is not a result of a sudden epidemic of heart disease, nor is it based on new data showing the benefits of lower cholesterol. Instead, it is a consequence of simply expanding the definition of who should take the drugs — a decision that will benefit the pharmaceutical industry more than anyone else.

The new guidelines, among other things, raise recommended statins for people with a lower risk of heart disease (a 7.5 percent risk over the next 10 years, compared with the previous guidelines' 10 to 20 percent risk), and for people with a risk of stroke. In addition, they eliminate the earlier criteria that a patient's "bad cholesterol," or LDL, be at or

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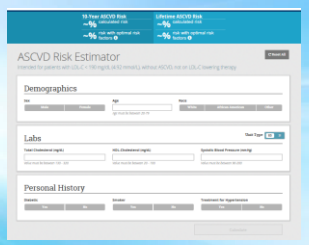
ASCVD Risk Calculator

- The ACC/AHA guidelines, by contrast, recommended basing the **decision on a patient risk** and created a scoring system that included such factors as age, gender, blood pressure, and family history, as well as LDL cholesterol levels, to determine a patient's **10 year risk of having a cardiovascular event**.
- Patients whose overall 10 year risk score was determined to be 7.5% or greater should start statin therapy



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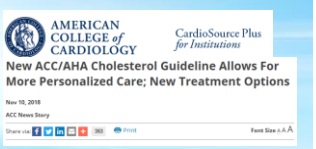
2018 Guideline Update

- The new 2018 ACC/AHA Guideline on the Management of Blood Cholesterol allows for more personalized care for patients compared to its 2013 predecessor.
- Among the biggest changes: more detailed risk assessments and new cholesterol-lowering drug options for patients at the highest risk for cardiovascular disease



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2018 Guideline Update: Benefit Groups

- Four Statin Benefit Groups
  - Secondary ASCVD Prevention
  - Severe Hypercholesterolemia (>190 LDL)
  - Diabetes Mellitus in adults 40-75 with LDL 70-189
  - Primary Prevention

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Dialysis patients and Statin Use

- **KDIGO (Kidney Disease improving Global Outcomes Work Group) recommendations for pharmacotherapy of lipids in adults with dialysis dependent CKD**
  - In adults with dialysis-dependent CKD, statins or statin/ezetimibe combinations should not be initiated (IIA).
- This recommendation was based on clinical studies that showed statins do not improve cardiovascular outcomes in hemodialysis patients despite lowering LDL cholesterol. The first of these studies was the 4D study.
  - In the 4D study, atorvastatin had no effect on the single components of the primary end point (a composite of cardiac death, non-fatal MI, and fatal and non-fatal stroke) in a four-year follow-up of 1,255 hemodialysis patients.
  - This was followed by a large-scale multicenter trial called the AURORA trial, which evaluated benefits of rosuvastatin in dialysis patients between 50 and 80 years of age. This was a placebo-controlled double-blinded randomized trial that studied the effect of rosuvastatin on multiple primary endpoints, namely non- fatal myocardial infarction, non-fatal stroke, and cardiovascular-specific mortality, in statin naive patients on hemodialysis. Some 2,776 hemodialysis patients were assigned to either rosuvastatin or placebo and followed for a median of 3.8 years. Rosuvastatin did not reduce the risk of individual components of the primary end point or all-cause mortality, despite a 43 percent reduction in the LDL cholesterol level

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Classification of Statin Therapy Intensity

High-, Moderate-, and Low-Intensity Statin Therapy*

Table 3

	High-Intensity	Moderate-Intensity	Low-Intensity
LDL-C Lowering†	≥50%	30% to 49%	<30%
Statins	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 (40 mg)**	**Atorvastatin 10 mg (20 mg)** **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg§**	Simvastatin 10 mg
	-	**Pravastatin 40 mg (80 mg)** **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1–4 mg	**Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

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Classification of Intensity: Caveats

- Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study.
- Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

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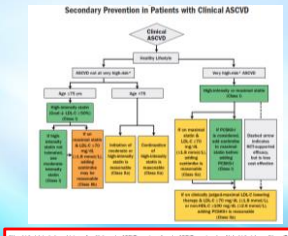
Secondary Prevention



Secondary ASCVD Prevention
First Statin Benefit Group

Very High-Risk for Future ASCVD Events*

Table 4

Major ASCVD Events
Recent acute coronary syndrome (within the past 12 months)
History of myocardial infarction (other than recent acute coronary syndrome event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ankle brachial index <0.85, or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)
Diabetes Mellitus
Hypertension
Chronic kidney disease (eGFR 15-59 mL/min/1.73 m²)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL (≥2.6 mmol/L)) despite maximally tolerated statin therapy and ezetimibe
History of congestive heart failure

*Very High Risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.

*Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 4 on following page).

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Secondary Prevention

Recommendations for Statin Therapy Use in Patients With ASCVD		
COR	LOE	Recommendations
I	A	In patients who are 75 years of age or younger with clinical ASCVD,* high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels.
I	A	In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels.

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Secondary Prevention

Recommendations for Statin Therapy Use in Patients With ASCVD		
COR	LOE	Recommendations
I	B-NR	In patients with clinical ASCVD who are judged to be very high risk and *considered for PCSK9 inhibitor therapy,* maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe.
IIa	A^{SR}	In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL (≥1.8 mmol/L) or higher or a non-HDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, it is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost.

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Secondary Prevention

Recommendations for Statin Therapy Use in Patients With ASCVD		
COR	LOE	Recommendations
IIa	B-R	In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level of 70 mg/dL (≥1.8 mmol/L) or higher, it is reasonable to add ezetimibe therapy.

Recommendations for Statin Therapy Use in Patients With ASCVD		
COR	LOE	Recommendations
IIb	B-R	In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL (≥1.8 mmol/L) or higher, it may be reasonable to add ezetimibe.

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IMPROVE IT

ORIGINAL ARTICLE

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Tim Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., et al., for the IMPROVE-IT Investigators*

Article Figures/Media Metrics

41 References 1321 Citing Articles Letters 11 Comments

June 18, 2015
N Engl J Med 2015; 372:2387-2397
DOI: 10.1056/NEJMoa1410489
Chinese Translation 中文翻译

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IMPROVE IT

IMPROVE-IT Cannon C, et al., 2015 (32) 26039521	**Aim:** To determine whether the addition of ezetimibe to a statin reduces the incidence of cardiovascular events as compared to statin monotherapy. **Study design:** Double blind placebo-controlled RCT multicenter study **Size:** N= 18,144	**Inclusion criteria:** 1. Men and women 50 y of age or older who had been hospitalized with the preceding 10 d for an acute coronary syndrome 2. Patients required to have LDL-C ≥ 50 mg/dL 3. For those not on lipid-lowering therapy at baseline, LDL-C ≤ 125 mg/dL. 4. For those on lipid-lowering therapy, LDL-C ≤ 100 mg/dL. **Exclusion criteria:** 1. Planned coronary bypass surgery for the acute coronary event 2. Creatinine clearance <30 ml/min 3. Active liver disease 4. Use of statin therapy that had potency greater than simvastatin 40 mg daily.	**Intervention/Comparator:** Simvastatin 40 mg daily (9072) plus placebo versus simvastatin 40 mg daily plus ezetimibe 10 mg daily (9072) over a median follow-up of 6 y.	**1° endpoint:** 1. Composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring re-hospitalization, coronary revascularization (≥30 d after randomization), or nonfatal stroke. **Results:** 1. Median time- weighted average LDL-C for placebo patients was 69.5 mg/dl vs. 53.7 for those taking ezetimibe. 2. Kaplan Meier event rate for the primary endpoint was 34.7% in those receiving placebos vs.32.7% in those on ezetimibe (absolute risk reduction 2%, hazard ratio: 0.936; 95% CI: 0.89-0.99; p=0.016.	1. Ezetimibe added to moderate-intensity statin therapy lowered LDL-C and reduced the incidence of cardiovascular events. 2. Ezetimibe therapy was safe and well-tolerated. **Limitations:** 1. 42% of the patients stopped the study medicine prematurely.

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Secondary Prevention

Recommendations for Statin Therapy Use in Patients With ASCVD		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences.**
IIa	**C-LD**	**In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences.**

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Statins Use in the Geriatric Population

- Potential harm is a crucial part of appropriate decision making.
- As frailty, comorbidity, and polypharmacy may increase the risk for adverse statin-associated symptoms, the "risk-benefit" balance in the elderly could theoretically tip in favor of withholding statin therapy if such conditions are present

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Statin Use in the Geriatric Population

- Efficacy of statin therapy in the very elderly, however, is well documented in secondary prevention trials
- The PROSPER (Pravastatin in elderly individuals at risk of vascular disease) trial, for example, specifically assessed the benefit of statins in elderly individuals and demonstrated improved outcomes among elderly with known vascular diseases

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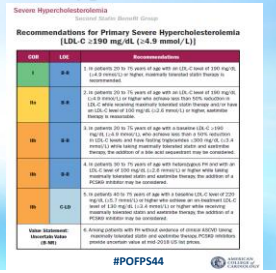
Severe Hypercholesterolemia


Severe Hypercholesterolemia

Second Statin Benefit Group

Recommendations for Primary Severe Hypercholesterolemia (LDL-C ≥190 mg/dL (≥4.9 mmol/L))

COR	LOE	Recommendation
I	B-R	1. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended.
IIa	B-R	2. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher who achieve less than 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, ezetimibe therapy is reasonable.
IIb	B-R	3. In patients 20 to 75 years of age with a baseline LDL-C ≥190 mg/dL (≥4.9 mmol/L) who achieve an on-treatment LDL-C <100 mg/dL (<2.6 mmol/L) and have fasting triglycerides ≥500 mg/dL (≥5.6 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered.
IIb	B-R	4. In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 190 mg/dL (≥2.8 mmol/L) or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.
IIb	C-LD	5. In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL (≥5.7 mmol/L) or higher who achieve an on-treatment LDL-C level of 130 mg/dL (≥3.4 mmol/L) or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.
Value Statement: Uncertain Value (B-NR)		6. Among patients with FH without evidence of clinical ASCVD timing: maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 US list prices.

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Severe Hypercholesterolemia

Value Statement: Uncertain Value (B-NR)	Among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at 2018 U.S. list prices.

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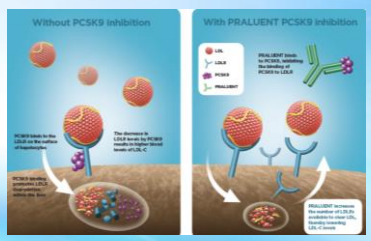
PCSK9 inhibitor



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Fourier

- FOURIER trial randomized patients with established atherosclerotic disease on background moderate- or high-intensity statin therapy (70% high intensity) to the PCSK9 inhibitor evolocumab versus placebo and assessed for a primary outcome of major CV events (cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization).
- At median follow-up 26 months, evolocumab was associated with an absolute 1.5% reduction in major cardiovascular events (cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization), driven primarily by reductions in nonfatal MI, stroke, and revascularization.

FOURIER TRIAL

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Fourier

- Treatment of 74 patients with evolocumab over 2 years would be expected to prevent one CV death, MI, or stroke.
- LDL was reduced by 59% from a median of 92 to 30 in the evolocumab group.

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Fourier

- There was no overall or CV-specific mortality benefit with evolocumab, although CV death rates were notably low (< 2%) in both groups.
- Effects of evolocumab were consistent regardless of baseline LDL level or intensity of background statin use. Other than a modest 2% incidence in injection-site reactions (which led to no excess drug discontinuations vs. placebo), there was no increase in key adverse events including new-onset diabetes or neurocognitive effects in patients receiving evolocumab.

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Fourier

- In summary, evolocumab in addition to moderate- or high-intensity statin therapy in patients with established atherosclerotic disease results in a modest reduction in CV events including MI and stroke although notably without a reduction in overall or CV-specific mortality

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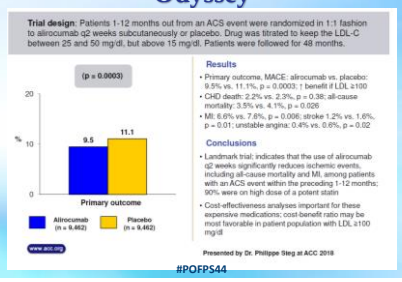
Odyssey



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Odyssey

- The results of this landmark trial indicate that the use of alirocumab, taken every other week, significantly reduces ischemic events, including all-cause mortality and MI, among patients with an ACS event within the preceding 1-12 months.
- First and total nonfatal events were lower with alirocumab. Nearly 90% of these patients were on a high dose of a potent statin (atorvastatin or rosuvastatin).
- Of note, the target LDL-C in this trial was 25-50 mg/dl, and the dose was adjusted to keep the LDL-C above 15 mg/dl.

ODYSSEY OUTCOMES

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Odyssey

- This is one of the first trials to show a therapeutic benefit with reduction in Lp(a) that is independent of LDL-C. This was particularly meaningful for patients with high baseline Lp(a) levels. This may represent a novel therapeutic target among ACS patients.

ODYSSEY OUTCOMES

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Odyssey

- A few points to consider:
  - This trial differs from the other PCSK9 inhibitor outcomes trial (FOURIER – evolocumab) in the patient population enrolled – post-ACS vs. stable established atherosclerotic disease.
  - Differences in mortality noted in this trial were not noted in FOURIER, possibly due to the higher risk patient population enrolled in ODYSSEY OUTCOMES
  - Reductions in LDL-C seemed qualitatively similar.
  - This trial further reinforces the "lower is better" hypothesis with LDL-C, and will likely once again reopen the debate about treating patients based on lipid levels rather than intensity of statin therapy alone. Interestingly, the CTT meta-analysis suggests an approximate 22% reduction in CHD events with every 1 mmol/L (38 mg/dl) reduction in LDL-C;
  - Finally, PCSK9 inhibitors are very expensive medications; the cost-effectiveness analysis is important, and suggests that the cost-benefit ratio is more favorable among patients with LDL-C ≥100 mg/dl.

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Diabetes Mellitus in Adults 40-75 Years of Age With LDL- C 70-189 mg/dL

Diabetes Mellitus in Adults

Third Statin Benefit Group

Diabetes-specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes

Table 5

- Long duration (≥10 years for type 2 diabetes or ≥ 20 years for type 1 diabetes)
- Albuminuria ≥30 mcg albumin/mg creatinine
- eGFR <60 ml/min/1.73 m^2
- Retinopathy
- Neuropathy
- ABI <0.9

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Lipid Management in Patients with Diabetes

- For all patients with diabetes aged 40-75 with LDL-C ≥70 mg/dL, the new guidelines suggest starting moderate intensity statin without formal estimation of 10-year ASCVD risk by the PCEs.
- Whereas prior guidelines suggested high intensity statins for this population if their 10-year ASCVD risk is ≥7.5%, new guidelines replace this qualifier with those "with multiple risk factors" or in those >50 years of age.

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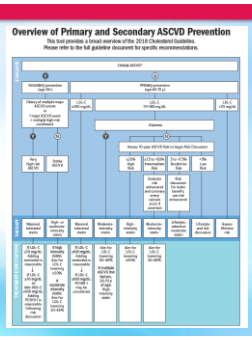

Diabetes and Statin Safety

- Statin use may increase the risk of type 2 diabetes (T2D)
- In 2008, investigators in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial reported a small, but statistically significant, increase in the rate of physician reported type 2 diabetes mellitus among those allocated to rosuvastatin as compared with placebo.

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Diabetes and Statin Safety

- The US Food and Drug Administration responded with a requirement in 2012 that labels state that statins may raise glycated hemoglobin (HbA1C) and fasting glucose levels.
- Despite reassurance that the benefits far outweigh any potential risk of T2D offered by the Statin Diabetes Safety Task Force, there remains an unresolved concern for clinicians

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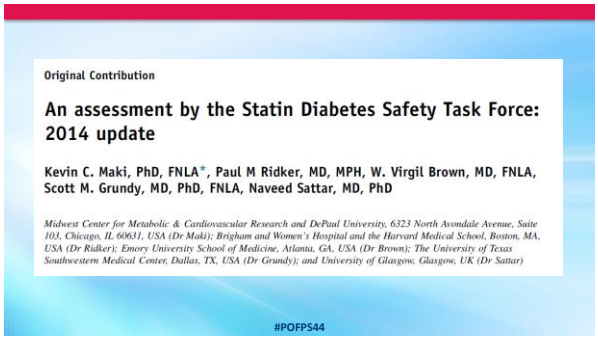
Original Contribution
An assessment by the Statin Diabetes Safety Task Force: 2014 update
Kevin C. Maki, PhD, FNLA*, Paul M Ridker, MD, MPH, W. Virgil Brown, MD, FNLA, Scott M. Grundy, MD, PhD, FNLA, Naveed Sattar, MD, PhD
Midwest Center for Metabolic & Cardiovascular Research and DePaul University, 6323 North Avondale Avenue, Suite 103, Chicago, IL 60631, USA (Dr Maki); Brigham and Women's Hospital and the Harvard Medical School, Boston, MA, USA (Dr Ridker); Emory University School of Medicine, Atlanta, GA, USA (Dr Brown); The University of Texas Southwestern Medical Center, Dallas, TX, USA (Dr Grundy); and University of Glasgow, Glasgow, UK (Dr Sattar)
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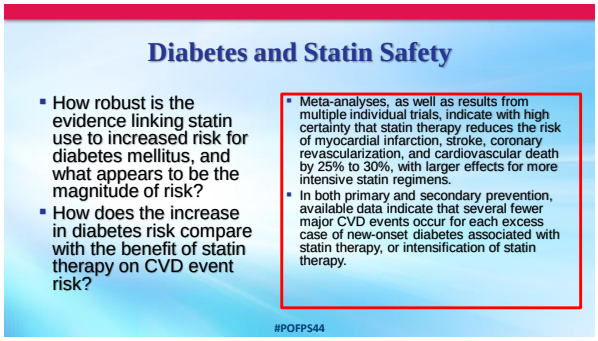
Diabetes and Statin Safety
How robust is the evidence linking statin use to increased risk for diabetes mellitus, and what appears to be the magnitude of risk?
How does the increase in diabetes risk compare with the benefit of statin therapy on CVD event risk?
Meta-analyses, as well as results from multiple individual trials, indicate with high certainty that statin therapy reduces the risk of myocardial infarction, stroke, coronary revascularization, and cardiovascular death by 25% to 30%, with larger effects for more intensive statin regimens.
In both primary and secondary prevention, available data indicate that several fewer major CVD events occur for each excess case of new-onset diabetes associated with statin therapy, or intensification of statin therapy.
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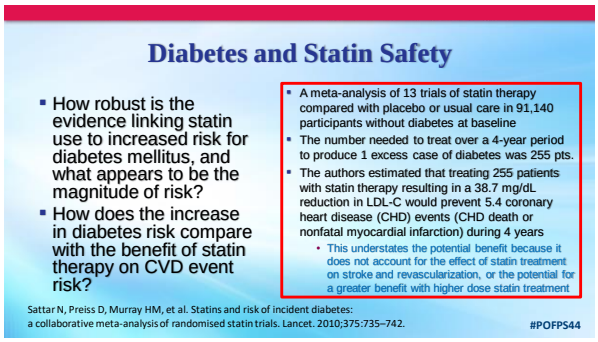
Diabetes and Statin Safety
How robust is the evidence linking statin use to increased risk for diabetes mellitus, and what appears to be the magnitude of risk?
How does the increase in diabetes risk compare with the benefit of statin therapy on CVD event risk?
A meta-analysis of 13 trials of statin therapy compared with placebo or usual care in 91,140 participants without diabetes at baseline
The number needed to treat over a 4-year period to produce 1 excess case of diabetes was 255 pts.
The authors estimated that treating 255 patients with statin therapy resulting in a 38.7 mg/dL reduction in LDL-C would prevent 5.4 coronary heart disease (CHD) events (CHD death or nonfatal myocardial infarction) during 4 years
This understates the potential benefit because it does not account for the effect of statin treatment on stroke and revascularization, or the potential for a greater benefit with higher dose statin treatment
Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375:735–742.
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Diabetes and Statin Safety

- Are there any subsets of patients in whom it would be prudent to consider alternatives to statin treatment because of concerns about increasing risk for new onset diabetes?

- No change is recommended to current practice on the basis of evidence for a modest increase in risk for diabetes associated with statin therapy because the benefits of statin therapy for CVD event reduction in patients at risk for diabetes (and with diabetes) have been amply demonstrated in randomized controlled clinical trials.
- Although diabetes mellitus is associated with a number of adverse outcomes, the changes observed in measures of glucose homeostasis with statin use have been small and are of uncertain clinical importance

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Diabetes and Statin Safety

- **New-onset diabetes mellitus**
- Depends on population; more frequent if diabetes mellitus risk factors are present, such as body mass index ≥30, fasting blood sugar ≥100 mg/dL; metabolic syndrome, or A1c ≥6%.
- Diabetes mellitus risk factors/metabolic syndrome
- High-intensity statin therapy
- RCTs/meta-analyses

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2018 Cholesterol Guideline

Statin Safety and Statin-Associated Side Effects

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Statin Intolerance

- This tool should be used by clinicians to assess, treat and manage patients with possible statin intolerance
- Although muscle symptoms may occur, true statin intolerance is ucnommon

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Statin Intolerance

- Answer questions to evaluate possible intolerance to a patient's current statin prescription.

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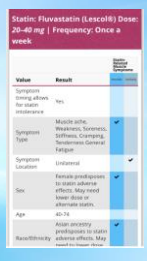
Statin Intolerance

- Answer questions to evaluate possible intolerance to a patient's current statin prescription.



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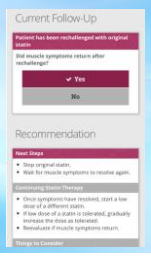
Statin Intolerance

- Follow steps to manage and treat a patient who reports muscle symptoms on a statin.



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Statin Intolerance

- Compare statin characteristics and drug interactions to inform management of LDL-related risk.

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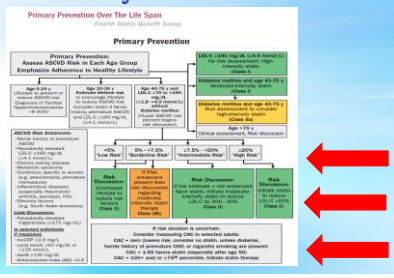
Primary Prevention



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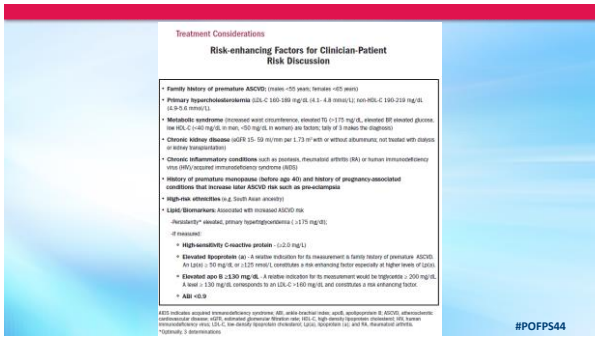

Primary Prevention

Primary Prevention Recommendations for Adults 40 to 75 Years of Age With LDL Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)		
COR	LOE	Recommendations
I	A	In adults at intermediate-risk, statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended.
I	A	In intermediate-risk patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in high-risk patients, levels should be reduced by 50% or more.

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Primary Prevention

Primary Prevention Recommendations for Adults 40 to 75 Years of Age With LDL Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)		
COR	LOE	Recommendations
IIa	B-R	In intermediate-risk adults, risk-enhancing factors favor initiation or intensification of statin therapy.
IIa	B-NR	In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy.

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Primary Prevention

Primary Prevention Recommendations for Adults 40 to 75 Years of Age With LDL Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)		
COR	LOE	Recommendations
IIa	B-NR	In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND • If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking); • If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; • If CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy.

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Primary Prevention

Selected Examples of Candidates for Coronary Artery Calcium Measurement Who Might Benefit from Knowing CAC Score is Zero

Table 8

1. Patients reluctant to initiate statin who wish to understand their risk and potential for benefit more precisely
2. Patients concerned about need to re-institute statin therapy after discontinuation for statin associated symptoms
3. Older patients (men 55 to 80; women 60-80 years old) with low burden of risk factors who question whether they would benefit from statin therapy
4. Middle-aged adults (40-55 years old) with PCE calculated 10-year risk for ASCVD 5 to <7.5% with factors that increase their ASCVD risk, even though they are in a borderline risk group

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Primary Prevention: Non Statin Therapies

Primary Prevention Recommendations for Adults 40 to 75 Years of Age With LDL Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)		
COR	LOE	Recommendations
IIb	B-R	In intermediate-risk adults who would benefit from more aggressive LDL-C lowering and in whom high-intensity statins are advisable but not acceptable or tolerated, it may be reasonable to add a nonstatin drug (ezetimibe or bile acid sequestrant) to a moderate-intensity statin.
IIb	B-R	In patients at borderline risk, in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy.

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Statin Use in the Geriatric Population

- PRIMARY PREVENTION IN THE VERY ELDERLY (>75 YEARS OF AGE).
- For apparently healthy very elderly individuals, only 1 (2014 NICE) of the 5 guidelines continues to provide a strong risk-based recommendation for initiating primary prevention with statins
- Very elderly people pose a troubling dilemma for the cardiovascular community, guideline writers, and clinical practitioners.
- Although they are at high risk of near-term ASCVD by virtue of their age alone, evidence of efficacy for primary prevention with statins is sparse in this age group, as only few have been included in RCTs

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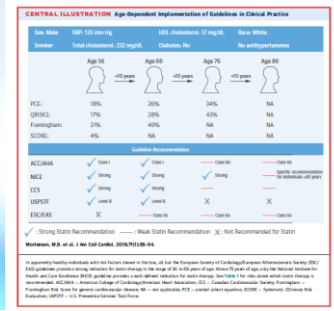

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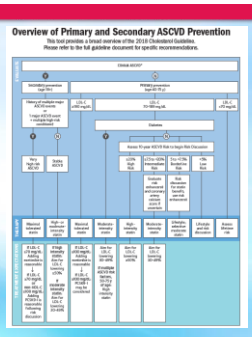

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Degree of LDL Reduction

- Important to the decision of choosing an adjunct agent is understanding the degree of expected LDL-C reduction
- Absolute mg/dL reduction in LDL-C is dependent on baseline LDL-C values and the potency of lipid lowering therapy
- Each reduction in LDL-C by 40 mg/dL is associated with approximately 20-25% relative reduction in ASCVD risk regardless of therapy chosen
- Furthermore, patients with highest absolute baseline risk are known to derive the most benefit.

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Degree of LDL Reduction

- High intensity statins typically reduce LDL-C by roughly 50%
- Ezetimibe reduces LDL-C levels by an additional 20-25%
- FDA approved doses of PCSK9 inhibitors evolocumab and alirocumab reduce LDL-C levels by approximately 60%.

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Checklist for Clinician Patient Shared Decision Making for Initiating Therapy

ASCVD Risk Assessment	• Assign to statin treatment group; use ASCVD risk estimator plus* ◦ In lower risk primary prevention adults 40-75 years with LDL-C ≥70 mg/dL (≥1.8 mmol/L). ◦ Not needed in secondary prevention, LDL-C ≥190 mg/dL (≥4.9 mmol/L) and those 40-75 years with diabetes. • Assess other patient characteristics which influence risk. See Risk Enhancing Factors *(Section 4.4.1.3 and Table 6)* • Assess coronary artery calcium *(section 4.4.1.4)* if risk decision uncertain and additional information is needed to clarify ASCVD risk ◦ Use decision tools to explain risk (ASCVD risk estimator plus- http://tools.acc.org/ASCVD-Risk-Estimator-Plus, Mayo Clinic Statin Choice Decision Aid)

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Checklist for Clinician Patient Shared Decision Making for Initiating Therapy

Lifestyle Modifications	• Review lifestyle habits (diet, physical activity, weight/BMI, tobacco use) • Endorse a healthy lifestyle and provide relevant advice/materials/referrals (CardioSmart, AHA Life's Simple 7, NLA Patient Tear Sheets, PCNA Clinicians' Lifestyle Modification Toolbox, cardiac rehab, dietitian, smoking cessation program)

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Checklist for Clinician Patient Shared Decision Making for Initiating Therapy

Potential Net-Clinical Benefit of Pharmacotherapy	• Recommend statins as first-line therapy • Consider the combination of statin and non-statin therapy in select patients • Discuss potential risk reduction from lipid-lowering therapy • Discuss the potential for adverse effects/drug-drug interactions

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Checklist for Clinician Patient Shared Decision Making for Initiating Therapy

Cost Considerations	• Discuss potential out-of-pocket cost of therapy to the patient (e.g., insurance plan coverage, tier level, copayment)

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Checklist for Clinician Patient Shared Decision Making for Initiating Therapy

Shared Decision Making	• Encourage patient to verbalize what was heard (personal ASCVD risk, available options and their risk/benefit) • Invite the patient to ask questions, express values/preferences, state ability to adhere to lifestyle changes and medications • Refer patients to trustworthy materials to aid in their understanding of issues regarding risk decisions • Collaborate with the patient to determine therapy and follow-up plan

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Omega 3 Supplementation and CVD prevention

- 5 Key points from AHA Science Advisory on omega-3 polyunsaturated fatty acid (PUFA) supplementation and the prevention of cardiovascular disease:
  1. Among patients with coronary heart disease (CHD), treatment with PUFA supplementation to reduce CHD-related mortality (in particular ischemic-mediated sudden cardiac death) is reasonable.
  2. For patients with heart failure with reduced left ventricular function, a large randomized controlled trial (RCT) observed benefit (reduced hospitalization and improved survival) with omega-3 PUFA supplementation.

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Omega 3 Supplementation and CVD prevention

3. For diabetic and prediabetic patients, there is no significant evidence to support omega-3 PUFA supplementation for the prevention of CHD. However, an ongoing RCT will address primary prevention with omega-3 supplementation in diabetic patients.
4. Among patients with a history of stroke, there are no published RCTs to support omega-3 supplementation. There is also no proven benefit for primary prevention of stroke.
5. There is no evidence to support the use of omega-3 PUFA supplementation for primary prevention of atrial fibrillation. Data from multiple RCTs do not support the use of omega-3 supplementation to prevent recurrent atrial fibrillation.

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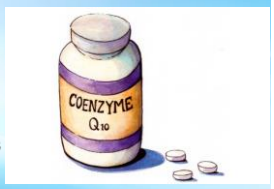
Coenzyme Q 10 supplementation

- How statins produce muscular side effects is not clear, but depletion of the mitochondrial transport element ubiquinone, or coenzyme Q10 (CoQ10) is one hypothesis
- CoQ10 supplementation is used by many patients and recommended by many clinicians despite the absence of definitive results.



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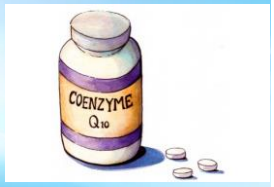
Coenzyme Q 10 supplementation

- The Co-Enzyme Q10 in Statin Myopathy study evaluated the effect of CoQ10 supplementation in subjects whose muscle complaints were confirmed using a lead-in, double-blind, placebo comparison of statin vs placebo.



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Coenzyme Q10 supplementation

- **BACKGROUND:**
Coenzyme Q10 (CoQ10) supplementation is the most popular therapy for statin myalgia among both physicians and patients despite limited and conflicting evidence of its efficacy.
- **OBJECTIVE:**
This study examined the effect of coenzyme Q10 (CoQ10) supplementation on simvastatin-associated muscle pain, muscle strength and aerobic performance in patients with confirmed statin myalgia.
- **METHODS:**
Statin myalgia was confirmed in 120 patients with prior symptoms of statin myalgia using an 8-week randomized, double-blind crossover trial of simvastatin 20 mg/d and placebo. Forty-one subjects developed muscle pain with simvastatin but not with placebo and were randomized to simvastatin 20 mg/d combined with CoQ10 (600 mg/d ubiquinol) or placebo for 8 weeks. Muscle pain (Brief Pain Inventory [BPI]), time to pain onset, arm and leg muscle strength, and maximal oxygen uptake (VO2max) were measured before and after each treatment.


atherosclerosis

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A Randomized Trial of Coenzyme Q10 in Patients with Confirmed Statin Myopathy

Beth A. Taylor, PhD[a,b,c], Lindsay Lorson, BS[b], C. Michael White, PharmD[a,c], and Paul D. Thompson, MD[a,c]
[a]Division of Cardiology, Henry Low Heart Center, Hartford Hospital, Hartford, CT
[b]Department of Health Sciences, University of Hartford, West Hartford, CT
[c]University of Connecticut School of Medicine, Farmington, CT

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Coenzyme Q10 supplementation

- **RESULTS:**

Serum CoQ10 increased from 1.3 ± 0.4 to 5.2 ± 2.3 mcg/mL with simvastatin and CoQ10, but did not increase with simvastatin and placebo (1.3 ± 0.3 to 0.8 ± 0.2) ($p < 0.05$). BPI pain severity and interference scores increased with simvastatin therapy (both $p < 0.01$), irrespective of CoQ10 assignment ($p = 0.53$ and 0.56). There were no changes in muscle strength or VO2max with simvastatin with or without CoQ10 (all $p > 0.10$). Marginally more subjects reported pain with CoQ10 (14 of 20 vs 7 of 18; $p = 0.05$). There was no difference in time to pain onset in the CoQ10 (3.0 ± 2.0 weeks) vs. placebo (2.4 ± 2.1 wks) groups ($p = 0.55$). A similar lack of CoQ10 effect was observed in 24 subjects who were then crossed over to the alternative treatment.

- **CONCLUSIONS:**

Only 36% of patients complaining of statin myalgia develop symptoms during a randomized, double-blind crossover of statin vs placebo. CoQ10 supplementation does not reduce muscle pain in patients with statin myalgia.

atherosclerosis

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[c]University of Connecticut School of Medicine, Farmington, CT

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Top 10 Take Home Messages

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.

A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.

In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician patient relationship and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.

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Top 10 Take Home Messages

2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

Use a maximally tolerated statin to lower LDL-C levels by ≥50%.

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Top 10 Take Home Messages

3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.

- Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L).
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost-effectiveness is low at mid-2018 list prices.

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Top 10 Take Home Messages

4. In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL[≥4.9 mmol/L]) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.

- If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), adding ezetimibe is reasonable
- If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) & the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered

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Top 10 Take Home Messages

5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.

In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.

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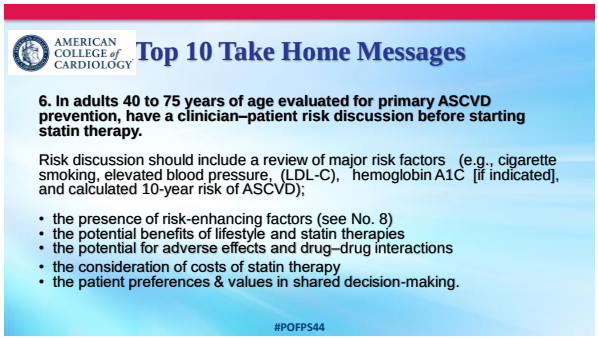
AMERICAN COLLEGE of CARDIOLOGY
Top 10 Take Home Messages
6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.
Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, (LDL-C), hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD);
• the presence of risk-enhancing factors (see No. 8)
• the potential benefits of lifestyle and statin therapies
• the potential for adverse effects and drug–drug interactions
• the consideration of costs of statin therapy
• the patient preferences & values in shared decision-making.
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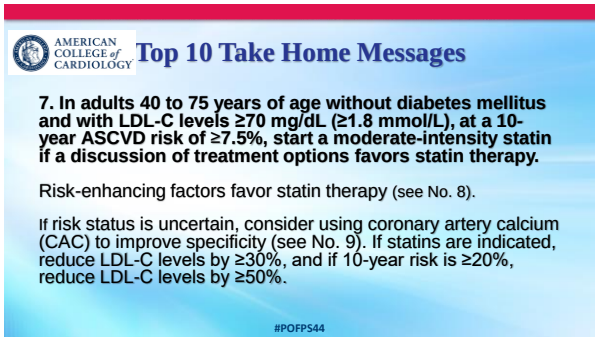
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Top 10 Take Home Messages
7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.
Risk-enhancing factors favor statin therapy (see No. 8).
If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.
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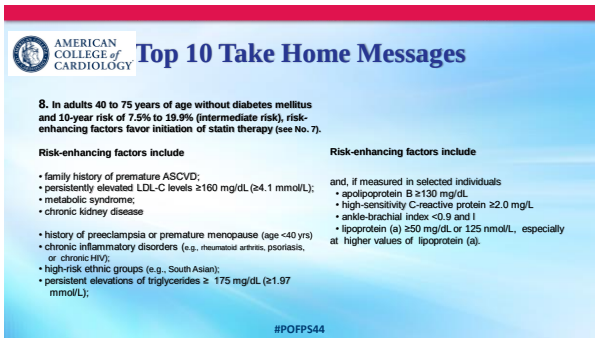
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Top 10 Take Home Messages
8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).
Risk-enhancing factors include
• family history of premature ASCVD;
• persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L);
• metabolic syndrome;
• chronic kidney disease
• history of preeclampsia or premature menopause (age <40 yrs)
• chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV);
• high-risk ethnic groups (e.g., South Asian);
• persistent elevations of triglycerides ≥ 175 mg/dL (≥1.97 mmol/L);
Risk-enhancing factors include
and, if measured in selected individuals
• apolipoprotein B ≥130 mg/dL
• high-sensitivity C-reactive protein ≥2.0 mg/L
• ankle-brachial index <0.9 and I
• lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a).
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Top 10 Take Home Messages

9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL- 189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

- If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age.
- For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.

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Top 10 Take Home Messages

10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

- Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.
- In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).

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Questions and Ideas

Contact Information:

Justin Guthier, DO
Justin_l.guthier@lvhn.org

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