Dyslipidemia: Beyond the Numbers

Chuck Carter, MD, FAAFP

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Dr. Carter is a graduate of the University of South Carolina School of Medicine in Columbia. He completed his residency at Palmetto Health Richland in Columbia and a fellowship at Georgetown University School of Medicine in Washington, DC. He practices in a residency teaching program and primarily cares for underserved patients. He has interests in diabetes, cardiovascular health, headache disorders, and urologic conditions. He feels family physicians are critical partners to help guide patients through complex evaluations and specialty care.
Learning Objectives

1. Provide a cholesterol screening for all patients over the age of 20 at least once every five years, with special attention to those who exhibit cardiovascular disease risk factors.

2. Risk stratify patients using the pooled cohort equation and evaluate for cholesterol therapy based on risk factors.

3. Counsel patients on different types of cholesterol, the impact of dietary and lifestyle choices on overall blood cholesterol and appropriate behavioral modifications that can be made to address cardiovascular disease risk.

4. Prepare treatment plans for those requiring management of dyslipidemia using evidence-based guidelines and shared decision making with patients.

Associated Sessions

• (PBL) Dyslipidemia: Beyond the Numbers
Audience Engagement System

Step 1

Step 2

Step 3

Cholesterol

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Poll Question 1

What is the LDL threshold defining dyslipidemia?

A. >70
B. >100
C. >130
D. >150
E. >180

Fasting Lipids?

• Limited impact on LDL values
• Increasing use of direct measurement
• Need if elevated triglycerides and using calculated LDL
• Fasting may impact other conditions and/or medication use

“Disease” defined by numbers

- LDL-C is dominant type of atherogenic cholesterol
- Dyslipidemia is LDL-C >130 or HDL-C < 40
- “Optimal” LDL-C around 100 b/c associated with low ASCVD rates
- “Treatment” primarily achieves reducing event risk


So what about dietary cholesterol?

- USDA reclassified cholesterol in 2015
- “Not a nutrient of concern for overconsumption”
- Current US dietary guidelines:
  www.health.gov/dietaryguidelines/2015/guidelines
- At time no evidence of a connection between dietary cholesterol and adverse outcomes, but…
- New study (Zhong) – Dietary cholesterol and egg consumption associated with CVD and all cause mortality in dose response manner

Scientific Report of the 2015 Dietary Guidelines Advisory Committee. February 2015, United States Department of Agriculture and Department of Health and Human Services
Why assess cardiovascular risk?

• The major cause of death in the US
  • ≥1 in 3 have some form of CV disease
  • 1 out of every 3 deaths

• A “common pathway” condition
  Adjusted population attributable fractions for ASCVD mortality
  • 40.6% for high blood pressure
  • 13.7% for smoking
  • 13.2% for poor diet
  • 11.9% for insufficient physical activity
  • 8.8% for abnormal glucose levels

Key Questions in Hyperlipidemia Treatment

• Why am I treating?
  – Primary prevention
  – Secondary prevention
  – True lipid disorder (ex. familial)

• Who am I treating? What are our goals?

• What is my treatment threshold and tolerance for over vs. under treatment?

Lipids are part of CV Risk assessment

• Value of lipid assessment predominantly linked to role as CV disease risk factor

• ACC/AHA Pooled Cohort Equation is recommended risk calculator:

http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#/calculate/estimate/
• Pooled cohort equation
• Concerns about over-estimation of risk
• Framingham likely underestimated risk
• Revisions to methods hold promise to address over-estimation

ASCVD Risk is Longitudinal

Risk is not static; Outcomes are

• Evidence of preclinical phase
• US adults with optimal CV risk factors will reach age 75 with only a 3-4% risk
• US adults with 2 or more CV risk factors will reach 75 with >20% risk


Risk

• Benefits of prevention will tend to confer more to those with higher risk
• Important consideration for those on the lower margins of risk

ATP III
ACC/AHA 2013
ACC/AHA 2018
USPSTF

Framingham Equation
Pooled Cohort Equation

http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#/calculate/estimate/
A Quick Note Regarding…

The 2018 ACC/AHA Cholesterol Management Guideline

The AAFP gives an “affirmation of value” to the new guideline but stopped short of a full endorsement.

Why? – Portions didn’t meet the AAFP standards for evidence

Including: 1) non-statin therapy, 2) treatment targets, 3) CAC scoring


Clinical “freedom”
“Breadth of evidence”
Individualization and sub-groups
Topics covered and Nuance

Clear guidance
Overall evidence quality
Focus on hard outcomes
General population focus
2013 ACC/AHA Risk Continuum – ASCVD Risk

- **Low Risk**: <5%
- **“Consider”**: 5% - 7.5%
- **Elevated Risk**: ≥7.5%

2018 ACC/AHA Risk Continuum - ASCVD

- **USPSTF >10%**
- **Low Risk**: <5%
- **Borderline Risk**: 5% - 7.5%
- **Intermediate Risk**: 7.5% - <20%
- **High Risk**: >20%

[https://www.ahajournals.org/doi/10.1161/CIR.0000000000000625](https://www.ahajournals.org/doi/10.1161/CIR.0000000000000625)
<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Recommendation</th>
<th>USPSTF SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults 40-75, no hx of ASCVD</td>
<td>Screen for lipid disorders</td>
<td>B</td>
</tr>
<tr>
<td>Adults 40–75, no symptoms or hx of ASCVD, one or more risk factor, and</td>
<td>Low- to moderate-dose statin for the prevention of CVD events</td>
<td>B</td>
</tr>
<tr>
<td>10-year risk of ≥10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults ages 40–75 years, no symptoms or hx of ASCVD, one or more risk</td>
<td>Statin may be beneficial for primary prevention, likelihood of benefit is</td>
<td>C</td>
</tr>
<tr>
<td>factor, and 10-year risk of 7.5%–10%</td>
<td>smaller</td>
<td></td>
</tr>
<tr>
<td>Adults 76 and older No hx of ASCVD</td>
<td>Insufficient evidence on benefits and harms of statins in this group</td>
<td>I</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Recommendation</th>
<th>USPSTF SOR</th>
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</thead>
<tbody>
<tr>
<td>Children/Adolescents younger than 20</td>
<td>Insufficient evidence on benefits and harms of screening</td>
<td>I</td>
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</table>


So, what are we treating?

- Risk or numbers?
- It’s probably not only about the numbers…
- Ideally, we want to address risk over the life span
Poll Question 2

62-year-old African-American man presents as a new patient. He has DM Type 2, HTN, coronary artery disease and is a non-smoker. Total Cholesterol is 180, Triglycerides are 185, LDL is 113, HDL is 30. BP is 126/78. Meds: metformin ER 1000 mg, ASA 81 mg, atorvastatin 20 mg, lisinopril 20 mg, amlodipine 10 mg.

Which intervention, if any, would most appropriate?

A. Start niacin
B. Start fenofibrate
C. Start ezetimibe
D. Increase atorvastatin to 40 mg
E. None of the above

Who’s Clearly At Risk?

• Proven ASCVD – Secondary Prevention
• LDL-C ≥190
• Persons 40-75 years with diabetes

https://www.ahajournals.org/doi/10.1161/CIR.0000000000000625
Prevention With Statins

• **Primary**
  - Reduce fatal events, non-fatal events and all-cause mortality
  - NNT = 18 over 5 years
  - Limitation: Long-term implications?

• **Secondary**
  - RCTs support statin treatment for patients with ASCVD


Primary Prevention

Diabetes age 40-75

Moderate Intensity Statin

LDL 70-189 – Assess ASCVD Risk

Adjust treatment

Adults 40-75 and LDL-C ≥70-<190

<5%

Low Risk

Risk/Lifestyle

5-<7.5%

Risk enhancers may favor treatment

Risk enhancers and risk favor treatment

>7.5-<20%

High intensity statin

>20%

Poll Question 3

Which one of the following tests would you consider ordering for a 40-year-old man who has a family history of premature ASCVD and otherwise normal risk factors?

A. Ankle-brachial index  
B. Lp(a)  
C. Treadmill stress test  
D. Apoliprotein B  
E. Genetic testing for familial hyperlipidemia

“Risk Enhancers”

- Family history of premature ASCVD
- LDL-C ≥160
- CKD
- Metabolic syndrome
- Preeclampsia, premature menopause
- Chronic inflammatory disease: Rheumatoid, Psoriasis, HIV, etc.
- High risk ethnicity (ex: South Asian)
- Persistently elevated triglycerides (≥175)
- In selected persons:
  - hs-CRP >2.0
  - Lp (a) >50 mg/dL or >125 nmol/L
  - apo B >130 mg/dL
  - ABI < 0.9

https://www.ahajournals.org/doi/10.1161/CIR.0000000000000625
What about uncertainty

• Regarding the risk or how to help your patient
  – New guidelines endorse Coronary Artery Calcium scoring as the preferred method to further evaluate persons in the Intermediate Risk Zone (ACC/AHA IIa/B-NR – translation AAFP SORT B)
  – Why?
    • Correlates with risk
    • A negative score lowers risk – generally to the low risk zone
      – Exceptions: Diabetes, Smoking, FH of premature CHD

https://www.ahajournals.org/ doi/10.1161/CIR.000000000000625

So, what about young people?

• NHANES Data
• Low prevalence of elevated CV risk in younger people in absence of HTN or smoking
  – Men under 40 = 0.09%
  – Women under 50 = 0.04%
  – 2.9% with LDL ≥190

Atherosclerosis occurs over decades

Risks and processes begin in youth and young adulthood

Pooled cohort equation can estimate lifetime risk for adults 20-39

Identify opportunities for intervention
  - Lifestyle & risk factor mitigation
  - Identify lipid disorder patterns
    - High LDL
    - FH of premature ASCVD
    - Familial hypercholesterolemia
  - No RCTs of this approach
What about older adults?

- Mixed signals – evidence quality is lower
- PROSPER (2002)
  - RCT of men and women 70-82 with or at increased risk for CV disease
  - Pravastatin (40 mg) vs placebo for 3 years
  - CHD mortality and non-fatal MI reduced (RR 19%); CHD mortality reduced (RR 24%)
  - Stroke unchanged
- ALLHAT-LLT (2017)
  - RCT starting a statin in patients over age 65 years for primary prevention
  - Pravastatin 40 mg/day or usual care in patients at increased risk
  - Open-label study, so some crossover to statin (32% aged 65 to 74, 15.2% aged 75 years or older)
  - No difference in all-cause mortality or cardiac events
- Risk reductions are more favorable for patients needing secondary prevention (surprise?!)
- Life expectancy considerations


Familial Hypercholesterolemia

- Assess family history
- Think about this if LDL ≥190 (or 160 if <20 yo)
- Xanthomas, xanthelasma or arcus in pts <45 yo
- Total cholesterol
  - >250 in >30 yo
  - >220 in 20-29 yo
  - >190 in <20 yo
- Treatments
  - Mipomersen, lomitapide
  - For homozygous familial disease
  - $$$$$$$, certified pharmacy, physicians, and REMs

Safeer R. J Fam Pract. 2015; 64(8): 464-469; Prescriber's Letter; April 2013; Vol: 29
Why so much emphasis on statins?

- Substantial data supporting statin use
- Lack of RCT data supporting other lipid medications
  - Niacin
  - Fibrates
  - Ezetimibe (except after MI – secondary prevention)
  - Omega – 3
  - Cholesteryl ester transfer protein (CETP) inhibitors

Keene D, et al. BMJ 2014; 349: g4379
Cannon CP et al. NEJM 2015; 372(25): 2387-97

- Meta-analysis of RCTs
  - 22 trials (134,537 patients)
  - Statins vs. control
  - Less intense vs. more intense (39,612 patients)
    - 73% men, 23% women
  - Similar LDL reduction effect for men and women
  - Reduction in events similar for men and women
  - Improved major vascular events regardless of baseline risk (with vs. without known ASCVD)
  - Another meta-analysis found greater lowering produced greater risk reduction except when baseline LDL was under 100 already.

Impact of LDL reduction with statins

• For every 38.6 mg/dL (1mmol/L) reduced:
  – Major vascular events by 0.7% (RRR≈20% )
  – Coronary events by 0.4% (RRR 25% )
  – Revascularizations by 0.5% (RRR 25%)
  – Stroke by 0.1% (RRR just under 20%)
  – All cause mortality by 0.2% (RRR 9%)


• So, for a patient with an LDL of 138…
• Reducing LDL to 100 (28% LDL reduction) should have a substantial relative impact on cardiovascular risk
• Another 1mmol/L reduction would be LDL of 62 (56% LDL reduction)
<table>
<thead>
<tr>
<th>Low-intensity statins</th>
<th>Moderate-intensity statins</th>
<th>High-intensity statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower LDL by &lt;30%</td>
<td>Lower LDL by 30-49%</td>
<td>Lower LDL by ≥ 50%</td>
</tr>
<tr>
<td>Fluvastatin 20-40 mg</td>
<td>Atorvastatin 10 – 20 mg</td>
<td>Atorvastatin 40-80 mg</td>
</tr>
<tr>
<td>Lovastatin 20 mg</td>
<td>Fluvastatin 40 mg (BID)</td>
<td>Rosuvastatin 20-40 mg</td>
</tr>
<tr>
<td>Pravastatin 10-20 mg</td>
<td>Lovastatin 40 mg</td>
<td></td>
</tr>
<tr>
<td>Simvastatin 10 mg</td>
<td>Pitavastatin 1-4 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin 5-10 mg</td>
<td></td>
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<tr>
<td></td>
<td>Simvastatin 20-40 mg</td>
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Poll Question 4

Which one of the following is a harm of statin treatment?

A. Cancer  
B. Dementia  
C. Ischemic stroke  
D. Autoimmune hepatitis  
E. Diabetes
Statin Harms

- Hepatic
- Cancer
- Diabetes
- Kidney disease
- Myopathy
- Myalgias
- Autoimmune myopathy
- Dementia/cognitive function

Meta-analysis of RCTs – statin vs. placebo
Mean follow-up of 4 years
Discontinuation rates
- 13.6% for statins
- 13.3% for placebo
No significant difference in myopathy rates
- OR 1.2% (p=0.25)
Does this correlate to practice (ex: dosing)

Riaz H. et al. Am J Cardiol 2017; 120:774-781
Numbers Needed to Harm

- Take 10,000 people and treat them with atorvastatin (40 mg) for 5 years
  - 50-100 cases of muscle pain
  - 5 cases of myopathy
  - 5-10 hemorrhagic strokes
  - 50-100 new cases of diabetes


Take the same 10,000

- 1000 fewer major vascular events for secondary prevention patients
- 500 fewer events in primary prevention patients

What about statin side effects?

- New guidelines emphasize re-framing away from statin intolerance to statin-associated side effects
- RCT evidence vs. other evidence and reports
  - RCTs = 1% or less
  - Observational studies – 5-20%
- Most patients can tolerate statin on retrial using same or different statin
- Helps avoid limiting best treatment options
- Consider different statin
- Consider alternative dosing strategies
- Consider other factors – ex. hydration
- CoQ10 – Recommendation against – evidence lacking


Caution when addressing perceived harm

- New guidelines emphasize good MSK assessment prior to starting treatment
- Balance of RCT evidence supports primary and secondary prevention
- Cessation carries potential risk
- Shift toward less effective and/or much more expensive interventions
• Analysis of 105,329 MCR patients started on moderate or high intensity statin after MI (Serban)
  – Comparing patients with “high adherence” (n=55,567) to those with “statin intolerance” (n=1741)
  – Higher adherence patients had fewer recurrent MIs (36%) and CHD events (43%). But, no significant difference in all-cause mortality
• Retrospective cohort of 22,266 Chinese primary care practice patients comparing stopping vs. continuing statins after an adverse event (Zhang)
  – Continuing associated with lower incidence CV events and death
  – 1.7% absolute risk difference
• Raises concerns about stopping statins
• Is it clinically significant?
• Overall risk is small so can stop to assess side effects


Non-statin treatments

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption inhibitors</td>
<td>Ezetimibe</td>
</tr>
<tr>
<td>PCSK9 Inhibitors</td>
<td>Alirocumab, evolocumab</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Cholestyramine, colesevelam, colestipol</td>
</tr>
<tr>
<td>Niacin</td>
<td>Niacin</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Fenofibrate, gemfibrozil</td>
</tr>
<tr>
<td>Omega 3 fatty acids</td>
<td>Icosapent ethyl, omega 3 ethyl esters</td>
</tr>
</tbody>
</table>

• Niacin
  – Best data is from the pre-statin era
  – No additional benefit on CV outcomes from adding
• Fibrates
  – No additional benefit on CV outcomes
• Omega 3 Supplements
  – No association with fatal or non-fatal CHD or any major vascular event


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**PCSK9 Inhibitors**

• New class of agents
  • Proprotein convertase subtilisin/kexin type 9 inhibitors
  • Injectable monoclonal antibodies
  • Evolocumab (Repatha) and alirocumab (Praluent) presently. Others in development
• Substantial LDL lowering
  – 50-60% by themselves
  – Testing in addition to statins – additional 39%
• Outcome data actively coming in
• Annual cost $10,000 – $14,000 (!)

PL Detail-Document, PCSK9 Inhibitors for High Cholesterol. August 2015
• Evolocumab in addition to statin (FOURIER Trial)
  – NNT = 74 to prevent one CV event in a higher risk patient
  – Composite end points were primary and secondary outcomes
  – No impact on CV mortality

• Systematic reviews of available RCT data
  – Decrease the risk of CVD events, MI, stroke vs. placebo
  – Little to no effect on mortality
  – Mostly high risk patients studied. How does this apply to primary prevention?
  – Modest changes in absolute risk (less than 1%)


• Lack of long term efficacy and safety trials
• Safety appears acceptable in available trials
• Short term trials show additional benefit but small in absolute impact
• Long term cost implications
• Long term efficacy – is there a ceiling effect or durability effect?
  – So far, so good
  – Anti-drug antibodies (bococizumab)?

Nissen
Are they cost effective?

• Balancing additional benefit with a long term treatment
• Estimates of cost
  – $10,000 - $14,000/year
• Cost effectiveness analysis of trials of evolocumab (FOURIER)
• Cost would need to be reduced 71% (to $4536) to reach the $100,000/QALY gained threshold)

Kazi DS, et al. JAMA 2016; 316(7): 743-753

• Already trials testing this treatment for patients with “statin intolerance”
• Concerns about who should get this treatment?
  – Consider defining high risk relative to a >$10K drug
  – Predictions of scenarios that will drive use
    • Statin intolerance
    • LDL targets return
    • “Statin failure” – i.e. events in those on statins
    • Non-adherence to statin treatment
• There will be those for whom this is the right answer, but probably a limited group
• New guidelines use in very high risk ASCVD patients
• Note low cost effectiveness

Ezetimibe

- ezetimibe (Zetia) – cholesterol absorption inhibitor
- LDL lowering = 18% solo / 25% further w/ statin
- Limited impact for primary prevention (? CKD)
- Some potential as add-on for secondary prevention in high risk patients
  - Add-on to statin after acute coronary syndrome
  - Prevents CV events (NNT 50 for seven years)
- Renewed emphasis in 2018 Guidelines


What about raising HDL?

- Based on findings that low HDL is a risk factor
- Theory: Raising HDL = Reducing events
- Reality: Doesn’t match up to theory
- Treatment options to raise HDL
  - Niacin
  - Fibrates
  - CETP inhibitors

Keene D, et al.  BMJ 2014; 349: g4379
**RCTs of HDL drugs?**

- Present treatment approaches don’t appear to work
- No significant impact on
  - All-cause mortality
  - CHD mortality
  - Stroke mortality
- Niacin may have role for those not on statins
- New meds would need to reduce rates 75%-95%

*Keene D, et al. BMJ 2014; 349: g4379*

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**Triglycerides**

- Unclear relationship to risk
- May be related to other conditions or marker of metabolic syndrome
- Treat if 500 -1000 or greater, but mainly addressing pancreatitis risk
- Persistent elevation may be cause to assess Apolipoprotein B
Practice Recommendations

• Treat hyperlipidemia in context of overall CV Risk and Prevention goals
• Screen for abnormal lipids and assess using the pooled cohort equation
  – Statin dosing for primary prevention according to risk
  – Consider adjunctive testing in select groups
  – Consider lifetime risk
  – Apply guidelines in the context of your patient
• Troubleshoot real and perceived statin side effects with patients
• Apply understanding of risk to avoid over and under treatment

Contact Information

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Questions