Controversy in contemporary guidelines
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Recent Lipid Guidelines

2013 AHA/ACC Guideline on the Treatment of Blood Cholesterol
ESC/EAS Guideline for the Management of Dyslipidaemias, 2011
2012 Update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia

AACE/ACE Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan—How is Dyslipidemia Managed in Patients With Diabetes? 2015
ADA Standard of Medical Care in Diabetes—2016—Cardiovascular Disease and Risk Management

What’s Common in These Guidelines?

Recommend concomitant healthy lifestyle habits
Secondary prevention
Consider FH high risk
Primary prevention in T2DM
Recommend appropriate statin dosing as the initial drug choice
Require baseline assessment of ASCVD risk For a minimum 10-year period
What’s Different in the Guidelines?

Method of risk assessment for primary prevention
  - Different calculators
  - 10-year vs lifetime risk

Use of LDL-C and/or non-HDL-C as targets of therapy

Recommendations on appropriateness of nonstatin drugs for some cases

Identifying high-risk patients (e.g., CKD, special populations)

NCEP/Framingham risk scores: Estimate of 10-yr CHD risk in men without CHD

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Points</th>
<th>Total-C (mg/dL)</th>
<th>Points</th>
<th>HDL-C (mg/dL)</th>
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<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Points</th>
<th>Systolic BP (mm Hg)</th>
<th>Points</th>
<th>Untreated</th>
<th>Treated</th>
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<tr>
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<td>1</td>
<td>1</td>
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<tr>
<td>60–69</td>
<td>1</td>
<td>130–139</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>70–74</td>
<td>1</td>
<td>140–159</td>
<td>1</td>
<td>2</td>
<td>2</td>
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<tr>
<td>75–79</td>
<td>1</td>
<td>≥160</td>
<td>2</td>
<td>3</td>
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</tr>
</tbody>
</table>

Point total: <0 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 16 16 >17
10-yr risk (%) <1 1 1 1 1 1 2 2 3 4 5 6 8 10 12 16 20 25 25 ≥30

### Framingham Risk Score (FRS)

- **Low risk**: < 10% 10-year risk
- **Intermediate risk**: 10 – 20% 10-year risk
- **High risk**: > 20% 10-year risk

### LDL-C Goals (ATP-III)

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Goal LDL (mg/dl)</th>
<th>Risk category</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD &amp; CAD risk equivalent</td>
<td>&lt; 100</td>
<td>high risk</td>
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<tr>
<td></td>
<td>&lt; 70 optional</td>
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<tr>
<td>2 or more major risk factors + 10 yr risk &gt;20%</td>
<td>&lt; 100</td>
<td>high risk</td>
</tr>
<tr>
<td></td>
<td>&lt; 70 optional</td>
<td></td>
</tr>
<tr>
<td>2 or more major risk factors + 10 yr risk 10-20%</td>
<td>&lt; 130</td>
<td>moderately high risk</td>
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<tr>
<td></td>
<td>&lt; 100 optional</td>
<td></td>
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<tr>
<td>2 or more major risk factors + 10 yr risk &lt;10%</td>
<td>&lt; 130</td>
<td>moderate risk</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 major risk factor</td>
<td>&lt; 160</td>
<td>low risk</td>
</tr>
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</table>
Keep it Simple: Start the Statin or Not?

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

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

Identified 4 statin benefit groups — Focus efforts to reduce ASCVD events
Four Major Statin Benefit Groups

Focus on ASCVD risk reduction

Classified into 4 statin benefit groups:

1. Individuals with clinical ASCVD
2. Individuals with primary elevation of LDL-C ≥ 190 mg/dl
3. Individuals 40-75 years of age with diabetes with LDL-C 70-189 mg/dl
4. Individuals without clinical ASCVD or diabetes who are 40-75 years of age with LDL-C 70-189 mg/dl and an estimated 10 year ASCVD risk of 7.5% or higher.

ACC/AHA Guidelines
4 Statin Benefit Groups

Secondary Prevention

- Individuals with clinical ASCVD (acute coronary syndromes, a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, peripheral arterial disease presumed to be of atherosclerotic origin) without NYHA class II-IV heart failure, or receiving hemodialysis

Primary prevention

- Individuals with primary elevations of LDL-C ≥ 190 mg/dL
- Individuals 40-75 years of age with diabetes and LDL-C 70-189 mg/dL without clinical ASCVD
- Individuals without clinical ASCVD or diabetes who are 40-75 years of age with LDL-C 70-189 mg/dL and an estimated 10 year ASCVD risk ≥ 7.5%

The guideline identifies high- and moderate-intensity statin therapy for use in primary and secondary prevention.
The ACC/AHA guidelines were last updated in 2013, with several notable differences when compared to their prior iteration and to the 2011 ESC/ EAS guidelines. These guidelines focus on a fixed-dose approach to cholesterol-lowering treatment, in which statin therapy is no longer titrated to achieve LDL goals.

One potential major advantage to this strategy is the avoidance of statin underdosing and undertreatment of LDL-C, which may be more likely to occur when clinicians are encouraged to reduce statin dosing if and when a target LDL-C is reached.
The ACC/AHA guidelines also now recommend less frequent routine LDL-C monitoring, however, which may create more difficulty in identifying adherence success, and leaves a greater degree of uncertainty regarding if and when to add non-statin therapies to improve LDL-C reduction.

This update also introduced a new Pooled Cohort Equation, which incorporates age, sex, smoking, blood pressure, total cholesterol, renal function, and the presence or absence of diabetes, left ventricular hypertrophy, and prior MI or stroke, in calculating an estimated risk of developing atherosclerotic cardiovascular disease (ASCVD) at 10 years.
This risk estimator provides a lower threshold for initiating therapy for primary prevention when compared to the prior guidelines. The 7.5% 10-year threshold for therapy, which carries a recommendation for a fixed-dose moderate-intensity statin in patients aged 40–75 years with LDL-C of 70–189 mg/dL, corresponds to a European SCORE of 2.5%, at which drug therapy can be considered at LDL-C >100 mg/dL, but is not strictly recommend.
**Non-statin therapies**

- For hyperlipidemia, *non statin therapies, alone or in combination with statins*, do not provide acceptable risk reduction benefits compared to adverse effects.
- These include:
  - Ezetimibe
  - Fibrates
  - Fish oil
  - Niacin
- For the most part, *these should be avoided* with few exceptions
What has changed compared to ATP-III guideline?

- Initiate either moderate-intensity or high-intensity statin therapy for patients who fall into the four categories.
- Unlike ATP-III, Do not titrate to a specific LDL cholesterol target.
- Measure lipids during follow-up to assess adherence to treatment, not to achieve a specific LDL target.

Evidence to support controversy in 2013 ACC/AHA Guideline

- Support
**2017 ADA**

*In addition to lifestyle therapy*

**ASCVD risk factors include LDL-C ≥100 mg/dL, high BP, smoking, CKD, albuminuria, and family history of premature ASCVD.**

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk factors</th>
<th>Recommended statin intensity*</th>
</tr>
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<tbody>
<tr>
<td>&lt;40 years</td>
<td>None, ASCVD risk factor(s)**ASCVD</td>
<td>None, High</td>
</tr>
<tr>
<td>40–75 years</td>
<td>None, ASCVD risk factors ASCVD ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L)</td>
<td>Moderate, High</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>None, ASCVD risk factors ASCVD ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L)</td>
<td>Moderate or high, ezetimibe</td>
</tr>
</tbody>
</table>

**HOPE-3:**

2 by 2 Factorial Design

14,682 Entered Single-blind 4 week Active Run-in
12,705 (87%) Randomized

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>n</th>
<th>Drug Combination</th>
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<tbody>
<tr>
<td>Candesartan 16 mg + HCTZ 12.5 mg</td>
<td>6,356</td>
<td>Placebo</td>
<td>6,349</td>
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<tr>
<td>Rosuvastatin 10 mg</td>
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<td>Rosuvastatin Cand+HCTZ</td>
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<tr>
<td>Placebo</td>
<td>6,344</td>
<td>Cand+HCTZ</td>
<td>3,176</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Double Placebo</td>
<td>3,168</td>
</tr>
</tbody>
</table>

Simple follow-up and few blood tests

2016
Does HOPE-3 give hope?

Statins reduce the risk of cardiovascular disease in intermediate risk patients

- This finding was independent of the cholesterol levels when patient started the trial.

You “set it and forget it”

- Importantly, the results show the benefits of using statins based on risk factors for disease, rather than the traditional approach of looking at lipid levels to guide decisions.

What's changed? Yet another new ESC lipid guidelines

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)
Total Cardiovascular Risk Estimation

Systemic Coronary Risk Estimation (SCORE) System

CV risk in the context of these guidelines means the likelihood of a person developing a fatal or non-fatal atherosclerotic CV event over a defined period of time.

2016 ESC/EAS Guidelines for the Management of Dyslipidemias

SCORE not used for Diabetic patients, Patient with documented CVD or CKD patients.

They already Very high risk or High risk.
Very high-risk
Subjects with any of the following:
- Documented cardiovascular disease (CVD), clinical or unequivocal on imaging.
- Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularisation procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD).
- Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound.
- DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia.
- Severe CKD (GFR <30 mL/min/1.73 m²).
- A calculated SCORE ≥10% for 10-year risk of fatal CVD.

High-risk
Subjects with:
- Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg.
- Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk).
- Moderate CKD (GFR 30–59 mL/min/1.73 m²).
- A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.

Moderate-risk
SCORE is ≥1% and <5% for 10-year risk of fatal CVD.

Low-risk
SCORE <1% for 10-year risk of fatal CVD.

4 Risk categories
Figure 1: Comparison of the American Heart Association/American College of Cardiology (ACC/AHA, left) and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS, right) Guidelines for the Management of Dyslipidemia.
Overall, the ACC/AHA guidelines recommend treating an increased number of individuals for primary prevention and recommend treating all patients with higher statin doses, while the ESC/EAS guidelines take a less conservative approach to primary prevention, and recommend generally lower statin doses, titrated to LDL-C levels. The ACC/AHA risk calculator has not been prospectively evaluated and appears to overestimate cardiovascular risk, particularly in some ethnic populations.
ESC comes out in favor of LDL targets

This raises the question: How will we reach these goals?

- If we do not reach our goals with diet alone, we are recommending the prescription of a statin as the first step.

- In the few cases where there is true statin intolerance, then the second step would be to use either ezetimibe or a bile acid sequestrant.

- If, with a statin at the highest tolerable dose, we do not reach the goal, then we have to think of combinations. Nowadays, we know that by combining ezetimibe and a statin, we can achieve a better result in terms of cardiovascular disease prevention.

- In patients at very high risk, with persistent high LDL-C levels despite treatment with the maximal tolerated statin dose, even in combination with ezetimibe, or in patients who really are completely statin intolerant, then this new family of drugs, the PCSK9 inhibitors, may be considered.

Statins inhibit cholesterol synthesis in the liver, ezetimibe blocks cholesterol absorption in the intestine, and PCSK9 inhibitors block the PCSK9-mediated degradation of LDL receptors.

Statins, ezetimibe, and PCSK9 inhibitors all increase the expression of LDL receptors and reduce LDL-cholesterol levels (by percentages shown).
LDL-C

The debate goes on

The Lower is The Better

Ezetimibe and PCSK9 inhibition join the mainstream of lipid-lowering therapy
IMPROVE-IT

IMPfoved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome

Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

- Standard Medical & Interventional Therapy
- Simvastatin 40 mg
- Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (at least 5250 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

*3.2mm
**2.0mm
Conclusions

IMPROVE-IT: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:

- **YES:** *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events
- **YES:** Even Lower is Even Better
  (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
- **YES:** Confirms ezetimibe safety profile

- Reaffirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events
- Results could be considered for future guidelines

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PCSX9 Inhibition: A Revolution in Cholesterol Therapy

This activity is supported by an educational grant from Merck US and Sanofi Pharmaceuticals.
Lowering LDL cholesterol: Statins vs PCSK9 Inhibitors

Statins

20%-45%

PCSK9

Up to 60%


Most Common Reasons for STOPPING STATIN USE

62%

Percent of former users

Side Effects 17%
Cost 12%
Efficacy 8%
Other 6%
Don't know/Can't remember

Reasons for stopping statin use among former statin users
**Novel Agents**

In addition to PSCK9 inhibitors, there are several other novel therapies for LDL reduction currently being investigated. One pharmacological therapy targets cholesterylester transfer protein (CETP), which normally works to facilitate the transfer of cholesteryl esters and triglycerides from HDL to lipoproteins. CETP inhibition has been shown to lead to increases in HDL and decreases in LDL-C and lipoprotein(a) levels. Early studies of CETP inhibitors have failed to show any clinical benefit, while one study of the CETP inhibitor anacetrapib is currently ongoing.
Conclusion

Cardiovascular disease continues to be the number one cause of morbidity and mortality in the United States and worldwide, with treatment of dyslipidemia being the most effective modifiable target for improving cardiovascular outcomes.

Statins are the cornerstone of LDL-C-lowering therapy, while PCSK-9 inhibitors are now available for addition to maximally-tolerated statin therapy in the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.
The most recent update to the ACC/AHA guidelines recommends treating a greater number of patients for primary prevention and aiming to achieve percentage-based LDL reduction rather than specific LDL levels.

For now, these new guidelines serve as a framework within which patients can be evaluated, while individual treatment decisions should always involve an individualized patient-centered approach, with consideration of individual risks, benefits, and values in choosing the most appropriate treatment strategy.
Questions!

Thank You!