WHOSE GUIDELINE IS IT ANYWAY?

A PRACTICAL APPROACH TO THE TREATMENT OF DYSLIPIDEMIA FOR THE PREVENTION OF CARDIOVASCULAR DISEASE

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DISCLOSURES

• None
OUTLINE

- The Players
  - Statins
  - PCSK9
  - BAS
  - Ezetimibe
  - Fibrates
  - Niacin
  - Omega-3 FAs
  - Lifestyle

- ACC/AHA
- ADA
- USPSTF
- AACE
- NLA
- Putting it all together

Logos of various organizations are shown, including:
- American College of Cardiology
- American Heart Association
- American Diabetes Association
- American Association of Clinical Endocrinologists
- U.S. Preventive Services Task Force
- National Lipid Association
SCREENING/MONITORING

• Fasting lipid profile  
  No disagreement

• Initial Screen – age 20-21 or at diagnosis of DM or MACE  
  If earlier

• When to repeat if not on therapy:
  – ACC: every 4-6 years only after age 40
  – AACE: every 5 years after age 20, 1-2 years for men >45, women >55, yearly after 65
  – NLA: every 5 years after age 21

• How often to repeat if on therapy:
  – 4-12 weeks after changes made or therapy started
  – 3-12 months when stable  
  Most err on the side of 12 months

My view: depends on the patient
THE PLAYERS - LIFESTYLE

• All guidelines essentially agree the following are beneficial for ASCVD reduction…
  
  – **Heart healthy diet:**
    • ↓ saturated/trans fat and cholesterol
    • ↑ omega-3s, viscous fiber, and plant stanols/sterols
  
  – **Regular exercise** habits (≥150 min/week)
  
  – **Avoidance of tobacco** products
  
  – Maintenance of a **healthy weight**
  
  – **Stress reduction** (mindfulness, meditation, etc.)
THE PLAYERS - STATINS

• AKA 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors
• **Primary lipid lowering agents** to reduce ASCVD events in **all guidelines**
• ↓ LDL 21-55% by competitively inhibiting rate-limiting step of cholesterol synthesis in the liver, leading to **upregulation of hepatic LDL receptors**
• **Multiple RCTs** showing **consistent reduction in ASCVD** events across the spectrum of baseline LDL levels >70 mg/dL for both primary and secondary prevention except for…
  – NYHA class II-IV heart failure
  – Maintenance hemodialysis
• **Cholesterol Treatment Trialists Meta-analysis** (2005): 12% reduction in all-cause mortality, 19% reduction in vascular mortality, 21% reduction in MACE for every 39 mg/dl ↓ in LDL
## The Players - Statins

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL-C on average, by &lt;30%</td>
</tr>
</tbody>
</table>

**Atorvastatin (40†) – 80 mg**
**Rosuvastatin 20 (40) mg**

80mg may be harmful

**Atorvastatin 10 (20) mg**
**Rosuvastatin (5) 10 mg**
**Simvastatin 20–40 mg†**
**Pravastatin 40 (80) mg**
**Lovastatin 40 mg**
**Fluvastatin XL 80 mg**
**Fluvastatin 40 mg bid**
**Pitavastatin 2–4 mg**

**Simvastatin 10 mg**
**Pravastatin 10–20 mg**
**Lovastatin 20 mg**
**Fluvastatin 20–40 mg**
**Pitavastatin 1 mg**

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**Justification for this classification?**
The reduction in ASCVD risk from statins is related to the degree by which LDL is lowered
THE PLAYERS – STATIN SIDE EFFECTS

• **Liver Dysfunction** (Cohen et al. *AM J Cardiology*. 2006)
  - AST/ALT >3x ULN = 1.4%
  - Significant liver damage extremely uncommon
  - No role for monitoring LFTs
  - Not contraindicated in CLD, compensated cirrhosis, NAFLD/NASH
  - **No evidence to alter or D/C statin for asymptomatic elevations in AST/ALT**

• **Cognitive Dysfunction**: Prosper Trial and Heart Protection Study over 25,000 pts avg. 3.5 year f/u

• **Diabetes** (ADA, 2017)
  - Meta-analysis of 13 statin trials (n=91,140): OR1.09 for a new diagnosis of diabetes
  - Treatment of 255 patients with statins for 4 years resulted in one additional case of diabetes…
  - **Simultaneously preventing 5.4 vascular events!**

Hepatologists weigh in

- Many studies show no difference
- 1 per million pt years liver failure, no death
- Doesn’t prevent severe idiosyncratic reaction
- Only decompensated or acute liver failure
- The benefits outweigh the risks

**no difference**
THE PLAYERS – STATIN SIDE EFFECTS

- **Myalgias and myopathy**
  - 2006 (Kashani et al. *Circulation*): 35 trials, 74,102 patients, 15.4% myalgias
  - 2014 (Ganga et al. *Am Heart J*): 42 trials, 59,237 patients, 12.7% myalgias
  - 2016 (Collins et al. *Lancet*): serious myopathy 0.5-1%, nearly all myalgias not statin related

  - 10,180 patients randomly assigned to atorvastatin 10mg or placebo for 3 years
  - All offered atorvastatin open label for 2 years afterward

3 Meta-analyses!

Bottom Line: Remind patients (and yourself) to be more careful about attributing muscle pain to statins

Don’t be a member of the Statin Intolerance Death Cult!
TRUE STATIN INTOLERANCE

• **Definition** (ACC/AHA):
  - Unacceptable muscle-related Sx that...
  - Resolve with D/C and occur with re-challenge...
  - On at least 2 to 3 statins...
  - One of which is at the lowest dose
  - With different metabolic pathways and different lipophilicity, and...

• Rule out other causes

• Evaluated drug–drug interactions

• There's an app for that

• **CYP450**: atorvastatin, simvastatin, lovastatin (3A4), and fluvastatin (2C9)

• **Not CYP**: pravastatin and rosuvastatin

• **Lipophilic**: atorvastatin, simvastatin, and lovastatin

• **Hydrophilic**: pravastatin, rosuvastatin, and fluvastatin

Hypothyroidism, Vitamin D Def, Rheum Disorders, etc.

The ACC Statin Intolerance App (www.acc.org/StatinIntoleranceApp)
THE PLAYERS – PCSK9 INHIBITORS

- **Proprotein convertase subtilisin/kexin type 9**: tags LDL-R for lysosomal destruction
- PCSK9 inhibitors (*alirocumab* and *evolocumab*): monoclonal antibodies
- ↓LDL 48-71%, ↓LDL 39% and 61% in Homozygous and Heterozygous Familial Hyperlipidemia
- Approved for use in combination with maximally tolerated statin therapy in patients with...
  - ASCVD
  - HeFH
  - HoFH (evolocumab only)

Who require *additional* LDL lowering
THE PLAYERS – PCSK9 INHIBITORS

ODYSSEY (ALIROCUMAB)
- 2341 patients with LDL >70
- 68.9% with CHD (41% w/risk equivalent)
- All on maximum tolerated statin
- Mean LDL: 122mg/dl to 48mg/dL
- MACE at 78 weeks = 1.7% vs 3.3%

FOURIER (EVOLOCUMAB)
- 27,564 patients with LDL >70
- 100% with ASCVD
- All on maximum tolerated statin
- Mean LDL: 92mg/dL to 30mg/dL
- MACE at 48 weeks = 9.8% vs 11.3%

No effect on CV mortality or all-cause mortality
Curves diverged progressively over time
↓ MACE per mg/dl ↓ LDL similar to statins

Maybe we just need to wait
THE PLAYERS – BILE ACID SEQUESTRANTS

- ↓ LDL 15-25% by binding bile acids and preventing reabsorption
- Causes upregulation of HMG-CoA reductase activity
- One primary prevention trial: the Lipid Research Clinics Coronary Primary Prevention
  - Cholestyramine vs. placebo in 3,806 asymptomatic middle-aged men followed for 7.4 years
  - ↓ CHD death or non-fatal MI 7% vs. 8.6%
  - No significant difference in all-cause mortality
  - High D/C rates due to adverse events
- Should not be used if fasting TGs ≥300 mg/dL (caution if >250)
  - Bloating and constipation
  - Severe TG elevations may occur
  - ↓ hepatic cholesterol = ↑ LDL-R
  - Limited efficacy as monotherapy
  - No evidence for benefit when added to statins
THE PLAYERS - EZETIMIBE

- ↓ LDL by inhibiting intestinal absorption of cholesterol via Niemann-Pick C1-like 1 transmembrane protein in enterocytes
- In combination with statins = additional ↓ LDL 25%
- **Monotherapy** in statin-intolerant individuals?
- **IMPROVE-IT Trial** (*NEJM* 2015):
  - >50 years of age, ACS within 10 days, and LDL >50 mg/dL
  - Ezetimibe 10mg vs. placebo in combination with simvastatin 40mg
  - Significant reduction in MACE (40 vs. 45%)
- ↓ hepatic cholesterol = ↑ LDL-R

No evidence for ASCVD prevention
The Players – Fibrates

- ↓TG 20-35%, ↑HDL-C 6-18%, ↓TC and LDL-C 20-25% by multiple mechanisms...
  - Stimulates lipoprotein lipase activity and decreases VLDL production
  - Stimulation of reverse cholesterol transport
  - Modulation of the LDL receptor/ligand interaction
- If GFR <30 = do not use and if GFR 30-59 = dose reduce
- Monotherapy: decreases CV events in men with or w/o ASCVD
  - VA-HIT study (Gemfibrozil)
  - Helsinki Heart Study (Gemfibrozil)
  - FIELD (Fenofibrate)
- Combination Therapy? Statin plus fenofibrate for men with DM and both TGs >204mg/dl and HDL <34mg/dl
  - ACCORD subgroup analysis

Benefit only in smokers
23% RRR in CV mortality 18 year f/u
Primary prevention only if TG >200, HDL <40
THE PLAYERS — OMEGA-3

• ↓ TG 27-45% in individuals with severe hypertriglyceridemia
• MOA for TG lowering:
  – Reduces hepatic VLDL-TG synthesis and secretion
  – Enhances TG clearance from circulating VLDL particles
• Hypotheses for CV protection mechanism:
  – Anti-arrhythmic (direct myocytes)
  – Decreased platelet aggregation
  – Reduced production of pro-atherogenic and inflammatory prostaglandins and leukotrienes

No strong data for CV protection
**THE PLAYERS - NIACIN**

"On the basis of currently available evidence of non-efficacy and potential harms, the committee judged that there are no clear indications for the routine use of niacin…" (ACC/AHA)

- One RCT (Coronary Drug Project 1966-74): 27% ↓ in non-fatal MI
- Meta-Analysis (Bruckert et al. Atherosclerosis. 2010.) 10 trials
  - 6/10 studies showed no effect on events
  - 4 studies showed a decrease in CV events, but none were as monotherapy
- Nasty side effects
- Mainly used for **reducing triglycerides**

**Third Line**

- Afib
- Flushing
- Acute Gout
- Hepatotoxicity
- Hyperglycemia
- Gastrointestinal Sx
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Basic Premise: LDL (and other ApoB containing lipoproteins) = main atherogenic particles

Highlights:
- Ease of use
- Evidence-based…

“Only one approach has been evaluated in multiple RCTs
The use of fixed doses of cholesterol-lowering drugs to reduce ASCVD risk”

• Dismissive of other strategies:
  - Treat-to-target
  - Lower is better

Primarily Statins

PCPs and Specialists

…so lowering LDL lowers risk

Under-treatment (not enough statin) or Over-treatment (non-evidence-based add-ons)

Mainly Over-treatment
• Four groups in which benefits of statins clearly outweigh the risks:
  
  – **Clinical ASCVD** (ACS, MI, stable or unstable angina, arterial revascularization, stroke, TIA, PAD)
    
    - High Intensity Statin
    - Unless older than 75
    - Moderate Intensity Statin

  – Primary elevations of **LDL >190 mg/dL**
    
    - High Intensity Statin
    - Evaluate Secondary Causes
    - Consider non-statin Rx

  – **Diabetes** aged 40 to 75 years with LDL 70-189 and without clinical ASCVD
    
    - Type 1 or 2
    - Moderate Intensity Statin
    - Unless 10-year risk >7.5%
    - High Intensity Statin

  – **Estimated 10-year ASCVD risk >7.5%** with LDL 70-189 and w/o clinical ASCVD or diabetes
    
    - Moderate Intensity Statin
    - High Intensity Statin

  ACC/AHA Pooled Cohort Equations Risk Estimator
ACC/AHA Pooled Cohort Equations Risk Estimator

• 10-year ASCVD risk (defined as first occurrence nonfatal and fatal MI, and nonfatal and fatal stroke)

• Advantages:
  – Simple to use
  – Inclusion of stroke as an endpoint (unlike Framingham)
  – Cohorts more contemporary than Framingham
  – Cohorts include substantial number of African Americans (unlike Framingham)

• Criticisms:
  – May overestimate risk for some
  – Omits CKD which is a strong risk factor for ASCVD

Physician’s/Women’s Health Studies and Women’s Health Initiative
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EXPERT CONSENSUS DECISION PATHWAY FOR NON-STATIN THERAPY

• **Treatment Thresholds** “in terms of both percentage LDL-C reduction from baseline and absolute on-treatment LDL-C measurement”

• Opened the door for **non-statin therapies**
  - **Ezetimibe** IMPROVE-IT Trial
  - **PCSK9 inhibitors** FOURIER and ODYSSEY
  - **BAS**: consider as a statin add-on in ezetimibe intolerant patients
  - Niacin not recommended for ASCVD event reduction in combination with statins
  - Fibrates and Omega-3s still mainly TG-lowering agents
• Revisiting the Big Four
  – Clinical ASCVD (ACS, MI, stable or unstable angina, arterial revascularization, stroke, TIA, PAD)
  – Primary elevations of LDL >190 mg/dL
  – Diabetes aged 40 to 75 years with LDL 70-189 and without clinical ASCVD
  – Estimated 10-year ASCVD risk >7.5% with LDL 70-189 and w/o clinical ASCVD or diabetes

Assuming maximally tolerated statin, LSM, and adherence

Goals: >50% LDL ↓ or LDL <70 or non-HDL <100
  Ezetimibe
  PCSK9i
  Preferred if comorbidities

If ASCVD, same as above plus...
  Mipomersen
  Lomitapide
  Apheresis
  Lipid Specialist

No ASCVD? Then goals LDL <100 or non-HDL <130

Goals: 30-50% LDL ↓ or LDL <100 or non-HDL <130
  ?Ezetimibe?
  No role for PCSK9i

No role for PCSK9i
Symptomatic heart failure: largely excluded from RCTs, except…

- **CORONA** (rosuvastatin 10mg): n = 5,011 ≥60 years old with ischemic CHF and EF <40% with NYHA class II to IV Sx
  - No difference from placebo

- **GISSI-HF** (rosuvastatin 10mg): n = 4,574 ≥18 years old with ischemic and nonischemic CHF and <40%
  - No difference from placebo

- **Meta-analysis** of these trials showed a 19% reduction in MI
  - Only in ischemic CHF

Reasonable to consider statins in *ischemic* CHF if life expectancy at least 3-5 years

- **ESRD-HD**: no data for statin benefit
  - AURORA and SHARP Trials
GUIDELINES

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk factors</th>
<th>Recommended statin intensity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factor(s)**</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td>40–75 years</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or in patients with a history of ASCVD who cannot tolerate high-dose statins</td>
<td>Moderate plus ezetimibe</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>Moderate or high</td>
</tr>
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<td>ASCVD</td>
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<td>Moderate plus ezetimibe</td>
</tr>
</tbody>
</table>

Risk Factors

- LDL ≥ 100
- HTN
- CKD
- Albuminuria
- Smoking
- Fam Hx

No need for risk calculator in DM
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Combination therapy besides ezetimibe?

• **Maybe fenofibrate** if TG > 204 and HDL < 32
  - **ACCORD subgroup**

• **Niacin = DO NOT DO**
  - SEs, lack of efficacy, ↑ CVA in AIM-HIGH

• **PCSK9 Inhibitors:** “considered…for patients with diabetes at high risk for ASCVD events who require additional lowering of LDL cholesterol or who require but are intolerant to high-intensity statin therapy”

**Likely to be more refined in 2018**
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- Adults aged 40 to 75 years with no history of CVD, one or more CVD risk factors, and a calculated 10-year CVD event risk of 10% or greater
  - Low Intensity Statin
  - Moderate Intensity Statin
- Adults aged 40 to 75 years with no history of CVD, one or more CVD risk factors, and a calculated 10-year CVD event risk of 7.5% to 10%
  - Discuss and selectively offer
- Adults 76 years and older with no history of CVD
  - No recommendation

Justifications?

- Most RCTs used low or moderate intensity
- ACC risk calculator may overestimate risk
- Hardly any trials in patients over 75 years
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General Principles/Highlights:
• Endorses a treat-to-target approach
• Supports the use of CAC scores, inflammatory markers, and other non-traditional risk factors
• “nuance-based clinical decision-making” and “real-world medical care”

Disadvantage:

Punishingly Intricate
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<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors^10-year risk^b</th>
<th>Treatment goals</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C (mg/dL)</td>
<td>Non-HDL-C (mg/dL)</td>
<td>Apo B (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Extreme risk</td>
<td>Progressive ASCVD including unstable angina in patients after achieving an LDL-C &lt;70 mg/dL</td>
<td>&lt;55</td>
<td>&lt;80</td>
<td>&lt;70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH</td>
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<tr>
<td></td>
<td>History of premature ASCVD (&lt;55 male, &lt;65 female)</td>
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</tr>
<tr>
<td>Very high risk</td>
<td>Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk &gt;20%</td>
<td>&lt;70</td>
<td>&lt;100</td>
<td>&lt;80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes or CKD 3/4 with 1 or more risk factor(s)</td>
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<tr>
<td></td>
<td>HeFH</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>High risk</td>
<td>≥2 risk factors and 10-year risk 10-20%</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes or CKD 3/4 with no other risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
<td>≤2 risk factors and 10-year risk &lt;10%</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>0 risk factors</td>
<td>&lt;130</td>
<td>&lt;160</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

Endorse 4 total calculators

No evidence for Apo B targets
And then there’s the risk factors...

<table>
<thead>
<tr>
<th>Major risk factors</th>
<th>Additional risk factors</th>
<th>Nontraditional risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age</td>
<td>Obesity, abdominal obesity</td>
<td>Lipoprotein (a)</td>
</tr>
<tr>
<td>Total serum cholesterol level</td>
<td>Family history of hyperlipidemia</td>
<td>Inflammation markers</td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>Small, dense LDL-C</td>
<td>(hsCRP, Lp-PLA₂)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Apo B</td>
<td>Homocysteine levels</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>LDL particle concentration</td>
<td>Apo E4 isoform</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Fasting/post-prandial hypertriglyceridemia</td>
<td>The apo</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>TG-rich remnants</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>PCOS</td>
<td>Coronary Artery Calcium Score?</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Dyslipidemic triad</td>
<td></td>
</tr>
</tbody>
</table>
The Agents

- Statins are recommended as primary agents to achieve goals
- Fibrates used to treat severe hyper-TG and reduce ASCVD events when TG >200, HDL <40
- No role for fish oil or niacin in ASCVD event reduction
- BAS and ezetimibe can be used as monotherapy or in combination with statins
- PCSK-9 can be used in FH or clinical ASCVD not achieving goal in combination with maximum tolerated statin

Cost Effective? No
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“Nuance-based clinical decision-making”
“Real-world medical care”

What is valuable?
• Highlighting Coronary Artery Calcium Score
• “Current evidence indicates that LDL-C can be aggressively lowered with statin therapy regardless of baseline levels and suggests that there is no baseline threshold level below which LDL-C lowering ceases to be effective”

Clear-cut and reliable predictor of CV events
Based on CTT and 2014 meta-analysis
Lowest LDL (<50) = Lowest ASCVD events

So complicated that it’s at odds with…
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Basic premises

• Elevated **Apo B-containing lipoproteins** (atherogenic/non-HDL cholesterol) are a root cause of atherosclerosis, the key contributor to most ASCVD events

• **Reducing atherogenic cholesterol will lower ASCVD risk** in proportion to the extent that it is reduced

• Intensity of risk-reduction therapy should be **adjusted to the patient’s absolute risk**

• **No evidence of an LDL reduction threshold** based on CTT data

• **Treat to target** hasn’t been tested in large trials …but that doesn’t invalidate the idea

“Treatment goals facilitate effective communication between patients and clinicians”
### GUIDELINES

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Criteria</th>
<th>Treatment goal</th>
<th>Consider drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>• 0–1 major ASCVD risk factors</td>
<td>&lt;130 Non-HDL-C, mg/dL</td>
<td>≥190 Non-HDL-C, mg/dL</td>
</tr>
<tr>
<td></td>
<td>• Consider other risk indicators, if known</td>
<td>&lt;100 LDL-C, mg/dL</td>
<td>≥160 LDL-C, mg/dL</td>
</tr>
<tr>
<td>Moderate</td>
<td>• 2 major ASCVD risk factors</td>
<td>&lt;130 Non-HDL-C, mg/dL</td>
<td>≥160 Non-HDL-C, mg/dL</td>
</tr>
<tr>
<td></td>
<td>• Consider quantitative risk scoring</td>
<td>&lt;100 LDL-C, mg/dL</td>
<td>≥130 LDL-C, mg/dL</td>
</tr>
<tr>
<td></td>
<td>• Consider other risk indicators*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>• ≥3 major ASCVD risk factors</td>
<td>&lt;130 Non-HDL-C, mg/dL</td>
<td>≥130 Non-HDL-C, mg/dL</td>
</tr>
<tr>
<td></td>
<td>• Diabetes mellitus (type 1 or 2)†</td>
<td>&lt;100 LDL-C, mg/dL</td>
<td>≥100 LDL-C, mg/dL</td>
</tr>
<tr>
<td></td>
<td>• 0–1 other major ASCVD risk factors and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No evidence of end-organ damage</td>
<td></td>
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<tr>
<td></td>
<td>• Chronic kidney disease stage 3B or 4‡</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• LDL-C of ≥190 mg/dL (severe hypercholesterolemia)†</td>
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</tr>
<tr>
<td></td>
<td>• Quantitative risk score reaching the high-risk threshold‖</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>• ASCVD</td>
<td>&lt;100 Non-HDL-C, mg/dL</td>
<td>≥100 Non-HDL-C, mg/dL</td>
</tr>
<tr>
<td></td>
<td>• Diabetes mellitus (type 1 or 2)</td>
<td>&lt;70 LDL-C, mg/dL</td>
<td>≥70 LDL-C, mg/dL</td>
</tr>
<tr>
<td></td>
<td>• ≥2 other major ASCVD risk factors or</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• Evidence of end-organ damage*</td>
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</tbody>
</table>
GUIDELINES

• **Step 1:** identify high- and very high–risk conditions, if present
  – Very high risk: ASCVD or DM (type 1 or 2) with ≥2 major ASCVD risk factors or GFR <60
  – High risk: LDL >190 mg/dL, DM with 0-1 risk factors, CKD Stage 3B-4

• **Step 2:** Count major ASCVD risk factors
  – 0-1 = low risk
  – ≥3 = high risk

• **Step 3:** if 2 risk factors are present…
  – **Risk refinement:** hs-CRP, CAC, Lp(a), micralbuminuria or…
  – **Quantitative risk scoring**
     – If neither of the above indicate high-risk, then assign to moderate-risk
ASCVD Risk Factors

- **Age:** Male $\geq 45$ y, Female $\geq 55$ y
- Current *cigarette smoking*
- **HTN:** $\geq 140/90$ mm Hg or on BP Rx
- **Low HDL:** Male $< 40$ mg/dL, Female $< 50$ mg/dL
- **Family history** of early CHD in 1st degree relative: $< 55$ y (male), $< 65$ y (female)

Additional Risk Factors for risk refinement

- **CAC** $\geq 300$ Agatston units
- **hs-CRP** $\geq 2$mg/L
- **Lp(a)** $\geq 50$mg/dL
- Microalbuminuria

**High Risk Score Thresholds**

- $\geq 10\%$ using Adult Treatment Panel III Framingham Risk Score
- $\geq 15\%$ using the 2013 Pooled Cohort Equations for hard ASCVD
- $\geq 45\%$ using the Framingham long-term cardiovascular disease
GUIDELINES

Medications

- First line therapy is moderate or high intensity statin
- No indication to reduce or D/C statin if LDL drops to <40mg/dl
- Statin intolerance: RCT evidence for monotherapy gemfibrozil, cholestyramine, niacin
- Combination Therapy (in order of preference):
  - Ezetimibe
  - Colesevelam
  - Niacin
  - Consider fenofibrate or omega-3 if HDL <40 and TG >200

Most add-on data was in patients with relatively low levels of LDL, so they may not have adequately assess risk reduction…
GUIDELINES

PCSK9 Inhibitors

• 4 categories of patients that would benefit:
  – Stable ASCVD on maximum tolerated statin plus ezetimibe
  – Progressive ASCVD on max statin plus ezetimibe
  – LDL-C > 190 mg/dL (mostly polygenic hypercholesterolemia, some HeFH/HoFH)
  – Very-high-risk patients with statin intolerance

Consider if LDL/non-HDL > 70/100
As above with caveat: not included in FOURIER
…it’s complicated

“who require substantial additional atherogenic cholesterol lowering, despite the use of other lipid lowering therapies”

Good luck getting this approved!
GUIDELINES

PCSK9 Inhibitors when LDL-C > 190 mg/dL

Why so complicated?

- Aged 40-79 years, no uncontrolled ASCVD risk factors or other key additional-high risk markers
  \[\text{LDL-C} > 100 \text{ mg/dL or non–HDL-C} > 130 \text{ mg/dL}\]
- Aged 40-79 years and either uncontrolled ASCVD risk factors, high-risk markers, or FH mutation
  \[\text{LDL-C} > 70 \text{ mg/dL or non–HDL-C} > 100 \text{ mg/dL}\]
- 18-39 years and either uncontrolled ASCVD risk factors, high-risk markers, or FH mutation
  \[\text{LDL-C} > 100 \text{ mg/dL or non–HDL-C} > 130 \text{ mg/dL}\]

Vast majority polygenic hypercholesterolemia

FH mutation confers a much higher risk

LDL values overlap, but...

HoFH is lipid specialist territory - mipomersen, lomitapide, and LDL apheresis

HoFH is lipid specialist territory - mipomersen, lomitapide, and LDL apheresis
SUMMARY

- The Big Four
  - Clinical ASCVD
    - Goals: >50% LDL↓ or LDL <70 or non-HDL <100
      - Primary elevations of LDL >190 mg/dL
      - Diabetes with LDL 70-189 w/o ASCVD
    - Mipomersen
    - Ezetimibe
    - PCSK9i
    - Preferred if comorbidities
  - Estimated 10-year ASCVD risk >7.5% with LDL 70-189 and w/o clinical ASCVD or diabetes
    - Goals: 30-50% LDL↓ or LDL <100 or non-HDL <130
      - Consider risk refinement: CAC, CKD, hs-CRP, Lp(a)
      - Be leery of risk calculator for elderly w/o risk factors

Maximize Statin, LSM, and Adherence
High Intensity Statin

Goals: >50% LDL↓ or LDL <70 or non-HDL <100
High intensity statin unless <40, >75, or no risk factors

Ezetimibe
PCSK9i
Preferred if comorbidities

Goals <100/<130 if age<40, no ASCVD or RFs, no FH mutation

Ezetimibe
No role for PCSK9i

Goals same as above plus...

Mipomersen
Lomitapide
Apheresis
Lipid Specialist

Goals <100/<130 if age<40, no ASCVD or RFs, no FH mutation

??Ezetimibe??
No role for PCSK9i

Don’t fear low LDLs
SUMMARY

Completely statin intolerant

- **Gemfibrozil**
  - If TGs are elevated and HDL is low
- **Bile Acid Sequestrant** otherwise
  - Cholestyramine
- **Ezetimibe** if the above two can’t be tolerated
  - No data
- **Niacin**
  - Minimal data as monotherapy
- **PSCK9 Inhibitor?**
  - Area for future investigation
QUESTIONS?

Statin Intolerance Death Cult

(Actual Member)