Get a Statin or Not?
Treatment Strategies in Dyslipidemia Management

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Learning objectives
1. Compare dyslipidemia treatment guidelines
2. Describe recent studies in the primary literature that affect dyslipidemia management
3. Select an appropriate intensity statin based on patient characteristics
4. Decide whether or not non-statin therapy should be added
5. Select appropriate non-statin therapy when warranted

Presentation overview
- Evidence behind dyslipidemia management
  – 2013 ACC/AHA
  – 2017 ACC Expert Consensus Decision Pathway
  – Primary literature
- Use of treatment goals to guide therapy
- Application using patient cases and audience response
2013 ACC/AHA

- "net ASCVD risk-reduction benefit"
  - Benefits of statins >>> non-statins
  - No large RCTs evaluating the outcome of drug titration to specific LDL-C target

4 Statin benefit groups

Statin benefit groups: Clinical ASCVD
Statin mechanism of action

Comparison of statin intensity

<table>
<thead>
<tr>
<th>Statin</th>
<th>Alovra</th>
<th>Fluvira</th>
<th>Lipira</th>
<th>Pravira</th>
<th>Rosuvira</th>
<th>Vytorin</th>
<th>Simvora</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL %</td>
<td>50</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>40</td>
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<td>40</td>
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<tr>
<td></td>
<td>40</td>
<td>80</td>
<td>80</td>
<td>10/10</td>
<td>40</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>20</td>
<td>20/40</td>
<td>60</td>
<td>55</td>
<td>45</td>
<td>60</td>
</tr>
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<td></td>
<td>60</td>
<td>40</td>
<td>40</td>
<td>60</td>
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</table>

Low intensity: lowers LDL-C by 30 to <50%
Moderate intensity: lowers LDL-C by ≥50%
High-intensity: lowers LDL-C by ≥50%

Since 2013 ACC/AHA

- HPS2-THRIVE (Heart Protection Study 2- Treatment of HDL to Reduce the Incidence of Vascular Events)
- IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)
- FOURIER
- SPIRE-1 and SPIRE-2
- ODYSSEY
**Cholesterol Absorption Inhibitor:**
**Ezetimibe**

**Mechanism of action:** Reduces cholesterol absorption at the epithelial brush border in the GI tract

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range (mg/day)</th>
<th>Monotherapy:</th>
<th>Combo:</th>
<th>Combination:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe (Zetia)</td>
<td>10</td>
<td>LDL ↓19%</td>
<td>HDL ↑1-4%</td>
<td></td>
</tr>
<tr>
<td>Combo:</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>Ezetimibe/atorvastatin</td>
<td>10/20, 10/40, 10/80</td>
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**IMPROVE-IT** (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)

- **Goal:** Determine efficacy and safety of ezetimibe/simvastatin 10/40mg vs. simvastatin 40mg alone
- **18,144** patients with ACS
- **Primary outcome:** CV mortality, major CV event, or nonfatal stroke reduced significantly with combination therapy
- **LDL-C levels** 53 mg/dL vs 70 mg/dL
- **No significant differences in adverse effects**

**LDL: How low can (should) you go?**

- **Threshold for atherogenesis** = 50-65 mg/dL
- **JUPITER trial**
  - evaluated adverse event rates in patients taking rosvastatin who attained an LDL-C below 50 or 30 mg/dL.
- **IMPROVE-IT trial**
  - achieving an LDL-C less than 30 mg/dl, at one month had a similar safety profile over six years, compared with patients achieving higher LDL-C concentrations
- **Consider ↓ dose if 2 consecutive LDLs <40 mg/dl (C)**
**LDL: How low can (should) you go?**

- **AACE/ACE 2017 guideline**
  - Extreme-risk patients: LDL-C goal <55 mg/dL (1.4 mmol/L)\(^1\)
  - Progressive disease after achieving an LDL-C <70 mg/dL, or CVD and diabetes, or CKD or heterozygous familial hypercholesterolemia (HeFH), or history of premature atherosclerotic CVD (<55 years in men or >65 years in women).

- No evidence of neurocognitive adverse events associated with alirocumab treatment and LDL-C levels <25 mg/dL in 3340 patients from 14 randomized Phase 2 and 3 controlled trials\(^2\)

- FOURIER Trial (PCSK9): start LDL-C of 90 mg/dL; final LDL-C of 30 mg/dL\(^3\)

- The long-term effects of very low levels of LDL-C induced by PCSK9 inhibitors are unknown (neurocognitive events study underway-Regeneron Pharmaceuticals; Phase 4 trial, 2016-2020)

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**PCSK9 Inhibitor MOA**

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**PCSK9 inhibitors**

**Evolocumab (Repatha)**
- Dosage form: Pre-filled Syringe, Solution auto-injector (Repatha SureClick)
- Dosing: 420 mg SQ monthly, (max: 150 mg q2weeks)
- Single-use on-body infusor (Repatha Pushtronex) with prefilled cartridge over 9 minutes, or 3 separate 140mg injections (prefilled syringe or solution auto-injector) in a row, using a different single-use prefilled syringe or single-use prefilled autoinjector for each injection. Give all of these injections within 30 minutes.

**Alirocumab (Praluent)**
- Dosage Form: Pre-filled syringe or Solution pen injector (75mg, 150mg)
- Dosing: 75 mg SQ q2weeks (max: 150 mg q2weeks)
### FOURIER-Evolocumab

- **27,564 high-risk secondary prevention patients 40 to 85 years of age**
  - Clinical ASCVD + at least 1 major risk factor or 2 minor risk factors
- **Evolocumab 140 mg every 2 weeks (or 420 mg monthly) vs placebo**
- **F/U median duration of 2.2 years**
- **Primary endpoint: composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization**


### FOURIER- Evolocumab

- **Reduction in primary endpoint in evolocumab group (HR: 0.85; 95% CI: 0.79 to 0.92; p<0.001) and the key secondary endpoint (composite of cardiovascular death, MI, or stroke) (HR: 0.80; 95% CI: 0.73 to 0.88; p<0.001)**
- **At 48 weeks, the mean percent reduction in LDL-C with evolocumab as compared with placebo was 59% (median baseline value of 92 mg/dL to 30 mg/dL (p<0.001))**
- **Consistent across key subgroups, including lowest quartile of baseline LDL-C levels**
- **No significant difference in adverse events**


### SPIRE-1 & SPIRE-2

- **Bococizumab: humanized monoclonal antibody (3% murine sequence)**
- **Significant attenuation of LDL-C lowering over time due to high-titer antidrug antibodies**
- **Wide variation in LDL-C lowering**
- **STOPPED at 7 months for SPIRE-1, 12 months for SPIRE-2**
- **No benefit in the combined analysis with respect to the primary composite endpoint of CV death, MI, stroke, or urgent revascularization.**
**ODYSSEY**
- 18,924 patients with recent MI or unstable angina (4-52 weeks) on statin
- Significant reductions in primary endpoint by 15%
  - Combined: CHD death, MI, ischemic stroke, or hospitalization for UA
- Significant improvement in all-cause mortality
- Pending publication

http://www.cardiobrief.org/2018/03/10/the-odyssey-trial-ends-well-but-is-it-enough/

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**2017 ACC Expert Consensus Decision Pathway**

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**2017 ACC ECDP**

Lloyd-Jones et al. JACC, vol. 70, No.14, 2017
Factors to consider with statins

- Adherence and lifestyle
- Statin intolerance
- Control of other risk factors
- Patient engagement and Discussion
- % LDL-C reduction
  - May consider absolute LDL-C or non-HDL-C level achieved
- Monitoring of response to therapy

Lloyd-Jones et al. JACC vol. 70. No.14. 2017

Adults ≥ 21 years of age, clinical ASCVD

Adults aged 40-75 years without clinical ASCVD or DM, est 10-year risk of ≥ 7.5%

DM Adults aged 40-75 years

Lloyd-Jones et al. JACC vol. 70. No.14. 2017

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LDL-C reduction or LDL-C ≤100 mg/dL, or non-HDL-C ≤130 mg/dL on max tol statin
- No other comorbidities: 1. ezetimibe 2. add or replace w PCSK9i
- With comorbidities or LDL-C ≥ 190mg/dL: ezetimibe or PCSK9i and addition of other second if needed

% LDL-C reduction: Target LDL-C ≤100 mg/dL, or non-HDL-C ≤130 mg/dL on max tol statin
- Consider specialist

LDL-C reduction: Target LDL-C ≤70 mg/dL or non-HDL-C ≤100 mg/dL on max tol statin
- Consider switching to a different statin

Adults aged 40-75 years without clinical ASCVD

≥ 50% LDL-C reduction (or LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on max tol statin
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Patient case

- PG is a 45 year old Caucasian male. He has type 2 diabetes which was diagnosed 2 years ago.
- Family history: MI (Father, at age 50)
- BP 155/95 mmHg, HR 76
- Labs: TC 255, TG 302, HDL 30, LDL 165, A1C 8.4%
  Scr 1.1, BMI 36
- Medications: metformin 1000 mg BID and empagliflozin 25mg daily

Patient case follow up

Thank You!

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