Lipids, Statins and HIV: 
Topics in Clinical Management

Medical Management of AIDS & Hepatitis
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• Work not related to this presentation

Outline

• Who should be on statins? Recent guidance
• Practical use of statins in patients with HIV
  – specific drug interactions with ARV’s
• What can statins achieve?
  – Lipid lowering, CV risk mitigation, malignancy reduction
• What downside risks do statins pose?
  – Myopathy, diabetes?, cognitive changes?
• If statins don’t achieve their goals, or can’t be used, what can ARV switching do to improve lipids?
• New drug class: PCSK9 inhibitors

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• New drug class: PCSK9 inhibitors
Older System: LDL-based goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL (mg/dL) Primary target</th>
<th>Non-HDL (mg/dL) Secondary target</th>
<th>LDL to Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High</td>
<td>&lt; 70</td>
<td>&lt; 100</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>High</td>
<td>100</td>
<td>&lt; 130</td>
<td>≥ 100</td>
</tr>
<tr>
<td>Moderately High</td>
<td>&lt; 130; optional</td>
<td>&lt; 160</td>
<td>≥ 130; 100-129; optional</td>
</tr>
<tr>
<td>Moderate ≥ 2 Risk Factors</td>
<td>130</td>
<td>160</td>
<td>≥ 160</td>
</tr>
<tr>
<td>Low 0-a Risk Factor</td>
<td>160</td>
<td>190</td>
<td>≥ 200</td>
</tr>
</tbody>
</table>

New statin guidelines in 2013

- **AHA/ACC guidelines Nov. 2013:**
  - assess risk of “hard” CV events
  - used a new “global risk prediction score”
  - recommend statins when 10-year risk is >7.5%
  - consider statins when 10-year risk is 5 - 7.5%

- **Controversies:**
  - do new guidelines mean there are many patients on statins who do not need to be?
  - do new guidelines mean many low risk patients not on statins should be initiated?
  - Huge resource questions involving millions of patients

Controversy over new guidelines

- **Ridker & Cook (Lancet, 2013):**
  - New calculator can overestimate risk and therefore recommend statins for too many people
  - No statin RCT used a ‘global risk prediction score’ as an entry criterion...
  - Smoking and HTN are major drivers of risk...but could end up being addressed by a statin rather than by habit reduction...
  - Can have odd individual situations where statin unexpectedly is or isn’t recommended...
  - Heavily influenced by age: 41% of men and 27% of women age 60-69 have risk≥10%, and many age≥65 with no risk factors will meet risk criteria...however, no statin trials ever enrolled persons of these ages with zero risk factors...
  - New risk calculator is widely recognized; use as a starting point to foster individual discussions

November 2018: New Cholesterol Guidelines

- **Key Changes to new 2018 guidelines:**
  - Amplifies patient-clinician discussion on patient specific risks, and risks/benefits of statin
  - Emphasis on early lifestyle modifications
    - Diet: high vegetable, fruit, lean protein, whole grains, limit sweets & processed fats
    - Exercise: 40 minutes, vigorous, 3-4 times per week
  - Understand high/moderate/low intensity statin options
  - Use new updated risk calculator (“risk plus”)
    - Still based on pooled population based risk equations, but now more of a “launch point” for discussion and decision making

Grundy SM et al., 2018 JACC: 2018 AHA/ACC Guideline on the Management of Blood Cholesterol

Ridker & Cook, Lancet, 2013
Overview of New 2018 Guidelines

Consider many factors simultaneously
- Focus on ASCVD risk, as well as certain numeric LDL targets
- Differentiate who needs statin for ASCVD (secondary prevention) vs. who needs it for primary prevention
- Differentiate high-intensity statin from moderate intensity statin
- Screen for LDL>190 and diabetes
- Calculate patient 20-year risk: is it >7.5%?
- Consider several “risk enhancers”
- Consider coronary artery calcium score

Also include in discussion
- Smoking cessation
- Diet
- HTN control
- Exercise

Grundy SM et al., 2018 JACC: 2018 AHA/ACC Guideline on the Management of Blood Cholesterol
- Initiate statin to achieve goals
- Then add ezetimibe if not achieving goals
- Then consider adding PCSK-9 inhibitor
- Consider coronary artery calcium score in patients >40 with uncertain risk status: if ≥100 Agatson units= ASCVD risk ≥7.5% = start statin

**November 2018: New Cholesterol Guidelines**

**Updated Web-based Calculator**
- Enter variables:
- Read out 10-year and lifetime risk:
- And how this risk can be optimized/lowered with therapies:

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Statin Choices: a review

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Statin potency in HIV+ patients

- Retrospective study: 700 HIV+ patients, 2 large US clinics initiating statin
- Both atorvastatin and rosuvastatin did better than pravastatin in reducing total cholesterol, LDL, TGs and non-HDL cholesterol
- Less accumulated data with rosuvastatin limits its use

Pitavastatin vs. Pravastatin

- INTREPID Study: First double blind RCT of 2 statins in HIV+ population; first trial of pitavastatin
- Randomized trial: 4mg daily pitavastatin vs. pravastatin 40mg daily
- Inclusions: Age 18-70, on ART≥6mo., CD4>200, VL<200,
- 4-week diet stabilization lead in; then advised lipid restricted diet throughout study
- After this period: dyslipidemia: LDL 130-220 mg/dL and triglycerides ≤400 mg/dL
- Exclusions: darunavir (due to pravastatin interaction), homozygous familial hypercholesterolemia, other secondary cause for hyperlipidemia, statin intolerance, diabetes, high fasting glucose, coronary artery disease

Singh et al., Clin. Infect. Dis., 2011
Intrepid Study (cont’d)

- Enrolled (pitavastatin/pravastatin arms):
  - n=126/126, 84%/88% male, 85%/76% white
  - CD4: 648/563; mean HIV duration: 12.6y (SD 7.5) y
  - ART: 54% on NNRTI, 40% on PI
  - Framingham 10 year risk: 6.6%/6.4%
  - Mean LDL: 154/154, total chol.: 240/240

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pitavastatin</th>
<th>Pravastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL 12 Weeks</td>
<td>-31.2%</td>
<td>-20.9%</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>-20.4%</td>
<td>-13.8%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-3.2%</td>
<td>-3.6%</td>
</tr>
<tr>
<td>LDL 52 Weeks</td>
<td>-29.7%</td>
<td>-20.5%</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>-19.1%</td>
<td>-13.7%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-2.0%</td>
<td>-8.3%</td>
</tr>
</tbody>
</table>

- Critiques of study:
  1. choice of pravastatin comparator (weak statin)
  2. short 12-week outcome
  3. no long term cardiovascular event outcomes
  4. diabetes and CAD exclusions
  5. rare patients on integrase inhibitors
  6. many patients on EFV (may have dropped prava levels more than pitava levels)
  7. study funding

• Outcomes:
  - pitavastatin showed stronger improvements in lipids at 12 weeks than pravastatin; effect durable at 52 weeks
  - Overall good safety; low discontinuation rate
  - Authors note: no change in diabetes, but N small

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Reducing CV Events and Death

- Statins prevent mortality by reducing LDL and by lowering inflammation
- Systemic inflammation persists in HIV infection despite successful virologic suppression
- Treatment with statin of normal LDL patients with high CRP levels reduced cardiac events
- Do statins lower mortality in HIV patients?
**Johns Hopkins HIV Clinical Cohort**

- 1,538 HIV-infected patients between 1998-2009 who achieved virologic suppression within 180 days of starting HAART were included.
- Followed to death or VL>500 c/ml
- 238 (15.5%) received a statin while taking HAART.
- There were 85 deaths (7 in statin users, 78 in non-users)... overall few
- Malignancy, non-AIDS infections, and liver failure were prominent causes of death

**Statins & Mortality Reduction in HIV+ Patients**

Moore et al., PLOS ONE, 2011

**Hopkins: Statins $\rightarrow$ 67% Lower Odds of Death (95% CI: 24%-86% lower odds)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategory</th>
<th>Relative Hazard (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of death</td>
<td></td>
<td>0.55 (0.39-0.92)</td>
<td>0.022</td>
</tr>
<tr>
<td>AP prior to years</td>
<td>Black</td>
<td>0.82 (0.61-1.11)</td>
<td>0.217</td>
</tr>
<tr>
<td>Age</td>
<td>Other</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>HIV risk group</td>
<td>HIV</td>
<td>2.81 (1.38-5.87)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1.8 (reference)</td>
<td></td>
</tr>
<tr>
<td>CD4 at HAART start</td>
<td>Reference</td>
<td>2.80 (1.37-5.77)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1.5 (reference)</td>
<td></td>
</tr>
<tr>
<td>CD4 at HAART start</td>
<td>&lt;100 cells/mm$^3$</td>
<td>0.46 (0.20-1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>&gt;100 cells/mm$^3$</td>
<td>0.96 (0.70-1.33)</td>
<td>0.53</td>
</tr>
<tr>
<td>Time on HAART treatment</td>
<td>&lt;1 year</td>
<td>0.00 (0.00-1.00)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>&gt;1 year</td>
<td>1.93 (1.72-2.17)</td>
<td>0.001</td>
</tr>
<tr>
<td>Overall impact of statin</td>
<td>stop observation time at viral rebound</td>
<td>0.75 (95% CI: 0.83-1.68)</td>
<td>0.46-2.07</td>
</tr>
<tr>
<td></td>
<td>allow observation time after viral rebound</td>
<td>1.17 (95% CI: 1.66-2.07)</td>
<td></td>
</tr>
<tr>
<td>No comorbidity</td>
<td></td>
<td>1.12 (0.34-3.62)</td>
<td>0.90 (0.28-2.88)</td>
</tr>
<tr>
<td>With comorbidity</td>
<td></td>
<td>0.34 (0.11-1.04)</td>
<td>0.64 (0.32-1.29)</td>
</tr>
</tbody>
</table>

Moore et al., PLOS ONE, 2011

**Statins and Mortality: Danish Cohort Study**

- 1,738 HIV+ persons initiated ART after 1/1/98 and achieved viral suppression in ≤180 days
- 145 (8.3%) initiated a statin
  - 124 (7.1%) of these after starting ART
- Regression models of death looked at:
  - censoring upon virologic failure (like Hopkins study)
  - not censoring; allowing observation to continue if viral rebound

Rasmussen et al., PLOS ONE, 2013
Statins and Mortality: VA Cohort Study

- ~25,000 vets who initiated ART over 15 years
- 30% taking statins
- Analyzed pts. on ART w/suppressed VL
- Looked at death, CVD, malignancy, fragility fractures
- Trend towards lower mortality

Drechsler et al., CROI 2013, Abstract 45

Statins and Mortality: ACTG ALLRT Cohort

- 3601 patients enrolled in prior ACTG trials followed for AIDS/non-AIDS defining events
- 95% on HAART, 66% suppressed
- ~15% initiated statins during follow up

CV Events

<table>
<thead>
<tr>
<th></th>
<th>Unweighted, baseline adjusted</th>
<th>Weighted, baseline adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysed</td>
<td>1.17 (0.61-2.23)</td>
<td>0.84 (0.44-1.58)</td>
</tr>
<tr>
<td>Expected HR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.44 (0.7-2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.82 (0.4-1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.89 (0.3-2.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drechsler et al., CROI 2013, Abstract 765

Is it enough to just "control for" comorbidities? These change over time, and they influence decisions to initiate statins... "time-dependent confounding"

This study used a technique called marginal structural modeling to account for this.

A trend towards fewer CV events, but unclear, and methodology difficult

Overton et al., CID, 2013

Statins and Mortality: ACTG ALLRT Cohort

Statins and Mortality: ACTG ALLRT Cohort

REPRIEVE Study: ACTG 5332

- First RCT to randomize HIV-positive patients to statin vs. placebo
- Adults age 40-75, no prior history of CV disease, on ART ≥6 mo.
- Randomize to pitavastatin 4mg vs. placebo
- One of largest HIV clinical trials ever undertaken
  - (goal size 7,500; 93% enrolled; ~36% female so far)
  - Sept. 11, 2018 Enrollment update: study has enrolled >7,000 of target 7,500 participants
- Primary outcome: “MACE” (major adverse cardiovascular events)
- Secondary outcomes: components of MACE, all cause mortality, LDL, immune function, non-CV events, safety

https://twitter.com/reprievetrial

Overton et al., CID, 2015

REPRIEVE Study: ACTG 5332
Statins and Malignancy:

- CA Kaiser cohort: statin use associated with a lower risk of NHL vs. patients on non-statin lipid therapy

<table>
<thead>
<tr>
<th>Event Category</th>
<th>No. of Events</th>
<th>Event Rate for Statin Users (per 100 PY)</th>
<th>Event Rate for Non-Statin Users (per 100 PY)</th>
<th>Odds Ratio (Uncertainty)</th>
<th>P-value</th>
<th>Hazard Ratio (Uncertainty)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL</td>
<td>67</td>
<td>0.6</td>
<td>0.9</td>
<td>0.64 (0.46 - 0.92)</td>
<td>0.02</td>
<td>0.70 (0.46 - 1.05)</td>
<td>0.08</td>
</tr>
<tr>
<td>Non-Cancerous</td>
<td>103</td>
<td>0.2</td>
<td>0.5</td>
<td>1.78 (1.35 - 2.36)</td>
<td>0.001</td>
<td>1.78 (1.35 - 2.36)</td>
<td>0.001</td>
</tr>
<tr>
<td>Incident Cancer</td>
<td>20</td>
<td>0.6</td>
<td>0.5</td>
<td>1.26 (0.53 - 3.08)</td>
<td>0.61</td>
<td>1.26 (0.53 - 3.08)</td>
<td>0.61</td>
</tr>
<tr>
<td>Malignancy</td>
<td>24</td>
<td>1.4</td>
<td>0.7</td>
<td>1.99 (1.09 - 3.65)</td>
<td>0.026</td>
<td>1.99 (1.09 - 3.65)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Alcohol: 17 (12.6%), current smokers: 32 (25.3%), ART exposure: 34 (26.3%), CD4 count < 50 cells/mm³: 7 (5.3%), diabetes: 11 (8.4%), hypertension: 48 (36.7%), hemoglobin < 12 g/dL: 2 (1.5%), hyperlipidemia: 40 (30.5%), insulin resistance: 15 (11.5%), obesity: 44 (33.7%), other malignancies: 10 (7.7%), pulmonary: 6 (4.5%), renal: 2 (1.5%), other cancers: 20 (15.3%).

Statins and Malignancy: ALLRT Cohort, 2013

- Overton et al., Clin. Infect. Dis., 2013
Statins and Malignancy: Italian cohort, 2014

- Milan, Italy HIV+ cohort:
  - n=5357 patients, initiated ART 1991-2012
  - naïve to statin, no prior cancer diagnosis at ART start
  - 740 started statin (14%)
  - Follow-up period >10 years (4.8-15.1 years)

- Incidence of cancer (either AIDS- or non-AIDS-defining)
  - Statin: 1.3 events/1000 PY
  - No statin: 8.4 events/1000 PY

Overall risk of cancer:
- HR 0.35 (0.17 - 0.70)
  - Corrected for "immortal time bias":
    - HR 0.59 (0.36 - 0.98)

Galli et al., AIDS, 2014

Statins and Myopathy: Hard to Study

- Mechanism not clear
- Data are conflicting:
  - Meta analysis of 42 RCTs: Muscle problems in 12.7% (statin) vs. 12.4% (placebo), but largely by CK values
  - Clinical experience: muscle symptoms not rare
    - Internet survey (n=10,318)
      - 88% on statin (25% reported muscle symptoms)
      - 12% former statin users (60% reported muscle symptoms)
      - many possible methodologic issues in this study

Cases that occur without CK elevation would not be part of most reported RCT data
- Data on myopathy without CK elevation are hard to find
- Hard to separate from background rates of muscle problems

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Mechanism for increasing diabetes risk?

- Largely unknown
- Reduction in GLUT-4, glucose transporter → phenotype of reduced insulin sensitivity?
- Reduction in pancreatic B-cell insulin secretion due to inhibition of glucose-stimulated cytoplasmic calcium channels?

Sattar et al., Atherosclerosis, 2012

Statins and diabetes (general population)

JUPITER Trial, NEJM 2008:
Men>50, women>60, LDL<130, CRP>2.0
Randomized to rosvastatin or placebo
Reduced all levels of cholesterol, reduced death, MI, stroke
Raised concern about incident diabetes... what were the data?


Diabetes events not adjudicated

Mills et al., QJM, 2011

Giant meta-analysis spanning 76 RCTs encompassing 170,255 patients in RCTs that randomized to statin vs. no statin regimen

Acknowledging limitations of meta-analyses, raises concern about incident diabetes

Lichtenstein et al., J.AIDS, 2015

Statins and diabetes: HIV+ population

- HOPS Cohort
  - n=4,692 (2002-2011), no prior statin or DM, median F/U 4 years
  - Comparison of incident diabetes in statin users vs. non-statin users, adjusted for propensity scores
  - n=590 (12.6%) received statins
  - n=355 developed new, incident DM during F/U
  - HR 1.14 per year of statin exposure (95%CI, 1.02-1.27)

Rochefort et al., AIDS, 2015
Summary of diabetes risk

• Likely a small 5-10% elevation in risk for diabetes with statin use
  – unclear if specific to particular statins
  – possible that risk is slightly higher in HIV+ patients

• When using statin, monitor HBA1c% regularly, along with clinical symptoms of diabetes

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Statins & Cognitive Issues

• Case reports, observational data led to 2012 FDA ‘safety warning’ for statins: "Memory loss and confusion have been reported with statin use. These reported events were generally not serious and went away once the drug was no longer being taken"

  • The post-marketing adverse event reports generally described individuals over the age of 50 years who experienced notable, but ill-defined memory loss or impairment that was reversible upon discontinuation of statin therapy. Time to onset of the event was highly variable, ranging from one day to years after statin exposure. The cases did not appear to be associated with fixed or progressive dementia, such as Alzheimer’s disease. The review did not reveal an association between the adverse event and the specific statin, the age of the individual, the statin dose, or concomitant medication use.

  • Data from the observational studies and clinical trials did not suggest that cognitive changes associated with statin use are common or lead to clinically significant cognitive decline.

  http://www.fda.gov/drugs/drugsafety/ucm293101.htm

Statins & Cognitive Issues: Hard to Study

• Challenging topic to study:
  – Attributing cognitive impairment accurately
  – Length of exposure needed
  – Hyperlipidemia also associated with dementia: could statins be neuro-protective?
  – If no statin leads to higher dementia/impairment, could that affect adherence and lead to statin non-adherence?
  – Time-dependent confounding
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Points on ART Optimization

• INSTIs have least lipid effects of all classes
• TDF lowers lipids; ABC and TAF raise lipids
• With change from NNRTI or PI → INSTI, and simultaneous TDF → TAF: overall effect?
• Difficult question: staying on TDF for lipid reasons?
• Future 2-drug regimens (e.g. DTG/RPV or DTG/3TC): we will need to examine lipid profiles

INSTI class: less lipid derangement vs. PI and NNRTI in ART initiators

NEAT 022: PI → DTG Switch

NEAT 022: 2 NRTI + PI → 2 NRTI + DTG
  – ~8-9 point drop in TC and LDL
  – NRTIs: ~65% TDF/FTC, ~31% ABC/3TC (no TAF)

DTG

TC Non–HDL-C TG LDL-C HDL-C TC/HDL
Ratio

Mean Change
From BL to Wk 48 (%)

Table 1: Mean lipid changes from baseline to week 48 in the EXPEDITE study

Table 2: Mean lipid changes from baseline to week 48 in the PHAROS study

Gatell J et al., AIDS, 2017
STRIIVING Study: ART → DTG switch

- Switch from any ART to Triumeq (dolutegravir): STRIIVING study:
  - Small worsening in lipids overall: total cholesterol up by 1.8% (early switch group) and 2.5% (late switch group)
  - However, 26% already on INSTI (so maybe lipid-improving effects wouldn’t be as large?)
  - And 74% of patients switched from TDF/FTC (so loss of TDF lipid-improving effects were lost)

Trottier et al., Antivir Ther, 2017

Switching to EVG and DTG

- Switch from NNRTI (mostly EFV) to Stribild (elvitegravir): STRATEGY-NNRTI study:
  - Little impact on lipids
  - May have been because of a balance of benefit of NNRTI→INSTI, at the same time as adding cobicistat

Pozniak et al., Lancet Infect Dis., 2014

SPIRAL study: PI → RAL switch

- Substantial improvements in TG, TC, LDL, & HDL with switch from PI to RAL

Martinez et al., AIDS, 2010

SPIRIT Study: PI → RPV switch

- Substantial improvements in TG, TC, LDL, & HDL with switch from PI to RAL

Palella et al., AIDS, 2014
Ezetimibe

- Cholesterol absorption inhibitor: inhibits dietary and biliary uptake of cholesterol
- Reliably lowers LDL, beyond what statin achieves... but does it lower CV outcomes?
- IMPROVE-IT Trial:
  - Patients with acute coronary syndrome (i.e., secondary prevention) randomized to statin + ezetimibe vs. statin alone
  - Composite outcome of CV death, MI, admission for unstable angina, revascularization ≥30d later, CVA
  - Outcomes lower with ezetimibe:
    - hazard ratio [HR] 0.94, 95% CI 0.89-0.99
    - 7-year event rate 32.7 vs. 34.7 percent
- Questions:
  - Is ezetimibe needed? Max out statin dose first? Or add EZ to statin for synergistic/additive effects, and avoid max statin dose?
  - beyond

Outline

- Who should be on statins? Recent guidance
- Practical use of statins in patients with HIV
  - specific drug interactions with ARV’s
- What can statins achieve?
  - Lipid lowering, CV risk mitigation, malignancy reduction
- What downside risks do statins pose?
  - Myopathy, diabetes?, cognitive changes?
- If statins don’t achieve their goals, or can’t be used, what can ARV switching do to improve lipids?
- Novel drug class: PCSK9 inhibitors

PCSK9 Inhibitors: New class of anti-lipid drugs

- Target populations:
  - Persons on statin and ezetimibe but not at goal LDL
  - Persons with heterozygous familial hypercholesterolemia (~1/500)
  - Persons with statin intolerance
- FDA approved medications:
  - Evolocumab: Repatha (Amgen)
    - 140mg S.O. q2weeks or 420mg S.O. qMonth
  - Alirocumab: Praluent (Regeneron)
    - 75mg S.O. q2weeks, can increase to 150mg in 4-8weeks
### PCSK9 Inhibitors: Substantial LDL Reductions

- **24 studies, 10,159 patients** (mix of PCSK9 vs. placebo and PCSK9 vs. ezetimibe)
- LDL reduction: -47.5% (95% CI -69.6% to -25.4%)
- Placebo trials only LDL reduction: -58.8% (95% CI -61.0% to -56.5%)

Navarese et al., Ann Int Med, 2015

### PCSK9 Inhibitors: Moving from LDL reduction to event reduction

- **24 studies, 10,159 patients** (mix of PCSK9 vs. placebo and PCSK9 vs. ezetimibe)
- Total mortality reduction: 0.53% down to 0.31% OR 0.48 (0.27-0.85)
- **All cause mortality reduction**
  - **24 studies, 10,159 patients** (mix of PCSK9 vs. placebo and PCSK9 vs. ezetimibe)
  - CV mortality reduction: 0.33% down to 0.19% OR 0.49 (0.23-0.73)

Navarese et al., Ann Int Med, 2015

### PCSK9 Inhibitors: Event Reductions

#### Evolocumab

- **OSLER-1 and -2 Trials**
  - N=4,411 patients from phase 2 or 3 trials
  - Evolocumab + standard therapy vs. standard therapy alone
  - **Primary outcome:** composite CV events
  - Median follow-up 11 months
  - LDL down 61% (120 to 48)
  - CV events down from 2.18% to 0.95% HR 0.47 (0.28-0.78)


#### Alirocumab

- **ODYSSEY Trial**
  - N=3,342 patients on maximized statin and with LDL≥70
  - **Primary outcome:** 24 week LDL
  - **Secondary outcomes:** long term LDL, CV events
  - LDL down 62% at 24 weeks, same at W78
  - CV events down from 3.3% to 1.7% HR 0.52 (0.31-0.90)


### PCSK9 Longer Follow up Results

- **FOURIER Trial**
  - N=21,954 patients; already on moderate-intensity statin, RCT of evolocumab vs. PBO injection
  - Median 2.2 years of follow up
  - Primary endpoint: composite of CV death, MI, CVA, revascularization, unstable angina
  - Lower rate of CV events (HR 0.79, CI 0.73-0.85)
  - Lower risk of non-fatal stroke (HR 0.75, CI 0.67-0.85)
  - All-cause mortality (HR 0.85, CI 0.78-0.92)
  - Reduced CV events but did not reduce mortality

Salatin, MS et al., New Engl J Med, 2017

- **ODYSSEY-OUTCOMES Trial**
  - N=18,924 patients; acute coronary syndrome in past year, on high intensity or dose-maximized statin, and with LDL ≥70, non-HDL ≥100, or apolipoprotein B ≥80; RCT of alirocumab SQ vs. PBO injection q2weeks
  - Primary endpoint: composite of CHD death, nonfatal MI, fatal or nonfatal CVA, or hospitalization from unstable angina
  - Median 2.8 years follow up
  - Reduced CV events and reduced mortality

Schwartz, GG et al., New Engl J Med, November 2018

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**CV events:** death from coronary heart disease, nonfatal myocardial infarction, unstable angina, coronary revascularization, stroke, transient ischemic attack, and heart failure

**Adverse events:** injection site reactions, myalgia, neurocognitive events, ophthalmologic events

What about PCSK9 in HIV+ Patients?

Slide and data courtesy of Dr. Priscilla Hsue, SF General Hospital, UCSF

PCSK9 Inhibition in HIV+ Patients: RCT

- PCSK9 in HIV Evaluation Study: A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study to Assess the Efficacy and Safety of PCSK9 Inhibition in HIV-Infected Subjects at UCSF
- Alirocumab or placebo (n=200)
  - Alirocumab or placebo injected subcutaneously every 2 weeks for a duration of 52 weeks
- Assessments: endothelial function (flow-mediated vasodilation [FMD] of the brachial artery), vascular inflammation (FDG-PET/CT scanning), and coronary plaque (CT angiography)
- Funded by Pfizer/Sanofi/Regeneron
- PI: Priscilla Hsue MD, UCSF

PCSK9: Summary

- Dramatic LDL lowering
- Studies w/2-3 year follow up (FOURIER [evolocumab] and ODYSSEY OUTCOMES [alirocumab]) showed:
  – CV event reduction (but smaller than expected)
  – Mortality reduction in alirocumab only
- In HIV-positive patients: longer term data needed
- Think of PCSK9 inhibitors for patients who:
  – Are already on statins and ezetimibe but not at goal
  – Can’t tolerate statins

Reduction in LDL-C in HIV+ patients treated with Evolocumab (n=6)

Reduction in Lp(a) in HIV+ patients treated with Evolocumab (n=6)

Unpublished data, Priscilla Hsue, MD
Inflammation in SATURN Study (HIV+ patients)

- In the SATURN Study, HIV+ patients on ART, suppressed, with normal LDL and elevated CRP:
  - decreased LDL (as expected)
  - did not statistically significantly decrease IL-6, CRP, d-dimers, and other biomarkers of inflammation and hypercoagulation
  - did decrease Lp-PLA2 levels, even accounting for LDL reduction, indicating possible anti-inflammatory effect

Eckard et al., J. Infect. Dis., 2014

Summary / Conclusions

Practical use of statins in HIV+ patients
- Specific drug interactions with ARV's
  - Atorvastatin, pravastatin
  - Caution darunavir—pravastatin
  - Caution EFV/statins

Who should be on statins?
Updates on new guidelines
- Controversial, evolving
  - Treat CV disease risk, not LDL

What can statins achieve?
- Robust cholesterol lowering
  - Lowering in CV events
  - Unclear impact on mortality
  - Likely reduces malignancy

What downside risks do statins pose?
- Diabetes, Cognitive changes
  - Higher DM risk: monitor HBA1c
  - Caution with cognitive changes

If statins don’t achieve their goals, or can’t be used, what can ARV switching do to improve lipids?
- Switching to INSTI class
  - Switching PI to to RPV

New PCSK9 inhibitor class of drugs
- Watch for emerging data...

Thank You!
- Happy to take any questions!
- Thank you to Dr. Priscilla Hsue, SF General Hospital, Division of Cardiology
- For questions after the conference:
  - Email me anytime