Lipids and CVD Prevention

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Regional CVD Colead

Overview

- Lipids and CAD risk
  - Large shortfall in lipid control / statin use
  - Lipid variability and risk
  - Large statin benefit - opportunity
- Optimizing Performance
  - Identifying patients
  - Promoting starts and adherence
  - Safety / intolerance of statins
  - Beyond statins

Heart disease kills roughly the same number of Americans each year as cancer, lower respiratory diseases (including pneumonia), and accidents combined.

- Also, stroke is #3 cause of mortality and much feared, significant morbidity.
- Heart disease and stroke are very costly.
“Mendelian Randomization”
Genetic variation of LDL and impact on CAD risk.

- Familial Hypercholesterolemia (FH) – high LDL, high risk. Baseline LDL ≥ 190.
- PCSK9 – low LDL, low risk.

Tendon Xanthomas
Last LDL > 190 in KPSC

- 20,500 KP So Cal members.
- If lifestyle not successful, statins recommended if age > 10 years old.
- Easy to tell in inbox if patient needs statin by this criteria. Is regardless of risk.
- For adults, lower LDL at least 50%. Start atorvastatin 80 mg daily (53% LDL lowering)

Protective PCSK9 mutations

- Lifelong decreased levels of LDL.
  - Do not break down LDL receptors as well.
  - 2-3% of population
- Variant 1: 28% reduced LDL → 88% reduction in CAD.
- Variant 2: 15% reduced LDL → 50% reduction in CAD.
- Event reduction impressive: favorable impact of low cholesterol over a long time
Evidence shows large statin benefit

Large statin benefit
Regardless of “Disease”

<table>
<thead>
<tr>
<th>Events (% per annum)</th>
<th>Statically</th>
<th>Control &lt;=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous vascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>0.91 (4.8%)</td>
<td>1.29 (5.3%)</td>
</tr>
<tr>
<td>Non-CVD/vascular</td>
<td>0.64 (3.6%)</td>
<td>0.80 (3.7%)</td>
</tr>
<tr>
<td>None</td>
<td>0.76 (4.1%)</td>
<td>0.75 (4.1%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.45 (4.5%)</td>
<td>1.67 (4.5%)</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>2.84 (4.2%)</td>
<td>2.50 (4.5%)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>3.72 (3.2%)</td>
<td>10.16 (4.0%)</td>
</tr>
<tr>
<td>No diabetes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CCT. Lancet Nov 9, 2010
Statin benefit across older ages

**CCT. Lancet Nov 9, 2010**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Events (% per annum)</th>
<th>RR (Q) per 1 mmol/L reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65</td>
<td>605 (2.9%) 745 (3.4%)</td>
<td>0.78 (0.75-0.82)</td>
</tr>
<tr>
<td>&gt; 65 to 75</td>
<td>402 (3.7%) 490 (4.6%)</td>
<td>0.78 (0.74-0.83)</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>88 (4.9%) 99 (5.4%)</td>
<td>0.84 (0.73-0.97)</td>
</tr>
</tbody>
</table>

Statins benefit across range of baseline lipids

**CCT. Lancet Nov 9, 2010**

<table>
<thead>
<tr>
<th>Baseline LDL mg/dL</th>
<th>Events (% per annum)</th>
<th>RR (Q) per 1 mmol/L reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 76</td>
<td>77-96</td>
<td>0.78 (0.70-0.86)</td>
</tr>
<tr>
<td>97-116</td>
<td>117-136</td>
<td>0.80 (0.76-0.83)</td>
</tr>
<tr>
<td>&gt; 135</td>
<td></td>
<td>0.78 (0.76-0.86)</td>
</tr>
</tbody>
</table>

**LDL 150 to 89 same benefit as LDL 77 to 45**

**CCT. Lancet Nov 9, 2010**

More statin, more benefit

**CCT. Lancet Nov 9, 2010**

<table>
<thead>
<tr>
<th>More or less statin</th>
<th>Events (% per annum)</th>
<th>RR (Q) per 1 mmol/L reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 mmol/l</td>
<td>704 (4.0%) 79 (5.2%)</td>
<td>0.71 (0.65-0.78)</td>
</tr>
<tr>
<td>2 to &lt; 4 mmol/l</td>
<td>238 (3.8%) 127 (4.8%)</td>
<td>0.77 (0.70-0.84)</td>
</tr>
<tr>
<td>4 to &lt; 6 mmol/l</td>
<td>527 (4.5%) 63 (5.4%)</td>
<td>0.81 (0.75-0.87)</td>
</tr>
<tr>
<td>&gt; 6 mmol/l</td>
<td>525 (4.9%) 49 (4.8%)</td>
<td>0.84 (0.79-0.90)</td>
</tr>
<tr>
<td>Total</td>
<td>1997 (3.2%) 1139 (4.0%)</td>
<td>0.78 (0.74-0.83)</td>
</tr>
</tbody>
</table>
HPS: NNT

NNT (simvastatin 40 mg) to prevent one MI, stroke or revascularization in 5 years.

<table>
<thead>
<tr>
<th>DX</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post MI</td>
<td>10</td>
</tr>
<tr>
<td>Angina</td>
<td>12.5</td>
</tr>
<tr>
<td>s/p Stroke, PAD, DM age ≥ 40</td>
<td>14</td>
</tr>
</tbody>
</table>

Young DM with 80% Lifetime risk of CAD

Simvastatin 40 mg in Heart Protection Study 2001

JUPITER

Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.45-0.68
P < 0.00001

Number Needed to Treat (NNT) = 26
avg A risk of 7.5%
Entry LDL < 130, mean 105

Fatal or Nonfatal Myocardial Infarction

HR 0.46, 95% CI 0.36-0.70
P < 0.0002

Placebo

-55%
Starting Statins

- Acute Ischemic Stroke / Acute Coronary Syndrome: atorvastatin 80 mg
- LDL > 190 (regardless of risk): atorvastatin 80 mg
- Other Ischemic Vascular Disease (IVD), DM, or FRS > 10%: atorvastatin 40 mg
- Consider lower doses, clinical judgment and/or shared decision making in patients with:
  - Baseline LDL < 70, Age > 76 years,
  - Liver disease or muscle disorders.
  - Asian ancestry.

### Med/Dose, cost/yr $, %↓LDL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost/yr</th>
<th>%↓LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>prava 80</td>
<td>$70</td>
<td>38%</td>
</tr>
<tr>
<td>simva 40</td>
<td>$14</td>
<td>41%</td>
</tr>
<tr>
<td>atorva 20</td>
<td>$24</td>
<td>41%</td>
</tr>
<tr>
<td>atorva 80 tab</td>
<td>$31</td>
<td>48%</td>
</tr>
<tr>
<td>atorva 40</td>
<td>$49</td>
<td>48%</td>
</tr>
<tr>
<td>rosuva 40 tab</td>
<td>$795</td>
<td>52%</td>
</tr>
<tr>
<td>atorva 80</td>
<td>$61</td>
<td>53%</td>
</tr>
<tr>
<td>rosuva 40</td>
<td>$1590</td>
<td>56%</td>
</tr>
</tbody>
</table>
Copays Generic Tier 1 vs 2

- 2 Tiers for generics for half of our Medicare members (Senior Advantage Individual Plans) for 2012-13.
  - Tier 1 copay: $3 for 30 day supply, or $6 for 100 day supply with Mail Order. Simvastatin.
  - Tier 2 copay: $7 for 30 day supply, or $14 for 100 day supply with Mail Order. Atorvastatin, pravastatin.
- Same copay for members age ≤ 64, and for the other half of Medicare patients (Group Plans)

Performance

Lipid Control in CVC
Lipid Control in Diabetes

IVD – Ischemic Vascular Disease
aka “Cardiovascular Conditions” to HEDIS

- post MI, post CABG, post PCTA, angina.
- Peripheral arterial disease.
- Status post stroke, lacunar infarcts, TIA, carotid artery occlusion

Finding the inclusion code:
Abdominal Aorta Screening

Screening increased from 51% to 60% in less than 6 months.

Abdominal Aortic Aneurysm (AAA) is considered CAD “risk equivalent” by NHLBI / ATP and KP guidelines
– statins and LDL < 100 control recommended.
– is part of our “CAD” POINT registry for targeting.

Diagnosis and Actions by Aortic Diameter

≤ 2.4 cm: Normal diameter. (check for aortic athero)

2.5–2.9 cm: Aortic Ectasia, place on problem list. Consider statin, esp if 10yr CVD risk > 10%.

≥ 3.0 cm: Abdominal Aortic Aneurysm (AAA), start statin, code and place on problem list.

≥ 4.0 cm: above actions, plus routine referral to vascular surgery.

≥ 6.0 cm: above actions, plus URGENT referral to vascular surgery.

Aortic Ectasia. 2.5 - 2.9 cm

<table>
<thead>
<tr>
<th>Risk</th>
<th>Hazard Ratio (crude)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td>1.60 (1.07 – 2.37)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.59 (1.16 – 2.18)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.85 (1.39 – 2.46)</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>1.46 (1.05 – 2.02)</td>
</tr>
<tr>
<td>Vascular Mortality</td>
<td>1.77 (1.20 – 2.63)</td>
</tr>
</tbody>
</table>

Duncan JL et al. BMJ 2012 May 4; 344:e2958
Aortic Atherosclerosis and Aortic Ectasia

- Although not automatic "risk equivalents", these diagnoses can be used to promote cardiovascular health.
- Imaging results can be used as opportunity to promote statin starts and adherence.

CAD 10 year Risk Assessment and Treatment Tools

Available now:
- KP Pocket Version
- Online Bookmarked

Men 65-69 Years Old
Framingham risk score calculator.
Recent expanded availability.
Revised to ASCVD risk, Spring 2013

Start atorvastatin 40 mg daily

Pre-statin and latest FRS are calculated and shown above.
FRS ≥ 10 %: atorvastatin 40 mg

Artery image in-person patient education.
Tear-off pads or posters, English or Spanish, illiterate.
Order from Health Education and use in exam rooms.
Give 100 day supply
To Keep Arteries Open in sig.
Spanish version: para mantener las arterias abiertas.
Q: “How long do I need to take?”
A: “As long as you want to keep your arteries open.”

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Encouraging Letter

Dear Mr. ,

Your cholesterol is much improved! Congratulations! Continue your cholesterol medicine to help keep your arteries open.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOL</td>
<td>&lt;200</td>
<td>338 [H]</td>
<td>179</td>
</tr>
<tr>
<td>TRIG</td>
<td>&lt;150</td>
<td>268 [H]</td>
<td>164 [A]</td>
</tr>
<tr>
<td>HDL</td>
<td>&gt;40</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>LDL CALC</td>
<td>&lt;100</td>
<td>235 [H]</td>
<td>94</td>
</tr>
<tr>
<td>CHOL, HDL</td>
<td>&lt;5.0</td>
<td>6.9 [H]</td>
<td>3.7</td>
</tr>
<tr>
<td>ALT</td>
<td>17 - 63 units/L</td>
<td>64 [H]</td>
<td>40</td>
</tr>
</tbody>
</table>

Be well,
Ron Scott, MD
800-954-8000

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Safety / Intolerance Issues and updates
Diabetes Risk of statins

- JUPITER analysis broke down population. Impact of rosuvastatin 20 mg daily:
  - in those without RF for DM, 86 CV events prevented, and 0 cases of increased DM.
  - In those with RF for DM, 134 CV events prevented (MI, stroke, death) and 54 new cases of DM (28% increase).
  - 40 day acceleration of progression to DM.
- Diabetes risk related to statin potency. Example:
  - 10 yr A risk > x% → atorvastatin 40 mg
  - 10 yr A risk y% → atorvastatin 20 mg


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Increased baseline ALT → increased statin benefit?

- GREACE study: rr of recurrent cardiovascular event:
  - Elevated liver tests NAFLD: 68%
  - Normal liver function: 39%
- Consistent with other studies that those with NAFLD and steatohepatitis are at higher CV risk and may benefit more from statins.
- The FDA statin labeling change 2/28/12 "revised to remove the need for routine periodic monitoring of liver enzymes."
statin muscle issues

- Check and treat low TSH before starting therapy. If sx, double check if recent TSH.
- Consider treating low vitamin D. About 90% resolution of myopathy sx in 3 small studies.
- Risk Factors: interacting meds, low GFR, statin dose relative to max, older age, female, cirrhosis . . .
- Co Q 10, creatine . . . Mixed or very little evidence.

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<table>
<thead>
<tr>
<th>Simvastatin</th>
<th>Fluya</th>
<th>Pitavastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Fluvarasila</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg</td>
<td>40 mg</td>
<td>4 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>40 mg</td>
<td>20 mg</td>
<td>2 mg</td>
<td>10 mg</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>20 mg</td>
<td>10 mg</td>
<td>1 mg</td>
<td>20 mg</td>
<td>10 mg</td>
<td>80 mg*</td>
</tr>
<tr>
<td>10 mg</td>
<td>5 mg</td>
<td>1 mg</td>
<td>20 mg</td>
<td>40 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>5 mg</td>
<td>4 mg</td>
<td>20 mg</td>
<td>40 mg</td>
<td>80 mg*</td>
<td>40 mg</td>
</tr>
<tr>
<td>1 mg</td>
<td>4 mg</td>
<td>80 mg</td>
<td>20 mg</td>
<td>40 mg</td>
<td>53%</td>
</tr>
<tr>
<td>20 mg</td>
<td>2 mg</td>
<td>80 mg</td>
<td>40 mg</td>
<td>53%</td>
<td>58%</td>
</tr>
<tr>
<td>10 mg</td>
<td>1 mg</td>
<td>40 mg</td>
<td>20 mg</td>
<td>58%</td>
<td>58%</td>
</tr>
</tbody>
</table>

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Muscle SE - options

- Try lower doses and less frequent dosing.
- Low dose statin often with better tolerance.
  - atorvastatin 10 mg daily 34% lowering.
  - rosuvastatin 5 mg daily 41% lowering.
- If still not tolerating decrease frequency (atorvastatin or rosuvastatin most studied) to 1-2 x a week.
- If not tolerate any statin, red yeast rice?
Red Yeast Rice – has issues

Arch Intern Med Oct 2010

Beyond Statins

- Priority is to optimize statin first, before going beyond statins to other lipid treatments.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost/yr</th>
<th>% LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin 10 mg</td>
<td>$12</td>
<td>34 %</td>
</tr>
<tr>
<td>Red yeast rice + s</td>
<td>$114</td>
<td>17 %</td>
</tr>
<tr>
<td><strong>“Add On Therapies”</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stanol Chews</td>
<td>$150-300 (OTC)</td>
<td>5-9 %</td>
</tr>
<tr>
<td>Or sterols</td>
<td>$95 (OTC)</td>
<td>9 %</td>
</tr>
<tr>
<td>ezetimibe 10 ½ tab</td>
<td>$540 (brand)</td>
<td>10 %</td>
</tr>
<tr>
<td>cholestipol bid</td>
<td>$550 (gen)</td>
<td>10 %</td>
</tr>
<tr>
<td>slo-niacin 500 bid</td>
<td>$50 (OTC)</td>
<td>5 %</td>
</tr>
</tbody>
</table>

Factors to consider: tolerability, patient preference and cost, desired lipid changes

Lyon Diet Heart Study: Cumulative Survival without Cardiac Death and Nonfatal MI

- Camola oil–based margarine, fiber, low cholesterol, low saturated fat, fruits, vegetables
- Experimental vs. Control
- P = 0.0001
**Dietary Interventions**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>%↓ LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce saturated fat from 11 to &lt;7%</td>
<td>8-10%</td>
</tr>
<tr>
<td>Dietary cholesterol &lt; 200 mg/day</td>
<td>3-5%</td>
</tr>
<tr>
<td>Losing 10 lbs</td>
<td>5-8%</td>
</tr>
<tr>
<td>Viscous fiber 5-10 g / day</td>
<td>3-5%</td>
</tr>
<tr>
<td>2 g plant stanols / sterols</td>
<td>10-15%</td>
</tr>
<tr>
<td>Soy</td>
<td>2-3%</td>
</tr>
<tr>
<td>Total</td>
<td>20-35%</td>
</tr>
</tbody>
</table>

**Plant Stanols / sterols**

- 2 chews BID, $300/yr ↓ LDL 9%
- 1 chew BID, $150/yr, ↓ LDL 5%
- 2 caps BID, $95/yr, ↓ LDL 9%

NIH recommends 2 g daily.
- Dietary source is fat rich vegetables, fruits, and nuts
- Avg American gets 0.2 g daily
- Should not use in sitosterolemia - where pts get xanthomas and CAD from inability to process plant stanols

**Ezetimibe (Zetia)**

- Well tolerated, moves LDL well.
- Mixed results in imaging studies.
- Simvastatin / ezetimibe reduced events in SHARP study.
- Await good event outcome data comparing statin alone to statin + ezetimibe (IMPROVE-IT).
- Brand – cost about $540/yr (for ½ tab).
- Cost to pt depends on drug benefit.
Resins / Bile Acid Sequestrants (BAS)

- Lowers LDL about 23% (monotherapy)
- Favorable mono and combo outcome studies.
- Cholestyramine powder (Questran), 1 scoop BID: $364
- Colestipol powder or tab bid: $550
- SE: Constipation, dyspepsia, can raise elevated TG, interferes with absorption of other meds (need to space timing).

Niacin Controlled Release

- 500 mg bid
- LDL 5%, HDL 15% $ 51 / y
- Contraindicated with liver disease and active peptic ulcer disease.
- Can use in DM and gout with monitoring.
- 500 mg scored tabs ½ tab after dinner for 1 week, ½ tab bid for 1 week, then 1 tab po bid from then on.
- Time aspirin (if taking) before dinner and niacin controlled release after dinner to ↓ flushing.
- Flushing wanes over 2-3 months.

TG Guidance
For those that have indication for statins

1. If indication for statin, start statin. If TG are still ≥ 200, optimize potential contributing factors (hyperglycemia, excess alcohol, hypothyroid, obesity, medicines) and lifestyle interventions. If TG are still ≥ 500,
2. Add/ or increase EPA/DHA to 3-4 g daily and retest. If TG still ≥ 500:
   - consider add niacin
   - consider intensify atorvastatin
   - Revisit / optimize 1 and 2 above.
   - consider adding fenofibrate (GFR ≥ 30-45, sub maximal dose statin)
Both the KP and Costco Kirkland Omega-3 Fish Oil contain 684 mg of Omega-3 Fatty Acids per softgel. Please look for Fish Oil supplements containing at least 684 mg of Omega-3 Fatty Acids per softgel.

5 caps / day = 3420 mg of Omega 3 for $113 / year.

Question

In JUPITER, rosuvastatin (Crestor) 20 mg (52% LDL lowering) showed risk reduction of MI, and of combined endpoint of MI, stroke, revascularization, CV death of:

A) MI 55% and combined endpoint 44%.
B) MI 50% and combined endpoint 40%.
C) MI 40% and combined endpoint 33%.

Question

Which of the following is True

A) CV Benefit is proportionate to statin LDL lowering, including LDLs down into the 40s.
B) HPS and JUPITER showed average NNT of 10 to 25, to prevent MI, stroke, revascularization, or death over 5 years.
C) NNT to reduce events and mortality among those with FRS < 10 in JUPITER is 39.
D) All of the above
Overview

- Lipids and CAD risk
  - Large shortfall in lipid control / statin use
  - Large statin benefit - opportunity

Optimizing Performance

- Identifying patients
- Promoting starts and adherence
- Safety / intolerance of statins
- Beyond statins

Use tools and prevention to improve outcomes

- Use tools and prevention:
  - Integrated data / IT – proactive care, CMSS, HC
  - Artery graphic, patient relationship, clinical skill
  - Teamwork – (care managers)
  - Inexpensive generic atorvastatin

- To improve outcomes:
  - Reduced CVD morbidity / mortality.
  - Reduce costly CVD procedures, hospitalizations, and morbidity care.