New Paradigms for Cardiovascular Prevention

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Disclosures

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Global Obesity Epidemic BMI trends

Cardiovascular Prevention

- Lifestyle is foundation for population-based CVD risk reduction
- Low adherence to healthy lifestyle habits in modern industrial societies
- High rates obesity in children, adolescents, and adults
- Medical therapy is needed to reduce CVD risk in absence of healthy lifestyles

Limitations “late” utilization of evidence-based medications

• Continued risk of CVD events on treatment
  • Large burden of atherosclerosis
  • Suboptimal adherence to medications
  • Suboptimal adherence to lifestyle
  • Suboptimal control of risk factors

Start statin earlier to prevent more events

Start moderate intensity statin
15% 10-year ASCVD risk

Start high intensity statin
5% 10-year ASCVD risk

No statin

ADDITIONAL ASCVD EVENTS & DEATHS PREVENTED

Advancing age

Adapted from Robinson JG, Gidding SS. Curing Atherosclerosis Should Be the Next Major Cardiovascular Prevention Goal. JACC. 2014;63(25, Part A):2779-2785
Start statin earlier
Evidence

Greater relative risk reduction CVD events from statins in lower risk than in higher risk individuals
But, CVD events still occur in low risk persons

<table>
<thead>
<tr>
<th>5-year MVE risk at baseline</th>
<th>Events (% per annum)</th>
<th>RR (CI) per 1.0 mmol/L reduction in LDL cholesterol</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin/more</td>
<td>Control/less</td>
<td></td>
</tr>
<tr>
<td>Participants without vascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>148 (0.35)</td>
<td>229 (0.53)</td>
<td>0.61 (0.45-0.81)</td>
</tr>
<tr>
<td>≥5% to &lt;10%</td>
<td>487 (1.02)</td>
<td>716 (1.53)</td>
<td>0.66 (0.57-0.77)</td>
</tr>
<tr>
<td>≥10% to &lt;20%</td>
<td>854 (2.52)</td>
<td>1003 (2.98)</td>
<td>0.82 (0.72-0.93)</td>
</tr>
<tr>
<td>≥20% to &lt;30%</td>
<td>294 (4.40)</td>
<td>351 (5.28)</td>
<td>0.81 (0.65-1.01)</td>
</tr>
<tr>
<td>≥30%</td>
<td>121 (7.29)</td>
<td>126 (8.16)</td>
<td>0.83 (0.58-1.18)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1904 (1.44)</td>
<td>2425 (1.84)</td>
<td>0.75 (0.70-0.80)</td>
</tr>
</tbody>
</table>

*1 mmol/L (39 mg/dl) LDL-C reduction was the average in the primary prevention RCTs excluding JUPITER CTT Collaborators. Lancet 2012; 380: 581-590.
Start statin earlier
Evidence

Total mortality reduction in lower risk individuals
CVD death still occur in low risk persons

<table>
<thead>
<tr>
<th>5-year MVE risk at baseline</th>
<th>Deaths (% per annum)</th>
<th>RR (CI) per 1.0 mmol/L reduction in LDL cholesterol</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants without vascular disease</td>
<td>Statin/more</td>
<td>Control/less</td>
<td></td>
</tr>
<tr>
<td>&lt; 5%</td>
<td>164 (0.38)</td>
<td>177 (0.41)</td>
<td>0.94 (0.71 - 1.26)</td>
</tr>
<tr>
<td>≥ 5%,&lt;10%</td>
<td>372 (0.77)</td>
<td>446 (0.93)</td>
<td>0.83 (0.69 - 0.99)</td>
</tr>
<tr>
<td>≥ 10%,&lt;20%</td>
<td>703 (1.99)</td>
<td>778 (2.19)</td>
<td>0.88 (0.76 - 1.02)</td>
</tr>
<tr>
<td>≥ 20%,&lt;30%</td>
<td>363 (5.13)</td>
<td>339 (4.73)</td>
<td>1.06 (0.86 - 1.32)</td>
</tr>
<tr>
<td>≥ 30%</td>
<td>192 (10.76)</td>
<td>192 (11.44)</td>
<td>0.94 (0.70 - 1.25)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1794 (1.33)</td>
<td>1932 (1.42)</td>
<td>0.91 (0.85 - 0.97)</td>
</tr>
</tbody>
</table>

*1 mmol/L (39 mg/dl) LDL-C reduction was the average in the primary prevention RCTs excluding JUPITER CTT Collaborators. Lancet 2012; 380: 581-590.
ECAD - Eliminate Coronary Artery Disease trial

- Men 35-50 y & women 45-59 years
  - Canada & Mexico
  - N=10,000-15,000; Recruitment started Aug 2014
- Primary prevention LDL-C $\geq$ 70 mg/dl
- Risk factor (smoking, hypertension, truncal obesity, family history premature MI, S Asian ancestry)
- Atorvastatin 20 mg vs control X 10 years
- 1° endpoint: Nonfatal MI or stroke, coronary revascularization, non-cancer/trauma death
- 2° endpoints: include new onset diabetes

Familial Hypercholesterolemia - Early treatment essential

Nordestgaard BG et al. EHJ 2013; Dec 1; 34(45): 3478–3490
Carotid Artery of 20 year old male with Heterozygous Familial Hypercholesterolemia

Courtesy of Sam Gidding MD
Or, try to cure atherosclerosis

• Why?
  • CVD remains the leading cause of death & major cause of morbidity in US & globally
  • Eliminating major CVD would increase life expectancy by almost 7 years
  • CVD #1 cause of healthcare expenditures
  • Total CVD costs expected to triple by 2030 as population ages

Atherosclerosis progression with age

ASCVD EVENTS
- MI/Unstable angina
- Ischemic stroke/TIA
- Critical leg ischemia
- Intermittent claudication
- CV death

Start LDL-C lowering early to regress disease “CURE”
LDL-C lowering started late
Large burden of atherosclerosis
STABILIZATION

Illustration Adapted from Libby P. Circulation. 2001;104:365-372.
No Apparent Lower LDL-C Limit
CVD Risk Reduction or Regression for Statins

Relative reduction CVD Risk by Achieved LDL-C level (mg/dl)

<table>
<thead>
<tr>
<th>LDL-C Level (mg/dl)</th>
<th>Relative Reduction CVD Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>-56</td>
</tr>
<tr>
<td>50-74</td>
<td>-49</td>
</tr>
<tr>
<td>75-99</td>
<td>-44</td>
</tr>
<tr>
<td>100-124</td>
<td>-42</td>
</tr>
<tr>
<td>125-149</td>
<td>-36</td>
</tr>
<tr>
<td>150-174</td>
<td>-29</td>
</tr>
<tr>
<td>&gt;175</td>
<td>REF</td>
</tr>
</tbody>
</table>

Individual level meta-analysis adjusted for sex, age, smoking, diabetes, SBP, HDL-C

18-24 months rosuvastatin 40 mg or atorvastatin 80 mg (n=1881)
TAV: Total atheroma volume on IVUS

No Apparent Lower LDL-C Limit to Regression with PCSK9 mAb Added to Statin - GLAGOV

Aggressive LDL-C lowering – Animal models

• LDL-C<30 mg/dl
• Regress atherosclerosis
• Completely regress early atherosclerosis
• Partially regress fibrotic, mature, advanced plaque
• Works better with functional HDL

Aggressive LDL-C lowering can normalize arterial function

• Humans
  • Statins modestly lower blood pressure in younger individuals

• Animal models
  • Endothelial dysfunction from prolonged hypercholesterolemia-induced atherosclerosis is a result of abnormal nitric oxide responses
  • Nitric oxide responses completely normalize with aggressive LDL-C lowering

Robinson JG, Gidding SS. JACC. 2014;63(25, Part A):2779-2785
Response to retention model of atherosclerosis initiation & progression

REGRESSION

• Reduce plasma LDL-C & other apoB-lipoproteins
• Reduce uptake
• Allow normal scavenger/clearance mechanisms to “heal” the plaque

Legacy effects in statin RCTs

Cardiovascular events WOSCOPS: Pravastatin vs placebo for 5 y; 15 y FU

All-cause mortality ASCOT: Atorvastatin vs placebo 3.3 y; 8 y FU

Average Non-HDL-C <130 mg/dl (3.4 mmol/L) (≈ LDL-C <100 mg/dl) before age 55 Low CHD risk

New paradigm: Curing atherosclerosis
Resetting the (vascular aging) clock

Robinson JG, Gidding SS. Curing Atherosclerosis Should Be the Next Major Cardiovascular Prevention Goal. JACC. 2014;63(25, Part A):2779-2785
Can we regress (cure) atherosclerosis?

Can we capitalize on a long-term legacy effect from plaque stabilization?

REGRESSION
PCSK-9 inhibitor + Statin

MAINTENANCE
Prevent new plaque formation
Max statin/ezetimibe

Normalization of artery

Options for LDL-C lowering

- Statins
  - Moderate intensity $\downarrow$ LDL-C 30-35%
  - High intensity $\downarrow$ LDL-C 50-55%
- Ezetimibe
- PSCK9 inhibitors

Ezetimibe vs Alirocumab
CVD patients on background statin therapy

Achieved LDL-C Over Time on Background of Maximally-Tolerated Statin

Week

0 4 8 12 16 20 24 28 32 36 40 44 48 52

Dose ↑ if LDL-C >70 mg/dL at W8

Ezetimibe 10 mg

2.1 mmol/L
82.5 mg/dL

2.2 mmol/L
85.3 mg/dL

1.3 mmol/L
51.6 mg/dL

1.4 mmol/L
53.3 mg/dL

Alirocumab 75/150 mg q2w

1.2 mmol/L
44.1 mg/dL

1.1 mmol/L
40.5 mg/dL

mg/dL

Cannon C, et al. COMBO II. Eur Heart J 2015; 36, 1186-1194
LDL-C lowering efficacy of PCSK-9 mAbs
Background statin therapy

Alirocumab 75 mg q2W
Alirocumab 75/150 mg q2W
Alirocumab 150 mg q2W
Evolocumab 140 mg q2W
Evolocumab 420 mg q4W

-48% -47%  
-54%  
-63% -62%  
-61%  
-60% -63%  

Heterozygous Familial Hypercholesterolemia  
Clinical ASCVD

Achieved LDL-C with PCSK-9 mAbs

**Heterozygous Familial Hypercholesterolemia Added to background statin/lipid-lowering therapy**

- **ODYSSEY FH I & II** – Alirocumab 75/150 mg LDL-C -51-58%
- **Statin/LLT+ Alirocumab** Mean LDL-C 135-154 mg/dl → 69 mg/dl

**High CV Risk Added to background statin therapy**

- **LAPLACE-2** – Evolocumab: High risk LDL-C >70 mg/dl
  - Randomized to moderate or high intensity statin
  - Re-randomized to Evolocumab (140 mg q2W vs 420 q4W) or placebo X 12 weeks
  - LDL-C -63-64% vs placebo
- **Moderate intensity statin + Evolocumab** Mean LDL-C 115-124 mg/dl → 39-49 mg/dl
- **High intensity statin + Evolocumab** Mean LDL-C 89-94 mg/dl → 33-35 mg/dl

PCSK9 mAbs: Preliminary data - CVD event reduction

ODYSSEY LONG TERM – Alirocumab 150 mg q2W
Mean 80 week follow-up

OSLER – Evolocumab 140 q2W/420 q4W
Mean 11 month follow-up

HR 0.52 (95% CI 0.31-0.90)
Nominal P =0.02

HR 0.47 (95% CI 0.28-0.78)
P=0.003

CVD=cardiovascular disease; HR=hazard ratio; PCSK9=proprotein convertase subtilisin/kexin Type 9.
Ezetimibe, PCSK-9 mAbs and the CTT Statin line

- IMPROVE-IT ezetimibe major CVD: 1.81 → 1.40 mmol/l
- IMPROVE-IT ezetimibe hard CVD
- ODYSSEY LONGTERM OSLER I & II: 3.1 → 1.24 mmol/l
- ODYSSEY pooled

Proportional reduction in event rate (SE) vs. Reduction in LDL cholesterol (mmol/L)
Magnitude of PCSK-9 mAb CV Risk Reduction & Longer-term Safety Awaits CV Outcomes Trials

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab</th>
<th>Evolocumab</th>
<th>Bococizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Min LDL-C</strong></td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>(mg/dL)</strong></td>
<td>ACS 18,000</td>
<td>CVD 27,500</td>
<td>CVD HR PP 12,000</td>
</tr>
<tr>
<td><strong>≥70</strong></td>
<td>≥70</td>
<td>≥70</td>
<td>≥70 &amp; &lt;100</td>
</tr>
<tr>
<td><strong>≥70 &amp; &lt;100</strong></td>
<td></td>
<td></td>
<td>≥70 &amp; &lt;100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

## Safety of PCSK9 mAbs

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Comparison</th>
<th>Duration</th>
<th>Placebo vs Alirocumab 150 mg Q2W, 80 weeks</th>
<th>Placebo vs Evolocumab 420 mg, 52 weeks</th>
<th>Standard care Evolocumab 420 mg Q4W or 140 mg Q2W, 11 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODISSEY LONG TERM</td>
<td>Placebo vs Alirocumab 150 mg Q2W, 80 weeks</td>
<td>80 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DESCARTES</td>
<td>Placebo vs Evolocumab 420 mg, 52 weeks</td>
<td>52 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSLER I &amp; II</td>
<td>Standard care Evolocumab 420 mg Q4W or 140 mg Q2W, 11 months</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (%)</th>
<th>Alirocumab (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>4.2%</td>
<td>5.9%</td>
<td>0.10</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2.9%</td>
<td>5.4%</td>
<td>0.006</td>
</tr>
<tr>
<td>Neurocognitive AEs</td>
<td>0.5%</td>
<td>1.2%</td>
<td>0.17</td>
</tr>
<tr>
<td>Ophthalmologic AEs</td>
<td>1.9%</td>
<td>2.9%</td>
<td>0.65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (%)</th>
<th>Evolocumab (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reaction</td>
<td>5.0%</td>
<td>5.7%</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>3.0%</td>
<td>4.0%</td>
<td></td>
</tr>
<tr>
<td>URIs</td>
<td>6.3%</td>
<td>9.3%</td>
<td></td>
</tr>
<tr>
<td>ALT &gt; 3X ULN</td>
<td>1.0%</td>
<td>0.8%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (%)</th>
<th>Evolocumab (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>NA</td>
<td>4.3%</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>3.0%</td>
<td>4.0%</td>
<td></td>
</tr>
<tr>
<td>URIs</td>
<td>6.0%</td>
<td>6.4%</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive AEs</td>
<td>0.3%</td>
<td>0.9%</td>
<td></td>
</tr>
</tbody>
</table>

### Post hoc CVD events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (%)</th>
<th>Alirocumab (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post hoc CVD events</td>
<td>3.3%</td>
<td>1.7%</td>
<td>0.02</td>
</tr>
<tr>
<td>HR 0.52 (0.31-0.90;P=0.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### “Exploratory” CVD events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (%)</th>
<th>Evolocumab (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Exploratory” CVD events</td>
<td>2.18%</td>
<td>0.95%</td>
<td>0.003</td>
</tr>
<tr>
<td>HR 0.47 (0.28-0.78;P=0.003)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AEs=adverse events; ALT=alanine aminotransferase; CVD=cardiovascular disease; HR=hazard ratio; Q2W=every 2 weeks; Q4W=every 4 weeks; SC=standard care; ULN=upper limit of normal; URIs=upper respiratory infections.

Safety of Very Low LDL-C - LDL-C <25/15 mg/dl
Pooled ODYSSEY trials & ODYSSEY LONG TERM

Select Treatment Emergent Adverse Events ≥2% Incidence

<table>
<thead>
<tr>
<th>Primary system organ class, % (n)</th>
<th>Pooled control (n=1894)</th>
<th>Pooled alirocumab ≥2 LDL-C &lt;25 mg/dL (n=796)</th>
<th>Pooled alirocumab ≥2 LDL-C &lt;15 mg/dL (n=288)</th>
<th>LONG TERM alirocumab ≥2 LDL-C &lt;25 mg/dL (n=562)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>25.2 (478)</td>
<td>24.2 (808)</td>
<td>21.1 (168)</td>
<td>20.1 (58)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>14.9 (283)</td>
<td>14.9 (497)</td>
<td>10.3 (82)</td>
<td>9.0 (26)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.1 (1)</td>
<td>0.1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.3 (24)</td>
<td>1.2 (39)</td>
<td>1.5 (12)</td>
<td>2.4 (7)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>0.9 (17)</td>
<td>0.8 (26)</td>
<td>1.5 (12)</td>
<td>2.4 (7)</td>
</tr>
</tbody>
</table>

# Propensity Analysis - Risk of Selected Adverse Events of Interest in Patients with LDL-C <25 mg/dL in Pooled Alirocumab Trials

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>LDL-C ≥25 mg/dL (n=2371)</th>
<th>LDL-C &lt;25 mg/dL (n=811)</th>
<th>HR (95% CI) for LDL-C &lt;25 versus ≥25 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological events</td>
<td>4.4 (104)</td>
<td>2.5 (20)</td>
<td>0.53 (0.30–0.93)</td>
</tr>
<tr>
<td>Neurocognitive disorders</td>
<td>1.1 (25)</td>
<td>0.6 (5)</td>
<td>0.38 (0.13–1.09)</td>
</tr>
<tr>
<td>Musculoskeletal events</td>
<td>17.0 (403)</td>
<td>14.2 (115)</td>
<td>0.75 (0.59–0.97)</td>
</tr>
<tr>
<td>DM or diabetic complications event (patients with or without diabetes at baseline)</td>
<td>4.0 (94)</td>
<td>6.0 (49)</td>
<td>1.09 (0.72–1.65)</td>
</tr>
<tr>
<td>DM or diabetic complications event (patients with diabetes at baseline)</td>
<td>9.2 (62)</td>
<td>12.0 (37)</td>
<td>1.05 (0.66–1.68)</td>
</tr>
<tr>
<td>Ophthalmologic events</td>
<td>2.0 (47)</td>
<td>1.6 (13)</td>
<td>0.64 (0.31–1.31)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>0.8 (19)</td>
<td>2.6 (21)</td>
<td>3.40 (1.58–7.35)*</td>
</tr>
</tbody>
</table>

Robinson JG, et al. Presented at European Society of Cardiology Congress, August 2016, Rome, Italy
Patients Homozygous for PCSK9 Loss-of-function Mutations

- Only a small number of patients who are homozygous (or compound heterozygotes) for PCSK9 have been discovered and studied
- These patients appear to have:
  - Very low LDL-C levels (~10-20 mg/dL)
  - Relatively low TG levels
  - Normal HDL-C levels
  - Otherwise healthy, normal individuals

LOF=loss of function; TG=triglyceride.
New paradigm? Curing atherosclerosis
Resetting the (vascular aging) clock

Robinson JG, Gidding SS. Curing Atherosclerosis Should Be the Next Major Cardiovascular Prevention Goal. JACC. 2014;63(25, Part A):2779-2785
Take home message

• Continue to emphasize healthy lifestyles & risk factor control
• Current efforts are not enough – CVD remain leading cause of death in the world
• RCTs testing new prevention paradigms needed