Lipoprotein Particles

- Chylomicron
- VLDL
- Remnants
- LDL
- -R
- HDL
- 2
- HDL3
- DL3
- IDL
- Lp(a)

Only these lipoprotein particles found in plaque at biopsy.
High Plasma Apo B Lipoprotein Levels Promote Atherogenesis
Anti-atherosclerotic therapy

From Davies et al (1998)
There Is a Strong Relationship Between CVD Risk and the Presence of Dyslipidemia: Framingham

CVD Risk (probability per 1000 over 8 years), %

Total Cholesterol (mg/dL)

Total Cholesterol Distribution: 
CHD vs Non-CHD Population

35% of CHD Occurs in People with TC<200 mg/dL
Low HDL-C Levels Increase CHD Risk Even When Total-C Is Normal

Risk of CHD by HDL-C and Total-C levels; aged 48–83 y

Castelli WP et al. JAMA 1986;256:2835–2838

HDL-C (mg/dL)

Total-C (mg/dL)

14-y incidence rates (%) for CHD
US age-standardized death rates attributable to CVD, 2000 to 2010

Mean age-adjusted LDL-C trends 2001–2011 in the United States: Analysis of 105 million patient records from a single national diagnostic laboratory

LDL cholesterol and benefit in clinical trials
Is lower better?

- LDL-C achieved mg/dL (mmol/L)
- WOSCOPS – Placebo
- AFCAPS – Placebo
- ASCOT – Placebo
- HPS – Placebo
- LIPID – Placebo
- CARE – Placebo
- PROVE-IT – PRA
- PROVE-IT – ATV
- TNT – ATV10
- TNT – ATVS0
- JUPITER

Rx - Statin therapy
PRA – pravastatin
ATV - atorvastatin

Event rate (%) vs. LDL-C achieved mg/dL (mmol/L)

Adapted from Rosensen RS. Exp Opin Emerg Drugs 2004; 9(2):269-279

TNT
PROVE-IT
JUPITER
Consistent Relationship Between LDL-C Reduction and CHD Relative Risk for all LDL-C-lowering Treatments

On-Treatment LDL-C and CHD Events in Primary Prevention

\[ y = 0.046x - 1.53 \]
\[ R^2 = 0.95 \]

% with CHD Events, Projected to 5 Years

Mean or Median LDL-C, mg/dL

Data abstracted from original publications
On-Treatment LDL-C and CHD Events in Secondary Prevention

![Graph showing the relationship between on-treatment LDL-C level at follow-up (mg/dL) and percentage with CHD event.]

TNT: Treatment Effects on LDL-C

Treating to New Targets (TNT) in Stable CHD Patients: LDL-C Results and Primary Endpoint

Mean LDL-C Value (mg/dL)

- Atorvastatin 10 mg: ~77 mg/dL
- Atorvastatin 80 mg: ~100 mg/dL

Patients with Major CV Event (%)

- RRR: 22%
- ARR: 3.2%
- NNT: 31

TNT: Changes in LDL-C by Treatment Group

![Graph showing changes in LDL-C levels over time for Atorvastatin 10 mg (n=5006) and Atorvastatin 80 mg (n=4995).]

- **Baseline**: Mean LDL-C level = 101 mg/dL (2.6 mmol/L)
- **Final Screen**: Mean LDL-C level = 77 mg/dL (2.0 mmol/L)

TNT: Primary Efficacy Outcome Measure: Major Cardiovascular Events*

*CHD death, nonfatal non–procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke.

### Criteria for ASCVD Risk Assessment, Treatment Goals, Levels at which to Consider Drug Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goal</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong></td>
<td>▪ 0-1 major ASCVD risk factors&lt;br&gt;▪ Consider other risk indicators, if known</td>
<td>&lt;130&lt;br&gt;&lt;100</td>
<td>≥190&lt;br&gt;≥160</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>▪ 2 major ASCVD risk factors&lt;br&gt;▪ Consider quantitative risk scoring&lt;br&gt;▪ Consider other risk indicators</td>
<td>&lt;130&lt;br&gt;&lt;100</td>
<td>≥160&lt;br&gt;≥130</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>▪ ≥3 major ASCVD risk factors&lt;br&gt;▪ Diabetes mellitus* (Type 1 or 2)&lt;br&gt;▪ 0-1 other major ASCVD risk factors, and&lt;br&gt;▪ No evidence of end organ damage&lt;br&gt;▪ Chronic kidney disease stage 3B or 4&lt;br&gt;▪ LDL-C ≥190 mg/dL (severe hypercholesterolemia)&lt;br&gt;▪ Quantitative risk score reaching the high-risk threshold</td>
<td>&lt;130&lt;br&gt;&lt;100</td>
<td>≥130&lt;br&gt;≥100</td>
</tr>
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<td>▪ ASCVD*&lt;br&gt;▪ Diabetes mellitus* (Type 1 or 2)&lt;br&gt;▪ ≥2 other major ASCVD risk factors or&lt;br&gt;▪ Evidence of end organ damage</td>
<td>&lt;100&lt;br&gt;&lt;70</td>
<td>≥100&lt;br&gt;≥70</td>
</tr>
</tbody>
</table>

*For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate- or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

Patient with HoFH

- 28 year-old female
- Cutaneous xanthomas beginning at age 3
- Obstructive coronary artery disease and CABG at age 12
- LDL cholesterol = 780 mg/dL
Clinical Characteristics FH

- Tendinous Xanthomas (any age)
- Corneal Arcus (<45yo)
- Tendinuous Xanthomas (any age)
- Xanthelasma (<25yo)
Four Major Statin Benefit Groups

1) Individuals with clinical ASCVD
2) Individuals with LDL >190
3) Individuals with dm, 40-75 yo with LDL 70-189 and without clinical ASCVD
4) Individuals without clinical ASCVD or dm with LDL 70-189 and estimated 10-year ASCVD risk >7.5%
4 Statin Benefit Groups

- Clinical ASCVD*
- LDL–C ≥190 mg/dL, Age ≥21 years
- Primary prevention – Diabetes: Age 40-75 years, LDL–C 70-189 mg/dL
- Primary prevention - No Diabetes†: ≥7.5%‡ 10-year ASCVD risk, Age 40-75 years, LDL–C 70-189 mg/dL,

* Atherosclerotic cardiovascular disease
† Requires risk discussion between clinician and patient before statin initiation.
‡ Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator.
**Intensity of Statin Therapy**

### Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
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<td><strong>Atorvastatin (40†)–80 mg</strong></td>
<td><strong>Atorvastatin 10 (20) mg</strong></td>
<td><strong>Simvastatin 10 mg</strong></td>
</tr>
<tr>
<td><strong>Rosuvastatin 20 (40) mg</strong></td>
<td><strong>Rosuvastatin (5) 10 mg</strong></td>
<td><strong>Pravastatin 10–20 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Simvastatin 20–40 mg‡</strong></td>
<td><strong>Lovastatin 20 mg</strong></td>
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<td><strong>Lovastatin 40 mg</strong></td>
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<td></td>
<td><strong>Fluvastatin XL 80 mg</strong></td>
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<td><strong>Fluvastatin 40 mg bid</strong></td>
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*For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate- or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

Primary Prevention
Initiating Statin Therapy

No Clinical ASCVD
Not currently on cholesterol-lowering drugs
Initial evaluation prior to statin initiation
- Fasting lipid panel*
- ALT
- Hemoglobin A1c (if diabetes status unknown)
- CK (if indicated)
- Consider evaluation for other secondary causes (Table 6) or conditions that may influence statin safety (Table 8, Rec 1)

Evaluate and Treat Laboratory Abnormalities
1. Triglycerides ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   - Secondary causes (Table 6)
   - If primary, screen family for FH
3. Unexplained ALT >3X ULN

Assign to statin benefit group
(Figure 2)
Counsel on healthy lifestyle habits

Diabetes and age 40-75 y†
OR
LDL-C ≥190 mg/dL

No diabetes, age 40-75 y, and
LDL-C 70-189 mg/dL

*Fasting lipid panel preferred. In a nonfasting individual, a nonfasting non-HDL-C >220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are >500 mg/dL, a fasting lipid panel is required.
Primary Prevention

Initiating Statin Therapy (con’t)

- Estimate 10-y ASCVD risk with Pooled Cohort Equations
  - ≥7.5% 10-y ASCVD risk
  - 5% < 7.5% 10-y ASCVD risk
  - < 5% 10-y ASCVD risk
  - Age <40 or ≥75 y and LDL-C < 190 mg/dL

- Clinicians and patients should engage in a discussion of the potential for:
  1. ASCVD risk reduction benefits
  2. Adverse effects
  3. Drug-drug interactions
  4. Patient preferences

- In selected individuals, additional factors may be considered to inform treatment decision making:

- Initiate statin therapy (Figure 2)
- Re-emphasize healthy lifestyle habits
- Monitor statin therapy (Figure 5)

Note:

1. Potential ASCVD risk reduction benefits (e.g., absolute risk reduction from moderate- or high-intensity statin therapy can be approximated by using the estimated 10-year ASCVD risk and the relative risk reduction of ~30% for moderate-intensity statin or ~45% for high-intensity statin therapy.
2. Potential adverse effects. The excess risk of diabetes is the main consideration. In ~0.1 excess case per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin treated patients for 1 year. Note: a case of diabetes is not considered equivalent to a fatal or nonfatal MI or stroke. Both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin should be evaluated in Table 8, Safety Rec 8.
INTENSITY OF STATIN THERAPY IN PRIMARY AND SECONDARY PREVENTION

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

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STATIN SAFETY RECOMMENDATIONS

• SELECT THE APPROPRIATE DOSE

• KEEP POTENTIAL SIDE EFFECTS AND DRUG-DRUG INTERACTION IN MIND (GRADE A)

• IF HIGH OR MODERATE INTENSITY STATIN NOT TOLERATED, USE THE MAXIMUM TOLERATED DOSE INSTEAD
Individuals Not in a Statin Benefit Group

• In those for whom a risk decision is uncertain, these factors may inform clinical decision making:
  • Family history of premature ASCVD
  • Elevated lifetime risk of ASCVD
  • LDL-C ≥160 mg/dL
  • hs-CRP ≥2.0 mg/L
  • CAC score ≥300 Agaston units
  • ABI <0.9
• Statin use still requires discussion between clinician and patient
Management of Muscle Symptoms on Statin Therapy

• It is reasonable to evaluate and treat muscle symptoms including pain, cramping, weakness, or fatigue in statin-treated patients according to the management algorithm

• To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy
Management of Muscle Symptoms on Statin Therapy (cont.)

If unexplained severe muscle symptoms or fatigue develop during statin therapy:

• Promptly discontinue the statin
• Address possibility of rhabdomyolysis with:
  • CK
  • Creatinine
  • Urinalysis for myoglobinuria
Management of Muscle Symptoms on Statin Therapy (cont.)

If mild-to-moderate muscle symptoms develop during statin therapy:

• Discontinue the statin until the symptoms are evaluated
• Evaluate the patient for other conditions* that might increase the risk for muscle symptoms
• If after 2 months without statin Rx, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms

*Hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency or primary muscle diseases
Statin-Treated Individuals
Nonstatin Therapy Considerations

- Use the maximum tolerated intensity of statin
- Consider addition of a nonstatin cholesterol-lowering drug(s)
  - If a less-than-anticipated therapeutic response persists
  - Only if ASCVD risk-reduction benefits outweigh the potential for adverse effects in higher-risk persons:
    - Clinical ASCVD <75 years of age
    - Baseline LDL-C ≥190 mg/dL
    - Diabetes mellitus 40 to 75 years of age
- Nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs are preferred
IMPROVE-IT Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 50 – 125 mg/dL (or 50-100 mg/dL if prior lipid-lowering Rx)

Standard Medical & Interventional Therapy

N= 18,144

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (at least 5250 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke
# LDL-C and Lipid Changes

<table>
<thead>
<tr>
<th>Time since randomization (months)</th>
<th>LDL-C (mg/dL)</th>
<th>TC (mg/dL)</th>
<th>TG (mg/dL)</th>
<th>HDL (mg/dL)</th>
<th>hsCRP (mg/dL)</th>
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<tr>
<td>QE</td>
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<tr>
<td>1</td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
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<td>12</td>
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<td>96</td>
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**1 Yr Mean**

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
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<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
</tr>
<tr>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Δ in mg/dL</th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>-16.9</td>
<td>-19.3</td>
<td>-16.7</td>
<td>+0.6</td>
<td>-0.5</td>
<td></td>
</tr>
</tbody>
</table>

**Median Time avg**

69.5 vs. 53.7 mg/dL

**Number at risk:**

| EZ/Simva | 8990 | 8889 | 8230 | 7701 | 7264 | 6864 | 6583 | 6256 | 5734 | 5354 | 4508 | 3484 | 2608 | 1078 |

- QE: Qualitative Evaluation
- R: Randomization
Primary Endpoint—ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

HR 0.936 CI (0.887, 0.988)  
p=0.016

Simva — 34.7%  
2742 events

EZ/Simva — 32.7%  
2572 events

NNT=50  
p=0.016

7-year event rates
# Summary of Key Differences

<table>
<thead>
<tr>
<th></th>
<th>ATP-III</th>
<th>AHA/ACC</th>
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</thead>
<tbody>
<tr>
<td><strong>Basis for recommendations</strong></td>
<td>Expert opinion based on pathophysiology, observational, &amp; RCT data</td>
<td>Evidence-based recommendations based on RCTs and systematic reviews</td>
</tr>
<tr>
<td><strong>Risk stratification</strong></td>
<td>CHD equivalents, risk factors, 10-year risk of MI</td>
<td>4 specific risk groups based on benefits in clinical trials</td>
</tr>
<tr>
<td><strong>Risk calculation</strong></td>
<td>Framingham risk score</td>
<td>Pooled cohort equation</td>
</tr>
<tr>
<td><strong>Goals of therapy</strong></td>
<td>LDL &amp; non-HDL levels (stratified by risk)</td>
<td>Statin intensity (% LDL reduction)</td>
</tr>
<tr>
<td><strong>Role for monitoring</strong></td>
<td>Fasting lipid panel to assess achievement of goal</td>
<td>Fasting lipid panel to assess adherence/therapeutic response</td>
</tr>
<tr>
<td><strong>Role of non-statin agents</strong></td>
<td>Encouraged use if needed to achieve LDL or non-HDL goal</td>
<td>Discourages use in most patients because of lack of evidence on improving outcomes</td>
</tr>
</tbody>
</table>
The Role of PCSK9 in the Regulation of LDL Receptor Expression
Impact of an PCSK9 mAb on LDL Receptor Expression

For illustration purposes only
Alirocumab Trials
ODYSSEY FH I and FH II Studies

Double-Blind Treatment Period (78 Weeks)

Alirocumab 75 mg Q2W SC with potential ↑ to 150 mg Q2W SC
(single 1-mL injection using prefilled pen for self-administration)

n = 323 (FH I); n = 167 (FH II)

Per-protocol dose ↑ possible based on prespecified LDL-C level

n = 163 (FH I); n = 82 (FH II)

Placebo Q2W SC

LDL-C ≥ 1.81 mmol/L [70 mg/dL] (history of CVD)
or
2.59 mmol/L [100 mg/dL] (no history of CVD)

Assessments

W0  W8  W16  W36  W52  W64  W78

Dose ↑ if LDL-C > 70 mg/dL at W8
Primary efficacy end point
Prespecified analysis
Efficacy: All patients to W52
Safety: Baseline-W78 (all patients at least W52)

ClinicalTrials.gov. NCT01623115; ClinicalTrials.gov. NCT01709500; Kastelein JJ, et al. ESC. 2014.
FH I and FH II

Baseline Characteristics

- Patients recruited from lipid centers (well treated)
- Mean age: 51.7 to 53.2 years
- Sex distribution: 51.5% to 57.7% male
- CHD history: 34.1% to 47.9%
- All patients with background of maximally tolerated statin with or without other LLT
  - High-intensity statin (atorvastatin 40 to 80 mg or rosvastatin 20 to 40 mg daily): 80.8% to 87.8%
  - Ezetimibe: 55.7% to 67.1%
- Mean LDL-C: 3.5 to 3.7 mmol/L
FH I and FH II

Results at W24

FH I

- LS mean difference (SE) vs. placebo: -57.9% (2.7%)
- 43.4% had dose increase at W12
- n = 322

FH II

- LS mean difference (SE) vs. placebo: -51.4% (3.4%)
- 38.6% had dose increase at W12
- n = 166

Alirocumab
Placebo

n = 163
n = 81

ITT analysis.
FH I and FH II
Results Over 52 Weeks

Achieved LDL-C Over Time on Background of Maximally Tolerated Statin With or Without Other LLT

- Placebo: FH I, FH II
- Alirocumab: FH I, FH II

LDL-C, LS mean (SE), mmol/L
- 4.0 mmol/L
- 3.5 mmol/L
- 1.8 mmol/L
- 1.7 mmol/L

mg/dL
- 174
- 155
- 135
- 116
- 97
- 77
- 58
- 39

Dose ↑ if LDL-C > 70 mg/dL at W8

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

ITT analysis.
FH I and FH II

Percentage Reaching LDL-C Goals at W24

<table>
<thead>
<tr>
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<th>FH II</th>
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<tr>
<td>Alirocumab</td>
<td>72.2%</td>
<td>81.4%</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.4%</td>
<td>11.3%</td>
</tr>
</tbody>
</table>

$P < .0001$

†Very high risk: < 1.81 mmol/L (70 mg/dL); high risk: < 2.59 mmol/L (100 mg/dL).

ITT analysis.
ODYSSEY Combo II Study

High CV risk patients on maximally tolerated statin†

- LDL-C ≥ 1.81 mmol/L [70 mg/dL] (history of CVD)
- or
- ≥ 2.59 mmol/L [100 mg/dL] (no history of CVD)

Double-Blind Treatment Period (104 weeks)

- Alirocumab 75 mg with potential ↑ to 150 mg Q2W SC + placebo ezetimibe PO (single 1-mL injection using prefilled pen for self-administration)
  - n = 479
  - Per-protocol dose ↑ possible based on prespecified LDL-C level

- Ezetimibe 10 mg/day PO + placebo Q2W SC
  - n = 241

Assessments

- LDL-C >70 mg/dL at W8
- Prespecified analysis
- Efficacy: All patients to W52
- Safety: Baseline-W102 (all patients at least W52)

Combo II
Results Over 52 Weeks

- Ezetimibe
  - 2.1 mmol/L
  - 82.5 mg/dL
  - -20.7%
- Alirocumab
  - 2.2 mmol/L
  - 85.3 mg/dL
  - -18.3%

LDL-C, LS mean (SE), mmol/L

Dose ↑ if LDL-C > 70 mg/dL at W8

ITT analysis.
ODYSSEY Long-term Study

Design

HeFH or high CV risk patients on maximally tolerated statin with or without other LLT

LDL-C ≥ 1.81 mmol/L [70 mg/dL]

Double-Blind Treatment (18 months)

n = 1553

Alirocumab 150 mg Q2W SC (single 1-mL injection using prefilled syringe for self-administration)

n = 788

Placebo Q2W SC

Assessments

W0  W8  W16  W24  W36  W52  W64  W78

Primary efficacy end point

Prespecified analysis
Efficacy: All patients to W52
Safety: Baseline-W78 (all patients at least W52)

86% (2011/2341) completed 52 weeks (both treatment arms)
26.1% (405/1553 alirocumab) and 25.6% (202/788 placebo) had completed 78 weeks by time of this analysis
Mean treatment duration: 65 weeks (both treatment arms)

ClinicalTrials.gov. NCT01507831.
ODYSSEY Long-term Study

LDL-C Reduction

- Placebo
- Alirocumab

Time, w

LDL-C, LS mean (SE), mmol/L

3.1 mmol/L
118.9 mg/dL

3.2 mmol/L
123.0 mg/dL

1.3 mmol/L
48.3 mg/dL

1.4 mmol/L
53.1 mg/dL

ODYSSEY Long-term Study
CV Death

Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event
Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)

Cox model analysis:
HR = 0.46 (95% CI 0.26 to 0.82)
Nominal P value < .01
Mean treatment duration: 65 weeks

No. at Risk
Placebo: 788 776 731 703 682 667 321 127
Alirocumab: 1550 1534 1446 1393 1352 1335 642 252

*Primary end point for the ODYSSEY Outcomes trial: CHD death, nonfatal MI, fatal and nonfatal ischemic stroke, UA requiring hospitalization.
Results of the GLAGOV Trial

Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound

Steven E. Nissen MD
Stephen J. Nicholls MBBS PhD

Disclosure

Sponsor: Amgen


Companies are directed to pay any honoraria directly to charity. No personal reimbursement is accepted for directing or participating in clinical trials.
968 patients at 197 global centers with symptomatic CAD and other high risk features. Coronary angiography showing 20-50% stenosis in a target vessel.

Stable, optimized statin dose for 4 weeks with LDL-C >80 mg/dL or 60-80 mg with additional high risk features.

Intravascular ultrasound via motorized pullback at 0.5 mm/sec through >40 mm segment.

Statin monotherapy
- 61 patients did not complete
- 423 statin completers

Statin plus monthly SC evolocumab 420 mg
- 61 patients did not complete
- 423 evolocumab completers

Follow-up IVUS of originally imaged “target” vessel (n=846)
Change in LDL-Cholesterol During Treatment

- Mean LDL-C 93.0 mg/dL
- Change from baseline 3.9%
- Mean LDL-C 36.6 mg/dL
- Change from baseline -59.8%
- 90 mg/dL
- 29 mg/dL
Primary Endpoint: Percent Atheroma Volume

<table>
<thead>
<tr>
<th>Change in Percent Atheroma Volume (%)</th>
<th>Statin monotherapy</th>
<th>Statin-evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.4</td>
<td>P = NS</td>
<td>-0.95</td>
</tr>
<tr>
<td>-0.6</td>
<td>P &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>-0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Secondary Endpoint: Total Atheroma Volume

Change in Total Atheroma Volume (mm$^3$)

- Statin monotherapy
- Statin-evolocumab

-0.9

$P = NS$

-5.8

$P < 0.0001$
FOURIER
Further cardiovascular OUTcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

MS Sabatine, RP Giugliano, AC Keech, N Honarpour, SM Wasserman, PS Sever, and TR Pedersen, for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 17, 2017
Objectives

In patients with established cardiovascular disease on statin therapy:

- Test whether the addition of evolocumab reduces the incidence of major cardiovascular events
- Examine the long-term safety & tolerability of evolocumab
- Investigate the efficacy and safety of achieving unprecedented low levels of LDL-C
27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

RANDOMIZED DOUBLE BLIND

Evolocumab SC 140 mg Q2W or 420 mg QM

Placebo SC Q2W or QM

Follow-up Q 12 weeks
Endpoints

• Efficacy
  – Primary: CV death, MI, stroke, hosp. for UA, or coronary revasc
  – Key secondary: CV death, MI or stroke

• Safety
  – AEs/SAEs
  – Events of interest incl. muscle-related, new-onset diabetes, neurocognitive
  – Development of anti-evolocumab Ab (binding and neutralizing)

• TIMI Clinical Events Committee (CEC)
  – Adjudicated all efficacy endpoints & new-onset diabetes
  – Members unaware of treatment assignment & lipid levels

Follow-up

Randomized 27,564 patients

- Evolocumab (N=13,784)
- Placebo (N=13,780)

Follow-up median 26 months (IQR 22-30)

2907 patients experienced primary endpoint
1829 experienced key secondary endpoint

<table>
<thead>
<tr>
<th>Premature perm. drug discontinuation</th>
<th>Evolocumab (N=13,784) 5.6%/yr</th>
<th>Placebo (N=13,780) 5.8%/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrew consent</td>
<td>0.29%/yr</td>
<td>0.35%/yr</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>5 patients</td>
<td>13 patients</td>
</tr>
</tbody>
</table>

Ascertainment for primary endpoint was complete for 99.5% of potential patient-years of follow up
Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>63 (9)</td>
</tr>
<tr>
<td><strong>Male sex (%)</strong></td>
<td>75</td>
</tr>
<tr>
<td><strong>Type of cardiovascular disease (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>81</td>
</tr>
<tr>
<td>Stroke (non-hemorrhagic)</td>
<td>19</td>
</tr>
<tr>
<td>Symptomatic PAD</td>
<td>13</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factor (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>80</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>28</td>
</tr>
</tbody>
</table>

Median time from most recent event ~3 yrs

Pooled data; no differences between treatment arms
# Lipid Lowering Therapy & Lipid Levels at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statin use (%)</strong></td>
<td></td>
</tr>
<tr>
<td>High-intensity</td>
<td>69</td>
</tr>
<tr>
<td>Moderate-intensity</td>
<td>30</td>
</tr>
<tr>
<td><strong>Ezetimibe use (%)</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>Median lipid measures (IQR) – mg/dL</strong></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>92 (80-109)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>168 (151-189)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>44 (37-53)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>133 (100-182)</td>
</tr>
</tbody>
</table>

*Per protocol, patients were to be on atorv ≥20 mg/d or equivalent. 1% were on low intensity or intensity data were missing. Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines.*
LDL Cholesterol

Placebo

59% mean reduction (95%CI 58-60), P<0.00001
Absolute reduction: 56 mg/dl (95%CI 55-57)

Evolocumab
(median 30 mg/dl, IQR 19-46 mg/dl)
Cohort of 11,077 patients who
- had all measurements through 120 weeks
- did not discontinue study drug
- did not △ concomitant background lipid-lowering Rx

Similar data out to 4 years in OSLER-1
(JAMA Cardiology online)
Primary Endpoint

Hazard ratio 0.85
(95% CI, 0.79-0.92)
P<0.0001

CV Death, MI, Stroke, Hosp for UA, or Cor Revasc

0 6 12 18 24 30 36

Evolocumab

Placebo

12.6%
14.6%
Key Secondary Endpoint

Hazard ratio 0.80
(95% CI, 0.73-0.88)
P<0.00001

Evolocumab
Placebo

CV Death, MI, or Stroke
## Types of CV Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Evolocumab (N=13,784)</th>
<th>Placebo (N=13,780)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, or stroke</td>
<td>7.9</td>
<td>9.9</td>
<td>0.80 (0.73-0.88)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2.5</td>
<td>2.4</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>Death due to acute MI</td>
<td>0.26</td>
<td>0.32</td>
<td>0.84 (0.49-1.42)</td>
</tr>
<tr>
<td>Death due to stroke</td>
<td>0.29</td>
<td>0.30</td>
<td>0.94 (0.58-1.54)</td>
</tr>
<tr>
<td>Other CV death</td>
<td>1.9</td>
<td>1.8</td>
<td>1.10 (0.90-1.35)</td>
</tr>
<tr>
<td>MI</td>
<td>4.4</td>
<td>6.3</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.2</td>
<td>2.6</td>
<td>0.79 (0.66-0.95)</td>
</tr>
</tbody>
</table>
## Types of CV Outcomes

<table>
<thead>
<tr>
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<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-yr Kaplan-Meier rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD, MI, stroke, UA, or revasc</td>
<td>12.6</td>
<td>14.6</td>
<td>0.85 (0.79-0.92)</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>7.9</td>
<td>9.9</td>
<td>0.80 (0.73-0.88)</td>
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<tr>
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<tr>
<td>Stroke</td>
<td>2.2</td>
<td>2.6</td>
<td>0.79 (0.66-0.95)</td>
</tr>
<tr>
<td>Hosp for unstable angina</td>
<td>2.2</td>
<td>2.3</td>
<td>0.99 (0.82-1.18)</td>
</tr>
<tr>
<td>Coronary revasc</td>
<td>7.0</td>
<td>9.2</td>
<td>0.78 (0.71-0.86)</td>
</tr>
<tr>
<td>Urgent</td>
<td>3.7</td>
<td>5.4</td>
<td>0.73 (0.64-0.83)</td>
</tr>
<tr>
<td>Elective</td>
<td>3.9</td>
<td>4.6</td>
<td>0.83 (0.73-0.95)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>4.8</td>
<td>4.3</td>
<td>1.04 (0.91-1.19)</td>
</tr>
</tbody>
</table>
Landmark Analysis

16% RRR
HR 0.84 (95%CI 0.74-0.96)
P=0.008

25% RRR
HR 0.75 (95%CI 0.66-0.85)
P<0.00001

CV Death, MI, Stroke

Placebo
Evolocumab

Months from Randomization
**Fatal or Nonfatal MI or Stroke**

- **19% RRR**
  - HR 0.81 (95%CI 0.70-0.93)
  - P=0.003

- **33% RRR**
  - HR 0.67 (95%CI 0.59-0.77)
  - P<0.00001
### Safety

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Evolocumab (N=13,769)</th>
<th>Placebo (N=13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>77.4</td>
<td>77.4</td>
</tr>
<tr>
<td>Serious</td>
<td>24.8</td>
<td>24.7</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>3.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Treatment-related and led to d/c of study drug</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Muscle-related</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Cataract</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Diabetes (new-onset)</td>
<td>8.1</td>
<td>7.7</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>1.6</td>
<td>1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory results</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding Ab</td>
<td>0.3</td>
<td>n/a</td>
</tr>
<tr>
<td>Neutralizing Ab</td>
<td>none</td>
<td>n/a</td>
</tr>
</tbody>
</table>

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC
Summary for Evolocumab

• ↓ LDL-C by 59%
  – Consistent throughout duration of trial
  – Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)

• ↓ CV outcomes in patients already on statin therapy
  – 15% ↓ broad primary endpoint; 20% ↓ CV death, MI, or stroke
  – Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  – 25% reduction in CV death, MI, or stroke after 1st year
  – Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C

• Safe and well-tolerated
  – Similar rates of AEs, incl DM & neurocog events w/ EvoMab & pbo
  – Rates of EvoMab discontinuation low and no greater than pbo
  – No neutralizing antibodies developed
Conclusions

In patients with known cardiovascular disease:

1. PCSK9 inhibition with evolocumab significantly & safely ↓ major cardiovascular events when added to statin therapy

2. Benefit was achieved with lowering LDL cholesterol well below current targets

2. Consider add-on therapy, i.e. ezetimibe, for patients not at goal or not able to tolerate maximal statin therapy.

3. PCSK9 inhibitors are now indicated for patients with familial heterozygous hyperlipidemia or clinical atherosclerotic cardiovascular disease on maximally tolerated statin therapy not at goal.

4. All therapies are only indicated when patient are on low cholesterol diets.