Only these lipoprotein particles found in plaque at biopsy.
High Plasma Apo B Lipoprotein Levels Promote Atherogenesis
lipid core
adventitia

Anti-atherosclerotic therapy

From Davies et al (1998)

Unstable lesion
Stable lesion
There Is a Strong Relationship Between CVD Risk and the Presence of Dyslipidemia: Framingham

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

14-y incidence rates (%) for CHD

HDL-C (mg/dL)

Total-C (mg/dL)
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?

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

JUPITER

TNT – ATV10
PROVE-IT – PRA
WOSCOPS – Placebo
WOSCOPS – Rx
ASCOT – Rx
LIPID – Placebo
CARE – Placebo
HPS – Placebo
AFCAPS – Placebo

Rx - Statin therapy
PRA – pravastatin
ATV - atorvastatin

TNT

Secondary Prevention

Primary Prevention

Event rate (%)

0
5
10
15
20
25
30

40 (1.0)
60 (1.6)
80 (2.1)
100 (2.6)
120 (3.1)
140 (3.6)
160 (4.1)
180 (4.7)
200 (5.2)

LDL-C achieved mg/dL (mmol/L)
On-Treatment LDL-C and CHD Events in Primary Prevention

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

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

TNT: New data on intensive lipid lowering in stable CHD patients
TNT: Design

Patient population
- 250 centers in 14 countries (N = 10,001)
- LDL 130–250 mg/dL
- TG <600 mg/dL

Atorvastatin 10 mg
Atorvastatin 80 mg

TNT: Treatment Effects on LDL-C

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

![Graph showing mean LDL-C values and patients with major CV event percentages for Atorvastatin 10 mg and 80 mg.]

TNT: Primary Efficacy Outcome Measure: Major Cardiovascular Events*

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


HR=0.78 (95% CI 0.69, 0.89); P<.001

Proportion of Patients Experiencing Major Cardiovascular Event

- Mean LDL-C level = 77 mg/dL
- Mean LDL-C level = 101 mg/dL

Relative risk reduction 22%

HR=0.78 (95% CI 0.69, 0.89); P<.001

Time (Years)
By Blocking Cholesterol Uptake in the Liver and Intestine, Ezetimibe Fosters Greater Elimination of Free Cholesterol
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)

<table>
<thead>
<tr>
<th>Standard Medical &amp; Interventional Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 18, 144</td>
</tr>
<tr>
<td>Simvastatin 40 mg</td>
</tr>
<tr>
<td>Uptitrated to Simva 80 mg if LDL-C &gt; 79</td>
</tr>
<tr>
<td>(adapted per FDA label 2011)</td>
</tr>
<tr>
<td>Ezetimibe / Simvastatin 10 / 40 mg</td>
</tr>
</tbody>
</table>

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>1 Yr Mean</th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Δ in mg/dL</td>
<td>-16.9</td>
<td>-19.3</td>
<td>-16.7</td>
<td>+0.6</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

Mean LDL-C (mg/dL)

Time since randomization (months)

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
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

7-year event rates
Conclusions

• **IMPROVE-IT:** First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:
  - **YES:** Non-statin lowering LDL-C with ezetimibe reduces cardiovascular events
  - **YES:** Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
  - **YES:** Confirms ezetimibe safety profile

• Reaffirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events

• Results could be considered for future guidelines
## 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></td>
<td></td>
<td>Non-HDL-C mg/dL</td>
<td>LDL-C mg/dL</td>
</tr>
<tr>
<td>Low</td>
<td>0-1 major ASCVD risk factors</td>
<td>&lt;130</td>
<td>≥190</td>
</tr>
<tr>
<td></td>
<td>Consider other risk indicators, if known</td>
<td>&lt;100</td>
<td>≥160</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 major ASCVD risk factors</td>
<td>&lt;130</td>
<td>≥160</td>
</tr>
<tr>
<td></td>
<td>Consider quantitative risk scoring</td>
<td>&lt;100</td>
<td>≥130</td>
</tr>
<tr>
<td></td>
<td>Consider other risk indicators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>≥3 major ASCVD risk factors</td>
<td>&lt;130</td>
<td>≥130</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus* (Type 1 or 2)</td>
<td>&lt;100</td>
<td>≥100</td>
</tr>
<tr>
<td></td>
<td>0-1 other major ASCVD risk factors, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No evidence of end organ damage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease stage 3B or 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDL-C ≥190 mg/dL (severe hypercholesterolemia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quantitative risk score reaching the high-risk threshold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very High</td>
<td>ASCVD*</td>
<td>&lt;100</td>
<td>≥100</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus* (Type 1 or 2)</td>
<td>&lt;70</td>
<td>≥70</td>
</tr>
<tr>
<td></td>
<td>≥2 other major ASCVD risk factors or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evidence of end organ damage</td>
<td></td>
<td></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.*

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,
Table 4. Very High-Risk* of Future ASCVD Events

<table>
<thead>
<tr>
<th>Major ASCVD Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent ACS (within the past 12 mo)</td>
</tr>
<tr>
<td>History of MI (other than recent ACS event listed above)</td>
</tr>
<tr>
<td>History of ischemic stroke</td>
</tr>
<tr>
<td>Symptomatic peripheral arterial disease (history of claudication with ABI &lt;0.85, or previous revascularization or amputation)</td>
</tr>
</tbody>
</table>
### Table 4 continued

<table>
<thead>
<tr>
<th>High-Risk Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 y</td>
</tr>
<tr>
<td>Heterozygous familial hypercholesterolemia</td>
</tr>
<tr>
<td>History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>CKD (eGFR 15-59 mL/min/1.73 m²)</td>
</tr>
<tr>
<td>Current smoking</td>
</tr>
<tr>
<td>Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe</td>
</tr>
<tr>
<td>History of congestive HF</td>
</tr>
</tbody>
</table>
Secondary Prevention

Clinical ASCVD

Healthy Lifestyle

ASCVD not at very high-risk*

Age ≤75 y
- High-intensity statin (Goal: ↓ LDL-C ≥50%) (Class I)
  - If high-intensity statin not tolerated, use moderate-intensity statin (Class I)
  - If on maximal statin therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable (Class IIa)

Age >75 y
- Initiation of moderate- or high-intensity statin is reasonable (Class IIa)
- Continuation of high-intensity statin is reasonable (Class IIa)

Very high-risk* ASCVD

High-intensity or maximal statin (Class I)

If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)

If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-I is reasonable (Class IIa)

If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I (Class I)

Dashed arrow indicates RCT-supported efficacy, but is less cost effective
Pooled Cohort Risk Assessment Equations

Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event

http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx
Primary Prevention: Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

- **Age 0-19 y**
  - Lifestyle to prevent or reduce ASCVD risk
  - Diagnosis of Familial Hypercholesterolemia → statin

- **Age 20-39 y**
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
  - Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

- **Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L)**
  - Without diabetes mellitus
  - 10-year ASCVD risk percent begins risk discussion

- **Diabetes mellitus and age 40-75 y**
  - Moderate-intensity statin (Class I)

- **Diabetes mellitus and age 40-75 y**
  - Risk assessment to consider high-intensity statin (Class IIa)

- **Age >75 y**
  - Clinical assessment, Risk discussion

**ASCVD Risk Enhancers:**
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

**Lipid/Biomarkers:**
- Persistently elevated triglycerides (≥175 mg/dL, ≥2.0 mmol/L)
- In selected individuals if measured:
  - hs-CRP ≥2.0 mg/L
  - Lp(a) levels >50 mg/dL or >125 nmol/L
  - apoB ≥130 mg/dL
  - Ankle-brachial index (ABI) <0.9

**Risk discussion:**
- **<5%** “Low Risk”
  - Emphasize lifestyle to reduce risk factors (Class I)

- **5% - <7.5%** “Borderline Risk”
  - Risk discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIb)

- **≥7.5% - <20%** “Intermediate Risk”
  - Risk discussion: If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% (Class I)

- **≥20%** “High Risk”
  - Risk discussion: Initiate statin to reduce LDL-C ≥50% (Class I)

If risk decision is uncertain:
- Considering measuring CAC in selected adults:
  - CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
  - CAC = 1-99 favors statin (especially after age 55)
  - CAC = 100+ and/or ≥75th percentile, initiate statin therapy
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>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL-C on average, by &lt;30%</td>
</tr>
<tr>
<td><strong>Atorvastatin (40†)–80 mg Rosuvastatin 20 (40) mg</strong></td>
<td><strong>Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg‡ Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg</strong></td>
<td><strong>Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg</strong></td>
</tr>
</tbody>
</table>
Table 6. Risk-Enhancing Factors for Clinician–Patient Risk Discussion

<table>
<thead>
<tr>
<th>Risk-Enhancing Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Family history of premature ASCVD</strong> (males, age &lt;55 y; females, age &lt;65 y)</td>
</tr>
<tr>
<td>• <strong>Primary hypercholesterolemia</strong> (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*</td>
</tr>
<tr>
<td>• <strong>Metabolic syndrome</strong> (increased waist circumference, elevated triglycerides [&gt;175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [&lt;40 mg/dL in men; &lt;50 in women mg/dL] are factors; tally of 3 makes the diagnosis)</td>
</tr>
<tr>
<td>• <strong>Chronic kidney disease</strong> (eGFR 15–59 mL/min/1.73 m² with or without albuminuria; not treated with dialysis or kidney transplantation)</td>
</tr>
<tr>
<td>• <strong>Chronic inflammatory conditions</strong> such as psoriasis, RA, or HIV/AIDS</td>
</tr>
<tr>
<td>• <strong>History of premature menopause</strong> (before age 40 y) and <strong>history of pregnancy-associated conditions</strong> that increase later ASCVD risk such as preeclampsia</td>
</tr>
<tr>
<td>• <strong>High-risk race/ethnicities</strong> (e.g., South Asian ancestry)</td>
</tr>
</tbody>
</table>
Table 6 continued

<table>
<thead>
<tr>
<th>Risk-Enhancing Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipid/biomarkers</strong>: Associated with increased ASCVD risk</td>
</tr>
<tr>
<td>- Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);</td>
</tr>
<tr>
<td>- If measured:</td>
</tr>
<tr>
<td>- <strong>Elevated high-sensitivity C-reactive protein</strong> (≥2.0 mg/L)</td>
</tr>
<tr>
<td>- <strong>Elevated Lp(a)</strong>: A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).</td>
</tr>
<tr>
<td>- <strong>Elevated apoB</strong> ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C &gt;160 mg/dL and constitutes a risk-enhancing factor</td>
</tr>
<tr>
<td>- <strong>ABI</strong> &lt;0.9</td>
</tr>
</tbody>
</table>
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
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
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
The Role of PCSK9 in the Regulation of LDL Receptor Expression
Impact of an PCSK9 mAb on LDL Receptor Expression
The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg, Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema, Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher, Ph. Gabriel Steg

On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018

ClinicalTrials.gov: NCT01663402
Residual Risk After Acute Coronary Syndrome

• Remains high despite evidence-based preventive therapies
• Is related, in part, to levels of low-density lipoprotein cholesterol (LDL-C)
• Is reduced when LDL-C is lowered by
  • Statin therapy, compared with placebo¹
  • High-intensity, compared with moderate-intensity statin therapy²
  • Ezetimibe, compared with placebo, added to statin³

Alirocumab

- PCSK9 is a validated target for risk reduction in stable atherosclerotic cardiovascular disease\(^1\)–\(^3\)
- A fully human monoclonal antibody against PCSK9
- Produces substantial and sustained reductions in LDL-C and other atherogenic lipoproteins\(^2\)
- Has been safe and well-tolerated in studies to date\(^4\)

PCSK9, proprotein convertase subtilisin/kexin type 9
Study Hypothesis

Alirocumab, versus placebo, reduces cardiovascular (CV) morbidity and mortality after recent acute coronary syndrome (ACS) in patients with elevated levels of atherogenic lipoproteins despite intensive or maximum-tolerated statin therapy.
Main Inclusion Criteria

• **Age** ≥40 years

• **ACS**
  • 1 to 12 months prior to randomization
  • Acute myocardial infarction (MI) or unstable angina

• **High-intensity statin therapy**
  • Atorvastatin 40 to 80 mg daily or
  • Rosuvastatin 20 to 40 mg daily or
  • Maximum tolerated dose of one of these agents for ≥2 weeks

• **Inadequate control of lipids**
  • LDL-C ≥70 mg/dL (1.8 mmol/L) or
  • Non-HDL-C ≥100 mg/dL (2.6 mmol/L) or
  • Apolipoprotein B ≥80 mg/dL

*Patients not on statins were authorized to participate if tolerability issues were present and documented Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.*
Primary Efficacy Outcome

Time of first occurrence of:

- Coronary heart disease (CHD) death, or
- Non-fatal MI, or
- Fatal or non-fatal ischemic stroke, or
- Unstable angina requiring hospitalization*

All outcomes adjudicated by the Clinical Events Committee, under the auspices of the Duke Clinical Research Institute (DCRI). Members were unaware of treatment assignment and lipid levels

*Required all of the following:
1. Hospital admission >23 h for MI symptoms, ↑ tempo in prior 48 hours and/or ≥20 min of chest discomfort at rest
2. New ECG findings consistent with ischemia or infarction
3. Angiographically significant obstructive coronary disease

Treatment Assignment

Post-ACS patients (1 to 12 months)

Run-in period of 2–16 weeks on high-intensity or maximum-tolerated dose of atorvastatin or rosvastatin

At least one lipid entry criterion met

Randomization

Alirocumab SCQ2W

Placebo SCQ2W

Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

A Target Range for LDL-C

A Target Range for LDL-C

Target range

Undesirably high baseline range

0 15 25 50 70

LDL-C (mg/dL)

Alirocumab

We thank the patients, their families, all investigators and coordinators involved in this study, and DCRI.
Patient Disposition

Randomized 18,924 patients

Alirocumab (N=9462)  Placebo (N=9462)

Follow-up*: median 2.8 (Q1–Q3 2.3–3.4) years
8242 (44%) patients with potential follow-up ≥3 years

1955 patients experienced a primary endpoint
726 patients died

- Premature treatment discontinuation
  - Alirocumab: 1343 (14.2%)
  - Placebo: 1496 (15.8%)

- Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)
  - Alirocumab: 730 (7.7%)
  - Placebo: Not applicable

- Patients lost to follow-up (vital status)
  - Alirocumab: 14
  - Placebo: 9

*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively
Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (Q1−Q3)</td>
<td>58 (52−65)</td>
<td>58 (52−65)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>2390 (25.3)</td>
<td>2372 (25.1)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>6205 (65.6)</td>
<td>6044 (63.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2693 (28.5)</td>
<td>2751 (29.1)</td>
</tr>
<tr>
<td>Current tobacco smoker</td>
<td>2282 (24.1)</td>
<td>2278 (24.1)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1790 (18.9)</td>
<td>1843 (19.5)</td>
</tr>
</tbody>
</table>
### Baseline Index Events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from index ACS to randomization, months, median (Q1–Q3)</td>
<td>2.6 (1.7–4.4)</td>
<td>2.6 (1.7–4.3)</td>
</tr>
<tr>
<td>ACS type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>4574 (48.4)</td>
<td>4601 (48.7)</td>
</tr>
<tr>
<td>STEMI</td>
<td>3301 (35.0)</td>
<td>3235 (34.2)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1568 (16.6)</td>
<td>1614 (17.1)</td>
</tr>
<tr>
<td>Revascularization for index ACS, n (%)</td>
<td>6798 (71.8)</td>
<td>6878 (72.7)</td>
</tr>
</tbody>
</table>
Baseline Lipid Characteristics

<table>
<thead>
<tr>
<th>Characteristic, mg/dL, median (Q1–Q3)</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>87 (73–104)</td>
<td>87 (73–104)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>115 (99–136)</td>
<td>115 (99–137)</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>79 (69–93)</td>
<td>80 (69–93)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>43 (37–50)</td>
<td>42 (36–50)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>129 (94–181)</td>
<td>129 (95–183)</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td>21 (7–59)</td>
<td>22 (7–60)</td>
</tr>
</tbody>
</table>

92.5% of patients qualified on the basis of LDL-C ≥70 mg/dL
Baseline Lipid-Lowering Therapy

<table>
<thead>
<tr>
<th>Therapy, n (%)</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose atorvastatin/rosvastatin</td>
<td>8380 (88.6)</td>
<td>8431 (89.1)</td>
</tr>
<tr>
<td>Low-/moderate-dose atorvastatin/rosvastatin</td>
<td>830 (8.8)</td>
<td>777 (8.2)</td>
</tr>
<tr>
<td>Other statin</td>
<td>19 (0.2)</td>
<td>27 (0.3)</td>
</tr>
<tr>
<td>Ezetimibe, with or without statin</td>
<td>269 (2.8)</td>
<td>285 (3.0)</td>
</tr>
<tr>
<td>No lipid-lowering therapy*</td>
<td>87 (0.9)</td>
<td>91 (1.0)</td>
</tr>
</tbody>
</table>

*Patients not on statins were authorized to participate if tolerability issues were present and documented
# Guideline-Recommended Post-ACS Medications

<table>
<thead>
<tr>
<th>Medication, n (%)</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>9050 (95.6)</td>
<td>9036 (95.5)</td>
</tr>
<tr>
<td>P2Y$_{12}$ antagonist</td>
<td>8296 (87.7)</td>
<td>8245 (87.1)</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>7356 (77.7)</td>
<td>7360 (77.8)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>7998 (84.5)</td>
<td>7992 (84.5)</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker
LDL-C: ITT and On-Treatment Analyses

*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo
LDL-C: On-Treatment Analysis

Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose
Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization
Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

ARR* 1.6%

HR 0.85 (95% CI 0.78, 0.93)
P = 0.0003

Based on cumulative incidence

<table>
<thead>
<tr>
<th>Years Since Randomization</th>
<th>Placebo Number at Risk</th>
<th>Alirocumab Number at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9482</td>
<td>9462</td>
</tr>
<tr>
<td>1</td>
<td>8805</td>
<td>8846</td>
</tr>
<tr>
<td>2</td>
<td>8201</td>
<td>8345</td>
</tr>
<tr>
<td>3</td>
<td>3471</td>
<td>3574</td>
</tr>
<tr>
<td>4</td>
<td>629</td>
<td>653</td>
</tr>
</tbody>
</table>
Primary Efficacy and Components

<table>
<thead>
<tr>
<th>Endpoint, n (%)</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
<th>HR (95% CI)</th>
<th>Log-rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>903 (9.5)</td>
<td>1052 (11.1)</td>
<td>0.85 (0.78, 0.93)</td>
<td>0.0003</td>
</tr>
<tr>
<td>CHD death</td>
<td>205 (2.2)</td>
<td>222 (2.3)</td>
<td>0.92 (0.76, 1.11)</td>
<td>0.38</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>626 (6.6)</td>
<td>722 (7.6)</td>
<td>0.86 (0.77, 0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>111 (1.2)</td>
<td>152 (1.6)</td>
<td>0.73 (0.57, 0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>37 (0.4)</td>
<td>60 (0.6)</td>
<td>0.61 (0.41, 0.92)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
All-Cause Death

- Nominal P-value
- Based on cumulative incidence

ARR†0.6%

HR 0.85
(95% CI 0.73, 0.98)
P=0.026*
Conclusions

Compared with placebo in patients with recent ACS, alirocumab 75 or 150 mg subcutaneous Q2W targeting LDL-C levels 25–50 mg/dL, and allowing levels as low as 15 mg/dL:

1. Reduced MACE, MI, and ischemic stroke
2. Was associated with a lower rate of all-cause death
3. Was safe and well-tolerated over the duration of the trial
Clinical Perspective

• In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥3 years, there was no safety signal with alirocumab other than injection site reactions
Clinical Perspective

• In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥3 years, there was no safety signal with alirocumab other than injection site reactions.

• Among patients with ACS and baseline LDL-C ≥ 100 mg/dL, alirocumab reduced MACE by 24% (ARR 3.4%) and all-cause death by 29% (ARR 1.7%) compared with placebo.

➢ These are the patients who may benefit most from treatment.

ARR, absolute risk reduction
Results of the GLAGOV Trial

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.
68 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%

Study Week
Primary Endpoint: Percent Atheroma Volume

-0.95

0.05

$P = \text{NS}$

$P < 0.0001$

-0.95

$P < 0.0001$

Statin monotherapy

Statin - evolocumab

$P < 0.0001$
Secondary Endpoint: Total Atheroma Volume

-0.9

$P = NS$

-5.8

$P < 0.0001$

Statin monotherapy vs. Statin--evolocumab: $P < 0.0001$
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
Trial Design

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)

Premature perm. drug discontinuation  5.6%/yr  5.8%/yr

Withdraw consent  0.29%/yr  0.35%/yr

Lost to follow-up  5 patients  13 patients

2907 patients experienced primary endpoint
1829 experienced key secondary endpoint

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

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>Ezetimibe use (%)</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 atorva ≥20 mg/d or equivalent. 1% were on low intensity or intensity data were missing. Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines.

Pooled data; no differences between treatment arms.
An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School

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)
Primary Endpoint

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- **Primary Endpoint**
  - **Evolocumab** vs **Placebo**

  - **Months from Randomization**
    - 0
    - 6
    - 12
    - 18
    - 24
    - 30
    - 36

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

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

- **12.6%** for Evolocumab vs **14.6%** for Placebo
Key Secondary Endpoint

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

P<0.00001

Evolocumab
Placebo

0 6 12 18 24 30 36

CVD death, MI, or stroke

0% 1% 2% 3% 4% 5% 6% 7% 8% 9% 10%

Months from Randomization
### 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><strong>Cardiovascular death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death due to acute MI</td>
<td>2.5</td>
<td>2.4</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>Death due to stroke</td>
<td>0.26</td>
<td>0.32</td>
<td>0.84 (0.49-1.42)</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>
<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>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>
</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>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>
<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

Evolocumab vs Placebo

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
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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

Fatal or Nonfatal MI or Stroke
### Safety

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab (N=13,769)</th>
<th>Placebo (N=13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events (%)</strong></td>
<td></td>
<td></td>
</tr>
<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>
<tr>
<td><strong>Laboratory results (%)</strong></td>
<td></td>
<td></td>
</tr>
<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
Top 10 Take-Home Messages

2018 Cholesterol Guidelines
Top 10 Take Home Messages

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.

A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.

In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.
2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

Use a maximally tolerated statin to lower LDL-C levels by $\geq 50\%$. 
3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.

- Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L).
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost-effectiveness is low at mid-2018 list prices.
4. In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL[≥4.9 mmol/L]) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.

• If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), adding ezetimibe is reasonable

• If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) & the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered, although the long-term safety (>3 years) is uncertain and economic value is low at mid-2018 list prices.
5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.

In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.
6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.

Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, (LDL-C), hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD);

- the presence of risk-enhancing factors (see No. 8);
- the potential benefits of lifestyle and statin therapies;
- the potential for adverse effects and drug–drug interactions;
- the consideration of costs of statin therapy; and
- the patient preferences & values in shared decision-making.
7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.

Risk-enhancing factors favor statin therapy (see No. 8).

If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.
8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).

Risk-enhancing factors include

- family history of premature ASCVD;
- persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L);
- metabolic syndrome;
- chronic kidney disease;
- history of preeclampsia or premature menopause (age <40 yrs)
- chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV);
- high-risk ethnic groups (e.g., South Asian);
- persistent elevations of triglycerides ≥ 175 mg/dL (≥1.97 mmol/L);
8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).

Risk-enhancing factors include

and, if measured in selected individuals

- apolipoprotein B $\geq 130$ mg/dL
- high-sensitivity C-reactive protein $\geq 2.0$ mg/L
- ankle-brachial index $< 0.9$ and 1
- lipoprotein (a) $\geq 50$ mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a).

Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5-7.5% (borderline risk)
9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL-189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

- If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age.
- For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.
10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

- Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.
- In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels $\geq 70$ mg/dL ($\geq 1.8$ mmol/L) on maximal statin therapy (see No. 3).

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.