• Presented on ESIM CME, February 2017.

• “Contents do not necessarily reflect positions of the Ethiopian Society of Internal Medicine (ESIM)”
Cardiovascular Disease Risk Management

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Gesund Cardiac Medical Center
A 65-year-old male diabetic with history of MI 6 months back presented for optimal CVD management. He is regularly taking simvastatin 40 mg/day plus low aspirin 81 mg/day

Lipid values:-
- T cholesterol 153 mg/dl, HDL 35mg/dl, LDL 65mg/dl & triglycerides 265mg/dl
HMG-CoA Reductase Inhibitor: Secondary Prevention

Relationship between LDL-C Levels and Event Rates in Secondary Prevention Trials of Patients with Stable CHD

Event (%) vs LDL-C (mg/dL)

- Statin
- Placebo
- 4S
- LIPID
- CARE
- HPS
- TNT (atorvastatin 10 mg/d)
- TNT (atorvastatin 80 mg/d)

LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease; TNT = Treating to New Targets; HPS = Heart Protection Study; CARE = Cholesterol and Recurrent Events Trial; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; 4S = Scandinavian Simvastatin Survival Study.

MIRACL

3086 PTS WITH UA: 24-96 HRS AFTER ADMISSION FOR 16 WEEKS

Placebo + DIET
17.4%

Atorvastatin 80 mg + Diet
14.8%

Relative risk = 0.84
\( p=0.048 \)

Time to first occurrence of:
- Death (any cause)
- Nonfatal MI
- Resuscitated cardiac arrest
- Worsening angina with new objective evidence requiring urgent rehospitalization

Schwartz GG et al. Jama 2001; 285: 1711-1718
HMG-CoA Reductase Inhibitor: Secondary Prevention

Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)—TIMI 22 Study

4,162 patients with an ACS randomized to atorvastatin (80 mg) or pravastatin (40 mg) for 24 months.

- Atorvastatin
- Pravastatin

Recurrent MI or Cardiac Death

Follow-up (months)

ACS=Acute coronary syndrome, CV=Cardiovascular, MI=Myocardial infarction, RRR=Relative risk reduction

TNT TRIAL
10,000 PTS, STABLE CAD, COMPARING HIGH AND LOW DOSE ATORVASTATIN

Primary Composite of CHD death, nonfatal MI, resuscitated cardiac arrest, and fatal or nonfatal stroke

- **High-dose**
  - MEDIAN LDL: 77 mg/dl
  - N = 4995

- **Low-dose**
  - MEDIAN LDL: 102 mg/dl
  - N = 5006

- **Mean follow-up of 4.9 years**
- **RRR = 22%**
  - HR = 0.78 (0.69–0.89)
  - P < 0.001

**CONCLUSIONS**

In patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke. (ClinicalTrials.gov number, NCT00147602.)
Comparison of the efficacy of statins

Comparison of the percent reduction in serum low density lipoprotein (LDL)-cholesterol with various statin drugs
# 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

## 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</strong> Rosuvastatin 20 (40) mg</td>
<td><strong>Atorvastatin 10 (20) mg</strong> 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</td>
<td><strong>Simvastatin 10 mg</strong> Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>
Secondary prevention

• Life style modification
• Aspirin &/or other antiplatelet agent
• High intensity statin
• A 65-year-old male diabetic with history of MI 6 months back presented for optimal CVD management. He is regularly taking simvastatin 40 mg/day plus low aspirin 81 mg/day.

• Lipid values:-
  – T cholesterol 153 mg/dl, HDL 35mg/dl, LDL 65mg/dl & triglycerides 265mg/dl

➤ Switch to high intensity statin treatment
Primary prevention
• In 2009, healthcare costs of CVD in Europe amounted to €106 billion, representing 9% of the total healthcare expenditure across the EU.  
  
  *European Heart Network, 2012*

• In the USA, direct annual costs of CVD are projected to **triple between 2010 and 2030**.  
  
  *Circulation 2011;123:933–944*
From 2011 to 2025, the projected cumulative economic losses from all NCD is $7.28 trillion in LIMC. Reducing CVD mortality by 10% would result in a $377 billion reduction in economic losses from 2011 to 2025.
CHD Risk Based on Major Risk Factors

CHD risk* (%)

<table>
<thead>
<tr>
<th>CHD Risk Level</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>B</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>C</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>D</td>
<td>37</td>
<td>27</td>
</tr>
</tbody>
</table>

- **Blood pressure (mm Hg)**: 120/80, 140/90, 140/90, 140/90
- **Total cholesterol (mg/dL)**: 200, 240, 240, 240
- **HDL cholesterol (mg/dL)**: 50, 50, 40, 40
- **Diabetes**: No, No, Yes, Yes
- **Cigarettes**: No, No, No, Yes

CHD, coronary heart disease.
*Estimated 10-year CHD risk in 55-year-old adults.
Findings from statin studies confirm

**CVD risk reduction by 20-30%**

A 45-yr old nonsmoking normotensive woman with T-Cholesterol of 240mg/dL and an HDL-C of 40 mg/dL

A 60-yr-old nonsmoking normotensive man with a T-cholesterol of 240 mg/dL and an HDL-C of 40 mg/dL

Relative risk

Framingham Risk Score
RR = 1%

Framingham Risk Score
RR = 12%

Absolute risk reduction

0.2 – 0.3 %

2.4 – 3.6 %
363 prediction models

• Their usefulness remains nuclear owing to:-
  – Methodological shortcomings
  – Incomplete presentation
  – Lack of external validation & model impact studies

• Notable exceptions are
  – Framingham
  – Score
Choice of risk calculator

Limitations of Framingham/ATPIII

- its derivation in an exclusively white sample population
- the limited scope of the outcome (in determining CHD alone)
The equations were developed from several long-standing population-based cohort studies. The first model to include data from large population of Caucasians & African Americans.
Parameters incorporated in ACC/AHA pooled cohort hard CVD risk calculator

- Age
- Gender
- Race
- Total cholesterol (mg/dl)
- HDL-C
- Systolic BP
- BP treatment (yes or no)
- Diabetes mellitus (yes or no)
- Current smoking (yes or no)

End points assessed
- CHD death
- Non fatal MI
- Fatal stroke
- Non fatal stroke
ACC/AHA guideline principles

• Separate equations for whites and blacks
• No LDL-C or non-HDL-C- targets
• Stroke is included in ASCVD as outcome
• In primary prevention
  – Optimal lifestyle emphasized
  – Clinician patient discussion needed for appropriate decision-making
• Use medication proven to reduce ASCVD risk
ACC/AHA guideline
Major Statin Benefit Groups

- Adults with clinical ASCVD
  ➢ high intensity

- Adults with LDL–C >190 mg/dL
  ➢ High intensity

- Adults 40 to 75 years of age with diabetes
  ➢ Moderate intensity, if 10 yr R > 7.5% high intensity

- Adults > 7.5 % estimated 10-year risk of ASCVD
  ➢ Moderate to high intensity
Table 2. Treatment Recommendations Based on Different Guidelines

<table>
<thead>
<tr>
<th>Treatment Categories</th>
<th>Guideline (^3)</th>
<th>(\text{ACC/AHA}^5)</th>
<th>(\text{ATP-III}^4)</th>
<th>(\text{ESC}^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men (n = 1894)(^b)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment recommended</td>
<td>96.4 (95.4-97.1)</td>
<td>52.0 (49.8-54.3)</td>
<td>66.1 (64.0-68.3)</td>
<td></td>
</tr>
<tr>
<td>Treatment considered</td>
<td>3.3 (2.6-4.2)</td>
<td>14.2 (12.6-15.8)</td>
<td>31.6 (29.5-33.7)</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>0.3 (0.1-0.7)</td>
<td>33.8 (31.7-35.9)</td>
<td>2.3 (1.6-2.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Women (n = 2315)(^b)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment recommended</td>
<td>65.8 (63.8-67.7)</td>
<td>35.5 (33.5-37.5)</td>
<td>39.1 (37.1-41.2)</td>
<td></td>
</tr>
<tr>
<td>Treatment considered</td>
<td>14.2 (12.8-15.7)</td>
<td>14.1 (12.7-15.6)</td>
<td>51.4 (49.3-53.4)</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>20.0 (18.3-21.6)</td>
<td>50.4 (48.4-52.5)</td>
<td>9.5 (8.3-10.8)</td>
<td></td>
</tr>
</tbody>
</table>
ACC/AHA guidelines superior to ESC/EAS guidelines for primary prevention with statins in non-diabetic Europeans: the Copenhagen Population Study

Eur heart J (2016) 0, 1-9
Compared with the ESC/EAS guidelines, the ACC/AHA guidelines were superior for primary prevention of ASCVD, that is, for assigning statin therapy to those who would benefit the most.
A 50 yr male
non diabetic and non smoker
hypertensive on amlodipine 5 mg daily & HCTZ 12.5 mg/day
BP of 150/90 mm Hg
T-cholesterol 180 mg/dl, HDL-C 44mg/dl, LDL-C 98 mg/dl, TG 190 mg/dl

Which of the following is the best treatment option?

a. He should receive both aspirin and statin
b. Increase amlodipine to 10 mg/day before consideration of primary prevention drugs
c. Start atorvastatin 20 mg/day or its equivalent
d. Intensified healthy heart habits should be enough
e. Start atorvastatin 80 mg/day or its equivalent
Aspirin Evidence: Primary Prevention

Physician’s Health Study (PHS)
22,071 male participants randomized to aspirin (325 mg every other day) followed for an average of 5 years

<table>
<thead>
<tr>
<th>End point</th>
<th>Relative Risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Mortality</td>
<td>0.96 (0.60-1.54)</td>
<td>0.87</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>0.34 (0.15-0.75)</td>
<td>0.007</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>0.59 (0.47-0.74)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Total</td>
<td>0.56 (0.45-0.70)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>1.51 (0.54-4.28)</td>
<td>0.43</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>1.20 (0.91-1.59)</td>
<td>0.20</td>
</tr>
<tr>
<td>Total</td>
<td>1.22 (0.93-1.60)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Aspirin reduces the risk of myocardial Infarction among men

CI=Confidence interval, CV=Cardiovascular
Effect of Aspirin on Mortality in the Primary Prevention of Cardiovascular Disease

Nine randomized controlled trials enrolling 100,076 participants were included.
- Myocardial Infarction $\downarrow$ 17%
- Ischemic stroke $\downarrow$ 12%
- Hemorrhagic Stroke $\uparrow$ 42%

No change

- Cardiovascular events $\downarrow$ 12%

Favour no aspirin

- Major Bleeding
- GI Bleeding

- All-cause mortality $\downarrow$ 6%

Am J Med 2011; 124:621
Aspirin and diabetes

• Absolute or relative aspirin resistance –
  – 40% of patients
  – ↑ risk with poor metabolic control of diabetes

• On the bases of this ongoing uncertainty large-scale randomized clinical trials are currently underway
  – ASCEND
  – ACCEPT-D
  – ASPREE
The ADA, AHA, and ACC recommend:

1. Aspirin is **reasonable** in diabetic patients whose 10-year risk of events is >10% (men age >50 years and women age >60 years with at least 1 additional risk factor)

2. Aspirin **should not** be recommended in diabetes patients at **low risk** of cardiovascular events

3. Aspirin **may be** considered for diabetes patients at **intermediate risk** of cardiovascular events
   - younger patients with at least 1 risk factor
   - older patients with no risk factors
   - patients with a 10-year risk of 5% to 10%
3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, statins
Outcomes of statin treatment

• Regression of atherosclerosis
• Reduced incidence of cardiovascular events and death
INTRAVASCULAR ULTRASOUND IMAGES AT BASELINE AND FU

A. Determination of Atheroma Area
   - Landmarks
   - EEM Area
   - Lumen Area
   - Atheroma Area

   - Vein
   - Side Branch

B. Change in Atheroma Area From Baseline to Follow-up
   - Baseline
     - Lumen Area 7.7 mm²
     - EEM Area 20.7 mm²
     - Atheroma Area 3.0 mm²
   - Follow-up
     - Lumen Area 9.6 mm²
     - EEM Area 17.1 mm²
     - Atheroma Area 7.4 mm²

NISSSEN SE ET AL, JAMA: 291: 1071-1080; 2004
Effect of statins on atherosclerosis

Figure 3. Categorical Changes in Left Ventricular Mass Index and Intimal Medial Thickness by Treatment Group, SANDS Randomized Trial

Howard, B. V. et al. JAMA 2008;299:1678-1689
Mean cIMT during 24 months of therapy

Longitudinal, repeated measures analysis

<table>
<thead>
<tr>
<th>Months</th>
<th>Mean IMT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.69</td>
</tr>
<tr>
<td>12</td>
<td>0.69</td>
</tr>
<tr>
<td>18</td>
<td>0.70</td>
</tr>
<tr>
<td>24</td>
<td>0.71</td>
</tr>
</tbody>
</table>

P=0.88

Data on vessel wall area (top), lumen area (middle), and maximal vessel wall thickness (bottom) at baseline and 6 and 12 months after simvastatin therapy for aortic (left) and carotid plaques (right).

Corti R et al. Circulation 2001;104:249-252
Meta-Analysis of Intensive Statin Therapy in ACS

Hulten E, et al. *Arch Intern Med*. 2006;166:1814-1821

**Any Cardiovascular Event**

<table>
<thead>
<tr>
<th>Time</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Month</td>
<td>1.02 (0.95-1.09)</td>
</tr>
<tr>
<td>4 Months</td>
<td>0.84 (0.72-1.02)</td>
</tr>
<tr>
<td>6 Months</td>
<td>0.76 (0.70-0.84)</td>
</tr>
<tr>
<td>12 Months</td>
<td>0.80 (0.76-0.84)</td>
</tr>
<tr>
<td>24 Months</td>
<td>0.81 (0.77-0.87)</td>
</tr>
<tr>
<td>Pooled</td>
<td>0.84 (0.76-0.94)</td>
</tr>
</tbody>
</table>
Summary

• The mechanisms of benefit are incompletely understood.
• Regression of atherosclerosis occurs in only a minority of patients.
• Clinical benefits of lipid lowering are seen earlier than six months, before significant regression could occur.
Clinical studies that indicated benefit of statins beyond lipid lowering

Other factors:

1. LIPID
2. CARE
3. MIRACL
4. HPS

Pleiotropic effects
- ✓ Plaque stabilization
- ✓ Reduced inflammation
- ✓ Reversal of endothelial dysfunction
- ✓ Decreased thrombogenicity
PROVE IT–TIMI 22
Clinical Relevance of Achieved LDL-C and Achieved CRP Combined after Statin Therapy

- LDL ≥70 mg/dl, CRP ≥2 mg/L
- LDL ≥70 mg/dl, CRP < 2 mg/L
- LDL < 70 mg/dl, CRP ≥2 mg/L
- LDL < 70 mg/dl, CRP < 2 mg/L
- LDL < 70 mg/dl, CRP < 1 mg/L

Achieved CRP on Statin Therapy vs. Number of Risk Factors

- **Standard therapy (Prava 40)**
- **Intensive Therapy (Atorva 80)**

**Risk factors**
1. BMI > 25
2. Current smoker
3. HDL < 50
4. TG > 150
5. Glucose > 110
6. BP > 130/85
7. LDL > 70

*KK Ray et al. JACC 2005*

\[ P_{\text{trend}} < 0.0001 \text{ for each} \]
The role of statins in improving clinical outcome in primary prevention: THE EVIDENCE
6595 men, 45 to 64 years of age, with a mean cholesterol of 272 mg/dl

Figure 2. Kaplan–Meier Analysis of the Time to a Definite Non-fatal Myocardial Infarction or Death from Coronary Heart Disease, According to Treatment Group.
JUPITER
Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.46-0.69
P < 0.00001

Number Needed to Treat (NNT\textsubscript{5}) = 25

- 44 %
CHD Prevention Trials with Statins in Diabetic Subjects: **Subgroup Analyses**

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>No.</th>
<th>Baseline LDL-C, mg/dl (mmol/L)</th>
<th>LDL-C Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>Lovastatin</td>
<td>155</td>
<td>150 (3.9)</td>
<td>25%</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin</td>
<td>3985</td>
<td>127 (3.3)</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Secondary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARE</td>
<td>Pravastatin</td>
<td>586</td>
<td>136 (3.6)</td>
<td>28%</td>
</tr>
<tr>
<td>4S</td>
<td>Simvastatin</td>
<td>202</td>
<td>186 (4.8)</td>
<td>36%</td>
</tr>
<tr>
<td>LIPID*</td>
<td>Pravastatin</td>
<td>782</td>
<td>150 (3.9)</td>
<td>25%</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin</td>
<td>1978</td>
<td>127 (3.3)</td>
<td>30%</td>
</tr>
</tbody>
</table>

*LDL-C values for overall group

The trial was terminated 2 years earlier than expected because the prespecified early stopping rule for efficacy had been met. Atorvastatin reduced the death rate by 27%.

“The debate about whether all people with this disorder warrant statin treatment should now focus on whether any patients are at sufficiently low risk for this treatment to be withheld.”

18 randomized controlled trials with 19 trial arms (56,934 patients)

- The mean age was 57 yrs
- 60.3% were men
- 85.9% were Caucasian
- the use of statins reduced
  - fatal non-fatal CVD events
  - all-cause mortality

Cochrane Database Syst Rev 2013;1:CD004816
meta-analysis of individual data from 27 randomised trials

Cholesterol Treatment Trialists’ (CTT) Collaborators

Vascular events avoided per 1000

LDL cholesterol reduction (mmol/L)
With statin treatment

Lancet 2012; 380: 581–90
Statin safety

Side effects of intensive statin therapy with the exception of simvastatin 80 mg daily:

- **Myopathy**: 0.5 per 1000 over 5 years
- **Rhabdomyolysis**: 0.1 per 1000 over 5 years
- **Hemorrhagic stroke**: 0.5 per 1000 over 5 years
- **Diabetes**: absolute risk of 0.1% per year
  
  *(more than 50-times smaller than the absolute benefit)*

*Lancet 2012; 380: 581–90*
Statin safety...

characteristics predisposing to statin adverse effects

- Multiple or serious comorbidities, including impaired renal or hepatic function
- History of statin intolerance or muscle disorders
- Unexplained ALT elevations >3 times ULN
- Patient characteristics or concomitant use of drugs affecting statin metabolism
- >75 years of age
- History of hemorrhagic stroke
- Asian ancestry
• A 50 yr male
• non diabetic and non smoker
• hypertensive on amlodipine 5 mg daily & HCTZ 12.5 mg /day
• BP of 150/90 mm Hg
• T-cholesterol 180 mg/dl, HDL-C 44mg/dl, LDL-C 98 mg/dl, TG 190 mg/dl

Which of the following is the best treatment option?

a. He should receive both aspirin and statin
b. Increase amlodipine to 10 mg/day before embarking on primary prevention drugs

c. Start atorvastatin 20 mg/day or its equivalent (10-year risk 11.8%)

d. Intensified healthy heart habits should be enough

e. Start atorvastatin 80 mg/day or its equivalent
Any action beyond statins?
A 65 yr male
- diabetic and hypertensive
- amlodipine 10mg/day, lisinopril 40 mg/day and furosemide 40 mg/day
- stopped smoking a month back
- BP 160/85 mm Hg
- Resting ECG is normal
- **T-cholesterol 185mg/dl, HDL-C 31mg/dl, LDL-C 106 mg/dl, TG 240 mg/dl**
- Creatinine 1.7 mg/dl

Indicate the next correct management step
a. moderate intensity statin
b. moderate intensity statin plus aspirin
c. high intensity statin
d. high intensity statin plus aspirin
e. high intensity statin plus aspirin plus consideration of a non statin antilipid agent
Undercutting the “statin hypothesis”

several previous trials have failed to show a significant ASCVD benefit of nonstatin lipid modifying agents when used alone or added to statins
The Statin Decade: For LDL: “Lower is Better”

Role of PCSK9 in regulation of LDL receptor

1. PCSK9
2. LDL particle
3. Clathrin-coated vesicle
4. LDL Receptor
Impact of PCSK9 monoclonal antibody on LDL receptor

1. Alirocumab
2. Evolocumab
3. Bococizumab

1. Alirocumab, Evolocumab, and Bococizumab bind to LDL particle.
2. Endocytosis of the LDL particle occurs.
3. Clathrin-coated vesicle forms.
4. LDL-R is recycled.
5. LDL Receptor is present in the membrane.
Alirocumab Significantly Reduced LDL-C from Baseline to Week 24 versus Placebo

Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C
All patients on background of maximally-tolerated statin ± other lipid-lowering therapy

\[
\text{LS mean (SE)} = -61.0
\]

\[
\text{% change from baseline to Week 24} = -61.9\% (1.3); \quad P<0.0001
\]

\[
\text{LS mean difference (SE) versus placebo:}
\]

\[
N=1530 \quad N=780
\]

Intent-to-treat (ITT) analysis
Evolocumab
OSLER-trial

![Graph showing LDL cholesterol levels over weeks for standard therapy and Evolocumab.]

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 weeks</th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>36 weeks</th>
<th>48 weeks</th>
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</thead>
<tbody>
<tr>
<td><strong>No. at Risk</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Standard therapy</td>
<td>1419</td>
<td>394</td>
<td>1388</td>
<td>1376</td>
<td>402</td>
<td>1219</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>2976</td>
<td>864</td>
<td>2871</td>
<td>2828</td>
<td>841</td>
<td>2508</td>
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<tr>
<td><strong>Absolute reduction (mg/dl)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>60.4</td>
<td>73.4</td>
<td>70.4</td>
<td>72.7</td>
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<td></td>
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<tr>
<td>Evolocumab</td>
<td></td>
<td></td>
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<tr>
<td><strong>Percentage reduction</strong></td>
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<tr>
<td>Standard therapy</td>
<td>45.3</td>
<td>60.9</td>
<td>58.8</td>
<td>54.0</td>
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<tr>
<td>Evolocumab</td>
<td></td>
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<tr>
<td><strong>P value</strong></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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*Graph from N Engl J Med 2015;372:1500-9*
Evolocumab
OSLER-trial
Cumulative Incidence of CVD Events

1. The observation that a nonstatin lipid-lowering agents can also reduce CVD risk does support the **LDL hypothesis** *(i.e., that lowering LDL cholesterol leads to a reduction in cardiovascular events)*

2. Most importantly it undercuts the “statin hypothesis,” *only statins are beneficial*
Consideration of non statin therapy

- less than 50% decrement in high intensify statin therapy
- Clinical ASCVD with comorbidities
  - Diabetes
  - Recent (< 3 months) ASCVD event
  - ASCVD event while on statin treatment
  - Poorly controlled other major risk factors
  - Elevated lipoprotein (a)
  - CKD not on hemodialysis
- Clinical ASCVD & baseline LDL > 190 mg/dl
Case 2, answer

- A 65 yr male
- diabetic and hypertensive for more than 10 yrs
- amlodipine 10mg/day, lisinopril 40 mg/day and furosemide 40 mg/day
- stopped smoking a month back
- BP 160/85 mm Hg
- Resting ECG is normal & no inducible ischemia on stress test
- T-cholesterol 185mg/dl, HDL-C 31mg/dl, LDL-C 106 mg/dl, TG 240 mg/dl
- Creatinine 1.7 mg/dl

Indicate the next correct management step
a. moderate intensity statin
b. moderate intensity statin plus aspirin
c. high intensity statin
d. high intensity statin plus aspirin
e. high intensity statin plus aspirin plus consideration of a non statin antilipid agent (10 yr risk 64.7%)
Analysis of 32,000 registered cases at Addis Cardiac Hospital
### Analysis of 32,000 registered cases at Addis Cardiac Hospital

<table>
<thead>
<tr>
<th>Type of drug</th>
<th>No</th>
<th>Percent</th>
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<tr>
<td>Statin</td>
<td>144</td>
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<td>Antiplatelet</td>
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<td>Diuretics</td>
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<tr>
<td>ACE inhibitors</td>
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<td>Beta blocker</td>
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<td>CCB</td>
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</table>
Summary

1. If Clinical evaluation reveals CVD at any age high intensity statin and aspirin

2. a fasting lipid value should be obtained at least once every 5 years in individuals 20 and above
   If LDL > 190 mg/dl statin therapy

3. In individuals 40 and above 10-year risk of CVD should be calculated
   if 10-year risk > 7.5% statin therapy
Thank you