ASCVD RISK REDUCTION THERAPY: BEYOND STATINS

“Vascular harmony”

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University of Texas Health Science Center
Director of Cardiac Catheterization labs
Director of clinical proteomics
Which is best to measure

Monitor therapy targets

Lower continues to be better
Lower global known risk factors
  Age
  Metabolics
  Wall stress
  Obesity
  Waist circumference
  Number of spouses

Fasting or non fasting?

What is current guidelines
QUESTION 1: WHICH IS BEST CV EVENT PREDICTOR

1. LDL
2. LDL direct
3. Apo B
4. Particle number-LDL
5. HDL
6. HDL particle number
7. Non fasting triglycerides
8. Fasting triglycerides

Acute event?

Atherosclerosis ↓ Metabolic / wall stress burden over time
CASE 1: CARDIOLOGY

- 56 y/o Hispanic male T2DM chest pain history
- Baseline ETT with 3 mm changes
- Metformin 2 gm/day
- HbA1c 7.8
- HDL low 32 mg/dl
- Triglycerides elevated 380 mg/dl
- LDL 102 mg/dl
- BP 154/78
INTERHEART trial: 9 modifiable risk factors account for 90% of myocardial infarctions

Adapted from Lancet 2004; 364: 937–52
Interlinked pathophysiologic mechanisms of increased CV risk in HTN & abnormal metabolics

Insulin resistance / HT
EC dysfunction
SPRINT / ACCORD BP
STENO-2

Translational biology
PROATHEROGENIC FLOW INCREASES ENDOTHELIAL STIFFNESS

Laminar flow - normal

Oscillatory flow - disturbed

Stained for uptake of LDL

oxLDL receptor CD36 (endothelial scavenger receptors)

↑ EC stiffness

↑ LDL uptake endothelial cells

↑ stillness (higher number) - AA
Normal - DA

Arterioscler Thromb Vasc Biol. 2018;38:64-75
Incident CVD in 27,673 initially healthy women in the Women's Health Study.
Within each triglyceride subgroup, the lower the LDL level, the lower the amount of cholesterol per particle.

Median values were 131 mg/dL for LDL-C and 1414 nmol/L for LDL-P.
**hsCRP: INFLAMMATION IS IMPORTANT**

**Risk RATIO** -adjusted for age, sex, and study, from a **meta-analysis of 54 prospective cohort studies** from the **Emerging Risk Factors Collaboration**

[Lancet. 2010;375:132–140](https://doi.org/10.1016/S0140-6736(10)61046-4)
METABOLICS ARE IMPORTANT: PATHOBIOLOGY: APO B

Small Dense LDL $\uparrow \uparrow$ Ischemic disease

RR

<255 A size

Large LDL

Small dense

Apo B $<116$ mg/dl

Apo B $>116$

Large LDL

Small dense

2034 men of the Quebec Cardiovascular Study

Circulation. 2001;104:2295-2299
New trials
# LDL-C and Lipid Changes

**IMPROVE-IT**

<table>
<thead>
<tr>
<th></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>-16.7</td>
<td>-19.3</td>
<td>-16.7</td>
<td>+0.6</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

Median Time avg
69.5 vs. 53.7 mg/dL

<table>
<thead>
<tr>
<th>QE</th>
<th>R</th>
<th>1</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>8990</td>
<td>8889</td>
<td>8230</td>
<td>7701</td>
<td>7264</td>
<td>6864</td>
<td>6583</td>
<td>6256</td>
<td>5734</td>
<td>5354</td>
<td>4508</td>
<td>3484</td>
<td>2608</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>9009</td>
<td>8921</td>
<td>8306</td>
<td>7843</td>
<td>7289</td>
<td>6939</td>
<td>6607</td>
<td>6192</td>
<td>5684</td>
<td>5267</td>
<td>4395</td>
<td>3387</td>
<td>2569</td>
</tr>
</tbody>
</table>

Number at risk:

## Individual Cardiovascular Endpoints and CVD/MI/Stroke

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HR</th>
<th>Simva*</th>
<th>EZ/Simva*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>0.99</td>
<td>15.3%</td>
<td>15.4%</td>
<td>0.782</td>
</tr>
<tr>
<td>CVD</td>
<td>1.00</td>
<td>6.8%</td>
<td>6.9%</td>
<td>0.997</td>
</tr>
<tr>
<td>CHD</td>
<td>0.96</td>
<td>5.8%</td>
<td>5.7%</td>
<td>0.499</td>
</tr>
<tr>
<td>MI</td>
<td>0.87</td>
<td>14.8%</td>
<td>13.1%</td>
<td>0.002</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.86</td>
<td>4.8%</td>
<td>4.2%</td>
<td>0.052</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.79</td>
<td>4.1%</td>
<td>3.4%</td>
<td>0.008</td>
</tr>
<tr>
<td>Cor revasc ≥ 30d</td>
<td>0.95</td>
<td>23.4%</td>
<td>21.8%</td>
<td>0.107</td>
</tr>
<tr>
<td>UA</td>
<td>1.06</td>
<td>1.9%</td>
<td>2.1%</td>
<td>0.618</td>
</tr>
<tr>
<td>CVD/MI/stroke</td>
<td>0.90</td>
<td>22.2%</td>
<td>20.4%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*7-year event rates (%)

Ezetimibe/Simva Better
Simva Better

Lessons from completed LDL lowering trials
Risk reduction is related to LDL decrease

Data from trials of:
• Statin vs placebo
• More vs less intense statin therapy.
• Combination therapy with ezetimibe

Regression line reveals:
1.0 mmol/l fall in LDLc translates into a 22% decrease in risk

CTTC Lancet (2005) 367;1267-78
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

Evolocumab SC 140 mg Q2W or 420 mg QM

Placebo SC Q2W or QM

Follow-up Q 12 weeks

Am Heart J 2016;173:94-101
Cohort of 11,077 patients who
• had all measurements through 120 weeks
• did not discontinue study drug
• did not Δ 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

Months from Randomization

Evolocumab
Placebo

14.6%
12.6%
Key Secondary Endpoint

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

Evolocumab
Placebo

CV Death, MI, or Stroke

0 6 12 18 24 30 36

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

Months from Randomization

An Academic Research Organization of Brigham and Women’s Hospital and Harvard Medical School
# 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>
# More Intensive LDL-C Lowering & CV Death

## No clear benefit on CV mortality

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>More Intensive Rx Arm</th>
<th>Less Intensive Rx Arm</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE-IT TIMI 22</td>
<td>2004</td>
<td>27</td>
<td>36</td>
<td>0.74 (0.45-1.22)</td>
</tr>
<tr>
<td>A2Z</td>
<td>2004</td>
<td>86</td>
<td>111</td>
<td>0.76 (0.57-1.01)</td>
</tr>
<tr>
<td>TNT</td>
<td>2005</td>
<td>101</td>
<td>127</td>
<td>0.80 (0.61-1.03)</td>
</tr>
<tr>
<td>IDEAL</td>
<td>2005</td>
<td>223</td>
<td>218</td>
<td>1.03 (0.85-1.24)</td>
</tr>
<tr>
<td>SEARCH</td>
<td>2010</td>
<td>565</td>
<td>572</td>
<td>0.99 (0.88-1.11)</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>2015</td>
<td>538</td>
<td>537</td>
<td>1.00 (0.89-1.13)</td>
</tr>
<tr>
<td>Summary</td>
<td></td>
<td>1540</td>
<td>1601</td>
<td>0.96 (0.90-1.03)</td>
</tr>
</tbody>
</table>

**NEJM** 2004;350:1495-504  
**JAMA** 2004;292:1307-16  
**NEJM** 2005;352:1425-35  
**JAMA** 2005;294:2437-45  
**Lancet** 2010;376:1658-69  
**NEJM** 2015;372:2387-97
LOWER LDL IS BETTER FOR PAD EVENTS

- **LDL-C Lowering With Evolocumab in Patients With PAD (FOURIER trial)**
- **History of diabetes mellitus, N = 27564/1580 and PAD 43%**
- **84% Hypertension**
- **LDL 94 mg/dL to 31 mg/dL @ 48 weeks**

**Circulation. 1.23.2018;137:338–350**
Locally Weighted Polynomial Regression (LOESS) Plot with 95% confidence limits
**BOTTOM LINE GOAL GUIDELINES (NOT LAW)**

- **ESC 2016**
  - Very high risk: <70
  - High risk: <100
  - >7.5% @ 10 yrs

- **CCS 2016**
  - ACS: <70
  - All groups: <80

- **AHA 2016**
  - ASCVD: 70
  - Diabetes: <100

- **ACCE 2017**
  - Very high risk: <55

**IMPROVE IT FOURIER**

- >50% reduction
- Non HDL <100
Closing comments
Patients who require <25% additional lowering of LDL-C, patients with recent ACS <3 months, cost considerations with recent availability of generic ezetimibe and future cost savings, ease of use as oral agent with low pill burden, patient preferences, heart failure, hypertension, age >75 years, diabetes, stroke, CABG, PAD, eGFR <60 ml/min/1.73 m², and smoking.

Clinical ASCVD and comorbidities require >25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial non-statin agent. The clinician–patient discussion should consider the extent of available scientific evidence for net ASCVD risk-reduction benefit, cost, administration by subcutaneous injection every 14-day or monthly dosing schedule, and storage requirements (refrigeration).

JACC 2017;70:1785 guidelines
BEST NON FASTING TRIGLYCERIDE CUT POINT FOR CV EVENTS IS 175 MG/DL

Kaplan Meier curve demonstrating Survival is significantly decreased in individuals with nonfasting triglycerides greater than or equal to the optimal threshold of 175mg/dL

High triglycerides may promote atherosclerosis via the accumulation of triglyceride-rich remnant particles within the endothelium

6,391 participants in the Women’s Health Study

Clin Chem. 2015 September ; 61(9): 1156–1