Come e perché raggiungere il target lipidico dopo sindrome coronarica acuta

Michele Brignole

Dipartimento di Cardiologia - Lavagna
INTERHEART

Attributable risk %

- Overall Women: 94%
- Overall men: 90%
- Lipids: 49%
- Smoking: 35%
- Psychosocial: 32%
- Obesity: 20%
- Hypertension: 18%
- No fruits & vegetables: 14%
- No physical activity: 12%
- Diabetes: 10%
- No alcohol: 7%
Diminishing risk reduction for the same relative LDL-C lowering with lower baseline LDL-C. Calculations based on the CTTC analysis.
IDEAL trial


Pts with previous myocardial infarction

- **Simva 20–40**: 99.8 mg/dl
  - 100 mg/dl
- **Atorva 80**: 80 mg/dl
  - 80 mg/dl
IDEAL trial


![Cumulative Hazard Graph](image)

- **Simvastatin**
- **Atorvastatin**

**Cumulative Hazard, %**

- 0
- 4
- 8
- 12
- 16

**Years Since Randomization**

0 1 2 3 4 5

**HR, 0.89; 95% CI, 0.78-1.01; P = .07**
Effects of rosuvastatin 20 mg on LDL, HDL, TG, and hsCRP

Primary prevention

LDL decrease 50 percent at 12 months

Ridker et al. NEJM 2008
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$_5$) = 25

Ridker et al NEJM 2008
Acute coronary syndrome

Median Time avg
69.5 vs. 53.7 mg/dL
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
Riduzione percentuale di colesterolo LDL


% riduzione LDL

- Pravastatina 10 mg: 20%
- Pravastatina 20 mg: 25%
- Simvastatina 10 mg: 29%
- Pravastatina 40 mg: 31%
- Simvastatina 20 mg: 35%
- Atorvastatina 10 mg: 38%
- Simvastatina 40 mg: 41%
- Atorvastatina 20 mg: 45%
- Rosuvastatina 10 mg: 46%
- Atorvastatina 40 mg: 52%
- Rosuvastatina 20 mg: 53%
- Rosuvastatina 40 mg: 55%
- Atorvastatina 80 mg: 55%
Riduzione percentuale di colesterolo LDL


% riduzione LDL

Prava 10 + ezetim 10
Prava 20 + ezetim 10
Simva 10 + ezetim 10
Prava 40 + ezetim 10
Simva 20 mg + ezetim 10
Atorva 10 + ezetim 10
Simva 40 mg + ezetim 10
Atorva 20 + ezetim 10
Rosu 10 + ezetim 10
Atorva 40 + ezetim 10
Rosu 20 + ezetim 10
Rossa 40 + ezetim 10
Atorva 80 + ezetim 10
Lifetime risk of death from cardiovascular disease among men at 55 years of age

Risk factors:
- blood pressure
- cholesterol level
- smoking status
- diabetes status

18 studies involving a total of 257,384 subjects
Lifetime risk of death from cardiovascular disease among women at 55 years of age

Risk factors:
- blood pressure
- cholesterol level
- smoking status
- diabetes status

18 studies involving a total of 257,384 subjects
### Comparative CHD Risk Reduction of Earlier and Later LDL-C Lowering

**Early LDL lowering (at birth - genetic studies)**

**Late LDL lowering (at mean age of 63 yrs – statin trials)**

<table>
<thead>
<tr>
<th>Lower LDL-C</th>
<th>Meta-Analysis</th>
<th>Sample Size (N)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mmol/L</td>
<td>Genetic Studies</td>
<td>312,321</td>
<td>0.46 (0.41-0.51)</td>
</tr>
<tr>
<td>(38.7 mg/dl)</td>
<td>Statin Trials</td>
<td>169,138</td>
<td>0.76 (0.74-0.78)</td>
</tr>
<tr>
<td>0.5 mmol/L</td>
<td>Genetic Studies</td>
<td>312,321</td>
<td>0.67 (0.64-0.72)</td>
</tr>
<tr>
<td>(19.3 mg/dl)</td>
<td>Statin Trials</td>
<td>169,138</td>
<td>0.87 (0.86-0.88)</td>
</tr>
<tr>
<td>0.25 mmol/L</td>
<td>Genetic Studies</td>
<td>312,321</td>
<td>0.82 (0.80-0.85)</td>
</tr>
<tr>
<td>(9.7 mg/dl)</td>
<td>Statin Trials</td>
<td>169,138</td>
<td>0.93 (0.93-0.94)</td>
</tr>
<tr>
<td>0.125 mmol/L</td>
<td>Genetic Studies</td>
<td>312,321</td>
<td>0.91 (0.89-0.92)</td>
</tr>
<tr>
<td>(4.8 mg/dl)</td>
<td>Statin Trials</td>
<td>169,138</td>
<td>0.96 (0.96-0.97)</td>
</tr>
</tbody>
</table>

*J Am Coll Cardiol 2012;60: 2631–9*
Comparative CHD Risk Reduction of Earlier and Later LDL-C Lowering

Prolonged exposure to lower LDL-C beginning early in life associated with 3-fold greater clinical benefit for each unit lower LDL than treatment with a statin started later in life.

![Graph showing the comparison between genetic studies and statin trials for different LDL-C levels across different ages.](image.png)

**J Am Coll Cardiol 2012;60: 2631–9**
PCSK9 Therapeutic Hypothesis

**PCSK9 Synthesis Inhibitors**
Durably block PCSK9 synthesis and all intracellular and extracellular PCSK9 functions

**Anti-PCSK9 Mabs**
Transiently block PCSK9 binding to LDL receptor (LDLR)
Effect of Evolocumab or Ezetimibe Added to Moderate- or High-Intensity Statin Therapy on LDL-C Lowering in Patients With Hypercholesterolemia
The LAPLACE-2 Randomized Clinical Trial

![Graph showing mean % change from baseline in LDL-C at the mean of wk 10 and 12 for different treatments.]

- Placebo (every 2 wk)
- Ezetimibe (daily) + placebo (every 2 wk)
- Evolocumab (every 2 wk)
- Placebo (monthly)
- Ezetimibe (daily) + placebo (monthly)
- Evolocumab (monthly)

**Treatments:**
- High-Intensity Statin: Atorvastatin (80 mg), Rosuvastatin (40 mg), Atorvastatin (10 mg), Rosuvastatin (5 mg), Simvastatin (40 mg)
- Moderate-Intensity Statin: Atorvastatin (80 mg), Rosuvastatin (40 mg), Atorvastatin (10 mg), Rosuvastatin (5 mg), Simvastatin (40 mg)
Effect of Evolocumab or Ezetimibe Added to Moderate- or High-Intensity Statin Therapy on LDL-C Lowering in Patients With Hypercholesterolemia
The LAPLACE-2 Randomized Clinical Trial
A Randomized, Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of a Monoclonal Antibody to PCSK9, SAR236553/REGN727, in Patients with Primary Hypercholesterolemia

James M. McKenney, PharmD, 1 Michael J. Koren, MD, FACC, 2 Dean J. Kereiakes, MD, FACC, 3 Corinne Hanotin, MD, 4 Anne-Catherine Ferrand, 4 Evan A. Stein, MD, PhD 5

1 National Clinical Research-Richmond, Inc., Richmond, VA, USA; 2 Jacksonville Center for Clinical Research, Jacksonville, FL, USA; 3 The Carl and Edyth Lindner Center for Research and Education at the Christ Hospital, Cincinnati, OH, USA; 4 Sanofi, Paris, France; 5 Metabolic and Atherosclerotic Research Center, Cincinnati, OH, USA.

Clinicaltrials.gov no. NCT01288443
Change in Calculated LDL-C at 2 Weekly Intervals from Baseline to Week 12

Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.
ALN-PCSsc, an RNAi Investigational Agent That Inhibits PCSK9 Synthesis With the Potential for Effective Bi-Annual Dosing: Interim Results

Kevin Fitzgerald, PhD

Co-authors: Amy Simon¹, Suellen White¹, Anna Borodovsky¹, Nirav Patel¹, Brian Bettencourt¹, Valerie Clausen¹, Jay Horton³, Peter Wijngaard², Robert Kauffman¹, David Kallend⁶

¹ – Alnylam Pharmaceuticals, 300 Third Street, Cambridge, MA 02142 USA
² – The Medicines Company, 8 Sylvan Way, Parsippany, NJ 07054 USA
³ – University of Texas South Western, 5323 Harry Hines Blvd, Dallas, TX 75390 USA

Declaration of Interest: Employees of Alnylam Pharmaceuticals¹
Employees of The Medicines Company²
Initial ALN-PCSsc Phase 1 Study Results
MD LDL-C Lowering Relative to Baseline

Max LDL-C reduction of 83.0% with mean max of 64.4% (+/- 5.4)

Data reported is from database transfer Sept. 24th 2015

qW, q2W, or qM

S° = On a stable dose of statins
Two MD subjects excluded:
One placebo subject elected to discontinue;
One subject in 300 mg statin group was incarcerated on Day 14
Come e perché raggiungere il target lipidico dopo sindrome coronarica acuta

- Il più presto possibile (prima dell’inizio dell’ATS)
- Al valore di LDL più basso possibile (40-50 mg/dl)