PREVENZIONE SECONDARIA DELLA CARDIOPATIA ISCHEMICA. VA RIVISTO IL VALORE SOGLIA DI 70 MG/DL PER LA COLESTEROLEMIA LDL ?

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Va rivisto il valore soglia di 70 mg/dl per la colesterolemia LDL?

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Prof. A. Zambon reports having received grants, consulting fees and/or honoraria and delivering lectures for:

- Abbott
- AstraZeneca
- Merck Sharp & Dohme
- Amgen
- Sanofi
- Alfasigma
- Mylan
- Chiesi
Va rivista la soglia di LDL-C <70 mg/dl?

Setting the stage

- The lower the LDL-C the better: Evidenze in era pre-PCSK9i

- PCSK9i Revolution: The lowest the LDL-C the best? Safe…Costs?

- In quali pazienti sarebbe opportuno rivedere (in basso) la soglia di LDL-C di <70 mg/dl

Take Home message
Every 39 mg/dl (1 mmol/L) reduction in LDL-C reduces annual CV risk by up to 28%, regardless of mechanism.

Data from studies of non-statin lipid-lowering medications superimposed upon data from the Cholesterol Treatment Trialists Collaboration (CTTC) 2005 meta-analysis. The IMPROVE-IT trial was adequately powered to show the efficacy on incremental LDL-C lowering on CV outcomes. [To convert, 100 mg/dL=2.59 mmol/L].

CV, cardiovascular; IMPROVE-IT, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol.

Va rivista la soglia di LDL-C<70 mg/dl?

- **Setting the stage:** tanto più si riduce (in assoluto – mg/dl) il colesterolo LDL tanto più si riduce il rischio CV, indipendentemente dall’approccio terapeutico

- **The lower the LDL-C the better:** evidenze in era pre-PCSK9i
Meta-analysis of 8 Statin Trials (Moderate- to High-Intensity Dosing): Patients Who Achieved Very Low LDL-C Levels Had Lower Risk for Major Cardiovascular Events

5% of patients achieving LDL-C<50 mg/dl

Adjusted* Hazard Ratio for Major CV Events

*adjusted for sex, age, smoking, diabetes, SBP, HDL-C, and trial

** >200 mg/dL for non-HDL-C

Very low LDL-C levels, lowest risk

Cutoffs: LDL-C, ApoB, non-HDL-C

Achieved On-Trial Atherogenic Cholesterol and Lipoprotein Concentration, mg/dL

Abbreviations: apo, apolipoprotein; CV, cerebrovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Va rivista la soglia di LDL-C<70 mg/dl?

- **Setting the stage:** tanto più riduco (in assoluto – mg/dl) il colesterolo LDL tanto più riduco il rischio CV indipendentemente dall’approccio terapeutico.

- **Evidenze in era pre-PCSK9i:** anche per LDL-C<70 mg/dl riduzione di LDL-C associata a riduzione rischio eventi CV.

- **PCSK9i Revolution:** *The lowest the LDL-C the best? E'* Sicuro...Costi?
Beyond The Statin ERA: For LDL: “The Lowest the Best”

R² = 0.9029  
p < 0.0001

IMPROVE IT (ezetimibe + statina)
≈90 FOURIER/ODYSSEY (PCSK9 inhibitor + statina)

Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial

Robert P Giugliano, Terje R Pedersen, Jeong-Gun Park, Gaetano M De Ferrari, Zbigniew A Gaciong, Richard Ceska, Kalman Toth, Ioanna Gouni-Berthold, Jose Lopez-Miranda, François Schiele, François Mach, Brian R Ott, Estella Kanevsky, Armando Lira Pineda, Ransi Somaratne, Scott M Wasserman, Anthony C Keech, Peter S Sever, Marc S Sabatine, on behalf of the FOURIER Investigators

Thank you to all the patients, investigators, coordinators, steering and executive committee members of the FOURIER and EBBINGHAUS trials, TIMI CEC, Adverse Events and statistical teams, Cambridge Cognition, and the sponsor, Amgen

Article available at www.thelancet.com
Slides available at www.TIMI.org
FOURIER:
Patients by LDL-C Levels

- LDL-C assessed at 4 wks (ultracentrifugation if <1 mM)
- Analyzed 5 groups by achieved LDL-C at 4 weeks
  1) <20 mg/dL (n=2669)
  2) 20-49 mg/dL (n=8003)
  3) 50-69 mg/dL (n=3444)
  4) 70-99 mg/dL (n=7471)
  5) ≥100 mg/dL was the referent group (n=4395)
- Pooled results across 2 Rx groups (evo, placebo)

FOURIER: CV DEATH, MI, or STROKE

LDL-C mg/dL | Adj HR (95% CI)
---|---
<20 | 0.69 (0.56-0.85)
20-49 | 0.75 (0.64-0.86)
50-69 | 0.87 (0.73-1.04)
70-99 | 0.90 (0.78-1.04)
≥100 | referent

P = 0.0001

SAFETY EVENTS

Adj P-values for trend >0.10 for each comparison

LDL-C (mg/dl) at 4 wks
- <20
- 20-49
- 50-69
- 70-99
- ≥100

SAE
AE->Discon
New DM
Cancer
Cataract

Neurocog
AST/ALT↑
CK↑
Non-CV death
Hem stroke

Efficacy and Safety of Further Lowering of Low-Density Lipoprotein Cholesterol in Patients Starting With Very Low Levels: A Meta-analysis

Marc S. Sabatine, MD, MPH; Stephen D. Wiviott, MD; KyungAh Im, PhD; Sabina A. Murphy, MPH; Robert P. Giugliano, MD, SM

The magnitude of clinical benefit of further LDL-C lowering in patients already with very low LDL-C levels remains debated

OBJECTIVE To evaluate efficacy and safety of further lowering LDL-C levels in patient populations presenting with median LDL-C levels of 1.8 mmol/L (70 mg/dL) or less.

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Participants</th>
<th>Type of Intervention</th>
<th>Drug</th>
<th>Achieved LDL-C, mmol/L</th>
<th>Median Duration of Follow-up, y</th>
<th>Overall No. of Major Vascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTTC (&lt;2 mmol/L)</td>
<td>NR</td>
<td>HMGCR Inhibitor (statin)</td>
<td>Various</td>
<td>1.7&lt;sup&gt;a&lt;/sup&gt;, NR</td>
<td>4.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1922</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>18 144</td>
<td>NPC1L1 inhibitor</td>
<td>Ezetimibe</td>
<td>1.8&lt;sup&gt;c&lt;/sup&gt;, 1.4</td>
<td>6.0</td>
<td>5104</td>
</tr>
<tr>
<td>FOURIER (&lt;1.8 mmol/L)</td>
<td>2034</td>
<td>PCSK9 inhibitor</td>
<td>Evolocumab</td>
<td>1.7&lt;sup&gt;d&lt;/sup&gt;, 0.5</td>
<td>2.1</td>
<td>184</td>
</tr>
<tr>
<td>REVEAL</td>
<td>30 449</td>
<td>CETP inhibitor</td>
<td>Anacetrapib</td>
<td>1.6&lt;sup&gt;e&lt;/sup&gt;, 1.4</td>
<td>4.1</td>
<td>4282</td>
</tr>
</tbody>
</table>

CTTC, Cholesterol Treatment Trialists Collaboration; CETP, cholesteryl ester transfer protein; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; LDL-C, low-density lipoprotein cholesterol; NPC1L1, Neimann-Pick C1-Like
Efficacy and Safety of Further Lowering of Low-Density Lipoprotein Cholesterol in Patients Starting With Very Low Levels
A Meta-analysis

Marc S. Sabatine, MD, MPH; Stephen D. Wiviott, MD; KyungAh Im, PhD; Sabina A. Murphy, MPH; Robert P. Giugliano, MD, SM

Meta-analysis of effect of 1-mmol/L LDL-C lowering on the risk of major vascular events

<table>
<thead>
<tr>
<th>Trial</th>
<th>Experimental Arm</th>
<th>Control Arm</th>
<th>RR (95% CI)</th>
<th>LDL-C Lowering Better</th>
<th>LDL-C Lowering Worse</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTTC &lt;2 mmol/L subgroup</td>
<td>910 (4.1)</td>
<td>1012 (4.6)</td>
<td>0.78 (0.65-0.94)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonstatin LDL-C lowering</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>2455 (4.5)</td>
<td>2649 (4.9)</td>
<td>0.79 (0.67-0.93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOURIER &lt;1.8 mmol/L subgroup</td>
<td>81 (3.7)</td>
<td>103 (4.9)</td>
<td>0.80 (0.61-1.04)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REVEAL</td>
<td>2068 (3.3)</td>
<td>2214 (3.5)</td>
<td>0.77 (0.63-0.96)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td>4604</td>
<td>4966</td>
<td>0.79 (0.70-0.88)</td>
<td></td>
<td></td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Overall summary</td>
<td>5514</td>
<td>5978</td>
<td>0.79 (0.71-0.87)</td>
<td></td>
<td></td>
<td>P &lt; .001</td>
</tr>
</tbody>
</table>

Δ LDL-C 39 mg/dl = -21% Major Vascular Events in patients with Baseline LDL-C 70 mg/dl
The newer, more costly therapies should be targeted to those who will benefit most, and only after other less expensive therapies have failed to meet risk-reduction goals.

Rather than using models to block access for patients, payers should work jointly with clinicians, who can identify those patients who will benefit most.

In so doing, we will assure the most cost-effective use of this important new class of drugs.
Va rivista la soglia di LDL-C<70 mg/dl?

- Setting the stage: tanto più riduco (in assoluto – mg/dl) il colesterolo LDL tanto più riduco il rischio CV indipendentemente dall’approccio terapeutico.

- Evidenze in era pre-PCSK9i: anche per LDL-C<70 mg/dl più basso LDL-C minor rischio eventi CV.

- The lowest the LDL-C the best: Sicuro (ad oggi)…Costi maggiori.

- Quali sono i pazienti a rischio CV estremo e potenziale massimo beneficio CV da soglia più bassa di LDL-C (es. LDL-C<50 mg/dl)?
The **TIMI Risk Score for Secondary Prevention (TRS 2P)** is a simple 9-point risk stratification tool for post-ACS patients.

**TRS 2°P Risk Indicators**
- CHF
- HTN
- Age ≥75
- DM
- Prior Stroke
- Prior CABG
- PAD
- eGFR <60
- Current Smoking

### ASCVD Risk Categories and LDL-C Treatment Goals

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors/10-year risk</th>
<th>Treatment goals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C (mg/dL)</td>
</tr>
<tr>
<td>Extreme risk</td>
<td>– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C &lt;70 mg/dL</td>
<td>&lt;55</td>
</tr>
<tr>
<td></td>
<td>– Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– History of premature ASCVD (&lt;55 male, &lt;65 female)</td>
<td></td>
</tr>
<tr>
<td>Very high risk</td>
<td>– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk &gt;20%</td>
<td>&lt;70</td>
</tr>
<tr>
<td></td>
<td>– DM or stage 3 or 4 CKD with 1 or more risk factor(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– HeFH</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>– ≥2 risk factors and 10-year risk 10%-20%</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>– DM or stage 3 or 4 CKD with no other risk factors</td>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
<td>≤2 risk factors and 10-year risk &lt;10%</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Low risk</td>
<td>0 risk factors</td>
<td>&lt;130</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not recommended.

Risk of CV Death, MI or Stroke With Each Risk Factor

- <2 yrs: HR 1.19 (1.04-1.37) P=0.01
- ≥2 yrs: 9.3%

- ≥2: HR 2.04 (1.78-2.35) P<0.001
- 1: 8.2%

- Yes: HR 1.47 (1.27-1.70) P<0.001
- No: 8.9%

Analyses in placebo arm
BENEFIT OF EVOLOOCUMAB BASED ON MULTIVESSEL DISEASE

**Multivessel Disease**

- **Placebo**
  - LDL-C≈30 mg/dl
  - HR 0.70 (95% CI 0.58-0.84)
  - P<0.001
  - ARR 3.4%
  - NNT 29

- **Evolocumab**
  - LDL-C≈90 mg/dl
  - HR 0.89 (95% CI 0.79-1.00)
  - P=0.055
  - ARR 1.3%
  - NNT 78

**No Multivessel Disease**

- **Placebo**
  - LDL-C≈90 mg/dl
  - HR 0.89 (95% CI 0.79-1.00)
  - P=0.055
  - ARR 7.6%

- **Evolocumab**
  - LDL-C≈30 mg/dl
  - HR 0.70 (95% CI 0.58-0.84)
  - P<0.001
  - ARR 9.2%
  - NNT 29
CV DEATH, MI OR STROKE IN PATIENTS WITH AND WITHOUT PERIPHERAL ARTERY DISEASE

PAD
N=3,642

27% RRR

HR 0.73
(0.59 – 0.91)
P=0.0040

No PAD
N=23,922

HR 0.81
95% CI (0.73 – 0.90)
P<0.001

Evolocumab
Bonaca MP et al. Circulation 2017;137

13.0%
3.5% ARR
NNT2.5y 29

+80%~

9.5%
7.6%
6.2%

1.4% ARR
NNT2.5y 72

NO PAD

Bonaca MP et al. Circulation 2017;137
Effect of Evolocumab on Primary Endpoint in Pts with Diabetes

Patients w/ DIABETES at Baseline

Hazard Ratio 0.83
(95% CI 0.75-0.93)
P=0.0008

17.1%

Patients w/o Diabetes at Baseline

Hazard Ratio 0.87
(95% CI 0.79-0.96)
P=0.0052

13.0%

P interaction = 0.60

LDL-C≈90 mg/dl

LDL-C≈30 mg/dl

Placebo

Sabatine MS et al, Lancet Diabetes Endocrinol 2017, 5:941-50
SUMMARY

Va rivista la soglia di LDL-C<70 mg/dl?

✓ Beneficio su eventi CV dipende da **quanto** si riduce LDL-C e non da «come» lo si riduce;

✓ **Studi con PCSK9i** confermano la **relazione lineare** tra riduzione LDL-C e benefici CV sino a livelli di **LDL-C<20 mg/dl**

✓ **Buona sicurezza e tollerabilità anche a livelli di LDL-C ≤ 30 mg/dl**
  - Eventi avversi simili vs placebo, inclusi DM & eventi neurocognitivi
  - No eventi avversi per LDL-C <0.5 mM (<20 mg/dL) dopo 2.2 anni
CONCLUSIONI

LDL Lowering < 70 mg/dl or LDL Eradication < 50 mg/dl (or more)?

- Bilancio costi/benefici della riduzione del LDL-C:
Inflammatory and Cholesterol Risk in the FOURIER Trial

Erin A Bohula et al, Circulation. 2018;138:131–140. DOI: 10.1161/CIRCULATIONAHA.118.034032
IT’S STILL A LONG, LONG WAY TO TIPPERARY!!!