State of the art and future of dyslipidemia management

PSCK9 inhibitors: Ready for primetime?

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Disclosures

I have received honorarium for advisory board and conferences from: Amgen, AstraZeneca, Daiichi Sankyo, MSD, Pfizer, and Sanofi.
Relationship between LDL-C and CV Event Rate in Primary and Secondary Prevention

Adapted from New Engl J Med 2005;352:1425
Table 8  Recommendations for treatment targets for LDL-C

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
<th>Ref(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level $\geq 10%$) the LDL-C goal is $&lt;1.8$ mmol/L (less than $\sim 70$ mg/dL) and/or $\geq 50%$ LDL-C reduction when target level cannot be reached.</td>
<td>I</td>
<td>A</td>
<td>15, 32, 33</td>
</tr>
<tr>
<td>In patients at HIGH CV risk (markedly elevated single risk factors, a SCORE level $\geq 2$ to $&lt;10%$) an LDL-C goal $&lt;2.5$ mmol/L (less than $\sim 100$ mg/dL) should be considered.</td>
<td>IIa</td>
<td>A</td>
<td>15, 16, 17</td>
</tr>
<tr>
<td>In subjects at MODERATE risk (SCORE level $&gt;1$ to $\leq 5%$) an LDL-C goal $&lt;3.0$ mmol/L (less than $\sim 115$ mg/dL) should be considered.</td>
<td>IIa</td>
<td>C</td>
<td>-</td>
</tr>
</tbody>
</table>

ESC/EAS guidelines for the management of dyslipidemias.
*Eur Heart J* 2011;32:1769
Drugs to reduce lipids

- Statins
- Ezetimibe
- Nicotinic acid
- CETP inhibitors (Torcetrapid, Dalcetrapib, Anacetrapib)
- PCSK9 mAb

Proprotein Convertase Subtilisin/Kexin Type 9 (PSCK9)
IMPROVE-IT Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Rzyllyo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators

Hazard ratio, 0.936 (95% CI, 0.89–0.99)
P=0.016

LDL-cholesterol – causality

Proof That Lower Is Better — LDL Cholesterol and IMPROVE-IT

John A. Jarcho, M.D., and John F. Keaney, Jr., M.D.
Original Article

Reasons for discontinuation of recommended therapies according to the patients after acute coronary syndromes


Expected impact of applying new 2013 AHA/ACC cholesterol guidelines criteria on the recommended lipid target achievement after acute coronary syndromes

Epidemiology of LDLC-cholesterol levels in Switzerland

Lipid-Lowering Therapy Modification and LDL-C Goal Achievement after an Acute Coronary Syndrome: A Swiss Prospective Cohort


for the SPUM-ACS (Special Program University Medicine-Acute Coronary Syndrome)

Purpose

1. European Society of Cardiology recommends treating low-density lipoprotein cholesterol (LDLC) to reduce the risk of atherosclerosis-related complications.
2. However, data on the current status of the control of hypercholesterolemia in Switzerland is scarce.
3. The objective of this study was to describe the achievement of the 2014 European Society of Cardiology LDL-C targets in a population-based cohort of patients with acute coronary syndrome (ACS), including the proportion of patients treated with high-dose statins.

Methods

A population-based cohort of patients (n=1472) presenting with an ACS, either non-ST-elevation ACS or ST-elevation ACS, aged 18 to 80 years was included in this study. Data were collected at the Hospital Centre Universitaire Vaudois, CHUV, University of Lausanne, Switzerland.

Conclusions

- Less than one third of patients with ACS failed to achieve intensive LDL-C target one year after their hospitalization.
- Intensive statin dosage was prescribed only in 34% of patients one year after ACS.
- Clinical inertia is frequent compared to therapy intensification following the hospitalization.
- New therapeutic approaches are probably needed to be able to reach the current LDL-C goals.

Acknowledgment/Declaration of interest

Contact: Baris Gencer, MD, University of Geneva, baris.gencer@hcuge.ch

The SPUM-ACS cohort is supported by the Swiss National Science Foundation (SNSF 33CM10-134112 and 33CM30-140336), Inflammation and acute coronary syndrome - Novel strategies for prevention and clinical management. This project is supported by this SNSF grant and by a grant from the Geneva University Hospital (CRG 71.225) for the development of research projects (for Dr Baris Gencer).

Dr Baris Gencer has no conflict of interest to declare in the presentation of this poster.
New Guidelines AHA and ACC (end of 2013)

ASCVD = Atherosclerotic cardiovascular disease
Application of New Cholesterol Guidelines to a Population-Based Sample

Michael J. Pencina, Ph.D., Ann Marie Navar-Boggan, M.D., Ph.D., Ralph B. D’Agostino, Sr., Ph.D., Ken Williams, M.S., Benjamin Neely, M.S., Allan D. Sniderman, M.D., and Eric D. Peterson, M.D., M.P.H.

CONCLUSIONS

The new ACC–AHA guidelines for the management of cholesterol would increase the number of adults who would be eligible for statin therapy by 12.8 million, with the increase seen mostly among older adults without cardiovascular disease. (Funded by the Duke Clinical Research Institute and others.)
"Fire and Forget" strategy worse than "Treat to Target"

- Patients in primary prevention are overtreated
- Patients in secondary prevention are undertreated

Compliance worse in fire and forget (OR 2.51), lower event rate in treat to target (HR 0.41)

Event rates per 1000 PY

<table>
<thead>
<tr>
<th></th>
<th>treat to target</th>
<th>fire-and-forget</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>45</td>
<td>56</td>
</tr>
<tr>
<td>2° Prevention</td>
<td>74</td>
<td>227</td>
</tr>
</tbody>
</table>

Pharmacoepidemiology and Drug Safety 2007;16:385
Clinical update

Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management

Statin-Associated-Muscle-Symptoms

Consider if statin-attributed muscle symptoms favour statin continuation / reinitiation

- Symptomatic & CK < 4 X ULN
  - 2-4 weeks washout of statin
  - Symptoms persist: statin re-challenge
    - Symptom-free: Continue statin
    - Symptoms improve: Second statin at usual or starting dose
      - 1) Low dose third efficacious (potent) statin;
      - 2) Efficacious statin with alternate day or once/twice weekly dosing regimen
      - Aim: achieve LDL-C goal* with maximally tolerated dose of statin
  - Symptoms re-occur
    - 1) Low dose second efficacious statin;
    - 2) Efficacious statin with alternate day or once/twice weekly dosing regimen

- CK ≥ 4 X ULN +/- rhabdomyolysis
  - 6 week washout of statin until normalisation of CK/creatinine and symptoms

Ezetimibe

- A] + bile acid absorption inhibitor
- B] + fibrate (not gemfibrozil)
- A + B

If still not at goal: consider additional (future) novel therapies: PCSK9 monoclonal antibody therapy, CETP inhibitor

Eur Heart J 2015;36:1012-22
Relative Risk of Death for Adherence
> 80% versus < 80%

Meta-analysis of 44 studies, n= 1 978 919; 135 627 CVD events; 94 126 cases of all-cause mortality

<table>
<thead>
<tr>
<th>(1) Adherence to statins</th>
<th>11</th>
<th>291,064</th>
<th>29,605**</th>
<th>0.55 (0.46, 0.67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2) Adherence to antihypertensive agents</td>
<td>11*</td>
<td>205,598</td>
<td>12,288**</td>
<td>0.71 (0.64, 0.78)</td>
</tr>
<tr>
<td>ACE inhibitors/Angiotensin receptor blockers</td>
<td>4</td>
<td>62,196</td>
<td>886**</td>
<td>0.97 (0.87, 1.09)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) Adherence to aspirin</td>
<td>3</td>
<td>12,980</td>
<td>1573</td>
<td>0.45 (0.16, 1.29)</td>
</tr>
<tr>
<td>(4) Adherence to any CVD medication</td>
<td>23*</td>
<td>533,381</td>
<td>94,126**</td>
<td>0.62 (0.57, 0.67)</td>
</tr>
</tbody>
</table>

9% of all CVD events in Europe could be attributed to poor adherence to vascular medications alone.
The Role of PCSK9 in the Regulation of LDL Receptor Expression
Loss of function mutations for PCSK9 in humans are associated with CHD risk reduction

<table>
<thead>
<tr>
<th>Study</th>
<th>PCSK9 mutation</th>
<th>LDL-C reduction</th>
<th>CHD risk reduction</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benn et al. JACC 2010</td>
<td>R46L</td>
<td>12%</td>
<td>46%</td>
<td>Copenhagen City Heart Study n=10'032</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Copenhagen general population n=26013</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Copenhagen ischemic heart disease n=9654</td>
</tr>
<tr>
<td>Cohen et al. NEJM 2006</td>
<td>R46L</td>
<td>15%</td>
<td>47%</td>
<td>White patients n=9524</td>
</tr>
<tr>
<td></td>
<td>Y142X or C679X</td>
<td>28%</td>
<td>88%</td>
<td>Black patients n=3363</td>
</tr>
</tbody>
</table>

*N Engl J Med* 2006;354:1264

*J Am Coll Cardiol* 2010;55:2833
Loss of function mutations for PCSK9 in humans are associated with CHD risk reduction.
Impact of Alirocumab on LDL Receptor Expression
Monoclonal antibody

Evolution of therapeutic mAbs

- **Mouse (mAb):** murine
  - Mouse variable
  - Mouse constant
  - No repeated dosing

- **Chimeric (mAb):** murine/human
  - All mouse variable
  - Human constant
  - Time-consuming to create

- **Humanised (mAb):** humanised
  - Part mouse variable
  - Human constant
  - Time-consuming to create

- **Human (mAb):** human
  - Human variable
  - Human constant
  - Decreased risk of immunogenicity

**Potential immune response to therapeutic antibody**
Anti-PCSK9 mAb and LDL-c

Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study

Lancet 2012;380:2007-17

Atorvastatin with or without an Antibody to PCSK9 in Primary Hypercholesterolemia

Anti-PCSK9 mAb and LDL-c

**Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events**

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Grégoire Langslet, M.D., Frederick J. Ral, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pordy, M.D., Umesh Chaudhary, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators

**Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events**

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Stephen D. Wiviott, M.D., Frederick J. Raal, M.B., B.Ch., M.Med., Ph.D., Dirk J. Blom, M.B., Ch.B., M.Med., Ph.D., Jennifer Robinson, M.D., M.P.H., Christine M. Ballantyne, M.D., Ransi Somaratne, M.D., Jason Legg, Ph.D., Scott M. Wasserman, M.D., Robert Scott, M.D., Michael J. Koren, M.D., and Evan A. Stein, M.D., Ph.D., for the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators

**Graphs:**
- Left: Least-squares mean calculated LDL cholesterol level (mg/dl) for placebo and alirocumab groups over weeks 0 to 78.
- Right: LDL cholesterol levels over weeks 0 to 48 for standard therapy and evolocumab groups, with no. at risk and absolute/reduction values.
Primary endpoints: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, UA requiring hospitalisation

Anti-PCSK9 mAb and MACE

ESC Late Clinical Breaking Trial 2014

**Sweetless’n low LDL-C targets for PCSK9 treatment**

Baris Gencer and François Mach

Cardiology Clinic, Department of Specialities in Medicine, Geneva University Hospitals, Switzerland
Significant risk reduction in patients with lipid polymorphisms

Effect of Naturally Random Allocation to Lower Low-Density Lipoprotein Cholesterol on the Risk of Coronary Heart Disease Mediated by Polymorphisms in NPC1L1, HMGCR, or Both

A 2 × 2 Factorial Mendelian Randomization Study

Brian A. Ference, MD, MPH, MSc,⇑⇑‡⇑‡‡ Fatemah Majeed, MBBS,⇑⇑⇑ Raji Parameswaran, MD,⇑⇑⇑ John M. Flick, MD, MPH,* Robert D. Brook, MD
# PCSK9 inhibitors in development

<table>
<thead>
<tr>
<th>Type of agent</th>
<th>Companies</th>
<th>Stage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAb: REGN727</td>
<td>Sanofi/Regeneron</td>
<td>Phase II</td>
<td>30–65% decrease in LDL-C levels for 12 weeks</td>
</tr>
<tr>
<td>mAb: REGN727 plus 80 mg atorvastatin</td>
<td>Sanofi/Regeneron</td>
<td>Phase II</td>
<td>73% decrease in LDL-C levels versus 17% decrease with atorvastatin alone</td>
</tr>
<tr>
<td>mAb: AMG145</td>
<td>Amgen</td>
<td>Phase II</td>
<td>Completion: 2012</td>
</tr>
<tr>
<td>mAb: RN316</td>
<td>Pfizer/Rinat Neuroscience</td>
<td>Phase II</td>
<td>Completion: 2012</td>
</tr>
<tr>
<td>LGT209</td>
<td>Novartis</td>
<td>Phase II</td>
<td>Completion: 2015</td>
</tr>
<tr>
<td>siRNA</td>
<td>Alnylam/Novartis</td>
<td>Preclinical</td>
<td>Cationic lipidoid formula</td>
</tr>
<tr>
<td>Small molecule</td>
<td>Cadila Healthcare</td>
<td>In development</td>
<td>No details available</td>
</tr>
<tr>
<td>Small molecule</td>
<td>Serometrix</td>
<td>In development</td>
<td>Peptide-derived small molecule</td>
</tr>
</tbody>
</table>
PCSK9 level changes according to physical activity

Differences before and during physical activity were significant (P value = 0.01)

Antibodies against PCSK9—a new era of therapy

Swiss Med Wkly 2015;145:w14094

Use and role of monoclonal antibodies and other biologics in preventive cardiology

Baris Gencer, Reijo Laaksonen, Aliki Buhayer, François Mach

Swiss Med Wkly 2015 (in press)
Conclusions

LDL-C causality

Statins as baseline therapy

The earlier and the lower the better

Targets translate evidence to clinical practice

Therapy with PCSK9 antibody will change our practice
FDA advisory panel backs approval of Sanofi, Regeneron's Praluent


June 9th, 2015

By: Joe Barber

An FDA advisory panel on Tuesday voted 13-3 in support of approval of Sanofi and Regeneron Pharmaceuticals cholesterol-lowering therapy Praluent (alirocumab). Meanwhile, many of the panellists suggested that the use of the PCSK9 inhibitor should be limited to certain patients, such as those with familial hypercholesterolaemia. Some members of the advisory committee additionally questioned whether the data submitted by the drugmakers confirm the effect of the therapy on cardiac risk.
Thank you
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small molecular</td>
<td>• Oral application</td>
<td>• Off target effects</td>
</tr>
<tr>
<td>weight drugs</td>
<td>• Clearly defined chemical structure</td>
<td>• Drug interactions</td>
</tr>
<tr>
<td></td>
<td>• Oral application</td>
<td>• Possibly toxic metabolites</td>
</tr>
<tr>
<td>Antibodies</td>
<td>• Long half-life</td>
<td>• Local and systemic adverse reactions</td>
</tr>
<tr>
<td></td>
<td>• Simple pharmacokinetics</td>
<td>• Chemical structure not clearly defined</td>
</tr>
<tr>
<td></td>
<td>• No kinetic drug interactions</td>
<td>• Tissue penetration limited</td>
</tr>
<tr>
<td>siRNA</td>
<td>• Long biological half-life</td>
<td>• Must penetrate cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Organ targeting usually necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Experience lacking</td>
</tr>
</tbody>
</table>
Loss of function mutations in PCSK9 in humans

- Coding region in 128 subjects with low LDL-C levels sequenced

- 5 missense mutations in PCSK9 gene identified (Y142X and C679X)

- Mutations in approximately 2% Africa Americans and 0.1% European Americans

*Nature Genetics* 2005;37:161
Family of proprotein convertases (PC)

- Protein activation is frequently achieved by cleavage of inactive precursors
- Scientific breakthrough was the description of the yeast subtilisin-like serine protease kexine (SK)
- Important functions in lipid metabolism, antiviral host defense, activation of hormones
- Attractive drug targets

Gain of function mutations in PCSK9 in humans

- 2 families with hypercholesterolemia (HC92 and HC60)
- The region between D1S197 and D1S2890 on chromosome 1 contains 41 genes, including PCSK9
- PCSK9 is related to PCSK1 which is known to be involved in cholesterol metabolism
- First demonstration in humans that PCSK9 is involved in cholesterol metabolism
Cholesterol metabolism in PCSK9 knock-out mice

- PCSK9\(^{-/-}\) mice are compared to wild type mice at 12 weeks of age
- Both groups were fed normal rodent chow ad libitum
- Body weight may be slightly higher in PCSK9\(^{-/-}\) mice
- Serum cholesterol is less than 50% in PCSK9\(^{-/-}\) mice
- This is due to a decreased in LDL-C which is associated with increased expression of the LDLR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WT</th>
<th>Pcsk9(^{-/-})</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of mice</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>25.5 ± 0.6</td>
<td>30.0 ± 1.6</td>
</tr>
<tr>
<td>Liver cholesterol, mg/g</td>
<td>2.20 ± 0.16</td>
<td>2.00 ± 0.02</td>
</tr>
<tr>
<td>Liver TG, mg/g</td>
<td>9.2 ± 0.6</td>
<td>7.2 ± 0.7</td>
</tr>
<tr>
<td>Plasma cholesterol, mg/dl</td>
<td>95.7 ± 9.4</td>
<td>46.3 ± 1.9(^*)</td>
</tr>
<tr>
<td>Plasma TG, mg/dl</td>
<td>70.0 ± 11</td>
<td>85.8 ± 7.5</td>
</tr>
</tbody>
</table>

PNAS 2005;102:5374
REGN727 in healthy volunteers

- Randomized single dose-ascending study with iv (n=40) and sc application (n=32)
- Intravenous: 0.3 mg/kg, then 1, 3, 6, 12 mg/kg
- Subcutaneous: 50, 100, 150, 250 mg
- Endpoints: safety, effect on LDL-C
- Safety: all subjects terminated study, no TESAR

*Images of graphs showing mean change from baseline in LDL cholesterol over study days for different doses of REGN727 compared to placebo.*

*N Engl J Med 2012;366:1108*
Alirocumab: Dynamic Relationship Between mAb Levels, PCSK9 and LDL-C

Free PCSK9, total alirocumab concentration and mean % change LDL-C vs time

- Total alirocumab
- Free PCSK9
- LDL-C

Time (hours)

Free/total PCSK9 Conc. (ng/mL) X 0.01