PCS9 Inhibitors: Impact on the Management of LDL Apheresis Candidates and LDL Apheresis Patients

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Disclosure

- Board and committee membership—National Lipid Association, Foundation of National Lipid Association
- Guideline development—ACC/AHA 2013 Cholesterol Guideline, Endocrine Society Triglyceride Clinical Practice guideline, National Lipid Association Familial Hypercholesterolemia Recommendations
- Research contracts—Merck, Genzyme/ISIS, Genzyme/Sanofi-Aventis, Glaxo-Smith-Kline, Regeneron/Sanofi-Aventis, Amarin, Amgen, Pfizer, IONIS, Regeneron, Genentech/Roche (all grants to medical school)
- Consulting—Sanofi-Aventis, OptumRx
- Editorial—Merck
Topics to be discussed

- Familial hypercholesterolemia
- LDL apheresis
- Efficacy of PCSK9 monoclonal antibodies
- Trials of PCSK9 antibodies and apheresis
- Comparison of apheresis and PCSK9 monoclonal antibodies

Familial Hypercholesterolemia

- Autosomal co-dominant high LDL
- Heterozygotes: untreated LDL-C 155 - 500 mg/dL
  - Premature CAD
- Homozygotes often have untreated LDL-C >500 mg/dL
  - CAD typically onset in childhood and adolescence
  - Insufficient response to usual lipid lowering medication, even in combination
- High LDL levels, often tendon xanthomas

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273
Treatment of FH

- **Lifestyle changes**
  - Decrease saturated fatty acids to ≤7% of total energy intake; limit dietary cholesterol <200 mg/day; add plant stanol/sterols (2 g daily); soluble fiber (10-20 g daily)
  - Physical activity and weight control
  - **Smoking cessation**

- **Medications:** Statins are best (rosuvastatin, atorvastatin)
- If LDL is not low enough add additional medications (ezetimibe, then colesvelam, niacin)
- LDL apheresis: heterozygotes every 2 weeks, homozygotes weekly
- Homozygous patients: statins, ezetimibe, resins, niacin apheresis, lomitapide, mipomersen

Lipid Lowering Therapies and LDL receptor function

**Statins**
Inhibit HMG-CoA reductase, rate limiting step in cholesterol synthesis

**Ezetimibe**
Inhibits the absorption of cholesterol

**Bile Acid Sequestrants**
Inhibit enterohepatic reuptake of bile acids and increase fecal loss of bile salts

**PCSK9 inhibitors**
Inhibit degradation of LDL receptors and increase recycling

All work by increasing expression of LDL receptors

**Niacin, lomitapide, mipomersen do not work by upregulating LDL receptors (possibly some effect of high dose statins)**
Typical percent LDL-C reduction by statin and dose

<table>
<thead>
<tr>
<th>Treatment (drug/dose)</th>
<th>5 mg</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>-40</td>
<td>-46</td>
<td>-52</td>
<td>-55</td>
<td>------</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>------</td>
<td>-37</td>
<td>-43</td>
<td>-48</td>
<td>-51</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>-26</td>
<td>-30</td>
<td>-38</td>
<td>-41</td>
<td>-47*</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>------</td>
<td>-21</td>
<td>-27</td>
<td>-31</td>
<td>-40</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>------</td>
<td>-20</td>
<td>-24</td>
<td>-30</td>
<td>-36</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>------</td>
<td>------</td>
<td>-22</td>
<td>-25</td>
<td>-35</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>(1 mg) -32</td>
<td>(2 mg) -36</td>
<td>(4 mg) -43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Simvastatin 80 mg only in patients already taking for > 1 year and no other contraindications (higher risk of rhabdomyolysis)

Compiled from various clinical trials and package inserts

Estimates of cumulative CHD-free survival in people with FH according to statin treatment (P < 0.001 for difference).

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273
© The Author 2013. Published by Oxford University Press on behalf of the European Society of Cardiology.
Homozygous FH

- Therapy begins at diagnosis regardless of age
- Statins, ezetimibe and other agents may help but LDL apheresis often necessary
- Cardiovascular disease monitoring critical
- Additional drugs approved for homozygous FH patients over age 18:
  - Mipomersen
  - Lomitapide

Algorithm for management of HoFH


**Risk of first MACE among Homozygous FH patients before and after the introduction of modern lipid lowering therapy**

![Graph showing survival probability over age with and without benefit from modern lipid therapy.](image)

**LDL Apheresis**

- LDL apheresis is a FDA-approved process of selectively removing Apo B-containing particles from the circulation through extracorporeal precipitation with either dextran sulphate cellulose or heparin.
- The procedure must be repeated every 1 to 2 weeks.
- In a single procedure, LDL apheresis typically removes at least 60% of the Apo B-containing lipoproteins.
**LDL-apheresis**

- LDL-apheresis: inadequate response to maximally tolerated therapy in patients with familial hypercholesterolemia
- Requires good vascular access (2 vein sites or A-V fistula)
- Usually done weekly for homozygous patients and every two weeks for heterozygous patients
- Over time 50% reduction of LDL-C

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**Lipoprotein-apheresis**

**Pre-Apheresis**

- Total Cholesterol 611 mg/dL
- LDL-C 507 mg/dL
- Fibrinogen 446 mg/dL
- CRP 2.0 mg/dL

**Post-Apheresis**

- Total Cholesterol 216 mg/dL
- LDL-C 134 mg/dL
- Fibrinogen 193 mg/dL
- CRP 0.5 mg/dL

Slide courtesy Dr. Patrick Moriarty
Mean Percentage Reduction of Plasma Proteins with Different Methods of Lipoprotein-apheresis

<table>
<thead>
<tr>
<th>mg/dL</th>
<th>MDF</th>
<th>Lipid Filtration</th>
<th>HELP</th>
<th>DALI</th>
<th>DSA</th>
<th>IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>56-62%</td>
<td>61%</td>
<td>55-61%</td>
<td>53-76%</td>
<td>49-75%</td>
<td>62-69%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>25-42%</td>
<td>6%</td>
<td>5-17%</td>
<td>5-29%</td>
<td>4-17%</td>
<td>9-27%</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>53-59%</td>
<td>61%</td>
<td>55-68%</td>
<td>28-74%</td>
<td>19-70%</td>
<td>51-71%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>37-49%</td>
<td>56%</td>
<td>20-53%</td>
<td>29-40%</td>
<td>26-60%</td>
<td>34-49%</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>52-59%</td>
<td>42%</td>
<td>51-58%</td>
<td>13-16%</td>
<td>17-40%</td>
<td>15-21%</td>
</tr>
</tbody>
</table>

High variation of values are partially due to differences in treated plasma and blood volumes. MDF, membrane differential filtration; HELP, heparin-induced extracorporeal LDL precipitation; DALI, direct adsorption of lipoproteins; DSA, dextrum sulfate adsorption; IA, immunoadsorption.

Moriarty PM. Clinical Lipidology, Ballantyne: A Companion to Braunwald’s Heart Disease; 363-74. 2009

LDL-apheresis (current rules)

- LDL-apheresis: inadequate response to maximally tolerated therapy in patients with familial hypercholesterolemia
  - Functional homozygotes with LDL-C > 500 mg/dl
  - Functional heterozygotes with LDL-C > 300 mg/dl and no evidence of vascular disease
  - Functional heterozygotes with LDL-C > 200 mg/dl and evidence of vascular disease
Candidates for LDL Apheresis: NLA FH recommendations

In patients who, after six months, do not have an adequate response to maximum tolerated drug therapy, LDL apheresis is indicated according to these guidelines:

- **Functional homozygous FH** patients with LDL-C ≥300 mg/dL (or non-HDL-C ≥330 mg/dL).
- **Functional heterozygous FH** patients with LDL-C ≥300 mg/dL (or non-HDL-C ≥330 mg/dL) and 0-1 risk factors.
- **Functional heterozygous FH** patients with LDL-C ≥200 mg/dL (or non-HDL-C ≥230 mg/dL) and high risk characteristics such as ≥2 risk factors or high lipoprotein (a) ≥50 mg/dL using an isoform insensitive assay.
- **Functional heterozygous FH** patients with LDL-C ≥160 mg/dL (or non-HDL-C ≥190 mg/dL) and very high risk characteristics (established CHD, other cardiovascular disease, or diabetes).


LDL Apheresis

- **Currently**, there are more than 400 patients in North America receiving LDL apheresis therapy at more than 40 centers.
- **There is a significant gap** between the number of patients receiving LDL apheresis therapy and the number that, according to FDA guidelines, may qualify for LDL apheresis.

Lipoprotein-Apheresis (LA) and the reduction of CV Events


LA Therapy for Elevated Lp(a) Levels

<table>
<thead>
<tr>
<th></th>
<th>Jaeger</th>
<th>Rosada</th>
<th>Leebmann</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apheresis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>120</td>
<td>37</td>
<td>170</td>
</tr>
<tr>
<td><strong>Duration (years)</strong></td>
<td>5.5</td>
<td>5.2</td>
<td>2</td>
</tr>
<tr>
<td><strong>LDL-C mg/dL</strong></td>
<td>125</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td><strong>Lp(a) mg/dL</strong></td>
<td>118</td>
<td>112</td>
<td>87</td>
</tr>
<tr>
<td><em><em>MACE</em> (total)</em>*</td>
<td>297</td>
<td>67</td>
<td>142</td>
</tr>
<tr>
<td><em><em>MACE</em> (per year)</em>*</td>
<td>1.05</td>
<td>2.80</td>
<td>0.41</td>
</tr>
</tbody>
</table>

**RRR = 72%**
**NNT = 4**

*MACE: Major Coronary Event, percentages are mean percent change

World-Wide Distribution of Lipoprotein-apheresis Therapy for FH Patients

Fewer than 3,500 FH patients, from a potential world population of 12-30 million, receive regular weekly/biweekly treatments

Slide courtesy Dr. Patrick Moriarty

Proprotein convertase subtilisin/kexin type 9

- Member of the family of proteases involved in degradation of LDL-C receptor
- Mutations leading to loss of function are associated with lifelong low LDL-C levels and decreased risk of cardiovascular disease
- Gain of function mutations lead to increased LDL-C levels
- Loss of function mutations lead to low LDL-C

Percent Change of LDL-C from Baseline to Week 12 with Alirocumab in Heterozygous FH Patients

Percent LDL-C Change from Baseline to Week 12 with Alirocumab in non-FH Hypercholesterolemic Patients

Stein et al Lancet 2012; 380: 29-36

McKenney et al. J Am Coll Cardiol 2012;59 2344-2353
Efficacy of Alirocumab
Reduction in LDL-C With 150 mg SQ Q2W

HeFH | Non-FH | Non-FH - no statin
---|---|---
-55.7% | -64.7% | -57.0%

Stein et al. NEJM 2012; 366: 1108-1118

Percent Reduction from Baseline in LDL Cholesterol on Evolocumab as Compared with Placebo by Background Lipid-Lowering Therapy.

PCSK9 Inhibition in FH

- Heterozygous FH
  - Dose dependent LDL-C reductions about 40 to 70% on top of background therapies

- Homozygous FH
  - Receptor defective patients: LDL-C reduction 23%
  - Receptor negative patients: no effect


Effects on patients with heterozygous FH

- Patient Profile (n=77)
  - >70% on max dose statin
  - >70% on ezetimibe
  - Baseline LDL-C about 155 mg/dL

- Treatment results
  - On-treatment LDL-C about 50 mg/dL
  - LDL-C < 100 = 97%
  - LDL-C < 70 = 81%

Stein et al Lancet 2012; 380: 29-36
Alirocumab and heterozygous FH

![Graph showing LDL-C levels over time for different groups of patients](image)


### Homozygous FH Patients

**Mean % in LDL-C from Baseline to Week 12 With Evolocumab**

<table>
<thead>
<tr>
<th>Patients</th>
<th>% Δ LDL-C Evolocumab 420 mg Q4W</th>
<th>% Δ LDL-C Evolocumab 420 mg Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects (n=8)</td>
<td>-16.5%</td>
<td>-13.9%</td>
</tr>
<tr>
<td>Receptor defective (n=6)</td>
<td>-22.9%</td>
<td>-23.6%</td>
</tr>
<tr>
<td>Receptor negative (n=2)</td>
<td>2.6%</td>
<td>15.3%</td>
</tr>
</tbody>
</table>

Stein et al. Circulation 2013; 128: 21123-2120
Studies with PCSK9 monoclonal antibodies

- LDL cholesterol lowered as much as 70%
- Decreases of non-HDL cholesterol—60%, triglycerides and lipoprotein (a)—25%
- Effects continue over time—52 week data have been presented
- Side effects infrequent and not much difference between placebo and treatment groups
  - Injection site reactions occasionally

Potential uses for PCSK9 Monoclonal Antibodies

- Familial hypercholesterolemia
  - Some effect in homozygous FH patients who are not receptor negative
  - Significant benefits in patients with heterozygous FH—on top of statins and other medications get LDL-C below 100 mg/dL
- Statin tolerance problems
- High risk patients—pre-existing vascular disease
**Alirocumab**

- FDA approval July 27, 2015
- Indications: adjunct to diet and:
  - maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL – C
- Dosage: 75 mg or 150 mg sc every two weeks
- Availability: 75 mg or 150 mg pre-filled syringe or injector pens

**Evolocumab**

- European approval
- FDA approval August 27, 2015
- Indications: adjunct to diet and:
  - maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL – C
  - Other LDL lowering therapies in patients with homozygous familial hypercholesterolemia who require additional LDL- C lowering
Evolocumab

- Dosage
  - Heterozygous FH: 140 mg sc every two weeks or 420 mg sc once per month
  - Homozygous FH: 420 mg sc once per month
- 140 mg pre-filled syringes or autoinjector
- 420 mg given as three 140 mg injections

Concerns with PCSK9 monoclonal antibodies

- LDL too low?
  - No increase in side effects seen in subjects with LDL-C <25 mg/dL
- Muscle, cognitive, fertility
  - No problems in the rare double loss-of-function patients
  - No significant increased muscle problems in clinical trials
- Antibodies to PCSK9—rare in the clinical trials
- Will this kind of LDL-C reduction with this treatment improve cardiovascular event rates?
  - Outcomes trials in progress
  - 52 week data suggest decrease CVD events (but very small numbers and post-hoc analysis)
- Cost
PCSK9 Outcomes Trials in Progress

**ODYSSEY Outcomes**
- Alirocumab SQ vs placebo
  - Endpoint: First occurrence of: CHD death, any non-fatal MI, fatal and non-fatal ischemic stroke, UA requiring hospitalization
  - Estimated completion: March 2018

**FOURIER**
- Evolocumab SC vs placebo
  - Endpoint: Time to CV death, MI, hospitalization for UA, stroke, or coronary revascularization
  - Estimated completion: February 2018

**SPIRE**
- Bococizumab SQ vs placebo
  - Endpoint: Time to CV death, MI, hospitalization for UA, stroke, or coronary revascularization
  - Estimated completion 2017

**SPIRE ESCAPE**
- Study of Alirocumab (REGN727/SAR236553) in Patients With Heterozygous Familial Hypercholesterolemia (HeFH) Undergoing Low-density Lipoprotein (LDL) Apheresis Therapy
- Randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of alirocumab in comparison with placebo on the frequency of LDL apheresis treatments in patients with HeFH undergoing LDL apheresis therapy.
- Rate of apheresis treatments during a 12-week period normalized by the number of planned apheresis treatments according to each patient’s established schedule at screening

www.clinicaltrials.gov
Alirocumab and apheresis

- Enrollment: 62
- Study Start Date: March 2015
- Estimated Study Completion Date: May 2017
- Inclusion Criteria:
  - Men and women ≥18 years of age at the time of the screening visit
  - Diagnosis of heterozygous familial hypercholesterolemia
  - Currently undergoing LDL apheresis therapy weekly or every 2 weeks for at least 8 weeks prior to the screening visit

www.clinicaltrials.gov

Alirocumab and apheresis

Main exclusion criteria:
- Homozygous FH (familial hypercholesterolemia)
- Background medical lipid-modifying therapy not stable for at least 8 weeks prior to screening visit
- LDL apheresis schedule/apheresis settings not been stable
- LDL apheresis schedule other than QW to Q2W
- New exercise program or exercise or diet not stable
- Presence of clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins
- Known positive test for human immunodeficiency virus
- Patients treated with at least 1 dose of alirocumab or any other anti-PCSK9 monoclonal antibody in any other clinical studies
- Pregnant or breastfeeding women

www.clinicaltrials.gov
Alirocumab and apheresis

- Primary outcome measure:
  - Rate of apheresis treatments during a 12-week period normalized by the number of planned apheresis treatments according to each patient's established schedule at screening

www.clinicaltrials.gov

Evolocumab and apheresis

- Trial Assessing Evolocumab (AMG145) Compared to LDL-C Apheresis in Subjects Receiving LDL-C Apheresis Prior to Study Enrollment
- Randomized, Actively Controlled, Open-label, Multicenter Study of Efficacy and Safety of Evolocumab Compared With LDL Apheresis, Followed by Single-Arm Evolocumab Administration in Subjects Receiving LDL Apheresis Prior to Study Enrollment
- **Purpose**: To evaluate the efficacy of subcutaneous (SC) evolocumab, compared to regularly scheduled low density lipoprotein cholesterol (LDL-C) apheresis, on reducing the need for future apheresis

www.clinicaltrials.gov
Evolocumab and apheresis

Inclusion Criteria:

- Male or female, ≥ 18 years of age
- Receiving regular apheresis for LDL-C lowering at least 3 months immediately prior to lipid screening; treatment goal of LDL-C < 100 mg/dL (2.6 mmol/L); receiving LDL-C apheresis during the last ≥ 4 weeks prior to lipid screening at regular QW or Q2W schedule and with no changes in apheresis type
- On lipid-lowering pharmacological therapy including high-intensity statin dose (moderate-intensity statin dose with attestation that higher dose not appropriate) unless history of statin intolerance
- Lipid-lowering therapy status (ie, any therapy for lowering lipids, including apheresis type and frequency) unchanged for ≥ 4 weeks prior to LDL-C screening
- Pre-apheresis LDL-C ≥ 100 mg/dL and ≤ 190 mg/dL at screening
- Fasting triglycerides ≤ 400 mg/dL at screening.

www.clinicaltrials.gov

Evolocumab and apheresis

Exclusion criteria:

- Known homozygous familial hypercholesterolemia
- Missing any apheresis session is medically contraindicated or inappropriate
- Stopping apheresis would be inappropriate in the opinion of the investigator even if LDL-C is controlled to < 100 mg/dL with other therapies
- Myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or stroke within 3 months prior to randomization.
- Uncontrolled hypertension

www.clinicaltrials.gov
Evolocumab and apheresis

- Evolocumab or Low Density Lipoprotein Cholesterol (LDL-C) Apheresis
  - Subjects will receive evolocumab q 2 weeks
  - Subjects will continue apheresis at the same schedule, every week (QW) or every two weeks (Q2W), as prior to study entry, for the first 6 weeks
- Endpoints
  - Apheresis avoidance at the end of randomized therapy, defined as no apheresis at week 5 and week 6

www.clinicaltrials.gov

Evolocumab and apheresis

- Estimated Enrollment: 50
- Study Start Date: December 2015
- Estimated Study Completion Date: March 2017
- Estimated Primary Completion Date: January 2017 (Final data collection date for primary outcome measure)

www.clinicaltrials.gov
PCSK9 Mab: Possible effects on apheresis

- Some patients are able to discontinue apheresis
- Decrease apheresis to once per month
- Insufficient effect
- Severe vascular disease with elevated LDL cholesterol and lipoprotein (a)—may be helped by use of both modalities
- Elevated lipoprotein (a)—some effect of PCSK9 Mab but more direct removal by apheresis

Effects on apheresis centers

- Small pheresis center
- Four patients—3 HeFH, 1 HoFH
  - One patient on PCSK9 Mab prescribed by her cardiologist—has discontinued apheresis
  - One patient on alirocumab 150 mg q 2 weeks, pheresis currently once every 4 weeks
  - One patient just starting PCSK9 and continuing pheresis every two weeks: some improvement pre pheresis LDL-C
  - Double heterozygous patient on q 2 week pheresis
Advantages of PCSK9

- Levels stable over time instead of going up between treatment sessions (especially every 2 week pheresis)
- Benefit in terms of time and travel (many patients do not have apheresis available)
- No need for venous access
- Costs less than apheresis

Advantages of LDL apheresis

- Fibrinogen decreases
- Better effect in receptor null homozygous patients and some severe heterozygous patients
- Feasible during pregnancy
- Use in pediatric patients
Cost considerations

- Pheresis about $2500 to 3000 per session – about $65,000 to 70,000 per year if every two weeks (does not necessarily include lab work, transportation costs, vascular access costs)
- Alirocumab and evolocumab about $14,000 per year
- Combination PCSK9 plus monthly apheresis would be about $50,000 per year
- Cost benefit analysis of PCSK9 will depend on outcomes trial data as well as eventual cost of the medication

Conclusions

- PCSK9 monoclonal antibodies reduce atherogenic lipoproteins
- They work in patients with heterozygous FH and some effect in homozygous FH
- Safety data look good to date
- Alirocumab and evolocumab now approved
- Long term outcome studies are in progress
- Potential to decrease frequency of or discontinue apheresis in many patients
- Likely significant benefit to patients who do not have access to apheresis
Thank you!

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