Cleveland Clinic

# Lipid Management: What's on the Horizon?

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# No disclosures

# Objectives

- **Review mechanism of action of new lipid lowering therapy**
- **Discuss clinical trial data**
- **Assess their place in therapy**

# Lipid lowering: Is there an ideal agent?

- Ease of administration / dosing
- Tolerable- low side effect profile
  - Muscle aches
  - Statin intolerance
  - Liver function (LFTs)
- Lack of drug interactions
  - Simvastatin
- Achieves LDL goals

# What's next on the horizon?

- **Proprotein convertase subtilisin/kexin 9**
  - **(PCSK9) Inhibitors**
    - **Bococizumab**
    - **Alirocumab (Praluent™)**
    - **Evolocumab (Repatha™)**

# What is PCSK9?

- **PCSK9**
  - **Produced in the liver**
  - **Binds hepatic LDL receptors and promotes degradation**
  - **Less LDL cholesterol is then removed by liver**
  - **Leads to increases in circulating LDL**

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# PCSK9 Inhibitors

- **Monoclonal antibody specifically blocks PCSK9 interaction with LDL receptor**
  - **Prevents degradation of LDL receptor**
    - **Statins may enhance PCSK9 production**
    - **May be why doubling statin dose doesn't double response**

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# PCSK9 Inhibitors

- **Cholesterol lowering profile**
  - **LDL: ~60%**
  - **Triglycerides: 12-17%**
  - **Total Cholesterol: 36-37.5%**
  - **HDL: 4-7%**
- **Unique dosing- Patient administered**
  - **Subcutaneous (SubQ) injection**
    - **Every two weeks**
    - **Once monthly**

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# Bococizumab

| Study | Objectives | Population | Endpoints / Results | Conclusions |
|---|---|---|---|---|
| Results of Bococizumab, A monoclonal antibody against proprotein convertase subtilisin/ kexsin type 9, from a randomized, placebo-controlled, dose-ranging study with statin-treated subjects with hypercholesterolemia<br><br>24 week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase 2b study<br><br>**Dose reduction if persistent LDL-C ≤25 mg/dL (after days 43 and 57**) | **Primary endpoint**:<br><br>Absolute change in LDL-C from baseline to 12 weeks after treatment with placebo or bococizumab<br><br>**Safety endpoint:**<br><br>Incidence of adverse events (AEs), serious AEs, laboratory abnormalities, incidence of antidrug antibodies (ADAs) , and injections site reactions | N= 100 placebo<br>N= 251 bococizumab<br><br>Patients with hypercholesterolemia on stable statin therapy with fasting LDL > 80 mg/dL, TGs < 400 mg/dL.<br><br>Excluded if cardiovascular event in last 6 months<br><br>Randomized to:<br>-Q14 day placebo or bococizumab 50, 100, 150 mg<br>-Q28 day placebo or bococizumab 200 or 300 mg | **Efficacy:**<br>LDL-C change from baseline bococizumab<br><br>150mg Q14day:<br>-53.4mg/dL (53.1%)<br><br>300 mg Q28 day:<br>-44.9mg/dL(41.1%)<br><br>Up to 44% had dose reductions for LDL-C ≤25 mg/dL<br><br>**Safety:** AEs similar bococizumab vs placebo:<br>Injection site reaction 0-8% vs 2%<br><br>Nonserious memory loss: 2 bococizumab patients | Bococizumab significantly reduced LDL-C<br><br>Q28 day dosing LDL-C reductions not well maintained between doses “saw tooth” pattern<br><br>Q14 day dose reduced fluctuations in LDL<br><br>If no dose reductions LDL lowering may have been<br>Q14day: -72.2 mg/dL<br>Q28day:- 55.4 mg/dL<br><br>AEs similar for LDL <25mg/dL |

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# Alirocumab-Monotherapy

| Study | Objectives | Population | Endpoints / Results | Conclusions |
|---|---|---|---|---|
| **ODYSSEY MONO:**<br><br>Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: Results of a 24 week, double blind, randomized Phase 3 trial | Evaluate efficacy and safety of alirocumab monotherapy vs ezetimibe | n= 52 alirocumab<br>n= 51 ezetimibe<br><br>Hypercholesterolemia with moderate CV Risk*<br><br>Not receiving statin or other lipid lowering therapy<br><br>Alirocumab 75 mg Q2wk (increased to 150 mg 2wk 12 if LDL > 70 mg/ dL) | **Efficacy:**<br>% LDL change from Baseline to 24 weeks:<br>• Alirocumab-54.1%<br>• Ezetimibe-17.2%<br><br>**Safety:**<br>Muscle related AE:<br>• Alirocumab-2(4 %)<br>• Ezetimibe- 2(4%)<br>CK 10 times ULN:<br>• Alirocumab-0 (0%)<br>• Ezetimibe- 1 (2%)<br>LFT elevation: none<br><br>Injection site reaction:<br>• Alirocumab- 1(2%)<br>• Ezetimibe- 2(4%)<br>Anti-drug antibodies:<br>• Alirocumab – 6 (12%) | Alirocumab showed greater LDL –C reduction vs ezetimibe<br><br>Alirocumab 75 mg Sub q 2 weeks ≥50% LDL-C reduction in most patients<br><br>Ldl <25 mg/dL in 3 patients with no safety concerns observed |

* Moderate cardiovascular risk (CV) 10 yr risk of fatal CV events ≥1% and ≤ 5%

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# Alirocumab- Familial Hypercholesterolemia

| Study | Objectives | Population | Endpoints /Results | Conclusions |
|---|---|---|---|---|
| Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol<br><br>3 separate phase 1 clinical studies:<br><br>Single dose studies<br>• Intravenous<br>• Subcutaneous<br>Multiple dose study<br>• 50, 100, 150 mg alirocumab or placebo days 1, 29, and 43 | **Primary outcome:**<br>• Incidence and severity of treatment-emergent adverse events<br><br>**Secondary outcome:**<br>• Effect on lipid profile | **Multiple dose study:**<br><br>**Atorvastatin arms with LDL> 100mg/dL:**<br><br>N= 21 Heterozygous familial hypercholesterolemia<br><br>N= 30 non-familial hypercholesterolemia<br><br>**Modified diet and LDL > 130 mg/dL arm:**<br><br>N= 10 non-familial hypercholesterolemia | No serious adverse events in multiple dose study<br><br>**Safety in all 3 studies**:<br>• No LFTS > 3 x ULN<br>• No creatinine elevations > 1.7 mg/dL<br>• 5/39 (13%) alirocumab + atorvastatin group creatine kinase (CK) elevation > 3 ULN<br>• No CK >10 ULN<br><br>**Lipid profile effect:**<br>In 50, 100, 150 mg groups on atorvastatin<br>LDL lowered to:<br>77.5, 61.3, 53.8 mg/dL<br>or (39.2%, 53.7%, 61.0% reduction) | LDL lowering response similar between familial and non-familial.<br><br>Maximal lowering seen in 2 weeks<br><br>Safety profile information limited due to short treatment duration<br><br>CK elevations were brief |

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# Alirocumab- Long Term

| Study | Objectives | Population | Endpoints / Results | Conclusions |
|---|---|---|---|---|
| **ODYSSEY LONG TERM**<br><br>Efficacy and safety of alirocumab in reducing lipids and cardiovascular events | **Primary efficacy endpoint:**<br>• % change in LDL cholesterol from baseline to 24 weeks<br><br>**Safety endpoints:**<br>• Adverse events<br>• Symptoms<br>  • Abnormalities in<br>  • Lab<br>  • Vital signs<br>  • EKG<br>• Adjudicated cardiovascular events<br><br>**Post Hoc**: major adverse cardiovascular events (composite of death from any coronary heart disease (CHD), non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization | N= 1553 alirocumab 150mg sub Q every 2 weeks<br><br>N=788 placebo<br><br>2:1 Randomization<br>Double blind<br><br>Every 2 weeks for 78 weeks in addition to statin therapy<br><br>Patients had heterozygous familial hypercholesterolemia or established CHD, or CHD risk equivalent all included if LDL >70 mg/dL | **Efficacy:**<br>Mean % change LDL Alirocumab vs Placebo<br>• 61.0% vs 0.8%<br><br>**Safety:**<br>Alirocumab vs Placebo<br>• Injection site reactions (5.9 vs 4.2%)<br>• Myalgias (5.4 vs 2.9%)<br>• Neurocognitive events (1.2 vs 0.5%)<br>  • Amnesia n=5<br>  • Memory impairment n=4<br>  • Confusional state n=4 | Alirocumab compared to placebo reduced LDL by 62 % at 24 weeks<br><br>Post hoc safety analysis rate of adverse CV events 48% lower for alirocumab vs placebo.<br><br>With all CV events included (CHF requiring hospitalization, ischemia driven revascularization), difference became non significant |

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# Evolocumab-Statin Intolerance

| Study | Objectives | Population | Endpoints Results | Conclusions |
|---|---|---|---|---|
| **GAUSS-2**<br><br>Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance | **Co-Primary endpoints:**<br>% change for baseline LDL-C at mean of weeks 10-12 and at week 12<br><br>**Safety endpoint:**<br>Treatment emergent and serious adverse events, CK and hepatic enzyme elevations, and anti-evolocumab antibodies | N= 205 evolocumab<br>N= 102 ezetimibe<br>Baseline LDL-C 193 ± 59 mg/dL<br><br>Patient on no or low-dose statin above NCEP ATP III* goals with intolerance ≥ 2 statins**<br><br>**Randomization** (placebo controlled)<br>• Evolocumab 140 mg Q2 weeks<br>• Evolocumab 420 mg once monthly<br>• Ezetimibe 10 mg daily | **Efficacy:**<br>Mean LDL-C reduction from baseline at mean of 10-12 weeks<br>• 56.1% -140mg Q2wk<br>• 55.3% - 240mg Q M<br><br>36.9%, 38.7% reduction- ezetimibe groups<br><br>Mean at 12 weeks similar<br><br>**Safety:**<br>Myalgia<br>8% evolocumab<br>18% ezetimibe (more likely to develop if on low-dose statin) | Evolocumab reduced LDL-C in patients with statin intolerance<br><br>Evolocumab may be useful for in hypercholesterolemic patients with intolerance to current agents as there was low incidence of muscle related side effects<br><br>**Limitations:**<br>Absence of blinded statin re-challenge group |

* National Cholesterol Education Program Adult Treatment Panel
** Inability to tolerate any dose of statin or increase dose above smallest tablet strength because of muscle-related side effects

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# Evolocumab

| Study | Objectives | Population | Endpoints Results | Conclusions |
|---|---|---|---|---|
| PCSK9 inhibition with evolocumab (AMG145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial | **Co-Primary endpoints:**<br>% change in plasma LDL from baseline to week 12 and at mean of 10-12 weeks.<br><br>**Secondary endpoints:**<br>Absolute change from baseline in LDL and % of patients achieving target LDL lower than 1.8 mmol/L at same timepoints | **Evolocumab**<br>N=110 (140mg q2 week Sub Q)<br>N= 110 (420 mg q M Sub Q)<br><br>**Placebo**<br>N= 54 (q 2 weeks SubQ)<br>N= 55 (q M Sub Q) | **Efficacy:**<br>Mean LDL-C reduction from baseline at mean of 10-12 weeks<br>Evolocumab vs placebo<br>Q 2wk: 60.2%<br>Q M: 65.6%<br><br>**Mean reduction at 12 weeks**<br>Q 2wk: 59.2%<br>Q M: 61.3%<br><br>**Safety:**<br>Evolocumab vs placebo:<br>Nasopharingitis: 9%vs 5%<br>Muscle related:<br>5% vs 1% | In patients with heterozygous familial hypercholesterolemia evolocumab reduced LDL by 60%<br><br>LDL of 1.8 mmol/L achieved in more than 60% of patients<br><br>Well tolerated |

**1.8 mmol/L = 70 mg/dL**

LANCET 2015;385:331-40

# Evolocumab

| Study | Objectives | Population | Endpoints Results | Conclusions |
|---|---|---|---|---|
| **OSLER**<br><br>Efficacy and safety of evolocumab in reducing lipids and cardiovascular events | **Primary endpoint:**<br>Incidents of adverse events<br><br>**Secondary endpoint:**<br>% change in LDL<br><br>Pre-specified exploratory outcome (adjudicated events):<br>Cardiovascular events-(death, MI, UA, coronary revascularization, stroke, TIA, and heart failure | N= 2976 evolocumab plus standard therapy<br>N= 1489 standard therapy<br><br>Enrolled after participation in one of 12 phase 2 or 3 "parent trials" for 12 weeks<br><br>Followed for median of 11.1 months<br><br>Evolocumab either:<br>140 mg Sub Q Q2wks<br>420 mg Sub Q q Month | **Safety:**<br>Evolucumab vs standard:<br>• LFTs 1.0% vs 1.2%<br>• CK 0.6% vs 1.1%<br>• Neurocognitive 0.9% vs 0.3%<br>• Injection site reaction: 4.3% evolocumab<br><br>**Efficacy:**<br>Evolocumab vs standard<br>• LDL reduction 61% at 12 weeks<br>• LDL reduced to 100 mg/dL 90.2% vs 26.0%<br>• LDL reduced to 70 mg/dL 73.6% vs. 3.8% | Reduction in LDL by 61% at 12 weeks<br>--sustained at 11 months<br><br>Evidence of reduction in cardiovascular events at one year<br>• Evolucumab vs standard:<br>0.95% vs 2.18 %<br>• HR 0.47; 95%CI 1.28-0.78<br><br>**Limitations**<br>--open label may have influenced reporting of events<br>-- #of events small<br>--patients enrolled in trial only if no adverse events in "parent trials" --12 weeks on study drug already |

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# Further Considerations

- **Outcome data still ongoing**
  - SPIRE I and II (bococizumab)
    - I- whether lowering LDL to below recommended targets will lead to further reduced cardiovascular outcomes
    - II- efficacy and safety in high risk patients not at target (<100mg/dL) on high dose statin or statin intolerant
  - ODYSSEY OUTCOMES (alirocumab) will assess CV benefit over 5 years
  - FOURIER study (evolocumab) full assessment of cardiovascular outcomes (5 years)

# Further Considerations

- Neurologic events to be further evaluated
- How low is too low for LDL?
- Cost?
- Future directions:
  - Potential oral options for small molecule PCSK9 inhibitors
    - Human trials (phase I) soon

# Conclusions

- PCSK9 inhibitors lower LDL by ~60%
- Useful for patient with familial hypercholesterolemia
- Potential option for statin intolerance
- Outcome data ongoing
- FDA biologics application license submission
  - Alirocumab- July
  - Evolocumab- August
  - Bococizumab- To be determined

# Cleveland Clinic

Every life deserves world class care.