PCSK9 INHIBITORS
THE NEW CLASS OF
CHOLESTEROL BUSTERS

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Cardiovascular disease is the #1 cause of death in the world

A major factor is high cholesterol

High levels of “bad” cholesterol can lead to the development of plaque in the arteries
FAMILIAL HYPERCHOLESTEROLEMIA (FH)

- Familial hypercholesterolemia is an autosomal dominant genetic disorder caused by a defect on chromosome 19.
- The defect makes the body unable to remove low density lipoprotein (LDL) cholesterol from the blood. This results in a high level of LDL in the blood.
- LDL-c of 190 mg/dL or greater in adults or 160 mg/dL or greater in children and a family history of elevated cholesterol or early heart disease.
- Individuals with FH have a 20x increased risk of early heart disease.
SYMPTOMS OF FH

Symptoms that may occur include:

- Xanthomas of the hands, elbows, knees, ankles and around the cornea of the eye
- Xanthelasmas
- Chest pain or other signs of CAD may be present at a young age
- Cramping of one or both calves when walking
- Sores on the toes that do not heal
- Sudden stroke-like symptoms
FACTS ABOUT FH

- Over 90% of people with FH have not been properly diagnosed.
- An estimated 1.3 million people in the U.S. have FH.
- 1 in 250 people in the world have FH.
- More prevalent in certain populations, including French Canadians, Ashkenazi Jews, Lebanese, & South African Afrikaners.
HETEROZYGOUS FH (HeFH) & HOMOZYGOUS FH (Ho FH)

<table>
<thead>
<tr>
<th>HeFH</th>
<th>HoFH</th>
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<tbody>
<tr>
<td>Inherit genetic mutation from <strong>one parent</strong> (50% chance)</td>
<td>Inherit genetic mutation from <strong>both parents</strong> (25% chance)</td>
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<tr>
<td>HeFH occurs in 1 in 250 people worldwide</td>
<td>HoFH very rare, occurring in about 1 in one million people worldwide</td>
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<td>Characterized by very high LDL cholesterol (above 190 for adults or above 160 for children) and a family history of high cholesterol, heart disease or stroke</td>
<td>Characterized by cholesterol levels into the 700’s or even 1,000’s</td>
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<td>Signs and symptoms often occur in the 4th or 5th decade of life</td>
<td>Aggressive atherosclerosis and consequences/start before birth and rapidly progress</td>
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WHAT IS PCSK9?

(PRO) 

The PCSK9 gene provides instructions for making a protein that helps regulate the amount of cholesterol in the bloodstream.

The PCSK9 protein appears to control the number of low-density lipoprotein (LDL) receptors, which are proteins on the surface of cells.

Primarily expressed in liver, intestine, and kidney.

First described in 2003.
Gain-of-function (GoF) missense mutations = genetic hypercholesterolemia (FH phenotype)

Loss-of-function (LoF) nonsense mutations = hypocholesterolemia with low LDL levels and major reduction in CHD incidence
THE ROLE OF PCSK9 IN THE REGULATION OF LDLR EXPRESSION

THE ROLE OF PCSK9 IN THE REGULATION OF LDLR EXPRESSION

**PCSK9 first described**

2003

First reports of familial hypercholesterolaemia due to gain-of-function mutations in PCSK9

**PCSK9 knockout in animals shown to decrease plasma levels of LDL cholesterol**

2004

2005

First reports of decreased LDL cholesterol and cardiovascular risk in humans with loss-of-function mutations in PCSK9

**Anti-PCSK9 monoclonal antibody shown to decrease LDL cholesterol in animals**

2006

2007

2008

2009

2010

2011

2012

2013

2014

2015

2016

2017

2018

Phase I human trial of anti-PCSK9 monoclonal antibody reported

Safety and sustained LDL-cholesterol lowering efficacy demonstrated over 52 weeks

Post hoc and meta-analysis data suggest substantial reduction in cardiovascular risk attributable to PCSK9 inhibitors

Results of major cardiovascular endpoint studies expected

LDL low-density lipoprotein

Food and Drug Administration approval for evolocumab and alirocumab in the USA
POTENTIAL TARGETS IN THE PCSK9 PATHWAY

- Reduction of PCSK9 protein production
- Reduction of PCSK9 mRNA expression
- Inhibition of PCSK9 binding to the LDL-R
- Inhibition of PCSK9-mediated degradation of the LDL-R
Low-density lipoprotein receptors (LDL-R) in hepatocytes bind to LDL particles and remove them from the circulation.

The LDL-R then return to the cell surface to repeat this process. PCSK9 functions as a binding protein; it is expressed primarily in hepatocytes and after secretion binds to the LDL-R and promotes their degradation.

By blocking PCSK9, these inhibitors result in increased availability of LDL-R to remove LDL-C from the circulation.
PCSK9 INHIBITORS

- PCSK9 inhibitors are a newer class of injectable drugs that are monoclonal antibodies (mABs), a type of biologic drug, that has shown to dramatically lower LDL cholesterol levels, by up to 60% when combined with a statin.

- Blocking the binding of PCSK9 to the LDL receptor reduces the degradation of the receptor, which markedly increases the clearance of LDL and substantially lowers plasma LDL cholesterol.

- An injection of PCSK9-specific antibody suppresses LDL-cholesterol concentrations for several weeks.
By inhibiting HMG-CoA reductase and decreasing intracellular cholesterol, statins upregulate LDL receptors and LDL clearance.

Statin

HMG-CoA reductase

Cholesterol precursors

Triglyceride

B100

VLDL

Cholesterol

B100

LDL

Without PCSK9 attached, the LDL receptor is recycled to the cell surface, and can continue to clear LDL particles.

Anti-PCSK9 antibody binds to PCSK9, preventing it from binding to the LDL receptor.

PCSK9 ‘tags’ LDL receptor, resulting in its degradation in the lysosome.

B100 apolipoprotein-B100

PCSK9 proprotein convertase subtilisin/kexin type 9

LDL low-density lipoprotein

VLDL very low-density lipoprotein
LANDMARK STUDIES OF PCSK9 INHIBITORS

☞ OSLER-1 & OSLER-2 (Evolocumab-Repatha)
☞ ODYSSEY (Alirocumab-Praluent)
☞ FOURIER
OSLER-1 & 2 TRIALS

- Multicenter, open-label, parallel-group, randomized (2:1), controlled trial to determine the safety and efficacy of evolocumab to decrease LDL and cardiovascular events in patients who were enrolled in phase 2 and phase 3 trials of evolocumab in the long-term

- OSLER-1: evolocumab 420 mg SQ once monthly

- OSLER-2: evolocumab 140 mg SQ once monthly OR 140 mg SQ every 2 weeks (based on patient preference)

- N=4,465
  - 1,324 in phase 2 trials into OSLER-1
  - 3,141 in phase 3 trials into OSLER-2

- Mean follow-up: 11.1 months

CONCLUSION: Evolocumab in addition to standard lipid-lowering therapy elicited a sustained 61% reduction in LDL-C levels
ODYSSSEY TRIALS

- ODYSSEY LONG TERM TRIAL
- ODYSSEY OUTCOMES
ODYSSEY LONG TERM TRIAL

- Multicenter, double-blind, parallel group, randomized, controlled, phase 3 trial to determine the long-term safety and tolerability of alirocumab in the high cardiovascular risk patient with uncontrolled hyperlipidemia

- N=2,310 at 320 sites in 27 countries
  - Alirocumab (n=1530)
  - Placebo (n=780)

- High-risk for CV events defined by ≥ 1 of the following:
  - HeFH
  - CHD
  - CAD risk equivalent (PAD, ischemic stroke, moderate CKD, DM plus ≥ 2 CHD risk factors such as HTN or a FH of premature CAD)

- Mean follow-up: 1.5 years

CONCLUSION: the use of the monoclonal antibody Alirocumab in addition to statin therapy resulted in an additional 62% reduction in LDL-C with no significant increase in adverse events
An ongoing, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of alirocumab on the occurrence of cardiovascular events in patients who have recently experienced an acute coronary syndrome (ACS)

Alirocumab vs Placebo

Estimated enrollment: 18,600

Study start date: October 2012

Estimated primary completion date: December 2017

Maximum study duration: 64 months
FOURIER TRIAL

- Further CV Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

- Ongoing multicenter, randomized, double-blind, trial to evaluate the efficacy and safety of evolocumab among subjects with elevated risk on statin therapy

- N=27,564 at 1,242 sites in 49 countries
  - Evolocumab (n=13,784)
  - Placebo (n=13,780)

- Mean follow-up: 26 months

- **CONCLUSION:** Evolocumab lowered LDL-C by 59% compared with placebo
META-ANALYSES OF PCSK9 TRIALS

April 2015: Navarese, et al
- 24 RCT’s
- 10,159 patients
- This meta-analysis of PSCK9 inhibition in the treatment of dyslipidemia showed mortality benefit

2016: Bernocchi, et al (Milan, Italy)
- 29 RCT’s from inception to September 8, 2016
- 15,838 patients
- The updated meta-analysis confirms evidence of efficacy of different PCSK9 inhibitors in reducing LDL-C across different types of patients and both versus active treatment and placebo
FDA APPROVED PCSK9 INHIBITORS

- Praluent (alirocumab)-Regeneron/Sanofi (FDA approved: July 22, 2015)
  - 75 mg SQ every 2 weeks or 150 mg SQ every 2 weeks
  - $14,600 per year
  - Indication: For use in addition to diet and max-tolerated statin therapy in adult patients
    - Heterozygous familial hypercholesterolemia
    - Clinical atherosclerotic CV disease, who require additional lowering of LDL cholesterol

- Repatha (evolocumab)-Amgen (FDA approved: August 27, 2015)
  - 140 mg SQ every 2 wks or 420 mg SQ every 4 wks (Pushtronex™ system)
  - $14,100 per year
  - Indication:
    - Heterozygous familial hypercholesterolemia
    - Clinical atherosclerotic CV disease, who require additional lowering of LDL cholesterol
    - Homozygous familial hypercholesterolemia
Before you use a single-use pre-filled Repatha® SureClick® Autoinjector, read this important information:

- It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider.

- The orange cap on the Repatha® SureClick® Autoinjector contains a needle cover (located inside the cap) that contains dry natural rubber, which is made from latex. Tell your healthcare provider if you are allergic to latex.

**Storage of Repatha™:**

- Keep the Repatha® SureClick® Autoinjector in the original carton to protect from light during storage.

- Keep the Repatha® SureClick® Autoinjector in the refrigerator between 36°F to 46°F (2°C to 8°C).

- If removed from the refrigerator, the Repatha® SureClick® Autoinjector should be kept at room temperature up to 77°F (25°C) in the original carton and must be used within 30 days.

- Do not freeze the Repatha® SureClick® Autoinjector or use a Repatha® SureClick® Autoinjector that has been frozen.

**Do not:**

- Do not shake the Repatha® SureClick® Autoinjector.

- Do not remove the orange cap from the Repatha® SureClick® Autoinjector until you are ready to inject.

- Do not use the Repatha® SureClick® Autoinjector if it has been dropped on a hard surface. Part of the Repatha® SureClick® Autoinjector may be broken even if you cannot see the break. Use a new Repatha® SureClick® Autoinjector, and call 1-844-REPATHA (1-844-737-2842).

- Do not use the Repatha® SureClick® Autoinjector after the expiration date.

A healthcare provider who knows how to use the Repatha® SureClick® Autoinjector should be able to answer your questions.

For more information or help, call 1-844-REPATHA (1-844-737-2842) or visit Repatha.com
Repatha® (evolocumab) Pushtronex™ system
(on-body infusor with prefilled cartridge)
PRALUENT® (alirocumab) Injection: Self-administered every 2 weeks

Each PRALUENT dose is delivered with a single, 1-mL subcutaneous injection

Dosage and Administration Options

75 mg/1 mL pen

150 mg/1 mL pen

Both doses available in a single-dose, 1-mL, prefilled pen and prefilled syringe

Please review complete Instructions for Use for the PRALUENT Pen and PRALUENT Syringe.

MyPRALUENT™: Comprehensive support for you and your patients

• PRALUENT can be self-administered but, if needed, we offer comprehensive support and training for your office and patients on how to inject PRALUENT

Call a MyPRALUENT nurse available 7 days a week at 1-844-PRALUENT (1-844-772-5836), press 1, to learn how to teach your patients to self-inject

IMPORTANT SAFETY INFORMATION
PRALUENT is contraindicated in patients with a history of a serious hypersensitivity reaction to PRALUENT. Reactions have included hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization.

Hypersensitivity reactions (e.g., pruritus, rash, urticaria), including some serious events (e.g., hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization), have been reported with PRALUENT treatment. If signs or symptoms of serious allergic reactions occur, discontinue treatment with PRALUENT; treat according to the standard of care, and monitor until signs and symptoms resolve.

The most commonly occurring adverse reactions (≥5% of patients treated with PRALUENT and occurring more frequently than with placebo) are nasopharyngitis, injection site reactions, and influenza.

Local injection site reactions including erythema/redness, itching, swelling, and pain/tenderness were reported more frequently in patients treated with PRALUENT (7.2% versus 5.1% for PRALUENT and placebo, respectively).
BOCOCIZUMAB

- PCSK9 inhibitor developed by Pfizer, Inc

- Discontinued phase III clinical trial in November 2016 due to higher levels of immunogenicity and higher rates of injection-site reactions

- Not likely to provide value to patients, physicians, or shareholders
“Maximally tolerated statin therapy”—not equivalent to "statin intolerant."

The FDA avoided including the term "statin intolerant" on the label because of concerns that this "could promote a condition that is not well-understood and encourage some patients to prematurely abandon statins."

Safety concerns/immunogenicity

Cost
PCSK9 inhibition is considered an attractive target for therapy.

Monoclonal antibodies are currently the most advanced pharmacologically developed PCSK9 inhibitors.

Recent studies suggest efficacy.

Long-term evaluation.
THANK YOU