Update on PCSK9 Inhibitors

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Disclosures

- None.

Management of Hypercholesterolemia

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PCSK9 inhibitors are approved for:

1. Statin intolerant patients
2. Patients with familial hypercholesterolemia
3. Patients with atherosclerotic heart disease on maximally tolerated dose of statins with insufficient LDL-C lowering.

A. All of the above
B. 1 only
C. 2 only
D. 2 and 3

True or False

PCSK9 inhibitors lower LDL-C, apolipoprotein B, and Lp(a).

A. True
B. False

An important addition to our current armamentarium

- Diet and Exercise
- Statins
- Cholesterol Absorption Inhibitor
- Bile Acid Sequestrants
- Niacin
- Microsomal Triglyceride Transfer Protein Inhibitor
- Oligonucleotide inhibitor of apo B-100
- LDL apheresis
- **PCSK9 inhibitors**

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Proprotein convertase subtilisin/kexin 9

- PCSK9 is an enzyme that is encoded to the PCSK9 gene.
- It binds to the LDL receptor in the liver
- When it binds to the LDLR, the receptor is broken down and can no longer remove LDL-C from the blood.

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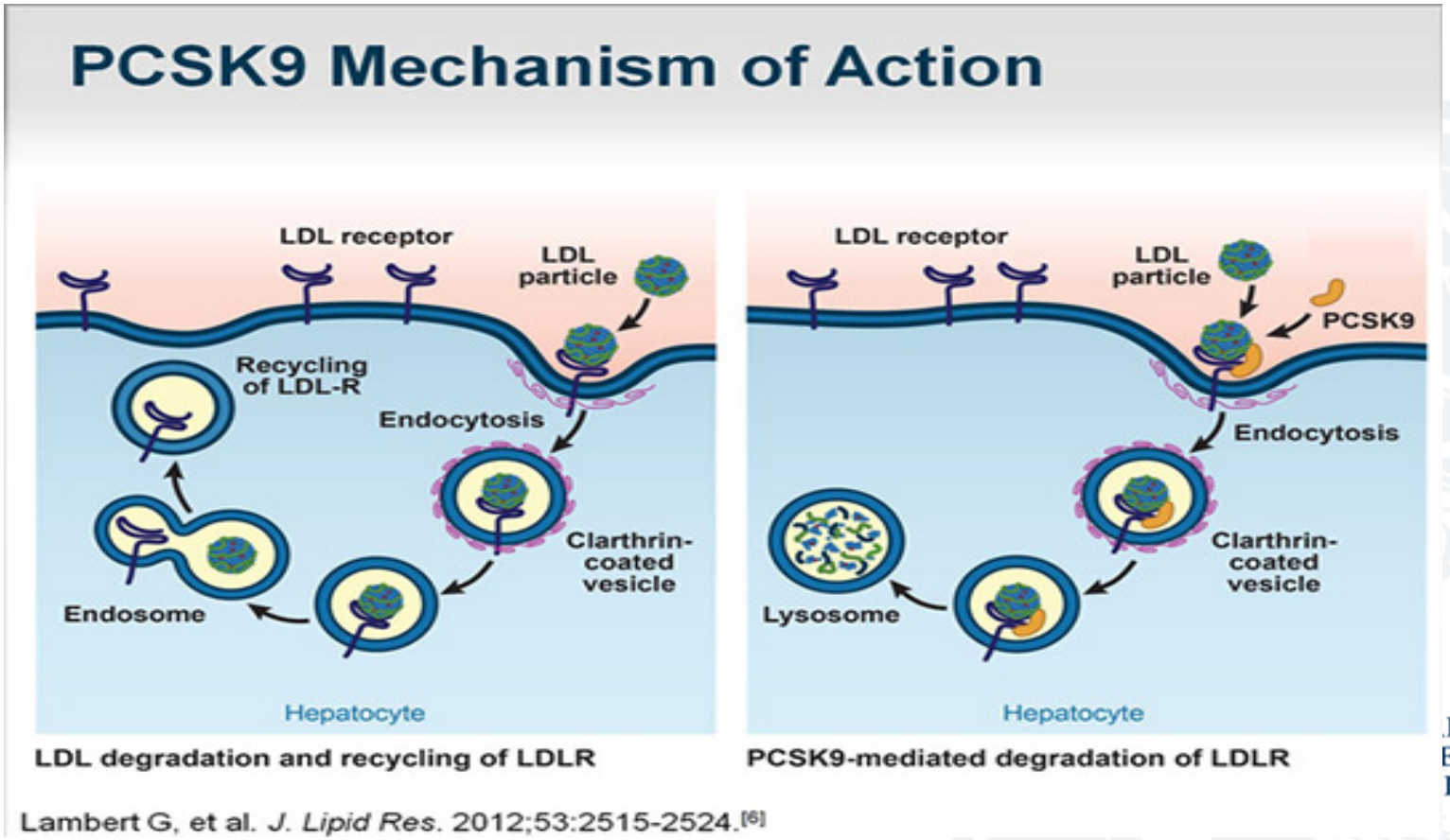
What does PCSK9 do?



Lambert G, et al. *J. Lipid Res.* 2012;53:2515-2524.[6]

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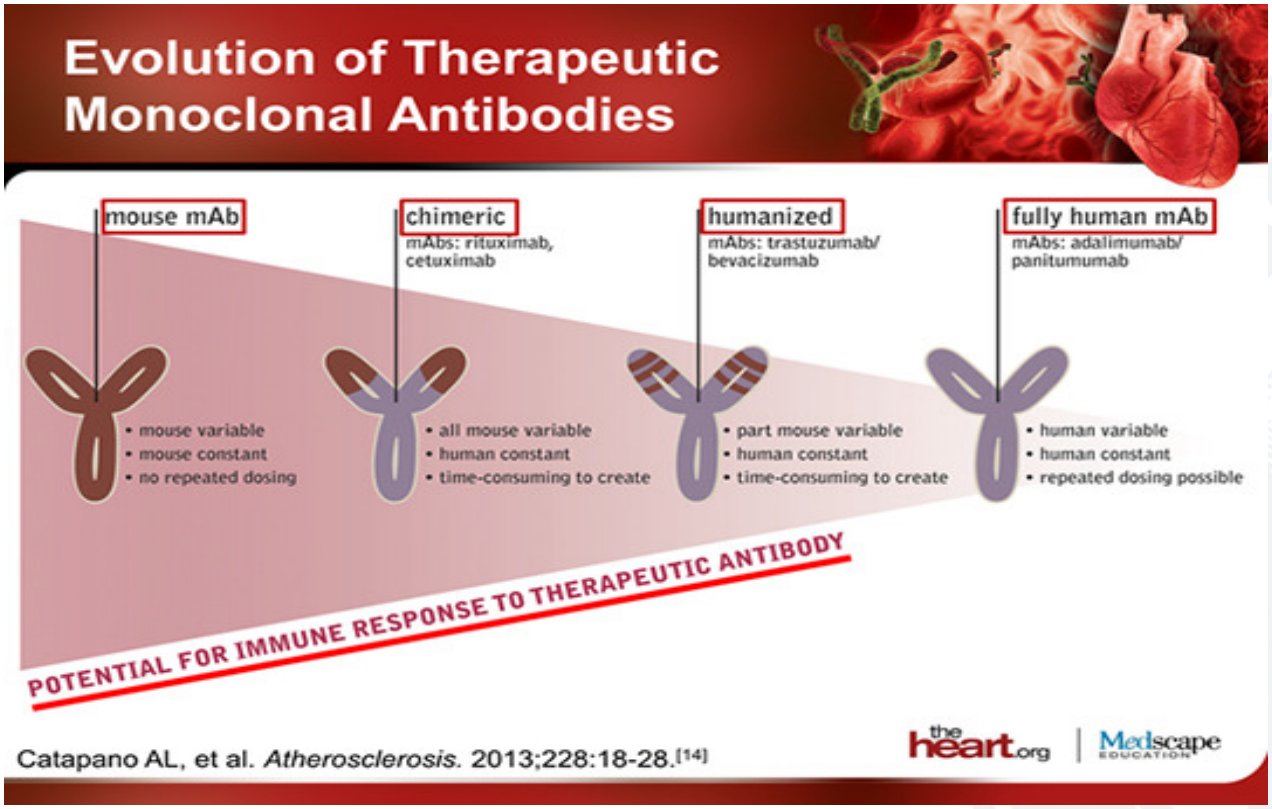
PCSK9 inhibitors are monoclonal antibodies



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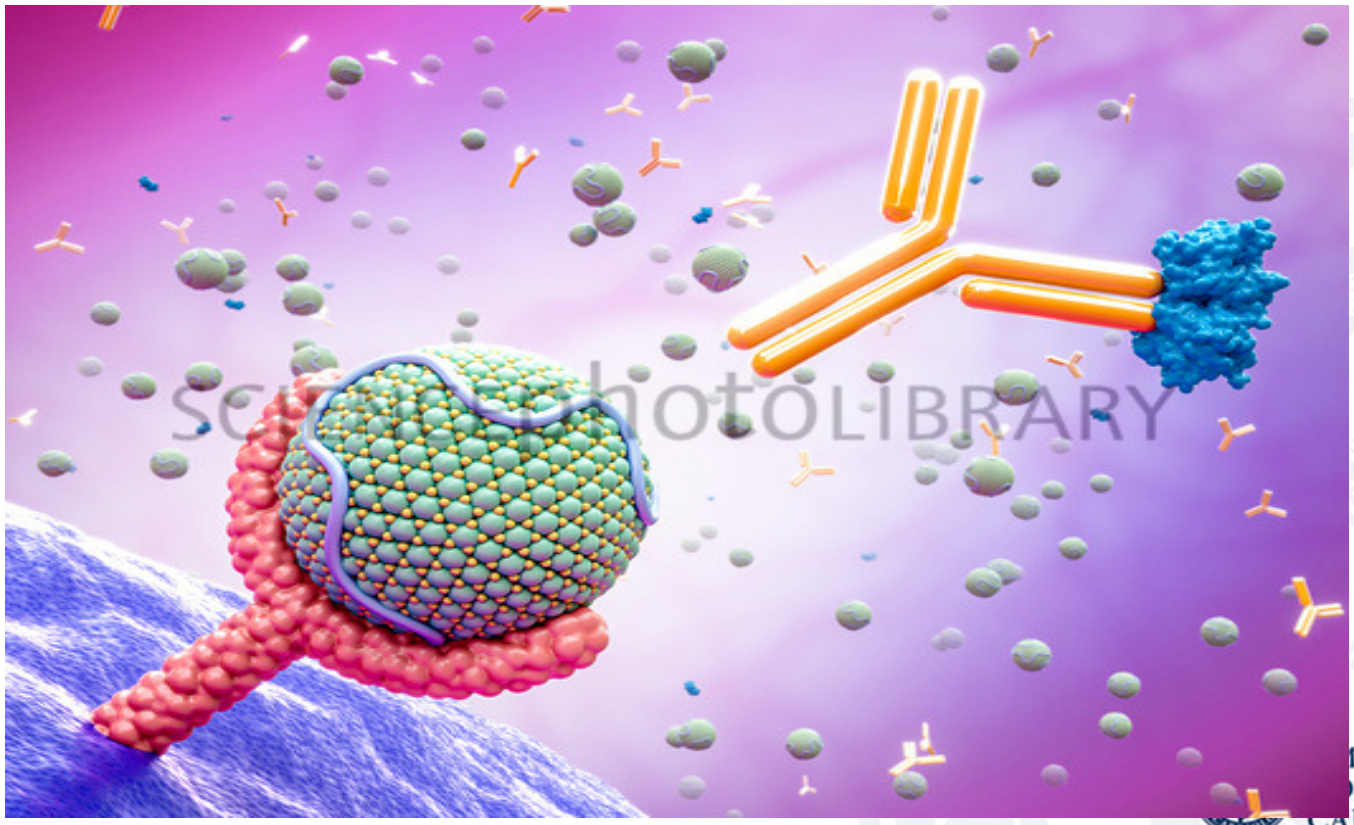
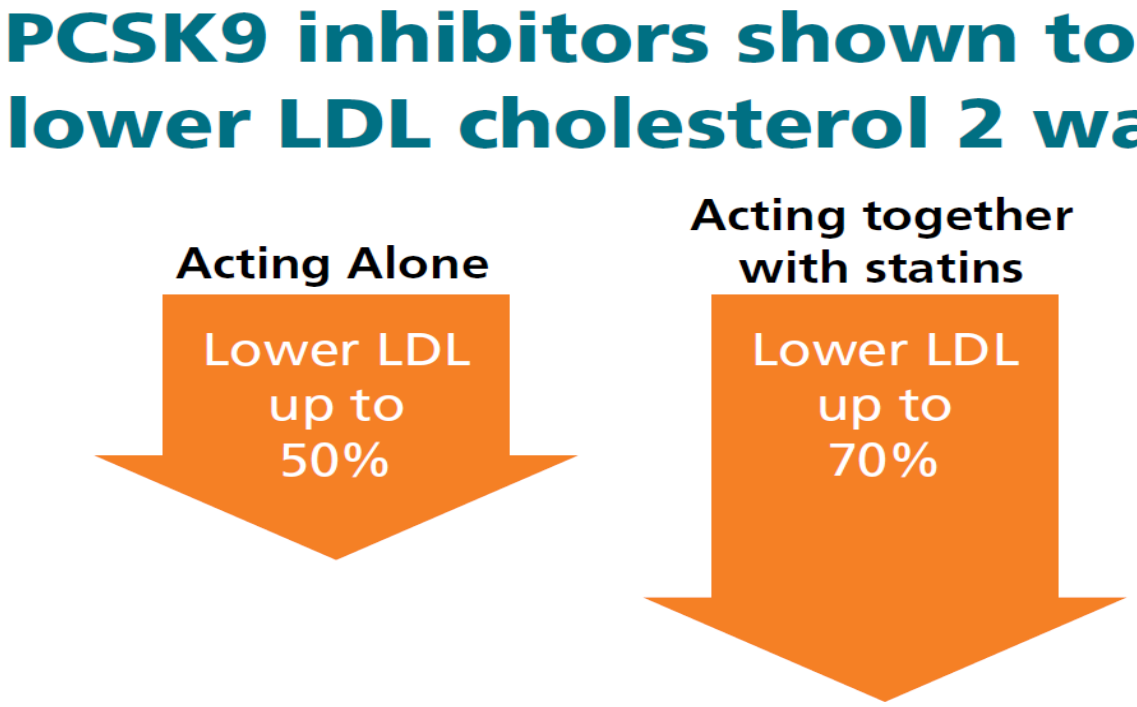
PCSK9 Inhibitors

- Are monoclonal antibodies
- Target and inactivate PCSK9 (proprotein convertase subtilisin kexin 9 in the liver
- Dramatically decrease LDL-C

PCSK9 inhibitors prohibit binding to the LDLR



PCSK9 inhibitors dramatically lower LDL-C



Source: McKenney JM. Understanding PCSK9 and anti-PCSK9 therapies. J Clin Lipidol. 2015;9:170-86.

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Statins lower LDL-C

Statins are Current Treatment of Choice for High Cholesterol

* Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1-45.

** LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA. 1999;282:2340-6.

\# Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol.

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LDL-C Lowering with Statins

Table. Classification of Statin Therapies

Statin	High-Intensity	Moderate-Intensity	Low-Intensity
	Lowers LDL >50%	Lowers LDL 30% to 49%	Lowers LDL <30%
Atorvastatin	40 mg – 80 mg	10 mg – 20 mg	
Rosuvastatin	20 mg – 40 mg	5 mg – 10 mg	
Lovastatin		40 mg	20 mg
Simvastatin		20 mg – 40 mg	10 mg
Pravastatin		40 mg – 80 mg	10 mg – 20 mg
Fluvastatin (XL)		80 mg	
Fluvastatin		40 mg (twice daily)	20 mg – 40 mg
Pitavastatin		2 mg – 4 mg	1 mg

LDL=low-density lipoprotein.
Source: Circulation. 2013;129(25 suppl 2):S1-S45.

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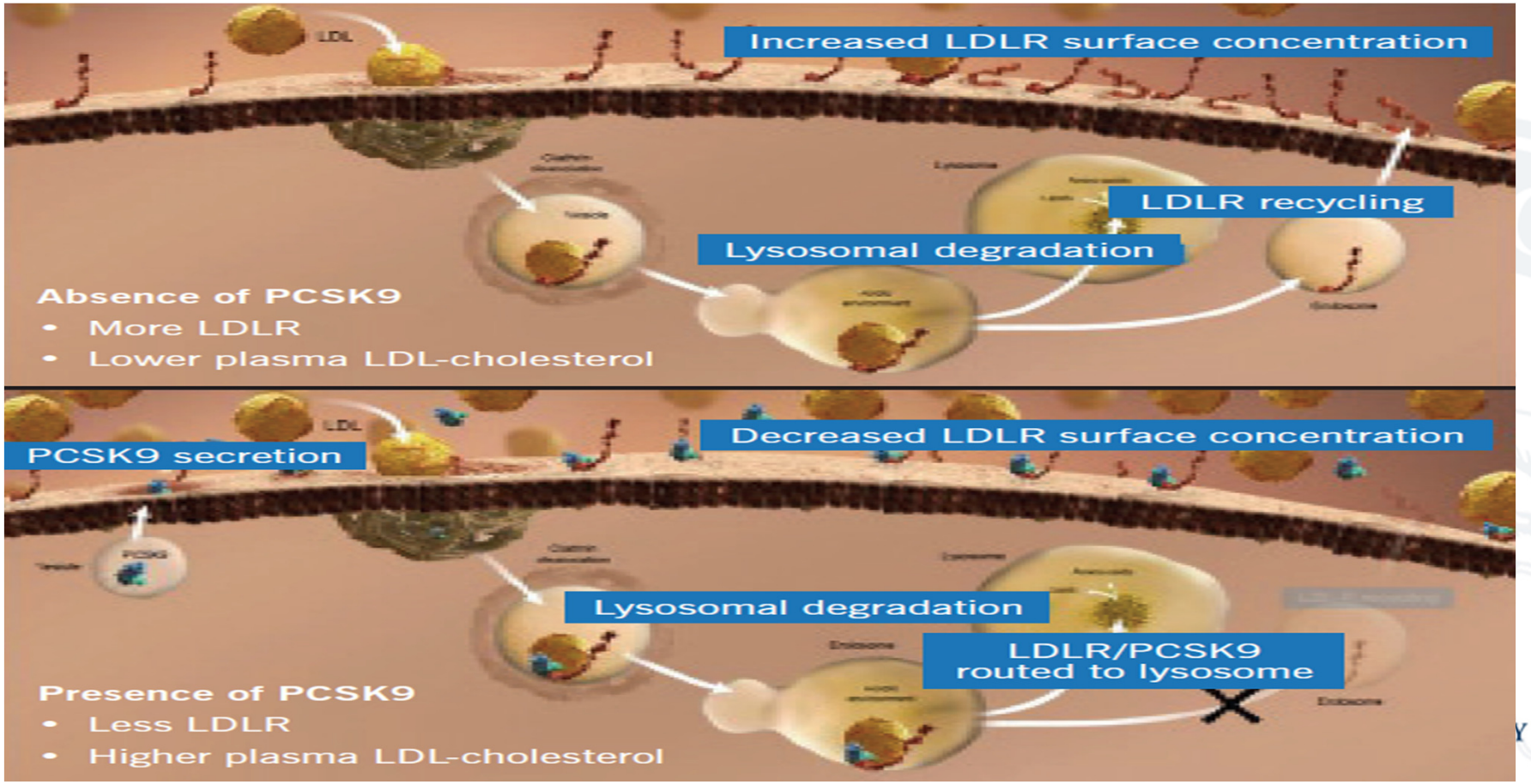
PCSK9 Inhibitors

- Are monoclonal antibodies
- Target and inactivate PCSK9 (proprotein convertase subtilisin kexin 9 in the liver
- Dramatically decrease LDL-C

PCSK9 decreases LDLR and increases LDL-C



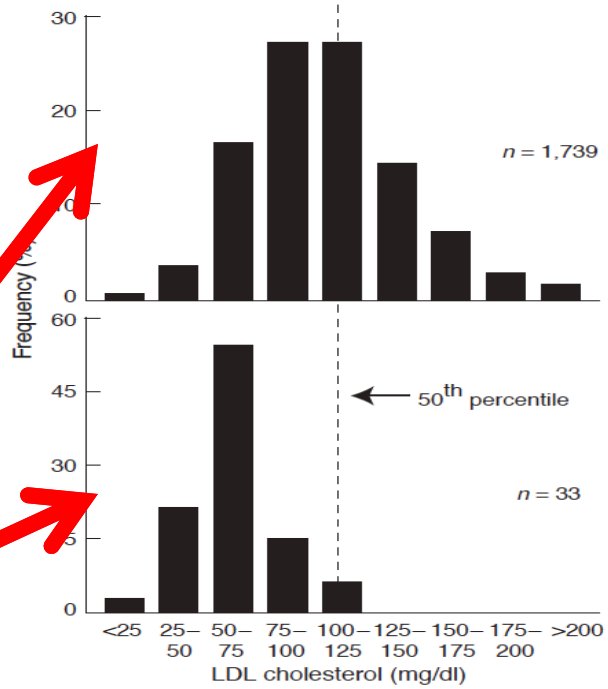
How did all of this come about?

- PCSK9 found to cause FH by a gain-of-function mutation, resulting in increased serum LDL-C and expression of FH phenotype
- Hypothesis: if a gain-of-function mutation leads to an increased LDL-C, then will a loss-of-function mutation lead to a decrease in LDL-C?
- Epidemiologic analysis supports this hypothesis, with rates of CHD for populations of individuals that have loss-of function mutations in PCSK9 being lower than that observed in the general public

PCSK9 Mutations: Dallas Heart Study

African Americans without PCSK9 mutation

African Americans with PCSK9 mutation



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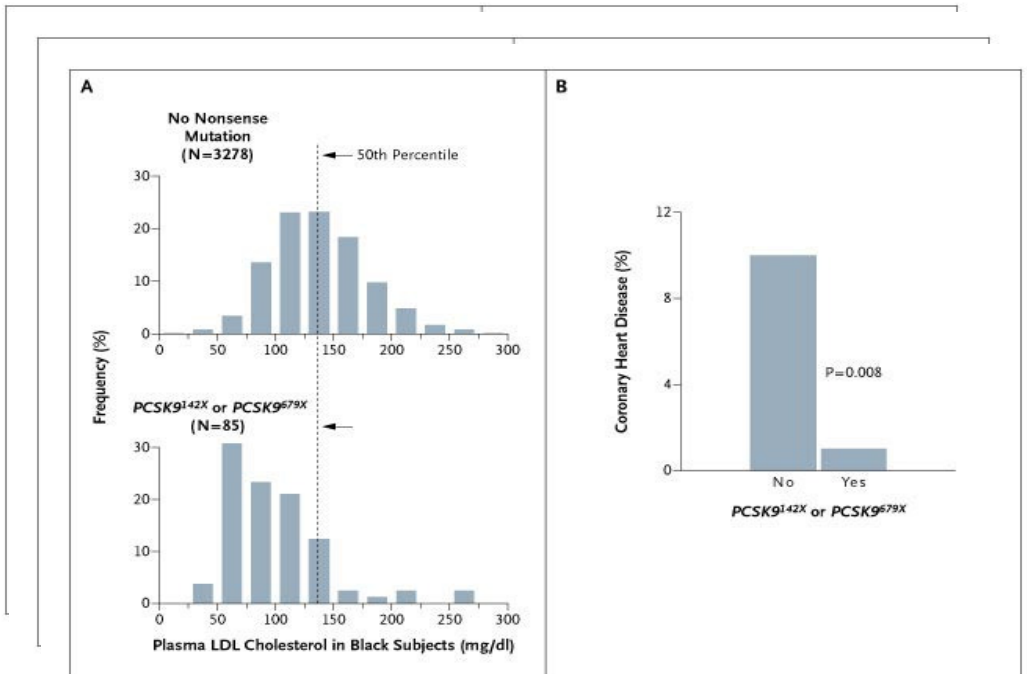
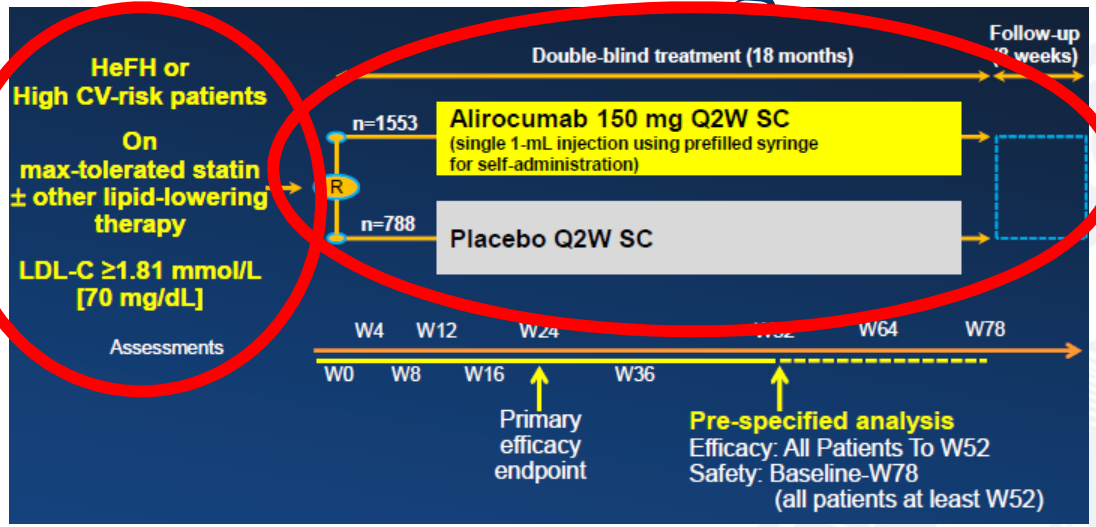
Distribution of Plasma LDL (panel A)and incidence of coronary artery disease (panel B) among Black Subjects, according to the presence or absence of a PCSK9 allele



What about individuals with little or no PCSK9?

- Question answered :
- 32-year-old women with LDL-C of 14 mg/dl and complete loss-of-function of PCSK9
  - Healthy college graduate
  - Normal fertility and development
  - No history of cancer or neurocognitive issues

ODYSSEY LONG TERM Design



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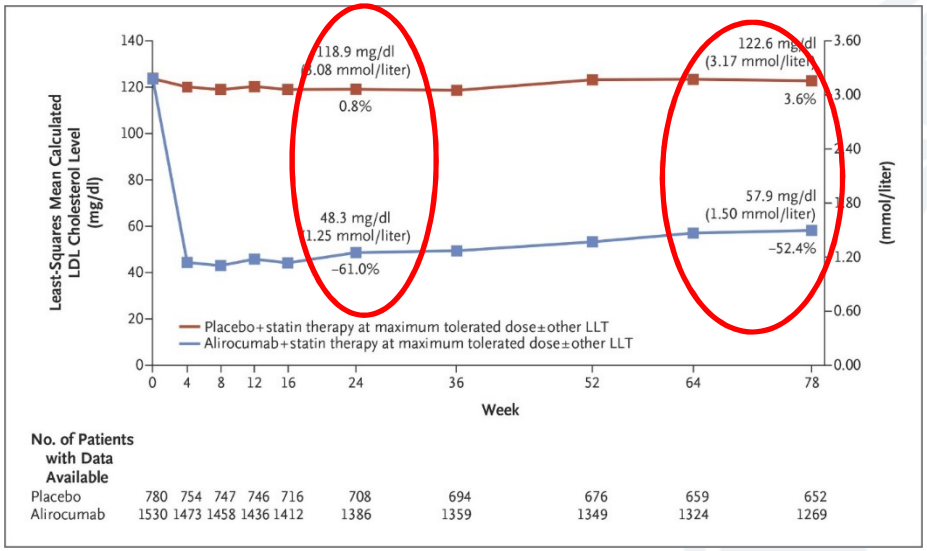
1° Efficacy Endpoint: LDL-C



Cardiovascular Outcomes

Cardiovascular adverse events of interest — no. of patients (%)			
Death from coronary heart disease, including death from unknown cause	4 (0.3)	7 (0.9)	0.26
Nonfatal myocardial infarction	14 (0.9)	18 (2.3)	0.01
Fatal or nonfatal ischemic stroke	9 (0.6)	2 (0.3)	0.35
Unstable angina requiring hospitalization	0	1 (0.1)	0.34
Congestive heart failure requiring hospitalization	9 (0.6)	3 (0.4)	0.76
Ischemia-driven coronary revascularization procedure	48 (3.1)	24 (3.0)	1
Positively adjudicated cardiovascular events, including all cardiovascular adverse events listed above	72 (4.6)	40 (5.1)	0.68
Adjudicated major adverse cardiovascular events in post hoc analysis‡	27 (1.7)	26 (3.3)	0.02

Event	Alirocumab (N=1550)	Placebo (N=788)	P Value†
Summary of adverse events — no. of patients (%)			
Any adverse event	1255 (81.0)	650 (82.5)	0.40
Serious adverse event	290 (18.7)	154 (19.5)	0.66
Adverse event leading to study-drug discontinuation	111 (7.2)	46 (5.8)	0.26
Adverse event leading to death	8 (0.5)	10 (1.3)	0.08
Other adverse events of interest			
General allergic reaction — no. of patients (%)	156 (10.1)	75 (9.5)	0.71
Local injection-site reaction — no. of patients (%)	91 (5.9)	33 (4.2)	0.10
Myalgia — no. of patients (%)	84 (5.4)	23 (2.9)	0.006
Neurologic event — no. of patients (%)§	65 (4.2)	35 (4.4)	0.83
Neurocognitive disorder — no. of patients (%)¶	18 (1.2)	4 (0.5)	0.17
Amnesia	5 (0.3)	0	0.17
Memory impairment	4 (0.3)	1 (0.1)	0.67
Confusional state	4 (0.3)	1 (0.1)	0.67
Ophthalmologic event — no. of patients (%)‖	45 (2.9)	15 (1.9)	0.65
Hemolytic anemia — no. of patients	0	0	NC
Diabetes in patients with no history of diabetes — no. of patients/total no. (%)**	18/994 (1.8)	10/509 (2.0)	0.84
Worsening of diabetes in patients with history of diabetes — no. of patients/total no. (%)**	72/556 (12.9)	38/279 (13.6)	0.83
Laboratory values of interest — no. of patients/total no. (%)			
Alanine aminotransferase >3× ULN	28/1533 (1.8)	16/779 (2.1)	0.75
Aspartate aminotransferase >3× ULN	22/1533 (1.4)	18/779 (2.3)	0.13
Creatine kinase >3× ULN	56/1507 (3.7)	38/771 (4.9)	0.18

ODYSSEY – Long Term Adverse Effects

- Serious adverse events balanced between active and placebo arms of this double blind study
- Fewer nonfatal MIs and CV events in those treated alirocumab
- Incidence of myalgias and local injection site reactions were higher in alirocumab versus the placebo arm.
- Lab abnormalities relative to liver or renal were balanced between the two arms.

Summary

- **ODYSSEY LONG TERM Study of Alirocumab:**
  - Enrolled high-risk participants in a double-blind, RCT
  - Essentially all participants were on statin therapy at baseline

- **Conclusions:**
  - Exciting
    - Robust reductions in LDL-C and other lipids like Lp(a) out to 18 months
    - Signal for reduced cardiovascular events
  - Concerning
    - Signal for adverse neurocognitive effects (though not associated with LDL-C levels)

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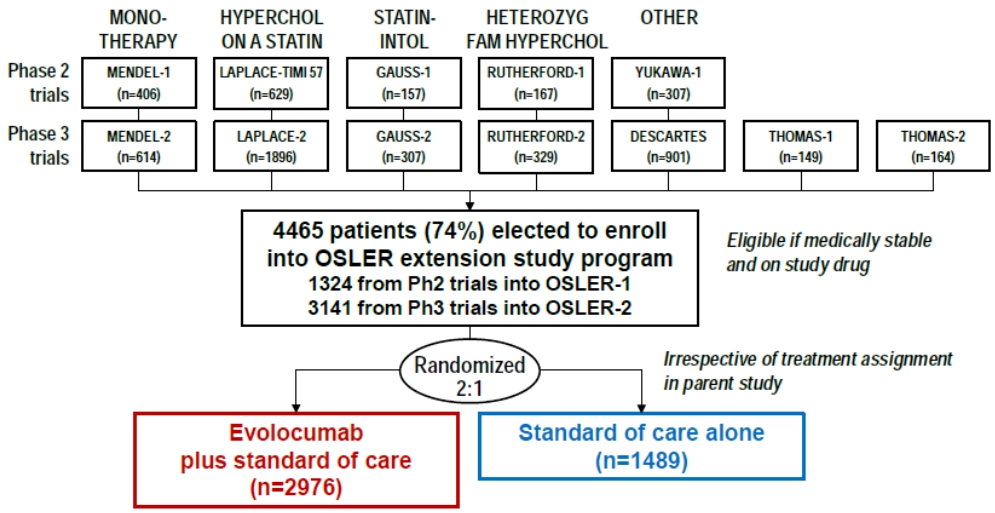
OSLER program- Longer term effects of evolocumab

- Studied subjects with LDL-C <25mg/dl, <50 mg/dl, and >50 mg/dl
- No significant differences in adverse effects among the 3 groups
- Neurocognitive events –more frequent with evolocumab subjects
  - No correlation between neurocognitive events and degree of LDL-C reduction
  - Lipoproteins and monoclonal antibodies don't cross blood-brain barrier, therefore difficult to find a mechanism to explain.
  - Open label design of the study and fact that subjects had more visits provided more opportunities to mention a neurocognitive event, particularly in the treatment group.

OSLER Program



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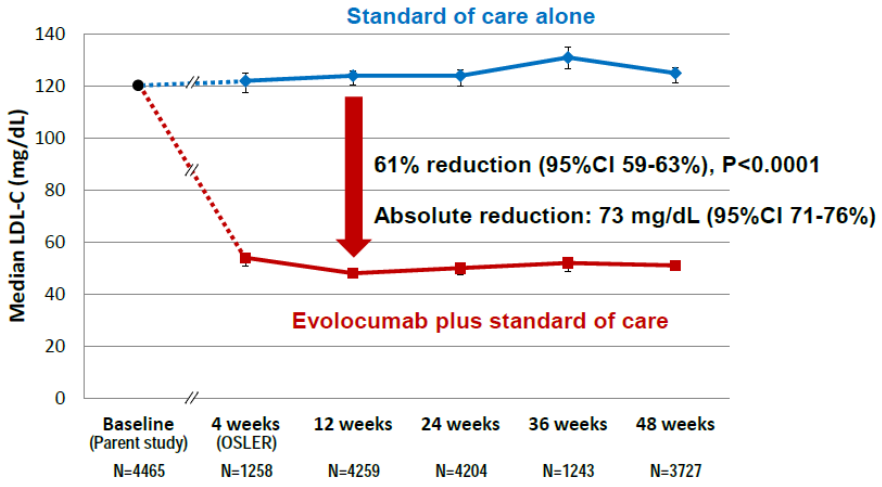
Methods

- **Intervention**
  - Open-label evolucumab via subcutaneous injections
  - Dosed either 140 mg q 2 wk or 420 mg q month
- **Endpoints**
  - Adverse events (primary)
  - LDL-cholesterol (secondary)
  - Cardiovascular (CV) clinical outcomes (prespecified, exploratory):
    - Death
    - Coronary: MI, UA requiring hospitalization, revascularization
    - Cerebrovascular: stroke or TIA
    - HF requiring hospitalization

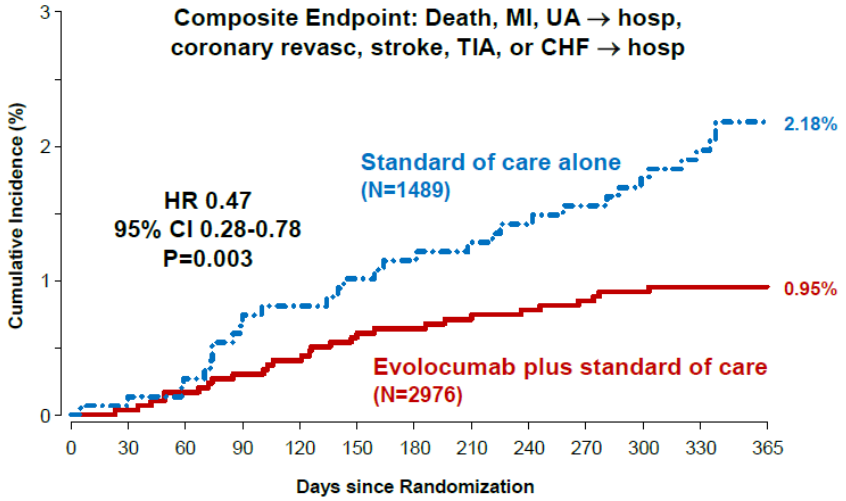
Baseline Characteristics

Characteristic	Value
Age, years, mean (SD)	**58 (11)**
Male sex (%)	**51**
Cardiovascular risk factor (%)	**80**
Hypertension	52
Diabetes mellitus	13
Metabolic syndrome	34
Current cigarette use	15
Family hx of premature CAD	24
Known familial hyperchol.	10
Known vascular disease (%)	**25**
Coronary	20
Cerebrovascular or Peripheral	9

LDL-C



Cardiovascular Outcomes



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Adverse Events

	Evolocumab subjects stratified by minimum achieved LDL-C				All EvoMab (n=2976)	Stnd of Care Alone (n=1489)
	<25 mg/dL (n=773)	25 to <40 mg/dL (n=759)	<40 mg/dL (n=1532)	≥40 mg/dL (n=1426)		
Adverse Events (%)						
Any	70.0	68.1	69.1	70.1	69.2	64.8
Serious	7.6	6.9	7.2	7.8	7.5	7.5
Muscle-related	4.9	7.1	6.0	6.9	6.4	6.0
Neurocognitive	0.5	1.2	0.8	1.0	0.9	0.3
Lab results (%)						
ALT/AST >3×ULN	0.9	0.8	0.8	1.3	1.0	1.2
CK >5×ULN	0.4	0.9	0.7	0.5	0.6	1.2

Neurocognitive Events

- Incidence slightly higher with alirocumab
  - Alirocumab: 1.2% vs. 0.5% (placebo)
  - Evolocumab: 0.9% vs. 0.3% (placebo)
- Good assessment of neurocognitive effects won't happen until the very large outcome studies are completed

Fourier Study

- Fourier study to be completed in 2018, will provide the long term cardiovascular outcomes of PCSK9 inhibitors.
- 22,500 patient trial evaluating evolocumab versus statin therapy in high-risk patients.
- Composite endpoint of cardiovascular death, myocardial infarction, and hospitalization for revascularization, unstable angina, or stroke.

Additional Long Term Studies

- ODYSSEY OUTCOMES Trial with alirocumab
- The Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High-Risk Subjects (SPIRE-1) and SPIRE-2 for bococizumab
- Will provide further insight into cardiovascular outcomes.

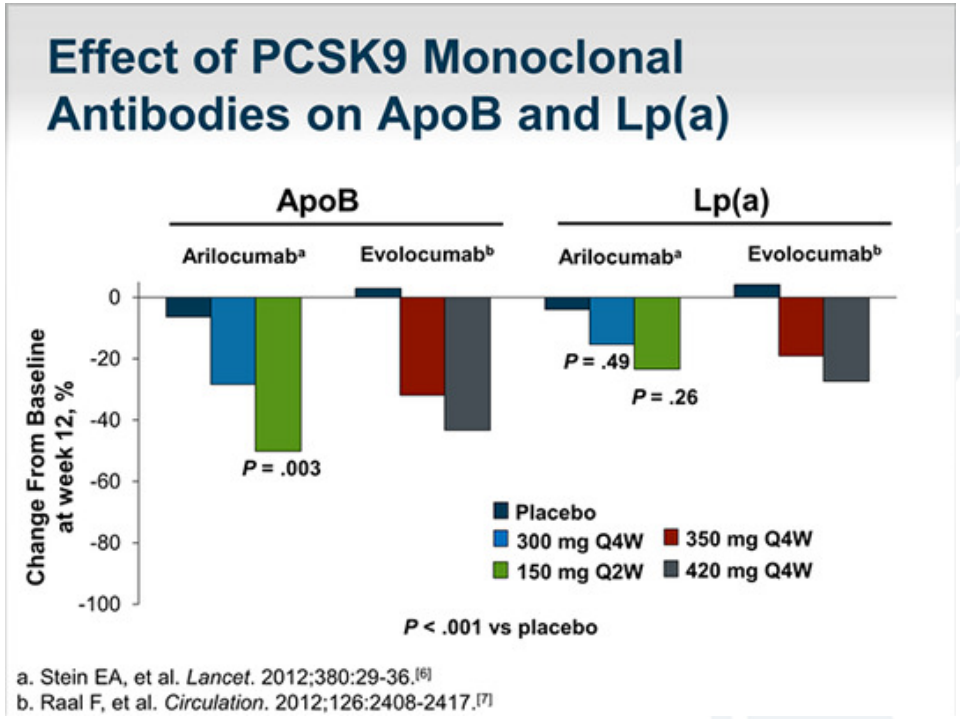
Advantages of PCSK9 Use

- Monoclonal antibodies have high specificity and affinity
- Reduce free PCSK9 to extremely low levels within hours
- Have a synergistic effect with statins
  - Statins upregulate LDLR activity, but also upregulate the production of PCSK9
  - PCSK9 inhibitors negate this effect
- Monoclonal antibodies circulate throughout the body for many days or weeks, making it possible to administer the PCSK9 inhibitor on a biweekly or monthly basis

Advantages of PCSK9 inhibitors

- Elimination of mAbs occurs via an antigen-specific targeted disposition or via the reticuloendothelial system
  - No elimination via liver or kidney
- Lowers lipoprotein (a) (Lp(a))

Apolipoprotein B and Lp(a) Lowering



a. Stein EA, et al. *Lancet*. 2012;380:29-36.[6]
b. Raal F, et al. *Circulation*. 2012;126:2408-2417.[7]

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Potential Disadvantages of Use

- Increased cost, due to complex and expensive manufacturing process
- Concerns over using parenteral vs. oral therapy
- Modest effects on HDL and triglycerides
- Long term effects on cardiovascular outcomes are yet unknown

Effects of Drug in Specific Populations

- Heterozygous familial hypercholesterolemia (HeFH)
- Homozygous familial hypercholesterolemia (HoFH)
- Statin Intolerant

Additional Issues regarding Safety and Tolerability of PCSK9 Inhibitors

- Immunogenecity
  - Direct immunogenicity does not occur as mAbs for PCSK9 are very specific and have no direct immune effects
  - Development of antidrug antibodies
- Possible adverse effects of very low LDL-C

FDA Approved Indications

Alirocumab – 7/24/15

Approved for use in addition to diet and maximally tolerated statin therapy in adult patients with HeFH or patients with clinical atherosclerotic disease, such as heart attacks or strokes, who require additional LDL lowering

Evolocumab – 8/27/15

Approved for use in addition to diet and maximally tolerated statin therapy in adult patients with HeFH, HoFH, or patients with clinical atherosclerotic disease, such as heart attacks or strokes, who require additional LDL lowering

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Praluent

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Repatha

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Comparisons of the 2 Approved Medications

Repatha

Praluent

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Repatha® (evolocumab) *Pushtronex™* system
(on-body infusor with prefilled cartridge)

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71 Million
Americans have high cholesterol[1]

- Statin intolerant
- Genetic disorder (FH)
- Uncontrolled on statins

11 Million
Americans uncontrolled on cholesterol therapy may be targeted[1]

1-2 Million[2]
Potential Targeted PCSK9 inhibitor population in U.S.

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Not always an easy task!

Be certain to include in your progress notes

Preauthorization

- Provide complete documentation of:
  - Diagnoses
  - LDL-C levels after treatment with lipid-lowering therapies
  - Trial of high intensity statin therapy
  - Documentation that patient will continue to receive maximum dose of statin while taking the PCSK9 inhibitor
  - All prescribed statins and dosing levels

Preauthorization

- Statin intolerance
  - Muscle related symptoms
  - CK levels
  - Symptoms while on separate trials of atorvastatin and rosuvastatin
  - Resolution of symptoms with discontinuance of each respective statin


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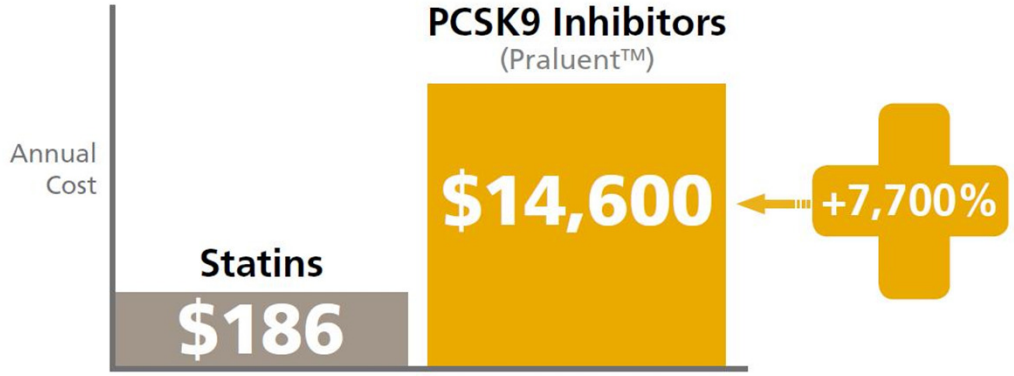
Expensive – explore assistance options with patients

Cost of Treatment

Average Annual Cost of Therapy

Costs could soar with widespread use of PCSK9 Inhibitors



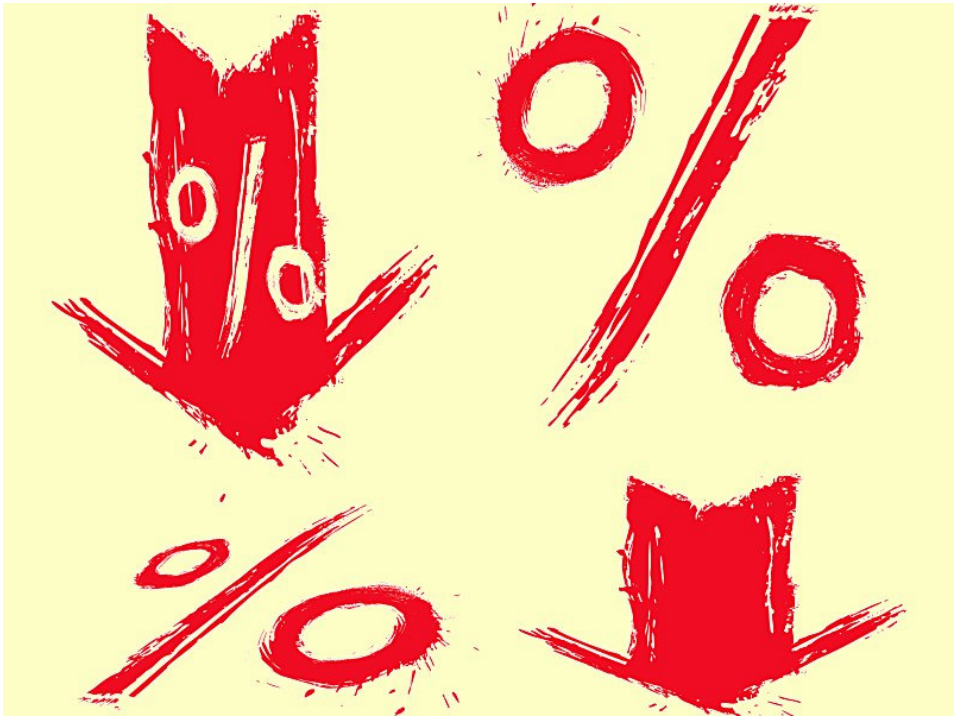
Statin cost: WAC drug costs for atorvastatin. OptumRx Q2-2015 utilization data.
Reuters. New heart drugs come in more expensive than expected. Jul 27, 2015.

Utilize supports to keep patients on track

Such as…

- Refill reminders
- Text messages
- Follow up phone calls
- If possible, enlist your specialty pharmacy

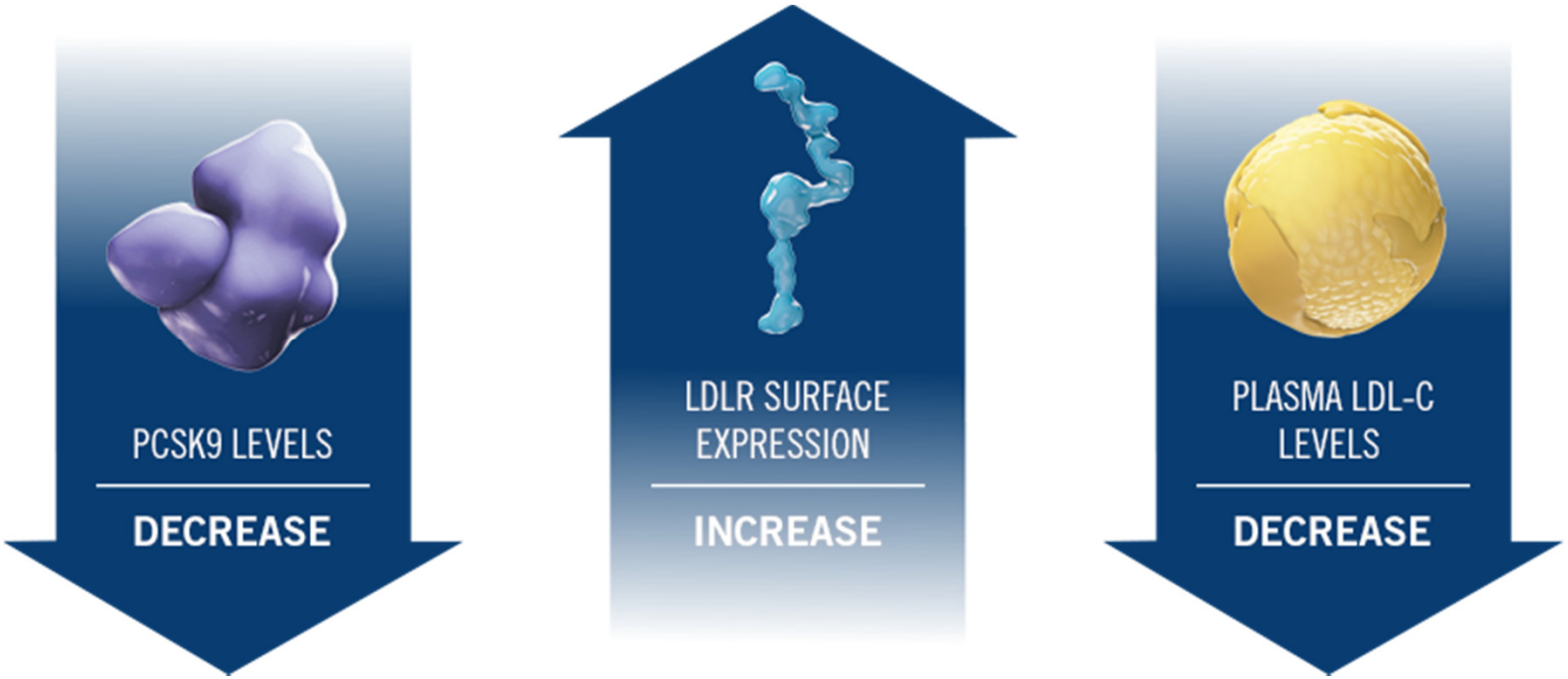
A common question from patients: how low is too low?



Additional patient questions

- Duration of therapy?
- Can other lipid-lowering meds be discontinued?
- What if I forget to take my medication?
- What should I do if I leave my injector pen out of the refrigerator for a whole day?
- What about pregnancy and breastfeeding?
- May other mAbs be used?

In a Nutshell…




OPTIMISM
BLVD

PCSK9 inhibitors are approved for:

1. Statin intolerant patients
2. Patients with familial hypercholesterolemia
3. Patients with atherosclerotic heart disease on maximally tolerated dose of statins with insufficient LDL-C lowering.

A. All of the above
B. 1 only
C. 2 only
D. 2 and 3

True or False

PCSK9 inhibitors lower LDL-C, apolipoprotein B, and Lp(a).

A. True
B. False

CHOLESTEROL
COUNTS

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