New Lipid-Lowering Drugs: PCSK9 Inhibitors

Blockbusters or Bust?

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The speaker has no actual or potential conflicts of interest in relation to this presentation.

What's our starting point?

Had you heard of PCSK9 inhibitors prior to this presentation?

A. Yes
B. No

Why You Should Care

- Two recently FDA-approved medications
  - alirocumab and evolocumab
  - bococizumab in the pipeline
- Novel mechanism resulting in potent LDL reduction
- Extensive clinical trial data
- Potential for great impact on public health
- Cost to patients and payers

Outline

- Current treatment guidelines for LDL reduction in hypercholesterolemia
- Mechanism of action of PCSK9 inhibitors
- Features of PCSK9 inhibitors
- Efficacy and safety data from clinical trials
- Place in therapy
- Cost

In a world without PCSK9 inhibitors…

CURRENT HYPERCHOLESTEROLEMIA TREATMENT GUIDELINES

2002 ATPIII Guidelines[1]

The higher the risk of cardiovascular disease…

- Atherosclerotic disease
- Risk factors such as smoking, hypertension, diabetes

…the more aggressive the LDL goal

2013 ATPIV Guidelines[2]

- Statin therapy
  - Dose intensity determined by presence of atherosclerotic cardiovascular disease or cardiovascular risk (ASCVD risk calculator)
- Adjunctive therapy if
  - Baseline LDL above 190 mg/dL
  - Inadequate response to statin
- Nonstatin therapy if contraindication to statin

Aren't Statins Enough?

- Atherosclerotic disease is still the leading cause of morbidity and mortality in developed countries.[3]
- Nearly **60 million** Americans are estimated to have LDL ≥160 mg/dL
  - Only **26%** of patients are receiving a high-intensity statin
  - Only **1/3** of very high-risk patients achieve an LDL <70 mg/dL in surveys conducted both within and outside of the U.S.

Aren't Statins Enough?

- Up to **40%** of patients receiving statins are not able to reach target LDL goals following current guideline recommendations.[4]
  - Residual risk
  - Statin intolerance
  - Non-compliance
  - Suboptimal dosing
  - Familial hypercholesterolemia

Adjunctive Therapy

Lack of demonstrated reduction in cardiovascular events when used in addition to a statin

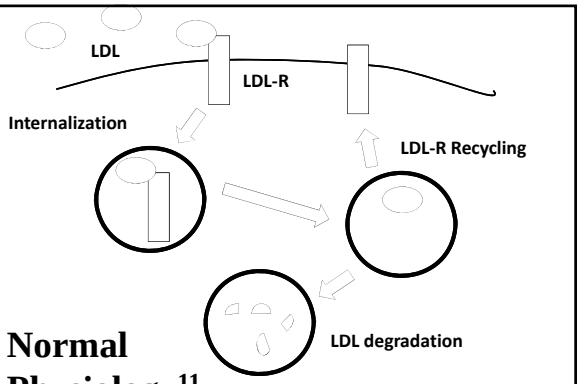
Trial	Drug, Population
ACCORD[5]	Fenofibrate, Type II Diabetes
AIM-HIGH[6]	Niacin, CVD and LDL <70mg/dL
HPS2-THRIVE[7]	Niacin + laropiprant, atherosclerotic vascular disease
ILLUMINATE[8]	Torcetrapib, high cardiovascular risk

IMPROVE-IT Trial[9]

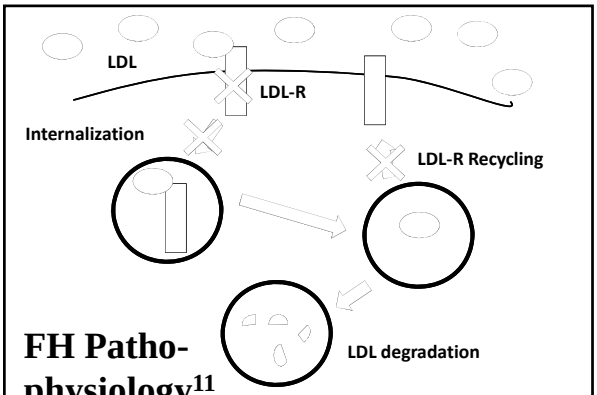
- 18,114 patients, acute coronary syndrome
- Ezetimibe + statin therapy reduced LDL levels and improved CV outcomes
  - Reduced LDL by 15.8 mg/dL, p<0.0001
  - Reduced primary endpoint over 6 years
  - Absolute risk reduction of 2%, HR of 0.936 (0.89 to 0.99, p=0.016), NNT of 50
- Limitation, used 40 mg simvastatin which is moderate intensity

Familial Hypercholesterolemia[10]

- ASCVD risk calculator likely underestimates risk in patients with FH.
- With the same lipid parameters and cardiac risk factors, patients with FH have greater risk.



Normal Physiology[11]



FH Patho-physiology[11]

Familial Hypercholesterolemia[10,12-13]

- Heterozygous forms: receptor function impaired ~50%
  - LDL levels 3x normal
  - 1 in 250 to 300 people
  - 40% experience cardiovascular events by age of 50
- Homozygous forms or compound heterozygous: receptor function impaired ~70-90%
  - LDL levels 4-8x normal
  - 1 in a million people
  - Accelerated atherosclerosis with cardiovascular events as early as childhood

FH Guidelines 2011[14]

- Patients with LDL ≥190 mg/dL require drug therapy to reduce LDL by ≥50%.
- LDL may need to be lowered to <100 mg/dL in patients with atherosclerotic disease, diabetes, family history of early coronary heart disease, or current smoking.
- Statins initially
- Can add ezetimibe, niacin, and bile acid sequestrants to intensify therapy

Familial Hypercholesterolemia[15]

- Combination therapy is often required.
  - Atorvastatin 80 mg daily
  - Homozygous FH→28% LDL reduction
  - LDL receptor negative→14% LDL reduction
  - Defective LDL receptors→41% LDL reduction

Familial Hypercholesterolemia

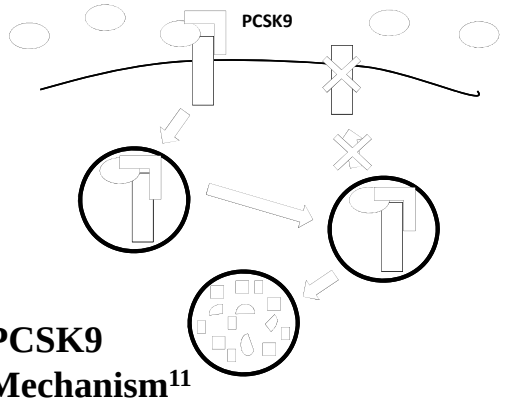
- Ezetimibe[15]
  - Can reduce LDL levels by 20%
- Lomitapide and ApoB antisense oligonucleotide[10]
  - Both reduce LDL by 25-40%,
  - REMS for both drugs—hepatotoxicity
- Lipoprotein apheresis[15]
  - Used in combination with other drugs
  - Reduces LDL by 45%

A Novel Mechanism To Meet An Unmet Need

PCSK9 INHIBITORS

PCSK9[11]

- **Proprotein convertase subtilisin/kinexin type 9**
- Enzyme that modulates the density of LDL receptors
- Produced in all people
  - May be a mechanism to maintain LDL receptor density equilibrium in normal individuals
- Statins, through an unknown mechanism, increase PCSK9 levels



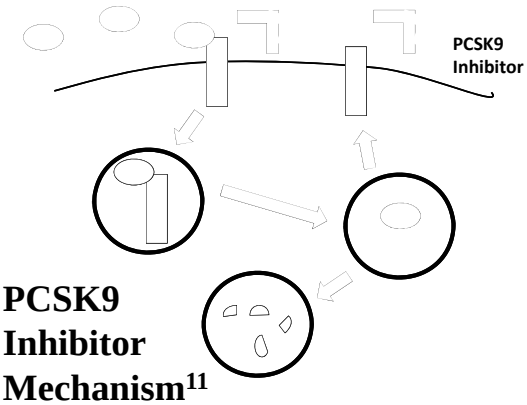
PCSK9 Mechanism[11]

PCSK9

- Loss of function PCSK9 mutations→ decreased LDL receptor degradation→ lower LDL levels[16]
  - 15-28% reduction in LDL-C
  - 47-88% reduction in CHD events
- Logically, inhibiting PCSK9 prevents LDL receptor degradation and preserves LDL receptor recycling to the hepatocyte surface

PCSK9 Inhibitors

- Fully human monoclonal antibodies to PCSK9
- Dose-dependent inhibition



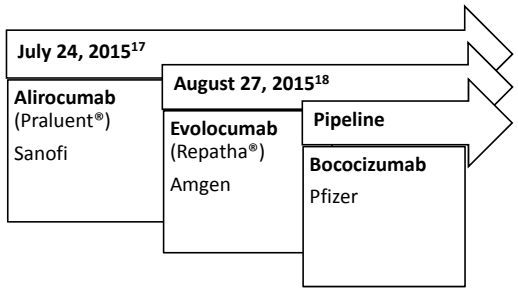
PCSK9 Inhibitor Mechanism[11]

Learning Assessment

How do PCSK9 inhibitors reduce LDL levels?

A. Reduce LDL receptor recycling
B. Reduce LDL absorption in the gut
C. Inhibit LDL receptor degradation
D. Inhibit synthesis of LDL cholesterol

Race To The Market



PCSK9 Inhibitors[19-20]

	Alirocumab	Evolocumab
Indications	Heterozygous FH in combination with a statin Hypercholesterolemia in patients with atherosclerotic CVD in combination with a statin	Heterozygous FH in combination with a statin Hypercholesterolemia in patients with atherosclerotic CVD in combination with a statin Homozygous FH in combination with other LDL-lowering drugs

PCSK9 Inhibitors[19-20]

	Alirocumab	Evolocumab
Dosing	75 mg SC Q2 weeks Max: 150 mg SC Q2 weeks	140 mg SC Q2 weeks or 420 mg SC monthly
Dosage Form	75 mg/mL or 150 mg/mL pen or prefilled syringe	140 mg/mL prefilled auto-injector

PCSK9 Inhibitors[19-20]

	Alirocumab	Evolocumab
Storage	Refrigerate, do not freeze, do not shake	Refrigerate, do not freeze, do not shake, protect from light
Administra-tion	Allow to warm to room temperature for 30-40 minutes Use within 24 hours SC injection into thigh, abdomen, or upper arm Rotate injection sites	Allow to warm to RT for 30 minutes Use within 30 days SC injection into thigh, abdomen, or upper arm Rotate injection sites

PCSK9 Inhibitors[19-20]

	Alirocumab	Evolocumab
Contra-indications	Hypersensitivity	Hypersensitivity, latex allergy
Adverse Effects	Common: injection site reactions, nasopharyngitis, influenza Serious: allergic reaction	Common: injection site reactions, influenza, nasopharyngitis, upper respiratory tract infection Serious: rash, urticaria

PCSK9 Inhibitors[19-20]

	Alirocumab	Evolocumab
DIs	No known DIs	No known DIs
Monitoring	LDL 4-8 weeks of initiation or dose change	LDL 4-8 weeks of initiation or dose change
PK	T_{max}: 3-7 days Metabolism: protein degradation $T_{1/2}$: 17 to 20 days	T_{max}: 3-4 days Metabolism: protein degradation $T_{1/2}$: 11 to 17 days

Learning Assessment

A patient is newly prescribed a PCSK9 inhibitor. Which of the following is a correct statement you could use to counsel the patient?

A. Store your medication at room temperature and rotate injection sites.
B. Allow medication to come to room temperature over 30 minutes and rotate injection sites.
C. Refrigerate your medication and shake to bring to room temperature
D. Refrigerate your medication and consistently inject at the same site

Efficacy, Safety, Cardiovascular Outcomes

WHAT THE DATA SHOW

Efficacy

Extensively studied in phase II and III clinical trials

Two meta-analyses in 2015

- Navarese et al.[21]
  - 24 randomized controlled trials, n=10,159 patients
  - Lipid, safety, and clinical outcomes
- Li et al.[22]
  - 20 randomized controlled trials, n=9,880 patients
  - Lipid and safety outcomes

Lipid-lowering Effects

Lipoprotein effects	Navarese *et al.*[21] n=10,159, 24 RCTs	Li *et al.*[22] n=9,880, 20 RCTs
LDL	**-47.9% (-69.6 to -25.4)**	**-65.29 mg/dL (-72.1 to -58.5)**
Total Cholesterol	-31.5% (-46.4 to -16.6)	-60.0 mg/dL (-70.0 to -50.1)
HDL	6.3% (5.6 to 7.0)	3.40 mg/dL (3.12 to 3.68)
Lp(a)	-25.5% (-30.2 to -27.7)	-0.94 mg/dL (-1.12 to -0.77)

Lipid-lowering Effects

Navarese et al.[21]

Comparator	Mean Difference in LDL (95% CI)	p-value
All comparators	-47.49% (-69.4 to -25.35%)	P<0.001
Placebo	-58.77% (-61.03 to -56.51%)	P<0.001
Ezetimibe	**-36.71% (-39.28 to -33.06)**	P<0.001

Why The Extra Indication For Evolocumab?

TESLA-B Trial[23]

- Randomized, double-blind, placebo-controlled, phase III trial
  - 50 patients, 12 years or older with homozygous FH who were on lipid-lowering therapy but not lipid apheresis
  - Randomized to either evolocumab 420 mg or placebo every 4 weeks for 12 weeks

Why The Extra Indication For Evolocumab?[23]

Polymorphism	LDL
Compound heterozygous FH with 2 defective alleles	MD -46.9% (-68 to -25.7)
Compound heterozygous FH with 1 defective and 1 receptor negative allele	MD -24.5% (-41.6 to -7.3)
LDL-receptor-negative mutations on both alleles and autosomal recessive homozygous hypercholesterolemia	**Increase in LDL over 12 weeks**

Adverse Events

Adverse Event	Navarese *et al.*[21] n=10,159, 24 RCTs	Li *et al.*[22] n=9,880, 20 RCTs
CK elevation	**OR 0.72 (0.54 to 0.96)**	Not reported
Composite of serious AEs	OR 1.01 (0.87 to 1.18)	RR 1.01 (0.88 to 1.17)
Discontinuation of therapy	Not reported	RR 1.07 (0.86 to 1.34)

Adverse Events

Zhang et al.[24]

- Meta-analysis that evaluated alirocumab and evolocumab safety separately
- Neither alirocumab nor evolocumab significantly affect the occurrence of the following as compared to placebo (p>0.26)
  - Adverse events in general
  - Adverse events leading to discontinuation
  - Musculoskeletal disorders
  - GI disorders

Adverse Events

Zhang et al.[24]

Adverse Effect	Alirocumab	Evolocumab
Injection site reactions	**RR 1.48 (1.05 to 2.09)**	RR 1.06 (0.67 to 1.67)
CK elevation >5X ULN	RR 0.72 (0.52 to 1.01)	RR 0.57 (0.21 to 1.51)
AST or ALT >3X ULN	RR 0.95 (0.26 to 3.47)	**RR 0.43 (0.20 to 0.93)**

Cardiovascular Outcomes

- No completed studies to date with cardiovascular outcomes as part of the primary analysis
- FOURNIER and ODYSSEY Outcomes trials for evolocumab and alirocumab
  - Sufficient design and duration to assess cardiovascular events
  - Final results not expected until 2018

Cardiovascular Outcomes

Navarese et al.[21]: mean follow-up 44 weeks

Outcome	+PCSK9i	-PCSK9i	OR (95% CI), p-value
All-cause Mortality	**0.31 %**	**0.53 %**	**0.45 (0.23 to 0.86), p=0.015**
Cardiovascular Mortality	0.19%	0.33%	0.50 (0.23 to 1.10), p=0.084
MI	0.58%	1%	0.49 (0.26 to 0.93), p=0.030
Unstable angina	0.04%	0.08%	0.61 (0.06 to 6.14), p=0.676

What The Data Appear To Show

- Profound reductions in LDL
- An apparently similar level of safety to background treatment
- A preliminary signal of survival benefit
  - No single RCT has been powered to show an effect on cardiovascular outcomes or mortality

Interpret with Caution

- Meta-analyses pooled data from the study level, not patient level
- Navarese et al. used fixed effects model
- Small number of events
- Duration of follow-up ranged from 2 months to 2 years
- Quantitative interaction

Who Might Benefit?

PLACE IN THERAPY

Place In Therapy: FDA Indications[19-20]

- Adjunctive therapy to diet and maximally tolerated statin therapy
- Adults with heterozygous FH or ASCVD who require additional LDL-lowering
- Evolocumab carries the added indication for patients with homozygous FH on other LDL-lowering therapies who require additional LDL-lowering

Place In Therapy: Hypercholesterolemia[25]

- Primarily competing against ezetimibe for adjunctive agent of first resort when maximally tolerated statins are insufficient
- Ezetimibe has a greater edge due to greater quality of evidence for cardiovascular event reduction
  - Longer time on market
  - Strong safety profile
  - Oral medication
  - Lower cost

Place In Therapy: Heterozygous FH[25]

- Difficult to say which is the adjunctive agent of first resort
  - PCSK9 inhibitors are clearly better able to reduce LDL concentrations than other adjunctive agents.
- The decision may be made by the clinician depending on the patient's LDL goal.

Place In Therapy: Homozygous FH[25]

- Statins and ezetimibe first line
- Evolocumab primarily competing against lipid apheresis
  - Except homozygous LDL-receptor-negative FH or autosomal recessive hypercholesterolemia→lipoprotein apheresis is superior option
- TESLA-B trial excluded patients receiving apheresis

Place In Therapy: Statin Intolerance[25]

- No labeled indication for patients intolerant of statins
- Potently decreases LDL in these patients either alone or in combination with ezetimibe

Learning Assessment

For which of the following patients would you most likely recommend a PCSK9 inhibitor?

A. Patient with FH experienced an MI at the age of 38, LDL is 120 mg/dL with atorvastatin 80 mg.
B. Patient has made diet changes, takes rosuvastatin 20 mg, and LDL is 70 mg/dL.
C. Patient takes atorvastatin 80 mg, is not compliant with insulin injections, and LDL is 100 mg/dL.
D. Patient reports nausea with statins and saw an ad on TV for these exciting new drugs.

The Real Question:

HOW MUCH DO THEY COST?

What's your guess?

How much do you think PCSK9 inhibitors cost per patient per year?

A. $100
B. $400
C. $1,400
D. $14,000
E. $140,000

Cost[26]

Current cost per year per patient

Alirocumab $14,600

Evolocumab $14,100

Estimated that 2.6 million U.S. individuals could potentially receive a PCSK9 inhibitor over the next 5 years

- $108 billion over 5 years
  - $19 billion FH
  - $15 billion CVD with statin intolerance
  - $74 billion for CVD with LDL not at target

Cost: ICER Report[26]

Institute for Clinical and Economic Review

- PCSK9 inhibitors should cost 85% less than current list price
- Typical cost-effectiveness ratio threshold: $100,000/QALY gained
  - To meet that threshold, yearly cost of between $3,615 to $4,811
- Even using a more generous threshold of $150,000/QALY gained
  - $5,200/year would be cost-effective

Cost: ICER Report[26]

- In order to not have to limit use in some way, drug cost would need to be $2,177, an 85% discount.
  - Make drugs more affordable
  - Cut costs elsewhere
  - Limit access

Cost To The Patient[27]

- Express Scripts
  - 25 million Americans
  - Will cover both agents—listed on National Preferred Formulary
- Have negotiated a lower price with drug manufacturers, though reported to not be as low as ICER report recommends
- Manufacturers will provide $5 copay cards and offer to cover up to $4,200/year in copays.

So…

BLOCKBUSTERS OR BUST?

Blockbuster?: Too Early to Tell

- Potential for great impact in reducing cardiovascular outcomes
  - Awaiting results of long-term studies
  - FOURNIER and ODYSSEY
- Strongest case for use in highest risk patients
- Impact on debate regarding reestablishment of LDL targets

Bust?: Too Early to Tell

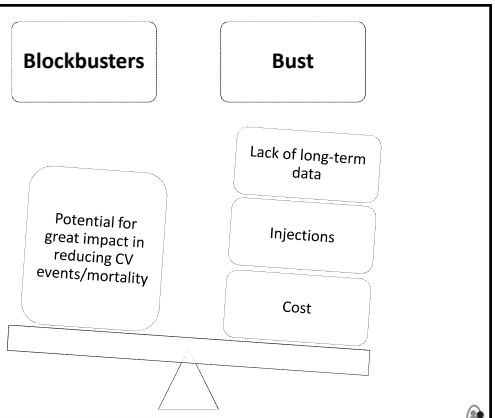
- High cost, chronic therapy
- No long-term safety or clinical outcome data
- Reasons PCSK9 inhibitors will not be used
  - Statin dose not yet optimized
  - Not following diet/exercise plan
  - Apprehensive about injections
  - Statin compliance
  - Patient will not be able to afford

What do you think?

Do you think PCKS9 inhibitors will be blockbusters or busts?

A. Blockbusters

B. Busts



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