PCSK9 Inhibitors

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Disclosures

I have no relevant disclosures.

Objectives

- Review the mechanism of action of PCSK9 inhibitors (PCSK9i)
- Discuss results from the PCSK9i outcome trials
- Understand the role of PCSK9i in current guidelines

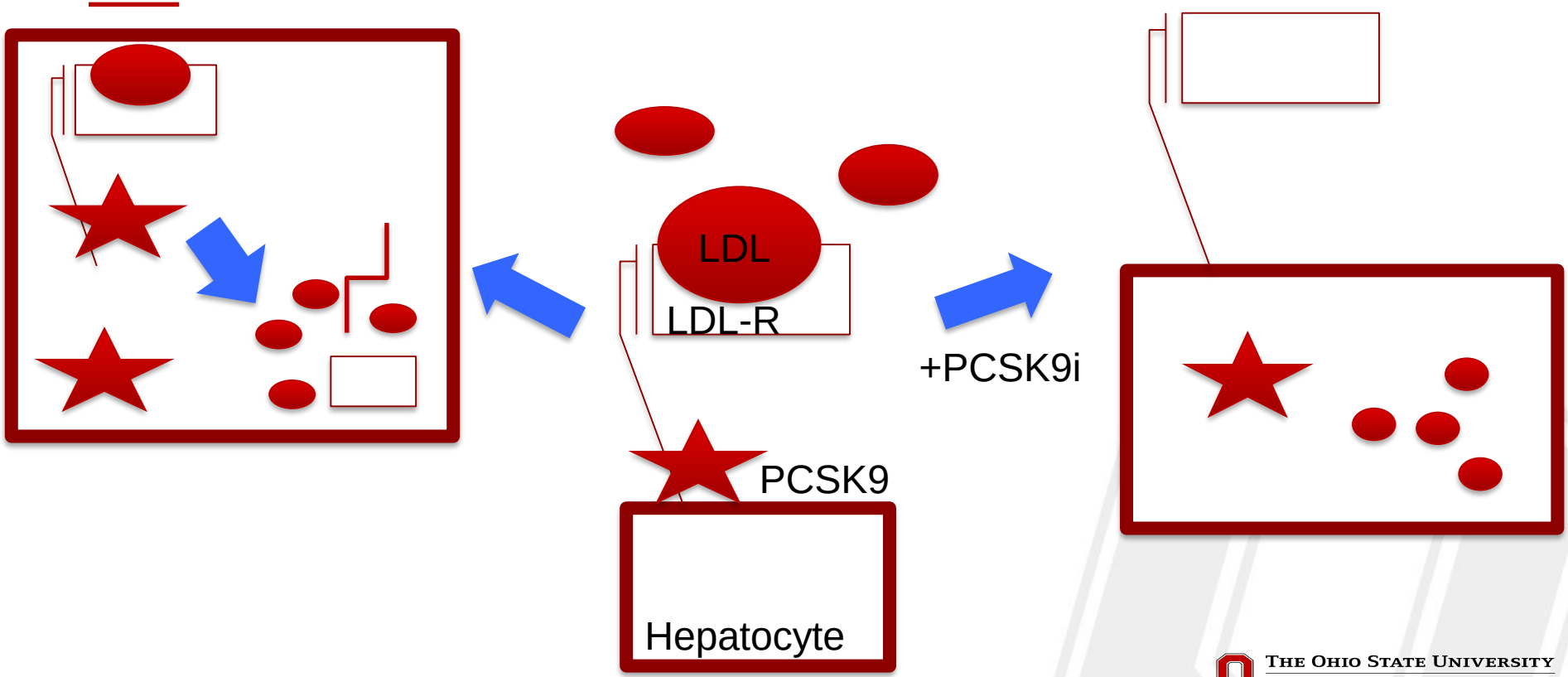
PCSK9 inhibitors

Overview + Approved Indications

- Alirocumab (Praluent) – approved July 2015
  - FDA approved for: Heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) requiring additional LDL lowering
  - Doses: 75mg Q2 weeks, 150mg Q2 weeks, 300mg Qmonth
- Evolocumab (Repatha) – approved August 2015
  - FDA approvals:
    - Reduce the risk of MI, stroke, and coronary revascularization in adults with established cardiovascular disease
    - Primary hyperlipidemia (including HeFH) to reduce LDL
    - Homozygous FH (HoFH) requiring additional LDL lowering
  - Doses: 140mg Q2 weeks, 420mg Qmonth

Praluent [package insert]. Bridgewater, NJ : Sanofi-aventis; 2018.
Repatha [package insert]. Thousand Oaks, CA : Amgen; 2017.

Mechanism of Action



Repatha [package insert]. Thousand Oaks, CA : Amgen; 2017.

Outcome Trials

FOURIER, ODYSSEY OUTCOMES, SPIRE

Evolocumab

FOURIER

- Multinational, multicenter, randomized, double-blind, placebo controlled trial
  - Enrolled February 2013 – June 2015
  - Average follow up of 25 months
- Inclusion criteria
  - At least one of: MI, non-hemorrhagic stroke, symptomatic PAD
  - 1 major or 2 minor risk factors
    - Major: DM, age >65yo, MI or non-hemorrhagic stroke within 6 months, recurrent MI or non-hemorrhagic stroke, current daily smoker, h/o PAD
    - Minor: h/o non-MI related coronary revascularization, residual CAD (stenosis $\geq$ 40% in $\geq$2 large vessels), most recent HDL <40 for men or <50 for women, most recent hs-CRP >2, most recent LDL $\geq$130 or $\geq$70 after two weeks of lipid lowering therapy, presence of metabolic syndrome, most recent TG $\leq$400
- Notable exclusion: NYHA class III or IV heart failure or LVEF <30%

Sabatine MS, et al. NEJM (2017).

Evolocumab

FOURIER

- Primary outcome: major CV events (CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization)
- N = 27,564
  - Average age 63
  - 75.4% male
  - 85% white
- Type of atherosclerosis at study entry
  - MI 81.1%, stroke 19.4%, PAD 13.2%
- At study entry:
  - 69.3% high intensity statin and 30.4% moderate intensity statin
  - 5.2% ezetimibe

Average Baseline Lipid Levels	
TC	168 mg/dL
TG	134 mg/dL
HDL	44 mg/dL
LDL	92 mg/dL
Lp(a)	37 nmol/L

Sabatine MS, et al. NEJM (2017).

Evolocumab

FOURIER - Outcomes

Outcome	Evolocumab N = 13,784	Placebo N = 13,780	HR	P value
Primary	1344 (9.8%)	1563 (11.3%)	0.85	<0.001
CV death, MI, stroke	816 (5.9%)	1013 (7.4%)	0.80	<0.001
CV death	251 (1.8%)	240 (1.7%)	1.05	0.62
All cause death	444 (3.2%)	426 (3.1%)	1.04	0.54
MI	468 (3.4%)	639 (4.6%)	0.73	<0.001
Stroke	207 (1.5%)	262 (1.9%)	0.79	0.01
Coronary revascularization	759 (5.5%)	965 (7.0%)	0.78	<0.001

Sabatine MS, et al. NEJM (2017).

Evolocumab

FOURIER - Conclusions

- Limitations:
  - Outcomes study with median follow up of 26 months
  - Most patients on high intensity statin
  - Study population relatively young, and predominantly male and Caucasian
  - Overall low CV mortality rates (<2%)
  - Benefit driven by prevention of non-fatal events
- Conclusions:
  - Reduced primary composite and key secondary composite endpoint
  - Kaplan-Meier curves diverge at ~6 months, with difference increasing with time
  - Results consistent across subgroups and baseline LDL
  - Again demonstrated trend that lower LDL results in better outcomes
  - NNT: 74 patients for 2 years to prevent a CV death, MI, or stroke

Sabatine MS, et al. NEJM (2017).

Alirocumab

ODYSSEY OUTCOMES

- Multinational, multicenter, randomized, double-blind, placebo controlled trial
  - Study period November 2012 – November 2017
  - Average follow up of 2.8 years
- Inclusion criteria
  - Age >40
  - Acute MI or unstable angina within 1-12 months prior to randomization
  - High intensity statin therapy or documented intolerance to statins
    - All patients had a 2-16 week run in period of high intensity statin
  - LDL ≥70mg/dL, non-HDL ≥100mg/dL, or apo B ≥80mg/dL
- Notable exclusion: NYHA class III or IV heart failure or LVEF <25%

Schwartz GG, et al. AHJ (2014).

Alirocumab

ODYSSEY OUTCOMES

- Primary outcome: occurrence of cardiovascular events (composite of CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization) in patients with ACS 4 to 52 weeks prior to entry
- N = 18,924
  - Average age 58
  - 74.8% male
  - Average time to randomization 2.6 months
- Patient history:
  - Prior MI 19.2%
  - ACS type (NSTEMI 48.5%, STEMI 34.6%, unstable angina 16.9%)
  - Revascularization for index ACS 72.3%
- At study entry: 88.9% high intensity statin, ezetimibe 2.9%

Average Baseline Lipid Levels	
TG	129 mg/dL
HDL	43 mg/dL
LDL	87 mg/dL

Schwartz GG, et al. AHJ (2014).

Alirocumab

ODYSSEY OUTCOMES - Outcomes

Outcome	Alirocumab N = 9,462	Placebo N = 9,462	HR	P value
MACE	903 (9.5%)	1052 (11.1%)	0.85	0.0003
CHD death	205 (2.2%)	222 (2.3%)	0.92	0.38
Non-fatal MI	626 (6.6%)	722 (7.6%)	0.86	0.006
Ischemic stroke	111 (1.2%)	152 (1.6%)	0.73	0.01
Unstable angina	37 (0.4%)	60 (0.6%)	0.61	0.02

- Intent to treat

Schwartz GG, et al. ACC.18

Alirocumab

ODYSSEY OUTCOMES – Secondary Outcomes

Outcome	Alirocumab N = 9,462	Placebo N = 9,462	HR	P value
CHD event	1199 (12.7%)	1349 (14.3%)	0.88	0.001
Major CHD event	793 (8.4%)	899 (9.5%)	0.88	0.006
CV event	1310 (13.7%)	1474 (15.6%)	0.87	0.0003
Death, MI, ischemic stroke	973 (10.3%)	1126 (11.9%)	0.86	0.0003
CHD death	205 (2.2%)	222 (2.3%)	0.92	0.38
CV death	240 (2.5%)	271 (2.9%)	0.88	0.15
All cause death	334 (3.5%)	392 (4.1%)	0.85	0.026*

*observational

Schwartz GG, et al. ACC.18

Alirocumab

ODYSSEY OUTCOMES

- Limitations:
  - Most patients on high intensity statin
  - Large proportion of men and Caucasians
  - Relatively young average age
  - Benefit driven by prevention of non-fatal events
- Conclusions:
  - Large portion of benefit in the group with baseline LDL >100mg/dL
  - Benefit in year one increases beyond year one
  - Results consistent across subgroups
  - NNT: 64, but for patients with LDL >100mg/dL, NNT = 29

Schwartz GG, et al. ACC.18

Bococizumab

SPIRE

- 27,438 patients in total received bococizumab
- SPIRE-1
  - Baseline LDL >70mg/dL
  - Median follow up 7 months
  - Major cardiovascular events: HR 0.99, p 0.94
- SPIRE-2
  - Baseline LDL >100mg/dL
  - Median follow up 12 months
  - Major cardiovascular events: HR 0.79, p 0.02
- Combined HR 0.88 with p 0.08
- Ultimately trials stopped due to neutralizing antibodies

P Ridker et al. NEJM (2017).

Study Comparison

	FOURIER	*ODYSSEY*
Patient Population	Established ASCVD or significant risk	Post- ACS
Median Follow Up	~ 26 months	~ 34 months
LDL Reduction	Maintained	Slight attenuation
NNT	74	64 (29 if LDL >100mg/dL)

Overall (both studies):

- Younger, male, Caucasian patients
  - Are results generalizable?
- Benefit driven by reduction in nonfatal events
- No safety issues
- RRR improves with time

PCSK9 inhibitors

Place in Therapy – 2017 ACC Focused Update

- Consider addition of PCSK9 to maximally tolerated* statin therapy for patients above LDL targets with:
    - Clinical ASCVD
        - No comorbidities – after trial of ezetimibe (add or replace)
        - With comorbidities – option as second agent
    - H/o LDL >190 – option as second agent
    - Not recommended in diabetic patients or patients 40-75yo with or without high risk features
- Not approved for use in pregnancy/lactation

*maximally tolerated may be none!

Questions?