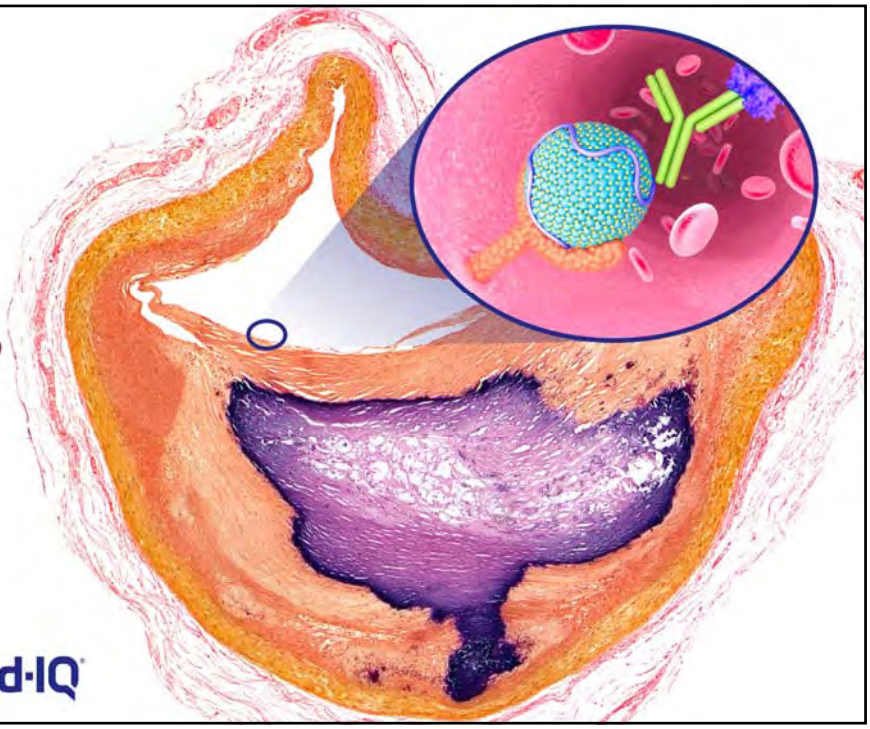
Complimentary CME/CPE

PCSK9 Inhibitors: For Whom, When, and Why



Developed in Collaboration

Cleveland Clinic Med-IQ

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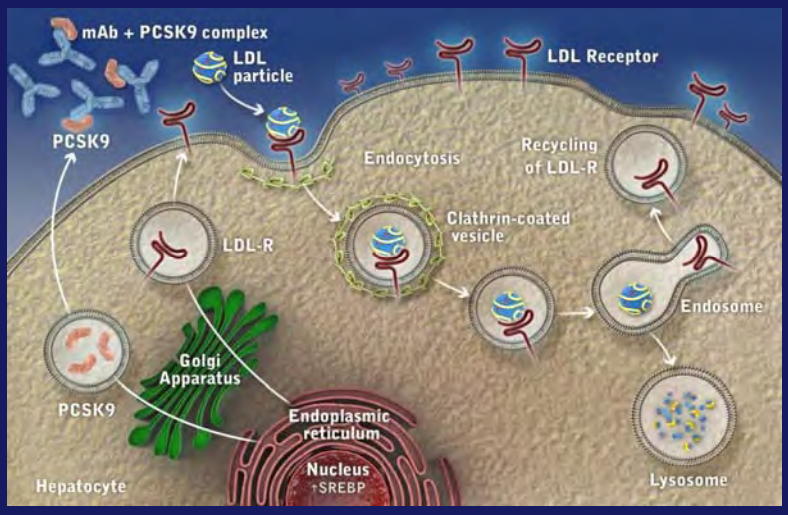
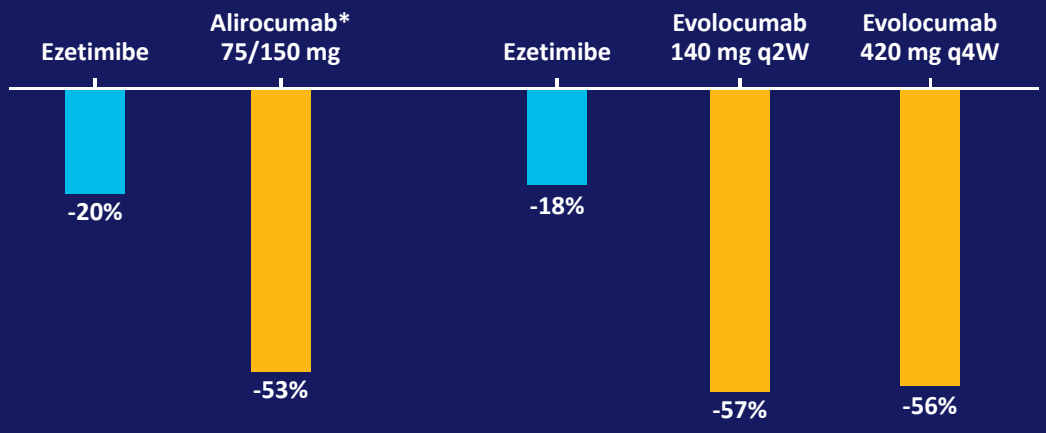
PCSK9 Inhibitors Inactivate PCSK9 → Increase LDL-Receptor Expression → ↓ LDL-C Levels



Adapted from Catapano AL, et al. *Atherosclerosis*. 2013;228:18-28.

LDL-C–Lowering Efficacy of PCSK9 Inhibitors

Monotherapy

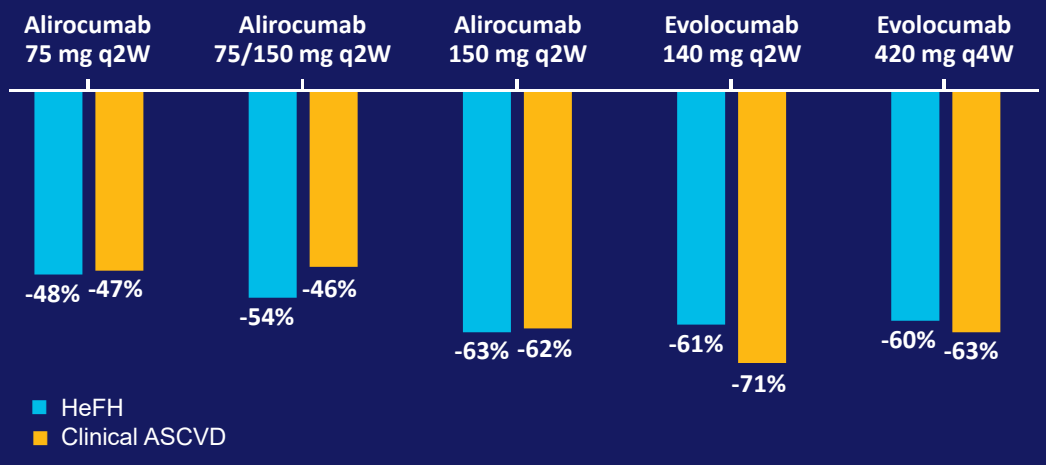


*LDL level is from week 12 of trial, prior to increase to alirocumab 150 mg.

Roth E, et al. *Int J Cardiol.* 2014;176:55-61; Koren M, et al. *J Am Coll Cardiol.* 2014;63:2531-40.

LDL-C–Lowering Efficacy of PCSK9 Inhibitors*

Background Statin Therapy



*Alirocumab data are from week 24; evolocumab data are from week 12.

Prescribing information; Kereiakes D, et al. *Am J Cardiol.* 2015;169:906-15; Robinson JG, et al. *N Engl J Med*. 2015;372:1489-99; Moriarty PM, et al. *J Clin Lipidol.* 2015;9:758-69.

Indications for PCSK9 Inhibitors Approved by US FDA in 2015

Alirocumab & Evolocumab

- Use as an adjunct to diet and maximally tolerated statin therapy in patients who require additional LDL-C lowering:
  - Adults with HeFH
  - Adults with clinical CVD

Evolocumab

- Patients with HoFH on statins, ezetimibe, and/or LDL apheresis
- The FDA further noted as a limitation of use that the effect of alirocumab or evolocumab on CV morbidity and mortality has not yet been determined

Prescribing information.

FH

PCSK9 Inhibitors in FH

Evolocumab

- TESLA study
- Patients with HoFH on statins and/or ezetimibe

Prescribing information; Raal FJ, et al. *Lancet*. 2015;385:341-50.

TESLA B: Baseline Characteristics

	Placebo Group (n = 16)	Evolocumab Group (n = 33)	All patients (N = 49)
Age (years)	32 (14)	30 (12)	31 (13)
Age range (years)	14-57	13-51	13-57
Female sex	8 (50%)	16 (48%)	24 (49%)
Ethnicity			
- White	15 (94%)	29 (88%)	44 (90%)
- Asian	1 (6%)	1 (3%)	2 (4%)
Clinically evident CAD	6 (38%)	15 (46%)	21 (43%)
- Previous coronary artery bypass surgery	4 (25%)	8 (24%)	12 (25%)
- Aortic valve replacement	3 (19%)	4 (12%)	7 (14%)
Lipid parameters			
- LDL-C, ultracentrifugation (mmol/L)	8.7 (3.8)	9.2 (3.5)	9.0 (3.5)
- LDL-C, calculated (mmol/L)	8.7 (3.7)	9.2 (3.5)	9.0 (3.6)
- apoB (g/L)	2.1 (0.8)	2.1 (0.7)	2.1 (0.7)
- lp(a) (nmol/L)	128 (80-201)	76 (26-145)	101 (31-146)
- apoA1 (g/L)	1.1 (0.4)	1.1 (0.2)	1.1 (0.3)
- HDL-C (mmol/L)	1.0 (0.4)	1.0 (0.3)	1.0 (0.3)
- Triglycerides (mmol/L)	1.3 (0.7)	1.2 (0.6)	1.2 (0.6)
- Free PCSK9 (nmol/L)	9.4 (2.5)	8.9 (2.9)	9.0 (2.7)

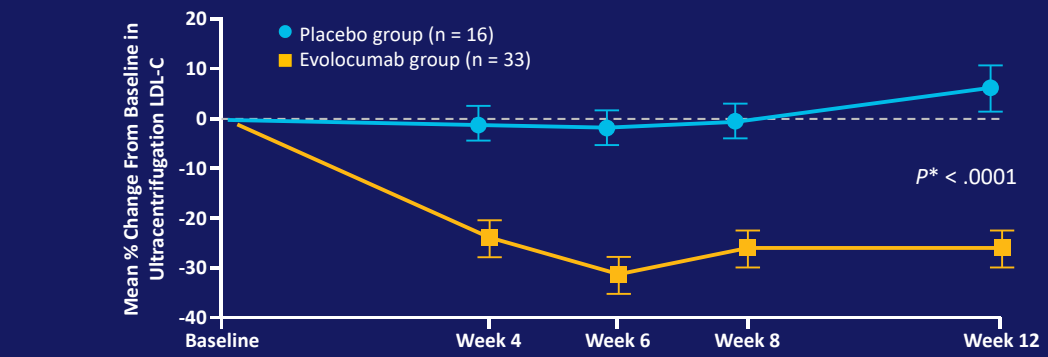
Raal FJ, et al. *Lancet*. 2015;385:341-50.

TESLA B: Genotype

	Placebo Group (n = 16)	Evolocumab Group (n = 33)	All Patients (N = 49)
LDL-R mutations	14 (88%)	31 (94%)	45 (92%)
True homozygous	7 (44%)	15 (45%)	22 (45%)
Compound heterozygous	7 (44%)	16 (48%)	23 (47%)
Heterozygous	0	1 (3%)	1 (2%)
apoB	2 (13%)	0	2 (4%)
Autosomal recessive hypercholesterolaemia	0	1 (3%)	1 (2%)

Raal FJ, et al. *Lancet*. 2015;385:341-50.

TESLA B: Change in LDL-C



Number of patients analyzed at each visit					
Placebo	16	16	15	16	15
Evolocumab	33	32	28	32	29

*Adjusted.

Raal FJ, et al. *Lancet*. 2015;385:341-50.

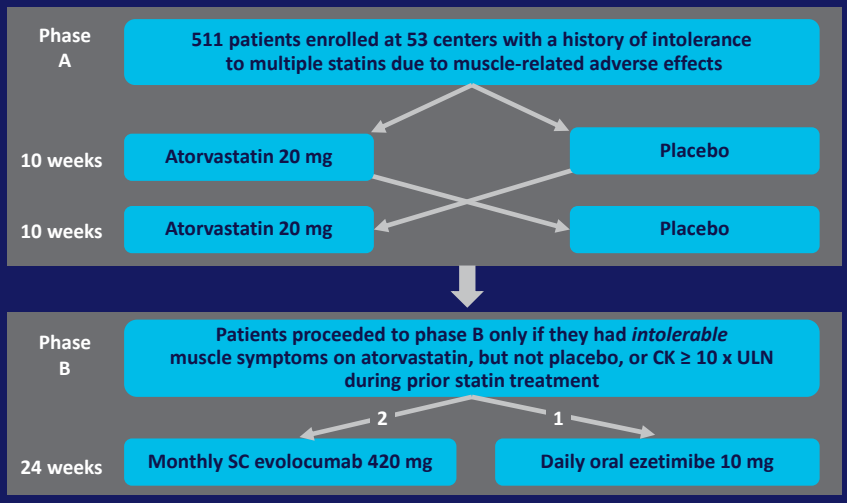
Statin Intolerant

Statin Intolerant

- GAUSS 1—*JAMA* 2012 (Sullivan D, et al)
- GAUSS 2—*JACC* 2014 (Stroes E, et al)
- GAUSS 3—*JAMA* 2016 (Nissen SE, et al)
- ODYSSEY ALTERNATIVE—AHA 2014 (Moriarty PM, et al)

Sullivan D, et al. *JAMA*. 2012;308:2497-506; Stroes E, et al. *J Am Coll Cardiol*. 2014;63:2451-48; Nissen SE, et al. *JAMA*. 2016;315:1580-90; Moriarty PM, et al. Presented at 2014 AHA Scientific Sessions.

Study Design: Two Double-Blind Phases—GAUSS 3



Nissen SE, et al. *JAMA*. 2016;315:1580-90.

Select Baseline Characteristics

Characteristic	Phase A (N = 491)	Phase B (N = 218) Ezetimibe (n = 73)	Phase B (N = 218) Evolocumab (n = 145)
Age (years)	61	59	59
Male gender	50%	47%	54%
CHD	35%	29%	33%
NCEP-ATP III high risk	63%	52%	58%
Intolerance to ≥ 3 statins	82%	82%	82%
Total cholesterol (mg/dL)	301	308	307
LDL-C (mg/dL)	212	222	219
HDL-C (mg/dL)	51	50	50

Nissen SE, et al. *JAMA*. 2016;315:1580-90.

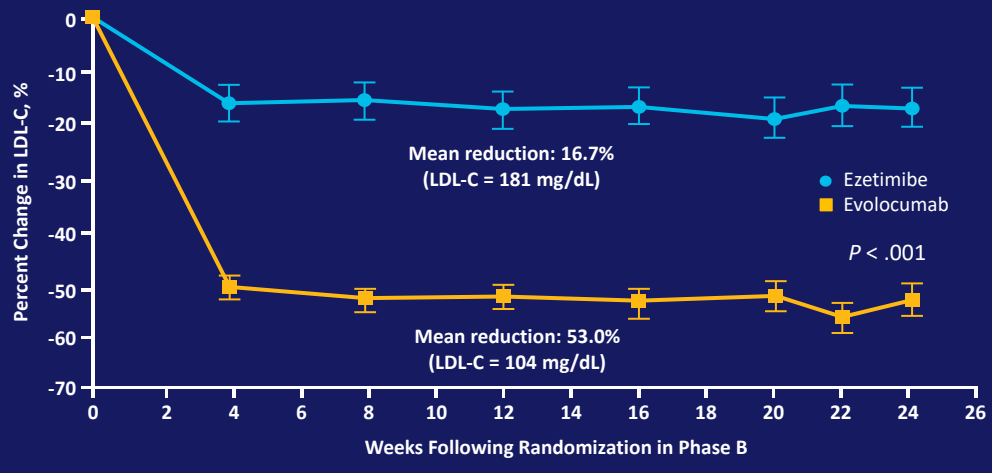
Phase A: Study Drug Discontinuation Events

Intolerable Muscle Symptoms	N = 491
On atorvastatin, but not placebo	209 (42.6%)*
On placebo, but not atorvastatin	130 (26.5%)
On both placebo and atorvastatin	48 (9.8%)
No symptoms on either treatment	85 (17.3%)
Did not complete phase A	20 (3.9%)*
Bypassed phase A due to CK elevation ≥ 10 x ULN	19 (3.9%)**

*N = 511.
**218 of these 228 eligible patients proceeded to phase B.

Nissen SE, et al. *JAMA*. 2016;315:1580-90.

LDL-C Values Over Time During Phase B



Nissen SE, et al. *JAMA*. 2016;315:1580-90.

Phase B: Adverse Effects and Drug Discontinuations

	Ezetimibe (n = 73)	Evolocumab (n = 145)
Total muscle-related events	21 (28.8%)	30 (20.7%)
Myalgia, muscle pain, or weakness	17 (23.3%)	25 (17.2%)
Investigator-reported CK increase	1 (1.4%)	4 (2.8%)
Discontinuation of Treatment for Any Reason		
Discontinued oral drug treatment	14 (19.2%)	23 (15.9%)
Discontinued SC drug treatment	4 (5.5%)	7 (4.8%)
Discontinuation of Treatment for Muscle Symptoms		
Discontinued oral drug treatment	5 (6.8%)	11 (7.6%)
Discontinued SC drug treatment	0 (0%)	1 (0.7%)

Nissen SE, et al. *JAMA*. 2016;315:1580-90.

ODYSSEY ALTERNATIVE

- Patients with statin intolerance (by medical history) with LDL-C > 70 mg/dL at very high CV risk or LDL-C > 100 mg/dL at moderate/high risk; mean baseline LDL-C was 190 mg/dL
- 314 patients were randomized to SC alirocumab 75 mg/150 mg every 2 weeks (n = 126), ezetimibe 10 mg once daily (n = 125), or atorvastatin 20 mg once daily (n = 63)

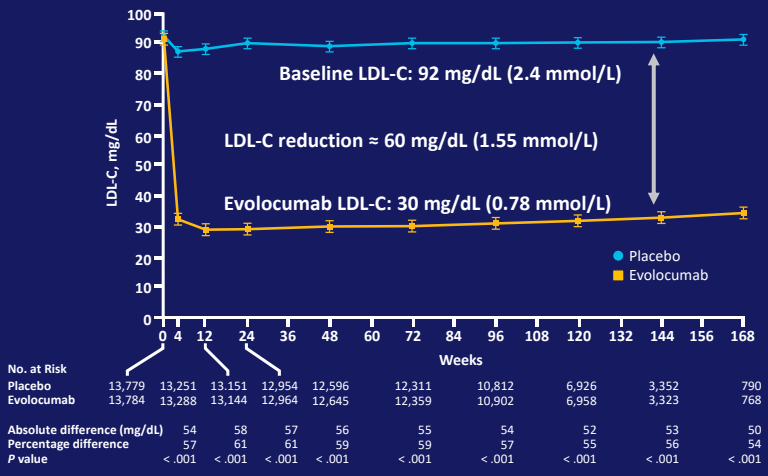
Moriarty PM, et al. Presented at 2014 AHA Scientific Sessions.

But What About
Everyone Else?

After FOURIER and ODYSSEY,
Who Else Should Get
PCSK9 Inhibitors?

FOURIER

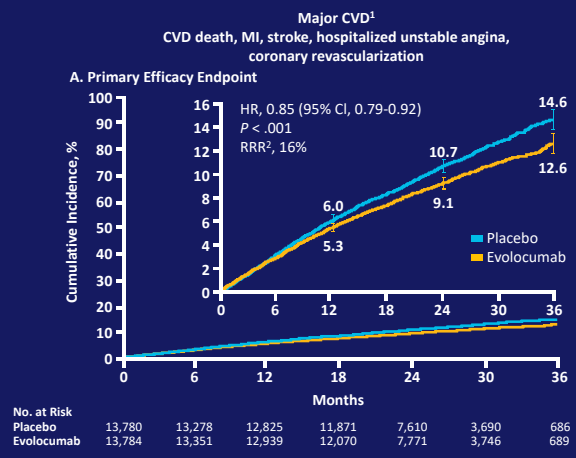
- Evolocumab vs placebo
- N = 27,564
- CVD "plus"—very high risk
  - 3.4% ASCVD/year
  - 34% 10-year ASCVD risk
- Guideline-based statin
  - High intensity (69%)
  - Moderate intensity (30%)
- Median follow-up: 2.2 years
- LDL-C reduction: 59%



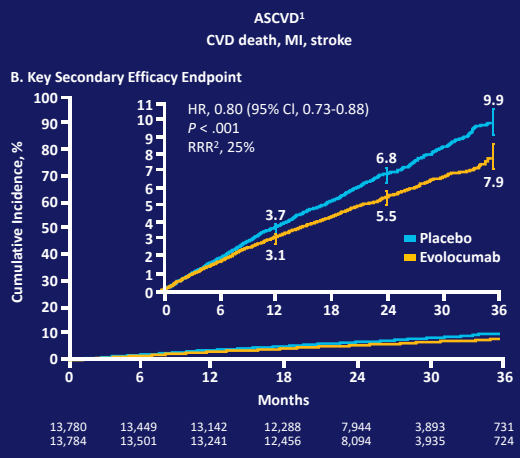
No. at Risk										
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6,926	3,352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6,958	3,323	768
Absolute difference (mg/dL)	54	58	57	56	55	54	52	53	50	
Percentage difference	57	61	61	59	59	57	55	56	54	
P value	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	

Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-22.

FOURIER



No. at Risk							
Placebo	13,780	13,278	12,825	11,871	7,610	3,690	686
Evolocumab	13,784	13,351	12,939	12,070	7,771	3,746	689



13,780	13,449	13,142	12,288	7,944	3,893	731
13,784	13,501	13,241	12,456	8,094	3,935	724

1. Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-22.
2. Sabatine MS, et al. Presented at 2017 AHA Scientific Sessions.

ODYSSEY: Study Hypothesis

- Alirocumab, versus placebo, reduces CV morbidity and mortality after recent ACS in patients with elevated levels of atherogenic lipoproteins despite intensive or maximum-tolerated statin therapy

Schwartz GG, et al. *Am Heart J.* 2014;168:682-9.e1

Main Inclusion Criteria

- Age ≥ 40 years
- ACS
  - 1 to 12 months prior to randomization
  - Acute MI or unstable angina
- High-intensity statin therapy*
  - Atorvastatin 40 to 80 mg daily or
  - Rosuvastatin 20 to 40 mg daily or
  - Maximum tolerated dose of one of these agents for ≥ 2 weeks
- Inadequate control of lipids
  - LDL-C ≥ 70 mg/dL (1.8 mmol/L) or
  - Non-HDL-C ≥ 100 mg/dL (2.6 mmol/L) or
  - apoB ≥ 80 mg/dL

*Patients not on statins were authorized to participate if tolerability issues were present and documented.

Schwartz GG, et al. *Am Heart J.* 2014;168:682-9.e1

Primary Efficacy Outcome

- Time of first occurrence of:
  - CHD death or
  - Nonfatal MI or
  - Fatal or nonfatal ischemic stroke or
  - Unstable angina requiring hospitalization*

All outcomes adjudicated by the Clinical Events Committee, under the auspices of the DCRI; members were unaware of treatment assignment and lipid levels

*Required all of the following:

1. Hospital admission > 23 hours for MI symptoms, ↑ tempo in prior 48 hours, and/or ≥ 20 minutes of chest discomfort at rest
2. New ECG findings consistent with ischemia or infarction
3. Angiographically significant obstructive coronary disease

Schwartz GG, et al. *Am Heart J.* 2014;168:682-9.e1; Schwartz GG, et al. Presented at 2018 ACC Scientific Sessions.

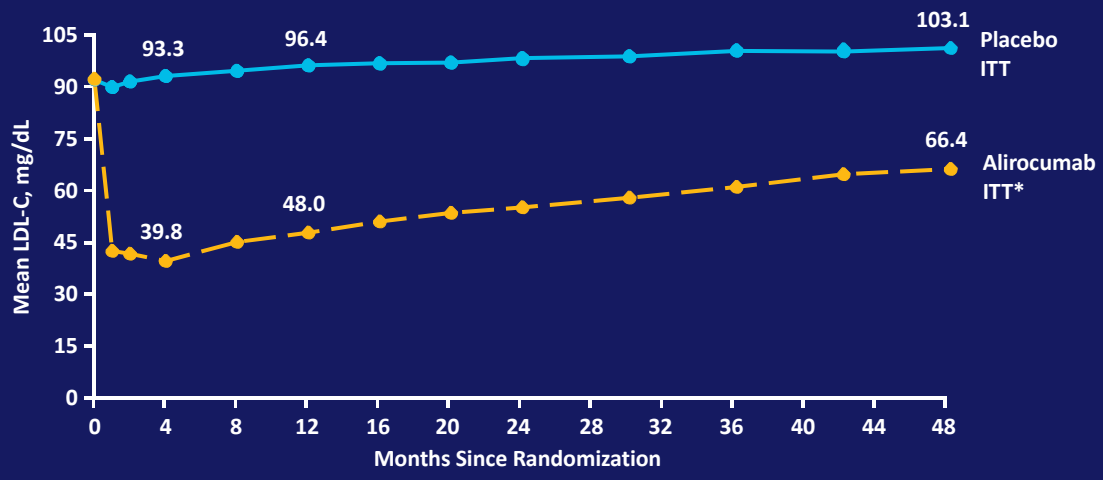
Baseline Lipid Characteristics

Characteristic, mg/dL, median (Q1-Q3)	Alirocumab (n = 9,462)	Placebo (n = 9,462)
LDL-C	87 (73-104)	87 (73-104)
Non-HDL-C	115 (99-136)	115 (99-137)
apoB	79 (69-93)	80 (69-93)
HDL-C	43 (37-50)	42 (36-50)
Triglycerides	129 (94-181)	129 (95-183)
lp(a)	21 (7-59)	22 (7-60)

- 92.5% of patients qualified on the basis of LDL-C ≥ 70 mg/dL

Schwartz GG, et al. Presented at 2018 ACC Scientific Sessions.

LDL-C: ITT Analyses

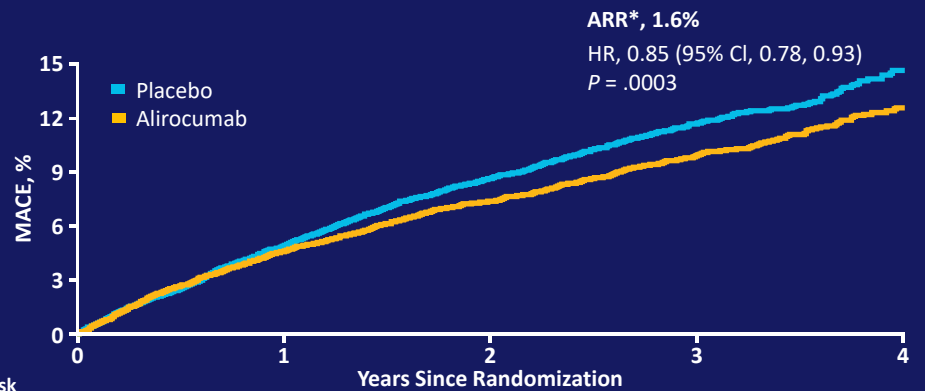


*All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo.

Modified from Schwartz GG, et al. Presented at 2018 ACC Scientific Sessions.

Primary Efficacy Endpoint: MACE

- MACE: CHD death, nonfatal MI, ischemic stroke, or unstable angina requiring hospitalization



No. at Risk					
Placebo	9,462	8,805	8,201	3,471	629
Alirocumab	9,462	8,846	8,345	3,574	653

*Based on cumulative incidence.

Schwartz GG, et al. Presented at 2018 ACC Scientific Sessions.

Primary Efficacy and Components

Endpoint, n (%)	Alirocumab (n = 9,462)	Placebo (n = 9,462)	HR (95% CI)	Log-Rank *P* Value
MACE	903 (9.5)	1,052 (11.1)	0.85 (0.78, 0.93)	.0003
CHD death	205 (2.2)	222 (2.3)	0.92 (0.76, 1.11)	.38
Nonfatal MI	626 (6.6)	722 (7.6)	0.86 (0.77, 0.96)	.006
Ischemic stroke	111 (1.2)	152 (1.6)	0.73 (0.57, 0.93)	.01
Unstable angina	37 (0.4)	60 (0.6)	0.61 (0.41, 0.92)	.02

Schwartz GG, et al. Presented at 2018 ACC Scientific Sessions.

PCSK9 Inhibitors: Safety

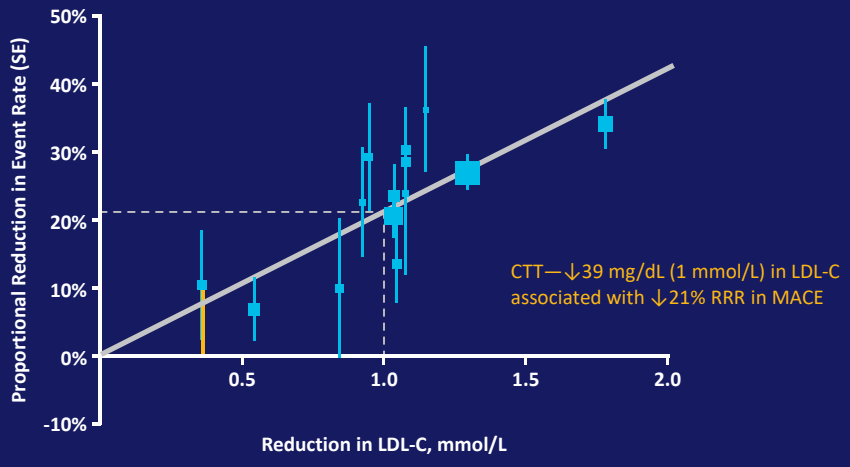
- FOURIER (median follow-up of 2.2 years, N = 27,564)[1]
  - Comparable rates of new-onset diabetes, neurocognitive events, cataracts, and allergic reactions for evolocumab and placebo groups
  - Significant increase (2.1% vs 1.6%) in injection-site reactions for evolocumab
- ODYSSEY OUTCOMES (follow-up of at least 2 years, N = 18,924)[2,3]
  - Comparable rates of new-onset diabetes, neurocognitive disorders, cataracts, and allergic reactions for alirocumab and placebo groups
  - Significant increase (3.8% vs 2.1%) in injection-site reactions for alirocumab
- Very low LDL-C[4,5]
  - ODYSSEY LONG TERM > 18 months: slight excess of cataracts in patients with LDL-C < 25 mg/dL
  - FOURIER: no excess adverse events across range of LDL-C levels to < 20 mg/dL

1. Sabatine M, et al. *N Engl J Med.* 2017;376:1713-22. 2. Schwartz GG, et al. Presented at 2018 ACC Scientific Sessions. 3. Jones PH, et al. *Am J Cardiol.* 2016;118:1805-11. 4. Guigliano R, et al. *Lancet.* 2017;390:1962-71. 5. Robinson JG, et al. *N Engl J Med.* 2015;372:1489-99.

When to Add Nonstatins in an Imperfect World

CTT Meta-Analysis of LDL-C and CVD Event Reduction

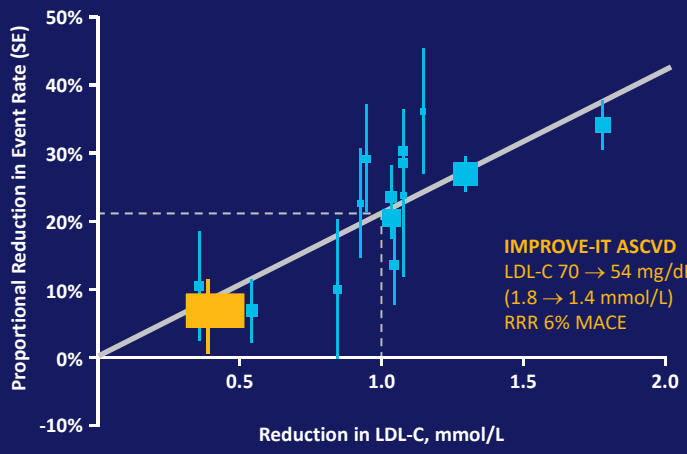
Statins (5 years)



Baigent C, et al; CTT Collaborators. *Lancet.* 2005;366:1267-78.

CTT Meta-Analysis of LDL-C and CVD Event Reduction

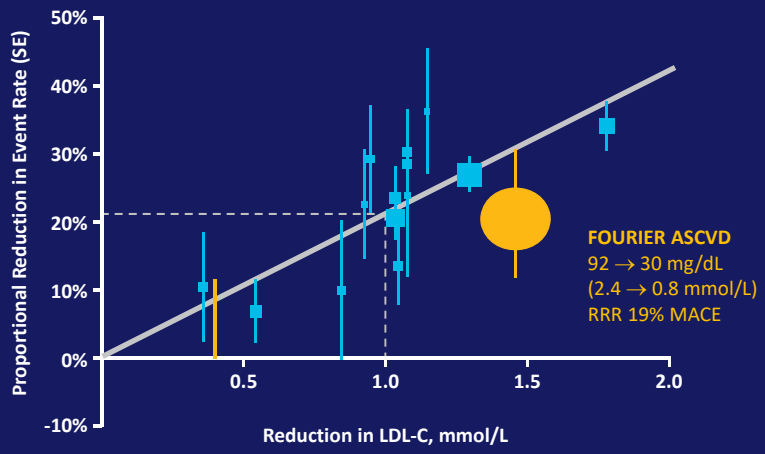
Ezetimibe (7 years)



Baigent C, et al; CTT Collaborators. *Lancet*. 2005;366:1267-78; Cannon CP, et al. *N Engl J Med*. 2015;372:2387-97.

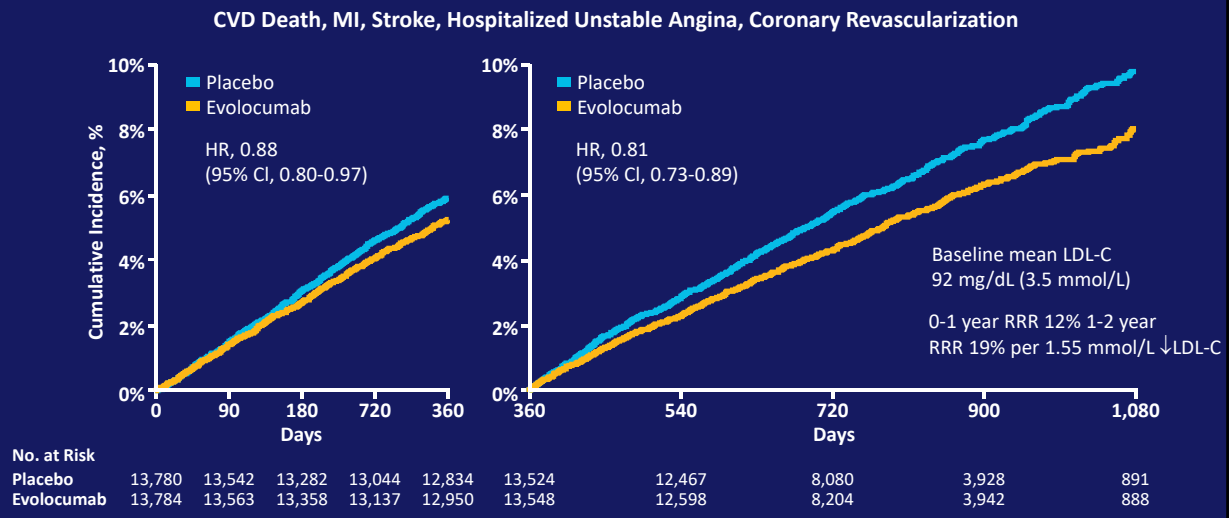
CTT Meta-Analysis of LDL-C and CVD Event Reduction

PCSK9 Inhibitors (11-26 months)



Baigent C, et al; CTT Collaborators. *Lancet*. 2005;366:1267-78; Sabatine MS, et al. *N Engl J Med*. 2015;372:1500-9.

FOURIER



Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-22.

So Who Should Get PCSK9 Inhibitors?

What Do the Guidelines Tell Us?


EXPERT CONSENSUS DECISION PATHWAY

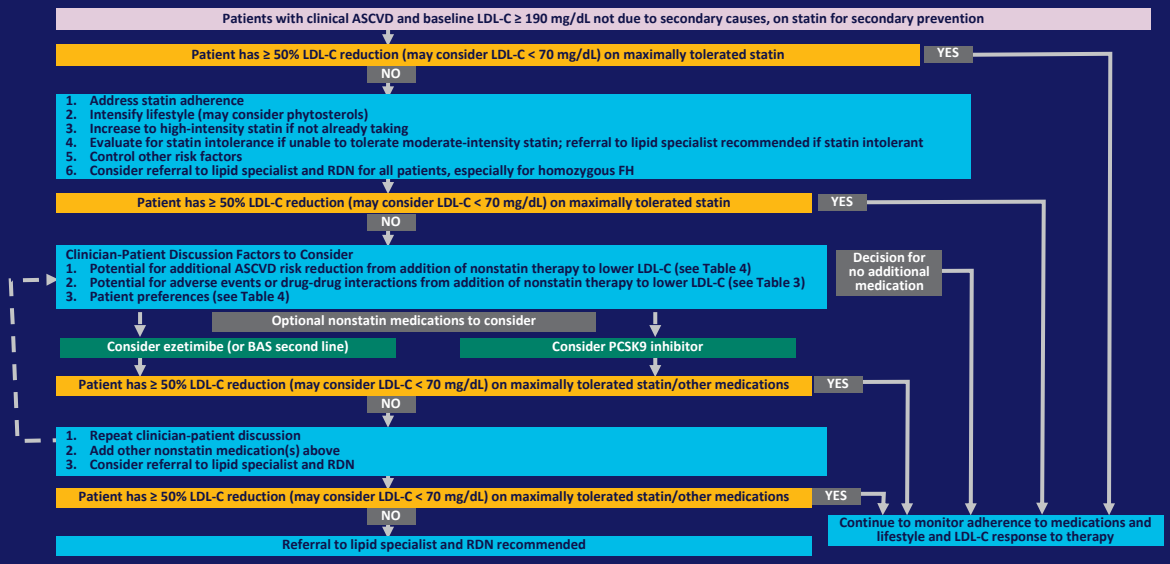
2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

2016 ACC Nonstatin Decision Pathway NET BENEFIT APPROACH

LDL-C reduction to trigger consideration of potential for net benefit from adding ezetimibe or PCSK9 mAb

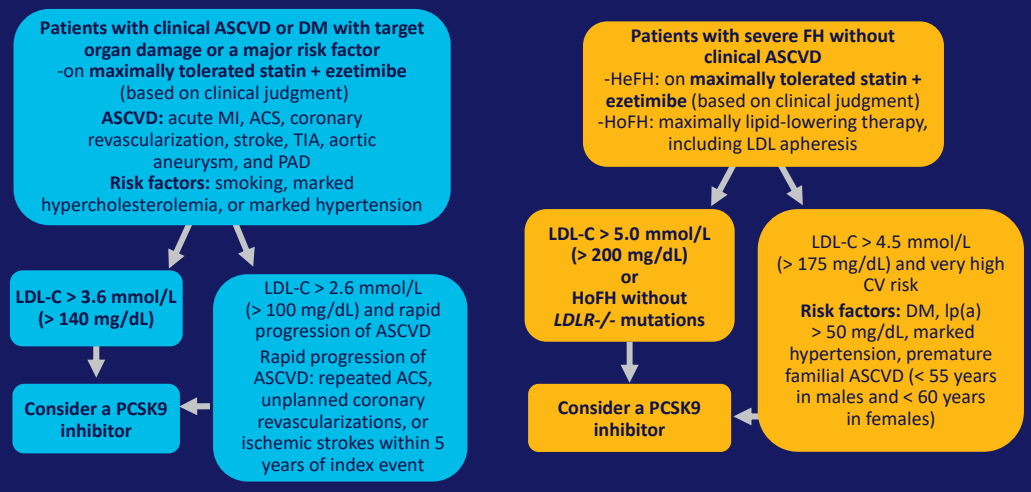
Lloyd-Jones DM, et al. *J Am Coll Cardiol.* 2016;68:92-125.

2016 ACC Consensus Guideline



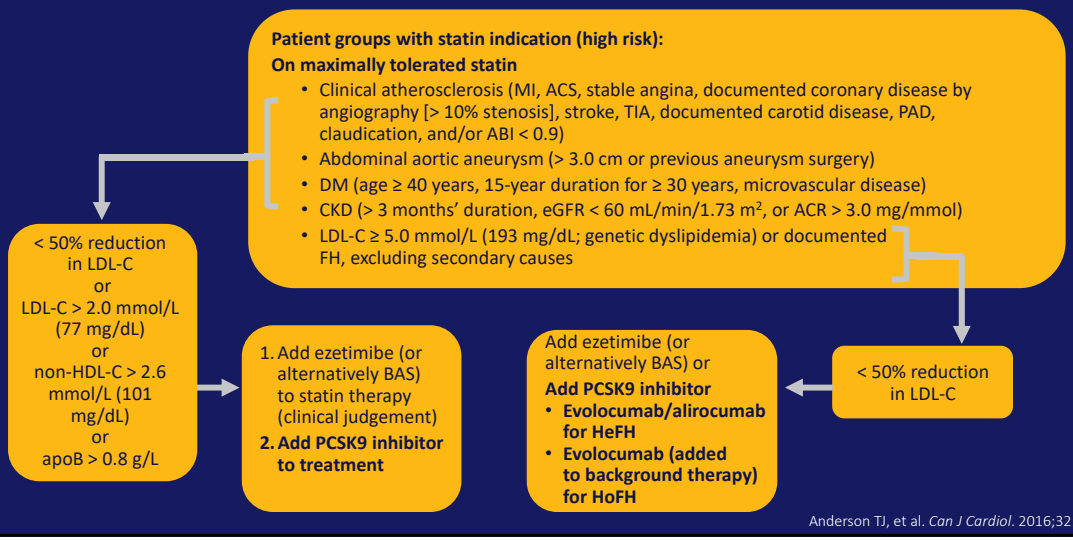
Lloyd-Jones DM, et al. *J Am Coll Cardiol.* 2016;68:92-125

Guidelines for PCSK9 Inhibitor Consideration in Patients With Very High CV Risk: ESC/EAS



Landmesser U, et al. *Eur Heart J.* 2017;38:2245-55.

Guidelines for Considering Nonstatin Treatment: Canadian Cardiovascular Society



Anderson TJ, et al. *Can J Cardiol*. 2016;32:1263-82.

Extreme High Risk—AACE/ACE 2017

- Progressive ASCVD in patients with LDL-C < 70 mg/dL
- CAD + DM
- CAD + CKD (stage 3 and up)
- CAD + HeFH

- Goal LDL-C < 55 mg/dL, non-HDL-C < 80 mg/dL, apoB < 70 mg/dL
- Based on Framingham, MESA, Reynolds Risk Score, UKPDS Risk Engine

Jellinger PS, et al. *Endoc Pract*. 2017;23:1-87.

Very High Risk—AACE/ACE 2017

- Established CAD, CVD, PAD with 10-year risk > 20%
- DM or CKD stage 3/4 with one or more risk factor
- HeFH

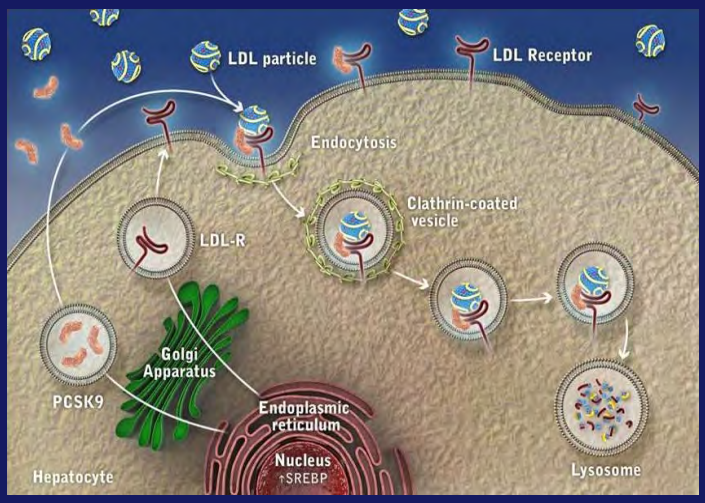
- Goal LDL-C < 70 mg/dL, non-HDL-C < 100 mg/dL, apoB < 80 mg/dL

Jellinger PS, et al. *Endoc Pract*. 2017;23:1-87.

Conclusion

- Consider PCSK9 inhibitors
  - FH/HeFH
  - Statin-intolerant patients
  - Very high risk CVD patients

PCSK9 Targets the LDL-Receptor for Lysosomal Degradation



Adapted from Catapano AL, et al. *Atherosclerosis*. 2013;228:18-28.

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PCSK9 Inhibitors: Abbreviations and Acronyms

ABI = ankle brachial index
ACR = albumin:creatinine ratio
ACS = acute coronary syndrome
apo = apolipoprotein
ASCVD = atherosclerotic cardiovascular disease
BAS = bile acid sequestrant
CAD = coronary artery disease
CHD = coronary heart disease
CK = creatine kinase
CKD = chronic kidney disease
CTT = Cholesterol Treatment Trialists
CV = cardiovascular
CVD = cardiovascular disease
DCRI = Duke Clinical Research Institute
DM = diabetes mellitus
ECG = electrocardiogram
eGFR = estimated glomerular filtration rate
FH = familial hypercholesterolemia
HDL-C = high-density lipoprotein
HeFH = heterozygous familial hypercholesterolemia
HoFH = homozygous familial hypercholesterolemia
ITT = intention to treat
LDL-C = low-density lipoprotein cholesterol
LDL-R = low-density lipoprotein receptor
lp(a) = lipoprotein(a)
mAb = monoclonal antibody
MACE = major adverse cardiac events
MESA = Multi-Ethnic Study of Atherosclerosis
MI = myocardial infarction
NCEP-ATP = National Cholesterol Education Program Adult Treatment Panel
PAD = peripheral artery disease
PCSK9 = proprotein convertase subtilisin-like/kexin type 9
q2W = every 2 weeks
q4W = every 4 weeks
RDN = registered dietitian nutritionist
RRR = relative risk reduction
SC = subcutaneous
SE = standard error
SREBP = sterol regulatory element-binding protein
TIA = transient ischemic attack
UKPDS = United Kingdom Prospective Diabetes Study
ULN = upper limit of normal