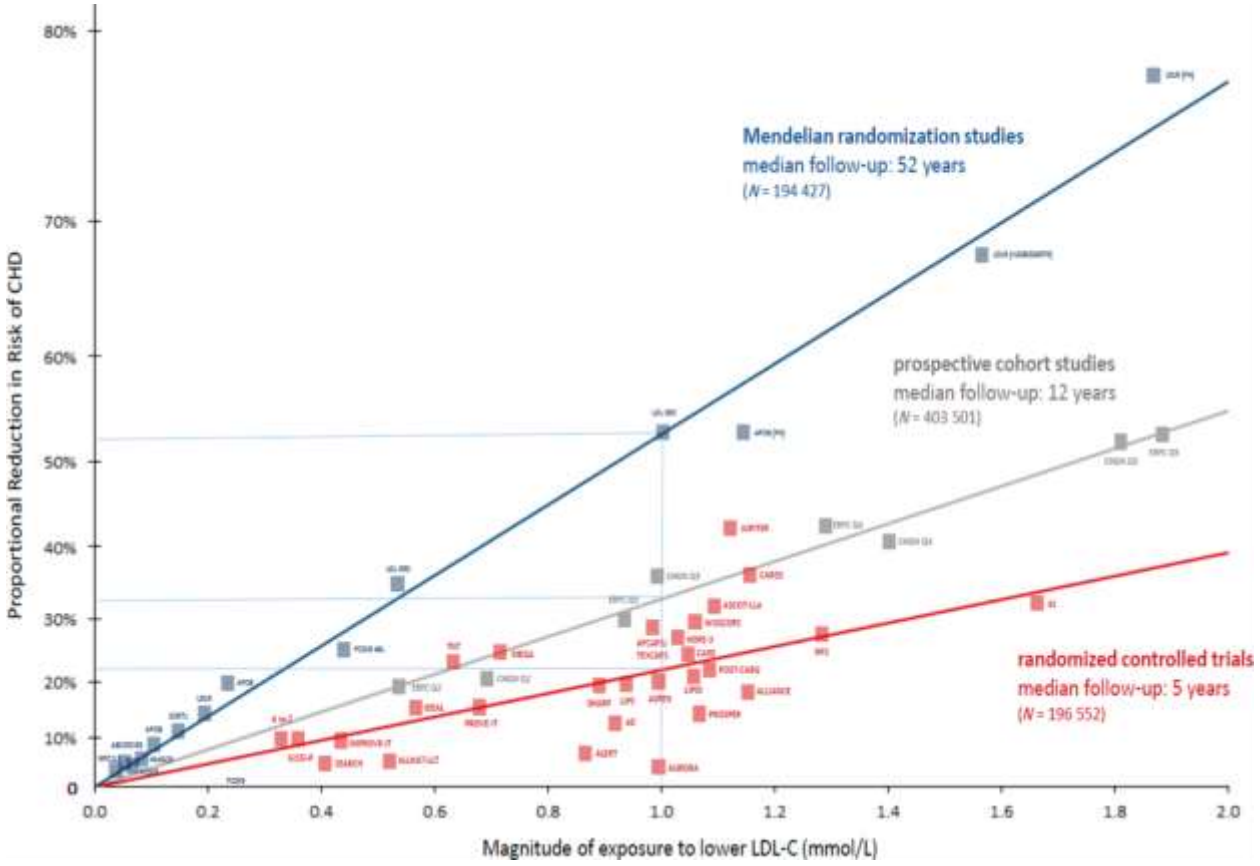
For a 2017 optimally treated patient with coronary heart disease

Do new trials published recently suggest that we should add additional drugs or lifestyle modification? And what in whom?

Current treatment:	Additional non-optimal risk factors:	You could consider for a patient based on individual decision:
Non-smoking Exercise Low-fat diet	High LDL cholesterol	Ezetimibe and/or PCSK9 inhibitor
	High C-reactive protein	Interleukin-1β inhibitor (if available)
Statin max dose Aspirin ACE-inhibitor +/- Beta-blocker	Diabetes	Sodium/glucose cotransporter 2 inhibitor or glucagon like peptide 1 receptor agonist
	Atherothrombosis risk	Long-term dual antiplatelet therapy or low-dose factor Xa antagonist with aspirin

From: The year in cardiology 2017: prevention
Eur Heart J. Published online January 02, 2018. doi:10.1093/eurheartj/ehx766



From: The year in cardiology 2017: prevention

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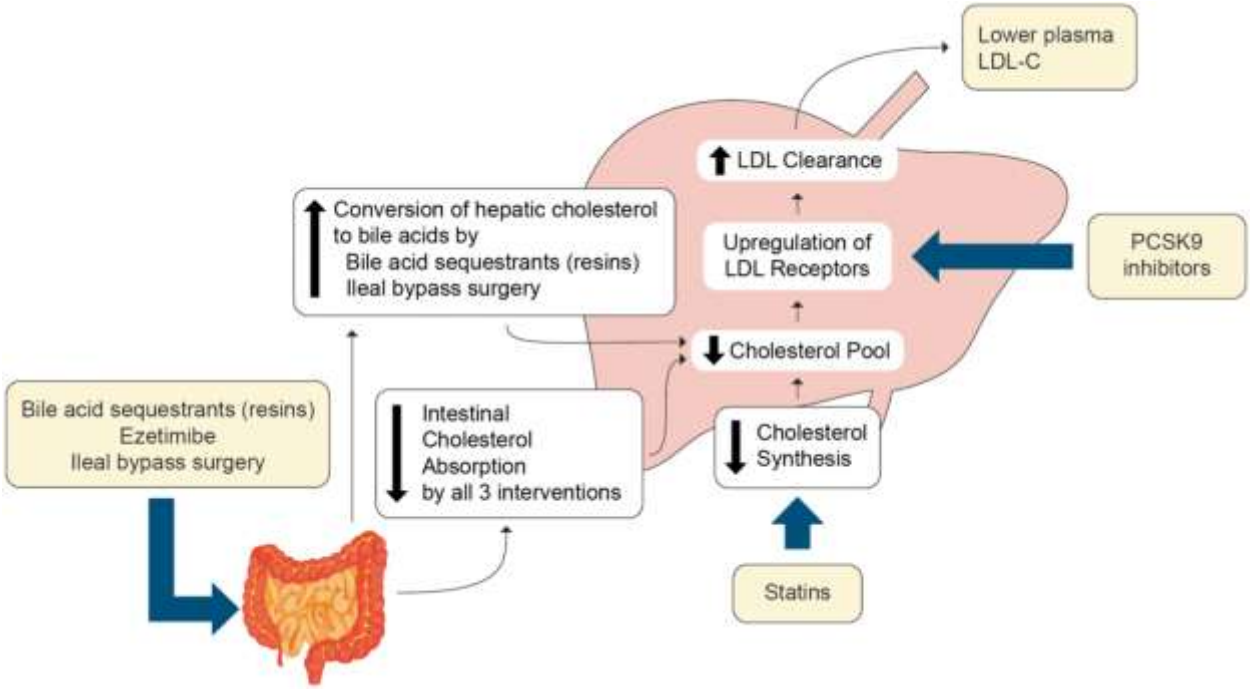
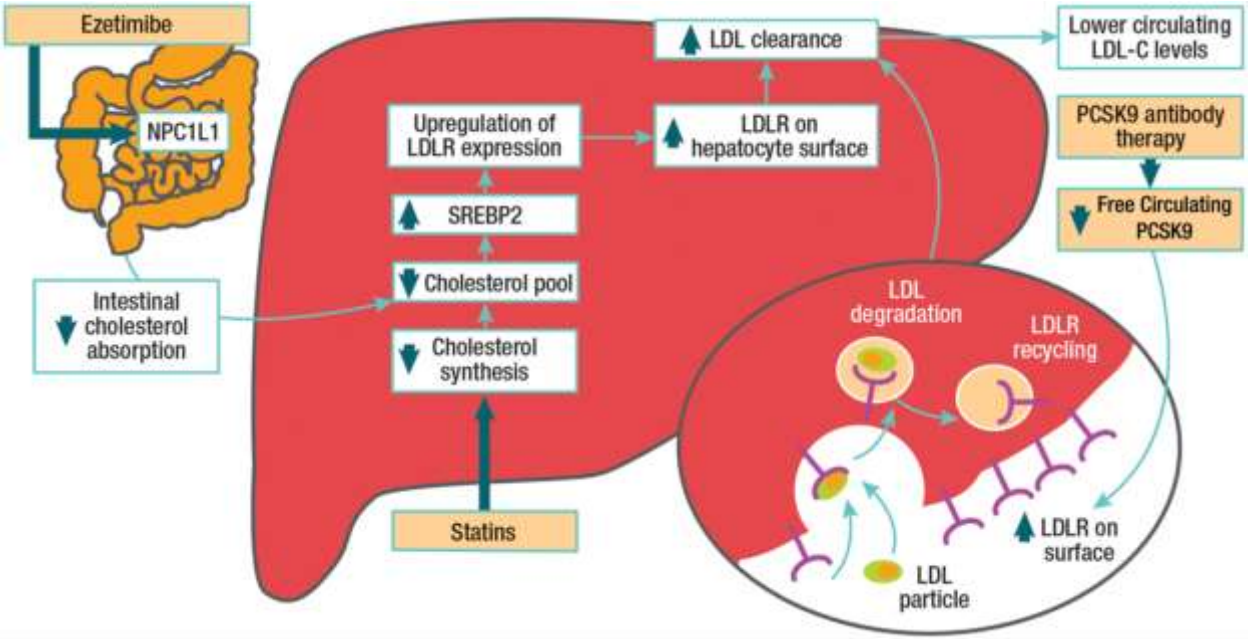


From: Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel

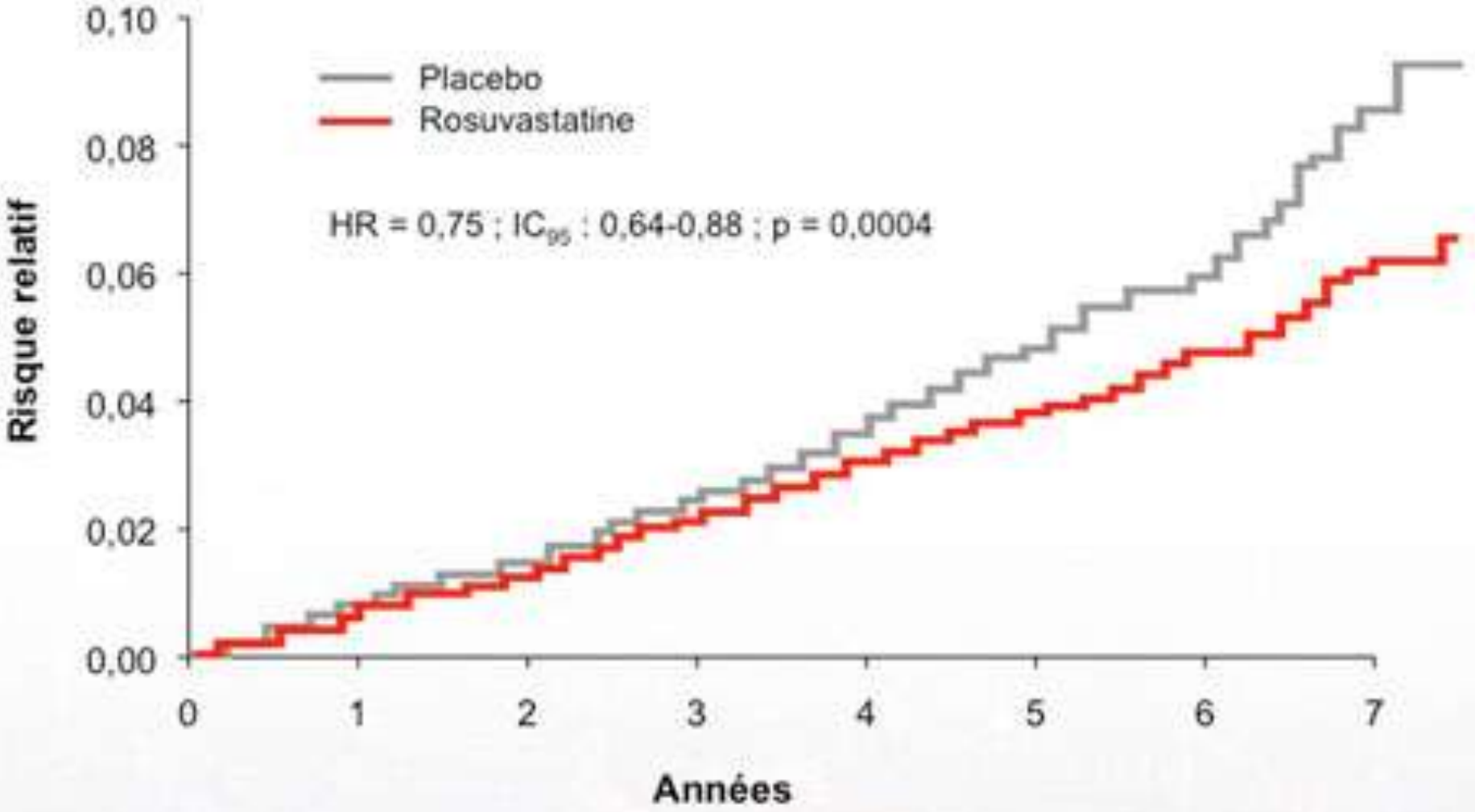
Eur Heart J. 2017;38(32):2459-2472. doi:10.1093/eurheartj/ehx144



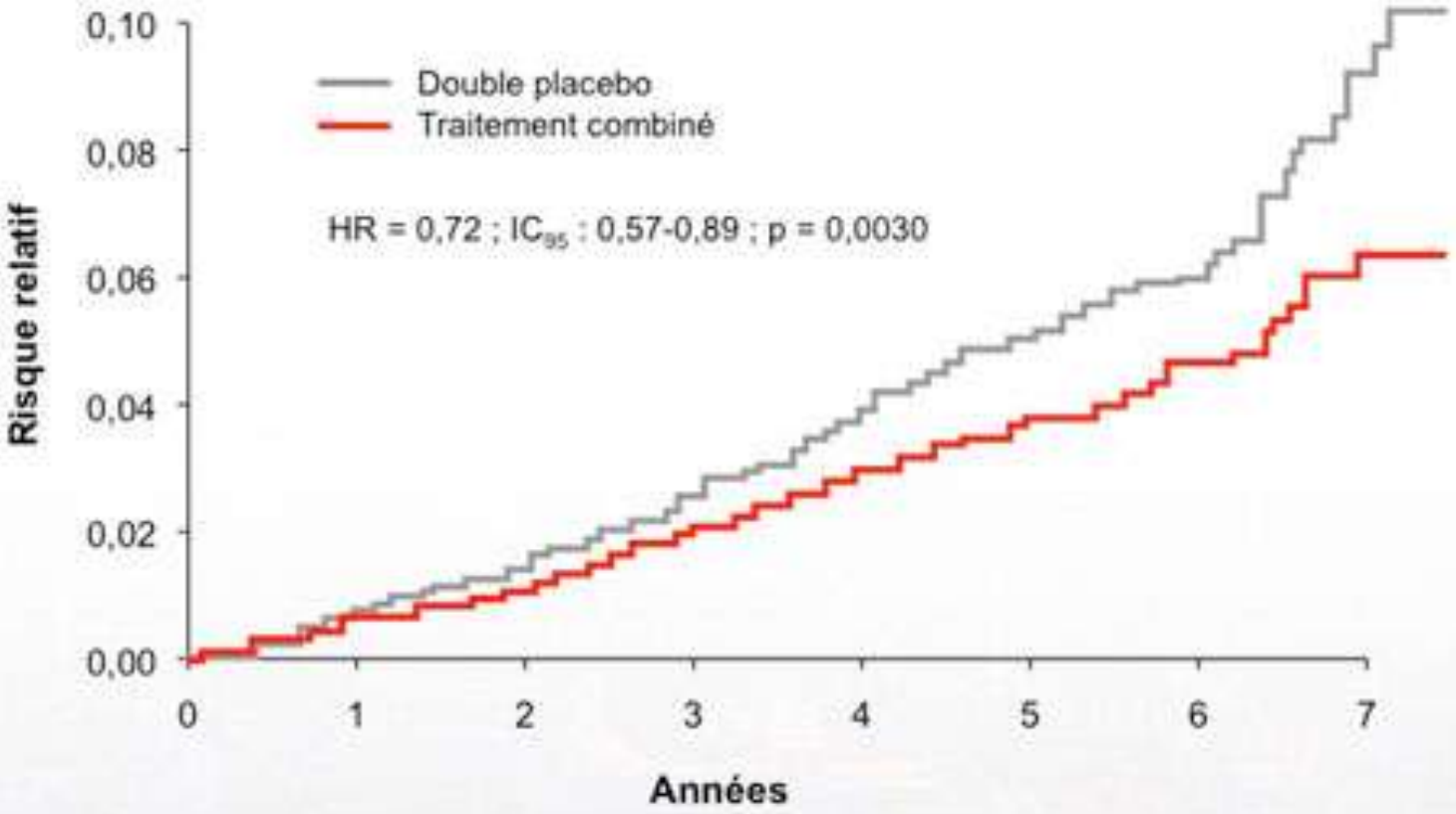
From: 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

Eur Heart J. Published online October 16, 2017. doi:10.1093/eurheartj/ehx549

Décès d'origine cardiovasculaire, infarctus, AVC, insuffisance cardiaque, revascularisation

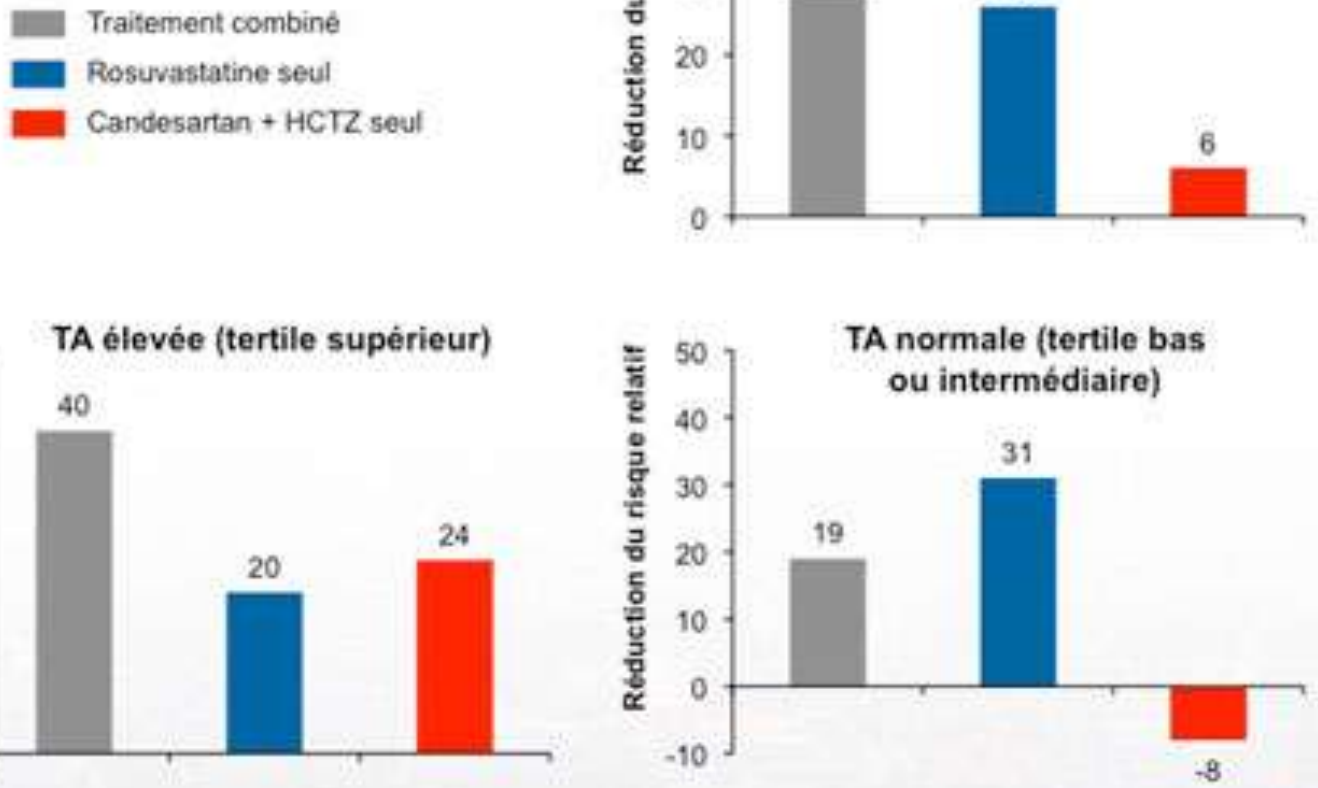


Décès d'origine cardiovasculaire, infarctus, AVC, Insuffisance cardiaque, revascularisation



ACC 2016 - D'après Yusuf S et al. Late Breaking Session I, actualisé

Réduction du risque relatif selon le traitement et la tension artérielle

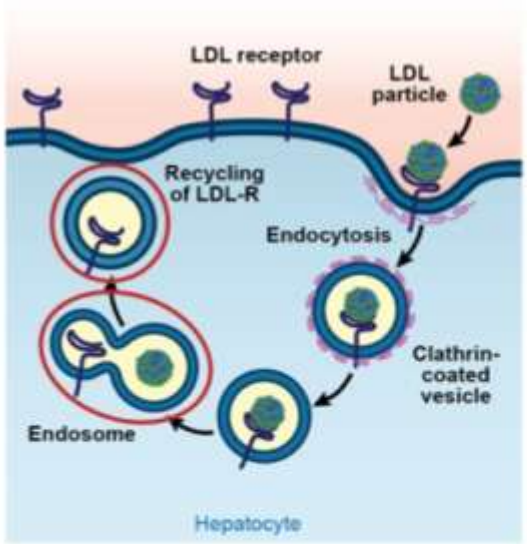


ACC 2016 - D'après Yusuf S et al. Late Breaking Session I, actualisé

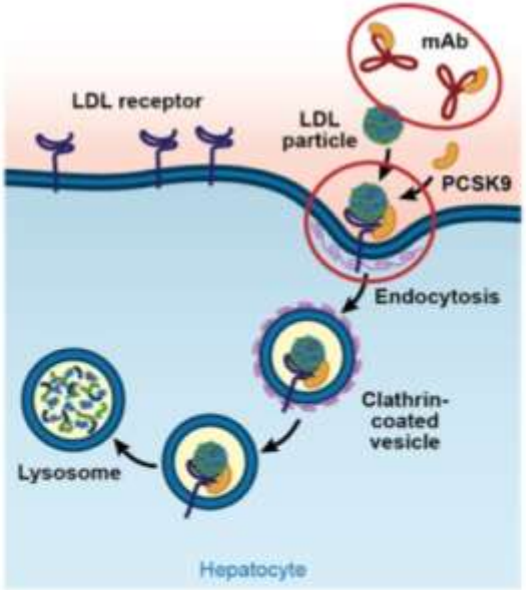
Background

PCSK9: Proprotein convertase subtilisin/kexin type 9

- Chaperones LDL-R to destruction → increase circulating LDL-C
- Loss-of-function genetic variants → increase LDL-R → reduce LDL-C and reduce risk of MI



LDL degradation and recycling of LDLR



PCSK9-mediated degradation of LDLR

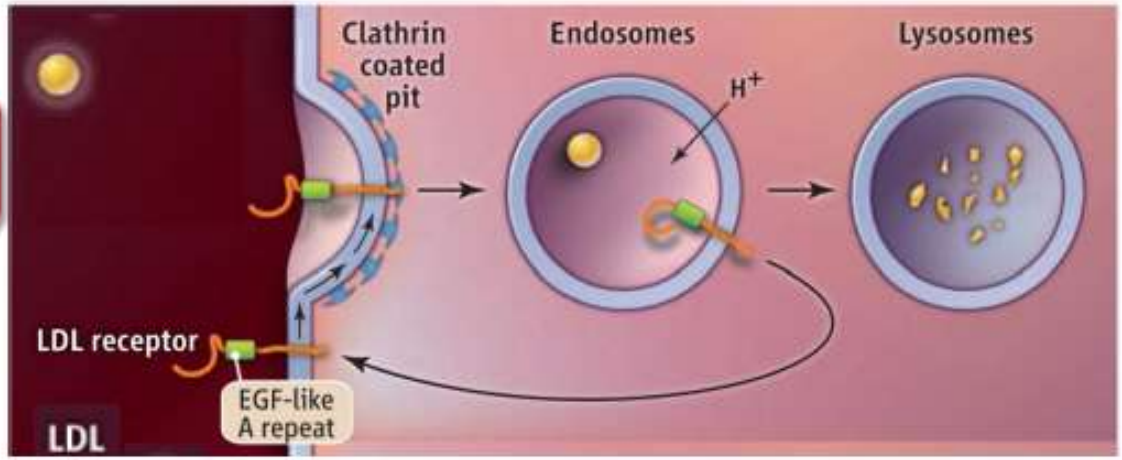
Evolocumab and Alirocumab

- Human anti-PCSK9 mAb
- 50% to 60% reduce LDL-C[a]
- Safe and well-tolerated in Phase 2 and 3 studies[b]

a. Giugliano RP, et al. *Lancet.* 2012;380:2007-2017.
b. Sabatine MS, et al. *N Engl J Med.* 2015;372:1500-1509.

PCSK9 blocks LDLR-Recycling

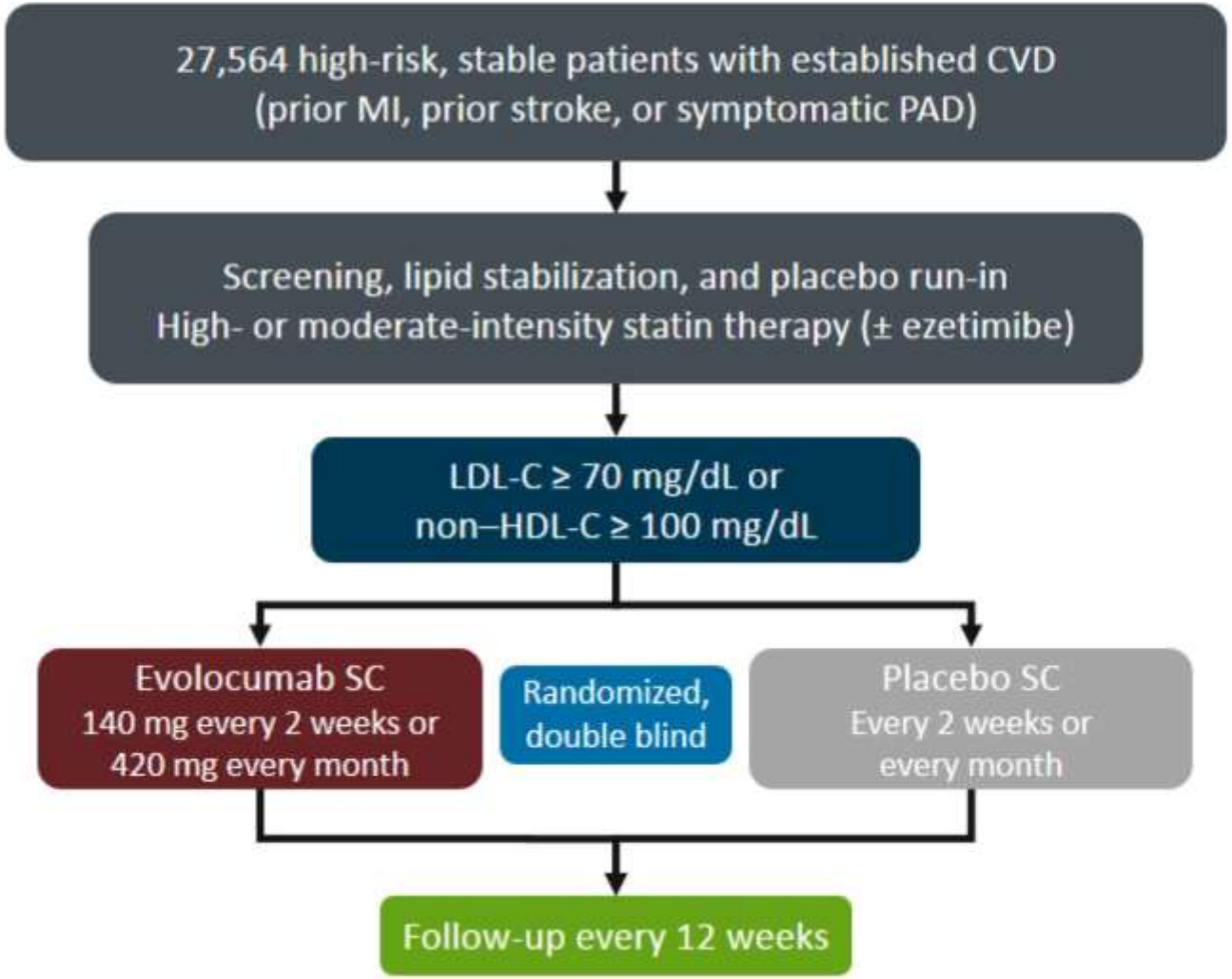
More LDL-Receptor
Less LDL-C



More LDL-Receptor
Less LDL-C

modifiziert nach Cohen JC, Hobbs HH. Science 2013 (6133):689-90

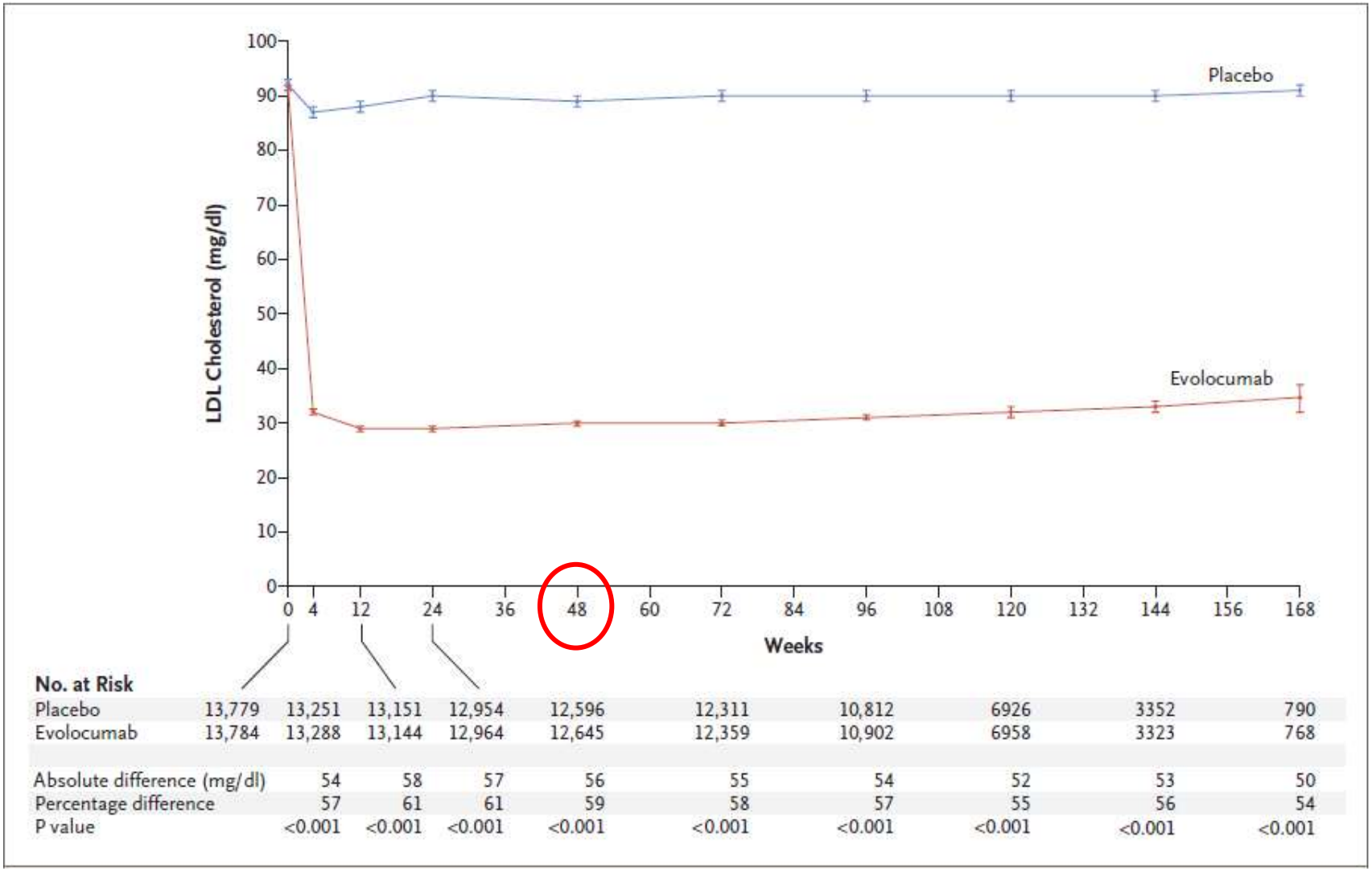
FOURIER Trial Design



Sabatine MS, et al. *Am Heart J.* 2016;173:94-101.

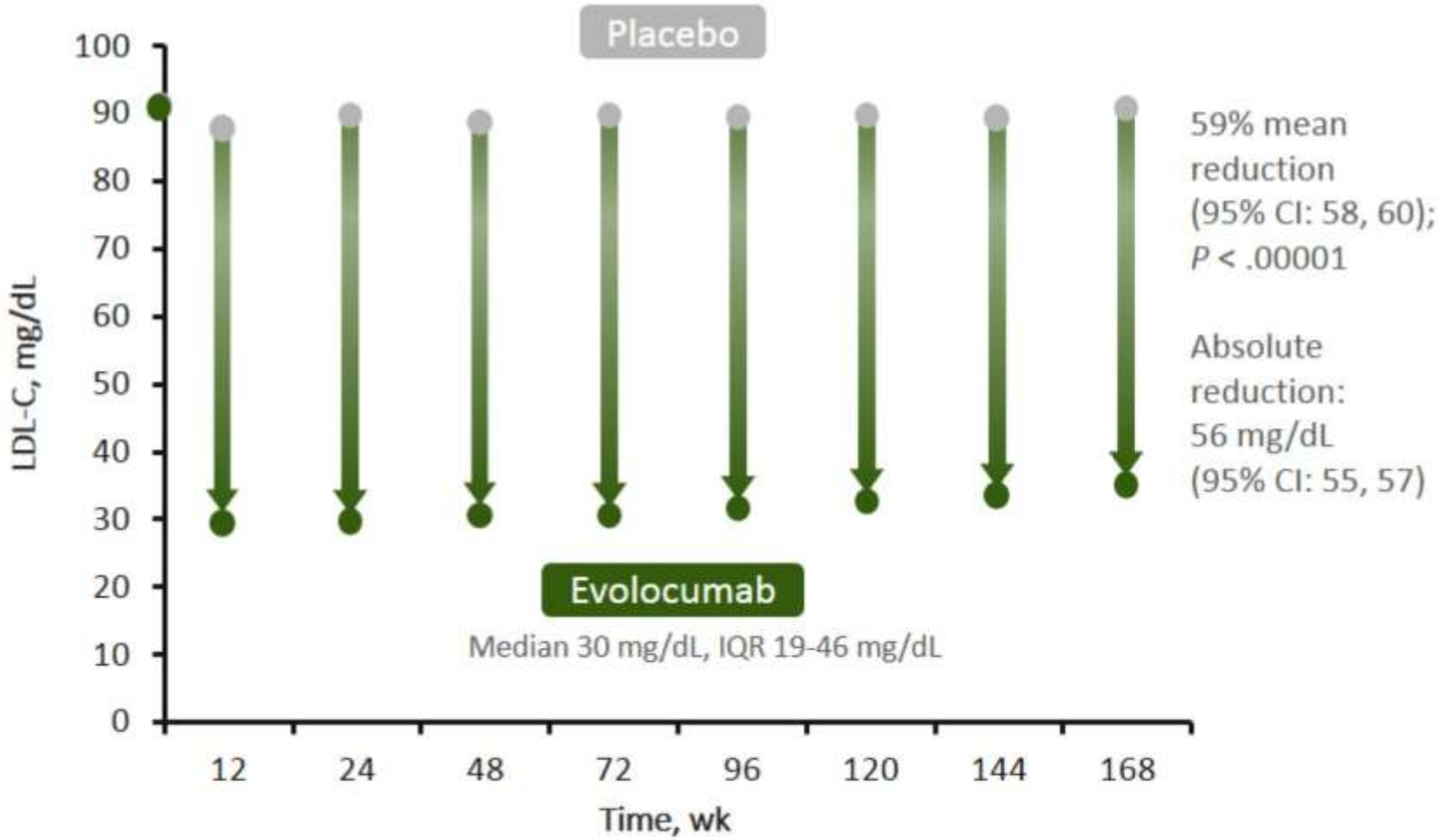
LDL-C Levels

LDL Cholesterol	Evolocumab	Placebo
≤ 70 mg/dL	87%	18%
≤ 40 mg/dL	67%	0.5%
≤ 25 mg/dL	42%	< 0.1%



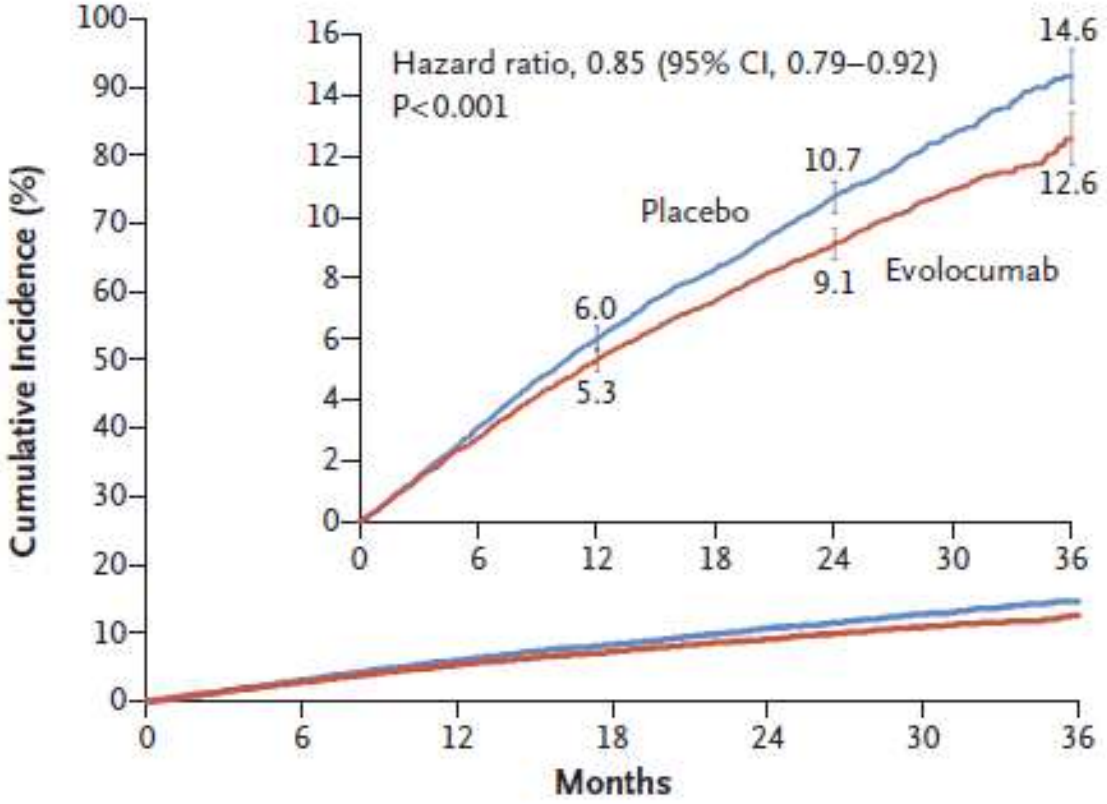
No. at Risk										
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

FOURIER
LDL-C Reduction



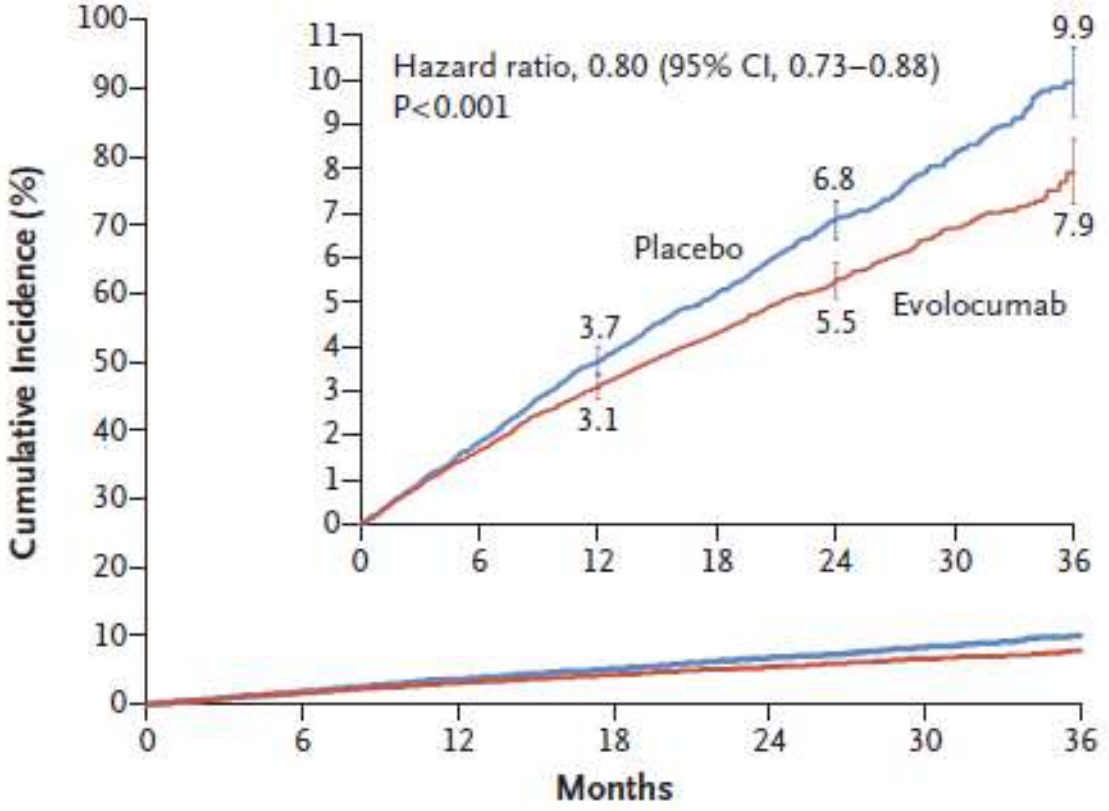
Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722.

Primary Endpoint



No. at Risk							
Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

Key Secondary Efficacy Endpoint

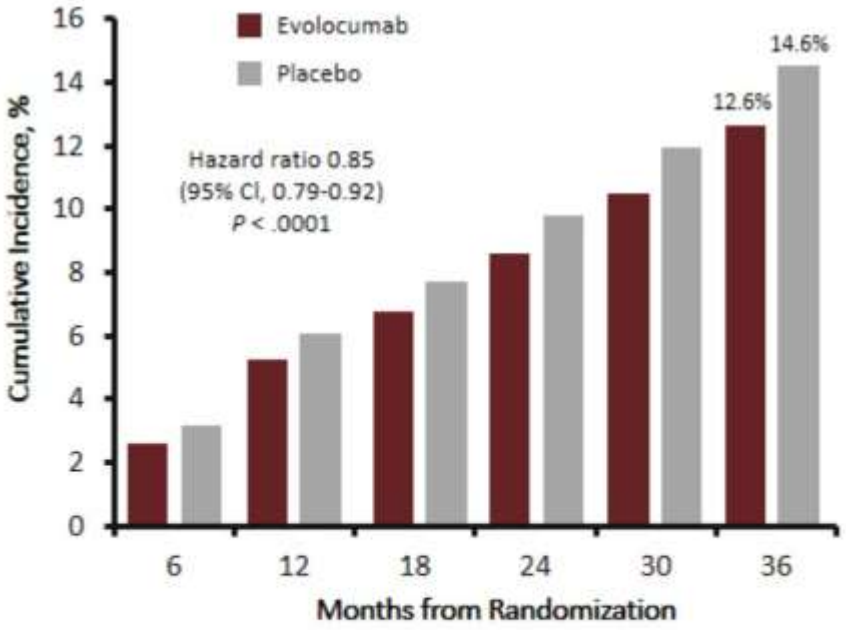


No. at Risk							
Placebo	13,780	13,449	13,142	12,288	7944	3893	731
Evolocumab	13,784	13,501	13,241	12,456	8094	3935	724

FOURIER: Results

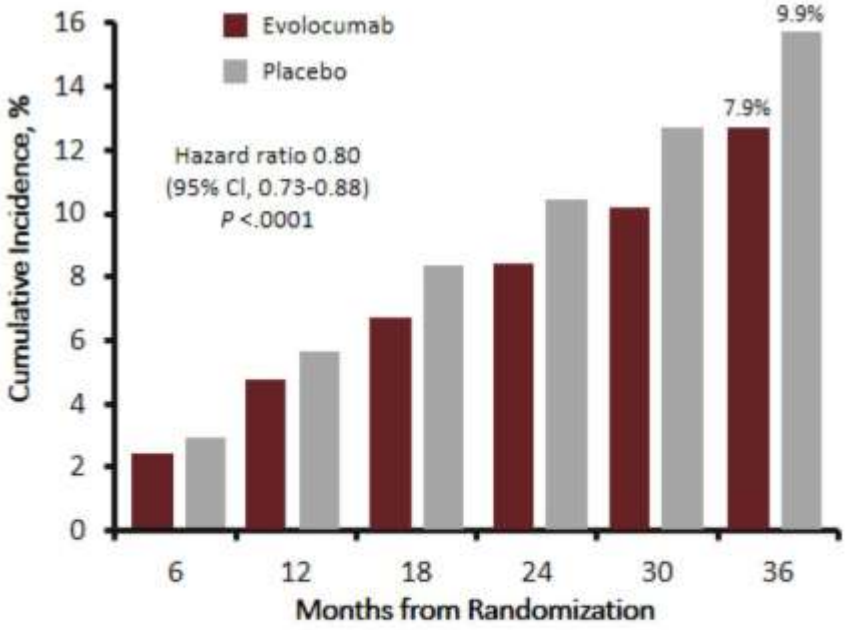
Primary Outcome

CV Death, MI, Stroke, Revascularization, or Hospitalization for UA



Secondary Outcome

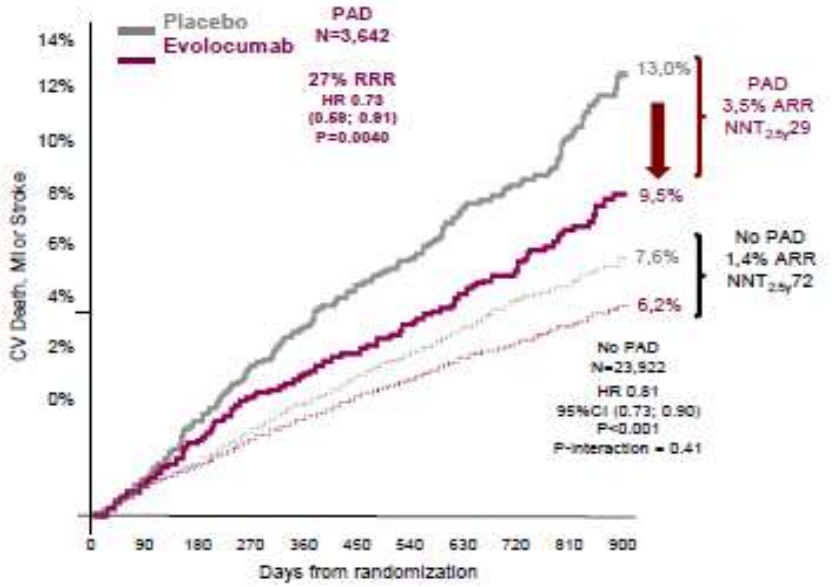
CV Death, MI, or Stroke



Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722.

FOURIER subanalysis PAD

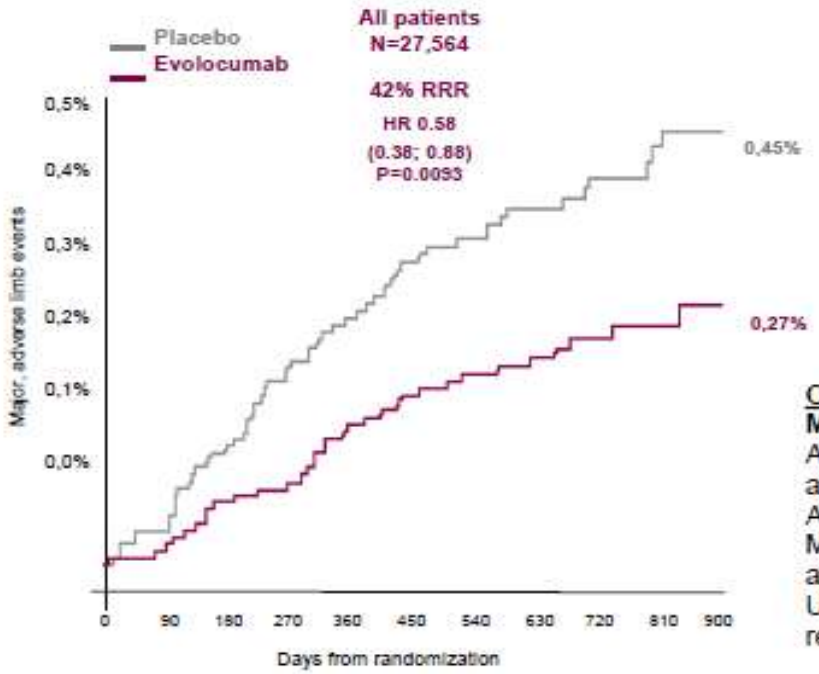
CV Death, MI or stroke in patients with and without PAD



Bonaca M | LBS-02
Bonaca M et al, Circulation 2017;137. DOI: 10.1161/CIRCULATIONAHA.117.032235

FOURIER subanalysis PAD

Major adverse limb events

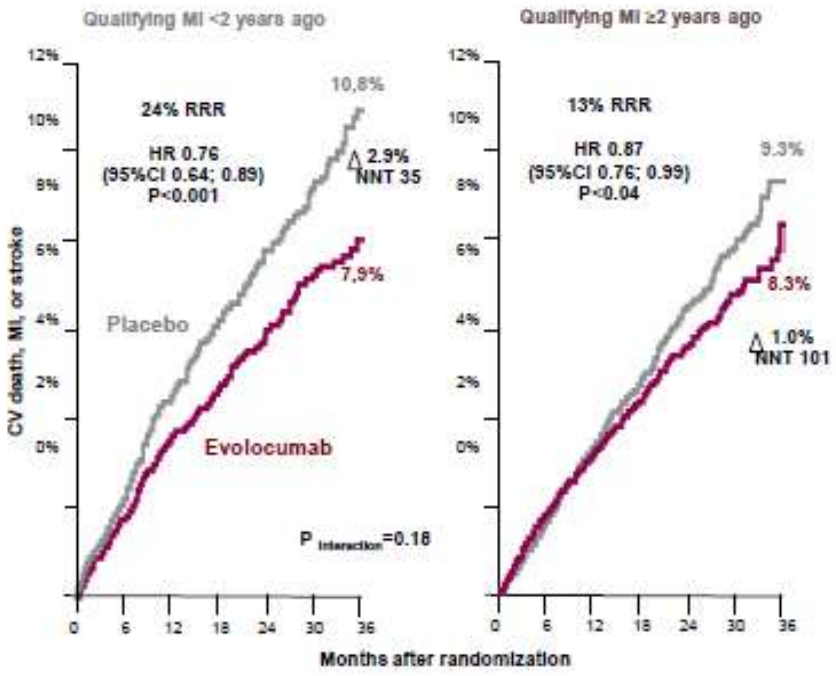


Outcome	HR	95%CI
MALE	**0.58**	**(0.38; 0.88)**
ALI or major amputation	0.52	0.31; 0.89
ALI	0.55	0.31; 0.97
Major amputation	0.57	0.17; 1.95
Urgent revascularization	0.69	0.38; 1.26

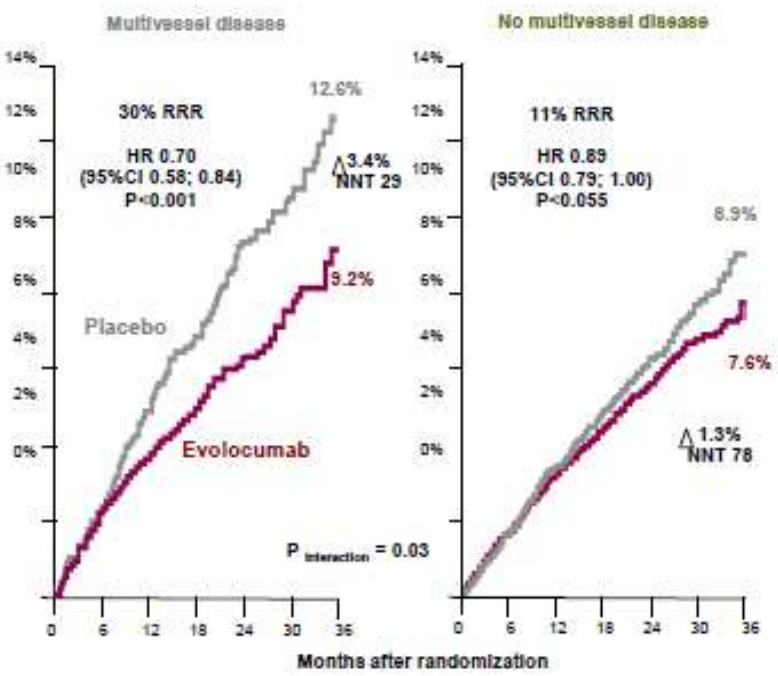
Bonaca M | LBS-02
Bonaca M et al. Circulation 2017;137. DOI: 10.1161/CIRCULATIONAHA.117.032235

FOURIER subanalysis history of MI – results

Benefit of EvoMab based on time from qualifying MI



Benefit of EvoMab based on multivessel disease

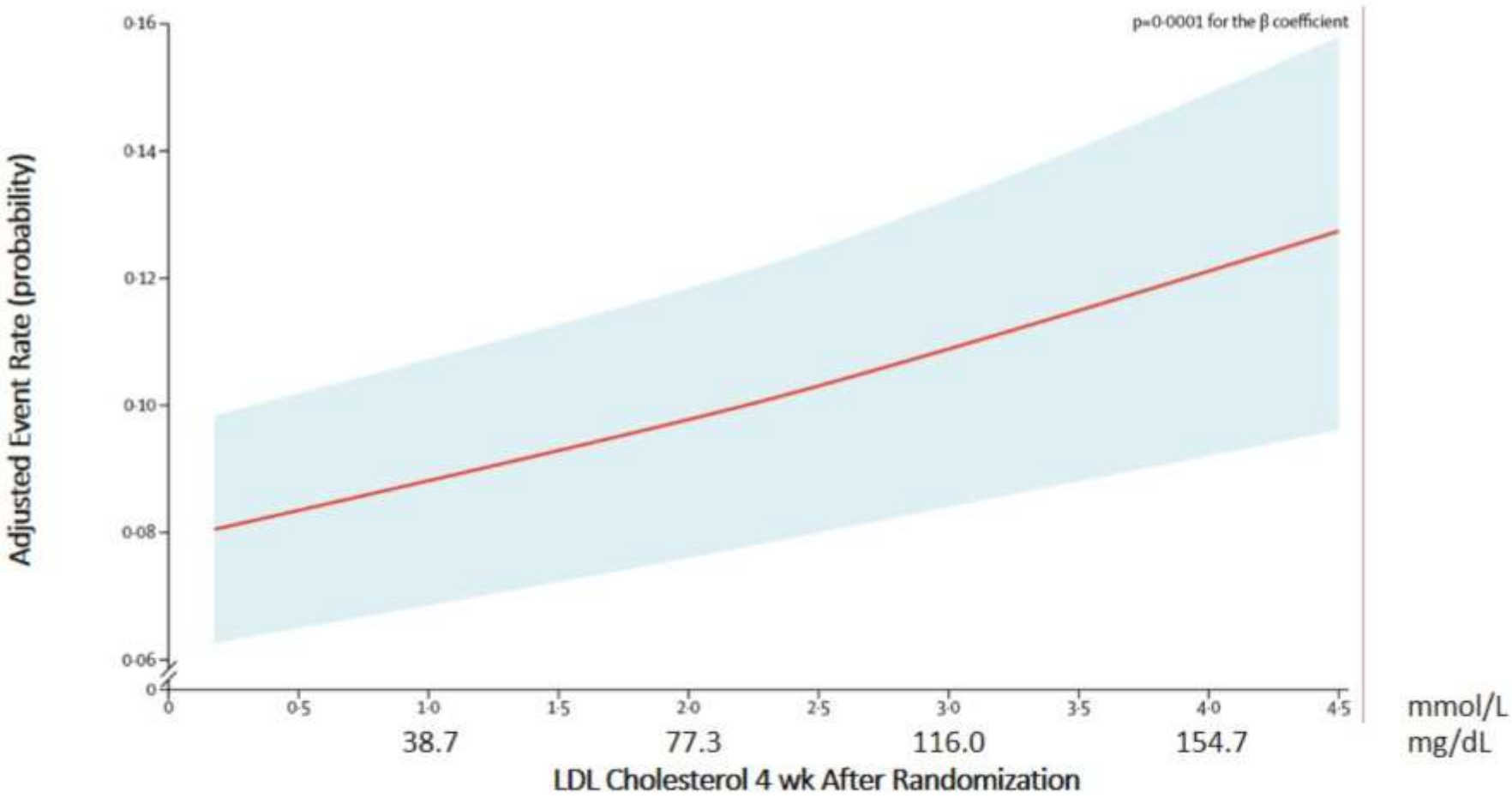


Safety: Adverse Events

Outcome	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events — no. of patients (%)		
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results — no. of patients/total no. (%)		
Aminotransferase level >3 times the upper limit of the normal range	240/13,543 (1.8)	242/13,523 (1.8)
Creatine kinase level >5 times the upper limit of the normal range	95/13,543 (0.7)	99/13,523 (0.7)

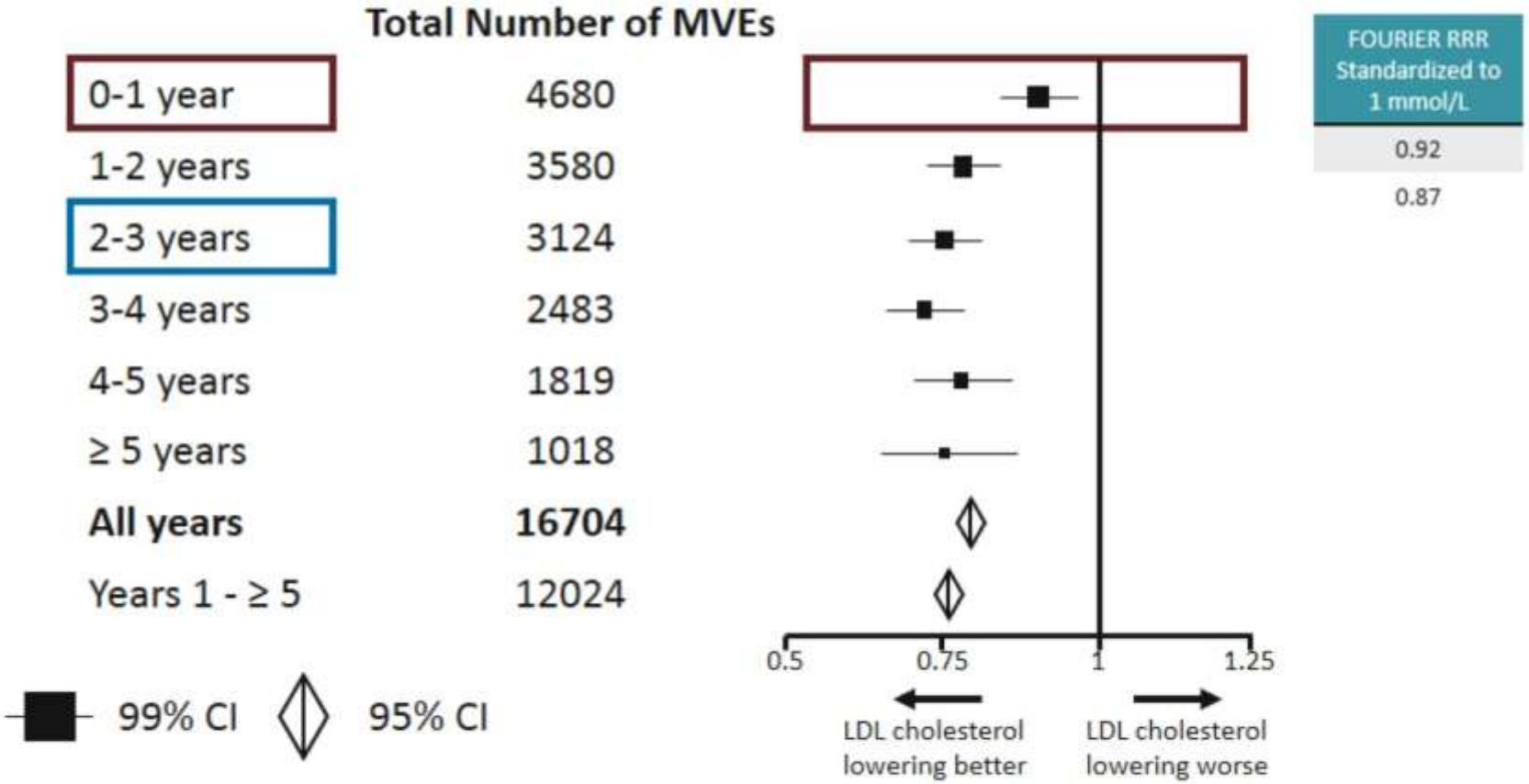
* The between-group difference was nominally significant (P<0.001).
† The total numbers of patients were 8337 in the evolocumab group and 8339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.

FOURIER: Lower CV Event Rates With Lower LDL-C Levels, as Low as 20 mg/dL (~0.5 mmol/L)



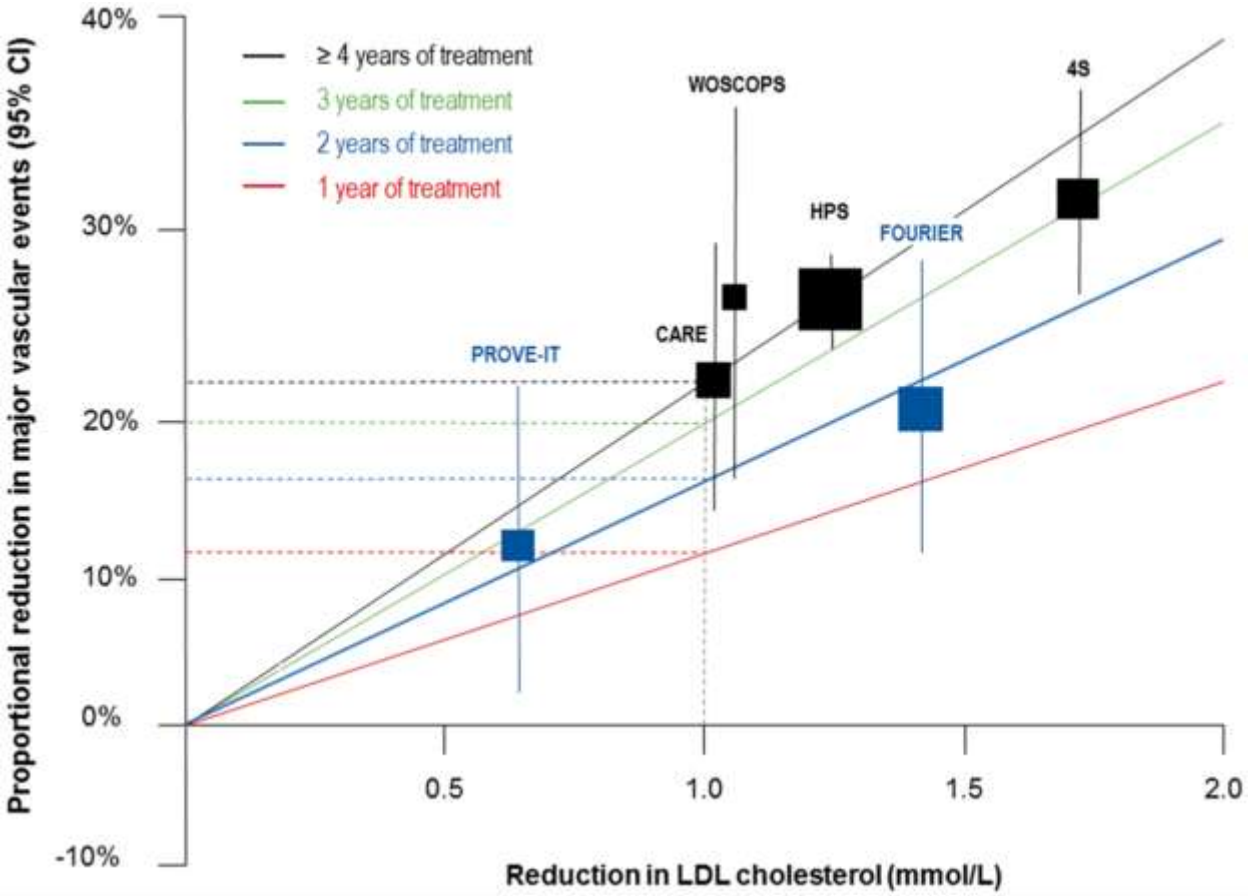
*Relationship between the achieved LDL-C concentration at 4 weeks and the risk of CV death, MI, or stroke. Reprinted from *Lancet*, 390 Giugliano RP et al, Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. 1962-1971, Copyright 2017, with permission from Elsevier

Proportional Reductions in Risks of MVEs* per mmol/L Reduction in LDL-C During Each Year of Scheduled Statin Treatment



FOURIER Primary Endpoint:
Overall RRR is 15%; RRR was 12% in the first year and 19% beyond the first year

Adapted From CTT Collaboration. The median duration across the studies included in the CTT meta-analysis was 4.9 years.
*MVEs (major vascular events) defined as coronary deaths, MIs, strokes, and coronary revascularizations.
Reproduced with permission from Collins R, et al. *Lancet.* 2016;388:2532-2561.



From: 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

Eur Heart J. Published online October 16, 2017. doi:10.1093/eurheartj/ehx549

Study Conclusions

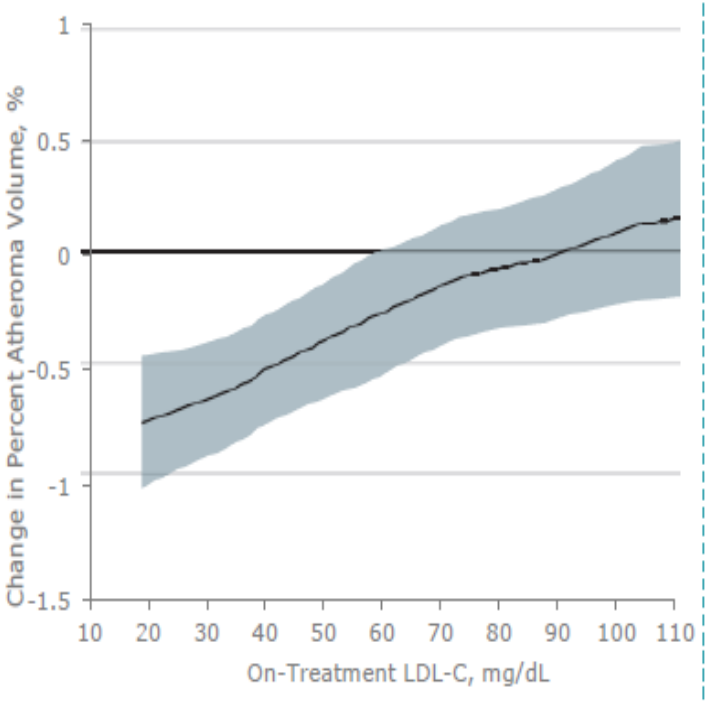
- When added to statin therapy, evolocumab lowered LDL cholesterol levels by 59% from baseline compared to placebo, from a median of 92 mg/dL to 30 mg/dL
- ↓ risk of the primary composite endpoint by 15% and ↓ risk of the key secondary endpoint by 20%
- Magnitude of risk reduction shown to increase over time
- No effect of additional LDL-C lowering on cardiovascular death or all-cause mortality
- Injection-site reactions were significantly higher in the evolocumab group compared to the placebo group

LDL REDUCTION – PCSK9 INHIBITION

GLAGOV Trial

Evolucumab reduces LDL-C and percent atheroma volume

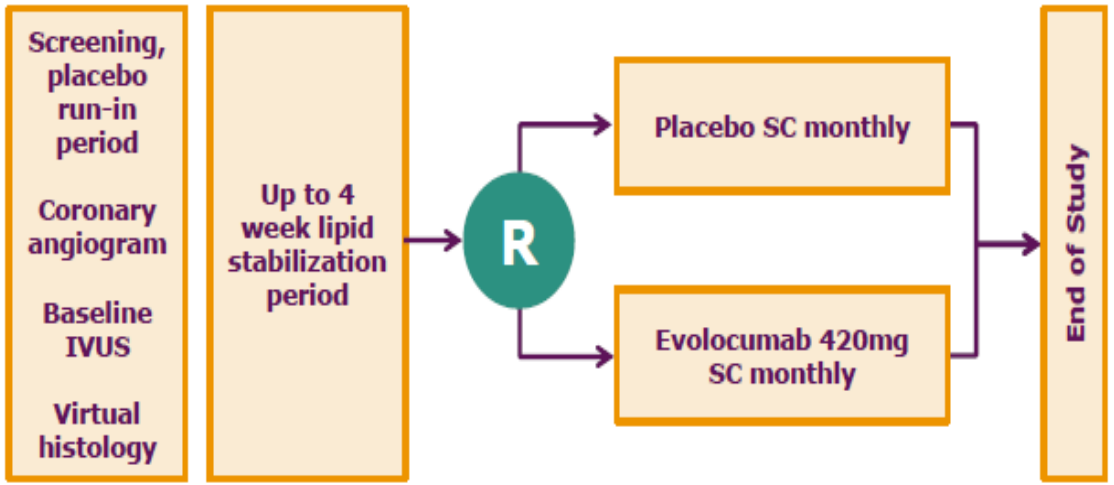
Post Hoc



JAMA 2017

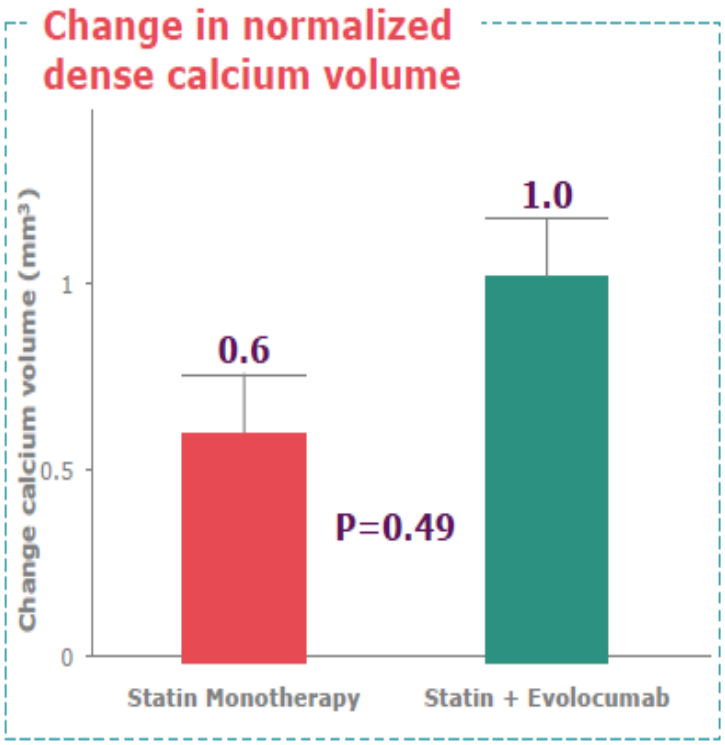
GLAGOV Trial Schematic

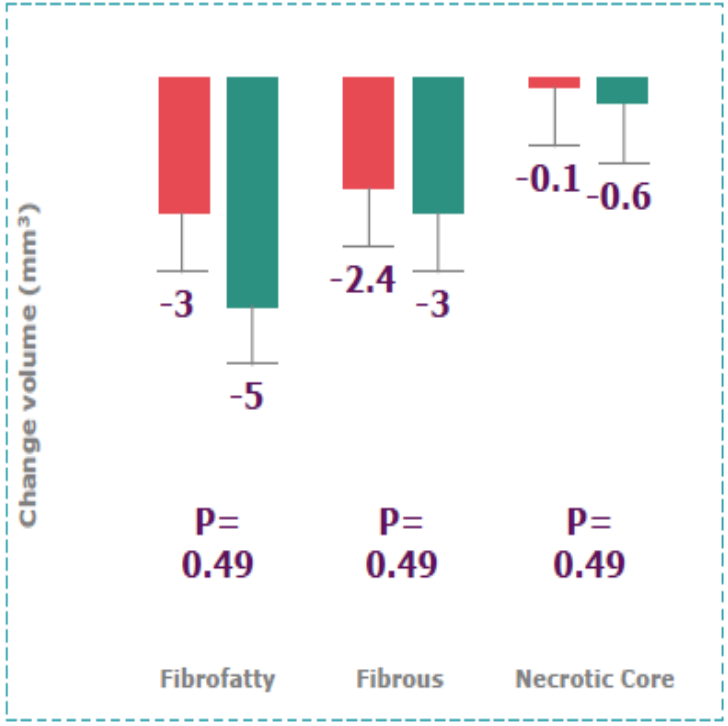
968 pattients with angiographic CAD, stable statin dose and LDL-C ≥80 mg/dL OR 60-80 mg/dL and 1 major or 3 minor risk factors



LDL REDUCTION – PCSK9 INHIBITION

GLAGOV Trial

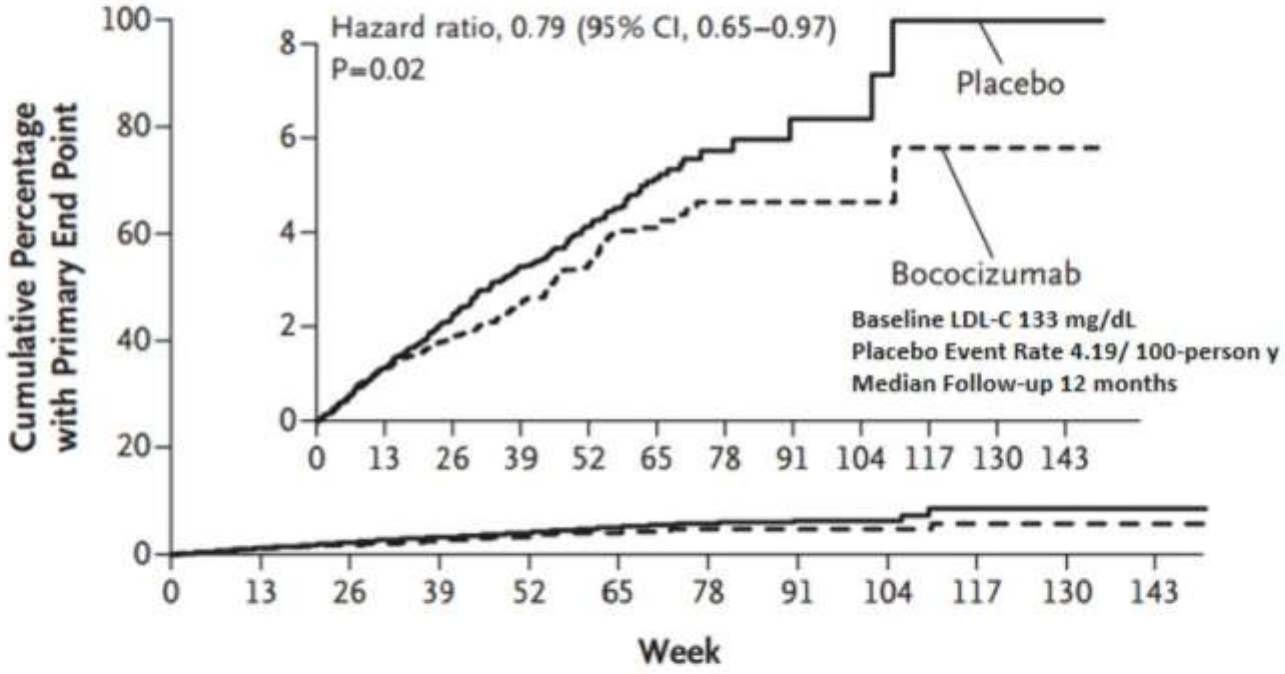




Evolocumab added to statin induces plaque regression but does not change plaque composition

S.J. Nicholls (Adelaide, AU) 5896

The SPIRE-2 Cardiovascular Outcomes Trial: Baseline LDL-C ≥ 100 mg/dL Primary Prespecified Endpoint*

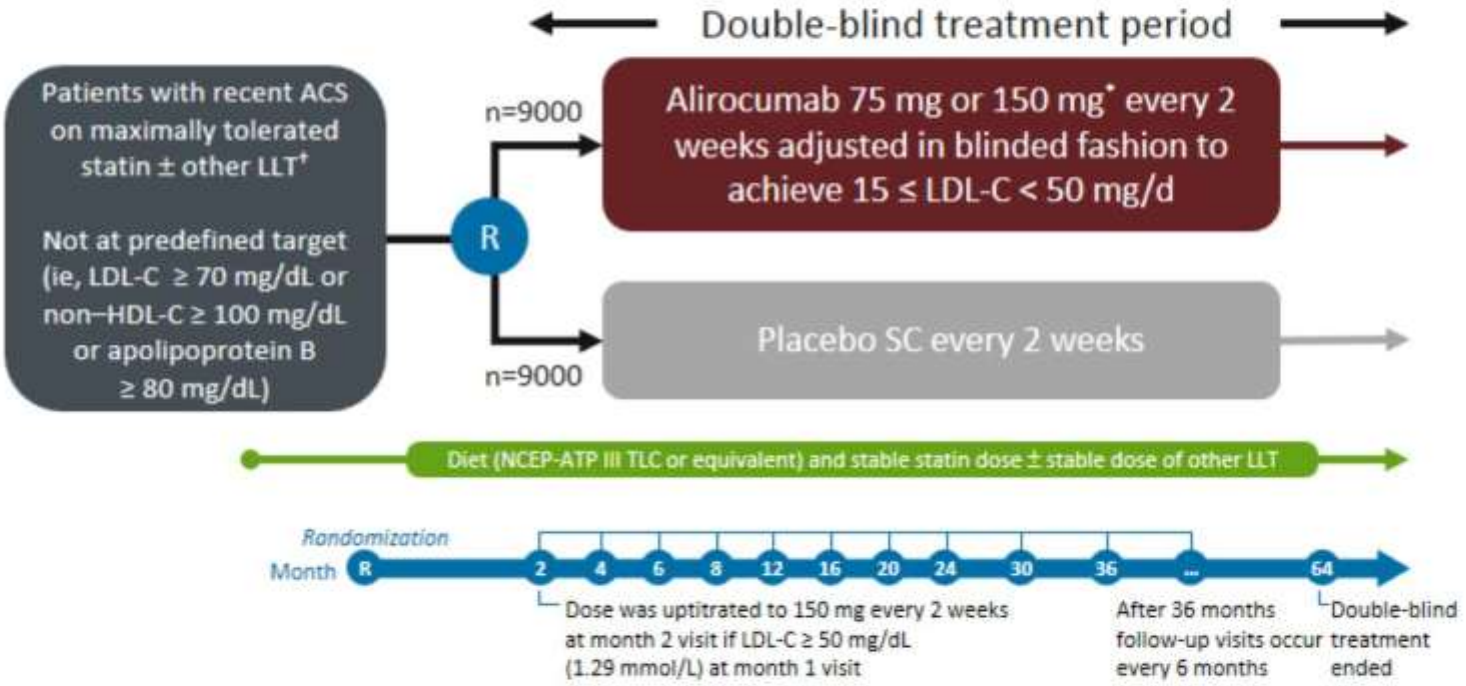


No. at Risk												
Placebo	5309	5220	5130	4214	2319	1174	419	216	116	49	14	4
Bococizumab	5312	5223	5161	4250	2346	1202	431	221	118	49	13	2

*Nonfatal MI, nonfatal stroke, hospitalization for UA requiring urgent revascularization, or CV death.

ODYSSEY OUTCOMES: Study Design

A randomized, double-blind, placebo-controlled study



*Dose titrated up to 150 mg every 2 weeks at month 2 if LDL-C ≥50 mg/dL (1.29 mmol/L) at month 1 visit.
†Atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg OR maximally tolerated dose of statin (can be 0 mg).
If LDL-C < 25 mg/dL on any 2 consecutive measurements on alirocumab 150 mg, the dose is reduced to 75 mg.
If LDL-C < 15 mg/dL on 2 consecutive measurements with alirocumab 75 mg, active treatment is discontinued at the next study visit and substituted with placebo.
Schwartz GG, et al. *Am Heart J.* 2014;168:682-689.e1; ClinicalTrials.gov. NCT01663402.

ODYSSEY OUTCOMES and FOURIER Demographics: Patient Histories

	ODYSSEY OUTCOMES[a] (n=18,312)	FOURIER[b] (n=27,564)
Age (mean)	58.6	62.5
Male, %	74.8	75.4
Hypertension, %	63.3	80.0
Diabetes, %	28.9	33.9
Current smoker, %	23.9	28.2
History of MI, %	100% ACS (mean time from index event 3.6 months, 75% <4 months) including 35% prior CAD + 20% with recurrent event	81.1 (31% MI < 1 y)
History of stroke, %	2.9	19.3
History of PAD, %	3.7	13.2

a. Goodman SG, et al. ACC 2017. Abstract 10269.
b. Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.

ODYSSEY OUTCOMES and FOURIER Demographics: LLTs and Lipids

	ODYSSEY OUTCOMES[a] (n=18,312)	FOURIER[b] (n=27,564)
LLTs		
High-intensity stain, %	89.5	69.2
Moderate-/low-intensity statin, %	7.8	30.7
Ezetimibe, %	2.9	5.1
Lipid parameters		
Median LDL-C, mg/dL	86.5	91.5
Total cholesterol, mg/dL	160.0	167.0
HDL-C, mg/dL	42.5	44.0
Triglycerides, mg/dL	129.2	133.0

Reprinted from *Am Heart J.*, Rationale and design of the Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk trial. 94-101. Copyright 2017, with permission from Elsevier

a. Goodman SG, et al. ACC 2017. Abstract 10269.

b. Sabatine MS, et al. *Am Heart J.* 2016;173:94-101.

ODYSSEY OUTCOMES and FOURIER: Primary Endpoints

	ODYSSEY OUTCOMES[a]	FOURIER[b]
CHD death	X	
CV death		X
MI	X (nonfatal)	X
Stroke	X (fatal/nonfatal)	X (ischemic and hemorrhagic)
UA requiring hospitalization	X	X
Coronary revascularization		X

CHD Death per ODYSSEY CVOT Protocol

- Any death with a clear relationship to underlying CHD
  - Death secondary to acute MI
  - Sudden death, heart failure, etc

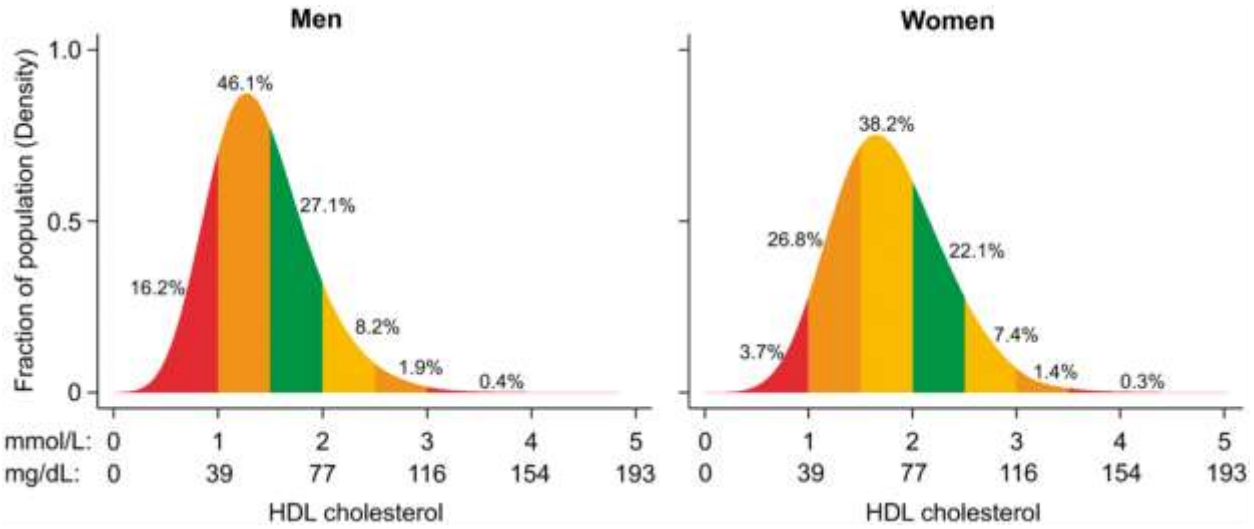
CV Death per ACC/AHA Clinical Data Standard 2014

Death resulting from an acute MI, sudden cardiac death, death due to heart failure, death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes

Reprinted from *Am Heart J.*, Rationale and design of the Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk trial. 94-101. Copyright 2017, with permission from Elsevier
a. Schwartz GG, et al. *Am Heart J*. 2014;168:682-689.e1; b. Sabatine MS, et al. *Am Heart J*. 2016;173:94-101; Sabatine MS, et al. *N Eng J Med*. 2015;372:1500-1509; ClinicalTrials.gov. NCT01663402; Marcinak JF, et al. *Nature*. 2012;91:514-520.

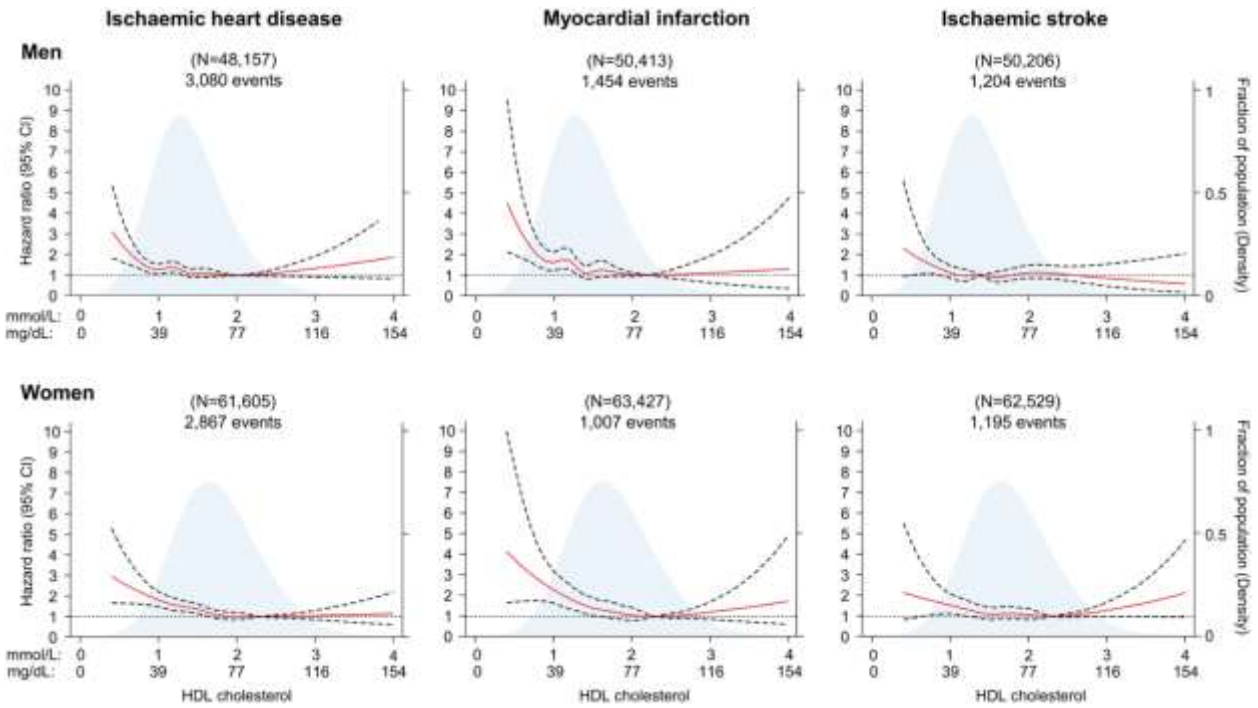
PCSK9 CVOTs: Key Scientific Points

- FOURIER results further support the LDL-C hypothesis (ie, lowering LDL-C reduces CV events)
  - RRR is 15% for 1° endpoint and 20% for 2° endpoint
- A potential limitation of FOURIER is the shorter duration of follow-up (median of 2.2 years); ODYSSEY OUTCOMES will have longer estimated mean double-blind follow-up of ~3 years and a maximum of 5 years at trial completion
- Elements of the ODYSSEY OUTCOMES trial are different from FOURIER, including:
  - A longer follow-up
  - A higher risk patient population
  - Treat-to-goal approach
  - Higher proportion of patients on high-intensity statin
  - Inclusion of CHD death as a component of the primary composite endpoint
- PCSK9 inhibition is an exciting new therapy—we need to get it to the right patients in clinical practice



From: Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies

Eur Heart J. 2017;38(32):2478-2486. doi:10.1093/eurheartj/ehx163



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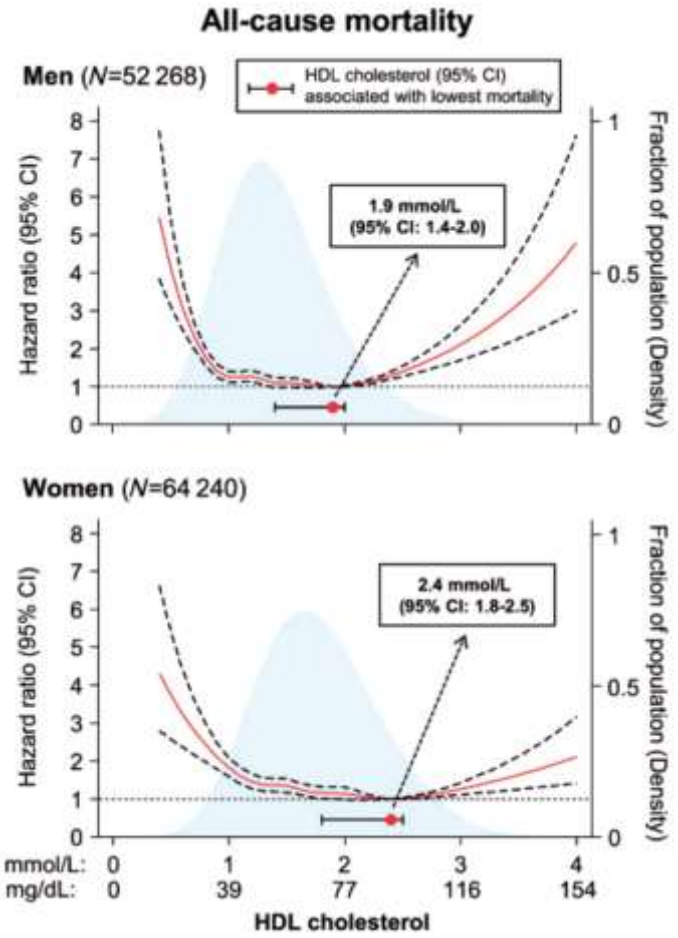
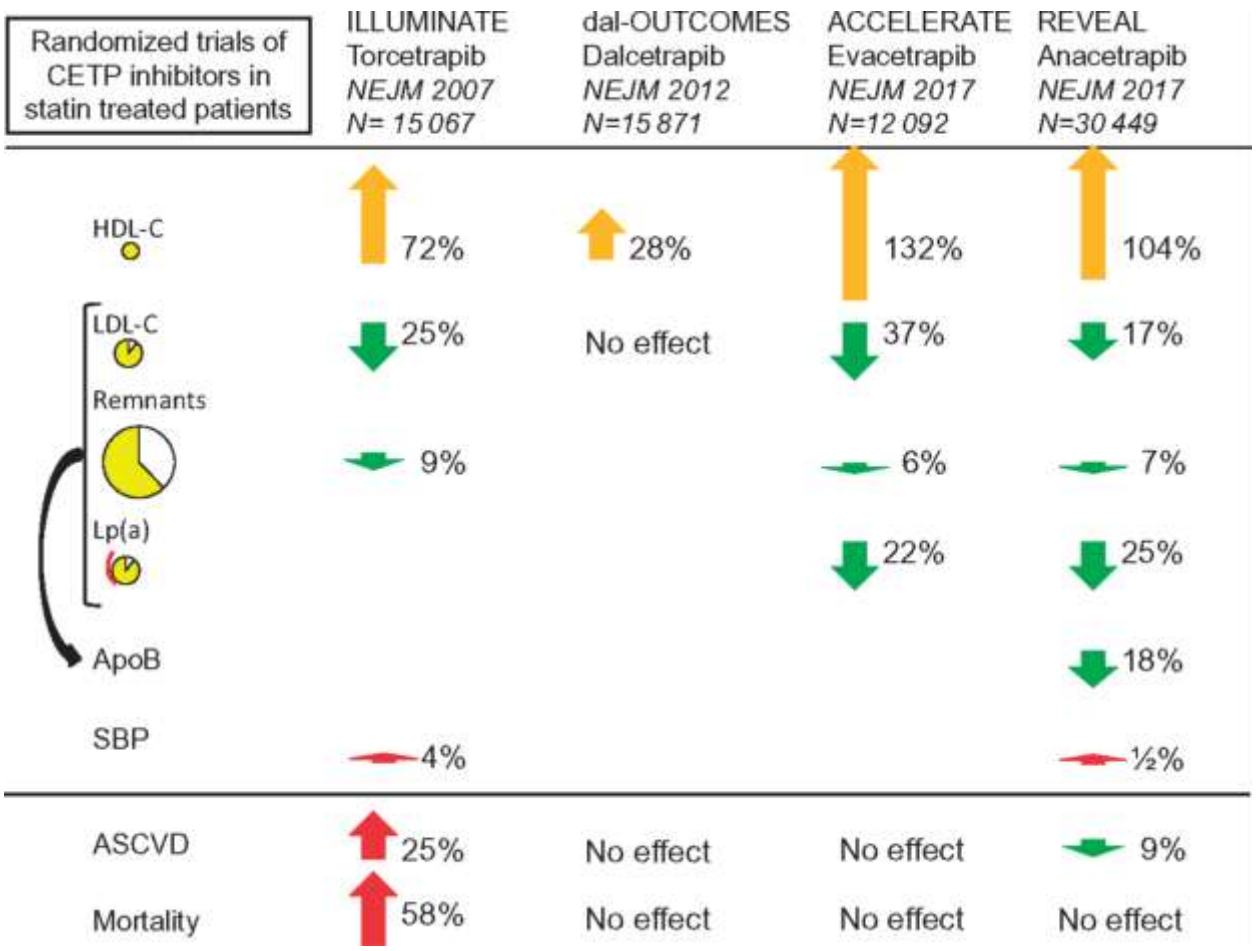


From: The year in cardiology 2017: prevention

Eur Heart J. Published online January 02, 2018. doi:10.1093/eurheartj/ehx766



From: The year in cardiology 2017: prevention

Eur Heart J. Published online January 02, 2018. doi:10.1093/eurheartj/ehx766

LDL REDUCTION – CETP INHIBITION

Hps3·TIMI55 REVEAL

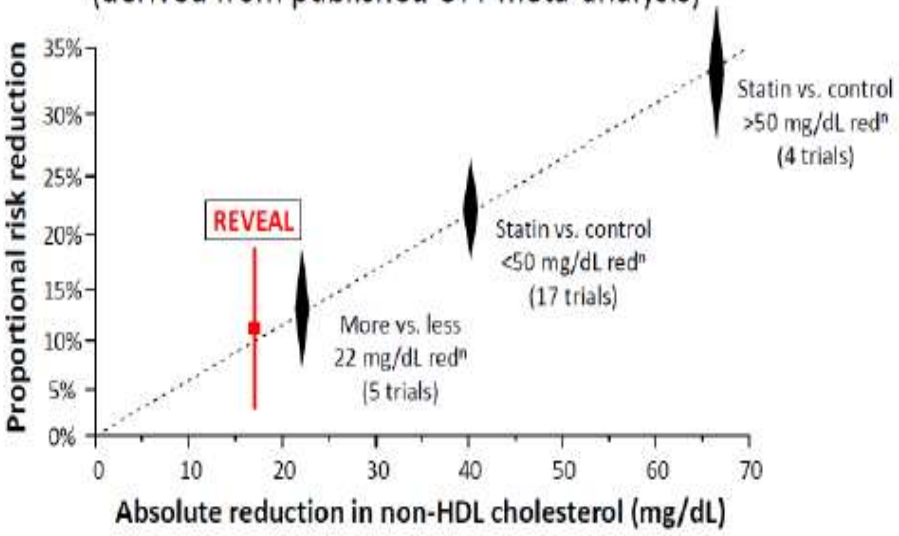
REVEAL: Randomized placebo-controlled trial of anacetrapib added to statin in 30,449 patients with atherosclerotic vascular disease

Effects of anacetrapib on lipids at trial midpoint

Measurement	Absolute difference		Proportional difference
	mg/dL	SI units	
HDL cholesterol	+43	+1.1 mmol/L	104%
Apolipoprotein AI	+42	+0.4 g/L	36%
LDL cholesterol			
- Direct (Genzyme)	-26	-0.7 mmol/L	-41%
- Beta-quantification*	-11	-0.3 mmol/L	-17%
Apolipoprotein B	-12	-0.1 g/L	-18%

Proportional reduction in Coronary death or MI vs. absolute reduction in non-HDL cholesterol

(derived from published CTT meta-analysis)



No excess of mortality, cancer or other serious adverse events
Small increase in blood pressure and small reduction in kidney function

M. Landray (Oxford, UK) 4728

2013 ACC/AHA Guidelines

STATINS are FIRST-LINE for CVD prevention

Journal of the American College of Cardiology

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Neil J. Stone, MD, MACP, FAHA, FACC; Jennifer G. Robinson, MD, MPH, FAHA; Alice H. Lichtenstein, DSC,FAHA; C. Noel Bairey Merz, MD, FAHA, FACC; Conrad B. Blum, MD, FAHA; Robert H. Eckel, MD, FAHA; Anne C. Goldberg, MD, FACP, FAHA; David Gordon, MD; Daniel Levy, MD; Donald M. Lloyd-Jones, MD, SCM, FACC, FAHA; Patrick McBride, MD, MPH, FAHA; J. Sanford Schwartz, MD; Susan T. Shero, MS, RN; Sidney C. Smith, JR, MD, FACC, FAHA; Karol Watson, MD, PhD, FACC, FAHA; Peter W. F. Wilson, MD, FAHA

2013 ACC/AHA Cholesterol Guideline

NET BENEFIT APPROACH

Strong evidence of net ASCVD risk reduction benefit

Use statins in 4 patient groups:

- Clinical ASCVD
- LDL-C >190 mg/dL
- Diabetes age 40 to 75 years
- >7.5% 10-year ASCVD (hard event) risk

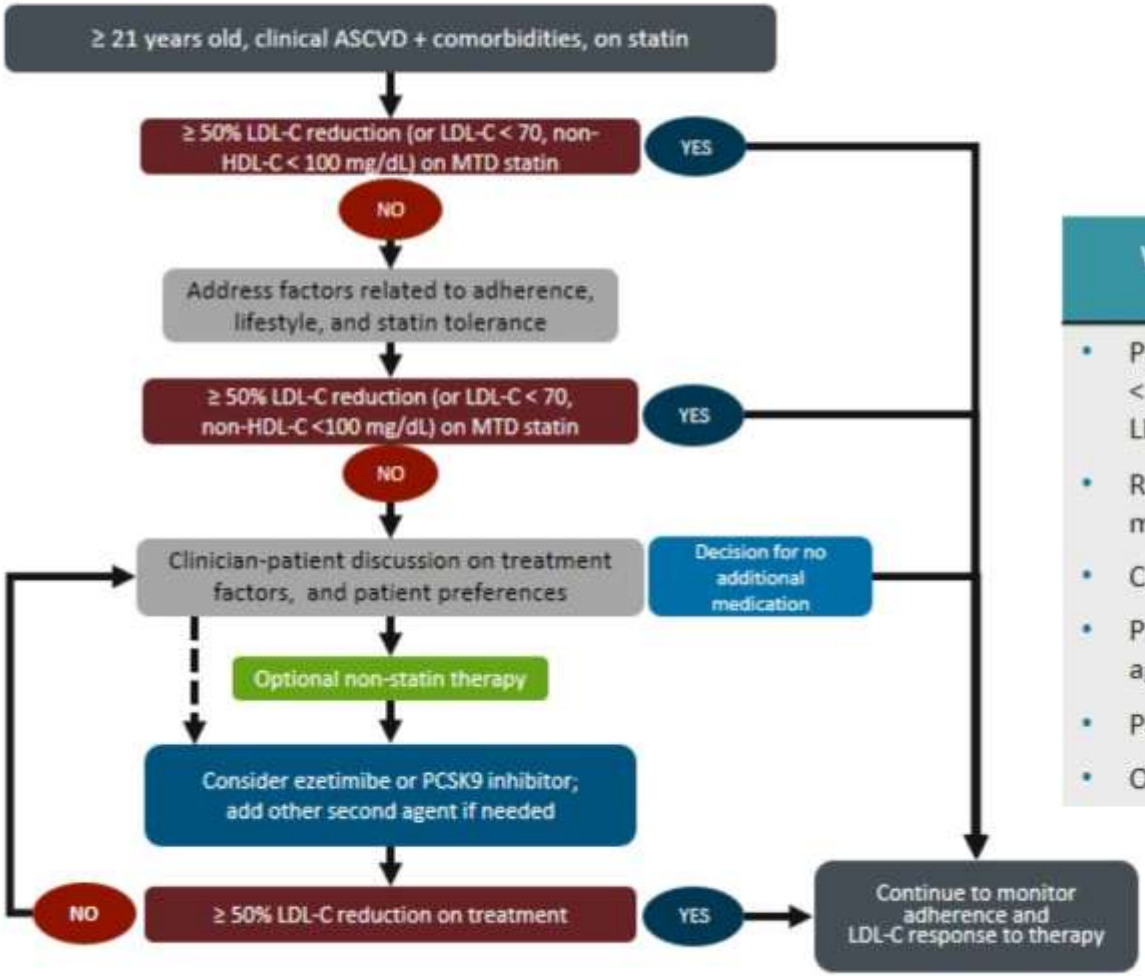
Stone NJ, et al. *J Am Coll Cardiol.* 2014;63:2889-2934.

2017 AACE Guidelines for the Management of Dyslipidemia

Risk Category	Risk Factors/10-Year Risk	Treatment Goals		
		LDL-C, mg/dL	Non-HDL-C, mg/dL	Apo B, mg/dL
Extreme risk	• Progressive ASCVD including unstable angina in patients after achieving an LDL-C < 70 mg/dL • Established clinical cardiovascular disease in patients with DM, CKD ¾, or HeF • History of premature ASCVD (< 55 male, < 65 female)	< 55	< 80	< 70
Very high risk	• Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk > 20% • Diabetes or CKD ¾ with 1 or more risk factor(s) • HeFH	< 70	< 100	< 80

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

2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway: Nonstatin Therapies for ASCVD



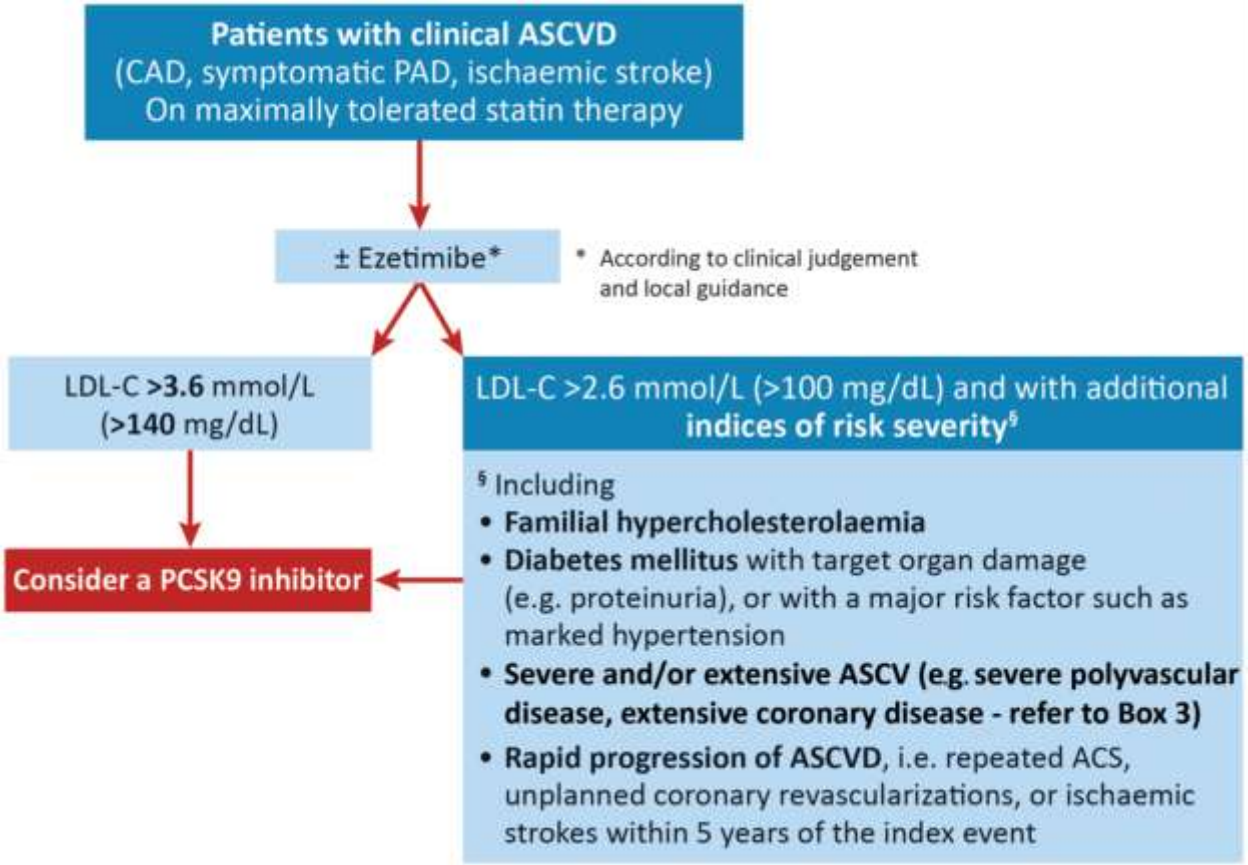
When to Choose Ezetimibe?	When to Choose PCSK9 Inhibitor?
• Patients requiring < 25% additional LDL-C lowering • Recent ACS < 3 months • Cost considerations • Preference of oral agent • Patient preference • Other risk factors	• Patients requiring > 25% additional LDL-C lowering • Cost-benefit considerations should be discussed • Administration, dosing schedule, and storage should be discussed

Reprinted from *J Am Coll Cardiol*, 70, Lloyd-Jones DM, et al., 2017 Focused Update of the 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: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways, 1785-1822., Copyright 2017, with permission from Elsevier.

2016 ESC/EAS Guidelines for the Management of Dyslipidemias

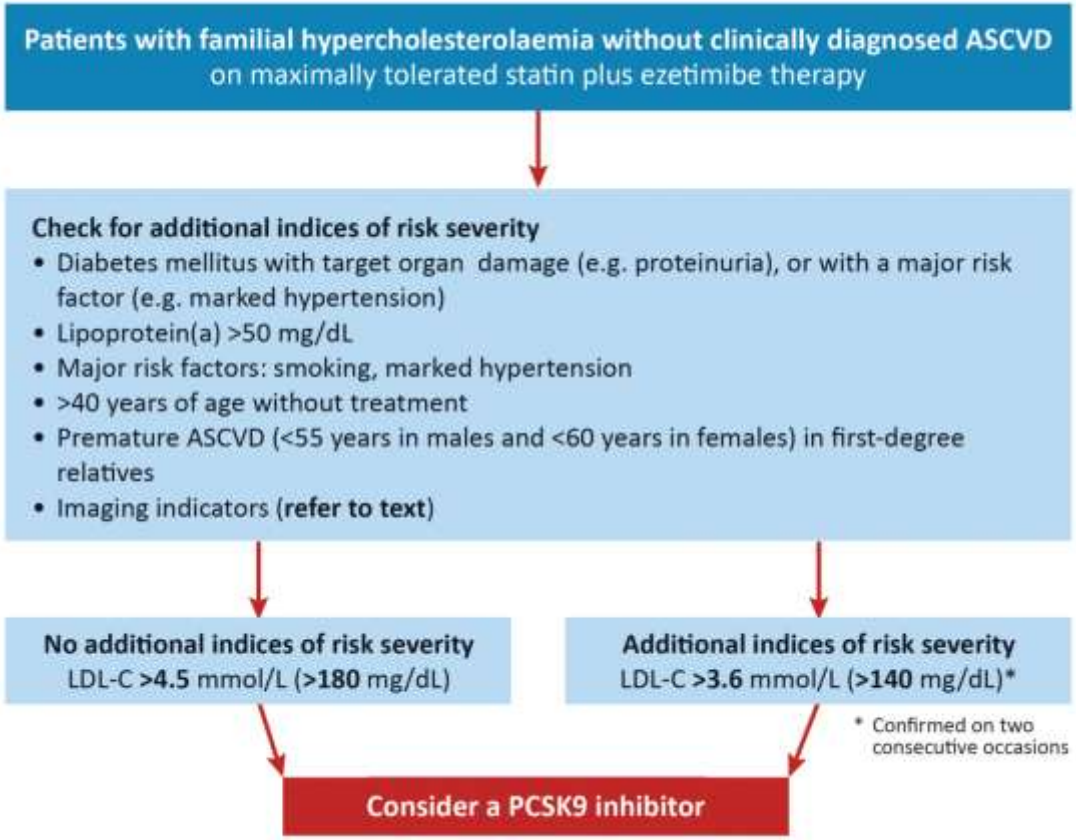
Risk Category	Definition	LDL-C Goal
Very high	• Documented CVD • T2D with target organ damage or a major risk factor • 10-year risk ≥ 10% for fatal CVD	< 70 mg/dL Or ≥ 50% reduction if LDL-C 70-135 mg/dL
High	• Cholesterol > 310 mg/dL or BP ≥ 180/110 mmHg • Most people with T2D • Moderate CKD • 10-year risk ≥ 5% for fatal CVD	< 100 mg/dL Or ≥ 50% reduction if LDL-C 100-200 mg/dL
Moderate	10-year risk ≥ 1% - < 5% for fatal CVD	< 115 mg/dL
Low	10-year risk < 1% for fatal CVD	< 115 mg/dL

Catapano AL, et al. *Eur Heart J.* 2016;37:2999-3058.



From: 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

Eur Heart J. Published online October 16, 2017. doi:10.1093/eurheartj/ehx549



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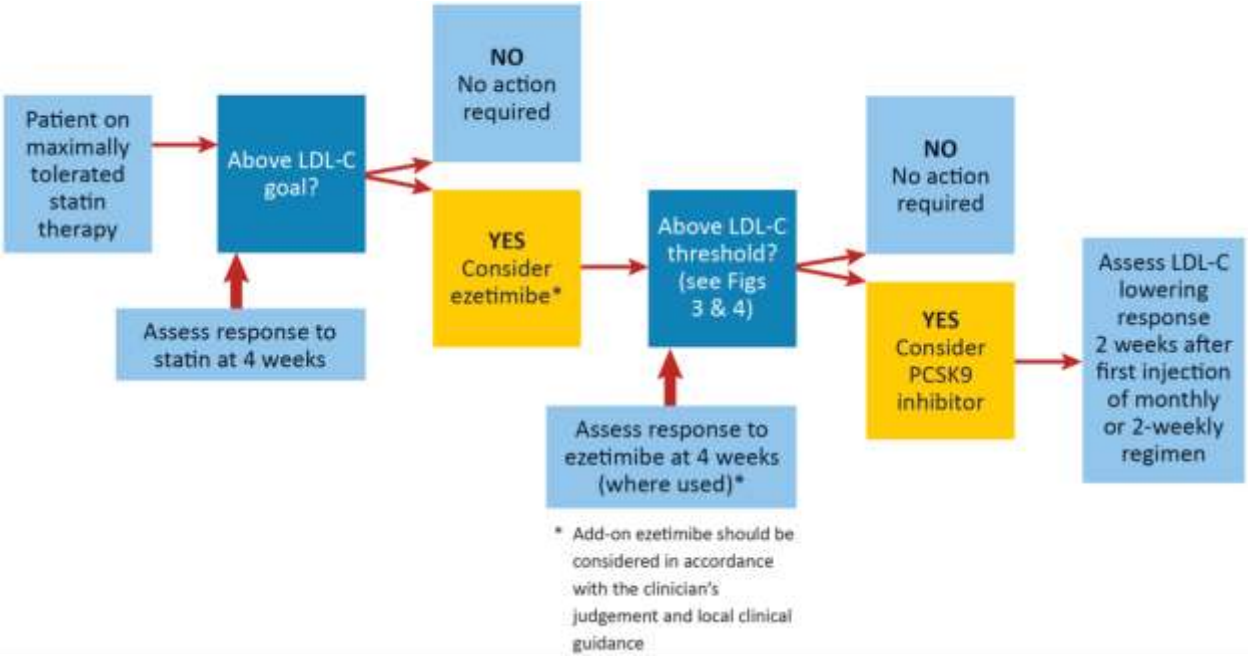

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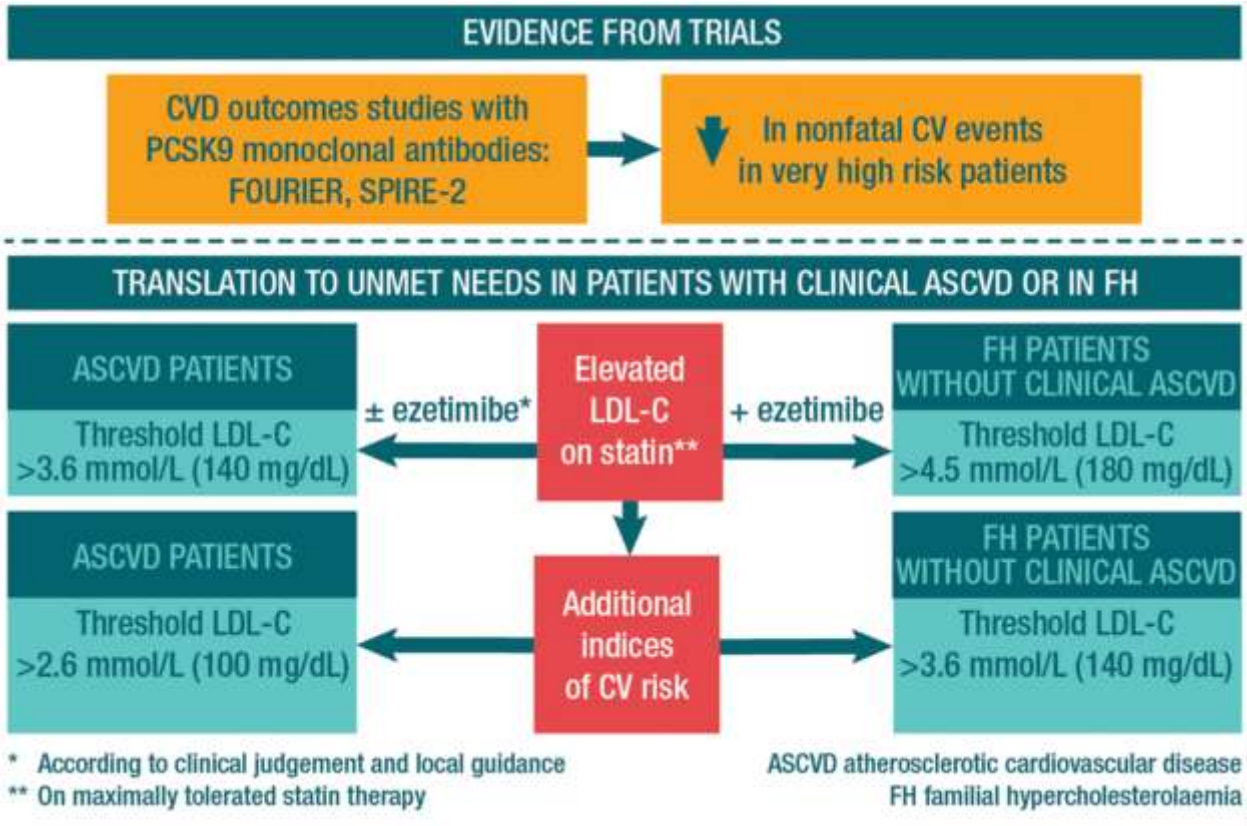

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