Landscape of Lipid Management Following an ACS Event

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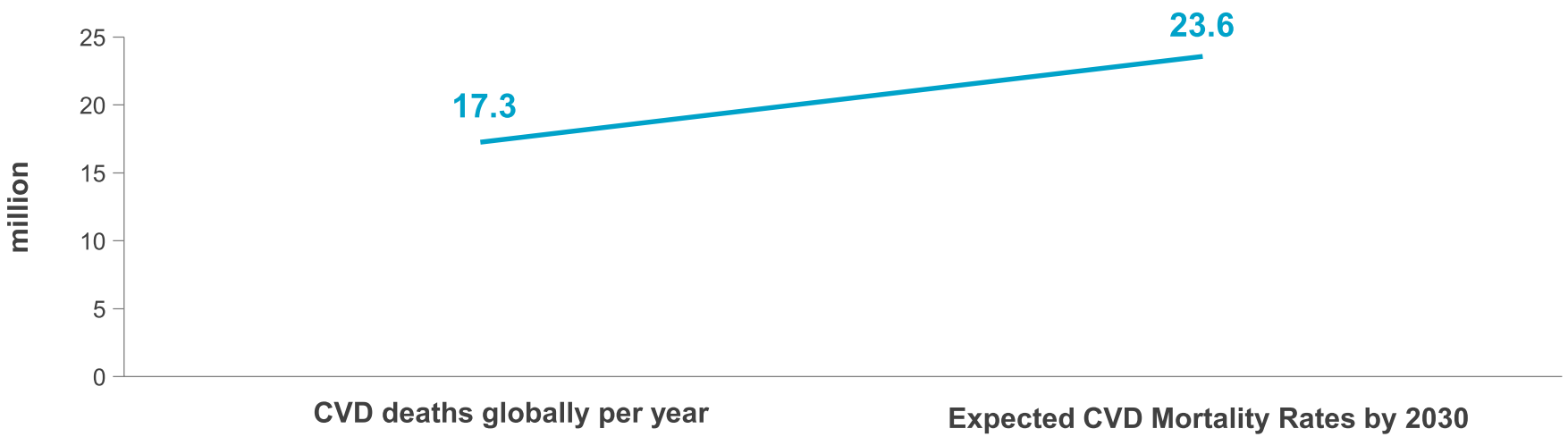
CONTENTS

CVD mortality is no longer decreasing.[1,2]

- Although advances in care have spurred improvements in CV outcomes, CVD remains the leading cause of death in the United States and around the world.[1]
- It accounts for 17.3 million deaths globally per year and is expected to grow to more than 23.6 million deaths per year by 2030.[2]

Expected CVD Mortality Rates by 2030 in the United States[2]

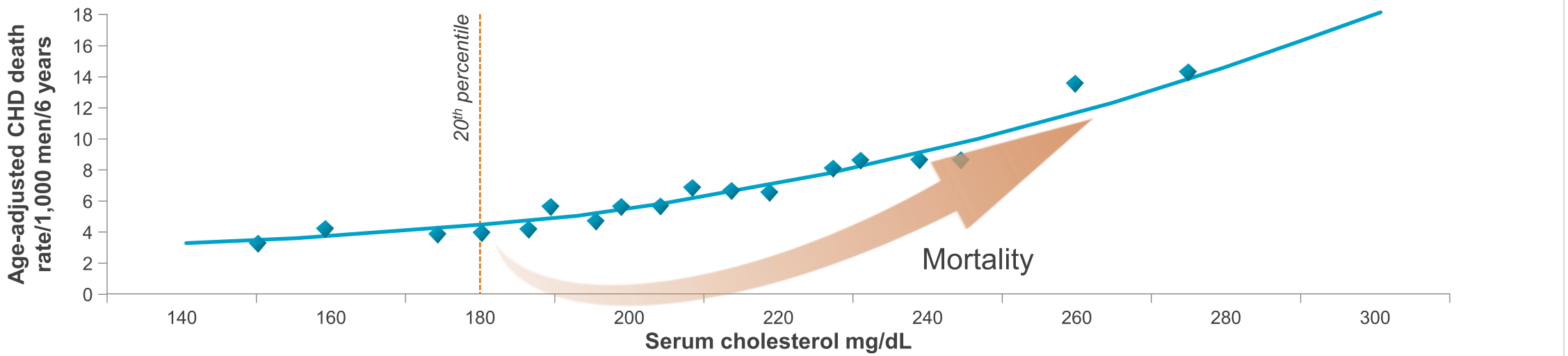


CVD, cardiovascular disease; CV, cardiovascular.

Reference. 1. Sidney S, *et al*. JAMA Cardiol. 2016 Aug 1;1(5):594-599. 2. McClellan M, *et al*. Circulation. 2019;139(9):e44-e54.

MRFIT screening data:
Association of serum cholesterol and CHD death in 361,662 men

MRFIT was a large, multicentre cohort study of middle-aged men with high CV risk. Its aim was to determine the risk relationship between serum cholesterol and CHD, and to compare it with the pattern observed between blood pressure and CHD risk



CHD mortality increased progressively above the 20th percentile for serum cholesterol (>181 mg/dL [4.68 mmol/L])

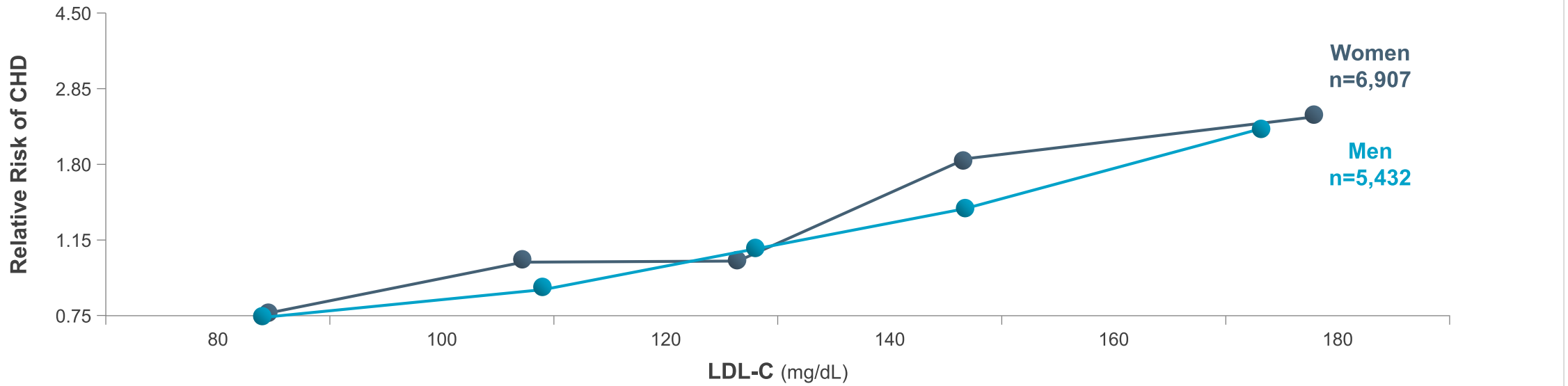
CHD, coronary heart disease; MRFIT, Multiple Risk Factor Intervention Trial for the Prevention of Coronary Heart Disease.

Reference. 1. Martin MJ, *et al*. Lancet. 1986;2(8513):933-6.

ARIC Study:
Relationship of LDL-C to CHD in men and women

- ARIC was a population-based sampling of 15,792 residents, 45 to 64 years old from 4 communities in NC, MS, MN, and MD

Adjusted for age and race 10-year follow-up



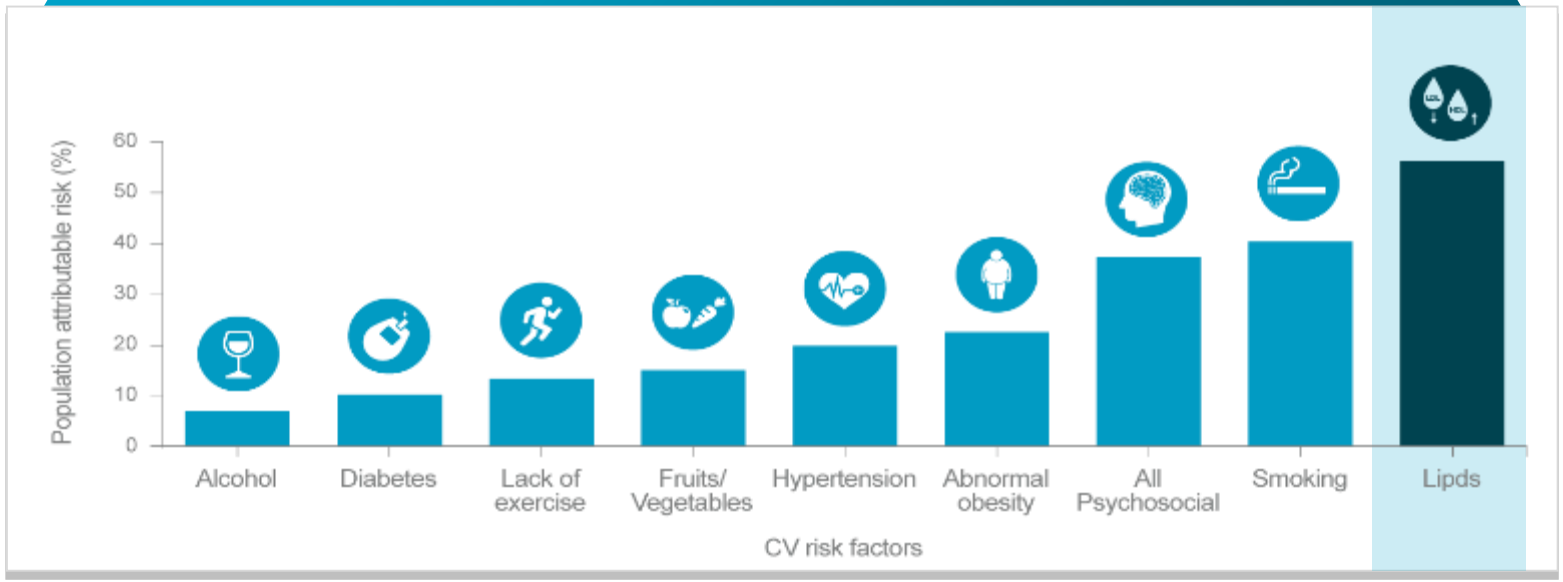
ARIC, Atherosclerosis Risk In Communities; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol

Reference. 1. Sharrett AR, *et al*. Circulation. 2001;104(10):1108–13.

High LDL-C levels increase cardiovascular risk and contribute to cardiovascular disease.[1]

- Cardiovascular risk factors determine cardiovascular disease progression and clinical event presentation.[1]
- Identification of modifiable cardiovascular risk factors such as high LDL-C levels has enabled the design of targeted prevention strategies in order to reduce the impact on disease progression.[2,3]

Population attributable risks for the association of risk factors to myocardial infarction[3]



Study Design

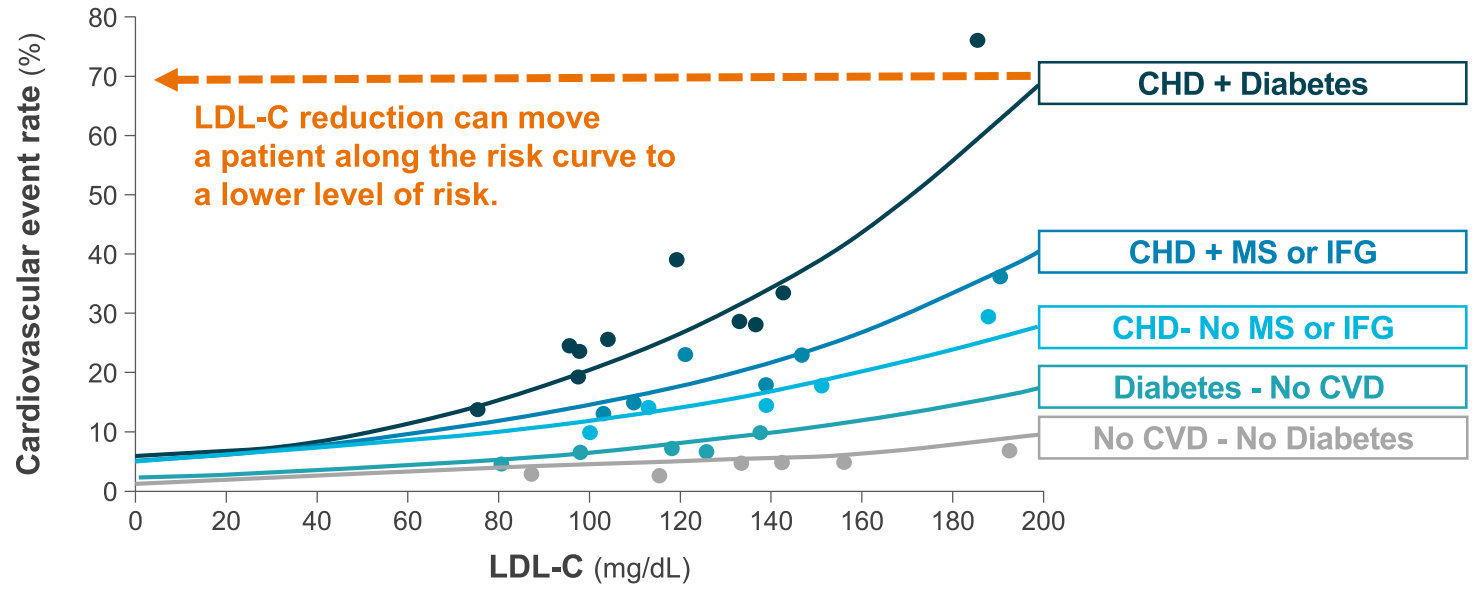
This study sought to assess the effect of potentially modifiable risk factors associated with myocardial infarction. It is a standardised case-control study of acute myocardial infarction in 52 countries, enrolling 15,152 cases and 14,820 controls.[3]

LDL-C, low-density lipoprotein cholesterol.

Reference. 1. Badimon L, *et al*. Int J Cardiol. 2016;217:S7–S9; 2. Mannsverk J, *et al*. Circulation. 2016;133:74–81; 3. Yusuf S, *et al*. Lancet. 2004;364:937–952.

Rate of CV events are related to risk level and LDL-C.[1]

Intent-to-treat LDL cholesterol level and risk for hard cardiovascular events (nonfatal myocardial infarction, CHD death, and stroke) by the presence of coronary heart disease (CHD), metabolic syndrome (MS), impaired fasting glucose (IFG), or diabetes in placebo-controlled statin trials of approximately 5 years in duration[1]



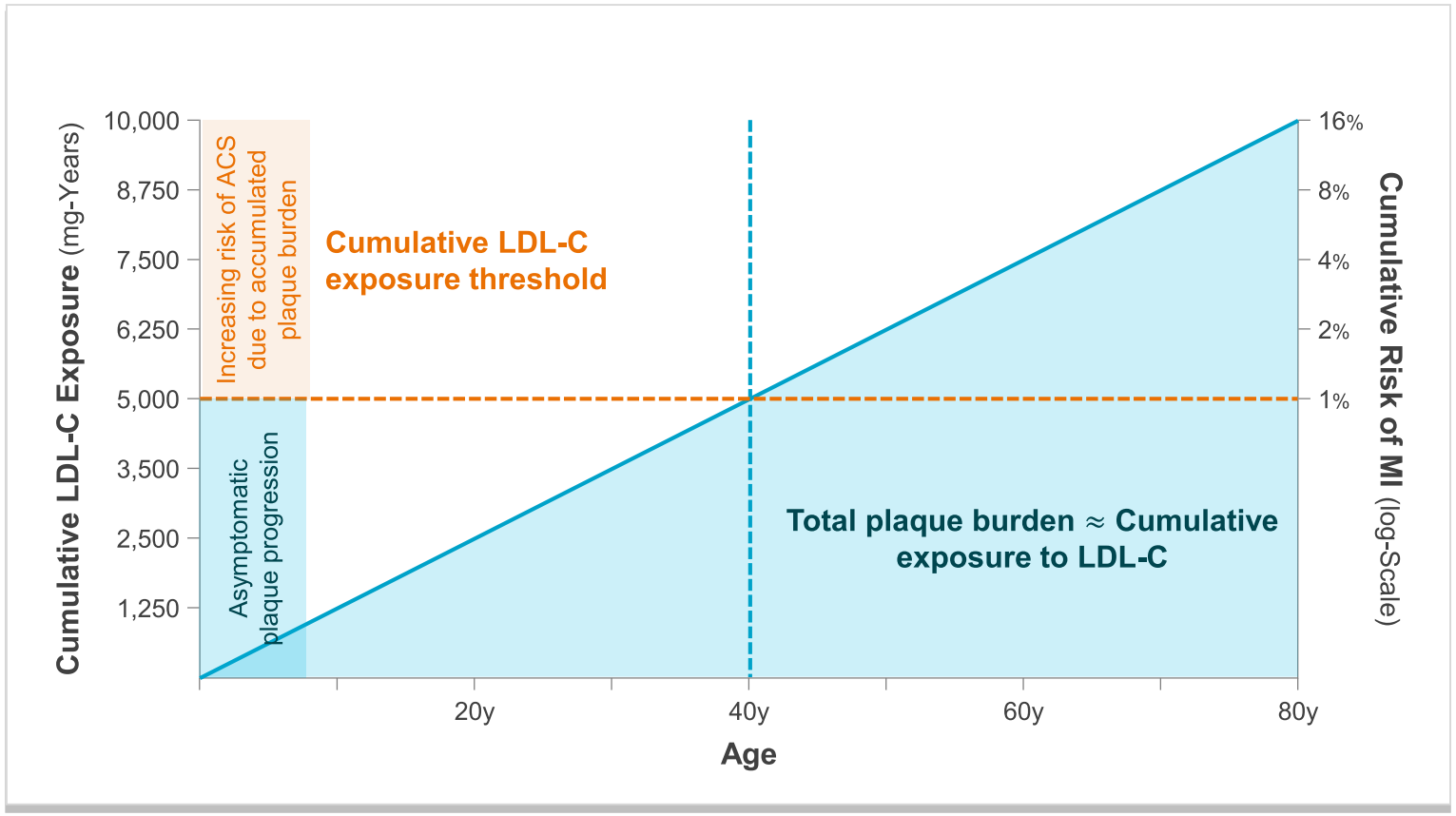
Study Design

Review article to identify patients for aggressive cholesterol lowering.[1]

CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol.

Reference. 1. Robinson JG, *et al*. Am J Cardiol. 2006 Nov 15;98(10):1405-1408.

Effect of Cumulative Exposure to LDL on Plaque Burden and Risk of Cardiovascular Disease

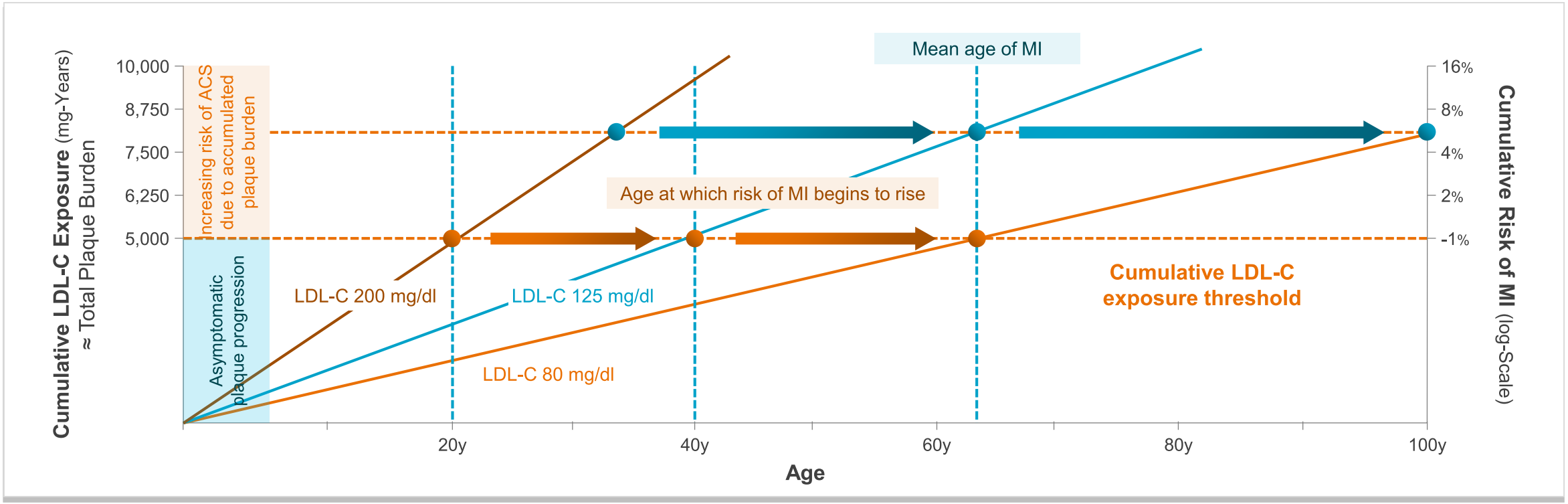


- The total plaque burden (shaded area under the solid blue line) is directly proportional to both age and cumulative exposure to LDL-c.
- Beyond the threshold, (horizontal orange dashed line) if the plasma LDL-c level remains constant, the risk of myocardial infarction rises log-linearly.

Reference. 1. Frence, Graham, Tokgozoglu, Catapano JACC 2018; 92: 1141-1156

Cumulative Effect of LDL on Risk of Atherosclerotic Cardiovascular Disease

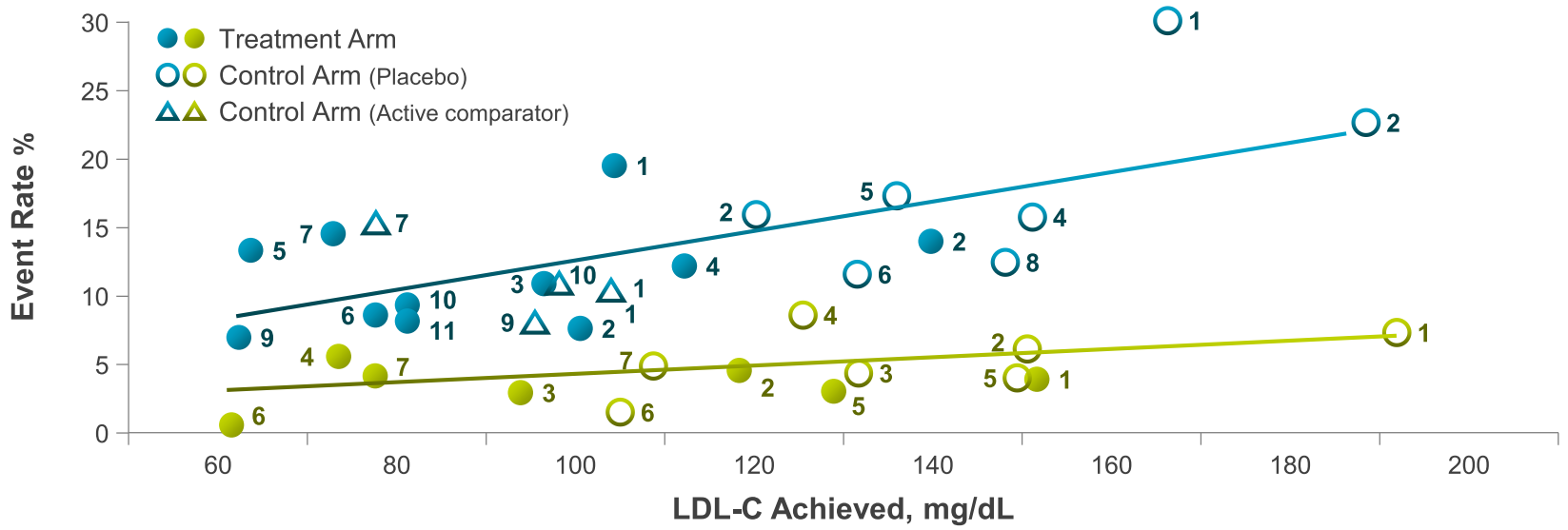
The lower cumulative exposure to LDL-c can slow plaque progression and delay the onset of myocardial infarction and other acute coronary syndromes.



Reference. 1. Frence, Graham, Tokgozoglu, Catapano JACC 2018; 92: 1141-1156

Lowering LDL-C levels in patients with or without prior CV events has been shown to significantly improve CV outcomes

From a meta-analysis of randomized controlled trials of statins used in primary (N=7) and secondary (N=11) prevention, produced by the NIH/ACC/AHA Task Force[1]



Secondary Prevention

1. POSCH (1990)
2. 4S (1994)
3. CARE (1996)
4. LIPID (1998)
5. MIRACL (2001)
6. HPS (2002)
7. A to Z (2004)
8. ALLIANCE (2004)
9. PROVE-IT (2004)
10. IDEAL (2005)
11. TNT (2005)

Primary Prevention

1. WOSCOPS (1995)
2. AFCAPS (1998)
3. ASCOT (2003)
4. CARDS (2006)
5. MEGA (2006)
6. JUPITER (2008)
7. SHARP (2011)

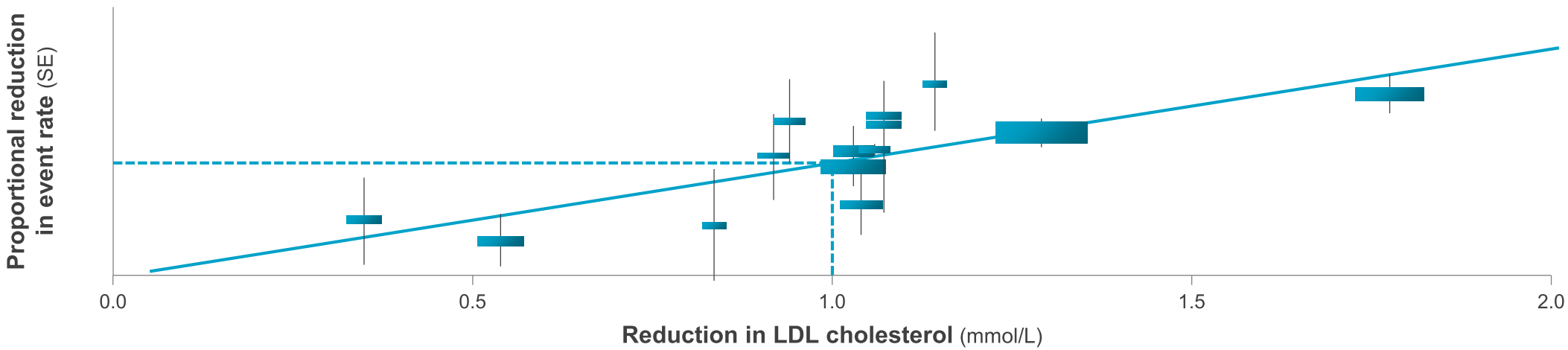
Lowering LDL-C levels in patients with (secondary prevention) **or without** (primary prevention) **prior CV events has been shown to significantly improve CV outcomes**

Reference. 1. Raymond C, *et al*. Clev Clin J Med. 2014;81:11–19.

There is a linear relationship between reduction in major CV events and LDL-C reduction in statin trials

A meta-analysis of data from 14 randomized controlled trials (RCT) of statins including 90,056 participants. Weighted estimates were obtained of effects on different clinical outcomes per 1.0 mmol/L reduction in LDL-C[1]

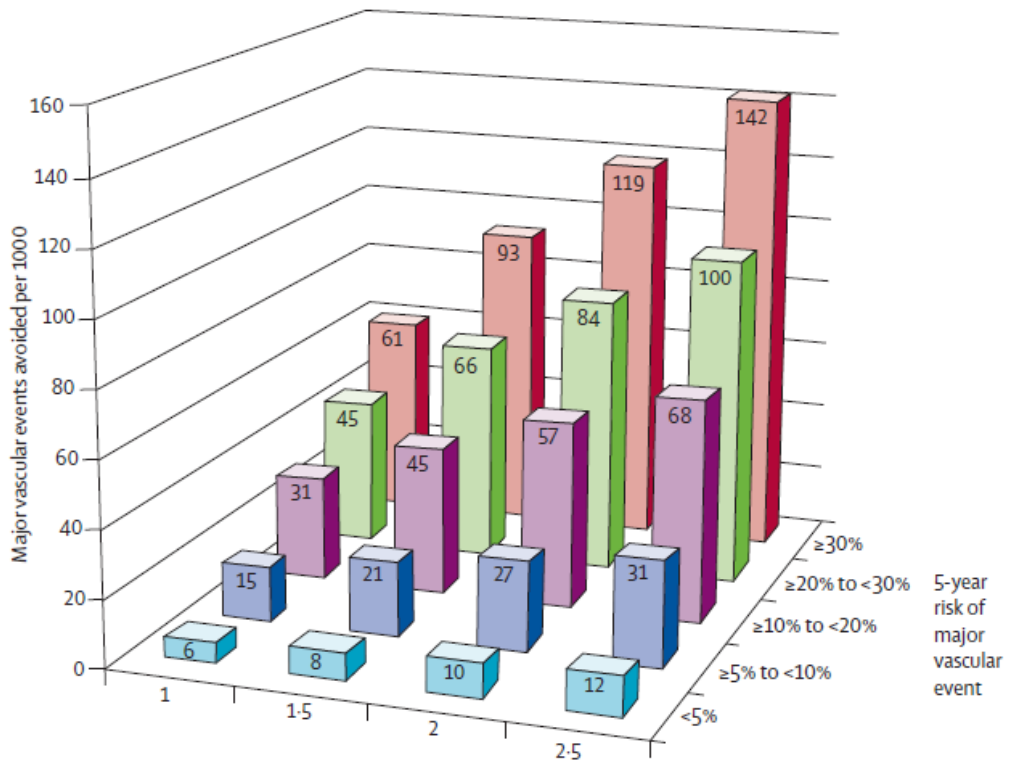
Major Vascular Events



A later meta-analysis of 26 RCTs involving 170,000 participants demonstrated that with every 1 mmol/L (39 mg/dL) **reduction in LDL-C, statins produce a relative risk reduction in major CV events of 22% at 1 year** (standard statin dose vs. control)[2]

Reference. 1. Cholesterol Treatment Trialists' (CTT) Collaboration. Lancet. 2005;366:1267–78. 2. Cholesterol Treatment Trialists' (CTT) Collaboration. Lancet. 2010;376:1670–81.

Reduction of LDL-C with statins reduce the risk of major vascular events; CTTC



Study Design

A meta-analysis by CTT included individual patient data from 22 trials of statin versus control (n=134,537; mean LDL-C difference 1.08 mmol/L; median follow up 4.8 years) and five trials more versus less statin (n=39,612; difference 0.51 mmol/L; 5.1 years)

Results

Reduction of LDL-C with statins reduced the risk of major vascular events
(RR, 0.79; 95% CI: 0.77-0.81; per 1.0 mmol/L reduction)

- there was no evidence that a reduction of LDL-C with statins increased cancer incidence, cancer mortality or other non-vascular mortality
- Higher absolute risk = greater absolute reduction = lower NNT

In these individual, each 1 mmol/L reduction in LDL-C produced an absolute reduction in major vascular events of about 11 per 1,000 over 5 years.

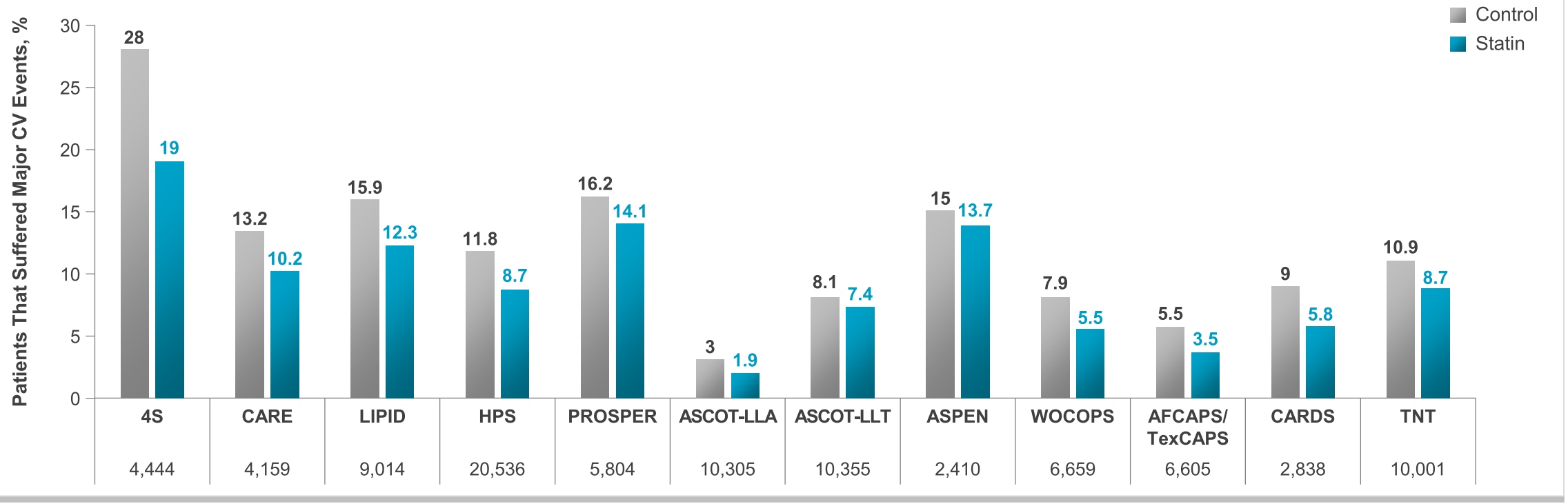
Benefit of LDL-C reduction through statin therapy exceed and known hazards

Reference. 1. Cholesterol Treatment Trialists(CTT) Collaboration, *et al*. Lancet. 2012; 380(9841);581.90.

CONTENTS

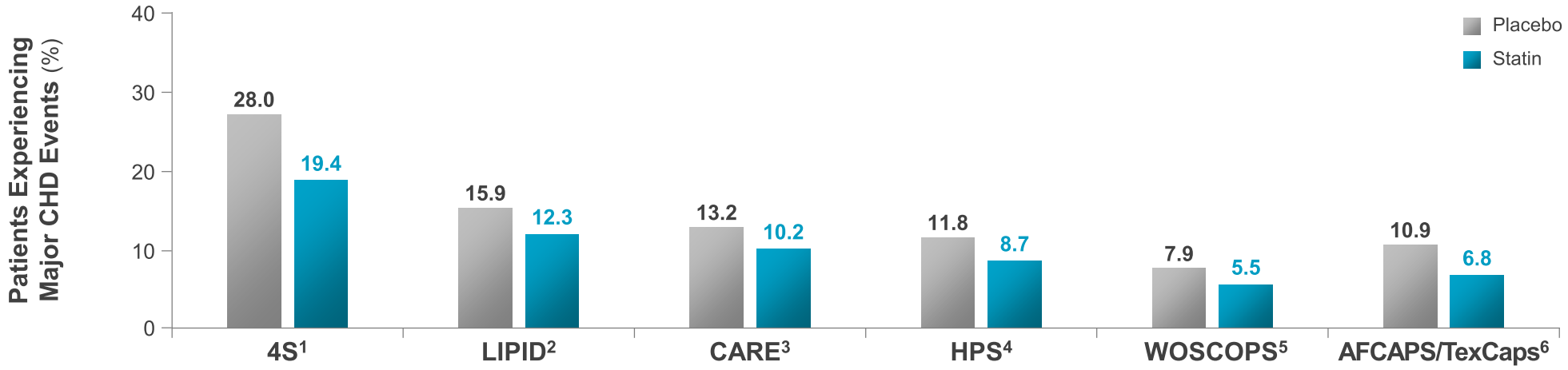
Residual CV Risk Remains Despite Treatment with Lipid Lowering Agents

CV Event Rates in Large Prospective Treatment Studies



Reference. 1. Sampson UK, *et al*. Curr Atheroscler Rep. 2012;14(1):1-10.

Patients experiencing major CHD events[1-6]

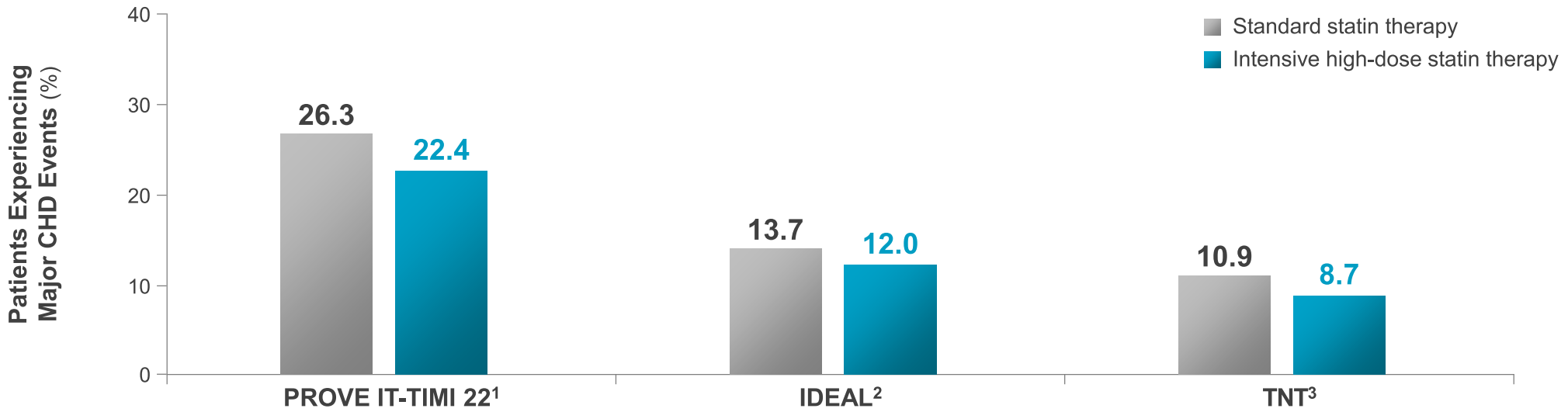


	4S[1]	LIPID[2]	CARE[3]	HPS[4]	WOSCOPS[5]	AFCAPS/TexCaps[6]
n	4,444	9,014	4,159	20,536	6,595	6,605
△LDL	-35%	-25%	-28%	-29%	-26%	-25%

Many CHD events still occur in statin-treated patients

References. 1. 4S Group. Lancet. 1994;344(8934):1383-1389. 2. LIPID Study Group. New England Journal of Medicine. 1998;339(19):1349-1357. 3. Sacks FM, *et al*. New England Journal of Medicine. 1996;335(14):1001-1009. 4. HPS Collaborative Group. Lancet. 2002;360(9326):7-22. 5. Shepherd J, *et al*. New England Journal of Medicine. 1995;333(20):1301-1307. 6. Downs JR, *et al*. Journal of the American Medical Association. 1998;279(20):1615-1622.

Patients experiencing major CVD events



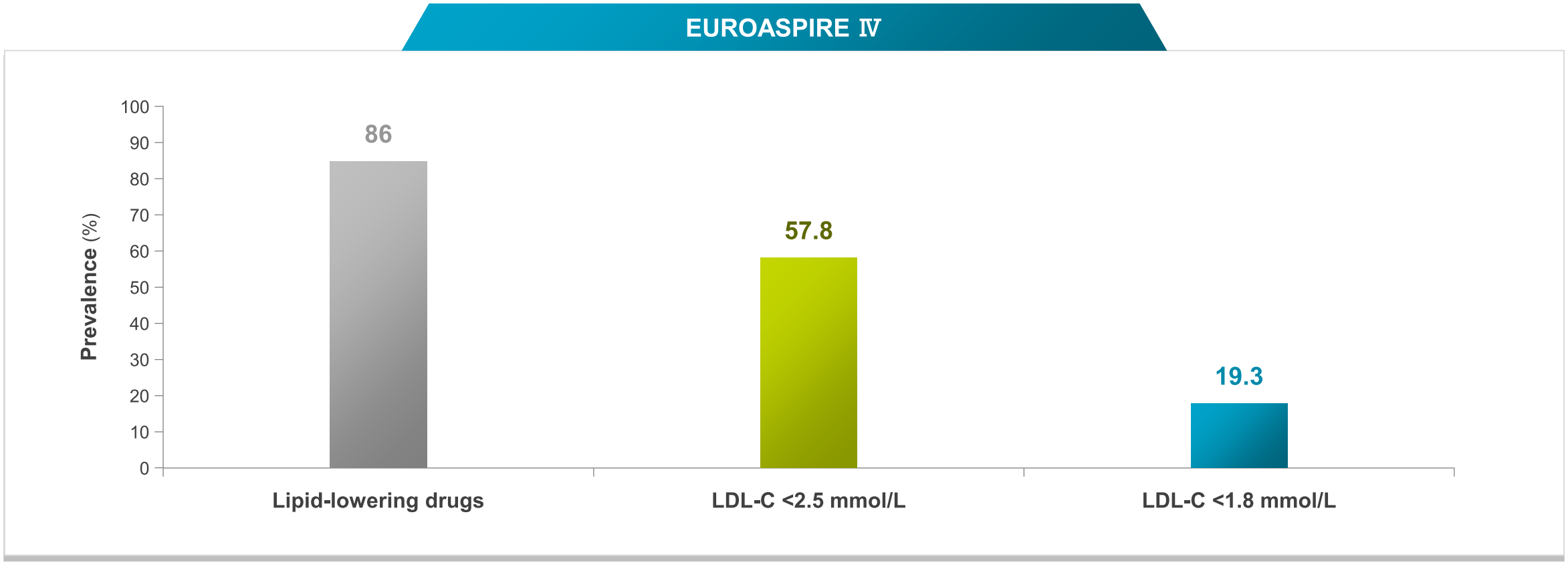
n	4,162		8,888		10,001	
LDL-C* mg/dL	95	62	104	81	101	77

Although intensive high-dose statin therapy reduced LDL-C concentration and the risk of any CHD events, but there were no significant in cardiovascular or all-cause mortality [2]

*Mean or median LDL-C after treatment

Reference. 1. Cannon CP, *et al*. New England Journal of Medicine. 2004;350(15):1495-1504. 2. Pedersen TR, *et al*. Journal of the American Medical Association. 2005;294(19):2437-2445. 3. LaRosa JC, *et al*. New England Journal of Medicne. 2005;352(14):1425-1435.

Post-ACS, only 1/5 patients achieve LDL-C <70 mg/dL despite statin prescription and good adherence

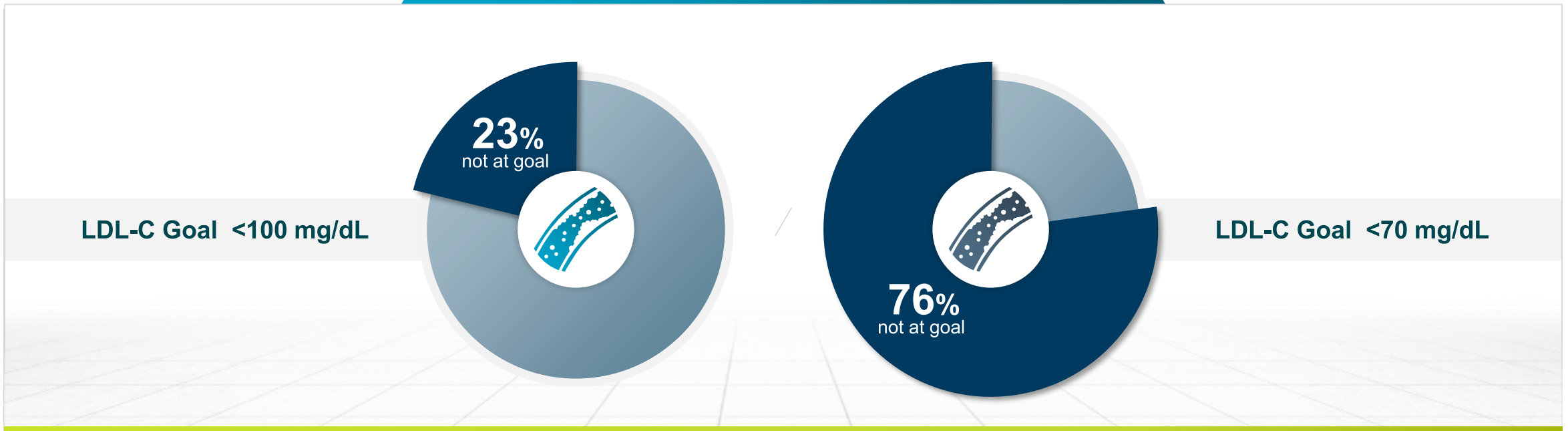


ACS, acute coronary syndrome; EUROASPIRE IV, A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries; LDL-C, low-density lipoprotein cholesterol

Reference. 1. Reiner EA, *et al.*

Not reaching their recommended LDL-C goal with statin therapy

High risk patients[1]



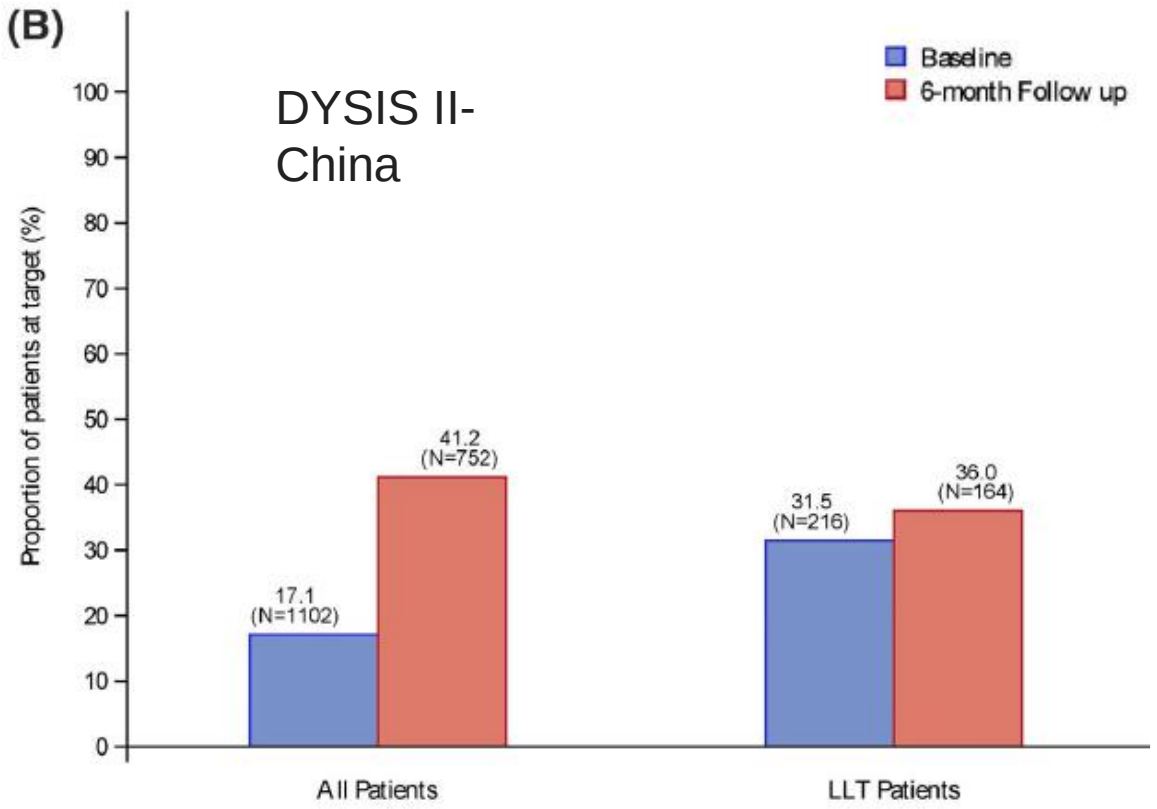
- **Statins are the standard of care for HC management**
- **However, many patients are not reaching their recommended LDL-C goal with statin therapy[1-3]**

CV, cardiovascular; HC, hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol

Reference. 1. Jones PH, *et al*. Journal of the American Heart Association. 2012;1(6):e001800. doi: 10.1161/JAHA.112.001800. 2. Stein EA, *et al*. American Journal of Cardiology. 2003;92(11):1287–1293. 3. Pijlman AH, *et al*. Atherosclerosis. 2010;209(1):189–194.

Clinical unmet needs

Not reaching their recommended LDL-C goal with statin therapy In Asian countries



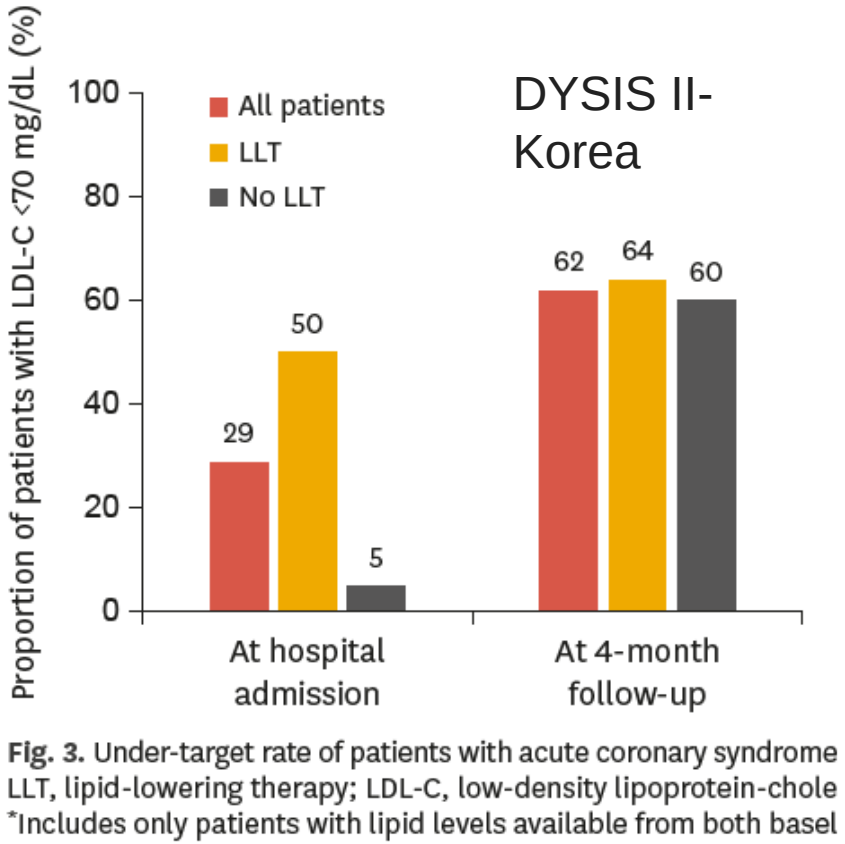


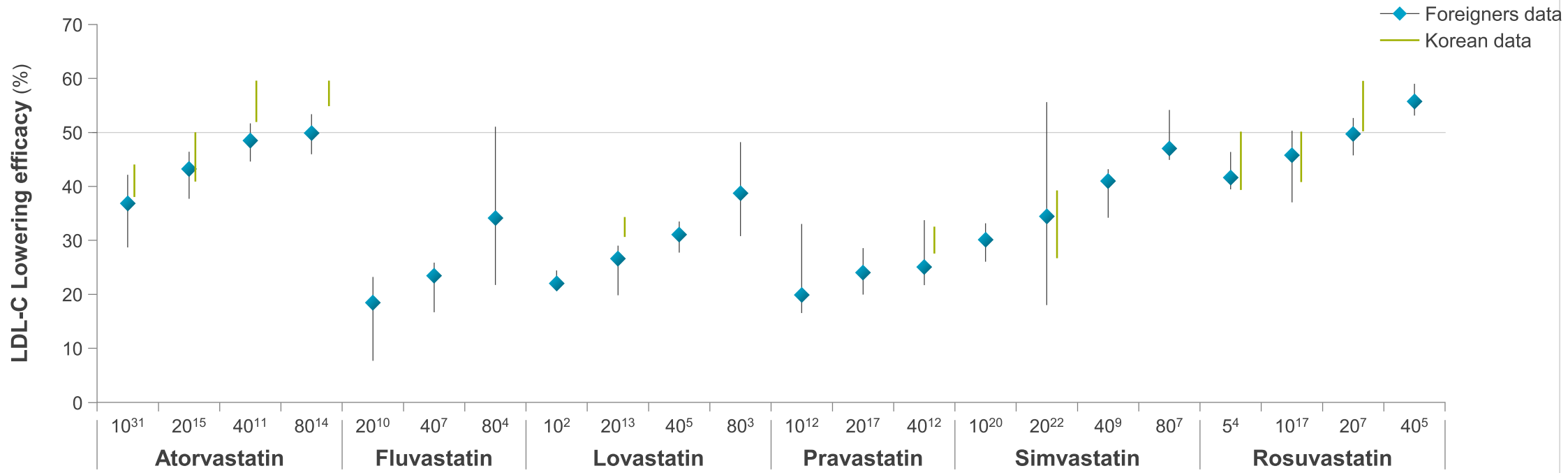
Fig. 3. Under-target rate of patients with acute coronary syndrome
LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein-chole
*Includes only patients with lipid levels available from both basel

Clin Cardiol . 2021 Nov;44(11):1575-1585

J Lipid Atheroscler. 2019 Sep;8(2):242-251

Meta-analysis of statins

Comparison of LDL cholesterol lowering rates by each statin in foreigners and Korean

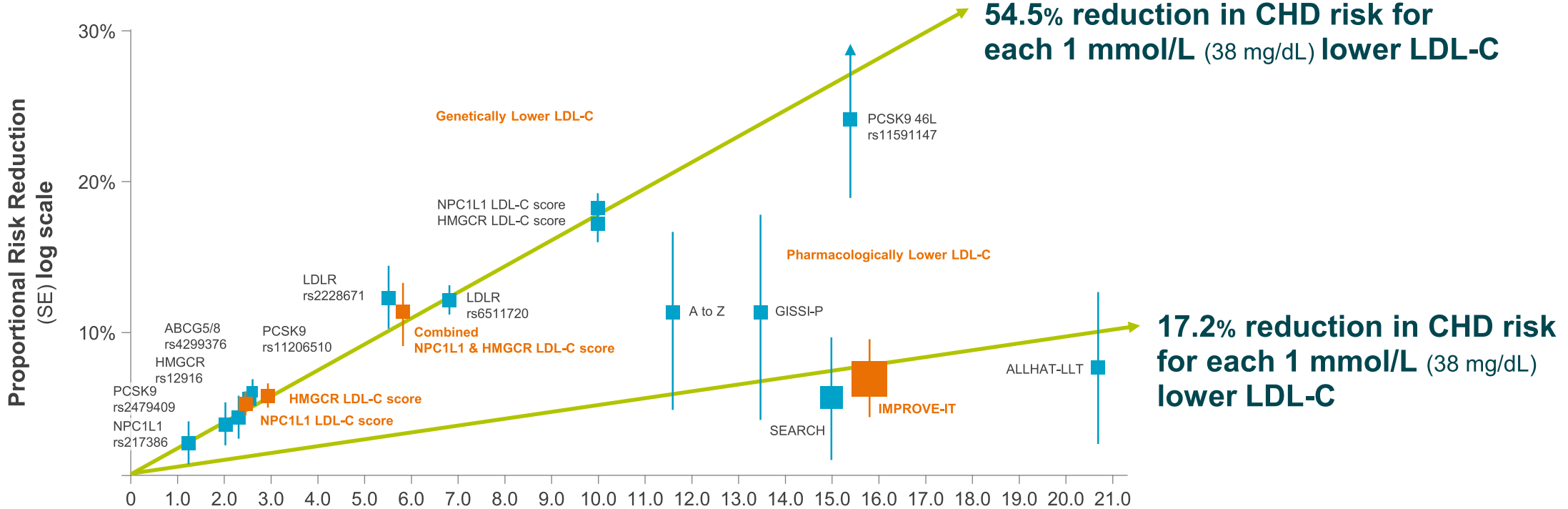


(Modified from reference 27. Permission from John Wiley and Sons Inc.)

Reference. 1. Weng TC, *et al*, j clin pharm ther. 2010;35:139-51, 한국지질동맥경화학회

The lower the better

Clinical benefit of lower LDL is determined by absolute exposure to lower LDL



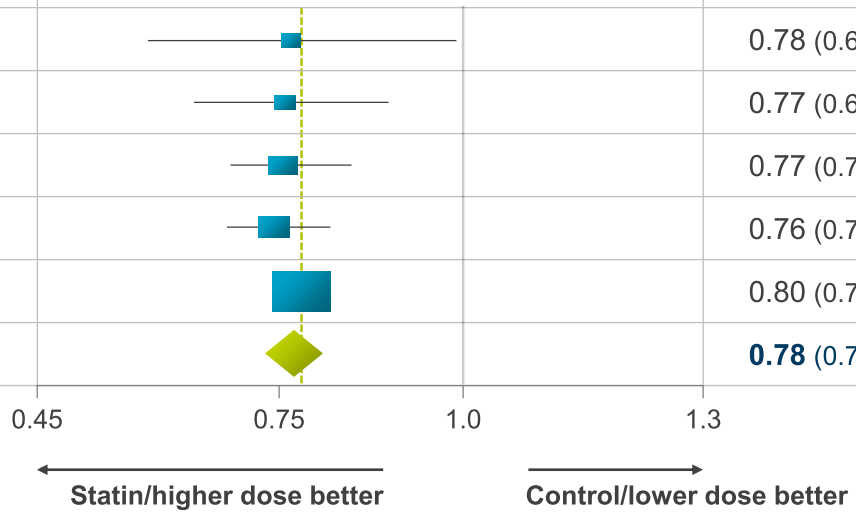
Reference. 1. Ference *et al*. J Am Coll Cardiol 2015;65:1552–1561.

The lower the better

Consistent CV risk reduction independent of baseline LDL-C level

CTT meta-analysis, N=169,138 in 26 trials

Baseline LDL-C	Events (% per annum)		RR (CI) per 39 mg/dL reduction in LDL-C
	Statin/Higher	Control/Lower	
All trials combined			
< 77 mg/dL	910 (4.1%)	1,012 (4.6%)	0.78 (0.61, 0.99)
≥77 to < 97 mg/dL	1,528 (3.6%)	1,729 (4.2%)	0.77 (0.67, 0.89)
≥97 to < 116 mg/dL	1,866 (3.3%)	2,225 (4.0%)	0.77 (0.70, 0.85)
≥116 to < 135 mg/dL	2,007 (3.2%)	2,454 (4.0%)	0.76 (0.70, 0.82)
≥135 mg/dL	4,508 (3.0%)	5,736 (3.6%)	0.80 (0.76, 0.83)
Total	**10,973** (3.2%)	**13,350** (4.0%)	**0.78** (0.76, 0.80)



Reference. 1. CTT Collaboration. Lancet 2010;376:1670–81.

The lower the better

Further risk Reduction with statin and non-statin agents in patients with LDL-C ≤70 mg/dL

Meta-analysis of lipid-lowering trials for further lowering LDL-C levels in patients with median LDL-C levels of ≤70 mg/dL

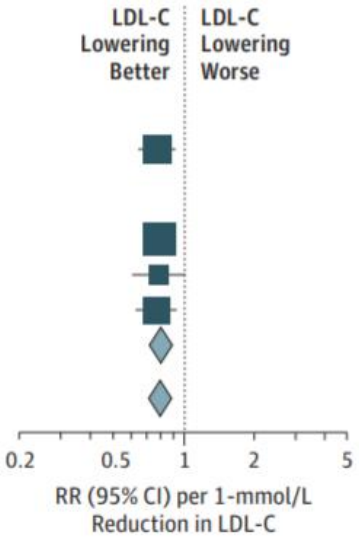
Table 1. Trial Characteristics

Trial	No. of Participants	Type of Intervention	Drug	Achieved LDL-C, mmol/L	
				Control Arm	Experimental Arm
CTTC (<2 mmol/L)	NR	HMGCR inhibitor (statin)	Various	1.7[a]	NR
IMPROVE-IT	18 144	NPC1L1 inhibitor	Ezetimibe	1.8[c]	1.4
FOURIER (<1.8 mmol/L)	2034	PCSK9 inhibitor	Evolocumab	1.7[d]	0.5
REVEAL	30 449	CETP inhibitor	Anacetrapib	1.6[e]	1.4

Figure 1. Effect of Low-Density Lipoprotein Cholesterol (LDL-C) Lowering on the Risk of Major Vascular Events

A Meta-analysis of effect of 1-mmol/L LDL-C lowering on the risk of major vascular events

Trial	Events, % per annum		RR (95% CI)	P Value
	Experimental Arm	Control Arm		
Statins				
CTTC <2 mmol/L subgroup	910 (4.1)	1012 (4.6)	0.78 (0.65-0.94)	
Nonstatin LDL-C lowering				
IMPROVE-IT	2455 (4.5)	2649 (4.9)	0.79 (0.67-0.93)	
FOURIER <1.8 mmol/L subgroup	81 (3.7)	103 (4.9)	0.80 (0.61-1.04)	
REVEAL	2068 (3.3)	2214 (3.5)	0.77 (0.63-0.96)	
Summary	4604	4966	0.79 (0.70-0.88)	P < .001
Overall summary	**5514**	**5978**	**0.79 (0.71-0.87)**	**P < .001**



1. JAMA Cardiol. 2018;3(9):823-828. doi:10.1001/jamacardio.2018.2258

The lower the better

Life-long low LDL-C is associated with significant reductions in cardiovascular risk

- **Modern hunter-gatherer populations with life-long LDL-C levels of approximately 50-75 mg/dL** (1.3-1.9 mmol/L) **show little evidence of atherosclerosis**[1]

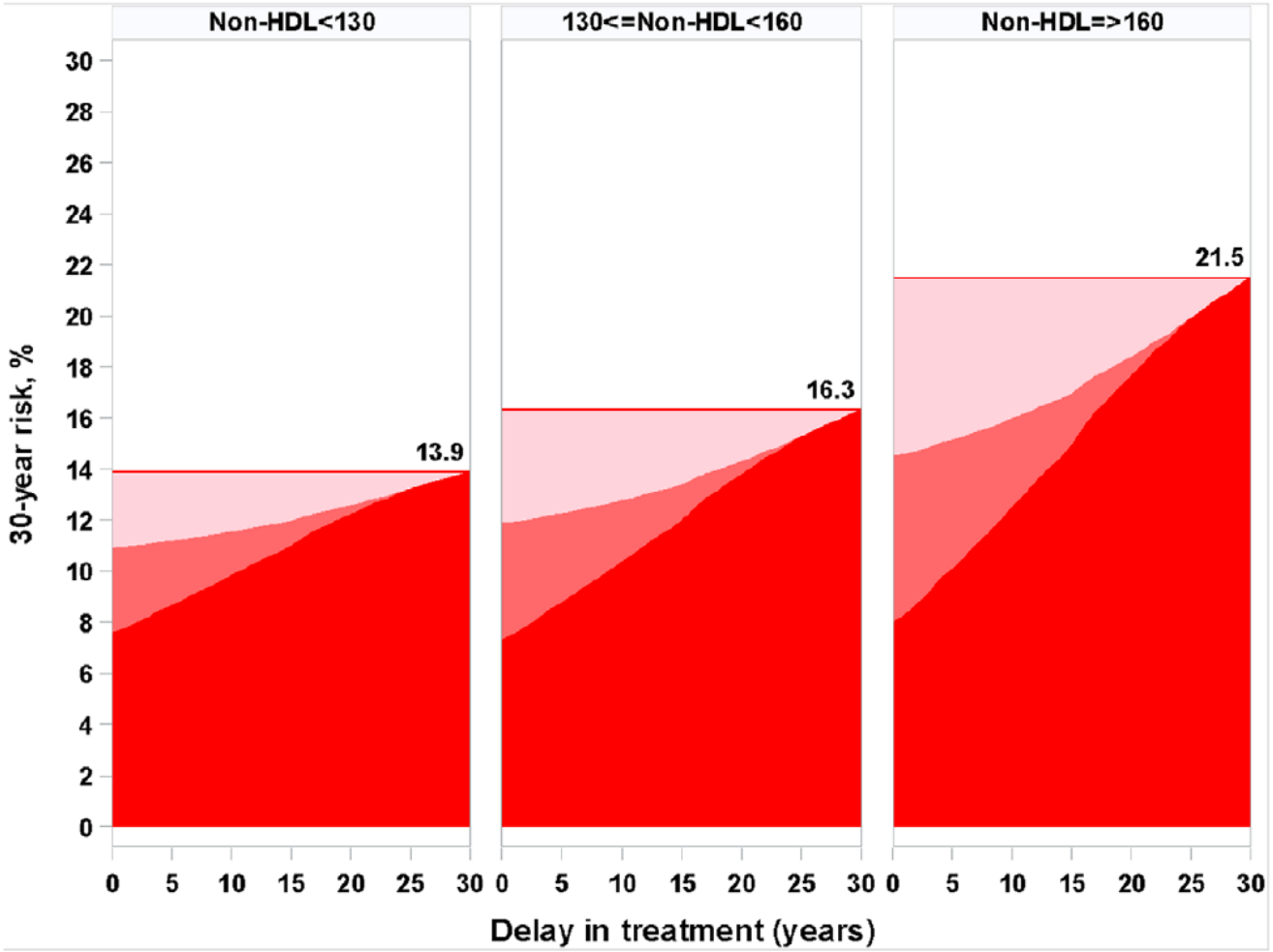
- **People with genetically determined low levels of LDL-C have shown that life-long low LDL-C levels are associated with low CV risk**[2,3]

- **A meta-analysis of 312,321 subjects showed that long-term exposure to naturally low levels of LDL-C, resulting from 9 different polymorphisms in 6 genes, was associated with a 54.5% reduction in the risk of CHD for each mmol/L lower of LDL-C**[2]
  - The latter study suggests a 3-fold greater reduction in the risk of CHD per unit lower LDL-C than that observed during treatment with a statin started later in life[2]

Reference. 1. O'Keefe JH, *et al*. 2004;43(11):2142–2146. 2. Ference BA, *et al*. J Am Coll Cardiol. 2012;60:2631–2639. 3. Benn M, *et al*. J Am Coll Cardiol. 2010;55:2833–2842.

The lower the better

Early initiation of statin therapy for long-term benefit



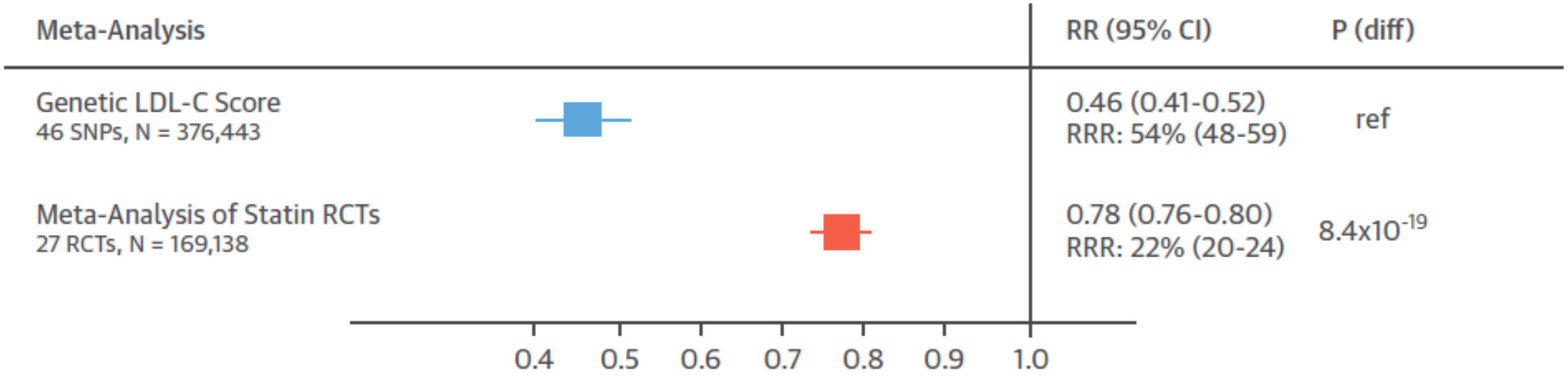
30-year risk reduction as a function of delay in initiation of lipid lowering by 40% (age 50-59 years, 10-year CV risk <7.5%)

Circulation . 2020 Sep;142(9):827-837

The lower the better

Life-long low LDL-C is associated with significant reductions in cardiovascular risk

FIGURE 6 Comparison of Proportional Risk Reduction in Cardiovascular Events per mmol/l Lower LDL by Duration of Exposure to Lower LDL



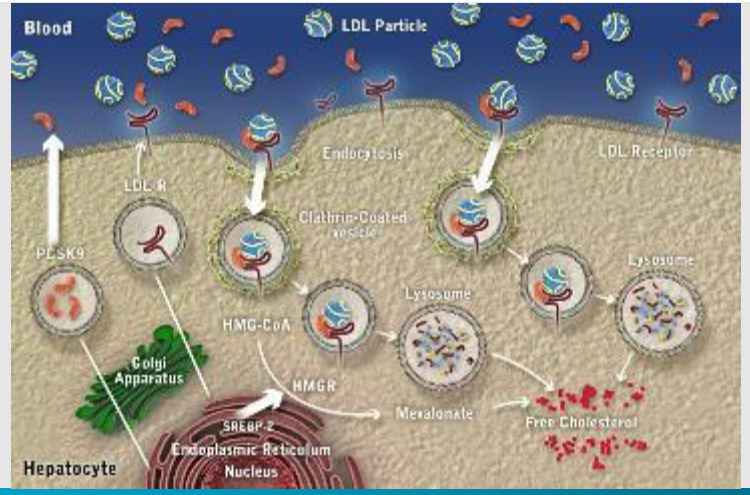
Long-term exposure to lower LDL-C associated with much greater reduction in CHD risk per unit lower LDL-C ($p_{(difference)} = 8.4x10^{-19}$)

J Am Coll Cardiol 2012;60: 2631–9
J Am Coll Cardiol 2018;72:1141–56

PCSK9 mutations and effect on LDL metabolism

Gain of Function

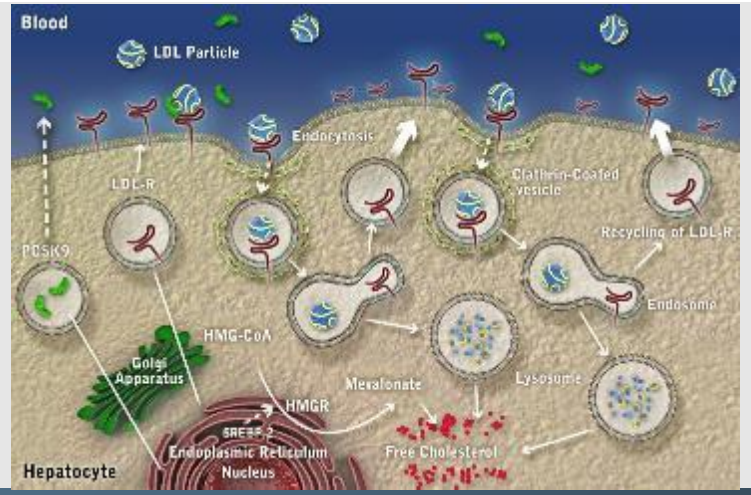
↓LDL-R levels ↓LDL clearance



↑LDL High risk for atherosclerosis and coronary heart disease (CHD)

Loss of Function

↑LDL-R levels ↑LDL clearance



↓LDL Protection from atherosclerosis and CHD

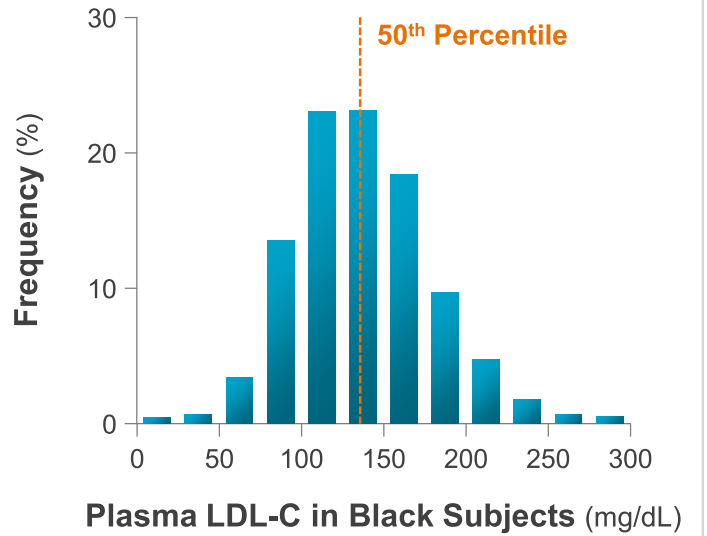
LDL, Low-density lipoprotein.

Reference. 1. Catapano AL and Papadopoulos N. Atherosclerosis. 2013;228(1):18–28. 2. Soufi M, *et al*. Gene. 2013;521(1):200–3.

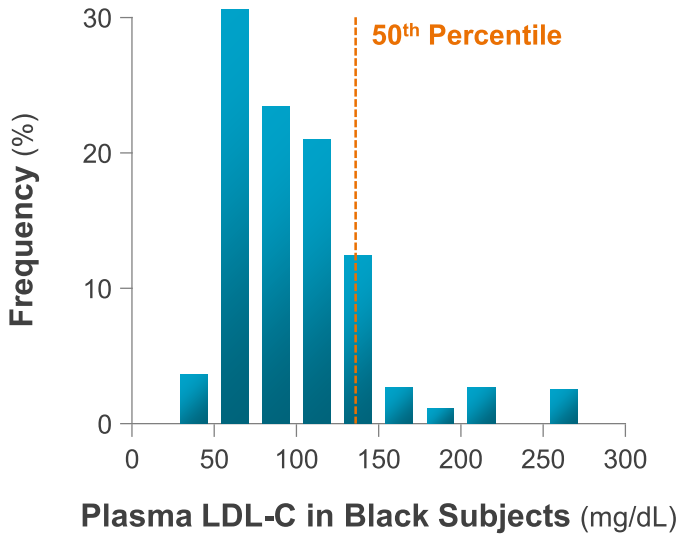
Cardiovascular benefits of PCSK9 loss of function mutations

- Prospective study of plasma LDL-C levels and incidence of CHD according to the presence or absence of a PCSK0142X or PCSK9679X allele (N=3,278) taken from a longitudinal, biracial cohort study designed to assess subclinical and clinical atherosclerosis (N=15,792)

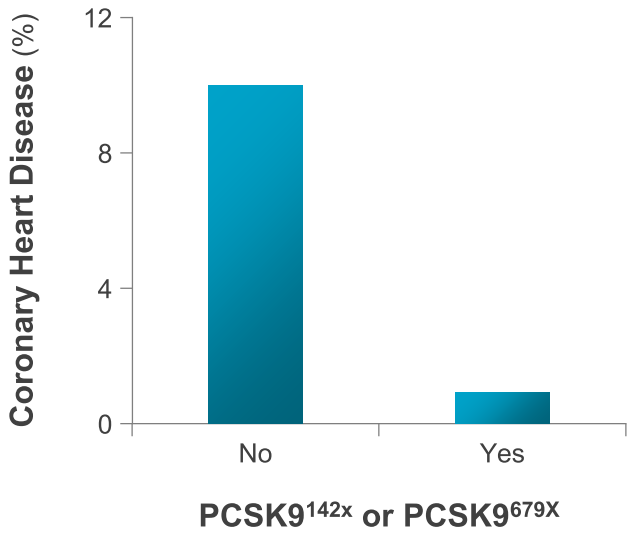
No Nonsense Mutation (N=3,278)



PCSK9^{142x} or PCSK9^{679X} (N=85)

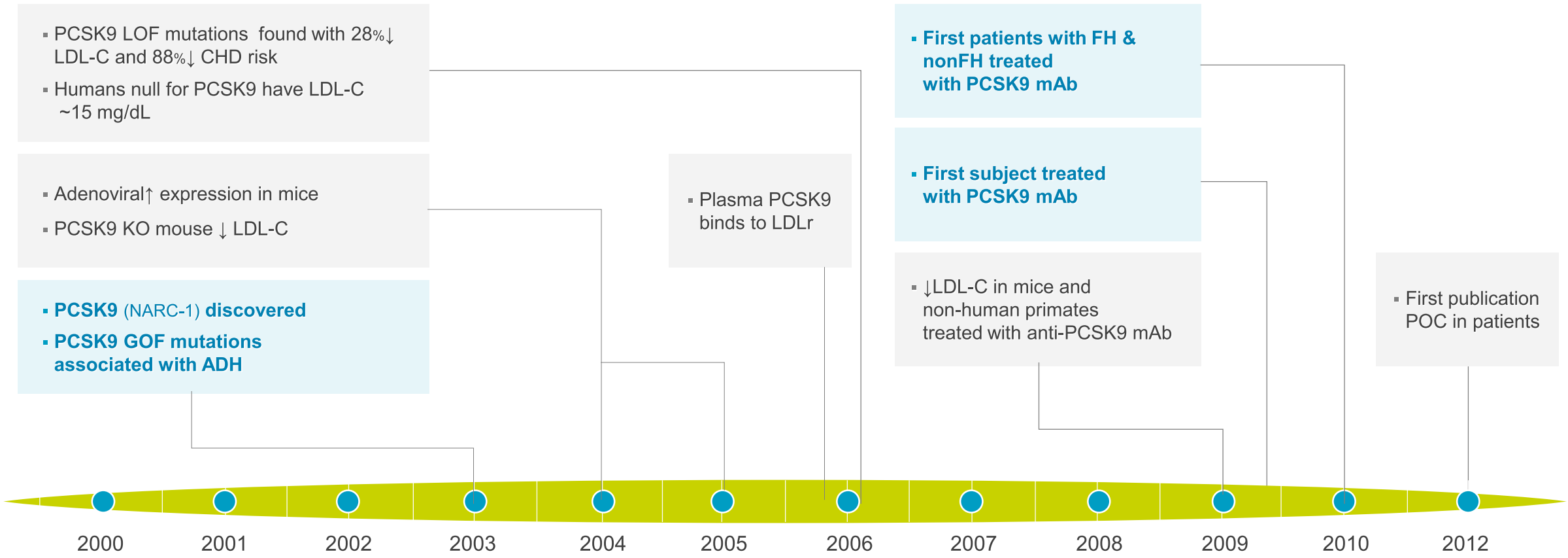


88% reduction in the risk of CHD



Reference. 1. Cohen J, *et al*. N Engl J Med 2006;354:1264–1272

PCSK9 Inhibition Rapid Progress From Discovery to Clinic



Reference. 1. Seidah NG. Proc Natl Acad Sci USA 2003;100(3):928-33, 2. Abifadel M. Nat Genet 2003;34(2):154-6, 3. Maxwell KN. Proc Natl Acad Sci USA 2004;101(18):7100-5, 4. Rashid S. Proc Natl Acad Sci USA 2005;102(15):5374-79, 5. Lagace TA *et al*. JCI 2006;116:2995-3005 Cohen JC. N Engl J Med 2006;354(12):1264-72, 6. Zhao Z. Am J Hum Genet 2006;79(3):514-23, Hooper AJ. Atherosclerosis 2007;193(2):445-8, 7. Chan JC. Proc Natl Acad Sci USA 2009;106(24):9820-5; Stein et al N Engl J Med 2012;366:1108-18

PCSK 9 inhibitor

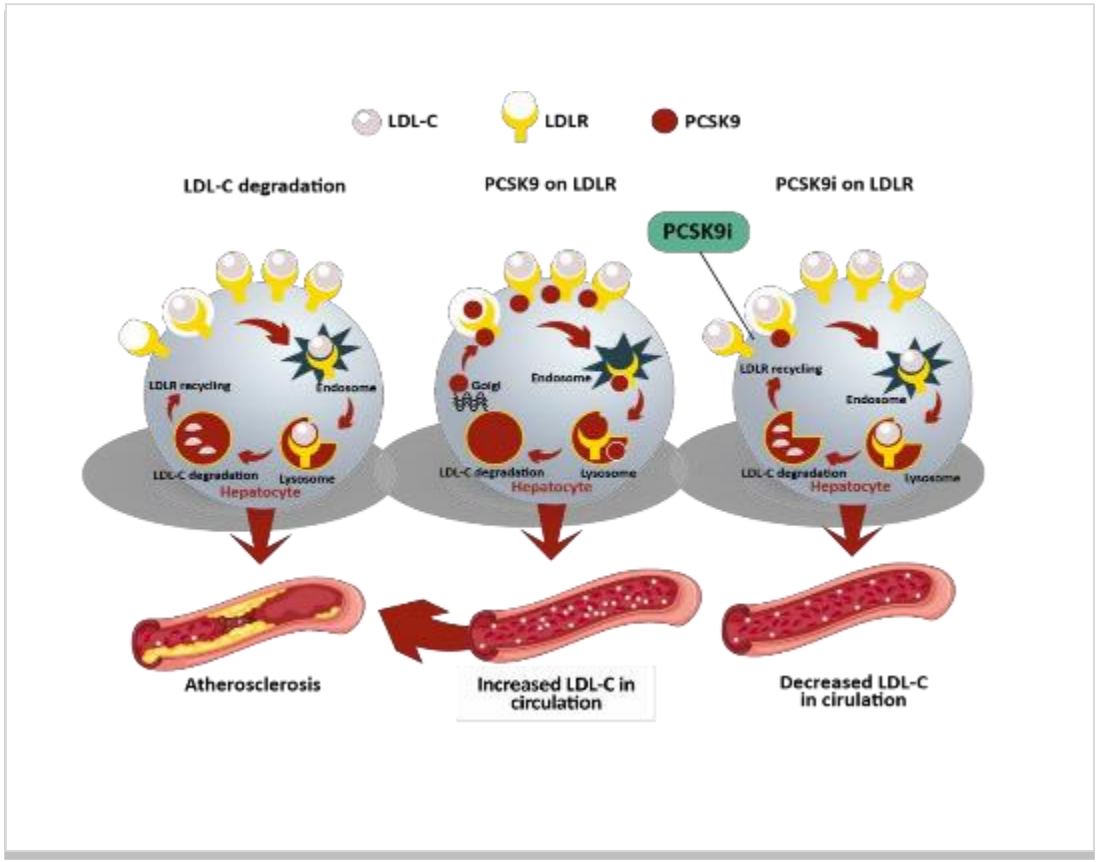
PRALUENT® has an established mechanism of action

Alirocumab makes LDL-R recycle to the surface of hepatocyte, which means lowering LDL-C consistently

- PCSK9 inhibition is an effective way of reducing LDL-C
- PSCK9 inhibitors decrease LDL-R degradation, resulting in improved lipid metabolism, reducing plasma LDL-C, leading to reduced risk of atherosclerosis[1]

Specific characteristics of PRALUENT®

- **Time to steady state:** Reached after 2 or 3 doses[2]
- **High bioavailability:** Absolute bioavailability of ~85%[2]
- **High binding affinity[2]:** Dissociation constant of 0.58 nM[3]



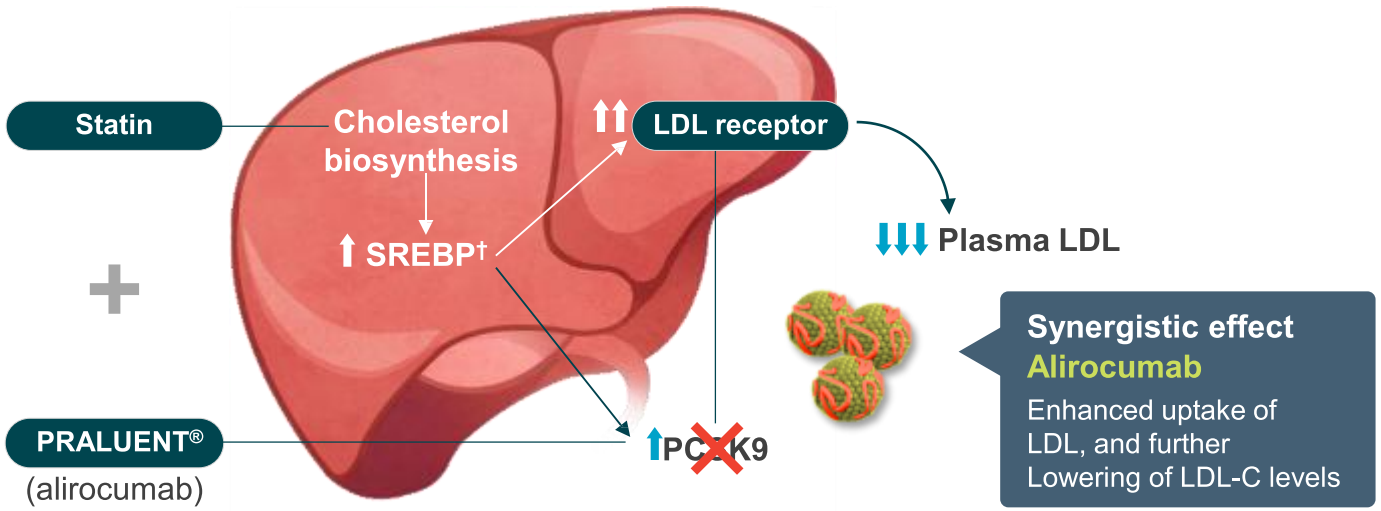
PCSK9, proprotein convertase subtilisin/kexin type 9; LDL-R, low-density lipoprotein receptor; LDL-C, low-density lipoprotein cholesterol

Reference. 1. Adapted from Amput P, *et al*. 2019.

Synergistic effect of PCSK9 inhibitor and Statin

Alirocumab would be predicted to lower LDL-C levels alone and in combination with statins by increasing cell-surface expression of LDLR

Lowering plasma LDL-C levels by increasing cellular LDL-Rs



*SREBP transcription factor : upregulates transcription of the LDL-R → LDL-C ↓

Reference. 1. Maxwell KN, *et al*. Circ Res. 2012;111(3):274-277.

LDL-C lowering agents trials

Again, focus on ‘Cholesterol’, not ‘Statin only’
Proven benefit of non-statin agent in ACS patients

- **IMPROVE-IT:** ezetimibe + simvastatin vs. simvastatin, after ACS Primary endpoint: CV death, MI, unstable angina requiring hospitalization, coronary revascularization (≥30 days), stroke. Median follow-up: 6 years **HR: 0.936** (95%CI: 0.89-0.99), *P*=0.016

- **FOURIER trial:** evolocumab vs. placebo, plus background statin therapy after ACS Primary endpoint: CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. Median follow-up: 2.2 years **HR: 0.85** (95%CI: 0.79-0.99), *P*<0.001

- **ODYSSEY OUTCOMES trial:** alirocumab vs placebo, on top of high-intensity statin therapy, after ACS Primary endpoint: death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. Median follow-up: 2.8 years **HR: 0.85** (95%CI: 0.78-0.93), *P*<0.001

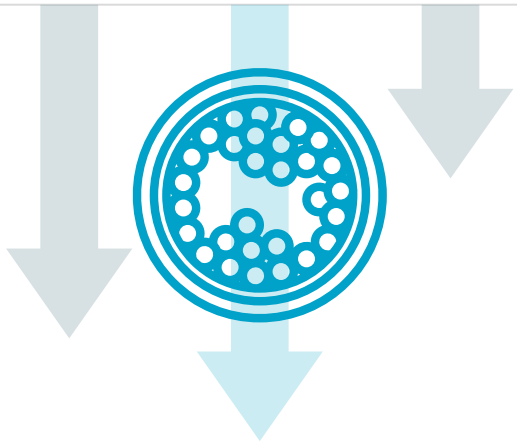
Reference. 1. . Christopher P. C. *et al*. N Engl J Med 2015; 372:2387-2397 2. Marc S. S, *et al*. N Engl J Med 2017; 376:1713-1722 3 G. Schwartz., *et al*. N Engl J Med 2018; 379:2097-2107

CONTENTS

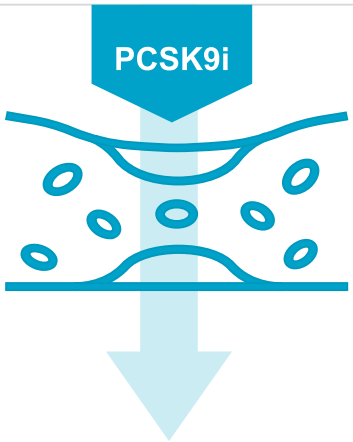
2019 ESC/EAS Guidelines

The guidelines recommend lower LDL-C goals and earlier treatment intensification for very high-risk patients not at goal.[1]

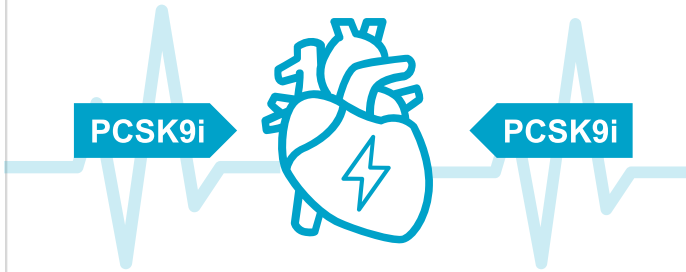
“ Three major changes in the recommendations for the management of dyslipidaemia in ACS patients[1] ”



Lower LDL-C goals for patients with ACS



Use of PCSK9i to further lower LDL-C in very high-risk patients

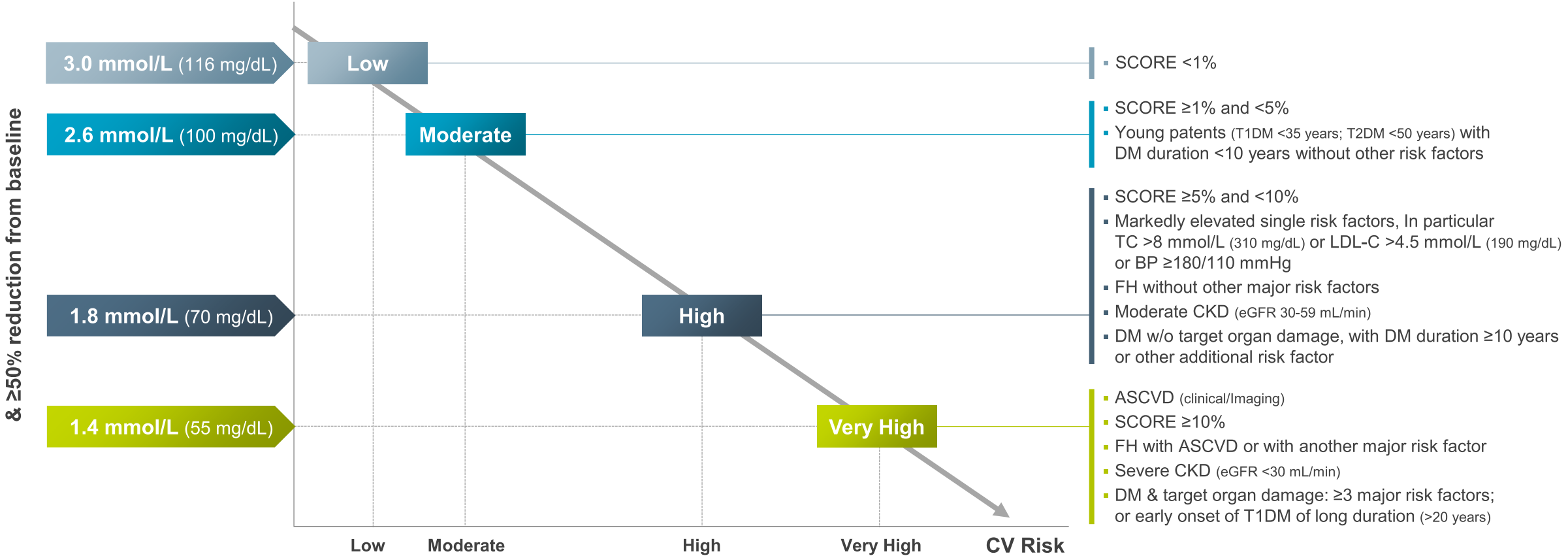


Early use of PCSK9i after an ACS event

ESC, European Society of Cardiology; EAS, European Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol; ACS, acute coronary syndrome; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

Reference. 1. Mach F, *et al*. Eur Heart J. 2020 Jan 1;41(1):111-188.

Treatment goals for LDL-C across CV risk categories



ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; SCORE, Systematic COronary Risk Evaluation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TC, total cholesterol. MAT-GLB-2002197-1.0 | October 2020

2016 and 2019 ESC/EAS risk-based LDL-C goals

	2016 LDL-C goals	2019 LDL-C goals
Low risk	<3.0 mmol/L (115 mg/dL)	
Moderate risk	<3.0 mmol/L (115 mg/dL)	<2.6 mmol/L (100 mg/dL)
High risk	50% reduction or <2.6 mmol/L (100 mg/dL)	50% reduction and <1.8 mmol/L (70 mg/dL)
Very high risk	50% reduction or <1.8 mmol/L (70 mg/dL)	50% reduction and <1.4 mmol/L (55 mg/dL)
Second CV event within 2 years	NA	50% reduction and <1.0 mmol/L (40 mg/dL)

2019 ESC/EAS Guidelines

Lower LDL-C goals are recommended for the patients with ACS.[1]

"More intensive LDL-C reduction is recommended across very high and high-risk CV categories[1]"

Class	Level	CV risk category	LDL-C goals		
I	A	In secondary prevention for patients at very high risk	Reduction of ≥50% from baseline	**and**	<55 mg/Dl (<1.4 mmol/L)
I	A	In patients at high risk	Reduction of ≥50% from baseline	**and**	<70 mg/dL (<1.8 mmol/L)

Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective; **Level A**: Data derived from multiple randomised clinical trials or meta-analyses.

Very high-risk: People with any of the following: ① Documented ASCVD, either clinical or unequivocal on imaging. **Documented ASCVD includes previous ACS** (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. ② DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years). ③ Severe CKD (eGFR <30 mL/min/1.73 m^2). ④ A calculated SCORE ≥10% for 10-year risk of fatal CVD. ⑤ FH with ASCVD or with another major risk factor; **High-risk: People with:** ① Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. ② Patients with FH without other major risk factors. ③ Patients with DM without target organ damage, with DM duration ≥10 years or another additional risk factor. ④ Moderate CKD (eGFR 3059 mL/min/1.73 m^2). ⑤ A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; SCORE, Systemic COronary Risk Evaluation; TC, total cholesterol.

Reference. 1. Mach F, *et al*. Eur Heart J. 2020 Jan 1;41(1):111-188.

2019 ESC/EAS Guidelines

PCSK9i use is recommended to further lower LDL-C in very high-risk patients, including those with ACS.[1]

"Adding a PCSK9i to maximally tolerated statins and ezetimibe is recommended by the 2019 ESC/EAS guidelines[1]"

Class	Level	CV risk category	Recommendation
I	A	In secondary prevention for patients at **very high-risk** not achieving their goal on a maximum tolerated statin and ezetimebe	A combination **with a PCSK9i** is recommended
I	C	In **very high-risk FH patients** (with ASCVD or another major risk factor) who do not achieve their goal on a maximum tolerated statin and ezetimibe	A combination **with a PCSK9i** is recommended

Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective; **Level A:** Data derived from multiple randomised clinical trials or meta-analyses; **Level C:** Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Very high-risk: People with any of the following: ① Documented ASCVD, either clinical or unequivocal on imaging. **Documented ASCVD includes previous ACS** (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. ② DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years). ③ Severe CKD (eGFR <30 mL/min/1.73 m^2). ④ A calculated SCORE ≥10% for 10-year risk of fatal CVD. ⑤ FH with ASCVD or with another major risk factor.

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; SCORE, Systemic COronary Risk Evaluation; TC, total cholesterol.

Reference. 1. Mach F, *et al*. Eur Heart J. 2020 Jan 1;41(1):111-188.

Importance of non-statin agents in the guideline

Recommendations for pharmacological low-density lipoprotein cholesterol lowering

Recommendations	Class[a]	Level[b]
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk.[32,34,38]	I	A
If the goals[c] are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.[33]	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention, patients at very-high risk not achieving their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.[119,120]	I	A

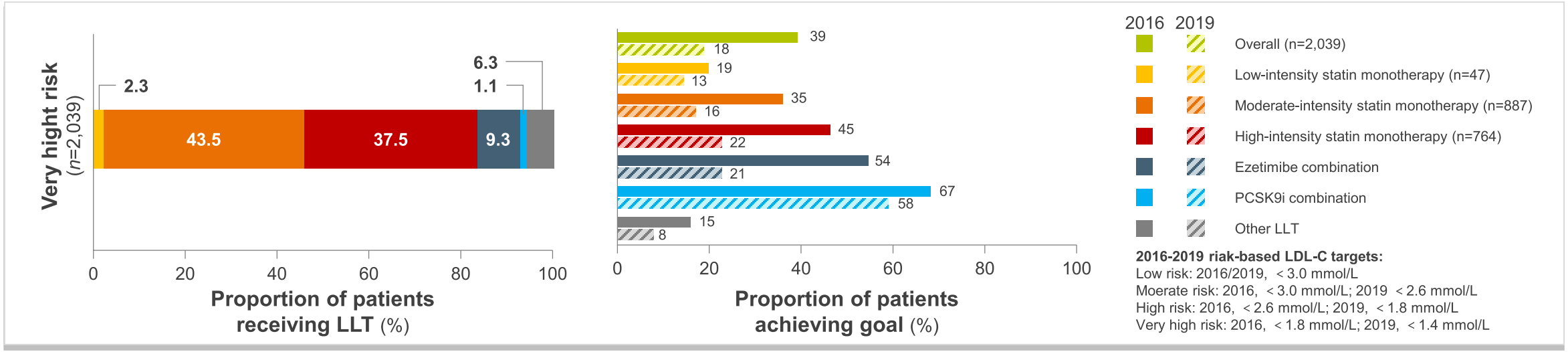
Addition of non-statin agent: ***WHEN, HOW LONG WE SHOULD USE?***

→ Considering statin tolerance, cost, adherence, and logistics for each patient and medical condition

ESC, European Society of Cardiology; EAS, European Atherosclerosis Society; ACS, acute coronary syndrome; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; LDL-C, low-density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; TIA, transient ischaemic attack; CT, computed tomography; DM, diabetes mellitus; T1DM, type 1 diabetes mellitus; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SCORE, Systematic COronary Risk Evaluation; CVD, cardiovascular disease; FH, familial hypercholesterolaemia.

Reference. 1. Mach F, *et al*. Eur Heart J. 2020 Jan 1;41(1):111-188.

DA VINCI study: combination therapy required



- With more stringent LDL-C goals by 2019 ESC/EAS guidelines, goal attainment is even lower.
- It is clear that the 2019 ESC/EAS LDL-C goal for high and very high-risk patients is largely unattainable on high-intensity statin monotherapy;
- Patients also require combination therapy

Reference. 1. Eur J Prev Cardiol 2020:doi:10.1093/eurjpc/zwaa047

DYSIS II for Global vs South Korea

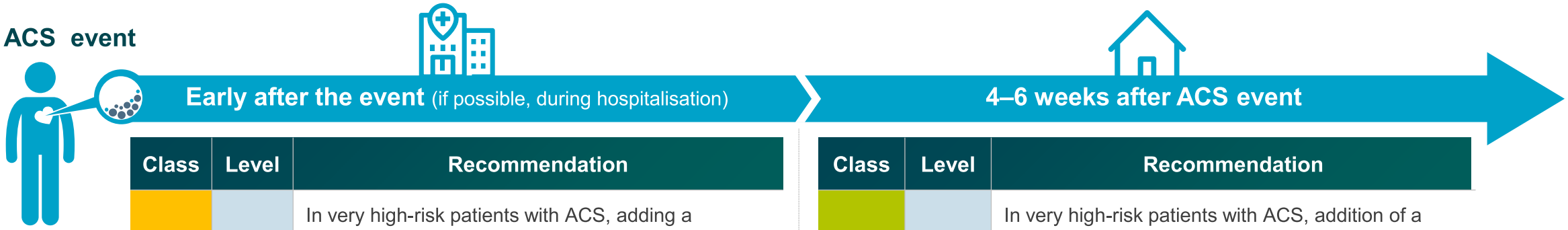
Dosage*

	Goal Attainment			
	Admission		4-Month F/U	>4-Month
	Pre ACS (LDL-C <70 or 100 mg/dL)	Post ACS (LDL-C <70mg/dL)		
Global	30% (n=3,866) »	19%	37% (n=1,071)	30% (n=6,792)
South KOREA	40% (n=308) »	24%	62% (n=79)	40% (n=500)

Reference. 1. Atherosclerosis. 2017 Nov;266:158-166

2019 ESC/EAS Guidelines

More urgency is required to initiate lipid-lowering treatment in ACS patients.[1]



Class	Level	Recommendation
IIa	C	In very high-risk patients with ACS, adding a **PCSK9i early after the event** (if possible, during hospitalisation for the event) should be considered for ACS patients whose LDL-C levels are not at goal, despite already taking maximally tolerated statins and ezetimibe

Class	Level	Recommendation
I	B	In very high-risk patients with ACS, addition of a PCSK9i is recommended if the LDL-C goal is not achieved **after 4 to 6 weeks**, despite maximally tolerated statins and ezetimibe

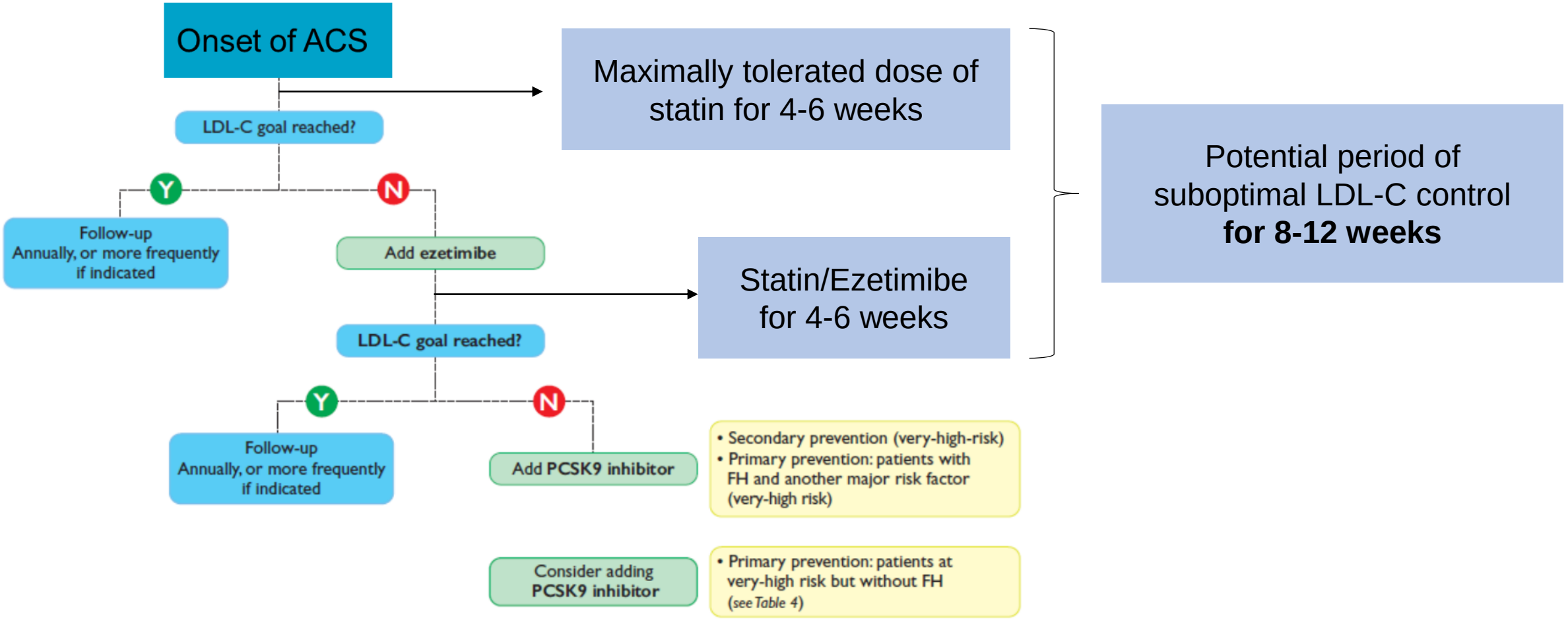
Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective; **Class IIa:** Weight of evidence/opinion is in favour of usefullness/efficacy;
Level B: Data derived from a single randomized clinical trial or large non-randomized studies; **Level C:** Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Very high-risk: People with any of the following: ① Documented ASCVD, either clinical or unequivocal on imaging. **Documented ASCVD includes previous ACS** (MI or unstable angina), stable angin a, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% st enosis), or on carotid ultrasound. ② DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years). ③ Severe CKD (eGFR <30 mL/min/1.73 m2). ④ A calculated SCORE ≥10% for 10-year risk of fatal CVD. ⑤ FH with ASCVD or with another major risk factor.

ESC, European Society of Cardiology; EAS, European Atherosclerosis Society; ACS, acute coronary syndrome; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; LDL-C, low-density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; TIA, transient ischaemic attack; CT, computed tomography; DM, diabetes mellitus; T1DM, type 1 diabetes mellitus; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SCORE, Systematic COronary Risk Evaluation; CVD, cardiovascular disease; FH, familial hypercholesterolaemia.

Reference. 1. Mach F, *et al*. Eur Heart J. 2020 Jan 1;41(1):111-188.

Current steps for cholesterol lowering in ACS patients



Proposed algorithm for further cholesterol lowering in ACS patients

During admission of ACS

Start MTD Statin/Ezetimibe

*+ PCSK9i single shot (in high risk features**)*

After PCSK9i injection

Recheck LDL-C level after 8 weeks
Consider to re-start PCSK9i

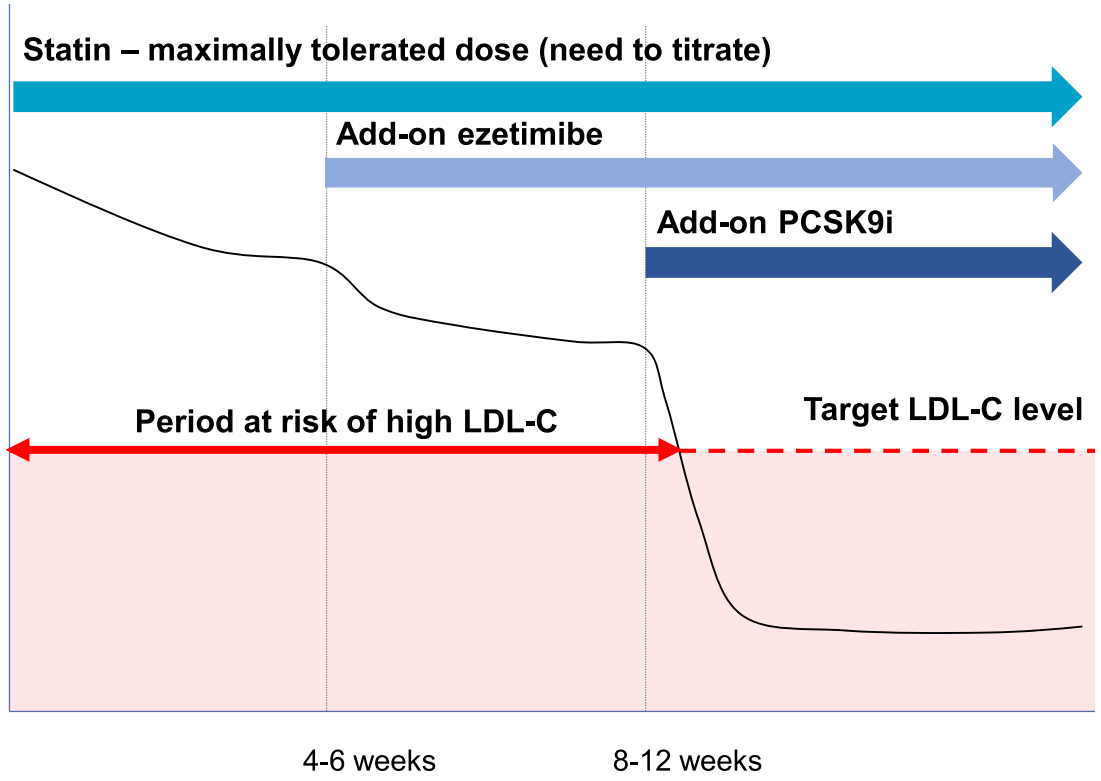
No PCSK9i injection

Recheck LDL-C level after 4-6 weeks
Consider to start PCSK9i

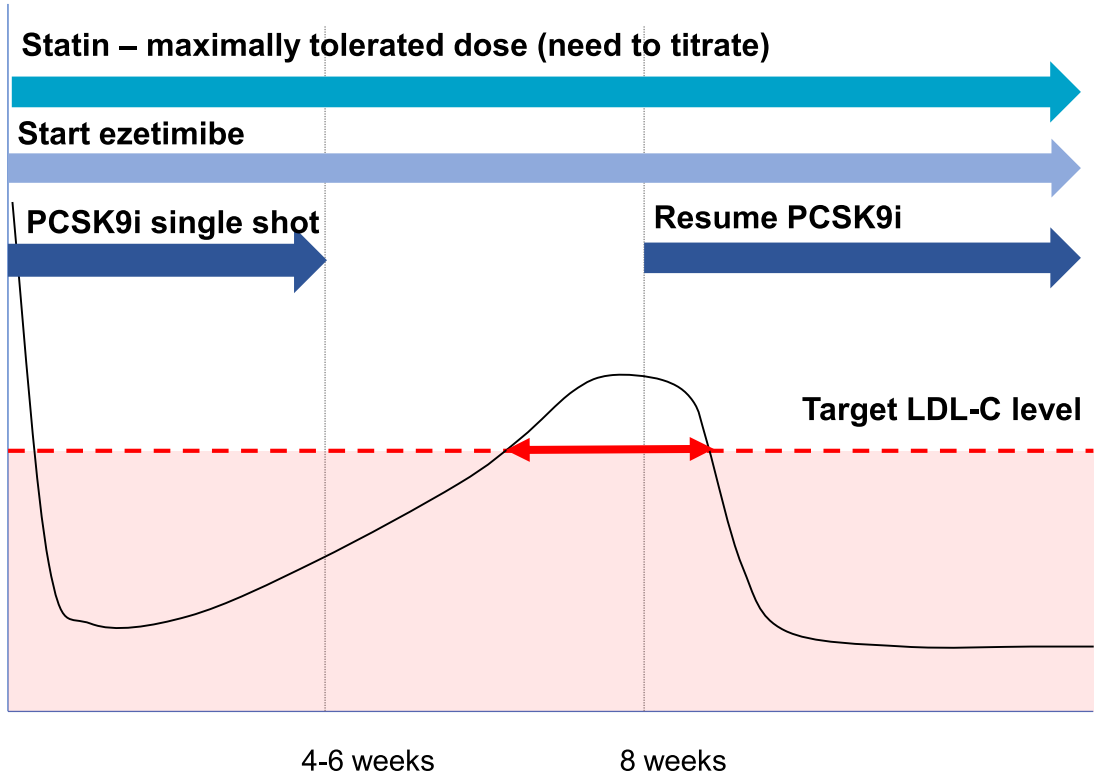
**Recurrent ACS, polyvascular disease Diffuse CAD, intermediate-vulnerable plaques, DM, CKD, high baseline LDL-C, statin-resistance

Potential change in LDL-C level in resistant patients

Stepwise, Guideline-directed algorithm



Intensified algorithm with early PCSK9i injection



SUMMARY

- Achievement of target LDL-C level is suboptimal, especially in those at very high-risk of CV events.
- Evidences support early initiation, sufficient intensity, and long-term use of LDL-C lowering therapy for better outcomes.
- Early use of PCS9Ki would be considered in selected, high risk patients after ACS