The Revolution in Cholesterol Management:
Putting **REPATHA** into practice

Amgen, Iran

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Cardiovascular

High unmet need:
burden of CVD & LDL-C in CVD

IHD is on the top of leading causes of death in Iran With **29.9%** increase since 2009[1]

Recurrent CV events occur at a high frequency (~**1.7 times** higher risk within first year) after the index event, lead to marked mortality & morbidity

Prevalence of **high LDL-C** is more than **96%** in patients with CVD, with more than **50%** of cases not report any usage of **LLT**.

Tehran Lipid and Glucose Study phase 5; 2011- 2014

A Substantial Percentage of **CHD (1/3)** and **ACS (1/4)** Patients Do **Not** Achieve LDL-C < **70** mg/dL Despite **LLT**

DYSIS II Study

1. Heathdata.org, 2. Rabani S, Sardarinia M, Akbarpour S, Azizi F, Khalili D, et al. (2018) 12-year trends in cardiovascular risk factors (2002-2005 through 2011-2014) in patients with cardiovascular diseases: Tehran lipid and glucose study. PLOS ONE 13(5): e0195543. 3. Gitt AK, et al. Atherosclerosis. 2017;266:158-166

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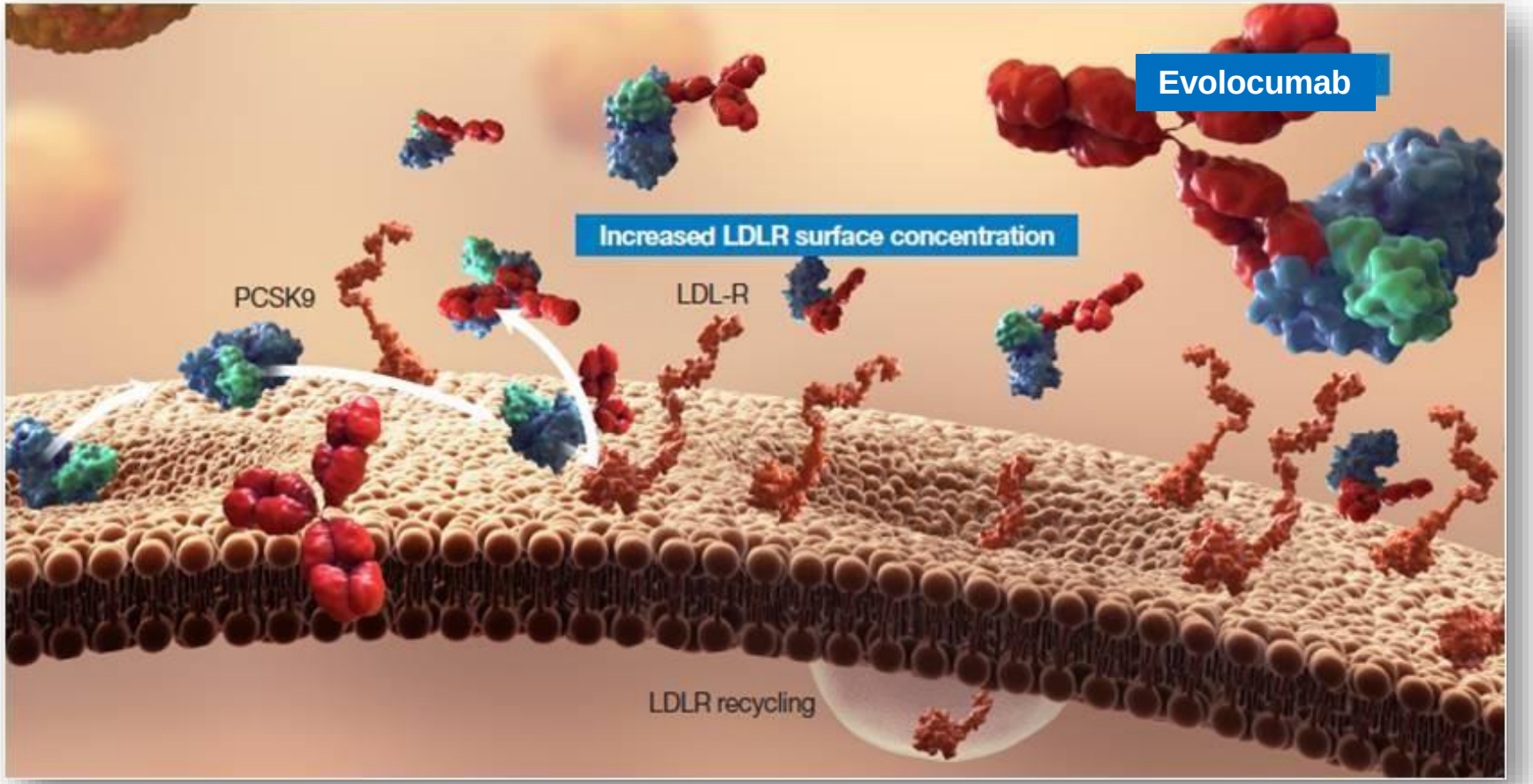
PCSK9 Inhibitors

- ***Proprotein convertase subtilisin/kexin type 9 (PCSK9)*** is a convertase protein which binds to LDL-R and renders it nonfunctional. So, ***inhibition*** of ***PCSK9 upregulates LDL-R*** and ***increases the clearance of LDL*** from plasma.
- In patients who *cannot tolerate statins*, PCSK9 inhibitors have been shown to be *more effective than ezetimibe* in terms of lowering LDL plasma levels.
- These agents *improved all-cause mortality* but not cardiovascular death or MI in short-term follow-up; however, their long-term impact on cardiovascular out- comes are not clear yet.
- PCSK9 inhibitors have been approved for the treatment of statin-intolerant patients and as an adjunctive agent in FH.

PCSK9i (Evolocumab) is a *Fully Human* Monoclonal Antibody Against PCSK9 and Blocks PCSK9/LDL-R Interaction



Chan JC et al. Proc Natl Acad Sci U S A. 2009;106:9820-9825.

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Repatha approved indications

REPATHA is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor indicated:

- in adults with established cardiovascular disease (CVD) to reduce the risk of myocardial infarction, stroke, and coronary revascularization

- as an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C

- as an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C

- as an adjunct to other LDL-C-lowering therapies in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH), to reduce LDL-C

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With Regard to Early, Intensive, and Sustained LDL-C Lowering, What Has Evolocumab Demonstrated?

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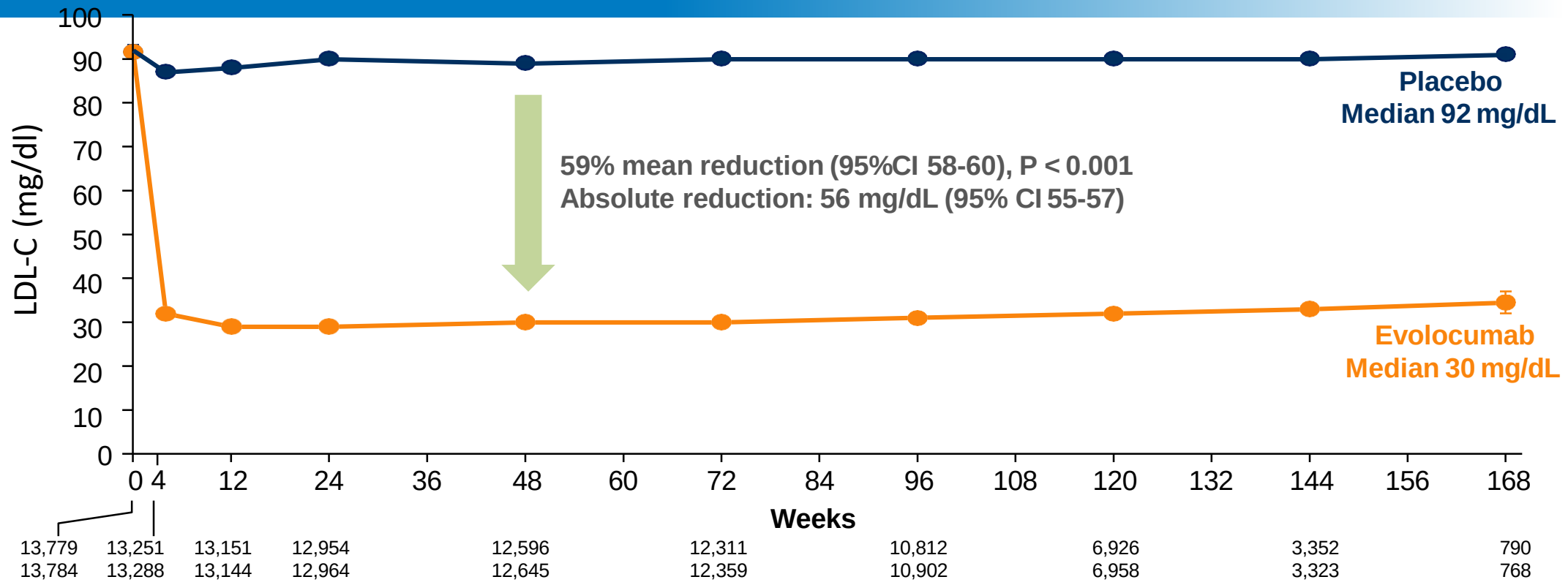
Intensive and Sustained LDL-C Reduction Was Demonstrated Over Time in FOURIER

Median LDL-C Levels Over Time: All Patients

42% ≤ 25 mg/dL
vs < 0.1%
in placebo



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

LDL-C was significantly reduced in the evolocumab group (median: 30 mg/dL) including 42% who achieved levels ≤ 25 mg/dL vs < 0.1% in the placebo group

LDL-C achieved at week 4 remained stable through week 168 for each of the very low achieved LDL-C categories

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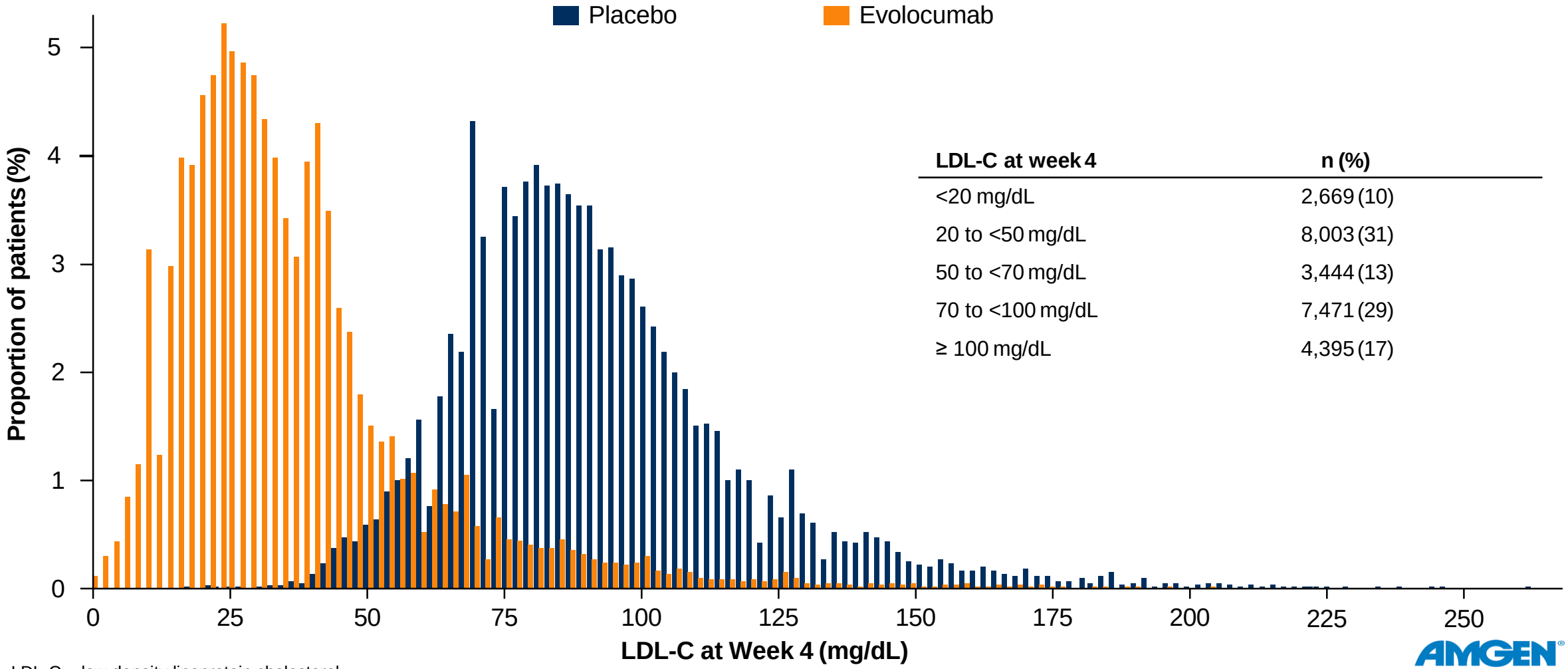
Data shown are median values with 95% confidence intervals in the two arms; ITT. LDL-C, low-density lipoprotein cholesterol

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

Distribution of Achieved LDL-C Level At Week 4 For Evolocumab and Placebo Groups



LDL-C at week 4	n (%)
<20 mg/dL	2,669 (10)
20 to <50 mg/dL	8,003 (31)
50 to <70 mg/dL	3,444 (13)
70 to <100 mg/dL	7,471 (29)
≥ 100 mg/dL	4,395 (17)

LDL-C = low-density lipoprotein cholesterol
n = 12,969 placebo; n = 13,013 evolocumab

Giugliano RP, et al. *Lancet*. [published online ahead of print August 28, 2017]. doi: 10.1016/ S0140-6736(17)32290-0

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Guidelines and Recommendations Worldwide Advise LDL-C Lowering Based on CV Risk

ACC/AHA Guideline 2018[1,2]	ESC/EAS Guidelines 2019[3]
secondary prevention: • ASCVD (High-intensity statin (LDL-C reduction ≥50%)) • Very high risk ASCVD (High-intensity statin (LDL-C < 70 mg/dL)) Primary prevention • Primary elevations of LDL-C ≥ 190 mg/dL (High-intensity statin (LDL-C reduction ≥50%)) • Low risk (life style modification) • Moderate risk (moderate intensity statin to reduce LDL-C by 30% - 49%) • High risk (high dose statin to reduce LDL-C ≥50%)	4 risk groups (LDL-C Goals) • Very High (LDL-C < 55 mg/dL) • High (LDL-C level < 70 mg/dL) • Moderate (LDL-C < 100 mg/dL) • Low (LDL-C < 116 mg/dL)
High (≥ 50% LDL-C ↓)or moderate (30-50% LDL-C ↓)intensity statin therapy	Absolute value for LDL-C goal
Target intensity of statin therapy and LDL-C reduction (percent reduction)	**Target LDL-C levels (absolute value)**

Statins are universally recommended as first line therapy across guidelines and recommendations (and commonly ezetimibe as second line therapy)

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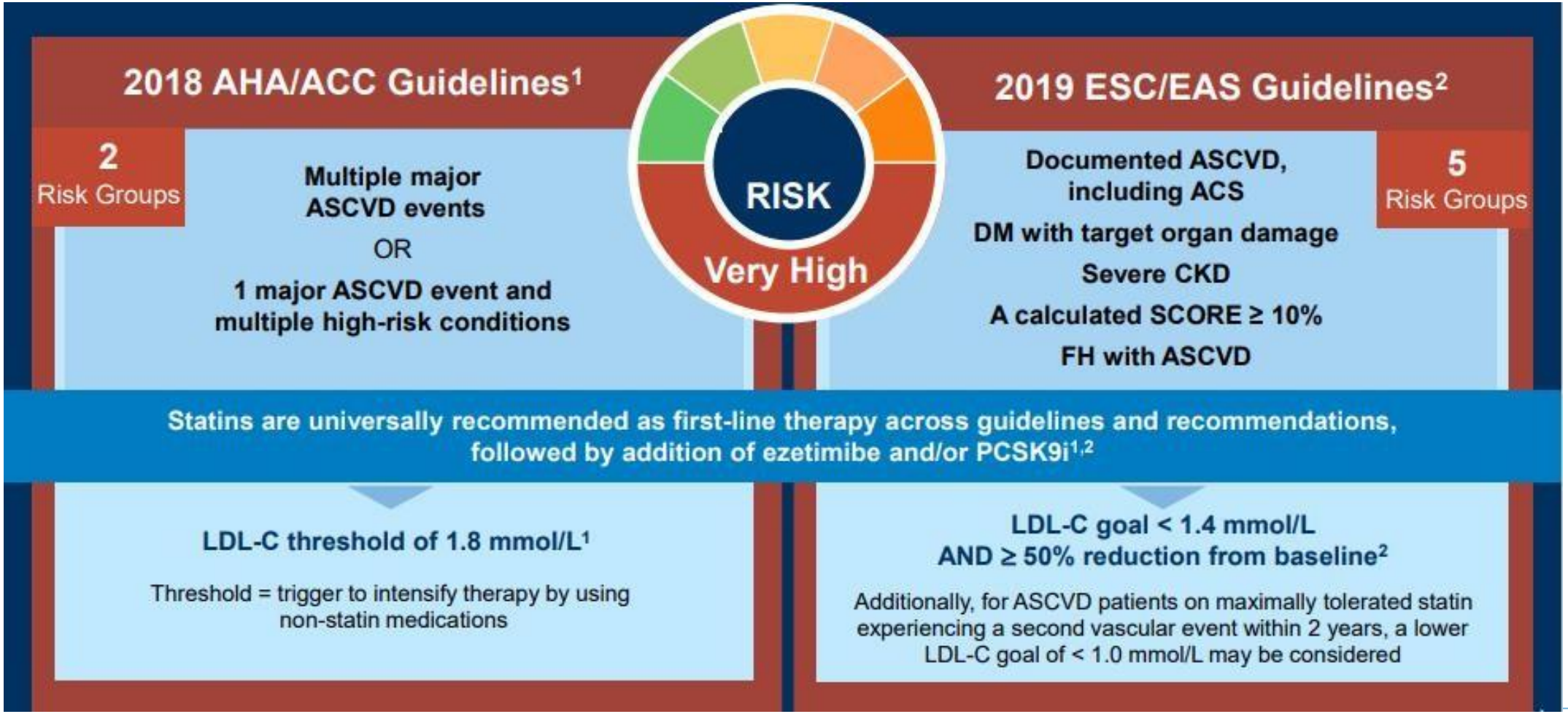
1. Stone NJ, et al. *J Am Coll Cardiol.* 2014;63:2889-2934. 2. Keaney JF Jr, et al. *N Engl J Med.* 2014;370:275-278.
3. Catapano AL, et al. *Atherosclerosis.* 2016;253:281-344. 4. Jacobson TA, et al. *J Clin Lipidol.* 2015;9:129-169.

PCSK9 Inhibitors Are Recommended on Top of Statin ± Ezetimibe Therapy Across Global Guidelines and Recommendations



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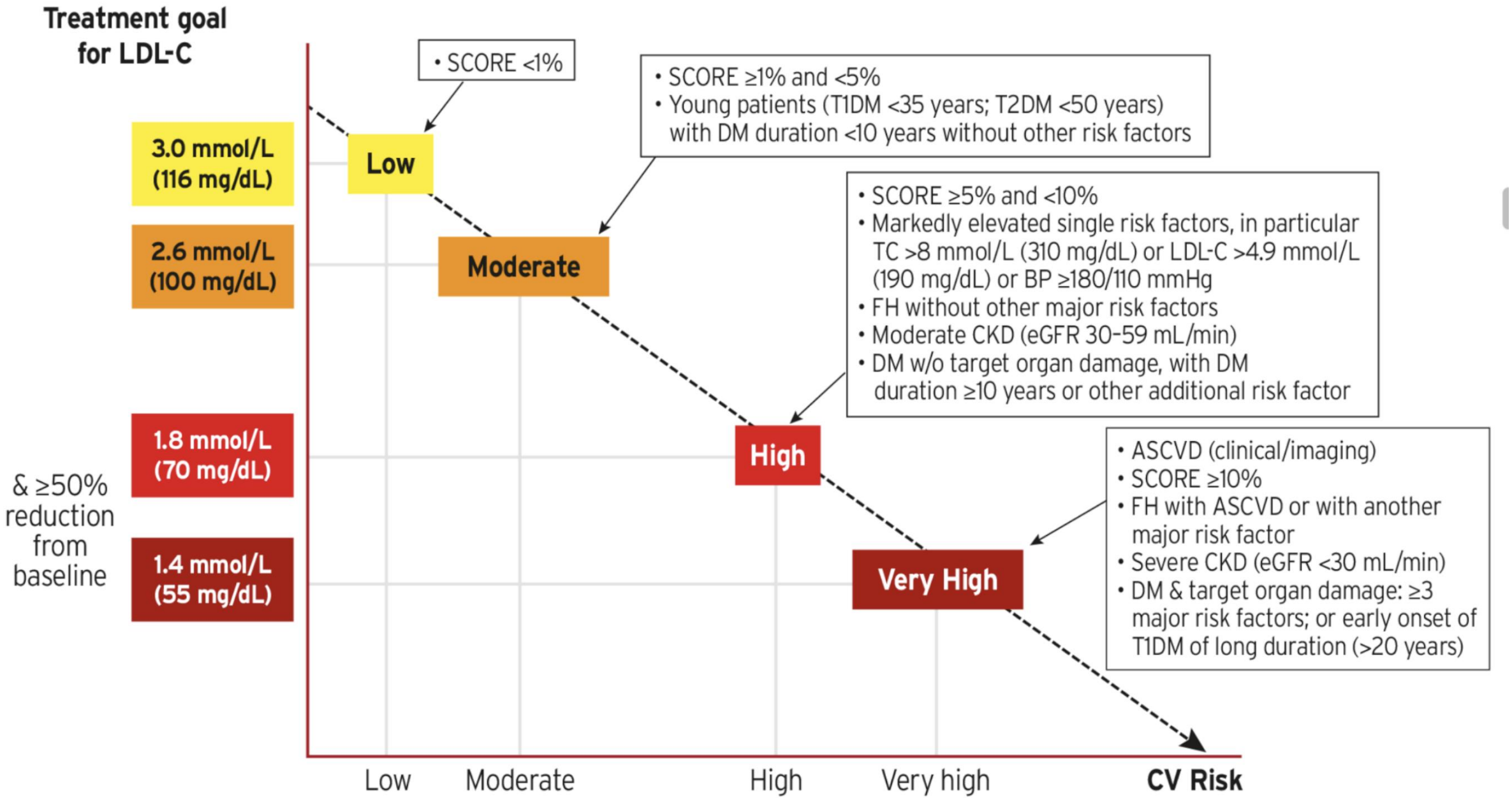
Recommendations for pharmacological low-density lipoprotein cholesterol lowering	
Recommendations	
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals[c] set for the specific level of risk.	
If the goals[c] are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.	
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 statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	
For secondary prevention, patients at very-high risk not achieving their goal[c] on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal[c] on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), ezetimibe should be considered.	
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), a PCSK9 inhibitor added to ezetimibe may also be considered.	
If the goal[c] is not achieved, statin combination with a bile acid sequestrant may be considered.	


Treatment goal for LDL-C
• SCORE <1%
• SCORE ≥1% and <5%
• Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years without other risk factors
• SCORE ≥5% and <10%
• Markedly elevated single risk factors, in particular TC >8 mmol/L (310 mg/dL) or LDL-C >4.9 mmol/L (190 mg/dL) or BP ≥180/110 mmHg
• FH without other major risk factors
• Moderate CKD (eGFR 30–59 mL/min)
• DM w/o target organ damage, with DM duration ≥10 years or other additional risk factor
• ASCVD (clinical/imaging)
• SCORE ≥10%
• FH with ASCVD or with another major risk factor
• Severe CKD (eGFR <30 mL/min)
• DM & target organ damage: ≥3 major risk factors; or early onset of T1DM of long duration (>20 years)
Low
Moderate
High
Very High
3.0 mmol/L (116 mg/dL)
2.6 mmol/L (100 mg/dL)
1.8 mmol/L (70 mg/dL)
1.4 mmol/L (55 mg/dL)
& ≥50% reduction from baseline
Low
Moderate
High
Very high
CV Risk

New Recommendations, and New and Revised Concepts (2019 ESC/EAS Guidelines)

UPGRADES

2016	2019
Lipid analyses for CVD risk estimation	**Lipid analyses for CVD risk estimation**
ApoB should be considered as an alternative risk marker whenever available, especially in individuals with high TG.	ApoB analysis is recommended for risk assessment, particularly in people with high TG, DM, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG, DM, obesity, or very low LDL-C.
Pharmacological LDL-C lowering	**Pharmacological LDL-C lowering**
If the LDL goal is not reached, stain combination with a cholesterol absorption inhibitor should be considered.	If the goals are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.
Pharmacological LDL-C lowering	**Pharmacological LDL-C lowering**
In patients at very-high risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimible or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	For secondary prevention, patients at very-high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.
	For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.
Drug treatments of hypertriglyceridemia	**Drug treatments of hypertriglyceridemia**
Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridemia.	Statin treatment is recommended as the first drug of choke for reducing CVD risk in high-risk individuals with hypertriglyceridemia [TG >23 mmol/L (200 mg/dL)].
Treatment of patients with heterozygous FH	**Treatment of patients with heterozygous FH**
Treatment should be considered to aim at reaching an LDL-C <2.6 mmol/L (<100 mg/dL) or in the presence of CVD <1.8 mmol/L (<70 mg/dL). If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations.	For FH patients with ASCVD who are at very-high risk, treatment to achieve at least a 50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended.
Treatment of patients with heterozygous FH	**Treatment of patients with heterozygous FH**
Treatment with a PCSK9 antibody should be considered in FH patients with CVD or with other factors putting them at very-high risk for CHD, such as other CV risk factors, family history, high Lp(a), or statin intolerance.	Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.

Treatment	Average LDL-C reduction
Moderate intensity statin	≈30%
High intensity statin	≈50%
High intensity statin plus ezetimibe	≈65%
PCSK9 inhibitor	≈60%
PCSK9 inhibitor plus high intensity statin	≈75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈85%

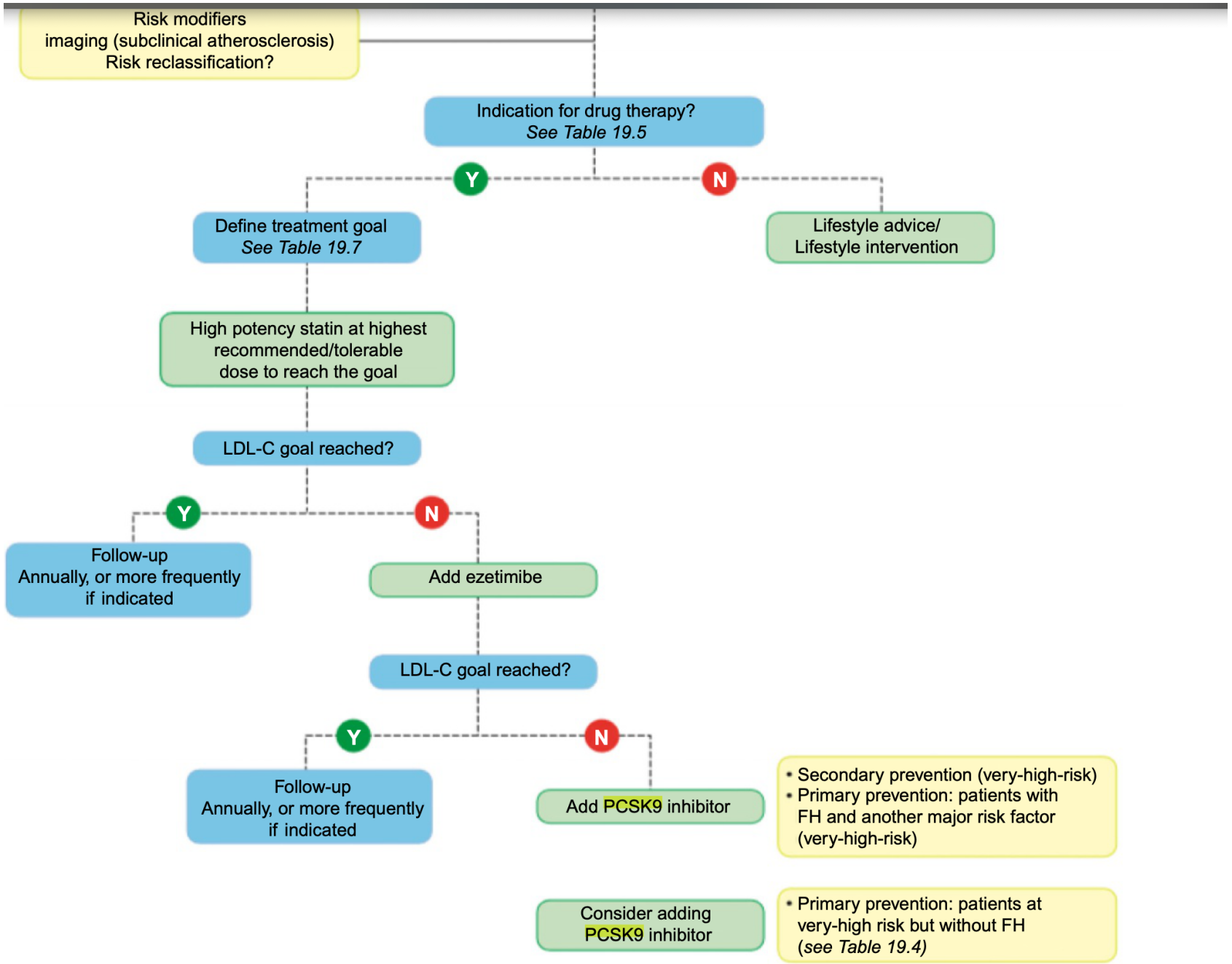


FIG. 19.4 Treatment Algorithm (ESC 2019).

TABLE 19.13
Recommendations for the Management of Dyslipidemia With Lipid-Lowering Drugs in Diabetic Patients (ESC 2019)

Recommendations	Class	Level
Targets		
In patients with T2DM at moderate CV risk, an LDL-C target of <2.5 mmol/L (<100 mg/dL) is recommended.[210–212]	I	A
In patients with T2DM at high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) or an LDL-C reduction of at least 50% is recommended.[210–212]	I	A
In patients with T2DM at very high CV risk, an LDL-C target of <1.4 mmol/dL (<55 mg/dL) or an LDL-C reduction of at least 50% is recommended.[200,201,210]	I	B
In patients with T2DM, a secondary goal of a non-HDL-C target of <22 mmol/L (<85 mg/dL) in very high CV-risk patients, and <2.6 mmol/L (<100 mg/dL) in high CV-risk patients, is recommended.[213,214]	I	B
Treatment		
Statins are recommended as the first-choice lipid-lowering treatment in patients with DM and high LDL-C levels: administration of statins is defined based on the CV risk profile of the patient and the recommended LDL-C (or non-HDL-C) target levels.[187]	I	A
If the target LDL-C is not reached, combination therapy with ezetimobe is recommended.[200,201]	I	B
In patients at very high CV risk, with persistent high LDL-C despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance a PCSK9 inhibitor is recommended.[203–206]	I	A
Lifestyle intervention (with a focus on weight reduction, and decreased consumption of fast-absorbed carbohydrates and alcohol) and fibrates should be considered in patients with low HDL-C and high triglyceride levels.[191,207]	IIa	B
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
Statins should be considered in patients with T1DM at high CV risk, irrespective of the baseline LDL-C level.[187,215]	IIa	A
Statins may be considered in asymptomatic patients with T1DM beyond the age of 30 years.	IIb	C
Statins are not recommended in women of childbearing potential.[189,190]	III	A

Intervention Strategies as a Function of Total Cardiovascular Risk and Untreated Low-Density Lipoprotein Cholesterol Levels

		UNTREATED LDL-C LEVELS					
	Total C V Risk (SCORE)%	**<1.4 mmol/L (55 mg/dL)**	**1.4 to <1.8 mmol/L (55 to <70 mg/dL)**	**1.8 to <2.6 mmol/L (70 to <100 mg/dL)**	**2.6 to <3.0 mmol/L (100 to <116 mg/dL)**	**3.0 to <4.9 mmol/L (116 to <190 mg/dL)**	**>4.9 mmol/L (≥190 mg/dL)**
Primary prevention	<1 low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention. Consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class/Level	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥1 to <5 or moderate risk (see Table 19.4)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class/Level	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
	≥5 to <10 or high-risk (see Table 19.4)	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class/Level	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
	≥10, or at very-high risk due to a risk condition (see Table 19.4)	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class/Level	IIa/B	IIa/A	IIa/A	I/A	I/A	I/A
Secondary prevention	Very-high-risk	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention

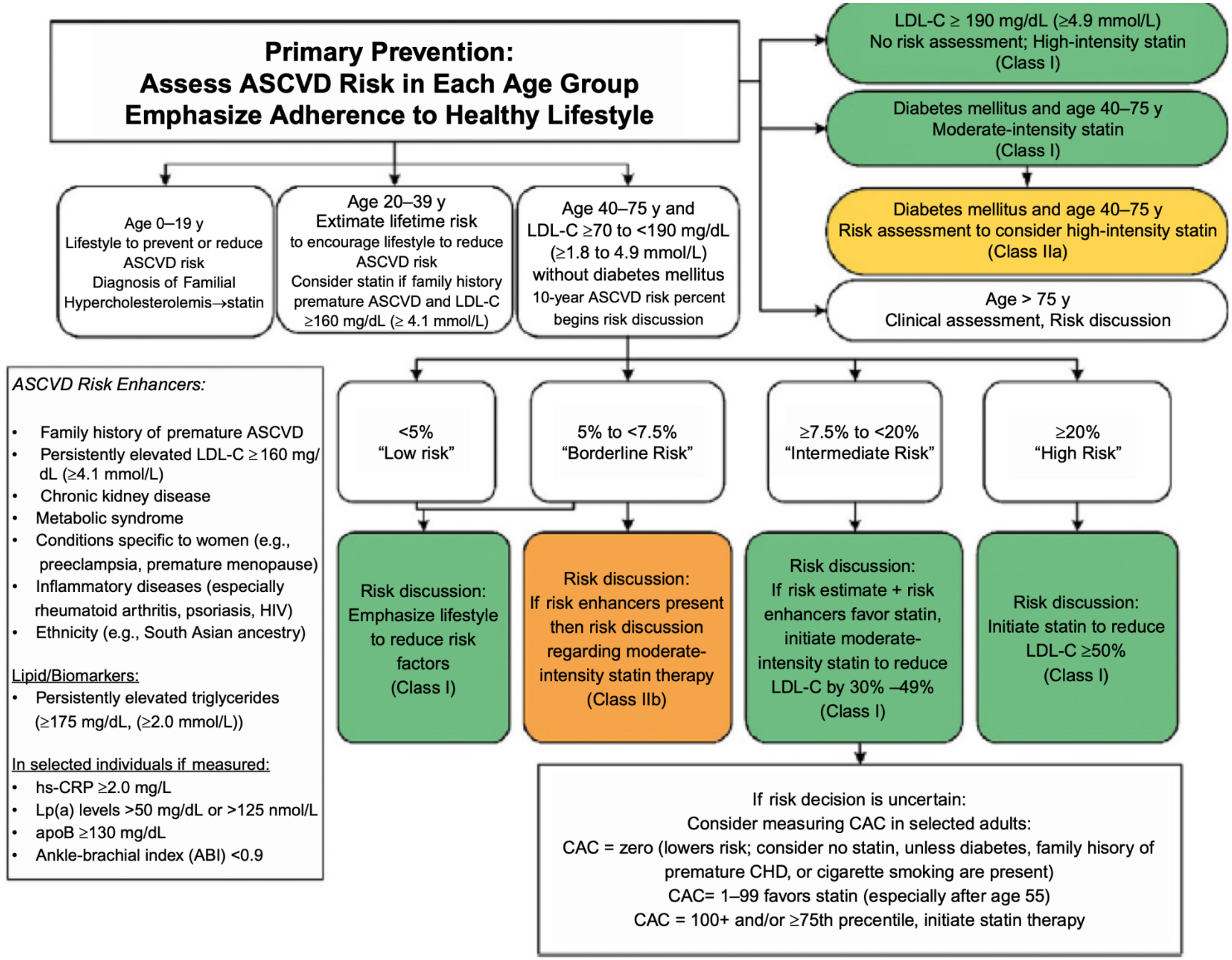


FIG. 19.5 Primary prevention (AHA 2019).

AMERICAN COLLEGE of CARDIOLOGY

ASCVD Risk Estimator Plus

Estimate Risk | Therapy Impact | Advice

15.9% Intermediate — **Current 10-Year ASCVD Risk****

Lifetime ASCVD Risk: **50%** Optimal ASCVD Risk: **5.2%**

Current Age * 59
Age must be between 20-79

Sex * ✔ Male | Female

Race * ✔ White | African American | Other

Systolic Blood Pressure (mm Hg) * 150
Value must be between 90-200

Diastolic Blood Pressure (mm Hg) * 90
Value must be between 60-130

Total Cholesterol (mg/dL) * 240
Value must be between 130 - 320

HDL Cholesterol (mg/dL) * 35
Value must be between 20 - 100

LDL Cholesterol (mg/dL) ○ 150
Value must be between 30-300

History of Diabetes? * Yes | ✔ No

Smoker? * Current | Former | ✔ Never

On Hypertension Treatment? * Yes | ✔ No

On a Statin? ○ Yes | ✔ No

On Aspirin Therapy? ○ Yes | No

Very-high risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation (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. DM with target organ damage*, ≥3 major risk factors or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: 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. Patients with FH without other major risk factors. Patients with DM without target organ damage*, with DM duration ≥10 years or other additional risk factors. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD.

Recommendations for cardiovascular imaging for risk assessment of atherosclerotic cardiovascular disease	
Recommendations	**Class[a]**
Arterial (carotid and/or femoral) plaque burden on arterial ultrasonography should be considered as a risk modifier in individuals at low or moderate risk.	**IIa**
CAC score assessment with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk.	**IIb**

Total CV risk (SCORE) %	<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥ 190 mg/dL)
Primary Prevention						
<1 low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A	IIa/A
≥1 to <5, or moderate risk (see Table 1)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A

Total CV risk (SCORE) %	Untreated LDL-C levels					
	<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥ 190 mg/dL)
≥5 to <10, or high- risk (see Table 1)	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
≥10, or at very-high risk due to a risk condition (see Table 1)	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class[a]/Level[b]	IIa/B	IIa/A	I/A	I/A	I/A	I/A

Total CV risk (SCORE) %	Untreated LDL-C levels					
	<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥ 190 mg/dL)
Secondary Prevention						
Very-high risk	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class[a]/Level[b]	IIa/A	I/A	I/A	I/A	I/A	I/A

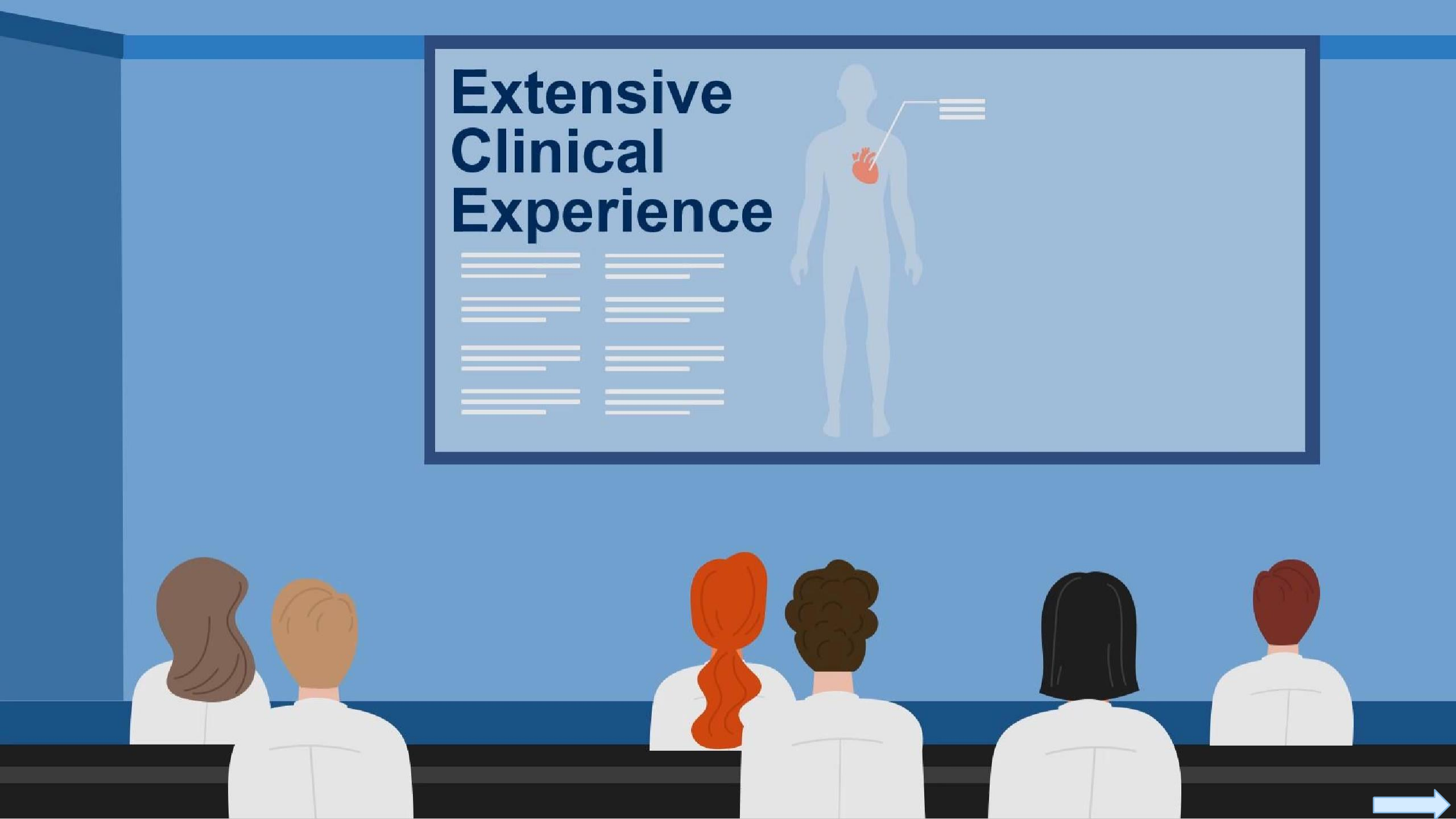
Recommendations for lipid-lowering therapy in very-high-risk patients with acute coronary syndromes	
Recommendations	**Class[a]**
In all ACS patients without any contra-indication or definite history of intolerance, it is recommended to initiate or continue high dose statin as early as possible, regardless of initial LDL-C values.	**I**
Lipid levels should be re-evaluated 4–6 weeks after ACS to determine whether a reduction of ≥50% from baseline and goal levels of LDL-C <1.4 mmol/L (<55 mg/dL) have been achieved. Safety issues need to be assessed at this time and statin treatment doses adapted accordingly.	**IIa**
If the LDL-C goal is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.	**I**
If the LDL-C goal is not achieved after 4–6 weeks despite maximal tolerated statin therapy and ezetimibe, adding a PCSK9 inhibitor is recommended.	**I**
In patients with confirmed statin intolerance or in patients in whom a statin is contra-indicated, ezetimibe should be considered.	**IIa**
For patients who present with an ACS and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe, adding a PCSK9 inhibitor early after the event (if possible, during hospitalization for the ACS event) should be considered.	**IIa**

Recommendations for the treatment of dyslipidaemias in diabetes	
Recommendations	**Class[a]**
In patients with T2DM at very-high risk[c], an LDL-C reduction of ≥50% from baseline and LDL-C goal of < 1.4 mmol/L (< 55 mg/dL) is recommended.	**I**
In patients with T2DM at high-risk[c] an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.	**I**
Statins are recommended in patients with T1DM who are at high or very-high risk[c].	**I**
Intensification of statin therapy should be considered before the introduction of combination therapy.	**IIa**
If the goal is not reached, statin combination with a ezetimibe should be considered.	**IIa**
Statin therapy is not recommended in pre-menopausal patients with diabetes who are considering pregnancy or not using adequate contraception.	**III**
Statin therapy may be considered in both T1DM and T2DM patients aged ≤30 years with evidence of end organ damage and/or LDL-C >2.5 mmol/L as long as pregnancy is not being planned.	**IIb**

Box 8 Summary of dyslipidaemia in metabolic syndrome and type 2 diabetes
Dyslipidaemia represents a cluster of lipid and lipoprotein abnormalities including elevation of both fasting and postprandial TG, ApoB, small dense LDL and low HDL-C and ApoA1.
Non-HDL-C or ApoB are good markers of TRLs and remnants and are a secondary objective of therapy. Non-HDL-C <2.6 mmol/L (<100 mg/dL) and ApoB < 80 mg/dL are desirable in those at high-risk, and non-HDL-C <2.2 mmol/L (<85 mg/dL) and ApoB<65 mg/dL in those at very-high risk. For those at very-high risk with recurrent ASCVD events, a goal of non-HDL-C <1.8 mmol/L (<70 mg/dL) and ApoB <55 mg/dL can be considered.
Atherogenic dyslipidaemia is one of the major risk factors for CVD in people with type 2 diabetes and in people with abdominal obesity and insulin resistance or impaired glucose tolerance.

Table 3 Treatment targets and goals for cardiovascular disease prevention

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish.
Physical activity	3.5–7 hours moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m^2, waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg[a]
LDL-C	**Very-high risk in primary or secondary prevention:** therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required. **High-risk:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL). **Moderate-risk:** A goal of <2.6 mmol/L (<100 mg/dL). **Low-risk:** A goal of <3.0 mmol/L (<116 mg/dL)
Non-HDL-C	Non-HDL-C secondary goals are <2.2, 2.6 and 3.4 mmol/L (<85, 100 and 130 mg/dL) for very high-, high- and moderate-risk people, respectively.
Apolipoprotein B	ApoB secondary goals are <65, 80 and 100 mg/dL for very high-, high- and moderate-risk people, respectively.
Triglycerides	No goal but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.


Extensive
Clinical
Experience

What CV Outcomes Have Been Demonstrated With Evolocumab and Which Data Are Available in Patients With Recent MI?

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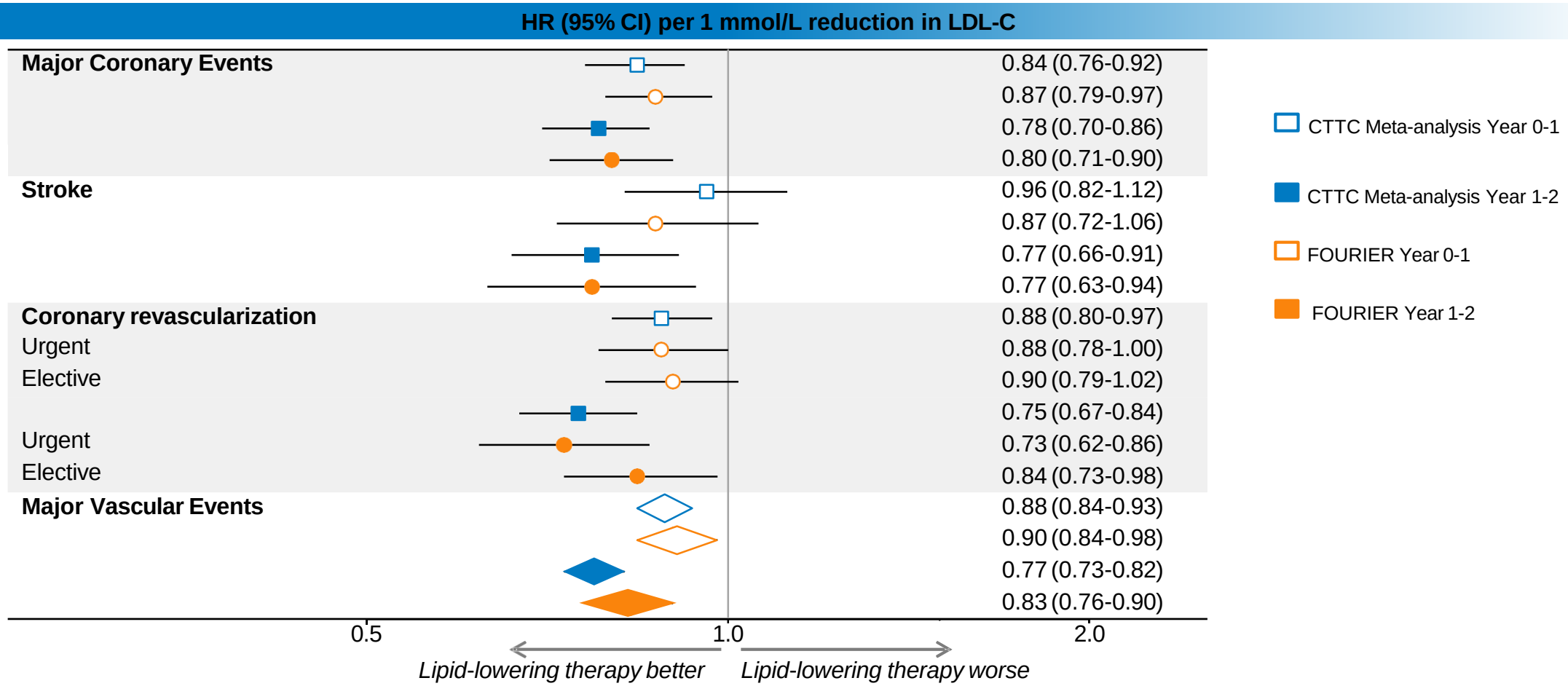
Evolocumab Outcomes Trial Analysis was in line with CTTC Meta-Analysis



The results of the evolocumab outcomes trial was in line with what was seen with statins in the CTTC meta-analysis, based on the study duration

CTTC, Cholesterol Treatment Trialists Collaboration; LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval

Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722.
(Supplementary Figure S6)

Cardiovascular

Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease: An Analysis from FOURIER

Marc S. Sabatine, Gaetano M. De Ferrari, Robert P. Giugliano, Kurt Huber, Basil S. Lewis, Jorge Ferreira, Julia F. Kuder, Sabina A. Murphy, Stephen D. Wiviott, Christopher E. Kurtz, Narimon Honarpour, Anthony C. Keech, Peter S. Sever, Terje R. Pedersen

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Sabatine MS, et al. Circulation. 2018;138:756-766.

What Long-Term Safety Data Are Available for Evolocumab?

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In FOURIER, Evolocumab Exhibited a Similar Safety Profile to That of Placebo Throughout the Duration of the Trial (Median 2.2 Years)

Adverse events, patients (%)	Evolocumab + statin (N = 13,769)	Placebo + statin (N = 13,756)
Any	**10,664** (77.4)	**10,644** (77.4)
Serious	**3,410** (24.8)	**3,404** (24.7)
Treatment related and led to discontinuation of study drug	**226** (1.6)	**201** (1.5)
Allergic reaction	420 (3.1)	393 (2.9)
Injection-site reactions	296 (2.1)	219 (1.6)
Muscle related	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Diabetes (new-onset)	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results (%)		
Aminotransferase level > 3 × upper limit of normal	240/13,543 (1.8)	242/13,523 (1.8)
Cr kinase > 5 × upper limit of normal	95/13,543 (0.7)	99/13,523 (0.7)
Binding Ab	43 (0.3)	N/A
Neutralizing Ab	0	N/A

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

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Binding Ab	**43** (0.3)	**N/A**
Neutralizing Ab	**0**	**N/A**

Two 5-year FOURIER OLE studies are ongoing to assess the extended long-term safety of evolocumab[2,3]

2. NCT02867813. Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk Open-label Extension (FOURIER OLE). https://clinicaltrials.gov/ct2/show/NCT028 67813. Accessed August 17, 2021. 3. NCT03080935. Fourier Open-label Extension Study in Subjects With Clinically Evident Cardiovascular Disease in Selected European Countries. https://clinicaltrials.gov/ct2/show/NCT030 80935. Accessed August 17, 2021

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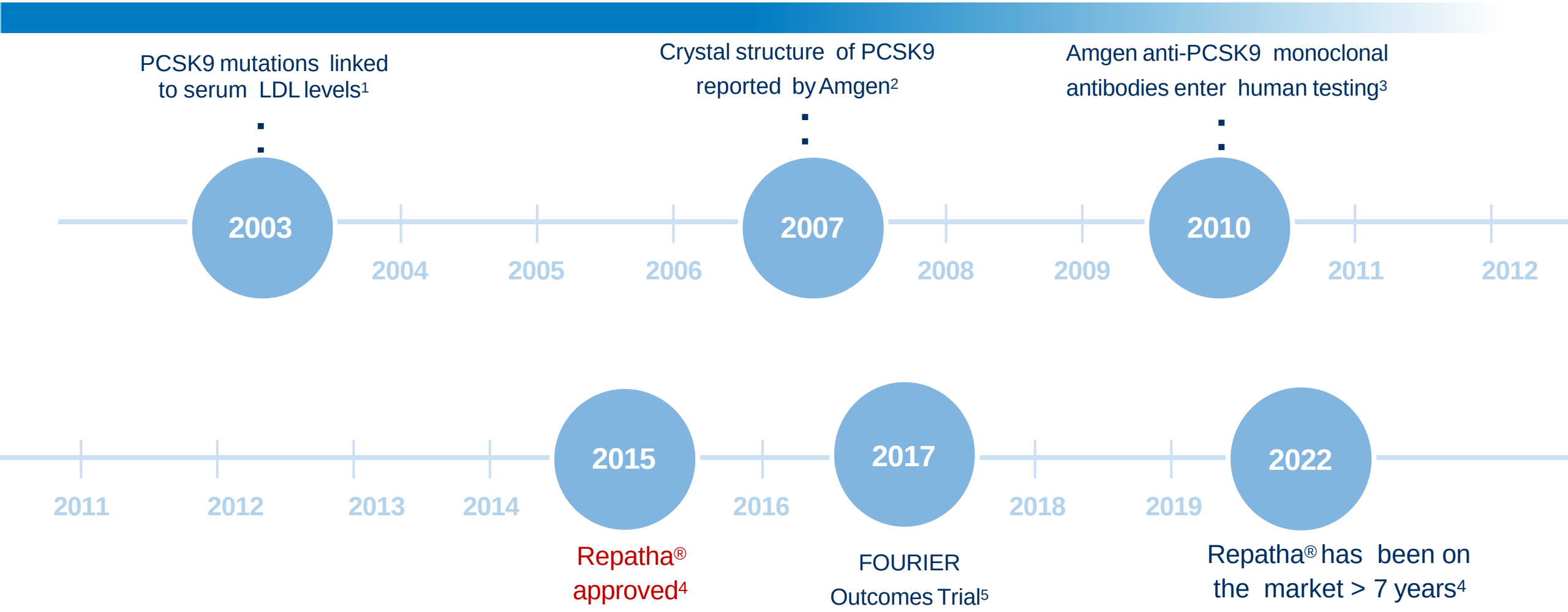
Robust Experience With Evolocumab



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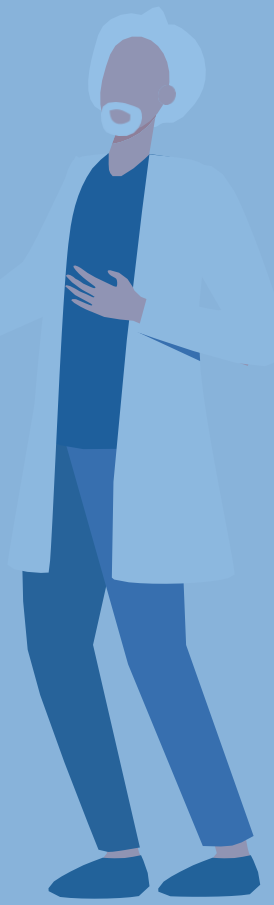
Program to Reduce LDL-C and
Cardiovascular Outcomes
Following Inhibition of PCSK9
In Different POpulations

The PROFICIO Clinical Development Program Demonstrates the Impact of Evolocumab on Cardiovascular Disease Across Multiple Patient Populations[8]



The PROFICIO Clinical Development Program Demonstrates the Impact of Evolocumab on Cardiovascular Disease Across Multiple Patient Populations[8]

	2011	2012	2013	2014	2015	2016	2017	2018	2019
CV OUTCOMES			*Secondary Prevention* **FOURIER** (N = 27,564)			*Secondary Prevention* **FOURIER OLE** (N = 5,037)	*Secondary Prevention* **FOURIER OLE** in select EU countries (N = 1,600)		*High CV Risk Without Prior MI or Stroke* **VESALIUS-CV** (N ~ 13,000)
CONSISTENT LDL-C EFFECT	*Combination Therapy* **LAPLACE** (N = 631) *Statin Intolerance* **GAUSS** (N = 160) *Monotherapy* **MENDEL** (N = 411)		*Combination Therapy* **LAPLACE-2** (N = 2,067) *Statin Intolerance* **GAUSS-2** (N = 307) *Statin Intolerance* **GAUSS-3** (N = 511) *Monotherapy* **MENDEL-2** (N = 615) *Self-administration* **THOMAS-1** (N = 149) **THOMAS-2** (N = 164)	*Lipoprotein Kinetics* **FLOREY** (N = 89)	*Statin Intolerance* **GAUSS-4** (N = 61)				
LONG-TERM	*Safety* **OSLER-1** (N = 1,324)	*Efficacy* **DESCARTES** (N = 905)	*Safety* **OSLER-2** (N = 3,681)	*Neurocognition* **EBBINGHAUS** (N = 1974)					
IMAGING			*Plaque* **GLAGOV** (N = 970)	*Plaque* **GLAGOV OLE** (N = 770)		*Arterial wall inflammation* **ANTISCHKOW** (N = 129)		*Plaque* **HUYGENS** (N = 150)	
FAMILIAL HYPERCHOLESTEROLEMIA	*Heterozygous FH* **RUTHERFORD** (N = 168)	*Heterozygous and Homozygous FH* **TAUSSIG** (N = 300) *Homozygous FH* **TESLA** (N = 58)	*Heterozygous FH* **RUTHERFORD-2** (N = 331)		*Apheresis* **DeLAVAL** (N = 39) *Pediatrics* **HAUSER OLE** (N = 115) *Pediatrics* **HAUSER RCT** (N = 150)			*Homozygous FH* **RAMAN** (N = 30)	
SPECIAL POPULATIONS		*Japanese/Asian* **YUKAWA** (N = 310)	*Japanese/Asian* **YUKAWA-2** (N = 409)			*Diabetes* **BANTING** (N = 424) *HIV* **BEIJERINCK** (N = 467)	*Diabetes* **BERSON** (N = 986)		

Year reflects start of study.

Data on File, Amgen; 2020.

familial hypercholesterolaemia

- Has two phenotype, heterozygous and homozygous form
- Heterozygous is a common codominant monogenic dyslipidaemia causing premature CVD due to lifelong elevation of plasma levels of LDL-C
- If left untreated, HeFH individuals typically develop early CAD before the ages of 55 and 60 years respectively.
- The risk of CHD among individuals with definite or probable HeFH is estimated to be increased at least 10-fold.
- The prevalence of HeFH in the population is estimated to be 1/200 to 250, translating to a total number of cases >300,000 in Iran.
- Only a minor fraction of these cases is identified and properly treated, average 10% worldwide
- With the exception of HoFH, FH is generally a silent disease
- at any given LDL-C level, having an identified FH mutation is associated with significantly higher cardiac risk than an individual with the same LDL-C but no apparent pathogenic FH mutation

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HeFH is clinically differentiable to HoFH

FH heterozygotes	FH homozygotes
Occur in ~ 1 in 230-500 persons worldwide[1,2]	Occur in ~ 1 in 300,000-1,000,000 persons worldwide[1,2]
One major genetic defect in LDL metabolism[1,2]	Two major genetic defects in LDL metabolism[1,2]
TC: 350 to 500 mg/dL[4] **(9-12.9 mmol/L)**	TC: > 500 to > 1,000 mg/dL[1] **(12.9-25.9 mmol/L)**
LDL-C: 200–400 mg/dL[1,3] **(5.1-10.3 mmol/L)**	LDL-C: > 600 mg/dL[3] **(15.5 mmol/L)**
Half the number of LDLR expressed[4]	LDLR activity severely decreased[4] or absent
Characterized by arcus cornealis and achilles tendon xanthomas present in <30% of cases and often develop CHD 30 to 60 years of age[3,5]	Characterized by tendon and cutaneous xanthomas often before age 10 years and CHD in childhood[3,5]
Most respond to drugs, but individual response variable	Poorly responsive to drugs; apheresis and other novel therapies often indicated

1. Rader DJ, et al. In: Longo DL, et al, eds. *Harrison's Principles of Internal Medicine*. Vol II.18th ed. New York, NY: McGraw Hill Medical. 2012:3145-3161.
2. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: Consensus Statement of the European Atherosclerosis Society. Eur Heart J. 2013 Aug 15
3. Robinson JG. *J Manag Care Pharm.* 2013;19:139-149.
4. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation*. 2002;106:3143-3421.
5. . Brown MS, et al. *Science*. 1986;232:34-47.

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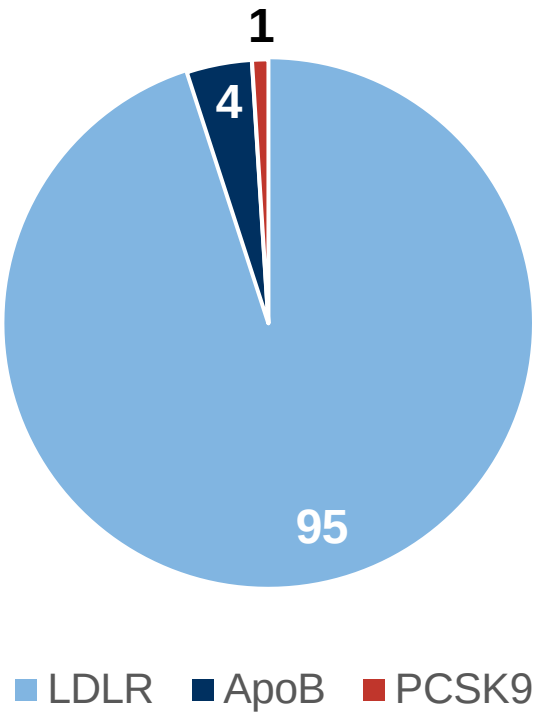
Genetic Mutations Associated With FH

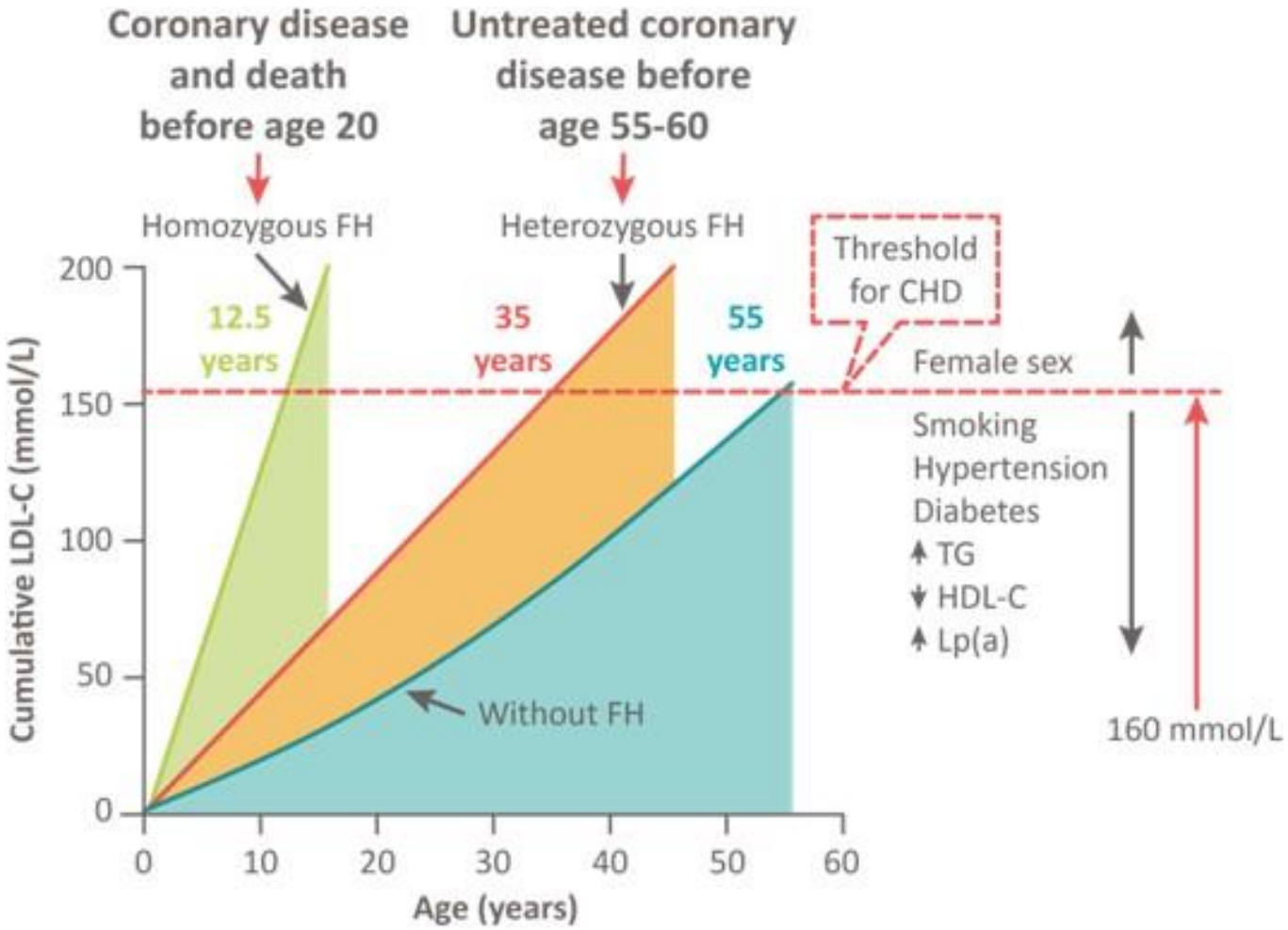
- FH is a monogenic disease caused by loss-of-function mutations in the LDLR or apoB genes, or a gain-of-function mutation in the PCSK9 gene
- More than 1000 different mutations that cause FH have been identified in LDLR.
- The different mutations cause reduced function or complete loss-of-function, the latter being associated with more severe hypercholesterolemia and CVD.

Diagnosis of FH is usually based on clinical presentation

- The diagnosis can be verified by showing causative mutations in the pathogenic genes.
- However, in most studies, the frequency of detectable mutations in patients with a clinically definite or probable HeFH is between 60% to 80%



Cumulative LDL-c burden determines CV risk in FH



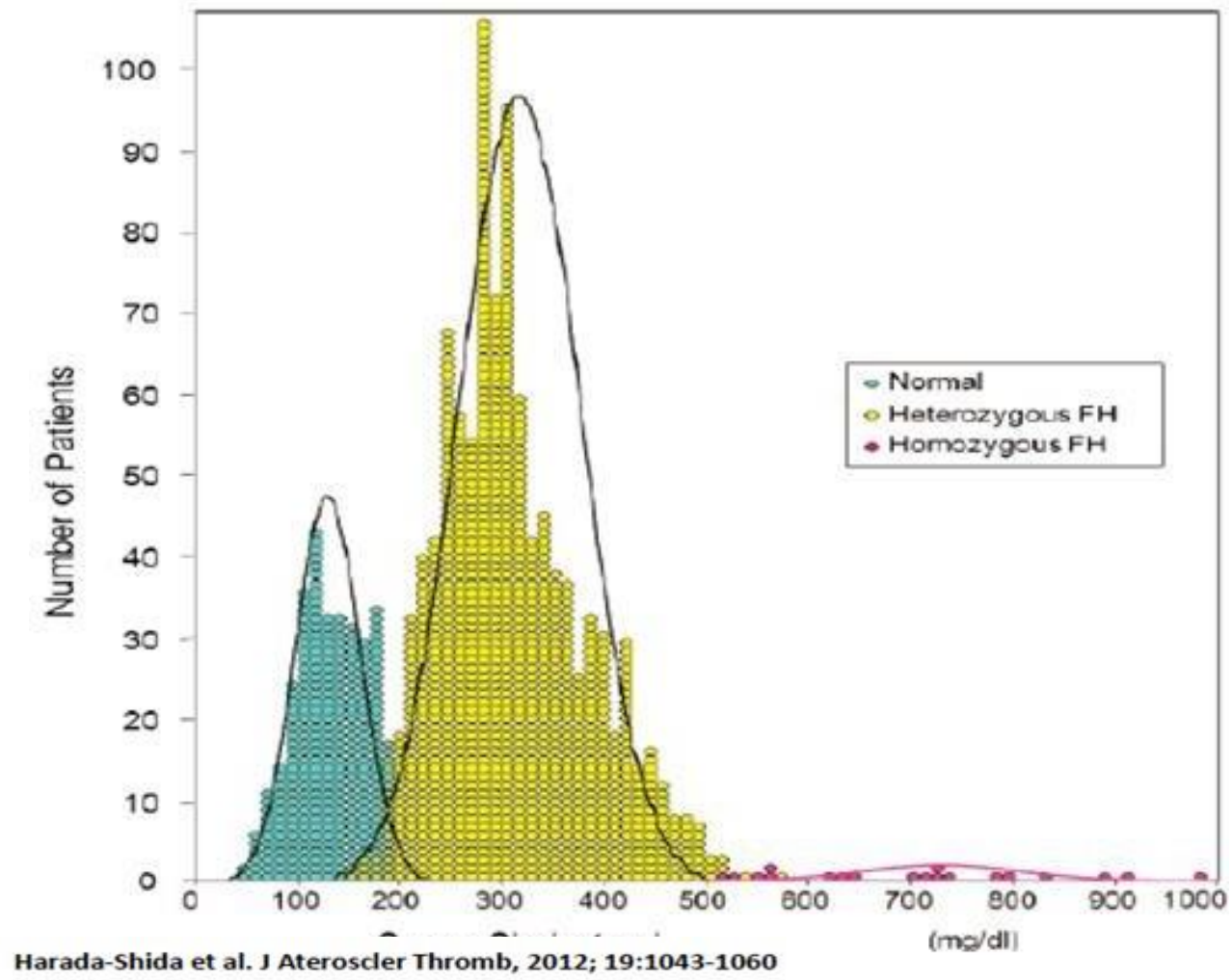
Nordestgaard BG *et al. Eur Heart J* 2013;**34**:3478-90.

Risk of CAD in those with Elevated LDL-c (≥190 mg/dl) According to FH Mutation Status

	N CAD free controls/N CAD Case	OR for CAD (95% CI)	P FH mutation+ vs. -	LDL-C adjusted OR for CAD (95%CI)	P FH mutation + vs. -
LDL-C> 190 mg/dL					
FH mutation-	1264 (422/842)	6.0 (5.2-6.9) P<0.001	0.001	1.6 (1.3-2.1) p<0.001	0.02
FH Mutation+	73 (8/65)	22.3 (10-7-53.2) P<0.001		4.2 (1.9-10.4) P<0.001	
LDL-C < 130 and FH mutation -	7485 (5175/2310)	Reference		Reference	

Adapted from Khera A et al. J Am Coll Cardiol. 2016 ;67(22):2578-89

Broad spectrum of LDL-C levels in FH



Harada-Shida et al. J Ateroscler Thromb, 2012; 19:1043-1060

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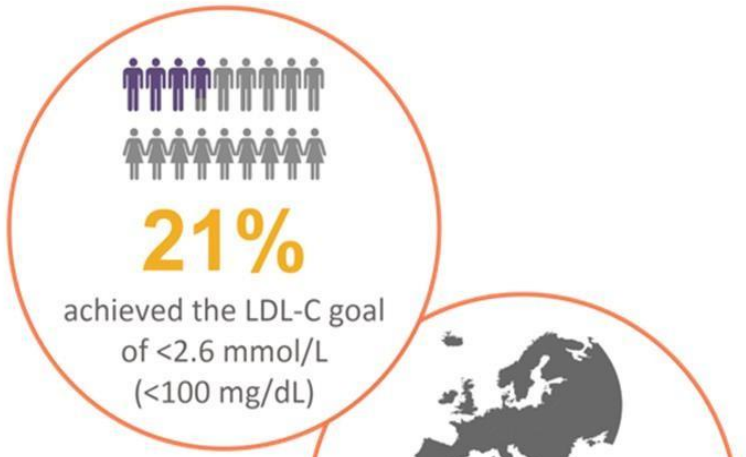
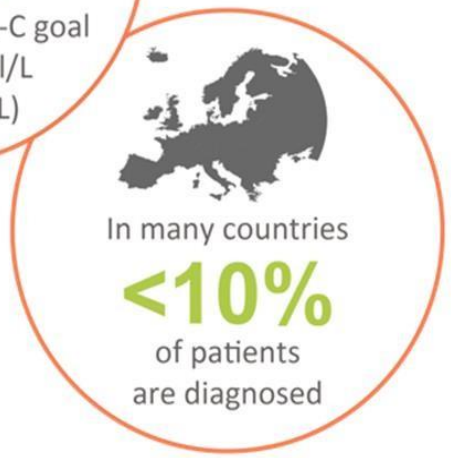
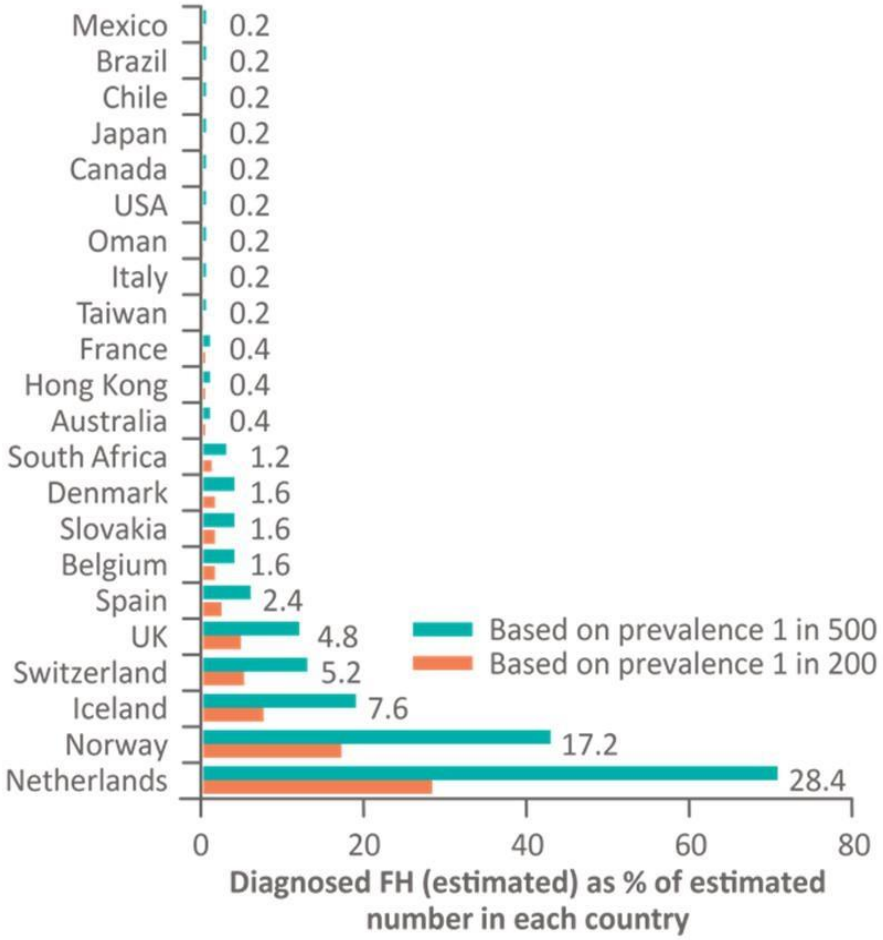
HeFH, under-diagnosed and under-treated







Pijlman *et al. Atherosclerosis* 2010;**209**:189-94. Nordestgaard *et al. Eur Heart J* 2013;**34**:3478-90.

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Dutch Lipid Clinic Network diagnostic criteria for HeFH

Criteria	Points
1) Family history	
First-degree relative with known premature (men aged <55 years; women <60 years) coronary or vascular disease, or first-degree relative with known LDL-C above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, or children aged <18 years with LDL-C above the 95th percentile	2
2) Clinical history	
Patient with premature (men aged <55 years; women <60 years) CAD	2
Patient with premature (men aged <55 years; women <60 years) cerebral or peripheral vascular disease	1
3) Physical examination[a]	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL-C levels (without treatment)	
LDL-C ≥8.5 mmol/L (≥325 mg/dL)	8
LDL-C 6.5–8.4 mmol/L (251–325 mg/dL)	5
LDL-C 5.0–6.4 mmol/L (191–250 mg/dL)	3
LDL-C 4.0–4.9 mmol/L (155–190 mg/dL)	1
5) DNA analysis	
Functional mutation in the *LDLR*, *apoB*, or *PCSK9* genes	8
Choose only one score per group, the highest applicable; diagnosis is based on the total number of points obtained	
A 'definite' FH diagnosis requires >8 points	
A 'probable' FH diagnosis requires 6–8 points	
A 'possible' FH diagnosis requires 3–5 points	

Comparison of Diagnostic Criteria for the Diagnosis of FH

iteria	MEDPED	DUTCH	SIMON BROOME	NLA*	AHA
amily history of premature CAD		+	+	+	+
amily history of tendon xanthomas		+	+		
amily history of hypercholesterolemia	+	+	+	+	
atient premature CAD		+		+	
atient premature PVD		+			
endon xanthomas		+	+	+	
orneal arcus		+		+	
evated LDL-C	+	+	+	+	+
enetic mutation		+	+	+	+

indicates American Heart Association; CAD, coronary artery disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MEDPED, Make Early Diagnosis to ent Early Death; NLA, National Lipid Association; PVD, peripheral vascular disease.

NLA recommends the use of MEDPED, Dutch Lipid Clinic Network (DLCN), and Simon Broome criteria for diagnosis of familial hypercholesterolemia.

Recommendations for the detection of patients with HeFH

ESC 2019

Children suspected of FH should be screened from the age of 5 years.

Recommendations	Class[a]	Level[b]
It is recommended that a diagnosis of FH is considered in patients with CHD aged <55 years for men and <60 years for women, in people with relatives with premature fatal or non-fatal CVD, in people with relatives who have tendon xanthomas, in people with severely elevated LDL-C [in adults >5 mmol/L (>190 mg/dL), in children >4 mmol/L (>150 mg/dL)], and in first-degree relatives of FH patients.	I	C
It is recommended that FH should be diagnosed using clinical criteria and confirmed, when possible, via DNA analysis.	I	C
Once the index case is diagnosed, family cascade screening is recommended.	I	C

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Recommendations for the treatment of patients with FH

Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.	I	C
In children, testing for FH is recommended from the age of 5 years, or earlier if HoFH is suspected.	I	C
Children with FH should be educated to adopt a proper diet and treated with a statin from 8—10 years of age. Goals for treatment should be LDL-C <3.5 mmol/L (<135 mg/dL) at >10 years of age.	IIa	C

- HoFH patients should be treated with intensive LDL-lowering drug therapy and, when available, with lipoprotein apheresis. This treatment (every 12 weeks) can decrease plasma LDL-C levels by 55 to 70%
- Statin treatment should be started with low doses and the dose should be increased to reach goals. The goal in children >10 years of age is an LDL-C<135 mg/dl and in <10 years a 50% reduction of LDL-C

REPATHA Trials

Name	Objective	End points	No. of patients	Duration	Arms	Result
FOURIE *Apr 2017*	To see • If established CVD patients on SOC benefit from adding Evomab in terms of reducing the risk of CV outcomes • Efficacy & safety of achieving very low LDL	**1°** : Composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization **2°** : Composite of CV death, MI, or stroke **Other**: Composite of CV death, MI, or stroke	27,500	Mean 26 months Up to 43 months	• SOC + Placebo • SOC + Evo	**LDL:** 59% mean reduction (95%CI 58-60), P < 0.001, 56 mg/dL absolute reduction (95% CI 55-57) **1°** : 15% RRR in Evo arm **2°** : 20% RRR in Evo arm **Safety:** No significant difference of AEs, SAEs, AEs leading discontinuation, incidence of neurocognitive events, cataracts, & new-onset diabetes
SUB-Analyses Of FOURIER *Aug 2017*	To explore the clinical efficacy and safety on progressively lower achieved LDL-C levels	*The same as FOURIER, but comparing in 5 groups: 1. LDL < 20 2. LDL 20-49 3. LDL 50-69 4. LDL 70-99 5. LDL ≥ 100 *10 safety adverse events evaluated: SAEs, AEs leading discontinuation, ALT/AST>3X, Cancer, Cataracts, CK>5X, Hem-Stroke, Neurocognitive AEs, Non-CV death & New onset of diabetes	27500	At week 4	• SOC + Placebo • SOC + Evo	**1 & 2°** : Lower RRR with lower LDL levels **LDL <10 Vs. LDL ≥100** 31% RRR in primary endpoints 41% RRR in secondary endpoints **Safety:** No significant difference in 10 safety adverse events evaluated

REPATHA Trials

Name	Objective	End points	No. of patients	Duration	Arms	Result
MENDEL *March 2014*	To evaluate mono-therapy of Evo	**1°** : Percent change from baseline in LDL-C at Week 12 & mean of Weeks 10 and 12 **2°** : At mean of Weeks 10 and 12 and at Week 12: • % change from baseline in ApoB, ApoA-I, lipoprotein(a), TG, and HDL-C • % patients with LDL-C <70 mg/dL of CV death, MI, or stroke **Other**: • Treatment-emergent and serious AEs • Muscle and hepatic enzyme elevations • Anti-evolocumab antibodies	MENDEL-1 406 MENDEL-2 614	12 weeks	• Placebo + Placebo • Placebo + Ez • Placebo + Evo	**LDL:** 39% mean reduction compare to Ez 57% mean reduction compare to placebo **Safety:** No significant difference
GAUSS *March 2014*	To evaluate efficacy & safety in Statin intolerant	**1°** : Percent change from baseline in LDL-C at mean of Weeks 10 and 12 and at Week 12 **2°** : At mean of Weeks 10 and 12 and at Week 12: • Change from baseline in LDL-C • % change from baseline in ApoB, ApoA-I, lipoprotein(a), TG, and HDL-C • % patients with LDL-C <70 mg/dL of CV death, MI, or stroke **Other**: • Treatment-emergent and serious AEs • Cereatine kinase & hepatic enzyme elevations • Anti-evolocumab antibodies	LAPLACE-1 307 LAPLACE-2 500	12 weeks	• Placebo + Ez • Placebo+ Evo	**LDL:** 37-39 % mean reduction compare to Ez 56% mean reduction compare to placebo **Achieved LDL<70:** 92% in low risk patients 88% in moderate risk patients 77% in high risk patients **Safety:** No significant difference

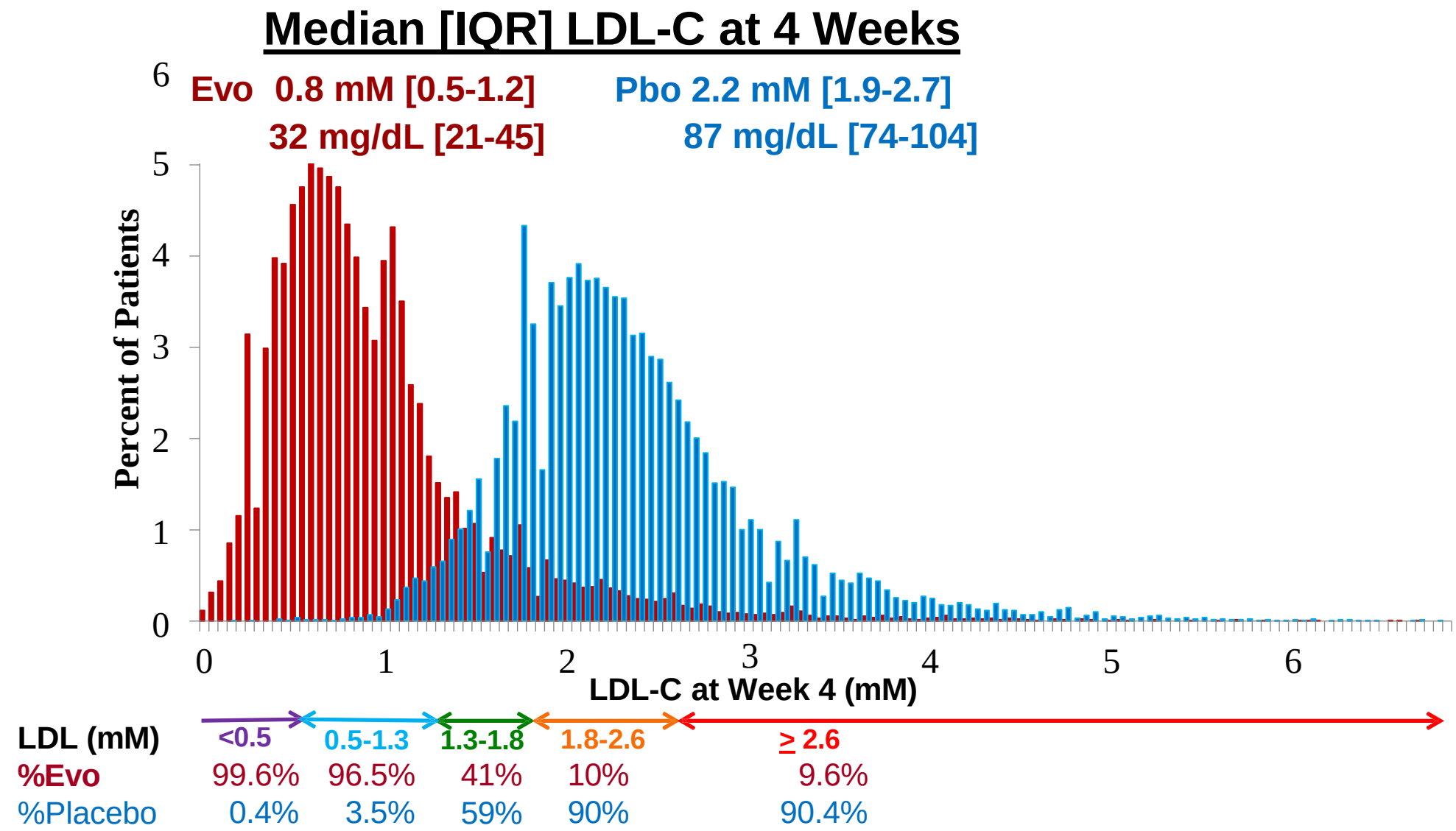
REPATHA Trials

Name	Objective	End points	No. of patients	Duration	Arms	Result
LAPLACE *Dec 2013*	To evaluate benefits & safety of combination therapy SOC + Evo	**1°**: Percent change from baseline in LDL-C at Week 12 & mean of Weeks 10 and 12 **2°**: At mean of Weeks 10 and 12 and at Week 12: • Change from baseline in LDL-C • % change from baseline in ApoB, ApoA-I, lipoprotein(a), TG, and HDL-C • % patients with LDL-C <70 mg/dL of CV death, MI, or stroke **Other**: • Incidence of treatment emergent AEs • laboratory values and vital signs at each scheduled visit • ECG parameters at each scheduled visit • Anti-evolocumab antibodies • Exploratory safety endpoints • Adjudicated CV events	LAPLACE-1 629 LAPLACE-2 1896	12 weeks	All patients on Statin plus: • Placebo • Evo • Placebo + Placebo • Placebo + Ez • Placebo +Evo	**1 & 2°**: Lower RRR with lower LDL levels **LDL <10 Vs. LDL ≥100** 31% RRR in primary endpoints 41% RRR in secondary endpoints **Safety:** No significant difference in 10 safety adverse events evaluated
DESCARTES *May 2014*	Long-term evaluation benefits & safety of combination therapy SOC + Evo	**1°**: %change from baseline in the LDL cholesterol level at week 52 **2°**: • LDL-C % change from baseline at Week 12 • Absolute LDL-C change from baseline at Week 52 • % patients achieving <70 mg/dL LDL-C target at Week 52 • % changes from baseline for TC, HDL-C, non-HDL-C, ApoB, VLDL-C, triglycerides, and Lp(a) at Week 52 • % changes in total cholesterol/HDL cholesterol ratio and apolipoprotein B/apolipoprotein A1 ratio at Week 52 **Other**: • Incidence of treatment emergent AEs • laboratory values and vital signs at each scheduled visit • ECG parameters at each scheduled visit • Anti-evolocumab antibodies • Exploratory safety endpoints • Adjudicated CV events	901	52 weeks	• SOC + Placebo • SOC + Evo	**LDL:** 57% LDL reduction compare to placebo 82% achieved LDL <70 in average **Safety:** No significant difference

REPATHA Trials

Name	Objective	End points	No. of patients	Duration	Arms	Result
Ratherford 2 *Dec 2013*	To evaluate benefits & safety of HeFH	**1°** : Percent change from baseline in LDL-C at Week 14 Secondary Endpoint % Patients achieving LDL-C Goal < 70 mg/dl at week 12	331	14 weeks	• 100% were on statins (87% at high intensity statin) • 62 % were on ezetimibe • Placebo • Evo	**LDL:** 61% LDL reduction compare to placebo 68% LDL<70 at week 12 **Safety:** No significant difference in 10 safety adverse events evaluated
Tesla B *May 2014*	To evaluate benefits & safety of HoFH	**1°** :Primary endpoint: % change from baseline in ultracentrifugation (UC) LDL-C at week 12 **Other**: • Incidence of treatment emergent AEs • laboratory values and vital signs at each scheduled visit • ECG parameters at each scheduled visit • Anti-evolocumab antibodies • Exploratory safety endpoints • Adjudicated CV events	901	52 weeks	• SOC + Placebo • SOC + Evo	**LDL:** 31% LDL reduction compare to placebo **Safety:** No significant difference

Achieved LDL-C at 4 Weeks in forier



Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017

Changes in recommendations (Upgrades)

Pharmacological LDL-C lowering (2016)

In patients at very-high risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or inpatients with statin intolerance, a PCSK9 inhibitor may be considered

(class IIb)

- **Pharmacological LDL-C lowering (2019)**

For secondary prevention, patients at very-high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended

(Class I)

Changes in recommendations (Upgrades)

Treatment of patients with heterozygous FH(2016)

- Treatment should be considered to aim at reaching an LDL-C <2.6 mmol/L (<100 mg/dL) or in the presence of CVD <1.8 mmol/L (<70 mg/dL)
- If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations

(class IIa)

• Treatment of patients with heterozygous FH(2019)

- For FH patients with ASCVD who are at very-high risk, treatment to achieve at least a 50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended
- If goals cannot be achieved, a drug combination is recommended

(Class I)

Changes in recommendations (Upgrades)

Treatment of patients with heterozygous FH(2016)

Treatment with a PCSK9 antibody should be considered in FH patients with CVD or with other factors putting them at very-high risk for CHD, such as other CV risk factors, family history, high Lp(a), or statin intolerance

(class IIa)

- **Treatment of patients with heterozygous FH(2019)**

Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe

(Class I)

Changes in recommendations (Upgrades)

Lipid-lowering therapy in patients with ACS (2016)

If the LDL-C target is not reached with the highest tolerated statin dose and/or ezetimibe, PCSK9 inhibitors may be considered on top of lipid-lowering therapy; or alone or in combination with ezetimibe in statin-intolerant patients or in whom a statin is contraindicated

(class IIb)

- **Lipid-lowering therapy in patients with ACS (2019)**

If the LDL-C goal is not achieved after 4 - 6 weeks despite maximal tolerated statin therapy and ezetimibe, addition of a PCSK9 inhibitor is recommended

(Class I)

Recommendations for pharmacological LDL-C lowering
ESC guideline 2019

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
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered.[197,265,353]	IIa	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may also be considered.[197,265,353]	IIb	C
If the goal[c] is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

I Is recommended or is indicated

IIa Should be considered

IIb May be considered

Thanks for your attention