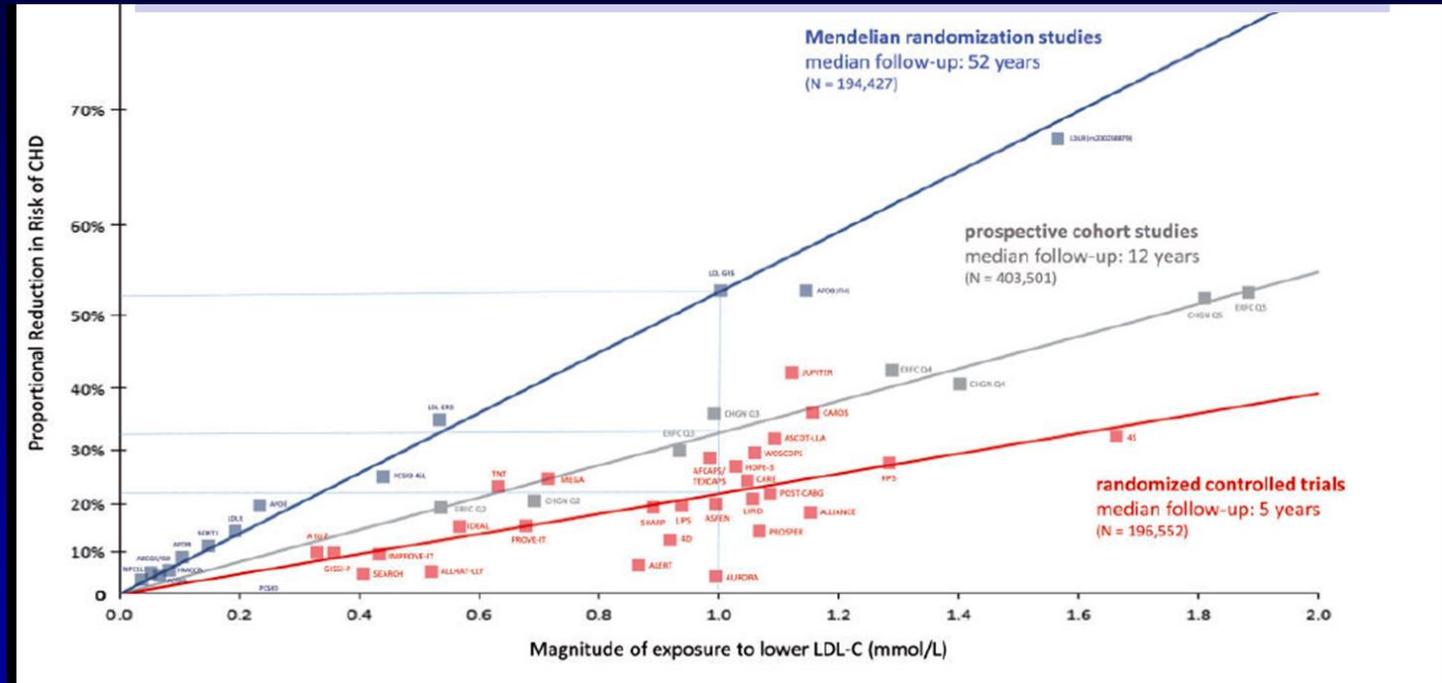


# **Ten take home messages from EAS/ ESC 2019 Dyslipidemia Guidelines**

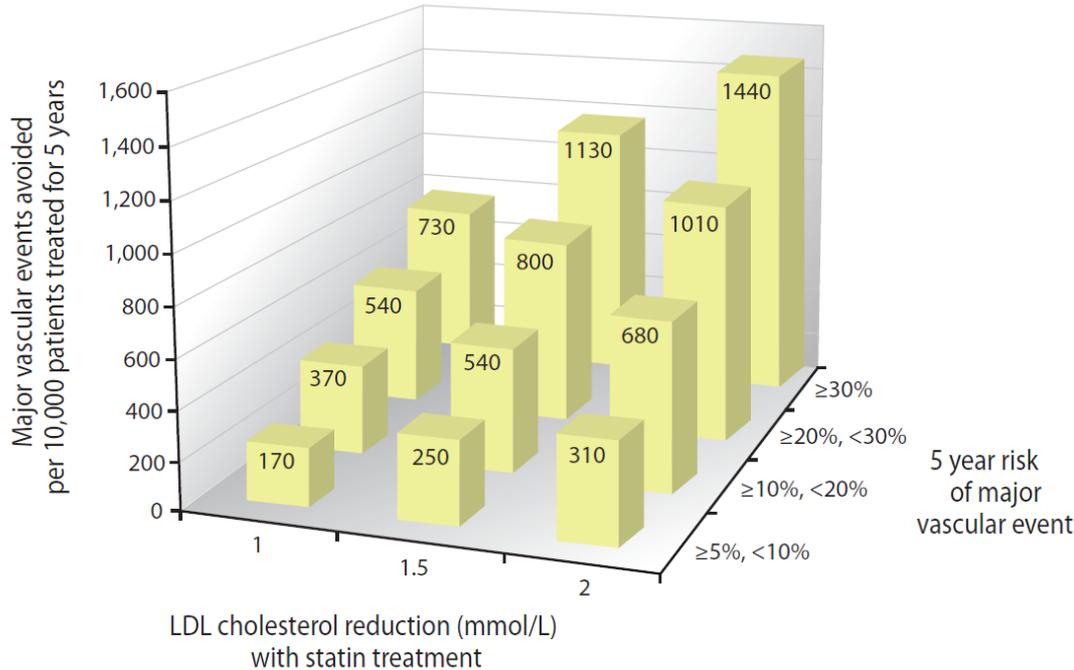
**Prof Lale Tokgozoglu MD,FACC,FESC  
President, European Atherosclerosis  
Society**

**Hacettepe University Dept of Cardiology**

# 1- LDL-C is causal



# Main principle of the Dyslipidemia Guidelines:



**Patient risk and absolute LDL reduction determine absolute risk reduction**

**Plan treatment intensity according to risk**

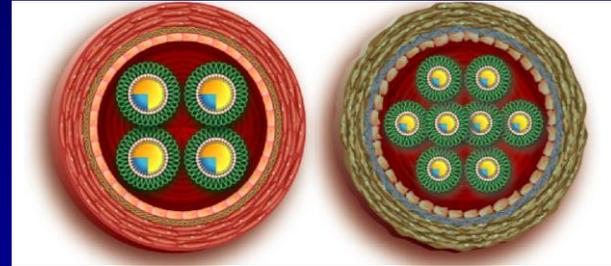
**As risk increases, increase intensity of treatment**

**2- Apo B is important in risk determination especially in IR**

# ApoB containing lipoproteins small enough to infiltrate arterial wall are atherogenic

Data not available

- ♥ Normally 90 % of apoB is in LDL-C.
- ♥ Non-HDL and LDL-C are concordant and predict risk similarly
- ♥ When apoB contains more or less than average amount of cholesterol, these markers disconcordant (10-20 %): DM, MS, obesity



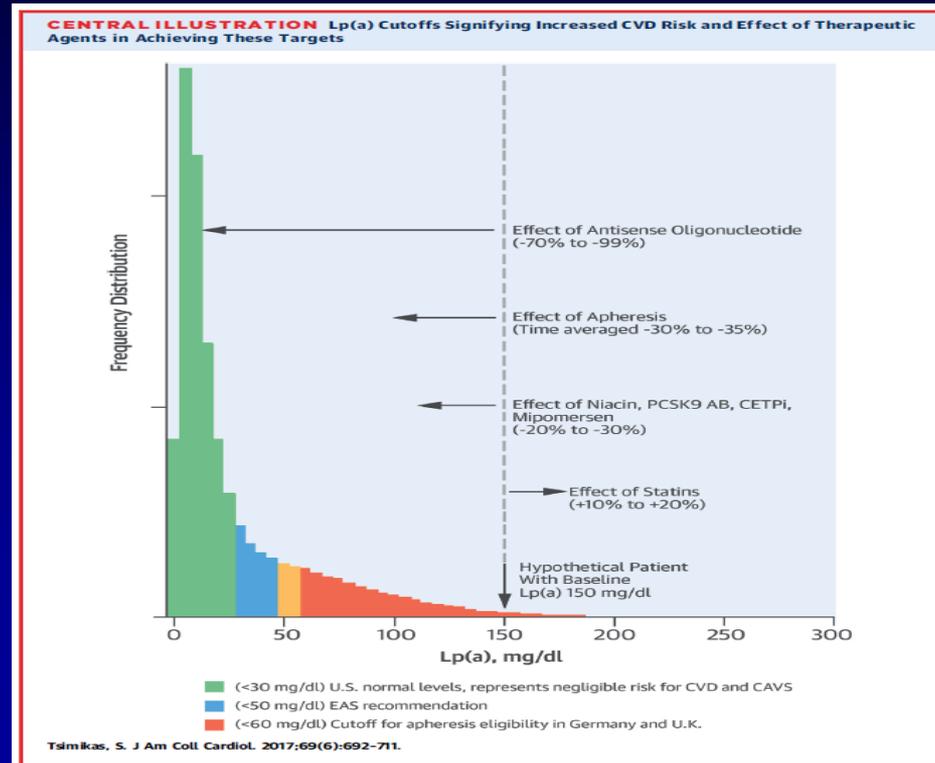
# Recommendations for lipid analyses for cardiovascular disease risk estimation (2)

Recommendations	Class	Level
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG, diabetes, obesity or very low LDL-C.	I	C
ApoB analysis is recommended for risk assessment, particularly in people with high TG, diabetes, 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, diabetes, obesity or very low LDL-C.	I	C

# Treatment targets and goals for cardiovascular disease prevention

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.
Diabetes	HbA1c: <7% (<53 mmol/mol).

# 4- Lp(a) is important in risk determination



# Recommendations for lipid analyses for cardiovascular disease risk estimation (3)

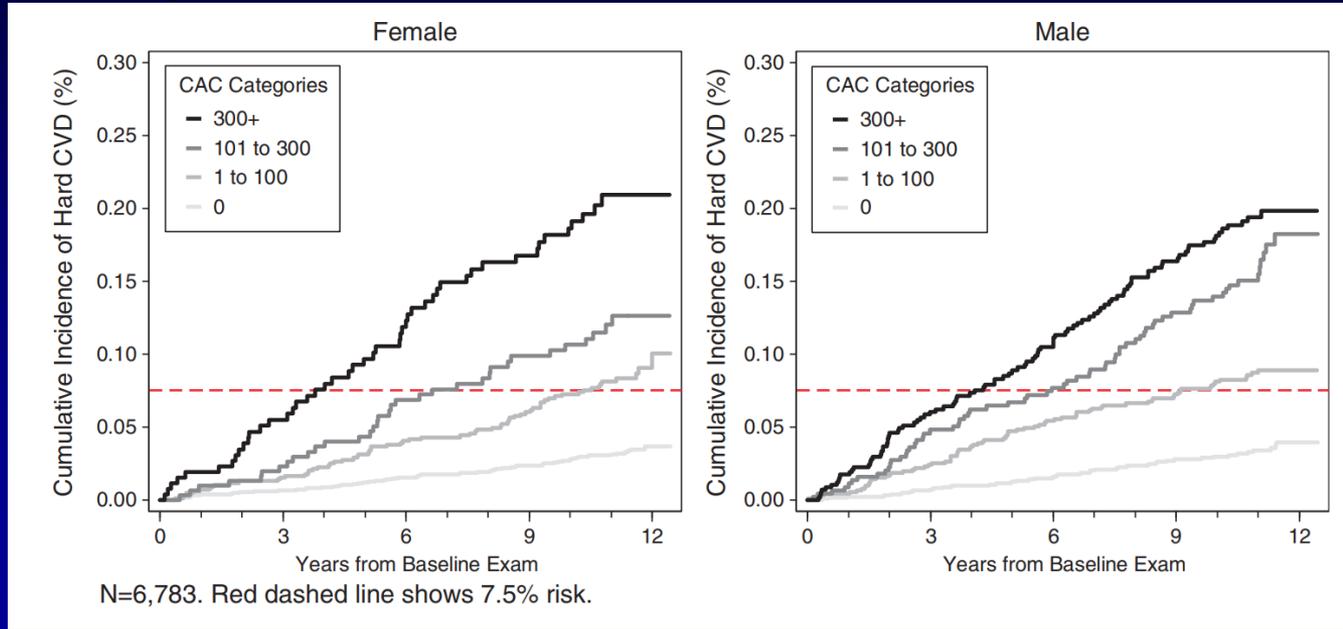
Recommendations	Class	Level
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.	<b>Ila</b>	<b>C</b>
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	<b>Ila</b>	<b>C</b>

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# 5- Imaging helps in risk determination

## Ten-year association of coronary artery calcium with ASCVD events: MESA

### (n=6814, age 45-84)

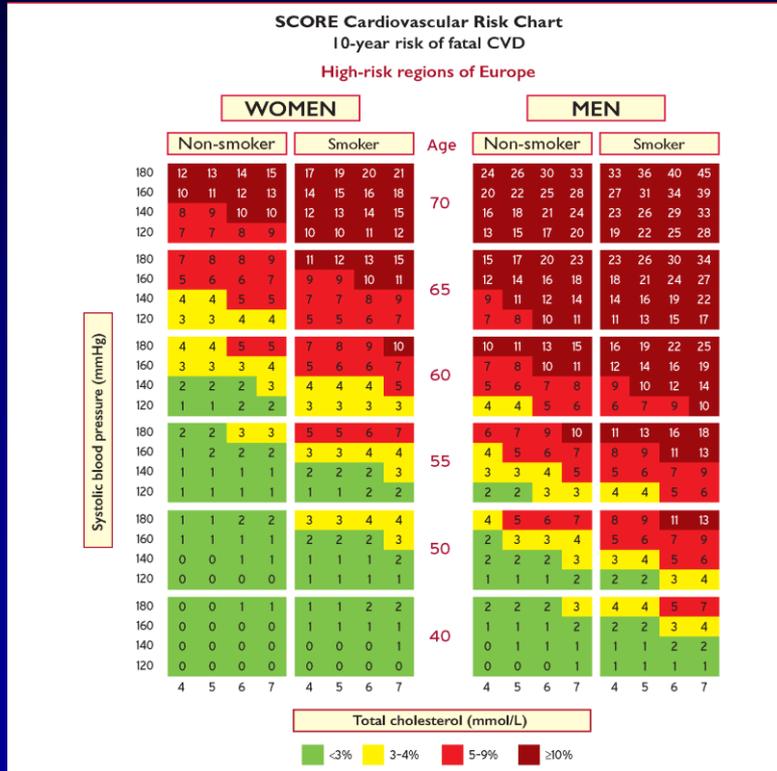


# Recommendations for cardiovascular imaging for risk assessment of atherosclerotic cardiovascular disease

Recommendations	Class	Level
Arterial (carotid and/or femoral) plaque burden on ultrasonography should be considered as a risk modifier in individuals at low or moderate risk.	<b>Ia</b>	<b>B</b>
CAC score assessment with CT should be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk.	<b>Ia</b>	<b>B</b>

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# 5- Determine risk, be more aggressive as risk increases

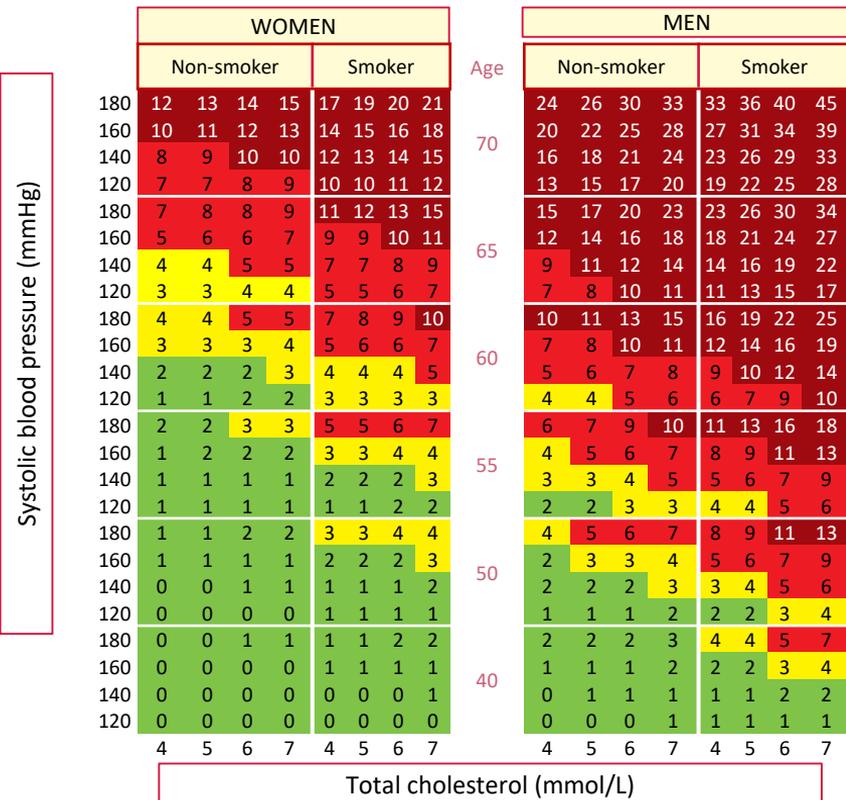


- ♥ CVD
- ♥ DM
- ♥ CKD
- ♥ FH
- ♥ Markedly elevated RF

# SCORE Cardiovascular Risk Chart

## 10-year risk of fatal CVD

### High-risk regions of Europe



## SCORE chart for European populations at high cardiovascular disease risk



# Cardiovascular risk categories (1)

## 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<sup>2</sup>).

A calculated SCORE ≥10% for 10-year risk of fatal CVD.

FH with ASCVD or with another major risk factor.

# Cardiovascular risk categories (2)

High-risk	<p>People with:</p> <ul style="list-style-type: none"><li>Markedly elevated single risk factors, in particular TC &gt;8 mmol/L (&gt;310 mg/dL), LDL-C &gt;4.9 mmol/L (&gt;190 mg/dL), or BP ≥180/110mmHg.</li><li>Patients with FH without other major risk factors.</li><li>Patients <u>with DM without target organ damage*</u>, with DM duration ≥10years or another additional risk factors.</li><li>Moderate CKD (eGFR 30–59 mL/min/1.73 m<sup>2</sup>).</li><li>A calculated SCORE ≥5% and &lt;10% for 10-year risk of fatal CVD.</li></ul>
Moderate-risk	<p>Young patients (T1DM &lt;35 years; T2DM &lt;50 years) <u>with DM duration &lt;10years, without</u> other risk factors. Calculated SCORE ≥1% and &lt;5% for 10-year risk of fatal CVD.</p>
Low-risk	<p>Calculated SCORE &lt;1% for 10-year risk of fatal CVD.</p>

\*Target organ damage is defined as microalbuminuria, retinopathy or neuropathy

## Factors modifying SCORE risks

Social deprivation – the origin of many of the causes of CVD.
Obesity and central obesity as measured by the body mass index and waist circumference, respectively.
Physical inactivity.
Psychosocial stress including vital exhaustion.
Family history of premature CVD (men: <55 years; women: <60 years).
Chronic immune-mediated inflammatory disorder.
Major psychiatric disorders.
Treatment for human immunodeficiency virus (HIV) infection.
Atrial fibrillation.
Left ventricular hypertrophy.
Chronic kidney disease.
Obstructive sleep apnoea syndrome.
Non-alcoholic fatty liver disease.

# Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

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)
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 <sup>a</sup> /Level <sup>b</sup>	I/C	I/C	I/C	I/C	Ia/A	Ia/A
	≥1 to <5, or moderate risk	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 <sup>a</sup> /Level <sup>b</sup>	I/C	I/C	Ia/A	Ia/A	Ia/A	Ia/A
	≥5 to <10, or high-risk	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 <sup>a</sup> /Level <sup>b</sup>	Ia/A	Ia/A	Ia/A	I/A	I/A	I/A
	≥10, or at very-high risk due to a risk condition	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 <sup>a</sup> /Level <sup>b</sup>	Ia/B	Ia/A	I/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			
	Class <sup>a</sup> /Level <sup>b</sup>	Ia/A	I/A	I/A	I/A	I/A	I/A

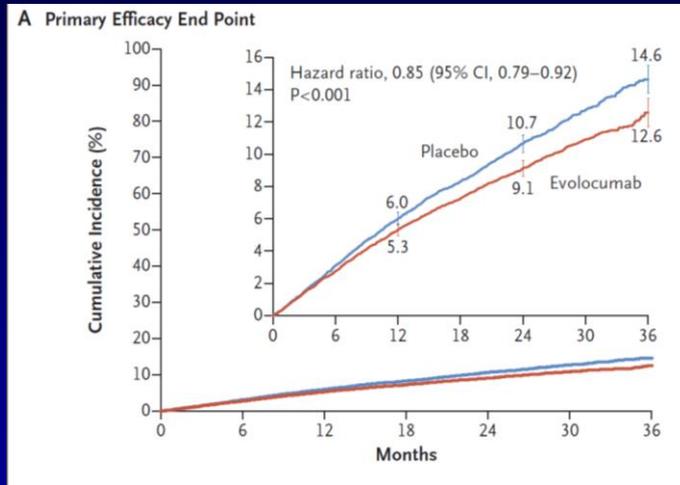
## 6- Intensification of treatment goals

### LDL-C Goals: Evidence from outcome trials

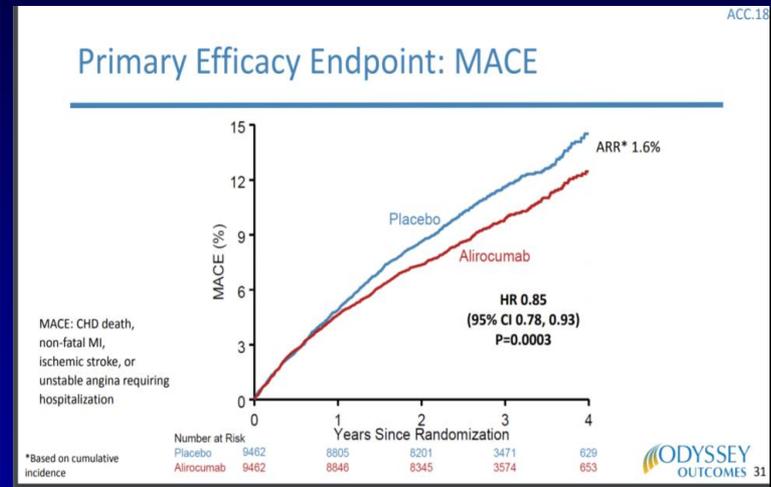
Data not available

# Evidence for benefit from further lowering LDL-C

## FOURIER



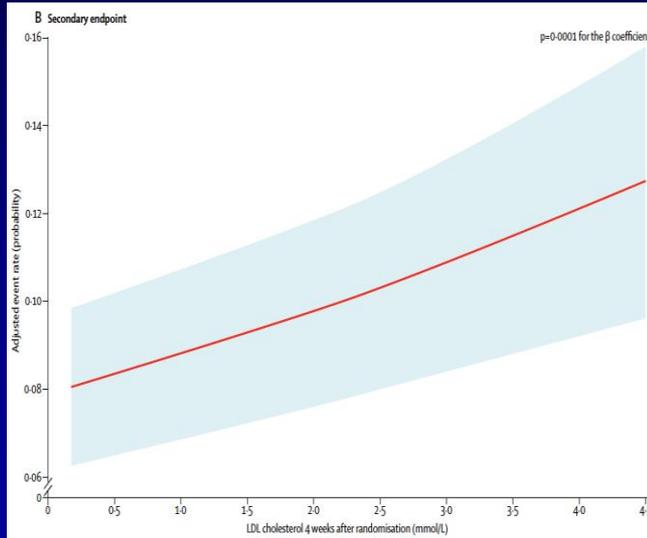
## ODYSSEY Outcomes



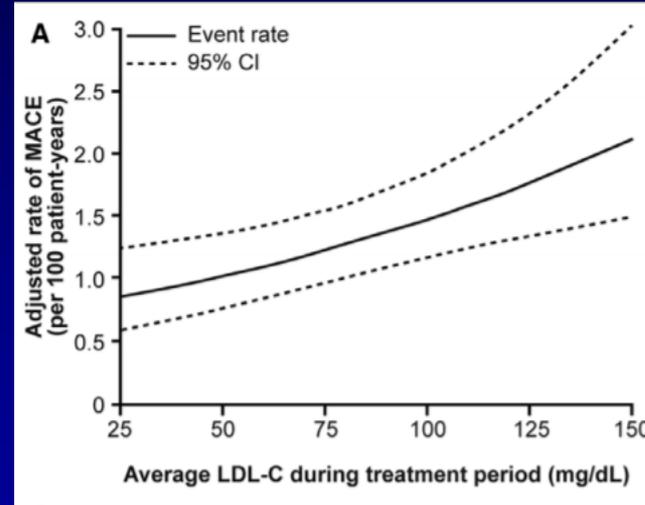
N Engl J Med 2018; 379:2097  
N Engl J Med 2017;376: 1713

# Risk reduction continues even at very low levels without threshold : No J curve

## FOURIER



## 10 ODYSSEY trials



Lancet. 2017;390:1962-1971  
Circulation. 2016;134:1931

# Recommendations for treatment goals for low-density lipoprotein cholesterol (1)

Recommendations	Class	Level
In secondary prevention patients at <u>very-high risk</u> <sup>c</sup> , an LDL-C reduction of at least 50% from baseline <sup>d</sup> and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	A
In primary prevention, for individuals at very-high risk but without FH <sup>c</sup> , an LDL-C reduction of at least 50% from baseline <sup>d</sup> and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	C
In patients at <u>high-risk</u> <sup>c</sup> , an LDL-C reduction of at least 50% from baseline <sup>d</sup> and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.	I	A

<sup>c</sup>For definitions see Table 1.

<sup>d</sup>The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

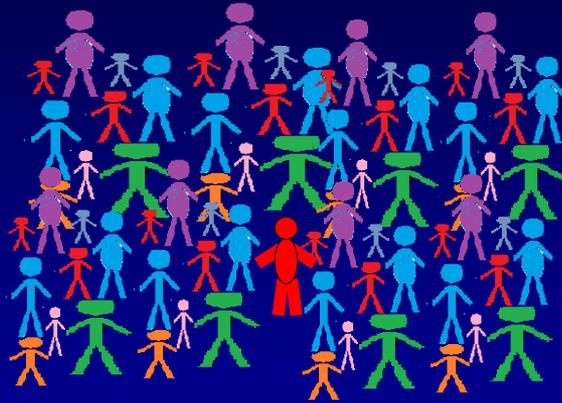
# Recommendations for treatment goals for low-density lipoprotein cholesterol (3)

Recommendations	Class	Level
In individuals at moderate risk <sup>c</sup> , an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.	<b>Ila</b>	<b>A</b>
In individuals at low risk <sup>c</sup> an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.	<b>Ilb</b>	<b>A</b>

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<sup>c</sup> For definitions see Table 1.

**Even secondary prevention patients are not homogenous in their risk!**



**Which high risk patients need to be treated more aggressively ?**

# Recommendations for treatment goals for low-density lipoprotein cholesterol (2)

Recommendations	Class	Level
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.	<b>IIb</b>	<b>B</b>

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<sup>c</sup> For definitions see Table 1.

<sup>d</sup> The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

# 7- Pharmacotherapy

# Recommendations for pharmacological low-density lipoprotein cholesterol lowering (1)

Recommendations	Class	Level
It is recommended to prescribe a high-intensity statin up to the highest tolerated dose to reach the goals <sup>c</sup> set for the specific level of risk.	I	A
If the goals <sup>c</sup> are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.	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 statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C

<sup>c</sup> For definitions see Full Text.

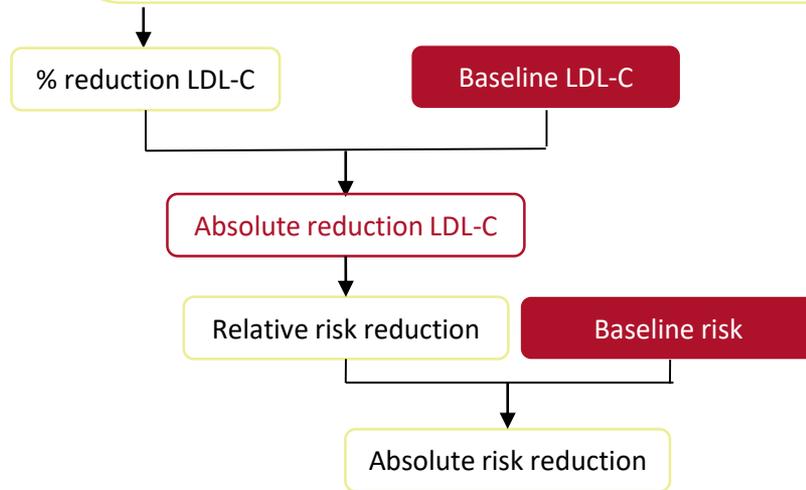
©ESC

# Recommendations for pharmacological low-density lipoprotein cholesterol lowering (2)

Recommendations	Class	Level
For secondary prevention, patients at very-high risk not achieving their goal <sup>c</sup> on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal on a maximum tolerated dose of 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 re-challenge), ezetimibe should be considered.	Ila	C

### Intensity of lipid lowering treatment

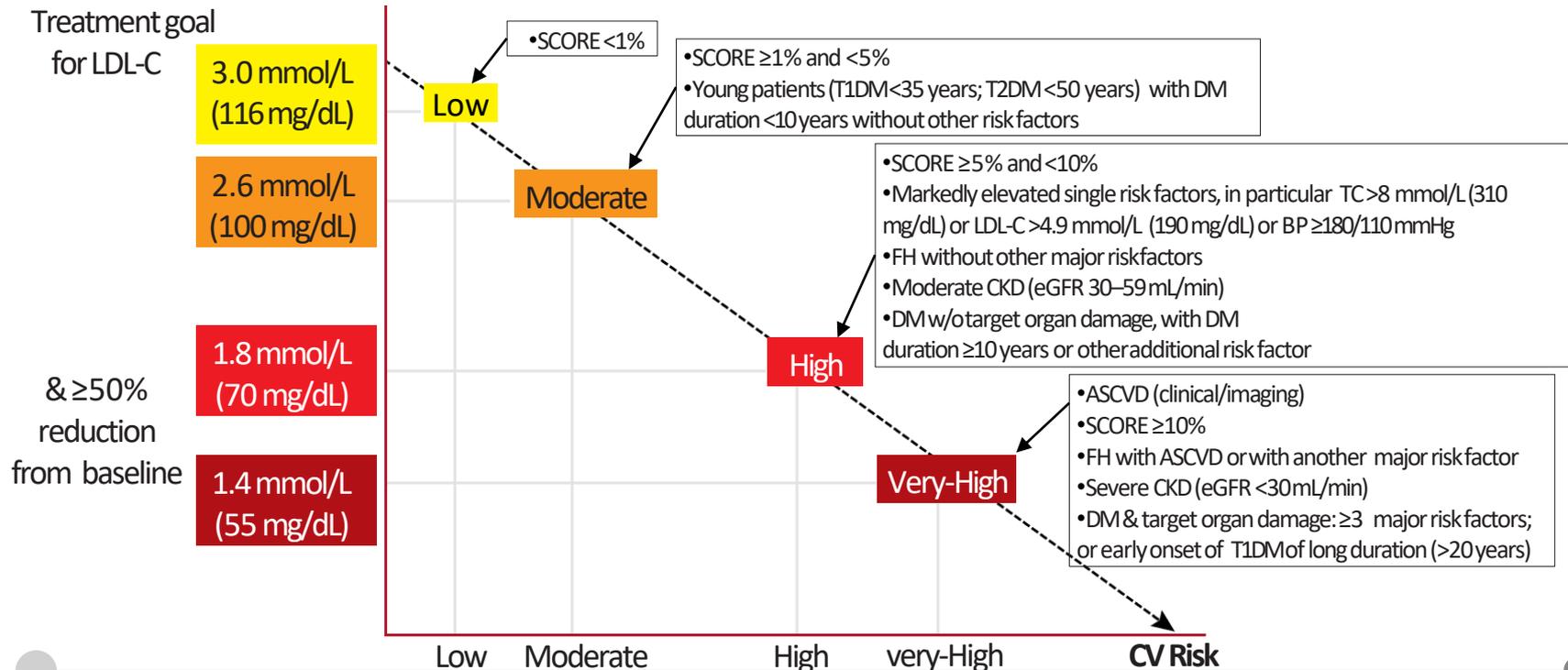
Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%



## Expected clinical benefit of low-density lipoprotein cholesterol lowering therapies

LDL-C = low-density lipoprotein cholesterol;  
 PCSK9 = proprotein convertase subtilisin/kexin type 9.

# Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk



**FH is underdiagnosed, undertreated and  
can be easily detected if we look for it !**

# Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia (1)

Criteria	Points
1) Family history	
First-degree relative with known premature (men <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 <18 years of age with LDL-C above the 95th percentile	2
2) Clinical history	
Patient with premature (men <55 years; women <60 years) coronary artery disease	2
Patient with premature (men <55 years; women <60 years) cerebral or peripheral vascular disease	1

# Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia (2)

Criteria	Points
3) Physical examination <sup>a</sup>	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL-C levels (without treatment)	
LDL-C $\geq$ 8.5 mmol/L ( $\geq$ 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

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<sup>a</sup> Exclusive of each other (i.e. maximum 6 points if both are present).

# Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia (3)

Criteria	Points
5) DNA analysis	
Functional mutation in the <i>LDLR</i> , <i>ApoB</i> or <i>PCSK9</i> 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	

# Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia (1)

Recommendations	Class	Level
It is recommended to consider the diagnosis of FH 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 confirm, when available, with DNA analysis.	I	C

# Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia (2)

Recommendations	Class	Level
Once the index case is diagnosed, family cascade screening is recommended.	I	C
It is recommended to treat FH patients with ASCVD or who have another major risk factor as very-high-risk, and those with no prior ASCVD or other risk factors as high-risk.	I	C
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.	I	C

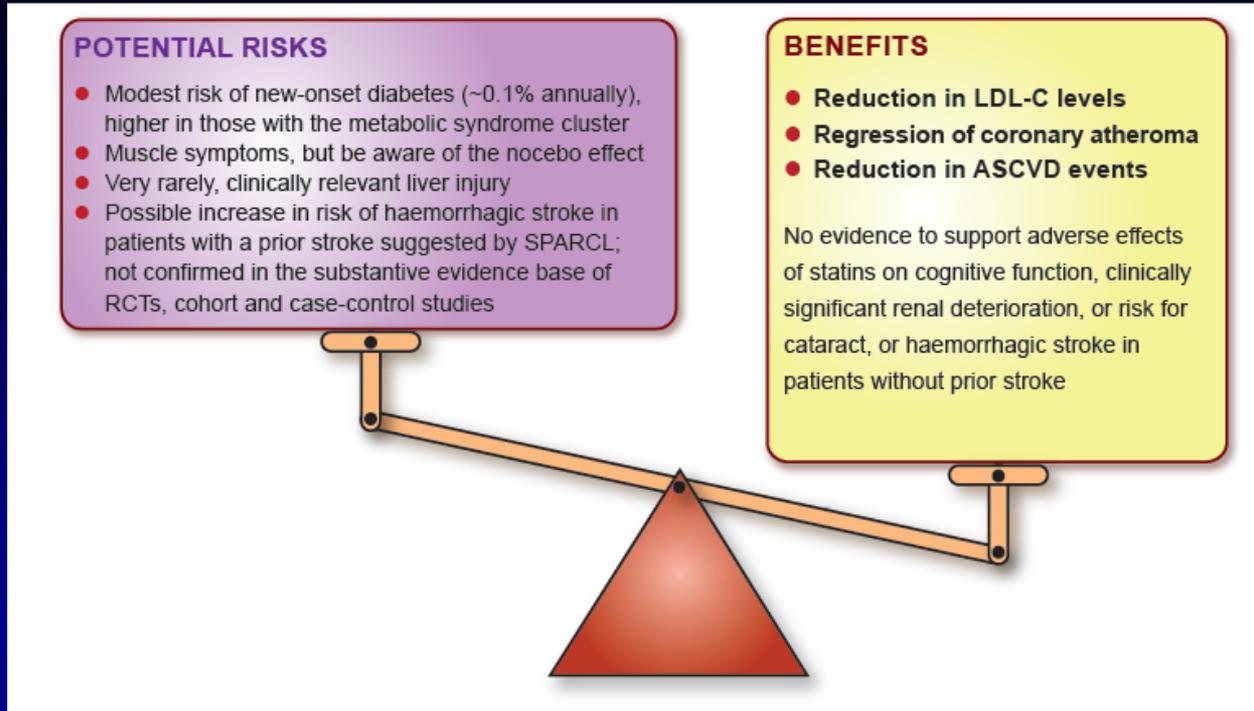
# Recommendations for lipid management in patients with moderate to severe (KDOQI stages 3–5)\* chronic kidney disease

Recommendations	Class	Level
It is recommended that patients with Kidney Disease Outcomes Quality Initiative stage 3–5 CKD are considered to be at high or very-high risk of ASCVD.	<b>I</b>	<b>A</b>
The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent stage 3–5 CKD.	<b>I</b>	<b>A</b>
In patients already on statins, ezetimibe or a statin/ ezetimibe combination at the time of dialysis initiation, continuation of these drugs should be considered, particularly in patients with ASCVD.	<b>IIa</b>	<b>C</b>
In patients with dialysis-dependent CKD and free of ASCVD, commencing statin therapy is not recommended.	<b>III</b>	<b>A</b>

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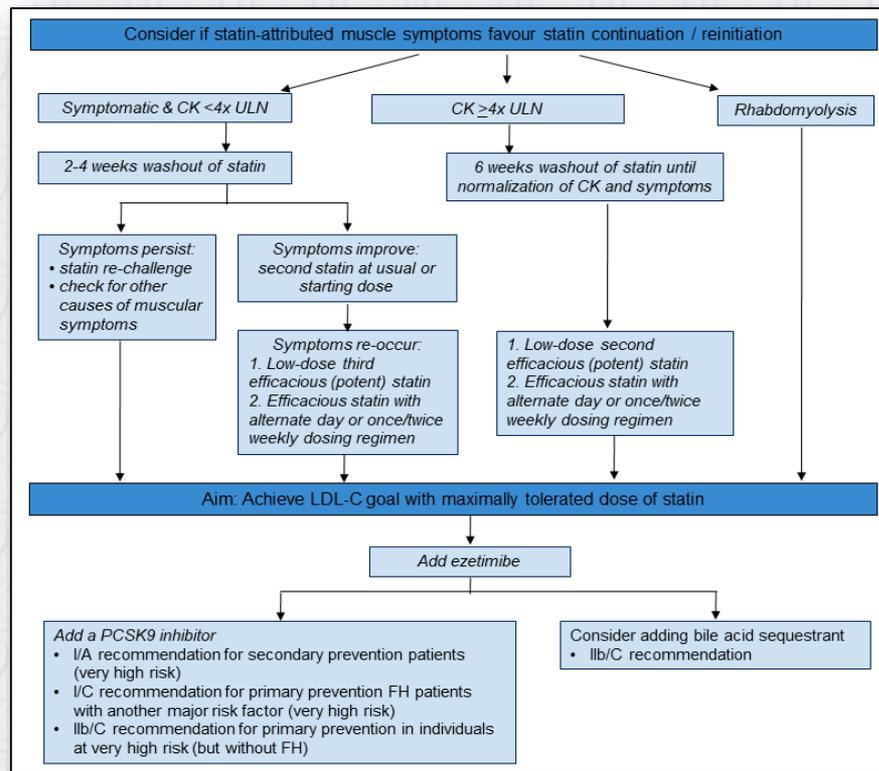
# 8-STATIN INTOLERANCE

## STATINS: HIGHLY FAVOURABLE BENEFIT VS. RISK RATIO



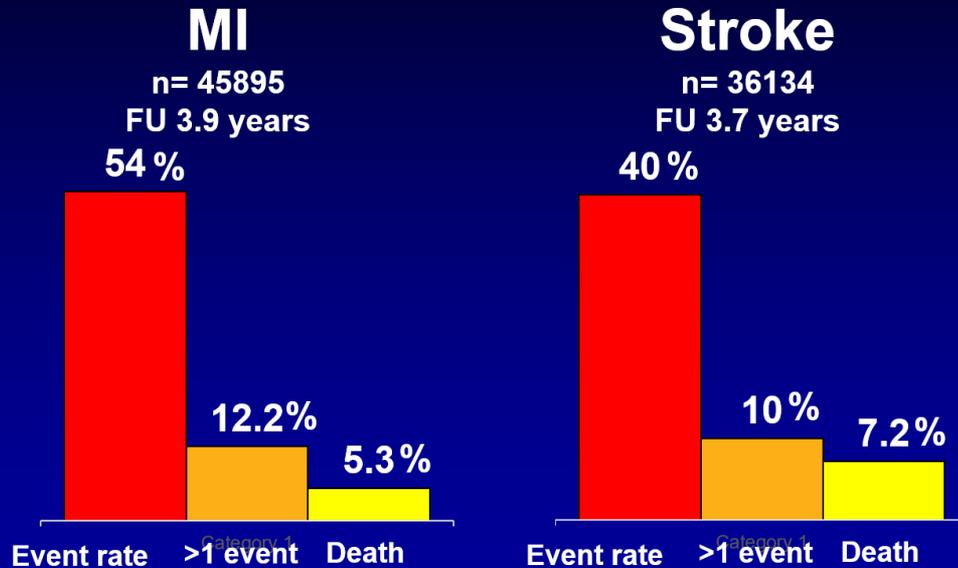
*the established cardiovascular benefits of statin therapy far outweigh the risk of any such adverse effects ‘*

# Algorithm for treatment of muscular symptoms during statin treatment: Distinction between SAMS and myopathy



# 9- ACS treatment

## CV Event Rates in a High Risk Population:



# Recommendations for lipid-lowering therapy in very-high-risk patients with acute coronary syndromes (1)

Recommendations	Class	Level
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.	<b>I</b>	<b>A</b>
Lipid levels should be re-evaluated 4–6 weeks after ACS to determine whether a reduction of at least 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.	<b>IIa</b>	<b>C</b>
If the LDL-C goal is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.	<b>I</b>	<b>B</b>

©ESC

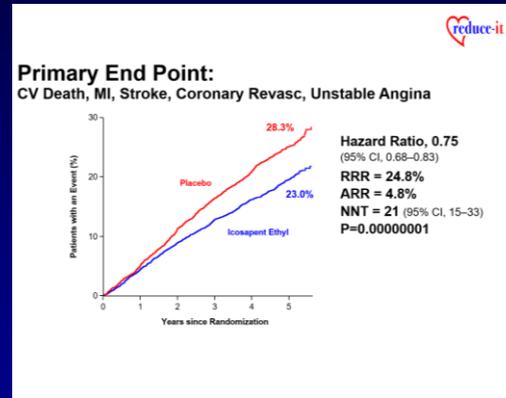
# Recommendations for lipid-lowering therapy in very-high-risk patients with acute coronary syndromes (2)

Recommendations	Class	Level
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.	<b>I</b>	<b>B</b>
In patients with confirmed statin intolerance or in patients in whom a statin is contra-indicated, ezetimibe should be considered.	<b>Ila</b>	<b>C</b>
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.	<b>Ila</b>	<b>C</b>

# 10- Hypertriglyceridemia treatment

# High dose omega -3 fatty acids in high risk patients: REDUCE-IT

- ♥ 8179 patients with CV event or DM+ one risk factor and high TG
- ♥ All on statin
- ♥ Randomised to 4 gr pure EPA or placebo
- ♥ 4.9 year follow up
- ♥ Primary end point :CV death,MI,stroke, revascularization,UA
- ♥ TGs reduced 20%,**CRP 40 %**



N Engl J Med 2019; 380:11

## Recommendations for drug treatments of patients with hypertriglyceridaemia

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia (TG >2.3 mmol/L (200 mg/dL)). <sup>{Vallejo-Vaz, 2018 #579}</sup>	<b>I</b>	<b>B</b>
In high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135-499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 x 2g/day) should be considered in combination with statin. <sup>{Bhatt, 2019 #57}</sup>	<b>IIa</b>	<b>B</b>
In primary prevention patients who are at LDL-C goal with TG >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins. <sup>{Catapano, 2014 #86;Chapman, 2010 #91;Keech, 2005 #284;Kotseva, 2010 #303}</sup>	<b>IIb</b>	<b>B</b>
In high-risk patients who are at LDL-C goal with TG >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins. <sup>{Catapano, 2014 #86;Chapman, 2010 #91;Keech, 2005 #284;Kotseva, 2010 #303}</sup>	<b>IIb</b>	<b>C</b>

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = ; polyunsaturated fatty acids; TG = triglycerides.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.