



PRESENT
AND FUTURE
APPROACHES TO
THE CONTROL OF
DYSLIPIDAEMIAS

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SOCIETÀ ITALIANA DI TERAPIA CLINICA E SPERIMENTALE

ESC/EAS 2019 Guidelines for the management of dyslipidaemias

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Disclosure of potential conflicts of interest

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2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (1)

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¹Representing the European Atherosclerosis Society (EAS)

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (2)

ESC entities having participated in the development of this document:

Associations: Acute Cardiovascular Care Association (ACCA), Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Interventions (EAPCI).

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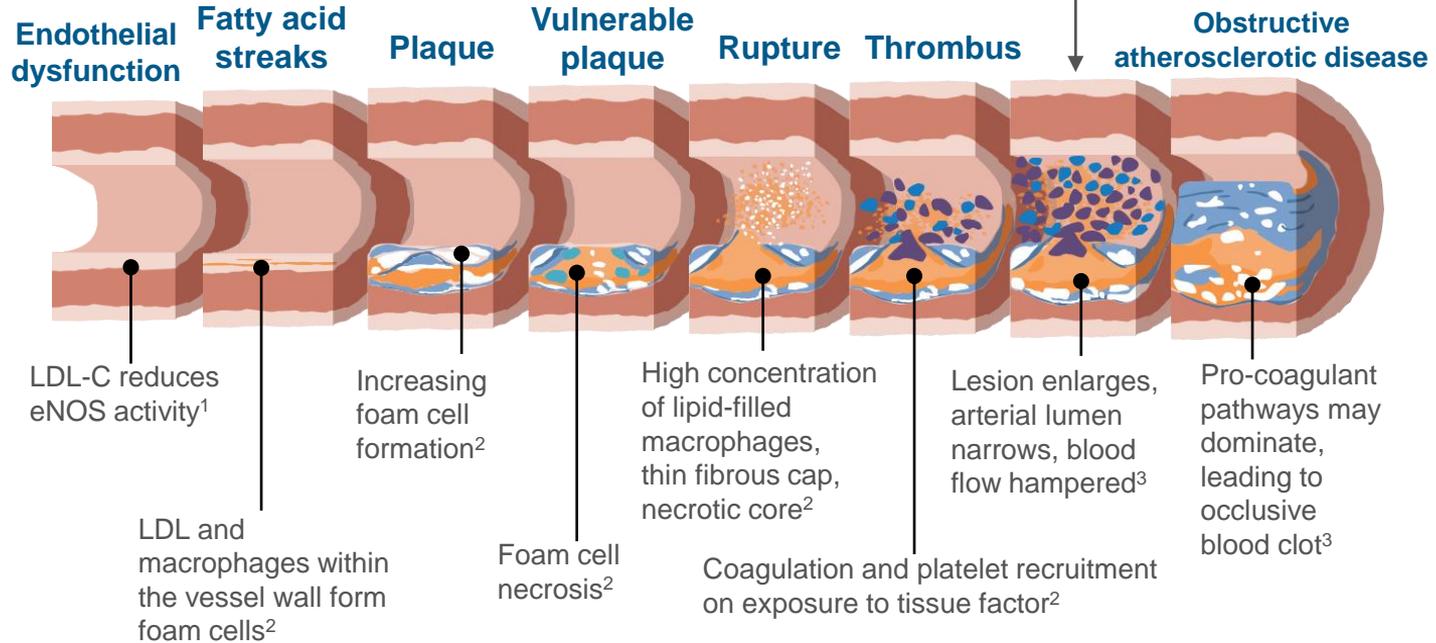
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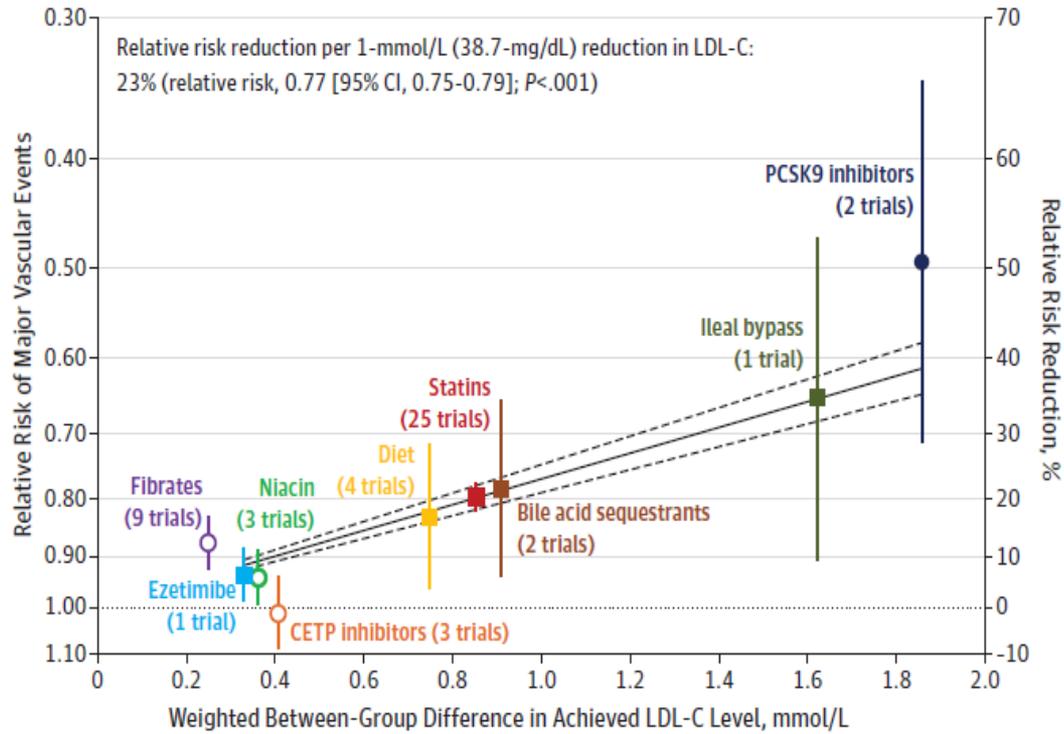
LDL-C is involved at every stage of atherosclerotic plaque formation

Acute event

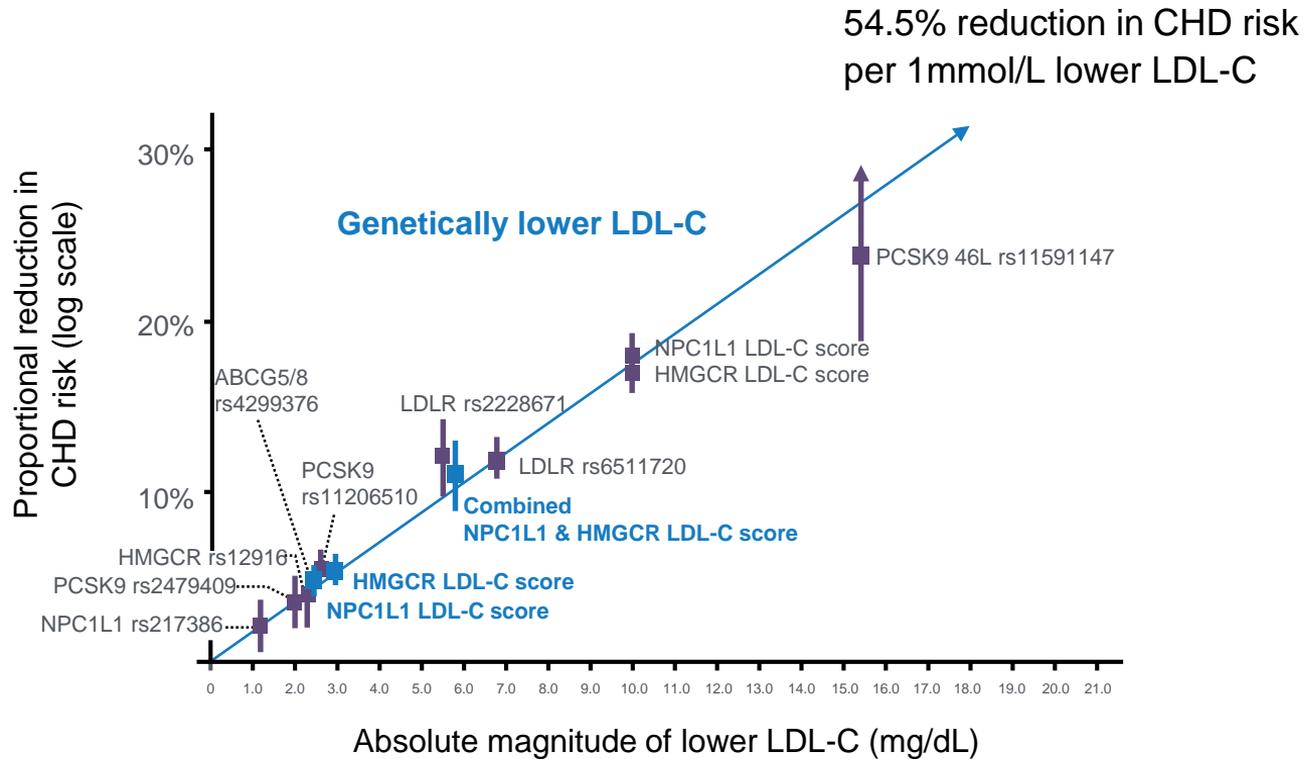
- Cardiac vessels – MI
- Brain vessels – stroke
- Peripheral vessels – critical limb ischaemia



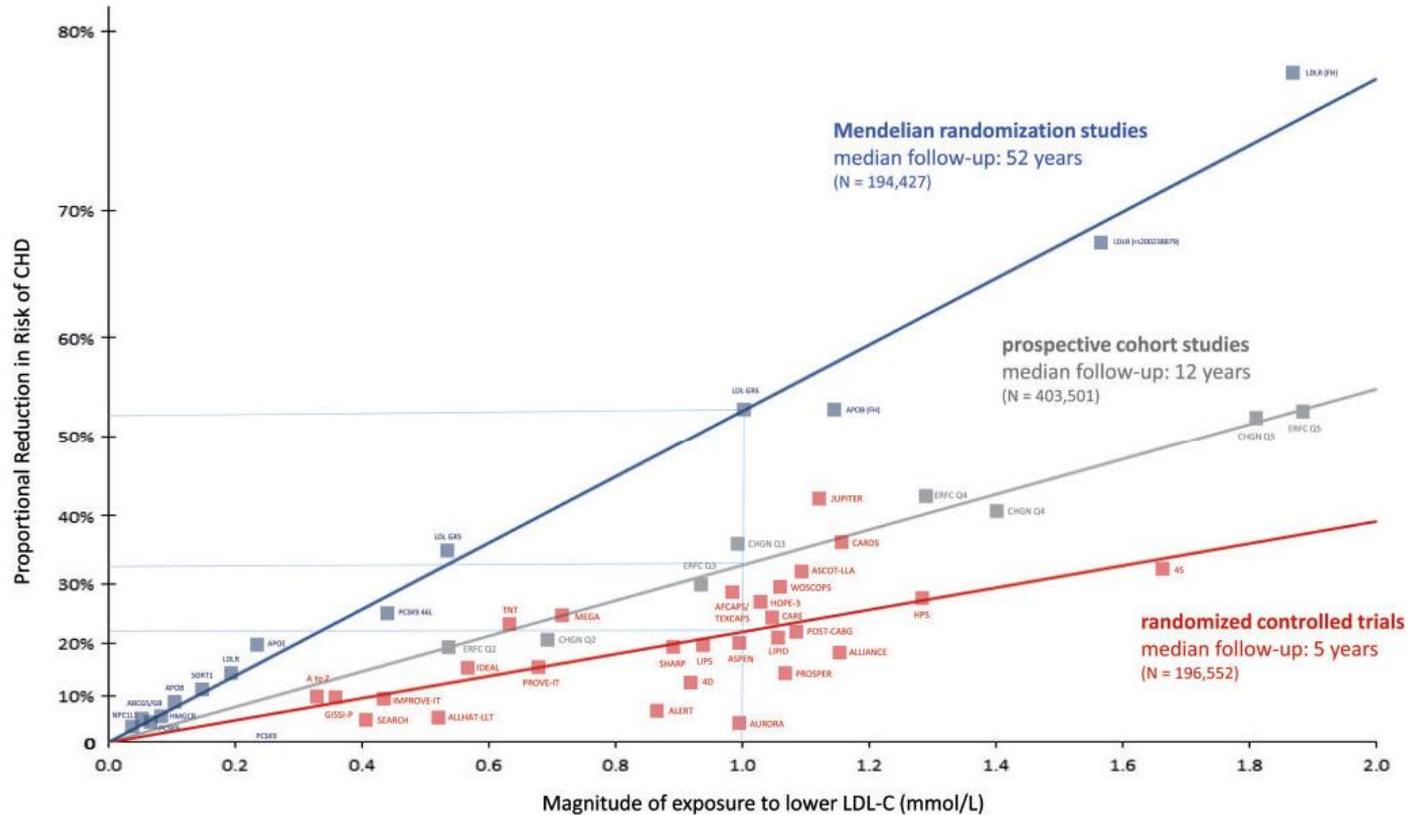
Meta-analysis of various methods to lower LDL-C

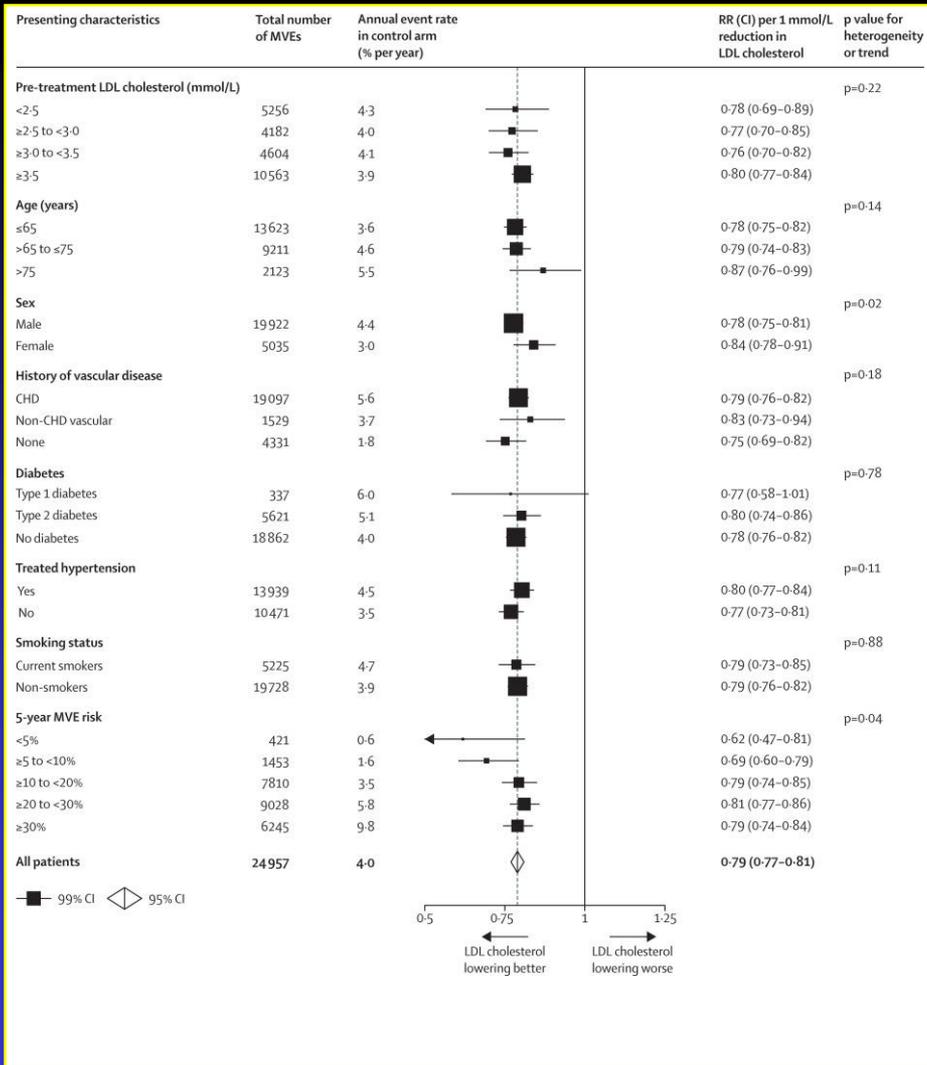


Genetic evidence supports LDL-C as a risk factor for CV events



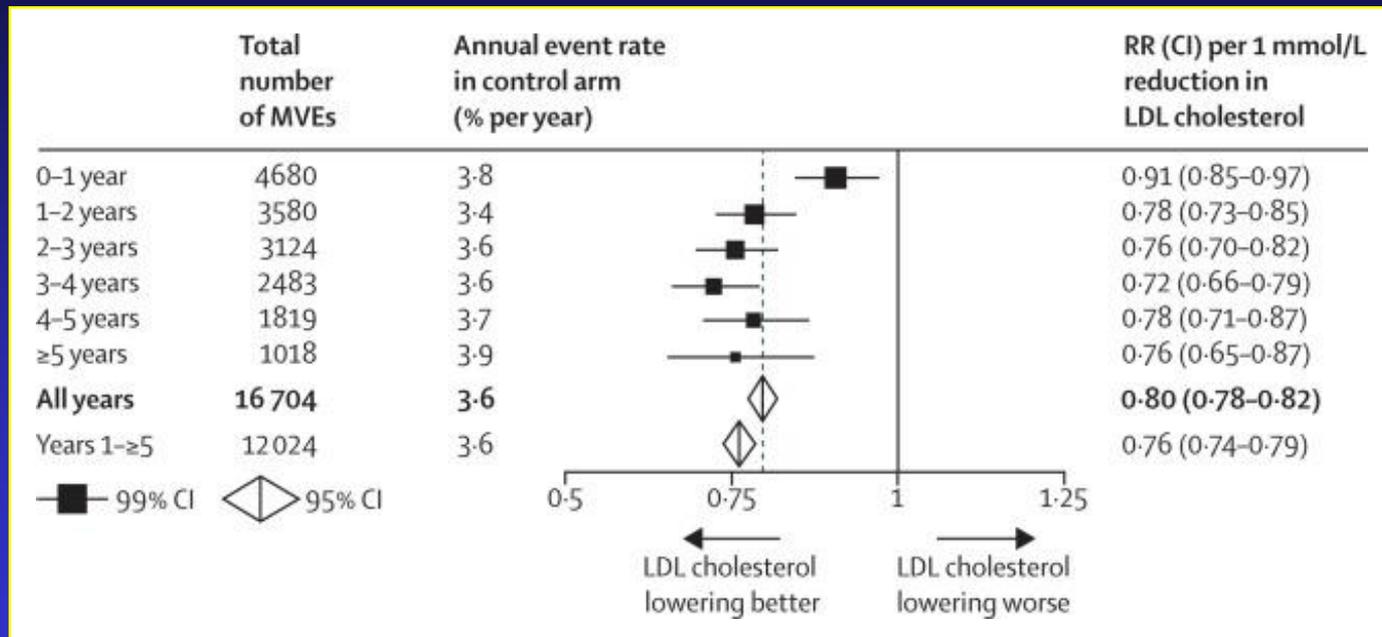
Effect of LDL-C by magnitude and duration of exposure



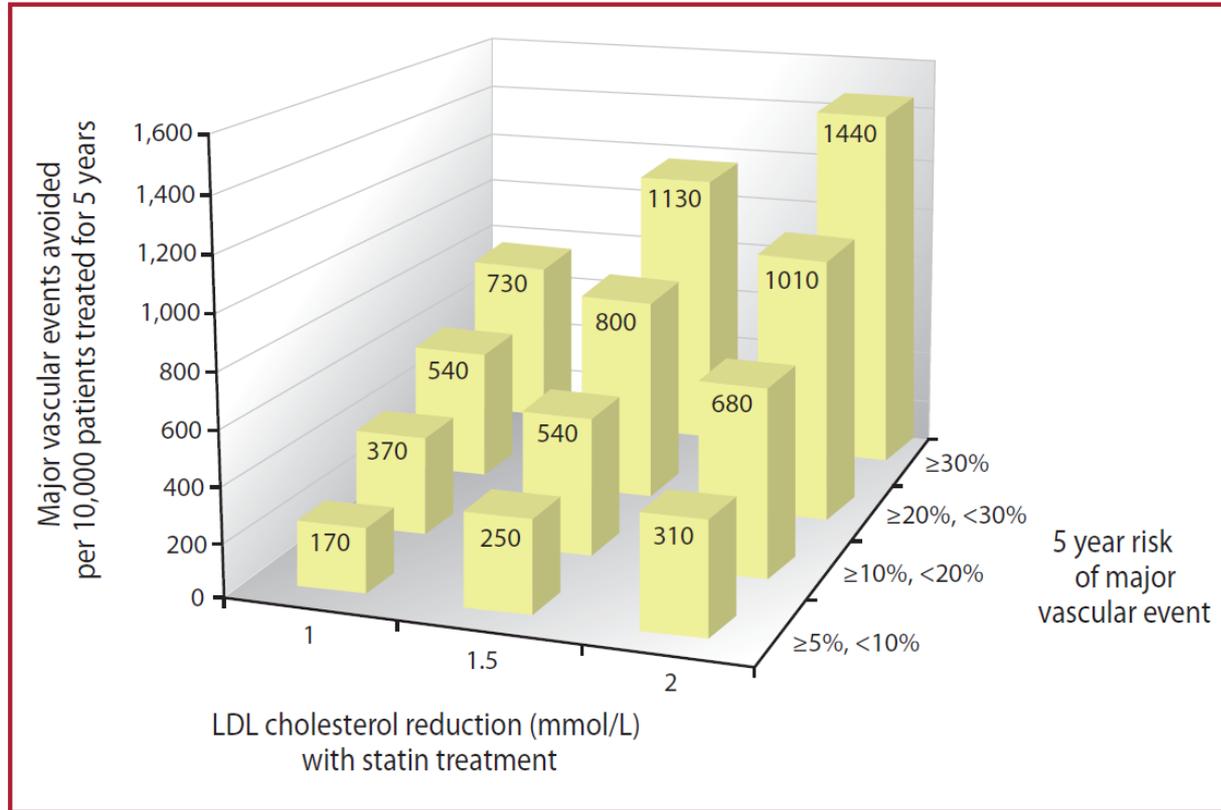


Similar proportional reductions in risks of major vascular events per mmol/L LDL cholesterol reduction in randomised trials of statin therapy among people with different presenting characteristics

Proportional reductions in risks of major vascular events per mmol/L reduction in LDL cholesterol during each year of scheduled statin treatment, in randomised trials of routine statin therapy versus no routine statin use



Absolute reductions in major vascular events with statin therapy



Main principles for LDL-lowering therapy

- Genetic, epidemiological and trial evidence indicates that LDL cholesterol is a CAUSE of atherosclerotic vascular disease
- Trials of LDL-lowering indicate RELATIVE RISK reduction is proportional to the ABSOLUTE REDUCTION in LDL-C
- Lower is better: lowering LDL-C with statins, ezetimibe, or PCSK9-inhibitors safe and effective to <1.4 mmol/L (55 mg/dL)
- Cholesterol Treatment Trialists' Collaboration
- Data on ezetimibe from the IMPROVE-IT trial
- Data from large randomized trials of PCSK9 inhibitors
- Intensity of LDL-lowering should be based on risk, irrespective of cause(s) of the risk (e.g., primary or secondary prevention, diabetes, or chronic kidney disease)

ESC Classes of recommendations

	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

ESC Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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 m²).

A calculated SCORE $\geq 10\%$ 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">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 \geq180/110mmHg.Patients with FH without other major risk factors.Patients with DM without target organ damage*, with DM duration \geq10years or another additional risk factors.Moderate CKD (eGFR 30–59 mL/min/1.73 m²).A calculated SCORE \geq5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	<p>Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10years, without other risk factors. Calculated SCORE \geq1% and <5% for 10-year risk of fatal CVD.</p>
Low-risk	<p>Calculated SCORE <1% for 10-year risk of fatal CVD.</p>

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

Recommended treatment goals for LDL-lowering therapy: main changes from 2016 to 2019

Risk category	LDL goals (starting with untreated LDL-C)	
	2016	2019
Very-high-risk	<1.8 mmol/L (70 mg/dL) or >50% ↓ if LDL-C 1.8-3.5 (70 - 135 mg/dL)	<1.4 mmol/L (55 mg/dL) and >50% ↓
High-risk	<2.6 mmol/L (100mg/dL) or >50% ↓ if LDL-C 2.6-5.2 (100 - 200 mg/dL)	<1.8 mmol/L (70 mg/dL) and >50% ↓
Moderate-risk	<3.0 mmol/L (115 mg/dL)	< 2.6 mmol/L (100 mg/dL)
Low-risk	<3.0 mmol/L (115 mg/dL)	<3.0 mmol/L (115 mg/dL)

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 ^a /Level ^b	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 ^a /Level ^b	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 ^a /Level ^b	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 ^a /Level ^b	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 ^a /Level ^b	Ia/A	I/A	I/A	I/A	I/A	I/A

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

Recommendations	Class	Level
In secondary prevention patients at very-high risk ^c , an LDL-C reduction of at least 50% from baseline ^d 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 ^c , an LDL-C reduction of at least 50% from baseline ^d and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	C
In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	Ila	C

^cFor definitions see Table 1.

^dThe 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 (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.	IIb	B
In patients at high-risk ^c , an LDL-C reduction of at least 50% from baseline ^d and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.	I	A

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^c For definitions see Table 1.

^d 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.

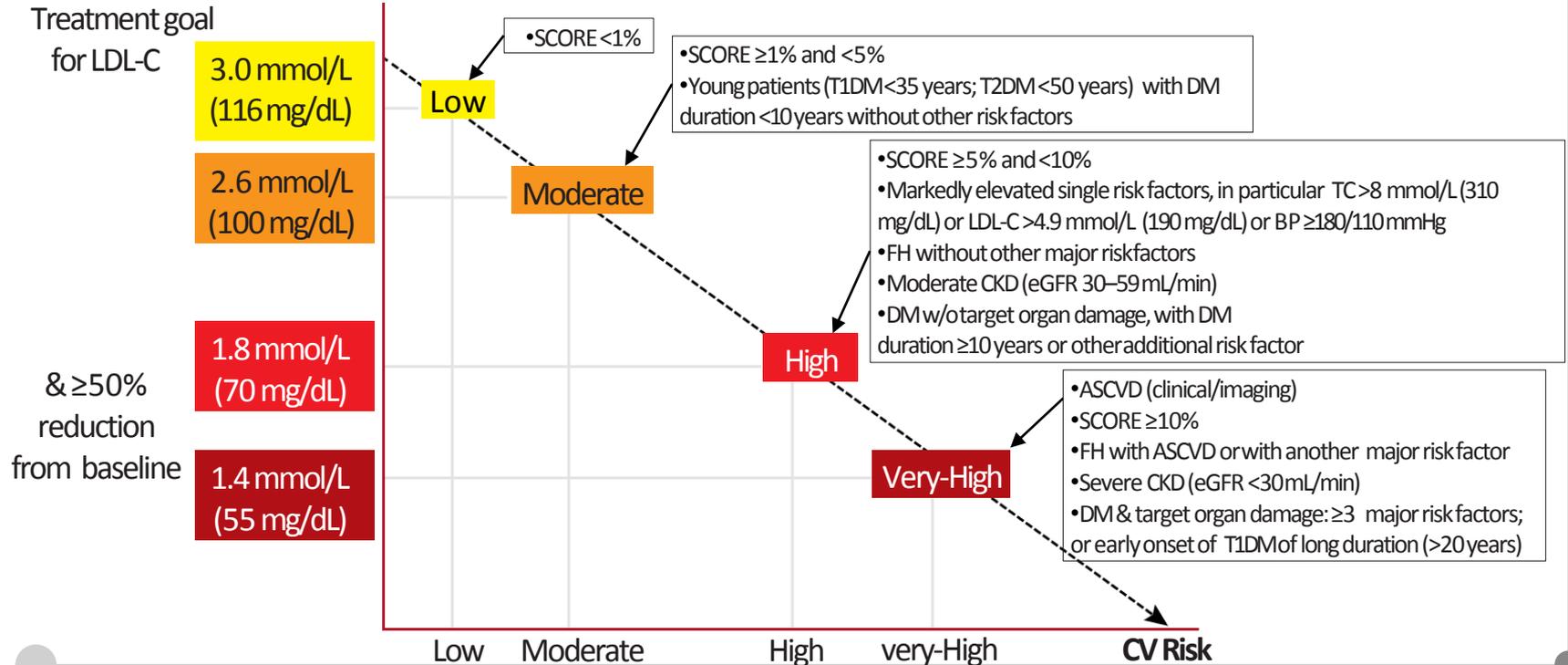
Recommendations for treatment goals for low-density lipoprotein cholesterol (3)

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

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^c For definitions see Table 1.

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



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 ^c set for the specific level of risk.	I	A
If the goals ^c 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

^c For definitions see Full Text.

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

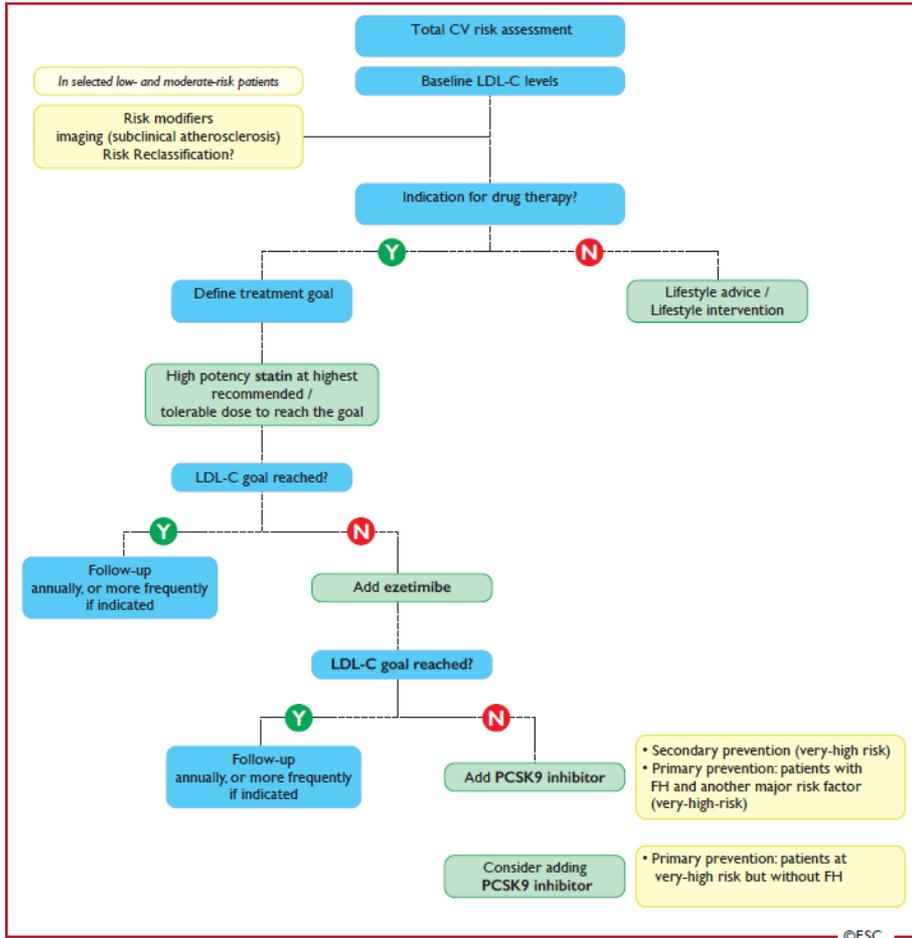
Recommendations	Class	Level
For secondary prevention, patients at very-high risk not achieving their goal ^c on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) 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

Recommendations for pharmacological low-density lipoprotein cholesterol lowering (3)

Recommendations	Class	Level
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.	IIb	C
If the goal ^c is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

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^c For definitions see Full Text.



Treatment algorithm for pharmacological LDL-C lowering

Recommendations for drug treatments of patients with hypertriglyceridaemia (1)

Recommendations	Class	Level
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)).	I	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 2 g/day) should be considered in combination with statin.	Ila	B

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Recommendations for drug treatments of patients with hypertriglyceridaemia (2)

Recommendations	Class	Level
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.	IIb	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.	IIb	C

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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

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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

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Recommendations for the detection & treatment of EAS patients with heterozygous familial hypercholesterolaemia (3)



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Recommendations	Class	Level
In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
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 homozygous FH 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

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Management of dyslipidaemia in women

Statin treatment is recommended for primary prevention of ASCVD in high-risk women.

Statins are recommended for secondary prevention in women with the same indications and goals as in men.

Lipid-lowering drugs should not be given when pregnancy is planned, during pregnancy or during the breastfeeding period. However, for severe FH patients, bile acid sequestrants (which are not absorbed) and/or LDL apheresis may be considered.

Recommendations for the treatment of dyslipidaemias in older people (aged >65 years)

Recommendations	Class	Level
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.	I	A
Treatment with statins is recommended for primary prevention, according to level of risk, in older people aged ≤ 75 .	I	A
Initiation of statin treatment for primary prevention in older people aged > 75 may be considered, if at high risk or above.	IIb	B
It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.	I	C

Recommendations for the treatment of dyslipidaemias in diabetes (1)

Recommendations	Class	Level
In patients with T2DM at very-high risk ^c , an LDL-C reduction of at least 50% from baseline and LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended.	I	A
In patients with T2DM at high risk ^c an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.	I	A
Statins are recommended in patients with T1DM who are at high or very-high-risk ^c .	I	A

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^c See Table in Full Text.

Recommendations for the treatment of dyslipidaemias in diabetes (2)

Recommendations	Class	Level
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
If the goal is not reached, statin combination with ezetimibe should be considered.	IIa	B
Statin therapy is not recommended in pre-menopausal patients with diabetes who are considering pregnancy or not using adequate contraception.	III	C
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	C

Summary of dyslipidaemia in metabolic syndrome and type 2 diabetes mellitus

Dyslipidaemia represents a cluster of lipid and lipoprotein abnormalities, including elevation of both fasting and post-prandial TG, ApoB, and small dense LDL, and low HDL-C and ApoA1 levels.

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 may 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.

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.	I	A
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.	IIa	C
If the LDL-C goal is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.	I	B

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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.	I	B
In patients with confirmed statin intolerance or in patients in whom a statin is contra-indicated, ezetimibe should be considered.	Ia	C
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.	Ia	C

Other patient groups addressed by the guidelines

- Chronic kidney disease
- Congestive heart failure
- Stroke
- Percutaneous coronary intervention

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 ^a /Level ^b	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 ^a /Level ^b	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 ^a /Level ^b	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 ^a /Level ^b	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 ^a /Level ^b	Ia/A	I/A	I/A	I/A	I/A	I/A