





WE **GUARD**

Web-basedGuidelinesUpdates,AdvancesEducation& Researches in Dyslipidemia

Module 1 Part 2:

Guidelines-Based Dyslipidemia Management

<u>AGENDA</u>



Recommended ESC/EAS treatment targets and goals for CVD prevention



Treatment algorithm for pharmacological LDL lowering.



Recommendations for drug treatment of patients with hypertriglyceridemia



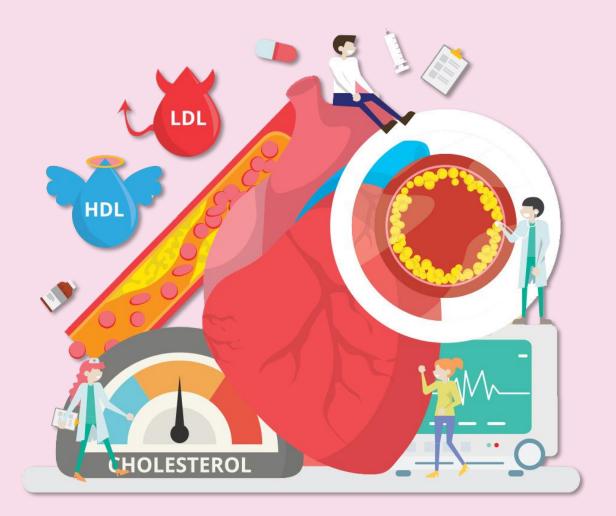
Non-pharmacological Management of Dyslipidemia



Pharmacological Management of Dyslipidemia

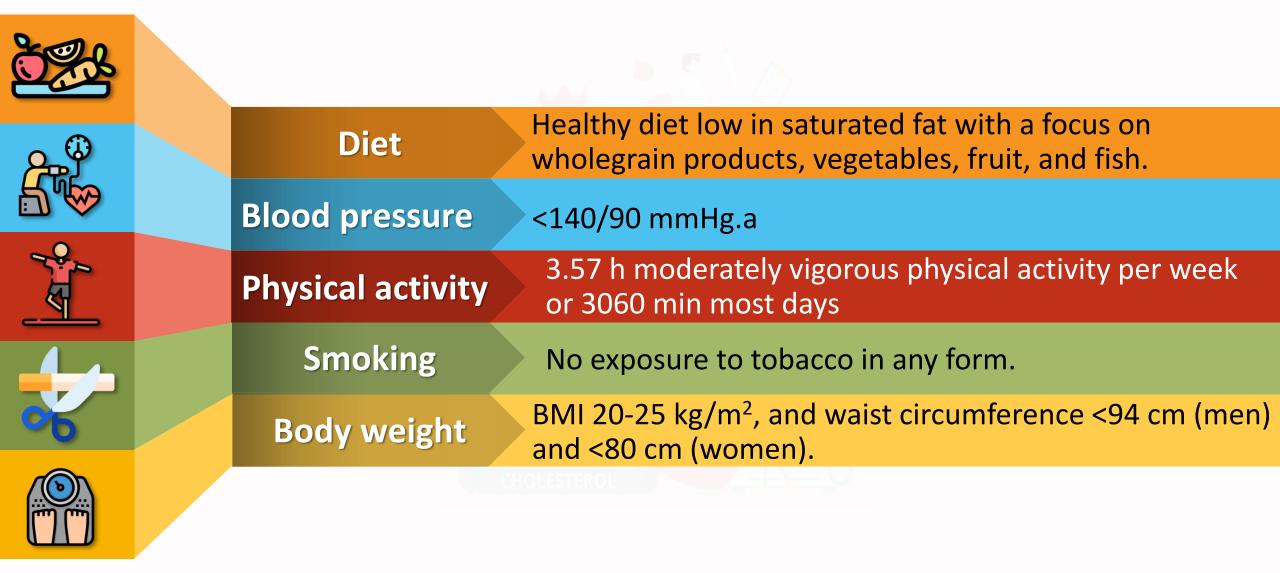


Recommendations for the treatment of dyslipidaemias in older people (aged >65 years)



1. Recommended ESC/EAS treatment targets and goals for GVD prevention





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1. Zodda, D., Giammona, R., & Schifilliti, S. (2018). Treatment Strategy for Dyslipidemia in Cardiovascular Disease Prevention: Focus on Old and New Drugs. Pharmacy (Basel, Switzerland), 6(1), 10. https://doi.org/10.3390/pharmacy6010010.

LDL-C

VERY-HIGH RISK IN PRIMARY OR SECONDARY PREVENTION:

- A therapeutic regimen that achieves ≥ 50% LDL-C reduction from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL).</p>
- 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:

1A

A therapeutic regimen that achieves \geq 50% LDL-C reduction from baseline 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

VERY-HIGH RISK

Secondary goal is <2.2 (<85 mg/dL)

HIGH RISK:

A goal of < 2.6 mmol/L (<100 mg/dL).

MODERATE RISK

A goal of < 3.4 mmol/L (< 130 mg/dL).



АроВ

VERY-HIGH RISK

Secondary goal is <65 mg/dL

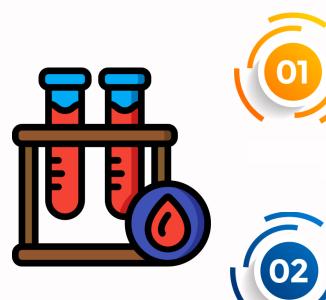
HIGH RISK: A goal of < 80 mg/dL

MODERATE RISK

A goal of 100 mg/dL



Triglycerides and Diabetes



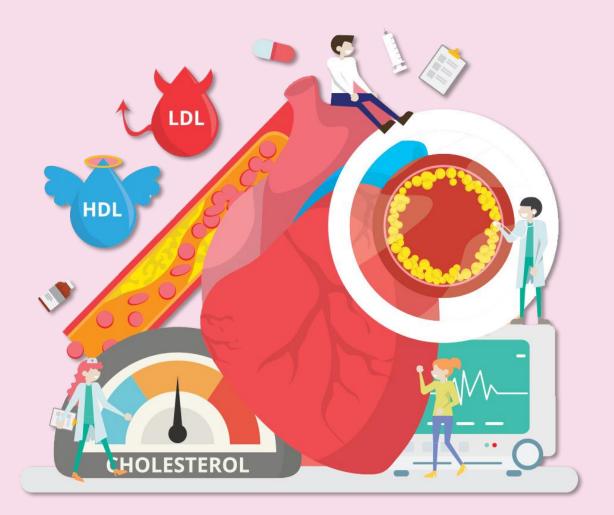
TRIGLYCERIDES:

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).

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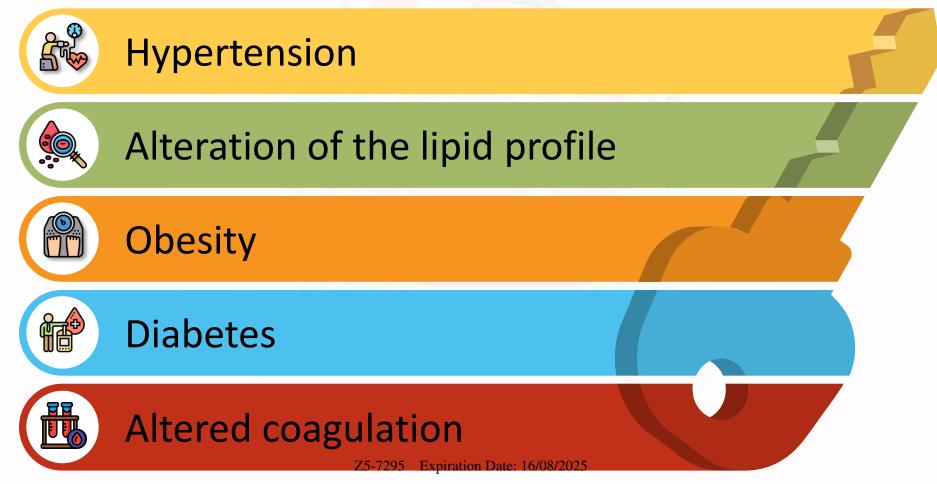


2. Non-pharmacological Management of Dyslipidemia



✓ One of the most important aspects of human life related to atherogenesis is the dietary pattern.

R Nutrients are linked to many atherosclerosis risk factors:







Diet is a multi-component mixture of many nutrients which may interact with one another. We still do not have a definitive study of the impact of nutrients on CVD.

✓ Many approaches have been used to examine the influence of nutrition on atherosclerosis :





 \checkmark Notes about these approaches :

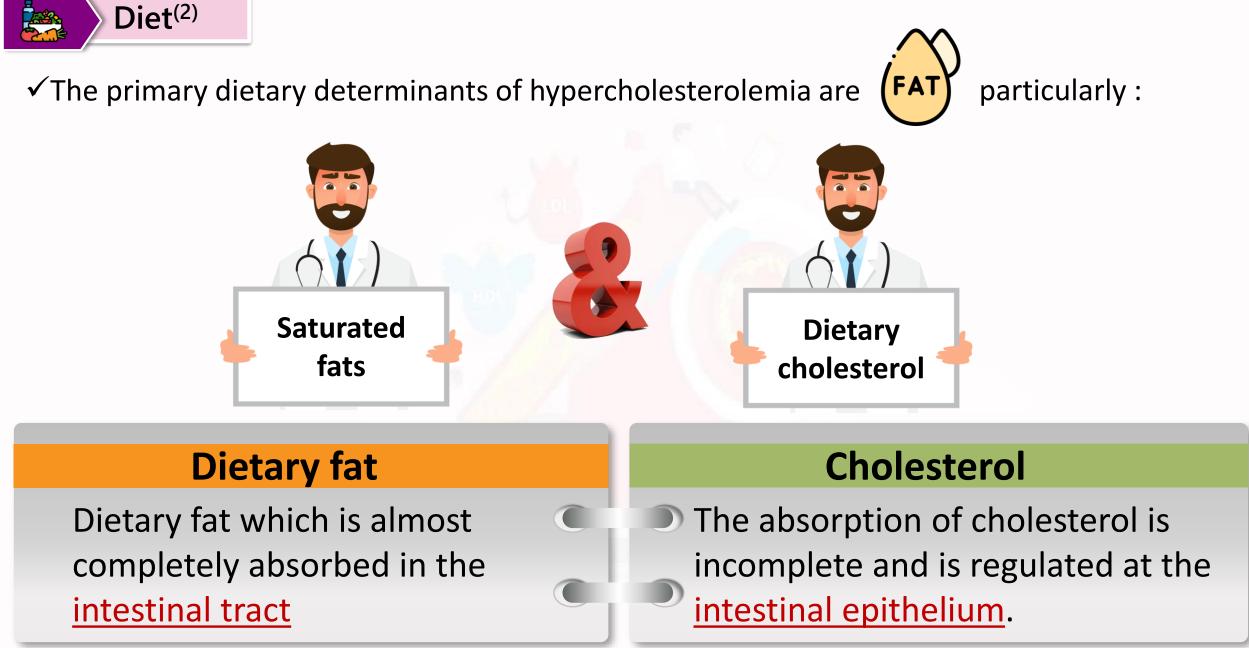
Some of these approaches can be very informative about individual nutrients.

DIET

Metabolic ward studies where the nutrients are varied in a specific fashion without changing total calories or nutrient balance, are most likely to yield relatively definitive answers.

However, they are not closely related to the real lives of free living peoples.

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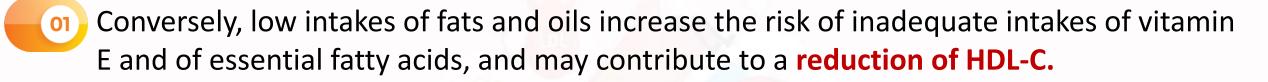
Saturated fat consumption should be **<10%** of the total caloric intake.

Saturated fat should be further reduced to **<7%** in the presence of high cholesterol level.

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fat intakes >35-40% of calories are associated with \clubsuit intakes of saturated fat and calories.





92 Fat intake should predominantly come from sources of monounsaturated fatty acids, including both n-6 and n-3 PUFAs.

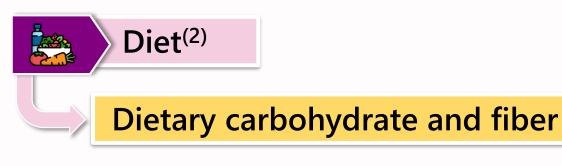


The cholesterol intake in the diet should be reduced (<300 mg/day), particularly in people with high plasma cholesterol levels.











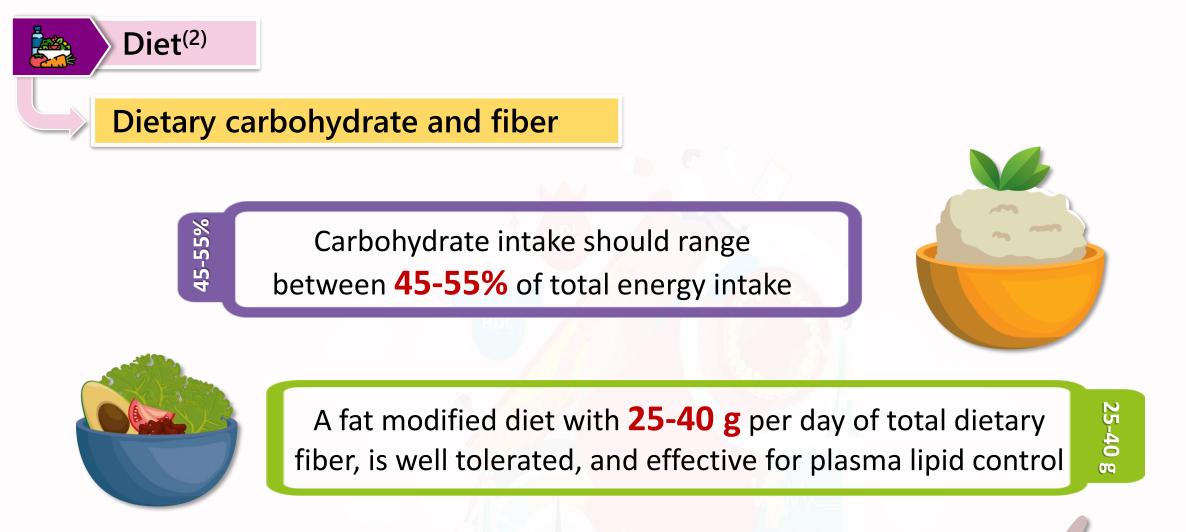
Dietary carbohydrate has a 'neutral' effect on LDL-C, although excessive consumption is represented by untoward effects on plasma TGs and HDL-C levels.

✓ Soluble Dietary fiber which is present in legumes, fruits, vegetables, and wholegrain cereals has a hypocholesterolaemic effect and represents a good dietary substitute for saturated fat.

To **A** the effects of the diet on LDL-C levels

To $\Psi\Psi$ the untoward effects of a high-carbohydrate diet on other lipoproteins.

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Intake of added sugar should not exceed **10%** of total energy

10%

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UGak



02



Smoking cessation has clear benefits regarding overall CV risk, and specifically on HDL.



Body weight reduction and physical activity⁽²⁾

Body weight reduction, even if modest (**5-10%** of basal body weight), improves lipid abnormalities and Ψ CV risk factors.

Weight reduction can be achieved by decreasing the consumption of energy-dense foods, inducing a caloric deficit of **300-500 kcal/day**.

People with dyslipidemia should engage in regular physical exercise of moderate intensity for ≥ 30 min/day, even if they are not overweight.



Food choices to \clubsuit LDL and improve lipoprotein profile (ESC/EAS)⁽²⁾

	To be preferred	To be used in moderation	To be chosen occasionally in limited amounts
Cereals	Wholegrains	Refined bread, rice, and pasta, biscuits, corn flakes	Pastries, muffins, pies, croissants
Vegetables	Raw and cooked vegetables	Potatoes	Vegetables prepared in butter or cream
Legumes	Lentils, beans, fava beans, peas		
Fruit	Fresh or frozen fruit	Dried fruit, jelly, jam, canned fruit, sorbets, ice lollies, fruit juice	
Sweets	Non-caloric sweeteners	Sucrose, honey, chocolate, sweets/ candies	Cakes, ice creams, fructose, soft drinks
Meat and fish	Lean and oily fish, poultry without skin ²⁵⁻⁷	Lean cuts of beef, lamb, pork, and veal, seafood, shellfish	Sausages, salami, bacon, spare ribs, hot dogs, organ meats



Food choices to \clubsuit LDL and improve lipoprotein profile (ESC/EAS)⁽²⁾

	To be preferred	To be used in moderation	To be chosen occasionally in limited amounts
Dairy food and eggs	Skimmed milk and yoghurt	Low-fat milk, low-fat cheese and other milk products, eggs	Regular cheese, cream, whole milk and yoghurt
Cooking fat and dressings	Vinegar, mustard, fat-free dressings	Olive oil, non-tropical vegetable oils, soft margarines, salad dressing, mayonnaise, ketchup	Trans fats and hard margarines (better to avoid them), palm and coconut oils, butter, lard, bacon fat
Nuts/seeds		All, unsalted (except coconut)	Coconut
Cooking procedures	Grilling, boiling, steaming	Stir-frying, roasting	Frying

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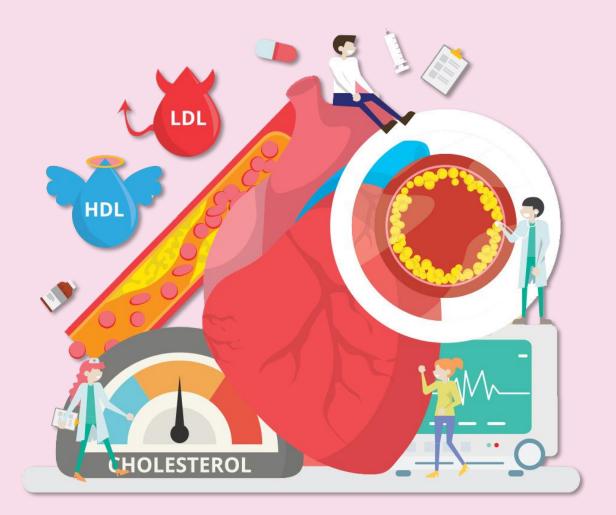
Impact of specific lifestyle changes on lipid levels (ESC/EAS) ⁽²⁾			
	Magnitude of the effect	Level	
Lifestyle interventions to reduce TC and LDL-C levels			
Avoid dietary trans fats	++	А	
Reduce dietary saturated fats	++	А	
Increase dietary fibre	++	Α	
Use functional foods enriched with phytosterols	++	А	
Use red yeast rice nutraceuticals	++	А	
Reduce excessive body weight	++	А	
Reduce dietary cholesterol	+	В	
Increase habitual physical activity Z5-7295 Expiration Date: 16/	+	В	

Impact of specific lifestyle changes on lipid levels (ESC/EAS) ⁽²⁾		
	Magnitude of the effect	Level
Lifestyle interventions to reduce TG-rich lipoprotein levels		
Reduce excessive body weight	+	А
Reduce alcohol intake	+++	А
Increase habitual physical activity	++	А
Reduce total amount of dietary carbohydrates	++	А
Use supplements of n-3 polyunsaturated fats	++	А
Reduce intake of mono- and disaccharides	++	В
Replace saturated fats with mono- or polyunsaturated fats	+	В

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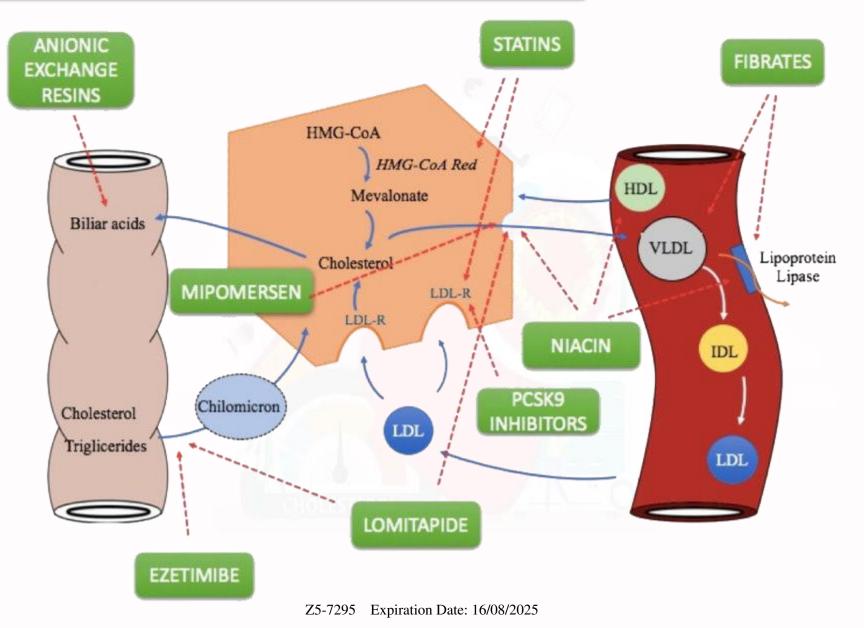
Impact of specific lifestyle changes on lipid levels (ESC/EAS) ⁽²⁾		
	Magnitude of the effect	Level
Lifestyle interventions to increase HDL-C levels		
Avoid dietary trans fats	++	А
Increase habitual physical activity	+++	А
Reduce excessive body weight	++	А
Reduce dietary carbohydrates and replace them with unsaturated fats	++	A
Modest consumption in those who take alcohol may be continued	++	В
Quit smoking	+	В

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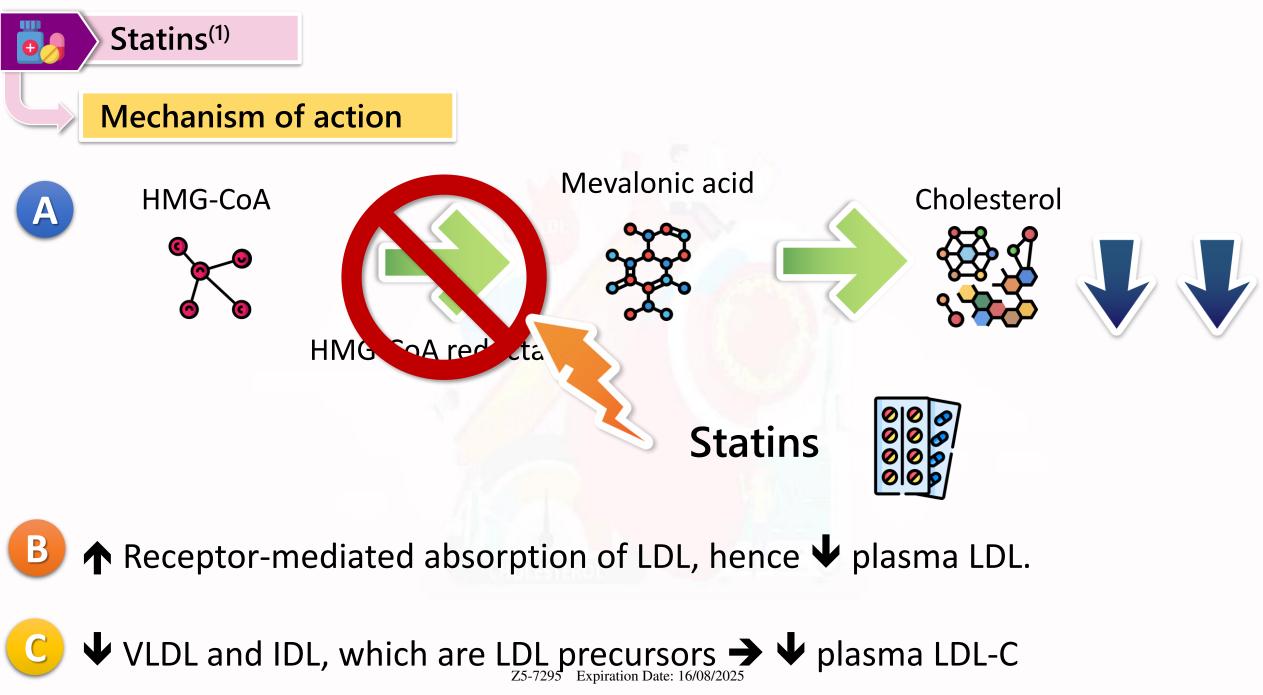


3. Pharmacological Management of Dyslipidemia

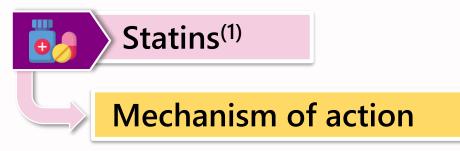
Pharmacological Management of Dyslipidemia

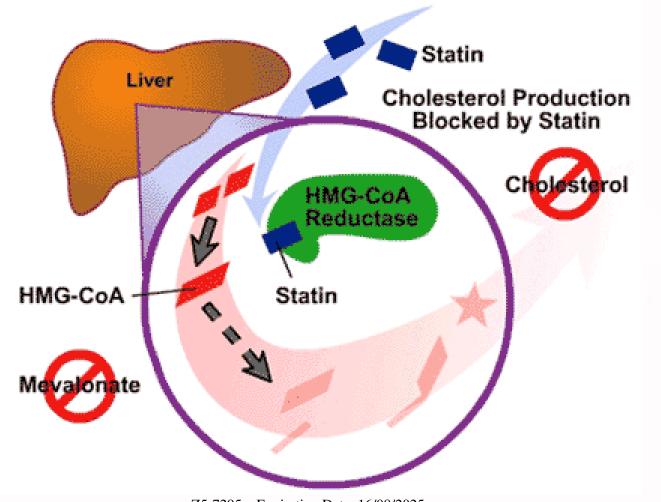


1. Zodda, D., Giammona, R., & Schifilliti, S. (2018). Treatment Strategy for Dyslipidemia in Cardiovascular Disease Prevention: Focus on Old and New Drugs. Pharmacy (Basel, Switzerland), 6(1), 10. https://doi.org/10.3390/pharmacy6010010.



1. Zodda, D., Giammona, R., & Schifilliti, S. (2018). Treatment Strategy for Dyslipidemia in Cardiovascular Disease Prevention: Focus on Old and New Drugs. Pharmacy (Basel, Switzerland), 6(1), 10. <u>https://doi.org/10.3390/pharmacy6010010</u>.









All statins possess very low systemic bioavailability due to an extensive first-pass effect.



Statins differ mainly in the degree of metabolism and the number of active and inactive metabolites.

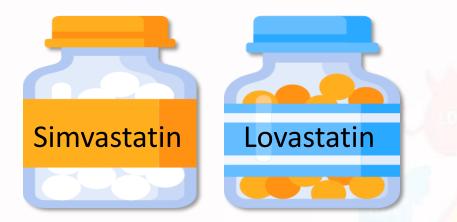


All statins have active metabolites so that their activity depends also on the profile of both parent compound and active metabolites.

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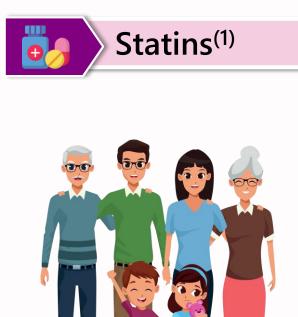


Unlike most statins, are administered as inactive lactone prodrugs.

Possess the longest terminal half-life (11–20 h).



Has the lowest protein-binding (around **50%**) when compared to other statins (**>90%**); furthermore, statins have a low half-life (**1-4 h**)



In Homozygous Familial Hypercholesterolemic



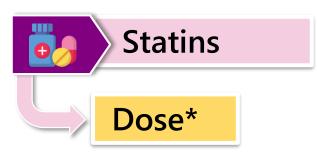
Do not lower LDL levels

Are effective

probably due to their ability to produce a significant decrease in liver production of LDL cholesterol.

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High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL on average by ≥50%	Daily dose lowers LDL on average by approximately 30-49%	Daily dose lowers LDL on average by <30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

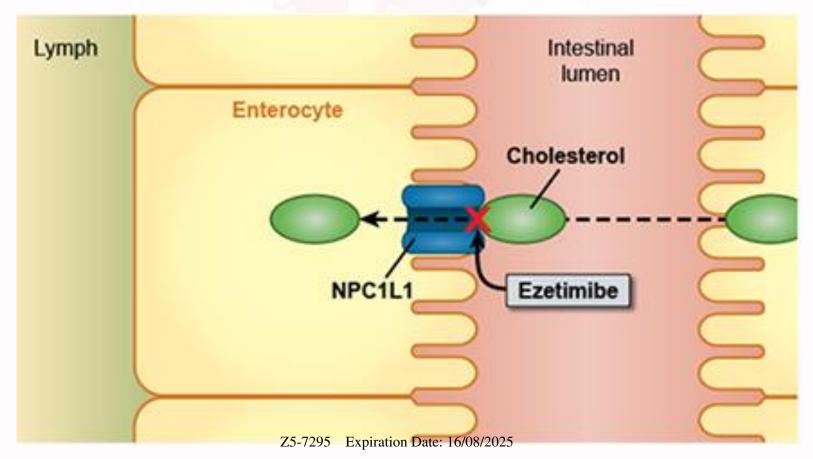
*Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am. Coll Cardiol, Nov 2018, 25709; doi: 10.1016/j.jacc.2018.11.003.



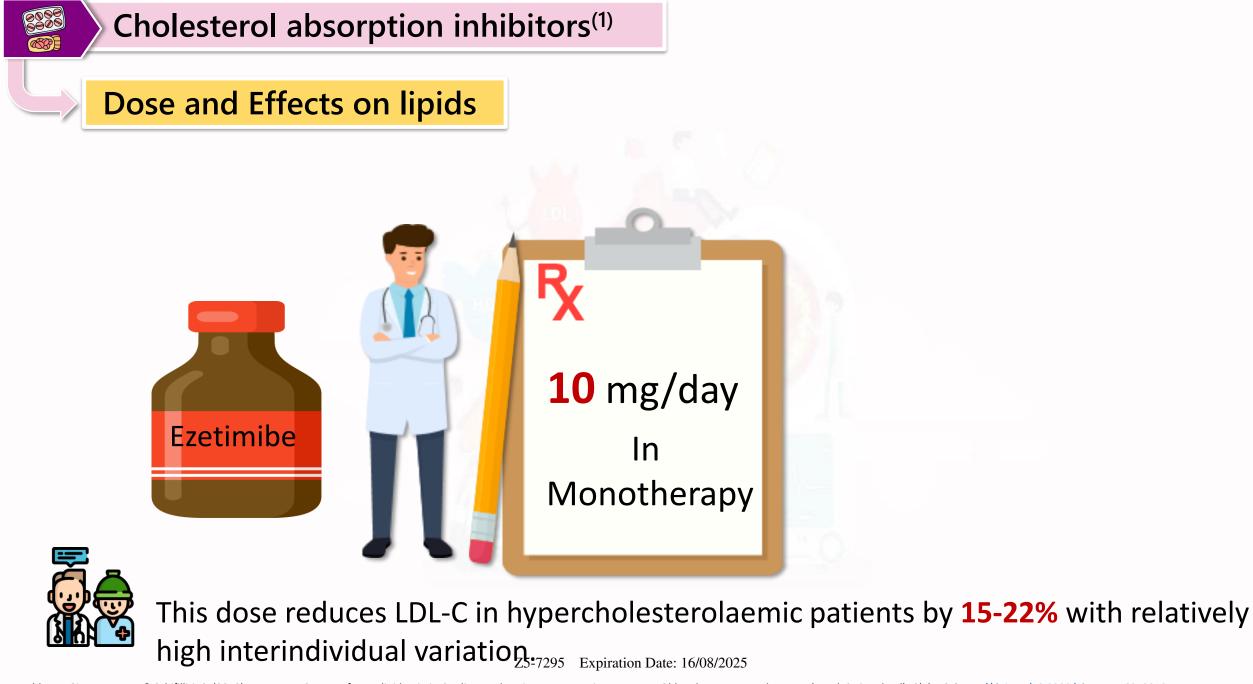
Cholesterol absorption inhibitors⁽¹⁾

Mechanism of action

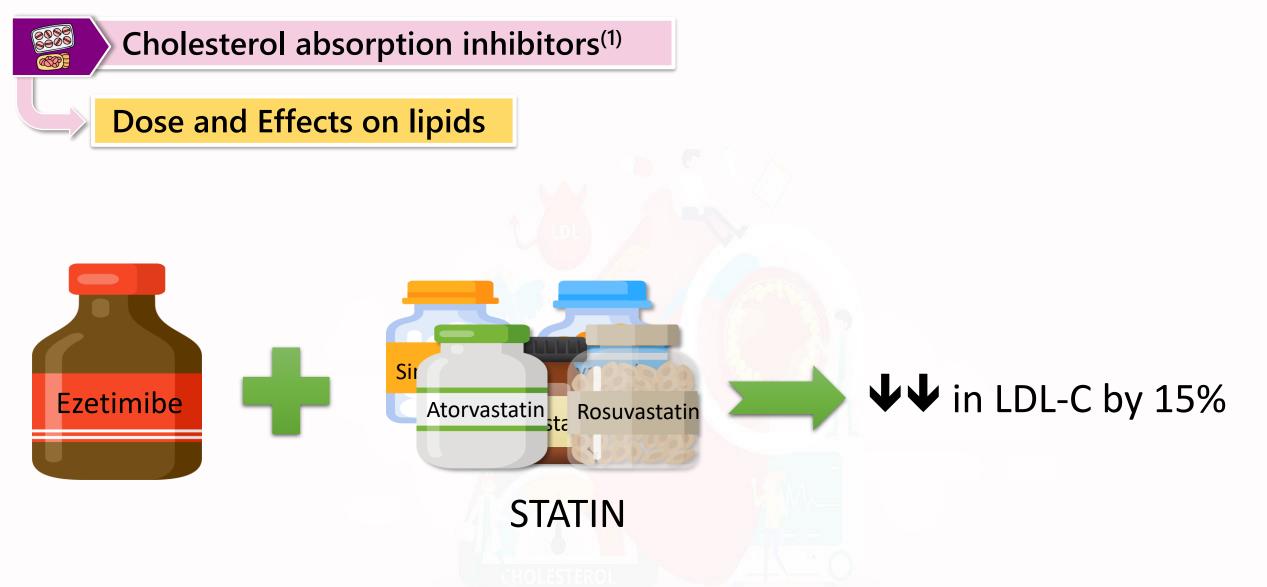
✓ **Ezetimibe** interact with NPC1L1



1. Zodda, D., Giammona, R., & Schifilliti, S. (2018). Treatment Strategy for Dyslipidemia in Cardiovascular Disease Prevention: Focus on Old and New Drugs. Pharmacy (Basel, Switzerland), 6(1), 10. https://doi.org/10.3390/pharmacy6010010.



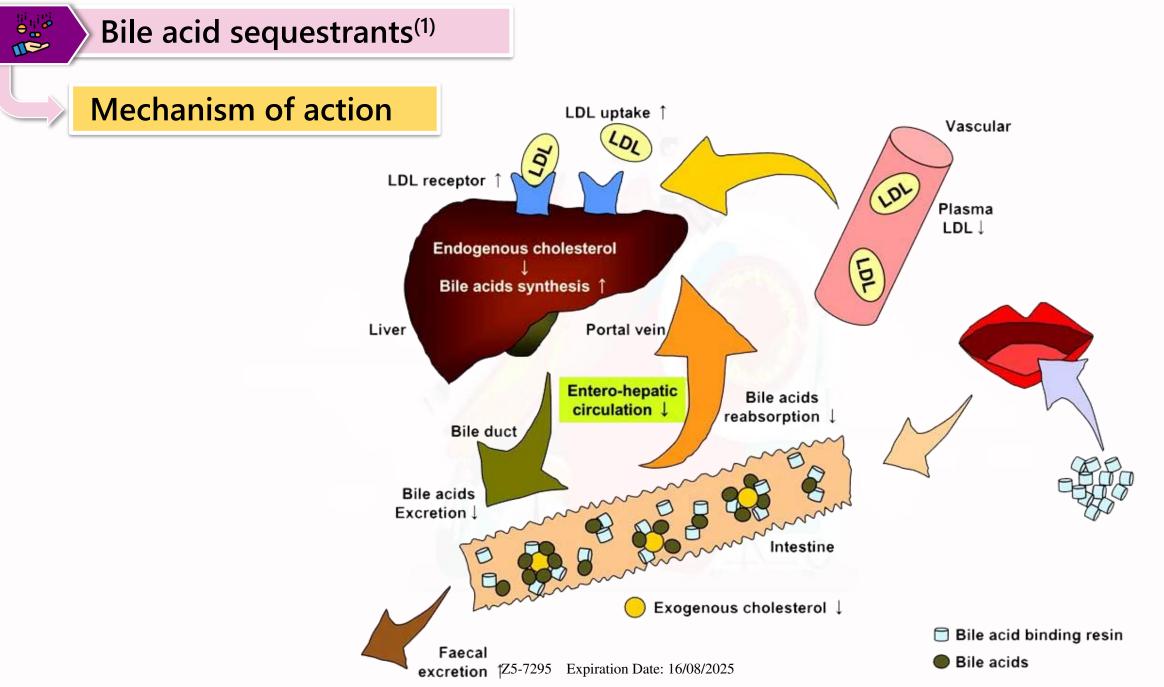
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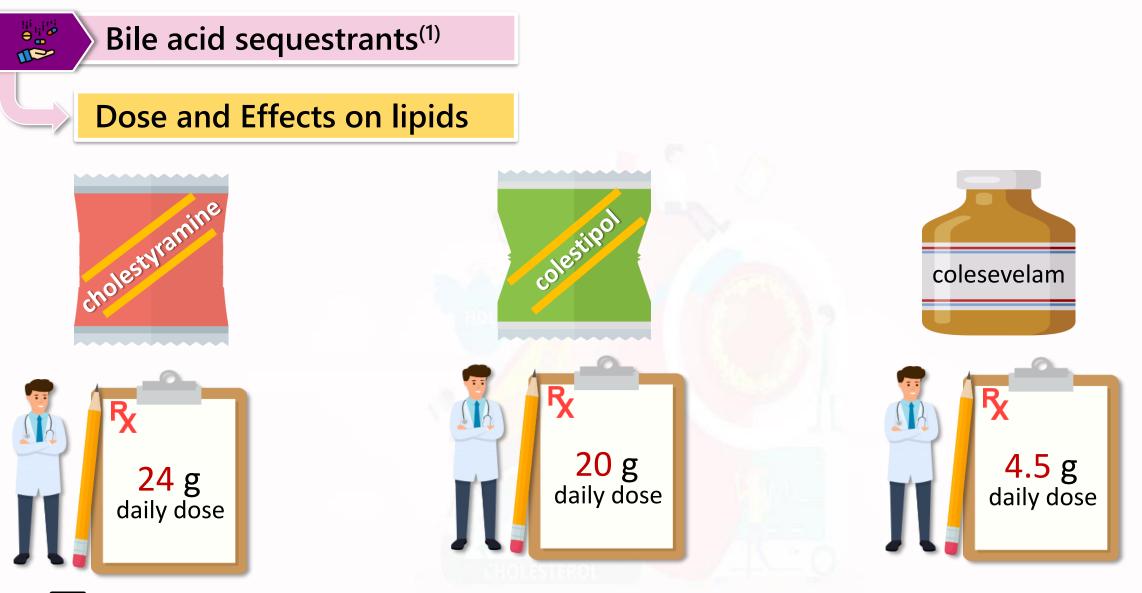
Compared with the same statins and doses in monotherapy or doubling of the statin dose

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1. Zodda, D., Giammona, R., & Schifilliti, S. (2018). Treatment Strategy for Dyslipidemia in Cardiovascular Disease Prevention: Focus on Old and New Drugs. Pharmacy (Basel, Switzerland), 6(1), 10. https://doi.org/10.3390/pharmacy6010010.



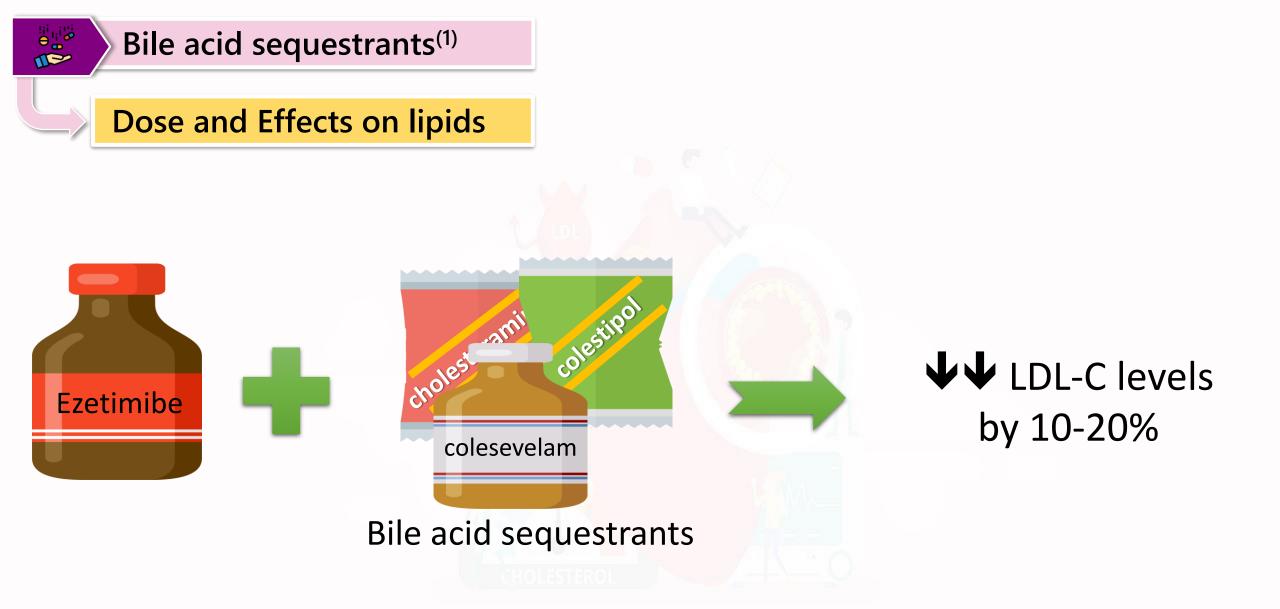
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A reduction in LDL-C of 18-25% has been observed. No major effect on HDL-C has been reported, while TGs may increase in some predisposed patients.

1. Zodda, D., Giammona, R., & Schifilliti, S. (2018). Treatment Strategy for Dyslipidemia in Cardiovascular Disease Prevention: Focus on Old and New Drugs. Pharmacy (Basel, Switzerland), 6(1), 10. https://doi.org/10.3390/pharmacy6010010.

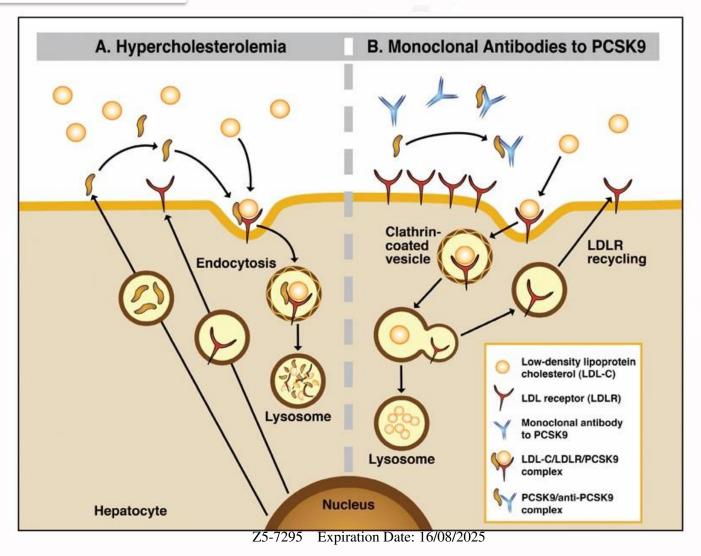


Compared with the stable bile acid sequestrant regimen alone

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Proprotein convertase subtilisin/kexin type 9 inhibitors⁽¹⁾

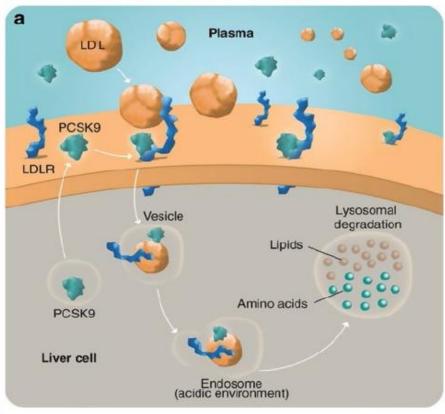
Mechanism of action



Proprotein convertase subtilisin/kexin type 9 inhibitors⁽¹⁾

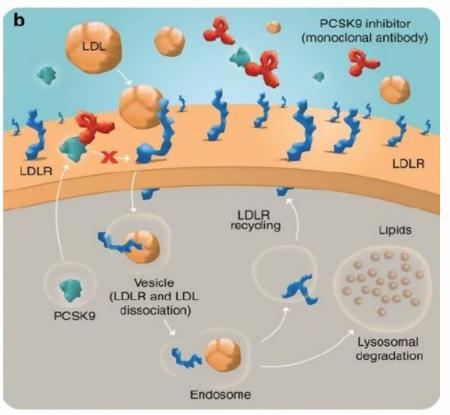
Mechanism of action

How does PCSK9 work?



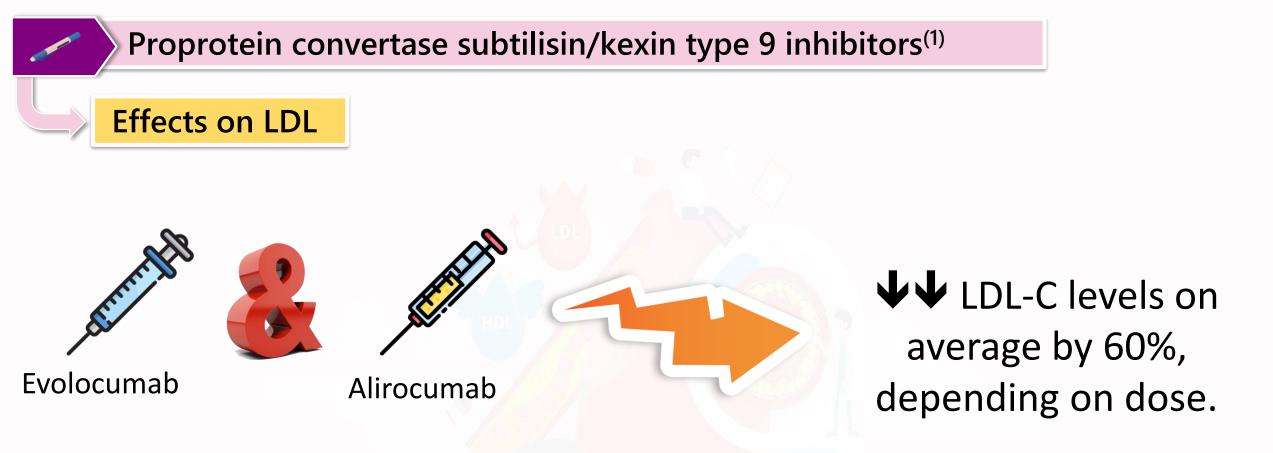
a) Secreted PCSK9 binds to LDLR on the liver cell surface and mediates the lysosomal degradation of the complex formed by PCSK9 - LDLR - LDL.

How does Inhibitors work?



b) In the presence of a monoclonal antibody that binds to PCSK9, the PCSK9-mediated degradation of LDLR is inhibited, resulting in an increased uptake of LDL-cholesterol by LDLR as more LDLR are recycled at the cell

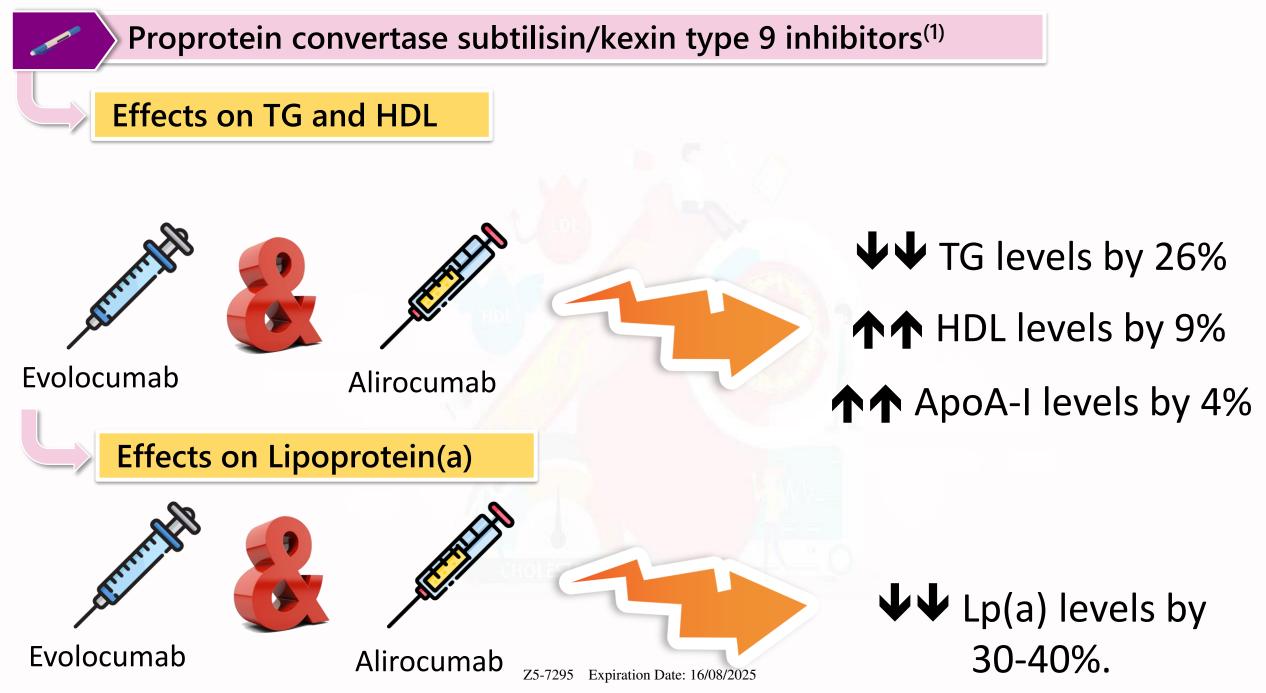
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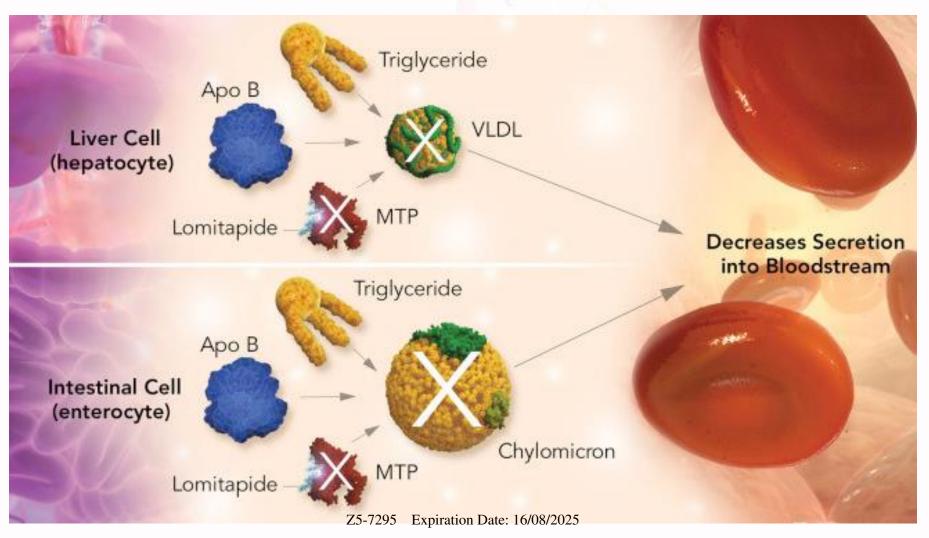
Effective in patients with HeFH and, albeit to a lower level, those with HoFH with residual LDLR expression. Receptor deficient HoFH responds poorly to the therapy.

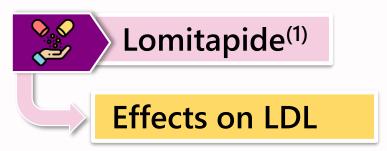
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Mechanism of action







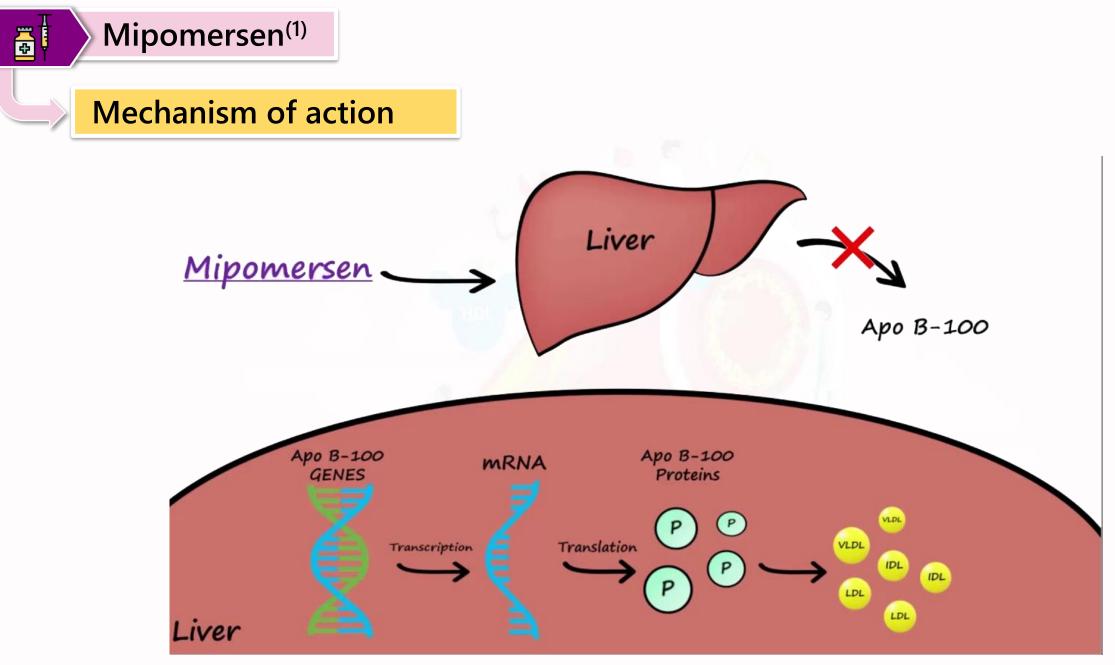


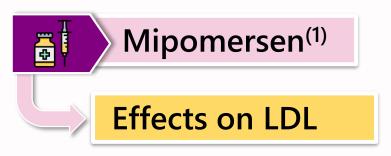
↓↓ LDL-C by 50% from baseline at 26 weeks and by 44% at 56 weeks



Lomitapide $\uparrow \uparrow$ ALT levels $\rightarrow \uparrow$ fat in the liver, as well as poor GI tolerability. preventing a further increase in the dose of lomitapide in clinical trials.

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↓↓ LDL-C in patients with Homozygous Familial Hypercholesterolemia

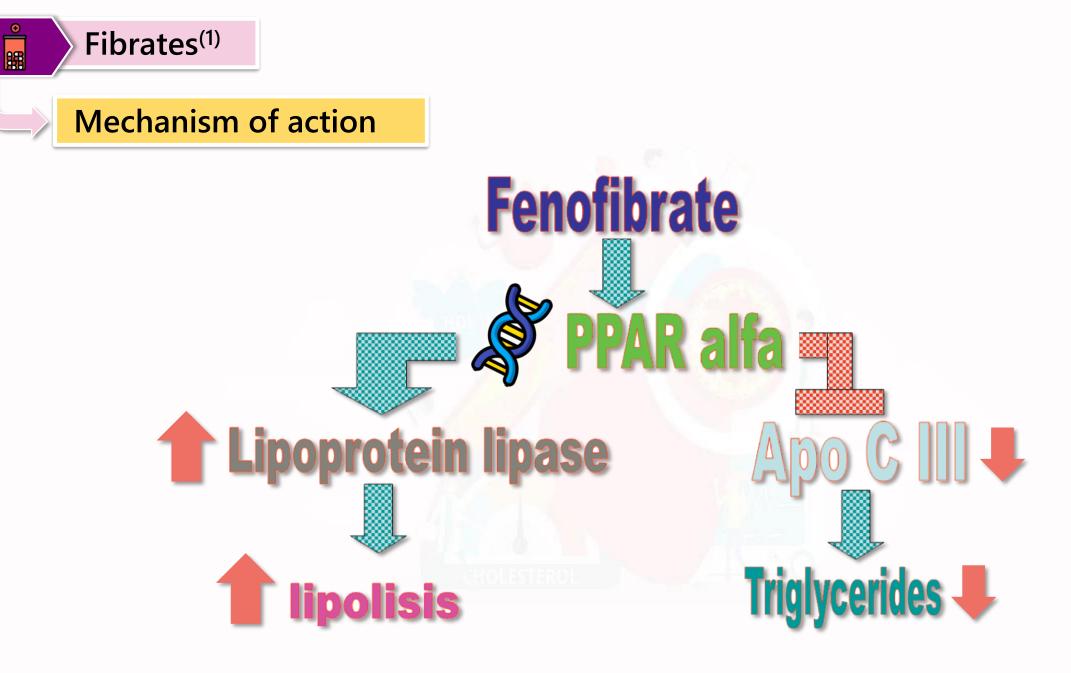
Mipomersen

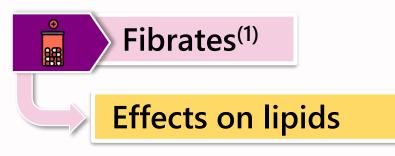


Reactions at the injection site are the most common adverse effects
 Mipomersen may cause liver

 development of steatosis.

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↓↓ TG level by 50%
↓↓ LDL-C level by 20%
↑↑ HDL-C level by 20%

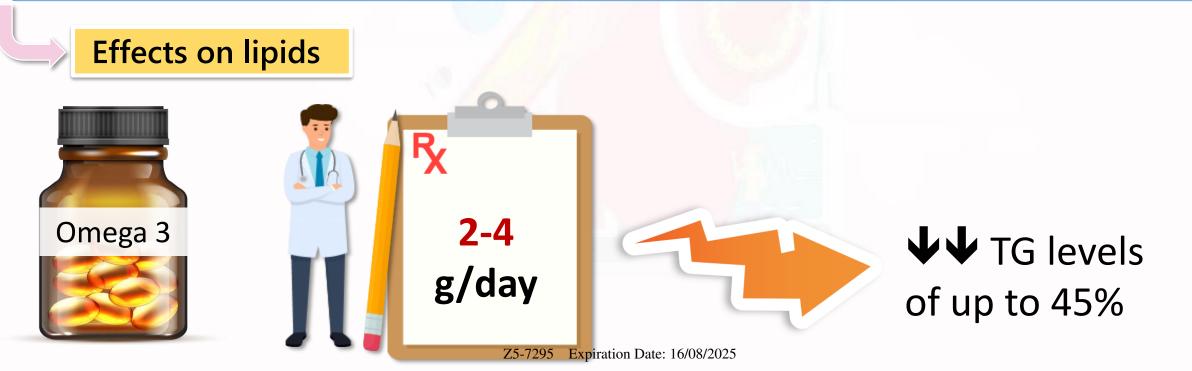
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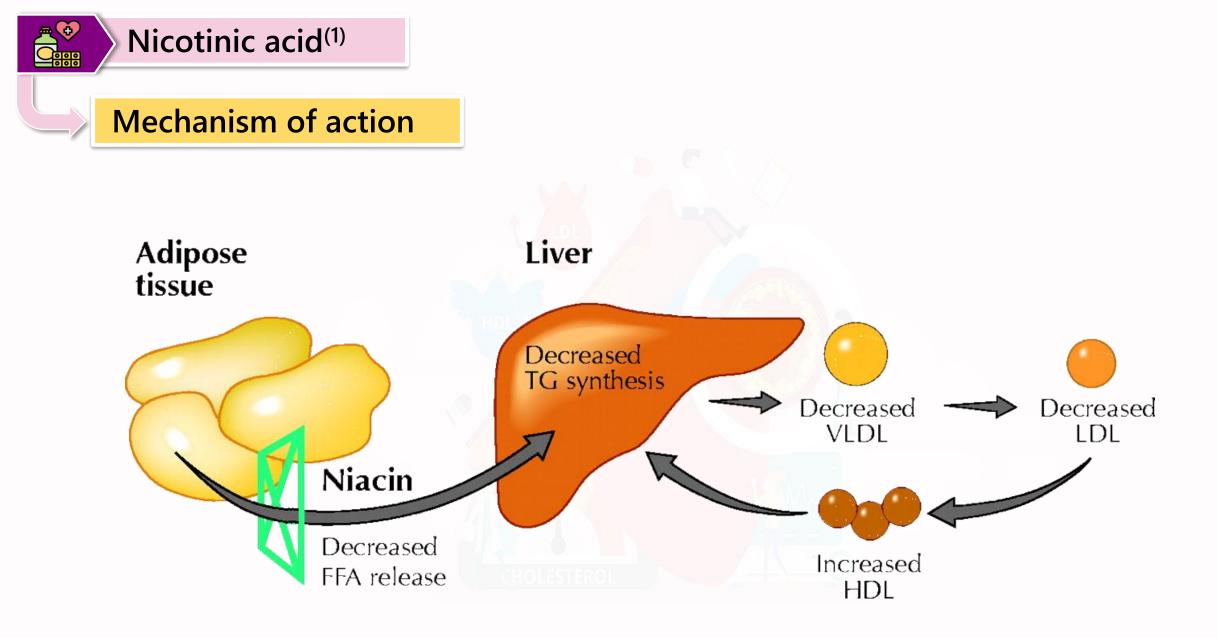


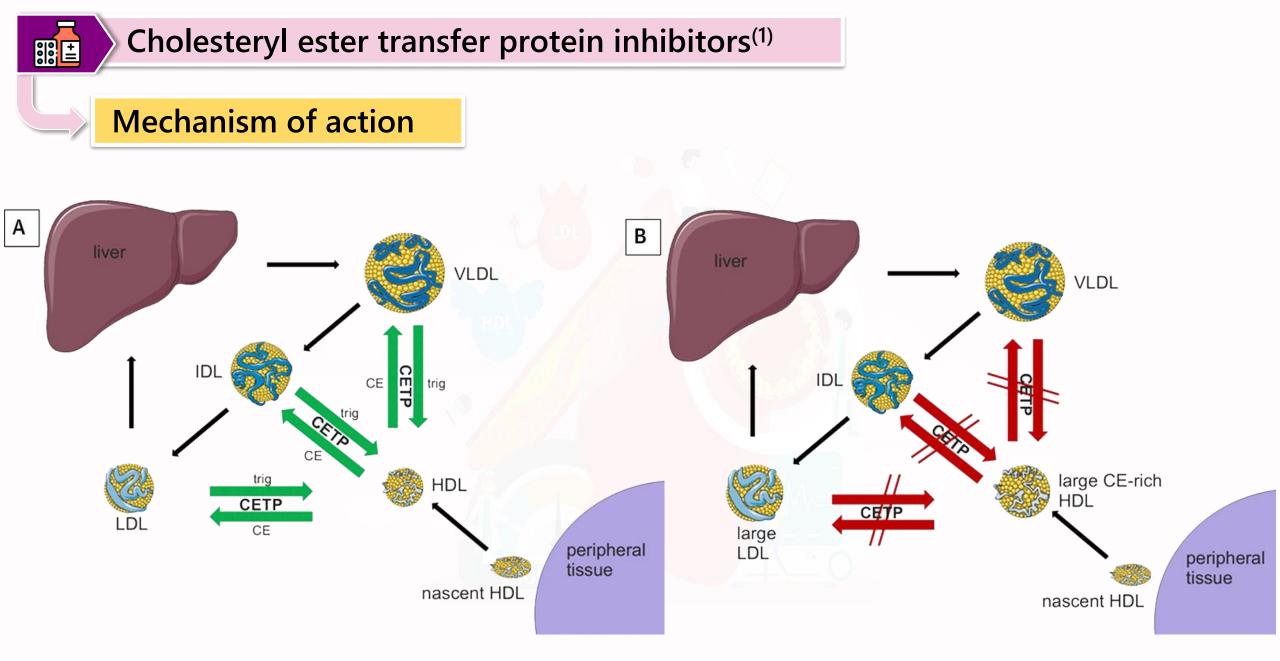
Mechanism of action



The underlying mechanism is poorly understood, although it may be related, at least in part, to their ability to interact with PPARs and to decreased secretion of ApoB.









Torcetrapib was studied to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial, which was stopped early due to increased mortality

Dalcetrapib ↑ HDL-C levels by 30-40% with no appreciable effect on LDL. it failed to show any benefit in ACS patients in the dal-OUTCOMES trial.

Evacetrapib A HDL-C levels by 130% and **V** LDL-C by 37%, was studied in the ACCELERATE trial, which was terminated due to futility.

04

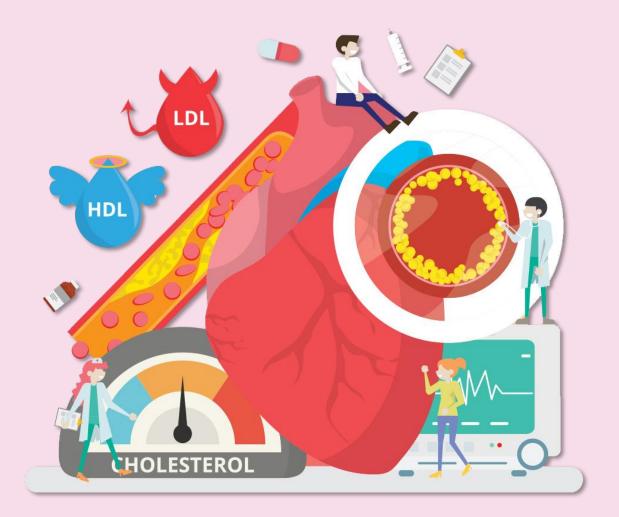
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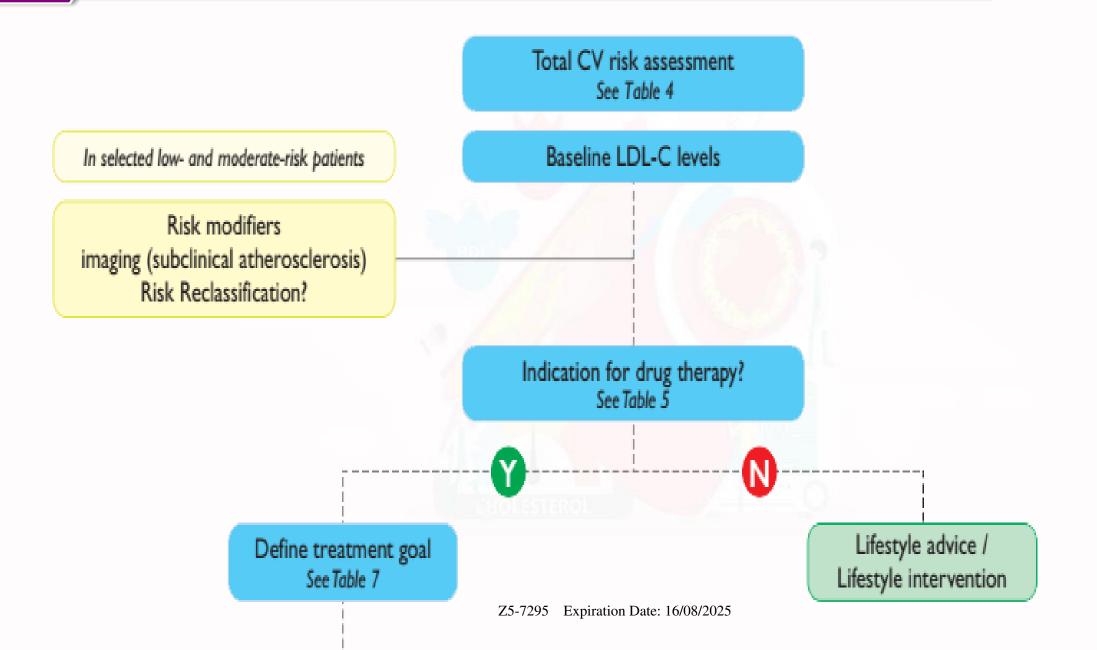
Anacetrapib \Uparrow HDL(104 %) & ApoA-I (36%), \checkmark LDL (17%) & ApoB (18%) was studied in the REVEAL trial. it \checkmark major coronary events by 9% over a median of 4.1 years. This drug has not been submitted for regulatory approval.

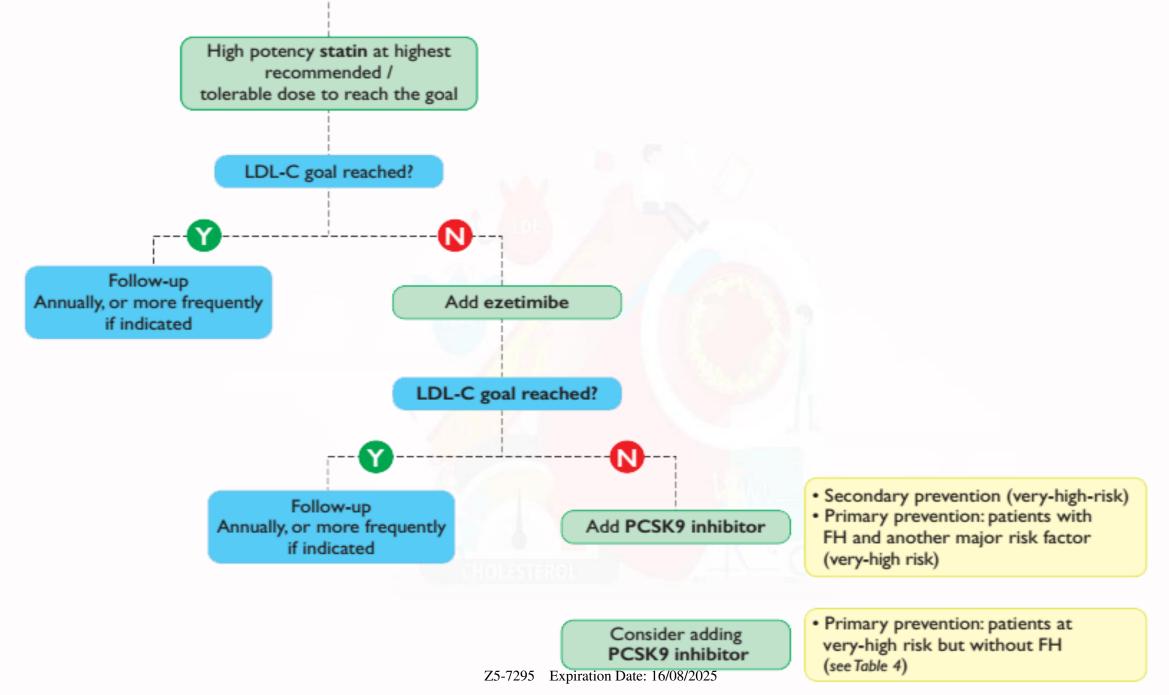
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4. Treatment algorithm for pharmacological LDL lowering.

Treatment algorithm for pharmacological LDL lowering⁽²⁾





2.Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–188. doi: 10.1093/eurheartj/ehz455.

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 revascularization (PCI. CABG. and other arterial revascularization procedures), stroke and TIA and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound.

DM with target organ damage* or at least three major risk factors, or early onset of T1 DM of long duration (>20 years).

Severe CKD (eGFR <30 ml_/min/1.73 m2).

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

FH with ASCVD or with another major risk factor.

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 another additional risk factor. Moderate CKD (eGFR 30—59 mL/min/1.73 m²).

A calculated SCORE >5% and <10% for 10-year risk of fatal CVD.

 Moderate
 Young patients (T1DM <35 years: T2DM <50 years) with DM duration <10 years, without other risk factors.</td>

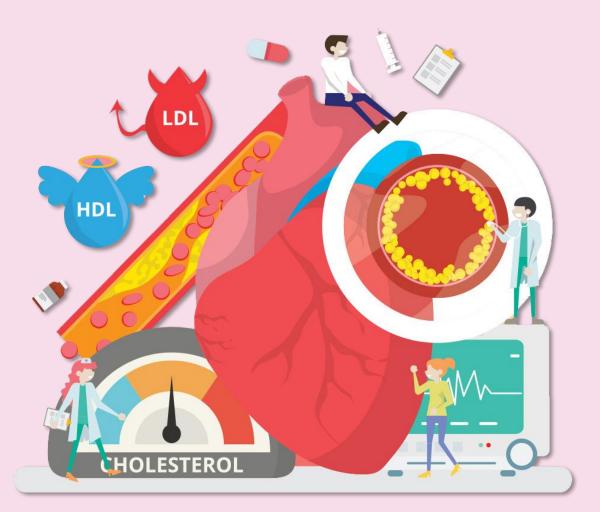
 -risk
 Calculated SCORE >1 % and <5% for 10-year</td>

 risk of fatal CVD.
 Image: Calculated Score in the second seco

Low-risk Calculated SCORE <1% for 10-year risk of fatal CVD.

	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)
P rimary prevention	<1, low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle inter- vention, con- sider adding drug if uncontrolled	Lifestyle inter- vention 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 <i>Table</i> 4)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle inter- vention, con- sider adding drug if uncontrolled	Lifestyle inter- vention, con- sider adding drug if uncontrolled	Lifestyle inter- vention and concomitant drug intervention
	Class ^a /Level ^b	I/C	I/C	Ila/A	Ila/A	IIa/A	IIa/A
	≥5 to <10, or high-risk (see Table 4)	Lifestyle advice	Lifestyle advice	Lifestyle inter- vention, con- sider adding drug if uncontrolled	Lifestyle inter- vention and con- comitant drug intervention	Lifestyle inter- vention and concomitant drug intervention	Lifestyle inter- vention and concomitant drug intervention
	Class ^a /Level ^b	IIa/A	IIa/A	Ila/A	I/A	I/A	VA
	≥10, or at very-high risk due to a risk condi- tion (see Table 4)	Lifestyle advice	Lifestyle inter- vention, con- sider adding drug if uncontrolled	Lifestyle inter- vention and concomitant drug intervention	Lifestyle inter- vention and con- comitant drug intervention	Lifestyle inter- vention and concomitant drug intervention	Lifestyle inter- vention and concomitant drug intervention
	Class ^a /Level ^b	IIa/B	Ila/A	I/A	I/A	I/A	I/A
Secondary	Very-high-risk Class ^a /Level ^b	Lifestyle inter- vention, con- sider adding drug if uncontrolled	Lifestyle inter- vention and concomitant drug interv25n7295n Expi		Lifestyle inter- vention and con- comitant drug intervention	Lifestyle inter- vention and concomitant drug intervention	Lifestyle inter- vention and concomitant drug intervention
	Class /Level	IIa/A	I/A	I/A	I/A	I/A	I/A

Smoking	No exposure to tobacco in any form.			
Diet	Healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit, and fish.			
Physical activity	3.5–7 h moderately vigorous physical activity per week or 30–60 min most days.			
Body weight	BMI 20-25 kg/m ² , and 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:				
	A 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 mm				
	(<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.			
АроВ	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	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. Z5-7295 Expiration Date: 16/08/2025 HbA1c: <7% (<53 mmol/mol). 2.Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–188. doi: 10.1093/eurheartjebr2455.			

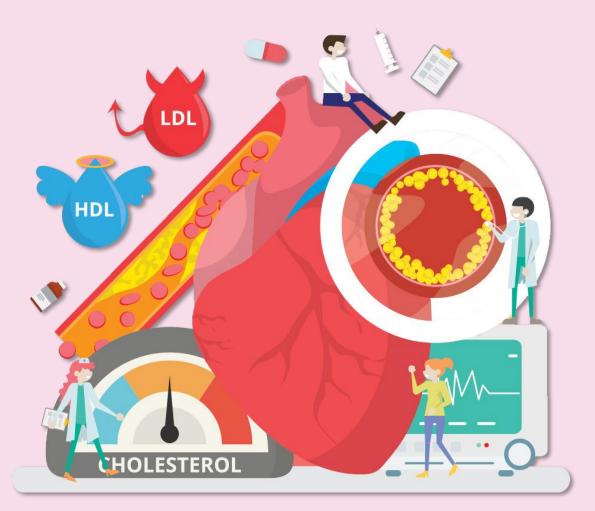


5. Recommendations for drug treatment of patients with hypertriglyceridemia



Recommendations	Class	Level
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].	I	В
In high-risk (or above) patients with TG levels between 1.55.6 mmol/L (135499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 22 g/day) should be considered in combination with a statin.	lla	В
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.	llb	В
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.	llb	С

2.Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–188. doi: 10.1093/eurheartj/ehz455.



6. Recommendations for the treatment 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	А
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged <_75 years.	I	А
Initiation of statin treatment for primary prevention in older people aged >75 years may be considered, if at high-risk or above.	llb	В
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	С

2.Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–188. doi: 10.1093/eurheartj/ehz455.

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Signatory Approval (Certificate)	Noha Mohamed Medical 16-Aug-2023 10:25:42 GMT+0000
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