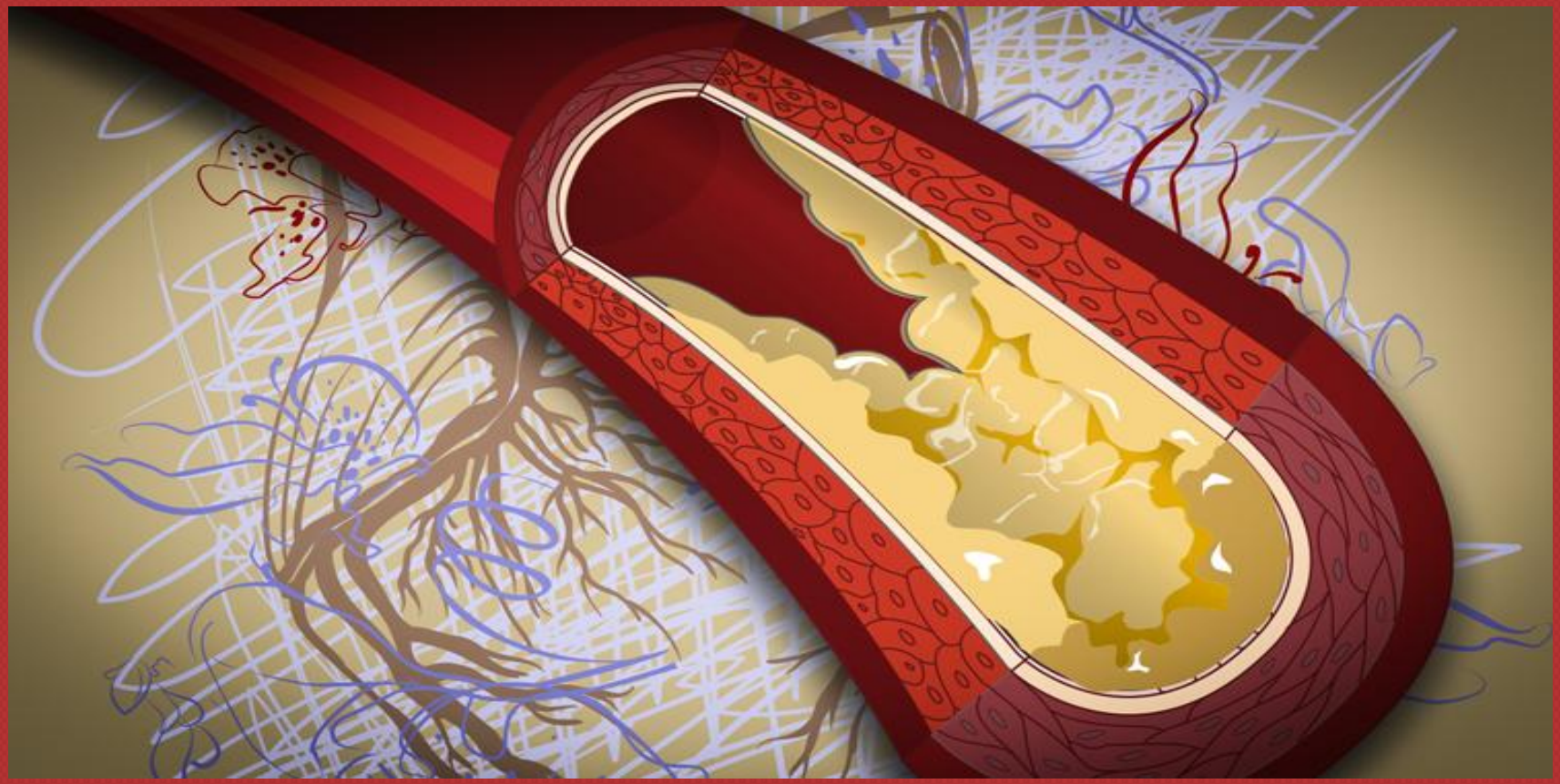
MANAGEMENT OF DYSLIPIDAEMIAS



Introduction

- CVD represents a considerable economic burden to society, and this necessitates an effective approach to CVD prevention.

- More than half of the reduction in CV mortality in the last three decades has been attributed to:

  - population-level changes in CV risk factors
  - reductions in cholesterol, blood pressure levels and smoking

- The present guidelines represent an evidence-based consensus of the European Task Force including the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS).

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Major Atherosclerotic Cardiovascular Disease Risk Factors

Major risk factors	Additional risk factors	Nontraditional risk factors
Advancing age	Obesity, abdominal obesity	⇧ Lipoprotein (a)
⇧ Total serum cholesterol level	Family history of hyperlipidemia	⇧ Clotting factors
⇧ Non–HDL-C	⇧ Small, dense LDL-C	⇧ Inflammation markers (hsCRP; Lp-PLA_2)
⇧ LDL-C	⇧ Apo B	⇧ Homocysteine levels
Low HDL-C	⇧ LDL particle concentration	Apo E4 isoform
Diabetes mellitus	Fasting/postprandial hypertriglyceridemia	⇧ Uric acid
Hypertension	PCOS	⇧ TG-rich remnants
Stage 3 or 4 chronic kidney disease	Dyslipidemic triad	
Cigarette smoking		
Family history of ASCVD		

Abbreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, highly sensitive C-reactive protein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp-PLA2, lipoprotein-associated phospholipase; PCOS, polycystic ovary syndrome.

AACE POSWC. *Endocr Pract*. 2005;11:126-134; ADA. Diabetes Care. 2017;40(Suppl 1):S1-S135; Brunzell JD, et al. *Diabetes Care*. 2008;31:811-822; Cromwell WC, et al. *J Clin Lipidol*. 2007;1:583-592; Einhorn D, et al. *Endocr Pract*. 2003;9:237-252; Grundy SM, et al. *Circulation.* 1998;97:1876-1887; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.; Kastelein JJ, et al. *Circulation.* 2008;117:3002-3009; NCEP. NIH Publication No. 02-5215. September 2002; Neaton JD, et al. *Arch Intern Med*. 1992;152:1490-1500; NHLBI. NIH Publication No. 04-5230. August 2004; Stamler J, el al. *JAMA*. 1986;256:2823-2828; Weiner DE, et al. *J Am Soc Nephrol.* 2004;15(5):1307-1315; Yusuf S, et al. *Lancet.* 2004;364(9438):937-952.

How is risk assessed?

Recommendations associated with this question:

The 10-year risk of a coronary event (high, intermediate, or low) should be determined by detailed assessment using one or more of the following tools **(Grade C; BEL 4, upgraded due to cost-effectiveness)**:

- Framingham Risk Assessment Tool
- MESA 10-year ASCVD Risk with Coronary Artery Calcification Calculator
- Reynolds Risk Score, which includes hsCRP and family history of premature ASCVD
- UKPDS risk engine to calculate ASCVD risk in individuals with T2DM

R7. When the HDL-C concentration is greater than 60 mg/dL, one risk factor should be subtracted from an individual's overall risk profile **(Grade B; BEL 2)**.

R8. A classification of elevated TG should be incorporated into risk assessments to aid in treatment decisions **(Grade B; BEL 2)**.

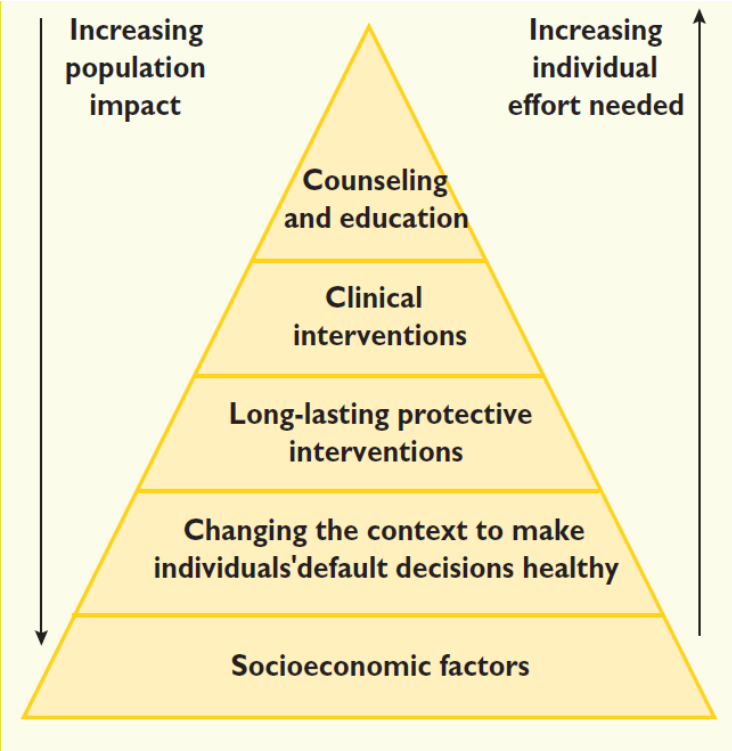
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity CRP; MESA, Multi-Ethnic Study of Atherosclerosis; T2DM, type 2 diabetes mellitus; TG, triglycerides.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

Health Impact

- Considerable evidence has quantified the relative efforts and costs in relation to health impact.
- Considerable evidence has quantified the relative efforts and costs in relation to health impact.
- The efforts may be depicted in the health impact pyramid (Figure), where interventions with the broadest impact on populations represent the base and interventions with considerable individual effort are at the top

Health impact pyramid



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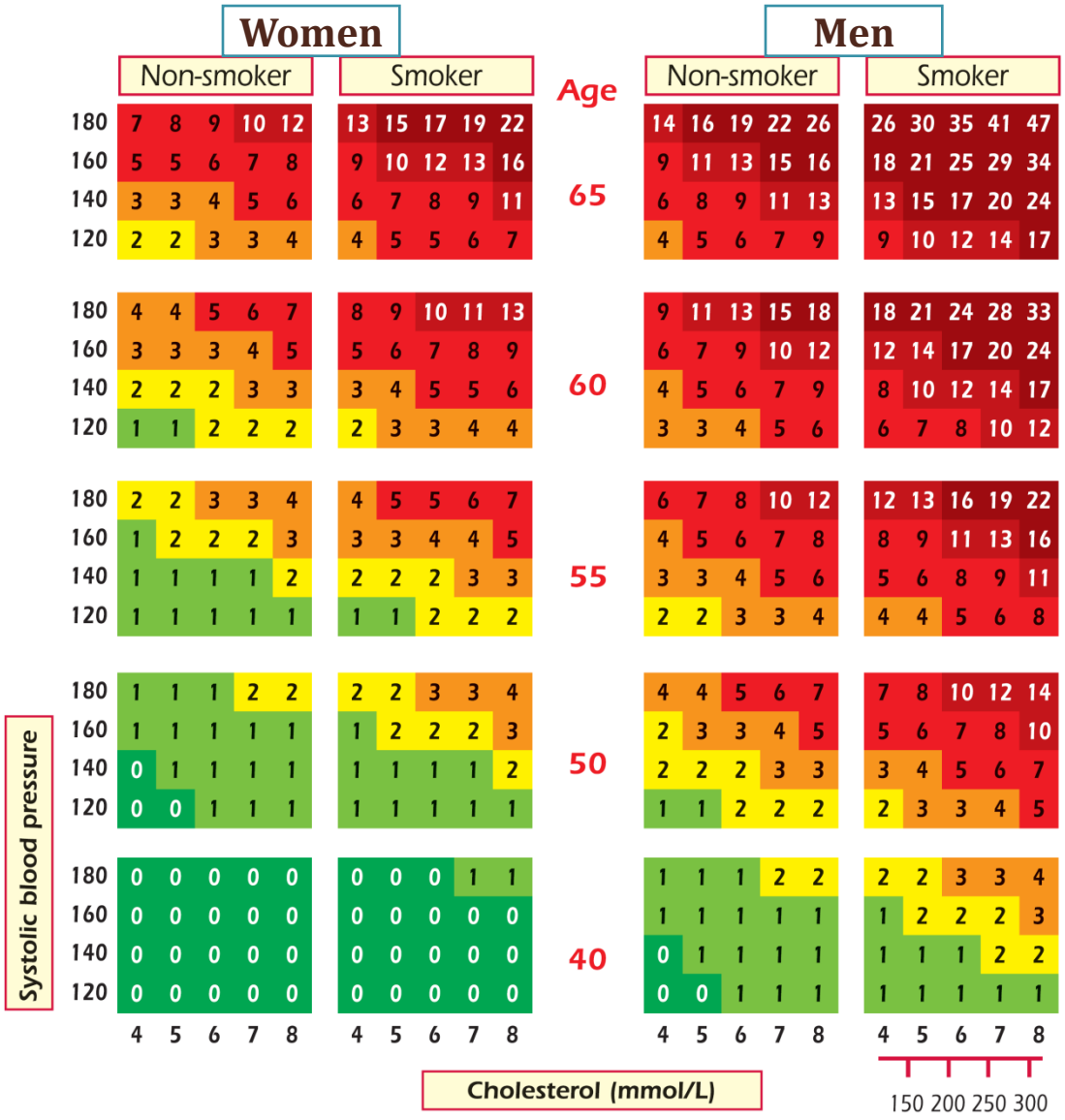
SCORE chart: 10 year risk of fatal cardiovascular disease (CVD) in populations at High CVD risk



SCORE

- 15% and over
- 10%-14%
- 5%-9%
- 3%-4%
- 2%
- 1%
- < 1%

10-year risk of fatal CVD in populations at **High CVD risk**

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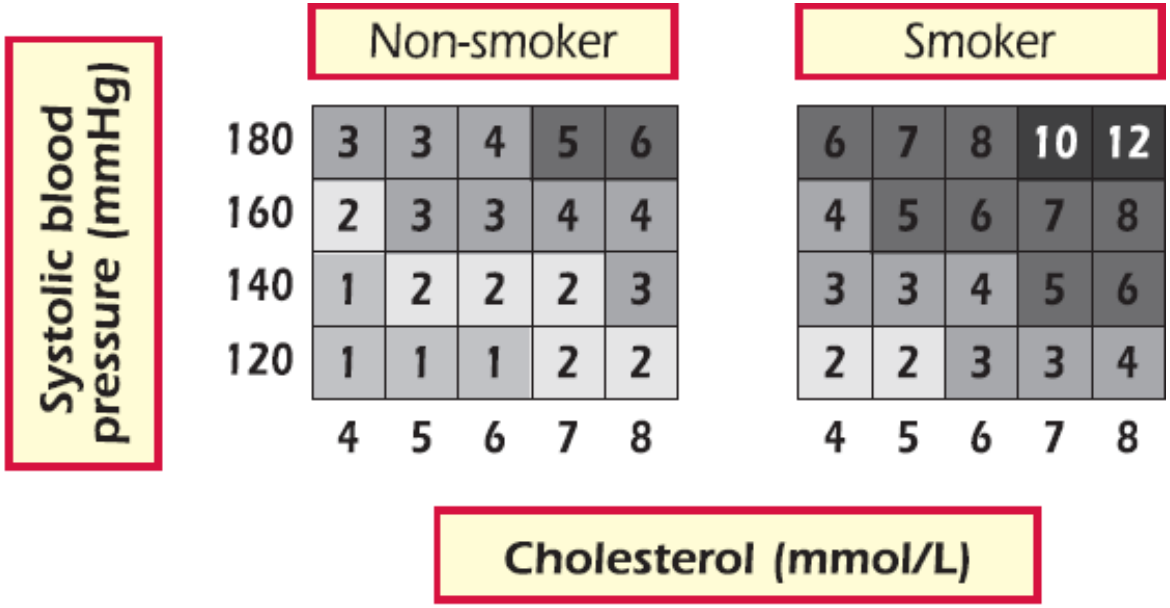
Relative risk chart

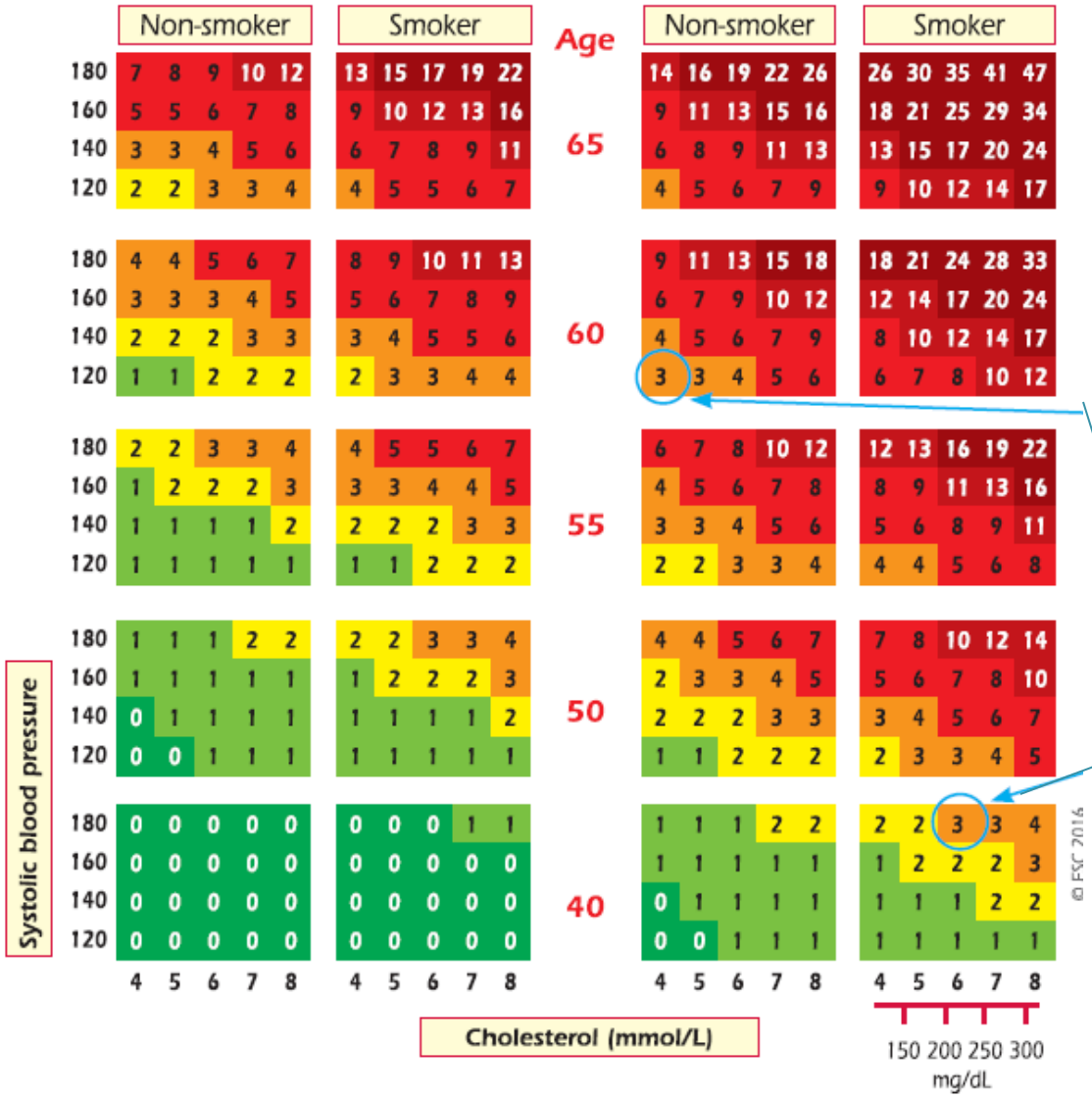
This chart may be used to show younger people at low absolute risk that, relative to others in their age group, their risk may be many times higher than necessary.

This may help to motivate decisions about avoidance of smoking, healthy nutrition and exercise, as well as flagging those who may become candidates for medication



Please note that this chart shows RELATIVE not absolute risk. Risks are RELATIVE to 1 in the bottom left. Thus a person in the top right hand box has a risk that is 12 times higher than a person in the bottom left.

Illustration of the risk age concept.



SCORE

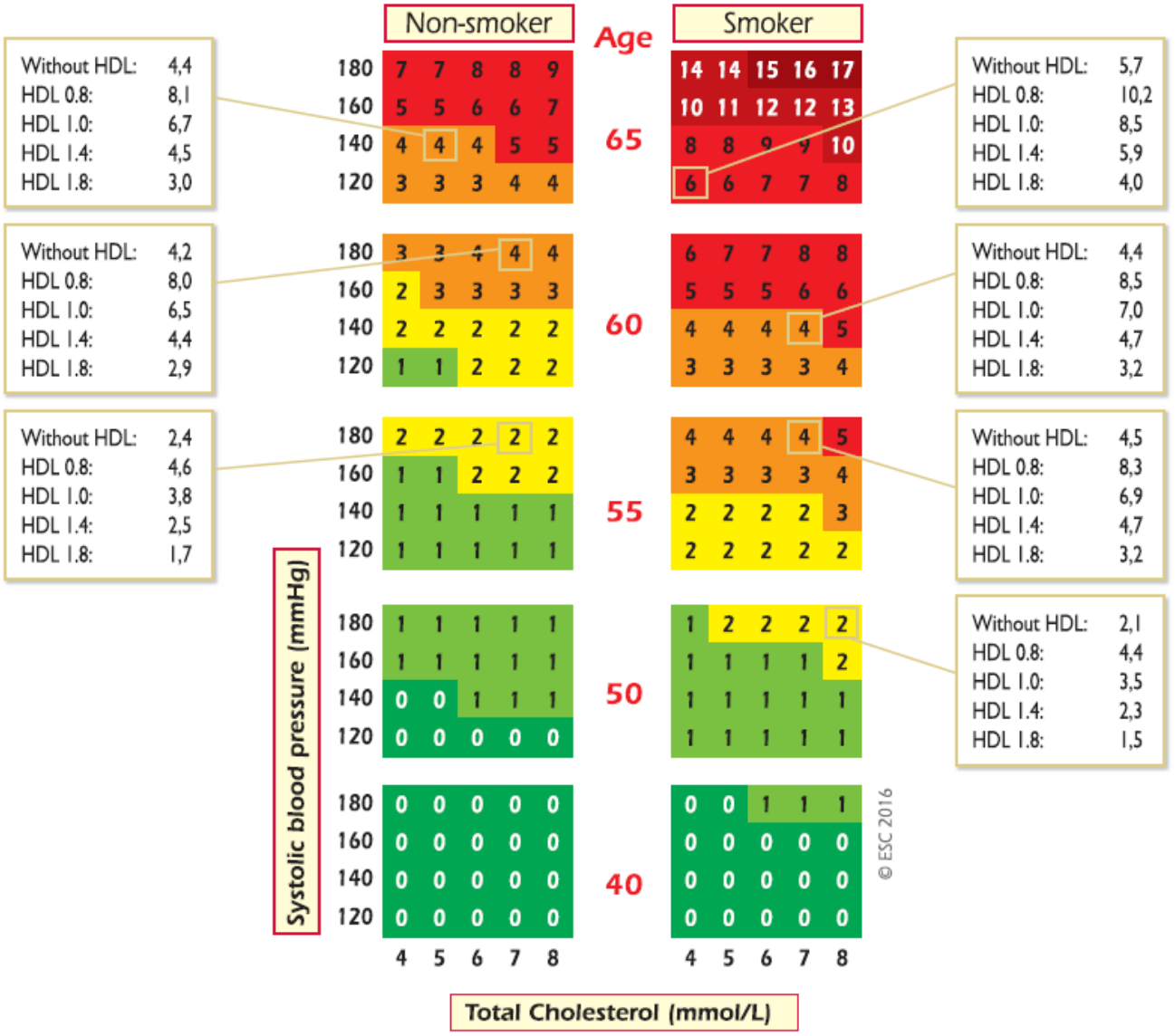
- 15% and over
- 10%-14%
- 5%-9%
- 3%-4%
- 2%
- 1%
- < 1%

10-year risk of fatal CVD in populations at **High CVD risk**

The risk of this 40 yr old male smoker with risk factors is same (3%) as that of a 60- yr old man with ideal risk factor levels

There fore, HIS RISK AGE IS 60 years

Risk function without HDL-C for women in populations at high CVD risk



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Risk Assessment

- The charts can assist in risk assessment and management but must be interpreted in light of the clinician's knowledge and experience and of the patient's pre-test likelihood of CVD.
- Risk will be overestimated in countries with a decreasing CVD mortality, and underestimated in countries in which mortality is increasing.
- Risk estimates appear lower in women than in men. However, risk is only deferred in women; the risk of a 60-year-old woman is similar to that of a 40-year-old man. Ultimately more women die from CVD than men.
- Relative risks may be unexpectedly high in young persons, even if absolute risk levels are low.
- The *relative risk chart* and the *estimated risk age* may be helpful in identifying and counselling such persons.

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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).
- Major psychiatric disorders.
- Left ventricular hypertrophy.
- Chronic kidney disease.
- Obstructive sleep apnoea syndrome.

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Intervention strategies as a function of total CV risk and LDL-C level

Total CV risk (SCORE) %	LDL-C levels				
	< 70 mg/dL < 1.8 mmol/L	70 to < 100 mg/dL 1.8 to < 2.5 mmol/L	100 to < 155 mg/dL 2.5 to < 4.0 mmol/L	155 to < 190 mg/dL 4.0 to < 4.9 mmol/L	> 190 mg/dL > 4.9 mmol/L
< 1	No lipid intervention	No lipid intervention	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled
Class/Level	I/C	I/C	I/C	I/C	IIa/A
≥ 1 to < 5	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class/Level	I/C	I/C	IIa/A	IIa/A	I/A
> 5 to < 10, or high risk	No lipid intervention	Lifestyle intervention consider drug*	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
≥ 10 or very high risk	Lifestyle intervention consider drug*	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/A	IIa/A	I/A	I/A	I/A

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Recommendations for treatment targets for LDL-C

Recommendations	Class [a]	Level[b]
In patients at VERY HIGH CV risk[d],a n LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[e] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B
In patients at HIGH CV risk[d], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C

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Examples of causes of secondary hypercholesterolaemia

- Hypothyroidism
- Nephrotic syndrome
- Pregnancy
- Cushing syndrome
- Anorexia nervosa
- Immunosuppressant agents
- Corticosteroids

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Management of dyslipidaemia

1. **Lipid profiling**.
2. Assess total CVD risk.
3. Treatment strategies. (according to 1 & 2)
4. Life style modifications.
5. Treatment targets.
6. Choice of treatment.
7. Dyslipidaemia in special population.

Management of dysli

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Lipid Profiling For Whom ??

1. In subjects with CVD
2. In clinical conditions associated with increased risk of CVD and dyslipidemia
3. For CVD risk stratification.

Recommendations for lipid analyses in cardiovascular disease risk estimation

Recommendations	Class [a]	Level [b]
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
LDL-C is recommended to be used as the primary lipid analysis for screening, risk estimation, diagnosis and management. HDL-C is a strong independent risk factor and is recommended to be used in the HeartScore algorithm.	I	C
TG adds information on risk and is indicated for risk estimation.	I	C
Non-HDL-C is a strong independent risk factor and should be considered as a risk marker, especially in subjects with high TG.	I	C
ApoB should be considered as an alternative risk marker whenever available, especially in subjects with high TG.	IIa	C
Lp(a) should be considered in selected cases at high-risk, in patients with a family history of premature CVD, and for reclassification in subjects with borderline risk.	IIa	C
The ratio apoB/apoA1 may be considered as an alternative analysis for risk estimation.	IIb	C
The ratio non-HDL-C/HDL-C may be considered as an alternative but HDL-C used in HeartScore gives a better risk estimation.	IIb	C

Risk modifiers

- For those at intermediate risk, other factors, including metabolic factors such as :

1. Increased apolipoprotein B (apoB),
2. Lipoprotein(a) (Lp(a)),
3. Triglycerides (TGs) or
4. High-sensitivity C-reactive protein (hs-CRP) or
5. The presence of albuminuria, may improve risk classification

Recommendations for lipid analyses for characterization of dyslipidaemias before treatment

Recommendations	Class [a]	Level [b]
LDL-C has to be used as the primary lipid analysis.	I	C
It is recommended to analyse HDL-C before treatment.	I	C
TG adds information about risk, and is indicated for diagnosis and choice of treatment.	I	C
Non-HDL-C is recommended to be calculated, especially in subjects with high TG.	I	C
When available, apoB should be an alternative to non-HDL-C.	IIa	C
Lp(a) should be recommended in selected cases at high-risk, for reclassification at borderline risk, and in subjects with a family history of premature CVD (**see Box 7**).	IIa	C
TC may be considered but is usually not enough for the characterization of dyslipidaemia before initiation of treatment.	IIb	C

Non-HDL cholesterol

- Non-HDL-C is used as an estimation of the total number of **atherogenic particles** in plasma ***[VLDL + intermediate-density lipoprotein (IDL) + LDL]*** .

- Non-HDL-C correlates relates well to **apo B levels.**

- Non-HDL-C is easily calculated from TC minus HDL-C.

Non-HDL cholesterol

- Non-HDL-C can provide a better risk estimation compared with LDL-C, in particular in **Mixed dyslipidaemias** combined with diabetes, the Metabolic Syndrome or CKD.

- This is supported by a recent meta-analysis including 14 statin trials, seven fibrate trials, and six nicotinic acid trials.

Apolipoproteins

1. Apolipoprotein B.
2. Apolipoprotein A1.

Apolipoprotein B

- Apo B is the major apolipoprotein of the atherogenic lipoprotein families VLDL, IDL, and LDL.

- The concentration of apo B is a good estimate of the number of these particles in plasma.

Apolipoprotein B

- several post-hoc analyses of statin trials suggest that apo B *may be not only a risk marker but also a better treatment target than LDL-C.*

- Another Met analysis showed that apo B *does not provide any benefit beyond non-HDL-C* or traditional lipid ratios.

Therefore, Apo B used as Secondary treatment target.

Apolipoprotein A1

- Apo A1 is the major protein of HDL and provides a good estimate of HDL concentration.

- Plasma apo A1 of < 120 mg/dL for men and < 140 mg/dL for women approximately correspond to what is considered as low for HDL-C.

Lipoprotein a

- The plasma level of Lp(a) is to a major extent genetically determined.

- Lp(a) has been found in several studies to be an additional independent risk marker; indeed,genetic data show it to be causal in the *pathophysiology of atherosclerotic vascular disease and aortic stenosis.*

Lipoprotein a

- Plasma Lp(a) is **not** recommended for risk screening in the general population ;however, Lp(a) measurement should be systematically considered in people with:

1. High CVD risk.
2. Strong family history of premature atherothrombotic disease.
3. Correct reclassification in patients on the borderline between high and moderate risk.

- **The risk is regarded as significant when Lp(a) is above the 80th percentile (50 mg/dL).**

Management of dyslipidemia

1. Lipid profiling.
2. **Assess total CVD risk.**
3. **Treatment strategies. (according to 1 & 2)**
4. Life style modifications.
5. Treatment targets.
6. Choice of treatment.
7. Dyslipidaemia in special population.

Management of dyslidemia

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Intervention Strategies

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.5 mmol/L	100 to <155 mg/dL 2.5 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	>190 mg/dL >4.9 mmol/L
<1	No lipid intervention	No lipid intervention	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
>5 to <10, or high risk	Lifestyle intervention, consider drug*	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high risk	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

Management of dyslipidemia

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Life Style modifications

1. Nutrition.
2 . Physical exercise.
3. Management of overweight & Obesity.
4 Smoking cessation.
5 Moderation of Alcohol consumption in Alcoholics.

Dietary recommendations to lower LDL-C and improve overall lipoprotein profile

	To be preferred	To be used with moderation	To be chosen occasionally in limited amounts
Cereals	Whole grains	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, chickpeas, soybean		
Fruit	Fresh or frozen fruit	Dried fruit, jelly, jam, canned fruit, sorbets, popsicles, fruit juice	
Sweets and sweeteners	Non-caloric sweeteners	Sucrose, honey, chocolate, candies	Cakes, ice creams, fructose, soft drinks
Meat and fish	Lean and oily fish, poultry without skin	Lean cuts of beef, lamb, pork or veal, seafood, shellfish	Sausages, salami, bacon, spare ribs, hot dogs, organ meats
Dairy food and eggs	Skim milk and yogurt	Low-fat milk, low-fat cheese and other milk products, eggs	Regular cheese, cream, whole milk and yogurt
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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- **Smoking cessation** has clear benefits on the overall CV risk and specifically on ***HDL-C.***

- **Aerobic physical activity** corresponding to a total energy expenditure of between 1500 and 2200 kcal/week, such as 25–30 km of brisk walking per week (or any equivalent activity) may ***increase HDL-C*** levels by 0.08 –0.15 mmol/L (3.1 – 6 mg/dL)

Management of dyslipidemia

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5. **Treatment targets.**
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Management of dyslidemia

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Treatment Targets

For prevention of CVD

(Primary or Secondary Prevention)

1. Primary Treatment targets.
2. Secondary Treatment targets.
3. Not recommended as Treatment targets.

Treatment targets

- Treatment targets of dyslipidaemia are primarily based on *results from clinical trials*.
- In nearly all lipid-lowering trials the **LDL-C** level has been used as an indicator of response to therapy.

Therefore, LDL-C remains the primary target of therapy in most strategies of dyslipidaemia management.

Treatment targets

- Non-HDL-C and apoB receive a moderate grading as treatment targets as they have not been extensively studied in RCTs compared to LDL-C.

Therefore, Non-HDL-C & Apo B are considered as Secondary treatment targets for dyslipidaemia management.

Primary Treatment Targets

- LDL-C→recommended as target for tx (class I A)

- TC→considered as tx target if other analyses are not available (class IIa A)

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Secondary Treatment Targets

- Non-HDL-C⟶ considered as a secondary tx target (class IIa B)
- Apo B⟶considered as a secondary tx target (class IIa B)

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Not recommended as Treatment Targets

- HDL-C → not recommended as targets for tx (class III C) because evidence is lacking on the efficacy of intervention on this variable to reduce CVD risk.

- Ratios (Apo B/ Apo A1)
  (Non- HDL/ HDL)

Treatment Targets for LDL-C

- In patients at <u>VERY HIGH CV risk</u>→the LDL-C goal is
  <1.8 mmol/L **(<~70 mg/dL)** and/or ≥50% LDL-C reduction when target level can not be reached (class I A)

- In patients at <u>HIGH CV risk</u>→the LDL-C goal <2.5 mmol/L **(<~100 mg/dL)** should be considered (class IIa A)

- In patients at <u>MODERATE CV risk</u>→the LDL-C goal <3.0 mmol/L **(<~115 mg/dL)** should be considered (class IIa C)

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Why (< 70 mg/dl) ???????

- Extrapolating from the available data, an absolute reduction to an *LDL-C level less than 70 mg/dL or at least a 50% relative reduction in LDL-C* provides the best benefit in terms of CVD reduction.

Treatment Targets ther Than LDL-C

- If non-HDL-C is used, the targets shouia be; <2.6 mmol/L (<~100 mg/dL) in those at VERY HIGH CV risk
  and <3.3 mmol/L (<~130 mg/dL) in those at HIGH CV risk
  (class IIa B)

- If apo B is available, the targets are;
  <80 mg/dL in those at VERY HIGH CV risk
  and
  <100 mg/dL in those at HIGH CV risk
  (class IIa B)

Management of dyslipidaemia

1Lipid profiling.

2Assess total CVD risk.

3Treatment strategies. (according to 1 & 2)

4- Life style modifications.

5 Treatment targets.

6 Choice of treatment.

7 Dyslipidaemia in special population.

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Choice of lipid-lowering drugs in the management of dyslipidaemias

1. Hypercholesetrolaemia.
2. Hypertriglyceridaemia.
3. Mixed dyslipidaemia.

Pharmacological Treatment of Hypercholesterolaemia

1. Statins.
2 Bile acid sequestrants.
3 Cholesterol absorption inhibitors.
4 PCSK9 inhibitors.
5 Nicotinic acid.
6 Drug combinations:
   - Statins + Cholesterol absorption inhibitors.
   - Statins + Bile acid sequestrants.
   - Others.

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Pharmacological Treatment of Hypercholesterolaemia

- **Statin** →prescribe up to the highest recommended dose or highest tolerable dose to reach the target level (class I A)

- Statin intolerance→

  bile acid sequestrants or

  cholesterol absorption inhibitor

  alone or in combination (class IIa)

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Pharmacological Treatment of Hypercholesterolaemia

In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a **PCSK9** inhibitor may be considered. (Class II b)

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Pharmacological Treatment of Hypertriglyceridaemia

1- Severe
2- Modest

Definition of hypertriglyceridaemia

According to the EAS consensus document:

- Mild to moderate HTG is defined as TGs >1.7 mmol/L (150 mg/dL) and <10 mmol/L (880 mg/dL).
- Severe HTG is defined as TGs > 10 mmol/L (880 mg/dL).

Severe Hypertriglyceridemia

- Treatment of Severe Hypertiglyceridemia (> 880mg/dl) should **begin immediately** to reduce risk of pancreatitis & usually **fibrate** is tried first.
- *Other treatment options include :*

1- Lipid lowering therapy. 2- Dietary modifications.
3- Insulin in poorly controlled DM 4- Apheresis.

Modest Hypertriglyceridemia

- Treatment of modest hypertriglyceridemia should begin with:

1- Assessment of total CVD risk.

2- Life style modifications.

3- Search for underlying cause.

Genetic predisposition
Obesity
Type 2 diabetes
Alcohol consumption
Diet high in simple carbohydrates
Renal disease
Hypothyroidism
Pregnancy (physiological triglyceride concentrations double during the third trimester)
Paraproteinaemia and autoimmune disorders such as systemic lupus erythematosus
Multiple medications including: • Corticosteroids • Oestrogens, especially those taken orally • Tamoxifen • Antihypertensives: adrenergic beta-blocking agents (to a different degree), thiazides • Isotretinoin • Bile acid-binding resins • Ciclosporin • Antiretroviral regimens (protease inhibitors) • Psychotropic medications: phenothiazines, second generation antipsychotics

After Life style modifications & in high risk patients:

- If TG remain elevated start *statin therapy* due to significant effect on mortality and CV risk lowering with the primary goal to reach LDL and Non-HDL cholestrol targets. (esp. Potent statins; Atorvastatin & Rosuvastatin)

- Combination therapy with a *fibrate* should follow if needed. Also Niacin is another option.

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Recommendations	Class [a]	Level [b]	Ref [c]
Drug treatment should be considered in high-risk patients with TG >2.3 mmol/L (200 mg/dL).	IIa	B	261, 262
Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia.	IIb	B	263, 264
In high-risk patients with TG >2.3 mmol/L (200 mg/dL) despite statin treatment, fenofibrate may be considered in combination with statins.	IIb	C	261–264

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Efficacy of fibrates on CV outcome

The clinical effects of fibrates are primarily illustrated by five prospective RCTs:

1Helsinki Heart Study **(HHS)**,

2Veterans Affairs Highdensity lipoprotein Intervention Trial **(VA-HIT),**

3Bezafibrate Infarction Prevention **(BIP)** study,

4Fenofibrate Intervention and Event Lowering in Diabetes **(FIELD)** and

5Action to Control Cardiovascular Risk in Diabetes **(ACCORD)** study, where fenofibrate was added to statin therapy

- Neither the FIELD nor the ACCORD study showed a reduction in total CVD outcomes.
- Results from other meta-analyses suggest reduced major CVD events in patients with high TGs and low HDL-C in fibrate-treated patients, but no decrease in CVD or total mortality.
- ***Thus the overall efficacy of fibrates on CVD outcomes is much less evident than that of statins.***

.

Drugs for Low HDL-C

- Low HDL-C constitute a strong, independent and inverse predictor of the risk of premature development of atherosclerosis.

Drugs for Low HDL-C

1. statins.
2. Fibrates.
3. Nicotinic acid.
4. CETP inhibitors

Drugs for Low HDL-C

Recommendations	Class [a]	Level [b]	Ref [c]
Statins and fibrates raise HDL-C with a similar magnitude and these drugs may be considered.	IIb	B	262, 292
The efficacy of fibrates to increase HDL-C may be attenuated in people with type 2 diabetes.	IIb	B	261, 262

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Pharmacological Treatment of Mixed Dyslipidaemia

Drug Combinations for the Management of Mixed Dyslipidaemias

- ↑ in HDL-C and ↓ in TG on top of ↓ in LDL-C can be achieved by **statins.**
- **Statin+fibrate**→monitor for myopathy; combination with gemfibrozil should be avoided
- TG are not controlled by statins or fibrates→**n-3 fatty acids**

Management of dyslipidaemia

1 Lipid profiling.

2 Assess total CVD risk.

3 Treatment strategies. (according to 1 & 2)

4- Life style modifications.

5- Treatment targets.

6- Choice of treatment.

7- **Dyslipidaemia in special population.**

Management of Dyslipidaemias in Different Clinical Settings

Familial dyslipidaemias
Children
Women
elderly
Metabolic syndrome and diabetes mellitus
Patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention
Heart failure and valvular disease
Autoimmune diseases
Renal disease
Transplantation patients
Peripheral arterial disease
Stroke
Human immunodeficiency virus patients

Familial Hypercholesterolemia

FH is suspected in subjects with:

- CVD aged <55 years (♂) or <60 years (♀),
- Relatives with premature CVD
- known FH in the family.
- Subjects with severe elevation of LDL-C (> 190 mg/dl in adults and >150 mg/dl in children).***(Class I c)***

Confirm the diagnosis with clinical criteria or with DNA analysis. ***(Class I c)***

Family screening is indicated when a patient with HeFH is diagnosed. ***(Class I c)***

Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia

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 (see 9.1.2.3)	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
3) Physical examination	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL-C levels	
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 gene	8
Choose only one score per group, the highest applicable Diagnosis (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	

Familial Hypercholesterolemia

Heterozygous Type:

1 AcoD type (Defect in LDL receptor)

2 AD type (Gain of function mutation of PCSK 9)

3 AR type (Mutation of ARH gene → decrease recycling of LDL-R)

4 Familial defective Apo B100 (decrease affinity to LDL-R)

Familial Hypercholesterolemia

Heterozygous Type:

Treatment :

Intense dose **statins** (often in cimbination with ezetimibe).***(Class I)***

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)***

Familial Hypercholesterolemia

Heterozygous Type:

Targets:

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

Familial Hypercholesterolemia

Heterozygous Type: (Children)

Children with FH should be educated to adopt a

1- Proper diet and

2- Treated with statin from **8–10 years** of age. Targets for treatment should be LDL-C <3.5 mmol/L (135 mg/dL) at >10 years of age)and at younger ages at least a 50% reduction of LDL-C.

Familial Hypercholesterolemia

Homozygous Type (Rare)

- Both Parents had HeFH
- Failure of LDL-R expression→ severe increase of LDL with death in early adulthood due to Myocardial ischemia or AS.
- Treatment:

High dose statins + combination

therapy LDL apharesis

CABG usually at young age

Novel ttt (Antisense RNA against Apo B synthesis in liver)

Children

- Only in FH consideration should be given to lipid-lowering drug treatment.
- In other cases of dyslipidaemia in children, focus should be on ***diet and treatment of underlying metabolic disorders.***

When to start Statin therapy ??

- The exact age at which to start statin treatment is, however, a matter for clinical judgement.

- **HoFH** patients should be treated with lipid- lowering drugs ***as early as possible***, and the same is true for **HeFH patients with extremely high LDL-C**, i.e. ≥400 mg/dL (10.3 mmol/L).

- In the case of other HeFH children,statin treatment is generally ***with held until*** sometime between the ages of 8 and 10 years.

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Women

- Statin tx→recommended for primary prevention of CAD in high risk women

- Statins→recommended for secondary prevention in women with the same indications and targets as in men

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Women

- *Lipid-lowering drugs should not be given when pregnancy is planned, during pregnancy or during the breast-feeding period*

Bile acid sequestrants (which are not absorbed) may be considered.

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The Elderly

- Tx with statins→recommended for elderly patients with established CVD in the same way as for younger patients (class I B)
- Elderly people often have comorbidities and have altered pharmacokinetics

- Recommended to *start lipid-lowering medication at a low dose and then titrate with caution* to achieve target lipid levels which are the same as in the younger subjects (class I C)

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DM & dyslipidemia

- Patterns of dyslipidemia in DM.

T1DM: Serum TGs (Normal), HDL (Upper normal or slightly elevated)

Due to Insulin therapy -> increase lipoprotein lipase activity in adipose tissue -> Increase turn over of VLDL (TRLs)

Increased CV risk is due to Qualitative changes in LDL & HDL i.e. become atherogenic.

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T1DM

- In patients with T1DM and in presence of microalbuminuria &/or renal disease LDL-C lowering (at least 50%) with statins as the first choice is recommended irrespective of base line LDL-C level.

Class I

(drug combination may be used if required)

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DM & dyslipidemia

T2DM: (Mixed dyslipidemia)

- Moderate increase of TGs.
- Increase of TRLs including LDL & VLDL.
- Decrease of HDL & Apo A.

Due to Insulin resistance → flux of FFA to liver → Non- alcoholic fatty liver disease → increase content of liver fat → Increase VLDL & TGs

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CVD risk assessment in DM

Very high risk: DM + other CVD risk factors or TOD

High risk: DM

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T2DM

Manag. ???

- Life style modifications
- Statins are recommended irrespective of baseline LDL-C (target acc. To level of risk)

High or very high risk

(drug combination may be used if required)

CKD & Dyslipidemia

- ***Pattern of dyslipidemia in CKD: Mixed dyslipidemia***

1.Increased TGs (due to increased production & impaired turn over of TRLs).

2.Decreased HDL-C.

3.Increased LDL-C (due to prolonged catabolic rate of LDL-C)

- ***Based on results of different RCTs & meta-analyses:***

In patients with CKD not on dialysis: treatment with statins reduced all-cause mortality by 34%, CV mortality by 31%,CV events by 45% and stroke by 34%.

In patients receiving dialysis: treatment with statins had **no** effect on all-cause mortality and **no** convincing evidence of reduced CVD events.,

Recommendations	Class [a]	Level [b]	Ref [c]
Patients with stage 3–5 CKD have to be considered at high or very high CV risk.	I	A	388–392
The use of statins or statin/ ezetimibe combination is indicated in patients with non-dialysis-dependent CKD.	I	A	393, 394, 397
In patients with dialysis-dependent CKD and free of atherosclerotic CVD, statins should not be initiated.	III	A	395, 396
In patients already on statins, ezetimibe or a statin/ezetimibe combination at the time of dialysis initiation, these drugs should be continued, particularly in patients with CVD.	IIa	C	
In adult kidney transplant recipients treatment with statins may be considered.	IIb	C	

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Patients with ACS & patients undergoing PCI

It was shown that either pretreatment

with high-dose statin (ranging from > 2 weeks to a single dose) in patients not on statin therapy (11studies) or loading of a high-dose statin in patients receiving chronic statin therapy ***decreased peri-procedural MI and 30-day adverse events in patients undergoing PCI.***

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Routine short pretreatment or loading (on the background of chronic therapy) with high-dose statins before PCI should be considered in elective PCI or in NSTE-ACS.

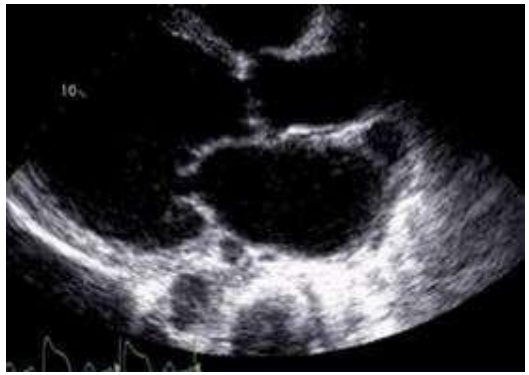
(Class II a)

Heart Failure and Valvular Diseases

n-3 PUFAs (1 g/day)→to be added to optimal tx in patients with HF ***(Class IIb B)***

Cholesterol-lowering therapy by statins→not indicated in patients with moderate to severe HF (NYHA III-IV) CORONA GISSI-HF

(Class III A)



Lipid-lowering tx→not indicated in patients with valvular disease without CAD ***(Class III B)***

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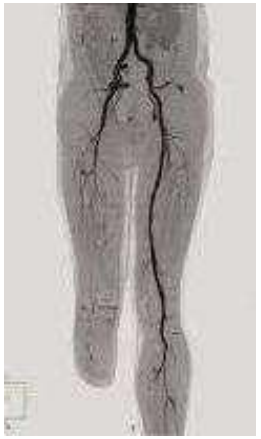
Peripheral Arterial Disease

PAD is a high risk condition and lipid-lowering therapy (mostly statins) is recommended
(Class I A)



Statins→recommended to reduce the progression of carotid atherosclerosis
(Class I A)

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Autoimmune disease & Dyslipidemia

- Rheumatoid arthritis, SLE, psoriasis and anti-phospholipid syndrome, are characterized by enhanced atherosclerosis and consequently higher CV morbidity and mortality rates compared with the general population.

- Statins are effective in reducing disease activity, CV events and mortality (particularly in primary prevention) in this setting However,there is no firm indication to use lipid-lowering therapy only on the basis of the presence of the disease.

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There are 4 defined Statin Benefit groups

1 Patients with clinical ASCVD.

2 LDL greater than 190 mg/dl.

3 Patients with diabetes, age 40-75 years.

4 Age 40-75 years that do not meet above criteria, but have a 10 year risk of >7.5 %

(according to the New pooled cohort risk equation)

Q: why 4 major statin benefit groups ???

- Because Statins RCTs showed the greatest ASCVD event reduction that EXCEEDS risk of adverse events.

There are 4 defined Statin Benefit groups

- All of these are indicated for statin treatment

- Results are mainly derived from **CTT metanalyses** which showed that each **39 mg/dl** reduction in LDL-C with statins Reduction of ASCVD events by **22%**

1. Patients with clinical ASCVD

- Coronary artery disease or peripheral artery disease
- Acute coronary syndromes
- Coronary or other arterial revascularization
- Stroke or TIA

- These patients get ***high intensity statin treatment***

If they cannot tolerate high intensity statin therapy, use other agent to achieve >50% reduction of baseline LDL.

2. LDL greater than 190 mg/dl

- These are patients with familial hyperlipidema (we should exclude secondary causes first to avoid unnecessary use of statins)

- These patients get ***high intensity statin treatment***

If they cannot tolerate high intensity statin therapy, use other agent to achieve >50% reduction of baseline LDL.

3. Patients with diabetes, age 40-75 years

- **All** have indication for statin
- Level of intensity of statin treatment depends on calculated 10 year risk.

- Diabetics with **> 7.5%** 10 year risk get *high intensity statin therapy*
- Diabetics with **< 7.5%** 10 year risk of CAD get *moderate intensity statin therapy*

4. Age 40-75 years that do not meet above criteria, but have a 10 year risk of >7.5 %

- 10 year and lifetime risk as determined by CV Risk Calculator.
- *Moderate to high intensity statin therapy* recommended

In these individuals whose 10 year risk is less

that 7.5%, or when the decision is unclear, other factors should be considered

- Family history of premature CAD
- LDL > 160 mg/dl
- Increased CRP greater than 2.0
- Coronary calcium greater than 300
- ABI < 0.9

Intensity of Statin therapy

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C 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* *Pitavastatin 1 mg*

Insufficient response to statins

1. Assess adherence to medications & life style modifications.
2. Exclude Secondary causes of Hyperlipidemia.
3. Intolerance to Statins.

Non-statin therapies

- For hyperlipidemia, non statin therapies, alone or in combination with statins, do not provide acceptable risk reduction benefits compared to adverse effects. CLASS IIb

- ***For the most part, these should be avoided*** with few exceptions when risk reduction outweigh the potential adverse events.

Non- statin therapy

Fibrates

Mech. : Agonists of PPAR- α → regulate gene expression

→ ++ LPL activity → ++ lipolysis of TGLs

Action: Decrease TGs (20 – 50%) & LDL (5 – 20%)

Side effects: Myopathy , GIT disturbances, Erectile dysfunction

Trials: FIELD & ACCORD (Fenofibrate showed no reduction of CV death & NFMI) but in subgroup analysis in pts with elevated TGs and Low HDL it showed reduction of CV risk.

Niacin

Mech. : Decrease hepatic secretion of VLDL from liver and
FFAs mobilization from periphery.

Action: Decrease TGs (20 – 25%) & LDL (5 – 20%)

Increase HDL (15 – 35 %)

Side effects: Flushing , GIT disturbances, Hyperuricemia,
Hepatotoxicity….

Trials: HPS2 – THRIVE & AIM HIGH (Adding Niacin to statins showed no significant reduction of CV events)

Cholestrol Absorption Inhibitors

Mech. : Decrease selective uptake of cholestrol by intestinal epithelial cells. (inhibit NPC1- like protein)

Action: Decrease LDL (18%).

Side effects: Increase Liver Transaminases Trials:

SEAS (Ezetimibe + Simv.) in AS → Decrease CV events but not decreasing progression of AS.

IMPROVE-IT

- Ezetimibe was added to simvastatin (40 mg) in patients after ACS.

A total of 18144 patients were randomized:

- 170 fewer events were recorded in the group taking simvastatin plus ezetimibe (P = 0.016).

- The average LDL-C during the study was 1.8 mmol/L in the simvastatin
  group and 1.4 mmol/L in patients taking ezetimibe plus simvastatin.

- Also, ischaemic stroke was reduced by 21% in this trial (P = 0.008).

- There was no evidence of harm caused by the further LDL-C reduction. the study supports the proposition that LDL-C lowering by means other than statins is beneficial and can be performed without adverse effects.

Bile Acid Binding Resins

Mech. : Interrupt enterohepatic circulation of Bile acids by inhibiting their reabsorption in intestine → lost in feaces → plasma cholestrol used in synthesis of Bile acids by liver.

Action: Decrease LDL (15 - 30%).

Side effects: Constipation, GIT disturbances

Hypertriglyceridemia (++ phosphatidic acid phosphatase leading to increased TG synthesis)

CETP inhibitors

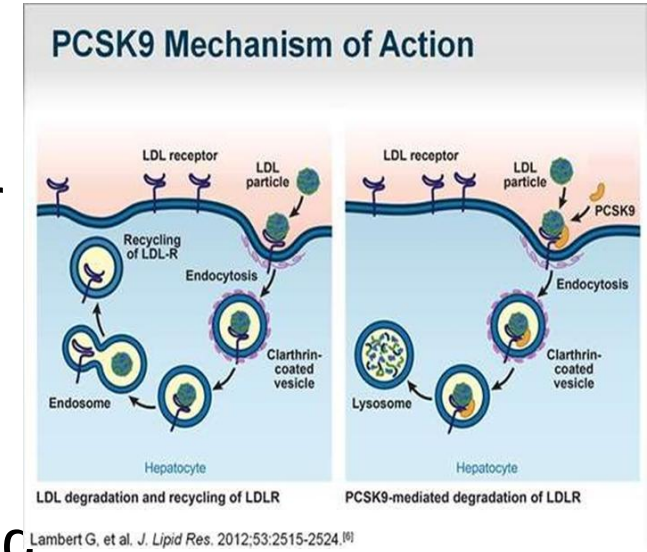
Torcetrapib : Toxic (ILLUMINATE)

Anacetrapib (REVEAL)

Dalcetrapib (DAL-OUTCOME)

PCSK 9 inhibitor

Mech. : Inhibit PCSK (Proprotein convertase subtilisin kexin 9) that functions in internalization & cellular processing of LDL-R.



Trials :

DESCARTES (Evolocumab 420 mg once every 4 weeks → significant reduction of Cholestrol regardless of type of lipid lowering drugs)

LAPLACE 2

PCSK9 Inhibitor is not a substitute of statin but only used as add on ttt or in cases of mixed or resistant hyperlipidemias

Lipoprotein disorders
Fridricksin & Leavy classification

Type	Abnormality	Changes
I: Familial Hyperchylomicronemia	Absent or deficient LPL or ↓↓ Apo CII (LPL +)	↑↑ TGs > 1000 mg/dl
II: Familial Hypercholesterolemia		↑↑ LDL
III: Dysbetalipoproteinemia	Abnormal Apo E ⟶ Decrease hepatic clearance of chylomicron remnants & IDL	↑↑ TG & TC
IV: Familial Hypertriglyceredemia	Overproduction &/or decreased catabolism of TGs	↑↑ TGs ↓↓ LDL & HDL
V: I + IV	Overproduction &/or decreased catabolism of chylomicrons & VLDL	↑↑ TGs
VI: Familial combined Hyperlipidemia	Overproduction of VLDL. ↑↑ flux of FFA to liver	↑↑ LDL & TGs

Type I & Type IV

- Rare.
- The most common complication is pancreatitis.
- Commonly don’t cause Atherosclerotic cardiovascular disease or increase cardiovascular risk.

Type III

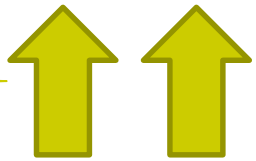
- AR disorder.
- Majority are homozygous for Apo E2 with defective binding to LDL receptors.
- Usually doesn’t cause a problem except if associated with other lipid disorders as in DM, Obesity or Metabolic syndrome.

Type IV and VI

- AD
- Mechanism is not clearly understood however it is mostly due to overproduction &/or decreased catabolism of affected lipoproteins.

LDL-C disorders
(Primary & Secondary)

- Familial Hypercholesterolemia
- Dysbetalipoproteinemia
- Familial combined hyperlipidemia

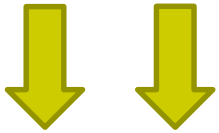


- Hypobetalipoproteinemia

(Due to defective Apo B)

- Abetalipoproteinemia

(Due to Absent Apo B)



Don’t forget Secondary causes

TRLs disorders
(Primary & Secondary)

- Familial Hyperchylomicronemia
- Familial Hypertriglyceredemia
- Familial combined Hyperlipidemia

Don’t forget Secondary causes

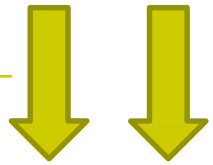
HDL Disorders

- Primary (Genetic) HDL dyslipidemia 1- Apo A1 defects.

2 LCAT deficiency

3 Tangier disease

4 Niemann-Pick type C disease

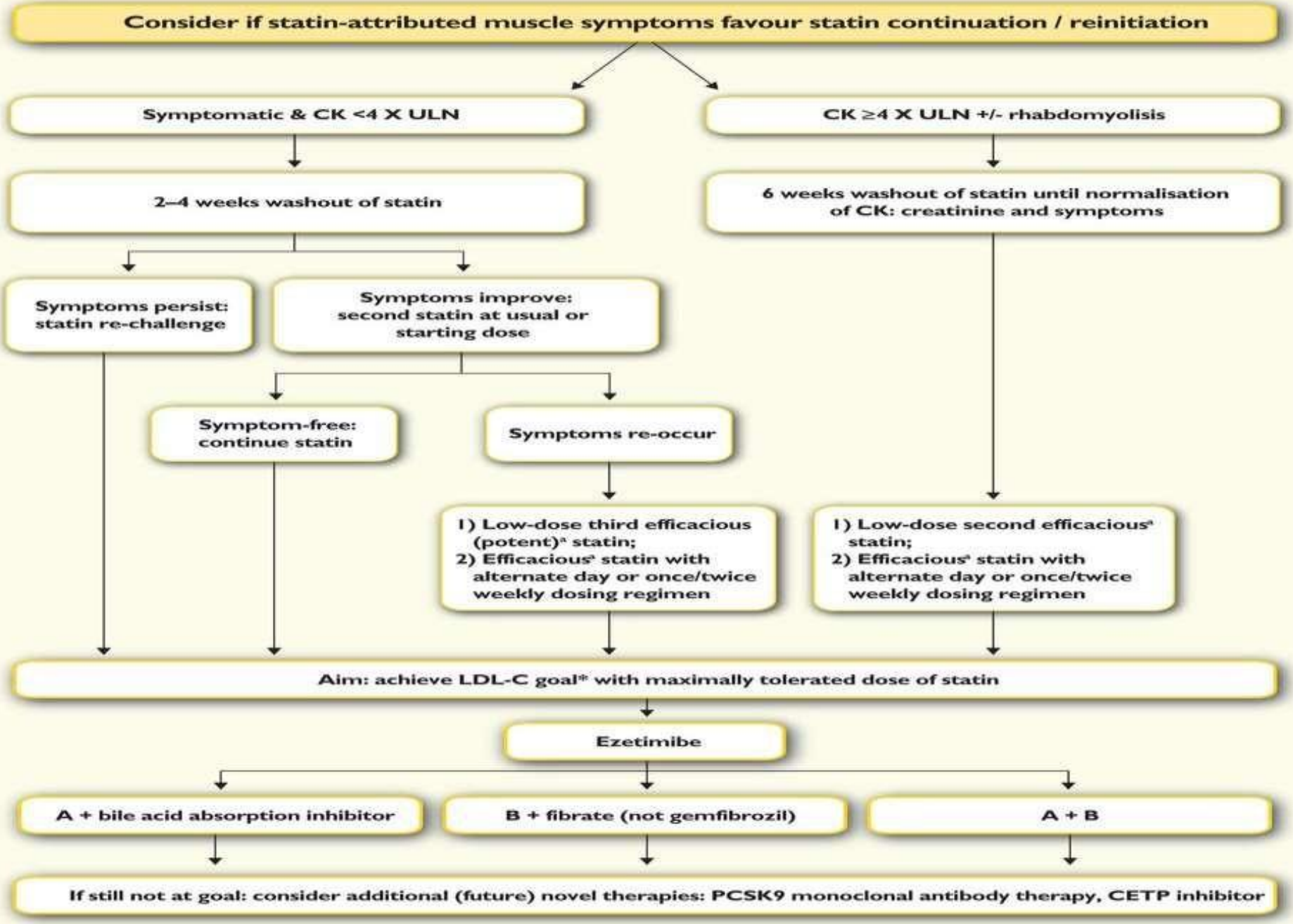


5 CETP deficiency

- *Part of other familial dyslipidemia (Type I, IV, VI)*

Secondary causes of Lipoprotein disorders(4D)

	⇧⇧ LDL- C	⇧⇧ TGs
Diet	Sat. fat Trans. Fat Weight gain	Very low fat diet Excess alcohol/ CHO Weight gain
Drugs	Diuretics Glucocorticoids Amiodarone	Thiazides BBs (except Carvidelol) Glucocorticoids Oral estrogen BAS.
Diseases	Biliary obstruction Nephrotic syndrome	CRF Nephrotic syndrome
Disorders & altered metabolism	Hypothroidism Obesity Pregnancy T2DM (poorly controlled)	



CETP = cholesteryl ester transfer protein; CK = creatine kinase; LDL-C= low-density lipoprotein cholesterol; PCKS9 = propotein onvertase subtilisin/kesin type 9; ULN = upper limit of the normal range.

[a]Efficacious statin such as atorvastatin or rosuvastatin.

*Reiner Z *et al.* (2011).

Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class [a]	Level[b]
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C

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Hypertriglyceridaemia

Possible Causes

- Genetic predisposition
- Obesity
- Type 2 diabetes
- Alcohol consumption
- Diet high in simple carbohydrates
- Renal disease
- Hypothyroidism
- Pregnancy (physiological triglyceride concentrations double during the third trimester)
- Paraproteinaemia and autoimmune disorders such as systemic lupus erythematosus
- Multiple medications including:

  • Corticosteroids • Oestrogens, especially those taken orally • Tamoxifen • Antihypertensives: adrenergic beta-blocking agents (to a different degree), thiazides • Isotretinoin • Bile acid-binding resins • Ciclosporin • Antiretroviral regimens • Psychotropic medications: phenothiazines, second generation antipsychotics

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Recommendations for drug treatment of HTG

Recommendations	Class	Level
In particular high risk patients, lowering of HTG by using the following drugs:		
is recommended: fibrates	I	B
should be considered: nicotinic acid	IIa	B
nicotinic acid + laropiprant	IIa	C
n-3 fatty acids	IIa	B
statin + nicotinic acid	IIa	A
statin + fibrate	IIa	C
may be considered: combinations with *n*-3 fatty acids	IIb	B

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Recommendations if drug treatment of low HDL-C is considered

Recommendations	Class	Level
Nicotinic acid is currently the most efficient drug to raise HDL-C and should be considered.	IIa	A
Statins and fibrates raise HDL-C with similar magnitude and these drugs may be considered.	IIb	B
The efficacy of fibrates to increase HDL-C may be attenuated in people with type 2 diabetes.	IIb	B

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Diagnostic criteria for familial hypercholesterolaemia

	Criteria	Score
Family history	First-degree relative known with premature CAD and/or first-degree relative with LDL-C > 95th centile	1
	First-degree relative with Tx and/or children < 18 with LDL-C > 95th centile.	2
Clinical history	Patient has premature CAD	2
	Patient has premature cerebral/peripheral vascular disease	1
Physical examination	Tx	6
	Arcus cornealis below the age of 45 years	4
LDL-C	> 8.5 mmol/L (more than ~ 330 mg/dL)	8
	6.5-8.4 mmol/L (~ 250-329 mg/dL)	5
	5.0-6.4 mmol/L (~ 190-249 mg/dL)	3
	4.0-4.9 mmol/L (~ 155-189 mg/dL)	1
DNA Analysis	Functional mutation in the LDLR, apoB or PCSK9 gene	8
Definite FH		Score > 8
Probable FH		Score 6-8
Possible FH		Score 3-5

2016 ESC/EAS Guidelines Catapano AL et al. Atherosclerosis. 2016 Sep 1. pii: S0021-9150(16)31267-9

Recommendations for detection and treatment of patients with HeFH

Recommendations	Class	Level
FH is recommended to be suspected in patients with CHD before the age of 55 years for men and 60 years for women, in subjects with relatives with premature fatal or non-fatal CVD, in subjects with relatives having tendon xanthomas, and in subjects with severely elevated LDL-C [in adults >5 mmol/L (190 mg/dL), in children >4 mmol/L (150 mg/dL)].	I	C
Diagnosis is recommended to be confirmed with clinical criteria and, when available, with DNA analysis.	I	C
Family cascade screening is recommended to be performed when an index case of FH is diagnosed.	I	C
FH patients are recommended to be treated with intense-dose statin, often in combination with ezetimibe.	I	C
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.	IIa	C
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.	IIa	C
In children, testing is recommended from age 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 statin from 8–10 years of age. Targets for treatment should be LDL-C <3.5 mmol/L (135 mg/dL) at >10 years of age.	IIa	C

Percentage reduction of LDL-C requested to achieve goals as a function of the starting value

STARTING LDL-C		% REDUCTION TO REACH LDL-C		
mmol/L	~ mg/dL	< 1.8 mmol/L (~ 70 mg/dL)	< 2.5 mmol/ (~ 100 mg/dL)	< 3 mmol/L (~ 115 mg/dL)
> 6.2	> 240	> 70	> 60	> 55
5.2–6.2	200–240	65–70	50–60	40–55
4.4–5.2	170–200	60–65	40–50	30–45
3.9–4.4	150–170	55–60	35–40	25–30
3.4–3.9	130–150	45–55	25–35	10–25
2.9–3.4	110–130	35–45	10–25	< 10
2.3–2.9	90–110	22–35	< 10	–
1.8–2.3	70–90	< 22	–	–

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Recommendations for lipid-lowering therapy in patients with ACS and patients undergoing PCI

Recommendations	Class	Level
It is recommended to initiate or continue high dose statins early after admission in all ACS patients without contraindication or history of intolerance, regardless of initial LDL-C values.	I	A
If the LDL-C target is not reached with the highest tolerable statin dose, ezetimibe should be considered in combination with statins in post-ACS patients.	IIa	B
If the LDL-C target is not reached with the highest tolerable 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 contra-indicated.	IIb	C
Lipids should be re-evaluated 4–6 weeks after ACS to determine whether target levels of LDL-C <1.8 mmol/L (<70 mg/dL) or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) have been reached and whether there are any safety issues. The therapy dose should then be adapted accordingly.	IIa	C
Routine short pretreatment or loading (on the background of chronic therapy) with high-dose statins before PCI should be considered in elective PCI or in NSTE-ACS.	IIa	A

Recommendations for lipid-lowering therapy in patients with ACS and patients undergoing PCI

Recommendations	Class	Level
Patients with stage 3–5 CKD have to be considered at high or very high CV risk.	I	A
The use of statins or statin/ ezetimibe combination is indicated in patients with non-dialysis dependent CKD.	I	A
In patients with dialysis-dependent CKD and free of atherosclerotic CVD, statins should not be initiated.	III	A
In patients already on statins, ezetimibe or a statin/ezetimibe combination at the time of dialysis initiation, these drugs should be continued, particularly in patients with CVD.	IIa	C
In adult kidney transplant recipients treatment with statins may be considered.	IIb	C

Thank You