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***Linee guida della terapia ipolipemizzante***

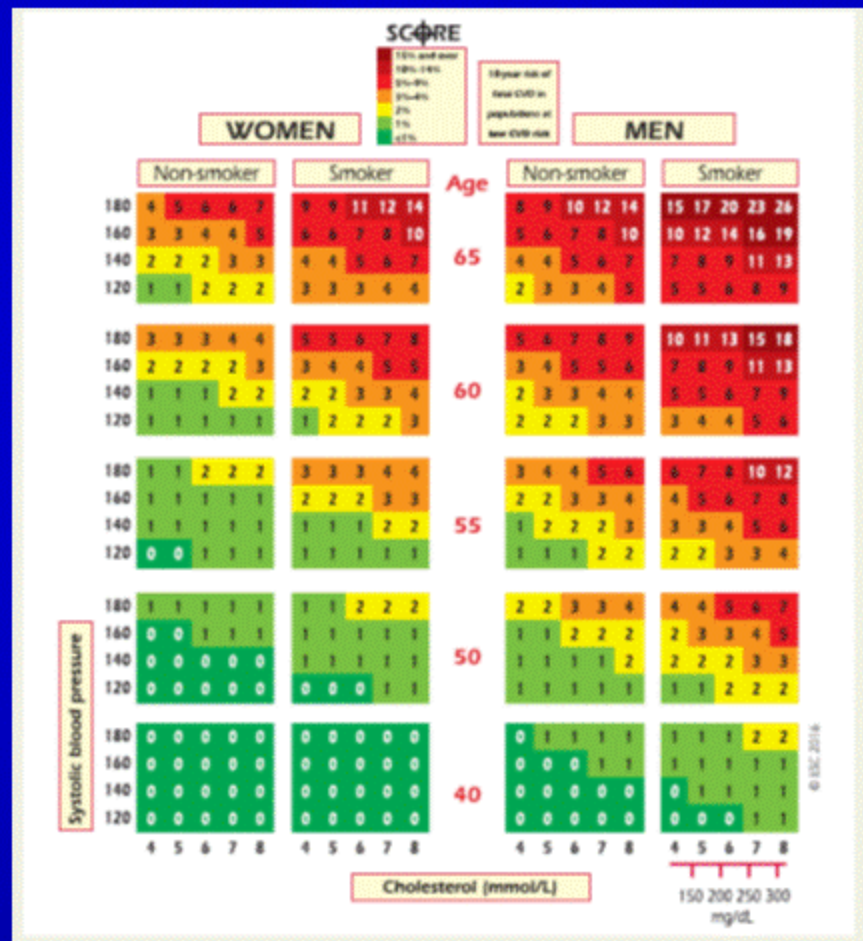
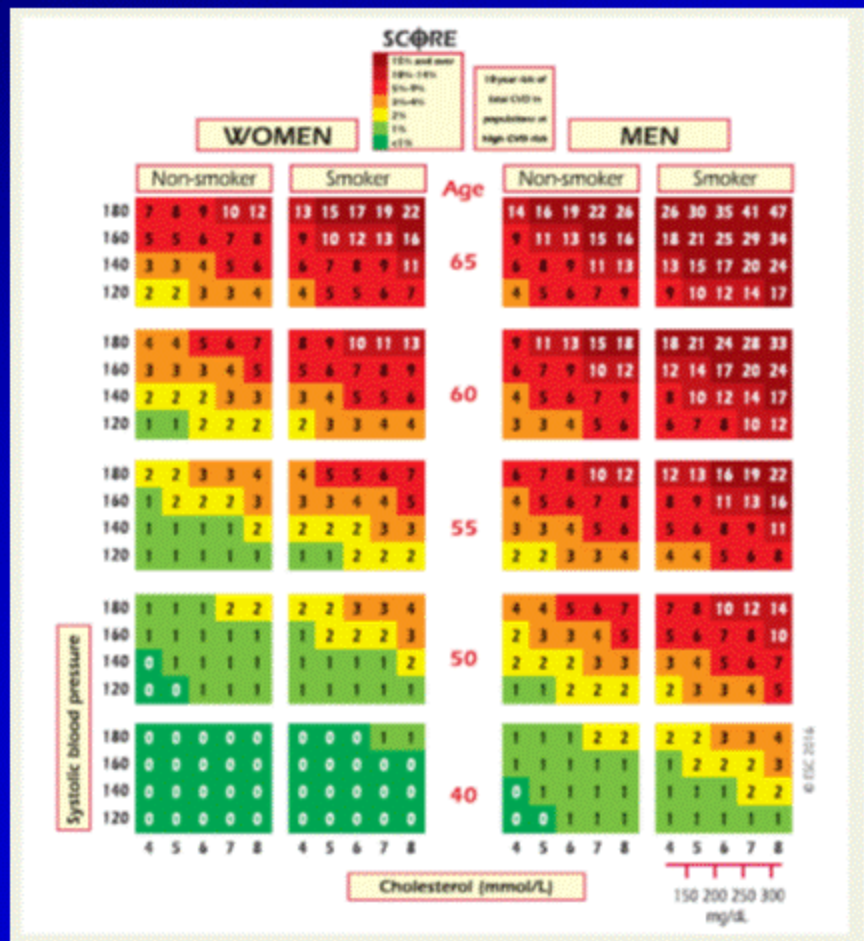
***Aggiornamenti in tema di terapia cardiovascolare***

***Salò, 4 marzo 2017***

# SCORE charts

- People at very high or high total CV risk
  - Documented CVD
  - Type 1 and 2 DM
  - Very high levels of individual RF
  - CKD

All other people





# Risk categories

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## 1. Very high risk

- Documented CVD: previous MI, ACS, coronary revascularization (PCI and CABG) and other arterial revascularization procedures, stroke and TIA, and peripheral arterial disease
- Diabetes mellitus with target organ damage (such as proteinuria) or with a major risk factor such a smoking, hypertension or dyslipidaemia
- Severe CKD (GFR < 30 mL/min/1.73 m<sup>2</sup>)
- A calculated SCORE ≥ 10% for 10-year risk of fatal CVD

# Risk categories

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## 2. High risk

- Markedly elevated single risk factors such as FH ( $> 310$  mg/dl) or hypertension ( $\geq 180/110$  mmHg)
- Type 1 diabetes mellitus (some young people may be at low or moderate risk)
- Moderate CKD (GFR 30-59 mL/min/1.73 m<sup>2</sup>)
- A calculated SCORE  $\geq 5\%$  and  $< 10\%$  for 10-year risk of fatal CVD

## 3. Moderate risk

- SCORE is  $\geq 1\%$  and  $< 5\%$  for 10-year risk of fatal CVD

## 4. Low risk

- SCORE is  $< 1\%$  for 10-year risk of fatal CVD



# Treatment targets and goals for CV disease prevention

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish.
Physical activity	2.5–5 h moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m <sup>2</sup> , waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg <sup>a</sup>
Lipids LDL-C is the primary target	<b>Very high-risk: LDL-C &lt;1.8 mmol/L (70 mg/dL)</b> or a reduction of at least 50% if the baseline <sup>b</sup> is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
	<b>High-risk: LDL-C &lt;2.6 mmol/L (100 mg/dL)</b> or a reduction of at least 50% if the baseline <sup>b</sup> is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
	<b>Low to moderate risk: LDL-C &lt;3.0 mmol/L (115 mg/dL).</b>
	Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively.
	HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk.
	TG: no target 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).

# Intervention strategies: 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 <2.6 mmol/L	100 to <155 mg/dL 2.6 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 <sup>a</sup> /Level <sup>b</sup>	IC	IC	IC	IC	Ib/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 <sup>a</sup> /Level <sup>b</sup>	IC	IC	Ib/A	Ib/A	IA
≥5 to <10, or high-risk	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class <sup>a</sup> /Level <sup>b</sup>	Ib/A	Ib/A	Ib/A	IA	IA
≥10 or very high-risk	Lifestyle intervention, consider drug <sup>c</sup>	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class <sup>a</sup> /Level <sup>b</sup>	Ib/A	Ib/A	IA	IA	IA

CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; SCORE = Systematic Coronary Risk Estimation.

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

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

<sup>c</sup>In patients with myocardial infarction, statin therapy should be considered irrespective of total cholesterol levels.



# Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A	62, 64, 68
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C	239, 256, 257
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B	63
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	115, 116

# Recommendations for the drug treatments of hypertriglyceridaemia and low HDL-C

## Triglycerides

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
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

## HDL-C

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
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



## Lifestyle modifications to improve the plasma lipid profile

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“Dietary fibre (particularly of the soluble type), which is present in legumes, fruit, vegetables, and wholegrain cereals, has a direct hypocholesterolaemic effect”.

“Weight reduction improves insulin sensitivity and decreases TG levels”.

“Alcohol intake has a major negative impact on Tg levels...Moderate ethanol consumption (up to 20-30 g/day in men and 10-20 g/day in women) is associated with increased HDL-C levels”.

“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 3.1-6 mg/dl”.

“Smoking cessation may also contribute to HDL-C elevation”.

# Nutraceuticals

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**“Innovative nutritional strategies to improve dyslipidaemias have been developed; they are based either on changing some ‘risky’ dietary components or encouraging the consumption of specifically targeted ‘healthy’ functional foods and/or dietary supplements; these so-called ‘nutraceuticals’ can be used either as alternatives or in addition to lipid-lowering drugs.”**



## Nutraceuticals (2)

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### Phytosterols:

“The principal phytosterols are sitosterol, campesterol, and stigmasterol, and they occur naturally in vegetable oils and, in smaller amounts, in vegetables, fresh fruits, chestnuts, grains, and legumes. Phytosterols compete with cholesterol for intestinal absorption, thereby modulating TC levels.” LDL-C lowering is near 7-10 %.

### Soy protein:

“...expected LDL-C lowering may be modest (3-5 %)”.

### Berberine:

It is an alkaloid compound from *Berberis Aristata*; LDL-C reduction up to 20% and Tg up to 15 %.

## Nutraceuticals (3)

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### **n-3 unsaturated fatty acids (PUFAs):**

“Supplementation with 2–3 g/day of fish oil (rich in long chain n-3 fatty acids) can reduce Tg levels by 25–30% . . . At least two portions of fish per week are recommended to the general population for the prevention of CVD, together with regular consumption of other food sources of n-3 PUFAs (nuts, soy, and flaxseed oil)”. High dosages may increase LDL-C.

### **Policosanol:**

“Policosanol is a natural mixture of long chain aliphatic alcohols extracted from sugarcane, rice, or wheat germ has no significant effect on LDL-C, HDL-C, Tg, apo B, Lp(a), homocysteine, hs-CRP, fibrinogen, or blood coagulation factors”.

### **Monacolin red yeast rice (RYR):**

The effects of RYR are related to a statin-like mechanism. Different commercial preparations of RYR have different concentrations of monacolins, the bioactive ingredients, and lower TC and LDL-C (up to a 20% reduction). The RYR quality may vary widely”.



# Drugs for treatment of hypercholesterolaemia

## Statins

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- **Interindividual variation in LDL-C reduction with the same drug dose**
- **Evaluate the total CV risk of the subject**
- **Involve the patient with decisions on CV risk management**
- **Identify the LDL-C goal for that risk level**
- **Calculate the percentage reduction of LDL-C required to achieve that goal**
- **Choose a statin and a dose that, on average, can provide this reduction**
- **Response to statin treatment is variable, therefore up-titration of the dose may be required**
- **If the highest tolerated statin dose does not reach the goal, consider drug combinations**
- **In addition, for subjects at very high and high risk, a  $\geq 50$  % reduction in LDL-C should be achieved**

# Drugs for treatment of hypercholesterolaemia

## Statins (2)

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- **LDL-C: 8-55 % of reduction**
- **HDL-C: 5-10 % of increase**
- **Tg: 30-50 % of reduction**
  
- **CV mortality: 20-27 % (meta-analyses)**
  
- **Adverse effects**
  - **Muscle: 10-15 %**
  - **Liver: 0.5-2.0 %**
  - **Kidney: up to 12 % of tubular proteinuria frequency with rosuvastatin 80 mg**
  - **Diabetes: 0.2 % of absolute risk increase**



# Drugs for treatment of hypercholesterolaemia

## Bile Acid Sequestrants

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- **LDL-C: 18-25 % of reduction**
- **HDL-C: no modification**
- **Tg: variable increase**
  
- **28-35 % of LDL-C reduction in association with statins**

# Drugs for treatment of hypercholesterolaemia

## Cholesterol Absorption Inhibitors

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- **LDL-C: 15-22 % of reduction**
- **HDL-C: 8-11 % of increase**
- **Tg: 20-28 % of reduction**
  
- **30-42 % of LDL-C reduction in association with statins**
  
- **IMPROVE-IT (simvastatin + ezetimibe):  
34.7 % decrease of CVD events**



# Drugs for treatment of hypercholesterolaemia

## PCSK9 inhibitors

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- **LDL-C: 50-70 % of reduction**
- **HDL-C: no modification**
- **Tg: no modification**
  
- **up to 55-75 % of LDL-C reduction more than statins**
- **up to 35-45 % of LDL-C reduction more than ezetimibe**

# Drugs for treatment of hypercholesterolaemia

## Nicotinic acid

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- **LDL-C: 15-18 % of reduction**
- **HDL-C: 15-35 % of increase**
- **Tg: 20-40 % of reduction**



# Drugs for treatment of hypertriglyceridaemia

## Fibrates

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- **Tg: up to 50 % of reduction**
- **HDL-C: up to 10-15 % of increase**
- **LDL-C: 0-10 % of reduction**
  
- **Helsinki Heart Study (gemfibrozil):  
34 % of CHD reduction**

## **Drugs for treatment of hypertriglyceridaemia** **n-3 unsaturated fatty acids (PUFAs)**

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- **Tg: up to 45 % of reduction**
  - **HDL-C: 5-10 % of increase**
  - **LDL-C: 10-20 % of reduction**
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- **REDUCE-IT and STRENGTH are ongoing**



## **Drugs for treatment of HDL-C increase**

### **Cholesteryl Ester Transfer Protein (CETP) Inhibitors**

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- **HDL-C: 30-129 % of increase**
  - **LDL-C: 13-36 % of reduction**
  - **Tg: no modification**
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- **REVEAL (anacetrapib) is ongoing**

# La stretta di mano tra Medicina e Chirurgia

Aula Scarpa  
Affresco del soffitto



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