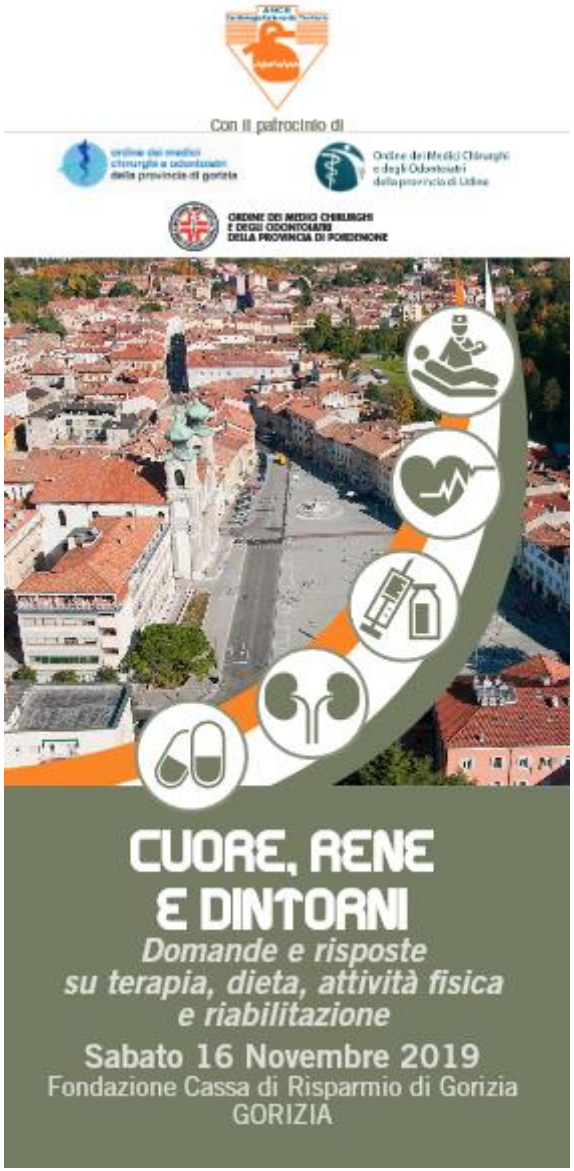

Gestione del paziente dislipidemico dal basso all'alto rischio coronarico

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GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) FREE

François Mach ✉, Colin Baigent ✉, Alberico L Catapano ✉, Konstantinos C Koskinas, Manuela Casula, Lina Badimon, M John Chapman, Guy G De Backer, Victoria Delgado, Brian A Ference ... Show more

Author Notes

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Classificazione delle iperlipidemie

- Linee guida dell'*European Atherosclerosis Society* per la classificazione delle iperlipidemie

Iperlipidemia	Concentrazione plasmatica di lipidi
Ipercolesterolemia	
Lieve	Colesterolo totale: 5,2-6,5 mmol/L (200-250 mg/dL)
Moderata	Colesterolo totale: 6,5-7,8 mmol/L (250-300 mg/dL)
Grave	Colesterolo totale: >7,8 mmol/L (>300 mg/dL)
Ipertrigliceridemia	
Moderata	Trigliceridi: 2,3-4,6 mmol/L (200-400 mg/dL)
Grave	Trigliceridi: >4,6 mmol/L (>400 mg/dL)

- Nell'iperlipidemia mista, colesterolo totale e trigliceridi sono entrambi elevati

ESC European Society of Cardiology

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ESC/EAS GUIDELINES

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

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

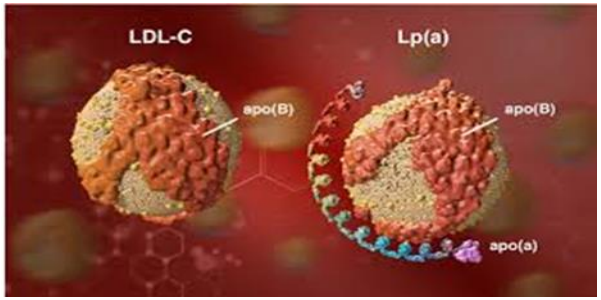
N E W S

New recommendations and new and revised concepts

LDL-C goals

revised CV **risk stratification**

especially **relevant to high- and very-high-risk** patients



Studies have demonstrated the critical role of LDL-C, and other cholesterol-rich Apo B-containing lipoproteins, in atherosclerotic plaque formation and related subsequent CV events

Laboratory measurement of lipids and lipoprotein

Quantification of plasma lipids can be performed on whole plasma and quantification of lipoproteins can be achieved by measuring their protein component. Operationally, lipoproteins are classified based on their hydrated densit

Physical and chemical characteristics of human plasma lipoproteins

	Density (g/mL)	Diameter (nm)	TGs (%)	Cholesteryl esters (%)	PLs (%)	Cholesterol (%)	Apolipoproteins	
							Major	Others
Chylomicrons	<0.95	80–100	90–95	2–4	2–6	1	ApoB-48	ApoA-I, A-II, A-IV, A-V
VLDL	0.95–1.006	30–80	50–65	8–14	12–16	4–7	ApoB-100	ApoA-I, C-II, C-III, E, A-V
IDL	1.006–1.019	25–30	25–40	20–35	16–24	7–11	ApoB-100	ApoC-II, C-III, E
LDL	1.019–1.063	20–25	4–6	34–35	22–26	6–15	ApoB-100	
HDL	1.063–1.210	8–13	7	10–20	55	5	ApoA-I	ApoA-II, C-III, E, M
Lp(a)	1.006–1.125	25–30	4–8	35–46	17–24	6–9	Apo(a)	ApoB-100

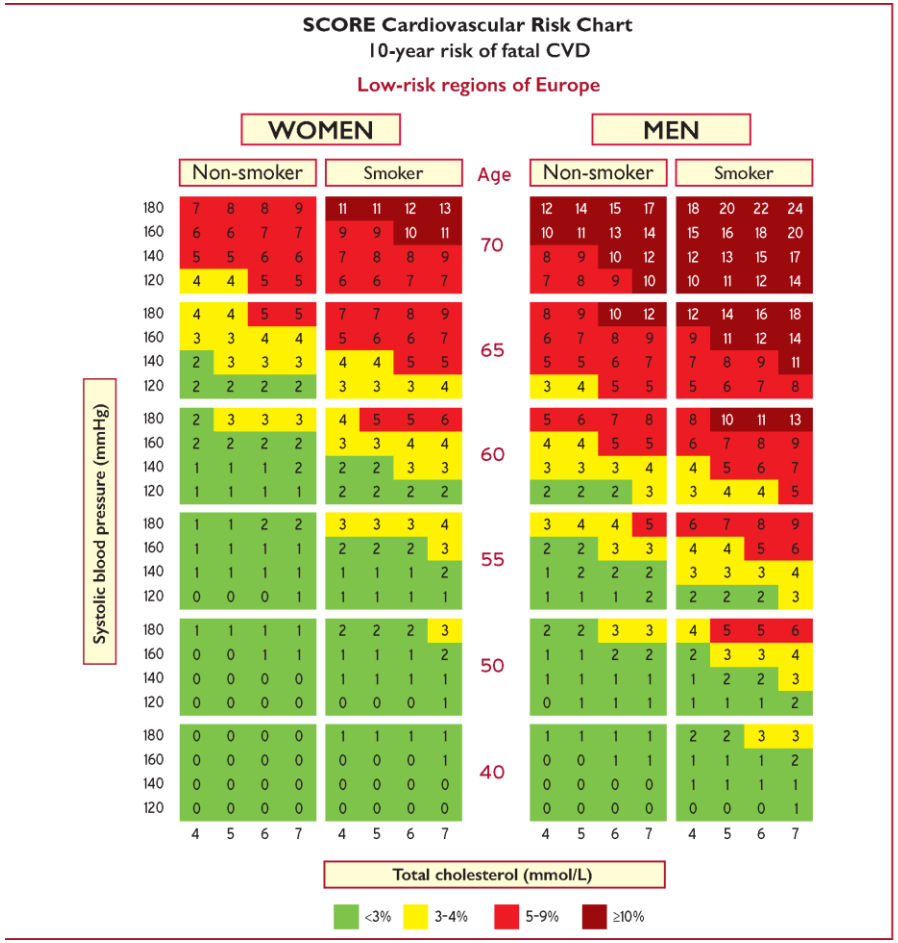
Apo = apolipoprotein; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); PLs = phospholipids; TGs = triglycerides; VLDL = very low-density lipoprotein.

Recommendations for lipid analyses for 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
HDL-C analysis is recommended to further refine risk estimation using the online SCORE system.	I	C
LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management.	I	C
TG analysis is recommended as part of the routine lipid analysis process.	I	C
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.	IIa	C
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	IIa	C

Upgrades	
2016	**2019**
Lipid analyses for CVD risk estimation	**Lipid analyses for CVD risk estimation**
ApoB should be considered as an alternative risk marker whenever available, especially in individuals with high TG.	ApoB analysis is recommended for risk assessment, particularly in people with high TG, DM, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG, DM, obesity, or very low LDL-C.
Pharmacological LDL-C lowering	**Pharmacological LDL-C lowering**
If the LDL goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	If the goals are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.
Pharmacological LDL-C lowering	**Pharmacological LDL-C lowering**
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.	For secondary prevention, patients at very-high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.
	For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.

Systematic Coronary Risk Estimation chart for European populations at low cardiovascular disease risk



Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary 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,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	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,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

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Recommendations	Class[a]	Level[b]
Arterial (carotid and/or femoral) plaque burden on arterial ultrasonography should be considered as a risk modifier in individuals at low or moderate risk.[29,30]	IIa	B
CAC score assessment with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk.[14–16,24,26]	IIb	B

CAC = coronary artery calcium; CT = computed tomography; CV = cardiovascular.

[a]Class of recommendation.

[b]Level of evidence.

CATEGORIE DI RISCHIO CARDIOVASCOLARE SECONDO IL PUNTEGGIO SCORE

CATEGORIA DI RISCHIO	PUNTEGGIO (SCORE)	CARATTERISTICHE DEI SOGGETTI
Molto alta	≥10%	Soggetti con: • malattia CV documentata mediante test invasivi e non invasivi; • precedente infarto del miocardio; • sindrome coronarica acuta; • rivascolarizzazione coronarica; • stroke ischemico; • arteriopatia periferica; • diabete di tipo II, diabete di tipo I con markers di danno d'organo; • patologia renale cronica moderata-severa (FG <60 ml/min/1.73m^2).
Alta	≥5% e <10%	Soggetti con: • SCORE ≥5% e <10% • singoli fattori di rischio marcatamente elevati come dislipidemie familiari e ipertensione severa.
Moderata	≥1% e <5%	Soggetti con: • SCORE ≥1% e <5% Il rischio è ulteriormente influenzato da: • storia familiare di patologia coronarica precoce; • obesità addominale; • attività fisica; • Col-HDL, TG, CRP ad alta sensibilità, Lp(a), fibrinogeno, omocisteina, Apo B; • classe sociale.
Bassa	<1%	

CV = cardiovascolare
FG = filtrato glomerulare
Col-HDL = colesterolo a lipoproteine ad alta densità
TG = trigliceridi
CRP = proteina C reattiva
Lp = lipoproteina
Apo = apolipoproteina

Risk estimation: key messages

In apparently healthy persons, **CVD risk** is most frequently the result of multiple, interacting risk factors. This is the basis for total CV risk estimation and management.

Risk factor screening including the lipid profile should be considered in men >40 years old, and in women >50 years of age or post-menopausal.

A risk estimation system such as SCORE can assist in making logical **management decisions**, and may help to avoid both under- and overtreatment.

Certain individuals declare themselves to be at high or very high CVD risk without needing risk scoring, and **all risk factors require immediate attention**. This is true for patients with documented CVD, older individuals with long-standing DM, familial hypercholesterolaemia, chronic kidney disease, carotid or femoral plaques, coronary artery calcium score >100, or extreme Lp(a) elevation.

The total risk approach allows flexibility; if optimal control cannot be achieved with one risk factor, trying harder with the other factors can still reduce risk.

Pazienti a rischio molto elevato: tabelle SCORE

- Coronaropatia documentata (test di immagine positivi, pregresse SCA, pregresse rivascolarizzazioni, arteriopatia periferica, pregressi stroke ischemici)
- Diabete Mellito (con associato uno o più fattori di rischio oppure segni di danno d'organo)
- Insufficienza renale cronica (GFR < 30 mL/min/1.73 m^2)
- Score calcolato > 10%

Pazienti a rischio elevato: tabelle SCORE

- Singolo fattore di rischio elevato (come ipercolesterolemia grave oppure ipertensione severa)
- Diabete Mellito (senza altri fattori di rischio oppure segni di danno d'organo)
- Insufficienza renale cronica (GFR < 59 > 30 mL/min/1.73 m^2)
- Score calcolato tra 5% e 10%

Recommendations for treatment goals for LDL -cholesterol

Recommendations	Class[a]	Level[b]
In secondary prevention for patients at very-high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[33–35,119,120]	I	A
In primary prevention for individuals at very-high risk but without FH,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[34–36]	I	C
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[119,120]	IIb	B
In patients at high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.[34,35]	I	A
In individuals at moderate risk,[c] an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.[34]	IIa	A
In individuals at low risk,[c] an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.[36]	IIb	A

Riduzione delle morti per coronaropatia 1990 – 2010 negli USA

Trattamento	% riduzione morti
Trattamento acuto SCA	10%
Trattamento cronico CAD	11%
Trattamento scompenso cardiaco	9%
Rivascolarizzazione su angina cronica	5%
Altre terapie	12%
Riduzione Colesterolo	24%
Controllo della pressione arteriosa	20%
Riduzione del fumo	12%
Attività fisica	5%

Terapia

47%

Prevenzione

44%

Treatment targets and goals for cardiovascular disease prevention

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 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	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.
ApoB	ApoB secondary goals are <65, 80, and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively.
Triglycerides	No goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<53 mmol/mol).

Stratificazione dei pazienti

FRONTIERA DEL RISCHIO CARDIOVASCOLARE ALTO e MOLTO ALTO e della prevenzione secondaria degli eventi

Trattamento con Statine

FRONTIERA DEL RISCHIO CARDIOVASCOLARE MEDIO

Farmaci alternativi per il controllo dell'ipercolesterolemia

FRONTIERA DEL RISCHIO CARDIOVASCOLARE BASSO

Nutraceutica

Farmaci ipolipemizzanti

Farmaci per l'ipercolesterolemia

- Farmaci che inibiscono il riassorbimento degli acidi biliari. **Resine a scambio ionico.**
- Farmaci che inibiscono la biosintesi di colesterolo. **Statine.**

Farmaci per l'ipertrigliceridemia e l'iperlipidemia mista.

- Derivati dell'acido fenossi isobutirrico. **Fibrati.**
- Derivati dell'**acido nicotinico.**

DRUGS POTENTIALLY INTERACTING WITH STATINS METABOLIZED BY CYTOCHROME P450 3 A 4 leading to increase risk of myopathy and rhabdomyolysis

Anti-infective agents	Calcium antagonists	Other
Itraconazole	Verapamil	Ciclosporin
Ketoconazole	Diltiazem	Danazol
Posaconazole	Amlodipine	Amiodarone
Erythromycin		Ranolazine
Clarithromycin		Grapefruit juice
Telithromycin		Nefazodone
HIV protease inhibitors		Gemfibrozil

Adapted from Egan and Colman,[257] and Wiklund *et al.*[258]
HIV = human immunodeficiency virus.

Cardine della terapia ipolipemizzante: LE STATINE

Recommendations for the pharmacological treatment of hypercholesterolaemia

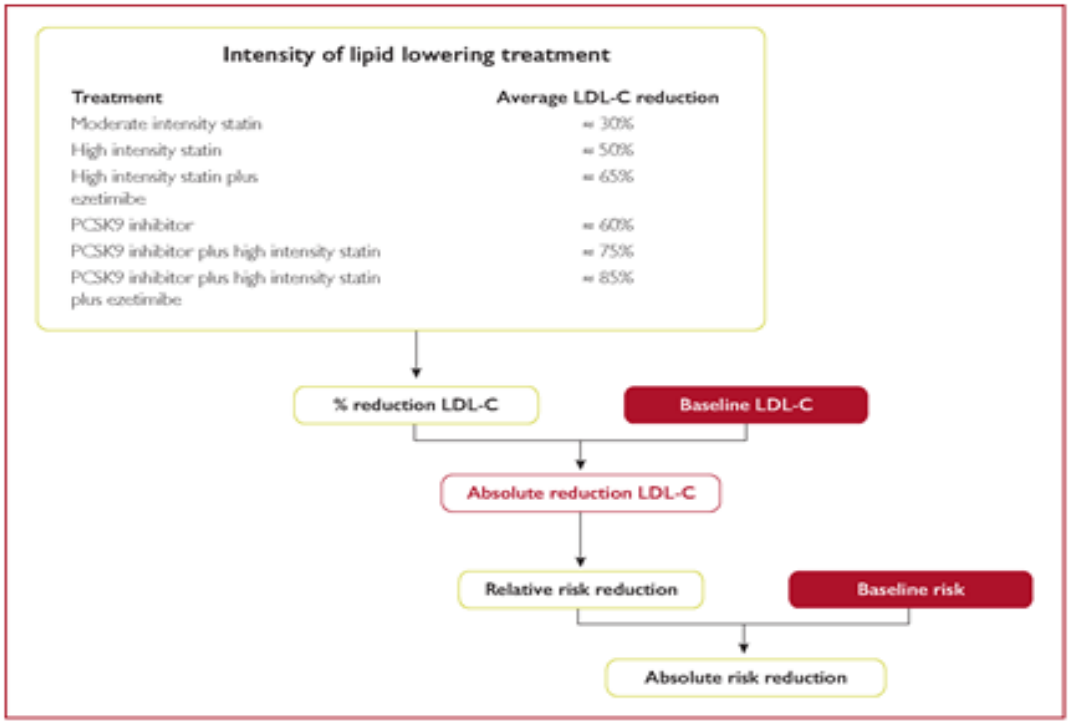
Recommendations	Class[a]	Level[b]
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk.[32,34,38]	I	A
If the goals[c] are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.[33]	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention, patients at very-high risk not achieving their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.[119,120]	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered.[197,265,353]	IIa	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may also be considered.[197,265,353]	IIb	C
If the goal[c] is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

Riduzione del colesterolo e dosaggi di statine: strategia treat to target

Riduzione C-LDL (%)	Atorvastatina (mg)	Fluvastatina (mg)	Lovastatina (mg)	Pravastatina (mg)	Rosuvastatina (mg)	Simvastatina (mg)
>40	>20	–	–	–	>5	>40
30-40	10	80	40/80	–	–	20
20-30	–	40	10/20	20/40	–	10
<20	–	20	–	10	–	–

Modificata da Weng et al.[31].

Figure 3 Expected clinical benefits of low-density lipoprotein cholesterol-lowering therapies. The expected clinical ...



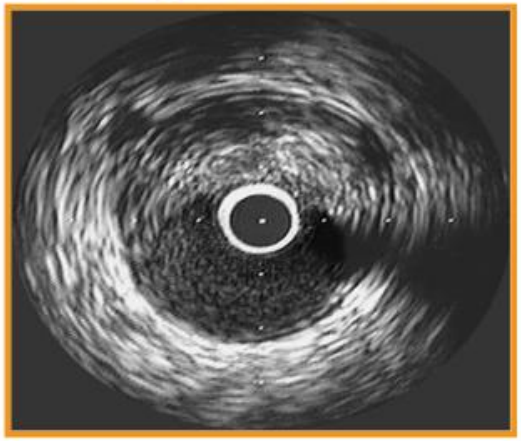
European Heart Journal, ehz455, https://doi.org/10.1093/eurheartj/ehz455

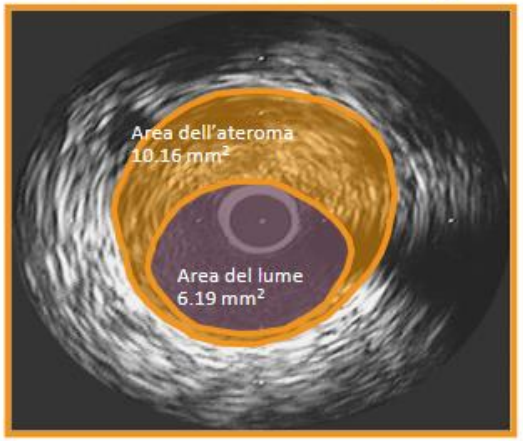
Recommendations for drug treatment of patients with hypertriglyceridaemia

Recommendations	Class[a]	Level[b]
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)].[355]	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.[194]	IIa	B
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.[305–307,356]	IIb	B
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.[305–307,356]	IIb	C

Studi sulla regressione della placca: Studio ASTEROID

Esempio di regressione di aterosclerosi in un paziente dello studio





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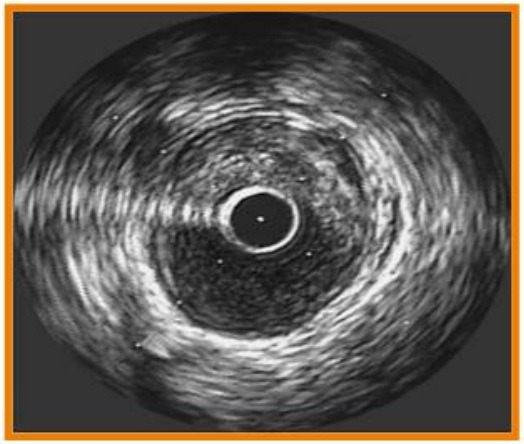
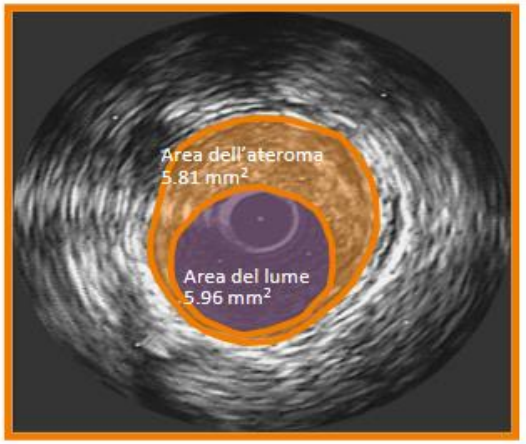
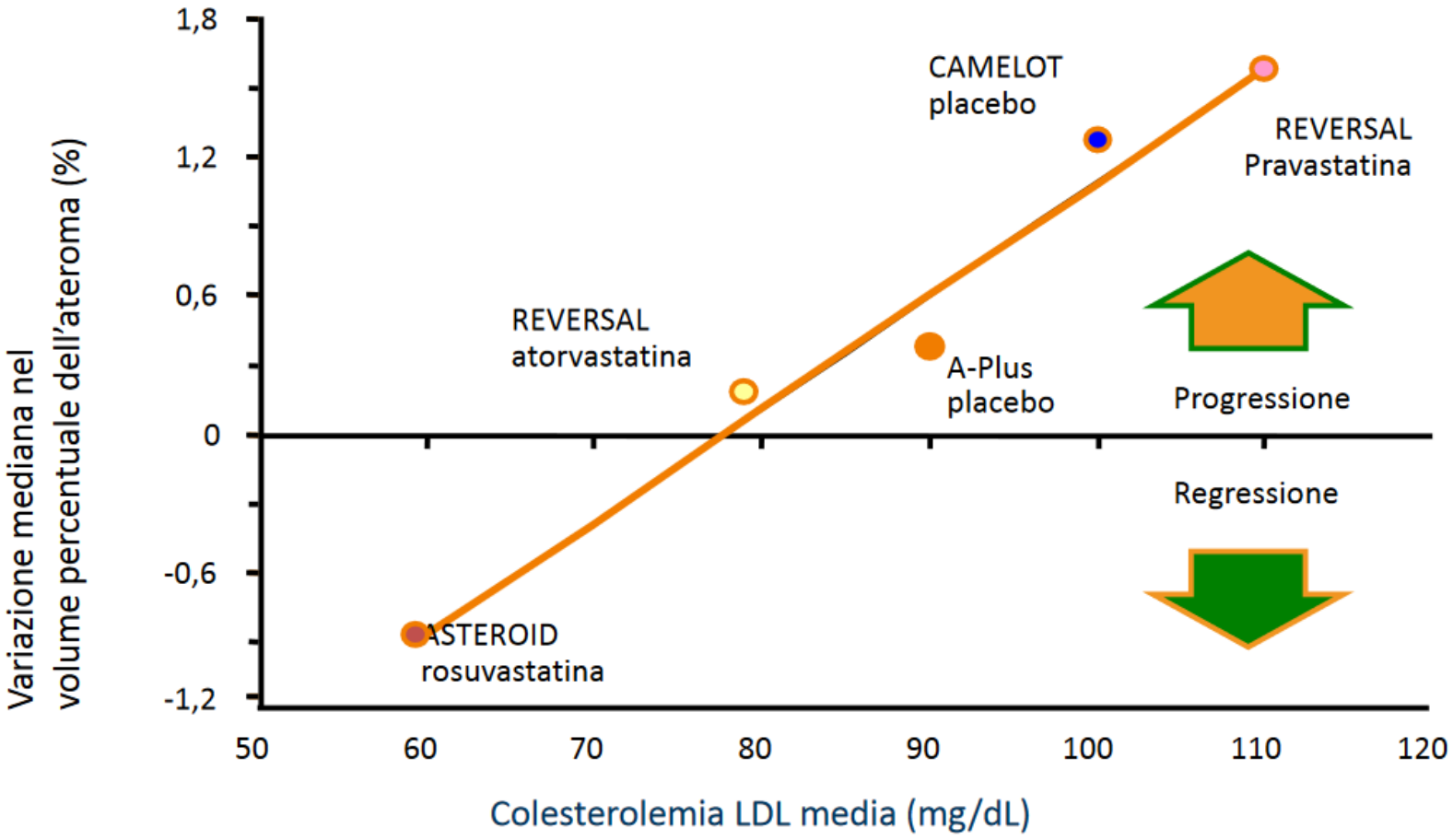




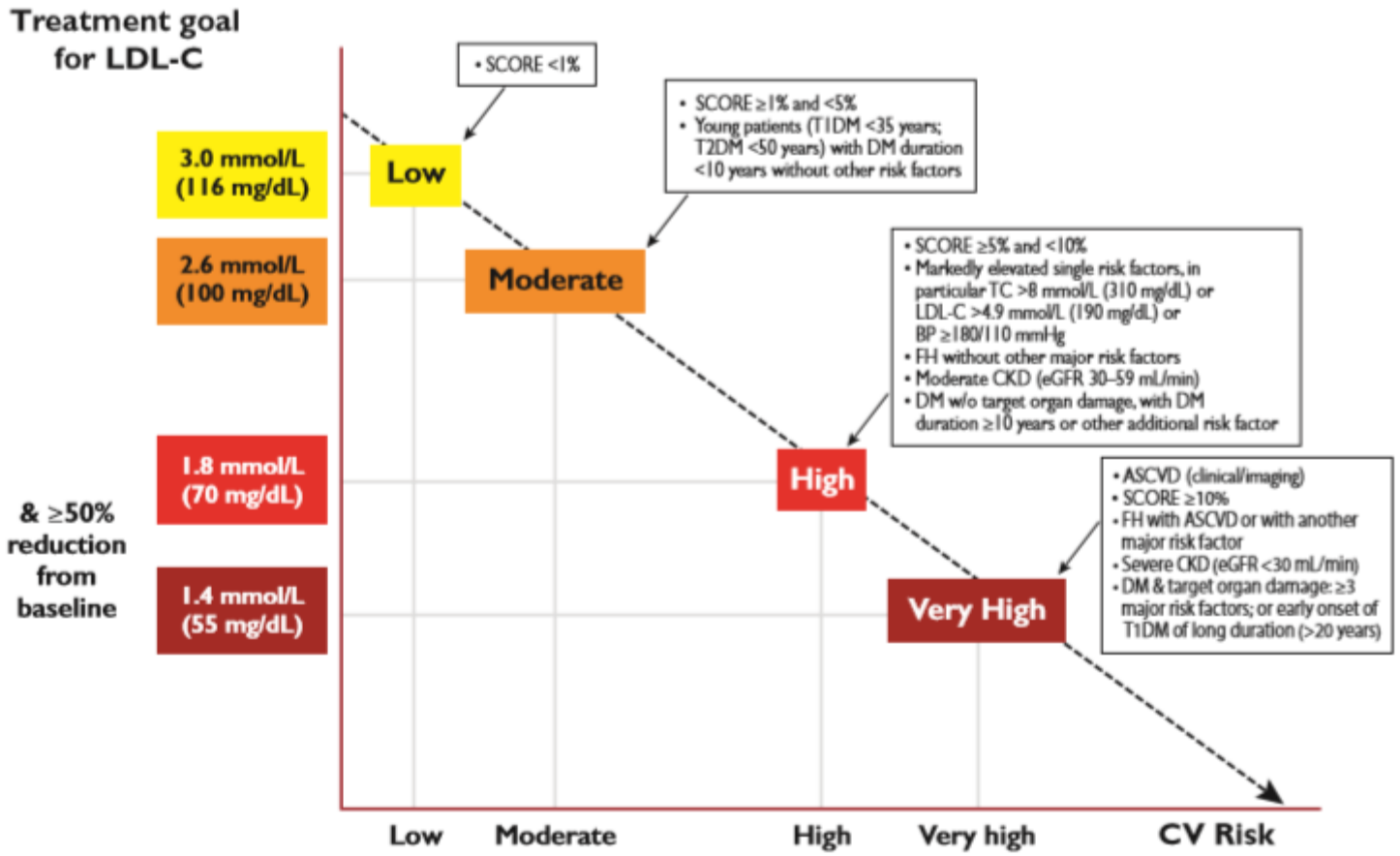
Follow-up IVUS
24 mesi di
rosuvastatina

Nissen SE et al. JAMA 2006;295:1556-1565

Relazione lineare tra la riduzione dei livelli di colesterolemia LDL e regressione dell'aterosclerosi coronarica



Nissen SE et al. JAMA 2006;295:1556-1565


Treatment goal for LDL-C
3.0 mmol/L (116 mg/dL)
2.6 mmol/L (100 mg/dL)
1.8 mmol/L (70 mg/dL)
1.4 mmol/L (55 mg/dL)
& ≥50% reduction from baseline
Low
Moderate
High
Very High
• SCORE <1%
• SCORE ≥1% and <5%
• Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years without other risk factors
• SCORE ≥5% and <10%
• Markedly elevated single risk factors, in particular TC >8 mmol/L (310 mg/dL) or LDL-C >4.9 mmol/L (190 mg/dL) or BP ≥180/110 mmHg
• FH without other major risk factors
• Moderate CKD (eGFR 30–59 mL/min)
• DM w/o target organ damage, with DM duration ≥10 years or other additional risk factor
• ASCVD (clinical/imaging)
• SCORE ≥10%
• FH with ASCVD or with another major risk factor
• Severe CKD (eGFR <30 mL/min)
• DM & target organ damage: ≥3 major risk factors; or early onset of T1DM of long duration (>20 years)
Low
Moderate
High
Very high
CV Risk

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[a] /Level[b]	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[a] /Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
≥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[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 concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class[a] /Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

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

	Total CV risk (SCORE) %	Untreated LDL-C levels					
		<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)
Primary prevention	<1, low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥1 to <5, or moderate risk (see *Table 4*)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
	≥5 to <10, or high-risk (see *Table 4*)	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
	≥10, or at very-high risk due to a risk condition (see *Table 4*)	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/B	IIa/A	I/A	I/A	I/A	I/A
Secondary prevention	Very-high-risk	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	I/A	I/A	I/A	I/A	I/A

Stratificazione dei pazienti

FRONTIERA DEL RISCHIO CARDIOVASCOLARE ALTO e MOLTO ALTO e della prevenzione secondaria degli eventi

Trattamento con Statine

+

Farmaci alternativi per il controllo dell'ipercolesterolemia

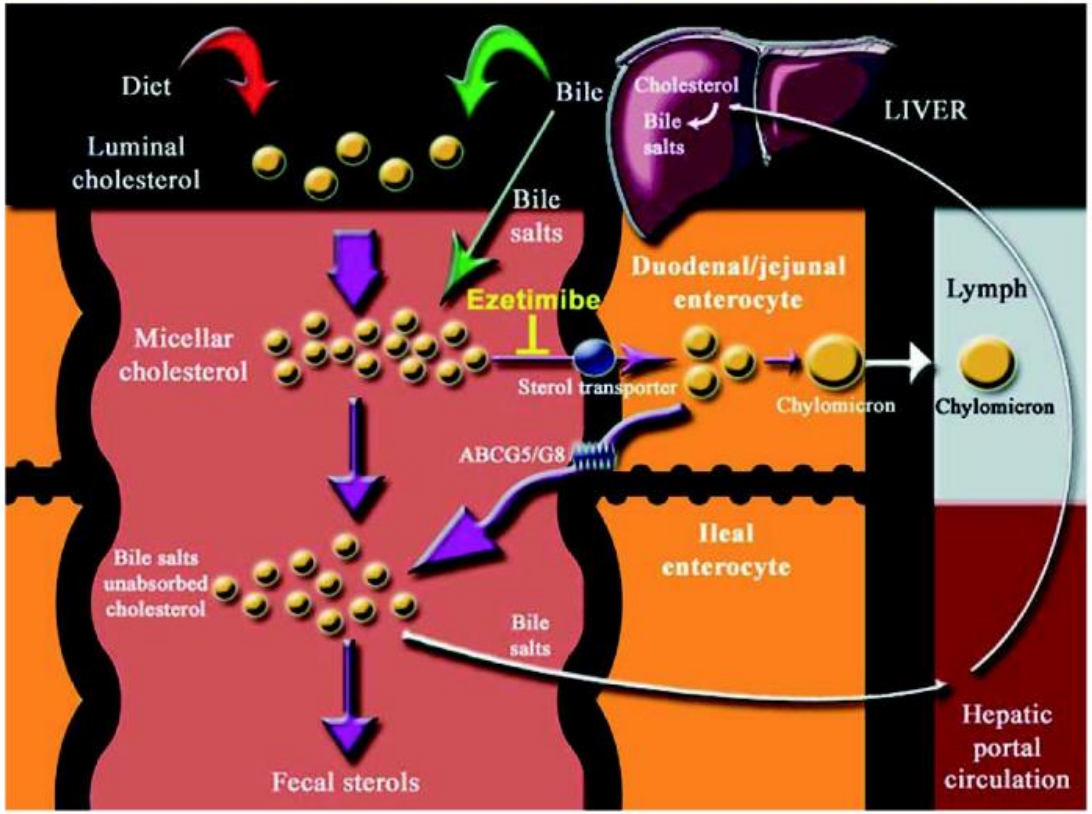
FRONTIERA DEL RISCHIO CARDIOVASCOLARE MEDIO

FRONTIERA DEL RISCHIO CARDIOVASCOLARE BASSO

Nutraceutica

Ezetimibe ….

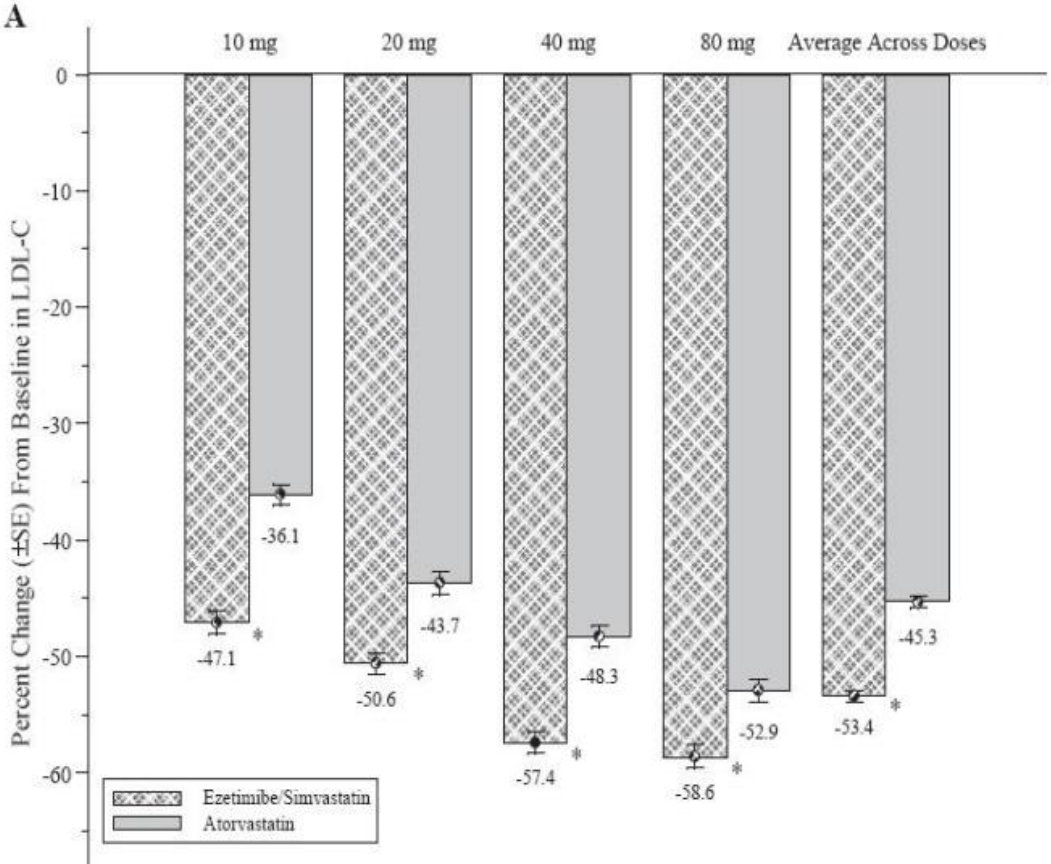
- Ezetimibe inhibits Niemann-Pick C_1-like 1 (NPC_1L_1) protein
  - located primarily on the epithelial brush border of the GI tract
  - resulting in reduced cholesterol absorption



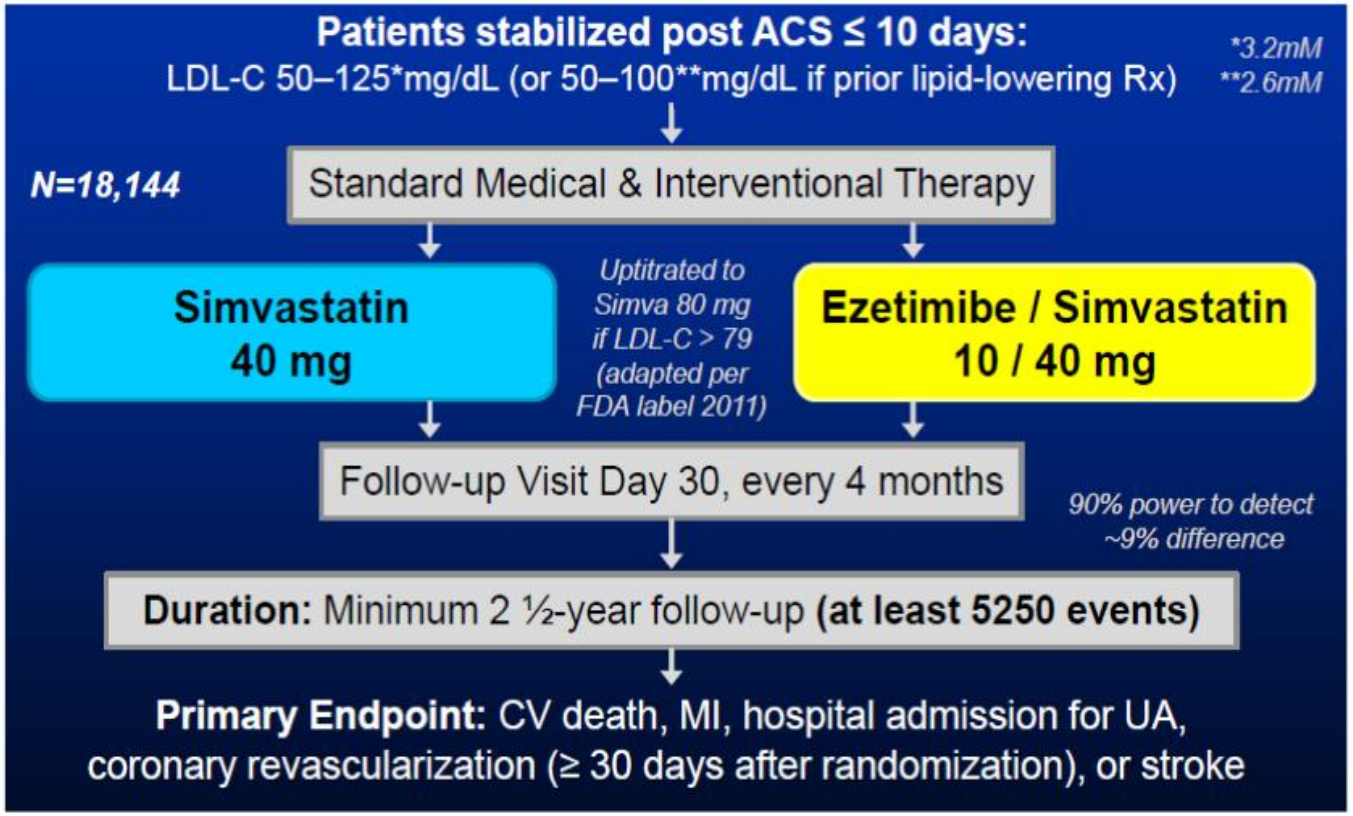
Terapia di associazione: Ezetimibe

- When added to statin, produces ~20% further reduction in LDL-C
- Two recent human genetic analyses have correlated polymorphisms in NPC_1L_1 with lower levels of LDL-C and lower risk of CV events*

Studio VYMET :
Studio multicentrico,randomizzato, in doppio cieco; 4 gruppi paralleli: E/S (10/20 mg) vs Atorvastatina (10 – 20 mg) e E/S (10/40 mg) vs Atorvastatina 40 mg.
Rand: 1128 pazienti ipercolesterolemici con sindrome metabolica. Follow up 6 w



IMPROVE-IT



Inclusion Criteria:

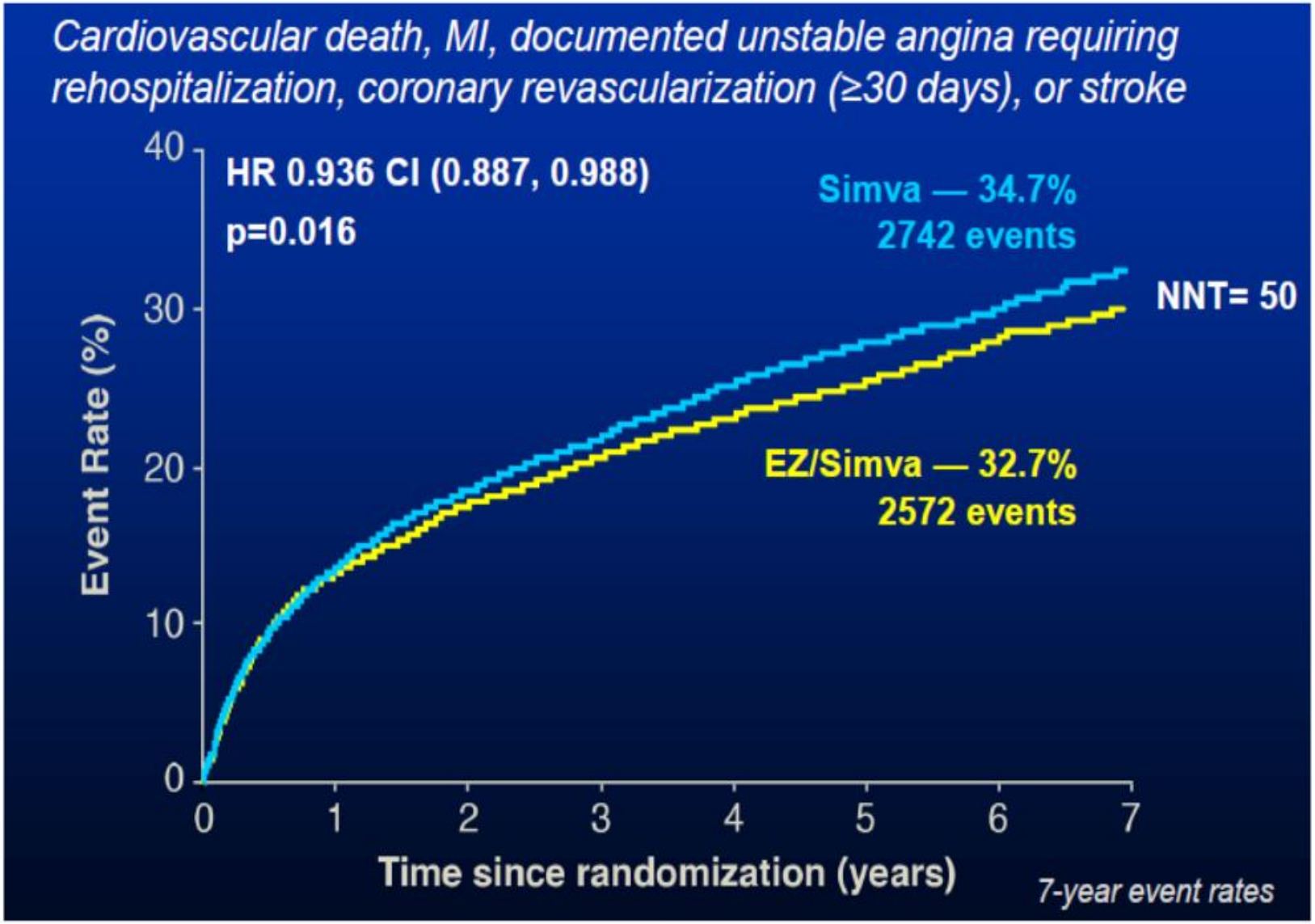
- Hospitalization for STEMI, NSTEMI/UA < 10 days
- Age ≥ 50 years, and ≥ 1 high-risk feature:
  - New ST chg, + troponin, DM, prior MI, PAD, cerebrovasc, prior CABG > 3 years, multivessel CAD
- LDL-C 50-125 mg/dL (50–100 mg/dL if prior lipid-lowering Rx)

Major Exclusion Criteria:

- CABG for treatment of qualifying ACS
- Current statin Rx more potent than simva 40mg
- Creat Cl < 30mL/min, active liver disease

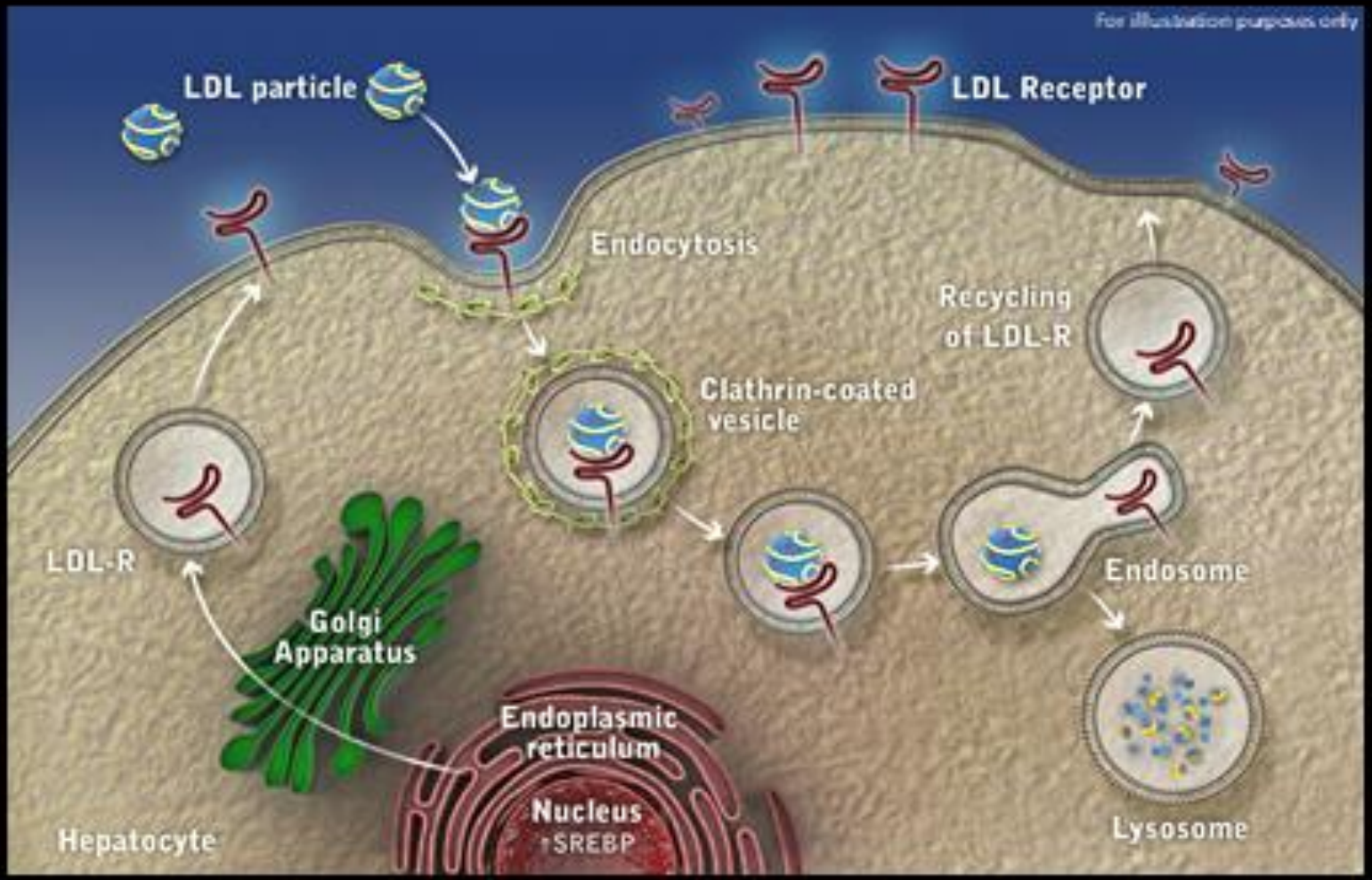
LDL-C and Lipid Changes

Primary Endpoint —ITT



Anti-PCSK9 ….

Funzione e Ciclo Biologico del Recettore LDL



STATE-OF-THE-ART PAPER

Targeting the Proprotein Convertase Subtilisin/Kexin Type 9 for the Treatment of Dyslipidemia and Atherosclerosis

Daniel Urban, MD, Janine Pöss, MD, Michael Böhm, MD, Ulrich Laufs,
Homburg/Saar, Germany

PCSK9 è una proteina appartenente alla famiglia delle subtilisine, che agisce mediante legame all'LDLR, **accelerandone la degradazione lisosomiale e riducendone, quindi, la densità recettoriale sulla superficie degli epatociti → questo aumenta la quota di LDL circolanti riducendone la captazione epatica ; anche sull'orletto a spazzola intestinale è espresso e ha lo stesso effetto: riduce l'assorbimento di lipidi**

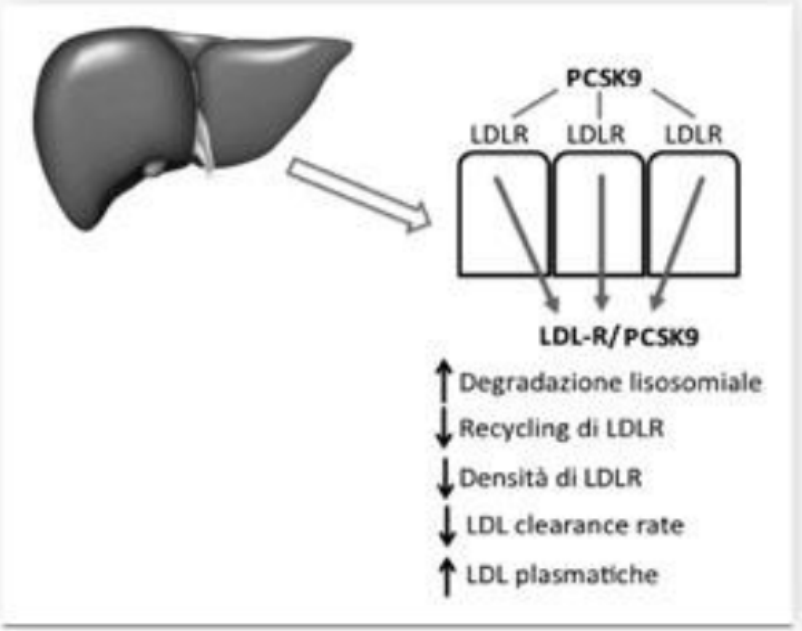
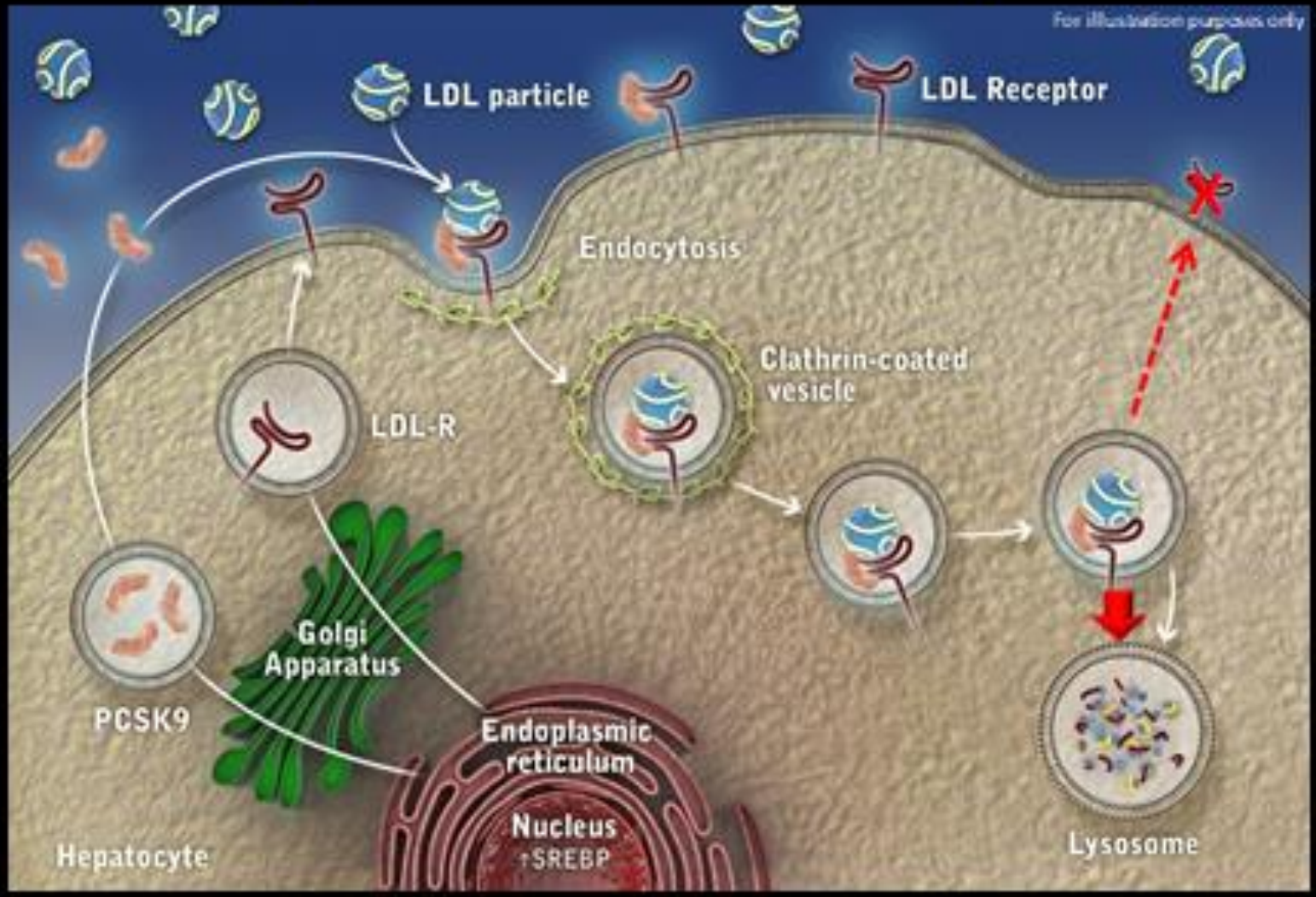
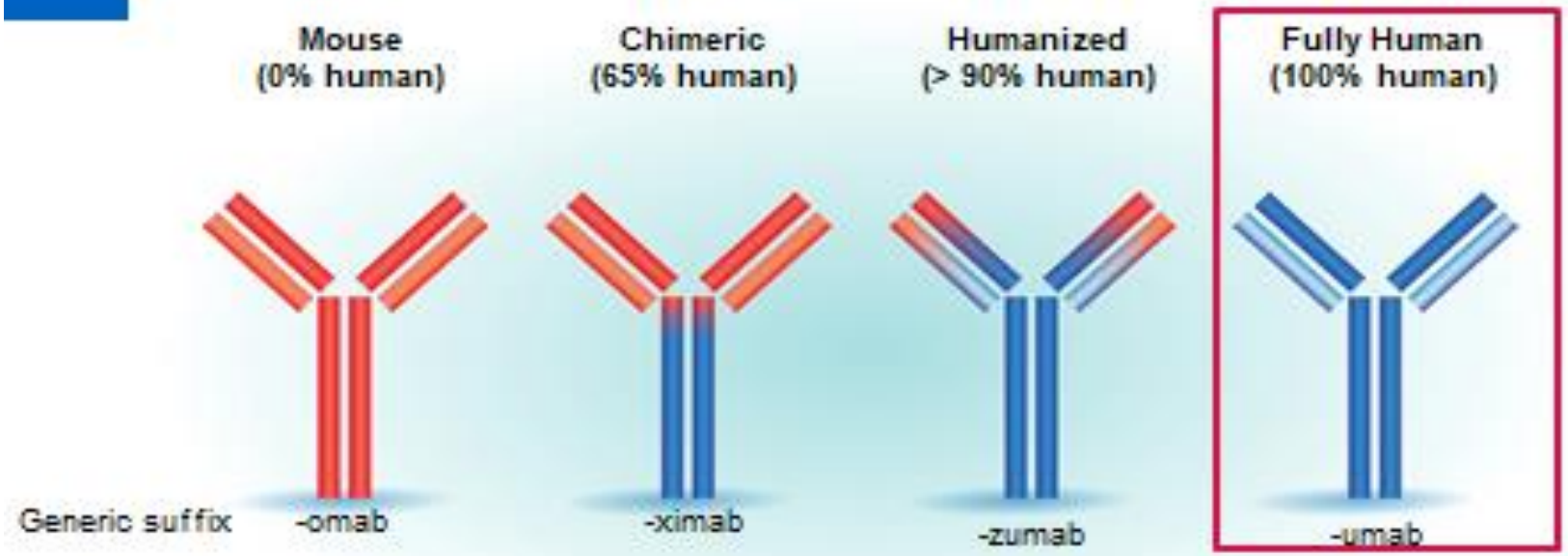


Figura 1. Meccanismo d'azione di PCSK9.
PCSK9 è una proteina appartenente alla famiglia delle subtilisine che, legandosi al recettore delle lipoproteine a bassa densità (LDLR), ne accelera la degradazione lisosomiale, riducendo quindi la densità recettoriale sulla superficie degli epatociti.

Il Ruolo di PCSK9 nella Regolazione dell'Espressione del Recettore per le LDL

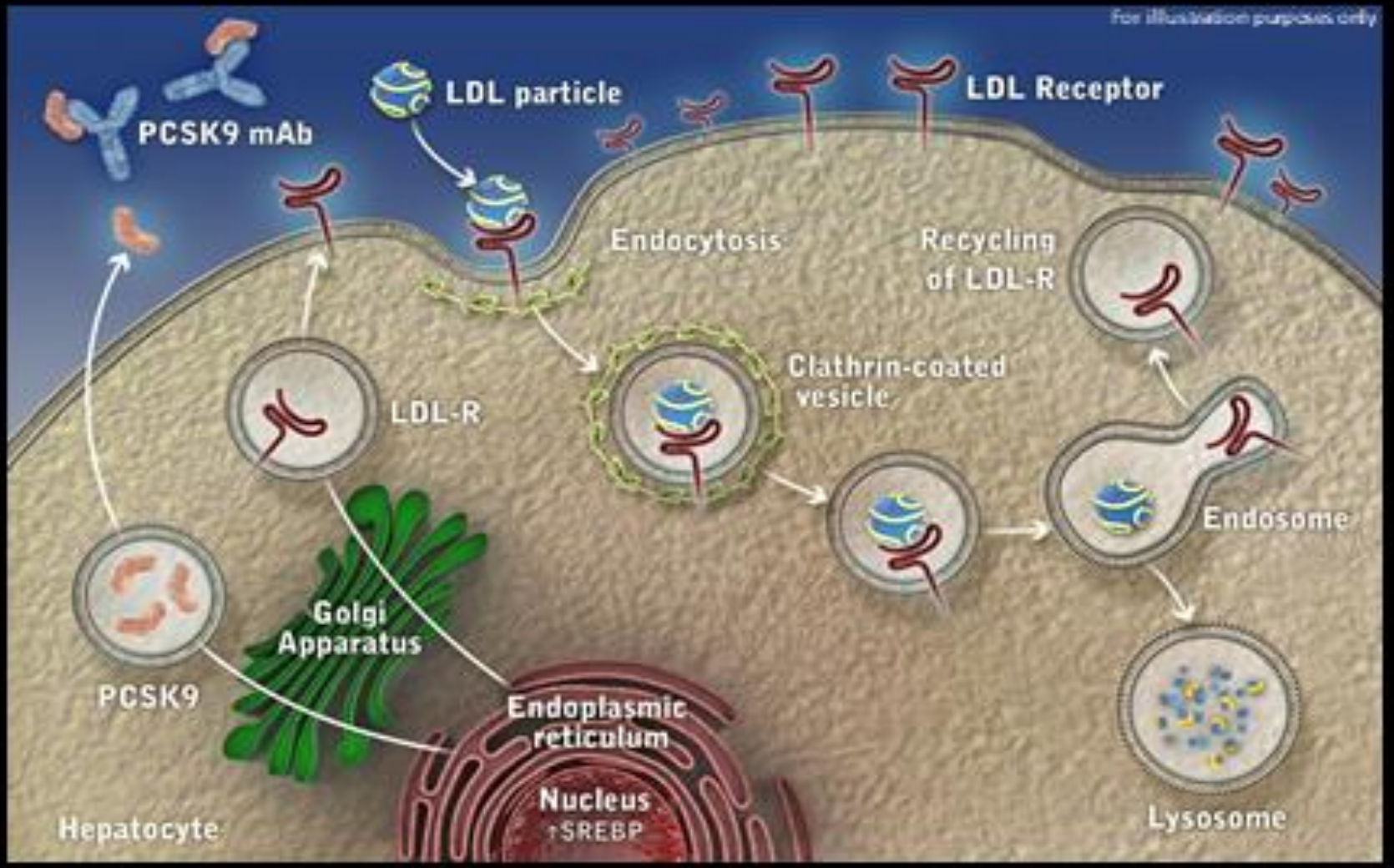


Fully Human Antibodies Have Reduced Immunogenicity



Elaborated from:
1. Weiner LM. *J Immunother*. 2006;29:1-9.
2. Yang XD, et al. *Crit Rev Oncol Hematol*. 2001;38:17-23.
3. Lonberg N. *Nat Biotechnol*. 2005;23:1117-1125.
4. Garber DE. *Am Fam Physician*. 2008;77:311-319.

Impatto dell'Anticorpo contro PCSK9 sull'Espressione del Recettore delle LDL



Molecole in commercio e in fase di studio

- **Sanofi (Regeneron)**
  - **Alirocumab (Ab monoclonale) (inibitore PCSK9) (Praluent)**
- **Amgen**
  - **Evolocumab (Ab monoclonale) (inibitore PCSK9) (Repatha)**
- **Pfizer**
  - **Bocucizumab (Ab monoclonale) (inibitore PCSK9) (non in commercio)**

Indicazioni di Evolucumab e Alirocumab

- Evolocumab and Alirocumab are indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
- - in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin
- - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contra-indicated

Utilizzo pratico di antiPCSK9

Evolocumab (Repatha)

- **Subcutaneous injection**
  - 140 mg every two weeks
  - 420 mg once a month (starting dose)
    - In HoFH, the initial recommended dose is 420 mg once a month; if an adequate LDL-lowering response is not achieved after 12 months in these patients, physicians have the option of increasing the dose to 420 mg every weeks

Alirocumab (Praluent)

- **Subcutaneous injection**
  - 75 or 150 mg every two weeks

Terapie geniche : PER IPERCOLESTEROLEMIE a trasmissione MENDELIANA

- L'Ipercolesterolemia Familiare (FH) è una malattia genetica mendeliana che in omozigosi (HoFH) è molto rara, mentre in eterozigosi (HeFH) è decisamente più frequente, ma non sempre riconosciuta. La conseguenza porta ad un numero aumentato e precoce di eventi quali morte improvvisa, infarto ed angina.
- HeFH: 350.000 individui
- HoFH: prevalenza 1:160.000-1:300.000

FH: Ipercolesterolemia FAMILIARE

Mutazione di vario tipo del gene che codifica per il recettore LDL (glicoproteina transmembrana), responsabile della rimozione dal plasma dei 2/3 circa delle LDL circolanti.

Forma eterozigote: 50% dei recettori funzionanti

(frequenza 1/500 soggetti sani; valori di colesterolemia nell'adulto tra 280 e 500 mg/dl, nel bambino tra 180 e 300 mg/dl).

Forma omozigote: assenza dei recettori

(frequenza 1/1.000.000 soggetti sani; valori di colesterolemia tra 600 e 1.000 mg/dl).

Terapia dell'ipercolesterolemia familiare

- **Bambini < 14 anni**
  - Statine (in base alle evidenze dei trials)
  - Ezetimibe
  - Resine sequestranti gli acidi biliari
  - Terapia di combinazione
- **Adulti ed adolescenti**
  - Statine ad alta efficacia ed alla massima dose tollerata
  - Ezetimibe
  - Resine sequestranti gli acidi biliari
  - Fibrati (se trigliceridi elevati)
  - LDL-aferesi (HoFH: tutti; HeFH: con CHD e resistenti al trattamento)
  - Nuove terapie (inibitori PCSK9, MTP, antisenso di Apo B)

Stratificazione dei pazienti

FRONTIERA DEL RISCHIO CARDIOVASCOLARE ALTO e MOLTO ALTO e della prevenzione secondaria degli eventi

Trattamento con Statine

FRONTIERA DEL RISCHIO CARDIOVASCOLARE MEDIO

Farmaci alternativi per il controllo dell'ipercolesterolemia

FRONTIERA DEL RISCHIO CARDIOVASCOLARE BASSO

Nutraceutica

Come si INSERISCONO i nutraceutici nell'ambito della terapia ipolipemizzante?

NOTA 13 AIFA: PRESCRIVIBILITA' della terapia con STATINE

La prescrizione della statina a carico del SSN è limitata ai pazienti affetti da:

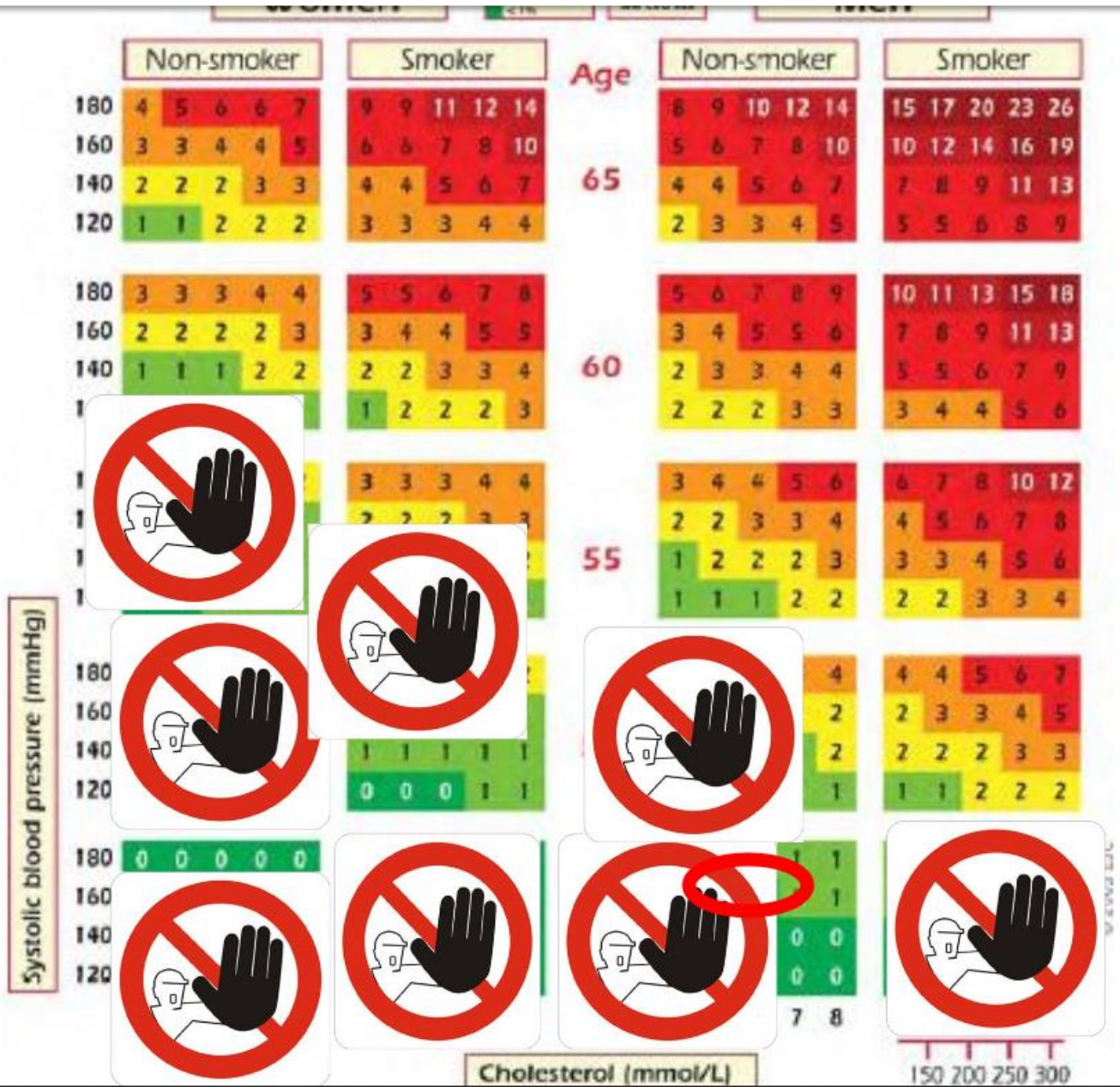
- **1) dislipidemie familiari**
- 2) in soggetti **a rischio elevato e molto elevato** di un primo evento cardiovascolare maggiore (rischio a 10 anni > 5 e 10% secondo SCORE) (prevenzione primaria)- prevenzione secondaria in soggetti con coronaropatia documentata o pregresso ictus o arteriopatia obliterante periferica o pregresso infarto o diabete
- **indotta da farmaci** (immunosoppressori, antiretrovirali e inibitori della aromatasi)
- in pazienti con **insufficienza renale cronica moderata o severa**

e.....NEI PAZIENTI CON RCV < 5%???

Le indicazioni della nota 13 sulla rimborsabilità delle statine

Quale paziente (livello di rischio decrescente)	Quando possibile prescrivere SSN	Quale farmaco
- score >10%, -malattia coronarica/bypass aorto-coronarico -stroke ischemico, -arteriopatie periferiche, -pregresso infarto, -diabete con uno o più fattori di rischio CV e/o markers di danno d'organo (come la microalbuminuria) -IRC grave (FG 15-29 ml/min/1.73m$_2$).	**Colesterolo LDL > 70 mg/dl** (obiettivo raccomandato < 70 mg/dl)	atorvastatina§ pravastatina fluvastatina lovastatina simvastatina rosuvastatina *nei pazienti in cui ci sia stata evidenza di effetti collaterali severi nei primi 6 mesi di terapia con altre statine* *-In caso l'obiettivo non sia stato raggiunto* ezetimibe più statine (in associazione estemporanea o precostituita *-In caso d'intolleranza a tutte le statine* è rimborsato il trattamento con ezetimibe in monoterapia *-Nei pazienti con sindromi coronariche acute o in quelli sottoposti a interventi di rivascolarizzazione percutanea* è indicata atorvastatina a dosaggio elevato (>40 mg).
- risk score ≥5% e < 10% -dislipidemie familiari -ipertensione severa -diabete senza fattori di rischio CV e senza danno d'organo, -IRC moderata (FG 30-59 ml/min/1.73m$_2$).	**Colesterolo LDL > 100 mg/dl** (obiettivo raccomandato < 100 mg/dl)	simvastatina pravastatina fluvastatina lovastatina atorvastatina *-Se necessaria riduzione LDL > 50%* preferire atorvastatina *-In caso l'obiettivo non sia stato raggiunto* rosuvastatina o ezetimibe più statine (in associazione estemporanea o precostituita *-In caso d'intolleranza a tutte le statine* è rimborsato il trattamento con ezetimibe in monoterapia
Risk score 4%-5%	**Colesterolo LDL > 115 mg/dl** (obiettivo raccomandato < 115 mg/dl)	simvastatina pravastatina fluvastatina lovastatina atorvastatina
Risk score 2%-3%	**Colesterolo LDL > 130 mg/dl** (obiettivo raccomandato < [illegible] mg/dl)	Modifica dello stile di vita per almeno 6 mesi *-In caso l'obiettivo non sia stato raggiunto* simvastatina pravastatina fluvastatina lovastatina [illegible]
Risk score ≤ 1	**MAI**	Indicato solamente la modifica dello stile di vita.

Uomo di 47 anni, iperteso con valori di PAS tra 140 e 150 e valori di LDL attorno a 170 mg/dl…??



NON RIMBORSABILE

GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

François Mach, Colin Baigent, Alberico L Catapano, Konstantinos C Koskinas, Manuela Casula, Lina Badimon, M John Chapman, Guy G De Backer, Victoria Delgado, Brian A Ference ... Show more

Author Notes

European Heart Journal, ehz455, https://doi.org/10.1093/eurheartj/ehz455

Published: 31 August 2019

5.5 Dietary supplements and functional foods for the treatment of dyslipidaemias

Innovative nutritional strategies to improve dyslipidaemias have been developed. They are based on either 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.[184] Nutritional evaluation of functional foods includes not only the search for clinical evidence of beneficial effects relevant to improved health or reduction of disease risk, but also the demonstration of good tolerability and the absence of major undesirable effects. The substantiation of health claims relevant for each food should be based on results from intervention studies in humans that are consistent with the proposed claims. Overall, the available evidence on functional foods so far identified in this field is incomplete; the major gap is the absence of diet-based intervention trials of sufficient duration to be relevant for the natural history of dyslipidaemia and CVD.

5.5.1 Phytosterols

5.5.2 Monacolin and red yeast rice

5.5.3 Dietary fibre

5.5.4 Soy protein

5.5.5 Policosanol and berberine

5.5.6 n-3 unsaturated fatty acids

NUTRACEUTICO:

Nutri-tional

Farma-ceutical

«Prodotto isolato o purificato da alimenti, venduto sotto forma di medicinale e non associato a un alimento, che abbia benefici fisiologici dimostrati o fornisca una protezione contro le malattie croniche.
Sono definiti anche alimenti funzionali o farma-alimenti, o alimenti-farmaco

Un nutraceutico per essere definito efficace deve avere una potenza farmacologica che superi la varianza spontanea del parametro che si vuole modificare.»

RUOLO DEI NUTRACEUTICI nella TERAPIA IPOLIPEMIZZANTE

	Effetto Ipolipemizzante ipotizzato	Meccanismi di azione ipotizzati	STUDI RANDOMIZZATI	TRIALS CLINICI
Policosanoli	- 25% LDL	Inibizione SINTESI EPATICA (HMGCA Reduttasi)	SI/NO	NO
Polifenoli	-25%LDL, -40% TG	Inibizione SINTESI EPATICA (HMGCA Reduttasi , ACAT2, MTP)	NO	NO
Aglio	-9%LDL	Inibizione SINTESI EPATICA (HMGCA Reduttasi) Inibizione ASSORBIMENTO INTESTINALE	NO	NO
Probiotici	-40% LDL	Inibizione ASSORBIMENTO INTESTINALE	NO	NO
Steroli vegetali	-5-15% LDL	Inibizione ASSORBIMENTO INTESTINALE	SI	NO
Berberina	-25% LDL, -35% TG	Inibizione SINTESI (Anti PCSK9)	SI	NO
Riso rosso fermentato	-20-30% LDL	Inibizione SINTESI EPATICA (HMGCA Reduttasi)	SI	SI

1: Fitosteroli o steroli vegetali

Food & Nutrition Research 2008

Cholesterol and Plant Sterol Absorption: Recent Insights

Klaus von Bergmann, MD,* Thomas Sudhop, MD, and Dieter Lütjohann, PhD

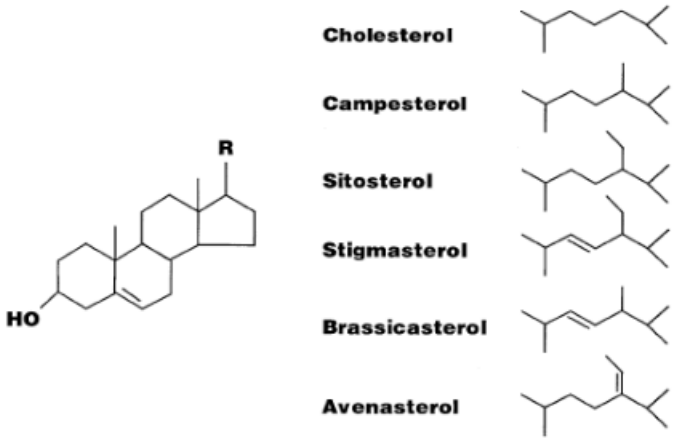
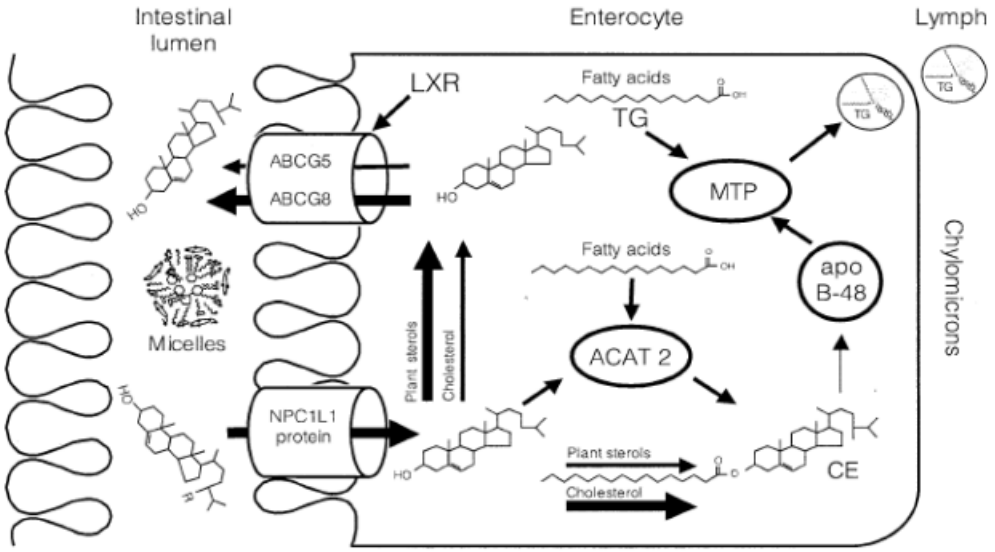


Figure 1. Chemical structures of cholesterol and different plant sterols.



1) Inibizione competitiva nella produzione di MICELLE
2) Recenti evidenze: inibizione di NPC1L1 e aumento di ABCG5 e ABCG8

La riduzione dell'assorbimento intestinale e del pool epatico del colesterolo comporta l'aumento del LDL-Recettore e quindi l'aumentata captazione di LDL con riduzione dei livelli circolanti

2.Ipolipemizzanti: Riso rosso fermentato

- Rappresenta il prodotto della fermentazione del comune riso da cucina (Oryza Sativa) da parte del lievito Monascus Purpureus. I prodotti di tale fermentazione sono definite **Monocoline, tra cui spicca la Monocolina K (Lovastatina), una statina naturale (non di sintesi).**

- La Monocolina presenta una efficacia Ipocolesterolemizzante che si attesta attorno a una riduzione del **17 – 29% del Col Tot e 24 – 40% del Col LDL a seconda dei dosaggi (20 mg – 80 mg die). TALE EFFICACIA è DOCUMENTATA IN STUDI CLINICI RANDOMIZZATI E TRIALS**

QUALI DIFFERENZE ci SONO TRA LE STATINE NATURALI E QUELLE DI SINTESI???

Bradford RH et al, Arch Inter Med 1991; 151:43 – 9
Downs JR AFCAPS – TexCAPS study group, JAMA 1998
European Heart Journal (2011) 32, 1769–1818

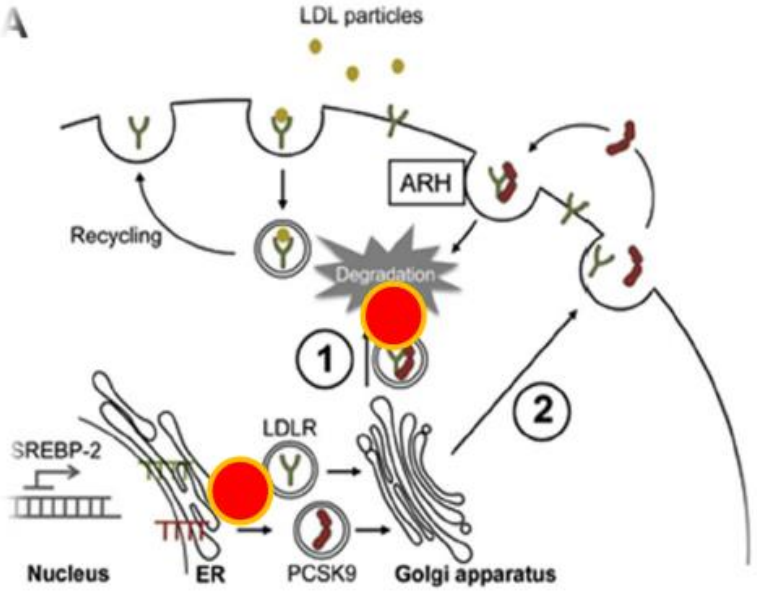
Atherosclerosis 201 (2008) 266–273
Nat Med 2004; 10: 1344-1351.

3.Ipolipemizzanti: Berberina

Meccanismi ipotizzati: INIBIZIONE SINTESI EPATICA ATTRAVERSO AUMENTO DELLA CAPTAZIONE PLASMATICA

-Stabilizzazione m-RNA di LDL-R.

-Riduzione della degradazione di LDL-r (inibizione di PCSK9) che le statine al contrario tendono a promuovere



Berberine decreases PCSK9 expression in HepG2 cells

Jamie Cameron, Trine Ranheim, Mari Ann Kulseth, Trond P. Leren, Knut Erik Berge *

Medical Genetics Laboratory, Department of Medical Genetics, Rikshospitalet University Hospital, Oslo, Norway

Received 14 November 2007; received in revised form 30 January 2008; accepted 9 February 2008
Available online 15 February 2008

Combination of simvastatin with berberine improves the lipid-lowering efficacy

Wei-Jia Kong[a,1], Jin Wei[b,1], Zeng-Yan Zuo[a], Yue-Ming Wang[a], Dan-Qing Song[a], Xue-Fu You[a], Li-Xun Zhao[a], Huai-Ning Pan[b], Jian-Dong Jiang[a,*]

[a]*Department of Pharmacology, Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China*

E' appropriato prescrivere «il» nutraceutico efficace, validato e sicuro, in tutti i casi in cui vi è:

- ✓ **Basso livello di rischio CVD**
- ✓ **«Resistenza» al cambiamento delle abitudini di vita**
- ✓ **In supporto alla adesione ad una dieta corretta per necessità psicologica del soggetto trattato di vedere e mantenere i risultati del suo impegno**
- ✓ **«Resistenza» al trattamento farmacologico**
- ✓ **«Intolleranza» al trattamento farmacologico**
- ✓ **Scarsa adesione e timore di assunzioni del farmaco.**
- ✓ **Necessità di aumentare l'efficacia del trattamento farmacologico senza aumentare il dosaggio e il numero di somministrazioni**

Cicero et al. Exp Opin Drug Safety 2012; 11(5):753-66

Take Home messages:

- Il cardine della terapia ipolipemizzante è costituito dalla terapia con STATINE
- I documenti delle società scientifiche internazionali nell'ultimo decennio hanno concordato su alcune evidenze importanti:
- 1) Il punto di PARTENZA e di ARRIVO è lo SCORE di rischio CV
- 3) Esistono FASCE di RISCHIO ESTREME NON ANCORA ADEGUATAMENTE TRATTATE NEI CONFRONTI DELLE QUALI SI RIVERSA L'INTERESSE IN QUESTO AMBITO:

Il rischio CV MOLTO BASSO , in cui il problema è trattare SENZA FARMACI
→ Stile di vita, NUTRACEUTICI

Il rischio CV ALTO , in cui il problema è portare a target i pazienti non ancora a target (per insufficienza delle terapie) .
→ Terapie di associazione con EZETIMIBE e anti PCSK9

GRAZIE PER L'ATTENZIONE