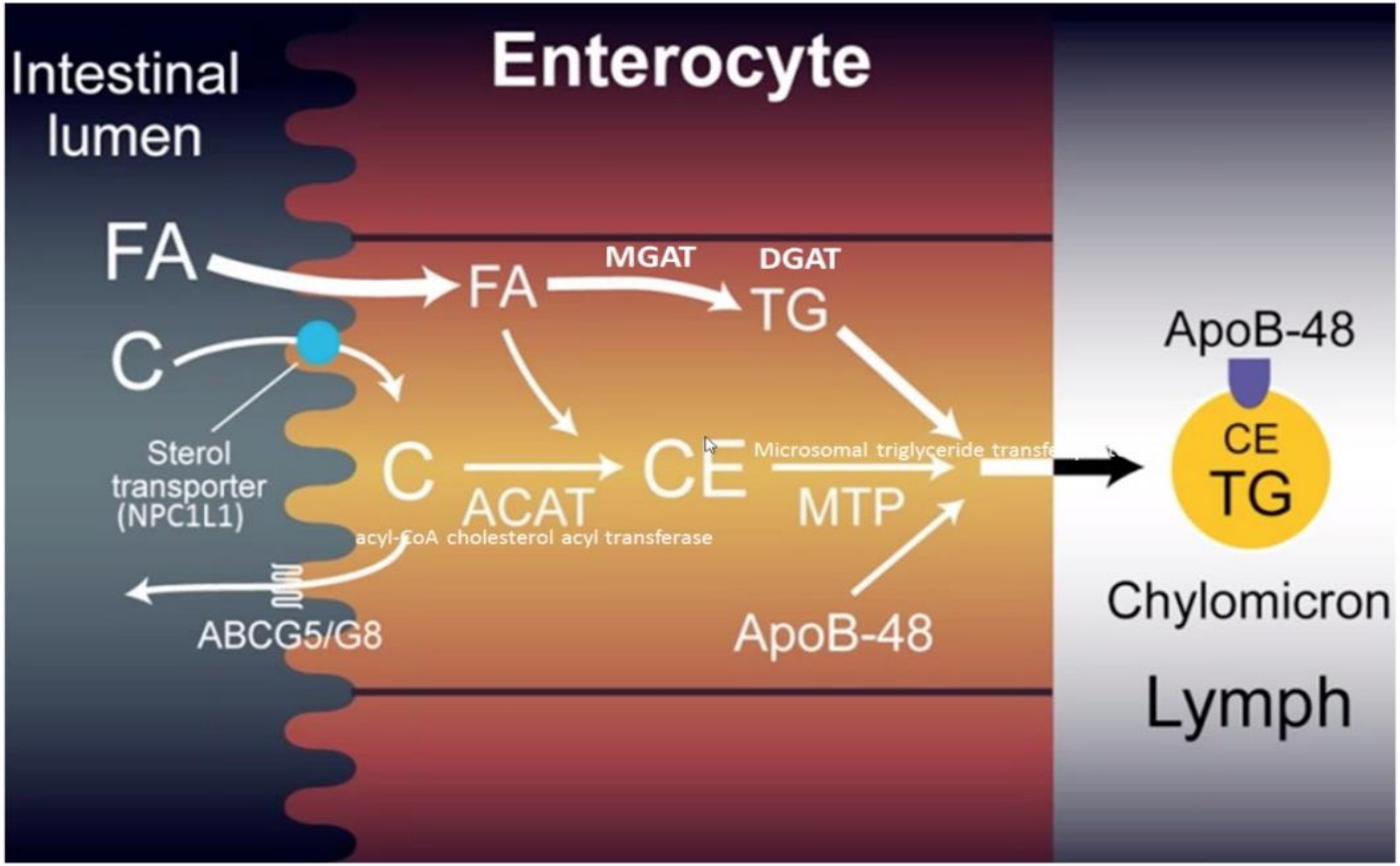
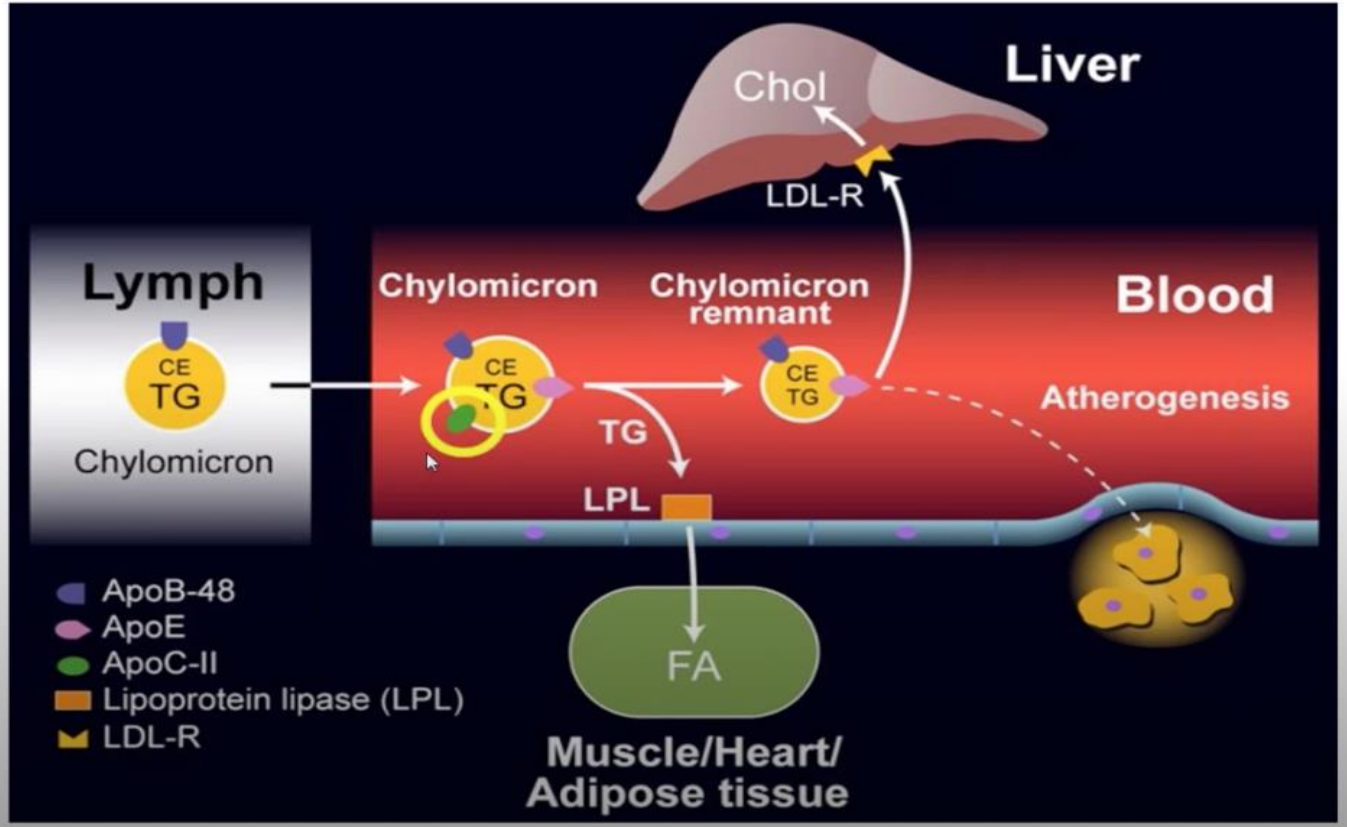
IL BAMBINO CON COLESTEROLO ALTO

PEDIATRIA DI LIBERA SCELTA
ASLTO4

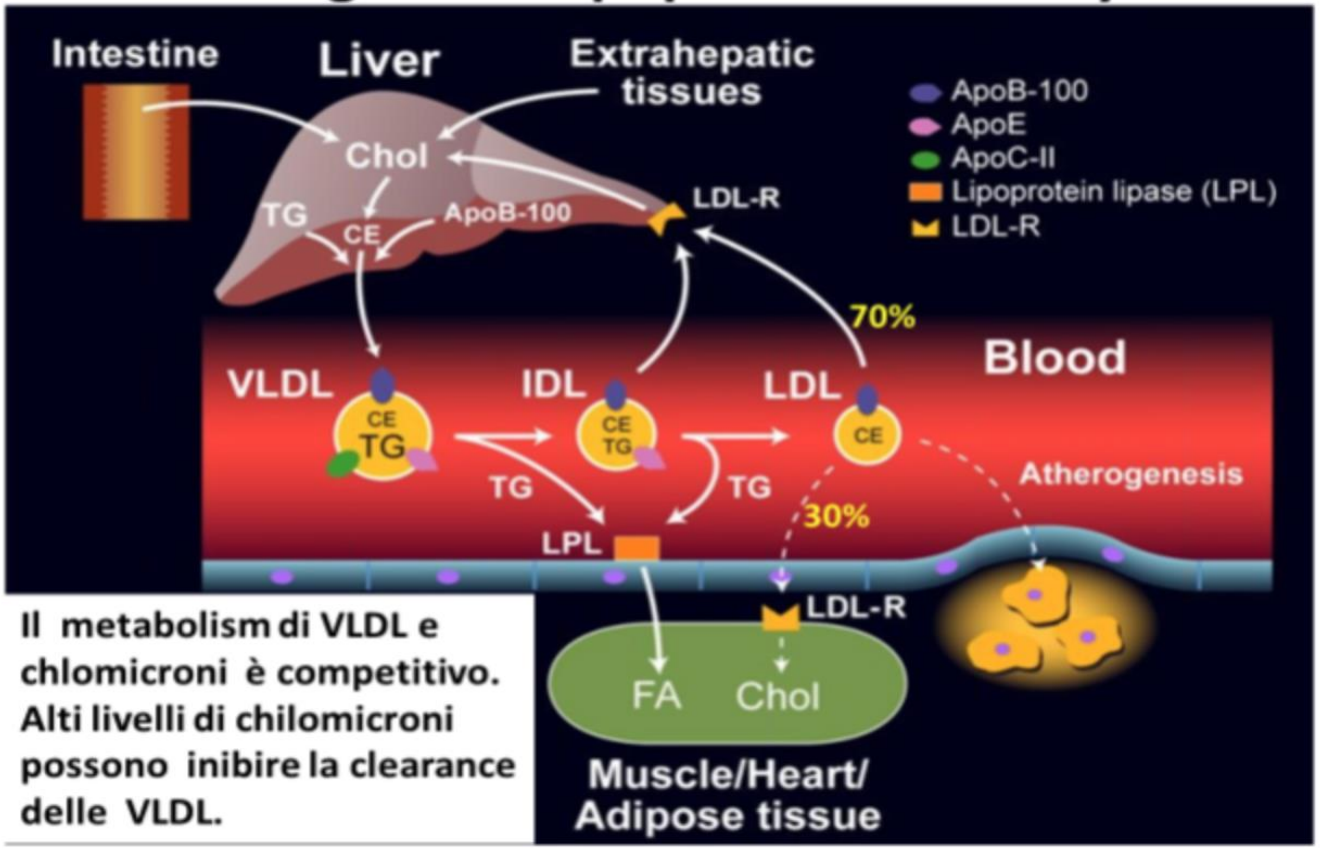
Dott.ssa Enza Giglione


Intestinal lumen
Enterocyte
FA
C
Sterol transporter (NPC1L1)
ABCG5/G8
FA
MGAT
DGAT
TG
C
ACAT
CE
acyl-CoA cholesterol acyl transferase
Microsomal triglyceride transfe
MTP
ApoB-48
ApoB-48
CE
TG
Chylomicron
Lymph

Exogenous Lipoprotein Pathway

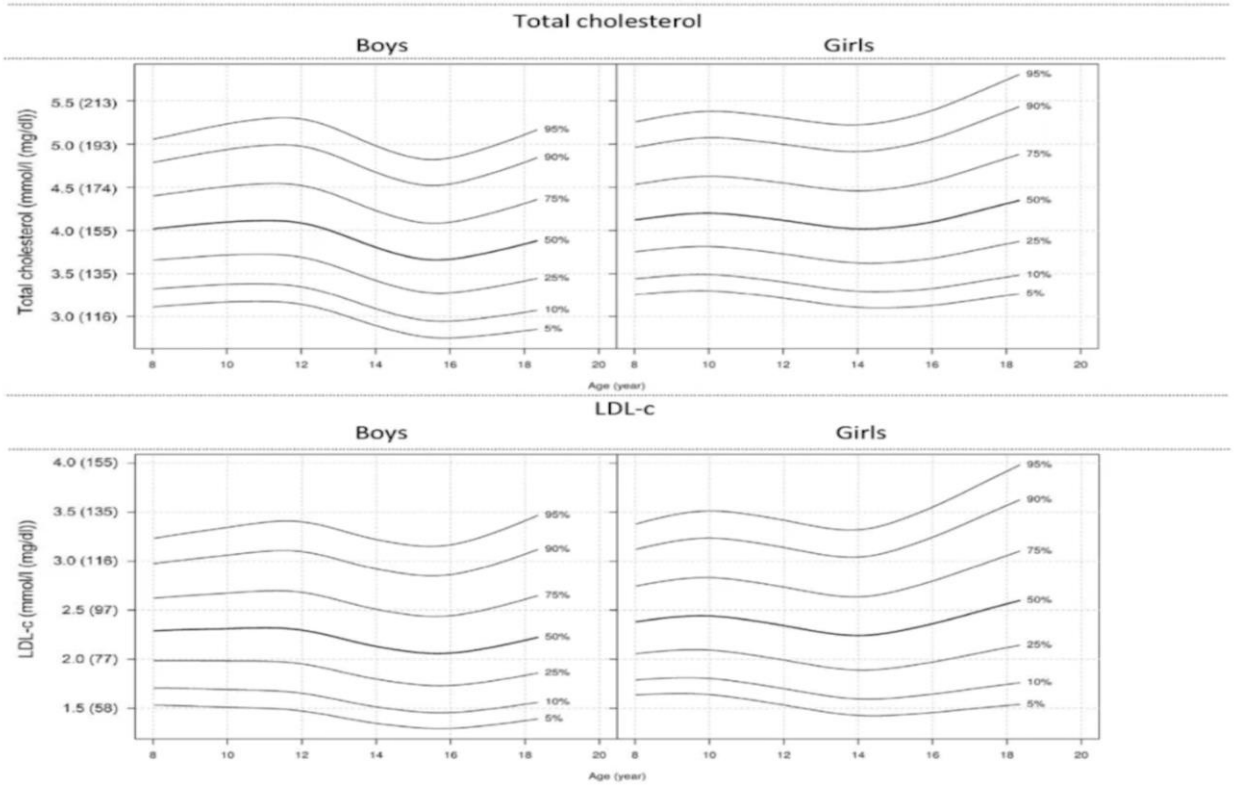


Endogenous Lipoprotein Pathway



Il metabolism di VLDL e chlomicroni è competitivo. Alti livelli di chilomicroni possono inibire la clearance delle VLDL.

○○○


Total cholesterol
Boys
Girls
Total cholesterol (mmol/l (mg/dl))
5.5 (213)
5.0 (193)
4.5 (174)
4.0 (155)
3.5 (135)
3.0 (116)
95%
90%
75%
50%
25%
10%
5%
8
10
12
14
16
18
20
Age (year)
LDL-c
Boys
Girls
LDL-c (mmol/l (mg/dl))
4.0 (155)
3.5 (135)
3.0 (116)
2.5 (97)
2.0 (77)
1.5 (58)
95%
90%
75%
50%
25%
10%
5%
8
10
12
14
16
18
20
Age (year)

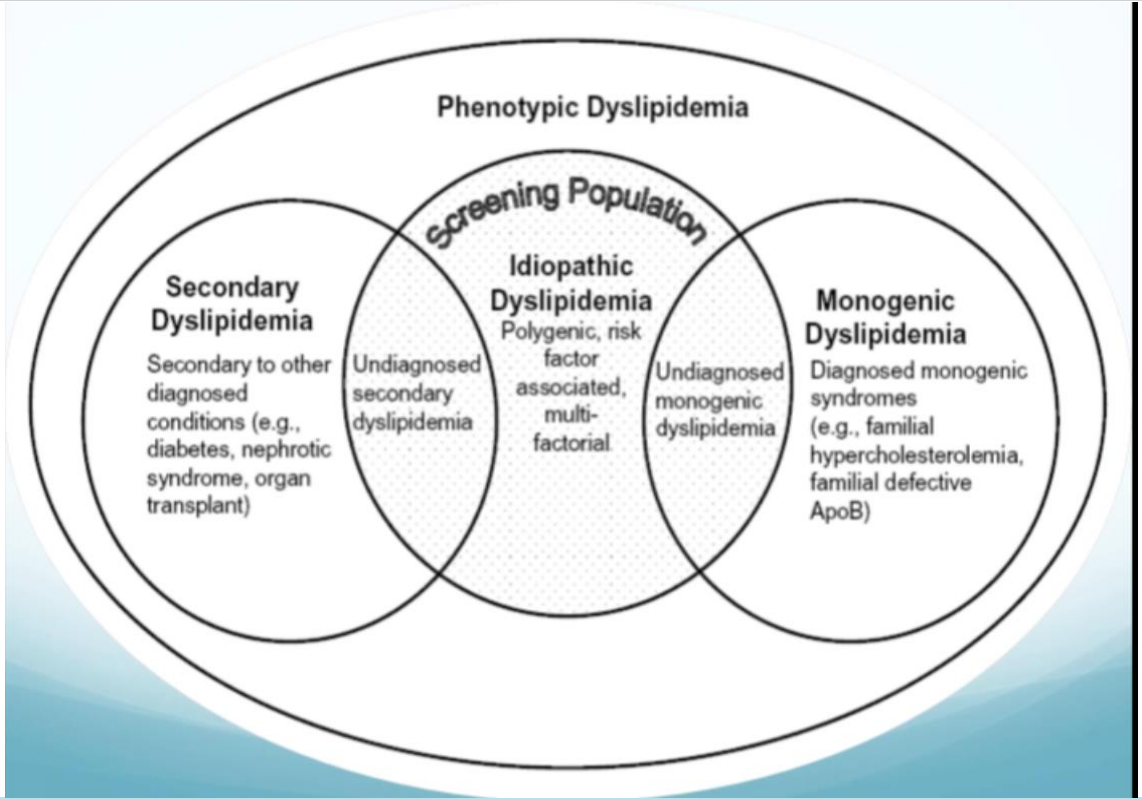
Plasma lipid, lipoprotein and apolipoprotein concentrations (mg/dl) in children and adolescents

Category	Years	Acceptable	Borderline	Unacceptable
TC		<170	170–199	≥200
LDL-c		<110	110–129	≥130
ApoB		<90	90–109	≥110
Triglycerides				
	0–9	<75	75–99	≥100
	10–19	<90	90–129	≥130
HDL-c		>45	35–45	<35
ApoA–I		>120	110–120	<110

From the National Cholesterol Education Program Expert on Cholesterol Levels in Children (Pediatrics, 1992 and 2011). Values for plasma ApoB, ApoA–I, HDL are from the National Health and Nutrition Examination Survey III (J Clin Endocrinol Metab, 2008).

Classificazione fenotipica (Frederickson, OMS)

Phenotype	Lipoprotein(s) elevated	Result	Atherogenicity	Associated with genetic disorders
I	Chylomicrons	↑↑ TG	?	Familial chylomicronemia (familial LPL deficiency, apo C-II deficiency)
IIa	LDL	↑ Cholosterol	+++	FH FCH Polygenic hypercholesterolemia Familial defective apo B
IIb	LDL VLDL	↑ Cholesterol ↑ TG	+++	FH FCH
III	IDL	↑ Cholesterol ↑ TG	+++	Familial dysbetalipoproteinemia
IV	VLDL	↑ TG N or ↑ Cholesterol	+	Familial endogenous hyperTG FCH
V	VLDL Chylomicrons	↑↑ TG N or ↑ Cholesterol	+	Familial mixed hyperTG

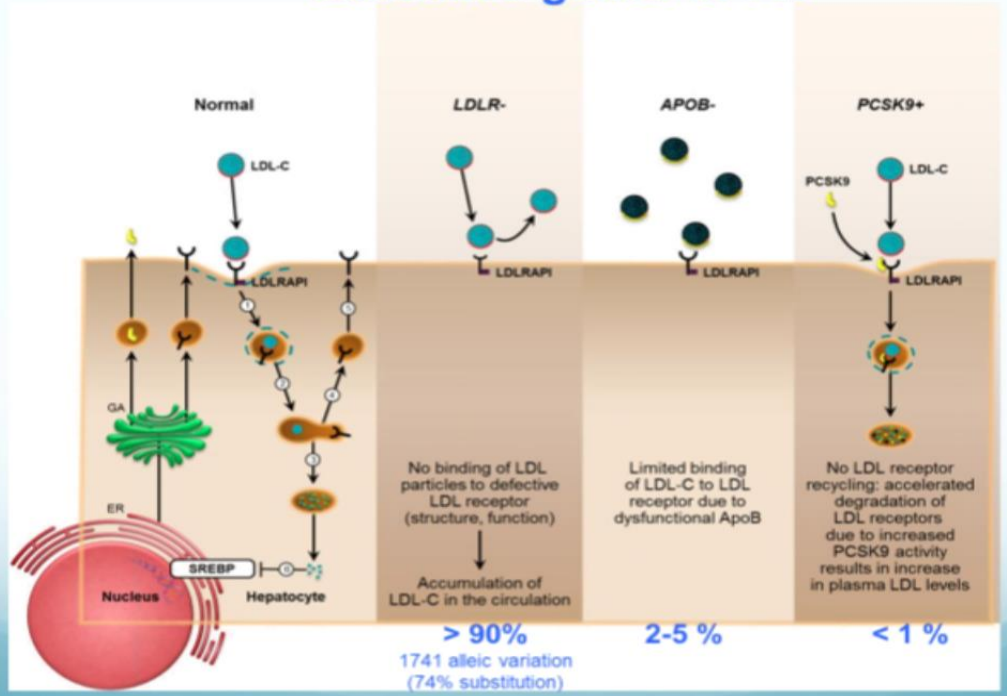

Phenotypic Dyslipidemia
Screening Population
Secondary Dyslipidemia
Secondary to other diagnosed conditions (e.g., diabetes, nephrotic syndrome, organ transplant)
Undiagnosed secondary dyslipidemia
Idiopathic Dyslipidemia
Polygenic, risk factor associated, multi-factorial
Undiagnosed monogenic dyslipidemia
Monogenic Dyslipidemia
Diagnosed monogenic syndromes (e.g., familial hypercholesterolemia, familial defective ApoB)

Le ipercolesterolemie genetiche

- Ipercolesterolemia Familiare di tipo 1 (FH o ADH1) →LDL-R
- Ipercolesterolemia autosomica dominante tipo B (FDB o ADH2) →ApoB100
- Ipercolesterolemia Autosomica Dominante 3 (ADH3) → PCSK9
- Ipercolesterolemia Autosomica Recessiva (ARH) → proteina che orienta LDL-R

- Iperlipidemia Familiare Combinata (FCHL) → ↑ApoB, modulato da fattori ambientali

Causative genes of FH

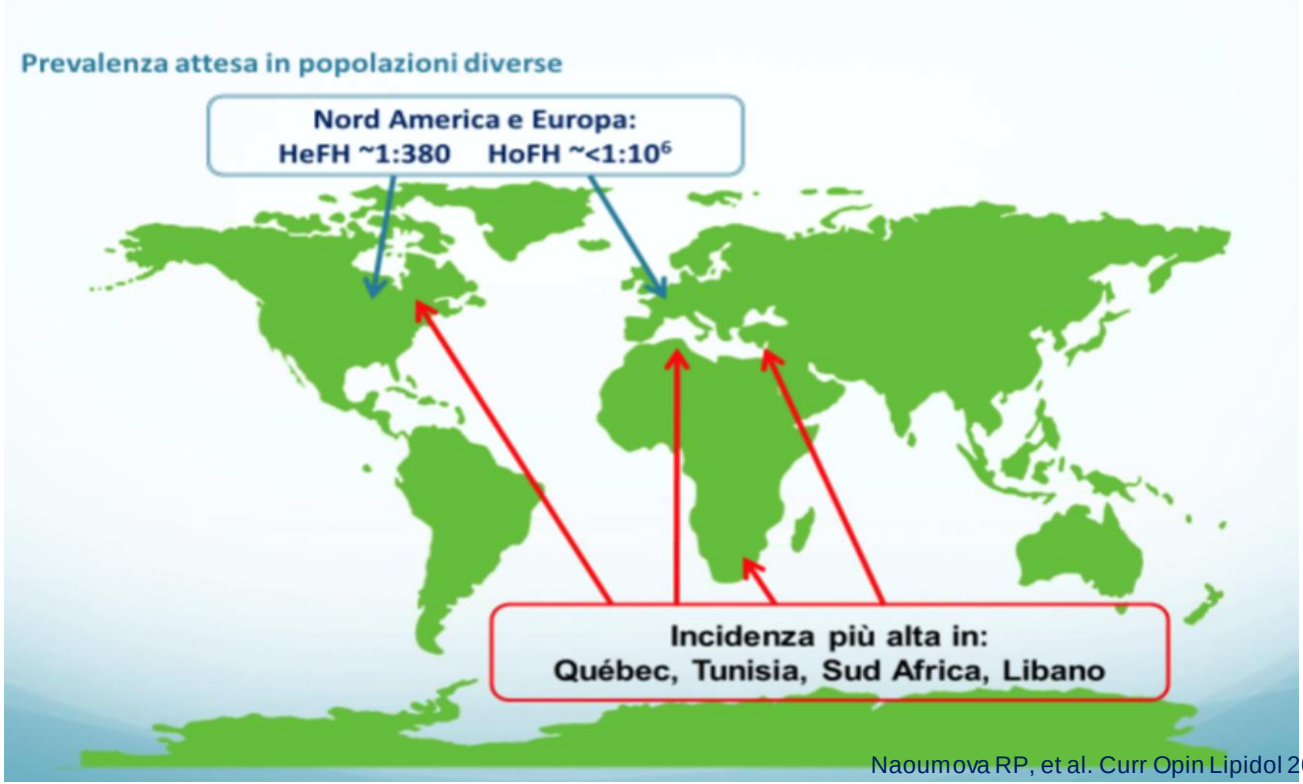


Ipercolesterolemia familiare

Dislipidemia ereditaria caratterizzata da un aumento isolato e permanente dei livelli di lipoproteina a bassa densità (LDL).

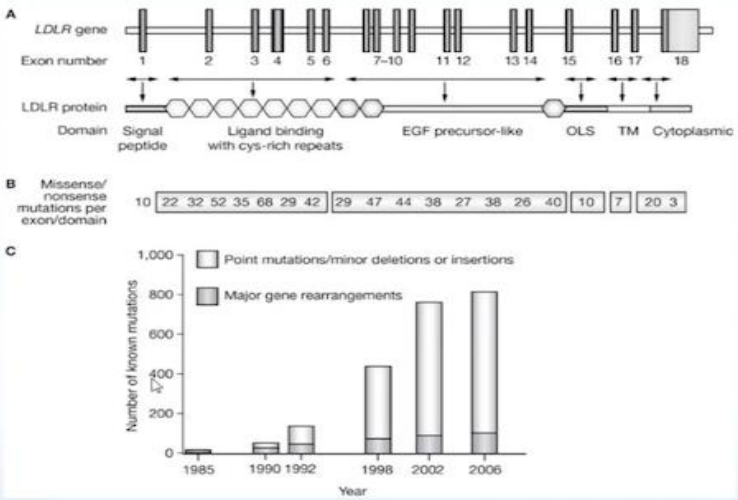
→Forma ***omozigote*** (1/1.000.000 – ***Update 1/160.000-1/300.000 in Nord Europa***) con esordio nei primi anni di vita, depositi extravascolari di colesterolo (xantomi cutanei o tendinei) e malattia arteriosa coronarica in età pediatrica

→Forma ***eterozigote*** (prevalenza 1 ogni 380) clinicamente silente ma comparsa di MCV precoce (<55 aa ♂ e <60 ♀)



Naoumova RP, et al. Curr Opin Lipidol 2004;15:413-422

IGene LDL-R (cr19p13)



90% dei casi → oltre 1700 mutazioni note

Soutar AK and Naoumova RP (2007) Mechanism of Disease: genetic causes of familial hypercholesterolemia. Nat Clin Pract cardiovasc Med 4:214-225

Ipercolesterolemia familiare fenotipo omozigote

Sintomatologia clinica:

- xantomi a partire dai 18 mesi, arcus cornealis

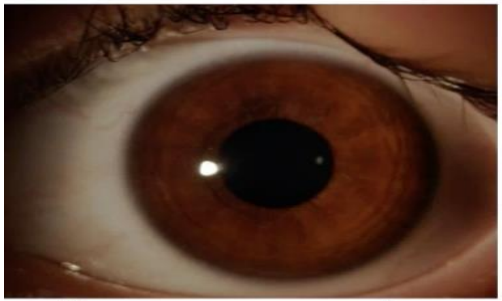
-età media di comparsa di MCV: primi 20 anni

Esami biochimici, LDL-C:

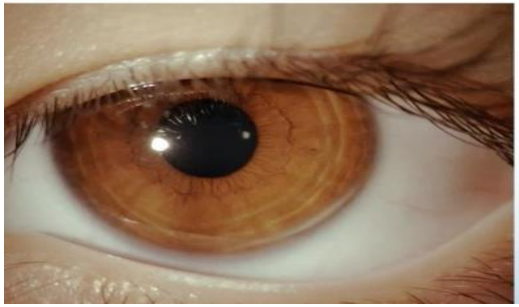
- >600 mg/dl

JMCP, march 2013, vol 19,No 2, 139-49

Ipercolesterolemia familiare fenotipo omozigote

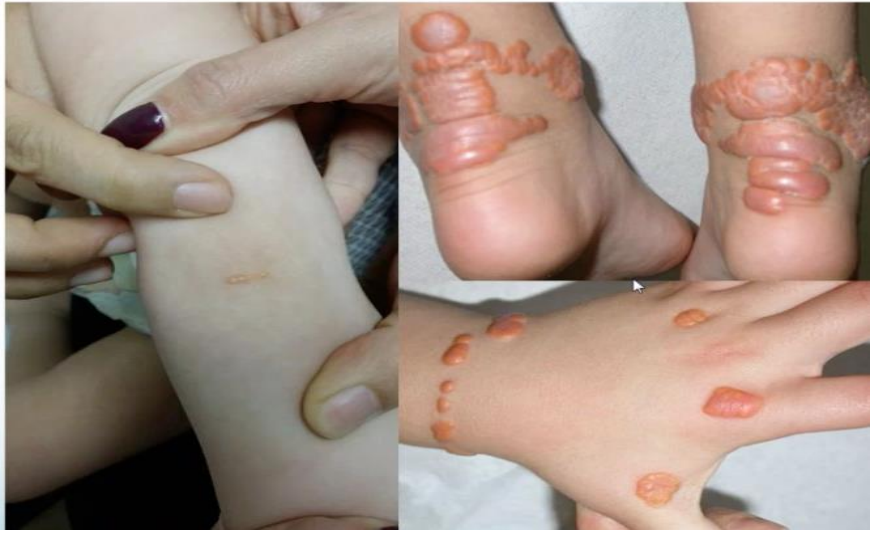


Arco corneale

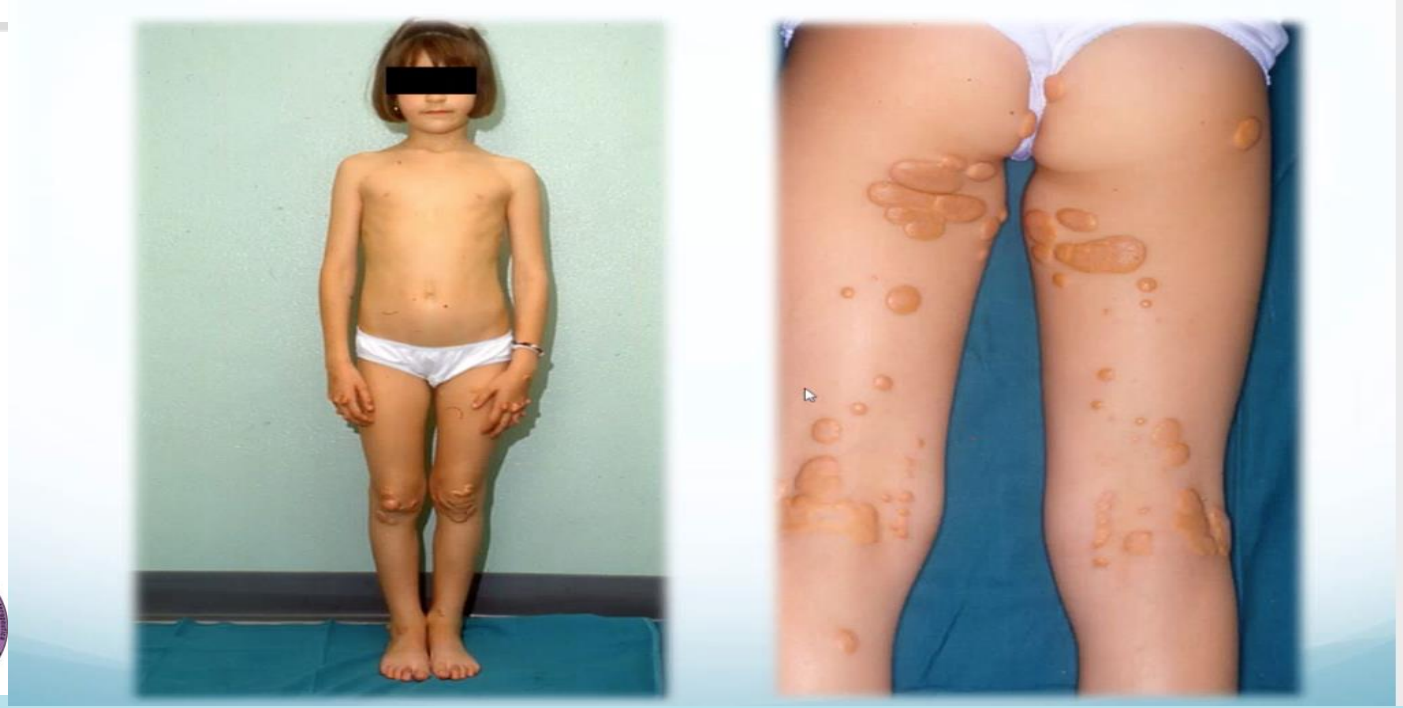


Depositi extravascolari

xantomi



Ipercolesterolemia familiare fenotipo omozigote



Ipercolesterolemia familiare fenotipo eterozigote

Sintomatologia clinica:

- **NULLA** in età pediatrica!
- xantomi a comparsa dopo l'età pediatrica
- malattia CV dopo 30 anni (♂ 42-46 aa, ♀ 51-52aa)

Esami biochimici, LDL-C:

- <20 aa	≥190 mg/dl
- 20-29aa	≥220 mg/dl
- >30 aa	≥250 mg/dl

JMCP, march 2013, vol 19,No 2, 139-49

AHA Special Report

Defining and Setting National Goals for Cardiovascular Health Promotion and Disease Reduction

The American Heart Association's Strategic Impact Goal Through 2020 and Beyond

CHILDREN

Goal/Metric	Ideal Cardiovascular Health Definition
Total cholesterol	< 170 mg/dl
Body mass index	< 85° percentile
Physical activity	≥ 60 min of moderate- or vigorous-intensity activity every day
Healthy diet score	4-5 components
Blood pressure	< 90° percentile
Fasting plasma glucose	< 100 mg/dl
Current smoking	Never tried; never smoked whole cigarette

Circulation 2010;121:586-613

Valutare il rischio cardiovascolare

Risk factors
Positive family history: myocardial infarction, angina, coronary artery bypass graft/stent/angioplasty, sudden cardiac death in parent, grandparent, aunt, or uncle at < 55 y for males, < 65 y for females
Hypertension that requires drug therapy (BP ≥ 99° percentile + 5 mmHg)
Current cigarette smoker
BMI at the ≥ 97th percentile
Presence of high risk conditions
Hypertension that does not require drug therapy
BMI at the ≥95° percentile, < 97° percentile
HDL cholesterol < 40 mg/dl
Presence of moderate risk conditions

Pediatrics 2011;128;S213

Terapia

«Quantità giuste di nutrimento e di esercizio, non troppo e non troppo poco»

Ippocrate (460-357 a.C.)

SUPPLEMENT ARTICLES

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report

Pediatrics 2011;128;S213

- **Ai bambini con ipercolesterolemia e elevati valori di LDL, deve essere proposta una dieta più stringente (CHILD-2)**
- **Invio paziente e famiglia presso dietista esperto**
- **In casi di pazienti obesi con dislipidemia, utilizzare raccomandazioni età- e BMI-specifiche al fine di ridurre l'introito calorico totale e incrementare l'attività fisica**

Età	CHILD-2 DIETA (corrispondente a dieta NCEP Step 2)
2 to 21 anni	Elevate LDL Consultare un dietista esperto 25-30% delle calorie derivanti da grassi (Grado B) ≤ 7% da grassi saturi = 10% da grassi mono-insaturi < 200 mg/die colesterolo Evitare ac.grassi trans il più possibile (Grado A) Azioni adiuvanti: -Introdurre esteri di steroli vegetali e/o esteri di stanoli vegetali fino a 2 gr/die, dopo i 2 anni d'età in bambini con ipercolesterolemia familiare - Fibre solubili in acqua psyllium possono essere addizionate alla dieta : dose di 6 g/d per bambini di 2-12 di età e 12 g/d se ≥ 12 anni d'età Elevati TG Consultare un dietista esperto = vedi sopra Ridurre l'apporto di zucchero (Grado B) Sostituire carboidrati semplici con complessi (Grado D) Non utilizzare bevande con zuccheri aggiunti Aumentare l'introito di pesce (aumentare apporto di omega-3)

Pediatrics 2011;128;S213

European Food Safety Authority

The EFSA Journal (2008) 781, 1-12

Scientific substantiation of a health claim related to plant sterols and lower/reduced blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006[1]

CONCLUSIONS

Based on the data presented, the Panel concludes the following:

- Plant sterols for which the health claim is proposed have been sufficiently characterised.
- Elevated blood LDL-cholesterol is one risk factor for coronary heart disease. Coronary heart disease is an important cause of mortality and morbidity. Lowering LDL cholesterol by dietary intervention has been shown to reduce the risk of coronary heart disease.
- A cause-effect relationship has been established between the consumption of plant sterols and lowering of LDL cholesterol, in a dose-dependent manner.
- A clinically significant LDL-cholesterol lowering effect of about 9 % can be achieved by a daily intake of 2 – 2.4 g of phytosterols in an appropriate food (e.g. plant sterols added to fat-based foods and low-fat foods such as milk and yoghurt). The size of the cholesterol lowering effect may differ in other food matrices.

Nutrition, Metabolism & Cardiovascular Diseases (2005) 15, 174–180

ELSEVIER

Nutrition,
Metabolism &
Cardiovascular Diseases

www.elsevier.com/locate/nmcd

Effect of dietary supplementation with glucomannan on plasma total cholesterol and low density lipoprotein cholesterol in hypercholesterolemic children

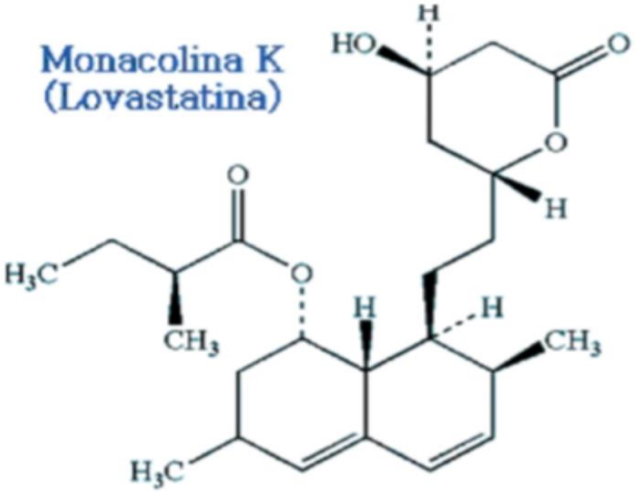
Francesco Martino [a,*], Eliana Martino [a], Francesco Morrone [a], Elisabetta Carnevali [a], Roberta Forcone [a], Tarcisio Niglio [b]

Summary *Aim:* This paper evaluates the effect of the adjunct of the hydrosoluble fiber glucomannan to a Step-One-Diet in 40 plasma hypercholesterolemic children, during a randomized controlled trial, to reduce plasma cholesterol.
Methods: All the subjects recruited underwent an 8-week run in diet period; a Step-One-Diet was prescribed. After that, they were randomly allocated to one of two groups: Step-One-Diet only (control), and Step-One-Diet plus glucomannan in gelatine capsules. After another 8 weeks of treatment, the results were compared within and between the two groups.

< 14 anni

2-3 g/giorno

Riso rosso fermentato



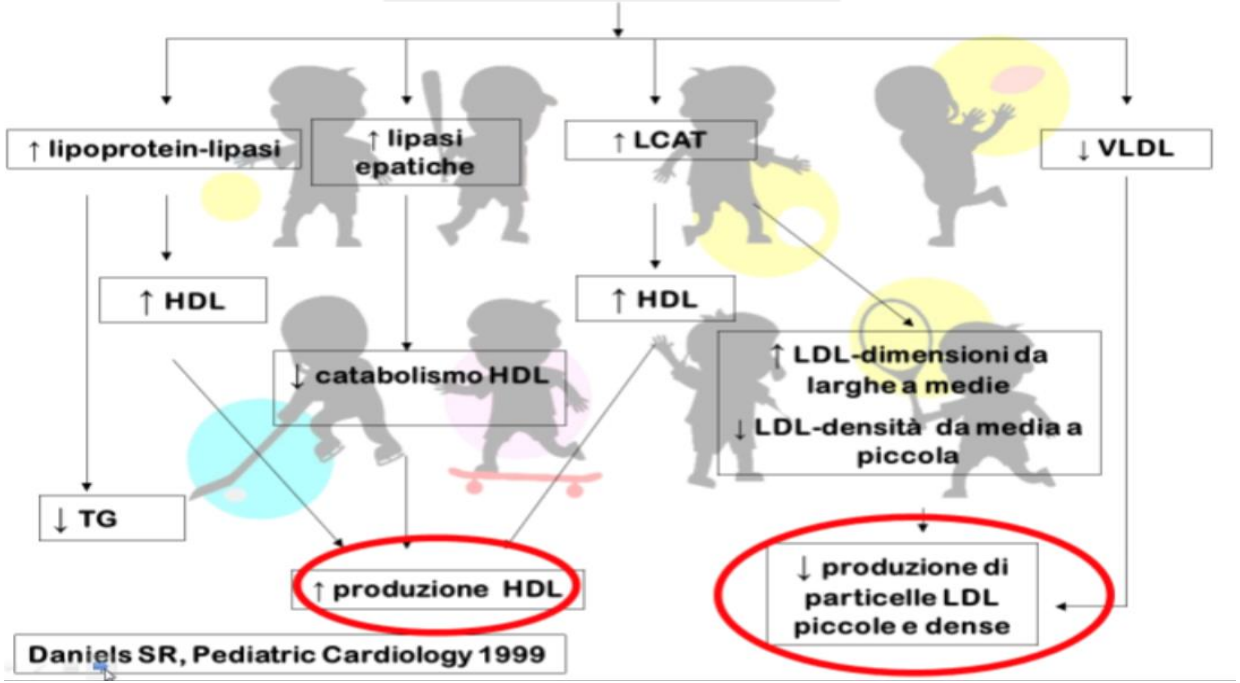
Riso rosso fermentato

- La fermentazione del riso (Oryza sativa) si ottiene in presenza del fungo Monascus purpureus, tradizionalmente impiegato in Cina da millenni per la produzione del vino di riso.

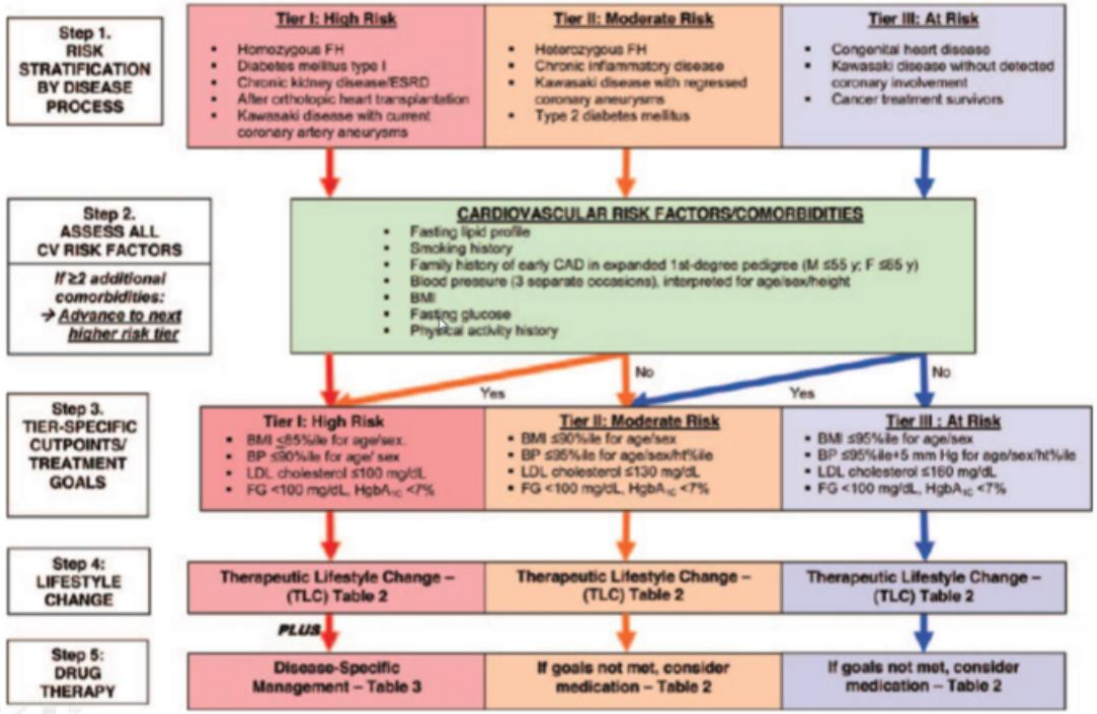
- Ai fini della medicina tradizionale cinese il processo di produzione del riso rosso fermentato è stato perfezionato con l'impiego di ceppi selezionati di muffe (come il Monascus purpureus, Went), in grado di produrre elevate concentrazioni della statina naturale monacolina k in assenza della micotossina nefrotossica citrinina.

- Durante la fermentazione del riso mediata dal *Monascus purpureus* si formano anche altre sostanze a seconda del medium utilizzato. Diverse tecniche produttive possono portare alla formazione di varie sostanze tra cui l'acido gamma-aminobutirrico (GABA), flavonoidi, fitosteroli, saponine ecc…

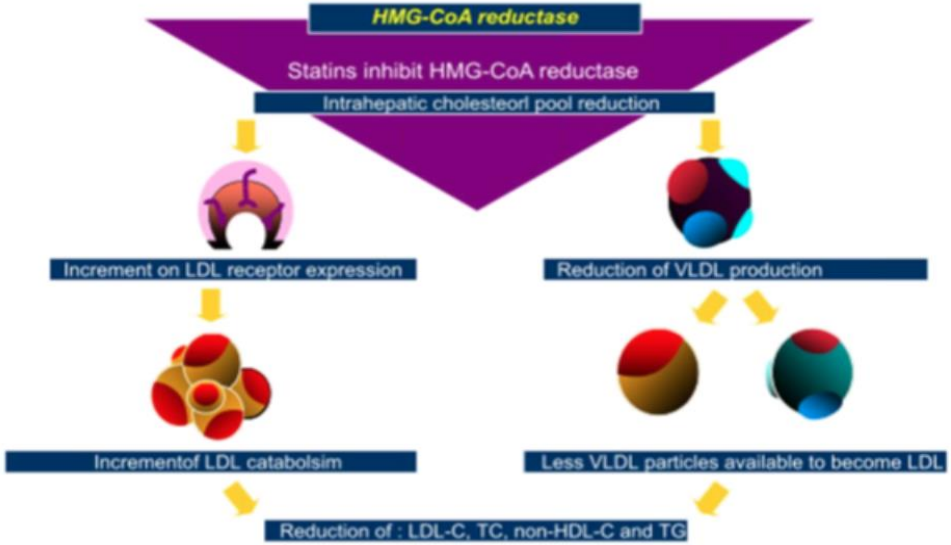
Attività fisica



HIGH-RISK PEDIATRIC POPULATIONS: RISK STRATIFICATION AND TREATMENT

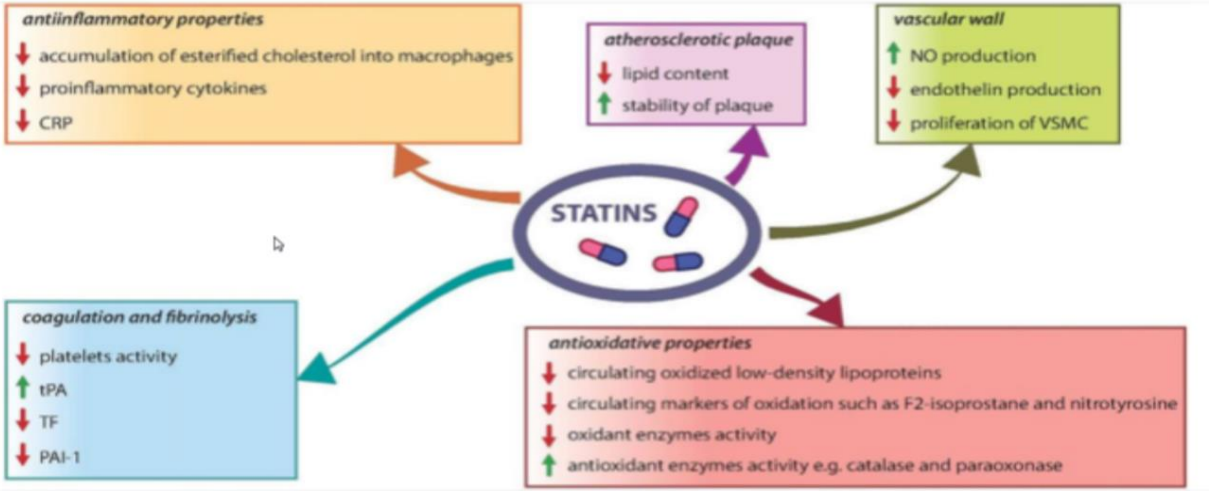


Statins: Mechanism of Action



Novità in tema di statine

L’effetto pleiotropico



JAMA®

Online article and related content current as of November 25, 2008.

Efficacy and Safety of Statin Therapy in Children With Familial Hypercholesterolemia: A Randomized Controlled Trial

Albert Wiegman; Barbara A. Hutten; Eric de Groot; et al.

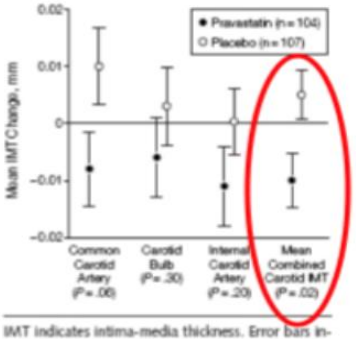
JAMA. 2004;292(3):331-337 (doi:10.1001/jama.292.3.331)

Table 1. Baseline Characteristics of Participants*

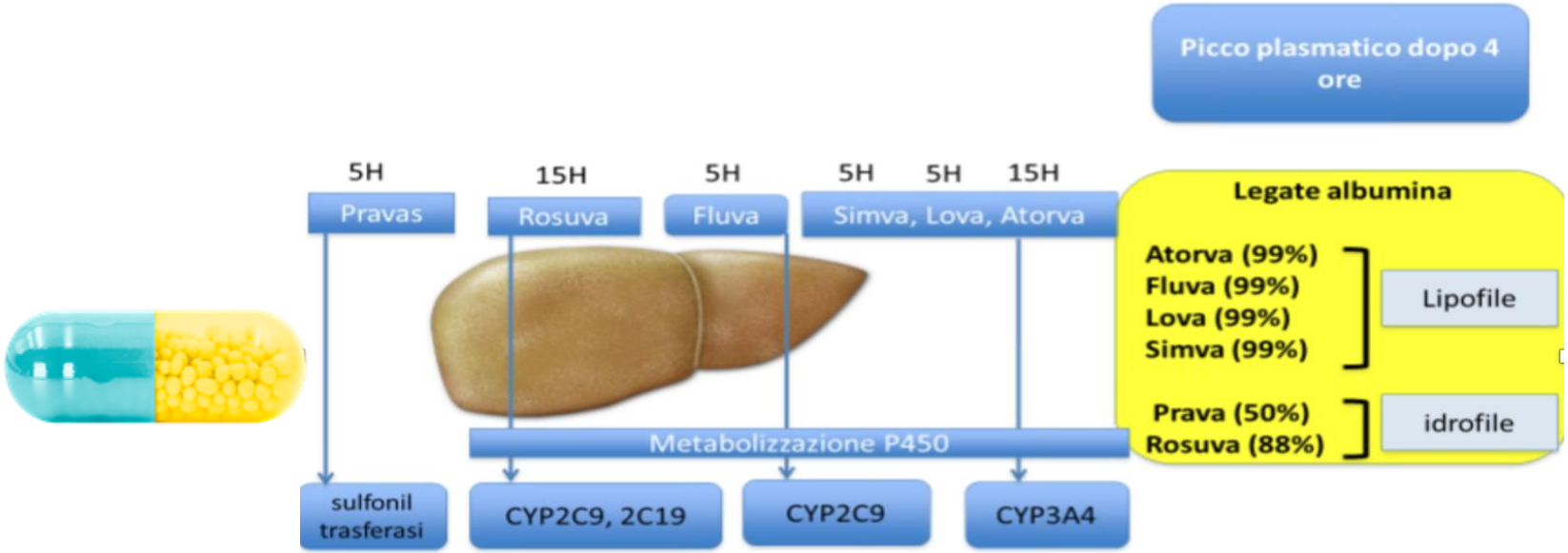
	Pravastatin (n = 106)	Placebo (n = 108)
Age, y	13.0 (3.0)	13.0 (2.9)
Younger than 14 y, No. (%)	65 (61)	63 (58)
Girls, No. (%)	57 (54)	57 (53)
Premenarche (girls), No. (%)	26 (46)	20 (35)
Smokers, No. (%)	11 (10)	13 (12)
Weight, kg	49.1 (15.5)	49.7 (14.7)
Height, cm	156 (16)	157 (13)
Height SDS	0.2 (1.1)	0.2 (0.9)
BMI	20 (3)	20 (4)
BSA, m^2	1.4 (0.3)	1.4 (0.3)
Blood pressure, mm Hg		
Systolic	111 (13)	110 (12)
Diastolic	61 (9)	62 (9)
Pulse, beats/min	72 (13)	72 (11)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; BSA, body surface area; SDS, standard deviation score.
*Data are expressed as mean (SD) unless otherwise noted.

Figure 2. Mean IMT Changes From Baseline for the Different Carotid Arterial Wall Segments in the Pravastatin and Placebo Groups



IMT indicates intima-media thickness. Error bars indicates SE. *P* values for the difference between the 2 groups in change from baseline were calculated using analysis of covariance adjusted for baseline values.

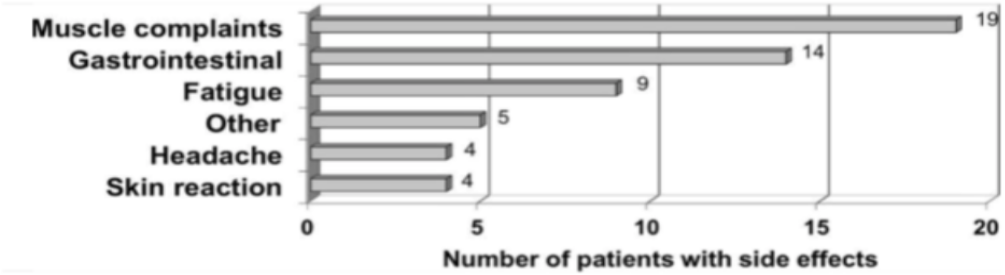


Ad eccezione della pravastatina, metabolizzata enzimaticamente nel citosol dell'epatocita, tutte le statine subiscono un metabolismo microsomiale isoenzimi del citocromo P450

Braamskamp MJAM et al.

Long-term statin treatment in children with familial hypercholesterolemia: more insight into tolerability and adherence

Pediatr Drugs 2015; 17: 159-166



- **19.5% patients had ever experienced side effects**
- **No major side effects**
- **1.5%stopped statin therapy because of side effects**
- **Adherence > 80%: 78.7%**

Cochrane Library

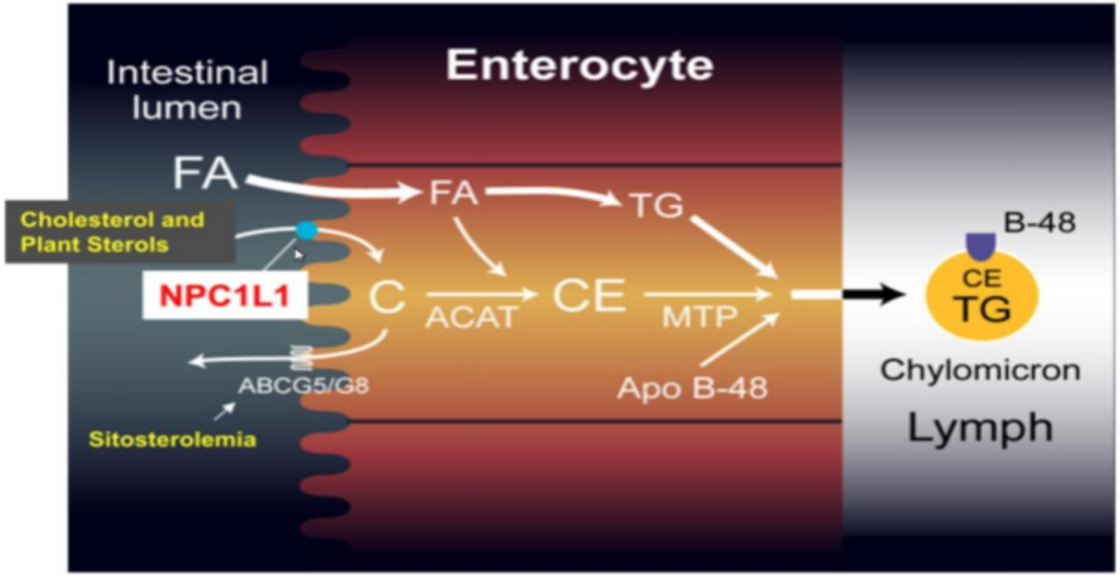
Cochrane Database of Systematic Reviews

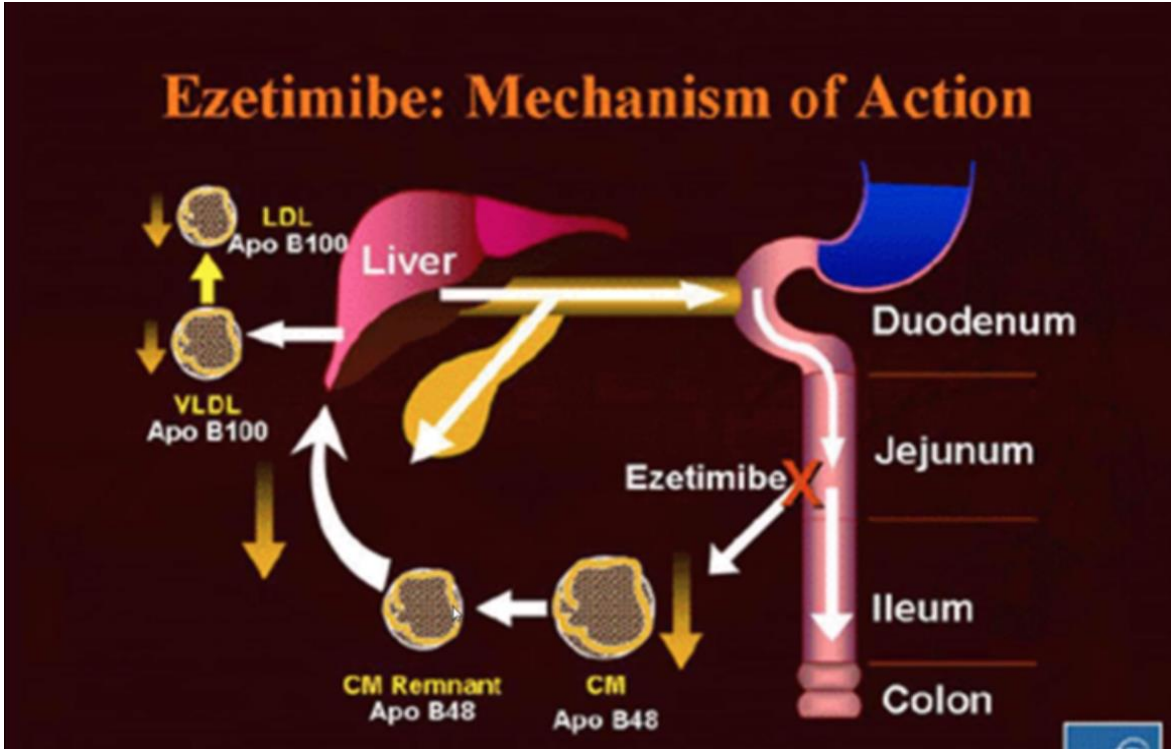
Statins for children with familial hypercholesterolemia (Review)

Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, Wiegman A, Drogari E, Ramaswami U

In the earliest study, children with FH were treated with **pravastatin doses from 5 mg/day to 20** mg/day (Knipscheer 1996).
In the later studies there was a tendency to use larger doses.
Wiegman (2004) used **pravastatin doses of 20 mg/day or 40 mg/day**
de Jongh (2002) titrated **simvastatin doses of up to 40 mg/day** (equivalent dose of pravastatin, 80 mg/day)
McCrindle (2004)titrated atorvastatin doses from **10 mg/day up to 20** mg/day (equivalent dose of pravastatin, up to 80 mg/day)
Braaskamp (2015), the **5 mg starting dose of rosuvastatin** was titrated at 3-monthly intervals to a maximum tolerated dose of 10 mg (six- to nine-year olds) or **20 mg** (10- to 17-year olds) to achieve an LDL-C goal of (2.85 mmol/L (110 mg/dL).

Phytosterols: Inhibition of NPC1L1 by Ezetimibe for Hypercholesterolemia and Sitosterolemia





Circulation
2002;105:2469-2475

Yeste D, Chacon P, Clemente M et al.

Ezetimibe as monotherapy in the treatment of hypercholesterolemia in children and adolescents.

J Pediatr Endocrinol Metab 2009; 22 (6):487-**92**

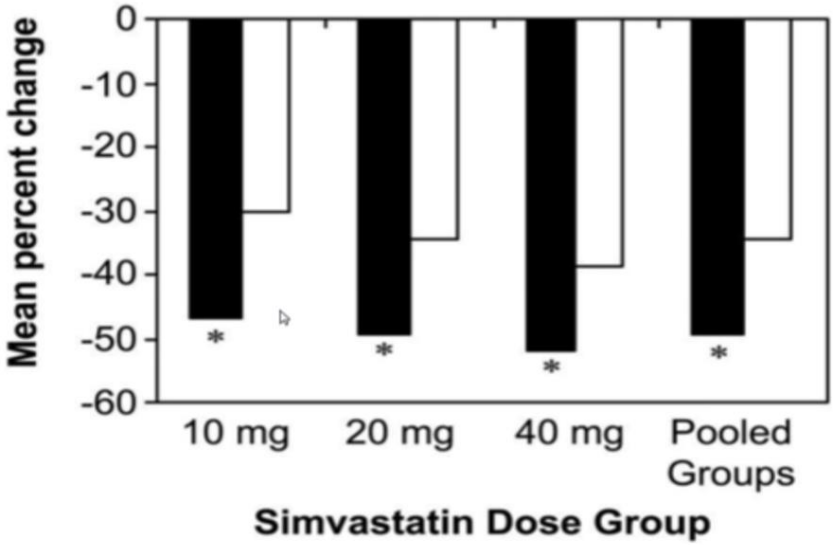
- Children with PH or poligenic hypercholetserolemia (n=6) or FH (n=11) aged 5-15 years were consecutively enrolled to receive ezetimibe as monotherapy at 10 mg/day for 11.3 +/- 7.3 and 15.9 +/- 10.1 months, respectively.
- Results:

	PH Pre-	Post-	p	FH Pre-	Post-	p
TC (mg/dl)	260.5 +/- 12.4	180.0 +/- 21.6	0.02	315.3 +/- 41.8	233.3 +/- 36.8	0.003
LDL-C (mg/dl)	177.1 +/- 17.7	102.6 +/- 16.7	0.02	243.0 +/- 41.8	170.0 +/- 29.8	0.003

- Biochemical profile (hemogram, transaminases, creatinine, calcium, phosphorus and liposoluble vitamins A and E) remained unchanged; no adverse effects were observed.

Efficacy and Safety of Coadministration of Ezetimibe and Simvastatin in Adolescents With Heterozygous Familial Hypercholesterolemia

Anouk van der Graaf, MD,* Cynthia Cuffie-Jackson, MD,‡ Maud N. Vissers, PhD,* Mieke D. Trip, MD, PhD,† Claude Gagné, MD,‖ Genming Shi, PhD,§ Enrico Veltri, MD,‡ Hans J. Avis, MD,* John J. P. Kastelein, MD, PhD*

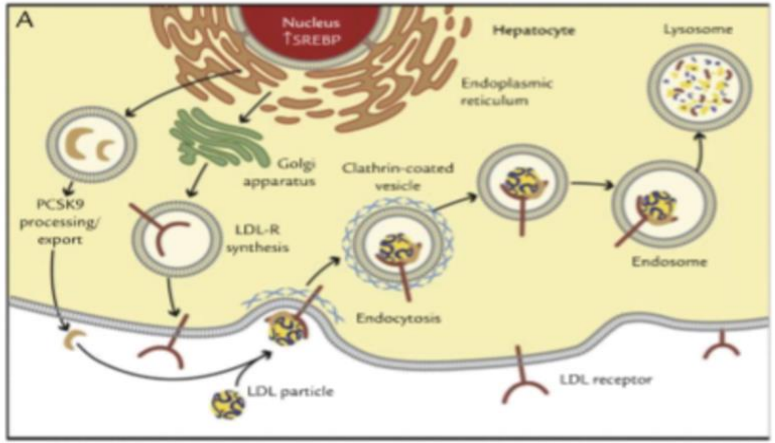


JACC Vol. 52, No. 17,2008

Altre opzioni terapeutiche

Should non-statin approaches continue to be investigated for LDL reduction? Inhibition of PCSK9 pathway

Lessons from nature



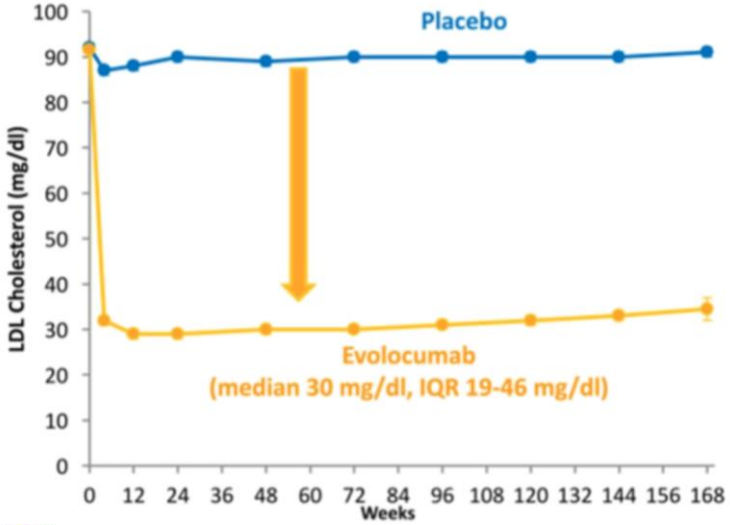
Proprotein convertase subtilisin/kexin type 9 (PCSK9) can bind to LDL-receptor on the surface of hepatocytes. On interaction, PCSK9 decreases LDLR density on the surface of hepatocytes either through **inhibition of receptor recycling** or **through directing LDLR to lysosomal catabolism clathrin-mediated endocytosis.**

From Sahebkor A. Clin Therap 2013;35,8:1082-1098

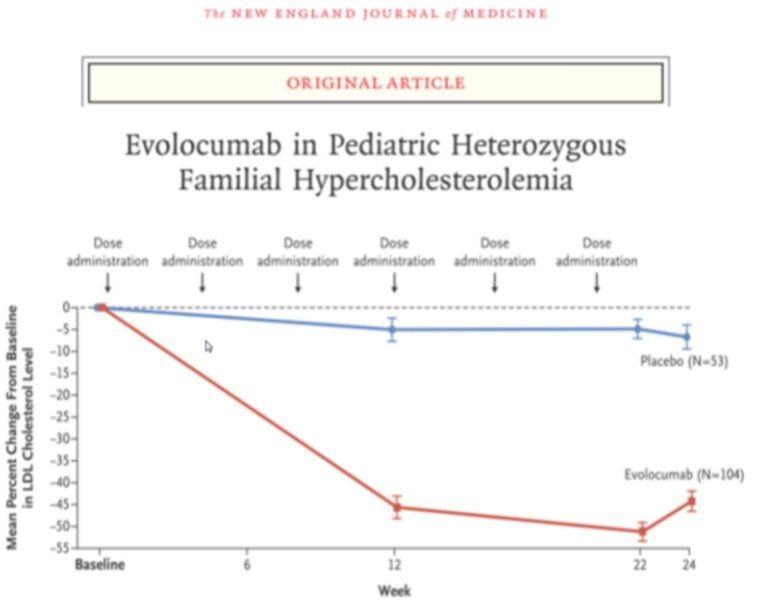
PCSK9 Promotes Degradation of LDLRs

↑ PCSK9 ↓ LDLR protein ↑ LDL-C

~~PCSK9~~ ↑ LDLR protein ↓ LDL-C



Sabatine, NEJM, 2017



Santos rd, 2020

CONCLUSIONI

- Trasmettere le indicazioni per la diagnosi precoce ed il trattamento delle dislipidemie in età pediatrica

- Sottolineare l'importanza della prevenzione della malattia cardiovascolare nell'adulto

L’occhio vede ciò che la mente conosce

Johann Wolfgang Goethe

Grazie per l’attenzione