

# Chimica Farmaceutica e Tossicologica 2

- Dislipidemie;
- Inibizione HMG-CoA: **Statine**;
- Agonisti PPAR: **Fibrati**;
- Resine; inibizione lipasi pancreatica (**Orlistat**);  
inibizione assorbimento intestinale colesterolo  
(**Ezetimibe**); inibitori sintesi ApoB-100 (**Kynamro**)

**Dislipidemie:** alterazione patologica quali/quantitativa dei livelli serici dei lipidi (colesterolo-trigliceridi) correlate al rischio vascolare, generalmente asintomatiche

## ATEROSCLEROSI

- 1900: *Virchow* osservò nelle pareti arteriose di pazienti, deceduti per patologie vascolari occlusive, aggregati di sostanza grassa gialla (gr. Atheroma, αθηρομα).
- 1913: *Anitschkow and Chalатов* dimostrarono la relazione tra alimentazione ricca di colesterolo e patologie ateromatose nel coniglio.
- 1950: Studio FRAMINGHAM nel quale si stabilì la correlazione tra elevate concentrazioni plasmatiche di colesterolo e mortalità da CHD (CORONARY HEART DISEASE).
- 1960-1980: Numerose indagini convergono (*ipotesi lipidica*) nell'evidenziare una relazione diretta tra mortalità per CHDs e colesterolo LDL (low-density lipoprotein) ed una relazione inversa con il colesterolo HDL (high-density lipoprotein).
- 1984: NIH Consensus Development Conference. Lowering blood cholesterol to prevent heart disease. NIH Consensus Development Conference Statement.

# Grassi alimentari

cistifellea

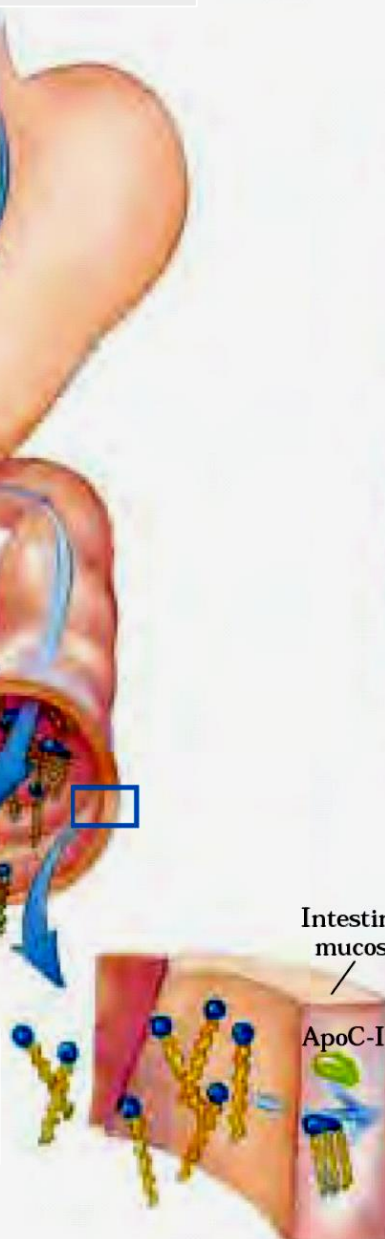


intestino tenue

sali biliari emulsionanti

lipasi-idrolisi  
 $TG \rightarrow FA$

Mucosa intestinale  
 $FA \rightarrow TG$



Intestinal mucosa

ApoC-II

$FA \rightarrow ox$  (anab),  
est (dep)

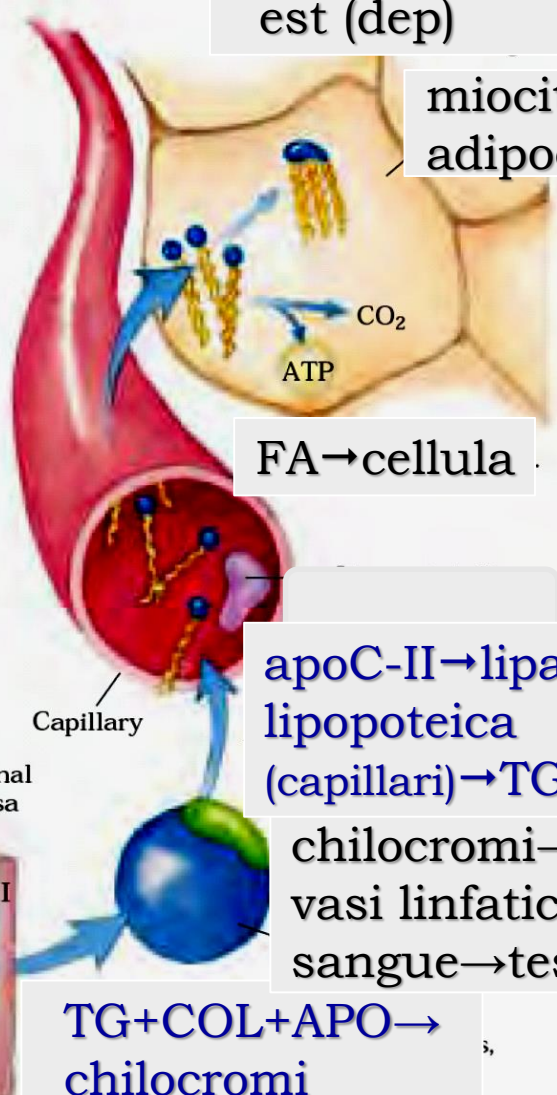
miocita-  
adipocita

$FA \rightarrow cellula$

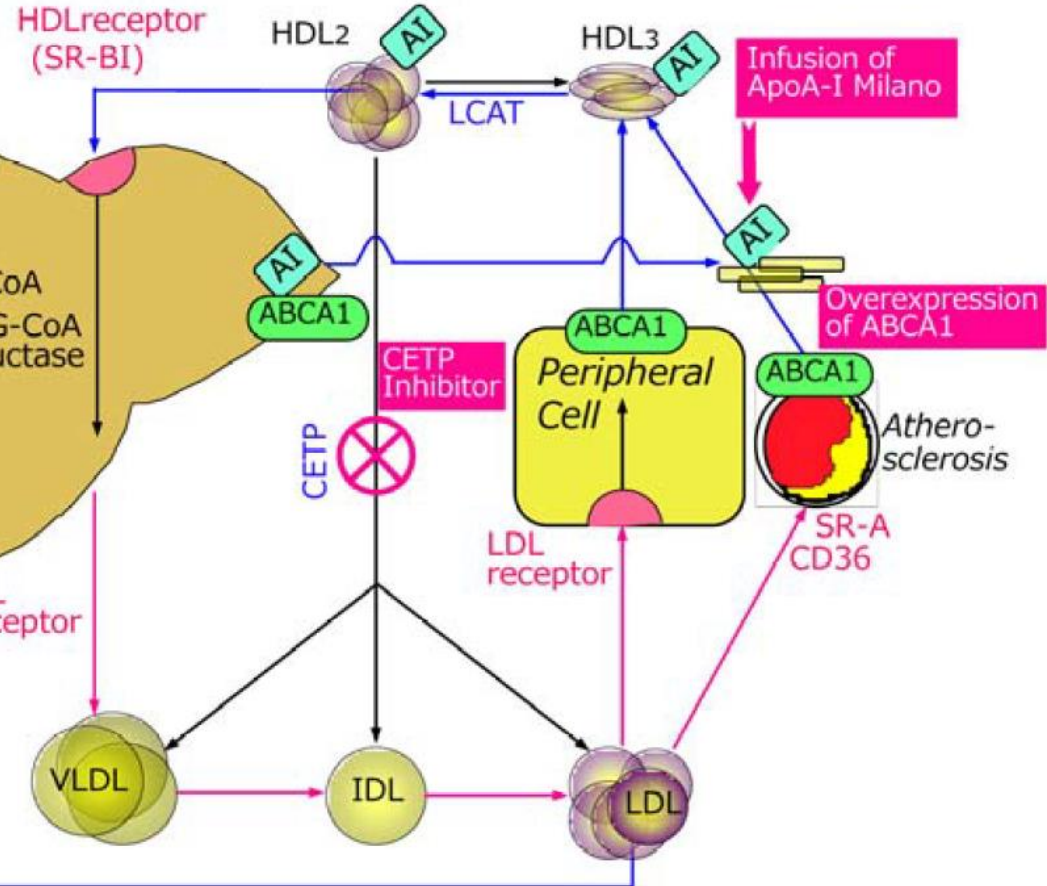
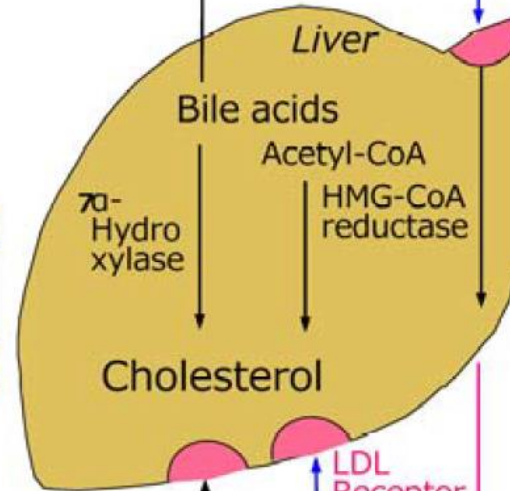
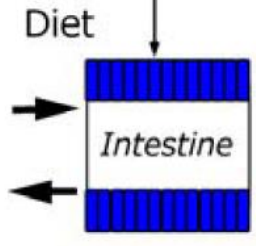
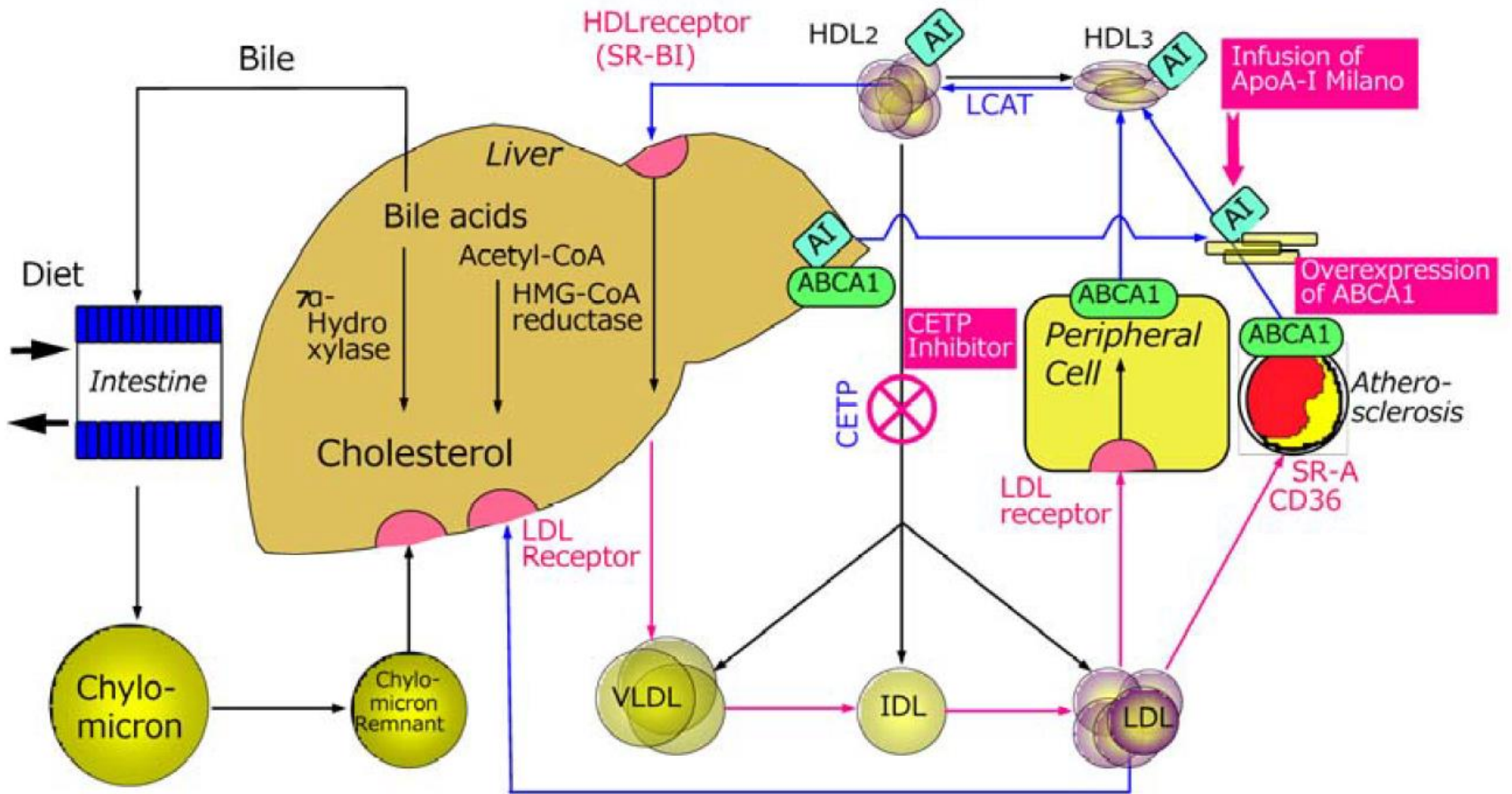
$apoC-II \rightarrow$  lipasi  
lipoproteica  
(capillari)  $\rightarrow TG \rightarrow TA + G$

chilocromi  $\rightarrow$   
vasi linfatici  $\rightarrow$   
sangue  $\rightarrow$  tessuti

$TG + COL + APO \rightarrow$   
chilocromi



$CO_2$   
ATP



Infusion of ApoA-I Milano

Overexpression of ABCA1

CETP Inhibitor

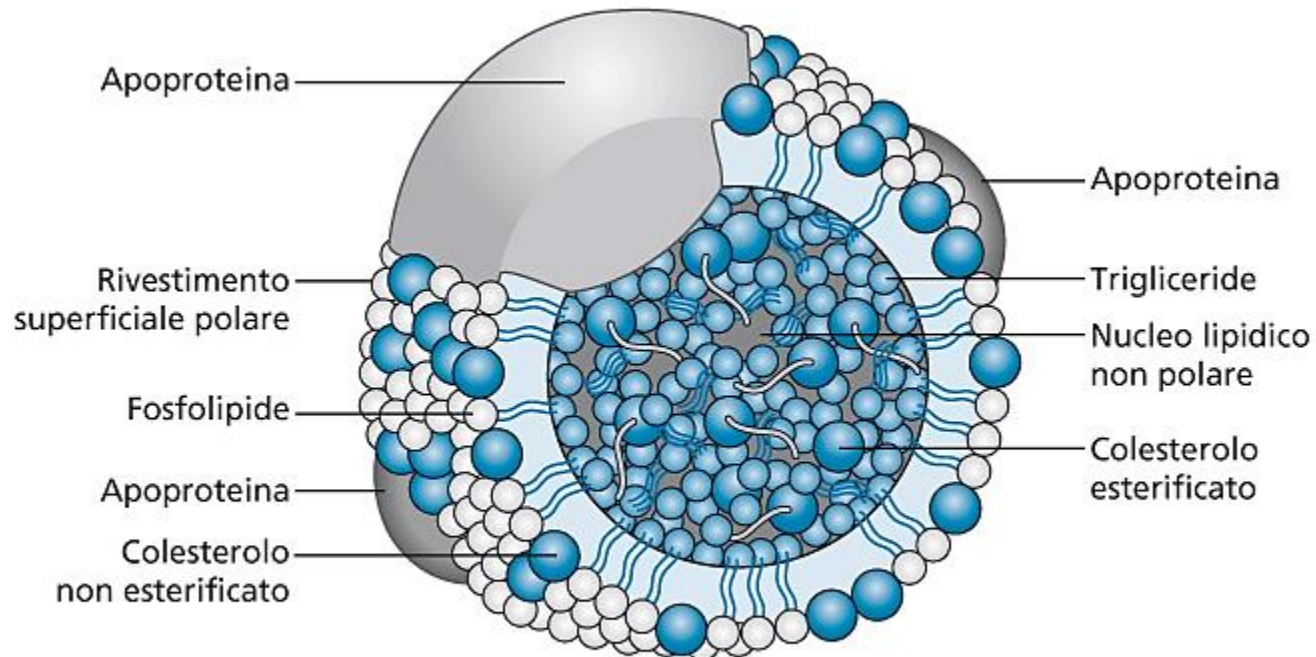
Atherosclerosis

SR-A  
CD36



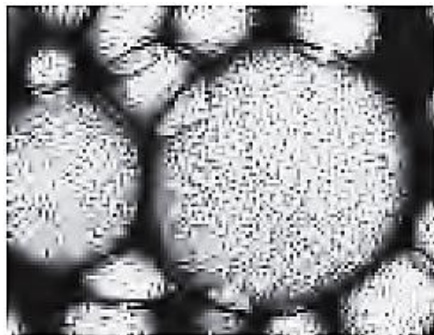
# STRUTTURA DELLE LIPOPROTEINE

Particelle globulari, caratterizzate da un nucleo che contiene lipidi non polari (esteri del colesterolo e trigliceridi in proporzioni diverse) e un involucro esterno di fosfolipidi, colesterolo libero e apoproteine

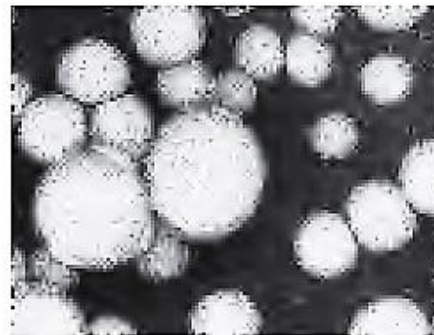


**FIGURA 39.1** Struttura generale di una lipoproteina.

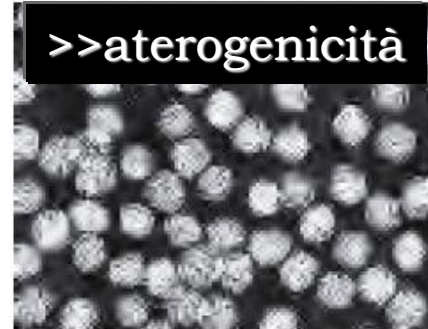
	Proteine	Triglic.	Coolest.	Fosfolipidi
<b>Chilomicroni</b> postprandiali	1%	90%	6%	3%
<b>VLDL</b> origine epatica	10%	65%	13%	12%
<b>LDL</b>	25% (di cui 98% ApoB)	10%	43%	22%
<b>HDL</b>	50% (di cui 90% ApoA)	2%	18%	30%



Chylomicrons (×60,000)



VLDL (×180,000)



LDL (×180,000)



HDL (×180,000)

Indice aterogenico plasmatico:  $\log(\text{trigliceridi}/\text{HDL-colesterolo})$

Frazione lipoproteica	Densità	Unità Svedberg	MW	Diametro (Å)
HDL	1.063-1.210	-	HDL <sub>2</sub> , 4X10 <sup>5</sup> HDL <sub>3</sub> , 2X10 <sup>5</sup>	70-130 50-100
LDL (o LDL <sub>2</sub> )	1.019-1.263	0-12	2X10 <sup>6</sup>	200-800
IDL (o LDL <sub>3</sub> )	1.006-1.019	12-20	4.5X10 <sup>6</sup>	250
VLDL	0.95-1.006	20-400	5X10 <sup>6-7</sup>	250-750
Chilomicroni	<0.95	>400	10 <sup>9-10</sup>	10 <sup>3-4</sup>

Analisi multivariate hanno dimostrato che elevate concentrazioni di TG:

- (1) Incrementano il rischio CHD (Coronary heart disease) indipendente dalla HDLc;
- (2) Incrementano significativamente il numero di eventi cardiovascolari se associate ad elevato rapporto LDLc/HDLc;
- (3) Sono un fattore indipendente di rischio in donne di età compresa tra 50-69 anni;
- (4) Sono un fattore indipendente di rischio in pazienti affetti da diabete mellito (DM) di tipo 2.

### Current NCEP Guidelines for Treatment

paziente	LDLc (mg/dL)	
	start	Goal
con rischio CHD o equivalenti	> 130	<100
senza CHD e ≥ 2 fattori di rischio	>130 (10-year risk: 10-20%)	<130
senza CHD e fattori di rischio <2	>190	<160

# DISLIPIDEMIE: STRATEGIE TERAPEUTICHE

## - Dieta

## - Eliminazione dei fattori aggravanti

*L'iperlipoproteinemia può essere aggravata da altre condizioni patologiche (es. diabete mellito, alcolismo, ipotiroidismo). Necessario ridurre tutti i fattori di rischio (ipertensione, iperglicemia, ecc.)*

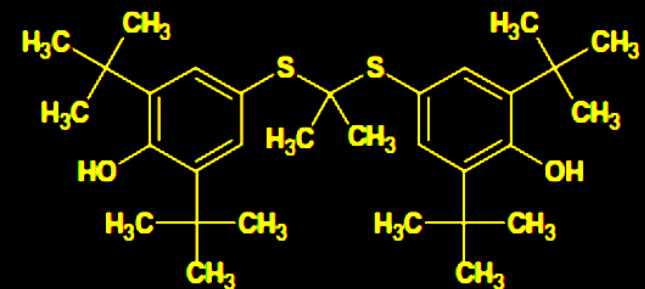
## - Terapie

### • fino al 1987:

- regime alimentare;
- Sequestranti acidi biliari (colestiramina and colestipolo);
- acido nicotinico (niacina);
- Fibrati (LDL  $\downarrow$ , HDL  $\uparrow$ );
- Probucol (LDL  $\downarrow$ , HDL  $\downarrow$ ) [X].

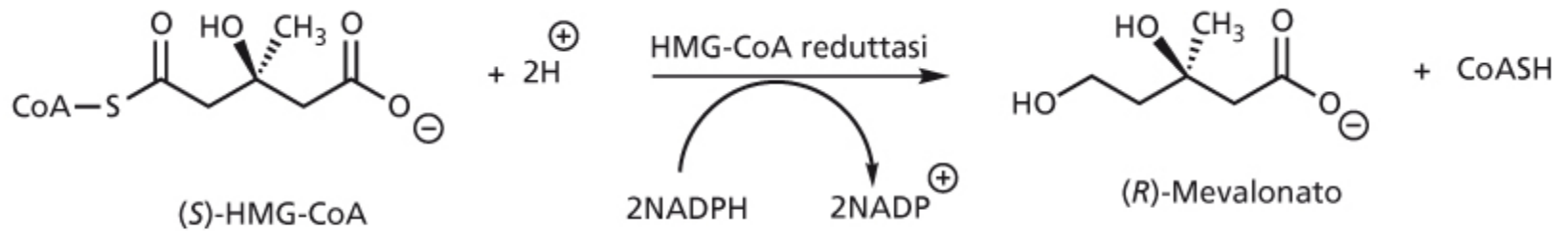
### • dal 1987:

- Statine;
- Ezetimibe.

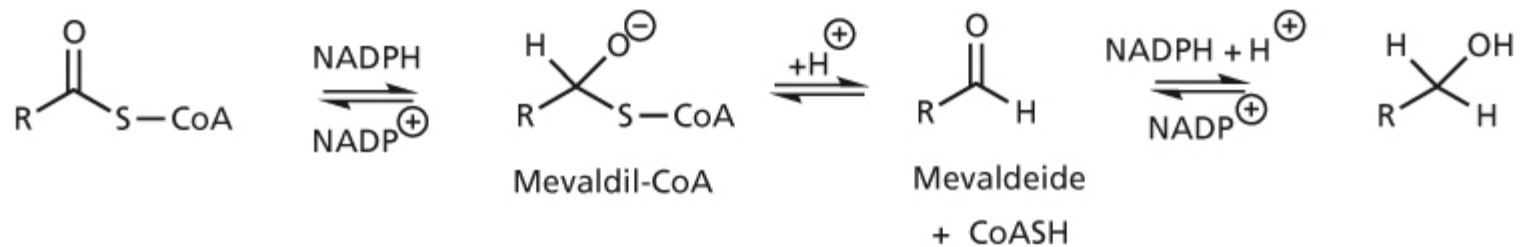




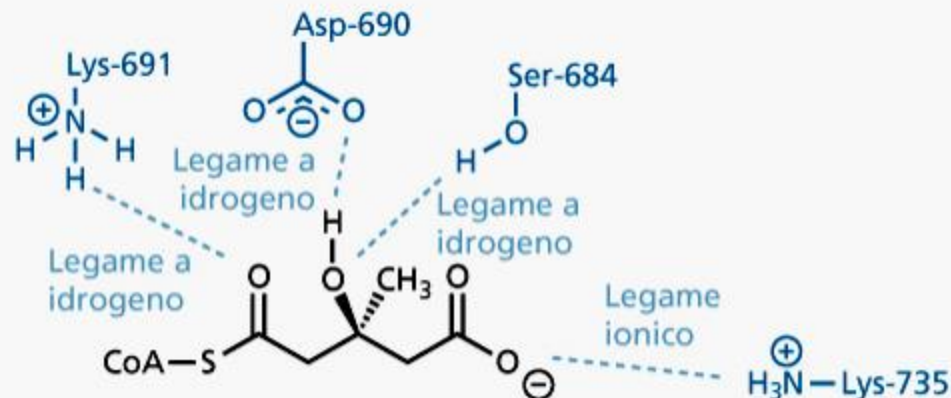




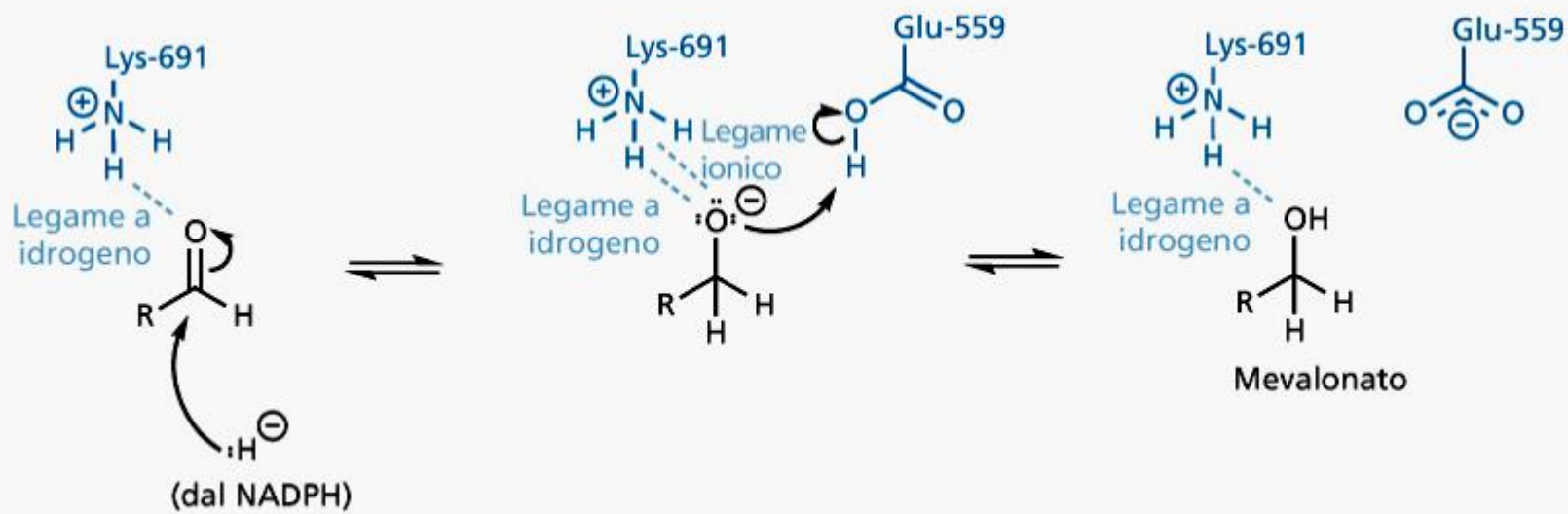
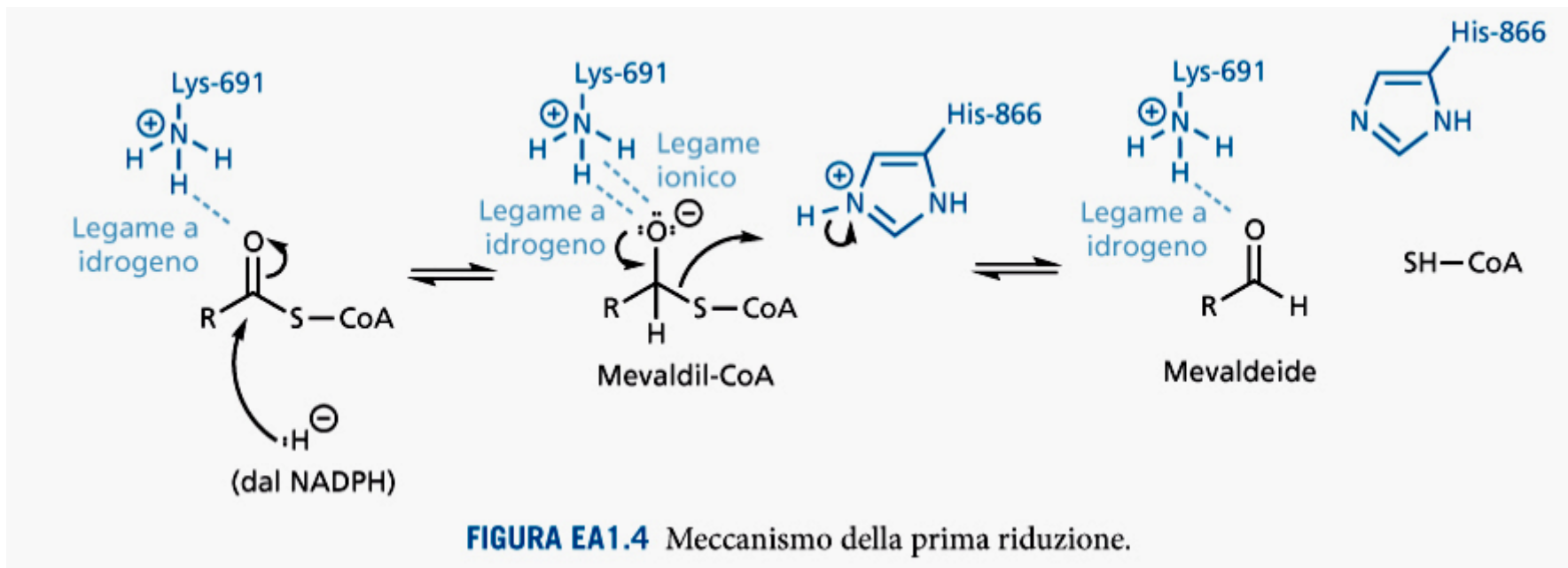
**FIGURA EA1.1** Reazione catalizzata dalla 3-idrossi-3-metilglutaril-coenzima A reduttasi (HMGR o HMG-CoA reduttasi).

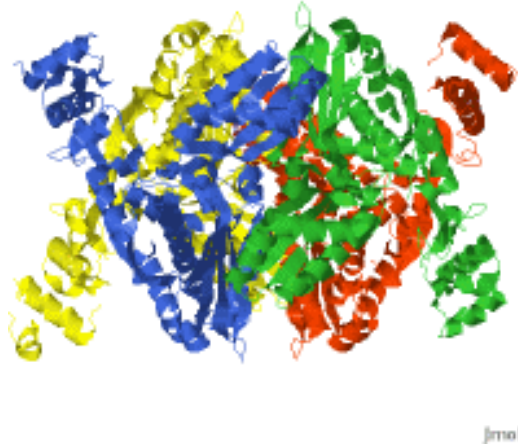


**FIGURA EA1.2** Meccanismo della reazione catalizzata dalla 3-idrossi-3-metilglutaril-coenzima A reduttasi (HMGR o HMG-CoA reduttasi).



**FIGURA EA1.3** Interazioni di legame del 3-idrossi-3-metilglutaril-coenzima A (HMG-CoA).





1jmol

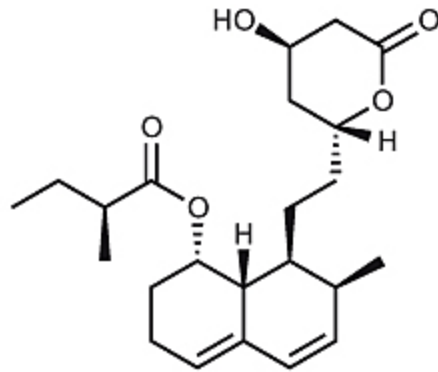
## **HMG-CoA Reductase** (or 3-hydroxy-3-methylglutaryl-CoA reductase or HMGR):

- class I HMGRs (eukaryotes, membrane bound) and class II HMGRs (prokaryotes, soluble)
- a transmembrane protein, containing 8 domains, that is anchored in the membrane of the endoplasmic reticulum;
- The catalytic portion of human HMGR forms a tetramer, with the individual monomers winding around each other;
- Each monomer contains three domains, the N-domain, the L-Domain, and the S-Domain (NADP binding site);

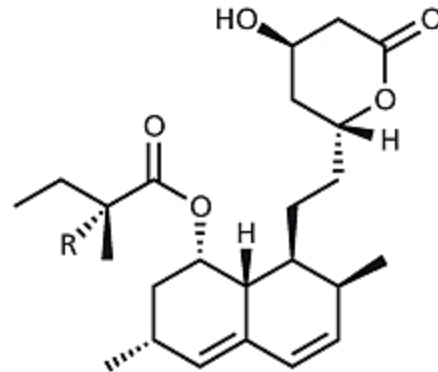
[http://proteopedia.org/wiki/index.php/HMG-CoA\\_Reductase](http://proteopedia.org/wiki/index.php/HMG-CoA_Reductase)



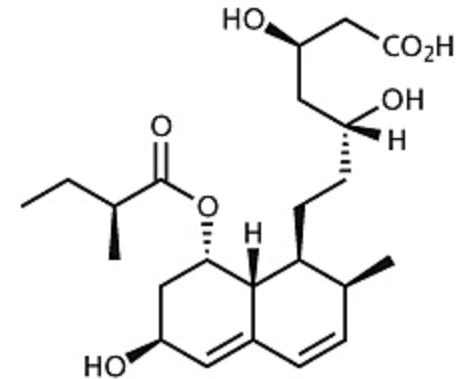
# Statine di tipo I



Compactina  $IC_{50} = 23$  nM  
(Mevastatina)

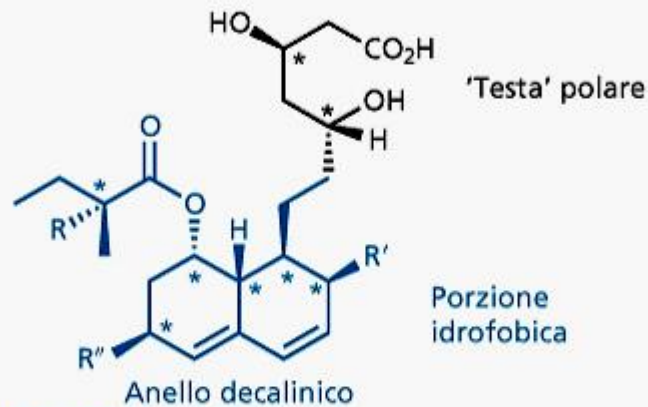


Lovastatina (R = H)  $IC_{50} = 24$  nM  
Simvastatina (R = Me)  $IC_{50} = 11$  nM

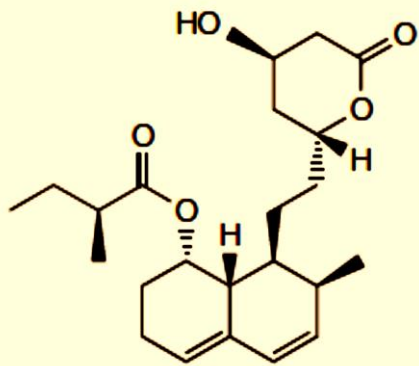


Pravastatina  $IC_{50} = 1900$  nM

**FIGURA EA1.7** Statine di tipo I.



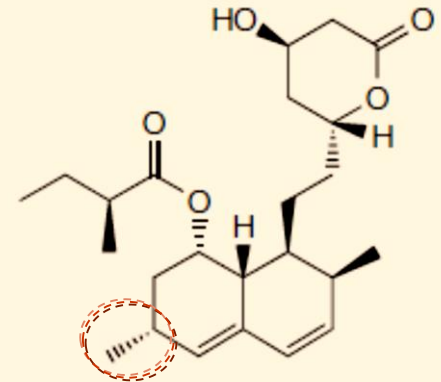
**FIGURA EA1.8** Struttura generale delle statine di tipo I  
(\* indica un centro asimmetrico).



**Compactin (mevastatin)**

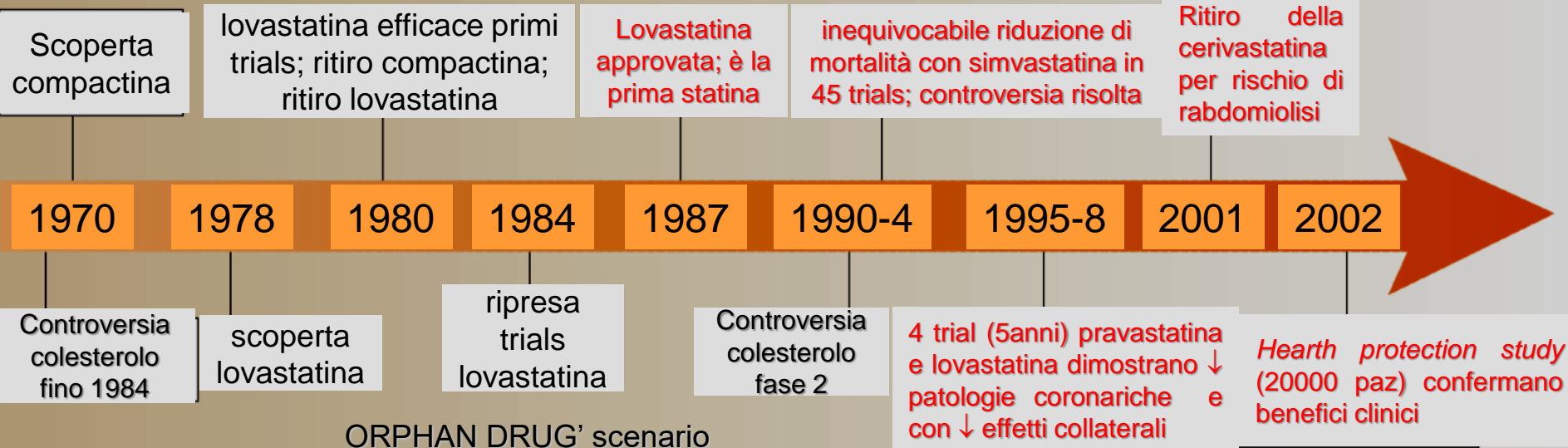
Akira Endo (*Penicillium citrinum*, Sankyo-Japan-1976); no attività antibiotica, ipolipidemico animale; stop trials (Sett1980)

Albert, Chen et al (**mevinolin**, *Aspergillus terreus*, Merck) 1978



**Lovastatin**

Timeline | **History of the statins**

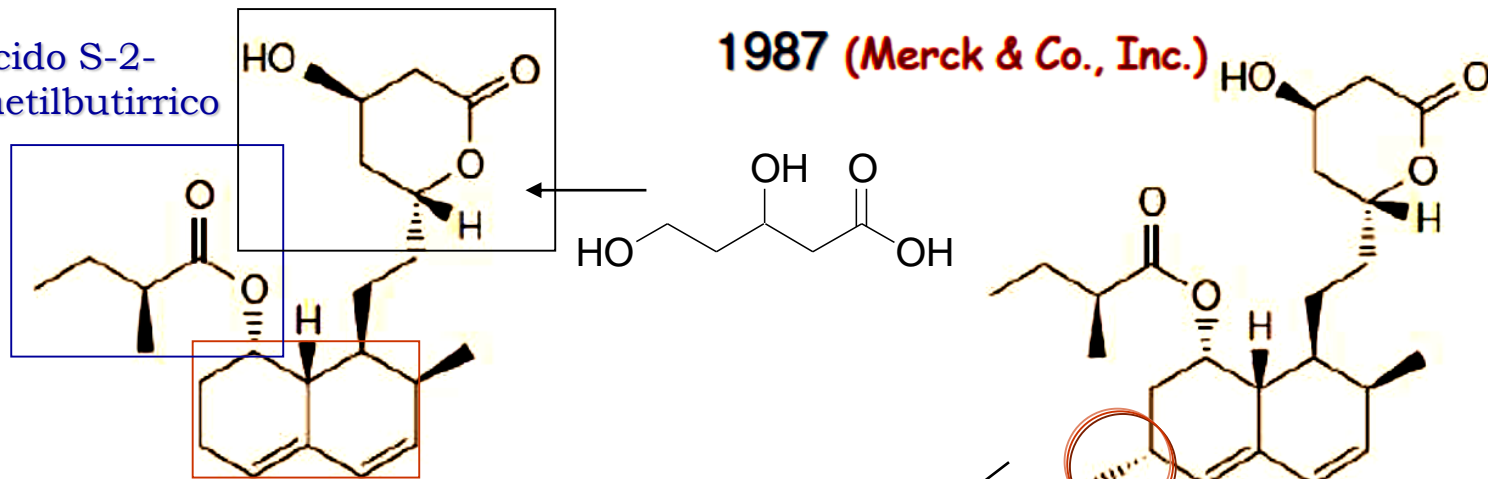


1982: Bilheimer and Grundy in Dallas, Texas, and Illingworth in Portland, Oregon asked Merck for lovastatin to test its effect in selected small groups of patients with severe heterozygous FAMILIAL HYPERCHOLESTEROLAEMIA → dramatic reductions in LDL cholesterol with very few adverse effects

4-idrossi- $\delta$ -valerolattone

acido S-2-metilbutirrico

1987 (Merck & Co., Inc.)



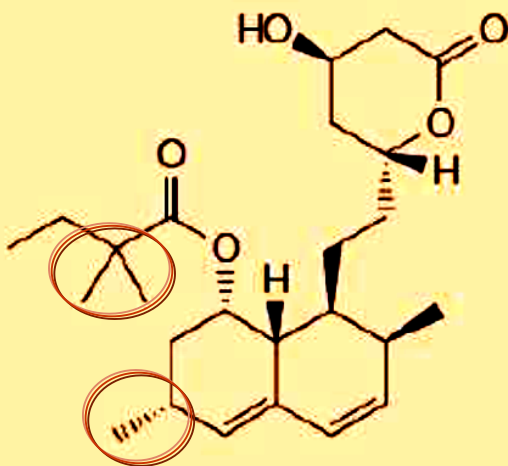
esaidronaftalene

**Compactin (mevastatin)**

semisintesi

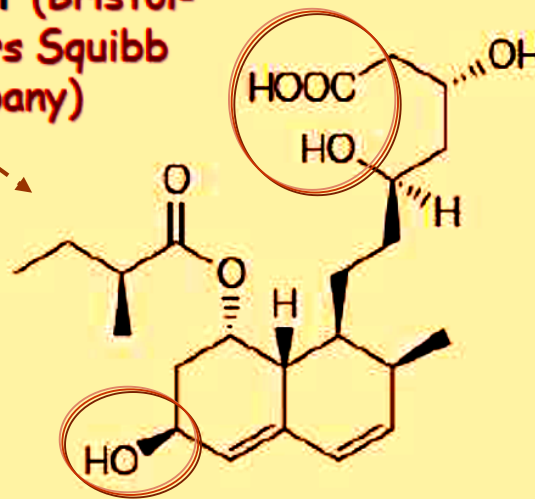
**Lovastatin (Mevacor®)**

1988 (Merck)



**Simvastatin (Zocor®)**

1991 (Bristol-Myers Squibb Company)



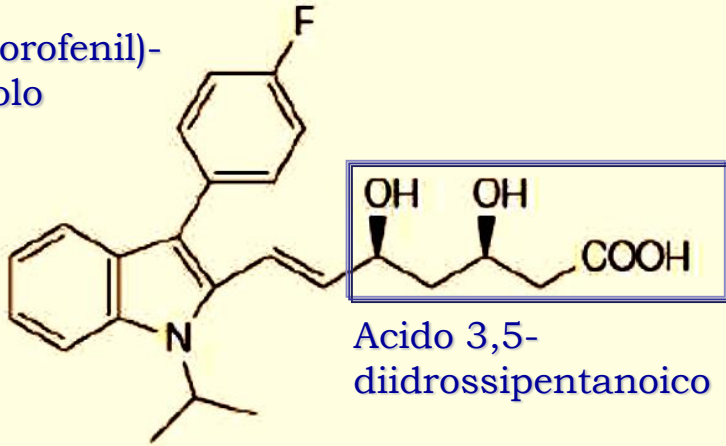
**Pravastatin (Pravachol®)**

The mean reduction in LDL cholesterol attainable with the maximal recommended dose of different statins ranges from 35 to 55%.

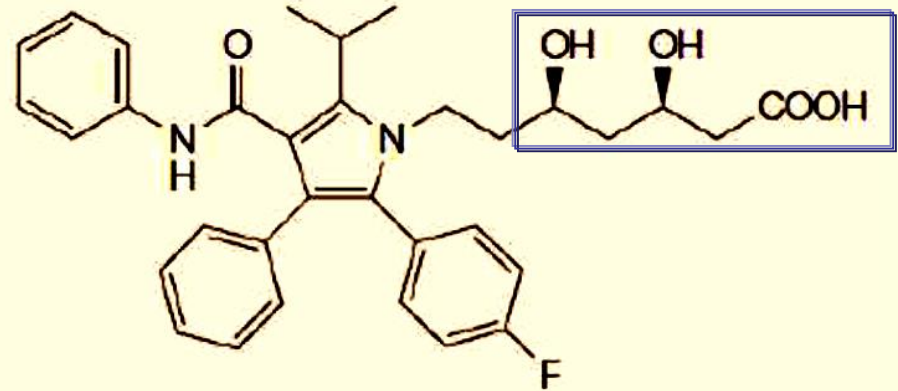
1994 (Novartis Pharmaceuticals Corporation)

1997 (Pfizer Inc.)

3-(4-fluorofenil)-  
1H-indolo



**Fluvastatin (Lescol®)**

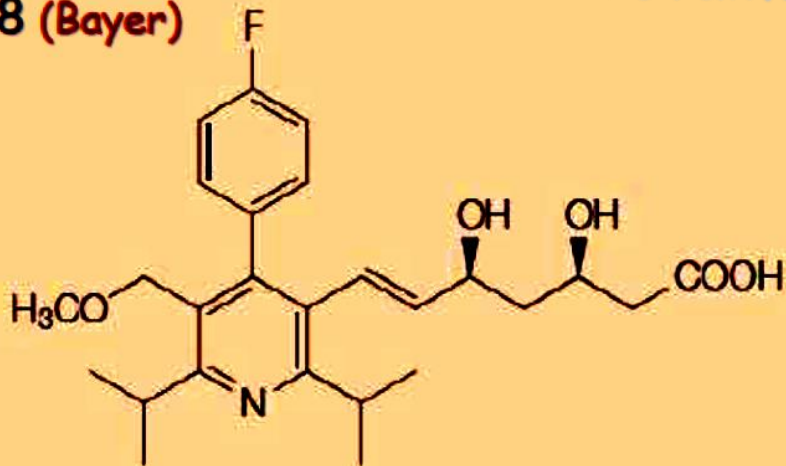


**Atorvastatin (Lipitor®)**

Totamente sintetici

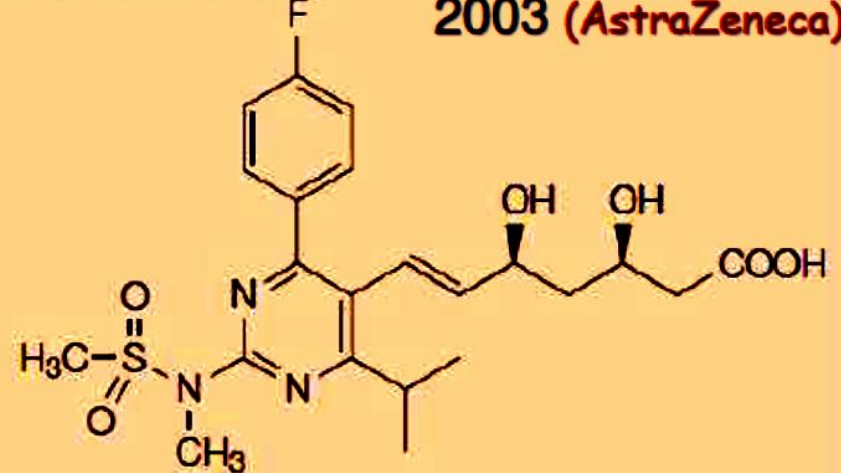
1998 (Bayer)

2003 (AstraZeneca)



**Cerivastatin (Lipobay®)**

miopatia, rabdomiolisi ritiro 2001

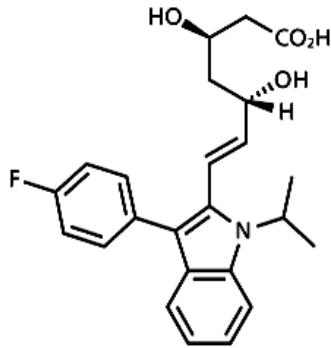


**Rosuvastatin (Crestor®)**

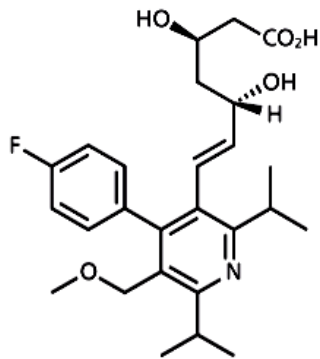
substrati CYP 3A4



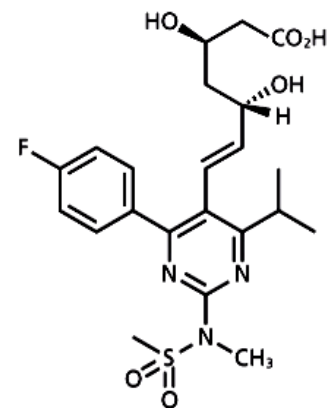
# Statine di tipo II



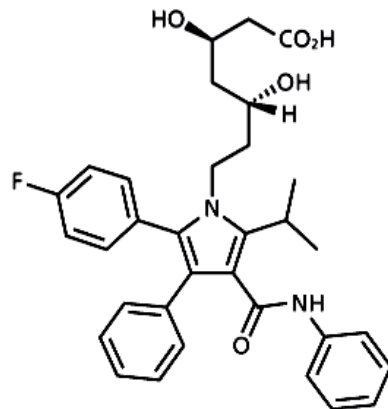
**Fluvastatina**  
(IC<sub>50</sub> 28nM)



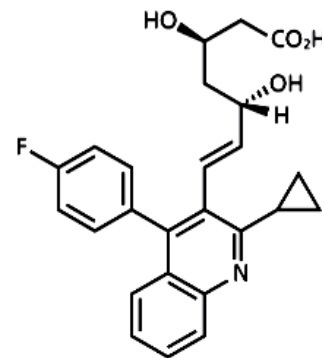
**Cerivastatina**  
(IC<sub>50</sub> 10nM)



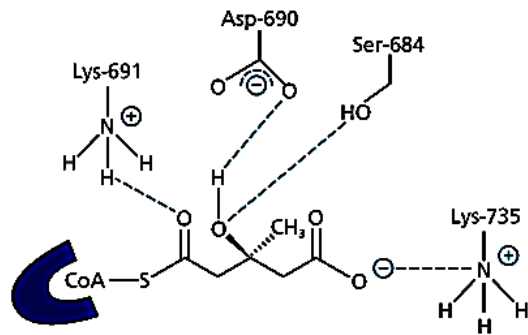
**Rosuvastatina**  
(IC<sub>50</sub> 5nM)



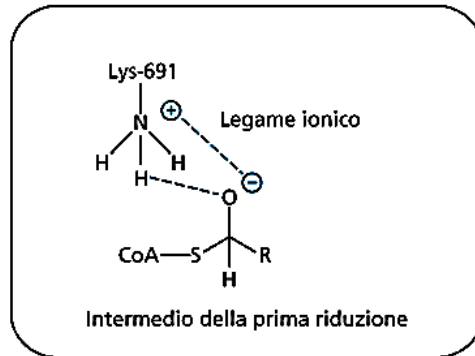
**Atorvastatina**  
(IC<sub>50</sub> 28nM)



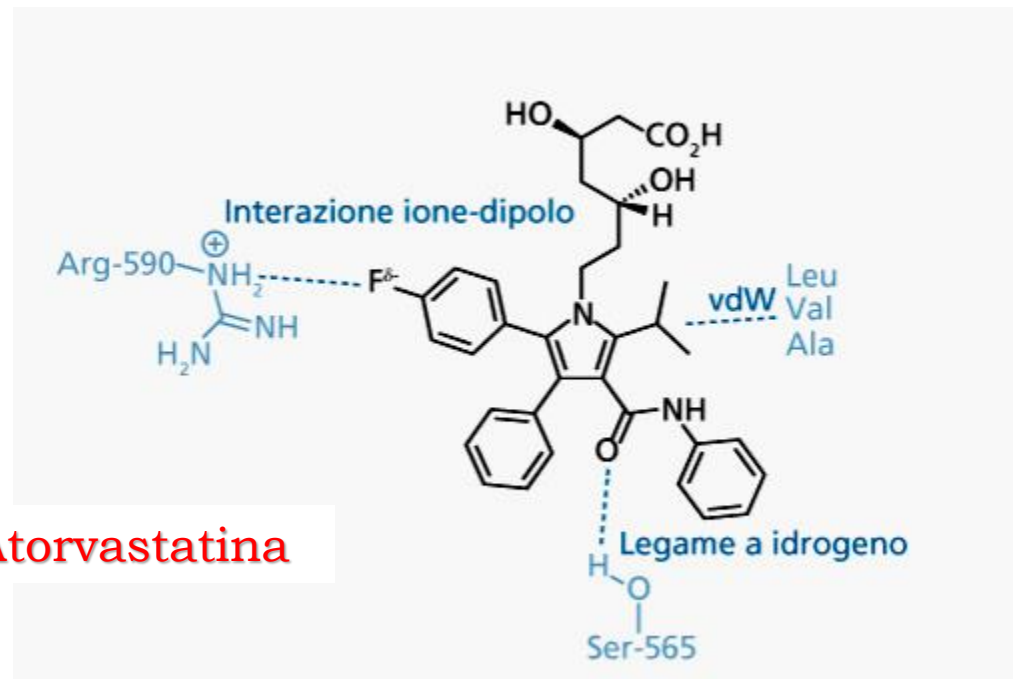
**Pitavastatina**  
(IC<sub>50</sub> 28nM)

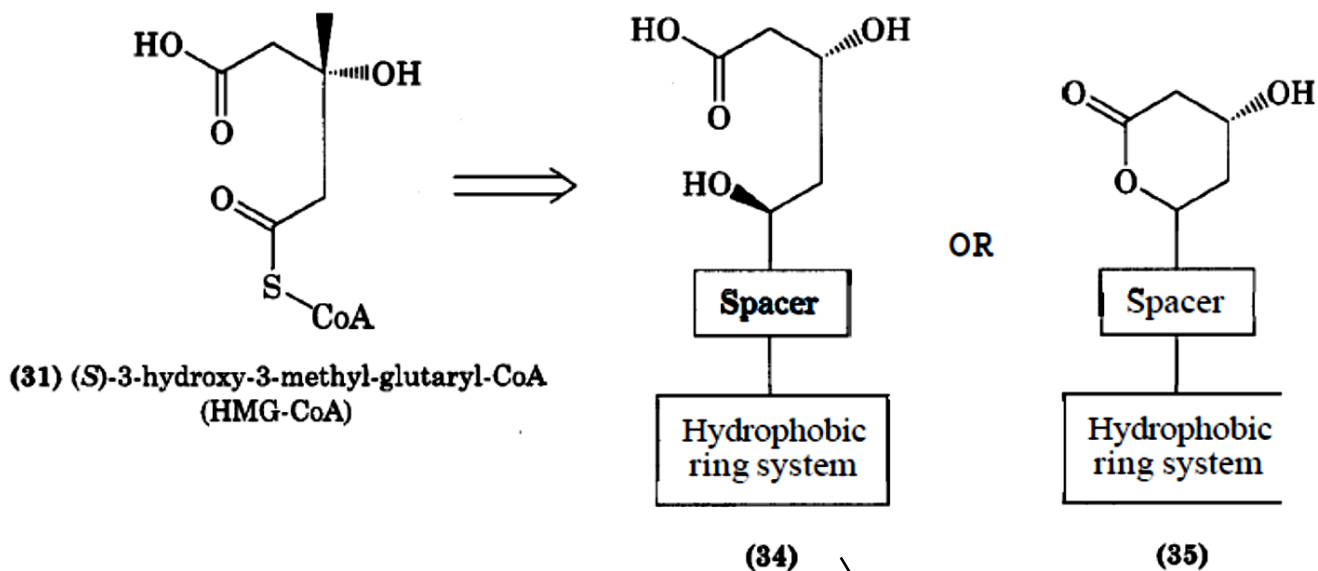


Stretta tasca idrofobica



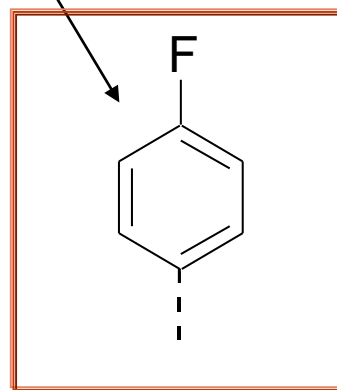
**FIGURA 39.4** Interazioni di legame del 3-idrossi-3-metilglutaril-coenzima A (HMG-CoA) e dell'intermedio della prima riduzione.





**Table 7.7 Enzyme Activity of Selected HMG-CoA Reductase Inhibitors**

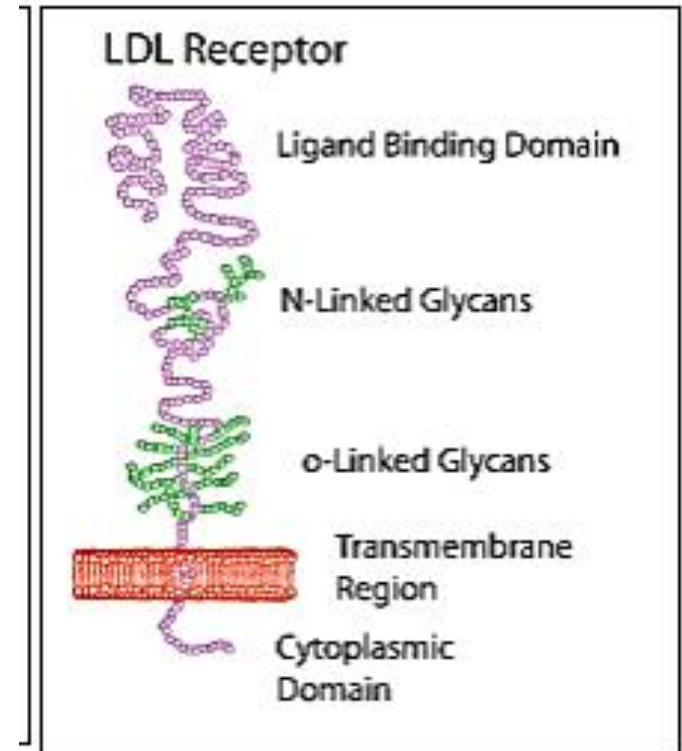
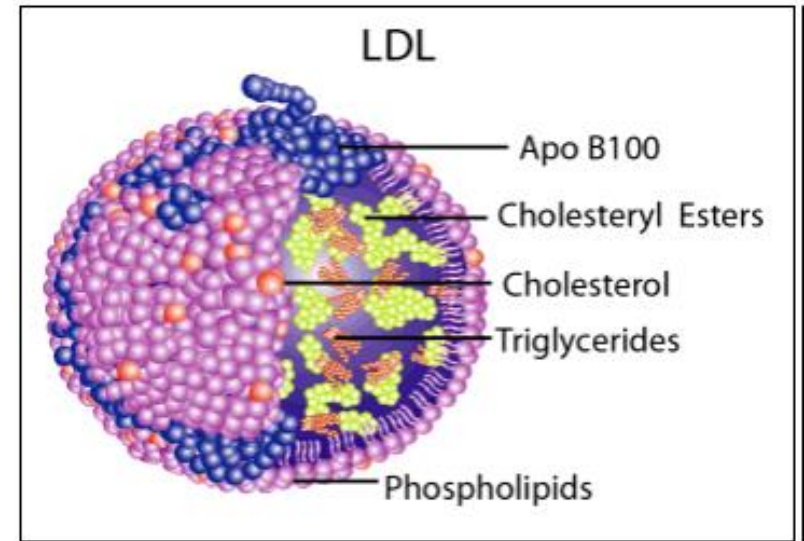
Statin	Potency on Enzyme $IC_{50}$ (nM) <sup>a</sup>
Pravastatin (3)	44
Simvastatin (4)	11
Fluvastatin (5)	28
Atorvastatin (6)	8
Rosuvastatin (7)	5
Cerivastatin (8)	10
Pitavastatin (9)	7



Michael Brown and Joseph Leonard Goldstein (Nobel Prize in 1985).

**Sovraregolazione Recettori LDL responsabili della rimozione il colesterolo dal sangue.**

- LDL: principale trasportatore del colesterolo (+esteri), >50% lipoproteine plasmatiche.
- LDL: assorbito dal fegato ed altri tessuti via endocitosi mediata da specifici recettori.
- Recettori LDL: il dominio citoplasmatico facilita la formazioni di regioni membranali particolarmente dense. Il dominio di binding riconosce apo-B100 su LDL → vescicole → endocitosi → dissociazione LDL dal recettore (pompe ATP, pH<).
- Idrolisi enzimatica esteri colesterolo (uptake).
- Riciclo recettori.
- **Recettori LDL non sono presenti in numero sufficiente in individui che sviluppano ipercolesterolemia.**
- Reihner → 10 pazienti da colecistomizzare, 20 mg trattamento pre-operatorio: attività HMG-CoA >12volte, recettori LDL >2





## # prescrizioni USA (2015)

<b>Drug Name</b>	<b>Sales</b>
Synthroid (levothyroxina)	21,561,481
Crestor (rosuvastatina)	21,478,776
Ventolin HFA (Salbutamolo)	18,203,939
Nexium (Esomeprazolo)	15,298,228
Advair Diskus (Fluticasone / Salmeterolo)	13,776,325
Lantus Solostar (Insulina Glargine)	10,939,840
Vyvanse (Lisdexamfetamine)	10,413,999
Lyrica (Pregabalin)	10,022,365
Spiriva Handihaler (Tiotropio Bromuro)	9,635,935
Januvia (Sitagliptin)	9,148,946
Abilify (Aripiprazolo)	9,099,978
Symbicort (Budesonide/Formoterol)	8,265,594
Tamiflu (Oseltamivir)	8,025,275
Cialis (Tadalafil)	7,472,719
Viagra (Sildenafil)	7,104,074
Suboxone (Buprenorfina/Naloxone)	6,985,631



## The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials



*Cholesterol Treatment Trialists' (CTT) Collaborators\**

### Summary

**Background** Statins reduce LDL cholesterol and prevent vascular events, but their net effects in people at low risk of vascular events remain uncertain.

*Lancet* 2012; 380: 581-90  
Published Online

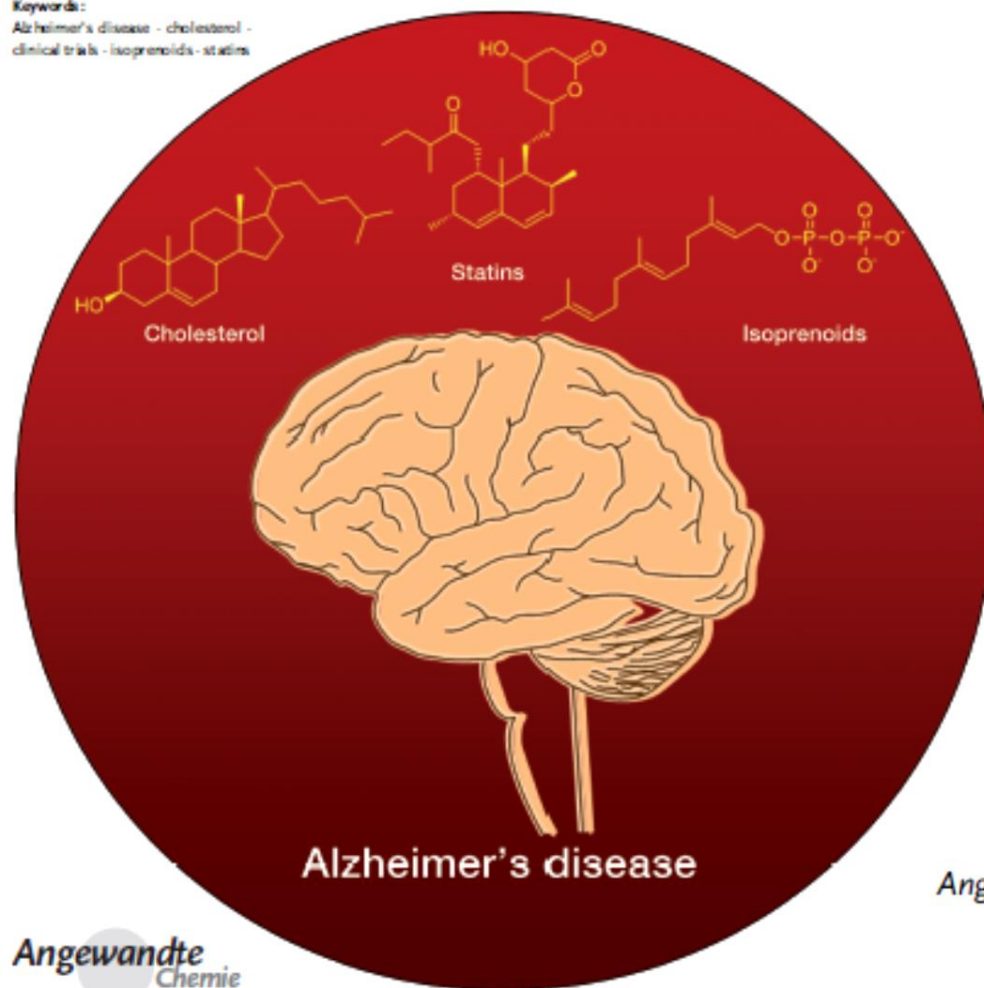
Crestor (**rosuvastatina**)

<http://www.repubblica.it/salute/2016/03/04/news/scomparsi-134727126/?ref=HREC1-4>

# Alzheimer's Disease, Cholesterol, and Statins: The Junctions of Important Metabolic Pathways

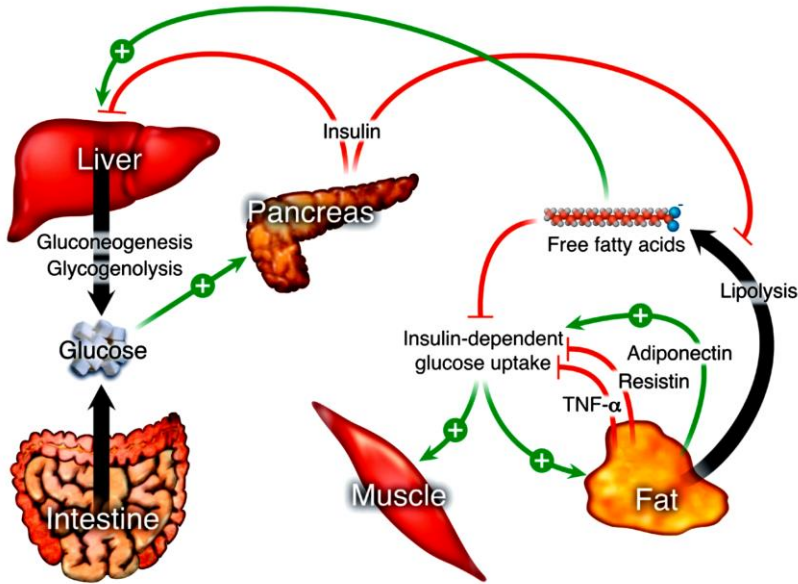
Tiago Silva, José Teixeira, Fernando Remião, and Fernanda Borges\*

Keywords:  
Alzheimer's disease · cholesterol ·  
clinical trials · isoprenoids · statins



Angew. Chem. Int. Ed. 2013, 52, 1110–1121

# Metabolismo ed omeostasi gluco-lipidica: recettori PPAR

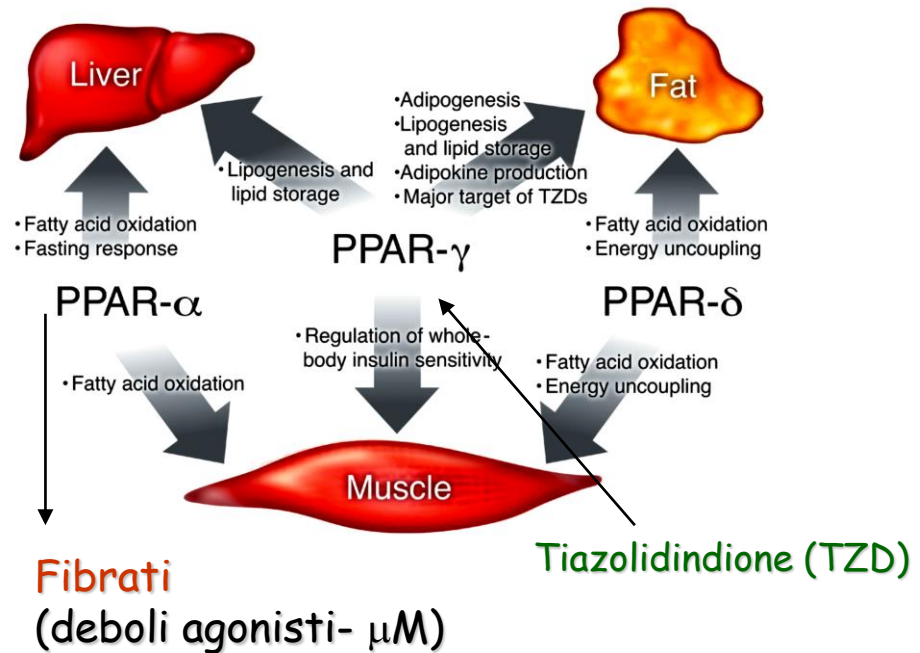


"lipotossicità" → accumulo patologico di TGR e lipidi-CoA nel muscolo e fegato → resistenza insulina;  
 PPAR: organelli che contribuiscono all'ossidazione degli acidi grassi, la loro proliferazione incontrollata può generare epatomegalia e carcinogenesi nei roditori.

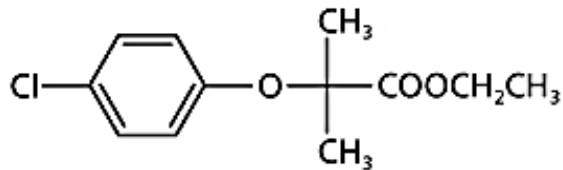
## Acidi grassi (dieta) e metaboliti → 'lipid-sensing' Peroxisome Proliferator-Activated Receptors

controllano una rete di geni target deputati alle attività trascrizionali associate al metabolismo. Attivazione indotta dagli acidi grassi introdotti con la dieta e dai loro metaboliti → sensori lipidici che se attivati possono reindirizzare il metabolismo

[http://www.repubblica.it/salute/2016/09/13/news/usa\\_l\\_industria\\_delle\\_zucchero\\_pago\\_scientiati\\_per\\_mentire-147667151/](http://www.repubblica.it/salute/2016/09/13/news/usa_l_industria_delle_zucchero_pago_scientiati_per_mentire-147667151/)

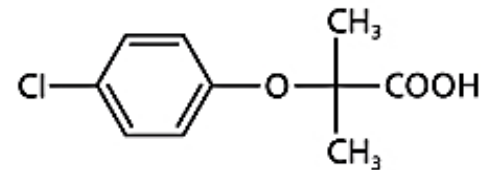
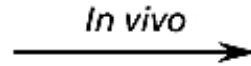


# Fibrati: agonisti recettori PPAR $\alpha$ (EC<sub>50</sub> $\mu$ M)

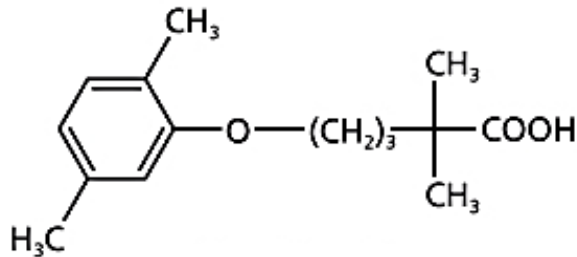


**clofibrato**

etil 2-(4-clorofenossi)-2-metilpropanoato



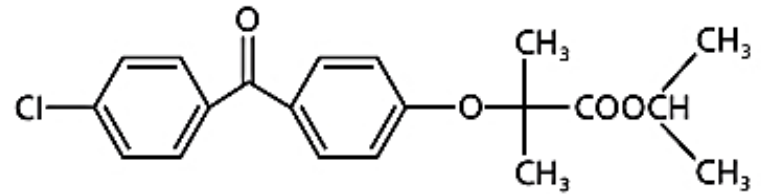
**acido clofibrico**



**gemfibrozil**

acido 5-(2,5-dimetilfenossi)-  
2,2-dimetilpentanoico

(*Genlip, Lopid*)



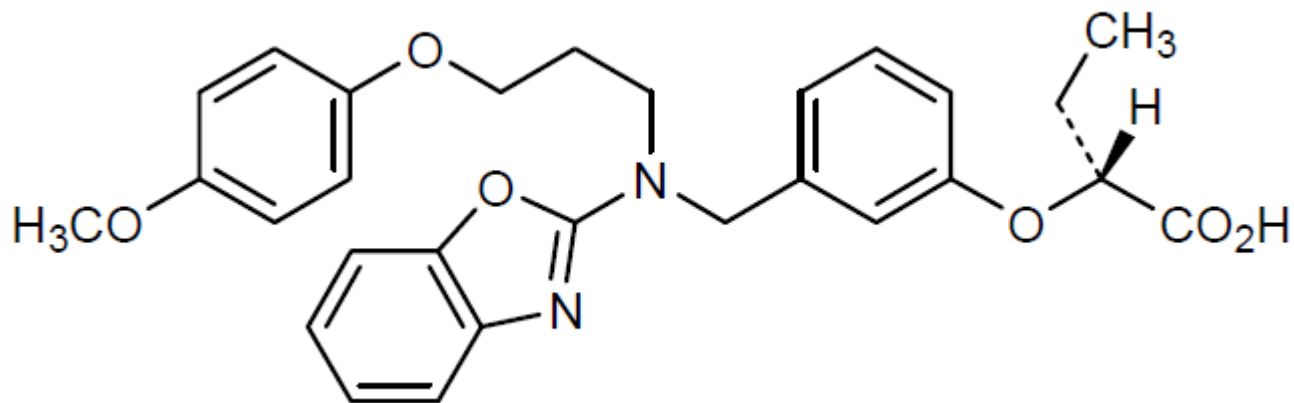
**fenofibrato**

Efficacia limitata da effetti avversi ( $\gg$  aminotransferasi, creatinina, omocisteina)



# Pemafibrato (fase II)

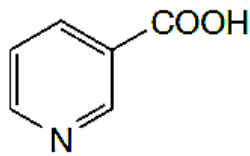
Modulatore PPAR $\alpha$



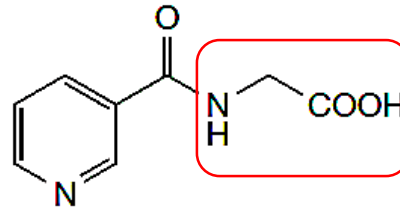
Acido (2R)-2-[3-(((1,3-benzoxazol-2-yl)[3-(4-metossifenossi)propil]ammino}metil) fenossi]butanoico

New Era of Lipid-Lowering Drugs. Pharmacol Rev 68:458–475, April 2016

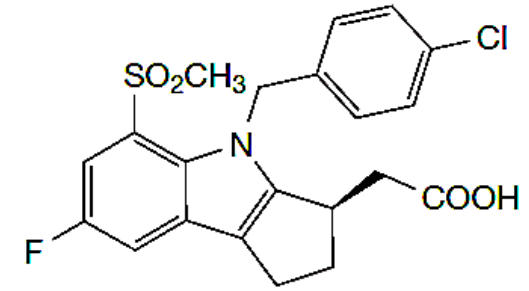
*Pelzont*



Acido nicotinico



Acido nicotinurico  
(metabolita)



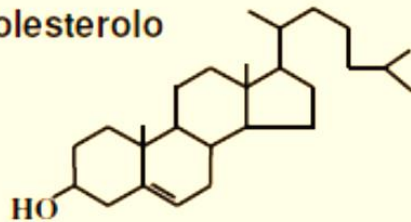
Laropiprant

**Figura 20.13** Struttura dell'acido nicotinico, del prodotto di coniugazione con la glicina (acido nicotinurico) e del laropiprant, antagonista selettivo del recettore delle prostaglandine PGD<sub>2</sub>.

- riduzione dei livelli ematici di colesterolo in modo indipendente dall'attività vitaminica (nicotinammide, niacina, vitamina PP/B<sub>3</sub>);
- aumento dei livelli plasmatici di colesterolo HDL, riduzione dei trigliceridi e del colesterolo LDL;
- parziale inibizione lipolisi tessuto adiposo e conseguente diminuzione dell'afflusso di FFA al fegato (< LDL);
- attivazione recettore HCA2 (hydroxycarboxylic acid, GPCR) → Pelzont  
< cAMP < PKA (proteina chinasi A o proteina chinasi dipendente dal cAMP)  
< lipolisi;
- associazione acido nicotinico-statine elevata complementarità;
- Elevata incidenza effetti collaterali: vampate calore (PGD<sub>2</sub>), prurito, intolleranza gastrointestinale, iperglicemia, iperuricemia.

# MECCANISMO D'AZIONE DELLE RESINE

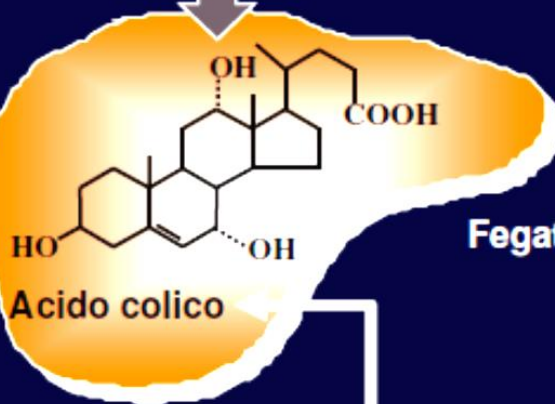
Colesterolo



Sottraendo acidi biliari al circolo enteroepatico, favoriscono il catabolismo del c.

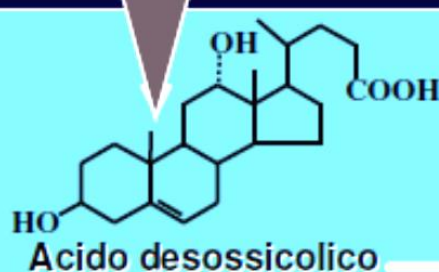
Utilizzate anche per trattare la diarrea provocata da anomalie della digestione e dell'assorbimento dei grassi in malattie come il morbo di Crohn.

Fegato



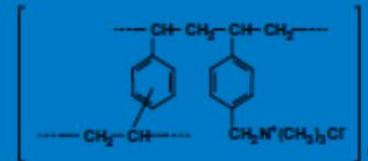
Acido colico

Intestino

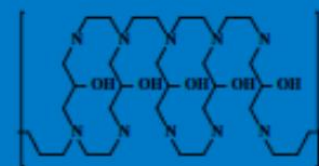


Acido desossicolico

Escrezione



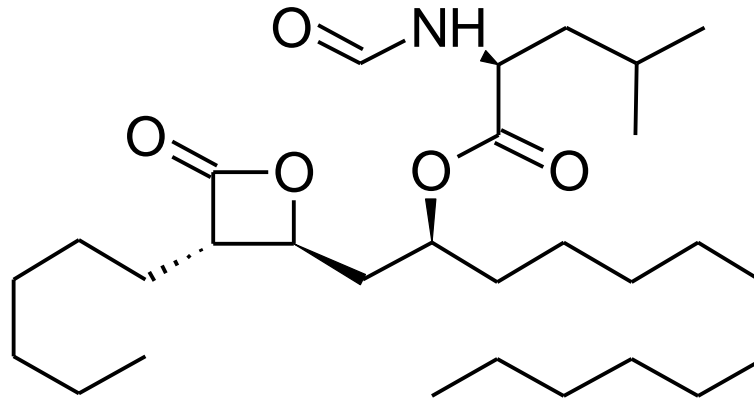
Colestiramina



Colestipol

# Orlistat

*(Xenical)*



Primo inibitore lipasi gastrointestinale (FDA 1999) per il trattamento dell'obesità:

- Efficacia a lungo termine (anni);
- Effetto antiipertensivo, << resistenza insulina, livello serico dei lipidi;
- Effetti indesiderati: diarrea, flatulenza, gonfiore e dolore addominale, dispepsia;

- Niemann-Pick C1-like 1 (NPC1L1) proteina trans membrana (versante luminale degli enterociti) responsabile dell'assorbimento della maggior aliquota di colesterolo nell'intestino tenue.

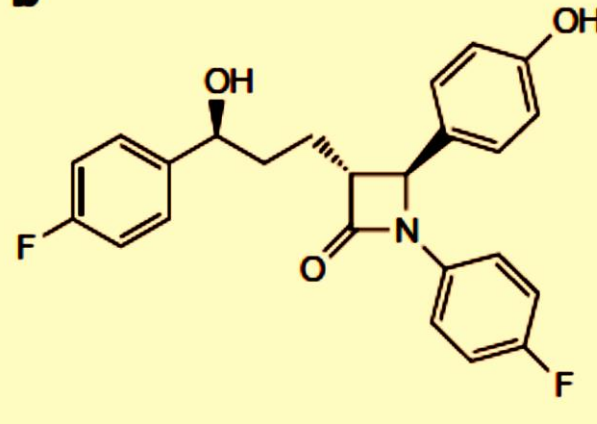
- **Ezetimibe**, si lega a NPC1L1 bloccando l'assorbimento del C.;

- Il C. promuove specificatamente l'internalizzazione di NPC1L1 con microfilamenti e un complesso clatrina/AP2;

- Il blocco dell'endocitosi NPC1L1 riduce significativamente l'internalizzazione del colesterolo.

- **Ezetimibe** previene l'inclusione di NPC1L1 in vescicole clatriniche

**b**



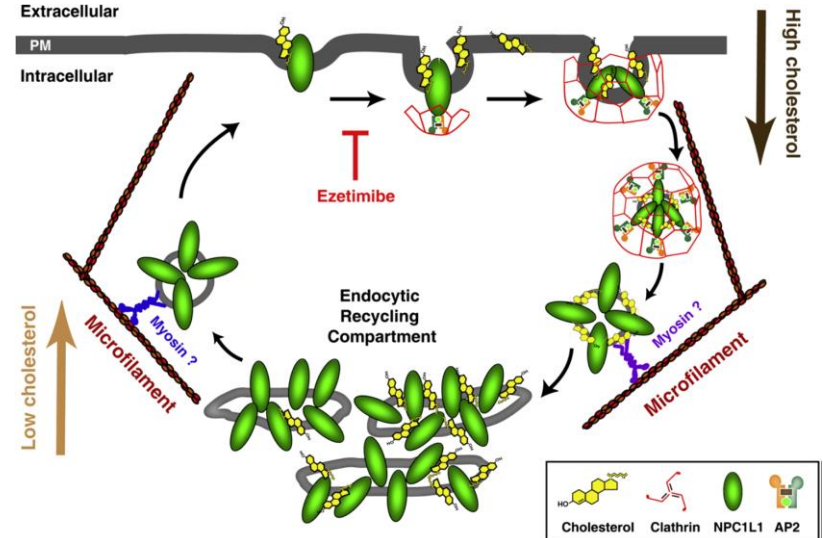
**Ezetimibe**  
 approvato FDA  
 Ottobre 2002

*(Ezestrol)*

**Ezetimibe (SCH 58235)**

1-(4-fluorophenyl)-(3*R*)-[3-(4-fluorophenyl)-(3*S*)-hydroxypropyl]-(4*S*)-(4-hydroxyphenyl)-2-azetidinone

$C_{24}H_{21}F_2NO_3$  CAS registry number: 163222-33-1



Cholesterol	Clathrin	NPC1L1	AP2



**Kynamro** (*mipomersen sodium*)

**Company:** Genzyme

**Approval Status:** **Approvato gennaio 2013;**

**Treatment Area:** ipercolesterolemia familiare omozigote

G\*-C\*-C\*-U\*-C\*-dA-dG-dT-dC-dT-dG-dmC-dT-dT-dmC-G\*-C\*-A\*-C\*-C\*

[d = 2'-deoxy, \* = 2'-O-(2-methoxyethyl)]

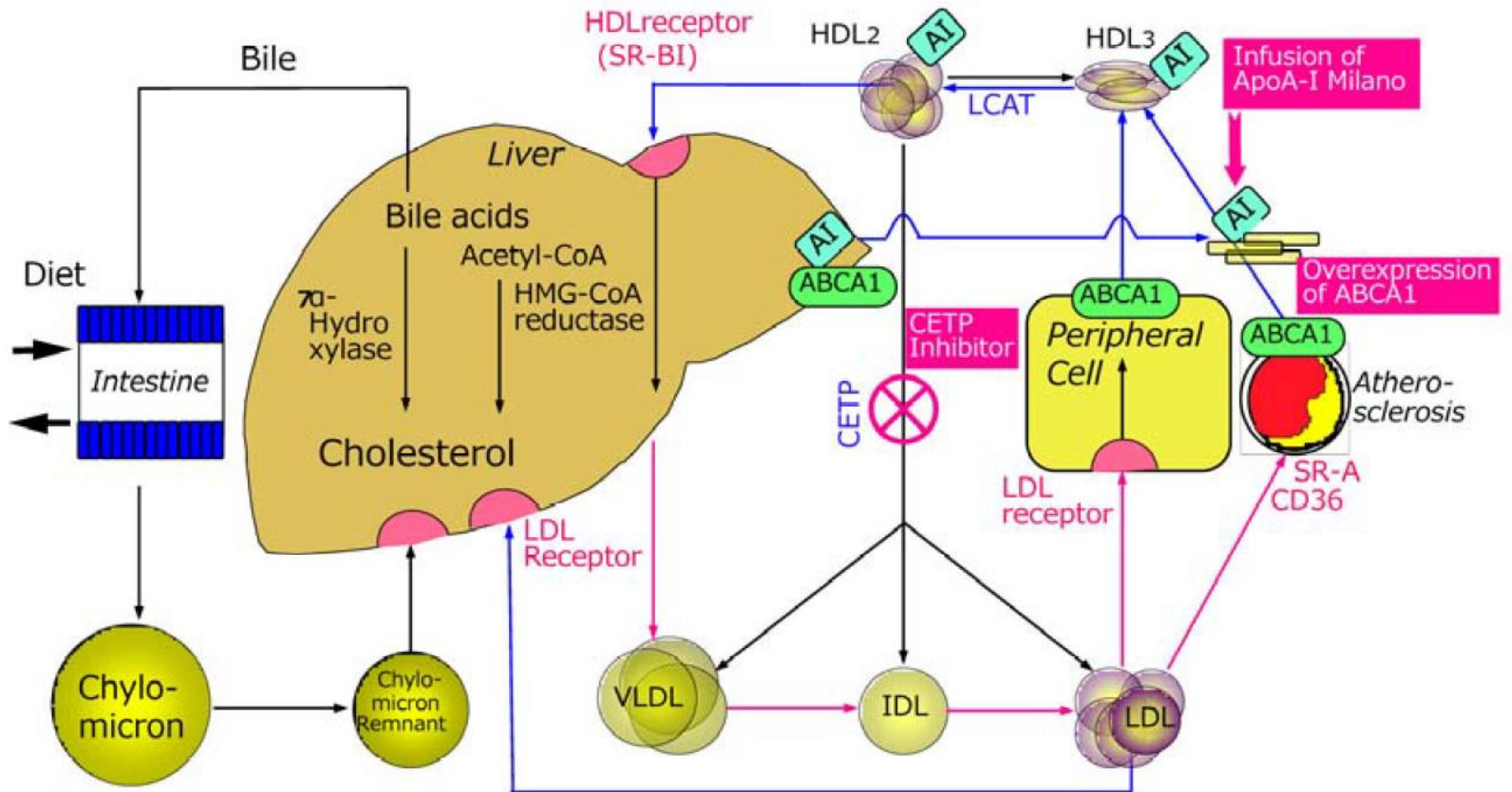
**Oligonucleotide antisense**

**Kynamro (mipomersen sodico)** inibisce la sintesi di ApoB-100, cruciale nella produzione di LDL. La conseguente riduzione di LDL-C previene la formazione di lipoproteine aterogeniche.

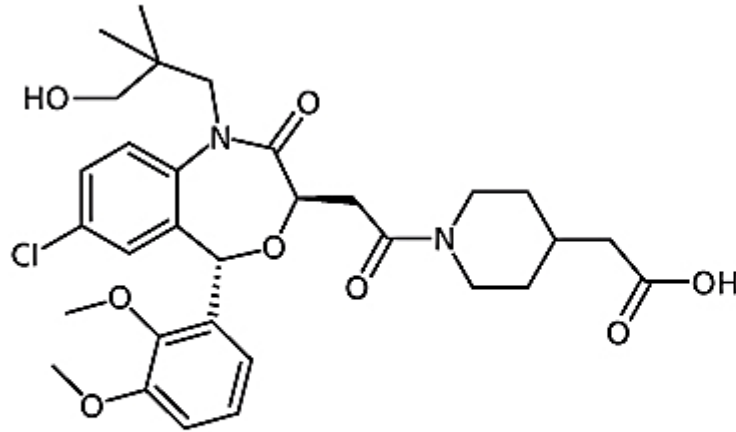
**Kynamro** è indicato in associazione ad altri ipolipidemici ed una specifica dieta per ridurre LDL-C, ApoB, colesterolo totale e lipoproteina-colesterolo ad non-alta densità (non-HDL-C) in pazienti con ipercolesterolemia omozigote familiare (HoFH).

(iniezioni sottocutanee 200 mg una volta settimana)

Cholesteryl ester transfer protein (CETP) mediates the exchange of cholesteryl ester for triglycerides between HDL and VLDL and LDL

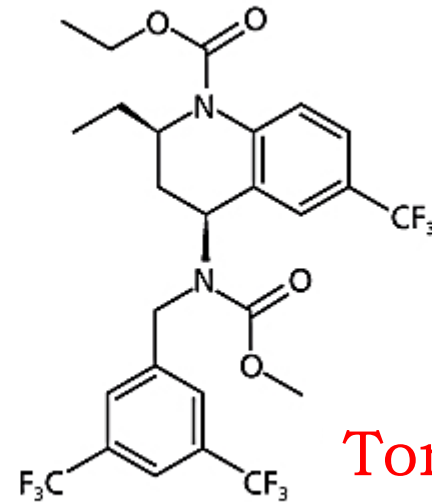


## Squalene synthase inhibitor



Lapaquistat

## Cholesteryl Ester Transfer Protein Inhibitors



Torcetrapib

**FIGURA 39.7** Nuove molecole oggetto di studio come ipolipidemizzanti.

**TABLE 1**

Effects of CETP inhibitors on plasma lipids and lipoproteins

Data are given as the effect on concentration with percentages in parentheses.

CETP Inhibitor	HDL-C	ApoA-I	LDL-C	ApoB	Lp(a)
Torcetrapib	Increase (72)	Increase (25)	Decrease (24)	Decrease (13)	Not available
Dalcetrapib	Increase (30)	Increase (10)	No change	No change	Not available
Anacetrapib	Increase (140)	Increase (45)	Decrease (30)	Decrease (21)	Decrease (39)
Evacetrapib	Increase (130)	Increase (40)	Decrease (30)	Decrease (25)	Not available
TA-8995	Increase (180)	Increase (60)	Decrease (45)	Decrease (35)	Decrease (35)

# Evolocumab

(*Repatha*)

PCSK9 (proprotein convertase subtilisin/kexin type 9): proteasi epatica che attacca e internalizza i LDLR in lisosomi, promuovendone la degradazione.

