ACCADEMIA di ALTA FORMAZIONE CLINICA per MEDICI del TERRITORIO

Meccanismi d'azione, potenza, associabilità, effetti collaterali dei farmaci tradizionali per le dislipidemie primarie

Prof Alberto Corsini
Università degli Studi di Milano

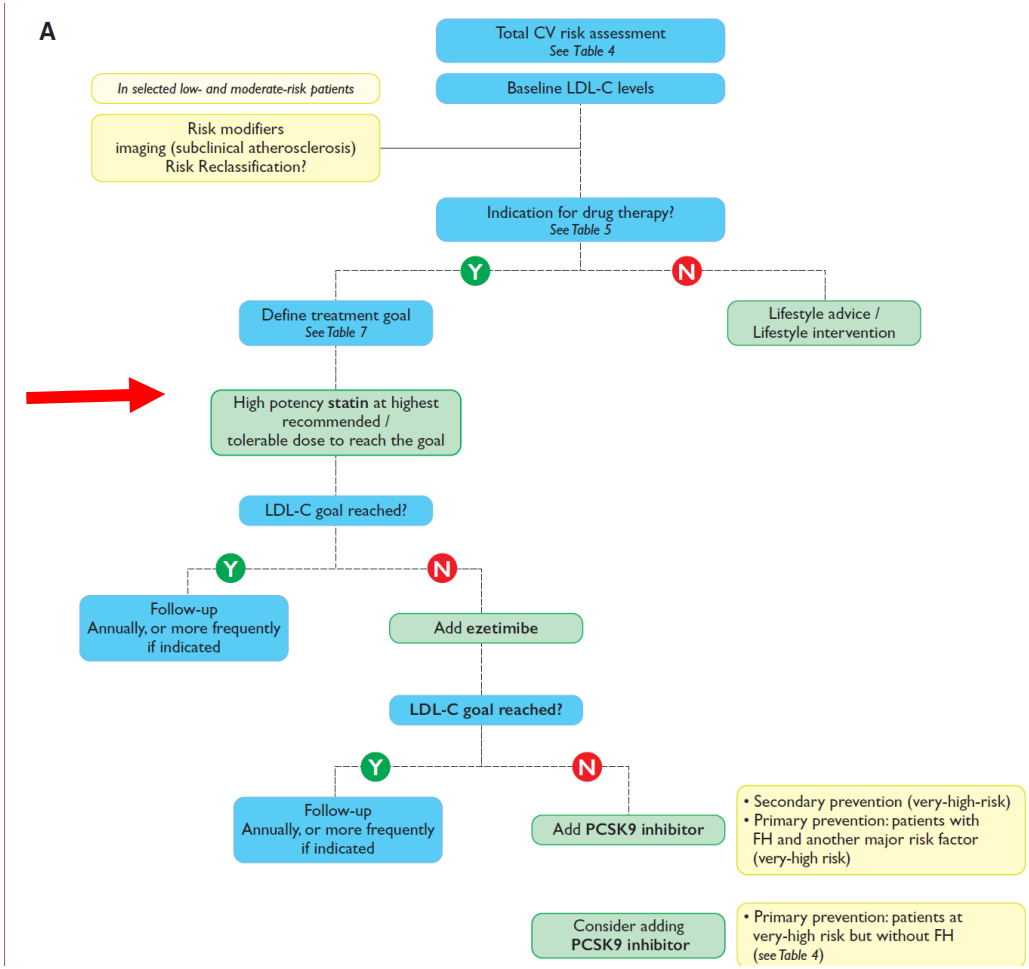
- **Farmaci ipocolesterolemizzanti**

- Farmaci ipotrigliceridemizzanti

Farmaci ipocolesterolemizzanti dalle molecole di sintesi ai farmaci biologici

- **Statine**
- Terapia di combinazione
- Farmaci biologici
- La terapia genica

Algoritmo del trattamento farmacologico per ridurre le LDL-C



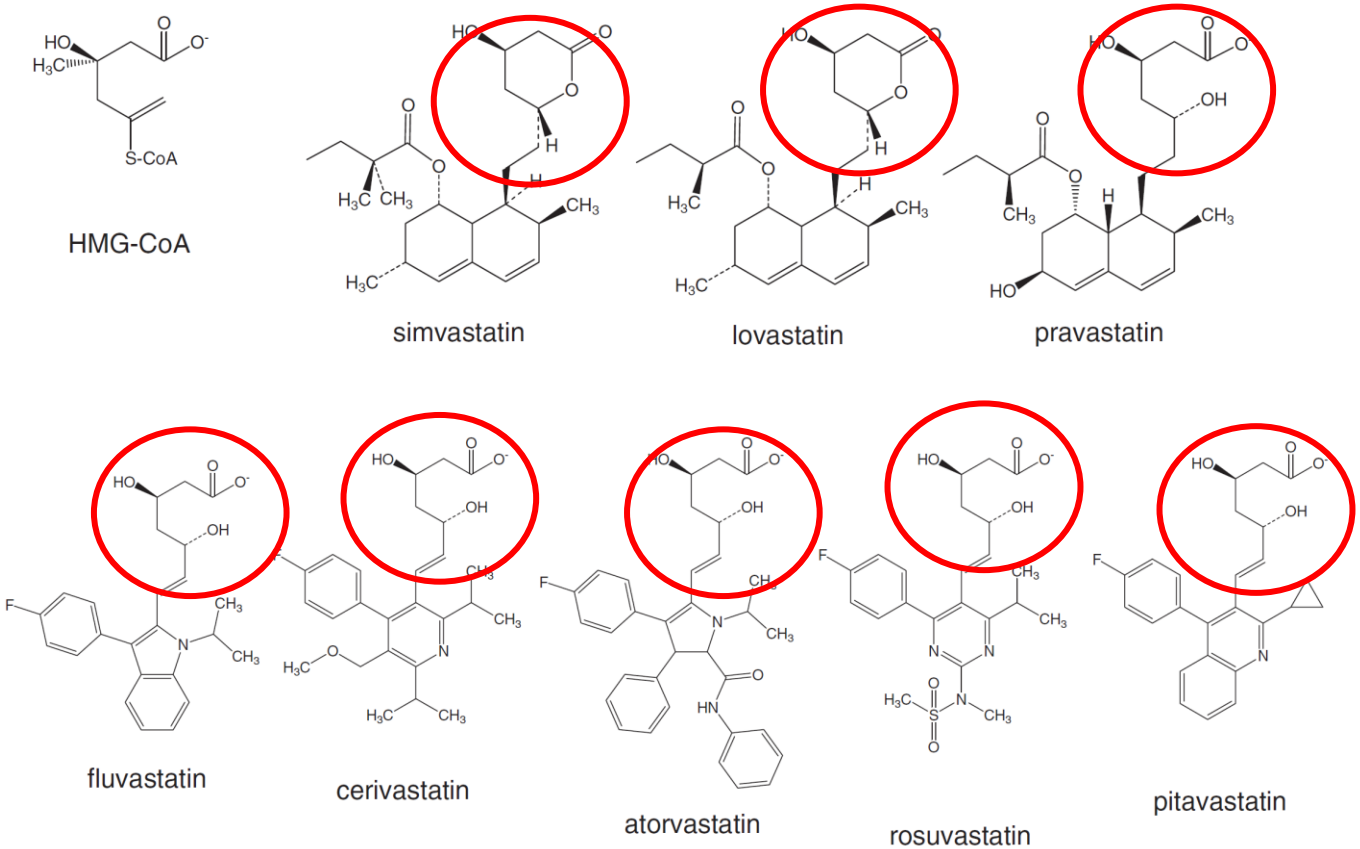
Eur Heart J. 2020 41: 111-188

Effetti dei farmaci per le dislipidemie

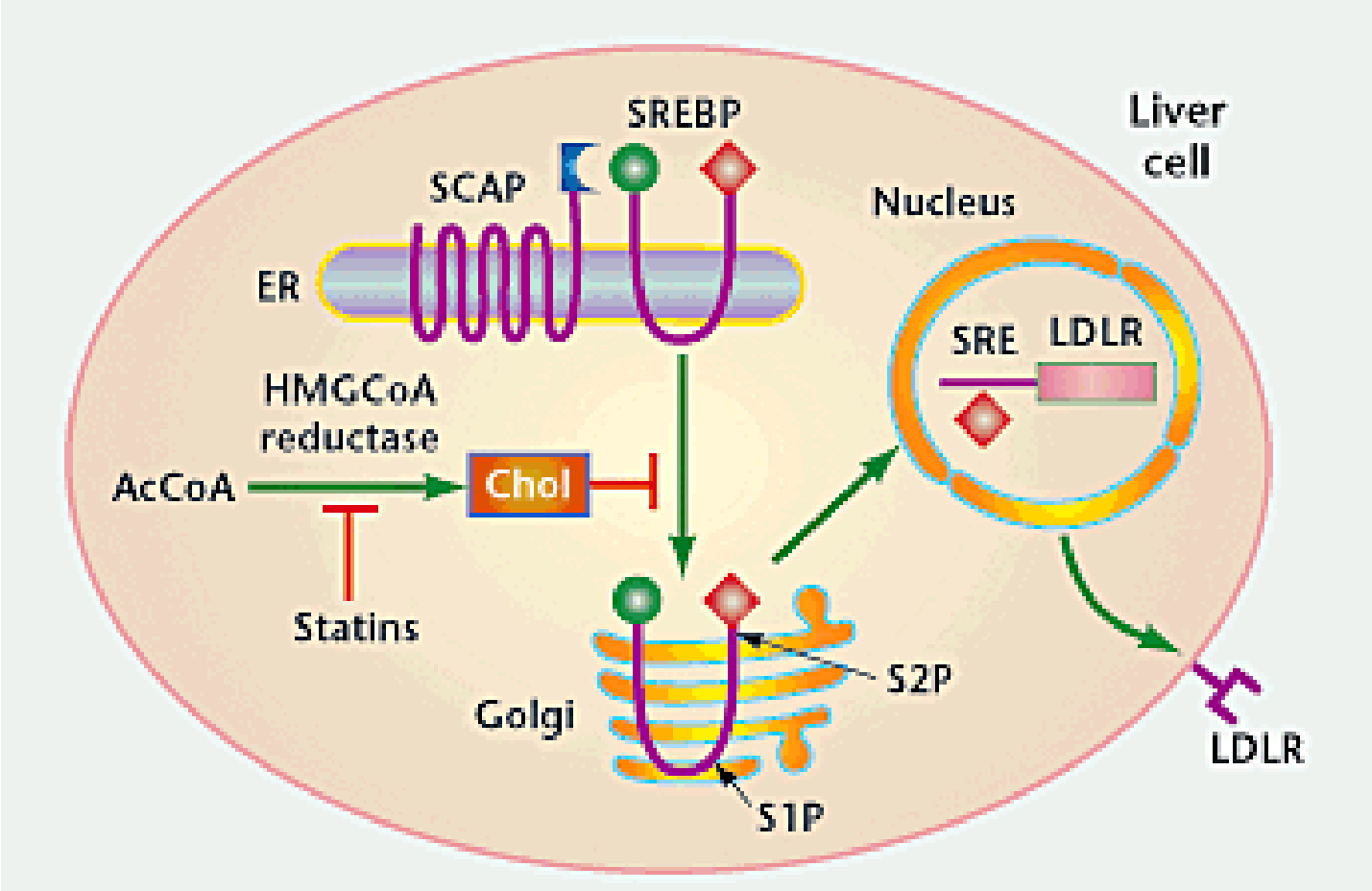
	Effect on LDL cholesterol	Effect on triglycerides and cholesterol remnants	Effect on lipoprotein(a)	Cardiovascular benefit	Ongoing studies
Antisense and mAbs to ANGPTL3	Moderate decrease	Strong decrease	Neutral	No	NCT02709850 (phase 2), phase 3 trials*
Antisense, mAbs, and siRNA to apolipoprotein C3	Neutral	Strong decrease	Neutral	No	NCT03385239 (phase 2), NCT03783377 (phase 1)
Antisense to apolipoprotein(a)	Neutral	Neutral	Strong decrease	No	NCT03070782 (phase 2)
Bempedoic acid	Moderate decrease	Neutral	Neutral	No	NCT02993406 (phase 3 CVOT)
Bile acid sequestrants	Moderate decrease	Mild decrease	Neutral	No†	No
CETP inhibitors	Moderate decrease	Neutral	Mild decrease	Yes‡	No
Ezetimibe	Moderate decrease	Neutral	Minimal increase	Yes	No
Fibrates: SPPARMs	Neutral	Moderate decrease	Neutral	No†§	NCT03071692 (phase 3 CVOT)
Fish oils: EPA	Neutral	Moderate decrease	Neutral	Yes	No
Fish oils: EPA and DHA	Neutral	Moderate decrease	Neutral	No	NCT02104817 (phase 3 CVOT)
Inclisiran	Strong decrease	Mild decrease	Mild decrease	No	NCT03814187 (phase 3 CVOT)
Lomitapide	Moderate decrease	Mild decrease	Mild decrease	No	No¶
Anti-PCSK9 mAbs	Strong decrease	Mild decrease	Mild decrease	Yes	No
Mipomersen	Moderate decrease	Mild decrease	Mild decrease	No	No¶
Nicotinic acid	Mild decrease	Mild decrease	Mild decrease	No‖	No
Statins	Strong decrease	Mild decrease	Minimal increase	Yes	No

Ray KK et al Lancet 2019; 394: 697–708

Struttura chimica delle statine e di HMG-CoA



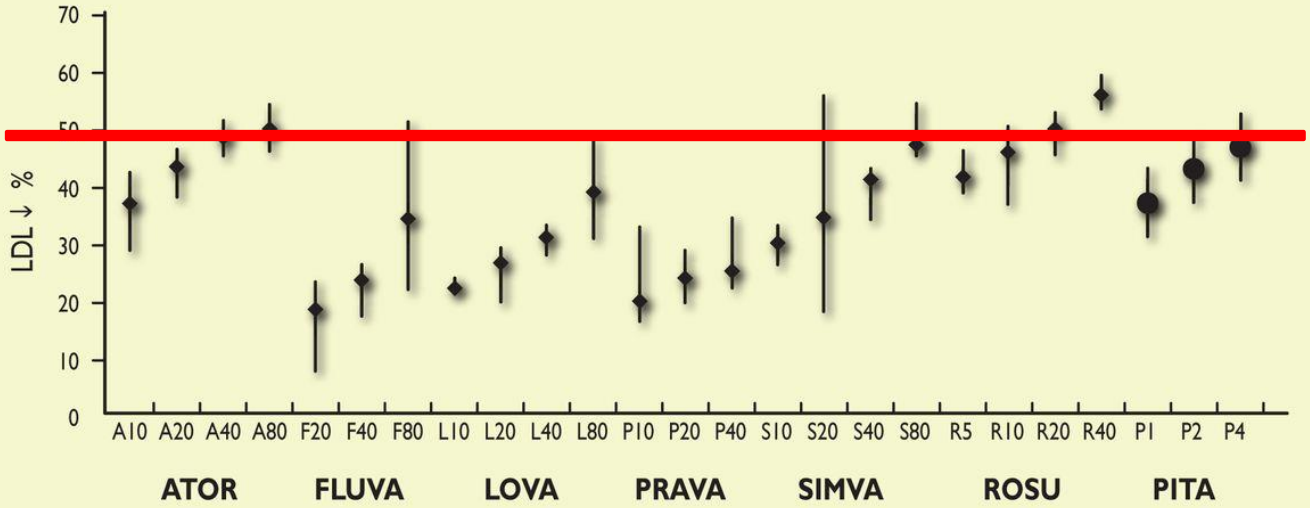
Shitara Y and Sugiyama Y Phar Ther 2006; 112:71-106



Modified from D. Rader Nat Med 2001, 7: 1282-1284

Revisione sistematica e meta-analisi dell'equivalenza terapeutica delle statine

European Heart Journal

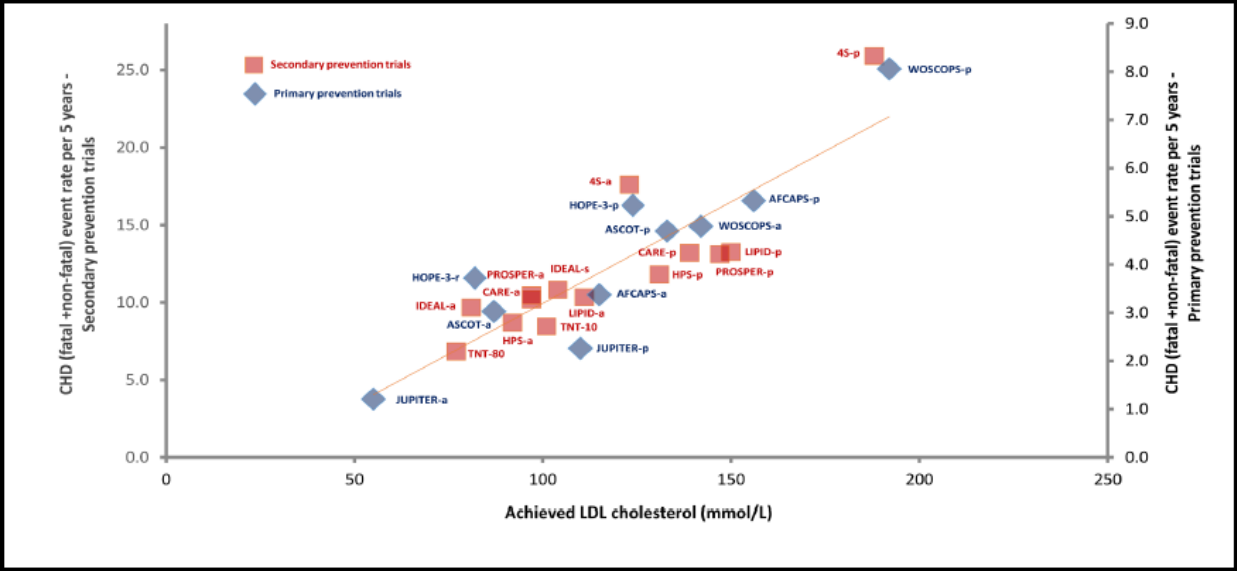


Weng TC, *et al. J Clin Pharm Ther* . 2010;35:139-151
Mukhtar RY, *et Al. Int J Clin Pract* . 2055;59(2):239-252

Alberico L. Catapano et al. Eur Heart J 2016

Randomized Controlled Trials

Absolute yearly event rate on LDL-lowering treatment was strongly and linearly associated with the absolute achieved LDL-C level

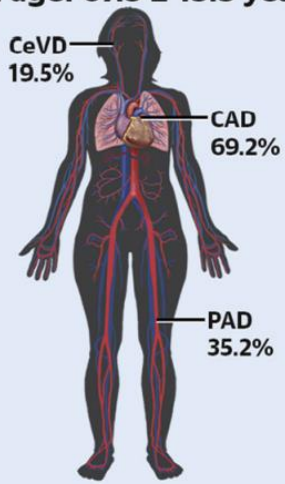


European Heart Journal. doi:10.1093/eurheartj/ehx144.

CENTRAL ILLUSTRATION **Statin Use in 601,934 Patients With Atherosclerotic Cardiovascular Disease on January 31, 2019**

Study Population

601,934 patients with ASCVD
Mean age: 67.5 ± 13.3 years



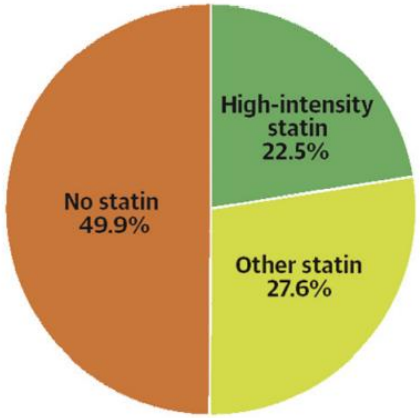
Outcomes

Statin usage on January 31, 2019 ± 30 days

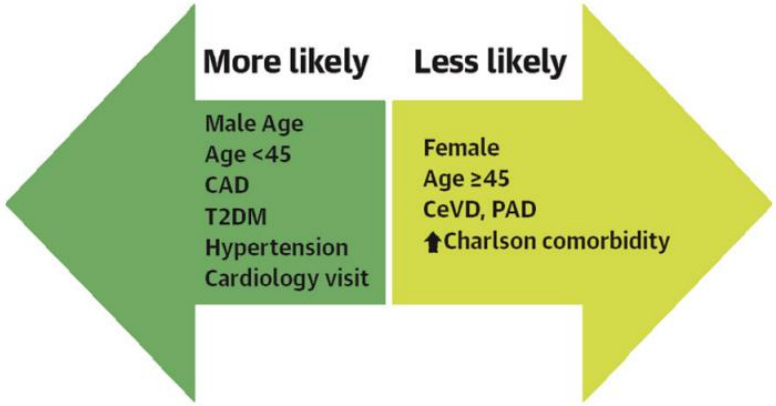
Proportion of days covered

Results

Proportion on high-intensity statin vs other statin vs no statin



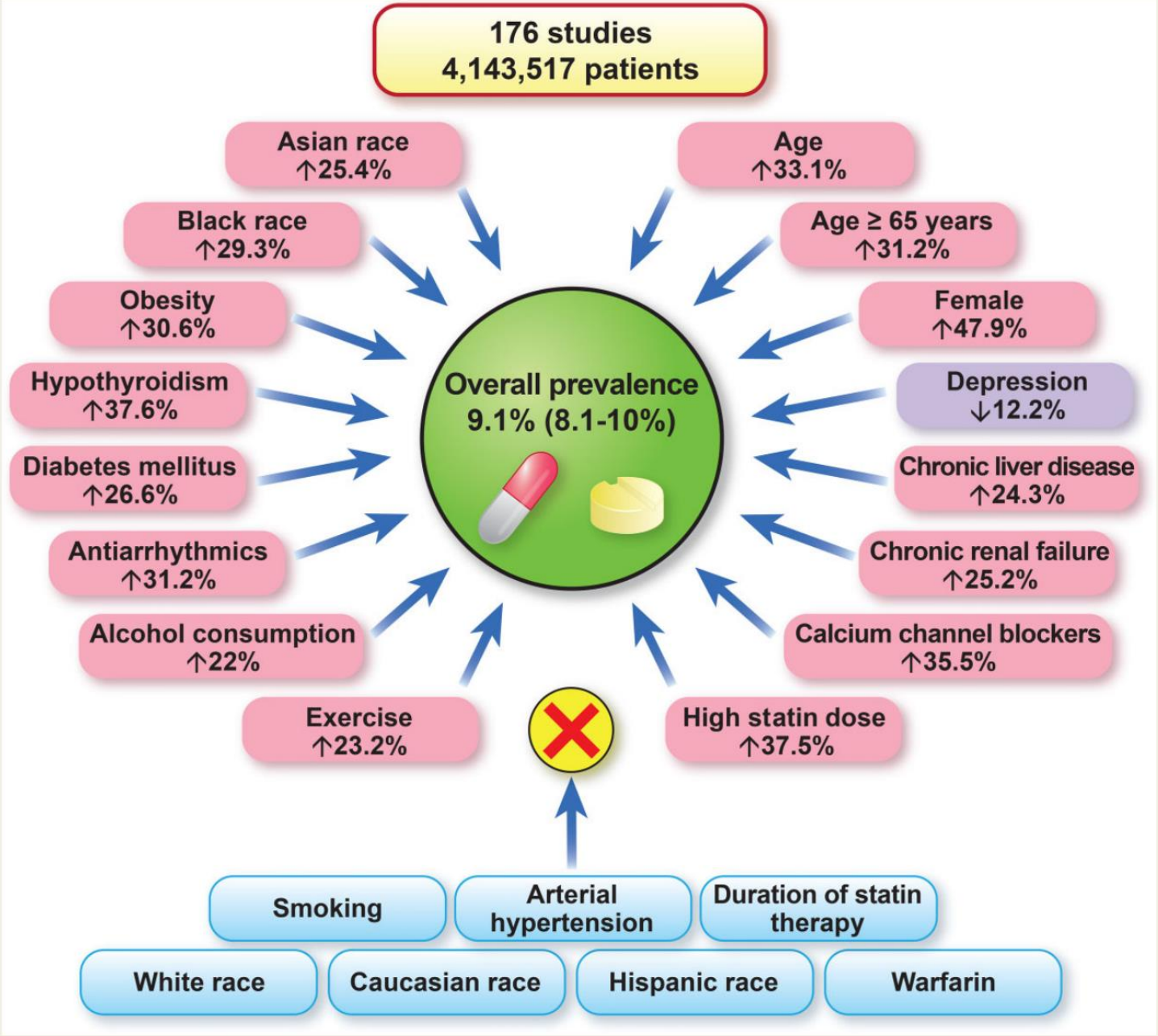
Odds of high (vs other) intensity statin use



Proportion of days covered

Nelson AJ, et al. J Am Coll Cardiol. 2022;79(18):1802-1813.

Proportion on high-intensity statin vs other statin vs no statin. Odds of high- (vs other) intensity statin use. Proportion of days covered among users of high-intensity statins. ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CeVD = cerebrovascular disease; PAD = peripheral artery disease; T2DM = type 2 diabetes mellitus.



Structured Graphical Abstract The worldwide prevalence of statin intolerance and risk factors/conditions that effect or do not effect the risk of statin intolerance.

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ESC European Society of Cardiology

Cardiovascular Research (2022) **00**, 1–17
https://doi.org/10.1093/cvr/cvac020

INVITED REVIEW

Side effects of statins: from pathophysiology and epidemiology to diagnostic and therapeutic implications

Massimiliano Ruscica[1], Nicola Ferri[2], Maciej Banach[3,4], Cesare R. Sirtori[1], and
AQ1 **Alberto Corsini[1]***

[1]Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Via Balzaretti 9, 20133 Milan, Italy; [2]Department of Pharmaceutical and Pharmacological Sciences, Universita degli Studi di Padova, Padova, Italy; [3]Department of Hypertension, Medical University of Lodz (MUL), Lodz, Poland; and [4]Cardiovascular Research Centre, University
AQ2 of Zielona Gora, Zielona Gora, Poland

Received 10 November 2021; editorial decision 8 February 2022

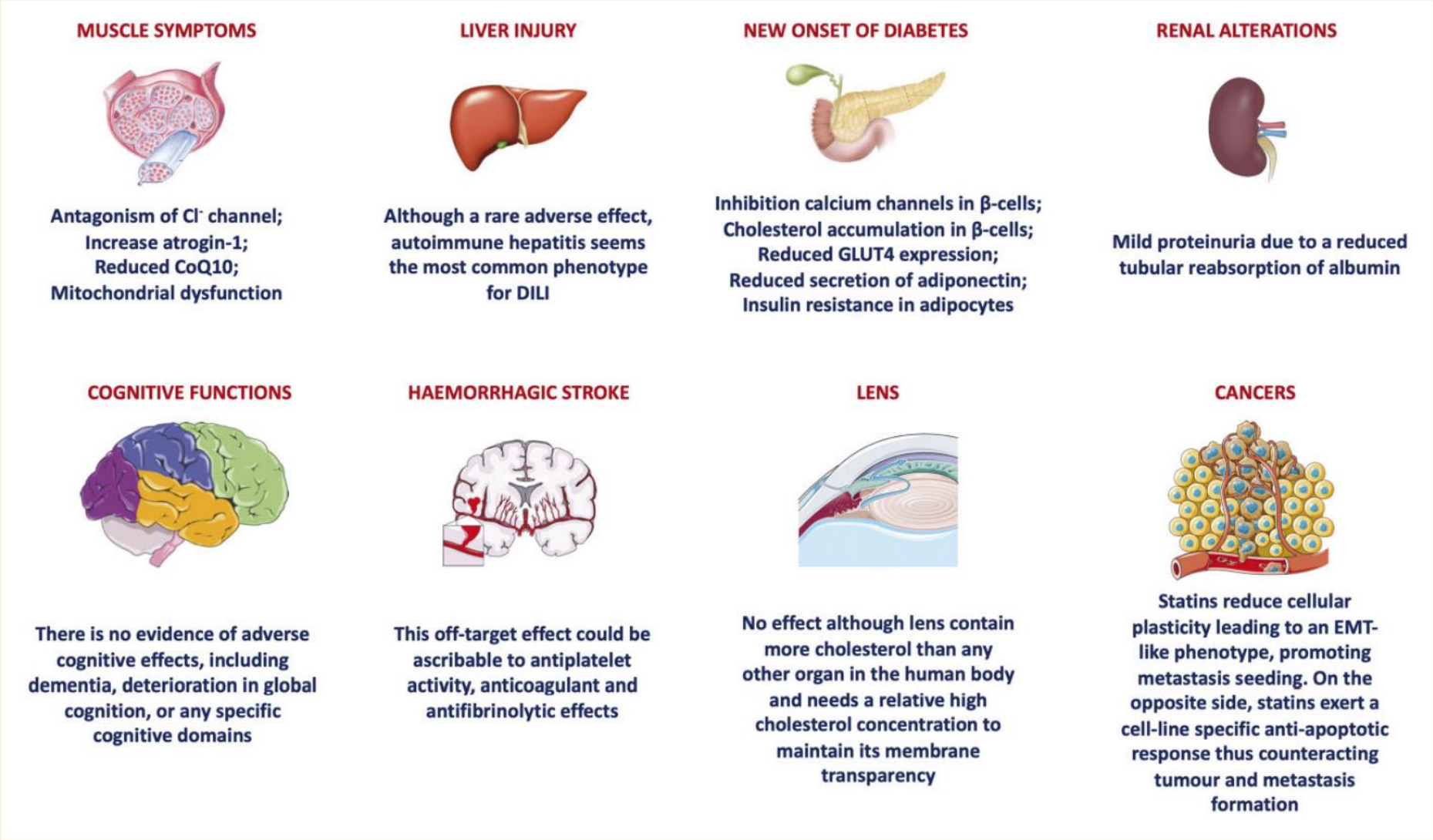


Figure 1 Summary of statin-associated adverse effects. DILI, drug-induced liver injury; EMT, epithelia-to-mesenchymal transition; GLUT-4, glucose transport-4. Some images were downloaded from Servier Medical Art by Servier (https://smart.servier.com/).

Table 1 Summary of the main statin-related adverse effects

SAMS	Although data based on observational studies and registries indicated an incidence of SAMS that can reach 30%, RCTs suggest a much lower rate (roughly 5%)	↑
Liver enzymes	Statins as a class raise transaminases (OR = 1.51, 95% CI: 1.24–1.84) compared to placebo. Higher doses of atorvastatin, fluvastatin, lovastatin, and simvastatin are associated with higher odds of transaminase elevations	↑
	In the case of NAFLD, interventional studies have shown that NAFLD patients prescribed statins have a reduction of ALT (–35.4%), AST (–31.8%), and gamma glutamyl transferase (GGT; -25.6%) levels, while observational studies showed a null effect, suggesting liver safety of statins in NAFLD patients	↔
Diabetes risk	Although treatment of 10 000 patients for 5 years with an effective regimen of a statin (e.g. 40 mg/day atorvastatin) would yield between 50 and 100 new cases of diabetes, this is far outweighed by the beneficial effects on CVD	↑
	Pre-diabetes, high TG levels, and a high BMI identify people at highest risk of statin-associated NOD	
Renal alterations	There is no effect of statins on renal function	↔
Cognitive functions	Statins are unlikely to cause dementia or cognitive decline	↔
Haemorrhagic stroke	Data are still limited and inconsistent, no causal link has been confirmed	↔
Lens	No clinical relevance	↔
Cancer	No clinical significance in long-term safety follow-up	↔

NAFLD, non-alcoholic fatty liver disease; NOD, new-onset diabetes; RR, relative risk; SAMS, statin associated-muscle symptoms.

ESC
European Society of Cardiology
European Heart Journal (2018) **0**, 1–18
doi:10.1093/eurheartj/ehy182

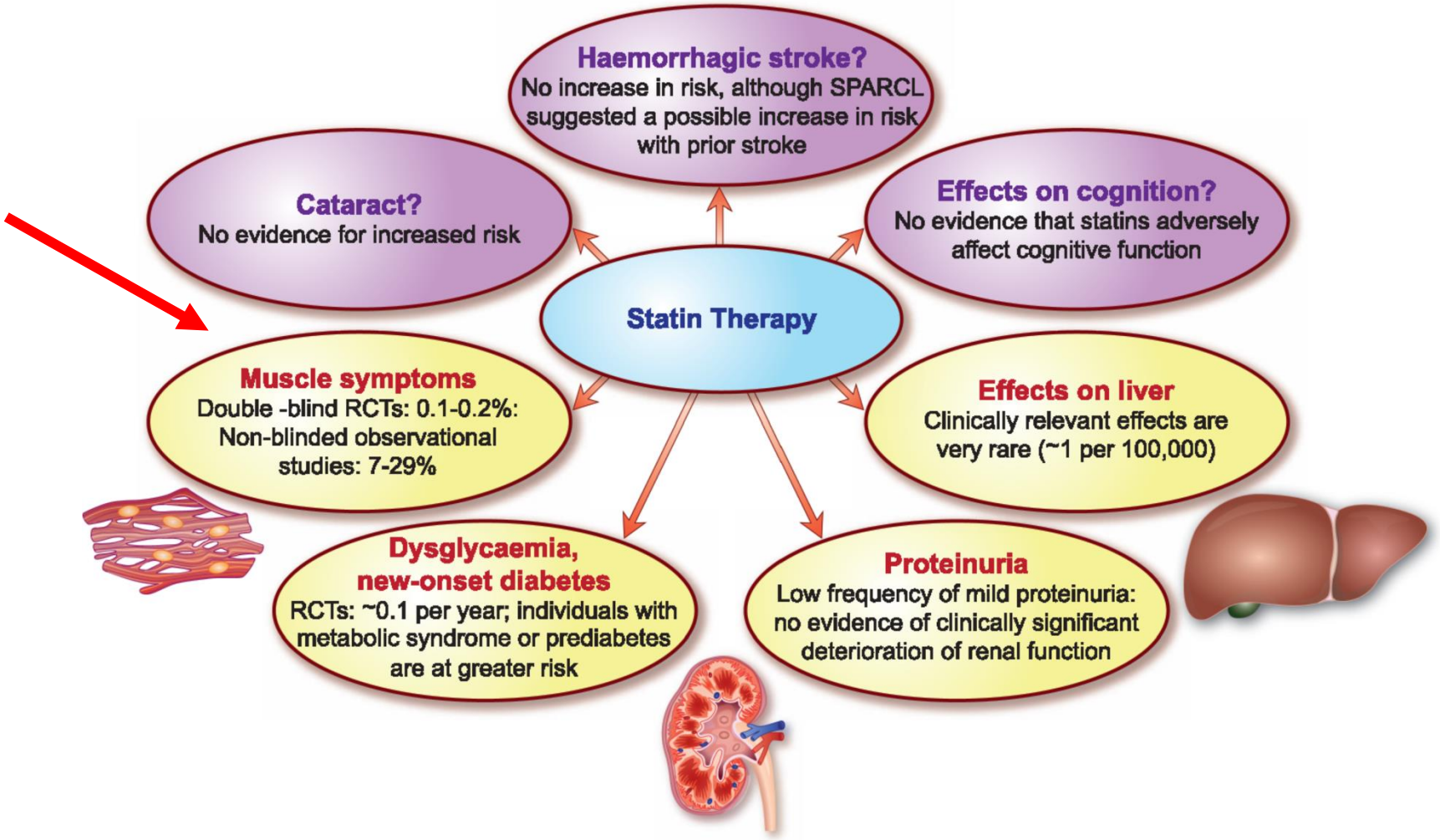
REVIEW

Clinical update

Adverse effects of statin therapy: perception vs. the evidence – focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract

François Mach[1]*, Kausik K. Ray[2], Olov Wiklund[3,4], Alberto Corsini[5], Alberico L. Catapano[5], Eric Bruckert[6], Guy De Backer[7], Robert A. Hegele[8], G. Kees Hovingh[9], Terry A. Jacobson[10], Ronald M. Krauss[11], Ulrich Laufs[12], Lawrence A. Leiter[13], Winfried März[14,15], Børge G. Nordestgaard[16,17,18], Frederick J. Raal[19], Michael Roden[20,21], Raul D. Santos[22,23], Evan A. Stein[24], Erik S. Stroes[9], Paul D. Thompson[25], Lale Tokgözoğlu[26], Georgirene D. Vladutiu[27], Baris Gencer[1], Jane K. Stock[28], Henry N. Ginsberg[29], and M. John Chapman[30]; European Atherosclerosis Society Consensus Panel

Overview of the relative prevalence of the main types of adverse effects reported with statin therapy. RCT, randomized controlled trial; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels.



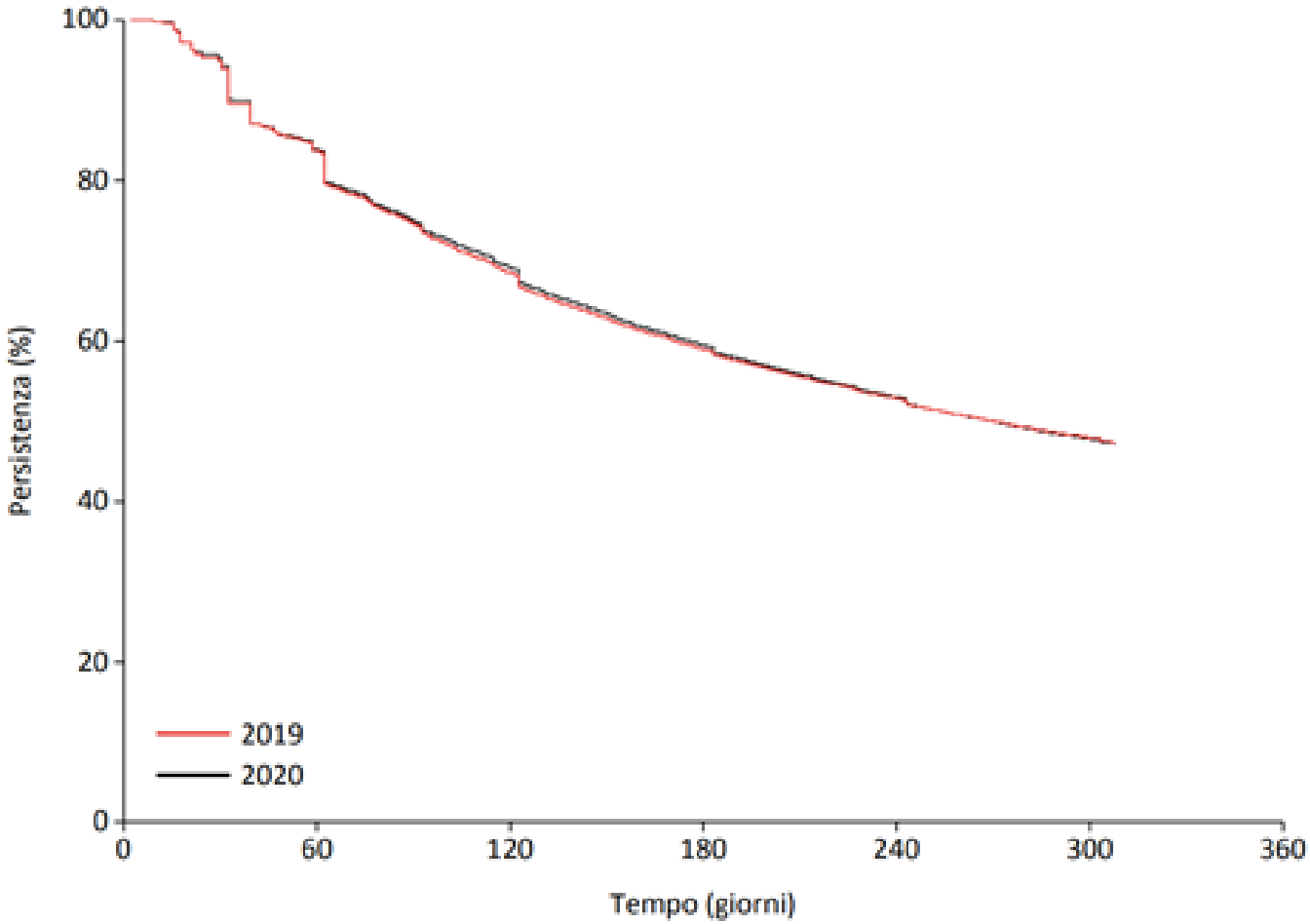
Eur Heart J. Published online April 27, 2018. doi:10.1093/eurheartj/ehy182

Discontinuation of statin therapy due to muscular side effects: A survey in real life

D. Rosenbaum [a,b,*], J. Dallongeville [c], P. Sabouret [d], E. Bruckert [a,b]

Muscular symptoms were reported in 10% of statin treated patients and led to discontinuation in 30% of the symptomatic patients

Nutrition, Metabolism & Cardiovascular Diseases 1-5, 2012



Nota: un'interruzione al trattamento si verifica se il soggetto non ha una prescrizione erogata entro 60 giorni (per maggiori dettagli consultare i metodi statistici). Per questo motivo, non possono osservarsi interruzioni negli ultimi 60 giorni dalla fine del follow-up (365 giorni)

A Survey of the FDA's AERS Database Regarding Muscle and Tendon Adverse Events Linked to the Statin Drug Class

Keith B. Hoffman[1], Christina Kraus[1], Mo Dimbil[1], Beatrice A. Golomb[2,3]*

Drug Name	Primary AEs	All AEs	PR	Primary AEs/PR	All AEs/PR	Ranked Risk (Primary)
Rosuvastatin	1,641	2,019	0.2901	5,657	6,959	100
Fluvastatin	103	184	0.0265	3,887	6,943	69
Atorvastatin	2,751	3,667	0.8604	3,197	4,262	57
Pravastatin	257	541	0.2275	1,130	2,378	20
Simvastatin	1,003	1,827	1	1,003	1,827	18
Lovastatin	67	189	0.2153	311	878	5

Fattori di rischio per miopatia/mialgia

- Increasing dose
- Increasing concentration:
    - **Increasing age,** female
    - CYP450 interactions (pharmacokinetic)
- Clinical conditions:
    - **Poly-therapy**
    - **Transplanted**
    - **Diabetes**
    - Hypothyroidism
    - History of muscular symptoms after LLT

European Heart Journal Advance Access published February 18, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv043

REVIEW

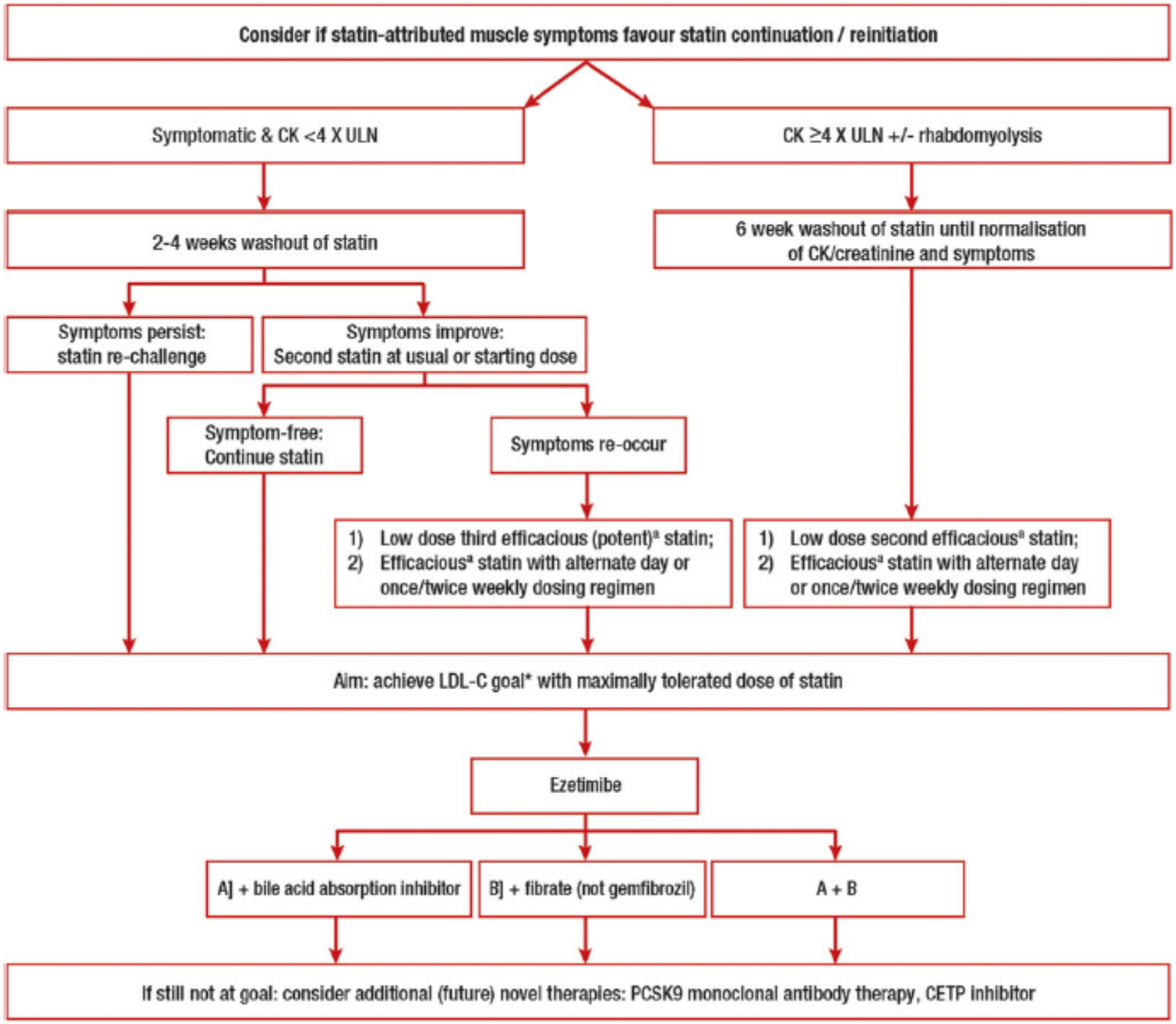
Clinical update

Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management

Erik S. Stroes[1*], Paul D. Thompson[2], Alberto Corsini[3], Georgirene D. Vladutiu[4], Frederick J. Raal[5], Kausik K. Ray[6], Michael Roden[7], Evan Stein[8], Lale Tokgözoğlu[9], Børge G. Nordestgaard[10], Eric Bruckert[11], Guy De Backer[12], Ronald M. Krauss[13], Ulrich Laufs[14], Raul D. Santos[15], Robert A. Hegele[16], G. Kees Hovingh[17], Lawrence A. Leiter[18], Francois Mach[19], Winfried März[20], Connie B. Newman[21], Olov Wiklund[22], Terry A. Jacobson[23], Alberico L. Catapano[3], M. John Chapman[24], and Henry N. Ginsberg[25], European Atherosclerosis Society Consensus Panel[†]

Downloaded

Therapeutic flow-chart for management of patients with statin-associated muscle symptoms



Eur Heart J. 2015 Feb 18.

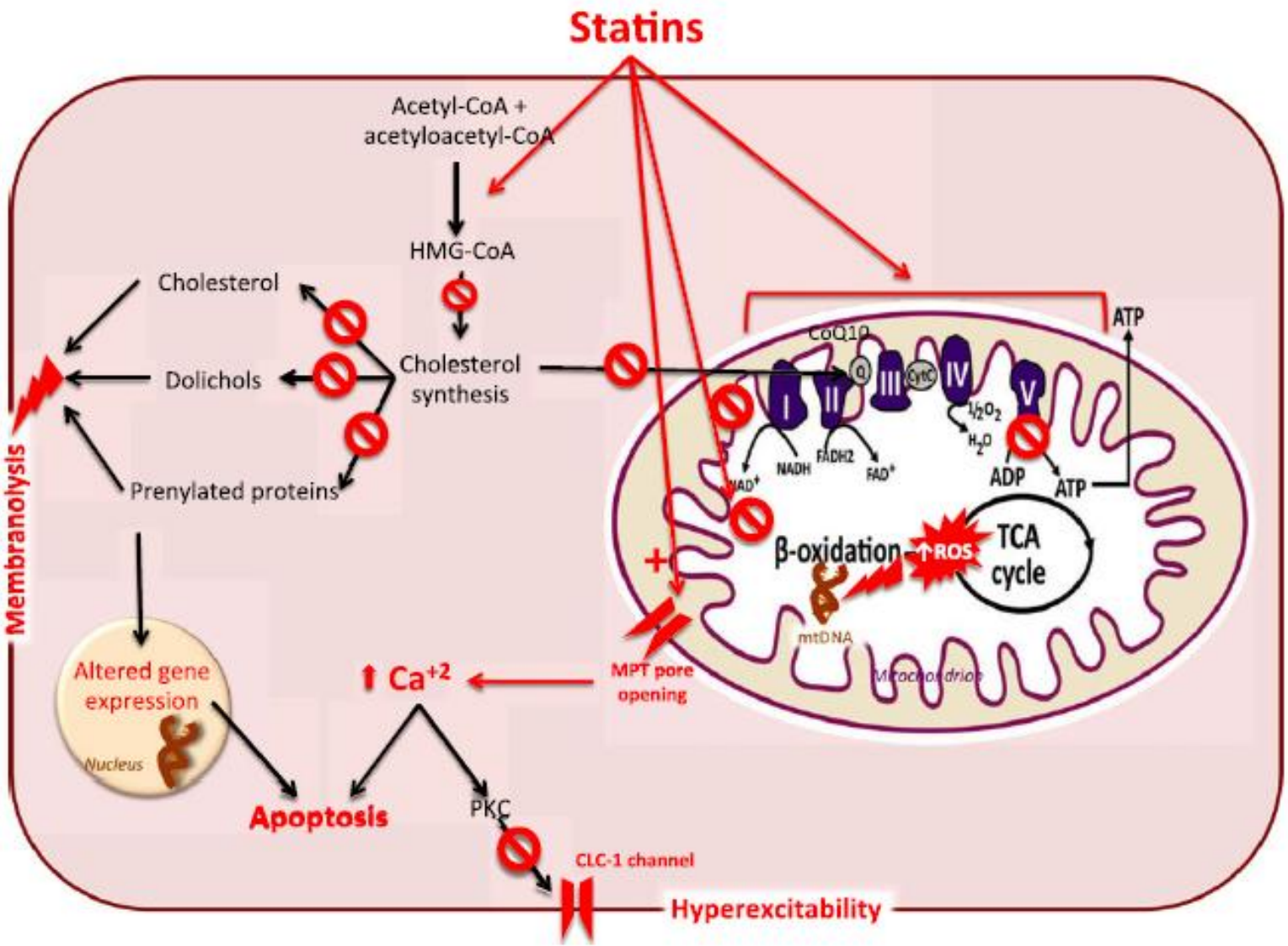
- Overview of the pathophysiology of SAMS
- Genetic susceptibility to SAMS

DOI: 10.1111/eci.12461

REVIEW

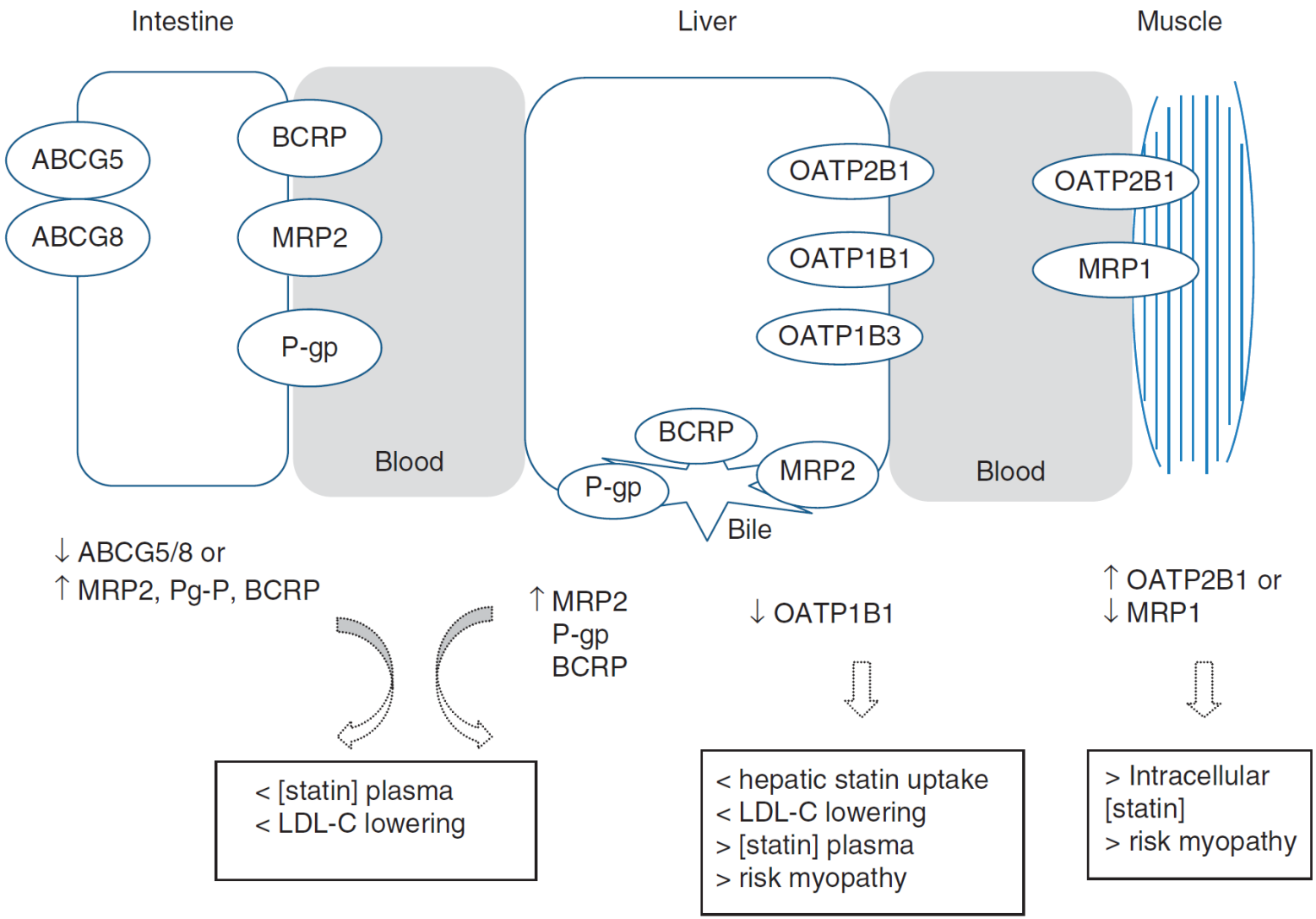
The role of mitochondria in statin-induced myopathy

Maria Apostolopoulou[*,†], Alberto Corsini[‡,§] and Michael Roden[*,†,¶]

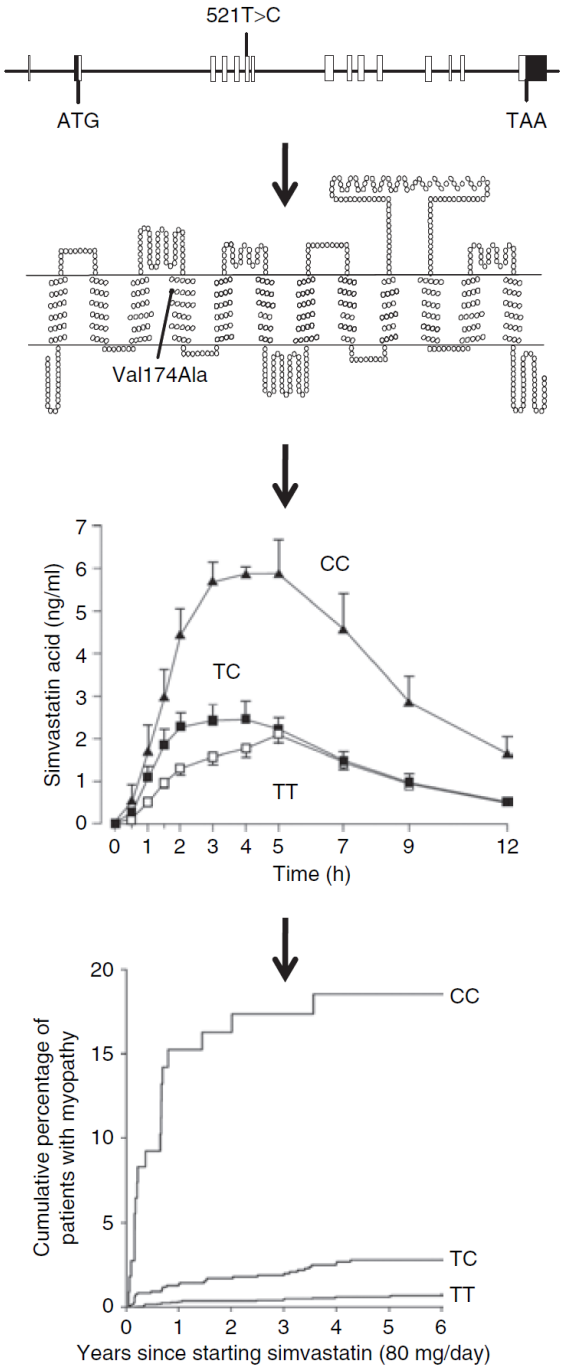


Eur J Clin Invest 2015; 45(7):745–754

Efflux and uptake transporters as determinants of statins response



Rodrigues AC Expert Opin Dru Metab Toxicol 6(5): 621-632; 2010



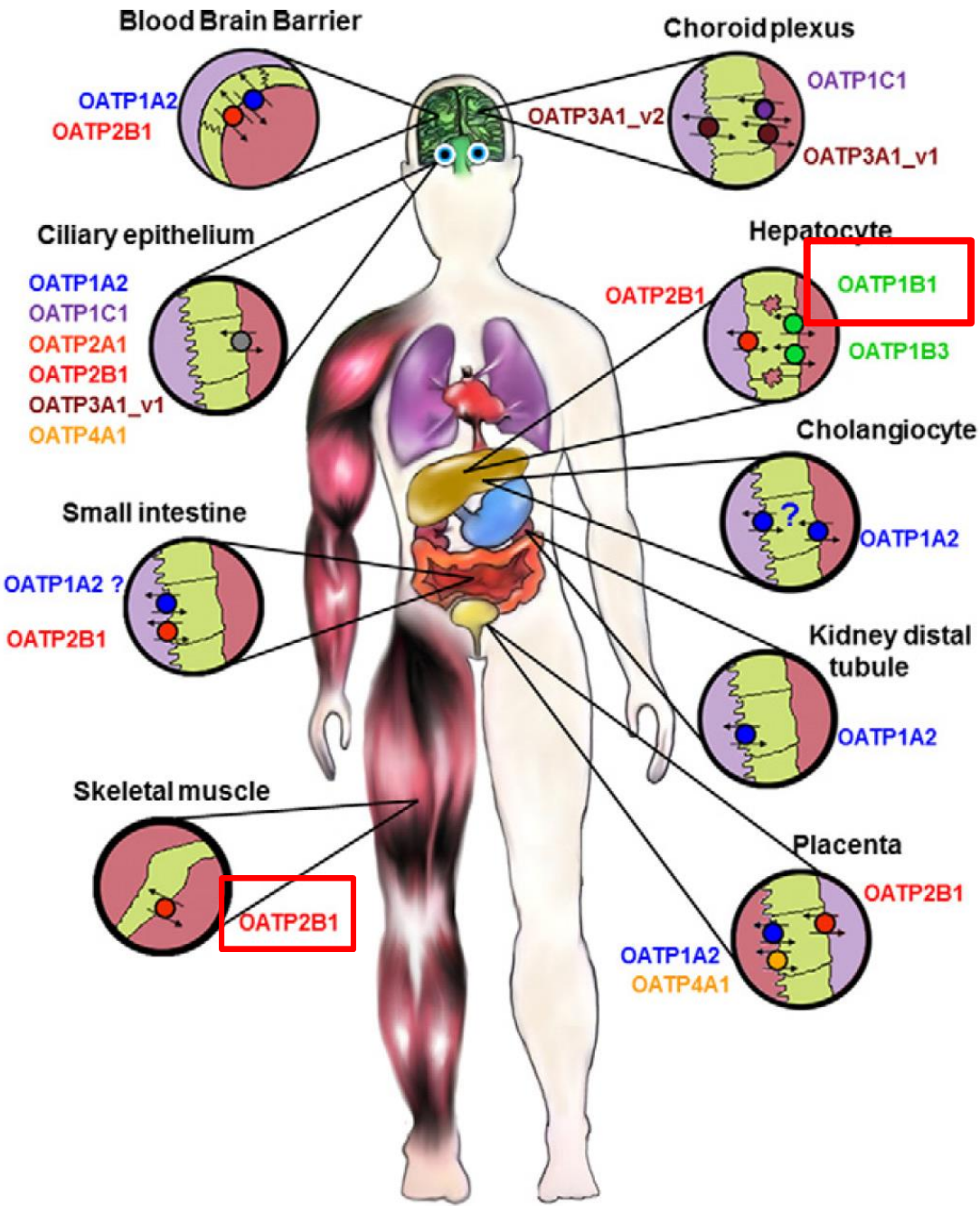
Genetically impaired activity of OATP1B1 reduces the hepatic uptake of active simvastatin acid, causing accumulation of simvastatin acid in plasma and an increased risk of myopathy.

Niemi M VOLUME 87 NUMBER 1 | january 2010 | www.nature.com/cpt

Enzymatic and drug transporter pathways involved in the pharmacokinetics of statins

	Atorvastatin	Fluvastatin XL	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
CYP-mediated metabolism	CYP3A4	CYP2C9	CYP3A4	Biliary, CYP2C9/2C8 (minor)	Sulphonation	Biliary, CYP2C9, 2C19 (minor)	CYP3A4
UGT1A1/1A3-mediated metabolism	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Transporter proteins	Yes	Yes	Yes	Yes	Yes	Yes	Yes
OATP1B1	Yes	Yes	Yes	Yes	Yes	Yes	Yes
OATP1B3	NA	Yes	NA	Yes	Yes	Yes	Yes
OATP1A2	NA	NA	Yes	NA	NA	Yes	NA
OATP2B1	Yes	Yes	NA	Yes	Yes	Yes	NA
OAT3	NA	Yes	Yes	NA	Yes	NA	Yes
BCRP	Yes	Yes	NA	Yes	Yes	Yes	NA
MDR1/P-gp	Yes	No	Yes	Yes	Yes	No	Yes
MRP2	Yes	NA	NA	Yes	Yes	NA	NA
BESP	?	Yes	?	NA	Yes	?	?

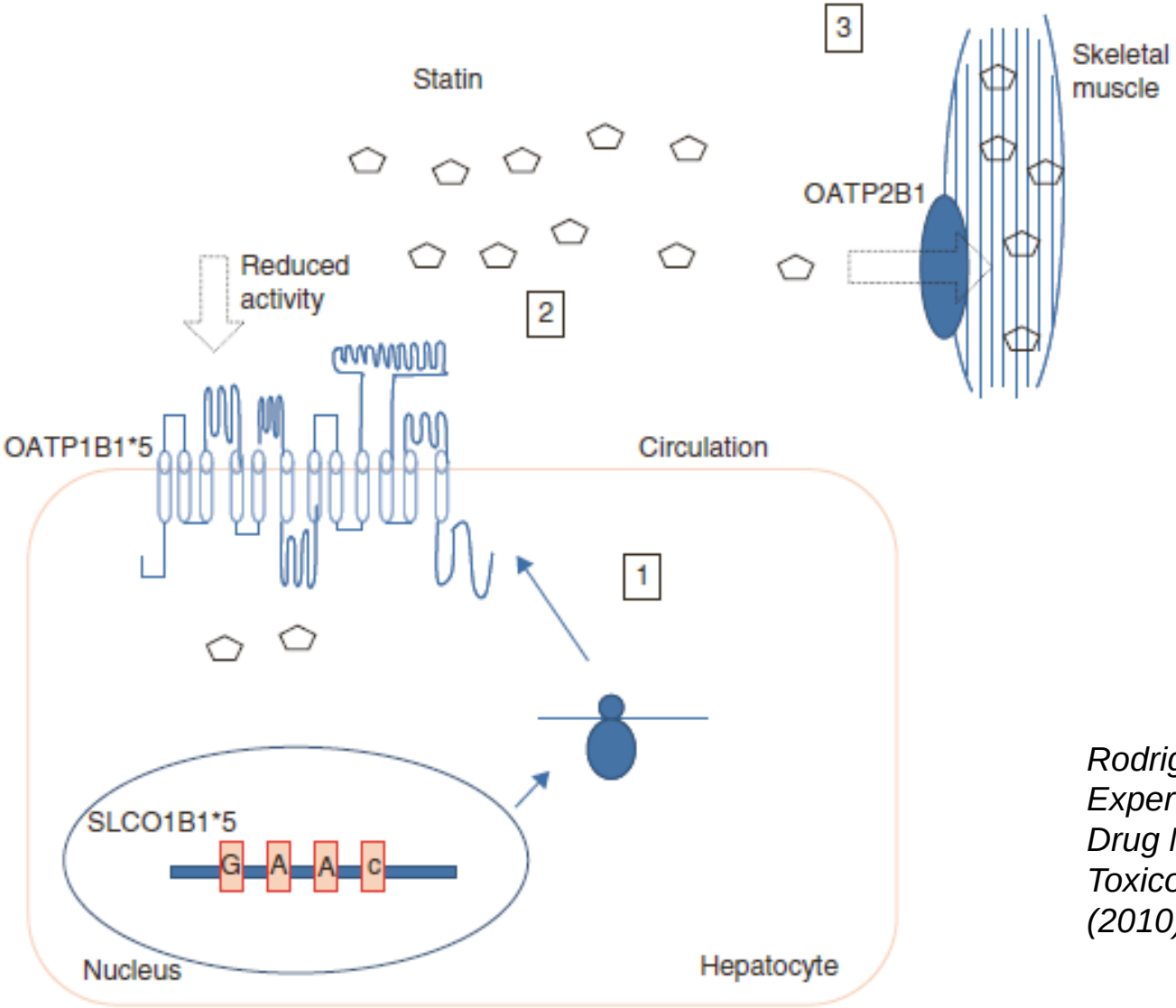
Corsini A and Ceska R Curr Med Res & Op Vol. 27:1551–1562 ; 2011



Distribution of OATPs in selected human epithelial tissues. The OATPs within the same subfamily are labelled with the same color

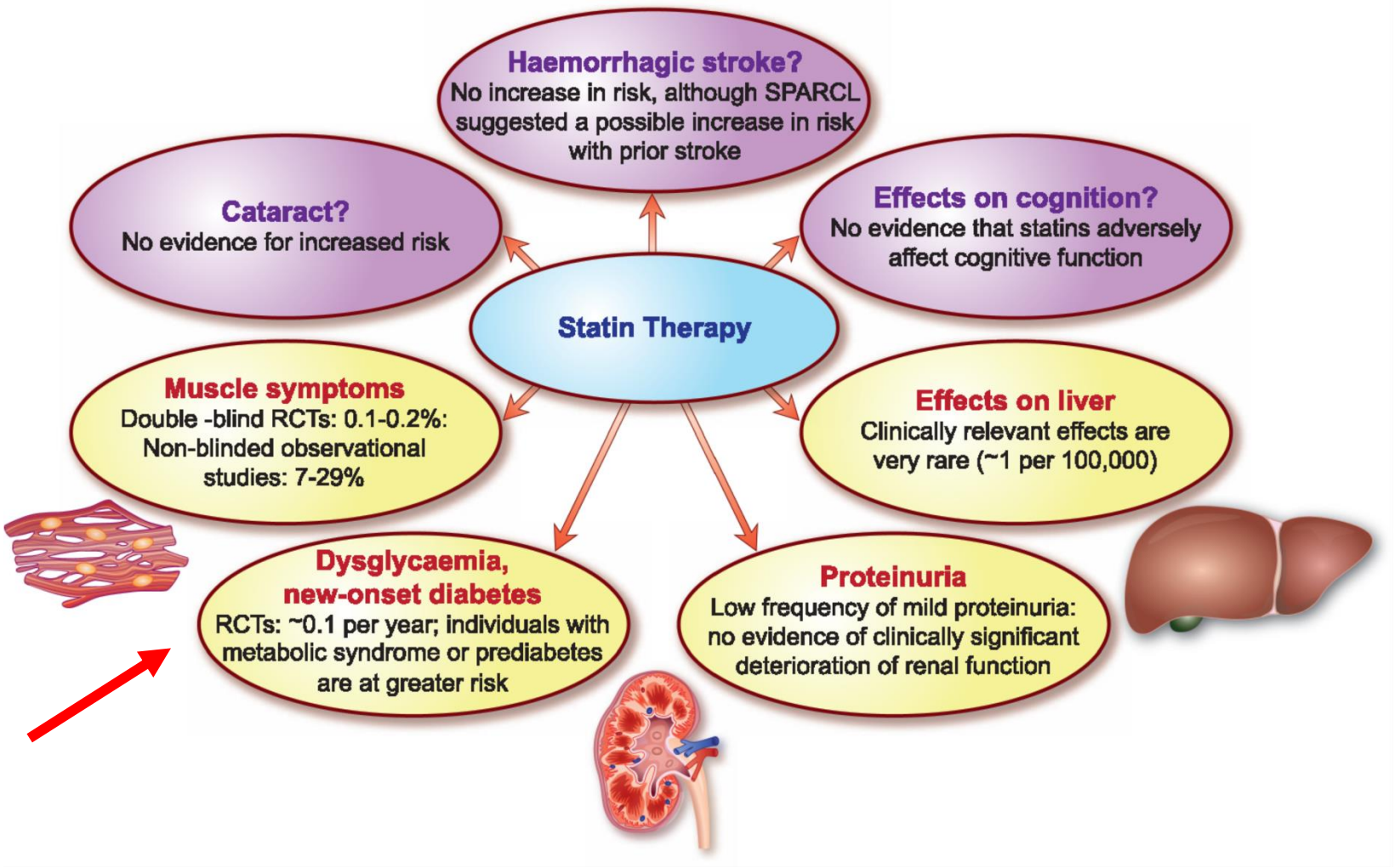
Hagenbuch B and Stieger B Molecular Aspects of Medicine 34 (2013) 396–412

Postulated mechanism of statin myotoxicity



Rodrigues AC Expert Opin. Drug Metab. Toxicol. (2010)

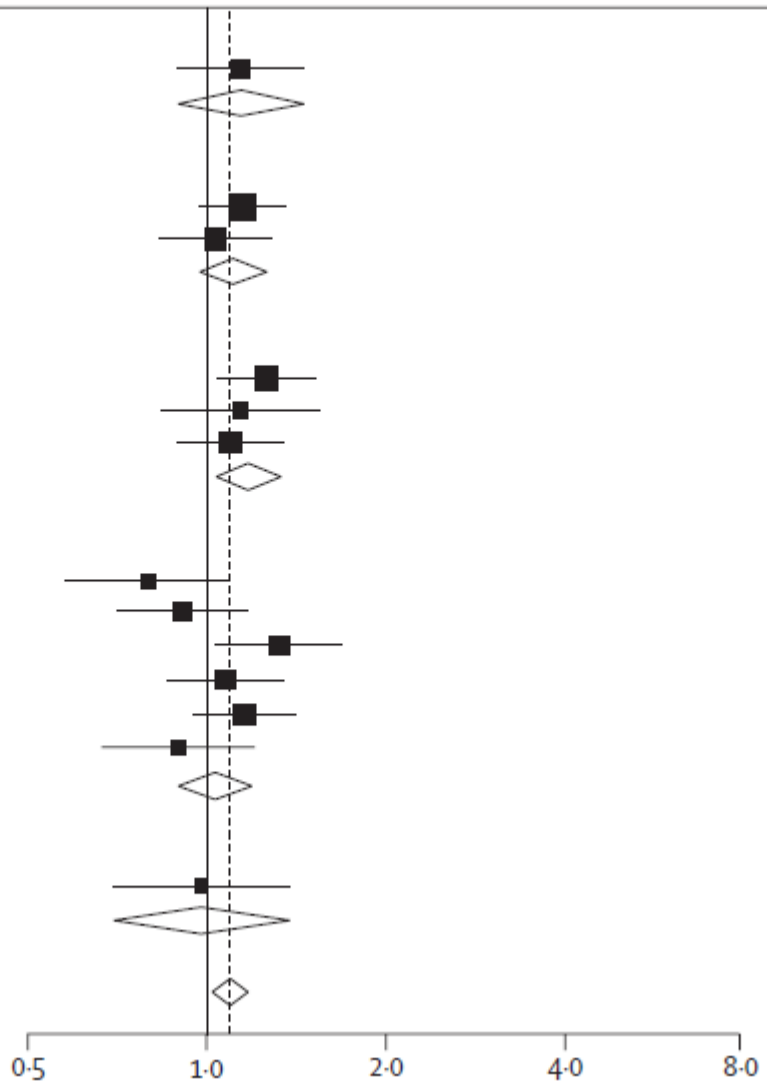
Overview of the relative prevalence of the main types of adverse effects reported with statin therapy. RCT, randomized controlled trial; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels.



Eur Heart J. Published online April 27, 2018. doi:10.1093/eurheartj/ehy182

No difference by statin

	n	Statin	Placebo or control	OR (95% CI)	Weight (%)
Atorvastatin					
ASCOT-LLA[7]	7773	154	134	1·14 (0·89–1·46)	7·07%
				1·14 (0·89–1·46)	7·07%
Simvastatin					
HPS[8]	14573	335	293	1·15 (0·98–1·35)	13·91%
4S[15]	4242	198	193	1·03 (0·84–1·28)	8·88%
Subtotal (I^2=0·0%, p=0·445)				1·11 (0·97–1·26)	22·80%
Rosuvastatin					
JUPITER[4]	17802	270	216	1·26 (1·04–1·51)	11·32%
CORONA[9]	3534	100	88	1·14 (0·84–1·55)	4·65%
GISSI HF[16]	3378	225	215	1·10 (0·89–1·35)	9·50%
Subtotal (I^2=0·0%, p=0·607)				1·18 (1·04–1·33)	25·46%
Pravastatin					
WOSCOPS[5]	5974	75	93	0·79 (0·58–1·10)	4·24%
LIPID[6]	6997	126	138	0·91 (0·71–1·17)	6·53%
PROSPER[12]	5023	165	127	1·32 (1·03–1·69)	6·94%
MEGA[13]	6086	172	164	1·07 (0·86–1·35)	8·03%
ALLHAT-LLT[14]	6087	238	212	1·15 (0·95–1·41)	10·23%
GISSI PREVENZIONE[16]	3460	96	105	0·89 (0·67–1·20)	4·94%
Subtotal (I^2=47·5%, p=0·090)				1·03 (0·90–1·19)	40·91%
Lovastatin					
AFCAPS/TexCAPS[18]	6211	72	74	0·98 (0·70–1·38)	3·76%
				0·98 (0·70–1·38)	3·76%
Overall (I^2=11·2%)				**1·09 (1·02–1·17)**	**100%**



Sattar N et al. Lancet. 2010;375:735-42

The diabetogenic action of statins — mechanisms and clinical implications

D. John Betteridge[1] and Rafael Carmena[2]

NATURE REVIEWS | **ENDOCRINOLOGY** VOLUME 12 | FEBRUARY 2016 | **99**

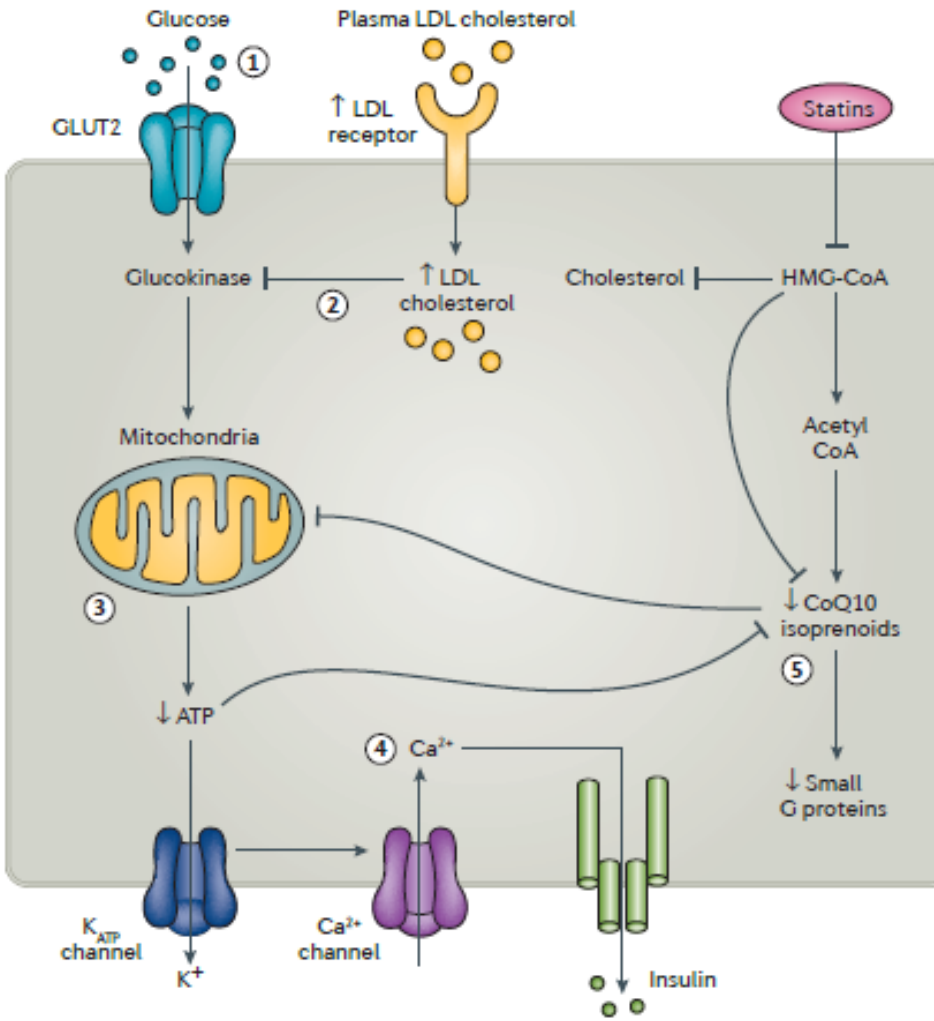
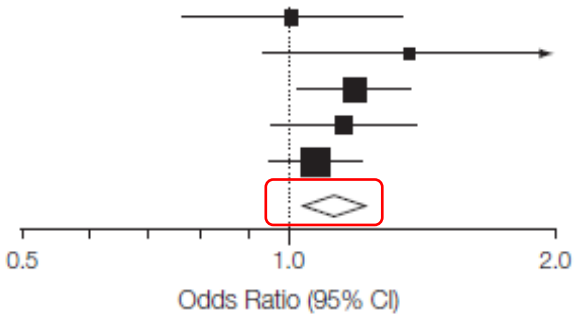
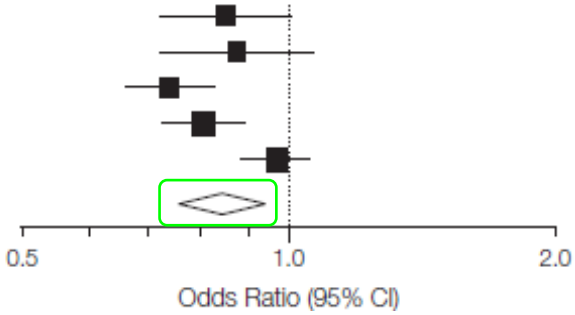


Figure 2 | **Potential sites of action of statins on β-cell function identified from *in vitro* studies.** (1) Statins reduce mRNA and protein expression of GLUT2, limiting glucose uptake. (2) Statins upregulate LDL receptors and cholesterol uptake. Cholester loading impairs β-cell function, proliferation and survival. (3) Statins reduce Coenzyme Q10 (CoQ10) levels secondary to inhibition of the mevalonate pathway impairing mitochondrial electron transport and ATP production. ATP is an essential regulator of insulin secretion through effects on K_{ATP} channels, membrane depolarization and subsequent calcium channel opening. (4) Statins inhibit L-type calcium channels and th rise in cytosolic calcium levels that is required for insulin secretion. (5) Statins reduce isoprene synthesis impairing the post-translational modification of small G proteins, which are important in insulin-containing granule exocytosis. Reprinted from Sattar, N.

Meta-analysis of New-Onset Diabetes and First Major CV Events in 5 Large Trials Comparing Intensive- to Moderate-Dose Statin Therapy

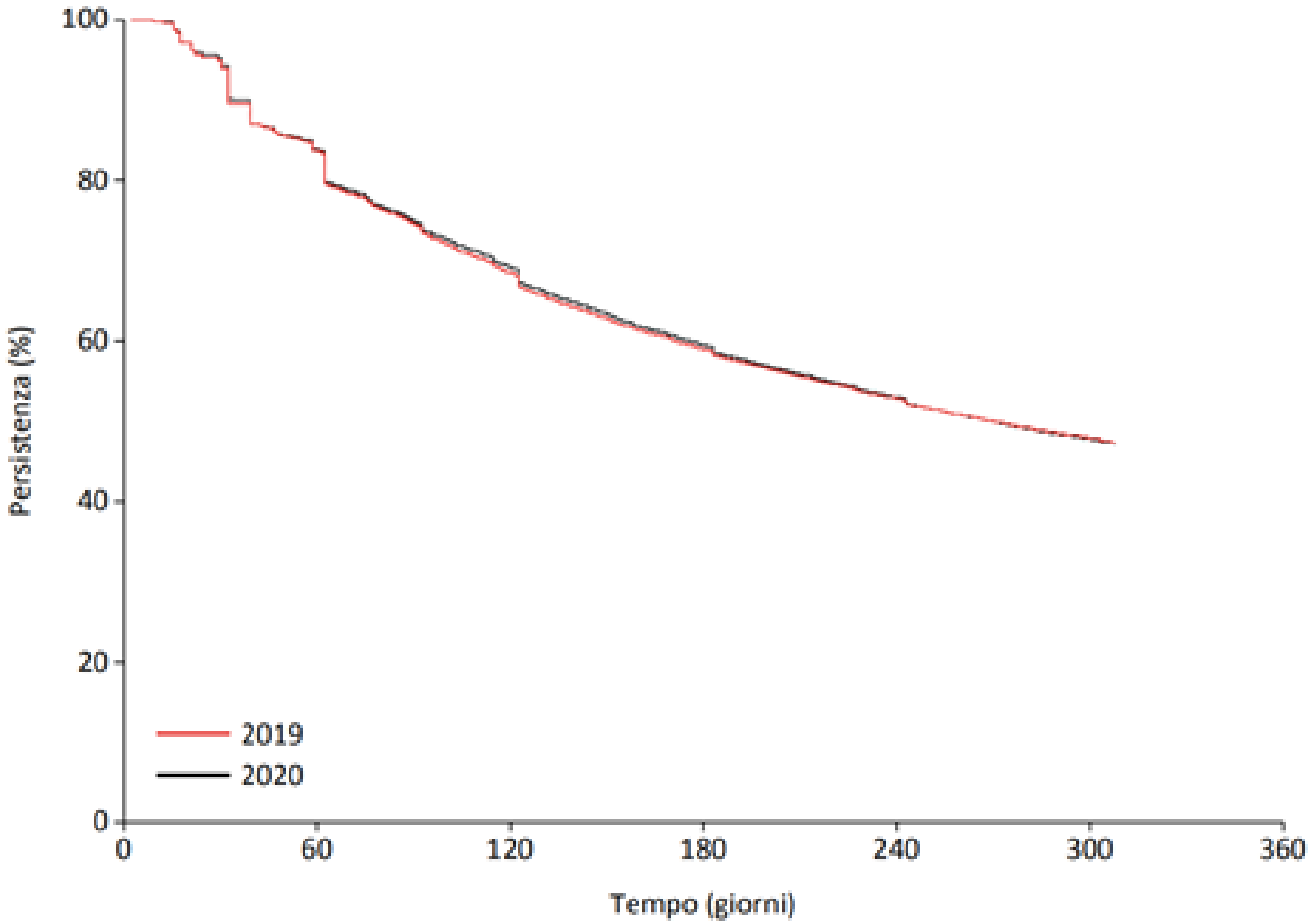
	Cases/Total, No. (%)		
	Intensive Dose	Moderate Dose	OR (95% CI)
Incident Diabetes			
PROVE IT–TIMI 22,[18] 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z,[17] 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT,[15] 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL,[16] 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH,[5] 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	1449/16 408 (8.8)	1300/16 344 (8.0)	1.12 (1.04-1.22)
Heterogeneity: $I^2 = 0\%$; $P = .60$			
Incident CVD			
PROVE IT–TIMI 22,[18] 2004	315/1707 (18.4)	355/1688 (21.0)	0.85 (0.72-1.01)
A to Z,[17] 2004	212/1768 (12.0)	234/1736 (13.5)	0.87 (0.72-1.07)
TNT,[15] 2005	647/3798 (17.0)	830/3797 (21.9)	0.73 (0.65-0.82)
IDEAL,[16] 2005	776/3737 (20.8)	917/3724 (24.6)	0.80 (0.72-0.89)
SEARCH,[5] 2010	1184/5398 (21.9)	1214/5399 (22.5)	0.97 (0.88-1.06)
Pooled odds ratio	3134/16 408 (19.1)	3550/16 344 (21.7)	0.84 (0.75-0.94)
Heterogeneity: $I^2 = 74\%$; $P = .004$			





NTT/yr 155 for CV events
NNH/yr 498 for new-onset diabetes

Preiss et al. JAMA 2011; 305:2556-64



Nota: un'interruzione al trattamento si verifica se il soggetto non ha una prescrizione erogata entro 60 giorni (per maggiori dettagli consultare i metodi statistici). Per questo motivo, non possono osservarsi interruzioni negli ultimi 60 giorni dalla fine del follow-up (365 giorni)

Recommended treatment goals for LDL-lowering therapy: main changes from 2016 to 2019

Risk category	LDL goals (starting with untreated LDL-C)	
	2016	**2019**
Very-high-risk	<1.8 mmol/L (70 mg/dL) or >50% ↓ if LDL-C 1.8-3.5 (70 - 135 mg/dL)	<1.4 mmol/L (55 mg/dL) and >50% ↓
High-risk	<2.6 mmol/L (100mg/dL) or >50% ↓ if LDL-C 2.6-5.2 (100 - 200 mg/dL)	<1.8 mmol/L (70 mg/dL) and >50% ↓
Moderate-risk	<3.0 mmol/L (115 mg/dL)	< 2.6 mmol/L (100 mg/dL)
Low-risk	<3.0 mmol/L (115 mg/dL)	<3.0 mmol/L (115 mg/dL)

ESC European Society of Cardiology
European Journal of Preventive Cardiology
doi:10.1093/eurjpc/zwaa047

FULL RESEARCH PAPER

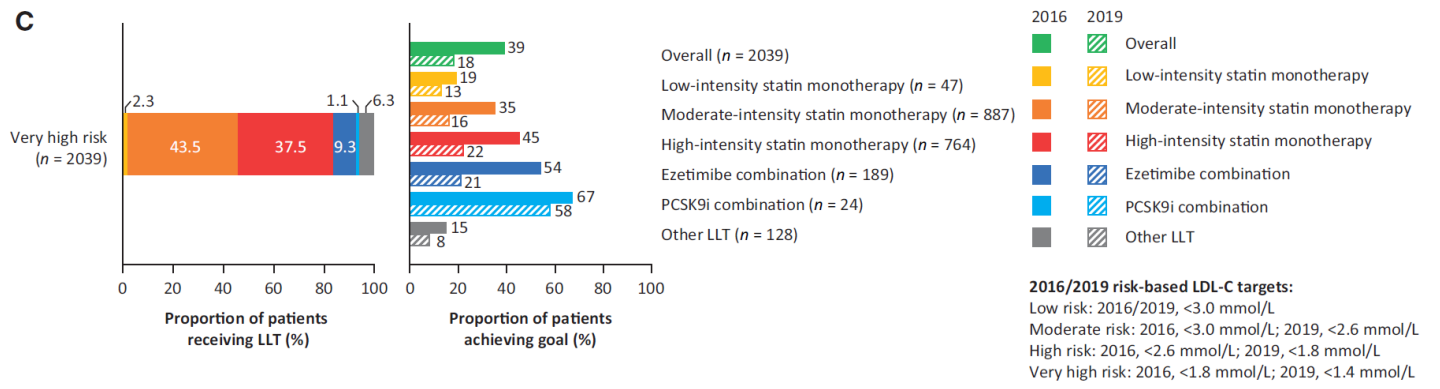
EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study

Aims To provide contemporary data on the implementation of European guideline recommendations for lipid-lowering therapies (LLTs) across different settings and populations and how this impacts low-density lipoprotein cholesterol (LDL-C) goal achievement.

Conclusion Gaps between clinical guidelines and clinical practice for lipid management across Europe persist, which will be exacerbated by the 2019 guidelines. Even with optimized statins, greater utilization of non-statin LLT is likely needed to reduce these gaps for patients at highest risk.

Eur J Prev Cardiol. 2021 Sep 20;28(11):1279-1289.

ESC/EAS 2016 and 2019 risk-based LDL cholesterol goal attainment among patients stabilized on lipid-lowering regimens

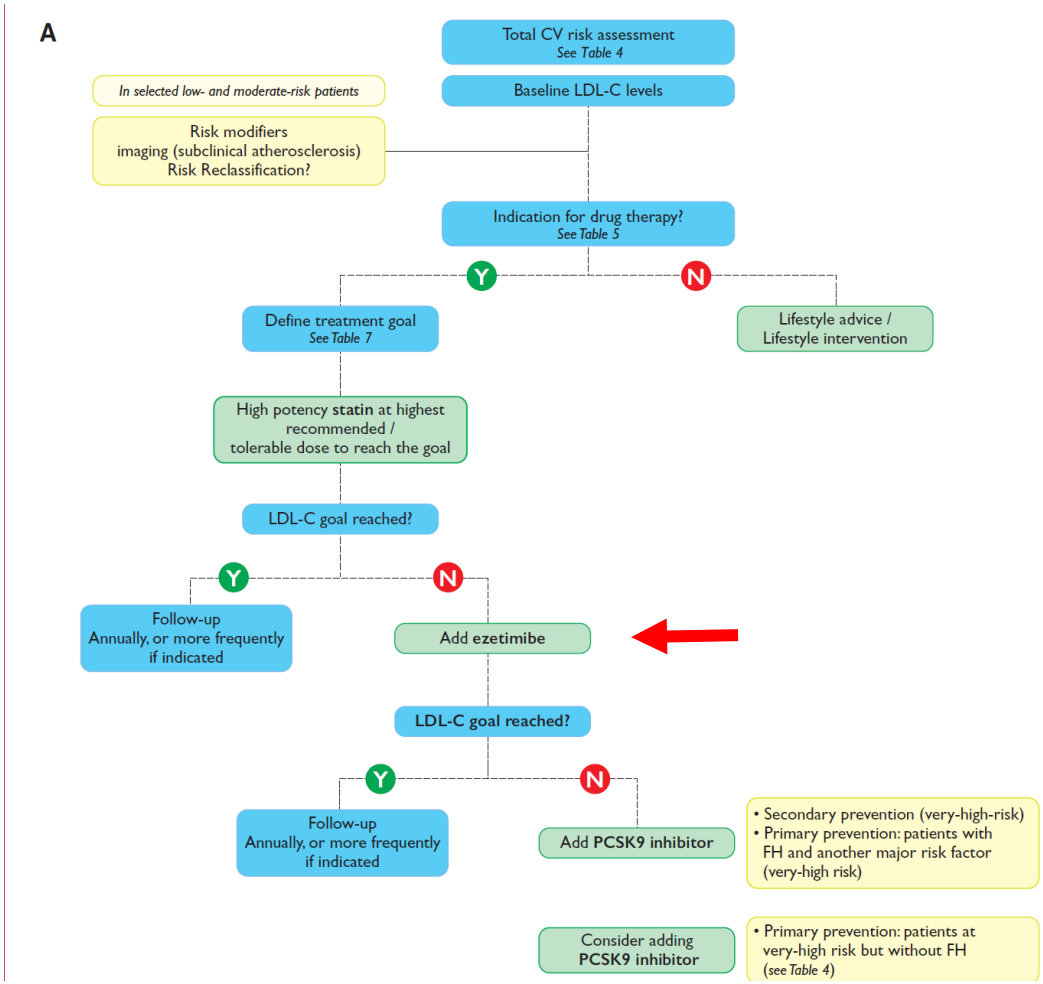


Eur J Prev Cardiol. 2021 Sep 20;28(11):1279-1289

Farmaci ipocolesterolemizzanti dalle molecole di sintesi ai farmaci biologici

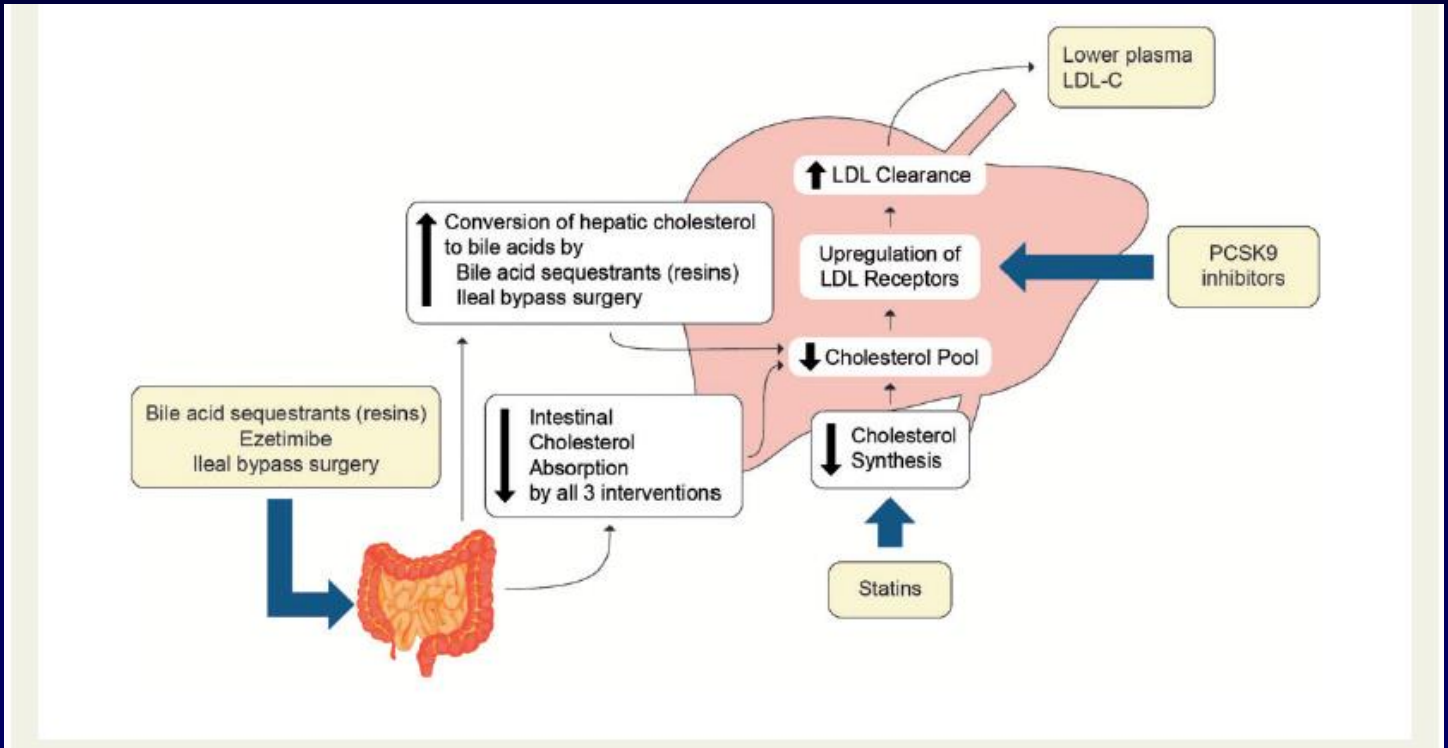
- **Statine**
- **Terapia di combinazione**
- Farmaci biologici
- La terapia genica

Treatment algorithm for pharmacological LDL-C lowering



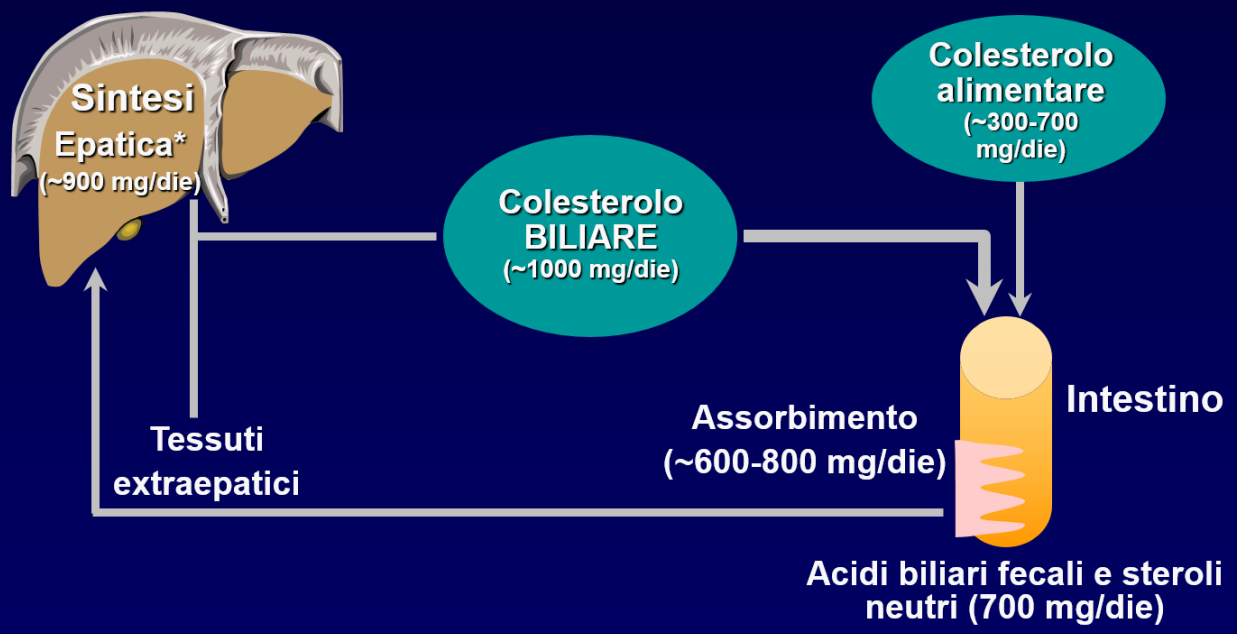
European Heart Journal (2019) 00, 1-78

All therapies that act predominantly to lower LDL up-regulate LDL receptors and thus increase LDL clearance



Ference B et al European Heart Journal (2017) 0, 1–14

Le due principali fonti di colesterolo



*e tessuti extraepatici

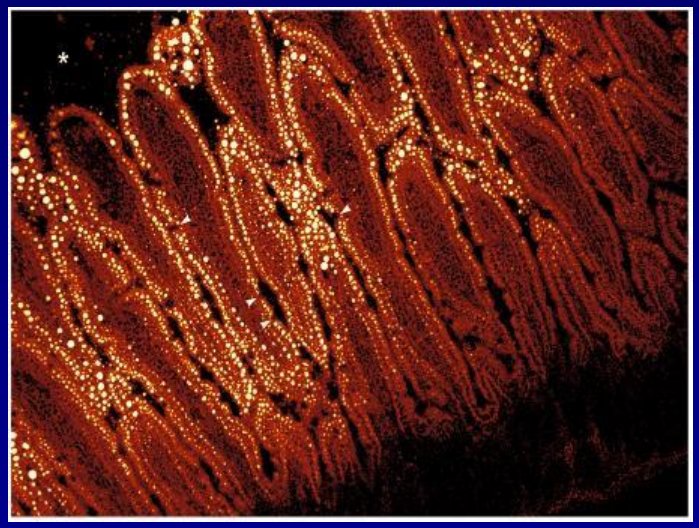
Riadattato da Champe PC, Harvey RA. In *Biochemistry*. 2nd ed. Philadelphia: Lippincott Raven, 1994; Glew RH. In *Textbook of Biochemistry with Clinical Correlations*. 5th ed. New York: Wiley-Liss, 2002:728-777; Ginsberg HN, Goldberg IJ. In *Harrison's Principles of Internal Medicine*. 14th ed. New York: McGraw-Hill, 1998:2138-2149; Shepherd J *Eur Heart J Suppl* 2001;3(suppl E):E2-E5; Hopfer U. In *Textbook of Biochemistry with Clinical Correlations*. 5th ed. New York: Wiley-Liss, 2002:1082-1150; Bays H *Expert Opin Investig Drugs* 2002;11:1587-1604.

Pharmacological effects of lipid-modification therapies

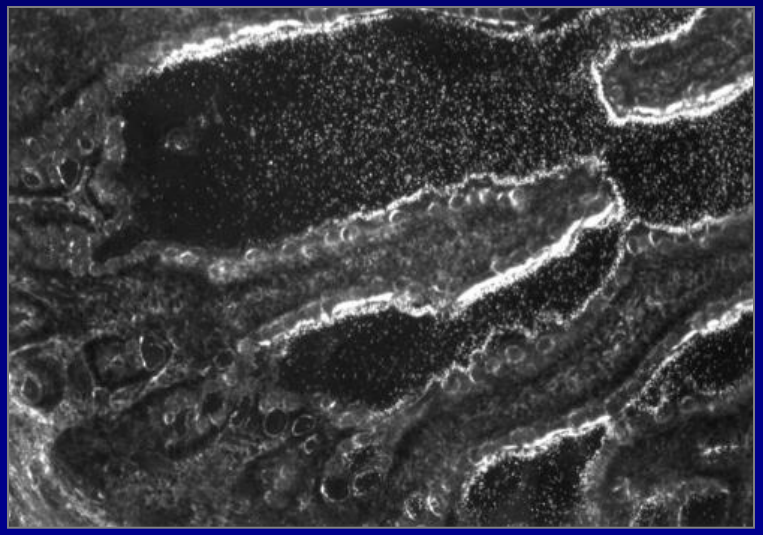
	Effect on LDL cholesterol	Effect on triglycerides and cholesterol remnants	Effect on lipoprotein(a)	Cardiovascular benefit	Ongoing studies
Antisense and mAbs to ANGPTL3	Moderate decrease	Strong decrease	Neutral	No	NCT02709850 (phase 2), phase 3 trials*
Antisense, mAbs, and siRNA to apolipoprotein C3	Neutral	Strong decrease	Neutral	No	NCT03385239 (phase 2), NCT03783377 (phase 1)
Antisense to apolipoprotein(a)	Neutral	Neutral	Strong decrease	No	NCT03070782 (phase 2)
Bempedoic acid	Moderate decrease	Neutral	Neutral	No	NCT02993406 (phase 3 CVOT)
Bile acid sequestrants	Moderate decrease	Mild decrease	Neutral	No†	No
CETP inhibitors	Moderate decrease	Neutral	Mild decrease	Yes‡	No
Ezetimibe	Moderate decrease	Neutral	Minimal increase	Yes	No
Fibrates: SPPARMs	Neutral	Moderate decrease	Neutral	No†§	NCT03071692 (phase 3 CVOT)
Fish oils: EPA	Neutral	Moderate decrease	Neutral	Yes	No
Fish oils: EPA and DHA	Neutral	Moderate decrease	Neutral	No	NCT02104817 (phase 3 CVOT)
Inclisiran	Strong decrease	Mild decrease	Mild decrease	No	NCT03814187 (phase 3 CVOT)
Lomitapide	Moderate decrease	Mild decrease	Mild decrease	No	No¶
Anti-PCSK9 mAbs	Strong decrease	Mild decrease	Mild decrease	Yes	No
Mipomersen	Moderate decrease	Mild decrease	Mild decrease	No	No¶
Nicotinic acid	Mild decrease	Mild decrease	Mild decrease	No‖	No
Statins	Strong decrease	Mild decrease	Minimal increase	Yes	No

Ray KK et al Lancet 2019; 394: 697–708

Ezetimibe appears to localize to the site of cholesterol absorption



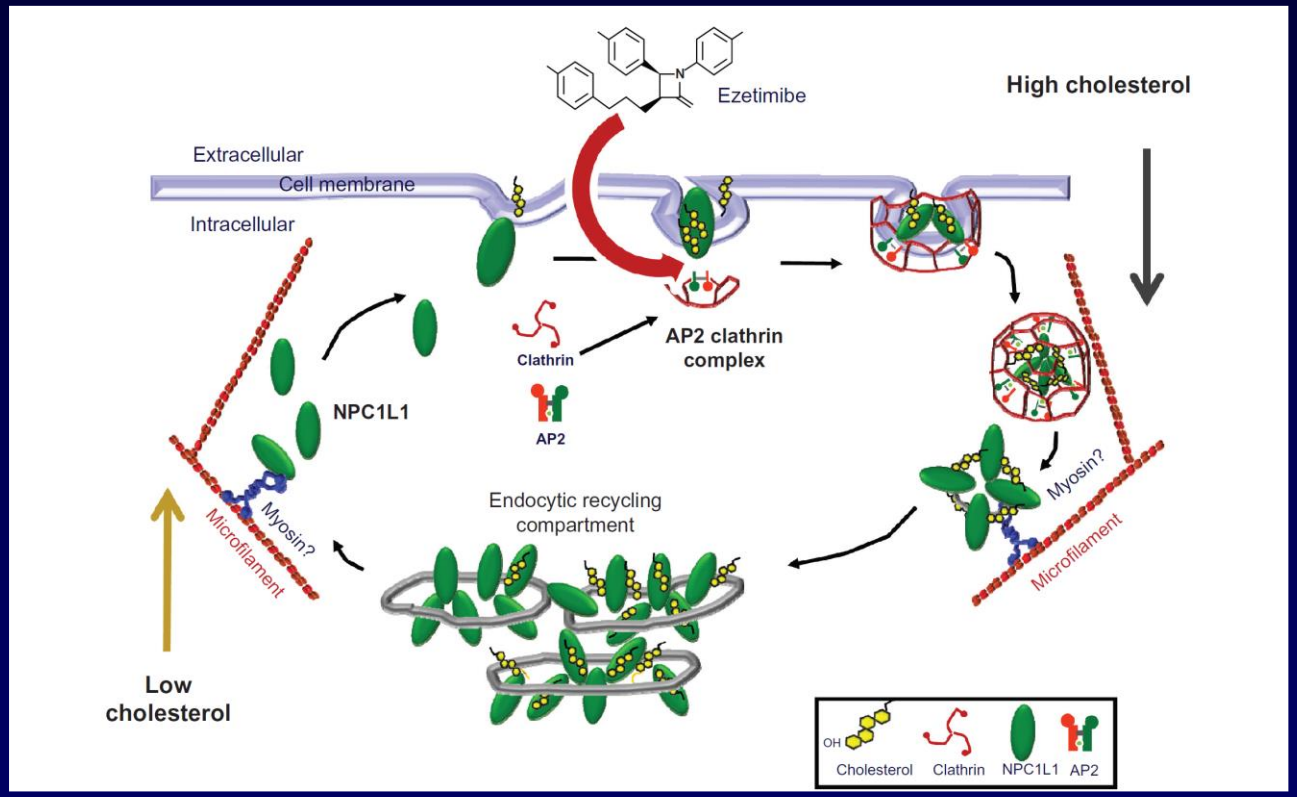
Uptake of a fluorescent cholesterol analog in hamster small intestine



125 I-Gluc-Ezetimibe Delivered I.V. Localizes to the Intestinal Brush Border in Bile-Duct Cannulated Rats

Sparrow et al. J Lipid Res. 1999; 10:1747

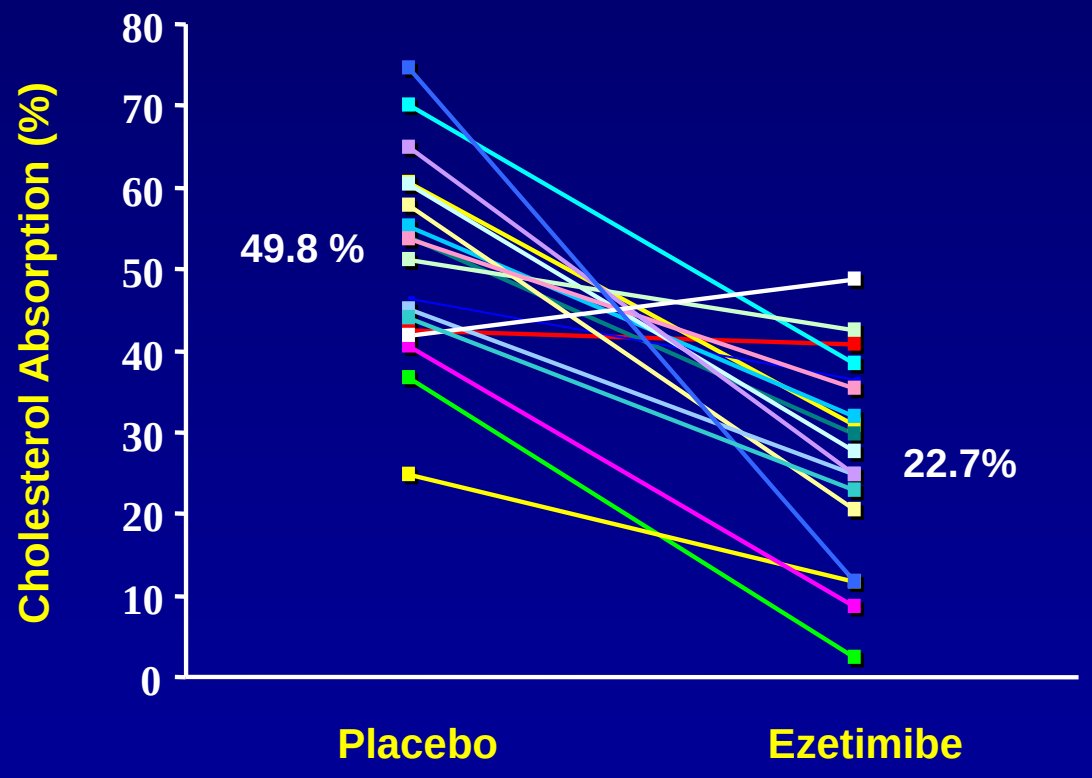
Model for NPC1L1-mediated cholesterol uptake



Phan BA et al Health Risk Manag. 2012;8:415-27

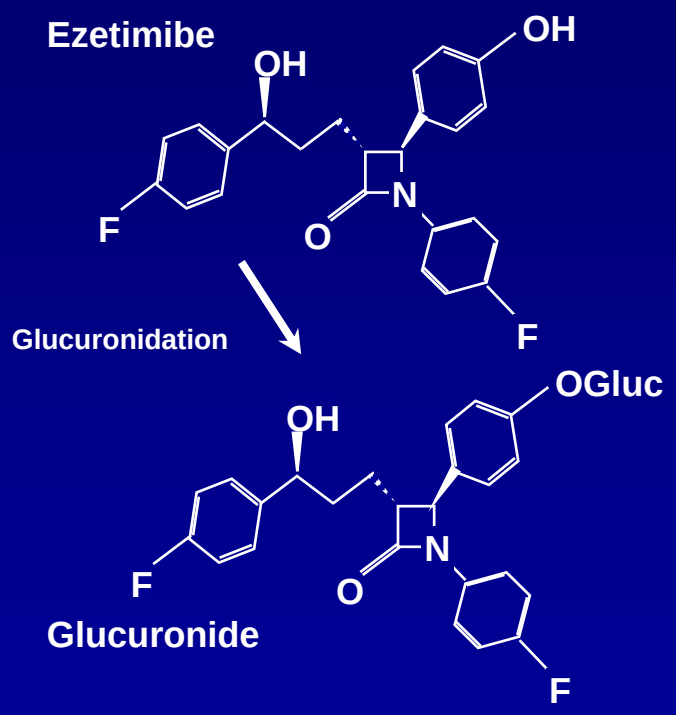
Cholesterol Absorption was Inhibited by 54%

($p < 0.001$)



Sudhop et al. Circulation 2002; 106;1943

Metabolism of Ezetimibe



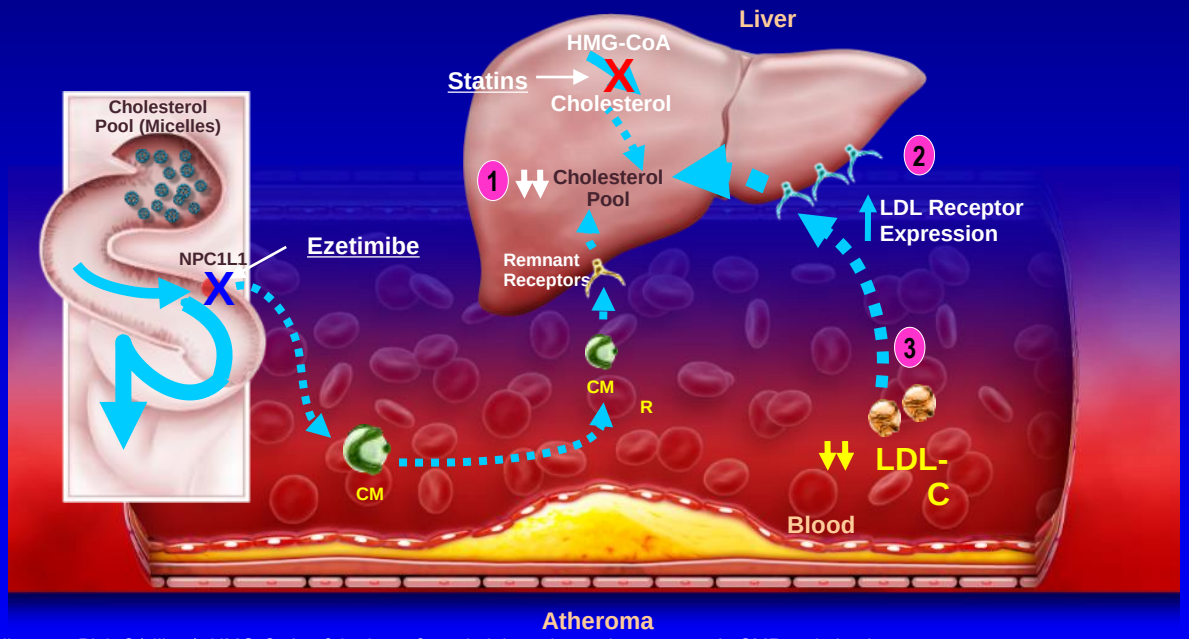
- Rapidly metabolized to an active glucuronide metabolite
- Both parent drug and metabolite inhibit cholesterol absorption
- Glucuronide metabolite more potent than parent drug in inhibiting cholesterol absorption
- Repeated enterohepatic circulation results in long duration of action

Adapted from Catapano AL *Eur Heart J Suppl* 2001;3(suppl E):E6-E10; van Heek M et al *Br J Pharmacol* 2000;129:1748-1754; Patrick JE et al *Drug Metab Dispos* 2002;30:430-437; Ezzet F et al *Clin Ther* 2001;23:871-885.

Ezetimibe and Statins Have Complementary Mechanisms of Action[1]

Together, ezetimibe in combination with a statin provides:

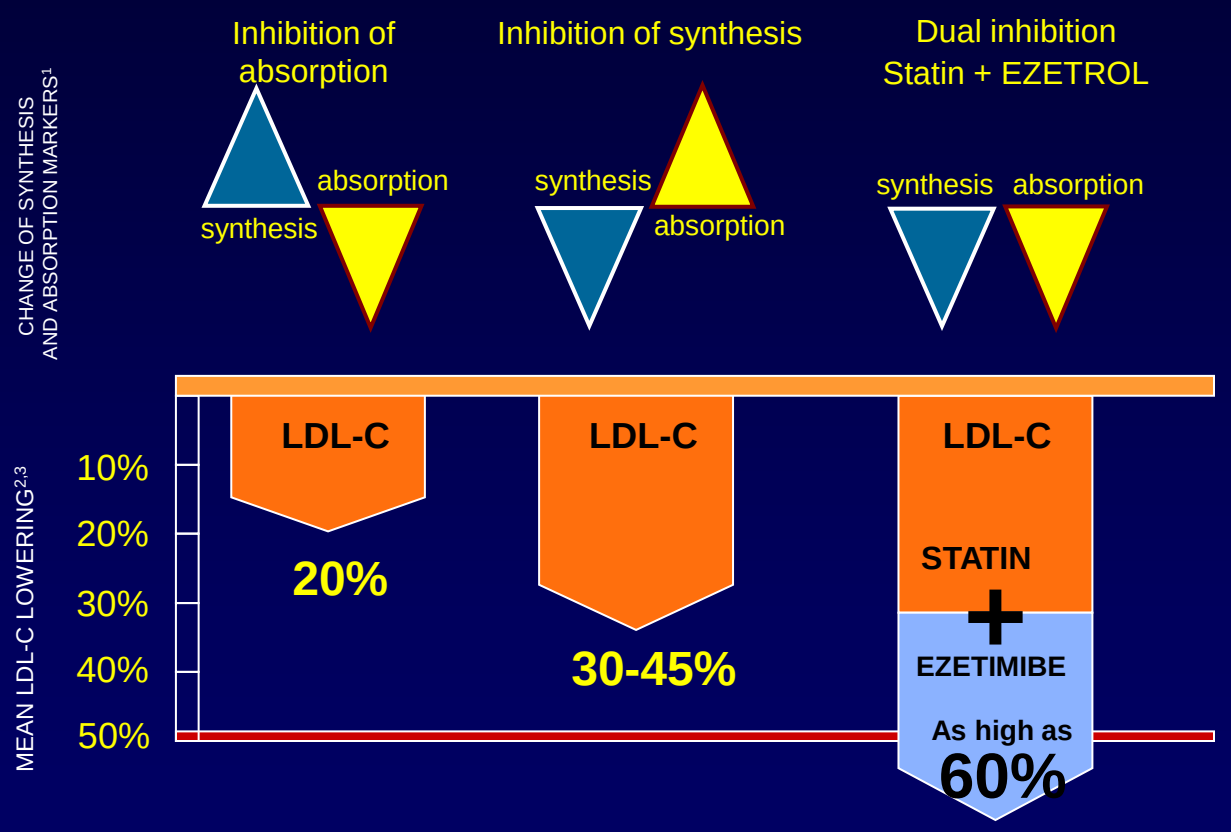
1. Reduction of hepatic cholesterol
2. Increased LDL receptor expression
3. Increased clearance of plasma LDL-C



NPC1L1 = Niemann-Pick C1-like 1; HMG-CoA = 3-hydroxy-3-methylglutaryl acetyl coenzyme A; CMR = chylomicron remnant.

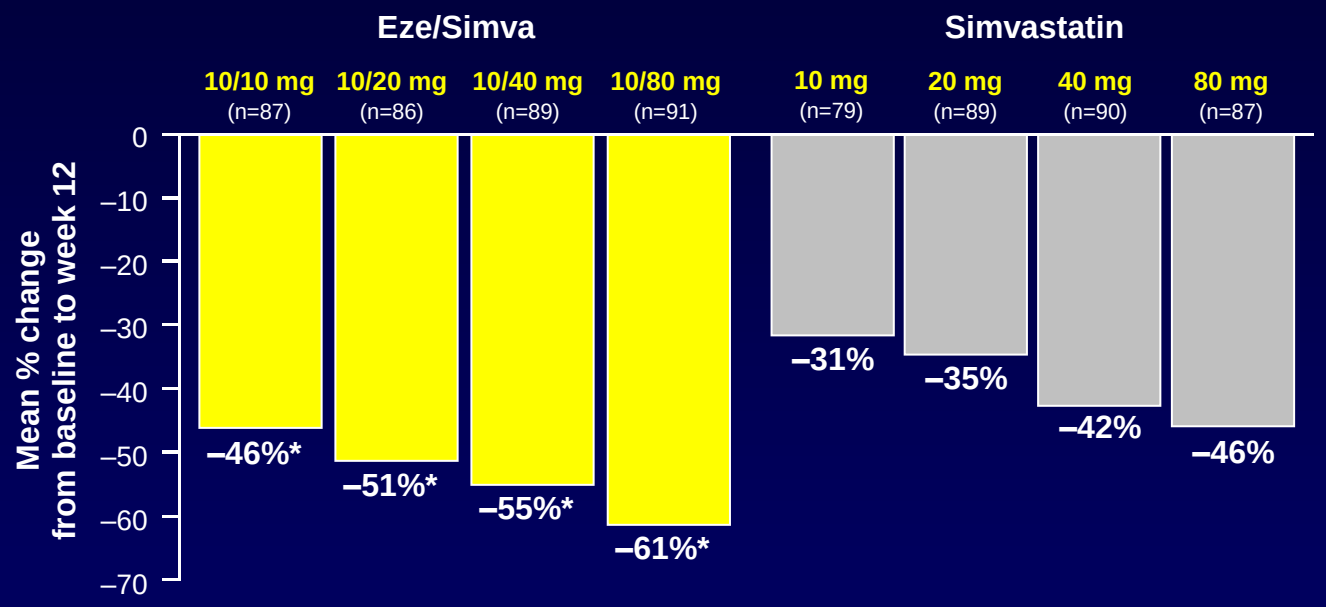
1. Grigore L et al. *Vas Health Risk Manag.* 2008;4:267–278.

As high as 60% LDL-C lowering via dual inhibition



1. Assmann G, et al. *J Am Coll Cardiol* 2004;43(5, Suppl. 2):A445-A446; **2.** Goldberg AC, et al. *Mayo Clin Proc.* 2004 May;79(5):620-9.; **3.** Davidson M et al. J Am Coll Cardiol 2002; 40:2125-34.

LDL-C Reduction Across the Dose Range

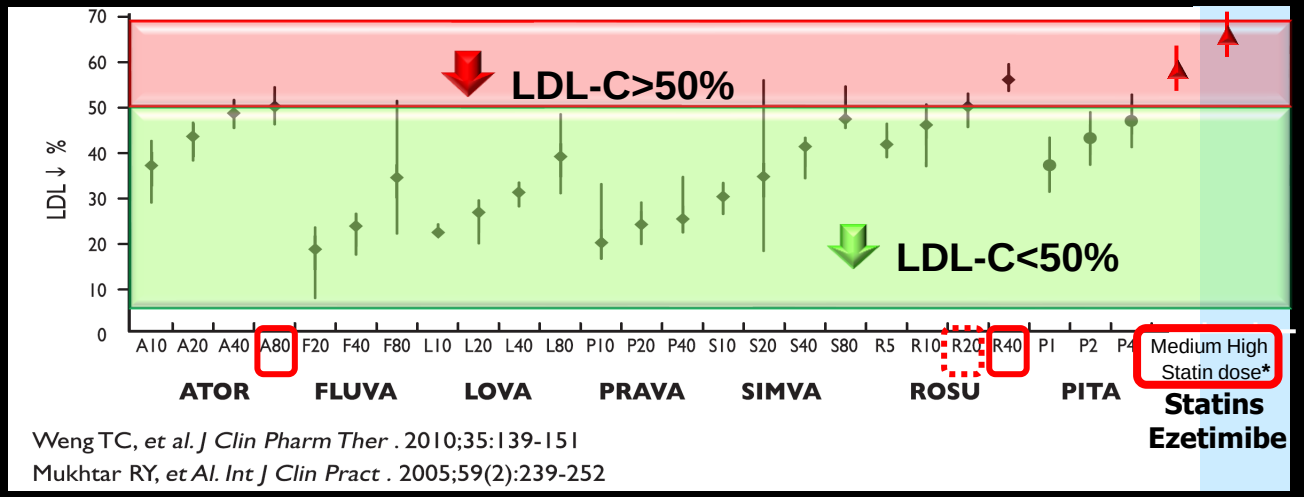


*p<0.001 vs. corresponding dose of simvastatin

Adapted from Goldberg AC et al. Poster presentation at the 53rd ACC, March 7–10, 2004.

LDL-C reductions with statin monotherapy

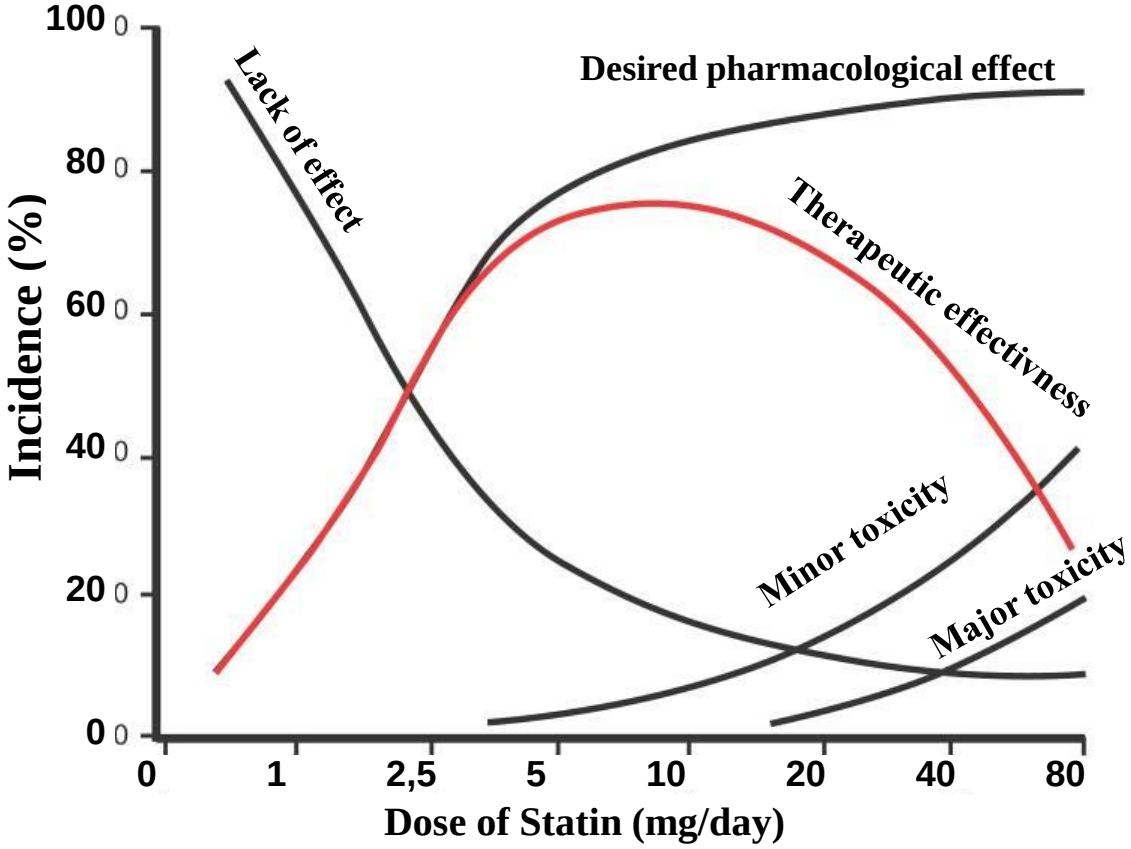
Doubling of a statin dose generally achieves a modest reduction in LDL-C of 5% to 6%



*High Efficacy Statins

Modified from ESC/EAS Guidelines for the Management of Dyslipidaemias: Addenda, European Heart Journal 2011

Statin: dose-effect relationship



Adapted from Rowland M et al., Clin. Pharmacokin.: Concepts and Applications. 2nd Ed. Philadelphia, Lea & Febiger, 1989

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REVIEWS / ONLINE FIRST

Statins plus ezetimibe in the era of proprotein convertase subtilisin/kexin type-9 inhibitors

Authors: Leonardo De Luca, Alberto Corsini, Massimo Uguccioni, Furio Colivicchi

DOI: 10.33963/KP.15529
Published online: July 24, 2020

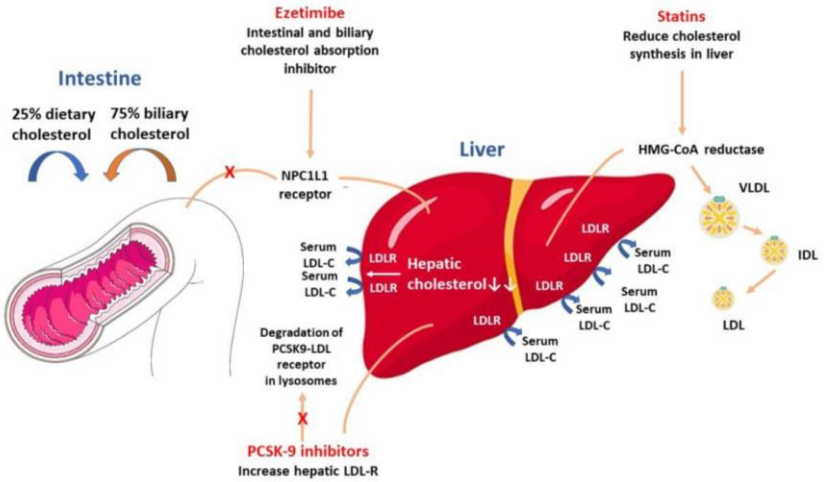


Figure 1. Lipid-lowering mechanisms of action for statins, ezetimibe, and PCSK-9 inhibtors.

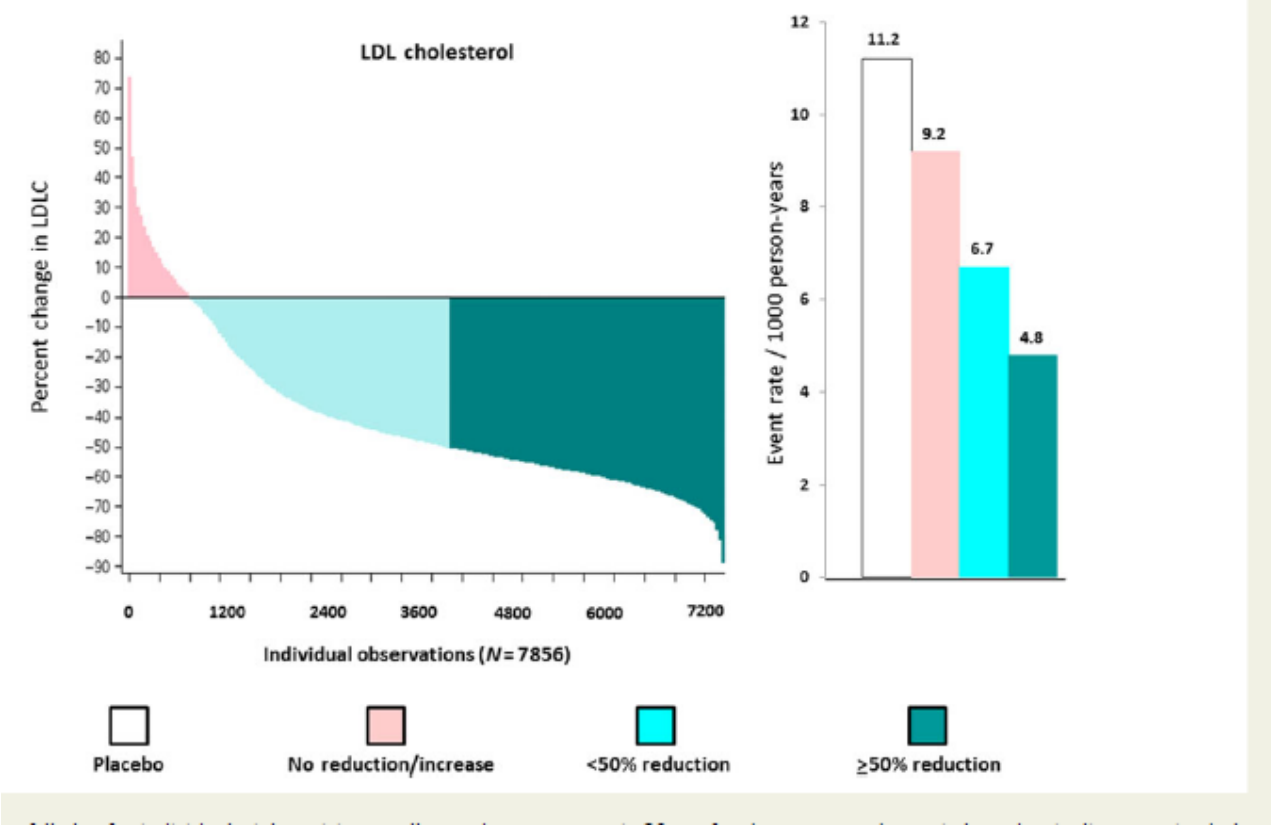
Kardiol Pol.
2020 Jul 24

Table 1. Mean percent change of total cholesterol and LDL-C from untreated baseline of the single-pill combination of ezetimibe/simvastatin, ezetimibe/atorvastatin and ezetimibe/rosuvastatin in patients with primary hypercholesterolemia.

Treatment	N	Total-C	LDL-C
Ezetimibe/simvastatin			
Pooled data (all ezetimibe/simvastatin doses)	609	-38	-53
Pooled data (all simvastatin doses)	622	-28	-39
Ezetimibe/simvastatin by dose			
10/10	152	-31	-45
10/20	156	-36	-52
10/40	147	-39	-55
10/80	154	-43	-60
Simvastatin by dose			
10	158	-23	-33
20	150	-24	-34
40	156	-29	-41
80	158	-35	-49
Ezetimibe/atorvastatin			
Pooled data (all ezetimibe/atorvastatin doses)	255	-41	-56
Pooled data (all atorvastatin doses)	248	-32	-44
Ezetimibe/atorvastatin by dose			
10/10	65	-38	-53
10/20	62	-39	-54
10/40	65	-42	-56
10/80	63	-46	-61
Atorvastatin by dose			
10	60	-26	-37
20	60	-30	-42
40	66	-32	-45
80	62	-40	-54
Ezetimibe/rosuvastatin			
Pooled data (all ezetimibe/ rosuvastatin doses)	195	-39	-57
Pooled data (all rosuvastatin doses)	194	-30	-44
Ezetimibe/rosuvastatin by dose			
10/5	65	-35	-52
10/10	66	-39	-57
10/20	64	-45	-64
Rosuvastatin by dose			
5	65	-29	-40
10	65	-31	-46
20	64	-35	-49

De Luca L et al. Kardiol Pol. 2020 Jul 24

Waterfall plot for participants allocated to rosuvastatin 20 mg for % change in LDL-C and incident event rates in JUPITER trial



Ridker PM et al Eur Heart J. 2016 Feb 24

Lipids in Health and Disease

BioMed Central

Research

Open Access

NPC1L1 haplotype is associated with inter-individual variation in plasma low-density lipoprotein response to ezetimibe

Robert A Hegele*[1,2], Justin Guy[1], Matthew R Ban[1] and Jian Wang[1]

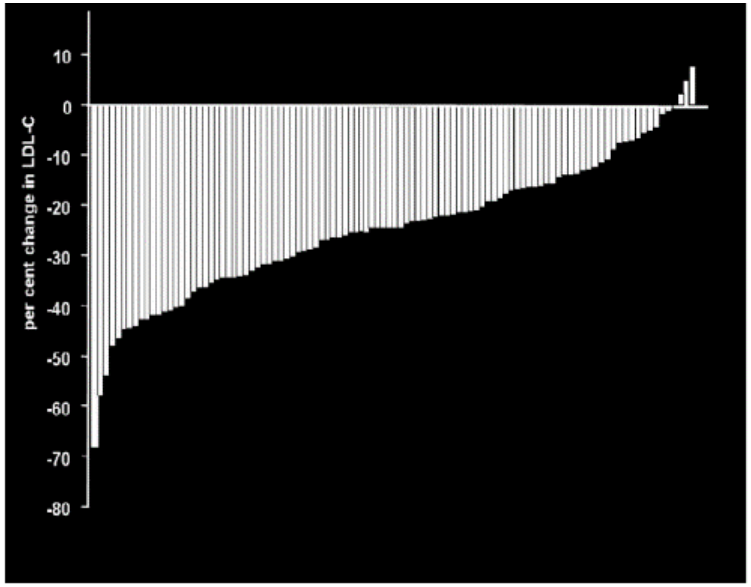


Figure 1
Individual LDL-cholesterol response to ezetimibe 10 mg. Each bar represents the percent change in LDL-cholesterol from baseline for one study subject; these data are arranged in rank order to show the range of responses.

Lipids in Health and Disease 2005, 4:16

There is a negative correlation between the LDL-C response to statins and the response to Ezetimibe

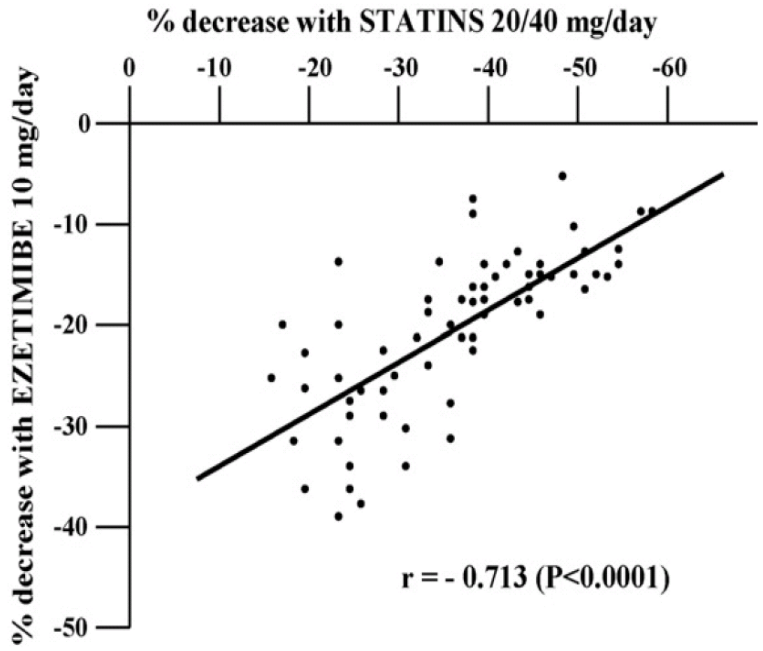
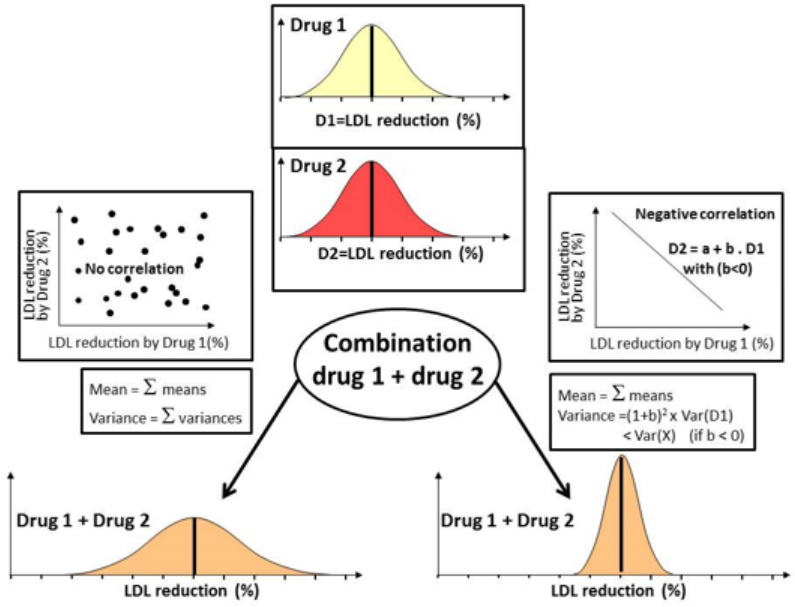


Fig. 2. Pearson's correlation between percent decrease of LDL-C induced by statins and by ezetimibe in genotype confirmed heterozygous FH patients.

Pisciotta L et al. Atherosclerosis 2006

Effect of a negative correlation between the LDL reduction of two drugs on the final variance of LDL reduction induced by the combination of the two drugs

Supplemental Figure 2.



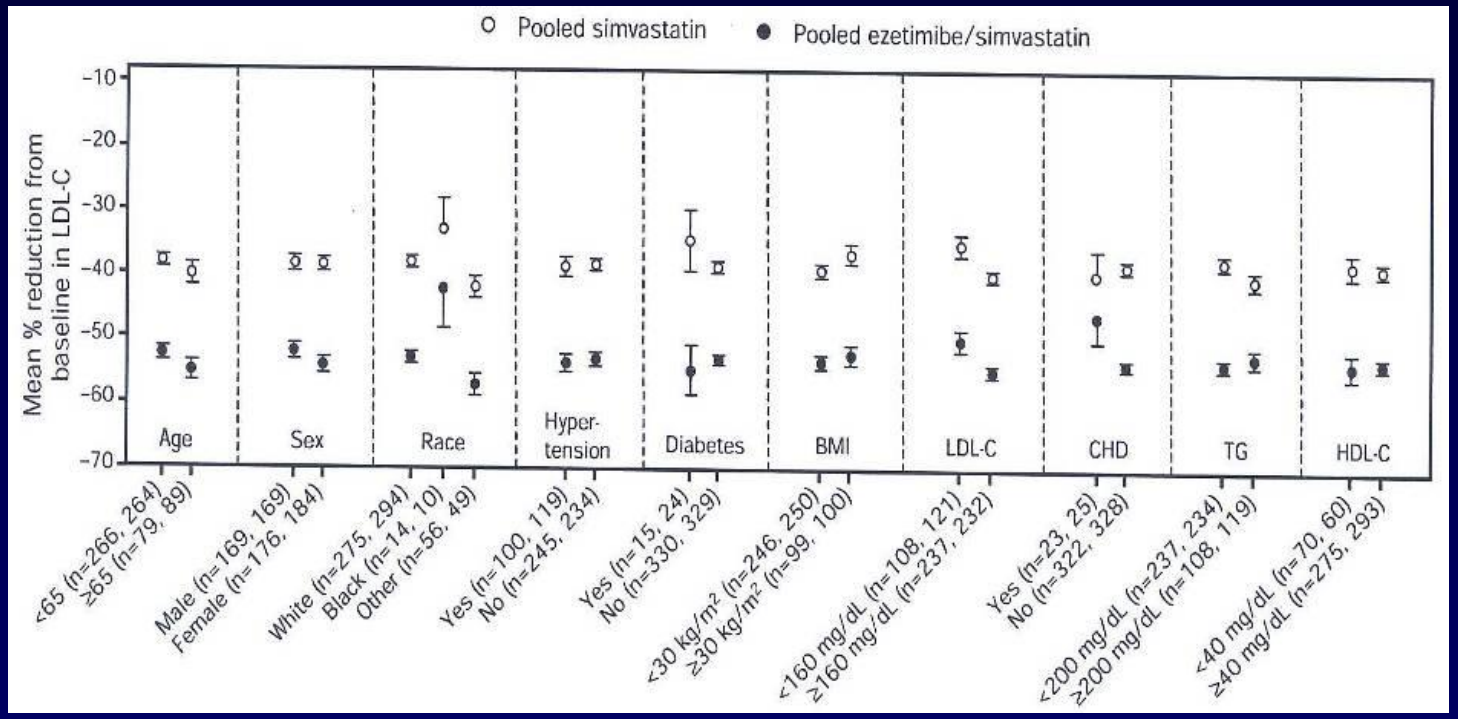
Mathematical demonstration of the effect of a negative correlation between the LDL reduction of two drugs on the final variance of LDL reduction induced by the combination of the two drugs.

Atherosclerosis 240 (2015) 482e489. Supplementary data

Lipid-Lowering Efficacy of Ezetimibe and Ezetimibe/Simvastatin

- Adding ezetimibe to ongoing statin therapy
- Adding ezetimibe to ongoing statin therapy vs doubling the statin dose vs switching to rosuvastatin
- Heterozygous FH
- Statin intolerance

Co-Administration of Ezetimibe with Simvastatin: % Reduction on LDL-C by Baseline Subgroup Parameters



Anne C. Goldberg et al., Mayo Clin Proc 2004;79:620-629

Ezetimibe in monoterapia		
Classi di organi e sistemi	**Reazioni avverse**	**Frequenza**
Esami diagnostici	ALT e/o AST aumentate Aumento della CPK ematica Aumento della gamma-glutamiltransferasi Anormalità nei test di funzionalità epatica	Non comune
Patologie respiratorie, toraciche e mediastiniche	Tosse	Non comune
Patologie gastrointestinali	Dolore addominale Diarrea Flatulenza	Comune
	Dispepsia Malattia da reflusso gastroesofageo Nausea	Non comune
Patologie del sistema muscoloscheletrico e del tessuto connettivo	Artralgia spasmi muscolari Dolore al collo	Non comune
Disturbi del metabolismo e della nutrizione	Diminuzione dell'appetito	Non comune
Patologie vascolari	Vampate di calore Ipertensione	Non comune
Patologie sistemiche e condizioni relative alla sede di somministrazione	Stanchezza	Comune
	Dolore al torace Dolore	Non comune

Del Farmaco

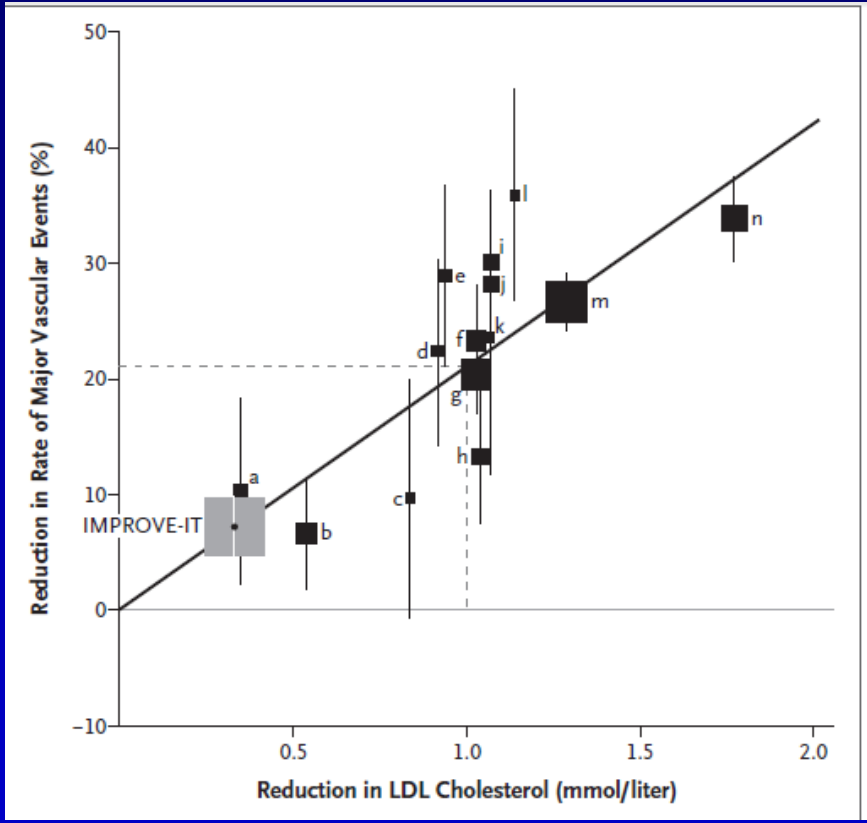
Ulteriori reazioni avverse con ezetimibe in somministrazione concomitante con una statina		
Classi di organi e sistemi	**Reazioni avverse**	**Frequenza**
Esami diagnostici	ALT e/o AST aumentate	Comune
Patologie del sistema nervoso	Mal di testa	Comune
	Parestesia	Non comune
Patologie gastrointestinali	Bocca secca Gastrite	Non comune
Patologie della cute e del tessuto sottocutaneo	Prurito Eruzione cutanea Orticaria	Non comune
Patologie del sistema muscoloscheletrico e del tessuto connettivo	Mialgia	Comune
	Dolore alla schiena Debolezza muscolare Dolore alle estremità	Non comune
Patologie sistemiche e condizioni relative alla sede di somministrazione	Astenia Edema periferico	Non comune

Eze-Simva: Clinical trials program in >28,000 high CVD risk patients

	N	Study Population	Treatments	Primary Endpoint
ENHANCE Ezetimibe + Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression	~725	HeFH	Ezetimibe/ simvastatin 10/80 mg Simvastatin 80 mg	CA IMT
SEAS Simvastatin + Ezetimibe in Aortic Stenosis	~1873	Asymptomatic aortic stenosis with LDL-C <6 mmol/L	Ezetimibe/ simvastatin 10/40 mg vs Placebo	CV death, aortic surgery, CV outcomes
SHARP Study of Heart and Renal Protection	~9000	Chronic kidney disease	Ezetimibe/ simvastatin 10/20 mg vs Placebo	CV outcomes (MI, stroke, coronary revascularization)
IMPROVE-IT Improved Reduction of Outcomes: VYTORIN™ Efficacy International Trial	~18,000	ACS	Ezetimibe/ simvastatin 10/40 mg vs Simva 40 mg	CV endpoints (death, MI, ACS, revascularization)

Adapted from Kastelein JJP, et al. *Am Heart J*. 2005;149:234–239; Baigent C, Landry M. *Kidney Int*. 2003;63(suppl 84):S207–S210; Oxford Clinical Trial Service Unit. The Study of Heart and Renal Protection (SHARP). Available at: http://www.ctsu.ox.ac.uk/ ~sharp/. Accessed June 2005; Rossebo A, et al, for the SEAS Steering Committee. Presented at: XIII International Symposium on Atherosclerosis; September 23–October 2, 2003; Kyoto, Japan. Poster 3P-0870; Schering-Plough. IMPROVE-IT: Examining outcomes in subjects with acute coronary syndrome: Vytorin (ezetimibe/simvastatin) vs simvastatin (Study P04103). Available at: http://www.clinicaltrials.gov/ct/show/NCT00202878. Accessed November 2006.

Plot of the IMPROVE-IT Trial Data and Statin Trials for Change LDL-C vs Clinical Benefit



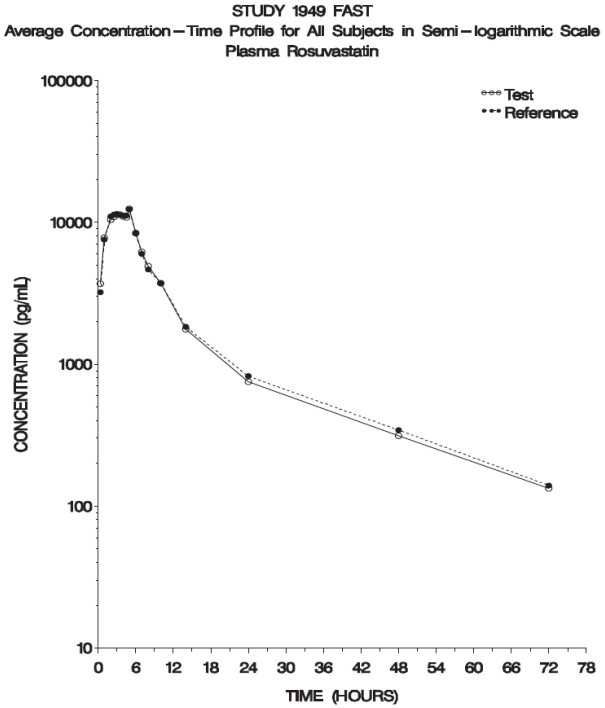
Cannon CP et al. N Engl J Med 2015;372:2387-2397

Title of Study:
A Single-Dose, Randomized, Open-Label, Two-Way Crossover, Pivotal, Bioequivalence Study of Rosuvastatin + Ezetimibe, Tablets, 20 mg + 10 mg (Adamed Sp. z o.o.) and Crestor® 20 mg Film-Coated Tablets (AstraZeneca BV) and Ezetrol® 10 mg Tablets (Merck Sharp & Dohme Limited) in Healthy Male and Non-pregnant Female Volunteers under Fasting Conditions.

Test Product (Treatment A):	Rosuvastatin + Ezetimibe, tablets, 20 mg + 10 mg; Lot No: 41566685 Manufacturer: Pabianickie Zaklady Farmaceutyczne Polfa S.A., Poland Dose: 1 x 20 mg + 10mg Mode of Administration: Oral under fasting conditions
Reference Products (Treatment B):	1) Crestor® 20 mg film-coated tablets; Lot No: LV980 MAH: AstraZeneca BV Dose: 1 x 20 mg Mode of Administration: Oral under fasting conditions 2) Ezetrol® 10 mg tablets; Lot No: 340811 MAH: Merck Sharp & Dohme Limited Dose: 1 x 10 mg Mode of Administration: Oral under fasting conditions

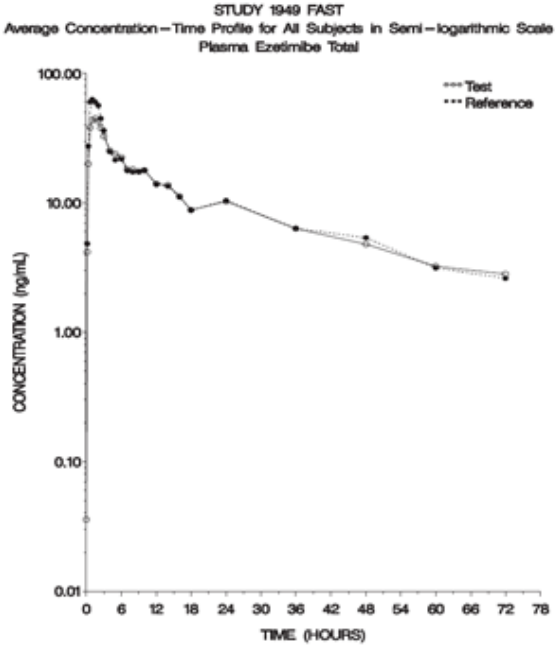
Duration of treatment:
The study consisted of two study periods. Each study period included a single-dose drug administration of either the Test product or the Reference product. There was a washout period of 14 days between each drug administration.
Subjects were confined to the clinic at least 10 hours prior to dosing until approximately 24 hours post-dose. Subjects were required to return to the clinical facility for the 36, 48, 60 and 72 hours post dose blood draws.

Criteria for Evaluation:
Bioequivalence:
To establish bioequivalence, the calculated 90% CI for the Test/Reference ratios of geometric means for AUC_t and C_{max} for rosuvastatin and ezetimibe free should fall within 80.00%-125.00%.

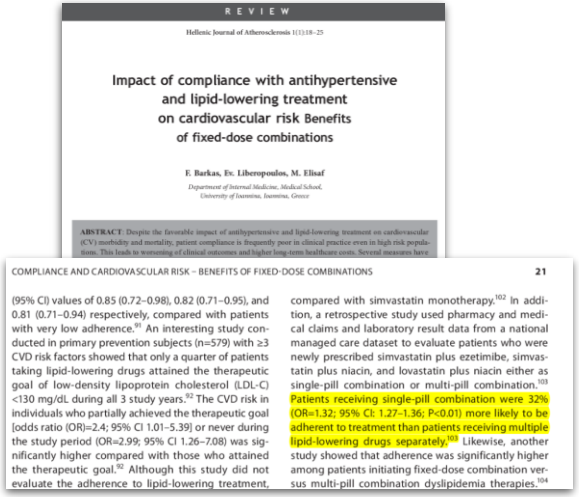


Confidential Information
The information in this study report is legally privileged and confidential. Any disclosure, copying or distribution of the information contained within is strictly prohibited without written consent from the sponsor and BioPharma Services Inc.

Figure 6: The mean plasma concentration profile for ezetimibe total in semi-log scale plot



Statina+ezetimibe: efficacia, tollerabilità e semplicità di somministrazione



REVIEW

Hellenic Journal of Atherosclerosis 1(1):18–25

Impact of compliance with antihypertensive and lipid-lowering treatment on cardiovascular risk Benefits of fixed-dose combinations

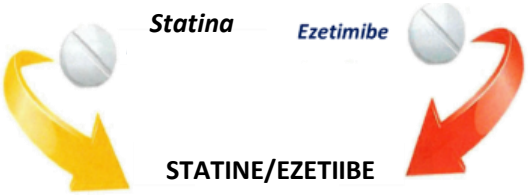
F. Barkas, Ev. Liberopoulos, M. Elisaf

Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece

ABSTRACT: Despite the favorable impact of antihypertensive and lipid-lowering treatment on cardiovascular (CV) morbidity and mortality, patient compliance is frequently poor in clinical practice even in high risk populations. This leads to worsening of clinical outcomes and higher long-term healthcare costs. Several measures have

(95% CI) values of 0.85 (0.72–0.98), 0.82 (0.71–0.95), and 0.81 (0.71–0.94) respectively, compared with patients with very low adherence.[91] An interesting study conducted in primary prevention subjects (n=579) with ≥3 CVD risk factors showed that only a quarter of patients taking lipid-lowering drugs attained the therapeutic goal of low-density lipoprotein cholesterol (LDL-C) <130 mg/dL during all 3 study years.[92] The CVD risk in individuals who partially achieved the therapeutic goal [odds ratio (OR)=2.4; 95% CI 1.01–5.39] or never during the study period (OR=2.99; 95% CI 1.26–7.08) was significantly higher compared with those who attained the therapeutic goal.[92] Although this study did not evaluate the adherence to lipid-lowering treatment, compared with simvastatin monotherapy.[102] In addition, a retrospective study used pharmacy and medical claims and laboratory result data from a national managed care dataset to evaluate patients who were newly prescribed simvastatin plus ezetimibe, simvastatin plus niacin, and lovastatin plus niacin either as single-pill combination or multi-pill combination.[103] Patients receiving single-pill combination were 32% (OR=1.32; 95% CI: 1.27–1.36; P<0.01) more likely to be adherent to treatment than patients receiving multiple lipid-lowering drugs separately.[103] Likewise, another study showed that adherence was significantly higher among patients initiating fixed-dose combination versus multi-pill combination dyslipidemia therapies.[104]

1 COMPRESSA AL GIORNO



+ 32% di ADERENZA

con l'associazione precostituita

Barkas F et al. 1 (1): 18-25

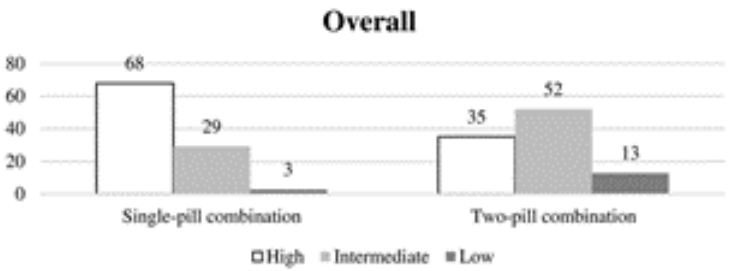
Adv Ther
https://doi.org/10.1007/s12325-021-01892-7

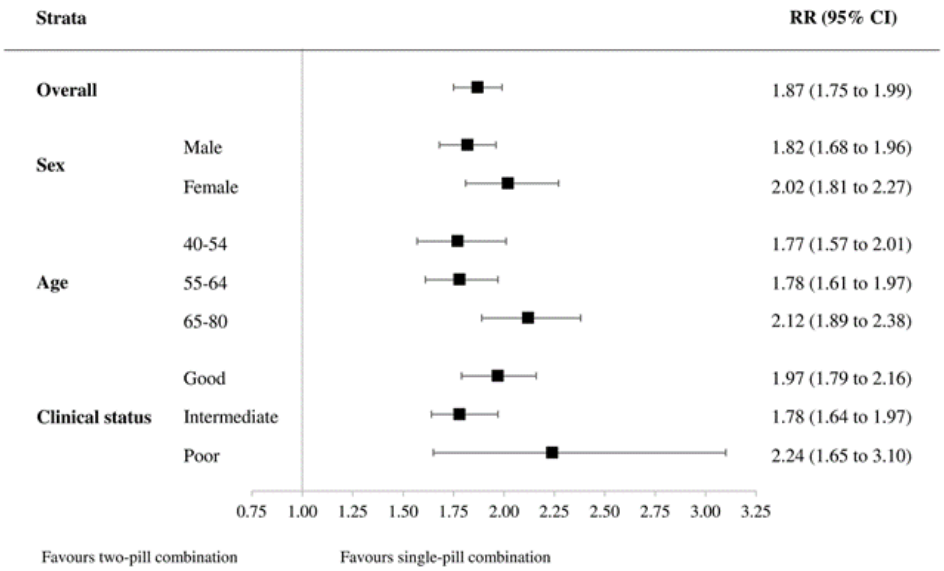
ORIGINAL RESEARCH

Adherence to Lipid-Lowering Treatment by Single-Pill Combination of Statin and Ezetimibe

Federico Rea · Laura Savaré · Giovanni Corrao · Giuseppe Mancia

Adherence to drug therapy according to the drug treatment strategy, i.e., single-pill versus two-pill combination of a statin and ezetimibe





The study suggests that the single-pill formulation of statin and ezetimibe improves adherence and persistence at all ages and at different levels of CVD risk

Adv Ther 2021 Oct;38(10):5270-5285

Atherosclerosis 325 (2021) 99–109

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journal homepage: www.elsevier.com/locate/atherosclerosis

From the EAS

Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force

Maurizio Averna [a], Maciej Banach [b], Eric Bruckert [c], Heinz Drexel [d,e,f], Michel Farnier [g], Dan Gaita [h], Paolo Magni [i], Winfried März [j,k], Luis Masana [l], Alberto Mello e Silva [m], Zeljko Reiner [n], Emilio Ros [o,p], Michal Vrablik [q], Alberto Zambon [r], Jose L. Zamorano [s], Jane K. Stock [t], Lale S. Tokgözoğlu [u], Alberico L. Catapano [i,*]

Background and aims: This European Atherosclerosis Society (EAS) Task Force provides practical guidance for combination therapy for elevated low-density lipoprotein cholesterol (LDL-C) and/or triglycerides (TG) in high-risk and very-high-risk patients.

Methods: Evidence-based review.

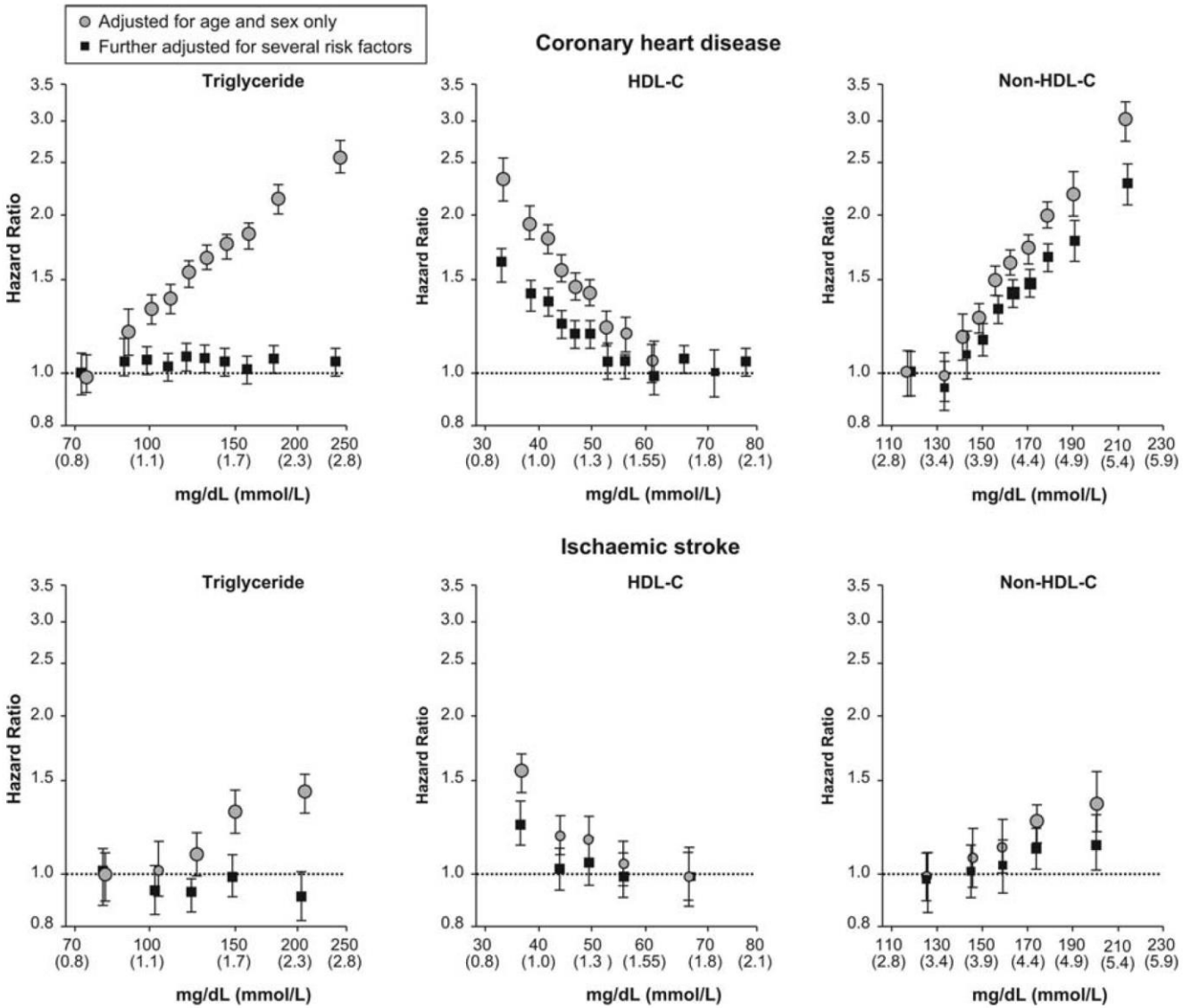
Results: Statin-ezetimibe combination treatment is the first choice for managing elevated LDL-C and should be given upfront in very-high-risk patients with high LDL-C unlikely to reach goal with a statin, and in primary prevention familial hypercholesterolaemia patients. A proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor may be added if LDL-C levels remain high. In high and very-high-risk patients with mild to moderately elevated TG levels (>2.3 and < 5.6 mmol/L [>200 and < 500 mg/dL) on a statin, treatment with either a fibrate or high-dose omega-3 fatty acids (icosapent ethyl) may be considered, weighing the benefit versus risks. Combination with fenofibrate may be considered for both macro- and microvascular benefits in patients with type 2 diabetes mellitus.

Conclusions: This guidance aims to improve real-world use of guideline-recommended combination lipid modifying treatment.

- Farmaci ipocolesterolemizzanti

- **Farmaci ipotrigliceridemizzanti**

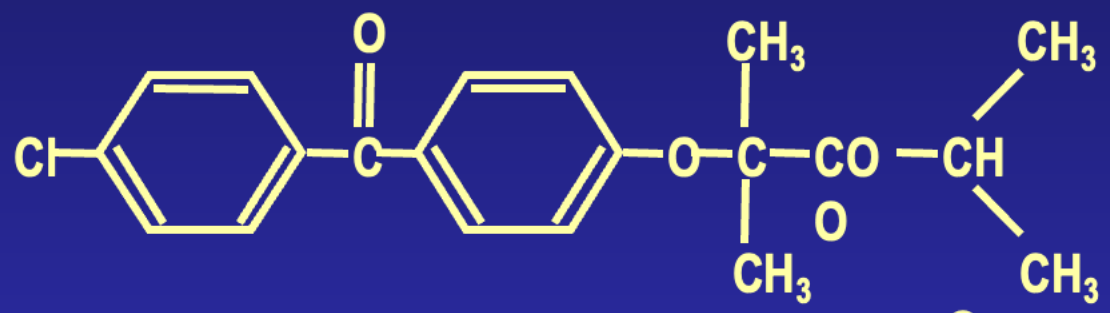
Hazard ratios for CVD risk across quintiles of triglycerides, HDL, and non-HDL cholesterol levels.



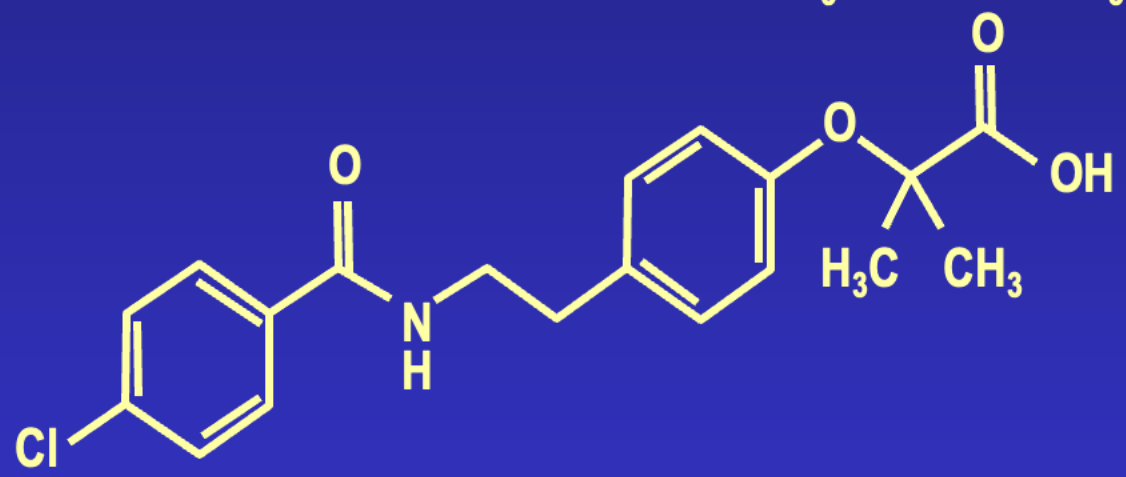
Chapman JM et al EHJ (2011) 32, 1345–1361

Fibrates

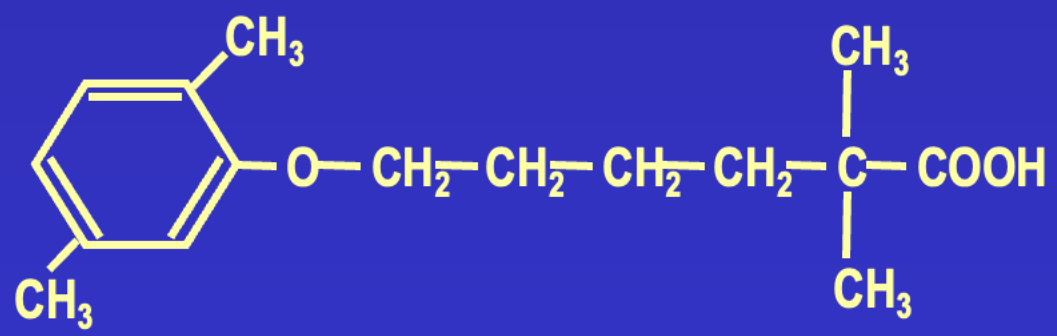
Fenofibrate



Bezafibrate



Gemfibrozil



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Impact of Existing Drug Therapies on Lipid Parameters

Drug class/agents	HDL-C effect	LDL-C effect	Triglyceride effect
Nicotinic acid	↑ 15–35%	↓ 5–25%	↓ 20–50%
Fibric acids	↑ 10–20%	↓ 5–20%	↓ 20–50%
Statins	↑ 5–15%	↓ 18–55%	↓ 7–30%
Bile acid sequestrants	↑ 3–5%	↓ 15–30%	No change or increase
Ezetimibe	↑ 3%	↓ 19%	↓ 8%
Omega-3 FA*	↑ or neutral	↑ or neutral	↓ 20–50 %

Jacobson et al. Clin Ther 2007; 29: 763-777

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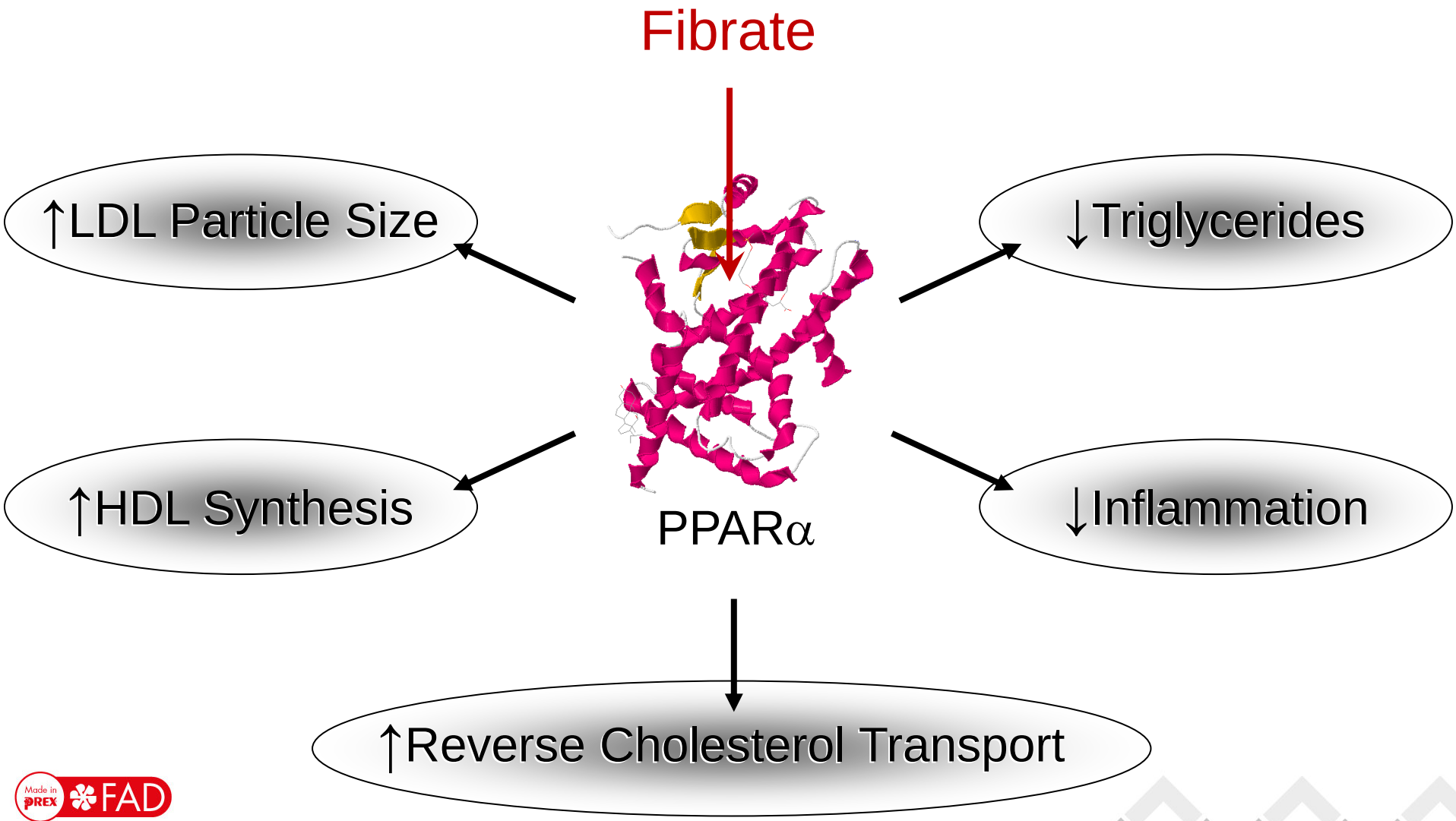
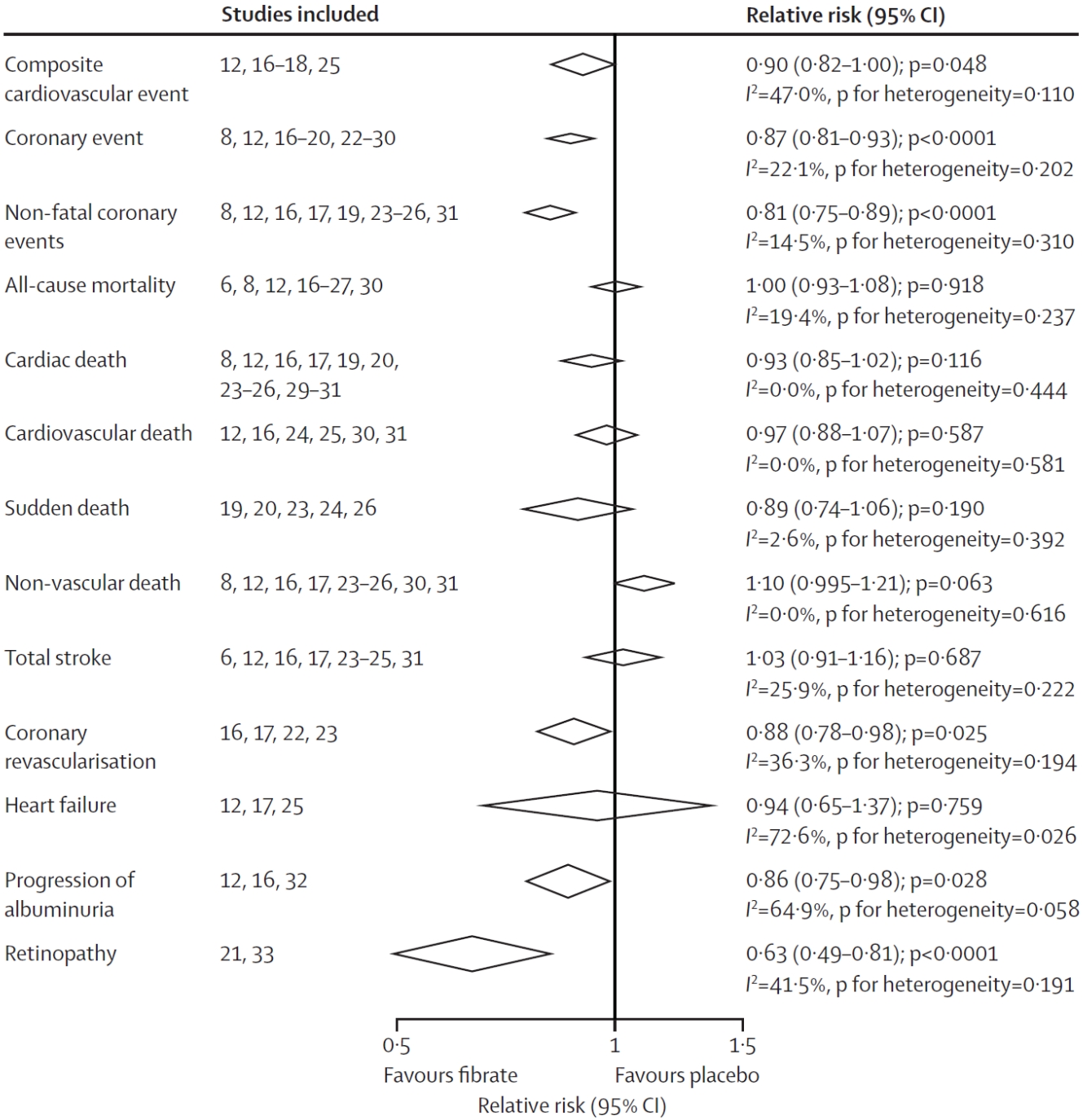
Fibrate Mechanisms of Action

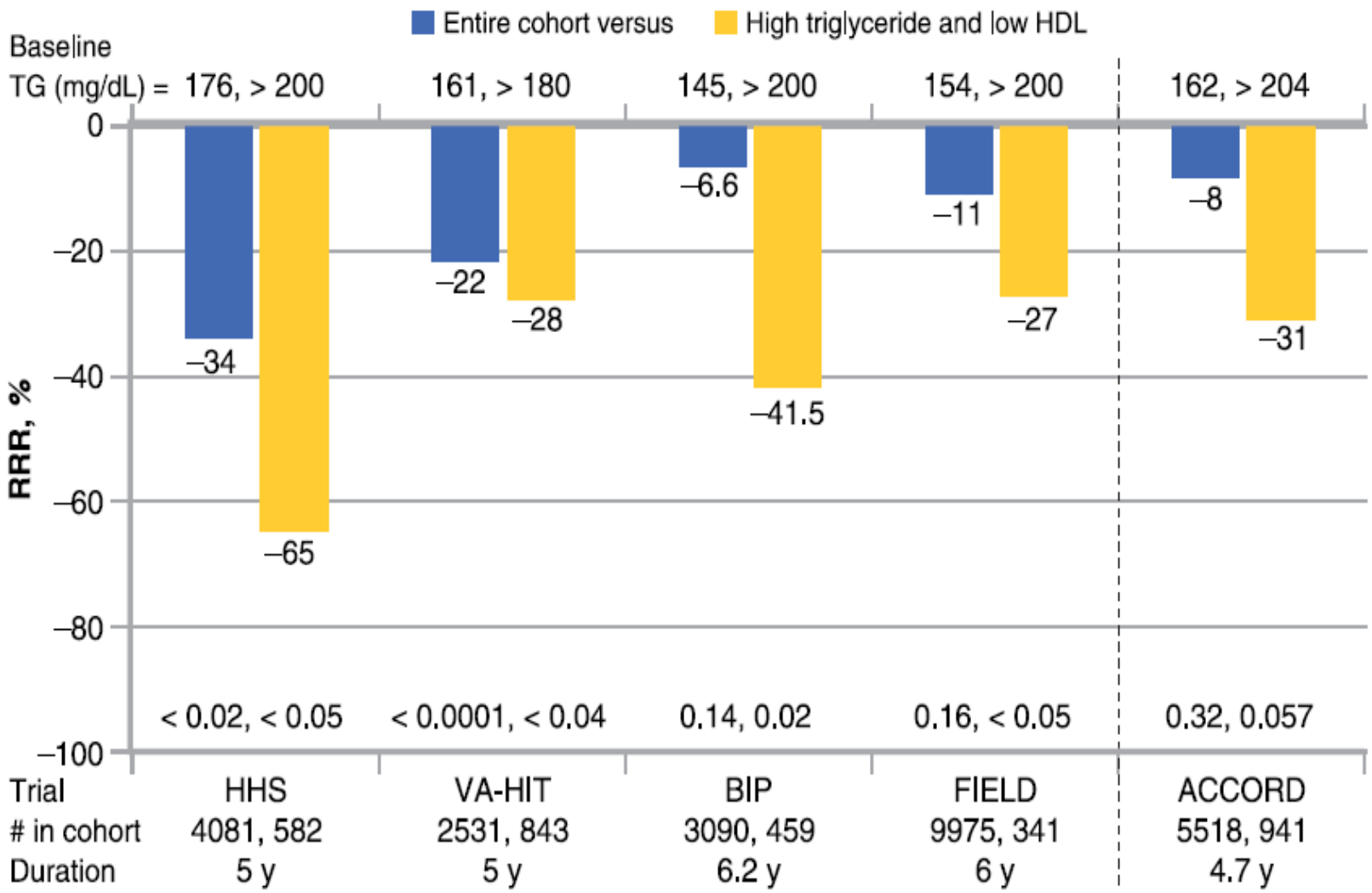


Effect of fibrates on clinical outcomes



Jun M et al. Lancet 2010; 375: 1875–84

Cardiovascular event risk reduction in large monotherapy fibrate clinical trials



Rosenblit PD Curr Cardiol Rep (2012) 14:112–124

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Fibrates: side effects

- mild gastrointestinal distress
- hepatic dysfunction
- muscular syndrome (myalgia)
- impotence
- (cholelithiasis)
- drug interactions

Made in PREX FAD

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Jacobson et al. Clin Ther 2007; 29: 763-777

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Current Atherosclerosis Reports (2021) 23:17
https://doi.org/10.1007/s11883-021-00918-3

STATIN DRUGS (R. CESKA, SECTION EDITOR)

Lipid Lowering Drugs: Present Status and Future Developments

Massimiliano Ruscica[1] · Nicola Ferri[2] · Raul D. Santos[3,4] · Cesare R. Sirtori[1] · Alberto Corsini[1,5]

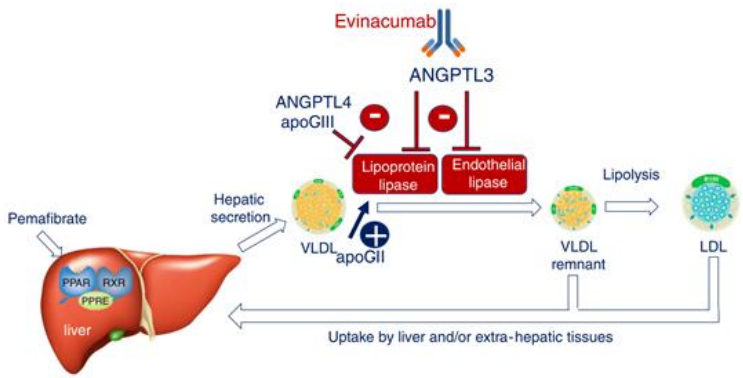

Fig. 2 Molecular mechanism of ANGPTL3 inhibition. ANGPTL3 inhibits both the lipoprotein and endothelial lipases and thus the conversion of VLDL into LDL. A similar effect is determined by ANGPTL4 and apoC-III, while apoC-II is a coactivator of lipoprotein lipase. The monoclonal antibody evinacumab binds and inhibits the ANGPTL3 generating VLDL remnant particles that are efficiently removed from the circulation. Thus, ANGPTL3 inhibition may lower LDL-C by limiting LDL particle production and endothelial lipase could be a key mediator of this novel pathway. ANGPTL, angiopoietin-like; apo, apolipoprotein; LDL, low-density lipoprotein; VLDL, very-low density lipoprotein. Adapted with permission of Elsevier [40].

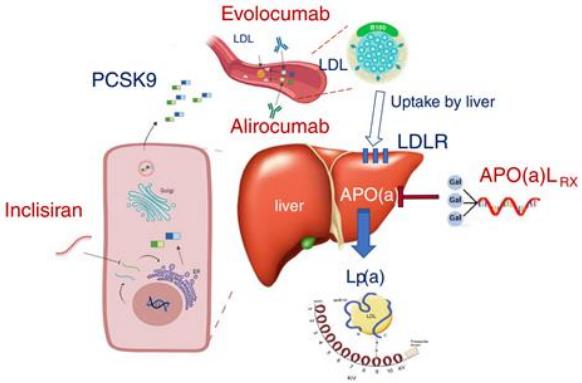

Fig. 1 Molecular mechanisms of PCSK9 and Lp(a) inhibition. PCSK9, mainly derived from the liver, acts by degrading the LDLR expressed on hepatocytes. PCSK9 inhibition leads to higher LDLR expression, thus lowering plasma LDL cholesterol. Inclisiran by inhibiting the transcription of the PCSK9 mRNA reduces the total amount of circulating PCSK9. Conversely, monoclonal antibodies (evolocumab and alirocumab) block PCSK9 interaction with LDLR. Both therapies have shown to strongly reduce the LDL-C levels. Relative to Lp(a) lowering, IONIS-APO(a)Lrx is a ligand-conjugated ASO with a triantennary N-acetylgalactosamine (GalNAc) covalently attached, to allow rapid and specific uptake by hepatocytes. ASO, antisense oligonucleotide; LDLR, low-density lipoprotein receptor; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9. Adapted with permission of Elsevier [40].

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