AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

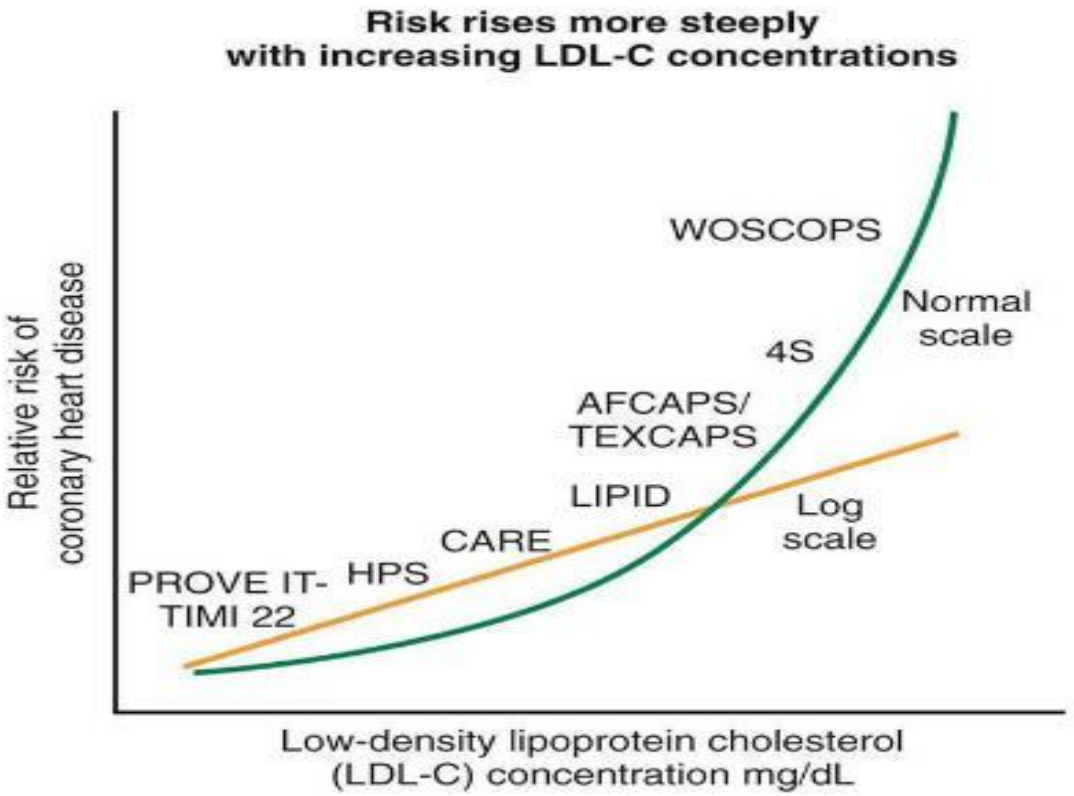
UNIVERSITÀ
DI TORINO

UPDATE 1

NOVITA' NELLA TERAPIA DELLE DISLIPIDEMIE

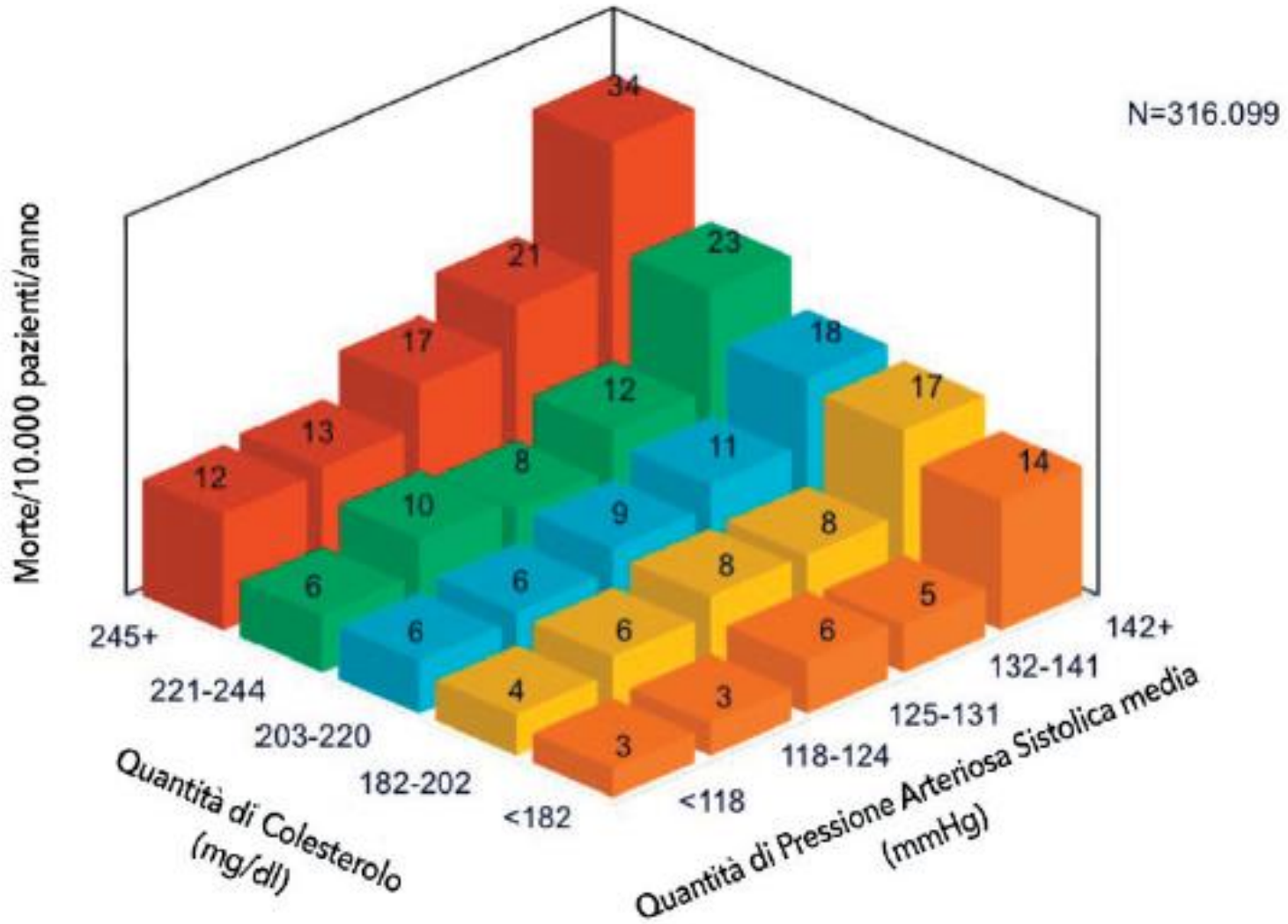
Franco Rabbia

Relazione tra livelli di colesterolo LDL e rischio relativo di malattia coronarica nei trial clinici



Huang JC, Hoogwerf BJ. Cholesterol guidelines update. More aggressive therapy for higher-risk patients. *Cleve Clin J Med*. 2005;72:253-262.

Effetto additivo dei livelli di colesterolo e della pressione arteriosa sistolica sul rischio di eventi coronarici nei grandi Trials



Neaton Arch Intern Med 1992

ESC European Society of Cardiology

European Heart Journal (2020) **41**, 111–188
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

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

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

Authors/Task Force Members: François Mach* (Chairperson) (Switzerland), Colin Baigent* (Chairperson) (United Kingdom), Alberico L. Catapano[1]* (Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula[1] (Italy), Lina Badimon (Spain), M. John Chapman[1] (France), Guy G. De Backer (Belgium), Victoria Delgado (Netherlands), Brian A. Ference (United Kingdom), Ian M. Graham (Ireland), Alison Halliday (United Kingdom), Ulf Landmesser (Germany), Borislava Mihaylova (United Kingdom), Terje R. Pedersen (Norway), Gabriele Riccardi[1] (Italy), Dimitrios J. Richter (Greece), Marc S. Sabatine (United States of America), Marja-Riitta Taskinen[1] (Finland), Lale Tokgozoglu[1] (Turkey), Olov Wiklund[1] (Sweden)

Eur heart J 2020

Società Italiana dell'Ipertensione Arteriosa
Lega Italiana contro l'Ipertensione Arteriosa

Documento ufficiale della
Società Italiana dell'Ipertensione Arteriosa:

Ipercolesterolemia nel paziente iperteso

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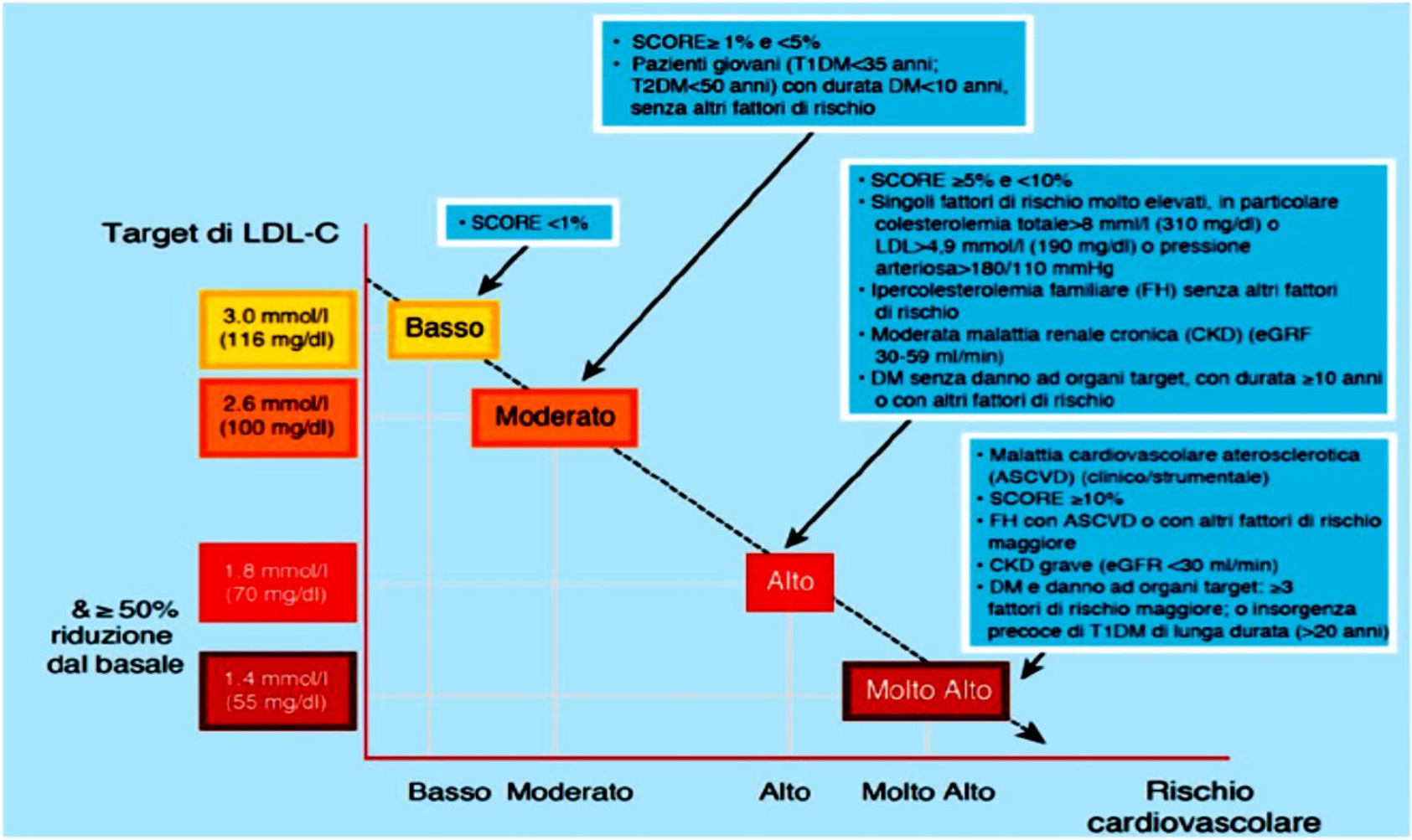
Massimo Volpe

STRATIFICAZIONE DEL RISCHIO CARDIOVASCOLARE A 10 ANNI (SCORE SYSTEM)

Rischio particolarmente elevato	• Precedente sindrome coronarica acuta seguita da ulteriore evento cardiovascolare entro 2 anni.
Rischio molto alto	• Malattia CV documentata, clinicamente o tramite imaging. Include: – sindrome coronarica acuta, angina stabile, rivascolarizzazione coronarica, ictus o attacco ischemico transitorio, arteriopatia periferica; – una placca rilevante alla coronarografia o alla TC (malattia coronarica multivasale, con due arterie epicardiche principali con stenosi >50%) o all'ecografia carotidea. • Diabete mellito con danno d'organo (microalbuminuria, retinopatia, neuropatia) o almeno 3 fattori di rischio CV, o diabete mellito di tipo 1 comparso precocemente e presente da più di 20 anni. • Nefropatia cronica severa (eGFR <30 ml/min/1.73 m²) • Rischio a 10 anni di malattia CV fatale calcolato con il sistema SCORE ≥10%. • Ipercolesterolemia familiare con ASCVD o un altro fattore di rischio CV.
Rischio alto	• Singoli fattori di rischio particolarmente elevati, come colesterolo totale >310 mg/dl, C-LDL >190 mg/dl o pressione arteriosa ≥180/110 mmHg. • Ipercolesterolemia familiare senza altri fattori di rischio CV. • Diabete mellito senza danno d'organo, ma presente da almeno 10 anni o in concomitanza ad un altro fattore di rischio CV. • Nefropatia cronica moderata (eGFR 30-59 ml/min/1.73 m²). • Rischio a 10 anni di malattia CV fatale calcolato con il sistema SCORE ≥5% e <10%.
Rischio moderato	• Diabete mellito in soggetti giovani (diabete di tipo 1 <35 anni, diabete di tipo 2 <50 anni), presente da meno di 10 anni e in assenza di altri fattori di rischio. • Rischio di malattia CV fatale a 10 anni, calcolato con il sistema SCORE ≥1% e <5%.
Rischio basso	• Rischio di malattia CV fatale a 10 anni, calcolato con il sistema SCORE <1%.

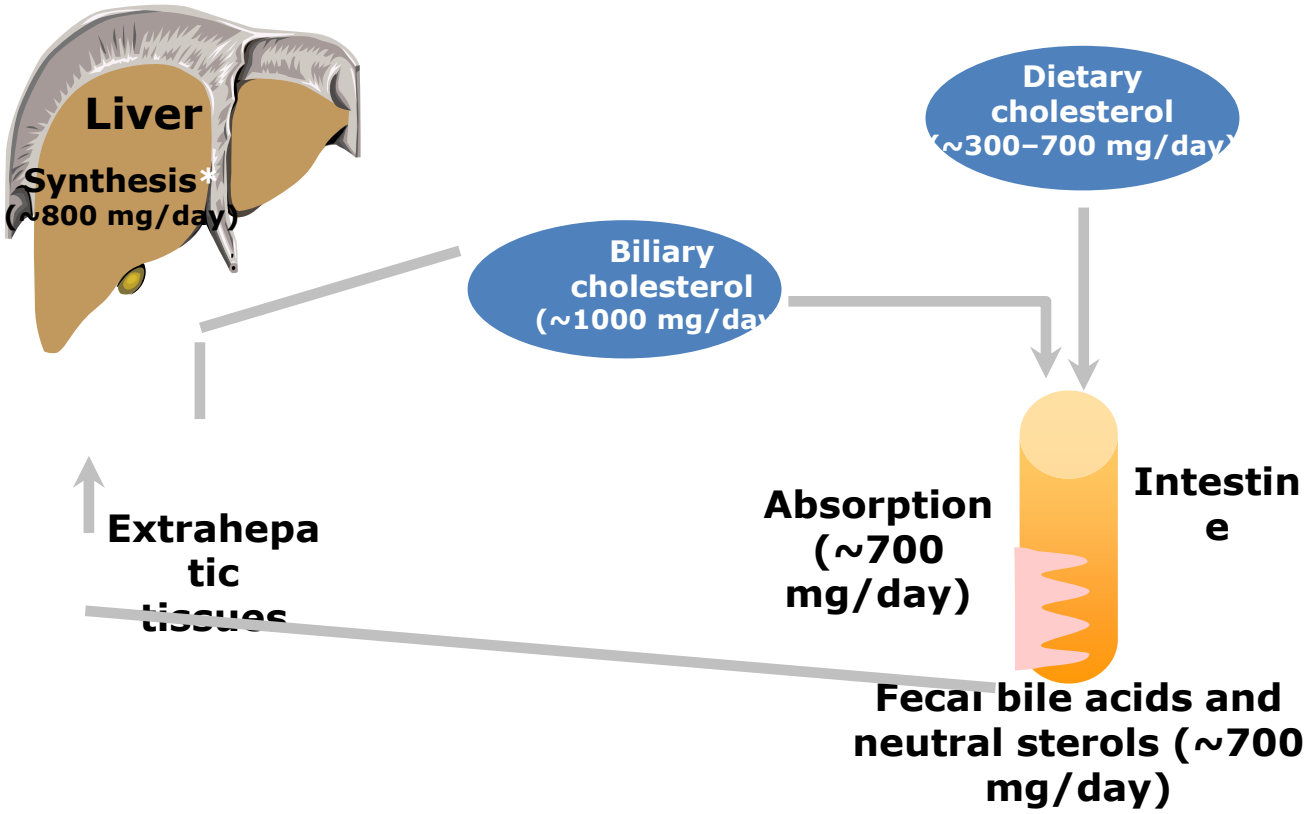
ASCVD, malattia cardiovascolare aterosclerotica; C-LDL, colesterolo legato alle lipoproteine a bassa densità; CV, cardiovascolare; eGFR, filtrato glomerulare stimato; SCORE, Systematic Coronary Risk Estimation; TC, tomografia computerizzata.

Ipercolesterolemia.
Obiettivi terapeutici in base al profilo di rischio cardiovascolare



2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modifi cation to reduce cardiovascularrisk. Eur Heart J. 2020; 41: 111-188

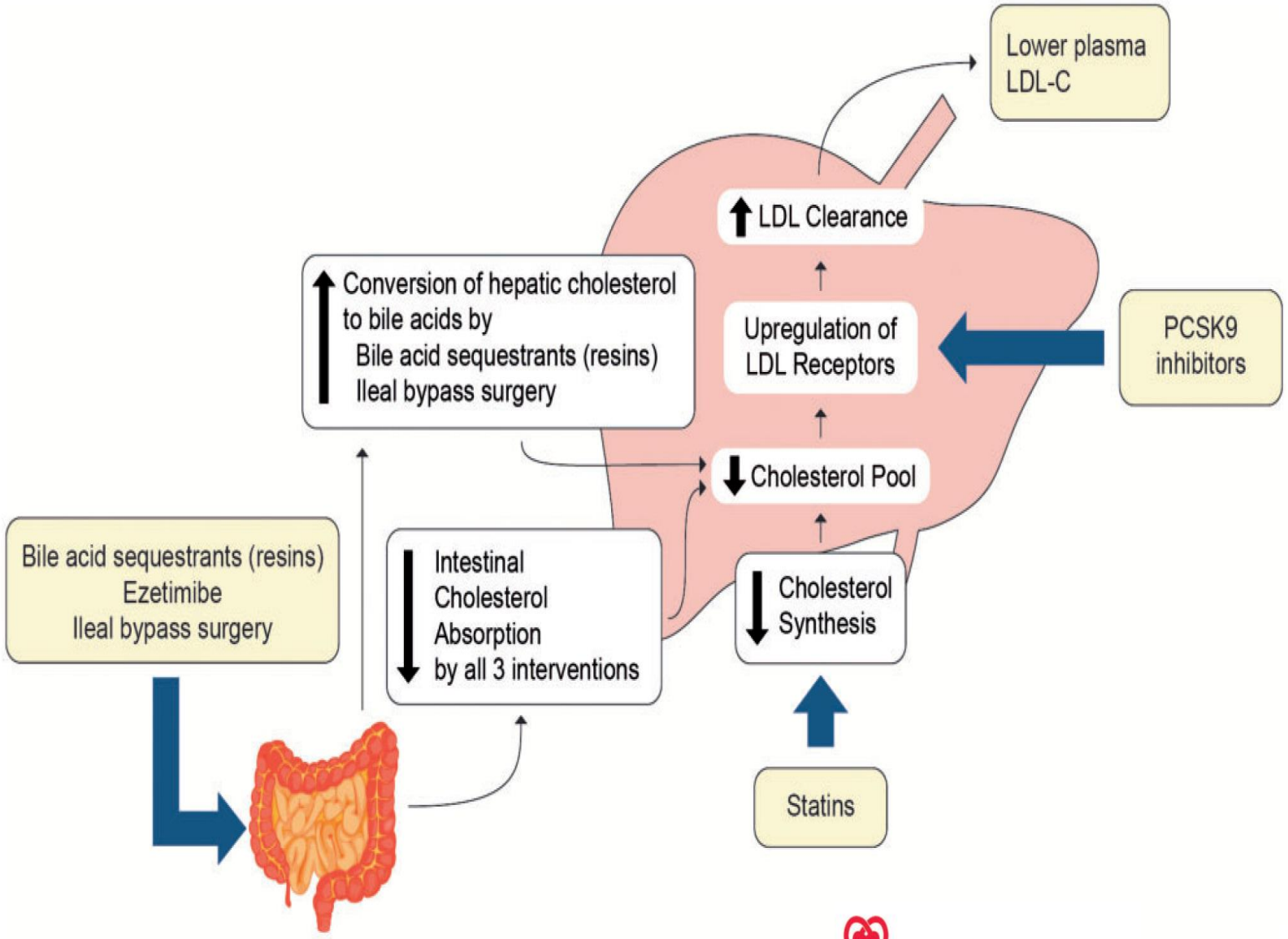
Fonti di colesterolo: sintesi e assorbimento



*

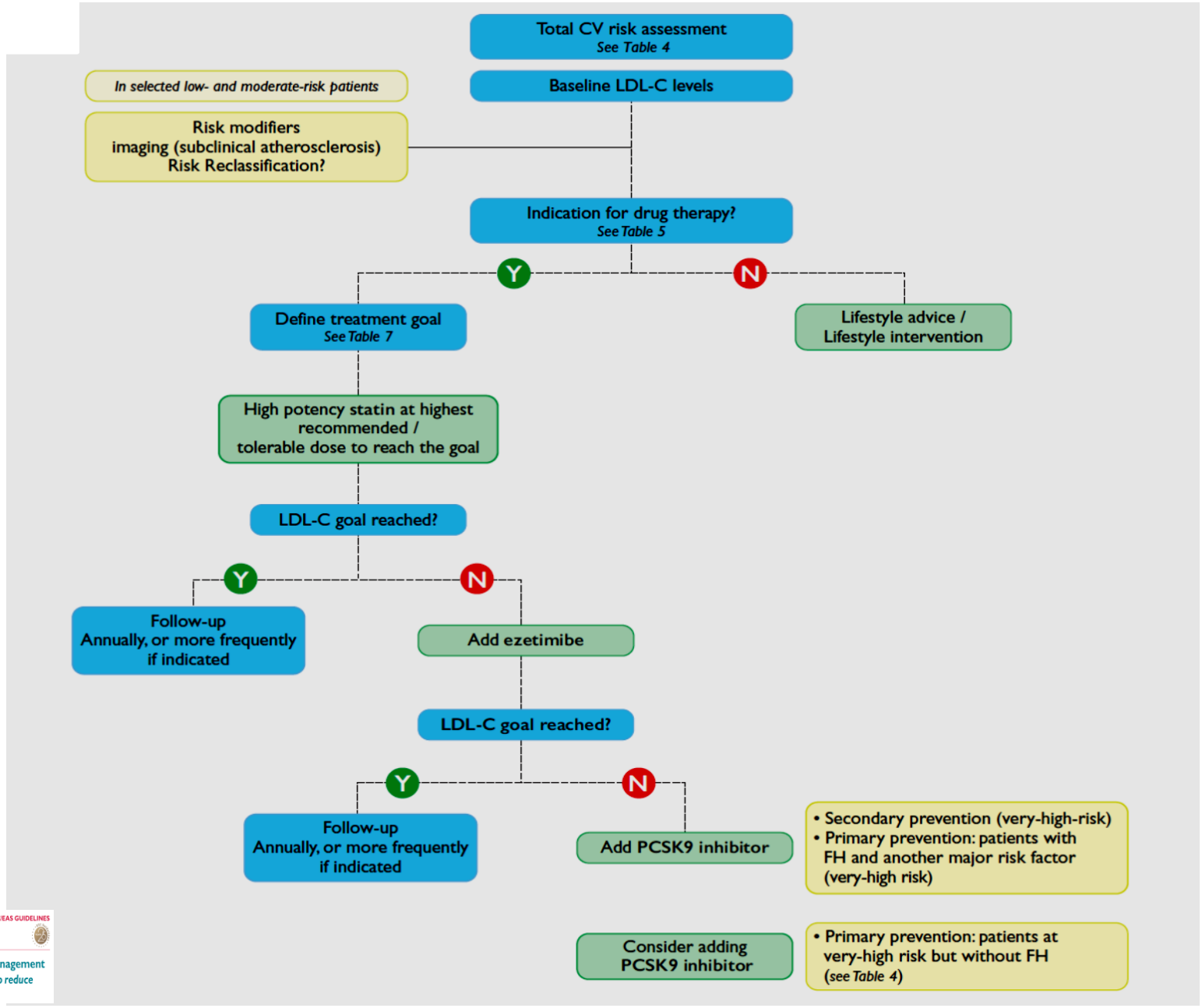
Bays H Expert Opin Investig Drugs 2002;11:1587–1604

Meccanismi d'azione dei farmaci ipocolesterolemizzanti in commercio



European Heart Journal (2017) **0**, 1–14
doi:10.1093/eurheartj/ehx144

Algoritmo di trattamento dell'ipercolesterolemia



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ESC/EAS GUIDELINES

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

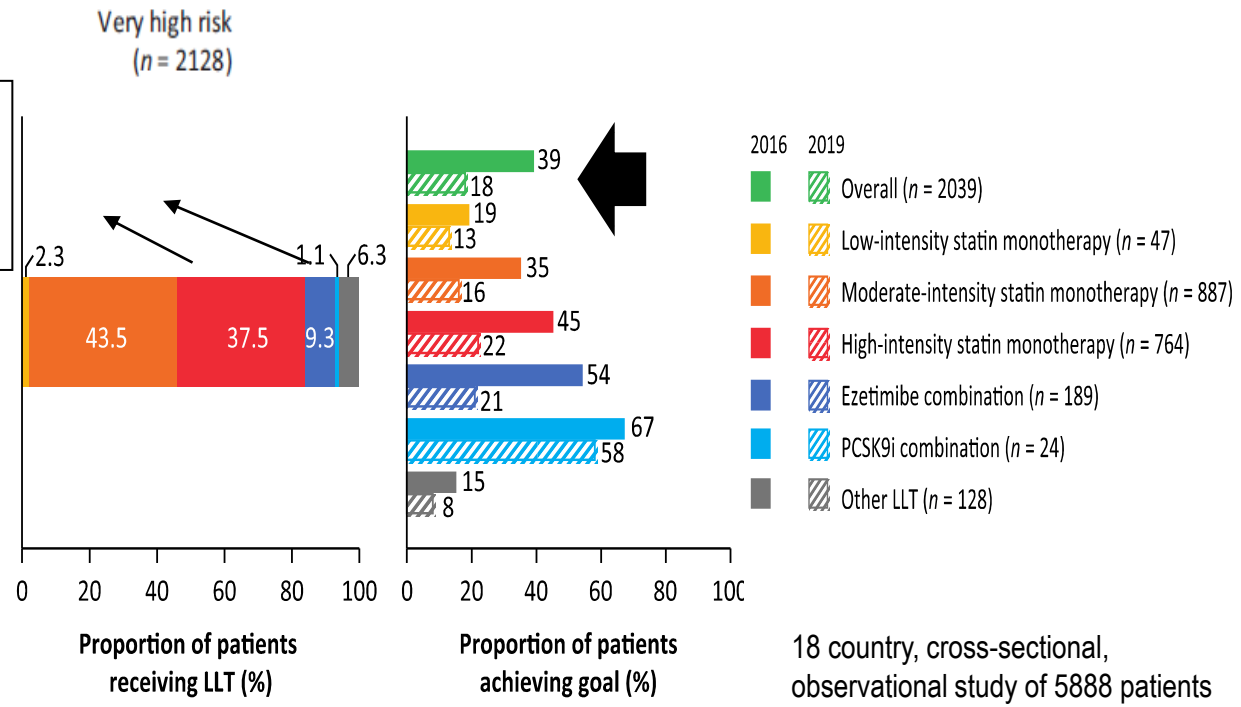
Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

Mach F, et al. *Eur Heart J*. 2019;00:1-78.

Il trattamento delle dislipidemie in Europa: lo studio DA VINCI

45.8% dei pazienti a rischio CV molto alto sono in statine a **bassa/moderata intensità**



18 country, cross-sectional, observational study of 5888 patients (3000 primary and 2888 **secondary prevention**) prescribed LLT between June 2017 and November 2018

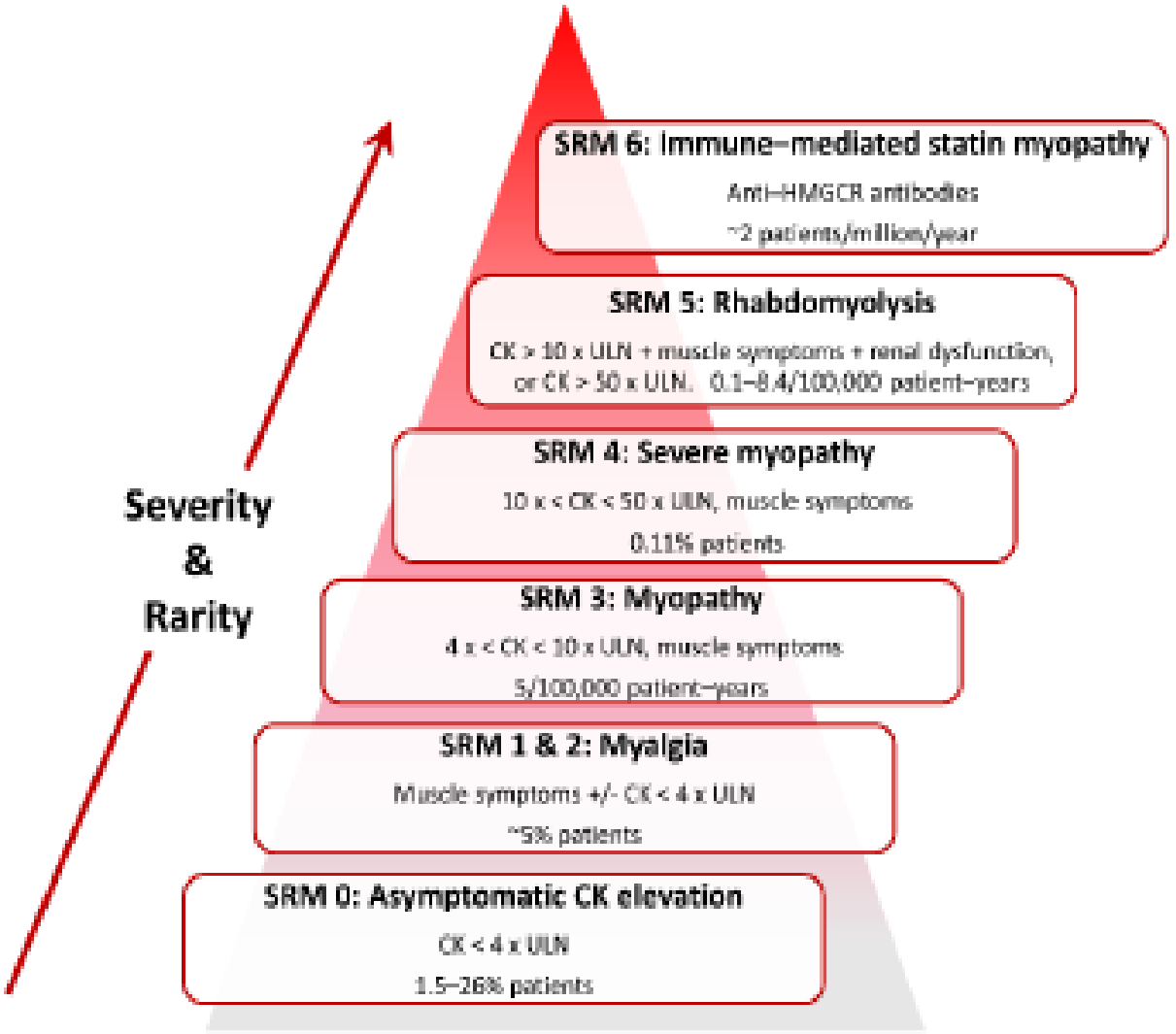
ESC European Society of Cardiology
European Journal of Preventive Cardiology (2021) **28**, 1279–1289
doi:10.1093/eurjpc/zwaa047

Principali effetti avversi associati all'uso di statine e relativa frequenza in base ad evidenze sperimentali ed osservazionali.

Effetto	Frequenza
Sintomi muscolari associati a statine (SAMS)	
Mialgie (senza alterazioni laboratoristiche): dolori, crampi, pesantezza, discomfort, debolezza, rigidità	1-10%
Miosite/miopatia con eventuale alterazione CK e debolezza	rara
Mionecrosi - Lieve (CK > 3x) - Moderata (CK ≥ 10x) - Severa (CK ≥ 50x)	rara
Rabdomiolisi (CK > 10x, danno renale acuto)	rara
Miopatia autoimmune	rara (case reports)
Diabete mellito	variabile (fattori predisponenti, statina ad alta intensità)
Aumento transaminasi (3x)	raro

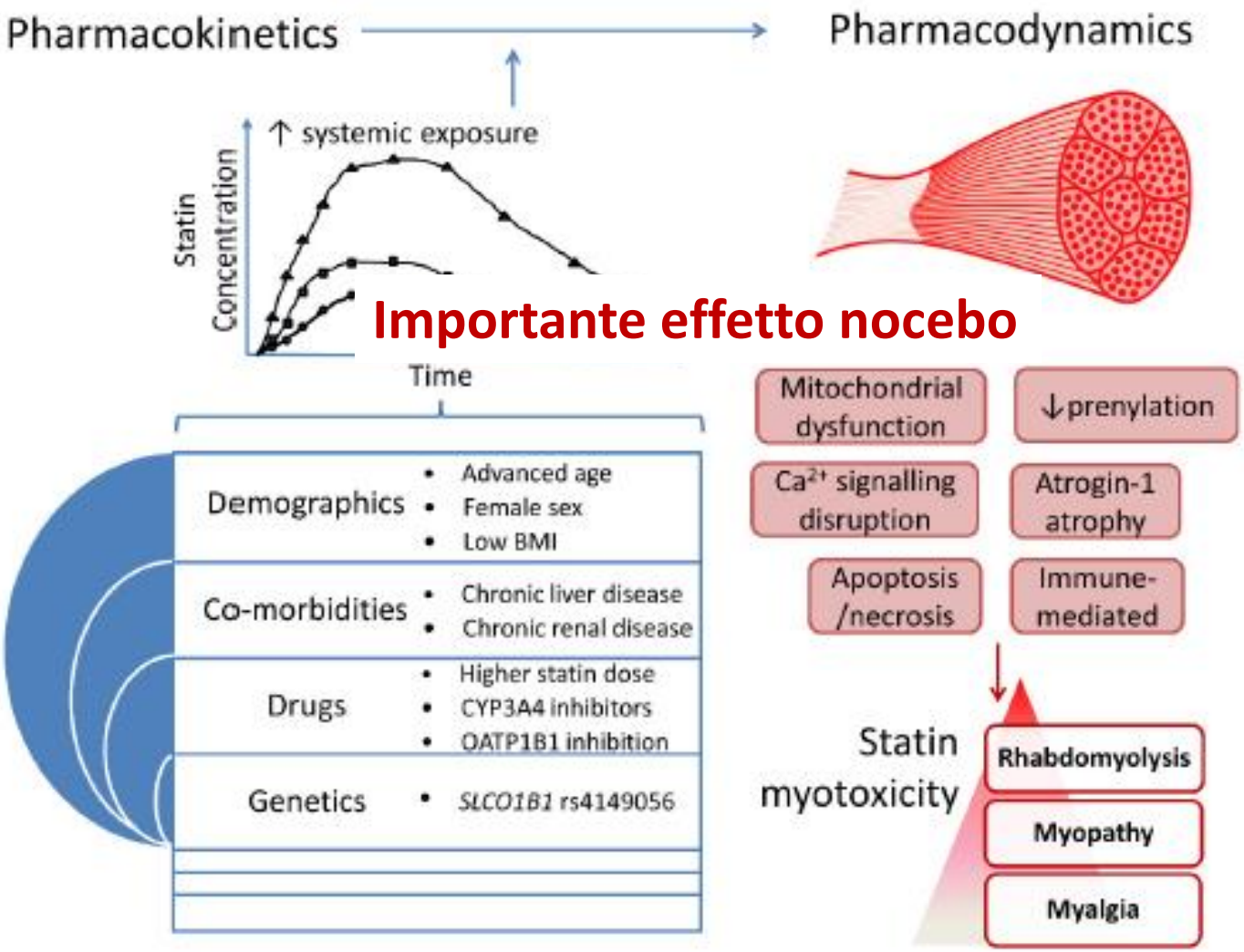
Da Ward CIRC RES 2019

Classificazione e frequenza dei fenotipi di miotossicità indotta da statine



Zhou J Clin Med 2020

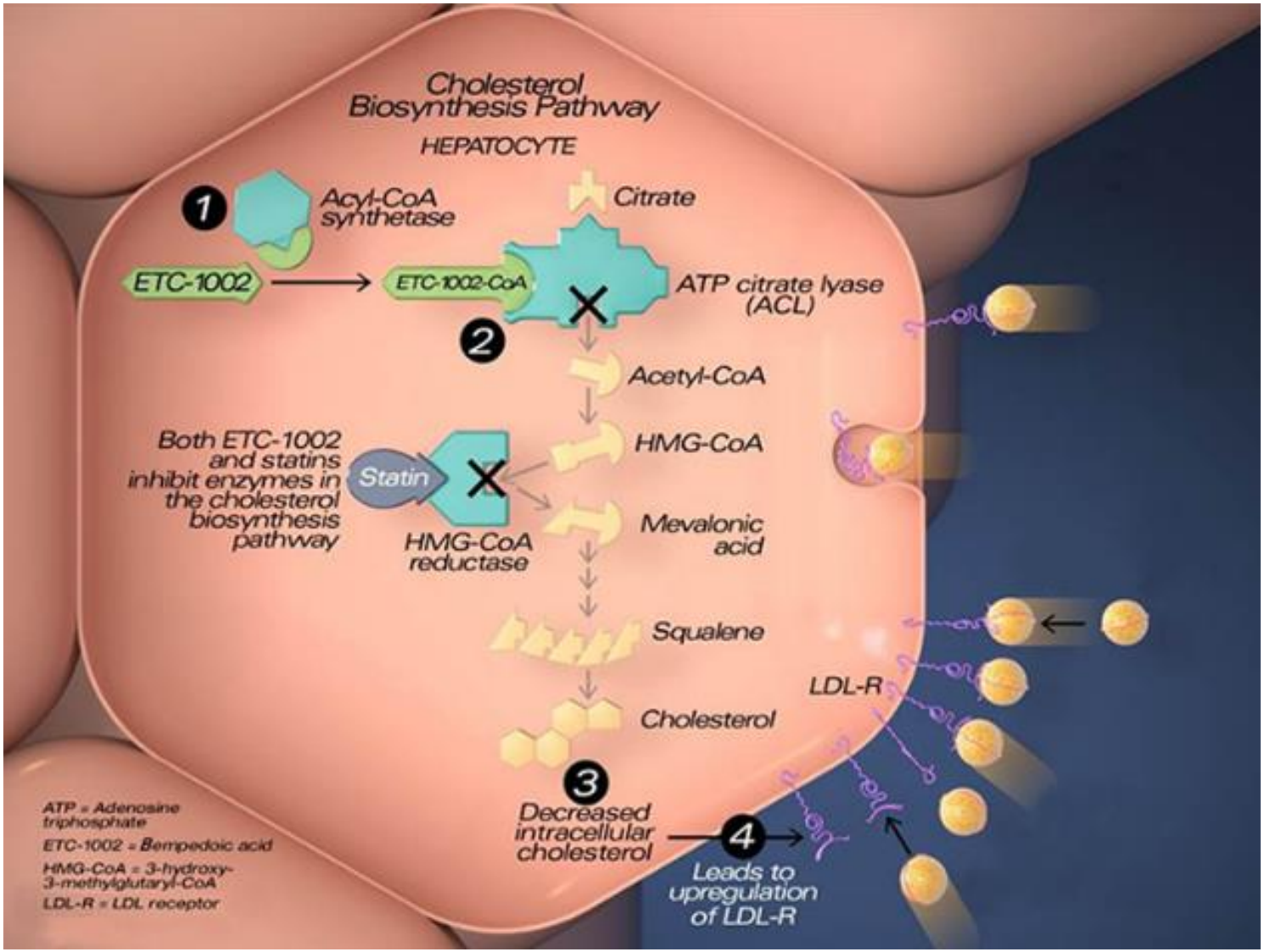
Fattori connessi alla miopatia da statine



Importante effetto nocebo

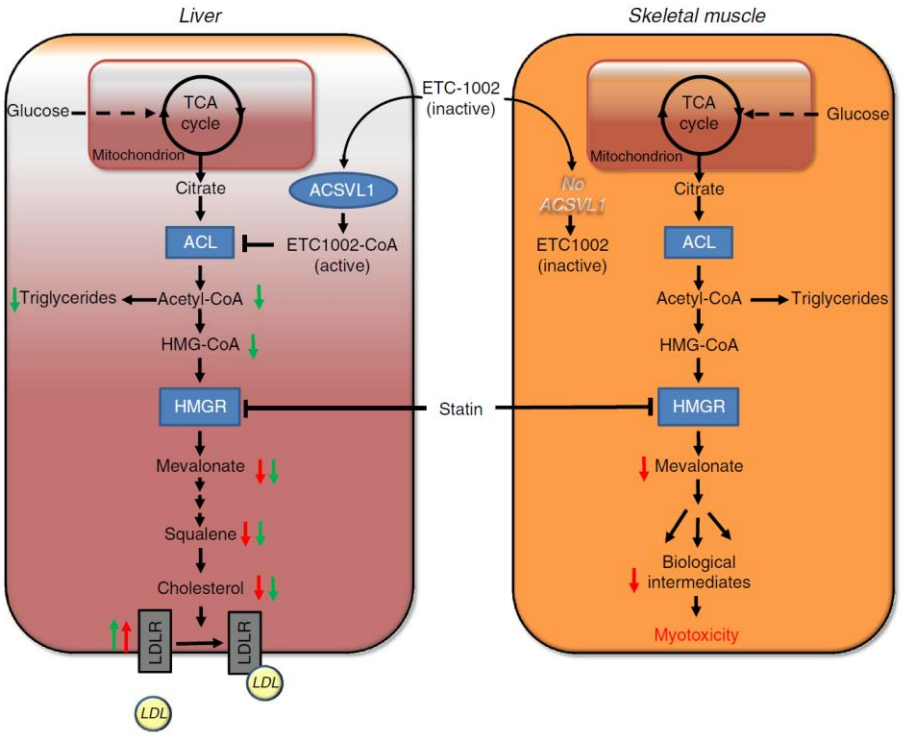
Zhou J Clin Med 2020

Acido Bempedoico.Meccanismo d'azione



Curr Atheroscler Rep (2016) 18: 61

Perchè l'acido bempedoico non provoca problematiche muscolari



In liver, bempedoic acid is activated to BA-CoA by ACSVL1, and subsequently inhibits ACL. Similar to inhibition of HMG-CoA reductase by statins, inhibition of liver ACL results in the suppression of cholesterol synthesis and compensatory LDLR upregulation and LDL particle clearance from the blood. **Skeletal muscle does not express ACSVL1 and is unable to convert bempedoic acid to its active form.** Therefore, bempedoic acid does not suppress the synthesis of cholesterol or the associated biological intermediates that are required to maintain normal muscle cell function, or promote the associated toxicity.

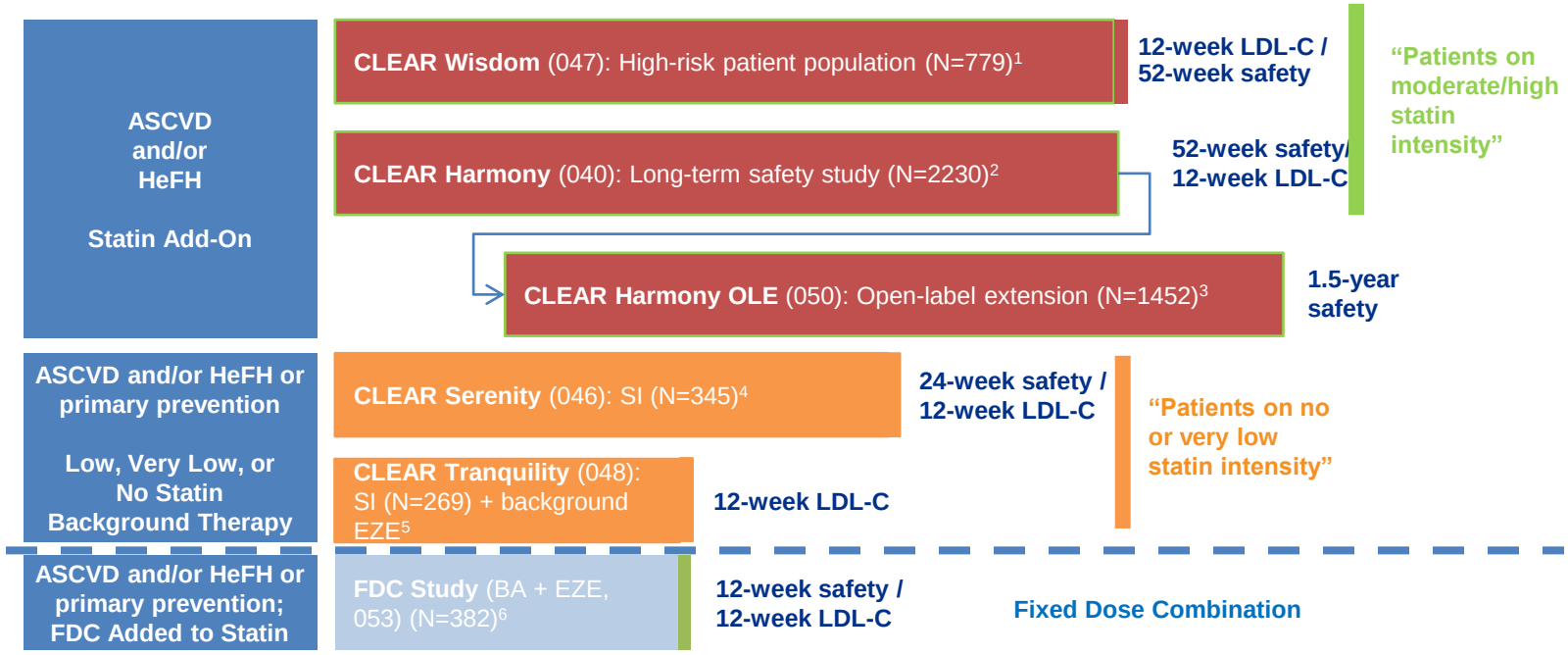
NATURE COMMUNICATIONS | 7:13457 | DOI: 10.1038/ncomms13457 | www.nature.com/naturecommunications

Caratteristiche farmacocinetiche dell'acido Bempedoico

Modalità di assunzione	Orale; dose singola (180 mg) giornaliera
Effetto del cibo	Nessuno
Tmax (180 mg)	3.5 h
Volume di distribuzione	18 L
Legame delle proteine plasmatiche	99%
Profarmaco	Si
Metaboliti attivi	Si. ETC-1002-CoA, ESP15228
Metabolismo	Glucuronidazione UGT2B7
Substrato trasportatori	OATP1B1/3, OAT2, OAT3
Via di eliminazione	Profarmaco: 5% eliminato equamente tra feci e urine Coniugati/metaboliti: 70% rene; 30% fegato
Emivita	15-24 h
Popolazioni speciali	Nessun effetto di età, sesso e etnia sulla farmacocinetica di acido bempedoico
Interazioni farmacologiche	Aumento significativo delle concentrazioni di simvastatina (2 volte) Nessuna inibizione/induzione dei citocromi Acido bempedoico e glucuronide sono deboli inibitori di OATP1B1/3 Acido bempedoico è un debole inibitore di OAT2, OAT3 (aumento acido urico e creatinina)

ATP, adenosin-trifosfato; OAT2/OAT3, organic anion transporter-2/3; OATP1B1/3, organic anion-transporting polypeptide 1B1/3; AUC, area sotto la curva; Tmax, tempo necessario per raggiungere la massima concentrazione plasmatica.

Acido bempedoico: studi di fase III

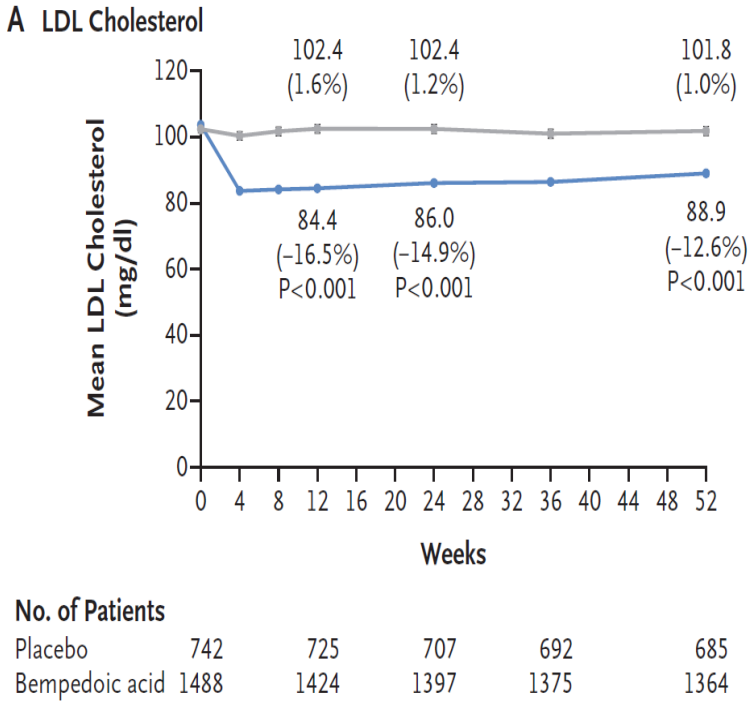


ASCVD = atherosclerotic cardiovascular disease; BA = bempedoic acid; EZE = ezetimibe; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; OLE = open-label extension; SI = statin intolerant.

1.Goldberg AC et al. JAMA. 2019;322(18):1780-1788. doi:10.1001/jama.2019.16585; 2. Ray KK, et al. *N Engl J Med*. 2019;380:1022-32; 3. ClinicalTrials.gov identifier NCT03067441;
4. Laufs U, et al. *J Am Heart Assoc*. 2019;8:e011662; 5. Ballantyne CM, et al. *Atherosclerosis*. 2018;277:195-2036. 6. Ballantyne et al. Eur J Prev Cardiol 2019 [Epub ahead of print].

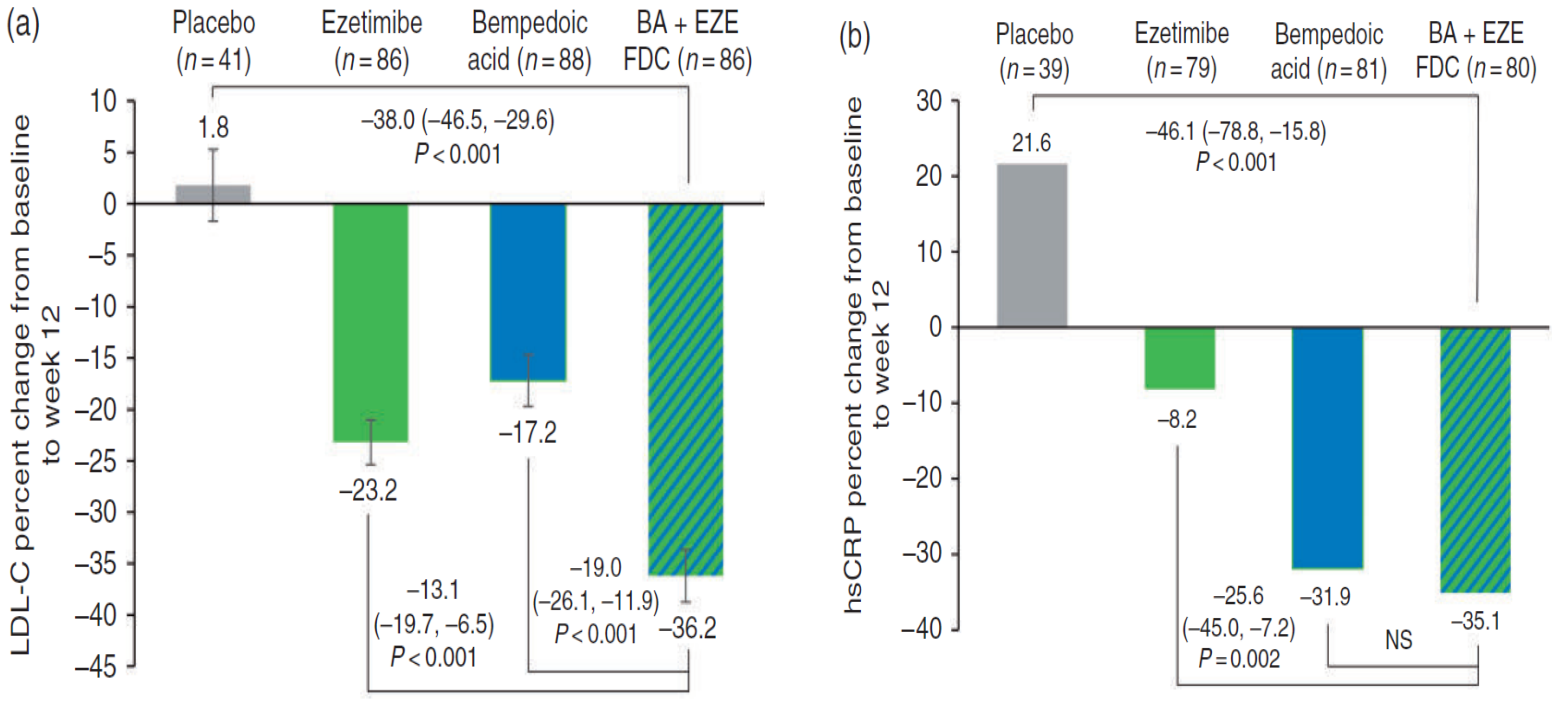
Acido Bempedoico in pazienti già in trattamento con statine: CLEAR Harmony

Characteristic	Bempedoic Acid (N=1488)	Placebo (N=742)
Age — yr	65.8±9.1	66.8±8.6
Male sex — no. (%)	1099 (73.9)	529 (71.3)
White race — no. (%)†	1423 (95.6)	716 (96.5)
Cardiovascular risk factor — no. (%)		
Atherosclerotic cardiovascular disease	1449 (97.4)	727 (98.0)
Heterozygous familial hypercholesterolemia	56 (3.8)	23 (3.1)
Diabetes	425 (28.6)	212 (28.6)
Hypertension	1174 (78.9)	594 (80.1)
Concomitant lipid-modifying therapy — no. (%)		
Statin	1485 (99.8)	742 (100)
Ezetimibe	116 (7.8)	56 (7.5)
Fibrate	54 (3.6)	26 (3.5)
None	2 (0.1)	0
Intensity of statin therapy at baseline — no. (%)		
Low	100 (6.7)	48 (6.5)
Moderate	646 (43.4)	324 (43.7)
High	742 (49.9)	370 (49.9)



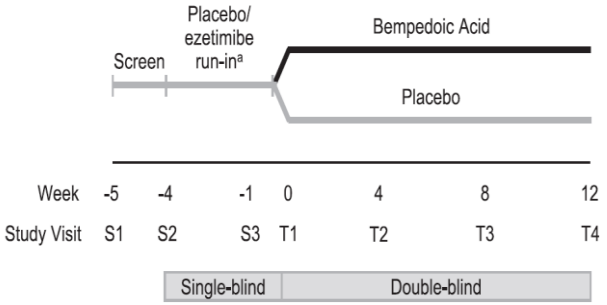
N Engl J Med 2019;380:1022-32.

Acido Bempedoico più ezetimibe in pazienti già in terapia on top con statine

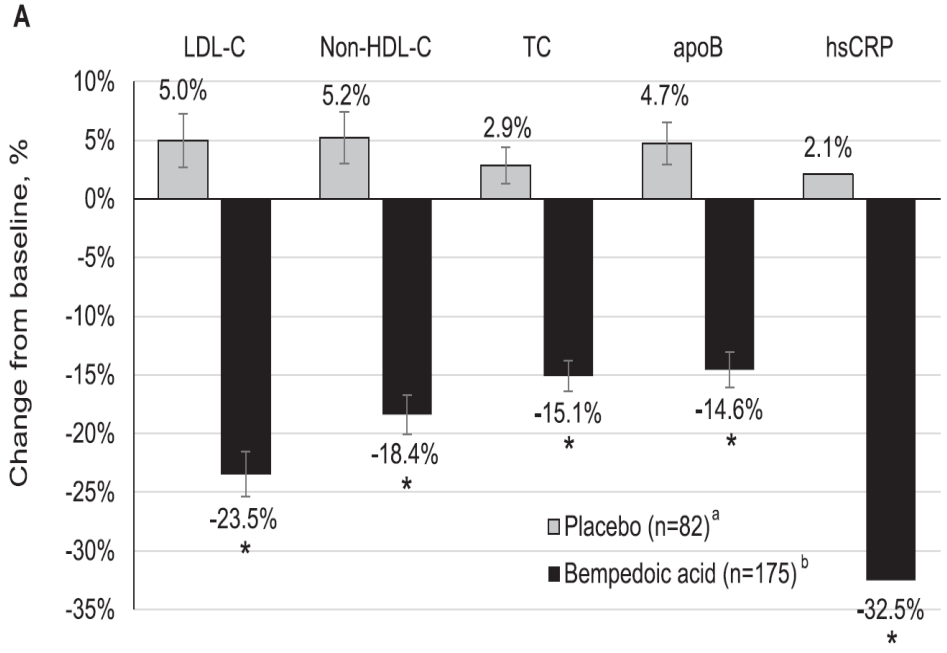


Ballantyne C. Eur J Prev Card 2019

Acido Bempedoico più ezetimibe nei pazienti intolleranti alle statine: CLEAR Tranquility



C.M. Ballantyne et al. / Atherosclerosis 277 (2018) 195–203



Ballantyne C. Atherosclerosis 2018

ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–4
doi:10.1093/eurheartj/ehab718

VIEWPOINT
Epidemiology and prevention

Combination lipid-lowering therapy as first-line strategy in very high-risk patients

Kausik K. Ray[1]*, Laurens F. Reeskamp [2], Ulrich Laufs [3], Maciej Banach [4], François Mach [5], Lale S. Tokgözoğlu [6], Derek L. Connolly[7], Anja J. Gerrits[8], Erik S. G. Stroes [2], Luis Masana [9], and John J. P. Kastelein [2]

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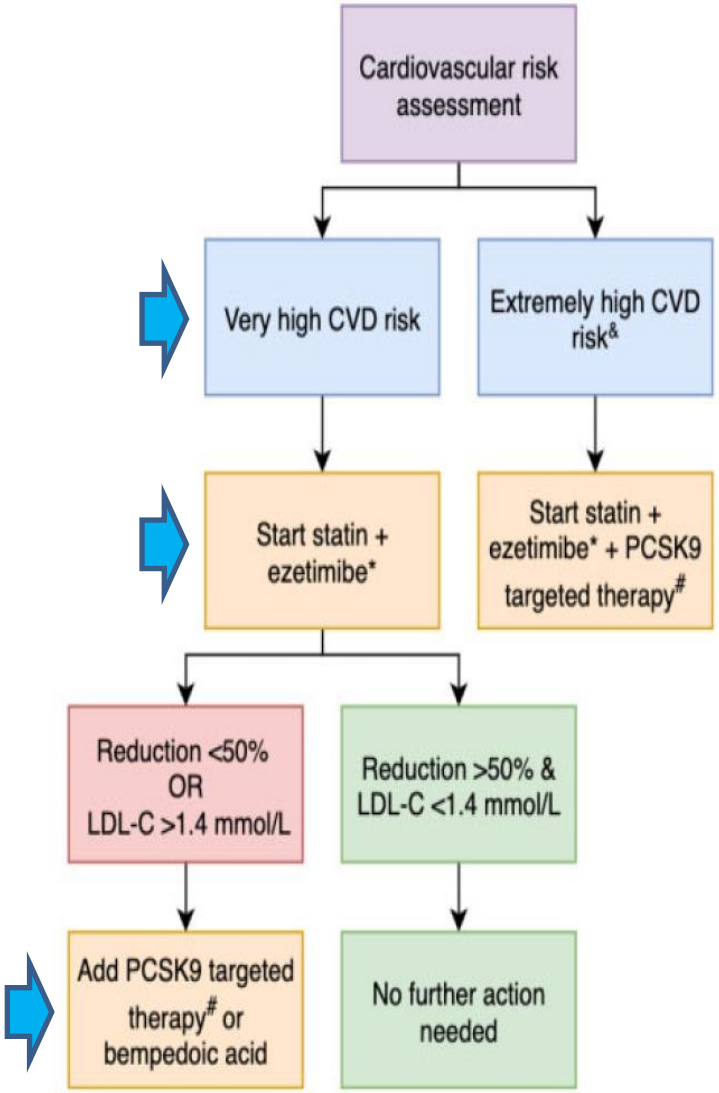
Clinical guidelines and position paper

Updated clinical evidence and place in therapy of bempedoic acid for hypercholesterolemia: ANMCO position paper

Furio Colivicchi[a,†], Stefania Angela Di Fusco[a,*], Pietro Scicchitano[b], Pasquale Caldarola[c,†], Adriano Murrone[d,†], Serafina Valente[e,†], Stefano Urbinati[f,†], Loris Roncon[g,†], Vincenzo Amodeo[h,†], Nadia Aspromonte[i,†], Manlio Cipriani[j,†], Stefano Domenicucci[k,†], Giuseppina Maura Francese[l,†], Massimo Imazio[m,†], Fortunato Scotto di Uccio[n,†], Andrea Di Lenarda[o,†], Michele Massimo Gulizia[l,p] and Domenico Gabrielli[q,†]

J Cardiovasc Med 2020, 21:000–000

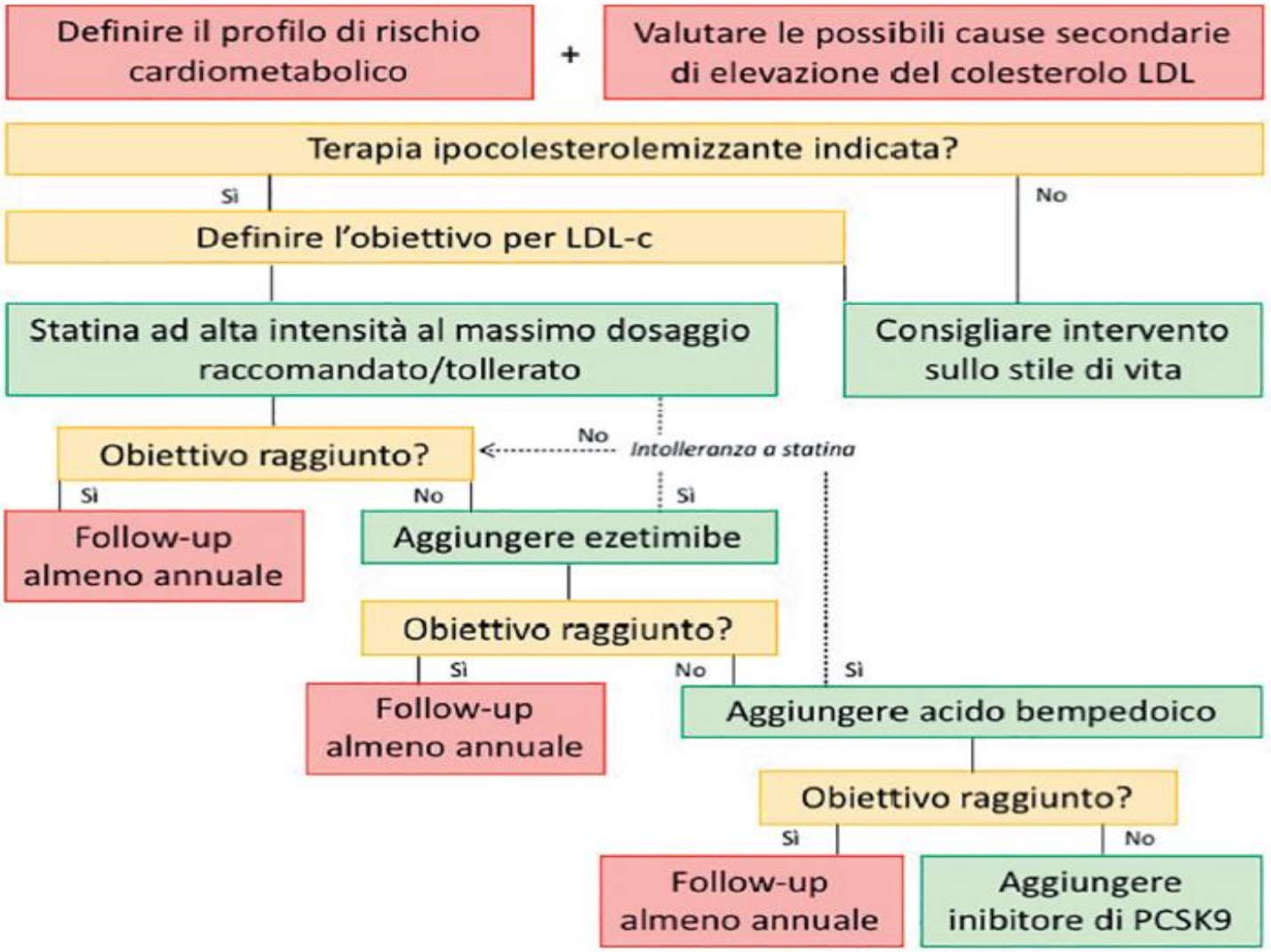


ESC European Society of Cardiology
ESC/EAS GUIDELINES
2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

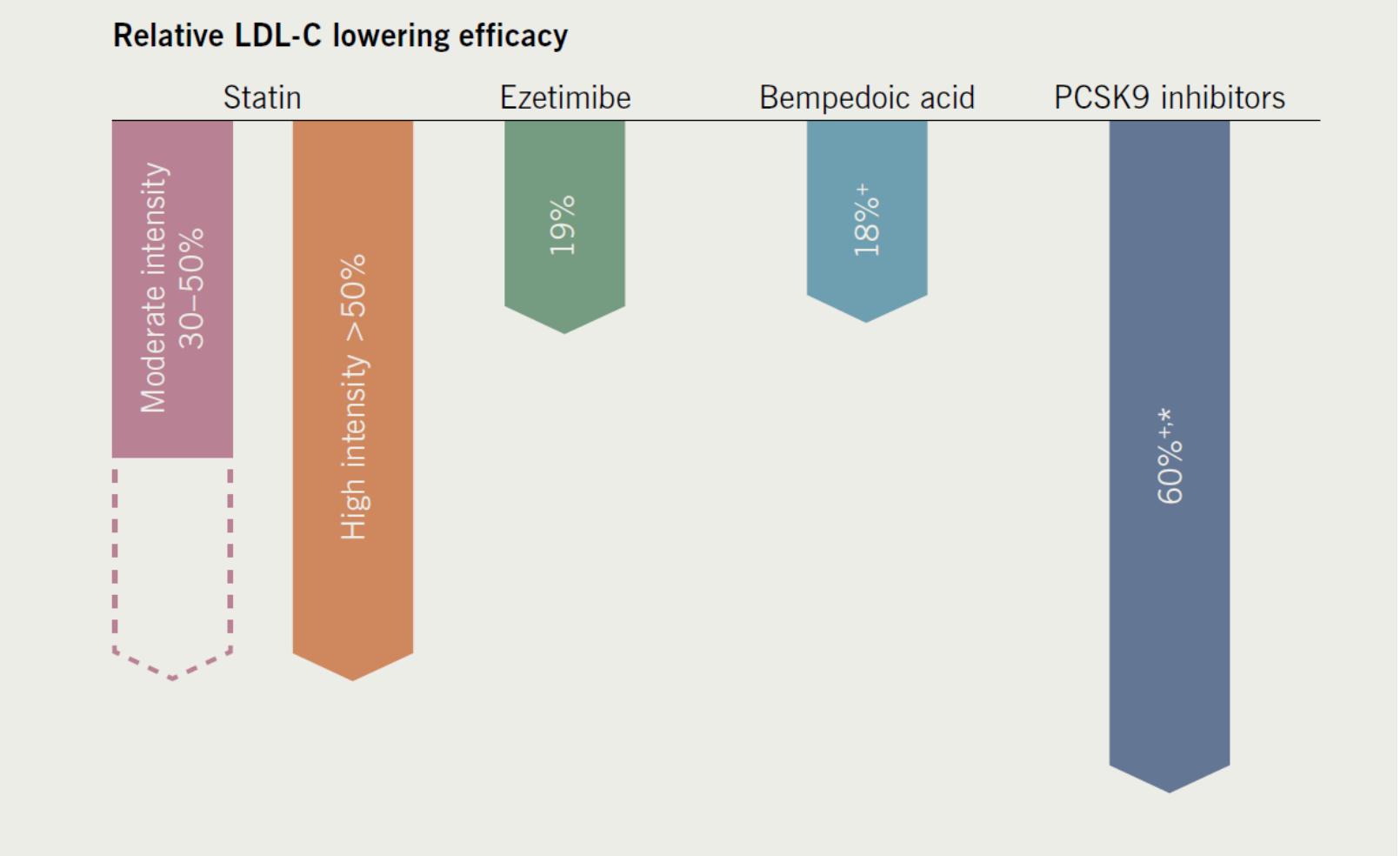
"If patients do not achieve the 2019 guideline-recommended LDL cholesterol goal of >50% reduction and levels <1.4mmol/L, ***a third lipid-lowering therapy, such as bempedoic acid or PCSK9 targeted therapies should be added****."*

Ray K et al, *European Heart Journal* -(2021) 00, 1–4 doi:10.1093/eurheartj/ehab718

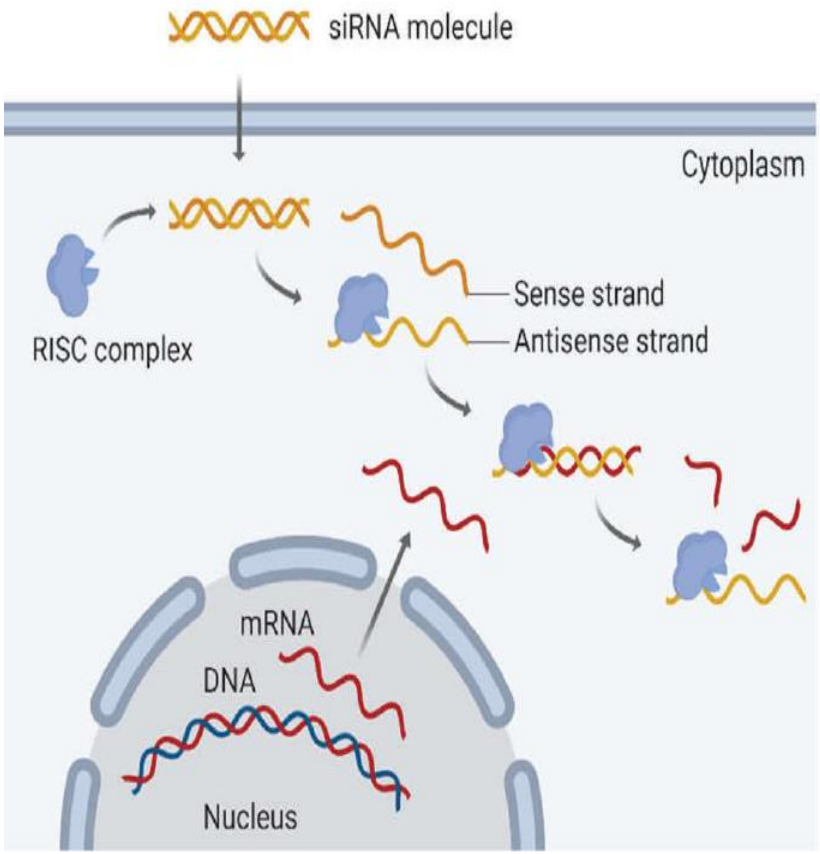
Documento di Consenso SIIA 2021



Agabiti Rosei C et al: Documento finale SIIA .indd

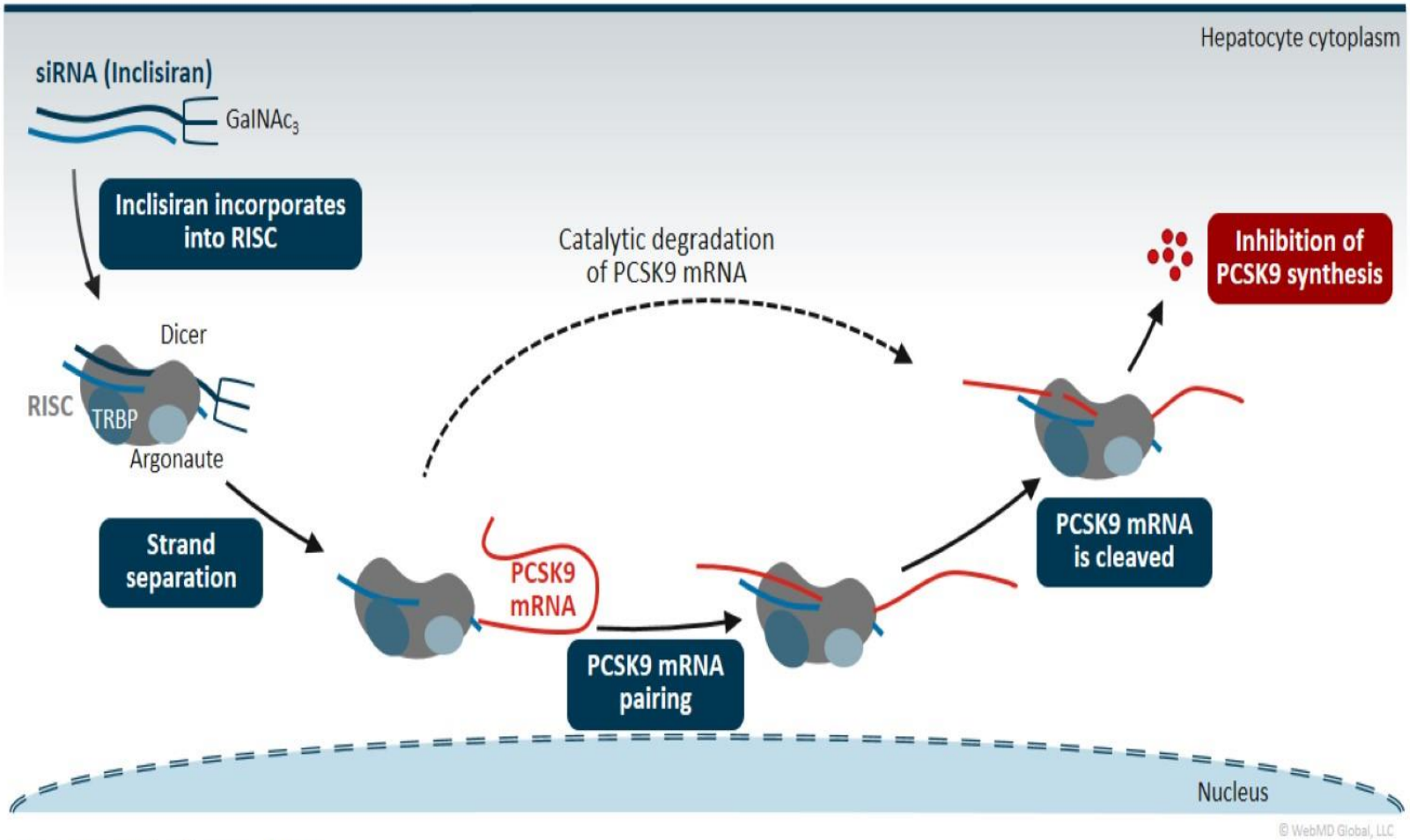

Relative LDL-C lowering efficacy
Statin
Ezetimibe
Bempedoic acid
PCSK9 inhibitors
Moderate intensity 30–50%
High intensity >50%
19%
18%+
60%+,*

Short Interfering RNA



Short-interfering RNA (siRNA) is a short (21–23 nucleotide) sequence of double-stranded RNA which is recognized
and incorporated by ***RNA-induced silencing complex (RISC).***
After incorporation, the sense strand is removed and the complex binds to a ***complementary mRNA sequence*** to be
enzymatically cleaved.
Importantly, the RISC-bound siRNA complex can be recycled and therefore cleave many mRNA transcripts thereby ensuring durable RNA silencing for extended periods of time (months).

Meccanismo di azione dell'Inclisiran



Kosmas CE, et al. *Diseases*. 2018;6.

PHASE III ORION-9, -10, and -11: Study Inclusion and Exclusion Criteria

Trial-Specific Inclusion Criteria		
ORION-9[a]	ORION-10[b]	ORION-11[b]
HeFH	ASCVD (CHD, CVD, PAD)	ASCVD (CHD, CVD, PAD)
Stable on a low-fat diet	--	ASCVD risk equivalents • Type 2 diabetes • 10-year risk ≥ 20% • HeFH
LDL-C ≥ 2.6 mmol/L (100 mg/dL)	LDL-C ≥ 1.8 mmol/L (70 mg/dL)	LDL-C ≥ 1.8 mmol/L (70 mg/dL) or ≥ 2.6 mmol/L (100 mg/dL) in risk equivalent

Common Key Inclusion Criteria:
≥ 18 years of age; had received statin treatment at the maximally tolerated dose or demonstrated documented intolerance. Ezetimibe therapy was allowed

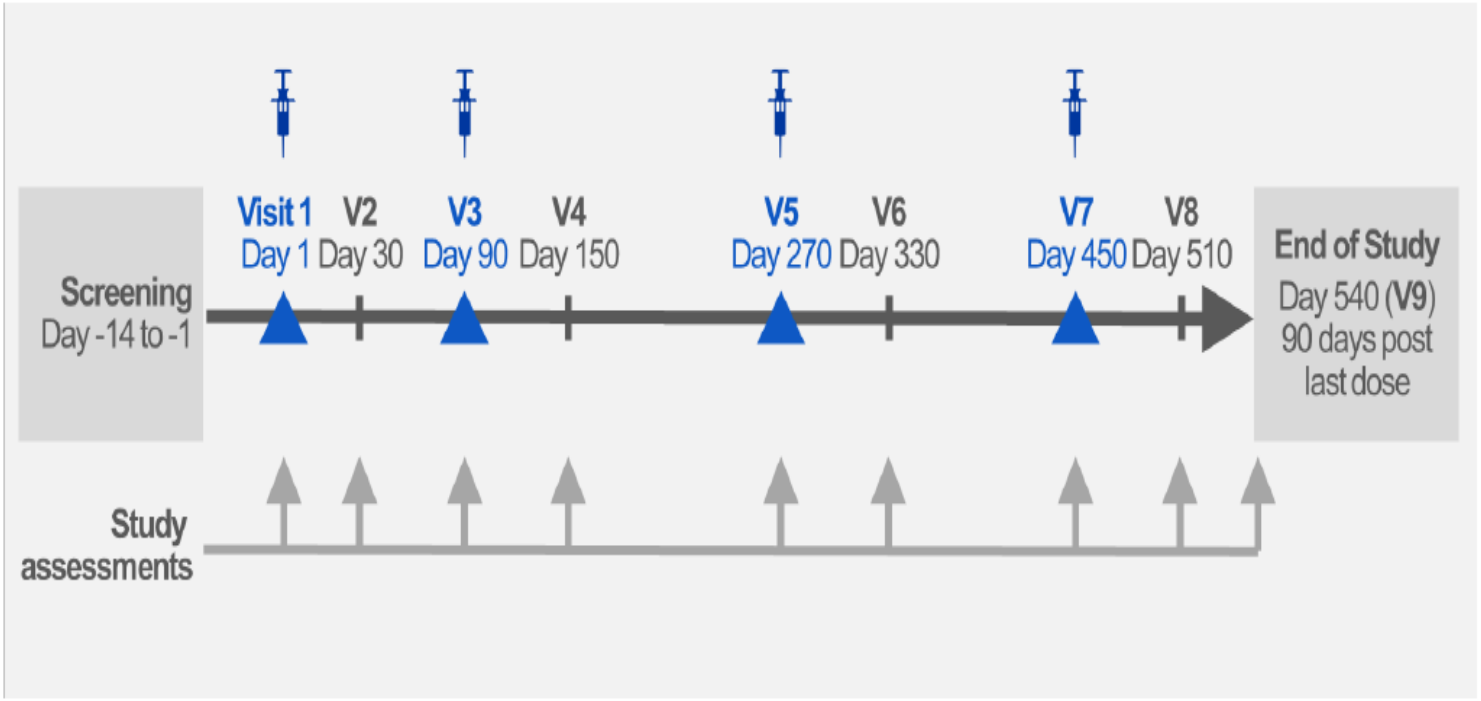
Common Key Exclusion Criteria:
Prior or planned use of a PCSK9 mAb; had received MACE within 3 months of randomization or had prior/planned used of other investigational drugs; NYHA class IV HF or LVEF < 25% (ORION-9, -10, -11); uncontrolled severe hypertension; severe concomitant non-CV disease, or fasting TG ≥ 4.52 mmol/L (400 mg/dL)

a. Raal FJ, et al. *N Engl J Med.* 2020;382:1520-1530; b. Ray KK, et al. *N Engl J Med*. 2020;382:1507-1519.

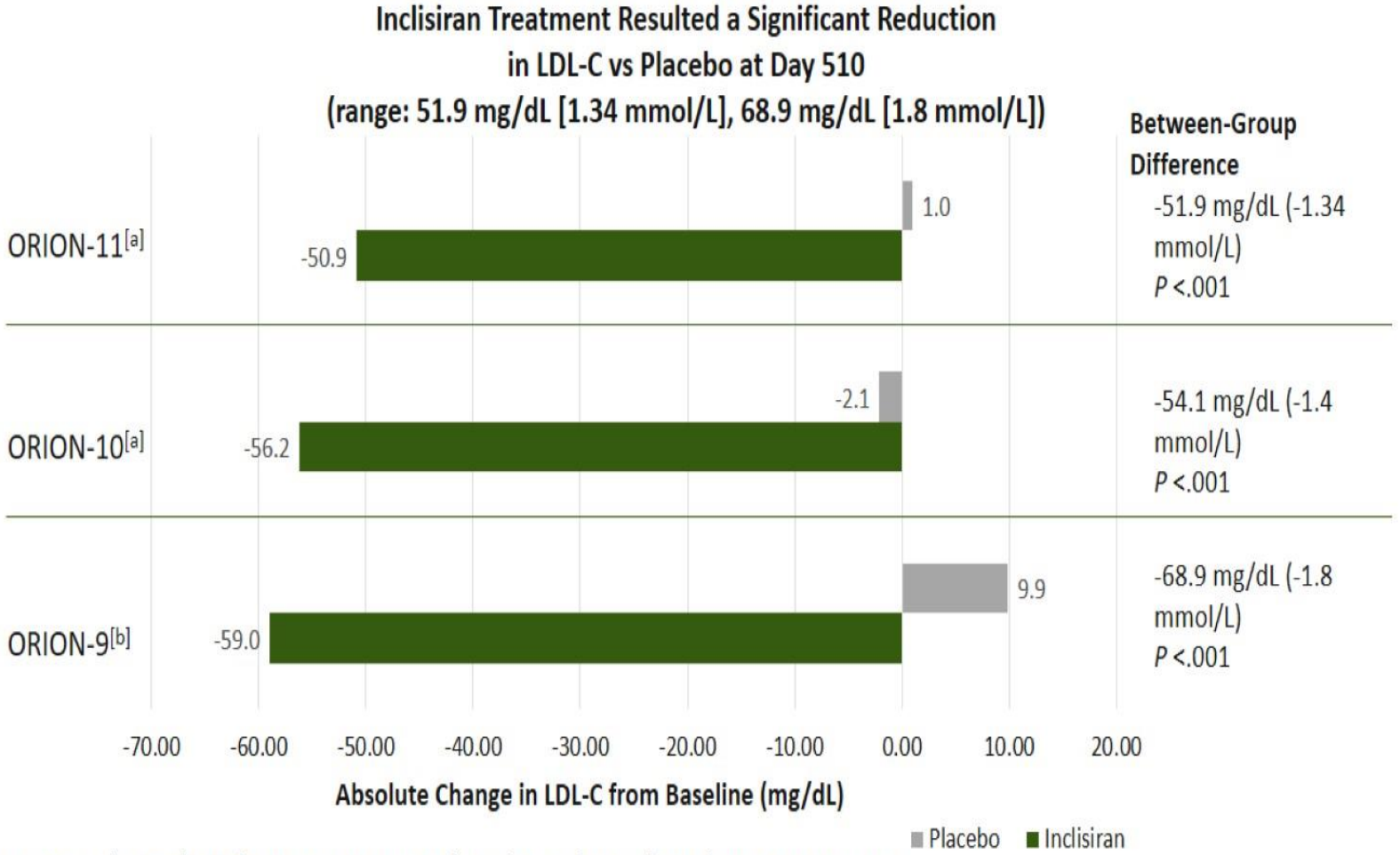
ORION Phase III pooled analysis: Common study design

18 months treatment & observation

Randomized 1:1 inclisiran 300 mg *vs.* placebo – with maximally tolerated statins



PHASE III ORION-9, -10, and -11 Inclisiran vs Placebo: Reduction in LDL-C Day 510



a. Ray KK, et al. *N Engl J Med*. 2020;382:1507-1519; b. Raal FJ, et al. *N Engl J Med*. 2020;382:1520-1530.

Conclusioni

- **la riduzione dei livelli di Colesterolo LDL è un intervento terapeutico fondamentale per contrastare il rischio cardiovascolare.**
- **il trattamento va commisurato al reale livello di rischio del singolo paziente**
- **Nonostante la disponibilità di numerose scelte terapeutiche un percentuale insufficiente di pazienti raggiunge il target terapeutico.**
- **I nuovi farmaci che a breve entreranno in commercio offrono ulteriori opportunità per ridurre il rischio cardiovascolare**

Paradigm Shift in the Treatment of Hypercholesterolemia

Statin

365 doses/year[a]

PCSK9 inhibitor

26 doses/year[b]

PCSK9 siRNA

2 doses/year[b]

a. Tiwari R, et al. *J Pharm Pharmacol*. 2011;63:983-998; b. Nishikido T, Ray KK. *Front Cardiovasc Med*. 2019;5:199.