Sabato 25 Marzo 2023
HOTEL CASCINA FOSSATA
Via Ala di Stura 5 - Torino
IL PAZIENTE FRAGILE IN CARDIOLOGIA
VI Edizione

PCSK 9, Inclisiran per il trattamento aggressivo dell'ipercolesterolemia

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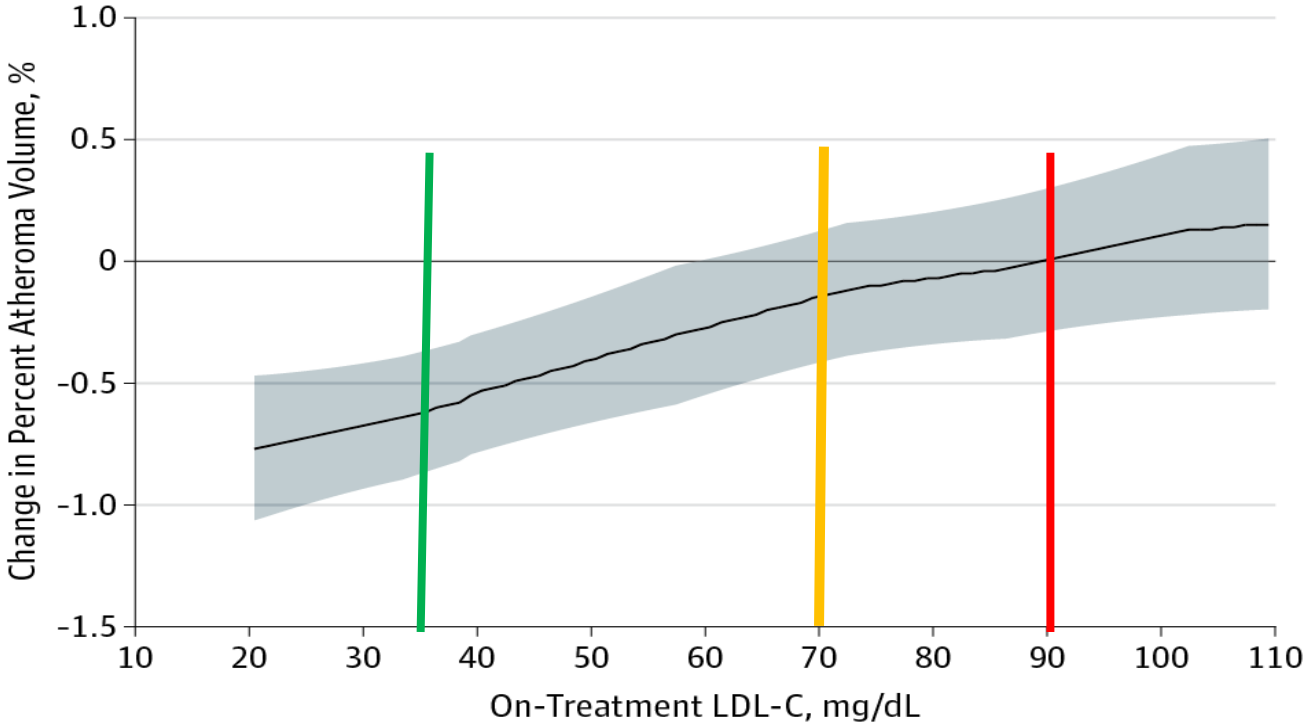
Il colesterolo LDL è un fattore causale per lo sviluppo dell'arteriosclerosi



THE LOWER,

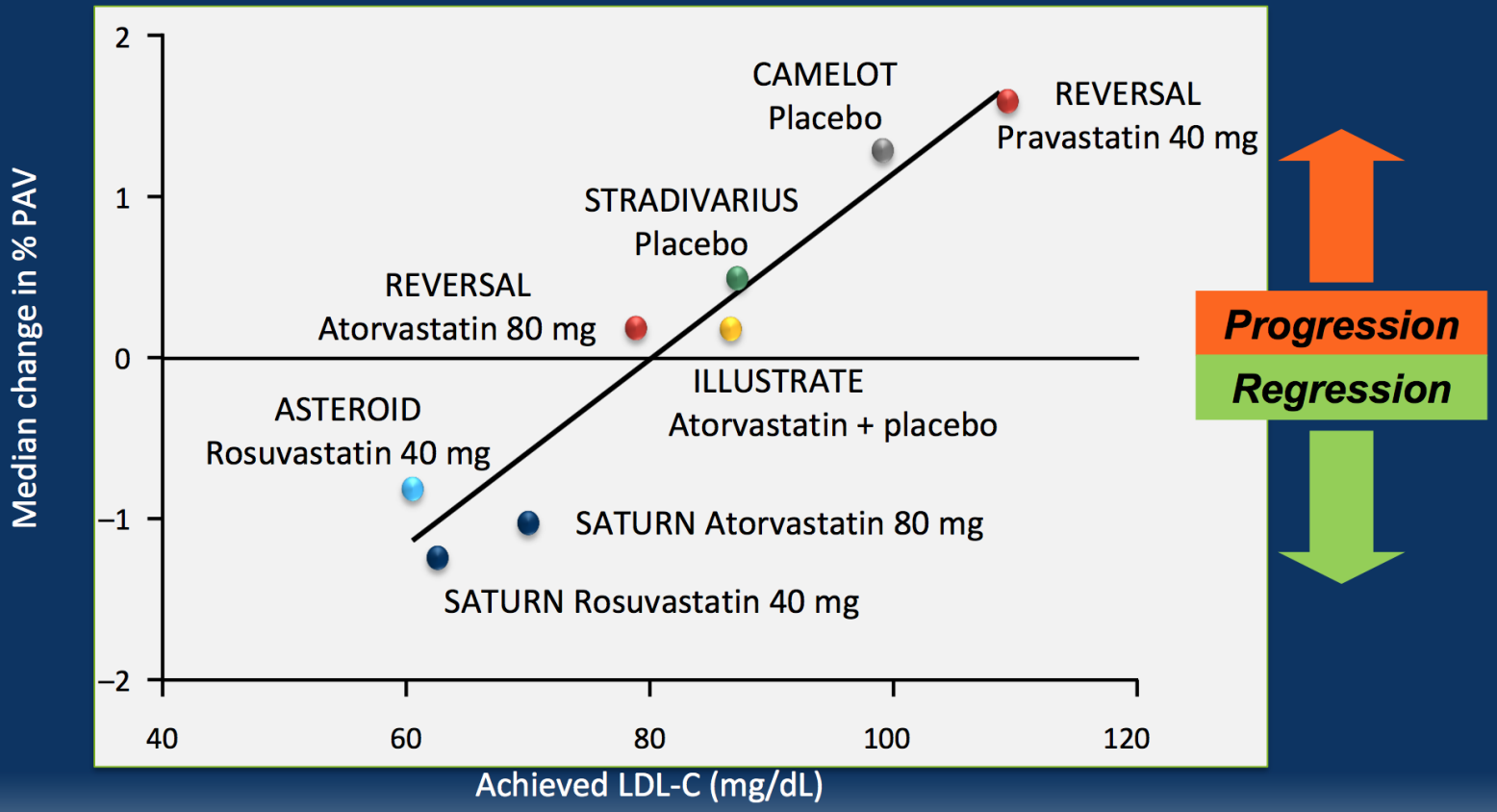
THE BETTER

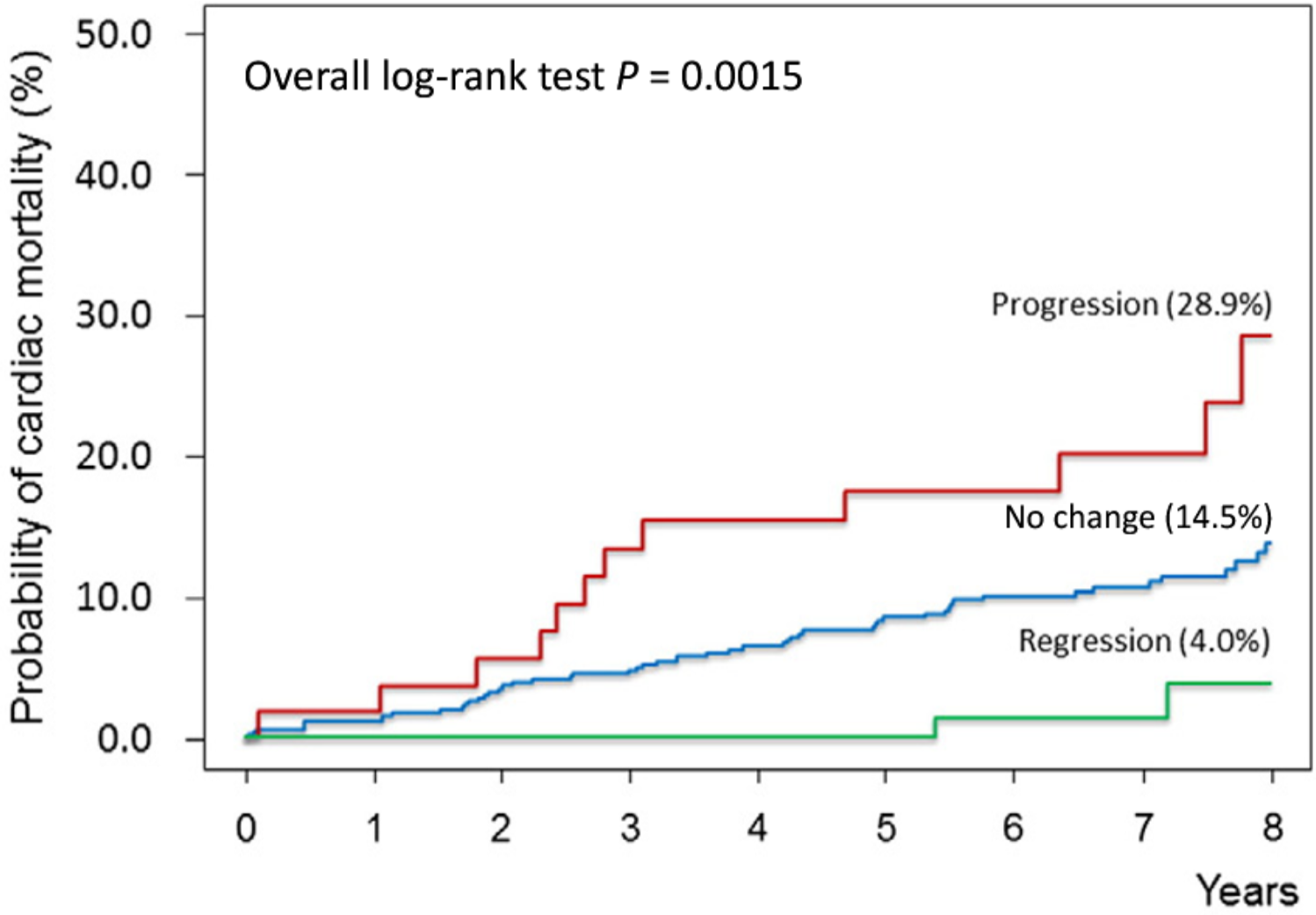
THE LOWEST

THE BETTER!!

Effect of Evelocumab on progression of coronary disease in statin-treated patients. The GLAGOV randomized clinical trial. JAMA. 2016;316(22):2373-2384

LDL-C and atherosclerotic burden

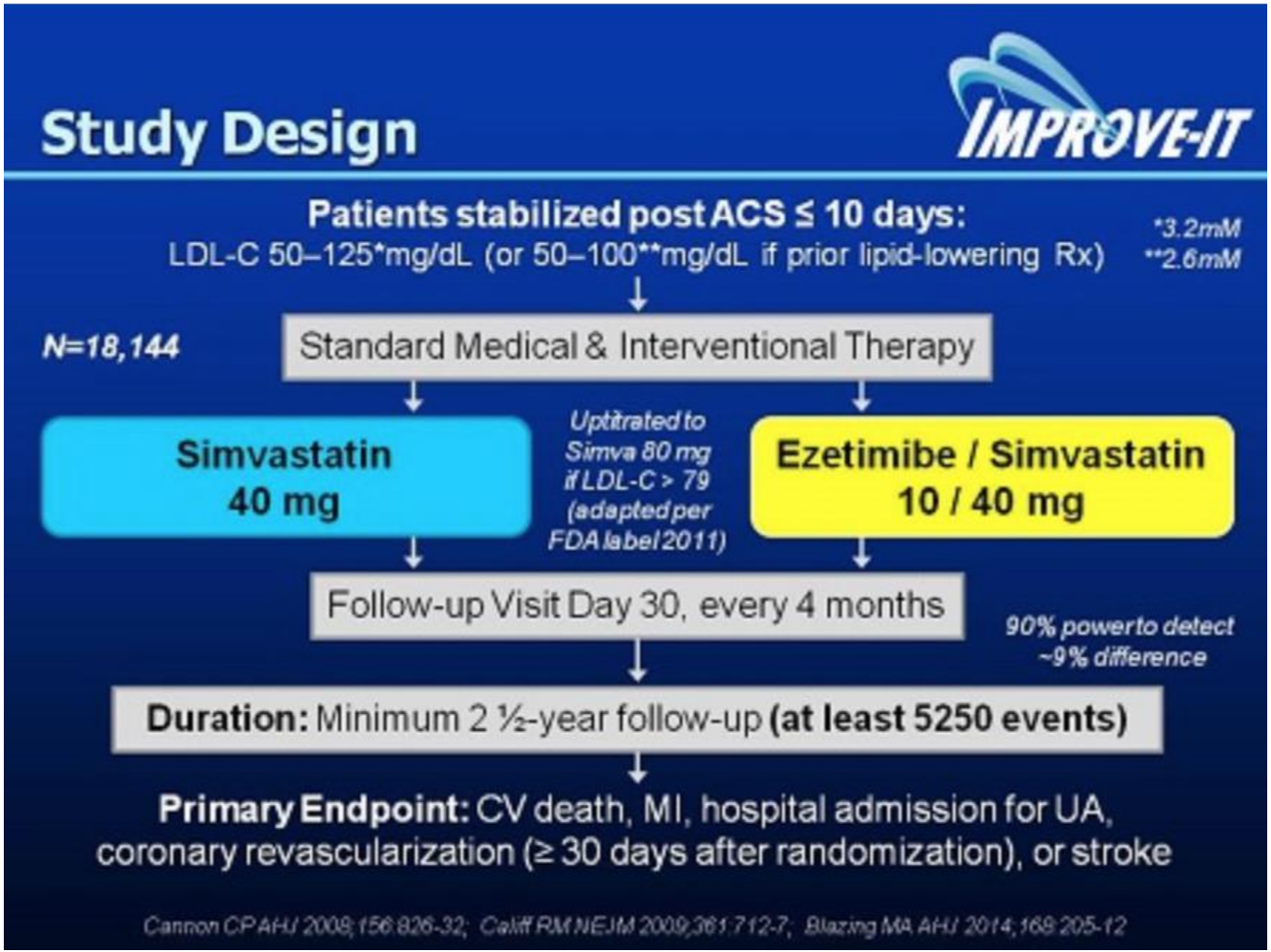



Overall log-rank test P = 0.0015
Probability of cardiac mortality (%)
50.0
40.0
30.0
20.0
10.0
0.0
Progression (28.9%)
No change (14.5%)
Regression (4.0%)
0
1
2
3
4
5
6
7
8
Years


FUORI
DI
TESTA

Caratteristica	*Atorvastatina*	*Fluvastatina*	*Lovastatina*	*Pravastatina*	*Rosuvastatina*	*Simvastatina*
Riduzione del colesterolo-LDL sierico ottenuta (%)	50	24	34	34	50	41
Riduzione del triacilgli-rerolo sierico ottenuta (%)	29	10	16	24	18	18
Aumento del colesterolo-HDL sierico ottenuto (%)	6	8	9	12	8	12
Emivita plasmatica (h)	14	1–2	2	1–2	19	1–2
Penetrazione nel sistema nervoso centrale	No	No	Sì	No	No	Sì
Escrezione renale della dose assorbita (%)	2	<6	10	20	10	13

Le statine sono farmaci che inibiscono la sintesi del colesterolo endogeno agendo sull'enzima idrossimetilglutaril-CoA reduttasi, che converte la molecola del 3-idrossi-3-metilglutaril-CoA in acido mevalonico, un precursore del colesterolo



L'ezetimibe è un farmaco capace di inibire selettivamente l'assorbimento intestinale del colesterolo assunto con la dieta e di quello proveniente dalla bile, senza causare gli effetti collaterali tipici delle resine sequestranti gli acidi biliari.
Riduzione LDL 10-20%

STATE-OF-THE-ART PAPER

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

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

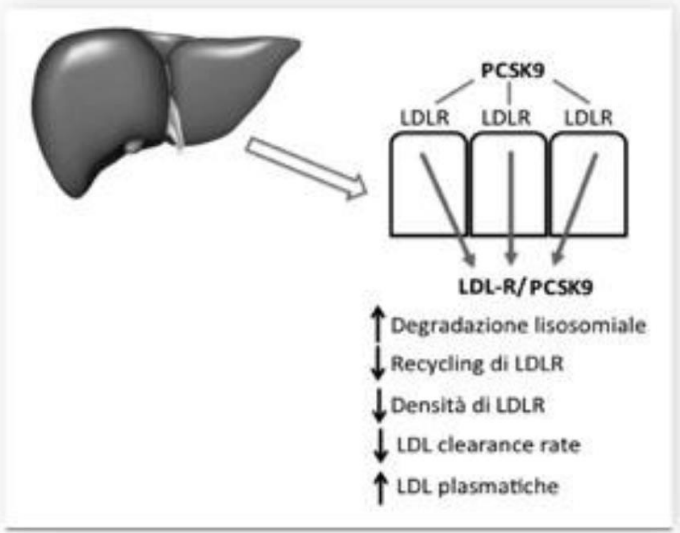


Figura 1. Meccanismo d'azione di PCSK9.
PCSK9 è una proteina appartenente alla famiglia delle subtilisine che, legandosi al recettore delle lipoproteine a bassa densità (LDLR), ne accelera la degradazione lisosomiale, riducendo quindi la densità recettoriale sulla superficie degli epatociti.

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

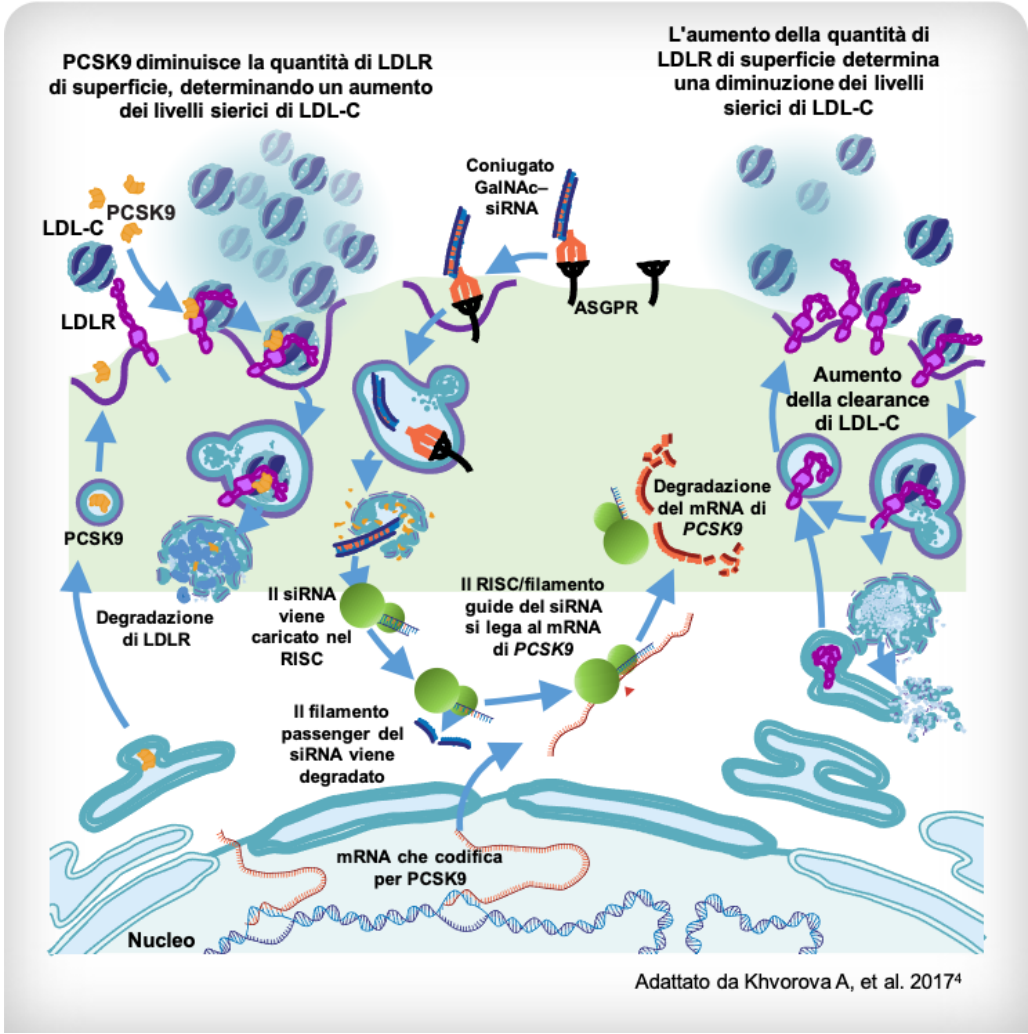
ALIROCUMAB ed EVOLOCUMAB

In circostanze naturali, PCSK9 si lega a LDLR determinando la sua degradazione lisosomiale e una riduzione della sua concentrazione sulla superficie cellulare

In assenza di PCSK9, LDLR si lega a LDL-C, viene internalizzato mediante endocitosi e riciclato sulla superficie cellulare

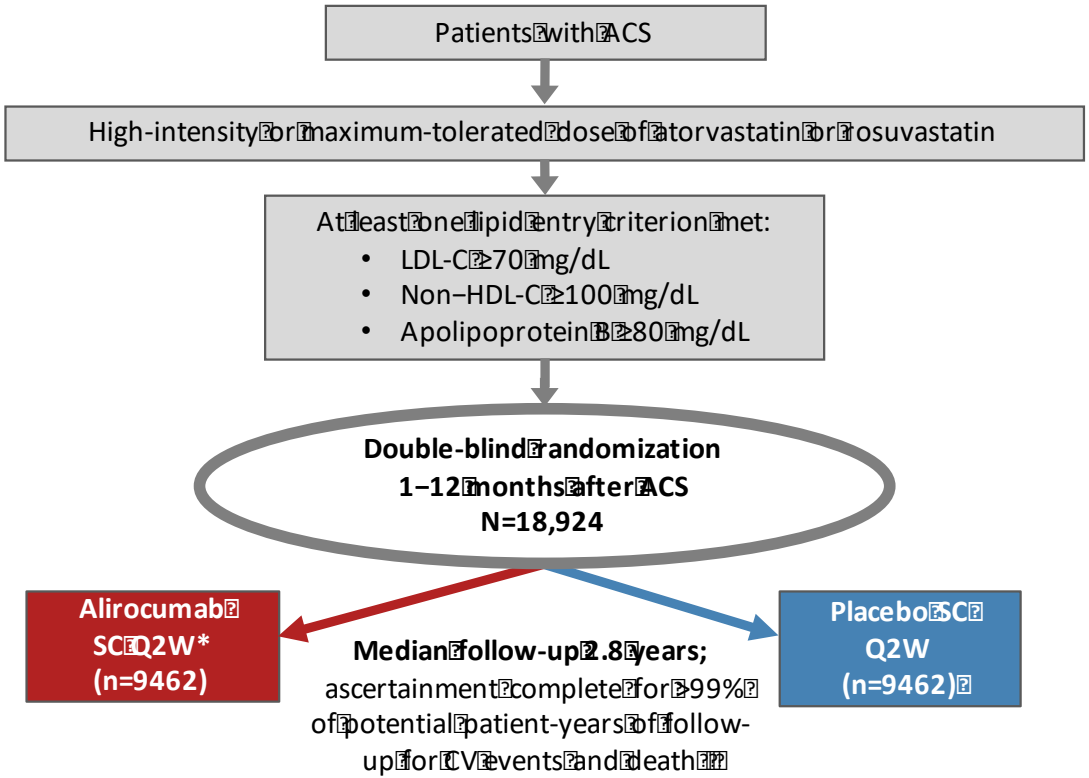
L'assorbimento di LDL-C da parte degli epatociti aumenta, con conseguente riduzione di LDL-C in circolo

ALIROCUMAB ed EVOLOCUMAB



Adattato da Khvorova A, et al. 2017[4]

Design of the ODYSSEY OUTCOMES trial



*Blinded adjustment of alirocumab dose to target achieved LDL-C 25–50 mg/dL and avoid sustained levels <15 mg/dL

CV, cardiovascular; Q2W, every 2 weeks; SC, subcutaneous.

Baseline characteristics by history of PAD or CeVD

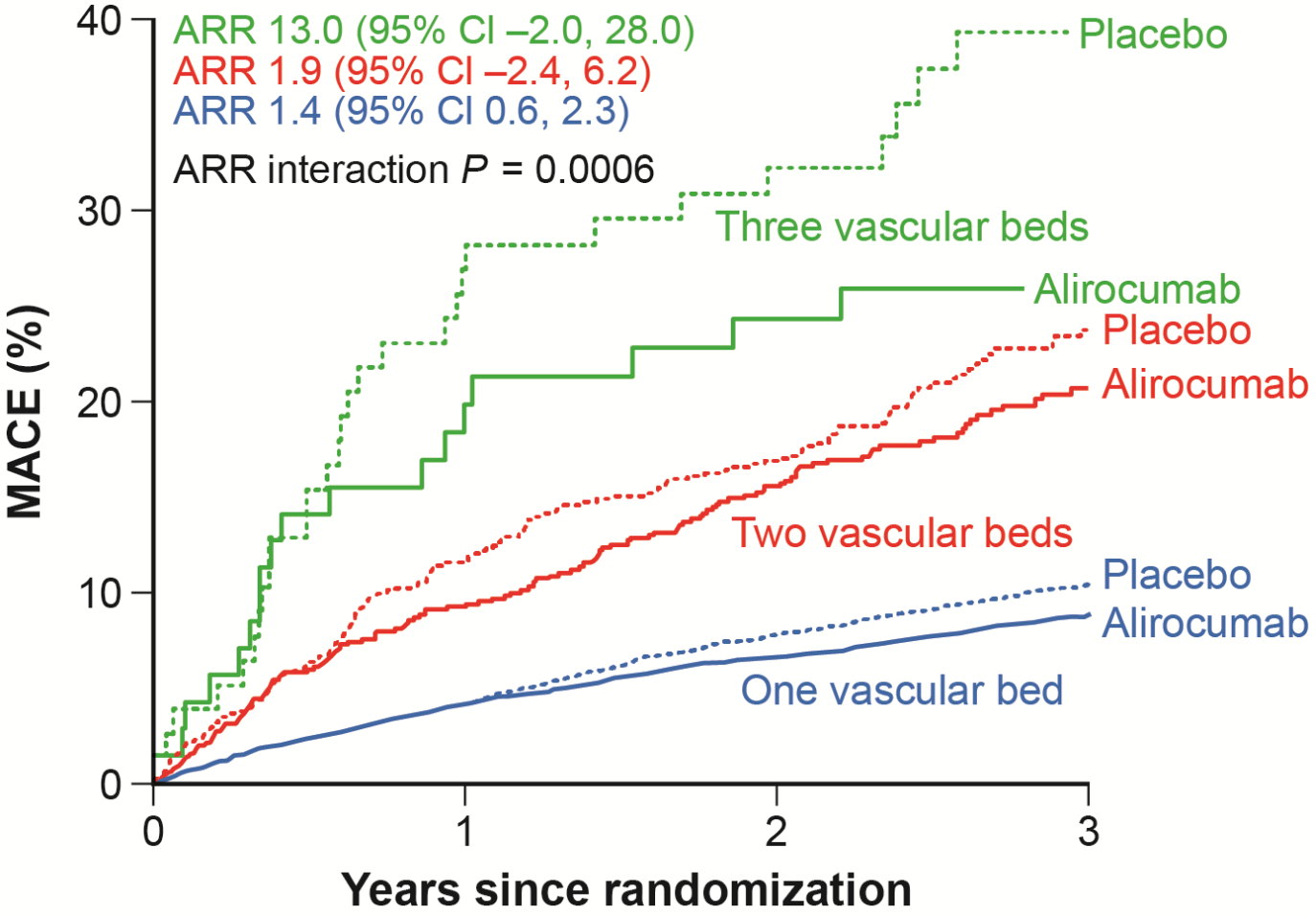
	Monovascular disease	Disease in two vascular beds		Disease in three vascular beds	*P**
	Coronary without PAD or CeVD (n=17,370)	Coronary and PAD (n=610)	Coronary and CeVD (n=795)	Coronary, PAD, and CeVD (n=149)	
Age, years	58 (51,65)	62 (56,68)	62 (56,69)	66 (60,71)	<0.0001
Women	24.7	26.7	33.2	24.8	<0.0001
Index event					<0.0001
NSTEMI	47.9	56.3	55.4	63.1	
STEMI	35.1	31.1	28.6	22.8	
Unstable angina	17.1	11.7	16.0	14.1	
LLT at randomization					<0.0001
High-dose atorvastatin or rosuvastatin	89.2	86.1	85.4	81.2	
Other LLT	10.0	12.3	12.8	16.1	
No LLT	0.9	1.6	1.8	2.7	

Values are median (quartile 1, quartile 3) or %; LLT, lipid-lowering therapy. *Across disease subgroups.

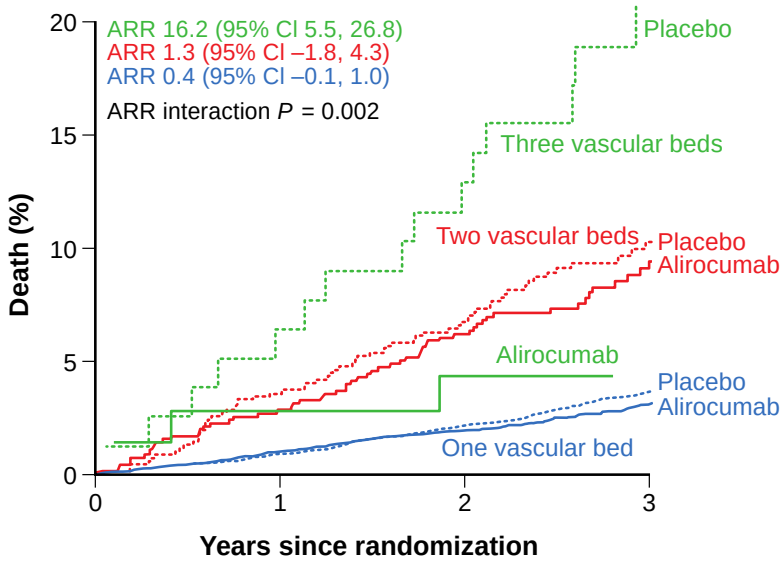
Baseline characteristics by history of PAD or CeVD

	Monovascular disease	Disease in two vascular beds		Disease in three vascular beds	*P**
	Coronary without PAD or CeVD (n=17,370)	Coronary and PAD (n=610)	Coronary and CeVD (n=795)	Coronary, PAD, and CeVD (n=149)	
LDL-C, mg/dL	86 (73, 103)	91 (76, 108)	90 (75, 109)	95 (80, 115)	<0.0001
LDL-C ≥100 mg/dL	29.1	35.7	36.5	40.9	<0.0001
HDL-C, mg/dL	42 (36, 50)	42 (36, 50)	43 (36, 51)	43 (37, 51)	NS
Non–HDL-C, mg/dL	114 (99, 136)	121 (105, 143)	120 (103, 144)	124 (108, 143)	<0.0001
Triglycerides, mg/dL	128 (94, 181)	134 (99, 187)	136 (98, 190)	135 (94, 182)	0.002
Apolipoprotein B, mg/dL	79 (69, 93)	83 (72, 96)	83 (71, 96)	82 (75, 95)	<0.0001
Lipoprotein(a), mg/dL	20.8 (6.6, 59.4)	25.5 (7.5, 68.1)	23.0 (7.1, 61.7)	29.4 (9.4, 74.5)	0.004
eGFR, mL/min per 1.73 m^2	78.5 (68.1, 90.4)	74.1 (61.6, 86.7)	72.9 (59.5, 85.8)	67.0 (52.2, 84.4)	<0.0001
eGFR <60 mL/min per 1.73 m^2	12.3	22.1	25.9	39.6	<0.0001

Values are median (quartile 1, quartile 3) or %. NS = p>0.05. eGFR, estimated glomerular filtration rate. *Across disease subgroups.


ARR 13.0 (95% CI –2.0, 28.0)
ARR 1.9 (95% CI –2.4, 6.2)
ARR 1.4 (95% CI 0.6, 2.3)
ARR interaction P = 0.0006
Placebo
Three vascular beds
Alirocumab
Placebo
Alirocumab
Two vascular beds
Placebo
Alirocumab
One vascular bed
MACE (%)
0
10
20
30
40
0
1
2
3
Years since randomization

Death: one, two or three vascular beds



Safety endpoints

- Overall, no differences in incidence of adverse events or laboratory abnormalities between alirocumab and placebo, with the exception of local injection-site reactions, which occurred more often in the alirocumab group

- No major differences were observed between the vascular groups

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Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

Endpoint	Description
Primary*	• Composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization
Key secondary†	• Composite of CV death, MI, or stroke
Other Secondary	• All-cause death; CV death; MI; stroke; coronary revascularization; CV death or hospitalization for heart failure; ischemic stroke or transient ischemic attack

Sample size based on key secondary endpoint and powered to detect a 15% risk reduction at 90% power

Assuming 2% per year event rate in placebo arm, 27,500 patients followed up for a median of ~43 months should have provided 1,630 key secondary endpoints

Efficacy analysis was hierarchical:

If primary endpoint was significantly reduced, then key secondary endpoint was to be tested, followed in order by CV death, all-cause mortality, then additional secondary endpoints

Inclusion Criteria

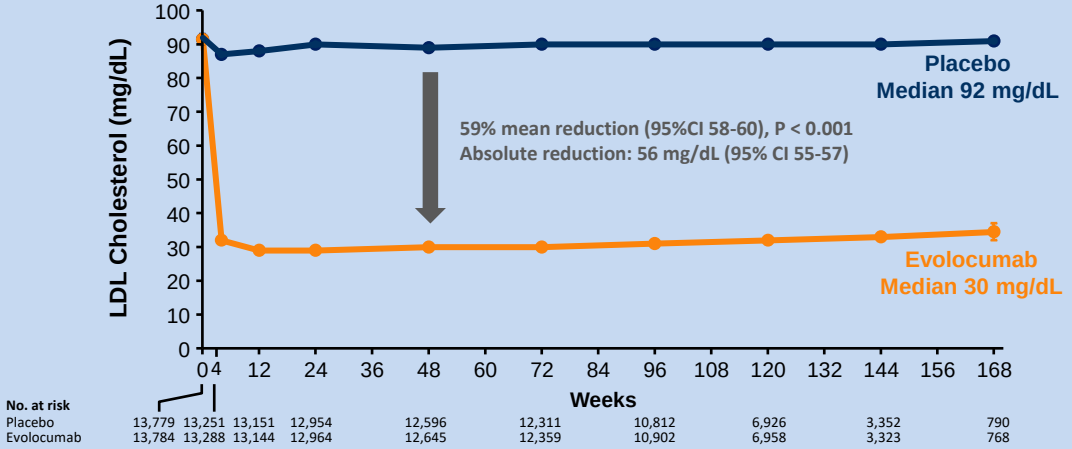
Atherosclerotic cardiovascular disease, defined as a history of myocardial infarction, nonhemorrhagic stroke, or symptomatic peripheral artery disease and had to have a fasting LDL cholesterol level of 70 mg per deciliter

*Time to CV death, MI, stroke, hospitalization for UA, or coronary revascularization, whichever occurs first
†Time to CV death, MI, or stroke, whichever occurs first
CV = cardiovascular; MI = myocardial infarction
Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Table 1. Characteristics of the Patients at Baseline.*

Characteristics	Evolocumab (N=13,784)	Placebo (N=13,780)
Age — yr	62.5±9.1	62.5±8.9
Male sex — no. (%)	10,397 (75.4)	10,398 (75.5)
White race — no. (%)†	11,748 (85.2)	11,710 (85.0)
Weight — kg	85.0±17.3	85.5±17.4
Region		
North America	2,287 (16.6)	2,284 (16.6)
Europe	8,666 (62.9)	8,669 (62.9)
Latin America	913 (6.6)	910 (6.6)
Asia Pacific and South Africa	1,918 (13.9)	1,917 (13.9)
Type of atherosclerosis‡		
Myocardial infarction — no. (%)	11,145 (80.9)	11,206 (81.3)
Median time from most recent previous myocardial infarction (IQR) — yr	3.4 (1.0–7.4)	3.3 (0.9–7.7)
Nonhemorrhagic stroke	2686 (19.5)	2651 (19.2)
Median time from most recent previous stroke (IQR) — yr	3.2 (1.1–7.1)	3.3 (1.1–7.3)
Peripheral artery disease — no. (%)	1,858 (13.5)	1,784 (12.9)
Cardiovascular risk factors		
Hypertension — no./total no. (%)	11,045/13,784 (80.1)	11,039/13,779 (80.1)
Diabetes mellitus — no. (%)	5,054 (36.7)	5,027 (36.5)
Current cigarette use — no./total no. (%)	3854/13,783 (28.0)	3923/13,779 (28.5)
Statin use — no. (%)§		
High intensity	9,585 (69.5)	9,518 (69.1)
Moderate intensity	4,161 (30.2)	4,231 (30.7)
Low intensity, unknown intensity, or no data	38 (0.3)	31 (0.2)
Ezetimibe — no. (%)	726 (5.3)	714 (5.2)
Median lipid measures (IQR)		
LDL cholesterol — mg/dl	92 (80–109)	92 (80–109)
Total cholesterol — mg/dl	168 (151–188)	168 (151–189)
HDL cholesterol — mg/dl	44 (37–53)	44 (37–53)
Triglycerides — mg/dl	134 (101–183)	133 (99–181)
Lipoprotein(a) — nmol/liter	37 (13–166)	37 (13–164)

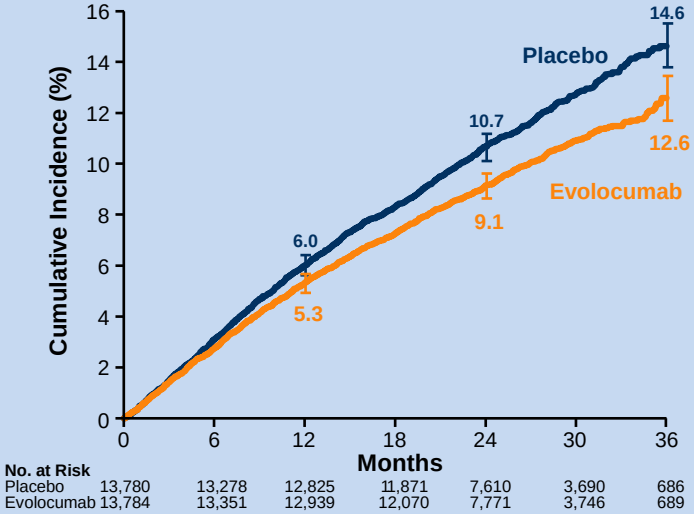
Median LDL-C Levels Over Time: All Patients



LDL-C was significantly reduced in the evolocumab group (median: 30 mg/dL) including 42% who achieved levels ≤ 25 mg/dL vs < 0.1% in the placebo group

Data shown are median values with 95% confidence intervals in the two arms; ITT.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa

Primary Endpoint: Composite of CV Death, MI, Stroke, Hospitalization for UA, or Coronary Revascularization
(the lowest)

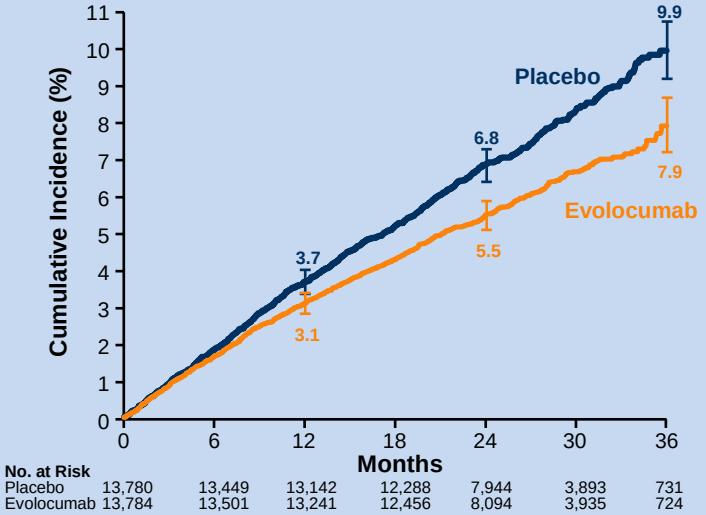


HR 0.85 (95% CI 0.79 to 0.92); *P* < 0.001

CV = Cardiovascular; MI = Myocardial infarction; UA = Unstable angina; HR = Hazard ratio

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Key Secondary Endpoint: Composite of CV Death, MI, or Stroke



HR 0.80 (95% CI 0.73 to 0.88); *P* < 0.001

CV = Cardiovascular; MI = Myocardial infarction; HR = Hazard ratio

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

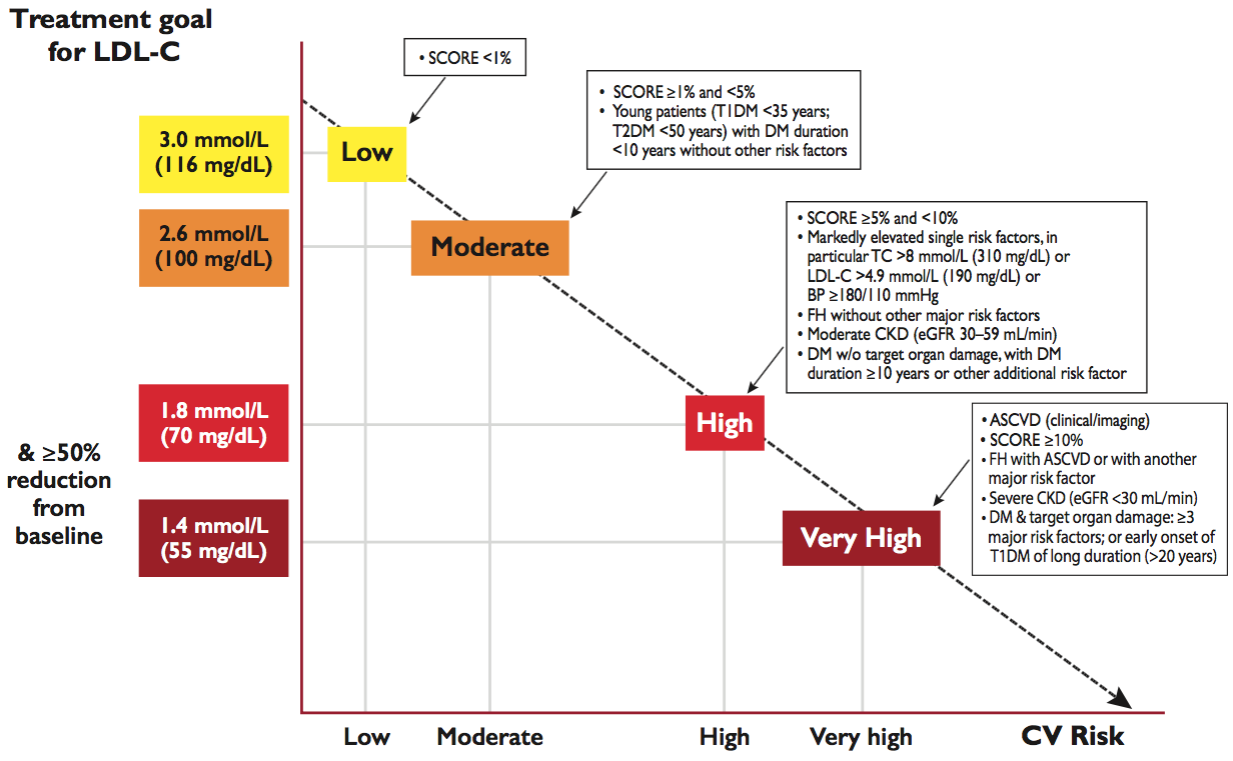
ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–78
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)



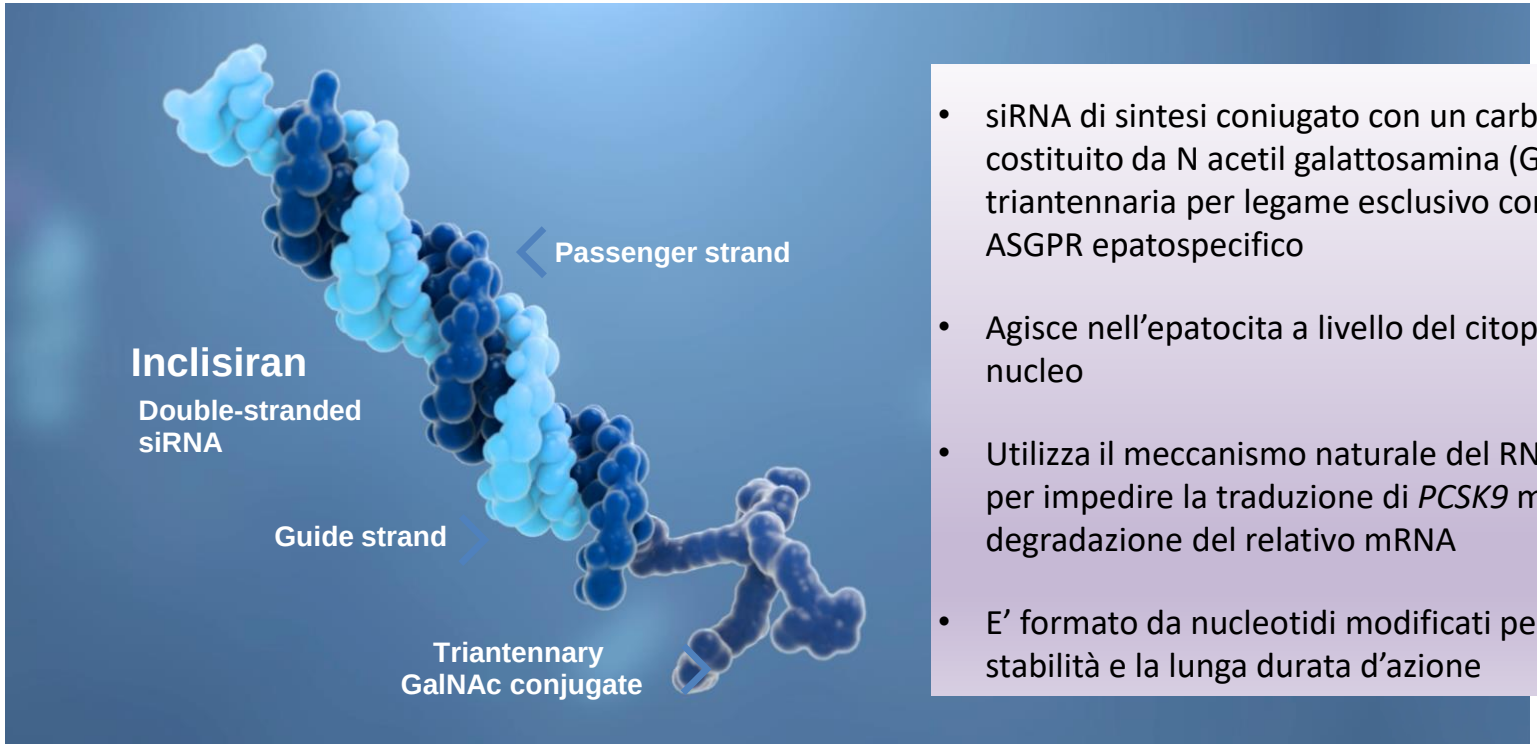
- **New/revised concepts**

More intensive reduction of LDL-C across CV risk categories

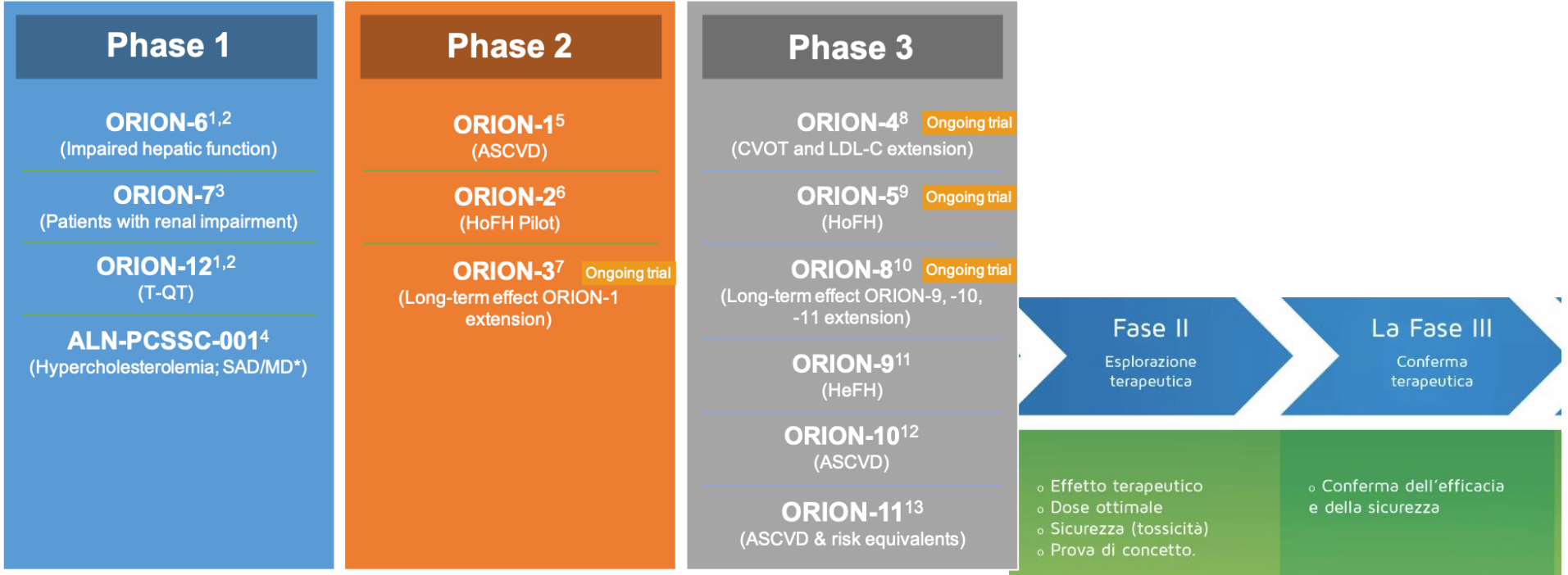
- For secondary prevention in very-high-risk patients, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.
  - For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.

INCLISIRAN

siRNA (SMALL INTERFERING RNA) mima il processo fisiologico di RNA interference. Legandosi al RNA-inducing silencing complex (RISC) ---- degradazione del mRNA che codifica per PCSK9 ----- impedendo la sintesi della relativa proteina

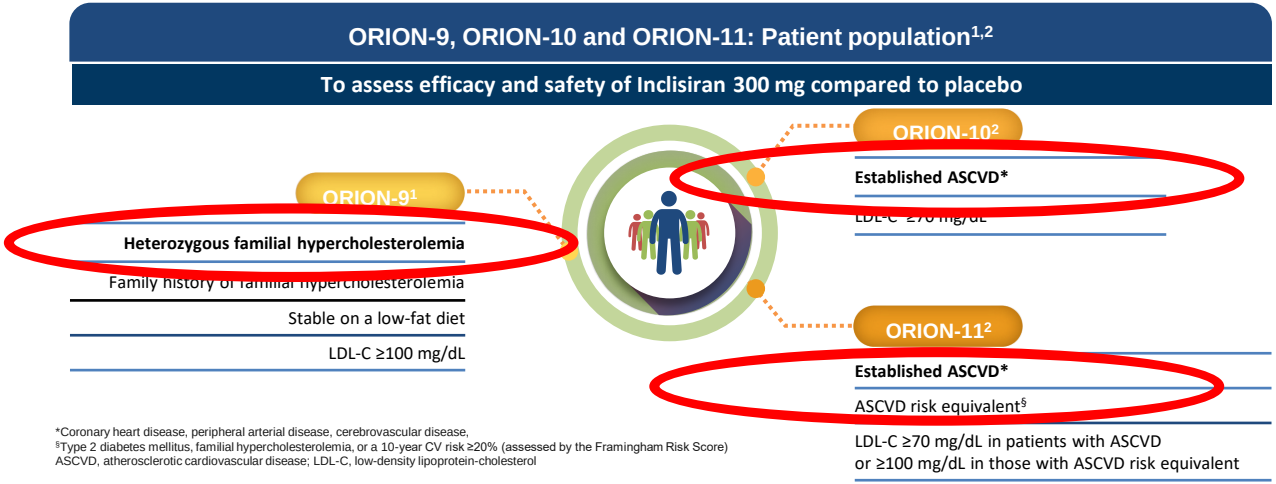


- siRNA di sintesi coniugato con un carboidrato costituito da N acetil galattosamina (GalNAc) triantennaria per legame esclusivo con recettore ASGPR epatospecifico
- Agisce nell'epatocita a livello del citoplasma e non nel nucleo
- Utilizza il meccanismo naturale del RNA interference per impedire la traduzione di *PCSK9* mediante la degradazione del relativo mRNA
- E' formato da nucleotidi modificati per prolungarne la stabilità e la lunga durata d'azione



ORION
(23.500 pazienti ad oggi)

Caratteristiche studi di fase 3 ORION 9-10-11: 18 mesi durata, doppio-cieco, randomizzati, vs placebo



Common key inclusion criteria:

≥18 years of age; fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening; had received statin treatment at the maximally tolerated dose or demonstrated documented intolerance. Ezetimibe therapy was allowed.

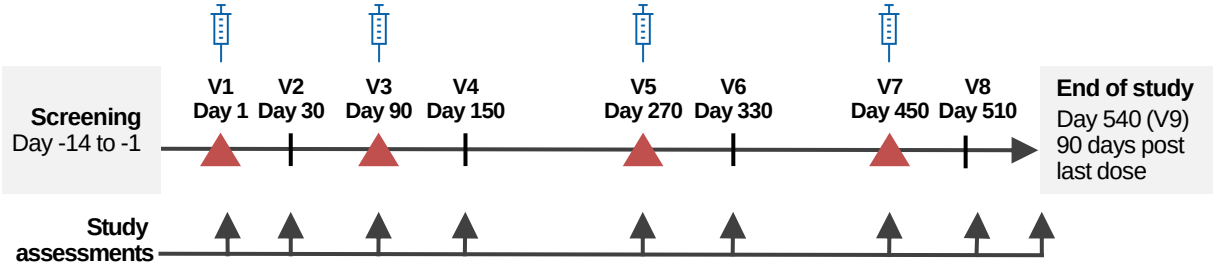
Common key exclusion criteria:

Prior or planned use of a PCSK9 mAb; MACE within 3 months of randomization; had prior/planned use of other investigational drugs; NYHA class IV heart failure or LVEF <25%; uncontrolled severe hypertension; severe concomitant non CV disease; fasting TG ≥4.52 mmol/L (400 mg/dL).

1. Raal FJ, et al. *N Engl J Med.* 2020;382(16):1520-1530. **2.** Raal FJ, et al. [supplementary appendix]. *N Engl J Med.* 2020;382:1520-1530. doi: 10.1056/NEJMoa1913805. **3.** Ray KK, et al. *N Engl J Med.* 2020;382(16):1507-1519. **4.** Ray KK, et al. [supplementary appendix]. *N Engl J Med.* doi: 10.1056/NEJMoa1912387.

Studi ORION 9-10-11: disegno degli studi
18 mesi, doppio-cieco, randomizzati, vs placebo

Randomized 1:1 inclisiran 300 mg* vs placebo – on top of maximal tolerated statin dose



Key primary endpoints

- Percentage change in LDL-C levels from baseline to Day 510
- Time-adjusted percentage change in LDL-C levels from baseline after Day 90 and up to Day 540

Key secondary endpoints

- Absolute change in LDL-C from baseline to Day 510
- Time-adjusted absolute change in LDL-C from baseline between Day 90 and up to Day 540
- Percentage change from baseline to Day 510 in PCSK9, TC, ApoB, and non-HDL-C
- Safety and tolerability profile of inclisiran, measured by AEs, SAEs, vital signs, and clinical laboratory values

*300 mg inclisiran sodium salt, equivalent to 284 mg of inclisiran.

1. Raal FJ, et al. *N Engl J Med.* 2020;382(16):1520-1530. **2**. Raal FJ, et al. [supplementary appendix] *N Engl J Med.* 2020;382:1520-1530. doi: 10.1056/NEJMoa1913805. **3**. Ray KK, et al. *N Engl J Med*. 2020;382(16):1507-1519. **4**. Ray KK, et al. [supplementary appendix] *N Engl J Med.* doi: 10.1056/NEJMoa1912387.

Caratteristiche studi di fase 3 ORION 9-10-11: 18 mesi durata, doppio-cieco, randomizzati, vs placebo

Trial Specific Inclusion Criteria

ORION-9[1,2]	ORION-10[3,4]	ORION-11[3,4]
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% • FH
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) in ASCVD or ≥2.6 mmol/L (100 mg/dL) in risk equivalent

Common key inclusion criteria:

≥18 years of age; fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening; 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; MACE within 3 months of randomization; had prior/planned use of other investigational drugs; NYHA class IV heart failure or LVEF <25%; uncontrolled severe hypertension; severe concomitant non CV disease; fasting TG ≥4.52 mmol/L (400 mg/dL).

1. Raal FJ, et al. *N Engl J Med.* 2020;382(16):1520-1530. **2.** Raal FJ, et al. [supplementary appendix]. *N Engl J Med.* 2020;382:1520-1530. doi: 10.1056/NEJMoa1913805. **3.** Ray KK, et al. *N Engl J Med.* 2020;382(16):1507-1519. **4.** Ray KK, et al. [supplementary appendix]. *N Engl J Med.* doi: 10.1056/NEJMoa1912387.

Studi ORION 9-10-11
Demografica al basale: caratteristiche dei pazienti arruolati[1,2]

Characteristic	ORION-9[1]	ORION-10[2]	ORION-11[2]
Population	**HeFH (n=482)**	**ASCVD (n=1561)**	**ASCVD/risk equivalent (n=1617)**
ASCVD status (%)	27.4%	100%	87.4% (ASCVD) 12.6% (risk equivalents)
Average age (yr)	56	66	65
Gender (male)	47.1%	69.4%	71.7%
LDL-C	4.0 mmol/L (153.1 mg/dL)	2.71 mmol/L (104.7 mg/dL)	2.73 mmol/L (105.5 mg/dL)
Statin use (%)	90.5%	89.2%	94.7%
High intensity statin use (%)	73.9%	68%	78.6%
Ezetimibe use	52.9%	9.9%	7.1%
Diabetes mellitus	10%	44.9%	35.1%

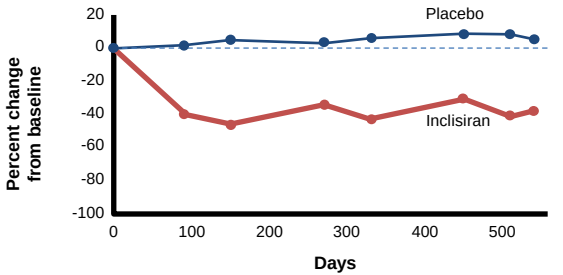
1. Raal FJ, et al. *N Engl J Med.* 2020;382(16):1520-1530.
2. Ray KK, et al. *N Engl J Med.* 2020;382(16):1507-1519.

Studi ORION 9-10-11: endpoint primario
Inclisiran fornisce un'efficace e prolungata riduzione delle LDL-C per 18 mesi

Variazione percentuale LDL nel tempo (over time)

ORION-9[1]

Change in LDL cholesterol

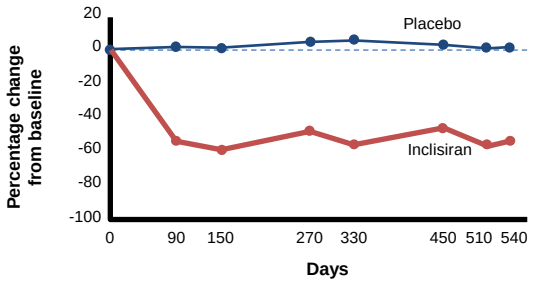


No. of patients								
Placebo	240	237	238	235	233	233	229	232
Inclisiran	242	240	239	240	237	237	231	232

Used with permission. Raal FJ, et al. *N Engl J Med.* 2020;382(16):1520-1530.

ORION-10[2]

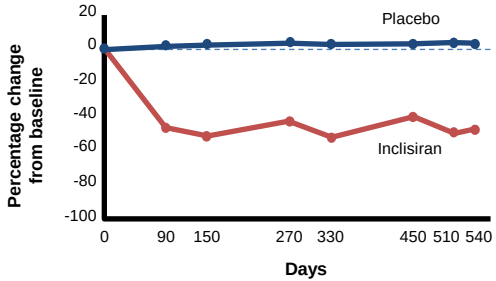
Percentage change in LDL cholesterol



No. of patients								
Placebo	780	762	745	724	715	698	666	670
Inclisiran	781	758	757	737	731	721	691	705

ORION-11[2]

Percentage change in LDL cholesterol



No. of patients								
Placebo	807	797	785	774	773	764	739	749
Inclisiran	810	790	796	778	773	768	724	742

Used with permission. Ray KK, et al. *N Engl J Med.* 2020;382(16):1507-1519.

Between group difference

-47.9% (*P*<0.001)	**-52.3%** (*P*<0.001)	**-49.9%** (*P*<0.001)

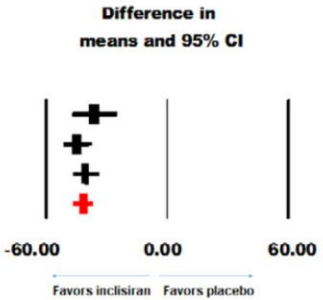
1. Raal FJ, et al. *N Engl J Med.* 2020;382(16):1520-1530.
2. Ray KK, et al. *N Engl J Med.* 2020;382(16):1507-1519.

Metanalisi studi Orion 9-10-11
Riduzione delle LDL-C e Major adverse Cardiovascular Event (MACE)

A: LDL cholestrol Level

Study name	Statistics for each study			
	Difference in means	Lower limit	Upper limit	p-Value
ORION-9	-47.90	-53.39	-42.41	0.000
ORION-10	-52.30	-55.75	-48.85	0.000
ORION-11	-49.90	-53.15	-46.65	0.000
Total	-50.53	-52.73	-48.34	0.000

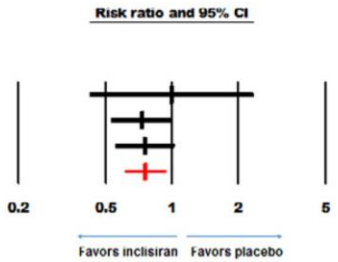
Heterogeneity ($Q = 2.0$, $P = 0.36$; $I^2 = 2.0$)



B: MACE

Study name	Statistics for each study			
	Risk ratio	Lower limit	Upper limit	p-Value
ORION-9	1.00	0.42	2.35	0.992
ORION-10	0.73	0.53	1.01	0.058
ORION-11	0.75	0.55	1.03	0.075
Total	0.76	0.61	0.94	0.012

Heterogeneity ($Q = 0.4$, $P = 0.80$; $I^2 = 0.0$)



Khan SA et al; AM.J Cardiol; 134:69-73

Profilo di safety. Analisi pooled studi ORION 9-10-11 (2)

	Inclisiran (n = 1,833)	Placebo (n = 1,822)	Risk Ratio (95% CI)
TEAE			
≥1 TEAE	1,430 (78.0)	1,409 (77.3)	1.01 (0.97-1.04)
≥1 TEAE leading to drug discontinuation	45 (2.5)	35 (1.9)	1.28 (0.83-1.98)
Serious TEAE			
≥1 serious TEAE	374 (20.4)	419 (23.0)	0.89 (0.78-1.00)
Death	27 (1.5)	27 (1.5)	0.99 (0.59-1.69)
New, worsening, or recurrent cancer	44 (2.4)	49 (2.7)	0.89 (0.60-1.33)
Clinically relevant TEAE at the injection site†			
Any reaction	91 (5.0)	12 (0.7)	7.54 (4.14-13.71)
Mild	67 (3.7)	11 (0.6)	6.05 (3.21-11.42)
Moderate	24 (1.3)	1 (0.1)	23.86 (3.23-176.15)
Severe	0 (0.0)	0 (0.0)	–
Persistent	0 (0.0)	0 (0.0)	–
Liver function			
Alanine aminotransferase >3× ULN	9 (0.5)	7 (0.4)	1.28 (0.48-3.42)
Aspartate aminotransferase >3× ULN	8 (0.4)	10 (0.5)	0.80 (0.31-2.01)
Alkaline phosphatase >2× ULN	8 (0.4)	5 (0.3)	1.59 (0.52-4.85)
Bilirubin >2× ULN	14 (0.8)	14 (0.8)	0.99 (0.48-2.08)
Kidney function: creatinine >2 mg/dl	36 (2.0)	42 (2.3)	0.85 (0.55-1.32)
Muscle: creatine kinase >5× ULN	24 (1.3)	22 (1.2)	1.08 (0.61-1.93)
Hematology: platelet count $<75 \times 10^9$/l	1 (0.1)	2 (0.1)	0.50 (0.05-5.48)

Profilo di safety. Analisi pooled studi ORION 9-10-11 (2)

Most Common Treatment-Emergent Adverse Events
(Safety Population) Occurrence >2%

TEAE (≥2% in any Subgroup)	Inclisiran (n = 1,833)	Placebo (n = 1,822)	Risk Ratio (95% CI)
Diabetes mellitus*	212 (11.6)	207 (11.4)	1.02 (0.85-1.22)
Nasopharyngitis	140 (7.6)	134 (7.4)	1.04 (0.83-1.30)
Upper respiratory tract infection	105 (5.7)	103 (5.7)	1.01 (0.78-1.32)
Hypertension	104 (5.7)	104 (5.7)	0.99 (0.76-1.29)
Arthralgia	91 (5.0)	72 (4.0)	1.26 (0.93-1.70)
Back pain	83 (4.5)	77 (4.2)	1.07 (0.79-1.45)
Urinary tract infection	81 (4.4)	66 (3.6)	1.22 (0.89-1.68)
Diarrhea	[illegible]	[illegible]	1.12 (0.80-1.56)
Bronchitis	78 (4.3)	50 (2.7)	1.55 (1.09-2.20)
Cough	[illegible]	[illegible]	1.12 (0.78-1.61)
Headache	59 (3.2)	56 (3.1)	1.05 (0.73-1.50)
Angina pectoris	58 (3.2)	57 (3.1)	1.01 (0.71-1.45)
Dizziness	59 (3.2)	55 (3.0)	1.07 (0.74-1.53)
Osteoarthritis	49 (2.7)	62 (3.4)	0.79 (0.54-1.14)
Pain in extremity	60 (3.3)	47 (2.6)	1.27 (0.87-1.85)
Dyspnea	59 (3.2)	47 (2.6)	1.25 (0.86-1.82)
Blood creatine phosphokinase increased	43 (2.3)	61 (3.3)	0.70 (0.48-1.03)
Noncardiac chest pain	44 (2.4)	58 (3.2)	0.75 (0.51-1.11)
Influenza	41 (2.2)	54 (3.0)	0.75 (0.51-1.13)

TEAE (≥2% in any Subgroup)	Inclisiran (n = 1,833)	Placebo (n = 1,822)	Risk Ratio (95% CI)
Fall	41 (2.2)	48 (2.6)	0.85 (0.56-1.28)
Sinusitis	36 (2.0)	51 (2.8)	0.70 (0.46-1.07)
Fatigue	39 (2.1)	45 (2.5)	0.86 (0.56-1.32)
Coronary artery disease	39 (2.1)	44 (2.4)	0.88 (0.58-1.39)
Pneumonia	46 (2.5)	36 (2.0)	1.27 (0.83-1.96)
Atrial fibrillation	38 (2.1)	42 (2.3)	0.90 (0.58-1.39)
Musculoskeletal pain	37 (2.0)	39 (2.1)	0.94 (0.60-1.47)
Myalgia	37 (2.0)	39 (2.1)	0.94 (0.60-1.47)
Peripheral edema	38 (2.1)	34 (1.9)	1.11 (0.70-1.76)
Anemia	38 (2.1)	33 (1.8)	1.14 (0.72-1.82)
Injection site pain	41 (2.2)	9 (0.5)	4.53 (2.21-9.29)
Injection site reaction	56 (3.1)	2 (0.1)	27.83 (6.80-113.88)
Cardiac failure congestive	25 (1.4)	36 (2.0)	0.69 (0.42-1.15)

Values are n (%) unless otherwise indicated. *Diabetes TEAE represents worsening of glycemic control as defined in the clinical protocol.

CI = confidence interval; TEAE = treatment-emergent adverse event.

Nessuna limitazione per livelli di GFR, per insufficenza epatica lieve e moderata

farmacocinetica

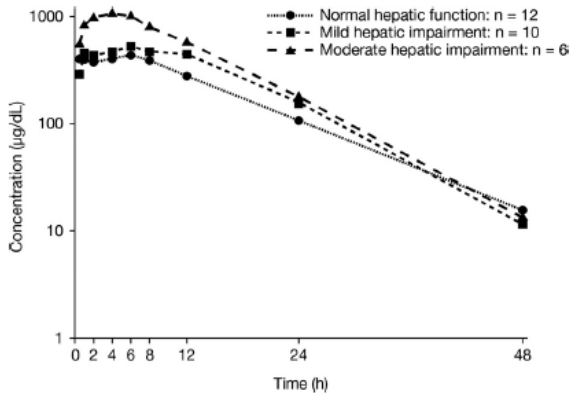


Fig. 1. Mean plasma concentration of inclisiran following a single subcutaneous injection of inclisiran 300 mg to participants with normal hepatic function and patients with hepatic impairment. h, hours.

farmacodinamica

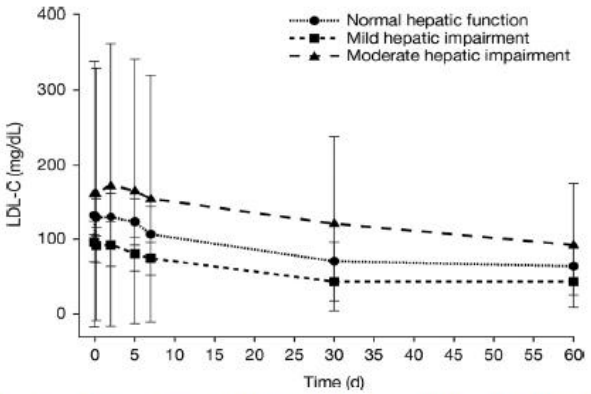


Fig. 2. Mean (standard deviation) LDL-C values over time according to hepatic function (pharmacodynamic population). d, days; LDL-C, low-density lipoprotein cholesterol.

Kallend et al, of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2022.01.001

Conclusioni

1. **L’associazione tra i livelli di colesterolo e gli eventi cardiovascolari/mortalità CV è indiscutibile**
2. **Gli studi recenti hanno dimostrato come l’ottenimento di valori di LDL i più bassi possibile continuino a ridurre gli eventi**
3. **I pazienti vanno stratificati in maniera attenta e va considerata in pazienti very high risk una dose d’attacco “aggressiva” ed un follow-up stretto del paziente**
4. **E’ fondamentale far squadra tra medici ospedalieri/specialisti sul territorio/MMG attorno al paziente nel coinvolgerlo permettendogli di capire l’importanza dei trattamenti che sta assumendo ed ottimizzare la compliance terapeutica.**
5. **Terapie di associazione o iniettive sono armi utili al fine di ottimizzare la compliance e raggiungere i target terapeutici da linee guida.**

Grazie per l’attenzione