



PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

**ROMA**

Centro Congressi  
di Confindustria

**Auditorium  
della Tecnica**

**9<sup>a</sup> Edizione**

**30 Settembre  
1 Ottobre  
2022**



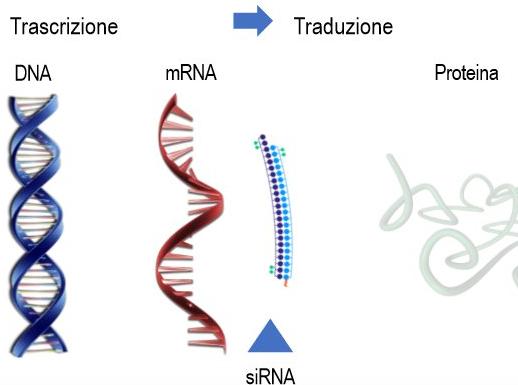
**Focus on Dyslipidemia**

# **Possibilità in fieri: Inclisiran**

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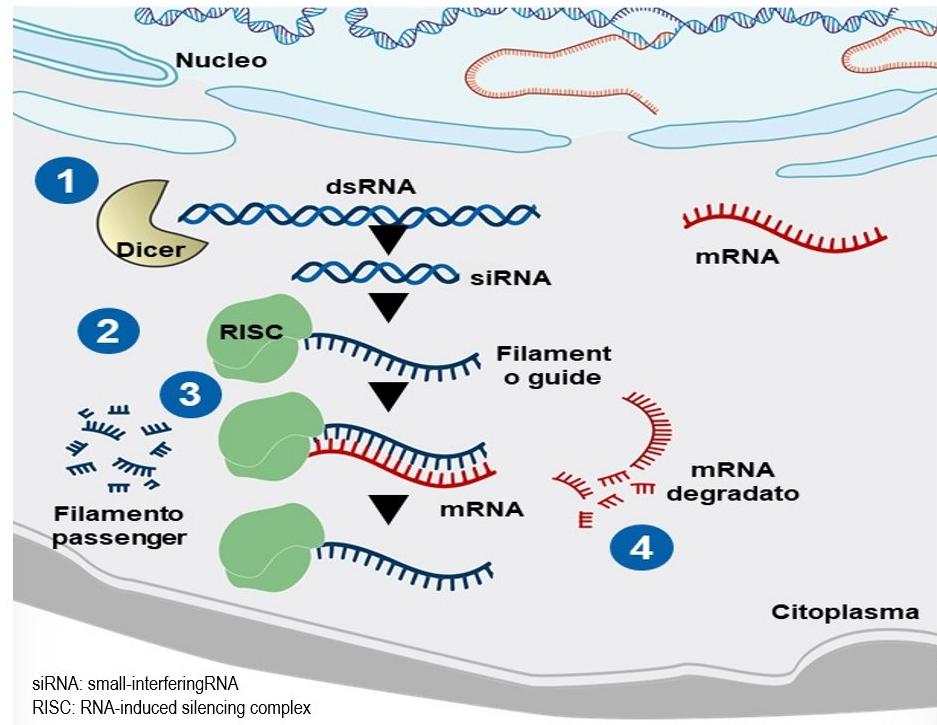
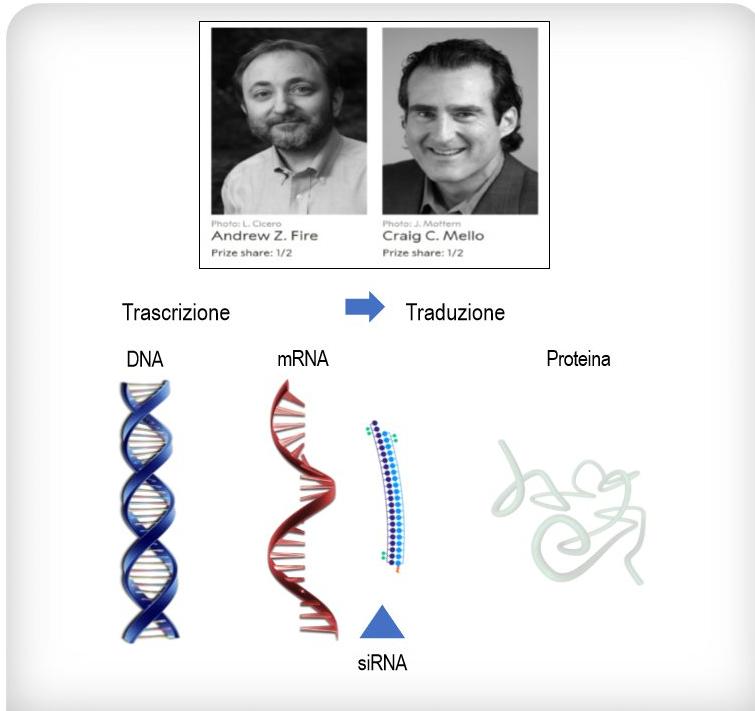
# RNA interference (RNAi)



- Nel 2006 Andrew Fire e Craig Mello sono stati insigniti del premio Nobel per la fisiologia e la medicina per la scoperta del RNAi, dando il via all'era delle terapie basate su RNA (farmaci altamente specifici)<sup>1</sup>
- Le terapie basate su RNA sfruttano il pathway biologico naturale del RNAi per regolare l'espressione di geni specifici<sup>2</sup>
- I progressi nelle terapie basate su RNA sono incentrati sul silenziamento genico mediante l'uso di piccoli ncRNA di sintesi, tra cui i siRNA, per regolare e/o silenziare geni bersaglio<sup>2,3</sup>

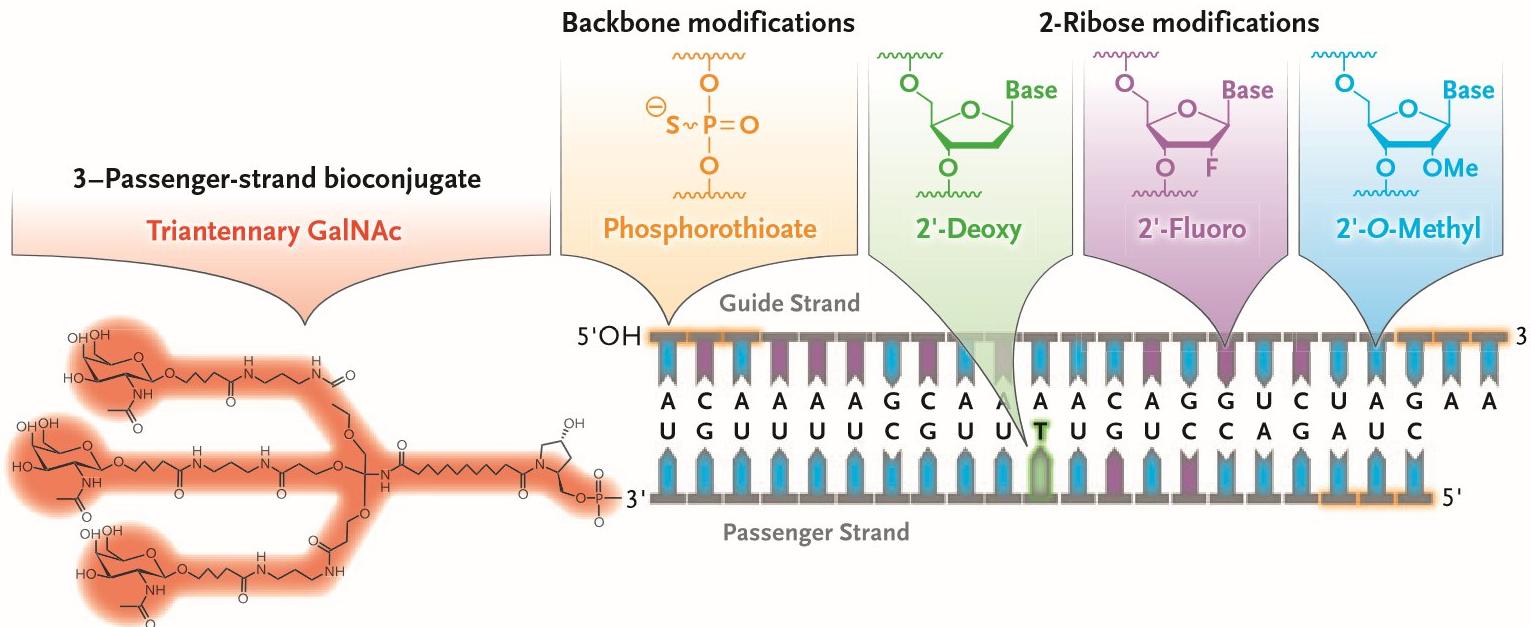
1. The Nobel Prize in Physiology and Medicine 2006. 2. Lam JKW, et al. Mol Ther Nucleic Acids. 2015;4:e252. 3. Crooke ST, et al. Cell Metab. 2018;27:714-739

# RNA interference (RNAi)



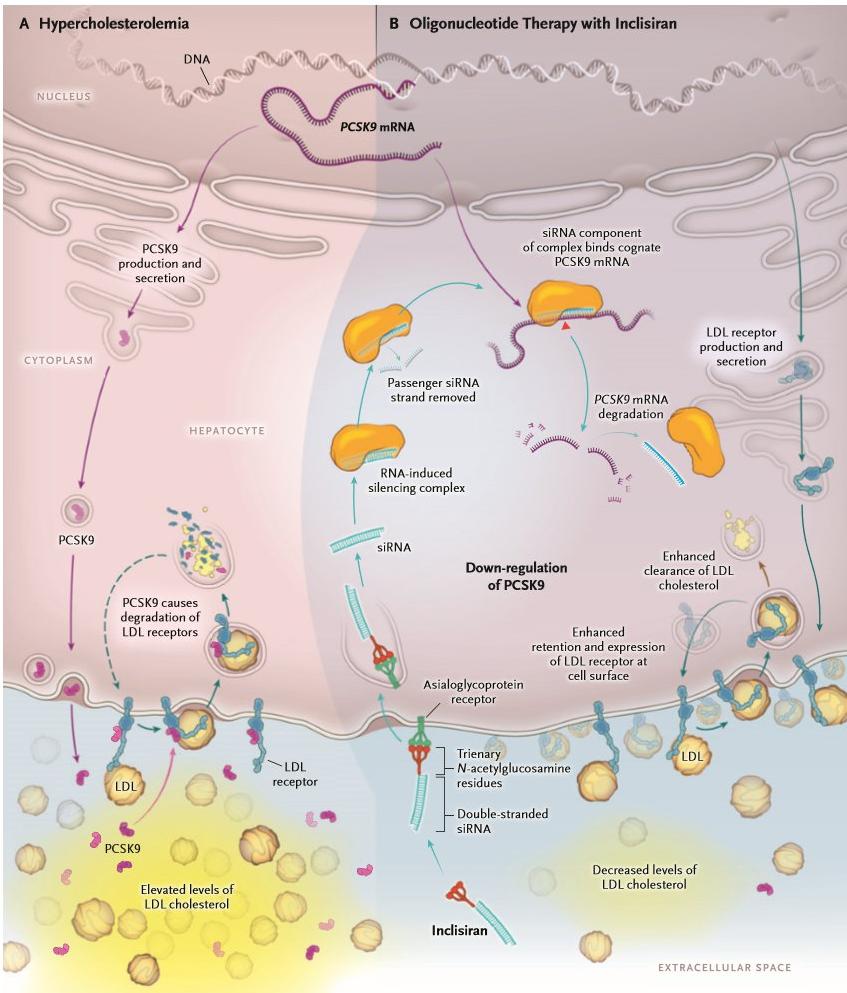
1. The Nobel Prize in Physiology and Medicine 2006. 2. Lam JKW, et al. Mol Ther Nucleic Acids. 2015;4:e252. 3. Crooke ST, et al. Cell Metab. 2018;27:714-739

# Inclisiran



Alta specificità, stabilizzazione e protezione dalla degradazione da endo/esonucleasi, stabilità di legame con il RISC

# Inclisiran



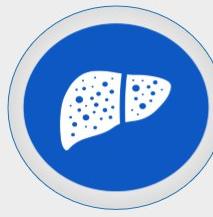
- double-stranded, small interfering RNA (**siRNA**) with one of the RNA strands complementary to a portion of PCSK9 mRNA.
- N-acetylgalactosamine (GalNAc) conjugated to oligonucleotides binds to the asialoglycoprotein receptors (ASGPR) on hepatocytes to transport and release the oligonucleotides into the intracellular compartment (**selectivity and lower dosage**)
- Once inclisiran enters the cell, the complementary strand (or guide strand) is loaded into the RNA-induced silencing complex (**RISC**), a protein complex that displays the strand to the intracellular milieu.
- Once a near-perfect complementary sequence (within an mRNA molecule) hybridizes with part of the guide strand, an enzyme that is part of RISC **cleaves the mRNA**.
- The mRNA cleavage products **cannot be translated**, and PCSK9 protein levels are thereby reduced.
- Inclisiran is chemically modified to increase its stability against endogenous nucleases, conferring a **durable effect** and months of therapeutic activity after each dose.

# Pharmacokinetic properties of inclisiran



## Plasma

- Inclisiran **appears in plasma** ~0.5 h post administration with a half-life of ~7.5 h<sup>1</sup>
- **Peak plasma concentrations** ~4 h and plateau until ~12 h post administration<sup>1,2</sup>
- Inclisiran is **undetectable in plasma between 24-48 h** post administration regardless of renal function<sup>1</sup>



## Liver

- **hepatic uptake of inclisiran within 8 h** of administration<sup>1</sup>
- In hepatocytes, inclisiran prevents translation of PCSK9 mRNA through RNA interference<sup>1</sup>
- Inclisiran undergoes **slow exonuclease degradation**<sup>1</sup>
- No effect cytochrome P450, **not expected to cause drug-drug interactions** <sup>1,2</sup>

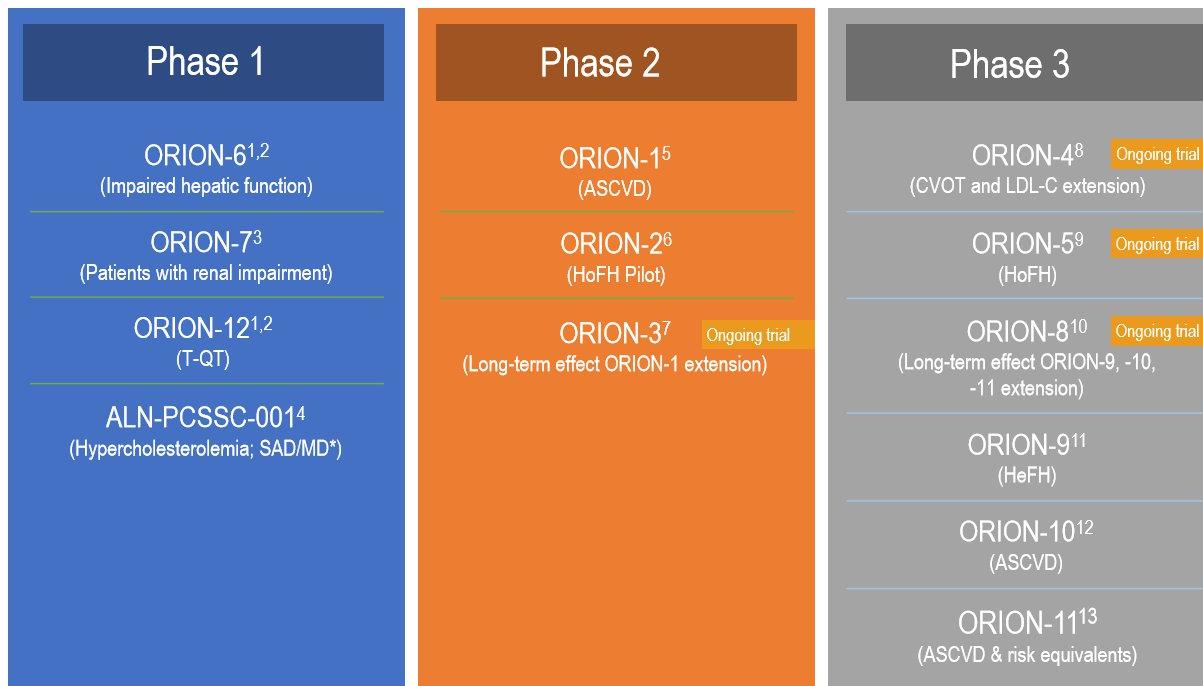


## Kidney

- The kidney is the **main organ of inclisiran elimination**<sup>1</sup>
- Inclisiran concentrations are also **found in the kidney** but are 2- to 5-fold lower than in the liver<sup>1</sup>
- 16% of inclisiran is cleared through the kidney and the terminal half-life is ~9 h<sup>2</sup>

# Il programma di studi clinici ORION

## (23,000 pazienti)

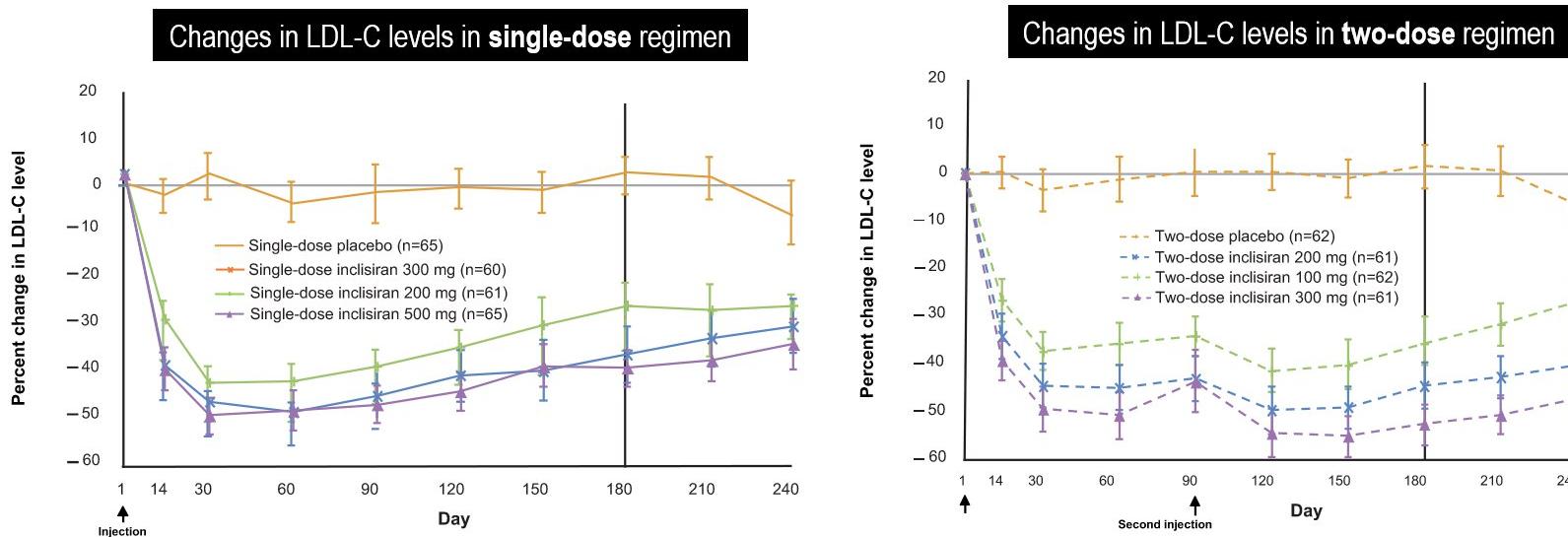


1. German CA, Shapiro MD. BioDrugs. 2020;34(1):1-9. 2. Stoekenbroek RM, et al. Future Cardiol. 2018;14(6):433-442. 3. NCT03159416. 4. NCT02314442. 5. NCT02597127. 6. NCT02963311. 7. NCT03060577. 8. NCT03705234. 9. NCT03851705. 10. NCT03814187. 11. NCT03397121. 12. NCT03399370. 13. NCT03400800.

\*SAD/MD=single ascending dose/multiple dose

# Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

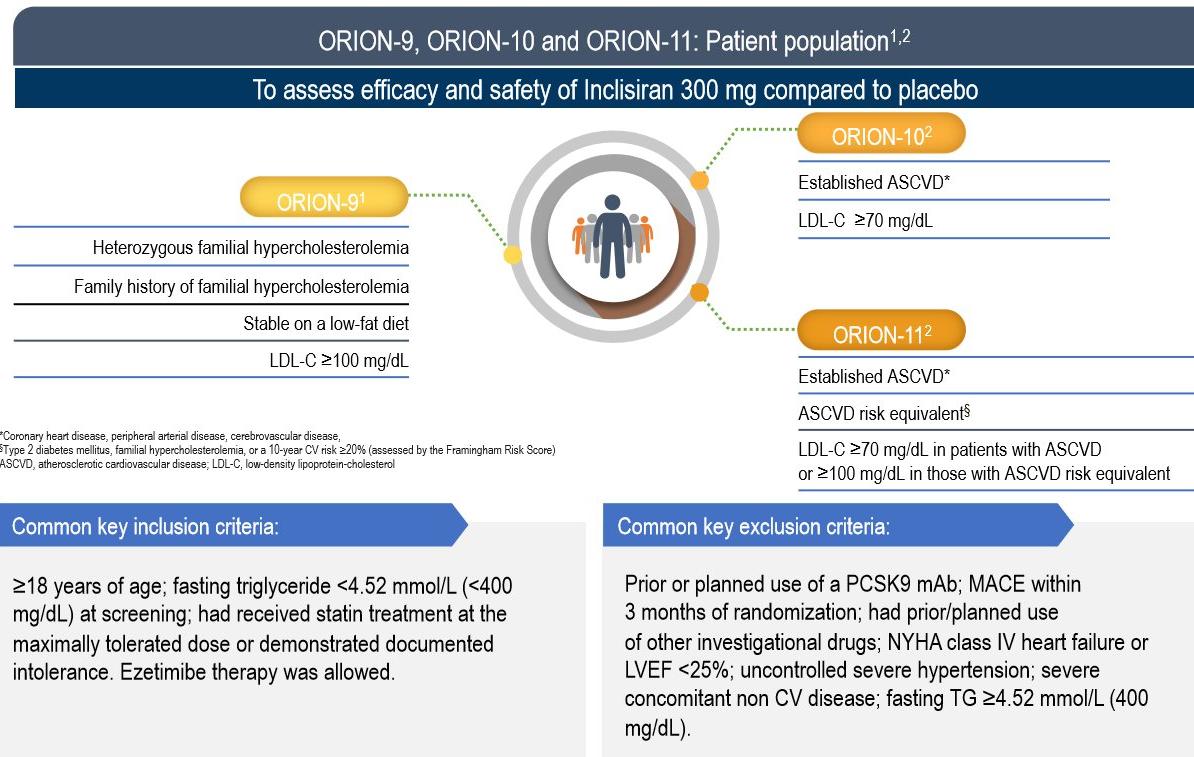
ORION-1 ClinicalTrials.gov



Two-dose 300 mg inclisiran regimen produced the greatest reduction in LDL-C levels

# ORION 9-10-11 studies

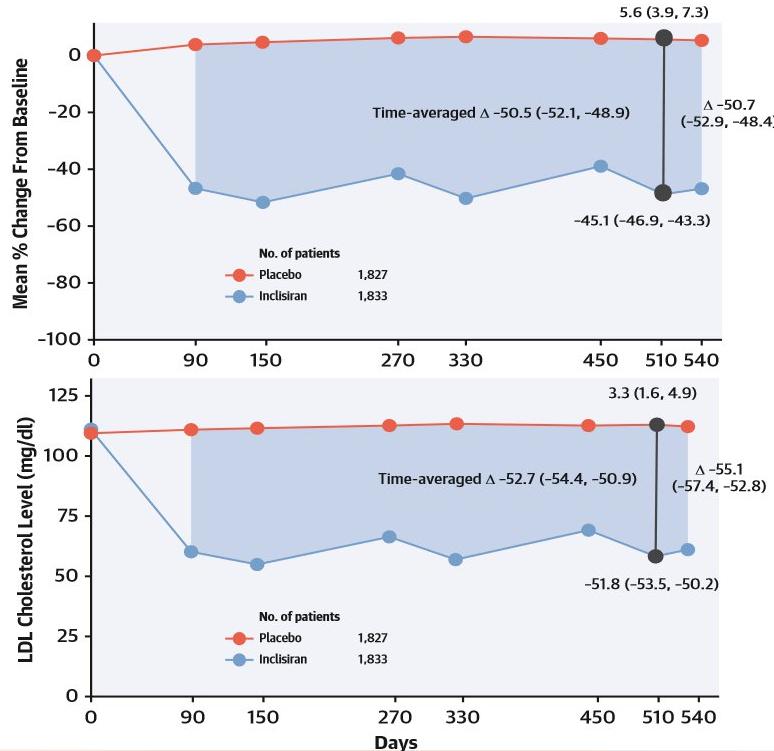
## 18 months follow-up, double blind doppio-cieco, randomized versus placebo



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

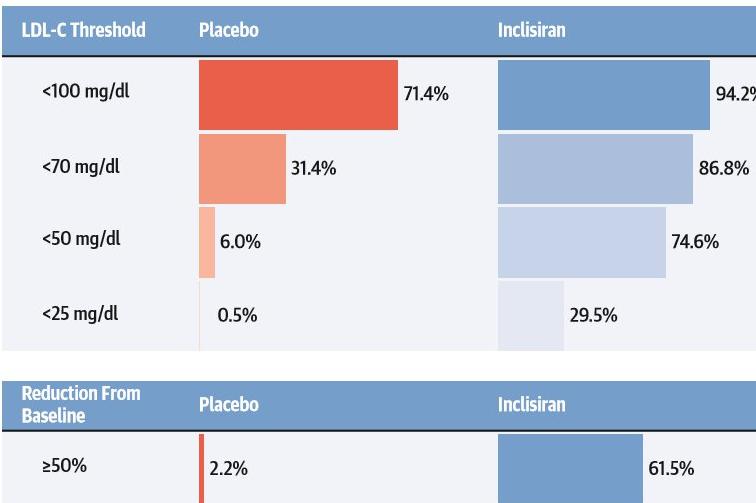
# Pooled Patient-Level Analysis of Inclisiran Trials in Patients With Familial Hypercholesterolemia or Atherosclerosis

	Inclisiran (n = 1,833)	Placebo (n = 1,827)
Age, yrs	64.1 ± 9.98	63.9 ± 9.87
Male	1,226 (66.9)	1,244 (68.1)
White race*	1,670 (91.1)	1,708 (93.5)
Concomitant lipid modifying therapy		
Statins	1,686 (92.0)	1,675 (91.7)
High-intensity statin	1,356 (74.0)	1,345 (73.6)
Ezetimibe	251 (13.7)	270 (14.8)
Cardiovascular risk factors		
ASCVD	1,552 (84.7)	1,555 (85.1)
ASCVD risk equivalent†	281 (15.3)	272 (14.9)
Risk score >20% for 10-yr risk of CV event	54 (19.2)	60 (22.1)
Congestive heart failure	213 (11.6)	227 (12.4)
Smoker (current)	311 (17.0)	271 (14.8)
Hypertension	1,456 (79.4)	1,463 (80.1)
Diabetes	687 (37.5)	631 (34.5)
Familial hypercholesterolemia	340 (19.3)	352 (20.2)
Lipid measures, mg/dl		
LDL cholesterol	111.9 ± 44.9	110.8 ± 43.6
Total cholesterol	190.1 ± 50.7	188.6 ± 49.3
Non-HDL cholesterol	141.5 ± 49.3	140.5 ± 48.1
HDL cholesterol	48.6 ± 15.0	48.0 ± 14.1
Apolipoprotein B	99.3 ± 29.4	98.7 ± 28.4
Lipoprotein(a), nmol/l	50.0 (18-185)	46.5 (19-185)
Triglycerides, mg/dl	130 (93-179)	130 (96-183)
PCSK9, µg/l	396.3 ± 146.1	389.3 ± 129.3

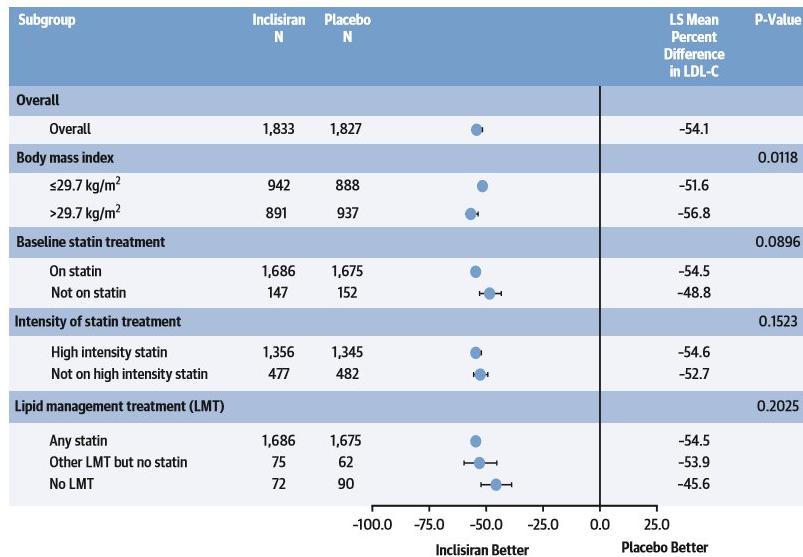


# Pooled Patient-Level Analysis of Inclisiran Trials in Patients With Familial Hypercholesterolemia or Atherosclerosis

% participants achieving specific LDL-C thresholds and LDL-C level  $\geq 50\%$  reduction from baseline at day 510



Subgroup analysis of placebo-corrected % change in LDL-C from baseline to day 510 with inclisiran (ITT)



# End points secondari ORION 9, 10 e 11

## variazione % a 510 giorni

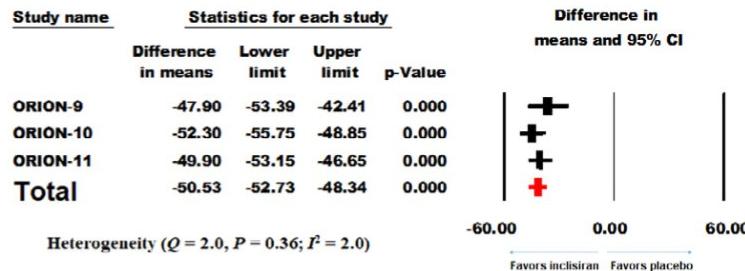
PARAMETRO	ORION-9 <sup>1</sup>		ORION-10 <sup>2</sup>		ORION-11 <sup>2</sup>	
	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo
PCSK9	-60.7%	+17.7%	-69.8%	+13.5%	-63.6%	+15.6%
Total cholesterol	-26.1%	+6.8%	-33.6%	+0.4%	-28.0%	+1.8%
<b>Non-HDL cholesterol</b>	<b>-36.1%</b>	<b>+7.5%</b>	<b>-47.4%</b>	<b>-0.1%</b>	<b>-41.2%</b>	<b>+2.2%</b>
ApoB	-34.0%	+2.9%	-44.8%	-1.7%	-38.2%	+0.8%
Lp(a)	-13.5%	+3.7%	-21.9%	+3.7%	-18.6%	+0.0
HDL-C	+8.6%	+6.0%	+7.5%	+2.4%	+10.2%	+4.1%

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

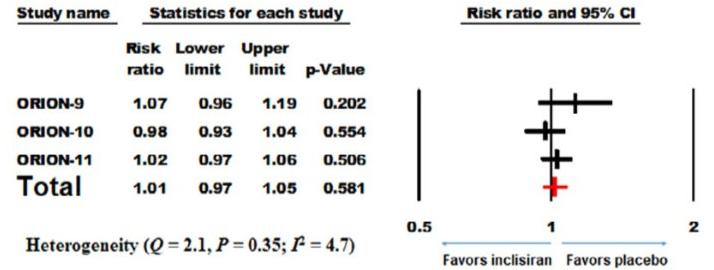
2. Ray KK, et al. N Engl J Med. 2020;382(16):1507-1519.

# Meta-Analysis of Inclisiran for the Treatment of Hypercholesterolemia

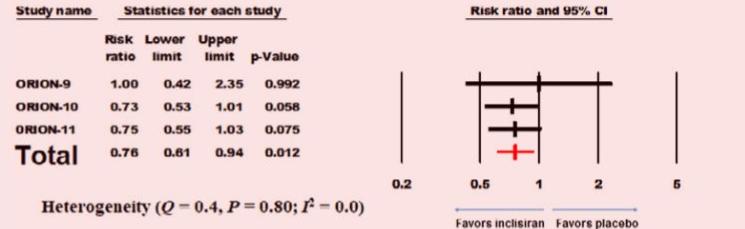
## A: LDL cholesterol Level



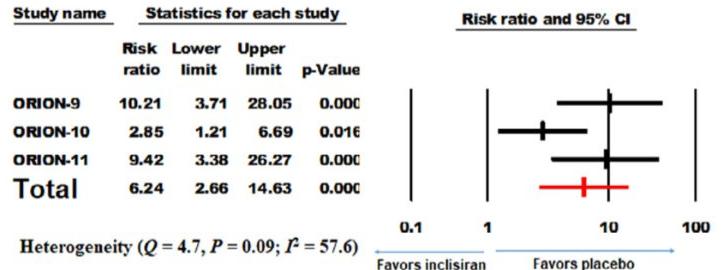
## A: Any Adverse Events



## B: MACE



## B: Injection Site Reactions



# Pooled Patient-Level Analysis of Inclisiran Trials in Patients With Familial Hypercholesterolemia or Atherosclerosis

## Treatment-Emergent Adverse Events and Key Safety Findings\*

	Inclisiran (n = 1,833)	Placebo (n = 1,822)	Risk Ratio (95% CI)
<b>TEAE</b>			
≥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)
<b>Serious TEAE</b>			
≥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)
<b>Clinically relevant TEAE at the injection site†</b>			
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)	—
<b>Liver function</b>			
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)
<b>Kidney function: creatinine &gt;2 mg/dL</b>			
	36 (2.0)	42 (2.3)	0.85 (0.55-1.32)
<b>Muscle: creatine kinase &gt;5× ULN</b>			
	24 (1.3)	22 (1.2)	1.08 (0.61-1.93)
<b>Hematology: platelet count &lt;75 × 10<sup>9</sup>/L</b>			
	1 (0.1)	2 (0.1)	0.50 (0.05-5.48)



## 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	71 (3.9)	63 (3.5)	1.12 (0.80-1.56)
Bronchitis	78 (4.3)	50 (2.7)	1.55 (1.09-2.20)
Cough	61 (3.3)	54 (3.0)	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)
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)

# Trattamento con inclisiran: dosaggio e somministrazione

## Formulazione

### Siringa preriempita

Ogni siringa contiene inclisiran sodico equivalente a

**284 mg di inclisiran in 1,5 mL di soluzione**

- Conservazione a **temperatura ambiente**

## Somministrazione

### Uso sottocutaneo.

Inclisiran è somministrato tramite iniezione **sottocutanea nell'addome**; siti di iniezione alternativi comprendono il braccio o la coscia.

Ogni dose da 284 mg viene somministrata utilizzando una singola siringa preriempita.

Ogni siringa preriempita è solo **monouso**.

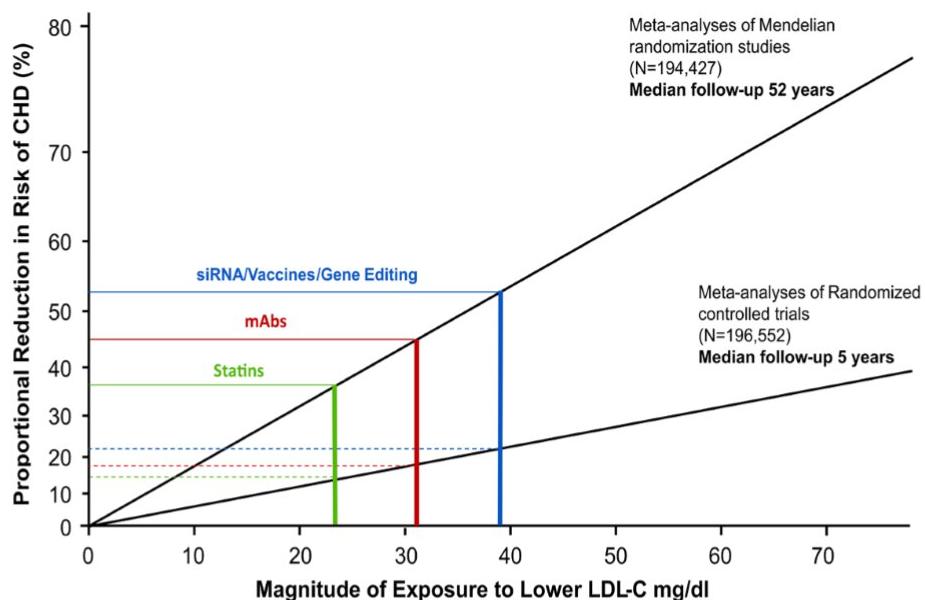
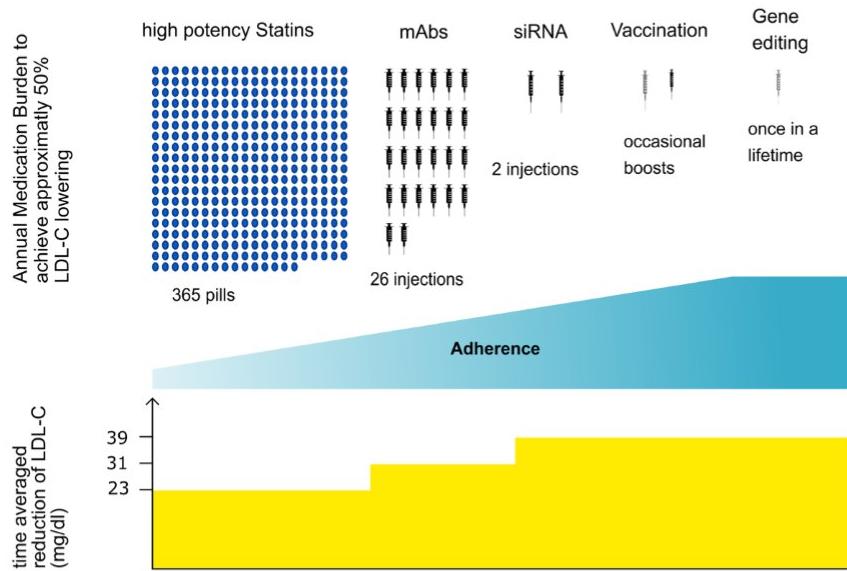
Inclisiran è destinato alla somministrazione **da parte di un operatore sanitario**.

## Regime posologico

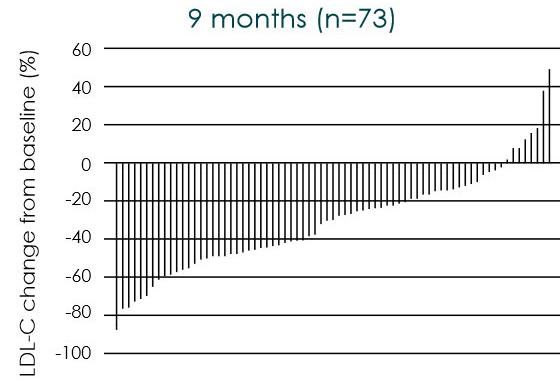
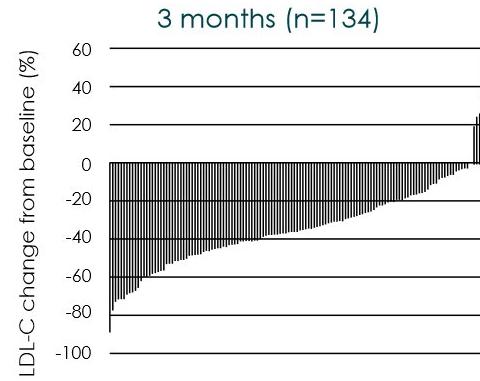
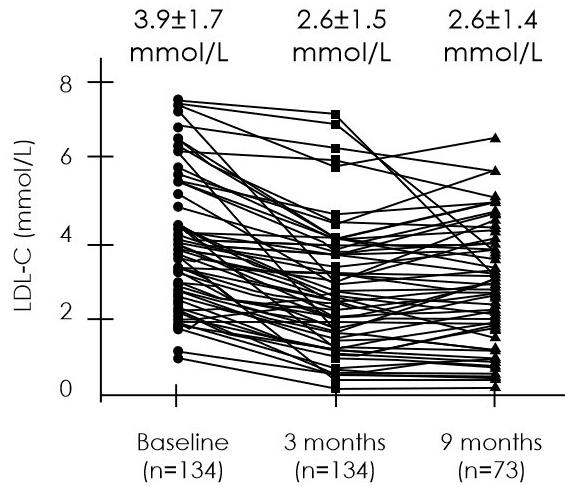


# Low Density Lipoprotein Cholesterol-Lowering Strategies and Population Health

## Time to Move to a Cumulative Exposure Model



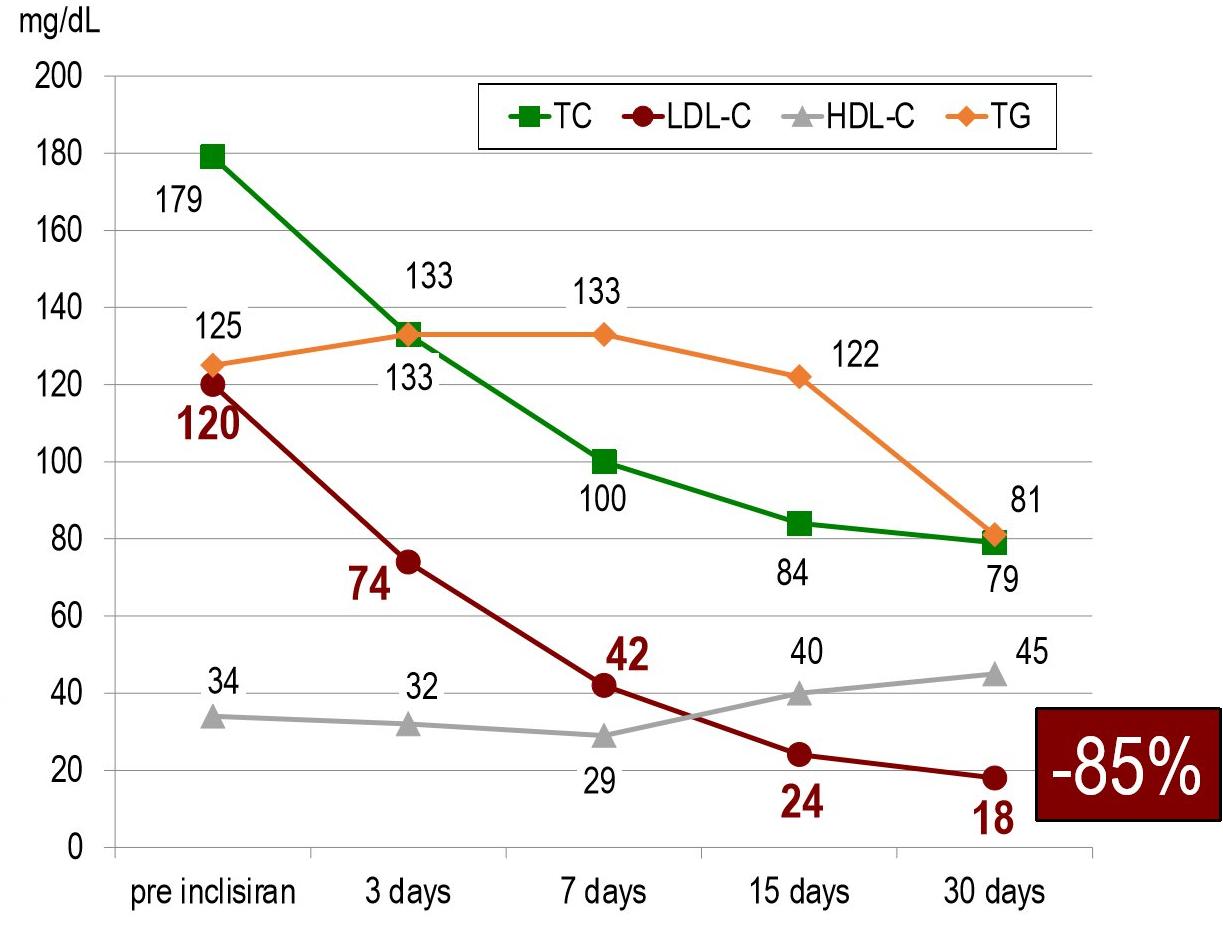
# High individual variability in LDL reduction after Inclisiran administration in a “real world setting”



- il *German Inclisiran Network* (GIN) ha arruolato 117 pazienti ipercolesterolemici in trattamento ipocolesterolemizzante con inclisiran afferenti a 10 centri prescrittori
- I valori medi basali di LDL-C erano  $3,9 \pm 1,7$  mmol/L ( **$150,5 \pm 65,6$  mg/dL**).
- Inclisiran ha ridotto mediamente i livelli di LDL-C del 33,8 ( $\pm 23,7\%$ ) a 3 mesi ( **$100,6 \pm 57,9$  mg/dL**) e del 31,0 ( $\pm 26,7\%$ ) a 9 mesi ( **$100,6 \pm 54,0$  mg/dL**) dall'inizio del trattamento



- Man, 68 years old
- Carotid artery disease
- High intensity statin intolerance
- Current lipid lowering therapy:
  - Pravastatin 30 mg/die
  - Ezetimibe 10 mg/die
  - Fenofibrate 145 mg/die

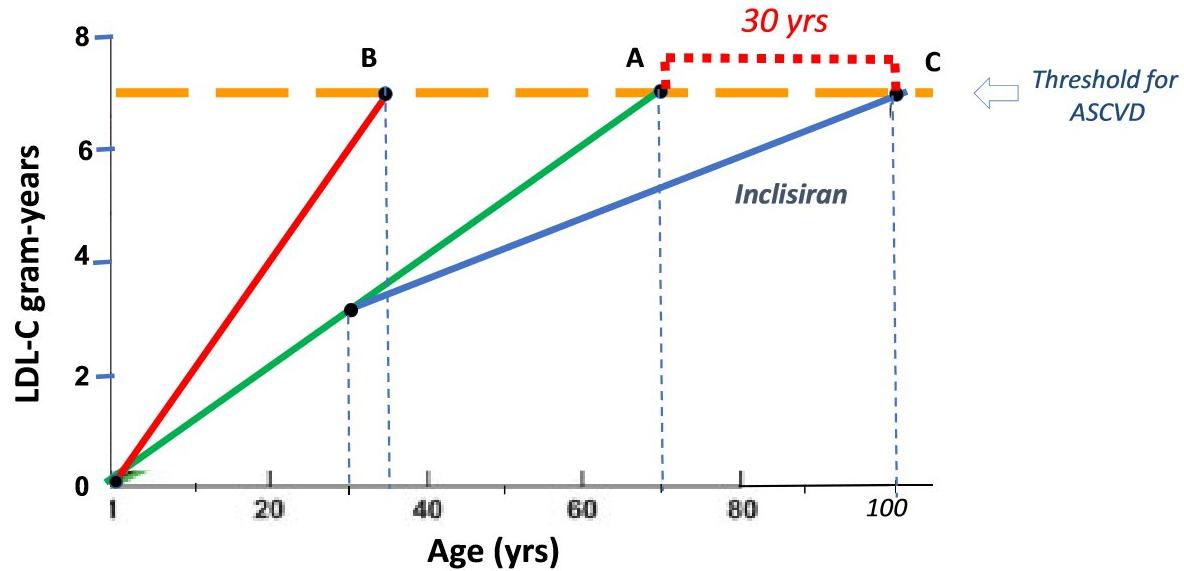


R. Tenaglia, personal communication

# How to live to 100 before developing clinical coronary artery disease: a suggestion

Eugene Braunwald  <sup>1,2\*</sup>

Cumulative LDL-C burden = [LDL-C] x age



# PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

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# 1000 grazie!!

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