



**HOT TOPICS
IN CARDIOLOGIA
2023**

13 e 14 Novembre 2023

Villa Doria D'Angri - Via F. Petrarca 80,
Napoli

**Prospettive e trattamento delle dislipidemie alla
luce dello studio ORION**

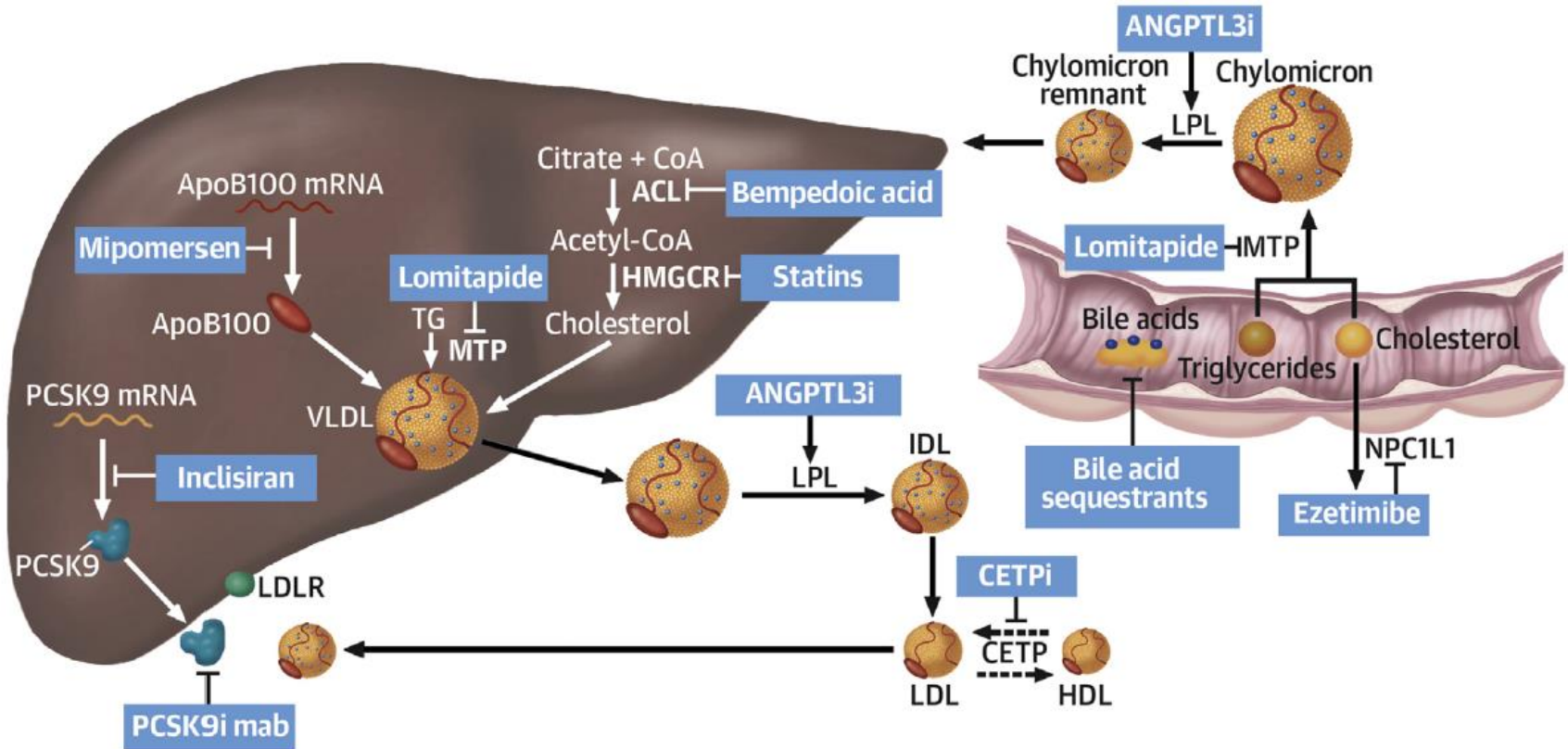
Dott. Emilio Di Lorenzo

Direttore U.O.C. Cardiologia/UTIC "D. Rotiroli"

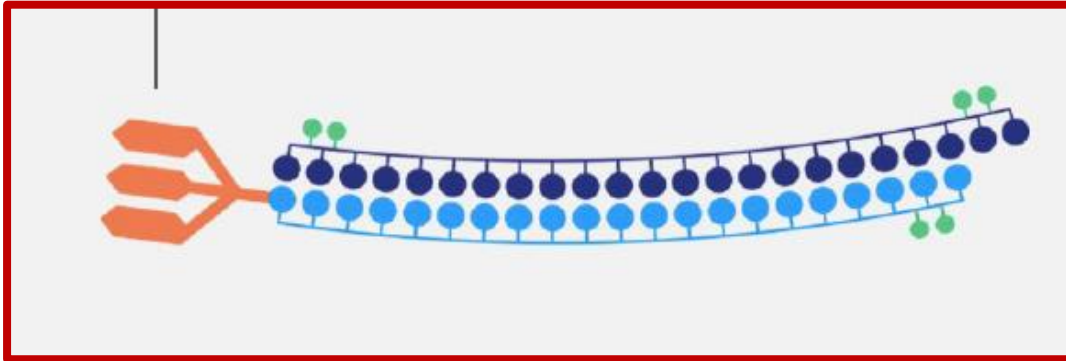
*Direttore Dipartimento Medico - Chirurgico del Cuore e dei Vasi
A.O.R.N. San Giuseppe Moscati - Avellino*

MECHANISM OF LOW-DENSITY LIPOPROTEIN CHOLESTEROL LOWERING THERAPIES

Nurmohamed, N.S. et al. *J Am Coll Cardiol.* 2021;77(12):1564–75.



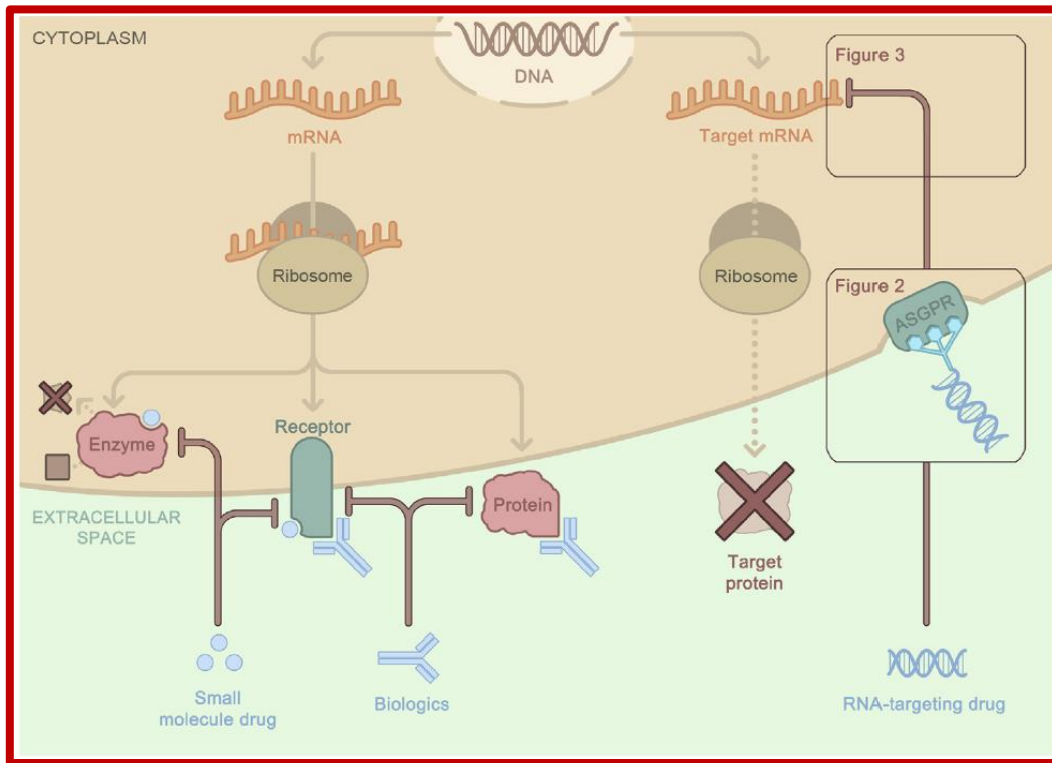
INCLISIRAN: THE FIRST siRNA APPROVED



Small interfering double-stranded RNA

1. Harnesses the natural process of RNAi
2. Nucleotides modified for durability and low immunogenicity
3. Distributed to liver due to GalNAc conjugation
4. Inhibits production of PCSK9 in hepatocytes

RNA-TARGETING DRUGS IN DYSLIPIDEMIAS



- mRNA-targeting drugs cross the cell membrane and are released into cytoplasm.
- After binding complementary target mRNA, degradation of the mRNA is initiated.
- As a consequence, the target protein is not translated.

ORION PHASE III POOLED ANALYSIS: ENTRY CRITERIA

ORION-9

HeFH¹

Stable on a low-fat diet

LDL-C \geq 100 mg/dL

ORION-10

ASCVD
(CHD, CVD, PAD)

LDL-C \geq 70 mg/dL

ORION-11

ASCVD
(CHD, CVD, PAD)

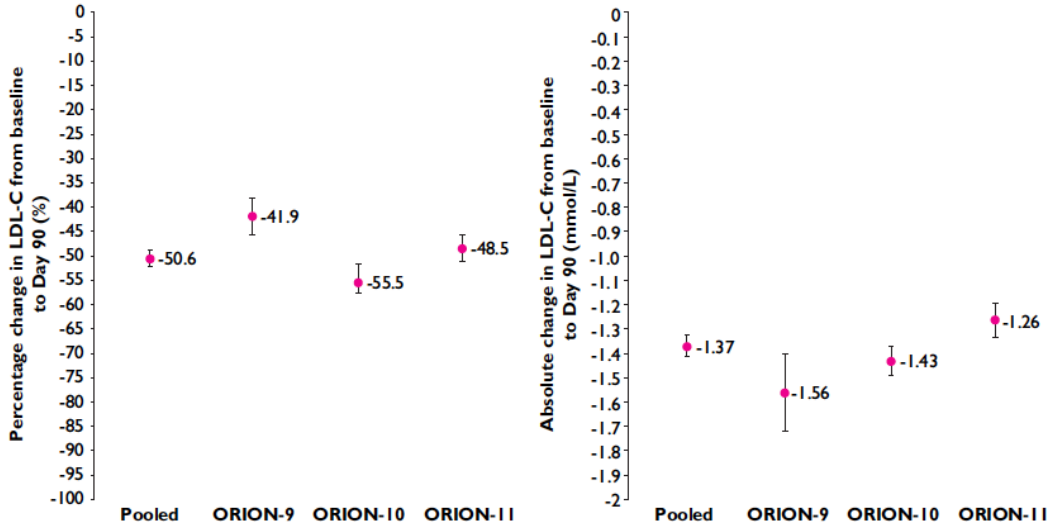
ASCVD risk equivalents

- Type 2 diabetes
- 10-year risk \geq 20%
- HeFH¹

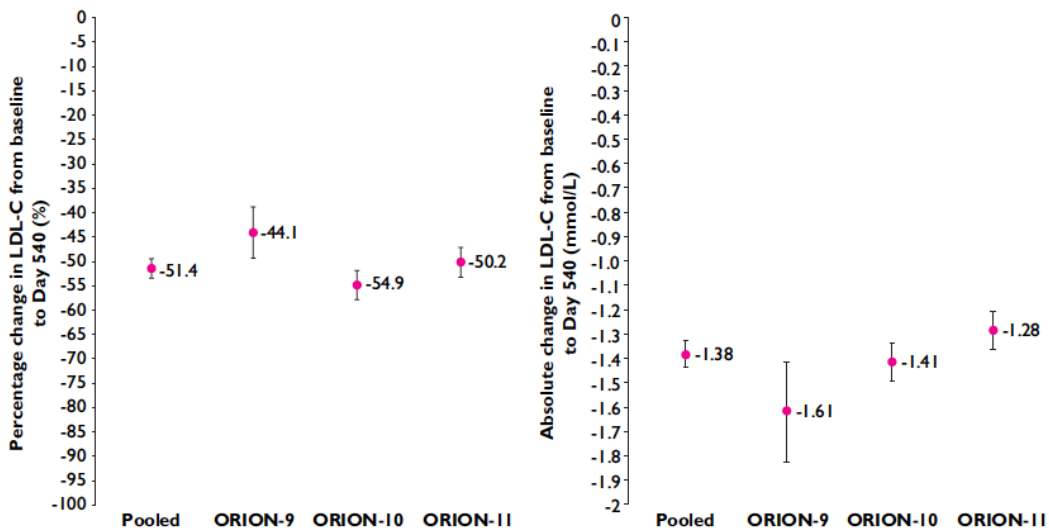
LDL-C \geq 70 mg/dL

Inclisiran and cardiovascular events: a patient-level analysis of phase III trials

A Percentage and absolute change in LDL-C from baseline to Day 90



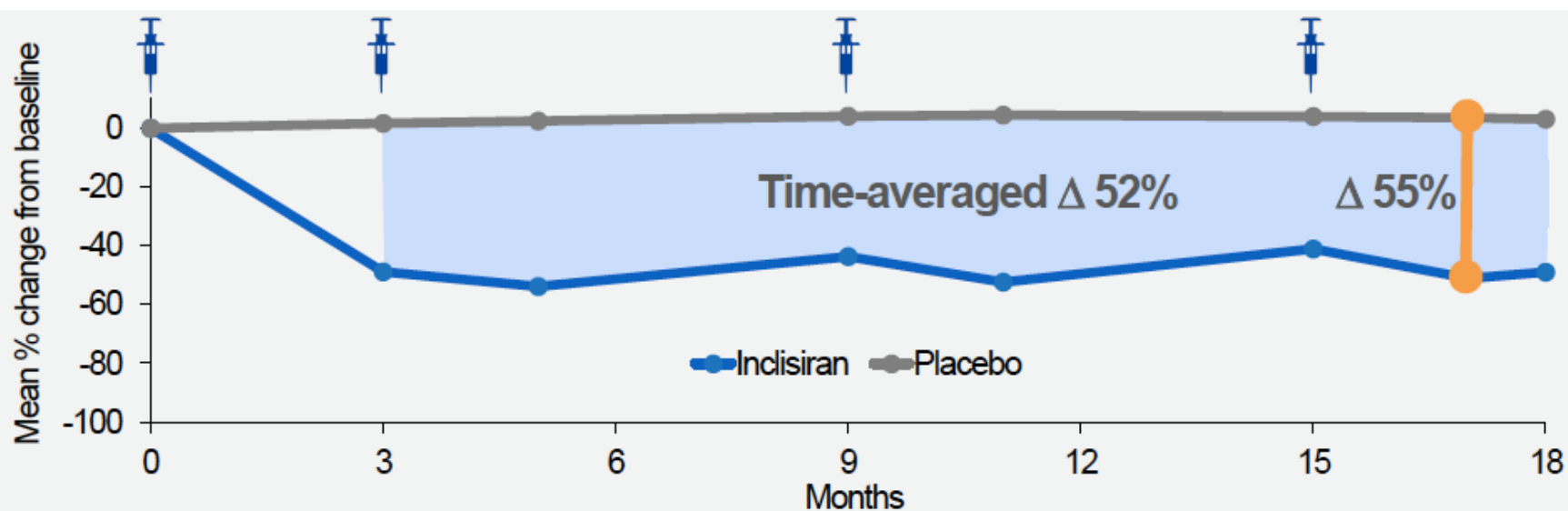
B Percentage and absolute change in LDL-C from baseline to Day 540



Patient-level, pooled analysis
of ORION-9, -10 and -11

ORION PHASE III POOLED ANALYSIS: EFFICACY

Percent change in LDL-C over time – observed values in ITT patients



P-value for placebo – incisiran comparison at each time point <0.0001

ORION PHASE III POOLED ANALYSIS: EFFICACY

EFFECTS ON OTHER LIPID PARAMETERS

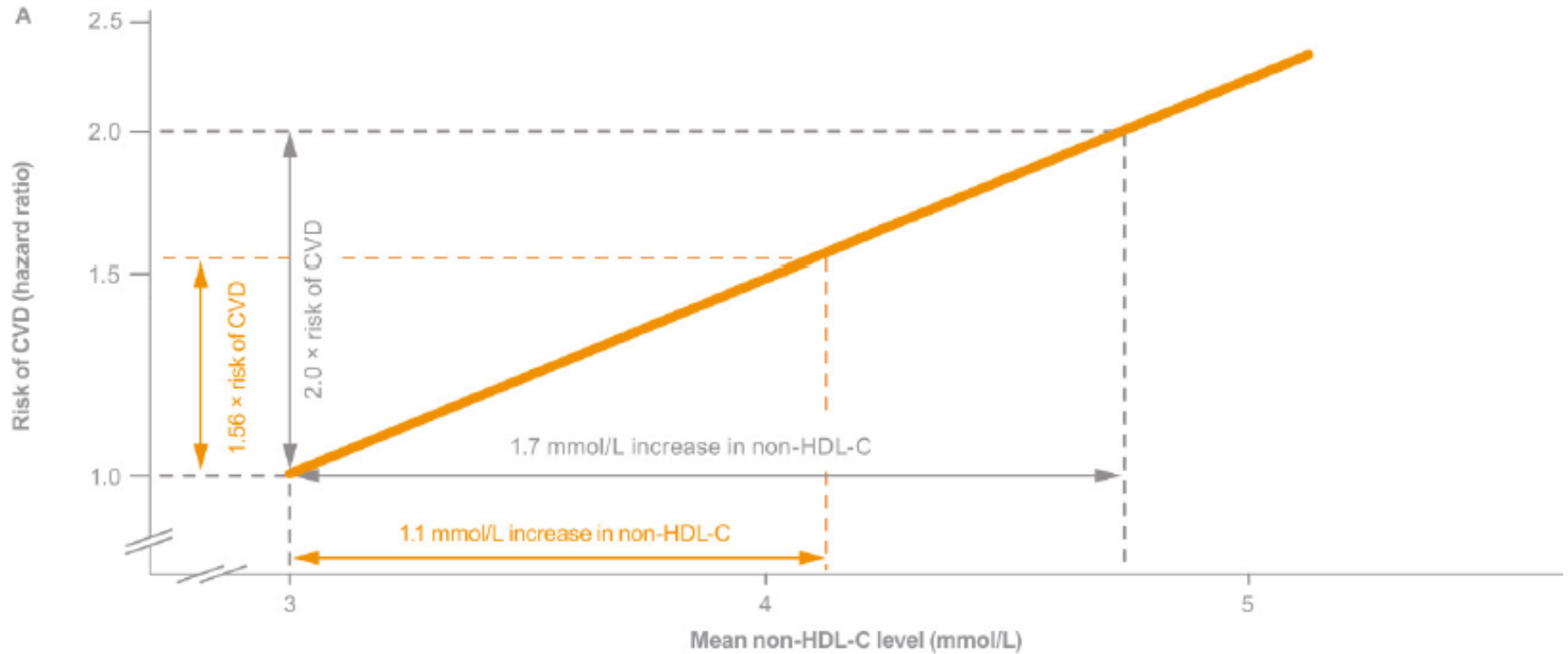
Percent Change from baseline to day 510		Placebo	Inclisiran	p-value
ITT population ¹	Imputed values ²	N = 1833	N = 1827	
PCSK9	Mean %	+ 14.8	- 68.2	<0.0001
Total cholesterol	Mean %	+ 2.9	- 29.5	<0.0001
Non HDL-C	Mean %	+ 3.6	- 42.8	<0.0001
ApoB	Mean %	+ 1.7	- 40.2	<0.0001
Lp (a) (day 540)	Median %	+ 0.0	- 20.0	<0.0001 ³

The definitive test of the hypothesis that twice-yearly administration of inclisiran reduces MACE in patients with clinical ASCVD or high CV risk awaits results of the ongoing ORION-4 and VICTORION-2 Prevent trials.

Each of these trials will enrol approximately 15 000 patients with clinical ASCVD and elevated LDL-C despite statin therapy, with an expected median follow-up of approximately 5 years

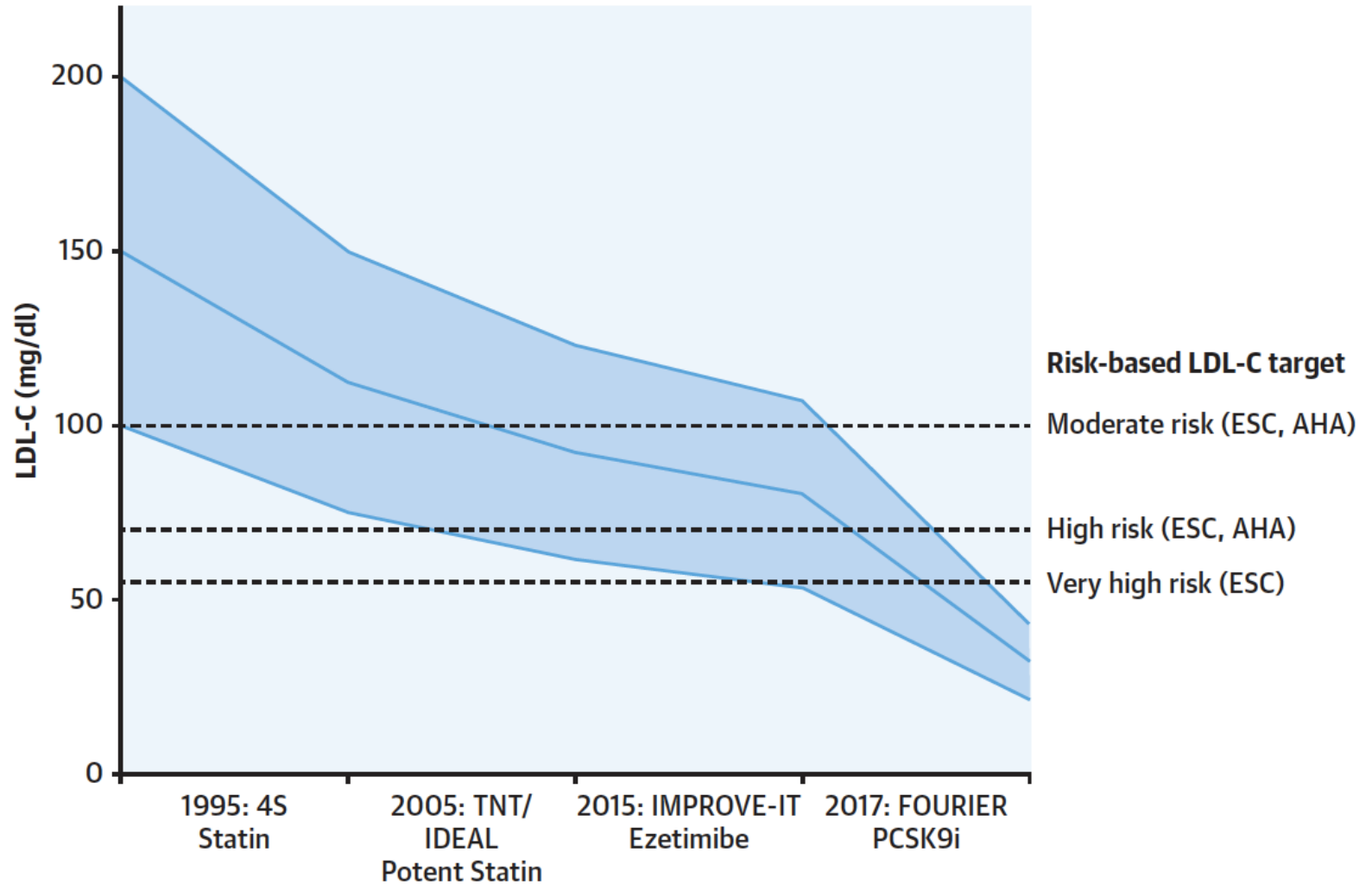
nonHDL exhibits a log-linear association (a doubling of risk per unit increase) with incidence of disease across the concentration range seen in the population

Packard C, et al. Heart 2021;107:1369–1375.



CUMULATIVE LDL-C REDUCTION OF THERAPIES OVER THE YEARS

Nurmohamed, N.S. et al. *J Am Coll Cardiol.* 2021;77(12):1564–75.



Grazie agli
**STEROLI
VEGETALI**

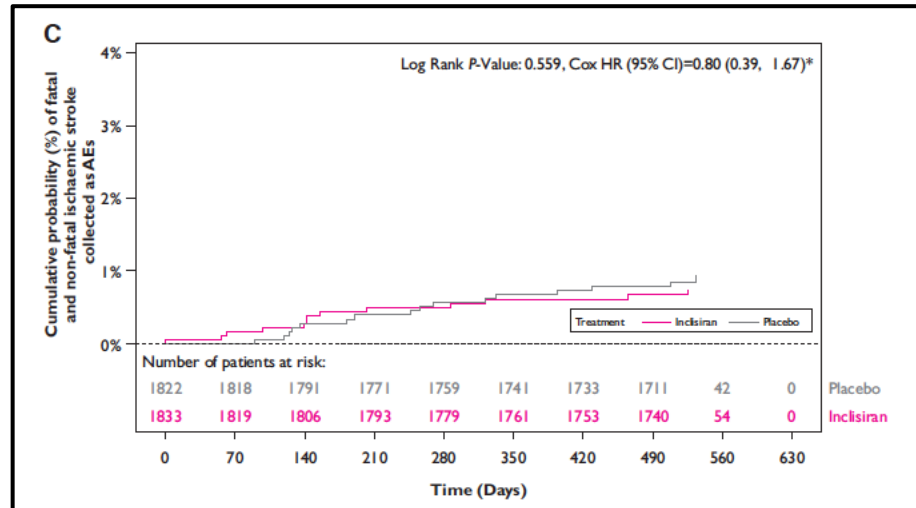
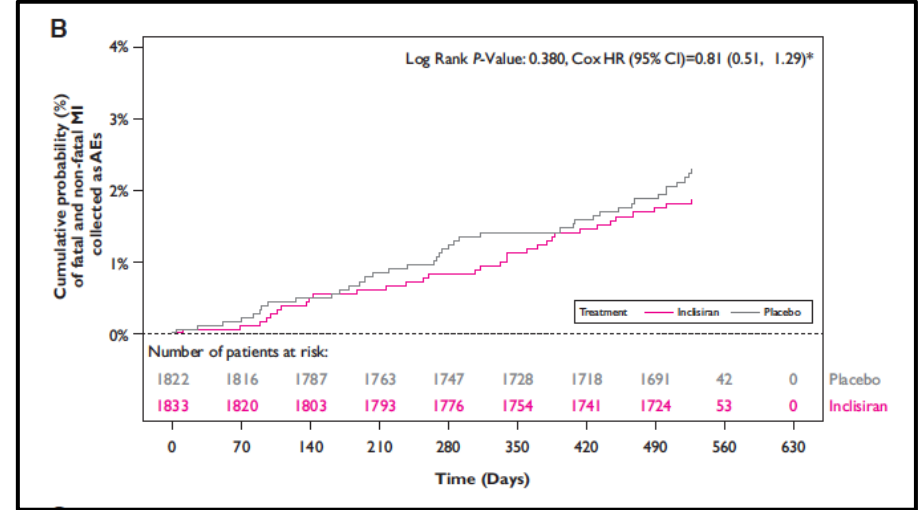
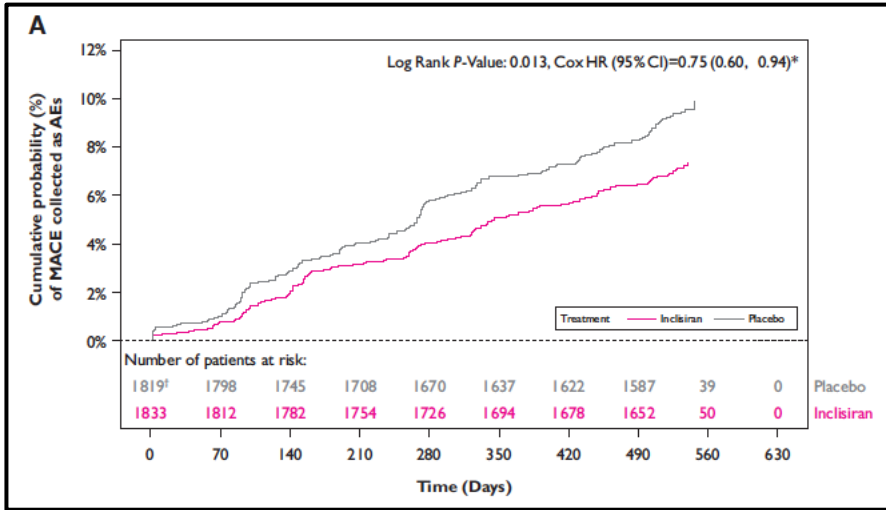
Riduce il colesterolo

1
AL GIORNO
DOPO
PASTO

FRAGOLA

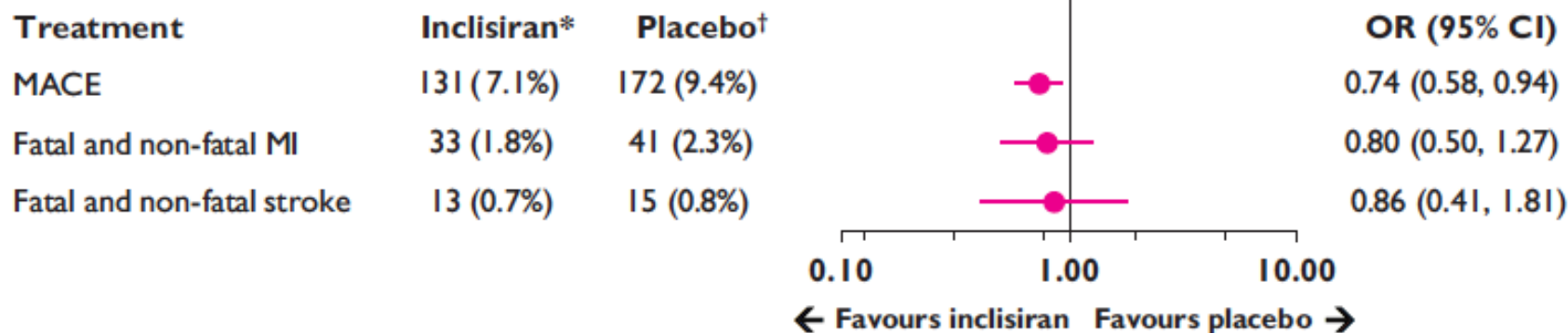


Inclisiran and cardiovascular events: a patient-level analysis of phase III trials

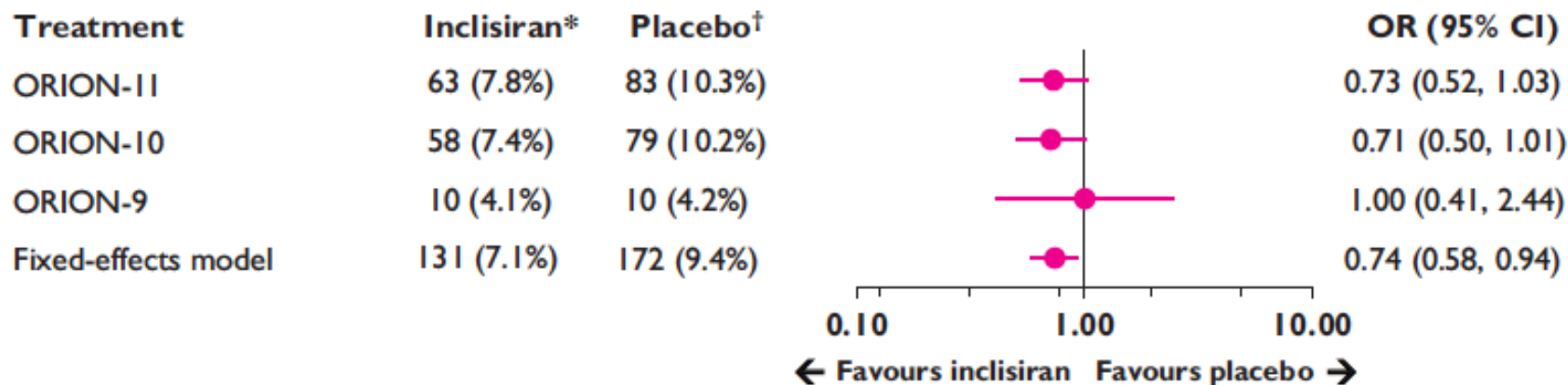


Inclisiran and cardiovascular events: a patient-level analysis of phase III trials

A Summary effects of MACE, fatal and non-fatal MI and fatal and non-fatal stroke



B MACE by individual study



Chapter I



Discovery of PCSK9

Characterization of NARC-1, a novel proprotein convertase

Chapter II



Genetic variants in the PCSK9 gene and LDL-C levels

Gain-of-function variants in the PCSK9 gene increase and loss-of-function variants decrease LDL-C levels

Chapter III



Development of monoclonal antibodies (MAbs) against PCSK9

MAbs against PCSK9 reduce LDL-C levels by 50-62%

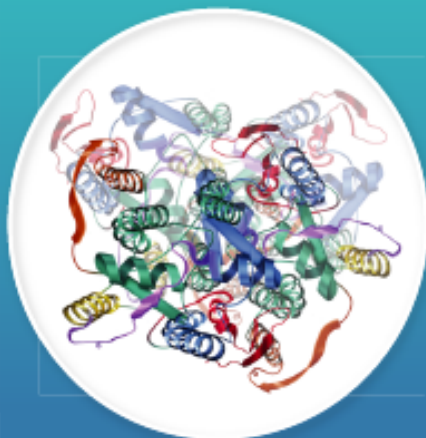
Chapter IV



Outcomes studies with MAbs against PCSK9

15% risk reduction in the primary endpoint

PCSK9 Story Book



Chapter V



siRNA against PCSK9 messenger RNA

↓ LDL-C ~ 50% at day 510

Chapter VI



Current study

Pooled data from phase 3 trials suggest 26% risk reduction of MACE with inclisiran

Chapter VII



Inclisiran reduces ASCVD?

ORION-4 and VICTORION 2P ongoing

Dal 4 ottobre 2022 è possibile utilizzare l'inclisiran in regime di rimborsabilità. Le indicazioni terapeutiche consentite ai fini della rimborsabilità da parte del Servizio Sanitario Nazionale sono le medesime degli anticorpi monoclonali anti-PCSK9, e nel dettaglio:

a) in prevenzione primaria, in soggetti adulti di età ≤ 80 anni con ipercolesterolemia familiare eterozigote e livelli di C-LDL ≥ 130 mg/dl nonostante terapia da almeno 6 mesi con statina ad alta potenza alla massima dose tollerata + ezetimibe oppure con dimostrata intolleranza alle statine e/o all'ezetimibe;

b) in prevenzione secondaria in pazienti di età ≤ 80 anni con ipercolesterolemia familiare eterozigote o ipercolesterolemia non familiare o dislipidemia mista e livelli di C-LDL ≥ 70 mg/dl nonostante la terapia da almeno 6 mesi con statina ad alta potenza alla massima dose tollerata + ezetimibe oppure dopo una sola rilevazione di C-LDL in caso di recente infarto acuto del miocardio (ultimi 12 mesi) o eventi cardiovascolari multipli oppure con dimostrata intolleranza alle statine e/o all'ezetimibe.

