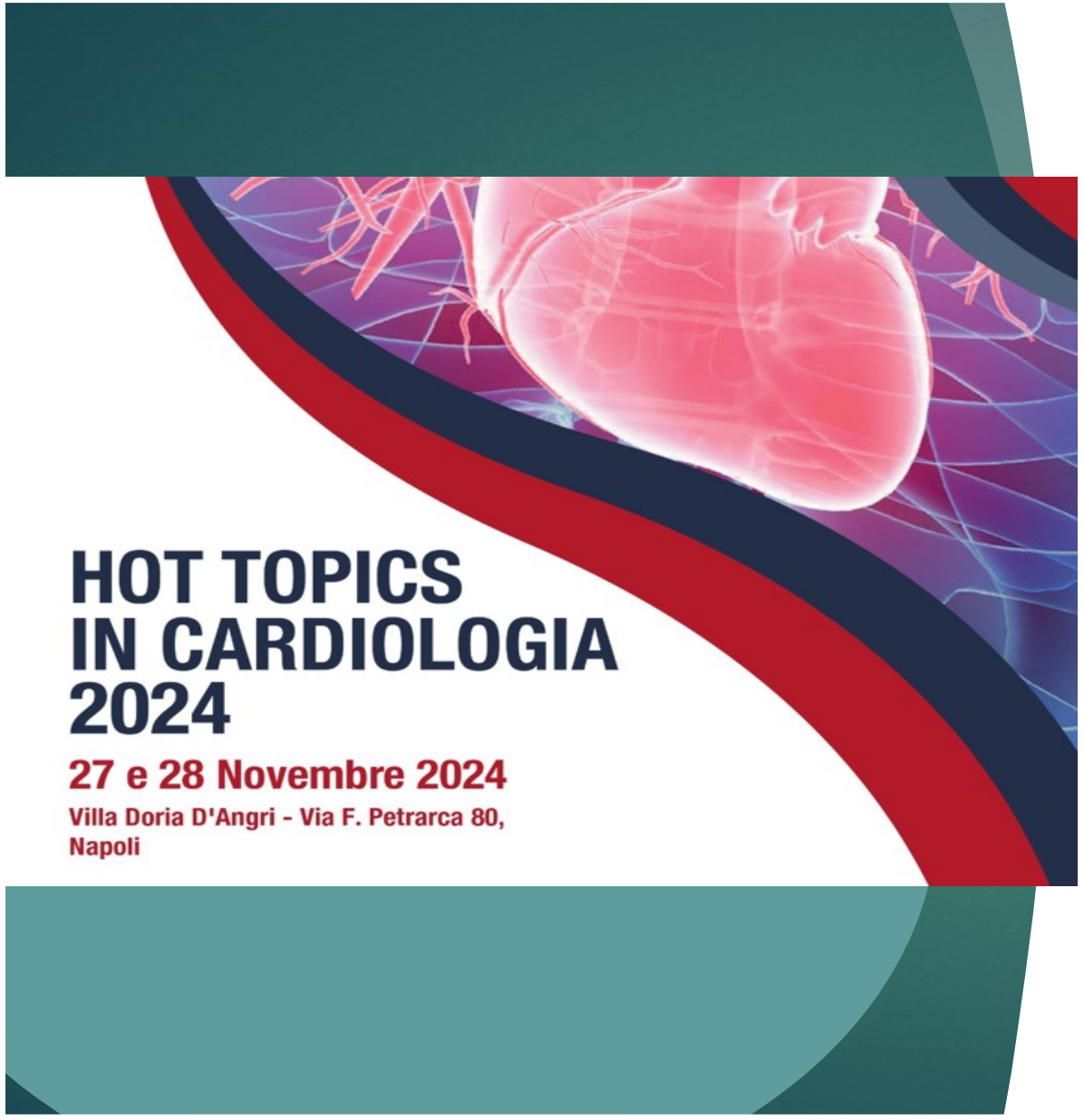


La strategia terapeutica ipolipemizzante basata sui siRNA: un nuovo strumento per abbattere il rischio cardio-vascolare nell'aterosclerosi

Claudio Bilato
Cardiologia, Ospedali dell' Ovest Vicentino,
ULSS 8 Berica

NATURE CARDIOVASCULAR RESEARCH | VOL 1 | JUNE 2022 | 554–561 | www.nature.com/natcardiovascres

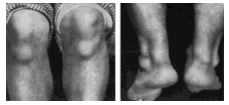
Chasing LDL cholesterol to the bottom — PCSK9 in perspective

Peter Libby[1] ✉ and Lale Tokgözoğlu[2]

Clinical milestones
Laboratory milestones

Nikolaj Nikolaevič Aničkov
1885-1964

"…non ci può essere aterosclerosi senza colesterolo…"



Carl Müller described clinical familial hypercholesteroemia

1938

1950s

Goffman uses ultracentrifuge to define lipoprotein classes

The serum lipoprotein transport system in health, metabolic disorders, atherosclerosis and coronary heart disease

1975

Brown and Goldstein discover the LDLR mutants as the molecular defect in familial hypercholesteromia (FH1)

1976

SCIENCE, VOL. 232 4 APRIL 1986

Nobel Lectures

A Receptor-Mediated Pathway for Cholesterol Homeostasis

MICHAEL S. BROWN AND JOSEPH L. GOLDSTEIN

1990

Innerarity et al. discover the molecular defect in familial defective ApoB (FH2)

Journal of Lipid Research Volume 31, 1990

Familial defective apolipoprotein B-100: a mutation of apolipoprotein B that causes hypercholesterolemia

1999

Verret and Boileau map the locus autosomal dominant hypercholesteroemia as distinct from *LDLR* or *APOB* loci

2003

Seidah and Boileau groups recognize PCSK9 as the gene mutation in autosomal dominant hypercholesterolemia (FH3)

Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

VOLUME 34 | NUMBER 2 | JUNE 2003 NATURE GENETICS

Seidah describes PCSK9

2004

Horton implicated LDLR as a target of PCSK9

2005

Hobbs and Cohen describe loss-of-function variants in PCSK9

2009

Anti-PCSK-9 antibodies developed

2015

PCSK-9 siRNA developed

2017

FOURIER trial reports (evolucumab)

The NEW ENGLAND JOURNAL of MEDICINE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

the FOURIER Steering Committee and Investigators*

2018

ODYSSEY outcomes trial reports (alirocumab)

N Engl J Med 2018;379:2097-107.

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

the ODYSSEY OUTCOMES Committees and Investigators*

2021

INCLISIRAN approval

PCSK-9 base editing in primates

JACC VOL. 77, NO. 9, 2021

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

2023

ORION 4 projected conclusion (inclisiran)

www.thelancet.com Vol 383 January 4, 2014

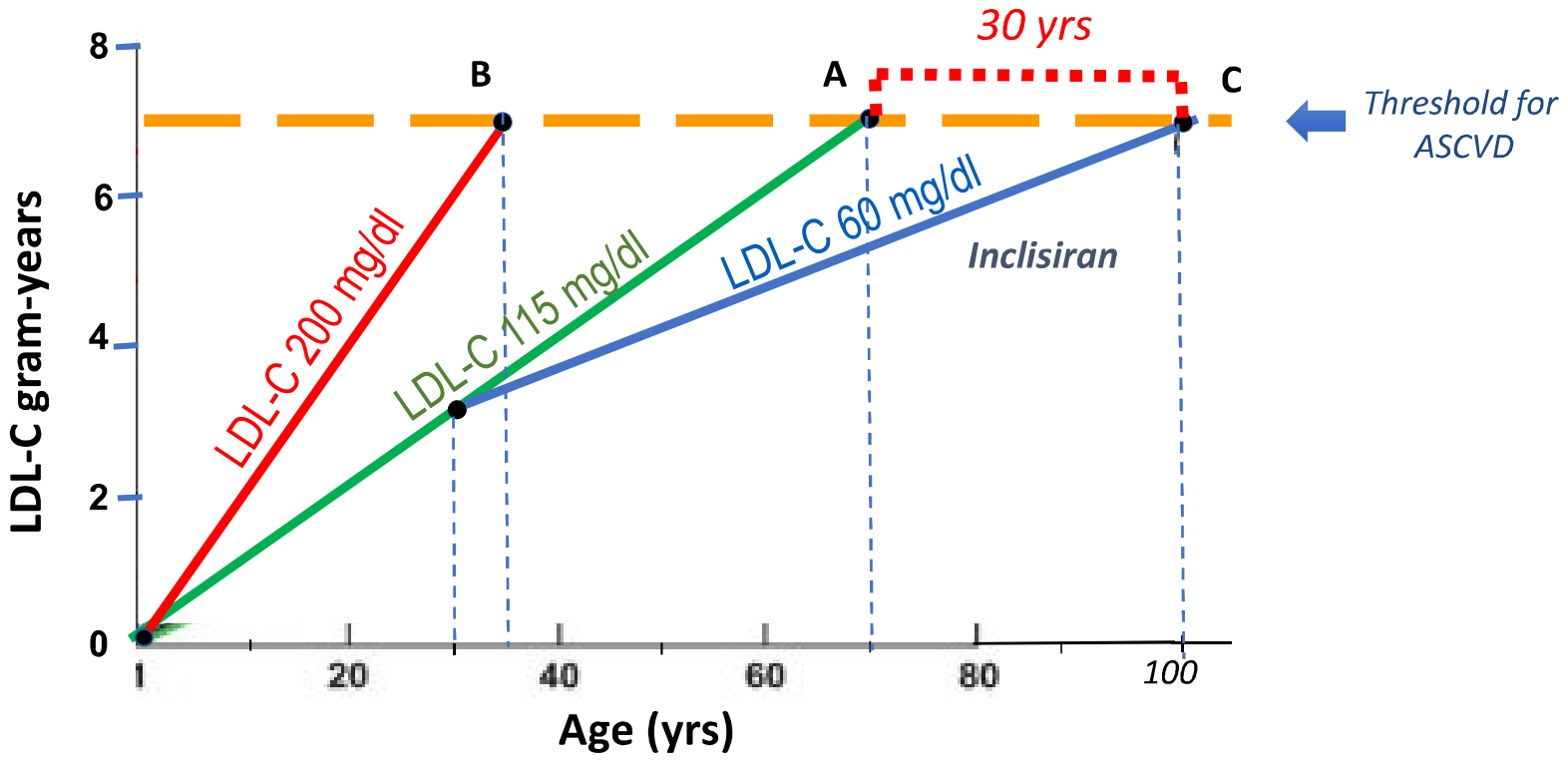
Effect of an RNA interference drug on the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the concentration of serum LDL cholesterol in healthy volunteers: a randomised, single-blind, placebo-controlled, phase 1 trial

European Heart Journal (2022) **43**, 249–250

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

Eugene Braunwald [1,2]*

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



NATURE | VOL 391 | 19 FEBRUARY 1998

Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*

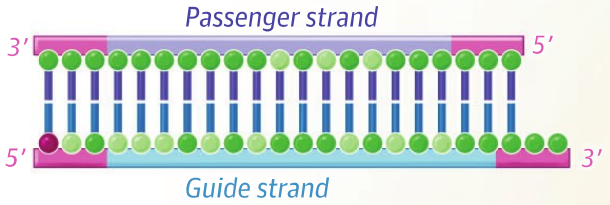
Andrew Fire*, SiQun Xu*, Mary K. Montgomery*, Steven A. Kostas*†, Samuel E. Driver‡ & Craig C. Mello‡

Experimental introduction of RNA into cells can be used in certain biological systems to interfere with the function of an endogenous gene[1,2]. Such effects have been proposed to result from a simple antisense mechanism that depends on hybridization between the injected RNA and endogenous messenger RNA transcripts. RNA interference has been used in the nematode *Caenorhabditis elegans* to manipulate gene expression[3,4].

JAMA Published online June 12, 2023

siRNAs—A New Class of Medicines

A Small interfering RNA (siRNA) backbone modifications for chemical stabilization



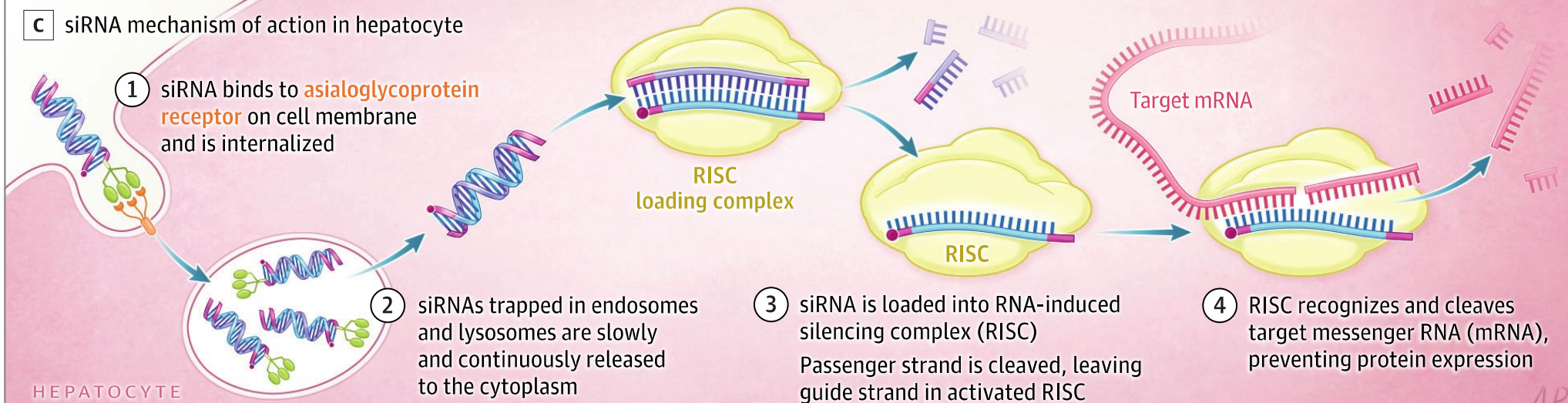
- 5′ Vinyl phosphonate end on guide strand
- Phosphorothioate linkages on strand ends
- 2′-O-methyl and 2′-fluoro substitutions for ribose molecules

B siRNA modification with conjugate to optimize targeted delivery to specific target tissues

GalNAc conjugation	Lipid conjugation		Protein conjugation	Multivalency
Hepatocytes	Central nervous system (CNS), lungs, and eyes	Muscle, fat, heart, and placenta	Muscle	CNS, lungs, and eyes
Trivalent GalNAc	16-Carbon fatty acid	22-Carbon fatty acid (PC-DCA)	Transferin antibody	Multiple siRNAs linked together

C siRNA mechanism of action in hepatocyte

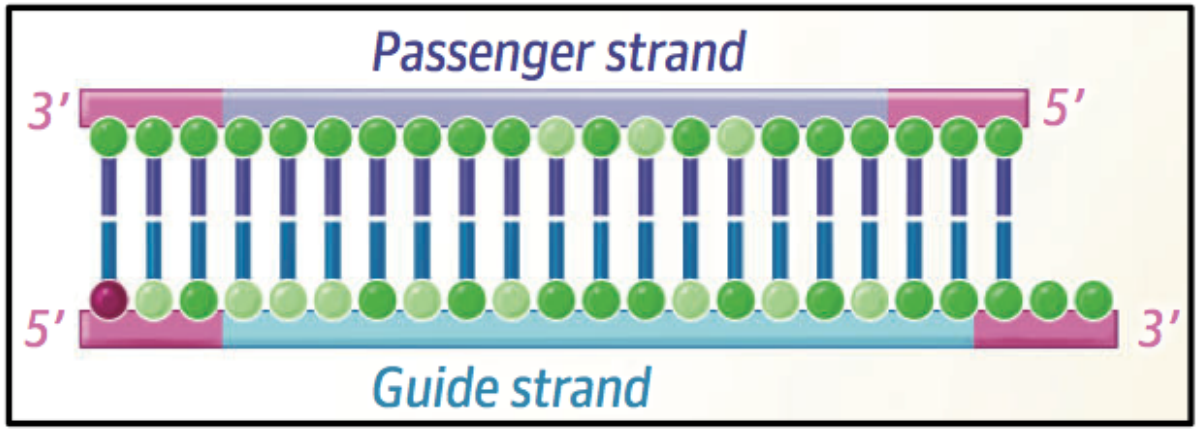
1. siRNA binds to asialoglycoprotein receptor on cell membrane and is internalized
2. siRNAs trapped in endosomes and lysosomes are slowly and continuously released to the cytoplasm
3. siRNA is loaded into RNA-induced silencing complex (RISC)
   Passenger strand is cleaved, leaving guide strand in activated RISC
4. RISC recognizes and cleaves target messenger RNA (mRNA), preventing protein expression

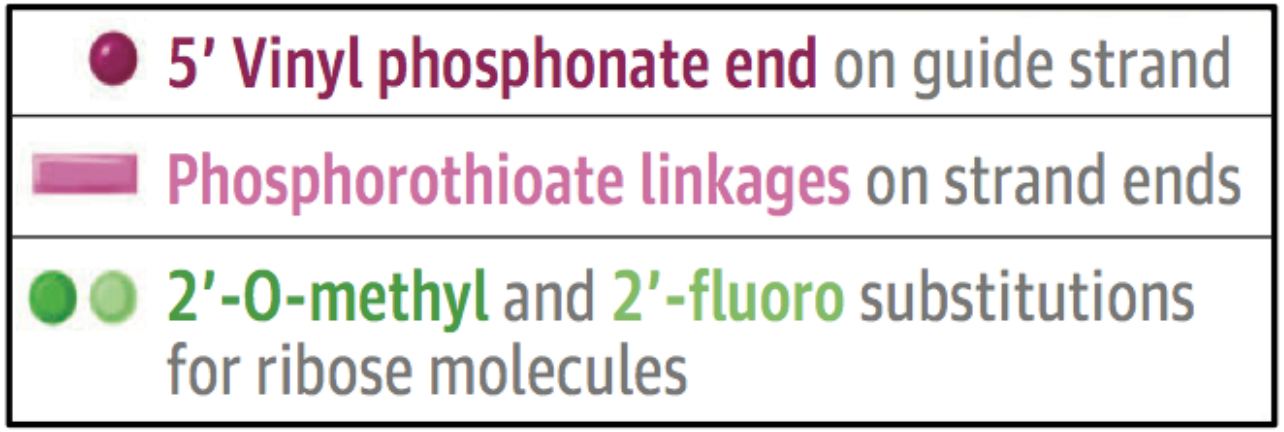


RISC = RNA-induced silencing complex

AR

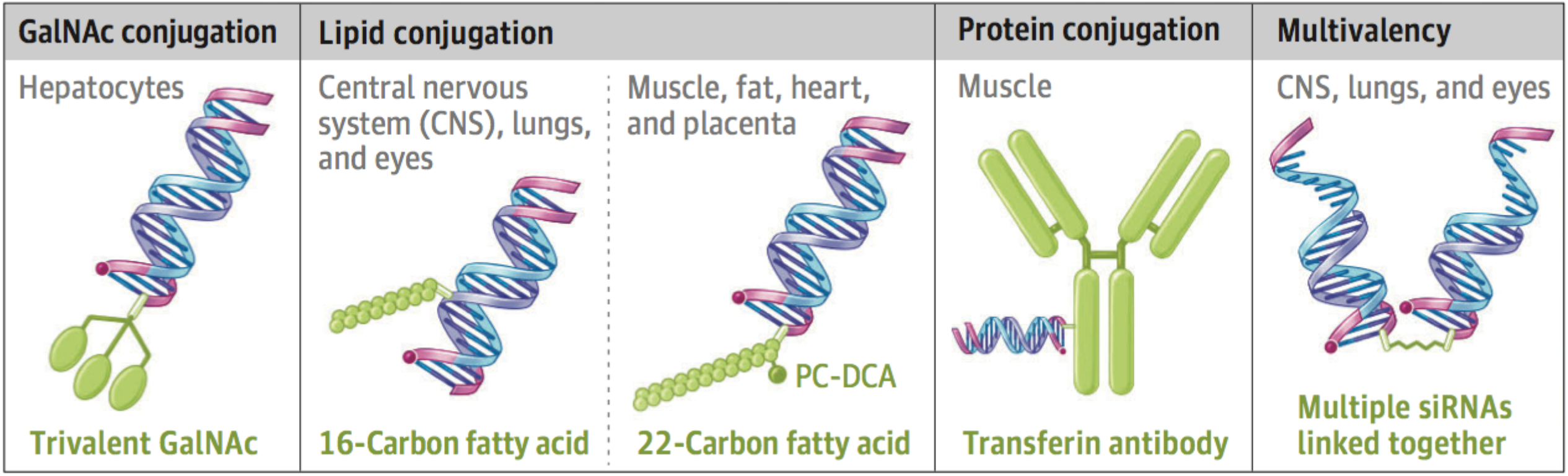
Small interfering RNA (siRNA) backbone modifications for chemical stabilization





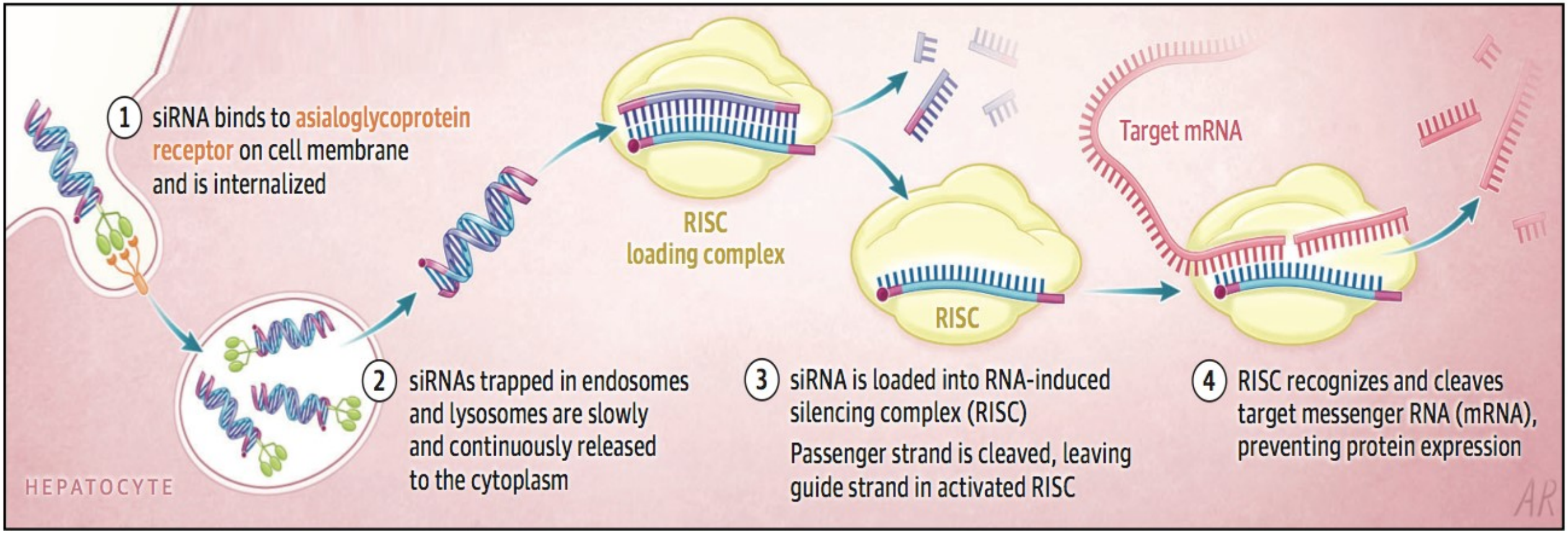
siRNA sequence defines its target, the chemical structure of an siRNA molecule drives its pharmacokinetics and pharmacodynamics. Therefore, once an siRNA architecture is optimized for delivery to a tissue of interest, any known gene sequence in that tissue can be silenced by changing the siRNA sequence only.

siRNA modification with conjugate to optimize targeted delivery to specific target tissues



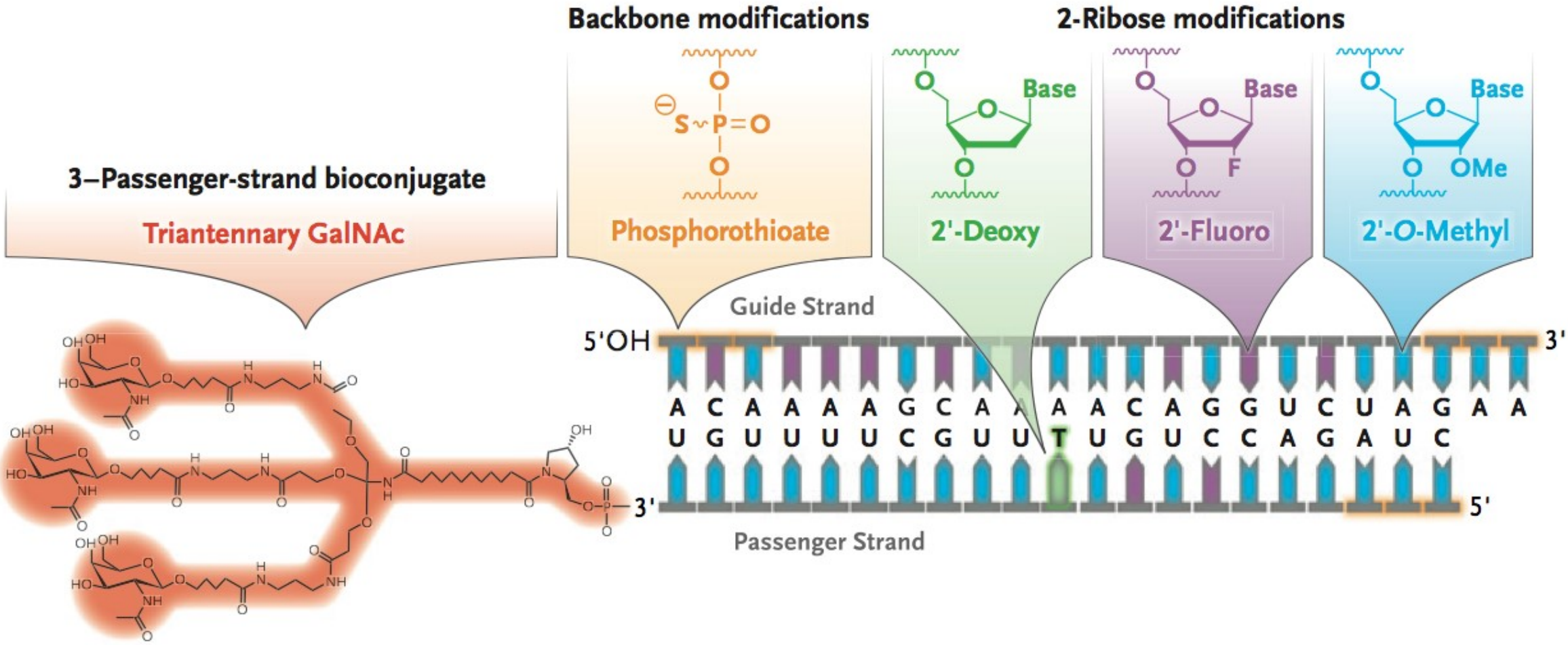
- Sugar derivative of galactose (GalNAc) is conjugated to siRNA to enable selective uptake into hepatocytes.
- Lipid conjugates (16-carbon or 22-carbon fatty acids) support broad tissue distribution, partially driven by hydrophobicity and lipid chain length.
- Protein-siRNA conjugate molecules incorporate antibodies, antibody fragments, or peptides (i.e. the siRNA–transferrin antibody conjugate robustly delivers siRNA to muscle in non human primates and is being evaluated in clinical trials for myotonic dystrophy type 1 treatment).
- Multivalency is a delivery concept that manipulates siRNA molecule size to slow clearance, increase tissue distribution, and promote cooperative cellular uptake.

siRNA mechanism of action in hepatocyte

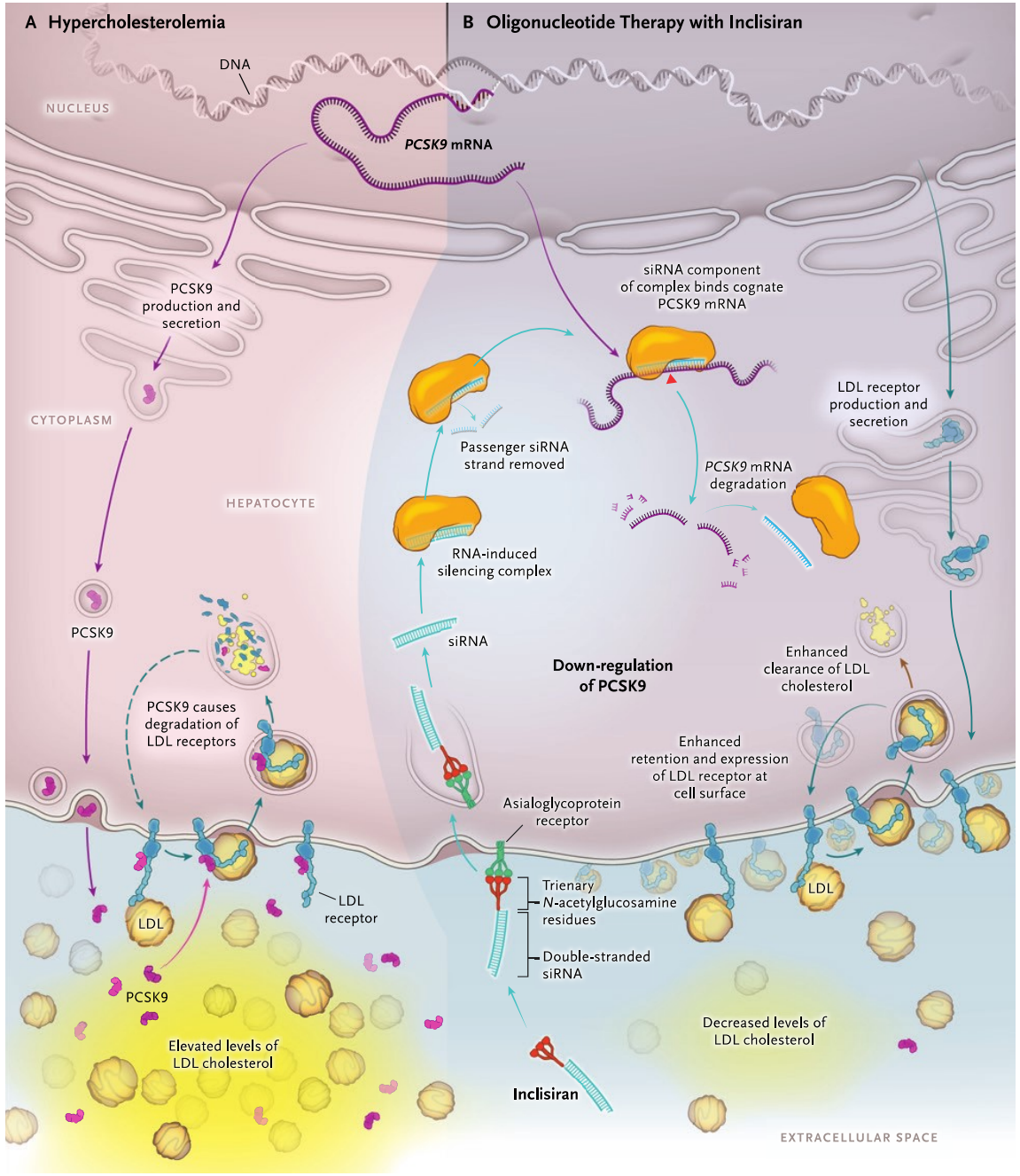


When conjugated siRNAs are administered, the first phase of distribution and clearance occurs in **a few hours**. The primary mechanism of cellular internalization independent of the conjugate is endocytosis, resulting in a large amount of siRNA cargo being trapped inside the endosomal or lysosomal compartments of cells. **This entrapment is key to the duration of effect of siRNA-based therapies**; it creates an intracellular depot of siRNA that gets slowly released over months into the cytoplasm for loading into RISC. Chemical modification of the siRNA structure is needed to prevent degradation in lysosomal environments while maintaining the ability to interact with RISC.

Inclisiran



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



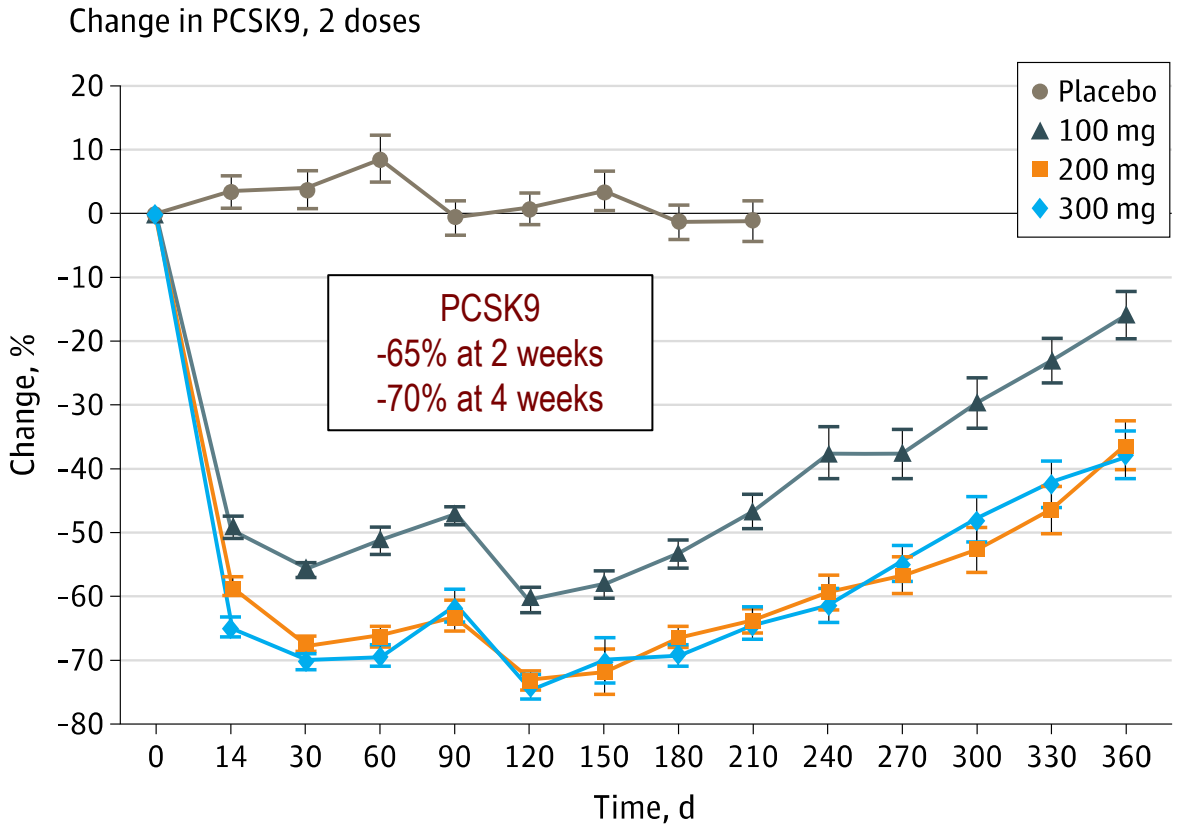
Inclisiran

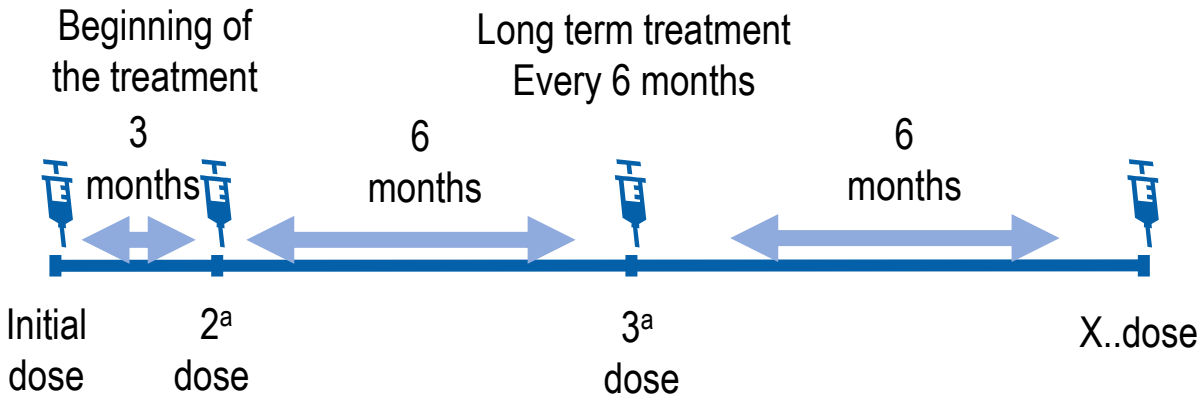
- **siRNA:** novel treatment strategy in CV disease (first in class).
- **Selectivity** and **lower dosage:** N-acetylgalactosamine (GalNAc) conjugated to oligonucleotides binds to the asialoglycoprotein receptors (ASGPR) on hepatocytes
- **Efficacy** and **safety**: by binding with pCSK9 mRNA, inclisiran/RISC cleaves the mRNA and blocks the translation mRNA-protein of PCSK9
- **Durability:** Chemical modified to increase stability against endogenous nucleases, conferring months of therapeutic activity after each dose
- **Handling:** refrigeration is not required. Pre-filled single-use syringe. Single dosage.
- **Adherence:** 2 is better than 26. Inclisiran must be administered only by health professionals.

JAMA Cardiology November 2019 Volume 4, Number 11

Effect of 1 or 2 Doses of Inclisiran on Low-Density Lipoprotein Cholesterol Levels

One-Year Follow-up of the ORION-1 Randomized Clinical Trial





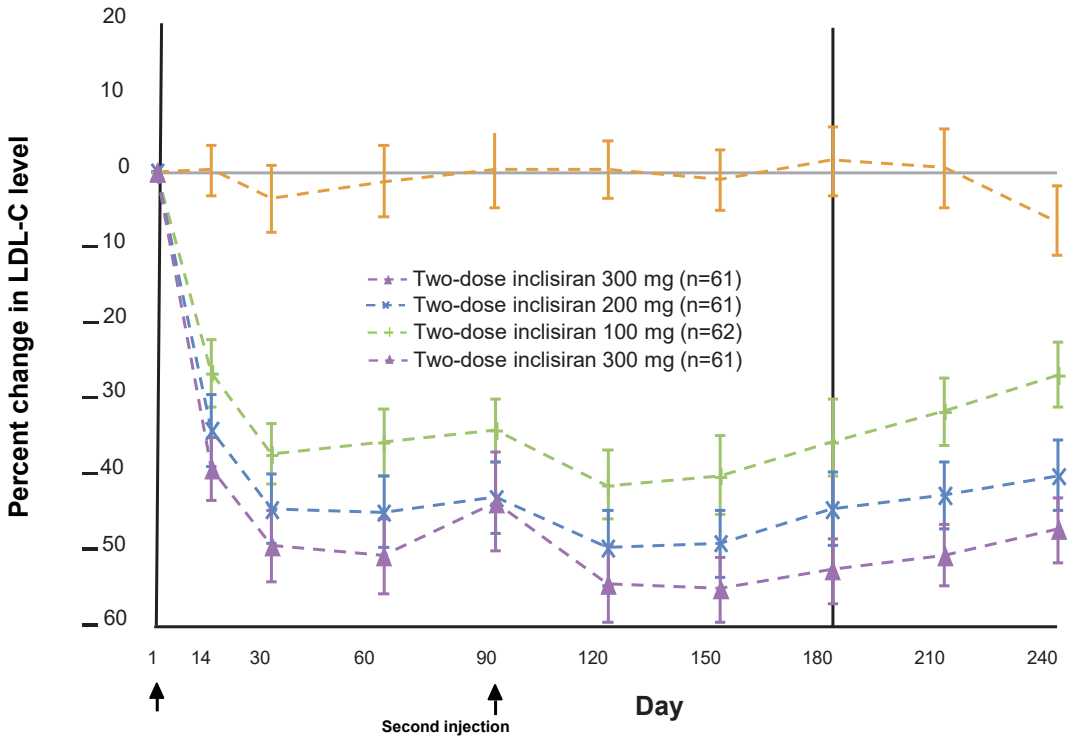
284 mg di inclisiran in 1,5 mL solution administered subcutaneously in the abdomen or upper arm or thigh

N ENGL J MED 376;15 NEJM.ORG APRIL 13, 2017

Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

ORION-1 ClinicalTrials.gov

Changes in LDL-C levels in **two-dose** regimen



JAMA Cardiology November 2019 Volume 4, Number 11

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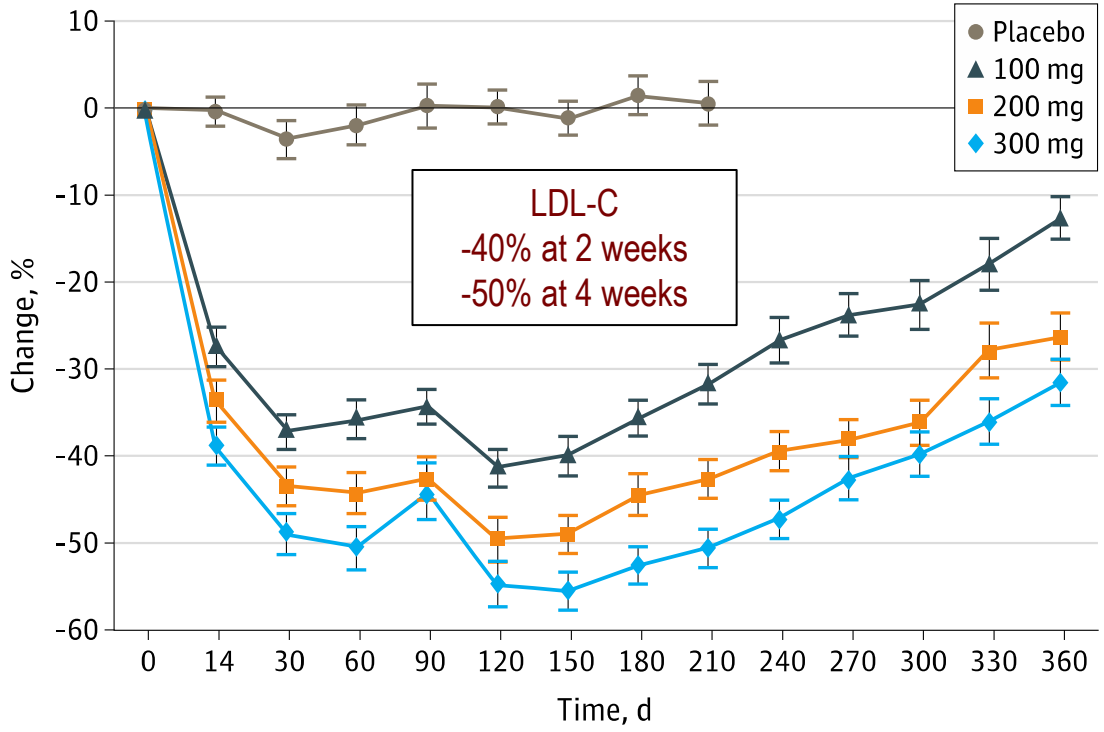
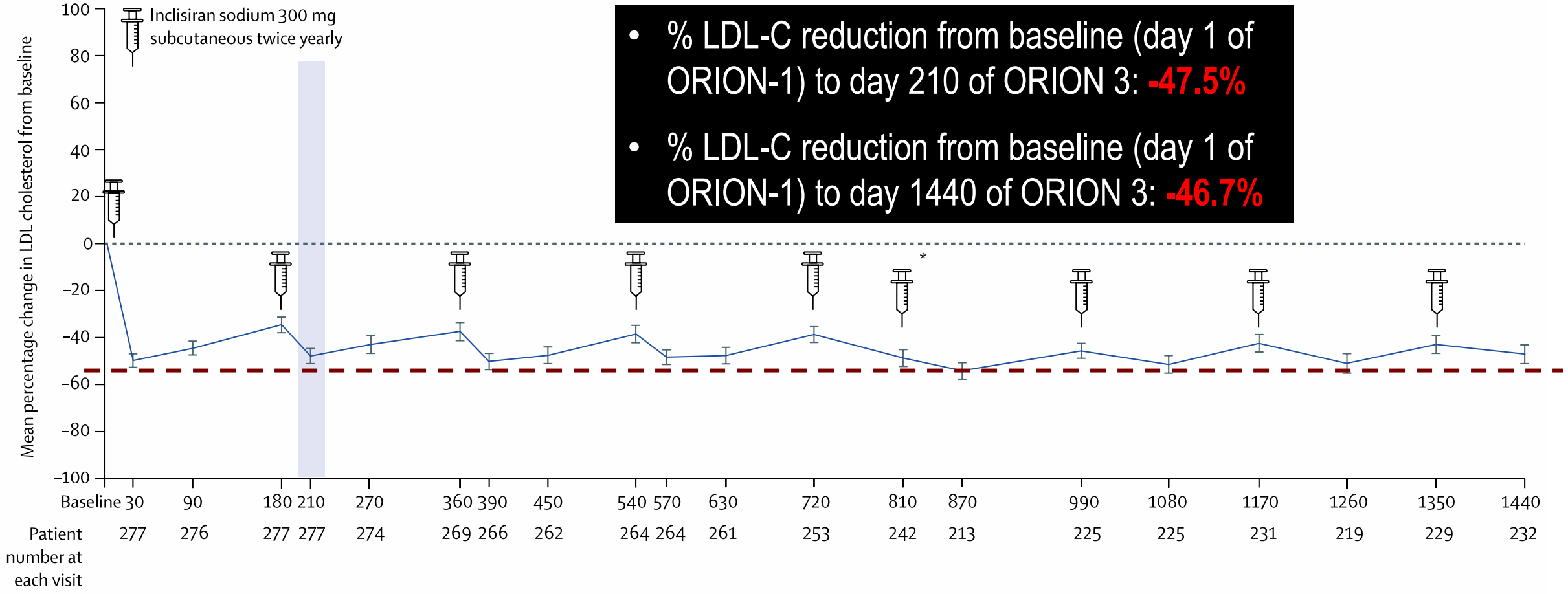
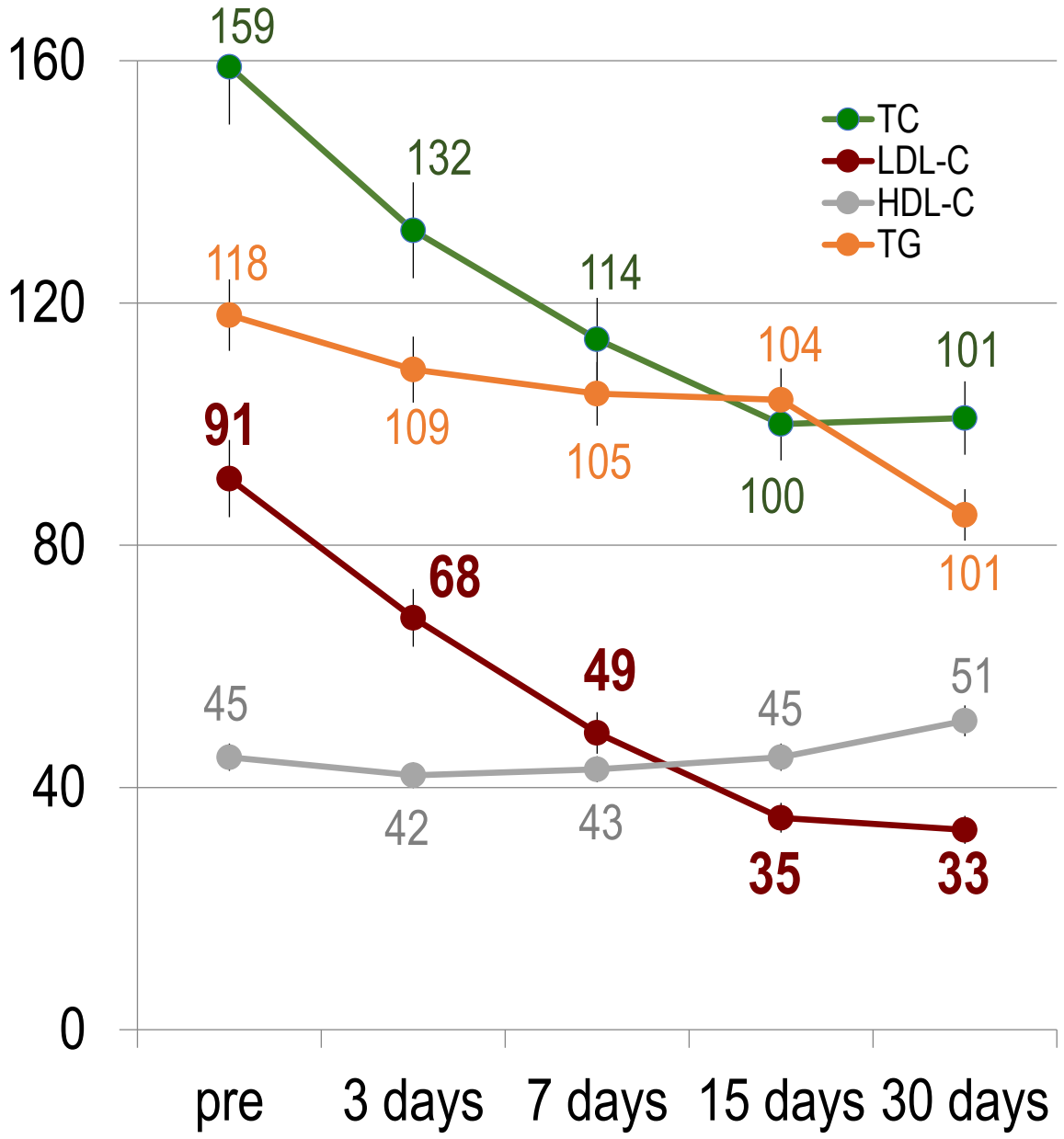


Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial



- % LDL-C reduction from baseline (day 1 of ORION-1) to day 210 of ORION 3: **-47.5%**
- % LDL-C reduction from baseline (day 1 of ORION-1) to day 1440 of ORION 3: **-46.7%**

	LDL-C (mg/dL, -Δ%)				
Patient	pre	3 days	7 days	15 days	30 days
# 1 (eze/prava 30)	120	-39%	-75%	-80%	-85%
# 2 (eze/prava 20)	70	-8%	-26%	-49%	-51%
# 3 (eze/atorva40)	90	-23%	-43%	-70%	-63%
# 4 (eze)	82	-23%	-39%	-38%	-43%
Overall	**91**	**-25%**	**-46%**	**-61%**	**-64%**



C. Dalla Valle, R. Tenaglia, personal communication

ORION 9-10-11 studies
18 months follow-up, double blind doppio-cieco, randomized versus placebo

ORION-9, ORION-10 and ORION-11: Patient population[1,2]

To assess efficacy and safety of Inclisiran 300 mg compared to placebo

ORION-9[1]

- Heterozygous familial hypercholesterolemia
- Family history of familial hypercholesterolemia
- Stable on a low-fat diet
- LDL-C ≥100 mg/dL

ORION-10[2]

- Established ASCVD*
- LDL-C ≥70 mg/dL

ORION-11[2]

- Established ASCVD*
- ASCVD risk equivalent§
- LDL-C ≥70 mg/dL in patients with ASCVD or ≥100 mg/dL in those with ASCVD risk equivalent

*Coronary heart disease, peripheral arterial disease, cerebrovascular disease,
§Type 2 diabetes mellitus, familial hypercholesterolemia, or a 10-year CV risk ≥20% (assessed by the Framingham Risk Score)
ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol

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.

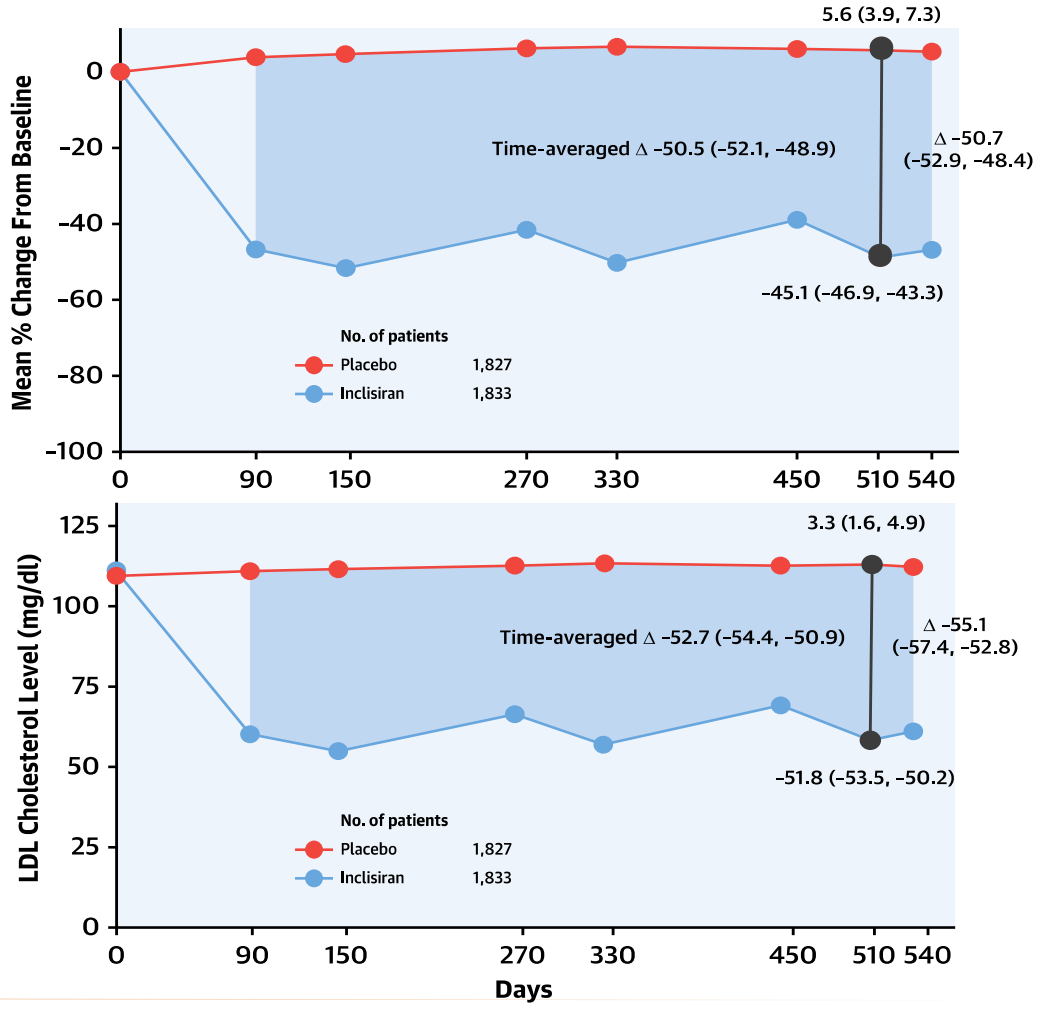
Common key exclusion criteria:

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, 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.

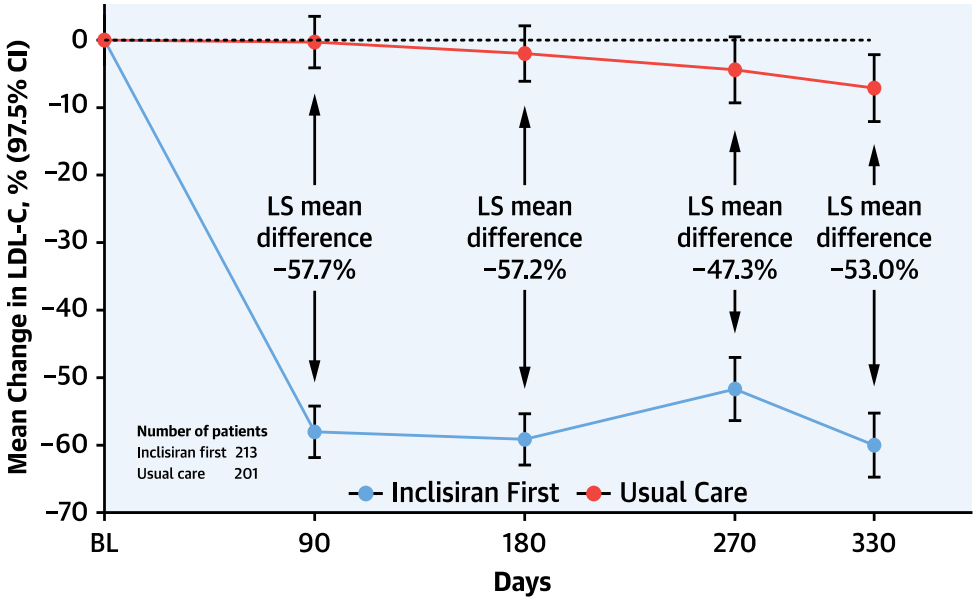
Pooled Patient-Level Analysis of Inclisiran Trials in Patients With Familial Hypercholesterolemia or Atherosclerosis

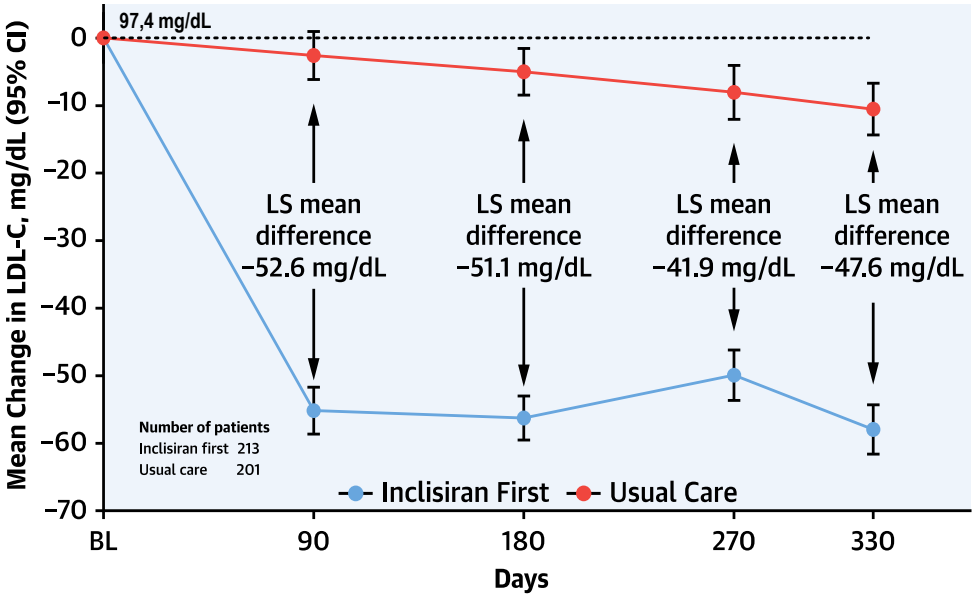
	Inclisiran (n = 1,833)	Placebo (n = 1,827)
Age, yrs	64.1 ± 9.98	63.9 ± 9.87
Male	1,226 (66.9)	1,244 (68.1)
White race*	1,670 (91.1)	1,708 (93.5)
Concomitant lipid modifying therapy		
Statins	1,686 (92.0)	1,675 (91.7)
High-intensity statin	1,356 (74.0)	1,345 (73.6)
Ezetimibe	251 (13.7)	270 (14.8)
Cardiovascular 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
Lipid measures		
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

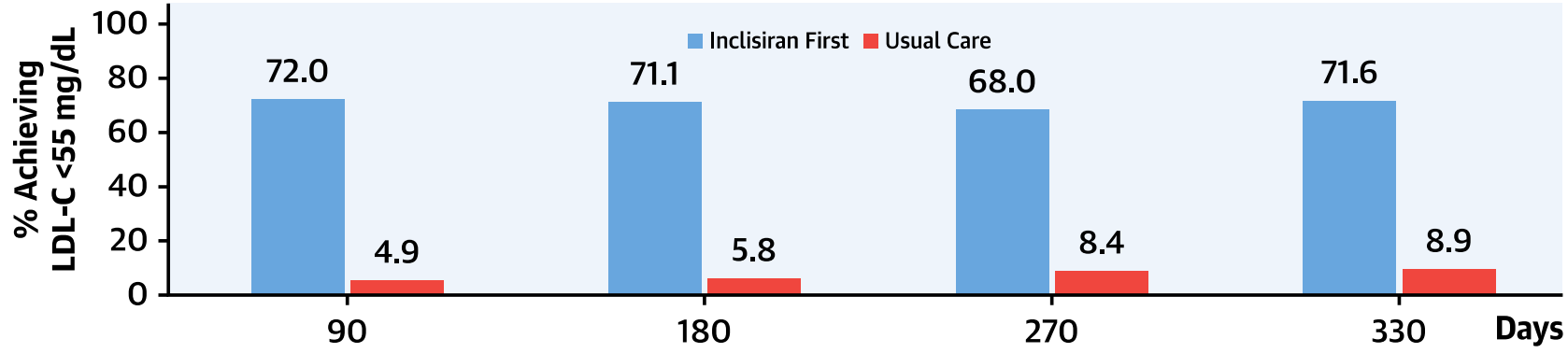


Journal of the American College of Cardiology Accepted Date: 14 March 2024

An Inclisiran First Strategy vs Usual Care in Patients with Atherosclerosis



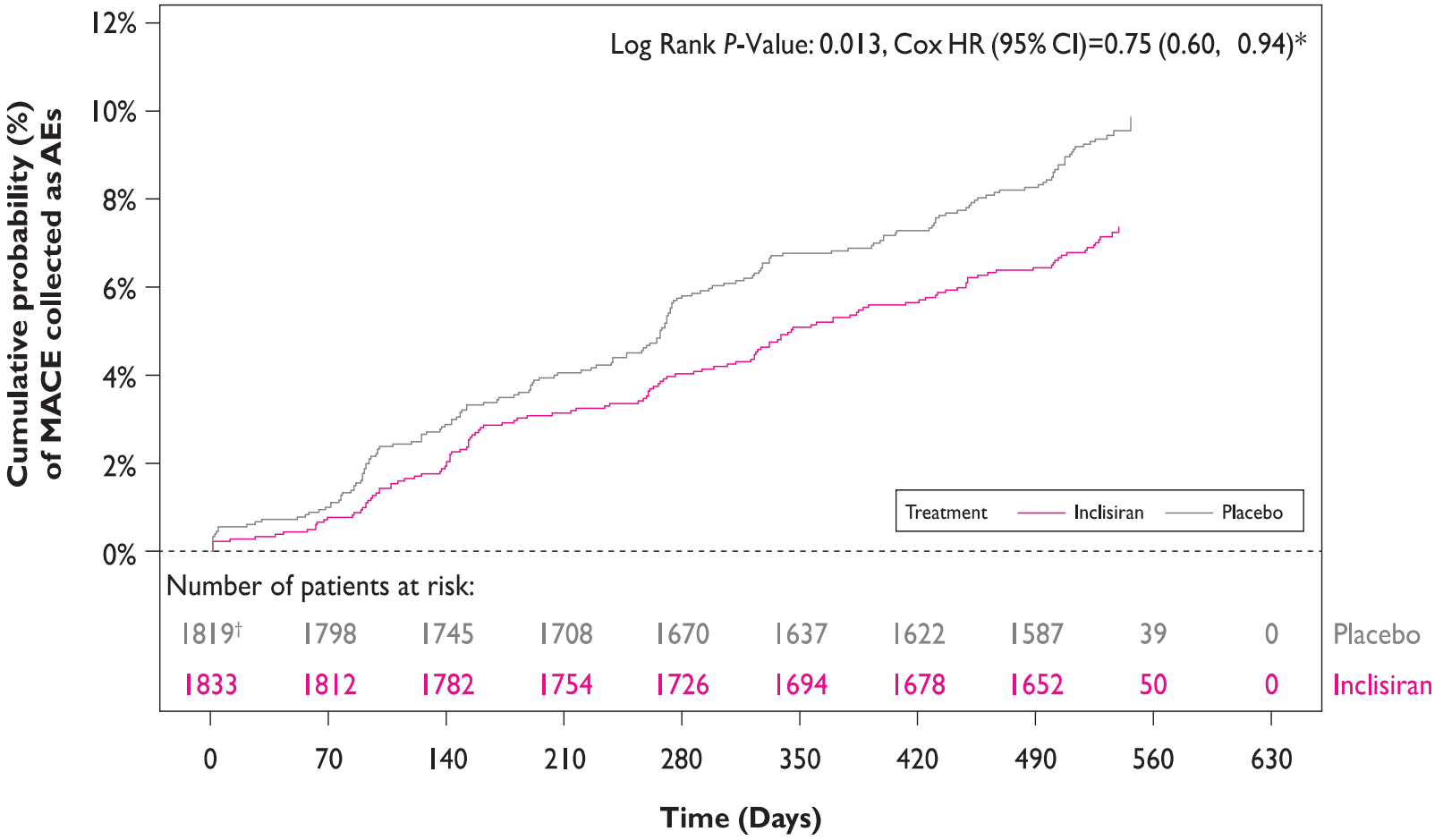




VICTORION-INITIATE is a prospective, randomized, US-based, multicenter, parallel-group, open-label, Phase 3b trial evaluating the effectiveness of an "inclisiran first" implementation strategy compared with usual care in 450 adults (≥18 years) patients with a history of coronary heart disease, cerebrovascular disease, or peripheral artery disease, and with LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL) and fasting TG <500 mg/dL, receiving (90% of pts) maximally tolerated statin therapy.

European Heart Journal (2023) **44**, 129–138

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



- Patient-level, pooled analysis of ORION-9, 10 and 11.
- Prespecified exploratory endpoint of MACEs included **CV death, cardiac arrest, non-fatal MI, and fatal and non-fatal stroke**.
- Although not prespecified, total fatal and non-fatal MI, and stroke were also evaluated.

VictORION

A dynamic clinical trial program co-created with healthcare partners worldwide to generate evidence on the impact of cholesterol lowering with inclisiran

60,000
patients being enrolled

across
>50
countries

in
>30
trials

Key trials

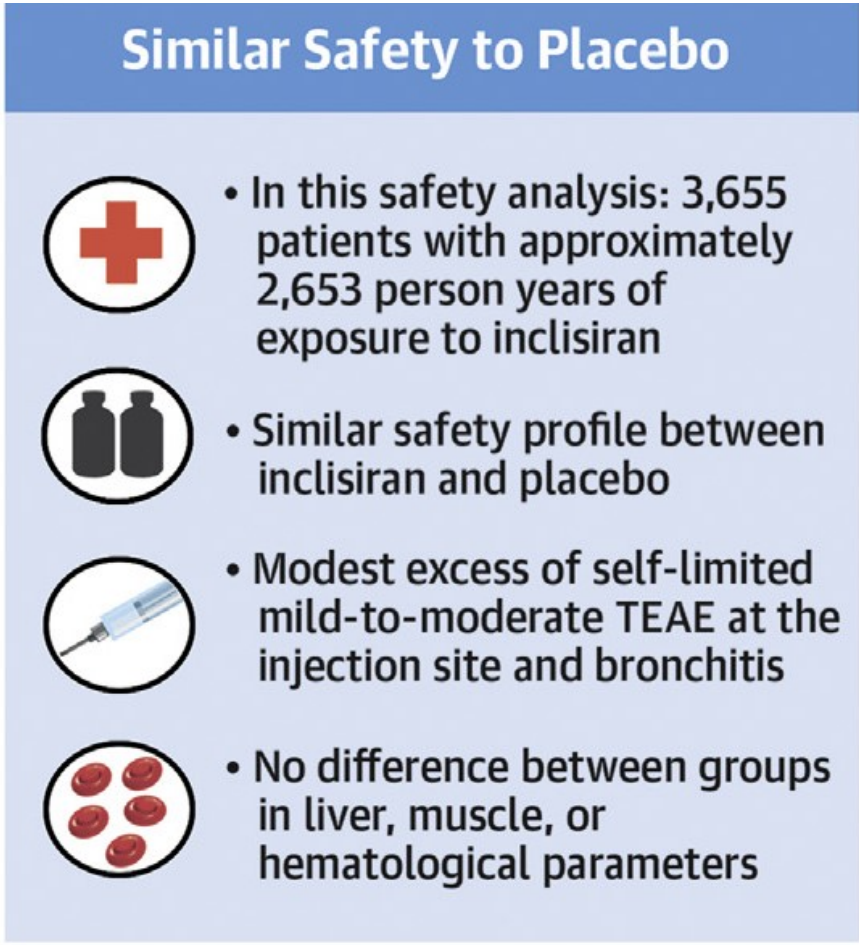
- ORION-4
- VictORION-1-PREVENT
- VictORION-2-PREVENT

Charles Everett Koop (October 14, 1916 – February 25, 2013)
13th Surgeon General of the United States under President Ronald Reagan from 1982 to 1989.

Drugs don't work in patients who won't take them

Treatment ADHERENCE is as important as therapy EFFICACY

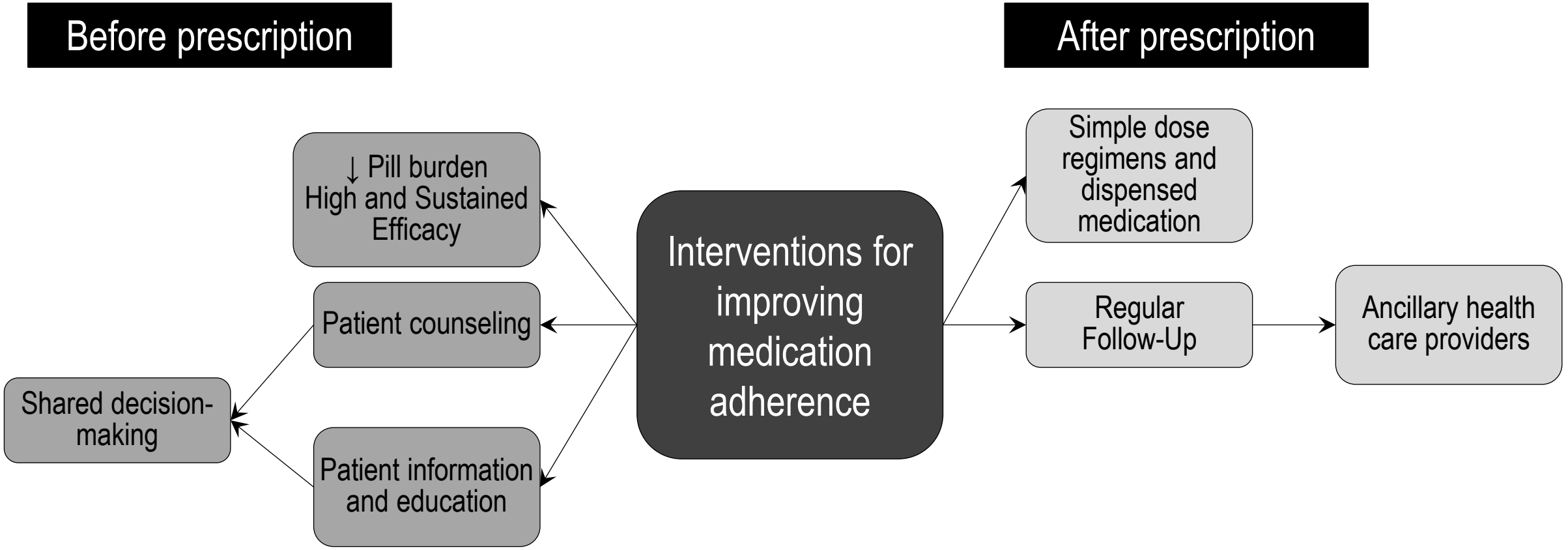
Pooled Patient-Level Analysis of Inclisiran Trials in Patients With Familial Hypercholesterolemia or Atherosclerosis



Patient-level pooled analysis of inclisiran efficacy and safety in the ORION phase 3 program

In a pooled analysis of patients from ORION-9, -10, and -11, inclisiran achieved a mean LDL-C reduction of 50.7% and a mean PCSK9 reduction of 80.9% after 17 months of treatment, with a **safety profile similar to placebo, except for an excess of self- limiting, mild-to-moderate treatment-emergent adverse events at the injection site and bronchitis**.

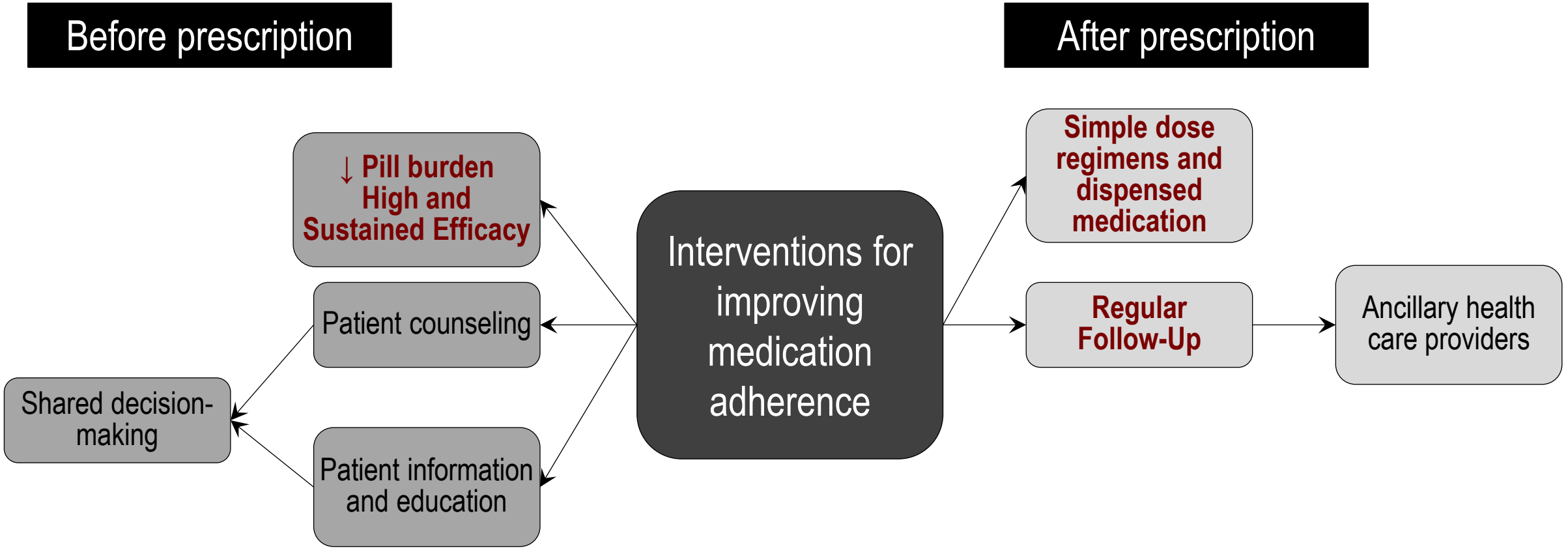
The Best Interventions to Improve Medication Adherence



Interventions can be 'before' and 'after' prescriptions are given.
Effective approaches involve strong partnerships between patients and health providers.

Adapted from Wouters H, et al. PloS One. 2016;11(1):e0146272.

The Best Interventions to Improve Medication Adherence



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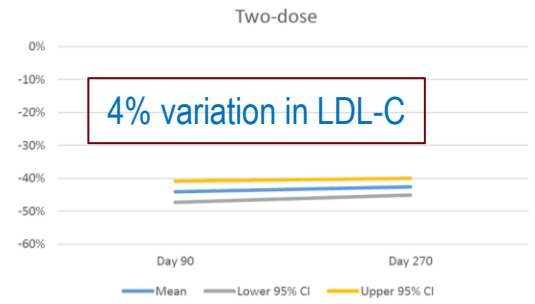
The Best Interventions to Improve Medication Adherence

Before prescription



↓ Pill burden
High and
Sustained Efficacy

Patient counseling

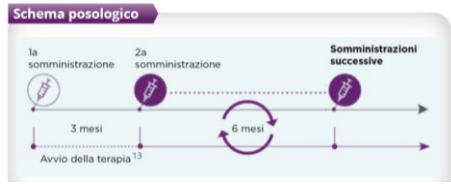
Shared decision-making

Patient information and education

Interventions for improving medication adherence

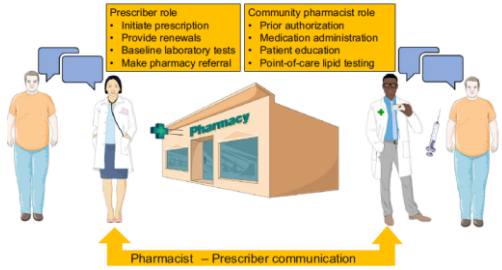
After prescription

Simple dose regimens and dispensed medication



Regular Follow-Up

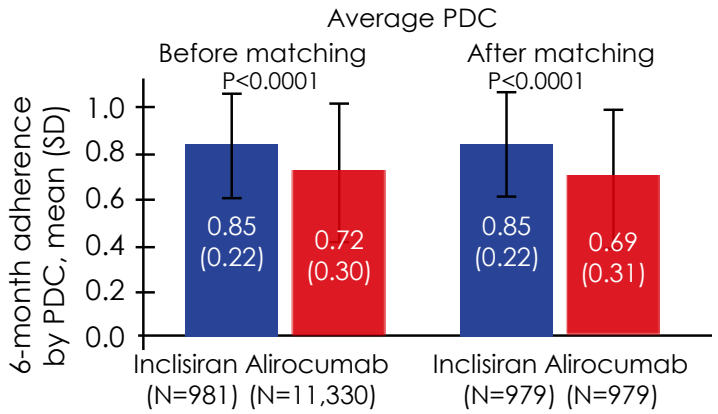
Ancillary health care providers

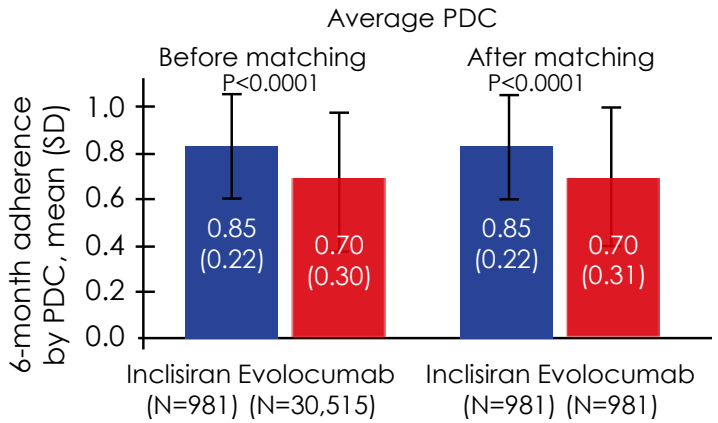


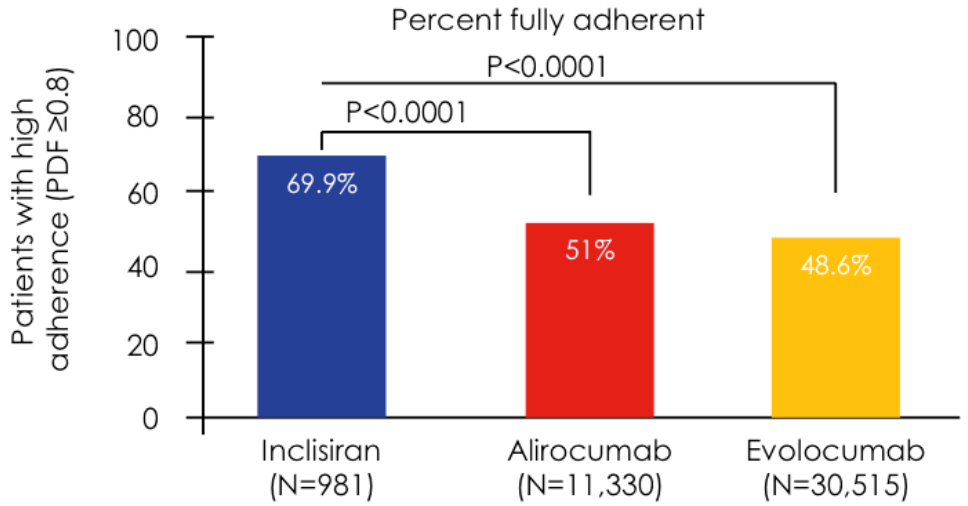
Interventions can be 'before' and 'after' prescriptions are given.
Effective approaches involve strong partnerships between patients and health providers.

Adapted from Wouters H, et al. PloS One. 2016;11(1):e0146272.

Six-Month Adherence Among Early Inclisiran Initiators vs. Anti PCSK9 mAbs Users: A Retrospective Analysis of US Claims Databases



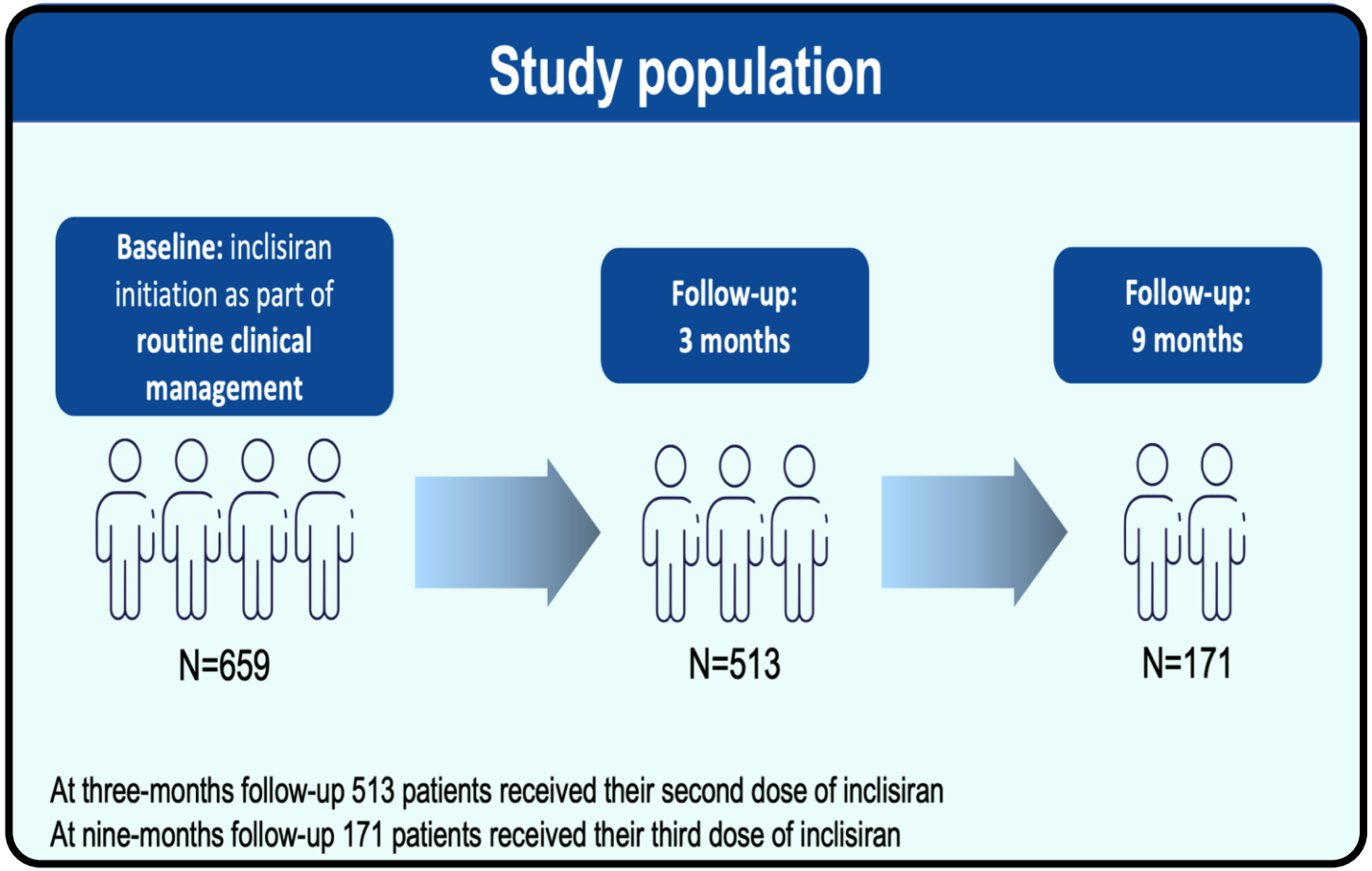




- US individuals (*Komodo Health database*) from jan 2021 to feb 2023. Adherence if > 80% *percentage of days covered*.
- *Propensity score matching* to compare anti PCSK9 population (n = 41,845) with inclisiran-treated patients (n = 981)

Efficacy and Safety of Inclisiran in Real-World: A Single Country, Multicenter, Observational Study (CHOLINET Registry)

Paola Gargiulo; Federica Marzano; Mario Crisci; Rossella Marcucci; Dario Bruzzese; Alessandro Maloberti; Filippo Maria Sarullo; Gennaro Galasso; Ciro Indolfi; Giuseppe Musumeci; Antonella Corleto; Ferdinando Varbella; Paolo Calabrò; Stefano Carugo; Gavino Casu; Giuseppe Colonna; Marco Matteo Ciccone; Claudio Bilato; Alberto Polimeni; Francesco Giallauria; Raffaele Napoli; Angelo Catalano; Leonardo De Luca; Giampaolo Niccoli; Elio Venturini; Marco Pepe; Roberta Montisci; Natale Brunetti; Giuseppe Patti; Italo Porto; Cosmo Godino; Marina Floresta; Saverio Muscoli; Matteo Cameli; Giuseppe Andò; Costantino Mancusi; Monica Franzese; Ornella Affinito; Luca Gallo; Mariafrancesca Di Santo; Ermanno Nardi; Stefania Paolillo; Giovanni Esposito; Alberto Corsini; PasqualePerrone-Filardi.



Age, years, mean (SD)	**63.1** (10.2)
Female, n (%)	202 (**30.7**)
Hypertension, n (%)	485 (73.6)
Type 2 DM, n (%)	129 (19.6)
Current smokers, n (%)	169 (25.6)
ASCVD, n (%)	556 (**84.4**)
ACS, n (%)	284 (**43.1**)
Ambulatory setting prescription n (%)	571 (87.4)
Very-high CV Risk	614 (**93.2**)
Statin n (%)	53 (8.1)
Statin+ezetimibe, n (%)	418 (**63.4**)
Ezetimibe, n (%)	103 (15.6)
Statin Intolerance, n (%)	240 (36.4)
LDL-C mg/dL median (Q1, Q3)	**103** (80, 149.5)

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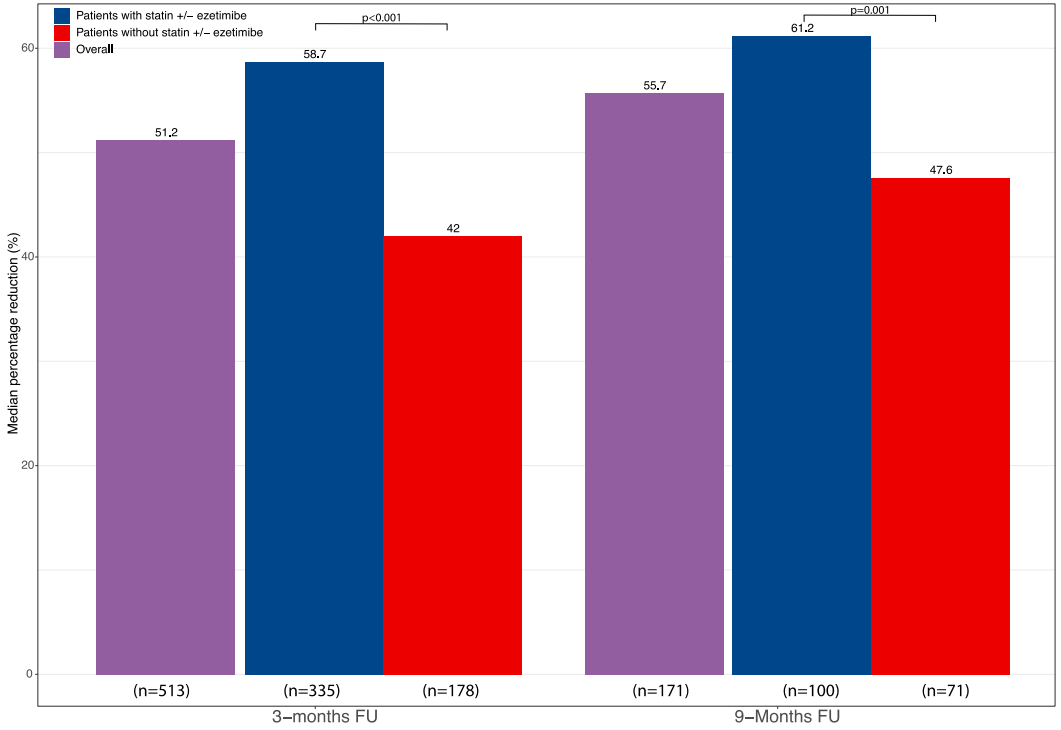
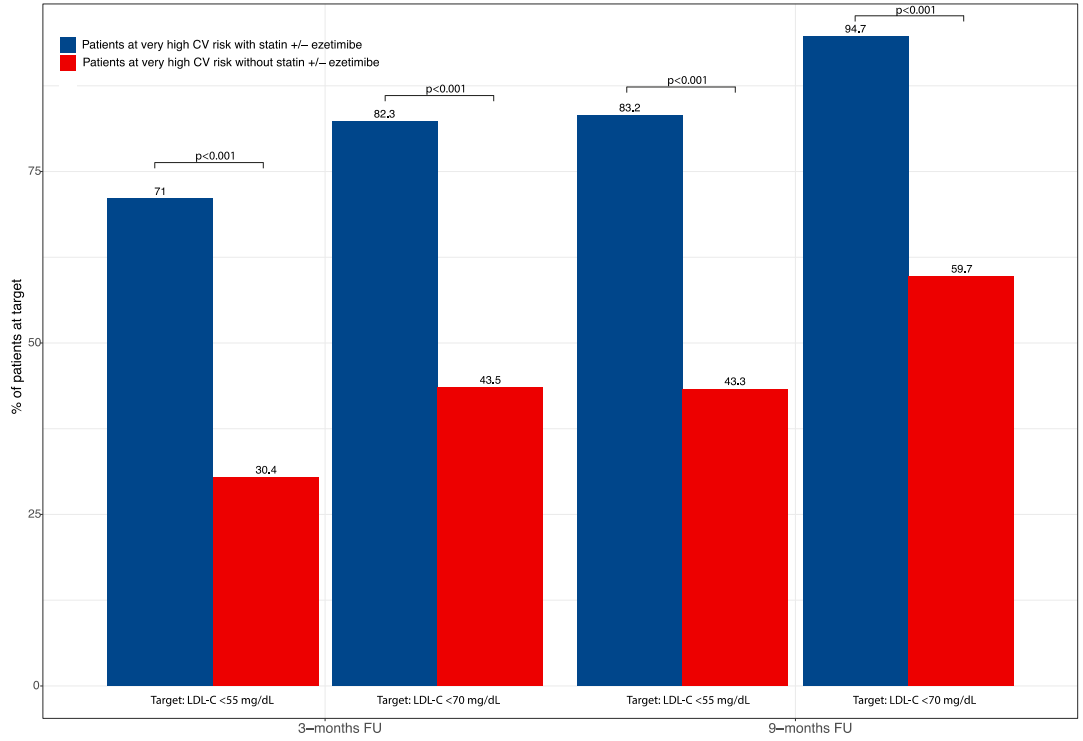
median % reduction of LDL-C



% of very high-risk patients achieving LDL-C targets



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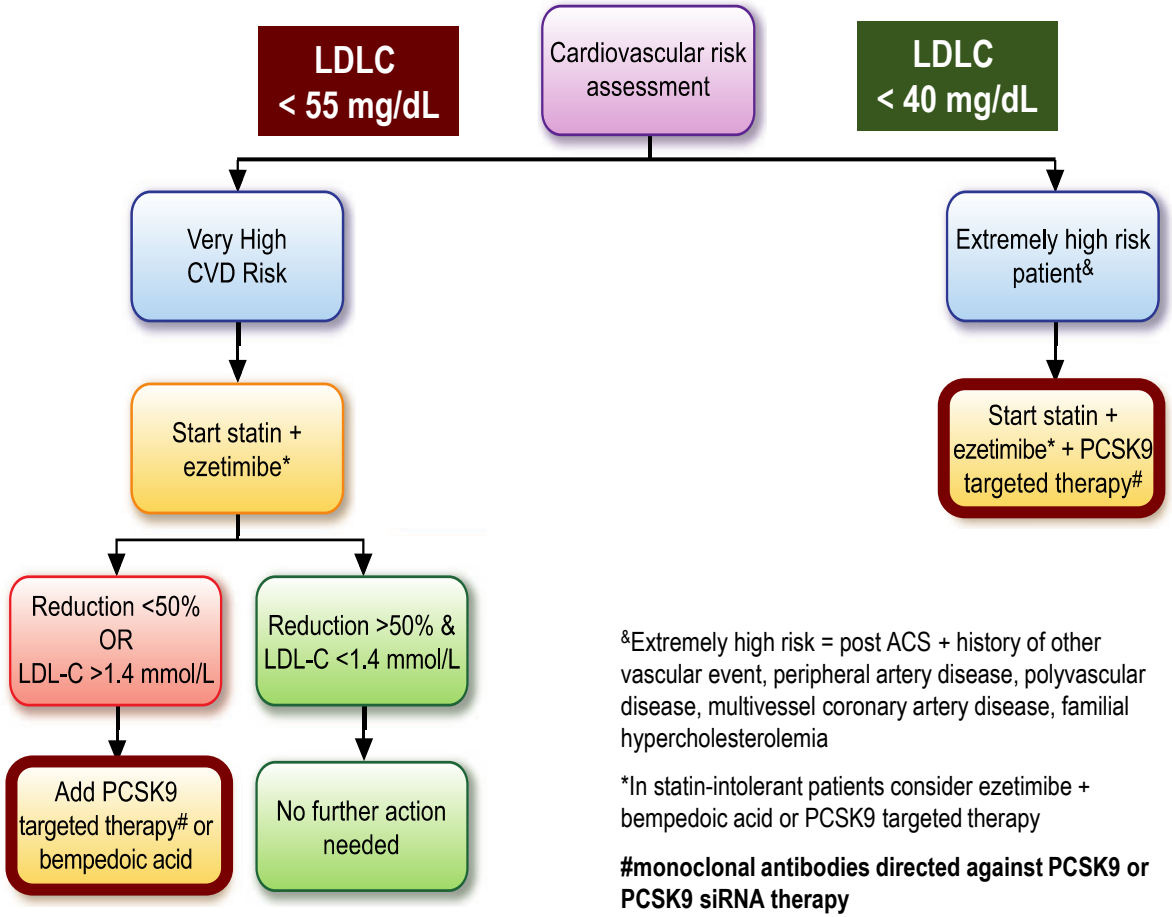
Predictors of achievement of LDL-C target at three-months follow-up

	Univariate			Multivariable		
Variable	OR	95% CI	P	OR	95% CI	P
Diabetes mellitus	1.53	0.99 to 2.37	0.058	1.2	0.71 to 2.05	0.495
Chronic Coronary Syndrome	2.35	1.63 to 3.38	<0.001	0.74	0.45 to 1.22	0.241
Male Sex	1.64	1.12 to 2.39	0.011	0.89	0.55 to 1.45	0.636
Age (10 years increase)	1.4	1.17 to 1.67	<0.001	1.25	0.99 to 1.58	0.06
Hypertension	1.89	1.27 to 2.82	0.002	1.2	0.71 to 2.02	0.496
Previous exposure to PCSK9i	0.47	0.28 to 0.81	0.006	0.57	0.29 to 1.1	0.093
Familial Hypercholesterolemia	0.19	0.11 to 0.32	<0.001	0.47	0.23 to 0.95	**0.036**
LLT - Statin alone	4.07	1.6 to 10.34	0.003	2.73	0.94 to 7.96	0.066
LLT - Statin and ezetimibe combination	6.33	3.65 to 11	<0.001	4.14	2.23 to 7.69	**<0.001**
LLT - Ezetimibe alone	1.49	0.79 to 2.83	0.217	1.07	0.52 to 2.18	0.854

European Heart Journal (2021) **00**, 1–4

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



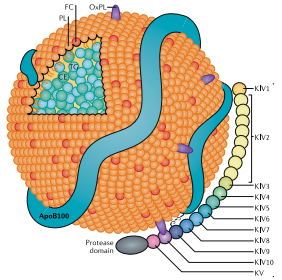
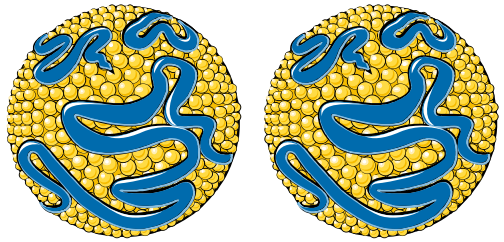
&Extremely high risk = post ACS + history of other vascular event, peripheral artery disease, polyvascular disease, multivessel coronary artery disease, familial hypercholesterolemia

*In statin-intolerant patients consider ezetimibe + bempedoic acid or PCSK9 targeted therapy

#monoclonal antibodies directed against PCSK9 or PCSK9 siRNA therapy

INCLISIRAN preferibile

- Pazienti per i quali con l'**aderenza terapeutica** può rappresentare un problema rilevante:
  - Pazienti che assumono un **elevato numero** di farmaci,
  - Pazienti con **limitata autonomia**,
  - Pazienti **lontani** da centri di riferimento/prescrizione
- Persone con **attività lavorative** caratterizzate da spostamenti/viaggi frequenti
- Situazioni ove sia difficile mantenere la **catena del freddo**
- **Giovani HeFH** ove sia essenziale una riduzione persistente di LDL-C e schema posologico snello (qualità di vita)

Particella lipidica	molecola	target
LDL 	Inclisiran	PCSK9
Lp(a) 	Olpasiran Lepodisiran Zerlasiran	apo(a) apo(a) apo(a)
TRL 	Plozasiran Zodasiran	apo C-III ANGPTL3

Antonio Cardarelli
AZIENDA OSPEDALIERA DI RILIEVO NAZIONALE

Grazie 1000!!

claudio.bilato@aulss8.veneto.it