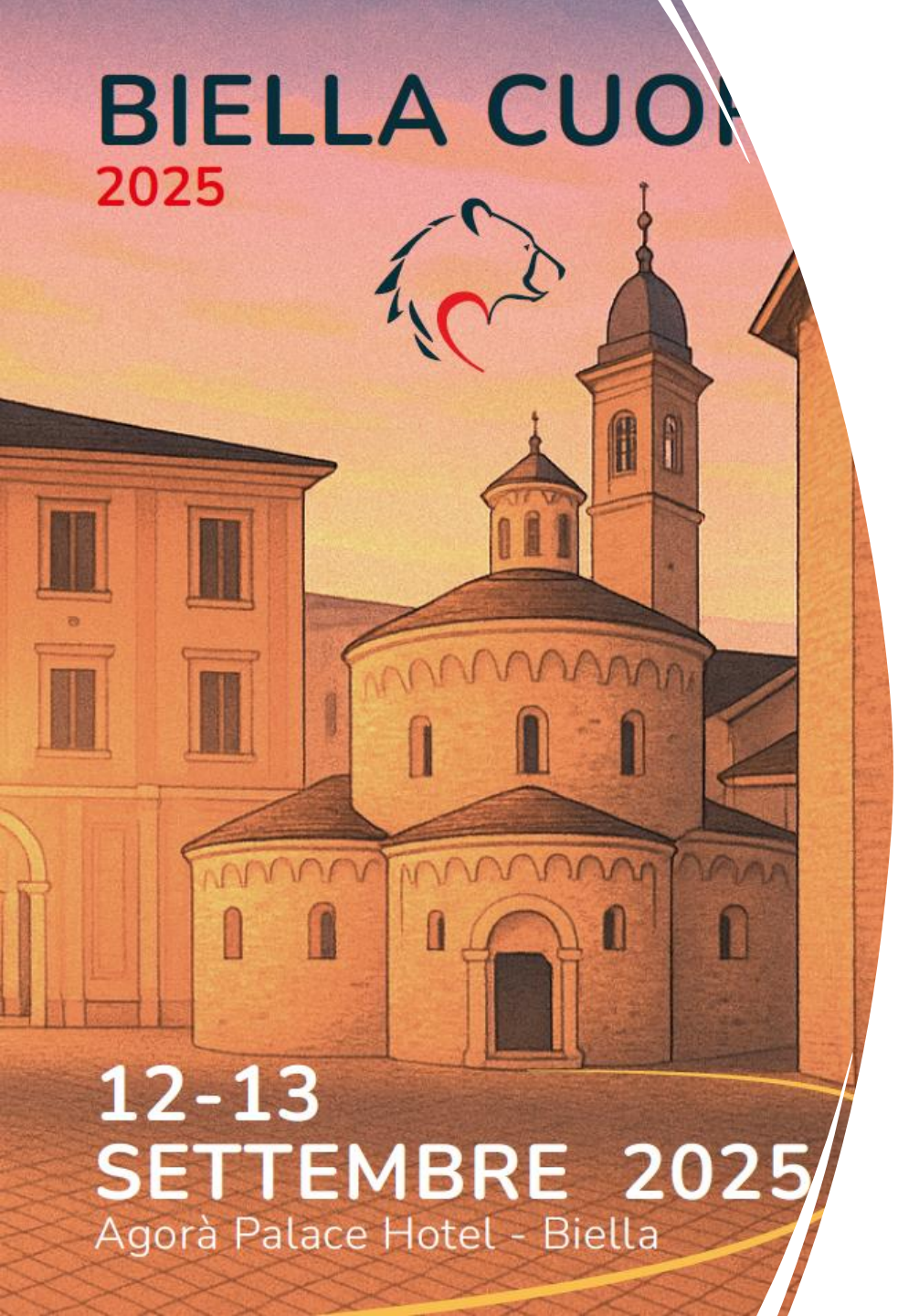


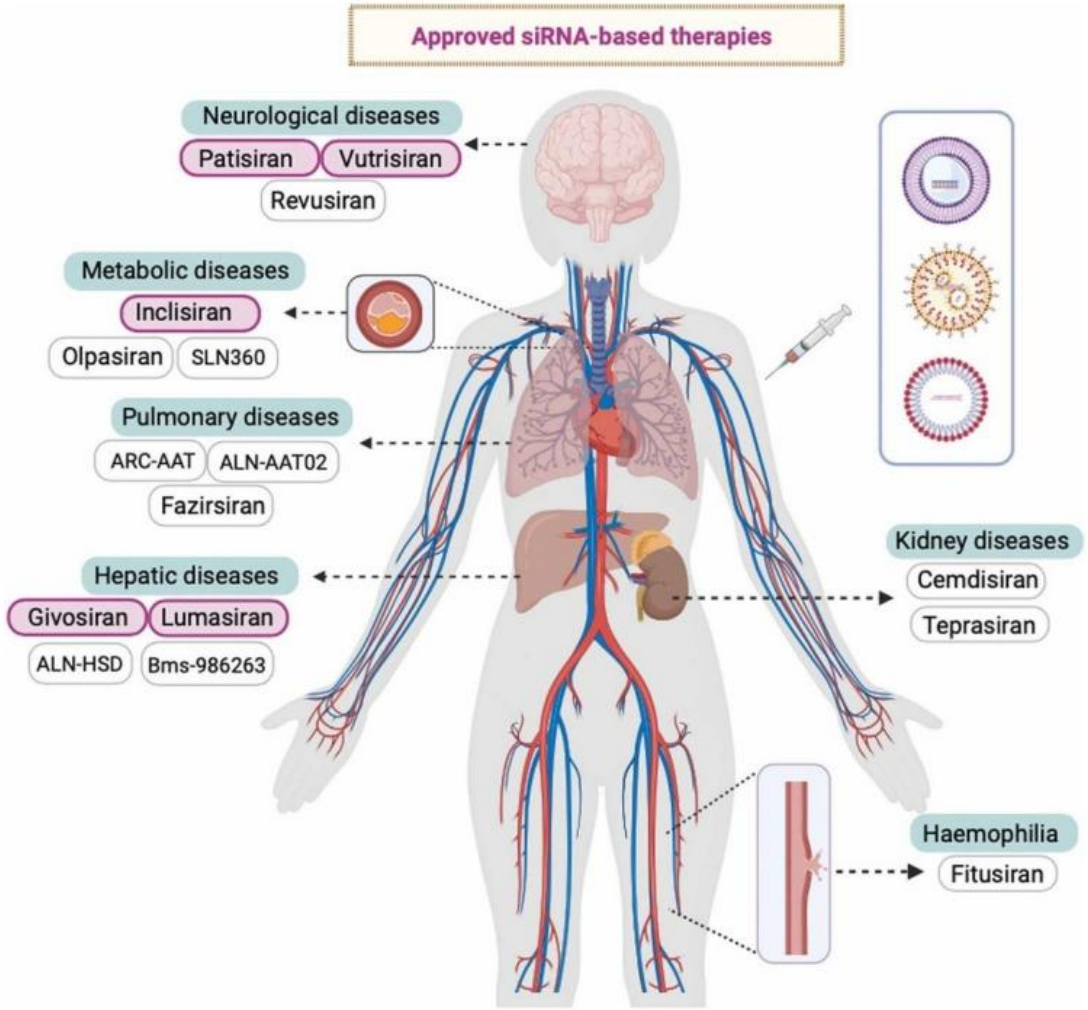
Il trattamento con siRNA: indicazioni ed effetti

Stefano Mazzarino

S.C. Cardiologia – Ospedale S. Spirito

Casale Monferrato (AL)

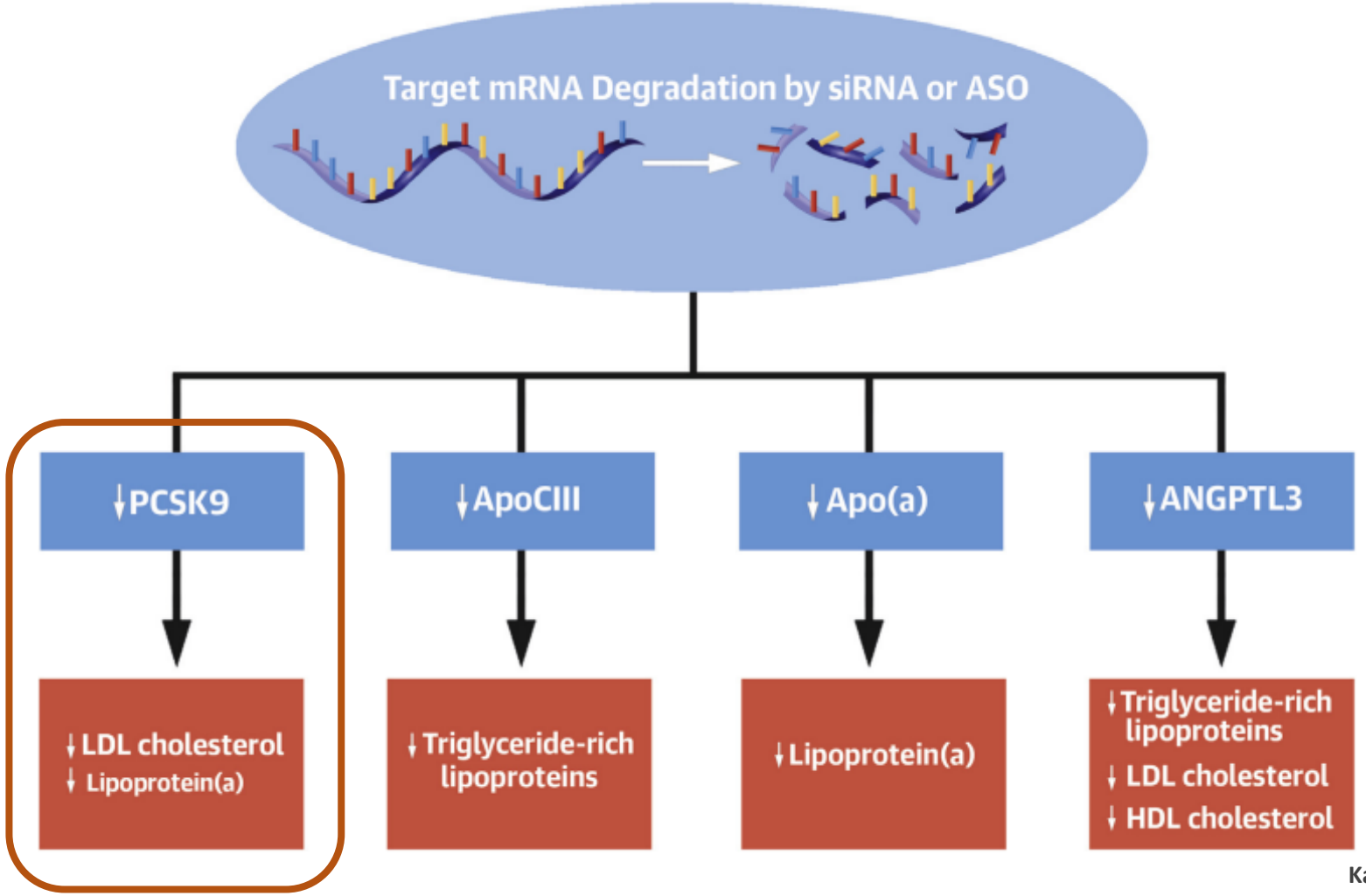
The Application of siRNA Technology to Other Therapeutic Areas is Expanding



With many new siRNA therapies in clinical development targeting diseases of different tissues, there is expected to be a substantial increase in the number of approved siRNA-based therapies in the next two decades

Pérez-Carrión et al. Pharmacol Res. 2024;201:107102

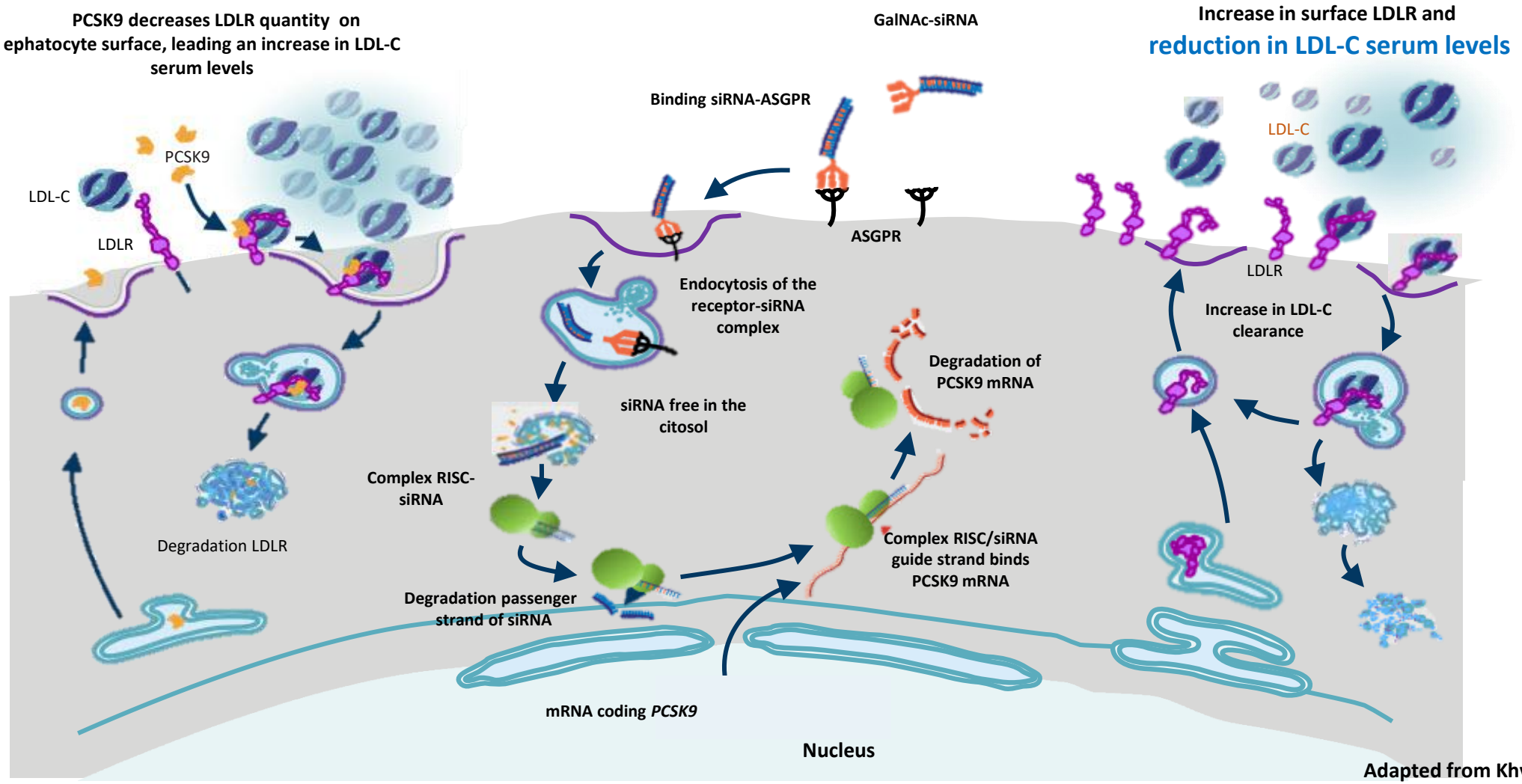
Targets of RNA-Based Drugs for Atherosclerotic Disease Prevention



ASO: Antisense Oligonucleotides

Katzman J, et al. J Am Coll Cardiol 2020;76:563

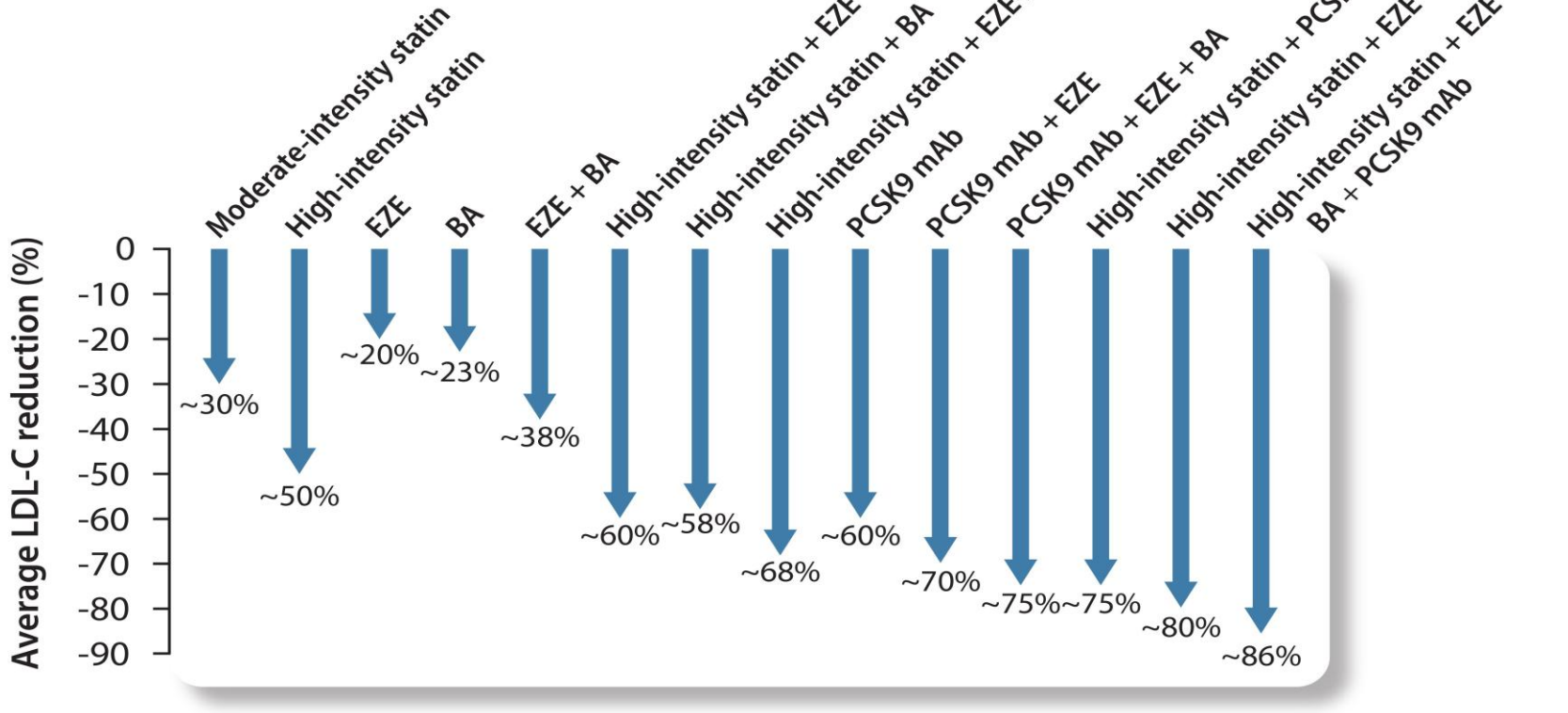
A Totally New Mechanism of Action



N-Acetylgalactosamine

Adapted from Khvorova A, et al. 2017

ESC guidelines



ESC EAS

OXFORD UNIVERSITY PRESS

Eur Heart J, ehaf190, https://doi.org/10.1093/eurheartj/ehaf190

ESC European Society of Cardiology
European Heart Journal (2025) 00, 1–20
https://doi.org/10.1093/eurheartj/ehaf190
ESC GUIDELINES

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias

Developed by the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

Inclisiran, a small interfering ribonucleic acid (RNA) molecule that inhibits the synthesis of PCSK9, may represent an alternative approach to PCSK9 mAbs (alirocumab and evolocumab). Inclisiran has been shown in phase III trials to lower LDL-C levels by approximately 50%.[48] Two CV outcome trials with inclisiran [>16 000 patients with CVD (NCT03705234) and 17 000 patients with established ASCVD (NCT05030428)] are currently ongoing and expected to report their primary outcomes in 2026 and 2027, respectively.

Extensive Clinical Development Program of Inclisiran, in all Settings of Dyslipidemic Patients

Phase 1

- **ORION-6**
  (Hepatic impairment, United States)
- **ORION-7**
  (Renal impairment, NZ)
- **ORION-12**
  (TQTc, United States)

Phase 2

- **ORION-1**
  (ASCVD, global)
- **ORION-2**
  (Pilot study, HoFH, global)
- **ORION-3**
  (LTE study of ORION-1, Global)

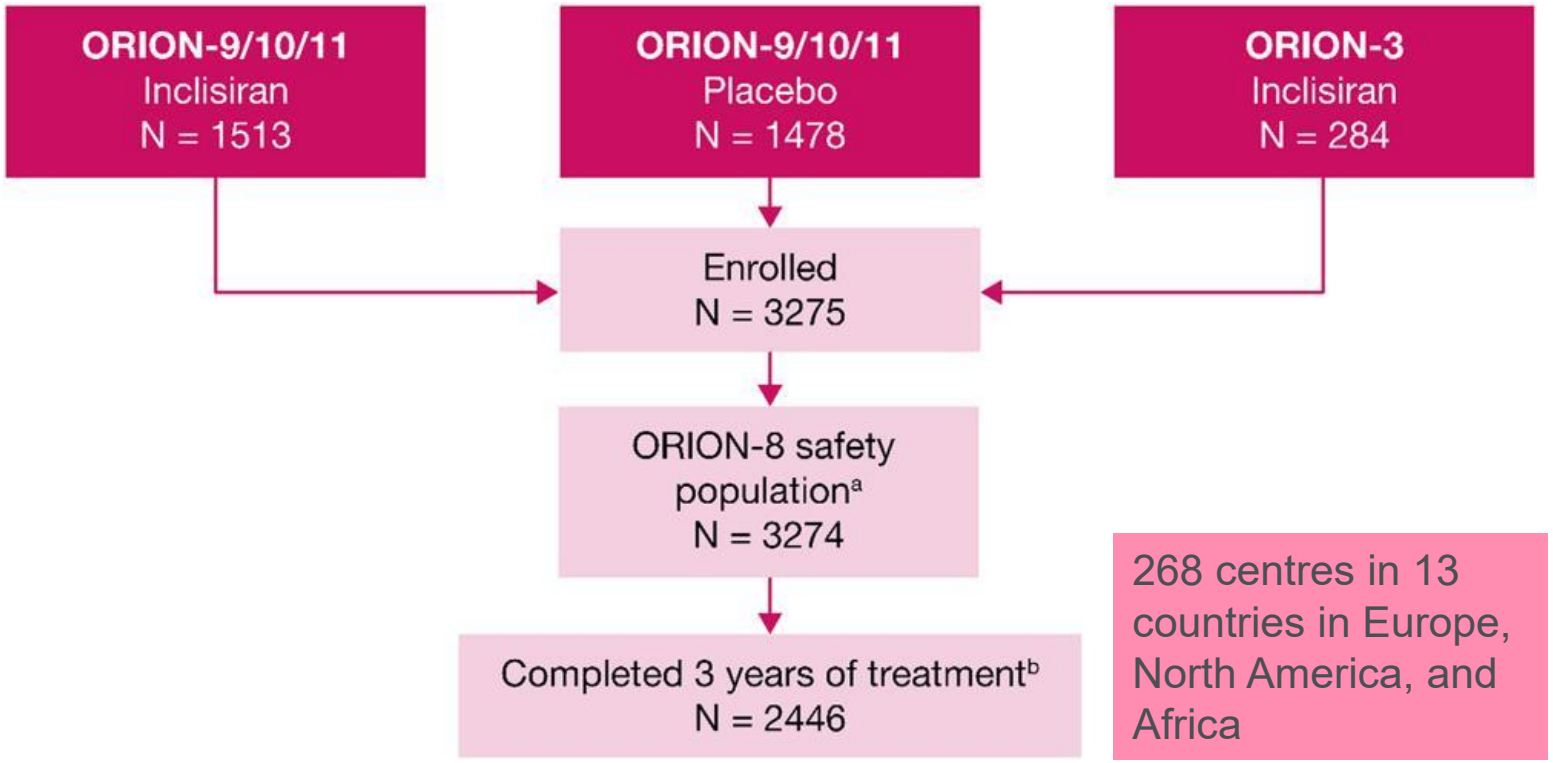
Phase 3-4

- **ORION-5**
  (HoFH, Global)
- **ORION-8**
  (Extension of ORION-9-11, ASCVD, Global)
- **ORION-9**
  (HeFH, Global)
- **ORION-10**
  (ASCVD, United States)
- **ORION-11**
  (ASCVD and risk-equivalents, Europe)
- **ORION-4**
  (CVOT/ASCVD, UK and United States)
- **VICTORION 2 PREVENT**
  (CVOT/ASCVD, Europe)
- **VICTORION 1 PREVENT**
  (primary prevention, global)
- **VICTORION PLAQUE**
  (Plaque progression, global)
- **ORION 13**
  (HoFH in ≥12 to <18 years, global)
- **ORION 16**
  (HeFH in ≥12 to <18 years, global)
- **VICTORION DIFFERENCE**
  (llt Optim. And QoL, (Europe)
- **VICTORION REAL**
  (Obs study, global)

- **>45,000 patients in ongoing trials**

German CA, Shapiro MD. Small Interfering RNA Therapeutic Inclisiran: A New Approach to Targeting PCSK9. BioDrugs. 2020 Feb;34(1):1-9
ClinicalTrial.Gov

Inclisiran administration potently and durably lowers LDL-C over an extended-term follow-up: the ORION-8 trial

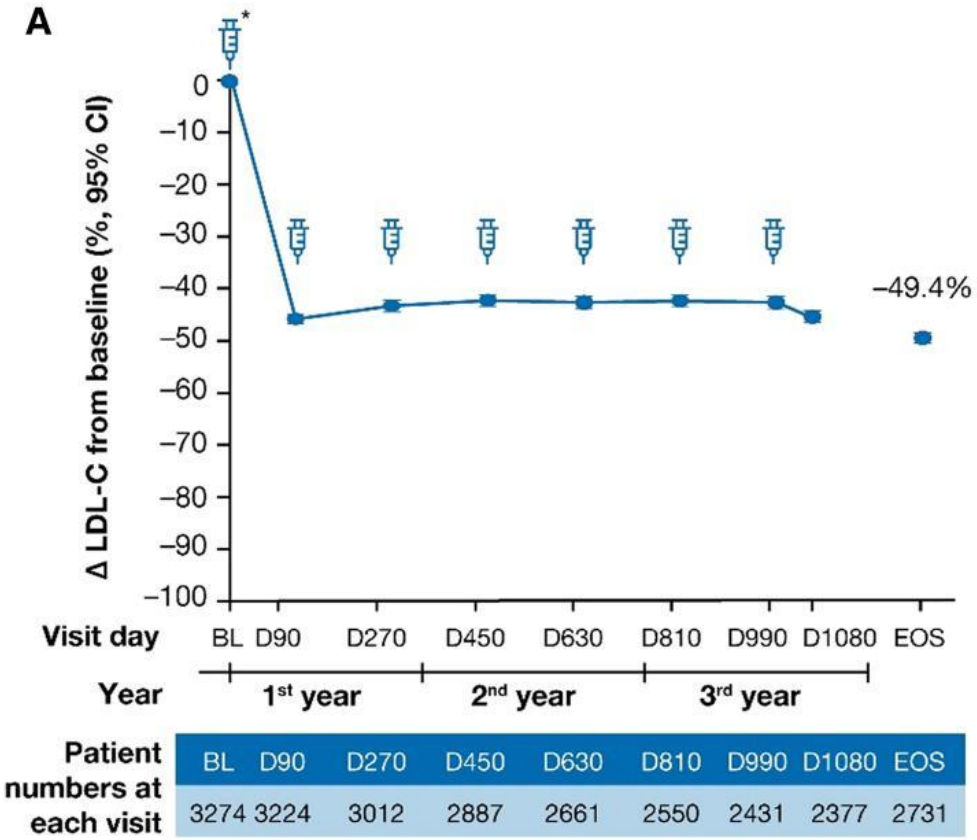


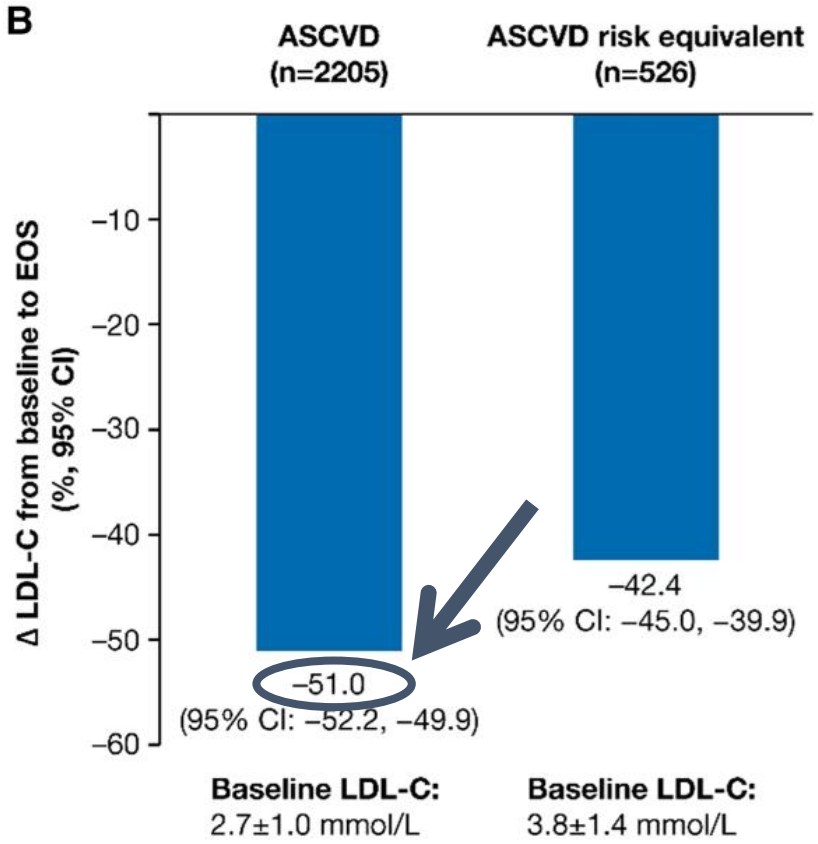
268 centres in 13 countries in Europe, North America, and Africa

[a]One patient from the inclisiran arm of pivotal trials ORION-9, ORION-10, and ORION-11 did not receive any injection in ORION-8. [b]The primary reasons for discontinuation were ORION-3 rollover patients not offered to complete the full study period (8.3%), death (5.0%), withdrawal of consent (4.8%), lost to follow-up, mostly during the COVID-19 pandemic period (3.1%), other (2.3%), and adverse events (1.4%).

Wright R.S. et al.; Cardiovasc Res 2024; 120 (12): 1400-1410

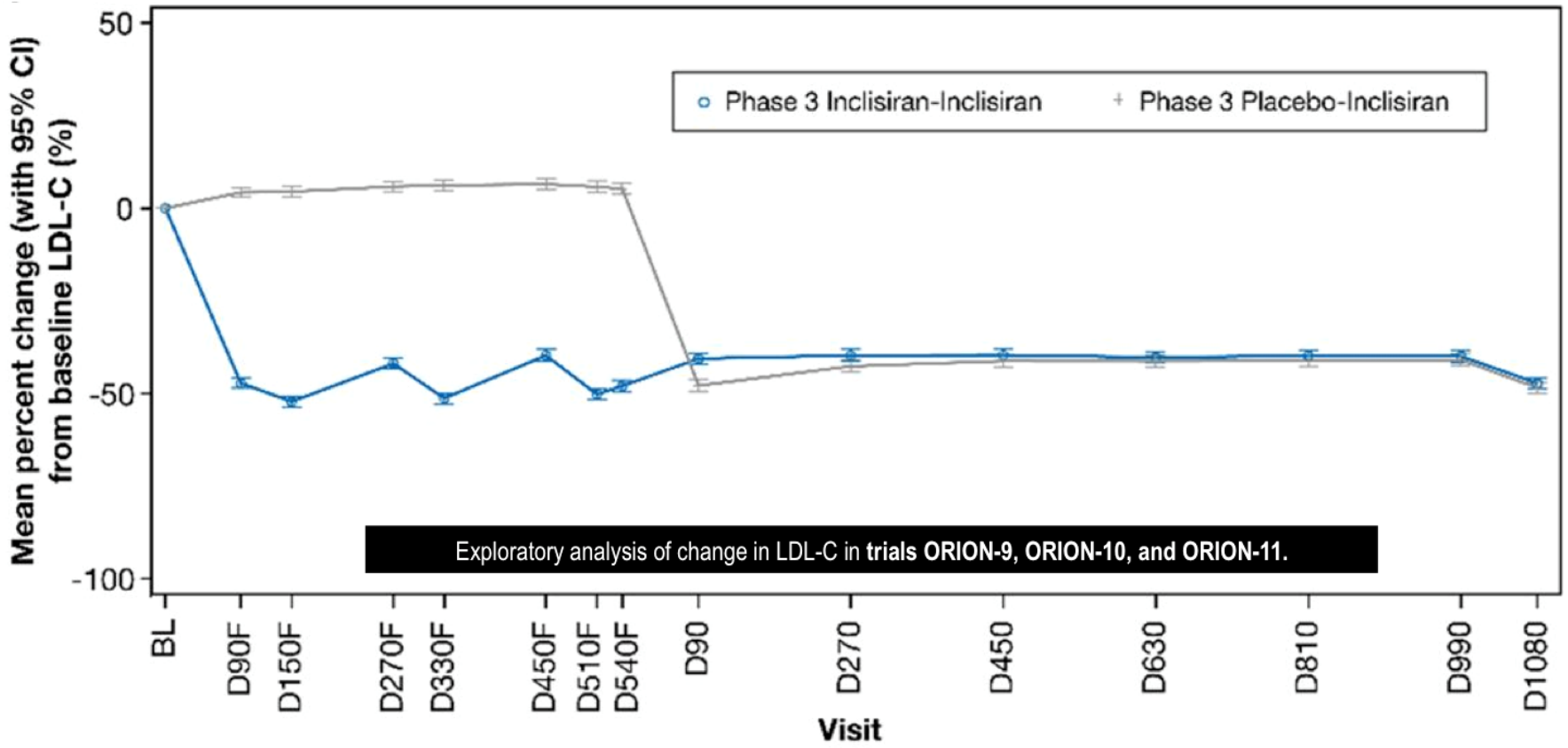
Inclisiran administration potently and durably lowers LDL-C over an extended-term follow-up: the ORION-8 trial





Wright R.S. et al.; Cardiovasc Res 2024; 120 (12): 1400-1410

Inclisiran administration potently and durably lowers LDL-C over an extended-term follow-up: the ORION-8 trial

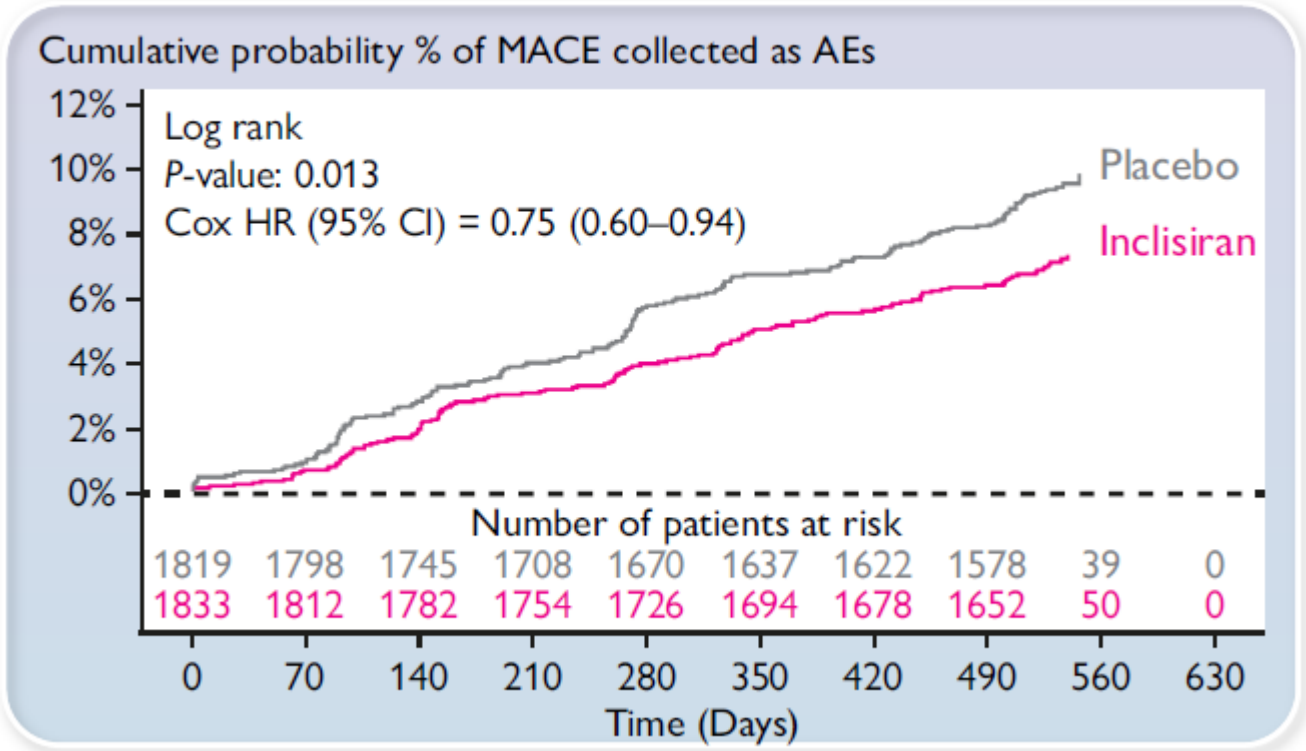


Wright R.S. et al.; Cardiovasc Res 2024; 120 (12): 1400-1410

Inclisiran and CV Events: A Patient-Level Analysis of Phase III Trials

Effects of inclisiran vs placebo on MACE (safety EP)

Kaplan-Meier curves showing the cumulative event rate for MACE



25% reduction in MACE with inclisiran

MACE: Non-fatal MI, non-fatal stroke, cardiac arrest, CV death evaluated as part of safety assessments using a standard Medical Dictionary for Regulatory Activities basket.

Ray KK et al Eur Heart J. 2023 Jan 7;44(2):129-138.

The VICTORION-INITIATE trial

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ORIGINAL RESEARCH

An "Inclisiran First" Strategy vs Usual Care in Patients With Atherosclerotic Cardiovascular Disease

Michael J. Koren, MD,[a] Fatima Rodriguez, MD, MPH,[b] Cara East, MD,[c] Peter P. Toth, MD, PhD,[d,e] Veena Watwe, MD,[f] Cheryl A. Abbas, PharmD,[g] Samiha Sarwat, PhD,[g] Kelly Kleeman, PharmD,[g] Biswajit Kumar, MSc, EMBA,[g] Yousuf Ali, PhD,[g] Naseem Jaffrani, MD[h]

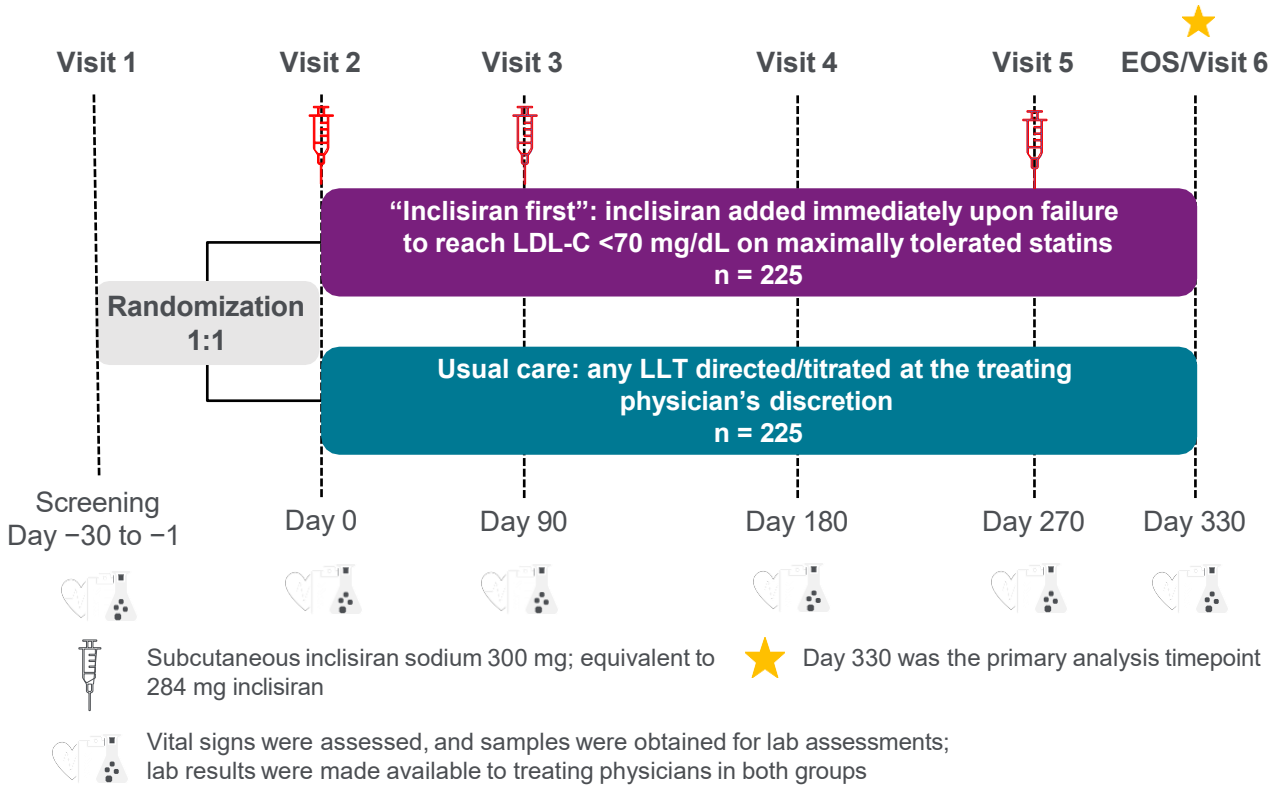
VICTORION-INITIATE (NCT04929249): prospective, randomized, open-label, Phase 3b trial that evaluated an "inclisiran first" **(i.e. adding inclisiran immediately if patients fail to reach LDL-C <70 mg/dL on maximally tolerated doses of statins)** implementation strategy compared with usual care in patients with ASCVD in representative US clinical settings

Population

- Adults ≥18 years of age with a history of ASCVD*
- LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL and fasting triglycerides <500 mg/dL
- Receiving maximally tolerated statin therapy† or had documented statin intolerance‡

Setting and procedures

- 45 sites selected from diverse settings
- Stratification by baseline health insurance status
- Study physician oversight without interference in lipid management beyond "inclisiran first" administration
- Managing physicians were provided lipid results and encouraged to follow AHA/ACC/Multisociety guidelines[1] and add therapies at their discretion



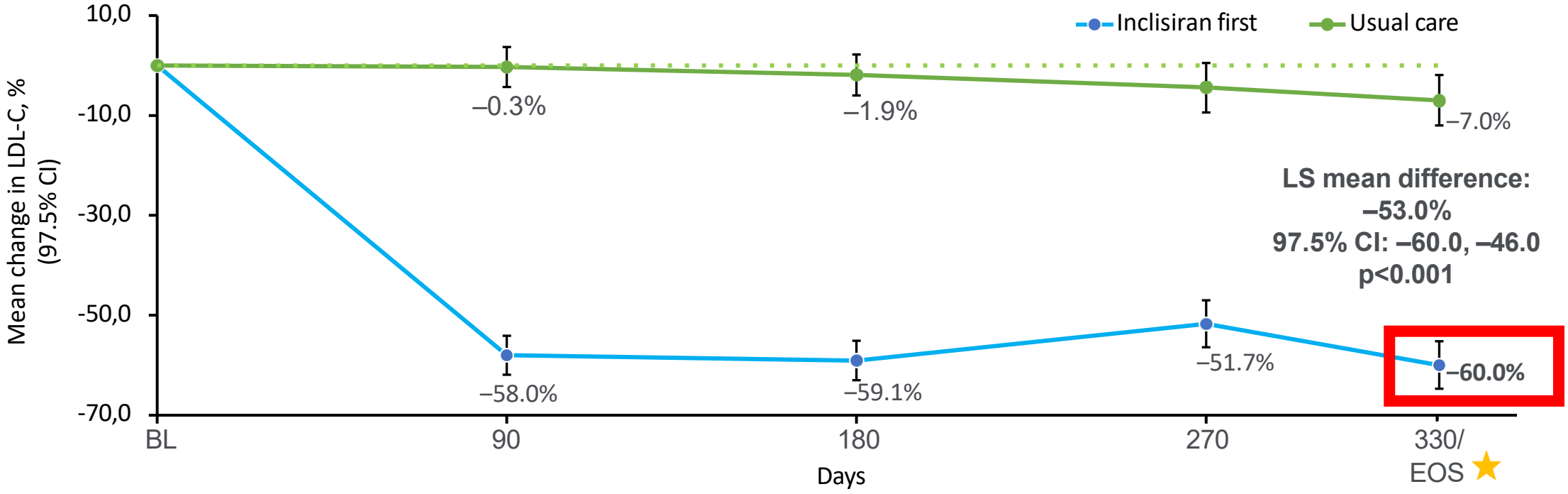
*Coronary heart disease, cerebrovascular disease, or peripheral artery disease. †Maximally tolerated statin therapy was determined by the investigator; no immediate plans to modify LLT were permitted.
‡Documented side effects on ≥2 different statins, including one at the lowest standard dose.
ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; EOS, end of study; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; US, United States.

1. Grundy SM, et al. Circulation. 2018;139;e1082–1143.

Koren MJ et al. J Am Coll Cardiol. 2024 May 21;83(20):1939-1952.

Co-primary endpoint: percent change in LDL-C

At Day 330/EOS the mean percent change in LDL-C from baseline was –60.0% (97.5% CI: –64.7, –55.2) with "inclisiran first" and –7.0% (97.5% CI: –12.0, –1.9) with usual care



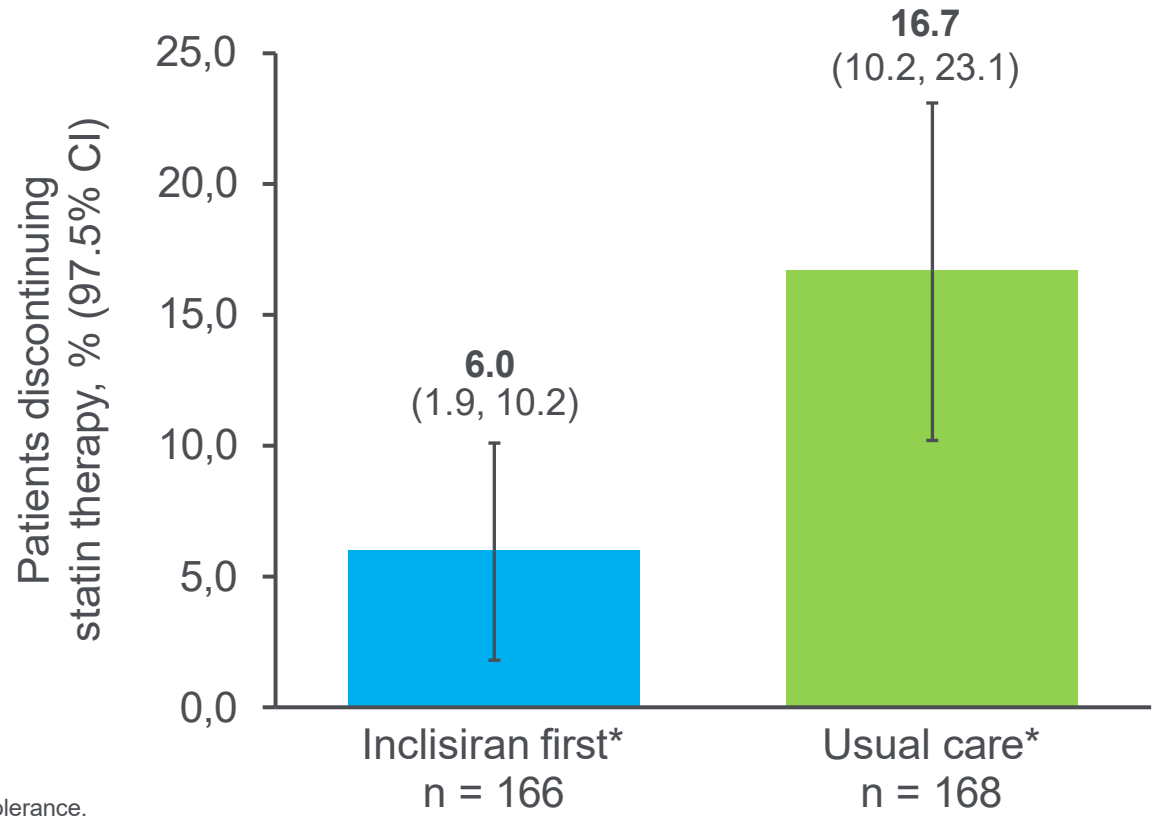
	BL	90	180	270	330/EOS
Inclisiran first, n		213	207	203	205
Usual care, n		201	191	178	174

★ Day 330 is the primary analysis timepoint. The dotted line represents baseline LDL-C.
BL, baseline; CI, confidence interval; EOS, end-of-study; LDL-C, low-density lipoprotein cholesterol; LS, least squares.

Gargiulo P. et al.; J Am Coll Cardiol. 2025; 85 (5): 536-540

Co-primary endpoint: statin discontinuation

The non-inferiority margin (15%) met comparing “inclisiran first” and usual care (−10.6% [97.5% CI: −18.3%, −3.0%])



*Only patients without a history of statin intolerance.
CI, confidence interval.

Koren MJ et al. J Am Coll Cardiol. 2024 May 21;83(20):1939-1952.

CHOLINET REGISTRY: 659 patients were enrolled across 31 Italian sites between November 2022 and February 2024

Main outcomes were:

- LDL-C reduction from baseline
- Percentage of patients reaching LDL-C target at 3 and 9 months

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BRIEF REPORT

Real-World Efficacy and Safety of Inclisiran

A Single-Country, Multicenter, Observational Study (CHOLINET Registry)

Paola Gargiulo, MD,[a] Federica Marzano, PhD,[a] Mario Crisci, MD,[b] Rossella Marcucci, MD,[c] Dario Bruzzese, PhD,[d] Alessandro Maloberti, MD,[e,f] Filippo Maria Sarullo, MD,[g] Gennaro Galasso, MD,[h] Ciro Indolfi, MD,[i] Giuseppe Musumeci, MD,[j] Antonella Corleto, MD,[k] Paolo Calabrò, MD,[l,m] Stefano Carugo, MD,[n,o] Gavino Casu, MD,[p] Amedeo Picciolo, MD,[q] Marco Matteo Ciccone, MD,[r] Claudio Bilato, MD,[s] Alberto Polimeni, MD,[t,u] Francesco Giallauria, MD,[v] Angelo Catalano, MD,[w] Leonardo De Luca, MD,[x] Giampaolo Niccoli, MD,[y] Elio Venturini, MD,[z] Marco Pepe, MD,[aa] Roberta Montisci, MD,[bb] Natale Daniele Brunetti, MD,[cc] Giuseppe Patti, MD,[dd] Italo Porto, MD,[ee] Alberto Margonato, MD,[ff] Marina Floresta, MD,[gg] Saverio Muscoli, MD,[hh] Matteo Cameli, MD,[ii] Giuseppe Andò, MD,[jj] Emilio Di Lorenzo, MD,[b] Martina Berteotti, MD,[c] Cristina Giannattasio, MD,[e,f] Silvia Sarullo, MD,[kk] Ciro Formisano, MD,[h] Assunta Di Costanzo, MD,[i] Fabrizio Delnevo, MD,[j] Ferdinando Varbella, MD,[k] Arturo Cesaro, MD,[l,m] Monica Franzese, MS,[ll] Costantino Mancusi, MD,[a] Sara Fontanarosa, MD,[a] Mariafrancesca Di Santo, MD,[a] Ciro Cotticelli, MD,[a] Fabrizio Perrone Filardi, PhD,[a] Stefania Paolillo, MD,[a] Giovanni Esposito, MD,[a] Alberto Corsini, MD,[mm] Pasquale Perrone Filardi, MD,[a] the CHOLINET Investigators

Gargiulo P. et al.; J Am Coll Cardiol. 2025; 85 (5): 536-540

Design

STUDY POPULATION

Baseline: inclisiran initiation as part of routine clinical trial management

Follow-up: 3 months

Follow-up: 9 months

N=659 → N=513 → N=171

At three-months follow-up 513 patients received their second dose of inclisiran
At nine-months follow-up 171 patients received their third dose of inclisiran

INCLUDED:

- 18 years or older
- had initiated inclisiran as part of routine clinical management

EXCLUDED:

patients enrolled in a PCSK9i or inclisiran interventional study

ENROLMENT PERIOD:

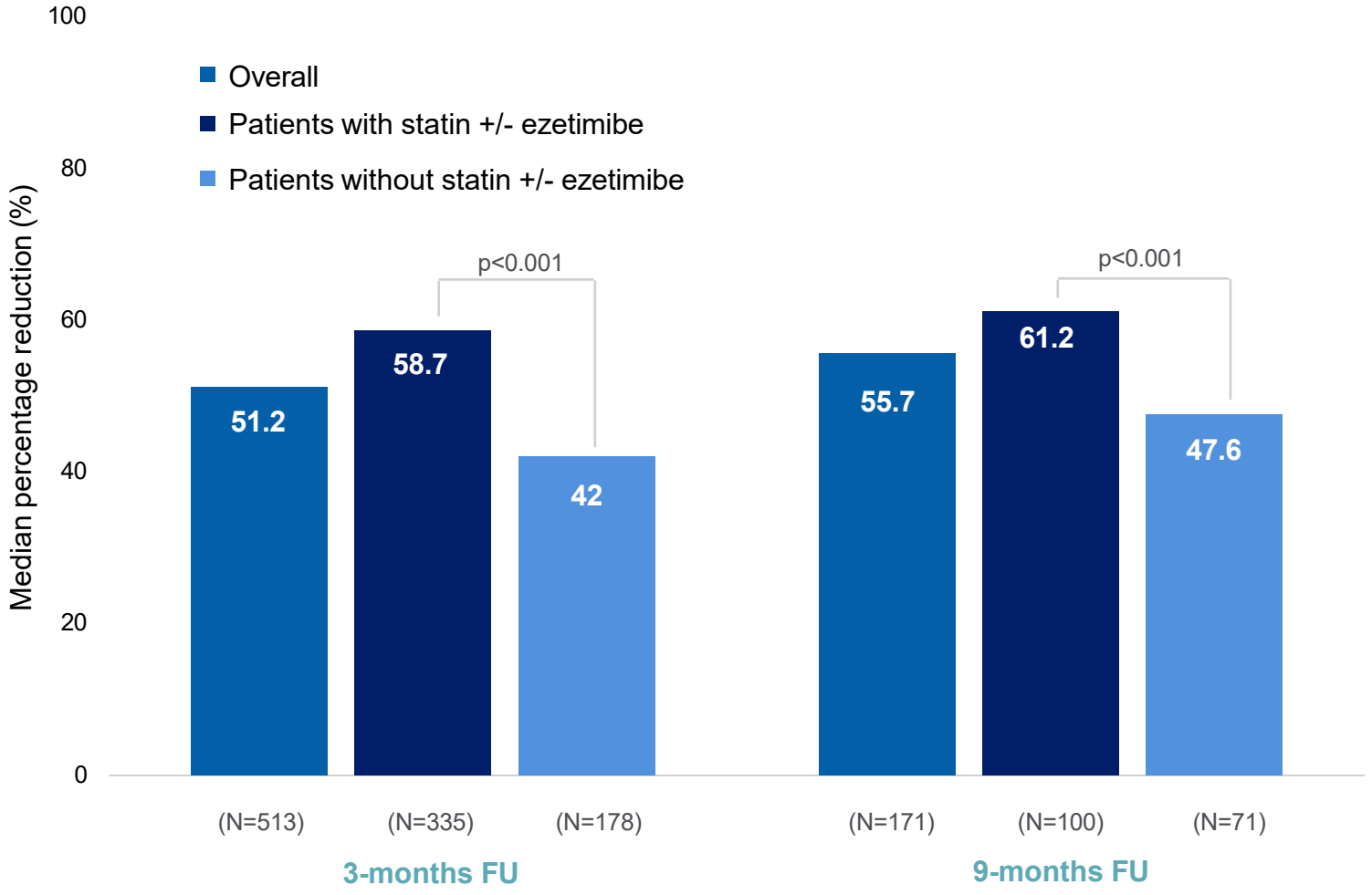
1st November 2022

FIRST CUT-OFF:

February 2024

Gargiulo P. et al.; J Am Coll Cardiol. 2025; 85 (5): 536-540

CHOLINET registry: percentage of LDL-C reduction



STUDY POPULATION

Baseline: inclisiran initiation as part of routine clinical trial management

Follow-up: 3 months

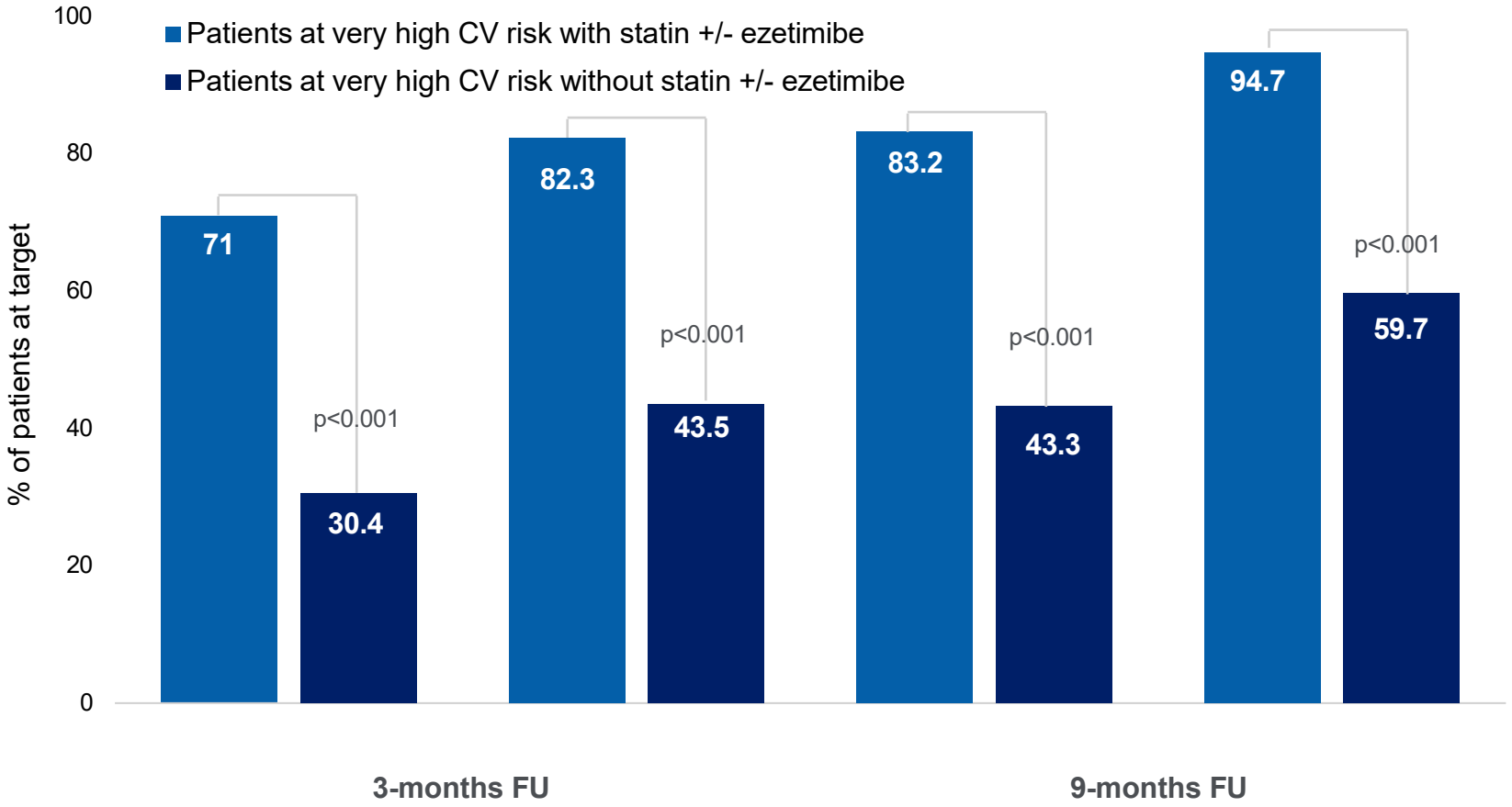
Follow-up: 9 months

N=659 N=513 N=171

In patients with concomitant statin +/- ezetimibe therapy, median percentage reduction of LDL-C is 58.7% and 61.2% at 3 and 9 months FUP respectively

Gargiulo P. et al.; J Am Coll Cardiol. 2025; 85 (5): 536-540

CHOLINET registry: percentage of patients reaching ESC/EAS LG Targets



STUDY RESULTS

79 out of 95 high CV risk patients **(83.2%)**, treated with statin +/- ezetimibe, **reached LDL-C target <55 mg/dL at 9 months follow up**

Gargiulo P. et al.; J Am Coll Cardiol. 2025; 85 (5): 536-540

RWE and registries confirm RCTs results

ORION-8[1] **-51,0%** ↓

(IC al 95%: -52,2%; -49,9%)

V-INITIATE[3] **-60,0%** ↓

(IC al 97,5%: -64,7%; -55,2%; P<0,001)

CHOLINET[4] **-61,2%** ↓

P=0,001

1. Wright RS et al Cardiovasc Res. 2024 Oct 14;120(12):1400-1410; 2. Ballantyne CN, et al. Poster presented at: ACC Congress; 3. Koren M et al. J Am Coll Cardiol. 2024; 4. Gargiulo P et al. Poster presented at: ESC Congress

Treatment patterns among early Inclisiran vs anti-PCSK9 mAbs users: a retrospective analysis of US claims databases

Xiaoli Niu, Lyuba Popadic, Xinshuo Ma, Yousuf Ali, Pam Kumparatana, Yuqin Wei, Sean McElligott

Poster presented at: National Lipid Association Scientific Sessions 2024; May 30–June 2, 2024. Las Vegas, NV. PO#158

Overview of the Komodo study

Komodo: **12-month *adherence*** and ***persistence*** for **Inclisiran** vs **Evolocumab** or **Alirocumab***

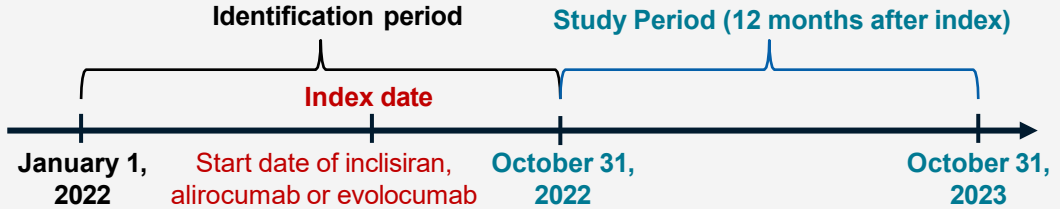
Study details

A retrospective, observational study using administrative claims data to evaluate the 12-month adherence and persistence for patients who ***newly*** initiated **Inclisiran, Alirocumab or Evolocumab**

Study objective and endpoint

- This study evaluated **treatment adherence and persistence at 12 months among patients who newly initiated inclisiran** (initial dose, then at 3 months, then twice yearly), alirocumab (every 2 weeks or once every month), or evolocumab (every 2 weeks or once every month) since 2022
- **Adherence** was defined as the proportion of days covered: **the number of days covered by the drug divided by the observational period** (12 months after the index date)
- **Persistence** was defined as **patients remained on therapy at month 12 without a gap of >60 days for alirocumab or evolocumab, and >90 days for inclisiran** between the last day of days' supply and the start of the next prescription

Study design



Inclusion criteria

- Patients were aged ≥18 years, had 12 months of continuous enrollment before the index date, 12 months continuous enrollment after the index date
- Patients had a first claim for newly initiated inclisiran, alirocumab or evolocumab in the identification period (January 1, 2022, to October 31, 2022)†

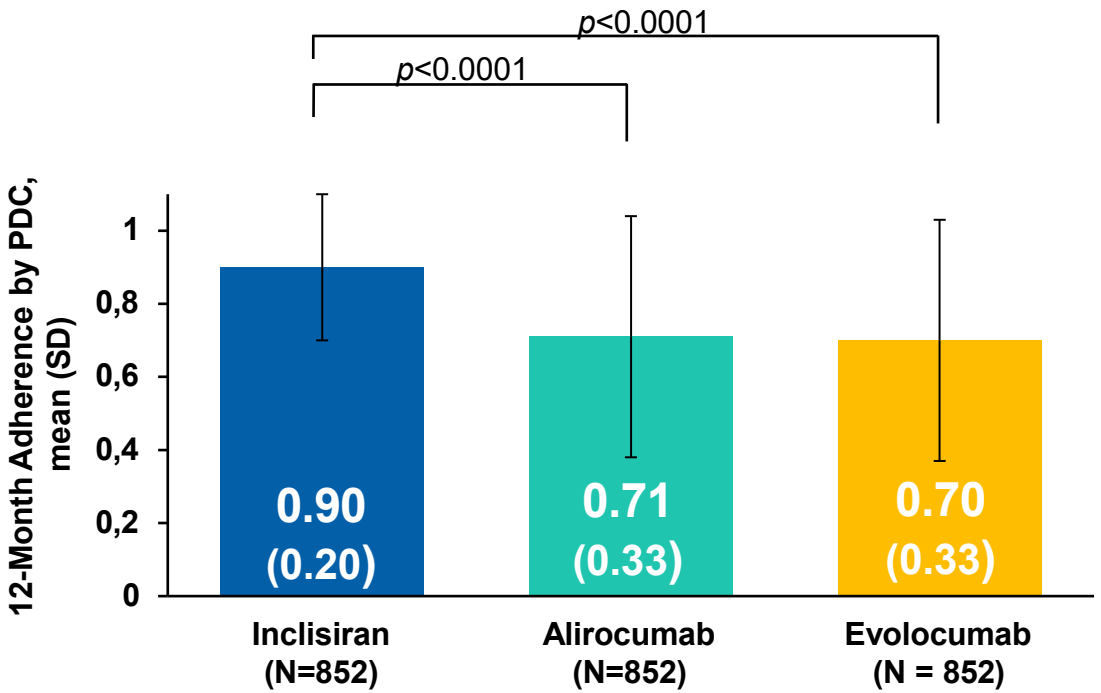
*The comparison pertains only to differences in adherence and persistence as defined by this analysis and should not be considered a comparison of safety or efficacy

PDC, proportion of days covered.
†Cohorts are mutually exclusive; the first claim determines which cohort the patient belongs to.
Niu X, et al. Poster presented at: National Lipid Association Scientific Sessions 2024; May 30–June 2, 2024. Las Vegas, NV. PO#158.

Komodo: **12-month adherence data* (1/2)**

12-month treatment adherence data

Adherence†



Adherence by subgroups

PDC, mean (SD)	Inclisiran (N=852)	Alirocumab (N=8878)	Evolocumab (N=27,171)
CAD only, n (%)	432 (50%)	3472 (39%)	11,402 (42%)
PDC, mean (SD)	0.90 (0.19)	0.73 (0.32)	0.73 (0.32)
PAD only, n (%)	25 (3%)	215 (2%)	772 (3%)
PDC, mean (SD)	0.88 (0.22)	0.71 (0.33)	0.70 (0.33)
CAD + PAD, n (%)	103 (12%)	717 (8%)	2353 (9%)
PDC, mean (SD)	0.91 (0.18)	0.70 (0.33)	0.70 (0.33)
IS/TIA, n (%)	19 (2%)	246 (3%)	784 (3%)
PDC, mean (SD)	0.92 (0.19)	0.69 (0.34)	0.68 (0.33)

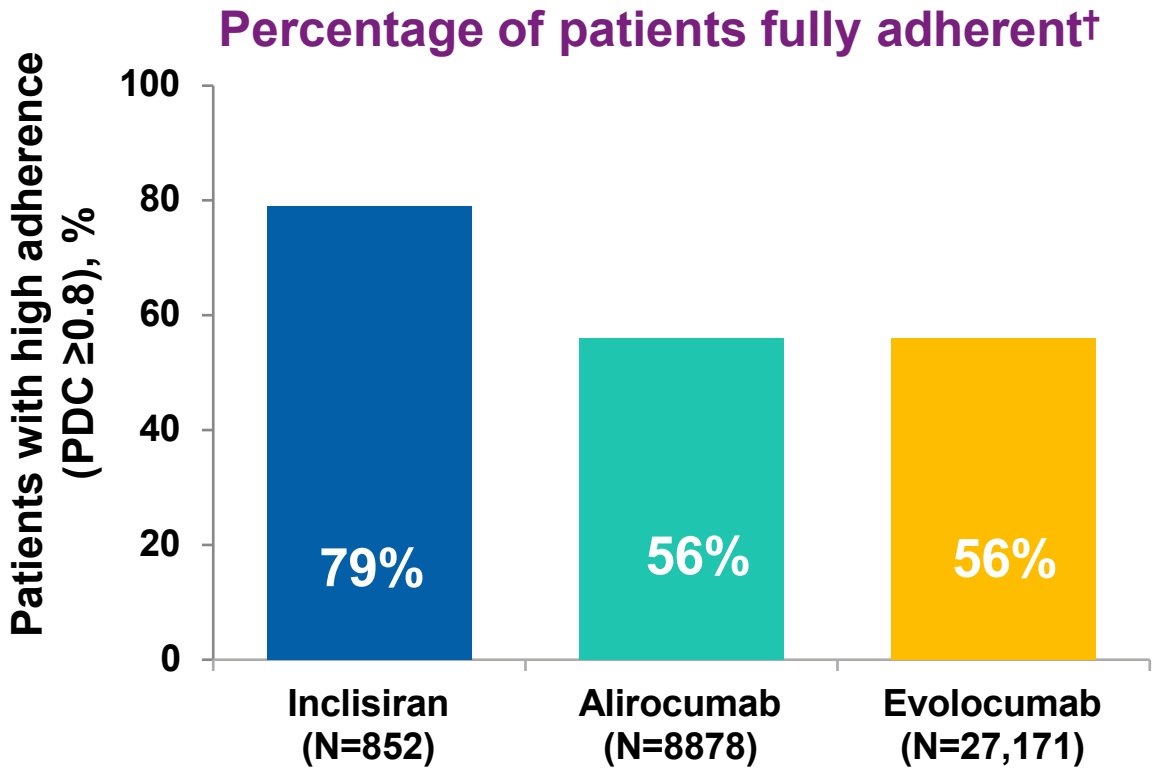
- High adherence were observed among patients with previous CAD, PAD or IS/TIA subgroups

*This comparison pertains only to differences in adherence as defined by this analysis and should not be considered a comparison of safety or efficacy.

CAD, coronary artery disease; IS, ischemic stroke; PAD, peripheral artery disease; PDC, proportion of days covered; TIA, transient ischemic attack.
†Propensity score-matched results; Propensity score matching was performed to adjust for the differences in baseline characteristics among cohorts. Niu X, et al. Poster presented at: National Lipid Association Scientific Sessions 2024; May 30–June 2, 2024. Las Vegas, NV. PO#158.

Komodo: **12-month adherence data* (2/2)**

12-month treatment adherence data

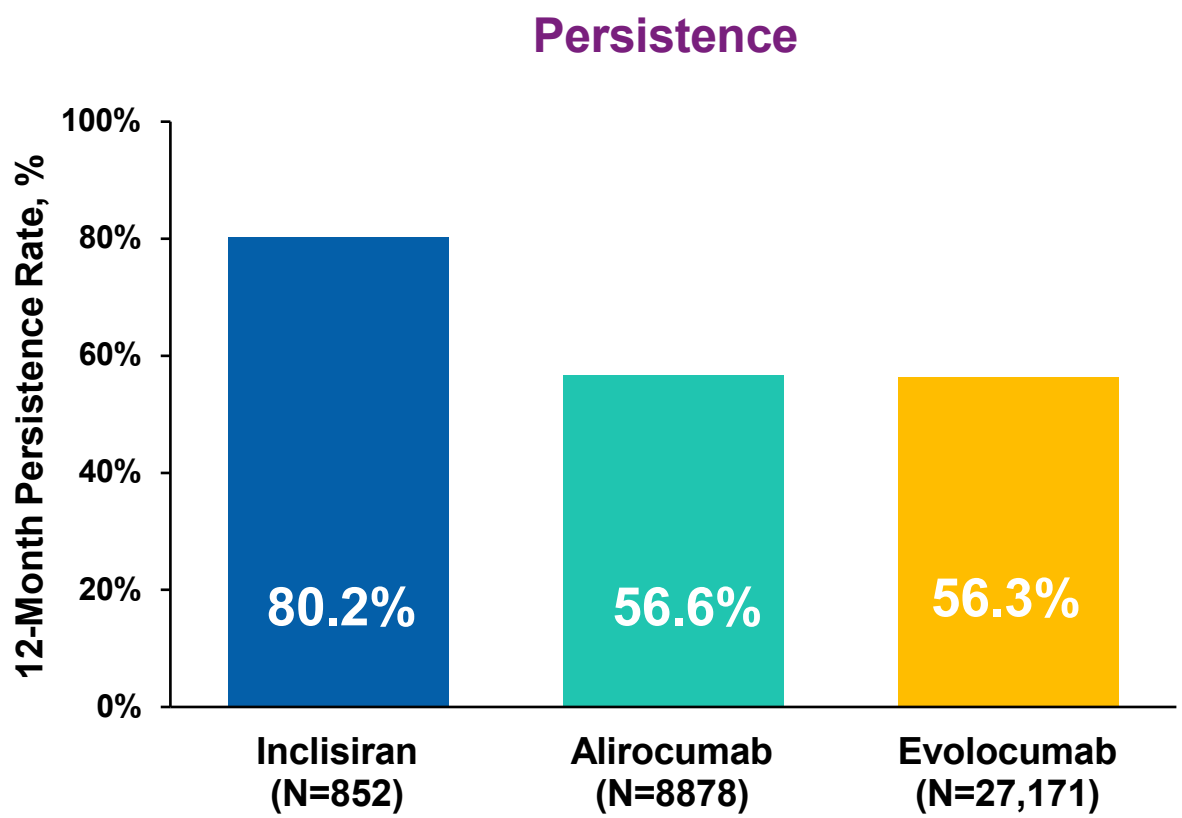


*This comparison pertains only to differences in adherence as defined by this analysis and should not be considered a comparison of safety or efficacy.

PDC, proportion of days covered.
†Adherence was defined as PDC: the number of days covered by the drug divided by the observational period (12 months after the index date). Fully adherent patients were defined as PDC ≥80%. PDC <80% was considered nonadherent.
Niu X, et al. Poster presented at: National Lipid Association Scientific Sessions 2024; May 30–June 2, 2024. Las Vegas, NV. PO#158.

Komodo: 12-month persistence data*

12-month treatment persistence data



Persistence was defined as ***patients who remained on therapy at month 12 without a gap of >60 days for alirocumab or evolocumab, and >90 days for inclisiran*** between the last day of days' supply and the start of the next prescription

*This comparison pertains only to differences in persistence as defined by this analysis and should not be considered a comparison of safety or efficacy.

Niu X, et al. Poster presented at: National Lipid Association Scientific Sessions 2024; May 30–June 2, 2024. Las Vegas, NV. PO#158.

Take home message

- Inclisiran non neutralizza PCSK9, ma ne inibisce la sintesi
- È efficace nel ridurre i livelli di C-LDL
- Ideale add-on alla terapia con statina ed ezetimibe
- Alta aderenza e persistenza terapeutica
- È un’altra arma per tentare di «eradicare» la malattia aterosclerotica