Current status and new possibilities in atherosclerotic cardiovascular disease prevention by targeting LDL-cholesterol

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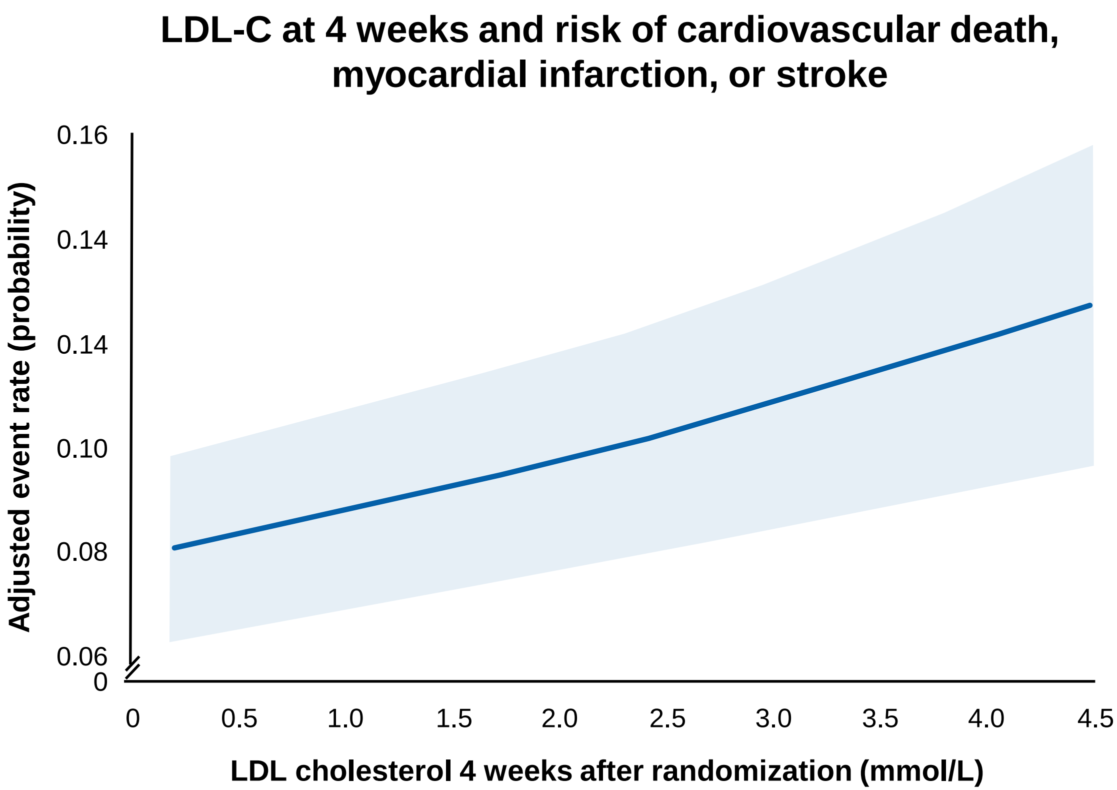
MEDICINSKI FAKULTET RIJEKA

KLINIČKI BOLNIČKI CENTAR RIJEKA

Intensive LDL-C lowering treatment beyond current recommendations prevents major vascular events



Used with permission. Giugliano RP, et al. *Lancet*. 2017;390(10106):1962-1971.

Prespecified secondary analysis from the FOURIER* trial (N=25,982)

Patients who achieved progressively lower LDL cholesterol concentrations at 4 weeks had progressively fewer cardiovascular events with no evidence of a plateau

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LDL-C reductions to as low as <0.5 mmol/L (<19 mg/dL) provided the greatest risk reduction of major CV event

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At median follow-up of 2.2 years, no safety concerns† were identified in subjects who achieved very low LDL-C levels

*The FOURIER (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) trial was a randomized, double-blind, trial assessing evolocumab vs placebo in 25,982 patients with stable atherosclerotic cardiovascular disease.
†Safety events assessed included: neurocognitive events (EBBINGHAUS study), new onset diabetes mellitus, cataract-related adverse events, new or progressive malignancy, and haemorrhagic stroke.

Giugliano RP, et al. *Lancet*. 2017;390(10106):1962-1971.

Recent European DA VINCI study confirms statins as the mainstay of lipid-lowering therapy

DA VINCI study overview

- Cross sectional study of patients receiving LLT between June 2017 and November 2018 across 18 European countries
- N=5888 (3000 primary prevention and 2888 secondary prevention)

Use of LTT

- **Statins were the mainstay of therapy**
  - 94% of primary prevention patients and 94% of patients with established ASCVD were on a statin
- **Most frequent regimen** across all risk categories was **moderate-intensity statins as monotherapy**
- Use of high-intensity statins: 22% in primary prevention and 42% in patients with ASCVD
- Combination therapy: ezetimibe in 9% of all patients on statins; PCSK9 inhibitors in 1% of all patients on statins and/or ezetimibe

Ray KK, et al. *Eur J Prev Cardiol*. 2020. zwaa047, https://doi.org/10.1093/eurjpc/zwaa047. https://academic.oup.com/eurjpc/advance-article/doi/10.1093/eurjpc/zwaa047/5898664. Accessed October 22, 2020.

DA VINCI study demonstrates current gaps in reaching 2016 and 2019 ESC/EAS LDL-C goals

Overall, **54%** attained overall risk-based **2016 goal**

– Low risk: 63%; moderate risk: 75%; high risk: 63%; very high risk: 39%

Only **33%** attained overall **2019 goal**

In patients with established **ASCVD, 2019 goal attainment was approximately half that of 2016** (18% vs 39%, respectively)

Potential reasons for failure to achieve ESC/EAS guideline recommended LDL-C values

- Lack of HCP familiarity with guidelines
- High cost of medications such as PCSK9 mAb inhibitors
- Patient reluctance to be treated with high-intensity LLT
- Concern about statin-related AEs

The authors concluded that **“even with optimized statins, greater utilization of non-statin LLT is likely needed to reduce these gaps for patients at highest risk”**

Ray KK, et al. *Eur J Prev Cardiol*. 2020.
zwaa047, https://doi.org/10.1093/eurjpc/zwaa047.
https://academic.oup.com/eurjpc/advance-article/doi/10.1093/eurjpc/zwaa047/5898664.
Accessed October 22, 2020.

Undertreatment with statins is common in patients recommended for therapy in the United States
Data from the PALM Registry*

	Treatment†		
	Not on statin	**Lower than recommended intensity**	**Treated appropriately**
Overall	25.3%	32.3%	42.4%
Indication			
Primary prevention	36.6%	27.3%	36.0%
Secondary prevention	16.4%	36.2%	47.3%

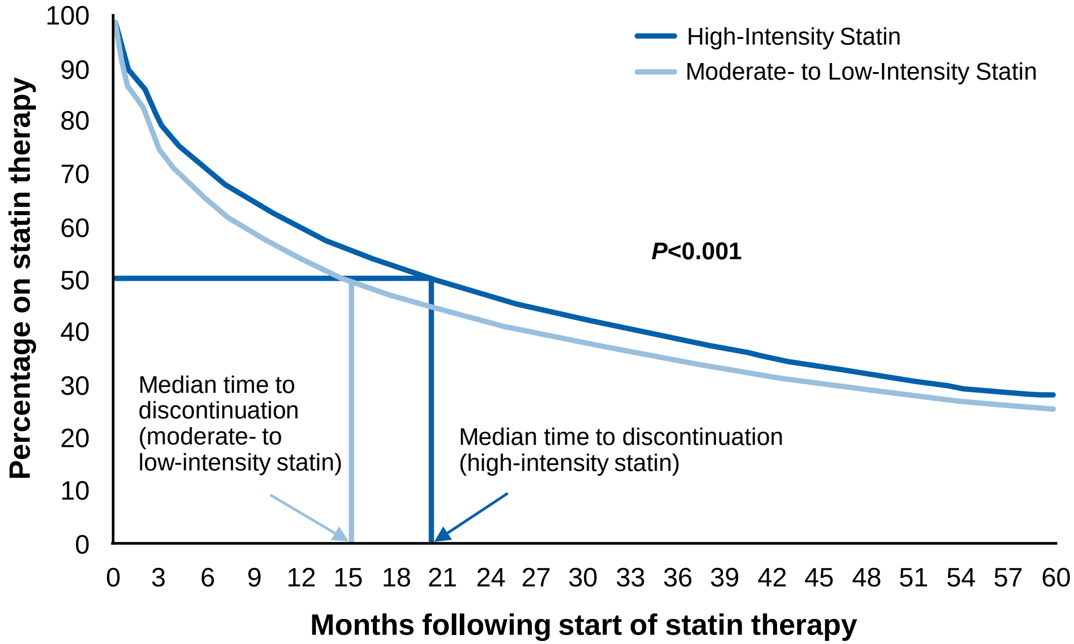
- In multivariate analysis
  - Factors associated with increased odds of receiving guideline recommended statin therapy include: male sex, increasing age, BMI ≥30 kg/m^2, diabetes, hypertension, and lower 10-year predicted ASCVD risk
  - Patients with CAD were more likely to receive guideline recommended statin therapy than those with other types of ASCVD (51.1% vs 34.9%, respectively)

*PALM (Patient and Provider Assessment of Lipid Management) registry: 7,938 patients from 140 cardiology, primary care, and endocrinology practices in the United States. The population is comprised of adults either on statins, at high risk of ASCVD, or with prior ASCVD.

†N=5,905 statin-eligible primary or secondary prevention patients from 138 PALM Registry practices.

Navar AM, Wang TY, Li S, et al. *Am Heart J*. 2017;193:84-92.

Most studies report statin discontinuation rates ≥50%[1]



Used with permission. . Lin I, et al. *J Manag Care Spec Pharm*. 2016;22(6):685-98.

53% of patients discontinued statin therapy during follow-up in a real-world retrospective study[2*]

15% of patients received high-intensity therapy and 85% of patients received moderate- to low-intensity therapy at index[†]

Median time to discontinuation was ~15 months

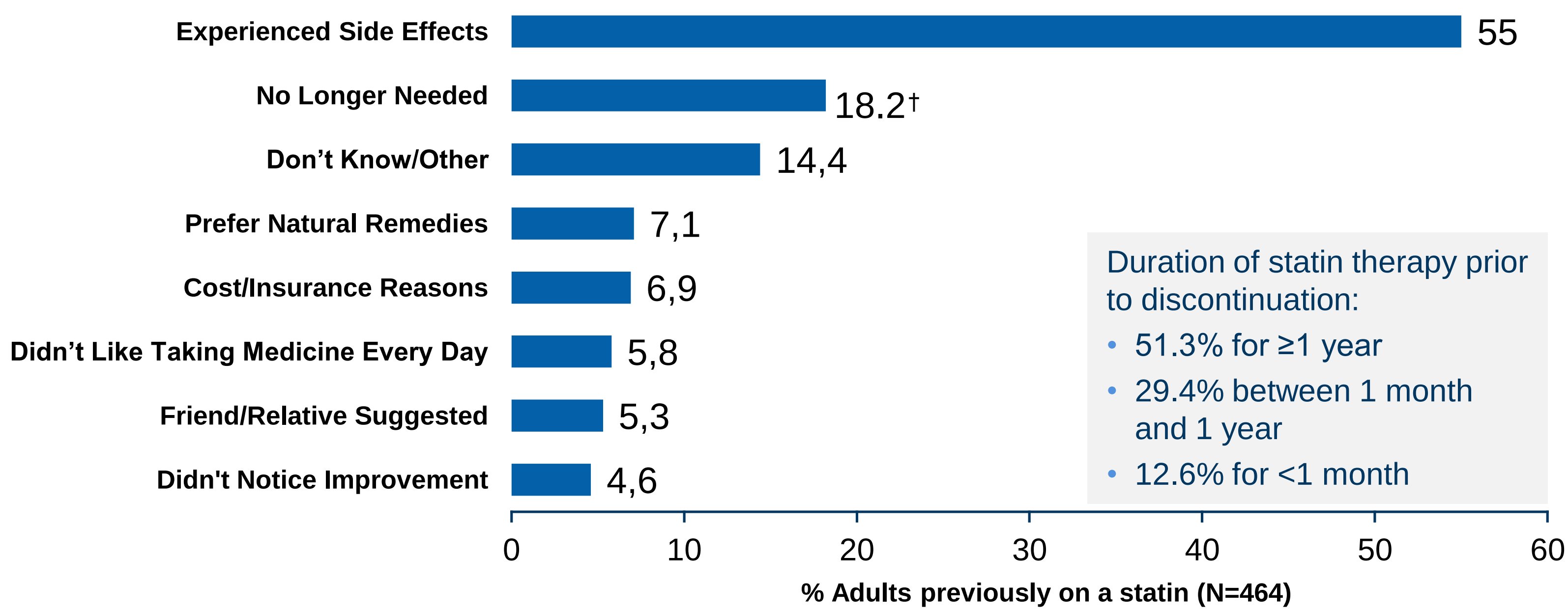
Index treatment with high-intensity therapy was associated with a longer median time to discontinuation and lower rates of discontinuation, 47.9% vs 53.9% compared with moderate- to low-intensity therapy (*P*<0.001)

*463,707 statin naive patients were identified from an analysis of almost 120 million patients in the Truven MarketScan and Medicare Supplemental databases (January 2007 through June 2013). †More than 20% of patients initially started with high-intensity therapy switched to moderate- to low-intensity therapy; 6.7% to 14.2% of patients starting with low-intensity therapy increased statin therapy during follow-up.

1. De Vera MA, et al. *Br J Clin Pharmacol.* 2014;78(4):684-698.
2. Lin I, et al. *J Manag Care Spec Pharm.* 2016;22(6):685-98.

Perceived side effects are the leading cause of statin discontinuation

Patient-reported reasons for statin discontinuation: insights from PALM registry*



*Among 5693 adults recommended for statin therapy in the PALM registry.

†Primary prevention patients were more likely than secondary prevention patients to state that the statin was no longer needed (23.4% vs 13.5%; *P*=0.007).

Bradley CK, et al. *J Am Heart Assoc*. 2019;8:e011765.

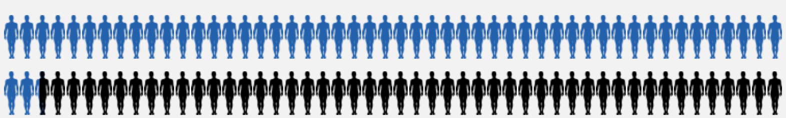
Therapy interruptions are observed with monoclonal antibodies directed against PCSK9

Retrospective analysis of 6151 patients from a commercial insurance database in the United States initiating PCSK9mAb inhibitors

52.2% of patients

experienced an interruption in PCSK9mAb inhibitor therapy of at least 30 days within 1 year of its initiation

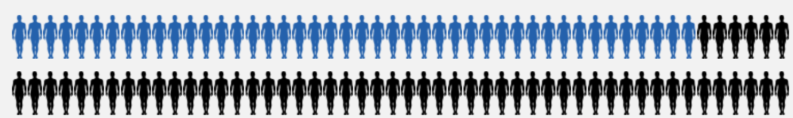
- **Only 63%** remained on a PCSK9mAb inhibitor 1 year after its initiation



44% of patients

experienced an interruption in all lipid-lowering therapy by 1 year of initiation of PCSK9mAb inhibitor

- **27%** were no longer on any lipid-lowering therapy 1 year after initiating a PCSK9mAb inhibitor



Rymer JA, et al. *J Am Heart Assoc*. 2020;9(9):e014347.

Treatment for cardiovascular disease can be burdensome

Predisposing factors for treatment burden associated with chronic illness have been identifed[1]

- Patient age
- Number of comorbidities
- Treatment characteristics:
  - Number of medications
  - Frequency of administration
  - Side effects
  - Perceived lack of efficacy

These factors may negatively impact adherence

A study group of 196 patients taking cardiovascular medications* for >1 year among which 65.8% of patients were retired and ~66% were taking ≥4 medications

35% reported an adverse impact on their social and daily lives[2]

*Patients 45+ years, predominantly of Dutch patients (89.8%); cardiovascular medications included antihypertensives, antihyperlipidemics, and anticoagulants.

1. Sav A, et al. *Health Expect.* 2015 Jun;18(3):312-324.
2. van der Laan DM, et al. *Int J Clin Pharm.* 2018;40(2):412-420.

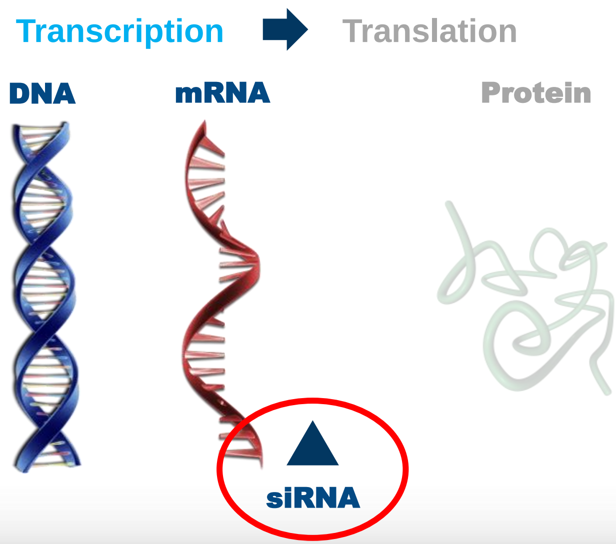
The unmet treatment needs

Gene-Protein synthesis inhibition

as a new promissing approach

RNA Therapeutics

Synthetic small RNA



In 2006, Andrew Fire and Craig Mello were awarded the Nobel Prize for Physiology or Medicine for their discovery of RNAi, initiating an era of RNA therapeutics (highly specific drugs)[1]

RNA therapeutics harness the natural biologic pathway of RNAi to regulate expression of specific genes[2]

Advances in RNA therapeutics focus on gene silencing using synthetic short ncRNA, including siRNA, to regulate and/or silence target genes[2,3]

Synthetic siRNA targets a unique mRNA nucleotide sequence and can theoretically target any gene of interest[2]

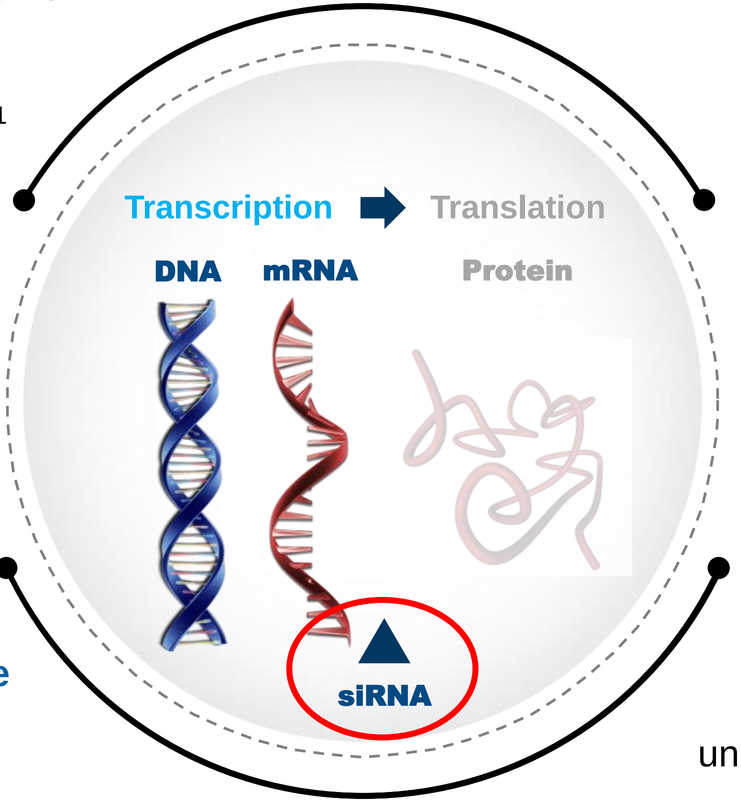
1. The Nobel Prize in Physiology or Medicine 2006. NobelPrize.org. https://www.nobelprize.org/prizes/medicine/2006/summary/.; 2. Lam JKW, et al. Mol Ther Nucleic Acids. 2015;4:e252; 3. Crooke ST, et al. Cell Metab. 2018;27:714-739

Gene-Protein Synthesis

Non-coding RNAs

Only **~2%** of the human genome encodes proteins while a significant portion codes for **non-coding RNAs** (ncRNA)[1]

Small interfering RNAs (siRNA) are short double-stranded ncRNAs that function in gene silencing[2,3]



ncRNAs are involved in **gene regulation**, RNA maturation and protein synthesis[1]

siRNAs prevent protein synthesis by degrading unique target mRNA through a natural mechanism called RNA interference[2,3]

1. Aryal and Suarez. Vascul Pharmacol. 2019;114:64-75; 2. Lam JKW, et al. Mol Ther Nucleic Acids. 2015;4:e252; 3. Wilson RC and Doudna JA. Annu Rev Biophys. 2013;42:217-239

RNA Therapeutics

Synthetic small RNA: Delivery mechanisms

GalNAc Conjugates[1,2]

- Trivalent *N*-Acetylgalactosamine (GalNAc) conjugated to siRNA mediate hepatocyte uptake through interactions with the asialoglycoprotein receptor (ASGPR, which is abundantly expressed in hepatocytes), causing durable whole-liver gene knockdown without adjunct toxicity
- The acidic pH in the endosome results in ASGPR dissociation and recycling back to the surface
- The GalNAc conjugate also offers some protection against liver exonucleases

Lipid Nanoparticles[1]

- Lipid nanoparticles (LNPs) are comprised of PEGylated lipids, cholesterol and nucleic acids
- LNPs associate with apolipoproteins in circulation which mediate endocytosis by hepatocytes
- The acidic pH in the endosome contributes to release of internal cargo

Liposomes[3,4]

- Liposomes are characterized by a lipid bilayer, mainly comprising phospholipids, surrounding an aqueous core
- Cationic liposomes facilitate intracellular and endosomal uptake through interactions with anionic components

1. Wittrup J and Lieberman J. Nat Rev Genet. 2015;16:543-552; 2. Data on file. Inclisiran. Investigator's Brochure. Novartis Pharmaceuticals Corp; 2018; 3. Barba AA, et al. Pharmaceutics. 2019;11:360; 4. Schroeder A, et al. J Intern Med. 2010;267:9-21

What is inclisiran?

Small interfering RNA

- Synthetic small interfering RNA (siRNA) conjugated with triantennary GalNAc carbohydrate[1,2]
- Utilizes the natural RNA interference mechanism to prevent translation of PCSK9 by degradation of *PCSK9* mRNA[2]

Chemical Modifications[3,4]

- 2′-fluoro and 2′-O-methyl modifications to **increase compound stability**
- Backbone phosphodiester linkages modified with phosphorothioates **to protect from degradation** by liver exonucleases
- Triantennary GalNAc conjugation for **targeted hepatic delivery**

Inclisiran

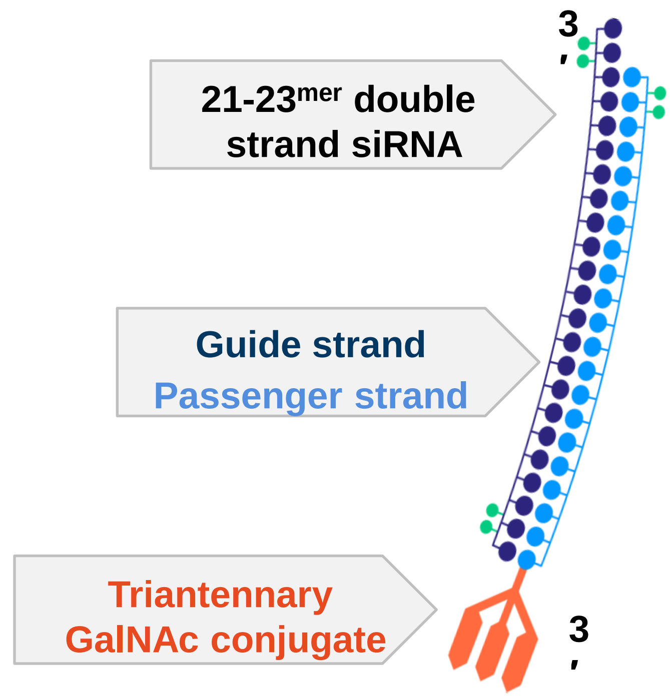
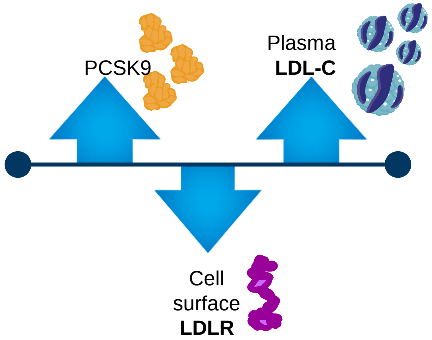


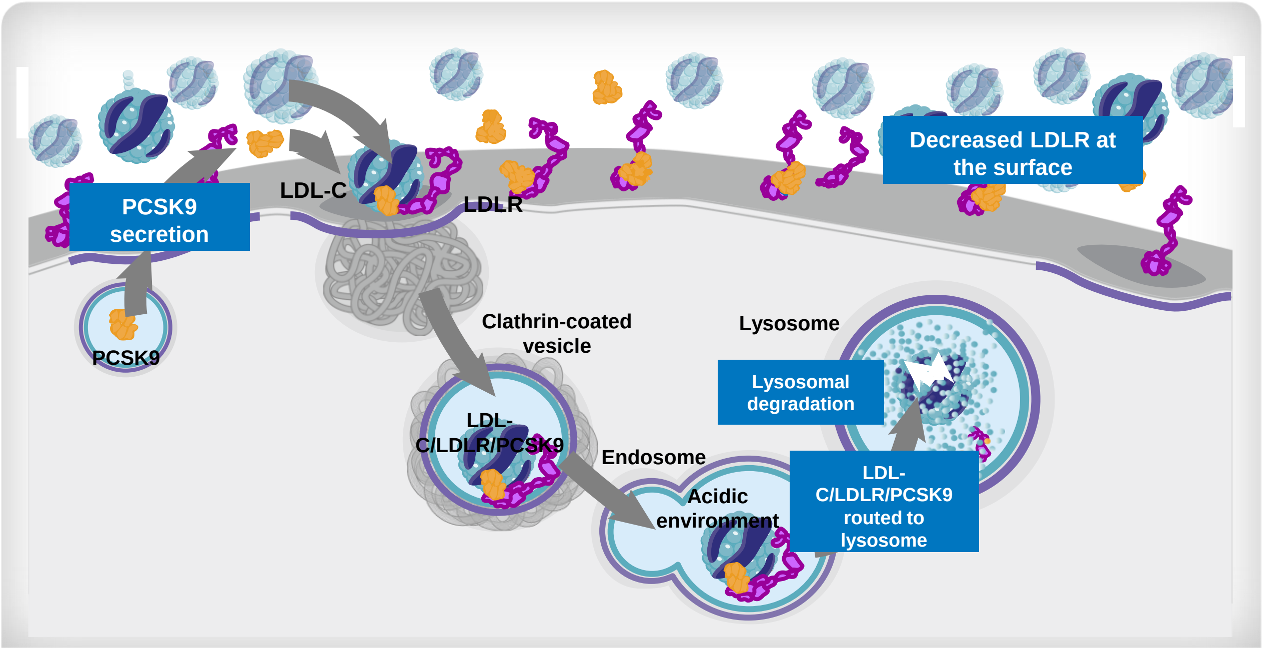
Figure from Wright RS, et al. 2020[5]

1. Wang N, et al. Circ Res. 2017;120:1063-1065; 2. Fitzgerald K, et al. N Engl J Med. 2017;376:41-51
3. Data on file. Inclisiran. Investigator's Brochure. Novartis Pharmaceuticals Corp; 2018; 4. Khorova A, et al. N Engl J Med. 2017;376:4-7; 5. Wright RS, et al. Presented at ACC 2020, 28-30 Mar 2020, Chicago, USA

Regulation of LDL-C by LDLR and PCSK9

- PCSK9 is primarily secreted in the liver and in trace amounts in the small intestine, kidney and brain, in response to cholesterol, metabolic state and dietary nutrients[1]
- Following hepatocyte secretion, PCSK9 binds to LDLR on the surface concurrently with LDL-C, initiating internalization by endocytosis[2]
- The acidic pH in the endosome increases binding affinity of PCSK9 for LDLR and the entire complex undergoes degradation in the lysosome[3]
- LDLR is not recycled, resulting in reduced LDLR concentration on the surface and increased levels of circulating LDL-C[2,3]





1. Krysa JA, et al. J Nutr. 2017;147:473-481; 2.Qian YW, et al. J Lipid Res. 2007;48:1488-1498; 3; Zhang DW, et al. J Biol Chem. 2007;282:18602-18612

*Studies carried out in a hamster model

ORION development program through ORION-12

	Trials	Relevant endpoints	Patients selected (number)	Expected start time
Pivotal trials	ORION-4	Cardiovascular M&M (Phase III)	HRASCVD or ASCVD RE (N=15,000)	Q2 2018
	ORION-5	LDL-C lowering (Phase III)	HoFH (N=60)	Q2/3 2018
	ORION-9	LDL-C lowering (Phase III)	HeFH (N=400)	Ongoing
	ORION-10	LDL-C lowering (US) (Phase III)	ASCVD (N=1,500)	Ongoing
	ORION-11	LDL-C lowering (EU) (Phase III)	ASCVD or ASCVD RE (N=1,500)	Ongoing
Extension trials	ORION-3	LDL-C lowering (extension of ORION-1)	ASCVD or ASCVD RE or HeFH (N=490)	Ongoing
	ORION-8	LDL-C lowering (extension of ORION -9, -10, -11)	ASCVD, ASCVD risk equivalent, HeFH (N=3,460)	Q4 2019
Supportive trials	ORION-1	LDL-C lowering (Phase II)	ASCVD or ASCVD RE or HeFH (N=501)	Completed
	ORION-2	LDL-C lowering (Phase II)	HoFH (N=10)	Ongoing
Special populations studies	ORION-6	Pharmacokinetics	Hepatic impairment (N=24-32)	Q2 2018
	ORION-7	Pharmacokinetics	Renal impairment (N=31)	Ongoing
	ORION-12	TQT	Healthy volunteers (N=200)	Q1/2 2018

Phase 3 ORION-9, -10, and -11

Study inclusion/exclusion criteria

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).

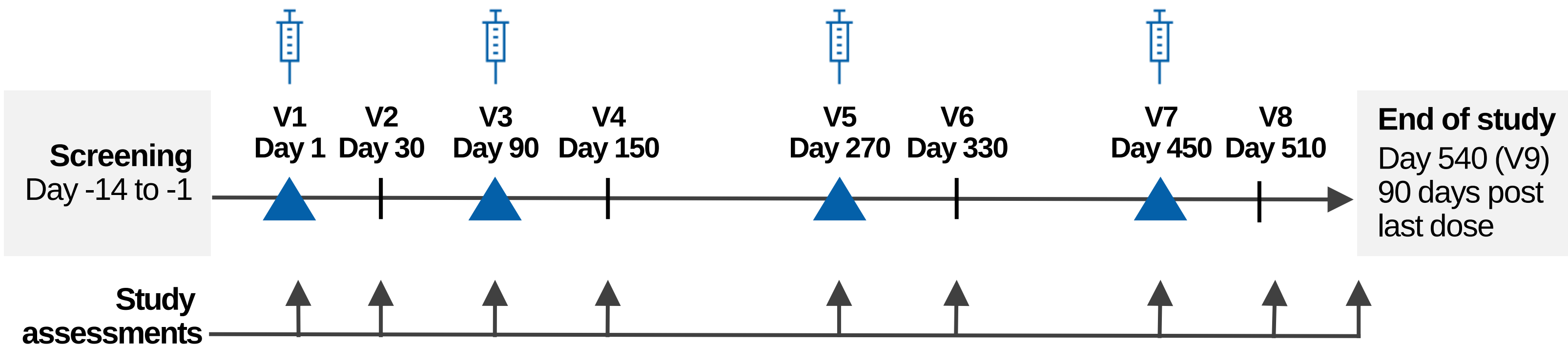
1. Raal FJ, et al. *N Engl J Med.* 2020;382(16):1520-1530. **2.** Raal FJ, et al. [supplementary appendix]. *N Engl J Med.* 2020;382:1520-1530. doi: 10.1056/NEJMoa1913805. **3.** Ray KK, et al. *N Engl J Med.* 2020;382(16):1507-1519. **4.** Ray KK, et al. [supplementary appendix]. *N Engl J Med.* doi: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

Phase 3 ORION-9, -10, and -11

Study design and endpoints[1-4]

18-month, double-blind, randomized, placebo-controlled

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.

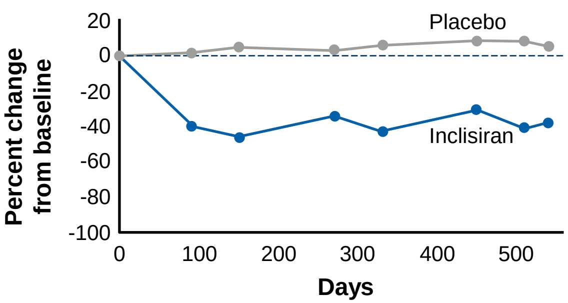
Phase 3 ORION-9, -10, and -11

Inclisiran provides effective and sustained LDL-C lowering over 18 months

Percent change in LDL-C over time

ORION-9[1]

Change in LDL cholesterol

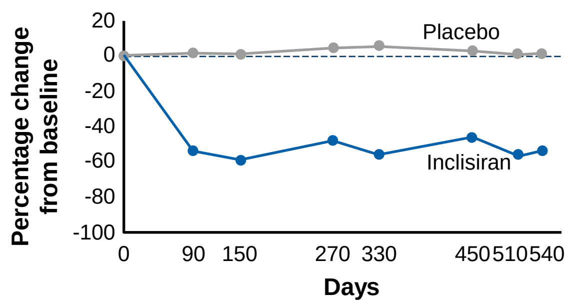


No. of patients

Placebo	240	237	238	235	233	233	229	232
Inclisiran	242	240	239	240	237	237	231	232

ORION-10[2]

Percentage change in LDL cholesterol

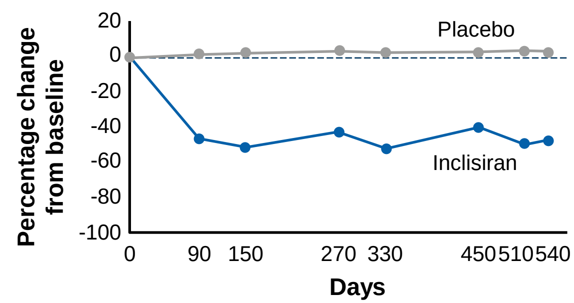


No. of patients

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

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.

Pharmacokinetic properties of inclisiran

Safety, pharmacology and toxicology

- No drug interactions expected[1]
- Co-administration with atorvastatin was not associated with exacerbated toxicities*[1]
- No dose-limiting toxicities*[2]
- Not genotoxic or carcinogenic*[1,2]
- No off-target effects observed*[1]
- No effect on fertility or embryonic development*[1]
- No dose adjustment necessary for patients with renal or hepatic impairment[2]
- Adverse events:

  Clinically relevant injection site reactions in ~5% of participants, including pain, erythema and rash[1]

*Testing was carried out *in vitro* or using animal models

1. Data on file. Inclisiran. Investigator's Brochure. Novartis Pharmaceuticals Corp; 2018; 2. Data on file. Inclisiran. Core Data Sheet. Novartis Pharmaceuticals Corp; 2020

Inclisiran treatment

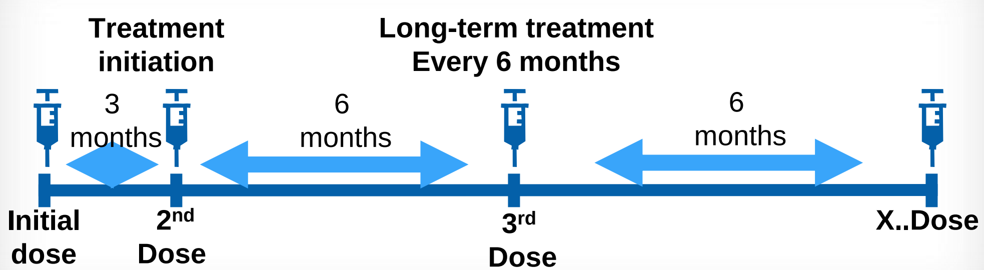
Dose & administration

Injection[1,2]

1.5 mL solution per syringe

- 300 mg inclisiran sodium*
- Water as the diluent
- Sodium hydroxide and phosphoric acid (pH 7)
- Stored at room temperature

Dose regimen[1,2]

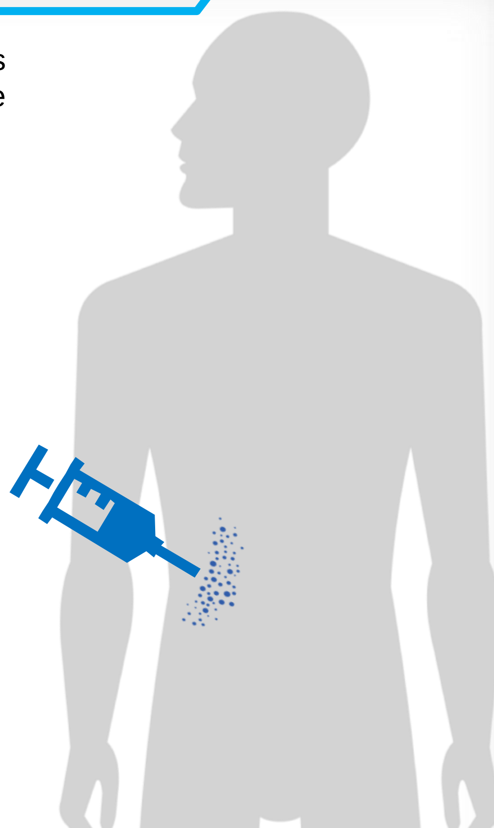


Development[1]

Under clinical investigation in the **ORION development program** to determine efficacy, safety and tolerability

Administration[1,2]

Subcutaneous injection in the abdomen by healthcare professionals



*equates to 284 mg inclisiran

1. Data on file. Inclisiran. Investigator's Brochure. Novartis Pharmaceuticals Corp; 2018; 2. Data on file. Inclisiran. Core Data Sheet. Novartis Pharmaceuticals Corp; 2020

EMA inclisiran approval

December, 2020

Inclisiran is approved for the treatment of adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet:

- ✓ in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximally tolerated dose of a statin,

or

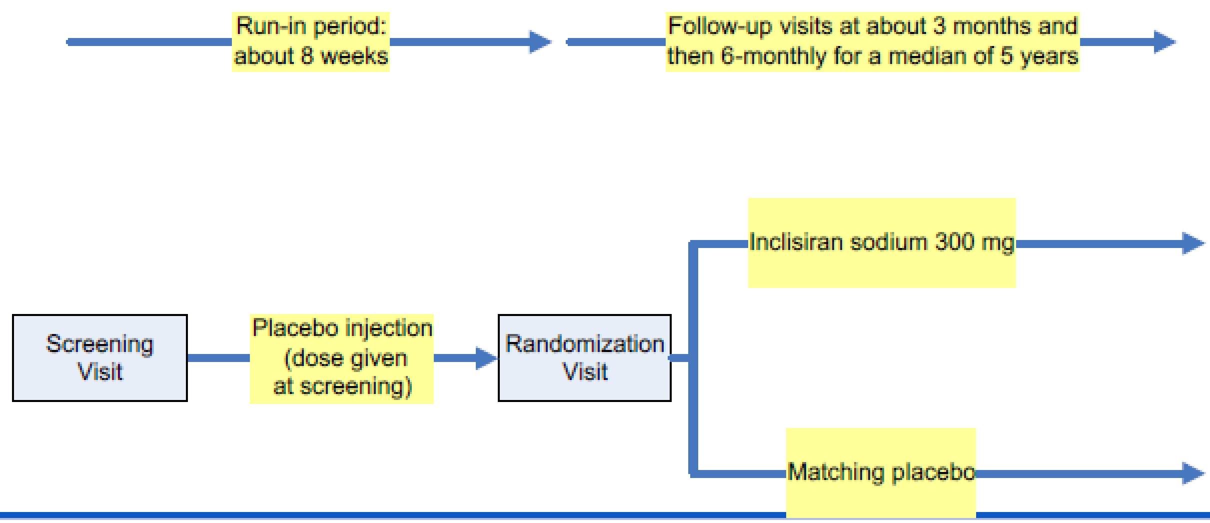
- ✓ alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

ORION-4

Long term cardiovascular outcomes study

Study Aims

- To assess the effect of inclisiran on major cardiovascular events
- The study will randomize ≥15,000 participants aged ≥55 years with pre-existing cardiovascular disease between inclisiran sodium 300 mg and matching placebo for a median of about 5 years.



Conclusions

Inhibition of PCSK9 with inclisiran is a very promising, and potentially the simplest and most effective approach to further reducing LDL-C, the cause of atherosclerosis:

- ✓ LDL-C variability within individuals is practically eliminated
- ✓ Injection burden reduced substantially
- ✓ Sustained effect between infrequent injections
- ✓ Opportunity to improve patient adherence