



PRESENT
AND FUTURE
APPROACHES TO
THE CONTROL OF
DYSLIPIDAEMIAS

S.I.Te.C.S.
SOCIETÀ ITALIANA DI TERAPIA CLINICA E SPERIMENTALE

PCSK9 inhibitors

Michel Farnier

*University of Bourgogne Franche-Comté and
Department of Cardiology, CHU Dijon-Bourgogne, Dijon, France*

Disclosure of potential conflicts of interest

Michel Farnier - University of Bourgogne Franche-Comté and Department of Cardiology, CHU Dijon-Bourgogne, Dijon, France

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PCSK9 inhibitors

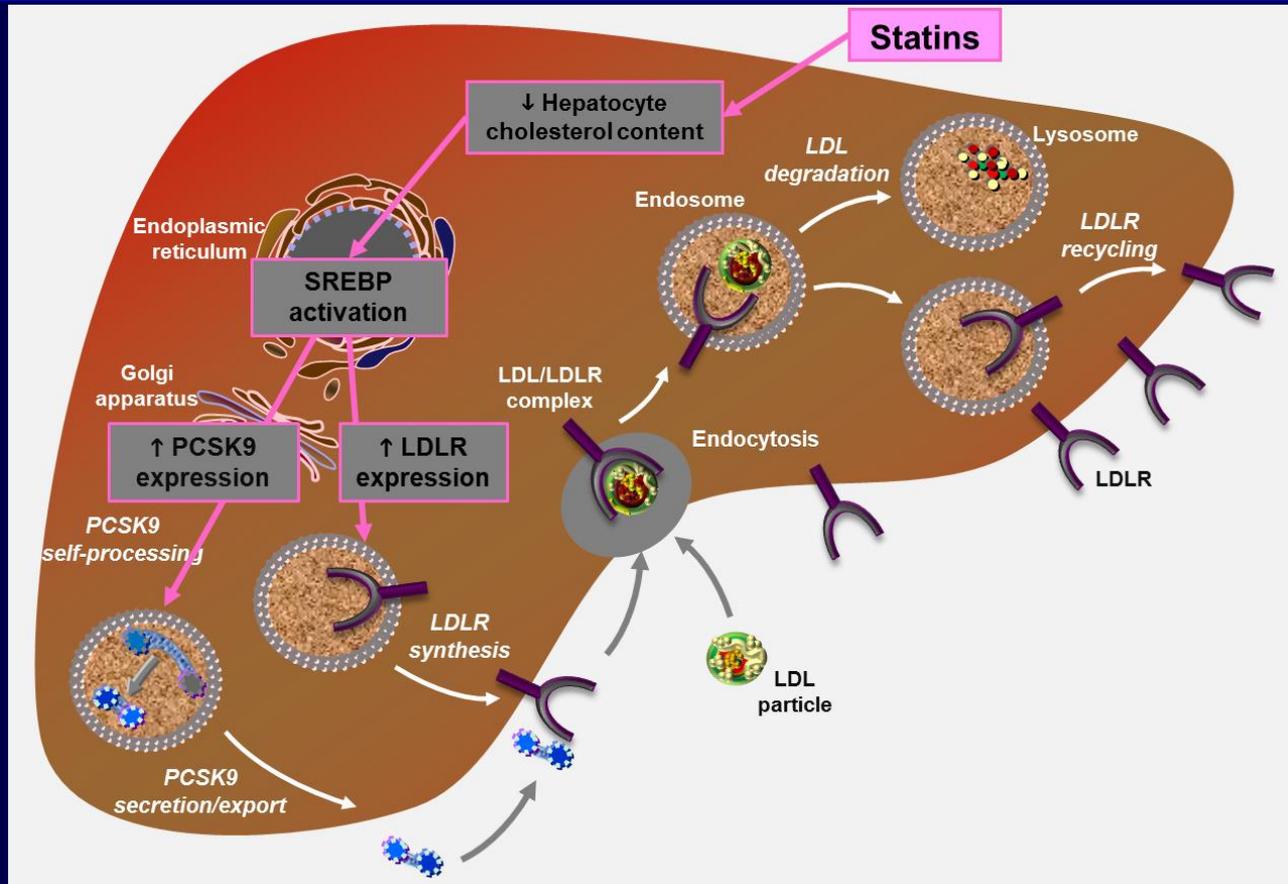
- ✧ Role of PCSK9 in LDL metabolism
- ✧ PCSK9 inhibitors : Monoclonal Antibodies (mAbs)
 - Alirocumab
 - Evolocumab
- ✧ PCSK9 inhibitors : Other strategies
 - Inclisiran
 - LIB003

Genetic variants of PCSK9 demonstrate its importance in regulating LDL levels

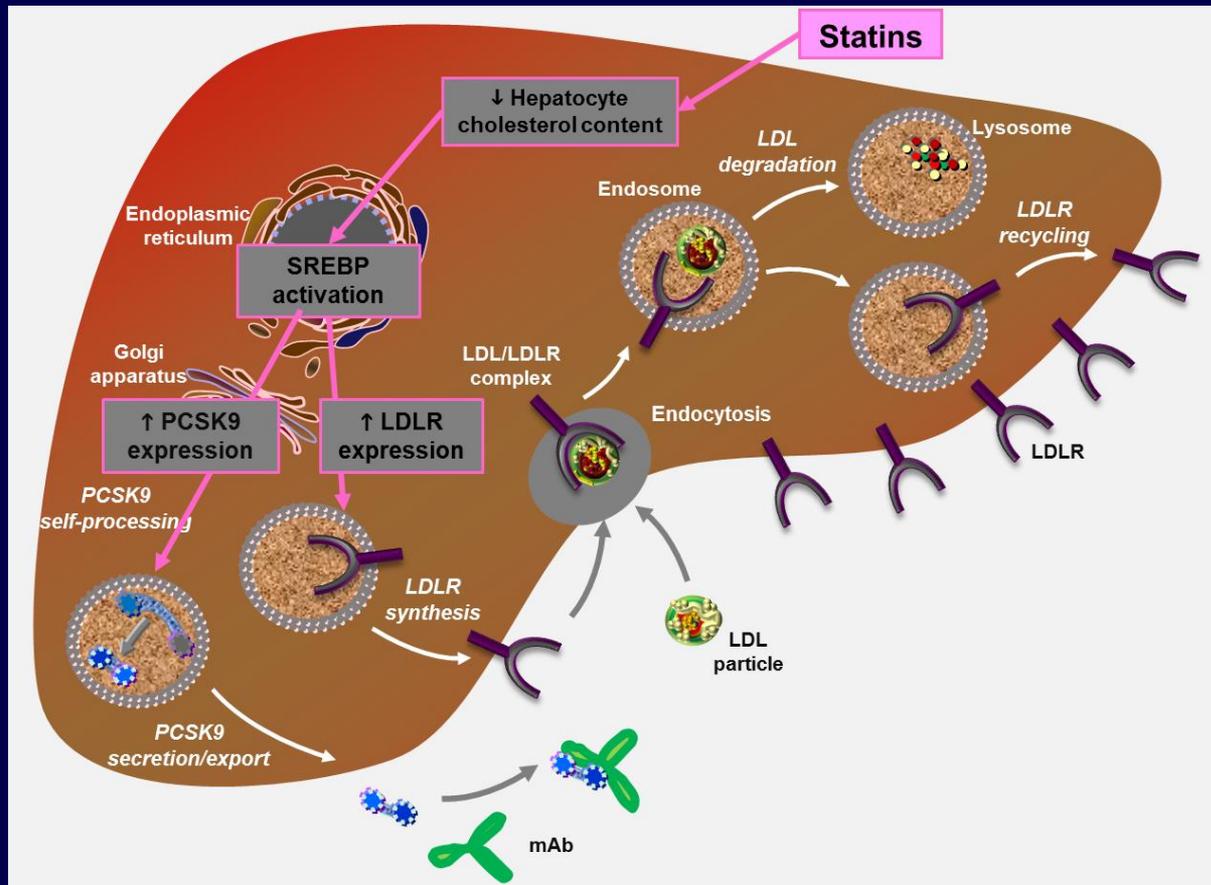
- PCSK9 GOF → fewer LDL-Rs (rare)
- PCSK9 LOF → more LDL-Rs (more common)

↓ PCSK9 ⇒ ↑ LDL-R ⇒ ↓ LDL-C

Regulation of the hepatocyte LDL Receptor



PCSK9 inhibitors monoclonal antibodies



PCSK9 inhibitors

⊠ Role of PCSK9 in LDL metabolism

⊠ PCSK9 inhibitors : Monoclonal Antibodies (mAbs)

- Alirocumab
- Evolocumab

⊠ PCSK9 inhibitors : Other strategies

- Inclisiran
- LIB003

PCSK9 inhibitors : Monoclonal Antibodies (mAbs)

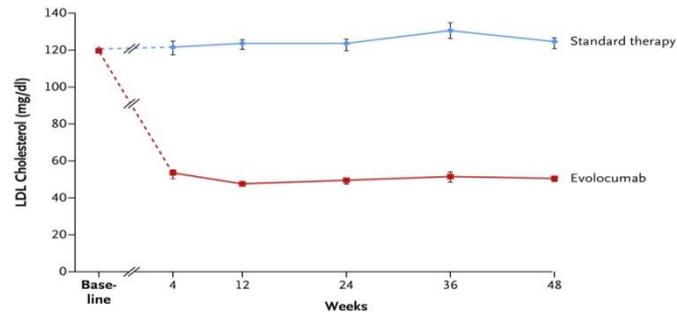
- ▶ ▶ Opportunities and barriers for a successful clinical utilisation
- ▶ ▶ Routine clinical practice :
 - ▶ What guidelines tell us ?
 - ▶ What are the priorities ?

PCSK9 inhibitors : Opportunities for the successful clinical utilisation

- ⊗ Further reduction of LDL-C by an average of 50% to 60%

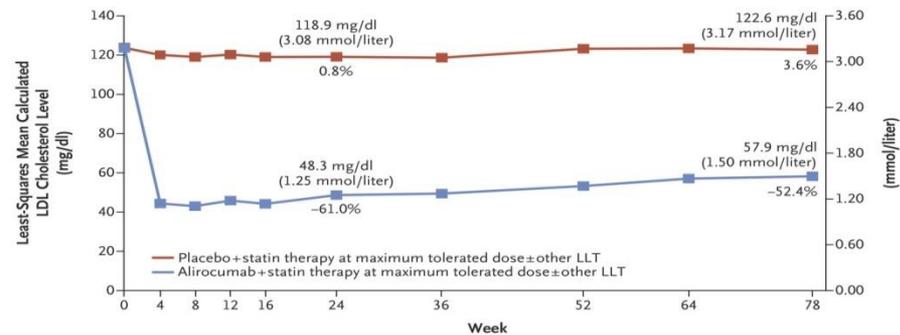
Alirocumab and Evolocumab produce dramatic and sustained LDL reductions

OSLER Trial LDL Cholesterol Levels with Evolocumab vs standard of care



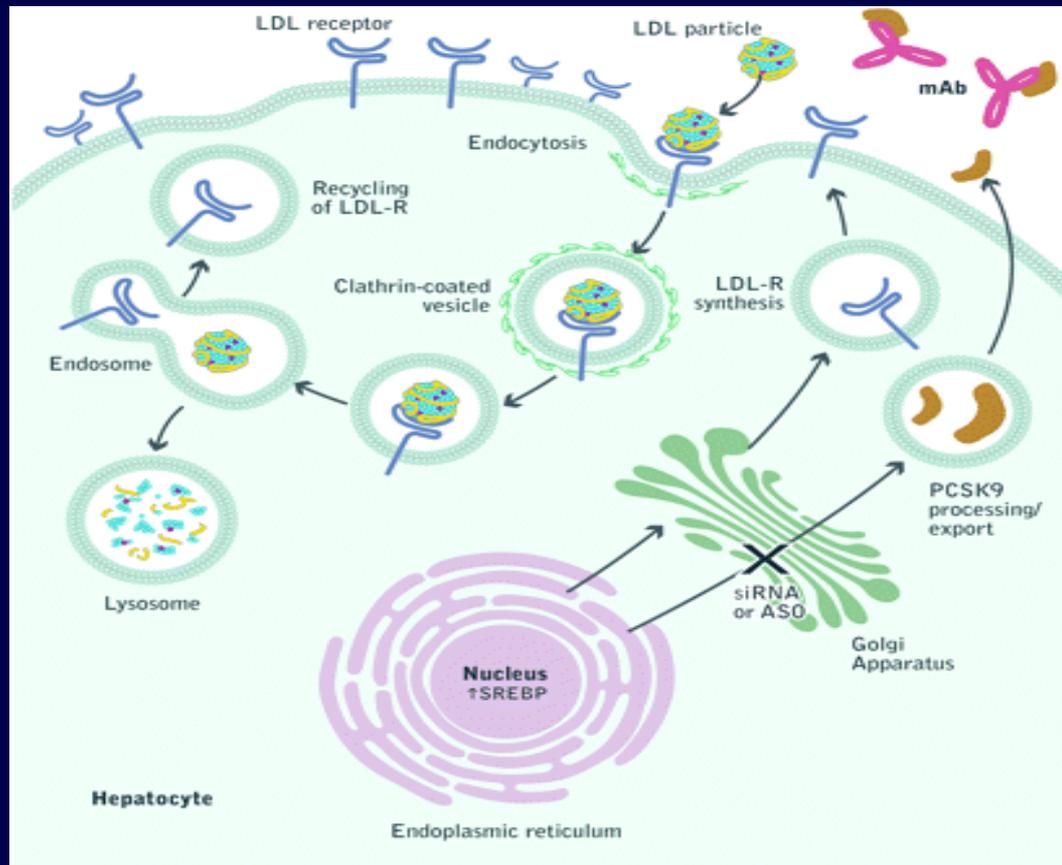
No. at Risk	Base-line	4	12	24	36	48
Standard therapy	1489	394	1388	1376	402	1219
Evolocumab	2976	864	2871	2828	841	2508
Absolute reduction (mg/dl)		60.4	73.4	70.4	72.7	70.5
Percentage reduction		45.3	60.9	58.8	54.0	58.4
P value		<0.001	<0.001	<0.001	<0.001	<0.001

ODYSSEY long term Alirocumab vs placebo, on top of statin therapy Calculated LDL Cholesterol Levels over Time (Intention-to-Treat Analysis).



No. of Patients with Data Available	0	4	8	12	16	24	36	52	64	78
Placebo	780	754	747	746	716	708	694	676	659	652
Alirocumab	1530	1473	1458	1436	1412	1386	1359	1349	1324	1269

Monoclonal Antibodies to PCSK9 Phase III results

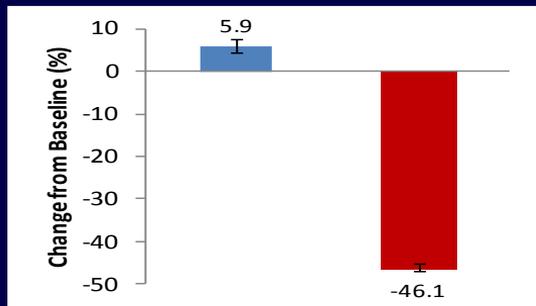


Effective :

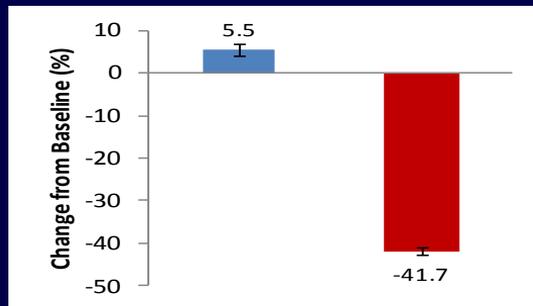
- ▶ in heterozygous FH (reduced LDL-R activity)
- ▶ in homozygous FH (LDL-R defective)
- ▶ as statin add-on
- ▶ in statin intolerance
- ▶ as monotherapy

Other Lipid Parameters

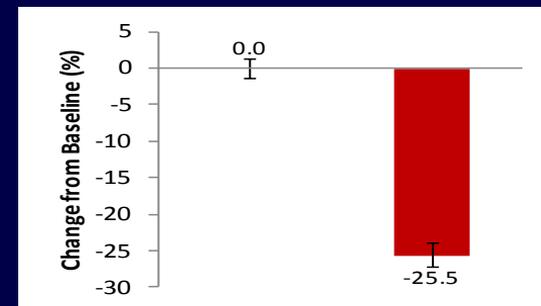
52% ↓ in Non-HDL-C



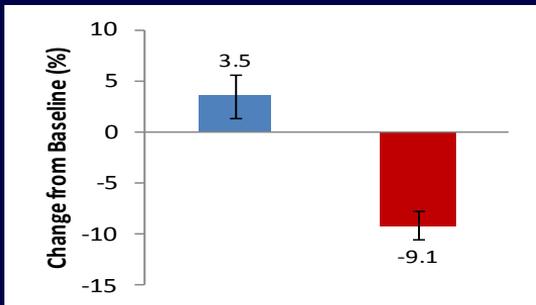
47% ↓ in ApoB



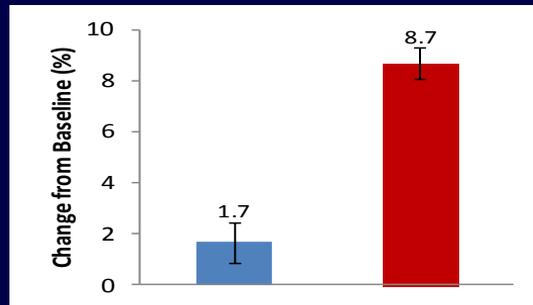
26% ↓ in Lp(a)



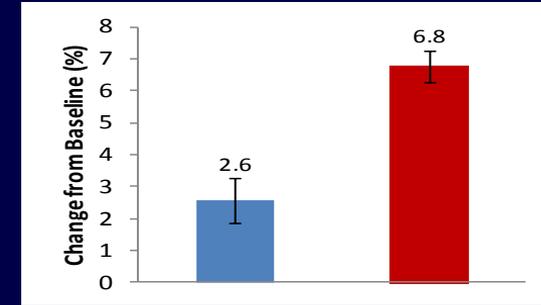
13% ↓ in Triglycerides



7% ↑ in HDL-C



4% ↑ in ApoA1



Week 12 data; values are means except for TG and Lp(a) which are medians

■ Evolocumab plus standard of care ■ Standard of care alone

PCSK9 inhibitors : Opportunities for the successful clinical utilisation

- ⊗ Further reduction of LDL-C by an average of 50% to 60%
- ⊗ Further reduction of the risk of CV events

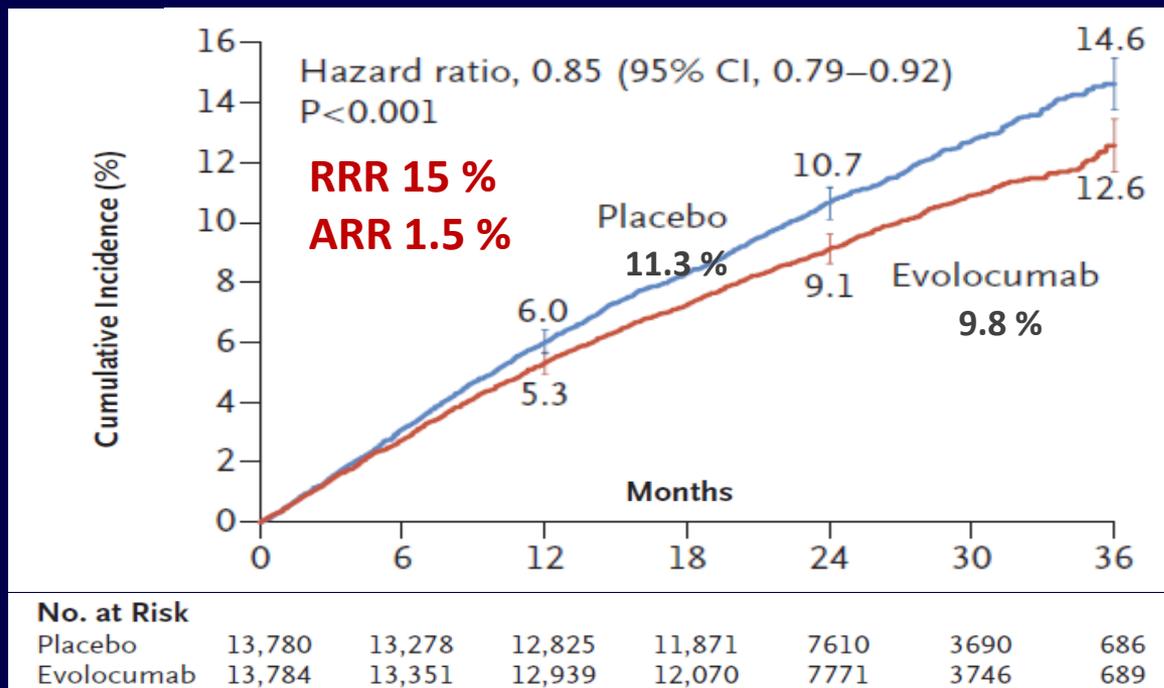
FOURIER trial

- 27,564 stable patients with established CV disease [prior MI (81%), prior stroke (19%), or symptomatic PAD (13%)]
- 69% on high-intensity statins
- LDL-C \geq 70 mg/dL or non-HDL-C \geq 100 mg/dL
- Randomized to evolocumab Q2W (or Q4W) vs placebo
- Median follow-up 2.2 years

Cumulative incidence of CV events

Primary Efficacy Endpoint

(cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)

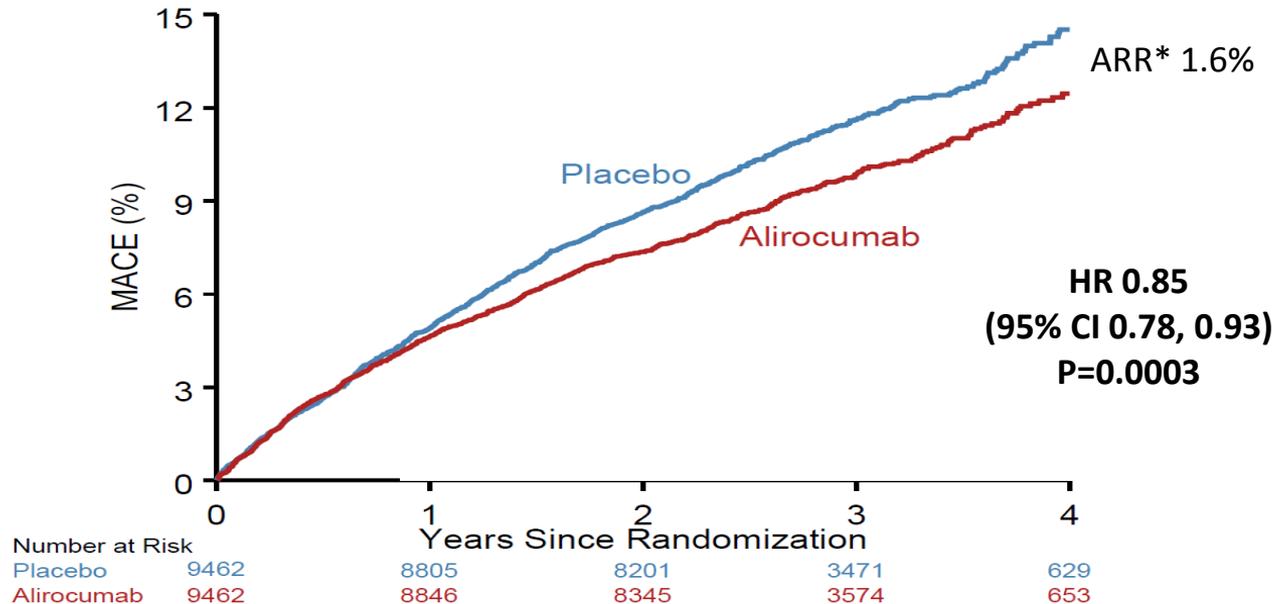


ODYSSEY Outcomes trial

- 18,924 subjects 1-12 months post-ACS (median time 2.6 months)
- 89% on high-intensity statins for ≥ 2 wks
- LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL or apoB ≥ 80 mg/dL
- Randomized to alirocumab Q2W vs placebo
- LDL-C target 25-50 mg/dL
- Median follow-up 2.8 years

Primary Efficacy Endpoint: MACE

MACE: CHD death,
non-fatal MI,
ischemic stroke, or
unstable angina requiring
hospitalization



* Based on cumulative incidence

PCSK9 inhibitors are safe

FOURIER: Evolocumab^[a]

Outcome	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Adverse events-no. of patients, %		
Any	77.4	77.4
Serious	24.8	24.7
Thought to be related to the study agent and leading to discontinuation of study regimen	1.6	1.5
Injection-site reaction	2.1	1.6
Allergic reaction	3.1	2.9
Muscle-related event	5.0	4.8
Rhabdomyolysis	0.1	0.1
Cataract	1.7	1.8
Adjudicated case of new-onset diabetes	8.1	7.7
Neurocognitive event	1.6	1.5

ODYSSEY Outcomes: Alirocumab^[b]

Variable	Alirocumab (N = 9451)	Placebo (N = 9443)
Adverse events-no. of patients, %		
Any adverse event	75.8	77.1
Serious adverse event	23.3	24.9
Adverse event that led to death	1.9	2.4
Adverse event that led to discontinuation of the trial regimen	3.6	3.4
Local injection-site reaction	3.8	2.1
General allergic reaction	7.9	7.8
Diabetes worsening or diabetic complication among patients with diabetes at baseline, %	18.8	21.2
New onset diabetes among patients without diabetes at baseline, %	9.6	10.1
Neurocognitive disorder	1.5	1.8
Hepatic disorder	5.3	5.7
Cataracts	1.3	1.4
Hemorrhagic stroke, adjudicated	< 0.1	0.2

a. Sabatine et al. *N Engl J Med* 2017; 376: 1713-1722

b. Schwartz et al. *N Engl J Med* 2018; 379: 2097-2107

FOURIER Study: adverse events

Adverse events, n(%)	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Any	10,664 (77.4)	10,644 (77.4)
Serious	3 410 (24.8)	3 404 (24.7)
Though to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201(1.5)
Injection site reactions *	296 (2.1)	219 (1.6)

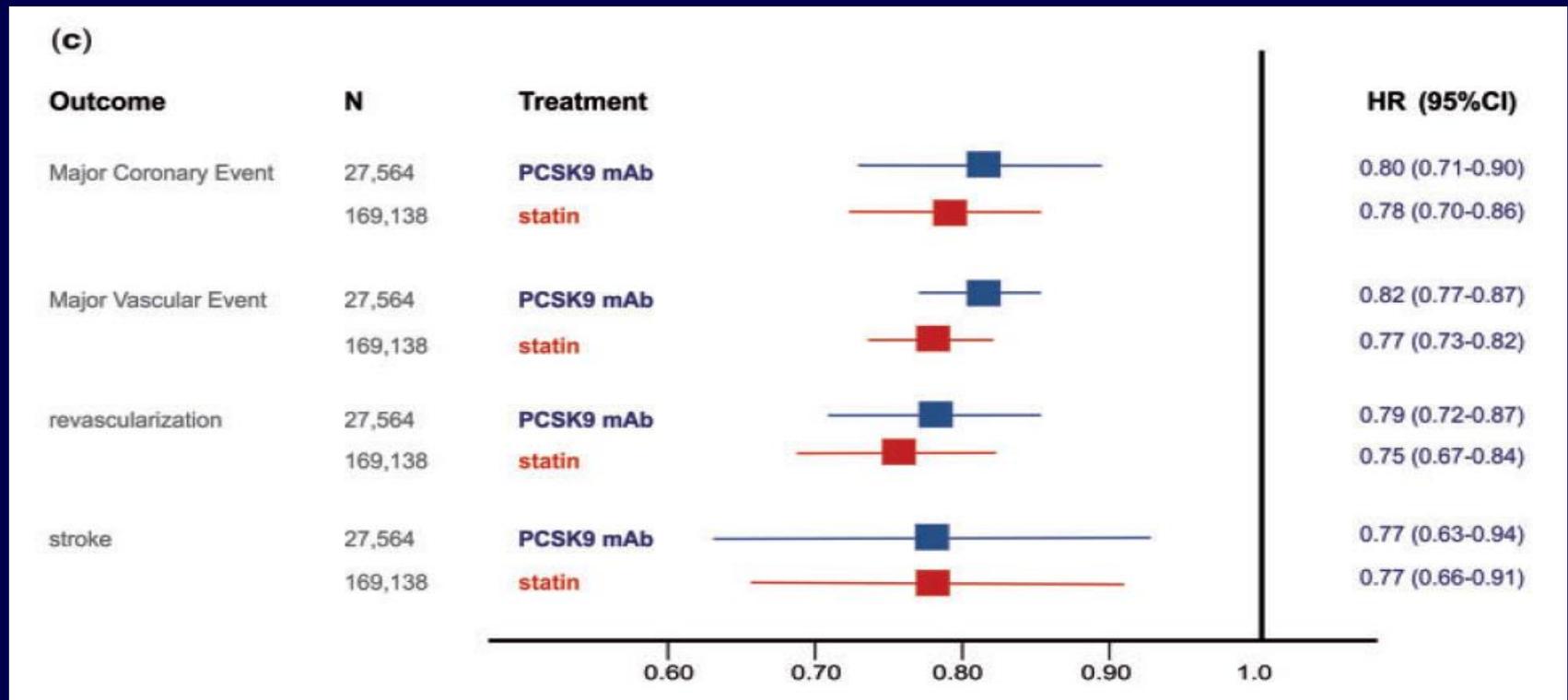
No notable differences in the rate of AEs, SAEs, or AEs leading to discontinuation

* nominally $p < 0.001$

PCSK9 inhibitors : Opportunities for the successful clinical utilisation

- ⊗ Further reduction of LDL-C by an average of 50% to 60%
- ⊗ Further reduction of the risk of CV events
- ⊗ CV benefits proportional to the absolute reduction in LDL-C and the duration of treatment

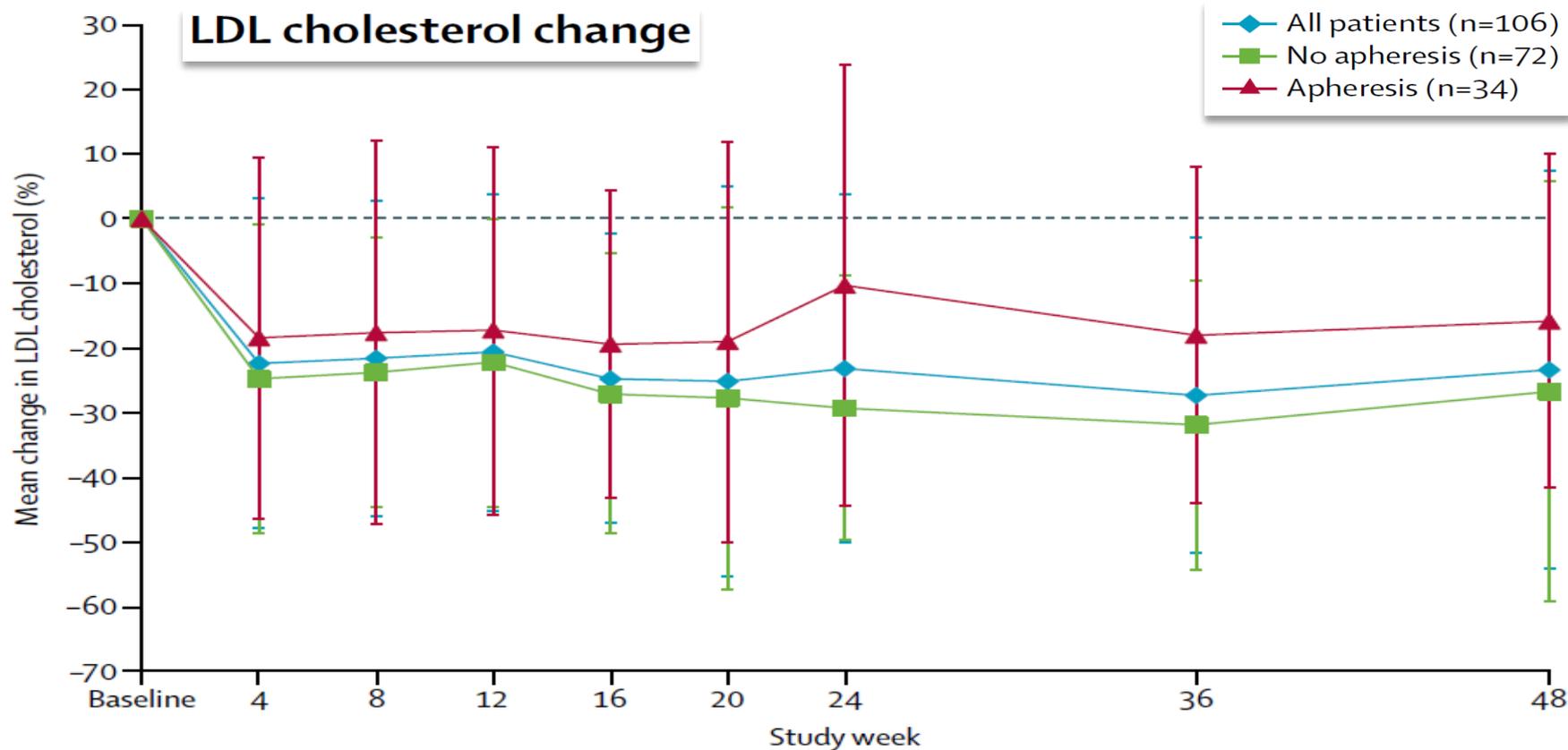
Effect of PCSK9 inhibitors in the FOURIER trial per mmol/l reduction in LDL-C during the second year of treatment as compared to the effect of statins during the second year of treatment per mmol/L reduction in LDL-C as reported by the CTT



PCSK9 inhibitors : Opportunities for the successful clinical utilisation

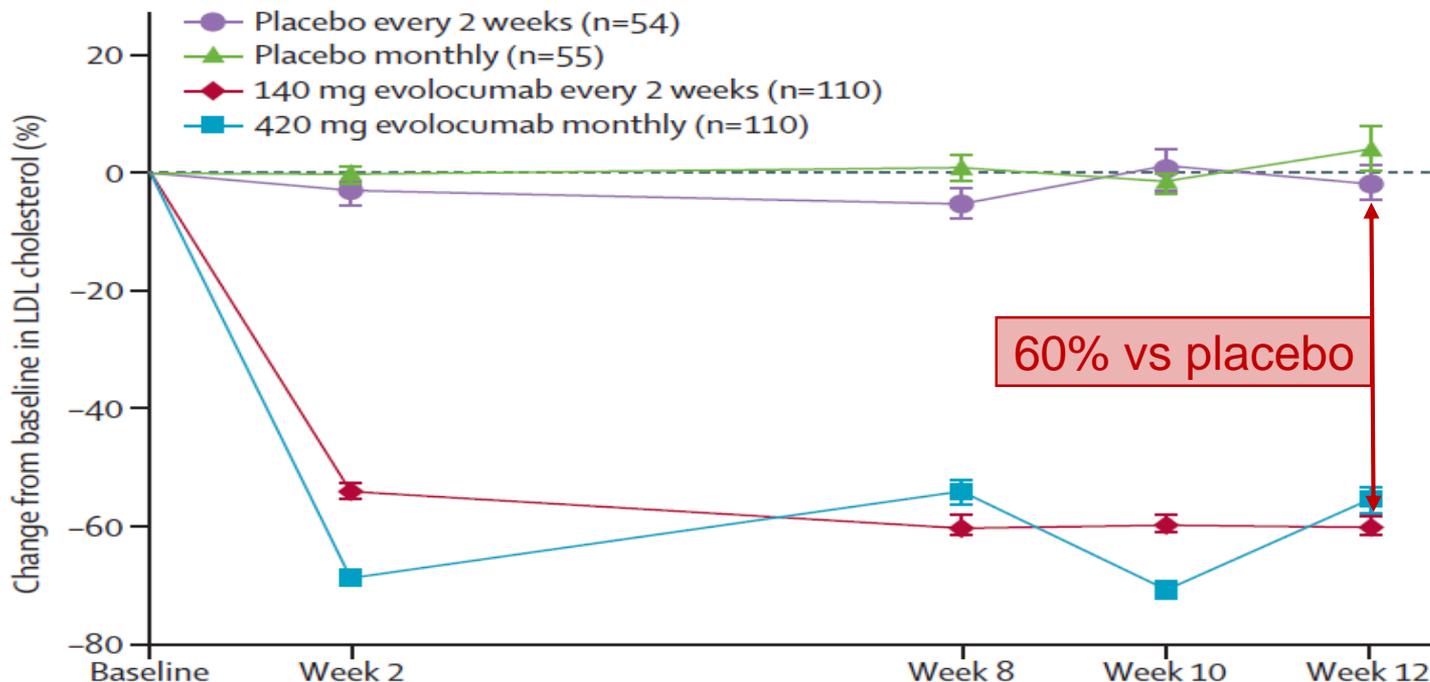
- ⊗ Further reduction of LDL-C by an average of 50% to 60%
- ⊗ Further reduction of the risk of CV events
- ⊗ CV benefits proportional to the absolute reduction in LDL-C and the duration of treatment
- ⊗ Treatment of familial hypercholesterolemia (FH)

TAUSSIG : HoFH with or without apheresis





Evolocumab significantly reduces LDL-C in patients with heterozygous FH

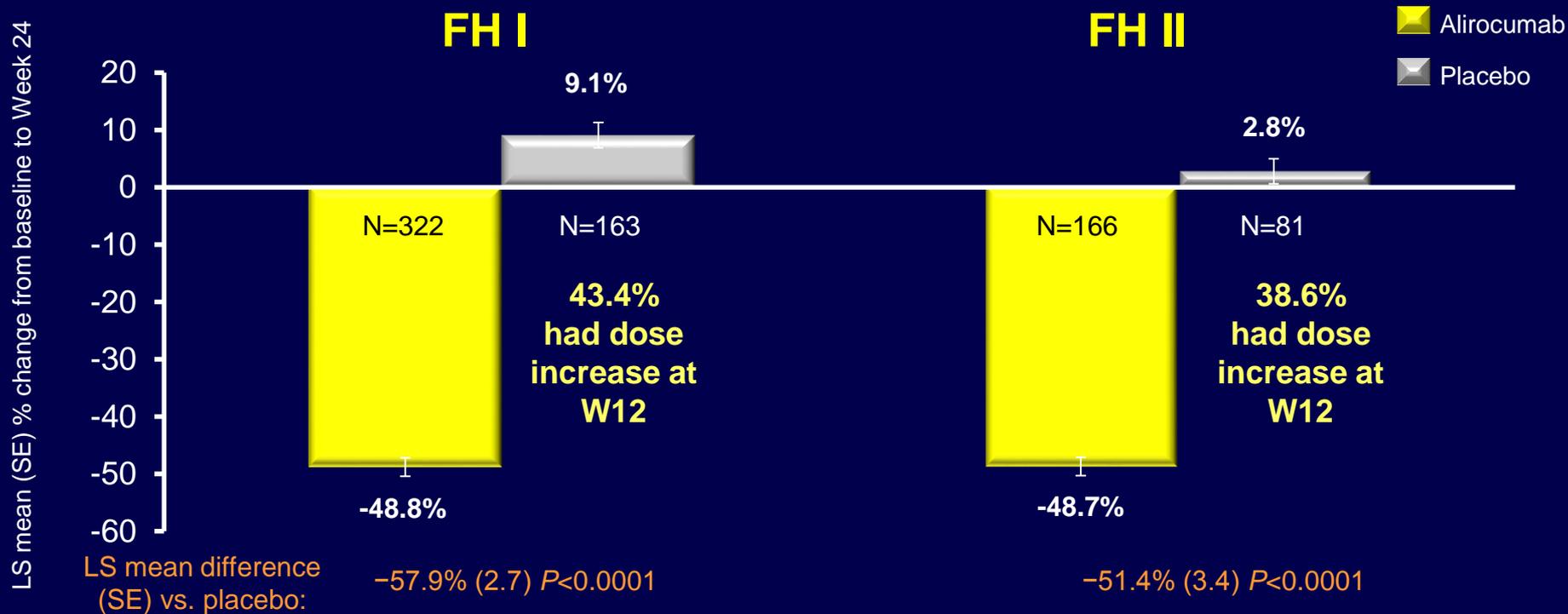


Evolocumab every 2 weeks .. ↑ ↑ ↑ ↑ ↑ ↑
Evolocumab monthly .. ↑ .. ↑ .. ↑ ..

FH I & II : Alirocumab Significantly Reduced LDL-C from Baseline to Week 24 versus Placebo



Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C
All patients on background max-tolerated statin ± other lipid-lowering therapy

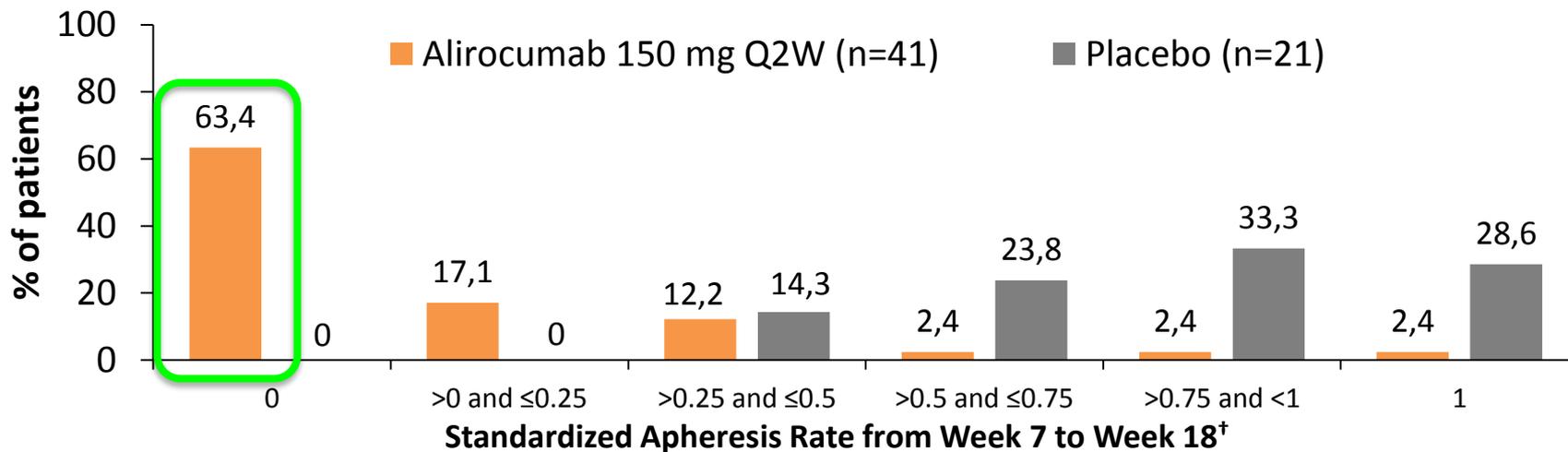


Standardized Apheresis Treatment Rates from Week 7–18

Standardised apheresis treatment rate in the period:
Hodges-Lehmann estimate of median treatment difference (95% CI):
p-value versus placebo:

Weeks 7–18
0.75 (0.67 to 0.83)
p<0.0001

Weeks 15–18
0.50 (0.50 to 1.00)
p<0.0001

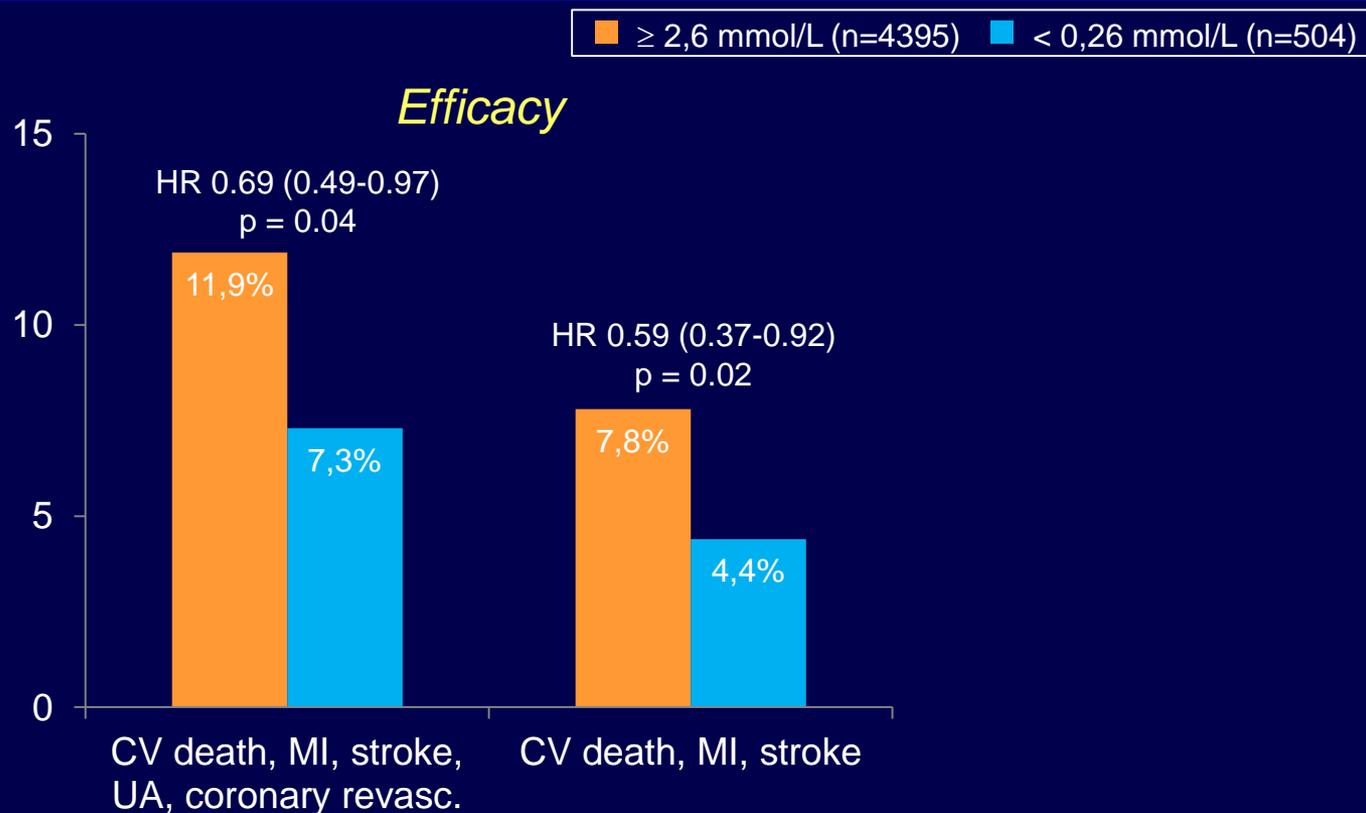


[†]An apheresis rate of 0 indicates that the patient skipped all planned apheresis treatments and an apheresis rate of 1 indicates that the patient received all planned apheresis treatments between Week 7 and Week 18 (apheresis rate of 0.75: the patient received 75% of planned apheresis treatments)

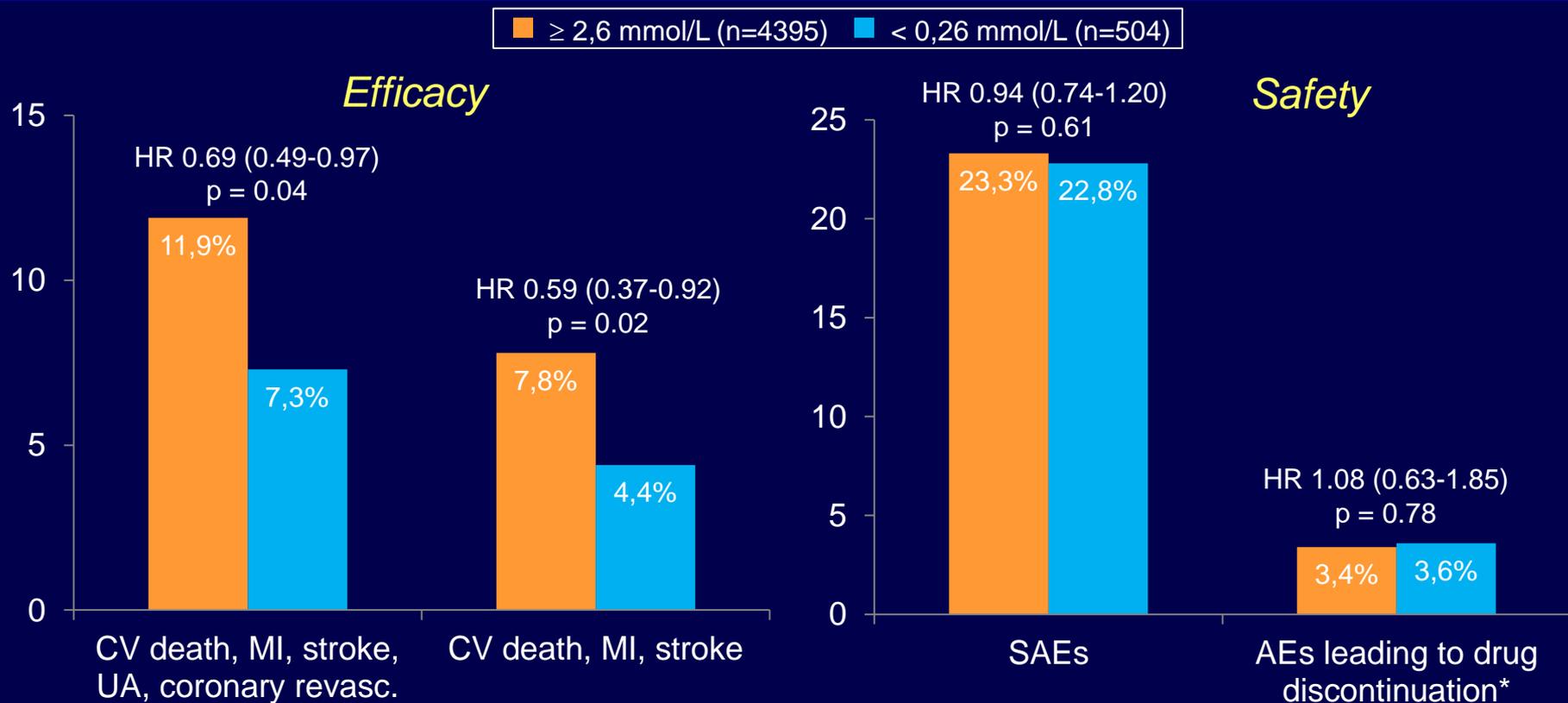
PCSK9 inhibitors : Barriers for the successful clinical utilisation

- ⊗ Cost of PCSK9i monoclonal antibodies
- ⊗ Long-term safety in clinical use (long-term safety of very low LDL-C levels)
- ⊗ Long-term impact of PCSK9 inhibition on disability and CV mortality
- ⊗ Long-term evaluation of risk for type 2 diabetes

FOURIER: Exploratory analysis of patients with LDL-C < 0.26 mmol/L (<10 mg/dL) at 4 weeks



FOURIER: Exploratory analysis of patients with LDL-C < 0.26 mmol/L (<10 mg/dL) at 4 weeks



* Excludes injection site reactions

PCSK9 inhibitors : Monoclonal Antibodies (mAbs)

- ▶ ▶ Opportunities and barriers for a successful clinical utilisation
- ▶ ▶ Routine clinical practice :
 - ▶ What guidelines tell us ?
 - ▶ What are the priorities ?

Changes in recommendations (3)

2016	2019
Pharmacological LDL-C lowering	Pharmacological LDL-C lowering
In patients at very-high risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	For secondary prevention, patients at very-high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended. For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.

Pharmacological LDL-C lowering

Recommendations	Class ^a	Level ^b
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk. ^{32,34,38}	I	A
If the goals ^c are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended. ³³	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention, patients at very-high risk not achieving their goal ^c on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended. ^{119,120}	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal ^c on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered. ^{197,265,353}	IIa	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may also be considered. ^{197,265,353}	IIb	C
If the goal ^c is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

PCSK9 inhibitors mAbs in Clinical Practice

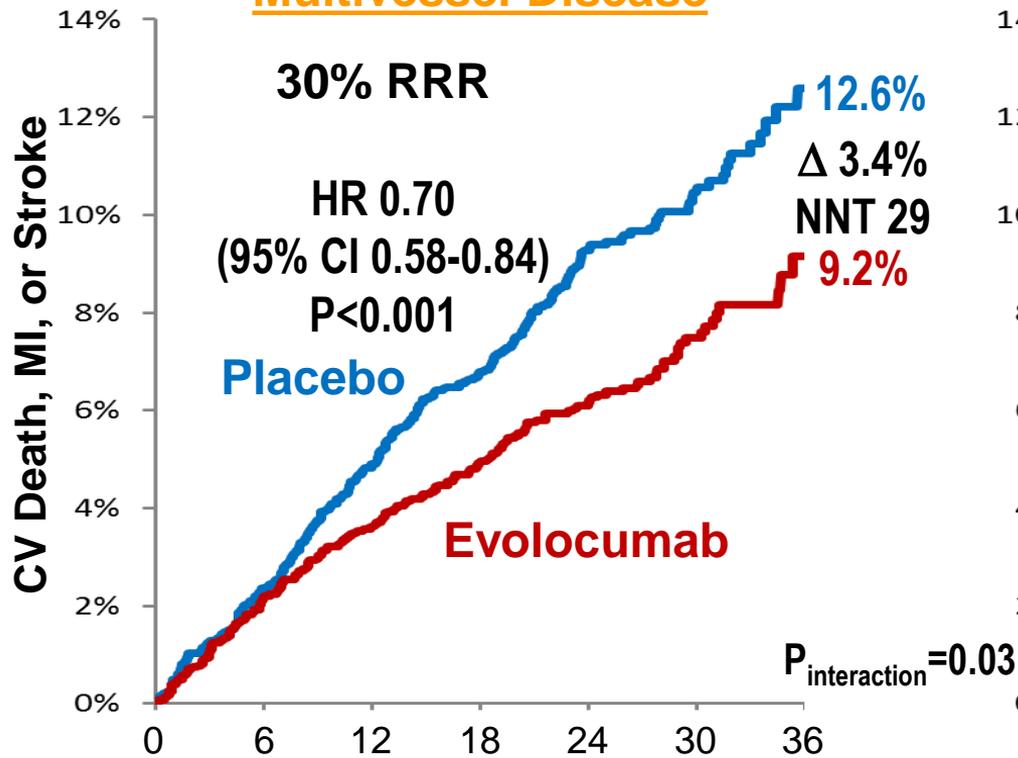
Categories of patients would benefit most
from PCSK9 mAbs



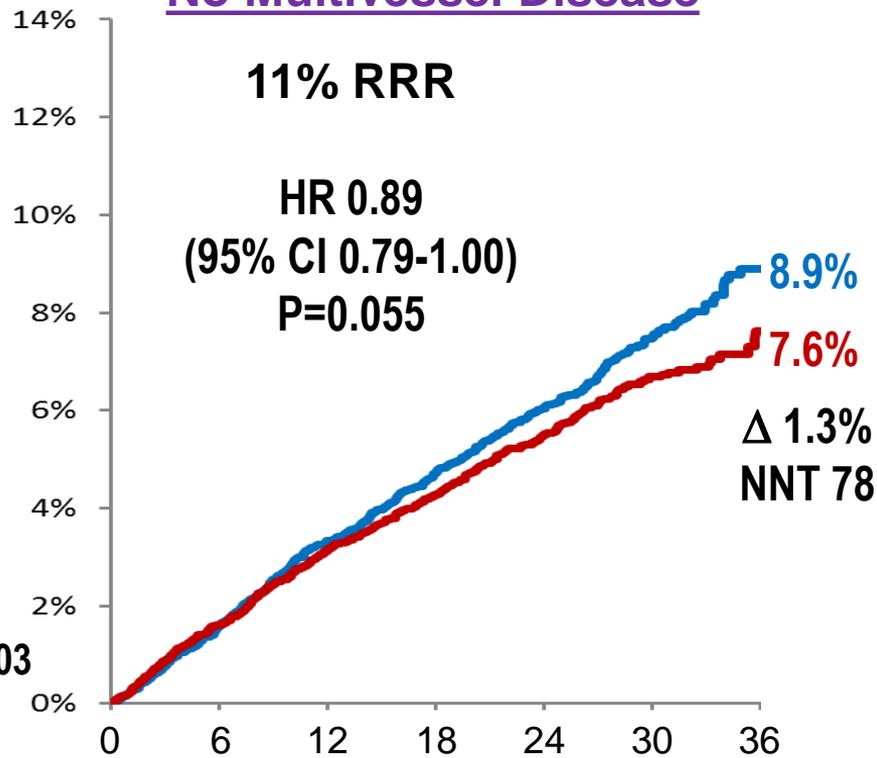
Benefit of EvoMab Based on Multivessel Disease



Multivessel Disease

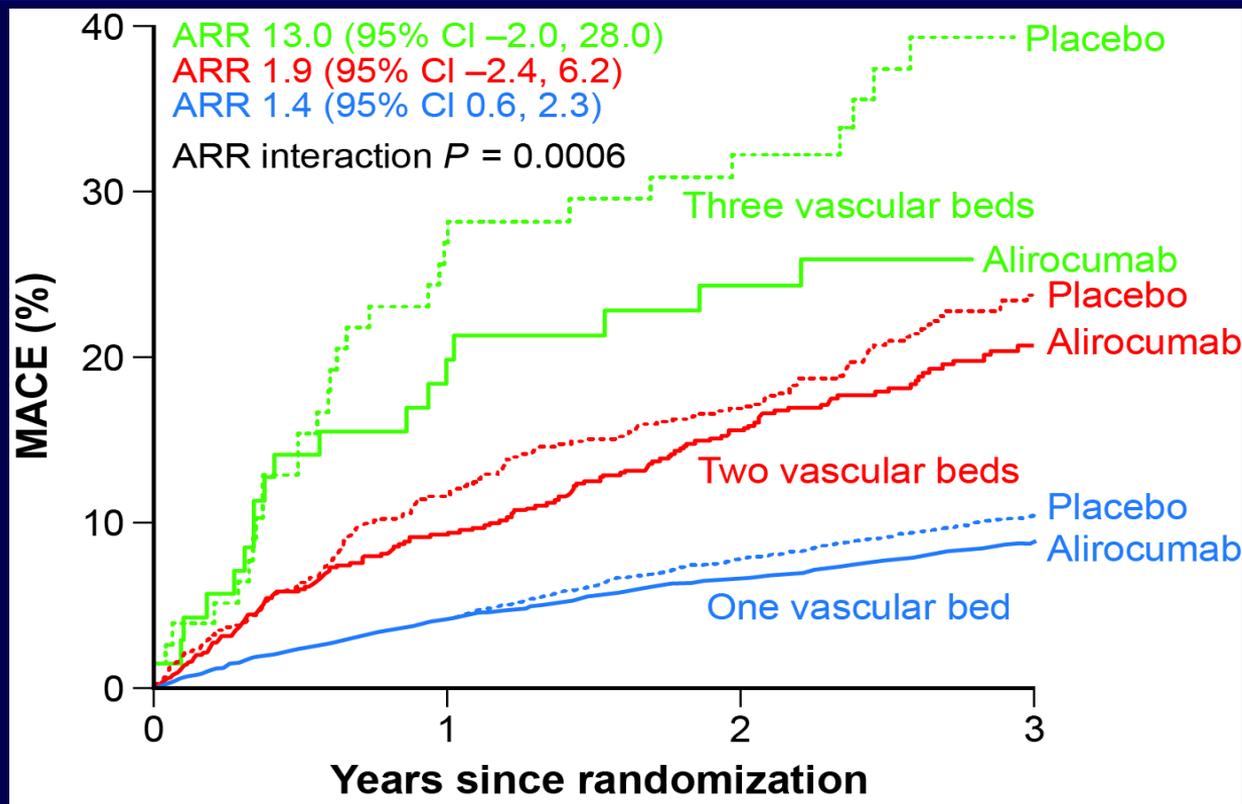


No Multivessel Disease

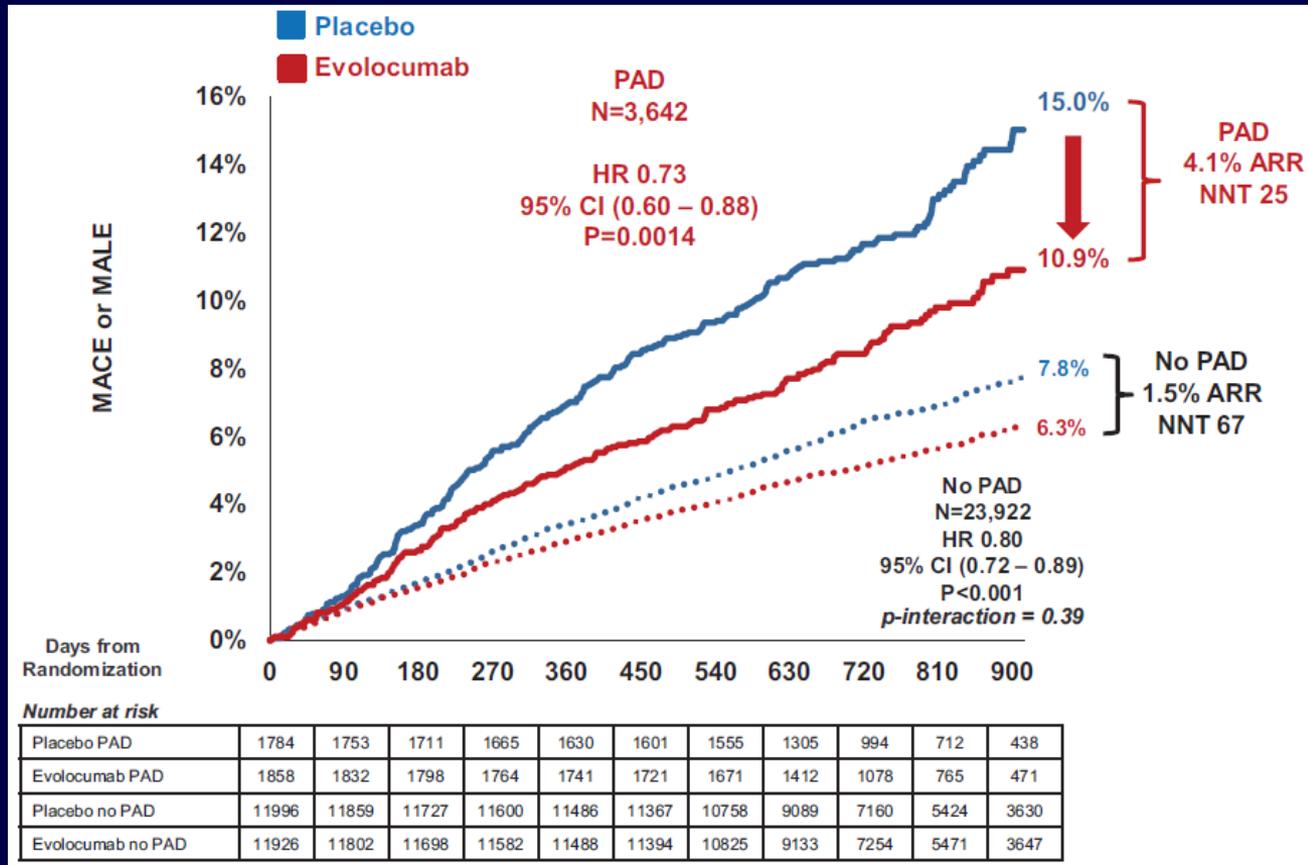


ODYSSEY-Outcomes: Alirocumab and Vascular Disease

Primary MACE endpoint : one, two or three vascular beds



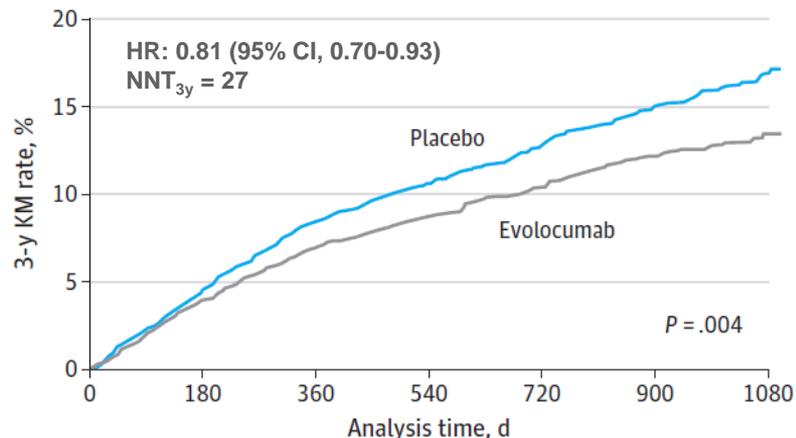
FOURIER : MACE or MALE in patients with and without PAD



FOURIER: Risk of the Primary End Point in patients with Recent and Remote MI randomized to Placebo vs Evolocumab

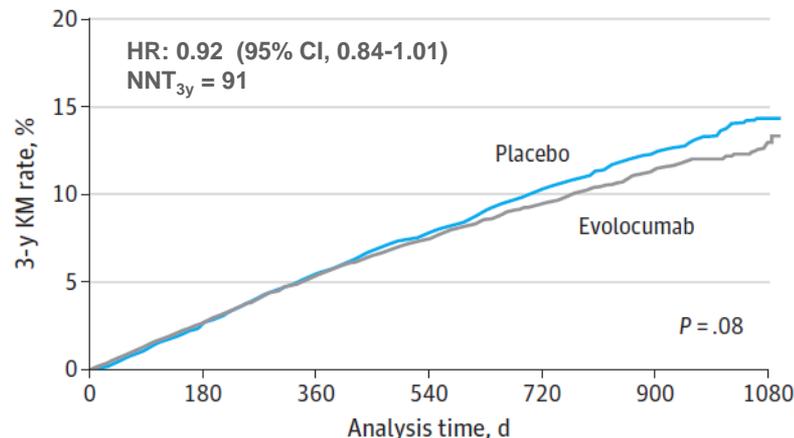
(Recent 1-12 months, Remote > 12 months prior to randomization)

A Primary end point in patients with recent MI



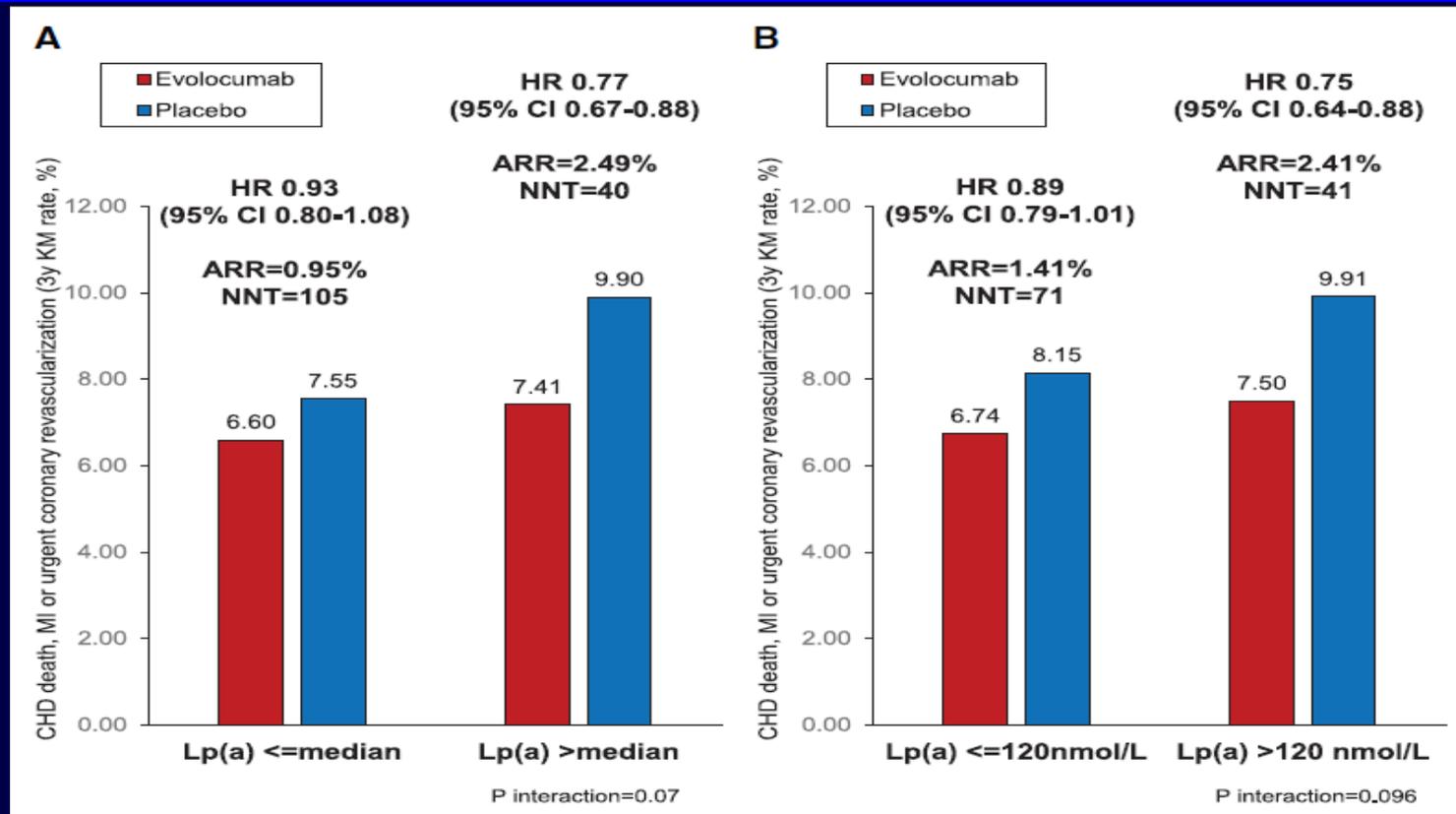
No. at risk							
Placebo	2890	2748	2628	2462	1716	999	309
Evolocumab	2821	2696	2602	2470	1705	988	299

B Primary end point in patients with remote MI



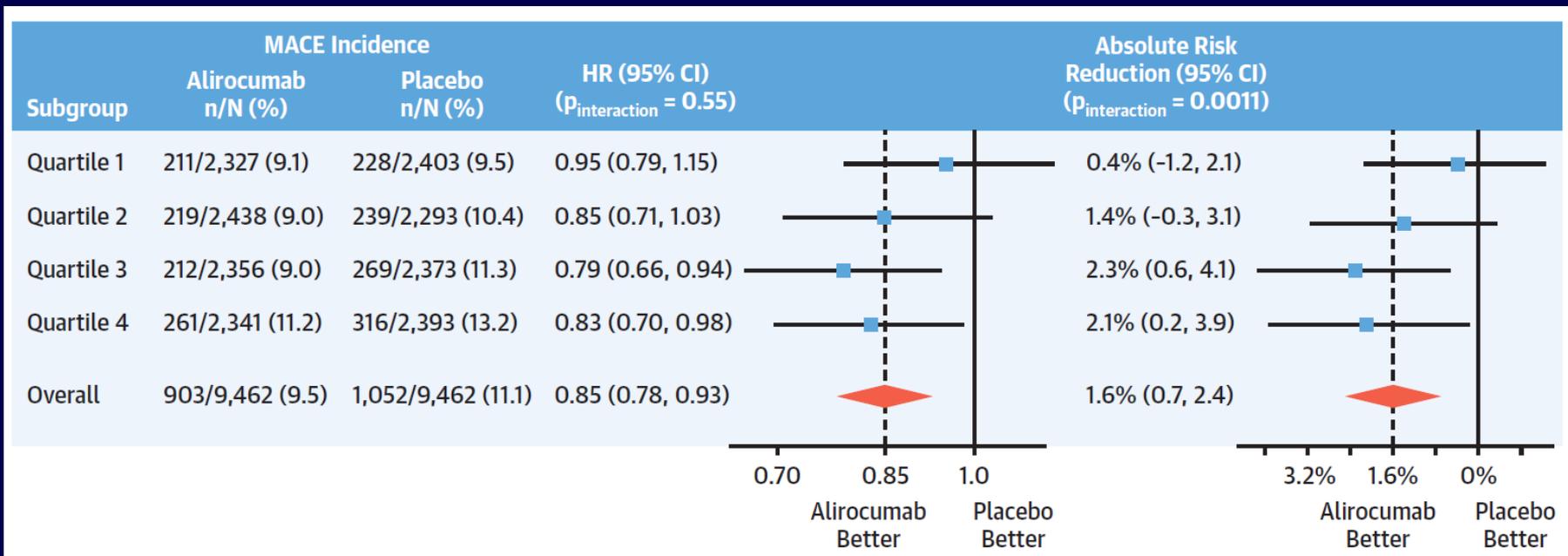
No. at risk							
Placebo	8301	8034	7770	7204	4695	2298	468
Evolocumab	8308	8058	7796	7286	4791	2332	480

FOURIER : Rate of cardiovascular events by Lp(a) levels and effect of evolocumab



Effect of Alirocumab on Lp(a) and CV risk after ACS

Greater Absolute Treatment Effect on MACE with Higher Baseline Lp(a)



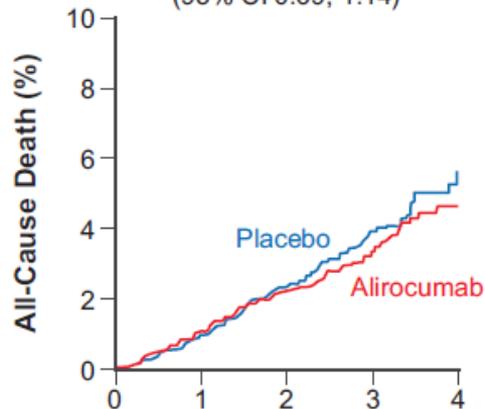
ODYSSEY-Outcomes: All-cause death by baseline LDL-C subgroup

RRR Interaction $P=0.12$

ARR Interaction $P=0.005$

<80 mg/dL

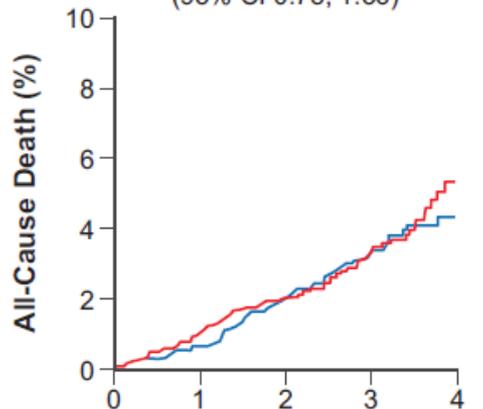
HR 0.89
(95% CI 0.69, 1.14)



Number at risk	Years Since Randomization				
	0	1	2	3	4
Placebo	3583	3486	3349	1426	285
Alirocumab	3581	3488	3358	1452	269

80 to <100 mg/dL

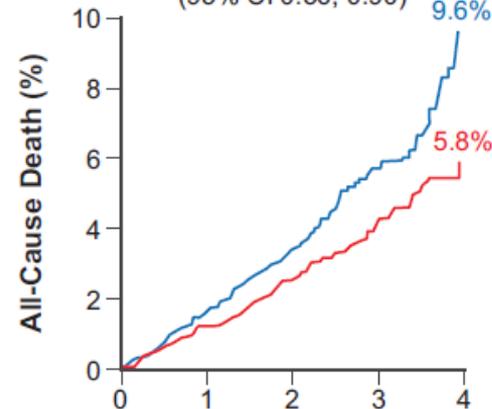
HR 1.03
(95% CI 0.78, 1.36)



Number at risk	Years Since Randomization				
	0	1	2	3	4
Placebo	3062	3001	2894	1325	228
Alirocumab	3066	2992	2907	1308	237

≥100 mg/dL

HR 0.71
(95% CI 0.56, 0.90)



Number at risk	Years Since Randomization				
	0	1	2	3	4
Placebo	2815	2732	2645	1147	224
Alirocumab	2814	2739	2655	1186	240

ASCVD patients : priorities for PCSK9 inhibition

On maximally tolerated statin + ezetimibe, LDL-C not at goal and ONE of :

- LDL-C > 100 mg/dL (2.5 mmol/L)
- Polyvascular disease, or PAD
- Post-CABG
- Diabetes
- Lp(a) > 50 mg/dL
- FH

Adult patients with FH and without ASCVD

On high-intensity statin* + ezetimibe

Check for additional indices of risk severity

- not on LDL-lowering treatment before the age of 40 years
- Lp(a) > 50 mg/dL
- major risk factors: smoking, marked hypertension, diabetes
- premature ASCVD (<55 years in males and < 60 years in females) in first degree relatives
- CAC score > 100 Agatston units or significant carotid plaque

NO

YES

LDL-C > 3.6 mmol/L
(140 mg/dL)

Add a PCSK9 inhibitor

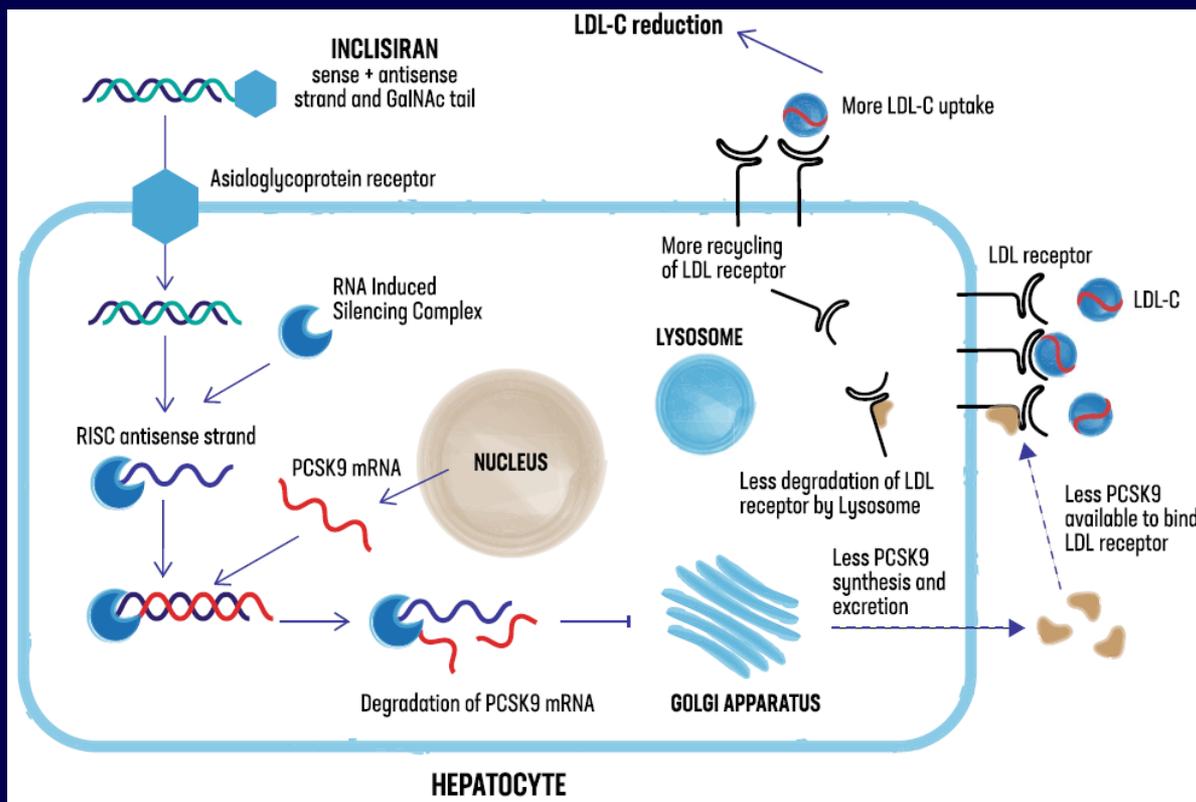
LDL-C > 2.6 mmol/L
(100 mg/dL)

*or maximally tolerated statin

PCSK9 inhibitors

- ⊗ Role of PCSK9 in LDL metabolism
- ⊗ PCSK9 inhibitors : Monoclonal Antibodies (mAbs)
 - Alirocumab
 - Evolocumab
- ⊗ PCSK9 inhibitors : Other strategies
 - Inclisiran
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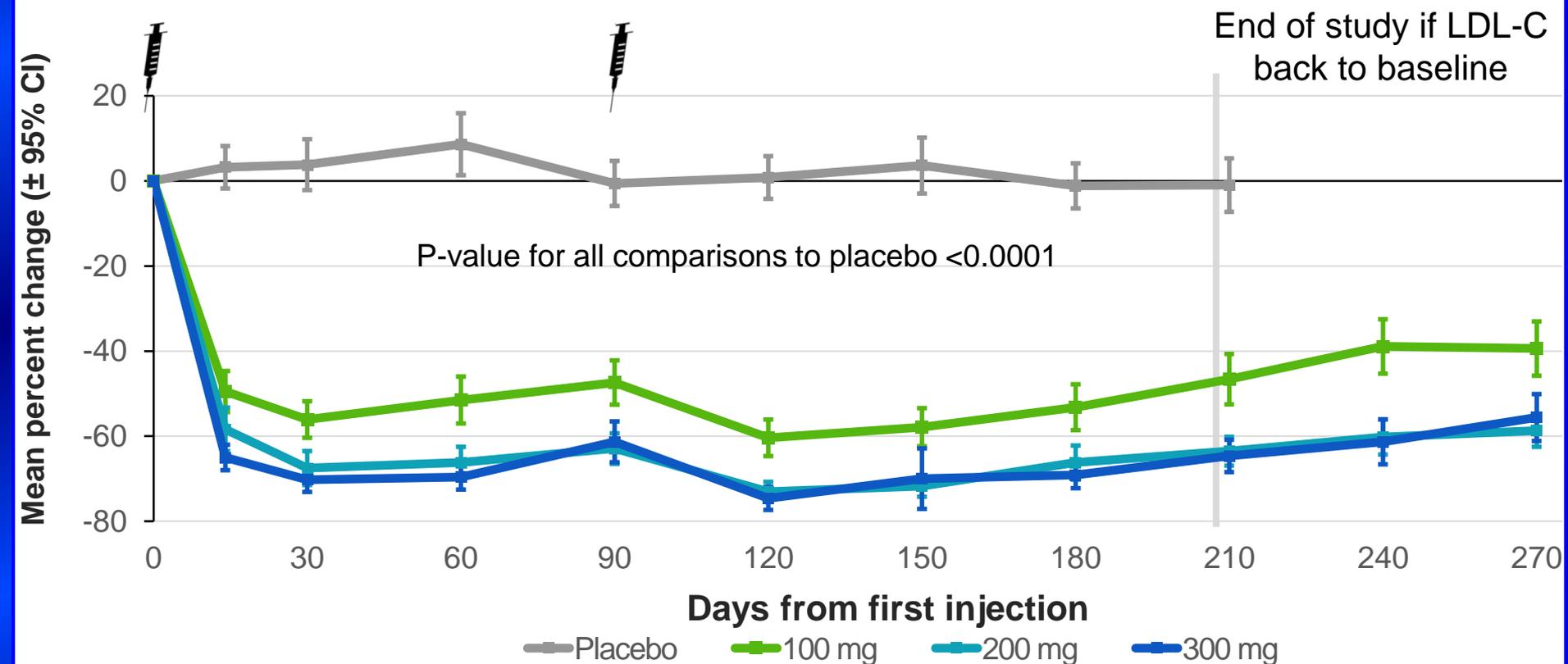
Inclisiran: mechanism of action



Inclisiran is a long-acting synthetic siRNA directed against PCSK9, conjugated to GalNAc, which bind to liver-expressed asialoglycoprotein receptors, leading to a rapid uptake specifically into hepatocytes

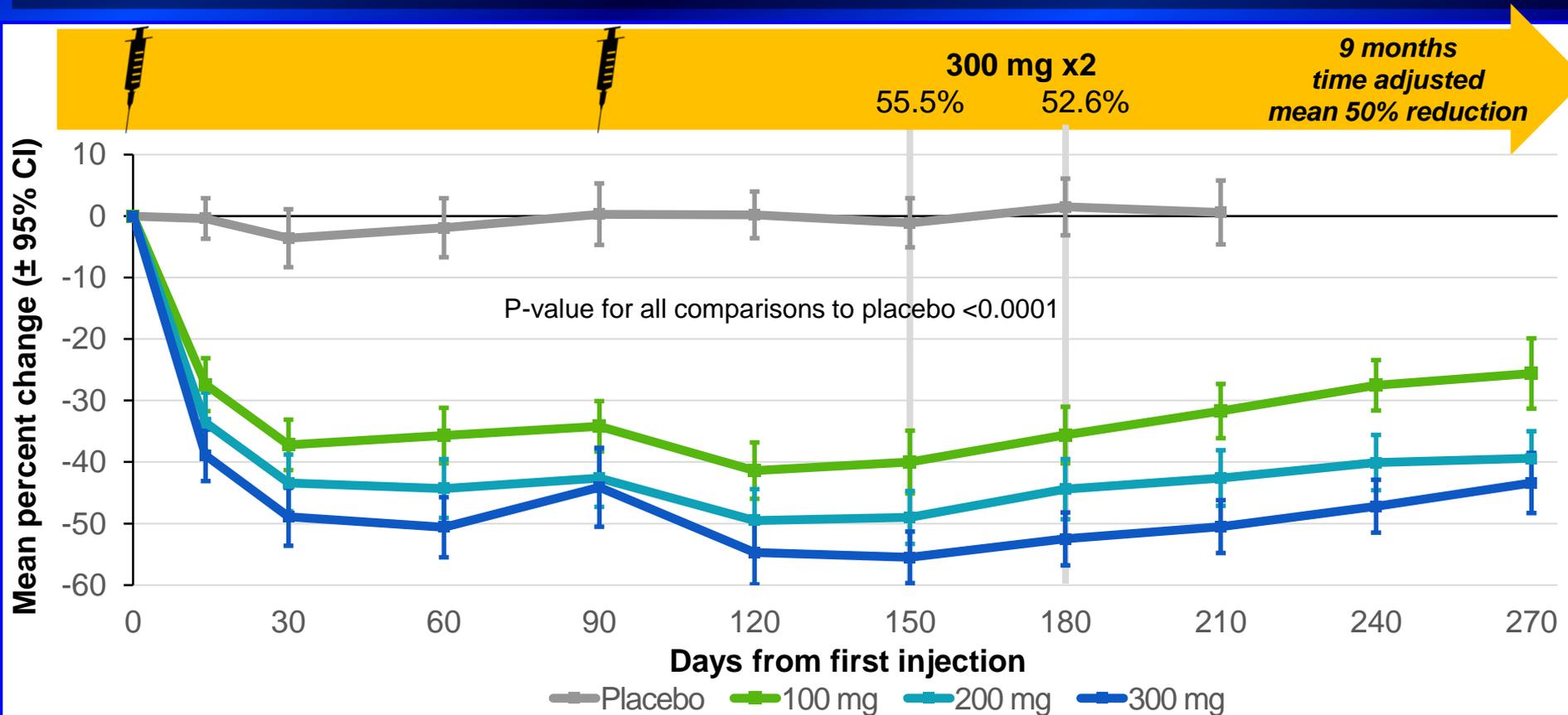
Efficacy: Two dose starting regimen

Clamped PCSK9 knockdown



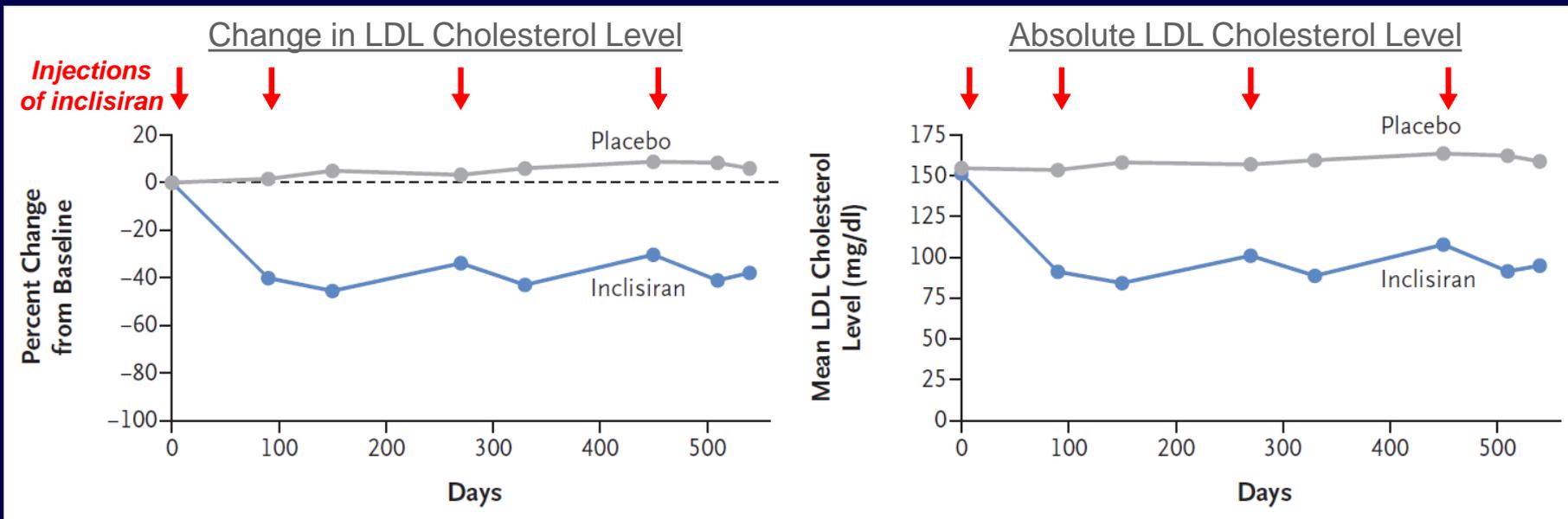
Efficacy: Two dose starting regimen

Robust, sustained LDL-C reductions – optimal start regimen



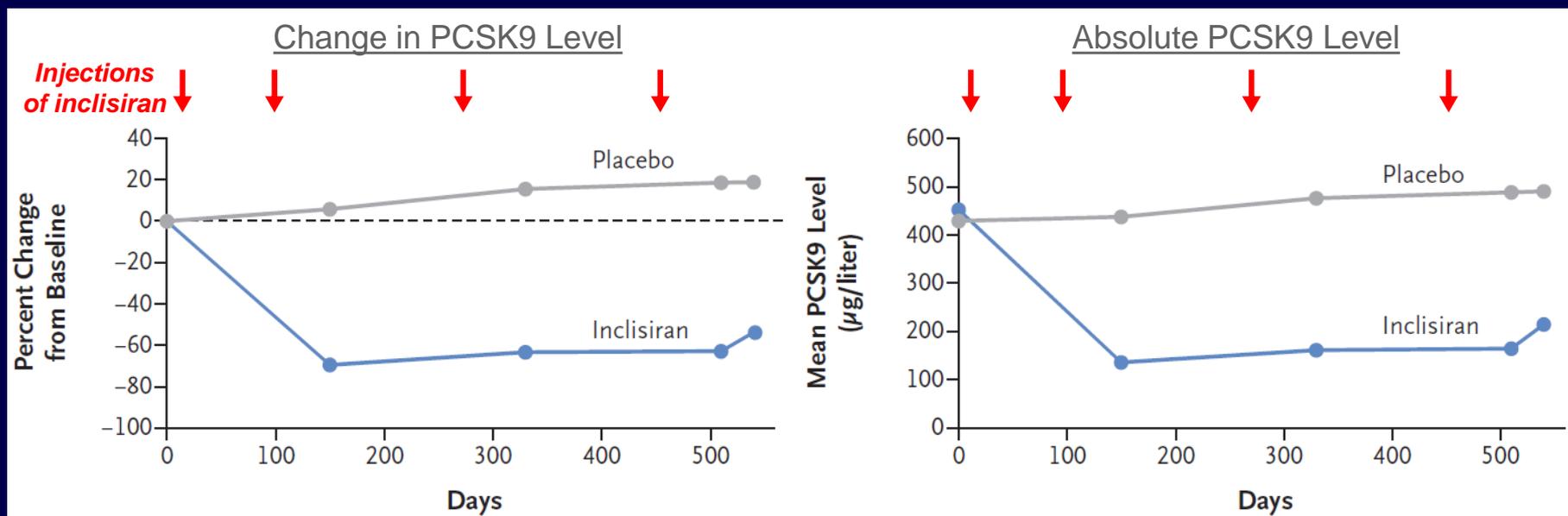
Inclisiran for the treatment of Heterozygous FH (ORION-9)

482 adults with heterozygous FH received 1.5 ml SC injections of inclisiran 300 mg or placebo (1:1) on days 1, 90, 270, and 450 (↓)



Inclisiran for the treatment of Heterozygous FH (ORION-9)

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Inclisiran for the treatment of Heterozygous FH (ORION-9)

482 adults with heterozygous FH received 1.5 ml SC injections of inclisiran 300 mg or placebo (1:1) on days 1, 90, 270, and 450

Mean LDL-C at baseline : 153 mg/dL

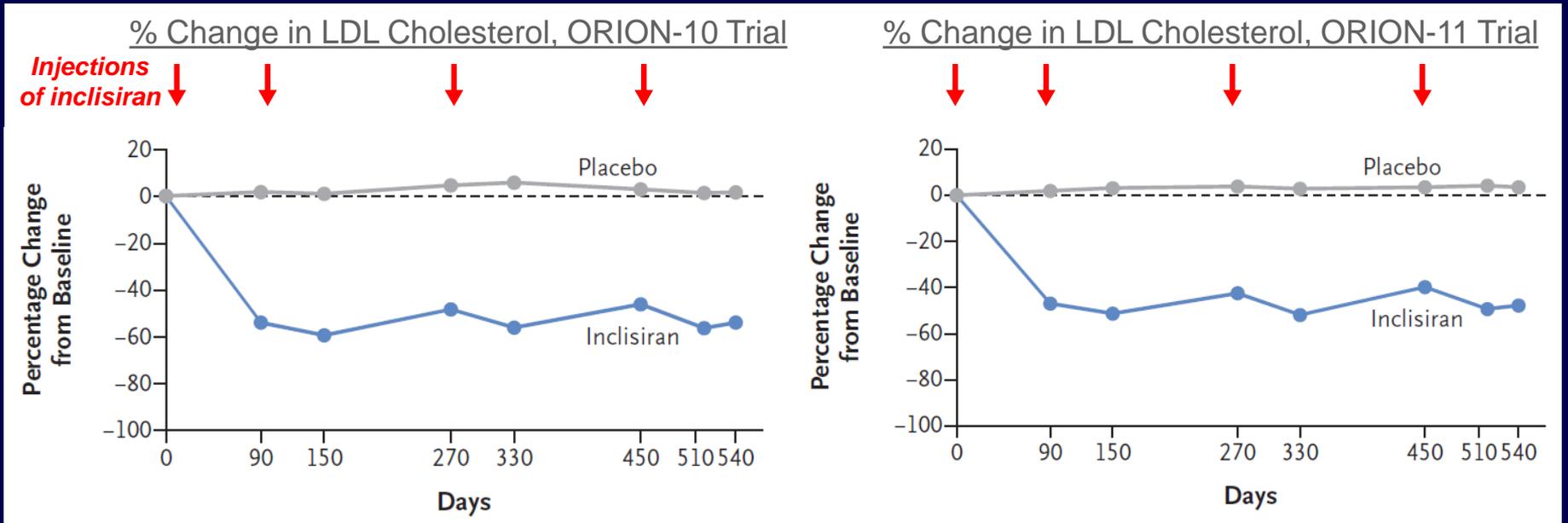
Primary endpoints:

- % change in LDL-C at day 510: - 47.9
- Time-averaged % change in LDL-C between day 90 and day 540 : - 44.3
(*between-group difference*)

AEs and SAEs: similar in the 2 groups

Inclisiran in patients with ASCVD (or risk equivalent) (ORION-10 and -11)

Injections on days 1, 90, 270, and 450 (↓)



Inclisiran in patients with elevated LDL-C (ORION-10 and -11)

1561 and 1617 patients randomized in the ORION-10 and -11, respectively to receive SC inclisiran or placebo on days 1, 90, 270 and 450

Patients with ASCVD or an ASCVD risk equivalent on maximally tolerated statin

Mean baseline LDL-C: \approx 104.7 and 105.5 mg/dL, respectively

Primary endpoints:

- % change in LDL-C at day 510:
- 52.3 (ORION-10), - 49.9 (ORION-11)
- Time-averaged % change in LDL-C between day 90 and day 540 :
- 53.8 (ORION-10), - 49.2 (ORION-11)

($p < 0.001$ for all comparisons vs placebo)

Inclisiran in patients with elevated LDL-C (ORION-10 and -11)

1561 and 1617 patients randomized in the ORION-10 and -11, respectively to receive SC inclisiran or placebo on days 1, 90, 270 and 450

Patients with ASCVD or an ASCVD risk equivalent on maximally tolerated statin

Mean baseline LDL-C: \approx 104.7 and 105.5 mg/dL, respectively

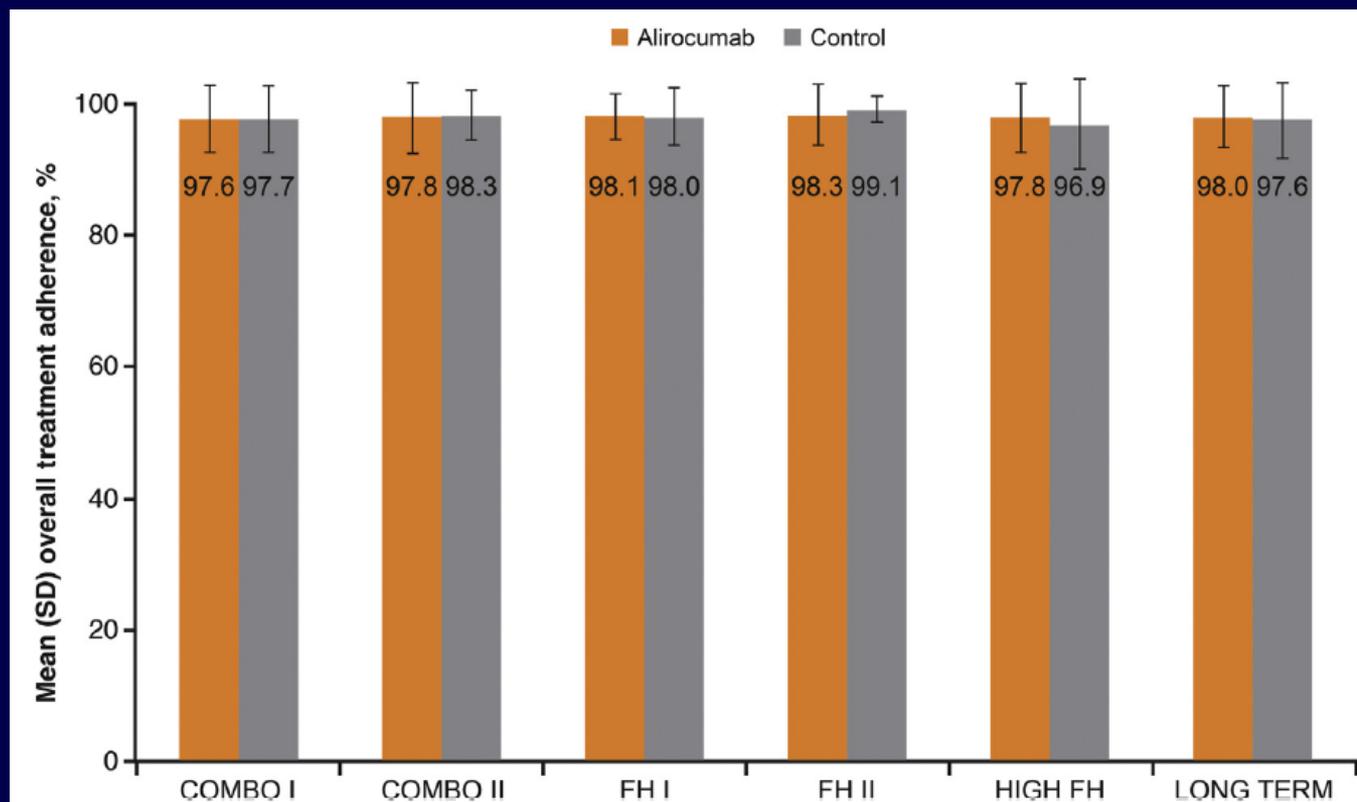
Safety:

AEs similar in the inclisiran and placebo groups, although injection-site AEs were more frequent with inclisiran than with placebo:

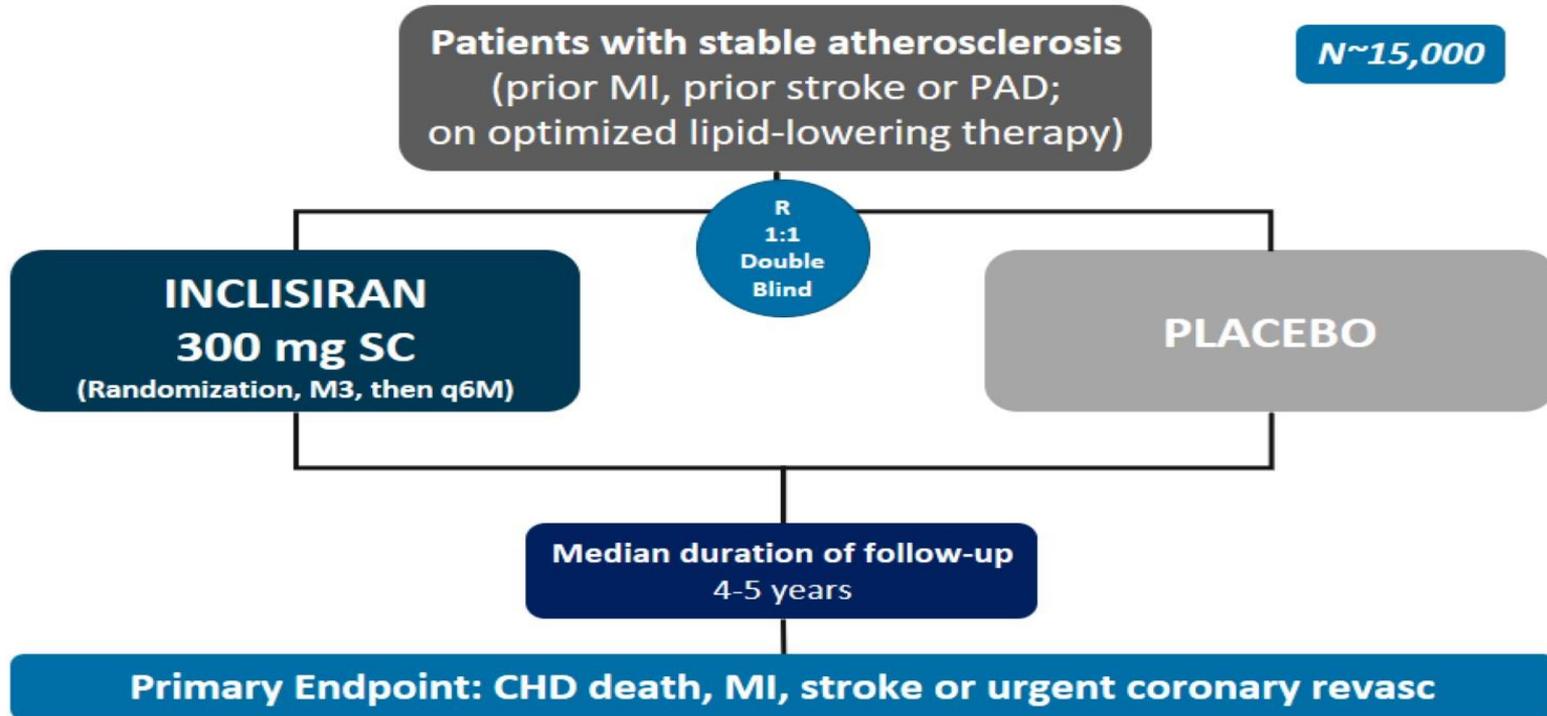
2.6% vs 0.9% (ORION-10)

4.7% vs 0.5% (ORION-11)

Adherence to Alirocumab (or Placebo) in Phase III studies



ORION-4 design



PCSK9 inhibitors

- ⊗ Role of PCSK9 in LDL metabolism
- ⊗ PCSK9 inhibitors : Monoclonal Antibodies (mAbs)
 - Alirocumab
 - Evolocumab
- ⊗ PCSK9 inhibitors : Other strategies
 - Inclisiran
 - LIB003

LIB003 : an anti-PCSK9 recombinant fusion protein

- A novel agent consisting of a PCSK9-binding domain (Adnectin) and human serum albumin
- LIB003 300 mg SC Q4W dose was selected from phase 2 trial (reduction in LDL-C of $> 70\%$ in the double-blind phase and of 64% in the open-label extension)

Conclusion : PCSK9 inhibition

- PCSK9-inhibiting mAbs are the only available alternative
- Real challenge : how identify which patients would benefit most from PCSK9 inhibitors ?
- Future : Inclisiran ?