Current and Future Therapeutic Approaches

PCSK9 Inhibitors

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Dr Farnier reports having received grants, consulting fees and/or honoraria and delivering lectures for Abbott, Akcea/Ionis, Amarin, Amgen, AstraZeneca, Daiichi-Sankyo, Eli Lilly, Kowa, Merck and Co, Mylan, Pfizer, Sanofi/Regeneron and Servier

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Disclosure of potential conflicts of interest

Research contracts:	Amgen, Sanofi/Regeneron
Consulting:	Abbott, Akcea/Ionis, Amarin, Amgen, AstraZeneca, Daiichi-Sankyo, Eli Lilly, Kowa, Merck, Mylan, Pfizer, Sanofi and Servier
Employment in industry:	None
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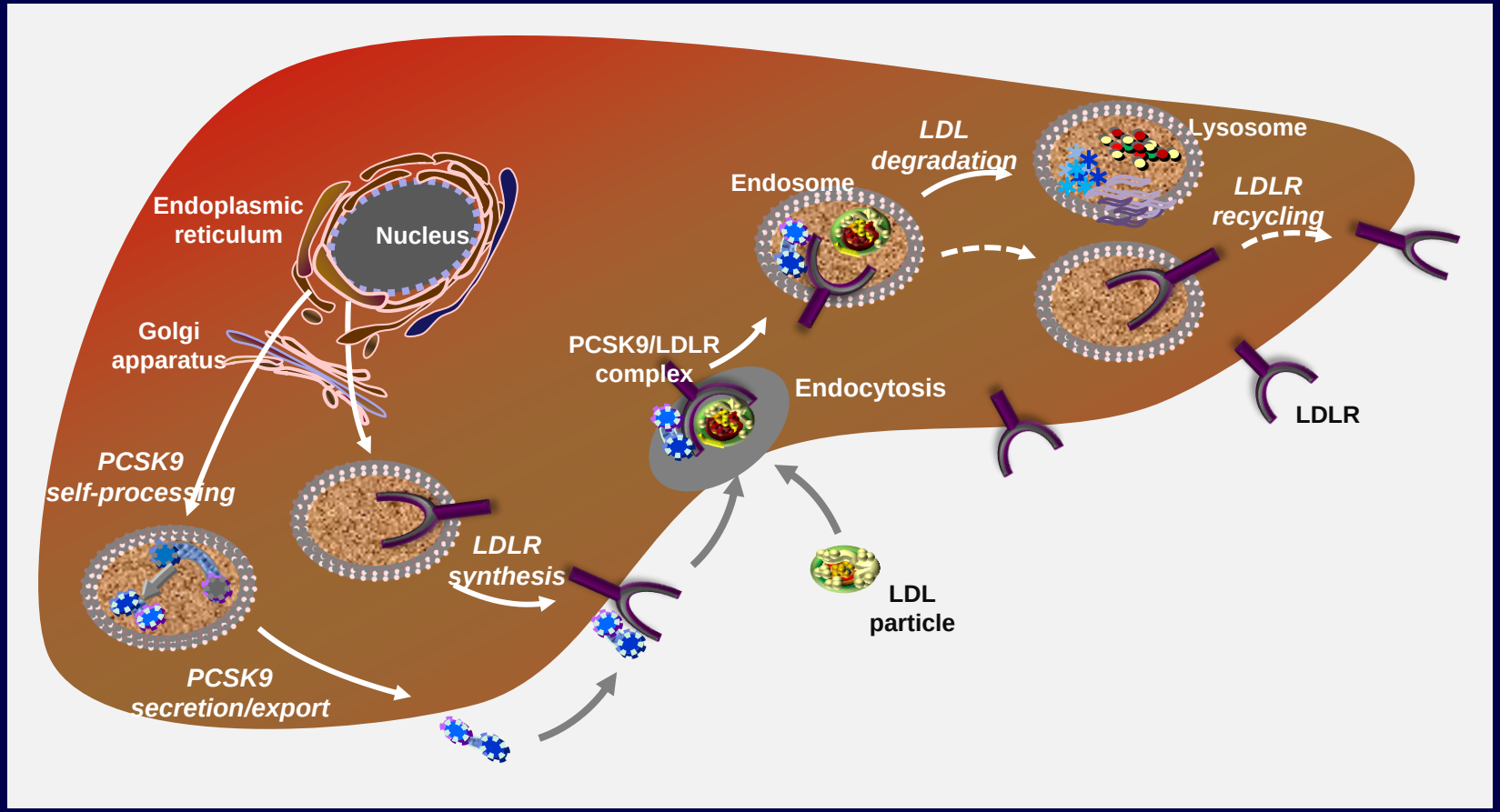
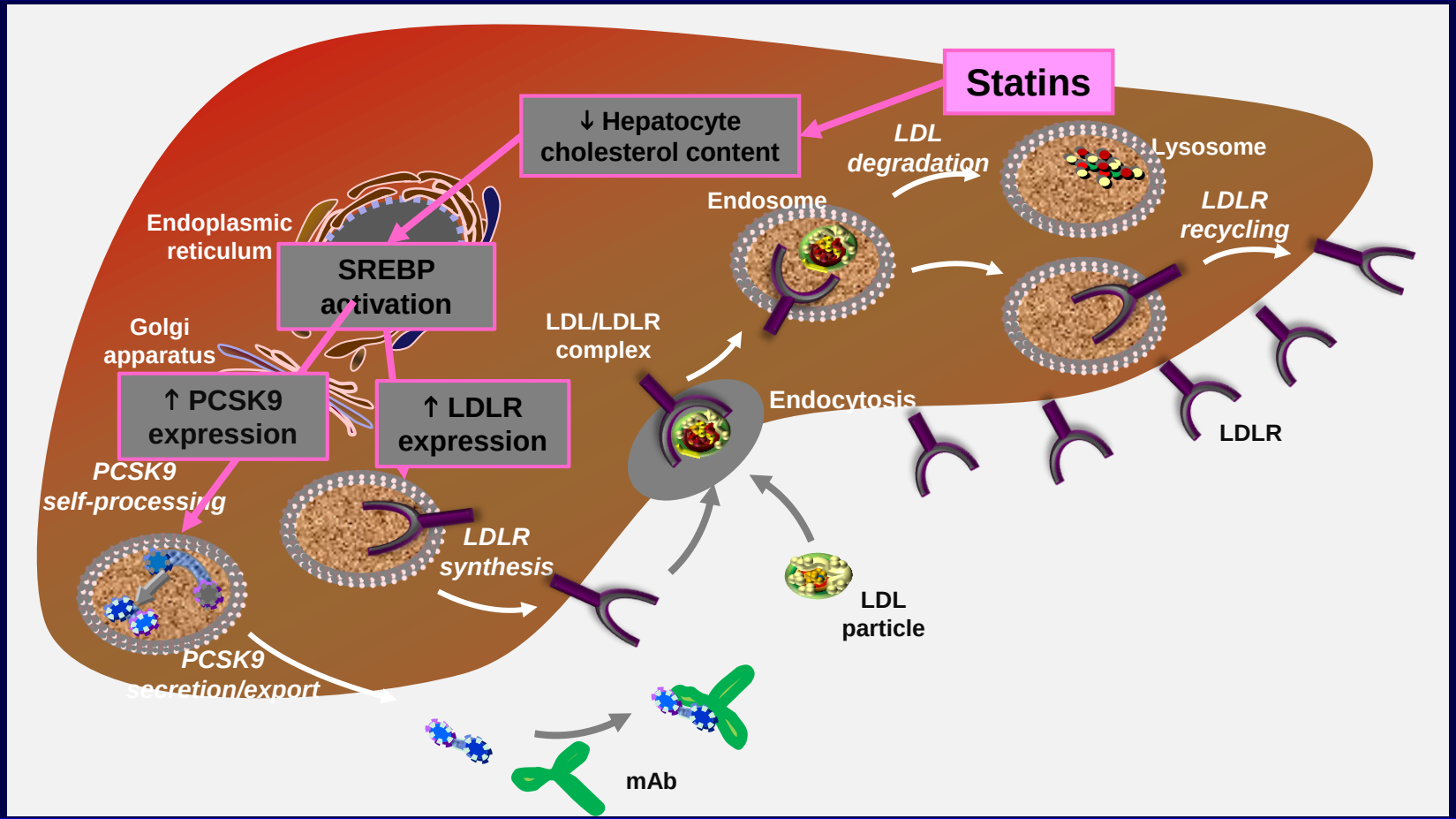
Owner of a healthcare company:	None
Participation in Clinical Trials:	ODYSSEY Programme (Sanofi/Regeneron) TESLA/TAUSSIG/VESALIUS (Amgen) Evinacumab Programme (Regeneron)

Regulation of the hepatocyte LDL Receptor



Farnier M. Arch Cardiovasc Dis 2014; 107: 58-66

Development of PCSK9 inhibitors



Farnier M. Arch Cardiovasc Dis 2014; 107: 58-66

PCSK9 inhibitors

- Monoclonal Antibodies (mAbs)
  - alirocumab
  - evolocumab
  - bococizumab
- siRNA (inclisiran)

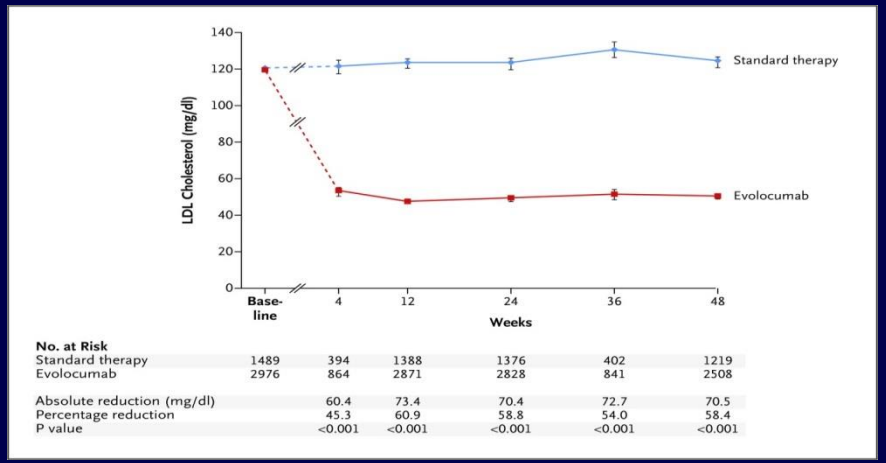
PCSK9 inhibitors : Opportunities for the successful clinical utilisation

- 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

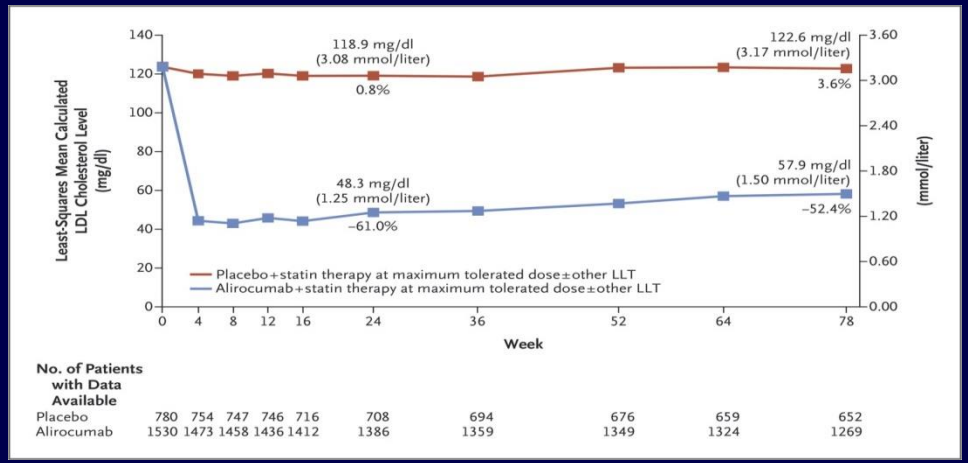


No. at Risk						
Standard therapy	1489	394	1388	1376	402	1219
Evolocumab	2976	864	2871	2828	841	2508
Absolute reduction (mg/dl)		60.4	73.4	70.4	72.7	70.5
Percentage reduction		45.3	60.9	58.8	54.0	58.4
P value		<0.001	<0.001	<0.001	<0.001	<0.001

Sabatine MS et al. N Engl J Med 2015.

ODYSSEY long term

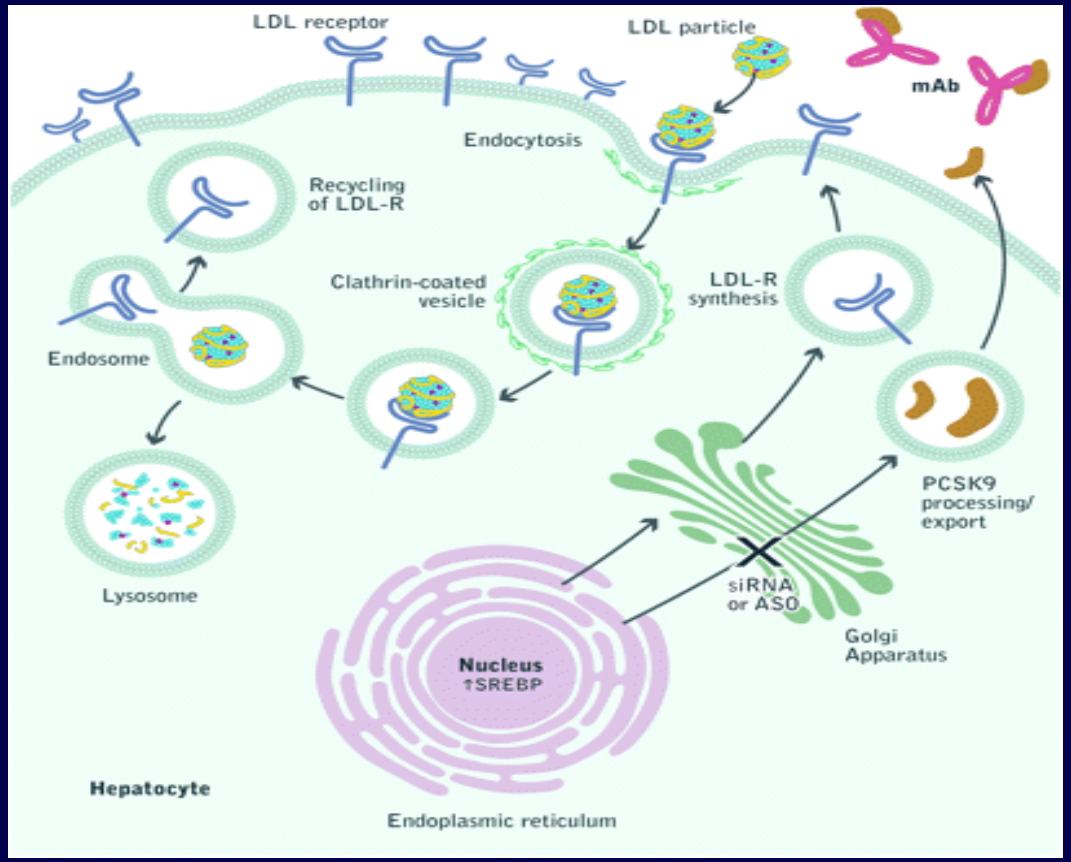
Alirocumab vs placebo, on top of statin therapy
Calculated LDL Cholesterol Levels over Time (Intention-to-Treat Analysis).



No. of Patients with Data Available										
Placebo	780	754	747	746	716	708	694	676	659	652
Alirocumab	1530	1473	1458	1436	1412	1386	1359	1349	1324	1269

Robinson JG et al. N Engl J Med 2015.

Monoclonal Antibodies to PCSK9 Phase III results

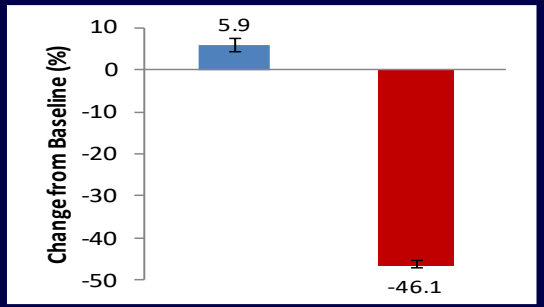


Effective :

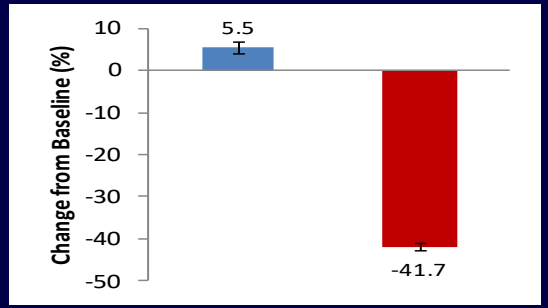
- in heterozygous FH (reduced LDL-R activity)
- in homozygous FH (LDL-R defective)
- as statin add-on
- in statin intolerance
- as monotherapy

Other Lipid Parameters

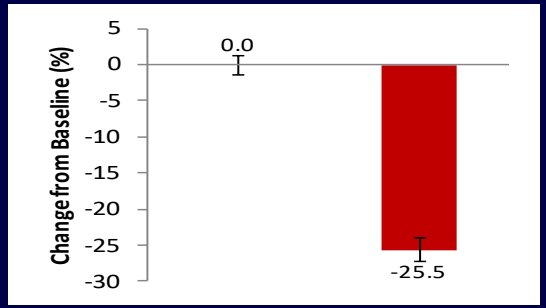
52% ↓ in Non-HDL-C



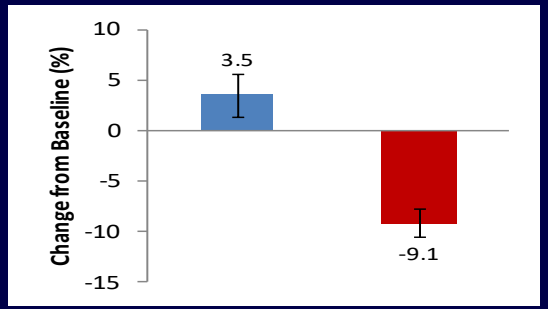
47% ↓ in ApoB



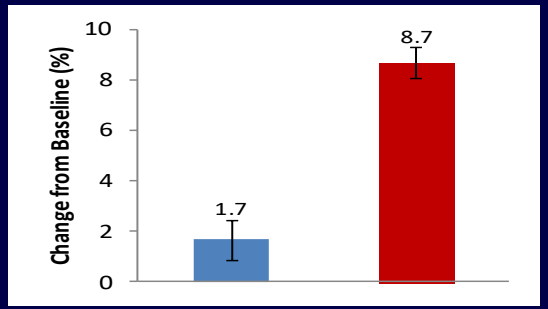
26% ↓ in Lp(a)



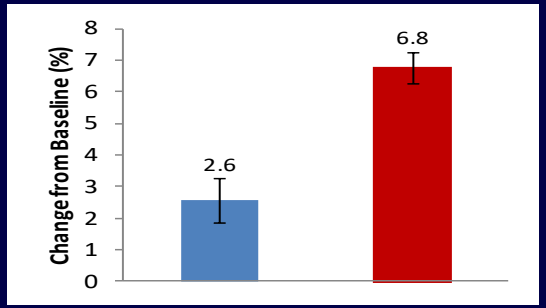
13% ↓ in Triglycerides



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**

Sabatine et al. N Engl J Med 2015; 372: 1500-9

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

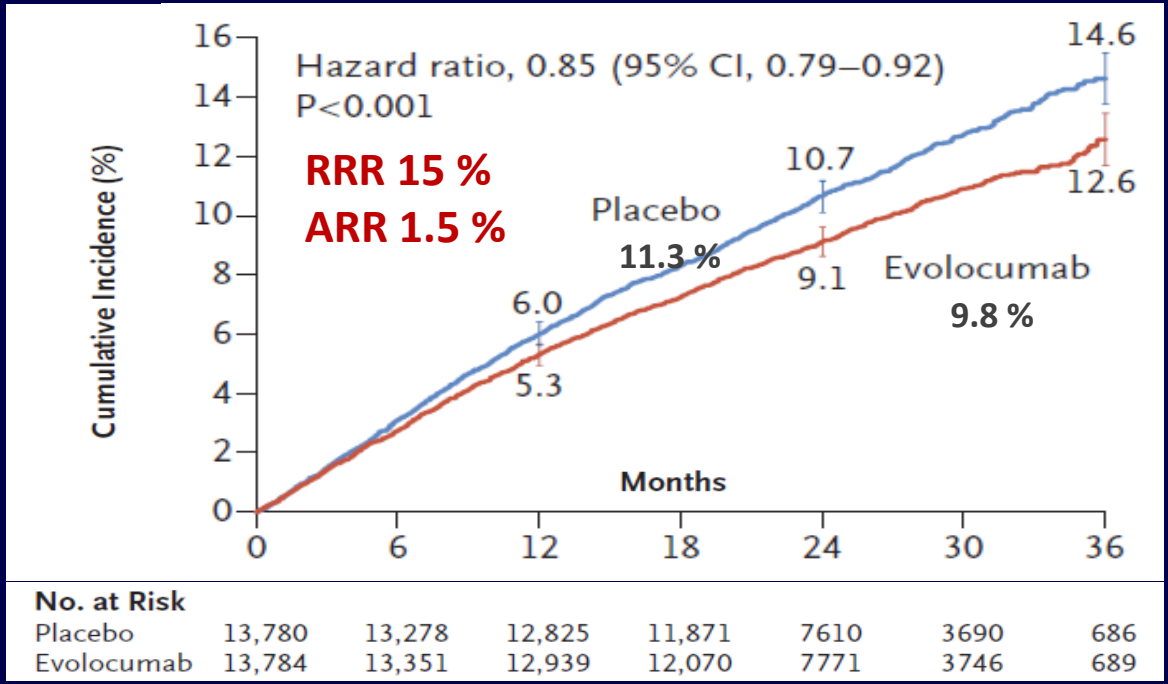
- 27,564 stable patients with established CV disease [prior MI (81%), prior stroke (19%), or symptomatic PAD (13%)]
- 69% on high-intensity statins
- LDL-C $\geq$ 70 mg/dL or non-HDL-C $\geq$ 100 mg/dL
- Randomized to evolocumab Q2W (or Q4W) vs placebo
- Median follow-up 2.2 years

Sabatine et al. N Engl J Med 2017; 376: 1713-22

Cumulative incidence of CV events

Primary Efficacy Endpoint

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



RRR : Relative Risk Reduction ; ARR : Absolute Risk Reduction

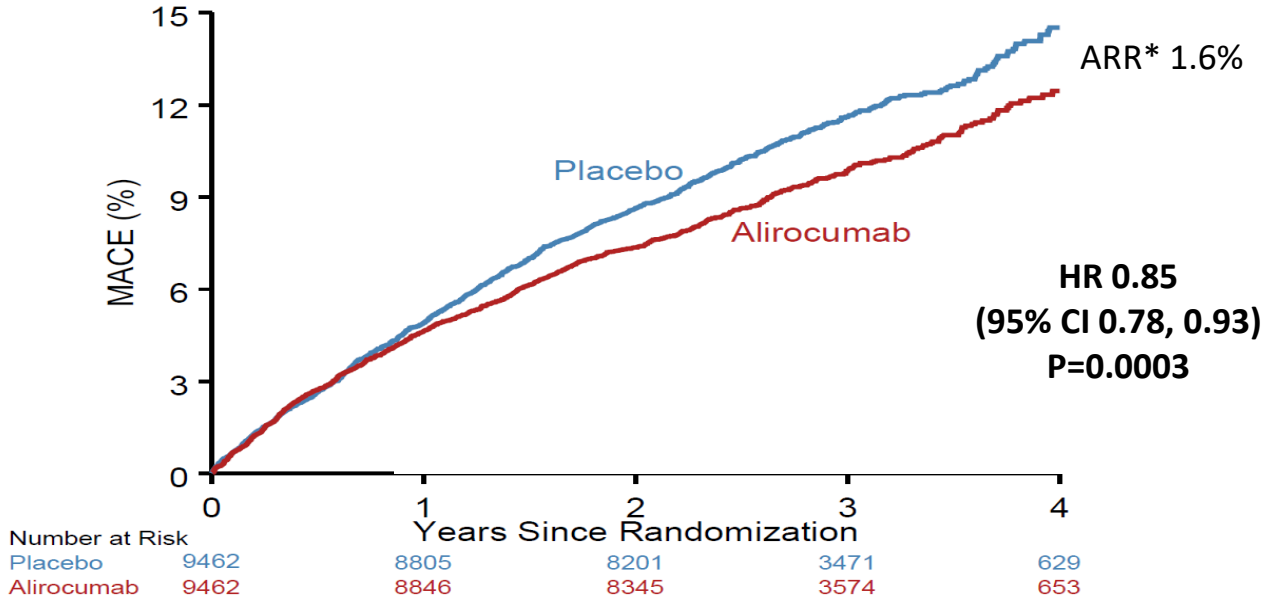
Sabatine et al. N Engl J Med. 2017; 376: 1713-22

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

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

Primary Efficacy Endpoint: MACE



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

* Based on cumulative incidence

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

ODYSSEY OUTCOMES

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
Rhabdomyolsis	0.1	0.1
Cataract	1.7	1.8
Adjucated case of new-onset diabetes	8.1	7.7
Neurocognitive event	1.6	1.5

ODYSSEY Outcomes: Alirocumab[b]

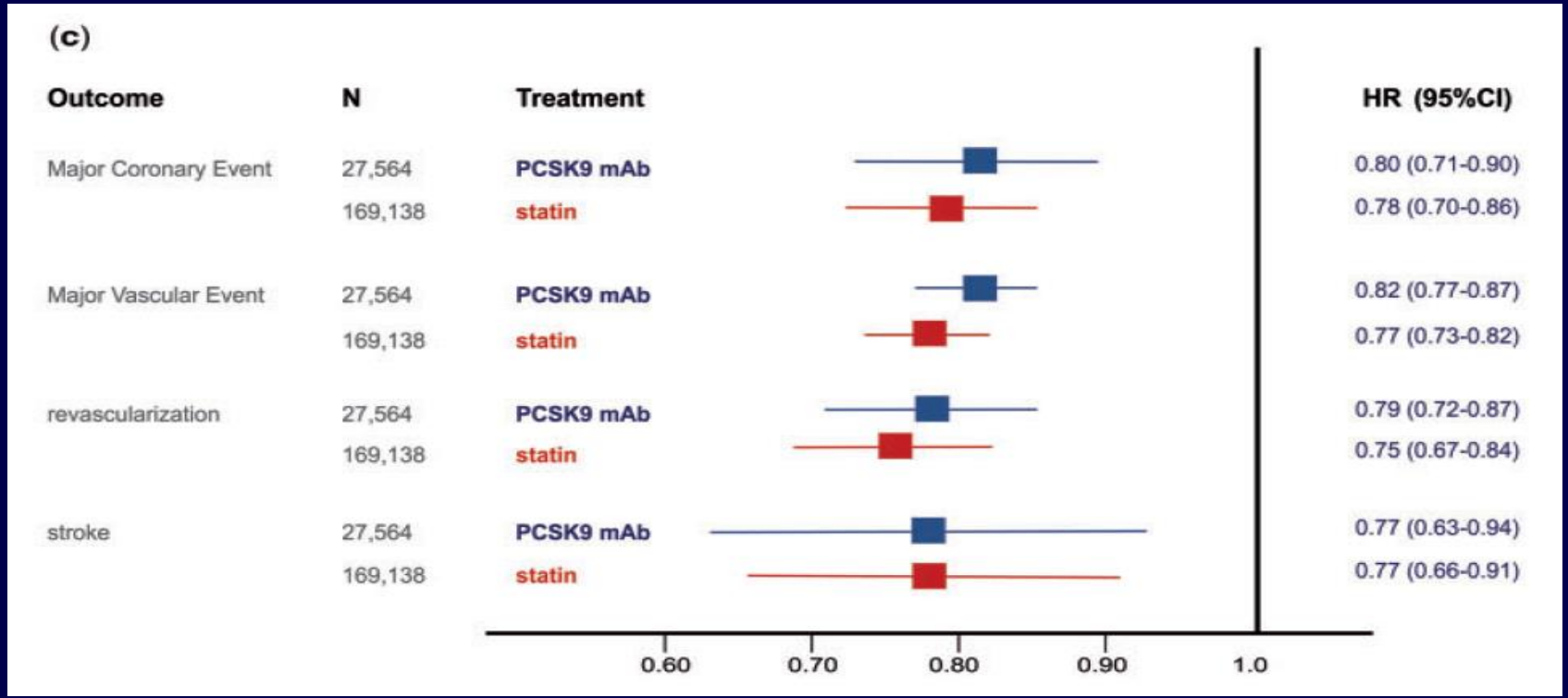
Variable	Alirocumab (N = 9451)	Placebo (N =9443)
Adverse events-no. of patients, %		
Any adverse event	75.8	77.1
Serious adverse event	23.3	24.9
Adverse event that led to death	1.9	2.4
Adverse event that led to discontinuation of the trial regimen	3.6	3.4
Local injection-site reaction	3.8	2.1
General 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*

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

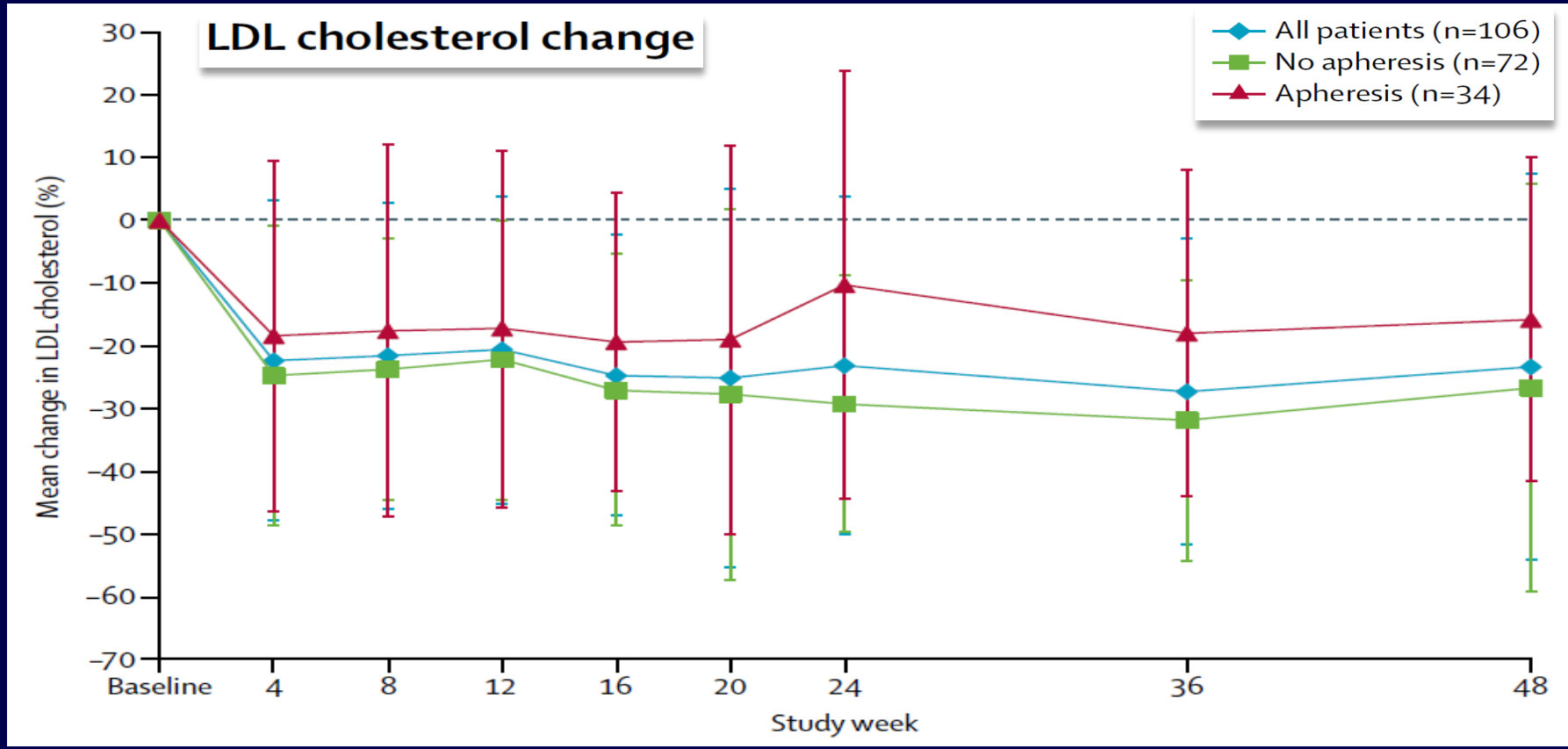


Ference et al. Eur Heart J 2017: online

PCSK9 inhibitors : Opportunities for the successful clinical utilisation

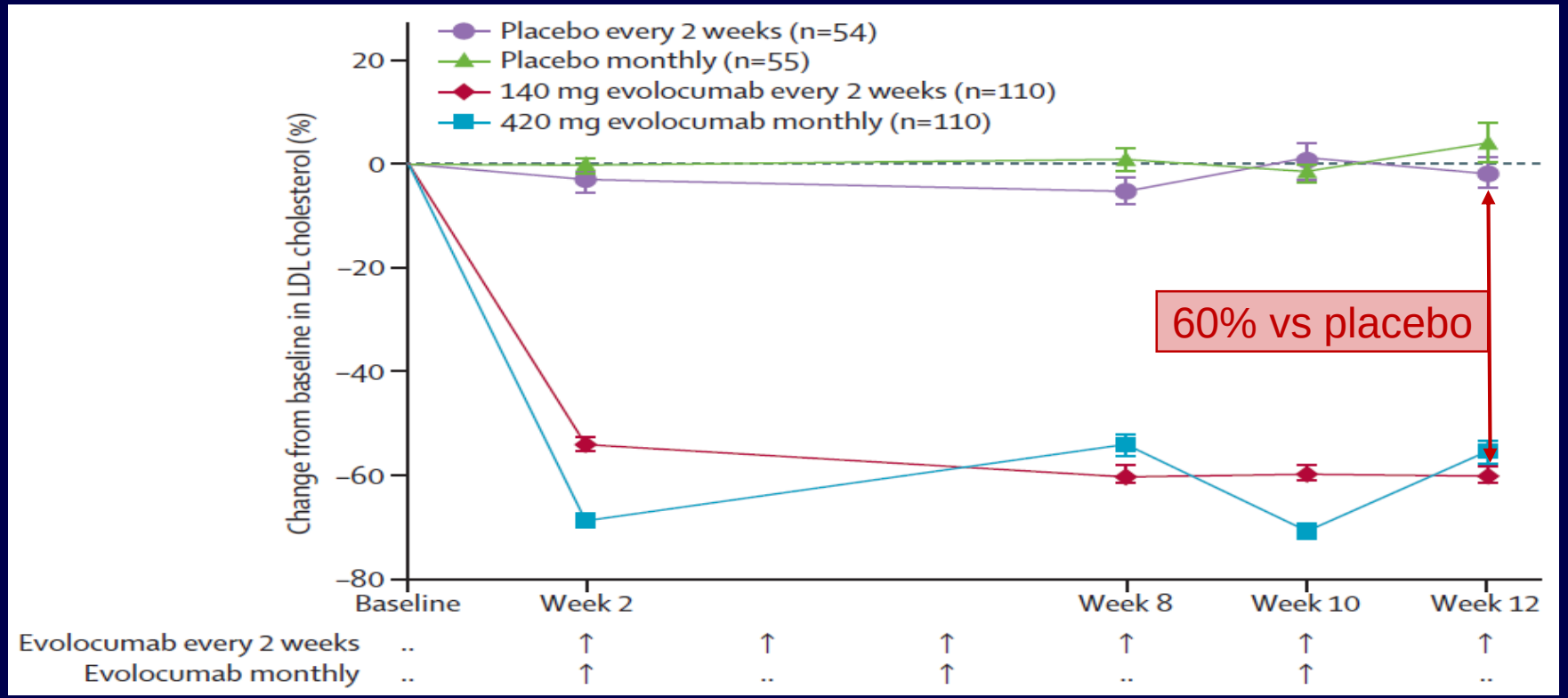
- Further reduction of LDL-C by an average of 50% to 60%
- Further reduction of the risk of CV events
- CV benefits proportional to the absolute reduction in LDL-C and the duration of treatment
- Treatment of familial hypercholesterolemia (FH)

TAUSSIG : HoFH with or without apheresis



Raal et al. Lancet Diabetes Endocrinol 2017; 5: 280-90

Evolocumab significantly reduces LDL-C in patients with heterozygous FH



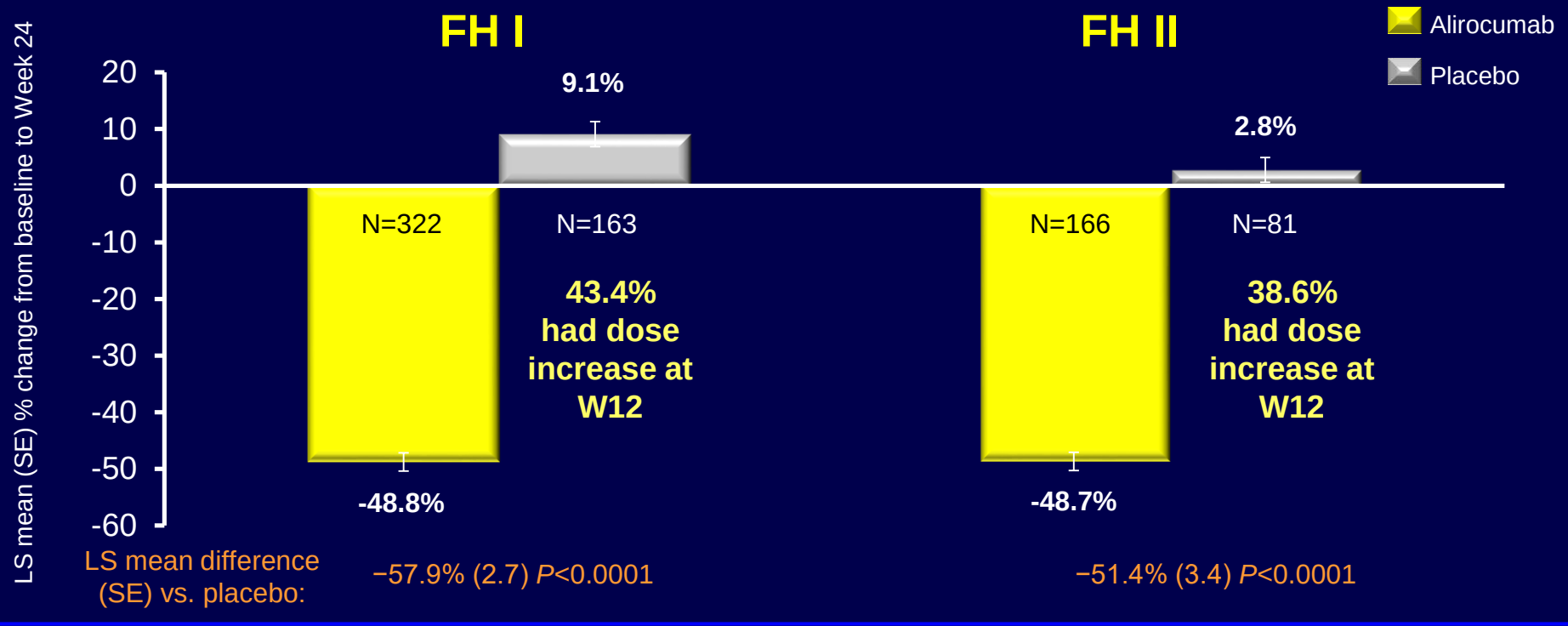
Raal et al. Lancet 2015; 385: 331-40

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

ODYSSEY

Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C

All patients on background max-tolerated statin ±other lipid-lowering therapy

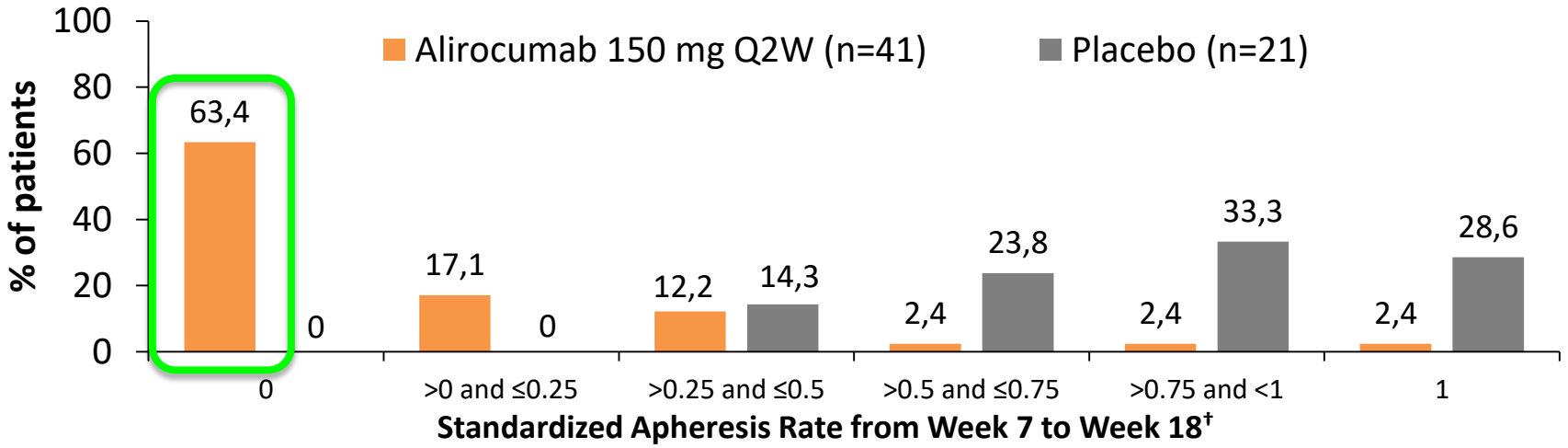


Intent-to-treat (ITT) Analysis

Kastelein et al. Eur Heart J 2015; 36: 2996-3003

Standardized Apheresis Treatment Rates from Week 7–18

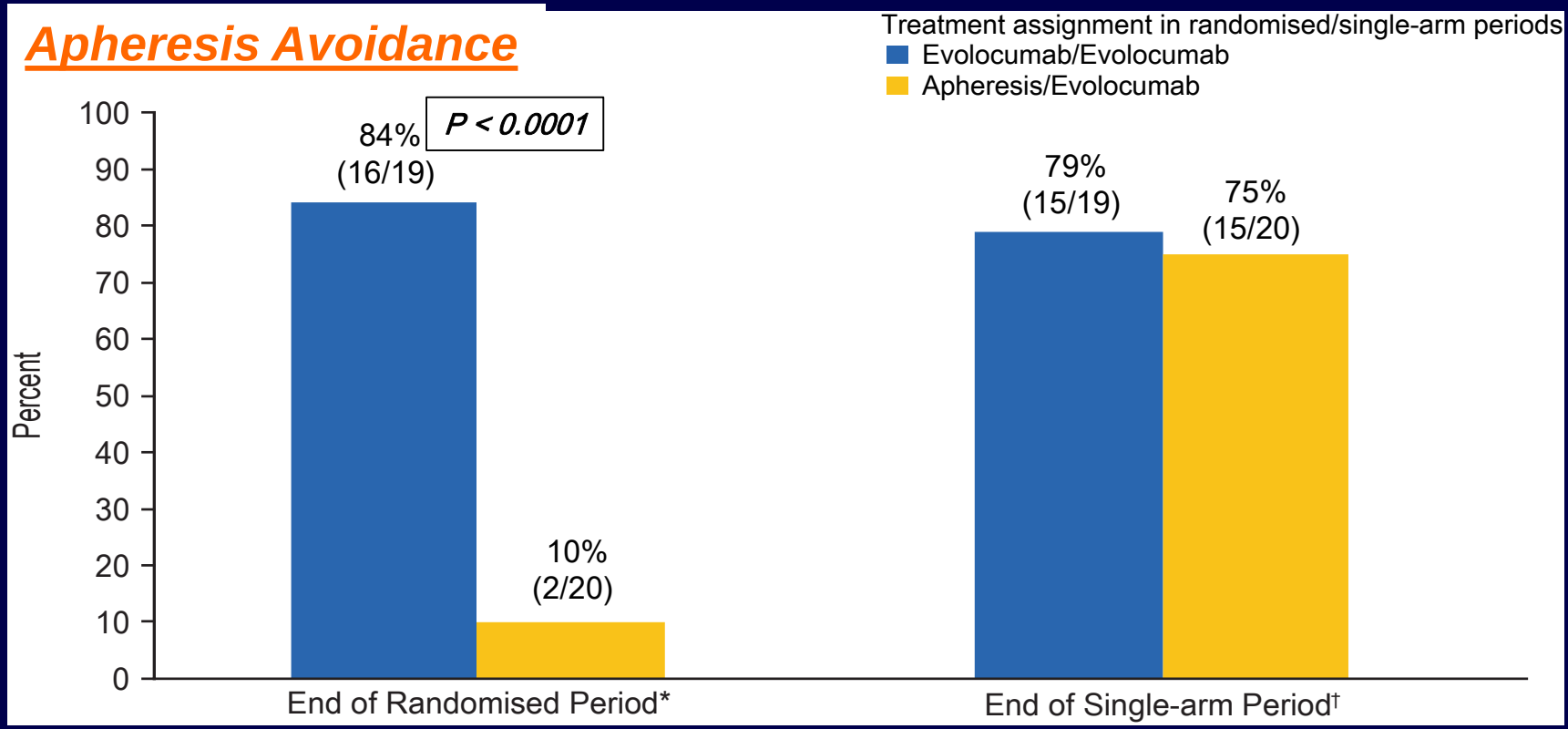
Standardised apheresis treatment rate in the period:	Weeks 7–18	Weeks 15–18
Hodges-Lehmann estimate of median treatment difference (95% CI):	0.75 (0.67 to 0.83)	0.50 (0.50 to 1.00)
p-value versus placebo:	p<0.0001	p<0.0001



†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)

Moriarty et al. Eur Heart J 2016; 37: 3588-95

Evolocumab compared with continued Lipoprotein Apheresis (LA)



* Based on Week 4 LDL-C < 2.6 mmol/L † Based on Week 22 LDL-C < 2.6 mmol/L

Moriarty et al. ESC 2017, p 1314

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

PCSK9 inhibitors: Barriers for the successful clinical utilisation

- Cost of PCSK9i monoclonal antibodies

Medical rationale
(*absolute CV risk*)
and
cost effectiveness

Pharmacological LDL-C lowering

ESC/EAS GUIDELINES
European Heart Journal (2019)

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

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; *Class of recommendation; †Level of evidence

Mach F, et al. Eur Heart J. 2019;0:1–78

PCSK9 inhibitors

How identify which patients would benefit most from PCSK9 inhibitors ?

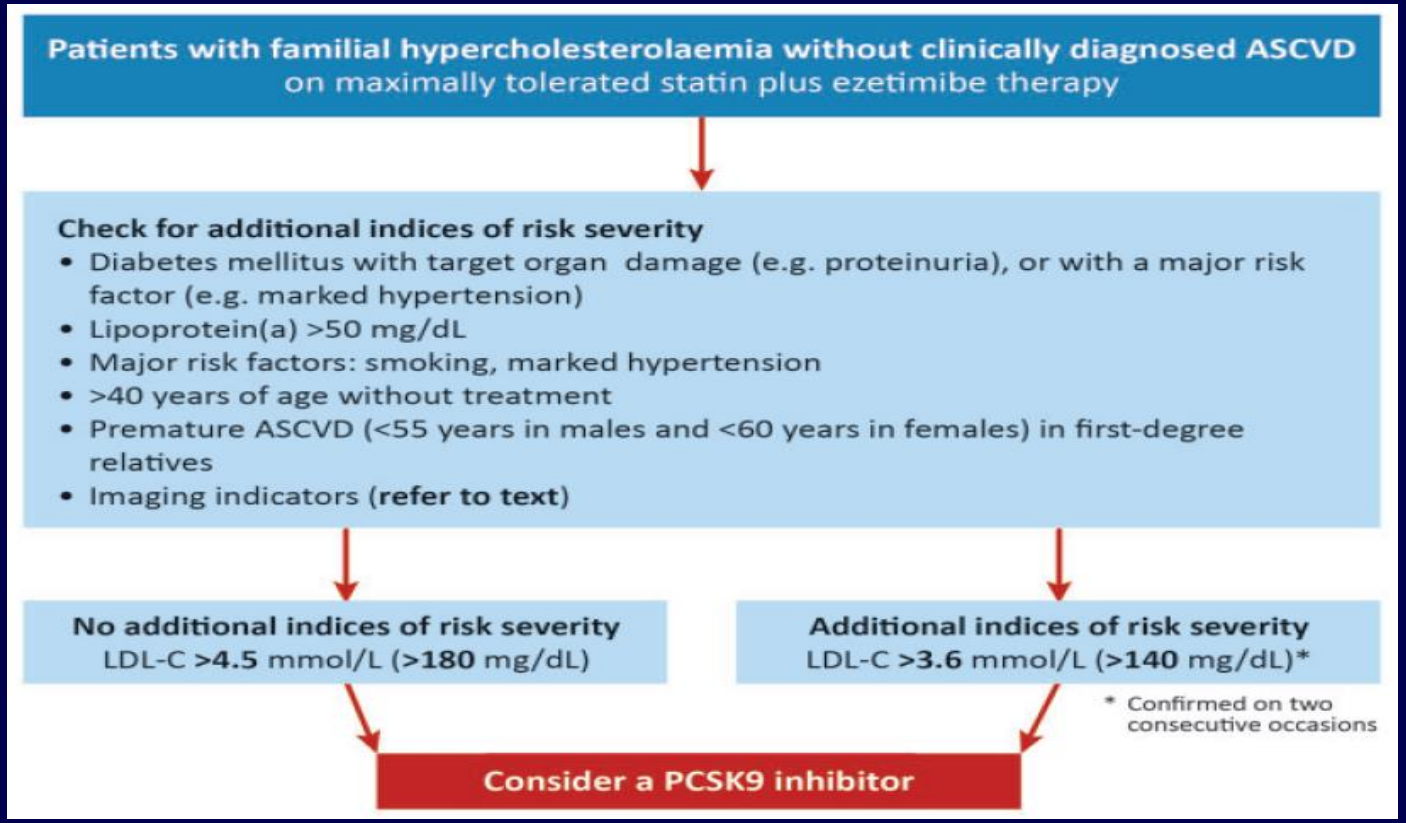
ESC European Society of Cardiology European Heart Journal 2018; 39: 1131-1143

CURRENT OPINION

2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

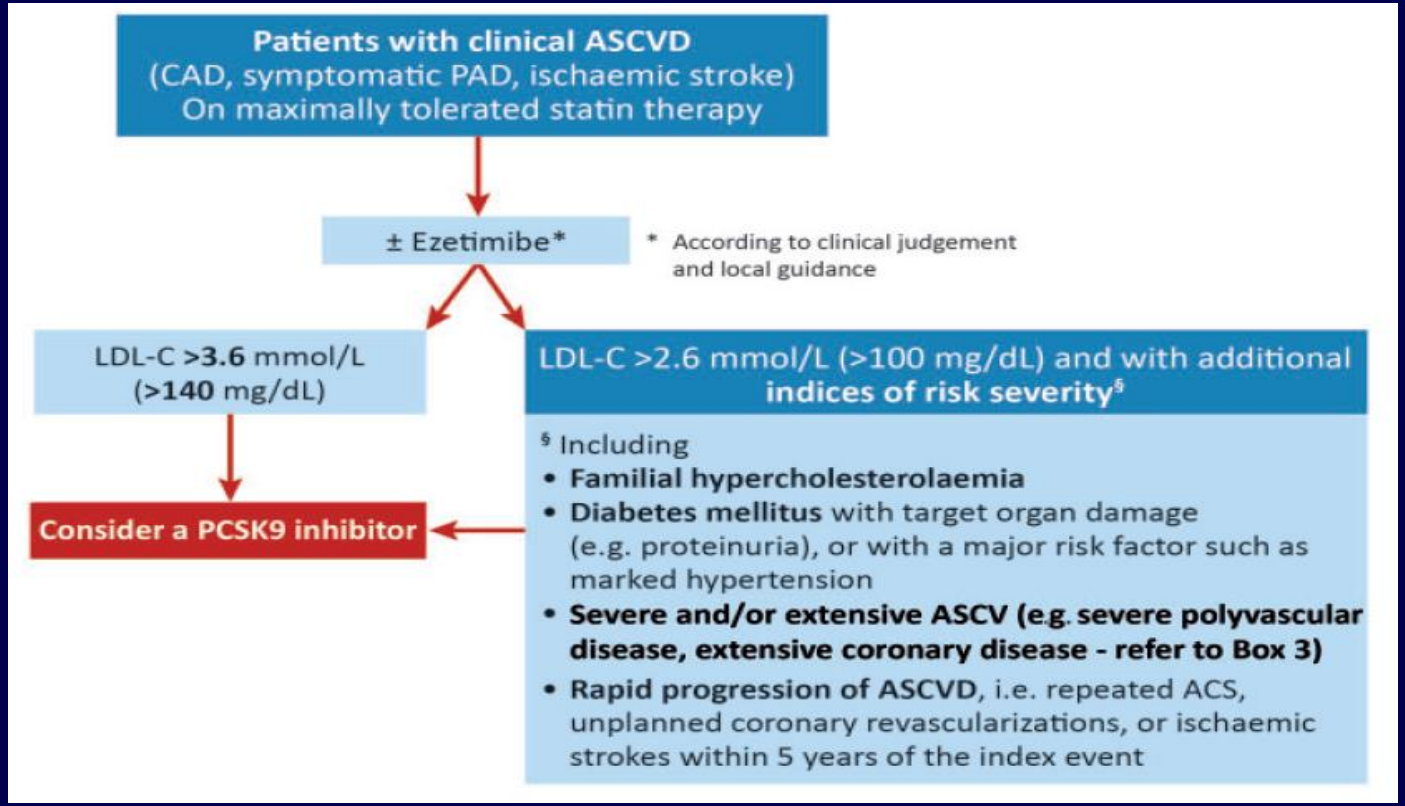
Ulf Landmesser[1*†], M. John Chapman[2†], Jane K. Stock[3], Pierre Amarenco[4], Jill J.F. Belch[5], Jan Borén[6], Michel Farnier[7], Brian A. Ference[8], Stephan Gielen[9], Ian Graham[10], Diederick E. Grobbee[11], G. Kees Hovingh[12], Thomas F. Lüscher[13], Massimo F. Piepoli[14], Kausik K. Ray[15], Erik S. Stroes[12], Olov Wiklund[16], Stephan Windecker[17], Jose Luis Zamorano[18], Fausto Pinto[19], Lale Tokgözoğlu[20], Jeroen J. Bax[21], and Alberico L. Catapano[22]

Clinical decision algorithm for the use of a PCSK9 inhibitor in FH patients without clinical ASCVD



Landmesser et al. Eur Heart J 2018; 39: 1131-43

Clinical decision algorithm for the use of PCSK9 inhibitors in patients with ASCVD

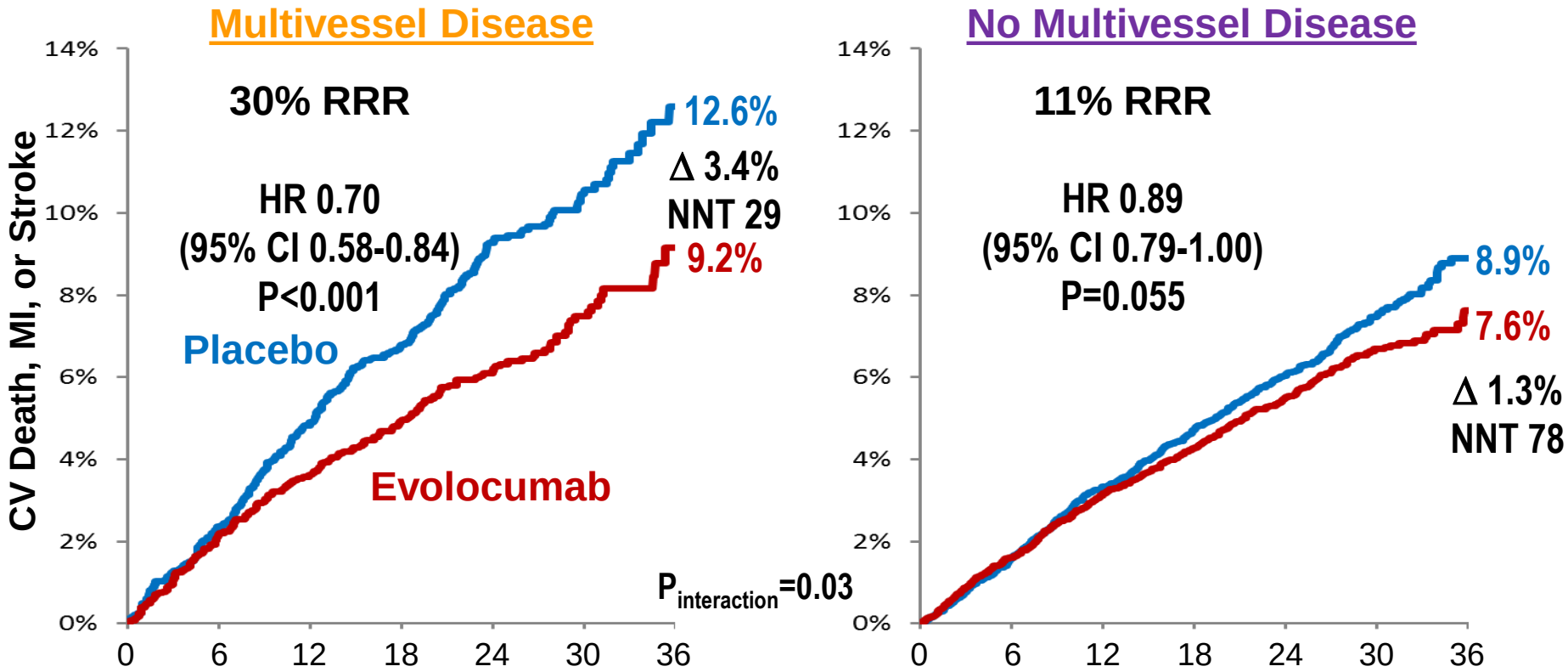


Landmesser et al. Eur Heart J 2018; 39: 1131-43

High-risk patients with ASCVD likely to derive greater absolute benefit from PCSK9 inhibition

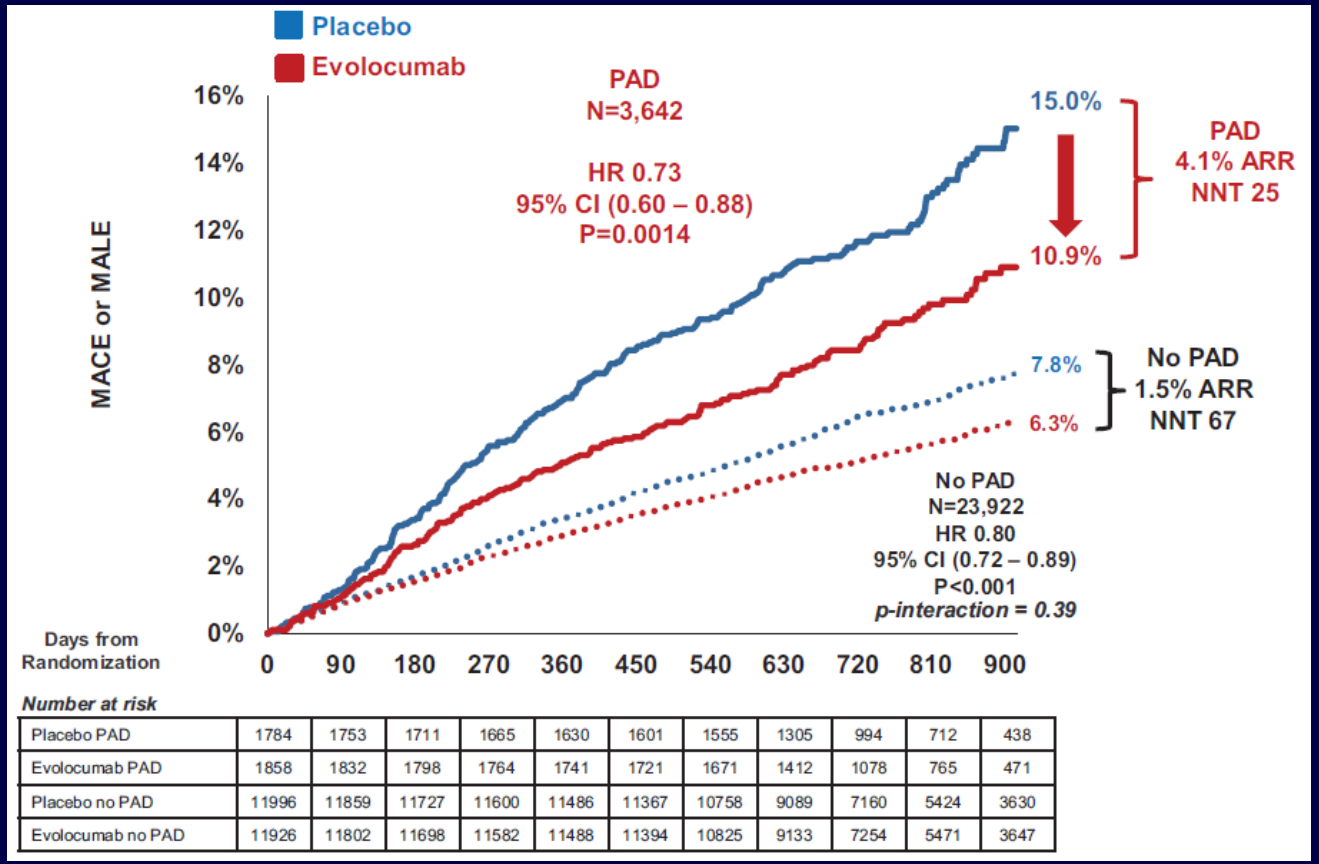
- Polyvascular patients
- Post-CABG patients, patients with PAD
- Patients with LDL-C > 100 mg/dl
- Patients with diabetes
- Patients with high Lp(a)

Benefit of EvoMab Based on Multivessel Disease



Sabatine et al. Circulation 2018; online April 6

FOURIER : MACE or MALE in patients with and without PAD

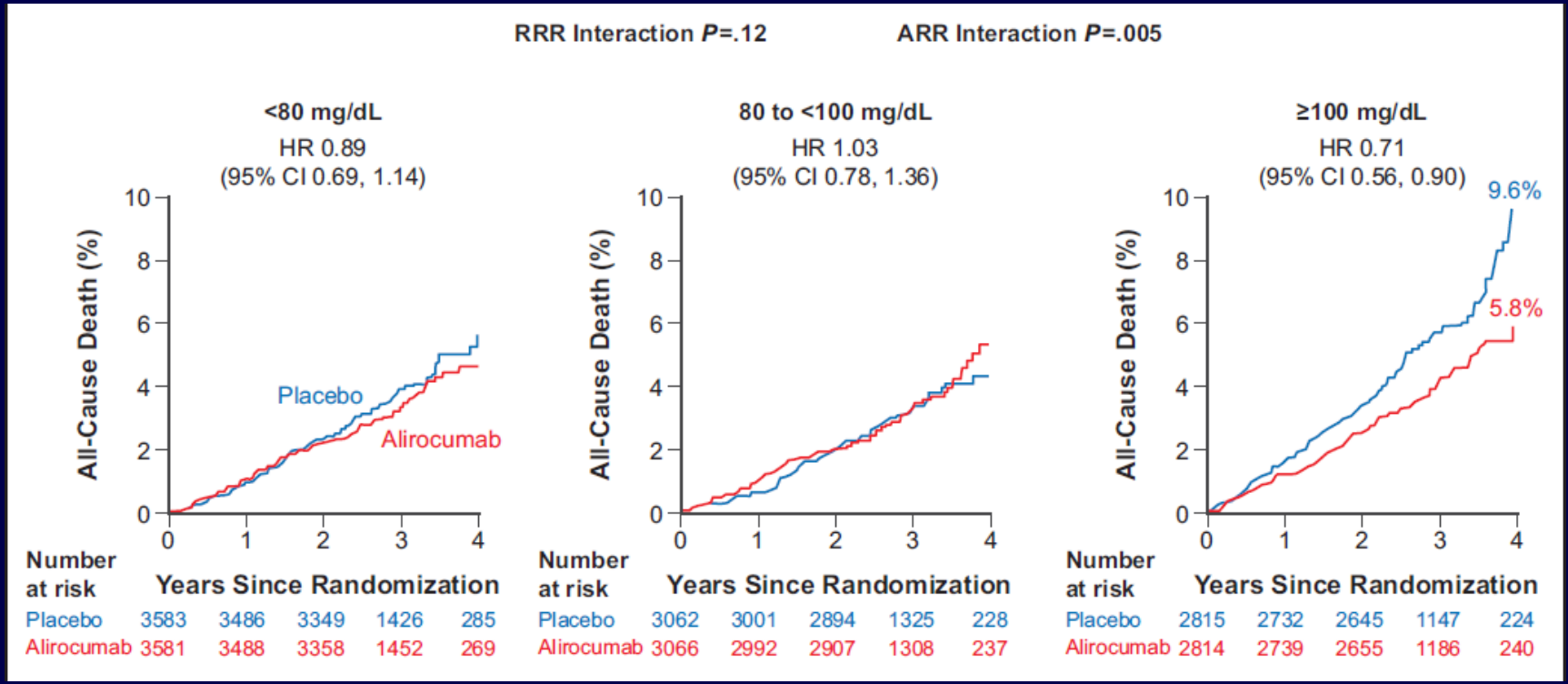


Number at risk

Placebo PAD	1784	1753	1711	1665	1630	1601	1555	1305	994	712	438
Evolocumab PAD	1858	1832	1798	1764	1741	1721	1671	1412	1078	765	471
Placebo no PAD	11996	11859	11727	11600	11486	11367	10758	9089	7160	5424	3630
Evolocumab no PAD	11926	11802	11698	11582	11488	11394	10825	9133	7254	5471	3647

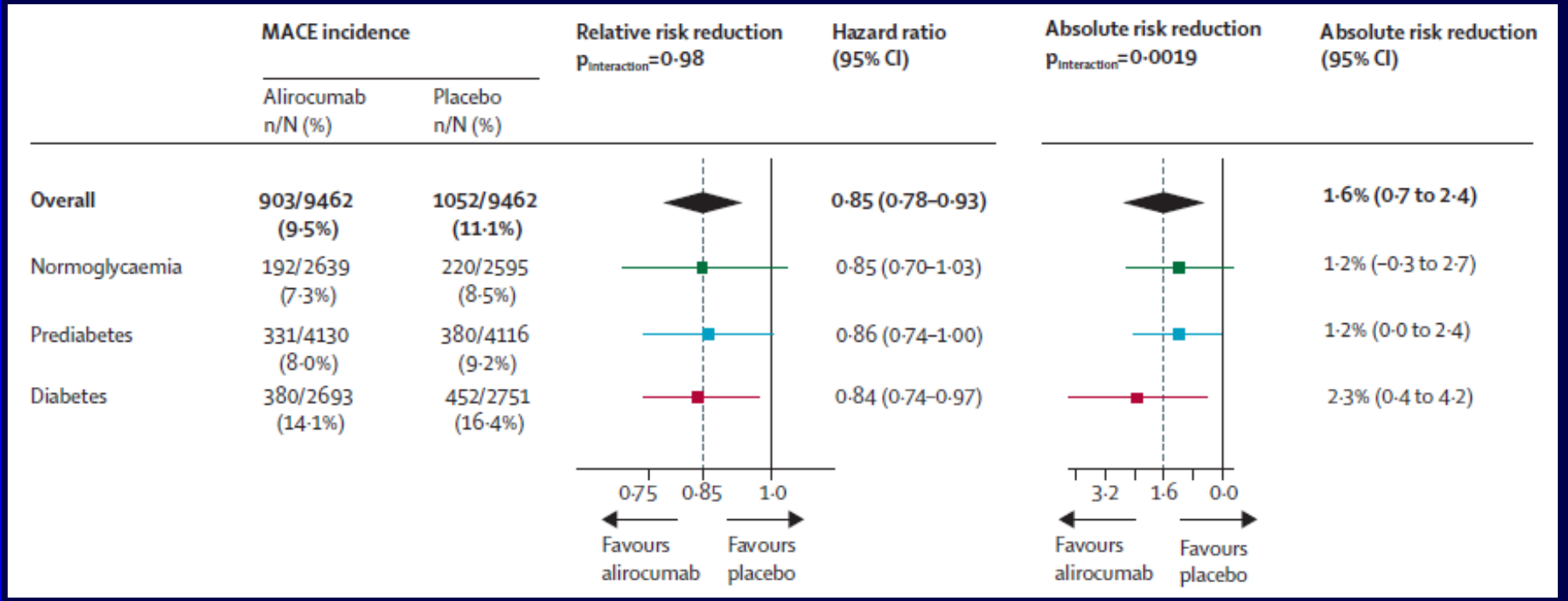
Bonaca MP, et al. Circulation. 2018; 137: 338-350

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



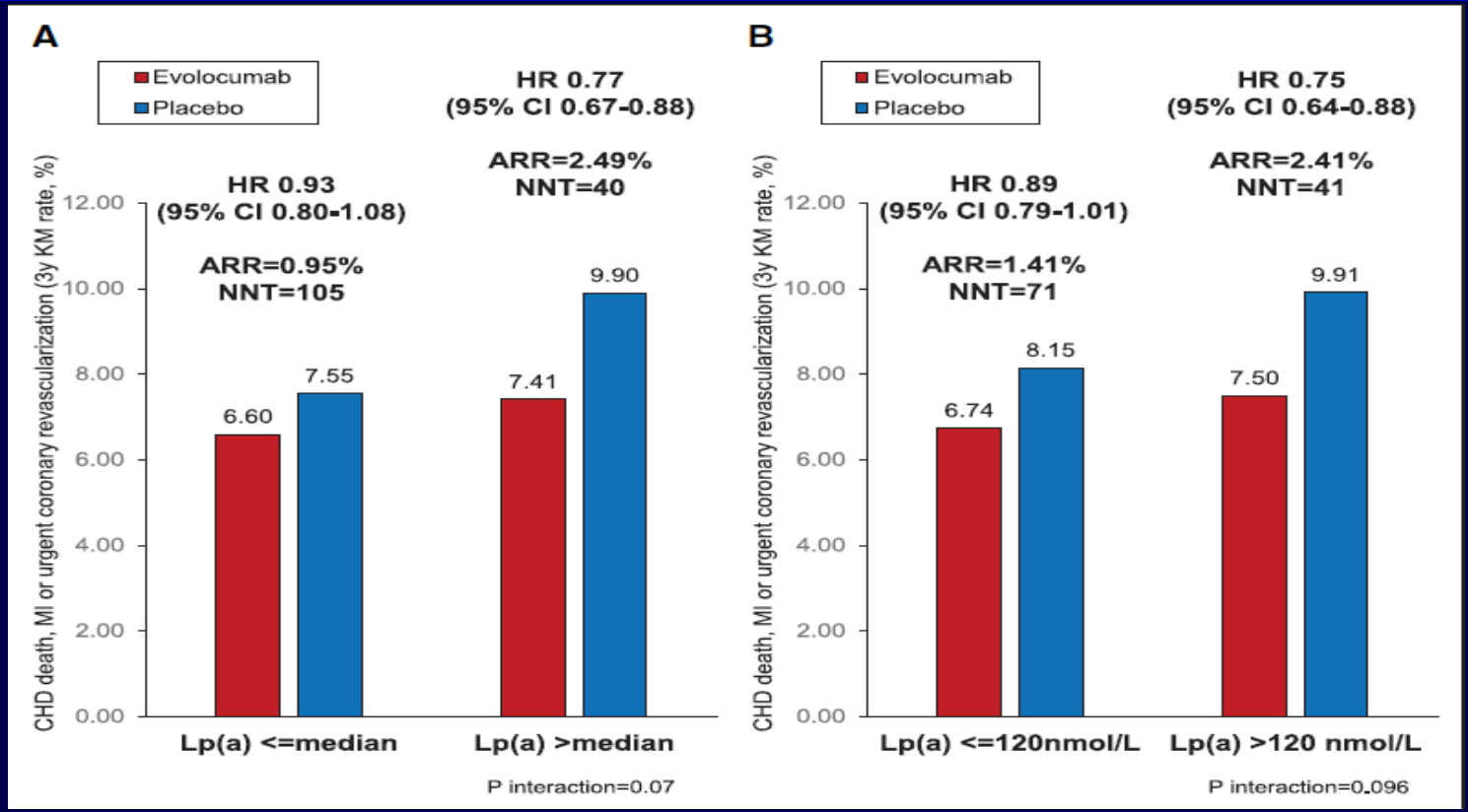
Steg et al. Circulation 2019; 140: 103-12

ODYSSEY-Outcomes: relative and absolute risk reduction by baseline glycaemic status



Ray et al. Lancet Dibates 2019; 7: 618-28

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

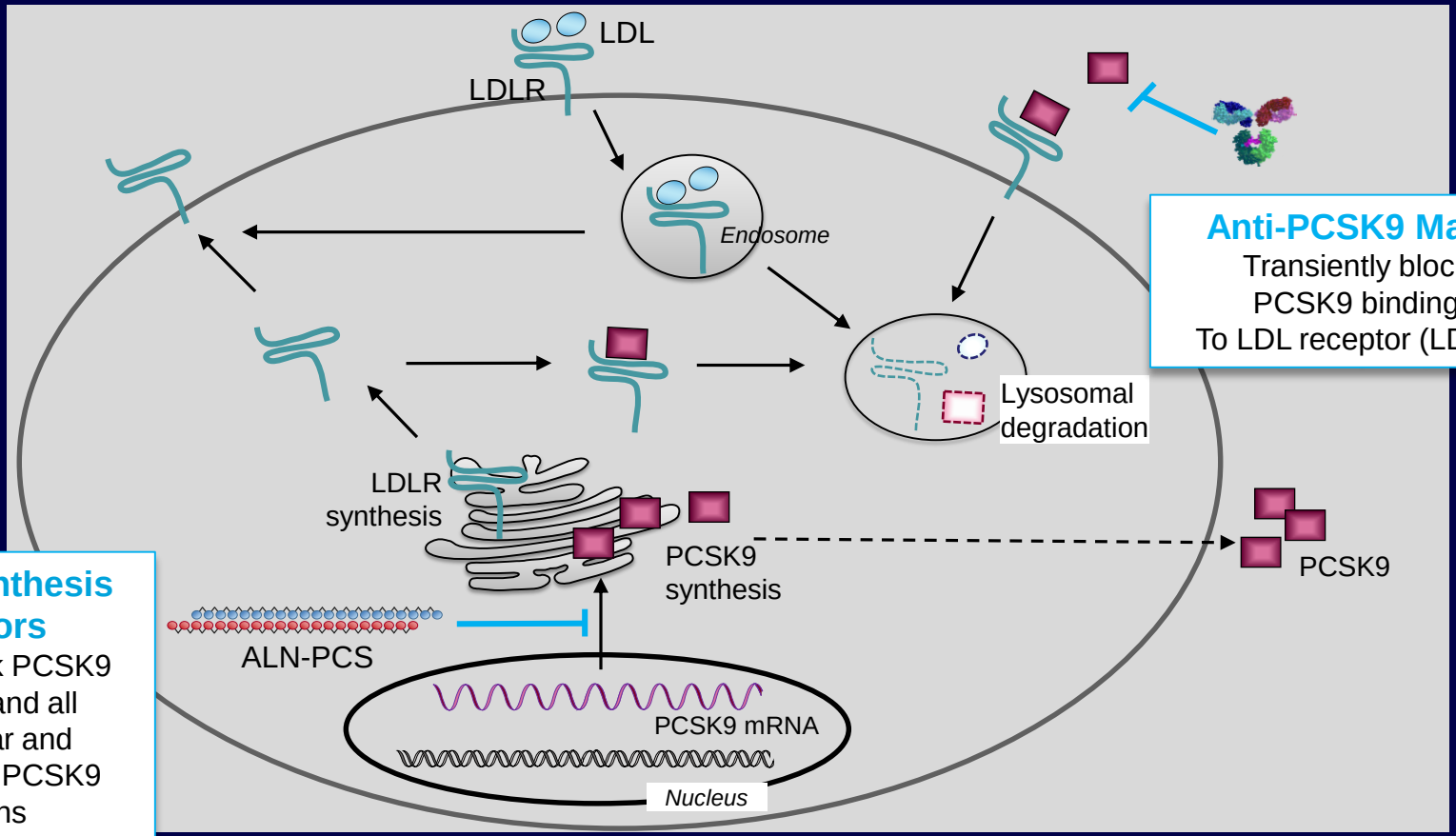


O'Donoghue et al. Circulation 2019; 139: 1483-92

PCSK9 inhibitors

- Monoclonal Antibodies (mAbs)
  - alirocumab
  - evolocumab
  - bococizumab ~~X~~
- siRNA (inclisiran)

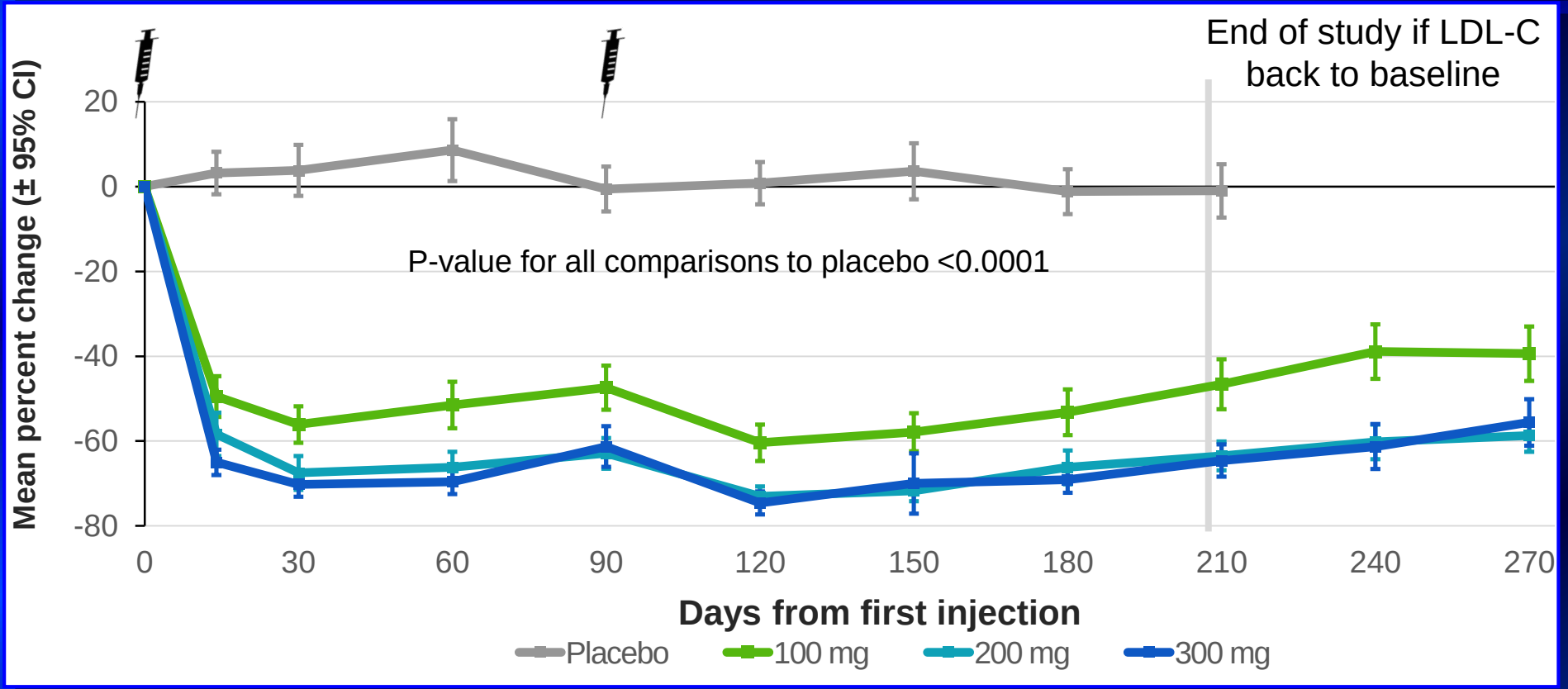
PCSK9 Therapeutic Inhibition



Anti-PCSK9 Mabs
Transiently block PCSK9 binding To LDL receptor (LDLR)

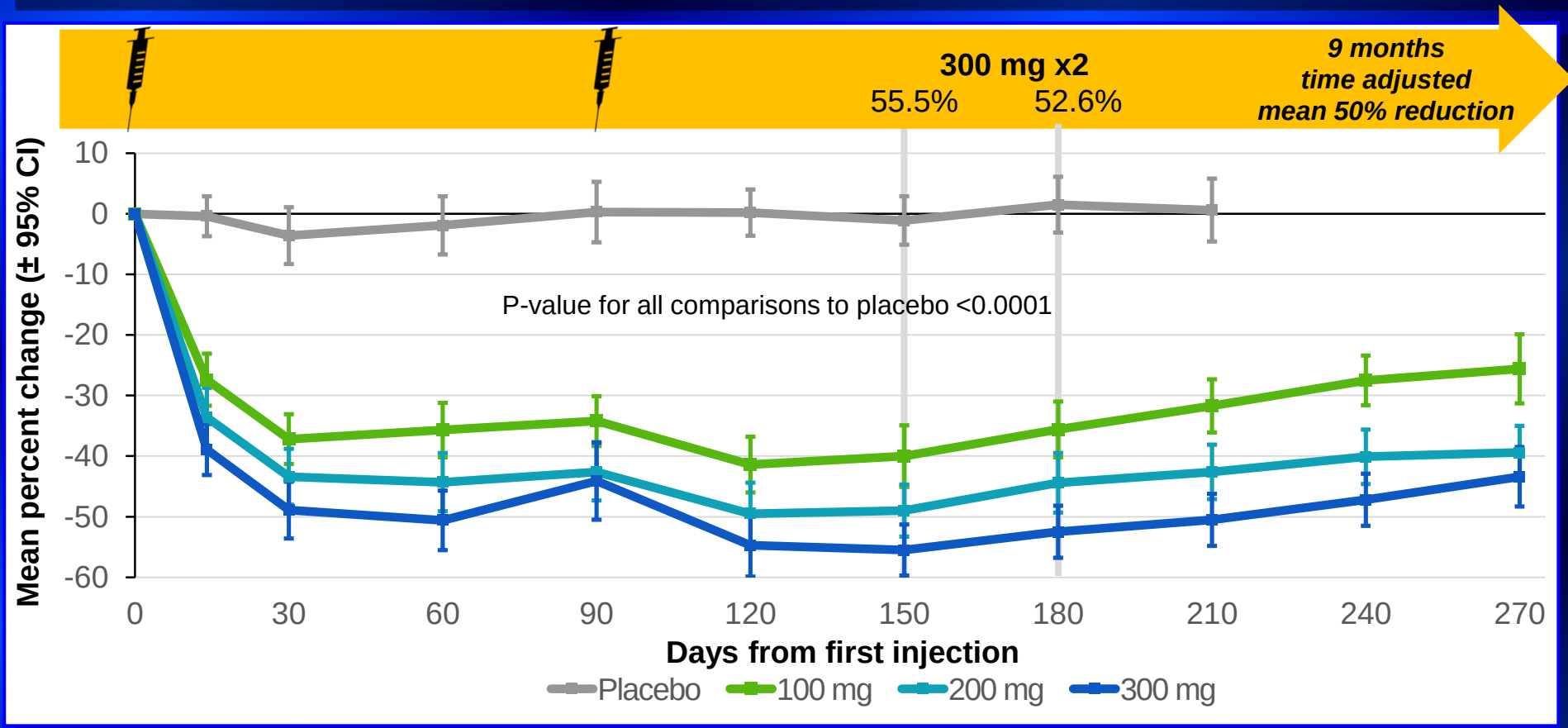
PCSK9 Synthesis Inhibitors
Durably block PCSK9 synthesis and all intracellular and extracellular PCSK9 functions

Efficacy: Two dose starting regimen
Clamped PCSK9 knockdown



Ray et al. N Engl J Med. 2017; 376: 1430-40

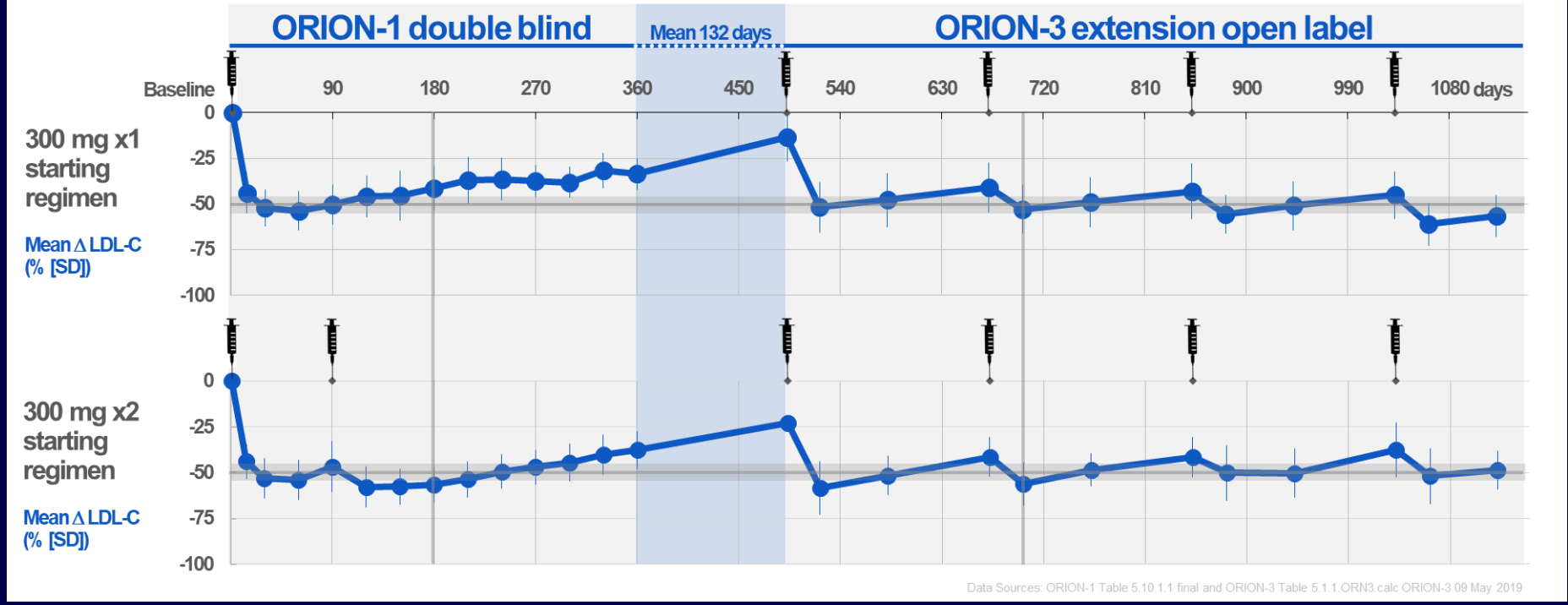
Efficacy: Two dose starting regimen
Robust, sustained LDL-C reductions – optimal start regimen



Ray et al. N Engl J Med. 2017; 376: 1430-40

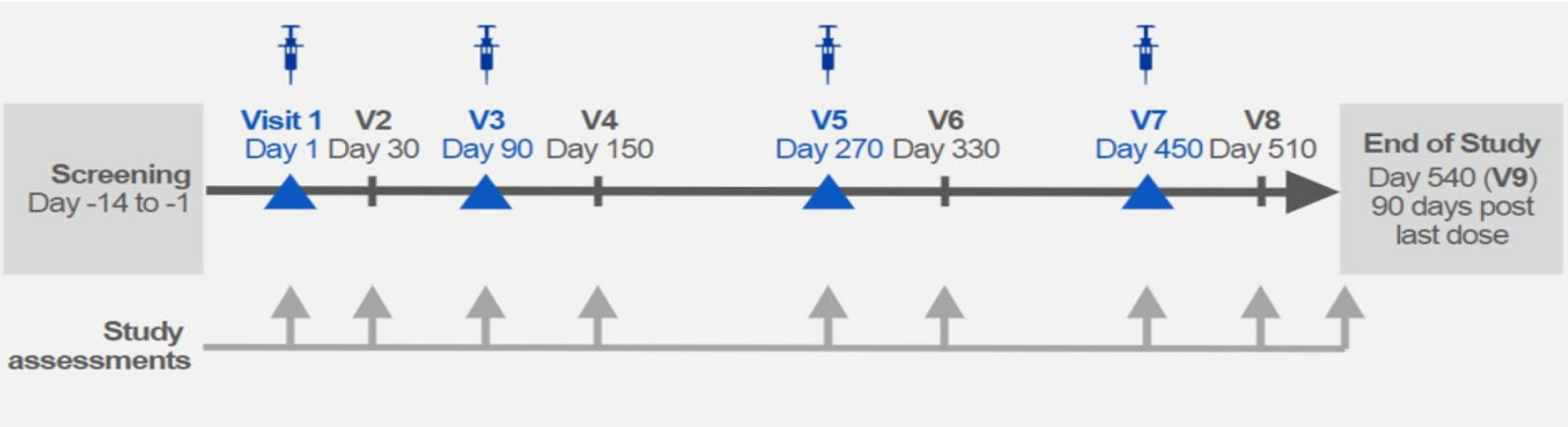
Long-term effect of 300 mg inclisiran on LDL-C

Consistent lowering of LDL-C >50% with no loss of effect over ~3 years



ORION-11 : Study design eighteen months treatment and observation

- Randomized 1:1 inclisiran 300 mg vs placebo – with maximally tolerated statins



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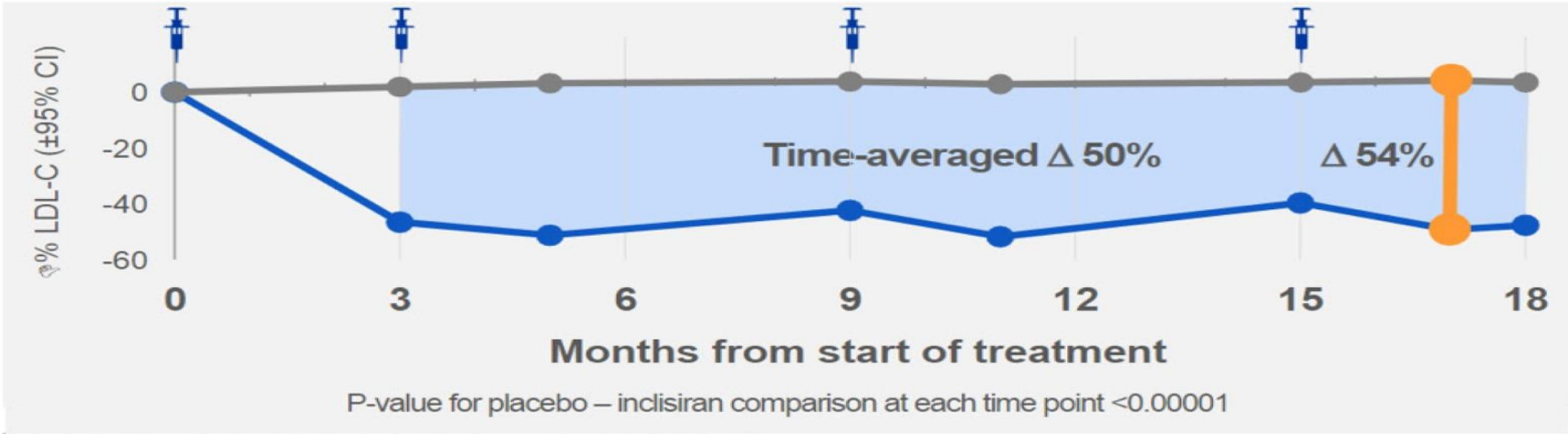
ORION-11 : Efficacy

Durable, potent, and consistent effect of over 18 months



1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

ORION-11 : Safety and tolerability

Adverse event profile similar to placebo

Treatment emergent adverse event (TEAE) Safety population[1] – AEs in ≥5% patients	Placebo N = 807		Inclisiran N = 810	
Patients with at least one TEAE	655	(82%)	671	(83%)
Diabetes mellitus adverse events	94	(12%)	88	(11%)
Nasopharyngitis	90	(11%)	91	(11%)
Hypertension	54	(7%)	53	(7%)
Upper respiratory tract infection	49	(6%)	52	(6%)
Arthralgia	32	(4%)	47	(6%)
Osteoarthritis	40	(5%)	32	(4%)

1. Safety population includes all patients who received at least 1 dose of study medication 2. Other TEAEs reported with lower frequencies than 5% in any group had no clinically meaningful differences

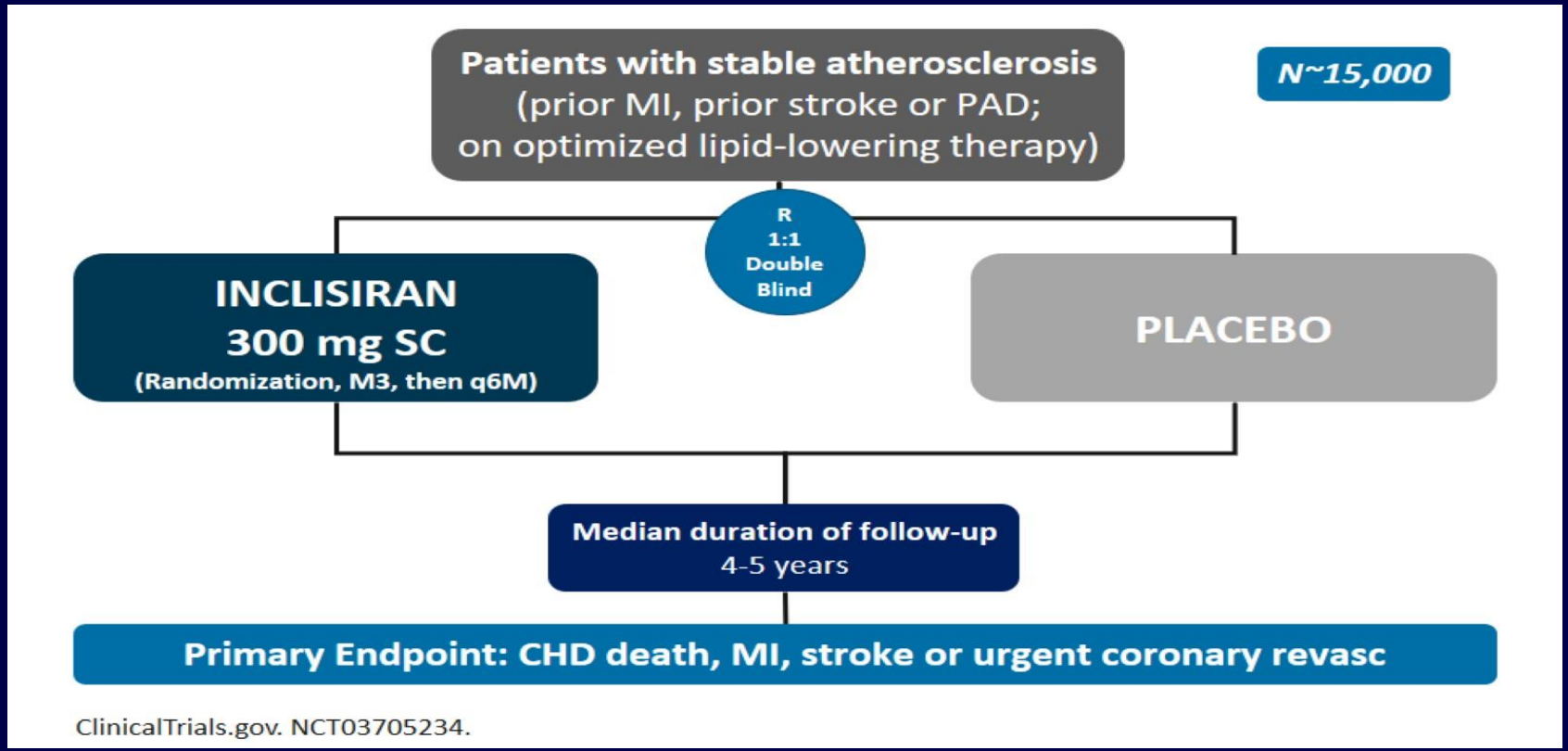
ORION-11 : Safety and tolerability

Injection site AEs localized, mostly mild and transient

Injection site TEAEs Safety population[1]	Placebo N = 807	Inclisiran N = 810	Difference
Protocol-defined skin event	**4 (0.50%)**	**38 (4.69%)**	**4.19%**
(Reaction, erythema, rash, pruritus, hypersensitivity)			
Mild	3 (0.37%)	23 (2.84%)	2.46%
Moderate	1 (0.13%)	15 (1.85%)	1.73%
Severe	0 ( )	0 ( )	
Persistent	0 ( )	0 ( )	

1. Safety population includes all patients who received at least 1 dose of study medication

ORION-4 design



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 ?


Thank you