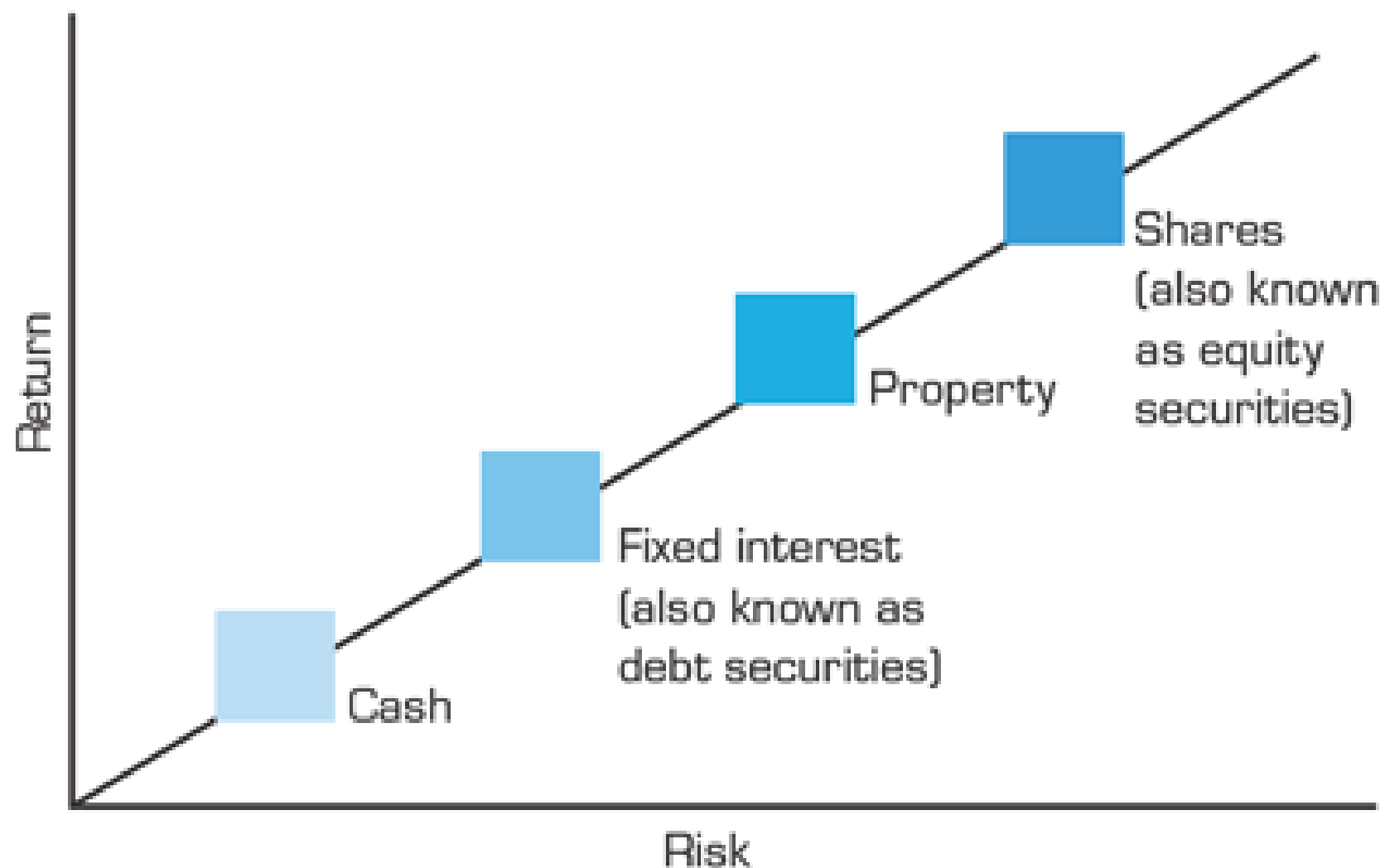


Paradim Shift in cholesterol behandeling: *van LDL-C target naar LDL-C eradication*

Prof. G.Kees Hovingh, MD PhD MBA
Dept. Vascular Medicine
Academic Medical Center
Amsterdam, the Netherlands

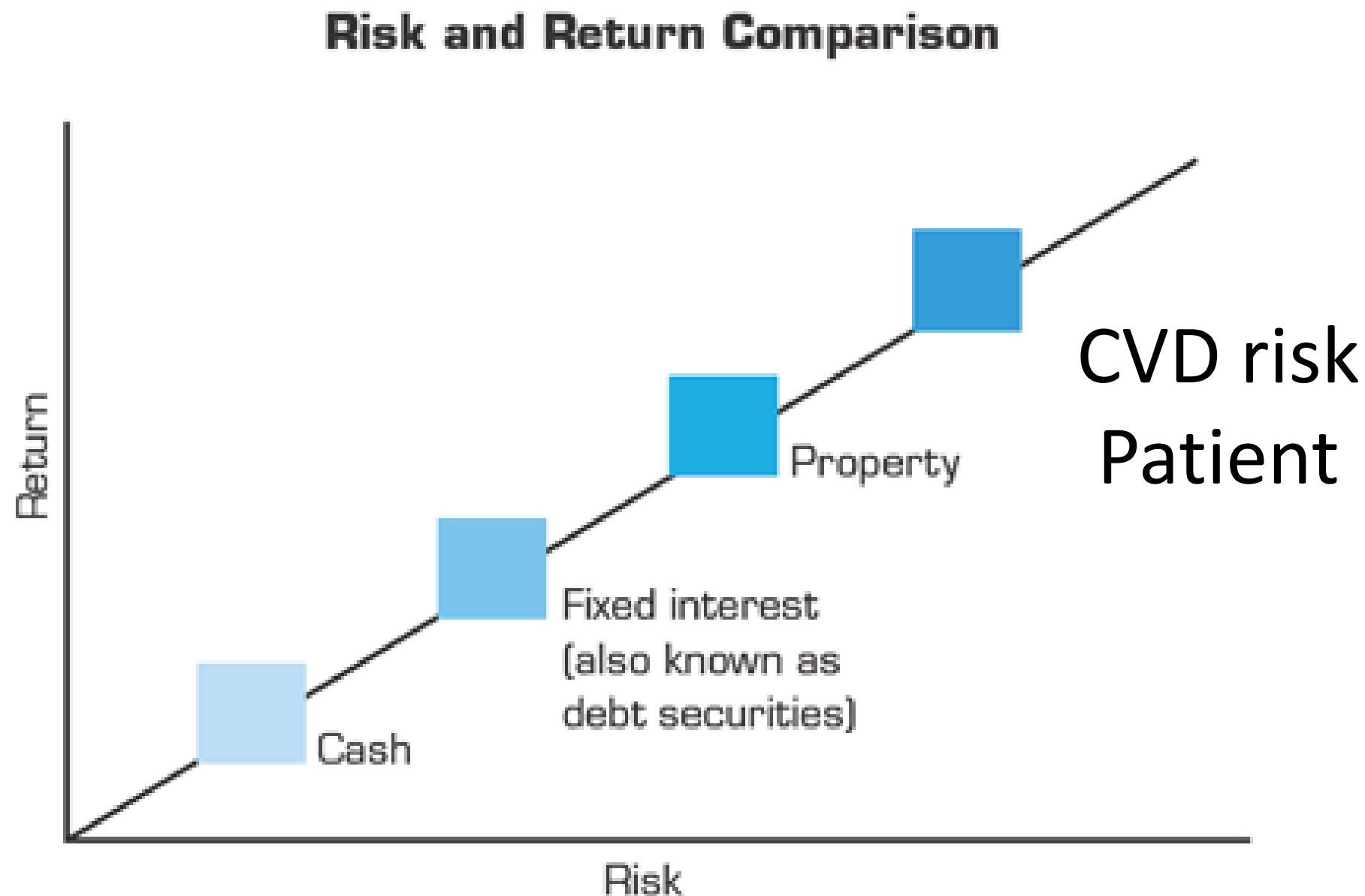
Risk and profit

Risk and Return Comparison

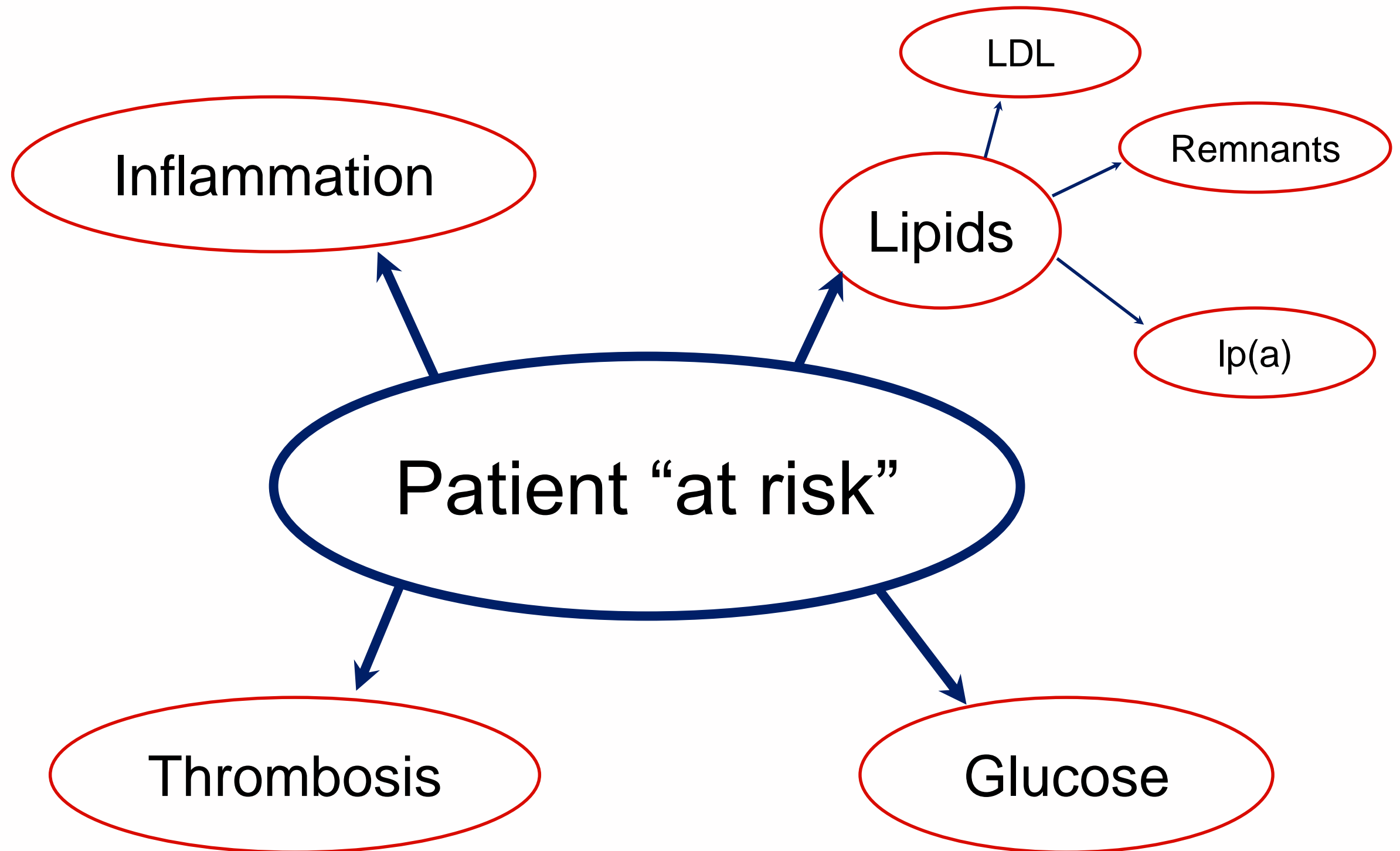


High risk CVD patients

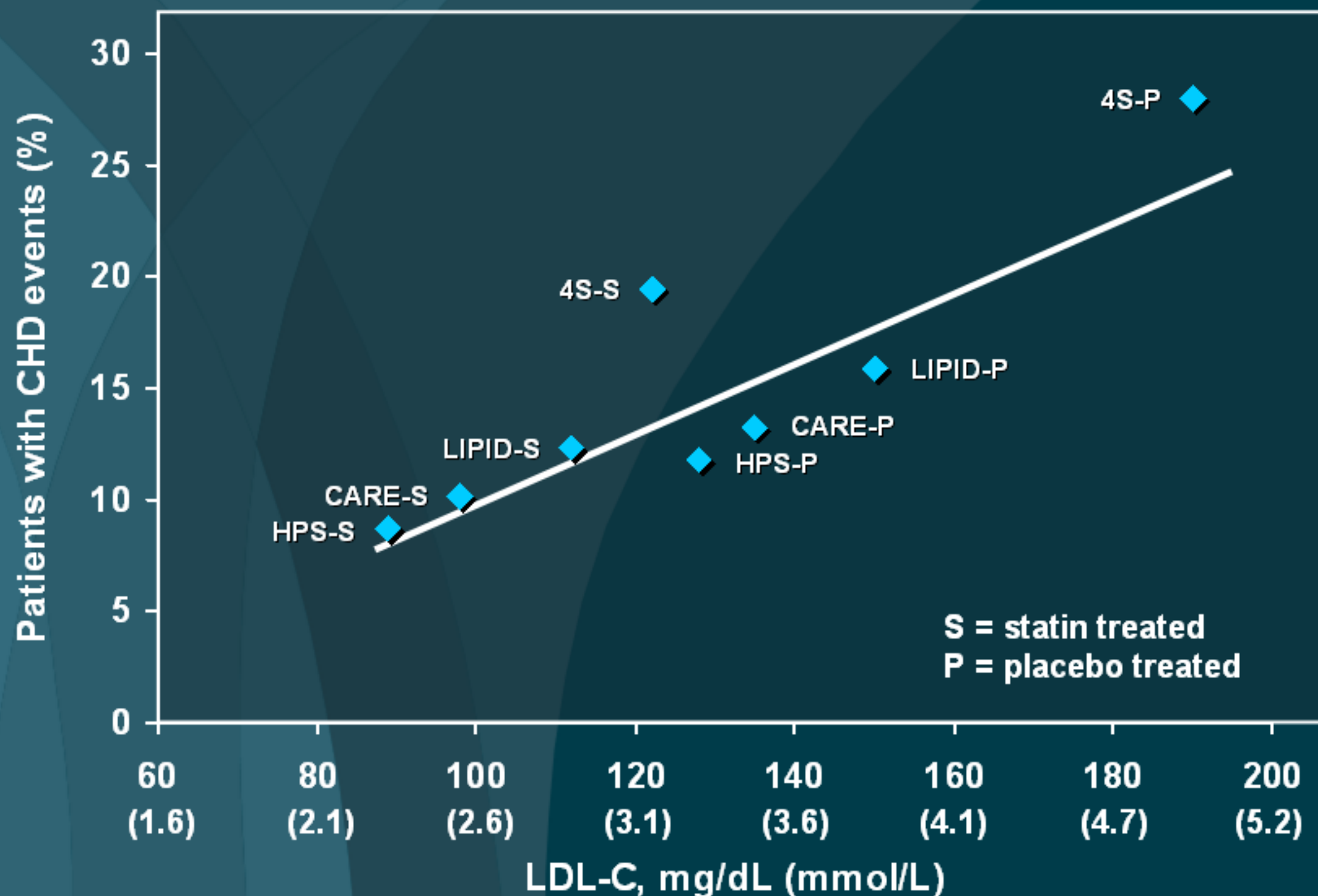
Risk and profit



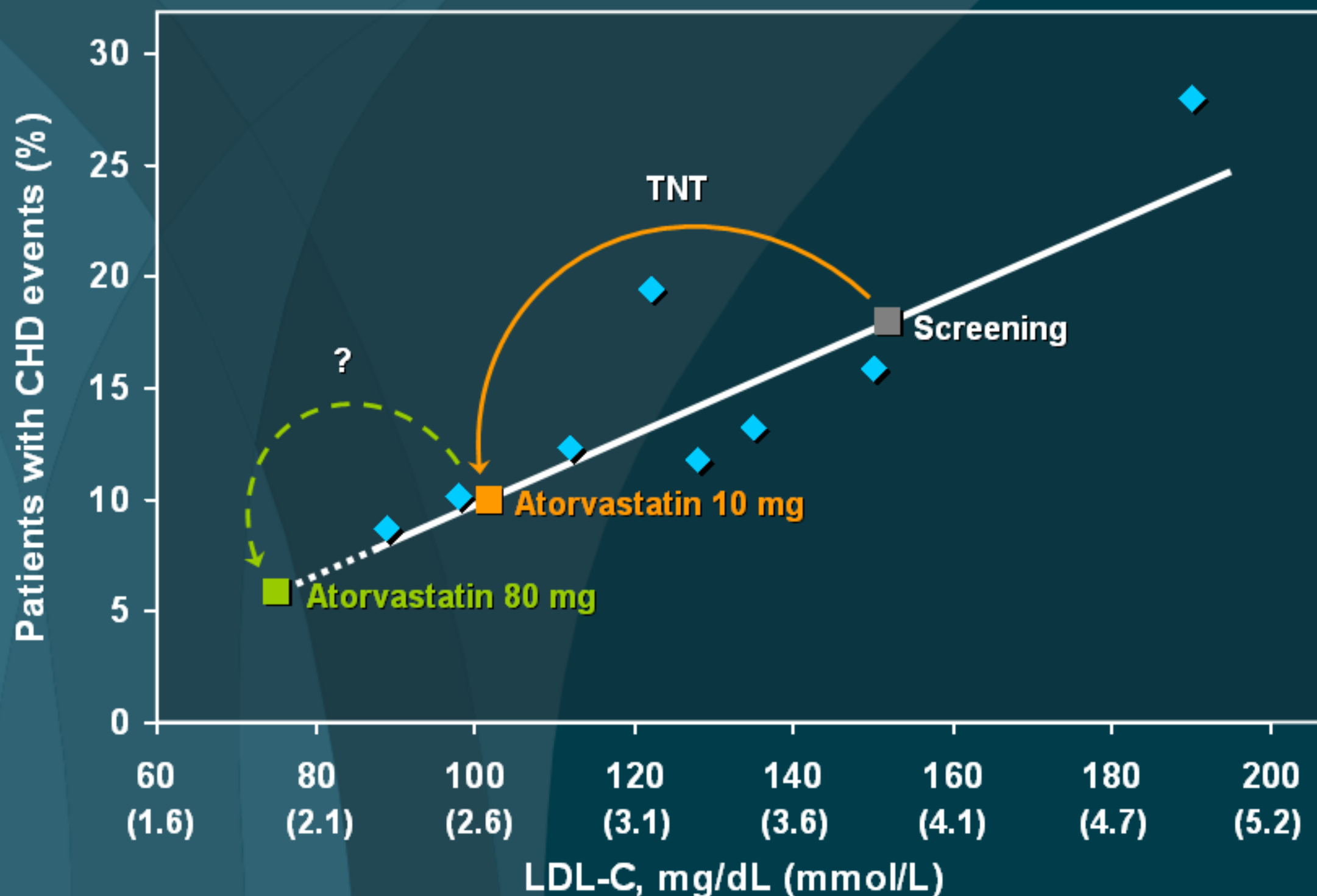
CVRM in the years to come.....



Effects of More Intensive Lipid Lowering in CHD Patients



The Treating to New Targets (TNT) Study: Rationale





TNT: Objective

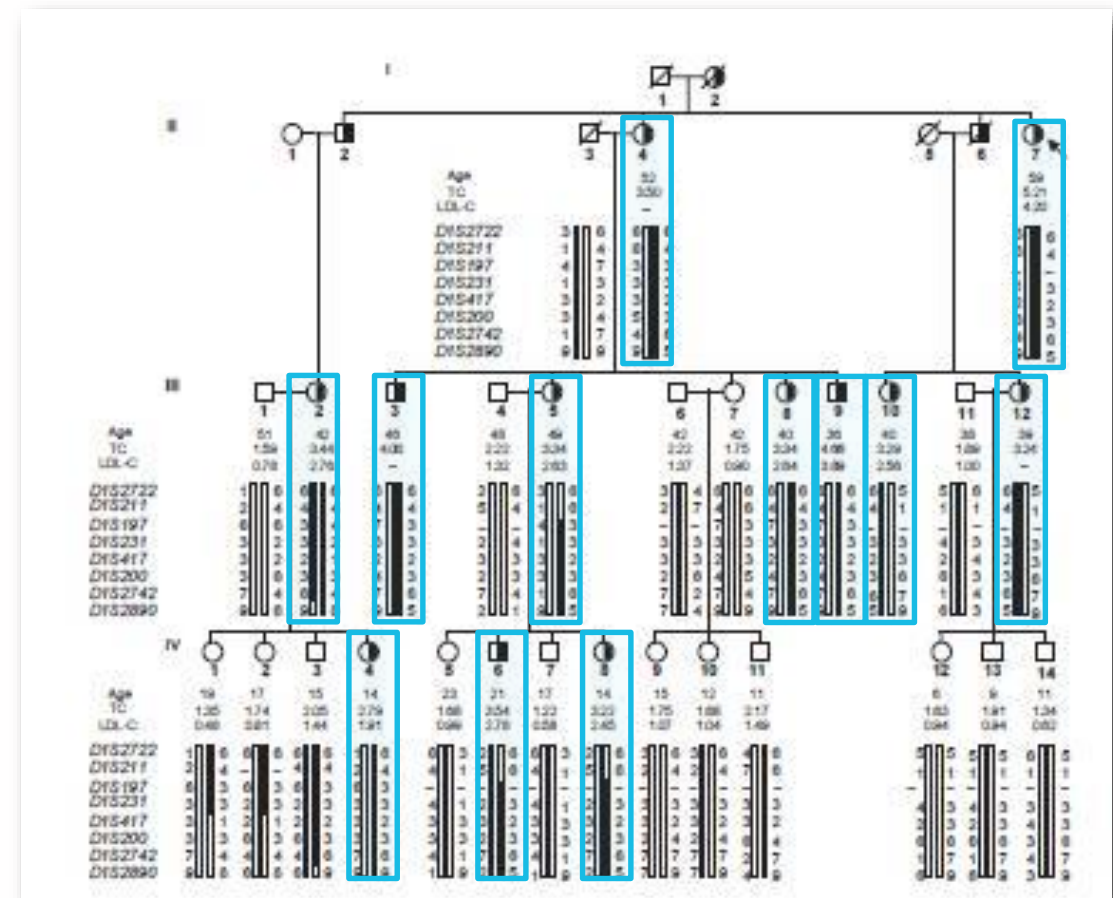
- TNT is the first randomized clinical trial to prospectively assess the efficacy and safety of treating patients with stable CHD to LDL-C levels well below 100 mg/dL (2.6 mmol/L)

PCSK9- a major breakthrough

Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

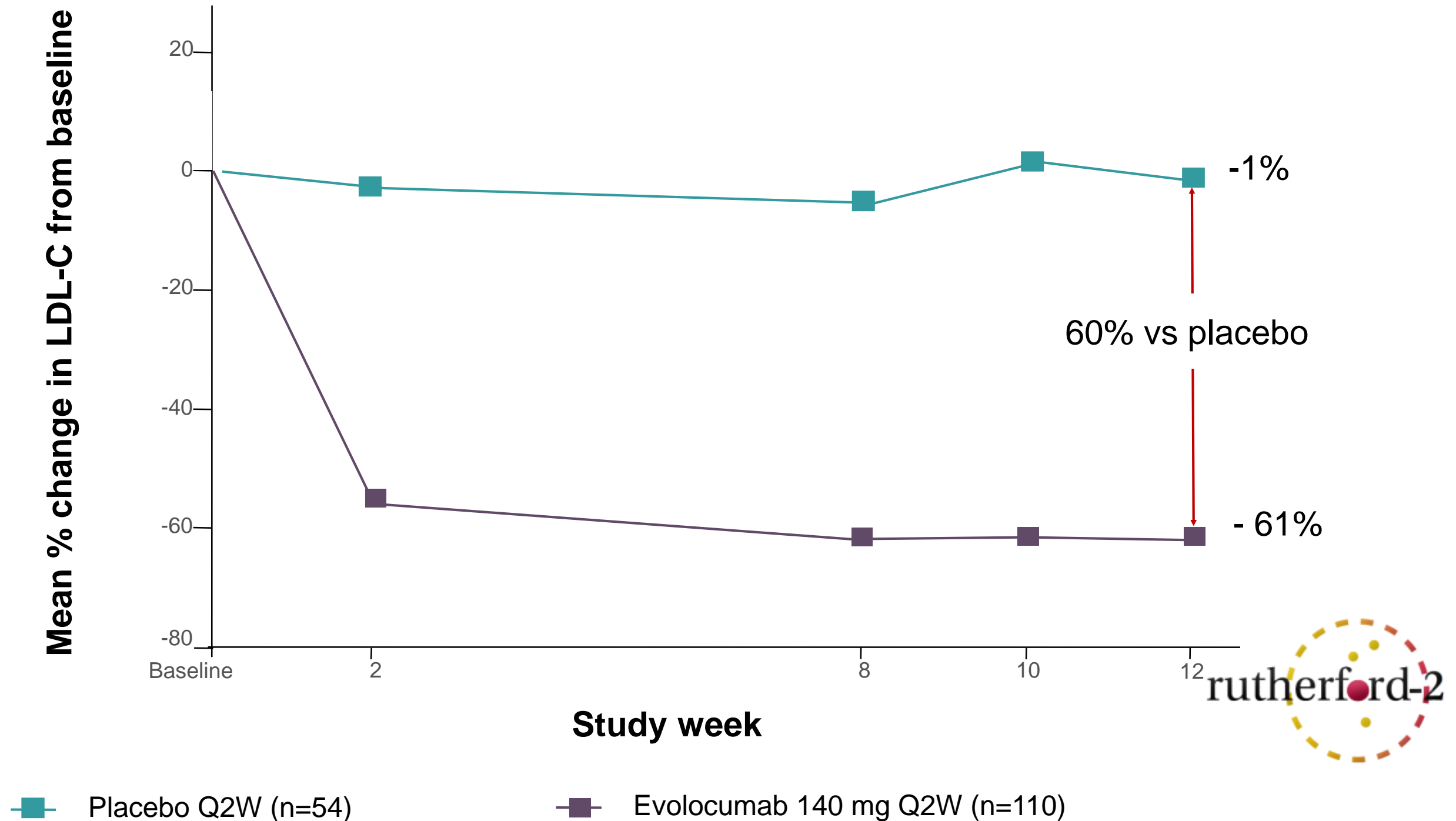
Marianne Abifadel^{1,2}, Mathilde Varret¹, Jean-Pierre Rabès^{1,3}, Delphine Allard¹, Khadija Ouguerram⁴, Martine Devillers¹, Corinne Cruaud⁵, Suzanne Benjannet⁶, Louise Wickham⁶, Danièle Erlich¹, Aurélie Derré¹, Ludovic Villéger¹, Michel Farnier⁷, Isabel Beucler⁸, Eric Bruckert⁹, Jean Chambaz¹⁰, Bernard Chanu¹¹, Jean-Michel Lecerf^{1,2}, Gerald Luc^{1,2}, Philippe Moulin^{1,3}, Jean Weissenbach⁵, Annick Prat⁶, Michel Krempf⁴, Claudine Junien^{1,3}, Nabil G Seidah⁶ & Catherine Boileau^{1,3}

Autosomal dominant hypercholesterolemia (ADH; OMIM144400), a risk factor for coronary heart disease, is characterized by an increase in low-density lipoprotein cholesterol levels that is associated with mutations in the genes *LDLR* (encoding low-density lipoprotein receptor) or *APOB* (encoding apolipoprotein B). We mapped a third locus associated with ADH, *HCHOLA3* at 1p32, and now report two mutations in the gene *PCSK9* (encoding proprotein convertase subtilisin/kexin type 9) that cause ADH. *PCSK9* encodes NARC-1 (neural apoptosis regulated convertase), a newly identified human subtilase that is highly expressed in the liver and contributes to cholesterol homeostasis.



- Affected family members with:
- Total cholesterol in 90th percentile, Tendon xanthomas, CHD Early MI Stroke

Evolocumab significantly reduces LDL-C in patients with heterozygous FH



Therapeutics...

Small molecules

hydrophobic organic, typically act by deactivating or inhibiting target proteins through competitive binding.
downside: only 2–5% of the protein-coding human genome has these sites

Protein based

antibody/ enzyme
high specificity to a variety of targets / replacement of mutated or missing proteins (e.g., insulin for diabetes)

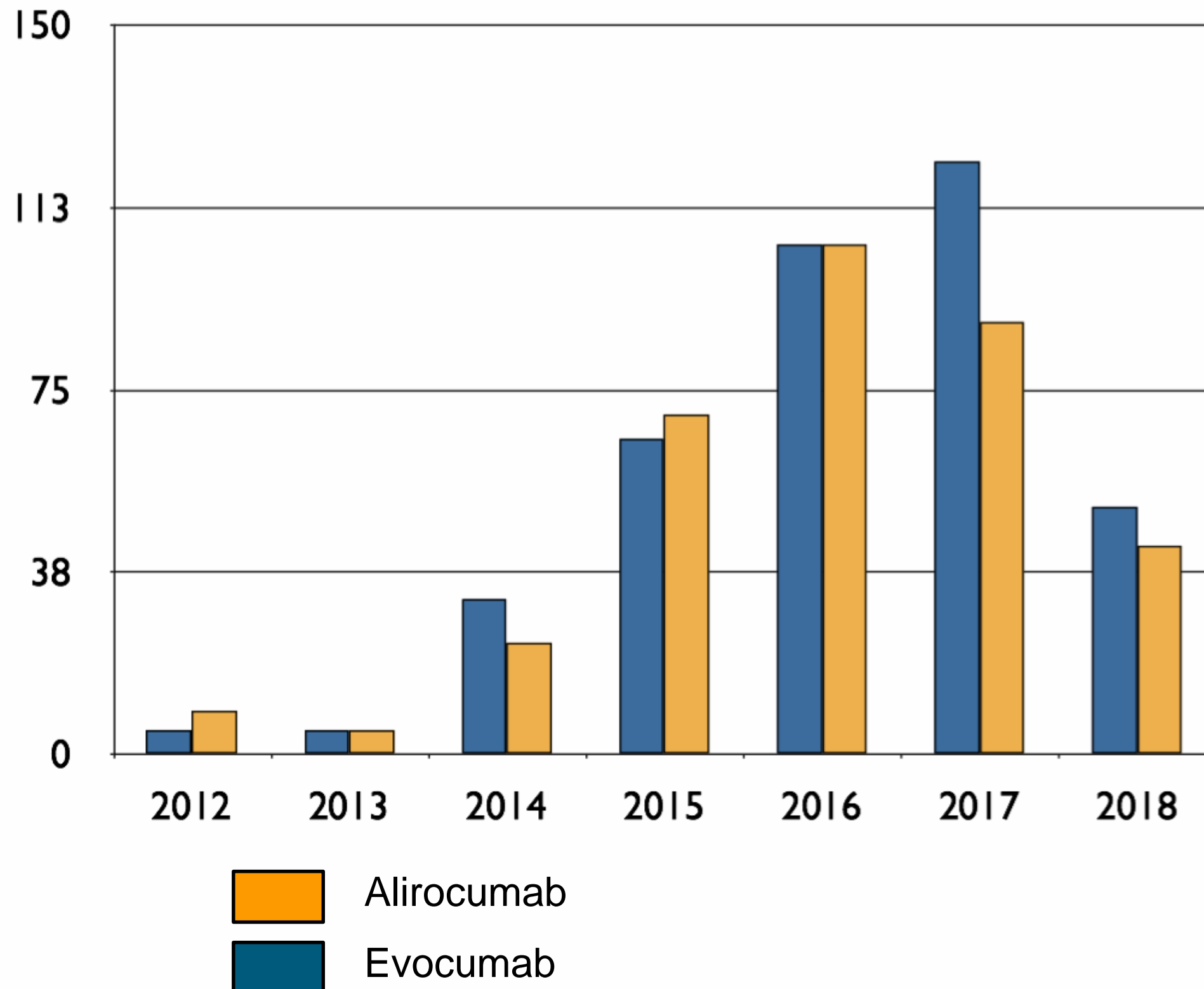
-: cost, size, stability

RNA drugs

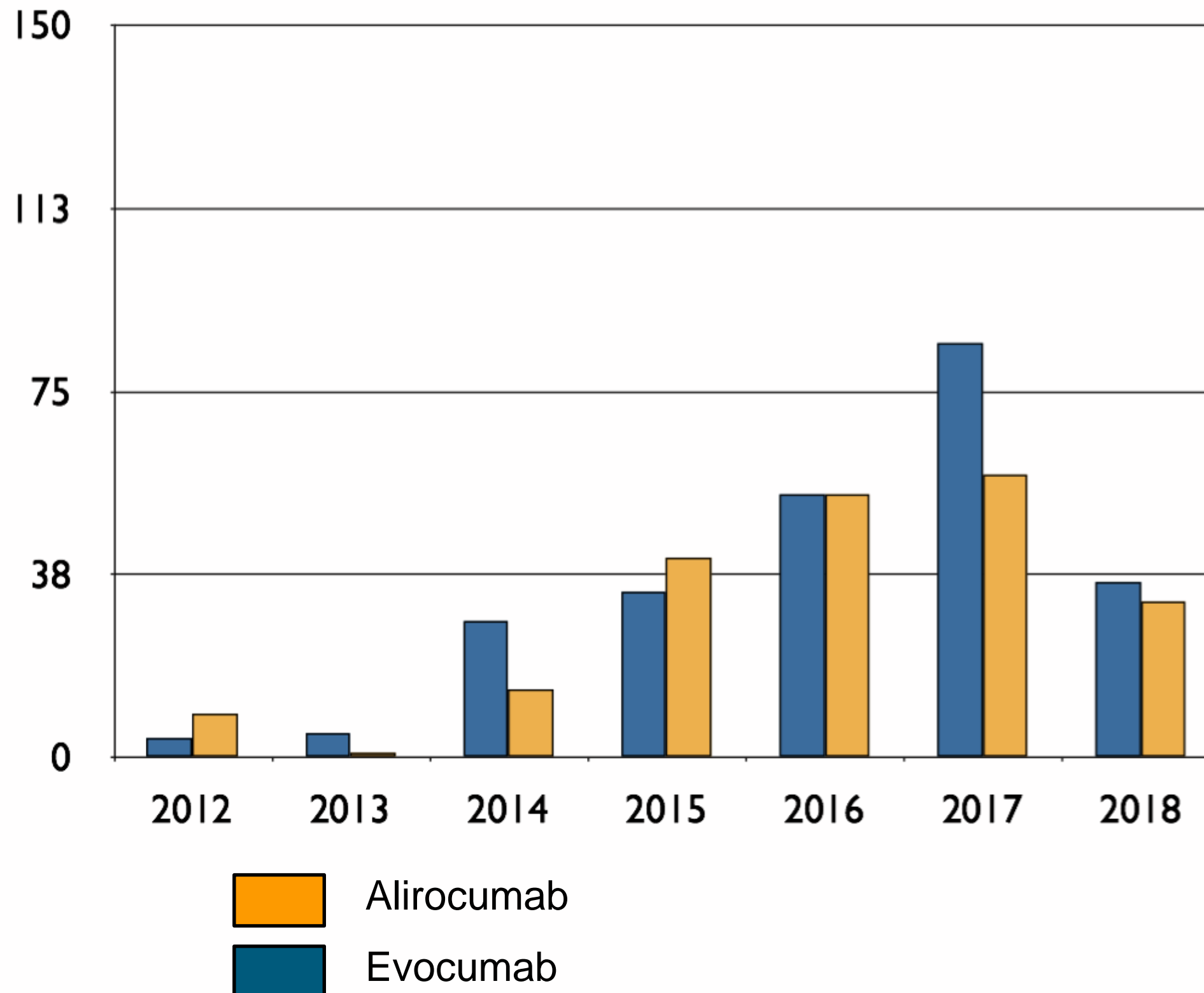
siRNA, ASO, CRISPR/Cas
extremely specific, exon skipping, knockdown

Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*.
Fire A, Mello CC
Nature. 1998 Feb 19; 391(6669):806-11.

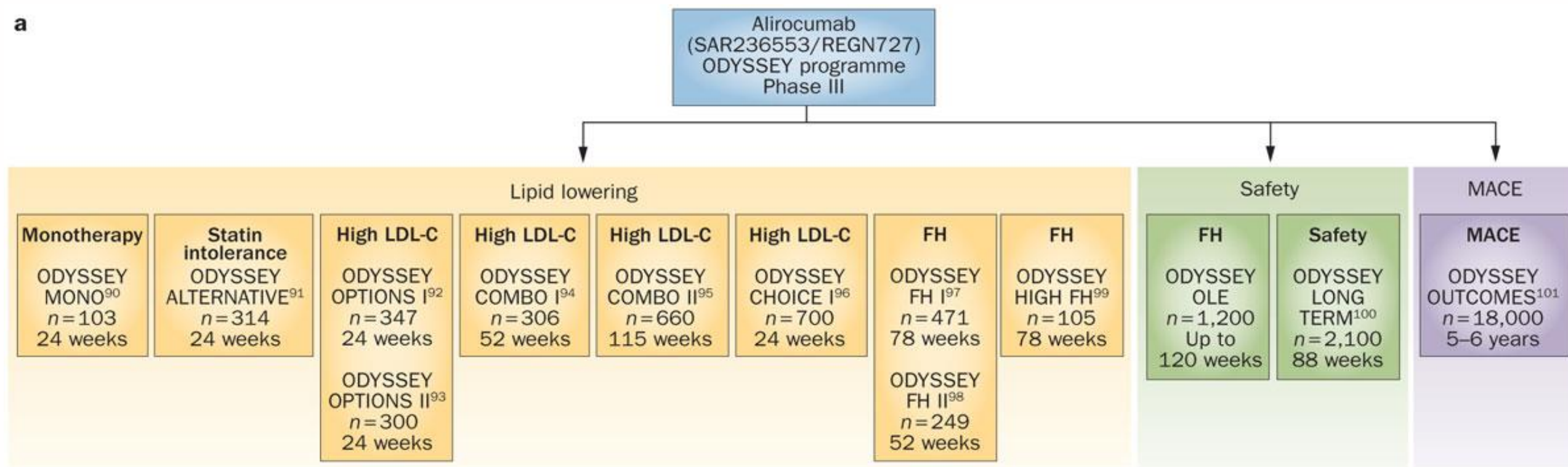
Aantallen papers (pubmed hits) per jaar “evolocumab” en “alirocumab”



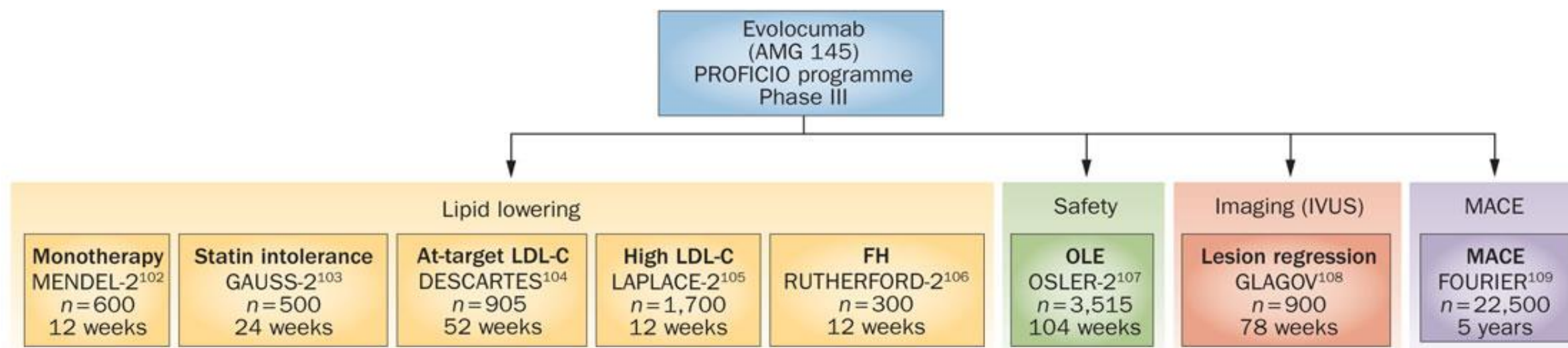
en nu zonder reviews....



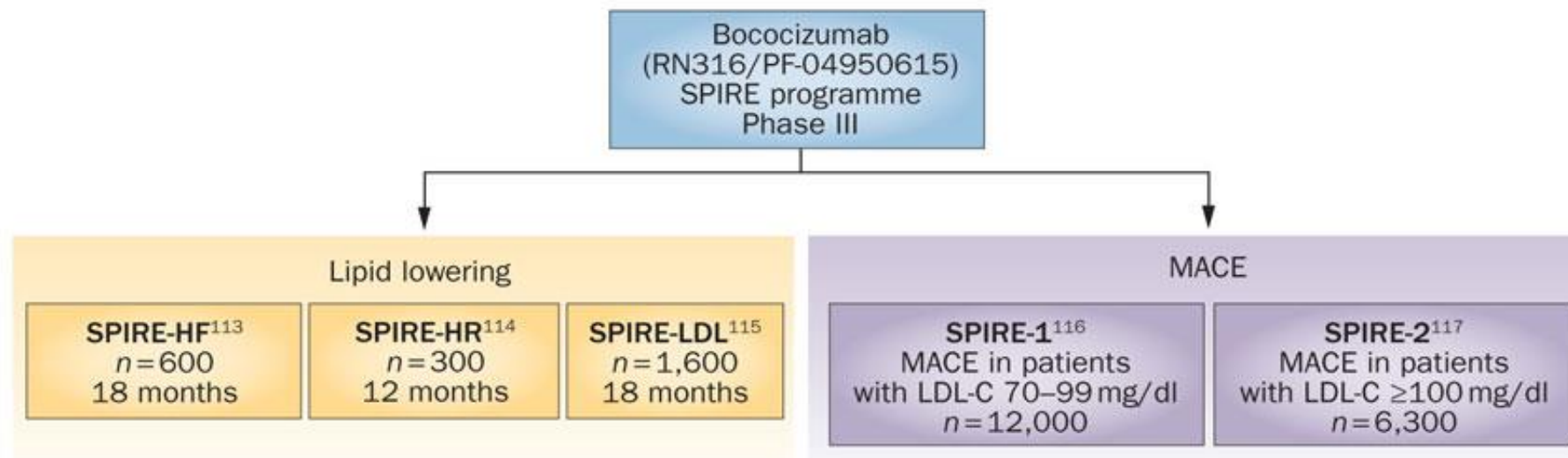
a



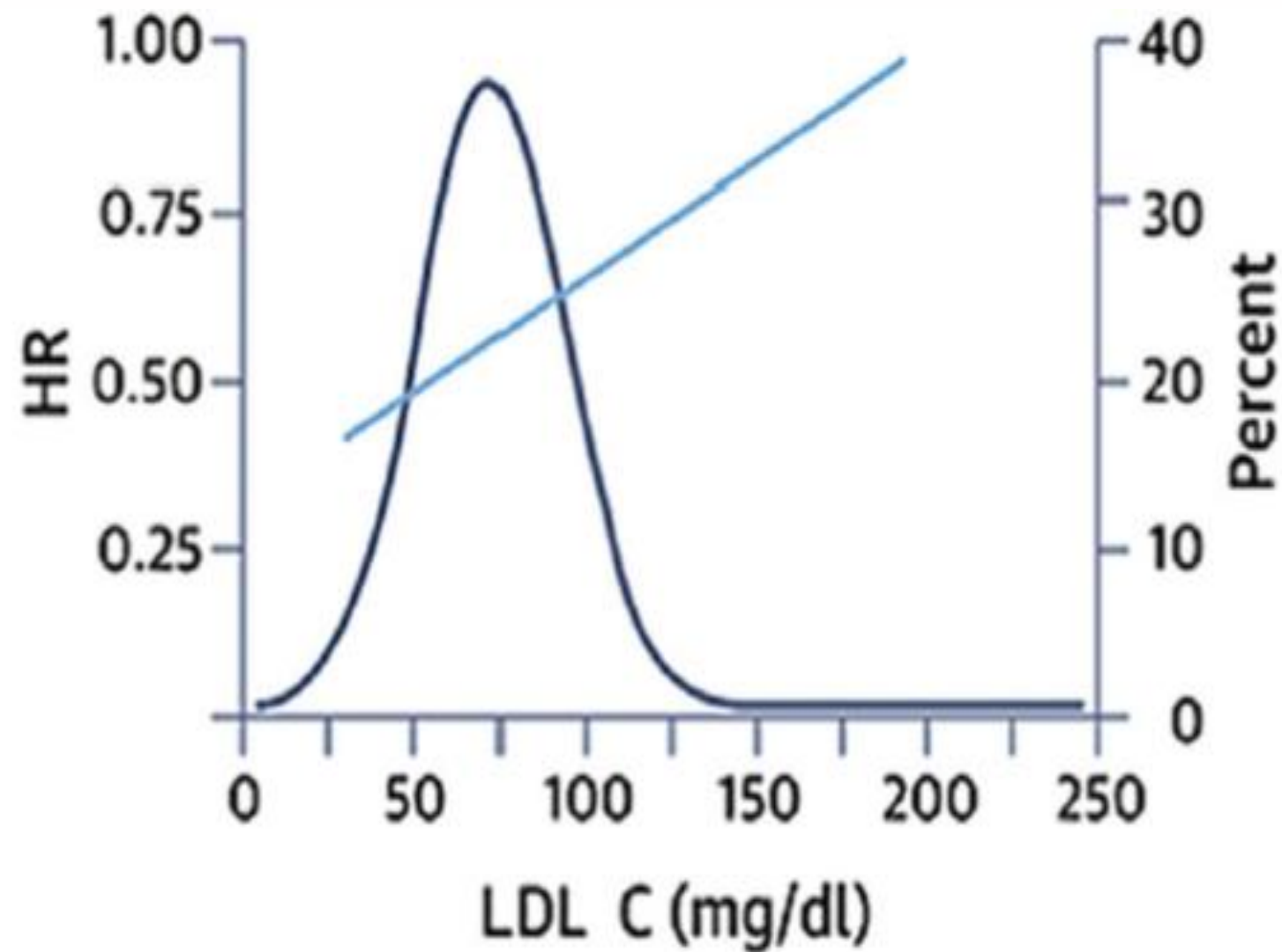
b



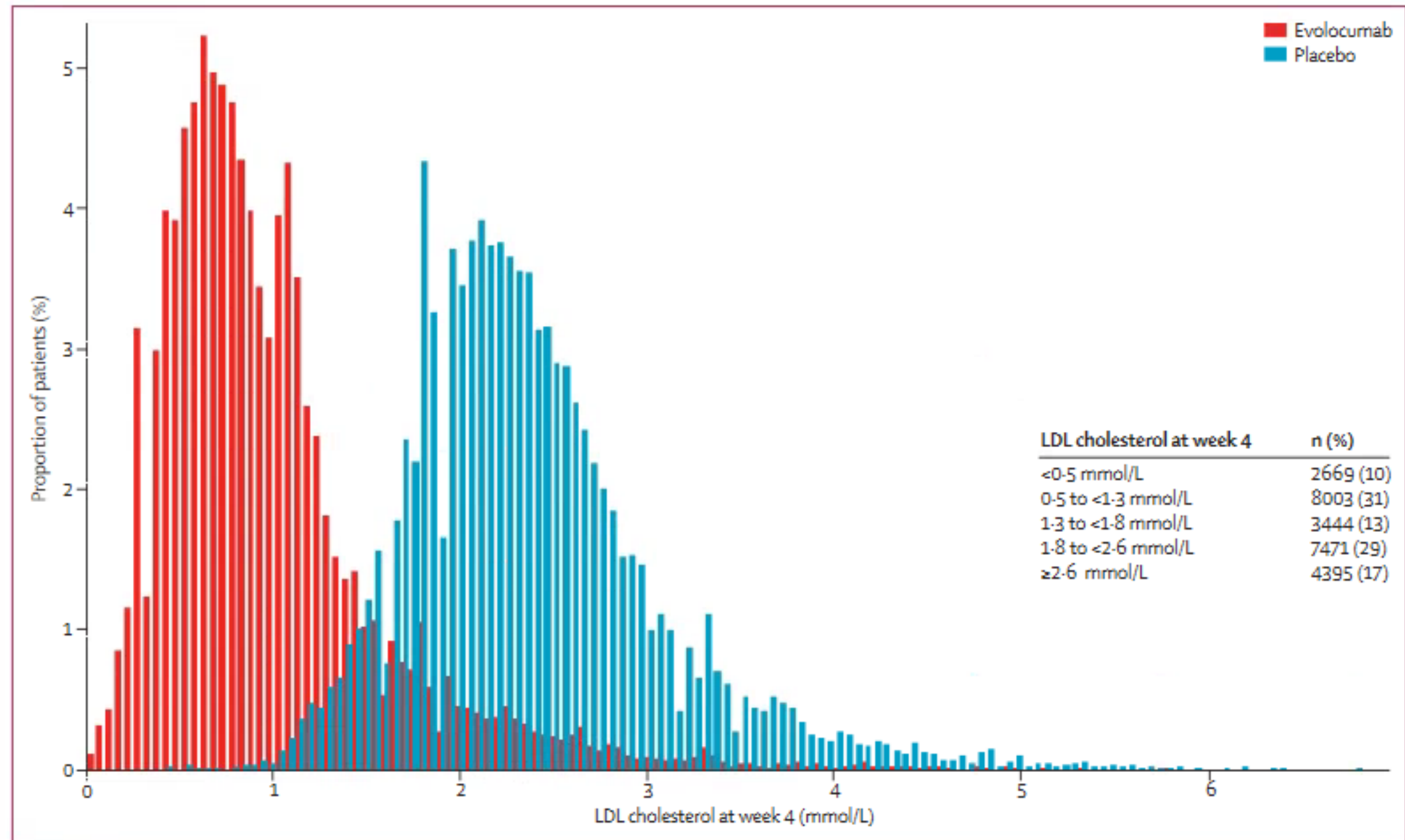
c

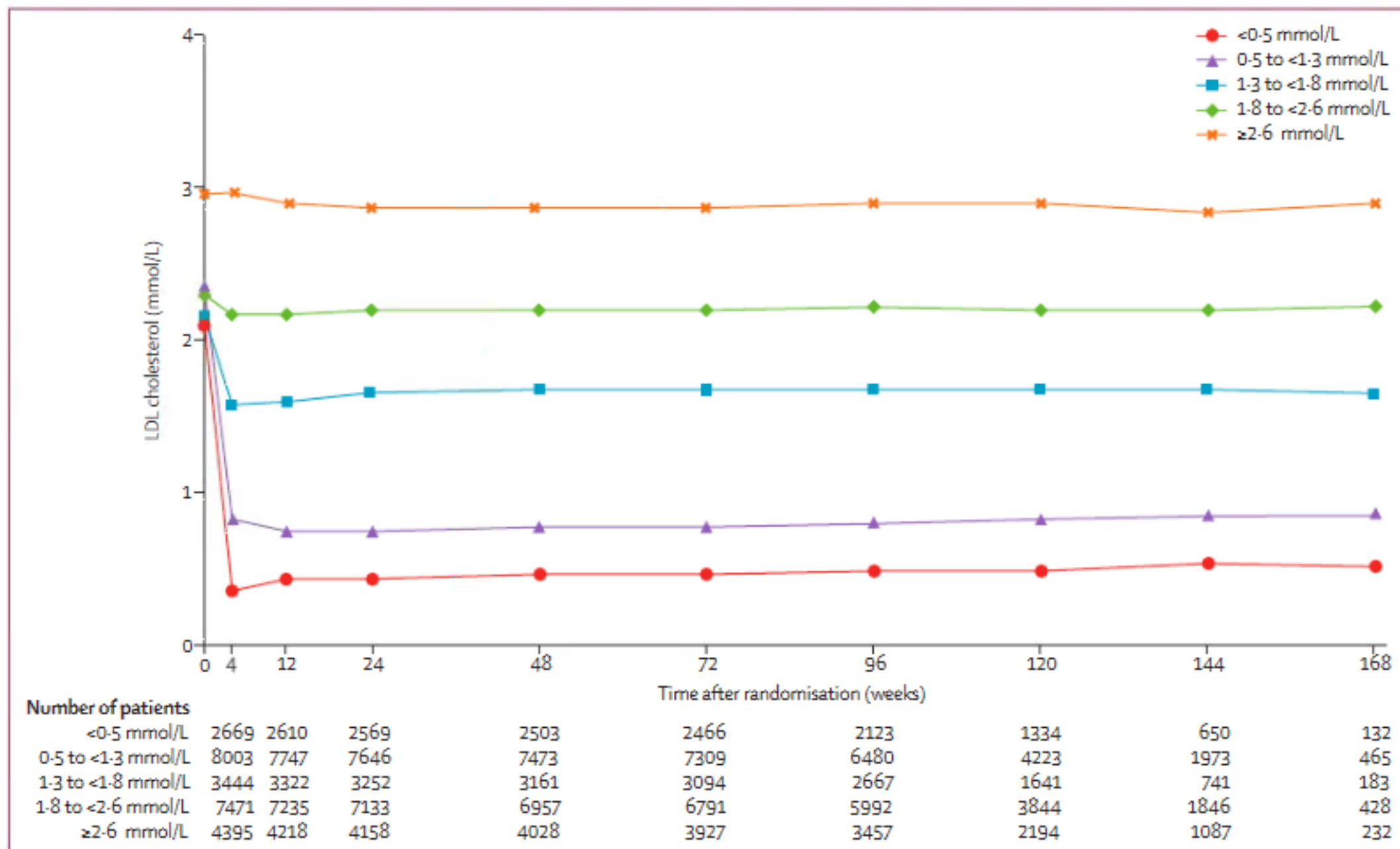


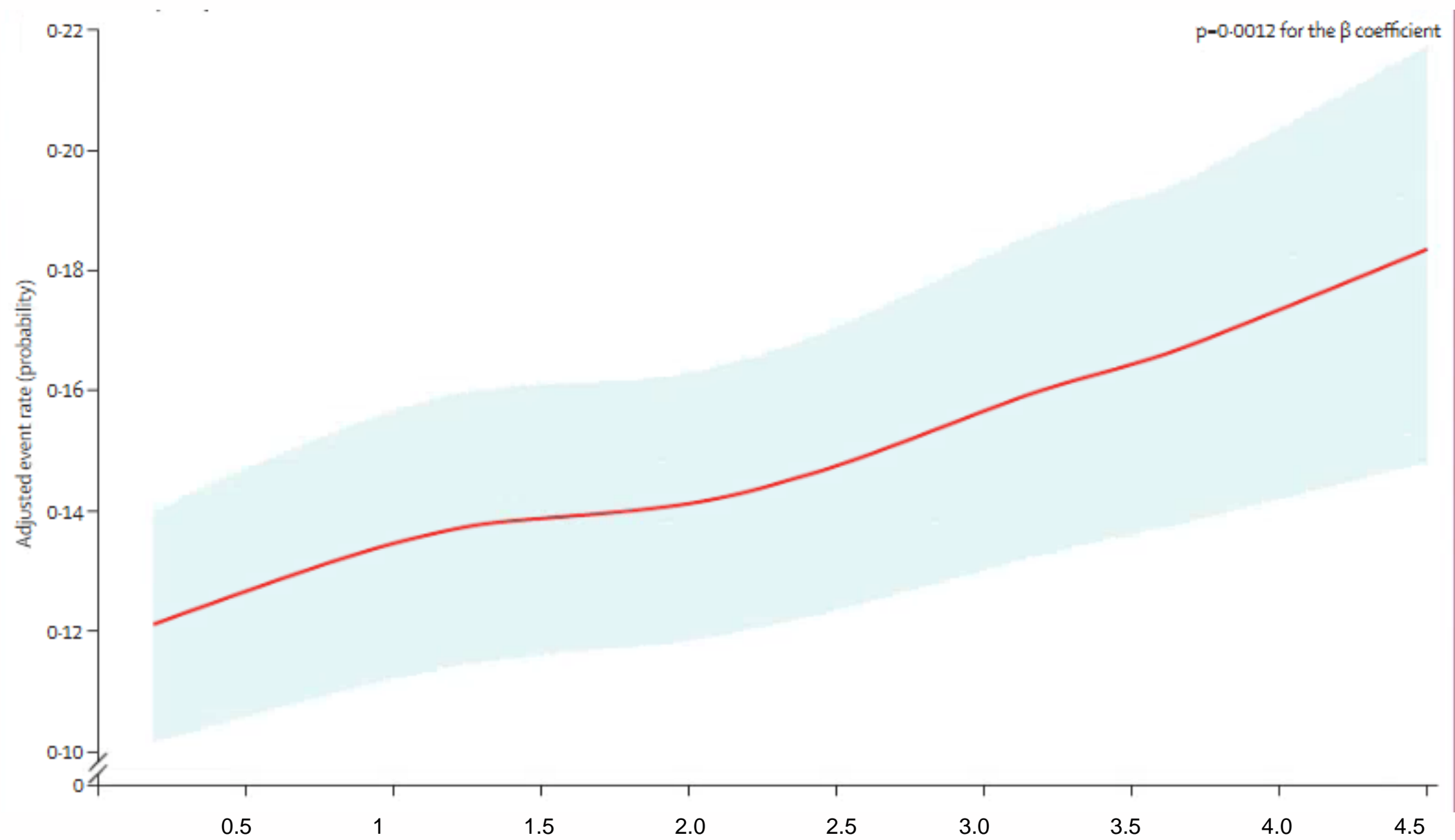
Achieved LDL-C matters



Evolocumab- FOURIER: achieved LDL-C







	LDL-cholesterol concentration at 4 weeks					p _{trend}
	<0.5 mmol/L (n=2669)	0.5 to <1.3 mmol/L (n=8003)	1.3 to <1.8 mmol/L (n=3444)	1.8 to <2.6 mmol/L (n=7471)	≥2.6 mmol/L (n=4395)	
Serious adverse events	614 (23%)	1948 (24%)	838 (24%)	1684 (23%)	1022 (23%)	0.13
Adjusted OR (95% CI)	0.97 (0.86-1.10)	1.01 (0.92-1.11)	1.01 (0.90-1.13)	0.93 (0.84-1.02)	1 (ref)	0.30
Adverse events* leading to discontinuation of study drug	98 (4%)	295 (4%)	124 (4%)	234 (3%)	149 (3%)	0.11
Adjusted OR (95% CI)	1.08 (0.82-1.43)	1.07 (0.86-1.33)	1.07 (0.83-1.39)	0.91 (0.73-1.14)	1 (ref)	0.13
AST or ALT elevation (>3 times ULN)	41 (2%)	120 (1%)	76 (2%)	119 (2%)	83 (2%)	0.19
Adjusted OR (95% CI)	0.96 (0.64-1.43)	0.87 (0.64-1.17)	1.25 (0.90-1.74)	0.91 (0.68-1.24)	1 (ref)	0.64
Creatine kinase elevation (>5 times ULN)	18 (1%)	55 (1%)	19 (1%)	58 (1%)	26 (1%)	0.99
Adjusted OR (95% CI)	1.02 (0.53-1.96)	1.07 (0.65-1.77)	0.88 (0.47-1.65)	1.23 (0.75-2.02)	1 (ref)	0.72
Neurocognitive events	49 (2%)	122 (2%)	51 (1%)	100 (1%)	52 (1%)	0.019
Adjusted OR (95% CI)	1.28 (0.84-1.96)	1.10 (0.78-1.55)	1.10 (0.73-1.65)	0.97 (0.68-1.39)	1 (ref)	0.15
New onset diabetes mellitus†	135/1655 (8%)	389/4863 (8%)	162/1886 (9%)	356/4603 (8%)	220/2778 (8%)	0.63
Adjusted OR (95% CI)	1.06 (0.83-1.35)	1.00 (0.83-1.20)	1.03 (0.83-1.30)	0.95 (0.78-1.14)	1 (ref)	0.48
Cataract-related adverse events	56 (2%)	124 (2%)	61 (2%)	134 (2%)	55 (1%)	0.15
Adjusted OR (95% CI)	1.54 (1.03-2.31)	1.14 (0.82-1.60)	1.34 (0.91-1.98)	1.35 (0.96-1.89)	1 (ref)	0.43
New or progressive malignancy	64 (2%)	205 (3%)	87 (3%)	166 (2%)	99 (2%)	0.22
Adjusted OR (95% CI)	0.90 (0.64-1.27)	1.01 (0.78-1.31)	1.04 (0.77-1.42)	0.88 (0.67-1.15)	1 (ref)	0.72
Haemorrhagic stroke	3 (<1%)	19 (<1%)	7 (<1%)	17 (<1%)	7 (<1%)	0.99
Adjusted HR (95% CI)	0.71 (0.17-2.90)	1.55 (0.62-3.85)	1.39 (0.47-4.14)	1.57 (0.62-3.98)	1 (ref)	0.91
Non-cardiovascular death	25 (1%)	86 (1%)	34 (1%)	66 (1%)	45 (1%)	0.67
Adjusted HR (95% CI)	0.89 (0.53-1.50)	1.06 (0.72-1.55)	1.03 (0.65-1.64)	0.89 (0.60-1.33)	1 (ref)	0.73

Clinical Efficacy and Safety of Evolocumab in High-Risk Patients Receiving a Statin

Secondary Analysis of Patients With Low LDL Cholesterol Levels and in Those Already Receiving a Maximal-Potency Statin in a Randomized Clinical Trial

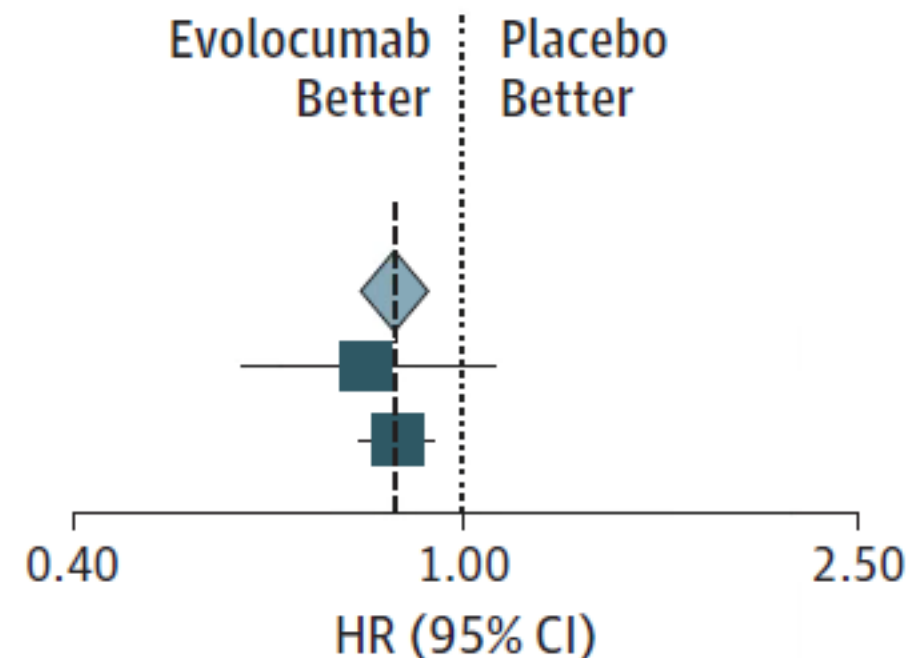
Robert P. Giugliano, MD, SM; Anthony Keech, MD; Sabina A. Murphy, MPH; Kurt Huber, MD; S. Zile Tokgozoglu, MD; Basil S. Lewis, MD; Jorge Ferreira, MD; Armando Lira Pineda, MD; Ransi Somaratne, MD; Peter S. Sever, PhD, FRC; Terje R. Pedersen, PhD; Marc S. Sabatine, MD, MPH

Dec 2017;1385

2034 with LDL-C <70mg/dL at baseline !!

A Efficacy outcomes by baseline LDL-C level

Primary composite end point	HR (95% CI)
All	0.85 (0.79-0.92)
Baseline LDL-C level, <70 mg/dL	0.80 (0.60-1.07)
Baseline LDL-C level, ≥70 mg/dL	0.86 (0.79-0.92)



The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg,
Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema,
Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher,

Ph. Gabriel Steg

On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018



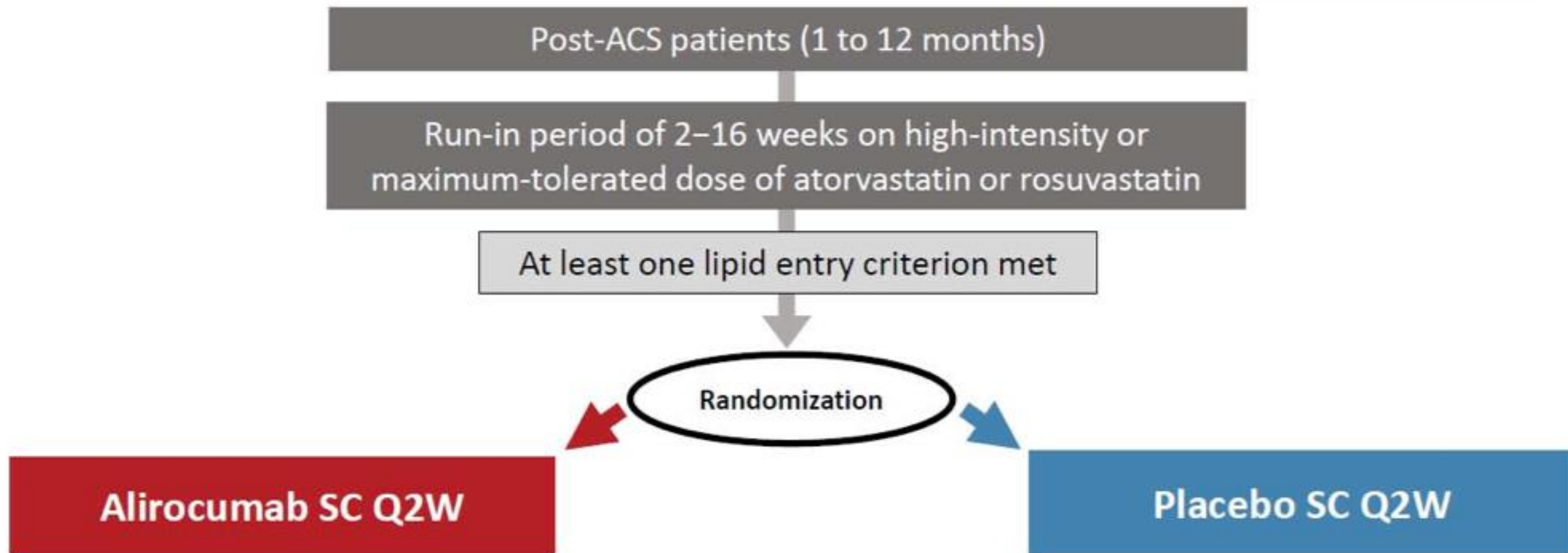
ClinicalTrials.gov: NCT01663402

Main Inclusion Criteria

- **Age** ≥ 40 years
- **ACS**
 - 1 to 12 months prior to randomization
 - Acute myocardial infarction (MI) or unstable angina
- **High-intensity statin therapy***
 - Atorvastatin 40 to 80 mg daily or
 - Rosuvastatin 20 to 40 mg daily or
 - Maximum tolerated dose of one of these agents for ≥ 2 weeks
- **Inadequate control of lipids**
 - LDL-C ≥ 70 mg/dL (1.8 mmol/L) or
 - Non-HDL-C ≥ 100 mg/dL (2.6 mmol/L) or
 - Apolipoprotein B ≥ 80 mg/dL

*Patients not on statins were authorized to participate if tolerability issues were present and documented
Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

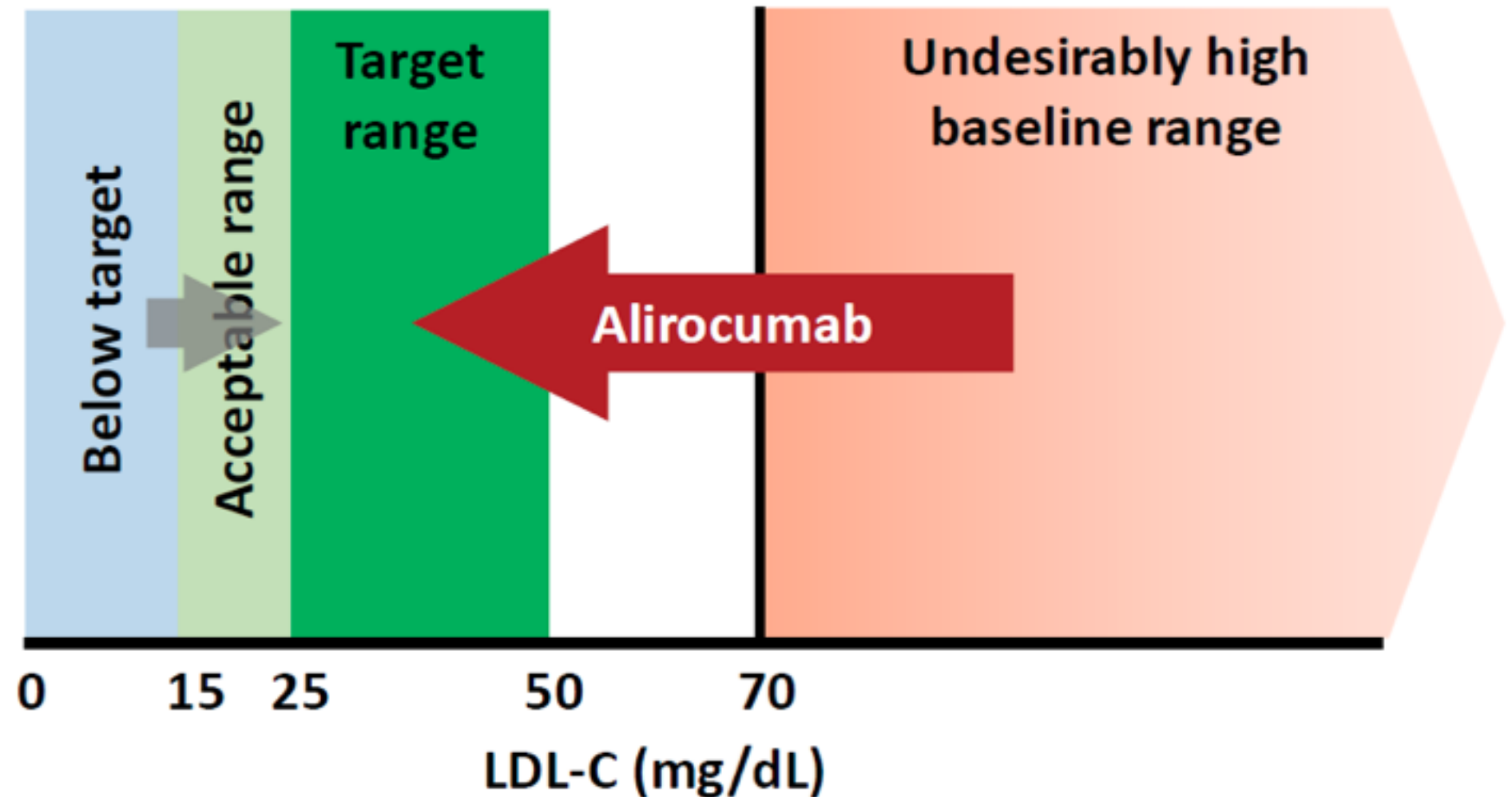
Treatment Assignment



Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

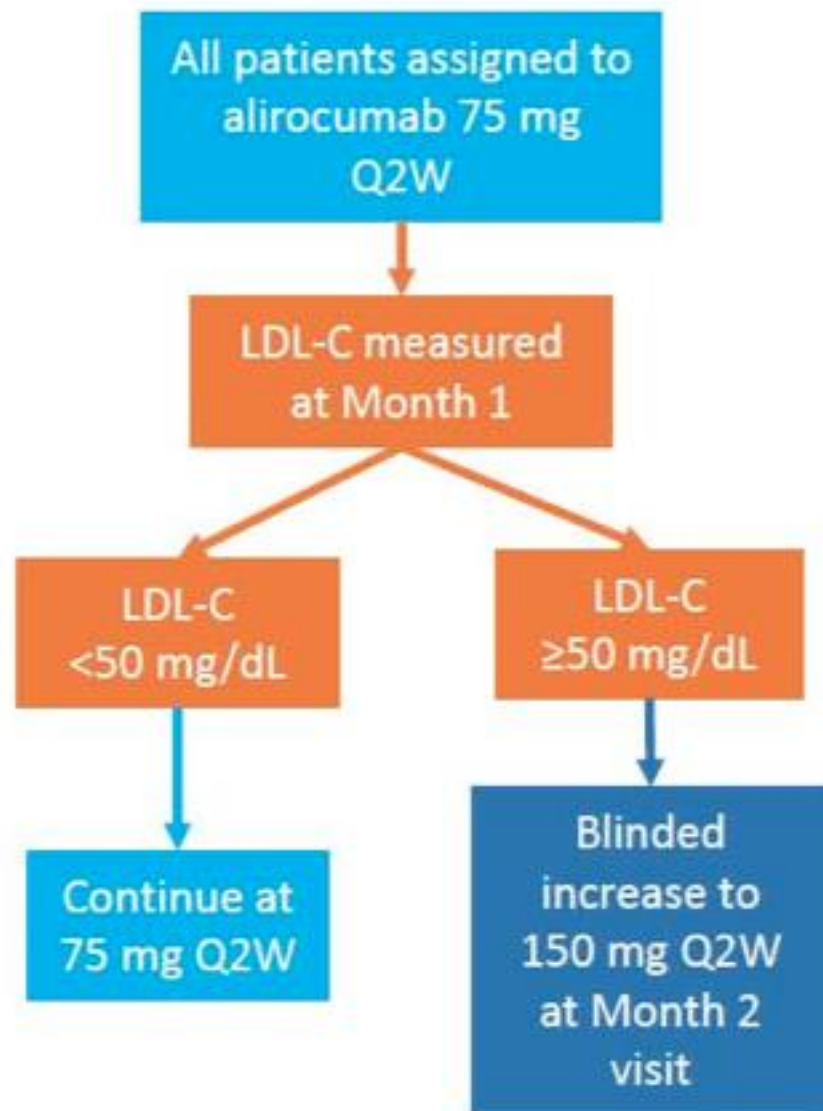
A Target Range for LDL-C

We attempted to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.

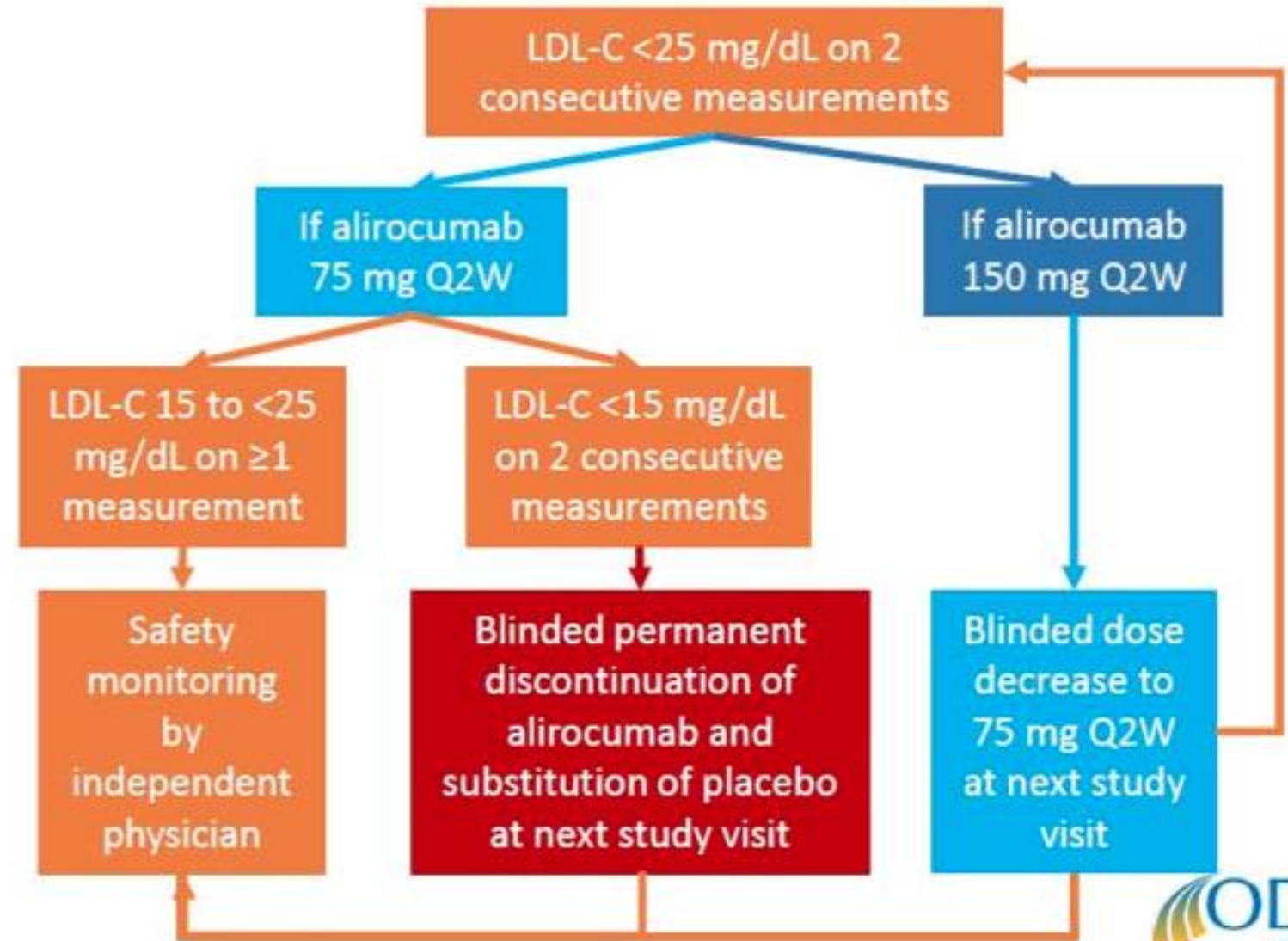


Blinded Alirocumab Dose Adjustments

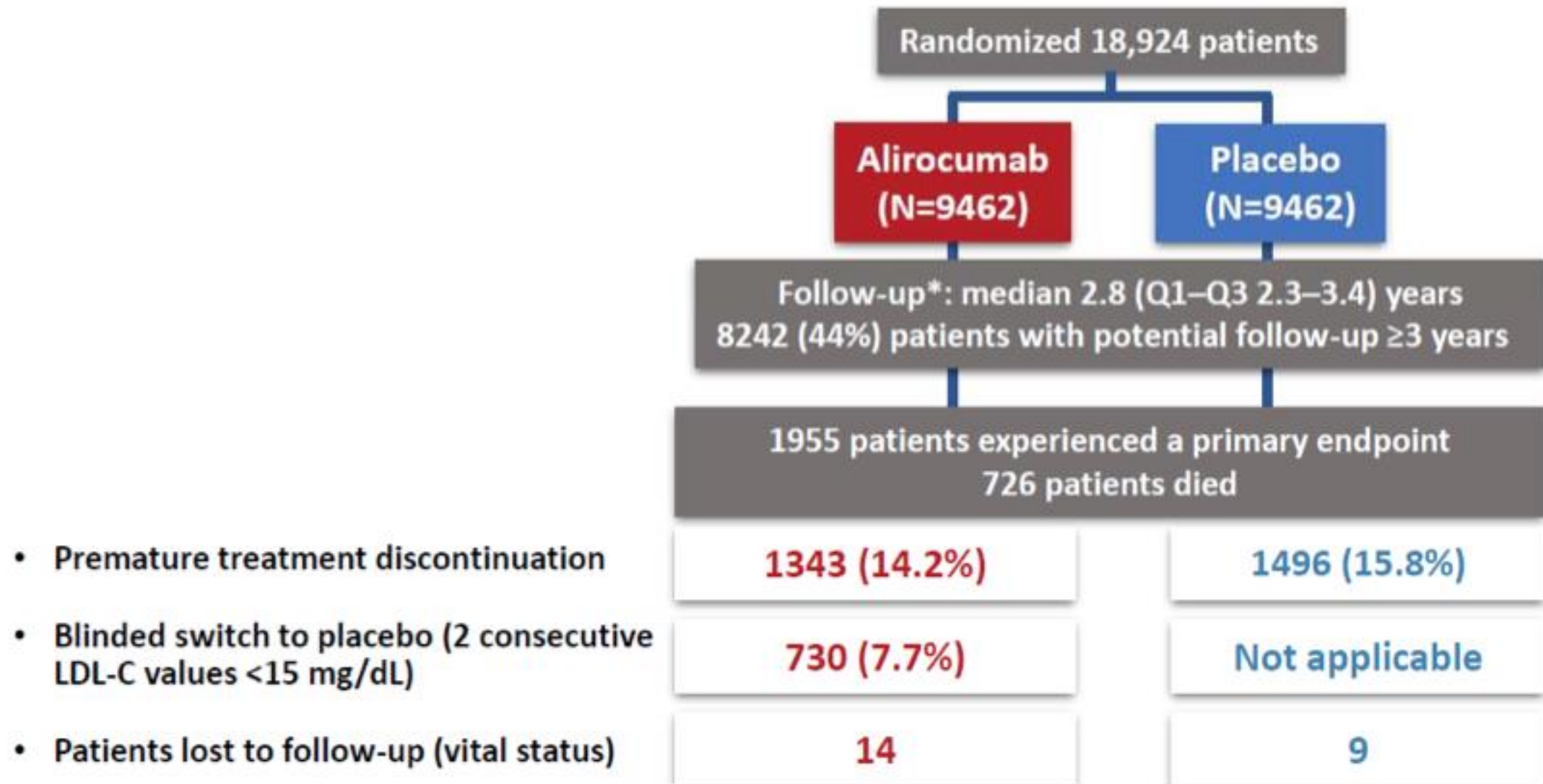
Up-titration of alirocumab for LDL-C ≥ 50 mg/dL



Down-titration of alirocumab and/or safety monitoring for LDL-C < 25 mg/dL



Patient Disposition



*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively

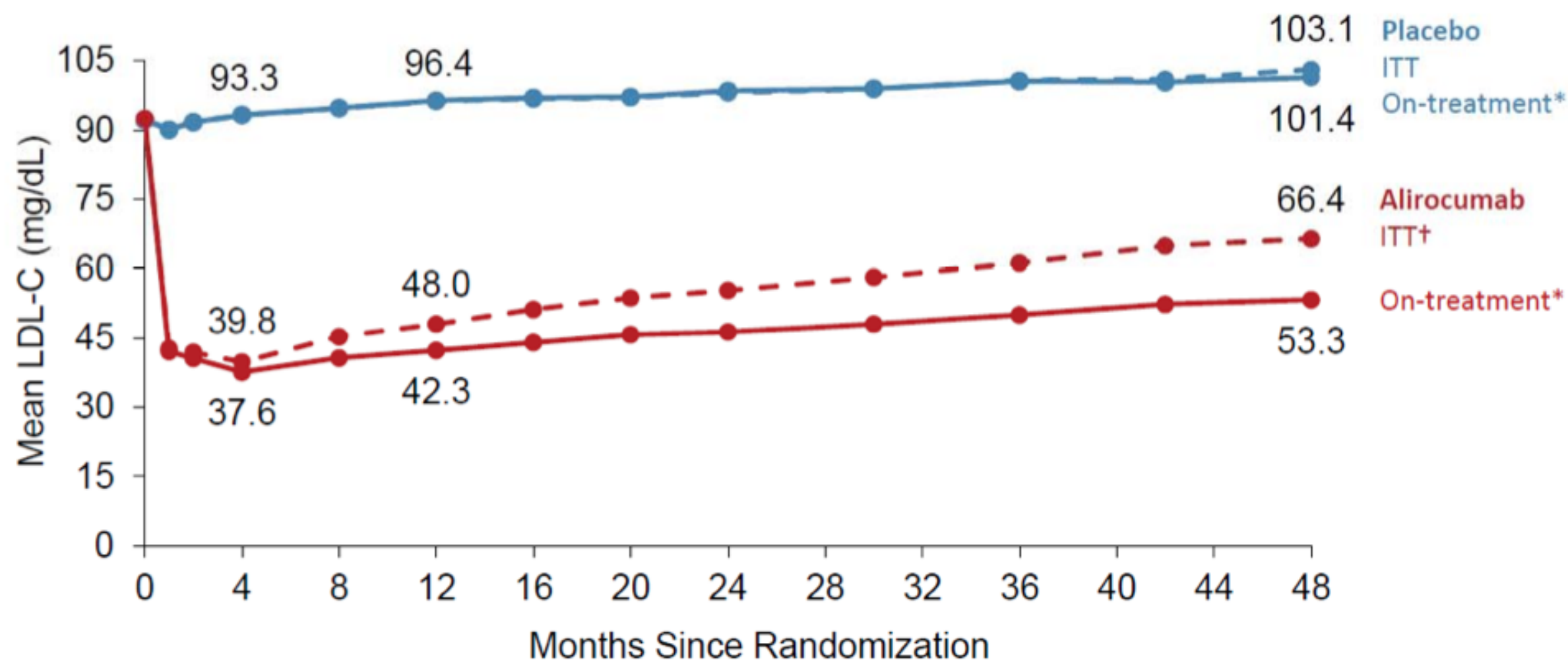
Baseline Demographics

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Age, years, median (Q1–Q3)	58 (52–65)	58 (52–65)
Female, n (%)	2390 (25.3)	2372 (25.1)
Medical history, n (%)		
Hypertension	6205 (65.6)	6044 (63.9)
Diabetes mellitus	2693 (28.5)	2751 (29.1)
Current tobacco smoker	2282 (24.1)	2278 (24.1)
Prior MI	1790 (18.9)	1843 (19.5)

Baseline Index Events

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Time from index ACS to randomization, months, median (Q1–Q3)	2.6 (1.7–4.4)	2.6 (1.7–4.3)
ACS type, n (%)		
NSTEMI	4574 (48.4)	4601 (48.7)
STEMI	3301 (35.0)	3235 (34.2)
Unstable angina	1568 (16.6)	1614 (17.1)
Revascularization for index ACS, n (%)	6798 (71.8)	6878 (72.7)

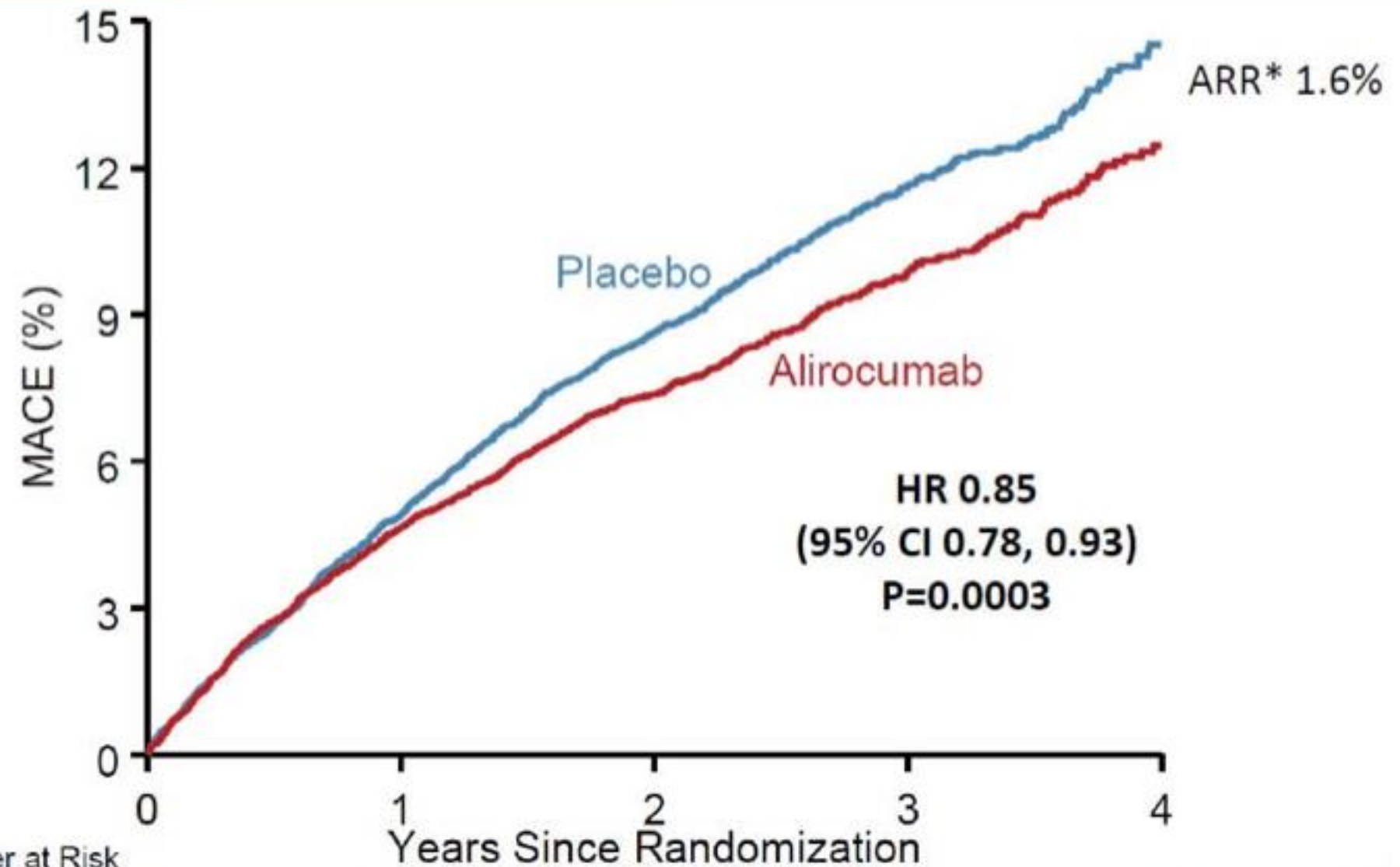
LDL-C: ITT and On-Treatment Analyses



*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo

†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo

Primary Efficacy Endpoint: MACE



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

*Based on cumulative incidence

Number at Risk		Years Since Randomization				
Placebo	9462	8805	8201	3471	629	
Alirocumab	9462	8846	8345	3574	653	

Conclusions Odyssey (preliminary...._

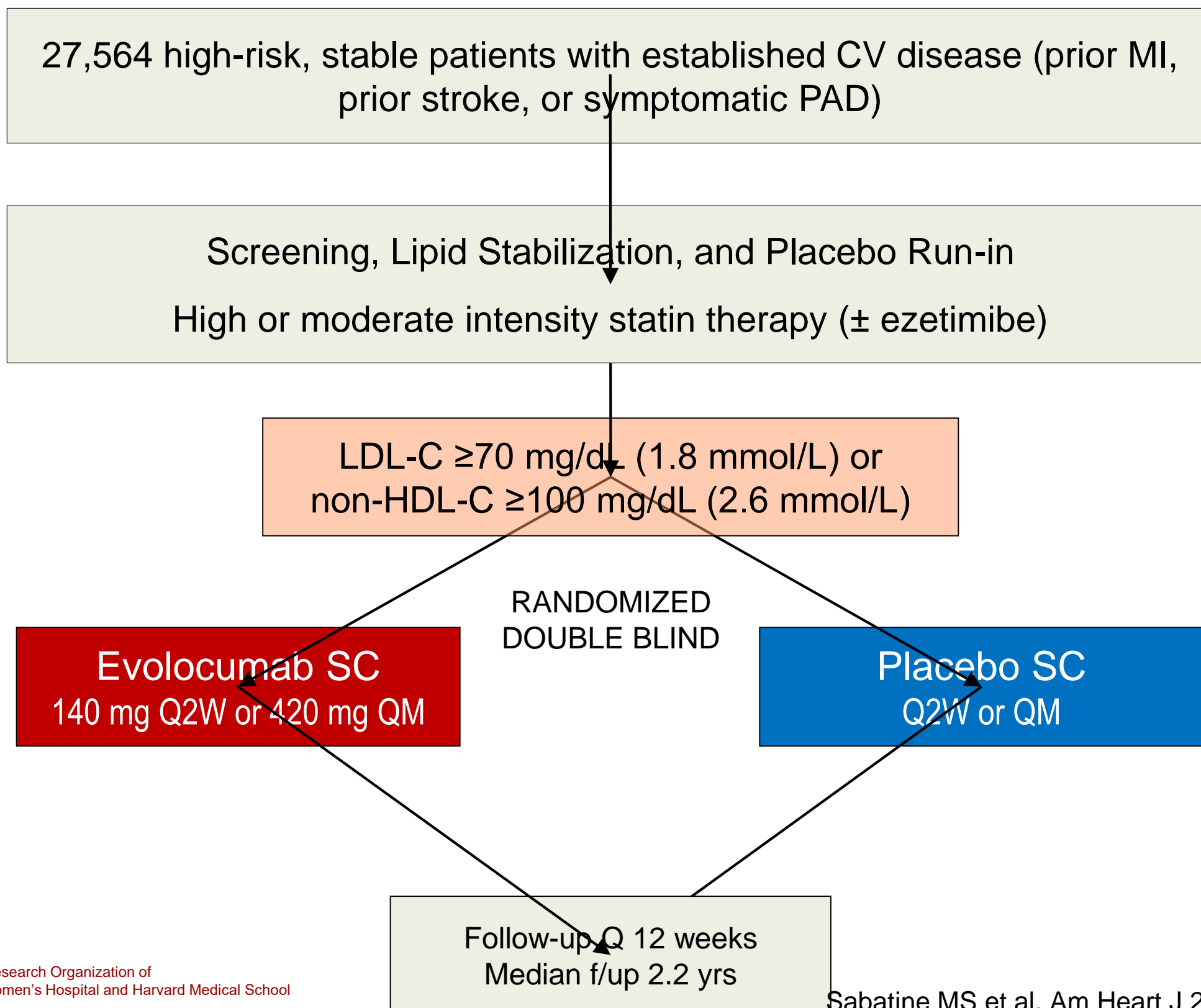
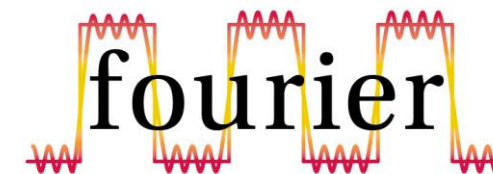
- In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥ 3 years, there was no safety signal with alirocumab other than injection site reactions
- Among patients with ACS and baseline LDL-C ≥ 100 mg/dL, alirocumab reduced MACE by 24% (ARR 3.4%) and all-cause death by 29% (ARR 1.7%) compared with placebo
 - These are the patients who may benefit most from treatment

ARR, absolute risk reduction

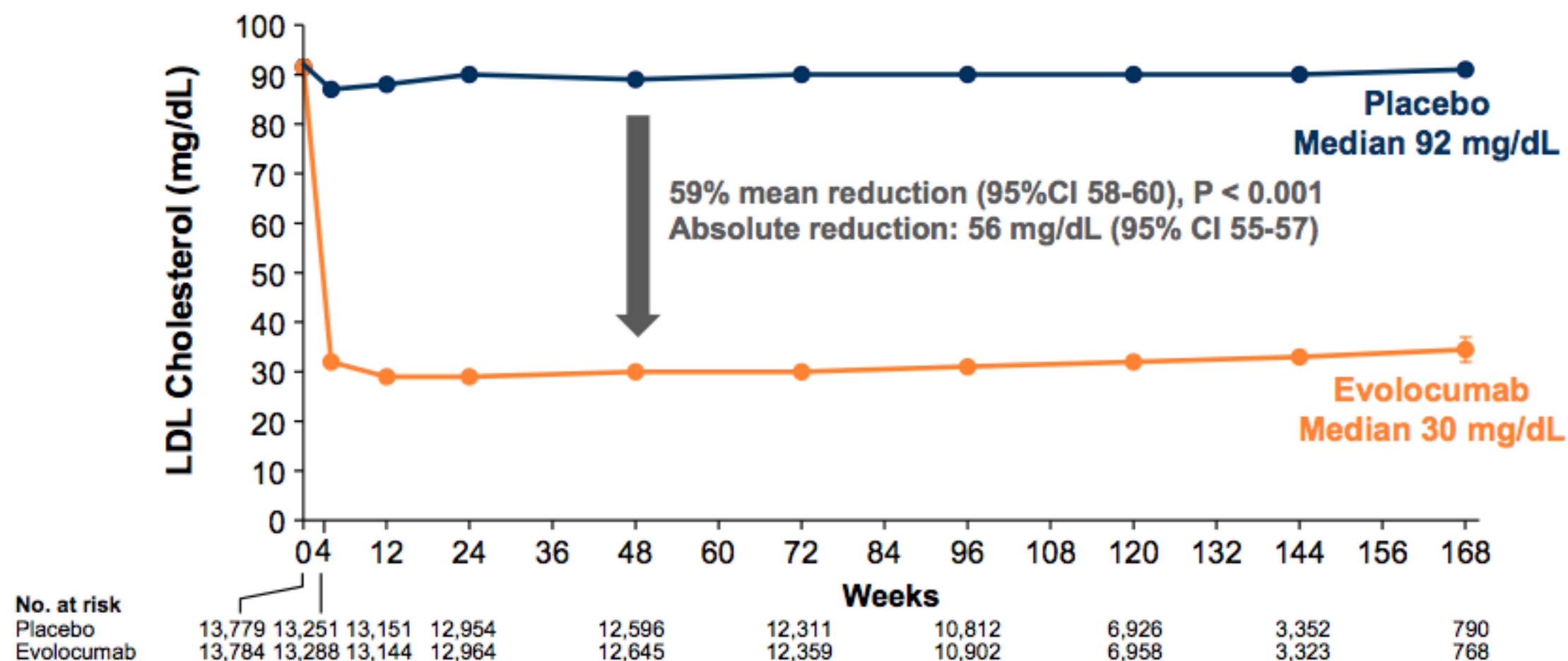




Trial Design



Median LDL-C Levels Over Time: All Patients

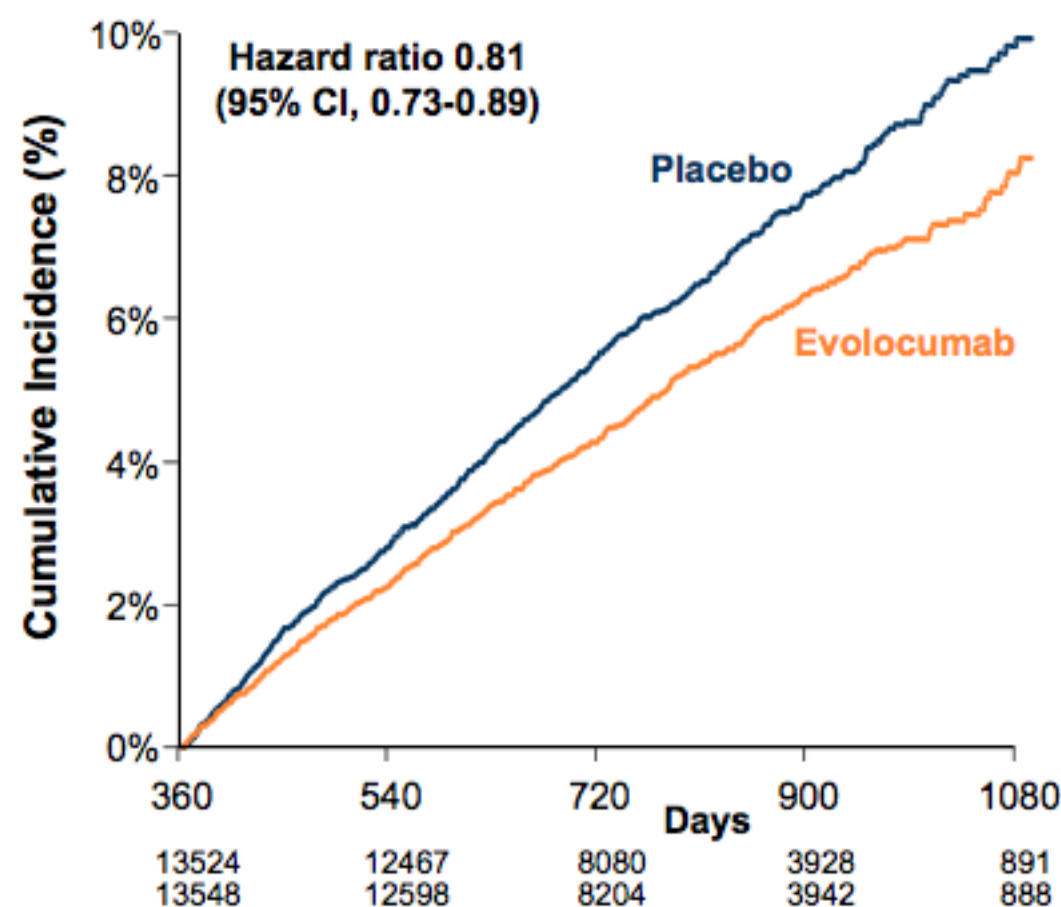
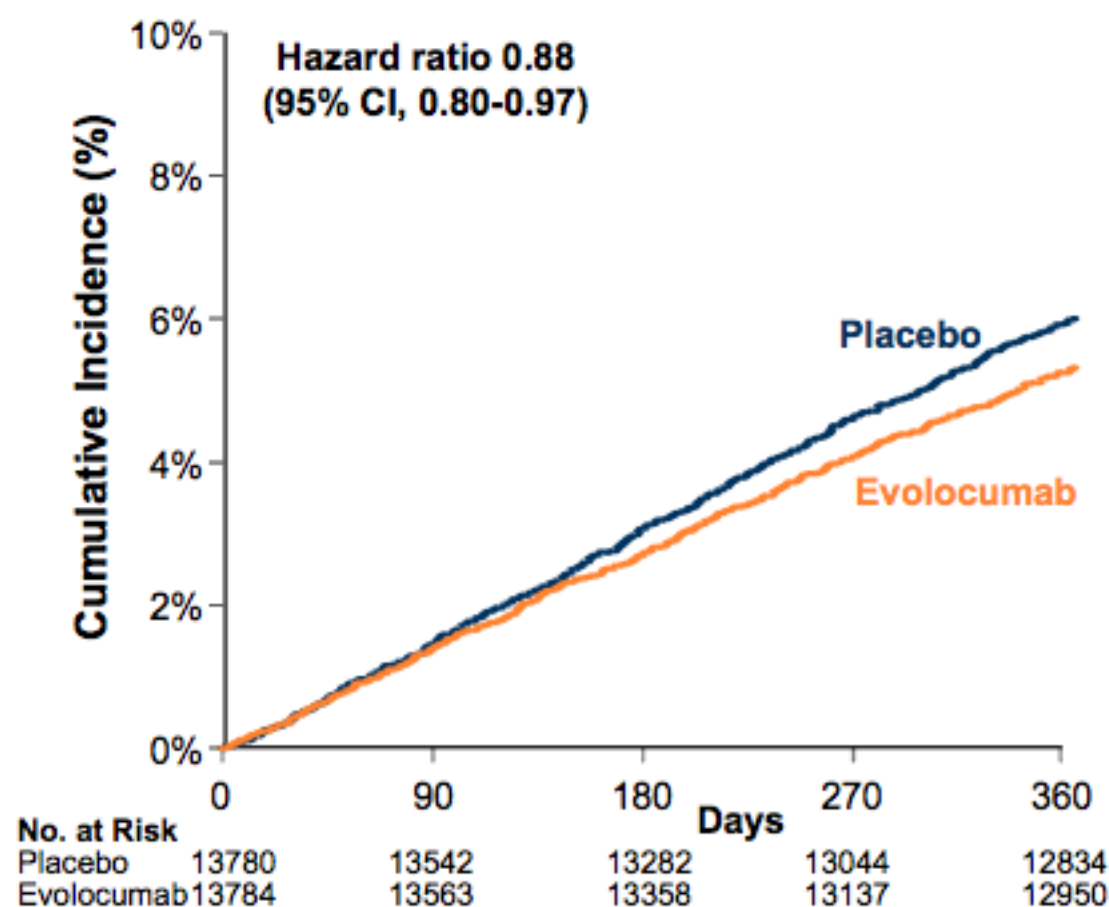


LDL-C was significantly reduced in the evolocumab group (median: 30 mg/dL) including 42% who achieved levels ≤ 25 mg/dL vs $< 0.1\%$ in the placebo group

Landmark Analysis of Primary Endpoint

Year 1: RRR 12%

> Year 1: RRR 19%



Longer duration of treatment and follow up suggests larger risk reduction

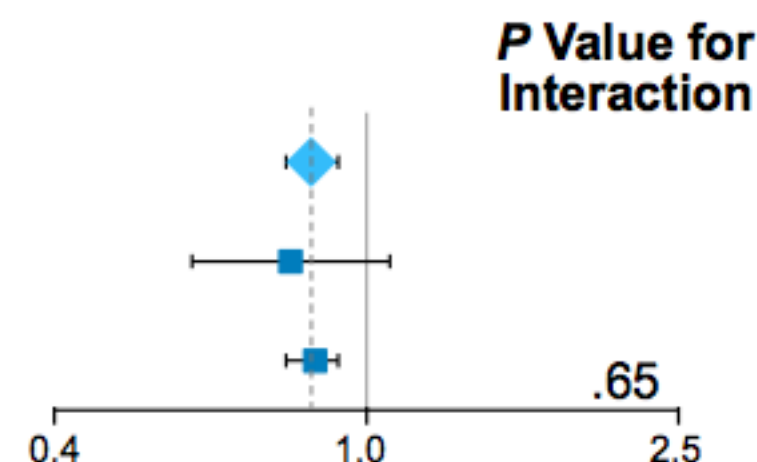
Landmark analyses were performed in which patients who were alive and in follow-up at the start of the period of interest formed the group at risk.
 Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722.
 (Supplementary Figure S4)

85

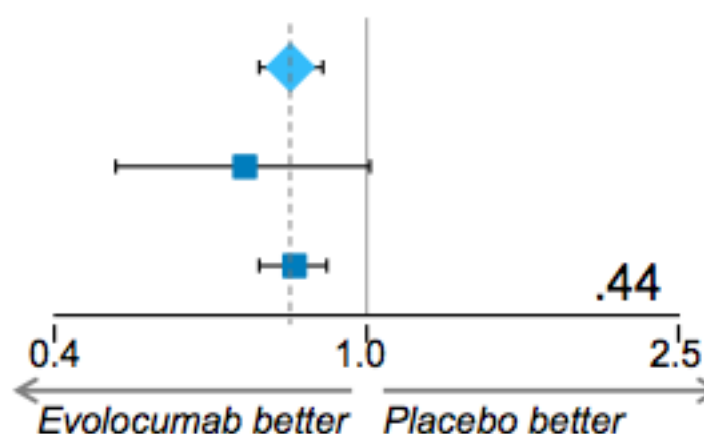
Primary and Key Secondary Endpoints Stratified by Baseline LDL-C

Efficacy outcomes by baseline LDL-C level

Number Events		Primary Endpoint	HR (95% CI)
Evo	Placebo	All	0.85 (0.79-0.92)
86	106	LDL-C < 70 mg/dL	0.80 (0.60-1.07)
1258	1457	LDL-C ≥ 70 mg/dL	0.86 (0.79-0.92)



Number Events		Key Secondary Endpoint	HR (95% CI)
Evo	Placebo	All	0.80 (0.73-0.88)
48	68	LDL-C < 70 mg/dL	0.70 (0.48-1.01)
768	945	LDL-C ≥ 70 mg/dL	0.81 (0.73-0.89)



Evolocumab significantly reduced risk for the primary and key secondary endpoints in those with baseline LDL-C < 70 mg/dL and ≥ 70 mg/dL, with no evidence of effect modification due to baseline LDL-C level

HRs and 95% CIs are shown for the primary (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, and coronary revascularization) and the key secondary (composite of cardiovascular death, myocardial infarction, and stroke) efficacy composite endpoints in the total population and in patients with baseline LDL-C levels < 70 mg/dL (1.8 mmol/L) vs those with LDL-C levels of at least 70 mg/dL (1.8 mmol/L). CI = confidence interval; HR = hazard ratio; LDL-C = low-density lipoprotein.

Giugliano RP, et al. *JAMA Cardiology*. [published online ahead of print November 8, 2017]. doi: 10.1001/jamacardio.2017.3944.

Therapeutics...

Small molecules

hydrophobic organic, typically act by deactivating or inhibiting target proteins through competitive binding.
downside: only 2–5% of the protein-coding human genome has these sites

Protein based

antibody/ enzyme
high specificity to a variety of targets / replacement of mutated or missing proteins (e.g., insulin for diabetes)

-: cost, size, stability

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siRNA, ASO, CRISPR/Cas
extremely specific, exon skipping, knockdown

Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*.
Fire A, Mello CC
Nature. 1998 Feb 19; 391(6669):806-11.

Current clinical RNA delivery trials

Current clinical trials involving RNA delivery

Name	Treatment	Genetic/protein target	Delivery vehicle	Administration method	Disease	ClinicalTrials.gov Identifier	Phase
Fitusiran (ALN-AT3SC)	siRNA	Plasma antithrombin	Conjugate (GalNAc)	Subcutaneous injection	Severe hemophilia A or B	NCT02554773	I/II
Inclisiran (ALN-PCSSC)	siRNA	PCSK9	Conjugate (GalNAc)	Subcutaneous injection	Hypercholesterolemia	NCT03060577	II
AKCEA- APOCIII-LRx	ASO	ApoCIII	Conjugate (GalNAc)	Subcutaneous injection	Elevated triglycerides	NCT02900027	I
IONIS ANGPTL3-LRx	ASO	ANGPTL3	Conjugate (GalNAc)	Subcutaneous injection	Elevated triglycerides/familial hypercholesterolemia	NCT02709850	I/II
AKCEA-APO(a)-LRx	ASO	ApoA	Conjugate (GalNAc)	Subcutaneous injection	Hyperlipoproteinemia(a)	NCT03070782	II
IONIS-GCGR Rx	ASO	GCGR	Naked (modified)	Subcutaneous injection	Type 2 diabetes	NCT02824003	II
Volanesorsen	ASO	ApoCIII	Naked (modified)	Subcutaneous injection	Familial chylomicronemia syndrome Familial partial lipodystrophy	NCT02658175 NCT02527343	III II/III

Kaczmarek *Genome Med* 2017; 9: 60

ASO antisense oligonucleotide, siRNA small interfering RNA, siRNA short interfering RNA, siRNA not disclosed

Phase II ORION-1 Study

Study design



Screening (Day -14 to Day -1)

Randomization (Day 1, n=501)

One dose starting regimen

Randomized (n=501)

Two dose starting regimen

Placebo
N=65

200
mg
N=60

300
mg
N=61

500
mg
N=65

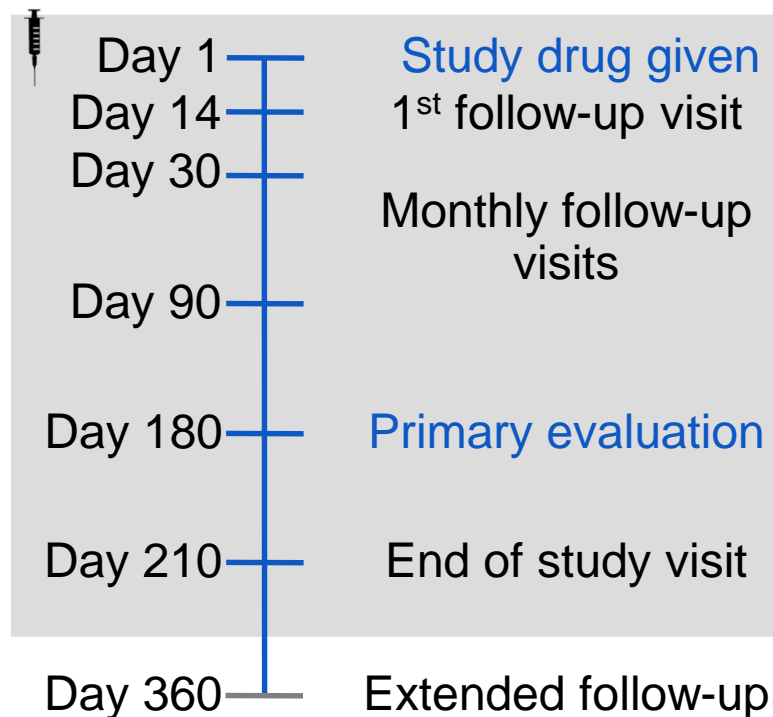
Treated (n=497)

Placebo
N=62

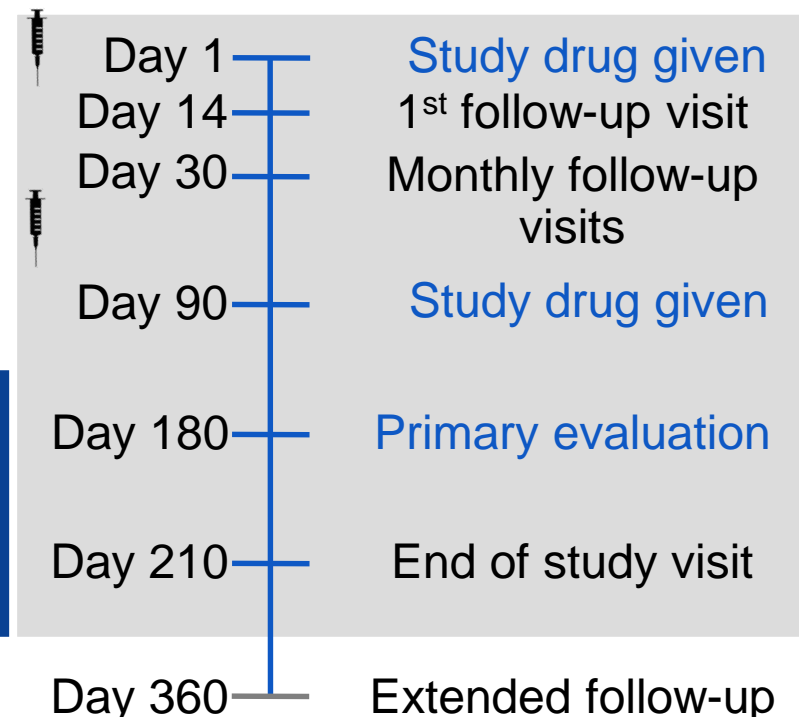
100
mg
N=61

200
mg
N=62

300
mg
N=61



Completed (n=483)

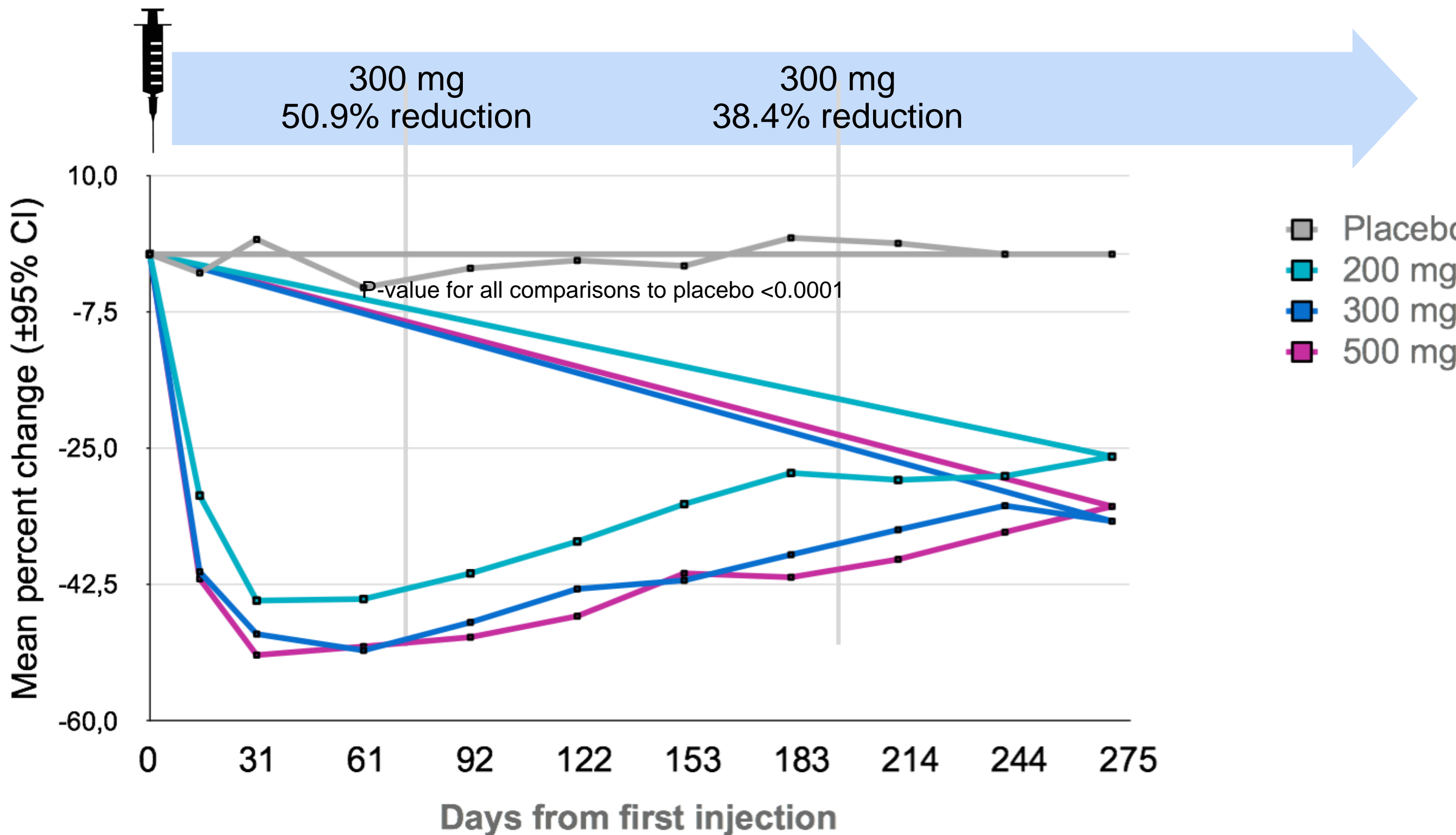


No safety concerns

- No thrombocytopenia
 - No neuropathy
 - No immunogenicity (no anti-drug antibodies)
 - No pro-inflammatory symptoms or elevated markers
-

Efficacy: One dose starting regimen

LDL-C reductions – 300 mg optimal





The NEW ENGLAND
JOURNAL of MEDICINE

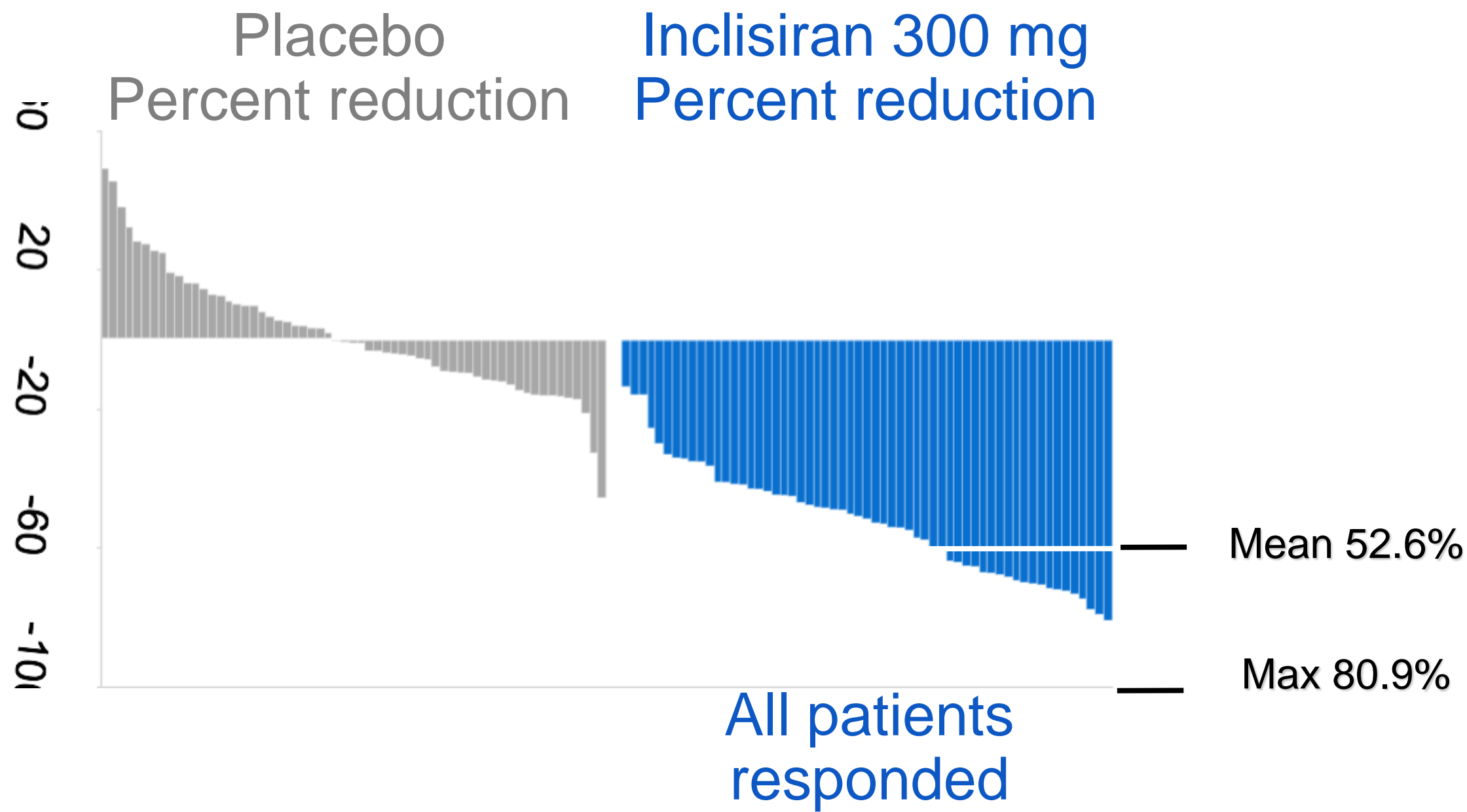
ORIGINAL ARTICLE

Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

Kausik K. Ray, M.D., Ulf Landmesser, M.D., Lawrence A. Leiter, M.D.,
David Kallend, M.D., Robert Dufour, M.D., Mahir Karakas, M.D., Tim Hall, M.D.,
Roland P.T. Troquay, M.D., Traci Turner, M.D., Frank L.J. Visseren, M.D.,
Peter Wijngaard, Ph.D., R. Scott Wright, M.D., and John J.P. Kastelein, M.D., Ph.D.

Efficacy: Two dose starting regimen

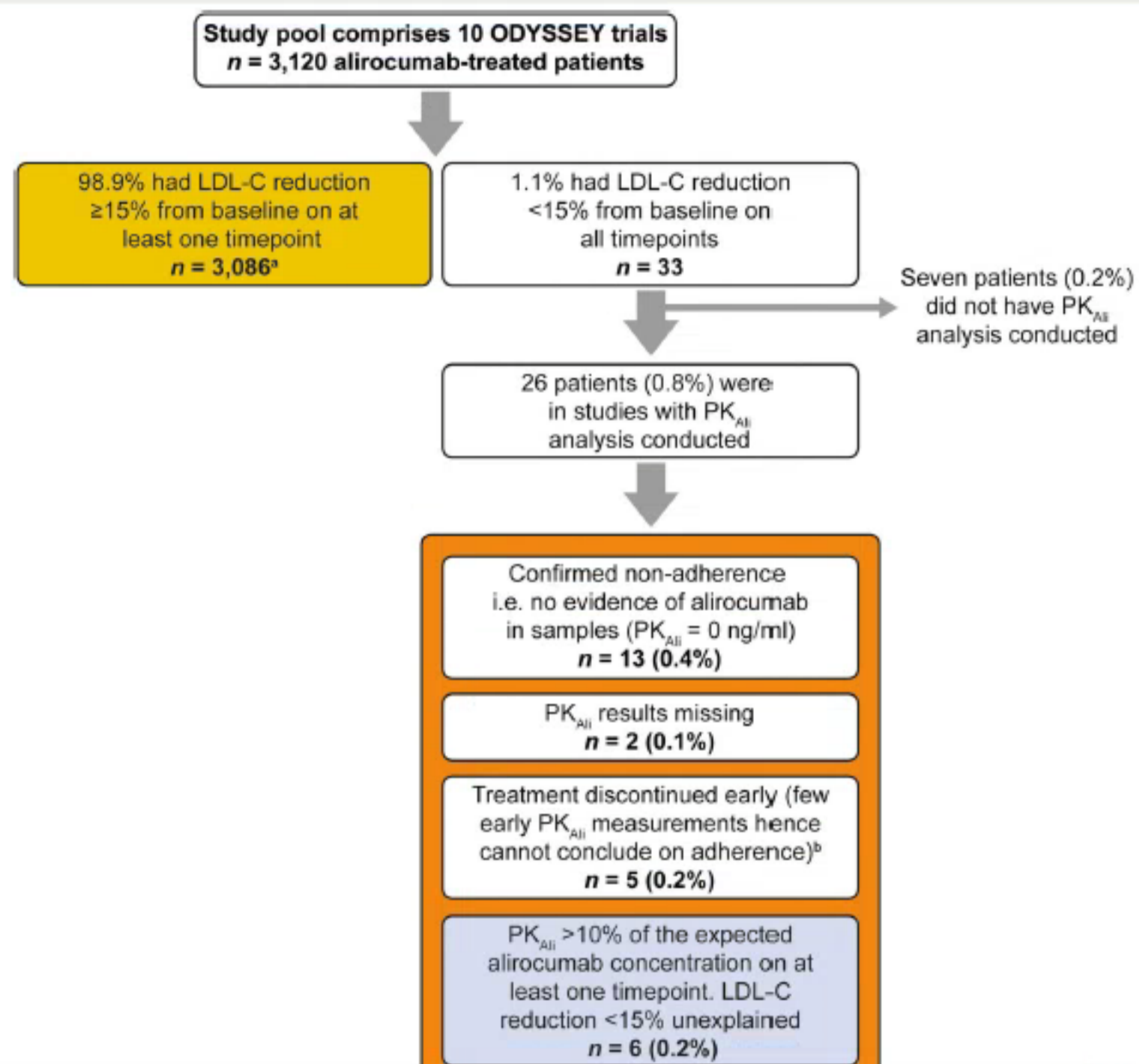
Individual patient responses (%) at day 180





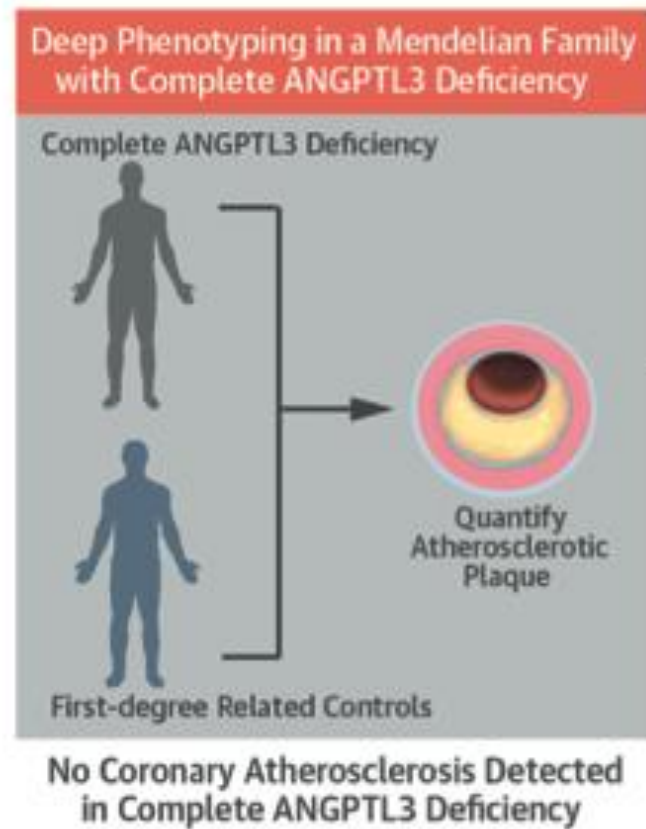
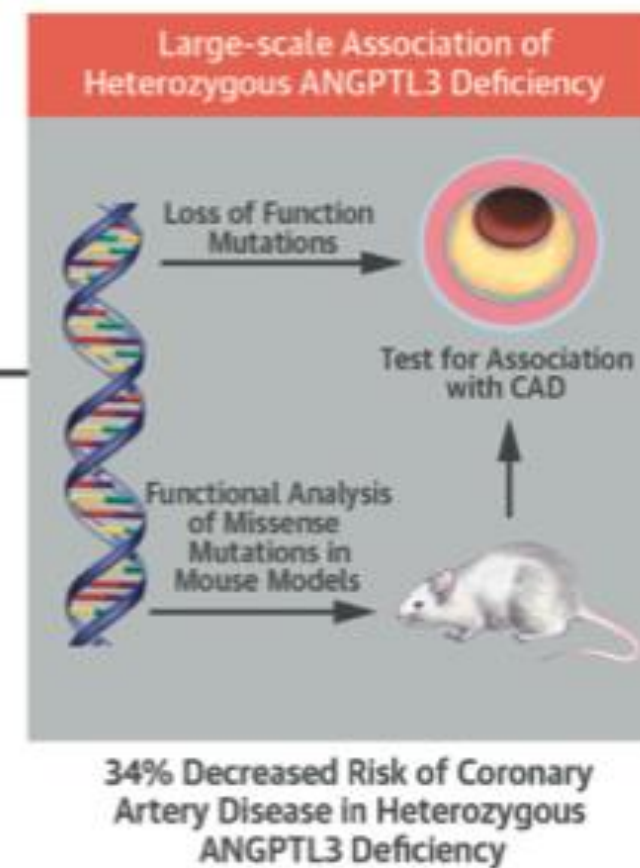
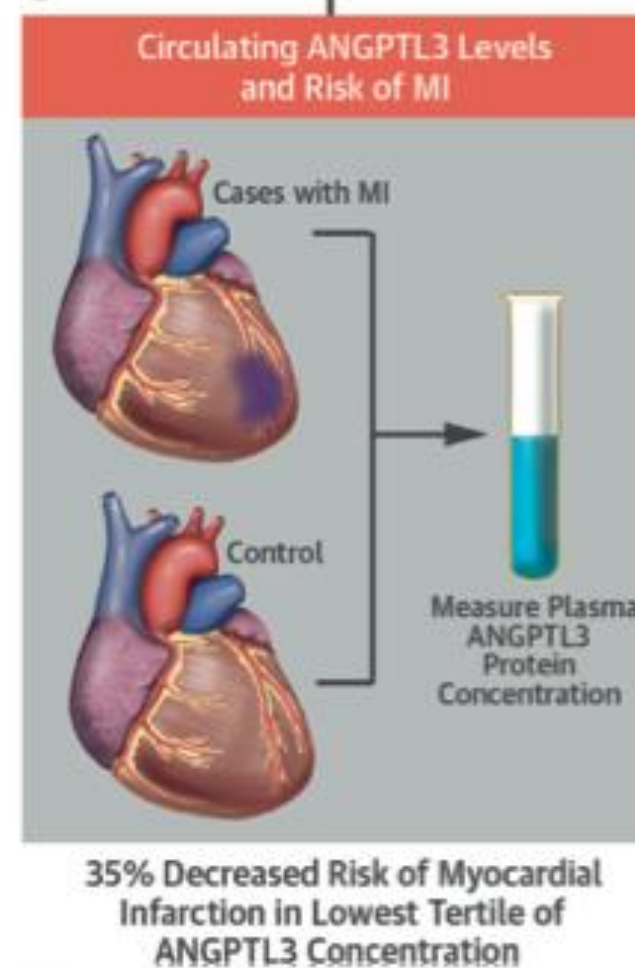
Assessment of the 1% of Patients with Consistent < 15% Reduction in Low-Density Lipoprotein Cholesterol: Pooled Analysis of 10 Phase 3 ODYSSEY Alirocumab Trials

Harold E. Bays¹ • Robert S. Rosenson² • Marie T. Baccara-Dinet³ • Michael J. Louie⁴ • Desmond Thompson⁴ • G. Kees Hovingh⁵



PCSK9 targeted therapy

Drug	Sponsor	Modality	Status
Alirocumab and evolocumab	Regeneron/Sanofi and Amgen	Monoclonal antibody	Approved
Inclisiran	Alnylam/The Medicines Company	RNA interference	Phase III planned
MEDI4166	AstraZeneca	PCSK9 antibody fused to GLP1 peptide	Phase I/II
AT04A and AT06A	Affiris	Vaccine	Phase I
DS-9001	Daiichi Sankyo/Pieris Pharmaceuticals	Anticalin (antibody mimetic)	Phase I
CRISPR-based approach	Academic project and AstraZeneca	CRISPR	Preclinical
PF-06446846	Pfizer	Small molecule	Discontinued
BMS-PCSK9Rx and SPC5001	BMS/Ionis Pharmaceuticals and Santaris Pharma/Roche	Antisense	Discontinued
BMS-962476	BMS	Adnectin (antibody mimetic)	Discontinued

A**B****C**

**3 Lines of Evidence:
ANGPTL3 Deficiency
Protects Against CAD**



Cardiovascular endocrinology: Is *ANGPTL3* the next *PCSK9*?

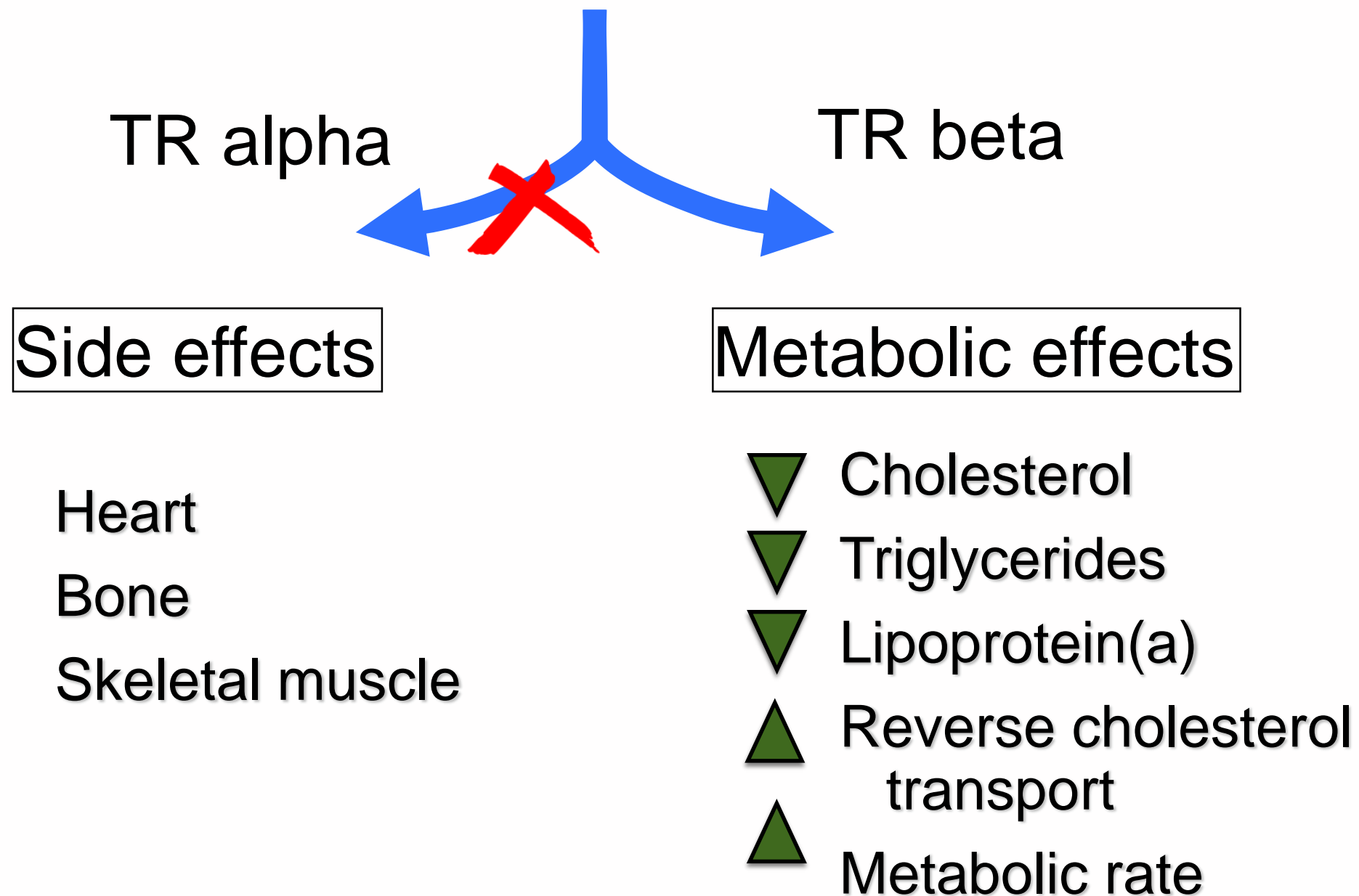
Kiran Musunuru & Sekar Kathiresan

[Affiliations](#) | [Corresponding author](#)

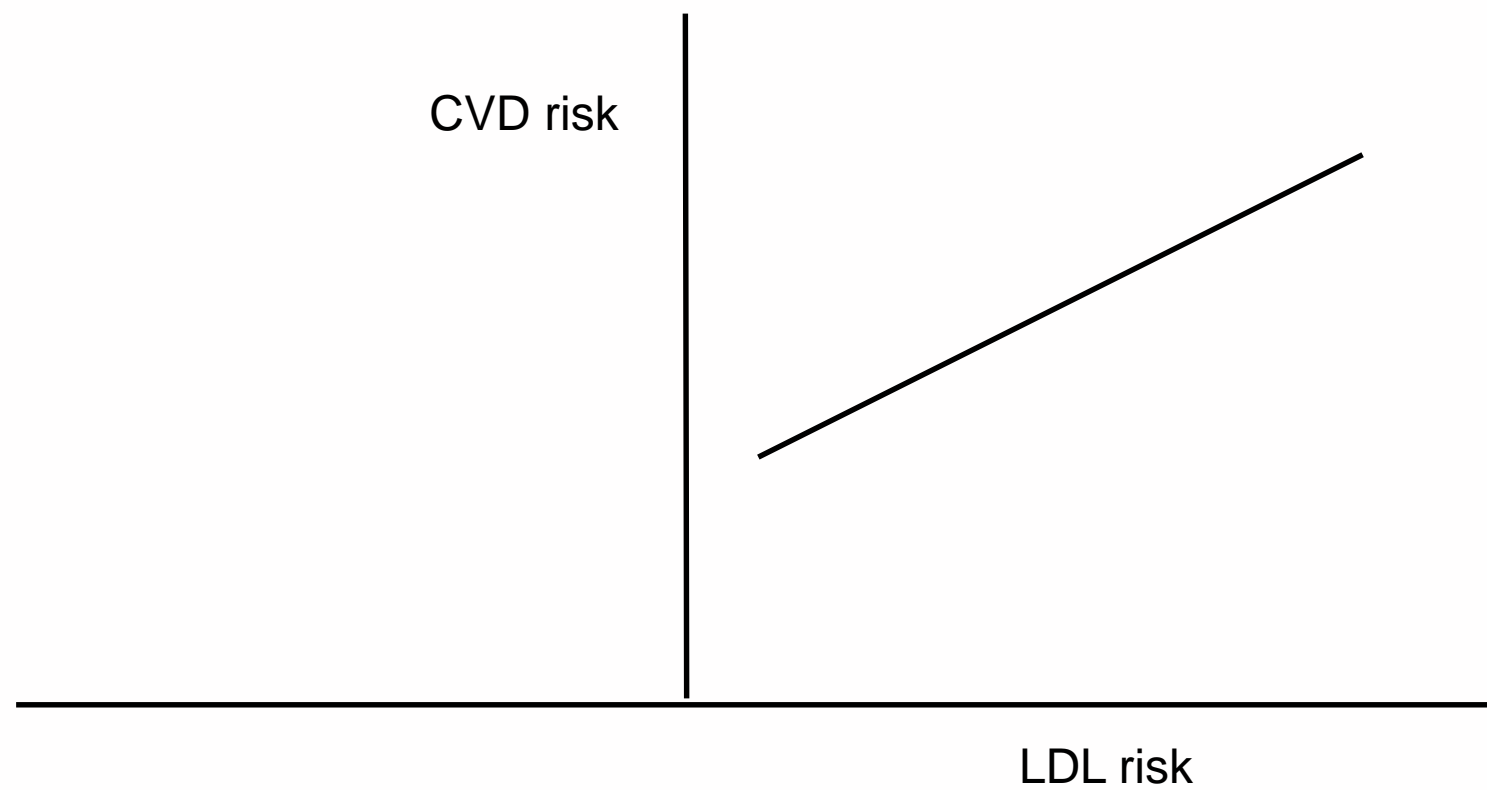
Nature Reviews Endocrinology (2017) | doi:10.1038/nrendo.2017.88

Published online 14 July 2017

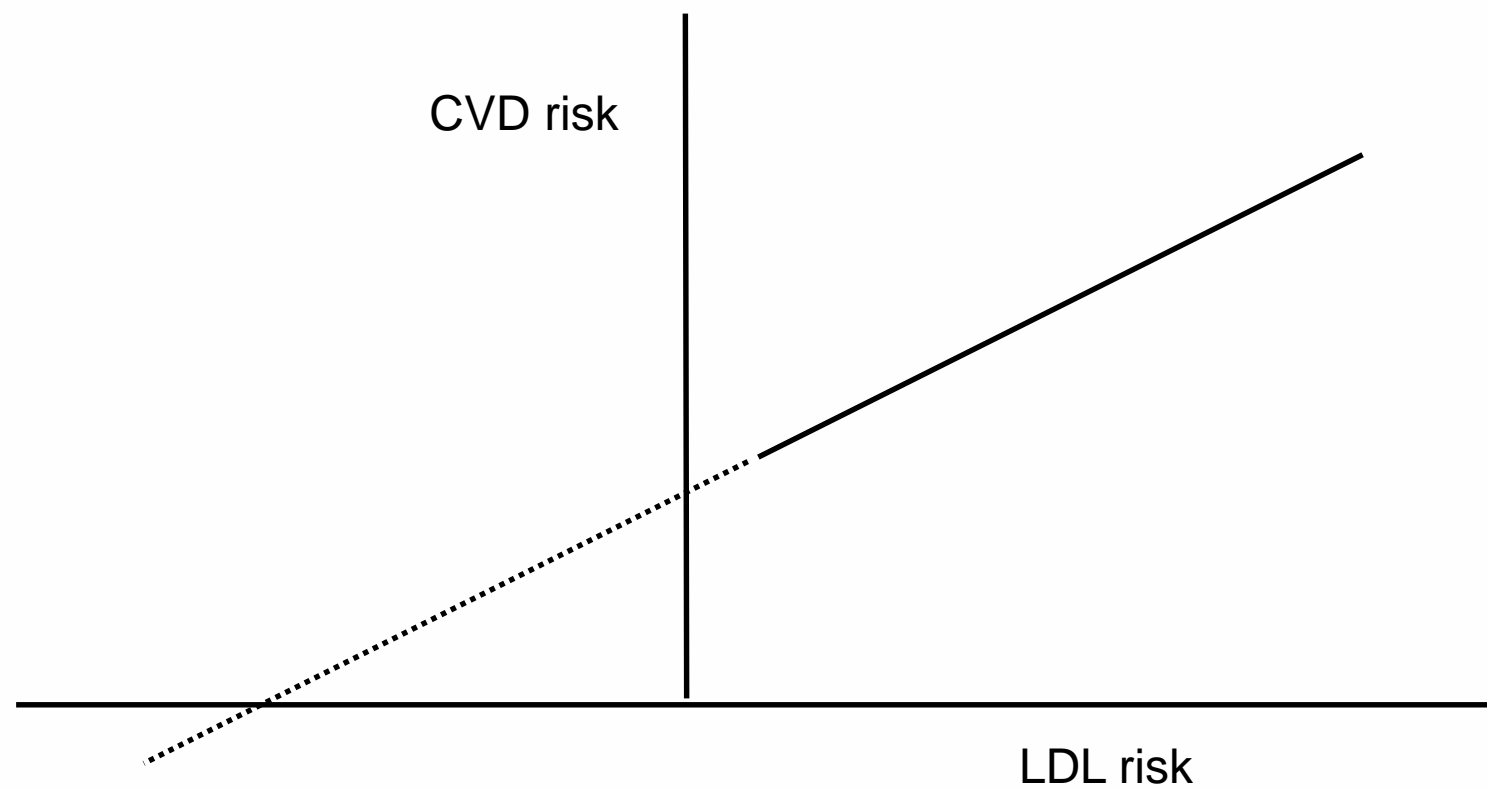
Selective Thyroid Receptor Agonist(s)



“how low can you go?”



“how low can you go?”



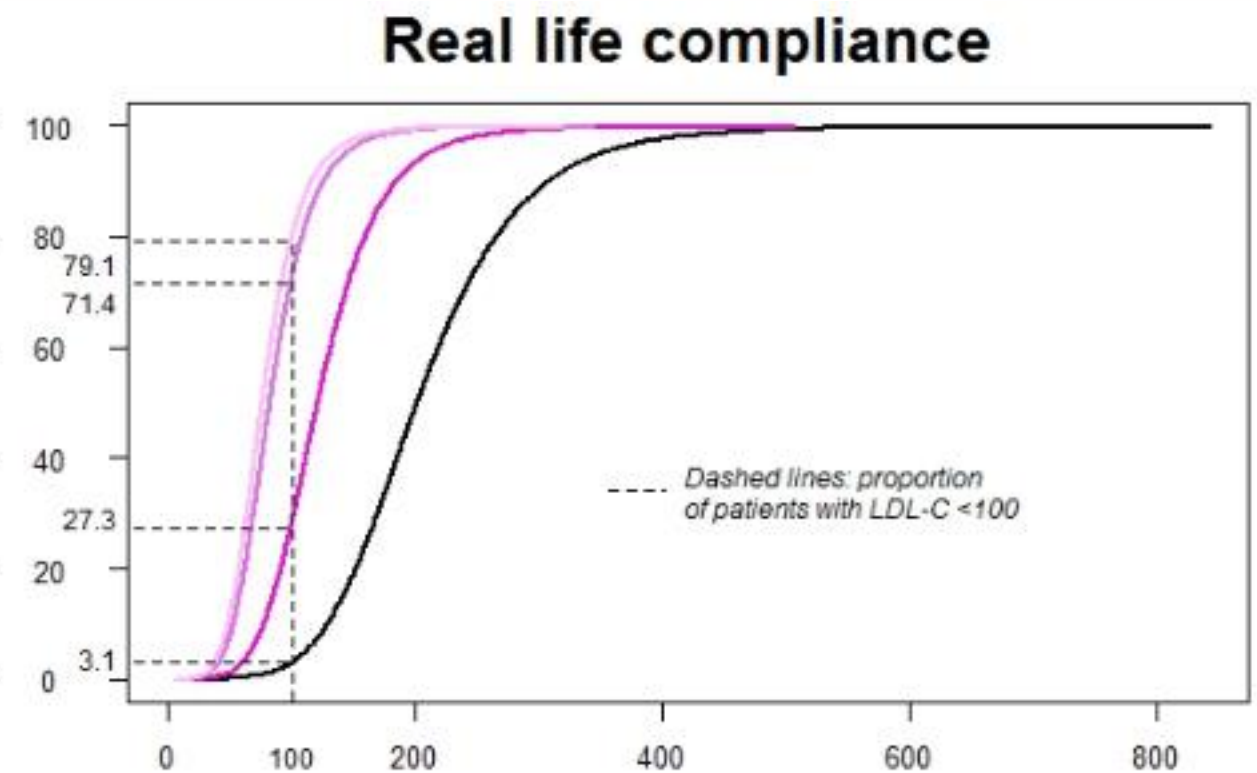
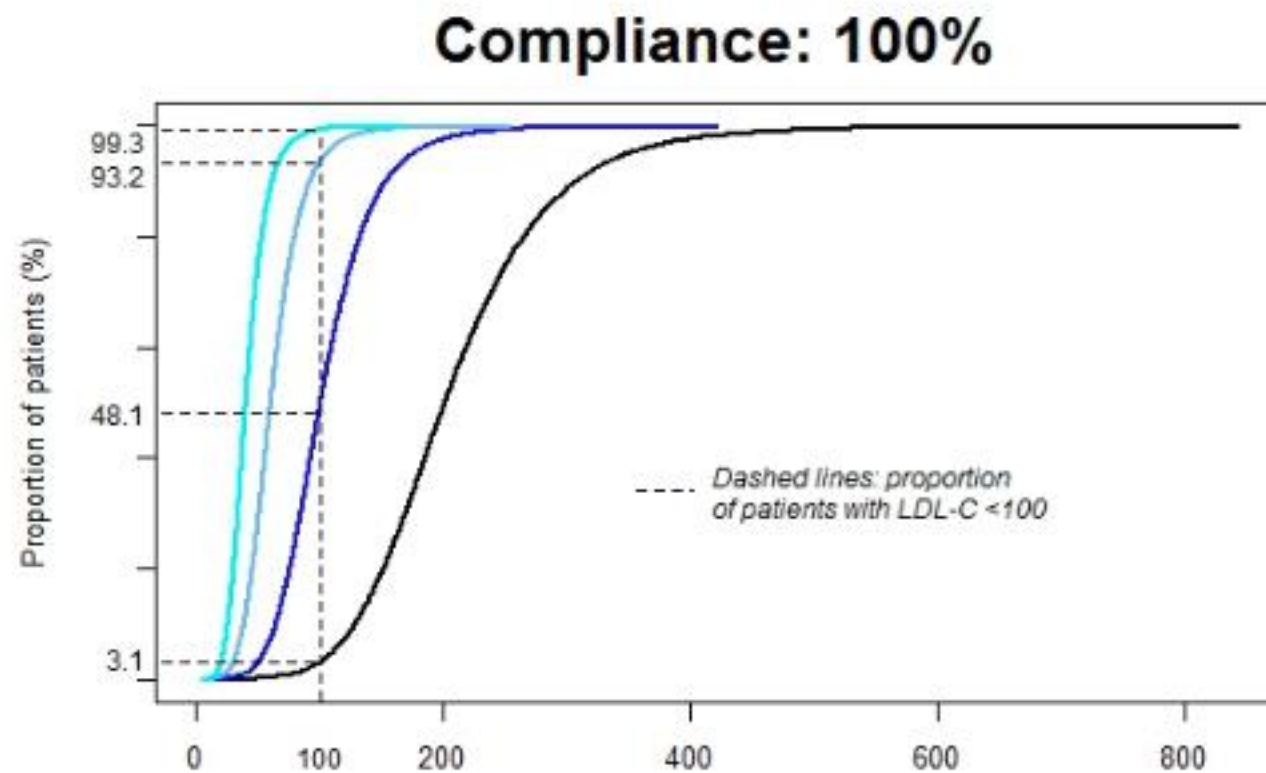
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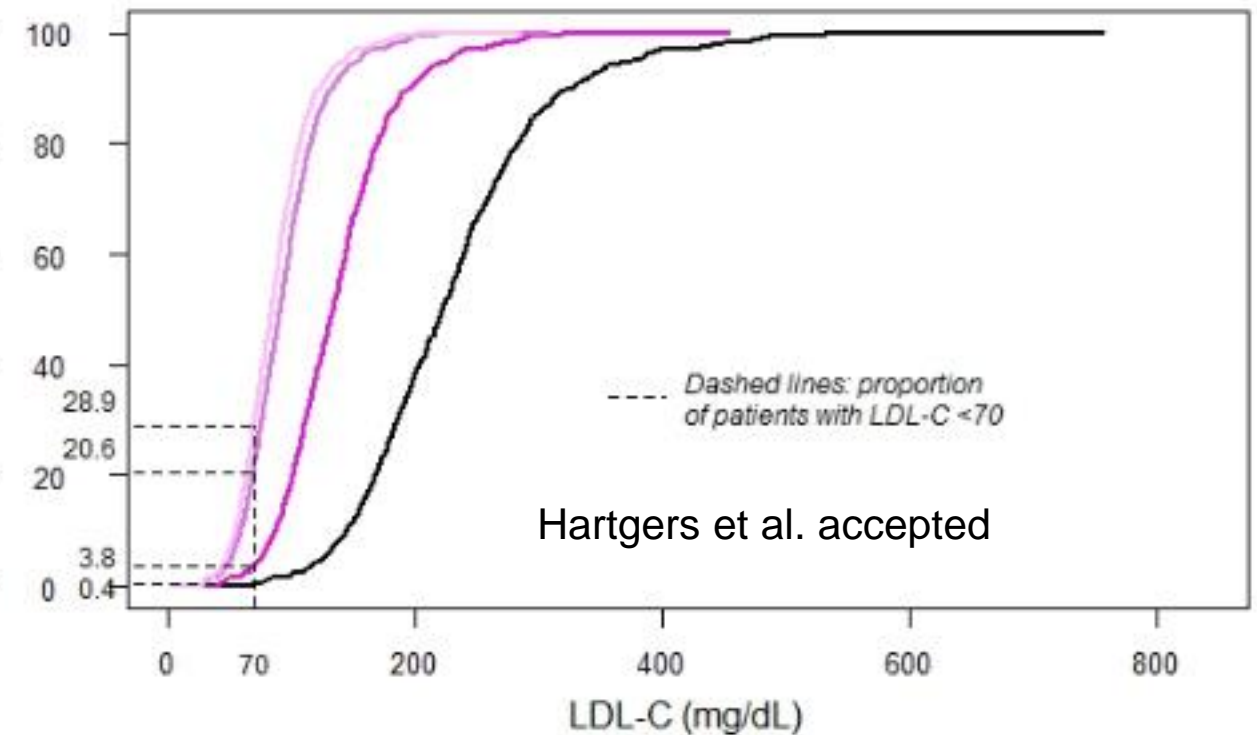
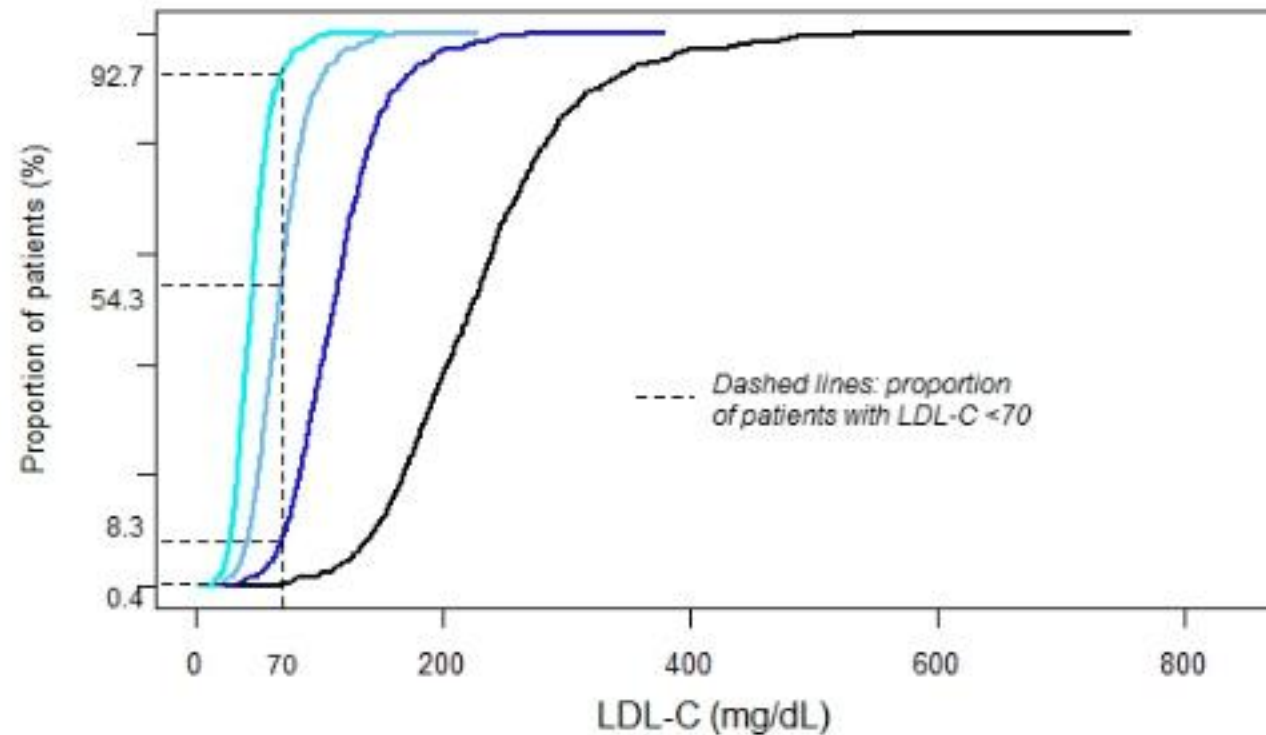
Conceptrichtlijn Cardiovasculair risicomanagement (CVVRM)

PCSK9i in heFH

Without CHD



With CHD

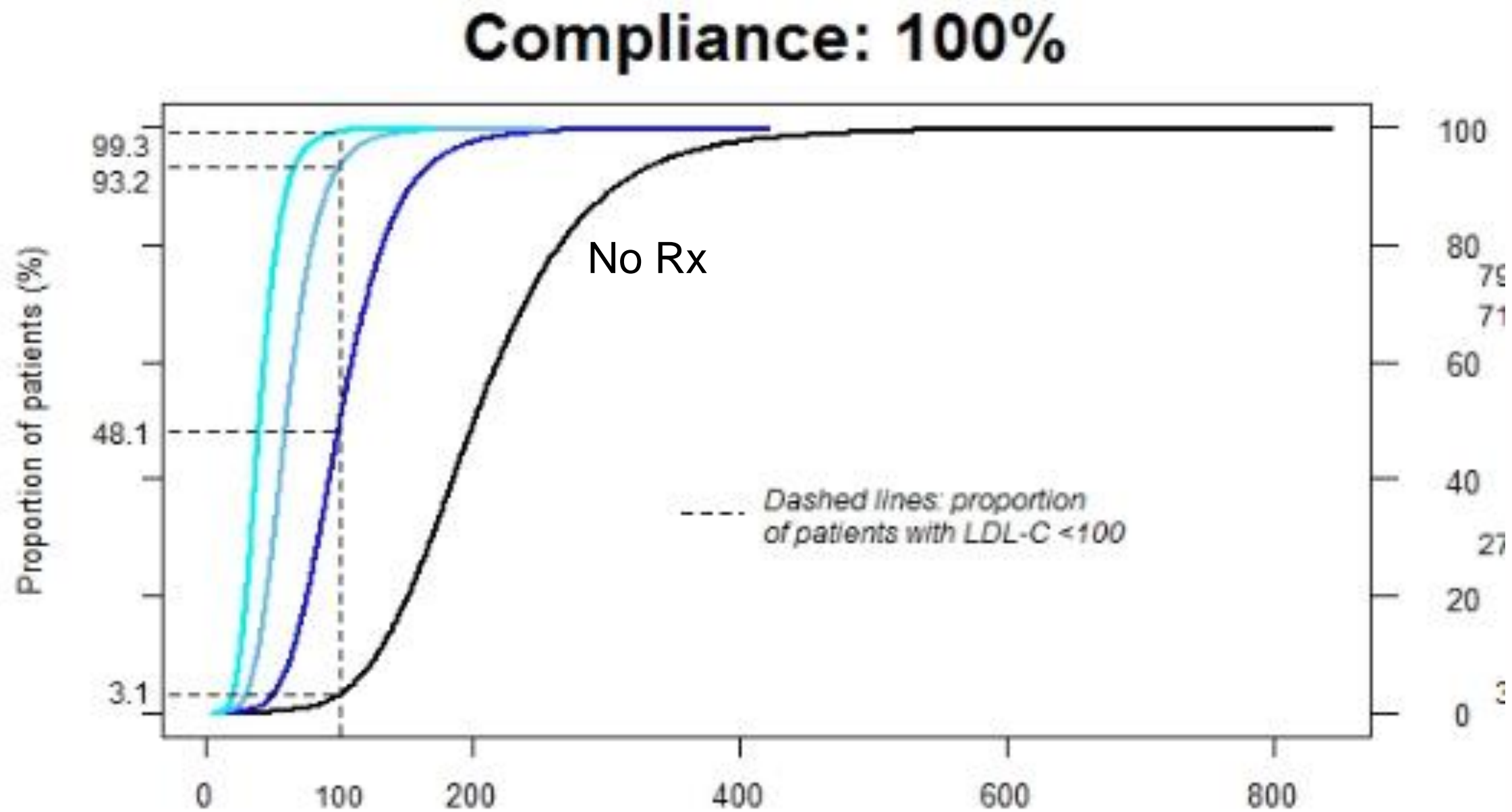


- Off treatment
- Reduction of 50% (maximal current therapy)
- Reduction of 50% and 40% (maximal current therapy and CETP inhibition)
- Reduction of 50% and 60% (maximal current therapy and PCSK9 inhibition)

- Reduction of 40% (maximal current therapy)
- Reduction of 40% and 32% (maximal current therapy and CETP inhibition)
- Reduction of 40% and 37.2% (maximal current therapy and PCSK9 inhibition)

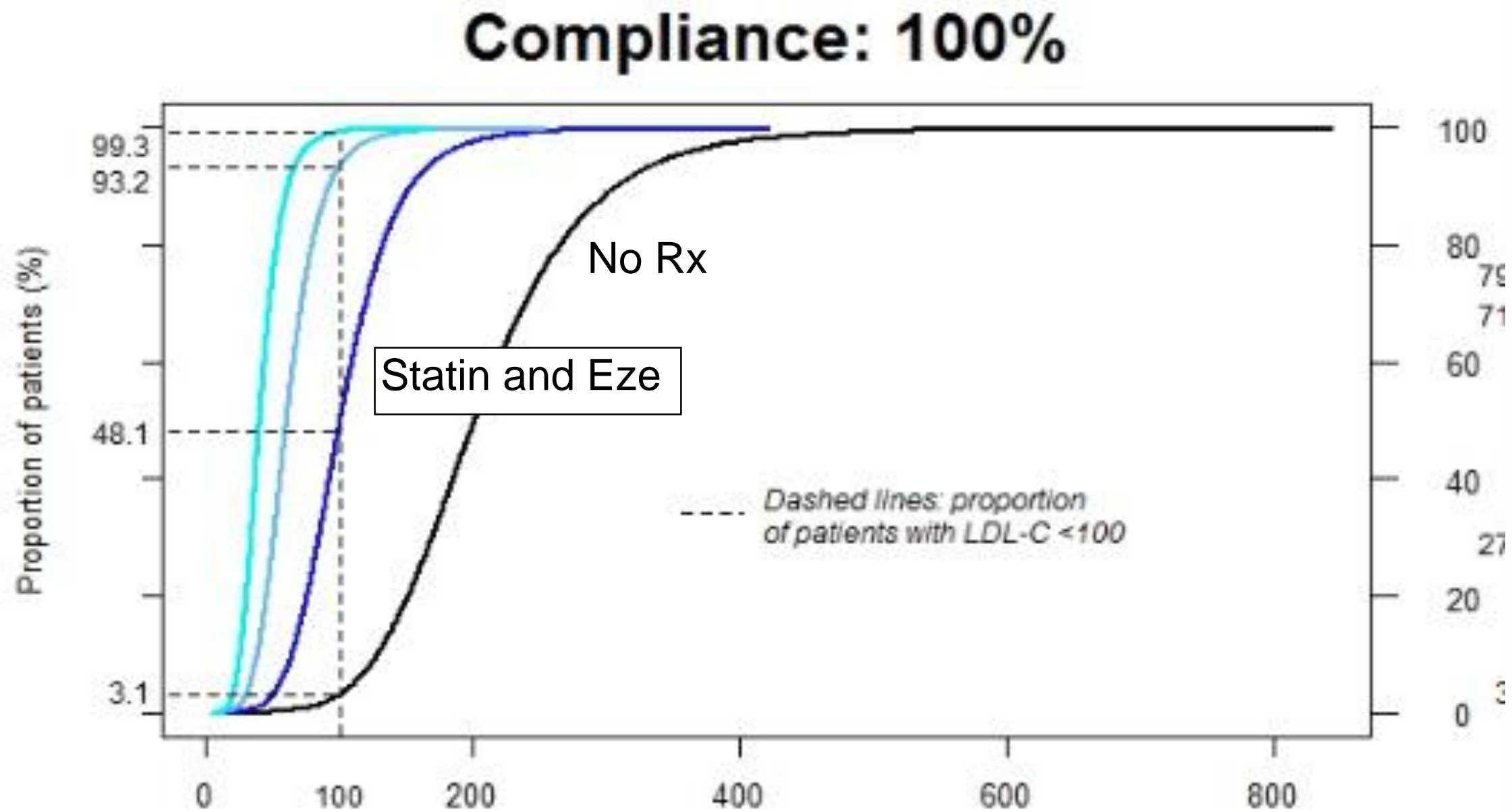
Hartgers et al. accepted

PCSK9i in heFH



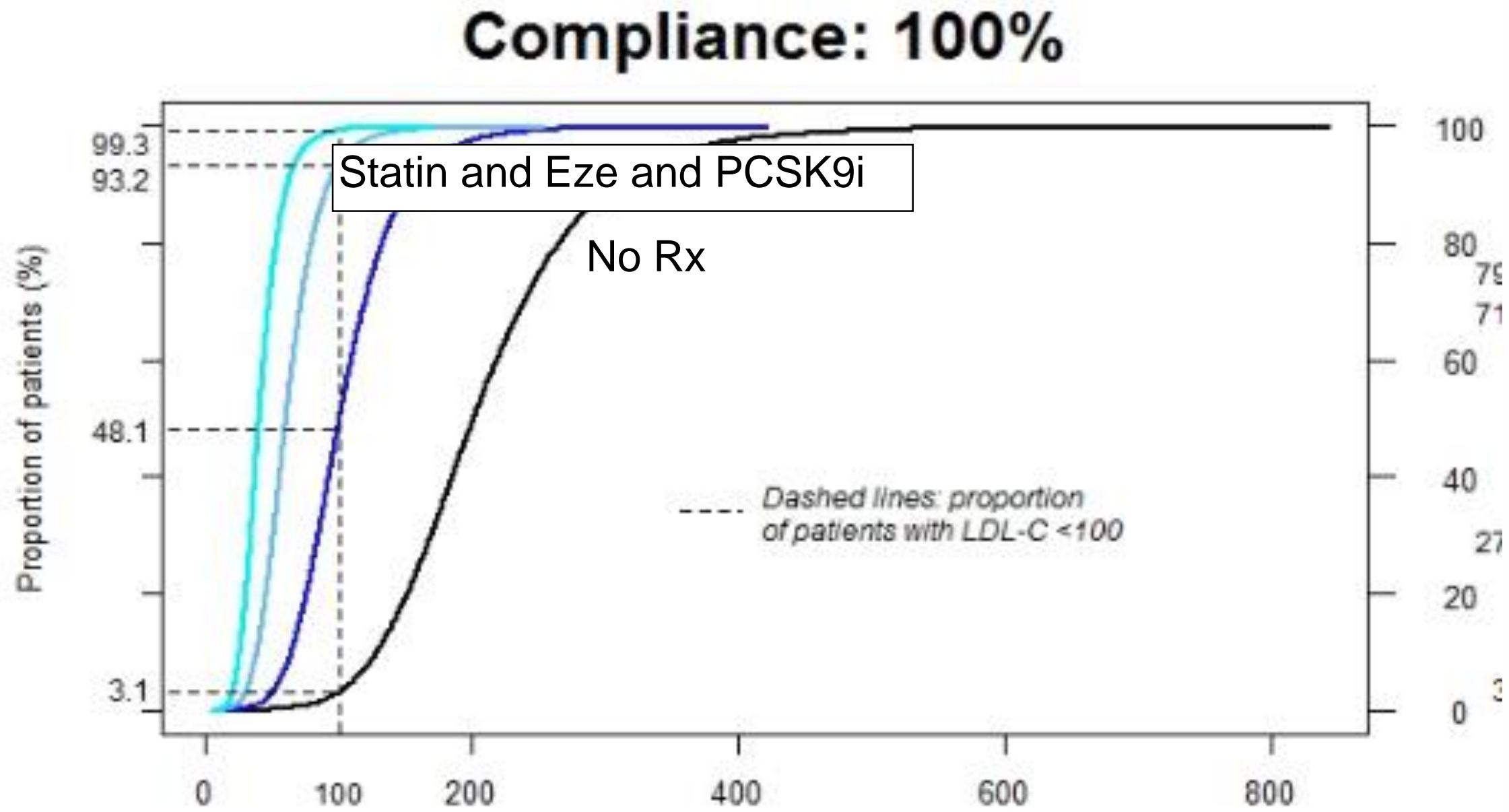
Without CVD

PCSK9i in heFH



Without CVD

PCSK9i in heFH



Without CVD

“all that good?”

Aan: G.K. Hovingh

dinsdag 15 mei 2018 10:07

- U hebt dit bericht doorgestuurd op 15-5-2018 21:55.

ernstige bijwerkingen praluent

Betreft: mevrouw T. Vos, de Gans (01-12-1947)

RE: PCSK9i resistentie FH patienten

@lumc.nl



Aan: G.K. Hovingh

dinsdag 15 mei 2018 9:53

Beste Kees,

Dank voor de reactie.

Ja ik heb een patiënte met HeFH die nauwelijks LDL daling laat zien op zowel alirocumab en evolocumab. Zeker therapietrouw. Intrigerend hoe dat tussen individuen kan wisselen.

Groet,

Adverse events and inefficacy of PCSK9
Inhibition with evolocumab or alirocumab in
hypercholesterolaemic patients. (AKITA trial)

(March 2018)
<https://nl.surveymonkey.com/r/YCFPY89>

