Indicações para um inibidor de PCSK9

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From Thought Leadership to Clinical Practice

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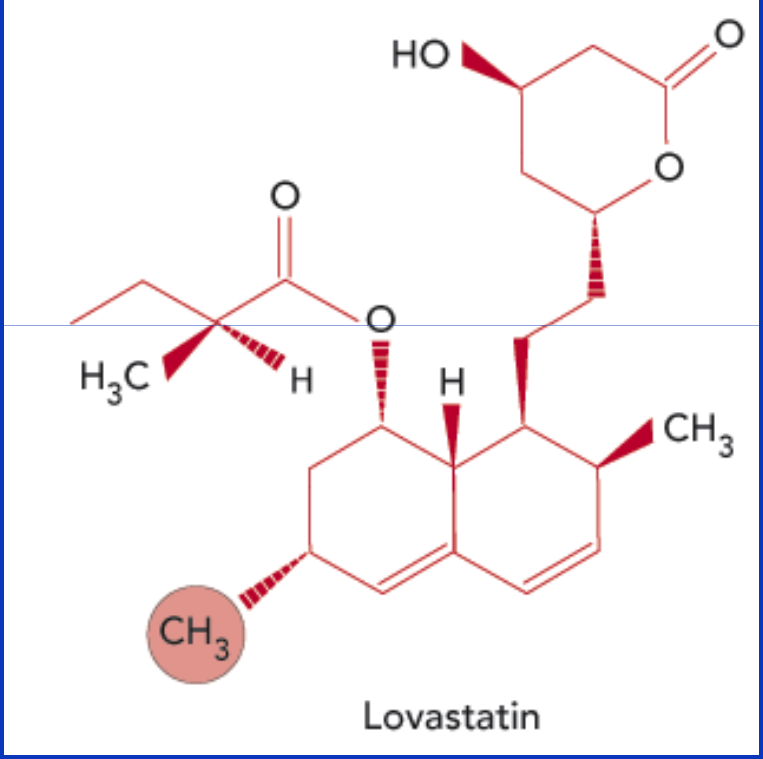
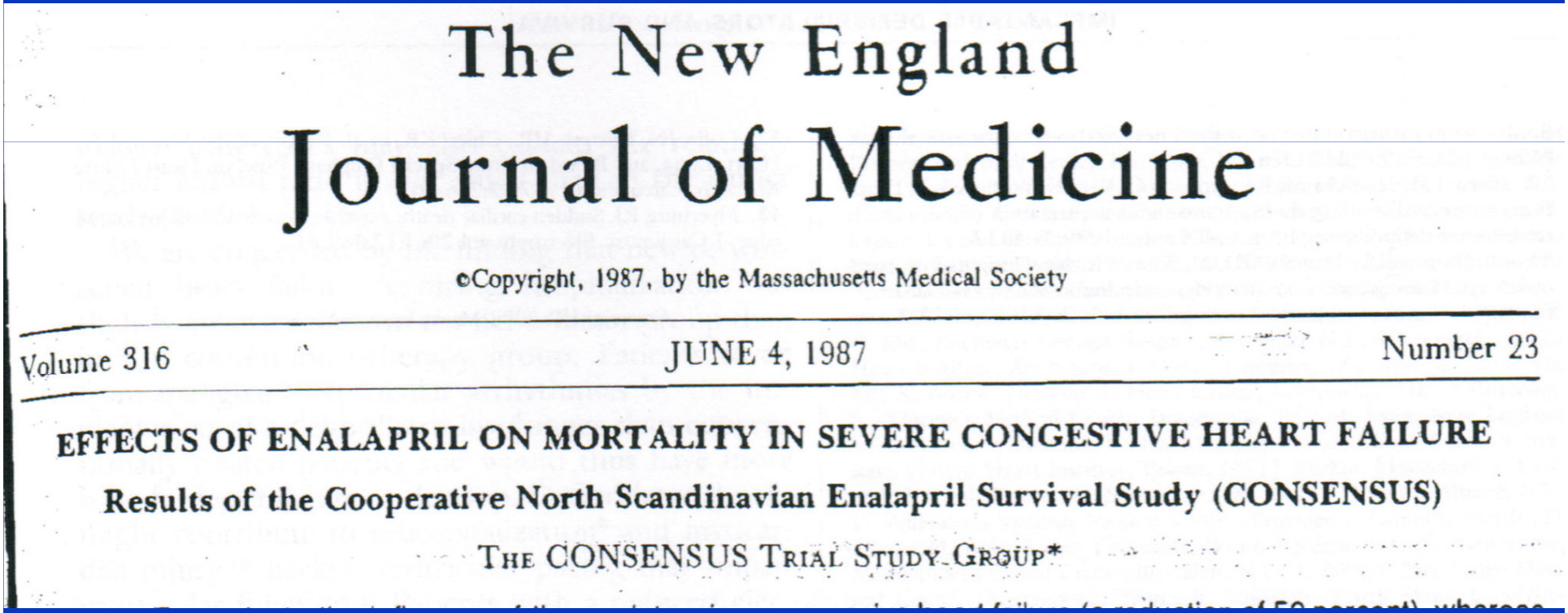
1987 – 2017:
30 years since first statin approved



Lovastatin

1987:
ACE-inhibitors shown to be beneficial in heart failure



The New England
Journal of Medicine

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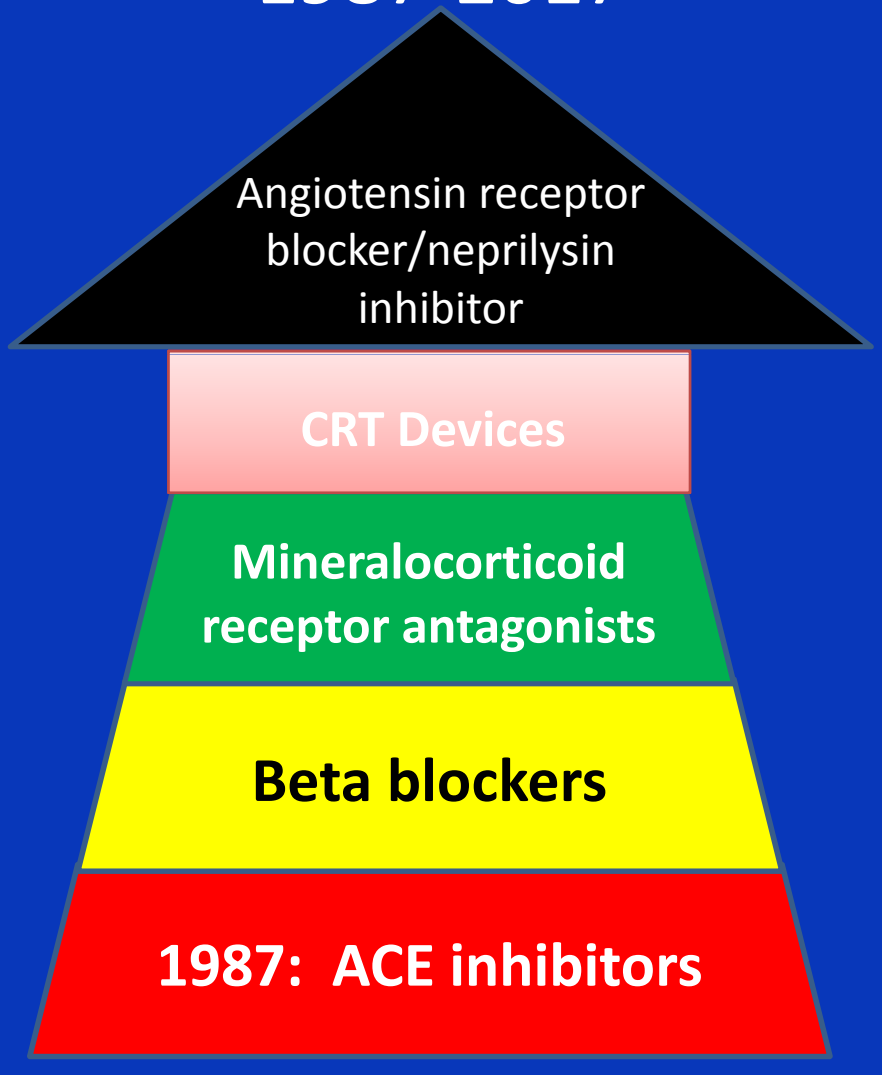
EFFECTS OF ENALAPRIL ON MORTALITY IN SEVERE CONGESTIVE HEART FAILURE

Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

THE CONSENSUS TRIAL STUDY GROUP*

How have we progressed?

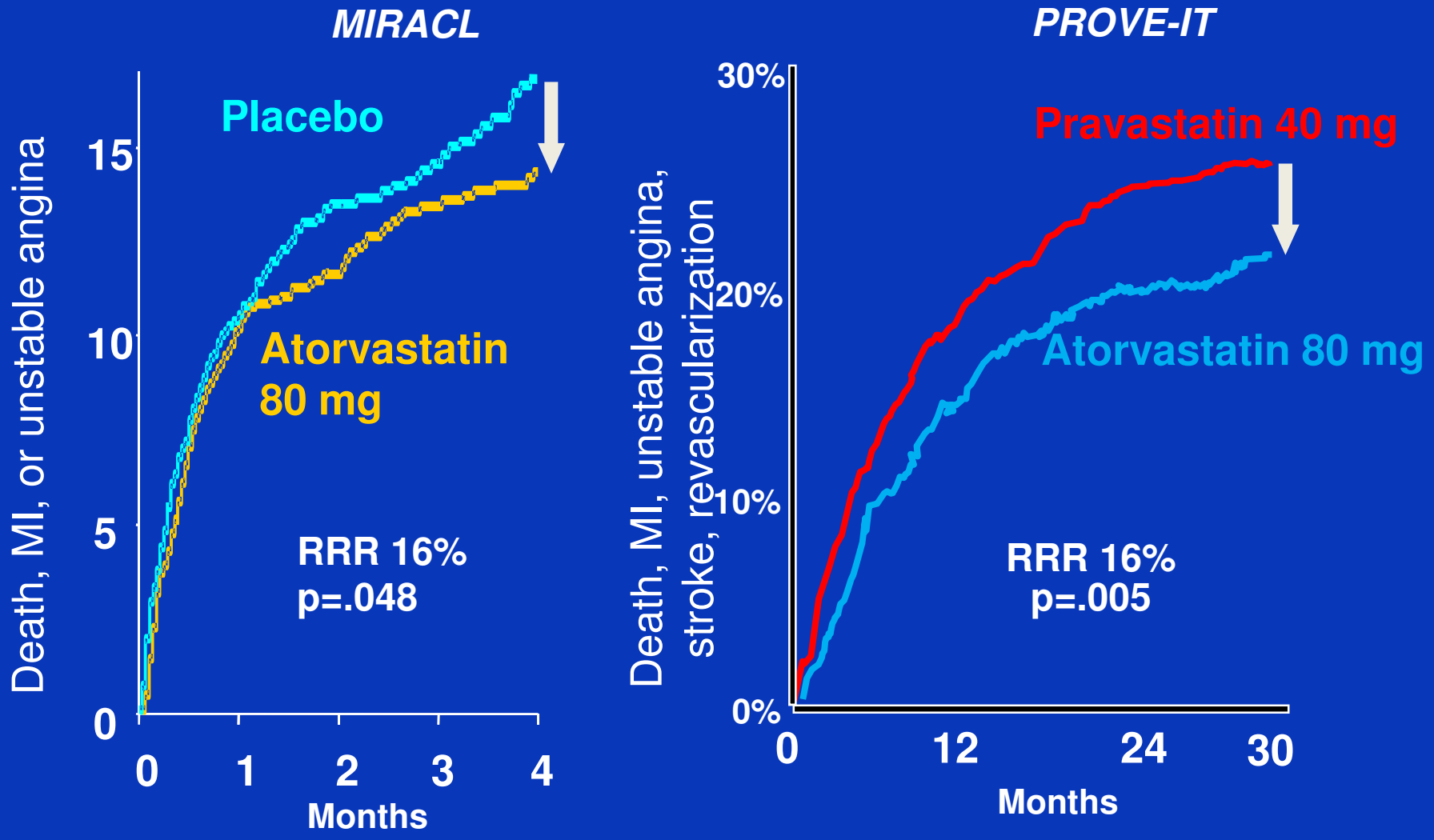
Heart failure 1987-2017



Atherosclerosis 1987-2017

1987: Statins

Intensive statin therapy reduces risk after ACS -- but residual risk remains high



Schwartz et al., JAMA 2001;285:1411; Cannon et al. *N Engl J Med*. 2004;350:1495.

Beyond statins:
Failed approaches to reduce CV risk

- Fenofibrate
- Niacin
- Succinobucol
- Omega-3 FAs
- CETP inhibitors
  - torcetrapib
  - dalcetrapib
- Secretory PLA2 antagonist
  - Varespladib
- PPAR activators
  - Aleglitazar, rosiglitazone

ACCELERATE

Evacetrapib

- CETP inhibitor – CETP is an enzyme that mediates transfer of cholesterol between LDL and HDL lipoproteins

- Genetic and animal data that support probable benefit

ACCELERATE

LDL from 84mg/dL to 54 mg/dL = 37% decrease
HDL from 46mg/dL to 104 mg/dl = 130% increase

ZERO EFFECT ON OUTCOMES

Similarities between CETP and PCSK9

Both with genetic data to support efficacy

Both have significant effects on LDLc

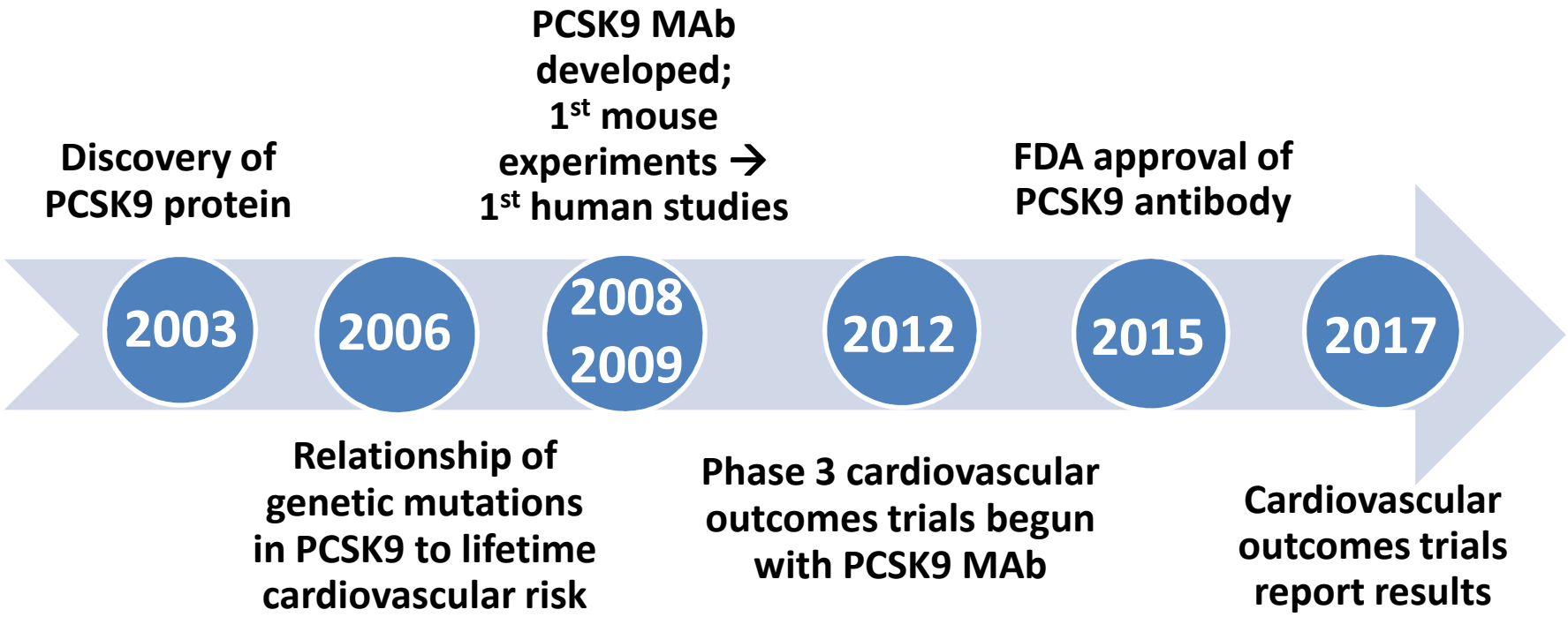
Neither effect hsCRP

PCSK9

- **Function:** How does PCSK9 participate in regulation of LDL-C levels?
- **Experiments of nature:** Effects of PCSK9 mutations
- **Experiments of man:** What can we expect from forthcoming CV outcomes trials?

The PCSK9 time-line:

Bench to bedside in record time!



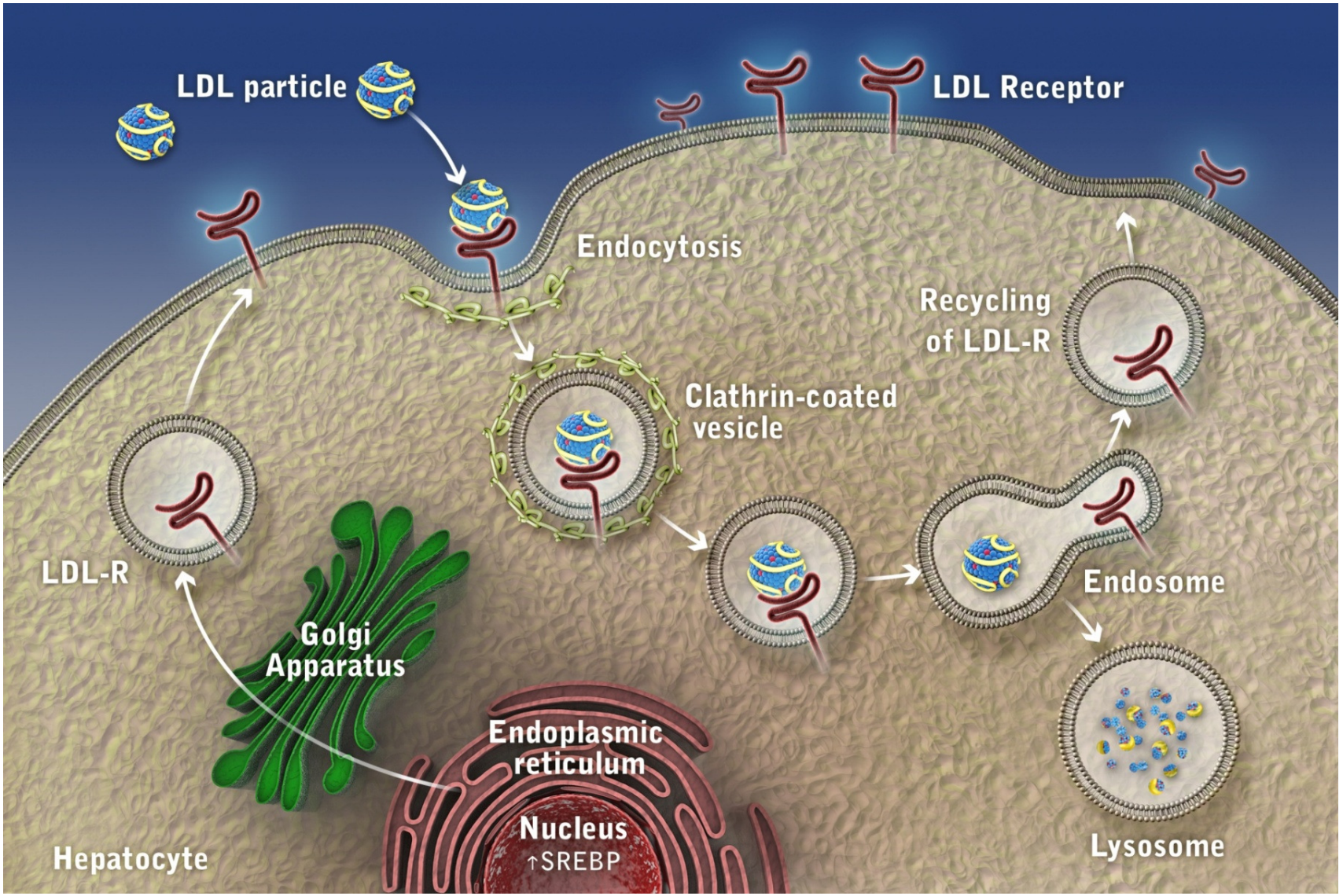
Function of PCSK9

- promote degradation of LDL receptors (LDLR)
- reduce clearance of LDL from circulation

Effect of PCSK9 inhibition

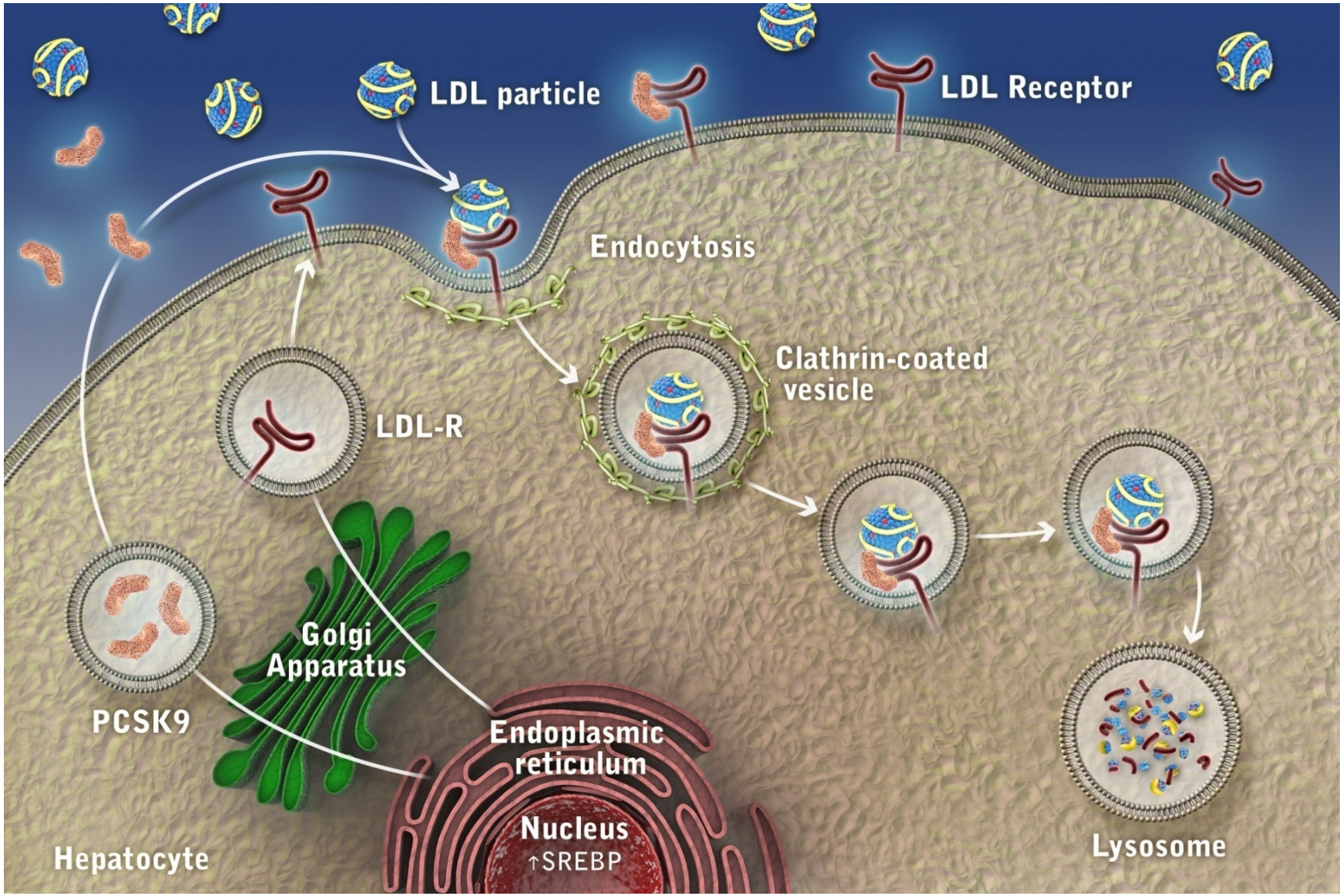
- increase LDLR density on hepatocytes
- promote clearance of LDL from circulation and reduce circulating LDL-C concentration

LDL Receptor Function and Life Cycle *without PCSK9*



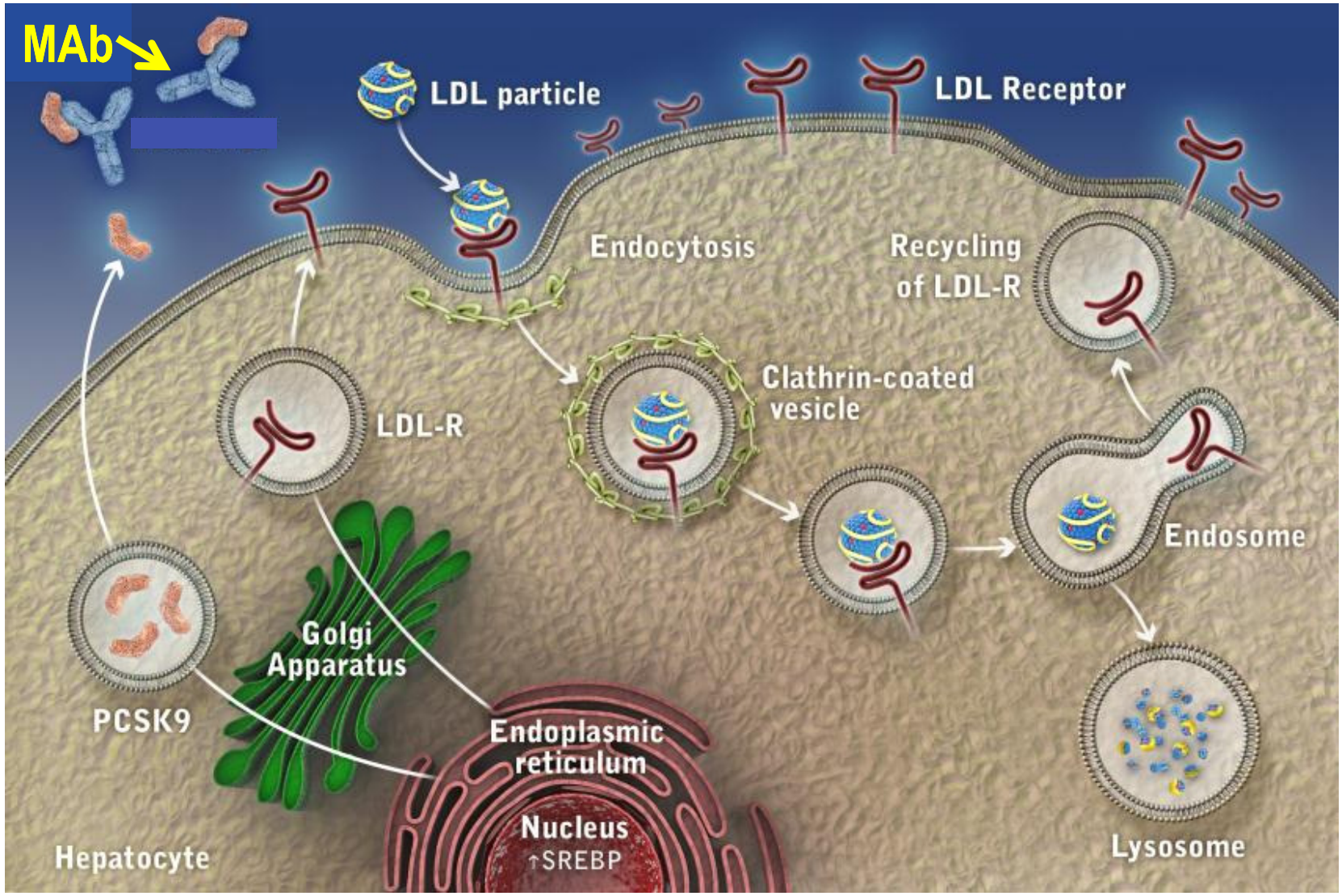
Do, et al. *Curr Cardiol Rep* 2013;15:345-56

LDL Receptor Function and Life Cycle *with PCSK9*



Do, et al: *Curr Cardiol Rep* 2013;15:345-56

Impact of PCSK9 inhibitor



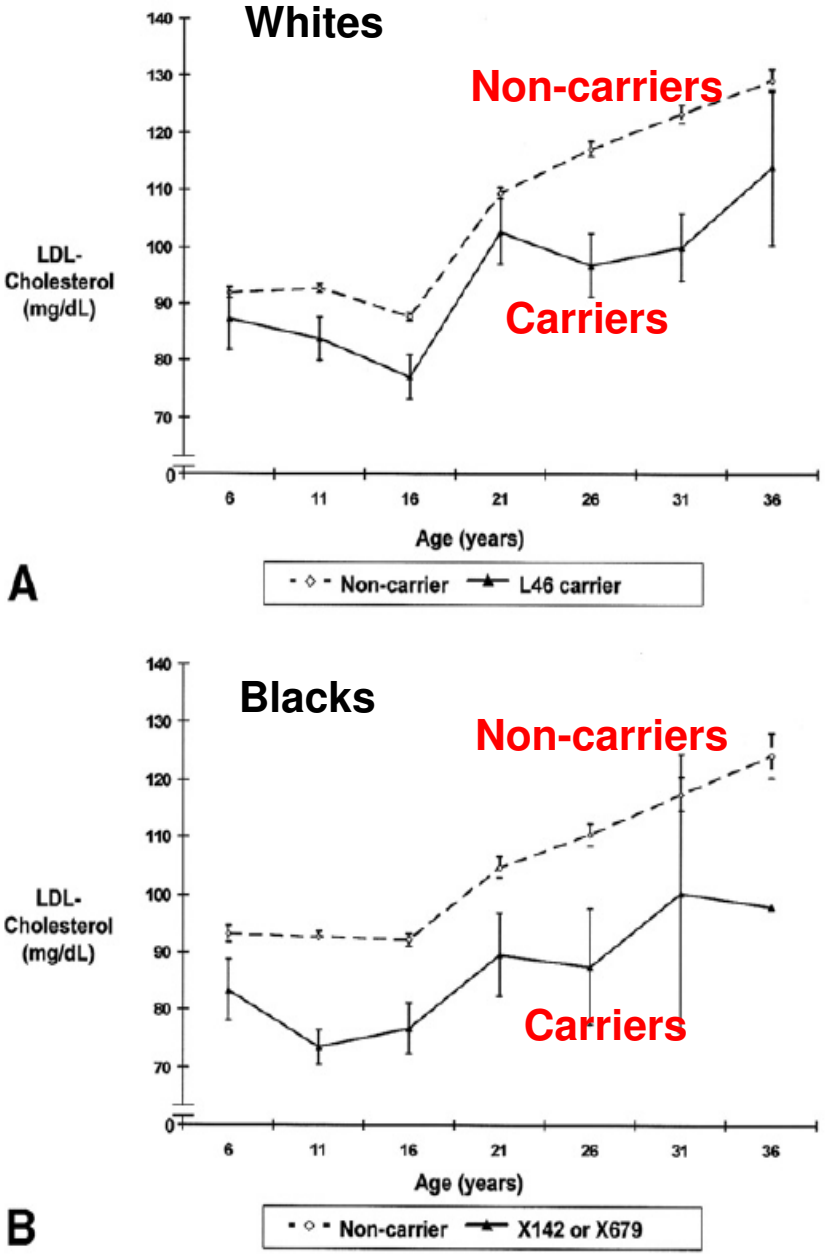
Do, et al. *Curr Cardiol Rep* 2013;15:345-56

Genetic validation of PCSK9 target

Loss of function PCSK9 mutations:

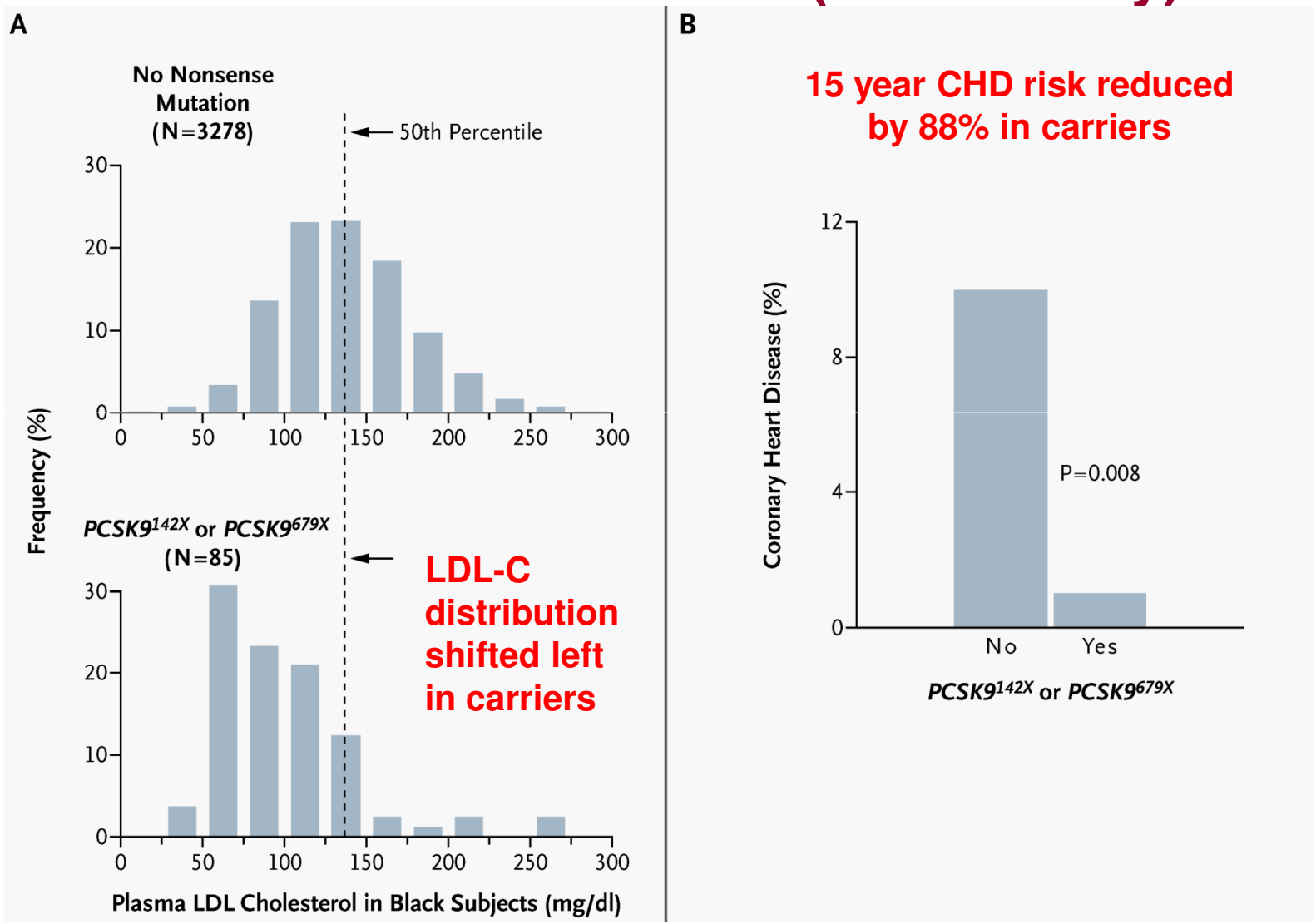
Lifelong reduced exposure to LDL-C

- Bogalusa Heart Study
- Followed from age ~9 to ~30 yrs of age
- Mutations had 1-2% prevalence and were associated with ~15%↓ LDL-C



Hallman et al. AJC 2007;100:69-72

PCSK9 loss of function mutation affects LDL-C and CHD risk in blacks (ARIC study)



Cohen et al. NEJM 2006;354:1264-72

Gain of function mutations in PCSK9

- A rare cause of familial hypercholesterolemia

PCSK9 therapeutics

Approaches to target (inhibit) PCSK9

- Monoclonal antibodies – Phase III-IV

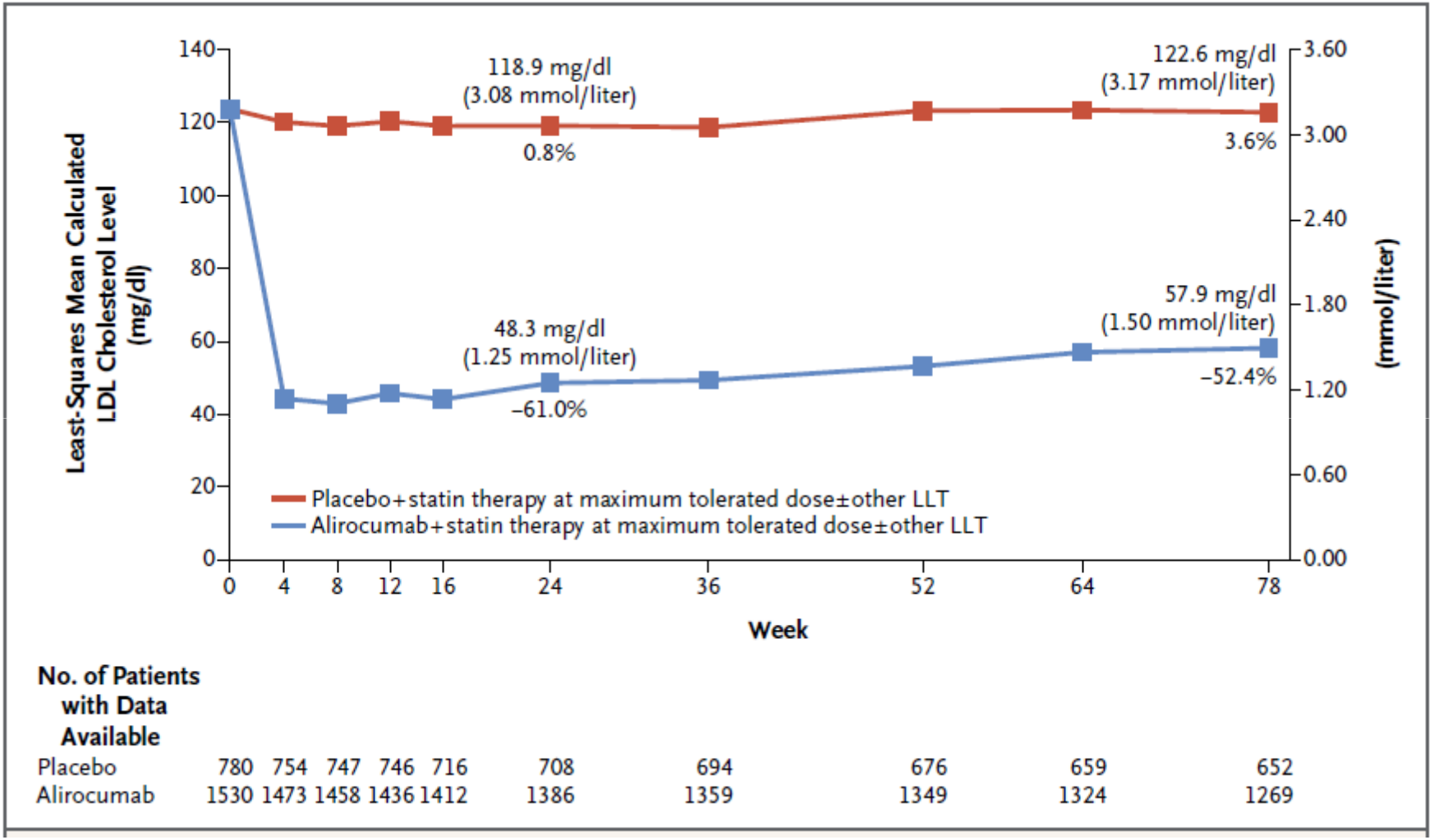
Name	Description	Developed by
Bocozicumab	Humanized	Pfizer
Evolocumab	Fully human	Amgen
Alirocumab	Fully human	Sanofi/Regeneron

- Small interfering RNA – Phase II (Medicines Company)
  - Potential administration every 3-6 months
- Other approaches -- Preclinical/Phase I
  - Adnectins
  - Small molecule inhibitors
  - PCSK9 vaccine

Potential clinical application of PCSK9 inhibitors

1. In patients who fail to reach LDL-C targets with statin
2. In patients who are statin intolerant
3. In patients with high Lp(a)
4. In patients with established coronary heart disease, to reduce CV risk on top of best statin treatment

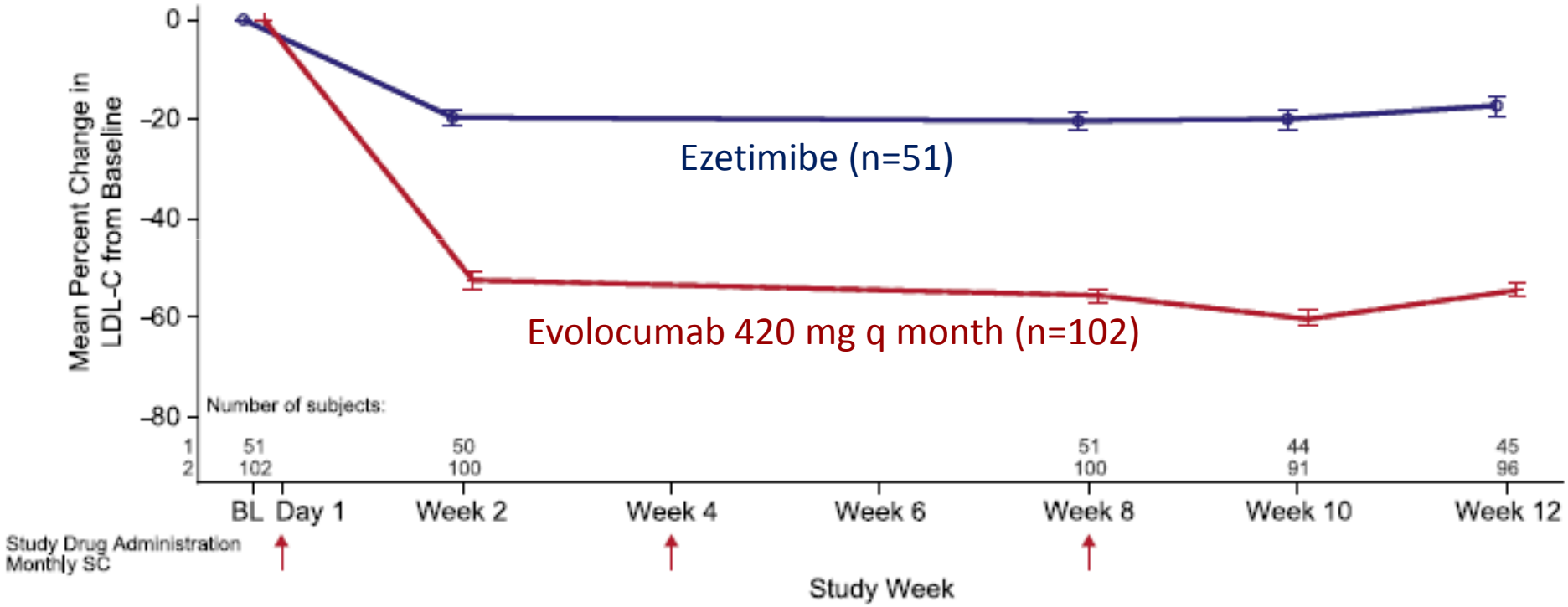
PCSK9 antibody in patients not at LDL-C goal on intensive statin



Robinson JG, et al., N Engl J Med 2015; 372:1489-1499

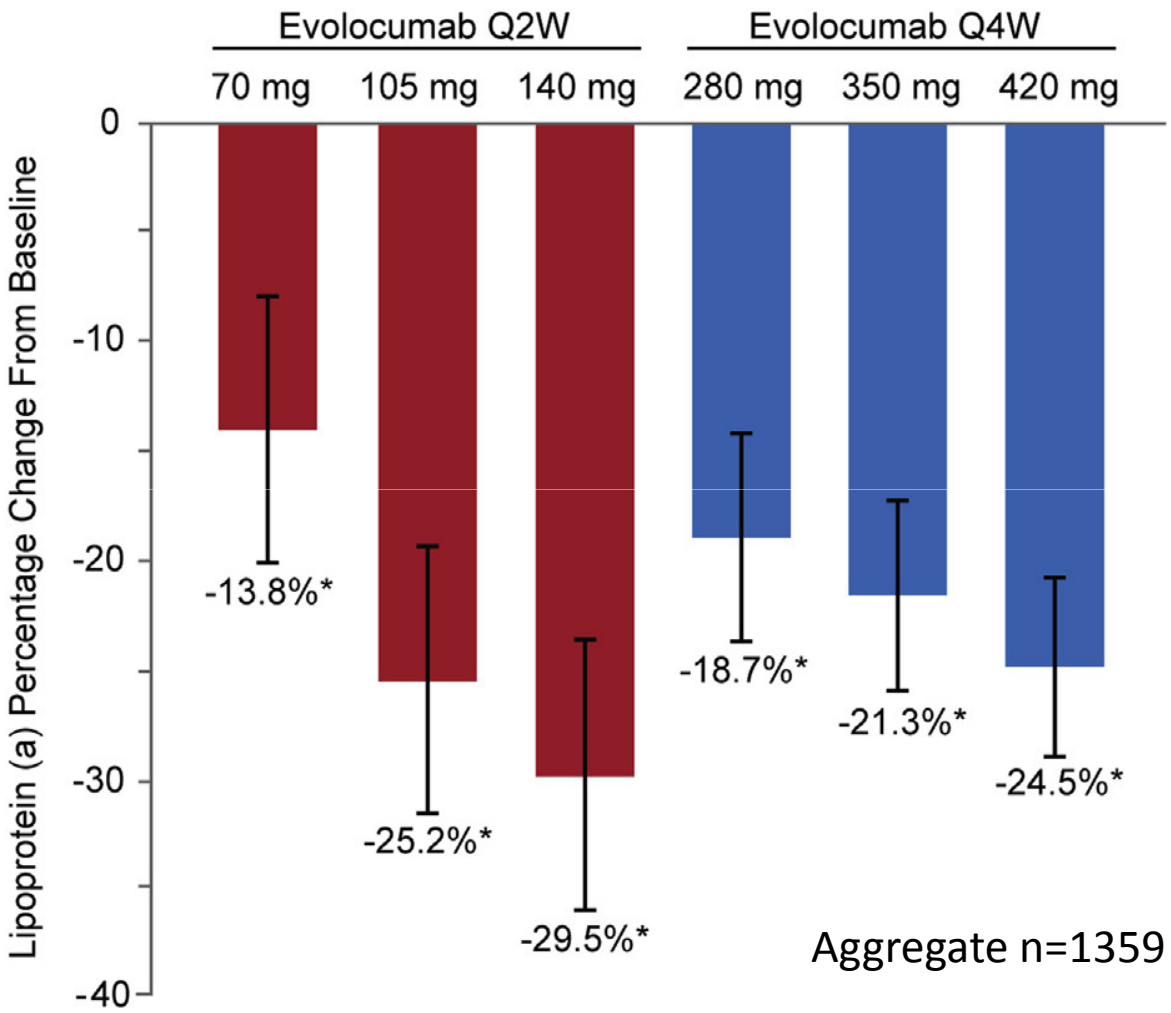
PCSK9 antibody in statin-intolerant patients

Mean baseline
LDL-C 195 mg/dL



Stroes E, et al., *J Am Coll Cardiol* 2014;63:2541-8

Effect of PCSK9 antibody on Lp(a)



Raal FJ, et al., *J Am Coll Cardiol* 2014;63:1278-88

CV outcomes trials with PCSK9 antibodies

FOURIER - Evolocumab	SPIRE I / II - Bococizumab		ODYSSEY OUTCOMES-Alirocumab
Population under study			
Secondary prevention: Established CV disease (MI, stroke, PAD)	Primary/secondary prevention: High CV risk		High risk secondary prevention: Recent ACS (within 4-52 weeks)
Lipid criteria at entry (mg/dL)			
LDL-C ≥ 1.8 or non-HDL-C ≥ 2.6 mmol/L	SPIRE I: 1.8 < LDL-C < 2.6 or 2.6< non-HDL-C < 3.4	SPIRE II: LDL-C ≥ 2.6 or non-HDL-C ≥ 3.4	LDL-C ≥ 1.8 or non-HDL-C ≥ 2.6
Statin dose regimen			
atorvastatin 20-80 mg (or equivalent statin); 69% high intensity treatment)	Not specified		Atorvastatin 40-80 mg, rosuvastatin 20-40 mg, or maximum tolerated 89% on intensive treatment
Sample size			
22,500	SPIRE I: 12,000	SPIRE 2: 6,300	18,000
Primary Endpoint			
CV death, MI, stroke, unstable angina, coronary revascularization	CV death, MI, stroke, or unstable angina needing urgent revascularization		CHD death, MI, stroke, unstable angina
Dosing regimen or doses			
140 mg Q2W or 420 mg QM	150 mg Q2W		75mg or 150mg Q2W

FOURIER

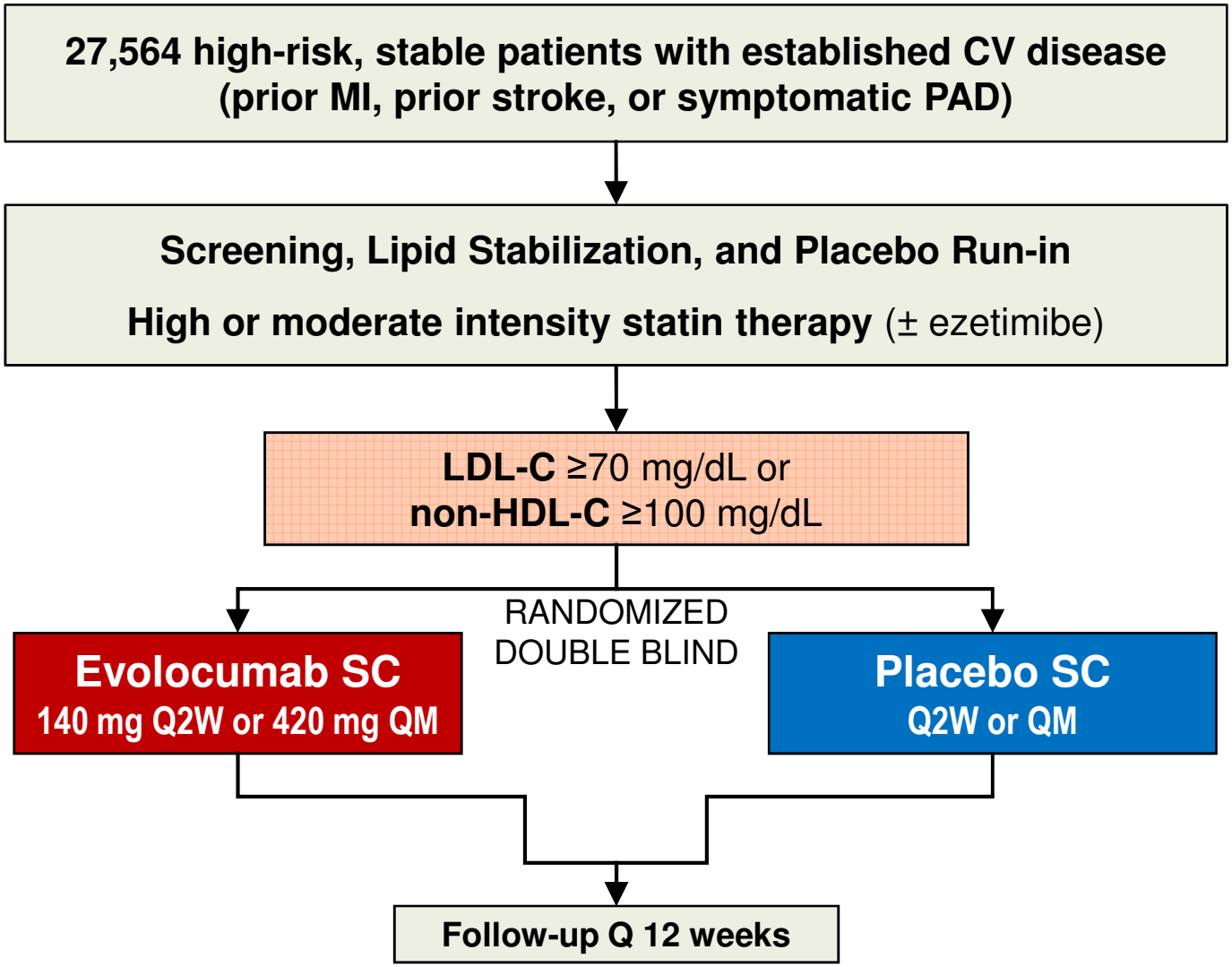
Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

MS Sabatine, RP Giugliano, AC Keech, N Honarpour,
SM Wasserman, PS Sever, and TR Pedersen,
for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 17, 2017

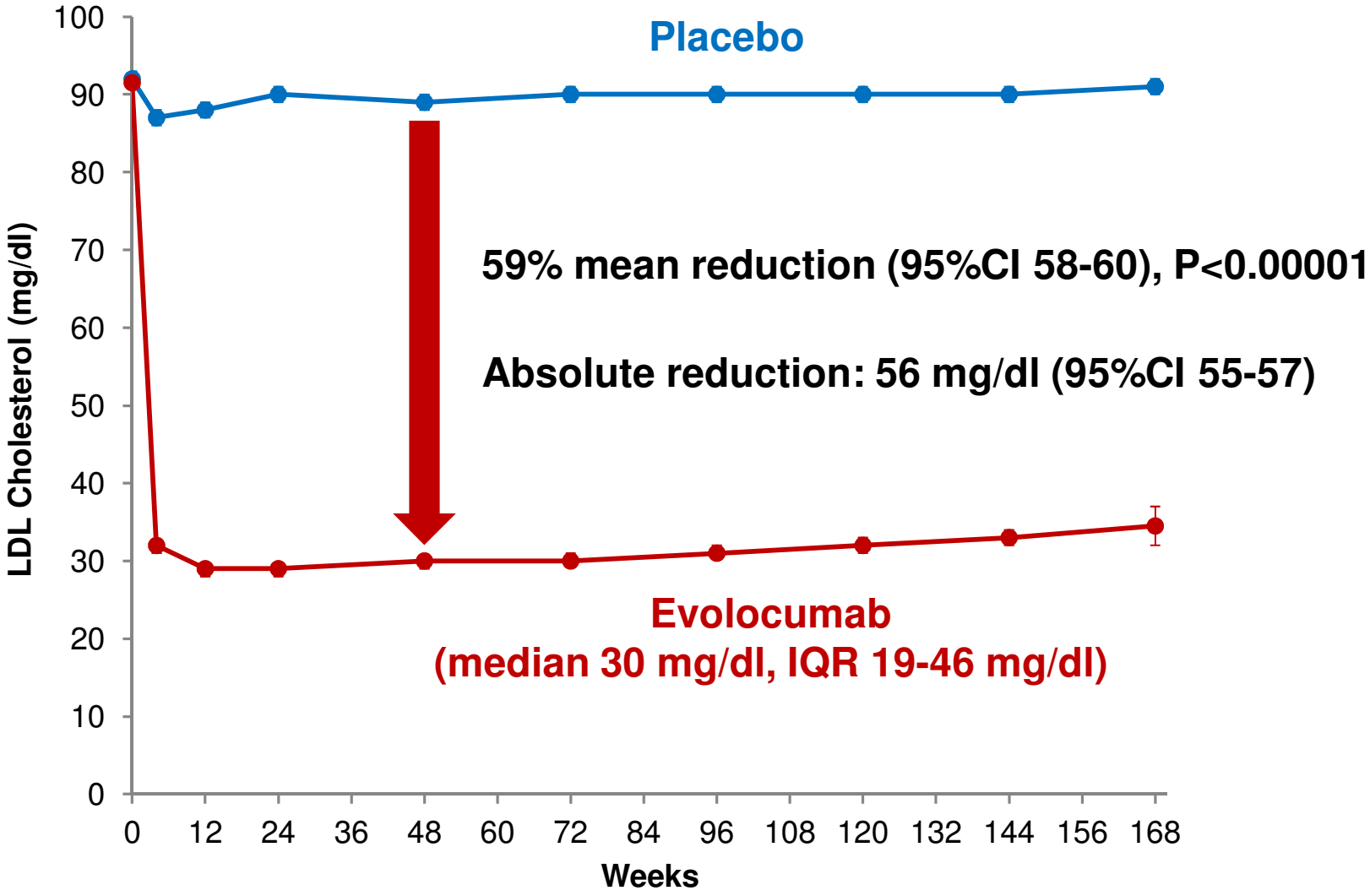
An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Trial Design

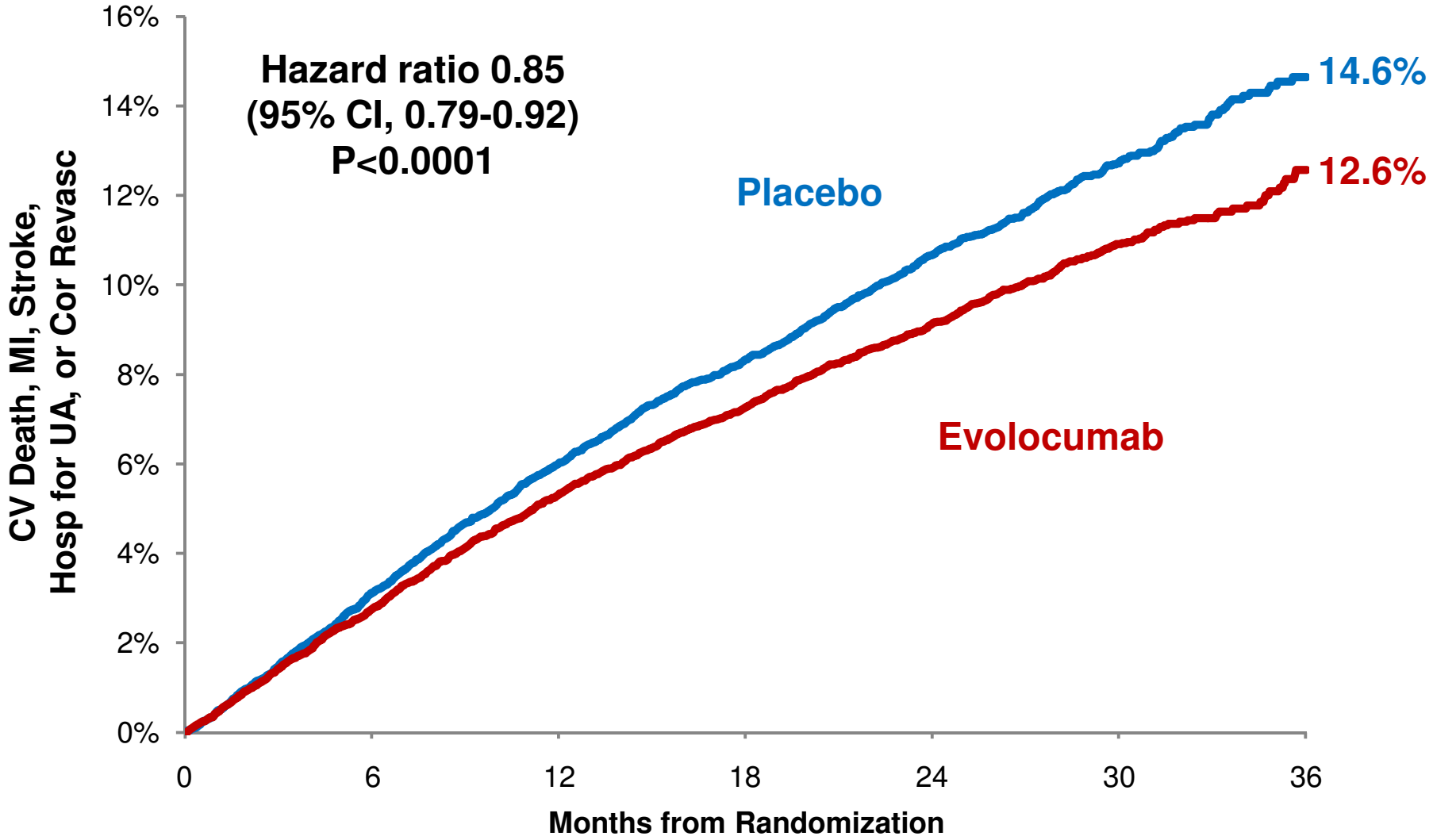


Sabatine MS et al. *Am Heart J* 2016;173:94-101

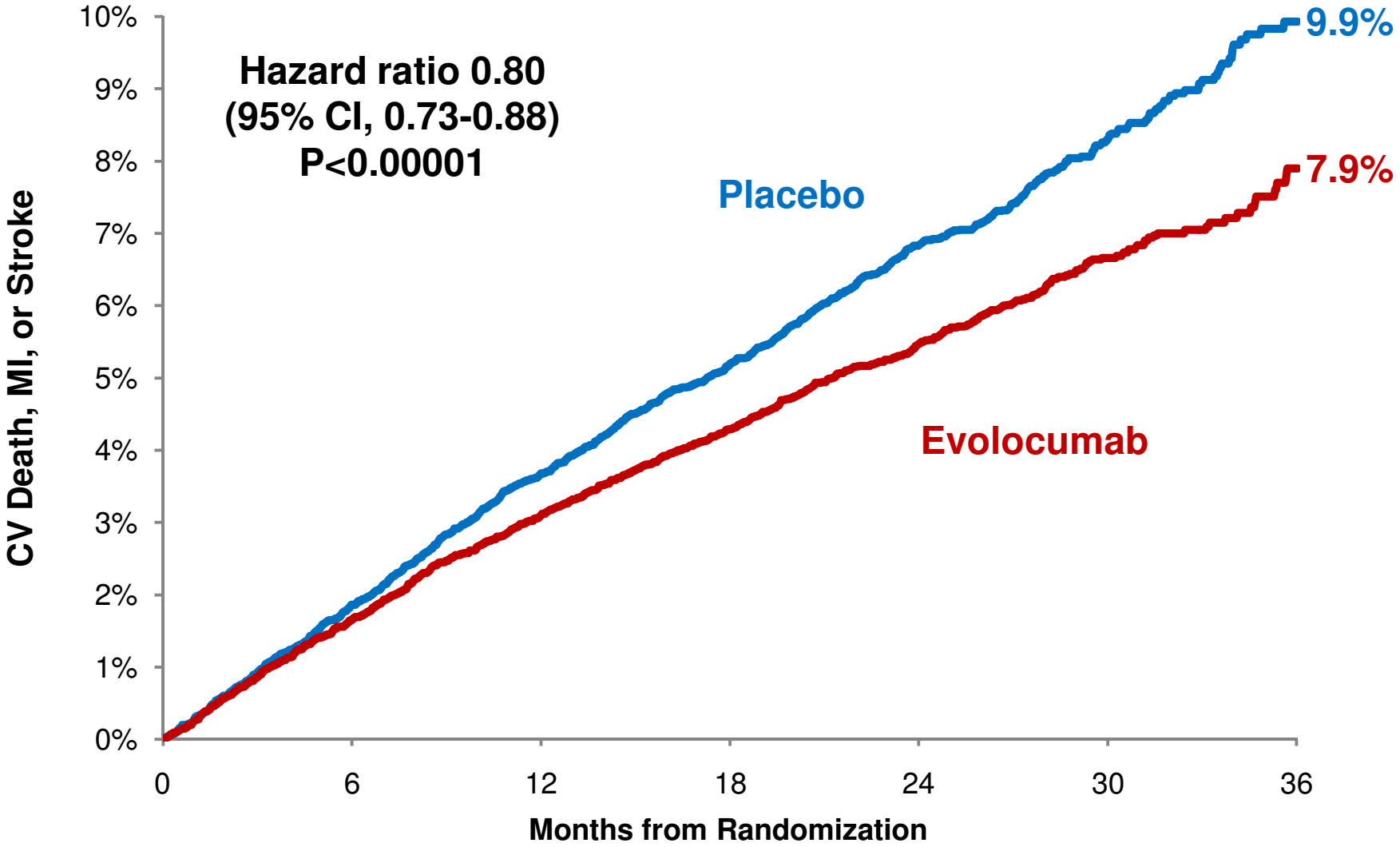
LDL Cholesterol



Primary Endpoint



Key Secondary Endpoint



Types of CV Outcomes

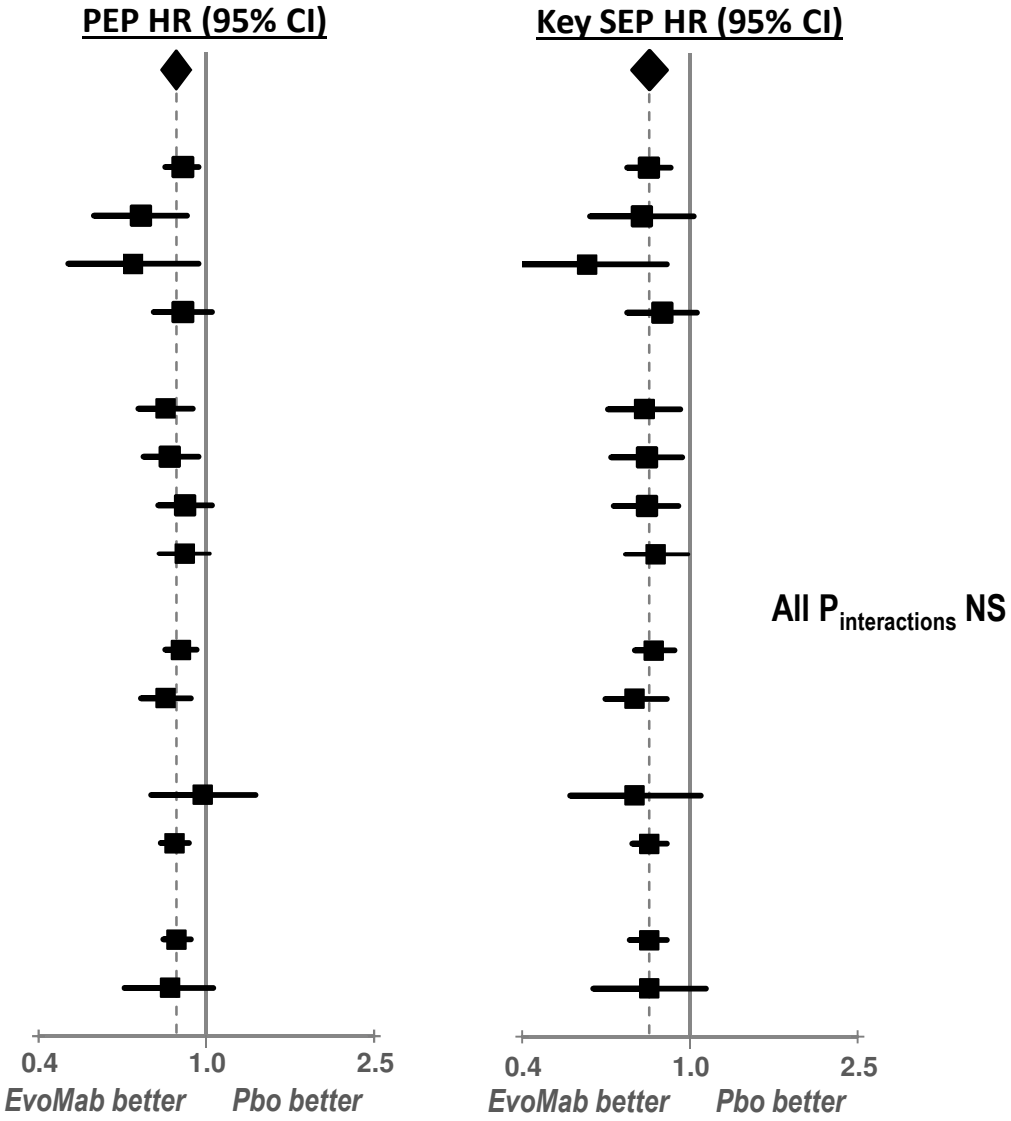
Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CV death, MI, or stroke	**7.9**	**9.9**	**0.80 (0.73-0.88)**
Cardiovascular death	**2.5**	**2.4**	**1.05 (0.88-1.25)**
Death due to acute MI	0.26	0.32	0.84 (0.49-1.42)
Death due to stroke	0.29	0.30	0.94 (0.58-1.54)
Other CV death	1.9	1.8	1.10 (0.90-1.35)
MI	**4.4**	**6.3**	**0.73 (0.65-0.82)**
Stroke	**2.2**	**2.6**	**0.79 (0.66-0.95)**

Types of CV Outcomes

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CVD, MI, stroke, UA, or revasc	**12.6**	**14.6**	**0.85 (0.79-0.92)**
CV death, MI, or stroke	**7.9**	**9.9**	**0.80 (0.73-0.88)**
Cardiovascular death	**2.5**	**2.4**	**1.05 (0.88-1.25)**
MI	**4.4**	**6.3**	**0.73 (0.65-0.82)**
Stroke	**2.2**	**2.6**	**0.79 (0.66-0.95)**
Hosp for unstable angina	**2.2**	**2.3**	**0.99 (0.82-1.18)**
Coronary revasc	**7.0**	**9.2**	**0.78 (0.71-0.86)**
Urgent	3.7	5.4	0.73 (0.64-0.83)
Elective	3.9	4.6	0.83 (0.73-0.95)
Death from any cause	**4.8**	**4.3**	**1.04 (0.91-1.19)**

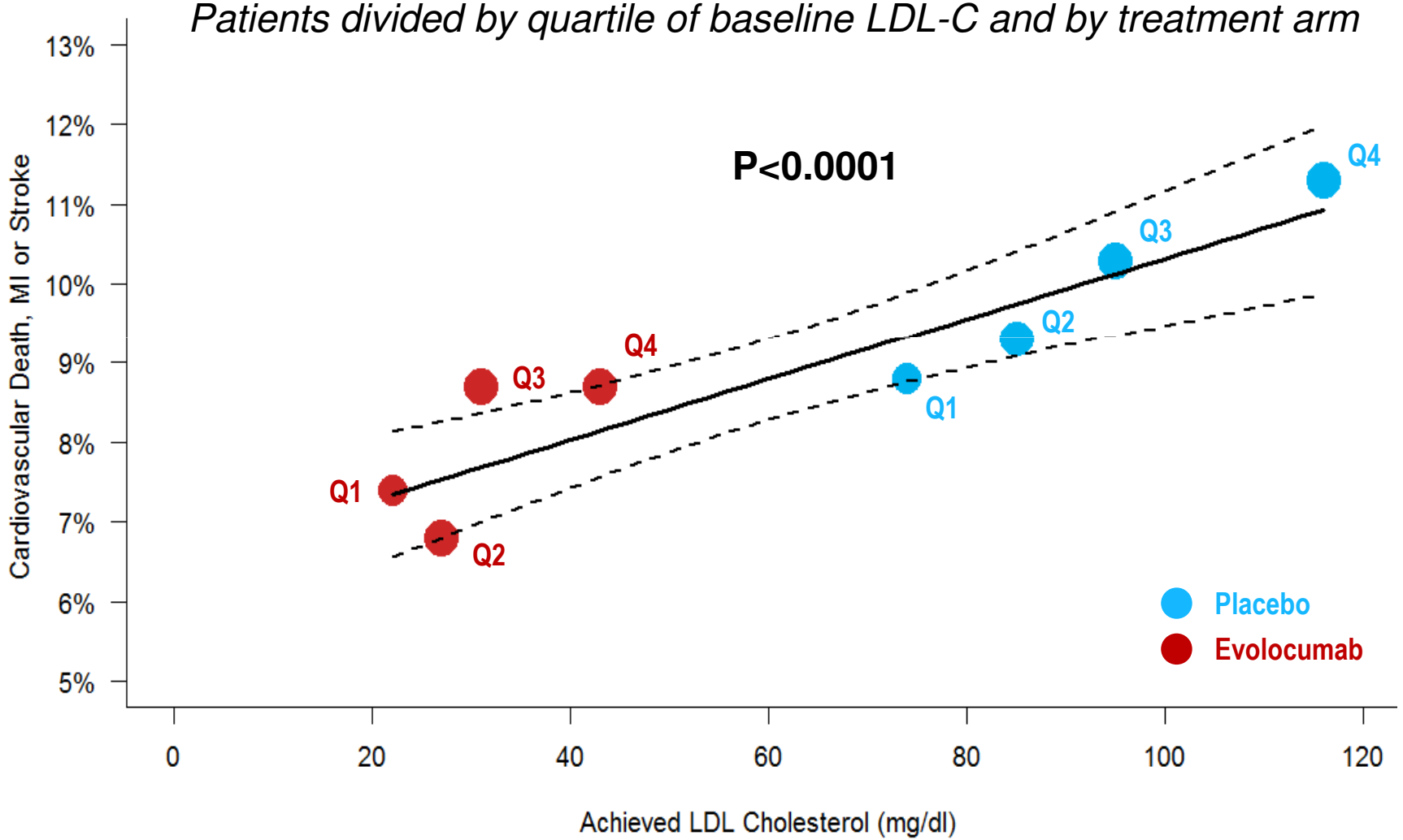
Key Subgroups

Subgroup	Patients
Overall	*27564*
Type of disease	
MI alone	19113
Stroke alone	3366
PAD alone	1505
Polyvascular disease	3563
Baseline LDL-C	
Q1 (<80 mg/dl)	6961
Q2 (80-<92 mg/dl)	6886
Q3 (92-109 mg/dl)	6887
Q4 (>109 mg/dl)	6829
Baseline statin intensity	
High	19103
Not high	8461
Ezetimibe	
Yes	1440
No	26124
Initial Dosing Regimen	
Every 2 weeks	24774
Monthly	2790

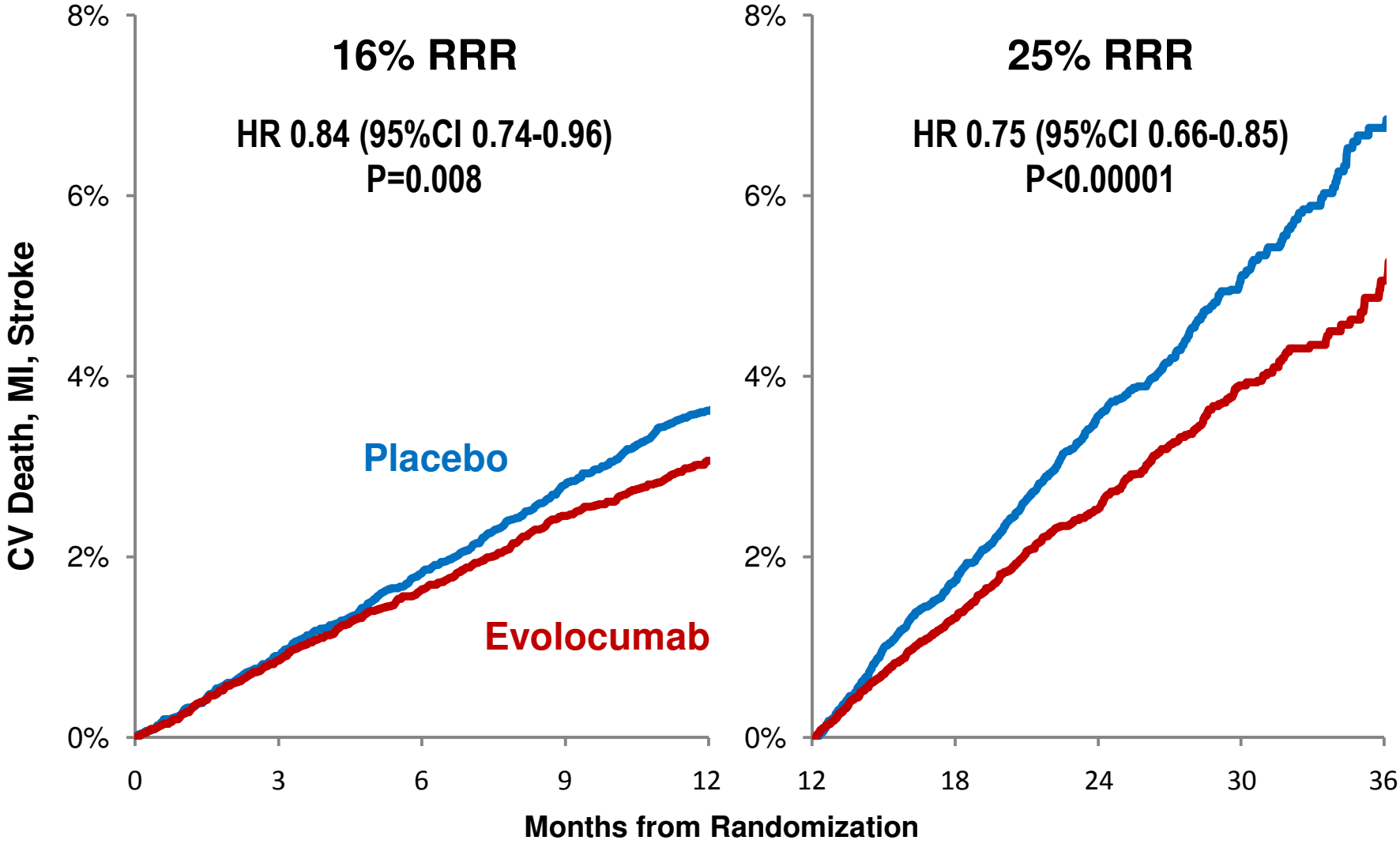


Lower LDL-C Is Better

Patients divided by quartile of baseline LDL-C and by treatment arm



Landmark Analysis



Summary for Evolocumab

- **↓ LDL-C by 59%**
  - Consistent throughout duration of trial
  - Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)
- **↓ CV outcomes in patients already on statin therapy**
  - 15% ↓ broad primary endpoint; 20% ↓ CV death, MI, or stroke
  - Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  - 25% reduction in CV death, MI, or stroke after 1st year
  - Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C
- **Safe and well-tolerated**
  - Similar rates of AEs, incl DM & neurocog events w/ EvoMab & pbo
  - Rates of EvoMab discontinuation low and no greater than pbo
  - No neutralizing antibodies developed

Conclusions

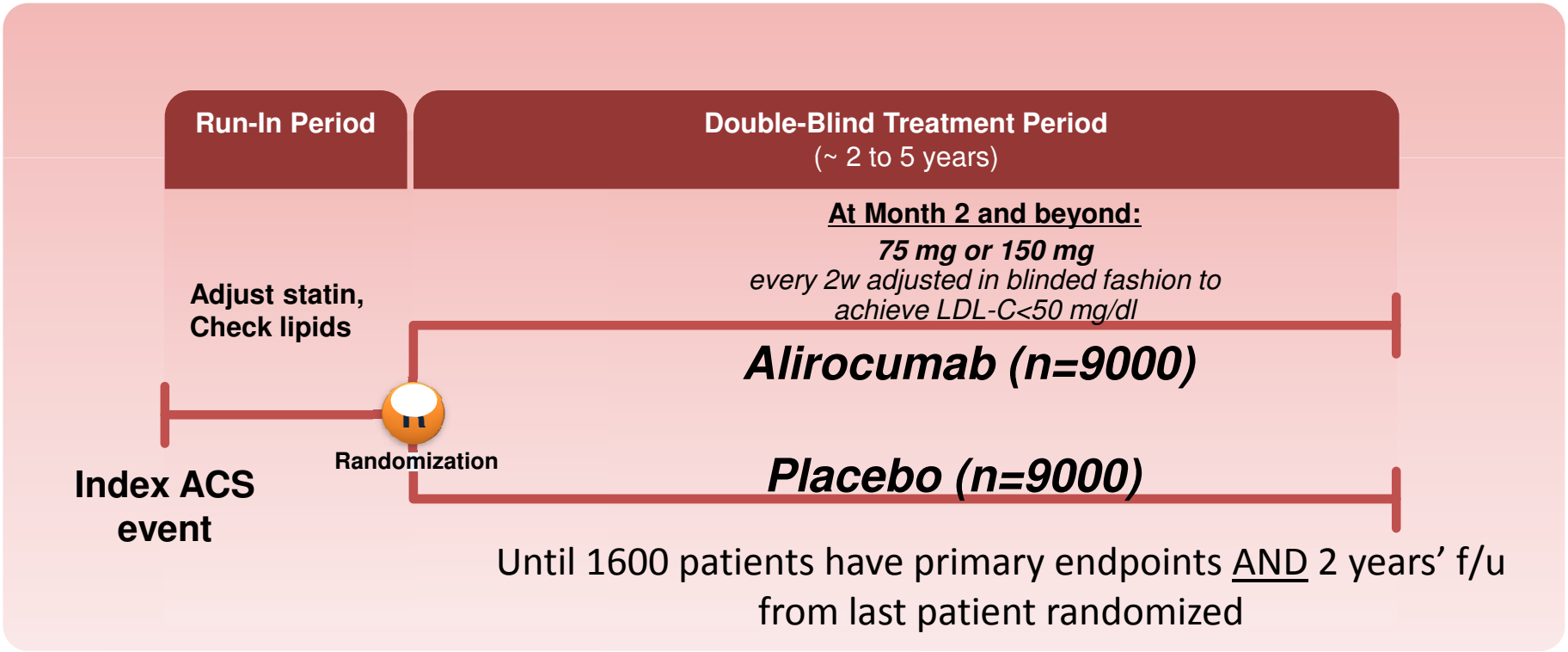
In patients with known cardiovascular disease:

1. **PCSK9 inhibition with evolocumab significantly & safely ↓ major cardiovascular events when added to statin therapy**

2. **Benefit was achieved with lowering LDL cholesterol well below current targets**

Alirocumab
ODYSSEY-Outcomes Study Design

- **Patient population:**
  - **Recent ACS** (1-12 mo before randomization)
  - **Lipids not optimally controlled on optimal statin:** LDL-C ≥70 mg/dL, non-HDL-C ≥100 mg/dL, or apo B ≥80
- **Primary endpoint:**
  - **CHD death**
  - **Non-fatal MI**
  - **Ischemic stroke**
  - **Unstable angina requiring hospitalization**



Schwartz GG et al., *Am Heart J* 2014; 168:682-689

Japan: indication for alirocumab July 2016

Praluent is indicated for the treatment of patients with FH or hypercholesterolemia who have high cardiovascular risk with LDL cholesterol not adequately controlled by HMG-CoA reductase inhibitors.

Precautions:

(1) Patients should undergo careful medical examinations, including tests confirming FH or non-FH before using Praluent.

(2) In patients with non-FH, the use of Praluent should be considered for patients with high cardiovascular risk based on confirmed risk factors (e.g., coronary artery disease, non-cardiogenic cerebral infarction, peripheral arterial disease, diabetes mellitus, chronic kidney disease, etc.)

Health Canada indication for evolocumab: Sept 2015

Evolocumab is indicated as an adjunct to diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C.

The effect of evolocumab on cardiovascular morbidity and mortality has not been determined.

Brasil: indicação para alirocumab Agosto 2016

Alirocumab está indicado para:

- adultos com hipercolesterolemia primária (familiar heterozigótica e não familiar) ou dislipidemia mista, como adjuvante à dieta

- pacientes incapazes de atingir os níveis alvos predefinidos da lipoproteína de baixa densidade (LDL-C) com o máximo de dose de estatina tolerada, em combinação à estatina ou à estatina associada a outras terapias hipolipemiantes

- pacientes intolerantes a estatina, seja como monoterapia ou em associação a outra terapia hipolipemiante

Fonte: ANVISA

Brasil: indicação para evolocumabe Abril 2016

Evolocumabe está indicado para adultos com hipercolesterolemia primária ou dislipidemia mista, como adjuvante à dieta:

- em combinação à estatina ou à estatina mais outras terapias hipolipemiantes em pacientes incapazes de atingir os níveis da lipoproteína de baixa densidade (LDL-C) com o máximo de dose de estatina tolerada

- isoladamente ou em combinação a outras terapias hipolipemiantes em pacientes que são intolerantes à estatina ou para aqueles cujo tratamento com estatina é contra-indicado

Fonte: ANVISA

"Humanity's greatest advances are not in its discoveries – but in how those discoveries are applied…"