From PCSK9 inhibition to the reduction of major cardiovascular events: what do trials teach us?

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EUROPEAN SOCIETY OF CARDIOLOGY®

Acute Cardiovascular Care Association
A Registered Branch of the ESC

Disclosure

Speaker fee: Astra Zeneca, BMS, Daichii Sankio, Bayer, Pfizer, Sanofi

Advisory board member: Bayer, BMS, Pfizer, Sanofi

Residual Risk After Acute Coronary Syndrome

- Remains high despite evidence-based preventive therapies
- Is related, in part, to levels of low-density lipoprotein cholesterol (LDL-C)
- Is reduced when LDL-C is lowered by
  - Statin therapy, compared with placebo[1]
  - High-intensity, compared with moderate-intensity statin therapy[2]
  - Ezetimibe, compared with placebo, added to statin[3]

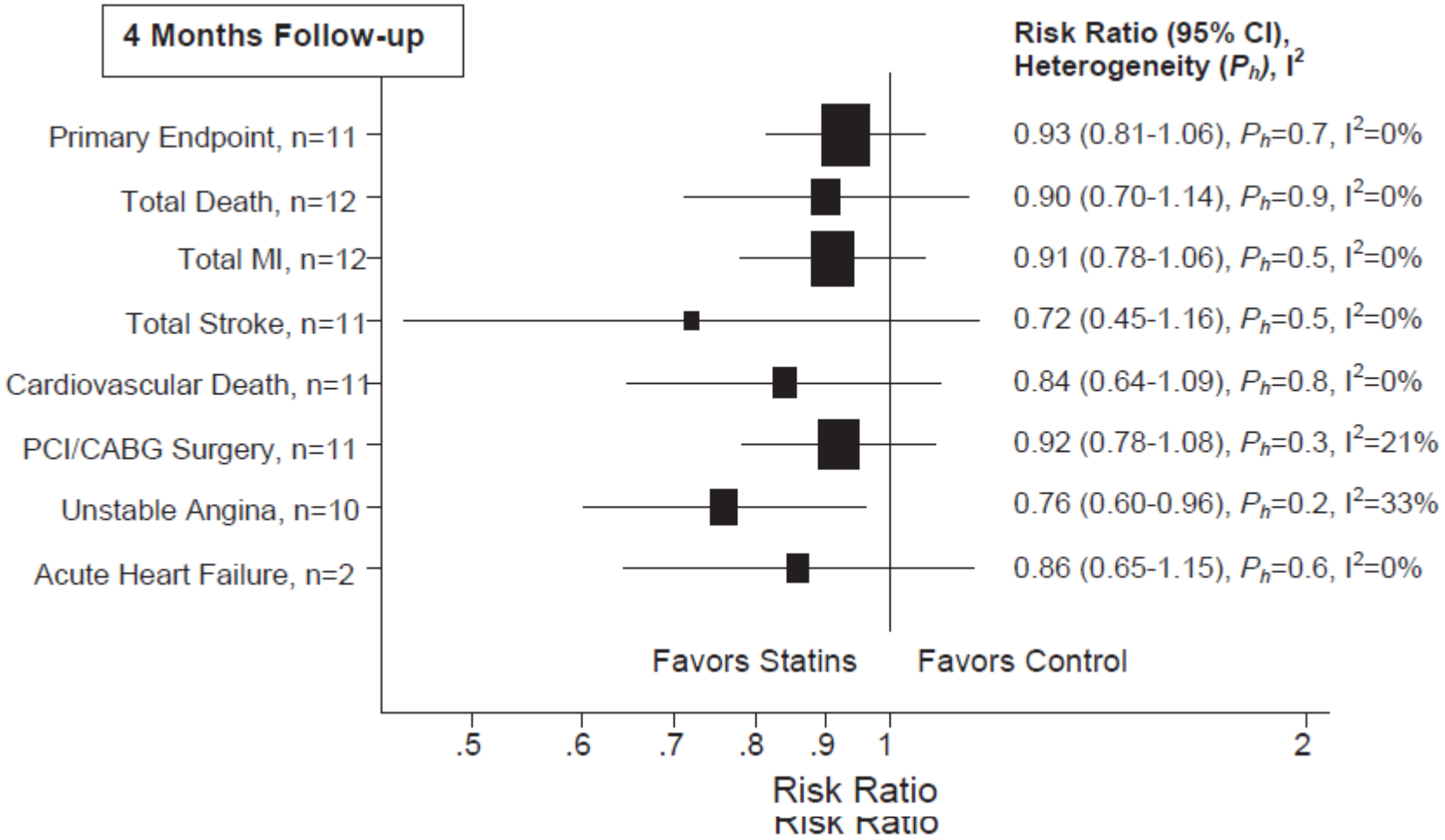
1. Schwartz GG, et al. JAMA 2001;285:1711-8. 2. Cannon CP, et al. NEJM 2004;350:1495-504.
3. Cannon CP, et al. NEJM 2015;372:2387-97.

Time

Intensity

Two main factors

Updated evidence on early statin therapy for ACS: a new meta-analysis



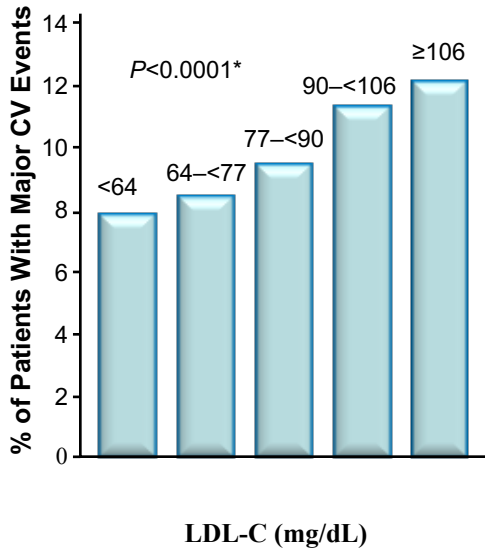
18 RCTs, 14303 pts

Briel M et al. Int J Cardiol 2011

The lower the LDL-C achieved, the lower the risk of CV events

TNT[1,a]

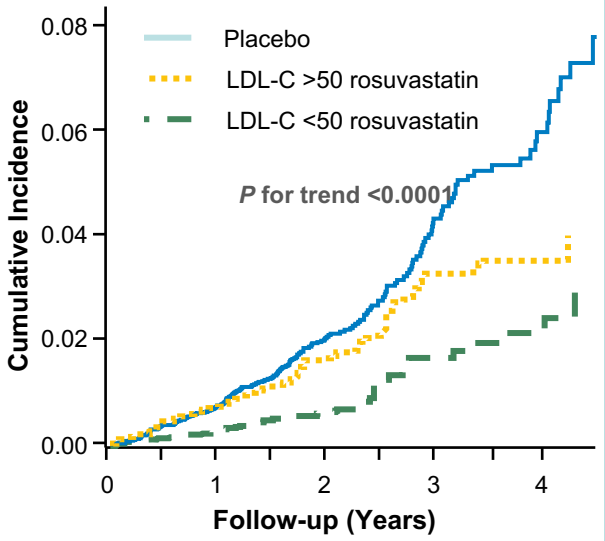
Rate of major CV events



*P value for trend across LDL-C

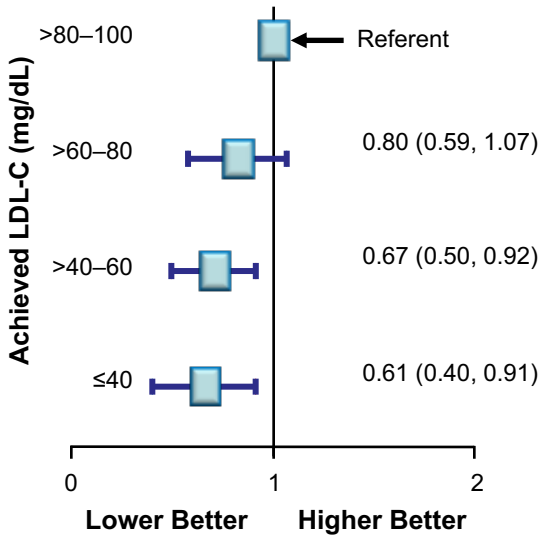
JUPITER[2,b]

Time to occurrence of major CV events



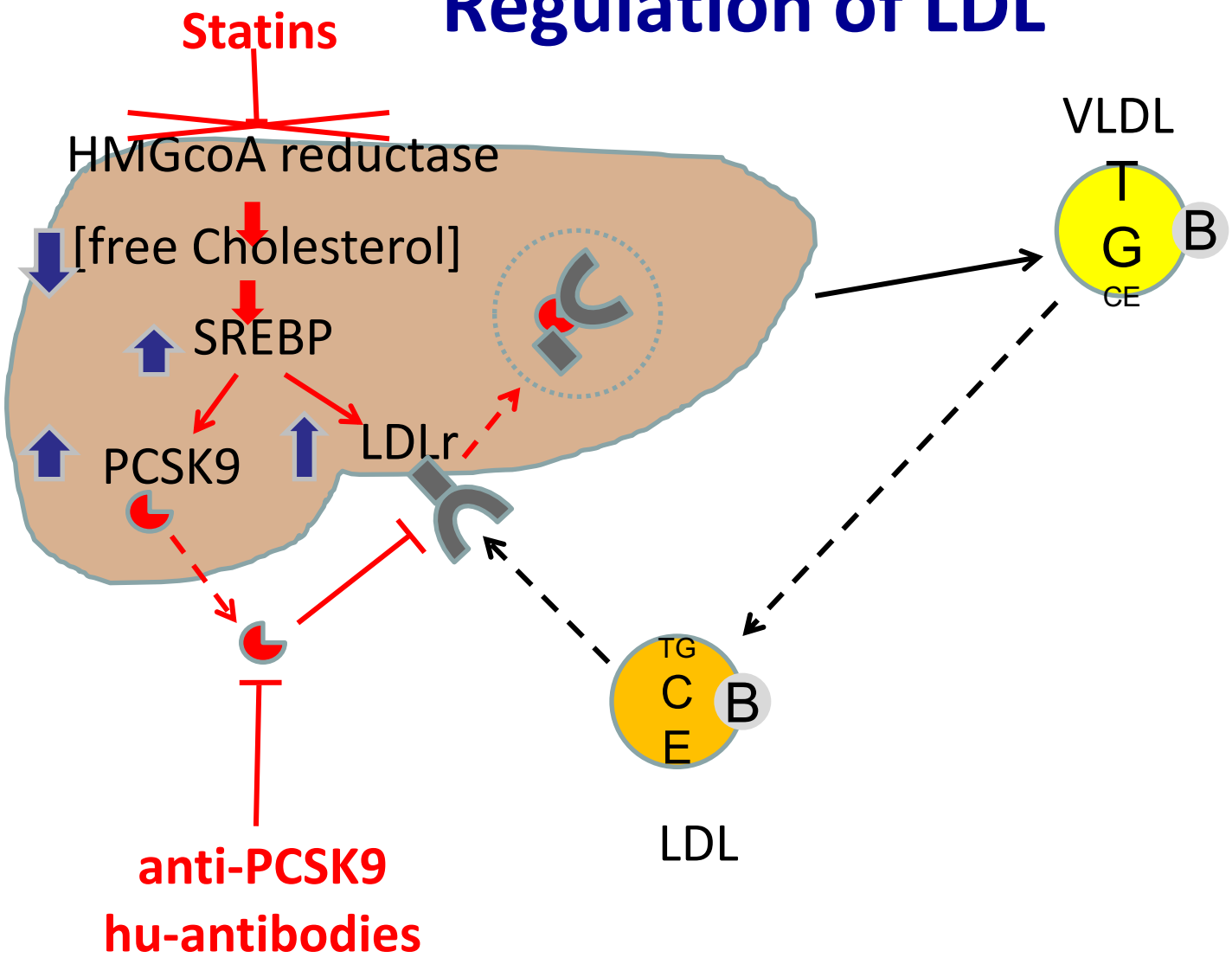
PROVE-IT[3,c]

Hazard ratio of primary endpoint



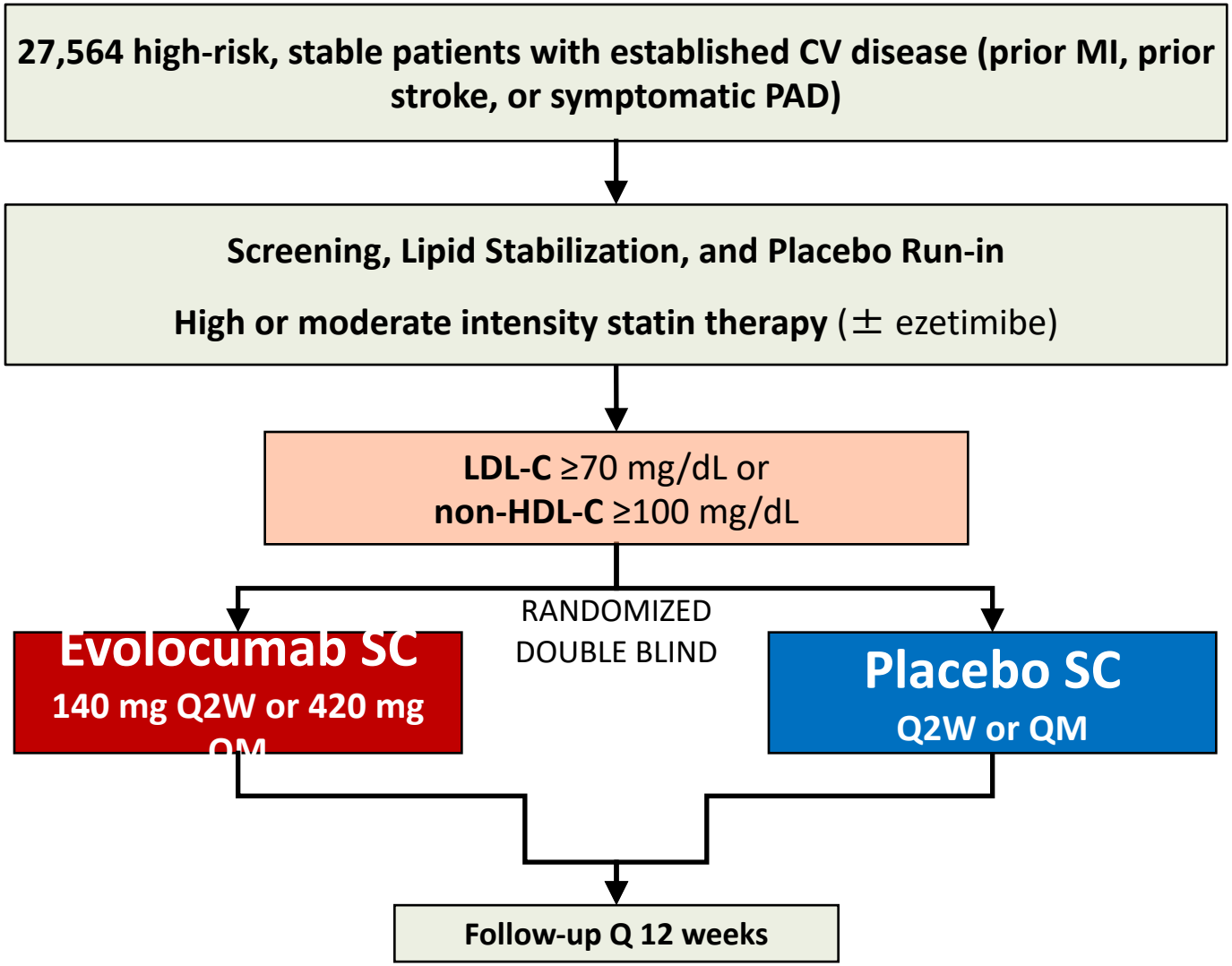
1. LaRosa JC, et al. J Am Coll Cardiol 2007;100:747–52.
2. Hsia J, et al. J Am Coll Cardiol 2011;57:1666–75.
3. Wiviott SD, et al. J Am Coll Cardiol 2005;46:1411–6.

Regulation of LDL



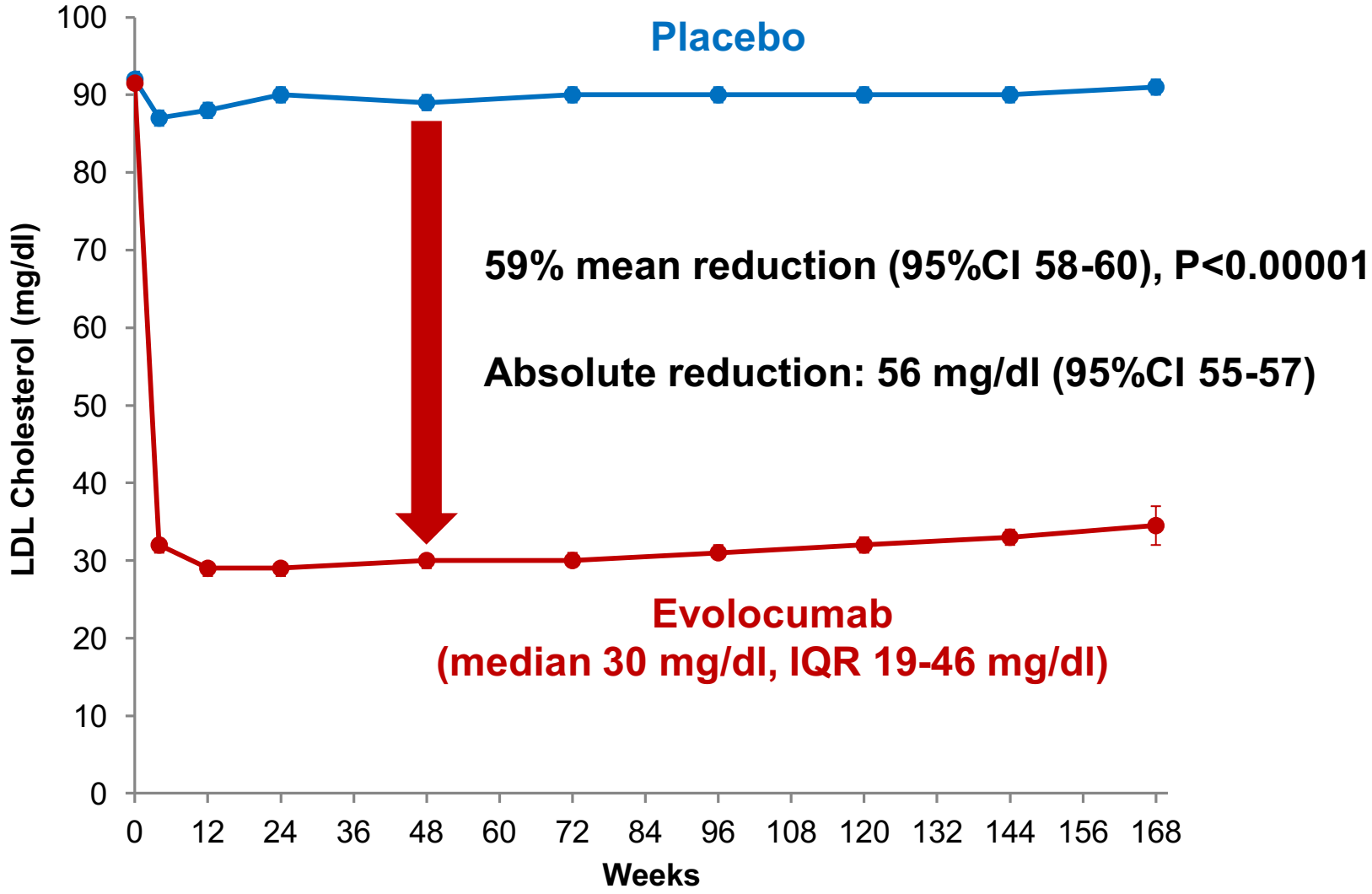
Horton JD *J Lipid Res* 2009;50:S172

Trial Design



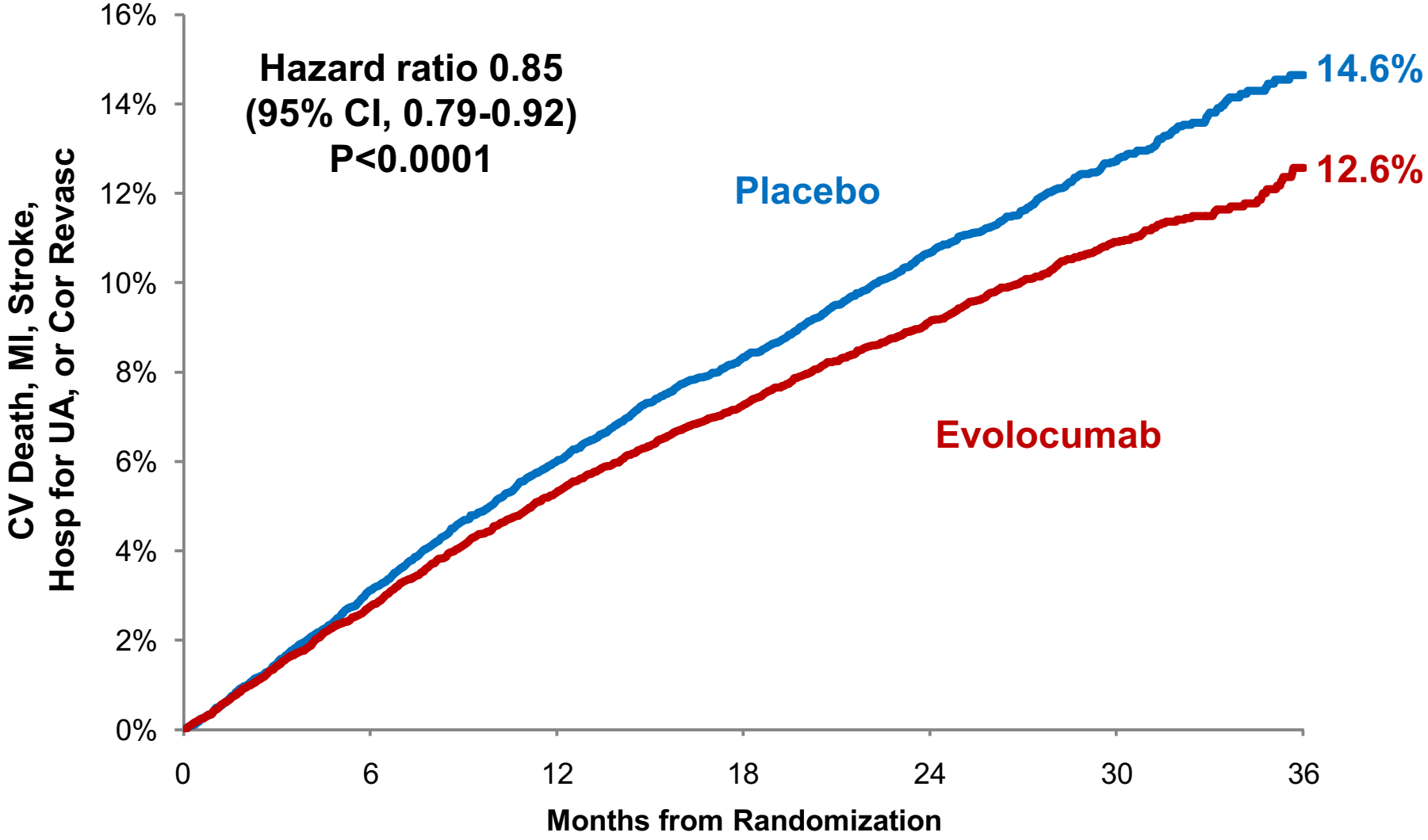
Sabatine MS et al. *Am Heart J* 2016;173:94-101

LDL Cholesterol



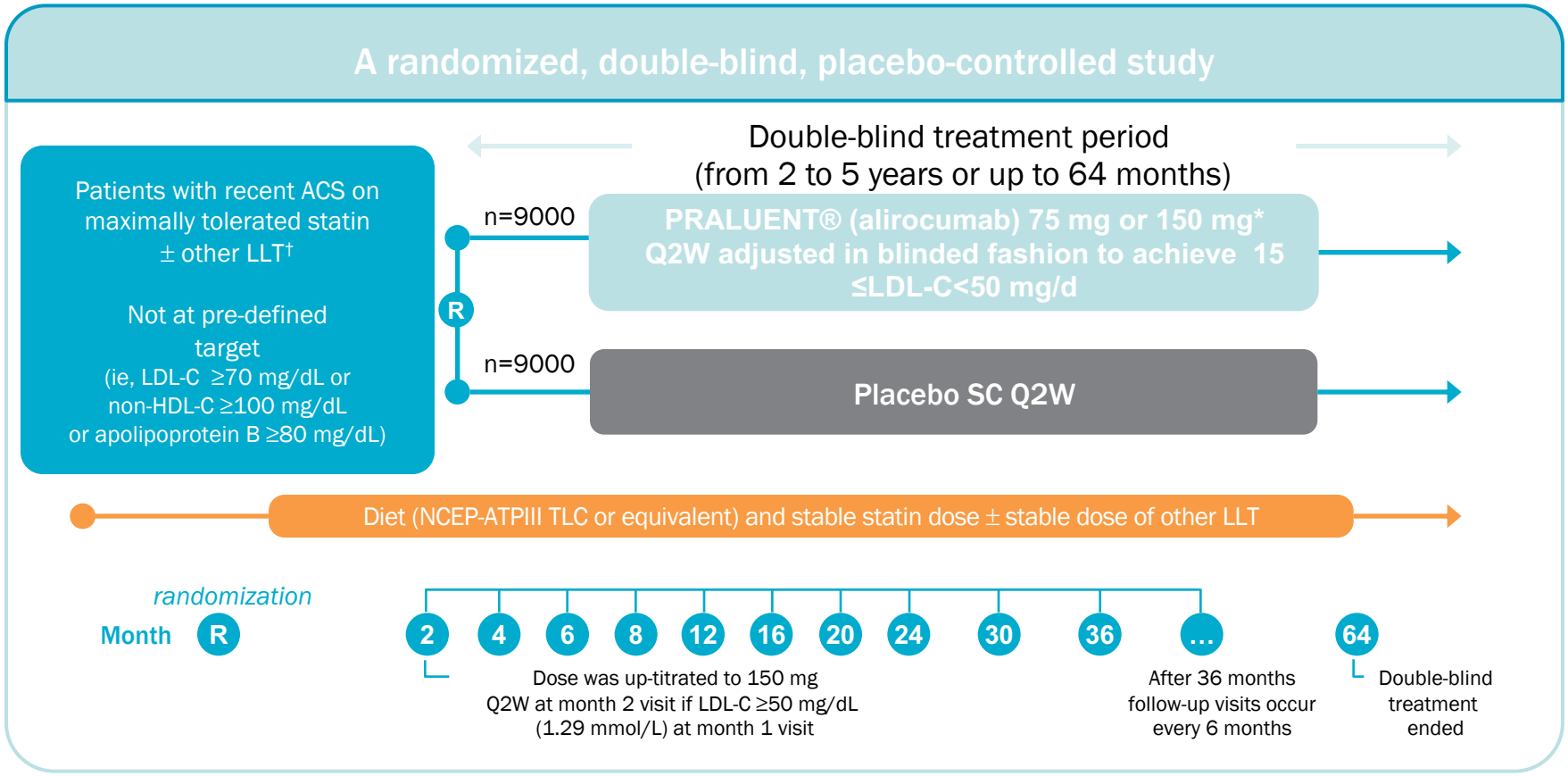
Sabatine MS et al. *NEJM 2017*

Primary Endpoint



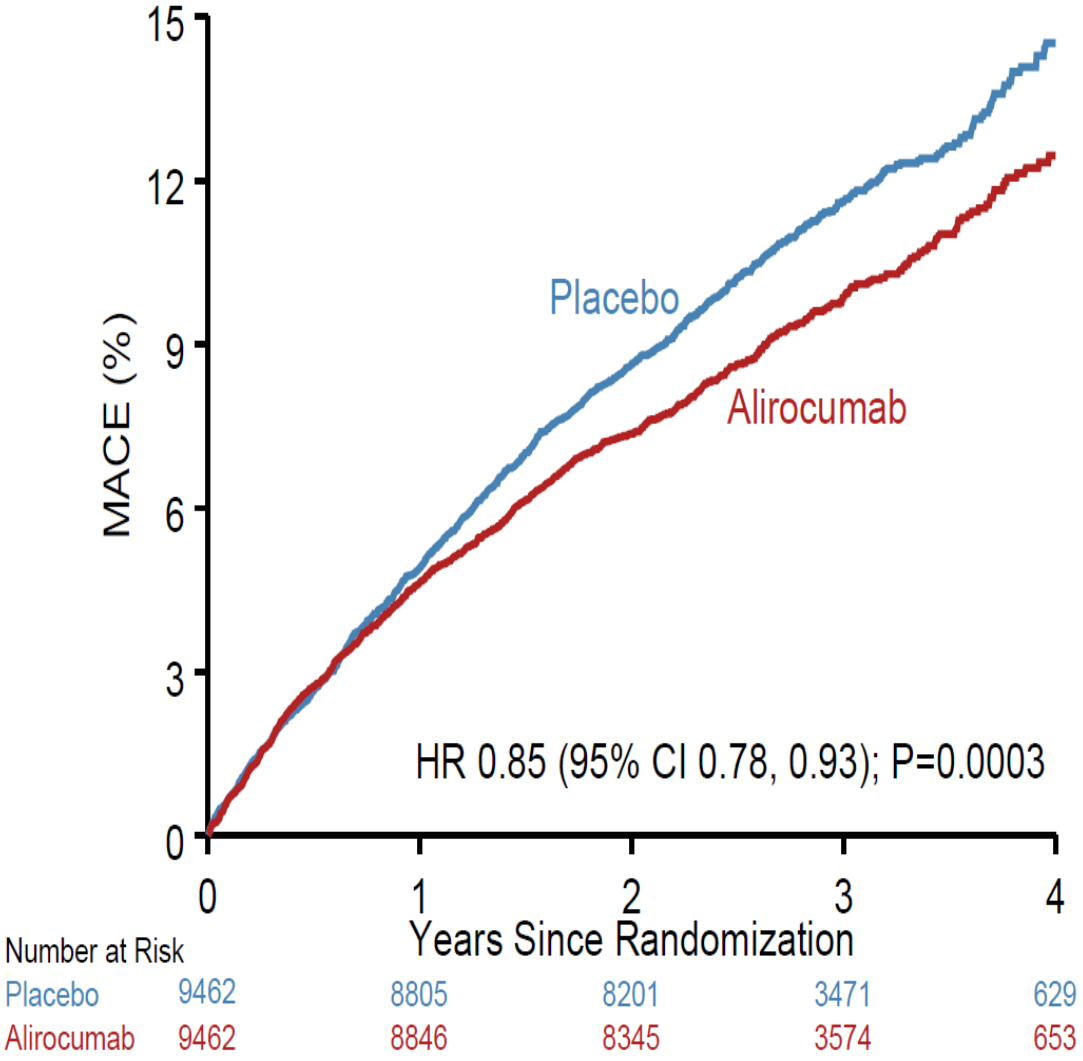
Sabatine MS et al. *NEJM 2017*

ODYSSEY OUTCOMES – Study Design



Schwartz GG, et al. *Am Heart J*. 2014;168:682-689.e1.

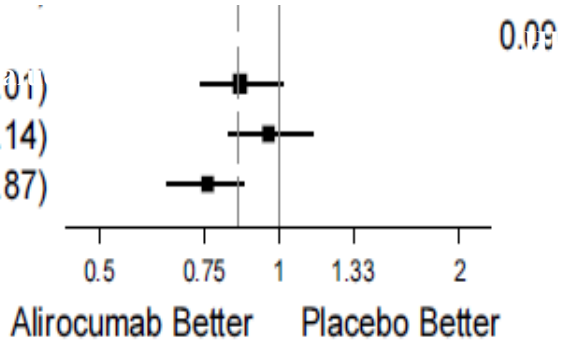
Primary Efficacy Endpoint: Coronary artery disease death, non-fatal MI, fatal &non fatal stroke, hospitalization for UA

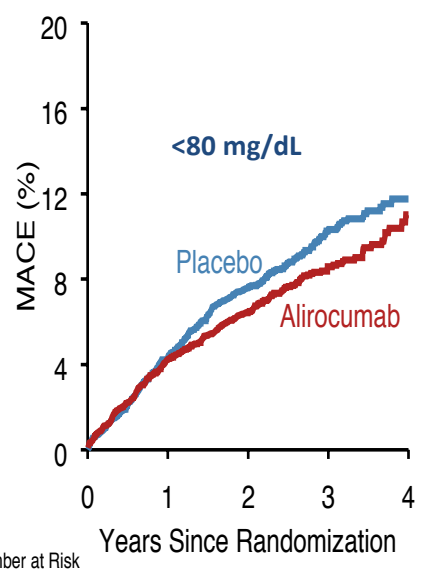


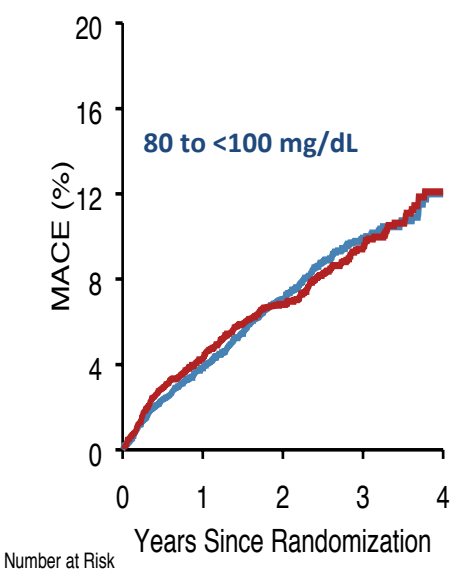
Steg P, ACC 2018

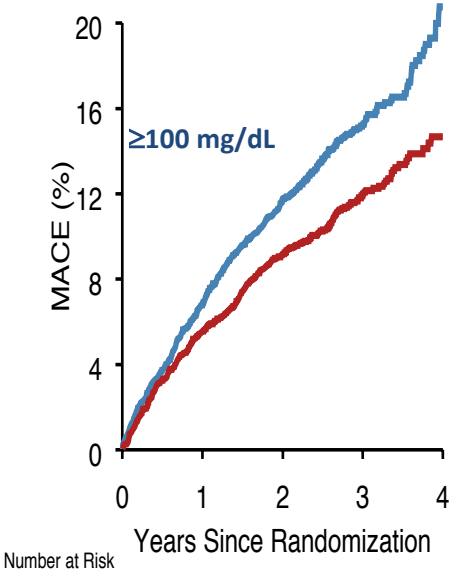
Primary Efficacy in Main Prespecified Subgroups

LDL (mg/dL)				
<80	7164	8.3	9.5	0.86 (0.74, 1.01)
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)





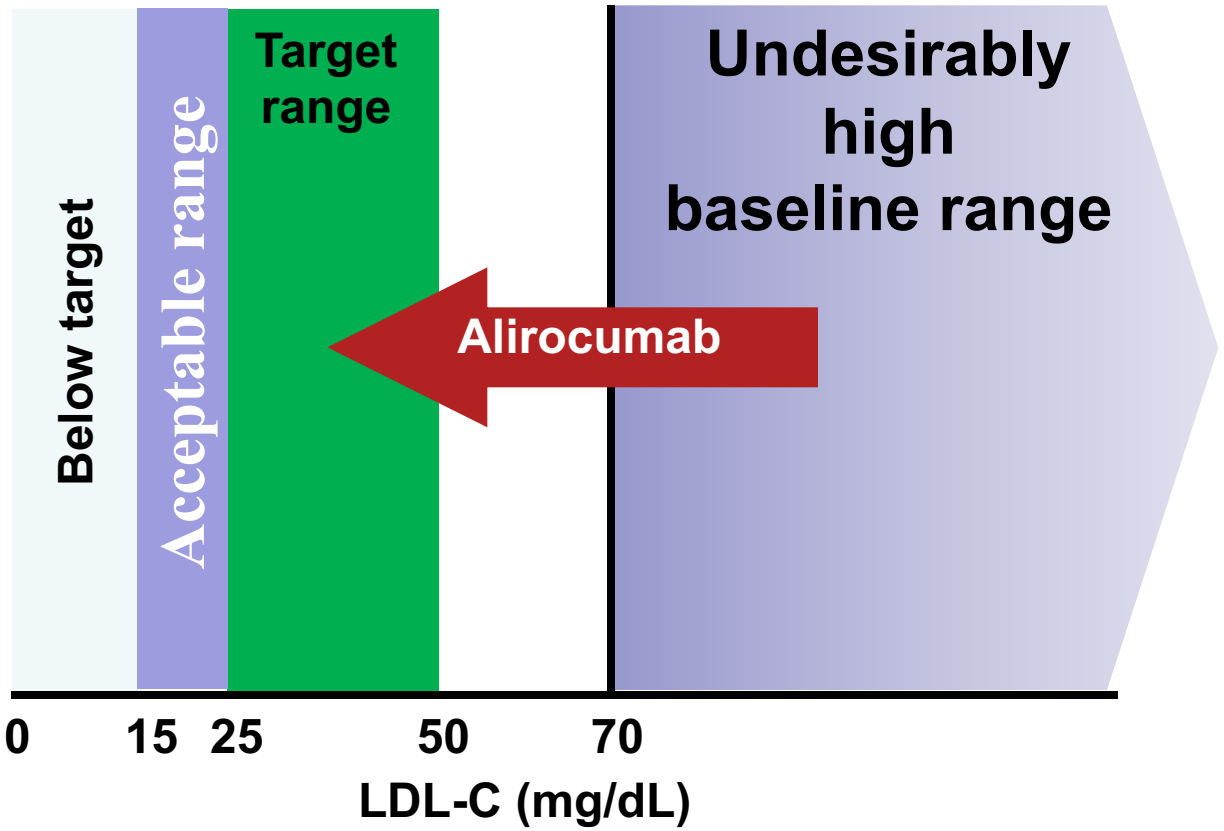




Steg P, ACC 2018

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.



Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

Key differences between ODYSSEY OUTCOMES and FOURIER

1.Goodman and al, Poster presented at the ACC, March 18,2017
2.Sabatine and al, NEJM, March 17,2017

	ODYSSEY OUTCOMES[1] N=18,536	FOURIER[2] N=27,564
Population	Patient with a coronary event within a year (ACS)	MI, stroke, PAD
Baseline Demographics	Diabetes: 24% Recurrent MI:20% Prior Stroke: 3% Prior PAD: 4% Prior CAD (coronary revascularization):20%	Diabetes: 37% MI: 81% Stroke: 19% PAD: 13%
Median baseline LDL-C (mg/dl)	87	92
Statin background	**Maximally tolerated** High-intensity 89% Moderate-intensity: 8%	High-intensity 69% Moderate-intensity: 30%
Dosing regimen	**Treat-to-target** 75Q2W → 150Q2W if LDL-C ≥50 mg/dl	**Lower the better** 140Q2W/420QM No titration
Primary endpoint Differences	**CHD death**	CV Death Coronary revascularization
Duration (exposure)	**2-to-5 years follow-up**	1-to-3.5 years follow-up

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

Table 11 Recommendations for treatment goals for low-density lipoprotein-cholesterol

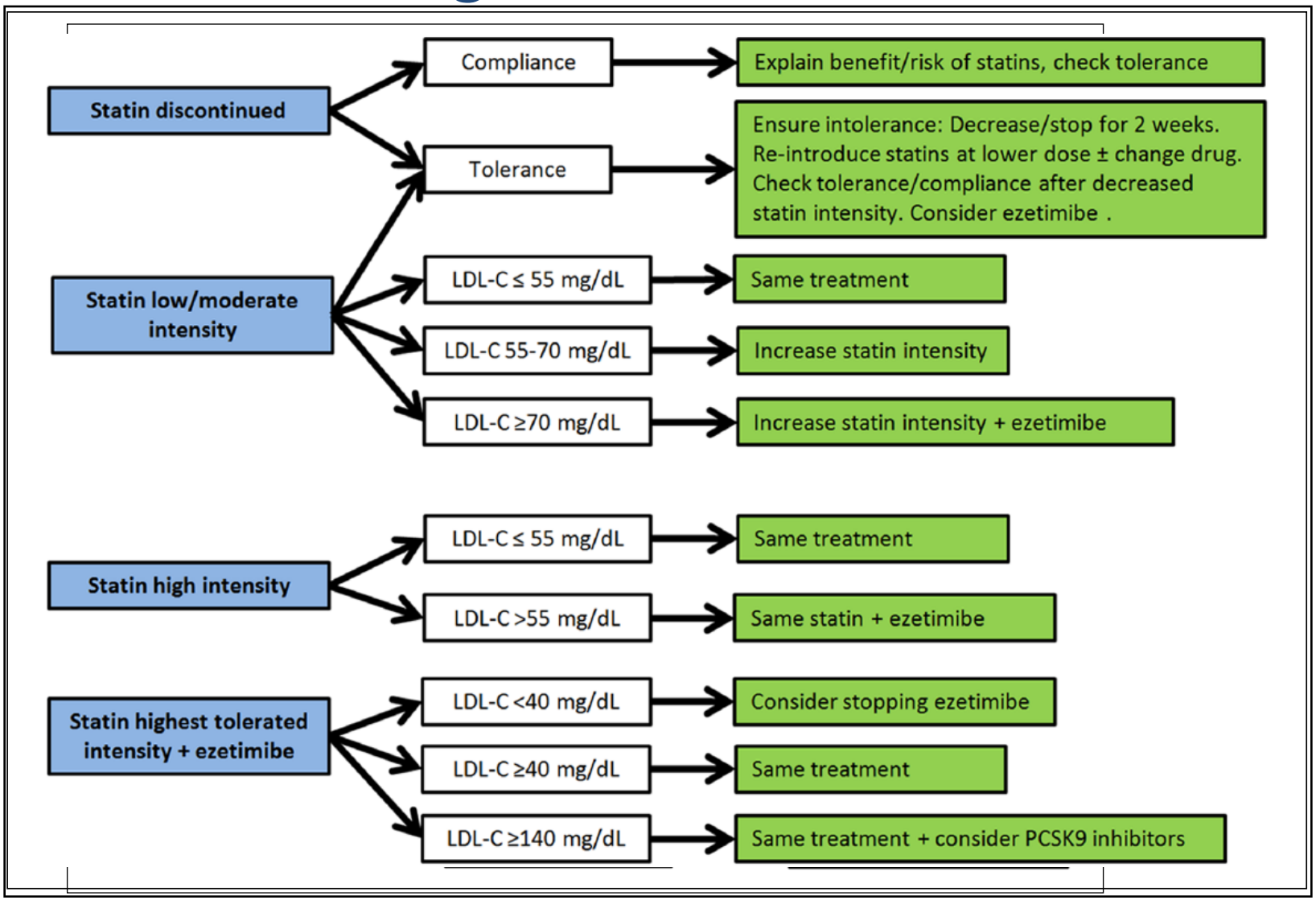
Recommendations	Class [a]	Level [b]	Ref [c]
In patients at VERY HIGH CV risk[d], an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[e] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B	61, 62, 65, 68, 69, 128
In patients at HIGH CV risk[d], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B	65, 129
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C	-

Eur Heart J 2016; 37: 2999-3058

ESC guidelines 2015 NSTE ACS

It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long term.	I	A	522, 527, 528
In patients with LDL cholesterol ≥70 mg/dL (≥1.8 mmol/L) despite a maximally tolerated statin dose, further reduction in LDL cholesterol with a non-statin agent[e] should be considered.	IIa	B	529

A consensus statement on lipid management after ACS



Sschiele F et al. Eur Heart Acute Cardiovasc Care 2018