Preparing for a Novel Era in CV Prevention:

Where do PCSK9 Inhibitors Fit in Lipid Management

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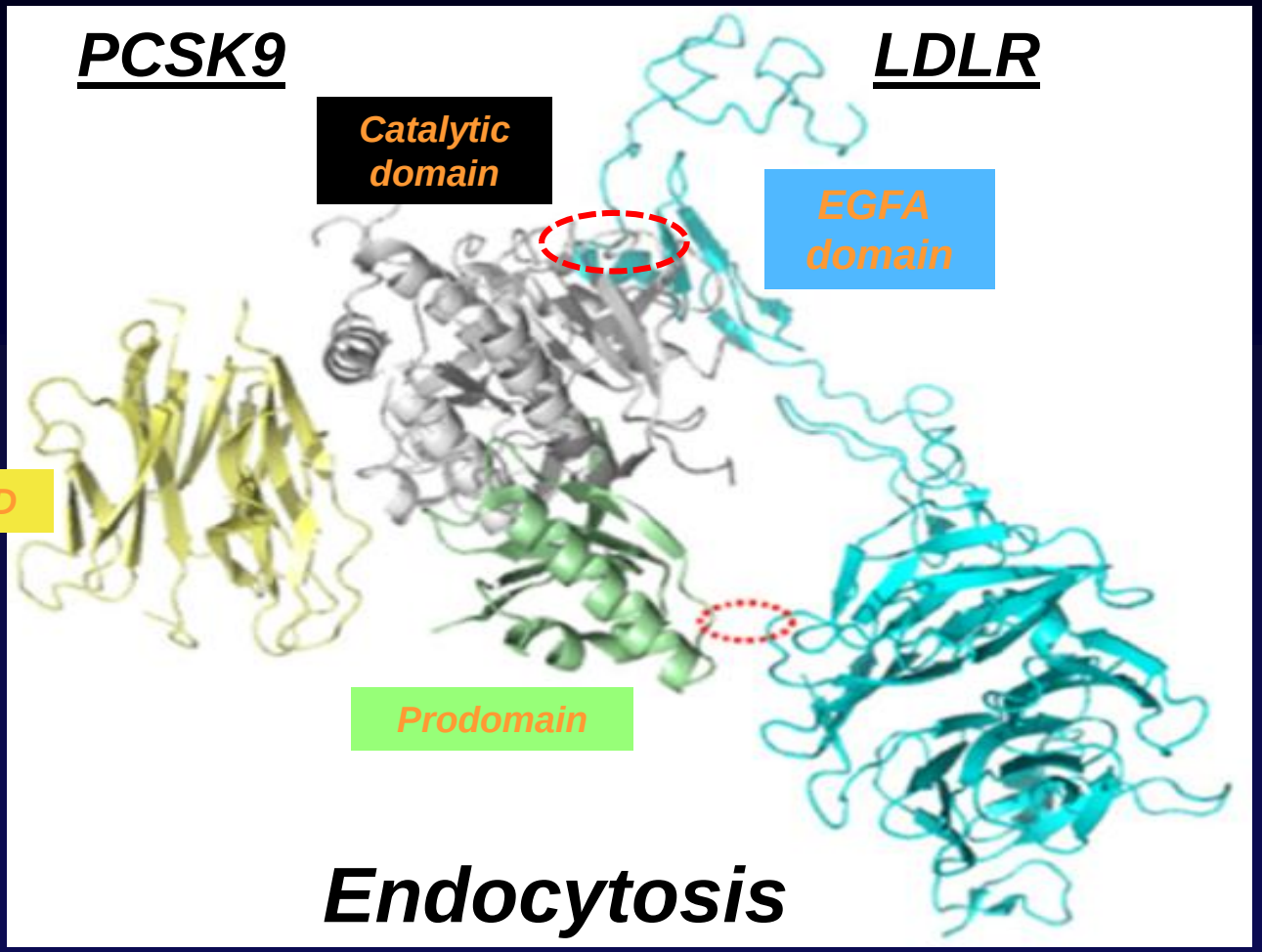
Disclosures

Dr. Kastelein consults with and speaks for biotechnological as well as pharmaceutical companies that develop molecules that influence lipoprotein metabolism and / or inflammation to prevent CVD, including Regeneron, Sanofi, Amgen, Pfizer, Eli Lilly, Iosis, AstraZeneca, CSL Behring, Cerenis, Esperion, The Medicines Company, Kowa, Affiris, UniQure, Madrigal Pharmaceuticals, Akcea Therapeutics, Staten Biotech, Akarna, Corvidia and Gemphire

PCSK9: Protein and Function

PCSK9: The Chaperone (Binds to the LDLR)



Seidah et al. (2014) Circ Res

PCSK9: Target for Pharmacotherapy?

SPIRE Phase 3 Bococizumab Clinical Development

SPIRE (Studies of PCSK9 Inhibition and the Reduction of Vascular Events) N=~30,000

SPIRE Lipid Lowering Studies

SPIRE HR (n=300)
On statin
High risk of CV event
LDL-C ≥70 or ≥100 mg/dL

SPIRE LDL (n=1,932)
On statin
High risk of CV event
LDL-C ≥70 mg/dL

SPIRE FH (n=300)
HeFH (genetic diagnosis or Simon Broome Criteria),
LDL ≥70 mg/dl

SPIRE LL (n=690)
On statin
High/very high risk of CV event
LDL-C ≥100 mg/dL

SPIRE SI (n=150)
Statin intolerant
LDL-C ≥70 mg/dL

SPIRE CV Outcome Studies

SPIRE-1 (n=17,000)
High Risk Primary and Secondary Prevention
LDL-C ≥70 to <100 mg/dL on statins (or statin intolerant)

SPIRE-2 (n=9,000)
High Risk Primary and Secondary Prevention
LDL-C ≥100 mg/dL on statins (or statin intolerant)

SPIRE
Studies on PCSK9 Inhibition and the Reduction of vascular Events

NCT#: https://clinicaltrials.gov
SPIRE HR: NCT01968954;
SPIRE LDL: NCT01968967.
SPIRE HF: NCT01968980;
SPIRE-LL: NCT02100514.
SPIRE-SI: NCT02135029
SPIRE-1: NCT01975376;
SPIRE-2: NCT01975389.

PCSK9 Inhibitors

- **High risk, high LDL-C**
- **Statin Intolerance**
- **Familial Hypercholesterolemia**

Familial Hypercholesterolemia

Familial Hypercholesterolemia

Number of Publications on FH per year

Ray and Hovingh, Eur Heart J. 2016; 37: 1395-97

Novel Insights in the Diagnosis and Management of FH to date.

Heterozygous Familial Hypercholesterolemia Patients

- **are at greater risk from their LDL than other individuals with similar LDL-C** (Khera et al, JACC 2016; 67: 2578)
- **are rearly diagnosed before they suffer from their first coronary event at age 44** (Krogh et al, Eur Heart J. 2016; 17: 1398)
- **have a post-ACS hazard ratio of 3.5 for a secondary event** (Nanchen et al, Eur Heart J. 2015; 36: 2438)
- **are only receiving high-dose statin therapy in 75% of cases** (Pijlman et al, Atherosclerosis 2009; 1: 189)
- **seldom reach the LDL-C guideline target of <70 mg/dl** (Nanchen et al, Circulation 2016; in press)
- **All of the above leads to their death from a recurent event at a mean age of 60** (Krogh et al, Eur Heart J. 2016; 17: 1398)

PCSK9 Inhibitors in the Management of FH

Alirocumab

FH I, 78 weeks
Alirocumab, n=323
Placebo, n=163

FH II, 78 weeks
Alirocumab, n=167
Placebo, n=82

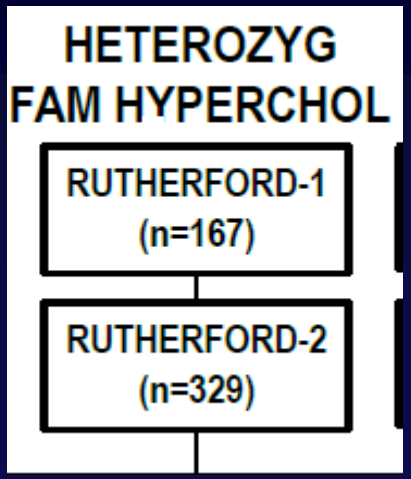
Patients with HeFH
Alirocumab, n=276
Placebo, n=139

HIGH FH, 78 weeks
Alirocumab, n=72
Placebo, n=35

Bococizumab

SPIRE FH (n=300)
HeFH (genetic diagnosis or Simon Broome Criteria),
LDL ≥70 mg/dl

Evolocumab



In total: 1634 heFH patients

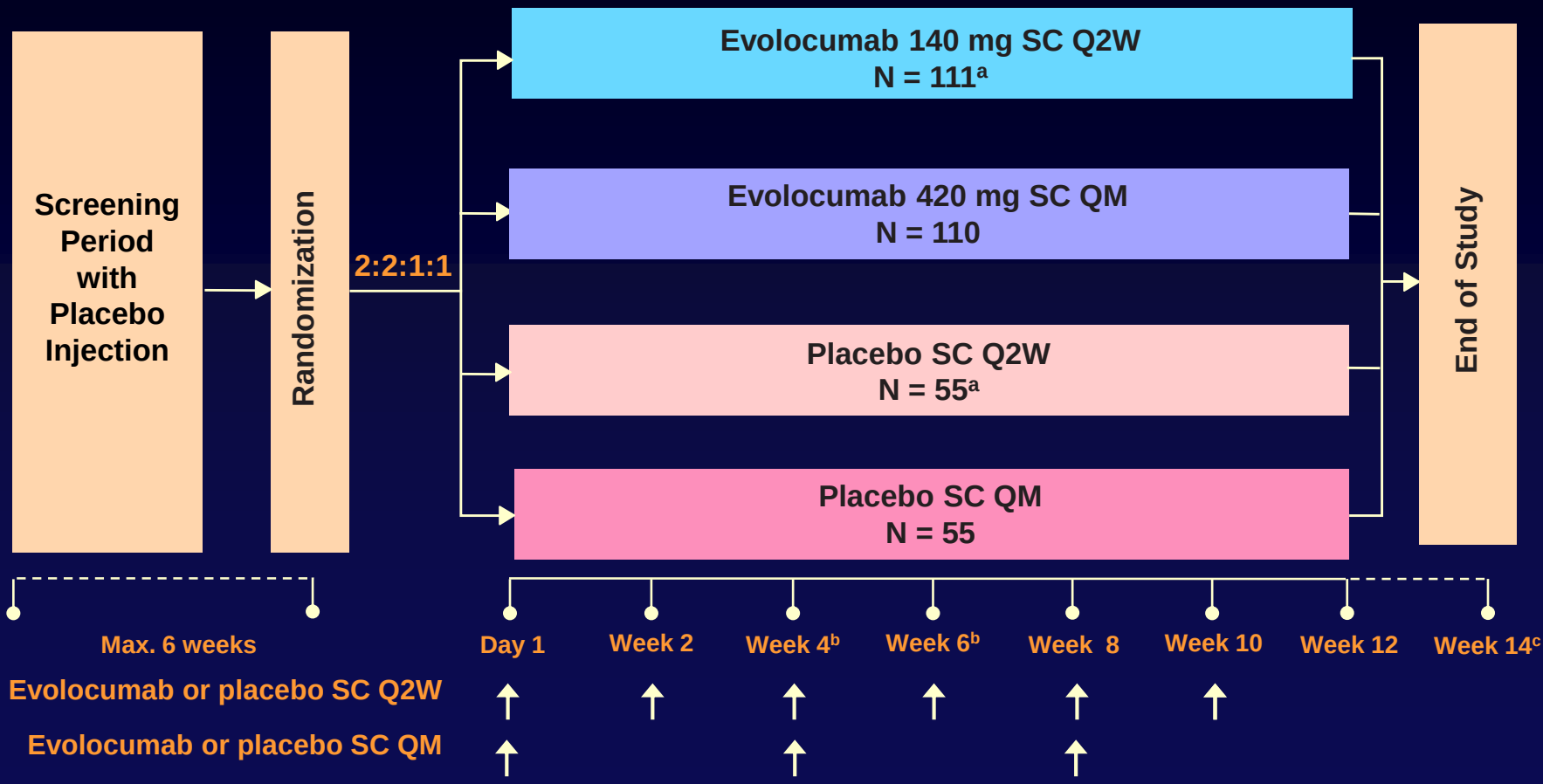
The RUTHERFORD-2 Study: Evolocumab

- **R**ed**u**ction of LDL-C with PCSK9 Inhibi**t**ion in **He**te**r**ozygous **F**amilial Hyperch**o**leste**r**olemia **D**isorder (NCT20110117)

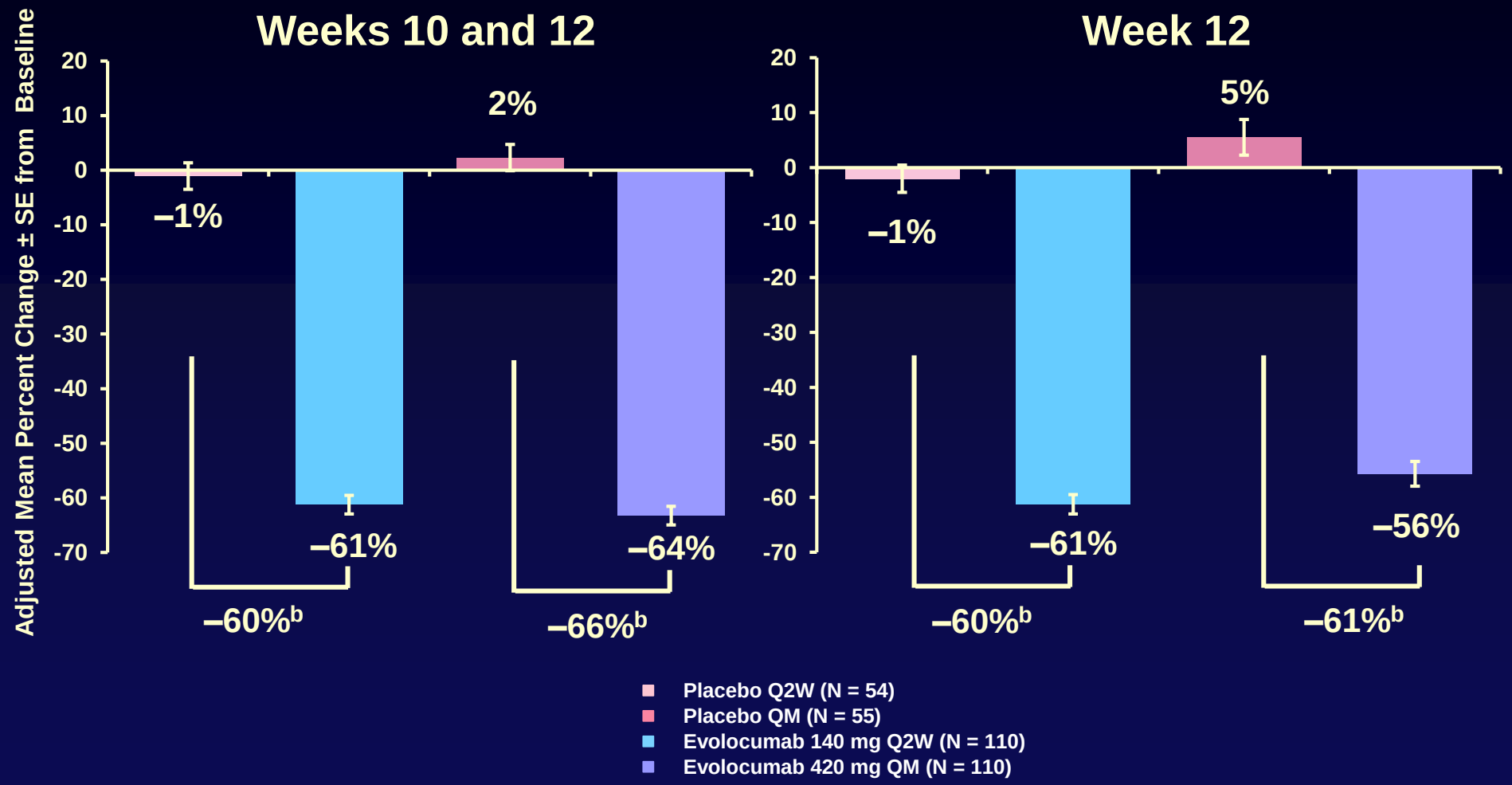
- **Design:**
  A 12-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study

- **Objective:**
  To evaluate the efficacy and safety of evolocumab (AMG 145) 140 mg Q2W and 420 mg QM administered subcutaneously in a large cohort of HeFH patients unable to achieve an LDL-C < 100 mg/dL despite statin therapy with or without ezetimibe

RUTHERFORD-2 Study Design

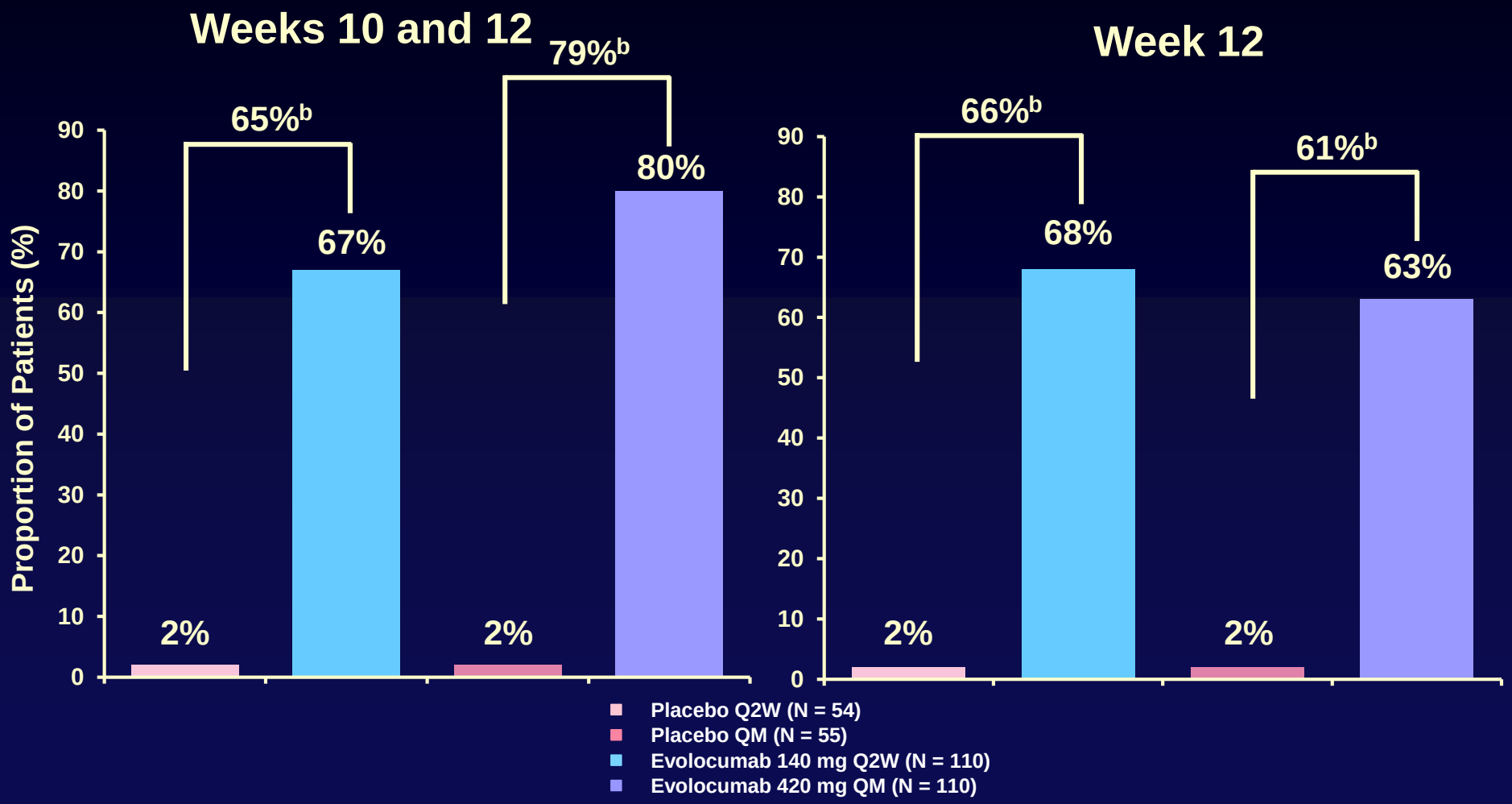


RUTHERFORD-2: Mean % Change in LDL-C[a] from Baseline to the Mean of Weeks 10 and 12, and Week 12 Alone



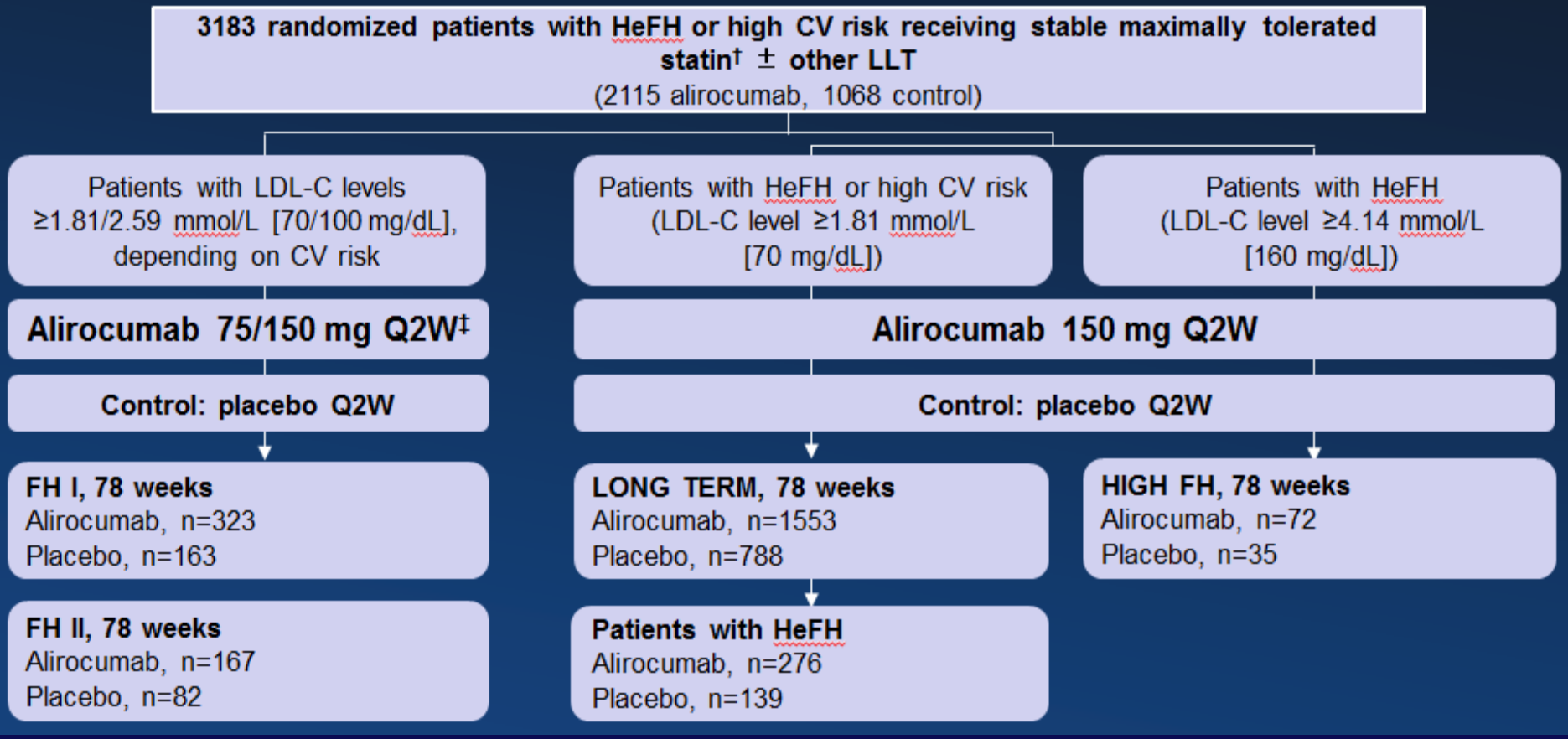
Raal et al, Lancet 2014;385:331-40

RUTHERFORD-2: LDL-C Goal Achievement < 70 mg/dL



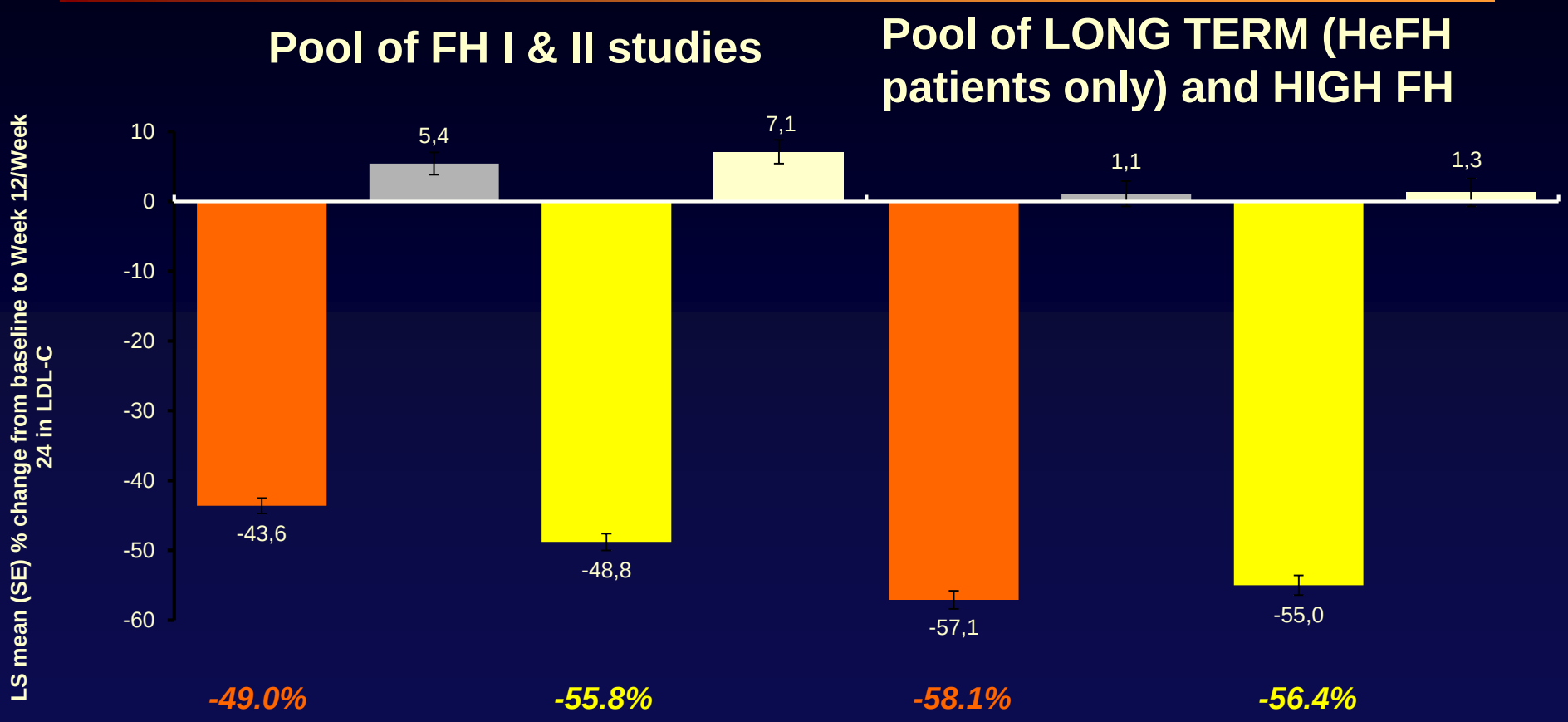
Raal et al, Lancet 2014;385:331-40

The Odyssey Program: Alirocumab Efficacy and Safety in 1257 heFH Patients



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

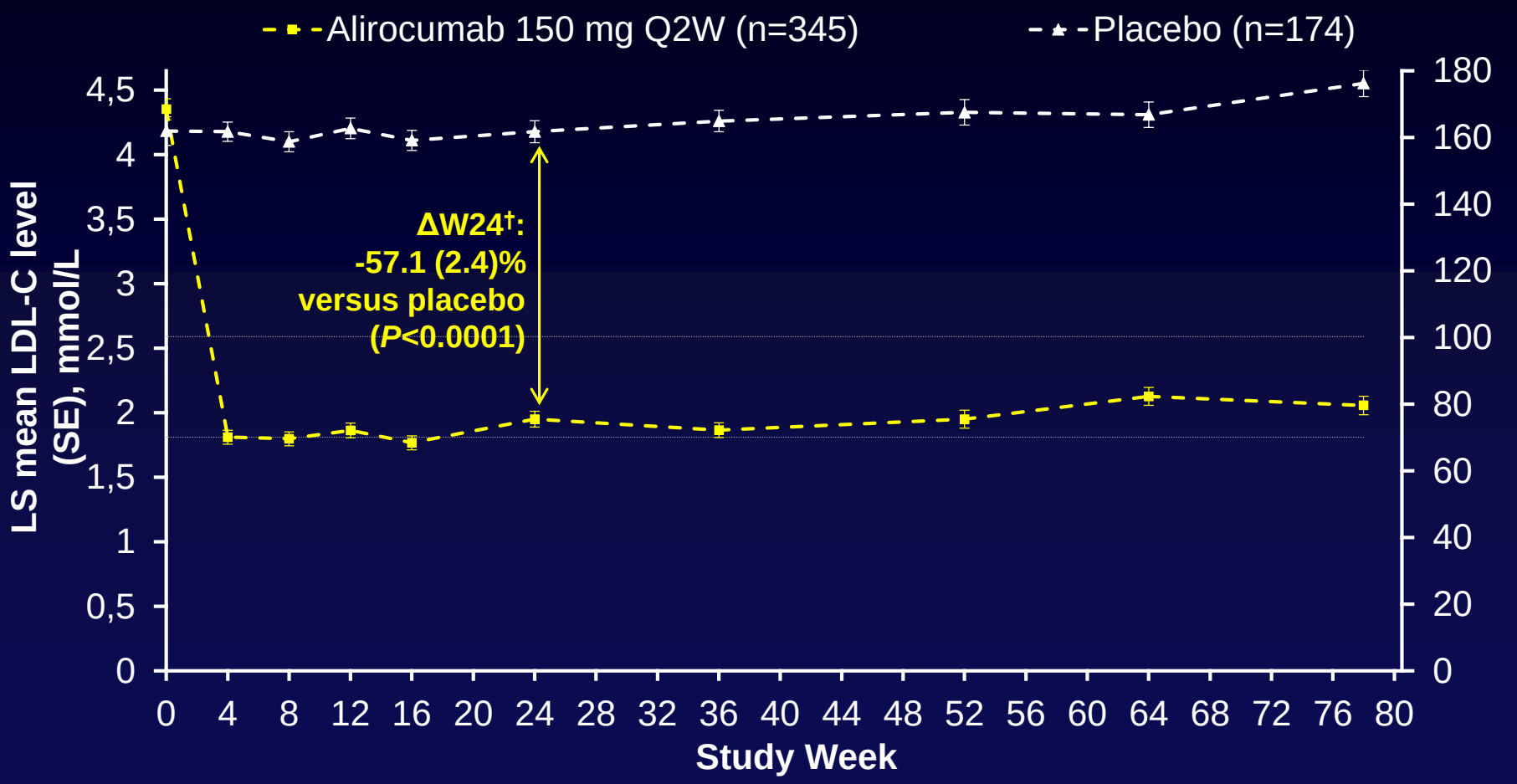
LDL-C Reduction with Alirocumab at Week 24 was Similar in Both Pooled Study Groups



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

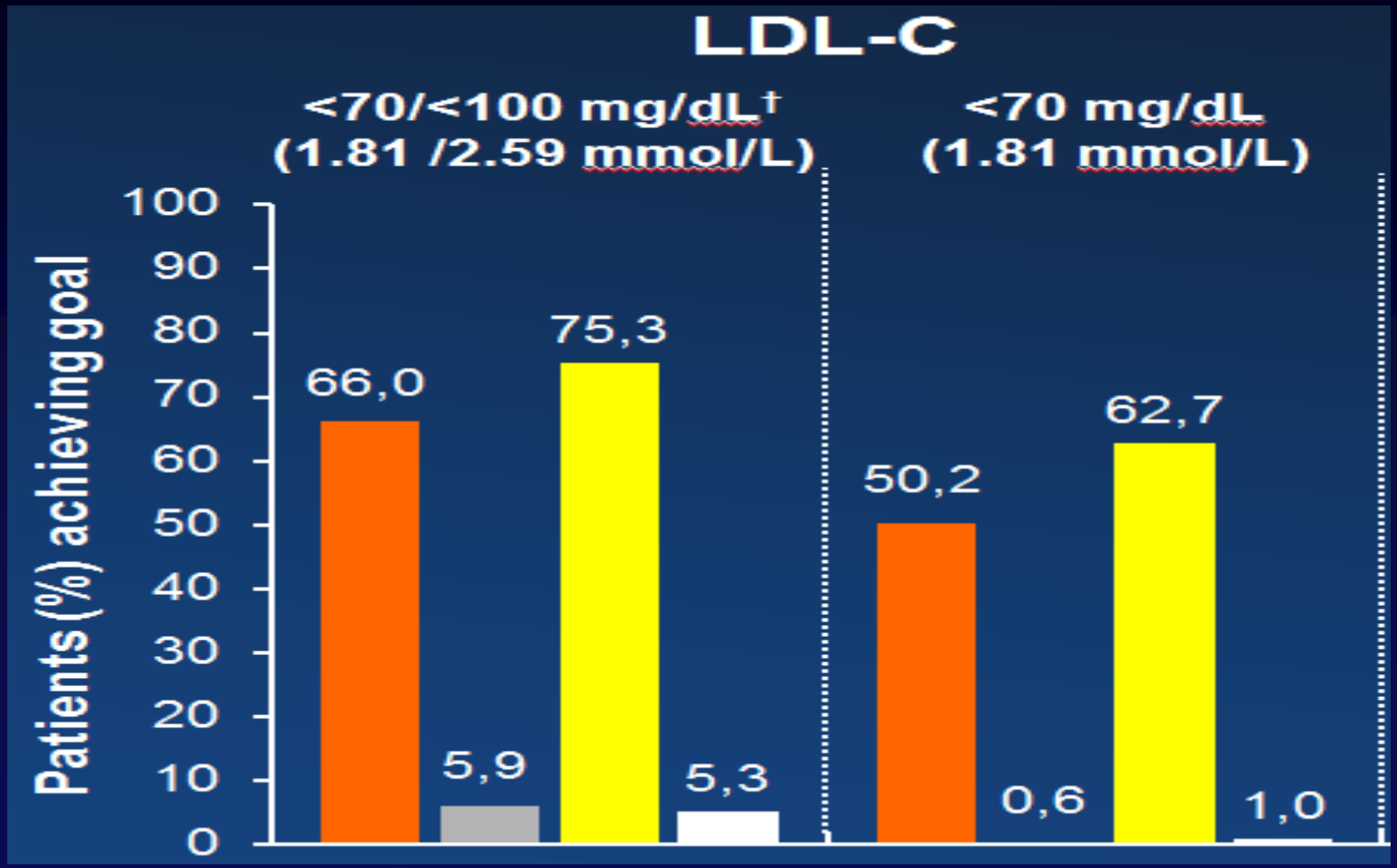
Mean Calculated LDL-C Levels

Pool of LONG TERM (HeFH patients only) and HIGH FH



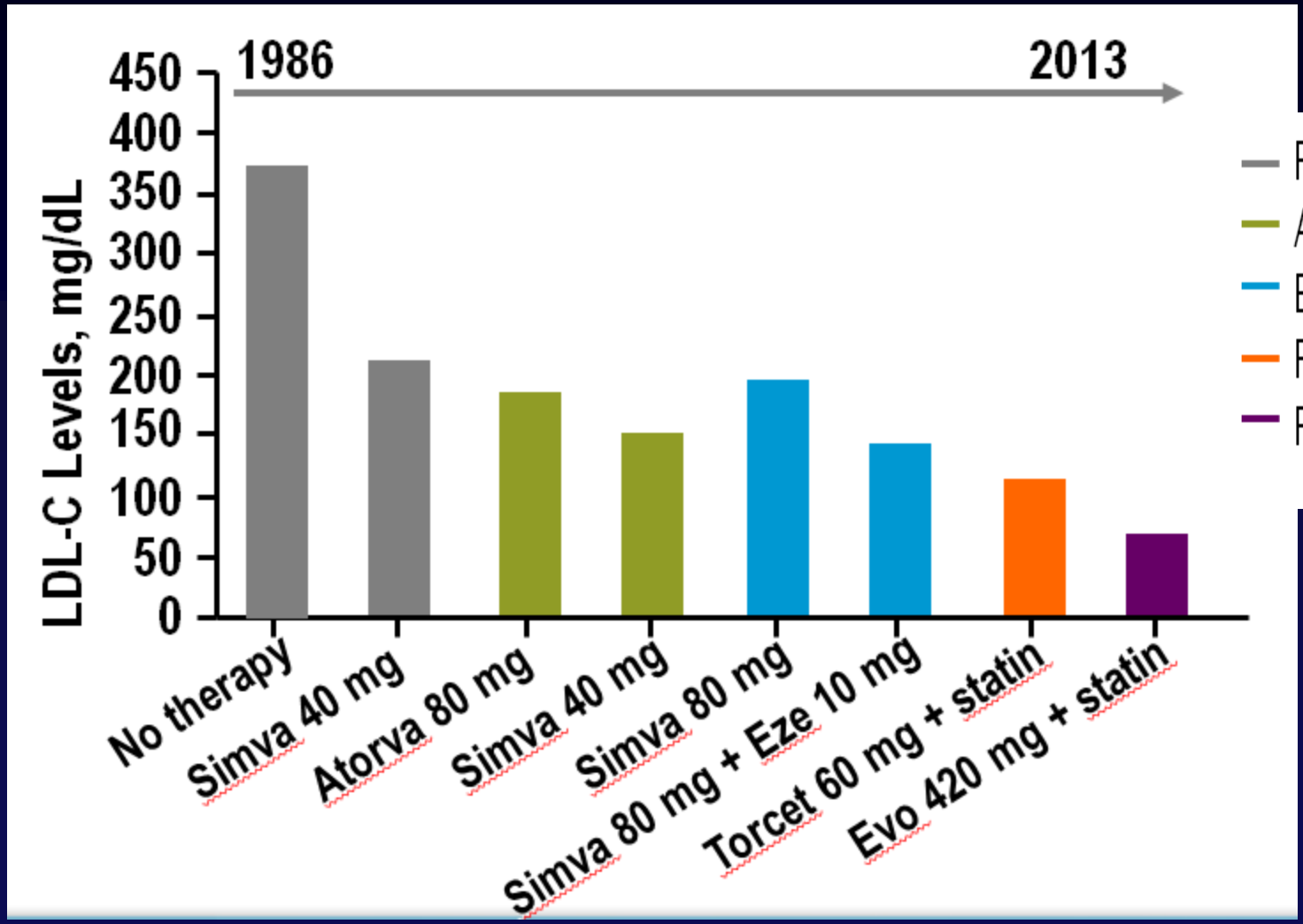
Kastelein, Eur Heart J. 2015; 36: 2996-3003

Odyssey Program
Pool of FH I & II Studies: Goal Achievement



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

LDL-C Levels in FH: From a Lethal Disorder to a Manageable Dislipidemia



Kastelein, Nat. Rev. Cardiol. 2014; 11:629-31

Conclusions

- The current management of heFH can be summarized by: too little, too late (Hovingh & Kastelein, Circulation 2016, in press)
- The future looks a lot brighter: both Evolocumab & Alirocumab therapy, on top of statins / ezetimibe, offers goal attainment hitherto impossible