Effect of the PCSK9 Inhibitor Evolocumab on Cardiovascular Outcomes

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Late-Breaking Clinical Trial
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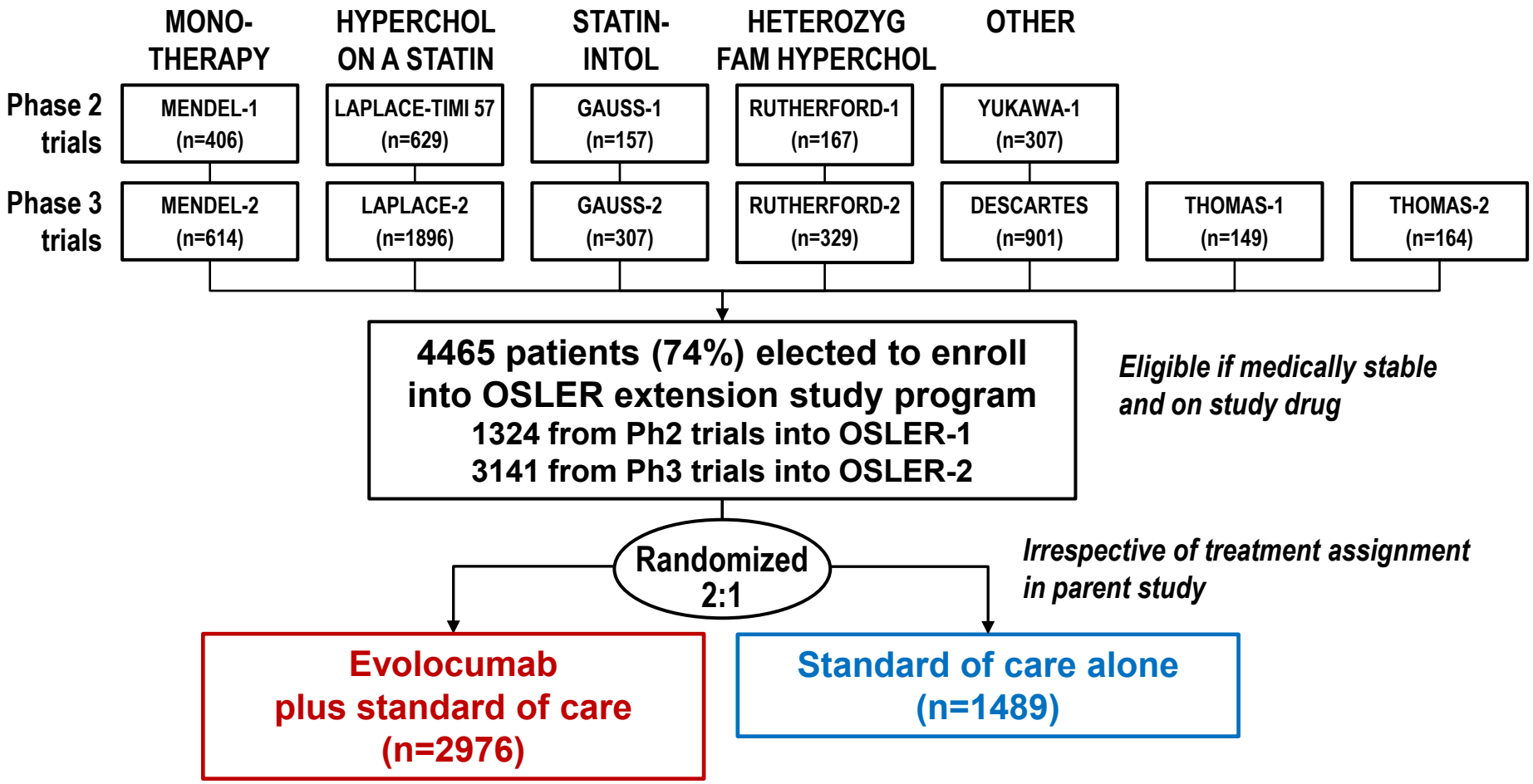
Background

- **Reduction in LDL cholesterol has proven highly effective in reducing cardiovascular events**
  - Randomized controlled trials (primarily w/ statins but also other drugs)
  - Mendelian randomization studies with SNPs in many different genes
- **Proprotein convertase subtilisin/kexin type 9 (PCSK9)**
  - Chaperones LDL receptor (LDL-R) to destruction → ↑ circulating LDL-C
  - Loss-of-fxn genetic variants → ↑ LDL-R activity → ↓ LDL-C & ↓ risk of MI
- **Evolocumab** (AMG 145)
  - Fully human monoclonal antibody against PCSK9
  - ↓ LDL-C by ~60% and was safe & well-tolerated in Ph 2 & 3 studies
  - Effect on cardiovascular outcomes remains undefined

OSLER Program



Median follow-up of 11.1 months (IQR 11.0-12.8)
7% discontinued evolocumab early
96% completed follow-up

Methods

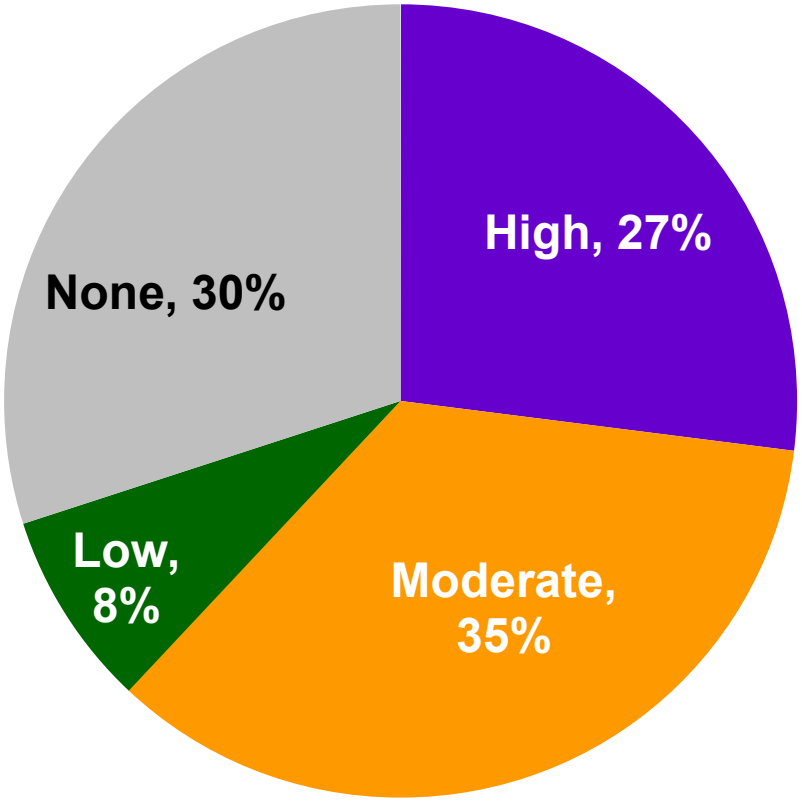
- **Evolocumab**
  - Open-label; subcutaneous injections
  - Dosed either 140 mg q 2 wk or 420 mg q month (similar ↓ LDL-C)
- **Endpoints**
  - Adverse events (primary) & tolerability
  - LDL-cholesterol (secondary) & other lipid parameters
  - Cardiovascular (CV) clinical outcomes (prespecified, exploratory): adjudicated by TIMI Study Group CEC, ***blinded to treatment***
    - Death
    - Coronary: myocardial infarction (MI), unstable angina (UA) requiring hospitalization, revascularization
    - Cerebrovascular: stroke or transient ischemic attack (TIA)
    - Heart failure (HF) requiring hospitalization

Baseline Characteristics

Characteristic	Value
Age, years, mean (SD)	**58 (11)**
Male sex (%)	**51**
Cardiovascular risk factor (%)	**80**
Hypertension	52
Diabetes mellitus	13
Metabolic syndrome	34
Current cigarette use	15
Family hx of premature CAD	24
Known familial hyperchol.	10
Known vascular disease (%)	**25**
Coronary	20
Cerebrovascular or Peripheral	9

Pooled data; no differences between treatment arms

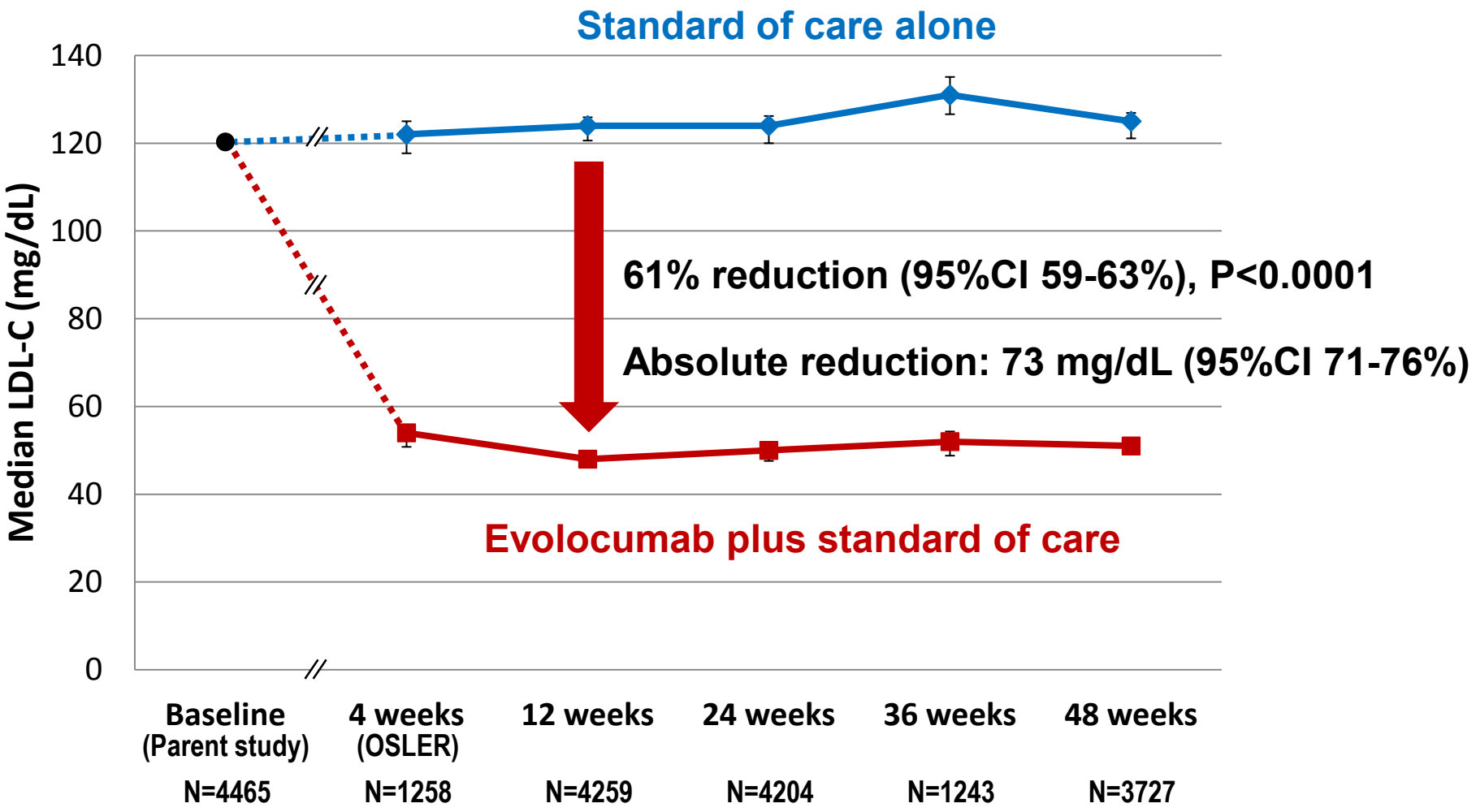
Statin Use & Intensity



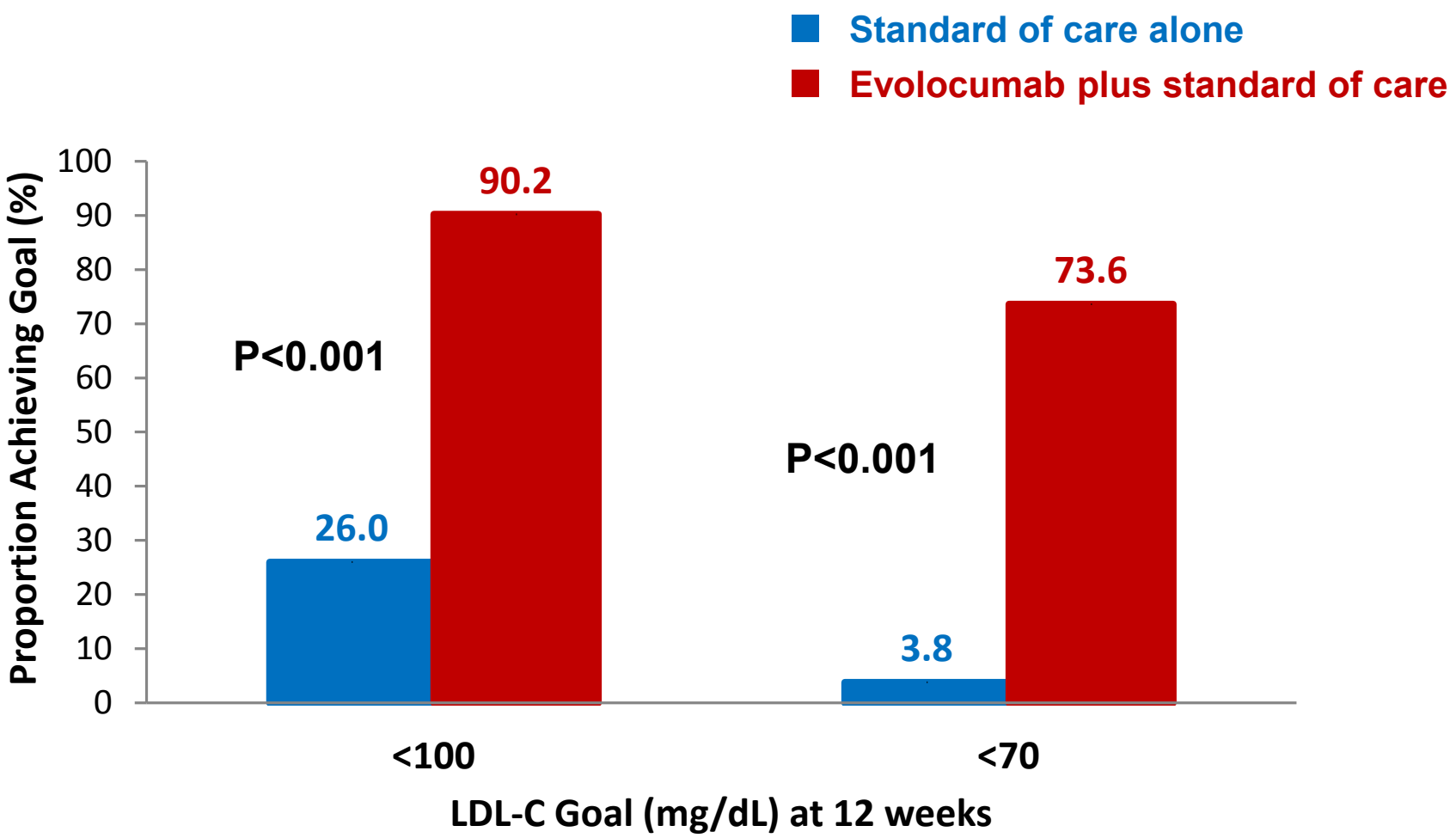
Pooled data at the start of OSLER; no differences between treatment arms

High: ↓ LDL-C by ~≥50% (eg, atorvastatin ≥40 mg/d or equivalent)
Moderate: ↓ LDL-C by ~30-50% (eg, simvastatin 20-40 mg/d or equivalent)
Low: ↓ LDL-C by ~<30% (eg, pravastatin ≤20 mg/d or equivalent)

LDL Cholesterol

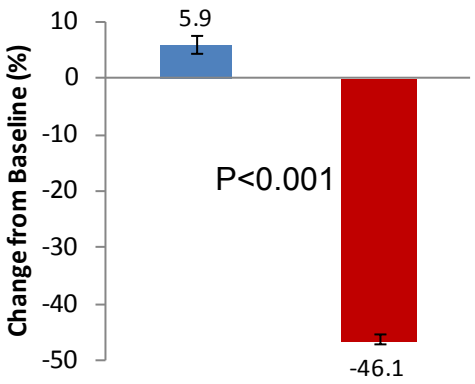


LDL Cholesterol Goals

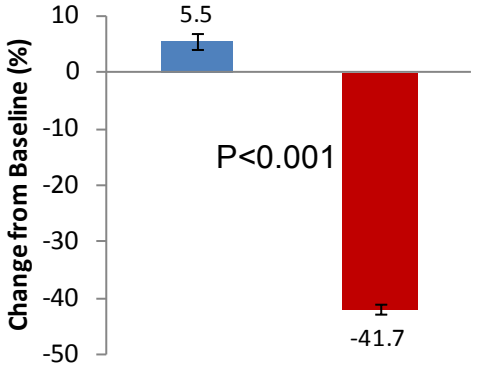


Other Lipid Parameters

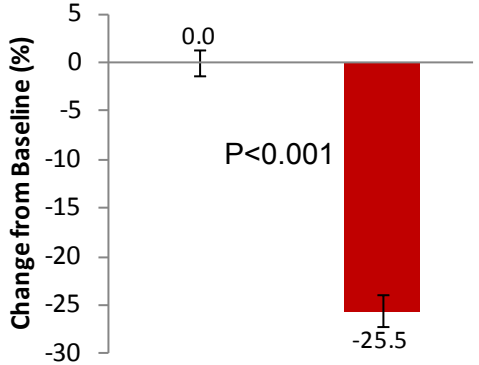
52% ↓ in Non-HDL-C



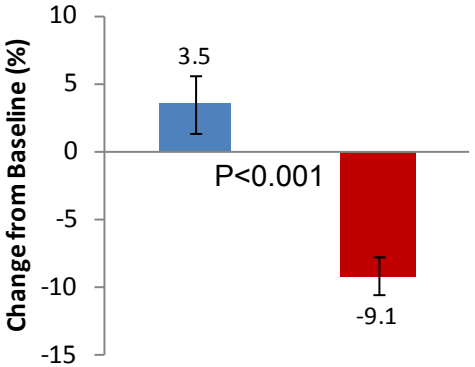
47% ↓ in ApoB



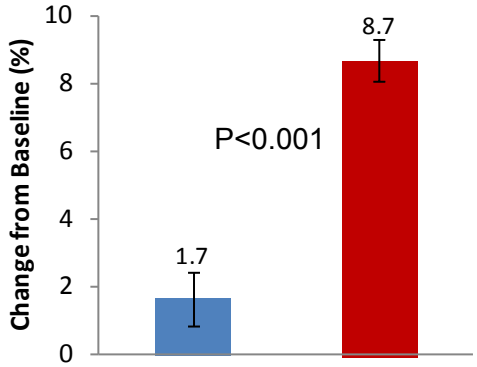
26% ↓ in Lp(a)



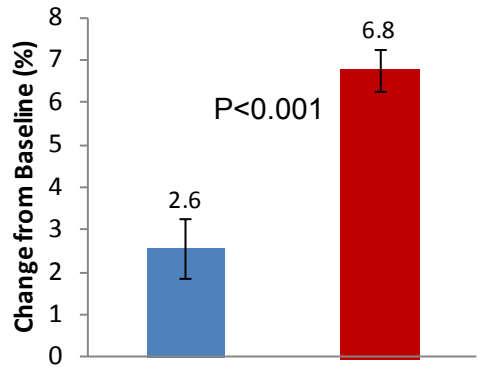
13% ↓ in Triglycerides



7% ↑ in HDL-C



4% ↑ in ApoA1

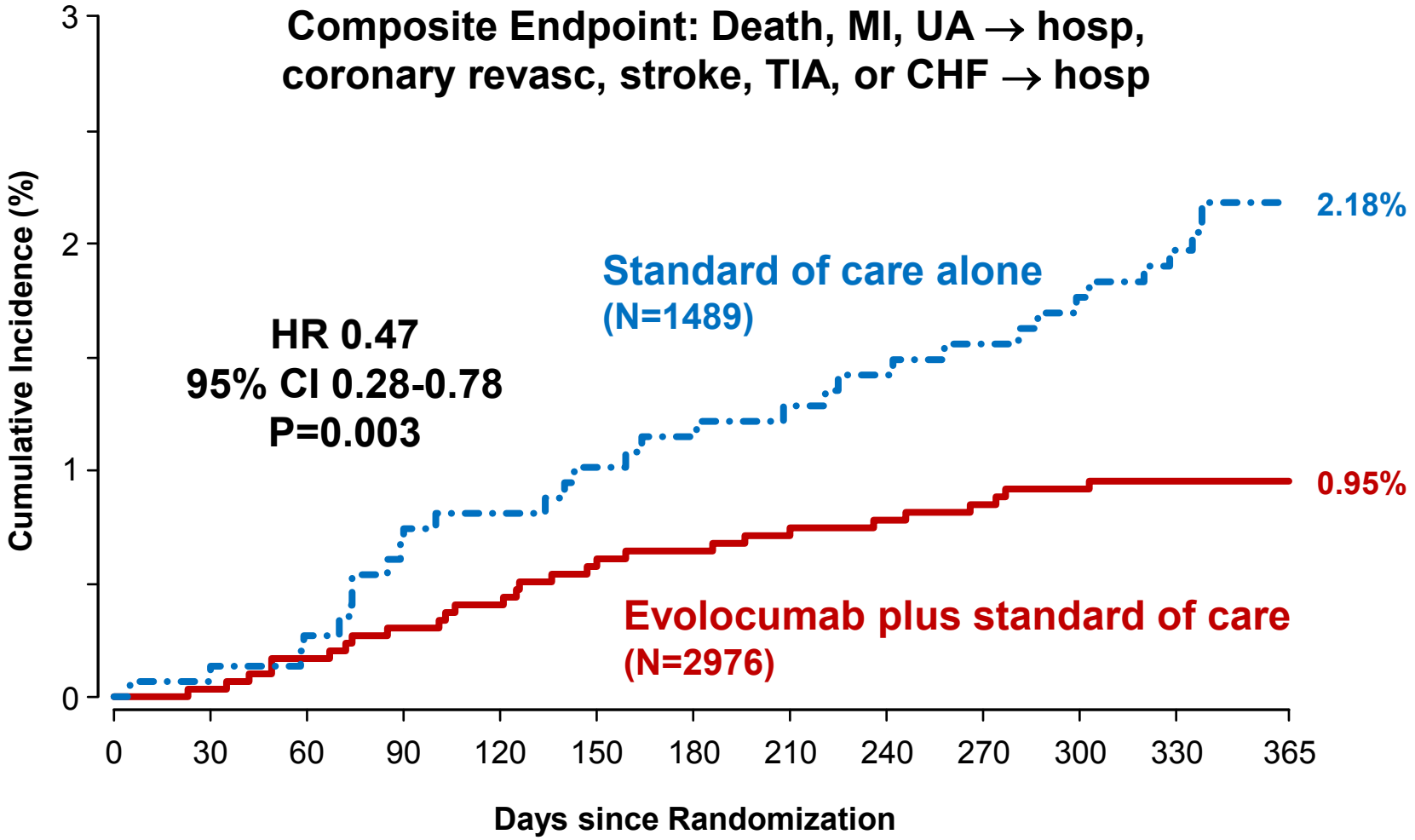


Week 12 data; values are means except for TG and Lp(a) which are medians

Standard of care alone

Evolocumab plus standard of care

Cardiovascular Outcomes



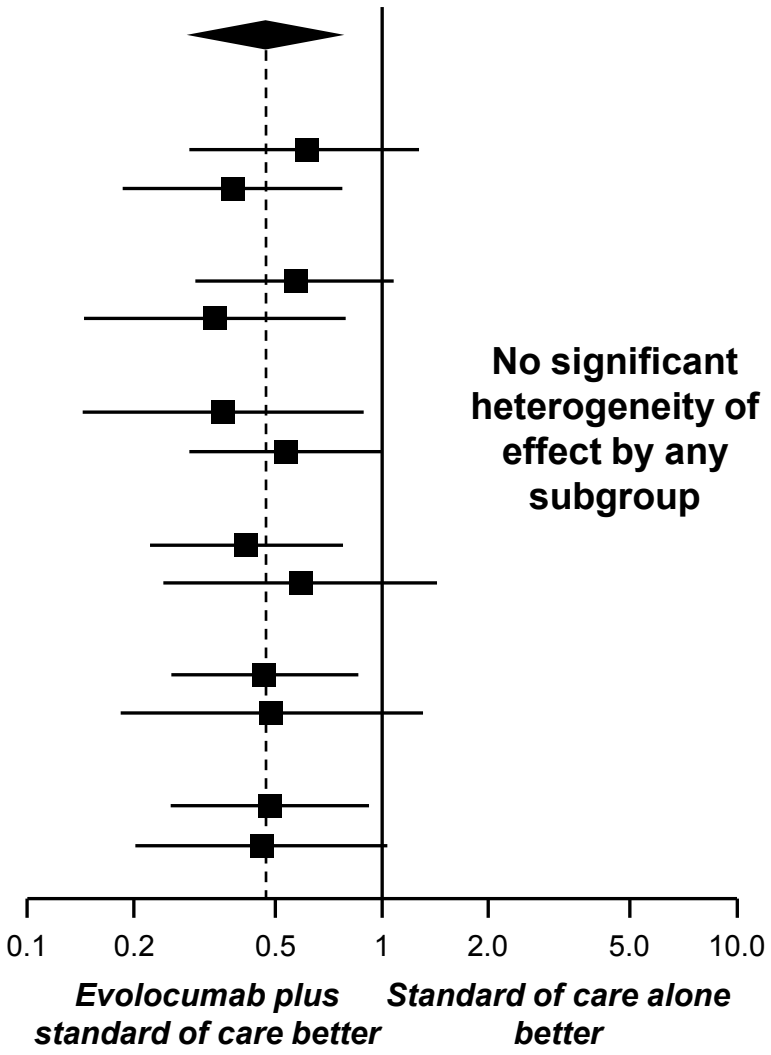
Types of CV Outcomes

Endpoint	Evolocumab + stnd of care (N=2976)		Standard of care alone (N=1489)		HR (95% CI)
	n	%	n	%	
All CV Events	29	0.95	31	2.18	0.47 (0.28-0.78)
Death	4	0.14	6	0.41	0.33 (0.09-1.18)
Coronary Events (MI, hosp for UA, or revasc)	22	0.75	18	1.30	0.61 (0.33-1.14)
Cerebrovasc Events (Stroke or TIA)	4	0.14	7	0.47	0.29 (0.08-0.98)
Heart failure hospitalization	1	0.03	1	0.07	0.52 (0.03-8.30)

% are KM event rates at 1 year except for HF, which is a crude %

CV Events in Subgroups

Baseline Subgroup	Number	Evolocumab	Stnd of care alone
Overall	4465	0.95%	2.18%
Age			
<65 yr	3103	0.73%	1.29%
≥65 yr	1362	1.47%	4.10%
Sex			
Male	2255	1.28%	2.37%
Female	2210	0.61%	1.96%
LDL cholesterol			
<120 mg/dL	2202	0.55%	1.53%
≥120 mg/dL	2263	1.35%	2.75%
Statin use			
Yes	3128	0.83%	2.21%
No	1337	1.24%	2.11%
NCEP class			
High or mod. high	2025	1.51%	3.51%
Mod. or lower	2440	0.49%	1.04%
Known vascular disease			
Yes	1125	2.31%	5.01%
No	3340	0.50%	1.19%



No significant heterogeneity of effect by any subgroup

% are KM event rates at 1 year

NCEP = National Cholesterol Education Program

Safety

	Evolocumab + stnd of care (N=2976)	Standard of care alone (N=1489)
Adverse events (%)		
Any	69.2	64.8
Serious	7.5	7.5
Leading to discontinuation of evolocumab	2.4	n/a
Injection-site reactions	4.3	n/a
Muscle-related	6.4	6.0
Neurocognitive	0.9	0.3
Laboratory results (%)		
ALT or AST >3×ULN	1.0	1.2
Creatine kinase >5×ULN	0.6	1.2

Adverse Events by Achieved LDL-C

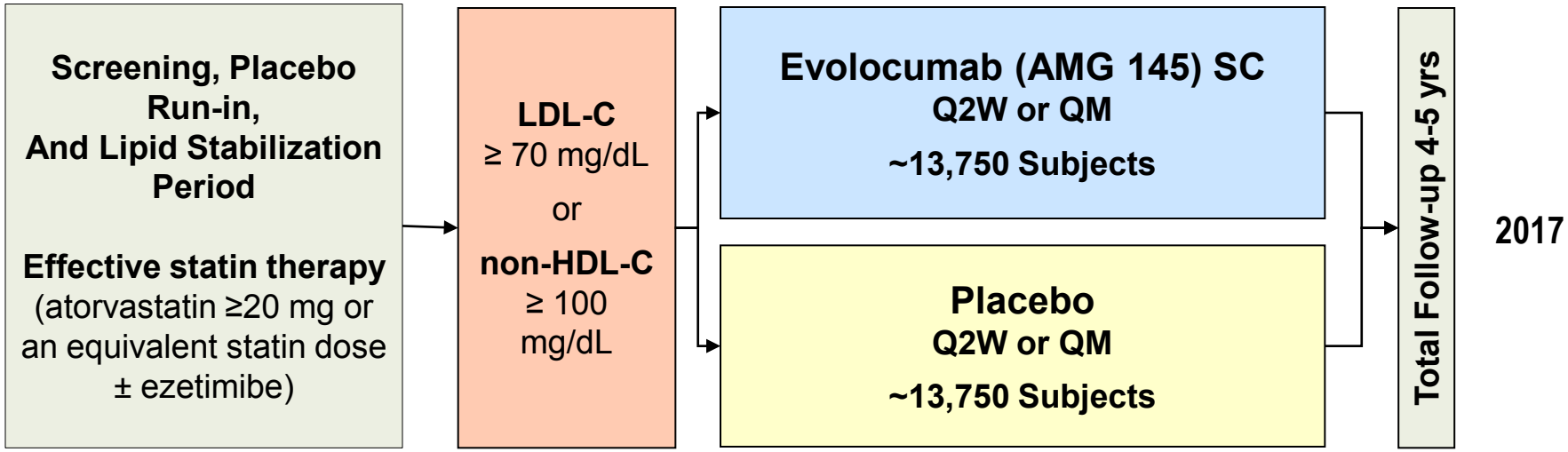
	Evolocumab subjects stratified by minimum achieved LDL-C				All EvoMab (n=2976)	Stnd of Care Alone (n=1489)
	<25 mg/dL (n=773)	25 to <40 mg/dL (n=759)	<40 mg/dL (n=1532)	≥40 mg/dL (n=1426)		
Adverse Events (%)						
Any	70.0	68.1	69.1	70.1	69.2	64.8
Serious	7.6	6.9	7.2	7.8	7.5	7.5
Muscle-related	4.9	7.1	6.0	6.9	6.4	6.0
Neurocognitive	0.5	1.2	0.8	1.0	0.9	0.3
Lab results (%)						
ALT/AST >3×ULN	0.9	0.8	0.8	1.3	1.0	1.2
CK >5×ULN	0.4	0.9	0.7	0.5	0.6	1.2

Summary for Evolocumab

- **↓ LDL-C by 61% at 12 weeks**
  - Absolute decrease of 73 mg/dL
  - Median achieved LDL-C of 48 mg/dL
- **↓ CV outcomes by 53% over 1 year**
  - Prespecified, exploratory outcome with relatively few events
  - Event curves diverged early & continued to separate over time
  - Consistent effect on death, coronary, and cerebrovasc. events
  - Consistent effect in major subgroups
- **Appeared to be safe and well-tolerated**
  - AEs largely balanced, good tolerability in this extension study
  - No gradient in incidence of any AE by achieved LDL-C, including in those with LDL-C <25 mg/dL

FOURIER

27,500 patients with cardiovascular disease (prior MI, stroke or PAD)
Age 40 to 85 years
≥1 other high-risk feature



Primary Endpoint: CV death, MI, hosp for UA, stroke, coronary revasc

NCT01764633

Conclusion

These data, in conjunction with epidemiological and genetic data, offer further support for the potential for PCSK9 inhibition as a safe and effective means to reduce major adverse cardiovascular outcomes through particularly robust LDL cholesterol lowering.