Evolocumab and clinical outcomes in patients with CV disease

FOURIER Study

Targeting the cholesterol pathway

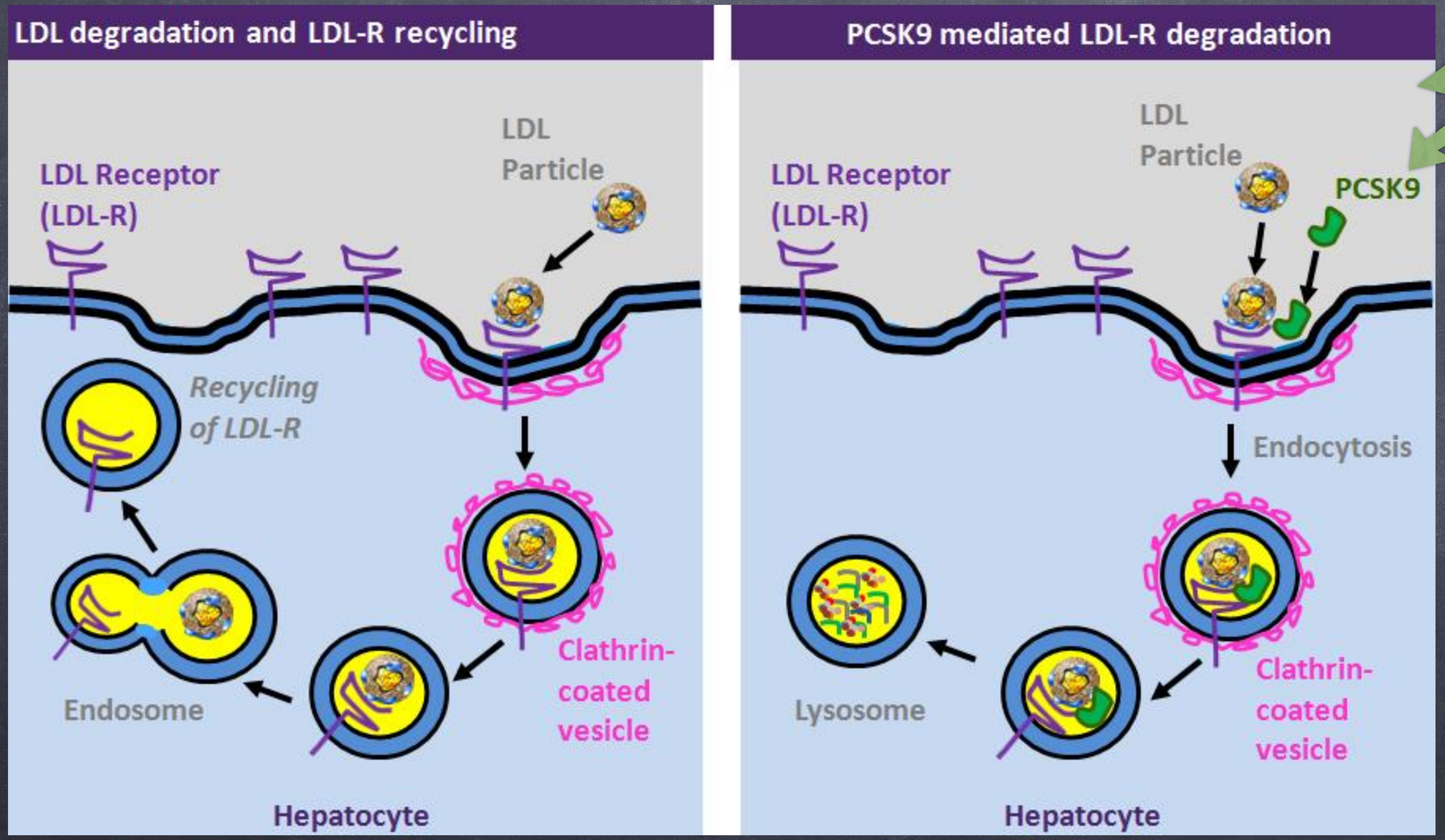
- **Statins** - competitive inhibition of HMG-CoA reductase and subsequent up-regulation of LDL receptors
    - Reduce CV morbidity & mortality in both primary & secondary prevention
    - Ineffective in homozygous FH
- **Ezetimibe** - inhibit cholesterol absorption
    - 2nd line when therapeutic LDL target is not achieved with statin therapy
- Bile acid sequestrants - inhibit bile acid reabsorption

Familial Dyslipidaemias

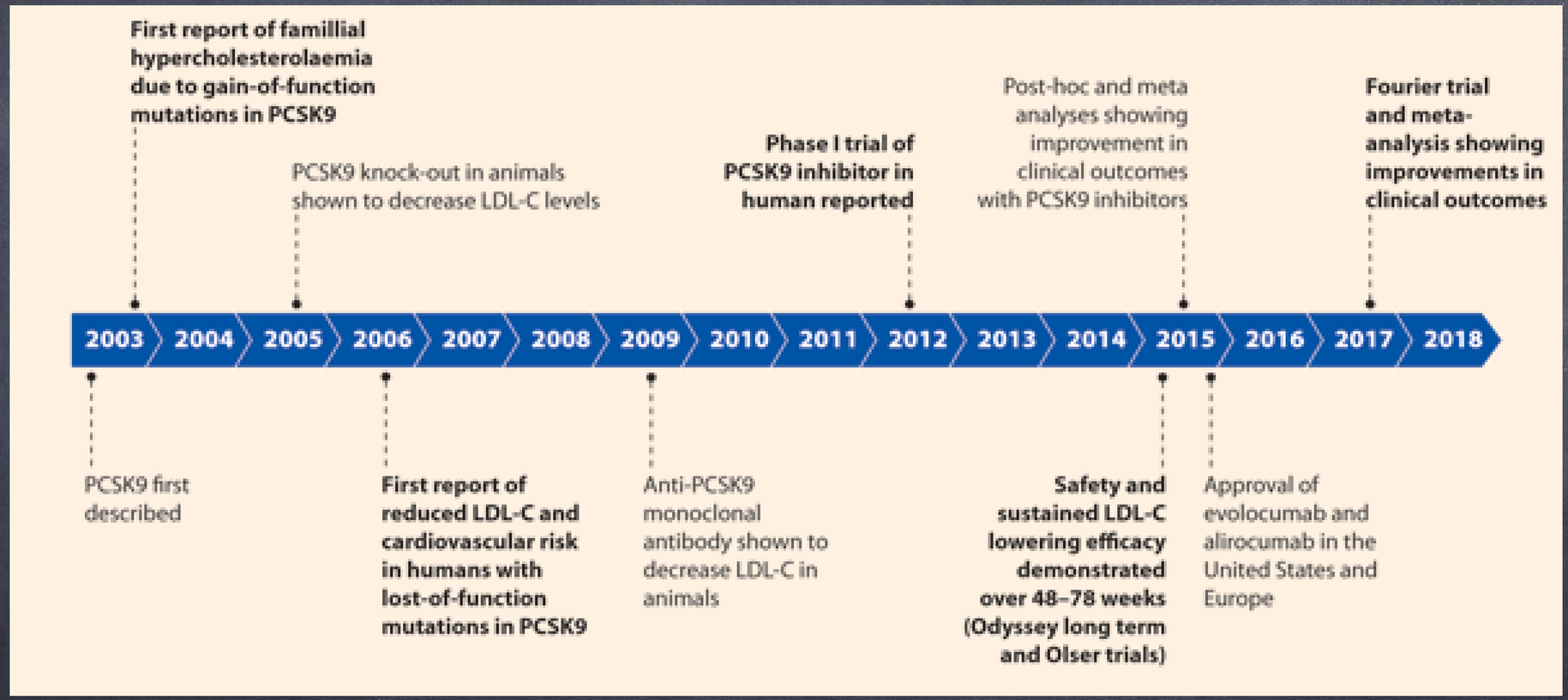
- **Familial combined hyperlipidaemia**
  - Phenotype is determined by the interaction between multiple susceptibility genes and the environment
  - Importance of FHx
- **Familial hypercholesterolaemia (FH)**
  - AD inheritance and is fully penetrant
  - Different types of mutations have been implicated: **LDL receptor** (1 in 500), **PCSK9** (1 in 2500), **apoB** (1 in 1000)

PCSK9 - the death knell for LDL-R

EVOLOCUMAB



Discovery of PCSK9



Primary objective of the FOURIER Trial

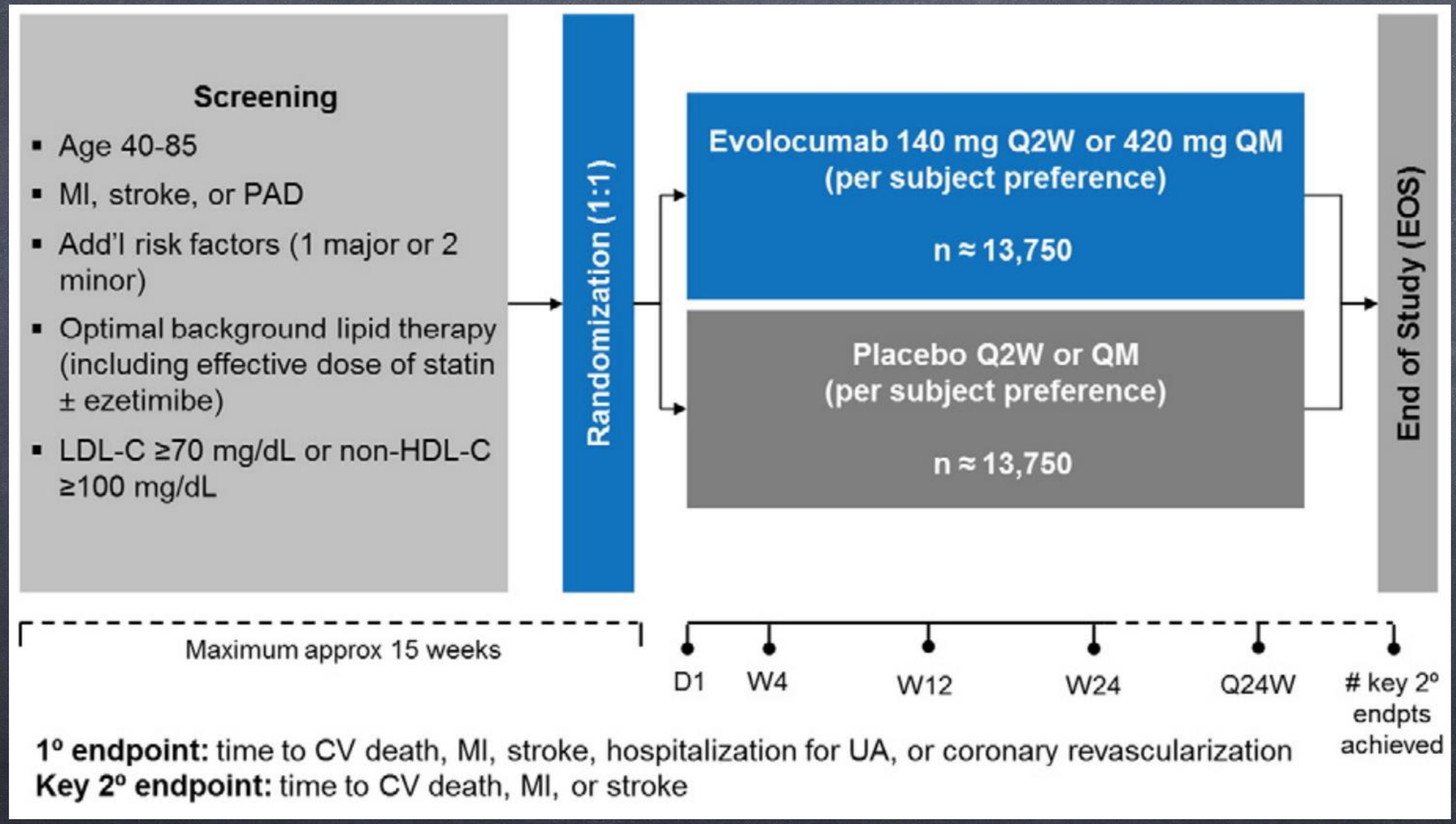
1) Establish the CV benefit associated with PCSK9 inhibitors

2) Efficacy of reducing LDL in patients with persistently high LDL levels DESPITE being on moderate/high intensity statin therapy

Methods

- Intervention: Evolocumab (140mg/2wks OR 420mg/month)
- Comparison: Placebo-controlled trial
- Follow-up: 2.2 years (median)
- Primary outcome: Composite of CV death, MI, stroke, hospitalisation for unstable angina, coronary revascularisation
- Secondary outcomes: MACE (CV death, MI, stroke)

Methods


Screening
Age 40-85
MI, stroke, or PAD
Add'l risk factors (1 major or 2 minor)
Optimal background lipid therapy (including effective dose of statin ± ezetimibe)
LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL
Randomization (1:1)
Evolocumab 140 mg Q2W or 420 mg QM (per subject preference)
n ≈ 13,750
Placebo Q2W or QM (per subject preference)
n ≈ 13,750
End of Study (EOS)
Maximum approx 15 weeks
D1
W4
W12
W24
Q24W
key 2º endpts achieved
1º endpoint: time to CV death, MI, stroke, hospitalization for UA, or coronary revascularization
Key 2º endpoint: time to CV death, MI, or stroke

Statistical Analysis

The primary efficacy analysis was based on the time from randomized study-group assignment to the first occurrence of any element of the primary composite end point. If the rate of the primary end point was significantly lower in the evolocumab group (P<0.05), then, in a hierarchical fashion, the key secondary end point and then cardiovascular death were to be tested at a significance level of 0.05. Additional details are

Significance

available. The size of the patient population in the trial was based on the key secondary end point, and we estimated that 1630 such end-point events were required to provide 90% power to detect a 15% relative risk reduction with evolocumab as compared with placebo.[11] Hazard

Effect size

Power

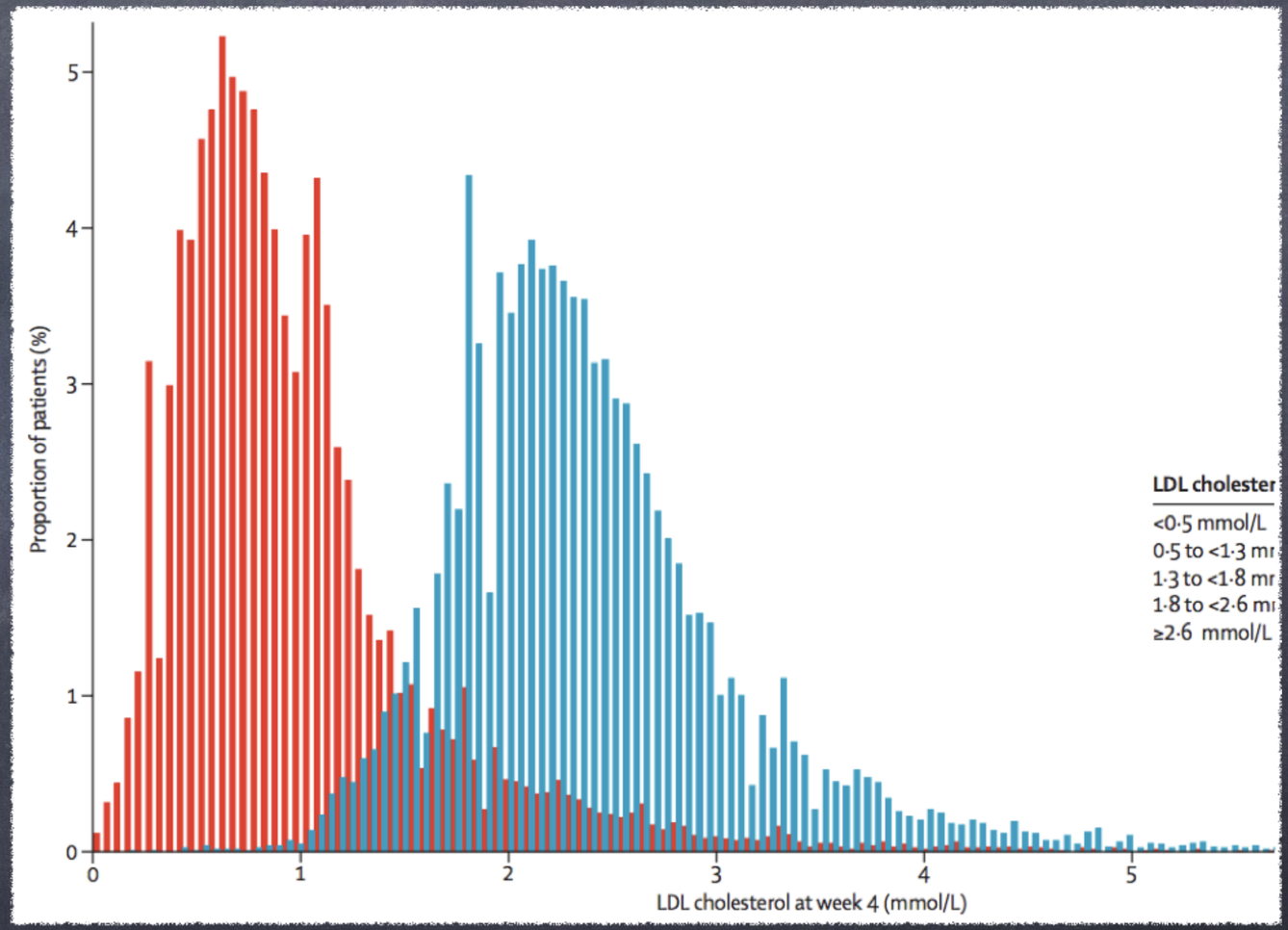
Sample Size

Baseline demographics

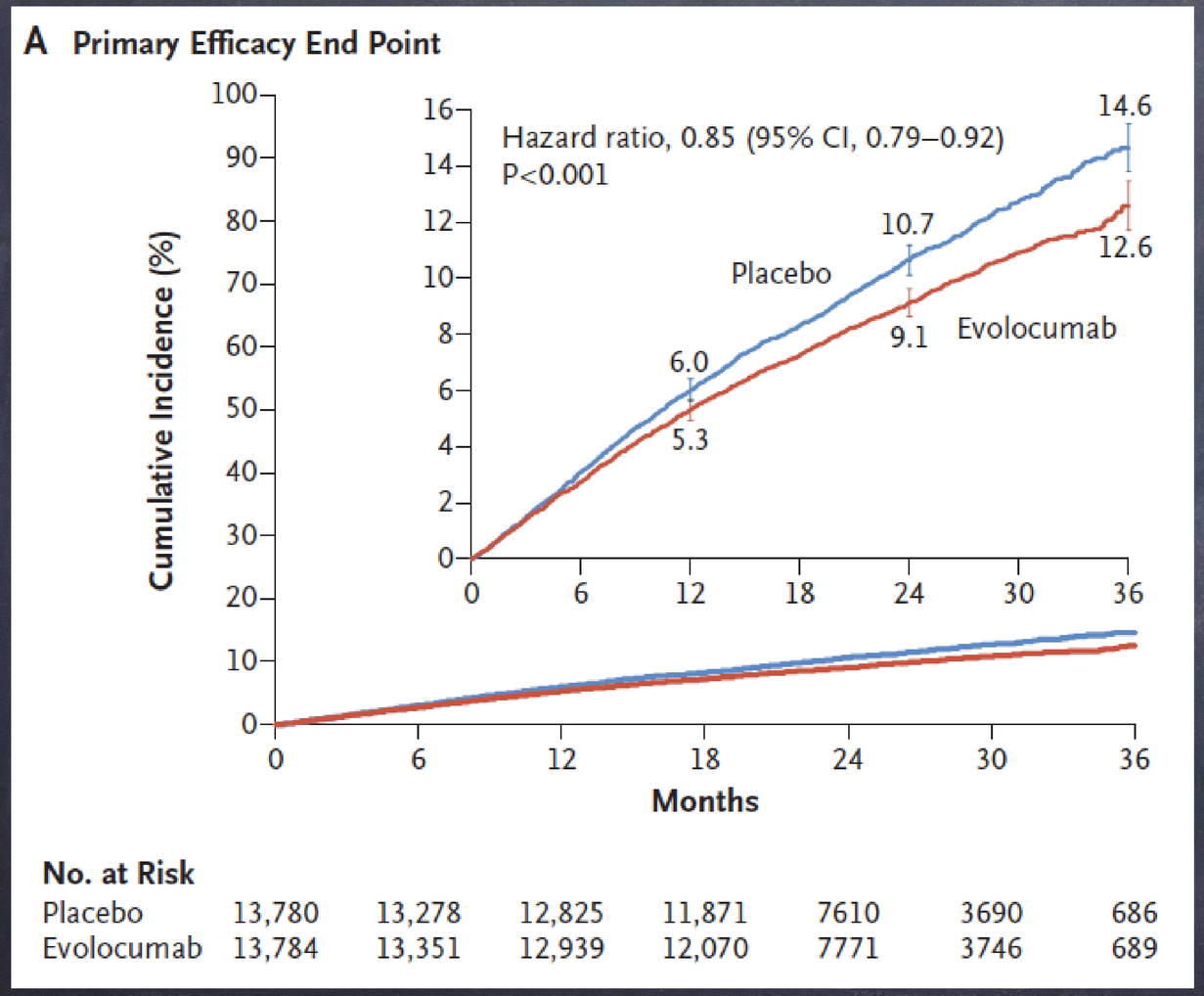
Cardiovascular risk factors		
Hypertension — no./total no. (%)	11,045/13,784 (80.1)	11,039/13,779 (80.1)
Diabetes mellitus — no. (%)	5,054 (36.7)	5,027 (36.5)
Current cigarette use — no./total no. (%)	3854/13,783 (28.0)	3923/13,779 (28.5)
Statin use — no. (%)§		
High intensity	9,585 (69.5)	9,518 (69.1)
Moderate intensity	4,161 (30.2)	4,231 (30.7)
Low intensity, unknown intensity, or no data	38 (0.3)	31 (0.2)
Ezetimibe — no. (%)	726 (5.3)	714 (5.2)
Other cardiovascular medications — no./total no. (%)		
Aspirin, $P2Y_{12}$ inhibitor, or both	12,766/13,772 (92.7)	12,666/13,767 (92.0)
Beta-blocker	10,441/13,772 (75.8)	10,374/13,767 (75.4)
ACE inhibitor or ARB, aldosterone antagonist, or both	10,803/13,772 (78.4)	10,730/13,767 (77.9)
Median lipid measures (IQR)		
LDL cholesterol — mg/dl	92 (80–109)	92 (80–109)
Total cholesterol — mg/dl	168 (151–188)	168 (151–189)
HDL cholesterol — mg/dl	44 (37–53)	44 (37–53)
Triglycerides — mg/dl	134 (101–183)	133 (99–181)
Lipoprotein(a) — nmol/liter	37 (13–166)	37 (13–164)

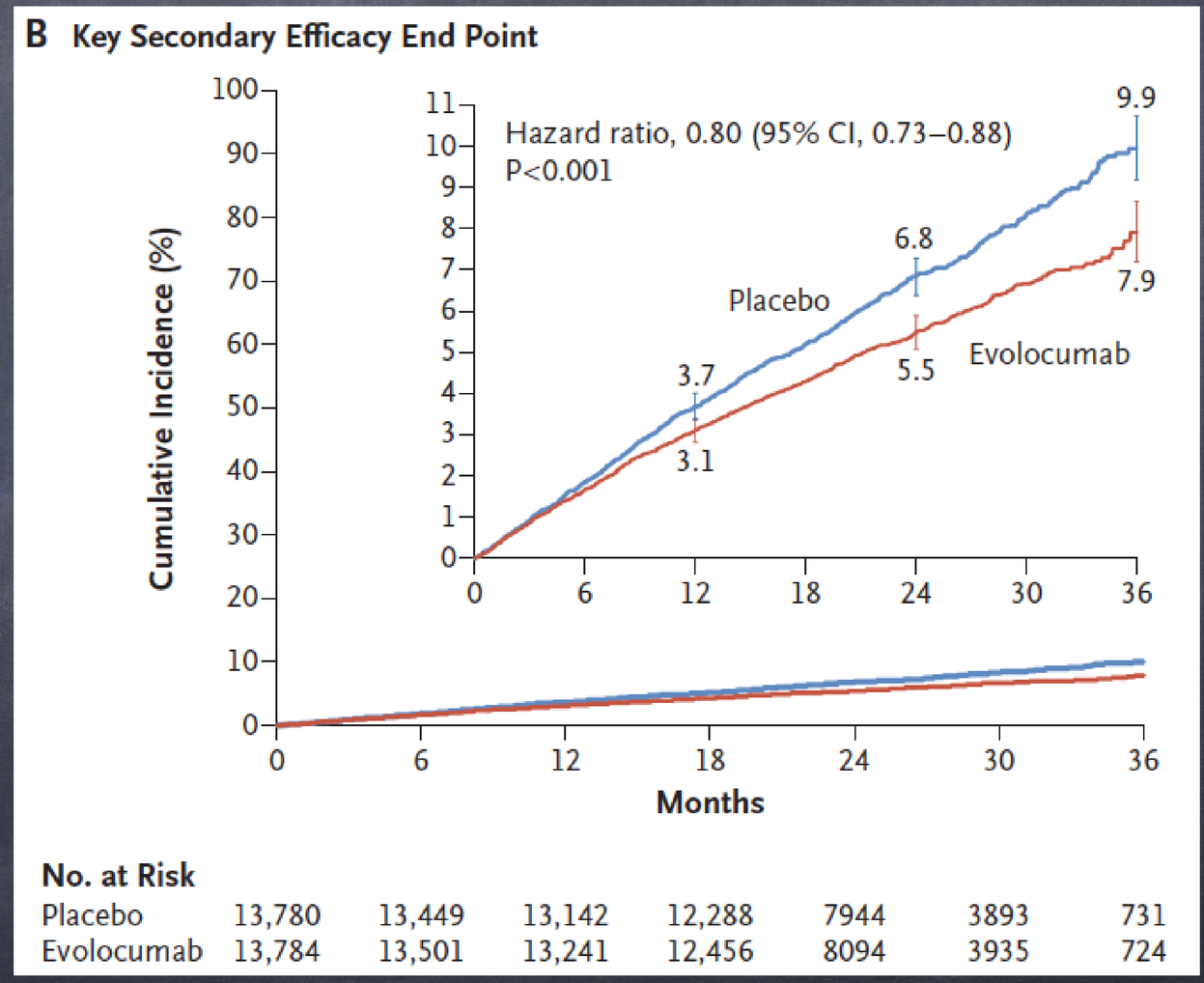
Efficacy in reducing LDL

- Median LDL (baseline) = 2.4 mmol/L
- After therapy
  - Median LDL = 0.78 mmol/L (absolute reduction of 1.45 mmol/L)
  - non-HDL = ↓ 52%
  - apoB levels = ↓ 49%
  - HDL = ↑ 8.4%



Endpoints


A Primary Efficacy End Point
Cumulative Incidence (%)
Hazard ratio, 0.85 (95% CI, 0.79–0.92)
P<0.001
Placebo
Evolocumab
14.6
12.6
10.7
9.1
6.0
5.3
Months
No. at Risk
Placebo 13,780 13,278 12,825 11,871 7610 3690 686
Evolocumab 13,784 13,351 12,939 12,070 7771 3746 689


B Key Secondary Efficacy End Point
Cumulative Incidence (%)
Hazard ratio, 0.80 (95% CI, 0.73–0.88)
P<0.001
Placebo
Evolocumab
9.9
7.9
6.8
5.5
3.7
3.1
Months
No. at Risk
Placebo 13,780 13,449 13,142 12,288 7944 3893 731
Evolocumab 13,784 13,501 13,241 12,456 8094 3935 724

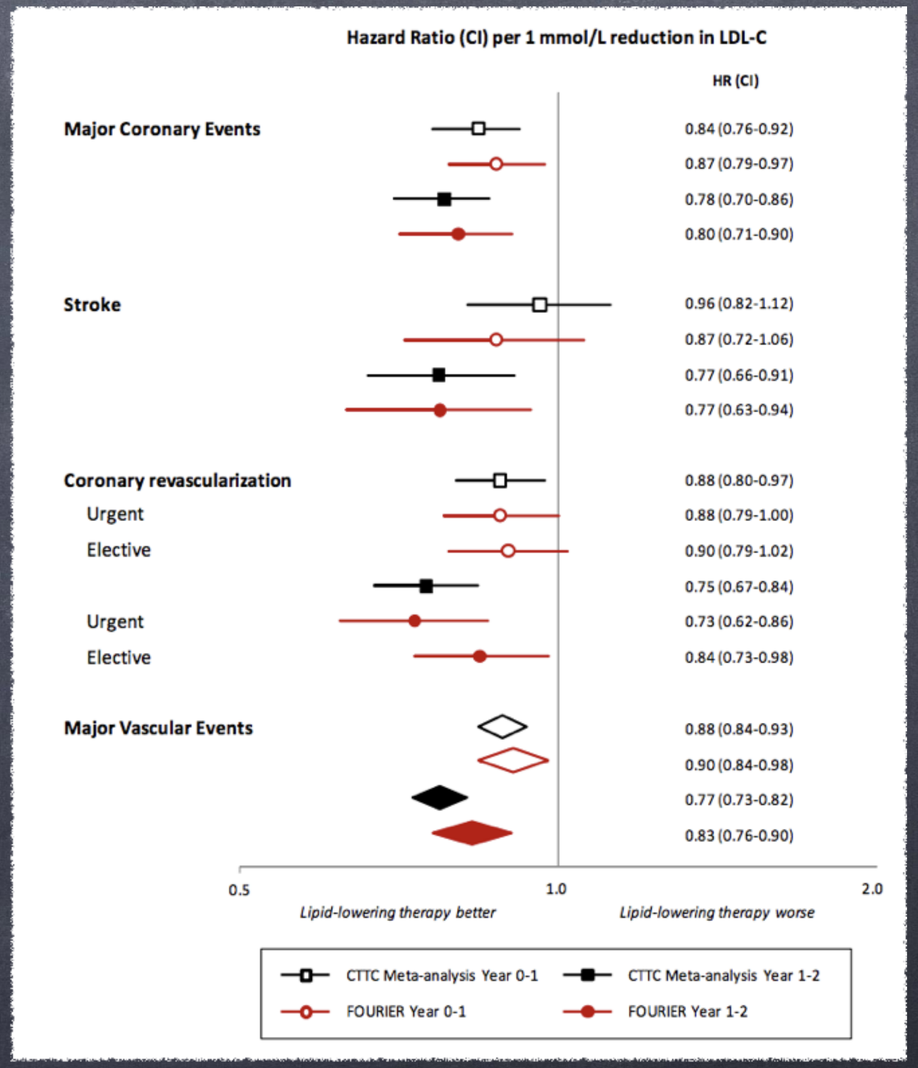
Outcome	Evolocumab (N=13,784)	Placebo (N=13,780)	Hazard Ratio (95% CI)	P Value*
	no. of patients (%)			
Primary end point: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization	1344 (9.8)	1563 (11.3)	0.85 (0.79–0.92)	<0.001
Key secondary end point: cardiovascular death, myocardial infarction, or stroke	816 (5.9)	1013 (7.4)	0.80 (0.73–0.88)	<0.001
Other end points				
Cardiovascular death	251 (1.8)	240 (1.7)	1.05 (0.88–1.25)	0.62
Due to acute myocardial infarction	25 (0.18)	30 (0.22)	0.84 (0.49–1.42)	
Due to stroke	31 (0.22)	33 (0.24)	0.94 (0.58–1.54)	
Other cardiovascular death	195 (1.4)	177 (1.3)	1.10 (0.90–1.35)	
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91–1.19)	0.54
Myocardial infarction	468 (3.4)	639 (4.6)	0.73 (0.65–0.82)	<0.001
Hospitalization for unstable angina	236 (1.7)	239 (1.7)	0.99 (0.82–1.18)	0.89
Stroke	207 (1.5)	262 (1.9)	0.79 (0.66–0.95)	0.01
Ischemic	171 (1.2)	226 (1.6)	0.75 (0.62–0.92)	
Hemorrhagic	29 (0.21)	25 (0.18)	1.16 (0.68–1.98)	
Unknown	13 (0.09)	14 (0.10)	0.93 (0.44–1.97)	
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71–0.86)	<0.001
Urgent	403 (2.9)	547 (4.0)	0.73 (0.64–0.83)	
Elective	420 (3.0)	504 (3.7)	0.83 (0.73–0.95)	
Cardiovascular death or hospitalization for worsening heart failure	402 (2.9)	408 (3.0)	0.98 (0.86–1.13)	0.82
Ischemic stroke or transient ischemic attack	229 (1.7)	295 (2.1)	0.77 (0.65–0.92)	0.003
CTTC composite end point†	1271 (9.2)	1512 (11.0)	0.83 (0.77–0.90)	<0.001

Side Effects

- No muscle-related events/intolerance
- **Risk of new-onset DM?**
- Neurocognitive impairment
  - Amnesia (<1%)) and memory impairment (<1%) seen in OSLER study
  - FOURIER substudy (EBBINGAUS study, NEJM, 2017) - no difference in cognitive function
- No induction of anti-drug/anti-neutralising antibodies (this side effect was seen with another drug, Bococizumab)

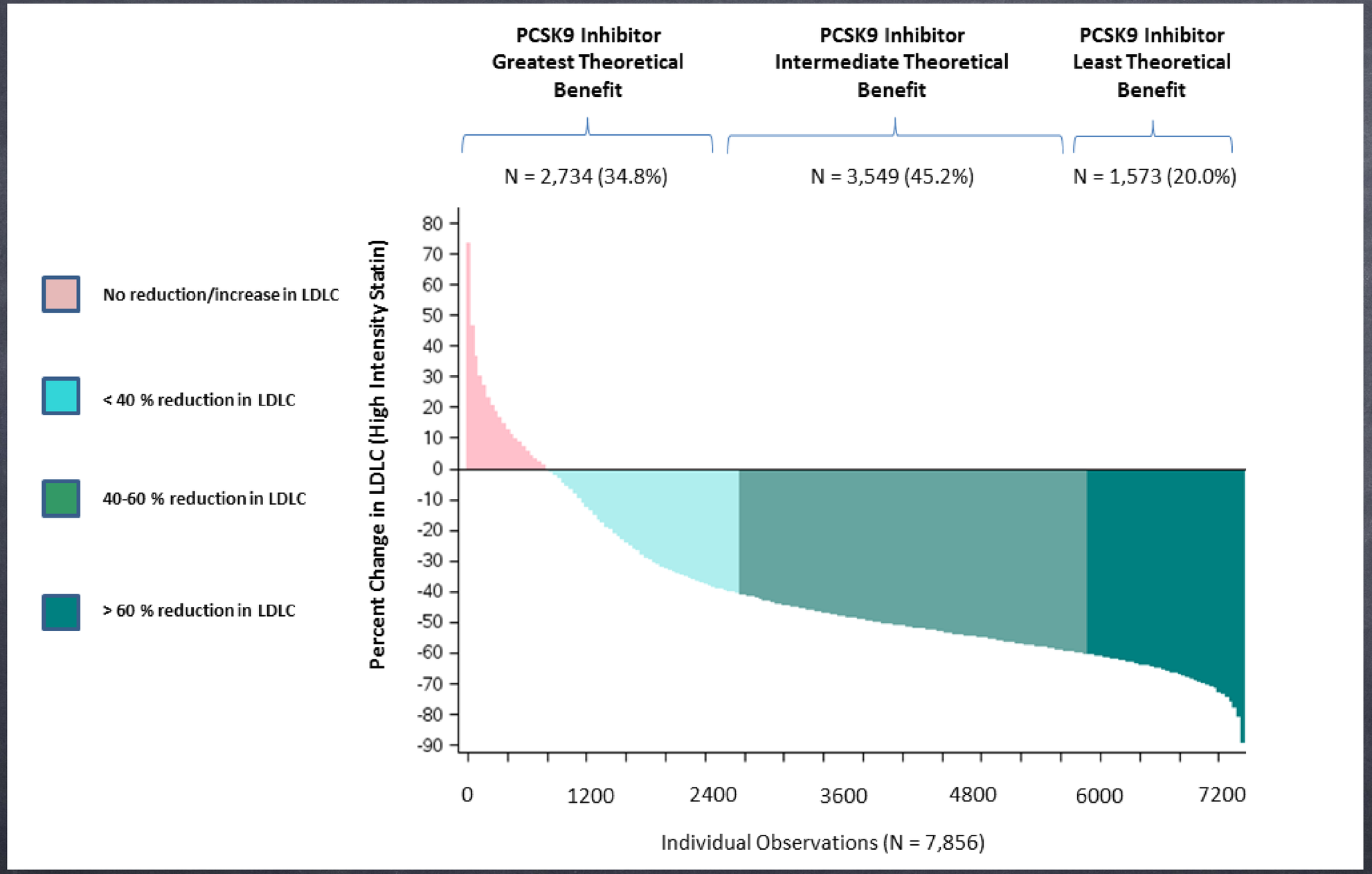
Comparison of benefit with statins

- **Statins reduce CV deaths by 20% per mmol/L LDL reduction irrespective of starting cholesterol** (CTT Collaboration)
- Similar benefit seen with Evolocumab therapy - incremental benefit evident after 1 year
- Mendelian randomisation study - variants in PCSK9 & HMGCR associated with protective effects wrt atherosclerosis but adverse effects wrt diabetes



Limitations

- Median follow-up = 2.2 years; significantly lower than other statin trials
- NNT: 74 patients need to be treated for 2 years to prevent 1 MACE
- ?Effect on hsCRP - meta-analysis of PCSK9 inhibitors suggest there is no effect on high sensitivity C-reactive protein (hsCRP) levels.
  - JUPITER trial (normal LDL but high hsCRP) - >>20% reductions in CV death with rousouvastatin as compared to placebo
- Cost of drug/year - $5850
  Cost of statin/year - “cheap as chips”



Ridker P, Mora S, Rose, L. Eur Heart J, 2016

Conclusion

1) PCSK9 inhibitors should be used as second-line therapy in patients who are intolerant to statin (at least 2 different statins) or receive little therapeutic benefit despite high-dose statin

2) 2nd line use in patients with FH or in patients with familial combined hyperlipidaemia with significant FHx of CV events.