

FOURIER

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

Focus on Cerebrovascular Disease

TR Pedersen*, RP Giugliano, PS Sever, AC Keech, M.S. Murphy,
and MS Sabatine,

for the FOURIER Steering Committee & Investigators

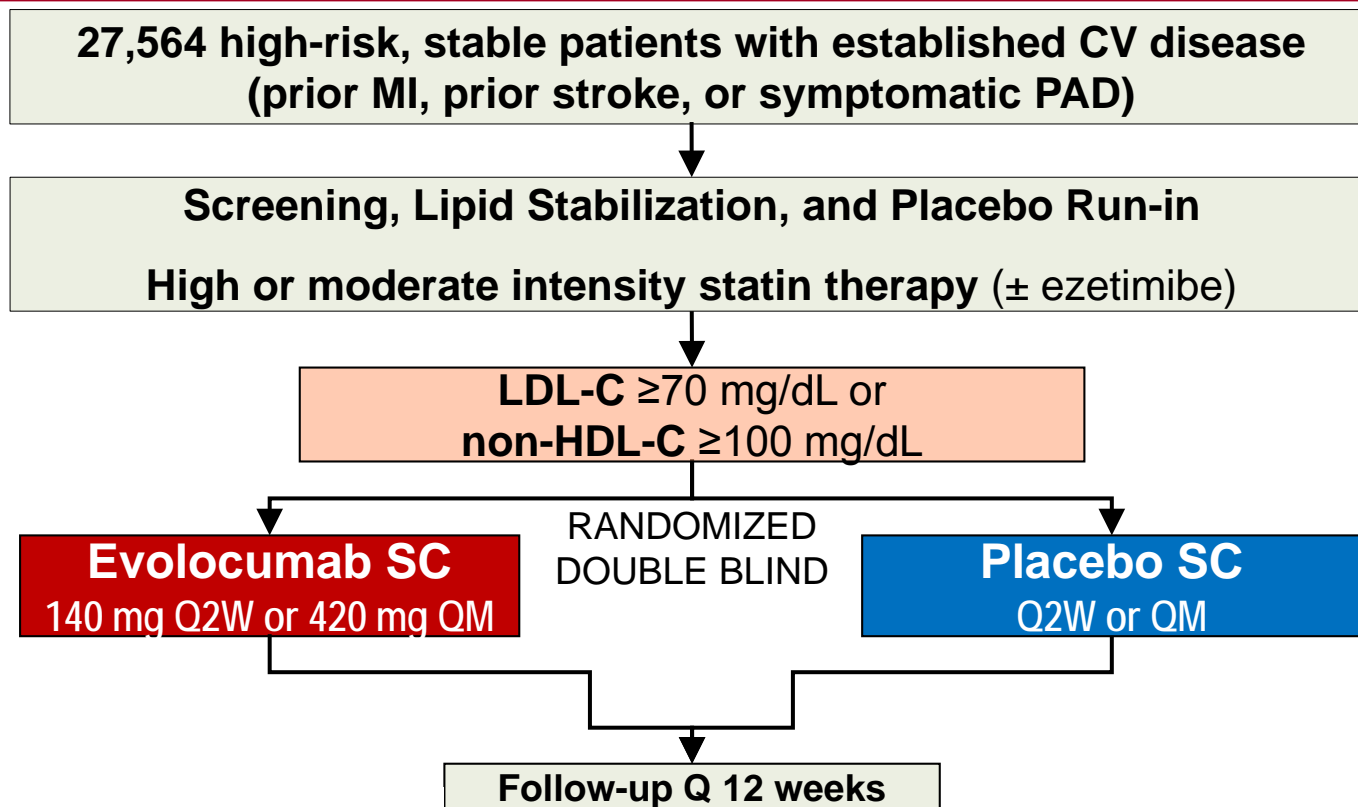
* : Oslo University Hospital, Center For Preventive Medicine

FOURIER Study:

- Financed by Amgen
- Data collection by Amgen
- Endpoint adjudication

and Data analysis by TIMI : an Academic Research Organization of Brigham and Women's Hospital, and Harvard Medical School

Trial Design

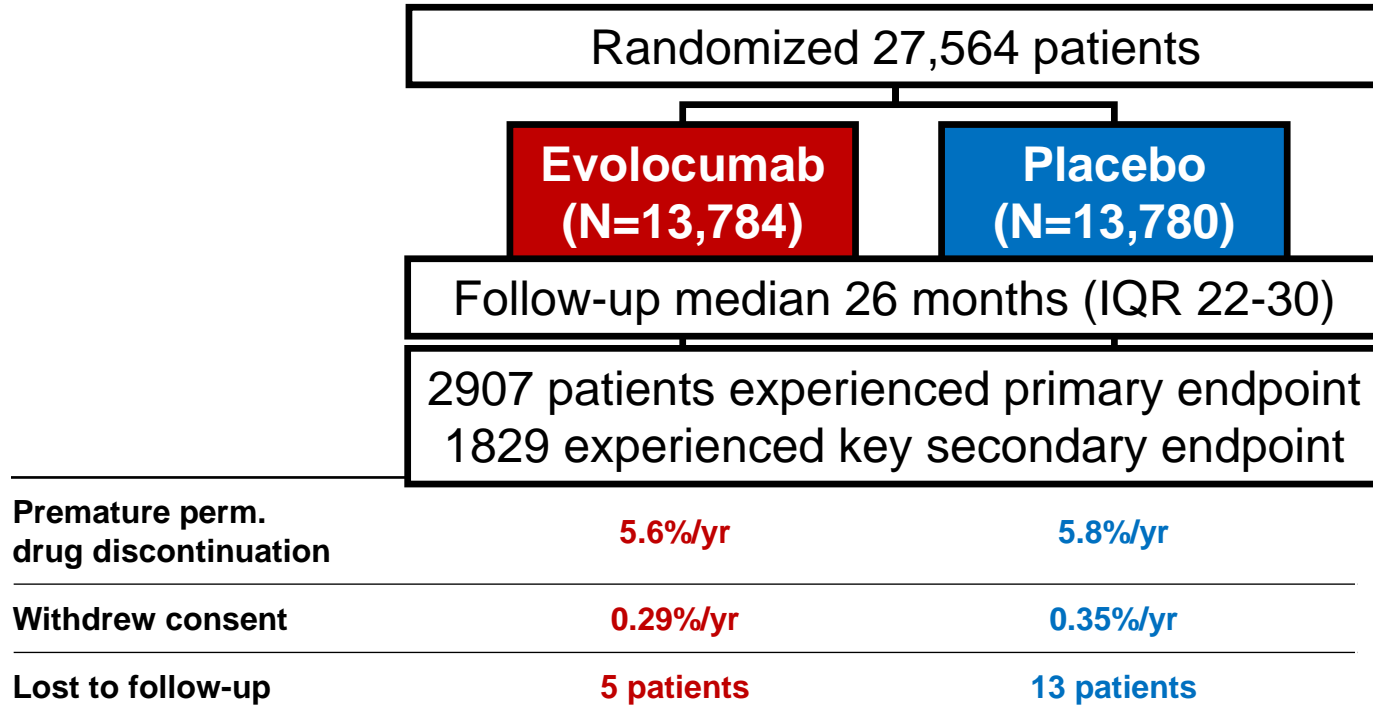


Endpoints



- **Efficacy**
 - **Primary: CV death, MI, all stroke, hosp. for UA, or coronary revasc**
 - **Key secondary: CV death, MI or all stroke**
- **Safety**
 - **AEs/SAEs**
 - **Events of interest incl. muscle-related, new-onset diabetes, neurocognitive**
 - **Development of anti-evolocumab Ab (binding and neutralizing)**
- **TIMI Clinical Events Committee (CEC)**
 - **Adjudicated all efficacy endpoints & new-onset diabetes**
 - **Members unaware of treatment assignment & lipid levels**

Follow-up



Ascertainment for primary endpoint was complete for 99.5% of potential patient-years of follow up

Baseline Characteristics

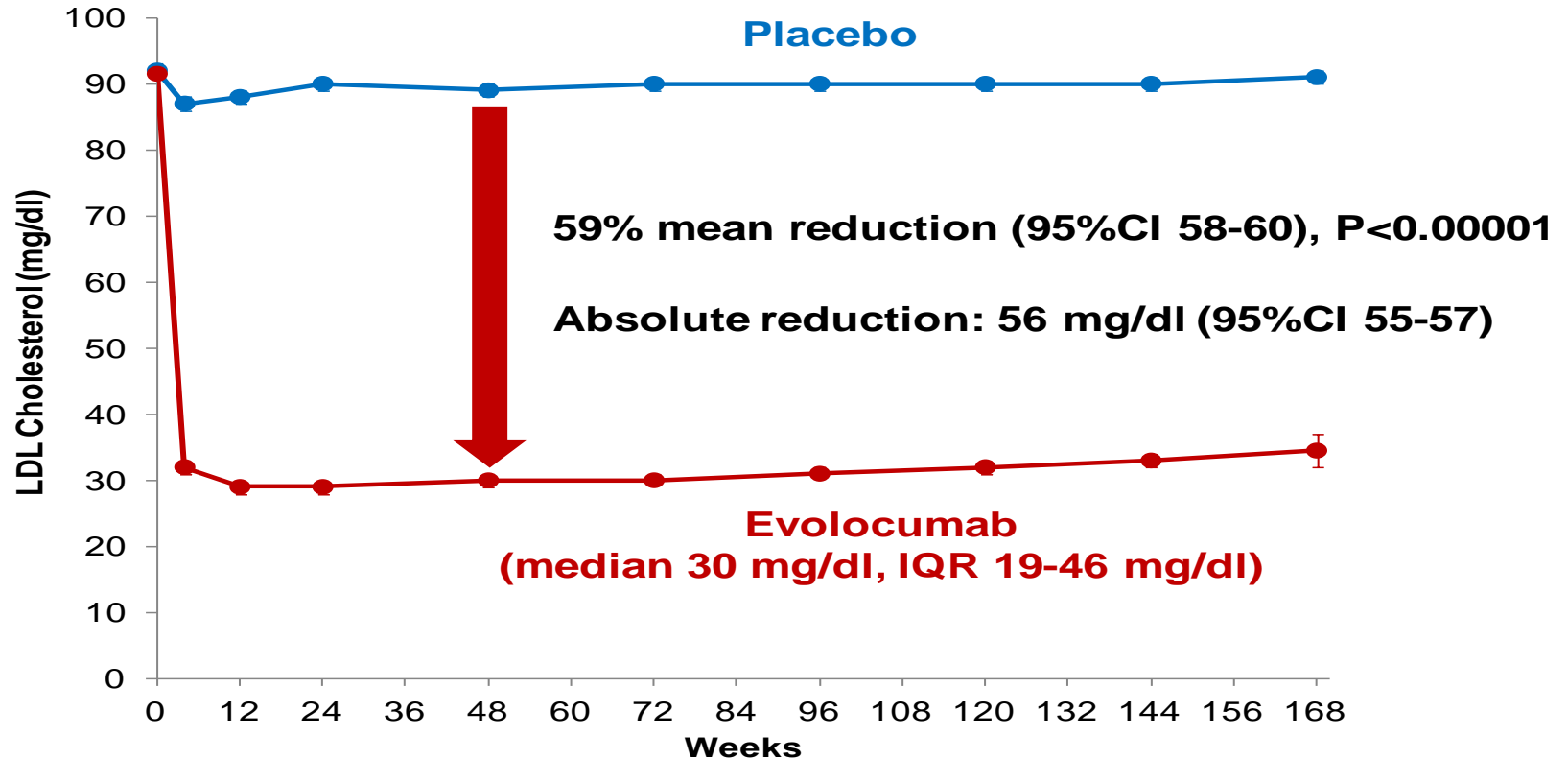


Characteristic	Value
Age, years, mean (SD)	63 (9)
Male sex (%)	75
Type of cardiovascular disease (%)	
Myocardial infarction	81
Stroke (non-hemorrhagic)	19
Symptomatic PAD	13
Cardiovascular risk factor (%)	
Hypertension	80
Diabetes mellitus	37
Current cigarette use	28

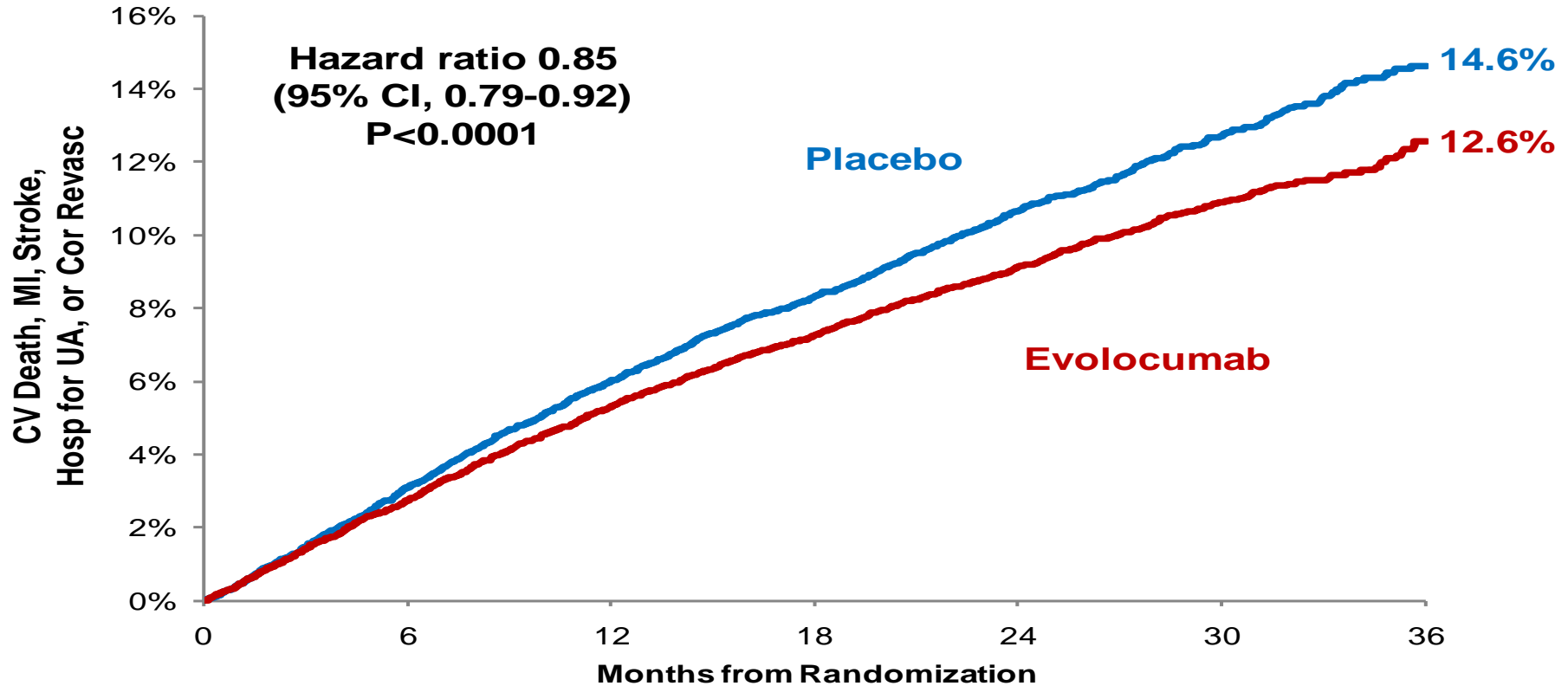
} Median time from most recent event ~3 yrs

Pooled data; no differences between treatment arms

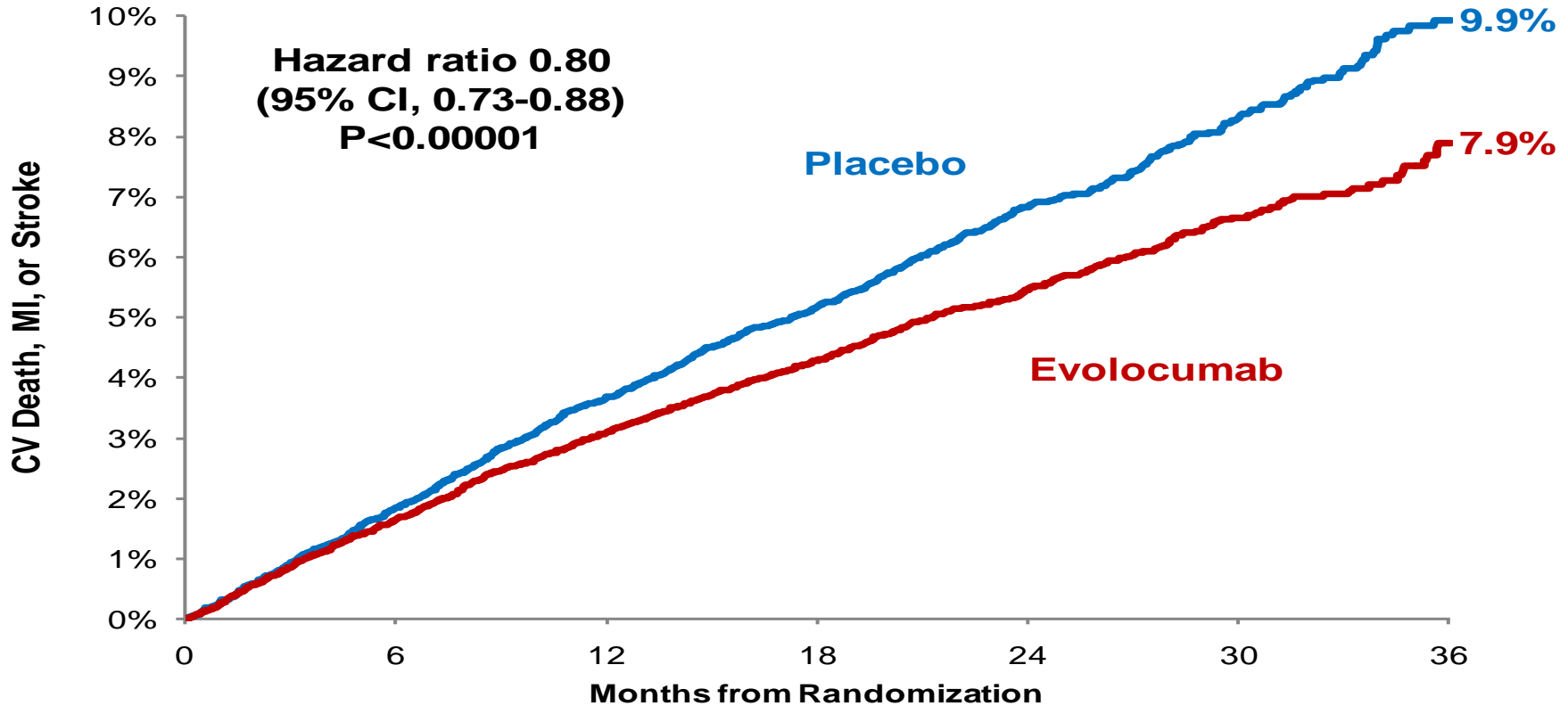
LDL-Cholesterol



Primary Endpoint Entire Study Population



Key Secondary Endpoint Entire Study Population

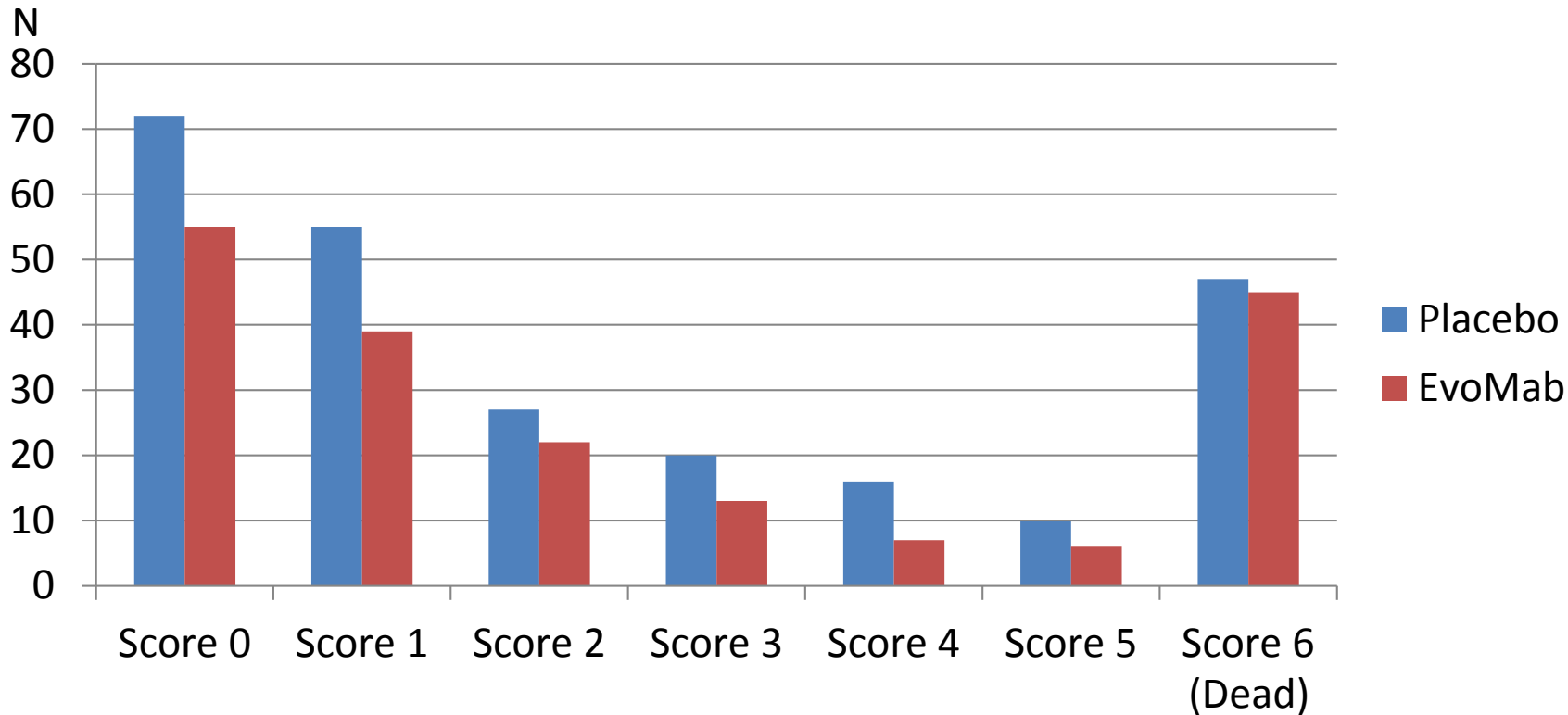


Types of CV Outcomes

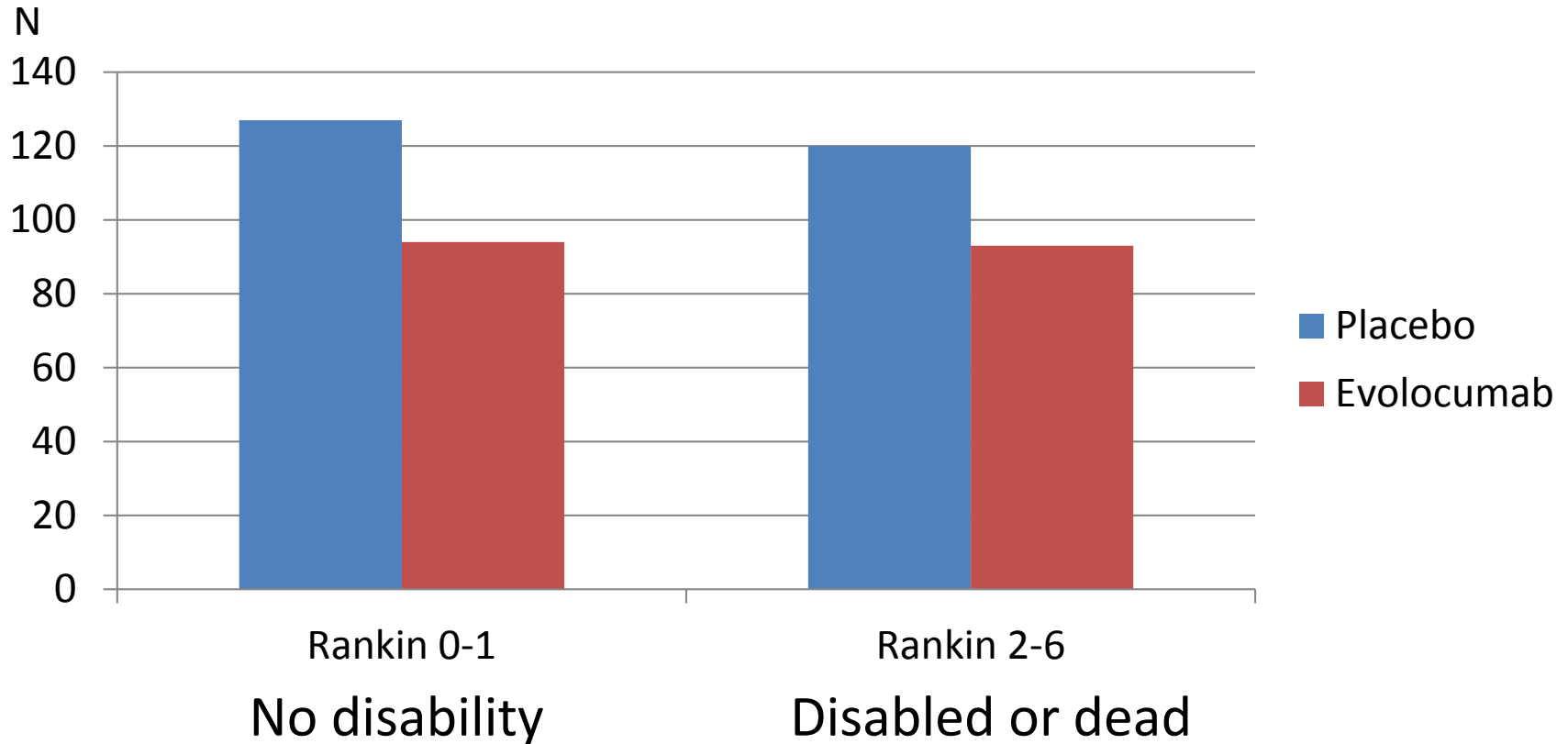


Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	<i>3-yr Kaplan-Meier rate</i>		
CV death, MI, or stroke	7.9	9.9	0.80 (0.73-0.88)
Cardiovascular death	2.5	2.4	1.05 (0.88-1.25)
Death due to acute MI	0.26	0.32	0.84 (0.49-1.42)
Death due to stroke	0.29	0.30	0.94 (0.58-1.54)
Other CV death	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)

Degree of Disability Post-Stroke (modified Rankin Score) among Patients with Stroke Endpoint



Stroke Outcome



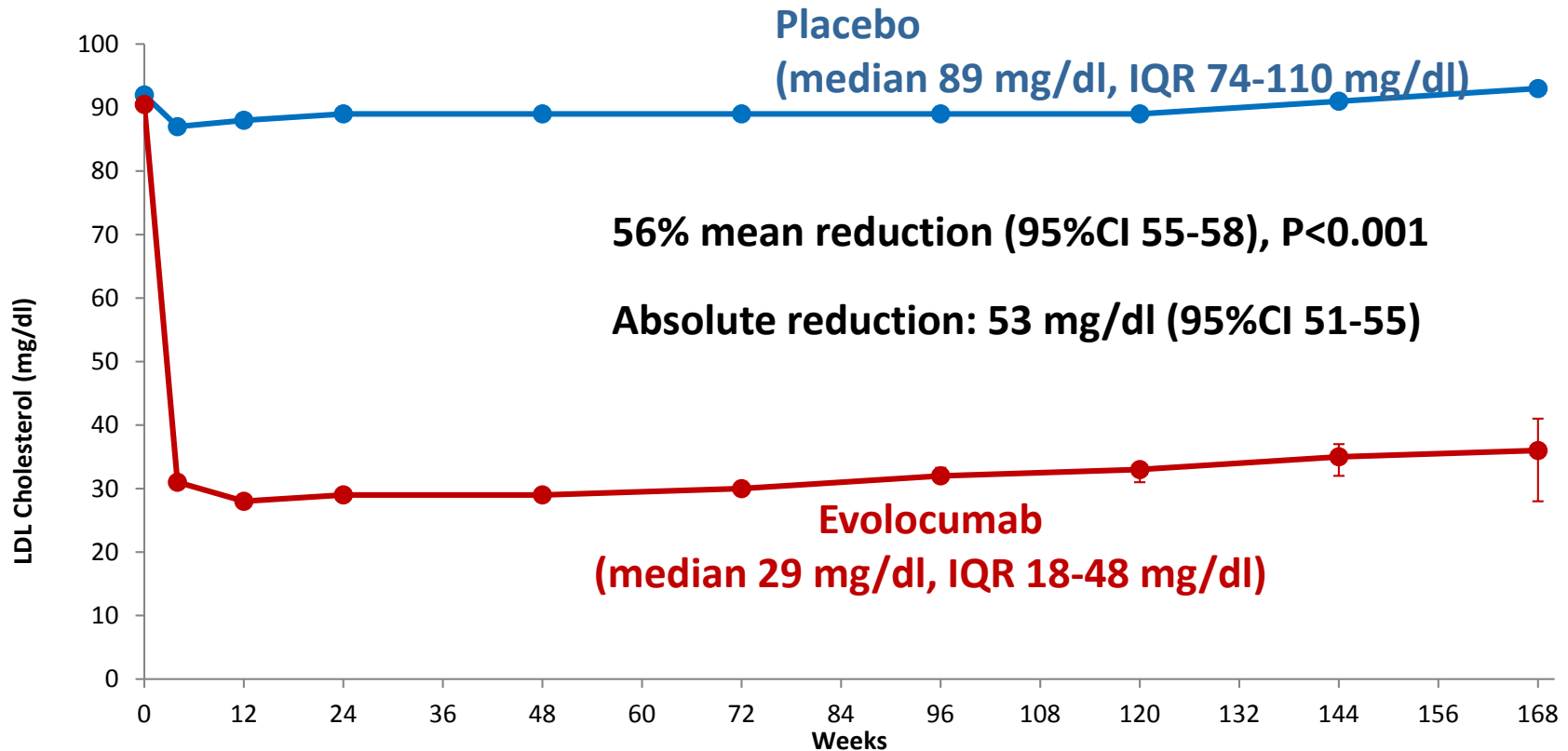
Baseline Characteristics

Characteristic	History of stroke N= 5 337 %	No history of stroke N= 22 227 %
Male	66	78
Age ≥ 65 years	50	43
Age ≥ 75 years	12	9
History of prior MI	31	93
Hypertension	87	79
Diabetes	42	35
Current smoker	25	29
Atrial fibrillation	14	7
Time from qualifying event to randomization < 1 year	27	26

Baseline Characteristics

Characteristic	History of stroke N= 5 337	No history of stroke N= 22 227
	Mean (SD)	Mean (SD)
LDL-C (mg/dl)	97.5 (28.4)	97.8 (27.9)
HDL-C (mg/dl)	47.8 (13.4)	45.3 (12.3)
Triglycerides (mg/dl)	146.5 (68.9)	150.3 (70.9)
Apo-B (mg/dl)	84.7 (21.1)	86.2 (20.9)
Fasting glucose (mg/dl)	118.5 (47.0)	115.5 (42.0)

Hx Stroke Cohort: LDL Cholesterol



Placebo

(median 89 mg/dl, IQR 74-110 mg/dl)

56% mean reduction (95%CI 55-58), P<0.001

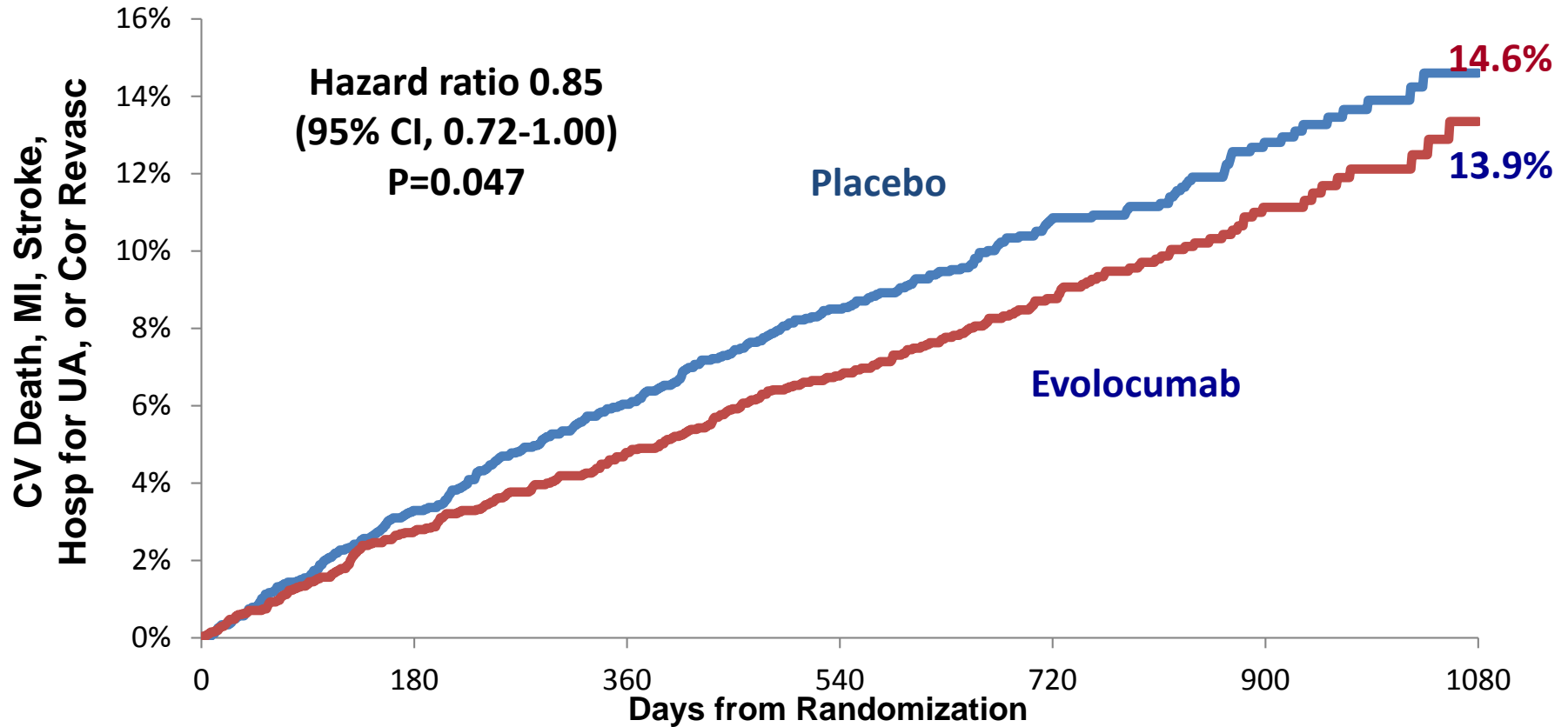
Absolute reduction: 53 mg/dl (95%CI 51-55)

Evolocumab

(median 29 mg/dl, IQR 18-48 mg/dl)

* Reduction at 48 week timepoint

Hx Stroke Cohort: Primary Endpoint



Endpoint Events



Patients With Hx Stroke (n= 5337)

Event	Evolocumab n	Placebo n	Hazard ratio*
Primary endpoint	259	300	0.85 (0.72 – 1.00)
Key 2nd. endpoint	202	224	0.89 (0.74 – 1.08)
CV death	73	65	1.11 (0.80 – 1.56)
Acute MI	75	100	0.74 (0.55 – 1.00)
Stroke	95	105	0.90 (0.68 – 1.19)
Coronary revasc.	89	128	0.68 (0.52 – 0.90)

*P for interaction = NS for all endpoint results in patients with/without stroke

Safety in Cohort With Stroke

Event	Evolocumab n	Placebo n	p-value
Neurocognitive AE	53	53	0.942
Headache	93	115	0.097
Arthralgia	121	99	0.159
Fatigue	65	52	0.255
New onset diabetes	114	106	0.640
AST or ALT >3X ULN	36	44	0.339
Cataract	55	44	0.254

Conclusion

Patients with previous history of stroke:
Effect of evolcumab is similar to that for patients
with other cardiovascular disease

