Studie **FOURIER**

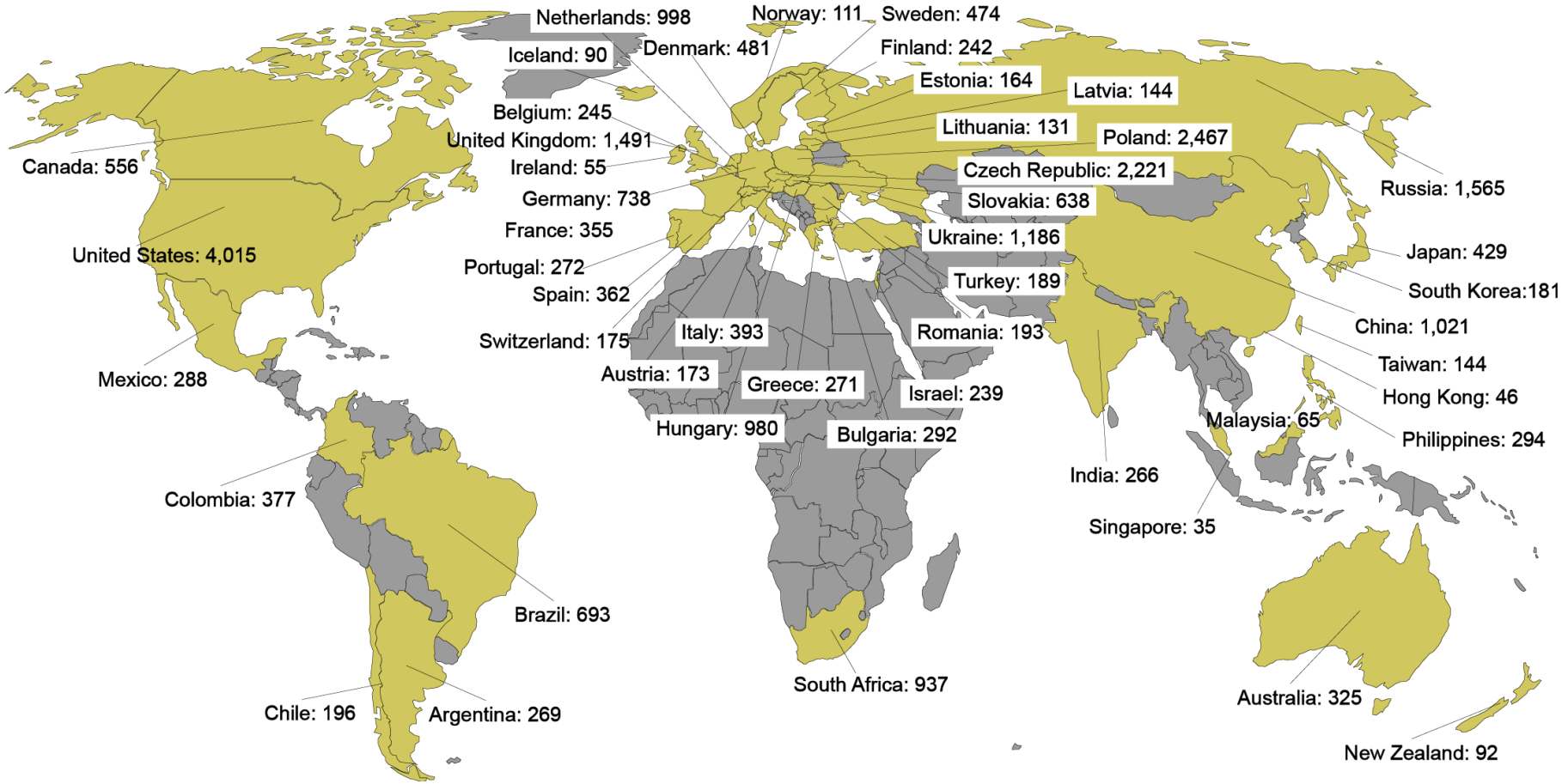
největší událost kongresu American College of Cardiology?

17.3.2017,Washington D.C.

Celosvětový nábor pacientů

27,564 patients randomized at 1242 sites
in 49 countries between 2/2013 – 6/2015

CZ 2221 pacientů



Charakteristika populace studie

- FOURIER: **F**urther cardiovascular **OU**tcomes **R**esearch with PCSK9 **I**nhibition in subjects with **E**levated **R**isk

27,564 patients aged 40–85 years

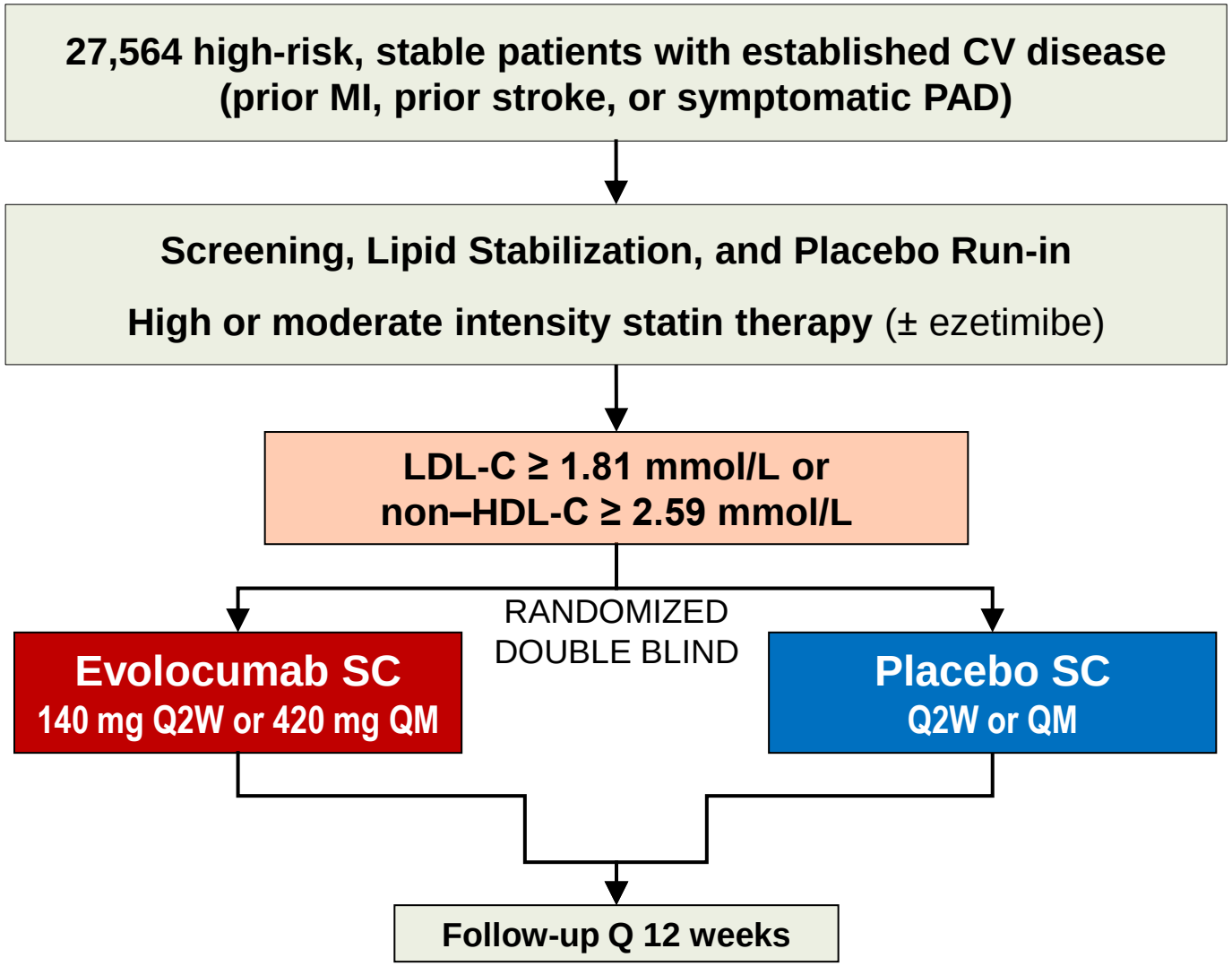
Clinically evident CV disease
- History of myocardial infarction
- Nonhemorrhagic stroke
- Symptomatic peripheral artery disease

Plus additional risk factors

Fasting LDL-C ≥ 1.81 mmol/L or non–HDL-C ≥ 2.59 mmol/L after > 2 weeks of optimized stable lipid-lowering therapy*

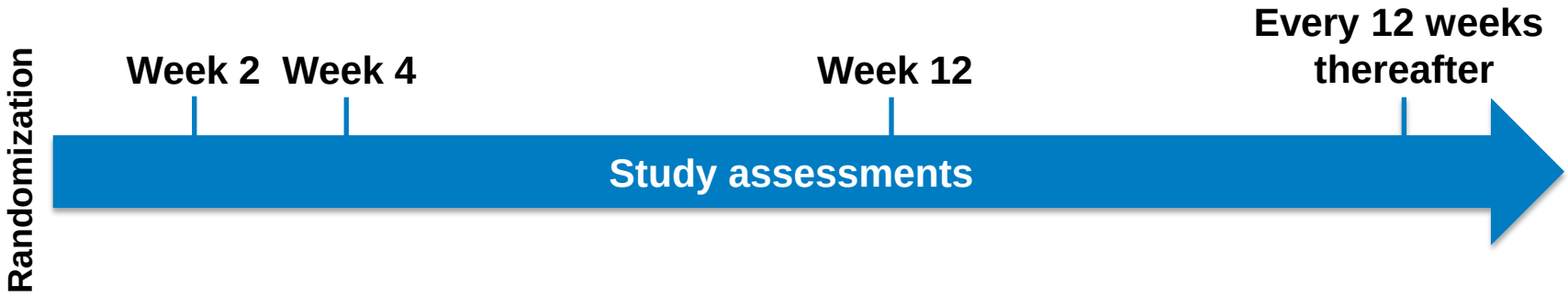
*Ideally a high-intensity statin, but must be at least atorvastatin 20 mg daily or equivalent
CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.
Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Design studie



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

FOURIER: Průběh studie



- All patients will be assessed at follow-up visits for:
  - AEs
  - Potential endpoint events
  - Blood and urine samples for central laboratory testing
- Central laboratory results of lipid panels are blinded
  - However, if a patient's LDL-C increases by 25% and 0.52 mmol/L from prior visit, the study site is notified to instruct the patient on compliance

AE, adverse event; LDL-C, low-density lipoprotein cholesterol.
Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.

Characteristika souboru

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

KV rizikové faktory

Characteristics	Evolocumab (N = 13,784)	Placebo (N = 13,780)
Type of atherosclerosis* – n (%)		
Myocardial infarction	11,145 (80.9)	11,206 (81.3)
Time from most recent prior MI – yr (IQR)	3.4 (1.0-7.4)	3.3 (0.9-7.7)
Non-hemorrhagic stroke	2,686 (19.5)	2,651 (19.2)
Time from most recent prior stroke – yr (IQR)	3.2 (1.1-7.1)	3.3 (1.1-7.3)
Peripheral artery disease – n (%)	1,858 (13.5)	1,784 (12.9)
Cardiovascular risk factors		
Hypertension – n/total n (%)	11,045/13,784 (80.1)	11,039/13,779 (80.1)
Diabetes mellitus – n (%)	5,054 (36.7)	5,027 (36.5)
Current cigarette use – n/total n (%)	3,854/13,783 (28.0)	3,923/13,779 (28.5)

*Patients could have more than one type of atherosclerosis.
CV = cardiovascular; MI = myocardial infarction.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Note: mmol/L version

Lipidy a hypolipidemická léčba

Characteristics	Evolocumab (N = 13,784)	Placebo (N = 13,780)
Statin use* – n (%)		
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 – n (%)	726 (5.3)	714 (5.2)
Other cardiovascular medications – n/total n (%)		
Aspirin and/or $P2Y_{12}$ inhibitor	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 and/or aldosterone antagonist	10,803/13,772 (78.4)	10,730/13,767 (77.9)
Lipid measures - Median (IQR) – mmol/L		
LDL cholesterol – mmol/L	2.38 (2.07, 2.82)	2.38 (2.07, 2.82)
Total cholesterol – mmol/L	4.34 (3.90, 4.86)	4.34 (3.90, 4.89)
HDL cholesterol – mmol/L	1.14 (0.96, 1.37)	1.14 (0.96, 1.37)
Triglycerides – mmol/L	1.51 (1.14, 2.07)	1.50 (1.12, 2.04)
Lp(a) - nmol/L	37 (13, 166)	37 (13, 164)

*Statin intensity was categorized per the ACC/AHA Guidelines. Note, that in some countries where FOURIER was conducted, higher statin doses are not approved. HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a) = Lipoprotein(a); IQR = Inter-quartile range

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664
Malinowski HJ, et all. *J Clin Pharmacol*. 2008;48:900-908

Cílové ukazatele

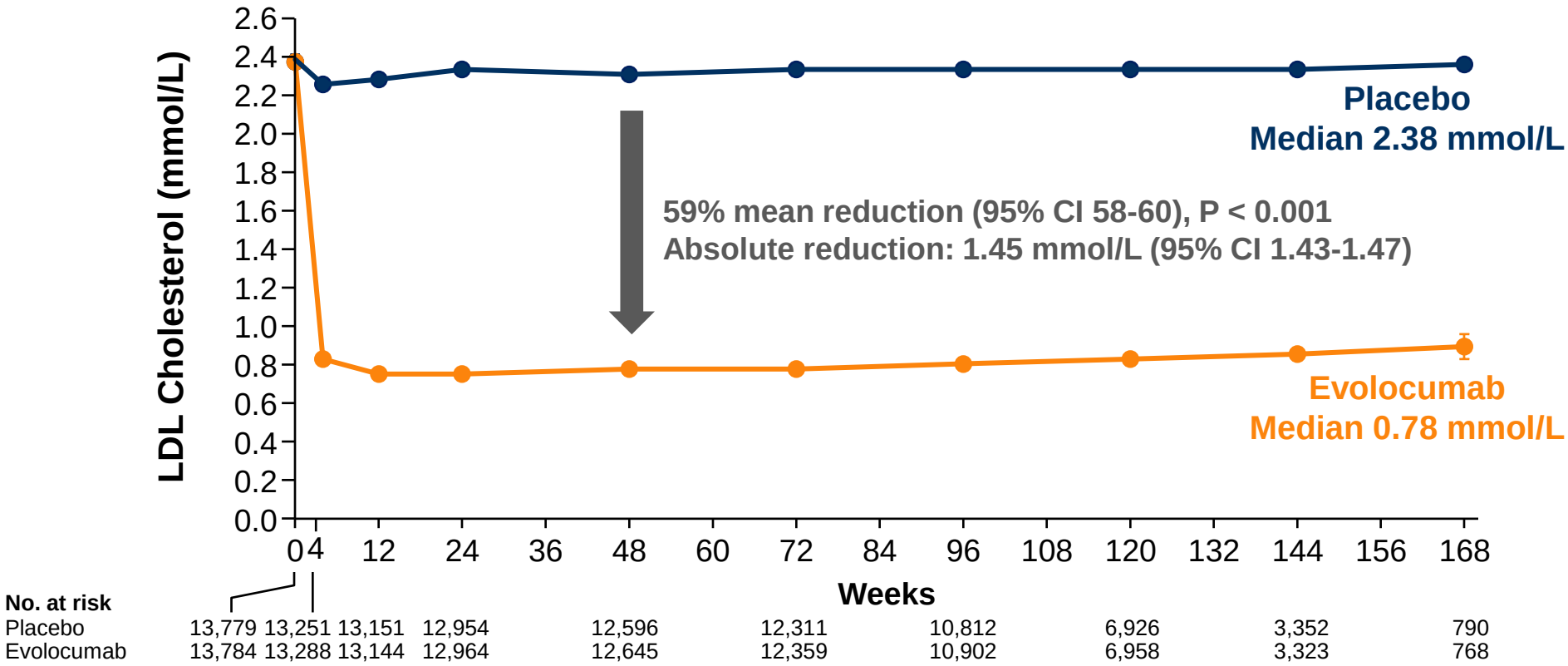
- **Účinnost**
- **Primary: CV death, MI, stroke, hosp. for UA, or coronary revasc**
  - **Key secondary: CV death, MI or stroke**

- **Bezpečnost**
  - **AEs/SAEs**
  - **Events of interest incl. muscle-related, new-onset diabetes, neurocognitive**
  - **Development of anti-evolocumab Ab (binding and neutralizing)**

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

Výsledky

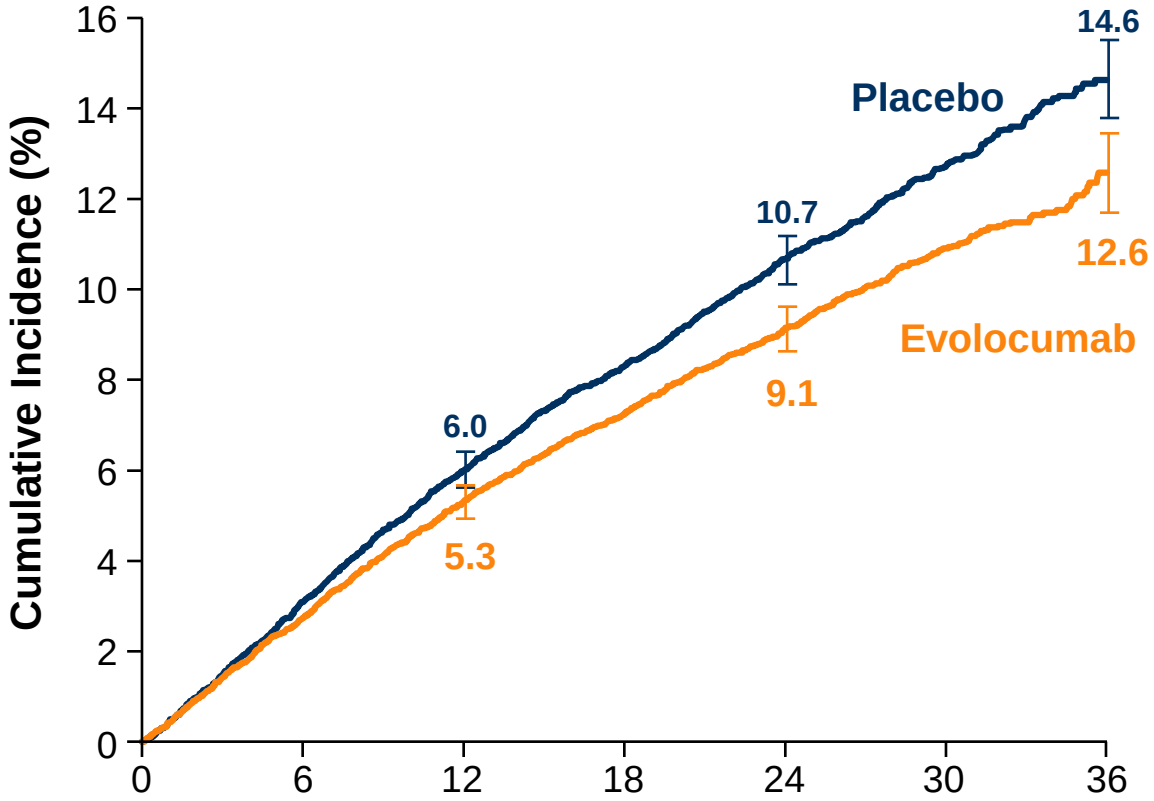
Medián LDL-C v čase:



LDL-C was significantly reduced in the evolocumab group (median: 0.78 mmol/L) including 42% who achieved levels ≤ 0.65 mmol/L vs < 0.1% in the placebo group

Data shown are median values with 95% confidence intervals in the two arms; ITT.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Primární cílový ukazatel: Composite of CV Death, MI, Stroke, Hospitalization for UA, or Coronary Revascularization



No. at Risk

Placebo	13,780	13,278	12,825	11,871	7,610	3,690	686
Evolocumab	13,784	13,351	12,939	12,070	7,771	3,746	689

HR 0.85 (95% CI 0.79 to 0.92); *P* < 0.001

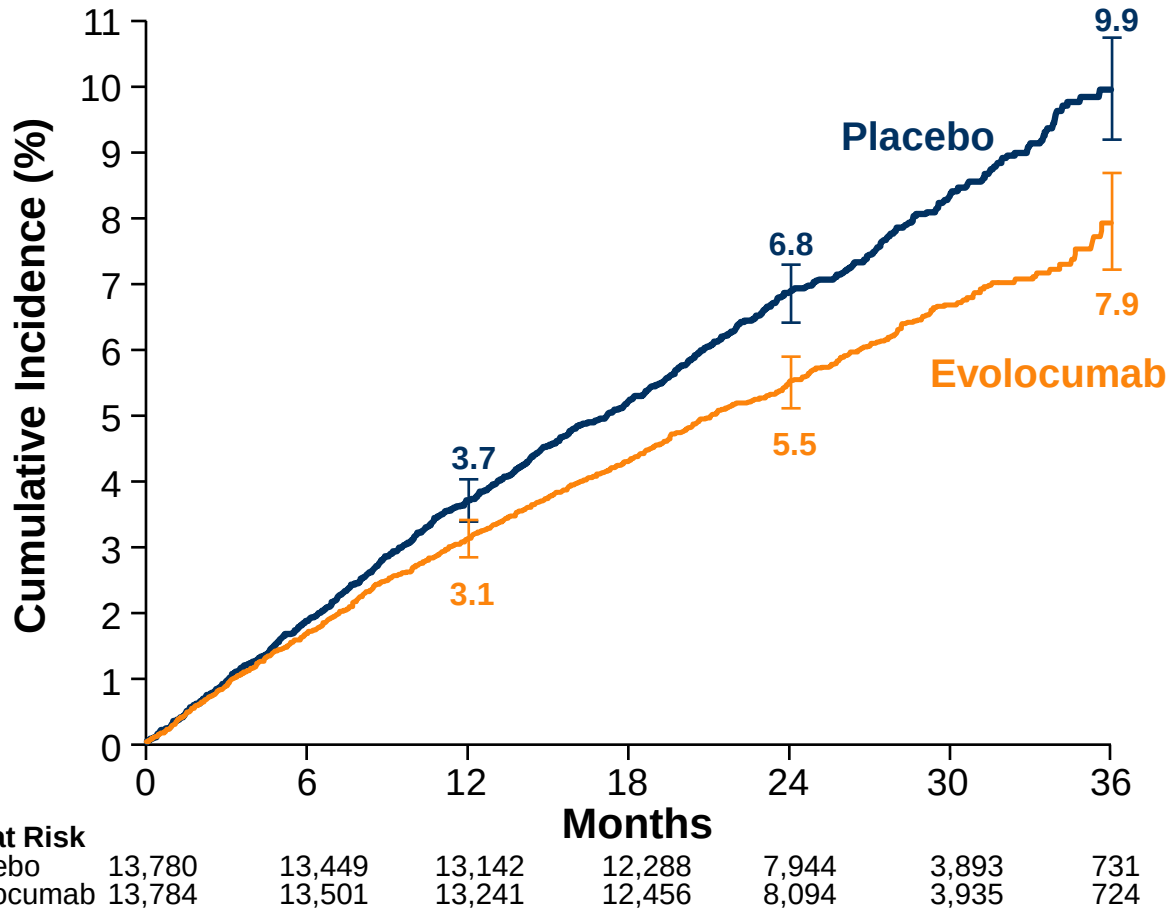
-15%

CV = Cardiovascular; MI = Myocardial infarction; UA = Unstable angina; HR = Hazard ratio

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Základní sekundární cílový ukazatel:

Composite of CV Death, MI, or Stroke



No. at Risk

Placebo	13,780	13,449	13,142	12,288	7,944	3,893	731
Evolocumab	13,784	13,501	13,241	12,456	8,094	3,935	724

HR 0.80 (95% CI 0.73 to 0.88); *P* < 0.001

-20%

CV = Cardiovascular; MI = Myocardial infarction; HR = Hazard ratio

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Analýza „endpointů“

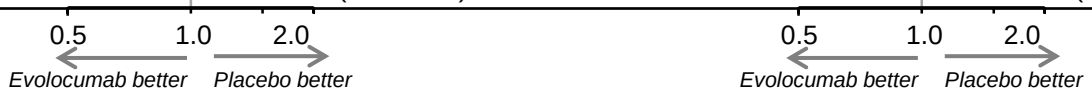
Outcome	Evolocumab (n = 13,784) n (%)	Placebo (n = 13,780) n (%)	HR (95% CI)	P-value‡
Primary endpoint*	1,344 (9.8)	1,563 (11.3)	0.85 (0.79-0.92)	<0.001
Key secondary endpoint†	816 (5.9)	1,013 (7.4)	0.80 (0.73-0.88)	<0.001
Other endpoints				
CV death	251 (1.8)	240 (1.7)	1.05 (0.88-1.25)	0.62
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91-1.19)	0.54
MI	468 (3.4)	639 (4.6)	0.73 (0.65-0.82)	<0.001
Hospitalization for UA	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
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71-0.86)	<0.001
CV Death or Hospitalization for Worsening Heart Failure	402 (2.9)	408 (3.0)	0.98 (0.86-1.13)	0.82
Ischemic stroke or TIA	229 (1.7)	295 (2.1)	0.77 (0.65-0.92)	0.003
CTTC composite endpoint**	1,271 (9.2)	1,512 (11.0)	0.83 (0.77-0.90)	<0.001

The primary endpoint was driven by reductions in MI, stroke, and coronary revascularization

*Time to CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, whichever occurs first †CV death, myocardial infarction, or stroke, whichever occurs first ‡Given the hierarchical nature of the statistical testing, the P values for the primary and key secondary endpoint should be considered statistically significant, whereas all other P values should be considered nominal.
**CTTC stands for Cholesterol Treatment Trialists Collaboration and the composite endpoint consists of coronary heart death, nonfatal MI, stroke, or coronary revascularization
MI = Myocardial infarction; UA = Unstable angina; TIA = Transient ischemic attack
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Analýza podskupin

		PRIMARY ENDPOINT: 3-yr KM rate (%)					KEY SECONDARY ENDPOINT: 3-yr KM rate (%)				
	Patients	Evo	Pbo	HR (95% CI)	HR (95% CI)	$P_{interaction}$	Evo	Pbo	HR (95% CI)	HR (95% CI)	$P_{interaction}$
OVERALL	27564	12.6	14.6		0.85 (0.79-0.92)		7.9	9.9		0.80 (0.73-0.88)	
Age						0.9					0.79
<65	15310	12.6	14.6		0.86 (0.78-0.94)		7.3	9.1		0.79 (0.69 -0.90)	
≥65	12254	12.6	14.6		0.85 (0.76-0.95)		8.7	10.9		0.81 (0.71 -0.92)	
Sex						0.48					0.44
Female	6769	9.9	12.5		0.81 (0.69-0.95)		6.5	9.2		0.74 (0.61 -0.90)	
Male	20795	13.5	15.3		0.86 (0.80-0.94)		8.4	10.2		0.81 (0.73 -0.90)	
Race						0.036					0.048
Caucasian	23458	12.7	14.4		0.88 (0.81-0.95)		7.8	9.6		0.83 (0.75-0.92)	
Non-Caucasian	4106	12.5	16.2		0.70 (0.57-0.86)		9.0	12.4		0.64 (0.50-0.81)	
Region						0.15					0.012
North America	4571	15.7	20.8		0.77 (0.66 -0.90)		8.6	13.5		0.62 (0.51-0.76)	
Europe	17335	11.9	13.1		0.91 (0.83 -1.00)		7.6	8.9		0.90 (0.80-1.01)	
Latin America	1823	14.9	14.3		0.85 (0.63-1.15)		11.3	10.8		0.85 (0.58-1.24)	
Asia/Pacific	3835	14.1	13.5		0.73 (0.58-0.91)		9.2	10.1		0.67 (0.51-0.88)	

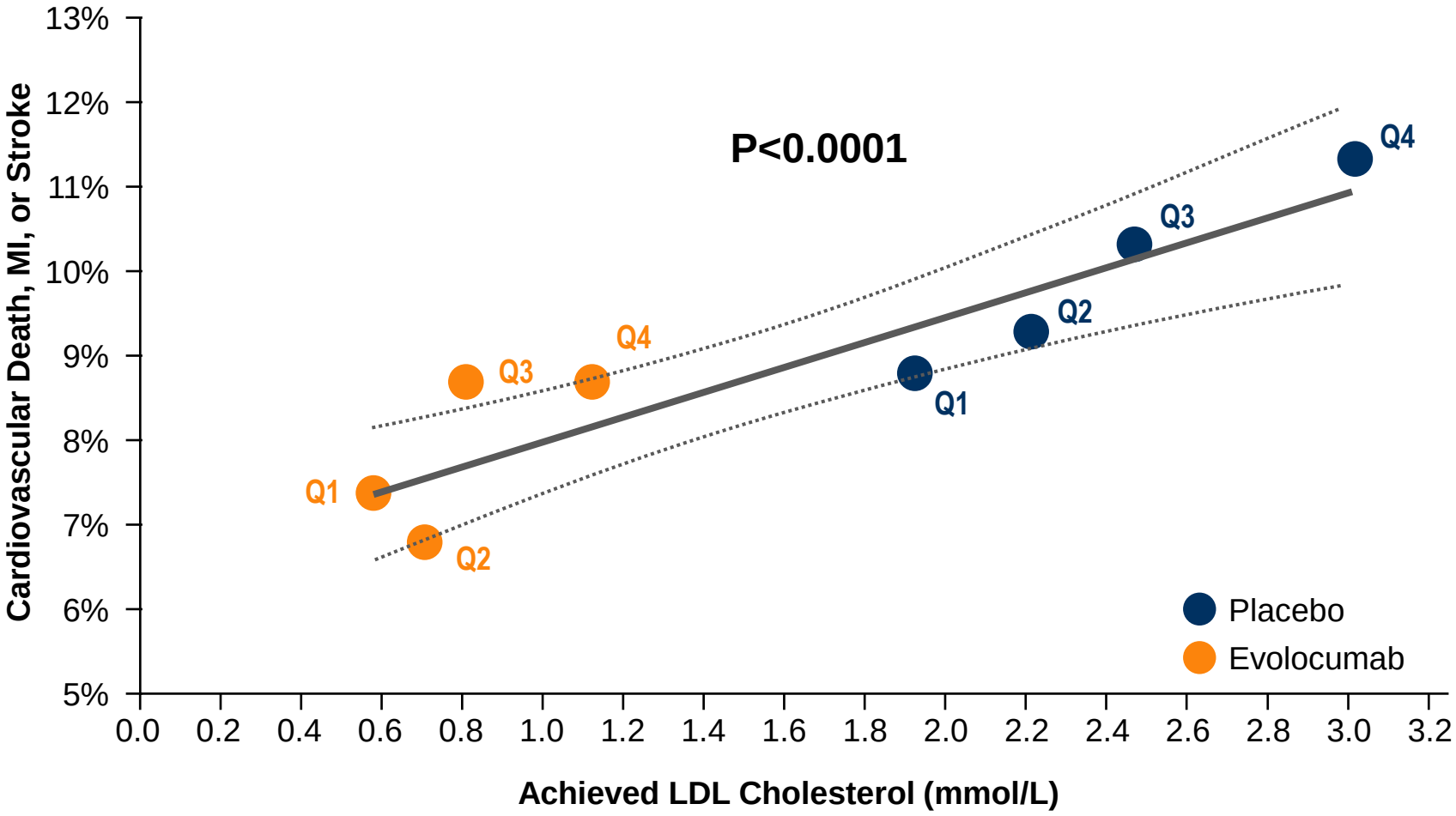


Primary and secondary composite endpoint results were consistent across all key subgroups

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664
(Supplementary Figure S5)

Asociace hladin LDL-C a KV příhod

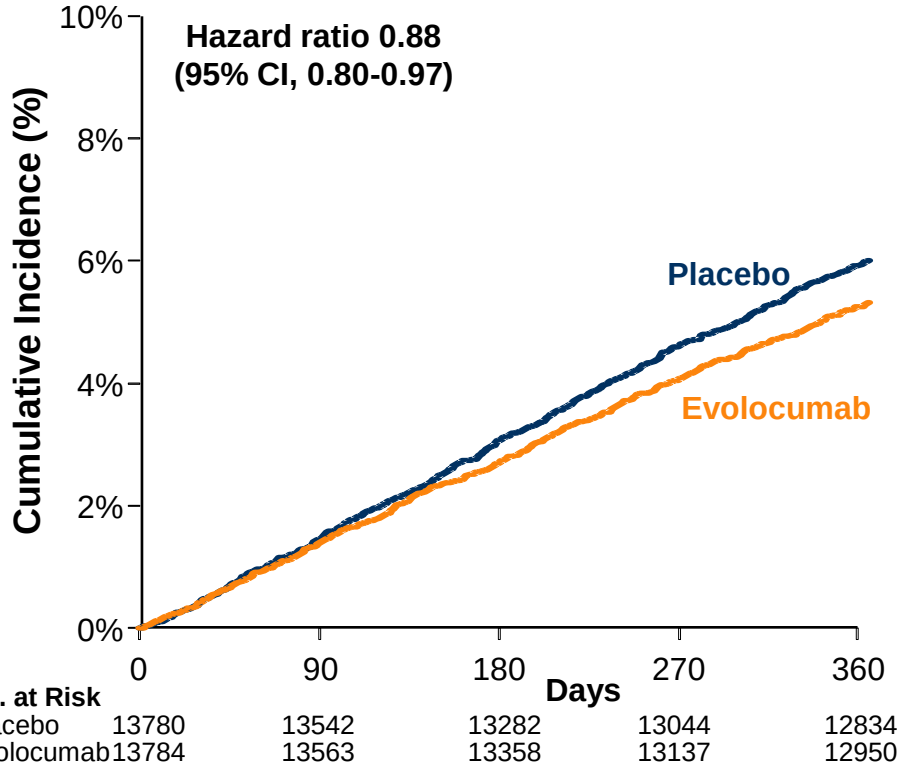
Patients divided by quartile of baseline LDL-C and by treatment arm



Sabatine MS, et al. *American College of Cardiology – 66th Annual Scientific Session Late-Breaking Clinical Trial*. Washington, D.C. March 17, 2017.

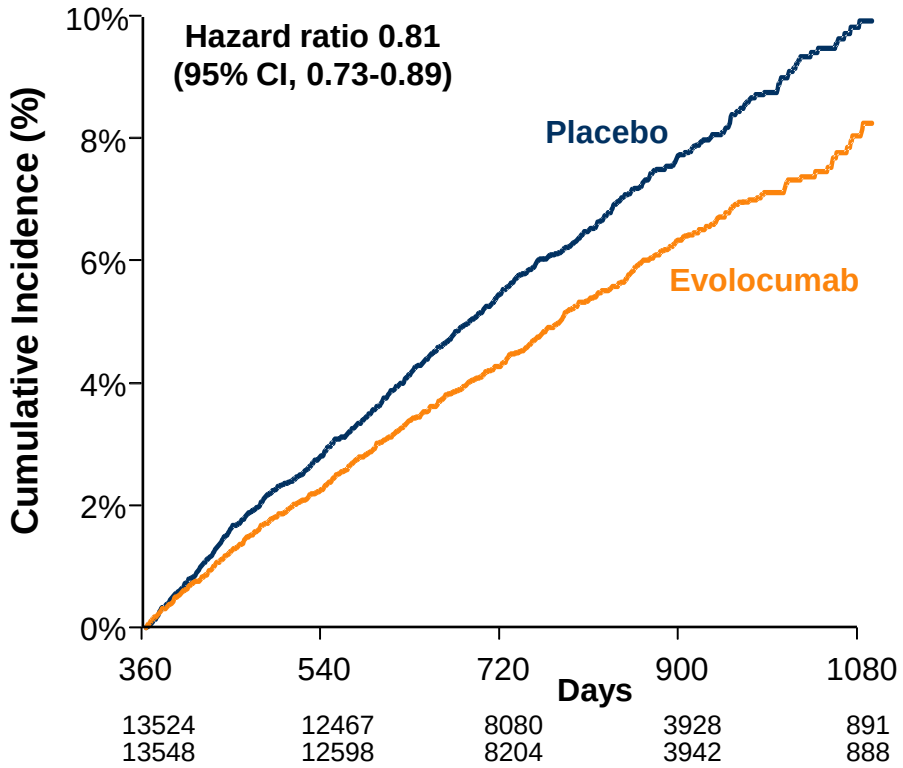
Analýza primárního „endpointu“ v čase

Year 1: RRR 12%



No. at Risk					
Placebo	13780	13542	13282	13044	12834
Evolocumab	13784	13563	13358	13137	12950

> Year 1: RRR 19%



Placebo	13524	12467	8080	3928	891
Evolocumab	13548	12598	8204	3942	888

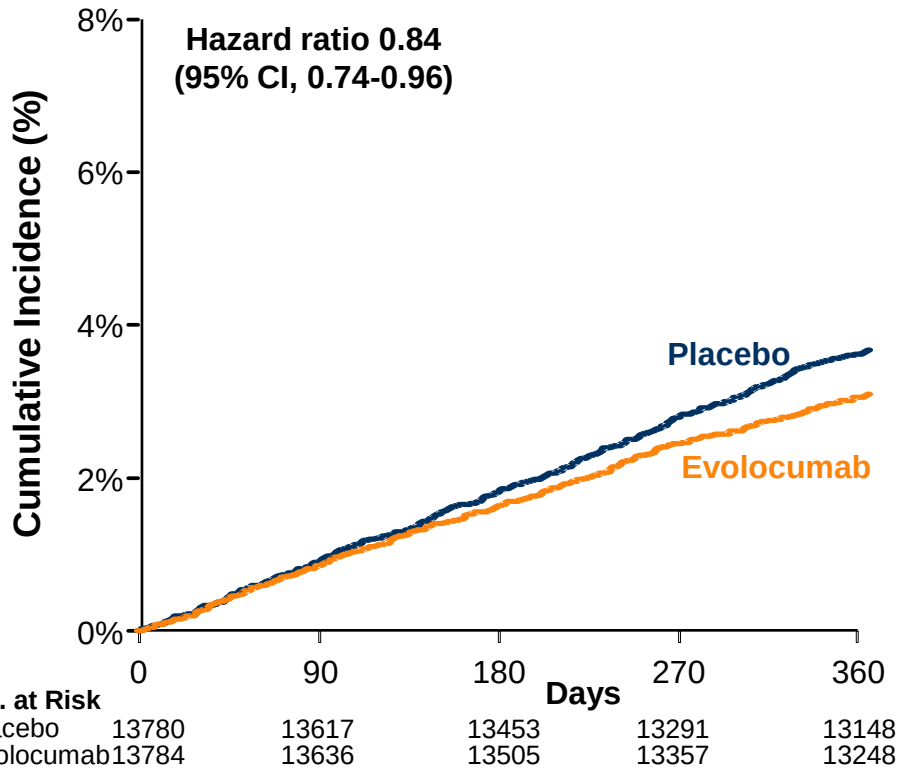
Longer duration of treatment and follow up suggests larger risk reduction

Landmark analyses were performed in which patients who were alive and in follow-up at the start of the period of interest formed the group at risk.

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017].
doi: 10.1056/NEJMoa1615664 (Supplementary Figure S4)

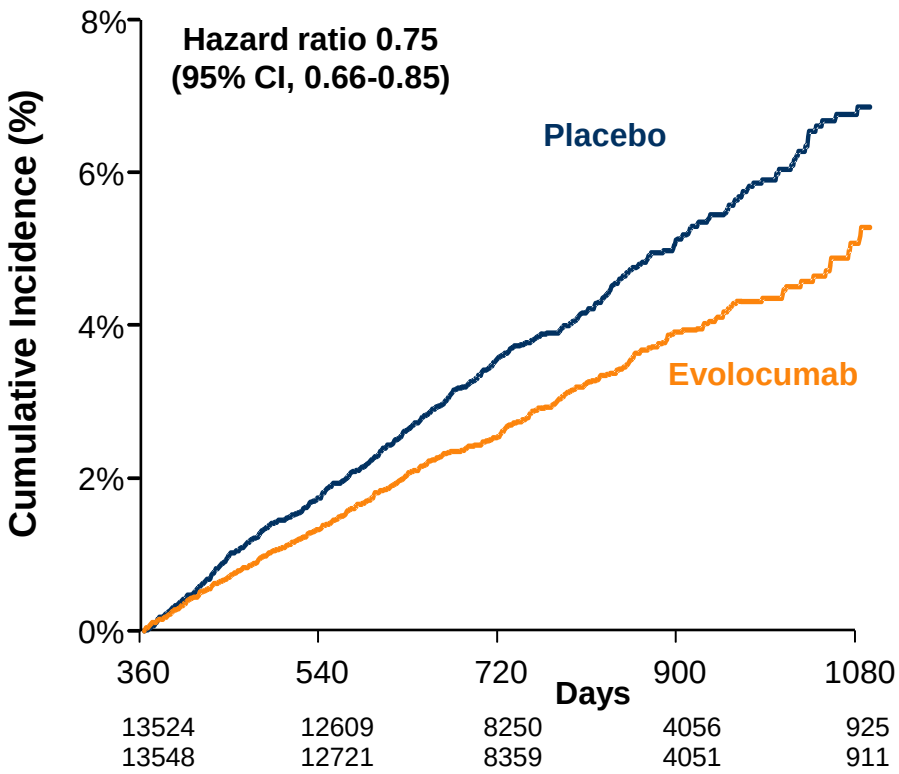
Analýza sekundárního „endpointu“ v čase

Year 1: RRR 16%



No. at Risk					
Placebo	13780	13617	13453	13291	13148
Evolocumab	13784	13636	13505	13357	13248

> Year 1: RRR 25%



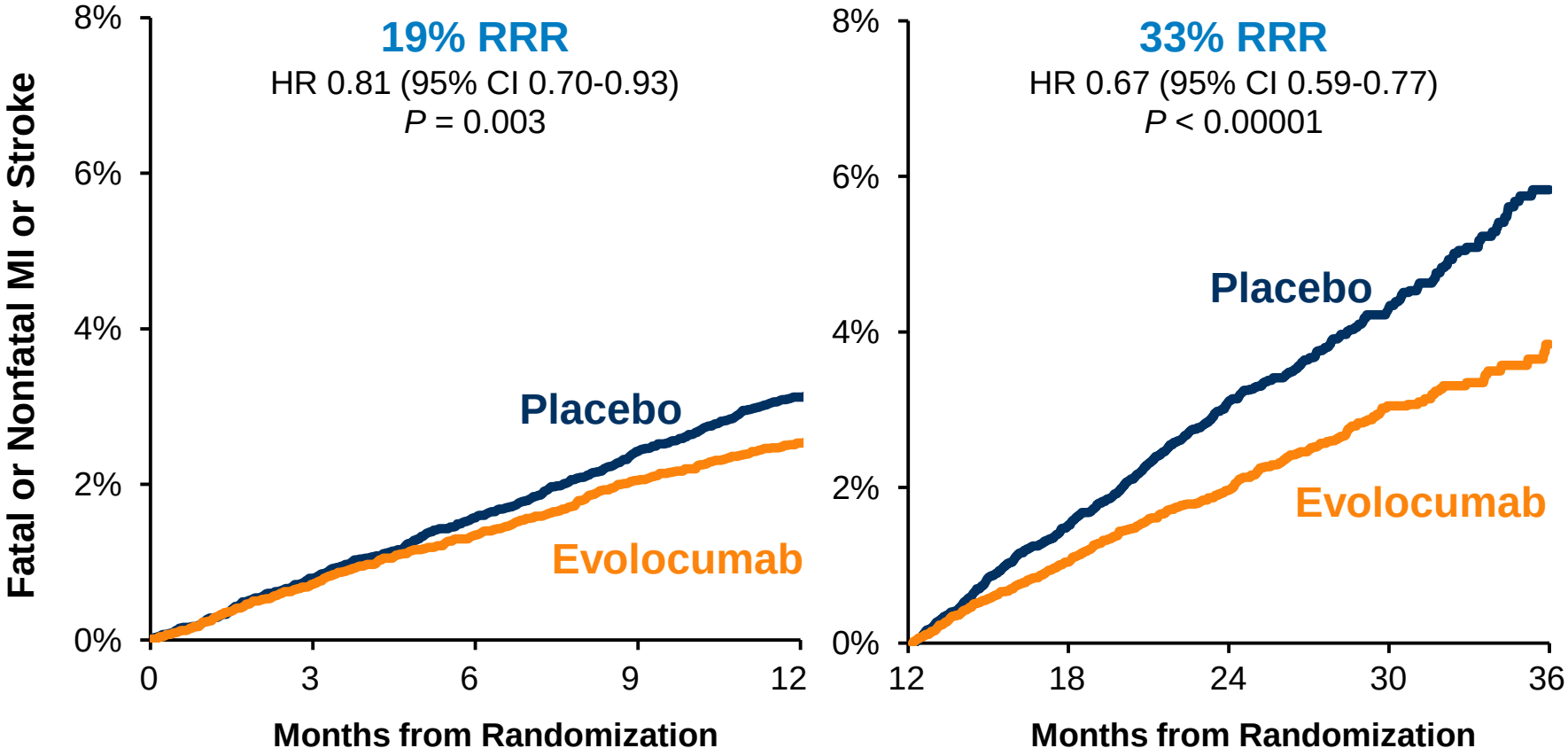
	13524	12609	8250	4056	925
	13548	12721	8359	4051	911

Longer duration of treatment and follow up suggests larger risk reduction

Landmark analyses were performed in which patients who were alive and in follow-up at the start of the period of interest formed the group at risk.

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017].
doi: 10.1056/NEJMoa1615664 (Supplementary Figure S4)

Fatální či nefatální IM nebo CMP
po 12 a po 36 měsících



Sabatine MS, et al. *American College of Cardiology – 66th Annual Scientific Session Late-Breaking Clinical Trial*. Washington, D.C. March 17, 2017.

Bezpečnost

Nežádoucí účinky

Adverse Events, n (%)	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Any	10,664 (77.4)	10,644 (77.4)
Serious	3,410 (24.8)	3,404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)

No notable differences in the rate of AEs, SAEs, or AEs leading to discontinuation

*Safety evaluations included all randomized patients who received at least one dose of study treatment and for whom post-dose data are available.

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Souhrn - Závěr

Souhrn

- **<u>Léčba evolocumabem vedla ke statisticky významnému poklesu</u>**
- **- 15 %** **Primární „endpoint“**
- **- 20%** **Sekundární „endpoint“**
- 50 NNT
- **Účinek léčby se prohluboval s časem**
- **Závažné KV** **po roce -16%** **na konci sledování - 25%**
- **IM+CMP** **-19%** **- 33%**

- **Výsledky jsou v souladu s výsledky CTTC**

Souhrn

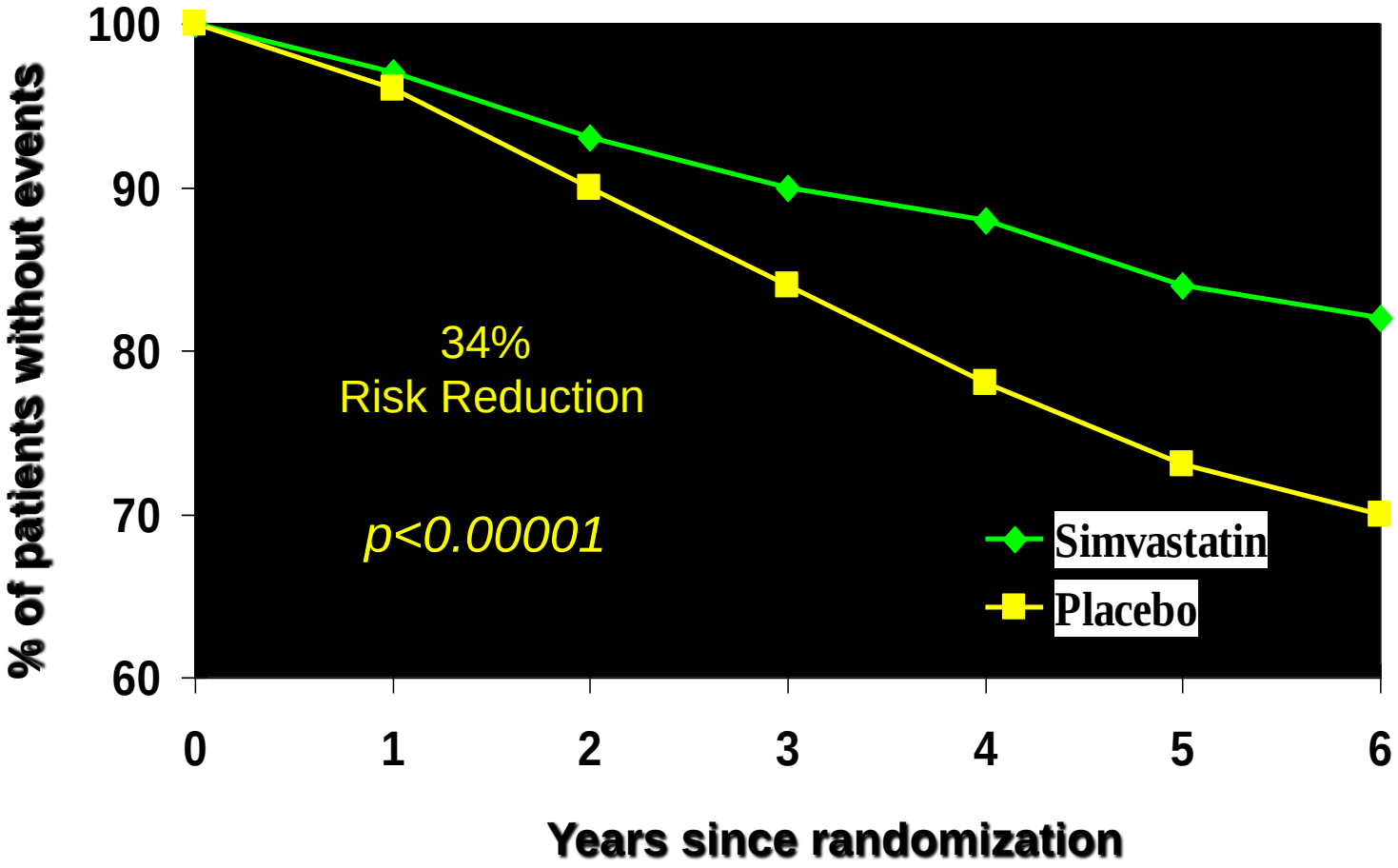
- **Léčba evolocumabem u nemocných s ICHS (léčených statinem)** trvala (medián) **2.2 roku** a vedla ke statisticky významné:
  - Redukci **LDL-C o 59%** z hodnoty medianu 2.38 na **0.78** mmol/L, i 42% dosáhlo LDL-C ≤ 0.65 mmol/L
- Léčba evolocumabem byla dobře tolerována
- **Léčba byla bezpečná (včetně sledovaných n.ú. neurokognitivních, rozvoje DM, myopatie…..)**

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Malá úvaha na závěr ☺
Nemohl být výsledek ještě výraznější?

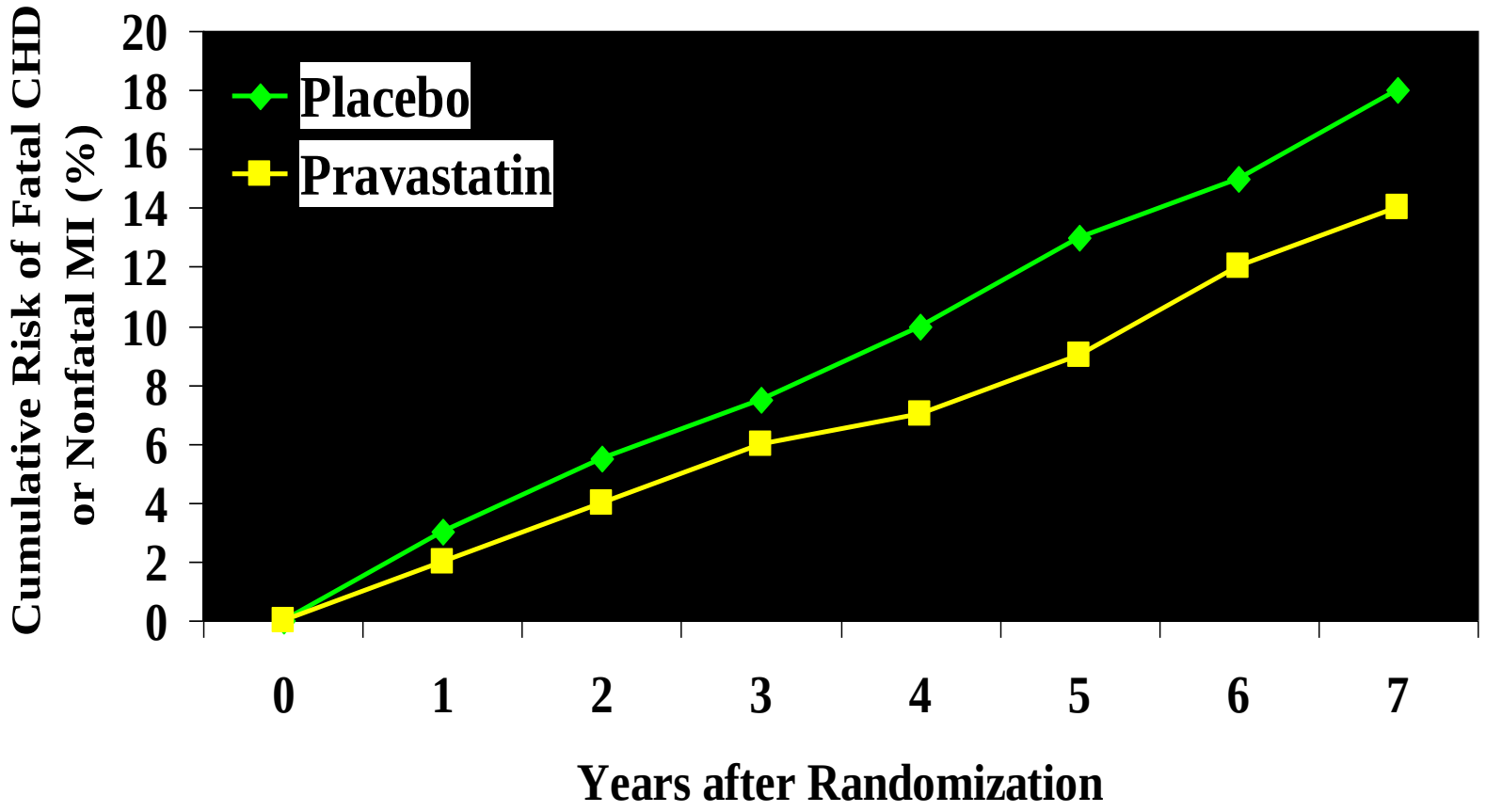
- **Možná až nereálná očekávání**
- **Přeceňování výsledků studií OSLER a ODYSSEY**
  - **zatížených malými čísly a krátkým sledováním**
- **Velmi krátká doba sledování 2,2 roku (3 roky)**
- **Vstupní hodnoty LDL-C 2,4, TC 4,3**
  - Téměř cílové hodnoty
  - Výrazně nižší než u dřívějších studií
  - Výborná léčba HLP statiny (méně kombinace, ezetimib)
- **Komplexní léčba ostatních RF**
- **Vlastní design studie**
- **Kolik známe z poslední doby studií které vůbec vyšly?**

4 S Koronární úmrtí a IM



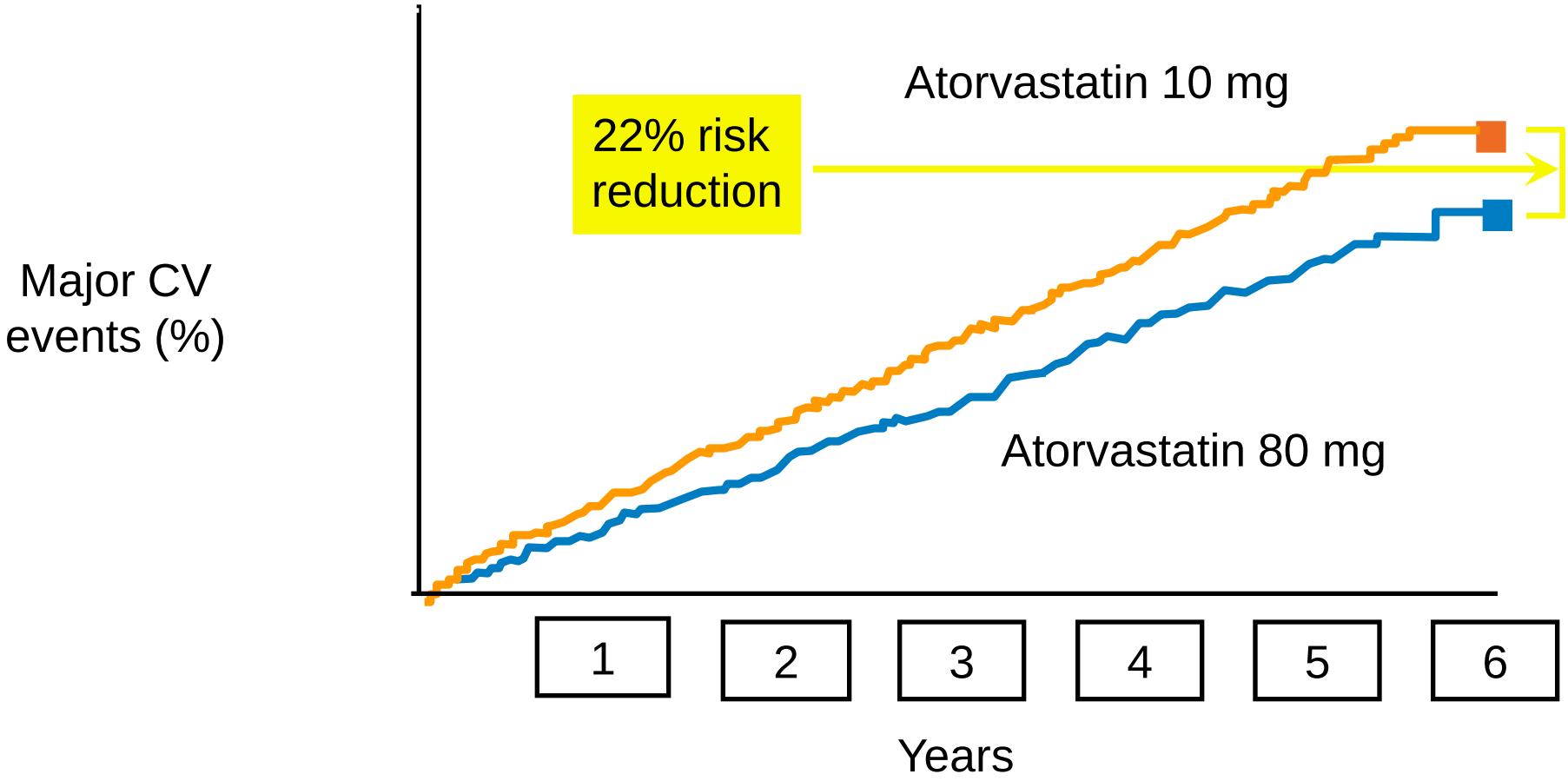
The Lancet, Vol 344, November 19, 1994

LIPID – KV úmrtí a nefatální IM



N Engl J Med 1998;339:1349-57

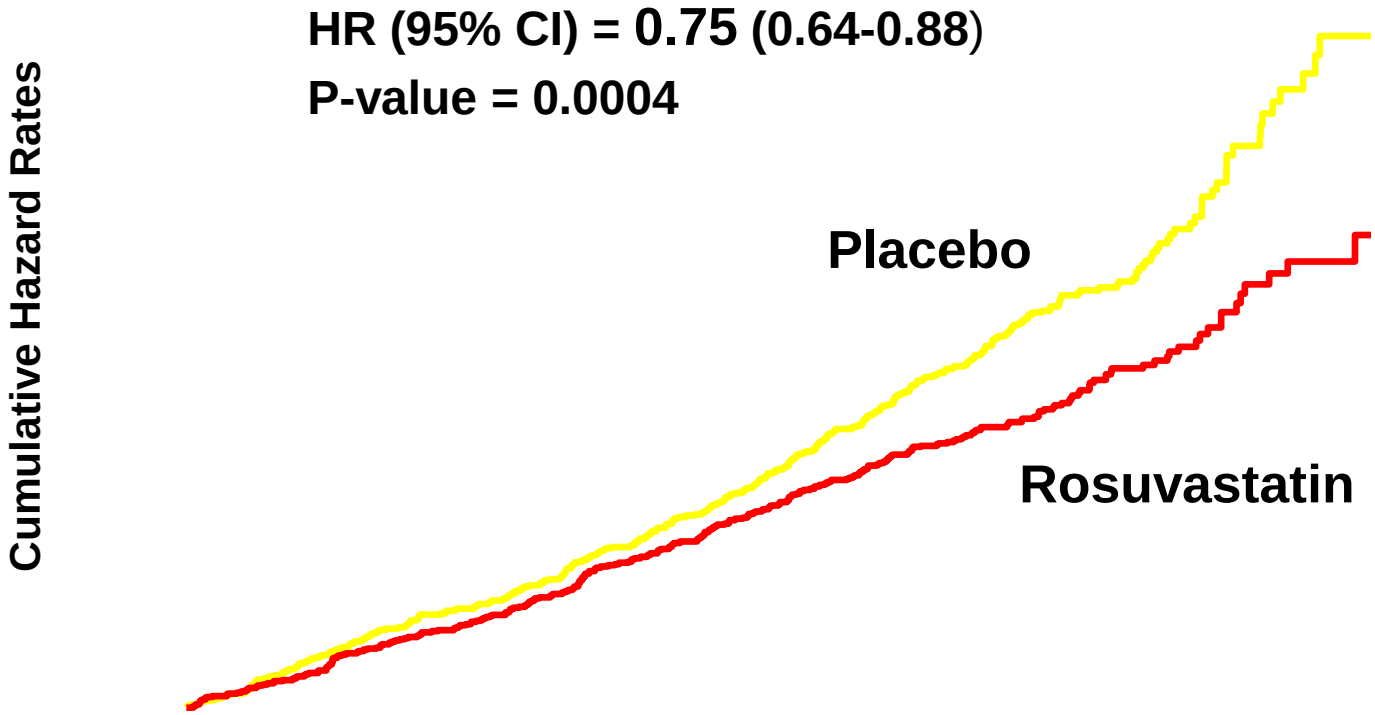
TNT: účinek na primární cílový ukazatel



LaRosa JC et al. *N Engl J Med.* 2005;352

HOPE 3:LIPID ARM: CV Death, MI, Stroke, Cardiac Arrest, Revasc, Heart Failure

-25%



Rosuva	6361	6241	6039	2122
Placebo	6344	6192	5970	2073

Malá úvaha na závěr ☺
Nemohl být výsledek ještě výraznější?

- **Výsledek plně odpovídá realitě**
- **Výsledek plně odpovídá reálnému očekávání**
  - **Je v souladu s analýzou CTTC**
- **Výsledek je statisticky významný**
- **Srovnání s posledními „lipidovými“ studiemi**
  - IMPROVE IT (snížení KVR o 6,4% za 8 let – hodnoceno, správně, jako relevantní, statisticky i klinicky významné v souvislostech)
- ***Proč potom někteří pochybují o dostatečném snížení KV příhod ve studii FOURIER? Nechápu ☹***

Studie FOURIER s evolocumabem prokázala

- **Účinnou redukci KV příhod inhibicí PCSK9**
- **Platnost LDL principu**
- **Pozitivní lipidové účinky léčby**
- ***Bezpečnost***
- ***Dobrou toleranci***

Studie FOURIER s evolocumabem

Představuje obrovský milník a zásadní přelom v prevenci KVO, v preventivní kardiologii, v léčbě HLP a DLP

Podobně, jako před více než 20 lety studie „4S“

XXIV. kongres

České internistické společnosti

ČLS J. E. Purkyně

29. 10. – 1. 11. 2017

Kongresové centrum Praha

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