85TH EAS CONGRESS

April
23-26
2017

PRAGUE
CZECH REPUBLIC

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PŘEHLED NOVINEK V OBLASTI HYPOLIPIDEMICKÉ LÉČBY PRO KARDIOLOGICKOU PRAXI

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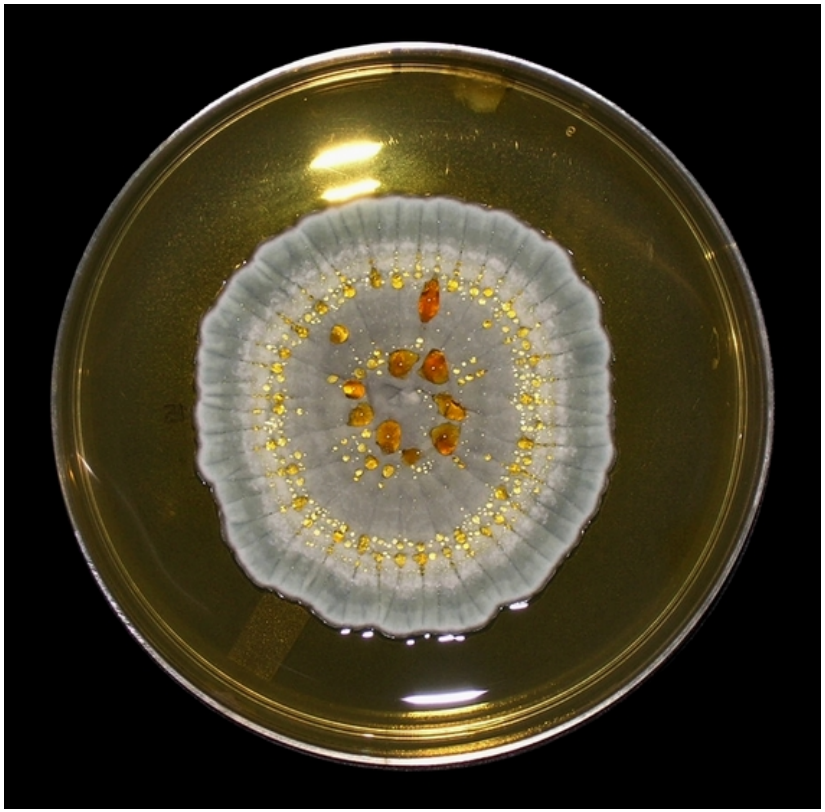
Centrum preventivní kardiologie 3. interní kliniky 1. LF UK a VFN

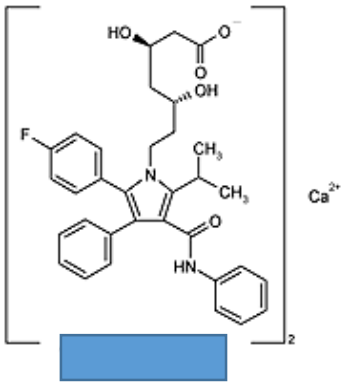
a

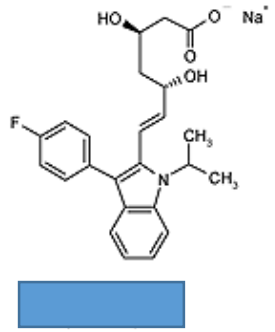
Česká společnost pro aterosklerózu

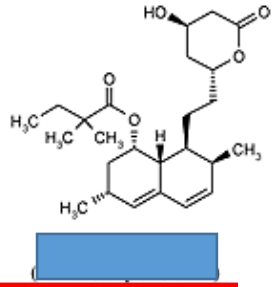
Čím musíme začít…

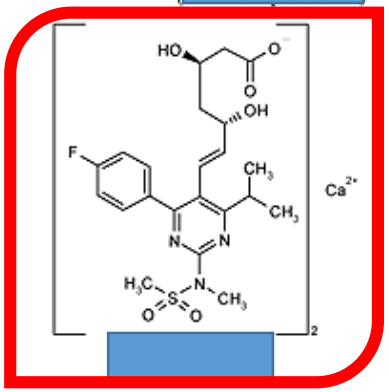


Poznáváte je?





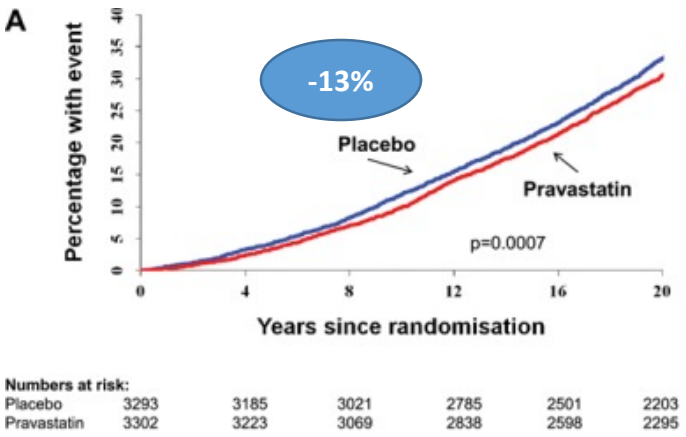


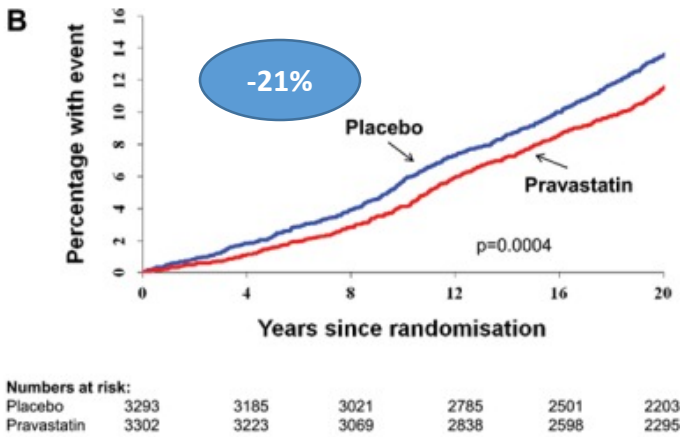


Statiny, které se (nejen) v kardiologii dají použít (téměř) v každé situaci

Nejdelší sledování zatím stále z WOSCOPS
6595 mužů, původně 55 let- sledování do 75. let

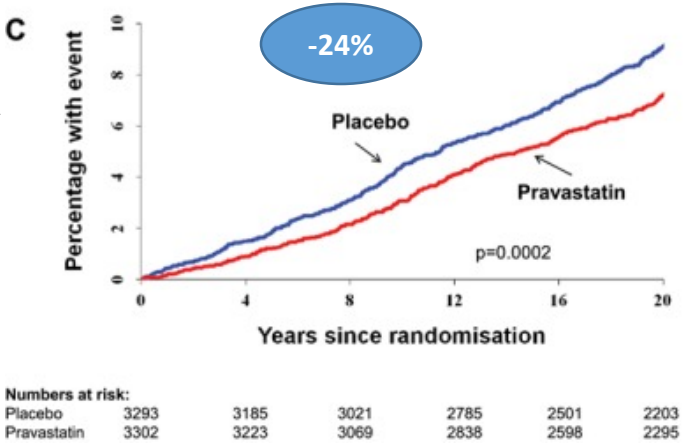
Celková mortalita

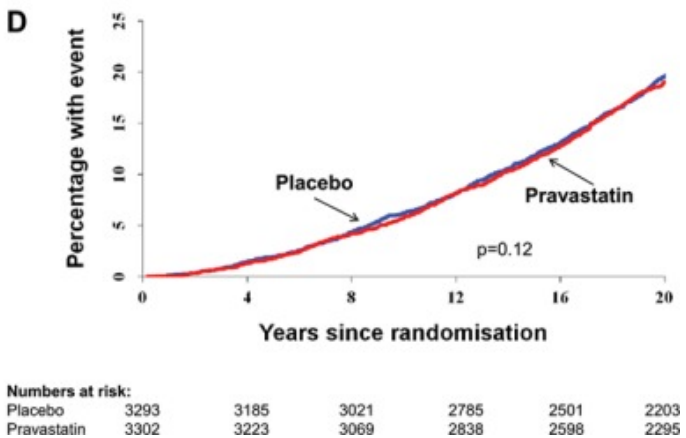




KV mortalita

Koronární příhoda





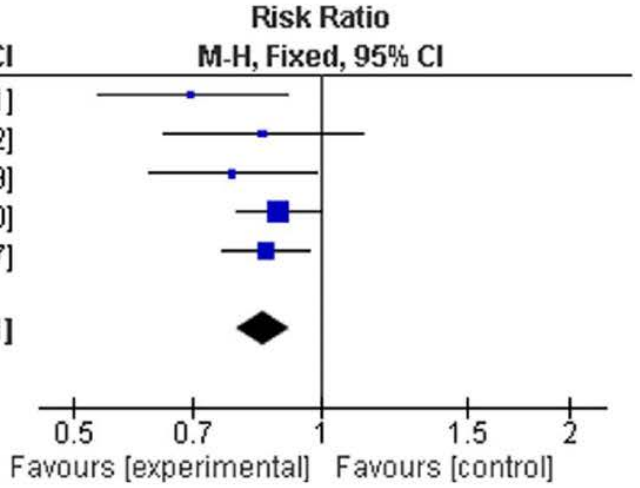
Nekardiální onem.

Circulation. 2016 Mar 15; 133(11): 1073–1080

Intenzivní terapie statinem jistě prospěšná i u DM 2

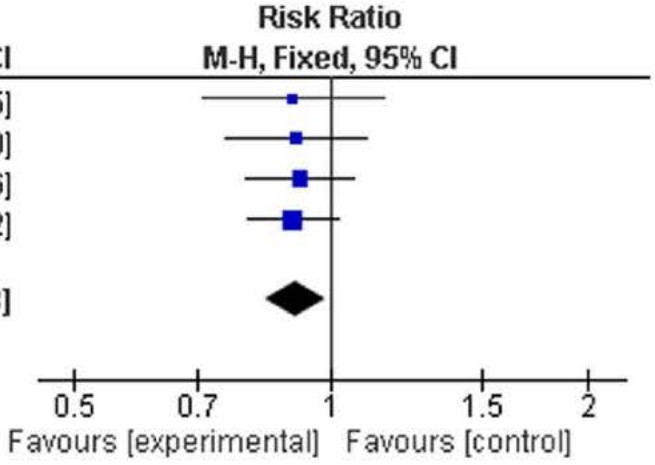
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4S	46	105	61	97	7.0%	0.70 [0.53, 0.91]
ASPEN	66	252	78	253	8.6%	0.85 [0.64, 1.12]
CARE	81	282	112	304	11.9%	0.78 [0.62, 0.99]
HPS	325	972	381	1009	41.2%	0.89 [0.79, 1.00]
LIPID	245	542	282	535	31.3%	0.86 [0.76, 0.97]
Total (95% CI)		**2153**		**2198**	**100.0%**	**0.85 [0.79, 0.91]**
Total events	763		914			

Heterogeneity: Chi² = 3.14, df = 4 (P = 0.53); I² = 0%
Test for overall effect: Z = 4.33 (P < 0.0001)



Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
A to Z 2004	99	529	110	530	13.1%	0.90 [0.71, 1.15]
PROVE-IT-TIMI 2006	142	499	150	479	18.3%	0.91 [0.75, 1.10]
SEARCH 2010	225	633	245	634	29.2%	0.92 [0.80, 1.06]
TNT 2006	298	748	332	753	39.5%	0.90 [0.80, 1.02]
Total (95% CI)		**2409**		**2396**	**100.0%**	**0.91 [0.84, 0.98]**
Total events	764		837			

Heterogeneity: Chi² = 0.04, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 2.37 (P = 0.02)



de Vries FM et al. . PLoS ONE 9(11): e111247.
doi:10.1371/journal.pone.0111247

HLAVNÍ ZÁSADY LÉČBY STATINY PŘI AKS

- Zahájit 1. den hospitalizace
- Bez ohledu na lipidogram

  Vyšetření lipidů v krvi při přijetí k hospitalizaci není pro rozhodování o léčbě statiny podstatné, je však užitečné jako základ pro další hodnocení účinnosti léčby

- Vysoká dávka statinu:

Nejlepší výsledky ze studií u AKS jsou dostupné pro 80 mg atorvastatinu. (alternativně 40 mg rosuvastatin)

- Pozor na lékové interakce
- V propouštěcí zprávě uvést jako konkrétní cíl léčby plazmat. koncentraci LDL-cholesterolu <1,8 mmol/l !!!

Piťha J et al. Léčba statiny u pacientů s akutním koronárním syndromem. *Interv Akut Kardiol 2012; 11(2): 89-90*

Jak na hypercholesterolemii podle doporučení?

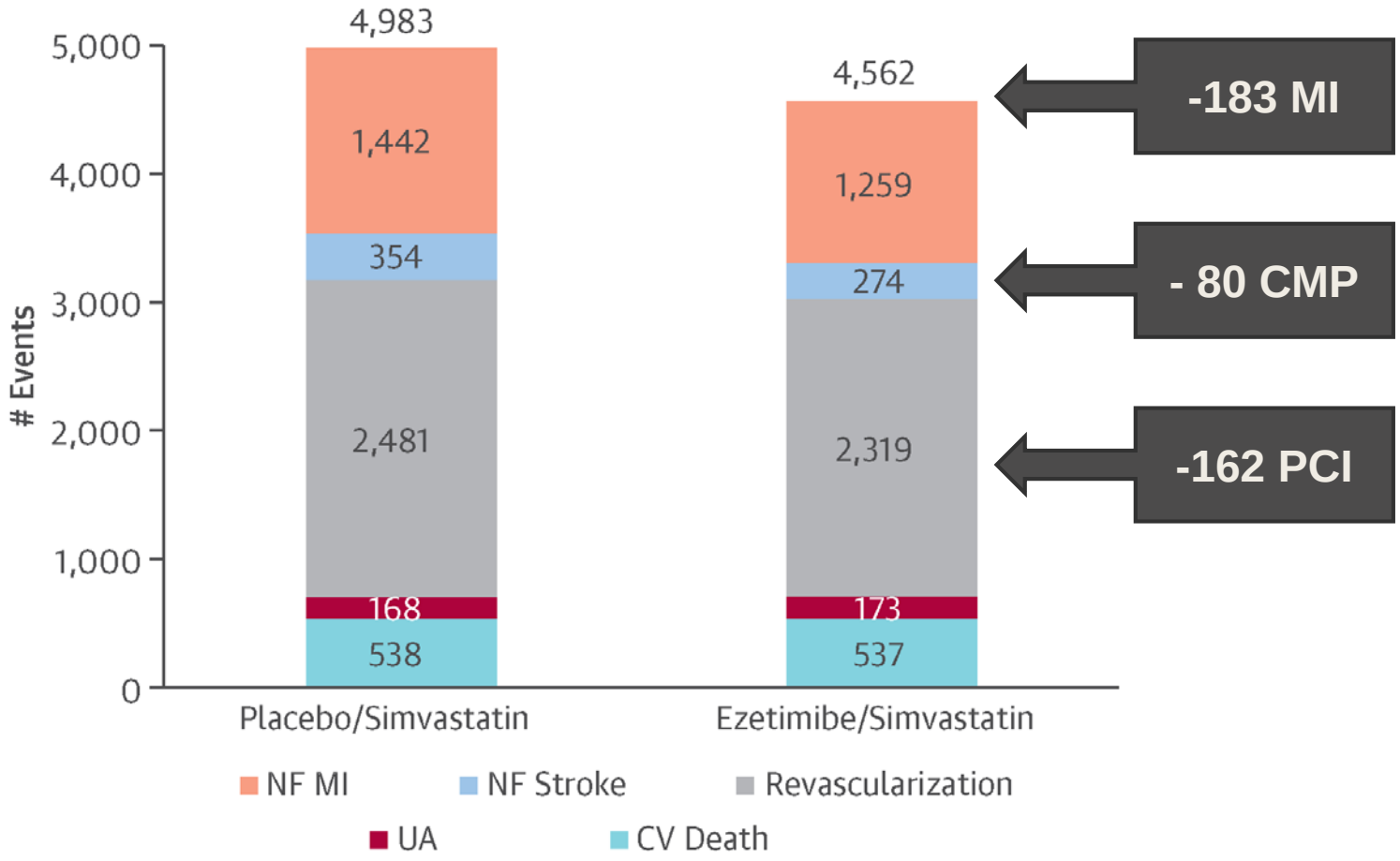
Změna postavení ezetimibu

Recommendations
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.

1. **Statin**
2. **Ezetimib**
3. **Pryskyřice**
4. **PCSK9i**

Cannon CP, N Engl J Med 2015;372: 2387–97.

IMPROVE-IT: statin + ezetimib = méně rekurentních příhod



Murphy et al . J A C C V O L . 6 7 , NO . 4 , 2 0 1 6

Pacienti po AKS podle guidelines 2016

Table 27 **Recommendations for lipid-lowering therapy in patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention**

Recommendations	Class [a]	Level [b]	Ref [c]
It is recommended to initiate or continue high dose statins early after admission in all ACS patients without contra-indication or history of intolerance, regardless of initial LDL-C values.	I	A	64, 358–360
If the LDL-C target is not reached with the highest tolerable statin dose, ezetimibe should be considered in combination with statins in post-ACS patients.	IIa	B	63
If the LDL-C target is not reached with the highest tolerable statin dose and/or ezetimibe, PCSK9 inhibitors may be considered on top of lipid-lowering therapy; or alone or in combination with ezetimibe in statin intolerant patients or in whom a statin is contra-indicated.	IIb	C	115, 116
Lipids should be re-evaluated 4–6 weeks after ACS to determine whether target levels of LDL-C <1.8 mmol/L (<70 mg/dL) or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) have been reached and whether there are any safety issues. The therapy dose should then be adapted accordingly.	IIa	C	
Routine short pretreatment or loading (on the background of chronic therapy) with high-dose statins before PCI should be considered in elective PCI or in NSTE-ACS.	IIa	A	363–365

Od 9/2016 fixní kombinace atorva+eze (Zoletorv)

Fixní „ASCOT trojkombinace“: perindopril+amlodipin+atorvastatin = LIPERTANCE

Perindopril 5	Amlodipin 5	Atorvastatin 10	**Lipertance 5/5/10**
Perindopril 5	Amlodipin 5	Atorvastatin 20	**Lipertance 5/5/20**
Perindopril 10	Amlodipin 5	Atorvastatin 20	**Lipertance 10/5/20**
Perindopril 10	Amlodipin 10	Atorvastatin 20	**Lipertance 10/10/20**
Perindopril 10	Amlodipin 10	Atorvastatin 40	**Lipertance 10/10/40**

- 5 dávkových variant
- Úvod léčby hypertonika s dyslipidemií
- Pokračování léčby s možností titrace
- Osvědčené účinné látky, ověřené klinickými studiemi i dlouhou zkušeností
- Zlepšení adherence nad rámec fixních kombinací antihypertenziv

Fixní „ASCOT trojkombinace“:

perindopril+amlodipin+atorvastatin = LIPERTANCE

Převod z terapie volnou kombinací

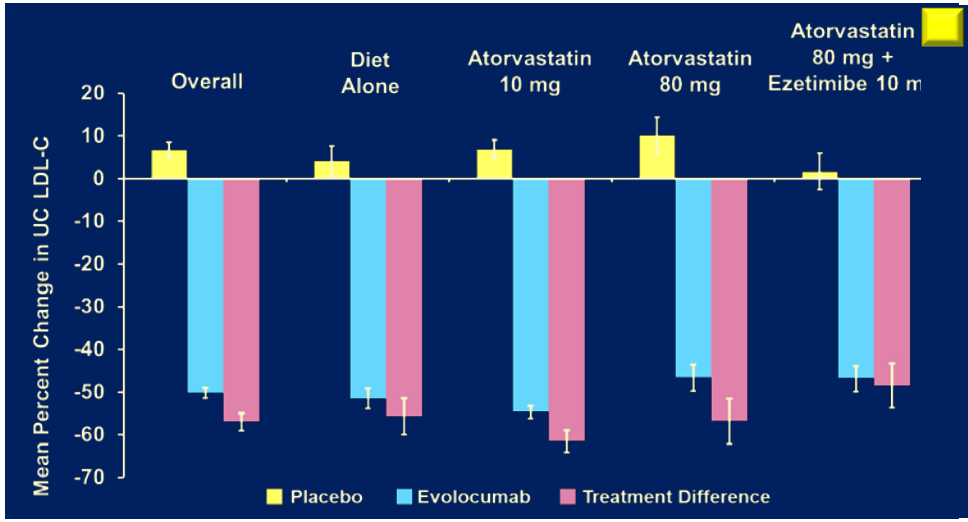
Zahájení léčby

Zahajování kombinace/ eskalace léčby

Co když pacient užívat statin nechce, nemůže nebo statin není dost?

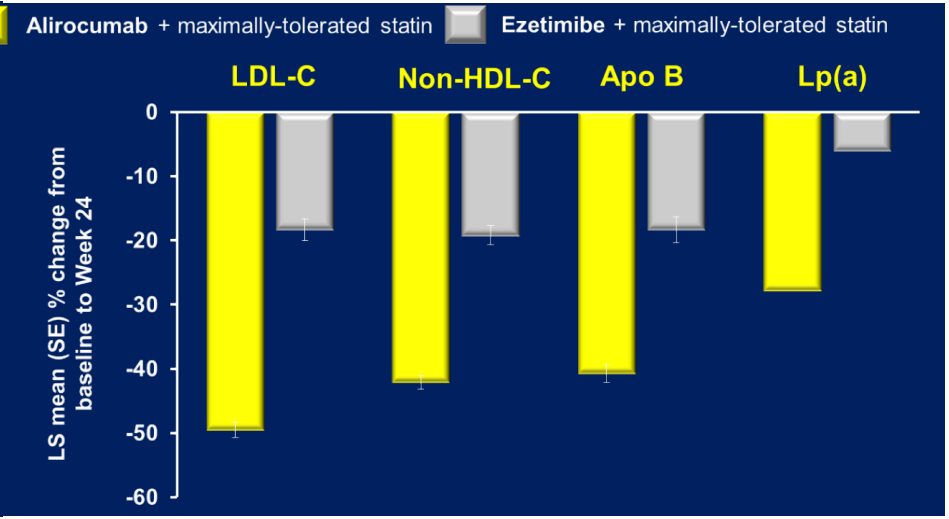
Pro nemocné nedosahující cíle LDL-c je tu PCSK9 inhibice

Evolocumab: LDLc snížení za 52 týdnů (DESCARTES)



Blom D et al. N Engl J Med. 2014

Alirocumab: LDLc snížení za 24 týdnů (ODYSSEY LONG TERM)



Robinson J et al. N Engl J Med. 2015

OSLER a OSLER-2: vedlejší účinky při velmi nízkých hodnotách LDL-C

52-týdenní open-label follow-up studie, evolocumab 420 mg 1xměsíčně vs stand. léčba u pacientů ve studii fáze 2 (OSLER) nebo fáze 3 (OSLER-2)

	Stratifikace dle minimálního LDL-C při léčbě Evolocumabem				EvoMab (n=2976)	Stand. léčba (n=1489)
	<0,65 mmol/l (n=773)	0,65 -1 mmol/l (n=759)	<1 mmol/l (n=1532)	≥ 1 mmol/l (n=1426)		
Nežádoucí účinky klinické (%)						
Všechny	70.0	68.1	69.1	70.1	69.2	64.8
Závažné	7.6	6.9	7.2	7.8	7.5	7.5
Myopatie	4.9	7.1	6.0	6.9	6.4	6.0
Neurokognitivní	0.5	1.2	0.8	1.0	0.9	0.3
Nežádoucí účinky laboratorní (%)						
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	1.1

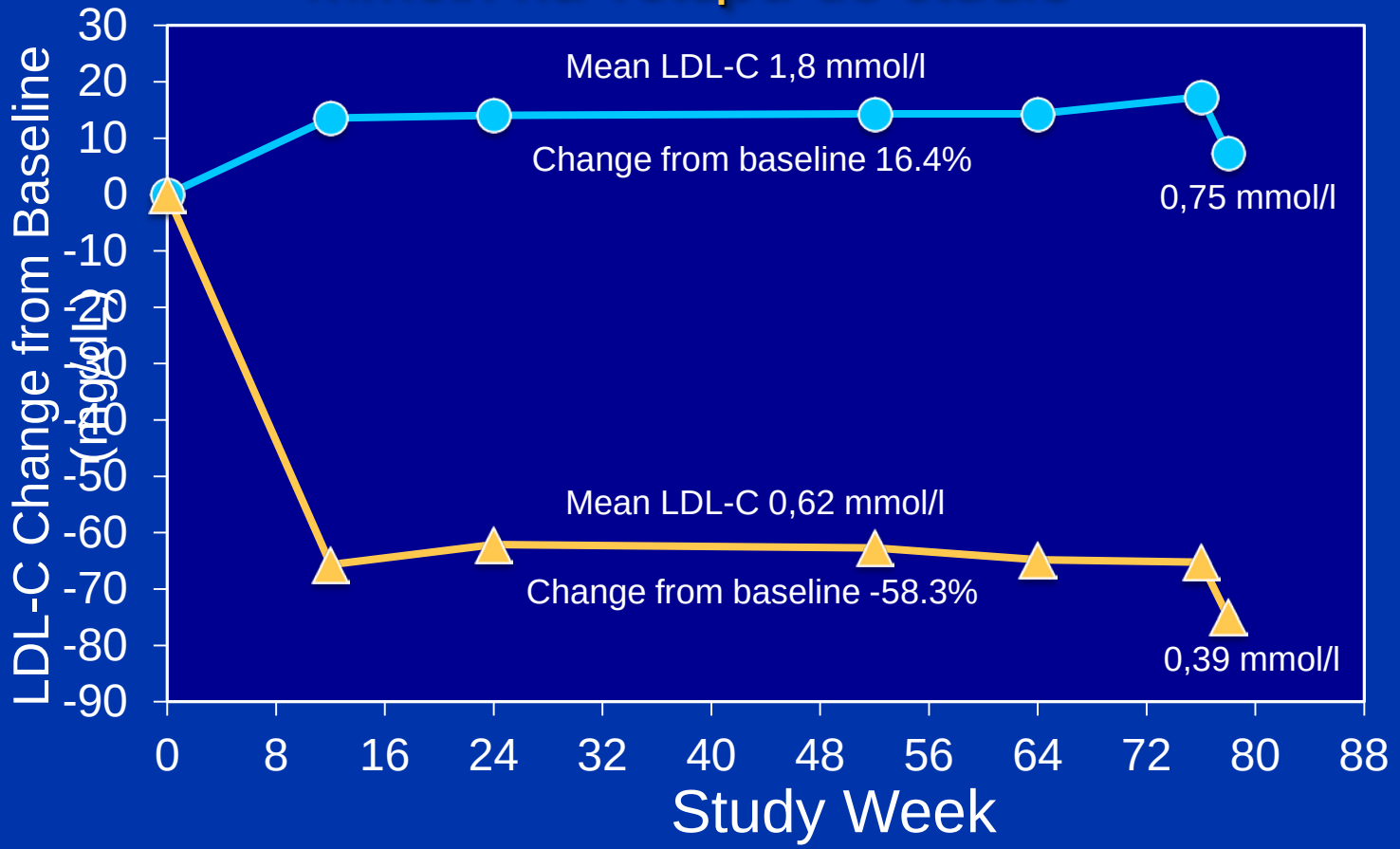
AE, adverse event; CK, creatine kinase; EvoMab, evolocumab; LDL-C, low-density lipoprotein cholesterol; QM , once monthly; SOC, standard of care; ULN, upper limit of normal.
Sabatine M, et al. N Engl J Med 2015;372:1500–9. (Suppl.):1–21.

Metaanalýza 14 studií s alirocumabem a výskyt NÚ podle dosažené hodnoty LDL-c

	Pooled control (n=1894)	Overall alirocumab (n=3340)	LDL-C ≥0.65 mmol/L† (n=2501)	LDL-C <0.65 mmol/L‡ (n=839)	LDL-C <0.39 mmol/L‡ (n=314)
Any TEAE, % (n)	77.1 (1461)	77.8 (2599)	**76.6 (1917)**	**72.7 (610)**	71.7 (225)
SAE, % (n)	15.4 (291)	16.0 (534)	**15.4 (386)**	**15.4 (129)**	13.1 (41)
Death, % (n)	1.2 (22)	0.7 (22)	**0.7 (18)**	**0.5 (4)**	0.3 (1)
TEAE leading to treatment discontinuation, % (n)	7.2 (137)	6.9 (232)	**7.9 (197)**	**4.2 (35)**	5.4 (17)
Values below are events per 100 patient-years§ (n)					
Neurological events (SMQ)	3.1 (71)	3.1 (134)	**3.4 (105)**	**1.9 (20)**	2.3 (9)
Neurocognitive disorders (CMQ)	0.7 (17)	0.7 (32)	**0.8 (26)**	**0.5 (5)**	0.3 (1)
Musculoskeletal (CMQ)	15.6 (328)	14.1 (559)	**14.6 (413)**	**12.1 (116)**	12.9 (45)
Ophthalmological TEAEs (SMQ)	1.1 (25)	1.4 (64)	**1.5 (47)**	**1.2 (13)**	1.3 (5)
Hepatic disorders (SMQ)	1.9 (45)	2.2 (95)	**2.4 (75)**	**1.6 (17)**	1.8 (7)
Cataracts (CMQ)	0.9 (21)	1.0 (43)	**0.6 (19)**	**2.0 (21)**	2.3 (9)
Patients with diabetes at baseline	n=559	n=998	**n=688**	**n=310**	n=129
Diabetes mellitus or diabetic complications (CMQ)	8.7 (58)	8.5 (106)	**7.7 (62)**	**10.1 (37)**	9.9 (15)
Patients without diabetes at baseline	n=1335	n=2342	**n=1813**	**n=529**	n=185
Diabetes mellitus or diabetic complications (CMQ)	2.0 (33)	1.5 (46)	**1.4 (32)**	**1.8 (12)**	1.8 (4)

Robinson J et al. Poster presented at the European Society of Cardiology Congress, 27–31 August 2016, Rome, Italy

GLAGOV exporatoraní subanalýza: LDL-c < 1,8 mmol/l na vstupu do studie



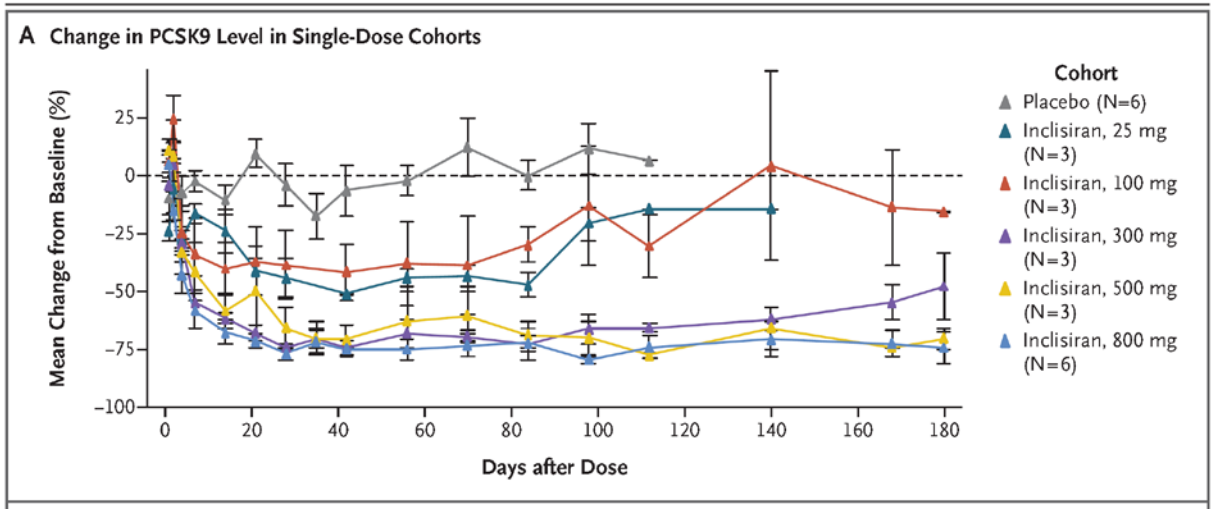
Mohou PCSK9 inhibitory snížit KV riziko ještě níže ?

- **Evolocumab**
  - FOURIER
    - 27654 pacientů/5let
    - 40-85 let
    - Sekundární prevence
    - LDL 1,8
    - Ukončení: 10/2017
- **Alirocumab**
  - ODYSSEY Outcomes
    - 18000 pacientů/5 let (+2roky FU)
    - Nad 40 let
    - Po AKS
    - LDL > 1,8 mmol/l
    - Ukončení: 12/2017

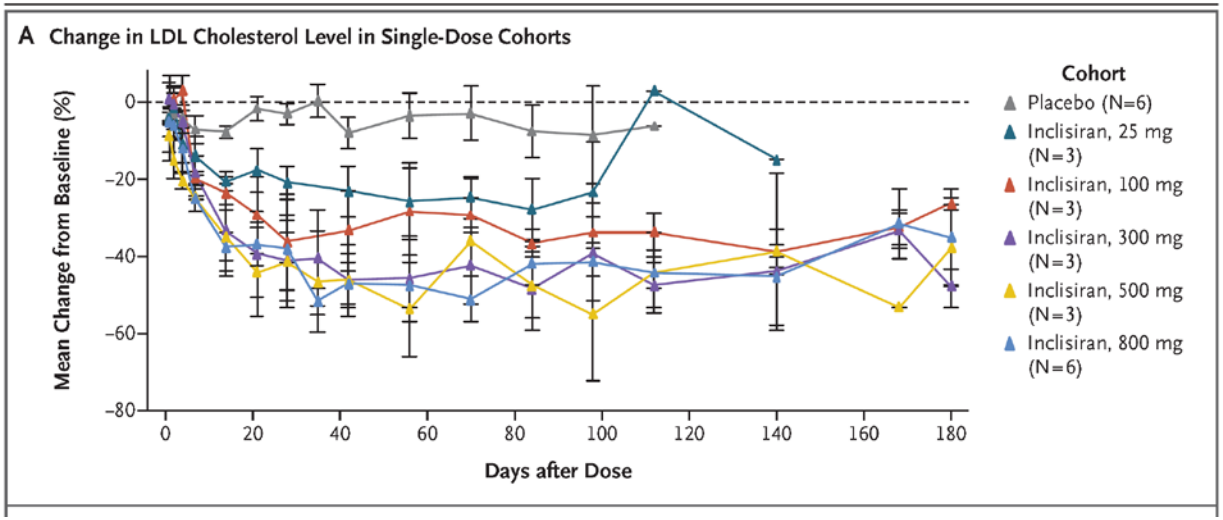
1. listopadu 2016 výzkumný program s bococizumabem s více než 28 000 nemocnými zastaven z rozhodnutí sponzora

Clinicaltrials.gov

Inclisiran: siRNA terapie proti PCSK9



- Změna hladin PCSK9



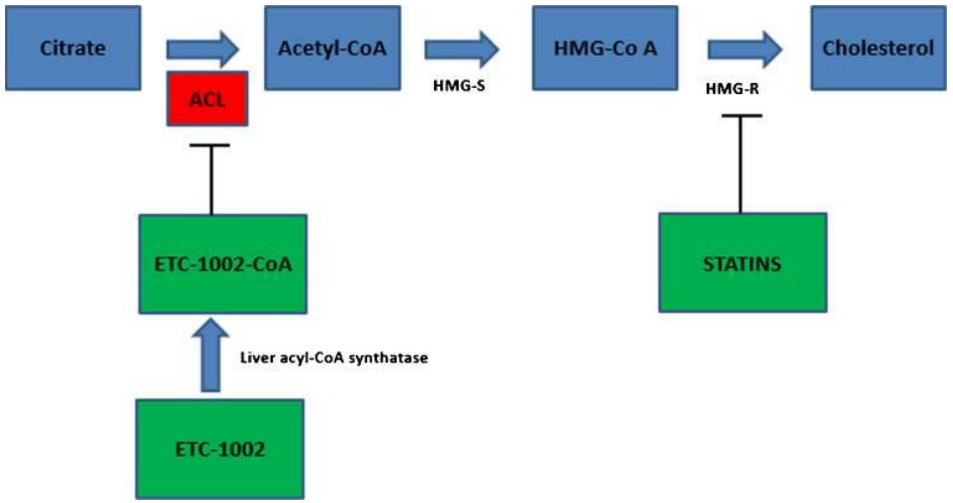
- Změna hladin LDL-c

Fitzgerald K et al. NEJM, Nov 13, 2016

Bempedenová kyselina: inhibice kyselé citrát lyasy: blok biosyntézy cholesterolu na novém místě

Study number	Short title (*N* = total/ETC-1002 treated)	LDL-C lowering[a]	Dose range (mg)	Treatment duration (weeks)
001 [23]	Phase 1a in healthy subjects (*N* = 18)			Single dose
002 [24]	Phase 1b in healthy subjects (*N* = 53/39)	Up to 17 %	20, 60, 100, 120	2 4
003 [26••]	Phase 2a in patients with hypercholesterolemia (*N* = 177/133)	Up to 27 %	40, 80, 120	12
004 [25]	Phase 1b in healthy subjects (*N* = 24/18)	Up to 36 %	40, 180, 220	2
005 [27]	Phase 2a in patients with hypercholesterolemia and type 2 diabetes (*N* = 60/30)	43 %	80, 120	4
006 [31]	Phase 2a in patients with hypercholesterolemia and a history of statin intolerance (*N* = 56/37)	32 %	60, 120, 180, 240	8
007 [29]	Phase 2a in patients with hypercholesterolemia added on to atorvastatin 10 mg (*N* = 58/42)	22 %	60, 120, 180, 240	8
008 [32••]	Phase 2b in patients with hypercholesterolemia with or without statin intolerance versus ezetimibe (*N* = 349/249)	Up to 30 % (ETC-1002) Up to 48 % (ETC-1002+ ezetimibe)	120, 180, 120 + ezetimibe, 180 + ezetimibe	12
009 [30]	Phase 2b in patients with hypercholesterolemia while on stable statin therapy (*N* = 134/88)	Up to 24 %	120, 180	12
014 [31]	Phase 2a in patients with hypercholesterolemia and hypertension (*N* = 143/72)	21 %	180	6

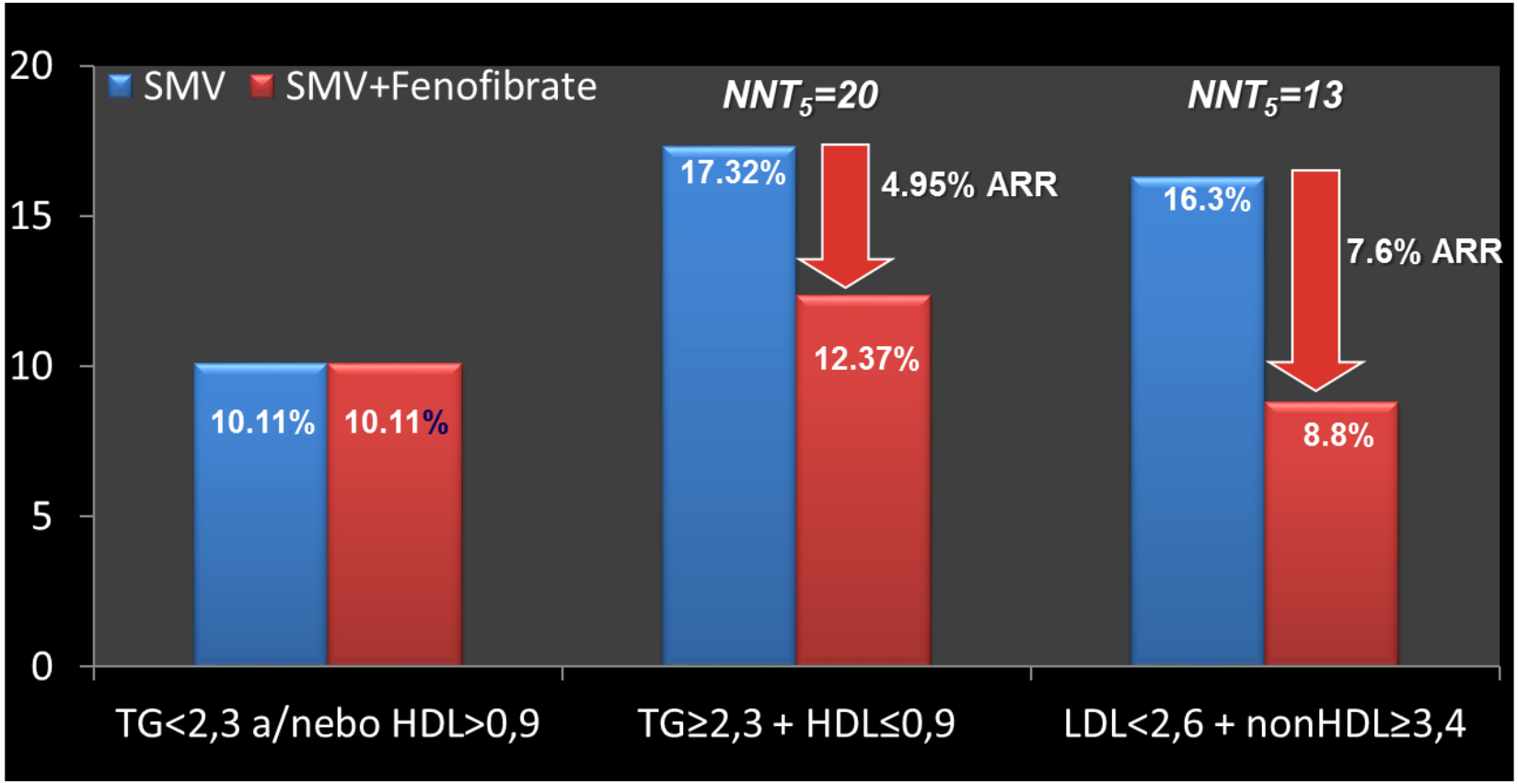
[a] Average LDL-C % change from baseline



Curr Atheroscler Rep (2016) 18: 61

Ale dyslipidemie není jenom elevace LDL-c…

Statiny jsou základem kombinací nejen ke snížení LDL-C



ACCORD Study Group. *N Engl J Med* **2010**; 362: 1563

Agonizace PPAR

Selective PPAR modulators (SPPARMs)

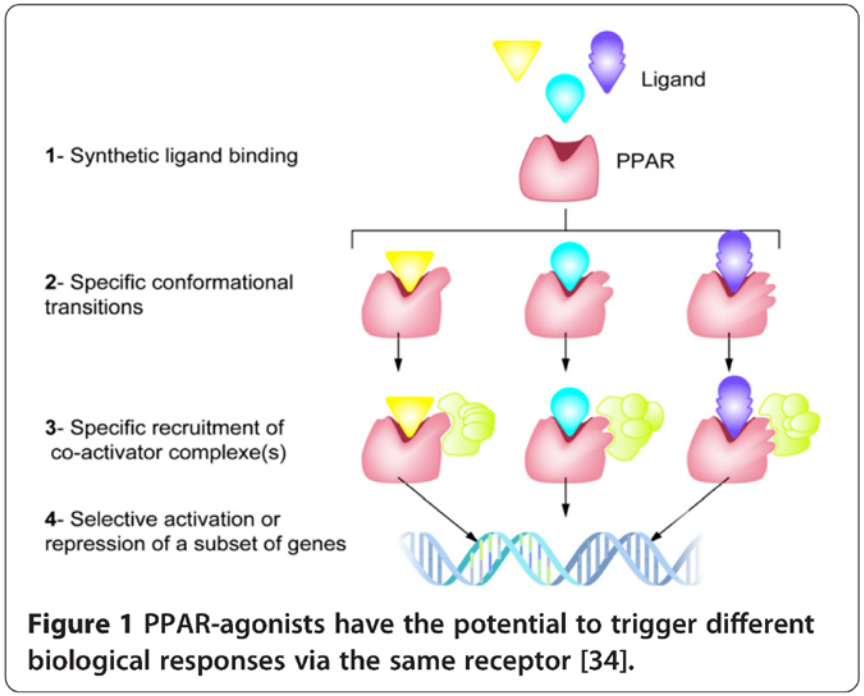
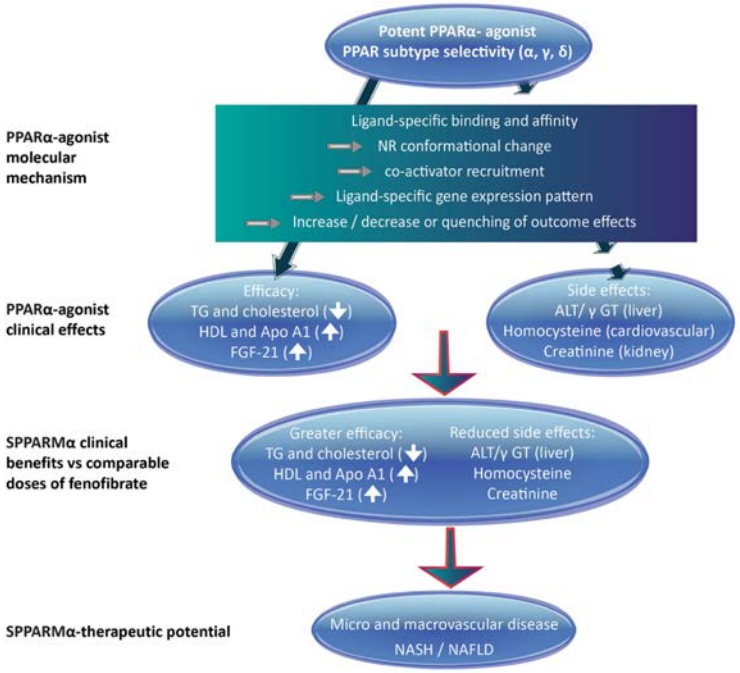


Figure 1 PPAR-agonists have the potential to trigger different biological responses via the same receptor [34].



Fruchart Cardiovascular Diabetology 2013, 12:82

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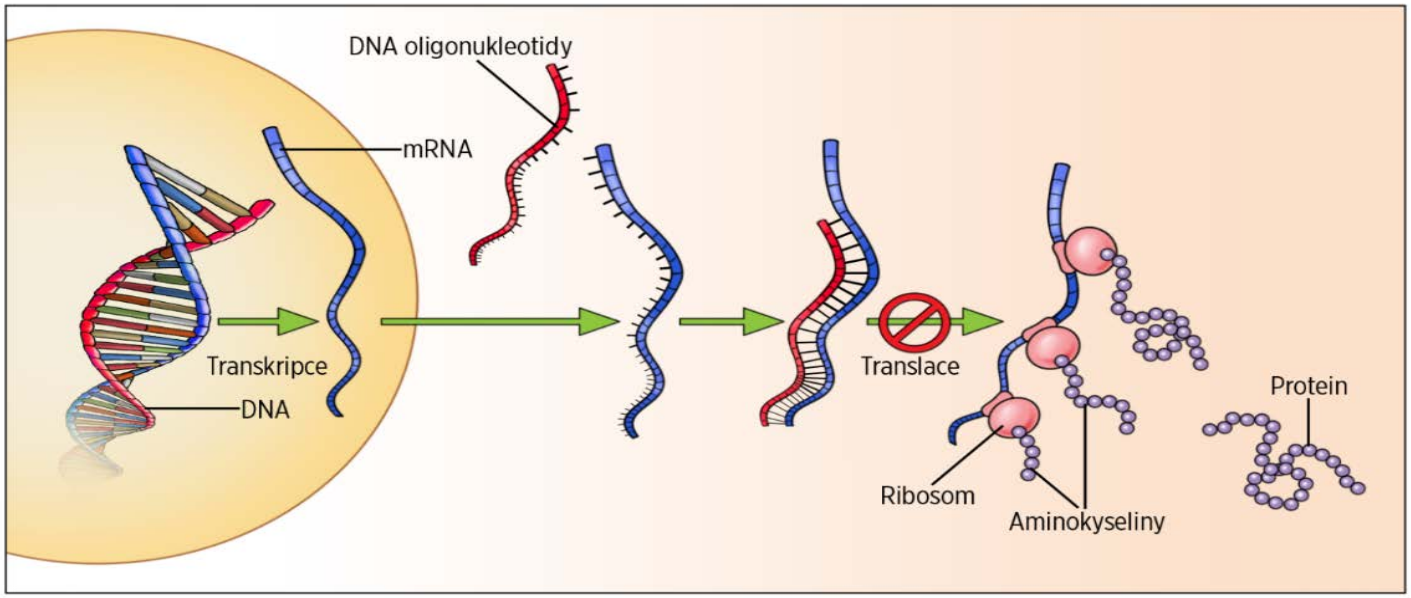
Landmark Trial Entitled "PROMINENT" To Explore The Prevention Of Heart Disease In Diabetic Patients With High Triglycerides And Low HDL-C

Trial will evaluate if lowering triglycerides and increasing functional HDL with Kowa's potent selective peroxisome proliferator activator receptor-alpha (PPAR-alpha) modulator, K-877 (pemafibrate) can reduce the elevated risk of cardiovascular disease in high-risk diabetic patients who are already taking statins

Jan 12, 2016, 09:00 ET from Kowa Research Institute, Inc.

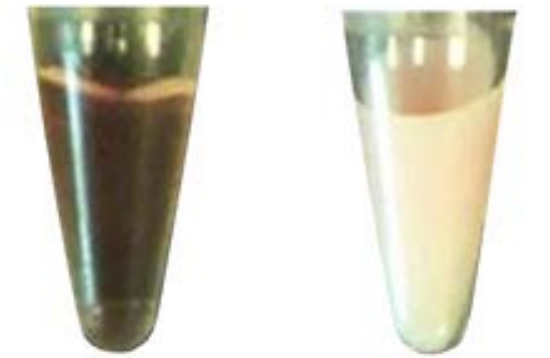
Antisense molekuly: společnost ~~ISIS~~…IONIS



CARDIOVASCULAR		
KYNAMRO®	ApoB-100	Genzyme
ISIS-APOCIII$_{Rx}$	ApoC-III	-
ISIS-FXI$_{Rx}$	Factor XI	-
ISIS-CRP$_{Rx}$	CRP	-
ISIS-APO(a)$_{Rx}$	Apo(a)	-
ISIS-ANGPTL3$_{Rx}$	ANGPTL3	-
ISIS-FVII$_{Rx}$	Factor VII	-

http://www.ionispharma.com/pipeline/

Těžké hypertriglycerdemie: familiární chylomikronemie



At left is a normal plasma sample, and at right is a plasma sample with a milky appearance (lipemia) due to chylomicronemia

- První genová terapie u člověka
  - GLYBERA
- MTP inhibice
  - Lomitapid
- Anti-sense terapie
  - Anti ApoB
  - Anti ANGPTL3
  - Anti apoCIII
- Inhibice DGAT

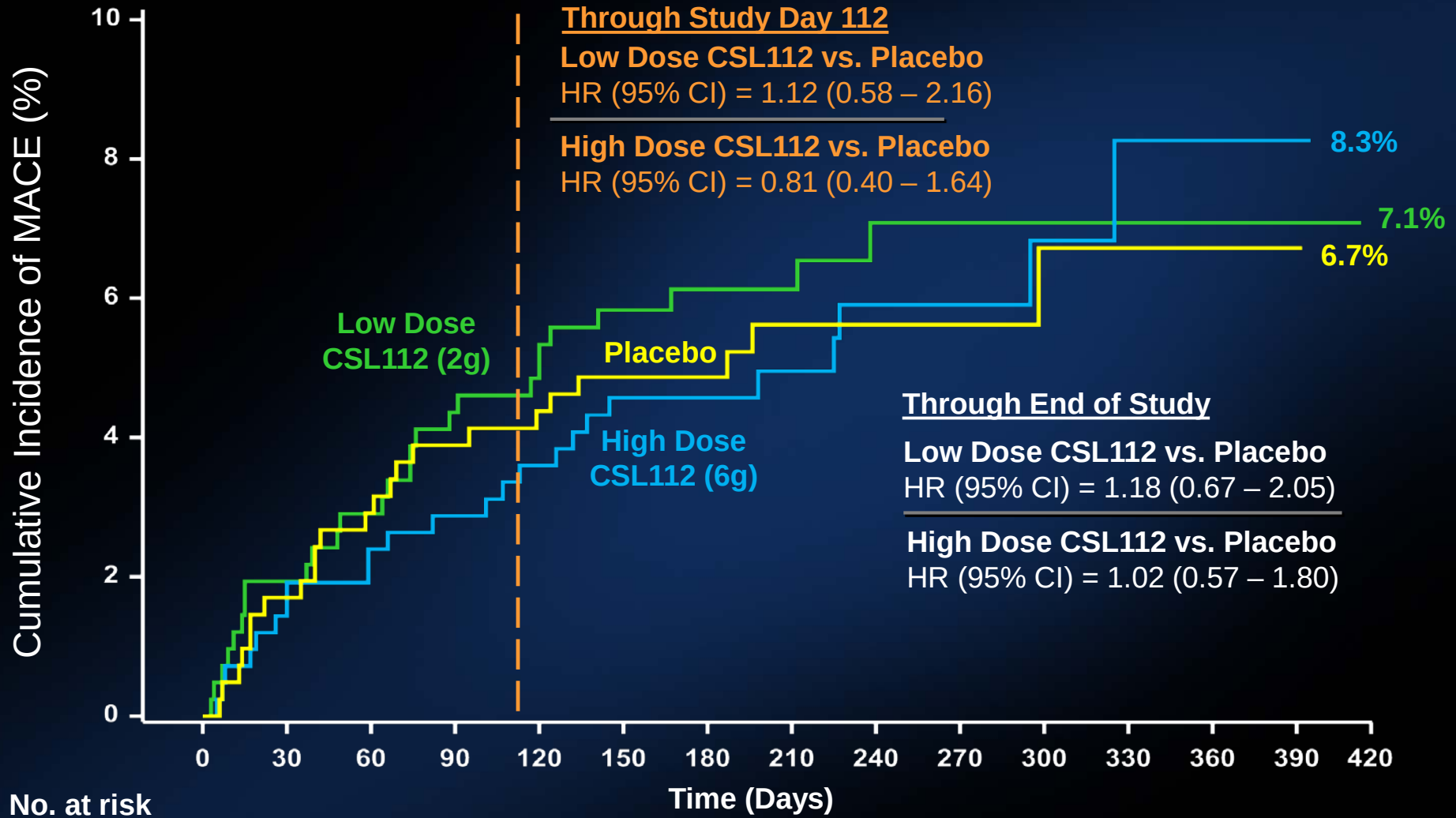
Některé ale také pro hoFH

Nezapomněli jsme na něco?
HDL ~~cholesterol~~ částice?

- ApoA1 Mimetics, such as APL-180 Novartis
- Full-length ApoA1, such as ApoA1 Cerenis Therapeutics
- Pre-Beta HDL, as generated by delipidation, HDL Therapeutics Inc.
- Reconstituted HDL, CSL Ltd.
- ApoA1 Milano MDCO216, The Medicines Company
- Trimeric ApoA1, Borean Pharma and now Roche
- RVX-208, as developed by Resverlogix
- Fx-5A, as developed by Kinemed Inc.

Time-to-First MACE

CV Death, Nonfatal MI, Ischemic Stroke, UA Hospitalization



No. at risk															
CSL112 2g	419	405	400	393	390	360	290	229	172	131	92	57	34	6	0
CSL112 6g	421	411	407	404	401	367	289	230	179	130	96	56	28	3	0
Placebo	418	404	399	394	391	360	283	220	171	123	84	53	24	2	0

Gibson et al. AHA 2016

Hypolipidemika v praxi kardiologa

Léčíme podle rizika: Statiny časněji a vyšší dávky

Kombinace hypolipidemik včetně fixních

Biologická hypolipidemická léčba

Nové terapie pro vzácné poruchy (hoFH, fam. chylomikronemie)

Chcete se dozvědět více?

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