Metabolická onemocnění u akutního srdečního selhání, AIM a srdeční zástavy: dyslipidemie

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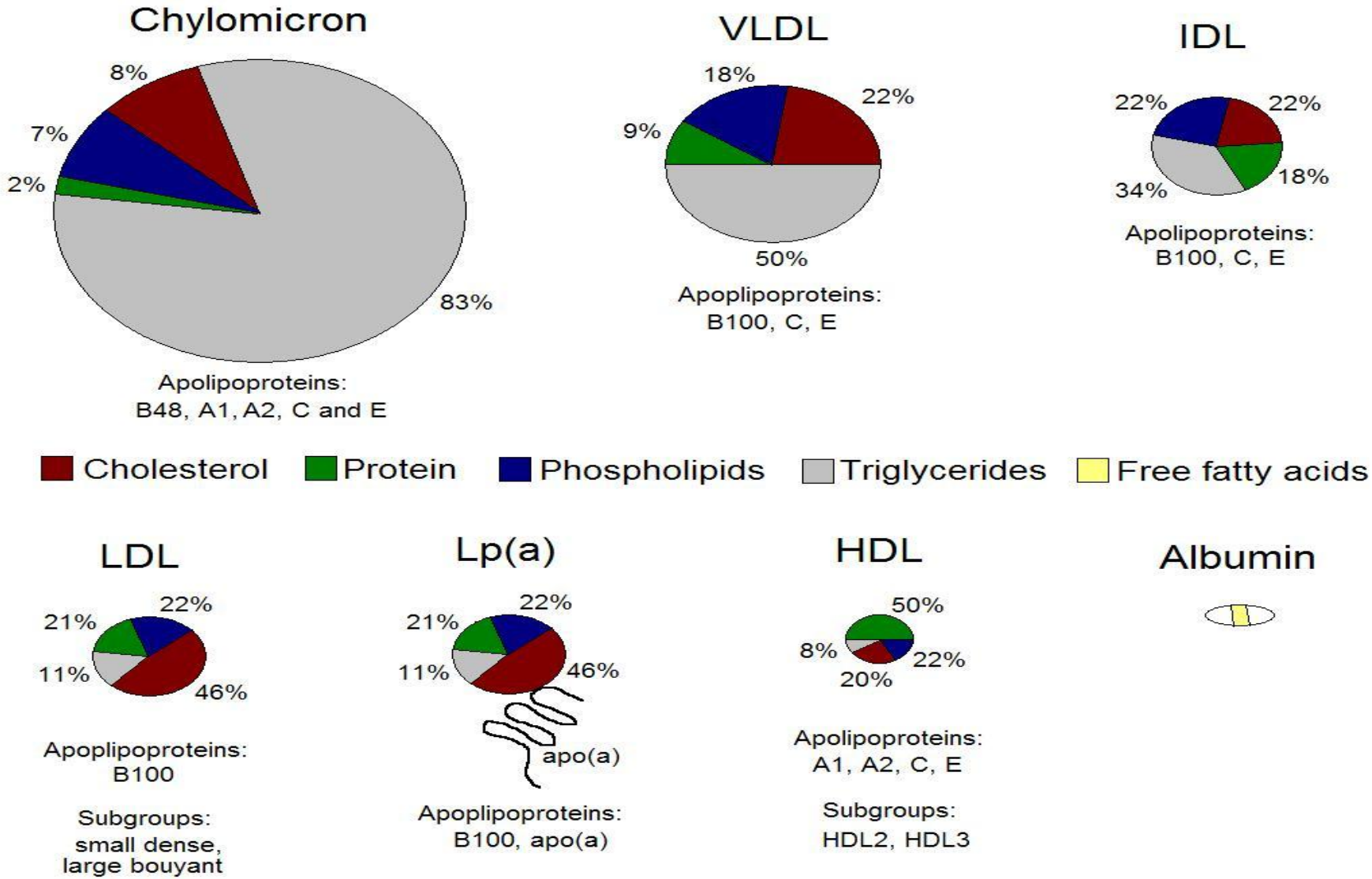
Česká asociace preventivní kardiologie ČKS

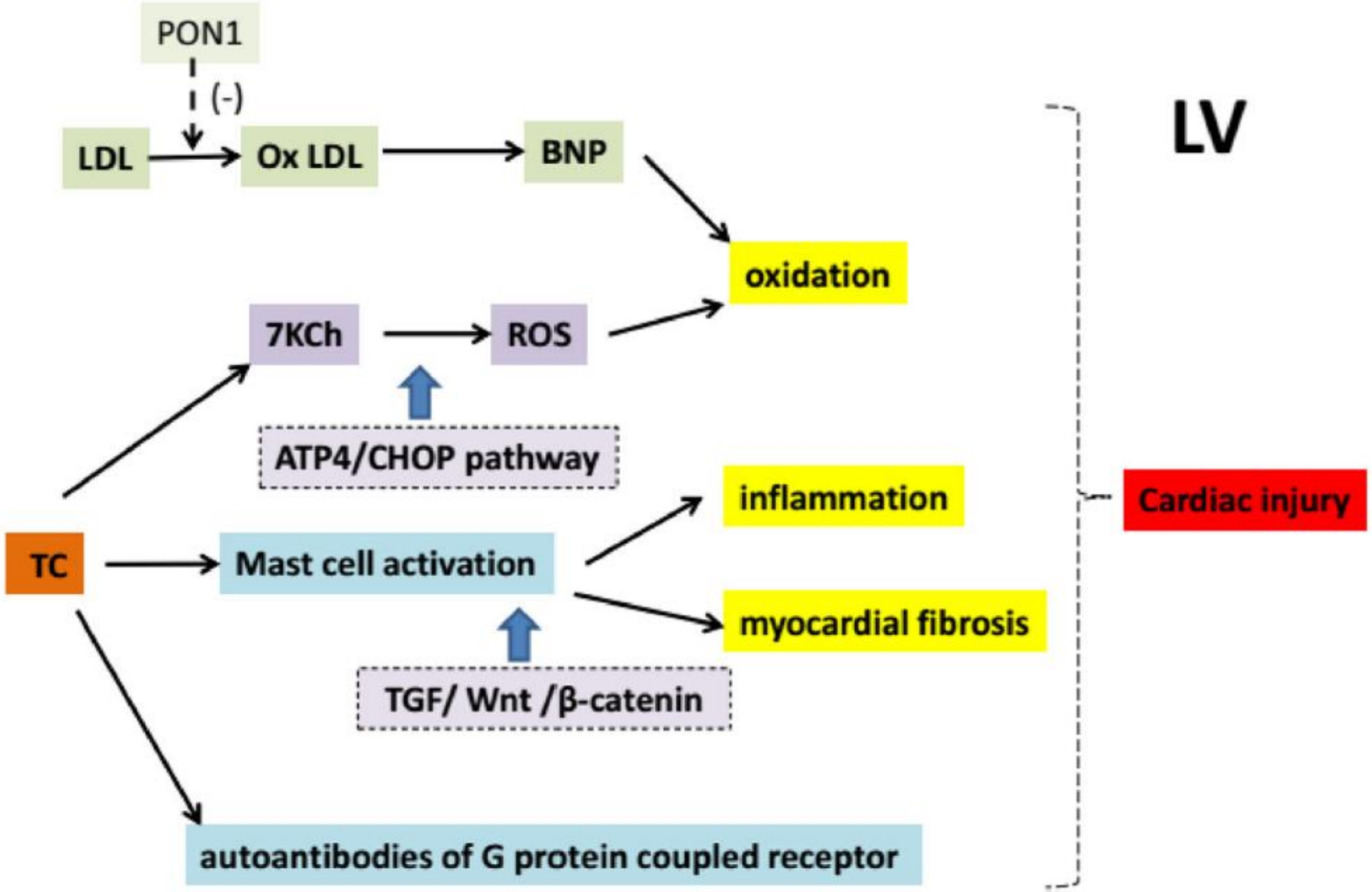
Na lipidy a AIM a srdeční zástavu máme jiné…

Proč hovořit o lipidech v kontextu srdečního selhání ?



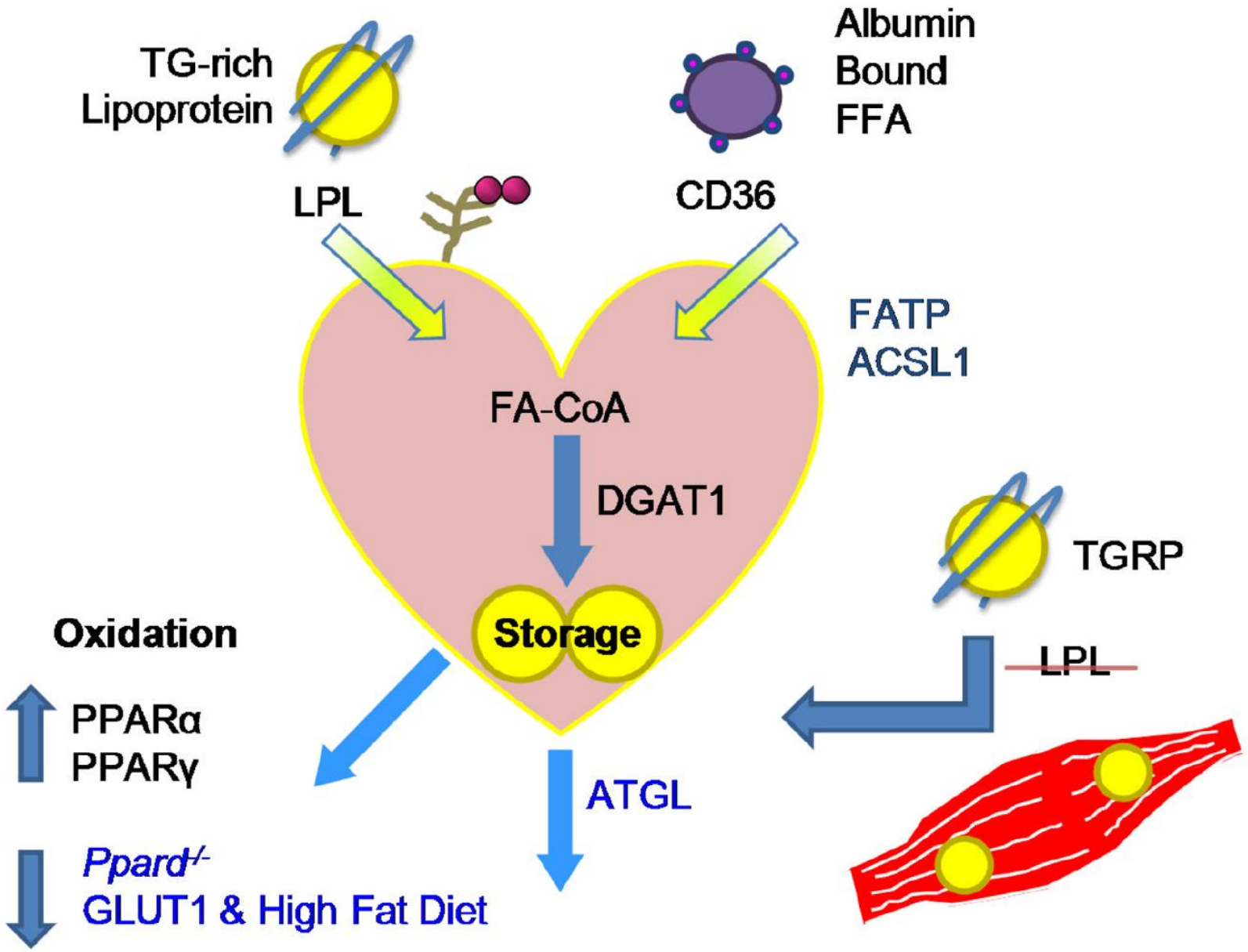
http://www.robertbarrington.net/wp-content/uploads/2013/03/Lipoprotein-Classes.jpg

Od plazmatických lipidů k poškození myokardu



Yao et al. Lipids in Health and Disease (2020) 19:23

Lipotoxicita u selhávajícího kardiomyocytu



Cell Metab. 2012 June 6; 15(6): 805–812. doi:10.1016/j.cmet.2012.04.006

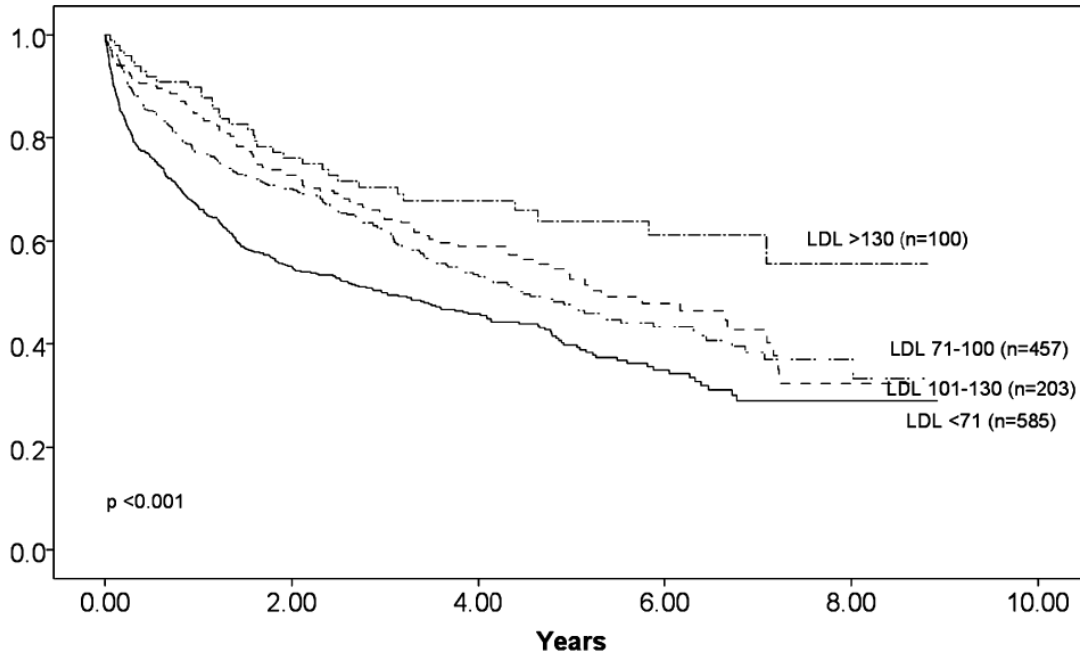
Lipidové parametry a riziko srdečního selhání ve studii AMORIS (n= 84740)

Biomarker	Men		Test of interaction (P)	Women		Test of interaction (P)
	HR (WO)	HR (W)		HR (WO)	HR (W)	
LC						
ApoB	1.36	1.34	0.043	1.23	1.22	0.242
ApoA-1	0.83	0.83	0.242	0.88	0.88	0.711
ApoB/apoA-1	1.41	1.39	0.045	1.25	1.24	0.171
LDL-C	1.32	1.31	0.115	1.19	1.18	0.956
HDL-C	0.77	0.78	0.227	0.84	0.83	0.075
Non-HDL-C	1.37	1.36	0.061	1.25	1.24	0.354
TG	1.28	1.26	0.161	1.25	1.23	0.001
TC/HDL-C	1.26	1.25	0.968	1.19	1.18	0.103
TC	1.28	1.26	0.166	1.18	1.16	0.725
Inflammation: Hp	1.19	1.20	0.002	1.12	1.14	0.309
Metabolism: glucose	1.11	1.10	0.035	1.05	1.03	0.083
Antioxidant: uric acid	1.19	1.19	0.424	1.20	1.19	0.174

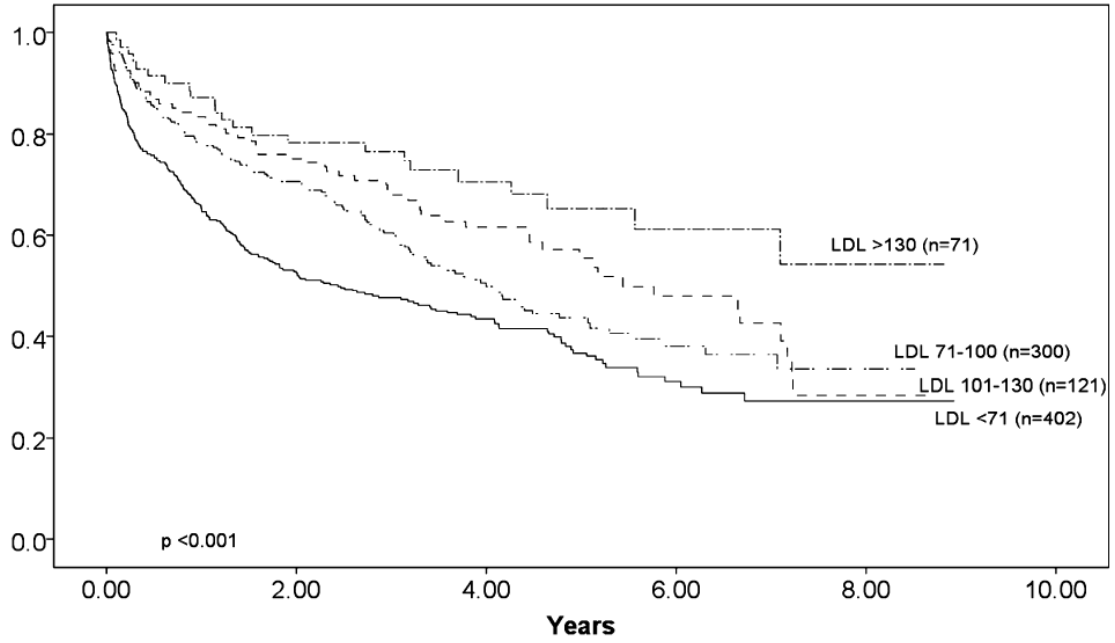
European Journal of Heart Failure (2009) 11, 1036–1042

Nízká hladina LDL-C- negativní prognostický ukazatel u akutního SS: (reverzní) kauzalita?

Mortalita nemocných s HFrEF dle LDL-C

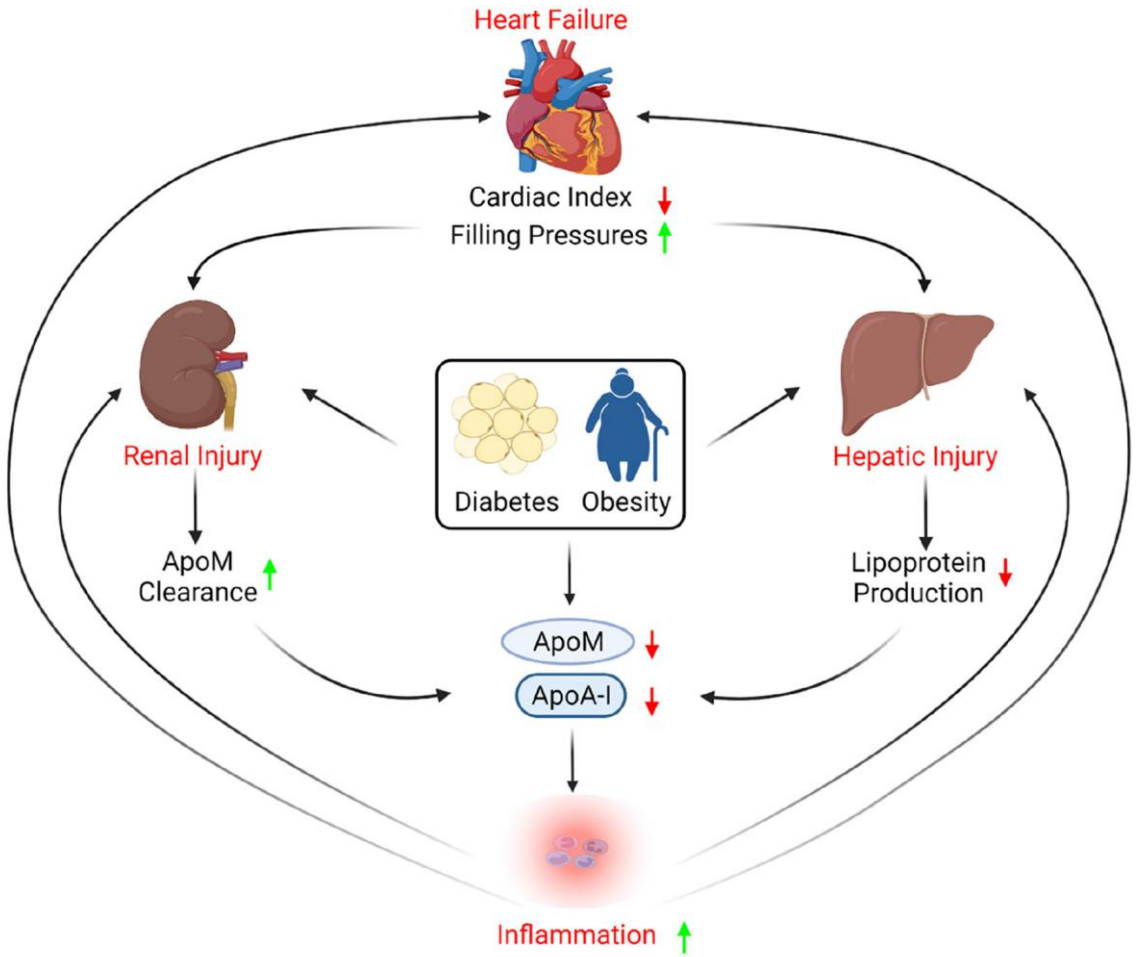


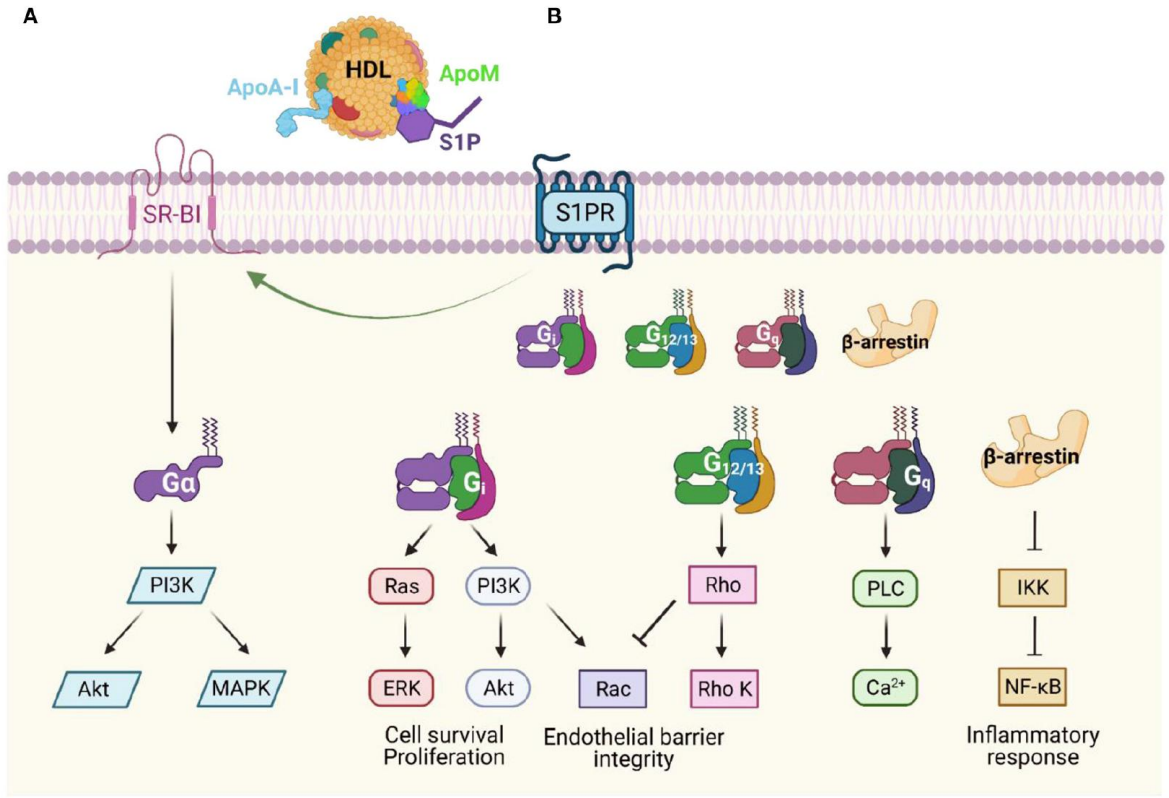
Mortalita nemocných s ICHS a HFrEF dle LDL-C



Congest Heart Fail. 2013;19:85–91 Vol. 19 | No. 2 | March . Apri

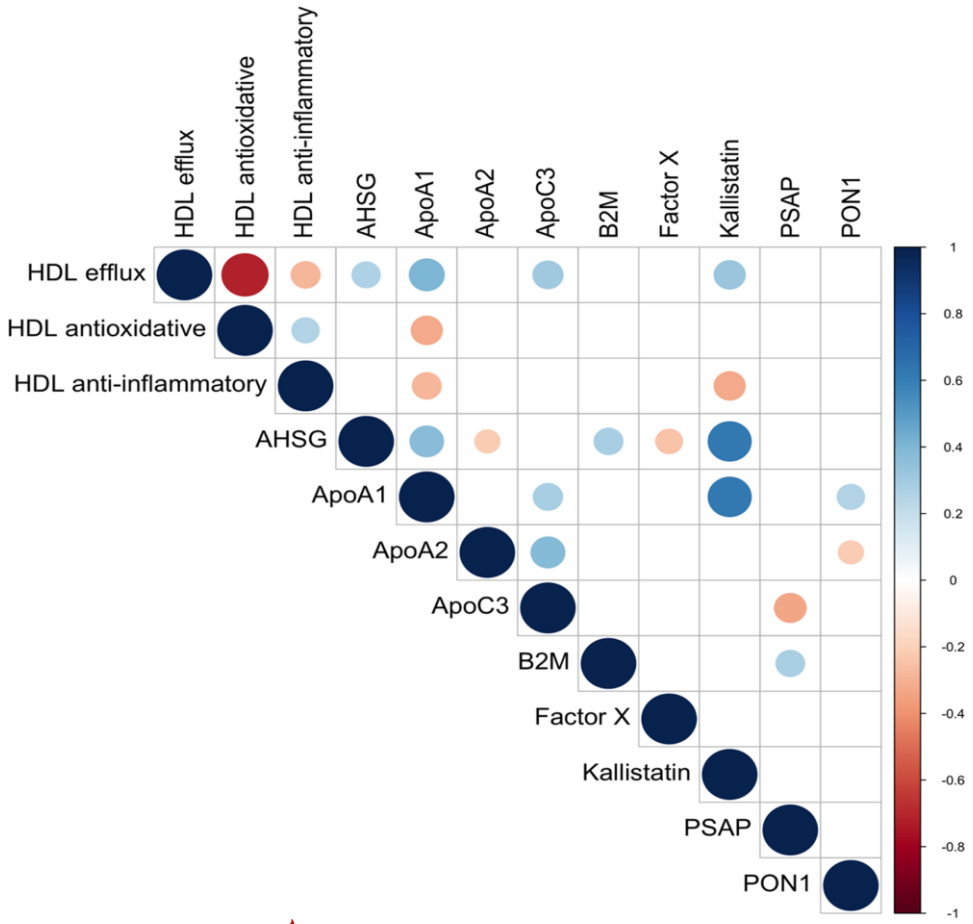
HDL, apoproteiny a srdeční selhání



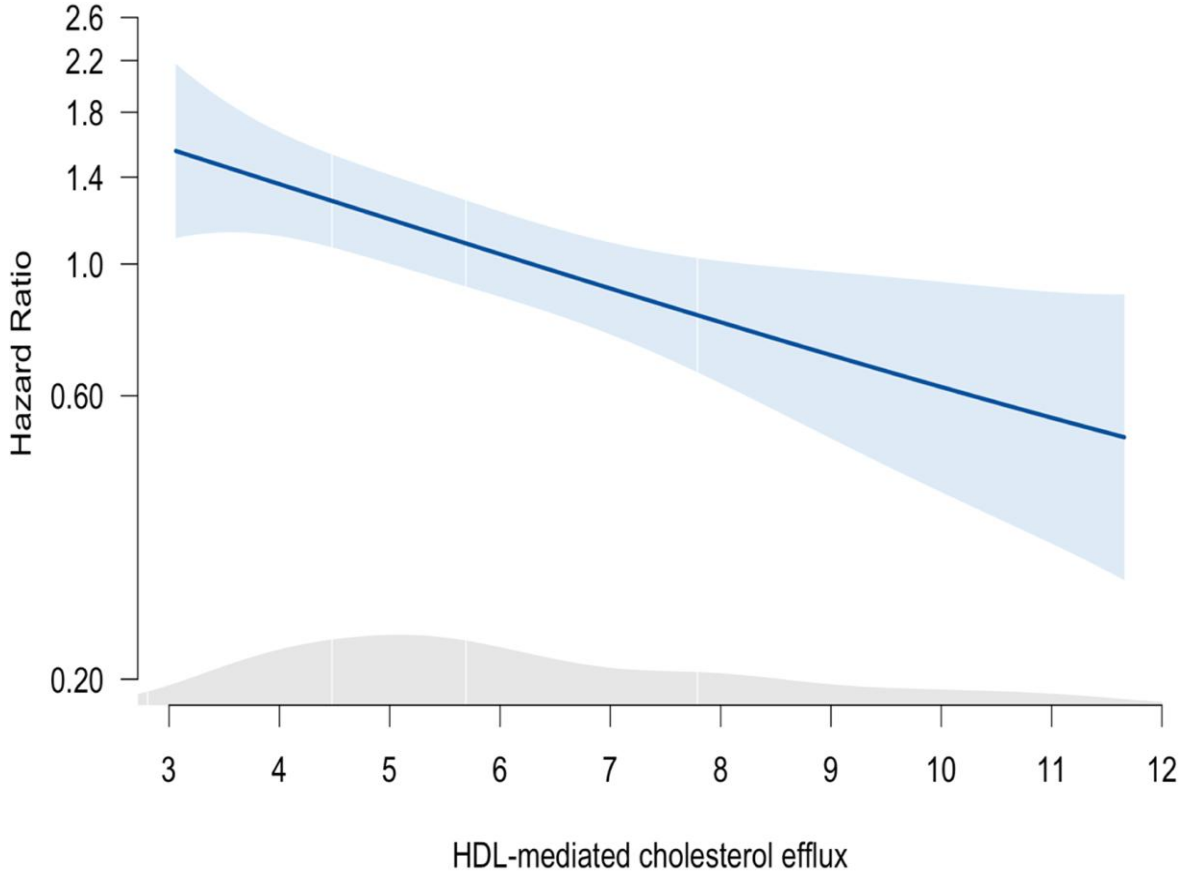


HDL částice a srdeční selhání: funkce je zásadní

Markery funkcionality HDL částice

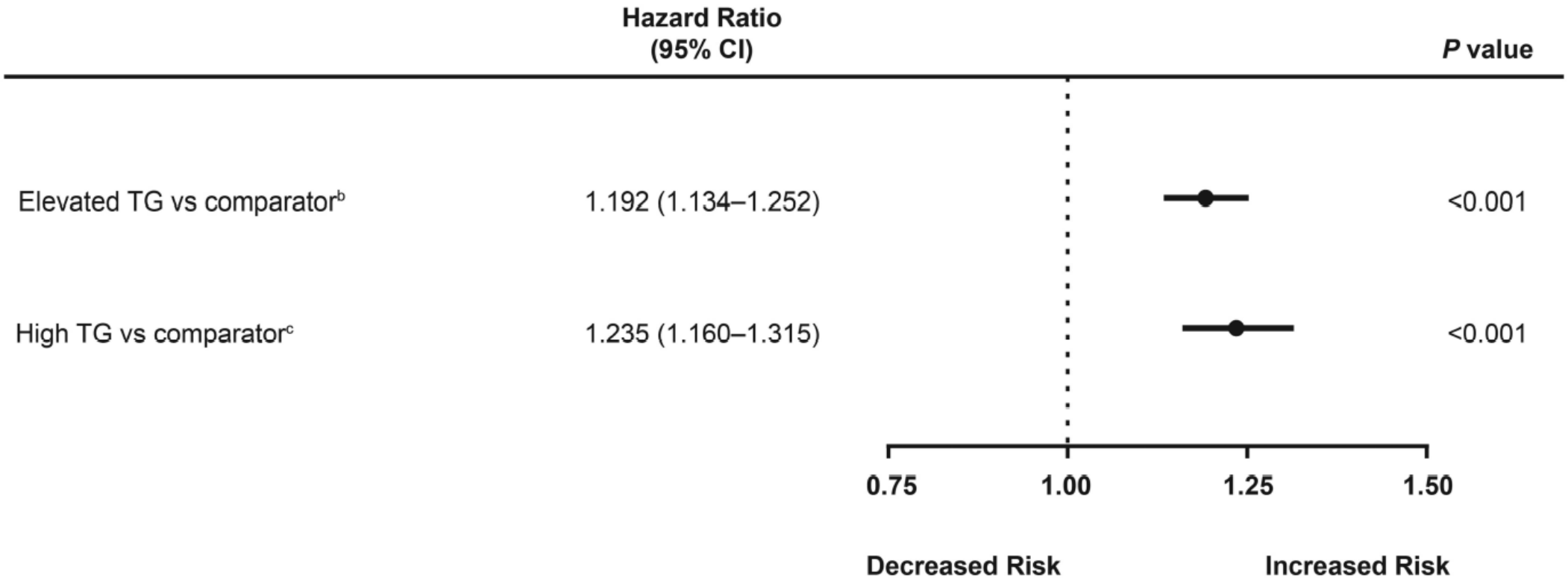


Mortalita a HDL zprostředkovaný eflux cholesterolu



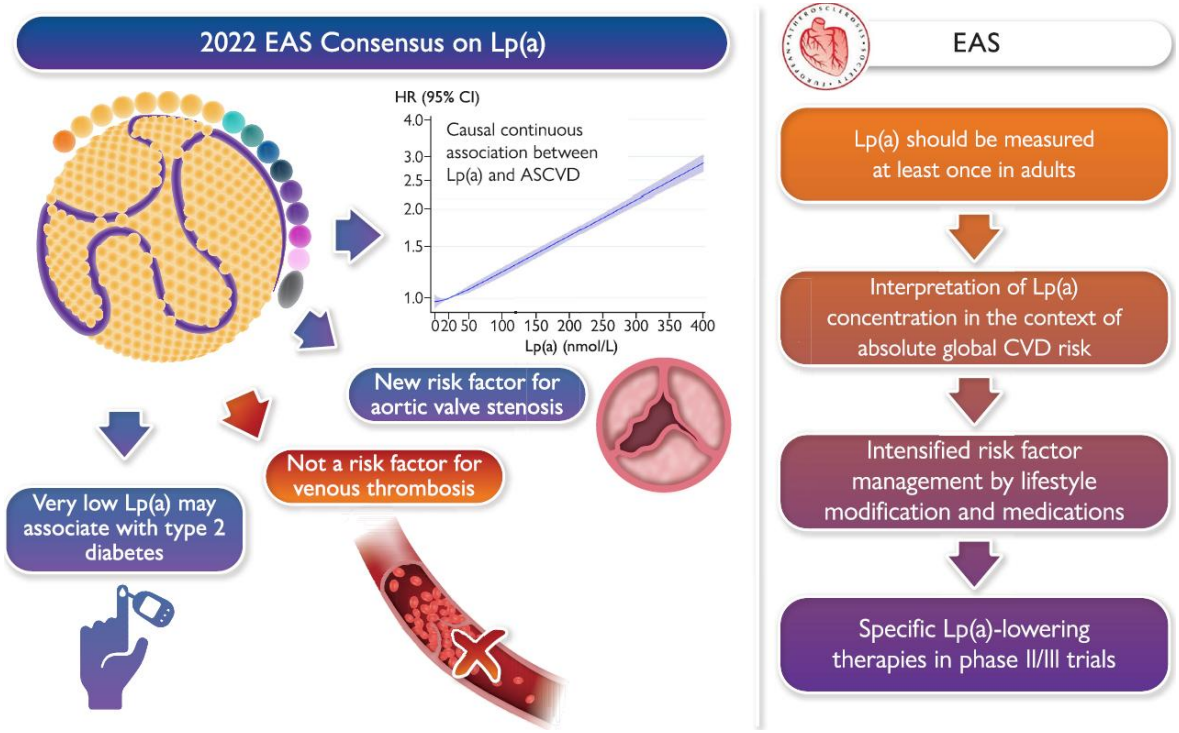
Johanna E. Emmens. Journal of the American Heart Association. Impaired High-Density Lipoprotein Function in Patients With Heart Failure, Volume: 10, Issue: 9, DOI: (10.1161/JAHA.120.019123)

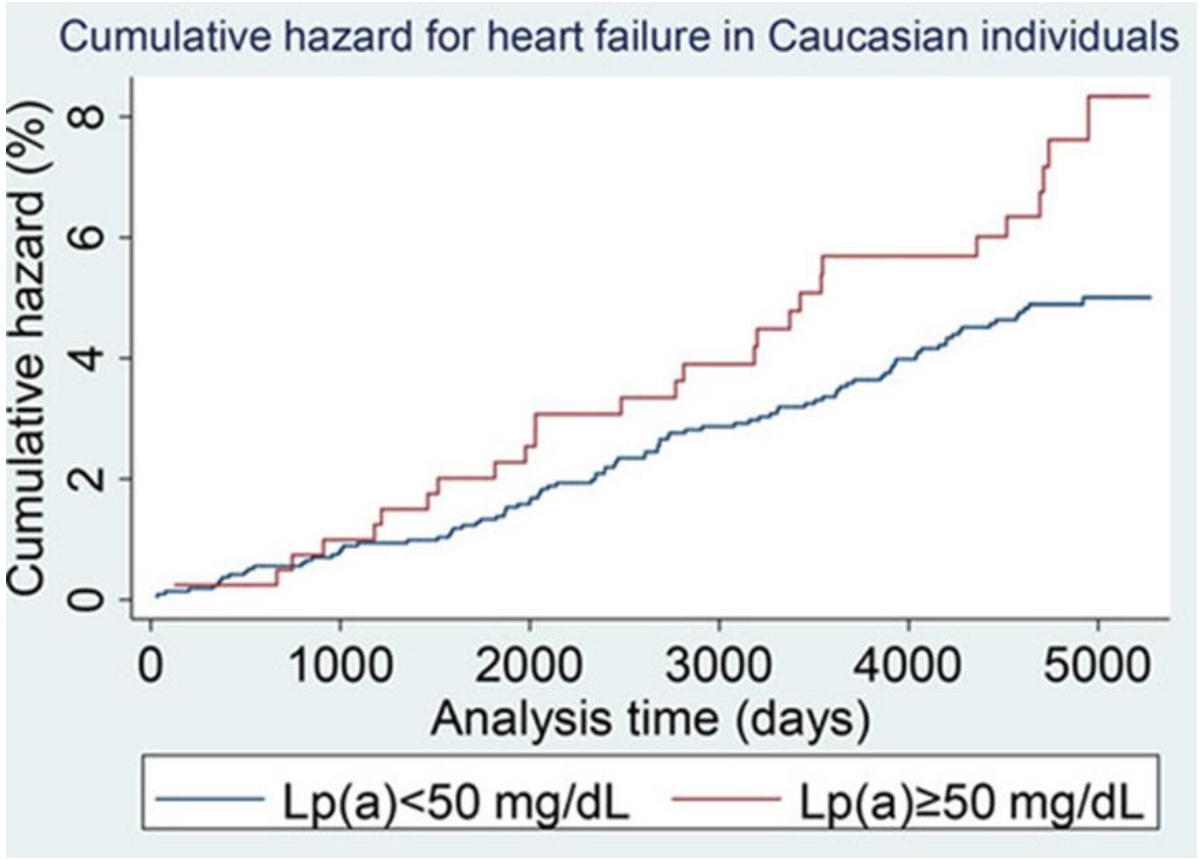
TG a riziko srdečního selhání u pacientů léčených statiny, n= 65918



Vascular Health and Risk Management 2019:15 533–538

Lipoprotein (a), o kterém ještě uslyšíme…





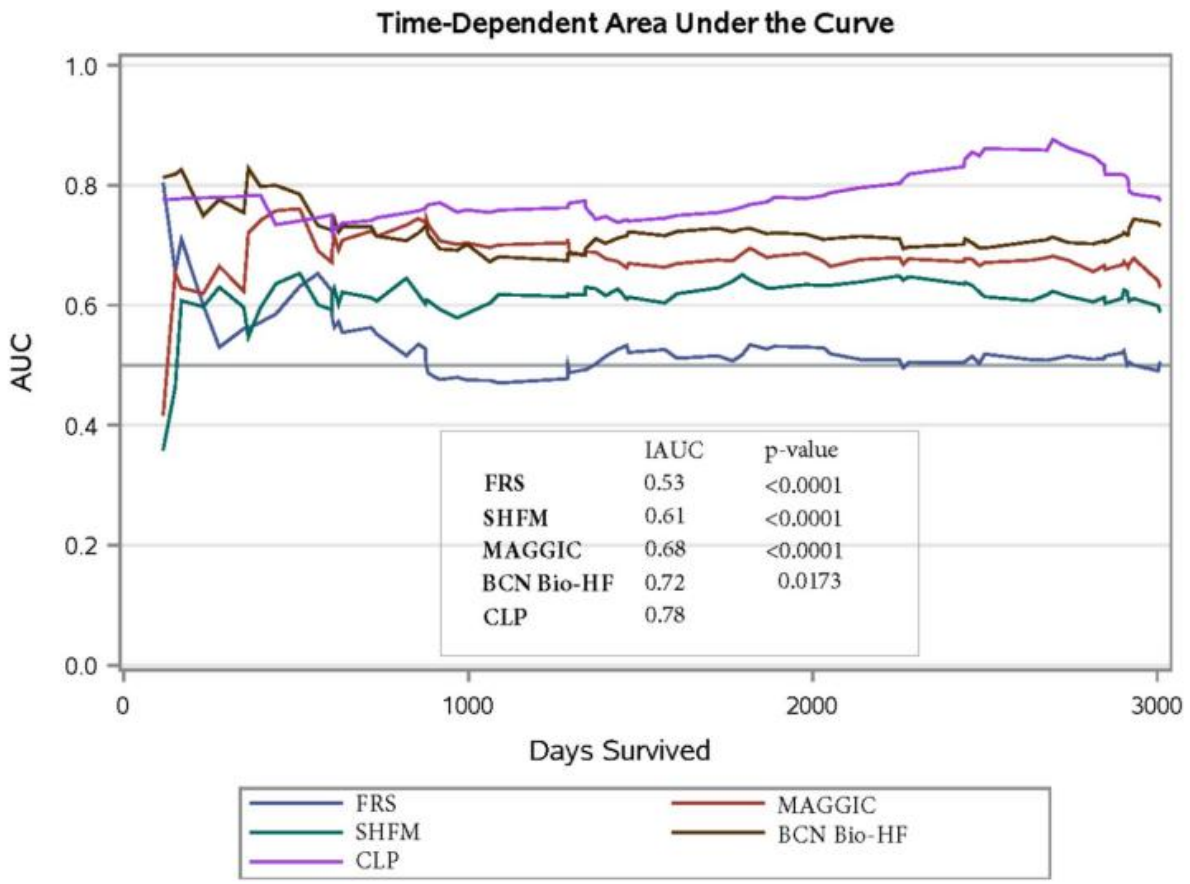
Kronenberg F et al. European Heart Journal (2022) **43**, 3925–3946
Brian T. Steffen. Arteriosclerosis, Thrombosis, and Vascular Biology. Lp(a) [Lipoprotein(a)]-Related Risk of Heart Failure Is Evident in Whites but Not in Other Racial/Ethnic Groups, Volume: 38, Issue: 10, Pages: 2498-2504, DOI: (10.1161/ATVBAHA.118.311220)

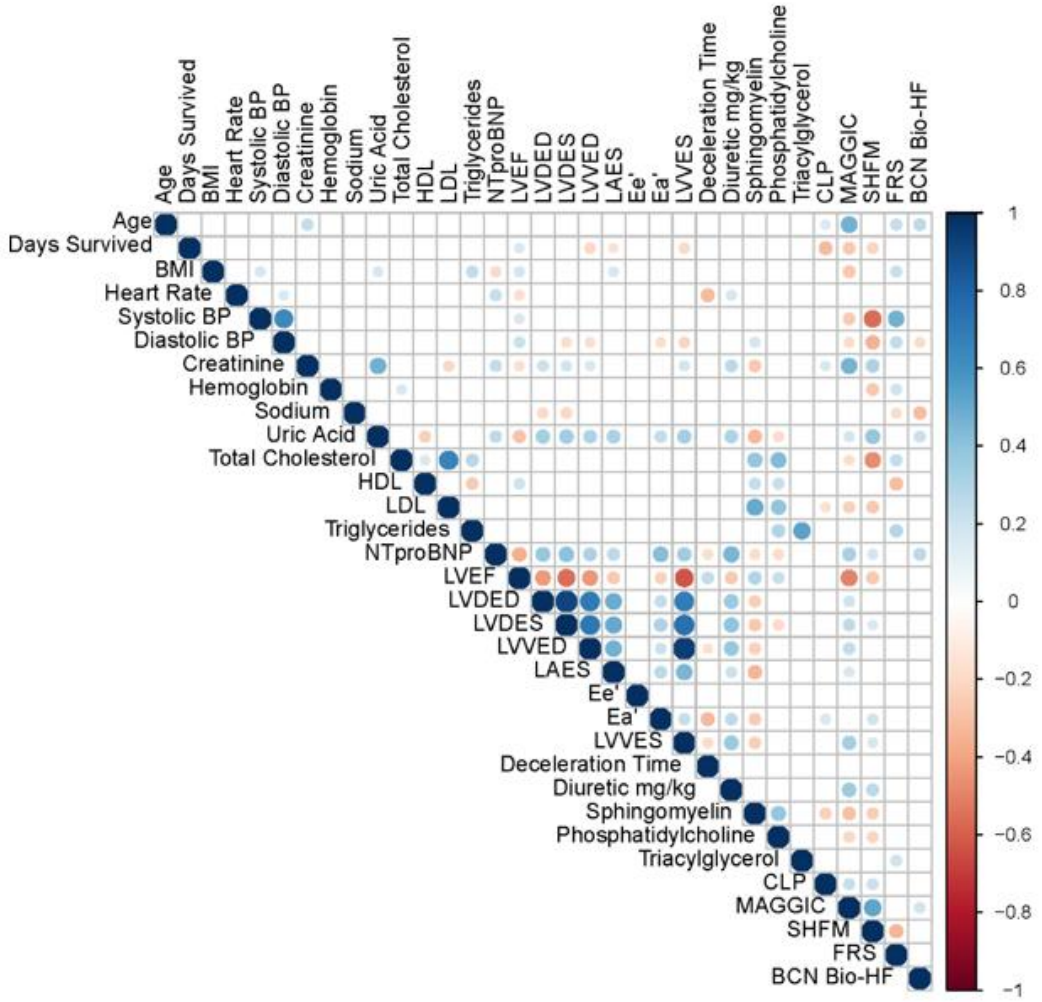
Lipidy jako nejsilnější prediktory prognózy CHSS: CLP +Nt pro BNP

Characteristic	Total	Prognostic score				
	n = 280	SHFM	FRS	MAGGIC	BCN Bio-HF	CLP
Age (years), mean ± SD	72 ± 4.9	✓	✓	✓	✓	
NYHA (II/III), n	188/91	✓		✓	✓	
Male, n (%)	206 (74)	✓	✓	✓	✓	
Body mass index (kg/m^2), mean ± SD	26.8 ± 3.4			✓		
Heart rate (bpm), mean ± SD	73 ± 13.0					
Systolic blood pressure (mm Hg), mean ± SD	134 ± 19	✓	✓	✓		
Diastolic blood pressure (mm Hg), mean ± SD	81 ± 11					
Years since first diagnosis of CHF	5.2 ± 5.6		✓			
Laboratory, mean ± SD						
Creatinine (µmol/L)	107 ± 27.9			✓		
Hemoglobin (g/dL)	13.4 ± 1.5	✓			✓	
Sodium (mEq/L)	141.4 ± 3.3	✓			✓	
Uric acid (µmol/L)	356 ± 127	✓				
Total Cholesterol (mmol/L)	5.1 ± 1.6					
HDL cholesterol (mmol/L)	1.2 ± 0.5		✓			
LDL cholesterol (mmol/L)	3.4 ± 1.3					
Triglycerides (mmol/L)	1.7 ± 1.0					
Lymphocytes (%)*		✓				
NT-proBNP (pg/mL)	793 (331–1765)†				✓	✓
PC 16:0/18:2 (µg/dl)	36,810 (32,435–40,015)†					✓
TAG 18:1/18:0/18:0 (µg/dl)	121 (76.5–256.4)†					✓
SM d18:1/23:1, SM d18:2/23:0, SM d17:1/24:1 (µg/dl)	1342 (1134–1596)†					✓

McGranaghan, P., Saxena, A., Düngen, HD. *et al.* Performance of a cardiac lipid panel compared to four prognostic scores in chronic heart failure. *Sci Rep* **11**, 8164 (2021).

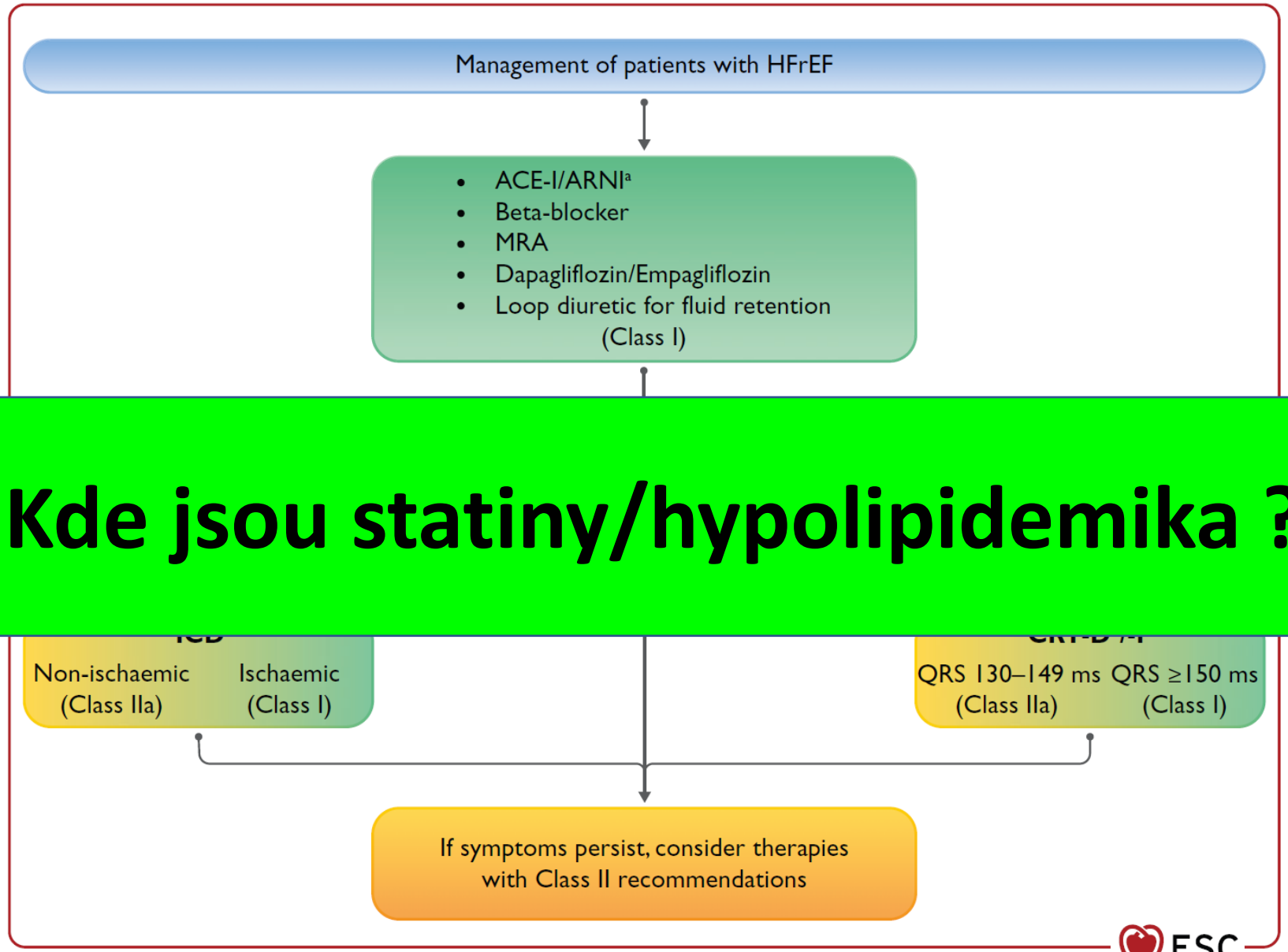
Lipidy jako nejsilnější prediktory prognózy CHSS Cardiac Lipid Panel (CLP)





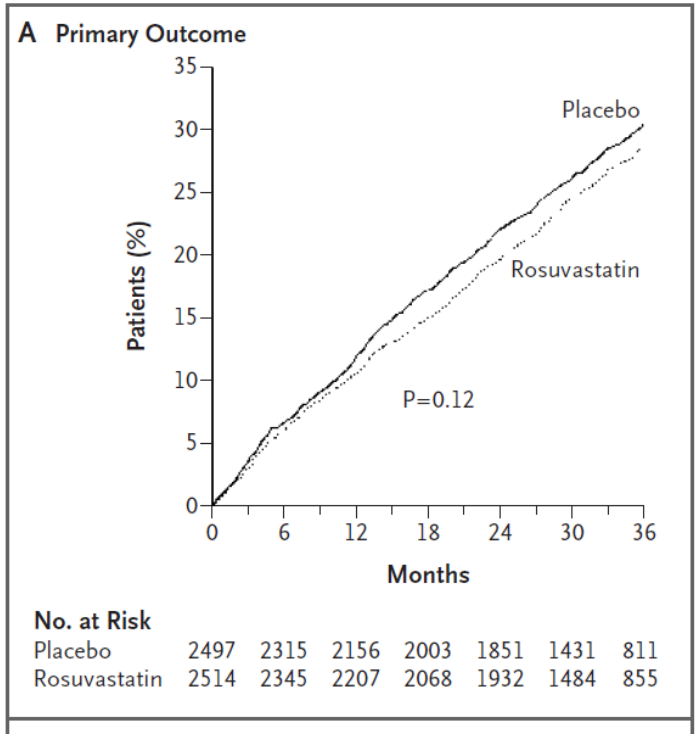
McGranaghan, P., Saxena, A., Düngen, HD. *et al.* Performance of a cardiac lipid panel compared to four prognostic scores in chronic heart failure. *Sci Rep* **11**, 8164 (2021).

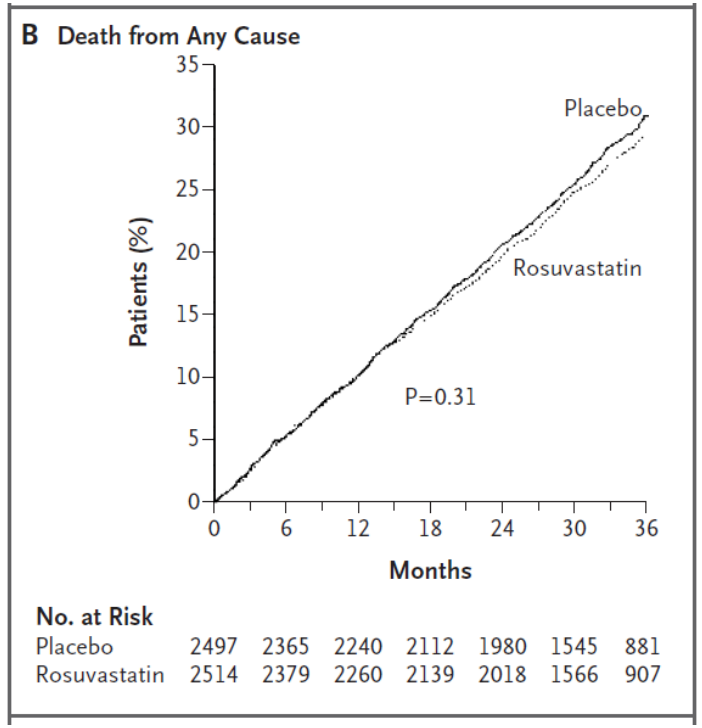
Taktika farmakoterapie srdečního selhání

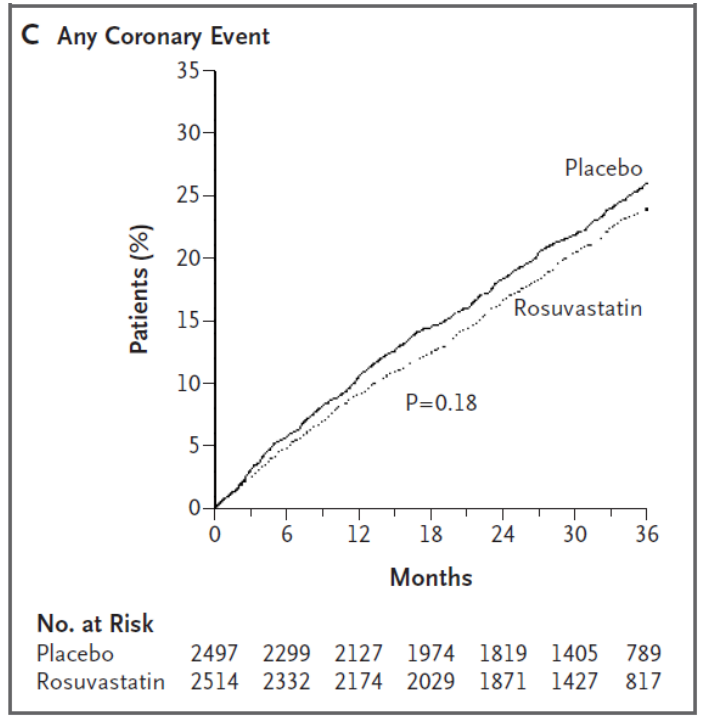


Kde jsou statiny/hypolipidemika ?

CORONA studie: rosuvastatin vs. placebo u HFrEF



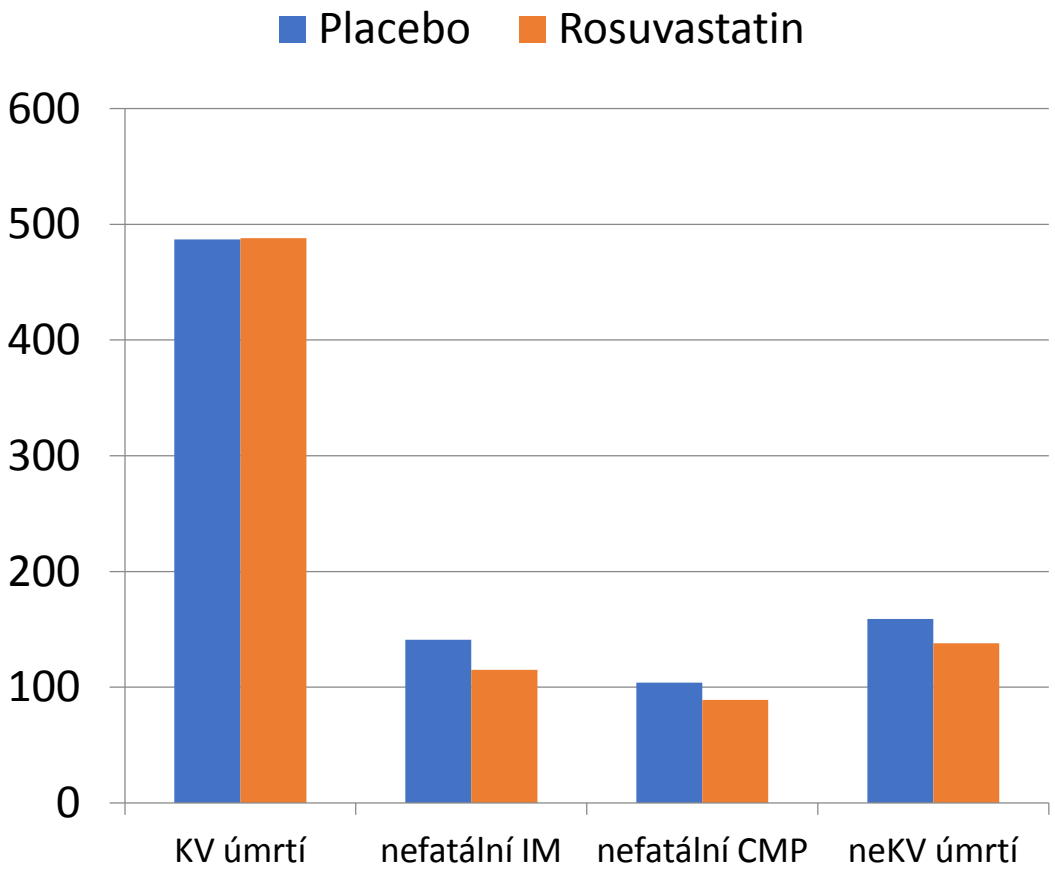




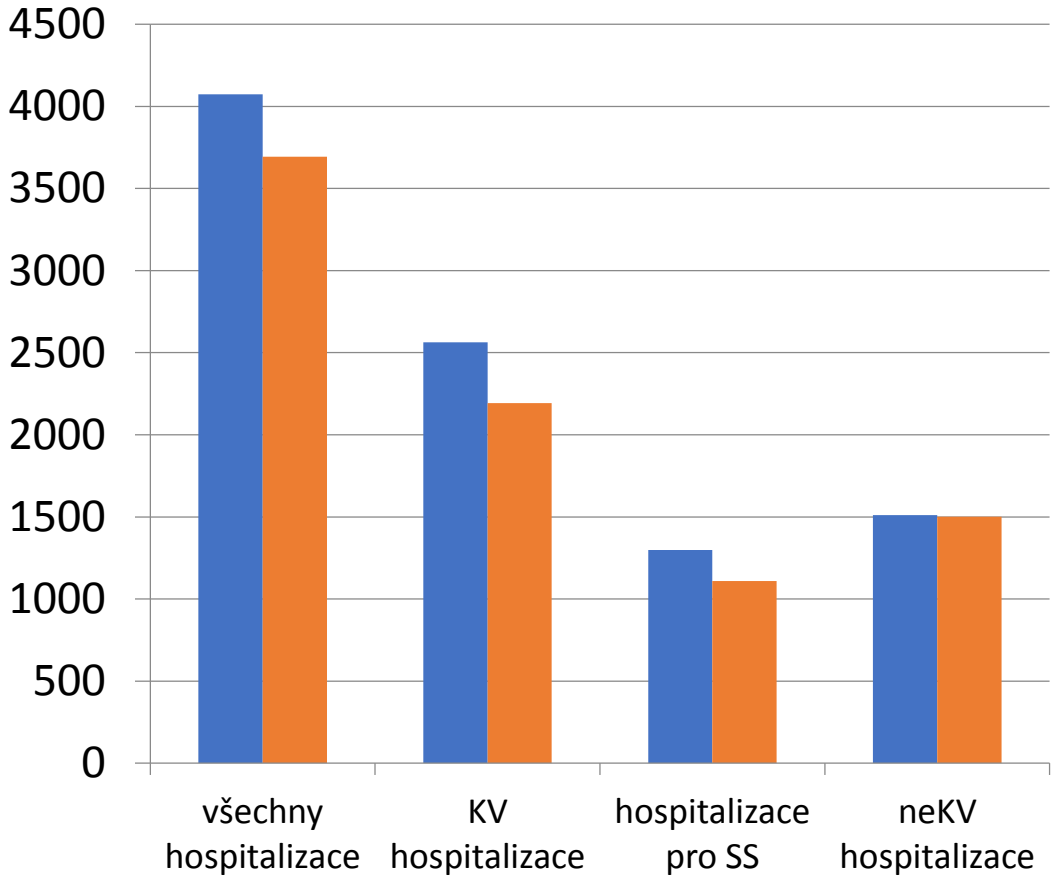
N Engl J Med 2007;357:2248-61.

Statiny u srdečního selhání: studie CORONA s rosuvastatinem

Počty příhod ve studii CORONA

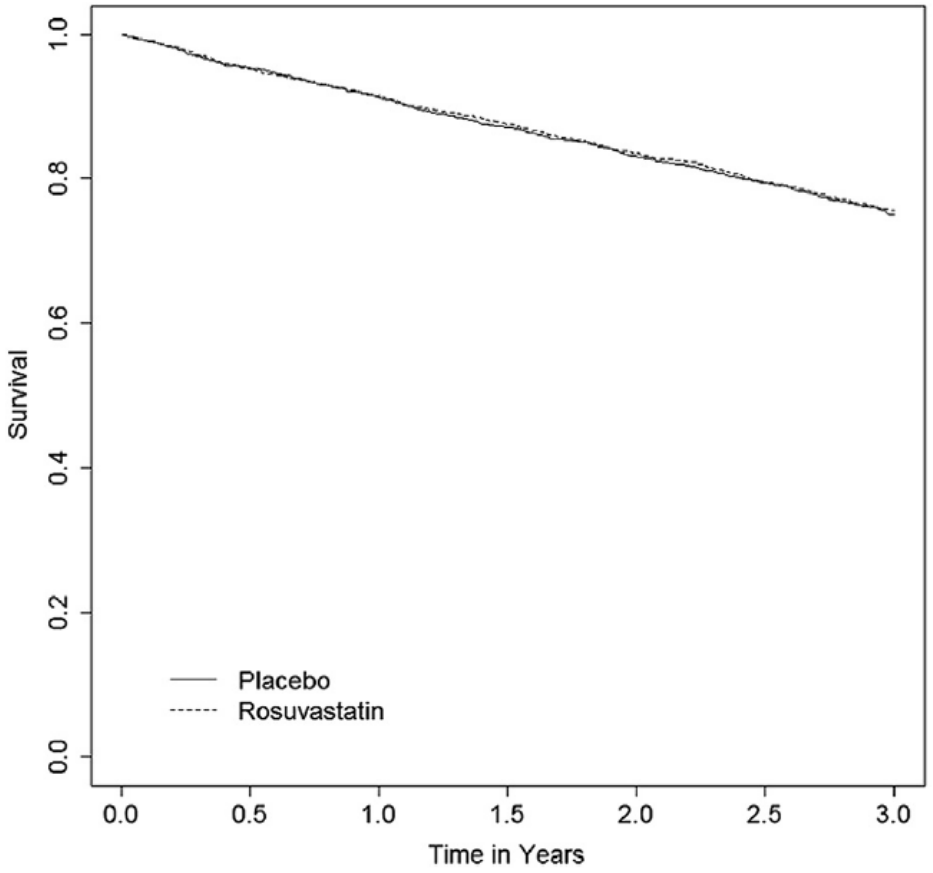


Počty hospitalizací ve studii CORONA

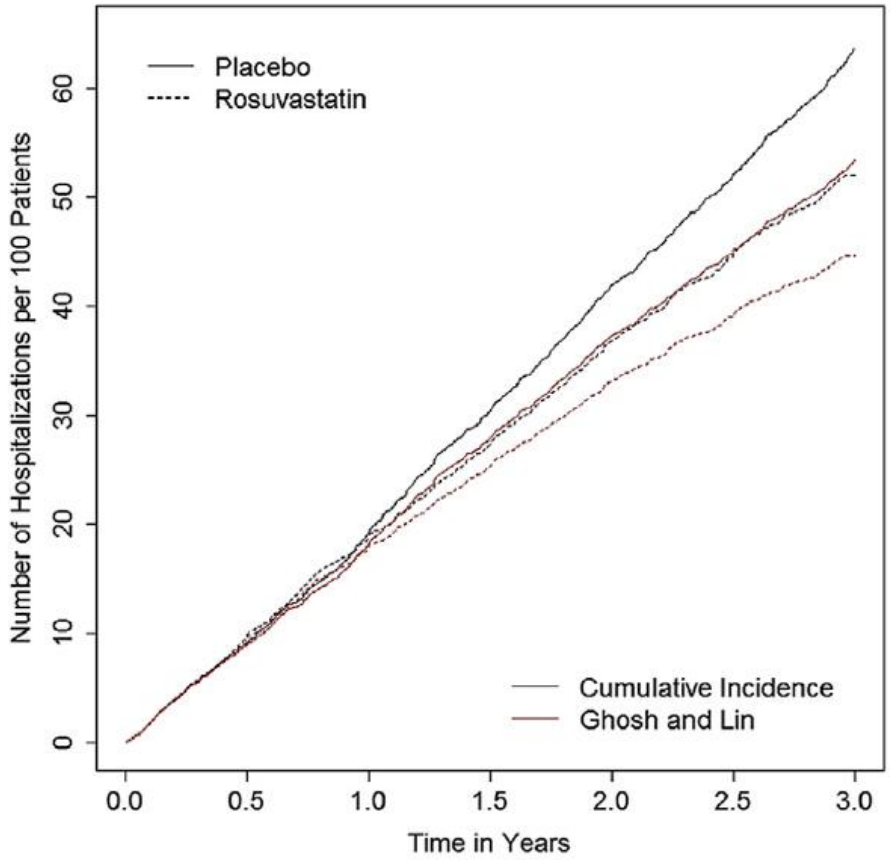


Studie CORONA v další analýze

Kardiovaskulární úmrtí



Hospitalizace pro srdeční selhání

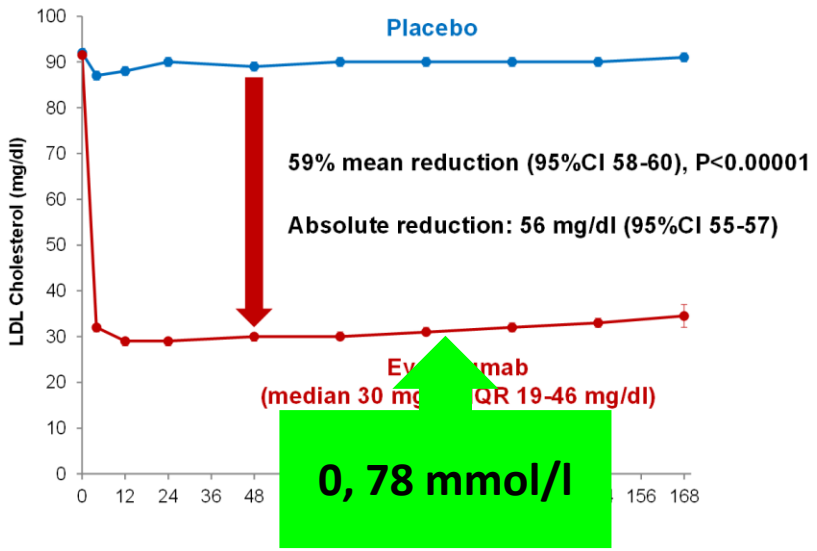


JACC: Heart Failure Vol. 2, No. 3, 2014

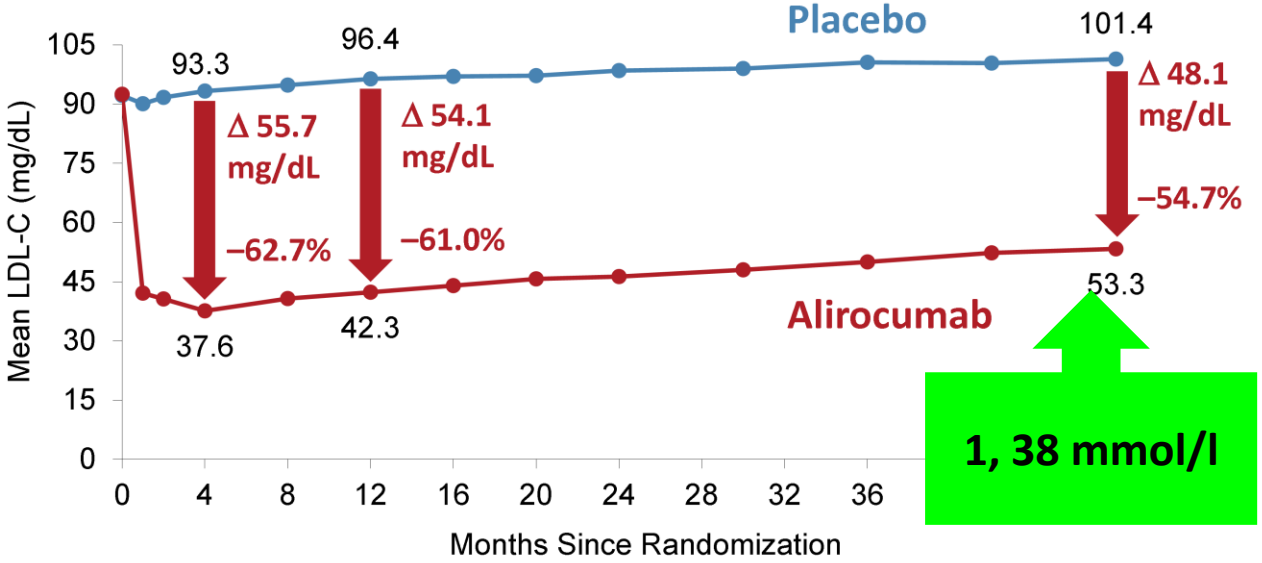
Vliv dlouhodobě výrazně snížené koncentrace LDL-C na riziko rozvoje SS ???

LDL cholesterol: kombinace statin +/- eze + PCSK9 i

FOURIER



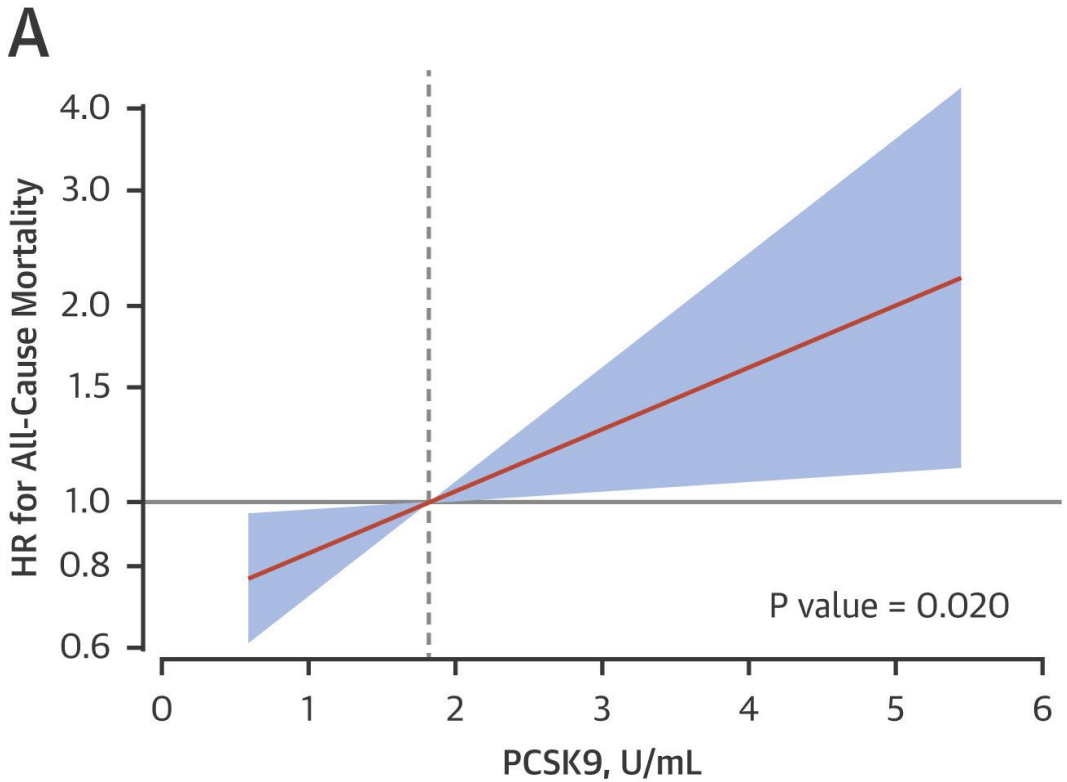
ODYSSEY Outcomes

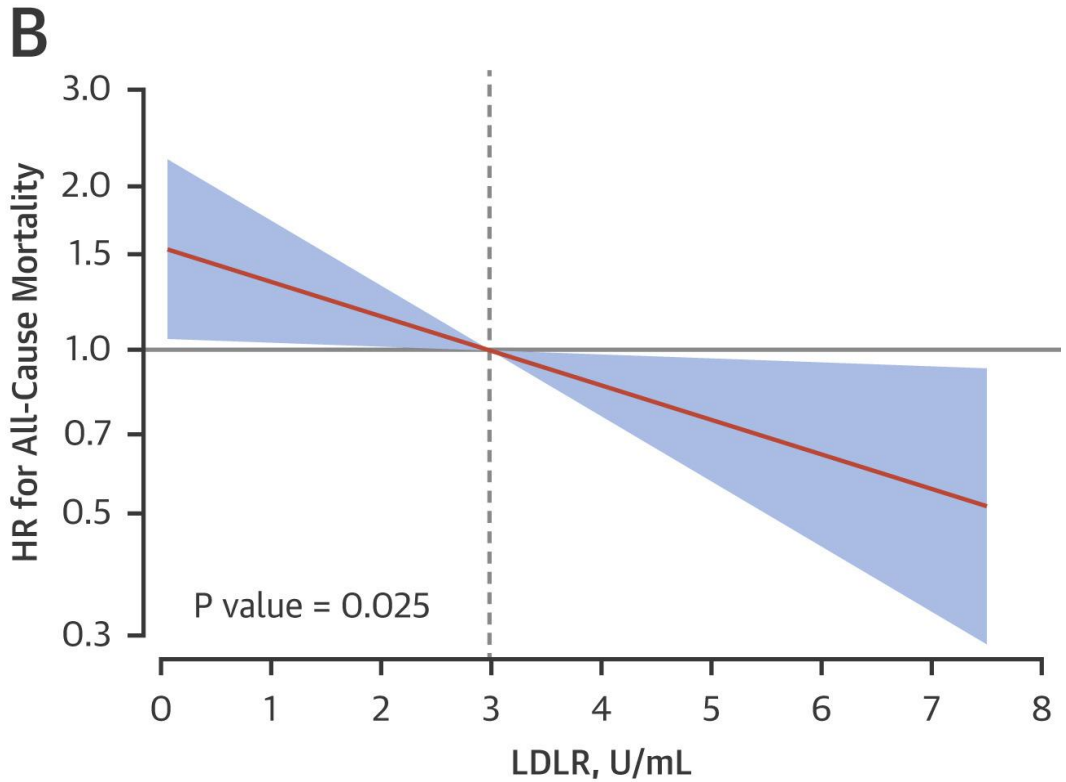


Sabatine MS *et al.* N Engl J Med. 2017 Mar 17. doi: 10.1056/NEJMoa1615664. Steg et al. ACC Orlando, 2018

PCSK9 a LDLR a mortalita u SS

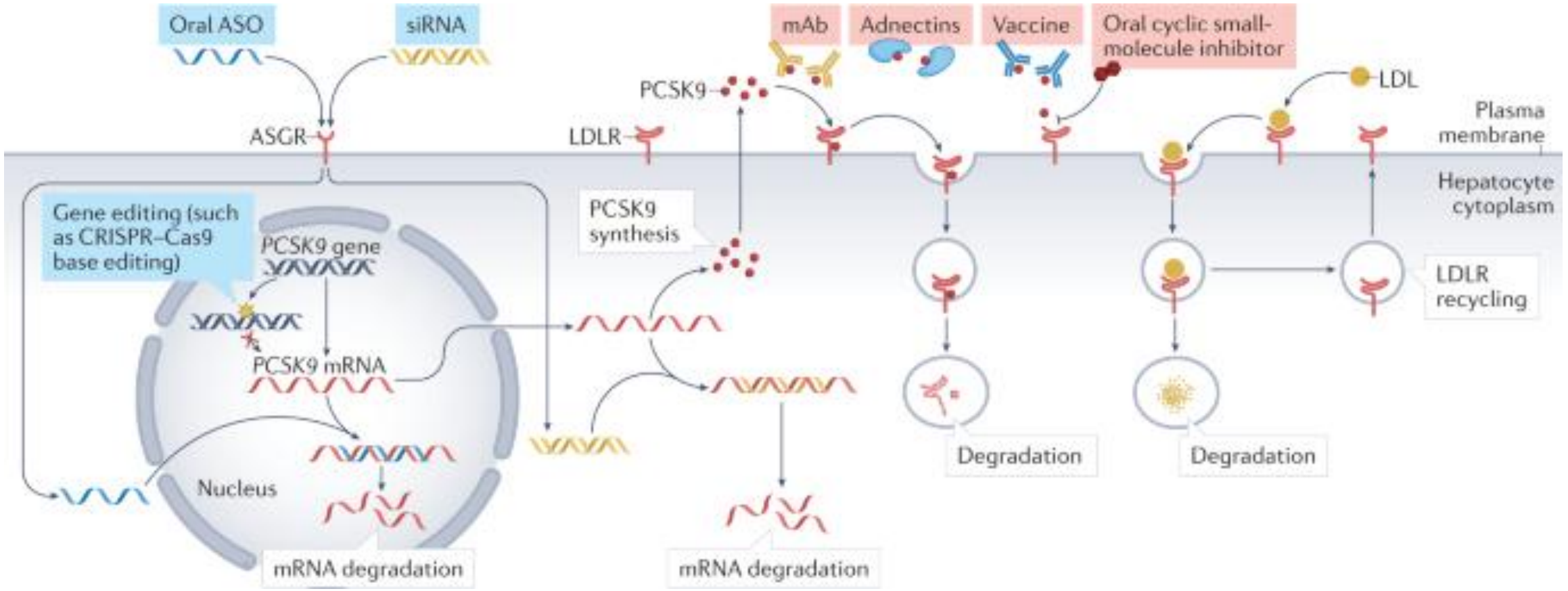
- BIOSTAT-CHF study
- 2174 pacientů, věk 68, 53 % Hx ICHS
- 569 úmrtí/896 kombinovaných endpointů za 21 měsíců sledování





J Am Coll Cardiol 2017;70:2128–36

Všichni proti proprotein konvertáze subtilisin kexin 9

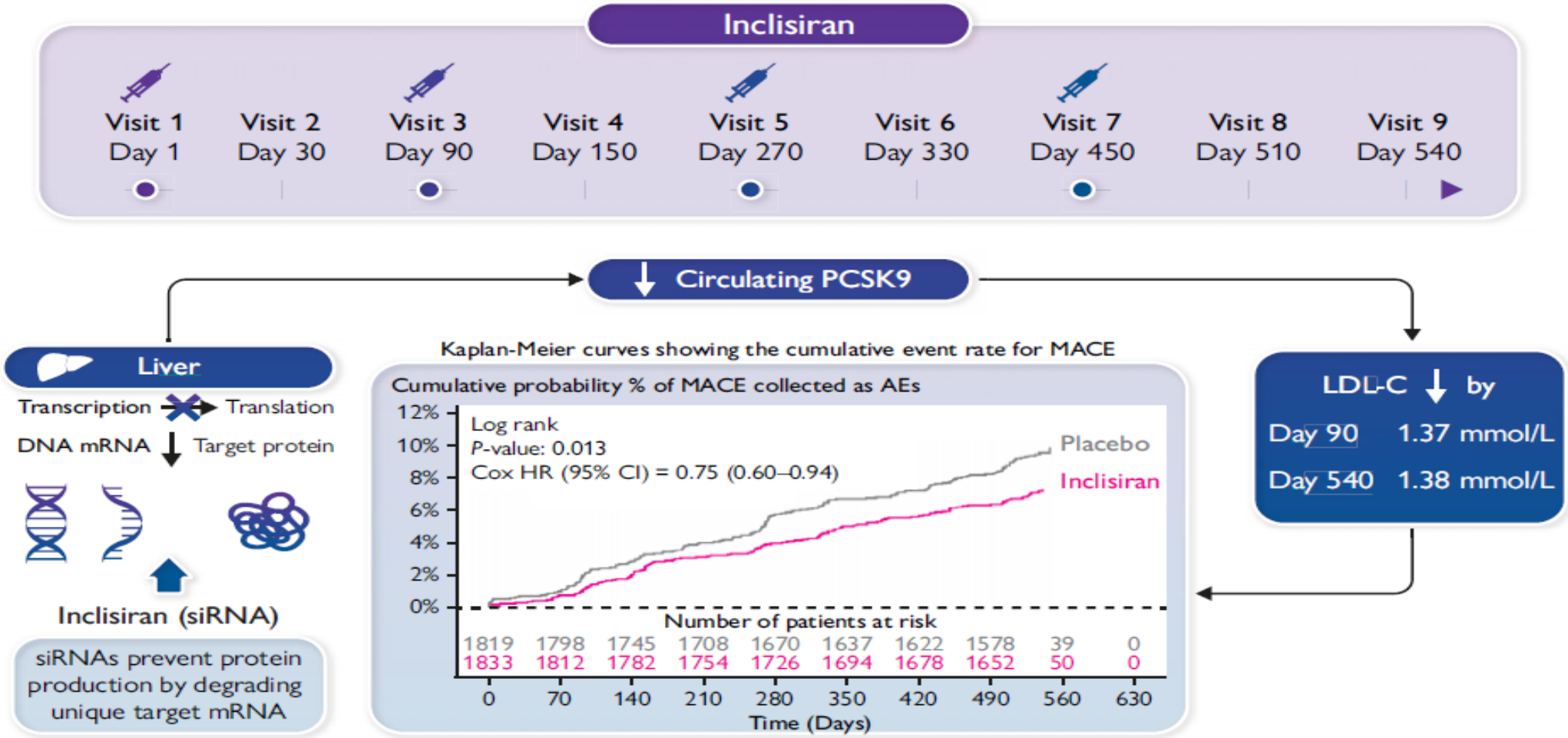


Rifai, M.A., Ballantyne, C.M. PCSK9-targeted therapies: present and future approaches. *Nat Rev Cardiol* (2021)

Inklisiran a jeho bezpečnost

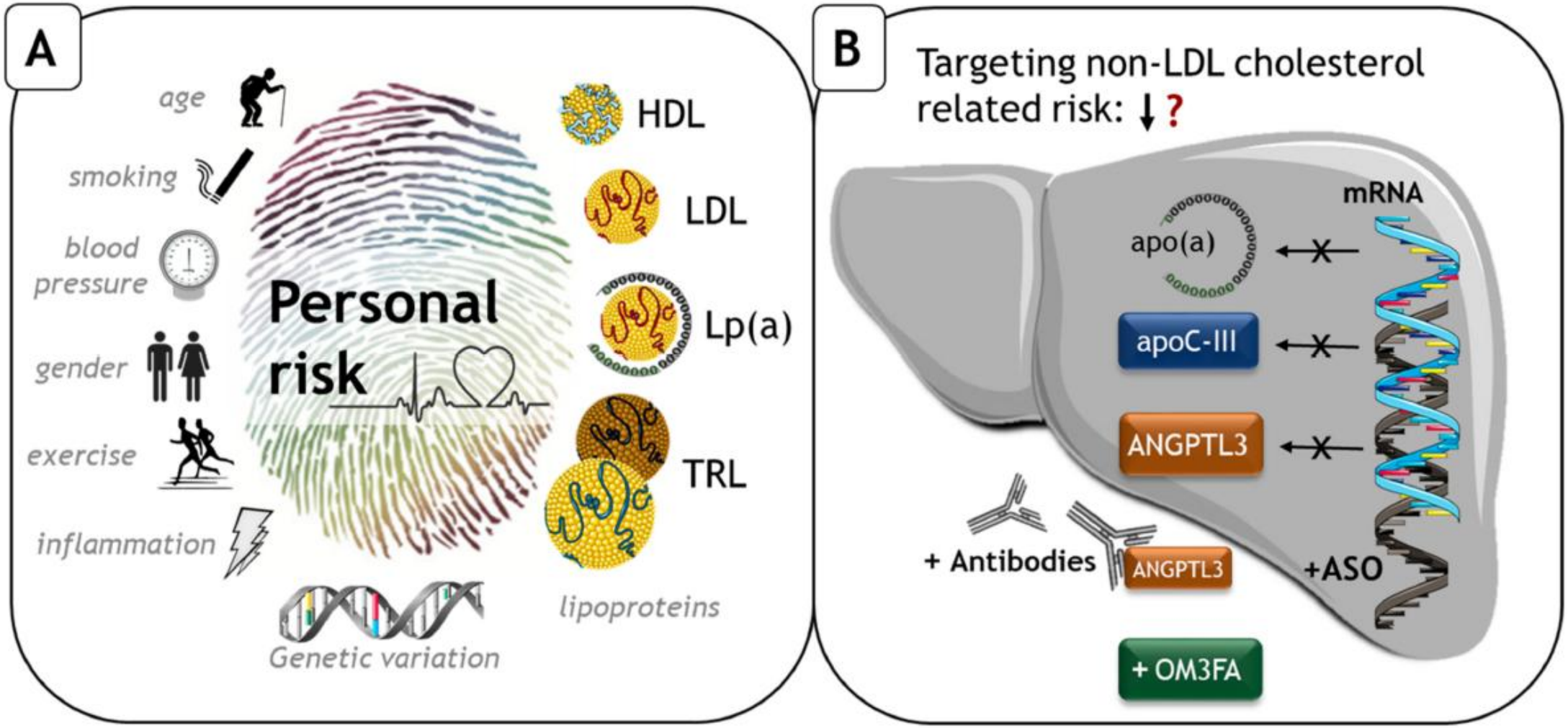
Velké kardiovaskulární příhody ORION 9-11

Data od 3660 pacientů, 1883 inklisiran



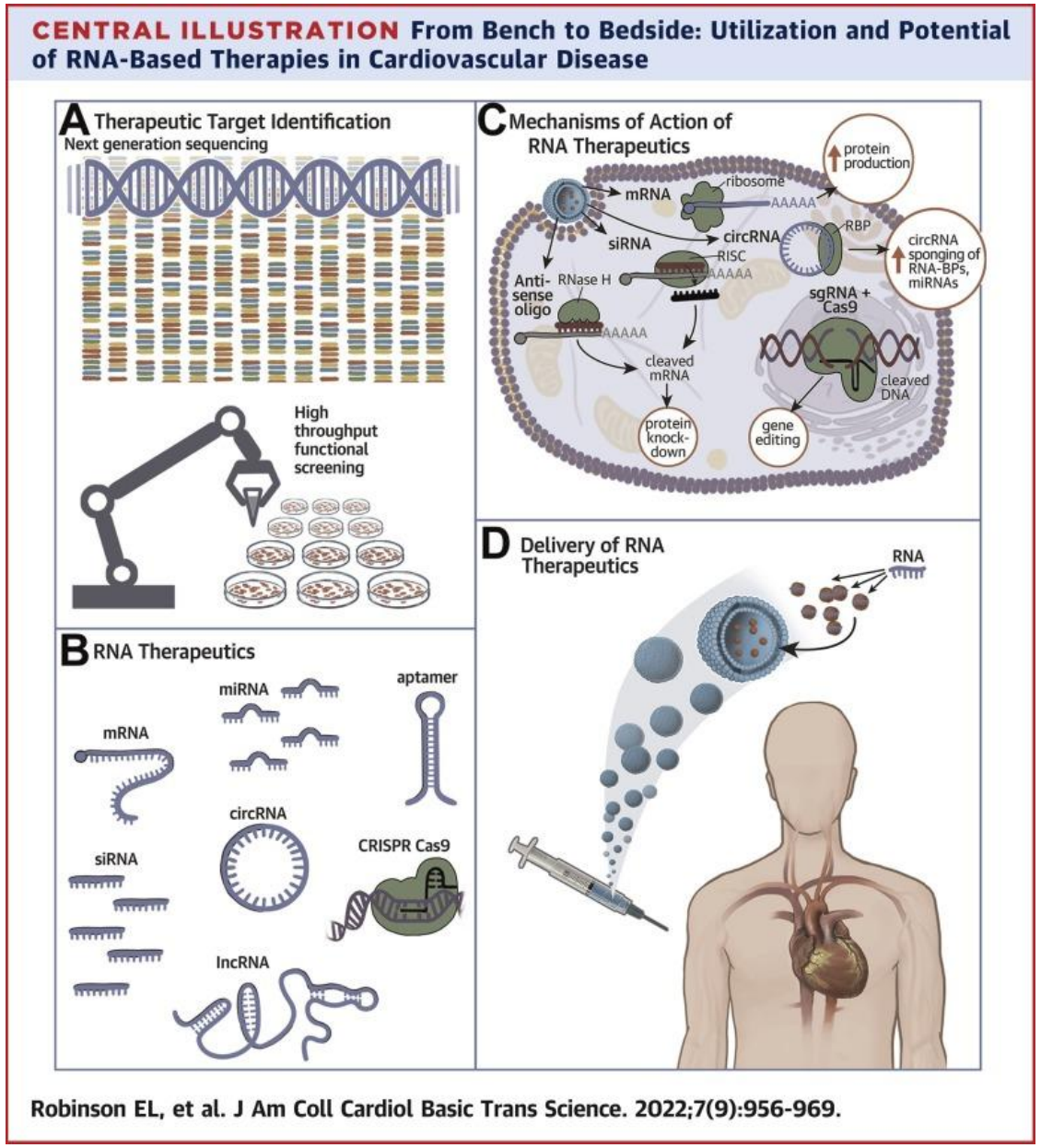
Ray KK et al. European Heart Journal (2022) 00, 1–

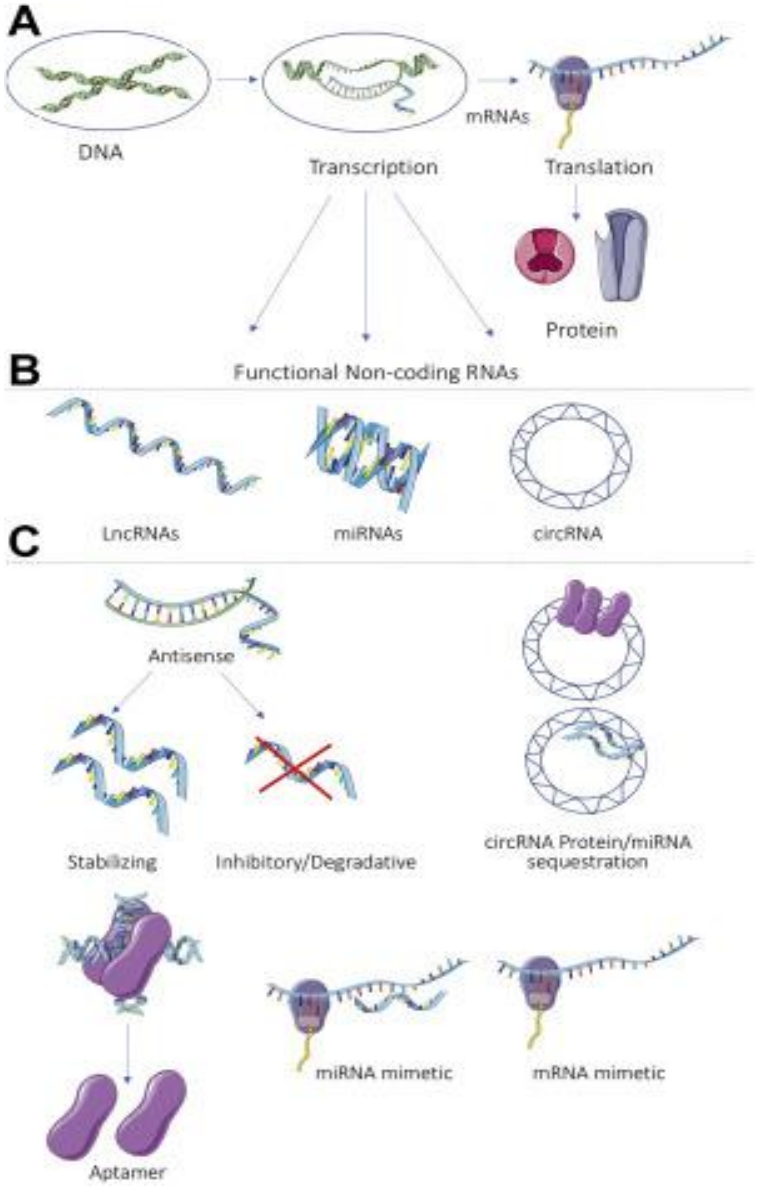
Nové terapeutické cíle: mimo LDL-C….



J. Clin. Med. **2019**, 8, 1085

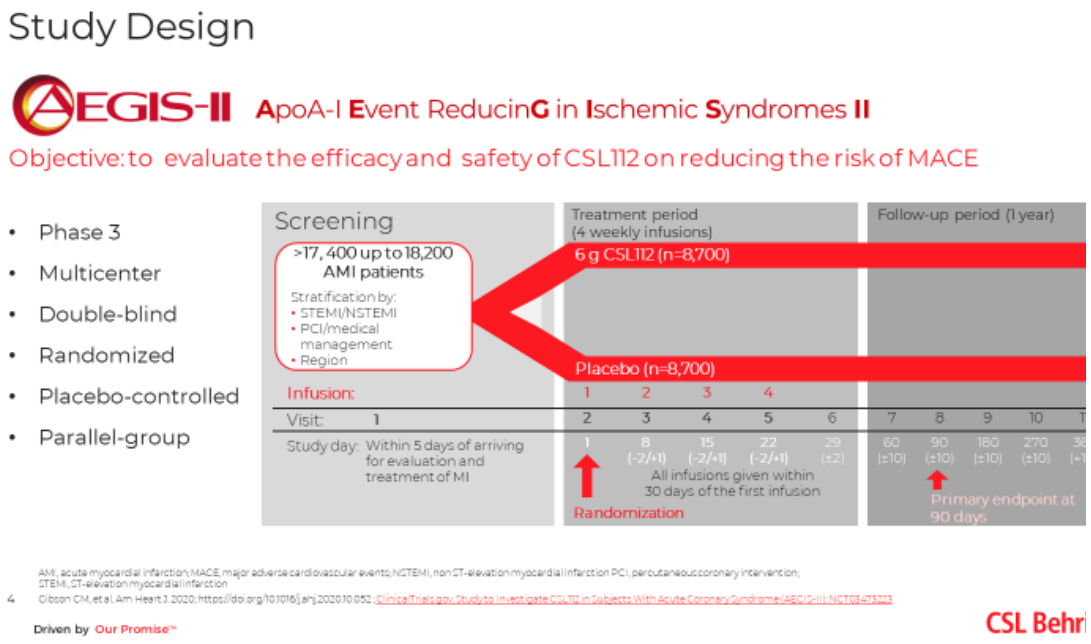
RNA terapeutika: současnost a budoucnost léčby DLP

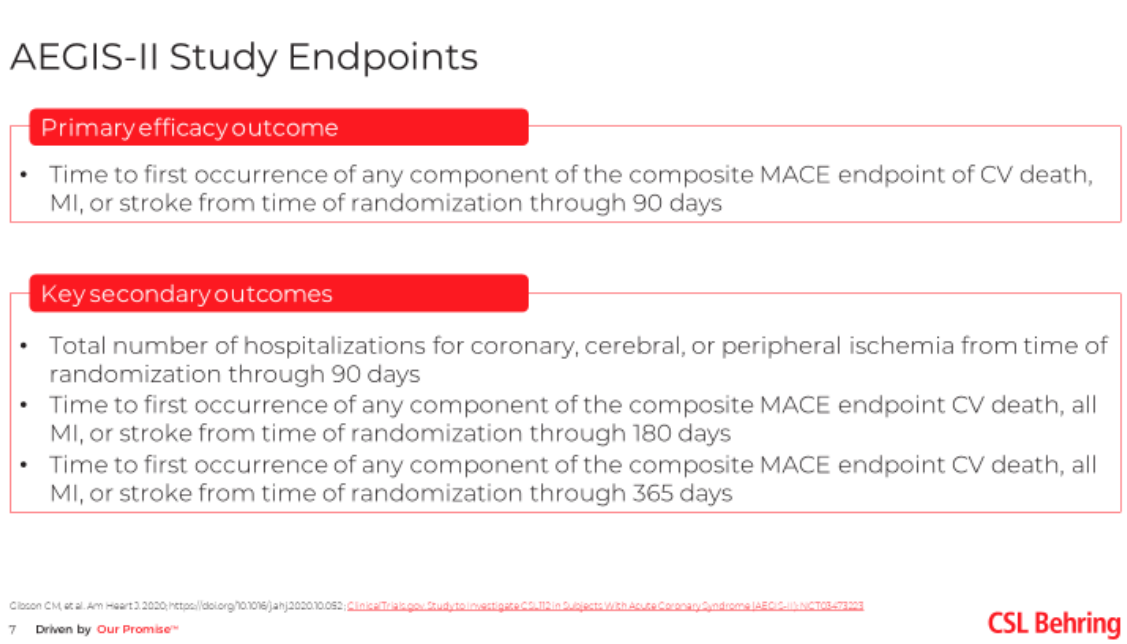




Neopouštěj staré věci … koncept apoA1 mimetik žije

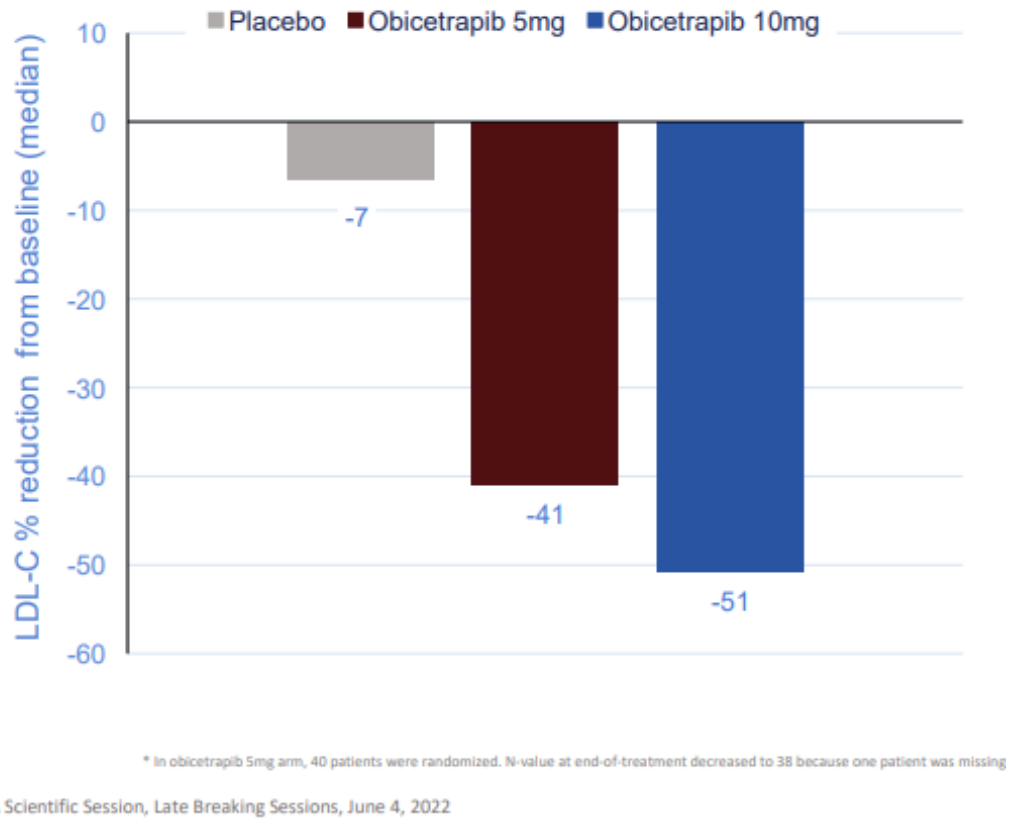
CSL112, nový intravenózní přípravek plazmatického apoA-I zvyšujícího cholesterol efflux kapacitu po AIM[1]





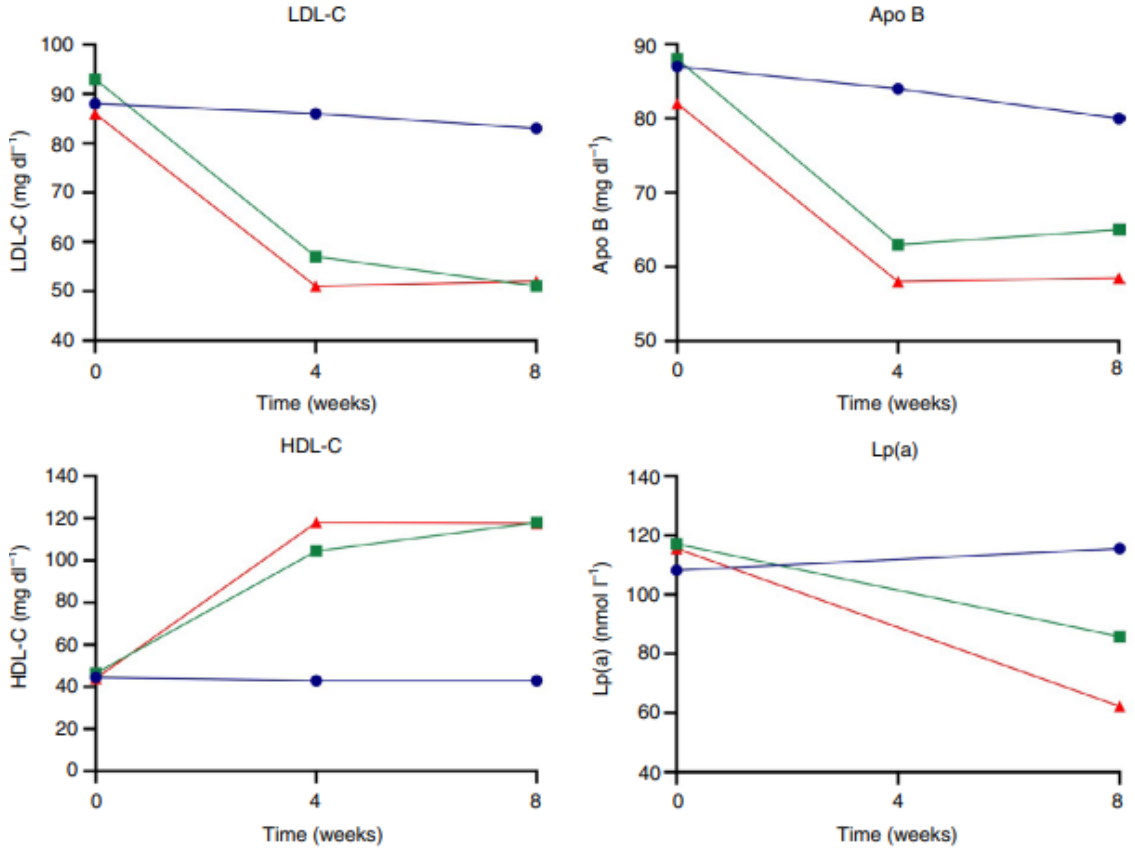
Gibson CM, et al. Circulation. 2016;134:1918-1930;

Obicetrapib ve studii ROSE



* In obicetrapib 5mg arm, 40 patients were randomized. N-value at end-of-treatment decreased to 38 because one patient was missing

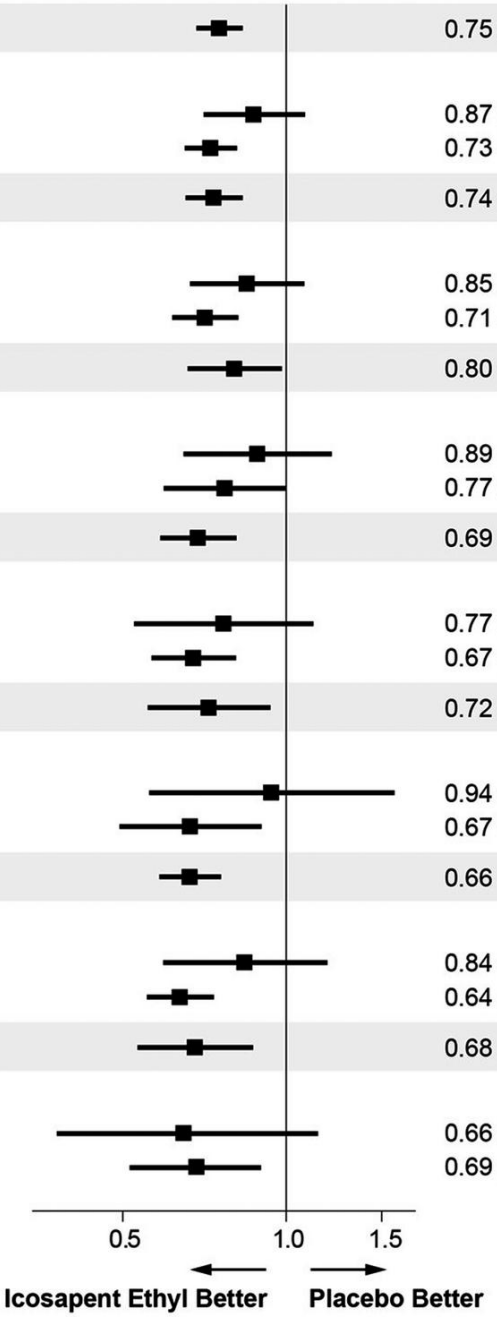
NLA Scientific Session, Late Breaking Sessions, June 4, 2022



Nicholls S et al. Nature Medicine | VOL 28 | August 2022 | 1672–1678

Kastelein J. Prezentace na ESC 2022, www.escardio.com

Endpoint/Subgroup	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	Interaction P-value
	n/N (%)	*n/N (%)*	*HR (95% CI)*	
Primary Composite Endpoint	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68, 0.83)	
History of heart failure				0.13
Yes	160/703 (22.8)	187/743 (25.2)	0.87 (0.70, 1.08)	
No	545/3386 (16.1)	714/3344 (21.4)	0.73 (0.65, 0.81)	
Key Secondary Composite Endpoint	459/4089 (11.2)	606/4090 (14.8)	0.74 (0.65, 0.83)	
History of heart failure				0.21
Yes	119/703 (16.9)	145/743 (19.5)	0.85 (0.66, 1.08)	
No	340/3386 (10.0)	461/3344 (13.8)	0.71 (0.62, 0.81)	
Cardiovascular Death	174/4089 (4.3)	213/4090 (5.2)	0.80 (0.66, 0.98)	
History of heart failure				0.50
Yes	72/703 (10.2)	85/743 (11.4)	0.89 (0.65, 1.21)	
No	102/3386 (3.0)	128/3344 (3.8)	0.77 (0.59, 1.00)	
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1)	355/4090 (8.7)	0.69 (0.58, 0.81)	
History of heart failure				0.56
Yes	46/703 (6.5)	63/743 (8.5)	0.77 (0.52, 1.12)	
No	204/3386 (6.0)	292/3344 (8.7)	0.67 (0.56, 0.81)	
Fatal or Nonfatal Stroke	98/4089 (2.4)	134/4090 (3.3)	0.72 (0.55, 0.93)	
History of heart failure				0.26
Yes	27/703 (3.8)	30/743 (4.0)	0.94 (0.56, 1.58)	
No	71/3386 (2.1)	104/3344 (3.1)	0.67 (0.49, 0.90)	
Coronary Revascularization	376/4089 (9.2)	544/4090 (13.3)	0.66 (0.58, 0.76)	
History of heart failure				0.14
Yes	58/703 (8.3)	72/743 (9.7)	0.84 (0.59, 1.18)	
No	318/3386 (9.4)	472/3344 (14.1)	0.64 (0.55, 0.73)	
Unstable Angina	108/4089 (2.6)	157/4090 (3.8)	0.68 (0.53, 0.87)	
History of heart failure				0.90
Yes	20/703 (2.8)	32/743 (4.3)	0.66 (0.37, 1.15)	
No	88/3386 (2.6)	125/3344 (3.7)	0.69 (0.52, 0.90)	



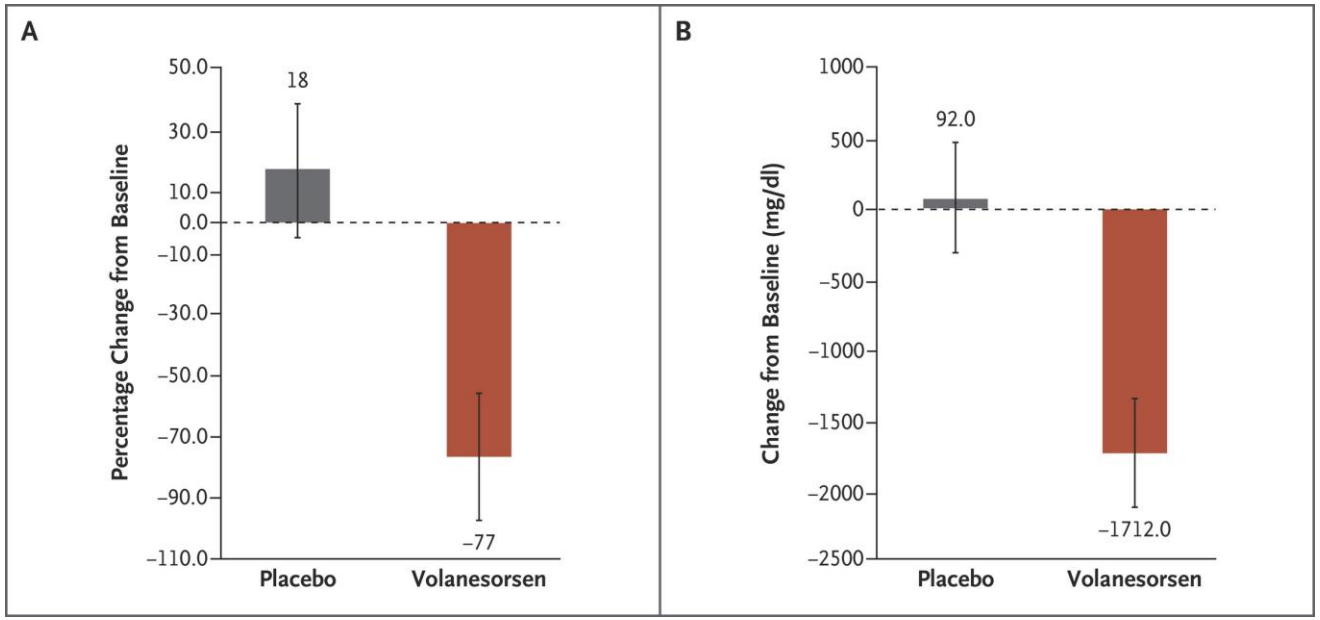
primár

vá mortalita

0
-5
-10
-15
-20
-25
-30
-35
-40

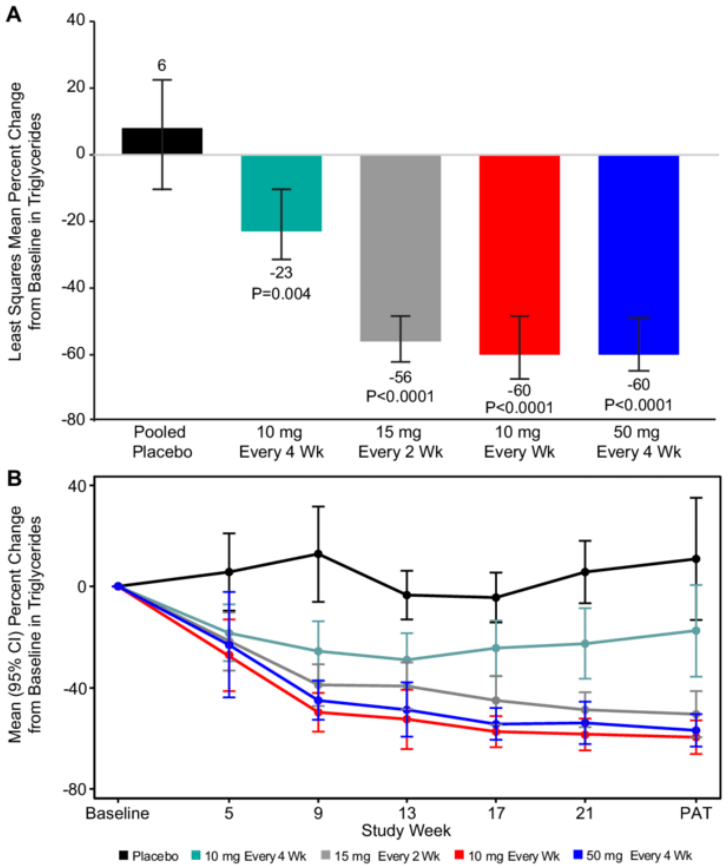
Selvaraj et al. JACC Volume 11, Issue 7, 5 April 2022

Změna triglyceridemie po 3měsících léčby **volanesorsenem**
66 pacientů s FCH, léčba 53 týdnů



Witzum JL et al. N Engl J Med 2019; 381:531-542

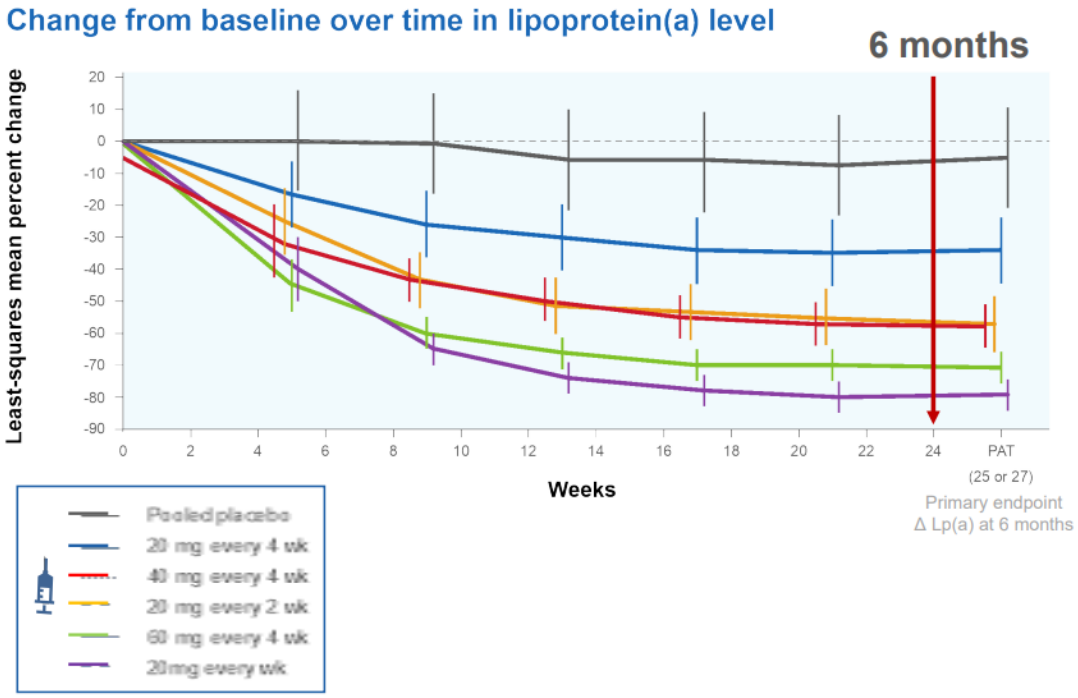
Změna triglyceridemie po 6měsících léčby **olazersenem**
114 pacientů s TG 2,5 – 3,7 mmol/l



Tardiff JC et al. European Heart Journal (2022) 43, 1401–1412

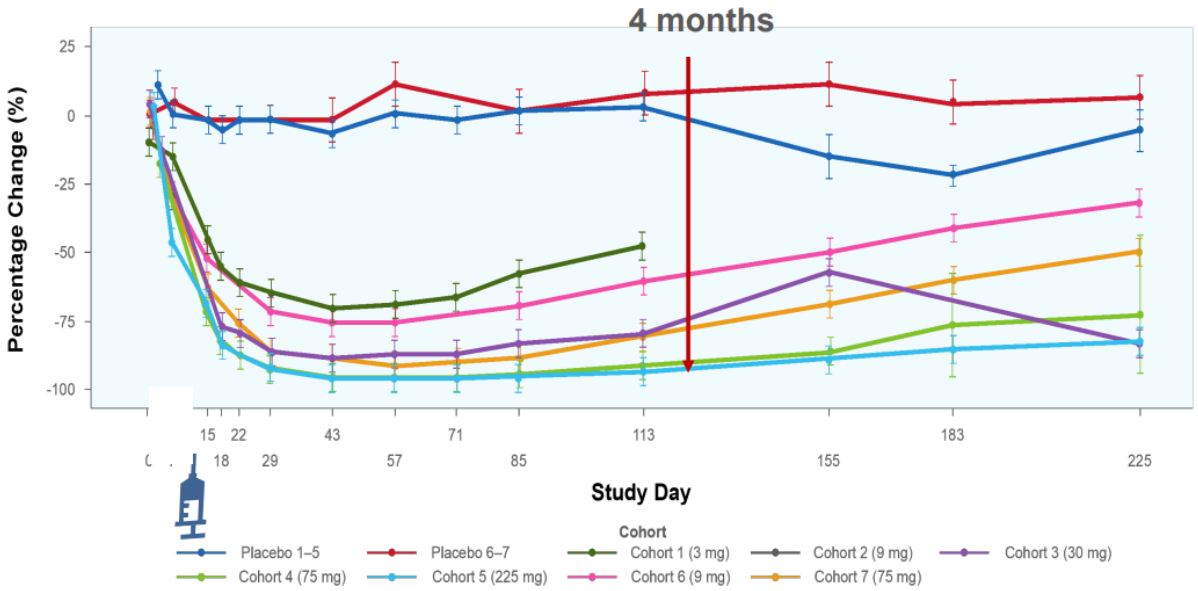
Nově na lipoprotein (a)

ASO: pelacarsen



Tsimikas S et al. N Engl J Med 2020; 382: 244–255.

siRNA: olpasiran



Koren MJ et al. Nat Med 2022; 28(1): 96–103

siRNA x Lp(a): olpasiran vstupuje na scénu

OCEAN(a)-DOSE: STUDY SCHEMA

Clinicaltrials.gov: NCT04270760

Patients aged 18-80 years with atherosclerotic disease & Lp(a) >150 nmol/L

N=281

RANDOMIZE 1:1:1:1:1 — DOUBLE BLIND

- Olpasiran 10mg Q12W
- Olpasiran 75mg Q12W
- Olpasiran 225mg Q12W
- Olpasiran 225mg Q24W
- Placebo

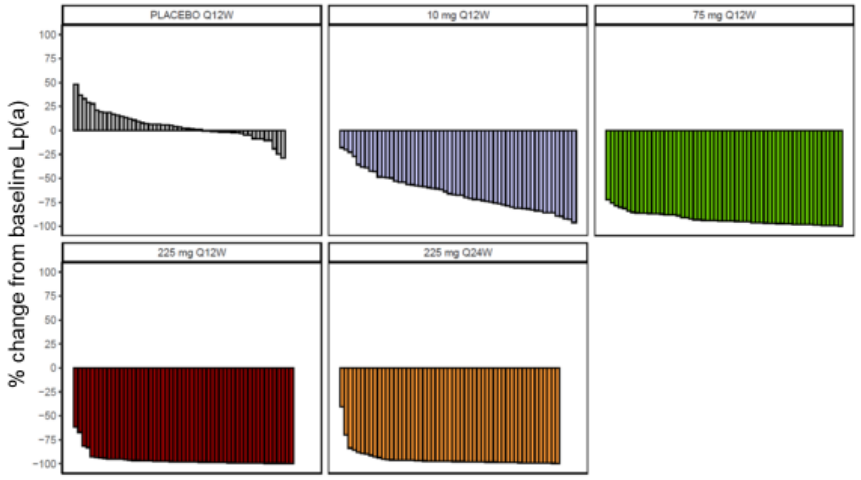
Primary Endpoint: % Change in Lp(a) from Baseline to Week 36

Key Secondary Endpoint: % Change in Lp(a) from Baseline to Week 48

An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School

O'Donoghue ML et al., *Am Heart J* 2022;251:61-69

Interindividual Variability in Lp(a) Response at Week 36



An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School

Vakcinace proti PCSK9: definitivní řešení

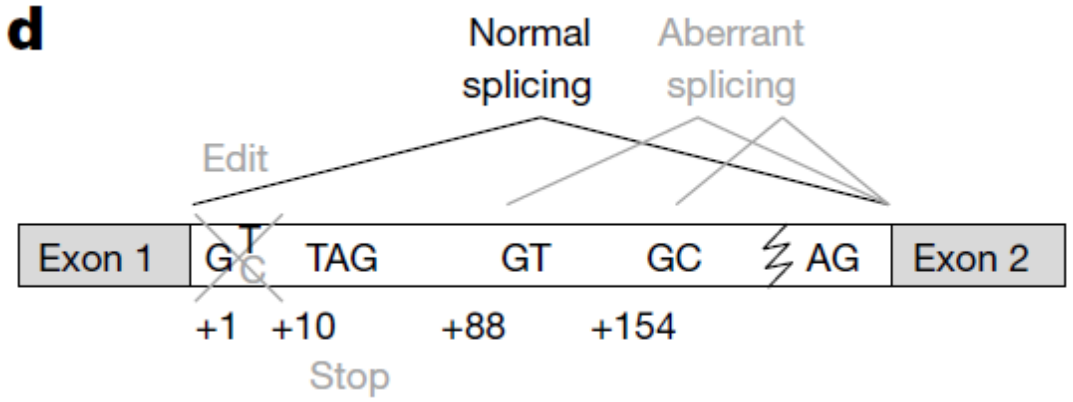
Article

In vivo CRISPR base editing of *PCSK9* durably lowers cholesterol in primates

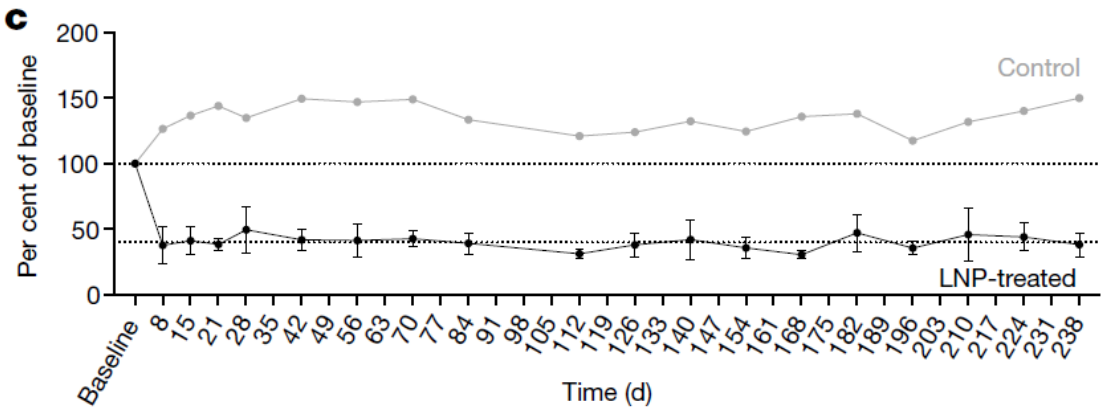
https://doi.org/10.1038/s41586-021-03534-y
Received: 6 December 2020
Accepted: 11 April 2021
Published online: 19 May 2021
Check for updates

Kiran Musunuru[1,2,3], Alexandra C. Chadwick[4], Taiji Mizoguchi[4], Sara P. Garcia[4], Jamie E. DeNizio[4], Caroline W. Reiss[4], Kui Wang[4], Sowmya Iyer[4], Chaitali Dutta[4], Victoria Clendaniel[4], Michael Amaonye[4], Aaron Beach[4], Kathleen Berth[4], Souvik Biswas[4], Maurine C. Braun[4], Huei-Mei Chen[4], Thomas V. Colace[4], John D. Ganey[4], Soumyashree A. Gangopadhyay[4], Ryan Garrity[4], Lisa N. Kasiewicz[4], Jennifer Lavoie[4], James A. Madsen[4], Yuri Matsumoto[4], Anne Marie Mazzola[4], Yusuf S. Nasrullah[4], Joseph Nneji[4], Huilan Ren[4], Athul Sanjeev[4], Madeleine Shay[4], Mary R. Stahley[4], Steven H. Y. Fan[5], Ying K. Tam[5], Nicole M. Gaudelli[6], Giuseppe Ciaramella[6], Leslie E. Stolz[4], Padma Malyala[4], Christopher J. Cheng[4], Kallanthottathil G. Rajeev[4], Ellen Rohde[4], Andrew M. Bellinger[4] & Sekar Kathiresan[4]✉

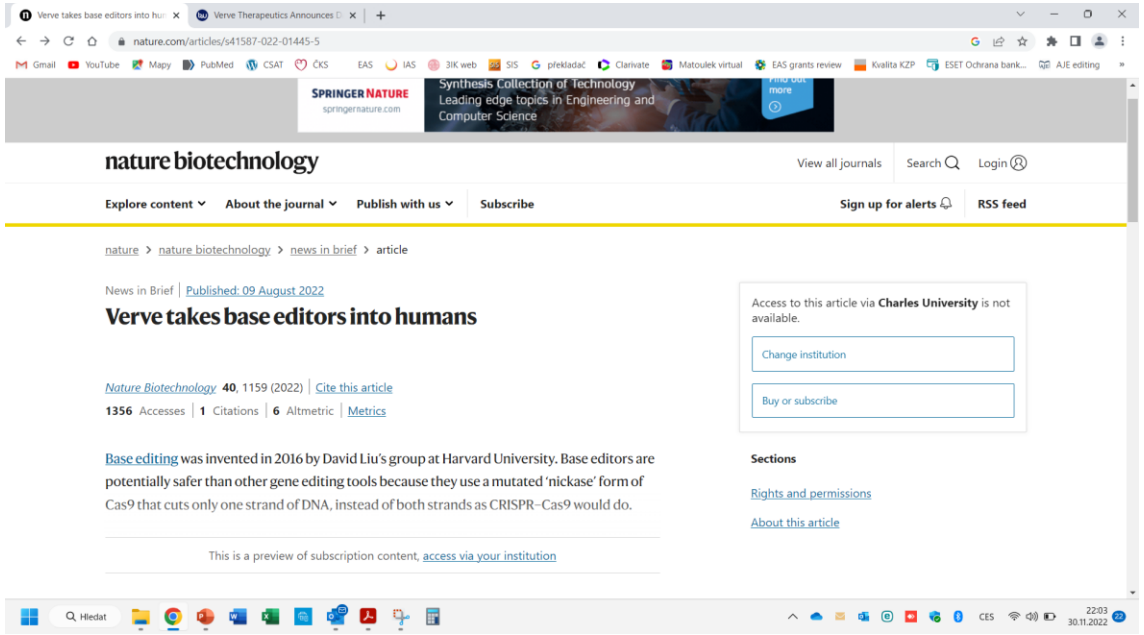
CRISPR PCSK9 gene editing

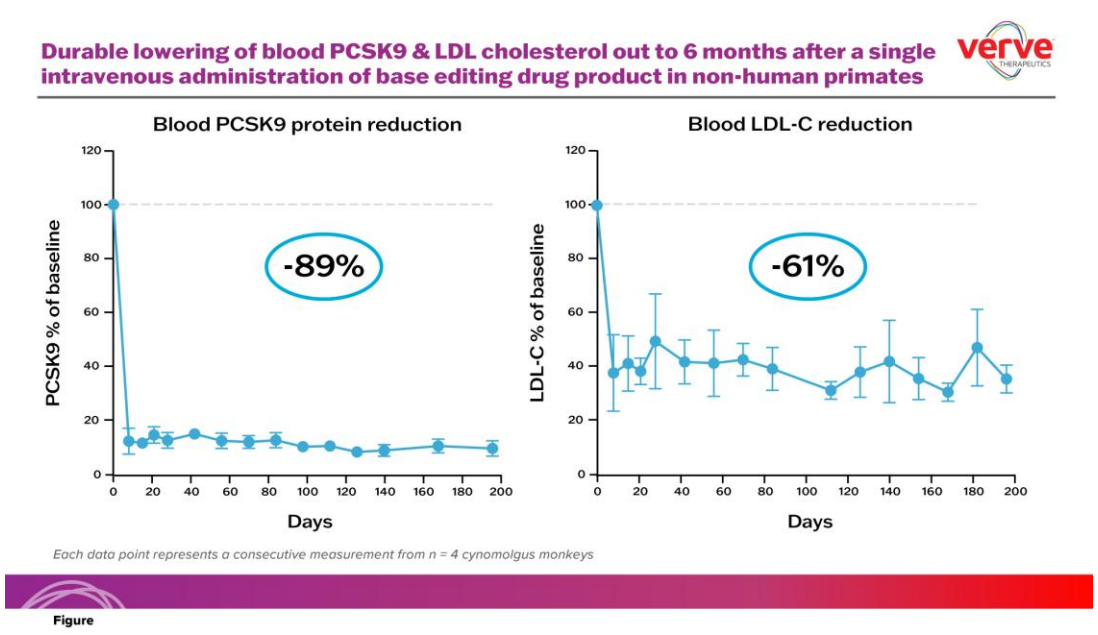


Levels of PCSK9 and LDL-C after PCSK9 gene editing



A již jsme v éře testování u lidí…





Lipidy a lipoproteiny ovlivňují funkci kardiomyocytu

Hypertriglyceridemie je nezávislým RF CHSS

Statiny nemají prokázaný benefit u CHSS

Nové terapie k razantnímu snížení koncentrací lipoproteinů u CHSS (?)

ČESKÁ SPOLEČNOST PRO ATEROSKLERÓZU

Odborné akce s účastí nebo pořádané ČSAT v roce 2023

leden:	35. Šamánkovy Poděbrady a 45. Motolský seminář	Poděbrady, **5. – 7. 1. 2023**
únor:	48. angiologické dny 2023 s mezinárodní účastí	Praha, **2. – 4. 3. 2023**
březen:	17. celostátní seminář ČIMS	Plzeň, **16. 3. 2023**
duben:	Pracovní setkání center projektu MedPed	Znojmo, **21. – 22. 4. 2023**
květen:	XXXI. výroční sjezd České kardiologické společnosti	Brno, **14. – 16. 5. 2023**
červen:	XXXVII. konference o hyperlipoproteinemiích - Šobrův den	Praha, **14. 6. 2023**
	29. Česko-slovenské angiologické sympozium	Lednice, **22. – 23. 6. 2023**
červenec:	10th IUA Course for Young Vascular Specialists	Praha, **12. – 16. 7. 2023**
říjen:	IX. Česko-slovenská lipidová akademie	Mikulov, **20. – 21. 10. 2023**
listopad:	XXX. kongres České internistické společnosti	Brno, **8. – 11. 11. 2023**
prosinec:	27. kongres o ateroskleróze	Hradec Králové, **7. – 9. 12. 2023**

Série webinářů s tematikou diagnostiky a léčby dyslipidemií v kontextu běžných i méně běžných situací a onemocnění. Na webu ČSAT (www.athero.cz) jsou zveřejněny bližší informace k webinářům, současně je zde možné v rámci projektu AtheroTV sledovat krátká videa z odborných akcí.