VŠEOBECNÁ FAKULTNÍ NEMOCNICE V PRAZE

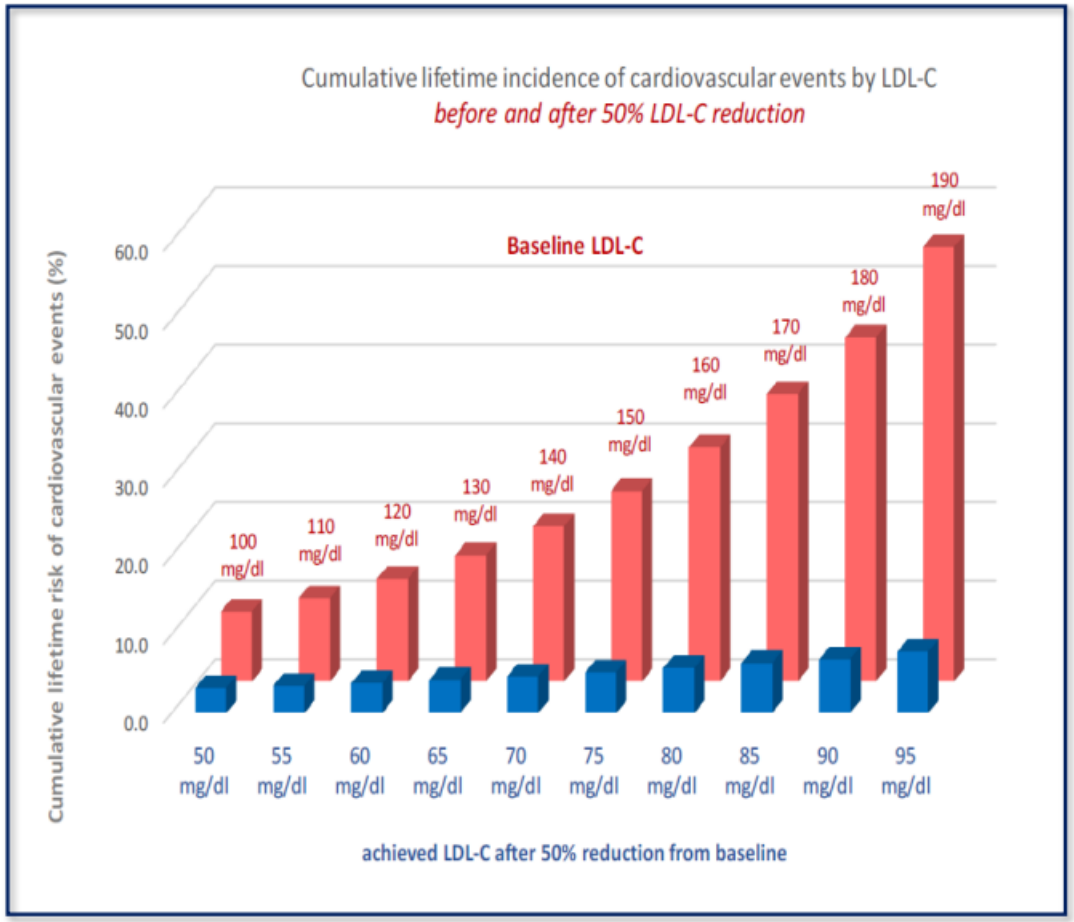
1. LÉKAŘSKÁ FAKULTA Univerzita Karlova

# Co nového v primární prevenci KVO: hypolipidemická léčba

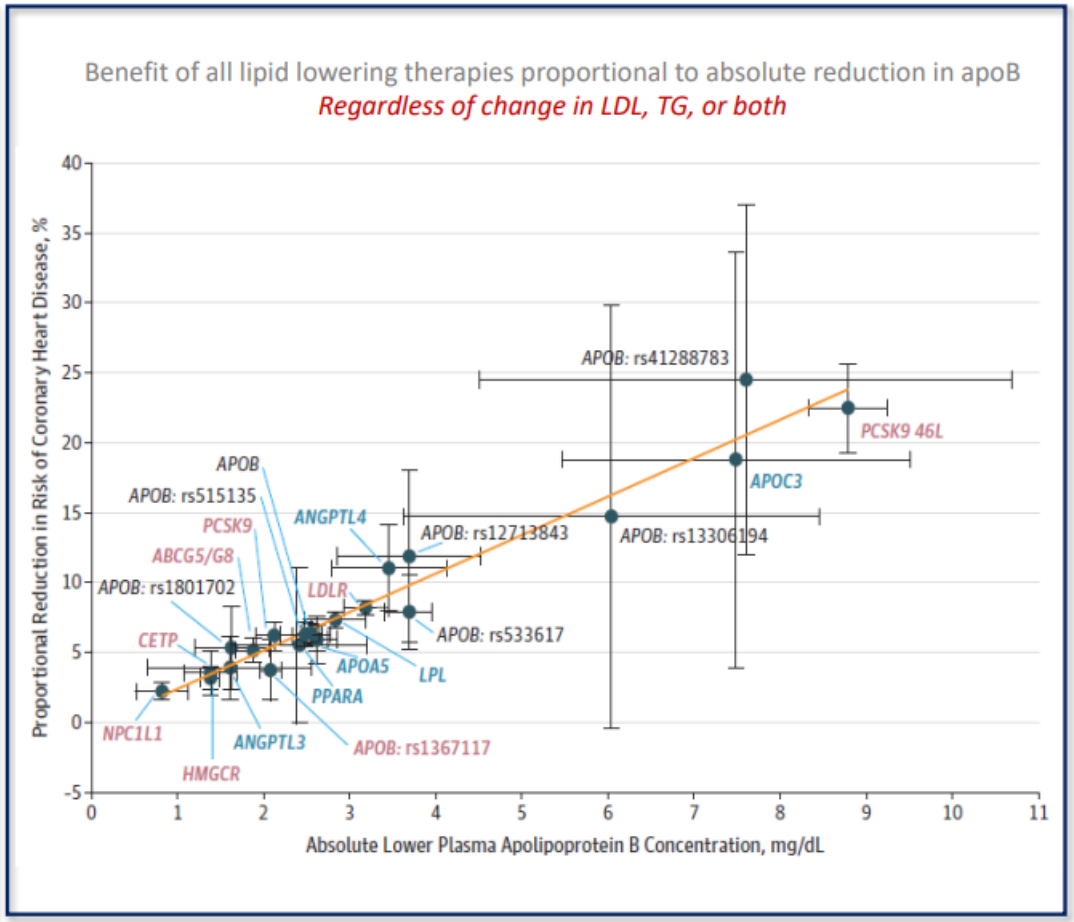
**Michal Vrablík**

# Absolutní redukce celoživotního rizika při 50 % snížení LDL-C

- Benefit je úměrný absolutní redukci LDL-C nezávisle na mechanismu, který vede k zvýšení katabolismu via LDLR
- Benefit je úměrný poklesu apoB pro všechny terapie nezávisle na změně LDL-C nebo TG koncentrací

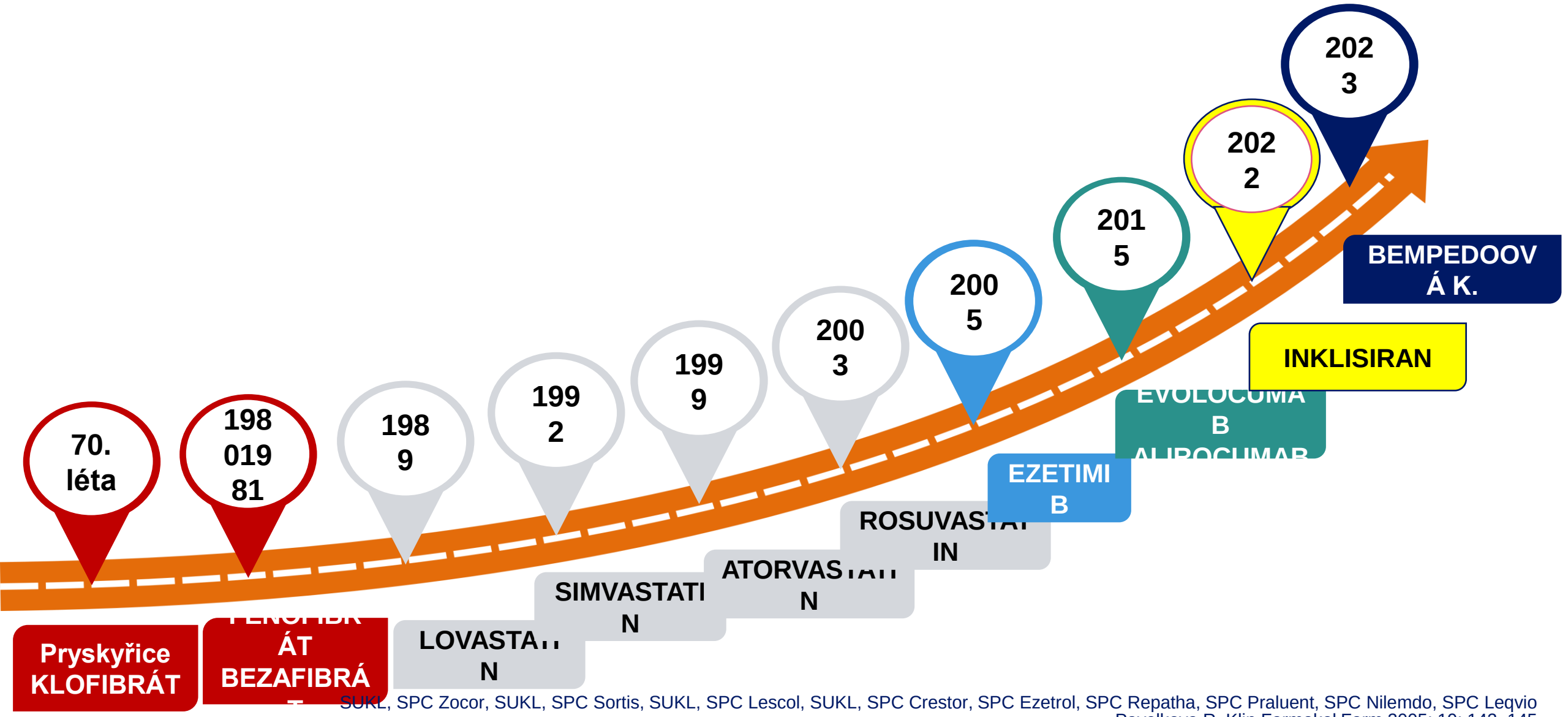



Ference BA, et al. ESC 2021, Late Breaking Clinical Trial, 29 August 2021




Ference BA, et al. JAMA 2019;321(4):1-11

# Možnosti hypolipidemické léčby se nadále rozšiřují

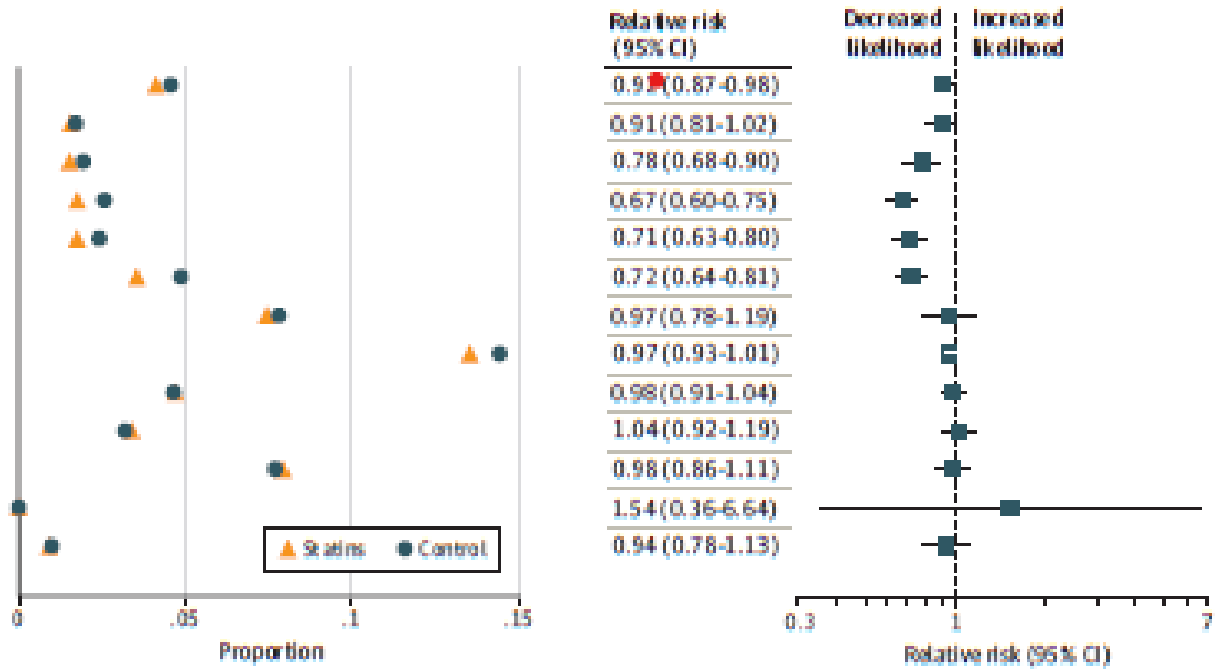



SUKL, SPC Zocor, SUKL, SPC Sortis, SUKL, SPC Lescol, SUKL, SPC Crestor, SPC Ezetrol, SPC Repatha, SPC Praluent, SPC Nilemdo, SPC Leqvio
Pavelkova R. Klin Farmakol Farm 2005; 19: 142–145

# Statiny v primární prevenci: mortalitní benefit
## 27 RCT (n=90624), 6 měsíců-6 let

Figure 4. Dot Plots for Primary Outcomes

| | No. of events/total (proportion) | | No. of trials | $I^2$, % | Strength of evidence | Relative risk (95% CI) |
|---|---|---|---|---|---|---|
| | Statins | Control | | | | |
| All-cause mortality | 1774/42991 (0.041) | 1924/42195 (0.046) | 18 | 0 | High | 0.92 (0.87-0.98) |
| CV mortality | 586/37582 (0.016) | 645/37556 (0.017) | 12 | 0 | Moderate | 0.91 (0.81-1.02) |
| Stroke (fatal or nonfatal) | 590/38295 (0.015) | 743/38315 (0.019) | 15 | 22 | High | 0.78 (0.68-0.90) |
| MI (fatal or nonfatal) | 665/37723 (0.018) | 971/37678 (0.026) | 12 | 14 | High | 0.67 (0.60-0.75) |
| Revascularization | 579/32966 (0.018) | 799/32958 (0.024) | 10 | 15 | High | 0.71 (0.63-0.80) |
| Composite CV outcomes | 1318/37162 (0.035) | 1813/37228 (0.049) | 15 | 51 | High | 0.72 (0.64-0.81) |
| Withdrawal due to AEs | 1648/22140 (0.074) | 1689/21643 (0.078) | 10 | 84 | High | 0.97 (0.78-1.19) |
| Serious AEs | 3815/28191 (0.135) | 3926/27228 (0.144) | 10 | 0 | High | 0.97 (0.93-1.01) |
| Cancer | 1637/35903 (0.046) | 1669/35830 (0.047) | 13 | 0 | High | 0.98 (0.91-1.04) |
| Diabetes | 1004/29536 (0.034) | 941/29547 (0.032) | 6 | 52 | Moderate | 1.04 (0.92-1.19) |
| Myalgia | 1871/23605 (0.079) | 1743/22733 (0.077) | 9 | 30 | High | 0.98 (0.86-1.11) |
| Rhabdomyolysis | 4/30213 (0.000) | 2/29469 (0.000) | 8 | 0 | High | 1.54 (0.36-6.64) |
| ALT elevation | 224/24276 (0.009) | 238/23873 (0.010) | 10 | 0 | High | 0.94 (0.78-1.13) |




AE indicates adverse event; ALT, alanine aminotransferase; CV, cardiovascular; MA, meta-analysis; MI, myocardial infarction; RR, relative risk; SOE, strength of evidence.

*Chou et al. JAMA*. 2022;328(8):754-771

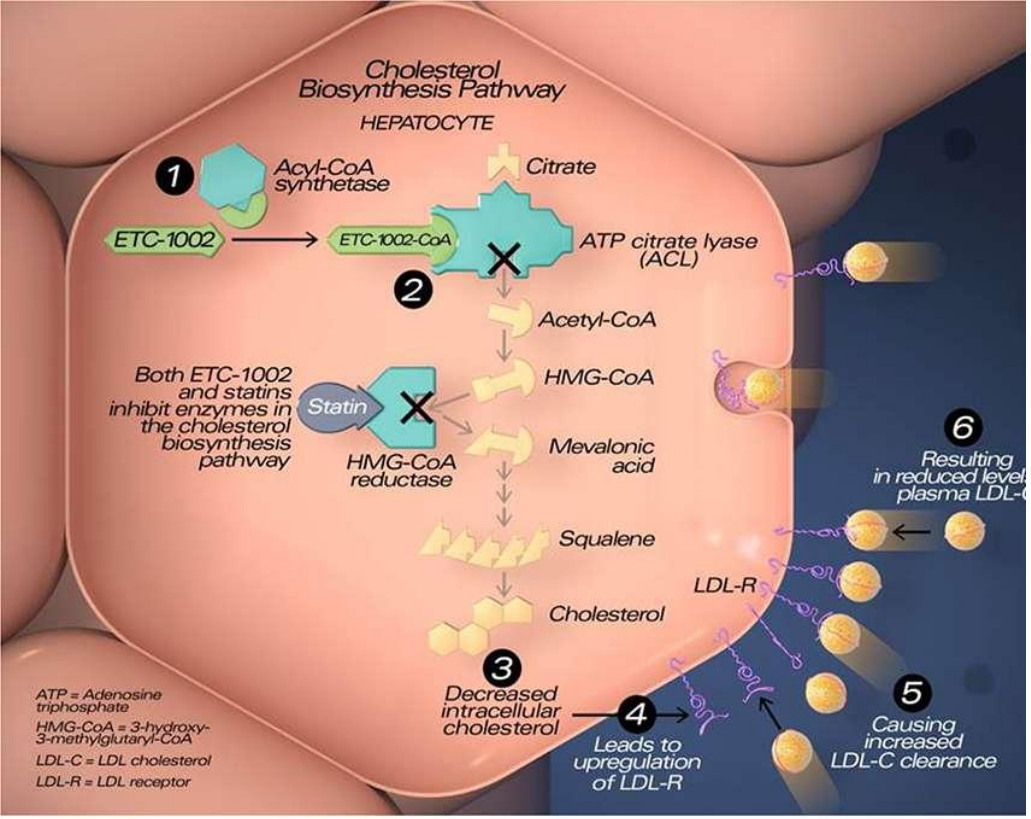
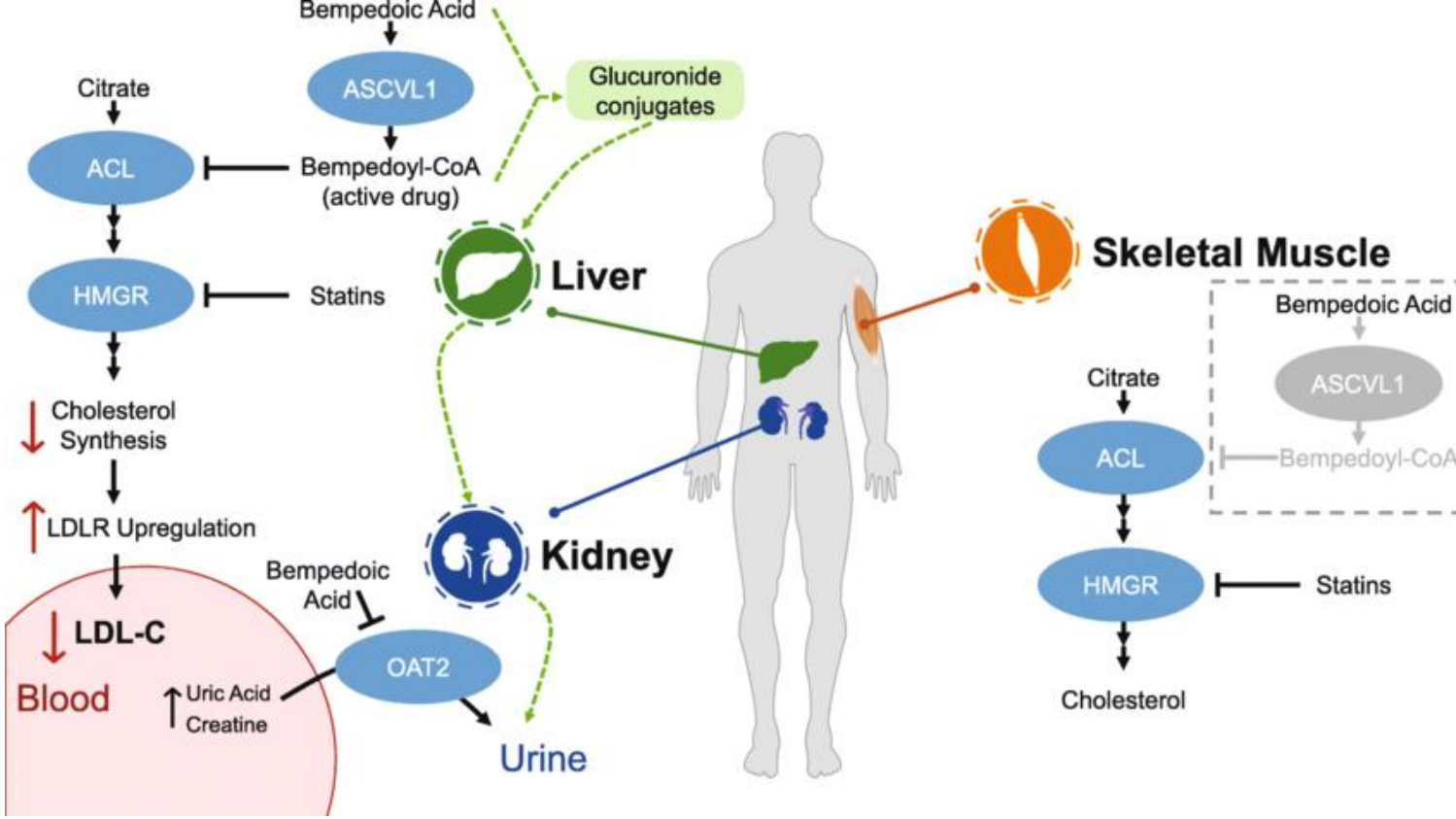



Image from www.esperio




# Bempedová kyselina: NILEMDO nově v našich rukách

- Inhibice endogenní biosyntézy cholesterolu
- Místo působení: hepatocyt
- Inihibuje ATP citrát lyázu, enzym stojící nad HMGCoA reduktázou
- Neaktivní ve skeletálním svalstvu – nízký potenciál k myalgiím

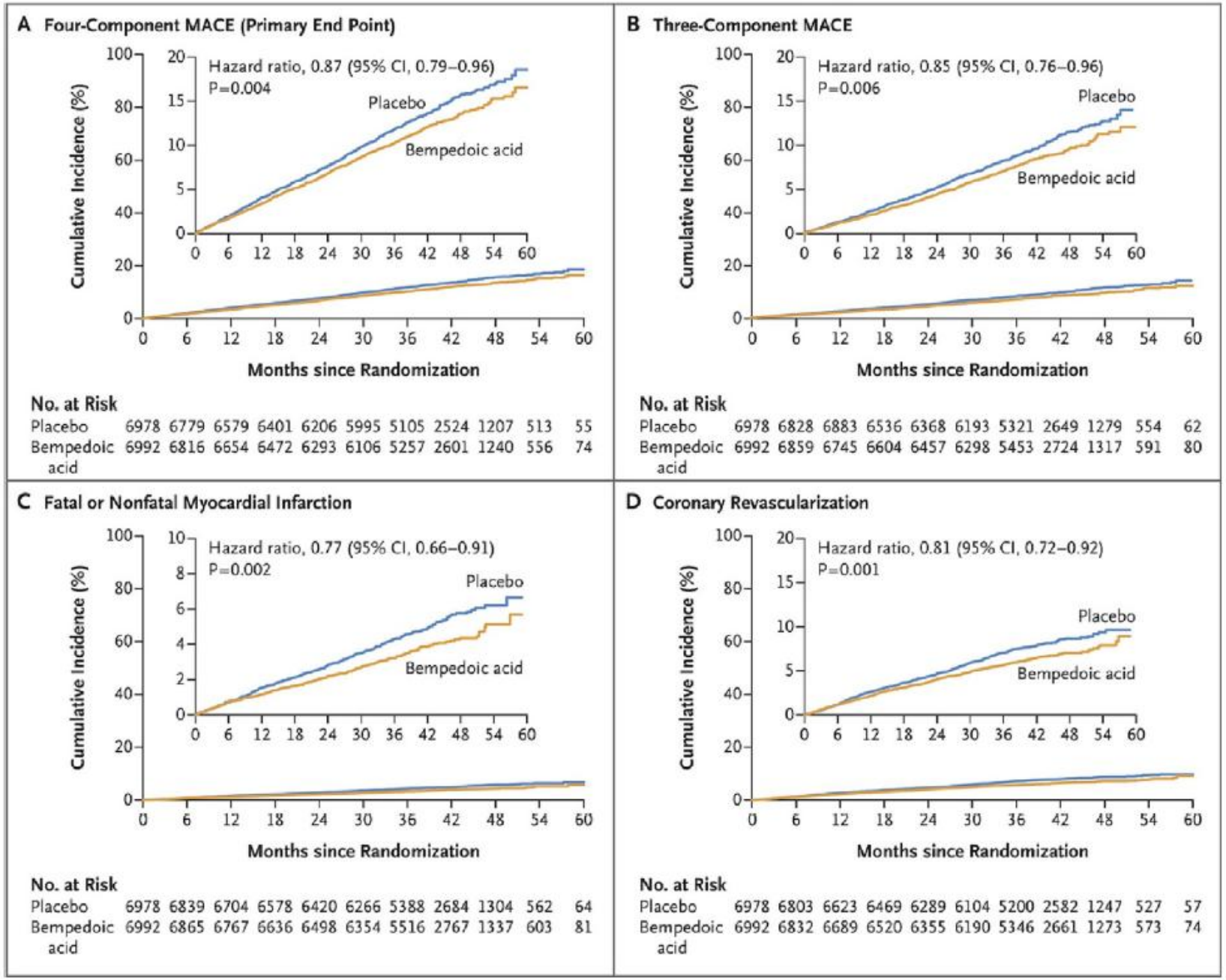
# Výsledky studie CLEAR OUTCOMES

The NEW ENGLAND JOURNAL of MEDICINE

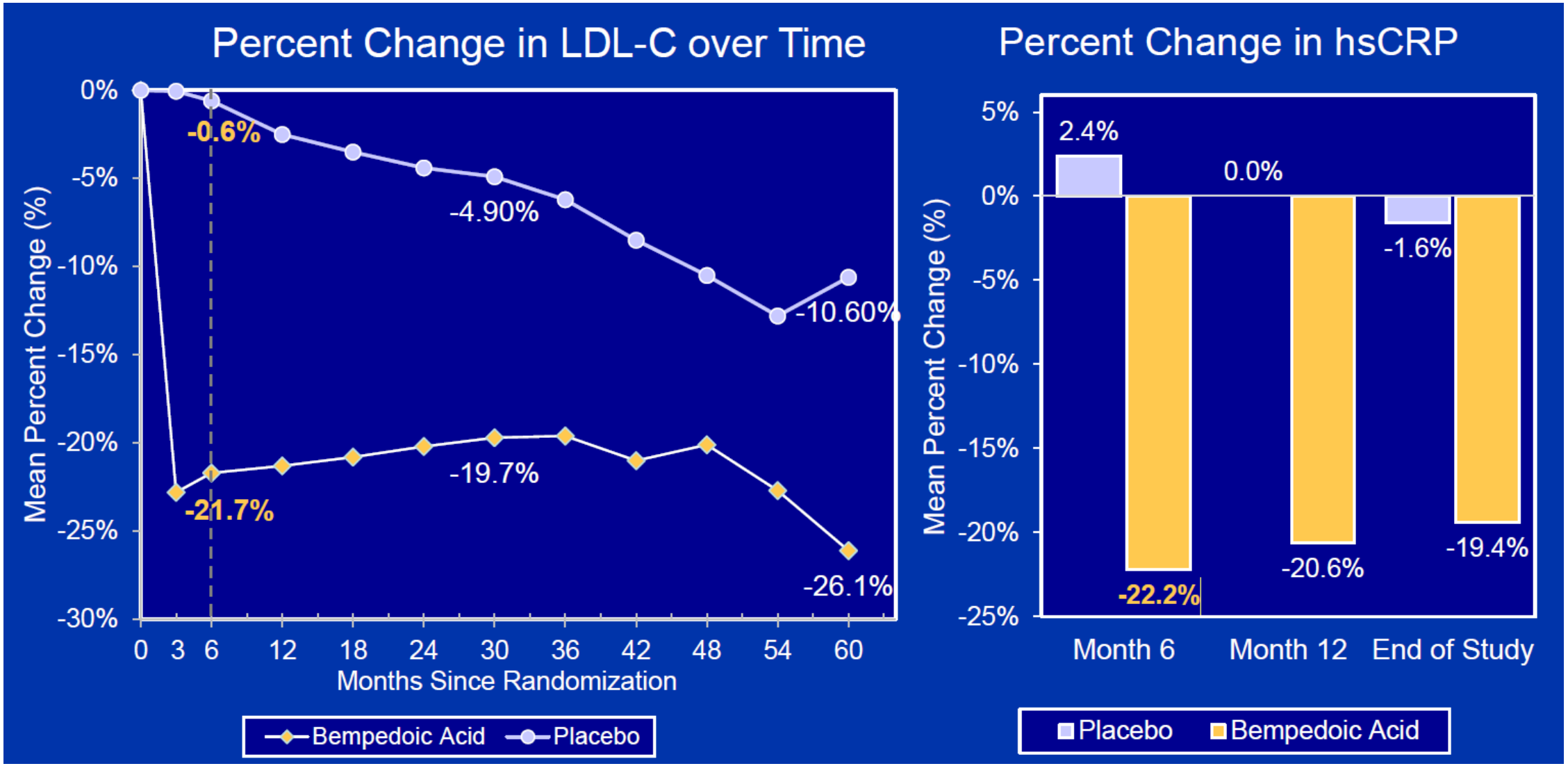
ORIGINAL ARTICLE

## Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

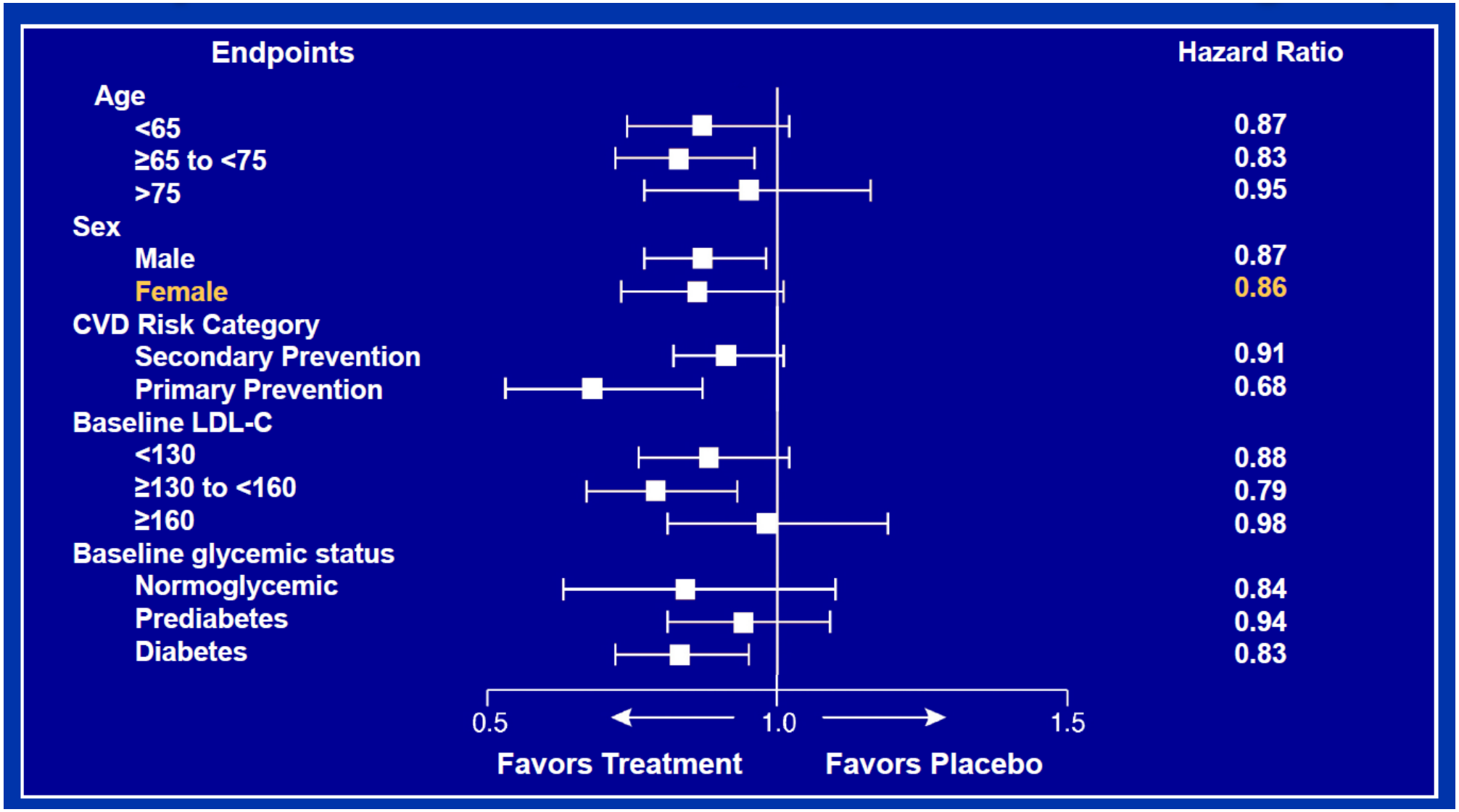
S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D.E. Grobbee, M.J. Louie, C.-F. Chen, N. Li, L.A. Bloedon, P. Robinson, M. Horner, W.J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, and S.J. Nicholls, for the CLEAR Outcomes Investigators*



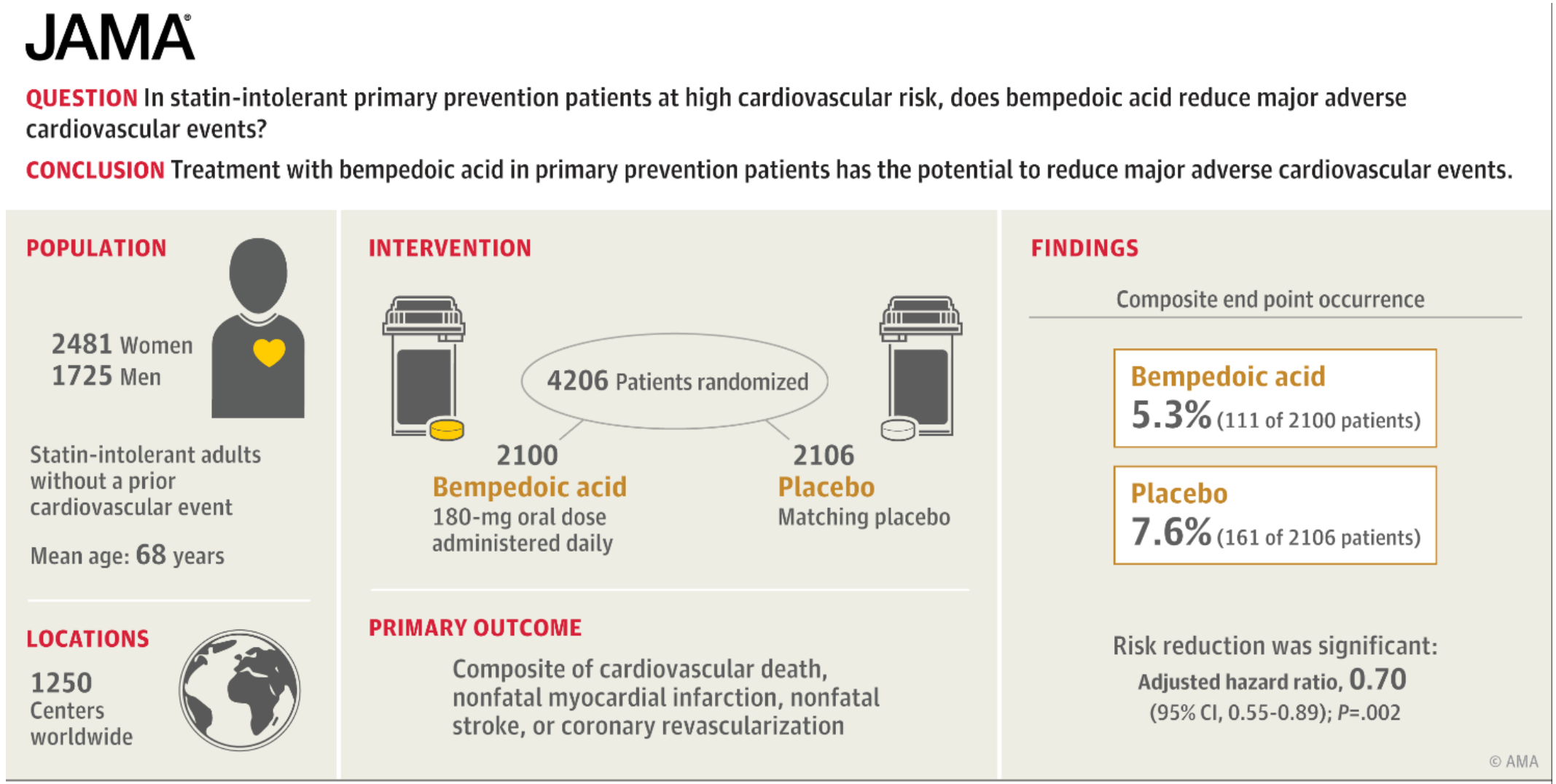
# Změna LDL-C a hsCRP



# Výskyt 4bodového primárního sledovaného MACE cíle



# Nové analýzy CLEAR OUTCOMES




Nissen SE, Menon V, Nicholls SJ, et al. Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients. *JAMA*. Published online June 24, 2023. doi:10.1001/jama.2023.9696

JAMA Cardiology

# BK a všechny příhody

## RCT: Impact of Bempedoic Acid on Total Cardiovascular Events

### POPULATION

**7050 Men, 6740 Women**

Adults with or at high risk for cardiovascular (CV) disease and statin intolerance

**Mean (SD) age, 65.5 (9.0) y**

### INTERVENTION

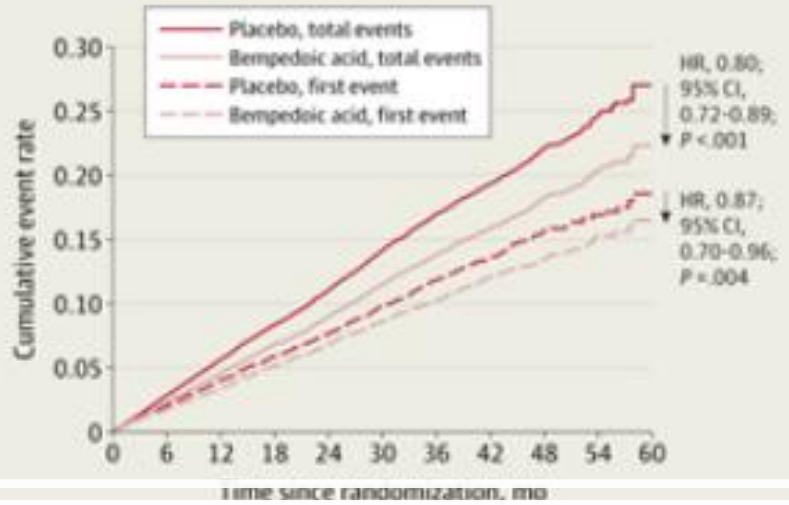
**13970** Patients randomized

**6992 Bempedoic acid**
Oral ATP citrate lyase inhibitor taken daily

**6978 Placebo**
Placebo pill taken daily

### FINDINGS

Treatment with bempedoic acid resulted in a lower incidence of total primary MACE-4 events compared with placebo. (hazard ratio, 0.80; 95% CI, 0.72-0.89; *P* <.001)




### SETTINGS / LOCATIONS

1250 Sites in 32 countries

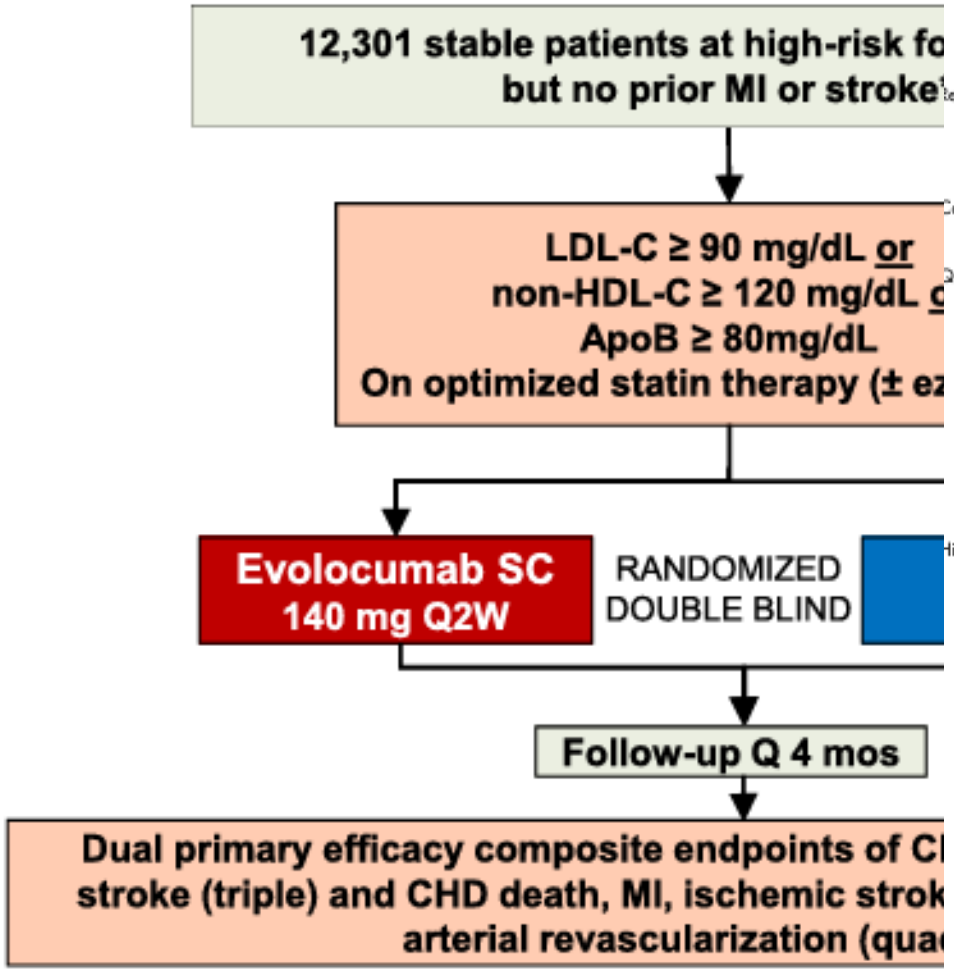
### PRIMARY OUTCOME

The primary end point was the composite of CV death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization (MACE-4). This prespecified analysis evaluated the total number of CV events.

Events per 100 patient years

Nicholls SJ, Nelson AJ, Lincoff AM, et al. Impact of bempedoic acid on total cardiovascular events: a prespecified analysis of the CLEAR Outcomes randomized clinical trial. *JAMA Cardiol*. Published online January 17, 2024. doi:10.1001/jamacardio.2023.5155

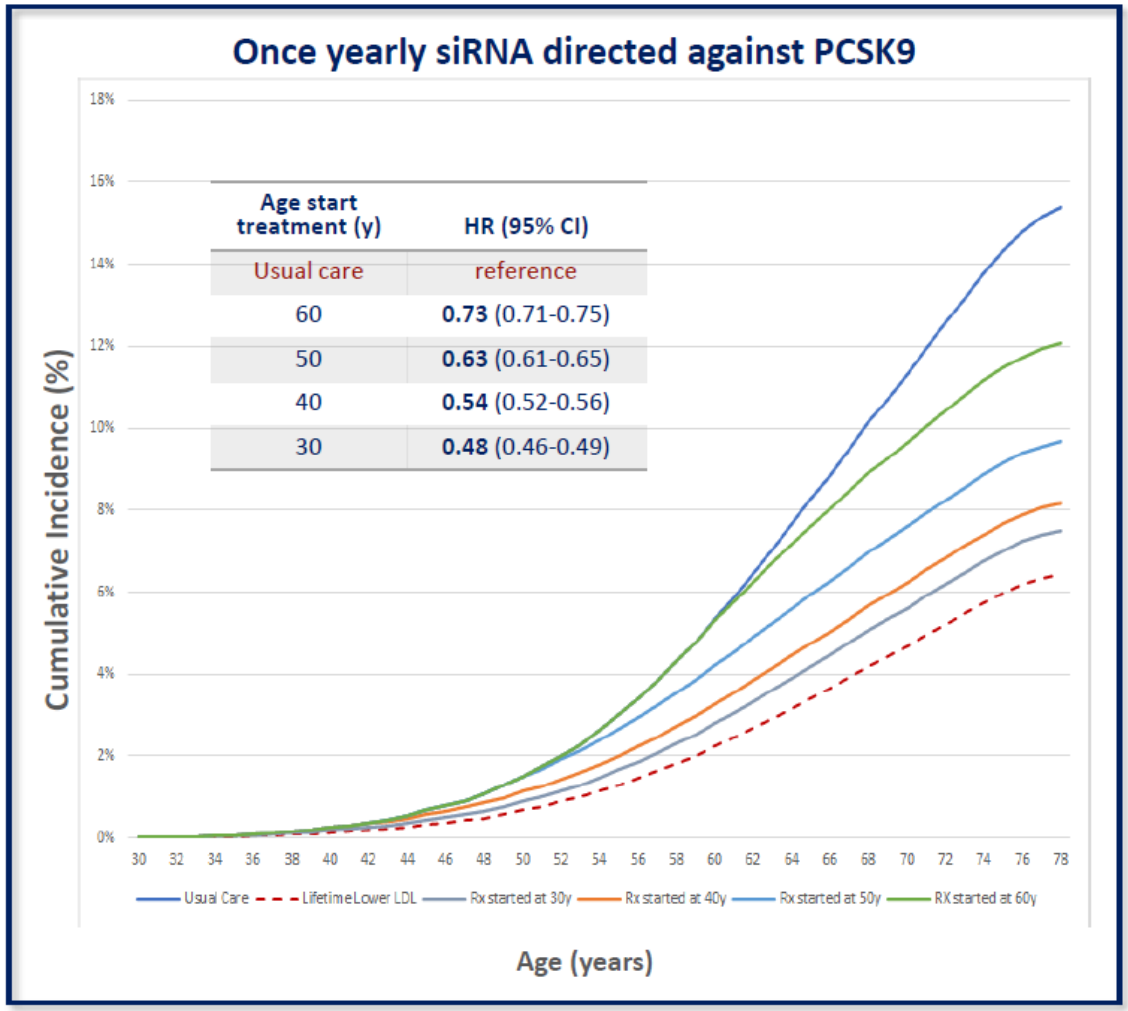
# Vesalius: evolokumab v

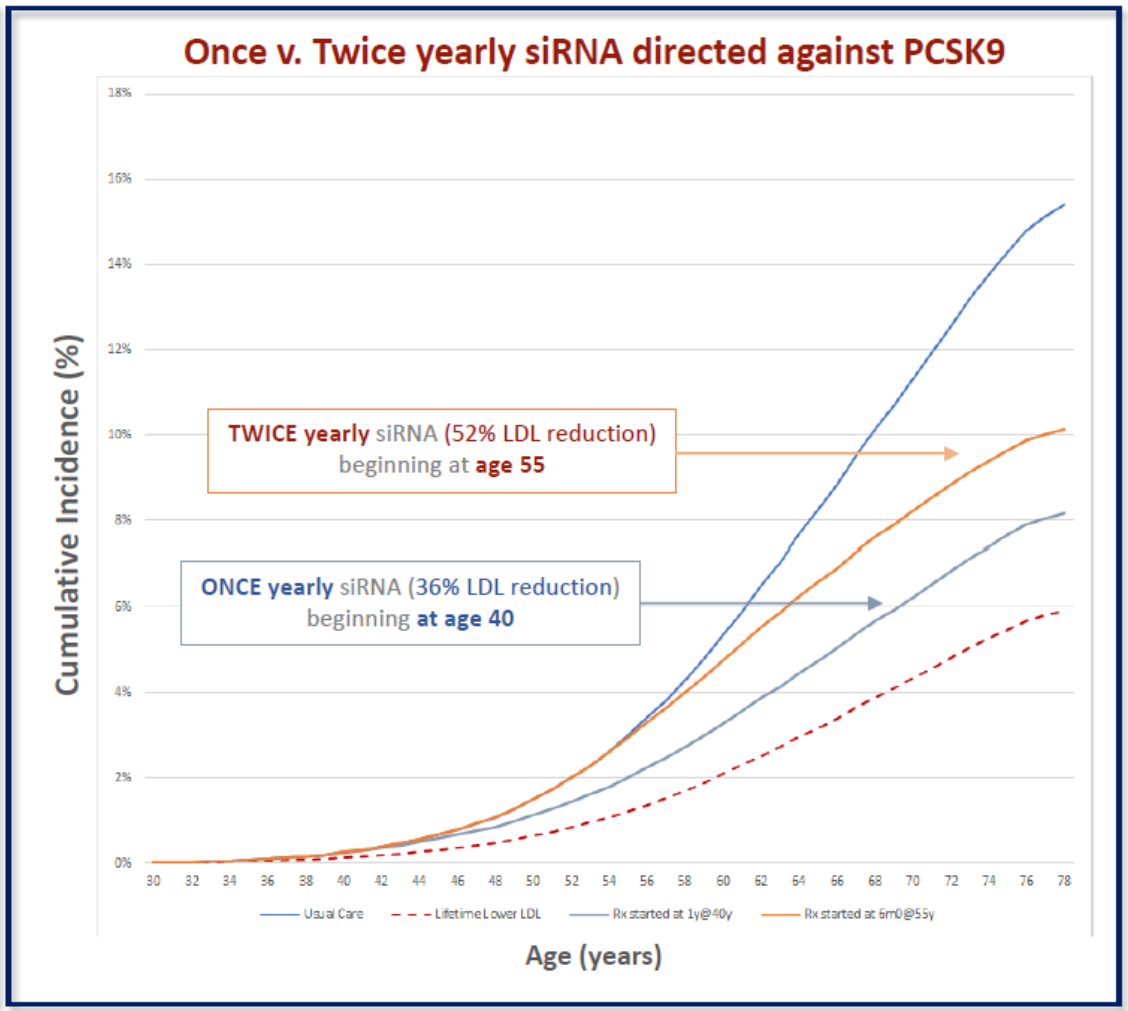



| | Overall cohort | Stratified by qualifying disease category at study inclusion* | | | |
|---|---|---|---|---|---|
| | All N = 12,301 (100%) | CAD N = 5,563 (45%) | CVD N = 1,207 (9.8%) | PAD N = 2,134 (17%) | High-risk DM N = 6,026 (49%) |
| Demographics | | | | | |
| Age (years, mean ± standard deviation) | 65 ± 7 | 66 ± 7 | 66 ± 7 | 65 ± 7 | 66 ± 7 |
| Female | 42 | 32 | 51 | 38 | 50 |
| Caucasian | 93 | 91 | 98 | 97 | 92 |
| Hispanic/Latino | 17 | 11 | 8.6 | 23 | 22 |
| Region | | | | | |
| North America | 11 | 11 | 6.1 | 5.7 | 14 |
| Europe | 69 | 70 | 85 | 72 | 64 |
| Asia/Pacific | 5.1 | 9.5 | 1.4 | 1.0 | 2.9 |
| Latin America/South America | 15 | 9.3 | 7.2 | 21 | 20 |
| Comorbidities | | | | | |
| Hypertension | 87 | 86 | 92 | 85 | 90 |
| Any diabetes mellitus (DM) | 58 | 37 | 31 | 44 | 100 |
| Qualifying disease categories for inclusion* | | | | | |
| CAD without prior myocardial infarction | 45 | 100 | 19 | 15 | 21 |
| Revascularization w/multivessel disease | 33 | 73 | 14 | 12 | 18 |
| Significant CAD without prior revascularization | 5.2 | 11 | 3.4 | 1.6 | 2.1 |
| Coronary artery calcium score ≥ 100 in the absence of prior revascularization, where available† | 8.2 | 18 | 1.5 | 1.1 | 2.2 |
| Cerebrovascular disease (CVD) without prior stroke | 10 | 4.1 | 100 | 7.9 | 4.3 |
| Peripheral arterial disease (PAD) | 17 | 5.7 | 14 | 100 | 11 |
| High-risk diabetes mellitus | 49 | 23 | 21 | 31 | 100 |
| High-risk criteria for inclusion (where known) | | | | | |
| LDL-C ≥ 130, non-HDL-C ≥ 160, or ApoB ≥ 120 mg/dL | 51 | 43 | 54 | 47 | 55 |
| Any DM or metabolic syndrome with qualifying CAD, CVD, or PAD | 30 | 44 | 40 | 50 | 33 |
| High-risk DM w/≥1 arterial stenosis of ≥50% | 9.5 | 12 | 18 | 16 | 19 |
| Polyvascular disease | 5.4 | 8.6 | 26 | 20 | 2.9 |
| Lipoprotein(a) > 125 nmol/L (50 mg/dL), where available† | 3.4 | 4.6 | 3.1 | 4.9 | 2.1 |
| Familial hypercholesterolemia | 8.7 | 10 | 6.8 | 6.9 | 6.9 |
| Family history of premature CAD | 22 | 26 | 21 | 16 | 19 |
| High sensitivity C-reactive protein ≥ 3 mg/L, where available† | 4.2 | 3.7 | 5.2 | 4.1 | 4.7 |
| Current tobacco use | 28 | 22 | 31 | 42 | 26 |
| Age ≥ 65 years | 56 | 58 | 55 | 56 | 57 |
| Menopause before 40 years | 3.1 | 1.8 | 3.3 | 3.2 | 4.1 |
| eGFR 15-<45 ml/min/1.73m$^2$ | 6.9 | 5.9 | 6.7 | 7.0 | 10 |
| Coronary artery calcium score ≥ 300 in the absence of prior revascularization, where available† | 4.4 | 10 | 1.0 | 0.7 | 1.2 |
| Background lipid-lowering therapy | | | | | |
| Any statin | 87 | 86 | 92 | 91 | 86 |
| High-intensity statin | 68 | 66 | 80 | 76 | 67 |
| Moderate-intensity statin | 17 | 17 | 10 | 14 | 18 |
| Ezetimibe | 20 | 27 | 14 | 16 | 16 |
| High-intensity lipid-lowering regimen† | 73 | 73 | 83 | 79 | 71 |
| Baseline lipid values in mg/dL, median (Q1, | | | | | |

Bohula EA, Marston NA, Ruzza A, Murphy SA, De Ferrari GM, Diaz R, Leiter LA, Elliott-Davey M, Wang H, Bhatia AK, Giugliano RP, Sabatine MS. Rationale and design of the effect of evolocumab in patients at high cardiovascular risk without prior myocardial infarction or stroke (VESALIUS-CV) trial. Am Heart J. 2024 Mar;269:179-190. doi: 10.1016/j.ahj.2023.12.004. Epub 2023 Dec 29. PMID: 38160917.

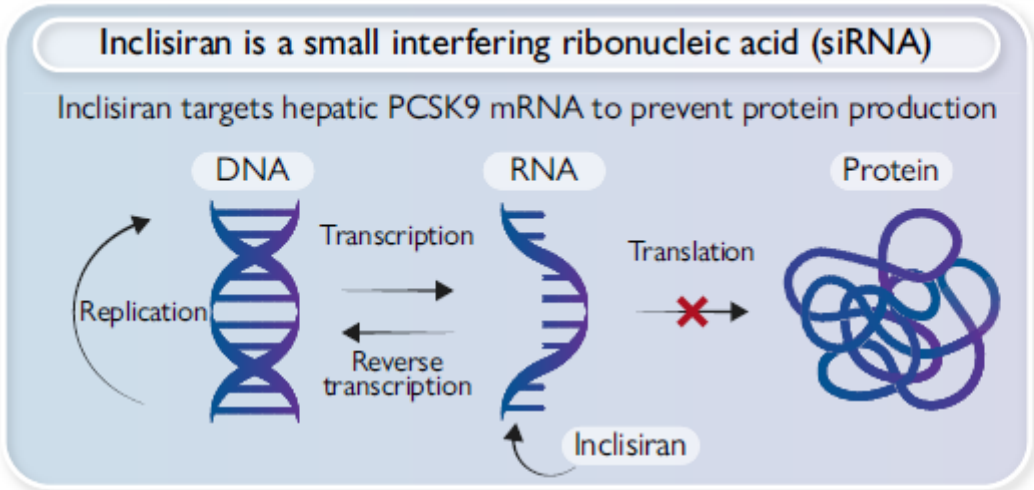
# Snížení hladiny cholesterolu: jak a kdy, to je oč tu běží

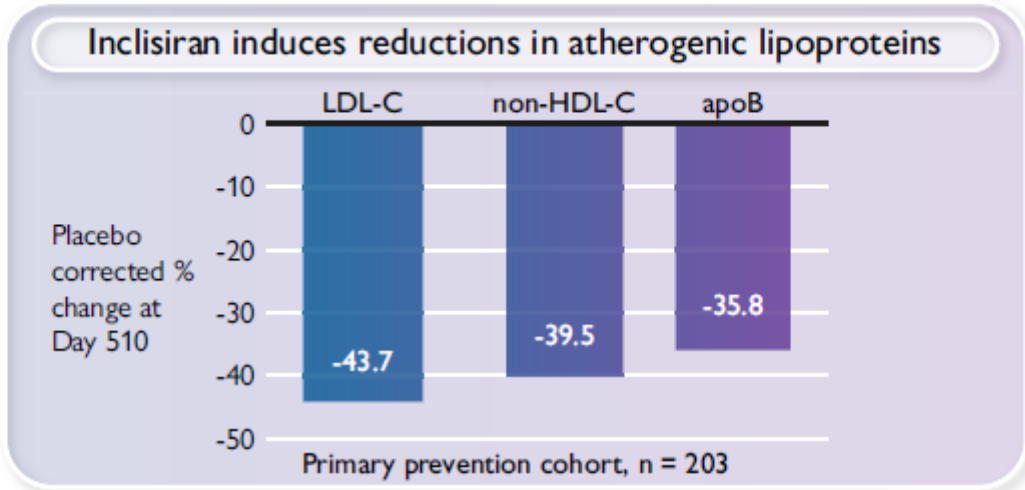



Ference BA, et al. ESC 2021 Late Breaking Clinical Trial August 2021

# Inklisican v primární prevenci: prví data máme




**Primary prevention cohort included patients with**

- Type 2 diabetes OR familial hypercholesterolaemia OR ≥ 20% 10-year risk of a CV event assessed by Framingham Risk Score or equivalent

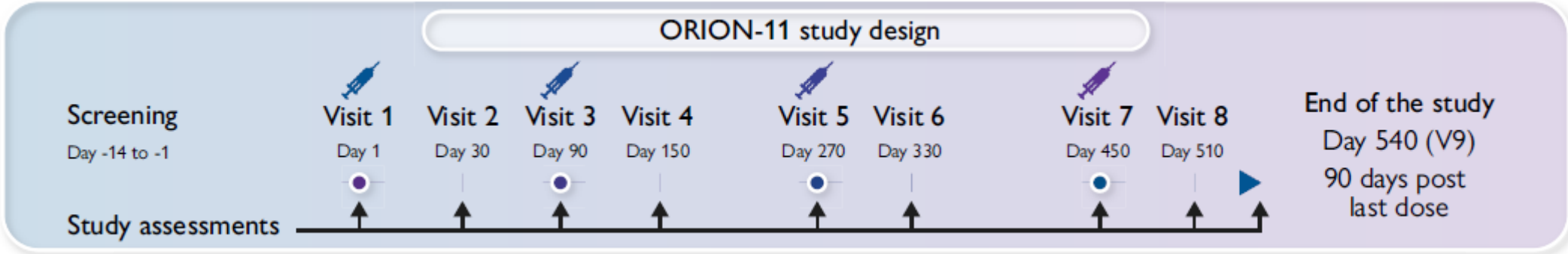
AND

- LDL ≥ 2.6 mmol/L

**Twice-yearly dosing of inclisiran** (after the initial and 3-month doses)

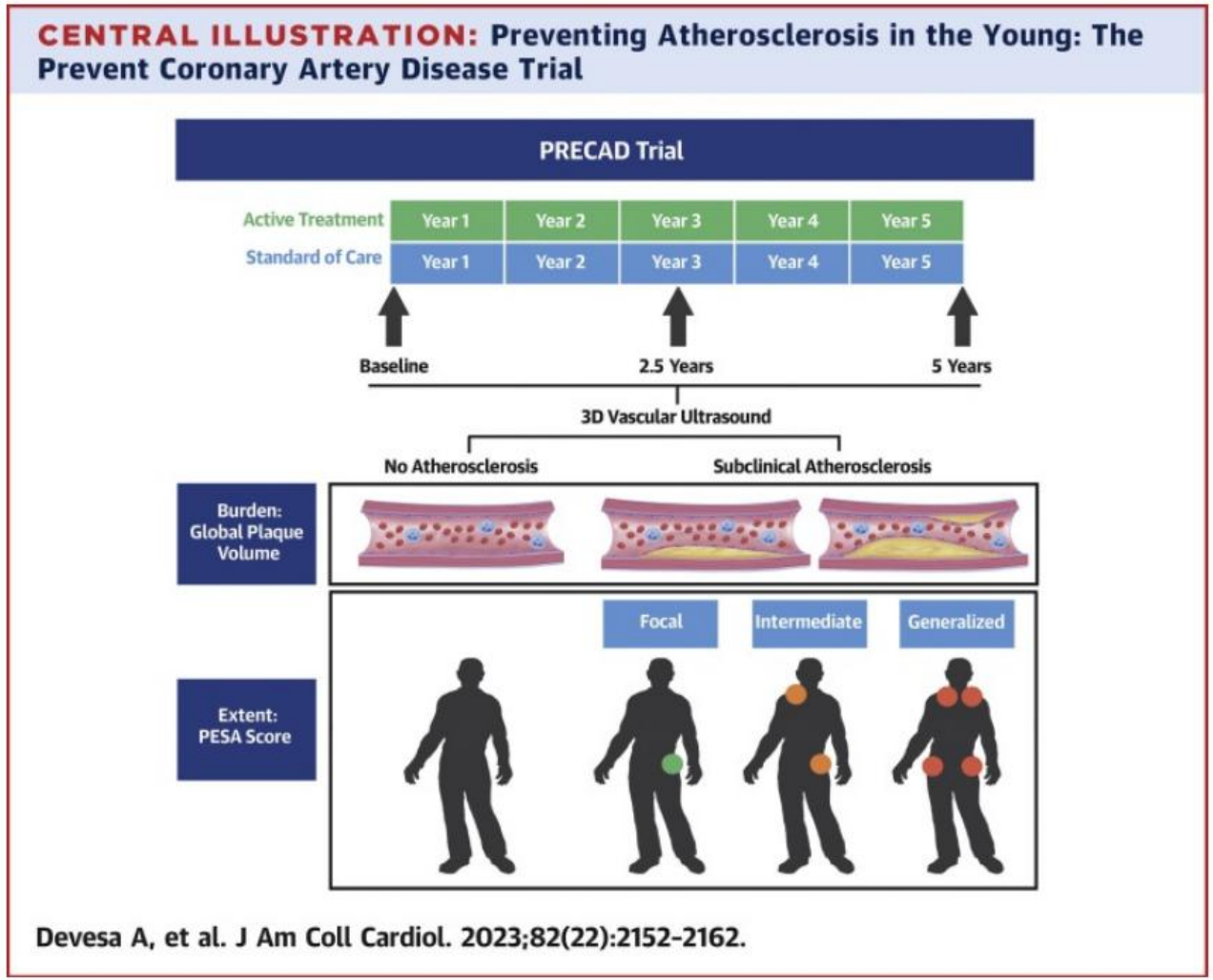
Significantly reduces atherogenic lipids

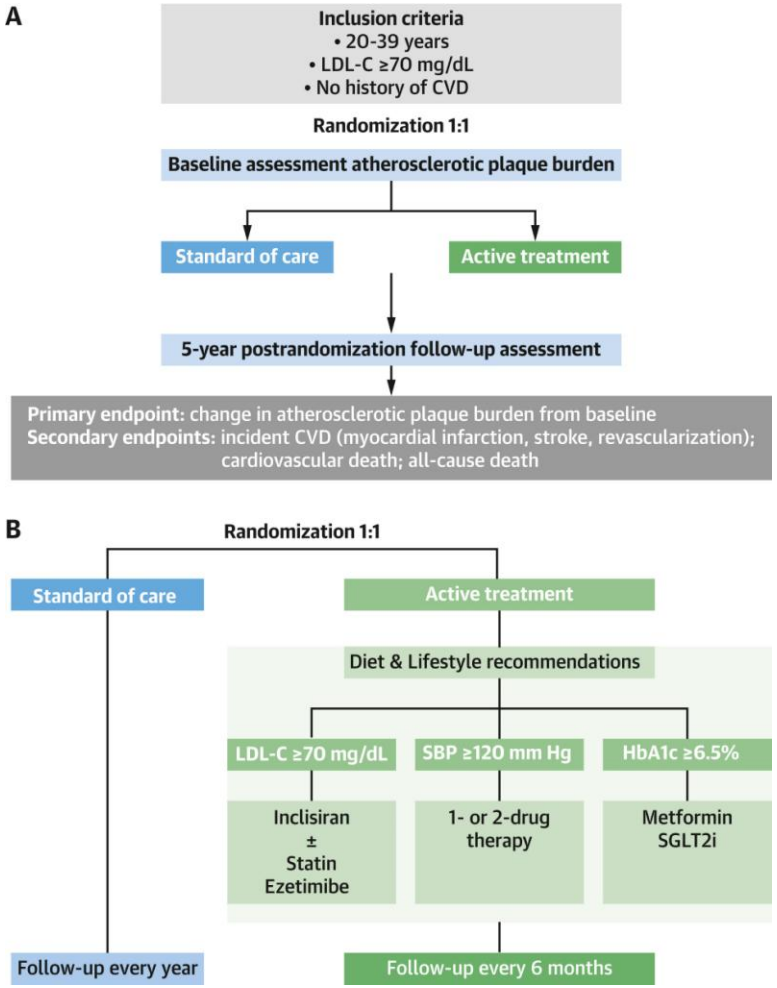
Is well-tolerated except for mainly mild, treatment-emergent adverse events at the injection site



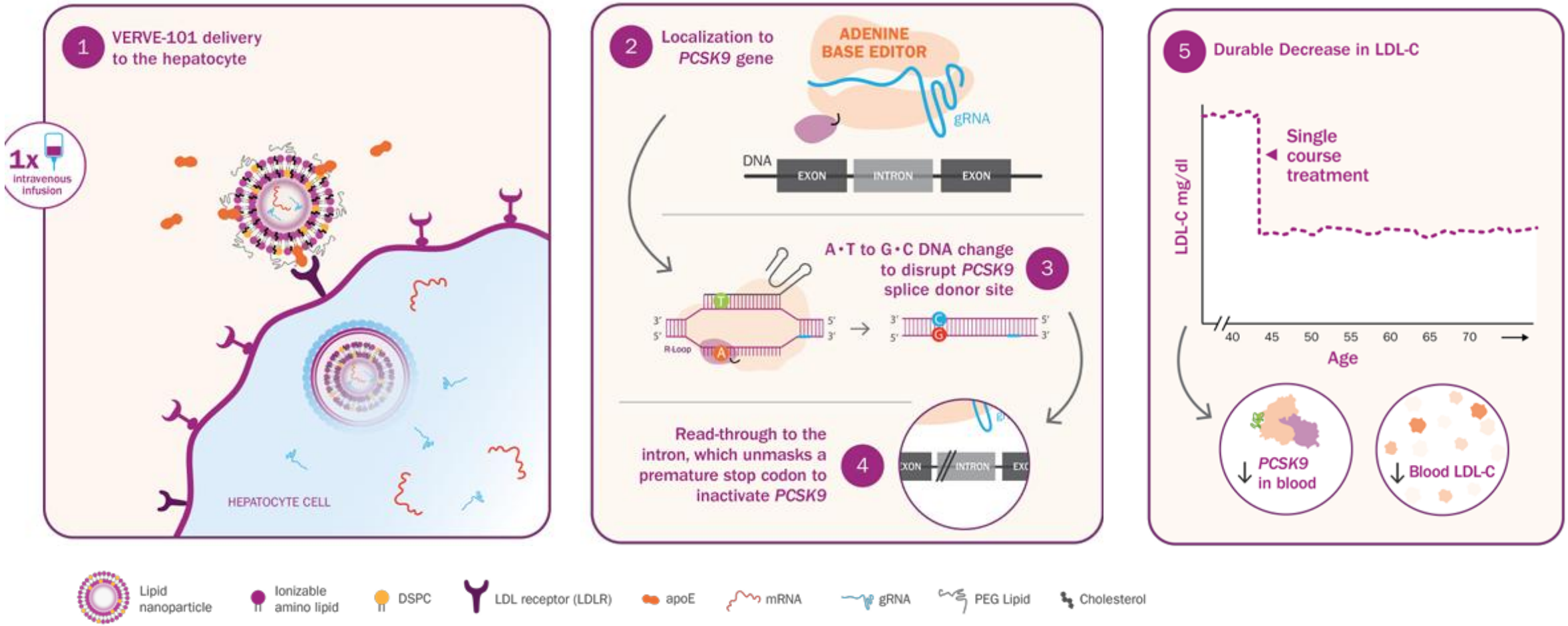

Ray KK et al. European Heart Journal (2022) **43**, 5047–5057

# Opravdová primární prevence ASCVD
# PRECAD studie: n=2100, sledování 5 let, 3DVUS



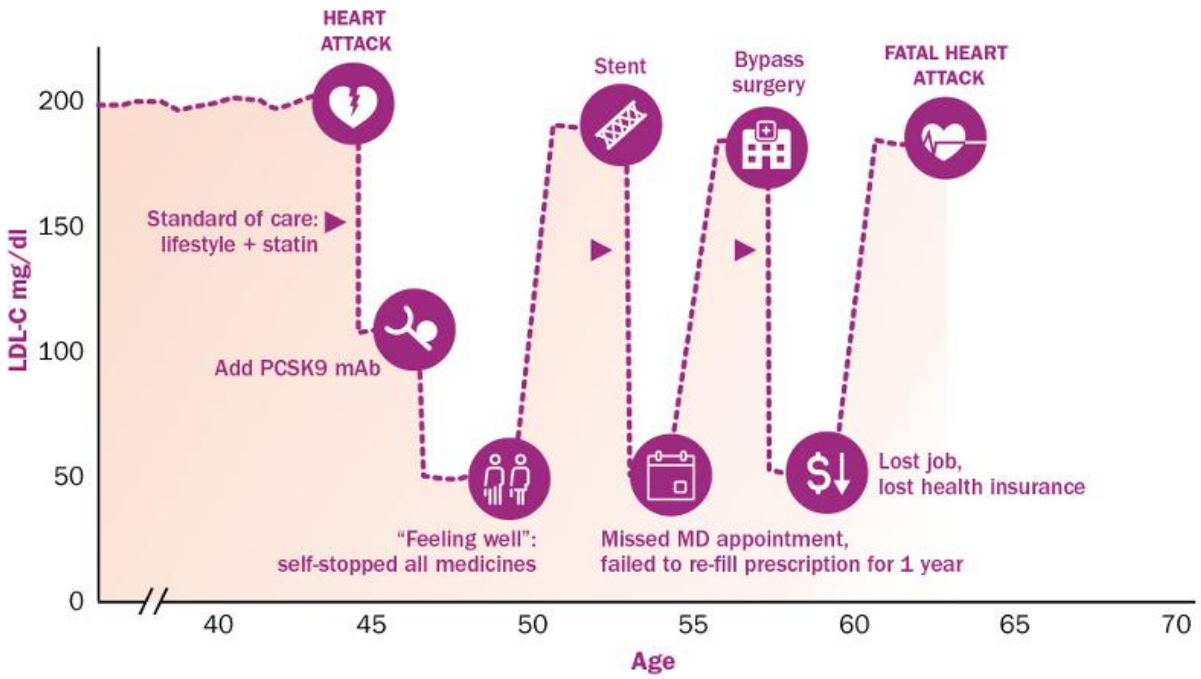



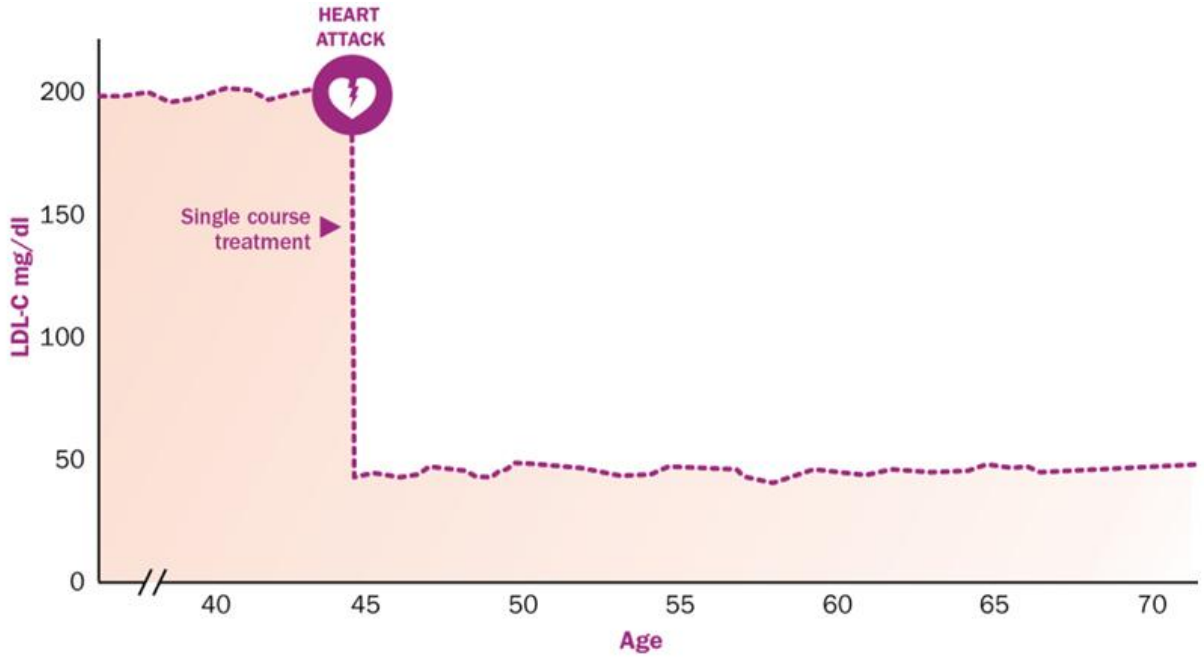
# Genová editace PCSK9- VERVE 101: editace genu pro PCSK9




https://www.vervetx.com

# Budoucnost je nyní




https://www.vervetx.com