Cardiology Lett. 2018;27(2):76–86

ODYSSEY OUTCOMES. Čo priniesla táto klinická štúdia

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ODYSSEY OUTCOMES clinical study: Implications for us

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Abstrakt. Pacienti s akútnym koronárnym syndrómom (AKS) i po optimálnej liečbe akútneho ochorenia a i pri optimálnej liečbe v rámci sekundárnej následnej prevencii majú naďalej vysoké kardiovaskulárne (KV) riziko morbidity a mortality.

Intenzívnejšia liečba dyslipidémie, ďalšia redukcia sérového LDL cholesterolu (LDL-Ch), by mali zlepšiť prognózu pacientov, čo bola hypotéza tejto štúdie s liečbou alirokumabom (PCSK9 inhibítorom) versus placebom pri ostatnej štandardnej liečbe. V štúdii bolo zaradených 18 924 pacientov, randomizovaných k tejto liečbe v období 1 – 12 mesiacov po AKS. V ramene aktívnej liečby došlo k ďalšej redukcii sérového LDL-Ch (z úrovne 2,62 na úroveň 1,37 mmol/l, redukcia 54,7 %). Tento pokles LDL-Ch viedol k redukcii primárneho end-pointu (koronárne úmrtie/nefatálny infarkt a cievna mozgová príhoda/hospitalizácia pre nestabilnú angínu pektoris) o 15 % (štatisticky významne, S), aj jeho komponenty boli významne priaznivo ovplyvnené a celková mortalita bola redukovaná tiež o 15 % (S). Benefit bol najvyšší v podskupine pacientov, ktorí do štúdie vstupovali s najvyššou sérovou hladinou LDL-Ch, t. j. ≥ 2,6 mmol/l: primárny endpoint bol tu redukovaný o 29 % (S) a KV mortalita o 31 % (S). Liečba bola bezpečná.

Odkazom štúdie je významná redukcia výskytu KV príhod (mortality, nefatálnych infarktov myokardu i mozgových príhod, nestabilnej angíny pektoris) u chorých s AKS pomocou alirokumabu – pričom všetci pacienti mali znamenitú štandardnú liečbu ochorenia, vrátane použitia silných

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Abstract. Patients suffering acute coronary syndrome (ACS), even with optimal treatment of ACS and optimal secondary prevention treatment afterwards, still have a very high cardiovascular (CV) risk of morbidity and mortality.

More intensive treatment of dyslipidemia, with further reduction of serum LDL-Ch levels, to improve the prognosis of these patients – was the hypothesis of this study, with alirocumab (PCSK9 inhibitor) treatment versus placebo treatment. There were 18 924 patients in this study, randomized for the mentioned treatment in the time period of 1 – 12 months after ACS. In the active arm treatment there was a further reduction of serum LDL-Ch level (from 2.62 to 1.37 mmol/l, reduction of 54.7%). This serum LDL-Ch reduction contributed to a reduction of primary end-point (coronary mortality/nonfatal myocardial infarction and stroke/hospitalization for unstable angina pectoris) of 15% (significantly, S), but also components of this endpoint were successfully reduced, and all-cause mortality too by 15% (S). The best benefit was in the subgroup of patients with the highest serum level of LDL-Ch, ≥ 2.6 mmol/l: the primary end-point was reduced by 29% (S) and CV mortality by 31% (S). The treatment was safe.

The message of this study is the great reduction of CV events (mortality, nonfatal myocardial infarctions and strokes, unstable angina pectoris) in patients with an ACS treated by alirocumab; and all patients had an excellent standard treatment of this

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Do redakcie došlo dňa 28. marca 2018; prijaté dňa 3. apríla 2018

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Manuscript received March 28, 2018; accepted for publication April 4, 2018

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statínov vo vysokých dávkach. Najviac z liečby profitovali pacienti s najvyššou vstupnou sérovou hladinou LDL-Ch (≥ 2,6 mmol/l). Obr. 7, Tab. 1, Lit. 21, online full text (Free, PDF), www.cardiologyletters.sk
Kľúčové slová: akútny koronárny syndróm – hypercholesterolémia – alirocumab – kardiovaskulárne príhody

disease, with strong and high doses of statins included. Patients with the highest basal serum LDL-Ch levels (≥ 2.6 mmol/l) profited the most. Fig. 7, Tab. 1, Ref. 21, online full text (Free, PDF), www.cardiologyletters.sk
Key words: acute coronary syndrome – hypercholesterolemia – alirocumab – cardiovascular events

Prečo sa táto štúdia naplánovala
(Uvedenie problému štúdie)

Napriek akútnej i následnej modernej liečbe chorých s akútnym koronárnym syndrómom (AKS), t. j. pohotová koronárna revaskularizácia a následne dlhodobá duálna antitrombotická liečba, liečba v rámci sekundárnej kardiovaskulárnej (KV) prevencie podľa odporúčaní, vrátane intenzívnej liečby silným statínom, sú títo pacienti ďalej vo vysokom riziku výskytu závažných KV príhod, najmä v období po prepustení (1, 2, 3). Údaje z registrov preukázali, že KV mortalita v období piatich rokov po prekonaní AKS je v úrovni až 13 %, a asi štyri z piatich úmrtí sa udeje v prvých mesiacoch po prepustení (4).

Intenzívna statínová liečba (atorvastatín či rosuvastatín vo vysokých dávkach tolerovaných pacientom) je schopná redukovať sérové hladiny LDL-Ch okolo 50 %, ale asociácia „redukcie LDL-Ch s redukciou KV (príhod)" nemá jasnú prahovú hodnotu, t. j. ak pôjdeme s redukciou LDL-Ch v sére ďalej, dosiahneme aj ďalšiu redukciu KV príhod (5). Treba tiež dodať, že u chorých po prekonanom AKS či u chorých s chronickou ischemickou chorobou srdca (ICHS), býva následné KV riziko vývoja ďalších (rekurentných) KV príhod veľmi vysoké a je vo vzťahu k sérovej hladine LDL-Ch (1, 6, 7). Okrem toho máme i chorých, ktorí statínovú liečbu netolerujú a máme i chorých, u ktorých napriek intenzívnej statínovej liečbe sú sérové koncentrácie LDL-Ch stále vysoké (8, 9).

Asi nie je prekvapením túžba (otázka) či k liečbe statínmi (hoci i silným a vo vysokej dávke) nemožno pridať ďalšiu liečbu, ktorá výrazne zredukuje sérovú koncentráciu LDL-Ch (oveľa viac ako pridanie ezetimibu) a možno i koncentrácie iných aterogénnych lipoproteínov – všetko s túžbou a cieľom významne a ešte viac redukovať KV riziko týchto chorých.

Proproteín konvertáza subtilizín/kexin typ 9 (PCSK9) je bielkovina – a je to regulátor expresie LDL receptorov na hepatocytoch, preto má potom významnú úlohu pri riadení (určovaní) sérových koncentrácií LDL-Ch (10). Isté pozorovania u osôb s genetickým polymorfizmom PCSK9 podporujú významnú úlohu tohto proteínu v náchylnosti/podpore k ateroskleróze. Sú dva vyhranené typy mutácie proteínu PCSK9: 1. tzv. "loss-of-function" mutácia (inaktivita či neprítomnosť funkcie PCSK9) znamená u osoby, že má celoživotne nízke sérové koncentrácie LDL-Ch a súčasne nízku incidenciu prí-

Why was this study planned?
(Introduction)

Despite acute, and the immediately-following modern treatment of patients with acute coronary syndrome (ACS), i.e. immediate coronary revascularization and successive long-term dual antithrombotic treatment, secondary cardiovascular (CV) prevention treatment according to the Guidelines and including high dose statin therapy, these patients are still at very high risk of serious CV events, especially during the period after discharge from hospital (1, 2, 3). Data from registries have shown that CV mortality in the 5 years following ACS is approximately 13%, and 4 from 5 deaths come in the first months after discharge (4).

Intensive statin treatment (atorvastatin or rosuvastatin in high doses tolerated by the patient) is able to reduce serum levels of LDL cholesterol (LDL-C) by 50%, but association of LDL-C reduction with CV events reduction does not have a clear threshold. This means that further reduction of LDL-C leads to a greater reduction of CV events (5). Also important to mention here is that in patients after a CV event or with ischemic heart disease (IHD) the subsequent risk of further (recurrent) CV events is very high and is related to serum LDL-C level (1, 6, 7). Moreover, there are also patients who do not tolerate statin treatment and also patients, who despite intensive statin treatment, have high LDL-C levels (8, 9).

Therefore, a valid and important question arises: whether some other drug can be added to intensive and high dose statins, which would significantly decrease (more than ezetimibe) LDL-C levels and maybe also concentrations of other atherogenic lipoproteins, with the goal of the further reduction of CV risk of those patients.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a protein which regulates the amount of LDL receptors on the hepatocytes, so playing an important role in regulation of LDL-C serum levels (10). Observations in persons with genetic polymorphism of PCSK9 support the idea of the important role of this protein in development of atherosclerosis. There are two well-marked types of PCSK9 mutations: 1/ "loss-of-function" mutation (inactivity or absence of PCSK9) causes life-long low levels of LDL-C and low incidence of IHD and CV events, and 2/ "gain-of-function" mutation (increased activity of PCSK9) with opposite effect of the former, i.e.

hod v rámci ICHS a 2. tzv. "gain-of-function" mutácia (kde je aktivita a pôsobenie proteínu PCSK9 výrazné) znamená opak predchádzajúceho, t. j. vysokú sérovú hladinu LDL-Ch celoživotne (tieto osoby majú málo alebo „žiadne" LDL receptory na hepatocytoch v dôsledku pôsobenia proteínu PCSK9 pri deštrukcii LDL receptorov intracelulárne v hepatocytoch) a následne vysokú a predčasnú incidenciu ICHS príhod (11, 12). Okrem toho aj statíny vedia upregulovať (t. j. zvýšiť) expresiu PCSK9, čím obmedzujú svoju účinnosť v redukcii sérového LDL-Ch (13).

Alirokumab je plnohodnotnou humánnou monoklonálnou protilátkou proti proteínu PCSK9. V štúdiách alirokumab preukázal redukciu LDL-Ch podobne ako intenzívna statínová liečba (t. j. ako silné statíny a vo vysokej dávke) (14). V kombinovanej liečbe, t. j. alirokumab a intenzívna statínová liečba dochádza potom navyše k významnej redukcii sérovej hladiny LDL-Ch (15, 16). Roth et al. (2012) preukázali u pacientov s LDL-Ch ≥ 2,6 mmol/l pri liečbe atorvastatínom 10 mg denne následné skutočnosti: a) zvýšenie dávky atorvastatínu na 80 mg denne viedlo k ďalšiemu 17 % zníženiu sérového LDL-Ch, ale b) pridanie alirokumabu 150 mg s.c. dvakrát mesačne k liečbe pacientov liečených atorvastatínom v dávke 80 mg denne viedlo k ďalšej redukcii sérového LDL-Ch o 73 % (17). Liečba alirokumabom je dobre tolerovaná a len ojedinele sa vyskytujú mierne lokálne kožné reakcie po vpichoch alirokumabu.

Čo si štúdia ODYSSEY OUTCOMES predsavzala riešiť

Táto štúdia testovala platnosť hypotézy, že „alirokumab v porovnaní s placebom" bude redukovať kardiovaskulárnu mortalitu i morbiditu u pacientov s nedávno prekonaným akútnym koronárnym syndrómom, ktorí súčasne napriek intenzívnej statínovej liečbe (atorvastatín, rosuvastatín) majú sérové hladiny lipoproteínov vyššie ako to požadujú dnešné odporúčania pre liečbu týchto chorých.

Akí pacienti v štúdii ODYSSEY OUTCOMES boli, aký bol dizajn štúdie

Štúdia **(obrázok 1)** bola medzinárodná, multicentrická, randomizovaná, dvojito-slepá a placebom kontrolovaná, zahŕňala 18 924 pacientov s nedávnym AKS: hospitalizovaní pre koronárnu obštrukciu v období 4 – 52 týždňov pred randomizáciou, pričom zaradenie pacienta vyžadovalo k tomu ešte aspoň prítomnosť elevácie biomarkerov nekrózy v sére alebo ischemické či infarktové EKG zmeny s regionálnou poruchou kinetiky steny ľavej komory či s perfúznym defektom, alebo s ≥ 70 % epikardiálnou koronárnou stenózou pri angiografii či s potrebou koronárnej revaskularizácie. Pacienti mali ≥

life-long increased LDL-C level (these persons have decreased amount of LDL receptors on hepatocytes caused by PCSK9 mediated increased intracellular destruction of these receptors in hepatocytes) with subsequent high and premature incidence of IHD and CV events (11, 12). Moreover, statins can upregulate the expression of PCSK9, leading to decreased efficacy in the reduction of serum LDL-C (13).

Alirocumab is a fully-functional human monoclonal antibody against PCSK9. Clinical studies with alirocumab have shown reduction of LDL-C similar to intensive statin treatment (14). Combined treatment with alirocumab and intensive statin therapy leads to further significant decrease of LDL-C (15, 16). Roth et al (2012) have shown that in patients with LDL-C > 2.6 mmol/l increasing the dose of atorvastatin to 80mg caused a further 17% decrease of LDL-C, but adding alirocumab 150mg twice a month subcutaneously in patients treated with atorvastatin 80mg led to further LDL-C reduction by 73% (17). Treatment with alirocumab was well tolerated and the most common adverse effects were minor local skin reactions after alirocumab injections.

What was the goal of this study?

Aim of this study was to test the hypothesis that alirocumab compared to placebo will reduce cardiovascular mortality and morbidity in patients with recent acute coronary syndrome who have despite intensive statin treatment (atorvastatin, rosuvastatin) higher levels of serum lipoproteins than those required by current Guidelines.

What kind of patients were in the study? What was its design?

The ODYSSEY OUTCOMES study **(Figure 1)** was an international, multicentric, randomized, double-blind placebo-controlled study, which included 18 924 patients with recent ACS: hospitalized due to coronary obstruction 4-52 weeks before randomization. Inclusion of the patient required either elevation of biomarkers of myocardial necrosis in serum or ischemic/infarction ECG changes with regional wall motion abnormality of left ventricle, or with perfusion defect or ≥ 70% epicardial coronary artery stenosis in angiography examination, or with the need of coronary revascularization. Patients had to have ≥ 40 years of age together with inadequately controlled serum lipid levels (LDL-C ≥ 1.8 mmol/l or non-HDL-C ≥ 2.59 mmol/l or apoB ≥ 0.8 mmol/l) despite intensive statin treatment (atorvastatin 40-80 mg or rosuvastatin 20-40 mg) on the highest tolerable dose. Most important exclusion criteria were: unstable hypertension (blood pressure ≥ 180/110 mmHg), severe heart failure (NYHA III-IV despite treatment, ejection fraction < 25%), history of hemorrhagic

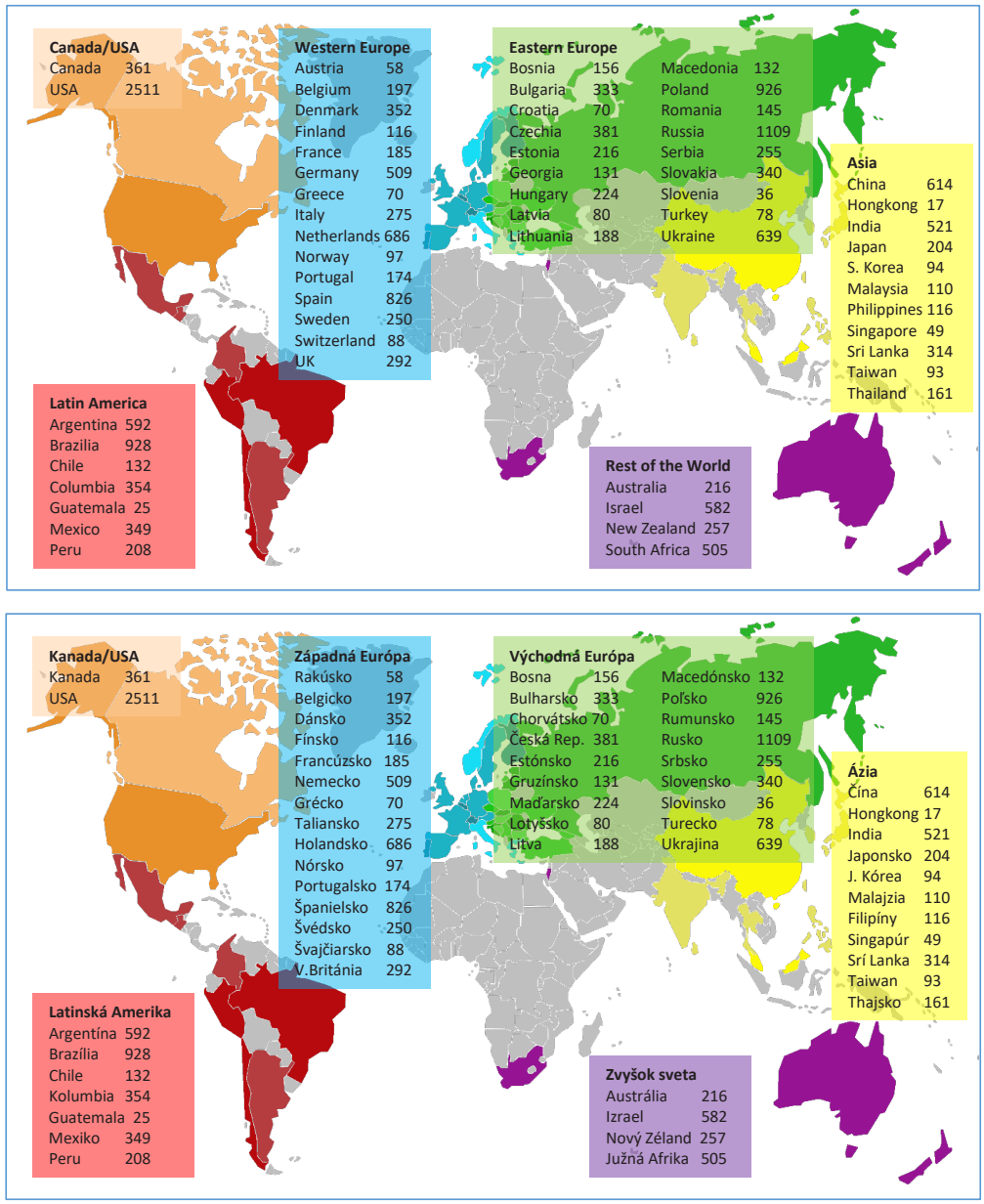

Figure 1 **Number of patients included into study and their distribution according to regions**
Obrázok 1 *Počet pacientov zapojených do štúdie a ich rozdelenie podľa regiónov*

40 rokov a súčasne nedostatočne kontrolované sérové lipidy (LDL-Ch ≥ 1,81 mmol/l, non-HDL-Ch ≥ 2,59 mmol/l alebo apoB ≥ 0,8 mmol/l) napriek liečbe silnými statínmi (atorvastatín 40 – 80 mg, rosuvastatín 20 – 40 mg), obvykle na najvyššej tolerovanej dávke. Hlavnými dôvodmi nezaradenia pacienta boli: nestabilná hypolipidemická liečba (≥ 2 týždne pred randomizáciou), nekontrolovaná hypertenzia (≥ 180/110 mmHg), srdcové zlyhávanie (NYHA III – IV napriek liečbe, ejekčná frakcia < 25 %), prekonaná hemoragická cievna

stroke, triacylglycerol serum level > 4.52 mmol/l at randomization, ACS or coronary revascularization 2 weeks before randomization or planned such procedure after randomization, AST, ALT or creatine kinase above 3 times the upper limit of normal, glomerular filtration rate < 30 ml/min, active viral hepatitis B or C, positive pregnancy test or treatment with fibrates (with the exception of fenofibrate).

The primary endpoint of the study was to evaluate whether treatment with alirocumab (75 mg or 150 mg subcutaneously

mozgová príhoda, triacylglyceroly > 4,52 mmol/l pri randomizácii, AKS či koronárna revaskularizácia do dvoch týždňov pred randomizáciou či plánovaný zákrok po randomizácii, AST a ALT aj kreatín-kináza > trojnásobok hornej normy, glomerulárna filtrácia < 30 ml/min, aktívna hepatitída B či C, pozitívny gravidárny test a liečba fibrátmi (s výnimkou fenofibrátu).

Primárnym end-pointom (cieľom) bolo zhodnotiť, či liečba alirokumabom (75 mg alebo 150 mg s.c. každý druhý týždeň), začatá 1 až 12 mesiacov po AKS, dokáže redukovať incidenciu „koronárneho úmrtia – nefatálneho myokardiálneho infarktu a nefatálnej mozgovej ischemickej cievnej príhody a tiež hospitalizácie pre nestabilnú angínu pektoris" (zložený end-point).

Dizajn štúdie je na **obrázku 2**: a) 2- až 16-týždňová úvodná (run-in) fáza, kde sa pacient učil podávať s.c. testované liečivo (placebo), nastolil sa vtedy metabolický „steady state" po AKS vrátane dobrej kontroly sérových lipidov (pri liečbe silnými statínmi). Pacienti vyhovujúci vstupným aj vylučovacím kritériám boli potom b) v druhej fáze štúdie (dvojito-slepej) randomizovaní k liečbe alirokumabom 75 mg s.c. každé dva týždne versus k liečbe placebom. Vizity sa naplánovali na 1., 2., 4., 8., 12., 16., 20. a 24. mesiac po randomizácii a potom dvakrát ročne. Zabezpečené bolo laboratórne testovanie krvi (lipoproteíny, hematologické bežné testy, obvyklé bežné biochemické testy, testy funkcie obličiek, pečene, svalstva, HbA1c, hsCRP, protilátky proti alirokumabu, gravidárne testy) a moču. LDL-Ch v sére sa kalkuloval Fiedewaldowou formulou (s výnimkou ak boli hodnoty veľmi nízke: < 0,38 mmol/l (15 mg/dl), alebo ak mal pacient sérové triacylglyceroly > 4,52 mmol/l – vtedy sa LDL-Ch stanovoval priamo) (18). Vyšetrovali sa aj: hladiny PCSK9, lipoproteínové subfrakcie, mediátory zápalu a KV rizika. Pacienti boli v oboch ramenách liečby na dobrej hypolipidemickej liečbe, a preto v štúdii neboli lekári-investigátori a ani pacienti informovaní o hodnotách sérových lipidov. V štúdii sa kontrolovali sérové lipoproteíny u zaradených pacientov: 1. v ramene liečby alirokumabom, ak bola hladina LDL-Ch po mesiaci liečby (od randomizácie) stále ≥ 1,29 mmol/l (50 mg/dl), tak sa dávka liečiva zvýšila na 150 mg s.c. každé dva týždne. 2. Ak po mesiaci liečby bola hodnota LDL-Ch v sére < 1,29 mmol/l (50 mg/dl), tak sa i ďalej podával alirokumab v dávke 75 mg/dl. 3. Ak sérová hladina LDL-Ch bola po mesiaci liečby < 0,64 mmol/l (25 mg/dl) (potrebné však boli dve takéto merania) pri liečebnej dávke 150 mg, tak sa táto dávka redukovala na 75 mg (každé dva týždne). 4. Ak bola sérová hladina LDL-Ch < 0,64 mmol/l (25 mg/dl), ale ≥ 0,38 mmol/l (15 mg/dl) (opäť dve merania po sebe), pokračovalo sa v dávke 75 mg s.c. alirokumabom (súčasne bol pacient podrobne monitorovaný pre nežiaduce účinky). 5. Ak sa sérová hladina LDL-Ch dvakrát po sebe nachádzala na hladine < 0,38 mmol/l (15 mg/l) pri liečbe alirokumabom 75 mg (každé dva týždne), liečba alirokumabom sa zastavila (pacient dostal placebo až do konca štúdie).

every 2 weeks) started 1-12 months after ACS, can reduce incidence of CV death, nonfatal myocardial infarction, nonfatal ischemic stroke and hospitalization for unstable angina pectoris (composite endpoint).

The design of the study is shown in **figure 2**. Initial run-in phase lasted 2-16 weeks, during which the patient was trained to apply subcutaneous (placebo) injections, and metabolic steady-state after ACS was reached (including good control of serum lipids by intensive statin treatment). Patients fulfilling inclusion and exclusion criteria advanced to the second double-blind phase, where they were randomized to treatment with alirocumab 75 mg subcutaneously every 2 weeks versus placebo treatment. Follow-up visits were planned on 1st, 2nd, 4th, 8th, 12th, 16th, 20th and 24th months after randomization and every 6 months from then. Patients had examinations of blood laboratory tests (lipoproteins, common hematologic and biochemistry tests, kidney and liver function tests, markers of muscle damage, HbA1c, hsCRP, antibodies against alirocumab, pregnancy tests, urine analysis) and of urine. Serum LDL-C level was calculated by the Friedewald formula (with exception of very low LDL-C levels: < 0.38 mmol/l (15 mg/dl) or if the patient had very high serum triacylglycerol levels > 4.52 mmol/l: in that case LDL-C was analyzed directly) (18). Other parameters analyzed included levels of PCSK9, lipoprotein subfractions, inflammatory mediators and markers of CV risk. Patients in both arms of the study were on intensive hypolipidemic treatment. Therefore during the study neither investigators nor patients were informed about the serum lipid levels.

After randomization patients' lipid levels were tested. According to the results, several possibilities arose: 1. If serum LDL-C level after 1st month of treatment from randomization remained ≥ 1.29 mmol/l (50 mg/dl), the dose of alirocumab was increased to 150 mg subcutaneously every 2 weeks. 2. If serum LDL-C level after 1st month of treatment from randomization was below 1.29 mmol/l (50 mg/dl), dose of alirocumab remained at 75 mg subcutaneously every 2 weeks. 3. If serum LDL-C level was below 0.64 mmol/l (25 mg/dl) (2 measurements were needed) and the alirocumab treatment dose was 150 mg, then the dose was reduced to 75 mg every 2 weeks. 4. If serum LDL-C level was below 0.64 mmol/l (25 mg/dl) but ≥ 0.38 mmol/l (15 mg/dl) (again, 2 measurements were needed), and the alirocumab treatment dose was 75 mg, the dose was continued; meanwhile, the patient was closely monitored for presence of adverse effects. 5. If serum LDL-C level was found consecutively twice below 0.38 mmol/l (15 mg/dl) and the alirocumab treatment dose was 75 mg, the alirocumab treatment was stopped and the patient continued on placebo treatment until the end of study.

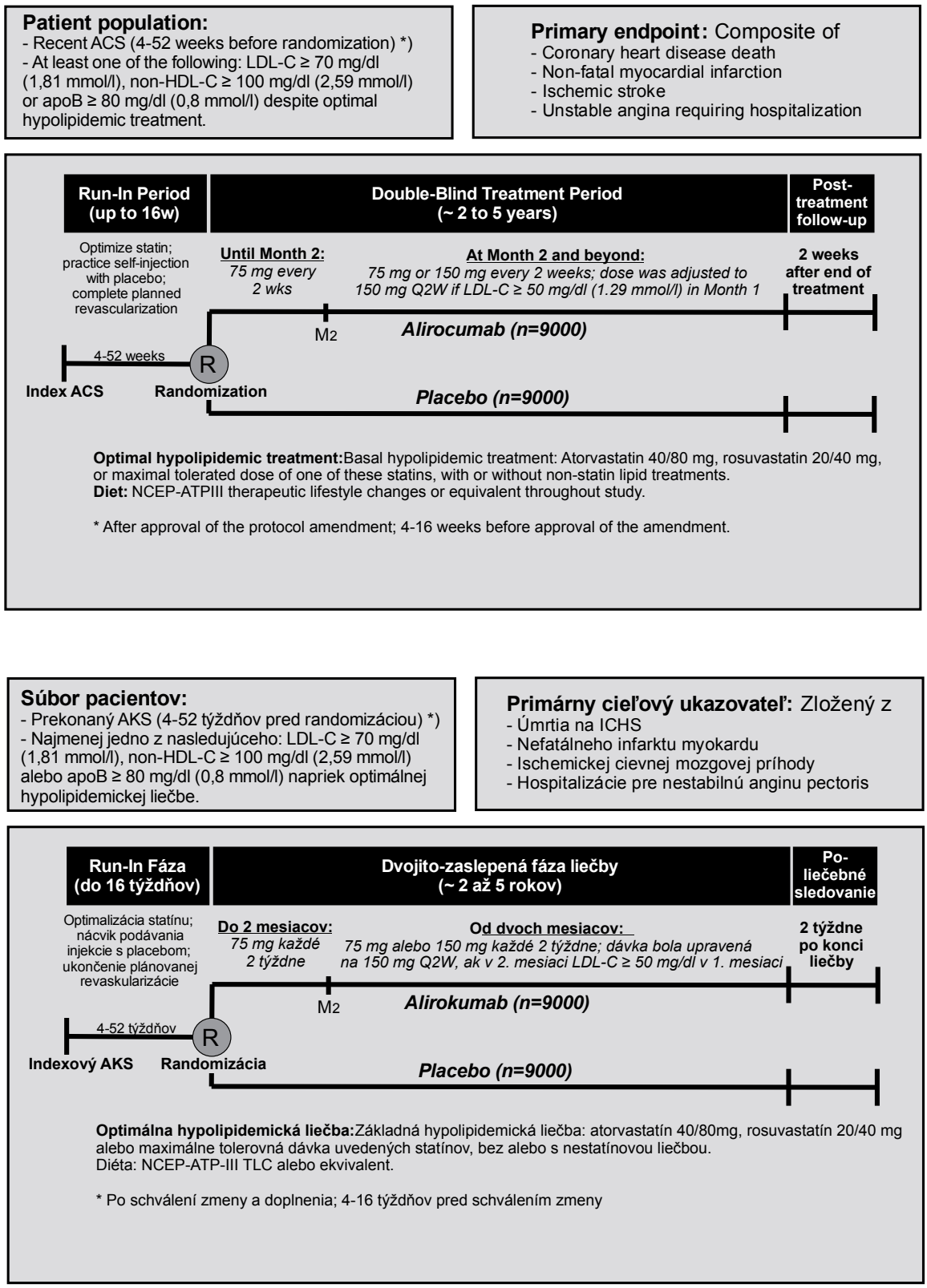

Figure 2 **Design of the ODYSSEY OUTCOMES Study (modified according to 20)**
Obrázok 2 *Dizajn štúdie ODYSSEY OUTCOMES (upravené podľa 20)*

Akým spôsobom sa monitoroval benefit liečby alirokumabom

V štúdii sa analyzovali KV príhody (primárny end-point: čas do koronárneho úmrtia, výskytu nefatálneho infarktu myokardu/nefatálnej ischemickej cievnej mozgovej príhody, hospitalizácie pre nestabilnú angínu pektoris), ale aj nežiaduce príhody. Sekundárne end-pointy boli nasledovné: potreba koronárnej revaskularizácie, hospitalizácia pre srdcové zlyhávanie, celková mortalita, tiež jednotlivé „súčasti" primárneho end-pointu. Ďalej sa analyzovali zmeny už uvedených sérových lipidov, HbA1c, hs CRP. Používal sa aj osvedčený dotazník kvality života (EUROQOL-5) (19).

Nežiaduce účinky sa zbierali najmä o alergickej príhode a o lokálnej kožnej reakcii v mieste podania alirokumabu. Hodnotili sa i prípady hemolytickej anémie a abnormality neurokognície (osobitne u pacientov, ktorí pri liečbe mali veľmi nízke sérové hladiny LDL-Ch). Protilátky proti alirokumabu sa merali: pri randomizácii, v mesiacoch 2., 4., 12. a potom raz ročne a pri odstúpení chorého zo štúdie.

Výskyt primárneho end-pointu sa analyzoval podľa princípu „intention – to – treat". Štatistiku zabezpečoval zdatný team Univerzity v New Yorku (SUNY) a vopred naplánoval hodnotenie (20).

How was the benefit of alirocumab treatment monitored?

The main observation of the study was the presence of primary endpoint: time to cardiovascular death or nonfatal myocardial infarction, nonfatal ischemic stroke or hospitalization for unstable angina pectoris; adverse events were also monitored. Secondary endpoints were as follows: need of coronary revascularization, hospitalization for heart failure, total mortality and also individual components of the primary endpoint. Further analyses were changes of serum lipid levels, HbA1c, hsCRP. Quality of life was monitored by the well-established EUROQOL-5 questionnaire (19).

Adverse events were collected; the main focus was on allergic reactions and local skin site reaction after alirocumab injections. Also evaluated were cases of hemolytic anemia and neuro-cognitive abnormalities (especially in patients who had very low serum LDL-C levels). Antibodies against alirocumab were measured at randomization, in 2nd, 4th and 12th months and then every year and at the patient's end of study.

The presence of the primary endpoint was analyzed by intention-to-treat principle. Statistical evaluation was made by a team from The University of New York (SUNY) and the evaluation was planned beforehand (20).

Výsledky štúdie ODYSSEY OUTCOMES

(zverejnené na Americkom kardiologickom kongrese 10. marca 2018) (21)

1. Do štúdie zahrnuli 18 924 pacientov, ktorí boli rovnomerne randomizovaní na liečbu alirokumabom či placebom (po 9 462 pacientoch). Medián sledovania chorých v štúdii bol 2,8 rokov. Nazbieralo sa 1 955 primárnych end-pointov: 726 úmrtí, prerušenie liečby bolo v úrovni 14 – 15 % pacientov, niekoľko „stratených pacientov" (14 v alirokumabovom ramene versus 9 v placebovom ramene). 2. Vstupné charakteristiky pacientov boli nasledovné: 58 rokov priemerný vek, 25 % pacientov boli ženy, hypertenziou trpelo 65 % zaradených, diabetom 28 %, fajčiarov bolo 24 % a u 19 % zaradených bol už predtým prekonaný infarkt. V priemere boli pacienti zaradení do štúdiovej liečby 2,6 mesiacov po vzniku AKS. Rozdelenie chorých podľa jednotlivých typov AKS bolo nasledovné: STEMI prípady (35 % pacientov), NSTEMI prípady (48 %), pacienti s nestabilnou angínou pektoris (16,6 % chorých). Revaskularizáciu pri AKS podstúpilo 71,8 chorých. Vstupné sérové lipidy: LDL-Ch (87 mg/dl, 2,24 mmol/l), HDL-Ch (43 mg/dl, 1,11 mmol/l), triacylglyceroly (129 mg/dl, 1,45 mmol/l), Lp(a) (21 mg/dl), ApoB (79 mg/dl). Hypolipidemická liečba bola vynikajúca, pretože 89 % pacientov užívalo silný statín a vo vysokej dávke, ezetimib užívalo 2,8 % pacientov, nízku dávku statínov užívalo 8,8 % chorých a bez tejto liečby bolo len

Results of the ODYSSEY OUTCOMES study

(presented at the American College of Cardiology meeting, March 10th, 2018) (21)

1. There were 18 924 patients in the study, who were evenly randomized on alirocumab and placebo treatment (9 462 patients in each group). Median follow-up in the study was 2.8 years. 1 955 primary endpoints were observed, including 726 deaths. Premature termination of the treatment was present in 14-15% of patients, only a few patients were lost-to-follow-up (14 patients in the alirocumab arm and 9 patients in the placebo arm). 2. Baseline characteristics of patients were: mean age 58 years, 25% of patients were females, 65% of patients had arterial hypertension, 28% had diabetes mellitus, 24% were smokers and 19% had previous myocardial infarction. Average time from the index ACS event to the randomization was 2.6 months. According to ACS types: 35% of patients had STEMI, 48% had non-STEMI and 16.6% patients had unstable angina pectoris. Revascularization for index event was present in 71.8% of patients. Entry serum lipid levels were: LDL-C 2.24 mmol/l (87 mg/dl), HDL-C 1.11 mmol/l (43 mg/dl), triacylglycerols 1.45 mmol/l (129 mg/dl), Lp(a) 21 mg/dl, apoB 79 mg/dl. Hypolipidemic treatment was good according to Guidelines: 89% of patients were treated by intensive statin therapy, ezetimib was used in 28% of patients, low statin dose was used in 8.8% of patients and no statin treatment was used

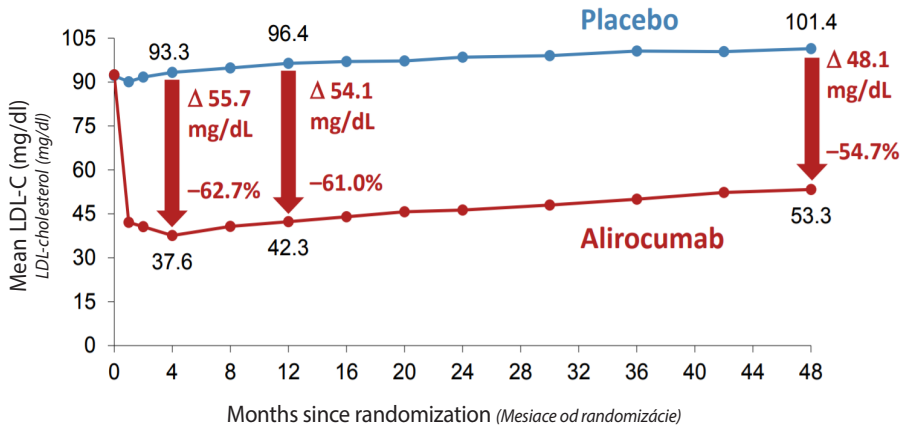

Figure 3 Comparison of LDL-Cholesterol values between Alirocumab and Placebo arms in patients who stayed on treatment (1 mg/dl = 0,02513 mmol/l)

Obrázok 3 *Porovnanie hladín LDL cholesterolu medzi alirokumabovým a placebovým ramenom u pacientov, ktorí užívali liečbu počas celej štúdie (1 mg/dl = 0,02513 mmol/l)*

0,9 % chorých. Aj ostatná liečba bola veľmi dobrá: kyselinu acetylsalicylovú užívalo 95,6 % zaradených, klopidogrel 87 % chorých, ACE inhibítor či sartan užívalo 77,7 % chorých, betablokátory 84,5 % pacientov a aj ostatná liečba bola vynikajúca v oboch podskupinách pacientov. 3. Výsledky sérových lipidov pri liečbe: alirokumab redukoval po štyroch rokoch sledovania sérový LDL-Ch z úrovne 101,4 mg/dl (2,62 mmol/l) na úroveň 53,3 mg/dl (1,37 mmol/l), t. j. o 54,7 % **(obrázok 3)**. 4. Klinické výsledky: A) v placebovom ramene liečby bol 11,1 % výskyt kardiovaskulárnych príhod a tento výskyt primárneho end-pointu alirokumab

only in 0.9% of patients. Other treatments: acetylsalicylic acid was used in 95.6% of patients, clopidogrel in 87% of patients, ACE inhibitor or sartan in 77.7% of patients and betablockers in 84.5% of patients. Also other treatment was excellent in both subgroups of patients. 3. Results of lipid levels. After 4 years of treatment, alirocumab reduced serum LDL-C level from 2.62 mmol/l (101.4 mg/dl) to 1.37 mmol/l (53.5 mg/dl), relative decrease was 54.7% **(Figure 3)**. 4. Clinical results. A) In the placebo arm, the incidence of primary endpoint was 11.1%, and alirocumab treatment reduced it by 15% (RR 0.85, statistically significant). An

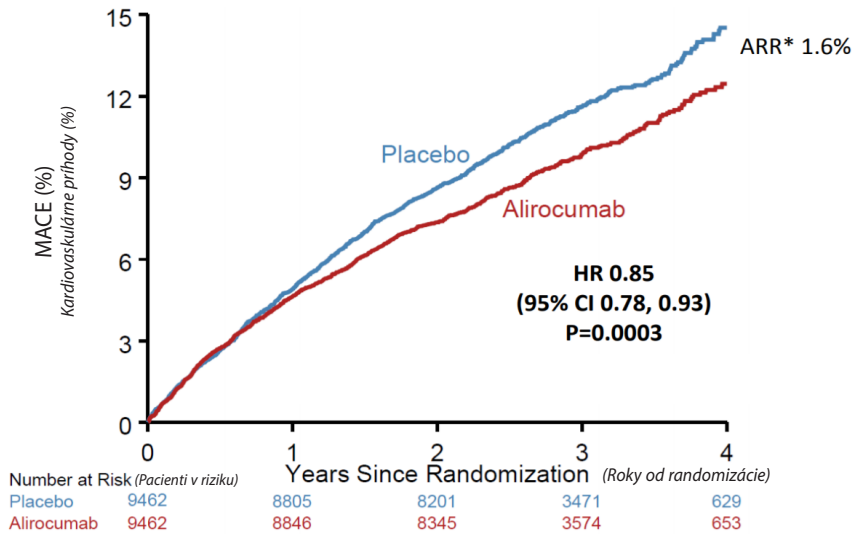

Figure 4 Primary efficacy composite endpoint of the study

Obrázok 4 *Primárny zložený cieľový ukazovateľ štúdie*

ARR – absolute risk reduction *(redukcia absolútneho rizika)*, HR – hazard ratio *(pomer rizika)*, CI – confidence interval *(interval spoľahlivosti)*

Table 1 Main secondary endpoints
Tabuľka 1 *Hlavné sekundárne ukazovatele*

Endpoint *(Ukazovateľ)*, n (%)	Alirocumab (n=9462)	Placebo (n=9462)	HR (95% CI)	Log-rank Significance *(Signifikancia)*
Coronary heart disease events *(Koronárne príhody)*	1199 (12.7)	1349 (14.3)	0.88 (0.81 – 0.95)	0.001
Major coronary heart disease events *(Závažné koronárne príhody)*	793 (8.4)	899 (9.5)	0.88 (0.80 – 0.96)	0.006
Cardiovascular events *(Kardiovaskulárne príhody)*	1301 (13.7)	1474 (15.6)	0.87 (0.81 – 0.94)	0.0003
Death, MI, ischemic stroke *(Mortalita, IM, iCMP)*	973 (10.3)	1126 (11.9)	0.86 (0.79 – 0.93)	0.0003
Coronary heart disease death *(Koronárna mortalita)*	205 (2.2)	222 (2.3)	0.92 (0.76 – 1.11)	0.38
Cardiovascular death *(Kardiovaskulárna mortalita)*	240 (2.5)	271 (2.9)	0.88 (0.74 – 1.05)	0.15
All-cause death *(Celková mortalita)*	334 (3.5)	392 (4.1)	0.85 (0.73 – 0.98)	0.026

HR – hazard ratio *(pomer rizika)*, CI – confidence interval *(interval spoľahlivosti)*

redukoval o 15 % (s RR: 0,85, štatisticky významne). Efekt sa dal poznať na konci prvého roku liečby. Absolútne riziko výskytu príhod bolo redukované o 1,6 % **(obrázok 4)**. B) Aj komponenty primárneho end-pointu boli dobre ovplyvnené: mortalita na ischemickú chorobu srdca (0,92, NS), výskyt nefatálneho infarktu (RR: 0,86, S), výskyt nefatálnej mozgovej príhody (0,73, S) a aj výskyt nestabilnej angíny pektoris (0,61, S). Druhotné end-pointy boli tiež dobre ovplyvnené (s RR medzi 0,85 – 0,92, väčšinou štatisticky významne) **(tabuľka 1)**, aj celková mortalita (RR: 0,85, S) **(obrázok 5)** a tiež potreba revaskularizácie pre ischémiu myokardu (RR: 0,88, S). C) Benefit liečby alirokumabu závisel od vstupnej sérovej hladiny LDL-Ch a bol najvyšší v podskupine chorých so sérovým LDL-Ch > 100 mg/dl

effect was already recognizable at the end of the 1st year of treatment. Absolute risk of CV events was reduced by 1.6% **(Figure 4)**. B) Individual components of primary endpoint were also positively influenced by alirocumab treatment: IHD mortality (RR 0.92, NS), nonfatal myocardial infarction (RR 0.86, SS), nonfatal stroke (RR 0.73, SS) and unstable angina pectoris (RR 0.61, SS). Secondary endpoints were also positively influenced, with RR 0.85 – 0.92, mostly statistically significant **(Table 1)**, as well as total mortality (RR 0.85, SS) **(Figure 5)** and need for myocardial revascularization for ischemia (RR 0.88, SS) (SS, statistically significant)). C) The benefit of alirocumab treatment was influenced by baseline levels of LDL-C; maximum effect was observed in patients with baseline LDL-C > 100 mg/dl (2.58 mmol/l):

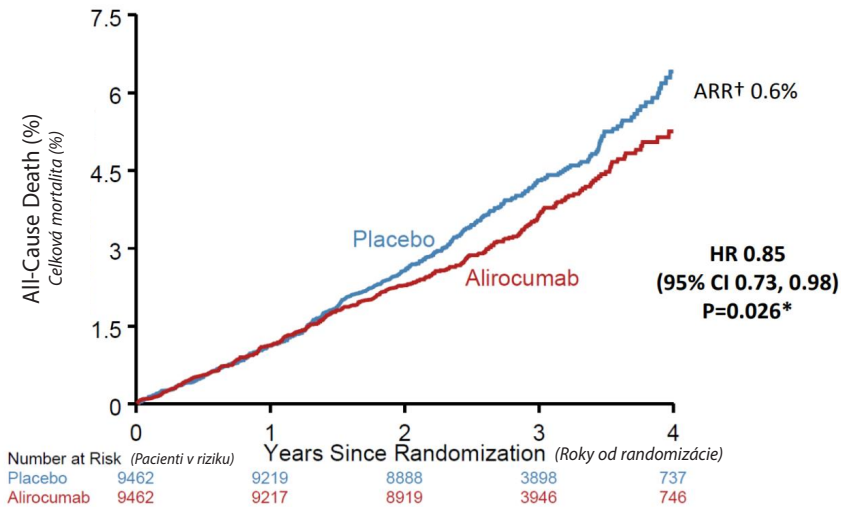

Figure 5 All-cause mortality
Obrázok 5 *Celková mortalita*
ARR – absolute risk reduction *(redukcia absolútneho rizika)*, HR – hazard ratio *(pomer rizika)*, CI – confidence interval *(interval spoľahlivosti)*

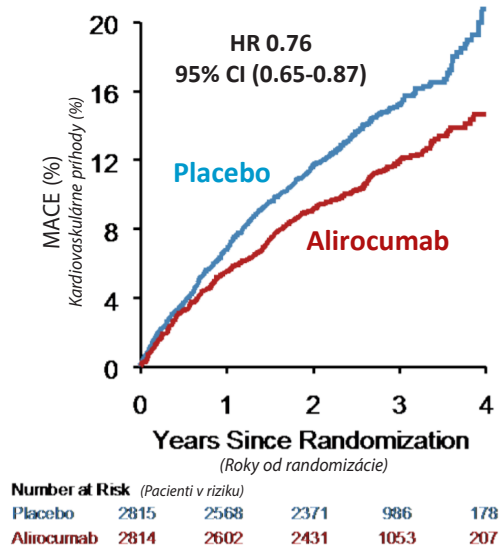

Figure 6 Primary endpoint in subgroup of patients with LDL-cholesterol > 100 mg/dl (2.59 mmol/l)
Obrázok 6 *Primárny ukazovateľ v podskupine pacientov s hladinou LDL cholesterolu > 100 mg/dl (2,59 mmol/l)*

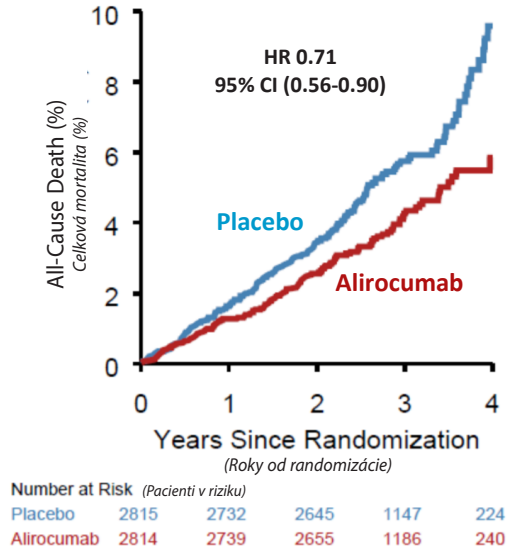

Figure 7 All-cause mortality in subgroup of patients with LDL-cholesterol > 100 mg/dl (2.59 mmol/l)
Obrázok 7 *Celková mortalita v podskupine pacientov s hladinou LDL cholesterolu > 100 mg/dl (2,59 mmol/l)*

(2,58 mmol/l): tu bola redukcia primárneho end-pointu 24 % (RR: 0,76, S) **(obrázok 6)**, podobne celková mortalita (RR: 0,71, S) **(obrázok 7)**, aj kardiovaskulárna mortalita (RR: 0,69, S). D) Benefit liečby alirokumabom bol prítomný vo všetkých podskupinách pacientov, rozdelených do podskupín podľa veku, pohlavia, rizikových faktorov a ochorení. 5. Bezpečnosť liečby bola vynikajúca – išlo viacmenej len o lokálne reakcie po vpichoch (alirokumab: 3,8 % vs placebo: 2,1 %), ostatné nežiaduce účinky boli podobne časté ako v placebovom ramene liečby.

Aký je odkaz štúdie do praxe

Možno konštatovať, že alirokumab významne redukoval výskyt kardiovaskulárnych príhod (mortality, nefatálnych infarktov myokardu i mozgových príhod, tiež nestabilnej angíny pektoris) u chorých s akútnym koronárnym syndrómom, ktorí dostávajú vynikajúcu liečbu akútneho koronárneho syndrómu a tiež silnú/intenzívnu statínovú liečbu. Aj celková mortalita chorých bola významne redukovaná. Najviac z liečby profitovala podskupina chorých s najvyššou vstupnou hladinou LDL-Ch v sére (> 100 mg/dl, 2,58 mmol/l), kde bola redukcia príhod primárneho end-pointu až 24 % a celkovej mortality až 29 %. Liečba bola veľmi bezpečná. Vhodnými pacientmi pre túto liečbu sú iste tí najrizikovejší chorí po AKS.

in this subgroup the primary endpoint reduction was 24% (RR 0.76, SS) **(Figure 6)**, all cause mortality (RR 0.71, SS) **(Figure 7)** and cardiovascular mortality (RR 0.69, SS). D) Benefit of alirocumab treatment was present in all prespecified subgroups according to age, gender, risk factors and concomitant diseases. 5. Treatment safety was excellent; most of the adverse effects were similarly present both in active and placebo arms. The only difference was in local skin reactions after alirocumab injection (alirocumab arm: 3.8%, placebo arm: 2.1%).

Conclusion and 'Take Home' message

Alirocumab significantly reduced the incidence of cardiovascular events (cardiovascular mortality, nonfatal myocardial infarctions, nonfatal ischemic strokes and unstable angina pectoris) in patients with acute coronary syndrome who were adequately treated for ACS and had intensive statin treatment. Total mortality was also significantly reduced by alirocumab. Maximum effect was observed in subgroup of patients with highest baseline LDL-C level (> 100 mg/dl, 2.58 mmol/l); the reduction of primary endpoint in this subgroup was 24% and total mortality 29%. Treatment with alirocumab was very safe. Patients with highest CV risk after ACS are suitable candidates for therapy with alirocumab.

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