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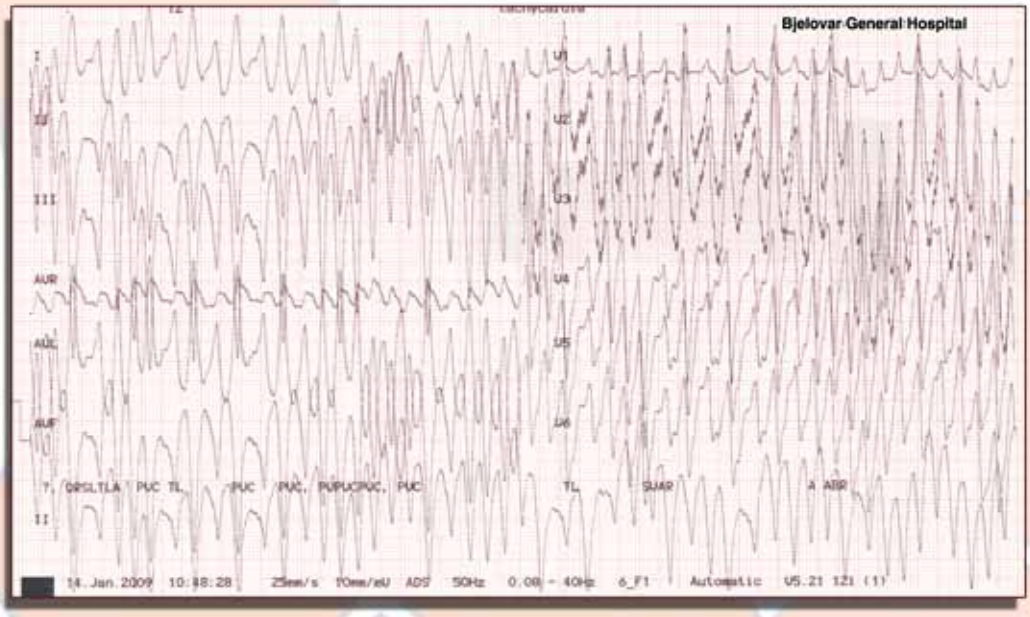

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Ima li novosti u farmakološkoj terapiji kroničnog zatajivanja srca

Are there any novelties in pharmacological treatment of chronic heart failure

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SAŽETAK: *Početni entuzijazam o mogućem terapijskom učinku statina u bolesnika sa zatajivanjem srca (ZS) temeljio se na dobro poznatim antiaterogenim i plejotropnim učincima statina. Nakon neutralnih rezultata CORONA studije, veliku pozornost privukli su nedavno priopćeni rezultati GISSI-HF istraživanja. Bolesnici sa simptomatskim ZS (NYHA II-IV) različite etiologije, liječeni su prosječno tijekom 3,9 godina rosuvastatinom u dozi od 10 mg na dan (n = 2.285) ili placebom (n = 2.289), povrh standardne terapije, neovisno o istisnoj frakciji lijeve klijetke i bez jasne indikacije za primjenu statina. Unatoč očekivanjima, nije bilo značajne razlike u pobolu i smrtnosti. Druga hipoteza GISSI-HF studije bila je da omega-3-masne kiseline mogu smanjiti pobol i smrtnost u bolesnika sa simptomatskim ZS (NYHA II-IV), neovisno o etiologiji i istisnoj frakciji lijeve klijetke. Stoga je 6.975 bolesnika randomizirano na jedan gram etilnih estera omega-3 masnih kiselina ili placebo, uz standardnu terapiju. Nakon prosječno 3,9 godina liječenja, omega-3-masne kiseline značajno su smanjile oba primarna ishoda, ukupnu smrtnost za 9% (p = 0,041) i ukupnu smrtnost ili hospitalizacije zbog kardiovaskularnih razloga za 8% (p = 0,009). Omega-3-masnim kiselinama trebalo je liječiti 56 bolesnika da se spriječi jedan smrtni ishod i 44 bolesnika da se izbjegne jedna smrt ili hospitaliza-*

ABSTRACT: *The initial entusiasm about a possible therapeutic effect of statins in patients with heart failure (HF) was based on well known antiatherogenic and pleiotropic effects of statins. After having obtained neutral results of the CORONA trial, a great interest was shown for the recently published results of the GISSI-HF trial. Patients with symptomatic HF (NYHA II-IV) of different etiology were treated during a median of 3.9 years with rosuvastatin 10 mg per day (n = 2285) or placebo (n = 2289), added to standard therapy, irrespective of LVEF and without clear indication for statin treatment. Despite expectations, there was no difference in morbidity and mortality. The second hypothesis of the GISSI-HF trial was that n-3 fatty acids can reduce morbidity and mortality in patients with symptomatic HF (NYHA II-IV), irrespective of etiology and LVEF. Therefore, 6975 patients were randomised to 1 gram of n-3 fatty acids ethyl esters or placebo, added to standard treatment. After the median follow-up of 3.9 years, n-3 fatty acids reduced significantly both primary endpoints, all-cause mortality by 9% (P = 0.041), and all-cause mortality or hospitalisations for cardiovascular reasons by 8% (P = 0.009). 56 patients needed to be treated to prevent one death*

cija zbog kardiovaskularnih razloga. Iako je povoljan terapijski učinak omega-3-masnih kiselina u GISSI-HF istraživanju bio manji od očekivanog, bio je značajan i postignut povrh optimalne standardne terapije, uz visoku sigurnost, podnošljivost, jednostavnost i povoljnu cijenu liječenja. Stoga etilni esteri omega-3-masnih kiselina trebaju biti dio terapije koja smanjuje smrtnost u bolesnika s kroničnim ZS.

KLJUČNE RIJEČI: *zatajivanje srca, statini, omega-3 masne kiseline*

Kronično zatajivanje srca (KZS) često je stanje, praćeno značajnim pobolom i smrtnošću. Unatoč dokazano učinkovitoj terapiji, koja podrazumijeva primjenu neurohormonskih antagonista, ACE inhibitora i beta adrenergičkih blokatora, a u posebnim indikacijama i antagonista aldosterona, implantabilnih kardioverter defibrilatora i uređaja za resinkronizaciju klijetki, broj smrti uzrokovanih zatajivanjem srca raste. Stoga u suvremenoj kardiologiji postoji velika potreba i interes za novim mogućnostima liječenja[1].

Najčešći uzrok KZS je koronarna bolest srca (KBS). Iako je hiperkolesterolemija vodeći čimbenik rizika za koronarnu aterosklerozu, bolesnici sa uznapredovalim zatajivanjem srca (ZS) imaju nizak kolesterol, što je paradoksalno povezano s lošijom prognozom[2]. Statini dokazano smanjuju pobol i smrtnost u koronarnih bolesnika, no takva istraživanja do sada su uglavnom isključivala bolesnike sa ZS. U više eksperimentalnih i nekoliko manjih prospektivnih kliničkih istraživanja statini su imali povoljan učinak na ventrikularnu funkciju, funkcionalno stanje bolesnika sa ZS i kliničke ishode[3]. Entuzijazam o mogućem terapijskom učinku statina u bolesnika sa ZS temeljio se na brojnim, dobro poznatim antiaterogenim i plejotropnim učincima statina. Nedostajale su, međutim, velike randomizirane studije.

Rezultati prvog takvog istraživanja, CORONA studije (*Controlled Rosuvastatin Multinational Trial in Heart Failure*), objavljeni su prošle godine[4]. U 5.011 bolesnika sa simptomatskim ZS (NYHA II-IV) uslijed sistoličke disfunkcije lijeve klijetke (LK) ishemijske etiologije, randomiziranih na rosuvastatin 10 mg na dan ili placebo, liječenih prosječno tijekom 33 mjeseca, nije bilo razlike u primarnom kombiniranom ishodu, ukupnoj smrtnosti, kardiovaskularnoj smrtnosti ili nefatalnim koronarnim događajima. Postignuto je statistički značajno, no malo smanjenje hospitalizacija zbog kardiovaskularnih razloga, a u *post hoc* analizi i nefatalnih ishemijskih događaja.

Nakon neutralnih rezultata CORONA studije, veliku pozornost privukli su nedavno priopćeni rezultati GISSI-HF istraživanja[5]. Radilo se randomiziranoj, dvostruko slijepoj, placebom kontroliranoj multicentričnoj studiji, provedenoj u 357 talijanskih centara. Bolesnici sa simptomatskim KZS (NYHA II-IV) različite etiologije (ishemijske i neishemijske), liječeni su prosječno tijekom 3,9 godina rosuvastatinom u dozi od 10 mg na dan (n = 2.285) ili placebom (n = 2.289), povrh optimalne standardne terapije, neovisno o istisnoj frakciji LK i bez jasne indikacije za primjenu statina. Unatoč očekivanjima, nije bilo značajne razlike u primarnim ishodima, ukupnoj smrtnosti i ukupnoj smrtnosti ili hospitalizacijama zbog kardiovaskularnih razloga. Također nije bilo razlike ni u sekundarnim ishodima, hospitalizacijama zbog bilo kojeg razloga, zbog kardiovaskularnih razloga ili zbog ZS.

or 44 patients to avoid one death or admission to hospital for cardiovascular reasons. Although therapeutic effect was lower than expected, it was significant and achieved beyond optimal standard therapy. The treatment was safe, well tolerated, simple and cheap. Therefore, n-3 fatty acids ethyl esters should be a part of the treatment for mortality reduction in HF patients.

KEYWORDS: *heart failure, statins, n-3 fatty acids*

Chronic heart failure (CHF) is a common condition, followed by substantial morbidity and mortality. Although treated with apparently effective therapy, consisting of neurohormonal antagonists, ACE inhibitors and beta adrenergic blockers, with addition of aldosterone antagonists, implantable cardioverter defibrillators and cardiac resynchronisation devices in specific cases, the number of deaths caused by heart failure (HF) is still increasing. Therefore, there is a great requirement and interest in contemporary cardiology regarding new methods and treatment possibilities[1].

The major cause of CHF is a coronary heart disease (CHD). Although hypercholesterolemia is the major risk factor for coronary atherosclerosis, patients with advanced HF have low cholesterol, paradoxically connected with pure prognosis[2]. It was clearly demonstrated that statins reduce morbidity and mortality in patients with CHD, but to date, all such trials generally excluded patients with HF. In several experimental studies and a few smaller prospective clinical trials, statins had favourable effect on ventricular function, functional state of heart failure patients and their clinical outcomes[3]. The initial entusiasm about a possible therapeutic effect of statins in patients with HF was based on multiple well known favourable antiatherogenic and pleiotropic effects of statins. However, no large randomised clinical trials with statins in HF have been conducted so far.

The results of the first such study, the CORONA trial (*Controlled Rosuvastatin Multinational Trial in Heart Failure*), were published last year[4]. In 5011 patients with symptomatic HF (NYHA II-IV) due to systolic left ventricular dysfunction of ischaemic etiology, randomised to rosuvastatin 10 mg daily or placebo, and followed over a median period of 33 months, there was no difference in primary composite endpoint, all-cause mortality, cardiovascular mortality or non-fatal coronary events. Treatment with rosuvastatin resulted in statistically significant, but in a small reduction in hospitalisations for cardiovascular reasons, and in post-hoc analysis, in non-fatal ischaemic events.

After having obtained neutral results of the CORONA trial, a great interest was shown for the recently published results of the GISSI-HF trial[5]. The investigation was designed as randomised, double-blind, placebo-controlled, multicenter study, conducted in 357 Italian centers. Patients with symptomatic CHF (NYHA II-IV) of different etiology (ischaemic and non-ischaemic) were treated during a median time of 3.9 years with rosuvastatin 10 mg per day (n = 2285) or placebo (n = 2289), added to optimal standard therapy, irrespective of left ventricular ejection fraction (LVEF) and without a clear indication for statin treatment. Despite expectations, there was no difference in primary endpoints, all-cause mortality and all-cause mortality or hospitalisations for cardiovascular reasons. No difference was also found in secondary endpoints, hospitalisations for any cause, cardiovascular cause, or HF.

Although statin treatment in the CORONA and GISSI-HF trial reduced LDL-cholesterol and CRP, and was good

Iako je liječenje statinom u CORONA i GISSI-HF studiji smanjilo LDL kolesterol i CRP, uz dobru podnošljivost i sigurnost, postavlja se pitanje zašto unatoč povoljnim hipolipemičkim i plejotropnim učincima statina, nije bilo kliničke koristi, odnosno povoljnog utjecaja na preživljenje bolesnika? Moguća objašnjenja su niska učestalost aterotrombotičkih događaja u ovih bolesnika u usporedbi s koronarnim bolesnicima bez ZS, nedovoljan učinak na patofiziološke mehanizme smrti te moguća protektivna uloga lipoproteina u smislu neutralizacije endotoksina, koji zbog povećane permeabilnosti crijevne sluznice ulaze u cirkulaciju[1].

Nekoliko ranijih eksperimentalnih i epidemioloških istraživanja pokazalo je povoljne učinke omega-3 masnih kiselina (n-3FA, prema engl. *n-3 fatty acids*) na aterotrombotsku kardiovaskularnu bolest i pojavu aritmija. U studijama primarne i sekundarne prevencije KBS n-3FA smanjile su učestalost nefatalnih i fatalnih kardiovaskularnih događaja za 10-20%[6]. Stoga je druga hipoteza GISSI-HF studije bila da n-3FA mogu smanjiti pobol i smrtnost u bolesnika sa simptomatskim KZS (NYHA II-IV), neovisno o etiologiji i istisnoj frakciji LK[7]. Ukupno 6.975 bolesnika randomizirano je na jedan gram n-3FA (850-882 mg eikosapentaenske i dokosaheksaenske kiseline u obliku etilnih estera i omjeru 1:1,2 - Omacor®) ili placebo, uz ostalu optimalnu standardnu terapiju. Nakon prosječno 3,9 godina liječenja, n-3FA značajno su smanjile oba primarna ishoda, ukupnu smrtnost za 9% (p = 0,041) i ukupnu smrtnost ili hospitalizacije zbog kardiovaskularnih razloga za 8% (p = 0,009). Tijekom navedenog razdoblja n-3FA trebalo je liječiti 56 bolesnika da se spriječi jedan smrtni ishod i 44 bolesnika da se izbjegne jedna smrt ili hospitalizacija zbog kardiovaskularnih razloga[8].

Ovo je već drugo veliko randomizirano kliničko istraživanje s povoljnim terapijskim učinkom etilnih estera n-3FA u kardiovaskularnih bolesnika. U poznatoj *GISSI Prevenzione studiji*[5] etilni esteri n-3FA su u postinfarktnih bolesnika, uz svu ostalu standardnu terapiju, značajno smanjili kardiovaskularnu smrtnost, nefatalni infarkt i nefatalni moždani udar za 20% (p = 0,006). Ukupna smrtnost smanjena je za 21% (p = 0,006), a iznenadna smrt za čak 44% (p = 0,0006). Iako je povoljan terapijski učinak n-3FA u GISSI-HF istraživanju bio manji od očekivanog, bio je značajan i postignut povrh optimalne standardne terapije, uz visoku sigurnost, podnošljivost, jednostavnost i povoljnu cijenu ovakvog liječenja. Stoga n-3FA trebaju biti uvrštene u terapijske intervencije koje smanjuju smrtnost bolesnika s KZS (**tablica 1**)[1]. Obzirom na veliki broj bezreceptnih pripravaka n-3FA, treba naglasiti da je povoljan terapijski učinak u postinfarktnih bolesnika i bolesnika s kroničnim sistoličkim ZS, dokazan samo za lijek s visoko pročišćenim etilnim esterima n-3FA (Omacor®), u skladu s medicinom temeljenom na dokazima.

tolerated and safe, we wonder why favourable hypolipemic and pleiotropic effects of statin resultet in no clinical benefit and patients' better survival? The possible explanations are that HF patients usually have lower rate of atherothrombotic events in comparison to coronary patients without HF, insufficient efficacy on pathophysiological mechanisms of death and possible protective role of lipoproteins in neutralisation of endotoxins, entering the circulation due to increased permeability of enteral mucosa[1].

Several previous experimental and epidemiological studies have shown favourable effects of n-3 polyunsaturated fatty acids (n-3FA) on atherothrombotic cardiovascular disease and arrhythmia occurrence. In primary and secondary prevention trials in patients with CHD, n-3FA reduced the incidence of non-fatal and fatal cardiovascular events by 10-20%[6]. Therefore, the second hypothesis tested in GISSI-HF trial was that n-3FA can reduce morbidity and mortality in patients with symptomatic CHF (NYHA II-IV), irrespective of etiology and LVEF[7]. The total 6975 patients were randomised to 1 gram of n-3FA (850-882 mg eicosapentaenoic acid and docosahexaenoic acid as ethyl esters in the ratio of 1:1.2 - Omacor®) or placebo, added to all optimal standard treatment. After the median follow-up of 3.9 years, n-3FA reduced significantly the both primary endpoints: all-cause mortality by 9% (P = 0.041), and all-cause mortality or hospitalisations for cardiovascular reasons by 8% (P = 0.009). During the mentioned follow-up period, 56 patients needed to be treated with n-3FA to prevent one death or 44 patients to avoid one deadly event or admission to hospital for cardiovascular reasons[8].

This is already the second large randomised clinical trial showing the favourable therapeutic effect of n-3FA ethyl esters in cardiovascular patients. In previous well known *GISSI Prevenzione Trial*[5], n-3FA ethyl esters were given to postinfarction patients besides all standard treatment, significantly reducing cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke by 20% (P = 0.006). All-cause mortality was reduced by 21% (P = 0.006), and sudden death even by 44% (P = 0.0006). Although therapeutic effect of n-3FA in the GISSI-HF trial was lower than expected, it was significant and achieved besides all optimal standard therapy. Treatment with n-3FA was safe, well tolerated, simple and cheap. Therefore, n-3FA ethyl esters should be included in the treatment options which reduce mortality in CHF patients (**table 1**)[1]. Considering a great number of n-3FA preparations without prescription existing on the market, it must be emphasized that the favourable therapeutic effect in postinfarction patients and those with chronic systolic HF was demonstrated only for the drug containing highly purified n-3FA ethyl esters (Omacor®), according to evidence-based medicine.

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Table 1. *Effective therapies for mortality reduction in chronic systolic heart failure.*

Treatment modalities	Reduction in all-cause mortality
ACE inhibitors or angiotensin receptor blockers	17 — 25 %
Beta blockers	34 — 35 %
Aldosterone antagonists*	15 — 30 %
Implantable cardioverter defibrillator*	23 %
Cardiac resynchronisation*	36 %
n-3 polyunsaturated fatty acids (ethyl esters)	9 %

*In patients with specific indications

Literature

1. Fonarow GC. Statins and n-3 fatty acid supplementation in heart failure. Lancet 2008;372:1195-6.

2. Velavan P, Huan LP, Clark A, Cleland JG. The cholesterol paradox in heart failure. Congest Heart Fail 2007;13:336-41.

3. Ramasubbu K, Estep J, White DL, et al. Experimental and clinical basis for the use of statins in patients with ischemic and nonischemic cardiomyopathy. J Am Coll Cardiol 2008;51:415-26.

4. Kjekshus J, Apetrei E, Barrios V, et al. CORONA Group. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2248-61.

5. GISSI-HF Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1231-9.

6. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet 1999;354:447-55.

7. Tavazzi L, Tognoni G, Franzosi MG, et al. GISSI-HF Investigators. Rationale and design of the GISSI heart failure trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. Eur J Heart Fail 2004;6:635-41.

8. GISSI-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1223-30.