Stručni rad / Professional article

Rezultati istraživanja SHIFT i mjesto ivabradina u liječenju bolesnika s kroničnim zatajivanjem srca u sinusnom ritmu

The SHIFT trial results and position of ivabradine in the treatment of patients with chronic heart failure in sinus rhythm

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SAŽETAK: U liječenju kroničnog zatajivanja srca (ZS), velikog problema suvremene medicine, postoji potreba za razvojem novih terapijskih pristupa, pa je svaki novi medikamentozni upliv u nepovoljni patofiziološki tijek ove bolesti vrijedan pažnje kardiologa. Nedavno je objavljeno istraživanje SHIFT (*Systolic Heart failure treatment with the IF inhibitor ivabradine Trial*), koje je ispitalo učinak dodatka ivabradina bolesnicima sa ZS, prethodno liječenih prema smjernicama. SHIFT je potvrdio da dodatno usporavanje srčane frekvencije ivabradinom može pojačati prednosti neurohormonalne blokade u kroničnom ZS. Na rezultate ovog istraživanja reagirala su neka svjetska kardiološka društva i to prilagođavanjem postojećih nacionalnih smjernica ili objavljivanjem konsenzusa, koji čvrsto definiraju mjesto ivabradina u liječenju bolesnika sa ZS.

KLJUČNE RIJEČI: zatajivanje srca, frekvencija srca, ivabradin.

SUMMARY: In the treatment of chronic heart failure (HF) as the major problem of modern medicine, there is a need to develop new therapeutic approaches, so each new medicamentous intervention undertaken in respect to adverse pathophysiological course of this disease is worth cardiologist's attention. The trial SHIFT (*Systolic Heart failure treatment with the IF inhibitor ivabradine Trial*) which investigated the effect of adding ivabradine to patients with HF who were previously treated according to the guidelines, has been published. SHIFT has confirmed that further slowdown of the heart rate by ivabradine may increase the benefits of neurohormonal blockade in chronic HF. Some international societies of cardiology reacted to the results of this trial by adapting the existing national guidelines or publicizing the consensus, which firmly define the place ivabradine in treating patients with HF.

KEYWORDS: heart failure, heart rate, ivabradine.

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Liječenje bolesnika sa zatajivanjem srca (ZS) predstavlja velik problem suvremene medicine. Ova se bolest ubraja među najmasovnije bolesti današnjice i predstavlja 30% bolničke smrtnosti, a liječenje bolesnika sa ZS predstavlja najveći trošak u sustavima zdravstva. Implementacija novih pristupa liječenju ZS, koji se zasnivaju na kombinaciji ACE inhibitora, beta-blokatora i aldosteronskih antagonista, rezultirala je značajnim smanjenjem smrtnosti[1]. Ipak, čak i uz suvremene metode liječenja, postoji hitna potreba za razvojem novih terapijskih pristupa u liječenju kroničnog ZS.

U tom smislu valja razmotriti rezultate istraživanja SHIFT (*Systolic Heart failure treatment with the IF inhibitor ivabradine Trial*). Radilo se o međunarodnom, randomiziranom, dvostruko slijepom prospektivnom istraživanju, kontroliranom placebom[2]. SHIFT je istraživao učinak ivabradina u kombinaciji s terapijom prema dosadašnjim smjernicama na

The treatment of patients with heart failure (HF) is a major problem of the modern medicine. This disease is ranked among the most widespread diseases of our time and makes up to 30% of in-hospital mortality, while the treatment of patients with HF incurs the highest cost in the healthcare system. The implementation of the new approaches to the treatment of HF based on a combination of ACE inhibitors, beta-blockers and aldosterone antagonists has resulted in significant reduction in mortality[1]. However, even with modern treatment methods, there is an urgent need to develop new therapeutic approaches to treatment of chronic HF.

Therefore, we should consider the results of SHIFT trial (*Systolic Heart failure treatment with the IF inhibitor ivabradine Trial*). It was an international, randomized, double-blind prospective trial, placebo controlled trial[2]. SHIFT investigated the effect of ivabradine combined with the therapy according to current guidelines on cardiovascular outcomes

kardiovaskularne ishode i kvalitetu života bolesnika sa ZS. Istraživanje je uključilo više od 6.500 bolesnika s kroničnim ZS u sinusnom ritmu, s frekvencijom srca ≥70/min i sistoličkom disfunkcijom lijeve klijetke (ejekcijska frakcija ≤35%). Primarni ishod je uključivao kardiovaskularnu smrtnost i hospitalizaciju zbog pogoršanja kroničnog ZS. U ovom je istraživanju 90% bolesnika već ranije uzimalo ACE inhibitore i beta-blokatore, prema suvremenim smjernicama. U protokolu se inzistiralo na titriranju beta-blokatora do maksimalno podnošljive doze. U konačnici su doze beta-blokatora u istraživanju SHIFT bile najviše doze ikada postignute u istraživanjima kroničnog ZS, osim u onim studijama koje su istraživale učinak samih beta-blokatora: 56% bolesnika liječeno je s najmanje polovicom ciljne dnevne doze, a 26% ih je bilo na ciljnoj dnevnoj dozi. Radi se o većim dozama od onih koje se koriste u rutinskoj kliničkoj praksi.

Istraživanje SHIFT je potvrdilo da se rizik od kardiovaskularne smrti i broj hospitalizacija zbog pogoršanja ZS povećava s bržom frekvencijom srca. Istovremeno je utvrđeno da se maksimalno smanjenje rizika od kardiovaskularne smrti i broja hospitalizacija zbog ZS postižu usporavanjem frekvencije do 60/min.

Rezultati istraživanja SHIFT ukazuju na uvođenje ivabradina kao dodatka liječenju zasnovanom na smjernicama. Složeni primarni ishod (kardiovaskularna smrtnost i broj hospitalizacija zbog pogoršanja ZS) smanjen je za 18% (P<0,0001). Ovaj je učinak postignut uglavnom smanjenjem rizika od smrti zbog ZS za 26% (P=0,014) i smanjenjem broja hospitalizacija zbog ZS za također 26% (P<0,0001).

Podnošljivost ivabradina bila je dobra. Neželjeni učinci, koji se mogu pripisati ivabradinu uključuju bradikardiju, koja je rezultirala ukidanjem lijeka u 0,62% ispitanika, u usporedbi s 0,15% u skupini na placebu (P=0,002).

Nedavno su objavljene i dvije podstudije istraživanja SHIFT. Istraživanje SHIFT-PRO[3] dokazuje da je usporavanje frekvencije srca ivabradinom udruženo s poboljšanjem kvalitete života bolesnika sa ZS iz osnovne studije te da je magnituda usporavanja srčane frekvencije direktno proporcionalna poboljšanju kvalitete života, koja se istraživala upitnikom *Kansas City Cardiomyopathy Questionnaire*. Istraživanje SHIFT-ECHO[4] pokazuje da ivabradin značajno utječe na remodeliranje, smanjuje end-sistolički volumni indeks lijeve klijetke i poboljšava istisnu frakciju u bolesnika sa ZS i sistoličkom disfunkcijom lijeve klijetke.

Ovim rezultatima istraživanje SHIFT je potvrdilo da dodatno usporavanje frekvencije srca ivabradinom može pojačati prednosti neurohormonalne blokade u kroničnom ZS. U svakom slučaju prije uvođenja ivabradina potrebno je pokušati titrirati beta-blokatore do maksimalne dnevne doze, a u slučaju da to nije moguće, preporučuje se dodavanje ivabradina. Uobičajena početna doza ivabradina je 2x5 mg. Doza se može povisiti do 2x7,5 mg.

Ivabradin je trenutno indiciran u liječenju bolesnika s anginom pektoris u kombinaciji s beta-blokatorima, ili kao alternativa beta-blokatorima u slučaju njihove nepodnošljivosti. Ipak, potaknuta istraživanjem SHIFT, brojna nacionalna kardiološka društva preporučuju korištenje ivabradina i u kroničnom ZS (**Tablica 1**).

Zaključak

Prihvaćenost bilo koje terapije za kronično ZS određuje se postizanjem najmanje dva od šest ciljeva liječenja, kako ih definira Europsko kardiološko društvo, a to su uklanjanje

and quality of life of patients with HF. The trial involved more than 6500 patients with chronic HF in sinus rhythm with heart rate ≥70/min and systolic left ventricular dysfunction (ejection fraction ≤35%). The primary outcome included cardiovascular death and hospitalization due to impairment of chronic HF. In this trial, 90% of patients were previously treated with ACE inhibitors and beta-blockers according to contemporary guidelines. The protocol insisted upon titration of beta-blockers up to the maximum tolerable dose. Finally, the doses of beta-blockers in the SHIFT trial were the highest doses ever achieved in trials of chronic FA, except in those trials that only investigated the effect of beta-blockers: 56% of patients were treated with at least half of the target daily dose, while 26% of them were treated with the target daily dose. Doses higher than those used in routine clinical practice are in question.

The SHIFT trial confirmed that the risk of cardiovascular death and number of hospitalizations due to worsening of HF rises with increasing the heart rate. At the same time it was established that the maximum reduction in risk of cardiovascular death and number of hospitalizations for HF is achieved by decreasing the rate up to 60/min.

The SHIFT trial results suggest the introduction of ivabradine in addition to the treatment based on the guidelines. Composite primary outcome (cardiovascular death and number of hospitalizations due to worsening of HF) has been reduced by 18% (P <0.0001). This effect is achieved mainly by reducing the risk of death due to the HF by 26% (P = 0.014) and reducing the number of hospitalizations due to HF also by 26% (P <0.0001).

Ivabradine tolerance was good. Adverse effects attributable to ivabradine include bradycardia, which resulted in the stopping of the drug in 0.62% of the respondents, compared with 0.15% of those in the placebo group (P=0.002).

Two SHIFT subtrials have been recently published. The SHIFT-PRO[3] trial proves that the decreasing of heart rate by ivabradine is connected with the improvement of the quality of life in patients with HF as indicated in the basic trial and that the magnitude of heart rate decreasing is directly proportional to the improvement of quality of life, which was investigated by the *Kansas City Cardiomyopathy Questionnaire*. The SHIFT-ECHO[4] trial shows that ivabradine significantly affects remodeling, reduces left ventricular end-systolic volume index and improves the ejection fraction in patients with HF and left ventricular systolic dysfunction.

Using such results, the SHIFT trial has confirmed that further decreasing the heart rate by ivabradine may increase the benefits of neurohormonal blockade in chronic HF. In any case, prior to introduction of ivabradine we should try to titrate beta-blockers to a maximum daily dose, and in case this is not possible, we recommended that ivabradine should be added. The usual initial dose of ivabradine is 2x5 mg. The dose may be increased up to 2x7, 5 mg.

Ivabradine is currently indicated for the treatment of patients with angina pectoris in combination with beta-blockers, or as an alternative to beta-blockers in case that they are not tolerable. Still, motivated by SHIFT trial, a great number of national societies of cardiology recommend that ivabradine in chronic HF should be used (**Table 1**).

Conclusion

Acceptance of any therapy for chronic HF is determined by achieving minimum two of the six treatment objectives, as defined by the European Society of Cardiology, which

Table 1. *International recommendation for ivabradine use in heart failure patients.*

Country	*Recommended by*	*Date*	*Ivabradine Recommendation*
Australia	National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand (Guidelines)[5]	March 2011	"In systolic heart failure patients, in sinus rhythm, with heart rate > 70 bpm despite efforts to maximize dosage of background β-blocker"
Austria	Austrian Society of Cardiology, Working Group on Heart Failure (Consensus)[6]	February 2011	"In addition to standard treatment - recommended in patients with systolic dysfunction (EF ≤35%), NYHA class II-III, (IV limited data) and sinus-rhythm with heart rate ≥70 bpm with maximum tolerated neurohormonal treatment, especially with maximum achievable β-blockade"
Canada	Canadian Cardiovascular Society (Guidelines)[7]	June 2011	"In patients with moderate to severe heart failure on optimum medical therapy including β-blockade with LVEF ≤35% and resting heart rate ≥70 bpm"
Denmark	Danish Society of Cardiology (National Cardiovascular Guidelines - NBV)[8]	May 2011	"Ivabradine can be considered for patients in sinus rhythm with continuous symptoms, (NYHA II-IV) after uptitration with ACE inhibitor /ARB, β-blocker and aldosterone-antagonist, EF <35%, and with HR >70 bpm measured after 5 minutes rest."
Russia	Russian Society of Heart Failure Specialists (Consensus)[9]	April 2011	"In patients with chronic heart failure, in sinus rhythm and HR >70 bpm, ivabradine can be administered whatever the previous therapy, including β-blockers, whatever its intensity, in accordance with the treatment algorithm for patients with chronic heart failure in sinus rhythm. If possible, the titration of β-blocker should be attempted before ivabradine administration"

simptoma i zaustavljanje napredovanja kroničnog ZS, odnosno smanjenje smrtnosti i smanjenje broja ponovnih hospitalizacija. Da bi se ovi ciljevi ispunili, važno je razmotriti potencijal svakog novog terapijskog pristupa, a pogotovo ako je zasnovan na dokazima o učinkovitosti u kliničkim istraživanjima. Usporavanje frekvencije srca ivabradinom svakako doprinosi postizanju optimalnog liječenja bolesnika sa ZS u sinusnom ritmu i prevenciji neželjenih ishoda.

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includes the elimination of symptoms and interruption of progression of chronic HF, or reduction of mortality and the reduction of the number of re-hospitalizations. In order to meet these objectives, it is important to consider the potential of every new therapeutic approach, especially if it is based on evidence of effectiveness in clinical trials. The decresing of heart rate by ivabradine certainly contributes to the achievement of optimal treatment of patients with HF in sinus rhythm and prevention of adverse outcomes.

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