županijama već započeto, tako da sve županije naše podružnice imaju isti pristup u liječenju i prevenciji.

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The program of registers will be initiated at the level of the Subsidiary and the process of establishing some other patients' associations will go on, which has been started in some counties, so all counties of our subsidiary will have a same approach to treatment and prevention.

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Povjerenje temeljeno na desetogodišnjem vlastitom iskustvu sa simvastatinom

Trust based on ten years of own experience with simvastatin

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SAŽETAK: *Hiperlipidemija je dokazano značajan čimbenik rizika za kardiovaskularne bolesti (KVB) razvijenog svijeta. Prema europskih smjernicama, statini su terapija prvog izbora za liječenje hiperlipidemije. U skupini statina, simvastatin je jedini statin s 10-godišnjim praćenjem liječenja koje se provodilo u 4S studiji. Ova studija predstavlja temeljnu osnovu u liječenju statinima obzirom da se radi o prvoj studiji koja je pokazala da liječenje hipelipidemije statinima smanjuje ukupnu smrtnost pacijenata s koronarnom bolesti srca. Danas je simvastatin dokazani statin s učinkovitošću i sigurnošću dokazanom kod velikog broja pacijenata u primarnoj i sekundarnoj prevenciji KVB. Godine 1999. Krkin simvastatin (Vasilip®) bio je prvi generički simvastatin na području Europe. U zadnjih 10 godina provedeno je nekoliko kliničkih studija kod različitih skupina pacijenata sa Vasilipom®. Najveća studija je bila meta-analiza koja je uključivala 11 kliničkih pokusa s 1.637 pacijenata iz 10 država, uključujući Hrvatsku. Kako se lijek koristi u preko milijun pacijenata dnevno, ovaj lijek je postao vodeći generički simvastatin u srednjoj, istočnoj i južnoistočnoj Europi.*

KLJUČNE RIJEČI: *hiperlipidemija, simvastatin, klinička studija.*

ABSTRACT: *Hyperlipidemia is a well-established major risk factor for cardiovascular disease in developed world. According to European guidelines, statins are the first-choice therapy for the treatment of hyperlipidemia. Among statins, simvastatin is the only statin with a ten-year long-term follow-up, which was conducted in the 4S study. This study represents a milestone in statin treatment, as it was the first study to show that treatment of hyperlipidemia with statins reduces the total mortality rate of patients with coronary heart disease (CHD). Nowadays, simvastatin is a well-established statin with efficacy and safety proven in a wide range of patients in primary and secondary prevention of cardiovascular diseases. In 1999, Krka's simvastatin (Vasilip®) was the first generic simvastatin launched in Europe. During the past ten years, several own clinical studies in different groups of patients have been conducted with Vasilip®. The largest study was a meta-analysis which included 11 clinical trials with 1637 patients in 10 countries, including Croatia. With over a million patients daily treated with it, it has become the leading generic simvastatin in Central, Eastern and Southeastern Europe.*

KEYWORDS: *hyperlipidemia, simvastatin, experience, clinical study.*

Hiperlipidemija je dokazano značajan čimbenik rizika za kardiovaskularne bolesti (KVB) kao i jedna od najčešćih bolesti u razvijenom svijetu. Epidemiološke studije su utvrdile da povišena vrijednost LDL kolesterola (LDL), kao jedna od značajki hiperlipidemije, predstavlja glavni čimbenik rizika povezan s razvojem i napredovanjem KVB. Stoga se sada smatra glavnim ciljem terapijske intervencije[1].

Prema smjernicama Europskog kardiološkog društva iz 2007. godine, statini predstavljaju terapiju prvog izbora za liječenje hiperlipidemije[2]. Među statinima, simvastatin je jedini statin s 10-godišnjim praćenjem, koji je bio korišten u *Scandinavian Simvastatin Survival Study* (4S). Ta studija se smatra najdužim praćenjem u kojem se koristio neki statin. 4S je multicentrična klinička studija koja je provedena tijekom 90-tih godina XX. stoljeća u Skandinaviji. Izrađena je radi procjene učinka sniženja vrijednosti kolesterola primjenom simvastatina na 4.444 pacijenata sa koronarnom bolesti srca (KBS). Rezultati su utvrdili da bi liječenje 100 pacijenata simvastatinom u trajanju od preko šest godina spriječilo:

Hyperlipidemia is a well-established major risk factor for cardiovascular disease (CVD) as well as one of the most prevalent conditions in developed world. Epidemiological studies have established that elevated LDL cholesterol (LDL-c), as one of the aspects of hyperlipidemia, is the major lipid risk factor associated with the development and progression of cardiovascular diseaseCVD. Therefore it is now considered to be the principal target of therapeutic intervention.[1]

According to European guidelines formulated by the European Society of Cardiology in 2007, the first-choice therapy for the treatment of hyperlipidemia are statins. (2). Among statins, simvastatin is the only statin with a ten-year long-term follow-up, which was conducted in the *Scandinavian Simvastatin Survival Study* (4S). This is considered the longest follow-up conducted with a statin. The 4S was a multicentre clinical study that was performed in the 1990s in Scandinavia. It was designed to evaluate the effect of cholesterol lowering with simvastatin on mortality and morbidity in 4444 patients with coronary heart disease (CHD). The results confirmed that over the first 6 years treatment of 100 patients with simvastatin would prevent:

- smrt kod 4 od 9 pacijenata od KBS,
- nefatalni infarkt miokarda kod 7 od 21 pacijenata, i
- revaskularizaciju miokarda kod 6 od 19 pacijenata[3].

Nakon završetka 4S studije nastavljeno je praćenje i kasnije pri čemu se steklo kliničko iskustvo od 10 godina. Budući da se nefatalni događaji nisu mogli proučavati nakon dovršetka pokusa, naknadno praćenje je bio usredotočeno na ukupnu smrtnost. Prosječno ukupno vrijeme praćenja bilo je 10,4 godine. U nastavku studije se većina pacijenata u obje skupine podvrgla liječenju snižavanja lipida koje je bilo otvorenog tipa. Tijekom više od 10 godina provođenja praćenja registrirano je 15% smanjenje relativnog rizika od smrtnosti od svih uzroka (p = 0,016), 17% smanjenja kardiovaskularne smrtnosti (p = 0,023) i 24% smanjenja koronarne smrtnosti (p = 0,002). Ova smanjenja relativnih rizika su bila niža nego tijekom razdoblja dvostrukog slijepog ispitivanja što nije iznenađujuće, budući da je više od 80% pacijenata u obje skupine bilo liječeno hipolipemicima (pretežito statinima). Važna poruka ove studije je da se apsolutna razlika između skupine na simvastatina u odnosu na onu na placebu nije puno promijenila. To znači da dobrobit preživljenja pacijenata pripisivana simvastatinu u odnosu prema skupini na placebu perzistira i tijekom daljnjeg praćenja. Ova studija predstavlja temeljni dokaz djelotvornosti liječenja statinima obzirom da se radi o prvoj studiji koja je pokazala da primjena statinske terapije u liječenju hiperlipidemije smanjuje ukupnu smrtnost pacijenata sa KBS[4].

Prvi generički simvastatin dostupan u Europi bio je Vasilip® (Krka, d. d., Novo mesto, Slovenija) koji je pokrenut 1990. godine. Tijekom posljednjih deset godina provedeno je nekoliko vlastitih kliničkih studija s ovim lijekom kod različitih skupina pacijenata, uključujući pacijente s hiperkolesterolemijom, one s dijabetesom tipa 2, starije pacijente sa KBS, pacijente u primarnoj prevenciji i pacijente u sekundarnoj prevenciji KVB[5]. Najveća studija bila je meta-analiza koja je uključivala jedanaest kliničkih pokusa s 1.637 pacijenata u deset država, uključujući Hrvatsku. Uključeni su pacijenti visokog rizika s hiperlipidemijom s ili bez pridružene KVB, koji su tijekom dvanaest tjedana primali Vasilip® u dozi 10 do 40 mg (prosječna doza 21.3 mg). Rezultati meta-analize koji su prikazani na *slici 1* potvrdili su učinkovitost i sigurnost lijeka. Ukupna vrijednost kolesterola (TC) bila je snižena za 26%, LDL-c za 35%, i trigliceridi (TG) za 12%, dok je vrijednost HDL-kolesterola (HDL) bila povišena za 10%. Ciljna vrijednost LDL-c od <3 mmol/l postignuta je kod 61% pacijenata[6].

Rezultati meta-analize su usporedivi rezultatima koji su prikazani u objavljenim studijama sa simvastatinom u primarnoj i sekundarnoj prevenciji (*tablica 1*).

- 4 of 9 patients from dying from CHD,
- 7 of 21 patients from having a non-fatal myocardial infarction and
- 6 of 19 patients from having myocardial revascularisation.[3]

After the 4S study was completed, a follow-up was performed, altogether yielding 10 years of clinical experience. Since non-fatal events could not be studied after the completion of the trial, the follow-up focused on total mortality. The median total follow-up time was 10.4 years. In the extension of the study, most patients in both groups received open-label lipid-lowering treatment. Over the entire 10-year follow-up there was a 15% relative risk reduction in all-cause mortality (p = 0.016), a 17% reduction in cardiovascular mortality (p = 0.023), and a 24% reduction in coronary mortality (p = 0.002). These reductions were lower than during the double-blind period, which is not surprising as more than 80% of the patients in both groups were treated with lipid-lowering agents (mostly statins). An important message of this study was that the absolute difference between the simvastatin and placebo group did not change much. That means that the survival benefit of patients allocated to simvastatin compared to those allocated to placebo observed during the double-blind period persisted during the follow-up. This study represents a milestone in statin treatment, as it was the first study to show that treatment of hyperlipidemia with a statin reduces the total mortality rate of patients with CHD.[4]

The first generic simvastatin available in Europe was Vasilip® (Krka, d. d., Novo mesto, Slovenia), which was launched in 1999. During the past ten years, several own clinical studied have been conducted with this medicine in different groups of patients, including patients with hypercholesterolemia, patients with type 2 diabetes, elderly patients with CHD, patients in primary prevention, and patients in secondary prevention of CVD.[5] The largest study was a meta-analysis which included 11 clinical trials with 1637 patients in 10 countries, including Croatia. The study included high-risk patients with hyperlipidemia and with or without CVD, who were treated for 12 weeks with 10 to 40 mg of Vasilip® (the mean dose was 21.3 mg). The results of the meta-analysis, which are shown in *Figure 1*, have confirmed its efficacy and safety. Total cholesterol (TC) was reduced by 26%, LDL-c by 35%, and triglycerides (TG) by 12%, while HDL-cholesterol (HDL-c) was increased by 10%. The treatment target of LDL-c <3 mmol/l was achieved in 61% of the patients[6].

The results of the meta-analysis are comparable to those reported in published studies on simvastatin in primary and secondary prevention (*Table 1*).

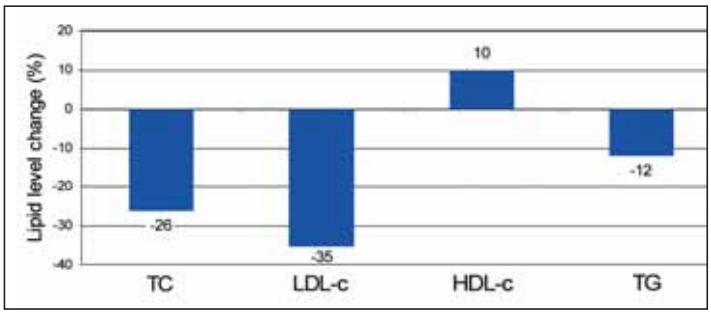

Figure 1. *Results of the meta-analysis of Krka's simvastatin.*

Source	TC	LDL-c	TG	HDL-c
Vasilip® meta-analysis of own clinical studies simvastatin average dose 21.3 mg[6]	-26%	-35%	-12%	+10%
Scandinavian Simvastatin Survival Study average dose 26 mg[3]	-25%	-35%	-10%	+8%
Meta-analysis of clinical studies simvastatin 20 mg[7]	-25.3%	-34.4%	-14.5%	+5.7%
Comparative efficacy of the six available statins simvastatin 20 mg[8]	-27%	-34%	-10 to 20%	+4 to 8%

Table 1. *Comparison of results of studies on simvastatin.*

Krkin simvastatin tijekom 10-godišnjeg postojanja liječnicima i njihovim pacijentima osigurava terapiju temeljenu na potvrđenim kliničkim dokazima. U više od milijun pacijenata koji su dnevno liječeni, ovaj lijek je postao vodeći generički simvastatin u srednjoj, istočnoj i južnoistočnoj Europi[9]. Odobren je u 44 države, uključujući mnoge zapadno europske države[5]. Sve ovo pruža dokaze o povjerenju u taj statin.

Having been present on the market for ten years, Krka's simvastatin provides a therapy based on well-established clinical evidence to the doctors and their patients. With over a million patients daily treated with it, it has become the leading generic simvastatin in Central, Eastern and Southeastern Europe[9]. It is approved in 44 countries, including many Western European countries[5]. All this provides evidence of confidence placed in this statin.

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