

Prevenција kardiovaskularnih bolesti u 2015. godini

Prevention of Cardiovascular Diseases in 2015

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Kardiovaskularne su bolesti (KVB) još uvijek vodeći uzrok mortaliteta u Hrvatskoj. Prema zadnjim podatcima za 2014. godinu, bile su uzrok smrti u 47 % umrlih (koronarna bolest srca 21 %, cerebrovaskularna bolest 14 % i zatajivanje srca 3 %). Pri tome je stopa smrtnosti od tih bolesti u našoj zemlji mnogo veća nego u razvijenim europskim zemljama (zemlje iz skupine EU15), dok je bolja od prosjeka ostalih zemalja u Europskoj regiji Svjetske zdravstvene organizacije u kojoj su tzv. tranzicijske zemlje (340/100 000 stanovnika za Hrvatsku; 160 za zemlje EU15; 630 za tranzicijske zemlje)¹. Premda postoji napredak u liječenju KVB-a u usporedbi s prijašnjim vremenima, one su i dalje čine vodeći javnozdravstveni problem te je nužno osigurati bolesnicima sve terapijske pristupe koji su u ovome trenutku na raspolaganju, a koje mi u našim uvjetima možemo omogućiti.

Naravno, uz liječenje, još je važnija prevencija KVB-a jer manjim sredstvima možemo ostvariti veće rezultate. Prema studijama provedenima u različitim populacijama, čak 44 – 76 % smanjenja smrtnosti od koronarne bolesti srca pripisuje se prevenciji i promjeni rizičnog ponašanja, dok se 23 – 47 % smanjenja smrtnosti pripisuje terapijskim intervencijama. Rezultati prevencije u nas sada nisu zadovoljavajući².

U prošloj su godini ostvareni veliki pomaci u prevenciji KVB-a. To je postignuto:

- smanjenjem kardiovaskularnih događaja u visokorizičnih bolesnika modifikacijom nezdravoga životnoga stila i dijetom,
- uvođenjem novih slikovnih metoda kojima se ranije detektira supklinička ateroskleroza, što omogućuje bolju prevenciju KVB-a,

Cardiovascular diseases (CVD) are still the leading cause of mortality in Croatia. According to the latest data for 2014, they were the cause of 47% of total deaths (coronary heart disease 21%, cerebrovascular disease 14%, and heart failure 3%). The mortality rate for these diseases is much higher in Croatian when compared with more developed European countries (from the EU15 group), but it is better than the average for other countries in the European region of the World Health Organization composed of the so-called transitional countries (340/100,000 inhabitants in Croatia; 160 for EU15 countries; 630 for transitional countries)¹. Although there have been advancements in CVD treatment in comparison with earlier times, they are still the leading public health problem, and it is crucial to ensure the availability of all existing treatment approaches that we can provide, given our conditions.

Of course, CVD prevention is even more important than treatment because it allows us to achieve greater results with fewer resources. According to studies performed in various populations, as much as 44-76% of coronary heart disease mortality reduction is ascribed to prevention and changes in health-risk behavior, while 23-47% of mortality reduction is a result of treatment interventions. Prevention results in Croatia have so far been unsatisfactory².

Significant advances in CVD prevention have been achieved over the last year. This is a result of:

- Reducing cardiovascular events in high-risk patients through diet and modification of unhealthy lifestyles.
- Introducing new imaging methods that allow earlier detection of subclinical atherosclerosis, which leads to better CVD prevention.

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- kliničkim dokazima da se ruptura plaka u tzv. *culprit* leziji događa samo u 50 – 77 % bolesnika s akutnim koronarnim sindromom,
- dokazima iz kliničkih ispitivanja o učinkovitosti terapije bazirane na monoklonskim protutijelima usmjerenima na PCSK9, što dovodi do znatne redukcije LDL kolesterola, a time i smanjenja KV događaja,
- znatnom redukcijom kardiovaskularnog i ukupnog mortaliteta u bolesnika s dijabetesom koji su bili na terapiji empagliflozinom (SGLAT-2 inhibitor), što je pokazano u EMPA-REG OUTCOME kliničkom istraživanju,
- boljom kontrolom arterijske hipertenzije, poglavito rezistentne, primjenom spironolaktona u PATHWAY-2 i PATHWAY-3 kliničkom ispitivanju te primjena kombinacije amilorida i hidroklorotiazida u bolesnika koji se koriste diuretikom u liječenju arterijske hipertenzije,
- smanjenom smrtnošću u bolesnika s arterijskom hipertenzijom kojima je ciljani sistolički tlak bio 120 mmHg u SPRINT kliničkom ispitivanju.

Sve spomenuto dovelo je do bolje kontrole dislipidemije, hiperglikemije i arterijske hipertenzije te do posljedične progresivne redukcije aterosklerotske vaskularne bolesti i kardiovaskularnih događaja u visokorizičnih bolesnika.

Chapman i sur. u preglednome članku o stanju prevencije KVB-a u 2015. godini³ najveću važnost u kardiovaskularnoj prevenciji pridaju dobroj regulaciji LDL kolesterola, pa kao važan napredak, pogotovo u bolesnika s obiteljskom hiperkolesterolemijom, navode registraciju dvaju lijekova koji djeluju na inhibiciju PCSK9 u plazmi te time i na sniženje razine LDL kolesterola. Ta su dva lijeka (monoklonska protutijela) s komercijalnim imenima Praluent® (alirokumab) i Repatha® (evolokumab) registrirana u Europskoj uniji 2015. godine te time automatski i u Hrvatskoj. Uputno je kada će doći na Listu lijekova Hrvatskog zavoda za zdravstveno osiguranje sa sadašnjom cijenom mjesečnog liječenja od oko 5.000 kuna.

Značenje koje se hipolipemijskoj terapiji pridaje u nas pokazuje potrošnja lijekova za regulaciju dislipidemije (pretežno statina) koja je u zadnjih deset godina (2004. – 2014.) izrazito porasla u DDD/1000 stanovnika s 28,13 na 61,79, što je više nego dvostruko.⁴ Ipak, kako su KVB vodeći uzrok mortaliteta i morbiditeta u nas, taj porast potrošnje hipolipemika svakako bi trebao biti veći, poglavito stoga što je povišeni kolesterol u nas, uz pušenje, najvažniji čimbenik rizika. Tako je u jednom ispitivanju u "zdravih" ispitanika nađena prevalencija razine kolesterola veća od 5,5 mmol/L u 67 % ispitanika⁵.

Uz regulaciju dislipidemije i dalje se velika važnost pridaje adekvatnoj regulaciji arterijskoga tlaka (AT) koja također u Hrvatskoj još nije dobra. Prema jednom nedavnom istraživanju, samo četvrtina bolesnika ima dobro regulirane vrijednosti AT-a⁶. Za regulaciju arterijske hipertenzije *Chapman i sur.*² navode dvije studije PATHWAY 2 i 3.^{7,8} U studiji PATHWAY 2 ispitivana je uloga spironolaktona u liječenju rezistentne arterijske hipertenzije (AH), gdje je pokazao dobre rezultate.⁷ Prema rezultatima istraživanja PATHWAY 3, kombinacija amilorida s hidrotijazidom bila je preferirani diuretik u liječenju hipertenzivnih bolesnika zbog njegovih neutralnih metaboličkih učinaka.⁸ Nažalost, taj lijek, koji je s imenom

- New clinical evidence that plaque rupture at the culprit lesion happens in only 50-77% of patients with acute coronary syndrome.
- Evidence from clinical trials on the effectiveness of treatment based on monoclonal antibodies targeting PCSK9, which leads to significant reduction in LDL cholesterol and consequently a reduction in CV events.
- Significant reduction of cardiovascular and total mortality in patients with diabetes treated with empagliflozin (a SGLAT-2 inhibitor), demonstrated in the EMPA-REG OUTCOME clinical trial.
- Improved management of arterial hypertension, especially resistant hypertension, through the application of spironolactone in the PATHWAY-2 and PATHWAY-3 clinical trials, and the application of the combination of amiloride and hydrochlorothiazide treatment in patients using diuretics to treat hypertension.
- Reduced mortality in patients with arterial hypertension with target systolic blood pressure values of 120 mmHg in the SPRINT clinical trial.

All of the above has led to better control of: dyslipidemia, hyperglycemia, and hypertension, resulting in progressive reduction of atherosclerotic vascular disease and cardiovascular events in high-risk patients.

In a review article on the state of CVD prevention in 2015, Chapman et al.³ attributed the greatest significance for cardiovascular prevention to good regulation of LDL cholesterol, citing the registration of two drugs that act on the inhibition of PCSK9 in the plasma, and consequently on the reduction of LDL cholesterol values, as an important advancement in cardiovascular prevention (especially in patients with a family hypercholesterolemia). These two drugs (monoclonal antibodies) under the trade names Praluent® (alirocumab) and Repatha® (evolocumab) have been registered in the European Union in 2015 and thus automatically in Croatia as well. It is not yet known when they will be placed on the medication List of the Croatian Health Insurance Fund, given the current price of monthly treatment of approx. 5,000 HRK.

The importance assigned to hypolipidemic therapy in our country is demonstrated by the expenditure of medication for the regulation of dyslipidemia (mostly statins), which has grown sharply over the last decade (2004-2014) in DDD/100 inhabitants from 28.13 to 61.79, which is more than double.⁴ However, since CVD are the leading cause of mortality and morbidity in Croatia, this increase in the use of hypolipidemic agents should definitely be larger, especially since elevated cholesterol values are also, along with smoking, the most important risk factor in our country. Thus, one trial on "healthy" participants found a prevalence of cholesterol levels above 5.5 mmol/L in 67% of the participants.⁵

In addition to dyslipidemia regulation, adequate regulation of blood pressure (BP) is still very significant and still not satisfactory in Croatia. A recent study found that only a quarter of patients have well-regulated BP values⁶. Chapman et al.² cite two studies regarding arterial hypertension regulation: PATHWAY 2 and PATHWAY 3.^{7,8} The PATHWAY 2 study examined the role of spironolactone in the treatment of resistant arterial hypertension (AH), where it showed good results.⁷ The results of the PATHWAY 3 study showed that the combination of amiloride and hydrochlor-

Moduretic® godinama bio dostupan u Hrvatskoj, povučen je s tržišta prošle godine, najvjerojatnije zbog komercijalnih razloga. Svakako treba vidjeti kako će autori smjernica o liječenju AH-a prihvatiti rezultate ove studije, a onda će lijek vjerojatno ponovno biti dostupan u nas.

Prema zadnjim europskim i američkim smjernicama, kontrola AH-a bila je manje striktna negoli prije. Ipak, ovu "relaksaciju" u preporučenim ciljnim vrijednostima AT-a dovode u pitanje rezultati nedavno objavljene SPRINT studije u kojoj su bolesnici koji su postigli vrijednost AT-a od 120/80 mmHg imali 25 % bolje kardiovaskularne ishode (infarkt miokarda, moždani udar, zatajivanje srca, akutni koronarni sindrom, kardiovaskularna smrt) od onih s vrijednostima AT-a 140/90 mmHg. Ovo je postignuto uz porast broja nuspojava (hipotenzija, sinkopa, poremećaji elektrolita, zatajenje bubrega) u bolesnika u skupini s intenzivnom kontrolom AT-a (4,7 prema 2,5 %)⁹. Spomenutu studiju autori članka također navode kao značajnu za kardiovaskularnu prevenciju.

Kao važno dostignuće prošle godine iz područja kardiovaskularne prevencije izdvojena je EMP-REG OUTCOME klinička studija u kojoj je dokazana znatna redukcija kardiovaskularnog i ukupnog mortaliteta u bolesnika s dijabetesom tipa 2 i velikim kardiovaskularnim rizikom koji su upotrebljavali selektivni SGLT-2 inhibitor empagliflozin. Znajući da nakon "rosiglitazonske afere" svi novi antidijabetici moraju imati studije kardiovaskularne sigurnosti, odnosno dokazati da ne povećavaju kardiovaskularni morbiditet i mortalitet, rezultat te studije pokazuje da ga jedan od njih i smanjuje¹⁰.

Zaključno, *Chapman i sur.* u članku o novostima u kardiovaskularnoj prevenciji 2015. godine ponovno najveći naglasak stavljaju na dobru kontrolu čimbenika rizika (dyslipidemije, hiperglikemije i arterijske hipertenzije), koja je, prema njima, ostvarila dramatičan napredak u prošloj godini. Značajno je da je većina lijekova kojima je to postignuto dostupna u Hrvatskoj pa stoga ne bi trebalo biti prepreka da znatno poboljšamo prevenciju kardiovaskularnih bolesti.

rothiazide treatment was the preferred diuretic in the treatment of hypertensive patients due to its neutral metabolic effects.⁸ This drug, which had been available under the name Moduretic® in Croatia for many years, has unfortunately been withdrawn from the market last year, most likely due to commercial reasons. It remains to be seen how the guideline authors for AH treatment will receive the results of this study, but it will likely result in this drug once again becoming available in Croatia.

According to the latest European and American guidelines, AH management was less strict than before. However, this relaxation in the recommended target AP values has been brought into question by the recently published results of the SPRINT study in which patients that achieved AT values from 120/80 mmHg had 25% better cardiovascular outcomes (myocardial infarction, stroke, heart failure, acute coronary syndrome, cardiovascular death) than those with AP values at 140/90 mmHg. This was accompanied with an increase in the number of side-effects (hypotension, syncope, electrolyte imbalance, renal failure) in patients from the group with intensive pressure control (4.7 vs. 2.5%)⁹. The authors also cite this study as significant for cardiovascular prevention.

A significant achievement from the field of cardiovascular prevention in the last year was the EMP-REG OUTCOME clinical study which demonstrated a significant reduction of cardiovascular and total mortality in patients with type 2 diabetes and high cardiovascular risk that used empagliflozin, a selective SGLT-2 inhibitor. Since all new antidiabetics must pass cardiovascular safety studies after the "rosiglitazone affair", i.e. must be proven not to increase cardiovascular morbidity and mortality, the results of this study show that one of them in fact reduces them¹⁰.

In conclusion, the Chapman et al. article on the news in cardiovascular prevention in 2015 once again stressed good risk factor management (dyslipidemia, hyperglycemia, and arterial hypertension), which saw dramatic advancements in the past year, according to the authors. It is significant that most medications that have achieved this are available in Croatia, so there should be no obstacles to significantly improving the prevention of cardiovascular diseases.

LITERATURE

- Hrvatski zavod za javno zdravstvo. Hrvatski zdravstveno-statistički ljetopis za 2014. godinu. [cited 2016 Apr 15]. Available from: http://www.hzjz.hr/wp-content/uploads/2015/05/ljetopis_2014.pdf
- Bergman Marković B. Prijedlog nacionalnog programa prevencije programa u obiteljskoj medicini. Simpozij Rano otkrivanje i prevencija kardiovaskularnih bolesti u obiteljskoj medicini. Zagreb, 2015. Available from: http://zdrava-sana.istra-istria.hr/uploads/media/BBM_Simpozij_HZJZ_Program_Prevencije_KVB_Zagreb_14.12.2015.pdf
- Chapman MJ, Blankenberg S, Landmesser U. The year in cardiology 2015: prevention. *Cardiol Croat.* 2016;11(7):218-233. DOI: <http://dx.doi.org/10.15836/ccar2016.218>
- HALMED - Agencija za lijekove i medicinske proizvode. Izvješća o prometu lijekova. Available from: <http://www.halmed.hr/Promet-proizvodnja-i-inspekcija/Promet/Potrosnja-lijekova/Izvjescia-o-prometu-lijekova/>
- Cokarić M, Banić A, Šešelja Perišin A, Kačić J, Portolan M, Modun D. [Primary prevention of cardiovascular diseases in pharmacies - measuring blood cholesterol and glucose]. Book of Abstracts of 1st Croatian congress of clinical pharmacy. Bačić Vrca V, Jakševac Mikša M, Ortner Hadžiabdić M, Vladimir Knežević S (Eds). Zagreb: Hrvatsko farmaceutsko društvo, 2014. P-18-P-18. Croatian.
- Knežević A, Banić A, Sarić - Kužina S. Comparison of efficacy and cost of antihypertensive therapy with fixed-dose combination versus free-drug combination. Abstract book of First macedonian and fourth adriatic congress on pharmacoeconomics and outcomes research. Ohrid: 2014. pp. 62-3.
- Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McCluskey G, et al; British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet.* 2015;386(10008):2059-68. DOI: [http://dx.doi.org/10.1016/S0140-6736\(15\)00257-3](http://dx.doi.org/10.1016/S0140-6736(15)00257-3)
- Brown MJ, Williams B, Morant SV, Webb DJ, Caulfield MJ, Cruickshank JK, et al; British Hypertension Society's Prevention and Treatment of Hypertension with Algorithm-based Therapy (PATHWAY) Studies Group. Effect of amiloride, or amiloride plus hydrochlorothiazide, versus hydrochlorothiazide on glucose tolerance and blood pressure (PATHWAY-3): a parallel-group, double-blind randomised phase 4 trial. *Lancet Diabetes Endocrinol.* 2016;4(2):136-47. DOI: [http://dx.doi.org/10.1016/S2213-8587\(15\)00377-0](http://dx.doi.org/10.1016/S2213-8587(15)00377-0)
- SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med.* 2015;373(22):2103-16. DOI: <http://dx.doi.org/10.1056/NEJMoa151939>
- Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med.* 2015 Nov 26;373(22):2117-28. DOI: <http://dx.doi.org/10.1056/NEJMoa1504720>