

Smanjenje tereta koronarne bolesti srca na dokazima utemeljenim principima liječenja

Evidence-based treatment approaches in reducing the burden of coronary heart disease

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SAŽETAK: Koronarna bolest srca (KBS) predstavlja vodeći uzrok smrti diljem svijeta. Nažalost, iznenadna srčana smrt je za mnoge pojedince prva manifestacija KBS. Prevencija idealno počinje primarnom intervencijom u osoba s povećanim rizikom od kardiovaskularnih bolesti (KVB), ali bez klinički manifestne bolesti. Usmjerena je na zbrinjavanje čimbenika rizika, koji uključuju dislipidemiju i artrijsku hipertenziju, koji su odavno utvrđeni kao važni promjenjivi kardiovaskularni (KV) čimbenici rizika. Međutim, postupci primarne prevencije su još uvijek nedovoljni i ne mogu pružiti optimalnu zaštitu od razvoja KBS. Naponi u sekundarnoj prevenciji, gdje zbrinjavanje KV čimbenika rizika postaje još važnije, usmjereni su na prevenciju daljnje progresije bolesti koja može dovesti do ponovne pojave KV događaja, pa čak i smrti. Tijekom proteklog desetljeća, klinička dobrobit hipolipemika i antihipertenzivnih lijekova u smislu smanjenja KV rizika je utvrđena u brojnim randomiziranim kontroliranim istraživanjima. Statini su jedina skupina hipolipemika koji poboljšavaju kliničke ishode u bolesnika sa i bez KVB. Oni dokazano smanjuju KV poboljšanje i smrtnost, kao i potrebu za intervencijama na koronarnim arterijama. Dokazi o djelotvornosti perindopрила u smanjenju pojavnosti KV događanja su dobro utemeljeni. Rezultati studije EUROPA u bolesnika sa stabilnom KBS pružaju jasne dokaze o djelotvornosti perindopрила u sekundarnoj prevenciji bolesnika sa stabilnom KBS. Mogućnosti liječenja zasnovane na dokazima, poput statina i inhibitora angiotenzin konvertirajućeg enzima bi mogle pomoći u smanjenju faktora rizika kod bolesnika sa KVB, a time i osigurati odgovarajuću zaštitu od daljnje progresije ove bolesti.

KLJUČNE RIJEČI: koronarna bolest srca, arterijska hipertenzija, hiperlipidemija, statini, perindopril.

SUMMARY: Coronary heart disease (CHD) is the leading cause of death worldwide. Unfortunately, sudden cardiac death is for many individuals the first manifestation of CHD. Prevention ideally begins with primary interventions in persons at increased risk for cardiovascular disease (CVD) but without clinically manifested disease. It is aimed at managing risk factors, including dyslipidemia and hypertension, which have long been established as important modifiable cardiovascular (CV) risk factors. However, primary prevention practices are still inadequate and may provide suboptimal protection against the development of CHD. Efforts in secondary prevention, where the management of CV risk factors becomes even more crucial, are focused on the prevention of further progression of the disease which can result in recurrence of the CV event or even death. Over the past decade, the clinical benefit of lipid-lowering and antihypertensive medicines in terms of CV risk reduction has been established in numerous randomised controlled trials. Statins are the only lipid-lowering medicines which improve clinical outcomes in patients with and without CVD. They have been shown to reduce CV morbidity and mortality as well as the need for coronary artery interventions. Evidence of the efficacy of perindopril in reducing the incidence of CV events is well established. The findings of the EUROPA study in patients with stable CHD provided clear evidence of the efficacy of perindopril in secondary prevention in patients with stable CHD. Evidence-based treatment options, such as statins and angiotensin-converting enzyme inhibitors, could help reduce risk factors in CHD patients and, consequently, provide adequate protection against further progression of the disease.

KEYWORDS: coronary heart disease, hypertension, hyperlipidemia, statins, perindopril.

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Koronarna bolest srca (KBS) predstavlja vodeći uzrok smrti diljem svijeta, a kako je u porastu postala je istinska pandemija koja nema granica.¹ KBS je i glavni uzrok smrti u Europi, gdje je odgovorna za 1.8 milijuna smrti svake godi-

Coronary heart disease (CHD) is the leading cause of death worldwide; it is on the rise and has become a true pandemic that respects no borders.¹ It is also the main cause of death in Europe where it accounts for 1.8 million deaths

ne.² Nažalost, iznenadna srčana smrt za mnoge je pojedinice prvi znak da se radi o KBS.¹

Prevenција KVB idealno počinje primarnim intervencijama u osoba s povećanim rizikom od kardiovaskularnih bolesti (KVB), ali bez kliničke manifestne bolesti. Uloga liječnika u primarnoj prevenciji je procijeniti kardiovaskularne (KV) čimbenike rizika, savjetovati promjenu načina života i pokrenuti liječenje u bolesnika s povećanim rizikom od KVB. Međutim, postupci primarne prevencije su još uvijek nedovoljni te ateroskleroza — temeljni uzrok bolesti — često napreduje tiho desetljećima dok se konačno ne manifestiraju simptomi KBS.¹ Osobe s već utvrđenom KBS imaju pet do sedam puta veći rizik od ponovljenih manifestacija KBS te stoga imaju veće apsolutne prednosti od intervencijskih strategija.³ Doprinos različitih čimbenika za KV rizik prikazan je u multicentričnoj, kontroliranoj studiji provedenoj u 52 zemlje. Studija je pokazala da abnormalne razine lipida i hipertenzija čine približno 70% rizika od infarkta miokarda (IM) u populaciji.⁴ Tijekom proteklog desetljeća, klinička dobrobit hipolipemika i antihipertenzivnih lijekova u smislu smanjenja KV rizika je utvrđena u brojnim randomiziranim kontroliranim istraživanjima.

Obzirom na činjenicu da su od svih hipolipemika jedino statini poboljšali kliničke ishode kod bolesnika s i bez KVB, ova skupina predstavlja prvu liniju farmakoterapije u liječenje hiperlipidemije.¹ Statini dokazano smanjuju kardiovaskularni pobol i smrtnost, kao i potrebu za intervencijama na koronarnim arterijama.⁵⁻⁸ Scandinavian Simvastatin Survival Study (4S) po prvi puta je dokazala da liječenje statinima dovodi do promjene učestalosti KV događaja u bolesnika s KBS, pa predstavlja prekretnicu u kardiologiji i medicini utemeljenoj na dokazima. Tijekom razdoblja od 5,4 godine prosječnog praćenja, statini su smanjili rizik velikih koronarnih događaja za 34%, kao i rizik od ukupne smrtnosti za 30%. Nije bilo razlike u nekardiovaskularnoj smrtnosti u liječenim skupinama i skupinama koje su primale placebo. Ova studija je jasno utvrdila da je terapija statinima sigurna i da smanjuje pobol i smrtnost u bolesnika s KBS. Glavni rezultati studije 4S su sažeto prikazani u **Tablici 1**.⁵

each year.² Unfortunately, sudden cardiac death is for many individuals the first manifestation of CHD.¹

Prevention of CHD ideally begins with primary interventions in persons at increased risk for cardiovascular disease (CVD) but without clinically manifested disease. The physician's role in primary prevention is to assess the cardiovascular (CV) risk factors, urge lifestyle changes and initiate medical treatment in patients at increased CV risk. However, primary prevention practices are still inadequate and atherosclerosis — the underlying cause of the disease — is often progressing silently for decades until CHD symptoms finally manifest.¹ Individuals with already established CHD have a five- to seven-fold increased risk for recurrent CHD events and, hence, derive greater absolute benefits from the intervention strategies.³ The contribution of different risk factors to CV risk was demonstrated in a multicenter, case-control study conducted in 52 countries. The study has shown that abnormal lipid levels and hypertension account for approximately 70% of the attributable risk for myocardial infarction (MI) in the population.⁴ Over the past decade, the clinical benefit of lipid-lowering and antihypertensive medicines has been, in terms of CV risk reduction, established in numerous randomised controlled trials.

Given the fact that lipid-lowering medicines other than statins have failed to improve clinical outcomes in patients with and without CVD, statins are the first-line pharmacotherapy in the treatment of hyperlipidemia.¹ They have been proven to reduce CV morbidity and mortality as well as the need for coronary artery interventions.⁵⁻⁸ The Scandinavian Simvastatin Survival Study (4S), which has demonstrated for the first time that treatment with statins changes the incidence of CV events in patients with CHD, turned out to be a milestone in cardiology and evidence-based medicine. Over the 5.4 years of median follow-up of the treatment, statins reduced the risk for major coronary events by 34% and the risk for mortality from all-causes by 30%. There was no difference in non-cardiovascular deaths in the treated and placebo groups. This study has clearly established that statin therapy is safe and that it reduces morbidity and mortality in patients with CHD. The main results of the 4S study are summarised in **Table 1**.⁵

Table 1. Summary of the main results of the 4S study⁵.

Causes of death	Number of patients	
	Placebo group (n=2223)	Statin group (n=2221)
All coronary	189	111
All cardiovascular	207	136
All deaths	256	182
Events		
Any major coronary event	502	353
Coronary surgery or angioplasty	383	252
Non-MI acute CHD	331	295
Any cerebrovascular	95	61
Other cardiovascular	33	24

Usljedio je niz drugih velikih randomiziranih kliničkih studija koje su utrle put širokoj primjeni statina u prevenciji kardiovaskularnih bolesti. U studiji CTT analizirani su i sažeti rezultati 14 randomiziranih kontroliranih istraživanja koji uključuju oko 90.000 ispitanika, od kojih je 47% imalo prethodno postojeću KBS. Statini dokazano smanjuju rizik od komplikacije KBS i povećavaju duljinu života.⁶ Sličan učinak bio je uočen u studiji CARE u bolesnika s utvrđenom KBS, u kojoj se pokazalo da se snižavanjem kolesterola statinima u bolesnika s preboljelim IM smanjuje rizik od fatalne KBS ili nefatalnog IM za 24%, fatalnog IM za 37% i aortokoronarnog premoštenja za 26%.⁷ Promatrane kliničke dobrobiti se mogu pripisati anti-arterogenom djelovanju statina, koji je ocijenjen u studijama pomoću koronarne angiografije ili ultrazvučnih tehnika. Studija u kojoj se istražuje intenzivna terapija statinima i regresija plaka je bilo ispitivanje SATURN u kojem je uspoređeno djelovanje rosuvastatina (40 mg dnevno) i atorvastatina (80 mg dnevno) kod 1.039 bolesnika s KBS u 104 tjedna. Rezultati su pokazali da smanjenje razine LDL kolesterola za više od 50% rezultira značajnom regresijom koronarne ateroskleroze.⁸ Činjenica da se mnogi bolesnici u sekundarnoj prevenciji ne liječe višim dozama statina, ostaje jedan od izazova za sekundarnu prevenciju.¹ Hiperlipidemija se često pojavljuje zajedno s arterijskom hipertenzijom.⁹ Dokazi ukazuju da liječenje usmjereno na oba spomenuta čimbenika KV rizika dovode do većeg smanjenja KV rizika.^{10,11} Pokazalo se da smanjenje sistoličkog arterijskog tlaka za 15 mmHg uzrokuje 10% smanjenje KV rizika. Osim toga, smanjenje ukupnog kolesterola za 0,6 mmol/l je bilo povezano s 10% smanjenjem KV rizika. Međutim, isto smanjenje oba čimbenika rizika je bilo daleko korisnije i imalo je za rezultat 45% smanjenje KV rizika.¹⁰ Stoga, ne čudi da je izračunato da bi se gotovo polovica KBS događaja koji se dogode kod hipertenzivnih bolesnika mogla spriječiti istodobnom kontrolom arterijskog tlaka i lipida.¹¹ Inhibitori angiotenzin konvertirajućeg enzima (ACEI) su se pokazali djelotvornima u sekundarnoj prevenciji KBS. Dokaz o djelotvornosti perindopрила u smanjenju pojavnosti KV događaja je već dobro utvrđen.¹² Rezultati studije EUROPA donijeli su jasne dokaze o djelotvornosti perindopрила u sekundarnoj prevenciji bolesnika sa stabilnom KBS.¹³ Perindopril u dozi kojom se smanjuje visoki arterijski tlak (8 mg/dan) rezultirao je 20% smanjenjem primarnog KV krajnjeg ishoda (KV smrtnosti, ne-fatalnog IM, ili reanimiranog srčanog zastoja) u usporedbi s placebom, a ta je dobrobit uočena kod bolesnika niskog, srednjeg i visokog rizika te u populaciji istodobno liječenoj hipolipemicima (koja je primijenjena kod 69% bolesnika). Pored toga, perindoprilom su smanjeni KV događaji kod normotenzivnih i hipertenzivnih bolesnika, a to smanjenje je potencijalno bilo veće nego što bi se očekivalo od promatranog smanjenja od početne vrijednosti arterijskog tlaka (prosječno smanjenje 5/2 mmHg). To ukazuje na izravno vaskularno i antiaterosklerotsko djelovanje perindopрила. Poznata korisna djelovanja perindopрила na vaskularnu strukturu uključuju smanjenje hipertrofije arterijske stijenke i krutosti arterija te poboljšanje elastičnosti arterija.¹² Korisna djelovanja perindopрила mogu biti povezana s njegovim djelovanjima koja dovode do poboljšanja funkcije endotela i prekida patofiziološkog kontinuuma. Time se usporava brzina napredovanja KBS i, sukladno tome, poboljšava prognoza bolesnika.¹³

Kako je prevencija KVB jedan od najvažnijih područja suvremene medicine, Krka je ponudila širok spektar lijekova koji se koriste u primarnoj i sekundarnoj prevenciji KBS. Asortiman proizvoda također uključuje dva najpotentnija statina na tržištu — atorvastatina (Atoris®) i rosuvastatin (Roswera®),

A host of other large randomised clinical trials followed, which paved the way to widespread use of statins in the CVD prevention. A study by the Cholesterol Treatment Trialists' (CTT) collaboration analysed and summarised the results of 14 randomised controlled trials involving about 90,000 subjects, of whom 47% had pre-existing CHD. Statins were proven to lower the risk of CHD complications and increase life expectancy.⁶ A similar effect was observed in the Cholesterol and Recurrent Events (CARE) study in patients with established CHD, which has shown that cholesterol lowering with statins in patients with previous MI reduces the risk for fatal CHD or nonfatal MI by 24%, fatal MI by 37% and coronary artery bypass surgery by 26%.⁷ The observed clinical benefits may be attributed to the antiatherogenic effect of statins, which was assessed in studies using coronary angiography or ultrasound techniques. A study investigating intensive statin therapy and plaque regression was the SATURN trial which compared the effect of rosuvastatin (40 mg daily) and atorvastatin (80 mg daily) in 1,039 patients with CHD for 104 weeks. The results have shown that a reduction of LDL cholesterol levels by more than 50% results in a significant regression of coronary atherosclerosis.⁸ Due to the fact that many patients in secondary prevention are not being treated with higher doses of statins, this remains one of the challenges in secondary prevention.¹

Hyperlipidemia often occurs together with hypertension.⁹ Consequently, evidence suggests that therapies targeted at both these CV risk factors lead to greater reductions in the CV risk.^{10,11} A reduction of the systolic blood pressure by 15 mmHg was shown to lead to a 10% CV risk reduction. In addition, a reduction of the total cholesterol by 0.6 mmol/l was associated with a 10% CV risk reduction. However, the same reduction of both risk factors was far more beneficial and resulted in a 45% reduction in the CV risk.¹⁰ Therefore, it's not surprising that it has been calculated that almost half of the CHD events occurring in hypertensive patients could be prevented by controlling blood pressure and lipids at the same time.¹¹ Angiotensin-converting enzyme inhibitors (ACEI) have been shown to be effective in secondary prevention of CVD. Evidence of the efficacy of perindopril in reducing the incidence of CV events is already well established.¹² The findings of the European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA) provided clear evidence of the efficacy of perindopril in secondary prevention in patients with stable CHD.¹³ Perindopril given at a dose that reduces high blood pressure (8 mg/day) resulted in a 20% reduction in the primary CV endpoint (CV mortality, non-fatal MI, or resuscitated cardiac arrest) when compared with placebo, and this benefit was observed across low-, medium-, and high-risk patients and in a population treated with concomitant lipid-lowering therapy (administered to 69% of patients). Additionally, perindopril reduced CV events in both normotensive and hypertensive patients and, overall, this reduction was potentially greater than it would be expected from the observed decrease from baseline in blood pressure (mean reduction of 5/2 mmHg). This suggests a direct vascular and antiatherosclerotic effect of perindopril. Well-known beneficial effects of perindopril on the vascular structure include reductions in arterial wall hypertrophy and arterial stiffness, and improvements in arterial elasticity.¹² The beneficial effects of perindopril can be linked to its effects leading to an improvement of the endothelial function and breaking the pathophysiological continuum. This slows the rate of progression of CVD and, consequently, improves patient prognosis.¹³

koji su dostupni u dvije dodatne doze, atorvastatin 30 mg i 60 mg te rosuvastatin 15 mg i 30 mg. Atorvastatin 60 mg ili rosuvastatin 30 mg posebno mogu pružiti odgovarajuću dozu održavanja u bolesnika s KBS, koji obično trebaju intenzivnije zbrinjavanje lipida. Krka je trenutno jedna od malobrojnih farmaceutskih tvrtki koja nudi cjelokupni portfelj perindoprila — perindopril (Perineva[®]), kombinaciju fiksne doze perindoprila i indapamida (Co-Perineva[®]) i kombinaciju fiksne doze perindoprila i amlodipina (Dalneva[®]), što omogućuje prilagođeni terapijski pristup kod velikog broja hipertenzivnih bolesnika.

Učinkovitost i sigurnost Krkinih kardiovaskularnih lijekova se kontinuirano prati u kliničkim studijama. Do sada je više od 110.000 bolesnika sudjelovalo u ovim studijama uključujući bolesnike s KBS.

Rezultati kliničkih ispitivanja predstavljaju važan doprinos poboljšanju zbrinjavanja hiperlipidemije i arterijske hipertenzije u različitim skupinama bolesnika. Mogućnostima liječenja zasnovanim na dokazima, poput statina i inhibitora angiotenzin konvertirajućeg enzima možemo smanjiti čimbenike rizika kod bolesnika sa KVB kako bi osigurali odgovarajuću zaštitu od daljnje progresije bolesti.

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As the prevention of CVD is being one of the most important fields of modern medicine, Krka has made available a wide range of medicines used in the primary and secondary prevention of CVD. Its range of products also includes two most potent statins on the market — atorvastatin (Atoris[®]) and rosuvastatin (Roswera[®]), which are available in two additional strengths, atorvastatin 30 mg and 60 mg and rosuvastatin 15 mg and 30 mg. Atorvastatin 60 mg or rosuvastatin 30 mg in particular can provide a suitable maintenance dose for patients with CHD, who usually need a more intensive lipid management. Krka is also one of the few companies offering the entire perindopril portfolio — perindopril (Perineva[®]), fixed-dose combination of perindopril and indapamide (Co-Perineva[®]) and fixed-dose combination of perindopril and amlodipine (Dalneva[®]), which enables a tailored therapeutic approach in a broad range of hypertensive patients.

The efficacy and safety of Krka's cardiovascular medicines are continuously monitored in clinical studies. Till now, more than 110,000 patients have participated in these studies, including patients with CHD.

The results of clinical studies are an important contribution towards improving the management of hyperlipidemia and hypertension in different groups of patients. With evidence-based treatment options, such as statins and ACEI, we could reduce risk factors in CHD patients in order to provide adequate protection against further progression of the disease.

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