



Mogu li pacijenti s arterijskom hipertenzijom i dijabetesom također imati dobit od primjene statina?

Do hypertensive and diabetic patients also benefit from statin therapy?

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SAŽETAK: Čimbenici rizika za kardiovaskularne bolesti (KVB) uključuju arterijsku hipertenziju, dijabetes i dislipidemiju. Moderne smjernice za prevenciju KVB preporučuju više mjera za smanjenje utjecaja navedenih čimbenika rizika, uključujući i farmakološko liječenje. Brojne kliničke studije su pokazale prednosti od snižavanja povišene razine kolesterola kod hipertenzivnih bolesnika. Pokazalo se da konkomitantna terapija za arterijsku hipertenziju i dislipidemiju značajno smanjuje rizik od KVB u usporedbi samo sa snižavanjem vrijednosti arterijskog tlaka i kolesterola u krvi. Kliničke studije s Krkinim atorvastatinom su također pokazale učinkovitost i sigurnost terapije smanjenja lipida kod hipertenzivnih bolesnika s dislipidemijom. Dobro je poznato da se rizik za aterosklerotску kardiovaskularnu bolest kod bolesnika s dijabetesom povećava dva do četiri puta. Kliničke studije su pokazale da je terapija statinom također bila korisna i u bolesnika s dijabetesom. Subanalize studija s uključenim bolesnicima s dijabetesom koji su bili liječeni Krkinim atorvastatinom dokazale su prednosti i sigurnost takvog liječenja. Stoga, snižavanje visokih razina kolesterola u krvi kod bolesnika s hipertenzijom i dijabetesom donosi dodatne koristi bolesnicima.

KLJUČNE RIJEČI: atorvastatin, dijabetes, arterijska hipertenzija, dislipidemija.

SUMMARY: The risk factors for cardiovascular diseases (CVD) include hypertension, diabetes and dyslipidemia. Therefore, the modern guidelines for CVD prevention suggest several steps to reduce these risk factors, including pharmacological treatment. Numerous clinical studies demonstrated benefits of cholesterol level reduction in hypertensive patients. It was shown that concomitant treatment of hypertension and dyslipidemia significantly reduced CVD risk in comparison with blood pressure or blood cholesterol reduction alone. Clinical studies with Krka's atorvastatin also demonstrated the efficacy and safety of lipid-lowering therapy in hypertensive patients with dyslipidemia. It is well known that the risk for atherosclerotic cardiovascular disease in diabetic patients is increased two to fourfold. Clinical studies demonstrated that statin treatment was also beneficial in diabetic patients. Similarly, sub-analyses of studies in diabetic patients treated with Krka's atorvastatin proved the advantages of such treatment, as well as its safety. Thus, reducing high blood cholesterol levels in hypertensive and diabetic patients clearly brings additional benefits for the patients.

KEYWORDS: atorvastatin, diabetes, hypertension, dyslipidemia.

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Moderno društvo i medicina se suočavaju s u potpunosti s drugačijim izazovima u odnosu na naše pretke. Kardiovaskularne bolesti (KVB) predstavljaju najčešći uzrok smrti u svijetu. Procjenjuje se da diljem svijeta uzrokuju gotovo trećinu svih uzroka smrti, što jasno ukazuje na njihovu važnost¹. Ove bolesti su proučavane desetljećima, a rezultati studija jasno su identificirali nekoliko značajnih čimbenika rizika, koji uključuju arterijsku hipertenziju, dijabetes i dislipidemiju². Stoga, moderne smjernice za prevenciju KVB preporučuju nekoliko mjera za smanjenje utjecaja ovih čimbenika rizika, uključujući i farmakološko liječenje³.

Jedna od kliničkih studija, provedena prije gotovo dvadeset godina na više od 300.000 bolesnika, dokazala je da zajedničko snižavanje povišenih vrijednosti arterijskog tlaka (AT) i razine kolesterola u krvi donosi najveću dobit⁴. Iako odvojeno snižavanje vrijednosti AT i kolesterola snižava smrtnost od koronarne bolesti srca, najbolji rezultati su dobiveni kad su oba čimbenika rizika liječena istovremeno (**Slika 1** na stranici 83). Nekoliko godina kasnije je utvrđena međusobna povezanost između sistoličkog AT/ukupnog smanjenja kolesterola i snižavanja rizika od

While our ancestors had their own set of issues to deal with, the modern society and medicine face completely new challenges. Cardiovascular diseases (CVD) represent the number one cause of death globally. It is estimated that almost one out of three deaths is caused by them, which clearly shows their importance¹. CVD have been studied for decades and the findings identified several risk factors connected to them, including hypertension, diabetes and dyslipidemia². Therefore, the modern guidelines for CVD prevention suggest several steps to reduce these risk factors, including pharmacological treatment³.

One of the early clinical studies from almost two decades ago, which was conducted in over 300,000 patients, already proved that reducing blood pressure (BP) and the blood cholesterol level concomitantly offered the most benefits for the patients⁴. Although separate reducing BP and blood cholesterol decreases mortality from coronary heart disease, the best results were demonstrated when both risk factors were treated at the same time (**Figure 1** on page 83). Several years later, a correlation was shown between sys-



KVB⁵. Pokazalo se da je sniženje sistoličkog AT od 15 mmHg dovelo do snižavanja rizika od KVB za 10%. Također, sniženje ukupnog kolesterola za 0,6 mmol/l je također bilo povezano s 10% snižavanjem rizika od KVB. Međutim, smanjenje oba čimbenika rizika za ove iste vrijednosti je bilo korisnije i rezultiralo je smanjenjem rizika od KVB za 45%. Jedna od poznatijih kliničkih studija koja se usredotočila na sniženje razine kolesterola kod hipertenzivnih bolesnika bila je ASCOT-LLA (Anglo Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm) koja je pokazala 36% smanjenje primarnih ishoda (nefatalni infarkt miokarda, uključujući nijemi infarkt i fatalnu koronarnu bolest srca) kod hipertenzivnih bolesnika s barem tri druga kardiovaskularna čimbenika rizika pri liječenju s 10mg atorvastatina u odnosu na placebo⁶. Bolesnici s hipertenzijom su također redovito uključivani u Krkine vlastite studije s atorvastatinom (Atoris[®]). Neke od ovih studija, uključujući studije ATLANTICA, ATOP, FARVATER i najnoviju studiju Atoris provedenu na starijim bolesnicima, su također dokazale učinkovitost i sigurnost Krkinog atorvastatina kod hipertoničara⁷⁻¹⁰.

Bolesnici s dijabetesom su već prema smjernicama klasificirani u visokorizične bolesnike³. Rezultati dosadašnjih istraživanja upućuju da dijabetičari tipa 2 imaju dva do četiri puta viši rizik od razvoja aterosklerotske kardiovaskularne bolesti te da su ishodi nakon infarkta miokarda ili moždanog udara još i lošiji¹¹. Dobrobit od primjene terapije statinima kod ovih bolesnika su prikazane u studiji HPS (Heart Protection Study): primjena statina smanjila je učestalost prvog velikog vaskularnog događaja za oko jednu četvrtinu u dijabetičara. Također, istraživači su zabilježili da bi terapiju statinom sada trebalo rutinski razmotriti kod svih bolesnika s dijabetesom koji su visokog rizika za velike vaskularne događaje, neovisno o njihovim početnim vrijednostima kolesterola¹². Štoviše, studija CARDS (Collaborative AtoRvastatin Diabetes Study) je pokazala smanjenu smrtnost, pobol te rizik od moždanog udara i rizik od akutnih koronarnih događaja u skupini bolesnika liječenoj atorvastatinom¹³.

Kao i kod hipertenzivnih bolesnika, Krka je također aktivno uključena u unaprjeđivanje mogućnosti liječenja dijabetičnih bolesnika. Za bolesnike s dijabetesom su obavljene zasebne sub-analize dvije Krkine najnovije studije s atorvastatinom — ATOP i Atoris kod starijih bolesnika^{7,9}. Rezultati ovih subanaliza su prikazani u **Tablici 1**. Ovi rezultati su potvrdili izvrsnu sigurnost terapije atorvastatinom kod bolesnika s dijabetesom. U studiji ATOP, 73 od 76 bolesnika nije prijavilo nikakve nuspojave. U studiji Atoris koja je provedena na starijim bolesnicima, 318 od 321 bolesnika nije prijavilo nikakve nuspojave. Uz gore navedene rezultate, također je dokazano da je liječenje povezano sa

tolic BP/total cholesterol reduction and CVD risk reduction⁵. Reduction of systolic BP by 15 mmHg was shown to lead to a 10% CVD risk reduction. In addition, reducing total cholesterol by 0.6 mmol/l was also associated with a 10% CVD risk reduction. However, reducing both risk factors by these same values was far more beneficial and resulted in a 45% reduction in the CVD risk. Perhaps one of the better known clinical studies which focused on reducing cholesterol levels in hypertensive patients was ASCOT-LLA (Anglo Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm) which demonstrated a 36% reduction in primary endpoint (non-fatal MI, including silent MI and fatal CHD) in hypertensive patients with at least three other cardiovascular risk factors treated with atorvastatin 10mg compared to placebo⁶. Patients with hypertension are also regularly included in Krka's own clinical studies with atorvastatin (Atoris[®]). Several of these studies, including ATLANTICA, ATOP, FARVATER, and the latest study with Atoris in elderly patients have proven the efficacy and safety of Krka's atorvastatin also in hypertensive patients⁷⁻¹⁰.

Diabetic patients are already classified by the guidelines as high-risk patients³. It has been reported that the risk for atherosclerotic cardiovascular disease is increased two to four-fold in patients with type 2 diabetes and the outcomes after myocardial infarction or stroke are even worse¹¹. The benefits of statin treatment in these patients were demonstrated by the HPS study (Heart Protection Study): statin therapy reduced the rate of first major vascular event by about a quarter in a wide range of diabetic patients. In addition, it was noted by the investigators that "statin therapy should now be considered routinely for all diabetic patients at sufficiently high risk of major vascular events, irrespective of their initial cholesterol concentrations"¹². What is more, the CARDS study (Collaborative AtoRvastatin Diabetes Study) demonstrated reduced mortality, morbidity, stroke risk and risk for acute coronary events in a group of patients treated with atorvastatin¹³.

As in the case of hypertensive patients, Krka is actively involved in improving the therapy options for diabetic patients as well. Separate sub-analyses of two of Krka's latest studies with atorvastatin — ATOP and Atoris in elderly patients — were performed in diabetic patients^{7,9}. The results of these sub-analyses are shown in **Table 1**. These results confirmed the excellent safety of atorvastatin treatment in diabetic patients. In the ATOP study, 73 out of 76 patients did not report any adverse events. In the study with Atoris in elderly patients, 318 out of 321 patients did not report any adverse events. In addition to the results presented above, treatment was also proven to be associated with BP

Table 1. Treatment with Krka's atorvastatin in diabetic patients; sub-analyses results.

	ATOP study	Atoris in elderly patients
LDL cholesterol reduction	-33%	-35%
Total cholesterol reduction	-25%	-30%
Triglyceride reduction	-12%	-26%
Mean dose of atorvastatin	21.2 mg/day	29.5 mg/day



snižavanjem vrijednosti AT kod bolesnika s dijabetesom. Prosječno sniženje sistoličkog AT-a je bilo sa 145,9 mmHg na 138,9 mmHg, a prosječno sniženje dijastoličkog AT-a sa 85,8 mmHg na 82,3 mmHg¹⁴.

Godine kliničke prakse su jasno pokazale koristi od terapije statinom kod hipertenzivnih bolesnika i dijabetičara. Smanjenje dodatnog čimbenika rizika — visoke razine kolesterola u krvi — povrh kontrole hipertenzije i dijabetesa donosi dodatne koristi bolesnicima u smislu smanjenog mortaliteta od koronarne bolesti srca, smanjenog rizika od KVB, smanjenog rizika od većih vaskularnih događaja, rizika od moždanih udara i rizika za akutnih koronarnih događaja. Predstavljeni rezultati su potvrdili učinkovitost i sigurnost Krkinog atorvastatina i kod hipertenzivnih bolesnika i dijabetičara.

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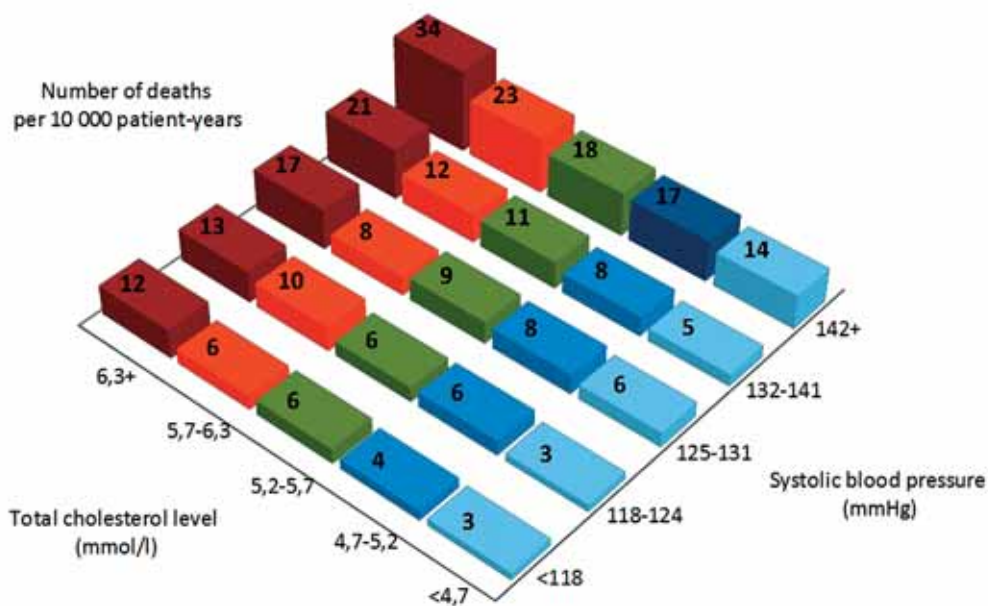


Figure 1. Number of deaths in association with total cholesterol and systolic blood pressure level (Adapted from: Ruilope L M. Reducing cardiovascular risk in hypertensive patients. A primary care handbook. Foundation for the Prevention of Cardiovascular Risk; 2007).