Značenje sartana u kardiovaskularnoj prevenciji

The Role of Sartans in Cardiovascular Prevention

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SAŽETAK: Primjena blokatora angiotenzinskih receptora (AT1) u kardiovaskularnoj prevenciji temelji se na liječenju arterijske hipertenzije. Telmisartan, u grupi sartana kojima pripada, povrh antihipertenzivnoga djelovanja, zaslužuje posebno mjesto zbog dokazanih pleiotropinih, metaboličkih, biohumoralnih, antiproliferativnih i vaskularnih učinaka, temeljnih procesa vaskularnoga starenja, ali i nastanka; progresije ateroskleroze čije još uvijek česte fatalne posljedice zahtijevaju rano prepoznavanje rizika i sveobuhvatnu primarnu i sekundarnu kardiovaskularnu prevenciju. Na temelju stručnoznanstvenih dokaza telmisartan se dokazao lijekom s dobrom podnošljivošću, dobrim antihipertenzivnim učinkom tijekom 24 sata, a indiciran je u prevenciji kardiovaskularnih bolesti.

SUMMARY: The application of angiotensin receptor blockers (AT1) in cardiovascular prevention is based on the treatment of arterial hypertension. Telmisartan, a medication from the sartan group, has not only an antihypertensive effect but proven pleiotropic, metabolic, biohumoral, antiproliferative, and vascular effects – the basic processes of vascular aging as well as the progression of atherosclerosis, a disease with a high mortality that requires early risk recognition and comprehensive primary and secondary cardiovascular prevention. Based on scientific evidence, telmisartan has been proven to provide a well tolerated antihypertensive effect over 24 hours, and is indicated in the prevention of cardiovascular diseases.

KLJUČNE RIJEČI: blokatori angiotenzinskih receptora, kardiovaskularna prevencija, telmisartan.

KEYWORDS: angiotensin receptor blockers, cardiovascular prevention, telmisartan.

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Prevencija kardiovaskularnih bolesti (KVB) i njihovih često fatalnih posljedica u vrhu je medicinskih i znanstvenoistraživačkih prioriteta. Koronarna bolest srca i KVB uopće vodeći su uzrok prerane smrtnosti u svijetu. Rana, najčešće asimptomatska bolest nalaže potrebu za prevencijom već od najranije životne dobi.[1] Posebno je važno otkriti pojedince s visokim rizikom. To su ponajprije oboljeli od dijabetesa, arterijske hipertenzije, metaboličkog sindroma, dislipidemije, karotidne i periferne vaskularne asimptomatske bolesti i one s uvjerljivom obiteljskom predispozicijom. S druge pak strane, svjedoci smo novih populacijskih trendova kao što je sve veća prisutnost treće životne dobi u populaciji kod koje se kardiovaskularne (KV) promjene najčešće susreću. Specifičnost populacije treće životne dobi jest prisutnost i kompleksnost komorbiditeta, koji nerijetko dovode i do neželjenih

Preventing cardiovascular diseases (CVD) and their often fatal effects is one of the top medical and scientific priorities. Coronary heart disease and CVD in general are the leading cause of premature mortality worldwide. The early onset of this often asymptomatic disease necessitates prevention from a very early age.[1] It is especially important to identify at-risk individuals. These are primarily patients with diabetes, arterial hypertension, metabolic syndrome, dyslipidemia, carotid and peripheral vascular asymptomatic disease, and those with a clear positive family history. On the other hand, we are witnessing new demographic trends such as an increase in the older population, in which cardiovascular (CV) changes are most common. In this age group comorbidities are more common and more complex and often

farmakoterapijskih nuspojava, što u konačnici dovodi do odustajanja od primjene lijeka.

Promjene KV aparata, srca i krvnih žila koja prati starenje nalikuje aterosklerotskom procesu, iako se po mnogim obilježjima od nje razlikuje. Ateroskleroza je sustavna bolest uz fokalne, nehomogene promjene žilne stijenke, za razliku od difuznoga procesa koji univerzalno prati životnu dob. Procesi se međusobno isprepleću i podržavaju. Ateroskleroza i vaskularno starenje slojeviti su procesi koji se temelje na zamoru vaskularnog „materijala", ali i na genskim predispozicijama. Proces starenja posljedica je vaskularnog pamćenja kumuliranih epizoda oksidativnoga stresa, izloženosti akutnim i kroničnim upalnim i metaboličkim bolestima, načina života te niza čimbenika rizika koji uzrokuju promjenu strukture žilne stijenke, fragmentaciju elastina, ali i povećanje udjela kolagena, prije svega velikih krvnih žila luka aorte i njezinih ogranaka. To je jedan od temeljnih događaja u KV patofiziologiji starenja. Aorta i velike elastične arterije luka aorte gube tako ulogu vaskularnog rezervaora kojemu je zadaća atenuacija pulsnog vala u sistoli klijetke, koji tada na svojem putu prema perifernim arterijama uzrokuje deformirajući stres i malih krvnih žila, poglavito u bubrezima i mozgu. Promjena krutosti perifernih arterija prati porast brzine pulsnog vala, reflektirajućeg vala (augmentacijskog indeksa), dovodeći do razvoja arterijske hipertenzije, hipertenzivne bolesti srca i svih dobro poznatih elemenata KV scenarija s prečesto fatalnim događajima poput infarkta miokarda, moždanog udara i kardiovaskularne smrti.[2] Poznati čimbenici rizika pogoduju nastanku ateroskleroze koja dodatno pridonosi gubitku endotelne funkcije s kardiometaboličkim posljedicama. Gubitak endotelne funkcije povezan je s endotelnom reparacijom („popravkom ozljede"), a to uvelike ovisi o potencijalu endotelnih progenitorskih stanica.[3] U konačnici progresija ateroskleroze, arterijska hipertenzija i pojava dijabetesa ubrzavaju spomenuti proces KV kontinuuma u kojima su srčano popuštanje, koronarna bolest srca, akutni infarkt miokarda te vaskularna bolest aorte, perifernih, karotidnih, cerebralnih i renalnih arterija praćena visokim pobolom i smrtnošću, neželjeni scenarij. Kako i kada zaustaviti ovakvu nepovoljnu kaskadu? Pravodobnim personaliziranim pristupom i prevencijom koja uz primarno preventivne, sociokulturološke akcije zahtijeva objektivizaciju i primjenu farmakoterapije, osobito u rizičnim skupinama.

U temeljnim, ali i kliničkim ispitivanjima za većinu događaja, napose za promjene koje nazivamo vaskularnim „starenjem", ali i u nastanku i progresiji ateroskleroze, ključnu poziciju zauzima reninsko-angiotenzinski sustav i angiotenzin II. Angiotenzin II potiče stanični rast aktivacijom čimbenika rasta, upalu, fibrozu, vazokonstrikciju podizanjem razine endotelina, oksidativni stres, odgovoran je za disfunkciju reparacijskog potencijala progenitorskih endotelnih stanica, potiče oslobađanje aldosterona te istim mehanizmom stimulira fibrozu te retenciju vode i soli.[4,5]

Većina učinaka angiotenzina II posredovana je aktivacijom AT 1 receptora.[6] Upravo je privilegij blokatora konvertirajućeg enzima (ACE inhibitora) i blokatora angiotenzinskih receptora u očuvanju endotelne funkcije, ali i u očuvanju centralnoga tlaka u aorti. Postoji niz eksprimentalnih dokaza o prevenciji metaboličkog sindroma i redukcije tjelesne težine uz primjelead to adverse side-effects, which may lead to the cessation of treatment with that medication.

Changes in the CV system that comes with aging are similar to atherosclerosis, although they differ in some important characteristics. Atherosclerosis is a systematic disease with focal, non-homogenous changes in the vascular wall, as opposed to the diffuse process that universally comes with old age. These two processes intertwine and support each other. Atherosclerosis and vascular aging are layered processes that are based on both material fatigue and genetic predispositions. The aging process is the result of cumulative episodes of oxidative stress, exposure to acute and chronic inflammatory and metabolic diseases, lifestyle choices, and a number of risk factors that cause changes in the arterial wall, elastin fragmentation, and an increase in the collagen ratio, primarily in the large blood vessels of the aortic arch and its branches. This is one of the basic events in the CV pathophysiology of aging. The aorta and the large elastic arteries of the aortic arch gradually lose the role of a vascular reservoir that attenuates the pulse wave during systolic ventricular ejection, which also causes deforming stress in small blood vessels, especially in the brain and kidneys. Changes in the stiffness of peripheral arteries correlate with the increase in pulse wave velocity and the augmentation index, leading to arterial hypertension, hypertensive heart disease, and all the well-known elements of CV scenarios with all too common fatal events such as myocardial infarction, stroke, and cardiovascular death.[2] Well-known risk factors lead to the development of atherosclerosis, which further contributes to the loss of endothelial function and associated cardiometabolic consequences. Loss of endothelial function is connected with endothelial repair, which largely depends on the potential of endothelial progenitor cells.[3] Atherosclerosis, arterial hypertension, and diabetes onset accelerate the abovementioned process of the CV continuum in which heart failure, coronary heart disease, acute myocardial infarction, and vascular diseases of the aorta as well as the peripheral, carotid, cerebral, and renal arteries, leading to high comorbidity and mortality, are an unwanted scenario. How and when to stop this unfortunate cascade? The solution is a timely personalized approach and prevention, which in addition to primarily preventive sociocultural initiatives also requires objectivization and pharmacotherapy, primarily in at-risk groups.

In both basic and clinical studies on most of these events, the rennin-angiotensin system and angiotensin II play key roles, especially in the changes we call vascular "aging" but also in the onset and progression of atherosclerosis. Angiotensin II encourages cellular growth by activating growth hormones, inflammation, fibrosis, vasoconstriction due to increased endothelin levels, and oxidative stress. It is also responsible for the dysfunction of the repair potential of endothelial progenitor cells, stimulates the release of aldosterone, and stimulates fibrosis and water and salt retention through the same mechanism.[4,5]

Most effects of angiotensin II are related to the activation of the AT1 receptor.[6] Angiotensin converting enzyme (ACE) blockers and ACE receptor blockers are crucial for preserving the endothelial function, as well as in preserving central pressure in the aorta. There is extensive experimental evi-

nu blokatora AT 1 receptora.[7,8] Značenje blokatora angiotenzin konvertirajućeg enzima i blokatora receptora angiotenzina II u liječenju arterijske hipertenzije nije upitno. Opravdana je i neizostavna primjena u liječenju srčanog popuštanja, u postinfarktnom razdobolju zbog utjecaja na remodeliranje miokarda, u prevenciji nefropatije u dijabetičara, u bolesnika s perifernom arterijskom bolešću i bolestima aorte, primjerice u Marfanovu sindromu. Primjena blokatora angiotenzin II receptora (ARB), AT 1 u liječenju Marfanova sindroma temelji se na povoljnom učinku na centralni tlak u aorti. U temeljnim istraživanjima paralelnim mjerenjem tlaka brahijalne arterije i centralnoga tlaka u aorti uz primjenu losartana i atenolola nisu utvrđene bitne razlike u vrijednostima tlaka mjerenima brahijalno, ali su vrijednost aortnoga tlaka i vrijednost reflektirajućeg vala bile mnogo niže uz primjenu losartana.[9] Udruženost arterijske hipertenzije i inzulinske rezistencije u metaboličkom sindromu, pošasti današnjega modernog čovjeka, povezana je s patofiziologijom nuklearnog hormon-receptora PPAR γ koji podešava, upravlja i modulira transkripciju gena čiji je stanični odgovor povezan s metabolizmom lipida, glukoze i vaskularnim procesima, i to prije svega produkcijom dušikova oksida (NO), razinom endotelina (ET1), aktivnošću kalcijskih kanala, ekspresijom receptora AT1, povišenom simpatoadrenalnom aktivnošću i perifernim vaskularnim otporom.[10] Visokorizične skupine, populacija dijabetičara ili bolesnika na programu kronične hemodijalize, imale su uz primjenu ACE inhibitora, a napose blokatora receptora (AT1) angiotenzina II, manji kardiovaskularni mortalitet.[11]

Telmisartan – sartan za prevenciju kardiovaskularnih bolesti

Revolucionarni pomak u KV prevenciji na početku trećeg milenija jest HOPE studija koja je ramipril na velika vrata uvela u liječenje, ali i u prevenciju KVB-a.[12]

Za razliku od blokatora konvertirajućeg enzima angiotenzina, blokatori angiotenzinskih receptora (AT1), a posebno telmisartan, ima, osim bolje podnošljivosti u usporedbi s ACE inhibitorima, i druge pleitropne, kardiometaboličke i hemodinamski povoljnije učinke, a koji nisu samo odraz antihipertenzivnoga djelovanja. Na temelju ONTARGET i TRANSCEND studije telmisartan, lijek s nizom poželjnih vaskuloprotektivnih učinaka povrh antihipertenzivnoga djelovanja, selekcioniran je u kategoriju lijeka za kardiovaskularnu prevenciju. Dokazani su učinci na pojavu hipertrofije miokarda uzrokovane arterijskom hipertenzijom te na regresiju i redukciju glomeruloskleroze.[13] Klinička primjenjivost telmisartana i u prevenciji i u liječenju usporediva je s primjenom ramiprila, uz manju učestalost nuspojava kao što su nadražajni kašalj i angioedem. U ONTARGET studiji ustrajnost bolesnika liječenih telmisartanom bila je veća od one uz ramipril u HOPE studiji. U ONTARGET studiji učinkovitost je bila komparabilna s ramiprilom uz signifikantno manje pojave nadražajnog kašlja. Telmisartan se pokazao kao lijek s boljim antihipertenzivnim učinkom u umjerenoj arterijskoj hipertenziji u usporedbi s valsartanom, losartanom, ramiprilom, perindoprilom i atenololom, kako u pogledu učinka na kontrolu arterijskoga tlaka kroz 24-satni interval, tako i zbog bolje podnošljivosti u

dence on prevention of metabolic syndrome and reduction in body weight from the application of AT1 receptor blockers.[7,8] The importance of angiotensin-converting enzyme and angiotensin II receptor blockers in the treatment of arterial hypertension is indubitable. Their use also is fully justified in the treatment of heart failure, in post-infarction periods due to the effect on cardiac remodeling, in preventing nephropathy in diabetics, in patients with peripheral arterial disease, and in diseases of the aorta, for instance Marfan syndrome. The use of angiotensin II receptor blockers (ARB), AT1 in the treatment of Marfan syndrome is based on their beneficial effect on aortic blood pressure. Studies where parallel measurement of blood pressure was performed in the brachial artery and for central aortic blood pressure with the application of losartan and atenolol showed no significant difference in brachial blood pressure values, but the central aortic blood pressure and reflecting wave values were significantly lower after the application of losartan.[9] The coexistence of arterial hypertension and insulin resistance in metabolic syndrome, the scourge of modern medicine, is related to the pathophysiology of the nuclear hormone receptor PPAR-γ which modulates and controls the transcription of genes whose cellular response is associated with lipid and glucose metabolism and vascular processes, primarily through the production of nitric oxide (NO), endothelin-1 (ET1) levels, calcium channel activity, AT1 receptor expression, elevated sympathoadrenal activity, and peripheral vascular resistance.[10] High risk populations, such as diabetics or patients on chronic hemodialysis programs, were shown to have reduced cardiovascular mortality with the use of ACE inhibitors, in particular angiotensin II (AT1) receptor blockers.[11]

Telmisartan – sartan for the prevention of cardiovascular diseases

A revolutionary development in CV prevention in the 21st century came in the form of the HOPE trial which introduced ramipril for the treatment and prevention of CVD.[12]

As opposed to angiotensin-converting enzyme inhibitors, angiotensin (AT1) receptor blockers and telmisartan in particular have other pleiotropic, cardiometabolic, and hemodynamic benefits which are not just a result of their antihypertensive effect, and are also better tolerated in comparison with ACE inhibitors. On the basis of the ONTARGET and TRANSCEND trials, telmisartan, a medication with a number of beneficial protective vascular effects over and above its antihypertensive effect, was selected for the category of medication used for cardiovascular prevention. Telmisartan was shown to have an effect on the onset of cardiac hypertrophy caused by arterial hypertension and on the regression and reduction of glomerulosclerosis.[13] The clinical applicability of telmisartan in both prevention and treatment is comparable to the application of ramipril, with a lower incidence of side-effects such as dry cough and angioedema. In the ONTARGET trial, patient compliance when treated with telmisartan was better than that of patients treated with ramipril in the HOPE trial. Effectiveness in the ONTARGET trial was comparable with ramipril, with a significantly lower incidence of dry

odnosu prema navedenim lijekovima. Nuspojave uz primjenu telmisartana bile su identične placebu. U kombinaciji s hidroklorotiazidom postignut je dobar učinak na vrijednosti arterijskoga tlaka u starijoj populaciji.[14] TRANSCEND studija u kojoj se uspoređuje primjena telmisartana u bolesnika koji ne podnose ACE inhibitore, a imaju već manifestnu KVB, hipertrofiju klijetki uz srčano popuštanje te druge čimbenice rizika kao što je dijabetes, u trajanju ispitivanja od 56 mjeseci, dokazala je redukciju KV događaja srčanog popuštanja, KV smrtnosti, infarkta miokarda ili moždanog udara. Učinak je postignut tek nakon šestomjesečnog intervala od početka primjene lijeka. U početku primjene lijeka pogoršanje dekompenzacije srca ili potreba za novom hospitalizacijom nije bila manja u usporedbi s placebom. Sve navedeno sugerira potrebu za dužom primjenom telmisartana blokatora angiotenzin-AT1 receptora do postizanja kliničkih ciljnih rezultata.[15] U usporedbi s ramiprilom godišnja stopa infarkta miokarda uz telmisartan bila je manja nego u HOPE studiji.[16] Važnost blokatora angiotenzinskih receptora u prevenciji velikih kardiovaskularnih događaja i kardiovaskularnog mortaliteta dokazana je i u visokorizičnoj populaciji bolesnika s kritičnom ishemijom udova, gdje je dokazana redukcija velikih KV događaja.[17] Povoljan učinak telmisartana u KV prevenciji u visokorizičnih vaskularnih bolesnika s novonastalom šećernom bolesti dokazana je i u kombinaciji s ramiprilom, a temelji se na selektivnoj modulaciji i parcijalnom agonizmu PPAR γ nuklearnoga hormonskog receptora potičući tako povoljan metabolizam glukoze i poboljšavajući osjetljivost na inzulin. Povoljan učinak na metabolizam lipoproteina povezan je s redukcijom i normalizacijom vrijednosti triglicerida u dijabetičara.[18] Ima povoljan učinak na endotelnu funkciju, utječe na krutost perifernih arterija i smanjuje oksidativni stres uzrokovan slobodnim masnim kiselinama.[19] Iz svega je vidljivo da blokator angiotenzin-AT1 receptora, telmisartan, utječe na većinu procesa u KV patofiziologiji od inicijalnih događaja koji uzrokuju promjenu vaskularne strukture i funkcije, ali i do povoljnih i željenih terapijskih učinaka u cjelokupnom KV kontinuumu.

Učinci poput normalizacije centralnoga tlaka aorte, liječenja arterijske hipertenzije, poticanja povoljnoga biohumoralnog odgovora i utjecaja na čimbenike rizika, upale, fibroze, dislipidemije, inzulinske rezistencije u metaboličkom sindromu, u očuvanju endotelne funkcije, arterijske krutosti, oksidativnoga stresa a potencijali su koji su ga na temelju kliničkih ispitivanja u paleti drugih blokatora angiotenzinskih receptora uz dobru podnošljivost svrstali na posebno važno mjesto, a to je kardiovaskularna prevencija.

cough. Telmisartan has been shown to have a superior antihypertensive effect in cases of moderate arterial hypertension in comparison with valsartan, losartan, ramipril, perindopril, and atenolol, both with regard to better tolerability and control of arterial blood pressure over a 24 hour interval. Side-effects under telmisartan were shown to be identical to placebo. In combination with hydrochlorothiazide it had a good effect on blood pressure in the elderly population.[14] The TRANSCEND trial looked at the application of telmisartan in patients that do not tolerate ACE inhibitors and have manifesting CVD, ventricle hypertrophy with heart failure, and other risk factors such as diabetes. Over a period of 56 months, the trial showed a reduction in heart failure, CV mortality, myocardial infarction, and stroke. The effect was detectable six months after the commencement of the treatment. At the start of the treatment, there was no reduction in the progression of cardiac decompensation or rates of hospitalization in comparison with placebo. These data indicate extended use of telmisartan angiotensin (AT1) receptor blockers until the desired clinical targets have been achieved.[15] In comparison with ramipril, the annual incidence of myocardial infarction with telmisartan was lower than in the HOPE trial.[16] The importance of angiotensin receptor blockers in the prevention of significant cardiovascular events and cardiovascular mortality has also been demonstrated in the high risk population of patients with acute limb ischemia in which a reduction in significant cardiovascular events was found.[17] A beneficial effect of telmisartan in CV prevention in at-risk vascular patients with newly developed diabetes was also found in combination with ramipril, and is based on the selective modulation and partial agonism of the nuclear hormone receptor PPAR-γ, which encourages glucose metabolism and improves insulin sensitivity. The beneficial effect on lipoprotein metabolism is also related to the reduction and normalization of triglyceride values in diabetics.[18] Telmisartan has a positive effect on endothelial function, influences the stiffness of peripheral arteries, and reduces oxidative stress caused by free fatty acids.[19] All this indicates that telmisartan, as an angiotensin (AT1) receptor blocker, influences most of the processes in CV pathophysiology, from the initial events that cause changes in vascular structure and function to beneficial therapeutic effects across the whole CV continuum.

Evidence-based effects such as central aortic blood pressure normalization, treatment of arterial hypertension, stimulation of a positive biohumoral response and effect on risk factors, inflammation, fibrosis, dyslipidemia, insulin resistance in metabolic syndrome, endothelial function, arterial stiffness, and oxidative stress, along with its good tolerability, have secured a special place for telmisartan among other angiotensin receptor blockers in cardiovascular prevention.

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