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Antagonisti angiotenzinskih receptora

Angiotensin receptor antagonists

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SAŽETAK: *Antagonisti angiotenzinskih receptora predstavljaju važnu skupinu kardiovaskularnih lijekova s dokazanom učinkovitošću u: liječenju arterijske hipertenzije, zatajivanja srca, primjeni u bolesnika nakon infarkta miokarda s disfunkcijom lijeve klijetke, prevenciji moždanog udara, kardiovaskularnoj protekciji u visokorizičnih bolesnika, prevenciji i liječenju bolesti bubrega s proteinurijim uključujući i dijabetičku nefropatiju. Zbog malog broja nuspojava omogućavaju dobru ustrajnost bolesnika u liječenju, što omogućava bolju kardiovaskularnu protekciju. Nedavna studija koja je pokazala nešto veću mogućnost izazivanja malignih bolesti u odnosu na komparabilnu terapiju nije prihvaćena od većine znanstvene zajednice i regulatornih tijela tako da se ti lijekovi i dalje mogu primjenjivati prema dosadašnjim uputama omogućavajući adekvatno liječenje i prevenciju kardiovaskularnih bolesti.*

KLJUČNE RIJEČI: *antagonisti angiotenzinskih receptora, ACE inhibitori, arterijska hipertenzija.*

SUMMARY: *Angiotensin receptor antagonists are the important group of cardiovascular drugs with proved efficiency in patients with hypertension, heart failure, after myocardial infarction with left ventricular dysfunction, stroke prevention, cardiovascular protection in high-risk patients, prevention and treatment of kidney diseases with proteinuria including diabetic nephropathy. Due to a small number of side-effects, they provide good patients' persistence in treatment which enables better cardiovascular protection. The recent study that has showed somewhat greater possibility of causing malignancy compared to comparative therapy has not been accepted by the majority of the scientific community and regulatory bodies, so that such medicines may still be applied according to the recent instructions, enabling adequate treatment and prevention of cardiovascular diseases.*

KEYWORDS: *angiotensin receptor antagonists, ACE inhibitors, hypertension*

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Opće je poznata uloga renin-angiotenzinskog sustav (RAAS) kao regulatornog mehanizma, primarno u arterijskoj hipertenziji (AH) i ravnoteži tekućina u tijelu. RAAS čini enzimski sustav koji počinje kad renin, hidrolizirajući angiotenzin, dovodi do nastajanja biološki inaktivnog dekapetida angiotenzin I (A I). Angiotenzin konvertirajući enzim (ACE) hidrolizira A I u biološki aktivni oktapeptid angiotenzin II (A II) koji predstavlja glavni čimbenik aktivnosti RAAS. Angiotenzin II je snažan vazokonstriktor koji svojim djelovanjem na remodeliranje lijeve klijetke (LK) i vaskulature te aktiviranjem ostalih neurohormonalnih agonista (noradrenalin, aldosteron i endotelin) značajno doprinosi razvoju ateroskleroze te nepoželjnom učinku na bubreg i srce u bolesnika s AH i zatajivanjem srca. Vremenom su definirani receptori za A II što je dalo mogućnost i za pronalaženje njihovih specifičnih inhibitora. Za sada su poznata četiri podtipa A II receptora: AT 1, AT 2, AT 3 i AT 4.

AT 1 receptori imaju ulogu u vazokonstrikciji, potiču otpuštanje aldosterona, endotelina i vazopresina, potiču aktivaciju simpatikusa, potiču reapsorpciju natrija u tubulima, potiču fibrozu u stijenci krvne žile i miokardu, povećavaju kontraktilnost miokarda i mogućnost nastajanja srčanih aritmija. Njihova inhibicija rezultira primarno sniženjem arterijskog tlaka (AT), ali i suprimira neželjene kemijske i strukturne promjene u stijenci krvnih žila i miokardu. Učinci stimulacije AT 2 receptora su slabije poznati. Njihovom stimulacijom postiže se antiproliferativni učinak, potiče se diferencijacija stanica te regeneracija tkiva nakon ozljede. Povećava se oslobađanje bradikinina i prostaglandina u bubregu, a moguće je postići i stanovitu vazodilataciju. Učinci AT 1 i AT 2 receptora u načelu su

Renin-angiotensin system (RAAS) as the regulation mechanism plays a pivotal role in hypertension and balance of fluids in the body. RAAS is the enzymatic system that starts when renin, hydrolyzing angiotensin causes occurrence of biologically inactive decapetide angiotensin I (A I). Angiotensin converting enzyme (ACE) hydrolyzes A I in biologically active octapeptide angiotensin II (A II) that represents the main factor of the RAAS activities. Angiotensin II is the strong vasoconstrictor that owing to its effects on remodeling of the left ventricle (LV) and vasculature as well as activation of other neurohormonal agonists (noradrenaline, aldesterone and endothelin) greatly contributes to the development of atherosclerosis and undesired effect on the kidney and heart in patients with AH and heart failure. With the time, the receptors for A II have been defined which made it possible to search for their specific inhibitors. At the moment there are four subtypes of A II receptors that are well-known for the time being: AT 1, AT 2, AT 3 and AT 4.

AT 1 receptors play a role in vasoconstriction, stimulate the release of aldesterone, endothelin and vasopressin, they stimulate the activation of simpaticus, reabsorption of sodium in tubules, fibrosis in the wall of the blood vessel and myocardium, increase contractility of myocardium and possibility of occurrence of cardiac arrhythmia. Their inhibition results primarily in lowering blood pressure (BP) and suppresses undesired chemical and structural changes in the wall of blood vessels and myocardium. The effects of the stimulation of AT 2 receptors are less known. Their stimulation results in antiproliferative effect, stimulates differentiation of cells and regeneration of tissue after injury. It increases the release of bradykinin and prostaglandin in kidney and vasodilatation may be achieved as well. The effects of AT 1 and AT 2 receptors are principally contradic-

oprečni. Blokadom AT 1 receptora i istovremenim neblokiranjem AT 2 receptora (što je učinak antagonista A II receptora) postiže se u konačnici pozitivan učinak za bolesnika, primarno sniženjem AT te sprečavanjem strukturnih promjena stijenke krvnih žila i miokarda. Uloga AT 3 i AT 4 receptora za sada je slabo poznata[1].

ACE- inhibitori su bili prva skupina lijekova kojima se djelovalo na štetne učinke A II. No oni su sprečavanjem nastanka A II (koje nije potpuno) istovremeno sprečavali i korisne učinke A II koji se ostvaruju stimulacijom AT 2 podskupine receptora (premda do sada ova hipoteza nije i klinički dokazana). Također, ACE inhibitori (primarno povećavajući nivo bradikinina) izazivaju nadražajni kašalj što ograničava njihovu primjenu. Da bi se prevladala ova ograničenja ACE inhibitora u terapijsku uporabu uključena je nova skupina lijekova antagonisti A II receptora-AT 1 podskupine (ARB). Stoga se danas ARB sve više upotrebljavaju u liječenju hipertenzije, zatajivanja srca, prevenciji cerebrovaskularnog inzulta, bolesti bubrega s proteinurijim uključujući i dijabetičku nefropatiju.

Skupina ARB predstavlja učinkovitu i dobro podnošljive lijekove za liječenje AH, što im je osiguralo važno mjesto u liječenju ove bolesti. U kliničkim studijama prevencije moždanog udara u bolesnika s hipertrofijom LK i dijabetičkom nefropatijom pokazali su se boljim od usporednih lijekova. Zbog svog dobrog sigurnosnog profila omogućavaju ustrajnost bolesnika u antihipertenzivnoj terapiji, što dovodi do bolje prevencije kardiovaskularnih komplikacija te u konačnici manjih troškova liječenja antihipertenzivima. Tako je jedna analiza liječenja AH pokazala da je najveća ustrajnost bolesnika u prvoj godini liječenja bila u onih liječenih ARB u odnosu na druge skupine antihipertenziva, a zbog nuspojava je odustalo 4% bolesnika liječenih ARB u odnosu na 8% liječenih ACE inhibitorima[2]. Stoga su uvršteni u sve smjernice antihipertenzivnog liječenja, a u Europskim smjernicama za liječenje AH (a time i hrvatskim) se preporučuju u bolesnika sa: zatajivanjem srca, nakon akutnog infarkta miokarda, atrijskom fibrilacijom, dijabetičkom nefropatijom, metaboličkim sindromom, mikroalbuminurijom, proteinurijom, hipertrofijom LK te kašljem kod primjene ACE inhibitora[3]. Kako se te indikacije uglavnom preklapaju s indikacijama odobrenim za ACE inhibitore, to osiguravateljska društva (pa tako i Hrvatski zavod za zdravstveno osiguranje) u svojim listama lijekova zbog, još uvijek, niže cijene prednost daju ACE inhibitorima, dok je uloga ARB ograničena na one bolesnike koje ne podnose ACE inhibotore, što se primarno odnosi na kašalj i angioedem. Pri tome moramo znati da kontraindikacije koje vrijede za ACE inhibitore, kao što su trudnoća i bilateralna renalna stenoza, vrijede i za ARB.

U liječenju zatajivanja srca ARB se sve više nameću kao alternativa ACE inhibitorima, primarno temeljem rezultata Val-HeFt i VALIANT studija gdje su pokazali usporedive rezultate[4,5]. Stoga se sve više nameću kao prvi izbor u liječenju tih bolesnika, a ne samo kao alternativno liječenje u onih koji imaju nuspojave na ACE inhibitore. Glavni argumenti za uporabu ARB u bolesnika sa zatajivanjem srca su: učinkovitost uz minimalne nuspojave, glavni nepoželjni učinci RAAS u bolesnika sa zatajivanjem srca nastaju stimuliranjem AT 1 receptora što ARB specifično blokiraju, nastanak angiotenzina II ide često mimo posretory. The blockade of AT 1 receptors and simultaneous non-blocking AT 2 receptors (which is an effect of antagonist A II receptor) finally results in a positive effect for a patient, primarily by lowering BP and preventing structural changes of the wall of blood vessels and myocardium. The role of AT 3 and AT 4 receptors are for the time being less known[1].

ACE inhibitors were the first group of drugs having effect on A II adverse effects. However, preventing the occurrence of A II (not complete) they simultaneously prevented even A II good effects that are achieved by stimulation of AT 2 receptor subgroup (although this hypothesis so far has not been clinically proved). ACE inhibitors (primarily by increasing the level of bradykinin) cause irritating cough which limits its application. In order to overcome these limitations of ACE inhibitors in the therapeutic use, a new group of drugs A II receptor antagonists of the AT 1 subgroup (ARB) was included. Therefore, today ARB medicines are more used in treatment of hypertension, heart failure, stroke prevention, renal diseases with proteinuria including diabetic nephropathy as well.

The ARB group represents the efficient and well tolerable antihypertensive drugs, which ensured them an important position in the treatment of this disease. In the clinical studies of prevention of the stroke in patients with LV hypertrophy and diabetic nephropathy they proved to be better than comparative drugs. Owing to their good safety profile, they enable persistence of patients in antihypertensive therapy causing better prevention of cardiovascular complications and finally reduced costs of antihypertensive treatment. So, one of the analysis of hypertension treatment showed that the greatest persistence of patients during the first year of treatment was in those treated with ARB medicines compared to the other groups of hypertensive medicines, while some 4% of patients treated with ARB medicines gave it up due to side-effects compared to 8% of those treated with ACE inhibitors[2]. Therefore, they are included in all antihypertensive treatment guidelines, and the European guidelines for the treatment of hypertension (consequently the Croatian guidelines as well) recommend them for the patients with: heart failure, after acute myocardial infarction, atrial fibrillation, diabetic nephropathy, metabolic syndrome, microalbuminuria, proteinuria, LV hypertrophy and cough when applying ACE-inhibitors[3]. Since such indications usually overlap with indications approved for ACE inhibitors, the insurance companies (the Croatian Health Insurance Institute as well) prioritize ACE inhibitors in their list of medicines due to their lower prices, while the role of ARB medicines is limited to those patients who do not tolerate ACE inhibitors, which primarily refers to cough and angioedema. We must know that side-effects applicable to ACE inhibitors, such as pregnancy and bilateral renal stenosis, are applicable to ARB medicines.

In treatment of heart failure, ARB medicines are more and more used as alternative medicines compared to ACE inhibitors, primarily based on results of Val-HeFt and VALIANT studies where they showed comparative results[4,5]. Therefore, they are more and more imposed as the first choice medicines in treatment of these patients, not only as alternative treatment in those who have ACE inhibitor side-effects. The main reasons for the application of ARB medicines in patients with heart failure are: efficacy with minimum side-effects, main undesired effects of RAAS in patients with heart failure occur by stimulating AT 1 receptor

dovanja ACE, ne djeluju na AT 2 receptore što može imati kliničku korist[6].

ARB imaju bolje dokaze iz kliničkih studija u prevenciji dijabetičke nefropatije u dijabetesu tipa 2, dok ACE inhibitori to imaju u dijabetesu tip 1. U renalnoj bolesti s proteinurijom, u bolesnika s dijabetesom ili bez njega, ARB i ACE inhibitori jednako su učinkoviti u reduciranju proteinurije. Također je u kliničkim studijama liječenja hipertenzije i zatajivanja srca zapaženo manje novonastalog dijabetesa u onih ispitanika koji su liječeni ARB u odnosu na komparativne lijekove (atenolol, amlodipin, hidroklorotijazid).

U pet kliničkih ispitivanja na 19.419 bolesnika izravno su uspoređivani ACE inhibitori i ARB u kardiovaskularnoj protekciji (uglavnom kaptopril 3x50 mg dnevno u usporedbi s losartanom 50 mg dnevno u tri studije, telmisartanom 80 mg dnevno u jednoj studiji i valsartanom 2x160 mg dnevno u jednoj studiji) te nije registrirana razlika među njima u kardiovaskularnim ishodima i ukupnoj smrtnosti. Ipak temeljem meta-analiza u kojim je pokazana nešto veća (za 4%), ali statistički neznačajna, povećana incidencija infarkta miokarda u osoba koje su upotrebljavale ARB u odnosu na ACE inhibitore, neki autori govore o "ARB paradoksu". Premda je to vjerojatno samo statistički fenomen i klinički bez značaja, ipak u ovom času ACE inhibitori imaju čvrste dokaze o kardiovaskularnoj protekciji u osoba s koronarnom bolesti i bez sistoličke disfunkcije lijeve klijetke i zatajivanja srca, dok ARB ti čvrsti dokazi još nedostaju[7]. To potvrđuju rezultati ONTARGET studije u kojoj su uspoređivani telmisartan 80 mg s ramiprilom 10 mg te njihova kombinacija u prevenciji kardiovaskularnih zbivanja u visokorizičnih bolesnika. Premda je telmisartan bolje snižavao AT od ramiprila, nije bio bolji u kardiovaskularnoj protekciji. Njihova kombinacija je imala više nuspojava, uz isti učinak, u odnosu na monoterapiju[8].

Uporaba kombinacije ACE inhibitora i ARB za sada je dokazana korisnom u liječenju zatajivanja srca i kronične bolesti bubrega s proteinurijom. Pri tome postoji povećana mogućnost nuspojava, poglavito hiperkalijemije. U liječenju zatajivanja srca dodatak valsartana ili kandersartana bolesnicima kojima se bolest ne može kontrolirati optimalnom ACE inhibicijom dovodi do boljeg ishoda, vjerojatno sprečavanjem djelovanja preostalog angiotenzina II. Također ARB (primarno kandesartan) ima smisla dati bolesnicima kojima se simptomi ne mogu optimalno kontrolirati ACE inhibitorom i beta blokatorom[9].

U kliničkoj uporabi postoji više ARB, koji su gotovo svi odobreni za uporabu u Hrvatskoj. U tekstu koji slijedi navest ćemo njihove karakteristike.

Losartan

To je prvi ARB s kliničkim studijama koje dokazuju njegovu učinkovitost u liječenju AH, dijabetičkoj nefropatiji i hipertrofiji LK. Doza mu je 25 do 100 mg. Kao i kod drugih ARB, povećanje doze je manje učinkovito u regulaciji AH, no što je dodatak male doze diuretika. Doza od 50 mg pokazala se manje učinkovitom u liječenju zatajivanja srca, dok 100 mg daje bolji učinak. Kao i kod svih ARB, puni antihipertenzivni učinak nastaje nakon 3 do 6 tjedana terapije.

that are specifically blocked by ARB medicines, the occurrence of antiotensin II frequently occurs without ACE mediation, they have no effect on AT 2 receptors which may have clinical benefit[6].

ARB have better evidence from clinical studies in prevention of diabetic nephropathy in diabetes type 2, while ACE inhibitors have it in diabetes type 1. In renal disease with proteinuria, in patients with diabetes or without it, ARB and ACE inhibitors are equally efficient in reducing proteinuria. Clinical studies of treatment of hypertension and heart failure record less newly occurred diabetes in those examinees treated with ARB compared to comparative drugs (atenolol, amlodipine, hydrochlorothiazide).

In five clinical tests including 19,419 patients, ACE inhibitors and ARB were directly compared in cardiovascular protection, (mainly captopril 3x50 mg a day compared with losartan 50 mg a day in three studies, with telmisartan 80 mg a day in one study and valsartan 2x160 mg a day in one study), and no difference was recorded among them in cardiovascular outcomes and total mortality. Anyway, based on meta-analyses that showed some greater (by 4%), but statistically insignificant, increased incidence of myocardial infarction in persons that used ARB compared to ACE inhibitors, some authors speak about "ARB paradox". Although it may be only a statistical phenomena and clinically unimportant, anyway at the moment, ACE inhibitors have stronger evidence for cardiovascular protection in persons with coronary heart disease and without systolic LV dysfunction and heart failure, while such strong evidence for ARB is still missing[7]. It is confirmed by the results of the ONTARGET study in which telmisartan 80 mg was compared with ramipril 10 mg and their combination in prevention of cardiovascular events in high-risk patients. Although telmisartan was better to lower BP than ramipril, it was not better in cardiovascular protection. Their combination showed a greater number of side-effects with the same effect in comparison with monotherapy[8].

The use of the combination of ACE and ARB has been so far proved to be beneficial in the treatment of heart failure and chronic kidney disease with proteinuria. However, there is an increased possibility of side-effects, especially of hyperkaliemia. In treatment of heart failure, an addition of valsartan or candersartan to patients whose disease may not be controlled by optimum ACE inhibition, leads to a better outcome, probably by preventing the effect of the remaining angiotensin II. ARB (primarily candesartan) are also to be given to patients whose symptoms may not be optimally controlled by ACE inhibitor and beta blocker[9].

In clinical use there are several ARB medicines, whereas almost all of them are approved for the use in Croatia. In the text that follows, we shall name some of their characteristics.

Losartan

This is the first ARB with clinical studies that prove its efficacy in treatment of hypertension, diabetic nephropathy and LV hypertrophy. Its dose is 25 to 100 mg. The same as in other ARB, the increase in dose is less efficient in regulation of hypertension, compared to the addition of a small dose of diuretics. The dose of 50 mg has proved to be less efficient in treatment of heart failure, while 100 mg provides a better effect. The same as in all ARB, a full antihypertensive effect occurs after 3 to 6 weeks of therapy.

Kandesartan

Primjenjuje se kao predlijek kandesartancileksetil koji se tijekom apsorpcije u probavnom sustavu hidrolizira u djelatnu tvar kandesartan. Indikacije su mu liječenje AH i zatajivanja srca, a primjenjuje se u dozama od 4 do 32 mg. U CHARM-Added studiji se pokazao učinkovit kao dodatna terapija bolesnicima sa zatajivanjem srca koji su već liječeni ACE inhibitorom i beta-blokatorom[10].

Valsartan

Primjenjuje se u dozama od 80 do 320 mg u indikacijama AH, zatajivanja srca kada se ne mogu primjeniti ACE inhibitori ili beta blokatori (ne u trojnoj terapiji) te nakon infarkta miokarda u bolesnika s disfunkcijom LK ili znakovima zatajivanja srca. Ovo je dokazano u dvije velike studije Val-HeFT i VALIANT. Bolesnici liječeni valsartanom u Val-HeFT studiji pokazali su signifikantno poboljšanje NYHA stupnja, kao i znakova i simptoma zatajivanja srca uključujući zaduhu, umor, edeme i hropce, u usporedbi s placebom. Bolesnici na valsartanu imali su bolju kvalitetu života nego bolesnici na placebu, što se pokazalo tijekom liječenja i promjenom rezultata ljestvice Minnesota Living with Heart Failure Quality of Life u odnosu na polazne vrijednosti. Udarni volumen u bolesnika liječenih valsartanom porastao je signifikantno, a LVIDD se značajno smanjio prema polaznoj vrijednosti u usporedbi s placebom[4]. U VALIANT studiji je dokazano da je valsartan jednako učinkovit kao i ACE-inhibitor kaptopril u smanjenu mortaliteta i kardiovaskularnog pobola u visokorizičnih bolesnika nakon akutnog infarkta miokarda[5].

Telmisartan

Ima vrlo dugo vrijeme poluživota u plazmi od 24 sata[11]. Pogodan je za liječenje AH što mu je i jedina indikacija. Primjenjuje se u dozama od 40 do 80 mg. U ONTARGET studiji se pokazao jednako učinkovit ramiprilu u kardiovaskularnoj protekciji kod visokorizičnih bolesnika[8].

Irbesartan

Indiciran je za liječenje AH i nefropatije u bolesnika s dijabetesom tipa 2. Primjenjuje se u dozama od 150 do 300 mg. Nema aktivnih metabolita, a poluživot u plazmi mu je 11 do 15 sati. U kliničkom ispitivanju IRMA2 u dijabetičara je prevenirao progresiju nefropatije[12].

Eprosartan

Indiciran je za liječenje AH u dozi od 600 mg, jednom dnevno. U kliničkom ispitivanju MOSES bio je bolji od kalcijskog antagonista nitrendipina u sekundarnoj prevenciji cerebrovaskularnog inzulta[13].

ARB i kancerogenost

U lipnju ove godine veliku pozornost je izazvala meta-analiza objavljena u časopisu *Lancet Oncology* prema kojoj bolesnici liječeni ARB imaju veću šansu oboljeti od kar-

Candesartan

Pre-drug is applied as candesartan cilexetil that is during the absorption in the digestive system hydrolyzed into active substance candesartan. The indications are the treatment of hypertension and heart failure, and it is applied in doses from 4 to 32 mg. In the CHARM-Added study it has already proved to be efficient as additional therapy to patients with heart failure that had already been treated with ACE inhibitor and beta-blocker[10].

Valsartan

It is applied in doses from 80 to 320 mg in indications of hypertension, heart failure when ACE inhibitors or beta blockers may not be applied (not in triple therapy) and following the myocardial infarction in patients with LV dysfunction or signs of heart failure. This has been proved in the two large studies Val-HeFT and VALIANT. The patients treated with valsartan in the Val-HeFT study showed more significant improvement of the NYHA scale and the symptoms of heart failure including dyspnoea, fatigue, edema and rattles in comparison with placebo. The patients using valsartan had better quality of life than the patients using placebo, which proved to be true during treatment and with a change to results of the scale Minnesota Living with Heart Failure Quality of Life in comparison with initial values. The impact volume in patients treated with valsartan has significantly increased, while LVIDD has greatly reduced to the initial value in comparison with placebo[4]. In the VALIANT study, valsartan has proved to be equally efficient as the ACE inhibitor captopril in reducing mortality and cardiovascular diseases in high-risk patients following acute myocardial infarction[5].

Telmisartan

It has a very long time of half-life of 24 hours[11]. It is suitable for the treatment of hypertension which is its only indication. It is applied in doses from 40 to 80 mg. In the ONTARGET study it has proved to be as efficient as ramipril in the cardiovascular protection in high-risk patients[8].

Irbesartan

It is indicated for the treatment of hypertension and nephropathy in patients with diabetes type 2. It is applied in doses from 150 to 300 mg. There are no active metabolites, while plasma half-life is 11 to 15 hours. In the clinical study IRMA2 in diabetic patients, it prevented progression of nephropathy[12].

Eprosartan

It is indicated for the treatment of hypertension in dose of 600 mg once a day. In the clinical test MOSES it was better than the calcium antagonist nitrendipine in the secondary prevention of stroke[13].

ARB medicines and carcinogenicity

In June this year, great attention was drawn by meta-analysis published in the journal *Lancet Oncology* according to which patients treated with ARB have a greater

cinoma nego oni liječeni placebom. Prema rezultatima pet randomiziranih kliničkih ispitivanja u kojima je sudjelovalo 62.000 bolesnika nađeno je da oni koji su uzimali ARB (85% telmisartan) imaju veći rizik za oboljevanje od karcinoma u odnosu na kontrolnu skupinu (7,2% : 6,0%). Pri tome je samo značajan bio rizik od novonastalog karcinoma pluća. Prema autorima 1 od 143 bolesnika koji će tijekom četiri godine biti liječeni ARB zbog toga će dobiti karcinom. Autori članka su rizik nastanka karcinoma ocjenili umjerenim, a mehanizam nastanka nepoznatim. Također su naglasili da se rizik ne može povezati sa pojedinim ARB, već se odnosi na skupinu[14]. Ipak i pored opreznog stava autora rada, u medijima su odmah objavljeni bombastični naslovi npr. "Lijekovi za visoki tlak mogu izazvati rak" ili " Lijekovi za visoki tlak izazivaju rak", srećom s komentarima naših uglednih stručnjaka (prof. Francetić, prof. Polić) koji su apelirali na stišavanje panike te obrazložili moguće slabosti studije, ali i značenje učinkovite terapije AH koja se postiže primjenom ARB. Iste stavove je imala i većina eksperata koji su se javili na tu temu u vodećim medicinskim publikacijama, a neki su bili toliko radikalni da su čak izjavili da se radi o smetlarskoj znanosti ("junk science").

Također se priopćenjem oglasila i FDA (Američka agencija za lijekove) koja je izjavila da temeljem njihovih podataka korist od primjene ARB daleko prelazi moguće nuspojave[15]. Stavovi koji dovode u pitanje rezultate studije navode da autori nisu raspolagali s izvornom studijskom dokumentacijom već samo zbirnim podacima iz publikacija, da su bolesnici koji su primali ARB bili uglavnom oni koji nisu mogli uzimati ACE inhibitore zbog kašlja, a da je to možda bio prvi znak plućnog maligniteta (jedini tumor statistički značajniji u bolesnika koji su rabili ARB), također da nisu uzeti u obzir ostali čimbenici koji doprinose malignitetu, npr. pušenje, izloženost azbestu itd. Na kraju je većina autora zaključila da je korist od uzimanja ARB daleko veća od moguće štete te da bolesnici mogu sa sigurnošću nastaviti uzimati ovu terapiju.

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chance to become ill of carcinoma than those treated with placebo. According to the results of five randomized clinical tests in which 62,000 patients participated, it was found out that those taking ARB (85% telmisartan) show a greater risk of becoming ill of carcinoma in comparison to the control group (7.2% : 6.0%). Then, it was only the risk of newly occurred pulmonary carcinoma that mattered. According to the authors, 1 out of 143 patients treated with ARB will become of carcinoma. The authors of the article evaluated the risk of occurrence of carcinoma as moderate and the mechanism of occurrence as unknown. They also emphasized that the risk may not be linked with a specific ARB, but it refers to the group[14]. Even though the authors carefully put forward their attitude, the media publicized some bombastic headings, such as: "Hypertension medicines may cause cancer" or " Hypertension medicines cause cancer", luckily along with the comments of our renowned experts (Prof. Francetić, Prof. Polić) who called for avoiding panic and explained potential weaknesses of the study and who also explained the importance of the efficient therapy of hypertension that is achieved by application of ARB. Most of the experts who referred to this topic in the leading international medical journals shared the same opinion, but some of them were so radical to declare that it was "junk science".

FDA (Federal Drug Administration) also stated its opinion by making a statement that based on the data they have available, the benefits from the application of ARB are far greater than any potential side-effects[15]. The attitudes making the results of the study doubtful imply that the authors did not have the original study documentation available, but only collective data from publications, that patients who took ARB medicines were only those who could not take ACE inhibitors as a consequence of cough, and that it was the first sign of the pulmonary malignity (the only tumor statistically more significant in patients who used ARB), some other factors that contribute to malignity, such as smoking, exposure to asbestos etc. were not taken into consideration. Eventually, most of the authors concluded that the benefit of taking ARB medicine largely exceeds any potential damage, so patients may safely continue to apply this therapy.

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