Procjena rizika od nastanka karcinoma povezanog s primjenom antihipertenziva

Risk assessment for cancer development associated with the use of antihypertensives

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SAŽETAK: Brojna su klinička istraživanja ispitivala mogući karcinogeni učinak anihipertenzivnih lijekova. Istraživan je njihov učinak na nastanak karcinoma prostate, kože, dojke, bubrega i pluća. Dokazano je da ukupni rizik od nastanka karcinoma pri uporabi svih antihipertenziva nije povišen. Za pojedine skupine karcinoma dokazano je smanjenje rizika od nastanka maligne bolesti uz uporabu antihipertenzivne terapije. Dobivene su vrijednosti jednake pri dugotrajnoj uporabi lijekova (> 7,5 godina); s duljinom primjene terapije ne dolazi do očekivanog porasta rizika, dok se u nekim istraživanjima vrijednost relativnog rizika s duljinom uporabe antihipertenziva smanjuje. Nijedna skupina antihipertenziva nije bila vezana s povišenim relativnim rizikom od nastanka karcinoma prostate, štoviše, uporaba beta-blokatora i dugogodišnja uporaba alfa-blokatora imala je protektivan učinak. Agencija za lijekove i medicinske proizvode i Europska agencija za lijekove obavještavaju o povišenom riziku od nastanka nemelanomskog raka kože uz uporabu hidroklorotiazida. Hrvatsko društvo za hipertenziju preporučuje razmotriti u kliničkoj praksi omjer koristi i rizika terapije hidroklorotiazidom, adekvatno informirati pacijenta te zajedno s njim donijeti odluku o daljnjoj uporabi hidroklorotiazida u terapiji. Relativni rizik za nastanak karcinoma dojke pri uporabi blokatora kalcijskih kanala, ali i drugih antihipertenziva nije bio povišen, vrijednosti su bile jednake onima u kontrolnim skupinama. Vjerojatnije je da je rizik od nastanka karcinoma bubrega vezan za samu patogenezu arterijske hipertenzije, a ne uz uporabu diuretske terapije. Zaključno, osim dokazane povezanosti uporabe hidroklorotiazida s nastankom nemelanomskog raka kože, valjanih dokaza za moguću karcinogenost drugih antihipertenziva još nema pa stoga preporučujemo u kliničkoj praksi nastaviti slijediti postojeće smjernice za liječenje arterijske hipertenzije uz reevaluaciju odluke o terapiji hidroklorotizadom u skladu s preporukama Hrvatskoga društva za hipertenziju.

SUMMARY: Numerous clinical trials have evaluated the potential cancerogenic effect of antihypertensive medications. Their influence on the development of prostate, skin, breast, kidney, and lung cancer has been examined. It was demonstrated that using antihypertensives does not elevate the total risk for cancer development. For some cancer groups there was even a reduction in risk of the development of malignant diseases under antihypertensive therapy. The results were the same in long-term use of the medications (>7.5 years), and longer application of the treatment did not lead to the expected increase in risk, with some studies finding a reduction in relative risk values with longer use of antihypertensives. No group of antihypertensives was associated with increased relative risk for the development of prostate cancer, and the use of beta-blockers and long-term use of alfa-blockers even had a protective effect. HALMED and the European Medicines Agency reported increased risk for the development of non-melanoma skin cancer with the use of hydrochlorothiazide. The Croatian Society of Hypertension recommends evaluating of the risk-benefit ratio of hydrochlorothiazide therapy in clinical practice, adequately informing the patient, and then deciding on the further use of hydrochlorothiazide in therapy together with the patient. The relative risk of breast cancer development was not increased due to the use of calcium channel blockers or other hypertensives, and the values did not differ from the control groups. It is more likely that the risk of kidney cancer development is associated with the pathogenesis of arterial hypertension rather than the use of diuretic therapy. In conclusion, apart from the demonstrated association between the use of hydrochlorothiazide and the development of non-melanoma skin cancer, there is still no valid evidence for the possible cancerogenic effect of other antihypertensives; in clinical practice we therefore recommend continuing to follow current guidelines for the treatment of arterial hypertension with a reevaluation of the use of hydrochlorothiazide therapy as recommended by the Croatian Society of Hypertension.

KLJUČNE RIJEČI: antihipertenzivi, karcinom, hidroklorotiazid.

KEYWORDS: antihypertensives, carcinoma, hydrochlorothiazide.

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Uvod

Arterijska hipertenzija, kao jedan od vodećih čimbenika rizika za nastanak kardiovaskularnih bolesti, danas se uspješno regulira antihipertenzivnom terapijom. Uz zadovoljavajuće vrijednosti arterijskoga tlaka (AT) navedeni rizik od nastanka kardiovaskularnih i cerebrovaskularnih incidenata znatno se smanjuje. Danas je u uporabi više skupina antihipertenzivnih lijekova: ACE inhibitori, blokatori angiotenzinskih receptora (ARB), blokatori kalcijskih kanala, beta-blokatori, diuretici i alfa-blokatori. Dok su pojedinim bolesnicima vrijednosti AT-a uredno regulirane uz monoterapiju, većina će biti liječena nekom od danas poznatih kombinacija antihipertenziva, dvojnom ili trojnom antihipertenzivnom terapijom, primjerice ACE inhibitor / kalcijski blokator, ACE inhibitor / diuretik tiazidne skupine, ARB / diuretik tiazidne skupine, ACE inhibitor / diuretik tiazidne skupine / blokator kalcijskih kanala. Sve skupine lijekova imaju određenu učestalost nuspojava: od neuroloških smetnji, gastrointestinalnih tegoba, kašlja, elektrolitskog disbalansa (kalija) i slično.

Posljednjih su nekoliko godina provođena istraživanja rizika od nastanka malignih bolesti vezanog za primjenu svih skupina antihipertenziva. Najveći je broj istraživanja rađen za ACE inhibitore i blokatore angiotenzinskih receptora, zatim za blokatore kalcijskih kanala, beta-blokatore, diuretike te alfa-blokatore. Većina će bolesnika, ovisno o trenutku postavljanja dijagnoze, antihipertenzivnu terapiju uzimati od nekoliko godina do nekoliko desetljeća pa su stoga u mnogim istraživanjima bolesnici praćeni tijekom duljeg razdoblja, što donosi vjerodostojnije rezultate i o mogućoj kasnoj pojavnosti nuspojava lijeka.

Procjena ukupnog rizika od nastanka karcinoma povezanog s primjenom antihipertenziva

Ukupni rizik od nastanka zloćudnih bolesti pri uporabi antihipertenziva prikazan je u idućim istraživanjima. Metaanalizom 70 randomiziranih kontrolnih istraživanja i 148 kontrolnih grupa potvrđeno je da nema razlike u riziku od nastanka karcinoma kod ARB-ova (proporcija 2,04 %; OR 1,01, 95 % CI 0,93 – 1,09), ACE inhibitora (2,03 %; 1,00, 0,92 – 1,09), beta-blokatora (1,97 %; 0,97, 0,88 – 1,07), blokatora kalcijskih kanala (2,11 %; 1,05, 0,96 – 1,13), diuretika (2,02 %; 1,00, 0,90 –1,11), drugih kontrola (1,95 %, 0,97, 0,74 – 1,24) u odnosu prema placebu (2,02 %), RR 5 – 10 %.[1] Uporabom podataka iz *Longitudinal Health Insurance Database 2000* napravljeno je kohortno istraživanje u 24 238 ispitanika u kojih je istraživan relativni rizik za nastanak karcinoma pri uporabi propranolola. Rezultati istraživanja ne upućuju na postojanje povišenoga relativnog rizika, štoviše, ukupni je rizik snižen (HR: 0,75; 95 % CI: 0,67 – 0,85; P < 0,001), dodatno uz znatno snižen rizik od nastanka pojedinih vrsta karcinoma, primjerice, karcinoma glave i vrata (HR: 0,58; 95 % CI: 0,35 – 0,95), karcinoma probavnoga trakta; jednjaka (HR: 0,35; 95 % CI: 0,13 – 0,96), želudca (HR: 0,54; 95 % CI: 0,30 – 0,98), kolona (HR: 0,68; 95 % CI: 0,49 –0,93) i karcinoma prostate (HR: 0,52; 95 % CI: 0,33 – 0,83).[2] Podatcima dobivenima iz *General Practice Research Database* (UK) provedeno je *nested case-control* istraživanje kojim je dokazano da dugotrajna uporaba antihipertenziva (> 7,5 god.) nije bila vezana s razvojem maligne bolesti.[3] Istraživanjem dviju grupa bolesnika, onih liječenih kombiniranom antihipertenzivnom terapijom

Introduction

Arterial hypertension, as one of the leading risk factors for the development of cardiovascular diseases, can now be successfully regulated by antihypertensive therapy. The risk of cardiovascular and cerebrovascular events is significantly reduced at satisfactory arterial pressure (AP) values. Multiple groups of antihypertensive medications are in use today: ACE inhibitors, beta-blockers, diuretics, and alpha-blockers. While some patients achieve AP regulation with monotherapy, most will be treated with one of the now well-known antihypertensive combination treatments, i.e. dual or triple antihypertensive therapy such as ACE inhibitor/calcium blocker, ACE inhibitor/thiazide diuretic, ARB/thiazide diuretic, ACE inhibitor/thiazide diuretic/calcium channel blocker. All these groups of medications have a chance of resulting in side-effects ranging from neurological disturbances, gastrointestinal issues, coughing, electrolyte imbalance (potassium), and so on.

Over the last few years, several studies have been conducted on the risk of malignant diseases associated with the application of all groups of antihypertensives. The greatest number of studies examined ACE inhibitors and angiotensin receptor blockers, followed by calcium channel blockers, beta-blockers, diuretics, and alpha-blockers. Most patients, depending on the timing of the diagnosis, will be receiving antihypertensive therapy for several years to several decades, so many studies followed patients over a longer period of time, which makes the results more reliable and allows detection of medication side-effects that manifest later.

Assessing total cancer risk associated with use of antihypertensives

The total risk for the development of malignant diseases with antihypertensive use was examined in the studies described below. A meta-analysis performed on 70 randomized control studies and 148 control groups confirmed that there was no difference in cancer development with ARBs (proportion 2.04%; OR 1.01, 95% CI 0.93-1.09), ACE inhibitors (2.03%; 1.00, 0.92-1.09), beta-blockers (1.97%; 0.97, 0.88-1.07), calcium channel blockers (2.11%; 1.05, 0.96-1.13), diuretics (2.02%; 1.00, 0.90-1.11), and other controls (1.95%, 0.97, 0.74-1.24) in comparison with placebo (2.02%), RR 5-10%.[1] Using data from the *Longitudinal Health Insurance Database 2000*, a cohort study was performed on 24 238 participants that examined the relative risk for cancer development with propranolol use. The results of the study do not indicate an increase in risk, but rather found a reduction in total risk (HR: 0.75; 95% CI: 0.67-0.85; P<0.001) with an additional significant reduction in risk of the development of individual types of cancer, for instance: head and neck cancer (HR: 0.58; 95% CI: 0.35-0.95), digestive track cancer and esophageal cancer (HR: 0.35; 95% CI: 0.13-0.96), stomach cancer (HR: 0.54; 95% CI: 0.30–0.98), colon cancer (HR: 0.68; 95% CI: 0.49–0.93), and prostate cancer (HR: 0.52; 95% CI: 0.33–0.83).[2] Data from the *General Practice Research Database*, UK, were used for a nested case-control study that demonstrated long-term use of antihypertensive (>7.5 years) was not associated with development of malignant diseases.[3] Assessment of two groups of patients, those treated with combined antihypertensive therapy with ACE inhibitors and calcium channel blockers compared with a group of patients treated with beta-blockers, found mildly elevated relative risk

ACE inhibitorima i blokatorima kalcijskih kanala u usporedbi s grupom pacijenata liječenih beta-blokatorima procijenjen je blago povišen relativni rizik za nastanak svih vrsta karcinoma od 1,27 (95 %, CI: 0,98 – 1,63) u skupini bolesnika liječenih blokatorima kalcijskih kanala i ACE inhibitorima s obzirom na snižen relativni rizik za nastanak karcinoma od 0,79 (0,58 – 1,06) u skupini liječenih beta-blokatorima. Blago povišeni relativni rizik za nastanak karcinoma u prvoj skupini može se opovrgnuti samom činjenicom da se, gledano kroz dulje razdoblje, relativni rizik uz uporabu terapije kalcijskim blokatorom nije očekivano povećavao, nego je, naprotiv, linearno padala vrijednost relativnog rizika s vremenom uzimanja terapije (RR za blokatore kalcijskih kanala 1 god. /1,46/, 1 – 3 god. /1,26/ i 4 god. i više /1,23/).[4] Prikazom kohortnog istraživanja (*General Practice Research Database*, UK) na velikome broju ispitanika, 377 649 (primjenjivani Coxovi modeli prilagodbe), koji su bili liječeni ARB-om ili ACE inhibitorima unatrag godinu dana procjenjivani relativni rizik za nastanak karcinoma uz uporabu ARB-ova nije bio povišen (HR 1,03, 95 %, Cl: 0,99 do 1,06, P = 0,10), štoviše, otkriven je sniženi rizik za nastanak karcinoma pluća (0,84, 0,75 do 0,94), dok učinka na nastanak karcinoma kolona nije bilo (1,02, 0,91 do 1,16), nešto povišeni rizik za nastanak karcinoma prostate i dojke (1,11, 1,01 – 1,21, P = 0,02; i 1,10, 1,00 – 1,20, P = 0,04), može se tumačiti time da je to zapravo nizak rizik u apsolutnoj procjeni (0,5 i 1,1 na 1000 osoba godišnje) te činjenicom da se u ovom istraživanju odnosilo na skupinu visokorizičnih bolesnika.[5]

Procjena rizika od nastanka karcinoma prostate povezanog s primjenom antihipertenziva

Ukupni relativni rizik od nastanka karcinoma prostate uporabom svih antihipertenzivnih skupina lijekova, procijenjen u kanadskom istraživanju u 2221 oboljelog s karcinomom i u 11 105 kontrolnih ispitanika, nije bio povišen: 0,98 (CI: 0,88 – 1,08). Uz uporabu beta-blokatora RR je bio je reduciran (OR = 0,86, Cl: 0,77 – 0,96), a s duljinom primjene lijeka rizik se nije povećavao: < 1 god. RR 0,89 (0,75 – 1,05), 1 – 4 god. RR 0,91 (0,75 – 1,09), > 4 god. RR 0,82 (0,69 – 0,96). Beta-blokatori i dugogodišnja uporaba alfa-blokatora mogu imati preventivni učinak na nastanak malignih bolesti, dok uporaba blokatora kalcijskih kanala i ACE inhibitora nema utjecaja na karcinom prostate.[6] Istraživanjem svakoga pojedinog anthipertenziva skupine ACE inhibitora povezanost s rizikom od nastanka karcinoma prostate ni za jedan od njih nije dokazana, štoviše, uz uporabu kaptoprila dokazan je sniženi rizik od nastanka malignosti: 0,7 (95 % CI: 0,4 – 1,2).[7] Metaanalizom provedenom na velikome broju ispitanika (20 267 bolesnika, uključujući 6 kohortnih istraživanja i 3 *nested case-control* istraživanja) na trima kontinentima, dokazan je protektivan učinak RAS inhibitora na karcinom prostate. Relativni rizik od nastanka karcinoma prostate manji je od 1, odnosno relativnog rizika nije bilo ni u jednom uključenom istraživanju.[8]

Procjena rizika od nastanka karcinoma kože povezanog s primjenom antihipertenziva

Dana 17. listopada 2018. Agencija za lijekove i medicinske proizvode (HALMED) i Europska agencija za lijekove (EMA) objavile su upozorenje o povećanom riziku za nemelanomski rak kože (NMSC; karcinom bazalnih stanica, karcinom pločastih stanica) – 1.27 (95% CI 0.98–1.63) – in the group of patients treated with calcium channel blockers and ACE inhibitors in comparison with a reduced relative risk for cancer development– 0.79 (0.58–1.06) – in the group treated with beta-blockers. Mildly elevated relative risk for cancer development in the first group can be refuted by the fact that the relative risk with use of calcium blockers did not rise as expected over a longer period of time; on the contrary, the relative risk value was reduced with extended application of the therapy (RR for calcium channel blockers at 1 year (1.46), at 1-3 years (1.26), and 4 years or more (1.23).[4] A cohort study (*General Practice Research Database*, UK) on a large number of participants, 377 649 (using the Cox model for adjustment), who were treated with ARBs or ACE inhibitors within the last year found no increase in their relative risk for cancer development with the use of ARBs (HR 1.03, 95% Cl 0.99 do 1.06, P=0.10); in fact, a reduction of risk was observed for the development of lung cancer (0.84, 0.75 to 0.94), while there was no effect on the development of colon cancer (1.02, 0.91 to 1.16) and somewhat elevated risk for the development of prostate and breast cancer (1.11, 1.01-1.21, P=0.02; and 1.10, 1.00-1.20, P=0.04), which can be interpreted as being risk that is actually low in absolute assessment (0.5 and 1.1 per 1000 persons annually) and given that this study examined a group of high-risk patients.[5]

Assessing risk for the development of prostate cancer associated with the use of antihypertensives

Total relative risk for the development of prostate cancer with the use of all groups of antihypertensive medications was assessed in a Canadian study with 2 221 cases of cancer and 11 105 controls and was not found to be elevated; 0.98 (CI, 0.88-1.08). RR was reduced with the use of beta-blockers (OR= 0.86, Cl 0.77-0.96), and risk did not increase with extended use of the medication: <1 year RR 0.89 (0.75-1.05), 1-4 years RR 0.91 (0.75-1.09), >4 years RR 0.82 (0.69-0.96). Beta-blockers and long-term use of alfa-blockers can have a preventive effect on the development of malignant diseases, whereas the use of calcium channel blockers and ACE inhibitors has no effect on prostate carcinoma.[6] Assessment of each individual antihypertensive in the ACE inhibitor group did not find an association with risk of prostate cancer for any of the medications, and the use of captopril was actually demonstrated to reduce risk for the development of malignancies: 0.7 (95% CI: 0.4-1.2).[7] A meta-analysis performed on a large number of participants, 20 267 patients including 6 cohort studies and 3 nested case-control studies on three continents, demonstrated a protective effect of RAS inhibitors for prostate cancer. The relative risk for the development of prostate cancer was less than 1, i.e. there was no relative risk in any of the included studies.[8]

Risk assessment for the development of skin cancer associated with the use of antihypertensives

On October 17, 2018, the Agency for Medicinal Products and Medical Devices of Croatia (HALMED) and the European Medicines Agency (EMA) published a warning on increased risk for non-melanoma skin cancer (NMSC; basal cell carci-

stih stanica) vezanom za uporabu hidroklorotiazida pri višim dozama lijeka (12,5 mg). Njihove preporuke za bolesnike koji uzimaju hidroklorotiazid u terapiji uključuju: adekvatno informiranje bolesnika o mogućem riziku od nemelanomskog raka kože (NMSC-a), savjete o poduzimanju redovitih dermatoloških pregleda, eventualne histološke pretrage, pregled suspektnih kožnih lezija te upozorenje o ograničenju i zaštiti od izlaganja Sunčevoj svjetlosti i UV zrakama. Preporuka za preispitivanje indikacije za uvođenje hidroklorotiazida u terapiju dana je samo za skupinu bolesnika s prije preboljenim kožnim malignitetom.

Dvanaestog prosinca 2018. Hrvatsko društvo za hipertenziju objavljuje stajalište o opaženom povećanom riziku za nemelanomske karcinome kože povezanom s liječenjem hidroklorotiazidom koje kaže da je rizik od nemelanomskog karcinoma kože i usnica veći u bolesnika liječenih tim lijekom nego u neliječenih tim lijekom, veći je također u starijih bolesnika, rizik se povećava s duljinom trajanja liječenja, a mehanizam karcinogenosti temeljen je na fotosenzitivnosti. U kliničkoj bi praksi trebalo razmotriti omjer između koristi i rizika od primjene hidroklorotiazida, bolesnike je potrebno informirati o postojećem riziku i o alternativnoj terapiji te se u dogovoru s bolesnikom odlučiti o nastavku ili prekidu terapije. Ako se odluči za nastavak terapije, potrebno je preporučiti pacijentima primjenu adekvatne fotoprotekcije i redovitu provjeru pojava ili promjena na koži.[9]

Procjena rizika od nastanka karcinoma dojke povezanog s primjenom antihipertenziva

Uporabom podataka iz *Taiwan National Health Insurance Research Database* na velikom uzorku ispitanika (330 699 pacijenata) dokazano je da uporaba neselektivnih beta-blokatora, selektivnih i neselektivnih alfa-blokatora, ACE inhibitora i angiotenzin II antagonista nije vezana s rizikom od nastanka karcinoma dojke, dok je uporaba blokatora kalcijskih kanala vezana s minimalnim rizikom (OR 1,09; 95 % CI: 1,03 – 1,16).[10] U dvama američkim kohortnim istraživanjima provedenima na uzroku od 210 641 žene (*U.S. Nurses' Health Study* /NHS 1988. – 2012./ i *Nurses' Health Study II* /NHS II 1989. – 2011./) uz uporabu multivarijabilnih hazard modela (primijenjena Coxova modifikacija) istražen je utjecaj diuretika, beta-blokatora, blokatora kalcijskih kanala i ACE inhibitora na rizik od nastanak karcinoma dojke. U 10 012 slučajeva invazivnog karcinoma dojke (6718 slučajeva u NHS i 3294 slučaja u NHS II) trenutačna uporaba nijednog antihipertenziva nije bila vezana za rizik od nastanka karcinoma dojke u usporedbi s kontrolnim skupinama: NHS (RR = 1,00, 95 % CI = 0,95 – 1,06) i NHS II (RR = 0,94, 95 % CI = 0,86 – 1,03). Rezultati su jednaki za dugotrajnu uporabu antihipertenziva.[11] U britanskom kohortnom istraživanju uspoređivane su tri skupine bolesnika: prva skupina na terapiji kalcijskim blokatorom (150 750), druga skupina bila je na terapiji drugim antihipertenzivom (557 931), dok je treća skupina bila na kombiniranoj antihipertenzivnoj terapiji, uključujući kalcijski blokator (156 966 bolesnika). Dobivenim rezultatima vrijednosti relativnog rizika za nastanak karcinoma nisu znatno povišene; RR 0,88 (0,86 – 0,89) i 1,01 (0,98 – 1,04). HR za nastanak karcinoma prostate, dojke, kolona uz primjenu blokatora kalcijskih kanala nije bio znatno povišen ni za jednu skupinu karcinoma; HR 0,95 (0,87 do 1,04), 1,07 (0,98 do 1,16) i 0,89 (0,81 do 0,98).[12]

noma, squamous cell carcinoma) associated with the use of hydrochlorothiazide at higher doses of the medication (12.5 mg). Their recommendations for patients taking hydrochlorothiazide in their treatment include: adequately informing the patient on the potential risk of NMSC, recommending regular dermatologic examinations, potentially performing histological tests for suspect skin lesions, and a warning on limiting and protecting against exposure to the sun and UV rays. A recommendation to reexamine the indication for introducing hydrochlorothiazide to the treatment was given only for the group of patients with previous skin malignancies.

On December 12, 2018, the Statement of the Croatian Society of Hypertension on the observed increased risk of NMSC associated with the use of hydrochlorothiazide in treatment was that the risk of non-melanoma skin and lip cancer was higher in patients treated with this medication than in those that were not treated with it, was higher in older patients, that risk increased with duration of treatment, and that the mechanism of carcinogenesis was based on photosensitivity. In clinical practice they recommended reassessing the risk-benefit ratio, adequately informing the patient on the existing risk and alternative treatments, and making a decision in consultation with the patient on whether to terminate or continue the treatment; if the treatment is continued, use of adequate sun protection and regular checkups of skin changes should be recommended to the patient.[9]

Risk assessment for the development of breast cancer associated with the use of antihypertensives

Using data from the *Taiwan National Health Insurance Research Database* and a large sample of 330 699 patients, it was shown that the use of non-selective beta-blockers, selective and non-selective alpha-blockers, ACE inhibitors, and angiotensin II antagonists was not associated with risk of developing breast cancer, whereas the use of calcium channel blockers was associated with minimal risk (OR 1.09; 95% CI 1.03-1.16).[10] Two American cohort studies on a sample of 210 641 women, the *U.S. Nurses' Health Study* (NHS 1988-2012) and *Nurses' Health Study II* (NHS II 1989-2011) using the multivariate hazard model (with the Cox modification), examined the influence of diuretics, beta-blockers, calcium channel blockers, and ACE inhibitors on the risk of breast cancer development. In 10 012 cases of invasive breast cancer (6 718 cases in NHS and 3 294 cases in NHS II), none of the hypertensives were associated with the risk of breast cancer in comparison with the control groups: NHS (RR = 1.00, 95 % CI = 0.95–1.06) and NHS II (RR = 0.94, 95 % CI = 0.86–1.03). The results were the same for long-term antihypertensive use.[11] A British cohort study compared three groups of patients: the first group used calcium channel blockers (150 750 patients), the second group received a different hypertensive (557 931 patients), while the third group received combined antihypertensive treatment that include a calcium channel blocker (156 966 patients). The resulting relative risk values for cancer development were not significantly increased: RR 0.88 (0.86 to 0.89) and 1.01 (0.98 to 1.04); HR for the development of prostate, breast, and colon carcinoma with the application of calcium channel blockers was not significantly increased for any of the cancer groups: HR 0.95 (0.87 to 1.04), 1.07 (0.98 to 1.16) and 0.89 (0.81 do 0.98).[12]

Procjena rizika od nastanka karcinoma bubrega povezanog s primjenom antihipertenziva

Uporaba antihipertenziva, napose diuretika, prema nedavnim je literaturnim podatcima, ispitivana kao rizični čimbenik za nastanak karcinoma bubrega. Međutim, gledajući sam mehanizam arterijske hipertenzije koja uzrokuje trajno proinflamatorno stanje na krvnim žilama i oslobađanje slobodnih radikala i brojnih drugih djelovanja pogodnih za nastanak mutacije stanica, moguća je povezanost same arterijske hipertenzije kao rizičnog čimbenika za nastanak karcinoma bubrega, što nije vezano s uporabom diuretika u terapiji. Istraživanja upućuju na veći rizik izražen u žena (OR 2,01, 95 % CI: 1,56 – 2,67) nego u muškaraca (OR 1,69, 95 % CI: 1,34 – 2,13), međutim relativni rizik od nastanka karcinoma bubrega u žena je bio 1,8, a uz adekvatnu antihipertenzivnu terapiju i uredno regulirane vrijednosti AT-a taj se rizik smanjuje na 1,1. Zaključno, važno je komparirati prednosti i nedostatke svake terapije pa tako i diuretske, uspoređujući relativno nizak ukupni rizik od karcinogenosti s nepobitno velikom koristi od diuretske terapije. Primjerice, na jedan slučaj karcinoma bubrega zbog uporabe diuretika prevenirano je 17 – 30 ishemijskih cerebrovaskularnih incidenata, 3 – 20 kardiovaskularnih smrti te 4 – 18 preveniranih smrti na općoj populaciji.[13-17]

Zaključak

Prema prikazanim rezultatima dosadašnjih istraživanja, ne nalazi se sigurna povezanost između primjene bilo koje skupine antihipertenziva s nastankom karcinoma, osim rizika od nastanka nemelanomskog karcinoma kože uz primjenu hidroklorotiazida. S duljinom primjene antihipertenzivne terapije ne dolazi do očekivanog porasta relativnog rizika od nastanka karcinoma, nego se, paradoksalno, rizik, prema nekim istraživanjima, linearno smanjuje. U dosadašnjim istraživanjima također ne nalazimo uključene ostale rizične čimbenike za nastanak malignosti, primjerice, pušenje, izloženost UV zrakama i Sunčevoj svjetlosti te ostalim noksama, pa se stoga rezultati budućih istraživanjima sa svim uključenim rizičnim čimbenicima uz primjenu antihipertenziva tek iščekuju. Važno je prisjetiti se da se valjanom regulacijom arterijske hipertenzije znatno smanjuju smrtnost od kardiovaskularnih i cerebrovaskularnih incidenata te ukupni mortalitet opće populacije pa stoga preporučujemo nastaviti slijediti postojeće smjernice za liječenje arterijske hipertenzije Europskoga društva za hipertenziju uz poseban oprez pri primjeni hidroklorotiazida. Prema preporukama Hrvatskoga društva za hipertenziju, važno je bolesnike pravodobno informirati o mogućim štetnim učincima hidroklorotiazida te zajednički s bolesnikom donijeti odluku o daljnjoj primjeni ili ukidanju terapije u onih koji nemaju ukupni rizik od razvoja karcinoma kože veći nego standardna populacija, dok bi u skupini visokorizičnih bolesnika, onih s prije preboljenim karcinomom kože, hidroklorotiazid trebalo zamijeniti nekim od drugih antihipertenziva dostupnih na našem tržištu, primjerice netiazidnim diuretikom: indapamidom ili antihipertenzivom druge skupine, ovisno o individualnoj procjeni za svakoga pojedinog bolesnika. Bolesnicima kojima se odlučimo nastaviti terapiju hidroklorotiazidom također treba savjetovati smanjenje izlaganja Sunčevoj svjetlosti i UV zračenju te ih uputiti na pregled dermatologu u slučaju pojave suspek-

Risk assessment for the development of kidney cancer associated with the use of antihypertensives

Using antihypertensives, especially diuretics, was examined as a risk factor for kidney cancer development in recent literature data. However, taking into account the mechanism of arterial hypertension, which causes a permanent proinflammatory state in the blood vessels and the release of free radicals as well as many other effects favorable to the cell mutation, it is possible that there is an association between arterial hypertension itself as a risk factor for the development of kidney carcinoma that is not associated with the use of diuretics in therapy. Studies have indicated higher risk in women (OR 2.01, 95% CI 1.56-2.67) than in men (OR 1.69, 95% CI 1.34-2.13), however the relative risk for kidney cancer development in women was 1.8, and with adequate antihypertensive therapy and well-regulated AP values this risk dropped to 1.1. In conclusion, it is important to compare the strengths and weaknesses of every treatment including diuretics, comparing the relatively low total risk of cancerogenic effect with the undoubtedly large benefits of diuretics. As an example, for every 1 case of kidney cancer the use of diuretics prevents 17-30 ischemic cerebrovascular incidents, 3-20 cardiovascular deaths, and 4-18 prevented deaths in the general population.[13-17]

Conclusion

The above results of current studies did not establish a definitive association between the use of any group of antihypertensives and cancer development, except the risk of nonmelanoma skin cancer with the use of hydrochlorothiazide. Increased duration of antihypertensive therapy did not lead to the expected increase in relative risk for cancer development; in fact, some studies found a paradoxical linear reduction in relative risk. Furthermore, current studies did not include other risk factors for the development of malignancies, e.g. smoking, exposure to UV rays and the sun, and other hazardous effects, and the results of future studies that include risk factors with the use of antihypertensives are yet to be seen. It is important to remember that proper regulation of arterial hypertension leads to a significant reduction in mortality from cardiovascular events, cerebrovascular events, and a reduction in total mortality in the general population; we therefore recommend adhering to the current guidelines for the treatment of arterial hypertension of the European Society of Hypertension, with additional caution when applying hydrochlorothiazide. According to the recommendations of the Croatian Society of Hypertension, it is important to inform the patient in a timely manner on the potential hazardous effects of hydrochlorothiazide and reach a joint decision with the patient on the further application or termination of the therapy in those patients who do not have a higher total risk of skin cancer than the standard population, whereas in the group of high-risk patients, those who have already had skin cancer, hydrochlorothiazide should be replace by one of the other antihypertensives available in Croatia such as a nonthiazide diuretic, indapamide, or an antihypertensive from a different group, based on an individualized assessment of every patient. If hydrochlorothiazide treatment is continued, patients should be advised to avoid sunlight and UV radiation

tnih kožnih lezija. Sve ostale antihipertenzive preporučujemo nastaviti dalje primjenjivati u skladu sa smjernicama za liječenje arterijske hipertenzije.

and instructed to visit a dermatologist in case suspect skin lesions appear. For all other antihypertensives, we recommend continuing their application according to guidelines for the treatment of arterial hypertension.

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