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Kronična bubrežna bolest i fibrilacija atrija

Chronic kidney disease and atrial fibrillation

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SAŽETAK: Kronična bubrežna bolest (KBB) definirana je strukturalnim ili funkcijskim abnormalnostima bubrega u razdoblju duljem od tri mjeseca sa znatnim utjecajem na zdravlje. Vodeći uzroci KBB su dijabetes i arterijska hipertenzija, stoga ne čudi činjenica kako je incidencija ove bolesti skoro svugdje u svijetu u porastu. Bolesnici s KBB podložniji su srčanožilnim bolestima (SŽB) više nego ostatak populacije, a zna se da su one i glavni uzrok smrti pacijenata na dijalizi. Fibrilacija atrija (FA), kao najčešća srčana aritmija, ima veću prevalenciju među bolesnicima s oštećenom bubrežnom funkcijom, stoga je izuzetno važan zdravstveni problem. Također, pacijenti s progredirajućim oblikom KBB i prisutnom dijagnozom FA imaju značajno viši rizik od smrti. Ne postoje jasne terapijske smjernice za liječenje FA u bolesnika s KBB, a pogotovo je upitna upotreba varfarina za sprječavanje moždanog udara, kao česte komplikacije ove srčane aritmije. Potrebna su daljnja istraživanja o KBB i SŽB te ova dva polja zahtijevaju zajedničku suradnju nefrologa i kardiologa.

KLJUČNE RIJEČI: kronična bubrežna bolest, srčanožilne bolesti, fibrilacija atrija.

ABSTRACT: Chronic kidney disease (CKD) is defined by structural or functional kidney abnormalities for more than three months with a significant impact on health. The major causes of CKD are diabetes and arterial hypertension. Therefore, the increasing incidence of this disease in almost all parts of the world is not surprising. Patients with CKD are more likely to develop cardiovascular diseases (CVD) than the rest of the population, and we know that they are the major cause of death in dialysis patients. Atrial fibrillation (AF), as the most common cardiac arrhythmia, has a higher prevalence among the patients with impaired renal function, therefore it is an extremely important health issue. On the other hand, patients with progressing CKD and who present a diagnosis of AF show a significantly higher risk of death. There are no clear guidelines for the treatment of AF in patients with CKD. The administration of warfarin to prevent stokes, a frequent complication of cardiac arrhythmia, is particularly debatable. Further trials of CKD and CVD are to be conducted and should include the close collaboration of nephrologists and cardiologists.

KEYWORDS: chronic kidney disease, cardiovascular diseases, atrial fibrillation.

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Kronična bubrežna bolest

Kronična bubrežna bolest (KBB) definirana je strukturalnim ili funkcijskim abnormalnostima bubrega u razdoblju duljem od tri mjeseca sa znatnim utjecajem na zdravlje. Vodeći uzroci KBB su dijabetes i arterijska hipertenzija, stoga ne čudi činjenica kako je incidencija ove bolesti skoro svugdje u svijetu u porastu. U mnogim zemljama svake se godine javlja dvjestotinjak novih slučajeva na milijun stanovnika, a u SAD-u čak četiristo. Procjenjuje se da oko 150.000 bolesnika u Hrvatskoj ima KBB.[1] Opći čimbenici rizika KBB u razvijenim zemljama su prekomjerna tjelesna težina, hipertenzija, dijabetes, visoka dob, pušenje, tjelesna neaktivnost i pozitivna obiteljska anamneza. KBB je povezana s brojnim komplikacijama od kojih su na prvom mjestu srčanožilne bolesti (SŽB).

Danas se KBB definira kao oštećenje bubrega karakterizirano albuminurijom i glomerularnom filtracijom manjom od 60 mL/min u trajanju duljem od tri mjeseca. Budući da glomerularna filtracija izuzetno dobro pokazuje stanje oštećenja, bubrežna bolest se na temelju nje klasificirala u pet stupnjeva.

Chronic kidney disease

Chronic kidney disease (CKD) is defined by structural or functional kidney abnormalities for more than three months with a significant impact on health. The major causes of chronic kidney disease are diabetes and arterial hypertension. Therefore, the increasing incidence of this disease in almost all parts of the world is not surprising. In many countries, about two hundred new cases per one million citizens occur every year, while four hundred such new cases occur in the United States. We estimate that there are about 150,000 patients in Croatia suffering from CKD[1]. The general risk factors for CKD in developed countries are overweight, hypertension, diabetes, advanced age, smoking, physical inactivity and a positive family history. CKD is associated with many complications, the most prominent of which is cardiovascular diseases (CVD).

Today, CKD is defined as renal impairment characterized by albuminuria and a glomerular filtration rate less than 60 mL/min lasting for more than three months. Since glomerular filtration can show the impairment very well, kidney di-

No, ta klasifikacija nije obuhvaćala čimbenike koji su bitni za prognozu bubrežne bolesti, poput npr. proteinurije, pa je uvedena nova klasifikacija koja istovremeno uzima u obzir i glomerularnu filtraciju i albuminuriju (**Tablica 1.**).

sease is accordingly classified in five degrees. However, this classification does not include the factors that are important for the prognosis of the kidney disease, such as proteinuria, so a new classification that simultaneously considers both glomerular filtration and albuminuria has been introduced (**Table 1**).

Table 1. *Prognosis of chronic kidney disease by glomerular filtration rate and albuminuria categorie.*

GFR categories (ml/min per 1,73 m^2), description and range				Persistent albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly-moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	≤15			

Low risk
Moderately increased risk
High risk
Very high risk

O klasifikaciji KBB puno se raspravljalo u zadnjih desetak godina. Pokušava se pronaći optimalan način kako bi se uzeli svi čimbenici bolesti u obzir (osnovna bolest, glomerularna filtracija i albuminurija kao pokazatelji trenutnog oštećenja bubrega, druge pridružene bolesti i stanja pacijenata, rizik pojedinca za komplikacije itd.) te na temelju toga donijele odluke o terapiji i postupanju s pacijentom.[2]

Osim već spomenutih najčešćih uzroka KBB uzroci mogu biti različiti oblici glomerulonefritisa, bakterijske infekcije, kamenci i parazitarne bolesti, što je često u nerazvijenim zemljama. Policistična bolest bubrega, analgetska nefropatija, tubulointersticijska bolest, autoimuna bolest, vaskulitis, amiloidoza, multipli mijelom, hemolitičko-uremički sindrom i endemska nefropatija također mogu dovesti do kroničnog bubrežnog zatajenja.

Od velike je važnosti što ranije prepoznavanje pacijenata s bubrežnom bolesti jer pravodobna intervencija može smanjiti izglede za kardiovaskularnim komplikacijama ili pogoršanjima bubrežne funkcije. Važne su i nefarmakološke mjere kao što su prestanak pušenja, prilagođena prehrana s ograničenjem unosa soli, umjerena tjelovježba itd. Jedna od ključnih mjera je dobra kontrola arterijskog tlaka (AT). Ciljne vrijednosti AT za bubrežne bolesnike su <125-135/75-85 mmHg. Lijekovi koji djeluju na renin-angiotenzinski sustav su lijekovi izbora za kontrolu AT u KBB zbog svog renopro-

This CKD classification has been much discussed in the last ten years. We are trying to find an optimal way to take all disease factors into account (primary disease, glomerular filtration rate and albuminuria as indicators of current renal impairment, other associated diseases and a patient's condition, individual risk of complications, etc.) and make decisions on a therapy and management of patients accordingly.[2]

Other causes of CKD may be different forms of glomerulonephritis, bacterial infections, stones and parasitic diseases, which are common in underdeveloped countries. Polycystic kidney disease, analgesic nephropathy, tubulointerstitial disease, autoimmune disease, vasculitis, amyloidosis, multiple myeloma, hemolytic uremic syndrome and endemic nephropathy can also lead to chronic renal failure.

Early identification of patients with renal disease is of great importance because timely intervention can reduce the chances of cardiovascular complications or renal function impairment. There are some non-pharmacological measures, such as smoking cessation, a tailored diet accompanied by limited salt intake, moderate exercise, etc., that are also very important. Another key measure is a good control of blood pressure (BP). BP target values for kidney patients are <125-135/75-85 mmHg. Drugs that have an effect on the renin-angiotensin system are the drugs of choice for BP control in CKD because of their renoprotective action and

tektivnog djelovanja i dokazanog učinka na smanjenje komplikacija. U dijabetičara s KBB kontrola glikemije je također od iznimne važnosti. Ciljne vrijednosti su HbA1c <7% i glikemija 4-7 mmol/L. Važna je i korekcija dislipidemije. Bubrežni bolesnici trebali bi se držati vrijednosti propisanih za opću populaciju, a kao medikamentna terapija na prvom mjestu su statini.[3] Acetilsalicilatna kiselina je također često propisivan lijek u KBB zbog svog dokazanog djelovanja na prevenciju kardiovaskularnih događanja, no davanje takve terapije mora biti individualizirano uzevši u obzir povišen rizik od krvarenja.[4] Liječenje bolesnika s KBB zahtjeva korekciju i metaboličkih komplikacija, od kojih su najčešće anemija i poremećaji mineralnog metabolizma.

Fibrilacija atrija

Fibrilacija atrija (FA) je najčešća srčana aritmija u cijeloj populaciji i jedan od najvažnijih čimbenika za ishemijski moždani udar i nezavisni prediktor smrti.[5] To je supraventrikularna aritmija koja u početku nastaje zbog nepravilne električne aktivacije s ishodištem u plućnim venama, a kao posljedicu ima nepravilnu aktivaciju i gubitak kontrakcije atrija. Incidencija i prevalencija rastu s dobi. U 12-kanalnom elektrokardiogramu se umjesto P-valova vidi nepravilna električna aktivnost, takozvani F-valovi. Akcija ventrikula može biti pravilna, ali je znatno češće nepravilna.[6]

Rizični čimbenici za FA uvelike se preklapaju s onima za razvoj KBB (visoka dob, pušenje, hipertenzija, dijabetes). FA je vrlo bitan zdravstveni problem, ne samo zbog svoje prevalencije, nego zbog mogućih posljedica kao što su tromboembolijski incidenti i srčano zatajivanje. Neki od simptoma ove aritmije koji značajno smanjuju kvalitetu života su palpitacije, zaduha, omaglice i slabost. Najčešće FA počinje kao paroksizmalna te bolesnici samo intermitentno imaju simptome. Postoji više podjela FA, a prema preporukama Europskog kardiološkog društva[7] ona se dijeli na paroksizmalnu, perzistentnu, dugotrajnu perzistentnu i permanentnu. Posebnu grupu čini prvi put zabilježena FA. Paroksizmalna FA je rekurentni oblik s atakama koji traju kraće od sedam dana, najčešće do 48 sati i sami prestaju. Perzistentna FA traje duže od 7 dana i zahtijeva električnu ili medikamentu konverziju u sinusni ritam. Dugotrajna perzistentnta FA jest ona koja traje dulje od godinu dana, ali i dalje postoji namjera liječnika i bolesnika za konverziju u sinusni ritam. Permanentna FA čini posljednju podskupinu, a radi se o FA kod bolesnika kojih ili nije odlučeno za kardioverziju, ili je ona pokušana, ali nije donijela rezultate.[8]

Terapijske opcije kod FA se svode na simptomatsko liječenje, zatim ili na kontrolu frekvencije ili na kontrolu srčanog ritma te obavezno antikoagulantnu terapiju. Općenito, ako FA traje duže od 48 sati, nije dozvoljeno učiniti konverziju ritma u sinusni bez uvođenja peroralne antikoagulacijske terapije. Tada su nam preostale dvije mogućnosti; isključivanje postojanja tromba transezofagealnim ultrazvukom srca i provođenje konverzije ili konverzija bez ultrazvučnog pregleda nakon mjesec dana antikoagulantne terapije. Drugi oslonac terapije FA je kontrola frekvencije. Studije nisu pokazale koja od ovih dviju opcija je bolja. Ukoliko medikamentna terapija nema uspjeha, kod određenih skupina bolesnika u obzir dolazi elektrokardioverzija, kateterska ablacija ušća plućnih vena (kod bolesnika s paroksizmalnom ili perzistentnom FA) te implantacija trajnog elektrostimulatora s ablacijom AV čvora.[9]

proven effect in reducing complications. In diabetic patients with CKD, glycemic control is also very important. The target values are HbA1c <7% and glycemia 4-7 mmol/L. The correction of dyslipidemia is important. Kidney patients should keep the values prescribed for the general population, while statins also have also have a primary place as a medical therapy.[3] Aspirin is commonly prescribed in CKD because of its proven effect in preventing cardiovascular events, but its administration must be individualized in view of the increased risk of bleeding.[4] The treatment of patients with CKD also requires correction of metabolic complications, the most common of which are anemia and disorders of mineral metabolism.

Atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population and one of the most important factors for ischemic stroke, and it is an independent predictor of death.[5] It is a supraventricular arrhythmia that is initially caused by improper electrical activation originating in the pulmonary veins and results in an incorrect activation and the loss of atrial contraction. Its incidence and prevalence increases with age. The 12-lead ECG shows irregular electrical activity, called the F-waves instead of P-waves. Ventricular action may be correct, but it is commonly irregular.[6]

AF risk factors largely overlap with those for the development of CKD (advanced age, smoking, hypertension, diabetes). AF is a very important public health problem not only because of its prevalence, but because of its potential consequences, such as thromboembolic incidents and heart failure. Some of the symptoms of this arrhythmia that significantly impair the quality of life are palpitations, shortness of breath, dizziness and fatigue. The most common form of AF starts as paroxysmal and patients have symptoms only intermittently. There are several classification of AF. According to the recommendations of the European Society of Cardiology,[7] it is classified into paroxysmal, persistent, long-term persistent and permanent AF. AF recorded for the first time constitutes a special group. Paroxysmal AF is a recurrent form with attacks that last less than seven days, usually up to 48 hours, that cease by themselves. Persistent AF lasts more than 7 days and requires electrical or medicament conversion to sinus rhythm. Long-term persistent AF lasts longer than a year, but still there is an intention of the doctor and patient for conversion to sinus rhythm. The last subgroup, permanent AF, includes patients for whom no decision has been made on cardioversion, or it has been attempted but yielded no results.[8]

Therapeutic options in AF are reduced to symptomatic treatment, followed either by control of frequency or control of heart rate mandatory including anticoagulant therapy. Generally, if the AF lasts longer than 48 hours, conversion of rhythm to sinus rhythm is not permitted without the introduction of oral anticoagulant therapy. Then two other options remain: to rule out the presence of thrombi by transesophageal ultrasound of the heart, and conducting the conversion or conversions without an ultrasound examination one month after the administration of anticoagulant therapy. Another mainstay of AF therapy is frequency control. Studies have not shown which of these two options is better. If drug therapy is not successful, electrocardioversion, catheter ablation of pulmonary venous confluence (in patients with paroxysmal or persistent AF) and implantation of a permanent pacemaker with an AV node ablation is an option to be considered in certain groups of patients.[9]

Kardiovaskularne komplikacije kronične bubrežne bolesti

Bolesnici s KBB podložniji su SŽB više nego ostatak populacije, a zna se da su one i glavni uzrok smrti pacijenata na dijalizi. Dokazano je da su niska glomerularna filtracija i povišena albuminurija povezane s povišenim rizikom od kardiovaskularnih incidenata, bilo novih ili ponavljajućih.[10] Mortalitet od SŽB među pacijentima u završnom stadiju bubrežne bolesti je 15-30 puta veći nego u općoj populaciji iste dobi.[11] Ova je razlika još izraženija među mlađom dobnom skupinom, od 25 do 34 godine, u kojoj je mortalitet čak 500 puta veći nego među zdravim pacijentima iste dobi.[12] Pacijenti u trećem i četvrtom stupnju KBB čak će prije umrijeti od SŽB nego progredirati u završni stadij bubrežne bolesti.[13]

Brojni su razlozi povećanog rizika kardiovaskularnih događaja u bolesnika s KBB. Pored tradicijskih rizičnih čimbenika kao što su debljina, pušenje, arterijska hipertenzija, dislipidemija i slično, u bolesnika s KBB prisutni su i mnogobrojni netradicijski čimbenici rizika kao što su anemija, poremećaj mineralnog metabolizma, malnutricija, oksidativni stres, proteinurija, odnosno albuminurija. Ovu potonju je bitno određivati i pratiti u pacijenata s povećanim rizikom za bubrežnu bolest, ne samo zbog dokazivanja i klasifikacije bolesti, već i zbog njene prediktivne vrijednosti u terapiji.[14]

Cilj ovog rada nije detaljno objašnjenje svih kardiovaskularnih čimbenika rizika u KBB. Želimo, naime, upozoriti samo na tri vrlo značajna: anemiju, poremećaj mineralnog metabolizma te proteinuriju, odnosno albuminuriju.

Anemija je u populaciji bolesnika s KBB gotovo pa redovita pojava. Najvažniji uzrok je nedostatak eritropoetina. Ukratko, anemija je uzrok smanjene oksigenacije tkiva; povećava se rad simpatikusa i samim time rad miokarda. Također, zbog smanjene viskoznosti povećan je venski priljev u srce što posljedično dovodi do hipertrofije lijeve klijetke.

Već u početnim stadijima KBB razvija se poremećaj mineralnog metabolizma, koji se manifestira poremećajem metabolizma kalcija i fosfora, parathormona, vitamina D te FGF 23 (engl. *Fibroblast growth factor 23*) hormona koji među ostalima regulira promet fosfora. Posljedica navedenih poremećaja je ubrzana kalcifikacija krvnih žila te ostalih tkiva npr. miokarda.

Postoje brojni eksperimentalni i klinički dokazi o povezanosti proteinurije, odnosno albuminurije i kardiovaskularnih događaja.[15] Prema Kanadskoj studiji Hemmelgarn et al, prisutstvo proteinurije je povezano s povećanim rizikom od smrti, infarkta miokarda i progresije bubrežne bolesti (povećan rizik od aterosklerotskih događaja u perifernoj vaskularizaciji). Kod hipertenzivne populacije albuminurija čak četiri puta povećava rizik od ishemijske bolesti srca. Također, kod pacijenata s hipertenzijom i dijabetesom, albuminurija dovodi i do zadebljanja lijeve klijetke. Pacijenti s dijabetesom tip 1 i albuminurijom imaju devet puta veći kardiovaskularni mortalitet nego normoalbuminurični pacijenti. Studija Svjetske zdravstvene organizacije Multinational Study of Vascular Disease in Diabetics je dokazala povezanost proteinurije i ishemijske bolesti srca i kod pacijenata s dijabetesom tip 2. Albuminurija je povezana i s kroničnim zatajivanjem srca te su studije pokazale kako ne samo da je čimbenik rizika zatajivanja srca, nego daje i prognostičke informacije.[15]

Postoji više načina na koje su povezane proteinurija i SŽB. To su upala, endotelna disfunkcija i trombogenički faktori. "Steno" hipoteza govori kako proteinurija dovodi do endotelne disfunkcije. Tome ide u prilog povećanje adiponektina,

Cardiovascular complications of chronic kidney disease

Patients with CKD are more likely to develop CVD than the rest of the population, and we know that they are the major cause of death in dialysis patients. It has been shown that low glomerular filtration rate and elevated albuminuria are associated with an increased risk of cardiovascular events, regardless of whether they are new or recurring ones.[10] Mortality caused by CVD among patients in end-stage kidney disease is 15-30 times higher than in the general population of the same age.[11] This difference is even more pronounced among the younger age group, from 25-34, in whom the mortality is 500 times higher than among the healthy patients of the same age.[12] Patients in the third and fourth stage of CKD are even more likely to die of CVD than to progress to end-stage kidney disease.[13]

There are many reasons for the increased risk of cardiovascular events in patients with CKD. In addition to traditional risk factors such as obesity, smoking, hypertension, dyslipidemia, etc., patients with CKD also show many non-traditional risk factors such as anemia, disorders of mineral metabolism, malnutrition, oxidative stress, proteinuria or albuminuria. This latter is to be diagnosed and monitored in patients at increased risk for kidney disease not only because of evidencing and classifying the disease, but also because of its predictive value in the therapy.[14]

The aim of this paper is not a detailed explanation of all cardiovascular risk factors in CKD. However, we only wish to warn about three very significant risk factors: anemia, mineral metabolism disorder and proteinuria or albuminuria.

Anemia is almost a normal event in the population of patients with CKD. The most important cause is the lack of erythropoietin. In short, anemia is the cause of reduced tissue oxygenation. It increases sympathicus activity, and consequently, myocardial activity. Reduced viscosity results in an increase in venous return to the heart, which consequently leads to left ventricular hypertrophy.

Mineral metabolism disorder develops in the early stages of CKD. It is reflected in a disorder of the metabolism of calcium and phosphorus, parathyroid hormone, vitamin D and FGF 23 (Fibroblast growth factor 23) hormone, which inter alia regulates phosphorus circulation. The consequence of these disorders is an accelerated calcification of blood vessels and other tissues such as the myocardium.

There is abundant experimental and clinical evidence about the association between proteinuria or albuminuria and cardiovascular events.[15] According to the Canadian study, Hemmelgarn et al, the presence of proteinuria is associated with an increased risk of death, myocardial infarction, and progression of renal disease (increased risk of atherosclerotic events in peripheral vascularization). In the hypertensive population, albuminuria increases the risk of ischemic heart disease by four times. Also, in patients with hypertension and diabetes, albuminuria leads to a thickening of the left ventricle. Patients with type 1 diabetes and albuminuria show cardiovascular mortality that is nine times higher than in normoalbuminuric patients. The World Health Organization (WHO) Multinational Study of Vascular Disease in Diabetics has also proven the association between proteinuria and ischemic heart disease in patients with type 2 diabetes. Albuminuria is associated with chronic heart failure and studies have shown that it is not only a risk factor for heart failure but also provides prognostic information.[15]

There are several ways in which proteinuria and CVD are associated, including inflammation, endothelial dysfunction

vrijednosti CRP, ADMA (engl. Asymmetric dimethylarginine) i vWF-a (von Willebrandov faktor). Povezanost preko trombogeničkih faktora dokazana je korelacijom ekskrecije proteina i koncetracije vWF, adhezivnih molkeula, fibrinogena i tkivnog aktivatora plazminogena, a to bi sve moglo dovesti do povećanog rizika tromboze.[16]

Povezanost kronične bubrežne bolesti i fibrilacije atrija

Prema REGARDS studiji kod 26.917 ispitanika u SAD dokazana je povećana prevalencija FA kod bolesnika s KBB i to najviše među pacijentima u trećem i četvrtom stupnju bolesti. Prevalencija FA među ispitanicima bez KBB iznosila je 1%, među pacijentima u 1. i 2. stupnju KBB iznosila je 2,8%, u 3. stupnju 2,7%, a u 4. i 5. stupnju 4,2%. Bolesnici u prva dva stupnja KBB imaju 2,67 puta veći rizik za razvoj FA, bolesnici u trećem 1,68 dok je taj rizik u četvrtom i petom stupnju 3,52 puta veći.[17]

FA i KBB dijele zajedničke čimbenike rizika; hipertenzija, dijabetes, postojeća SŽB, pretilost, metabolički sindrom.[18] Retrospektivne studije su pokazale da je KBB nezavisni čimbenik rizika za pojavu FA te da je pojava FA u KBB povezana s povećanom stopom smrtnosti.[19]

Provedena istraživanja su uputila na to da bi FA mogla biti čimbenik koji ubrzava progresiju KBB u terminalni stadij te je kasnije i dokazano da je FA povezana sa 67% višom relativnom stopom progresije do završnog stupnja bubrežne bolesti. Novija istraživanja potvrđuju da FA može doprinijeti bržoj progresiji KBB do terminalnog stadija. Također, FA pospješuje sustavnu upalu koja pogoduje pogoršanju bubrežne funkcije. Budući da FA inducira fibrozu miokarda moguće je da je isti proces fibroze potaknut i u bubregu, možda kroz sustavnu profibrotičku težnju u organizmu. FA pridonosi sistoličkoj i dijastoličkoj disfunkciji što može pogoršati KBB zbog promijenjene hemodinamike, venske kongestije i aktivacije RAAS.[20] Isto tako je poznato da je FA povezana s dugoročnim lošijim kliničkim ishodima u pacijenata s terminalnim stupnjem KBB.[21]

Više je hipoteza koje objašnjavaju vezu između KBB i FA. Neurohormonalna aktivacija je upletena u progresiju bubrežnog oštećenja i njegovih kardiovaskularnih posljedica. Također, aktivacija sustava renin-angiotenzin-aldosteron u pacijenata s KBB uzrokuje porast proliferacije srčanih fibroblasta i srčane hipertrofije. Ovaj efekt bi mogao biti dokazan povećanom sekrecijom profibrotičkog faktora TGF-β1.[22] To nam potvrđuje činjenica da se spironolakton pokazao kao djelotvoran u reduciranju FA zbog blokade mineralokortikoidnog receptora i antifibrotičkog učinka.[23] Aritmogenezi pridonosi i aktivacija simpatikusa koja je, kao i povećanje koncentracije adrenergičnih hormona u serumu, prisutna u pacijenata s KBB.[22] Sistemna upala prisutna u bubrežnoj bolesti također ima ulogu u patogenezi FA, a marker CRP je povišen u KBB i FA. Ova pretpostavka je potvrđena analizom uzoraka biopsije srca u pacijenata s FA gdje su pronađene upalne promjene.[24] Također je hs-CRP identificiran kao dobar marker za prognozu kardiovaskularnih incidenata, uključujući smrt zbog svoje povezanosti sa sistemnom upalom, disfunkcijom endotela i rizikom za tromboembolijske incidente.[25] Nadalje, strukturalne abnormalnosti na srcu, otprije povezane s KBB, kao što su hipertrofija lijeve klijetke i pretklijetke jednako tako povećavaju rizik aritmijskih događanja.[24] Metaboličke abnormalnosti koje su prisutne u KBB kao što su metabolička acidoza, poremećaj prometa kalija i kalcija također vode do povećanog rizika za razvoj

and thrombogenic factors. "Steno" hypothesis suggests that proteinuria leads to endothelial dysfunction. This hypothesis is reinforced by an increase in adiponectin, CRP, ADMA (Asymmetric dimethylarginine) and vWF (von Willebrand factor). The association via thrombogenic factors has been proven by the correlation of protein excretion and vWF concentration, adhesive molecules, fibrinogen and tissue plasminogen activator, all of which may lead to an increased risk of thrombosis.[16]

Association of chronic kidney disease and atrial fibrillation

The REGARDS study conducted on 26,917 patients in the US demonstrated the increased prevalence of AF in patients with CKD, mostly among the patients in the third and fourth stage of the disease. The prevalence of AF among the subjects without CKD was 1%, among the patients in the first and second stage of CKD it was 2.8%, in the third stage the prevalence was 2.7%, and in the fourth and fifth stage it was 4.2%. Patients in the first two stages of CKD show a 2.67 times greater risk of AF, patients in the third stage show a 1.68 times greater risk, and the risk in the fourth and fifth stage is 3.52 times higher.[17]

AF and CKD share some common risk factors, such as hypertension, diabetes, current CVD, obesity, and metabolic syndrome.[18] Retrospective studies have shown that CKD is an independent risk factor for the occurrence of AF and that the occurrence of AF in CKD is associated with an increased mortality rate.[19]

The investigations suggested that AF could be a factor that accelerates the progression of CKD in the end-stage, and it was later proven that AF is associated with a 67% higher relative rate of progression to the end-stage renal disease. Recent studies confirm that AF may contribute to a faster progression of CKD to the end-stage. AF also stimulates systemic inflammation that contributes to the impairment of renal function. Since AF induces myocardial fibrosis, it is possible that the same process of fibrosis is stimulated in the kidney, perhaps through the systematic profibrotic tendency in the body. AF contributes to systolic and diastolic dysfunction that can impair CKD due to altered hemodynamics, venous congestion and activation RAAS.[20] AF is also known to be associated with long-term impaired clinical outcomes in patients in end-stage CKD.[21]

There are several hypotheses that explain the association between CKD and AF. Neurohormonal activation is involved in the progression of renal impairment and its cardiovascular consequences. The activation of the renin-angiotensin-aldosterone system in patients with CKD causes an increase in the proliferation of cardiac fibroblasts and cardiac hypertrophy. This effect could be proven by an increased secretion of profibrotic factor TGF-β1.[22] This is confirmed by the fact that spironolactone proved to be effective in reducing AF due to blocking of the mineralocorticoid receptor and its antifibrotic effect.[23] Arrhythmogenesis is also stimulated by the sympathetic activation that, like the increase in the concentration of adrenergic hormones in serum, is present in patients with CKD.[22] Systemic inflammation present in renal disease also plays a role in the pathogenesis of AF, while the marker CRP is elevated in CKD and AF. This assumption is confirmed by a cardiac biopsy sample analysis in patients with AF where inflammatory changes are found.[24] Hhs-CRP was identified as a good marker for the prognosis of cardiovascular events, including death, due to its associa-

FA.[26] Oksidativni stres igra važnu ulogu u patogenezi FA, a on se povećava s pogoršanjem renalne funkcije. Na primjer, u lijevom atriju je povećana ekspresija nikotinamid adenin dinukleotid fosfata oksidaze.[27]

Terapija

Pacijenti s progredirajućim oblikom KBB i koegzistirajućom dijagnozom FA imaju značajno viši rizik od smrti.[19] Dokazano je da je proteinurija povezana s 50% višim rizikom za tromboembolijske incidente. Terapija FA u bolesnika s KBB je doista kompleksna. Prije svega jer pacijenti koji boluju od KBB imaju znatno viši rizik od krvarenja za vrijeme antikoagulacijske terapije, što također pridonosi višoj stopi smrtnosti. Varfarin u pacijenata s KBB dovodi do povećanog rizika od krvarenja, a dokazano je da može doprinijeti i kalcifikaciji krvnih žila i srčanih zalistaka te povećati uremičnu arteriolopatiju.[28] Korist, odnosno rizik uporabe varfarina u pacijenata s KBB, ostaje nerazjašnjen.[29] Istraživanje iz 2012. godine pokazuje kako bi noviji oralni antikoagulantni lijekovi poput dabigatrana, apixabana i rivoroxabana, mogli u budućnosti zamijeniti zamijeniti varfarin kod pacijenata u trećem i četvrtom stupnju bubrežne bolesti, koji uz to boluju i od FA.[30]

Kod pacijenata na dijalizi slična je situacija. Prevalencija FA među pacijentima na hemodijalizi je 11-27%, za razliku od opće populacije u kojoj iznosi 1%. Kako znamo da je FA povezana s moždanim udarom, u općoj se populaciji koristi varfarin kao prevencija moždanog udara, a stopa krvarenja je zanemariva. No, to nije slučaj s pacijentima na dijalizi. Zadnja istraživanja pokazala su kontradiktorne rezultate o smanjenju cerebrovaskularnih događaja pri upotrebi varfarina kod pacijenata na hemodijalizi. Ipak, definitivno je dokazana veća učestalost krvarenja pri njegovoj upotrebi u pacijenata s KBB, nego kod populacije bez oštećene funkcije bubrega. Samim time izgledno je da opasnost upotrebe varfarina kod ovih pacijenata nadilazi njegov pozitivan utjecaj.[31]

Uporaba antiaritmika koji se koriste u terapiji FA je uvelike ograničena u pacijenata s KBB jer se većina njih eliminira kroz bubrege te njihova upotreba može lako podići serumske vrijednosti kreatinina i dovesti do štetnih učinaka.[32] *L'Allier i sur* izvješćuju o smanjenoj incidenciji FA u 10.926 pacijenata s hipertenzijom liječenih ACE inhibitorima.[33]

Jedna od terapijskih opcija jest i kateterska ablacija. Pacijenti s KBB imaju veće vjerojatnosti od ponovnog vraćanja FA nakon jednog provedenog zahvata, pa je vrijednost i tog terapijskog postupka upitna.[34] Neke studije ukazuju na potpuno nezadovoljavajući ishod kateterske ablacije u pacijenata s KBB i s nižom glomerularnom filtracijom,[35] dok je u drugim studijama pokazano da uspješna eliminicija aritmije kateterskom ablacijom, poboljšava bubrežnu funkciju u pacijenata s blagim do umjerenim bubrežnim oštećenjem.[36] Sve u svemu, teško je predvidjeti i prevenirati relaps FA nakon kateterske ablacije u pacijenata s terminalnom KBB i veća je vjerojatnost da će se postupak morati ponoviti.[32]

Zaključak

Kronična bubrežna bolest je veliki javnozdravstveni problem u razvijenom dijelu svijeta, a postaje sve veći i u zemljama u razvoju. Učestalost kardiovaskularnih komplikacija u bolesnika s KBB je velika. Postoji brojni dokazi kako je FA u bolesnika s KBB češća nego u ostaloj populaciji.

tion with systemic inflammation, endothelial dysfunction and the risk of thromboembolic incidents.[25] Cardiac structural abnormalities associated with CKD from an earlier date, such as left ventricular and atrial hypertrophy, increase the risk of arrhythmic events in the same way.[24] Metabolic abnormalities that are present in CKD, such as metabolic acidosis, impaired potassium and calcium circulation, can also lead to an increased risk of the development of AF.[26] Oxidative stress plays an important role in the AF pathogenesis, and it increases with the impairment of renal function. For example, the expression of nicotinamide adenine dinucleotide phosphate oxidase is increased in the left atrium.[27]

Therapy

Patients with a progressing form of CKD and a co-existing AF diagnosis have a significantly higher risk of death.[19] It has been proven that proteinuria is associated with a 50% higher risk of thromboembolic incidents. AF therapy in patients with CKD is indeed a complex therapy primarily because patients suffering from CKD have a significantly higher risk of bleeding during anticoagulant therapy, which also contributes to a higher rate of mortality. Warfarin in patients with CKD leads to an increased risk of bleeding. It has also been proven that it can contribute to calcification of blood vessels and heart valves and increase uremic arteriolopathy.[28] The benefit or the risk of administering warfarin in patients with CKD is still debatable.[29] A 2012 trial shows that more recent oral anticoagulant drugs such as dabigatran, apixaban and rivoroxaban might replace warfarin in the future in patients in the third and fourth stage of renal disease, who are also suffering from AF.[30]

We see a similar situation in dialysis patients. AF prevalence among hemodialysis patients is 11-27%, as opposed to that in the general population, which is 1%. Since we know that the AF is associated with stroke, warfarin is administered in the general population to prevent it, while the bleeding rate is negligible. However, this is not a case in dialysis patients. Some recent trials have shown contradictory results on the reduction of cerebrovascular events when administering warfarin in patients on hemodialysis. However, a higher incidence of bleeding during its administration in patients with CKD has been definitely proven compared to the population without impaired renal function. Thus, it is likely that the risk of administering warfarin in these patients outweighs its positive impact.[31]

The administration of anti-arrhythmic drugs used in the treatment of AF is severely limited in patients with CKD because most of them are eliminated through the kidneys and their administration can easily raise serum creatinine values and have adverse effects.[32] *L'Allier et al* report a decreased incidence of AF in 10,926 patients with hypertension treated with ACE inhibitors.[33]

Another treatment option is catheter ablation. Patients with CKD are more likely to have recurring AF after one procedure is performed, so the value of this therapeutic procedure is open to question.[34] Some studies suggest a completely unsatisfactory outcome of catheter ablation in patients with CKD and with a lower glomerular filtration rate,[35] while other studies have demonstrated that the successful elimination of arrhythmias by catheter ablation improves renal function in patients with mild to moderate renal impairment.[36] Overall, it is difficult to predict and prevent a relapse of AF after catheter ablation in patients with end-stage CKD and there is a

Nažalost, postoji manjak dokaza o učinkovitosti, odnosno nuspojavama lijekova i učinkovitosti različitih intervencija u bolesnika s KBB. Novi lijekovi i nove metode dolaze u kliničku praksu nakon strogih kliničkih studija na ispitanicima s očuvanom bubrežnom funkcijom, bez da su uključeni pacijenti s oštećenom bubrežnom funkcijom, kao i oni na dijalizi. Sve češće se ističe važnost uključivanja i ove grupe bolesnika u sva klinička istraživanja, kako bi se definirale jasne smjernice, indikacije kao i kontraindikacije.[37] Jednako tako ne postoje ni jasne terapijske smjernice za liječenje FA u bolesnika s KBB, a pogotovo za uporabu varfarina za sprečavanje moždanog udara, kao česte komplikacije ove srčane aritmije. Zbog češćeg krvarenja pri upotrebi varfarina kod pacijenata s KBB nego kod opće populacije, njegova korist i dalje ostaje upitna. Potrebna su daljnja istraživanja o kroničnoj bubrežnoj bolesti i SŽB, a u svakodnevnom kliničkom radu neophodna je uska suradnja nefrologa i kardiologa. Na taj način će se uspješno spriječiti i liječiti mnogobrojne komplikacije u bolesnika s KBB.

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greater likelihood that the procedure will have to be performed again.[32]

Conclusion

Chronic kidney disease is a major public health problem in the developed world, and is becoming an ever greater problem in developing countries. The incidence of cardiovascular complications in patients with CKD is high. There is ample evidence that AF in patients with CKD is more common than in the general population.

Unfortunately, there is a shortage of evidence of the efficacy and side effects of drugs and the efficacy of various procedures in patients with CKD. Recent drugs and new methods have entered into clinical practice after rigorous clinical trials on subjects with preserved renal function without involving patients with impaired renal function and those on dialysis. The importance of involving this group of patients in all clinical trials is commonly emphasized in order to define clear guidelines and for indications and contraindications.[37] There are no clear guidelines for the treatment of AF in patients with CKD, especially for the administration of warfarin to prevent strokes, a common complication of cardiac arrhythmias. Because of more common bleeding with the administration of warfarin in patients with CKD than in the general population, its benefit remains a subject of debate. Further investigations of chronic kidney disease and CVD are required, while close coordination in daily clinical work between nephrologists and cardiologists is necessary. In this way, many potential complications in patients with CKD can be successfully prevented and treated.

Literature:

1. http://www.svjetskidanbubrega.org/p3-bubrezna-bolest.htm

2. Pavlović D. Kronična bubrežna bolest: definicija, podjela, prevencija. Nefrologija danas 2005. Prevencija kronične bubrežne bolesti. Hrvatski liječnički zbor. 2005;1.1-1.9

3. James MT, Hemmelgarn BR, Tonelli M. Early recognition and prevention of chronic kidney disease. Lancet. 2010;375:1296-309.

4. AntithromboticTrialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373:1849-60.

5. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrilation on the risk of death: the Framingham Hearth Study. Circulation 1998;98:946-52.

6. Bernat R. Farmakoterapija fibrilacije atrija. Medicus. 2010;19:203-14.

7. Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Eur Heart J. 2012;33:2719-47.

8. Fuster V, Ryden LE, Cannom DS, et al. American College of Cardiology Foundation/American Heart Association Task Force 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011;120:269-367.

9. Shukla A, Curtis AB. Avoiding permanent atrial fibrillation: treatment approaches to prevent disease progression. Vasc Health RiskManag. 2014;10:1-12.

10. Levey AS, Coresh J. Chronic kidney disease. Lancet. 2012;379:165-80.

11. Foley RN, Parfrey PS, Sarnak M. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J KidneyDis.1998;32:112-9.

12. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology and Epidemiology and Prevention. Hypertension. 2003;42:1050-65.

13. Schiffrin EL, Lipman ML, Mann JFE. Chronic kidney disease: effects on the cardiovascular system. Circulation. 2007;116:85-97.

14. Pavlović D. Laboratory standards in the diagnosis and monitoring of therapy. Ejifcc 20/01 2009. http://www.ifcc.org/ifccfiles/docs/200109012.pdf

15. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA. 2010;303:423-9.

16. Currie G, Delles C. Proteinuria and its relation to cardiovascular disease. Int J Nephrol Renovasc Dis. 2014;7:13-24.

17. Baber U, Howard VJ, Halperin JL,et al. Association of chronic kidney disease with atrial fibrillation among adults in the United States: reasons for geographic and racial differences in stroke (REGARDS) study. Circ Arrhythm Electrophysiol. 2011;4:26-32.

18. Fabbian F, Catalano C, Lambertini D, et al. Clinical characteristics associated to atrial fibrilation in chronic hemodialysis patients. Clin Nephrol. 2000;54:234-9.

19. Nelson SE, Shroff GR, Li S, Herzog CA. Impact of chronic kidney disease on risk of incident atrial fibrillation and subsequent survival in medicare patients. J Am Heart Assoc. 2012 Aug;1(4):e002097. Epub 2012 Aug 24.

20. Bansal N, Fan D, Hsu C, Ordonez JD, Marcus GM, Go AS. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. Circulation. 2013;127:569-74.

21. Genovesi S, Vincenti A, Rossi E, et al. Atrial fibrillation and morbidity and mortality in a cohort of long-term hemodialysis patients. Am J Kidney Dis. 2008;51:255-62.

22. Schlaich MP, Socratous F, Hennebry S, et al. Sympatetic activation in chronic renal failure. J Am SocNephrol. 2009;27:933-9.

23. Williams RS, deLemos JA, Dimas V, Reisch J, Hill JA, Naseem RH. Effect of spironolactone on patients with atrial fibrilation and structural heart disease. Clin Cardiol. 2011;34:415-9.

24. Ananthapanyasut W, Napan S, Rudolph EH, et al. Prevalence of atrial fibrilatrion and its predictors in nondialysis patients with chronic kidney disease. Clin J Am Soc Nephrol. 2010;5:173-81.

25. Hermida J, Lopez FL, Montes R, Matsushita K, Astor BC, Alonso A. Usefulness of high-sensitivity C-reactive protein to predict mortality in patients with atrial fibrillation (from the Atherosclerosis Risk In Communities [ARIC] Study). Am J Cardiol. 2011;109:95-9.

26. Voroneanu L, Covic A. Arrhythmias in hemodialysis patients. J Nephrol. 2009;6:716-25.

27. Fukunaga N, Takahashi N, Hagiwara S, et al. Establishment of a model of atrial fibrillation associated with chronic kidney disease in rats and the role of oxidative stress. Heart Rhythm. 2012;9:2023-31.

28. Holden RM, Sanfilippo AS, Hopman WM, Zimmerman D, Garland JS, Morton AR. Warfarin and aortic valve calcification in hemodialysis patients. J Nephrol. 2007;20:417-22.

29. US Renal Dana System. USRDS 2011 Annual Dana Report: Atlas of chronic kidney disease and end stage renal disease in the United States. 2011. ED. Bethesda: National institution of diabetes and digestive and kidney disease; 2011.

30. Hart RG, Eikelboom JW, Ingram AJ, Herzog CA. Anticoagulants in atrial fibrillation patients with chronic kidney disease. Nat. Rev. Nephrol. 2012;8:569-78.

31. Allon M. Evidence-based cardiology in hemodialysis patients. J Am Soc Nephrol. 2013;24:1934-43.

32. Hayashi M, Kaneko S, Shimano M, et al. Efficacy and safety of radiofrequency catheter ablation for atrial fibrillation in chronic hemodialysis patients. Nephrol Dial Transplant. 2014;29:160-7.

33. L'Allierpl, Ducharme A, Keller PF, Yu H, Guertin MC, Tardif JC. Angiotensin-converting enzyme inhibition in hypertensive patients is associated with a reduction in the occurrence of atrial fibrilation. J Am CollCardiol. 2004;44:159-64.

34. http://czasopisma.viamedica.pl/cj/article/view/ DOI 10.5603/CJ.a2013.0116

35. Berkowitsch A, Kuniss M, Greiss H, et al. Impact of impaired renal function and metabolic syndrome on the recurrence of atrial fibrillation after catheter ablation: a long term follow-up. Pacing Clin Electrophysiol. 2012;35:532-43.

36. Takahashi Y, Takahashi A, Kuwahara T, et al. Renal function after catheter ablation of atrial fibrillation. Circulation. 2011;124:2380-7.

37. Vardi M, Yeh RW, Herzog CHA, et al. Strategies for postmarketing surveillance of drugs and devices in patients with ESRD undergoing dialysis. Clin J Am Soc Nephrol. 2013;8:2213-220.