Kardiologija 2015.: periferna cirkulacija

Cardiology 2015: Peripheral Circulation

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Uvod

Na inicijativu Hrvatskoga kardiološkog društva (HKD) Radna skupina za angiologiju i periferne vaskularne bolesti odlučila je osvrnuti se na stanje u hrvatskoj angiologiji tijekom 2015. godine, a po uzoru na inicijativu Radne skupine za perifernu cirkulaciju Europskoga kardiološkog društva objavljenu u časopisu *European Heart Journal*. Cilj je bio osvrt na stajalište i ciljeve koje slijedi HKD, prema aktualnim spoznajama i događajima u Europskoj kardiološkoj zajednici, a koji su obilježili proteklu, 2015. godinu.[1]

U ovom ćemo se uvodniku osvrnuti na prevenciju kardiovaskularnih bolesti i na značenje novih biljega u kardiovaskularnom prepoznavanju, na dijagnostiku i liječenje bolesti perifernih arterija i, napokon, na vrlo aktualnu problematiku vezanu za liječenje venskog tromboembolizma.

Prevencija kardiovaskularnih bolesti

Prevencija kardiovaskularnih bolesti i dalje je vrlo aktualna tema, a posljednjih godina ona sve češće razmatra i proširene "vaskularne teritorije", prije svega karotidnu i perifernu cirkulaciju u procjeni kardiovaskularnog rizika. U **tablicu 1** uvrstili smo neke od preporuka uobličenih u aktualne smjernice za prevenciju kardiovaskularnih bolesti[2], koje je Europsko kardiološko društvo (ESC) objavilo u svibnju 2016. godine.

Debljina intima medija karotidne arterije (CIMT) postao je zanimljiv klinički podatak i "marker" koji je u žarištu kardiovaskularnog interesa kao potencijalni izazov u reklasifikaciji kardiovaskularnog rizika, iako ga aktualne smjernice ne preporučuju u rutinskoj primjeni. U

Introduction

At the initiative of the Croatian Cardiac Society (CCS), the Working Group on Angiology and Peripheral Vascular Diseases decided to address the state of Croatian angiology during 2015, based on the example of the Working Group on Peripheral Circulation of the European Society of Cardiology that was published in the European Heart Journal. The goal was to provide an overview of the positions and goals that CCS holds, based on the current knowledge and events in the European cardiologic community that marked the year 2015.[1]

This editorial will briefly address the prevention of cardiovascular diseases and the importance of new markers in cardiovascular identification, diagnosis and treatment of peripheral artery disease, and finally the current issues related to venous thromboembolism treatment.

Prevention of cardiovascular diseases

Prevention of cardiovascular diseases is still very topical, and has in recent years increasingly included the expanded "vascular territories", primarily carotid and peripheral circulation, in the assessment of cardiovascular risk. **Table 1** includes some of the recommendations published in current guidelines for the prevention of cardiovascular diseases[2] by the European Society of Cardiology (ESC) in May 2016.

Carotid intima-media thickness (CIMT) has become interesting clinical evidence and a marker in the focus of cardiovascular research as a potential challenge in the reclassification of cardiovascular risk, although current guidelines do not recommend it for routine application. A prospec-

TABLE 1. Methods of cardiovascular risk assessment – using insight into the state of peripheral blood vessels (modified from reference 2).

Recommendations	Class / Level
Atherosclerotic plaque detection by carotid artery scanning may be considered as a risk modifier in cardiovascular risk assessment.	IIb / B
Ankle-brachial index may be considered as a risk modifier in cardiovascular risk assessment.	IIb / B
Carotid ultrasound intima-media thickness screening for cardiovascular risk assessment is not recommended.	III / A

prospektivnom multicentričnom ispitivanju mjerenje CIMT-a pokazalo se povezanim s kardiovaskularnim događajima u ispitanika mlađih od 45 godina.[3]

Porast CIMT-a nije upozorio na dodatne informacije povrh standardnih rizičnih čimbenika, no ipak je otvoren prostor koji ga pozicionira kao biomarker za osobe koje još nisu kvalificirane za probir standardnih kardiovaskularnih čimbenika jer se oni uglavnom primjenjuju u osoba koje su starije od 40 godina.[1]

Stajališta HKD-a potpuno slijede smjernice ESC-a objavljene 2012. i 2016. godine[2,4] (**tablica 2**), premda je u svrhu procjene kardiovaskularnog rizika procjena CIMT-a još uvijek u kategoriji stručnog i znanstvenog interesa, pa tako i u našoj relativno maloj kardiološkoj sredini, i nema širu kliničku primjenu u rutinskoj procjeni rizika. HKD dijeli stajališta i priklanja se pravilima ESC-a koja navode da bi mjerenje CIMT-a moglo uzrokovati neadekvatnu zabrinutost i liječenje u slučaju pozitivnog rezultata, ali bi i negativan rezultat mogao dovesti do nepotrebne opuštenosti i lažne sigurnosti glede pravilnog odnosa prema zdravom načinu života. Ne preporuča se sustavna procjena kardiovaskularnog rizika u osoba mlađih od 40 godina za mušku populaciju i u žena mlađih od 50 godina prema najnovijim smjernicama o kardiovaskularnoj prevenciji publiciranih 2016. godine.

O aktualnoj temi kardiovaskularne prevencije u Hrvatskoj akademiji znanosti i umjetnosti 9. travnja 2015. godine u Zagrebu održan je znanstveni skup na kojemu se izlagalo o značenju biomarkera u prevenciji ateroskleroze. Tema je znanstvenoga skupa bila Asimptomatska ateroskleroza, a stručna su izlaganja sažeta i objavljena u zborniku radova. Zaključak skupa označio je potrebu za pozicioniranjem CIMT-a kao nove metode u kliničkoj praksi za koju su još uvijek potrebna klinička i ekonomska istraživanja, ali i ipak mogući potencijal u reklasifikaciji kardiovaskularnog rizika populacije s intermedijarnim rizikom.[5]

Na istom je skupu iznjedrena i potreba o personaliziranoj prevenciji asimptomatske ateroskleroze ističući potencijalne vrijednosti novih metoda koje još uvijek nisu pozicionirane u rutinskoj kliničkoj praksi i procjeni vaskularnoga statusa zdravih pojedinaca. Dokazana je povezanost kardiovaskularne "vulnerabilnosti" uz hemodinamske pokazatelje koji se po-

TABLE 2. From the current cardiovascular disease prevention guidelines of the European Society of Cardiology (modified from reference 2).

Recommendations	Class / Level
Systematic cardiovascular risk assessment is recommended in individuals at increased cardiovascular risk, i.e. with family history of premature cardiovascular disease, familial hyperlipidaemia, major cardiovascular risk factors (such as smoking, high blood pressure, diabetes or raised lipid levels) or comorbidities increasing cardiovascular risk.	I / C
It is recommended to repeat cardiovascular risk assessment every 5 years, and more often for individuals with risks close to thresholds mandating treatment.	I / C
Systematic cardiovascular risk assessment may be considered in men >40 years of age and in women >50 years of age or post-menopausal with no known cardiovascular risk factors.	IIb / C
Systematic cardiovascular risk assessment in men <40 of age and women <50 years of age with no known cardiovascular risk factors is not recommended.	III / C

tive multi-center study found that CIMT measurement was associated with cardiovascular events in participants under 45 years of age.[3]

CIMT increase did not provide further information beyond that from the standard risk factors, but the study supported its use as a biomarker for persons that are still not qualified for screening for standard cardiovascular risk factors, given that these are usually used in persons above 40 years of age.[1]

The position of CCS on this issue is fully in line with the ESC guidelines published in 2012 and 2016[2,4] (**Table 2**), although CIMT is still in the category of professional and scientific interest regarding cardiovascular risk assessment in our relatively small cardiovascular community and has no wider clinical application in routine risk assessment. CCS shares the positions and adheres to the rules of ESC, which states that CIMT measurement could cause inadequate concern and treatment in cases of false-positive results, but even a negative result could lead to unnecessary laxity and a false sense of safety regarding the proper relationship to a healthy lifestyle. Thus, the systematic assessment of cardiovascular risk in men younger than 40 years of age and women younger than 50 remains advocated by the newest guidelines on cardiovascular prevention published in 2016.

A scientific conference was held on the topic of cardiovascular prevention at the Croatian Academy of Sciences and Arts in Zagreb on April 9, 2015, where the significance of biomarkers in atherosclerosis prevention was discussed. The topic of the conference was "Asymptomatic Atherosclerosis", and the professional lectures were summarized and published in the Conference Proceedings. The conclusion of these discussions was that there was a need to position CIMT as a new method in clinical practice that still requires clinical and economic stud-

TABLE 3. Overview of some research results on endothelial function and the importance of vascular markers.

Vascular marker related to the endothelial function	Healthy population / coronary patients Value (± SD)	P value
ß index (e-tracking)	4.46 / 11,91 (± 1.56 / 5.08)	0.02
Augmentation index (Aix)	-1.38 / 23.15 (± 6.95 / 13.32)	0.02
Pulse wave velocity (PWV)	4.6 / 7.65 (± 0.92 / 1.44)	0.04

vezuju s kardiovaskularnim bolestima i čine markere bolesti, a to su: brzina pulsnog vala (PWV; engl. *pulse wave velocity*), dilatacija ovisna o protoku (FMD; engl. *flow mediated dilatation*) i pedobrahijalni indeks (ABI; engl. *ankle brachial index*). Klinička rutinska primjena u Republici Hrvatskoj još je uvijek predmet znanstvenih istraživanja u procjeni rizika zdravih asimptomatskih pojedinaca.[6]

Vlastita istraživanja (**tablica 3**) samo su dokaz naše prisutnosti i znanstvenog interesa za funkciju endotela u procjeni i značenju vaskularnih biljega u kardiovaskularnim bolestima.[7]

Mjerenje ABI-ja koji se potvrdio kao vaskularni pokazatelj, biomarker čije su vrijednosti repozicionirale rizik procijenjen Framingamskom bodovnom skalom u bolesnika s intermedijarnim rizikom, i to u širokome dobnom rasponu (od 35. do 74. godine života) posebno je istraživan u kohorti španjolske populacije.[8] U Hrvatskoj je mjerenje ABI-ja, iako davno etablirana i priznato neizostavna metoda, još uvijek zanemarena pretraga i u procjeni kardiovaskularnog rizika, ali, nažalost, i u funkcijskoj procjeni statusa perifernih arterija donjih udova. Ova je činjenica potvđena anketom koja je provedena u Hrvatskoj tijekom 10. kongresa HKD-a u listopadu 2014. godine.

Rezultati ankete u kojoj je sudjelovalo 88 liječnika (62 kardiologa, 14 internista i 12 liječnika drugih specijalnosti) upravo svjedoče o zanemarenosti spomenute metode u cjelokupnoj kardiološkoj praksi. Od ukupnoga broja sudionika anketi se odazvalo oko 20 % liječnika. Aktivno sudjelovanje u dijagnostičkom procesu i u procjeni bolesti perifernih arterija 56 % anketiranih nije primjenjivalo nijednu metodu u dijagnostici periferne arterijske bolesti, a samo 7 % rabilo je ABI kao metodu probira i kao inicijalnu, ključnu metodu u procjeni težine periferne arterijske bolesti. Ukupno 55 % bilo je onih koji su smatrali da bi im u svakodnevnoj procjeni arterijskoga statusa mjerenje ABI-ja pridonijelo ukupnoj procjeni kardiovaskularnoga statusa u bolesnika. Sve navedeno upućuje na potrebu ponovnog nametanja potrebe pridržavanja preporuka smjernica ESC-a za dijagnostiku i liječenje periferne arterijske bolesti predstavljenih još 2011. godine, a prevedene kao sažete smjernice predstavljene u Republici Hrvatskoj 2013.[9,10]

Smatramo vrijednim senzibilizirati kardiološku javnost o značenju primjene vaskularnih biomarkera u primarnoj i sekundarnoj kardiovaskularnoj prevenciji. Zato smo u **tablici 4**

TABLE 4. The applicability of vascular biomarkers in primary and secondary cardiovascular prevention (modified from reference 1).

Vascular biomarker	Class / Level	Risk stratification value / Simplicity of method
Ankle-brachial index	IIa / A	+++ / ++++
Arterial stiffness		
Pulse wave velocity (carotid, femoral artery)	IIa / A	++++ / +++
Carotid ultrasound	IIa / A	+++ / ++

ies but has potential for cardiovascular risk reclassification in the population under intermediate risk.[5]

The need for personalized prevention of asymptomatic atherosclerosis also became apparent over the course of this conference, stressing the potential value of new methods that have not yet been applied to routine clinical practice and vascular status assessment in healthy individuals. An association was demonstrated between cardiovascular vulnerability and hemodynamic indicators associated with cardiovascular diseases that thus represent disease markers, which are: pulse wave velocity (PWV), flow mediated dilatation (FMD), and ankle brachial index (ABI). Routine clinical application in the Republic of Croatia is still the subject of scientific studies on risk assessment in healthy asymptomatic individuals.[6]

Our own studies (**Table 3**) are proof in our scientific interest for endothelial function in the assessment and the importance of vascular markers for cardiovascular diseases.[7]

ABI measurement was confirmed to be a vascular indicator, a biomarker whose values reclassified risk assessed using the Framingham Risk Score in patients with intermediate risk in a wide age-range (35 to 74 years of age) in a special cohort study in a Spanish population.[8] In Croatia, ABI measurement is, though long-established as an accepted and indispensable method, still underused in the assessment of cardiovascular risk and unfortunately also in functional assessment of the state of the peripheral arteries of the lower extremities. This fact has been confirmed by a poll conducted in Croatia during the 10th CCS congress in October 2014.

The results of the poll, in which 88 physicians took part (62 cardiologists, 14 internists, and 12 other physicians with other specialties) bear witness to the neglect for this method in the overall cardiologic practice. Approximately 20% of the participants responded to the poll. Active participation in the diagnostic process and assessment of peripheral artery disease did not include any method in the diagnosis of peripheral arterial disease for 56% of those polled, and only 7% used ABI as a screening method and as the initial, key method in the severity assessment in peripheral artery disease. A total of 55% respondents believed that ABI measurement would contribute to total cardiovascular status assessment in patients during routine assessment of arterial disease. All this indicates the

prikazali samo najvažnije dosadašnje prihvaćene biomarkere čija je razina dokaza razine A.

Bolesti perifernih arterija

Dijagnostički proces i procjena bolesti perifernih arterija, unatoč objavljenim preporukama, i dalje se temelji samo na kliničkim pokazateljima, dupleksu arterijske cirkulacije te angiografiji.

Zanemariv je broj centara koji u dijagnostički proces uključuju pletizmografiju, segmentalne tlakove i ABI, iako je, prema preporukama ESC-a, spomenuta metoda neizostavna u procjeni periferne arterijske bolesti. U Republici Hrvatskoj su, na temelju podataka Centralnoga informatičkog sustava Hrvatskog zavoda za zdravstveno osiguranje (CEZIH/HZZO), tijekom 2015. godine izvedene ukupno 644 angiointervencije na perifernim arterijama (527 s ugradnjom jednog stenta i 117 s ugradnjom dvaju ili više stentova). U ovaj su broj uključene i intervencije na karotidnim arterijama. Karotidna endarterektomija, prema podatcima iz istog izvora, izvedena je na 1213 karotidnih arterija, a to je sukladno i preporukama i dokazima iz publikacije na koju se referiramo, sugerirajući endarterektomiju kao metodu koja se još uvijek preferira pred endovaskularnim liječenjem karotidne stenoze.

Venska tromboza

Niska je osviještenost javnosti vezana za pojavu VTE-a (venskog tromboembolizma), odnosno DVT-a (duboka venska tromboza) i PE-a (plućna embolija), a ona se procjenjuje na oko 44 do 59 % i niža je nego to informiranost glede pojave infarkta miokarda (88 %) i moždanog udara (90 %), kao i arterijske hipertenzije (90 %).[11] Upravo je stoga nužna dodatna javna ili medijska djelatnost kojom bi se povećala osviještenost javnosti za značenje VTE-a, pa tako i smanjila opterećenost pojavljivanjem proširene bolesti koja se može spriječiti.

U Republici Hrvatskoj o prevalenciji venske tromboze nemamo čvrstih objektivnih podataka jer ne postoji registar o venskoj trombozi. Spoznaja o stvarnoj prevalenciji bolesti samo je djelomično moguća jer se odnosi na samo bolnički liječenu populaciju. Prema podatcima dobivenima iz informatičke baze CEZIH/HZZO-a za 2015. godinu procjenjuje se da je u bolničkim uvjetima od venske tromboze bilo liječeno oko 1925 bolesnika. Na temelju toga broja bolesnika, koji su kao prvu dijagnozu imali vensku trombozu, nije moguće prosuđivati podatke o pravoj incidenciji bolesti. Ako prihvatimo činjenicu da je incidencija venske tromboze u Hrvatskoj slična incidenciji koja se navodi u europskim i američkim publikacijama, tada valja očekivati godišnju pojavnost bolesti između 6000 i 7000 oboljelih u općoj populaciji.

Važno je još jednom upozoriti i na već prije spominjane rezultate ankete vezane za način liječenja VTE-a. Podatci govore da 68 % liječnika primjenu antagonista vitamina K (VKA) u liječenju DVT-a i tromboembolijskoj profilaksi smatra zabrinjavajućom jer da bolesnici liječeni primjenom VKA u samo 30 % postižu terapijske vrijednosti INR-a. Oko 88 % bilo je onih koji su smatrali da bi primjena novih oralnih antikoagulansa pridonijela boljoj ustrajnosti, komforu i sigurnosti liječenja venske tromboze. Oko 70 % njih smatralo je da bi se i troškovi liječenja bolesnika s DVT-om pri tome smanjili s obzirom na

need to once again ensure adherence to recommendations in the ESC guidelines for the diagnosis and treatment of peripheral artery disease that were presented as early as 2011 and were translated as summarized guidelines in the Republic of Croatia in 2013.[9,10]

We believe it would be worthwhile to alert the cardiologic public to the importance of the application of vascular biomarkers in primary and secondary cardiovascular prevention, so in **Table 4** we showed only the most important biomarkers with A-level evidence that have been accepted so far.

Peripheral artery disease

The diagnostic process and disease assessment for peripheral artery diseases, despite the published guidelines, still relies only on clinical signs, arterial circulation duplex ultrasound, and angiography.

Only a negligible number of centers use plethysmography, segmental blood pressure, and ABI in the diagnostic process, despite the fact that this method is an indispensable part of peripheral artery disease assessment. Based on data from the Information Health System of the Republic of Croatia (CEZIH) of the Croatian Health Insurance Fund (HZZO), a total of 644 angiointerventions on peripheral arteries were performed in 2015 in the Republic of Croatia (527 with the implantation of 1 stent and 117 with the implantation of 2 or more stents). This number also includes carotid artery interventions. Carotid endarterectomy, based on the same data, was performed in 1213 carotid arteries, which is in line with the recommendations and evidence from the publication we are referring to, suggesting that endarterectomy is a method that is still preferred over endovascular treatment for carotid stenosis.

Vein thrombosis

Public awareness is low regarding venous thromboembolism (VTE) and deep vein thrombosis (DVT) as well as pulmonary embolism (PE) and is estimated at 44% to 59%, which is lower than awareness of myocardial infarction (88%) and stroke (90%) as well as arterial hypertension (90%).[11] Additional public or media engagement is necessary in order to increase public awareness of the significance of VTE and thus reduce the disease burden of this widespread but preventable disease.

We do not have clear objective data on the prevalence of venous thrombosis for the Republic of Croatia, since a registry for venous thrombosis does not exist. Knowing the true prevalence of the disease is only partially possible, since data only applies to the hospitalized part of the population. According to data from the CEZIH/HZZO database for 2015, it is estimated that approximately 1925 patients were treated for venous thrombosis in hospital conditions. It is not possible to determine the data on the true incidence of the disease based on this number of patients that had venous thrombosis as their initial diagnosis. If we accept that the incidence of venous thrombosis in Croatia is similar to the incidence reported in European and US publications, we can expect that the annual incidence in the general population is between 6000 and 7000 cases.

It is important to once again point out the abovementioned results of the poll on the way VTE is being treated. The data show that 68% of physicians believe that the application of vitamin K antagonists (VKA) in the treatment of DVT and thromboembolism prophylaxis is a cause for concern, since only 30% that pa-

postignutu učinkovitost, a pogotovo zbog manje pojave nuspojava.

Inicijativa Radne skupine za angiologiju i periferne vaskularne bolesti HKD-a u poboljšanju interesa i spoznaje o venskoj tromobozi vezana je za pripremu Nacionalnih preporuka za dijagnostiku i liječenje venske tromboze i venskog tromboembolizma, koje će uskoro biti predstavljene javnosti, a one se u nedostatku smjernica ESC-a za dijagnostiku i liječenje venske tromboze uglavnom oslanjaju na preporuke publicirane u časopisu *Chest* tijekom 2016. godine te smjernica za liječenje akutne plućne embolije.[12,13]

Zaključak

Smatramo da nije nevažno to što je čak 78 % kardiologa smatralo da bi trebalo osigurati dodatnu edukaciju iz angiologije u liječenju i dijagnostici bolesti vena i perifernih arterija. Kako bi se udovoljilo potrebama koje bi dovele do bolje kliničke prakse, usklađenosti prema postojećim smjernicama, potrebno je svakako postići sinergiju između mogućnosti koje određuje HZZO, ali i osnažiti inicijativu HKD-a, potaknuti i razvijati registre u području angiologije te potaknuti stručnu osjetljivost za probleme vezane za angiologiju u RH.

Smatramo važnim napomenuti da je uz HKD i Hrvatska akademija znanosti i umjetnosti tijekom svoje znanstveno-stručne djelatnosti u 2015. godini pridonijela promociji javnog i stručnog mnijenja akademske zajednice glede aktualnih tema periferne bolesti arterija i biomarkera u procjeni kardiovaskularnog rizika.

tients treated with VKA achieve target international normalized ratios (INR). Approximately 88% hold that the application of new oral anticoagulants would contribute to better compliance, comfort, and safety for venous thrombosis treatment. Approximately 70% of the respondents believed this would also reduce treatment costs for patients with DVT due to the increase in effectiveness, especially due to lower incidence of side effects.

The initiative of the Working Group on Angiology and Peripheral Vascular Diseases of the CCS to improve interest and awareness of venous thrombosis is related to the preparation of the National Guidelines for the Diagnosis and Treatment of Venous Thrombosis and Venous Thromboembolism, which will soon be presented to the public and which, given the lack of ESC guidelines on the diagnosis and treatment of venous thrombosis, mostly rely on the recommendations published in the *Chest* Journal during 2016 and treatment guidelines for acute pulmonary embolism.[12,13]

Conclusion

We believe it is not irrelevant that as many as 78% of cardiologists thought that further education in angiology should be ensured for the treatment and diagnostics of venous diseases and peripheral artery diseases. To satisfy these needs, which would lead to better clinical practice and compliance with current guidelines, it is necessary to achieve synergy between the possibilities determined by the Croatian Health Insurance Fund, but also strengthen the initiative of the CCS, encourage and develop registries in the field of angiology, and encourage professionals to be sensitive to the issues related to angiology in the Republic of Croatia.

We also believe it is important to emphasize that in addition to the CCS, the scientific and professional activities of the Croatian Academy of Sciences and Arts in 2015 also contributed to public and professional awareness of the academic community regarding the current topics in peripheral artery diseases and biomarkers in cardiovascular risk assessment.

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