

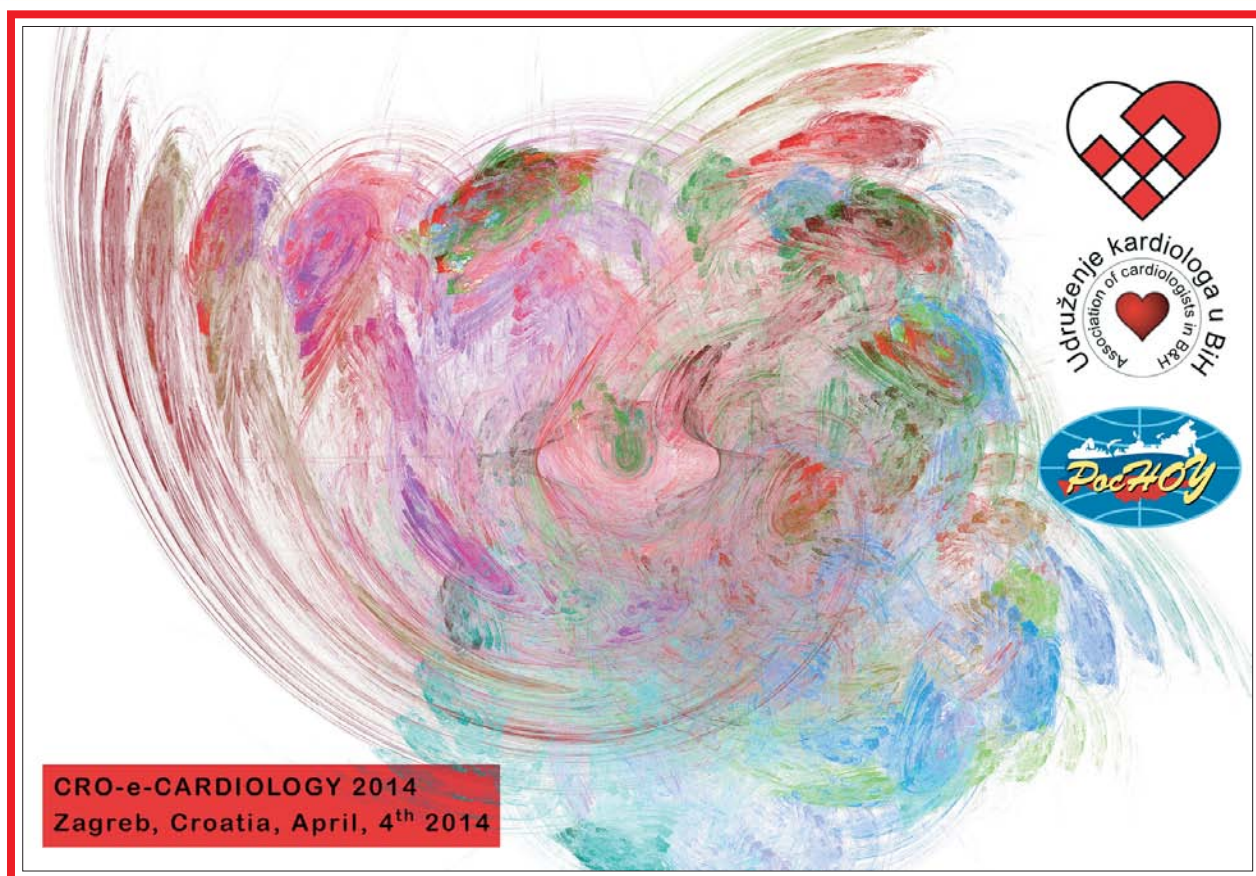
# CARDIOLOGIA CROATICA

BROJ / NUMBER 3-4  
GODINA / VOLUME 9  
OŽUJAK - TRAVANJ 2014.  
MARCH - APRIL 2014



ČASOPIS HRVATSKOGA KARDIOLOŠKOG DRUŠTVA  
JOURNAL OF THE CROATIAN CARDIAC SOCIETY

ISSN 1848-543X (Print)  
ISSN 1848-5448 (Online)  
UDK/UDC 616.12(051)=164.42=111



MEMBER OF THE ESC NATIONAL SOCIETIES CARDIOVASCULAR JOURNALS

[www.kardio.hr/cardiologia-croatica/arhiva.html](http://www.kardio.hr/cardiologia-croatica/arhiva.html)

# CARDIOLOGIA CROATICA

Časopis Hrvatskoga kardiološkog društva | Journal of the Croatian Cardiac Society

Godina — Volume 9 • Broj — Number 3-4 • Ožujak - Travanj 2014. — March - April 2014

formerly *Kardio list*

## Sadržaj / Table of contents

### International Scientific Symposium CRO-e-CARDIOLOGY 2014

April, 4<sup>th</sup> 2014 — Croatian Heart  
House, Zagreb, Croatia

CRO-e-CARDIOLOGY 2014 Uvodnik  
CRO-e-CARDIOLOGY 2014 Editorial  
stranica / page **83**

Konačni program  
Final Programme  
stranica / page **84-85**

Oral presentations  
stranica / page **86-108**

e-Posters  
stranica / page **109-115**

Akutni koronarni sindrom i  
intervencijska kardiologija u  
Dubrovniku. 2013. godina stručnog  
kontinuiteta i teritorijalnog  
diskontinuiteta

Acute coronary syndrome and  
interventional cardiology in Dubrovnik  
2013 as the year of professional  
continuity and territorial discontinuity  
stranica / page **117-126**

Transseptalna kateterizacija  
Transseptal catheterization  
stranica / page **127-133**

Kronična bubrežna bolest i fibrilacija  
atrija  
Chronic kidney disease and atrial  
fibrillation  
stranica / page **134-141**

Zdravo povrće za zdravo srce: šparoge  
Healthy vegetables for healthy heart:  
asparagus  
stranica / page **142-149**

Suvremeno liječenje arterijske  
hipertenzije fiksnom kombinacijom  
telmisartan-hidroklorotiazid

Contemporary treatment of  
hypertension by fixed-dose  
combination of telmisartan-  
hydrochlorothiazide  
stranica / page **150-153**

Nakladnik i izdavač / Editing and publishing company:  
Hrvatsko kardiološko društvo / Croatian Cardiac Society

Adresa / Address:  
Kišpatičeva 12, HR-10000 Zagreb, Croatia  
Telefon / Phone: +385-1-2388-888  
E-mail: [kardio@kardio.hr](mailto:kardio@kardio.hr)  
URL: <http://www.kardio.hr/cardiologia-croatica/arhiva.html>

Za nakladnika / For Publisher:  
Davor Miličić (HR)

Glavni urednik / Editor-in-Chief:  
Mario Ivanuša (HR)

Urednički odbor / Editorial Board:  
Marko Boban, Sandro Brusich, Mario Ivanuša, Anita Jukić,  
Sandra Makarović, Ivica Premuzić Meštrović, Deiti  
Prvulović, Alen Ružić, Kristina Selthofer-Relatić i Hrvoje  
Vražić

Savjet / Advisory Board:  
Mijo Bergovec (HR), Bojan Jelaković (HR), Žarko Mavrić  
(HR), Davor Miličić (HR), Jure Mirat (HR), Vjeran Nikolić-  
Heitzler (HR), Dubravko Petrač (HR), Stojan Polić (HR),  
Željko Reiner (HR) i Luka Zaputović (HR)

Tehnički urednik / Technical Editor:  
Stjepan Horvat (HR)

Priprema / Editing prepared by:  
ČVOR d.o.o. Bjelovar — [www.cvor.hr](http://www.cvor.hr)

Tisak / Printed by:  
Denona d.o.o. Zagreb — [www.denona.hr](http://www.denona.hr)

Prijevod / Translated by:  
Studium d.o.o. Zagreb — [www.studium-jezici.hr](http://www.studium-jezici.hr)

Naklada / Print run: **1.100 copies**

Informacije o pretplati / Subscription info:  
Tiskano izdanje je besplatno za liječnike, a mrežno izdanje  
je u cijelosti dostupno svima. / Physicians can receive the  
print editions of *Cardiologia Croatica* free of charge.  
*Cardiologia Croatica* is open access journal with free and  
unrestricted access for all online readers.

Članci su kategorizirani prema "Uputama za uredništva  
časopisa" koji su dostupni na portalu Hrcak / The articles  
are categorized according to "Instructions for journal  
editorial boards" available at the Hrcak web site:  
<http://hrcak.srce.hr/admin/upute.doc>

Copyright:  
Hrvatsko kardiološko društvo / Croatian Cardiac Society.

This publication was printed with an unrestricted educational  
grant from: Krka-Farma d. o. o., Zagreb, Croatia



Hrvatsko kardiološko društvo  
Croatian Cardiac Society

Adresa / Address: Hrvatsko kardiološko društvo  
HR-10000 Zagreb, Kišpatičeva 12, Croatia

• [www.kardio.hr](http://www.kardio.hr) • E-mail: [kardio@kardio.hr](mailto:kardio@kardio.hr)

Žiro-račun: 2360000-1101412726  
OIB: 18767182406

Predsjednik / President:  
Dopredsjednik / Vice-President:  
Tajnik / Secretary:  
Rizničar / Treasurer:

Davor Miličić  
Diana Delić-Brkljačić  
Darko Počanić  
Eduard Margetić

Upravni odbor / Management: Robert Bernat, Duška  
Glavaš, Mladen Jukić, Viktor Persić, Pejo Samardžić, Maja  
Strozzi, Josip Vincelj, Luka Zaputović i predsjednici  
podružnica HKD.



# Simpozij CRO-e-CARDIOLOGY 2014

## CRO-e-CARDIOLOGY 2014 Symposium

Goran Krstajić\*

Direktor Simpozija CRO-e-CARDIOLOGY 2014  
*Symposium Director CRO-e-CARDIOLOGY 2014*

Zanimna mi je čast ugostiti Vas na Simpoziju CRO-e-CARDIOLOGY 2014, znanstvenom i stručnom međunarodnom simpoziju u suorganizaciji Hrvatskog kardiološkog društva, Udruženja kardiologa u Bosni i Hercegovini i Ruskog Novog Sveučilišta iz Moskve.

Simpozij CRO-e-CARDIOLOGY 2014 se organizira kao interaktivni, edukacijski simpozij visoke razine kvalitete koji će obuhvatiti najzanimljivija područja uporabe informacijske tehnologije (IT) kao široko rasprostranjene mogućnosti primjene u različitim područjima kardiologije. To podrazumijeva primjenu IT u istraživanju, ali i svakodnevnoj kliničkoj praksi unutar ili izvan bolničkog okružja.

Područje rada i istraživanja e-Kardiologije je promocija specijaliziranih računalnih postupaka u kardiovaskularnom slikovnom prikazu, računalnom otkrivanju znanja, umjetnoj inteligenciji, strojnom učenju, modeliranju i analizi biosignala, bazi podataka, intra- i interbolničkoj komunikaciji i razvoju prediktivnih modela. Ove aktivnosti omogućavaju logističku potporu znanstvenicima iz različitih područja u suradnji na novim temama i primjenama u kardiologiji.

Stručni sadržaj Simpozija CRO-e-CARDIOLOGY 2014 donosi pregled najvažnijih suvremenih tema iz elektrokardiologije, kardiometrije, elektrofiziologije, intervencijske kardiologije, ehokardiografije i ostalih slikovnih prikaza, analize podataka, komunikacijskih servisa u kardiologiji i računarstva u kardiologiji. Simpozij je namijenjen kardiolozima, specijalizantima kardiologije, internistima, anesteziolozima, medicinskim informatičarima, medicinskim fizičarima i svim drugim liječnicima koji u svakodnevnom stručnom i znanstvenom radu koriste IT.

Veselim se Vašem dolasku u Zagreb, u Hrvatsku kuću srca.

I am greatly honored to welcome you to CRO-e-CARDIOLOGY 2014 Symposium, the scientific and expert international symposium co-organized by the Croatian Cardiac Society, Association of Cardiologists in Bosnia and Herzegovina and Russian New University from Moscow.

CRO-e-CARDIOLOGY 2014 Symposium is organized as a high quality interactive and educational symposium that will cover the most interesting areas of using information technology (IT) applied in various areas of cardiology. It includes the application of IT in research, and also in daily clinical practice inside or outside the hospital environment.

The field of work and research of e-Cardiology is the promotion of specialized computer procedures in cardiovascular imaging, computer-aided discovery of knowledge, artificial intelligence, machine learning, modeling and analysis of bio-signals, database, intrahospital and interhospital communication and development of predictive models. These activities provide logistical support to scientists and clinicians from different fields to cooperate on new topics and applications in cardiology.

The professional contents of CRO-e-CARDIOLOGY 2014 Symposium gives an overview of the most significant contemporary issues in electrocardiology, cardiometry, interventional cardiology, electrophysiology, echocardiography and other imaging modalities, data analysis, communication services in cardiology and computing in cardiology. The Symposium is intended for cardiologists, cardiology specialists, cardiology residents, internists, anesthesiologists, medical IT experts, medical physicists and all other physicians who use IT in their daily professional and scientific work.

I look forward to seeing you in Zagreb, in Croatian Heart House.

Received: 3<sup>rd</sup> Mar 2014

\*Address for correspondence: Poliklinika za prevenciju kardiovaskularnih bolesti i rehabilitaciju, Draškovićeve 13, HR-10000 Zagreb, Croatia.

Phone: +385-1-4612290

E-mail: eCardiology@kardio.hr



# Symposium CRO-e-CARDIOLOGY 2014

4. travnja 2014. — Hrvatska kuća srca, Ilica 5/II, Zagreb, Hrvatska

April, 4<sup>th</sup> 2014 — Croatian Heart House, Ilica 5/II, Zagreb, Croatia

Međunarodni znanstveni simpozij / **International Scientific Symposium**

Organizator / **Organisation:**

**Radna skupina e-Kardiologija Hrvatskoga kardiološkog društva**

**Croatian Cardiac Society Working Group on e-Cardiology**

<http://ekardiologija.kardio.hr/>



Suorganizatori / **Co-Organizers:**

**Radna grupa e-Kardiologija Udruženje kardiologa u BiH**

**Association of Cardiologists of Bosnia and Herzegovina Working Group on e-Cardiology**

<http://e-kardiologija.ukbih.com/>



**Rusko Novo Sveučilište, Moskva, Rusija**

**Russian New University (RosNOU), Moscow, Russia**

[www.rosnou.ru](http://www.rosnou.ru)



Predsjednik / **Symposium Director:** Goran Krstajić (HR)

Supredsjedatelji / **Co-Directors:** Davor Miličić (HR), Zumreta Kušljugić (BiH), Mikhail Rudenko (RUS), Enno van der Velde (NL)

Tajnik / **Symposium Secretary:** Mario Ivanuša (HR)

Organizacijski odbor / **Organizing Committee:** Goran Krstajić (HR), Mario Ivanuša (HR)

Znanstveni odbor / **Scientific Committee:** Nico Bruining (NL), Enrico Gianluca Caiati (I), Duško Cerovec (HR), Christof Colb (DE), Diana Delić Brkljačić (HR), Dragan Gamberger (HR), Inge Heim (HR), Mario Ivanuša (HR), Tatiana Kharcenko (RUS), Goran Krstajić (HR), Zumreta Kušljugić (BiH), Nihad Mešanović (BiH), Davor Miličić (HR), Jure Mirat (HR), Viktor Peršić (HR), Hrvoje Pintarić (HR), Mihail Rudenko (RUS), Alen Ružić (HR), Elnur Smajić (BiH), Robert Steiner (HR), Jadranka Šeparović-Hanževački (HR), Peter van Dam (NL), Enno van der Velde (NL), Josip Vincelj (HR), Hrvoje Vražić (HR), Ivo Vuković (HR)

Službeni jezici / **Official languages:** Hrvatski i engleski / **Croatian and English**

Kotizacija / **Fees:** standardna / **standard 150 EUR**; specijalizanti do 35 godine / **Residents up to 35 years 100 EUR**; izlagači & sponzori / **Exhibitor & Sponsor 125 EUR**; osobe u pratnji / **accompanying persons 50 EUR**.

Kontakt / **Contact:** [ecardiology@kardio.hr](mailto:ecardiology@kardio.hr)

Potvrđnice / **Accreditation:** Svi sudionici primit će potvrdu o sudjelovanju i bodove / **All participants will receive a certificate of attendance and the credits**

Službena turistička agencija simpozija i tehnička organizacija / **Travel agency and technical organization:** Gold Tours, Zagreb, Croatia, <http://www.gold-tours.com/>

## Finalni program / Final Programme

8.00-9.00 — Registracija sudionika / **Registration of participants**

9.00-9.45

Goran Krstajić (HR) — Pozdravna riječ / **Welcome Note**

Davor Miličić (HR) — Pozdravna riječ / **Welcome Note**

Zumreta Kušljugić (BiH) — Pozdravna riječ / **Welcome Note**

Mikhail Rudenko (RUS) — Pozdravna riječ / **Welcome Note**

Fractal and chaos music show performed by **Mejrema Reuter & Emil Vargović**

Gradonačelnik **Milan Bandić / Milan Bandić, The Mayor of Zagreb** — Pozdravna riječ i službeno otvaranje

Simpozija / **Welcome Note and Official Opening of the Symposium**



## 9.45-10.30 OPENING LECTURES

Goran Krstačić (HR), Enno van der Velde (NL)

9.45-10.00 — Davor Miličić (HR): Heart failure: state of the art

10.00-10.15 — Zumreta Kušljugić (BiH): Exercise testing to stratify risk in asymptomatic moderate et severe aortic stenosis

10.15-10.30 — Mikhail Rudenko (RUS): Cardiometry: a new fundamental research area in cardiology

10.30-11.00 **Coffee break & e-posters**

## 11.00- 12.45 ELECTROCARDIOLOGY / ELECTROPHYSIOLOGY

Duško Cerovec (HR), Tatiana Kharcenko (RUS)

11.00-11.15 — Goran Krstačić (HR): Chaos and string theory: Sunset or new dawn?

11.15-11.30 — Hrvoje Vražić (HR): Cardiovascular implantable electronic devices and electromagnetic interference.

11.30-11.45 — Christof Colb (DE): Single versus dual chamber ICD for the avoidance of inappropriate shocks — results from the OPTION trial?

## 11.45-12.30 CARDIOVASCULAR IMAGING

Viktor Peršić (HR), Josip Vincelj (HR)

11.45-12.00 — Nico Bruining (NL): Identifying post-MI patients at risk by imaging techniques

12.00-12.15 — Jadranka Šeparović-Hanževački (HR): 3D Echocardiography — valve morphology

12.15-12.30 — Diana Delić Brkljačić (HR): Emergency echocardiography

## 12.30 — 13.15 CARDIOVASCULAR IMAGING II

Jadranka Šeparović-Hanževački (HR), Diana Delić Brkljačić (HR)

12.30-12.45 — Viktor Peršić (HR): MRI of the heart: more than the morphological analysis

12.45-13.00 — Mladen Jukić (HR): To stent or not to stent"; what is the role CCTA in clinical decision-making?

13.00-13.15 — Peter van Dam (NL): Inverse procedures for engineers and clinicians

13.30 — 14.30 **Lunch & e-posters**

## 14.30 — 15.15 DATA ANALYSIS

Mario Ivanuša (HR), Nihad Mešanović (BiH)

14.30-14.45 — Enno van der Velde (NL): Using data from electronic health record systems in clinical research

14.45-15.00 — Dragan Gamberger (HR): Descriptive and predictive modeling

15.00-15.15 — Inge Heim (HR): Data collecting for the acute myocardial infarction register

## 15.15-16.15 INFORMATION TRANSFER IN CARDIOLOGY

Zumreta Kušljugić (BiH), Dragan Gamberger (HR)

15.15-15.30 — Nihad Mešanović (BiH): Information processing in cardiology

15.30-15.45 — Mario Ivanuša (HR): mHealth in cardiology

15.45-16.00 — Elnur Smajić (BiH): Design and implementation of health information systems in cardiology

16.00-16.15 — Alen Ružić (HR): Internet — based interventions for cardiovascular prevention: focus on overweight and obesity

## 16.15 — 17.00 INVASIVE CARDIOLOGY

Peter van Dam (NL), Ivo Vuković (HR)

16.15-16.30 — Robert Steiner (HR): Radiation exposure in interventional cardiology

16.30-16.45 — Jure Mirat (HR): Urgent situation in invasive cardiology

16.45-17.00 — Hrvoje Pintarić (HR): Why transradial instead of transfemoral approach for the percutaneous coronary intervention

17.00 — Zaključak, završna riječ i završetak Simpozija CRO-e-CARDIOLOGY 2014 / **Conclusion & final word Symposium CRO-e-CARDIOLOGY 2014**

18.00 — Svečana večera u restoranu "Kaptolska klet" / **Gala Dinner at the Restaurant "Kaptolska klet"**

Prošireni sažetak / Extended abstract

## *Exercise testing to stratify risk in asymptomatic moderate and severe aortic stenosis*

Zumreta Kušljugić<sup>1\*</sup>, Fahir Baraković<sup>1</sup>, Larisa Dizdarević-Hudić<sup>1</sup>, Mirza Dilić<sup>2</sup>, Elnur Smajić<sup>1</sup>, Melika Avdagić<sup>1</sup>, Katarina Kovačević-Divković<sup>1</sup>, Amira Bijedić<sup>1</sup>

<sup>1</sup>University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina

<sup>2</sup>Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

**Introduction:** The literature contains various data regarding the value of the exercise testing in patients with asymptomatic aortic stenosis (AS). *The aim:* To determine the importance of exercise testing in cardiovascular risk stratification in patients with moderate severe to severe aortic stenosis.

**Methods and Results:** Out of a total 33 patients with moderate severe to severe asymptomatic aortic stenosis (mean aortic area EOA  $0.9 \pm 0.34$  cm<sup>2</sup>) we followed up 31 patients (two were excluded) during the 12 months' period by clinical, transthoracic echocardiogram and treadmill stress testing. 18 (58%) patients discontinued the test due to limiting symptoms, and had severe aortic stenosis (EOA  $\leq 0.8$  cm<sup>2</sup>).

During the follow-up, 11 patients spontaneously developed severe symptoms within 12 months' period, of whom 8 underwent aortic valve replacement, one patient died (sudden cardiac death), and two patients had a stroke. A total of 20 patients remained free of any symptoms. The highest predictive value is EOA  $\leq 0.8$  cm<sup>2</sup> for the provoked symptom test and it is 85%. ST depression had the highest negative predictive value.

**Conclusion:** Only limiting symptoms with critical aortic of area (EOA  $\leq 0.8$  cm<sup>2</sup>) have a positive predictive value.

**KEYWORDS:** asymptomatic aortic stenosis, treadmill stress testing, prognosis.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):86.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Javna zdravstvena ustanova Univerzitetski klinički centar Tuzla, Trnovac bb, 75 000 Tuzla, Bosnia and Herzegovina.

Phone: +387-35-303-500

E-mail: [zumreta.kusljugic@ukctuzla.ba](mailto:zumreta.kusljugic@ukctuzla.ba)

# Cardiometry as a new fundamental scientific field in cardiology

Mikhail Y. Rudenko\*, Vladimir A. Zernov, Olga K. Voronova

Russian New University, Moscow, Russian Federation

Our fundamental research in hemodynamics allows us to develop a new mathematical model of blood flow in the cardiovascular system which is in line with actual data in practice. It provides us some new data on the performance of various cardiovascular system segments responsible for the circulation maintenance. Our research has resulted in the development of an innovative technology and a device for accurate non-invasive measuring of hemodynamic parameters which was not possible earlier. The use of the device helps us obtain some new information that is the basis for a radically new ECG and Rheo classification. It is based on

the cardiac cycle phase analysis. It is precisely the methodology that is capable of revealing the heart performance mechanism, which could not be explored earlier, and investigating progression of various pathological processes. Mechanisms of sudden cardiac death and those of energetic resources responsible for maintaining the normal hemodynamics have been detected by our R & D team. The method for non-invasive assessment of cardiac muscle metabolic processes has been developed. The core principles which constitute the basis of cardiometry as a new scientific field have been defined in our research.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Russian New University, Moscow, Radio Street 22, Postal index 105005, Russian Federation.

Phone/Fax: +7 495 925-03-83

E-mail: [cardiocode.rudenko@gmail.com](mailto:cardiocode.rudenko@gmail.com)

**KEYWORDS:** cardiometry, ECG, Rheo, hemodynamics, mathematical model of blood flow.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):87.

## Literature

1. Rudenko MY, Zernov VA, Voronova OK, et al. Theoretical Principles of Heart Cycle Phase Analysis. ISBN 978-3-937909-57-8.
2. Krstacic G, Krstacic A, Smalcelj A, Milicic D, Jembrek-Gostovic M. The «Chaos Theory» and non-linear dynamics in heart rate variability analysis: does it work in short time series in patients with coronary heart disease? *Ann Noninvasive Electrocardiol.* 2007;12(2):130-6.
3. Gamberger D, Lavrač N, Krstacic G, Šmuc T. Inconsistency tests for patient records in a coronary heart disease database. In R. Brause & E. Hanisch (Eds.), *Medical Data Analysis SE-22 2000*;1933:183-9. Springer Berlin Heidelberg. Doi:10.1007/3-540-39949-6\_22.
4. Macfarlane PW, Clark EN. ECG measurements in end QRS notching and slurring. *J Electrocardiol.* 2013;46:385-9.
5. Macfarlane PW, Oosterom A, Janse M, Kligfield P, Camm J, Pahlm O. (Eds.). *Cardiac Electrophysiology, ECG Systems and Mathematical Modeling.* 2012, XI, 497p., ISBN 978-0-85729-870-6
6. Yong CM, Perez M, Froelicher V. Prognostic implications of the J wave ECG patterns. *J Electrocardiol.* 2013;46:408-10.
7. Rudenko MY, Zernov VA, Mamberger KK, Rudenko SM. ECG as a quest for extracting new data: non-invasive measurement of acid-alkaline parameters; *Cardiometry.* 2013;(3):45-57; doi: 10.12710/cardiometry.2013.3.4557. Available from: [www.cardiometry.net/no3-november-2013/ecg-as-a-quest-for-extracting-new-data](http://www.cardiometry.net/no3-november-2013/ecg-as-a-quest-for-extracting-new-data)
8. Zomer AC, Vaartjes I, van der Velde ET, et al. Prognosis of heart failure in adults with congenital heart disease. *J Am Coll Cardiol.* 2011;57(14 Suppl):E410.

# Theory of chaos and theory of string

Goran Krstajić<sup>1\*</sup>, Antonija Krstajić<sup>2</sup>

<sup>1</sup>Institute for Cardiovascular Prevention and Rehabilitation, Zagreb, Croatia

<sup>2</sup>University Hospital Centre "Sestre milosrdnice", Zagreb, Croatia

At the turn of the millennium it became apparent that science is fully losing its foundations — objective reality and the consequent determinism. The illusion of objectivity has already been eliminated by quantum science, showing how human consciousness plays a significant role in the quantum realm of subatomic matter. Scientists Descartes and Newton founded the science on assumption that the consciousness has no effect on reality. The consciousness itself was shown isolated, even from the domain of religion. It was believed that everything in nature could be explained by mechanistic terms, the universe itself was assumed to be a huge mechanical clock. Causal determinism, already damaged by quantum science with the uncertainty principle in quantum space was finally destroyed by the theory of chaos.<sup>1</sup>

The theory of chaos suggests that all events in nature are chaotic and unpredictable and that physical laws can only operate within the confined boundaries, giving space for creativity and spontaneity. Cause and consequence are reversed, since the fractal as a cause attracts consequential effects. Chaos means a kind of temporal behavior in which the difference between the two states initially grows exponentially with time. Chaotic system is extremely sensitive to the initial state and unpredictable in the long time scale, where the initial state is rarely known with absolute precision.<sup>2</sup> The systems we find in nature exhibit the characteristics of nonlinear and chaotic behavior. We can attempt to show all systems as linear, near-equilibrium systems. However, if a continuous "flow" of energy is sufficient to arouse the system sufficiently, it will become nonlinear or even chaotic. Chaos can be more easily understood when compared with the other two forms of behavior by a random, uncontrolled system and system of periodicity. Random behavior is never repeated in the same form and it is unpredictable and disorganized. A typical example is normal sinus rhythm recorded by ECG. If we know the amplitude, frequency and phase of the sine wave, we can at any time predict the incidence and amplitude of the sine wave.<sup>3</sup> Chaos is different from the behavior of periodicity and randomness, but it also includes the features of the both systems at the same time. Although

chaotic behavior seems to be disorganized, random behavior, it is actually a deterministic, periodic behavior. The most important criteria of chaotic behavior are: Chaos can be deterministic and aperiodic. Unlike the Newton's laws of physics, the chaotic behavior is never exactly repeated. There are no visible cycles that circulate at regular time intervals. Chaotic systems are very dependent on the initial conditions.<sup>4</sup> This means that very small changes in the initial condition can result in large differences at a later time period. Even chaotic behavior is limited. As the system is becoming controlled, behavior is becoming limited and predictability grows and eventually every chaotic behavior has an ultimate form.<sup>5</sup> Chaotic behavior in general has a definite form, while parts of a pattern have a similar form.<sup>6</sup> Thus, the theory of chaos shows that our universe is in no way deterministic, but it is creative and eternally evolving.<sup>7</sup>

In an attempt to unify Einstein's theory of relativity and that of quantum physics, and in accordance with the mainstream physics, the Holy Grail of contemporary physics would be the theory of string". The theory of string should allow the Einstein's unification theory that would connect the four existing force fields (strong and weak nuclear forces, electromagnetic forces and forces of gravity) in a unified theory of everything (theory of everything; T.O.E.).<sup>8</sup> In theory, string is the building block of a matter, a vibrating variable, which can have loose ends or is one-dimensional closed loop. Depending on a variety of spins and frequencies of vibrating string, various subatomic particles are reflected. In theory of string, there is only one fundamental cause, vibration of the string, but the note played on the string is actually accountable for a different type of a particle. The string itself is so small that it is impossible to imagine its existence. The string is hypothetically said to be as big as an atom, if the atom is as big as the Earth. This means that the string is incredibly small. Should the theory ever be effective, the basic inquiry will be whether scientists will be able to prove the existence of strings in their laboratories. The theory of string predicts the existence of at least 10 or more dimensions. Physicists around the world today still agree that such physical dimensions themselves still cannot explain our physical reality. The problem of the theory of string is also the existence of several theories of string in order to obtain a more efficient model and those theories of string are so complex that their complete understanding and explanation is still eagerly expected. In fact, we are going to face an interesting future!

**KEYWORDS:** theory of chaos, fractal, theory of string.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):88-89.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Poliklinika za prevenciju kardiovaskularnih bolesti i rehabilitaciju, Draškovićevea 13, HR-10000 Zagreb, Croatia.

Phone: +385-1-4612-290

Fax: +385-1-4612-343

E-mail: [goran.krstacic@zg.t-com.hr](mailto:goran.krstacic@zg.t-com.hr)



## Literature

1. Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. *Lancet*. 1996; 347:1312-4.
2. Krstacic G. Dissertation: Non-linear dynamics in short time series in patient with stable coronary heart disease. Zagreb University School of Medicine (2002).
3. Krstacic G, Krstacic A, Smalcelj A, Milicic D, Jembrek-Gostovic M. The "Chaos Theory" and non-linear dynamics in heart rate variability analysis: does it work in short time series in patients with coronary heart disease? *Ann Noninvasive Electrocardiol*. 2007;12(2):130-6.
4. Krstacic G, Parati G, Gamberger D, Castiglioni P, Krstacic A, Steiner R. Heart rate variability and nonlinear dynamic analysis in patients with stress-induced cardiomyopathy. *Med Biol Eng Comput*. 2012;50(10):1037-46.
5. Martinis M, Knezević A, Krstacic G, Vargović E. Changes in the Hurst exponent of heartbeat intervals during physical activity. *Phys Rev E Stat Nonlin Soft Matter Phys*. 2004;70(1 Pt 1):012903. Epub 2004 Jul 21.
6. Glass L. Chaos and heart rate variability. *J Cardiovasc Electrophysiol*. 1999;10:1358-60.
7. Krstacić G. Heart rate variability based on chaos theory and non-linear dynamics. *Cardiol Croat*. 2012;7(3-4):93-4.
8. Krstacić G, Krstacić A. From chaos to string theory. *Cardiol Croat*. 2012;7(Suppl 1):82.



# Cardiovascular implantable electronic devices and electromagnetic interference

Hrvoje Vražić<sup>1,2\*</sup>, Christof Kolb<sup>2</sup>

<sup>1</sup>University Hospital Dubrava, Zagreb, Croatia

<sup>2</sup>German Heart Centre of the State of Bavaria and the Technical University Munich, Munich, Germany

**Introduction:** Most frequently used cardiovascular implantable electronic devices for the treatment of arrhythmias are pacemakers and implantable cardioverter defibrillators (ICDs). It has been shown that the function of these cardiac rhythm devices can be impaired by electromagnetic interference from the devices and systems emitting magnetic fields, causing either temporary or permanent system malfunction.

**Methods:** Literature review<sup>1-3</sup> and own results<sup>4</sup> from the studies examining the potential electromagnetic interference of hand metal detectors among the patients with implanted cardiovascular implantable electronic devices performed in Deutsches Herzzentrum Munich will be used.

**Results:** Sources of electromagnetic interference are frequently encountered in daily life, emanating from cellular phones, anti-theft devices, metal detectors, various remote controls, improperly wired/grounded appliances coming into the contact with the body, MP3 players, induction ovens and many other devices<sup>1-3</sup>. Increasing global efforts to intensify security screening measures in the past decade have also brought into focus the use of metal detectors (which create a magnetic field that might interfere with the function of car-

diovascular implantable electronic devices); they are nowadays routinely used in many settings to detect ferrous and other dangerous items. Patients with pacemakers and implantable cardioverter defibrillators are often advised to avoid screening with metal detectors because of the risk for electromagnetic interference. Another important group of sources of electromagnetic interference is that which is encountered in workplace and/or industrial environments, such as high voltage power lines, transformers, welders, electric motors, and many others. Last, but not least, are those sources are found in the medical environment: magnetic resonance image scanners, electrosurgery, defibrillation, neurostimulators, TENS devices, radiofrequency catheter ablation, and therapeutic diathermy.

**Conclusions:** Although the majority of data available is based on case reports, there are a few studies examining effects of electromagnetic interference on cardiovascular implantable electronic devices. Majority of problems that occur are transient in nature, and, more important, easily avoidable. Physicians should be aware of and familiarized with the most common interactions of electromagnetic interference and cardiovascular implantable electronic devices.

**KEYWORDS:** cardiovascular implantable electronic device, pacemaker, implantable cardioverter defibrillator, electromagnetic interference

**CITATION:** *Cardiol Croat.* 2014;9(3-4):90.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Klinička bolnica Dubrava, Avenija Gojka Šuška 6, HR-10000 Zagreb, Croatia.

Phone: +385-1-2902-444

E-mail: [vrazic@gmail.com](mailto:vrazic@gmail.com)

## Literature

1. Pinski SL, Trohman RG. Interference in implanted cardiac devices, Part I. *Pacing Clin Electrophysiol.* 2002;25:1367-81.
2. Thaker JP, Patel MB, Jongnarangsin K, Liepa VV, Thakur RK. Electromagnetic interference with pacemakers caused by portable media players. *Heart Rhythm.* 2008;5:538-44.
3. Trigano A, Blandeau O, Dale C, Wong MF, Wiart J. Reliability of electromagnetic filters of cardiac pacemakers tested by cellular telephone ringing. *Heart Rhythm.* 2005;2:837-41.
4. Jilek C, Tzeis S, Vrazic H, et al. Safety of screening procedures with hand-held metal detectors among patients with implanted cardiac rhythm devices: a cross-sectional analysis. *Ann Intern Med.* 2011;155(9):587-92.

# Single versus dual chamber implantable cardioverter defibrillator for the avoidance of inappropriate shocks - results from the OPTION trial

Christof Kolb\*

German Heart Centre of the State of Bavaria and the Technical University Munich, Munich, Germany

**Introduction:** Implantable Cardioverter Defibrillators (ICD) are considered to be the treatment of choice for primary and secondary prevention of sudden cardiac death. However, the therapy is burdened by inappropriate ICD shocks (for example for supraventricular tachyarrhythmias) which reduce patient's quality of life and acceptance of the device, although dual chamber (DC) ICD have access to atrial and ventricular information for tachyarrhythmia discrimination. Recent studies have failed to show a clear benefit in reducing inappropriate shocks by these devices<sup>1-3</sup>. But adequately powered trials with a long-term follow-up are scarce.

**Methods:** Patients (pts) were recruited in 54 international centres and supplied with a DC ICD. A total of 453 pts were randomised to receive either standard SC programming or optimised DC programming<sup>4</sup>. Optimised DC programming was defined by the activation of the discrimination algorithm (PARAD+) and a mode (SafeR) to minimise ventricular pacing (Vp). ICD indications were primary (75%) or secondary (25%) prevention of sudden cardiac death; pts were aged 63±11 years (86% males). For the both groups, zones of arrhythmia detection were set with the following inferior cut-

offs: VF 240; Fast VT 200; VT 170; slow VT 120 bpm. ATP and/or shock therapies were recommended to be activated in all these zones. Pts' outcome measures were the occurrence of inappropriate shocks, all-cause mortality and cardiovascular morbidity.

**Results:** During an average follow-up (FU) of 23±8 months, DC ICD-therapy, as compared to SC ICD-therapy, was associated with significantly fewer pts experiencing inappropriate shocks (10/230 pts=4.3% vs. 23/223 pts=10.3%; p=0.0146) and longer time to first occurrence of inappropriate shock (p=0.0122 in Kaplan Meier analysis). Comparing DC- and SC ICD-therapy referring to mortality or cardiovascular events statistical equivalence was reached (p<0.0001), with similar rates in the sub-items of all cause deaths (21/230 pts=9 % vs. 18/223 pts=8%) and cardiovascular events (33/230 pts=14% vs. 40/223 pts=18%).

**Conclusion:** DC-therapy with optimized arrhythmia discrimination and minimised Vp, as compared to standard SC-therapy, was associated with a significantly lower occurrence of inappropriate shocks over the 2 years follow up. This benefit was reached with an equivalent rate of all-cause mortality and cardiovascular events.

**KEYWORDS:** arrhythmia discrimination, inappropriate shocks, implantable cardioverter defibrillator, pacing, shock, survival, tachyarrhythmias.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):91.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Deutsches Herzzentrum München, Klinik für Herz- und Kreislauferkrankungen, Lazarettstr. 36, DE-80636 München, Germany.

Phone: +49-89-1218-2020

Fax: +49-89-1218-4593

E-mail: kolb@dhm.mhn.de

## Literature

1. Deisenhofer I, Kolb C, Ndrepepa G, et al. Do current dual chamber cardioverter defibrillators have advantages over conventional single chamber cardioverter defibrillators in reducing inappropriate therapies? A randomized, prospective study. *J Cardiovasc Electrophysiol.* 2001;12:134-42.
2. Theuns DA, Klootwijk AP, Goedhart DM, Jordaens LJ. Prevention of inappropriate therapy in implantable cardioverter-defibrillators: results of a prospective, randomized study of tachyarrhythmia detection algorithms. *J Am Coll Cardiol.* 2004;44:2362-7.
3. Friedman PA, McClelland RL, Bamlet WR, et al. Dual-chamber versus single-chamber detection enhancements for implantable defibrillator rhythm diagnosis: the Detect SupraVentricular Tachycardia study. *Circulation.* 2006;113:2871-9.
4. Kolb C, Tzeis S, Sturmer M, et al. Rationale and design of the OPTION-study: optimal antitachycardia therapy in ICD patients without pacing indications. *Pacing Clin Electrophysiol.* 2010;33:141-8.

# Identifying post-myocardial infarction patients at risk by imaging techniques

Nico Bruining\*

Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands

Most myocardial infarction patients will undergo emergency percutaneous intervention (PCI) today. However, most of these patients will have diffuse cardiovascular disease and will often show more disease than a single culprit lesion. It is important to identify those patients at risk after a myocardial infarction (MI). The current guidelines suggest that the resting left ventricular (LV) function must be assessed as part of the risk stratification by both the ESC (ESC ST-elevation myocardial infarction (STEMI) in 2012)<sup>1</sup> as well by the ACCF/AHA (2013)<sup>2</sup>. The guidelines suggest that patients with an LV ejection fraction (LVEF) <30-40% and New York Heart Association (NYHA) functional class I or II should receive an implantable cardioverter-defibrillator (ICD) treatment.

However, there are two major concerns to this classification and those are: 1) Are the current imaging methods accurate enough to measure this threshold in LVEF? And 2) the great majority of patients with a sudden cardiac death (SCD) have an LVEF >30%.<sup>3</sup> So the major question is how we can identify the patient at risk and whether we have any other possibilities to identify them by imaging<sup>4</sup>?

There are currently many additional imaging methods available who aimed at identifying vulnerable coronary lesions<sup>5</sup>,

such as: intravascular ultrasound (IVUS), optical coherence tomography (OCT) and near infrared spectroscopy (NIRS), to name a few. Some of these imaging methods can be used for in-depth analysis of plaque components as by example IVUS-Virtual Histology. Most of these intracoronary imaging techniques are used to identify the so-called thin-cap fibro-atheroma's (TCFA's)<sup>6,7</sup>. Also functional measurements of coronary blood flow, e.g. fractional flow reserve (FFR)<sup>8</sup> or even virtual FFR by multi-slice computed tomography (MSCT)<sup>9</sup>.

However, not a single imaging method could identify these vulnerable plaques at itself, the results up until now are somewhat disappointing. We expect that combination of the results of the individual methods by multi-modality imaging, might improve this<sup>10</sup>. The ultimate multi-modality assessment of the LV and the heart might be "electro-mechanical imaging"<sup>11</sup>.

Identifying the vulnerable patient at risk after MI is a difficult task<sup>3</sup>. Although the imaging guidelines today recommend to measuring the LVEF at rest to identify patients at risk and who might benefit from additional treatment, there is still a large scientific debate if this is appropriate enough. More recent imaging methods are necessary and perhaps multi-modality imaging could provide better insight into the very important topic of identifying patients at risk.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Erasmus MC, Thoraxcenter, Department of Cardiology, Room BA-571, Rotterdam, The Netherlands.

Phone: +31107033934

Email: n.bruining@erasmusmc.nl

**KEYWORDS:** myocardial infarction, risk stratification, imaging, left ventricular function.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):92.

## Literature

1. The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC); Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012;33:2569-619.
2. O'Gara PT, Kushner FG, Ascheim DD, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice G. 2013 accf/aha guideline for the management of st-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127:e362-425.
3. Dagues N, Hindricks G. Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death? *Eur Heart J.* 2013;34:1964-71.
4. Bruining N, Knaapen M, de Winter S, et al. A histological "fly-through" of a diseased coronary artery. *Circ Cardiovasc Imaging.* 2009;2:e8-9.
5. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation.* 2001;104:365-72.
6. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: A comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol.* 2000;20:1262-75.
7. Choi BJ, Prasad A, Gulati R, et al. Coronary endothelial dysfunction in patients with early coronary artery disease is associated with the increase in intravascular lipid core plaque. *Eur Heart J.* 2013;34:2047-54.
8. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the fame study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol.* 2010;55:2816-21.
9. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter discover-flow (diagnosis of ischemia-causing stenoses obtained via noninvasive fractional flow reserve) study. *J Am Coll Cardiol.* 2011;58:1989-97.
10. Bruining N, de Winter S, Serruys PW. Intravascular ultrasound registration/integration with coronary angiography. *Cardiol Clin.* 2009;27:531-40.
11. Galeotti L, van Dam PM, Loring Z, Chan D, Strauss DG. Evaluating strict and conventional left bundle branch block criteria using electrocardiographic simulations. *Europace.* 2013;15:1816-21.

# Magnetic resonance imaging of the heart: more than the morphological analysis

Viktor Peršić\*

Thalassoterapija Opatija, Opatija, Croatia

Magnetic resonance imaging (MRI) of the heart is one of the key non-invasive techniques in modern cardiology. In the last period it developed from the useful research method into a clinically evidence-based, safe and comprehensive diagnostic test. The development of the technology has resulted in its wider application in various fields of cardiology, in evaluation of regional and global systolic function of the heart, perfusion and tissue characterization of the heart muscle, evaluation of pericardial disease, heart tumor and follow-up of patients with congenital heart disease and diseases of the aorta. In ischemic heart disease there are great possibilities for identifying segmental contractility failures af-

ter administration of dobutamine, or applying vasodilating tests such as adenosine, with a satisfactory safety profile and a good degree of diagnostic accuracy. The principle of gadolinium-based imaging is based on a lower speed of wash out of gadolinium from myocardium replaced by fibrosis or scar. On these grounds, a delayed imaging 5 to 20 minutes after injection of contrast agent will clearly show a fibrosis or a scar and thus also give an answer to the question as to the benefits of further revascularization procedures. The main advantages of cardiac MRI versus other non-invasive imaging methods are high spatial resolution, excellent reproducibility (suitable for monitoring patients), non-ionizing radiation, high intrinsic contrast, numerous techniques within one method and 3D reconstruction.

**KEYWORDS:** magnetic resonance imaging, perfusion, tissue characterization.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):93.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Thalassoterapija Opatija, Maršala Tita 188/1, HR-51410 Opatija, Croatia.

Phone/Fax: +385 51 202 724

E-mail: viktor.persic@ri.t-com.hr

## Literature

1. Nagel E, Lehmkuhl HB, Bocksch W, et al. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. *Circulation.* 1999;99:763-70.
2. Lima JA, Desai MY. Cardiovascular magnetic resonance imaging: current and emerging applications. *J Am Coll Cardiol.* 2004; 44:1164-71.
3. Lockie T, Ishida M, Perera D, et al. High-resolution magnetic resonance myocardial perfusion imaging at 3.0-Tesla to detect hemodynamically significant coronary stenoses as determined by fractional flow reserve. *J Am Coll Cardiol.* 2011;57:70-5.
4. Schwitler J, Wacker CM, Wilke N, et al. MR-IMPACTII: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J.* 2012; 34:775-81.
5. Kwong RY, Chan AK, Brown KA, et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. *Circulation* 2006; 113:2733-43.

## *“To stent or not to stent” debate, and how it can refer to the role of coronary computed tomography angiography in clinical decision-making for stable coronary artery disease*

Mladen Jukić<sup>1\*</sup>, Ladislav Pavić<sup>1</sup>, Ivan Bitunjac<sup>2</sup>, Joško Bulum<sup>3</sup>

<sup>1</sup>*Sunce Clinic Zagreb, Croatia*

<sup>2</sup>*General Hospital “Dr Josip Benčević”, Slavonski Brod, Croatia*

<sup>3</sup>*University Hospital Centre Zagreb, Zagreb, Croatia*

Coronary Computed Tomography Angiography (CCTA) is now the fastest and only growing application for computed tomography in the United States, with approximately 500,000 Americans undergoing CCTA each year<sup>1</sup>. On the other hand, this has stimulated professional and public concern about appropriateness of its widespread use.

AHA/ACC Appropriate Use Criteria (AUC) for CCTA from 2006 defined 37 clinical situations where this method was considered appropriate, whereas in 2010 this has extended to 93, demonstrating and obvious growth.

However, although recommendations for CCTA still remain cautious, on the other hand, diagnostic Invasive Coronary Angiography (ICA) is now recommended only if the results of non-invasive testing suggest high likelihood of significant 3-vessel disease, or left main affliction, and also if the patient is willing to accept the possibility of immediate revascularisation<sup>2</sup>. In general, therefore, the AHA/ACC guideline update was less prescriptive than the earlier NICE guideline, perhaps partly because it put less emphasis on the cost efficiency of its recommendations.

Although the indications might vary among different institutions, ICA and CCTA are now being commonly, and widely, used by clinicians to assess anatomic disease burden in pa-

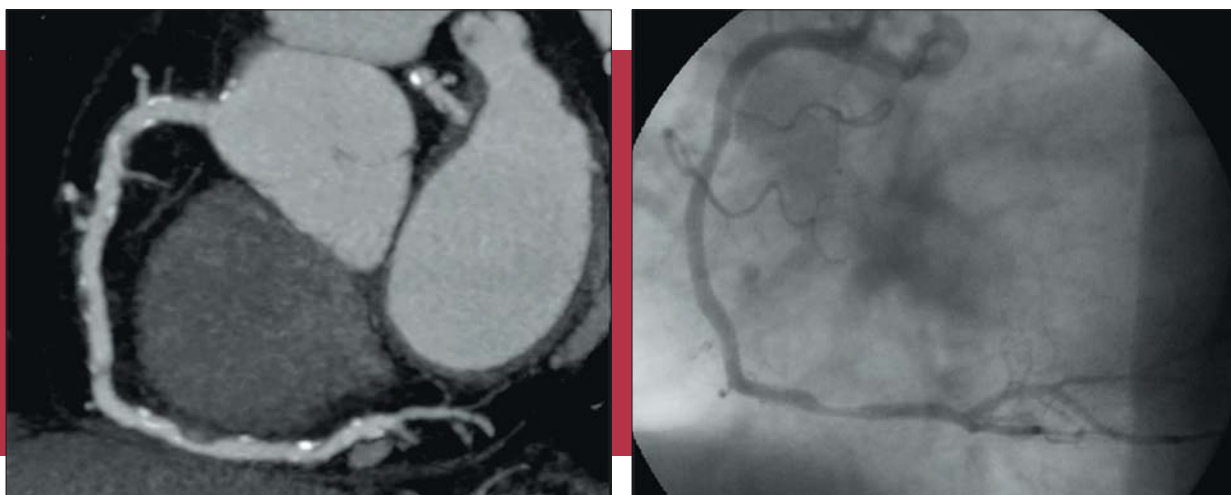
tients with coronary artery disease (CAD), while other non-invasive imaging techniques are primarily used to ascertain ischemic burden.

Beside a recent analysis has de facto called into question the rationale for many of the revascularization procedures performed until recently, at least in patients with stable CAD<sup>3</sup>. In the meta-analysis including more than 5,000 patients, PCI seemed to be no better than medical therapy alone, patients with documented ischemia on stress testing or fractional flow reserve (FFR).

As a curiosity in this respect, when George W. Bush was stented in August 2013 a fierce dispute arose whether this intervention was really necessary or if he would have fared better off with only medical therapy. Also possibly interesting, the primary diagnostic work-up used in his case was CCTA, not ICA.

Luckily, we believe, this dispute was settled after the COURAGE-trial systematically showed that patients with stable angina fare as well with optimal medical therapy alone, as they do with angioplasty/stenting, or by-pass.

In our own series of roughly 800 patients, we also tried to evaluate how CCTA influenced the management and treat-



**Figure 1.** *Coronary computed tomography angiography and invasive coronary angiography. Borderline distal right coronary artery stenosis, on coronary computed tomography angiography and invasive coronary angiography.*

ment of patients with CAD, where we showed that CCTA can reliably replace diagnostic ICA in majority of stable patients, no regardless of the pre-test risk stratification<sup>4</sup>.

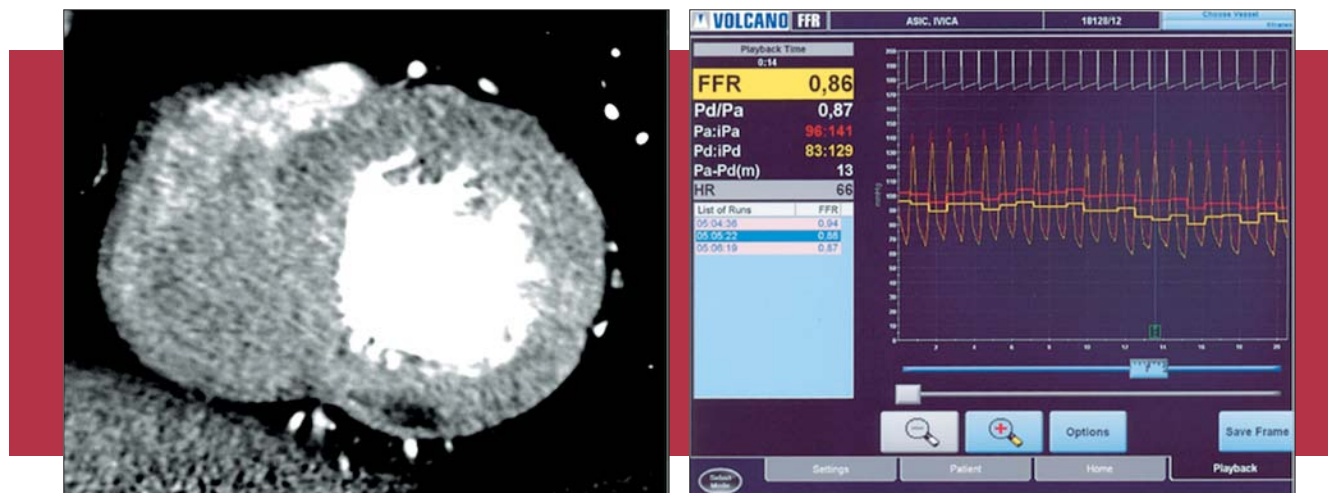
In this respect, we would like to present a case "To stent or not to stent" our own debate (Figure 1 and 2).

Having in mind the most recent evidence-based data that suggests that revascularization (coronary stenting, as well as by-pass) should probably be reserved only for patients with non-stable CAD, while patients with stable CAD should be treated conservatively, we think that also diagnostic

work-up for these patients should be kept as non-invasive as possible, as the majority of the patients can be adequately managed in this way alone.

To conclude, based upon this data and our clinical experience, we believe that CCTA can provide reliable diagnostic and prognostic information for adequate clinical decision-making and treatment of the majority of patients with stable CAD.

The still ongoing 8,000-patient ISCHEMIA and other trials, will hopefully yield some more insights in this respect.



**Figure 2.** Cardiac computed tomography (CCT) and fractional flow reserve. Contrast-enhancement deficit on inferior left ventricular wall (under 10%) on CCT in the same patient, and hemodynamically non-significant stenosis on invasive coronary angiography-fractional flow reserve, which was not regarded to require stenting.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Poliklinika Sunce, Trnjanska cesta 108, HR-10000 Zagreb, Croatia.

Phone: +385-1-304-6666

Email: [mladen.jukic@sunce.hr](mailto:mladen.jukic@sunce.hr)

**KEYWORDS:** coronary artery disease, coronary computed tomography angiography, invasive coronary angiography.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):94-95.

## Literature

1. Berenson A, Abelson R. Weighing the Costs of a CT Scan's Look Inside the Heart. *New York Times*. Sunday, June 29, 2008. [http://www.nytimes.com/2008/06/29/business/29scan.html?pagewanted=all&\\_r=0](http://www.nytimes.com/2008/06/29/business/29scan.html?pagewanted=all&_r=0)
2. Fihn SD, Gardin JM, Abrams J, et al.; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American College of Physicians; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2012;60:e44-164.
3. Stergiopoulos K, Boden WE, Hartigan P, et al. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. *JAMA Intern Med.* 2014;174(2):232-240.
4. Jukic M, Pavic L, et al. Influence of coronary computed tomography-angiography on patient management. *Croat Med J.* 2012;53(1):4-10.

# Quantitative spatial cardiac localization of premature ventricular contractions using the cardiac isochrone positioning system

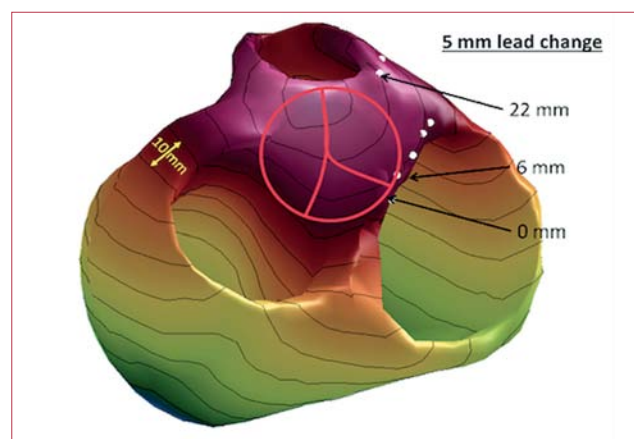
Peter van Dam\*

University of Nijmegen, Nijmegen, The Netherlands

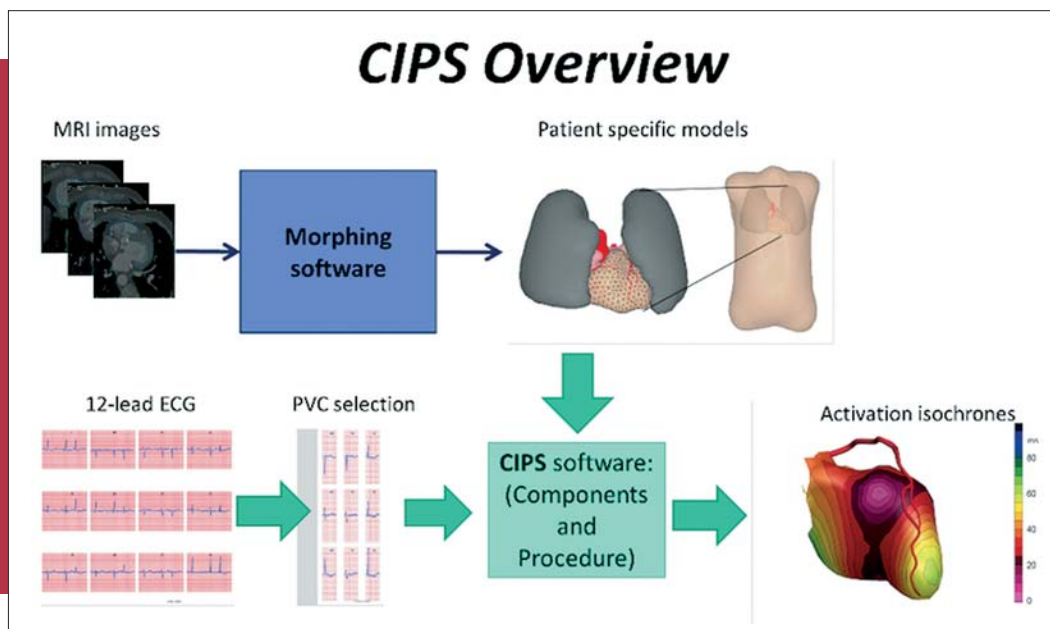
**Introduction:** The precise localization of the site of origin of a premature ventricular contraction (PVC) or ventricular tachycardia (VT) prior to ablation would facilitate the planning and execution of the electrophysiological procedure<sup>1</sup>. Current electrocardiographic imaging (ECGI) techniques use body surface mapping that is costly, complex, and requires as many as 256 leads to localize the PVC origin. We have developed and tested the novel cardiac isochrone positioning system (CIPS) utilizing the readily available 12 lead ECG to localize the PVC origin.

**Methods:** The myocardial activation based ECGI requires a patient specific model of the heart and thorax. For the PVC or VT origin localization, the fastest route algorithm<sup>2,3</sup> is used on patient specific models created by the newly developed morphing software<sup>4</sup>.

For this study population the electrodes were not recorded accurately. The influence of electrode misplacement was



Consequently we developed and tested new Kinect camera software to document and determine the ECG electrode locations on the chest wall<sup>5</sup>. This software fuses the recorded



tested on one of the cases by moving the precordial electrodes up and down. The amount of electrode misplacement alters significantly the PVC location determined by CIPS, shown with white dots. An electrode misplacement of 5 mm resulted in a range of 0-22 mm PVC location.

3D Kinect camera image with the MRI derived thorax model<sup>4</sup>.

**Results:** Ten patients that underwent electrophysiological mapping and ablation of PVCs were studied. The PVCs origins were localized on the endocardium of the mid left later-



al wall, the anterior right ventricular outflow tract (RVOT), the left ventricular superior septum, septal RVOT and mid wall of the RVOT. In one patient the PVC origin was located on the epicardial RVOT. PVC localization by the 12-lead ECGI was correlated to the site of successful ablation. All patients (10/10) had accurate prediction of the PVC origin. However, in two patients without patient specific models the localization was reversed between the RV free wall and septum of the RVOT. With patient specific models and accurately reconstructed electrode positions, these latter two cases would likely be localized correctly.

**Conclusion:** This feasibility study of CIPS shows its ability to localize the PVC origin based on only the standard 12 lead ECG. This ECGI method yields activation estimates of

isochrones on both ventricles from which the PVC origin location is derived. This new ECGI technique can localize the PVC from any part of the ventricular endocardium, intramyocardium or epicardium. Accurate localization of the precordial ECG electrodes, however, is still required. The Kinect camera offers the functionality to quickly and reliably localize these electrodes on the chest wall, potentially increasing the accuracy of CIPS. We are currently in the process of designing a prospective study using CIPS with the Kinect camera to localize PVCs and VT origins.

**KEYWORDS:** cardiac isochrone positioning system, inverse problem, Kinect, non-invasive premature ventricular contraction localization.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):96-97.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: University of Nijmegen, 126 Dept. of Cognitive Neuroscience, Geert Grooteplein 21, 6525 EZ Nijmegen, The Netherlands..

Phone: +31-622198396

Email: [peter.van.dam@peacs.nl](mailto:peter.van.dam@peacs.nl)

## Literature

1. Adams J, Srivathsan K, Shen W. Advances in management of premature ventricular contractions. *J Interv Card Electrophysiol.* 2012;35(2):137-49.
2. van Dam PM, Oostendorp TF, Linnenbank AC, van Oosterom A. Non-invasive imaging of cardiac activation and recovery. *Annals Biomedical Engineering.* 2009;37(9):1739-56.
3. van Dam PM, Oostendorp TF, van Oosterom A. Application of the fastest route algorithm in the interactive simulation of the effect of local ischemia on the ECG. *Med Biol Eng Comput.* 2009;47(1):11-20.
4. van Dam PM, van Der Graaf AWM, Gotte MJW, editors. A new 3D patient specific morphing tool enabling clinical application of non-invasive cardiac activation imaging. ESC; 2012; Munich.
5. van Dam PM, Maan AC, van der Putten NHJJ, Bruining N, Dijk WA, Laks M. New Computer Program for detecting 12 Lead ECG Misplacement using a 3D Kinect Camera. In: Murray A, editor. *Computing in cardiology; Zaragoza 2013.* p. 1175-8.



# Using electronic health records in clinical research

Enno T. van der Velde\*

Leiden University Medical Center, Leiden, The Netherlands

**Background:** Information technology has transformed the way healthcare is carried out and documented. Presently, the practice of healthcare generates, exchanges and stores huge amounts of patient-specific information. In addition to the traditional clinical narrative information, databases in modern health centres automatically capture structured data relating to all aspects of care, including: diagnosis, medication, laboratory test results, imaging data and many other.

Electronic health record (EHR) data comprise various data types, structured data as well as unstructured data, and can be exploited for care, statistics and research.

Despite the great potential, researchers who wish to analyse large amounts of patient data are still faced with technical challenges of integrating scattered, heterogeneous data, in addition to ethical and legal obstacles that limit the access to the data.

In short, the use of data from EHR systems is still hampered by the lack (or lack of implementation of) standards for interoperability and schemes for privacy and consent.

**Interoperability:** When an EHR system is implemented, it is often customized for the users. This means that even EHR's developed by the same vendor could collect the same information in different ways for different institutions. Without the use of common vocabularies, it is impossible for a given hospital's computer to understand a patient record from another hospital, but also for researchers to compare data across organizations. Therefore, the use of common vocabularies should be implemented as much as possible in each EHR.

There are many interoperability domains: Organizational interoperability (who does what when), semantic interoperability (meaning of the data), syntax interoperability (structure of the data), and technical interoperability (connecting computers on a technical level).

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Department of Cardiology, Leiden University Medical Center, P.O. Box 9600, 2300 RC, Leiden, The Netherlands

Phone: +31-71-5261795

Email: [ETvanderVelde@lumc.nl](mailto:ETvanderVelde@lumc.nl)

To solve these interoperability issues, many healthcare IT standards have been developed; some of them are overlapping. There are standards on medical/clinical content (e.g. CDA, HL7), and standards on structure & implementation (CCR, DCM)<sup>1</sup>.

**Privacy:** Privacy legislation in many countries has traditionally placed a great weight on personal autonomy, and has required informed consent for accessing personal health data for research. A legitimate public concern related to the use of personal health data is the risk of privacy breaches. A technical solution is to de-identify research data according to the specifications in the Health Insurance Portability and Accountability Act privacy rule. De-identification (anonymization) allows researchers to circumvent costly and timely consent procedures, but the lack of identifiers makes the inclusion of follow-up data difficult. In practice, the following measures are taken to overcome this problem: attributes with identifying information such as 'name', 'phone number', 'SSN' will be omitted. Necessary fields for later linkage such as PatientID will be encrypted, with the decryption codes only accessible for certain people<sup>2,3</sup>.

**Conclusion:** The present widespread use of electronic health record systems holds great promise for the use of this data for clinical research. Despite the great potential, researchers who wish to analyse large amounts of patient data are still faced with technical challenges of integrating scattered, heterogeneous data, in addition to ethical and legal obstacles that limit access to the data. However, it is to be expected that large-scale adoption of health information technology infrastructure in the form of EHRs and standards for interoperability and schemes for privacy and consent will allow to fully exploit EHR data in clinical research.

However, it is difficult to predict when a major shift in availability of EHR data may take place. EHR's and EHR related data mining can further improve the quality of care and also reduce overall cost of healthcare in the long-term.

**KEYWORDS:** electronic health record systems, clinical research, data standardization, privacy.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):98.

## Literature

1. Ouagne D, Hussain S, Sadou E, Jaulent MC, Daniel C. The Electronic Healthcare Record for Clinical Research (EHR4CR) information model and terminology. *Stud Health Technol Inform.* 2012;180:534-8.
2. Shoffner M, Owen P, Mostafa J, et al. The secure medical research workspace: an IT infrastructure to enable secure research on clinical data. *Clin Transl Sci.* 2013;6(3):222-5.
3. Fernandez-Aleman JL, Senor IC, Lozoya PAO, Toval A. Security and privacy in electronic health records: A systematic literature review. *J Biomed Inform.* 2013;46:541-62.

# Descriptive and predictive modeling

Dragan Gamberger\*

Ruđer Bošković Institute, Zagreb, Croatia

**Introduction:** Intelligent data analysis (IDA) is an important tool for data based medical research. It is often combined with statistical techniques. The primary goal of IDA is data understanding and hypothesis creation while statistics is used for hypotheses validation. *Aim:* Presentation of novel approaches for pattern recognition, example clustering, and data understanding tasks in cardiological applications.

**Methods:** A new generation of machine learning algorithms, like Random Forest<sup>1</sup> and Random Rules, is based on efficient and systematic construction of many independent classifiers. Besides increased predictive quality, the algorithms have some distinguished properties like inherent estimation of the probability of correct classification for each example and estimation of the similarity of pairs of examples. The probability of correct classification is measured by the difference in the number of votes for different classes while similarity of examples is measured by the percentage of classifiers that correctly predict both examples. These new options are potentially very useful for pattern recognition and example clustering results that may be applied for the predictive and descriptive analysis of medical data.

**Results:** The problem of fetal heart rate (FHR) monitoring is known as an important and difficult problem<sup>2</sup>. Typically it is solved by sophisticated signal processing techniques. We demonstrate how it may be solved by transforming the four

simultaneous noninvasive fetal ECG signals into a single probability sequence. From such probability sequence it is much easier to identify positions of actual fetal QRS complexes. A model based on many independent classifiers is used for this transformation. The starting point for constructing the model is a few ECG sequences on which medical experts have already identified the positions of fetal QRS complexes.

The second application is clustering of coronary heart disease (CHD) patients. The experiments start from a set of 238 patients. A classification problem is formed so that the original set of examples is used as positive examples while negative examples are obtained by randomized shuffling of attribute values of the original set. The goal of constructing a predictive model for discriminating original from randomized data is to obtain a similarity table for original examples. In the second step clusters of examples are iteratively constructed by minimization of the internal variance of the similarity table for all 238 examples. The main result is identification of relevant subgroups of CHD patients, description of properties of these subgroups, and detection of outlying examples.

**Conclusion:** The presented methodology and its appropriate applications enable novel approaches to data analysis in cardiology. The applications that are discussed in this work are only an illustration of its potentials. A long term goal is better understanding of the methodology and its comparative evaluation with standard techniques.

**KEYWORDS:** pattern recognition, clustering of examples, data understanding, random forest algorithm, example similarity table.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):99.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Institut Rudera Boškovića, Bijenička 54, HR-10000 Zagreb, Croatia.

Phone: +385-1-4561-111

E-mail: dragan.gamberger@irb.hr

## Literature

1. Breiman L. Random Forests. *Machine Learning.* 2001;45(1):5-32.
2. Sameni R, Clifford GD. A review of fetal ECG signal processing: issues and promising directions. *Open Pacing Electrophysiol Ther J.* 2010;3:4-20

# The process of collecting data for the Acute Myocardial Infarction / Acute Coronary Syndrome Register for the City of Zagreb

Inge Heim\*

Institute for Cardiovascular Prevention and Rehabilitation, Zagreb, Croatia

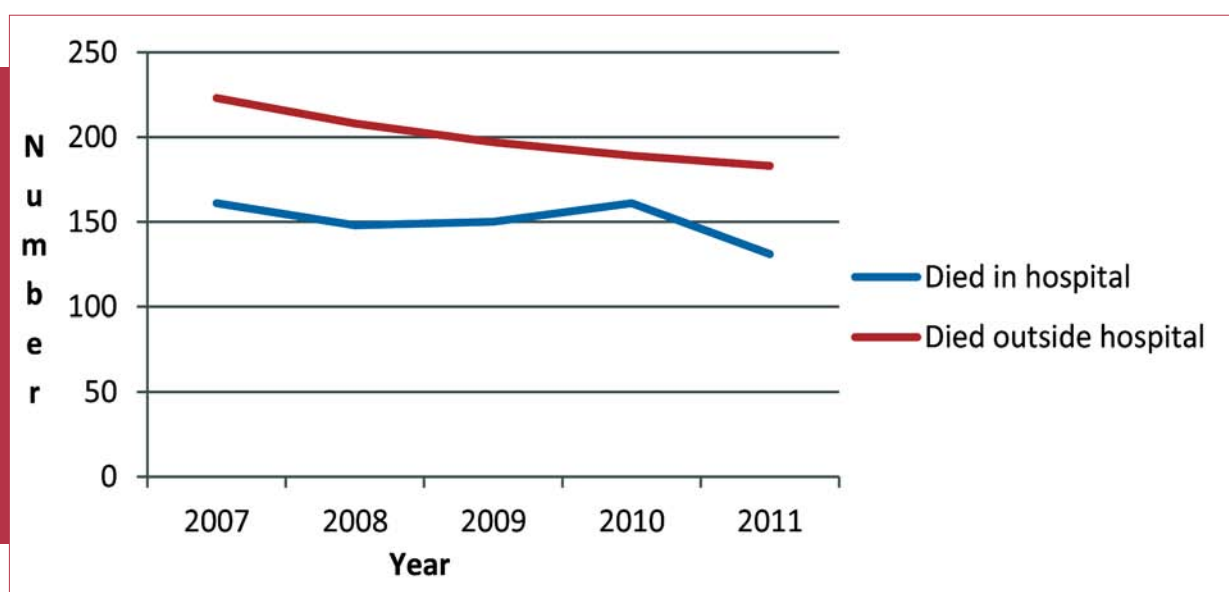
**Introduction:** The Acute Myocardial Infarction Register for the City of Zagreb was established in 1979 in the Institute for Cardiovascular Prevention and Rehabilitation as a population-based register including all cases among Zagreb residents. It contained mostly epidemiological data. As time passed and diagnostic procedures and therapy in cardiology advanced, cardiologists were interested to get more clinical information. In 2003 we established the Acute Coronary Syndrome Register for the City of Zagreb containing a series of clinical data. All age groups are covered. Sources of information are: mortality data and hospital discharge of consecutive patients admitted to all Zagreb hospitals with Acute Cardiology Units. Main inclusion criteria:

- suspected or confirmed acute coronary syndrome (ACS)
- those who died outside hospital with ACS as the main cause of death (confirmed or not confirmed by autopsy).
- sudden cardiac death (in- and out-of-hospital)

**Methods:** Physicians regularly visit all Zagreb hospitals which have Acute Cardiology Units. In the hospital admission list they look for Zagreb residents who were discharged with a diagnosis of ACS. Data collection method is cold pursuit.

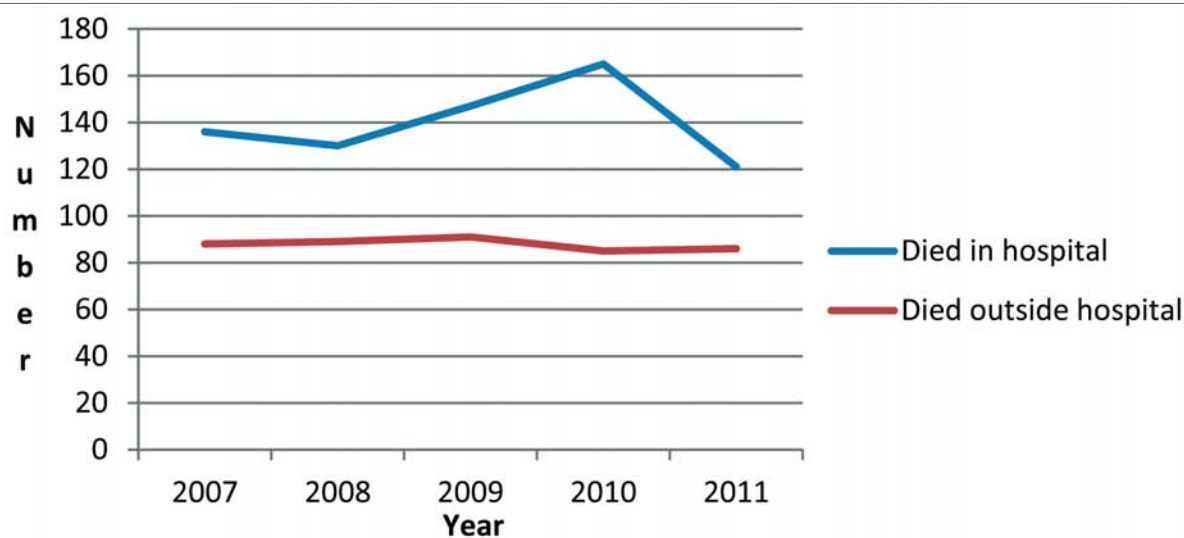
They fill in a questionnaire with the following data: history data (risk factors, previous percutaneous coronary interventions or coronary artery bypass graft surgery), exact date and time of the onset of symptoms, date and time of admission, time of entering coronary care unit, 12-lead ECG on admission, markers of necrosis (CK-MB, troponin), PCI or PTCA, working diagnosis from the emergency clinic, diagnostic procedures during hospitalization, laboratory findings (TC, HDL, LDL, triglycerides), therapy in the first 24 hours, complications, final diagnosis, groups of drugs taken in the last 3 months prior to arrival at the hospital and medications recommended at discharge, date and place of death (hospital death occurring within 28 days) and whether autopsy was performed. In fatal cases, autopsy report is checked and if it is proven that the cause of death is not an ACS, the patient is not entered in the Register.

**Results:** The comparison between in-hospital and out-of-hospital death from ACS by gender shows great differences. Out-of-hospital death in men is much higher than in-hospital death and the both show a declining trend seen from 2007 to 2011 (**Figure 1**). In women we see the opposite (**Figure 2**). In-hospital death is much higher than out-of-hospital



Source: Croatian Bureau of Statistics.

**Figure 1.** Comparison of in- and out-of-hospital death from acute coronary syndrome among men — Zagreb residents (2007-2011).



Source: Croatian Bureau of Statistics.

**Figure 2.** Comparison of in- and out-of-hospital death from acute coronary syndrome among women — Zagreb residents (2007-2011).

death. There is no change in out-of-hospital death but the in-hospital death shows a declining trend. Each year only about 10% of the patients included in the ACS Register join the outpatient cardiac rehabilitation program in Zagreb.

**Discussion:** Advantages of the Register - It is intended for health professionals and policy makers and gives the information on the characteristics, the burden and consequences of ACS in the City of Zagreb. It provides a more precise and valid monitoring of ACS. Continuing hospital computerization and personal identification number should allow record linkage and better data quality. Data is published in the Croatian Health Service Yearbook. Limitations: Financial

problems, lack of data collection staff, unrecognized value of such population-based registers among health professionals, lack of validation of discharge diagnoses. One of the problems is, also, that we no longer have the possibility to check the diagnosis on the death certificate at the Hospital Department of Pathology because the Central Bureau of Statistics refuses to give us the names of deceased patients due to data protection.

**Conclusion:** Out-of-hospital mortality has declined in the last few decades, but it still remains high representing great concern in men. From the epidemiological point of view emphasis should be placed on CV prevention, population education and better out-of hospital emergency care. The use of a reliable information system has enabled the development of such a register and contributed to a relatively simple data processing. Medical professionals and patients should be better informed on the advantages of the cardiac rehabilitation program.

**KEYWORDS:** acute coronary syndrome, population-based register, epidemiology, mortality, outpatient cardiac rehabilitation program

**CITATION:** *Cardiol Croat.* 2014;9(3-4):100-101.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Poliklinika za prevenciju kardiovaskularnih bolesti i rehabilitaciju, Draškovićeva 13, HR-10000 Zagreb, Croatia.

Phone: +385-1-4612-308

Fax: +385-1-4612-343

E-mail: [inge.heim@srcana.hr](mailto:inge.heim@srcana.hr)

## Literature

1. Heim I, Jembrek-Gostović M, Kern J, Jonke V, Svetina M. Trends in acute myocardial infarction mortality and morbidity from 1979 to 2001 in the City of Zagreb, Croatia: retrospective study. *Croat Med J* 2005; 46(6):970-6.
2. Jembrek-Gostović M, Heim I, Hrabak-Žerjavić V, Jonke V. Epidemiološko značenje akutnog koronarnog sindroma u populaciji grada Zagreba. *Acta Med Croat.* 2004;58:91-3.
3. Heim I, Jonke V, Gostović M, Jembrek-Gostović M. Epidemiologija akutnog koronarnog sindroma u Gradu Zagrebu. *Acta Med Croat.* 2009;63:105-9.
4. Heim I, Jembrek-Gostović M. Osvrt na bolničku smrtnost s aspekta kliničara i epidemiologa. *Cardiol Croat.* 2007;2(4):26-7.
5. Heim I, Kruhek Leontić D, Jonke V, Romčević M, Jembrek-Gostović M, Henezi I. Patients in cardiac rehabilitation programme - where we were 1999 and where 10 years later. *Coll Antropol.* 2012;36(Suppl1):59-63.
6. Heim I, Jembrek-Gostović M. Registar akutnog infarkta miokarda i akutnog koronarnog sindroma za grad Zagreb (akutni infarkt miokarda i nestabilna angina). *HČJZ* 2011;7.
7. Heim I, Jembrek-Gostović M, Jonke V, Gostović M. Epidemiological data of acute coronary syndrome in Zagreb, the Capital of Croatia in 2000 and 2001. *Eur J Cardio Prev Rehab.* 2004;11(Suppl 1):101.
8. Vervueren PL, Elbaz M, Wagner A, et al. The major element of 1-year prognosis in acute coronary syndromes is severity of initial clinical presentation: results from the French MONICA registries. *Arch Cardiovasc Dis.* 2012;105(10):478-88.

# Cardiac image processing techniques

Nihad Mešanović\*, Elnur Smajić

University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina

Heart disease is the leading cause of death in the modern world. Cardiac image processing is now routinely applied for detecting, classification and diagnosis of heart diseases. One of the most common uses of processing methods that are now widely applied are cardiac segmentation<sup>1</sup> and registration methods<sup>2</sup>, that are used in order to extract the detailed anatomy and function of the heart.

Automatic segmentation plays a central role when inspecting reconstructed 3D cardiac images from CT or MR scanners. An accurate classification of the different cardiac regions is usually the first step of tasks like: cardiac visualization, coronary artery inspection, measurement of the ejection fraction for the left and right ventricles and wall motion analysis.

In a clinical context, physicians often mentally integrate image information from different modalities. Automatic registration, based on computer programs, might, however, offer better accuracy and repeatability and save time<sup>3</sup>. Cardiac image registration remains a challenge because of the numerous specific problems mainly related to the different motion sources (patient, respiration, heart) and to the specificity of each imaging modality. Up to now, no general method could automatically register any modality with any other modality so far.

Received: 14<sup>th</sup> Jan 2014

\*Address for correspondence: Javna zdravstvena ustanova Univerzitetski klinički centar Tuzla, Trnovac bb, 75 000 Tuzla, Bosnia and Herzegovina.

Phone: +387-35-303-500

E-mail: [Nihad.Mesanovic@ukctuzla.ba](mailto:Nihad.Mesanovic@ukctuzla.ba)

This paper presents a survey of shape modeling applications to cardiac image analysis from MRI, CT, echocardiography, PET, and SPECT and aims to introduce new methodologies in this field, classify major contributions in image-based cardiac modeling, provide a tutorial to beginners to initiate their own studies, and introduce the major challenges of registration and segmentation and provide practical examples.

Image-driven processing methods, such as thresholding, region-based or edge-based techniques, or else pixel classification<sup>4-6</sup>, provide a limited framework for further medical image analysis. They can include geometrical information, as well as high level information, in the so-called shape prior based segmentation framework, or through active shape models and active appearance models. At last, atlas guided segmentation also make use of a set of manually segmented images.

By using different analysis software of cardiac images, CAD prototypes can be used in clinical routines in order to provide a computer output as a second reader to assist physicians in the detection of abnormalities, quantification of disease progression and differential diagnosis of lesions<sup>7</sup>. Computerized analysis of cardiac images in combination with artificial intelligence can be used in clinical practice and may contribute to more efficient diagnosis.

**KEYWORDS:** cardiac image processing, analysis, artificial intelligence.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):102.

## Literature

1. Mesanovic N, Grgic M, Huseinagic H, Males M, Skejic E, Smajlovic M, Automatic CT image segmentation of the lungs with region growing algorithm. 18th International Conference on Systems, Signals and Image Processing - IWSSIP 2011, University of Sarajevo, Bosnia and Herzegovina. 2011, pp. 395-400.
2. Dhawan AP. Medical image analysis. IEEE press series in Biomedical Engineering, John Wiley & Sons. Inc. Publications, 2003.
3. Mesanovic N, Huseinagic H, Kamenjakovic S. Disease quantification by automatic segmentation of lung CT image. 4th Congress of radiology of Bosnia and Herzegovina with international participation BHCR2011. 2011, pp. 61.
4. Suri JS. Computer vision, pattern recognition and image processing in left ventricle segmentation: The last 50 years. *Pattern Anal Appl.* 2000;3:209-42.
5. Jolly MP. Automatic segmentation of the left ventricle in cardiac. MRI and CT images. *Int J Comp Vis.* 2006;70(2):151-63.
6. Zheng Y, Barbu A, Georgescu B, Scheuering M, Comaniciu D. Four-chamber heart modeling and automatic segmentation for 3-D cardiac CT volumes using marginal space learning and steerable features. *IEEE Trans. Medical Imaging.* 2008;27(11):1668-81.
7. Mešanović N, Smajić E. Overview of open source software for computer aided detection in cardiology. *Cardiol Croat.* 2012;7(3-4):120.

# mHealth in cardiology

Mario Ivanuša\*

Institute for Cardiovascular Prevention and Rehabilitation, Zagreb, Croatia

The development of mobile telecommunications and multimedia technologies has resulted in providing one segment of medical services when a patient and a physician are at remote locations. Mobile health (mHealth) is a system of remote monitoring the health status during the 24/7 and is primarily designed for patients with chronic diseases, but also those who are at home care after acute events and/or emergency medical intervention, patients involved in programs for the improvement of health status or for clinical trials.

The basis of the mHealth is supported by enthusiasm of a growing use of technologies in the community that keeps up with the 21<sup>st</sup> century developments and medical equipment that gathers information from the body (the sensor for a patient, communication device, medical application), and accessories. Blood pressure, heart rate, electrocardiogram, blood glucose, oxygen saturation and other variables are collected by sensors and can be simultaneously or in a certain period of time transmitted to the server, enabling the option of integration with electronic medical record and signaling in case of any disorders.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Poliklinika za prevenciju kardiovaskularnih bolesti i rehabilitaciju, Draškovićeve 13, HR-10000 Zagreb, Croatia.

Phone: +385-1-4612-346

Fax: +385-1-4612-343

E-mail: [mivanusa@gmail.com](mailto:mivanusa@gmail.com)

In addition to the unequal development of broadband communication networks, the main problems of mHealth are:

- Lack of technical skills of medical professionals, particularly middle-aged and elderly ones;
- Technical problem of sensors — devices dependent on the size, design and battery life;
- The need for interoperability — linking diverse technologies for the purpose of exchanging and using information (from textual to complex multimedia messages), technology (WLAN, Bluetooth, satellite communications, etc.) and connectivity (wireless, wired, PC, PDA devices);
- Necessity of certifying the devices — the credibility of procedure (information of mobile monitoring are credible medical information or additional indicators), data protection, lack of standards and unclear legislation;
- Lack of financial incentives for the application of mHealth technology.

Telecardiology and mHealth principles and technology in cardiac rehabilitation can be used as a tool for promoting ever greater involvement of patients with coronary heart disease, which, in addition to the availability and price is the global problem for the mentioned cardiovascular activity. Mobile technology has proved to be potentially useful in intervention programs that detect and modify risk factors in psychosocial support, physical activity programs and therapeutic education. Time will show whether this mHealth potential will increase availability, participation and outcomes of patients with coronary heart disease.

**KEYWORDS:** mHealth, telecardiology, coronary heart disease.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):103.

## Literature

1. Ericsson Mobile Health. [http://www.ericsson.com/hr/ict\\_solutions/e-health/emh/index.shtml](http://www.ericsson.com/hr/ict_solutions/e-health/emh/index.shtml) (10.2.2014).
2. Huljencić D. m-zdravstvo u EU. [www.logincee.org/file/24558/library](http://www.logincee.org/file/24558/library) (10.2.2014).
3. Lee MH, Kim J, Jell SH, Yoo SK. Integrated solution for physical activity monitoring based on mobile phone and PC. *Healthc Inform Res.* 2011;17(1):76-86.
4. Walters DL, Sarela A, Fairfull A, et al. A mobile phone-based care model for outpatient cardiac rehabilitation: the care assessment platform (CAP). *BMC Cardiovascular Disorders* 2010;10:5.
5. Steinhubl SR, Muse ED, Topol EJ. Can mobile health technologies transform health care? *JAMA.* 2013;310(22):2395-6.

# Design and implementation of health information systems in cardiology

Elnur Smajić\*, Nihad Mešanović

University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina

The practice of collecting and maintaining information on health is as old as the history of medicine itself. Since the earliest times, those who were engaged in the art of healing found it necessary to record various outcomes in relation to the number of patients attended. At the beginning, health information systems were oriented to collect information on diseases and on health service outputs. In the meantime, there has been a tremendous progress in medicine as well as in informatics. In contemporary times, health information systems were transcended to the domain of modern health practices, and they hold great significance in the planning and decision-making of health delivery services<sup>1-3</sup>.

Health information systems are there to bridge the gap between disease occurrence and the response of health professionals to fight diseases. The drive for the reform of health information systems coincided with a revolution in information and communication technology, as a result the computer has made its entry, but many of the resulting computerised systems are suffering from the lack of appropriate-

ly trained staff, thereby also facing hardware and software maintenance problems.

However, it is important to make sure that, computerisation of health information systems does not dominate the health information system reform improvement process<sup>4</sup>. The problems of implementation of information systems are well known and invariably they concern the interplay of human, organisational, and technical factors, which cannot be easily separated. It is important especially in field of cardiology. The heart is a specific organ, besides morphologic characteristics, the functional status is very important and the relationship between heart and blood vessels, well known as arterioventricular coupling.

We can describe this complex interlinking by conceptualising computer-based information systems as social systems in which technology is only one of the elements<sup>5</sup>. Information systems are much more than computers and telecommunications equipment, as they also involve people and their actions in the organizational settings in which they work. One of the good and in developing health information systems is provided in University Clinical Center Tuzla at Tuzla county in Bosnia and Herzegovina<sup>6,7</sup>.

Received: 14<sup>th</sup> Jan 2014

\*Address for correspondence: Javna zdravstvena ustanova Univerzitetski klinički centar Tuzla, Trnovac bb, 75 000 Tuzla, Bosnia and Herzegovina.

Phone: +387-35-303-500

**KEYWORDS:** health information system, computer, cardiology.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):104.

## Literature

1. Wilson R, Rohde J, Puchert R, Hedberg C. South Africa's district health information systems: case study from Eastern Cape province. In: The RHINO workshop on issues and innovation in routine health information in developing countries, The Bolger Center, Protomac, MD, USA 14-16 March 2001. Arlington, VA 22209, USA: MEASURE Evaluation, JSI Research and Training Institute, 2001, 81-93.
2. Sauerborn R, and Lippeveld T. Introduction. In: T. Lippeveld, R. Sauerborn, C. Bodart, eds. Design and implementation of health information system, Geneva: World Health Organisation 2000, 1-14.
3. Reinhold H. Health information systems - past, present, future. *Int J Med Inform.* 2006;75(3-4):268-81.
4. Buntin Beeuwkes M, Burke MF, Hoaglin MC, Blumenthal D. The benefits of health information technology: a review of the recent literature shows predominantly positive results. *Health Aff (Millwood).* 2011;30(3):464-71.
5. Maryati MY, Kuljis J, Papazafeiropoulou A, Stergioulas LK. An evaluation framework for Health Information Systems: human, organization and technology-fit factors (HOT-fit). *Int J Med Inform.* 2008;77(6):386-98.
6. Smajić E. Primjena informacionih sistema u svakodnevnoj kliničkoj praksi. Zajednički sastanak radničkih grupa e-Kardiologija HR-BiH: Vizija budućnosti i/ili potreba sadašnjosti: IT u kardiologiji. VI kongres kardiologa i angiologa BiH, Tuzla, 2013. [www.ukbih.com](http://www.ukbih.com)
7. Mešanović N, Smajić E. Overview of open source software for computer aided detection in cardiology. *Cardiol Croat.* 2012;7(3-4):120.



# Internet-based interventions for cardiovascular prevention: focus on overweight and obesity

Alen Ružić\*

University Hospital Centre Rijeka, Rijeka, Croatia

At a time when the Internet has become an inseparable part of the everyday lives in the population of developed countries, the awareness of the need for its use in health promotion and disease prevention is continuously increasing. Although there are numerous studies in this field that are still in progress, at the time being we have more open questions than safe answers. Health issues are on the internet dominated largely by unfounded commercial promotions and

sales campaigns, while professional content tends to be limited to the official web site of professional societies. Promotion health campaigns that are based on proven and effective — evidence based platforms are still sporadic. Because of its specificity and longevity, the prevention and treatment of obesity is area of a special interest. It seems that the Internet-based education, practical materials, web — medical and psychological counseling, and controlled support groups within social networks represent the next major step in the development of effective therapeutic strategies for obesity.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Klinički bolnički centar Rijeka, Tome Strišića 3, HR-51000 Rijeka, Croatia.

Phone: +385-51-407-149

E-mail: [alen.ruzic1@ri.t-com.hr](mailto:alen.ruzic1@ri.t-com.hr)

**KEYWORDS:** internet, obesity, cardiovascular disease, eHealth, home-based, self-delivered.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):105.

## Literature

1. Tang J, Abraham C, Greaves C, Yates T. Self-directed interventions to promote weight loss: a systematic review of reviews. *J Med Internet Res.* 2014;16: e58.
2. Stephens SK, J Cobiac LJ, Veerman JL. Improving diet and physical activity to reduce population prevalence of overweight and obesity: an overview of current evidence. *Prev Med.* 2014;62:167-78.
3. Ajie WN, Chapman-Novakofski KM. Impact of computer-mediated, obesity-related nutrition education interventions for adolescents: a systematic review. *J Adolesc Health.* 2014 Feb 14. [Epub ahead of print].
4. Chang T, Ohopra V, Zhang C, Woolford SJ. The role of social media in online weight management: systematic review. *Med Internet Res.* 2013;15:e262.
5. Ružić A, Ružić T. Menadžment pretilosti — primjer suvremenog upravljanja u zdravstvu. U: Balen S, ur. *Priručnik Menadžment u zdravstvu.* Osijek; Medicinski fakultet Osijek i Medicinski fakultet Rijeka, 2012; 123-33.
6. Pokrajac-Bulian A, Ambrosi-Randić N, Ružić A. Weight loss and maintenance in overweight and obese patients with cardiovascular disease. *Psychological Topics.* 2010;19:355-72.

# Radiation exposure in interventional cardiology

Robert Steiner\*

University Hospital Centre Osijek, Osijek, Croatia

Radiation exposure rises with growing number of computed tomography, nuclear cardiological exams, coronary angiography and fluoroscopy leading to a higher risk of patient overexposure to radiation. It is estimated that 40% of radiation exposure is due to cardiological procedures. Interventional cardiologists and cardiac electrophysiologists are two to three times more exposed to radiation than diagnostic radiologists. In high volume cath labs the most experienced interventional cardiologists have annual exposure about 5mSv and lifetime exposure increases cancer risk by 1%. There are two main biological effects of radiation: tissue reaction (deterministic effects) that becomes evident days or months after exposure and include skin injuries and cataract, and stochastic effect which is related with potential and future harm damaging DNA or indirectly (free radicals and reactive oxygen species) leading to cancer manifestation after many years. Increased cancer risk is for doses more than 50mSv. Risk is 3-4 times higher in children than in adults, 38% higher in females than in males, 50% lower in octogenarians than in 50 year-old old patients. Some tissues are more sensitive than others. Highest radiosensitivity organs are breast, colon, lung and stomach.

Patients and doctors protection can reduce the radiation exposure by 90%. Radiation doses in cath lab depend on operator experience, arterial approach, distance of image intensifier from patient, cine-duration, performing ventriculography or not, projection, magnified views and also some patient characteristics: BMI, coronary lesion type and sort of arrhythmia to be ablated as maintained and quality controlled technology.

In our investigation we compared doses of exposure to patients and operators in 2007 compared with 2009 and found that as we had more experience and awareness of harmful effect of radiation, doses were lower and 2.7% of patients had exposure more than 2Gy and they are included in the follow up. Doses were similar to other cath labs.

We need more epidemiological, and biodosimetry data on radiological protection in patients (children and adults), interventional cardiologists and staff (including genetic studies), non-cancer effects, innovative devices and procedures.

**KEYWORDS:** interventional cardiology, risk, radiological protection, radiation, imaging.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):106.

**Table 1.** Standard reference doses for common cardiological examinations.

Diagnostic procedure	Effective dose (mSv)	Equivalent number of PA chest radiography each (0.02mSv)	Approximate equivalent period of natural background radiation (years)
Chest X-ray	0.02	1	0.008
Coronary angiography	7 (2-16)	350 (100-800)	2.9
Percutaneous coronary intervention	15 (7-57)	750 (350-2800)	6.3
Radiofrequency ablation	15 (7-57)	750 (350-2800)	6.3
Dilatation chronic coronary occlusion	81 (17-149)	4050 (850-9600)	33.7
Aortic valvuloplasty	39	1950	16.2
Endovascular thoraco-abdominal aneurism repair	76-119	3800-5950	31.6-49.5
64-slice coronary CT	15 (3-32)	750 (150-1600)	6.3
Coronary calcium CT	3 (1-12)	150 (50-600)	1.2
Sestamibi stress test (1 day)	9	450	3.7

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Klinički bolnički centar Osijek, Josipa Huttlera 4, HR-31000 Osijek, Croatia.

Phone: +385-31-511-511

E-mail: steiner\_robert5@hotmail.com

## Literature

- Picano E, Eliseo V, Rehni MM, et al. The appropriate and justified use of medical radiation in cardiovascular imaging: a position document of the ESC Associations of Cardiovascular Imaging, Percutaneous Cardiovascular Interventions and Electrophysiology. *Eur Heart J.* 2014;35(10):665-72.
- Russo GL, Tedesco I, Russo M, Cioppa A, Andreassi MG, Picano E. Cellular adaptive response to chronic radiation exposure in interventional cardiologists. *Eur Heart J.* 2012;33:408-14.
- Vano E. Reduction of exposure of patients and staff to radiation during fluoroscopically guided interventional procedures. *Curr Radiol Rep.* 2013;1:11-22.
- Brnić Z, Krpan T, Faj D, et al. Patient radiation doses in the most common interventional cardiology procedures in Croatia: first results. *Radiat Prot Dosimetry.* 2010;138(2):180-6.

# Interventional cardiology in acute coronary syndrome — what is next to do?

Jure Mirat\*

*Polyclinic Kardioton, Zagreb, Croatia*

A change of the paradigm in the treatment of some diseases rarely changed so radically as the strategy for the treatment of acute myocardial infarction (AMI) has changed over the last few decades. A long period with a completely passive and expectative attitude was followed by two radical revolutions. The first occurred in the eighties by introducing fibrinolytic therapy, while the other was even more spectacular, when primary percutaneous coronary interventions (PCI) were introduced, being accompanied by a significant decrease in mortality. The second wave affected us in Croatia 10 years ago, whereas intervention skills, technology and enthusiasm were the trias in the genesis of success. If we drew a cross-section today, we can ask ourselves — What is next to do? Have we reached the maximum which is followed by the plateau or is there still room for upward curve of success? This second variant seems to be more realistic. The reasons for this can be found primarily in spreading PCI to non-ST segment elevation myocardial infarction (NSTEMI),

that are subject to less invasive strategy or strategy of longer waiting for PCI, significantly longer in practice than what is prescribed in the guidelines, which can explain epidemiological data of the difference in mortality between ST-segment elevation myocardial infarction (STEMI) and NSTEMI in some follow-ups. Another moment is the limitations of electrocardiographic methods in the classification of AMI, which determines the treatment strategy. The differences reflected by the electrocardiographic method are not always an expression of real pathophysiologic events, so the treatment strategy should not be different. In addition to the methods of unmasking false NSTEMI and real STEMI showing terminology inadequacy of the existing names, we should take into account the technological advance in the diagnostics of AMI, as a potential moment for further jump. Imaging methods in cardiology have not yet, at least in our regions, taken their full advantage and we can expect that diagnostic hodograms will change when they become available. To conclude, we can say that there is still a lot of work to do for us to optimize the approach to the treatment of acute coronary syndrome.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Poliklinika Kardioton, Kaptol 26, HR-10000 Zagreb, Croatia.

Phone / Fax: +385-1-5802-736

E-mail: [jure\\_mirat@yahoo.com](mailto:jure_mirat@yahoo.com)

**KEYWORDS:** acute coronary syndromes, primary percutaneous coronary interventions, ischaemic heart disease.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):107.

## Literature

1. Nikolić Heitzler V, Babić Z, Miličić D, et al. Results of the Croatian Primary Percutaneous Coronary Intervention Network for patients with ST-segment elevation acute myocardial infarction. *Am J Cardiol.* 2010;105(9):1261-7.
2. Mirat J. Invasive versus noninvasive approach in the treatment of nonstable angina pectoris and NSTEMI: pro and con. *Acta Med Croat.* 2009;63(1):67-70.
3. Hamm CW, Bassand JP, Agewall S, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32:2999-3054.
4. The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC); Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012;33:2569-619.

# Why transradial instead of transfemoral approach for the percutaneous coronary intervention

Hrvoje Pintarić\*

University Hospital Centre Sestre milosrdnice, Zagreb, Croatia.

Despite the fact that transradial approach (TRA) requires a longer learning curve than transfemoral approach (TFA), the transradial challenges are usually overcome with experience. Nowadays, in view of its benefits, there is no longer any justification for ignoring the transradial approach<sup>1</sup>. Multiple randomized clinical trials and reports consistently demonstrate benefits to the patient and improved outcomes from TRA<sup>2</sup>. TRA is particularly appealing in patients with coagulopathy, elevated international normalized ratio due to warfarin, or morbid obesity<sup>3</sup>. A recent meta-analysis of nine studies involving 2,977 patients with ST elevation myocardial infarction (STEMI) demonstrated an impressive nearly 50% reduction in mortality for the TR approach<sup>4</sup>.

TR percutaneous coronary intervention (PCI) can be performed by low-to-intermediate volume operators with standard equipment with a low failure rate<sup>5</sup>. Age over 75 years, prior coronary artery bypass graft surgery, and short stature are independent predictors of TR-PCI failure<sup>6</sup>. Appropriate patient selection and careful risk assessment are needed to maximize benefits offered by TR-PCI.

In the Sestre milosrdnice University Hospital Centre, Zagreb, Croatia, seven interventional cardiologists perform almost 900 coronary percutaneous coronary interventions a year (40% pPCI). Our Cath Lab is one of the largest high-volume interventional cardiology centers in Croatia. In the last few years, our center has become dedicated to the radial approach with nearly 90% of PCI performed with either left or right radial access route. In time radial approach has become the first choice even in patients with STEMI. At the 2<sup>nd</sup> Advanced International Masterclass, September 2013 in

New York we have had the opportunity to present our results dedicated to TR approach. In patients with STEMI undergoing primary PCI in our, radial dedicated center, there is no difference in effectiveness, safety, and blood loss between radial and femoral approach. Also there is no significant difference in either left or right radial access type<sup>7</sup>. There are situations when radial arterial approach is not possible (e.g. congenital anomalies, tortuous configurations, radioulnar loop, weak or absent radial pulse secondary to previous puncture or catheterization). In such situations, a common second-line approach is used (femoral or ulnar). Many clinicians considered transbrachial (TB) angiography as a high-risk and obsolete procedure. However, our overall success rate was 95.5% (21/22). There were no major complications and we noticed only two minor complications (9%), both hematomas. According to our results TB approach, when used by dedicated transradialists, seems to be easily feasible, safe, and effective. Local vascular complications could be avoided by cautious and sensitive puncture technique. Other important factors are using 6 Fr catheters, defensive anticoagulation, and careful observation by the nursing team after sheath withdrawal. TB approach has all advantages of the arm approach over the femoral (early ambulation, patient preference, suitable for patients with severe occlusive aortoiliac disease and for patients with difficulty in lying down)<sup>8</sup>.

Radial access use has been growing steadily but, despite encouraging results, still varies greatly among operators, hospitals, countries and continents. Twenty years after its introduction, it was felt that the time had come to develop a common evidence-based view on the technical, clinical and organisational implications of using the radial approach for coronary angiography interventions<sup>9</sup>.

**KEYWORDS:** transradial approach, percutaneous coronary intervention, learning curve.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):108.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Klinički bolnički centar Sestre milosrdnice, Vinsogradska 29, HR-10000 Zagreb, Croatia

Email: [hrvojepintaric@yahoo.com](mailto:hrvojepintaric@yahoo.com)

## Literature

1. Rao SV, Ou FS, Wang TY, et al. Trends in the prevalence and outcomes of radial and femoral approaches to percutaneous coronary intervention: a report from the National Cardiovascular Data Registry. *JACC Cardiovasc Interv.* 2008;1(4):379-86.
2. Rao SV, Cohen MG, Kandzari DE, et al. The transradial approach to percutaneous coronary intervention: Historical perspective, current concepts, and future directions. *J Am Coll Cardiol.* 2010;55:2187-95.
3. Chese AJ, Fretz EB, Warburton WP, et al. Association of the arterial access site at angioplasty with transfusion and mortality: the M.O.R.T.A.L. study (Mortality benefit of Reduced Transfusion after percutaneous coronary intervention via the Arm or Leg). *Heart.* 2008;94:1019-25.
4. Mamas MA, Ratib K, Routledge H, et al. Influence of access site selection on PCI-related adverse events in patients with STEMI: meta-analysis of randomised controlled trials. *Heart.* 2012;98:303-11.
5. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol.* 2011;58:e44-122.
6. Dehghani P, Mohammad A, Bajaj R, et al. Mechanism and predictors of failed transradial approach for percutaneous coronary interventions. *JACC Cardiovasc Interv.* 2009;2(11):1057-64.
7. Gabrić ID, Pintarić H, Babić Z, et al. STEMI patients undergoing primary PCI in a radial approach skilled center can be equally treated with either femoral, left, or right radial access. *J Invasive Cardiol.* 2013;25:E6.
8. Trbušić M, Gabrić ID, Planinc D, Krčmar T, Pintarić H. What happens when transradialists use transbrachial approach. *J Invasive Cardiol.* 2013;25: E30.
9. Hamon M, Pristipino C, Di Mario C, et al. Consensus document on the radial approach in percutaneous cardiovascular interventions: position paper by the European Association of Percutaneous Cardiovascular Interventions and Working Groups on Acute Cardiac Care and Thrombosis of the European Society of Cardiology. *EuroIntervention.* 2013;8:1242-51.

# Cardiometry: new options in cardiology

Mikhail Y. Rudenko\*, Vladimir A. Zernov, Olga K. Voronova  
Russian New University, Moscow, Russian Federation

Cardiometry as a new fundamental field of cardiology is described in the paper. The laws of cardiometry are identified herein. Cardiometry is based on an adequate mathematical model of hemodynamics that is described by the Poyedin-tev-Voronova equations. The mode of elevated blood fluidity was first described by the mathematics. This allows both to properly interpret the mechanism of the heart performance and to calculate phase-related volumes of blood in each cardiac cycle. The new interpretation of the SA and AV nodes functioning as baroreceptors is provided by the authors.

A new classification for all of the varieties of ECG curve shapes has been proposed<sup>1-13</sup>. Clearly identified boundaries

in each phase are provided according to the new theory of hemodynamics, and some new symbols for newly defined ECG points has been proposed. Point L which denotes the beginning of the rapid ejection phase has been introduced. The exact location of point j that is the end of the rapid ejection phase has been given by the authors<sup>5,13-16</sup>.

The existing ECG recording methods has been revised, and an original single-lead ECG of the ascending aorta has been developed. A rheogram is recorded in synchronism with obtaining the original single-lead ECG. Phase synchronization of the ECG and Rheo curves supplies us with a new source of data on all phase-related changes in arterial pressure. A new diagnostic device CARDIOCODE has been developed on the basis of the new theoretical basis. CARDIOCODE delivers non-invasively data on 7 phase-related volumes of blood in every cardiac cycle that was absolutely incredible in the past<sup>1-11</sup>.

**KEYWORDS:** cardiometry, ECG, Rheo, hemodynamics, baroreceptors.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):109.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Russian New University, Moscow, Radio Street 22, Postal index 105005, Russian Federation.

Phone/Fax: +7 495 925-03-83

E-mail: [cardiocode.rudenko@gmail.com](mailto:cardiocode.rudenko@gmail.com)

## Literature

- Rudenko MY, Zernov VA, Voronova OK. Study of hemodynamic parameters using phase analysis of the cardiac cycle. *Biomedical Engineering.* 2009;43(4):151-5.
- Rudenko M, Voronova O, Zernov V, et al. The diagnostic performance of cardiovascular system and evaluation of hemodynamic parameters based on heart cycle phase analysis. In: *The cardiovascular system - physiology, diagnostics and clinical implications.* David C. Gaze (Ed.). ISBN: 978-953-51-0534-3, InTech. Available from: <http://www.intechopen.com/books/the-cardiovascular-system-physiology-diagnostics-and-clinical-implications/the-diagnostic-performance-of-cardiovascular-system-and-evaluation-of-hemodynamic-parameters-based-o>
- Rudenko M, Zernov V, Voronova O. Fundamental research on the mechanism of cardiovascular system hemodynamics self-regulation and determination of the norm-pathology boundary for the basic hemodynamic parameters and analysis of the compensation mechanism as a method of revealing the underlying causes of the disease. *Heart Rhythm.* 2012;9(11):1909-10.
- Rudenko MY, Zernov VA, Mamberger KK, Rudenko SM. Heart and aortic baroreceptors: operation in providing hemodynamic processes in cardiovascular system. *Cardiometry.* 2013;(3):31-44. Available from: [www.cardiometry.net/no3-november-2013/heart-and-aortic-baroreceptors](http://www.cardiometry.net/no3-november-2013/heart-and-aortic-baroreceptors)
- Rudenko SM. A new point on ECG: point L as identifier of rapid and slow ejection phases boundary. *Cardiometry.* 2013;(2):30-9. Available from: <http://www.cardiometry.net/issues/no2-may-2013/new-point-on-ecg.pdf>
- Rudenko MY, Voronova OK, Zernov VA. ECG periodic table: a new ECG classification based on heart cycle phase analysis. *Cardiometry.* 2013;(2):19-28. Available from: <http://www.cardiometry.net/issues/no2-may-2013/ecg-periodic-table.pdf>
- Rudenko MY, Voronova OK, Zernov VA, Mamberger KK, Makedonsky DF, Rudenko SM. Theoretical principles of cardiometry. *Cardiometry.* 2012;(1):7-23. Available from: <http://www.cardiometry.net/issues/no1-november-2012/theoretical-principles-of-cardiometry.pdf>
- Vecherkin VA, Ptitsin VA, Voronova OK. Study of central hemodynamic parameters in pediatric burn shock patients using the method of the heart cycle phase analysis. *Cardiometry.* 2012;(1):48-56. Available from: <http://www.cardiometry.net/issues/no1-november-2012/study-of-central-hemodynamic-parameters.pdf>
- Zernov VA. Cardiometric diagnostics and control of anti-androgenic drug adverse effects on cardiovascular system. *Cardiometry.* 2012;(1):57-63. Available from: <http://www.cardiometry.net/issues/no1-november-2012/cardiometric-diagnostics-and-control.pdf>
- Rudenko MY, Zernov VA, Voronova OK, et al. Theoretical principles of heart cycle phase analysis. Fouque Publishers, 2011. ISBN 978-3-937909-57-8.
- Rudenko MY, Zernov VA, Mamberger KK, Rudenko SM. ECG as a quest for extracting new data: non-invasive measurement of acid-alkaline parameters. *Cardiometry.* 2013;(3):45-57. Available from: [www.cardiometry.net/no3-november-2013/ecg-as-a-quest-for-extracting-new-data](http://www.cardiometry.net/no3-november-2013/ecg-as-a-quest-for-extracting-new-data)
- Krstacic G, Krstacic A, Smalcelj A, Milicic D, Jembrek-Gostovic M. The «Chaos Theory» and non-linear dynamics in heart rate variability analysis: does it work in short time series in patients with coronary heart disease? *Ann Noninvasive Electrocardiol.* 2007;12(2):130-6.
- Gamberger D, Lavrač N, Krstacić G, Šmuc T. Inconsistency tests for patient records in a coronary heart disease database. In: R. Brause & E. Hanisch (Eds.), *Medical Data Analysis SE-22 2000;1933:183-9.* Springer Berlin Heidelberg. Doi:10.1007/3-540-39949-6\_22.
- Macfarlane PW, Clark EN. ECG measurements in end QRS notching and slurring. *J Electrocardiol.* 2013;46:385-9.
- Macfarlane PW, Oosterom A, Janse M, Kligfield P, Camm J, Pahlm O. (Eds.). *Cardiac Electrophysiology, ECG Systems and Mathematical Modeling.* 2012, XI, 497p., ISBN 978-0-85729-870-6.
- Yong CM, Perez M, Froelicher V. Prognostic implications of the J wave ECG patterns. *J Electrocardiol.* 2013; 46(5):408-10.

# Relevance of heart rate variability in assessment of autonomic nervous system function in subjects in perioperative period

Meldijana Omerbegović\*, Jasminka Džemidžić

University Clinical Centre Sarajevo, Sarajevo, Bosnia and Herzegovina

Assessment of the autonomic nervous system function could be of great importance in evaluation of the risk factors of the patients in perioperative period. Surgery and anaesthesia as integral medical procedures aimed at restoring and improving different disorders of homeostasis and physical conditions of subjects with different ailments and functional cardiac reserves have strong influence on haemodynamic function in perioperative period and it is of a great importance to clearly define if an individual patient is at a great risk of autonomic dysfunction in addition to the underlying morbidity, which increase the risk of morbidity and mortality in the perioperative period.

Clinical tests for evaluation of autonomic nervous dysfunction have not become widely used by clinicians for several reasons. Some of the clinical tests are quite demanding what makes them less possible for performing in patients with poor reserve and more comorbidities and there are also

difficulties in interpretation of subjective findings. Monitoring of heart rate variability as a parameter of autonomic nervous system activity has been clearly advocated in the risk assessment and follow up of the patients who develop diabetes mellitus and patients with coronary syndrome<sup>1</sup>.

In subjects with diabetes mellitus who could have cardiac autonomic diabetic neuropathy, the quite serious condition of haemodynamic instability could increase the risk of aggravation and complications of the general condition in perioperative period<sup>2</sup>. On the other hand, most subjects with different stages of coronary syndrome have been shown to have different alterations of heart rate variability, and monitoring of heart rate variability in perioperative period could be a part of predicting tools of risk factors for surgery and anaesthesia<sup>3</sup>. The aim of this paper is to give a review of the importance of assessment of heart rate variability in relatively healthy subjects and subjects with different comorbid states, focusing on presenting of different findings of linear measures of the analysis of parameter by means of two different softwares.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Klinički centar Univerziteta u Sarajevu, Bolnička 25, 710000 Sarajevo, Bosnia and Herzegovina.

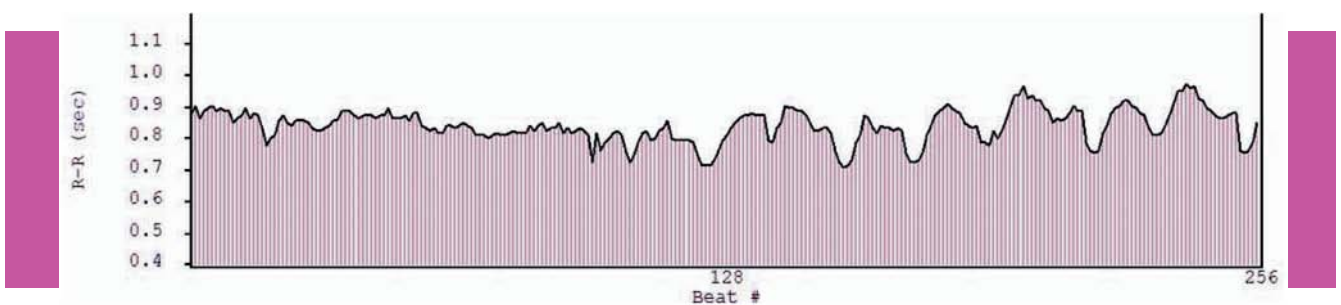
Phone: +387-33-297-000

E-mail: [meldi@bih.net.ba](mailto:meldi@bih.net.ba)

**KEYWORDS:** heart rate variability, autonomic nervous system, perioperative period.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):110.

**Figure 1.** Tachogram during calm and deep respiration in relatively healthy subject (*HrvFreqVers 4.01, 2006*).



## Literature

1. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996;93:1043-65.
2. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation*. 2007;115:387-97.
3. Hanss R, Block D, Bauer M, et al. Use of heart rate variability analysis to determine the risk of cardiac ischaemia in high-risk patients undergoing general anaesthesia. *Anaesthesia*. 2008;63:1167-73.

# Contributing factors in heart failure development—results from CRO-HF Registry

Duška Glavaš<sup>1\*</sup>, Davor Miličić<sup>2</sup>, Stojan Polić<sup>1</sup>, Branka Jurčević Zidar<sup>3</sup>, Katarina Novak<sup>1</sup>

<sup>1</sup>University Hospital Centre Split, Split, Croatia

<sup>2</sup>University Hospital Centre Zagreb, Zagreb, Croatia

<sup>3</sup>Public Health Institute of Split and Dalmatian County, Split, Croatia

**Introduction:** There are many causes of heart failure (HF), and these vary in different populations. The aim of the study was to analyse the contributing factors in heart failure development.

**Methods:** We analyzed the results from CRO-HF Registry<sup>1,2</sup>. This on-line registry was established in 2005.

**Results:** A total of 2203 in-hospital HF patients from CRO-HF Registry were analyzed: 1,028 (46.7%) females (F) and 1,175 (53.3%) males (M); median age was 76 years. Preserved left ventricular systolic function (LVEF 50%) was recorded in 37.8% patients.

History of arterial hypertension was recorded in 67.5% patients, diabetes mellitus in 34.4%, myocardial infarction in 22.7%, renal insufficiency in 19.2%, chronic obstructive pulmonary disease (COPD) in 17.3%, and cerebrovascular disease in 16.5% patients. Atrial fibrillation or undulation was noted in 53.7% patients. Active smoking habit was recorded in 11.1% patients and 15.6% patients were former smokers.

Overweight was recorded in 46.3% patients and obesity in 25%.

The frequent precipitating factors of HF were arterial hypertension (55.5% patients), arrhythmias (51.3%), valvular heart disease (32.8%), acute coronary syndrome (19.7%), and infections (19.6%).

Lower levels of haemoglobin was recorded in 51.9% patients, higher levels of creatinine in 46.8%, ALT in 29.8%, cholesterol in 32.7%, tryglicerides in 31.9%, uric acid in 79.3% and hyperglycaemia in 99.8% patients. Females had higher values of ALT (F-33%, M-27%, P=0.012), cholesterol (F-36.8%, M-29.1%, P=0.009), tryglicerides (F-36.1%, M-28.3%, P=0.014), and uric acid (F-82.9%, M-76.4%, P=0.007). Opposite to expectation, males had lower haemoglobin levels (M-58%, F-44.8%, P 0.001).

In-hospital mortality rate was 13.8%.

**Conclusion:** The considerable underlying diseases of HF were hypertension, diabetes mellitus, myocardial infarction, renal insufficiency and COPD. one-third of HF patients were smokers (active or former) and two-third of them were overweight or obese. Hypertension was the most important “trigger” of our HF patients, close to arrhythmia, ACS, and infections.

**KEYWORDS:** heart failure, risk factors, Croatia.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):111.

Received: 21<sup>st</sup> Jan 2014

\*Address for correspondence: Klinički bolnički centar Split, Spinčićeva 1, HR-21000 Split, Croatia.

Phone: +385-21-556-111

E-mail: [duskag@net.hr](mailto:duskag@net.hr)

## Literature

1. Polić S, Zaputović L, Miličić D, Glavaš D. Croatian Heart Failure Registry: initial results — part II. *Liječ Vjesn.* 2007;129 Suppl 4:34.
2. Polić S, Glavaš D. Some specific features of identification and treatment of heart failure in the Republic of Croatia. *Cardiol Croat.* 2011;6(11):286-8.

# Machine learning approach for fetal QRS complexes detection

Dragan Gamberger<sup>1\*</sup>, Goran Krstačić<sup>2</sup>

<sup>1</sup>Ruder Bošković Institute, Zagreb, Croatia

<sup>2</sup>Institute for Cardiovascular Diseases and Rehabilitation, Zagreb, Croatia

**Aims:** The study presents a novel methodology for the detection of QRS events from four simultaneous noninvasive fetal ECG signals.

**Methods:** We have developed a three step procedure consisting of: **A)** transformation of ECG signals into a set of instances with 5 msec distance, so that each instance is defined by 93 features that describe characteristics of signals in the concrete time slot, **B)** evaluation of a multi-rule model on the set of instances so that a value in the range -200 to +200 is generated which is proportional to the probability that the instance is a fetal QRS event, **C)** transformation of a string of generated values into a string of QRS events taking into account that typical distance between fetal QRS is 250-600 msec. The central part of the approach is the preparation of the multi-rule model that consists of about 70,000 rules that vote either yes or no for fetal QRS<sup>1</sup>. Probability of fetal QRS is proportional to the difference between yes and no votes.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Institut Ruder Bošković, Bijenička 54, HR-10000 Zagreb, Croatia.

Phone: +385-1-4561-111

E-mail: dragan.gamberger@irb.hr

The model is constructed by a machine learning approach from a set of 10,000 examples described by the same set of features. Positive examples are coming from time slots with known fetal QRS events, while negative examples are from time slots that are 50 msec far from the positive examples.

**Results:** For the Physionet Challenge in the year 2013<sup>2</sup> the methodology enabled reasonable quality of QRS detection. For Task 4 the error in respect of the square of beats per minute has been 244.13 (best score 18.08) while for Task 5 mean squared error in milliseconds has been 11.72 (best score 4.34).

**Conclusion:** The achieved result demonstrates that the implemented approach is already able to recognize fetal QRS events with a reasonable quality, especially in respect of the precise position of the peaks. The further work is expected to result in an improvement of the quality of all three steps A-C. The main problem is very high time complexity of step b in which multi-rule model with many rules has to be evaluated on many instances.

**KEYWORDS:** ECG signals, fetal QRS, random rules algorithm, pattern recognition.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):112.

## Literature

1. Pfahringer, B., Holmes, G., Wang, C. (2004). Millions of random rules. In Proc. of the Workshop on Advances in Inductive Rule Learning, 15<sup>th</sup> European Conference on Machine Learning (ECML), Pisa, 2004.
2. Physionet Challenge 2013: Noninvasive Fetal ECG (<http://www.physionet.org/challenge/2013/>).



# Corticosteroids and heart rate variability in spinal cord injury

Antonija Krstajić<sup>1\*</sup>, Goran Krstajić<sup>2</sup>

<sup>1</sup>University Hospital Centre Sestre milosrdnice, Zagreb, Croatia

<sup>2</sup>Institute of Cardiovascular Disease and Rehabilitation, Zagreb, Croatia

**Introduction:** Spinal cord injury (SCI) is an insult to the spinal cord resulting in a change, either temporary or permanent, in the cord's normal motor, sensory, or autonomic function. SCI may cause loss of cardiovascular reflexes mediated by sympathetic drive due to interruption supraspinal control of spinal sympathetic motoneurons. *Aim:* The purpose of this study was to analyze sympathovagal balance after acute spinal cord injury demonstrated by the linear measures in time and frequent domain of heart rate variability (HRV) and effect of corticosteroids on the HRV parameters.

**Methods:** We have analyzed a sample of 40 tetraplegic patients after acute spinal cord injury and 40 healthy persons of the controls. In the group with cervical spine injury 29 patients received a corticosteroid therapy, and 11 did not. Cardiac autonomic balance was evaluated by analysis of HRV in time and frequents domain.

**Results:** The ratio of low and high frequencies (LF/HF) was significantly reduced in the groups of patients with acute trauma with and without corticosteroid therapy, as compared to controls. However there was no statistically significant difference in the two SCI groups. [(1.74 (0524) with corticosteroids therapy and 1.75 (0534) without)].

This study establishes analyzing of the heart rate variability (HRV) by linear methods as objective measures of normal and abnormal function of autonomic nervous system.

**Conclusion:** This study shows that sympathovagal balance is altered in quadriplegic patients in acute phase of cervical spinal cord trauma. SCI causes dysfunction of the autonomic cardiovascular regulation demonstrated by the spectral measures of heart rate variability and leads to disturbances of modulatory sympathetic activity on cardiovascular system. Finally, the effect of corticosteroids on the parameters of HRV in SCI patients was not found.

**KEYWORDS:** cervical spinal cord injury, corticosteroid therapy, heart rate variability, sympathovagal balance.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):113.

Received: 27<sup>th</sup> Jan 2014

\*Address for correspondence: Klinika za traumatologiju, Klinički bolnički centar Sestre milosrdnice, Draškovićeva 19, HR-10000 Zagreb, Croatia

Phone/Fax: +385-1-4697-000

E-mail: [akrstacic@gmail.com](mailto:akrstacic@gmail.com)

# *CroDiab NET as a powerful tool for tracking cardiovascular risk factors in diabetic patients: data from Bjelovar-Bilogora County collected during the period from 2001 to 2012*

Saša Magaš\*

*Bjelovar General Hospital, Bjelovar, Croatia*

Diabetes mellitus (DM) and its chronic complications are the major world health problem having an upward trend in the whole world. It is believed that currently 366 millions of people suffer from DM worldwide, and by the year 2030 the number of diabetics will increase to 552 million. The number of patients with DM rises in all countries, and 80% of the world's population suffering from diabetes live in developing countries or newly industrialized countries.<sup>1</sup>

The Republic of Croatia and the Bjelovar-Bilogora County are not exempt from this trend and the prevalence of DM in Croatia is 6.1%.<sup>2</sup> The influx of patients in the Center for Diabetes of the Bjelovar-Bilogora County is rising. The values of body mass index (BMI), Hba1c levels and the incidence of hypertension and dyslipidemia are worrisome. Therefore the incidence of modifiable cardiovascular risk factors increases too. Cardiovascular complications are the leading cause of morbidity and mortality among patients with DM, and the risk of coronary artery disease is 2-4 times higher than in the general population.<sup>3</sup>

This study has involved 4,408 outpatients whose e-records are maintained by the national register of diabetic persons. CroDiab NET, a computer software designed on the basis of

world quality indicators, integrates electronic patient records and generates discharge summaries parallel to collecting data for the national diabetes registry.<sup>4</sup> Type 2 diabetes was recorded in 93% of patients, while type 1 diabetes was recorded in only 3% of patients. Hypertension was present in 51% of patients with upward trend in the last three years. The highest rate of dyslipidemia was 39% in 2004, with downward trend at about 25% in the last 3 years. The frequency of patients with myocardial infarction was stable at around 10%, with the lowest value of 7.4% in 2010. The prevalence of patients with stroke also showed a downward trend from 14.9% to 7.4%. Only 10% of patients had BMI <25 kg/m<sup>2</sup>, while 32% of them were overweight persons with BMI from 25 to 30 kg/m<sup>2</sup>, and 50% were obese persons with BMI >30 kg/m<sup>2</sup>. Good disease control was achieved by only 18% of patients, a further 18% of them had borderline disease control.

The level of regulation of diabetes, BMI, as well as other observed modifiable cardiovascular disease risk factors (arterial hypertension, dyslipidemia) is not satisfactory. Therefore further efforts for better glycemic control, control of hypertension, and dyslipidaemia are needed. CroDiab NET is a powerful tool for tracking cardiovascular risk factors in diabetic patients.

**KEYWORDS:** diabetes mellitus, cardiovascular risk factors, cardiovascular complications, body mass index, glycosylated hemoglobin, hypertension.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):114.

Received: 2<sup>nd</sup> Feb 2014

\*Address for correspondence: Opća bolnica Bjelovar, Mihanovićevo 8, HR-43000 Bjelovar, Croatia.

Email: [sasa.magas@zg.t-com.hr](mailto:sasa.magas@zg.t-com.hr)

## Literature

1. IDF Diabetes atlas. Fifth edition. <http://www.idf.org/diabetesatlas> (8.5.2013).
2. Metelko Z, Pavlic-Renar I, Poljicanin T, Szivovitz L, Turek S. Prevalence of diabetes mellitus in Croatia. *Diabetes Res Clin Pract.* 2008;81(2):263-7.
3. Li YW, Aronow WS. Diabetes mellitus and cardiovascular disease. *J Clin Exp Heart Dis.* 2011;2:114.
4. CroDiab NET. [http://www.idb.hr/web\\_english/crodiabnet.htm](http://www.idb.hr/web_english/crodiabnet.htm) (10.1.2014).

# Evaluation of satisfaction with information system

Nada Hrstić<sup>1,2\*</sup>, Marija Heinrich<sup>1,2</sup>, Mario Ivanuša<sup>1,3</sup>, Goran Krstajić<sup>1,2</sup>

<sup>1</sup>Institute for Cardiovascular Prevention and Rehabilitation, Zagreb, Croatia

<sup>2</sup>University of Applied Health Studies, Zagreb, Croatia

<sup>3</sup>Study Programme in Nursing, Technical College in Bjelovar, Bjelovar, Croatia

**Introduction:** Information System Irata<sup>®</sup> was implemented at Institute for Cardiovascular Prevention and Rehabilitation, Zagreb, Croatia in 1995 as a DOS application, and since 2010 as a NET application which is aimed to facilitate the daily workup of patients and improve the quality of services rendered. Every workplace, at both institution locations is linked in a Novell 6 network.<sup>1,2</sup> The aim of this study was to determine the satisfaction of employees with the existing IT system.

**Methods:** The study was conducted on a sample of 29 medical professionals with secondary school qualification and higher expertise education (Bachelor of Science) by using the method of a structured questionnaire, which was anonymous. In addition to demographic data, the questions were aimed to find out the length of work experience, professional qualification and satisfaction and benefit of using the existing information program.

**Results:** 83% of employees were surveyed. Only one respondent was male, while the remaining respondents were women. A total 17/29 (58%) of respondents have the higher expertise education and 12/29 (41%) have the secondary school qualification. Most of the respondents (19/29; 66%)

have more than 20 years of experience and are over 40 years of age. The majority of the respondents (20/29; 69%) have attended some IT course, and the majority (25/29; 86%) have a computer at home, which they commonly use for emailing (26/29; 98%), listening to music (24/29; 83%), education in medical contents (23/29; 79%), browsing the Internet and reading news (21/29; 72%), watching movies (20/29; 69%), and for browsing professional medical journals, preparation of articles and lectures (11/29; 40%). The existing information system is used by almost all respondents when entering patients data for examinations and cardiovascular diagnostics. Nurses and physical therapists rarely browse patients' findings (10/29; 35%), and use the IT system to write medical records very rarely (5/29; 17%). Only a quarter of respondents (7/29; 24%) considers the existing information system adapted to their daily work. A large number of respondents (23/29; 79%) find additional IT training and information system training necessary.

**Conclusion:** Today, the information system has entered into all spheres of our life, and so the most of the respondents have and use a computer at home for emailing, browsing the Internet, watching movies, etc. The information system should facilitate the work of medical professionals and thus shorten the time of admittance which would free up the time for work with patients and enable certain type of triage. The obtained results similar to the results of some other authors<sup>3-5</sup> indicate the need for additional IT training and additional training in using the information system.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):115.

**KEYWORDS:** information system, satisfaction, evaluation.

Received: 15<sup>th</sup> Feb 2014

\*Address for correspondence: Poliklinika za prevenciju kardiovaskularnih bolesti i rehabilitaciju, Draškovićeve 13, HR-10000 Zagreb, Croatia.


Phone: +385-1-4612-290

Fax: +385-1-4612-343

E-mail: [nhrstic@gmail.com](mailto:nhrstic@gmail.com)

## Literature

1. Heim I, Jembrek Gostović M, Jonke V. Informacijski sustav u Poliklinici za prevenciju kardiovaskularnih bolesti i rehabilitaciju. *Medix.* 2004;10(54/55):117-8.
2. Heim I. Informacijski sustav u poliklinici. Nastavni tekstovi iz kolegija Upravljanje informacijskim sustavom i sustavom kliničkih podataka. Zagreb, Zdravstveno veleučilište, 2013.
3. Brumini G, Kovic I, Zombori D, Lulic I, Petrovecki M. Nurses' attitudes towards computers: cross sectional questionnaire study. *Croat Med J.* 2005;46:101-4.
4. Ivanuša M, Kern J. User satisfaction with clinical informatical system. *European Notes in Medical Informatics* 2006;2(2):304-9. [CD-ROM; ISSN 1861-3179].
5. Abdrbo AA, Hudak CA, Anthony MK, Douglas SL. Moderating and mediating roles of nurses' beliefs: information systems use among Ohio nurses. *West J Nurs Res.* 2009;31(1):110-27.



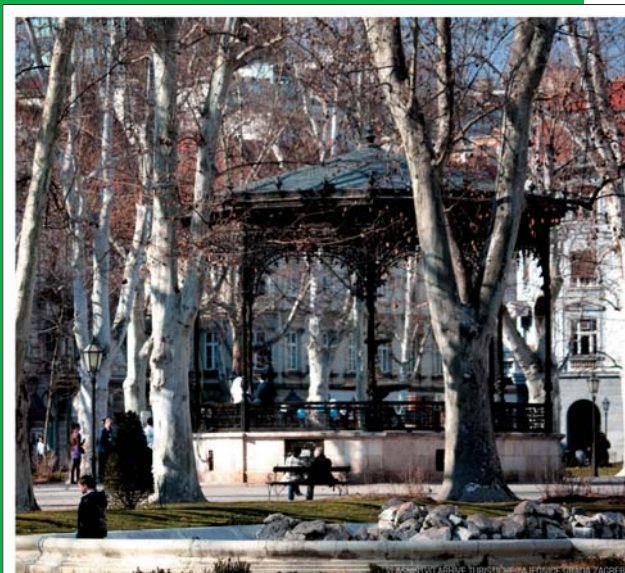


**22<sup>ND</sup> ANNUAL MEETING  
OF THE  
ALPE ADRIA ASSOCIATION  
OF CARDIOLOGY**

**OPATIJA HOTEL ADMIRAL | 04 - 07. 06. 2014.**

[WWW.ALPEADRIACARDIOLOGY2014.ORG](http://WWW.ALPEADRIACARDIOLOGY2014.ORG)

ORGANIZED BY THE CROATIAN CARDIAC SOCIETY  
TEHNIČKI ORGANIZATOR / TECHNICAL ORGANIZER  
SPEKTAR PUTOVANJA D.O.O. / TKALČEVA 15 / ZAGREB / CROATIA  
PHONE +385 1 4862 605 / FAX +385 1 4862 622 / E-MAIL ANA.HADJIC@SPEKTAR.HOLIDAYS.HR

**10. KONGRES  
HRVATSKOGA  
KARDIOLOŠKOG  
DRUŠTVA**

S MEĐUNARODNIM SUJELOVANJEM  
POKROVITELJ KONGRESA: EUROPSKO KARDIOLOŠKO DRUŠTVO  
ORGANIZATOR KONGRESA: HRVATSKO KARDIOLOŠKO DRUŠTVO

**10<sup>TH</sup> CONGRESS OF THE  
CROATIAN  
CARDIAC  
SOCIETY**

WITH INTERNATIONAL PARTICIPATION  
UNDER THE PATRONAGE OF THE EUROPEAN SOCIETY OF CARDIOLOGY  
CONGRESS ORGANIZER: CROATIAN CARDIAC SOCIETY

**5. KONGRES HRVATSKE UDRUGE  
KARDIOLOŠKIH MEDICINSKIH SESTARA**

**5<sup>TH</sup> CONGRESS OF THE CROATIAN  
ASSOCIATION OF CARDIOLOGY NURSES**

**ZAGREB / HOTEL WESTIN / 06 - 09. 11. 2014.**

TEHNIČKI ORGANIZATOR / TECHNICAL ORGANIZER  
SPEKTAR PUTOVANJA D.O.O. / TKALČEVA 15 / ZAGREB / CROATIA  
PHONE +385 1 4862 605 / FAX +385 1 4862 622 / E-MAIL ANA.HADJIC@SPEKTAR.HOLIDAYS.HR  
[WWW.KARDIO-KONGRES2014.COM](http://WWW.KARDIO-KONGRES2014.COM)



# Akutni koronarni sindrom i intervencijska kardiologija u Dubrovniku.

## 2013. godina stručnog kontinuiteta i teritorijalnog diskontinuiteta

### *Acute coronary syndrome and interventional cardiology in Dubrovnik*

### *2013 as the year of professional continuity and territorial discontinuity*

Josip Lukenda\*

Opća bolnica Dubrovnik, Dubrovnik, Hrvatska  
Dubrovnik General Hospital, Dubrovnik, Croatia

**SAŽETAK:** Uz uspjeh Hrvatske mreže primarne perkutane kornarne intervencije ipak su zaostale "sive zone", kao što je Dubrovačko-neretvanska županija, a grad je uz dva granična prijelaza udaljen 210 km od sljedećeg najbližeg centra. Stoga je od 1. siječnja 2013. godine pokrenut redoviti rad invazivnog laboratorija u Općoj bolnici Dubrovnik, 24 h/7 dana.

Od 361 invazivne obrade u 2013. godini 227 (66,8%) učinjeno je kod hitnih bolesnika. Među bolesnicima s akutnim koronarnim sindromom 33,5% imalo je nestabilnu anginu pektoris, 39,2% akutni infarkt miokarda bez elevacije ST-segmenta i 27,2% (N=62) akutni infarkt miokarda s elevacijom ST-segmenta (STEMI). Perkutana koronarna intervencija (PCI) je učinjena kod 167 bolesnika, kod 62% svih bolesnika s AKS. Implantirane su 223 proširnice, 1,33 po postupku, kod 16,2% na dvije ili više žila, uz penetraciju proširnica obloženih lijekovima od 25,6%. Među koronarnim bolesnicima 30% je ostalo na medikamentoznoj terapiji, kod 55% je učinjena PCI, a kod 15% je preporučena kardiokirurški zahvat. Unutarbolnički mortalitet akutnog infarkta miokarda bio je 2,61%, a kod STEMI 4,8%. Bilo je 2,4% tromboza u stentu te 0,8% kirurški liječenih perifernih komplikacija.

Gotovo da samo hitni bolesnici opravdavaju postojanje laboratorija u Općoj bolnici Dubrovnik, uz potrebu daljeg povećanja broja elektivnih PCI, osoblja i aparature.

**KLJUČNE RIJEČI:** akutni koronarni sindrom, perkutana koronarna intervencija, Dubrovnik.

**SUMMARY:** Along with the success of the Croatian Network of Primary Percutaneous Coronary Intervention, there are still "grey zones" remaining, such as the Dubrovnik-Neretva County where the City of Dubrovnik is 210 kilometers away with two border crossings from the nearest center. Therefore, from the first of January 2013, the General Hospital Dubrovnik started a regular operation of the invasive laboratory 24 hours/7 days.

Of 361 invasive procedures in 2013, some 227 (66.8%) of them were performed in emergency patients. Among the patients with acute coronary syndrome (ACS), 33.5% had unstable angina pectoris, 39.2% had acute myocardial infarction without ST-segment elevation and 27.2% (N = 62) had acute myocardial infarction with ST-segment elevation (STEMI). Percutaneous coronary intervention (PCI) was performed in 167 patients, in 62% of all patients with ACS. 223 stents were implanted, 1.33 per procedure, in 16.2% of patients on two or more vessels, with the penetration of the drug-eluting stents in 25.6%. Among coronary patients, 30% remained on medical therapy, 55% underwent PCI and 15% of them received a recommendation for cardiac surgery. In-hospital mortality of acute myocardial infarction was 2.61%, and 4.8% for STEMI. 2.4% stent thrombosis and 0.8% of surgically treated peripheral complications were recorded.

It is almost only the emergency patients that justify the existence of the laboratory in Dubrovnik General Hospital, along with a need for further increase in the number of elective PCI, personnel and apparatus.

**KEYWORDS:** acute coronary syndrome, percutaneous coronary intervention, Dubrovnik.

**CITATION:** Cardiol Croat. 2014;9(3-4):117-126.

## Uvod

Krajem osamdesetih godina prošlog stoljeća koncept "otvorene koronarne arterije" u liječenju akutnog infarkta miokarda (AIM) selio se iz farmako-koagulacijskih u laboratorije za invazivnu kardiologiju.<sup>1,2</sup> Od 1997. godine u izvorištu naše invazivne kardiologije, Kliničkoj bolnici Sestre milosrdnice u Zagrebu, započele su primarne perkutane koronarne intervencije (pPCI) kod akutnog infarkta miokarda s elevacijom ST-segmenta (STEMI).<sup>3</sup> Krajem 2000. godine u tom centru započinje i kontinuirana pripravnost invazivnih kardiologa za STEMI (24 sata/7 dana).<sup>4</sup> Krug oko te bolnice širi se početkom 2001. na krugove oko Kliničkog bolničkog centra Zagreb i Kliničke bolnice Dubrava u Zagrebu<sup>5</sup> te se postupno pokriva i cijelo područje Zagreba. Struka se paralelno razvija i u Rijeci gdje je prva pPCI učinjena već 1998. godine.

Od 2004. inicijativom članova Hrvatskog kardiološkog društva osniva se Hrvatska mreža pPCI koja od 2005. godine širi krugove teritorija gdje se radi pPCI, od Zagreba i Rijeke na nove invazivne kardiološke laboratorije, koji pokrivaju većinu hrvatskog teritorija, rezultirajući fascinirajućim rezultatima.<sup>6</sup> Mreža je povećala dostupnost i smanjila razlike u liječenju AIM naših građana, kako po teritorijalnoj pripadnosti, tako i po dobi i spolu.<sup>7</sup> Ipak, ostale su i "sive zone našeg teritorija" gdje Mreža nije obuhvaćala svo pučanstvo i sve bolesnike, što zbog nerazumijevanja lokalnih voditelja bolnica, sve do sredine 2013. (Slavonski Brod), što zbog nedostatka kvalificiranih invazivnih kardiologa, sve do kraja 2012. godine (Dubrovnik).

Invazivni kardiološki laboratorij Opće bolnice Dubrovnik ustanovljen je 2009. godine i sljedećih par godina radio je prigodice, tijekom ljeta i vikendima, kada bi dolazili kolege iz Zagreba. Budući da je transport do Splita u razumnom roku bio gotovo nemoguć (samo putovanje traje 3-4 sata), uključujući 210 km djelomično "planinske ceste" od Ploča do Vrgorca, te dva granična prijelaza, do 1. siječnja 2013. godine reperfuzijska terapija u Dubrovniku uglavnom je značila fibrinolizu. Od tada i u Dubrovniku započinje stalni kontinuirani rad laboratorija i stalna pripravnost za akutni koronarni sindrom (AKS) (24/7), s jednim invazivnim kardiologom u prvoj polovici godine i nakon ispunjavanja uvjeta i sljedećom kolegicom.<sup>7</sup> Laboratorij je integriran s koronarom jedinicom u Odsjek za akutne srčane bolesti i intervencijsku kardiologiju, a rezultati prve godine rada deskriptivno su predstavljeni u ovom članku.

## Rezultati

Tijekom 2013. god. u OB Dubrovnik primljeno je 227 bolesnika s AKS, od čega 151 bolesnik (66,5%) zbog AIM i 76 bolesnika (33,5%) s nestabilnom anginom pectoris (NAP). Među bolesnicima s AIM bilo je 89 bolesnika (39,2% AKS) s akutnim infarktom bez elevacije ST-segmenta (NSTEMI) i 62 bolesnika (27,2% AKS) sa STEMI (**Tablica 1**).

U prvoj godini rada invazivna kardiološka obrada učinjena je kod ukupno 361 bolesnika, od čega dvije trećine kod hitno primljenih bolesnika (241 bolesnik; 66,8%), a trećina kod naručenih bolesnika (120 bolesnika; 33,2%). Prosječna dob bolesnika bila je 65,5 godina (raspon 25-89 god.). Žene su bile prosječno nešto starije (67,4 god.) i bilo ih je manje (33,2%) od muškaraca (**Tablica 2**).

## Introduction

In the late eighties of the last century, the concept of an "open coronary artery" in the treatment of acute myocardial infarction (AMI) moved from phamaco-coagulation laboratory to the invasive cardiology laboratory.<sup>1,2</sup> Since 1997 our principle invasive cardiology institution, University Hospital Sestre milosrdnice in Zagreb initiated primary percutaneous coronary intervention (pPCI) in acute myocardial infarction with ST-segment elevation (STEMI).<sup>3</sup> In late 2000 this center also started with continuous preparedness of invasive cardiologists for STEMI (24 hours/7 days).<sup>4</sup> This concept was also extended in early 2001 to the laboratories in University Hospital Zagreb and University Hospital Dubrava in Zagreb<sup>5</sup> whereas the entire Zagreb region was gradually covered. The profession is simultaneously evolving in Rijeka, where the first pPCI was performed already in 1998.

Since 2004, upon the initiative of the members of the Croatian Cardiac Society the Croatian pPCI network was established and after that it started extending to some other territories since 2005, from Zagreb and Rijeka to some new invasive cardiology laboratories, covering major part of the Croatian territory, recording fascinating results.<sup>6</sup> The network resulted in a greater availability and reduced differences in the treatment of AMI for our citizens, both in terms of territorial allegiance and by age and gender.<sup>7</sup> However there are certain "grey zones of our territory" where the network did not include all of its population and all of its patients, partly because of a lack of understanding by local hospital principals till the mid of 2013 (Slavonski Brod), partly because of a lack of skilled invasive cardiologists till the end of 2012 (Dubrovnik).

The invasive cardiac laboratory of Dubrovnik General Hospital was established in 2009 and in the next few years it worked on certain occasions, in summer and at weekends, when colleagues from Zagreb would come to this hospital. Since the transport to Split within a reasonable time was almost impossible (only the journey takes 3-4 hours), including 210 km partly along the "mountain road" from Ploče to Vrgorac and two border crossings, the reperfusion therapy in Dubrovnik mainly included fibrinolysis prior to the 1<sup>st</sup> of January 2013. Since that date a continuous operation of the laboratory and constant preparedness for acute coronary syndrome (ACS) (24/7) started with one invasive cardiologist in the first half of the year and another colleague after she fulfilled some conditions.<sup>7</sup> The laboratory is integrated with the coronary unit into Department for acute cardiac care and interventional cardiology, and the results of the first year of operation are descriptively presented in this article.

## Results

During the year 2013, the Dubrovnik General Hospital received 227 patients with ACS, of whom 151 patients (66.5%) with AMI and 76 patients (33.5%) with unstable angina pectoris (UAP). Among the patients with AMI there were 89 patients (39.2% ACS) with acute myocardial infarction without ST-segment elevation (NSTEMI) and 62 patients (27.2% ACS) with STEMI (**Table 1**).

In the first year of operation, the invasive cardiac workup was performed in a total of 361 patients, of whom two-thirds of patients were admitted in an emergency department (241 patients, 66.8%), and one third as ordered patients (120 patients; 33.2%). The average age of patients was 65.5 (range 25-89 years of age). Women were on average slightly older (67.4) and there were fewer of them (33.2%) than men (**Table 2**).

**Table 1.** Structure of admitted, invasively processed and invasively treated patients in Department of Cardiology, GH Dubrovnik during 2013.

	Admitted Pts	Coronary angiography (CA)		Percutaneous coronary intervention (PCI)		RCS (%CA)
		N (% Pts)	TRA (%CA)	N (%CA)	TRA (%PCI)	
UAP	76	76 (100)	43 (56.6)	32 (42.1)	19 (59.4)	10 (13.2)
NSTEMI	89	78 (87.6)	50 (64.1)	53 (67.9)	33 (62.3)	15 (19.2)
STEMI	62	61 (98.4)	31 (50.8)	55 (90.2)	26 (47.3)	6 (9.6)
SAP	(80)*	87	35 (40.2)	26 (29.9)	15 (57.7)	12 (13.7)
VD/CMP	(30)*	58	33 (56.9)	2 (3.4)	2 (100.0)	26 (44.8)
Total	—	361	192 (53.2)	168 (46.5)	95 (56.5)	69 (19.1)

UAP — unstable angina pectoris; NSTEMI — non-ST segment elevation myocardial infarction; STEMI — ST segment elevation myocardial infarction; SAP — stable angina pectoris; VD/CMP — valvular disease and cardiomyopathy; TRA — transradial approach; RCS — recommended cardiac surgery. \* scheduled patients

**Table 2.** Invasive cardiac procedures and percutaneous coronary interventions (PCI) in GH Dubrovnik during 2013.

	Coronary angiography		PCI		pPCI
	N	Age (mean)	N (%)	Age (mean)	N (% PCI) [TIMI 0/1/2/3]
Total	361	65.5	167 (46.3)*	65.0	55 (32.9) [2/0/2/51]
Male	241 (66.8%)	64.5	121 (72.4%)	64.0	38 (31.4) [0/0/1/37]
Female	120 (33.2%)	67.4	46 (27.6%)	67.7	17 (40.0) [2/0/1/14]

\* % of coronary angiographies

Invasivna obrada učinjena je kod 215 hitno primljenih koronarnih bolesnika (94,7%), i to kod svih 76 bolesnika s NAP (100%) i kod većine bolesnika sa AIM (92%) te kod 61 od 62 bolesnika sa STEMI (98,4%). Među 120 bolesnika naručenih radi invazivne obrade kod njih 80 indikacija je bila stabilna angina pektoris, a istu dijagnozu imalo je i 7 hitno primljenih bolesnika, primljenih iz drugog razloga, a obrada je učinjena većinom kao priprava za nekardijalnu kirurgiju. Kod 30 naručenih bolesnika obrada je učinjena zbog valvularnih bolesti i kardiomiopatija. Gotovo jednak broj bolesnika invazivno je obrađen zbog valvularnih bolesti i kardiomiopatija nakon prijema iz hitne službe (28 bolesnika). Transradijalnim pristupom učinjeno je ukupno 192 obrade, 53,2% (**Tablica 1**).

Obradom 361 bolesnika nađeno je 570 značajnih stenoza/okluzija, 1,6 po bolesniku. Nađena je 31 (5,4%) stenoza na deblu lijeve koronarne arterije (LM) te polovica na velikim arterijama, gotovo trećina (27,4%) na lijevoj prednjoj descendentnoj arteriji (LAD) i četvrtina (23,9%) na desnoj koronarnoj arteriji (RCA) (**Tablica 3**). Perkutane koronarne intervencije učinjene su kod 167 bolesnika, s udjelom od 46,3% svih invazivnih obrada i na trećini svih nađenih značajnih stenoza/okluzija (34%). Prosječna dob bolesnika kojima je učinjena PCI bila je 65 godina (raspon 36-87), žene su bile starije, prosječno 67,7 godina, i bilo ih je ukupno manje, 27,6% (**Tablica 2**).

Sa PCI rezultiralo je više od polovice intervencija kod koronarnih bolesnika (54,4%; 165/303), a udio PCI kod bolesnika sa AKS bio je i veći, 62%. Kod 140 bolesnika PCI je uči-

Coronary angiographies were performed in 215 of emergency coronary patients (94.7%), in all 76 patients with UAP (100%), in the majority of patients with AMI (92%) and in 61 of 62 patients with STEMI (98.4%). Among 120 patients ordered for invasive workup, 80 of them had indication for stable angina pectoris, and the same diagnosis was made in 7 emergency patients, received for some other reason, while the workup and preparation was done mostly for non-cardiac surgery. The workup was done in 30 ordered patients for valvular diseases and cardiomyopathy. Almost the same number of patients underwent the invasive workup for valvular disease and cardiomyopathy after being admitted from the emergency department (28 patients). Transradial access was done in a total of 192 procedures, 53.2% (**Table 1**).

The workup of 361 patients found 570 significant stenosis/occlusions, 1.6 per patient. We found 31 (5.4%) stenosis of the left main coronary artery (LM) and a half of them on the large arteries, almost one third of them (27.4%) on the left anterior descending artery (LAD) and one fourth of them (23.9%) on the right coronary artery (RCA) (**Table 3**). Percutaneous coronary interventions were performed in 167 patients, accounting for 46.3% of all invasive procedures and also on one third of all found significant stenosis/occlusions (34%). The average age of patients who underwent PCI was 65 years (range 36-87), women were older, on average 67.7 years, and there were fewer of them, 27.6% (**Table 2**).

PCI has resulted in more than one half of interventions in coronary patients (54.4%, 165/303), and the proportion of PCI in patients with ACS was higher, 62%. 140 patients under-

njena na jednoj, a kod 27 na dvije ili više arterija (16,2%). Implantirane su 223 proširnice, 1,33 po intervenciji, od toga 52 proširnice obložene lijekom (DES), s penetracijom od 25,6%. U 15 bolesnika (9%) učinjena je perkutana transluminalna angioplastika balonom (PTCA), bez implantacije proširnice.

Polovica od 156 značajnih stenoza/okluzija na LAD je liječeno primjenom PCI (48,7%) što je 45,5% svih intervencija, a od 136 lezija na RCA sa PCI liječeno je 41,2%, što je 33,5% svih PCI. Ostatak od 21% PCI učinjeno je na arteriji cirkumfleksi (ACx) (12,9%) i na manjim žilama, nešto više na marginalnim (OM) granama (10,8%) nego na dijagonalnoj (D) i posterodescendentnoj (PD) grani (ukupno 7,7%) (Tablica 3). Neliječene lezije ostale su kod bolesnika kojima je pre-

went PCI on one, and 27 patients on two or more arteries (16.2%). 223 stents were implanted, 1.33 per intervention, of which 52 of them were drug-eluting stents (DES), with a penetration of 25.6%. 15 patients (9%) underwent percutaneous transluminal coronary angioplasty, without stent implantation.

A half of the 156 significant stenosis /occlusions on the LAD was treated with PCI (48.7%), which is 45.5% of all interventions, and out of 136 lesions on the RCA 41.2 % was treated with PCI, which is 33.5% of all PCIs. The remaining 21% of PCI was performed in circumflex coronary artery (CCA) (12.9%) and on the smaller vessels, somewhat more on marginal (OM) branches (10.8%) than on the diagonal (D) and posterodescending (PD) branch (a total of 7.7%) (Table 3). Untreated lesions remained in patients who were recommen-

**Table 3.** Coronary angiography results and performed percutaneous coronary interventions.

	Stenosis N (%)	PCI N (%)
Left main (LM)	31 (5.4)	1 (0.5)
Left anterior descending (LAD)	156 (27.4)	76 (39.2)
Diagoal branch (D)	54 (9.5)	6 (3.1)
Circumflex artery (Acx)	80 (14.0)	25 (12.9)
Obtuse marginal artery (OM)	73 (12.8)	21 (10.8)
Right coronary artery (RCA)	136 (23.9)	56 (28.8)
Posterior descending artery (PD)	40 (7.0)	9 (4.6)
Total	570	194 (34.0)*

\* % of all stenosis

poručena kardiokirurška revaskularizacija (CABG), nerekanalizirane kronične totalne okluzije, bolesnicima sa stupnjevanom PCI (ugavnom nakon STEMI) te kod dva bolesnika koje smo uputili u tercijarni centar s kardiokirurškom potporom, u Kliničku bolnicu Dubrava (jedna PCI debla LKA i jedna PCI jedine ostatne žile, ukupno 1,2%). Transradijalnim pristupom učinjeno je ukupno 95 PCI (56,5%).

Od 61 invazivno obrađenog bolesnika zbog STEMI kod 55 je učinjena PCI, jedna bolesnica je imala Takotsubo kardiomiopatiju i nije trebala intervenciju, kod 3 je preporučena hitna kardiokirurška revaskularizacija, bez prethodne PCI, a kod 3 bolesnika je učinjena intervencija i preporučena CABG zbog nalaza na ostalim žilama. Kod 2 bolesnice nije postignuta rekanalizacija žile uz TIMI 0 protok (Tablica 2 i 5), a

ded to undergo surgical cardiac revascularization (CABG), non-recanalized chronic total occlusions, patients with staged PCI (mainly after STEMI) and in two patients who were referred to a tertiary center with cardiosurgical support, University Hospital Dubrava (one PCI of the left main and one PCI on the only residual vessel, total 1.2%). Transradial access was performed in a total of 95 PCIs (56.5%).

Out of 61 patients invasively processed for STEMI, 55 of them underwent PCI, one patient had Takotsubo cardiomyopathy and did not need an intervention, 3 of them were recommended to undergo urgent CABG without prior PCI, and 3 patients underwent PCI and were recommended to undergo CABG for their findings in other vessels. In 2 patients no vessel flow was achieved (TIMI 0 flow) (Table 2 and 5) and

**Table 4.** Foreigners invasively processed and invasively treated in Dubrovnik General Hospital during 2013.

	CA*	PCI
UAP	4	2
NSTEMI	10	4
STEMI	9	9
SAP	2	0
VD; CMP	0	0
Total	25	15

\*For abbreviations see Table 1.



dvoje bolesnika je imalo krajnji TIMI 2 protok. Ukupno TIMI 3 protok imalo je 93.4% bolesnika sa STEMI (**Tablica 5**).

two patients had final TIMI 2 flow. 93.4% of patients with STEMI had a total TIMI 3 flow (**Table 5**).

**Table 5.** In-hospital mortality and other complications of invasively treated patients in Dubrovnik General Hospital during 2013.

Outcome	Age, gender	Primary dg & complication	Therapy
Death	83; F	— STEMI anteroseptalis — Shock	— Equipment out of order — Fibrinolysis — Death 3 <sup>rd</sup> day
	88, F	— STEMI anteroseptalis, 3 vessel disease — Shock	— Failed PCI of LAD — Fibrinolysis — Death 3 <sup>rd</sup> day
	76; F	— STEMI anteroseptalis, 3 vessel disease — Asystolia	— Failed PCI of LAD — Death after procedure
	80; F	— NSTEMI and shock — Multiorgan failure	— Conservative th. — Death 3 <sup>rd</sup> day
Stent thrombosis	45; M	— STEMI anteroseptalis. pPCI on LAD and PCI on Acx. Chronic renal failure — STEMI inferior 4 <sup>th</sup> day	— Stent thrombosis in Acx — rePCI on Acx (PTCA and another stent)
	55; M	— NAP. PCI on RCA — STEMI inferior 3 <sup>rd</sup> day	— Stent thrombosis in RCA — rePCI on RCA (PTCA and another stent)
	74; M	— STEMI inferior. PCI on RCA — reSTEMI inferior 1 <sup>st</sup> day	— Stent thrombosis in RCA — rePCI on RCA (PTCA)
	80; M	— NSTEMI and ventricular fibrillation out of hospital — PCI on RCA (in 24 hours) — STEMI inferior on 2 <sup>nd</sup> day	— Stent thrombosis in RCA — rePCI in RCA (PTCA)
Vascular complications	69; M	— Femoral artery dissection and occlusion	— Surgery, aortofemoral by pass
	72; F	— Femoral artery pseudoaneurysm	— Surgery, aneurysmectomy
	65; F	— Radial artery pseudoaneurysm	— Surgery, aneurysmectomy

\* For abbreviations see Table 1 and Table 3.

Kardiokirurški zahvat, elektivni ili direktni premještaj, preporučan je kod 69 bolesnika (19,1% ukupno obrađenih). Nije bilo urgentnih ili helikopterskih prevoza. Među bolesnicima obrađivanim zbog koronarne bolesti preporuku za CABG dobilo je 43 bolesnika (14,2%), a među bolesnicima obrađenim zbog valvularne bolesti ili kardiomiopatijom kod njih 26 preporučena je valvularna kirurgija, s ili bez CABG (44,8%).

Konačno, od svih koronarnih bolesnika oko 30% je ostalo na medikamentoznoj terapiji, kod oko 55% učinjena je PCI, a kod 15% preporučan je kardiokirurški zahvat.

Grad Dubrovnik veliko je turističko središte, a Dubrovačko-neretvansku županiju godišnje posjeti više od milijun turista. Iako nisu dostupni podaci o demografskoj strukturi gostiju, možemo reći da smo 2013. godine invazivno obradili 25 stranih državljana i da je kod njih 15 učinjena PCI (60%). PCI je učinjena kod dva od četiri bolesnika sa NAP, četiri od

Cardiac surgery, elective or direct transfer was recommended in 69 patients (19.1% of totally worked up). There were no urgent or helicopter transported patients. Among the patients worked up for coronary heart disease, 43 patients (14.2%) received the recommendation for CABG, and among the patients treated for valvular disease or cardiomyopathy there were 26 of them who were recommended to undergo valvular surgery with or without CABG (44.8%).

Finally, of all coronary patients about 30% remained on medical therapy, with approximately 55% who underwent PCI and 15% of them were recommended to undergo cardiac surgery.

The city of Dubrovnik is a major tourist destination and the Dubrovnik-Neretva County is visited by more than one million tourists each year. Although no data on the demographic structure of guests is available yet, we can say that in 2013 some 25 foreign citizens underwent invasive treatment and PCI was performed in 15 of them (60%). PCI was per-

10 bolesnika sa NSTEMI i svih 9 bolesnika sa STEMI (**Tablica 4**).

Naravno, dešavali su se i neželjeni događaji (**Tablica 5**). Nestandardizirani unutarbolnički letalitet bolesnika sa AIM bio je 2,61% (4/153), sve su bile žene, srednje dobi 81,2 godine (raspon 76-88), kod tri od četiri s infarktom prednje stijenke, kod dvije uz neuspješnu PCI na LAD i kod jedne nakon neuspješne terapije fibrinolizom tijekom kvara aparata. Unutarbolnički letalitet bolesnika sa STEMI bio je 4,8%. Nije bilo smrti kod bolesnika s NAP i stabilnom anginom pectoris. Tijekom godine bilo je 2,4% akutnih i subakutnih tromboza u stentu (4/168), sve kod bolesnika s AKS i sve kod muškaraca, u 3 slučaja u RCA i jednom u Acx. Jedan bolesnik imao je klinički vođenu rePCI zbog restenoze, nakon 3 mjeseca. Imali smo 3 periferne komplikacije koje su zahtijevale kirurški tretman (0,8%), dvije kod bolesnika sa AKS i jednu kod naručene bolesnice (**Tablica 5**).

Utrošak glavnih stavki materijala 2013. godine vidi se u **Tablici 6**. Prema potrošnji iz 2013. godine planirali smo potrošnju za 2014. godinu, 900 dijagnostičkih i 280 vodećih katetera. Na kraju, prema nacionalnom tenderu, odobreno nam je 200 dijagnostičkih katetera, bez vodećih katetera (sic!). Planirali smo sljedeće godine implantirati oko 300 metalnih proširnica (BMS) i 45 DES, no odobreno nam je samo 130 BMS.

formed in two of four patients with UAP, four of 10 patients with NSTEMI and all 9 patients with STEMI (**Table 4**).

Of course, there were some adverse events we faced (**Table 5**). Non-standardized in-hospital lethality of patients with AMI was 2.61% (4/153), all of them were women, mean age 81.2 (range 76-88), in three of the four with anterior wall AMI, in two with unsuccessful PCI on the LAD and in one after unsuccessful treatment with fibrinolysis during malfunction of the appliance. In-hospital lethality of patients with STEMI was 4.8%. There were no deaths in patients with UAP and stable angina pectoris. During the year there were 2.4% of acute and subacute stent thrombosis (4/168), all of them in patients with ACS and all of them in men, in three cases on the RCA and one in Acx. One patient had clinically guided rePCI for restenosis after 3 months. There were three peripheral complications that required surgical treatment (0.8%), two in patients with ACS and one in a patient who was ordered (**Table 5**).

The consumption of major supplies in 2013 can be seen in **Table 6**. Based on consumption in 2013, we planned to spend 900 diagnostic and 280 guiding catheters in 2014. Finally, according to the national tender, 200 diagnostic catheters and no guiding catheters (sic!) were approved to us. We planned to implant 300 bare-metal stents (BMS) and 45 drug-eluting stents, however only 130 BMS were approved to us.

**Table 6.** *Interventional products consumption in Dubrovnik General Hospital during 2013. Planned consumption during 2014, and the finally approved material in the National tender for 2014.*

		Consumption in 2013	Planned for 2014	Approved for 2014
Diagnostic catheters		800	900	200
Guiding catheters		200	280	0
Stents	Total	223	345	130
	BMS	171	300	130
	DES	52	45	0

BMS — bare-metal stent; DES — drug-eluting stent

## Rasprava

Jedan od rijetkih uspješno provedenih nacionalnih programa u zadnjem desetljeću, ne samo u zdravstvu, program je Hrvatske mreže primarne PCI.<sup>6</sup> Inicijativom vodstva Hrvatskog kardiološkog društva koje je pratilo integrirani razvoj mreže pPCI u drugim zemljama, kao u Republici Češkoj, a uz već etablirane hrvatske laboratorije za pPCI, invazivni i neinvazivni kardiolozi, kao i liječnici hitne medicinske pomoći i obiteljske medicine uspješno su, uz pomoć tadašnjeg Ministarstva zdravstva, organizirali Hrvatsku mrežu za primarnu PCI 2005. godine. Na počecima intervencijske kardiologije, prije organiziranja Mreže, hrvatski su građani bili diskriminirani pri liječenju AKS i po spolu, i po dobi i po teritorijalnoj pripadnosti. To se izgubilo nakon uvođenja Mreže i početka unisonog postupanja po smjernicama Europskog kardiološkog društva (ESC).<sup>7-9</sup> Međutim, i sedam godina nakon uvođenja Mreže teritorij čitave zemlje još nije bio potpuno pokriven, primjerice na područjima Dubrovačko-neretvanske županije i

## Discussion

One of few successfully implemented national programs in the last decade, not only in health care, is the program of the Croatian network of primary PCI.<sup>6</sup> At the initiative of the Leadership of the Croatian Cardiac Society, which monitored the integrated development of the pPCI network in other countries as in the Czech Republic, invasive and non-invasive cardiologists, emergency physicians and family physicians along with already established Croatian laboratories for pPCI have successfully, with the help of then Ministry of Health organized the Croatian network for primary PCI in 2005. At the beginning of interventional cardiology, before the Network was organized, the Croatian citizens were discriminated against in the treatment of ACS, both by gender and by age and by territorial affiliation. It was lost after the introduction of the Network and start of unison procedures according to the European Society of Cardiology guidelines.<sup>7-9</sup> However, seven years after the introduction of the

regije Zapadne Slavonije. Entuzijazmom kolega, a unatoč zadnjim objavljenim shemama u kojima su ta područja označena kao da pružaju tu uslugu samo za radnog vremena,<sup>10</sup> u OB Dubrovnik usluga pPCI tijekom 24 h/7 dana dostupna je od početka 2013., a u OB Slavonski Brod od početka 2014. godine.<sup>11</sup> Uvrštavanjem novih centara za pPCI sada ih u Hrvatskoj imamo 11, a jednom centru tendira 391.000 stanovnika. To je odličan rezultat na europskoj razini i sada bolju dostupnost pPCI u Europi imaju samo: Austrija, Belgija, Francuska, Njemačka, Italija i Švicarska.<sup>12</sup> Koliko je to razložno u ovom času ostaje zadaća za izračun i prosudbu od strane naših stručnjaka za ekonomiku zdravstva, koji će trebati procijeni odnos koristi/troškova za pPCI u Hrvatskoj.<sup>8</sup> Švedska analiza pokazuje da su u njihovom okruženju konačni rezultati liječenja s pPCI bolji i da je ukupna cijena liječenja manja u odnosu na fibrinolizu.<sup>13</sup>

Dubrovačko-neretvanska županija ima 122.500 stanovnika od kojih se 70% (86.000) uglavnom liječi u OB Dubrovnik. No, kada se pribroje posjeti više od milijun turista godišnje možemo ugrubo govoriti o populaciji od cca 100.000 stanovnika koja tendira našoj bolnici. U 2013. primljeno je oko 230 bolesnika sa AKS, od kojih 27% zbog STEMI, što je udio sličan američkom registru (29%),<sup>14</sup> iako GRACE registar govori o udjelu od 38% bolesnika sa STEMI.<sup>15</sup> Od 2010. godine konačno su nam dostupni podaci Hrvatskog zavoda za zdravstveno osiguranje, pa sada znamo da je u Hrvatskoj te godine hospitalizirano 7.300 bolesnika s AIM (170/100.000) i 2.552 sa NAP (26% AKS), dakle 9.852 bolesnika s AKS (229/100.000). Radi račlanjivanja i praćenja pojedinih skupina bolesnika i uspješnosti terapije jasna je potreba formiranja Hrvatskog nacionalnog registra za AKS i PCI. U 2013. godini u OB Dubrovnik primljena su 62 bolesnika sa STEMI, sa sličnom učestalošću kao u Švedskom registru (66/100.000), dok je stopa NSTEMI od 89 bolesnika ipak bila niža nego u drugim registrima (120-130).<sup>16</sup> Prema Europskom kardiološkom društvu očekuje se europski prosjek od 190 bolesnika sa AIM na 100.000 stanovnika,<sup>12</sup> a naš broj od 151 bolesnika povoljniji je od očekivanog europskog prosjeka, ali i hrvatskog prosjeka, od 170 bolesnika. Međutim, ostaje pitanje koliko se naših bolesnika sa NSTEMI nije niti javilo liječniku, iz razloga slabe informiranosti, a također da li je kod dijela bolesnika s NAP propušteno registrirati porast kardioselektivnih enzima, iz razloga štednje i pravilno ih sistematizirati kao NSTEMI.

Prema smjernicama ESC rijetki su bolesnici sa AKS čiji izbor liječenja ne bi trebala biti PCI, barem u roku od 72 sata. Među bolesnicima sa AKS u OB Dubrovnik invazivno je obrađeno 94%, a konačno je liječeno metodom PCI 62%, dok je CABG preporučeno kod 13,7% bolesnika. Trećina svih obavljenih PCI bile su primarne PCI (33%), što je više od hrvatskog prosjeka 2007. godine (22%), dok se udio u Europi kreće od 9-39%.<sup>12</sup> Među bolesnicima sa STEMI invazivno je obrađeno 98,4% a kod 90,2% učinjena je pPCI, što je dalji korak u približavanju idealnom cilju da svi bolesnici sa STEMI budu liječeni pPCI. U Sjedinjenim Američkim Državama 2005. godine invazivno je obrađeno 43% bolesnika sa NSTEMI i 65% bolesnika sa STEMI.<sup>17</sup> U Hrvatskoj je 2007. godine bilo 3.600 STEMI (82/100.000), prema broju stanovnika više nego u našoj županiji i 1.150 pPCI (22,5/100.000), značajno manje nego sada u našoj županiji.<sup>12</sup> Usporedba navedenih rezultata govori o našoj usmjerenosti prema intervencijskom liječenju hitnih bolesnika i AKS, što je sačinjavalo oko 2/3 ukupno obavljenih intervencija, a manju usmjerenost na stabilnu anginu pektoris i naručene bolesnike. Pošteno rečeno i štrajk liječnika krajem 2013. godine imao je utjecaj na manji broj narudžbi za koronarografiju. Ova či-

Network, the entire territory of the country was not yet fully covered, for example in the regions of Dubrovnik-Neretva County and the region of Western Slavonia. Owing to the colleagues' enthusiasm and despite the latest published schemes in which these areas are designated as those that provide this service only during normal working hours<sup>10</sup>, the pPCI service has been available in the General Hospital Dubrovnik 24 hours/7 days since early 2013, and in General Hospital Slavonski Brod since early 2014.<sup>11</sup> By including new pPCI centers now we have 11 of them in Croatia, while 391,000 inhabitants gravitate to one center. This is an excellent result at the European level and only the following European countries have a better availability to pPCI: Austria, Belgium, France, Germany, Italy and Switzerland.<sup>12</sup> How reasonable it is at this point remains the task for our experts for Health Economics to evaluate the costs benefit analysis for pPCI in Croatia.<sup>8</sup> The Swedish analysis shows that in their environment the final results of treatment with pPCI are better and that the total cost of treatment is lower compared to fibrinolysis.<sup>13</sup>

Dubrovnik-Neretva County has 122,500 inhabitants, of whom 70% (86,000) are mainly treated in General Hospital Dubrovnik. However, when the visits by over one million tourists a year are added, we can roughly speak about the population of approximately 100,000 inhabitants that gravitate towards our hospital. In 2013, about 230 patients with ACS were admitted, of whom 27% for STEMI, which is a proportion similar to the one in the American registry (29%),<sup>14</sup> although the GRACE registry suggests the proportion of 38% of patients with STEMI.<sup>15</sup> Since 2010, the figures of the Croatian Institute for Health Insurance have been finally available to us, so now we know that some 7,300 patients with acute myocardial infarction (170/100.000) and 2,552 with unstable angina (26% ACS), that is, 9,852 patients with ACS (229/100.000) were hospitalized in Croatia in that year. It is necessary to establish the Croatian national registry for ACS and PCI for better classification and follow-up of some groups of patients and achieving success in the therapy. In 2013, 62 patients with STEMI were admitted to the General Hospital Dubrovnik, with a similar frequency as in the Swedish registry (66/100.000), while the rate of 89 NSTEMI patients was lower than in other registries (120-130).<sup>16</sup> European Society of Cardiology expects the European average of 190 patients with AMI per 100,000 population,<sup>12</sup> while our figure of 151 patients is better than the expected EU average, but also the Croatian average of 170 patients. However, the question remains how many of our patients with NSTEMI have not even contacted a doctor, for reasons of not being properly informed, and also because an increase in troponin level was not registered in one portion of patients with unstable angina for reasons of cost saving and they were not classified as NSTEMI patients.

According to the ESC guidelines, patients with ACS whose choice of treatment should not be PCI, at least within 72 hours are rare. Among the patients with ACS, 94% of them underwent invasive workup in General Hospital Dubrovnik, and 62% were finally treated by the PCI, whereas CABG was recommended to 13.7% of patients. A third of all performed PCI were primary PCI (33%), which is above the Croatian average in 2007 (22%), while the proportion in Europe ranges from 9-39%.<sup>12</sup> Among the patients with STEMI, 98.4% underwent the invasive workup and 90.2% underwent pPCI, which is a further step towards reaching the ideal goal that all patients with STEMI are treated by pPCI. 43% of patients with NSTEMI and 65% of patients with STEMI underwent invasive treatment in the United States of America in 2005.<sup>17</sup>

njenica utjecala je i na neostvarivanje našeg plana od najmanje 200 PCI godišnje, koliko je potrebno da bi se jedan PCI centar svrstao u srednje veliki centar bez kardiokirurške potpore, i po američkim standardima bio sposoban zasebno funkcionirati.<sup>9</sup>

Raspodjela PCI po liječenim žilama slična je drugim registrima bolesnika s AKS, a usmjerenost prema hitnim bolesnicima pokazuje i udio PCI na velikim žilama, najviše na LAD na kojoj je učinjeno 45,5% svih procedura.<sup>5</sup> Objašnjava to i penetraciju DES od 25,6%, koja je za europsku razinu bila minimalna, no aktualno realna.

Među 58 bolesnika sa STEMI kojima je izbor liječenja bio pPCI konačni TIMI 3 protok postignut je kod 93,4% bolesnika, što je rezultat bolji i od europskog prosjeka od 85%. Iako na maloj skupini bolesnika taj podatak uz intrahospitalni letalitet AIM od 2,61% i 4,8% od STEMI zasigurno ne govori o lošoj, nego više o izvrsnoj kvaliteti rada, a uspoređujući to sa smrtnošću u Europi, za AIM od 5 do 14% i za STEMI od 4,2 do 13,5% te u SAD (2005. godine) 9,7% za STEMI i 9,5% za NSTEMI.<sup>12,17</sup> U Hrvatskoj je 2007. mortalitet kod STEMI bio 10%,<sup>12</sup> a podaci iz susjedne Splitsko-dalmatinske županije pokazuju da je mortalitet od AIM značajno pao uvođenjem PCI, sa 15% na 10% u 2005. godini, prvoj godini rada njihovog laboratorija.<sup>18</sup> U Splitu se kroz sljedećih 5 godina mortalitet AIM spustio na 4%,<sup>18</sup> dok je mortalitet od STEMI bio 6,3%.<sup>19</sup> Dostupni podatak za Kliničku bolnicu Dubrava iz 2003. pokazuje intrahospitalni letalitet od STEMI 6,2%, a u Kliničkom bolničkom centru Zagreb 2005. godine za STEMI 13,9% a za NSTEMI 9,6%.<sup>5,20</sup>

Osim TIMI protoka i smrtnosti, učestalost komplikacija također je mjera kvalitete rada. Učestalost akutne i subakutne tromboze u stentu od 2,4% među svim bolesnicima i 3,6% među bolesnicima sa STEMI bila je ipak veća nego u općim registrima, gdje se kreće od 0,5-2%.<sup>21</sup> Ova komplikacija nije prikazana u analizi iz Splita, a na jednom skupu u Hrvatskoj prikazana je veća učestalost, i do 13,3% kod bolesnika sa STEMI.<sup>22</sup> Svi naši bolesnici sa trombozom u stentu bili su na potrebnoj dvojnjoj antiagregacijskoj terapiji, uz klopidogetrel, kao i u registrima (prasugrel i tikagrelor bi mogli imati bolje rezultate) te će biti potrebno i dalje pratiti ovu komplikaciju i tražiti joj uzroke, da bi i u tome dosegli europske rezultate. Međutim, potrebnu pomoć u tome morati će nam pružiti uvođenje novih metoda unutaržilnog prikaza (IVUS i/ili OCT), kojima bi se prekontrolirali neki postPCI nalazi, koji angiografski izgledaju odlično, a kasnije rezultiraju trombozom. Srećom, svi bolesnici su riješeni reintervencijom, bez daljih komplikacija. Perifernih komplikacija imali smo 1,2% kod femoralnog pristupa i 0,5% kod radijalnog pristupa, i to jednu ekstremno rijetku pseudoaneurizmu radijalne arterije, uz ukupnu potrebu kirurškog liječenja u 0,8% bolesnika. U globalnim registrima, uz modernu farmakološku terapiju, lokalne komplikacije kod femoralnog pristupa javljaju se u 5,5-7,4% bolesnika, uz potrebu kirurškog liječenja od 1,3%.<sup>23-25</sup> U susjednoj županiji, u Splitu, ovih je komplikacija bilo 1,6%.<sup>19</sup>

Uz pokrivenost ostatka Hrvatske Mrežom, populaciju od 100.000 stanovnika, ali uz 210 km polovično loše ceste, dva granična prijelaza EU i više od milijun turista godišnje i nepostojanje laboratorija u graničnim regijama susjednih država smatramo da je postojala opravdana potreba uvođenja centra za intervencijsku kardiologiju u Dubrovačko-neretvanskoj županiji, a opseg rada samo s hitnim bolesnicima u 2013. godini gotovo da to i potvrđuje. Dubrovnik koji osigurava značajan prihod od brodova za krstarenje, kao popratnu uslugu mora imati integralno visoko kvalitetnu akutnu

There were 3,600 STEMI (82/100.000) patients in Croatia in 2007, more than in our county and 1,150 pPCI (22.5/100.000), significantly less than now in our county.<sup>12</sup> The comparison of results suggests our focusing on interventional treatment of emergency patients and ACS, which accounted for about 2/3 of all interventions performed, and placing a less emphasis on stable angina pectoris and ordered patients. To be fair, even doctors' strike in 2013 had an impact on a smaller number of orders for coronary angiography. This fact also affected the failure to achieve our plan to perform at least 200 PCI per year, which is needed to classify a single PCI center into the medium-sized center without cardiac support, and which according to American standards it would be able to function independently.<sup>9</sup>

Classification of PCI by treated vessels is similar to the one in other registries of patients with ACS, and focusing on emergency patients shows the proportion of PCI on large vessels, mostly on LAD on which 45.5% of all procedures were performed.<sup>5</sup> This explained the DES penetration of 25.6%, which for the European level was minimal, but actually realistic.

Among 58 patients with STEMI whose treatment of choice was pPCI, final TIMI 3 flow was achieved in 93.4% of patients, which is a better result than the European average of 85%. Although this data is one on the small group of patients together with intra-hospital lethality of AMI of 2.61% and 4.8% of STEMI certainly does not suggest the poor, but rather outstanding quality of work even when we compare it with mortality in Europe, regarding AMI from 5-14% and regarding STEMI from 4.2 to 13.5% and in the U.S. (in 2005) 9.7% for STEMI and 9.5% for NSTEMI.<sup>12,17</sup> In 2007, mortality in STEMI patients was 10% in Croatia,<sup>12</sup> and the data from the neighboring Split-Dalmatia County shows that the mortality of AMI significantly dropped by introducing PCI, from 15% to 10% in 2005, the first year of work of their laboratory.<sup>18</sup> Mortality from AMI dropped to 4% in Split over the next five years,<sup>18</sup> while the mortality from STEMI was 6.3%.<sup>19</sup> The available data for the University Hospital Dubrava in 2003 shows intra-hospital lethality of STEMI 6.2%, while in 2005, intra-hospital lethality of STEMI was 13.9% and 9.6% of NSTEMI in University Hospital Zagreb.<sup>5,20</sup>

In addition to TIMI flow and mortality, the incidence of complications is also a measure of quality of work. The incidence of acute and subacute stent thrombosis of 2.4% among all patients and 3.6% among patients with STEMI was still higher than in the general registries, ranging from 0.5-2%.<sup>21</sup> This complication is not shown in analysis of Split, and at one meeting in Croatia higher incidence was shown, namely, up to 13.3% in patients with STEMI.<sup>22</sup> All our patients with stent thrombosis underwent the required dual antiaggregation therapy with clopidogrel, as in the registries (prasugrel and ticagrelor might have better results) and it will be necessary to continue to monitor this complication and look for its causes in order to reach the European results. However, the necessary assistance in this matter will have to be provided to us by introducing new intravascular imaging methods (IVUS and/or OCT), which will check some postPCI results, which angiographically look great, but will later result in thrombosis. Fortunately, all those patients were managed by reintervention, without further complications. Peripheral complications were present in 1.2% in case of femoral access and 0.5% in case of radial access, and we had one extremely rare radial artery pseudoaneurysm, with a total need for surgical treatment in 0.8% of patients. Global registries report that with modern pharmacotherapy local complications in femoral access occur in 5.5 to 7.4% of patients, with the need for

zdravstvenu skrb, a konačno od svih pPCI kod STEMI na strane državljanke otpada gotovo 15% (9/61). Lijepo je čuti pohvale stranih kardiologa glede naših intervencija, kada se bolesnici s nalazom intervencije na CD vrata u SAD,<sup>26</sup> Veliku Britaniju, Francusku i Španjolsku, što je zasigurno povećalo ugled naše zemlje kao sigurne turističke destinacije. No, naša primarna zadaća u Dubrovačko-neretvanskoj županiji i OB Dubrovnik u sljedećoj godini bila je zamišljena kao povećanje udjela hospitalizacija u koronarnoj jedinici, odvajanjem ostalih nekardioloških bolesnika osnivanjem opće internističke intenzivne skrbi, a s intervencijske strane povećanje opsega rada u segmentu naručenih bolesnika (na kraju godine lista čekanja bila je 80 bolesnika), prezentacija usluge pPCI susjednim zemljama, kao i nova oprema, injektor, IVUS i FFR. Kako laboratorij nije funkcionirao u vrijeme početka nacionalnog tendera za materijal u intervencijskoj kardiologiji, prvotno nismo niti prepoznati kao stalni intervencijski centar. Nakon analize 2013. godine planirali smo materijal za narednu godinu, no upozoreni smo da moramo smanjiti predviđene količine, a početkom 2014. dobili smo rješenje u kojem smo zamijetili da je odobrena količina materijala upola manja i od one koju smo reducirali (**Tablica 6**). Nevjerojatno zvuči podatak da je za nas predviđeno katetera za svega 90-100 dijagnostičkih procedura, da nam nisu odobrili niti jedan kateter za intervencije, koje pretpostavljam, ne bi trebali niti raditi no tada ostaje smiješna činjenica čemu bi nam trebalo služiti onih 130 odobrenih proširnica? Kada bi i imali katetere to bi bilo dostatno samo za bolesnike sa STEMI. Da bi se takva situacija štednje zaokružila, ukinut je i Odsjek za akutne srčane bolesti i intervencijsku kardiologiju, koji se pripojio Internom odjelu. Uz nove okolnosti ostaje za vidjeti kakvi će biti dalji rezultati, za 2014. i dalje godine, ne samo u zdravstvu nego i turizmu, jer bi se na webu mogli pojaviti komentari turista i turoperatera o zdravstvenoj nesigurnosti u našim zdravstvenim ustanovama na obali.

Received: 24<sup>th</sup> Feb 2014; Updated 2<sup>nd</sup> Mar 2014; Accepted: 5<sup>th</sup> Mar 2014

\*Address for correspondence: Opća bolnica Dubrovnik, Dr. Roka Mišetića 2, HR-20000 Dubrovnik, Croatia.

Phone: +385-20-431-777

E-mail: lukendaj@hotmail.com

## Literature

1. Hartzler GO, Rutherford BD, McConahay DR. Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. *Am Heart J.* 1983;106:965-73.
2. Grines CL, Browne KF, Marco J. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med.* 1993;328:673-9.
3. Mišatović Š, Starčević B, Nikolić-Heitzler V, et al. Percutaneous coronary interventions in treatment of acute myocardial infarction. *Neurol Croat.* 2001;50:151-4.
4. Mišatović Š, Starčević B, Nikolić-Heitzler V, et al. Interventional reperfusion strategy in acute myocardial infarction. *Acta Clin Croat.* 2001;40(Suppl.):102.
5. Raguž M, Starčević B, Todorović N, Vesković M, Vagić JS, Bergovec M. [Percutaneous coronary interventions (PTCA and stent) myocardial infarct with ST segment elevation]. *Acta Med Croatica.* 2004;58:107-9.
6. Nikolić Heitzler V, Babic Z, Milicic D, et al. Results of the Croatian Primary Percutaneous Coronary Intervention Network for patients with ST-segment elevation acute myocardial infarction. *Am J Cardiol.* 2010;105:1261-7.
7. Potocki-Karacic T, Lukenda J. Yentl's syndrome in Croatia: younger male patients from capital were favoured for PCI. *Int J Cardiol.* 2011;146:450-2.

surgical treatment in 1.3% patients.<sup>23-25</sup> There were 1.6% of such complications in the neighboring county, in Split.<sup>19</sup>

Covering the rest of Croatia by the Network, namely our population of 100,000 inhabitants, but mentioning 210 km half poorly built roads, two EU border crossings and more than a million of tourists a year as well as the lack of laboratories in the border regions of the neighboring countries, we believe that there was a reasonable need to establish the Center for Interventional Cardiology in Dubrovnik-Neretva County, and the scope of work only with emergency patients in 2013 almost confirms it. Dubrovnik which generates considerable revenues from cruise ships must render an integral high quality acute medical care as an accompanying service, and finally there are almost 15% (9/61) foreign nationals of all pPCI for STEMI. It is nice to be paid compliments by foreign cardiologists regarding our interventions, when patients with the CD intervention findings come back to the USA<sup>26</sup>, United Kingdom, France and Spain, which certainly increased the reputation of our country as a safe tourist destination. However, our primary task in the Dubrovnik-Neretva County and General Hospital Dubrovnik in the next year was conceived as to increase the proportion of hospitalizations in the coronary care unit, separate other non-cardiac patients by establishing a general internal intensive care, and in the segment of interventions we are about to increase the volume of work in the field of ordered patients (by the end of the year, 80 patients were in the waiting list), present the pPCI service to some neighboring countries, new equipment purchase, injector, IVUS and FFR. As the laboratory was not functioning at the time of initiating the national tender for supplies in interventional cardiology, we were not recognized as a permanent interventional center at the beginning. After we made an analysis on 2013, we forecasted the supplies for the next year, but were warned that we had to reduce the quantity of forecasted supplies, and in early 2014, we received the decision in which we noticed that the approved quantity of supplies was half the size of the one we had already reduced (**Table 6**). We faced an incredible fact that we have been approved catheters for only 90-100 diagnostic procedures, that we have not been approved a single catheter for interventions, which I suppose should not be performed by us, but then we wondered what the purpose of 130 approved stents was? If we had catheters, those stents would be sufficient only for patients with STEMI. To round up this situation regarding cost savings, the Department for acute heart diseases and interventional cardiology has been abolished, and now it is annexed to the Internal Medicine Department. Given the new circumstance we shall see what the results in 2014 will be like not only in healthcare, but also in tourism, because tourists' and tour operators' comments may appear on the websites about medical insecurity in our medical facilities on the coast.

8. Ivanaša M, Miličić D, Nikolić-Heitzler V, Bergovec M, Babić Z, Tršinski D. Liječenje akutnog infarkta miokarda u Hrvatskoj - sadašnje stanje i kako ga unaprijediti. *Medix*. 2005;58:115-8.
9. Harold JG, Bass TA, Bashore TM, et al.; Presidents and Staff of American College of Cardiology Foundation; American Heart Association; Society of Cardiovascular Angiography and Interventions. ACCF/AHA/SCAI 2013 update of the clinical competence statement on coronary artery interventional procedures: a report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training (writing committee to revise the 2007 clinical competence statement on cardiac interventional procedures). *Circulation*. 2013;128:436-72.
10. PLIVAMED.net [Web stranica na internetu]. Zagreb, Hrvatska. [Pristupljeno 29.10.2013.]. Babić Z. Radna skupina za akutni koronarni sindrom HKD-a. Raspoloživo na: <http://www.plivamed.net/vijesti/clanak/8426/Radna-skupina-za-akutni-koronarni-sindrom-HKD-a.html>.
11. Prvulović Đ. Farmakoinvazivna strategija i njeno mjesto u zbrinjavanju bolesnika s akutnim infarktom miokarda s elevacijom ST-segmenta. *Cardiol Croat*. 2013;8(12):414-23.
12. Widimsky P, Wijns W, Fajadet J, et al.; European Association for Percutaneous Cardiovascular Interventions. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. *Eur Heart J*. 2010;31:943-57.
13. Aasa M, Henriksson M, Dellborg M, et al. Cost and health outcome of primary percutaneous coronary intervention versus thrombolysis in acute ST-segment elevation myocardial infarction-Results of the Swedish Early Decision reperfusion Study (SWEDES) trial. *Am Heart J*. 2010;160(2):322-8.
14. Go AS, Mozaffarian D, Roger VL, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. 2013;127:e6-e245.
15. Fox KA, Eagle KA, Gore JM, et al.; GRACE and GRACE2 Investigators. The Global Registry of Acute Coronary Events, 1999 to 2009 - GRACE. *Heart*. 2010;96:1095-101.
16. Steg PG, James SK, Atar D, et al.; Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569-619.
17. McManus DD, Gore J, Yarzebski J, et al. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. *Am J Med*. 2011;124:40-7.
18. Mirić D, Novak K, Kovačević LM, et al. In-hospital mortality of patients with acute myocardial infarction before and after introduction of PCI in Split University Hospital Center, Croatia. *Coll Antropol*. 2013;37:207-12.
19. Giunio L, Vuković I, Duplancić D, et al. [Primary percutaneous coronary intervention (pPCI) in hospital without regional cardiac surgery support, data from Split region]. *Liječ Vjesn*. 2012;134:75-8.
20. Strozzi M, Bulum J, Ernst A, et al. [Overall and therapy specific mortality of patients hospitalized for acute myocardial infarction in Zagreb University Hospital Centre]. *Liječ Vjesn*. 2007;129:260-4.
21. Moreno R, Jimenez-Valero S, Sanchez-Recalde A, et al. Periprocedural (30-day) risk of myocardial infarction after drug-eluting coronary stent implantation: a meta-analysis comparing cobalt-chromium and stainless steel drug-eluting coronary stents. *EuroIntervention*. 2011;6:1003-10.
22. Koshi R, Strozzi M. Stent thrombosis between drug-eluting and bare-metal stents. *Cardiol Croat*. 2013;8:283.
23. Dangas G, Mehran R, Kkolis S, et al. Vascular complications after percutaneous coronary interventions following hemostasis with manual compression versus arteriotomy closure devices. *J Am Coll Cardiol*. 2001;38:638-41.
24. Choussat R, Black A, Bossi I, et al. Vascular complications and clinical outcome after coronary angioplasty with platelet IIb/IIIa receptor blockade. Comparison of transradial vs transfemoral arterial access. *Eur Heart J*. 2000;21:662-7.
25. Philippe F, Larrazet F, Meziane T, et al. Comparison of transradial vs. transfemoral approach in the treatment of acute myocardial infarction with primary angioplasty and abciximab. *Catheter Cardiovasc Interv*. 2004;61:67-73.
26. Opća bolnica Dubrovnik [Web stranica na internetu]. Dubrovnik, Hrvatska. [Pristupljeno 04.07.2013.]. Arhiv. Raspoloživo na: <http://www.bolnica-du.hr/clanak1.php?id=443>

**HRVATSKO KARDIOLOŠKO DRUŠTVO**

**HRVATSKA KUĆA SRCA**  
CROATIAN HEART HOUSE

**Vi imate pitanje?  
Mi imamo odgovor!**

**www.kardio.hr**

Najčešća pitanja bolesnika o srčanom udaru,  
koronarografiji i perkutanoj koronarnoj intervenciji

# Transseptalna kateterizacija

## *Transseptal catheterization*

Nikola Pavlović<sup>1,2\*</sup>, Šime Manola<sup>1</sup>, Vjekoslav Radeljić<sup>1</sup>, Ivica Benko<sup>1</sup>, Michael Kühne<sup>2</sup>, Christian Sticherling<sup>2</sup>

<sup>1</sup>Klinički bolnički centar Sestre milosrdnice, Zagreb, Hrvatska

<sup>2</sup>Klinička bolnica Basel, Basel, Švicarska

<sup>1</sup>University Hospital Centre Sestre milosrdnice, Zagreb, Croatia

<sup>2</sup>University Hospital Basel, Basel, Switzerland

**SAŽETAK:** Transseptalna punkcija (TSP) je postupak koji omogućuje perkutani transvenski pristup strukturama lijevog srca. TSP je razvijena primarno radi hemodinamske procjene valvularnih grešaka i mitralne valvuloplastike, dok je danas, u eri izolacije plućnih vena (PVI), postala rutinska procedura većine elektrofiziologa. Obzirom na porast broja PVI u Hrvatskoj, tehnika TSP postaje svakodnevica elektrofiziologa. Stoga liječnici i osoblje moraju biti upoznati s TSP i potencijalnim komplikacijama. Svrha ovog preglednog članka je prikazati kratku povijest i razvoj TSP, samu tehniku, indikacije te potencijalne komplikacije.

**KLJUČNE RIJEČI:** transseptalna punkcija, fibrilacija atrija, izolacija plućnih vena.

### Povijest

Transseptalna punkcija TSP je razvijena tijekom 50-ih godina XX. stoljeća primarno radi kateterizacije lijevog atrija i procjene valvularnih bolesti srca<sup>1</sup>. Razvili su je Ross, Morrow i Braunwald<sup>1</sup>. Daljnji napredak transseptalne punkcije i učinio je Brockenbrough razvojem igle i katetera<sup>2</sup> te Mullins<sup>3</sup> daljnjim razvojem dilatatora i uvodnice. Sam sustav za TSP se nije previše mijenjao do danas te, iako postoje različiti proizvođači kao i veličine sustava, sam sustav i tehnika TSP ostaju gotovo isti kao u originalnim opisima. Danas se velika većina TSP izvodi u elektrofiziologiji radi ablacije lijevostranih aritmija<sup>4</sup>. Indikacije i kontraindikacije za TSP danas su prikazane u **Tablici 1**.

### Anatomija

Transseptalnom punkcijom cilj je pristupiti lijevom atriju kroz najtanji dio interatrijskog septuma, a to je fossa ovalis. Fossa ovalis omeđena je anteriorno trikuspidnom valvulom, anterosuperiorno korijenom aorte, posteriorno stražnjim stjenkama desnog i lijevog atrija te dublikaturom perikarda dok se inferiorno nalazi bazalni dio desnog atrija i donja šuplja vena, a superiorno limbus fossae ovalis. Fossa ovalis zauzima oko 25% površine interatrijskog septuma i veličine je

**SUMMARY:** Transseptal puncture (TSP) is a procedure that allows transvenous access to the structures of the left heart. TSP has been primarily developed for the evaluation of valvular disease and mitral valvuloplasty, while today, in the era of pulmonary vein isolation (PVI), it has become a routine procedure performed by a great number of electrophysiologists. Since there is a constant increase in a number of PVIs in Croatia, TSP is becoming a standard procedure for electrophysiologists. Physicians and staff must therefore be trained in TSP and its potential complication. This review focuses on the historical development of TSP, its technical aspect, indications and complications.

**KEYWORDS:** transseptal puncture, atrial fibrillation, pulmonary vein isolation.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):127-133.

### History

TSP was developed in the 1950s for left atrial catheterization, and evaluation of valvular heart disease<sup>1</sup>. It was developed by Ross, Morrow and Braunwald<sup>1</sup>. Further improvements were made by Brockenbrough with the development of a special needle and catheter<sup>2</sup> and Mullins<sup>3</sup> contributing with a designated dilatator and sheath. Although there are many products by different manufacturers available today, the system and the technique remain essentially the same. Nowadays, TSP is mainly being used by electrophysiologists for left atrial ablation procedures and access to the left ventricle<sup>4</sup>. Indications and contraindications for TSP today are shown in **Table 1**.

### Anatomy

The goal of transseptal puncture is to access the left atrium through the thinnest part of the interatrial septum, the fossa ovalis. Fossa ovalis is limited by the tricuspid valve anteriorly, the aortic root antero-superiorly, right and left atrial free wall with pericardial duplicature posteriorly, while inferior border is the lower right atrium and inferior vena cava and superior border is limbus fossae ovalis and above it superior vena cava. The fossa takes up 25% of the septal area and has

**Table 1.** *Indications and contraindications for transeptal puncture.*

### Indications for transeptal approach

#### Eletrophysiology

- Pulmonary vein isolation
- Left atrial tachycardia/flutter ablation
- Left accessory pathway ablation
- Ventricular tachycardia (antegrade app)
- Slow pathway/AV node ablation (rare)

#### Left atrial appendage occluder

#### Valvular interventions

- Mitral balloon valvuloplasty
- Mitraclip

#### Hemodynamic assessment

- Invasive evaluation of LA pressure (Pts with mitral or aortic v prosthesis)

#### Hemodynamic support

- TandemHeart (percutaneous VAD)

### Contraindications for transeptal approach

#### Left atrial thrombus

#### Left atrial tumor

#### Uncooperative patient

#### Severe bleeding diathesis

10-25 mm (prosječno 16 mm)<sup>5</sup>. Kod TSP najvažnije je izbjeći punkciju korijena aorte anteriorno te slobodne stjenke desnog ili lijevog atrija posteriorno. Transezofagusnim (TEE) i intrakardijalnim ultrazvukom (ICE) je moguće direktno prikazati navedene strukture. Obzirom da korištenje ultrazvuka povećava kompleksnost i cijenu procedure, kao i da nije uvijek dostupan razvijeno je nekoliko metoda za indirektno označavanje fossae ovalis korištenjem fluoroskopije.

Jedna od metoda je direktno označavanje korijena aorte — postavljanjem duge žice ili pigtail katetera transfemoralnim pristupom direktno u korijen aorte. Ova metoda, međutim, zahtijeva punkciju arterije i povećava rizik krvarenja. Druga metoda je pozicioniranje dijagnostičkog elektrofiziološkog katetera u područje Hisovog snopa koji se nalazi u neposrednoj blizini desnog koronarnog kuspisa aorte. Ipak, najčešće korištena metoda je jednostavno postavljanje katetera u koronarni sinus (CS). CS prolazi stražnjom stranom atriiventrikularne brazde i označava razinu mitralnog anulusa koji je anteriorna granica interatrijskog septuma. Iako ova metoda ne označava direktno položaj korijena aorte, ona omogućava anatomsku orijentaciju i smjer TSP pogotovo u kombinaciji s kateterom na His poziciji (**Slika 1**).

### Opis postupka

TSP se izvodi korištenjem posebno dizajniranih i preformiranih igala, uvodnica i dilatatora. Iako postoje različiti oblici i veličine i dalje su najčešće u upotrebi tzv. Brockenbroughova igla i Mullins uvodnice (**Slika 2**). Procedura počinje kanulacijom femoralne vene Seldingerovom tehnikom. Postavlja se najcesce jedna kratka uvodnica putem koje se postavi kateter u koronarni sinus, a služi i za i.v. primjenu lijekova ili nadoknadu volumena. Dvije duge uvodnice zajedno s dva dilatatora postavljaju se u gornju šuplju venu (SVC) preko duge žice (J žica 0,032). Nakon toga, žica se izvuče, sustav

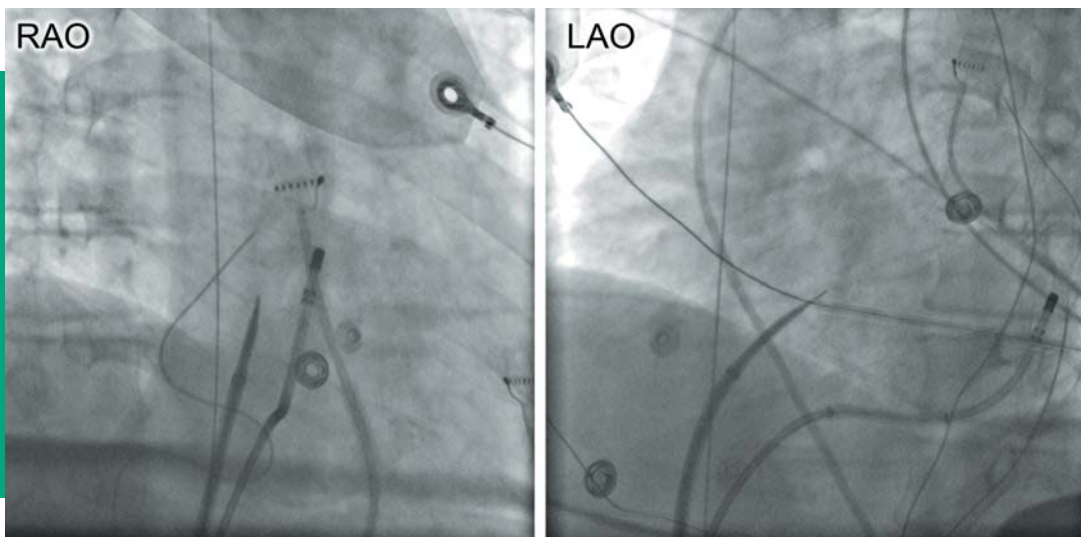
a diameter of 10-25mm (average 16mm)<sup>5</sup>. It is of utmost importance to avoid aortic root puncture anterosuperiorly and right and left atrial free wall puncture posteriorly. All critical structures can be visualized during the procedure by using transesophageal (TOE) or intracardiac echocardiography (ICE). Since the use of these modalities adds cost and complexity to the procedure and they may not always be available, several methods have been developed to delineate the boundaries of the fossa ovalis using fluoroscopy.

One of the methods includes directly marking the aortic root by positioning a long J-tip guidewire or pigtail catheter in the aortic root. However, this technique requires arterial access and increases bleeding complications. Another method is to position a diagnostic EP-catheter in the His-bundle position, which is in close proximity to the right coronary cusp. The most frequently used method is to simply position an EP-catheter in the coronary sinus (CS). The CS runs along the posterior aspect of the atrioventricular groove and delineates the level of the annulus of the atrioventricular valves, the anterior boundary of the interatrial septum. While this does not directly visualize the aortic root, it allows for proper anatomical orientation and direction of TSP, particularly in conjunction with catheter in his-position (**Figure 1**).

### Technique description

TSP is performed by using specially designed and preformed needles, sheaths and dilators. Although there are many forms, designs and sizes in use, still the most frequently used are Brockenbrough needle and Mullins sheaths (**Figure 2**). The procedure typically starts with access to the femoral vein using a Seldinger technique. One short sheath is placed for a coronary sinus catheter and as a vascular access for drug and fluid administration. Two long sheaths together with dilators are placed in the SVC





**Figure 1.** Right anterior oblique and left anterior oblique projections. In the right anterior oblique projection, coronary sinus catheter is pointing away from the operator and is marking the position of atrioventricular groove. The assembly for transseptal puncture is at the fossa ovalis, in the right anterior oblique, it is parallel to coronary sinus catheter and approximately half way between the coronary sinus catheter and posterior wall. In the left anterior oblique, it is above the level of the coronary sinus ostium.

aspirira te se postavlja igla za punkciju do samog vrha dilatatora.

Daljnja orijentacija i procedura ovise o tehnici kojom se operator koristi. Ovdje ćemo opisati TSP uz korištenje fluoroskopije te kontrastnog sredstva i mjerenja tlaka putem igle za punkciju. Koristeći LAO 45 projekciju cijeli sustav (igla, dilatator, uvodnica) se polako povlače iz gornje šuplje vene prema desnom atriju. Važna je orijentacija cijelog sustava i u većini slučajeva se orijentacija igle i dilatatora drži tako da je bočni izlaz dilatatora usmjeren prema 4-5 sati (vrh igle i uvodnice moraju biti usmjereni u istom pravcu). Kod povlačenja sustava radiološki se mogu uočiti dva "preskoka" vrha dilatatora. Prvi je kod prelaska iz gornje šuplje vene u desni atrij, a drugi kod prelaska s muskularnog dijela septuma preko limbusa fossae ovalis u fossu ovalis. Vrh dilatatora sada u LAO projekciji mora biti iznad katetera u koronarnom sinusu, a u RAO projekciji mora biti posteriornije i paralelno s kateterom u distalnom koronarnom sinusu (**Slika 1**). Smjer transseptalne uvodnice i dilatatora ne bi smio prelaziti anteriornije od katetera u koronarnom sinusu jer se povećava mogućnost preanteriorne punkcije (punkcija korijena aorte).

over a long 0.032 inch J tip wire. The wire is then removed, blood aspirated and the transseptal needle is positioned just at the tip of the system. It is important to forward the needle in the sheath with a stylet in place in order to avoid inadvertent avulsion of the lining of the dilator by the sharp needle tip. Further orientation and procedure depends on the technique used. We will describe TSP with the use of fluoroscopy with contrast injection and pressure measurement from the tip of the needle. In the LAO 45 projection, the whole system (needle, dilator and sheath) is slowly pulled back from the SVC to the RA. Orientation of the system is important, and it is held so the dilator handle points to the 4-5 o'clock (needle and sheath should be pointing in the same direction). While pulling the system down, two "jumps" can be seen on the fluoroscopy image. The first jump occurs, when the system enters the RA from the SVC, and the other when system jumps from muscular part of the septum, over the limbus fossae ovalis into the fossa. At this point the tip of the dilator should be above the CS catheter in the LAO projection and behind and parallel to it in the RAO projection (**Figure 1**). The direction of the system (projected from the tip) should not cross

**Figure 2.** Tip of transseptal dilator, sheath and the transseptal needle.



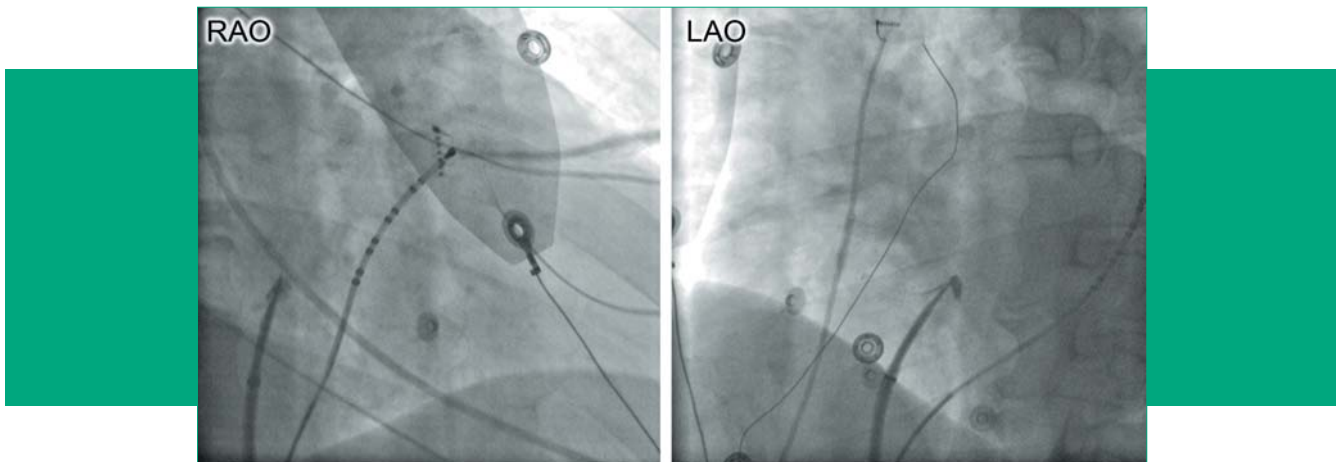
Kada smo zadovoljni s pozicijom sustava, potrebno je polako pozicionirati iglu prema naprijed. U isto vrijeme primjenjuje se kontrast kroz transseptalnu iglu kojim se nakon prelaska u lijevi atrij ispunjava šupljina lijevog atrija. Nakon prelaska, dodatno se položaj igle potvrđuje mjerenjem tlaka u lijevom atriju.

U slučaju otežane punkcije "staining" odnosno opacificiranje septuma kontrastom je korisna metoda. Kako je vidljivo na **Slici 3**, kontrast se primjenjuje još prije prelaska septuma te se jasno može vidjeti "tenting" interatrijskog septuma prema lijevom atriju tijekom prelaska igle.

the line of CS catheter as it increases the risk of an anterior puncture (aortic root puncture).

When the operator is satisfied with catheter position, the needle is advanced. At the same time, the contrast is applied through the needle which opacifies the left atrium. Additionally, the position is verified by removing the syringe and performing a pressure measurement from the needle tip.

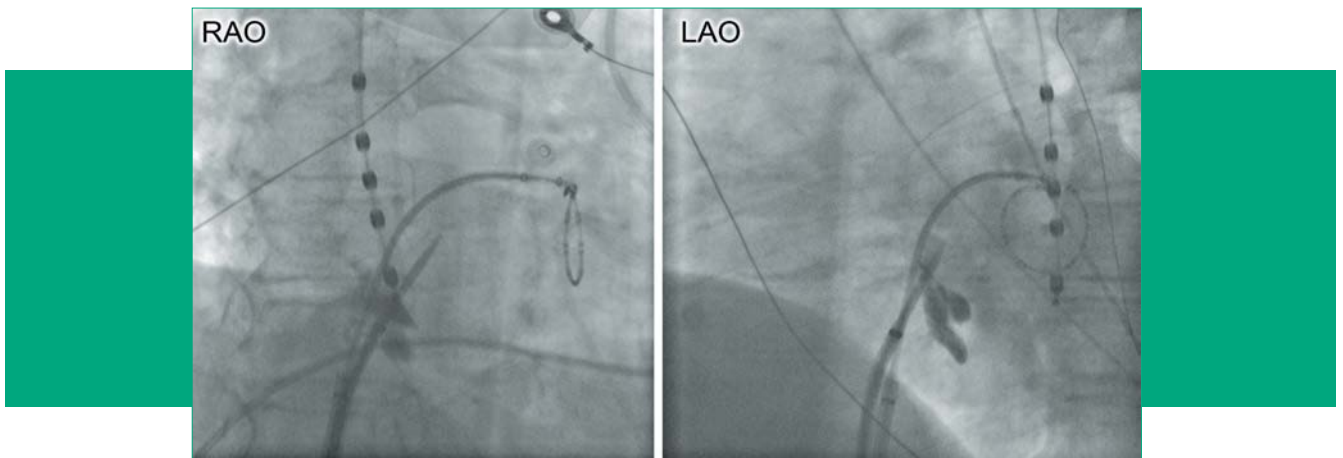
In case of a difficult puncture or a rigid interatrial septum, staining of the septum may prove very helpful. As depicted in **Figure 3**, the operator can then observe a "tenting" of the stained septum into the left atrial cavity when advancing the needle.



**Figure 3.** Right anterior oblique and left anterior oblique projections. Catheter positions are same as described in Figure 1. While advancing the needle and applying pressure at the fossa ovalis with the system, the contrast is applied. "Tenting" can be best seen in left anterior oblique and "staining" of the fossa ovalis just at the tip of the needle indicating the correct spot for the transseptal puncture.

U slučaju neadekvatne pozicije sustava za TSP ili nesigurnosti kao i u slučaju da nakon izvlačenja igle kontrast opacificira neku drugu strukturu potrebno je iglu povući te cijeli sustav ponovo repositionirati. Dok god je učinjena punkcija neke strukture (**Slika 4**) osim fosse ovalis samo iglom rizik komplikacije je minimalan. Prolaskom dilatatora i uvodnice (8,5 Fr) u aortu ili slobodnu stijenku atrija komplikacije postaju potencijalno fatalne. U slučaju pojave kontrasta u korijenu aorte ili u/iza stražnje stijenke atrija savjetujemo rano intraprocuduralno učiniti ehokardiografiju radi isključivanja ozbiljnih komplikacija.

In case of uncertainty or inadequate position of the system for TSP as well as in case of staining of other structures apart from the fossa ovalis after needle advancement, the needle and the system should be withdrawn and the whole system repositioned again. As long as other structures have only been punctured with the needle, (**Figure 4**) the latter can be withdrawn and the risk of complications is minimal. In case of dilator and sheath advancement (8.5 Fr) into the aorta or through the atrial free wall, the complications become potentially fatal. In case of staining of the aortic root or atrial free wall/pericardium we advise early use of echocardiography to exclude serious complications.



**Figure 4.** Staining of the infero-posterior part of the interatrial septum before the current transseptal puncture. The contrast is seen in the septum and the current transseptal puncture is above and anterior to the staining. Staining was done only with the needle and the patient had no complications after the procedure (echo control).

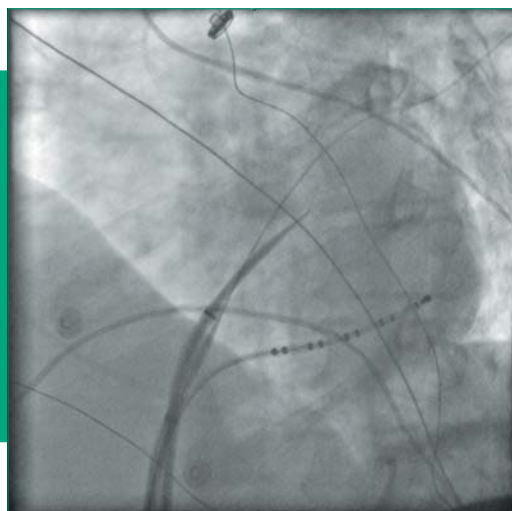
Nakon uspješnog prolaska igle kroz septum, igla i dilator se dodatno pomiču prema naprijed dok operater nije siguran da je vrh dilatatora prošao septum. Zatim se igla izvlači, aspirira oksigenirana, arterijska krv (mjerenje saturacije također potvrđuje poziciju u LA) te se duga J žica postavlja u gornju ili donju plućnu venu (**Slika 5**). Cijeli sustav se zatim postavlja u lijevi atrij preko žice čime se smanjuje rizik punkcije slobodne stjenke LA ili aurikule tijekom prelaska u LA.

Nakon uspješne TSP, igla i dilator se povlače, uvodnica se aspirira te se spaja na kontinuirano propiranje hepariniziranim fiziološkom otopinom. Ovime je TSP završena te daljnji postupak ovisi o proceduri koja se izvodi. Za lijevostrane

After the needle has crossed the septum, the whole system is slightly advanced, ensuring positioning of the dilator tip in the left atrial cavity and then removed. After aspiration of oxygenated blood (at this point O<sub>2</sub> saturation can be measured to prove the correct position), the J tip wire should be positioned in the left superior or left inferior pulmonary vein (**Figure 5**). The whole system is then advanced across the septum over the wire. The wire positioned in a pulmonary vein minimizes the risk of an inadvertent injury to the left atrial wall or appendage when forcing the sheath into the left atrium.

After successful TSP, the needle and the dilator are removed. The sheath is aspirated and continuously flushed with heparinized saline. At this point the further management is dependent on the procedure being performed. A second

**Figure 5.** Left anterior oblique view. After successful first transseptal puncture, guide wire can be seen in left superior pulmonary vein (beyond the left heart border). Second sheath, dilator and needle are at the fossa level before second transseptal puncture.



ablacije najčešće je potrebno učiniti još jednu TSP koristeći prvu kao marker. Kod otežanih TSP, postavljanje druge uvodnice se može pokušati prolaskom žice ili elektrofiziološkog katetera uz prethodnu TSP.

Neki laboratoriji za TSP koriste i druge mogućnosti kao korištenje TEE<sup>6</sup>, ICE<sup>7</sup> ili angiografije desnog atrija<sup>8</sup>. Korištenjem ultrazvuka moguće je potencijalno smanjiti komplikacije ali ICE značajno povećava cijenu procedure, a TEE povećava nelagodu kod bolesnika. Angiografija desnog atrija može biti od koristi kod bolesnika s anatomskim varijacijama ili rotacijom srca. Kod otežanih TSP danas se koriste i posebno dizajnirane "oštre" žice kroz lumen igle<sup>9</sup> ili se primjenjuje radiofrekvencija energija putem vrha igle<sup>10</sup>. Nedavno su opisane i metode transseptalne punkcije bez korištenja fluoroskopije uz pomoć ultrazvuka i navigacijskih sustava<sup>11</sup>.

### Priprema bolesnika i postupak nakon intervencije

Kao i za svaki drugi invazivni postupak, priprema bolesnika je iznimno važna da bi se smanjio rizik komplikacija. Prije TSP kod bolesnika s AF kod svakog bolesnika potrebno je učiniti TEE, primarno radi isključenja postojanja tromba u LA i aurikuli. Također, anatomija interatrijskog septuma, postojanje otvorenog foramena ovale (PFO), atrijskog septalnog defekta ili hipertrofije septuma te ostalih anatomskih odnosa mogu uvelike pomoći operatoru. TEE je potrebno učiniti i kod ostalih bolesnika koji veći rizik za razvoj tromba u LA. Tijekom postupka, mi koristimo TEE samo rijetko, kod bolesni-

transseptal puncture is to be performed for left atrial ablation procedures, typically, using the first as a "roadmap". In cases of a very difficult TSP, left atrial access of two long sheaths can be achieved by trying to pass the first puncture site along the guidewire with a second guidewire or a steerable EP catheter.

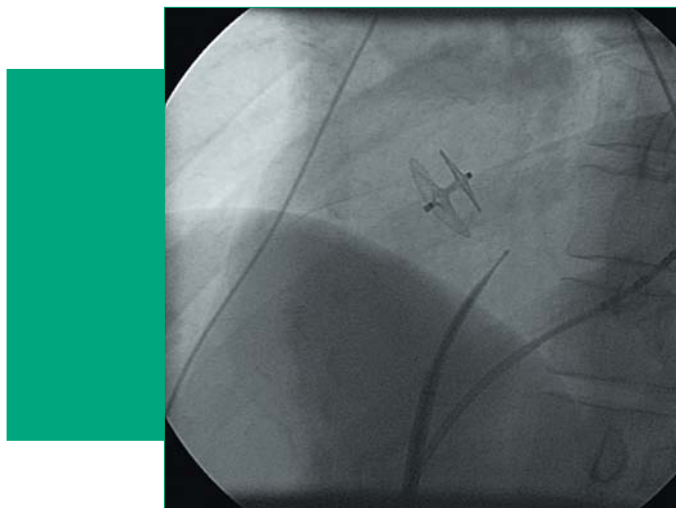
Some labs use additional methods for TSP like the use of transesophageal<sup>6</sup> and intracardiac<sup>7</sup> echocardiography or right atrial angiography<sup>8</sup>. While the use of echocardiography potentially reduces the risk of complications, ICE significantly increases the costs of the procedure, while TOE increases the patient's discomfort. Angiography of the right atrium can be used in patients with unusual anatomy. Specially designed "sharp" J tip wires can be used<sup>9</sup> or radiofrequency energy over the tip of the needle can be applied<sup>10</sup> in difficult TSP. Recently, fluoroscopy free transseptal punctures have been described by using echocardiography and 3D navigation systems<sup>11</sup>.

### Patient preparation and postprocedure treatment

As in any other invasive procedure, a thorough preparation is important to minimize the risk for complications. Before performing TSP in patients with AF, transesophageal echocardiography should be performed to exclude a left atrial thrombus. During the TOE, anatomy of the interatrial septum, presence of PFO, ASD or septal hypertrophy can be defined and assist the operator in the procedure. TOE should also be performed in other patients who are at risk for the left atrial thrombus. During the procedure, we only use TOE in

ka koji imaju postavljen PFO okluder i kod kojih nije uspjela TSP uz korištenje samo fluoroskopije (Slika 6).

some patients who have a PFO occluder in place and TSP could not be performed using fluoroscopy only (Figure 6).



**Figure 6.** Left anterior oblique view before transseptal puncture in patient with patent foramen ovale occluder.

Obzirom da se radi o invazivnom postupku koja također zahtijeva sistemsku heparinizaciju, važni su i nalazi kompletne krvne slike kao i koagulogram (broj trombocita, INR). Radi prevencije tromboembolijskih komplikacija, nakon uspješne TSP bolesnici dobivaju 100 IJ/kg heparina. U daljnjem tijeku procedure svakih 20-30 minuta mjeri se ACT te se održava većim od 300 s<sup>12</sup>. Iako je povišen INR (>2.5) do nedavno bila kontraindikacija za proceduru<sup>4,13</sup>, prema rezultatima COMPARE studije (NCT01006876) bolesnici s učinkovitim ablacijom uz nastavak varfarina imaju manje tromboembolijskih incidenata. Stoga, danas sve više centara izvodi TSP i PVI bez prekidanja antikoagulantne terapije, uz terapijske vrijednosti INR.

Nakon TSP i završetka postupka vade se uvodnice te se krvarenje zaustavlja manualnom kompresijom. Bolesnik mora mirovati 6-8 sati, a ukoliko postupak prođe bez komplikacija idući dan se može otpustiti kući. Nakon TSP kod svih bolesnika je potrebno učiniti ehokardiografski pregled radi isključenja perikardnog izljeva. Kod bolesnika nakon PVI nastavlja se antikoagulantna terapija minimalno tri mjeseca, a dalje ovisno o riziku tromboembolije (CHADS2VASc score). Kod bolesnika nakon ablacije lijevostranih akcesornih putova dovoljna je terapija acetilsalicilatnom kiselinom tijekom 4 tjena.

## Komplikacije

Komplikacije su opisane u oko 1% TSP<sup>14,15</sup>. Moguće komplikacije uključuju perikardni izljev i tamponadu, zatim punkciju korijena aorte, moždani udar ili tranzitornu ishemijsku ataku, tranzitornu elevaciju ST spojnice, bol u prsištu, perzistiranje atrijskog septalnog defekta te smrt. U početku TSP, prvi radovi koji su opisivali komplikacije transseptalne punkcije opisali su incidenciju tamponade u oko 1,2% bolesnika<sup>16</sup>. Prema najvećem istraživanju kojim je obuhvaćeno 5.520 TSP, incidencija tamponade bila je 0,74%<sup>14</sup> s jednim smrtnim ishodom (0.018%). Incidencija komplikacija razlikuje se također ovisno i o proceduri. Tako je tamponada opisana u 1.2% do čak 6 % bolesnika prilikom PVI što je znatno više nego kod ablacija lijevostranih akcesornih putova. Viši rizik povezan je s potrebom za dvije TSP, sistemskom antikoagulacijom, kao i opsežnijom ablacijom u lijevom atriju. Dio tog rizika sigurno je povezan sa samim postupkom ablacije, kao i manipulacije kateterima u LA, a ne samom TSP.

Since TSP is an invasive procedure which also requires systemic heparinization, complete blood count and coagulogram (thrombocytes, INR) should be obtained in all patients. For prevention of thromboembolic incidents, after successful TSP, patients receive 100 IU/kg of heparin. After that, ACT is measured every 20-30 minutes and should be kept >300 s<sup>12</sup>. Although increased INR (>2.5) was considered a contraindication for TSP<sup>4,13</sup>, the COMPARE trial (NCT01006876) showed a decreased risk for thromboembolic incidents and major bleeding in patients who continued warfarin therapy. Today, an increasing number of centers perform TSP and PVIs without discontinuation of warfarin therapy and with INRs in the therapeutic range.

After TSP and the procedure, sheaths are removed and manual compression applied to stop the bleeding. A patient should rest 6-8 hours, and if there are no complications, he can be released home next day. A pericardial effusion should be excluded by transthoracic echocardiography. In patients after PVI, anticoagulation therapy is continued for at least three months and further management depends on thromboembolic risk (CHADS2VASc score). Patients who were ablated for left sided accessory pathways receive aspirin for 4 weeks.

## Complications

Complications have been described to occur in around 1% of TSP<sup>14,15</sup>. Complications include pericardial effusion and tamponade, aortic root puncture, stroke, TIA, ST segment elevation, chest pain, persistence of ASD and death. In early days of TSP, first reports described an incidence of tamponade in 1.2%<sup>16</sup> patients. In the largest survey of TSPs which included 5,520 TSPs, the incidence of tamponade was 0.74%<sup>14</sup> with one death (0.018%). The incidence of tamponade also differs depending on the procedure. Tamponade is described in 1.2-6% of patients undergoing PVI which is much higher than in patients undergoing left sided accessory pathway ablation. The higher risk is probably attributable to double TSP, need for systemic anticoagulation, treatment of patients with structural heart disease (dilated chambers) and more extensive ablation in the left atrium. A part of the risk is related to ablation duration and catheter manipulation in the left atrium rather than TSP itself.

Incidencija tamponade može se potencijalno smanjiti korištenjem ultrazvuka prilikom punkcije<sup>17</sup> međutim incidencija tamponade kod TSP s korištenjem samo fluoroskopije i fluoroskopije i ultrazvuka nikada nije uspoređena u randomiziranoj studiji. Znatno važniji način smanjivanja broja komplikacija je vjerojatno trening, iskustvo i volumen operatora. Prema podacima iz nekoliko istraživanja krivulja učenja uključuje 25-50 procedura nakon čega se broj komplikacija znatno smanjuje<sup>17,18</sup>.

Iako rizik tromboembolije postoji, on je više povezan s kasnijom procedurom nego sa samom TSP. Radi smanjenja incidencije moždanog udara/transitorne ishemijske atake potrebna je adekvatna antikoagulacija, kao i pažljivo propiranje dilatatora i uvodnica. Izvođenje procedure uz terapijske vrijednosti INR kao dodatak heparina znatno smanjuju incidenciju tromboembolijskih incidenata.

## Zaključak

Transseptalna punkcija je jedna od osnovnih tehnika invazivnih elektrofiziologa. Porastom broja valvularnih intervencija (mitralna valvuloplastika, MitraClip), kao i pojavom okludera lijeve aurikule postaje potrebna i sve većem broju invazivnih kardiologa. U iskusnim rukama većina transseptalnih punkcija može se učiniti sigurno uz korištenje samo fluoroskopije.

Received: 28<sup>th</sup> Feb 2014; Accepted: 4<sup>th</sup> Mar 2014

\*Address for correspondence: Zavod za kardiovaskularne bolesti, Klinički bolnički centar Sestre milosrdnice, Vinogradska cesta 29, HR-10000 Zagreb, Croatia.

Phone: +385-1-3787-111

E-mail: [nikola.pavlovic@usb.ch](mailto:nikola.pavlovic@usb.ch)

## Literature

1. Ross J Jr, Braunwald E, Morrow AG. Transseptal left heart catheterization: a new diagnostic method. *Prog Cardiovasc Dis.* 1960;2:3158.
2. Brockenbrough EC, Braunwald E, Ross J Jr. Transseptal left heart catheterization. A review of 450 studies and description of an improved technic. *Circulation.* 1962;25:15-21.
3. Mullins CE. Transseptal left heart catheterization: experience with a new technique in 520 pediatric and adult patients. *Pediatr Cardiol.* 1983;4(3):239-45.
4. Kuhne M, Oral H. Indications and contraindications of transseptal catheterization. In: Thakur RK, Natale A (Eds). *Transseptal catheterization in cardiac electrophysiology.* Cardiotext Publishing 2010, Minneapolis, Minnesota.
5. Sweeney LJ, Rosenquist GC. The normal anatomy of the atrial septum in the human heart. *Am Heart J.* 1979;98(2):194-9.
6. Hahn K, Gal R, Sarnoski J, Kubota J, Schmidt DH, Bajwa TK. Transesophageal echocardiographically guided atrial transseptal catheterization in patients with normal-sized atria: incidence of complications. *Clin Cardiol.* 1995;18(4):217-20.
7. Dravid SG, Hope B, McKinnie JJ. Intracardiac echocardiography in electrophysiology: a review of current applications in practice. *Echocardiography.* 2008;25(10):1172-5.
8. Rogers DPS, Lambiase PD, Dhinoja M, Lowe MD, Chow AWC. Right atrial angiography facilitates transseptal puncture for complex ablation in patients with unusual anatomy. *J Interv Card Electrophysiol.* 2006;17(1):29-34.
9. De Ponti R, Marazzi R, Picciolo G, Salerno-Uriarte JA. Use of a novel sharp-tip, J-shaped guidewire to facilitate transseptal catheterization. *Europace.* 2010;12(5):668-73.
10. McWilliams MJ, Tchou P. The use of a standard radiofrequency energy delivery system to facilitate transseptal puncture. *J Cardiovasc Electrophysiol.* 2009;20(2):238-40.
11. Reddy VY, Morales G, Ahmed H, et al. Catheter ablation of atrial fibrillation without the use of fluoroscopy. *Heart Rhythm.* 2010;7(11):1644-53.
12. Earley MJ. How to perform a transseptal puncture. *Heart.* 2009 Jan;95(1):85-92.
13. Tzeis S, Andrikopoulos G, Deisenhofer I, Ho SY, Theodorakis G. Transseptal catheterization: considerations and caveats. *Pacing Clin Electrophysiol.* 2010;33(2):231-42.
14. Roelke M, Smith AJ, Palacios IF. The technique and safety of transseptal left heart catheterization: the Massachusetts General Hospital experience with 1,279 procedures. *Cathet Cardiovasc Diagn.* 1994;32(4):332-9.
15. De Ponti R, Cappato R, Curnis A, et al. Trans-septal catheterization in the electrophysiology laboratory: data from a multicenter survey spanning 12 years. *J Am Coll Cardiol.* 2006;47(5):1037-42.
16. De Ponti R, Zardini M, Storti C, Longobardi M, Salerno-Uriarte JA. Trans-septal catheterization for radiofrequency catheter ablation of cardiac arrhythmias. Results and safety of a simplified method. *Eur Heart J.* 1998;19(6):943-50.
17. Bayrak F, Chierchia G-B, Namdar M, et al. Added value of transoesophageal echocardiography during transseptal puncture performed by inexperienced operators. *Europace.* 2012;14(5):661-5.
18. Yao Y, Ding L, Chen W, et al. The training and learning process of transseptal puncture using a modified technique. *Europace.* 2013;15(12):1784-90.

The incidence of tamponade and other complications can potentially be reduced with the use of ICE during the puncture<sup>17</sup>. However, TSP with the use of fluoroscopy and ICE versus fluoroscopy only has never been compared in a randomized manner. It must be training, volume and experience of the operator that is more important for the reduction of complications. According to several published papers, the steepest part of the learning curve includes 25-50 TSPs after which complication rates significantly decrease<sup>17,18</sup>.

Thromboembolic risk during TSP exists, although it is more related to the procedure which is performed after the TSP. An adequate anticoagulation during the procedure and careful aspiration/flushing of the whole system is required for the reduction of the risk of stroke/TIA. Additional reduction in thromboembolic incidents is achieved by performing the procedures with therapeutic INR and additional heparinization during the procedure.

## Conclusion

Transseptal puncture has become an indispensable technique for interventional electrophysiologists. The technique has become even more widely used with an increase in valvular interventions (mitral valvuloplasty and MitraClip) and the advent of left atrial appendage occlusion devices. When used by experienced hands, transseptal puncture can be performed safely and reliably when using fluoroscopy only.

# Kronična bubrežna bolest i fibrilacija atrijska

## *Chronic kidney disease and atrial fibrillation*

Bruna Sanader, Lana Pintarić, Josipa Josipović, Draško Pavlović\*

Klinički bolnički centar Sestre milosrdnice, Zagreb, Hrvatska  
*University Hospital Centre Sestre milosrdnice, Zagreb, Croatia*

**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 atrijska (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 atrijska.

### 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.<sup>1</sup> 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.

**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 strokes, 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.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):134-141.

### 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<sup>1</sup>. 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.

				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
GFR categories (ml/min per 1,73 m <sup>2</sup> ), description and range	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.<sup>2</sup>

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 izgled 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.<sup>2</sup>

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.<sup>3</sup> 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.<sup>4</sup> Liječenje bolesnika s KBB zahtjeva korekciju i metaboličkih komplikacija, od kojih su najčešće anemija i poremećaji mineralnog metabolizma.

## Fibrilacija atrijsa

Fibrilacija atrijsa (FA) je najčešća srčana aritmija u cijeloj populaciji i jedan od najvažnijih čimbenika za ishemijski moždani udar i nezavisni prediktor smrti.<sup>5</sup> To je supraventrikularna aritmija koja u početku nastaje zbog nepravilne električne aktivacije s ishodištem u plućnim venama, a kao posljedica ima nepravilnu aktivaciju i gubitak kontrakcije atrijsa. 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.<sup>6</sup>

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<sup>7</sup> 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 medikamentnu konverziju u sinusni ritam. Dugotrajna perzistentna 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.<sup>8</sup>

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.<sup>9</sup>

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 a primary place as a medical therapy.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup> 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.<sup>6</sup>

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,<sup>7</sup> 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 medication 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.<sup>8</sup>

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.<sup>9</sup>



## 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.<sup>10</sup> Mortalitet od SŽB među pacijentima u završnom stadiju bubrežne bolesti je 15-30 puta veći nego u općoj populaciji iste dobi.<sup>11</sup> 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.<sup>12</sup> Pacijenti u trećem i četvrtom stupnju KBB čak će prije umrijeti od SŽB nego progredirati u završni stadij bubrežne bolesti.<sup>13</sup>

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.<sup>14</sup>

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.<sup>15</sup> Prema Kanadskoj studiji Hemmelgarn et al, prisustvo 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 zadržavanja lijeve klijetke. Pacijenti s dijabetesom tip 1 i albuminurijom imaju devet puta veći kardiovaskularni mortalitet nego normoalbuminurici 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.<sup>15</sup>

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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>12</sup> 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.<sup>13</sup>

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.<sup>14</sup>

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 sympathetic 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.<sup>15</sup> 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.<sup>15</sup>

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 koncentracije vWF, adhezivnih molekula, fibrinogena i tkivnog aktivatora plazminogena, a to bi sve moglo dovesti do povećanog rizika tromboze.<sup>16</sup>

## Povezanost kronične bubrežne bolesti i fibrilacije atrijske

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.<sup>17</sup>

FA i KBB dijele zajedničke čimbenike rizika; hipertenzija, dijabetes, postojeća SZB, pretilost, metabolički sindrom.<sup>18</sup> 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.<sup>19</sup>

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 pogoršava pogoršanje 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.<sup>20</sup> Isto tako je poznato da je FA povezana s dugoročnim lošijim kliničkim ishodima u pacijenata s terminalnim stupnjem KBB.<sup>21</sup>

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- $\beta$ 1.<sup>22</sup> To nam potvrđuje činjenica da se spironolakton pokazao kao djelotvoran u reduciranju FA zbog blokade mineralokortikoidnog receptora i antifibrotičkog učinka.<sup>23</sup> Aritmogenezu pridonosi i aktivacija simpatikusa koja je, kao i povećanje koncentracije adrenergičnih hormona u serumu, prisutna u pacijenata s KBB.<sup>22</sup> 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.<sup>24</sup> 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.<sup>25</sup> Nadalje, strukturalne abnormalnosti na srcu, otprilike povezane s KBB, kao što su hipertrofija lijeve klijetke i pretklijetke jednako tako povećavaju rizik aritmijskih događanja.<sup>24</sup> 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.<sup>16</sup>

## 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.<sup>17</sup>

AF and CKD share some common risk factors, such as hypertension, diabetes, current CVD, obesity, and metabolic syndrome.<sup>18</sup> 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.<sup>19</sup>

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.<sup>20</sup> AF is also known to be associated with long-term impaired clinical outcomes in patients in end-stage CKD.<sup>21</sup>

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- $\beta$ 1.<sup>22</sup> 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.<sup>23</sup> 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.<sup>22</sup> 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.<sup>24</sup> Hs-CRP was identified as a good marker for the prognosis of cardiovascular events, including death, due to its associa-

FA.<sup>26</sup> 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.<sup>27</sup>

## Terapija

Pacijenti s progredirajućim oblikom KBB i koegzistirajućom dijagnozom FA imaju značajno viši rizik od smrti.<sup>19</sup> Dokazano je da je proteinurija povezana s 50% višim rizikom s 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.<sup>28</sup> Korist, odnosno rizik uporabe varfarina u pacijenata s KBB, ostaje nerazjašnjen.<sup>29</sup> Istraživanje iz 2012. godine pokazuje kako bi noviji oralni antikoagulantni lijekovi poput dabigatrana, apixabana i rivoroxabana, mogli u budućnosti zamijeniti varfarin kod pacijenata u trećem i četvrtom stupnju bubrežne bolesti, koji uz to boluju i od FA.<sup>30</sup>

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.<sup>31</sup>

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 serumске vrijednosti kreatinina i dovesti do štetnih učinaka.<sup>32</sup> *L'Allier i sur* izvješćuju o smanjenoj incidenciji FA u 10.926 pacijenata s hipertenzijom liječenih ACE inhibitorima.<sup>33</sup>

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.<sup>34</sup> Neke studije ukazuju na potpuno nezadovoljavajući ishod kateterske ablacije u pacijenata s KBB i s nižom glomerularnom filtracijom,<sup>35</sup> dok je u drugim studijama pokazano da uspješna eliminacija aritmije kateterskom ablacijom, poboljšava bubrežnu funkciju u pacijenata s blagim do umjerenim bubrežnim oštećenjem.<sup>36</sup> 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.<sup>32</sup>

## 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.<sup>25</sup> 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.<sup>24</sup> 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.<sup>26</sup> 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.<sup>27</sup>

## Therapy

Patients with a progressing form of CKD and a co-existing AF diagnosis have a significantly higher risk of death.<sup>19</sup> 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.<sup>28</sup> The benefit or the risk of administering warfarin in patients with CKD is still debatable.<sup>29</sup> 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.<sup>30</sup>

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.<sup>31</sup>

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.<sup>32</sup> *L'Allier et al* report a decreased incidence of AF in 10,926 patients with hypertension treated with ACE inhibitors.<sup>33</sup>

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.<sup>34</sup> Some studies suggest a completely unsatisfactory outcome of catheter ablation in patients with CKD and with a lower glomerular filtration rate,<sup>35</sup> 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.<sup>36</sup> 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.<sup>37</sup> 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 SZB, 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.

Received: 9<sup>th</sup> Feb 2014; Accepted: 25<sup>th</sup> Feb 2014

\*Address for correspondence: Zavod za nefrologiju i dijalizu, Klinički bolnički centar Sestre milosrdnice, Vinogradska cesta 29, HR-10000 Zagreb, Croatia.

Phone: +385-1-3787-526

E-mail: drasko.pavlovic@kbcsm.hr

greater likelihood that the procedure will have to be performed again.<sup>32</sup>

## 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.<sup>37</sup> 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.svjetskidanubrega.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. Antithrombotic Trialists' (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 fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98:946-52.
6. Bernat R. Farmakoterapija fibrilacije atrijske. *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 Kidney Dis*. 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 fibrillation 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. Sympathetic activation in chronic renal failure. *J Am Soc Nephrol*. 2009;27:933-9.
23. Williams RS, deLemos JA, Dimas V, Reisch J, Hill JA, Naseem RH. Effect of spironolactone on patients with atrial fibrillation and structural heart disease. *Clin Cardiol*. 2011;34:415-9.

24. Ananthapanyasut W, Napan S, Rudolph EH, et al. Prevalence of atrial fibrillation 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 Data System. *USRDS 2011 Annual Data 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'Allier PL, 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 fibrillation. *J Am Coll Cardiol.* 2004;44:159-64.
34. [http://czasopisma.viamedica.pl/cj/article/view/ DOI 10.5603/CJ.a2013.0116](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.

# Zdravo povrće za zdravo srce: šparoge

## Healthy vegetables for healthy heart: asparagus

Marina Palfi<sup>1\*</sup>, Helena Tomić-Obrdalj<sup>1</sup>, Dijana Horvat<sup>2</sup>

<sup>1</sup>Podravka d.d., Koprivnica, Hrvatska

<sup>2</sup>Visoko gospodarsko učilište u Križevcima, Križevci, Hrvatska

<sup>1</sup>Podravka d.d., Koprivnica, Croatia

<sup>2</sup>College of Agriculture at Križevci, Križevci, Croatia

**SAŽETAK:** Šparoga (*Asparagus officinalis* L.) je povrće koje se uzgaja zbog ukusnih bijelih ili zelenih izboja. Iznimne je hranjive i zdravstvene vrijednosti. Jedno serviranje kuhane šparoge odličan je izvor vitamina K, folne kiseline, vitamina C i vitamina A. Od minerala bogat je izvor selena, bakra i mangana. Šparoga je poznata po sastavu fitonutrijenata, karotenoida (capsanthin, caprorubin, zeaxanthin), steroidnih saponina i flavonoida (rutin). Pokazuje jaču antioksidativnu aktivnost od brokule zbog većeg udjela flavonoida. Zahvaljujući snažnom antioksidativnom kapacitetu pomažu u prevenciji srčanožilnih bolesti smanjenjem nakupljanja homocisteina, prevenciji arterijske hipertenzije, dislipidemije i dr. Potencijalno djeluje na pospješivanje izlučivanja žučnih kiselina i uklanjanje suviška kolesterola.

**KLJUČNE RIJEČI:** šparoge, povrće, hranjiva i zdravstvena vrijednost, antioksidativni kapacitet, srčanožilne bolesti.

**SUMMARY:** Asparagus (*Asparagus officinalis* L.) is a vegetable that is grown for tasty white or green shoots. It has exceptional nutritional and health value. One serving of cooked asparagus is an excellent source of vitamin K, folic acid, vitamin C and vitamin A. Concerning minerals, it is a rich source of selenium, copper and manganese. It is known for the composition of phytonutrients, carotenoids (capsanthin, caprorubin, zeaxanthin), steroidal saponins and flavonoids (rutin). It shows a more potent antioxidant activity than broccoli due to a larger portion of flavonoids. Owing to its more potent antioxidant capacity, it helps in the prevention of cardiovascular disease by reducing the formation of homocysteine, prevention of hypertension, dyslipidemias, etc. It potentially has an effect on stimulating the secretion of bile acids and the removal of excess cholesterol.

**KEYWORDS:** asparagus, vegetables, nutritional and health value, antioxidant capacity, cardiovascular diseases.

**CITATION:** *Cardiol Croat.* 2014;(9):142-149.

### Porijeklo i rasprostranjenost

Šparoga (*Asparagus officinalis* L.) je višegodišnja dvodomna biljka koja po novoj klasifikaciji pripada porodici Asparagaceae.<sup>1</sup> Porijeklom je iz južne Europe, Azije i sjeverozapadne Afrike (Alžir, Maroko, Tunis). Prvi tragovi šparoge potječu iz egipatskih grobnica iz 4. stoljeća p.n.e., a kasnije su je kultivirali i stari Grci i Rimljani.<sup>2</sup>

Najveći svjetski proizvođači šparoge su Kina, Peru, SAD i Meksiko. Šparoge se u svijetu proizvode na 195.819 ha, od toga 121.694 ha zelenih i 74.125 ha bijelih. U Europi se šparoga proizvodi na 56.198 ha, od čega je 39.544 ha bijelih i 16.654 ha zelenih. Najveći europski proizvođači šparoge su Njemačka, Španjolska, Francuska i Italija.<sup>3</sup>

Osim kultivirane vrste šparoga, u našem priobalnom području rastu i one samonikle. Tu valja biti oprezan jer je u Republici Hrvatskoj dozvoljena berba za jelo oštrolosne šparoge (*Asparagus acutifolius* L.) i za njeno branje nije potrebno ishoditi dozvolu. Kod nas su zaštićene tri vrste šparoga: morska (*Asparagus maritimus* (L.) Mill), ljekovita šparoga (*Asparagus officinalis* L.) i tankolisna (*Asparagus teneuifolius* Lam.).<sup>4</sup>

### Origin and distribution

Asparagus (*Asparagus officinalis* L.) is a perennial dioecious plant that according to the new classification belongs to the family Asparagaceae.<sup>1</sup> It originates from southern Europe, Asia and north-west Africa (Algeria, Morocco, Tunisia). The first traces of asparagus originate from the Egyptian tombs in the 4<sup>th</sup> century BC and later the plant was grown by the ancient Greeks and Romans.<sup>2</sup>

The world's largest asparagus producers are China, Peru, the United States and Mexico. Asparagus is produced on 195,819 ha worldwide, of which green asparagus on 121,694 ha and white asparagus on 74,125 ha. In Europe, asparagus is produced on 56,198 ha, of which white asparagus on 39,544 ha and green on 16,654 ha. Europe's largest asparagus producers are Germany, Spain, France and Italy.<sup>3</sup>

In addition to cultivated species of asparagus, there are species of self-grown asparagus that grow in our coastal area. One must be cautious here, because harvesting of wild asparagus (*Asparagus acutifolius* L.) is permitted in the Republic of Croatia and no license is required for its harvesting. Three species of asparagus are protected in our country: sea (*Asparagus maritimus* (L.) Mill), medicinal garden as-

## Uzgoj šparoga

Šparoga je višegodišnja biljka koja na jednom mjestu ostaje deset i više godina. Podzemni dio šparoge je podanak na čijoj se gornjoj strani razvijaju brojni pupovi, a na donjoj strani korijenje. Iz pupova se u proljeće razvijaju mladi, sočni izboji iz kojih se, ako se u proljeće ne odrežu, razvija stabljika koja može narasti i do 1,5 m.

Za komercijalni uzgoj šparoga se uzgaja izravno iz sjemena ili presadnicama koje je moguće proizvesti i u kontejnerima i kulturom tkiva (naročito hibride samo muških biljaka). Presadnice se presađuju u jarke ili brazde od sredine ožujka do sredine travnja i odmah prekriju s 5-7 cm tla, a s porastom biljaka do kraja prve vegetacijske sezone jarci se postupno zatrpavaju. Za proizvodnju bijelih etiliranih izboja potrebno je nasad u proljeće nagnuti zemljom ili prekriti crnom polietilenskom folijom.<sup>5</sup> Berba šparoga koje su proizvedene iz presadnica može započeti već druge godine nakon sadnje presadnica, a one koje su proizvedene iz sjemena tek treće godine. Važno je napomenuti da se u prvoj godini berbe sa svake biljke reže samo nekoliko izboja, a ostali se ostave da biljka ojača i skupi što više hranjivih tvari potrebnih za rast i razvoj u sljedećim godinama.

Pri punoj berbi svi izboji dužine oko 15 cm režu se specijalnim nožem pod kutem od 45° na 5 cm u tlu. Izboje je nakon berbe potrebno što prije spremirati u hladnjače i čuvati na temperaturi od 0-2 °C.

U toku vegetacije potrebno je usjev održavati zdravim, zaštićen od štetnika, bolesti i korova. Najznačajniji štetnici šparoge su šparogine zlatice (*Crioceris asparagi*, *Crioceris duodecimpunctata*), šparogina muha (*Platyparaea poeciloptera*), šparogin kornjaš (*Parahypopta / Hypopta / caestrum*), stjenica (*Lygus*), minirajuće muhe i dr., a od bolesti najznačajnije su hrđe (*Puccinia asparagai*), crvena trulež (*Helicobasidium brebissonii*) i Fusarium vrste koji se smatraju glavnim uzrocima degeneracije usjeva šparoge.<sup>6</sup> Zaštita usjeva od korova, naročito je važna agrotehnička mjera u prvim godinama uzgoja šparoge gdje je moguće uspješno regulirati rast korijena i malč folijama.<sup>7</sup>

U početku sezone berbe šparoga ima znatno višu cijenu, pa se u Nizozemskoj, Belgiji i Francuskoj razvijaju tehnologije i za zimsku proizvodnju šparoge.<sup>8</sup>

Iako se u Njemačkoj, na primjer organiziraju festivali šparoga, biraju kraljice šparoga i provodi postupak zaštite šparoge u smislu zaštite zemljopisnog podrijetla i oznake izvornosti poljoprivrednih i prehrambenih proizvoda<sup>9</sup>, u Republici Hrvatskoj nema veće organizirane proizvodnje šparoga. Trenutačno postoji organizirana proizvodnja samo u okolici Vinkovaca.

Kod nas je više zastupljena sadnja šparoge uz rub vrtova i okućnica. Pretpostavlja se da bi za jednu peteročlanu obitelj bilo dovoljno uzgajati 6-10 biljaka šparoge.<sup>10</sup>

## Čuvanje i priprema šparoga

Svježe šparoge treba pažljivo skladištiti i brzo konzumirati. U šparogama se i nakon berbe odvija intenzivna metabolička aktivnost koja je vrlo visoka u odnosu na drugo povrće. Umatanjem krajeva šparoga u vlažnu krpu ili ručnik tijekom skladištenja u hladnjaku može se zaustaviti razgradnja škroba i šećera i ispuštanje ugljikovog dioksida. Najbolje je konzumirati šparoge u roku od otprilike 48 sati nakon kupnje.<sup>11</sup>

Šparoga se u domaćim uvjetima prilikom pripreme najčešće sjecka i kuha. Utvrđeno je da sjeckanje značajno utječe na

paragus (*Asparagus officinalis* L.) and narrow-leaved (*Asparagus tenuifolius* Lam.).<sup>4</sup>

## Growing asparagus

Asparagus is a perennial plant that stays in one place for more than 10 years. The underground part of asparagus consists of upper side with numerous buds and roots on the bottom. Young, succulent shoots develop from the buds in the spring from which, if not cut off in spring, the stem is developed that can grow up to 1.5 meters.

For commercial cultivation, asparagus is grown directly from seed or seedlings that can be produced in containers and by tissue culture (especially hybrids of only male plants). Seedlings are transplanted into ditches or furrows from mid March to mid April and are immediately covered with 5-7 cm of soil, and as the plants grow by the end of the first growing season, the ditches are gradually buried. The plantation is to be covered by soil in spring for production of white etiolated shoots or it is to be covered by black polyethylene foil.<sup>5</sup> The harvesting of asparagus that are produced from seedlings may start already in the second year after planting seedlings, and those that are produced from the seed only during the third year. It is worth noting that in the first year of the harvest only a few shoots are cut off from every plant, while the others are left to allow the plant to become stronger and collect as more nutrients as possible needed for growth and development in the years to come.

In full harvest all of the shoots in a length of about 15 cm are cut off with a special knife at an angle of 45° in 5 cm in the soil. The shoots after harvest should be stored in refrigerators at a temperature of 0-2 °C as soon as possible.

During the growing season, the crop is to be maintained healthy and protected from pests, diseases and weeds. The most important asparagus pests are asparagus beetle (*Crioceris asparagi*, *Crioceris duodecimpunctata*), asparagus fly (*Platyparaea poeciloptera*), cossid moth (*Parahypopta / Hypopta / caestrum*), lygus bug (*Lygus*), stem-mining flies, etc., and concerning the diseases, the most important diseases are asparagusrust (*Puccinia asparagai*), violet root rot (*Helicobasidium brebissonii*) and Fusarium species that are considered to be the main causes of degeneration of the asparagus crops.<sup>6</sup> Protection of crops from weed is a particularly important agro-technical measure in the first years of growing asparagus where it is possible to successfully regulate the growth of root and mulch by foil.<sup>7</sup>

At the beginning of the harvesting season, the asparagus is much more costly, so the technologies are being developed in the Netherlands, Belgium and France for the winter production of asparagus.<sup>8</sup>

While festivals of asparagus are organized in Germany, asparagus queens are elected and the procedure of protection of asparagus is conducted in terms of protection of geographical origin and designation of origin for agricultural and food products<sup>9</sup>, we lack some well organized production of asparagus in the Republic of Croatia. At present, there is some organized production only in the surrounding of Vinkovci.

In our country growing of asparagus is more common along the edge of gardens and yards. It is assumed that it would be enough to grow 6-10 asparagus plants for one five-member family.<sup>10</sup>

## Storing and preparing asparagus

Fresh asparagus should be carefully stored and soon consumed. Intense metabolic activity, which is very high compared to the other vegetables, occurs in asparagus even fol-

sadržaj rutina, pad je bio 18,5% za 60 minuta, a kuhanje od 60 minuta reducira sadržaj flavonola za 43%. Sjeckanje ne utječe na ukupni antioksidativni potencijal biljke, ali kuhanje utječe.<sup>12</sup>

Pripremiti šparoge moguće je na bezbroj načina. Najbolje ju je pripremiti kuhanjem na pari tako da se snopići šparoge urone u lonac napunjen 1/3 vodom i kuhaju poklopljene 5 minuta. Tek tada ih lomiti i preliti umacima ili začiniti na salatu.

U našim mediteranskim krajevima, gdje se bere samonikla šparoga, najpoznatija je fritaja od šparoga i salata od šparoga i tvrdo kuhanih jaja uz dodatak maslinovog ulja i domaćeg vinskog octa.

## Hranjivi sastav šparoga

Šparoga se uzgaja zbog sočnih, veoma ukusnih i nježnih bijelih, zelenih, a u novije vrijeme i ljubičastih izboja. Način uzgoja djeluje na hranjivu vrijednost šparoge, prije svega na sastav fitokemikalija. Iako zelena šparoga ima bolju hranidbenu i zdravstvenu vrijednost, naročito u sadržaju vitamina C na vrhovima izboja, u Europi se više cijeni bijela šparoga.<sup>8</sup>

Podaci u **Tablici 1** prikazuju usporedbu svježih plodova zelene i bijele šparoge. Šparoga ima mali sadržaj energije, s tim da je bijela šparoga nešto bogatija bjelančevinama, a sadržaj ugljikohidrata i masti je nizak.

lowing the harvest. Wrapping the ends of the asparagus in a damp cloth or towel during storage in the refrigerator can stop the degradation of starch and sugar and release of carbon dioxide. Asparagus should be consumed within approximately 48 hours after the plant is purchased.<sup>11</sup>

Asparagus is usually chopped and boiled in households during preparation. It has been found that chopping significantly affects the rutin content. The decrease was 18.5% in 60 minutes, and boiling in duration of 60 minutes reduces the flavonol content by 43%. Chopping does not affect the total antioxidant potential of the plant, but boiling does.<sup>12</sup>

Asparagus can be prepared in number of ways. It is best to be prepared by steaming, so that the asparagus bundles are immersed in a pot 1/3 filled with water and cooked for 5 minutes under the lid. Only then they are to be crushed and sauce is to be poured over it and spiced as a salad.

In our Mediterranean regions, where wild asparagus is harvested, the most famous dish is the asparagus fritatta and asparagus salad as well as hard-boiled eggs with an addition of olive oil and local wine vinegar.

## Asparagus nutritional ingredients

Asparagus is grown for succulent, very tasty and delicate white, green and more recently purple shoots. The cultivation method affects the nutritional value of asparagus, primarily the composition of phytochemicals. Although green asparagus has better nutritional and medicinal value, especially regarding the higher content of vitamin C on the tops of shoots, white asparagus is more priced in Europe.<sup>8</sup>

The data in **Table 1** shows the comparison of fresh fruits of green and white asparagus. Asparagus has low energy content, whereas the white asparagus is somewhat richer in proteins, while the carbohydrate and fat content is low.

**Table 1.** Chemical content in 100 g of fresh green and white asparagus (*Asparagus officinalis*) (DK7)

	Green asparagus	White asparagus
Water (g)	92.1-93.0	91.7-93.1
Energy (kcal/kJ)	26/109	26/109
Protein (g)	1.7-1.9	2.3-2.4
Carbohydrate (g)	4.9	4.3
Fat (g)	0.3	0.3
Dietary fibers (g)	1.4-2.2	1.4-2.2
Ash (g)	0.4-0.6	0.5-0.7

**Tablica 2** prikazuje sadržaj vitamina i minerala i postotke od preporučenog dnevnog unosa. Podaci su izraženi za uobičajenu količinu za konzumiranje. Prema Pravilniku o navođenju hranjivih vrijednosti hrane značajni udio mikronutrijenta za hranu je minimalno 15%.<sup>13</sup> Prema tome možemo uočiti da je šparoga bogat izvor vitamina K, zatim folne kiseline, odnosno folata, jednog od vitamina B kompleksa. Nadalje u značajnoj količini se nalazi vitamin C, snažni antioksidans, osobito u konzerviranom obliku te vitamin A i vitamin B1. Od minerala šparoga je bogat izvor selena, mangana, bakra i željeza kojeg ima u značajnoj količini u konzerviranoj šparogi. Vrijedi istaknuti da kuhana šparoga sadrži znatno manje natrija od konzervirane, stoga se osobama koji paze na unos natrija preporuča odabrati kuhane šparoge.

**Table 2** shows the content of vitamins and minerals and the percentage of the reference daily intake. Data is expressed for the usual amount for consumption. According to the Regulation on Nutrition Labelling for Foodstuffs, a significant proportion of micronutrients in food is at least 15%.<sup>13</sup> Thus, we can see that asparagus is a rich source of vitamin K, folic acid, or folate, one of the vitamin B complex. Besides, vitamin C, a potent antioxidant, is present in a significant amount especially in canned asparagus. Vitamin A and vitamin B1 are also present. Out of minerals, asparagus is a rich source of selenium, manganese, copper and iron, which are present in a significant amount in a canned asparagus. It is worth noting that cooked asparagus contains much less sodium than canned asparagus, so the people who must take care of the sodium intake are recommended to choose cooked asparagus.



**Table 2.** Vitamin and mineral content of asparagus per serving (*Asparagus officinalis*). (USDA 8)

	Cooked, boiled (1 cup; 180 g)		Canned (1 cup; 242 g)	
	Content	%RDI*	Content	%RDI
<b>VITAMINS</b>				
Vitamin C (mg)	14.00	23.30	44.50	74.0
Vitamin B1 (thiamin) (mg)	0.30	20.00	0.15	10.0
Vitamin B2 (riboflavin) (mg)	0.25	14.70	0.24	14.1
Vitamin B3 (niacin) (mg)	2.00	10.00	2.30	11.5
Vitamin B6 (mg)	0.14	7.00	0.26	13.0
Folic acid (µg)	89.40	37.25	140.00	58.3
Vitamin A (µg)	50.00	19.40	99.00	16.4
Vitamin K (µg)	50.60	63.25	100.00	125.0
<b>MINERALS</b>				
Calcium (mg)	42.0	4.2	39.0	3.9
Iron (mg)	1.6	8.0	4.4	24.4
Magnesium (mg)	26.0	6.5	24.0	6.0
Phosphorus (mg)	98.0	9.8	104.0	10.4
Potassium** (mg)	404	11.5	416	12.0
Copper (mg)	0.3	15.0	0.23	11.5
Zinc (mg)	1.1	7.3	0.9	6.0
Selenium (µg)	11.0	15.7	4.1	27.3
Manganese (mg)	0.3	15.0	0.4	20.0
Sodium (mg)	26.0	1.1	695.0	29.0

USDA National Nutrient Database for Standard Reference Release 26

\*RDI — Reference Daily Intake; \*\*DV — Daily value for potassium; \*\*\* Significant source is 15% from RDI

Tijekom vegetativnog razvoja šparoge stapke izlaze na površinu i pod utjecajem sunčeve svjetlosti dolazi do procesa fotosinteze, koja utječe na promjenu boje, a time i nutritivnog sastava biljke. Ispitivanja su utvrdila da tijekom vegetativnog sazrijevanja sadržaj minerala raste te da se u vrhu izboja šparoge u odnosu na bazalni dio nalazi najveći sadržaj minerala. To se pripisuje procesima razvoja biljke i diobi stanica za koju je potrebna veća koncentracija minerala.<sup>14</sup> Uočeno je da sadržaj natrija u tim procesima opada, a kalija ostaje isti. Šparoga ima vrlo visoku nutritivnu gustoću, to je podatak koji ukazuje na nutritivnu raznolikost i bogatstvo sadržaja. Za sve elemente je visoko iznad 100%, osim za natrij.<sup>15</sup> Osim toga, pokazalo se da i veći promjer izboja šparoge znači bogatiji mineralni sastav. Slični rezultati su dobiveni i za bijelu šparogu. Također su utvrđene razlike u hranjivoj vrijednosti između vrha biljke i bazalnog dijela. Mineralni sastav se postupno smanjuje od vrha prema dnu biljke, a to se različito manifestira prema sortama i debljini stapke. Valja napomenuti da te razlike nisu nutritivno značajne i da su podaci unutar preporučenih vrijednosti.<sup>16</sup>

Konzerviranje je jedna od često korištenih metoda za čuvanje hrane pa tako i šparoge. Sama tehnologija konzerviranja ne utječe značajno na hranjivi sastav tj. na ugljikohidrate, vlakna, bjelančevine i vlagu. Također se zadržava i oko 95% vitamina B1, B2, B6 i vitamina C.<sup>17</sup>

Druga uobičajena metoda čuvanja povrća je zamrzavanje. Ispitivanja su pokazala da na većinu minerala utječe skladištenje od 45 dana na -18 °C. Ovi gubici se djelomično mogu pripisati i postupcima u industrijskoj obradi šparoge (pranje i blansiranje), koji se provode prije zamrzavanja. Po-

During vegetative development of asparagus, the stem comes to the surface and the process of photosynthesis occurs under the influence of sunlight, which affects the change of the color, and thus the nutritional composition of the plant. Tests have determined that during vegetative maturation, the mineral content rises and that the largest mineral content is contained in the top of the asparagus shoot compared to its basal portion. This is attributed to the processes of plant development and cell division that requires higher concentration minerals.<sup>14</sup> It was observed that the sodium content in these processes drops and potassium content remains the same. Asparagus has a very high nutritional density. This data suggests nutritional diversity and richness of content. Regarding all the elements, it exceeds 100%, except for sodium.<sup>15</sup> In addition, it was shown that a larger diameter of asparagus stem implies a richer mineral composition. Similar results were obtained for the white asparagus. The differences in nutritional values between the top and the basal part of the plant have been identified. Mineral composition gradually decreases from the top to the bottom of the plant, and it is manifested in different ways according to the kinds and the thickness of the stem. It should be noted that these differences are not nutritionally significant, and that the data is within the recommended values.<sup>16</sup>

Canning is one of the most commonly used methods for preserving food including asparagus. The preservation technology itself does not significantly affect the nutrient composition i.e. carbohydrates, fibers, proteins and moisture. About 95% of vitamins B1, B2, B6 and vitamin C are preserved.<sup>17</sup>

Another common method of preserving vegetables is freezing. Tests have shown that the majority of minerals are af-

daci za skladištenje od 90 dana na istoj temperaturi od -18 °C, pokazuju da nema značajnog gubitka većine minerala.<sup>18</sup>

Šparoga je, nadalje, izvor raznih fitonutrijenata koje imaju vrlo povoljno djelovanje na zdravlje. Ubrajaju se u snažne antioksidanse koji štite organizam od štetnih posljedica oksidativnih procesa u organizmu. Među njima se ističu flavonoidi, karotenoidi i antocijani.

Manje poznata ljubičasta šparoga svoju boju dobiva iz visoke razine antocijana u izdancima. U odnosu na bijelu i zelenu šparogu ima niži sadržaj vlakna, slađa je i ima svjež, voćni okus.<sup>19</sup>

ected by the 45-day storage at -18 °C. These losses are partially attributable to the procedures in the industrial processing of asparagus (washing and blanching), that is carried out before freezing. Data on storage for 90 days at the same temperature of -18 °C, shows that there is no significant loss of most minerals.<sup>18</sup>

Asparagus is, besides, a source of a variety of phytonutrients that have a beneficial effect on health. They are included in potent antioxidants that protect the body from the harmful effects of oxidative processes in the body. Flavonoids, carotenoids and anthocyanins are distinguished among them.

Less well-known purple asparagus gets its color from the high level of anthocyanins in shoots. Compared to the white and green asparagus, it has a lower fiber content, it is sweeter and has a fresh, fruity flavor.<sup>19</sup>



Glavni bioaktivni sastojci šparoge su skupina steroidnih saponina. Od primarnih kemijskih sastojaka šparoge sadrže i eterična ulja, asparagin, arginin, tirozin, flavonoide (kaempferol, kvercetin i rutin), smole i tanin.<sup>20</sup>

Ispitivanja plodova šparoga, dobivenih iz komercijalnog uzgoja u južnoj Mađarskoj, na sastav karotenoida provedena je HPLC tehnikom. Utvrđeni su: capsanthin, caprorubin, capsanthin 5,6-epoxid, antheraxanthin, violaxanthin, neoxanthin, mutatoxanthin epimeri, zeaxanthin, lutein, beta-cryptoxanthin, beta-karoten i neki cis-izomeri.<sup>21</sup>

Šparoga je prva u odnosu na ostale uspoređivane vrste povrća po ukupnoj kvaliteti i kvantiteti antioksidansa i četvrta po sadržaju ukupnih fenola.<sup>22</sup>

Pokazuje jaču antioksidativnu aktivnost od primjerice brokule, iako posjeduju podjednaki sadržaj fenola, šparoga sadrži veći udio flavonida koji su u direktnoj korelaciji s antioksidativnom aktivnosti.<sup>23</sup>

### Zdravstvena vrijednost šparoga i utjecaj na srčanožilne bolesti

Šparoga je po svojoj zdravstvenoj vrijednosti poznata od davnina. U staroj Kini, 3000 godina p.n.e., jedna vrsta šparoga (*Asparagus lucidus*) se koristila protiv napadaja suhog kašlja, za liječenje otekline na koži i čireva, za jačanje pluća i za ublažavanje vrućine i bolova u nogama.<sup>24</sup>

U kontekstu zdravstvene vrijednosti treba istaknuti da je šparoga povrće koje zahvaljujući izuzetnom nutritivnom sastavu ima potencijal u doprinosu prevenciji bolesti srčanožilnog sustava.

The main bioactive ingredients of asparagus are a group of steroidal saponins. Out of primary chemical ingredients, asparagus contain essential oils, asparagine, arginine, tyrosine, flavonoids (kaempferol, quercetin and rutin), resins and tannin.<sup>20</sup>

Testing of asparagus fruits, obtained from commercial farming in South Hungary was conducted on the carotenoid composition by applying HPLC technique. The following has been identified: capsanthin, capsorubin, capsanthin 5.6-epoxide, antheraxanthin, violaxanthin, neoxanthin, mutatoxanthin epimers, zeaxanthin, lutein, beta-cryptoxanthin, beta-carotene and some cis-isomers.<sup>21</sup>

Asparagus takes the first place in relation to other compared types of vegetables judging by the overall quality and quantity of antioxidants and takes the fourth place judging by overall content of phenols.<sup>22</sup>

It shows a more potent antioxidant activity than broccoli, though they contain an equal content of phenols. However, asparagus contains a greater proportion of flavonoids, which are in direct correlation with antioxidant activity.<sup>23</sup>

### Health value of asparagus and impact on cardiovascular diseases

Asparagus has been known for its health value since ancient times. In ancient China in 3000 BC, one species of asparagus (*Asparagus lucidus*) was used against the seizure of dry cough, for the treatment of skin swelling and ulcers, to strengthen the lungs and to alleviate the fever and pain in the legs.<sup>24</sup>

Regarding the health values we should point out that asparagus is a vegetable that thanks to the extraordinary nutri-

Šparoga je također odličan izvor folne kiseline tj. reduciranog oblika folata. Folati sudjeluju u procesima stvaranja eritrocita i sprječavanju pojave anemije. Održava zdravu cirkulaciju krvi jer doprinosi smanjenju nakupljanja homocisteina koji je rizični čimbenik za pojavu srčanožilnih bolesti. Utvrđeno je da konzumacija 400 µg folne kiseline dnevno može smanjiti broj infarkta miokarda za 10%. Folati su posebno važni za trudnice jer doprinose pravilnom razvoju živčanog sustava kod fetusa.

Šparoga sadrži vitamin B6 koji pomaže u procesima sprječavanja nakupljanja homocisteina. Kad je razina ovog B vitamina niska, razina homocisteina u krvi raste, a to ovo stanje značajno povećava rizik od bolesti srca. Homocistein potiče aterosklerozu smanjujući integritet krvnih žila te ometajući stvaranje kolagena. Porast razine homocisteina uočen je u približno 20-40% osoba koje boluju od srčanih bolesti.<sup>25</sup>

Konzumacija voća i povrća, naročito zelenog lisnatog povrća, bogatog vitaminom C, potencijalno ima zaštitni učinak protiv koronarne bolesti srca. Povećanje konzumacije voća i povrća za 1 serviranje na dan smanjuje rizik od koronarne bolesti za 4%.<sup>26</sup> Studija provedena u Španjolskoj ispitala je utjecaj konzumacije voća i povrća na arterijski tlak. Ispitanici su ispunjavali upitnik o prehrani na osnovu kojeg je utvrđeno da se mast konzumira u velikim količinama, 37% od dnevnih energetskih potreba. Ispitanici kojima je izmjeren sistolički tlak  $\geq 140$  ili dijastolički  $\geq 90$  mmHg smatrani su kao osobe s nedijagnosticiranom arterijskom hipertenzijom, iako nisu imali postavljenu medicinsku dijagnozu. Nakon prilagodbe čimbenika rizika za arterijsku hipertenziju, utvrđeno je da je visoki unos voća i povrća obrnuto proporcionalan arterijskom tlaku.<sup>27</sup>

S obzirom da je šparoga bogata funkcionalnim sastojcima, pokušalo se razjasniti da li pomaže u snižavanju visokih vrijednosti arterijskog tlaka. Ispitivanja su provedena na spontano hipertenzivnim laboratorijskim životinjama. Zabilježeno je da su sistolički tlak, izlučivanje proteina u urin i aktivnost ACE (angiotenzin-konvertirajući enzim) značajno smanjene. Zaključak je da 2-hidroksinikotinamin iz šparoga inhibira ACE te na taj način doprinosi prevenciji hipertenzije i očuvanju funkcije bubrega.<sup>28</sup>

Tijekom proizvodnje šparoge odvajaju se drvenasti dijelovi stabljike i lišća kao nusproizvodi, a pokazuju veliki potencijal za zdravlje. U lišću je utvrđeno tri puta više rutina nego u stabljikama zelene šparoge.<sup>29</sup> Ispitivani su efekti unosa lišća i podnožja stabljike šparoga u prahu na metabolički sindrom kojega karakterizira hiperglikemija, arterijska hipertenzija i dislipidemija. Volonteri su bili nasumično podijeljeni u dvije grupe, jedna je konzumirala 6 g/dan praha lišća, a druga 6 g/dan podnožja stabljike šparoga tijekom 10 dana. Mjeren je arterijski tlak i CAVI (cardio-ankle-vascular indeks). Utvrđeno je da podnožje stabljike šparoge značajno smanjuje sistolički i dijastolički tlak. Također lišće i podnožje stabljike utječu na smanjenje ukupnih ugljikohidrata. Rezultati pokazuju značajan potencijal šparoge u prevenciji bolesti sastavnica metaboličkog sindroma.<sup>30</sup>

Fitonutrijenti iz *Asparagus racemosus* tj. fitosteroli, saponini, polifenoli, flavonoidi i askorbinska kiseline mogu potencijalno djelovati na povećanje izlučivanja žučnih kiselina, uklanjanje suviška kolesterola i povišene vrijednosti jetrenog antioksidativnog statusa u uvjetima povišenih vrijednosti kolesterola.<sup>31</sup>

Saponin protodioscin kojeg u šparogi ima oko 0,01% posjeduju i snažno citotoksično djelovanje za mnoge vrste tumorskih stanica i djeluje na razinu androgena. Druga vrsta saponina diosgenin doprinosi smanjenju izlučivanja ukupnog

tional composition has a potential to contribute to the prevention of cardiovascular disease.

Asparagus is also an excellent source of folic acid that is, the reduced form of folate. Folate participates in the process of creating red blood cells and prevention of anemia. It maintains healthy blood circulation because it contributes to reducing the buildup of homocysteine, which is a risk factor for cardiovascular diseases. It was found that the consumption of 400 µg of folic acid a day can reduce the number of myocardial infarctions by 10%. Folate is especially important for pregnant women because they contribute to the proper development of the nervous system in the fetus.

Asparagus contains vitamin B6 which helps in the processes of preventing the accumulation of homocysteine. When the level of this B vitamin is low, the level of homocysteine in the blood increases, and this condition increases the risk of heart disease. Homocysteine stimulates atherosclerosis by reducing the integrity of blood vessels and interferes with the formation of collagen. The increased homocysteine levels was observed in approximately 20-40 % of patients suffering from heart diseases.<sup>25</sup>

Eating fruit and vegetables, especially leafy green vegetables rich in vitamin C may have a protective effect against coronary heart disease. An increased consumption of fruit and vegetables by one dish per day reduces the risk of coronary heart disease by 4%.<sup>26</sup> A study conducted in Spain examined the impact of the consumption of fruit and vegetables on blood pressure. The subjects filled out the self-reported questionnaire on diet on the basis of which it was found that the fat was consumed in large amounts, 37% of daily energy needs. The subjects in whom the systolic blood pressure was measured  $\geq 140$  or diastolic was measured  $\geq 90$  mmHg were considered to be the persons with undiagnosed hypertension, although they did not have medical diagnosis. After adjusting for risk factors for hypertension, it was found that a high intake of fruit and vegetables is inversely proportional to blood pressure.<sup>27</sup>

Since asparagus is rich in functional ingredients, we attempted to clarify whether it helps in lowering high blood pressure. Tests were conducted on spontaneously hypertensive laboratory rats. It was noted that the systolic blood pressure, protein excretion in the urine and the activity of ACE (angiotensin-converting enzyme) have been significantly reduced. The conclusion is that 2-hydroxynicotinamine from asparagus inhibits ACE and thus contributes to the prevention of hypertension and preservation of renal function.<sup>28</sup>

During the production of asparagus, woody parts of stems and leaves are separated as byproducts, but they show a great potential for health. The foliage is found to contain three times more rutin than in the stems of green asparagus.<sup>29</sup> The effects of powdered leaves and stem base of asparagus on a metabolic syndrome characterized by hyperglycemia, hypertension and dyslipidemia have been tested. Volunteers were randomly divided into two groups, one of them consumed 6 g/day of leave powder and the other group consumed 6 g/day the stem base for 10 days. Blood pressure and CAVI (cardio-ankle-vascular index score) was measured. It was found that the asparagus stem base significantly reduced systolic and diastolic pressure. The leaves and asparagus stem base contribute to the reduction of the total carbohydrates. The results show a significant potential of asparagus in prevention of diseases of the metabolic syndrome.<sup>30</sup>

Phytonutrients from *Asparagus racemosus* i.e., phytosterols, saponins, polyphenols, flavonoids and ascorbic acids can potentially have an effect on increased excretion of bile acids, removal of excess cholesterol and elevated liver antioxidant status in conditions of elevated cholesterol values.<sup>31</sup>

kolesterola i LDL-kolesterola, ali ne i HDL-kolesterola. Preliminarni rezultati istraživanja pokazuju da rutin i kvercetin, potencijalno smanjuju pojavnost karcinoma debelog crijeva kod eksperimentalnih životinja.<sup>32</sup>

U prevenciji srčanožilnih bolesti izuzetno je važno u prehranu uvrstiti dovoljne količine voća, povrća i ribe, a ograničiti unos soli, smanjiti potrošnju zasićenih masti i rafiniranih šećera. Konzumacija šparoga doprinosi raznolikosti prehrane, povećanju potrošnje povrća i stjecanju zdravih prehrambenih navika.

## Zaključak

Bolesti srca i krvnih žila su vodeći uzrok smrtnosti i bolničkog liječenja u Republici Hrvatskoj. Jedan od vrlo važnih rizičnih čimbenika za njihovu pojavu uz arterijsku hipertenziju, pušenje i nedostatnu tjelesnu aktivnost je nepravilna prehrana. Uravnotežen unos hrane i raznolikost namirnica, kao temelj pravilne prehrane, podrazumijeva konzumiranje najmanje tri obroka povrća dnevno.

Šparoge su povrće koje zahvaljujući odličnom sastavu vitamina, minerala i fitonutrijenata, visokom antioksidativnom kapacitetu, maloj kalorijskoj vrijednosti doprinose prevenciji srčanožilnih bolesti i općem zdravlju. Iako je utvrđen pozitivan utjecaj šparoge na kardiovaskularno zdravlje, za očekivati je da će u budućnosti biti više istraživanja koja idu u tom smjeru.

Received: 9<sup>th</sup> Mar 2014; Accepted: 15<sup>th</sup> Mar 2014

Podravka d.d., Ante Starčevića 32, HR-48000 Koprivnica, Croatia.

Phone: +385-48-651-617

Fax: ++385-48-651-941

E-mail: [marina.palfi@podravka.hr](mailto:marina.palfi@podravka.hr)

## Literature

1. Dubravec KD. Botanika. Zagreb: Agronomski fakultet; 1996, str. 328.
2. Kew. Royal Botanic Gardens. *Asparagus officinalis* (garden asparagus). <http://www.kew.org/plants-fungi/Asparagus-officinalis.htm> (10.2.2014).
3. Benson BL. 2009 Update of the world's asparagus production areas, spear utilization and production periods. [http://www.calif-asparagus-seed.com/img/2009\\_world\\_asparagus\\_production.pdf](http://www.calif-asparagus-seed.com/img/2009_world_asparagus_production.pdf) (18.2.2014).
4. Državni zavod za zaštitu prirode. Branje proljetnica i šparoga. <http://www.dzpz.hr/novosti/k/branje-proljetnica-i-sparoga-936.html> (7.1.2014).
5. Matotan Z. Suвременa proizvodnja povrća. Zagreb: Nakladni zavod Globus; 2004, str. 169-74.
6. Macejski M, Cvjetković B, Ostojčić Z i sur. Štetočinje povrća. Čakovec: Zrinski; 2004, str. 453-8.
7. Dudaš S, et al. Effect of mulch in the cultivation of *Asparagus officinalis* L. *Glasnik Zaštite Bilja*. 2009;32(4):22-32.
8. Lešić R, Borošić J, Buturac I, Čustić M, Poljak M, Romić D. Povrčarstvo. II. dopunjeno izdanje, Čakovec: Zrinski; 2004, str. 150-68.
9. UREDBA VIJEĆA (EZ) br. 510/2006 o zaštiti oznaka zemljopisnog podrijetla i oznaka izvornosti poljoprivrednih i prehrambenih proizvoda ( 2 ) "BORNHEIMER SPARGEL"/"SPARGEL AUS DEM ANBAUGEBIET BORNHEIM", EZ br.: DE-PGI-0005-0803-17.03.2010 ZOZP ( X ) ZOI ( ), C 286/12. Službeni list Europske unije 2.10.2013.
10. Lešić R, Pavlek P, Borošić J. Povrće iz vlastitog vrta. Zagreb: Nakladni zavod znanje; 1987, 180-2.
11. The World's Healthiest Foods. *Asparagus*. <http://www.whfoods.com/genpage.php?name=foodspice&dbid=12> (12.2.2014).
12. Makris DP, Rossiter JT. Domestic processing of Onion Bulbs (*Allium cepa*) and *Asparagus* Spears (*Asparagus officinalis*): effect on flavonol content and antioxidant status. *J Agric Food Chem*. 2001;49 (7):3216-22.
13. Pravilnik o navođenju hranjivih vrijednosti hrane (NN 29/09). <http://www.propisi.hr/print.php?id=8245> (12.2.2014).
14. Amaro-Lopez MA, Zurera-Cosano G, Moreno-Rojas R, Garcia-Gimeno RM. Influence of vegetative cycle of asparagus (*Asparagus officinalis* L.) on copper, iron, zinc and manganese content. *Plant Foods for Hum Nutr*. 1995;47:349-55.
15. Lopez MA, Cosano GZ, Rojas RM, Garcia-Gimeno RM. Mineral content modifications during ripening of asparagus (*Asparagus officinalis*, L.). *Int J Food Sci Nutr*. 1998;49(5):353-63.
16. Amaro-Lopez MA, Zurera-Cosano G, Moreno-Rojas R. Trends and nutritional significance of mineral content in fresh white asparagus spears. *Int J Food Sci Nutr*. 2013;64(8):944-52.
17. Martin-Belloso O, Llanos-Barriobero E. Proximate composition, minerals and vitamins in selected canned vegetables. *Eur Food Res Technol*. 2001;212:182-7.
18. Amaro Lopez M, Moreno Rojas R, Zurera Cosano G. Mineral composition of frozen green asparagus. *Eur Food Res Technol*. 2004;219:260-4.
19. Australian Asparagus. The official website of the Australian Asparagus Council. <http://www.asparagus.com.au/> (25.2.2014).
20. Negi JS, Singh P, Joshi GP, Rawat MS, Bisht: WK. Chemical constituents of *Asparagus* *Pharmacogn Rev*. 2010;4(8):215-20.
21. Deli J, Matus Z, Toth G. Carotenoid composition in the fruits of *Asparagus officinalis*. *J Agric Food Chem*. 2000;48(7):2793-6.
22. Vinson JA, Hao Y, Su X, Zubik L. Phenol antioxidant quantity and quality in foods: Vegetables. *J Agric Food Chem*. 1998;46:3630-4.
23. Sun T, Powers JR, Tang J. Evaluation of the antioxidant activity of asparagus broccoli and their juices. *Food Chemistry*. 2007;105:101-6.
24. Wilfort R. Ljekovito bilje i njegova upotreba. 2. izd., Zagreb: Mladost, 1978, str. 80-82.

Saponin protodioscin is contained in the asparagus as much as 0.01% and possesses a potent cytotoxic effect on many types of tumor cells which has an effect on androgen levels. Diosgenin, another type of saponin, contributes to the reduction of secretion of total cholesterol and LDL-cholesterol, but not HDL-cholesterol. Preliminary results of the trial show that rutin and quercetin potentially reduce the incidence of colon cancer in experimental animals.<sup>32</sup>

In prevention of cardiovascular disease, it is extremely important to introduce adequate amounts of fruit, vegetables and fish in the diet, and limit the intake of salt, reduce the consumption of saturated fats and refined sugars. Consumption of asparagus contributes to the diversity of the diet, increase in consumption of vegetables and acquiring healthy eating habits.



## Conclusion

Cardiovascular diseases are the leading cause of death and in hospital treatment in the Republic of Croatia. An unbalanced diet is one of the most important risk factors for their development along with hypertension, smoking and low physical activity. A balanced intake of food and the variety of foodstuff as the foundation of proper nutrition includes eating at least three meals of vegetables a day.

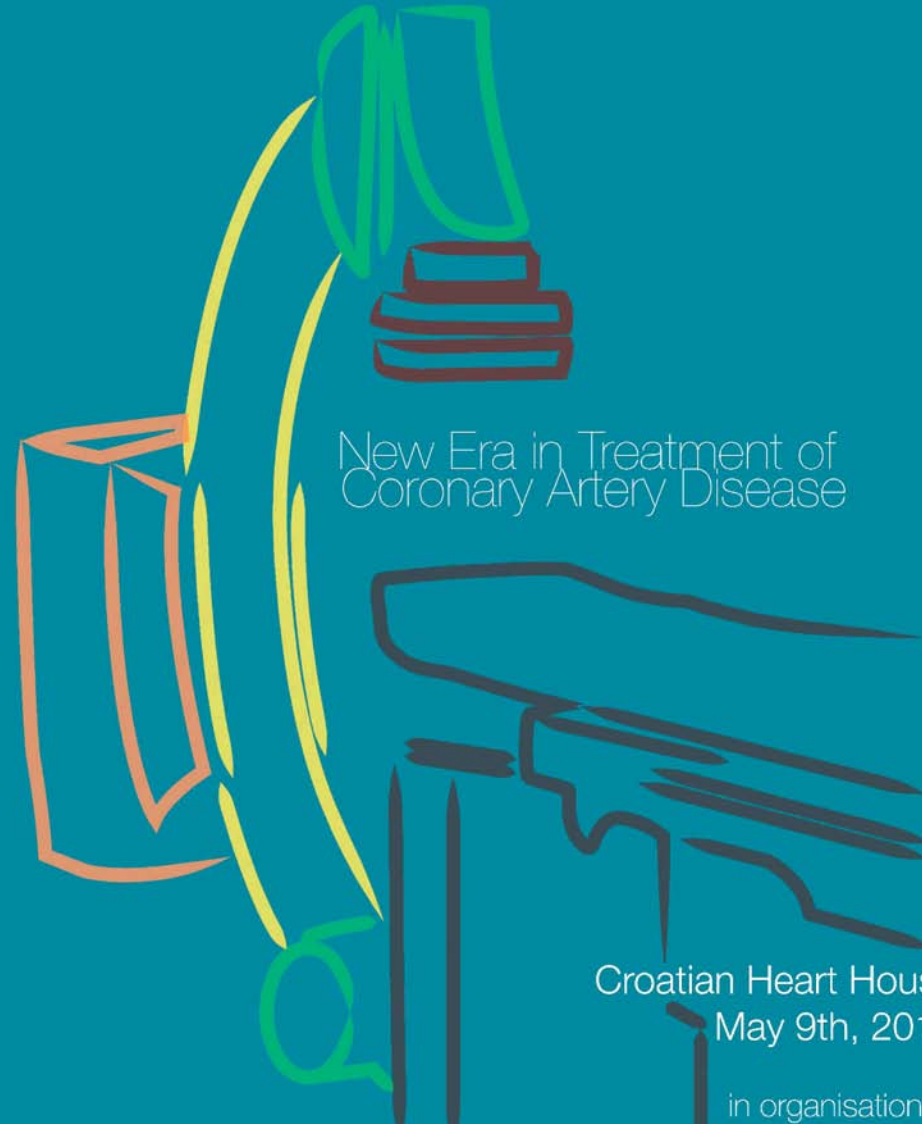
Asparagus is a vegetable that owes excellent composition of vitamins, minerals and phytonutrients, high antioxidant capacity, low calorie value contribute to the prevention of cardiovascular diseases and general health. Although a positive impact of asparagus on cardiovascular health has been confirmed, more trials addressing that topic are expected to be conducted in the future.

25. Mateljan G. The world's healthiest foods: essential guide for the healthiest way of eating. GMF Publishing; 2007, pp. 120-7.
26. Joshipura KJ, Hu FB, Manson JE, et al. The effect of fruit and vegetable intake on risk for coronary heart disease. *Ann Intern Med.* 2011;134(12):1106-114.
27. Alonso A, de la Fuente C, Martín-Armau AM, de Irala J, Martínez JA, Martínez-González MA. Fruit and vegetable consumption is inversely associated with blood pressure in a Mediterranean population with a high vegetable-fat intake: the Seguimiento Universidad de Navarra (SUN) Study. *Br J Nutr.* 2004;92(2):311-9.
28. Sanae M, Yasuo A. Green asparagus (*Asparagus officinalis*) prevented hypertension by an inhibitory effect on angiotensin converting enzyme activity in the kidney of spontaneously hypertensive rats. *J Agric Food Chem.* 2013;61(23):5520-5.
29. Motoki S, Kitazawa H, Maeda T, et al. Effects of various asparagus production methods on rutin and protodioscin contents in spears and cladophylls. *Biosci Biotechnol Biochem.* 2012;76:1047-50.
30. Nishimura M, Ohkawara T, Kagami-Katsuyama H, Sato H, Nishihira J. Improvement of blood pressure, glucose metabolism, and lipid profile by the intake of powdered asparagus bottom-stems and cladophylls. *J Tradit Complement Med.* 2013;3:250-5.
31. Visavadiya, NP, Narasimhacharya AVR. Asparagus root regulates cholesterol metabolism and improves antioxidant status in hypercholesteremic rats. *eCAM.* 2009;6(2):219-26.
32. Chin CK, Garrison SA. Functional elements from asparagus for human health. *Acta Hort. (ISHS)* 776:219-26.

Sveti Duh Cardiology Cath Lab's 10th Anniversary

# Drugs on Devices



New Era in Treatment of  
Coronary Artery Disease

Croatian Heart House  
May 9th, 2014

in organisation of  
University Hospital Sveti Duh  
Croatian Cardiac Society

# Suvremeno liječenje arterijske hipertenzije fiksnom kombinacijom telmisartan-hidroklorotiazid

## *Contemporary treatment of hypertension by fixed-dose combination of telmisartan-hydrochlorothiazide*

Goran Krstaić\*

Poliklinika za prevenciju kardiovaskularnih bolesti i rehabilitaciju, Zagreb, Hrvatska  
*Institute for Cardiovascular Prevention and Rehabilitation, Zagreb, Croatia*

**SAŽETAK:** Fiksna kombinacija telmisartana i hidroklorotiazida predstavlja još jednu suvremenu mogućnost učinkovitog liječenja arterijske hipertenzije. To je kombinacija antagonista receptora angiotenzina II, telmisartana i tiazidskog diuretika, hidroklorotiazida. Telmisartan smanjuje kardiovaskularni rizik ne samo smanjenjem vrijednosti arterijskog tlaka (AT), nego i smanjenjem drugih metaboličkih parametara koji imaju pozitivan učinak na srčanožilne bolesti, primjerice selektivna modulacija PPAR- $\gamma$ . Hidroklorotiazid ima učinak na renalne tubularne mehanizme reapsorpcije elektrolita, izravno povećavajući ekskreciju natrija i klorida u približno jednakim količinama. Različite kombinacije telmisartana i hidroklorotiazida (40/12,5; 80/12,5 i 80/25 mg) se primjenjuju u liječenju arterijske hipertenzije odraslih osoba čiji AT nije dobro kontroliran uz primjenu samog telmisartana ili kod bolesnika koji su prethodno stabilizirani telmisartanom i hidroklorotiazidom davanim zasebno.

**KLJUČNE RIJEČI:** telmisartan, hidroklorotiazid, arterijska hipertenzija, arterijski tlak, kardiovaskularni rizik.

**SUMMARY:** Fixed-dose combination of telmisartan and hydrochlorothiazide is another contemporary option of effective treatment of hypertension. It is a combination of an angiotensin II receptor blocker, telmisartan and thiazide diuretic, hydrochlorothiazide. Telmisartan reduces cardiovascular risk not only by reducing blood pressure (BP), but also by reducing other metabolic parameters that have a positive effect on cardiovascular diseases, especially selective modulation of PPAR- $\gamma$ . Hydrochlorothiazide has an effect on the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equal amounts. Different combinations of telmisartan and hydrochlorothiazide (40/12,5; 80/12,5 and 80/25 mg) are used in the treatment of hypertension in adults whose BP is not well controlled by using telmisartan alone or in patients who have been previously stabilized by telmisartan and hydrochlorothiazide administered separately.

**KEYWORDS:** telmisartan, hydrochlorothiazide, hypertension, blood pressure, cardiovascular risk.

**CITATION:** *Cardiol Croat.* 2014;9(3-4):150-153.

Fiksna kombinacija telmisartana i hidroklorotiazida predstavlja još jednu suvremenu mogućnost učinkovitog liječenja arterijske hipertenzije.<sup>1</sup> To je kombinacija antagonista receptora angiotenzina II, telmisartana i tiazidskog diuretika, hidroklorotiazida. Obje tvari pomažu u kontroli povišenog arterijskog tlaka (AT).

Telmisartan pripada skupini lijekova koji se nazivaju antagonisti receptora angiotenzina II. Angiotenzin II je tvar koja se proizvodi u organizmu, a dovodi do sužavanja krvnih žila i na taj način povišenja AT. Telmisartan blokira učinak angiotenzina II tako što opušta krvne žile i snižava AT. Hidroklorotiazid pripada skupini lijekova koji se nazivaju tiazidski diuretici koji uzrokuju povećano izlučivanje urina, što također dovodi do snižavanja AT.

Kombinacija ovih sastojaka ima aditivni antihipertenzivni učinak koji snižava AT u većoj mjeri nego što to čini svaka

Fixed-dose combination of telmisartan and hydrochlorothiazide is another contemporary option of effective treatment of hypertension.<sup>1</sup> It is a combination of an angiotensin II receptor blocker, telmisartan and thiazide diuretic, hydrochlorothiazide. The both substances help to control high blood pressure (BP).

Telmisartan belongs to a group of angiotensin II receptor blockers. Angiotensin II is a substance produced in the body, leading to the narrowing of the blood vessels, thereby elevating BP. Telmisartan blocks the effect of angiotensin II so that it relaxes blood vessels and lowers BP. Hydrochlorothiazide belongs to a group of thiazide diuretics, which cause increased urine output, which also leads to lowering BP.

The combination of these ingredients has an additive antihypertensive effect, which lowers BP to a greater extent than what every component does separately. Dosing once a day

od komponenti zasebno. Doziranje jedanput dnevno dovodi do učinkovitog i ujednačenog sniženja AT u rasponu terapijskih doza.

Telmisartan je dugotrajno oralno učinkovit i specifičan jaki antagonist receptora angiotenzina II (AT1) pri čemu ne pokazuje parcijalnu agonističku aktivnost na AT receptore. On ne pokazuje niti afinitet za druge receptore, uključujući AT2 i druge manje karakteristične AT receptore. Vrijednosti aldosterona u plazmi se smanjuju uzimanjem telmisartana. Telmisartan ne inhibira renin u ljudskoj plazmi niti blokira ionske kanale. Također on ne inhibira enzim koji pretvara angiotenzin (kininaza II), pa ne dolazi do degradiranja bradikina i sukladno tome nema pojačavanja nuspojava posredovanih bradikininom. Učestalost suhog kašlja je znatno niža kod bolesnika liječenih telmisartanom nego kod onih kojima su davani inhibitori angiotenzin konvertirajućeg enzima, sukladno rezultatima kliničkih ispitivanja koja izravno uspoređuju ova dva antihipertenzivna liječenja.<sup>2,3</sup>

Doza od 80 mg telmisartana primjenjena u zdravih pojedina gotovo u potpunosti inhibira povišenje AT uzrokovano angiotenzinom II. Inhibitorski učinak se održava tijekom 24 sata i može se objektivizirati i do 48 sati. Nakon prve doze telmisartana, antihipertenzivna aktivnost postupno postaje vidljiva unutar 3 sata. Maksimalno smanjenje AT se općenito postiže za 4-8 tjedana nakon početka liječenja te se održava tijekom dugotrajnog liječenja. Antihipertenzivni učinak zadržava se neprekidno tijekom 24 sata nakon doziranja te uključuje posljednja 4 sata prije sljedeće doze, kao što je pokazano kontinuiranim mjerenjima AT.

Kod bolesnika s hipertenzijom telmisartan snižava sistolički i dijastolički AT bez utjecaja na srčanu frekvenciju. Antihipertenzivna djelotvornost telmisartana usporediva je s djelotvornošću antihipertenziva koji spadaju u druge skupine primjerice s amlodipinom (blokator kalcijevih kanala), atenololom (blokator beta-receptora), enalaprilom (ACE inhibitor) ili hidroklorotiazidom (tijazidski diuretik).<sup>4</sup> Nakon naglog prekida liječenja telmisartanom AT se postupno vraća na vrijednosti prije liječenja tijekom perioda od nekoliko dana, bez objektivizacije tzv. naglog povratnog fenomena visokog AT. U kliničkoj studiji ONTARGET dokazano je da je telmisartan jednako učinkovit kao i ramipril u smanjenju kardiovaskularnih događaja kod različitih skupina rizičnih krvožilnih bolesnika, uz bolju podnošljivost.<sup>5</sup>

Telmisartan smanjuje kardiovaskularni rizik ne samo smanjenjem vrijednosti AT, nego i smanjenjem drugih metaboličkih parametara koji imaju pozitivan učinak na srčanožilne bolesti, primjerice selektivnu modulaciju PPAR- $\gamma$ . To podrazumijeva sposobnost aktivacije ovog intracelularnog receptora koji je glavni regulator metabolizma lipida i ugljikohidrata odnosno regulator diferencijacije masnih stanica što ga čini jedinstvenim unutar skupine ARB. Aktivatori PPAR- $\gamma$  imaju antiinflamacijske, antioksidativne i antiproliferatorne učinke na vaskularne stanice. To uzrokuje boljitak učinka na metabolizam glukoze i lipida, što je posebice korisno kod bolesnika s arterijskom hipertenzijom i/ili metaboličkim sindromom odnosno u procesu smanjenja rizika od ateroskleroze.<sup>6</sup> Telmisartan je jedini ARB s indikacijom smanjenja rizika od krvožilnih događaja.

Hidroklorotiazid je tijazidski diuretik. Tijazidi imaju učinak na renalne tubularne mehanizme reapsorpcije elektrolita, izravno povećavajući ekskreciju natrija i klorida u približno jednakim količinama. Diuretsko djelovanje hidroklorotiazida reducira volumen plazme, povećava aktivnost renina u plazmi, povećava sekreciju aldosterona s posljedičnim povećanjem gubitka kalija i bikarbonata urinom te smanjenjem kalija u

leads to an efficient and uniform BP reduction in the therapeutic dose range.

Telmisartan is a long-term orally efficient and specific potent antagonist of the angiotensin II receptor (AT1) where it does not show partial agonist activity on the AT receptors. It shows no affinity for other receptors, including AT2 and other less characterized AT receptors. Aldosterone levels in plasma are reduced by taking telmisartan. Telmisartan neither inhibits renin in human plasma nor does it block ion channels. Also it does not inhibit angiotensin converting enzyme (kininase II), so no degradation of bradykinin is caused, and accordingly there is no enhancement of side effects mediated by bradykinin. The incidence of dry cough was significantly lower in patients treated with telmisartan than in those who were administered angiotensin converting enzyme according to the results of clinical trials that directly compare these two antihypertensive treatment methods.<sup>2,3</sup>

Dose of 80 mg of telmisartan administered to healthy volunteers almost completely inhibit BP elevation caused by angiotensin II. The inhibitory effect is maintained during 24 hours and can be objectified up to 48 hours. After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction of BP is generally achieved in 4-8 weeks after the start of treatment and is maintained during long-term treatment. The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose, as shown by continuous measurements of BP.

Telmisartan reduces systolic and diastolic BP in patients with hypertension without affecting the heart rate. Antihypertensive efficacy of telmisartan is comparable to the efficacy of antihypertensive agents that belong to some other groups for instance with amlodipine (calcium channel blocker), atenolol (beta-receptor blocker), enalapril (ACE inhibitor) or hydrochlorothiazide (thiazide diuretic).<sup>4</sup> Following abrupt cessation of the treatment with telmisartan, BP gradually returns to the pre-treatment values over a period of several days, without the objectification of the so-called rapid return of the phenomenon of high BP. The clinical study ONTARGET demonstrated that telmisartan is as efficient as ramipril in reducing cardiovascular events in different groups of high-risk cardiovascular patients with better tolerability.<sup>5</sup>

Telmisartan reduces cardiovascular risk not only by reducing blood pressure (BP), but also by reducing other metabolic parameters that have a positive effect on cardiovascular diseases, especially selective modulation of PPAR- $\gamma$ . This implies the ability of activation of this intracellular receptor which is a major regulator of lipid and carbohydrate metabolism, that is, the regulator of differentiation of fat cells which makes it unique within the ARB group. Activators of PPAR- $\gamma$  have antiinflammatory, antioxidant and antiproliferative effects on vascular cells. This causes the benefit of effect on glucose and lipid metabolism, which is especially useful in patients with arterial hypertension and/or metabolic syndrome or in the process of reducing the risk of atherosclerosis.<sup>6</sup> Telmisartan is the only ARB with an indication of reducing the risk of cardiovascular events.

Hydrochlorothiazide is a thiazide diuretic. Hydrochlorothiazide drugs have an effect on the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equal amounts. Diuretic action of hydrochlorothiazide reduces plasma volume, increases the renin activity in plasma, increases aldosterone secretion with consequential increase in the loss of potassium and bicarbonate in urine and decrease in potassium in

serumu. Pretpostavlja se da putem blokade sustava renin-angiotenzin-aldosteron istodobna primjena telmisartana ima tendenciju poništavanja gubitka kalija povezanog s tiazidnim diureticima. Uz hidroklorotiazid početak diureze javlja se za oko 2 sata, a vršni učinak pojavljuje se nakon otprilike 4 sata, dok se djelovanje zadržava oko 6-12 sati. Epidemiološke studije pokazale su da dugotrajno liječenje hidroklorotiazidom reducira rizik od kardiovaskularne smrtnosti i morbiditeta.

serum. The presumption is that by the renin-angiotensin-aldosterone blocking, the concomitant use of telmisartan has a tendency to annul the potassium loss associated with the thiazide diuretics. With hydrochlorothiazide, the onset of diuresis occurs in about 2 hours, and the peak effect occurs after approximately 4 hours, while the action persists for approximately 6-12 hours. Epidemiological studies have shown that long-term treatment by hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

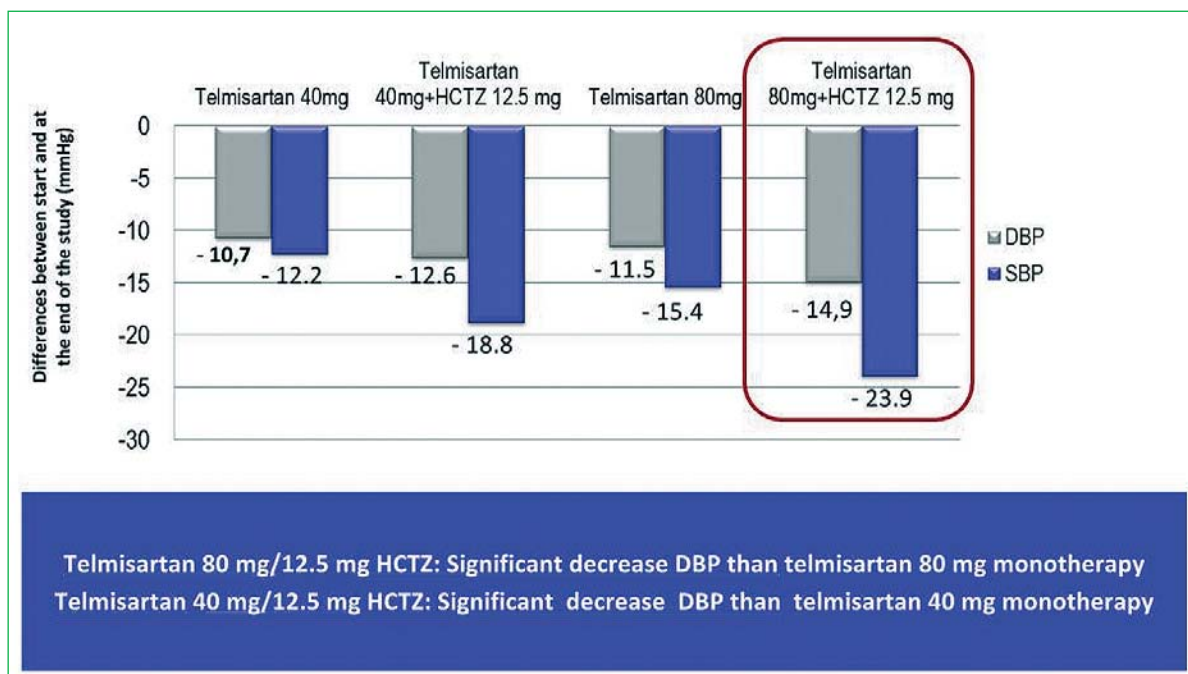


Figure 1. Combination of telmisartan/hydrochlorothiazide gives the better antihypertensive effect than monotherapy.

Kombinacija telmisartana i hidroklorotiazida (40/12,5; 80/12,5 i 80/25mg) se primjenjuje u liječenju esencijalne hipertenzije kod odraslih osoba čiji AT nije dobro kontroliran uz primjenu samog telmisartana ili kod bolesnika koji su prethodno stabilizirani telmisartanom i hidroklorotiazidom davanim zasebno.<sup>7</sup>

Nakon intravenske i peroralne primjene 14C označenog telmisartana većina primijenjene doze (>97 %) eliminira se fecesom putem bilijarne ekskrecije. Samo su minorne količine pronađene u urinu. Ukupni plazmatski klirens telmisartana nakon peroralne primjene je >1.500 ml/min. Poluvrijeme eliminacije je >20 sati. Hidroklorotiazid se izlučuje gotovo u potpunosti u nepromijenjenom obliku putem urina. Oko 60% oralne doze se eliminira unutar 48 sati. Renalni klirens je oko 250-300 ml/min. Poluvrijeme eliminacije hidroklorotiazida je 10-15 sati. Koncentracije telmisartana u plazmi su općenito 2-3 puta veće kod žena nego kod muškaraca. Međutim, u kliničkim ispitivanjima nisu pronađena značajna povećanja u odgovoru AT ili incidenciji ortostatske hipotenzije kod žena.<sup>8</sup> Nije potrebno prilagođavanje doze. Postojao je trend prema većim koncentracijama hidroklorotiazida u plazmi kod žena nego kod muškaraca što se ne smatra klinički značajnim.

U dvostruko-slijepom kontroliranom kliničkom ispitivanju (djelotvornost ocjenjivana na n = 687 bolesnika) kod osoba koje nisu reagirale na kombinaciju 80 mg / 12,5 mg, pokazao se inkrementalni učinak snižavanja AT kombinacije 80

Different combinations of telmisartan and hydrochlorothiazide (40/12.5; 80/12.5 and 80/25 mg) are used in the treatment of essential hypertension in adults whose BP is not well controlled by using telmisartan alone or in patients who have been previously stabilized by telmisartan and hydrochlorothiazide administered separately.<sup>7</sup>

After intravenous or oral administration of 14C labeled telmisartan most of the administered dose (>97%) is eliminated by the faeces by biliary excretion. Only minor amounts were found in urine. Total plasma clearance of telmisartan after oral administration is >1,500 ml/min. Elimination half-life is >20 hours. Hydrochlorothiazide is excreted almost entirely in unchanged form in the urine. About 60% of the oral dose is eliminated within 48 hours. Renal clearance is about 250-300 ml/min. Elimination half-life of hydrochlorothiazide is 10-15 hours. The concentrations of telmisartan in plasma are generally 2-3 times higher in women than in men. However, clinical studies have not found significant increases in response to BP or the incidence of orthostatic hypotension in women.<sup>8</sup> No dosage adjustment is necessary. There was a trend toward higher concentrations of hydrochlorothiazide in plasma in women than in men, which is not considered clinically significant.

Double-blind controlled clinical trial (efficacy was evaluated on n = 687 patients) in persons who have not responded to the 80/12.5 mg combination, showed the incremental effect of lowering BP by 80/25 mg combination compared to con-



mg / 25 mg u odnosu na stalno liječenje s kombinacijom 80 mg / 12,5 mg, u vrijednosti 2,7/1,6 mmHg (SKT/DKT) (razlika u prilagođenim prosječnim promjenama u odnosu na početnu vrijednost). U ispitivanju praćenja, s kombinacijom 80 mg / 25 mg, AT se nastavio snižavati (što je rezultiralo ukupnim smanjenjem od 11,5/9,9 mmHg (SKT/DKT)).<sup>9</sup>

Telmisartan i kombinacija telmisartan/hidroklorotiazid imaju niski potencijal za interakcije s drugim lijekovima. Telmisartan se ne metabolizira putem citokromskog P 450 sustava, dok se hidroklorotiazid poglavito ne metabolizira i gotovo u potpunosti se izlučuje putem bubrega u obliku nepromijenjene tvari.<sup>8</sup>

U konačnici možemo kazati da na hrvatsko tržište u portfelju Krke dolazi još jedna dobra nova vijest, spomenuta kombinacija telmisartana i hidroklorotiazida, pod nazivom Tolucombi® i to u tri doze u rasponu od 40/12,5 mg, preko 80/12,5 mg do 80/25 mg od kojih se može očekivati učinkovito liječenje arterijske hipertenzije.

tinuous treatment with 80/12.5 mg combination, evaluated at 2.7/1.6 mmHg (SBP/DBP) (difference in adjusted mean changes compared to the baseline). BP continued to be lowered in follow-up by the 80/25 mg combination (which resulted in a total reduction of 11.5/9.9 mmHg (SBP/DBP)).<sup>9</sup>

Telmisartan and the telmisartan/hydrochlorothiazide combination have a low potential for interactions with other drugs. Telmisartan is not metabolized via cytochrome P 450 system, while hydrochlorothiazide is particularly not metabolized and is almost completely excreted by the kidneys in the form of an unchanged substance.<sup>8</sup>

In the end we can say that there is another good news that comes to the Croatian market, namely, the above mentioned telmisartan and hydrochlorothiazide combination, called Tolucombi® in three doses in the range of 40/12.5 mg, via 80/12.5 mg to 80/25 mg which can be expected to efficiently treat hypertension.

Received : 6<sup>th</sup> Mar 2014; Accepted 15<sup>th</sup> Mar 2014

Poliklinika za prevenciju kardiovaskularnih bolesti i rehabilitaciju, Draškovićeva 13, HR-10000 Zagreb, Croatia.

Phone: +385-1-4612-290

Fax: +385-1-4612-343

E-mail: [goran.krstacic@zg.t-com.hr](mailto:goran.krstacic@zg.t-com.hr)

## Literature

1. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypert*. 2013;31:1281-357.
2. Battereshill AJ, Scott LJ. Telmisartan: a review of its use in the management of hypertension. *Drugs*. 2006;66(1):51-83.
3. Primožič A, Knavs-Vrhunec P, Barbič-Žagar B. Suvremeno liječenje arterijske hipertenzije telmisartanom. *Cardiol Croat*. 2013;8(10-11):380-2.
4. Lacourciere Y, Lenis J, Orchard R, et al. A comparison of the efficacies and duration of action of the angiotensin II receptor blockers telmisartan and amlodipine. *Blood Press Monit*. 1998;3:295-302.
5. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547-9.
6. Schupp M, Janke J, Clasen R, Unger T, Kintscher U. Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. *Circulation*. 2004;109:2054-7.
7. McGill JB, Reilly PA. Telmisartan plus hydrochlorothiazide versus telmisartan or hydrochlorothiazide monotherapy in patients with mild to moderate hypertension: a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. *Clin Therap*. 2001;(27):833-50.
8. Schumacher H, Mancia G. The safety profile of telmisartan as monotherapy or combined with hydrochlorothiazide. A retrospective analysis of 50 studies. *Blood Press Suppl*. 2008;1:32-40.
9. Kjeldsen SE, Schmieder RE, Unger T, Mancia G. Telmisartan and hydrochlorothiazide combination therapy for the treatment of hypertension. *Curr Med Res Opin*. 2010;26(4):879-87.



Više od 10 milijuna bolesnika svakodnevno se liječi  
Krkinim kardiovaskularnim lijekovima (1)

cjelovit



protektivan



**Atordapin**<sup>®</sup>

amlodipin i atorvastatin

Filmom obložene tablete 5 mg/10 mg, 10 mg/10 mg

**NOVO!**  
Na Osnovnoj listi  
lijekova HZZO-a. (2)

Širok pogled, precizno djelovanje

**Naziv gotovog lijeka:** Atordapin 5 mg/10 mg filmom obložene tablete, Atordapin 10 mg/10 mg filmom obložene tablete. **Kvalitativni i kvantitativni sastav:** Jedna filmom obložena tableta sadrži 5 mg ili 10 mg amlodipina u obliku amlodipinbesilata i 10 mg atorvastatina u obliku atorvastatinkalcija. **Terapijske indikacije:** Atordapin je indiciran za sprječavanje kardiovaskularnih događaja u bolesnika koji boluju od hipertenzije te imaju tri prateća čimbenika kardiovaskularnog rizika, normanu do blago povišenu razinu kolesterola, bez klinički jasne koronarne bolesti srca u kojih se prikladnim smatra kombinirana primjena amlodipina i niske doze atorvastatina, u skladu s aktualnim smjernicama liječenja. Atordapin se smije primjenjivati kod nedostatnog odgovora na dijetu i druge nefarmakološke mjere. **Doziranje i način primjene:** Uobičajena početna doza je 5 mg/10 mg jednom na dan. Ako je bolesniku potrebna bolja kontrola krvnog tlaka, može se primjenjivati 10 mg/10 mg jednom na dan. Lijek se može primjenjivati u bilo koje doba dana, sa ili bez hrane. Atordapin se može primjenjivati sam ili u kombinaciji s antihipertenzivnim lijekovima, no ne smije se primjenjivati u kombinaciji s drugim blokatorom kalcijevih kanala kao ni s drugim statinom. Atordapin se primjenjuje kroz usta. **Kontraindikacije:** Atordapin je kontraindiciran u bolesnika koji su preosjetljivi na dihidropiridine, djelatne tvari amlodipin i atorvastatin ili na neku od pomoćnih tvari; imaju akutnu bolest jetre ili nerazjašnjeno trajno povećanje serumskih transaminaza koje premašuju vrijednosti 3 puta veće od gornje granice normale u trudnica i dojilji; bolesnika koji se istodobno liječe trakeozolom, ketokonazolom, telitromicinom, imaju tešku hipotenziju ili su u stanju šoka (uključujući kardiogeni šok); imaju opstrukciju izlaznog dijela lijeve klijetke (npr. visoki stupanj stenozе aorte); imaju hemodinamički nestabilno zatijevanje srca nakon akutnog infarkta miokarda. **Posebna upozorenja i mjere opreza pri uporabi:** Učinci na jetru: Pretrage jetrene funkcije moraju se obaviti prije početka liječenja, periodički nakon početka liječenja, kao i u bolesnika u kojih se razviju znak ili simptomi koji ukazuju na oštećenje jetre. U slučaju povećane razine transaminaza, potrebno je praćenje sve dok se vrijednosti ne vrate u granice normale. Zbog djelatne tvari atorvastatina, Atordapin se mora oprezno primjenjivati u bolesnika

koji konzumiraju značajne količine alkohola, u bolesnika s oštećenjem jetre (ili onih koji imaju bolest jetre u anamnezi). Učinci na poprečno-prugaste mišice: Kao i ostali inhibitori HMG-CoA reduktaze, atorvastatin može djelovati na poprečno-prugaste mišice te uzrokovati mišaljgu, miozitis i miopatiju koji rijetko mogu uznapredovati do rhabdomiolize, koju karakterizira značajno povišena razina kreatin fosfokinaze, CKP (> 10 puta viša od GGn), mioglobinemija i mioglobinurija, što može dovesti do zatajanja bubrega te u rijetkim slučajevima biti smrtonosno. Prije liječenja Atordapin se mora propisati s oprezom u bolesnika s predisponirajućim čimbenicima za razvoj rhabdomiolize. Ako su razine CKP znatno povišene (> 5 puta GGn) prije početka liječenja, liječenje se ne smije započeti. Nije preporučena kombinacija Atordapina i dantrolena (infuzija), gemfibrozila i drugih fibrata. Ne preporučuje se primjena atorvastatina u kombinaciji s fusidatnom kiselinom. Tijekom liječenja fusidatnom kiselinom može biti potrebno privremeno prekinuti liječenje atorvastatinom. **Nuspojave:** U kliničkim ispitivanjima amlodipina/atorvastatina nisu primijećeni štetni događaji koji bi bili neobični za ovu kombinaciju. Prijavljeni štetni događaji bili su oni koji su i ranije primijećeni kod amlodipina i/ili atorvastatina. Slijedeće nuspojave, česte i vrlo česte mogu se javiti u bolesnika koji uzimaju ovu kombinaciju: glavobolja, bolovi u abdomenu, crvenilo popraćeno osjećajem mržnje, hipotenzija, mučnina, dispneja, proljev, zatvor, nadutost, otečanje zglobova. **Način i mjesto izdavanja:** Lijek se izdaje na recept, u ljekarni. **Nositelj odobrenja za stavljanje gotovog lijeka u promet:** KRKA-FARMA, d.o.o., Radnička cesta 48, 10 000 Zagreb, Hrvatska. **Broj odobrenja za stavljanje gotovog lijeka u promet:** Atordapin 5 mg/10 mg filmom obložene tablete UPA-530-09/12-01/405; Atordapin 10 mg/10 mg filmom obložene tablete UPA-530-09/12-01/406. **Datum posljednje izmjene teksta:** veljača, 2014. Ovaj promotivni materijal sadrži podatke o lijeku koji su odgovarajući cjelokupnom odobrenom sažetku svojstava lijeka te cjelokupnoj odobrenoj uputi sukladno članku 15. Pravilnika o načinu oglašavanja o lijekovima i homeopatskim proizvodima (NN broj 118/09).

Samo za zdravstvene djelatnike. Za detaljnije informacije o lijeku, molimo, pročitati Sažetak opisa svojstava lijeka ili Uputu o lijeku.

Literatura: 1. ePharma market, CEGEDIM, IMS, Intellix, Medicube, PharmStandard, PharmaZoom 1-6 2013. 2. Osnovna lista lijekova HZZO-a, NN br. 9/2014.

Detaljnije informacije možete dobiti od tvrtke: KRKA-FARMA d.o.o., Radnička cesta 48/II, 10000 Zagreb, Telefon (01) 63 12 100, Faks (01) 61 76 739, E-mail: info.hr@krka.biz, www.krka-farma.hr

**KRKA**

Naša inovativnost i znanje posvećeni su zdravlju. Zbog toga naša odlučnost, ustrajnost i iskustvo zajedno doprinose jednom cilju – razvoju djelotvornih i neškodljivih proizvoda vrhunske kakvoće.



Atoris® - jedini atorvastatin dostupan u 6 različitih doza! (1)



ATORIS®  
nove doze,  
nove terapijske mogućnosti

# ATORIS®

filmom obložene tablete atorvastatin  
10 mg, 20 mg, 30 mg, 40 mg, 60 mg i 80 mg

**Sastav:** Svaka filmom obložena tableta sadrži 10 mg, 20 mg, 30 mg, 40 mg, 60 mg ili 80 mg atorvastatina u obliku atorvastatinkalcija. **Indikacije:** Hiperlipidemija. Prevencija kardiovaskularne bolesti. **Doziranje i način primjene:** Prije početka liječenja Atorisom bolesnik mora biti na dijeti za snižavanje koncentracije kolesterola u krvi, a dijetu mora nastaviti i tijekom terapije. Preporučena početna doza je 10 mg na dan, doza se može povećati do 80 mg. Lijek se uzima u jednokratnoj dozi u bilo koje doba dana, svaki dan u isto vrijeme. Može se uzeti nakon obroka ili natašte. Zamjetan odgovor na liječenje opaža se nakon dva tjedna liječenja, a najveći učinak postiže se nakon četiri tjedna. **Kontraindikacije:** preosjetljivost na bilo koji sastojak lijeka, aktivna bolest jetre, trajno povećane vrijednosti serumskih transaminaza triput veće od gornje granice normalnih vrijednosti (ULN-upper limit of normal), bolesti skeletnih mišića, trudnoća i dojenje. **Posebna upozorenja i mjere opreza pri uporabi:** Prije početka i tijekom liječenja nužno je provoditi testove jetrene funkcije. Bolesnike kojima se povise razine transaminaza treba nadzirati dok se poremećaji ne povuku. Ako porast transaminaza triput veći od gornje granice normalnih vrijednosti perzistira, preporučuje se smanjenje doze ili ukidanje Atorisa. Atoris treba koristiti s oprezom kod bolesnika koji konzumiraju veće količine alkohola i/ili su u prošlosti imali bolest jetre. Atorvastatin može uzrokovati mijalgiju, miozitis i miopatiju, što može napredovati do rhabdomiolize, koja može ugroziti život, obilježena izrazito povišenim razinama CPK (>10 puta ULN), mioglobinemijom i mioglobinurijom koja može dovesti do zatajenja bubrega. Ovaj lijek sadržava laktazu. **Nuspojave:** Manje od 2% bolesnika prekinulo je sudjelovanje u kliničkim ispitivanjima zbog nuspojava koje su pripisane atorvastatinu. Najčešće nuspojave (>1%) uključuju nesanicu, glavobolju, konstipaciju, proljev,

flatulenciju, mučninu, dispneju i abdominalnu bol, mijalgiju i asteniju. **Način izdavanja:** Izdaje se na recept. **Ime i adresa nositelja odobrenja za stavljanje lijeka u promet:** Krka-farma d.o.o., Radnička cesta 48, 10000 Zagreb, Hrvatska. **Broj odobrenja za stavljanje lijeka u promet:** Atoris® 10 mg tablete: UPI/I-530-09/04-01/132 (830x10 mg) – UPI/I-530-09/07-01/309 (60x10 mg) – UPI/I-530-09/07-01/310 (90x10 mg), Atoris® 20 mg tablete: UPI/I-530-09/04-01/133 (30x20 mg) – UPI/I-530-09/07-01/311 (60x20 mg) – UPI/I-530-09/07-01/312 (90x20 mg), Atoris® 40 mg tablete: UPI/I-530-09/05-01/1073 (30x40 mg); Atoris 30 mg filmom obložene tablete: UPI/I-530-09/11-01/156, Atoris 60 mg filmom obložene tablete: UPI/I-530-09/11-01/157, Atoris 80 mg filmom obložene tablete: UPI/I-530-09/11-01/158. **Datum prvog odobrenja za stavljanje gotovog lijeka Atoris 30 mg tablete, Atoris 60 mg tablete i Atoris 80 mg tablete u promet:** 12.06.2013. **Datum obnove odobrenja za stavljanje gotovog lijeka Atoris® 10 mg tablete, Atoris® 20 mg tablete, Atoris® 40 mg tablete u promet:** 30.12.2009.

Ovaj promotivni materijal sadržava bitne podatke o lijeku koji su istovjetni cjelokupnom odobrenom sažetku opisa svojstava lijeka te cjelokupnoj odobrenoj uputi u skladu s člankom 15. Pravilnika o načinu oglašavanja o lijekovima i homeopatskim proizvodima (NN broj 118/2009).

#### Literatura:

1. Narodne novine br. 47 od 19. travnja 2013.

Sama za zdravstvene djelatnike.

Telefon (01) 63 12 100, Telefaks (01) 61 76 739,  
E-mail: info.hr@krka.biz, www.krka-farma.hr

Detaljnije informacije možete dobiti od firme:

Krka-Farma d.o.o., Radnička 48/1, p.p. 205, 10000 Zagreb, Croatia



Naša inovativnost i znanje posvećeni su zdravlju. Zbog toga naša odlučnost, ustrajnost i iskustvo zajedno doprinose jednom cilju – razvoju djelotvornih i neškodljivih proizvoda vrhunske kakvoće.



Krka je vodeći proizvođač sartana na tržištima  
Srednje, Istočne i Jugoistočne Europe. (1)

**Više od  
24 sata...**

**Tolura®**

telmisartan  
tablete 40 mg, 80 mg

**Tolucombi®**

telmisartan i hidroklorotiazid  
tablete 40 mg/12,5 mg, 80 mg/12,5 mg i 80 mg/25 mg

**NOVO**

Na Osnovnoj listi  
lijekova – bez nadoplate! (2)



NEW MEDICINE FOR BLOOD PRESSURE CONTROL

7:00

NEWS

**DOBRE VIJESTI SVAKI DAN**

**Naziv lijeka:** Tolura® 40 mg tablete, Tolura® 80 mg tablete, Tolucombi® 40 mg/12,5 mg tablete, Tolucombi® 80 mg/12,5 mg tablete, Tolucombi® 80 mg/25 mg tablete. **Sastav:** Svaka Tolura tableta sadrži 40 mg telmisartana ili 80 mg telmisartana. Svaka Tolucombi tableta sadrži 40 mg telmisartana i 12,5 mg hidroklorotiazida ili 80 mg telmisartana i 12,5 mg hidroklorotiazida ili 80 mg telmisartana i 25 mg hidroklorotiazida. **Indikacije:** Tolura: liječenje esencijalne hipertenzije u odraslih osoba. **Kardiovaskularna prevencija** koja podrazumijeva smanjenje kardiovaskularnog morbiditeta i odraslih osoba s manifestnom aterosklerotičkom kardiovaskularnom bolešću (koronarna bolest srca, miokardni udar, periferna arterijska bolest) i dijabetes melitusom tip 2 s dokazanim oštećenjem ciljnih organa. **Tolucombi:** liječenje esencijalne hipertenzije kod odraslih bolesnika čiji se krvni tlak ne može adekvatno kontrolirati samo telmisartanom. **Doziranje i način uporabe:** Tolura: Esencijalna hipertenzija: uobičajena učinkovita doza je 40 mg jednom dnevno. U slučajevima gdje nije postignuta ciljna vrijednost tlaka, doza telmisartana može se povisiti na maksimalno 80 mg jednom dnevno. **Kardiovaskularna prevencija:** preporučena doza je 80 mg jednom dnevno. U bolesnika s bubrežnim oštećenjem preporučuje se početna doza od 20 mg i nije potrebno prilagođavati doziranje u bolesnika s blagim do umjerenim oštećenjem bubrega. U bolesnika s blagim do umjerenim oštećenjem jetre doza ne smije prelaziti 40 mg jednom dnevno. U starijih bolesnika nije potrebno prilagođavati doziranje. **Tolucombi:** namijenjen bolesnicima čiji se krvni tlak ne može adekvatno kontrolirati samo telmisartanom. Tolucombi tablete 40 mg/12,5 mg ili 80 mg/12,5 mg ili 80 mg/25 mg se primjenjuju jedanput dnevno. Tolura ili Tolucombi tablete primjenjuju se personalno jednom dnevno i trebaju se uzimati s tekućinom, sa ili bez hrane. **Kontraindikacije:** Preosjetljivost na djelatnu tvar ili neku od pomoćnih tvari, preosjetljivost na druge derivate sulfonamida (s obzirom da je hidroklorotiazid derivat sulfonamida), trudno i drugo tromjesečno do šest mjeseci trudnoće, kolestaza i bilijarni opstruktivni poremećaji, teško oštećenje jetrene funkcije, teško oštećenje bubrežne funkcije (klirens kreatinina <30 ml/min), refraktorna hipokalemija, hiperkalcemija. Istodobna primjena telmisartana s aliskirenom kontraindicirana je u bolesnika s dijabetes melitusom ili oštećenjem bubrega (brzina glomerularne filtracije (GFR) <60 ml/min/1,73 m<sup>2</sup>). **Posebna upozorenja i posebne mjere opreza pri uporabi:** Primjena antagonista receptora angiotenzina II ne smije započinjati tijekom trudnoće. Kada se utvrdi trudnoća, liječenje antagonistima receptora angiotenzina II mora se trenutno prekinuti te, ako je potrebno, započeti s primjenom drugog lijeka. Tolura se treba primjenjivati oprezno u bolesnika s blagim do umjerenim oštećenjem jetre. Postoji povećani rizik od teške hipotenzije i lizurije u bolesnika s bilateralnom stenozom bubrežne arterije ili stenozom arterije jednog funkcionalnog bubrega. Kada se Tolura primjenjuje u bolesnika s poremecenom funkcijom bubrega, preporučuje se povremeno pratiti vrijednost kalija i kreatinina u serumu. U bolesnika s deplecijom volumena (ili natrija zbog snažne terapije diureticima, prehrane s ograničenim unosom soli, proljeva ili povraćanja) može se pojaviti simptomatska hipotenzija. Takva stanja moraju se korigirati prije primjene Tolure. Dvostruka blokada sustava RAAS (sustav renin-angiotenzin-aldosteron) primjenom telmisartana s drugim blokatorima RAAS, ne preporučuje se. U bolesnika s primarnim aldosteronizmom ne preporučuje se primjena telmisartana. Potreban je

poseban oprez u bolesnika koji imaju aortalnu ili mitralnu stenozu ili opstruktivnu hipertrofičnu kardiomiopatiju. Terapija tiazidima može narušiti toleranciju glukoze. U bolesnika s dijabetesom kod liječenja telmisartanom može se pojaviti hipoglikemija, stoga, u ovih bolesnika treba adekvatno kontrolirati glukozu u krvi. Preporučuje se pažljivo pratiti kalij u serumu rizičnih bolesnika. Bolesnici s rijetkim nasljednim poremećajem nepodnošenja fruktoze ne bi trebali uzimati Toluru. Bolesnici s rijetkim nasljednim poremećajima nepodnošenja galaktoze, nedostatkom Lapp laktaze ili glukoza-galaktoza malapsorpcijom ne bi trebali uzimati Toluru ili Tolucombi. Tolucombi se mora primjenjivati s oprezom kod bolesnika s oštećenom jetrenom funkcijom ili progresivnom bolešću jetre, s obzirom da manje promjene u ravnoteži tekućine i elektrolita mogu dovesti do hepatičke kome. Izkustvo s lijekom Tolucombi je skromno kod bolesnika s blagim do umjerenim oštećenjem bubrega, stoga se preporučuje periodično praćenje serumskih vrijednosti kalija, kreatinina i mokraćne kiseline. Hidroklorotiazid, koji je sulfonamid, može uzrokovati idiosinkratičnu reakciju uzrokujući akutnu prolaznu mioipiju i akutni glaukom zatvorenog kuta. **Nuspojave:** U kontroliranim kliničkim ispitivanjima ukupna učestalost nuspojava u bolesnika s hipertenzijom bila je usporediva placebom. Prikupljene nuspojave iz kontroliranih kliničkih ispitivanja i iz podataka prikupljenih nakon stavljanja lijeka u promet su manje česte ili rijetke. Manje česte nuspojave su: infekcije mokraćnog sustava, infekcije gornjeg dišnog sustava, anemija, hiperkalemija, nesanicna, depresija, sinkopa, vrtoglavica, bradikardija, hipotenzija, ortostatska hipotenzija, dispneja, kašalj, abdominarna bol, proljev, dispepsija, flatulencija, povraćanje, pruritus, hipohidроза, oteplj, bol u leđima, grčevi mišića, malajija, oštećenje bubrega, bol u prsima, otežnja (duboki). Hidroklorotiazid može uzrokovati hipovolemiju što može dovesti do neravnoteže elektrolita. **Način i mjesto izdavanja:** Lijek se izdaje na liječnički recept, u ljekarni. **Ime i adresa nositelja odobrenja za stavljanje lijeka u promet:** KRKA, d.d., Novo mesto, Smarjska cesta 6, 8501 Novo mesto, Slovenija. **Brojevi odobrenja za stavljanje gotovog lijeka u promet:** Tolura® 40 mg, 30 tableta: EU/1/10/632/010; Tolura® 80 mg, 30 tableta: EU/1/10/632/017; Tolucombi® 40 mg/12,5 mg tablete, 30 tableta: EU/1/13/821/005; Tolucombi® 80 mg/12,5 mg tablete, 30 tableta: EU/1/13/821/015; Tolucombi® 80 mg/25 mg tablete, 30 tableta: EU/1/13/821/025; Tolucombi® 40 mg/12,5 mg tablete, 60 tableta: EU/1/13/821/007; Tolucombi® 80 mg/12,5 mg tablete, 60 tableta: EU/1/13/821/017; Tolucombi® 80 mg/25 mg tablete, 60 tableta: EU/1/13/821/027. **Zadnji odobreni sažetak opisa svojstava lijeka i uputu o lijeku možete u cijelosti pročitati na internetnoj stranici Europske agencije za lijekove (EMA):** www.ema.europa.eu. Datum sastavljanja oglas: 17.02.2014.

Samo za zdravstvene djelatnike. Ovaj promotivni materijal sadrži bitne podatke o lijeku koji su istovjetni cjelokupnom odobrenom sažetku svojstava lijeka te cjelokupnog odobrenog uputa sukladno članku 15. Pravilnika o načinu oglašavanja o lijekovima i homeopatskim proizvodima ("Narodne novine" broj 118/2009). Za detaljne informacije o lijeku, molimo, pročitati sažetak opisa svojstava lijeka ili uputu o lijeku.

**Referencje:** 1. IMS, IMS MV, Intellix, Medclub, Pharmazoom, Pharmexpert, Pharmstandard 2012. 2. Narodne Novine br. 09/2014 (24.01.2014.)

Detaljnije informacije možete dobiti od firme: KRKA-FARMA d.o.o., Radnička cesta 48/II, 10000 Zagreb, Telefon (01) 63 12 100, Faks (01) 61 76 739, E-mail: info.hr@krka.biz, www.krka-farma.hr



Naša inovativnost i znanje posvećeni su zdravlju. Zbog toga naša odlučnost, ustrajnost i iskustvo zajedno doprinose jednom cilju – razvoju djelotvornih i neškodljivih proizvoda vrhunske kakvoće.