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June 4-7, 2014 — Hotel Admiral, Opatija, Croatia

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Book of Abstracts

22nd Annual Meeting of the Alpe Adria Association of Cardiology

Hotel Admiral, Opatija, Croatia

June 4-7, 2014

Organized by the Croatian Cardiac Society

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22nd Annual Meeting of the Alpe Adria Association of Cardiology

Hotel Admiral, Opatija, Croatia
June 4-7, 2014

Dear colleagues,

The Alpe Adria Cardiology Association celebrates its 22nd anniversary in 2014. Just to remind, the Association was founded as a result of the initiative of a few distinguished cardiologists from the Alpe Adria region, being aware of the common tradition, history and culture, as a motive for a scientific networking among cardiologists within the Alpe Adria region.

Besides, the Alpe Adria Cardiology was also aimed to stimulate young cardiologists and cardiology fellows to present their scientific results and their presentation skills before international peers. Therefore, we were quite happy this year to have an opportunity to select 91 abstracts for the Final Programme. These abstracts, received mostly from younger representatives of the Alpe Adria cardiac community, represent a wide variety of cardiology topics. The best abstracts will be presented as short oral communications, and the others in a form of moderated poster presentations. Finally, the best original contributions will be awarded during the Closing Ceremony of the Congress. Beside a scientific content within this Abstract Book, The Congress will also contain about 40 invited lectures given by the leading names in cardiovascular medicine from the Alpe Adria region and wider.

The Alpe Adria Cardiology annual congresses varied a lot in their attendance, quality of organization and scientific content. However, we keep most of them in our memory as remarkable scientific and social events. Despite the fact that the Alpe Adria Association lives practically only through its annual meetings, those meetings helped many of us to get to know each other, as well as to communicate and collaborate in many other ways and occasions, e.g. by inviting each other to national congresses and other local meetings, collaborating within the ESC, etc. Therefore, each year we repeatedly conclude that the Alpe Adria Cardiology should be kept alive and be further developed.

Croatia, as one of the founding countries of the Alpe Adria Cardiology Association, organizes the Alpe Adria congress for the fourth time: for the first time it was the 2nd Alpe Adria Cardiology Meeting on Brijuni Islands 1994 (Ivo Čikeš, President), for the second time it was the 9th Alpe Adria Meeting in Cavtat 2001 (Šime Mihatov, President), for the third time it was the 14th Alpe Adria Meeting, again in Cavtat (Davor Miličić, President), and this, 22nd Meeting is being held in Opatija — a pearl of the northern Adriatic and a traditional meeting place of the Croatian Cardiac Society. I feel really pleased and honoured to chair the Alpe Adria Cardiology Congress for the second time, after 8 years, and want to wish a warm welcome to the Founding Fathers of the Association, to the Faculty members, chairmen and invited speakers, to all the presenters and to all participants.

I hope that this Congress will be a strong motive for all of us to creatively continue our collaboration through the Alpe Adria Cardiology Association, as a challenge and an added value for each of our national cardiac societies, for individual cardiologists within the Alpe Adria region, but also as a way how to enrich a broader, European, and even global cardiology context with our experience.

Sincerely yours,

Professor **Davor Miličić**, FESC, FACC
President, 22nd Alpe Adria Cardiology Congress
Councillor, ESC Board
President, Croatian Cardiac Society

CARDIOLOGIA CROATICA | CROATIAN CARDIAC SOCIETY | EUROPEAN SOCIETY OF CARDIOLOGY

Proširenisažetak / Extended abstract

Ischemic heart disease mortality trends in Croatia between 1995 and 2011: a joinpoint regression analysis

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Aim: In the last few decades, mortality from ischemic heart disease has been decreasing in many countries. The aim of this study was to analyze trends in ischemic heart disease mortality rates in Croatia between 1995 and 2011.

Materials and methods: The data on deaths from ischemic heart diseases in Croatia were extracted from the WHO mortality database, and estimates of the Croatian population were derived from the Population Division of the Department of Economic and Social Affairs of the United Nations. Ischaemic heart diseases were defined as I20-I25 diagnoses in ICD-10. We used Joinpoint Regression analysis to describe mortality time trends, with up to 4 joinpoints and a Monte Carlo simulation to calculate p-values for a series of permutation tests. The joinpoint analysis was applied to the age-standardised rates (world population) and their standard errors, separately for each sex.

Results: There were 165,432 deaths due to ischemic heart disease in Croatia in this 17-year period (51.2% females). The age-standardized ischemic heart disease mortality rates declined from 139.9/100,000 in men and 79.4/100,000 in women in 1995 to 118.9/100,000 and 67.6/100,000 in 2011, respectively. The trends showed a constant decrease, without any joinpoints in both men and women. In men, the best fitting model showed that in the period from 1995-2011 mortality rates significantly decreased (annual percent change (APC) of -1.0%; 95% CI -1.4 to -0.6), while in women trends were also decreasing (APC of -0.8%;95% CI -1.3 to -0.3) throughout the entire study period.

Conclusion: Mortality rates for ischaemic heart disease showed a continuous decrease during this period, especially in men. However, it is still the leading cause of death, and it is important to monitor trends and focus on reduction of preventable risk factors.

KEYWORDS: ischemic heart disease, mortality rate, trends.

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Prošireni sažetak / Extended abstract

The comparison between in-hospital and out-of-hospital death from acute coronary syndrome in the city of Zagreb

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Institute for Cardiovascular Prevention and Rehabilitation, Zagreb, Croatia

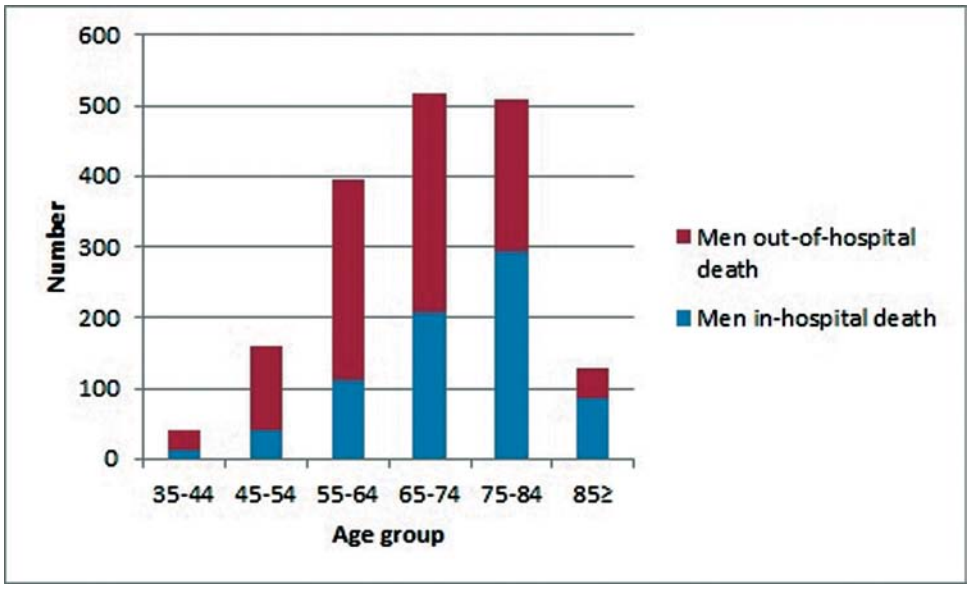
Background: The Acute Myocardial Infarction Register for the City of Zagreb was established in 1979 in the Institute for Cardiovascular Prevention and Rehabilitation as a population-based register (retrospective study) and in 2003 we established the Acute Coronary Syndrome Register for the City of Zagreb.

Aim: To compare in-hospital and out-of-hospital death from acute coronary syndrome (ACS) by gender and age in the City of Zagreb between 2007 and 2011.

Patients and Methods: Sources of information are: mortality data (Central Bureau of Statistics) and hospital discharge of consecutive patients admitted to all Zagreb hospitals with Acute Cardiology Units. The methodology was previously described-3.

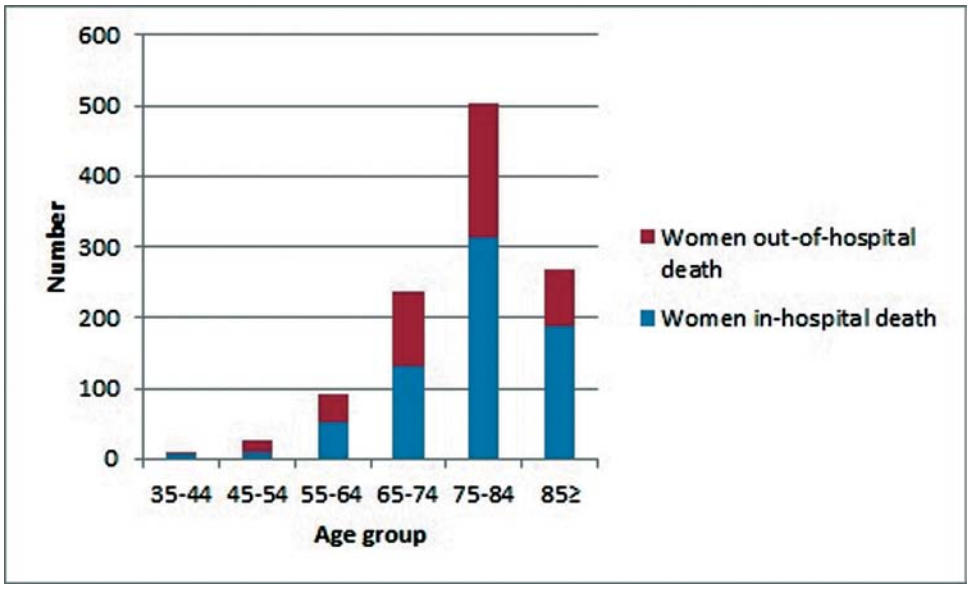
Results: Among 1750 male post-ACS patients, the out-of-hospital death is much higher than in-hospital death (57% vs. 43%). Men who died outside of hospital are much younger than those who died in hospital (mean age: 66.38 and 72.32, respectively). In-hospital death in 1133 female post-ACS patients is much higher than out-of-hospital death (62% vs. 38%) and there is no significant difference in age among the women who died in hospital and those who died outside of hospital (mean age: 77.85 and 75.61, respectively). The age distribution among the patients who died in hospital and those who died outside of hospital (**Figure 1**) shows differences especially in out-of-hospital death from ACS in men reaching peak between 55 and 74 years of age and both in- and out-of-hospital death between 65 and 74 years of age. In women in-hospital death reaches a peak between 75-84 years of age (**Figure 2**).

Conclusion: The comparison between in-hospital and out-of-hospital death from ACS by gender and age shows great differences. In-hospital death in women is significantly higher than out-of-hospital death. Men who died outside of hospital are 10 years younger than women and younger than men who died in hospital. Obviously, the outcome of the acute coronary syndrome depends on gender, age and clinical presentation. From the epidemiological point of view, the emphasis should be placed on cardiovascular prevention, population education which would enable a quick transport to hospital with a a catheterization laboratory. The AMI/ACS population-based register gives the information on the characteristics, burden and consequences of ACS in the City of Zagreb and is intended for health professionals and policy-makers.



Source: Croatian Bureau of Statistics.

Figure 1. *Comparison of in- and out-of-hospital death from ACS among men by age — Zagreb residents (2007 - 2011).*



Source: Croatian Bureau of Statistics.

Figure 2. *Comparison of in- and out-of-hospital death from ACS among women by age — Zagreb residents (2007 - 2011).*

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KEYWORDS: acute coronary syndrome, epidemiology, population-based register, mortality, in-hospital death, out-of-hospital death.

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Prošireni sažetak / Extended abstract

Macrovascular complications in diabetics in the Centre for Diabetes Bjelovar during the period from January 2003 to April 2014

Saša Magaš*, Zrinka Sudar Magaš, Branko Fila

Bjelovar General Hospital, Bjelovar, Croatia

The goal: To present the incidence of macrovascular diabetic complications in outpatients in the Centre for Diabetes in the Bjelovar-Bilogora County during the period from January 2003 to April 2014.

Patients and Methods: Data were collected by using the database of the computer software CroDiab NET as a part of the national registry for diabetes. Risk factors prevalence and glycemic regulation data in diabetics of the Centre for Diabetes in Bjelovar Bilogora county have been already published.[1] This study included 4,631 electronic health records processed during the follow-up period, considering the history of myocardial infarction, stroke, below ankle amputations, above ankle amputations and claudications.

Results: The most common macrovascular complication in this patient group is myocardial infarction (about 10% of patients). The second most common macrovascular complication was stroke (9%), followed by claudications (4.58%), below ankle amputations (2.46%) and above ankle amputations (2.06%). The lowest value of myocardial infarction was 7.4% in 2010. The prevalence of patients with stroke also showed a downward trend from 14.9% in 2007 to 7.4% in 2012. Amputations below the ankle show the highest rate of 3.83 % in 2007, but with a clear downward trend to 1.56% in 2013, and with further decline to 0.86% in the first four months of 2014. The frequency of amputations above the ankle shows even greater fall from 6.82% in 2003 to 0.88 % in 2013, followed by a further downward trend. Frequency of patients with claudications shows downward trend from 7.39% in 2003 to 3.45% in April 2014.

Conclusions: The most common macrovascular complication was myocardial infarction, followed by stroke, and peripheral arterial insufficiency (claudications and amputations). The registered downward trend of macrovascular complications can be explained by good and even better glycemic control and management of cardiovascular risk factors. Good disease control pays off!

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KEYWORDS: diabetic macrovascular complications, myocardial infarction, stroke, ankle amputations, claudications.

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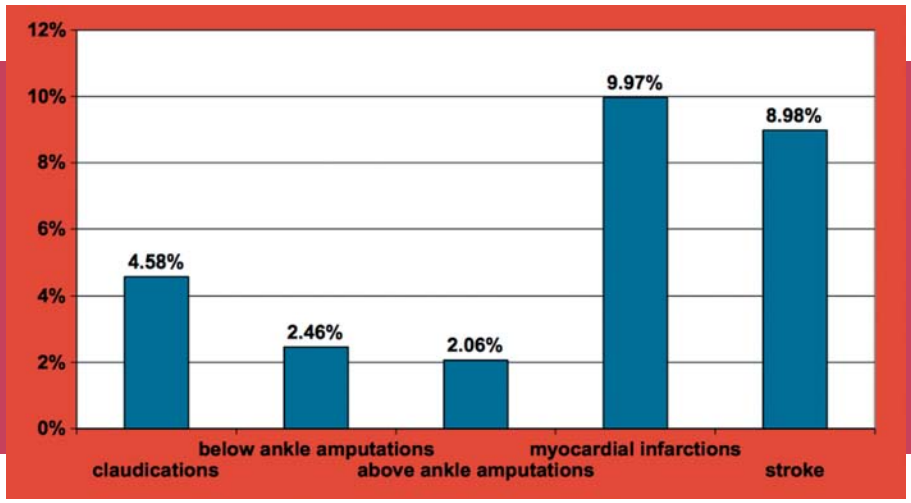

Figure 1. *Macrovascular complications in Centre for Diabetes Bjelovar.*

Proširenisažetak / Extended abstract

Is there any influence of elevated diastolic blood pressure on ventricular arrhythmias in hypertensive patients with left ventricular hypertrophy?

Juraj Kunišek[1]*, Leon Kunišek[2]

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Objective: To investigate the prevalence of ventricular arrhythmias in a patient with isolated systolic hypertension (ISHT) and left ventricular hypertrophy (LVH) in comparison to patients with systolic and diastolic hypertension and LVH.

Patients and Methods: 192 (87 men) patients with essential hypertension and LVH were divided into two groups: 98 patients with ISHT and 94 patients with systolic and diastolic hypertension. After discontinuing all medications for a period of 48 hours, the blood pressure was measured, electrocardiography, echocardiography, Holter monitoring and bicycle ergometry were performed. The number of ventricular arrhythmias was recorded. Antihypertensive drugs and the duration of previous treatment were taken into consideration.

Results: Isolated systolic hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure <90 mmHg) was recorded in 98 patients (51%), 47 men and 51 women (**Table 1**). The frequency of ventricular arrhythmias did not differ according to Lowns classification categories I-II and III-IV in patients with and without isolated systolic hypertension (**Table 2**). There was no difference in the treatment duration between the groups (p=0.858), or in the type of the applied medication. We found 44% complex ventricular arrhythmias in patients with ISHT. No significant difference was found in the frequency of ventricular arrhythmias between the groups that were observed.

Conclusions: No significant difference was found in the frequency of ventricular arrhythmias in patients with isolated systolic hypertension and LVH in comparison to patients with systolic and diastolic hypertension and LVH. Diastolic blood pressure does not seem to have any influence on the frequency of ventricular arrhythmias in such patients.

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KEYWORDS: isolated systolic hypertension, left ventricular hypertrophy, ventricular arrhythmias.

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Table 1. *Numerical review of patients.*

No of patients		No of patients with ISHT	%	SH+DH	%	p
Total	192	98	(51)	94	(49)	NS
Man		47	(54)	40	(46)	
Women		51	(49)	54	(51)	

ISHT=isolated systolic hypertension, SH=systolic hypertension, DH=diastolic hypertension.

Table 2. *Frequency of ventricular arrhythmias in patients with and without isolated systolic hypertension.*

	SH+DH No	%	ISHT No	%	Total	p
Lown I-II	98	(63)	20	(56)	118	0.419
Lown III-V	58	(37)	16	44)	74	

SH=systolic hypertension, DH=diastolic hypertension, ISHT=isolated systolic hypertension.

Prošireni sažetak / Extended abstract

The correlation between systolic and diastolic blood pressure and diastolic parameters in arterial hypertension in the presence of normal systolic function

Snežana Lazić*, Bratislav Lazić

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Introduction: Diastolic abnormalities in arterial hypertension are more prominent in the presence of the accompanying left ventricular hypertrophy (LVH). In the hypertrophic left ventricle due to hypertension, the elevated blood pressure exhibits additional unfavorable effect on complex diastolic process in the presence of normal systolic function. E/A ratio is considered to be global index of diastolic function.

Objective: To evaluate the relationship between systolic and diastolic blood pressure and E/A ratio in arterial hypertension with left ventricular hypertrophy with normal systolic function.

Method: Standard Doppler echocardiography, blood pressure levels measured by the standard mercury sphygmomanometer 15 minutes before the examination.

Results: This study analyzed 111 subjects with hypertension (65 with concentric LVH and 46 with eccentric LVH). The individuals with ischemic heart disease, valve abnormalities, diabetes mellitus, and heart rhythm and conductance abnormalities were initially excluded from the study. The study inclusion criteria were EF >50% and LVH confirmed by echocardiography. The mean EF was 61±6%; systolic blood pressure 168±13 mmHg; diastolic blood pressure 101±7 mmHg; E/A ratio 0.7±0.13; IVRT 110±4.2 ms; and DT 291±8.9 ms. The study showed negative correlation between SBP and E/A ratio (r -0.225; $p<0.05$) and between DBP and E/A ratio (r -0.205; $p<0.05$). No significant correlation between SBP and DT (r -0.003; $p>0.05$) or between SBP and IVRT (r +0.42; $p>0.05$) was shown. Furthermore, no significant correlation was shown between DBP and DT (r -0.17; >0.05) or DBP and IVRT (r +0.045; $p>0.05$).

Conclusion: Arterial hypertension and left ventricular hypertrophy have been associated with E/A ratio <1. The observed negative correlation between SBP and DBP and E/A ratio suggests hemodynamic effect of blood pressure on diastolic function. The results of this study alert about possibility of heart failure during the elevated blood pressure attacks with preserved systolic function.

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KEYWORDS: arterial hypertension, echocardiography, diastolic function.

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Literature

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Proširenі sažetak / Extended abstract

Is there still a gender gap in patients with ST-elevation myocardial infarction?

Martin Marinšek[1]*, Andreja Sinkovič[1], Nejc Piko[2], Matevž Privšek[2]

[1]University Clinical Centre Maribor, Maribor, Slovenia

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Background: A decade ago, women with ST-elevation myocardial infarction (STEMI) were significantly older than men, with more comorbidities, less likely treated by primary percutaneous coronary intervention (PPCI) and their prognosis was worse. The progress in treatment of STEMI patients resulted in an increased survival after STEMI. Our aim was to evaluate and compare possible differences in the treatment and in 30-day and 6-months mortality between the genders in the STEMI patients.

Patients and Methods: We retrospectively evaluated 255 STEMI patients — 187 men and 68 women, admitted in 2012. Reperfusion strategy was PPCI, combined with aspirin and clopidogrel or prasugrel or ticagrelor and a heparin with glycoprotein receptor IIb/IIIa antagonist or bivalirudin. We compared baseline clinical data between the genders. We also compared the use and time to PPCI, in-hospital complications, 30-day and 6-month mortality.

Results: The STEMI patients were treated by PPCI in 92.6%. Their 30-day mortality was 9% and 6-month mortality was 12.9%. We observed insignificant differences in mean age, comorbidities, the use and time to PPCI, in-hospital complications, discharge treatment, 30-day, and 6-month mortality between the genders. We even observed significantly increased admission troponin I (10.0±20.2, women 3.7±9.1 µg/l, p=0.015) and peak troponin I levels (54.4±38.8 vs 39.7±39.2 µg/l, p=0.009) in men.

Conclusion: Women account for 1/3 of STEMI population; the gap between the genders in presentation, treatment and outcome in STEMI population is significantly decreasing.

KEYWORDS: gender, gap, ST-elevation, myocardial infarction.

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Prošireni sažetak / Extended abstract

Who has the leading role in acute myocardial infarction: troponin I or brain natriuretic peptide?

Snežana Brđanović*, Mehmed Kulić, Zorica Hondo, Azra Durak-Nalbantić, Sanela Rošić-Ramić

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Background: For the assessment of the left ventricular function and infarct size in acute myocardial infarction, brain natriuretic peptide (BNP) and cardiac troponin I (cTnI) are useful for the prediction of a prognosis. The aim of the present study was to correlate left ventricular function and infarct size to the level of cTnI and BNP in acute myocardial infarction.

Patients and Methods: We studied 40 patients (pts), with the first ST-segment elevation myocardial infarction (STEMI). We measured the level of BNP and cTnI on a single occasion at 96 hours after the onset of symptoms, and then compared it with echocardiography estimated systolic and diastolic ventricular function and infarct size — which was determined with numbers of ECG leads and classification into small and large infarct size (small infarct size 3-4 leads, large infarct size 6-9 leads).

Results: Distribution of data was estimated by using the Shapiro-Wilk test. The data do not have normal distribution, so they are representative as a median and range. We used non-parametric statistic tests (Mann-Whitney tests) to compare and improve differences among the groups. For statistical correlation, we used the Sperman rank correlation. Data were analyzed using statistical program Arcus Quick Stat. There was significant inverse correlation between the level of BNP and EF (r = -0.504, P = 0.0016) and between BNP i E/A (r = -0.290, P = 0.00705). There was a strong inverse correlation between BNP and LV-EF in STEMI, such as between BNP and E/A, against cTnI no significant correlation with LV-EF and E/A in STEMI was found. There is no significant statistical difference between BNP and cTnI in small and large infarct size.

Conclusion: A single BNP value at 96 hours after the onset symptoms of myocardial infarction proved useful for the estimation of LV systolic and diastolic function. In a direct comparison BNP disclosed a better performance for the estimation of LV-EF and E/A against cTnI. cTnI is useful for diagnosing early myocardial damage in acute myocardial infarction, suggesting an implementation of dual marker strategy in acute myocardial infarction for diagnostic and prognostic work-up.

KEYWORDS: brain natriuretic peptide, cardiac troponin I, left ventricular systolic function, left ventricular diastolic function, ST-segment elevation myocardial infarction.

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Left transradial access is safe and effective in acute STEMI patients undergoing primary percutaneous coronary intervention: results from CROSS-STEMI (CROatian Single center Study in STEMI patients)

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Aim: In the last few years University Hospital Center Sestre milosrdnice, Zagreb has become dedicated to the radial approach with nearby 90% of percutaneous coronary interventions (PCI) performed with either left or right radial access route. In time, left radial approach has become the first choice option for most of the patients (pts) with acute ST-segment elevation myocardial infarction (STEMI). The aim of this study was to compare the efficacy and safety of left transradial access (L-TRA) with the right transradial (R-TRA) and transfemoral (TFA) access in the setting of primary (PCI) for acute (STEMI).

Patients and Methods: This single-center, retrospective study included 767 consecutive acute STEMI patients, treated with primary PCI from January 2011 to May 2013, who were divided in three groups according to the arterial access site: L-TRA group (413 patients, 53.85%), R-TRA group (110 patients, 14.34%) and TFA group (244 patients, 31.81%). We collected data on the procedure success, procedure, door-to-balloon and fluoroscopy time and bleeding complications. Of all the patients, 43.5% of them were admitted directly through the emergency department and 56.5% of them were transported from other hospitals being the part of the Croatian PCI network.

Results: Procedural success was similar among the three groups (L-TRA vs TFA 93.2% : 88.5%, p=0.495; and L-TRA vs R-TRA 93.2% : 90.1%, p=0.855). Additionally, all investigated procedural characteristics were similar among compared groups, including total procedure time (L-TRA vs TFA 71.9±18.4 : 73.3±21min, p=0.366; and L-TRA vs R-TRA 71.9±18.4 : 72.7±21.3min, p=0.966) and fluoroscopy time (L-TRA vs TFA 11.1±6.9 : 11.6±9.3min, p=0.461; and L-TRA vs R-TRA 11.1±6.9 : 12.8±8.2min, p=0.128). When considering the bleeding complications (change in the concentration of haemoglobin), there were no differences between the three groups (L-TRA vs TFA 10±10.1 : 11±10.8 g/L, p=0.308; and L-TRA vs R-TRA 10±10.1 : 10±11.8 g/L, p=0.254).

Conclusion: In a PCI center committed to PCI, left transradial approach for acute STEMI patients undergoing primary PCI, is as equally effective and safe as transfemoral or right transradial approach.

KEYWORDS: ST-segment elevation myocardial infarction, radial access, primary percutaneous coronary intervention.

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Prošireni sažetak / Extended abstract

Anticoagulation therapy and invasive management of acute non-ST elevation coronary syndromes: guidelines and everyday practice

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Introduction and goal: The latest 2011 non-ST-segment elevation acute coronary syndromes (NSTE-ACS) management guidelines indicated that all patients should receive anticoagulation drugs irrespective of the treatment strategy. In this report, 2-year data on anticoagulation therapies for NSTE-ACS are presented, in relation to invasive management selection and treatment outcomes in a clinical setting without registered bivalirudin.

Patients and Methods: Data for 374 patients with NSTE-ACS treated in the Coronary Care Unit in General Hospital Slavonski Brod, Croatia were analyzed from January 2012 to December 2013. Treatment strategies, outcomes and complications among patients treated with different anticoagulation agents (enoxaparine, fondaparinux or unfractionated heparin) were analyzed and compared.

Results: In all, 72% of all NSTE-ACS patients were treated invasively, out of which 66% underwent angiography within 72 hours. Urgent and early angiography was performed in 44% of all invasively treated patients. Generally, 58% and 5% of patients received enoxaparine and unfractionated heparin (UFH), respectively, whereas fondaparinux was administered in 37% of patients. Median age of patients treated with enoxaparine was 66, compared to 76 in the fondaparinux group. There were significantly more patients treated with enoxaparine and UFH than with fondaparinux in the invasive strategy group. We observed that the number of patients treated with fondaparinux in the invasive group increased together with the period between symptom onset and angiography. The number of patients treated conservatively with either fondaparinux or enoxaparine was almost equal. There were no patients treated conservatively with UFH. In general, in-hospital mortality was low, 2.6% with no significant differences in bleeding events regarding the selection of anticoagulation therapy.

Conclusions: Although the guidelines gave preference to fondaparinux, everyday practice in our hospital showed that enoxaparine was a preferred agent, particularly in younger patients selected for early invasive strategy, most probably because of the risk/benefit ratio and opportunity of avoiding the mixing of anticoagulation agents. Only 5% of patients were selected for urgent invasive approach with UFH, which should probably increase in the future. Considering a higher cost of bivalirudin, the introduction of this agent for non-ST segment elevation myocardial infarction management does not seem to be mandatory in our clinical setting, since this small group of patients was adequately managed with UFH.

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KEYWORDS: acute coronary syndrome, anticoagulation therapy, percutaneous coronary intervention.

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Prošireni sažetak / Extended abstract

Continuous clopidogrel dose modification after platelet function testing improves clinical outcome in acute coronary syndrome treated with percutaneous coronary intervention and initially determined high on-treatment platelet reactivity

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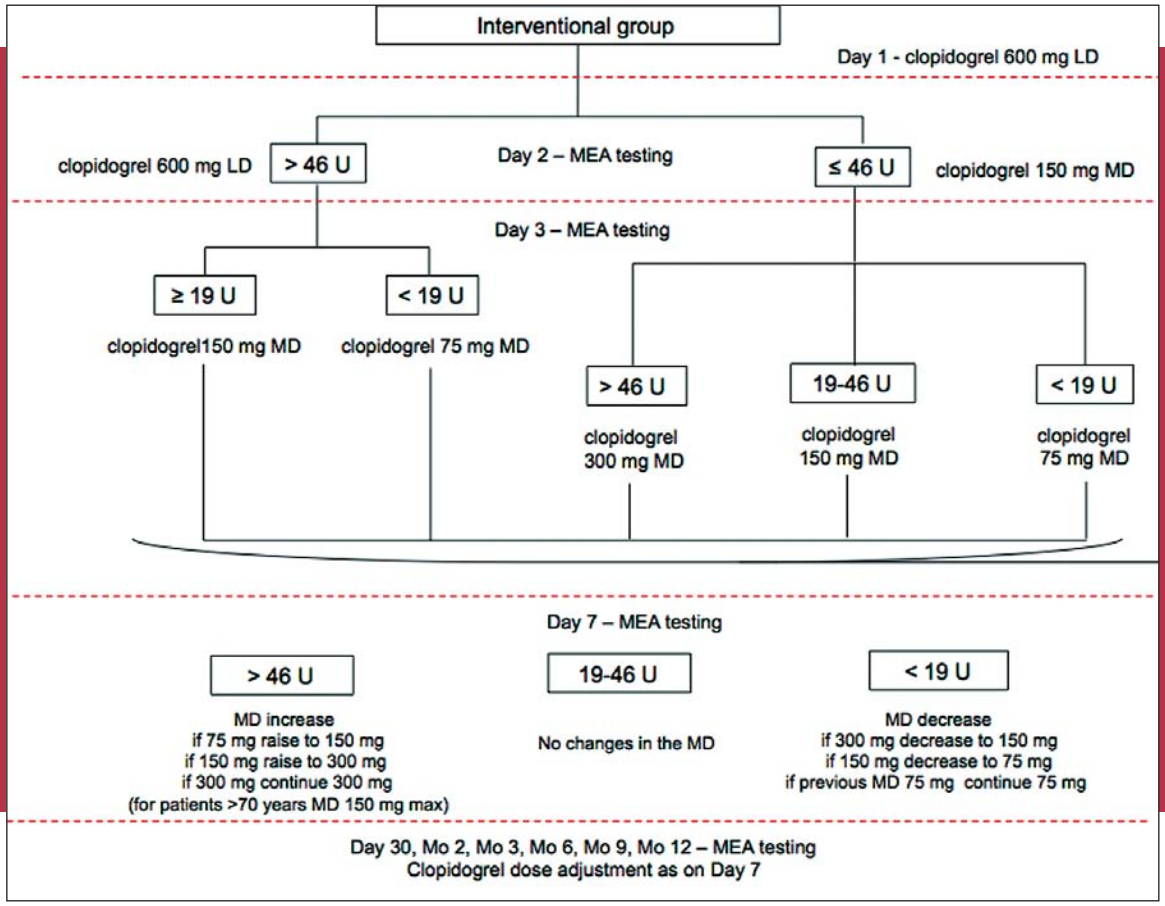
Introduction: High on-treatment platelet reactivity (HTPR) on clopidogrel correlates with adverse clinical outcomes in patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI)[1]. Whether HTPR on clopidogrel is a modifiable risk factor for ischemic events is not clear. We sought to evaluate the effect of the serial clopidogrel dose tailoring after platelet function testing (PFT) on a clinical outcome of the patients with determined HTPR after successful PCI in ACS.

Patients and Methods: We screened 461 consecutive ACS patients. Exclusion criteria was present in 120 patients (continuous postinterventional glycoprotein (GP) IIbIIIa receptor inhibitor perfusion, thrombocytopenia (<150x109/L), significant renal insufficiency (creatinine>200 μmol/L), anemia (Htc<30%), hemorrhagic diathesis, concomitant chronic anticoagulation therapy and advanced age (>80 years of age). Patients without exclusion criteria (341) underwent PFT 12-24 hours following PCI. Patients with determined HTPR on



LD — loading dose; MEA — Multiplate elecrode aggregometry; MD — maintenance dose

Figure 1. *Flow chart of the personalized treatment with clopidogrel in the interventional group after coronary revascularization.*

clopidogrel (n=87; 25.5%) were included in the study and randomized to the standard dose clopidogrel (control) group (n=44) and the interventional group (n=43). Blood samples for PFT using Multiplate® function analyzer (MEA) were drawn at day 1, 2, 3, 7, 30 and at month 2, 3, 6, 9 and 12 following PCI. The clopidogrel dose was modified at each PFT the interventional group with patients taking up to three 600 mg loading doses and a range of 75-300 mg maintenance dose of clopidogrel to achieve an optimal platelet reactivity (19-46 U) as set by the consensus statement[2].

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Results: Nine (20.9%) and 18 (41.8%) patients experienced either ischemic or bleeding adverse event in the interventional and control group during the 12-month follow up, respectively (p = 0.044). Composite ischemic events (hospitalization due to ischemia, target vessel revascularization, non-fatal myocardial infarction, stent thrombosis, stroke, cardiovascular death) were also significantly higher in the control group (16 vs 7 patients; p = 0.034). There was no difference in total bleeding outcomes (p=1.000).

Conclusion: We hypothesize that HTPR to clopidogrel is a modifiable risk factor and personalized antiplatelet therapy based on PFT might be implemented in ACS patients treated with PCI. Larger, similarly designed randomized studies are needed to confirm these results.

KEYWORDS: acute coronary syndrome, platelet reactivity, antiplatelet therapy, clinical outcome.

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Prošireni sažetak / Extended abstract

Takotsubo after general anesthesia for chronic subdural hematoma: case report

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The goal: Takotsubo cardiomyopathy is an acute cardiovascular disease generally characterized by reversible wall motion abnormalities of the left ventricle, electrocardiographic changes and clinical presentation that can mimic myocardial infarction in the absence of an obstructive coronary artery disease. It is often precipitated by an intense acute emotional or physical stress. Our goal was to present a patient with Takotsubo cardiomyopathy which developed after the induction of general anesthesia.

Patient and Methods: The patient's available medical record was used to present the clinical course of Takotsubo that developed after induction of general anesthesia.

Results: We present a case of a 61-year-old woman who developed Takotsubo cardiomyopathy during operation of chronic subdural hematoma. After induction of general endotracheal anesthesia and preparation of the operative field, hemodinamic instability was detected. The ECG lead to suspect on acute myocardial infarction. Coronarography with the left ventriculography was performed indicating development of takotsubo cardiomyopathy. The patient was admitted to the cardiac intensive care unit and treated according to the ongoing hemodynamic disturbances. By the day eight, clinical recovery was observed with anterior wall hypokinesis. The patient was hemodynamically stabile with normal blood pressure and pulse.

Conclusion: There are already many case reports presenting numerous possible triggering factors for Takotsubo cardiomyopathy. Severe stress, emotional or physical, can precede this disease. This is an interesting case where iatrogenic stress related to medical procedures causes transient systolic dysfunction of the heart, mimicking myocardial infarction.

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KEYWORDS: acute myocardial infarction, Takotsubo cardiomyopathy, general anesthesia.

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Prošireni sažetak / Extended abstract

Takotsubo cardiomyopathy after severe emotional stress: a case report and a brief literature review

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The goal: Takotsubo cardiomyopathy is recognized as an important differential diagnosis of acute myocardial infarction. It is characterized by a transient systolic dysfunction of apical, mid or basal segments of the left ventricle with an absence of obstructive coronary artery disease. Despite a rapid onset and severity of symptoms, it is considered to be a relatively benign condition with swift resolution of symptoms and wall motion abnormalities, even though it may have complicated clinical course and lead to mortal outcome. Our aim was to present a patient under severe emotional stress in which the clinical course was complicated with an irreversible cardiogenic shock.

Patient and Methods: Single patient clinical characteristics are analysed using available medical record.

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Results: A 78-year-old woman was presented with signs and symptoms of acute heart failure. The ECG and laboratory findings lead to suspect on ST elevation myocardial infarction. Coronarography excluded the acute myocardial infarction and left ventriculography indicated takotsubo cardiomyopathy as a cause of the existing symptoms. Despite the intensive treatment, respiratory insufficiency and irreversible cardiogenic shock developed and in five days the patient succumbed to the illness.

Conclusion: Takotsubo cardiomyopathy has a benign clinical course in the most of the cases, which leads to a total recuperation of the systolic function and resolution of symptoms. Complications such as cardiogenic shock are rare. In this case we present a patient with irreversible cardiogenic shock as a rare complication of Takotsubo cardiomyopathy.

KEYWORDS: acute myocardial infarction, Takotsubo cardiomyopathy, severe emotional stress.

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Prošireni sažetak / Extended abstract

What is the limit of capability of using the bioresorbable vascular scaffold?

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The number of deaths caused by coronary artery disease (CAD) in the USA is 145/100.000, while in Hungary it is 332/100.000. CAD is progressive, characterized by narrowing or even blockage of the arteries causing restricted blood flow to the heart. Several risk factors can be modified by lifestyle changes, but due to other risk factors, the progression of the disease cannot be stopped despite all of the aggressive pharmacological therapies. There is expectation for brand new devices and techniques in the therapy of CAD.

The first bioresorbable vascular scaffold (BVS) implantation around the world was performed by P. Serruys and his team in the Netherlands. In Hungary the first BVS was implanted in 2012. This was the second generation BVS. The BVS is a temporary scaffold indicated for improving coronary luminal diameter that will eventually resorb and potentially facilitate normalization of the vessel function in patients with ischemic heart disease due to de novo native coronary artery lesions.

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One of the first institutes in Hungary was the Heart Institute of the University of Pécs, which had the opportunity to apply several BVS. In our lab some of the procedures were controlled by optical coherence tomography (OCT), which ensured the perfect apposition and sizing of the stents. The treated lesion length should be less than the nominal scaffolding length, (12-28 mm) with reference vessel diameters ≥2.0 mm and ≤3.8 mm. The scaffold is contraindicated for the patients who are contraindicated to receive antiplatelet or anticoagulant therapy, who show hypersensitivity to aspirin, clopidogrel, ticlopidine, prasugrel, ticagrelor, everolimus, poly(L-lactide), poly (D,L-lactide), or platinum. In total, we have implanted 14 BVS in 7 patients so far, which is 2 scaffolds per patient on the average. We have both used the BVS with the typical indications and with off-label indications as well. We would use this poster to share our experience we have gained by applying the scaffold. As the second point, we would like to highlight the most frequent complications and the special implantation technique which is mandatory to be carried out while a bioresorbable vascular scaffold system is being implanted.

KEYWORDS: coronary artery disease, bioresorbable vascular scaffold, optical coherence tomography.

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Prošireni sažetak / Extended abstract

Complex percutaneous coronary intervention for unprotected distal left main bifurcation lesion in a patient with cardiac allograft vasculopathy

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Introduction: Cardiac allograft vasculopathy (CAV) is a progressive form of coronary disease that defines the long term prognosis in heart transplant patients. The mortality of surgical revascularization in post-transplant patients is very high. Percutaneous coronary intervention (PCI) has a relatively low periprocedural mortality and high acute angiographic success, but still high restenosis rate and poor long-term results. Bypass surgery (CABG) is considered the gold-standard for unprotected left main coronary artery (LMCA) disease in non-transplant patients, especially with the distal bifurcation lesion. Optimal PCI techniques are needed to improve the results and complex double kissing crush technique seems to be promising.

Case Report: We present a case of a 27-year-old patient who received heart transplant at the age of 24. During the second post-transplant year, he developed acute inferior ST-elevation myocardial infarction and primary PCI of RCA was performed. An eccentric LMCA stenosis with an involvement of large ramus intermedius (RI) and almost occluded, minor left circumflex (LCx) were detected on control angio. We decided to perform PCI on this complex lesion with double kissing crush technique. Two wires were positioned distally to the lesions in both the LAD and ramus intermedius (RI). A stent was positioned in the RI with few proximal millimeters protruding into the LMCA, a balloon with a length long enough to cover the protruding stent segment was concurrently positioned in the LAD. The RI stent was deployed. The SB stent-balloon and wire were removed. The balloon in LAD was then inflated at a high pressure to crush the protruding RI stent. The RI ostium was rewired and dilated with a balloon. The bifurcation was then kissed with two balloons. Afterwards, a stent was deployed in the LMCA toward LAD at a high pressure. The RI ostium was rewired for the second time through the LMCA stent strut and dilated with a balloon at a high pressure. The final kissing balloon inflation in the bifurcation was performed at a high pressure and finished with proximal optimization of LMCA. The control angio performed 6 months later showed no signs of restenosis.

Summary: The treatment of CAV is very challenging and while CABG remains a poor revascularization option, PCI of complex lesions such as those of LMCA require optimal technique to reduce the incidence of adverse cardiac events and prevent further graft deterioration.

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Prošireni sažetak / Extended abstract

Frequency of anatomic variations of radial artery in patients undergoing transradial heart catheterisation

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Over the last ten years, transradial cardiac catheterisation has been increasingly applied, primarily because of its lower incidence of complications compared to the femoral approach. However, one of the greatest flaws of the transradial approach is a relatively high incidence of catheterisation failure (1-5%). Anatomic variations of the radial artery are ranked second among the reasons for this. Previous studies have not provided unambiguous data on the frequency of them. It is therefore the aim of this study to determine the frequency of anatomic variations using routine angiographies of the radial artery (RA) during the left heart catheterisation at the Interventional Cardiology Unit of the University Hospital Centre Zagreb in 2013. Seven hundred and forty-nine such cardiac catheterisations were carried out during the studied period. All the images were examined and, after selection, 602 remained for further research. The process of selection required all patients to be of age and to have an accurate image of radial artery angiography. Correctly performed radial artery imaging involved the imaging of the division of the brachial artery into the ulnar and radial arteries. It also implied the visibility of at least half of the radial and half of the brachial artery. Anatomic variations are classified in accordance with the classification provided by Burzotta et al. Of the total of 602 patients, 414 (68.8%) were men and 188 were women. The youngest patient was 18 and the oldest one was 87 (mean±SD; 64±10.78), with a normal distribution of subjects across the age groups. In 538 (89.4%) of patients, cardiac catheterisation was performed through the right arm. The frequency of anatomic variations of RA was 8.8%, exclusive of tortuosities whose frequency was 12.7%. The most frequent anatomic variation was the high origin of the radial artery, found in a total of 31 (5.1%) subjects. Radioulnar loops, being one of potential contraindications for the procedure, were reported in 2% of the cases. Regression analysis revealed that age ($p<0.001$), female sex ($p=0.015$) and high origin ($p=0.034$) statistically significantly contributed to the development of tortuosity. The results indicate that the incidence of tortuosity increases linearly with age. Although this is not a contraindication for continuing with the procedure, we recommend that elderly patients should have angiography performed at the beginning of the procedure due to a higher frequency of tortuosity.

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Prošireni sažetak / Extended abstract

Transbrachial approach — taken from the history

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Purpose: Radial arterial approach has become the default option for coronary procedures in our cath lab (>90%). However, 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 the 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 an obsolete procedure. In literature, the complication rate was unacceptably high (up to 36%). The aim of this retrospective investigation was to evaluate the safety and efficiency of TB approach as an alternative to radial approach, especially after the unsuccessful radial artery puncture.

Method: During the period of two years, TB coronary angiography in the antecubital region was performed in 25 patients with stable and unstable angina or valvular heart disease. In 12 patients, diagnostic procedure was followed by a coronary intervention. Reasons for TB approach were weak or absent radial pulse (12 cases) or unsuccessful radial artery puncture (13 cases). Procedures were performed by three experienced transradial invasive cardiologists (transradial success more than 95%). The catheter size was 6 Fr in all patients. Anticoagulation protocol was used while following the guidelines (aspirin, clopidogrel, unfractionated heparin) but without glycoprotein IIb/IIIa receptor inhibitors. Major complications were defined as vascular complications requiring blood transfusion or surgery or permanent neurological deficit in the lower limb. Minor complications were defined as vascular complications not requiring blood transfusion or surgery and transient neurological deficit in the lower limb. A standard post-procedural protocol was the removal of the artery sheath 3 hours after the diagnostic procedure, 6 hours after PCI and manual puncture site compression for 10 minutes.

Results: Overall success rate was 96% (24/25). There were no major complications and we noticed only two minor complications (8%), both hematomas.

Conclusion: TB approach, when used by dedicated transradialists, seems to be easily feasible, safe, and effective. Local vascular complications could be avoided by the cautious and sensitive puncture technique. Other important factors include the use of 6 Fr catheters, defensive anticoagulation and careful observation by the nursing team after the 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 when lying down).

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KEYWORDS: transbrachial approach, puncture site.

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Efficacy of percutaneous coronary intervention in diabetic patients — local results with global impact

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Introduction: Diabetes mellitus is combined with high risk for the development of coronary artery disease (CAD). Revascularization in diabetic patients is challenged by a more diffuse atherosclerotic coronary disease, a higher propensity to develop re-stenosis and unremitting atherosclerotic progression causing new stenosis.

The goal: To assess efficacy, safety and long-term survival of diabetic patients with mutivessel CAD treated with percutaneous coronary intervention (PCI) and drug-eluting stent implantation (DES).

Patients and Methods: We included 28 patients with stable/unstable angina or non-ST segment elevation myocardial infarction (age 66±15) and with basal characteristics and inherent risk comorbidities as stated in **Table 1.** After the coronarography was done and multivessel CAD was confirmed (significant stenosis in more than 2 epicardial vessels and/or stenosis of the left main coronary artery) patients were offered, regarding optimal evidence-based medical possibilities, surgical revascularization or PCI. The latter ones entered the PCI arm of the study and were treated with PCI using DES. After the patients underwent coronarography, SYNTAX score was calculated which classifies patients into low, medium and high SYNTAX score group (SYNTAX score <22, 23-32 and >33). Following PCI, all the patients were treated by using optimal medical therapy (**Table 2**). The patients were subjected to secondary coronarography after one year of follow-up or earlier based on clinical indication.

Results: After the median follow-up of 3.4 years, we found that the highest incidence of major adverse cardiac and cerebrovascular event (MACCE) was observed in high SYNTAX score group (100%) as opposed to absence of MACCE in the low SYNTAX score group (**Table 3**). The need for repeated revascularization was 14.3% and the overall registered primary outcome prevalence (composite of death, myocardial infarction and stroke) was 21.4%. None of the patients had stroke and the incidence of myocardial infarction was 14.2% (all observed in high SYNTAX score group).

Conclusion: The results of our study are comparable to the results of large randomized clinical trials conducted worldwide which studied the efficacy of PCI in multivessel disease as well as compared PCI strategy with surgical revascularization. Therefore, we find that these results indicate the possibilities of implementing and performing "state-of-the-art" cardiovascular procedures even in somewhat small clinical centers as ours whilst obtaining results comparable to the ones achieved in large global centers.

KEYWORDS: diabetes, multivessel coronary artery disease, drug-eluting stent.

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Table 1. *Baseline characteristics, comorbidities and calculated SYNTAX score in the group of patients treated with percutaneous coronary intervention and drug-eluting stent implantation.*

Characteristic	DID-DES
No. of patients	28
Age	66±15
Male	57%
Hemoglobin A1c	8.0±1.8
Current smoker	21%
Hypertension	71%
Hyperlipidemia	64%
SYNTAX	28±10

DID-DES = Coronary proceDures and Interventions in Diabetics — DES implantation

Table 2. *Percentage of patients receiving optimal medications after percutaneous coronary intervention.*

Medication	DID-DES
Aspirin	100%
Thienopyridine	100%
Statin	93%
Beta blocker	86%
ACE inhibitor	89%

DID-DES = Coronary proceDures and Interventions in Diabetics — DES implantation

Table 3. *Final results after median follow-up of 3.4 years.*

OUTCOME	DID-DES
Primary outcome (Death/Stroke/MI)	21.4% (8 pts)
Myocardial infarction	14.2% (4 pts)
Stroke	0% (0 pts)
Repeat revascularization	14.3% (4 pts)

DID-DES = Coronary proceDures and Interventions in Diabetics — DES implantation

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Prošireni sažetak / Extended abstract

Coronary artery perforation following percutaneous coronary intervention: a case report

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Introduction: Coronary artery perforation is a severe complication of percutaneous coronary intervention (PCI). It occurs after an intimal tear of the coronary artery that leads to perforation of the arterial wall. A major risk factor for perforation during PCI is the balloon-to-artery ratio. Ellis classification is used to classify the types of perforation, the type III being the most severe one. Here we report on the case of a patient with the type III perforation after elective PCI.

Case report: A 60-year-old man admitted to our clinic for diagnostic coronary angiography. A significant stenosis of the right coronary artery (RCA) was found. Stent implantation and postdilatation was performed. Postprocedural coronary angiogram showed contrast extravasation, whereas perforation of the RCA was suspected. Urgent pericardiocentesis was performed and blood was aspirated from the pericardium. Patient went into cardiorespiratory arrest and cardiopulmonary resuscitation was started. Sternotomy was carried out by a cardiac surgeon, followed by open heart massage, evacuation of the hematoma and compression of the bleeding site. Return of spontaneous circulation was established and the patient was taken to the operating room. A complete perforation of the RCA was found. The stent was removed, right ventricle was reconstructed and coronary artery bypass graft with left internal mammary artery to RCA was performed. After the procedure, the patient was admitted to the intensive care unit and transferred back to our clinic after recovery. Two months later he was discharged without any major neurological deficit.

Conclusion: Coronary perforation is a rare complication of PCI, but is associated with significant morbidity and mortality. Type I and type II perforation have a much better prognosis than the type III perforation. It is important to immediately recognize this complication, so the patient could be managed in the best possible way. Treatment strategies for coronary perforation include reversal of anticoagulation, prolonged balloon inflation, implantation of stent grafts, local injection of thrombogenic molecules, placement of microcoils or open heart surgery. In cases where sealing of the perforation by conservative measures cannot be achieved, urgent bypass surgery must be performed.

KEYWORDS: coronary artery perforation, percutaneous coronary intervention, cardiorespiratory arrest, open heart surgery.

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Proširenи sažetak / Extended abstract

How to select a good candidate for left atrial appendage occlusion device: case report

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Atrial fibrillation is one of the most common arrhythmias and carries a great risk for cardioembolisation, with stroke and acute limb or mesenteric ischemia as one of the most severe consequences. Anticoagulation therapy is a gold standard therapy for embolic event protection, with new oral anticoagulants as a more attractive option for both patients and physicians. However, there are data that support the introduction of left atrial appendix occluders, like Watchman device, as a good therapeutic option for selected population of patients.

We present a case of a 73-year-old women, who was first admitted in the coronary care unit in General Hospital Slavonski Brod because of non-ST segment elevation myocardial infarction (NSTEMI). She was in sinus rhythm. She was treated with acetylsalicylic acid (ASA), clopidogrel and low-molecular-weight heparin (LMWH), and was scheduled for a coronary angiogram during the same hospital stay. On the third day of hospitalization, before planned coronarography, she developed a large retroperitoneal hematoma with no computed tomography signs of active bleeding from any large vessel. She was treated conservatively with good recovery. During the treatment, several episodes of atrial fibrillation were documented. After introduction of amiodarone, she was in stable sinus rhythm. After partial resolution of retroperitoneal heamatoma, coronary angiography was performed showing normal coronary arteries. She was discharged home in sinus rhythm, with ASA, angiotensin-converting-enzyme inhibitor, beta-blocker, and a statin. After 2 months she presented to emergency room with clinical signs of acute left arm ischemia. Color Doppler investigation showed signs of acute closure of left axillar artery. Basal ECG showed sinus rhythm. Urgent thromboendarterectomy with a Foley catheter was performed with prompt restoration of the circulation. Early transesophageal echocardiography was performed showing a large thrombus in the left atrial appendage. Continuous ECG monitoring showed short episodes of atrial fibrillation and undulation. Along with LMWH, anticoagulation therapy with warfarin was introduced. Previous NSTEMI with normal coronary angiography and acute left arm ischemia were attributed to thromboembolisation from the left atrial appendage. Because of her history of spontaneous retroperitoneal bleeding on antiaggregation and anticoagulation therapy, she was referred to Clinical Hospital Dubrava for left atrial appendage occlusion with Watchman device.

We have discussed the appropriateness of criteria for lifetime anticoagulation therapy in atrial fibrillation and selection criteria for occlusion device implantation.

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KEYWORDS: atrial fibrillation, cardioembolisation, embolic protection device.
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Prošireni sažetak / Extended abstract

Balloon aortic valvuloplasty for severe aortic stenosis: acute and long-term outcomes

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Introduction: The use of the balloon aortic valvuloplasty (BAV) has risen with the development of transcatheter aortic valve stenosis (TAVR). The role of BAV should be reevaluated as a part of the complex treatment of severe aortic stenosis in high risk patients.

Aim: We evaluated the patient characteristics, peri-procedural complications and long-term outcome after BAV. We also present our results of the external beam radiation therapy (EBRT) impact on restenosis after BAV.

Methods: We retrospectively analyzed all of the patients who underwent BAV from January 2009 to June 2013 and stratified our cohort into 3 groups: BAV as a bridge to TAVR/SAVR, BAV as a final therapy and consecutive BAV.

Results: We analyzed 228 patients (mean age 82.5±6.3, logistic EuroSCORE 17.0±11.4). After BAV aortic valve area increased (0.60±0.20 cm^2 to 0.72±0.21 cm^2, $p<0.001$) and mean aortic gradient decreased (48.8±15.7 mmHg to 37.1±11.9 mmHg, $p<0.001$). Major intra-hospital complications occurred in 11.4% with three procedure-related deaths (1.3%). BAV bridged to TAVR had a better outcome than BAV alone. EBRT showed no effect on the long-term outcome.

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Proširenisažetak / Extended abstract

Transcatheter intervention in carotid artery disease: when and how?

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Carotid artery disease, due to atherosclerotic changes and consequent stenotic lesion, is responsible for about 20% of all ischemic strokes. Rare causes of carotid stenosis are irradiation therapy, vasculitis, accidental dissection or fibromuscular dysplasia. Its impact on public health and patient's quality of life is considerable and causes long-term disability.

In general population, in 5.7% of patients between 70 and 80 years of age and 9.5% of patients over 80 years of age, carotid stenosis over 50% is diagnosed. Carotid stenosis can be asymptomatic or diagnosed when TIA (transient ischemic attack) or cerebral stroke occurs (symptomatic). In patients with symptomatic carotid stenosis, the risk of recurrent stroke is much higher.

Carotid stenosis could be easily and promptly diagnosed with Doppler ultrasound, CT scan or MR imaging. The degree of stenosis, morphology and homogeneity of adjacent plaque, presence of thrombus, intracranial pathologies and asymptomatic cerebral embolic events must be evaluated.

Optimal medical treatment has to be provided to patients, both with symptomatic and asymptomatic carotid stenosis. Antiplatelet and statin therapy should be administered to all patients, irrespective of symptoms or disease progression. Risk factors (arterial hypertension, diabetes, obesity, smoking etc.) must be recognized and promptly cured.

Although many large scale trials (CAVATAS, EVA-3S, ICSS, SAPPHIRE, CREST, etc.) recognize carotid endarterectomy advantages in the treatment of carotid stenosis, carotid stenting as a revascularization option has its place in certain subgroups of patients. The patients with high perioperative risk, infavourable neck anatomy, prior neck dissection, restenosis after carotid endarterectomy or post-irradiation stenosis benefit from transcatheter interventions. The aim of this research is to explore the indications and to detail the most used techniques in carotid artery stenosis transcatheter interventions.

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KEYWORDS: carotid artery disease, stenosis, treatment.
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Prošireni sažetak / Extended abstract

Catheter directed thrombolysis for acute limb ischemia: eight cases in two years

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Introduction: Acute limb ischemia (ALI) is a challenging problem in angiology. It can be associated with significant morbidity or death even after successful limb revascularization. Management of ALI depends on the clinical status of the affected limb and patient comorbidities. We assessed the efficacy and complication of catheter directed thrombolysis for ALI in our institution during 2012 and 2013.

Patients and Methods: During the period of 24 months, eight ALI patients were treated by catheter directed infusion with recombinant tissue plasminogen activator (r-tPA). Standard endovascular access and catheter techniques were involved starting with 5 mg bolus of r-TPA, followed by continuous infusion of 0.5-2 mg/h. Concomitant heparin at low dose was applied to prevent catheter-associated thrombus development. During r-TPA, infusion angiography was repeated to determine success of thrombus dissolution.

Results: There were 5 males and 3 females, mean age of 74.8 years (range, 54-90 years). One patient had upper extremity ischemia, others had lower ALI. The average duration of symptoms was 3.6 days (1-10 days). Mean duration of r-TPA infusion was 24.2 hours (16 to 4 hours), with mean dosage of 36.6 mg (range 17 to 60 mg).Three patients (38%) had complete reestablishment of blood flow with catheter thrombolysis and mean ankle — brachial index (ABI) improved from 0.22 to 0.85. The other 4 patients (50%) had partial restoration of flow and needed additional endovascular or surgical intervention with final mean ABI improvement from 0.39 to 0.98. In one case catheter directed thrombolysis failed to reestablish blood flow and the patient underwent the bypass surgery. Only one patient had severe periprocedural complication (gastrointestinal bleeding) requiring a blood transfusion. Small access site hematoma was noticed in all of the treated patients. In the follow-up period (7 to 20 months) one patient had unfavorable course of affected limb which ended with an amputation 15 months after thrombolysis. The other seven patients were stabile, without significant impairment of the treated limb.

Conclusion: Selective thrombolysis should be considered for ALI patients with the symptom onset less than 14 days and without motor deficit of the affected limb. It is a time-consuming procedure with potential severe hemorrhagic complications. With the proper patient selection and coordinated multidisciplinary team, it could result in the reestablishment of flow and an acceptable bleeding complication rate.

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KEYWORDS: thrombolysis, acute, ischemia, limb.

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Proširenisažetak / Extended abstract

Prevention of musculoskeletal neck disorders in echocardiographers

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Echocardiographic operators using the most traditional right handed scanning are five times more likely to be at risk from the back pain and almost a half of them are reporting neck musculoskeletal disorders (MSD). Painful posture leads to abnormal muscle contraction and a new pain. If the condition persists, it may cause organic disorders resulting in structural degenerative changes.

The aim of this pilot study was to develop on the basis of the physiotherapeutic analysis of the postures of 50 echocardiographers while providing scanning of simple preventive interventions that can be self-performed at the work places. Practice in a wrong posture characterized by a lateral shift of the trunk in the frontal plane, kyphotic holding of the thoracic spine, elevation of one or both arms, and outpost of the head with extension of its joints can result in overload of muscular and skeletal neck segments with tissue damage and discs protrusion, causing long lasting MSD.

Based on this, we have given the following recommendations. Firstly, it is about control of physiological posture that means to hold the torso upright with the correct position of the head, cervical spine and shoulders. It is not always possible to minimize lateral shift of the trunk in the frontal plane; therefore easy compensatory exercises are the most suitable. Secondly, simple relaxation exercises for the neck muscles performed in a defined position and direction and synchronized with breath are highly appropriate. They are quite effective for the restoring of the physiological length and tension of the muscles. Thirdly, a self performed massage is highly recommended additionally to reduce the increased muscle tension of the neck. It can be performed by one or two-handed spawning or kneading applications and resulting in an improving muscle blood supply, thus eliminating the pain that occurs on the basis of ischemia. The time required for the self-performing of the proposed preventive program does not exceed five minutes and it should be performed during the breaks between the examinations at least once per hour.

The next step of our initiative will be a practical application of the recommended preventive interventions. Furthermore, a well-constructed study at a large sonographic population is to be considered to properly test a proposed preventive program to confirm if it will reduce the reported MSD to which echocardiographers are susceptible.

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KEYWORDS: musculosceletal disorders, echocardiographers, prevention.

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Prošireni sažetak / Extended abstract

Three-dimensional speckle-tracking echocardiography allows volumetric and strain analysis of the left atrial function in noncompaction cardiomyopathy

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The goal: Noncompaction cardiomyopathy (NCCM) is a rare cardiomyopathy characterized by a distinctive 2-layered appearance of the myocardium, hypertrabecularization and deep intertrabecular recesses due to arrest of the compaction process of the embryonic endomyocardial morphogenesis. The present study was designed to assess left atrial (LA) volumetric and strain-based functional properties by three-dimensional (3D) speckle-tracking echocardiography (3DSTE) in NCCM.

Patients and Methods: The study comprised 9 consecutive NCCM patients. Due to a low image quality, one patient was excluded from the analysis (mean age: 60.2 ± 8.2 years, 3 males). Their results were compared to 20 age- and gender-matched healthy controls (mean age: 50.8 ± 14.6 years, 11 males). Complete two-dimensional Doppler echocardiography and 3DSTE were performed in all cases.

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Results: Calculated LA maximum (90.3 ± 19.1 ml vs. 35.8 ± 6.3 ml, p <0.0001) and minimum (71.3 ± 19.5 ml vs. 16.3 ± 4.7 ml, p <0.0001) volumes and LA volume before atrial contraction (81.6 ± 19.8 ml vs. 24.0 ± 6.5 ml, p <0.0001) significantly increased in NCCM patients. Total, active and passive LA emptying fractions proved to have decreased in NCCM. Global radial (8.0 ± 6.8% vs, 21.4 ± 11.5%, p =0.005), circumferential (9.7 ± 7.7% vs. 28.7 ± 9.7%, p <0.0001), longitudinal (8.4 ± 4.1% vs. 24.5 ± 6.6%, p <0.0001), 3D (5.7 ± 5.2% vs. 13.7 ± 10.5%, p =0.05) and area (17.7 ± 12.5% vs. 58.2 ± 17.3%, p <0.0001) strains were significantly reduced in NCCM patients as compared to the matched controls.

Conclusions: 3DSTE allows detailed evaluation of LA (dys)function. Increased LA volumes and reduced LA emptying fractions respecting cardiac cycle and reduced LA strain parameters could be demonstrated by DSTE in NCCM.

KEYWORDS: three-dimensional, speckle-tracking, echocardiography, left atrium, noncompaction cardiomyopathy.

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Prošireni sažetak / Extended abstract

Andersen-Tawil syndrome (LQT7) is associated with alterations in left ventricular rotational mechanics

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The goal: Andersen-Tawil syndrome (ATS), also called Andersen Syndrome and Long QT Syndrome 7 (LQT7) is a rare condition. ATS is characterized by episodic flaccid muscle weakness, distinctive dysmorphic features, ventricular arrhythmias and prolonged QT interval in the presence of normal conventional left ventricular (LV) structural and functional parameters. In the normal heart, the LV base rotates clockwise, while the apex rotates counterclockwise during systole, producing a "towel-wringing" motion of the heart. The net difference between the LV base and LV apex is called "net twist angle". The present study was designed to assess LV rotational mechanics in ATS by three-dimensional speckle-tracking echocardiography (3DSTE).

Patients and Methods: The study comprised 6 patients with ATS, their results were compared to 20 healthy volunteers. Complete two-dimensional Doppler echocardiography and 3DSTE were performed in all cases. 3DSTE was used to measure apical and basal LV rotations and LV twist.

Results: During 3DSTE, apical LV rotation proved to be 8.43 ± 1.54 degree, while basal LV rotation was -2.31 ± 1.31 degree, therefore LV twist was 11.12 ± 5.32 degree in healthy subjects. In 3 out of 6 ATS patients, LV basal and LV apical rotation were in the same direction resulting in the near absence of LV twist showing „rigid body rotation". In the remaining 3 ATS patients, LV apical rotation (2.06 ± 1.30 degree, $p < 0.05$) together with LV twist (6.51 ± 1.28 degree, $p < 0.05$) were significantly decreased as compared to controls. Mean basal rotation showed no significant difference compared to the values of controls (-4.45 ± 1.87 degree, p =NS).

Conclusions: Significant alterations in LV rotational mechanics could be demonstrated in ATS by 3DSTE.

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Prošireni sažetak / Extended abstract

Detailed evaluation of right atrial dysfunction in patients with corrected tetralogy of Fallot by three-dimensional speckle tracking echocardiography

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The goal: Three-dimensional (3D) speckle tracking echocardiography (STE) could encompass the benefits of STE and 3D echocardiography allowing to see the heart as it is: a 3D organ. In the recent studies, alterations in ventricular deformations could be demonstrated in adult patients with corrected tetralogy of Fallot (cTOF) by 3DSTE. The present study was designed to assess 3DSTE-derived right atrial (RA) volumetric and strain parameters in cTOF.

Patients and Methods: A total of 17 cTOF patients were involved into the present study. Their results were compared to 18 age- and gender-matched healthy controls. All subjects have undergone complete 2-dimensional Doppler echocardiographic and 3DSTE measurements.

Results: Significantly increased RA volumes respecting heart cycle could be detected in cTOF patients. Total and passive atrial emptying fractions proved to be significantly decreased in patients with cTOF (26.4 ± 12.4% vs. 39.1 ± 8.8%, p=0.001 and 11.2 ± 6.8% vs. 19.8 ± 9.0%, p=0.003, respectively). Global and mean segmental peak longitudinal (17.0 ± 10.9% vs. 30.8 ± 11.2%, p=0.0008 and 20.6 ± 10.7% vs. 34.4 ± 10. 5%, p=0.0005) and area strains (20.2 ± 18.8% vs. 41.0 ± 19.8%, p=0.003 and 28.1 ± 19.8% vs. 49.1 ± 19.7%, p=0.004) and global radial peak strain (9.5 ± 5.6% vs. 15.0 ± 10.0%, p=0.05) proved to be reduced in cTOF patients as compared to controls. Global pre-atrial contraction circumferential strain was significantly decreased in cTOF patients (3.9 ± 6.9% vs. 10.8 ± 11.0%, p=0.03).

Conclusions: Complex evaluation of RA dysfunction could be allowed by 3DSTE including volumetric and strain analysis.

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Proširenи sažetak / Extended abstract

Image methodes in chest deformation diagnosis — a case report

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Case Report: A 34-year-old patient was admitted to our Institution because of weakness, shortness of breath and exercise intolerance. Echocardiography shows mitral valve prolapse and regurgitation, dilated right ventricle. MSCT coronarography detected changes in the anatomic relations of large blood vessels. The Xiphoideum is drawn back and form pectus excavatum with pressure on the chest structures. No changes in coronary anatomy were found. Cardiac MRI showed that the ventricular systolic function is preserved. No fibrosis was found. This finding reflects the compression-induced changes in anatomy and geometric distortion of the RV. The outflow of large blood vessels is normal, whereas the aorta moved to the left. The exercise test showed a reduced functional capacity. We concluded that there is no structural heart disease and that the symptoms were due to pectus excavatum.

Discussion: The patient was admitted to differentiate the etiology between the structural heart disease or the presence of a pectus excavatum. In a large number of cases the symptoms appear in adolescence or early adulthood. Wilting in the thorax can lead to shifts in the thorax structure which may lead to reduced cardiac ejection or disrupt lung function. In the available literature the reduction of functional capacity is well documented. The reduction in functional capacity is caused by a decrease in stroke volume and respiratory capacity. Earlier research has shown the reduction VO_2max at 75% predicted for age. Pectus excavatum is associated with mitral valve prolapse and regurgitation with the prevalence of 20%. The changes in cardiac MRI findings are a consequence of compression of the pectus excavatum on structures in the mediastinum with a displacement of the heart to the left with a rotation about the longitudinal axis which leads to the compression of the RV and the change of the anatomical relationship of large blood vessels.

Conclusion: Pectus excavatum, the most common congenital malformations of the chest with the prevalence of 0.1 — 0.3% of the general population. In a large number of cases the repercussions appear in adolescence or early adulthood which are manifested by reduced exercise tolerance and dyspnea. These problems are caused by cardiac compression and a reduction in stroke volume and restrictive respiratory disorders. Functional testing and imaging methods are necessary together with the clinical picture in assessing the degree of malformation and its repercussions on the cardiovascular system.

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KEYWORDS: chest, deformation, heart.

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Can the ankle-brachial index be a predictor of the grade and localisation of thoracic aortic atherosclerosis?

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Introduction: The ankle-brachial index (ABI) is a strong marker of cardiovascular disease and is a predictor of cardiovascular events and mortality. In several studies, low ABI (<0,9) values were a predictor of atherosclerosis, such as peripheral artery disease (PAD), coronary artery disease and carotid artery disease. The atherosclerosis is a systemic disease, and recently we have learnt about the association of the PAD and cardiovascular diseases. One of the most important manifestations of the atherosclerotic process can be seen in the thoracic aorta. Patients with severe aortic arch plaque are at a high risk for stroke. We have investigated whether we can use the measurement of the ABI to predict the atherosclerosis of throracic aorta and its grade and localization as well.

Patients and Methods: Transoesophageal echocardiography examination was made for the consecutive patient population of 62 adults due to other reasons, such as atrial fibrillation, detection of intracardiac sources of embolism, artificial valves function, pulmonary embolism. We observed the grade of the atherosclerosis in three different sites of the throracic aorta, in the visualized part of the ascendens aorta, on the aortic arch and in the descendens throracic part. We used the universally accepted classification of aortic atherosclerosis (grade 1-4). After it ABI measurement was performed for all patients with a a handheld Doppler device. We investigated the correlations between the aortic plaques severity, localization and age of patients and the ABI values.

Results: In our consecutive population we found predictive value of ankle-brachial index for manifestation of atherosclerosis in the thoracic aorta. ABI measurements showed the same values independently for the observed atherosclerotic process in the thoracic aorta.

Conclusion: The ABI measurement, as an indicator of PAD and the commonly used factor of cardiovascular risk assessment can not consequently predict the form appearing in the thoracic aorta of general atherosclerosis, neither considering the severity nor the localization. Morphologically detected various severities of aortic plaques in our study could not be explored by ABI measurements.

KEYWORDS: ankle-brachial index measurement, aortic plaque, transoesophageal echocardiography.

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Prošireni sažetak / Extended abstract

Non-stenotic coronary lesion — is it really non-ischemic?

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Coronary angiography has a diagnostic limitation in identifying non-stenotic coronary lesion (NSCL) responsible for ischemia. Although an abnormal fractional flow reserve (FFR) increases the probability of significant obstructive lesions, it cannot reliably distinguish intermediate epicardial stenosis from ischemic, diffuse atherosclerosis or microvascular disease. Myocardial perfusion defects in patients (pts) with NSCL have often been unreasonably considered by invasive cardiologists to be "falsely positive".

We evaluated a prognostic value of gated single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in unselected group of the pts with NSCL over a 24 month period of follow-up. 170 pts (115 males, 67.6%; aged 42-68; mean age 56.4±9.2 years) with NSCL (stenosis of 50% or less of left anterior descending artery and 70% or less of any other coronary artery or its major branches, FFR cut-off 0.80) were enrolled into the study. Retrospective analysis of 86 pts with NSCL and subsequent positive MPS performed within 6 months from the time of coronary angiography (study group) and 84 pts with normal scan results (control group) was performed. The follow-up period lasted for 24 months from the time of MPI or up to the time of major coronary event (MCE) — first occurrence of cardiac death or myocardial infarction. Over a two-year follow-up, approximately 11% of the pts in the study group had MCE as compared to 3.2% in the control group (P <0.01). Abnormal MPI, EF <35% and high levels of hs-CRP were independent predictors for MCE in the study group. In multivariate analysis only an abnormal MPI remained to be an independent predictor regardless of the size or severity of perfusion abnormalities (P <0.005). Pts with NSCL on coronary angiography and myocardial perfusion defects have relatively high event rate (11%) of MCE over a period of 24 months from the time of MPI.

So, we highly recommend gated SPECT MPI to be performed in cases of NSCL to look for possible ischemia and to avoid life-threatening coronary complications in the forthcoming future. It can also prevent unnecessary repeatedly performed coronary interventions for identifying lesion responsible for angina in NSCL.

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KEYWORDS: non-stenotic coronary lesion, ischemia, myocardial perfusion imaging.

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Experience of a single-center in coronary computed tomography angiography

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Purpose: Coronary computed tomography angiography with calcium scoring measured with Agatston score index provides a diagnosis of coronary atherosclerosis in the patients with subclinical coronary plaque. To evaluate the diagnostic accuracy of Agatston score in comparison with the conventionally used Framingham risk score (FRS) and blood biomarkers in predicting existence of coronary artery disease (CAD) and significant coronary stenosis >50%.

Patients and Methods: This retrospective single-center study is evaluating the role of Agatstone score in the prognosis of CAD in patients with previously unknown CAD. 2,597 patients underwent coronary multidetector computed tomography (MDCT) and obtained Agatston score in our Center from June 2012 to April 2014. Scanning was done with dual-source MDCT equipped with two 128-detector row units using the ECG-gating protocol. The mean amount of radiation that was obtained was 6.8 ± 4.5 mSv. The exclusion criteria included Agatston score above 800, atrial fibrillation, pre-existing kidney failure (eGFR< 50 mL/min/1.73 m^2), as well as the incomplete data. All of the patients with heart rate higher than 80/min received beta blocker. The mean heart rate during scanning was 68 ± 9/min, and the patient's body mass index was 28 ± 5,1. The participants were divided into two groups based on coronary artery stenosis, significant >50% or less than 50%. The frequency of demographic and clinical characteristics, blood biomarkers and risk factors were tested between the groups by using chi-squared test and Student T-test as appropriate. To test for factors associated with predicting coronary artery stenosis, likelihood ratio, and receiver operating characteristics analyses were used. Relative risk was calculated in the context of developing coronary artery stenosis greater than 50% in the participants with Agatston score above 100.

Results: Out of 2,597 patients participating, 361 patients (mean age 63 ± 8; 227 (63%) of females) with complete data were included in this study. Significant coronary artery stenosis was recorded in 84 (23%) of patients. Mean FRS values were 20 ± 13. Agatstone score (Se 85%, Sp 95%, NPV 95%, PPV 85%, AUC 0.99, 95% CI 0.968 to 1.000, p<0.0001).

Conclusion: Among all considered demographic and clinical characteristics, Agatstone score was the most accurate predictor for developing of CAD and significant coronary stenosis.

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Prošireni sažetak / Extended abstract

Subclinical detection of atherosclerosis and myocardial ishemia in asymptomatic patients with intermediate and high cardiovascular risk: therapeutic and prognostic implications

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Background: We wanted to evaluate the presence of coronary atherosclerosis and myocardial ischemia in asymptomatic patients with intermediate and high cardiovascular (CV) risk, the influencing clinical factors and the impact of ischemia on the final management decision and prognosis.

Patients and Methods: 75 asymptomatic patients (35 with intermediate and 40 patients with high CV risk-SCORE risk system), underwent single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) for the detection of suspected coronary artery disease. We used a 17-segment model for the scan perfusion and function analysis using perfusion scores. All of the patients have full blood laboratory analyses including lipid values, and presence of urine albuminuria. Multislice computer tomography with coronary calcium Agatston score (CAC) for coronary atherosclerosis detection was also performed. The patients were followed up for 12-18 months for cardiovascular events (new chest pain, hospitalization for acute coronary syndrome, revascularization, cardiac death). Logistic regression analysis was used to assess predictive parameters for myocardial ischemia and cardiovascular events.

Results: Stress-inducible ischemia was found in 19 patients (33%), fixed defects were found in 13% and mixed defects in 9% of cases. The average ischemia amount was 10%. Mild ischemia was found in 12 patients (64%) - summed stress score (SDS) <4, moderate ischemia in 5 patients (26%) - SDS 5-7 and severely abnormal scans in 2 patients (10%) - SDS >7. Severe ischemia was only related to the duration of diabetes (DM). Patients with at least moderate ischemia had Agatston CAC score 465+/-112. The patients with normal MPI scan had CAC score 98+/-45. 3 pts with moderate risk were reclassified to high risk by using CAC and MPI scan results. Stepwise logistic regression analysis for the prediction of stress-induced ischemia showed OR 2.4 (95% CI 1.7_3.6) for the stress-induced ECG changes, OR 2.8 for CAC >400 (95% CI 1.9-3.2) and OR 3.9 for the presence of DM over 10y (95% CI 2.3_6.6). Seven patients with ischemia >10%, were referred for coronary angiography. One patient was hospitalized due to the acute coronary syndrome and no cardiac death was registered during the 12 months follow-up.

Conclusions: MPI is a valuable method for preclinical assessment of myocardial ischemia in asymptomatic intermediate and high risk patients, which can improve the prognosis and guide the treatment decision. Coronary calcium score can predict the presence of myocardial ischemia and reclassify the patient's risk.

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KEYWORDS: myocardial single-photon emission computed tomography imaging, ischemia, coronary calcium score, prognosis.

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Proširenі sažetak / Extended abstract

Role of multidetector computed tomography in diagnosis acute aortic syndrome

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Acute aortic syndrome (AAS) is the modern term that includes aortic dissection, intramural hematoma (IMH), and penetrating atherosclerotic ulcer (PAU and aortic rupture); trauma to the aorta with intimal laceration may also be considered.

The common denominator of AAS is a disruption of the media layer of the aorta with bleeding within IMH, along the aortic media resulting in the separation of the layers of the aorta (dissection), or transmurally through the wall in the case of a ruptured PAU or trauma.

Multidetector computed tomography (MDCT) is a gold standard due to its intrinsic diagnostic value; its performance approaches 100% sensitivity and specificity, and it is accepted as the first-line modality for the suspected acute aortic disease. MDCT allows an early recognition and characterisation od AAS as well as the presence of any associated complications.

Long-standing arterial hypertension, variety of genetic disorders with altered connective tissues, vascular inflammation, deceleration trauma and iatrogenic factors are the most prevalent risk conditions. Patients with AAS often present in a similar fashion, regardless of the underlying condition of dissection, IMH, PAU or contained aortic rupture. Pain is the most commonly presenting symptom of acute aortic dissection and should prompt immediate attention, including diagnostic imaging modalities (such as multislice computed tomography, transoesophageal ultrasound, or magnetic resonance imaging).

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KEYWORDS: multidetector computed tomography management, acute thoracic aortic syndromes, aortic dissection, intramural hematoma, penetrating aortic ulcer.

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Prošireni sažetak / Extended abstract

Multidetector computed tomography in early diagnosis of patients with acute chest pain

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Acute nontraumatic chest pain is a common presenting symptom to the emergency department. The examination must be able to exclude life-threatening conditions, including pulmonary embolism, aortic dissection, and acute coronary syndrome.

Several "triple rule-out" protocols have been proposed to provide high-quality images covering the thoracic aorta, coronary, and pulmonary arterial trees. Studies have shown that coronary computed tomography (CT) using a 256-detector row dual-source is a safe and efficient method for triage patients with acute chest pain who have a low to intermediate likelihood of coronary artery disease (CAD), with a high diagnostic efficacy, time efficiency and cost-effectiveness.

The protocol included three axial nongated volume acquisitions to cover the chest with triggering at the pulmonary arteries followed by a prospectively ECG-gated cardiac scan for the coronary arteries. Multidetector computed tomography (MDCT) has rapidly evolved from the 4-detector row systems in 1998 to the 256-slice and 320-detector row CT systems. With a smaller detector element size and higher gantry rotation speed, spatial and temporal resolution of the 256-slice MDCT scanners, has enabled volumetric imaging of the entire heart free of stair-step artifacts at a single time point within one cardiac cycle. Such scanners hold promise in performing a rapid high quality "triple rule-out" test without a high contrast load and with a small radiation dose. These emerging technical advances and novel applications will continue to change the way we study CAD beyond detecting luminal stenosis.

We shall focus on three aspects of managing the patients with acute chest pain:

1. Imaging to increase the number of correct diagnoses in the acute situation;

2. Imaging to rule out other coronary causes of chest pain;

3. Use of imaging for risk stratification, once myocardial infraction has been ruled out in the chest pain unit.

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KEYWORDS: computed tomography, acute chest pain, aortic dissection, pulmonary embolism, wide area detector, triple rule-out protocol.

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Prošireni sažetak / Extended abstract

Eosinophilic endocardiomyopathy: a case presentation

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Eosinophilic endocardiomyopathy is a major cause of morbidity and mortality among patients with hypereosinophilic syndrome (HES), a group of disorders characterized by the sustained overproduction of eosinophils, where eosinophilic infiltration causes the damage to multiple organs. We present the case of a 63-year-old man who had been investigated at the out-patient clinic for malaise, effort intolerance, dry cough and cognitive disturbances six months before his presentation to our hospital. He had been diagnosed with hypereosinophilia (51.14 x 10^9/L) and leukocytosis (69.7 x 10^9/L). Bone marrow biopsy resulted negative for abnormal myeloid maturation or lymphoproductive disorder. A brain magnetic resonance confirmed postischemic lesions and gastroscopy revealed esophageal varices grade I. According to immunologist's recommendation, who previously excluded systemic autoimmune disease, the patient was referred to our Cardiology Clinic for further investigations. The transthoracic echocardiography showed a dilated cardiomyopathy with global hypokinesia and ejection fraction of 40%. A multi-slice computer tomography coronarography (MSCT) excluded the presence of coronary artery disease. Cardiac magnetic resonance imaging demonstrated biventricular enlargement and global hypokinesia (trueFISP cine), myocardial oedema in the mid-cavity and in the apical segments (T2 STIR), diffuse endocardial late gadolinium enhancement of the left ventricular mid-cavity and apical segments and of almost the entire right ventricle (true FISP PSIR) indicating fibrosis/necrosis. Thrombi at both ventricular apices were also identified. These findings present the final stage in the time course of eosinophilic endomyocardial disease. The patient was dismissed with anticoagulation and immunosuppressive therapy. Two months later the patient was feeling better and the eosinophil counts significantly decreased. Eosinophilic endocardiomyopathy is characterized by three stages: an acute necrotic stage significant for direct endomyocardial infiltration and damage, an intermediate phase, in which thrombi form along the damaged endocardium and a fibrotic stage characterized by endomyocardial fibrosis. Cardiac magnetic resonance imaging is an important non-invasive tool for detection of all stages of eosinophil-mediated heart damage.

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KEYWORDS: endocardiomyopathy, hypereosinophilia, cardiac magnetic resonance imaging.

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Prošireni sažetak / Extended abstract

Paradoxical embolism of the right kidney

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Case presentation: A 40-year-old man presented with shortness of breath, pleuritic chest pain and tachycardia. Five weeks before, the patient was admitted to the hospital due to the fracture of the fifth metatarsal bone of the left foot. The patient was put in a cast for 4 weeks. Pulmonary embolism (PE) was confirmed by a ventilation/perfusion lung scan. Immediately after admission, the patient started to complain about a sharp pain in his right lumbar region. Echocardiography revealed a dilated right ventricle and pulmonary hypertension of 70 mmHg (**Figure 1**). A CT-angio scan confirmed a massive PE and showed an infarction of the right kidney (**Figure 2**). Thrombosis of the left popliteal vein was confirmed by ultrasound. Transesophageal echocardiography revealed a patent foramen ovale (**Figure 1**). After the initial treatment with low molecular weight heparin, the patient became hypotensive and elevated levels of troponin were registered. The patient was transferred to the Coronary Care Unit and treated with alteplase. After the treatment, a normalisation in the both right ventricle diameter and right ventricular systolic pressure was noted. The patient was hemodynamically stable with full regression of his symptoms. A postprocedural Doppler ultrasound showed recanalisation of the right renal artery.

Conclusion: Paradoxical embolism and intracardiac shunt should be immediately considered when PE and systemic arterial embolism co-occur. Treatment mainly consists of thrombectomy or thrombolysis.

KEYWORDS: paradoxical embolism, patent foramen ovale.

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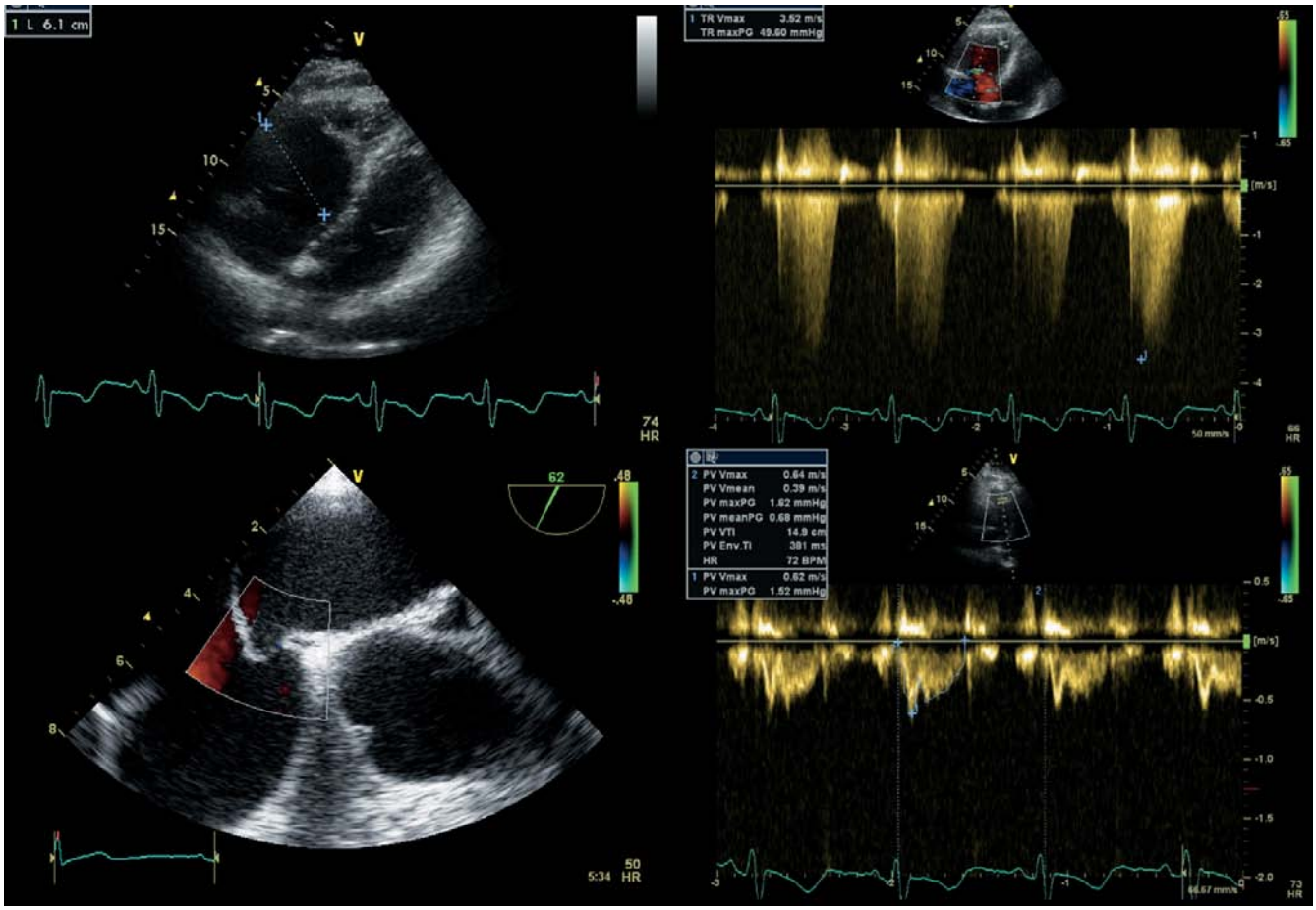

Figure 1. *Showing clockwise from top left: distention of the right ventricle, pulmonary hypertension, flow across the pulmonary valve (transthoracic echocardiogram) and patent foramen ovale (transesophageal echocardiography).*

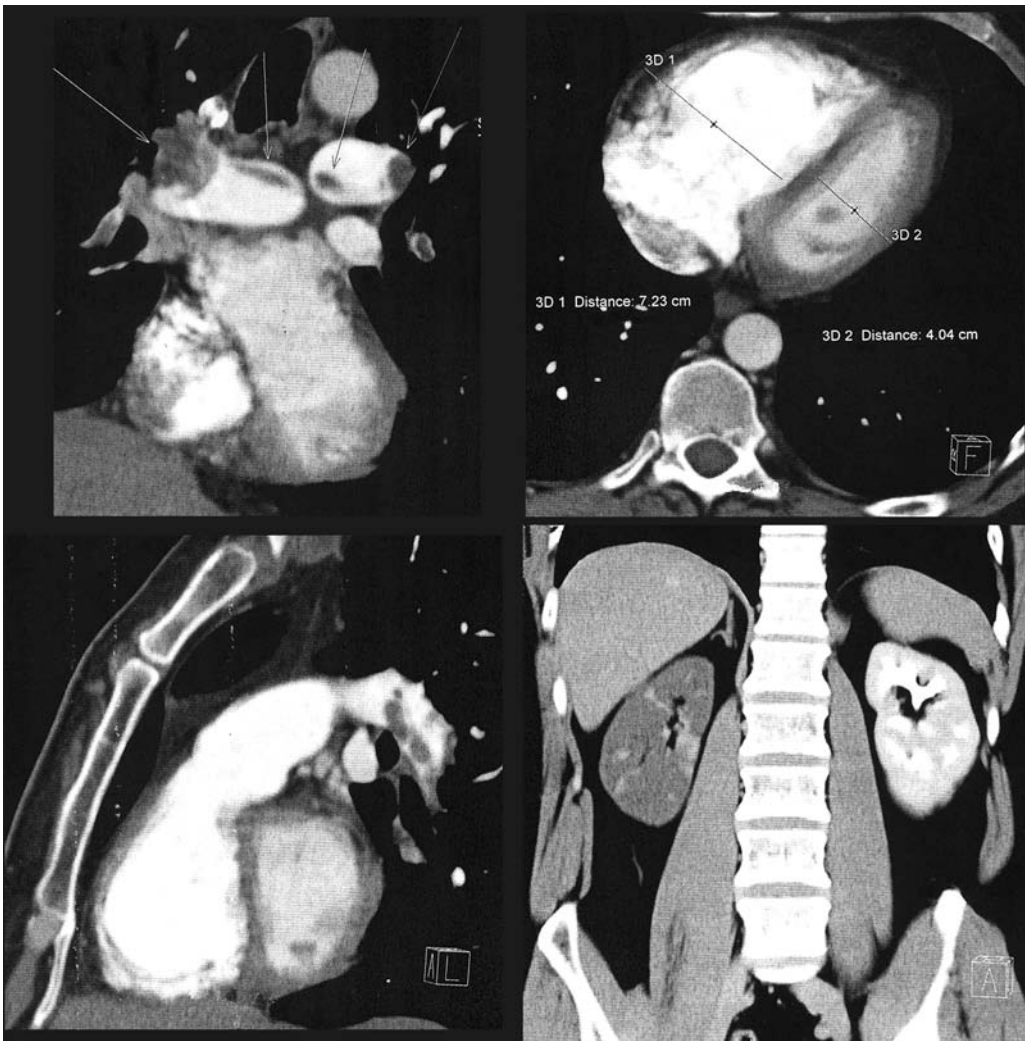

Figure 2. *Contrast enhanced computed tomography showing clockwise from top left: emboli in the both pulmonary arteries, distention of the right ventricle, infarction of the right kidney, emboli in both pulmonary arteries.*

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Prošireni sažetak / Extended abstract

Noncompaction cardiomyopathy, mitral valve prolapse and bicuspidal aortic valve in a 22-year-old men — case report

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Left ventricular noncompaction is a rare congenital cardiomyopathy which is characterized by the presence of a thin, compacted epicardial layer and a non-compacted thicker endocardial layer of the myocardium, with prominent trabeculation and deep recesses communicating with the cavity of the left ventricle.

The American Heart Association classifies noncompaction cardiomyopathy as a genetic cardiomyopathy, while the European Society of Cardiology considers noncompaction cardiomyopathy as an unclassified cardiomyopathy. The prevalence of this cardiomyopathy is about 0.014-1% in the general population. Noncompaction of the left ventricle probably results from an improper development of the myocardium in 3-8 week of intrauterine life.

The clinical picture varies from mild forms to severe forms with heart failure, complex ventricular arrhythmias and thromboembolic incidents. It can exist in an isolated form or is associated with other congenital cardiac and neuromuscular diseases. Left ventricular noncompaction is reported to be highest among the patients with Ebstein's anomaly, tetralogy of Fallot, malformation of the left ventricle outflow tract including unicuspid and bicuspid aortic valve and aortic coarctation.

In our case report, we are presenting a young male, 22 years old where we made the diagnosis of noncompaction cardiomyopathy associated with bicuspidal aortic valve and mitral valve prolapse using the imaging method of echocardiography and cardiac MRI.

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KEYWORDS: noncompaction cardiomyopathy, bicuspidal aortic valve, mitral valve prolapse.

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A rare case of angina in a patient with coronary artery microfistulas — role of echocardiographic examination

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The goal: To point out the role of echocardiographic examination in diagnosing coronary microfistulas.

Case presentation: The patient (male; 58) with so far unremarkable medical history presented to our department due to newly developed exertional chest pain and concordant abnormal ECG findings — negative T waves with ST segment depression <1 mm in lateroapical chest leads. Following the complete clinical examination which showed normal findings, the patient was sent to perform the cardiac stress test which showed no changes in relation to the ones observed in resting. Afterwards the patient was instructed to perform thallium-201 stress myocardial perfusion test. The latter indicated the presence of reversible hypoperfusion area in anteroapical segment of left heart myocardium. Therefore, the patient was scheduled for elective coronary angiography. Before the invasive diagnostics were undertaken, an echocardiography was done on which a characteristic cluster of intramyocardial high velocity "color spots" were appreciated in standard color Doppler gain and depth settings within the anteroapicolateral region of the left ventricle (**Figure 1**). Coronary blood flow was easily demonstrated in these malformations using pulsed wave Doppler (**Figure 2**) and normal left ventricle wall thickness was observed. All the other echocardiography findings were described as normal. Afterwards, coronary angiography was undertaken. Initial injections into left coronary artery revealed characteristic direct diffuse shunting of contrast from diagonal branch and distal left anterior descending artery into the left ventricle cavity through multiple microfistulas (**Figure 3**). The right coronary artery was not affected by the phenomenon. Also the cardiovascular magnetic resonance imaging was done which depicted multiple punctiform hyperintensities on cine sequences within the anterior and anterolateral region of the left ventricle. The patient was discharged from the hospital and treated symptomatically by vasodilators. He was reviewed through to 1 year period after the index hospitalization and remained well.

Conclusion: Coronary artery microfistulas are rarely seen as malformations which are usually asymptomatic, but can also cause a diverse variety of clinical symptoms. The true

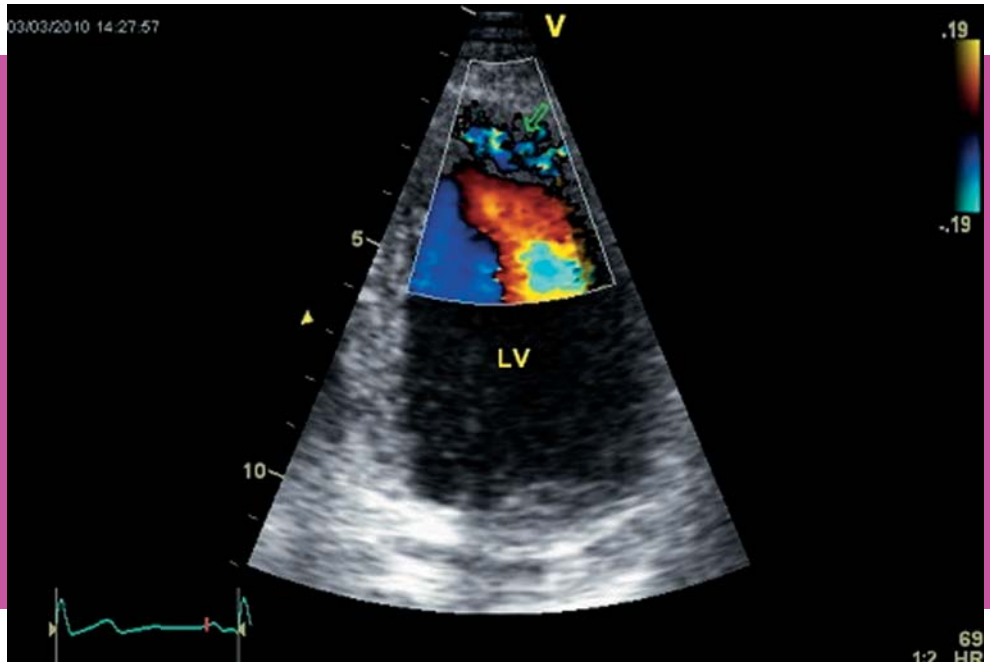

Figure 1. *Standard Color Doppler gain and depth settings showing coronary microfistulas as characteristic cluster of intramyocardial high velocity "color spots".*

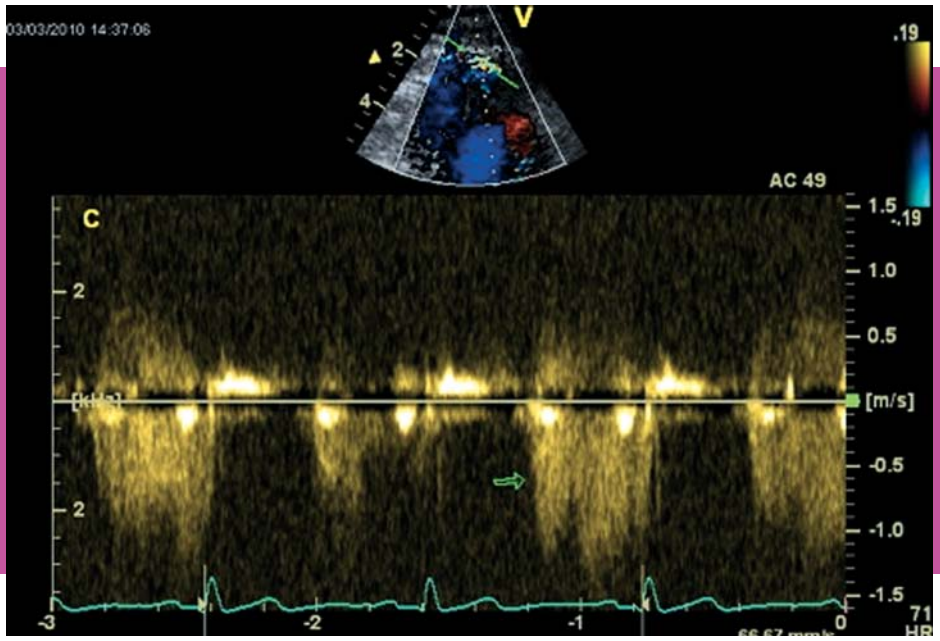

Figure 2. *Power Doppler zoom mode showing coronary blood flow within microfistulas.*

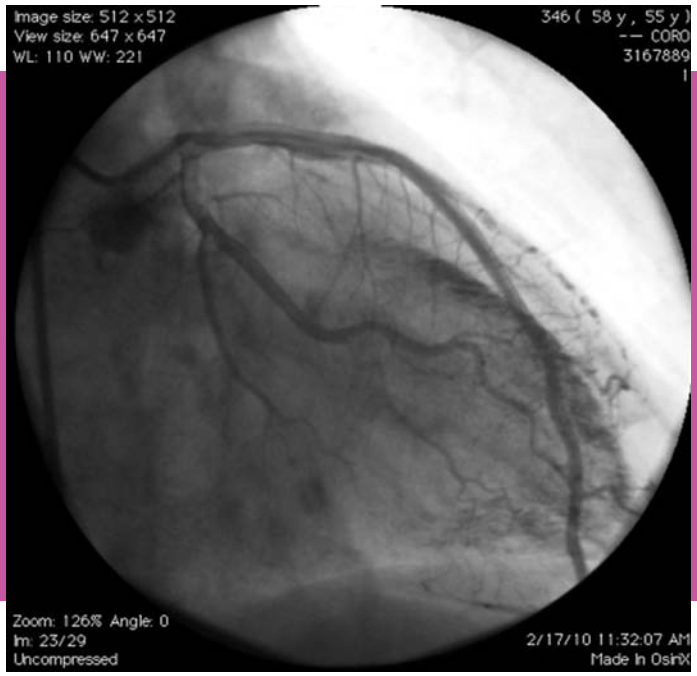

Figure 3. *Coronary angiogram depicting direct shunting of contrast from diagonal branch and distal LAD into the left ventricle cavity.*

prevalence of these anomalies is yet to be determined. Coronary angiography remains to be the cornerstone in determining the definite diagnose. Nevertheless, as we demonstrated in our patient, an echocardiographic examination can be used to indicate the presence of this kind of malformation.

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Prošireni sažetak / Extended abstract

Ascending aorta and aortic arch pseudoanaeurysm — case report

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We present a 53-year-old patient who was admitted with high fever, cough and nasal discharge. She received her kidney transplant ten years ago with subsequent taking of common immunosupressive therapy with several past hospitalizations due to respiratory infections and respiratory failure. Twenty years ago, she underwent an urgent neurosurgical procedure due to subarachnoid bleeding with underlying ruptured intracranial anaeurysm. One month before actual hospitalization, the patient was complaining of chest pain. Diagnostic work-up of the infection included native computerised tomography (CT) of the thorax and abdomen with coincidental finding of the ascending aorta and aortic arch anaeurysm. Subsequent CT aortography with reconstructions was performed showing pseudoanaeurysm of the ascending aorta and aortic arch (6.2x2.7cm) anteriorly and laterally of the ascending aorta and arch until the origin of the left common carotid and left subclavian artery with wide communication of the aorta and pseudoanaeurysm. Anaeurysmatic dilatation of the splenic artery was diagnosed as well (2.6 cm).

Cardiothoracic operation was planned and coronary angiography (transfemoral) was performed as well with the normal finding of the epicardial coronary arteries but with postprocedural haemorrhagic complication with large ipsilateral haematoma of the rectus abdominis and retroperitoneum requiring percutaneous occlusion with BeadBlock Terumo spheric particles of the inferior epigastric artery with an optimal result. Several heamodialysis procedures were undertaken after all contrast imaging procedures in order to protect the transplanted renal graft. Due to a blood loss, the patient was transfused with seven units of blood altogether. She was treated with meropenem and is afebrile with good general condition pending operation of the aorta.

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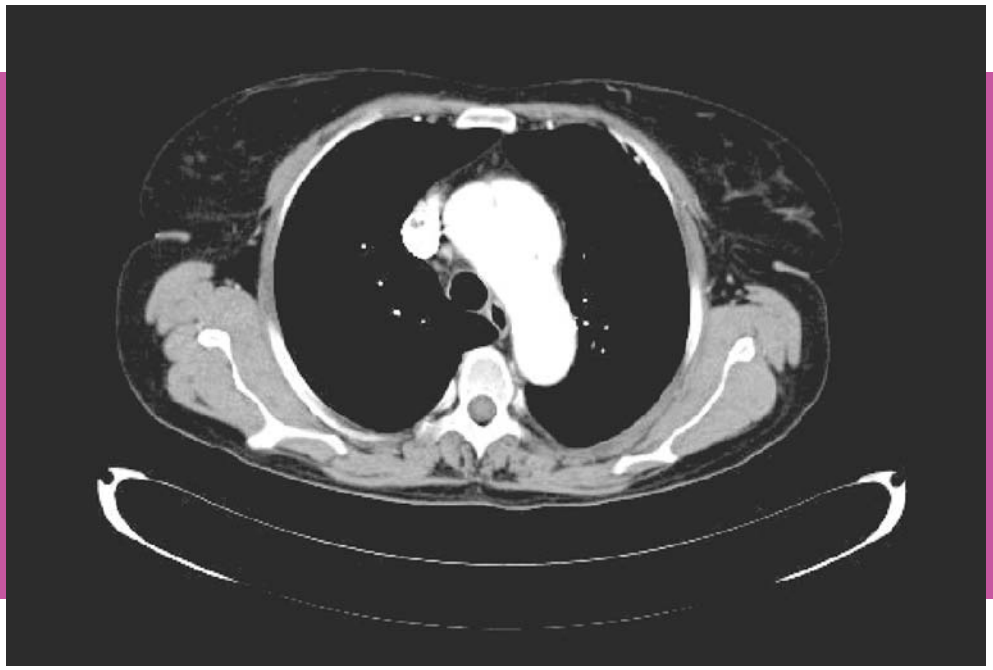

Figure 1. *Computerized tomography aortography showing pseudoanaeurysm anteriorly to the ascending aorta and aortic arch..*

Prošireni sažetak / Extended abstract

Prognostic impact of CHA_2DS_2VASC and renal dysfunction in non valvular atrial fibrillation patients: which is the best equation to stratify risk of future events?

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Purpose: Renal dysfunction (RD) is associated with an increased risk of thromboembolic (TE) and hemorrhagic events (HE) in non-valvular atrial fibrillation (NVAF). Which method of RD evaluation can better stratify the risk of cardiovascular (CV) events in NVAF is still unknown. We evaluated the additive prognostic role of RD in a wide "real world" population of NVAF outpatients.

Methods: From November 2009 and October 2013, we enrolled 3,398 consecutive NVAF patients (pts). Clinical data were derived from the E-data chart for outpatient clinic (Cardionet®) of Cardiovascular Center of Trieste, Italy. In 1,509 pts the glomerular filtration rate (GFR) was estimated at first clinic evaluation with Cochkroft-Gault (CG), Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) equations. RD was defined as GFR <60 ml/min. We recalculated CHA_2DS_2-VASc score, adding 1 point for RD, using all the three equations. The median follow-up was 27 months (Interquartile Range-IR- 15 to 40). We evaluated incidence of death, CV hospitalization (CVH), HE (fatal bleeding or leading to transfusion, a decrease in hemoglobin level of 20 g/L or hospitalization) and thromboembolism.

Results: The median age was 75 years (IR 68-81), 39.7% were male; 38% of pts had paroxysmal, 31.9% persistent and 30.1% permanent NVAF. 1,217 (80.1%) pts had hypertension, 466 (30.8%) diabetes mellitus, 295 (19.5%) heart failure, 196 (13%) prior stroke or transient ischemic attack and 23 (1.5%) previous bleedings. Median GFR was 61.8 mL/min (IR 47-77) with CG, 72.4 (IR 59-87) with MDRD and 69.1 (IR 55-84) with CKD-EPI. Median HAS-BLED score was 3 (IR 2-4) and 3 in 70% of the pts; median CHA2DS2-VASc score was 4 (IR 3-5) and 2 points in 91.1% pts. 623 (41%) pts were on anticoagulant therapy (OAT). During the follow-up, we recorded 531 (35%) deaths or CVH, 113 (7.5%) TE and 24 (1.6%) HE. Adding 1 point for RD to CHA_2DS_2VASc score pts were reclassified in a worse-class of risk in 47% with CG, 34% with CKD-EPI and 27% with MDRD ($p<0.001$). Pts with combined TE/HE during the follow-up were reclassified by the presence of RD in a worst class of risk in 62% with CG, 46% with CKD-EPI and 35% with MDRD ($p=0.009$). Stratifying these pts by antithrombotic therapy, the presence of RD, estimated by CG and CKD EPI, were associated to a significant higher risk of TE/HE during the follow-up ($p=0.006$) only in pts not treated with OAT; conversely using MDRD there was a significant higher risk only in anticoagulated pts ($p=0.04$). These results could be related to an higher rate of TE in the past medical history in the OAT group versus antiplatelets or not therapy (11,4% v 9,5% vs 5,1%, respectively, $p<0.001$). Adding RD (1 point) to CHA_2DS_2VASc score, considering the pts that experienced death/CVH, 58.5%, 44.7% and 36.4% of pts with RD were reclassified in a worst class of risk with CG, CKD-EPI and MDRD respectively ($p<0.001$), independently from OAT.

Conclusions: In NVAF pts the risk reclassification by CHA_2DS_2VASc and moderate RD seems to have an additive prognostic impact, considering death and CVH, TE and HE. CG was the best formula for global performance to reclassify pts for risk of events during the follow-up.

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KEYWORDS: non valvular atrial fibrillation, renal dysfunction, thromboembolic risk, antithrombotic drugs, mortality.

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Prošireni sažetak / Extended abstract

Atrial remodeling in permanent atrial fibrillation: mechanism and implications

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Atrial fibrillation (AF) is the most common arrhythmia in the clinical practice. It can occur at any age; however, it becomes extremely common in the elderly, with a prevalence approaching more than 20% in patients older than 85-years. AF is associated with a wide range of cardiac and extra-cardiac complications and thereby significantly contributes to morbidity and mortality. Present therapeutic approaches to AF have major limitations, which have inspired substantial efforts to improve our understanding of the mechanisms underlying AF, with the premise that improved knowledge will lead to innovative and improved therapeutic approaches.

Our understanding of AF pathophysiology has advanced significantly over the past 10 to 15 years through an increased awareness of the role of "atrial remodeling". Any persistent change in atrial structure or function constitutes atrial remodeling. Both rapid ectopic firing and reentry can maintain AF. Atrial remodeling has the potential to increase the likelihood of ectopic or reentrant activity through a multitude of potential mechanisms.

The present lecture reviews the main novel results on atrial tachycardia-induced electrical, structural and contractile remodeling focusing on the underlying pathophysiological and molecular basis of their occurrence. Special attention is paid to novel strategies and targets with therapeutic significance for atrial fibrillation.

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KEYWORDS: atrial, remodeling, permanent, fibrillation, mechanism.

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Prošireni sažetak / Extended abstract

Genetic screening for mutations in known long QT syndrome causing genes in patiens with known or suspected long QT syndrome with high throughput sequencing

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The long QT syndrome (LQTS) is a disease of the cardiac ion channels with a heterogeneous genetic background. Although case reports describing mutations in known LQTS genes in Hungarian LQTS patients are available, the distribution of the disease causing genes in a larger cohort of Hungarian LQTS patients is still unknown. Our goal was to screen all LQTS causing disease genes in a cohort of Hungarian patients with definite or suspected LQTS for presence of mutations.

Thirty-six patients (12 males, 24 females, median age 40±15 years) were screened. The patients had either a definite diagnosis of LQTS, based on prolonged QTc interval on their resting ECG (n=23), developed QTc prolongation on pharmacological provocation (n=5), or were survivors of sudden cardiac death in whom the suspicion of LQTS had been raised (n=8).

All of the 13 genes, known to cause LQTS, were sequenced. A putative disease causing mutation was defined as a nucleotide variant which was either novel, or had a minor allele frequency less than 0.5% according to the published databases. Among the 36 patients, a putative disease causing mutation was identified in 19 patients (53%). Twenty-four mutations were found in 19 patients: 14 patients had single mutations and 5 patients had compound mutations in two different genes. The three major LQTS genes made up the majority of the identified mutations as KCNQ1 (LQT1), KCNH2 (LQT2), and SCN5A (LQT3) mutations were identified in 17%; 21% and 8% of the cases, respectively. The distribution for mutations in rare LQTS genes were as follows: ANK2 (LQT4): 13%; KCNE1 (LQT5): 4%; KCNE2 (LQT6): 4%; KCNJ2 (LQT7): 13%; CACNA1C (LQT8): 4%; AKAP9 (LQT11): 13%; STNA1 (LQT12): 4%.

The results of our large-scale genetic screening provide the first available data for disease gene distribution in Hungarian patients with LQTS. It also highlights the genetic heterogeneity of LQTS and demonstrates that gene-negative patients are not infrequent.

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KEYWORDS: long QT syndrome, ion channel, mutation.

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Great arterial potential in radiofrequency ablation of ventricular arrhythmias

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Ablation success for coronary cusp ventricular arrhythmias is predicted by timing, not by a mere presence of great arterial potential.

Purpose: To investigate the predictive value of presence and timing of typical potentials registered during ablation for ventricular arrhythmias above coronary cusps.

Methods: Between May 2011 and December 2013, we performed radiofrequency (RF) ablation for ventricular arrhythmias above coronary cusps in 11 patients. In each case careful search for potentials that represent activation of myocardial extension into aortic root was done, the so called great arterial potential (GAP).

Results: GAP was registered in 9/10 patients (**Figure 1**). Timing range in respect to QRS onset was 50-116 ms. In 3 patients, the first ablation attempt at sites with GAP being less than 50 ms before QRS onset had no effect on ectopic activity. No lesion with GAP being 50 ms or more in front of QRS onset was without effect, exhibiting partial or complete suppression of arrhythmia.

Conclusions: By using careful mapping, GAP can be registered in most of the patients with coronary cusps ventricular arrhythmias. In our series it was registered in 90% of patients. In 3/8 patients the ablation attempt at sites with GAP being less than 50 ms before QRS failed to show any effect. Conversely, all lesions at sites with GAP being 50 ms or more before QRS showed effect, mostly complete suppression of arrhythmia within seconds after RF delivery start. Thus, when ablating above coronary cusps, one should not only rely on mere presence of GAP yet map extensively till registering signal being 50 ms or more before QRS.

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KEYWORDS: ventricular arrhythmias, radiofrequency ablation, coronary cusps, great arterial potential.

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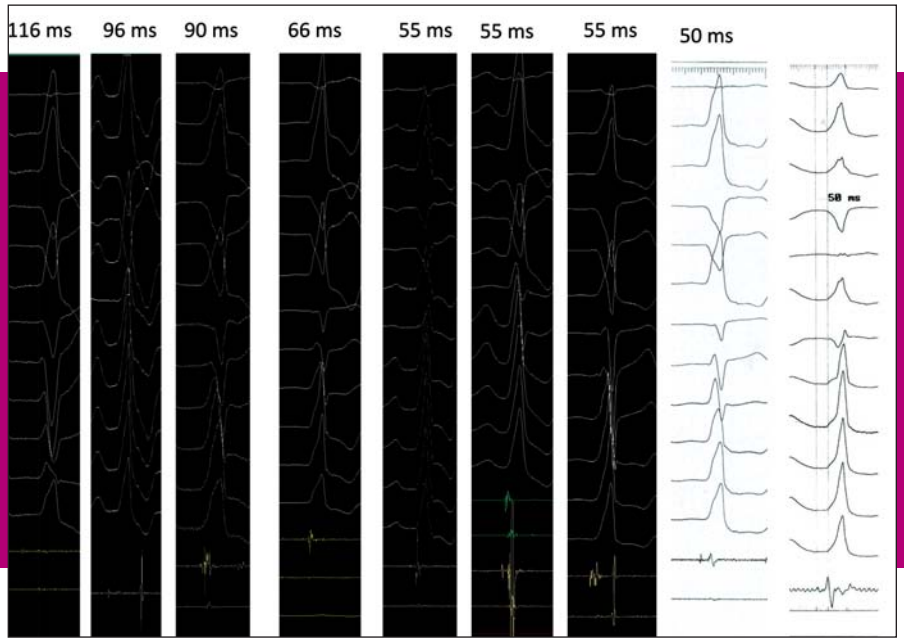

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Prošireni sažetak / Extended abstract

Heart rate variability in critically ill subjects

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Heart rate variability, a phenomenon of variations of the length of consecutive heat cycles reflects the autonomic modulation of the heart function. Parameters of monitoring the heart rate variability are suggested to be important in the assessment of autonomic neuropathy that may complicate several pathological conditions, with established clinical importance in predicting morbidity and mortality in patients with coronary syndrome and in patients with diabetes mellitus. The complexity of the critical illness of the subjects in the intensive care unit demands complex pharmacological and procedural therapeutic interventions and measures, which all have a significant impact on the parameters of heart rate variability. Such complex interactions limit the possibility to reach conclusions on a potential degree of the influences of the deteriorated organ function and the influence of the therapeutic interventions. Despite difficulties and limitations of interpretation of the variations and depression of the heart rate variability parameters, research in this field has been continuing.

In this paper, different parameters of short-term heart rate variability monitored in 25 consecutive patients who were admitted to an adult intensive care medicine unit for different conditions of critical illness are presented.

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KEYWORDS: heart rate variability, critical illness, autonomic nervous modulation.

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Prošireni sažetak / Extended abstract

30-day mortality and neurological outcome in survivors of out-of-hospital cardiac arrest

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Purpose: Mortality is high in survivors of out-of-hospital cardiac arrest (OHCA) — it is even up to 86% and it strongly correlates with ischemic brain damage. In the last decade, quality of cardiopulmonary resuscitation by emergency medical services (EMS) enormously improved as well as the postcardiac arrest treatment of survivors of OHCA in intensive care units, in particular by introducing mild induced therapeutic hypothermia to prevent ischemic brain injury. Our purpose was to evaluate 30-day mortality and neurological outcome in survivors of OHCA.

Methods: We retrospectively studied 119 survivors of OHCA (73.1% men, mean age 64.1±13.5), admitted from 2011 to 2013. On admission, they were comatose with palpable pulse, breathing either spontaneously or mechanically ventilated. Postcardiac arrest treatment included iv. infusion of fluids, vasopressors and inotropes if necessary, percutaneous coronary interventions (PCI) in case of acute coronary syndromes (ACS), mild induced hypothermia of 34°C for the first 24 hours. Neurological evaluation by cerebral performance category (CPC) scale 1-5 was performed. Mild to moderate neurological disability was registered as CPC scale 1-2, severe cerebral disability, vegetative state and brain death as CPC scale 3-5.

Results: OHCA was witnessed in 45.4%. It was the consequence of ventricular fibrillation or pulseless ventricular tachicardia (VF/VT) in 54.6% and of asystole or pulseless electrical activity (PEA) in 45.6%. Mean time from OHCA to EMS arrival was 8.6±4.5 minutes, mean time from EMS arrival to return of spontaneous circulation (ROSC) due to resuscitation by EMS 17.6±17 minutes. On arrival to intensive care, the patients were comatose, 92.4% mechanically ventilated. Mild therapeutic hypothermia was performed in 82.4% during the first 24 hours. Mean admission troponin I level was 6.5±20.8 μg/l, admission lactate 6.5±4.2 mmol/l and peak troponin I 35.3±4.8 μg/l. ACS were the cause for 41.1% of OHCA. PCIs were performed in 40.3% after emergency coronary angiography. Mean ejection fraction within the first few hours was 33.7±15%. Vasopressors were administered in 75.6%, inotropes in 57.1%, intraaortic baloon pump in 6.7%. 30-day mortality was 46.2% and 6-month mortality 52.9%. CPC scale 1-2 was achieved in 35.3%, CPC scale 3-5 in 64.7%.

Conclusion: Improvements in resuscitation and postresuscitation care resulted in an increased survival and better neurological outcome of successfully resuscitated patients due to OHCA.

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KEYWORDS: out-of-hospital, cardiac, arrest, outcome.

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Proširenи sažetak / Extended abstract

Is it time to calculate renal function in non valvular atrial fibrillation patients to stratify the risk of future events?

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Purpose: Chronic kidney disease with renal dysfunction (RD) is associated with an increased risk of thromboembolic and hemorrhagic events in non-valvular atrial fibrillation (NVAF). Although the current European Guidelines on NVAF suggest that an accurate evaluation of the renal function is useful in hemorrhagic risk stratification, it has not been yet considered in thromboembolic risk score CHA_2DS_2VASc. The aim of our study was to evaluate the prognostic role of RD in a wide "real world" population of NVAF outpatients.

Methods: From November 1, 2009 and October 31, 2013, we enrolled 3,398 consecutive NVAF patients. Clinical data were derived from the E-data chart for outpatient clinic (Cardionet®) of Cardiovascular Center of Trieste, Italy, and collected in a regional Data Warehouse. In 1,509 patients, glomerular filtration rate (GFR) was available at the first visit. Renal dysfunction (RD) was defined as GFR <60ml/min estimated using MDRD equation. The events recorded during the follow-up were death, cardiovascular hospitalization (CVH), major bleeding (including fatal bleeding or leading to transfusion, a decrease in hemoglobin level of 20 ≥g/L or hospital admission) and thromboembolism.

Results: The median patient age was 75 (range 68-81), 39.7% were male, 38% had paroxysmal, 31.9% persistent and 30.1% permanent NVAF; 1,217 (80.1%) had hypertension, 466 (30.8%) diabetes mellitus, 295 (19.5%) heart failure, 491 (32%) coronary artery disease, 196 (13%) prior stroke or transient ischemic attack, 23 (1.5%) previous bleeding episode, 31.9% and 13.2% had Charlson Comorbid Index from 3 up to 5 and >5, respectively. 1,014 patients (67.2%) were treated with more than 5 drugs. Median HAS-BLED score was 3 (range 2-4) and ≥3 in 70% of patients; median CHA_2DS_2VASc score was 4 (range 3-5) and ≥2 points in 91.1% of patients. During a median follow-up of 27 months, 531 (35%) deaths or CVH, 113 (7.5%) thromboembolic events and 24 (1.6%) major bleedings were recorded. The presence of RD identified a group of older patients with more cardiovascular (CV) risk factors, more severe heart disease, higher Charlson Index, more concomitant medical therapies. During the follow-up, we recorded 48% vs 30% of deaths or CVH (p<0.001), 10% vs 7% of thromboembolic events (p=0.02) and 2.5% vs 1% of hemorrhagic events in those with and without RD (p=0.09). Patients with RD showed a global worse prognosis for CVH/death-free survival independently from the prescription of anticoagulant (p<0.001). Instead, considering thromboembolism/major bleeding free survival, patients with RD had a worse prognosis only if taking anticoagulants (p=0.038). We can hypothesize that it could be probably related to a relatively higher number of thromboembolic events in the past medical history in the anticoagulant group versus antiplatelets or not therapy (11,4% vs 9,5% vs 5,1%, respectively, p<0.001).

Conclusions: In a "real world" of NVAF outpatients, RD identified a subgroup of older patients, with more complex CV and non CV disease at higher risk of CV, thromboembolic and hemorrhagic events. RD was associated with a higher rate of thromboembolism/major bleeding in patients on anticoagulants.

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KEYWORDS: non valvular atrial fibrillation, renal dysfunction, thromboembolic risk, antithrombotic drugs, mortality.

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Proširenі sažetak / Extended abstract

Proarrhytmic effect of amiodarone can cause "electrical storm" in patient with ischaemic cardiomyopathy and implantable cardioverter defibrillator

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The goal: Electrical storm (ES) is a life-threatening syndrome that involves recurrent episodes of ventricular arrhythmias. Data on its prognostic significance strongly suggest that these patients have a poor outcome and had an increased risk of non-sudden cardiac death. The goal of this case report is to show the importance of clinical judgment in the treatment of post myocardial arrhythmia in complex patients, such as those with an implantable cardioverter defibrillator (ICD).

Case presentation: A 61-year-old male patient experienced sustained ventricular tachycardia after myocardial infarction. Due to severely impaired left ventricular function, he underwent maximal medical treatment for heart failure together with amiodarone and ICD implantation. Following ICD implantation, he presented with ES and we noticed a prolongation of the QT interval in ECG. We excluded amiodarone because of the evident proarrhythmic effect. During hospitalization and in outpatient follow-up, we detected no ventricular tachycardia, neither in ECG monitoring, nor in the ICD device record. In the one month follow-up we detected normalization of the QT interval. However, after 9 months, the patient experienced VT episodes and one of them was terminated by ICD shock. This event was complicated by head trauma and subsequent subdural hematoma and posttraumatic subarachnoid hemorrhage. The patient underwent urgent neurocranial surgery. Unfortunately, the patient died on the third day after the surgery.

Conclusion: Cardiac mortality of patients with all types of ventricular tachyarrhythmias is high. The use of antiarrhytmic agents may predispose the patient to proarrhythmic complications that might pose a significant threat to life. Though amiodarone has become the first line drug to treat ventricular tachyarrhythmias in patients with cardiac dysfunction, it is important to be aware of its proarrhythmic effect, which may lead to an ES of monomorphic VT. Drug-induced effects on the QT interval with the associated possibility of inducing fatal arrhythmias have become a new challenge for the practitioner, the drug development process and the regulatory agencies.

KEYWORDS: electrical storm, amiodarone, proarrhytmic effect.

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Prošireni sažetak / Extended abstract

Potential role of potassium currents in the repolarization reserve: the importance of cardiac repolarization reserve in safety pharmacology

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Cardiac repolarization is a delicate process and the determinants of repolarization in various species are poorly understood. This study compared the contribution of IK1, IKr and IKs to cardiac repolarization in canine and human ventricular preparations by applying conventional microelectrode, whole cell patch-clamp and molecular biological techniques. Pharmacological inhibition of IKr evokes modest prolongation of repolarization in the dog ventricle, while it largely lengthens it in the human. These results suggest that in human, in addition to its known effect to establish the resting membrane potential, IK1 is contributing only to the repolarization reserve, while in the dog, IK1 also plays a role to secure the normal repolarization. Therefore, the smaller IK1 in human comparing to the dog makes the ventricle more susceptible to repolarization lengthening in the human than in the dog. This should be taken into consideration when pharmacological results from the dog studies are extrapolated to the human, i.e. the effect on repolarization of drugs potentially blocking IKr/HERG channels can be underestimated in the human based on experiments performed in the dog. We conclude that humans show much greater repolarization-delaying effects of IKr-block than dogs, because of lower repolarization-reserve contributions from IK1 and IKs. These results are relevant to understanding species-specific determinants of repolarization and emphasize the limitations of animal models for the human disease.

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KEYWORDS: potassium, currents, cardiac, repolarization, reserve.

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Prošireni sažetak / Extended abstract

Arrhythmogenic ion-channel remodeling in heart failure

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Heart failure carries a poor prognosis, namely, about a half of the affected patients die within five years after the initial diagnosis, and a half of these deaths are due to severe arrhythmia. The underlying proarrhythmic mechanisms in the heart failure consist of abnormal excitability and impulse conduction resulting in a triggered activity, reentrant wave fronts and/or rotors, that are related to aberrant intracellular Ca_2+-cycling. Cardiac disease modifies the operation of ion channels and transporters in a way that promotes the occurrence of cardiac rhythm disturbances, the process called "arrhythmogenic remodeling". Arrhythmogenic remodeling involves alterations in ion channel and transporter expression, regulation and association with important protein partners and has important pathophysiological implications that in major ways contribute to cardiac morbidity and mortality.

We review the changes in ion channel and transporter properties associated with the congestive heart failure. We pay a particular attention to K, Na and Ca channels; Ca transporters; connexins; and hyperpolarization-activated nonselective cation channels and discuss the mechanisms through which the changes in ion handling processes lead to cardiac arrhythmias. We highlight the areas of future investigation, important opportunities for improved therapeutic approaches that are being opened by an improved understanding of the mechanisms of arrhythmogenic remodeling.

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Prošireni sažetak / Extended abstract

Improved quality of life in patients with implanted cardiac resynchronization therapy devices

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Considering the fact that the implanted cardiac pacemaker can have a significant impact on a patient's life quality, the aim of the research was to determine how much the implantation of a cardiac resynchronization therapy (CRT) device really changes patients' life. The questionnaire SF-36 was used to test the subjective evaluation of life quality after the implantation of a CRT device on a sample of 50 participants. The hypothesis in the study was that the implantation of a CRT device improves tolerance of the physical activity, decreases the patient's dependency on the help of other people, correlates to the visible qualitative improvement of the social and family environment, and improves communication.

The results show that in regards to the bodily functioning, limitations due to body impediments, social functioning, mental health, vitality, body pain, and total perception of health, the quality of life was significantly improved statistically ($p < 0.05$). The only exception was the domain of limitations due to emotional problems where there was no statistically significant difference after the implantation of a CRT device. There was no difference in relation to age, while in relation to gender there was a correlation to the total perception of health and changes in health, where statistically significant difference in the changes of life quality was observed in male patients.

This research proved that the total life quality in its various aspects improved significantly after the implantation of a CRT device, which was the starting hypothesis of the study.

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KEYWORDS: heart failure, cardiac resynchronisation therapy, quality of life.

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Prošireni sažetak / Extended abstract

Channelopathies and comma — case report

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Introduction: Cardiac arrhythmias usually occur in the presence of abnormal substrate that is responsible for creating and disturbed conduction of impulses. Ischemic heart disease is the primary cause of the development of ventricular fibrillation, and also the other, as hypertrophic and dilated cardiomyopathy make up the most of the cases. In a post-mortem series of victims of cardiac arrest, structural abnormalities were absent in 5-8 % and they have been, for many years, called idiopathic ventricular fibrillation (IVF). Now, with the help of molecular biologists, substrate IVF is practically defined. In less than a decade, the essential facts suggest that genetically determined abnormalities in the proteins that control the electrical activity can cause cardiac arrest in a structurally intact heart. Finally, at least nine genes are associated with inherited arrhythmogenic diseases and the number of genes is expected to be even higher. The advances in molecular biology reveal the causes of sudden cardiac death (SCD) in patients with morphologically normal myocardium. The term channelopathies is introduced for the diseases such as long QT syndrome, Brugada syndrome, etc.

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Case presentation: We report a 65-year-old male, a case of the patient with syndrome sudden cardiac death understood as a stroke with comma, which was initially treated at the Department of Neurology, and then relocated to the Department of Internal Medicine. Having excluded stroke as the cause of coma, heart attack and pulmonary embolism, and on the basis of ECG recorded earlier, the incident that was recorded such as ventricular fibrillation is suspected of channelopathies. The diagnostic evaluation and clinical testing based on proper findings of coronary angiography indicated structural heart disease. The patient was relocated to the Clinic for Cardiovascular Surgery for implantation of implantable cardioverter defibrillator.

Conclusion: On the basis of the exclusion of cerebrovascular accident, myocardial infarction and coronary artery disease, pulmonary embolism, as well as metabolic causes of coma, and bearing in mind the positive family history of sudden cardiac death, the diagnosis of channelopathies as a cause of malignant cardiac arrhythmias was made and the transfer of the patient to the Clinic for Cardiovascular Surgery for the implantation of permanent cardioverter defibrillator was performed.

KEYWORDS: channelopathies, sudden, cardiac, death, implantable cardioverter defibrillator.

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Prošireni sažetak / Extended abstract

Both atrioventricular nodal reentrant and atrioventricular reentrant tachycardias in one patient: a case report

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The two most common supraventricular tachycardias are typical (slow-fast) atrioventricular nodal reentrant tachycardia (AVNRT) and orthodromic atrioventricular reentrant tachycardia (AVRT) using accessory pathway (AP). Nowadays, a leading method in the treatment of supraventricular re-entrant tachycardias is radio-frequent (RF) catheter ablation during the electrophysiological (EP) study.

We report the case of a 46-year old woman on whom an EP study was performed due to the presence of paroxysmal supraventricular tachycardia documented in 12-lead ECG. During the EP study, at baseline, supraventricular tachycardia was induced very easily and it corresponded to orthodromic AVRT (frequency of 190-200/min) using concealed, left lateral AP (PPI - TCL = 100 ms; VAV pattern, preceding positive for AP). However, during the study, AVRT spontaneously converted to the typical slow-fast AVNRT (frequency 150/min) using the slow AV node pathway (PPI - TCL >150 ms; VA < 30 ms; preceding negative for AP; jump noted at programmed pacing (500+280 ms) from right atrium as well as echo beat). During the EP study, a slow pathway was localized and then ablated using the RF catheter ablation. By performing the transseptal puncture of the interatrial septum, the left lateral wall AP was also successfully localized and then ablated using the RF catheter ablation. The patient remained asymptomatic for more than 6 months after the successful ablation procedures.

To the authors' best knowledge, the coexistence of AVRT and AVNRT is not reported in the literature.

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KEYWORDS: accessory pathway, slow pathway, atrioventricular reentrant tachycardia, atrioventricular nodal reentrant tachycardia, catheter ablation.

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Prošireni sažetak / Extended abstract

Pentadecapeptide BPC 157 antiarrhytmic effect in rats treated with bupivacaine toxic doses

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Introduction: Bupivacaine, still a drug of choice in all of the techniques of regional anaesthesia, acts mainly through blockade of Na+ channels, K+ and Ca^{2+} channels as well, changing the way the heart conduction system works to cardiac rhythm disturbances in a case of inadvertent i.v. application because we do not have an antidote. Pentadecapeptide BPC 157 antiarrhythmic effects, through its the interaction with NO-system, were already established in the previous studies of digoxin toxicity, hyper- and hypokalemia. The aim of the study is to establish BPC 157 antiarrhythmic effect when cardiac rhythm disturbances are caused by bupivacaine toxic dose and to explore whether this effect is dose-dependent and related with NO-system.

Materials and Methods: The study was conducted on female Wistar albino rats, divided into groups of 6. We had two protocols with 4 experimental groups each, treated with BPC 157 i.p. (50 μg/kg, 10 μg/kg, 10 ng/kg, 10 pg/kg) and the control group treated with saline 5 ml/kg i.p. either 30 minutes before (preventive) or 1 minute after bupivacaine 100 mg/kg i.p administration (therapeutic). Three standard ECG leads were recorded for 90 minutes. The wave amplitudes P, R, S and T, the duration of waves and intervals P, PR, QRS and RR, the presence of ventricular ectopies, tachycardia, AV block and asystolia were analyzed.

Results: Bupivacaine caused bradycardia, PQ prolongation, all degrees of AV block, QRS widening, ST-T wave changes, multiform ventricular ectopies (VES), ventricular tachycardia (VT) and asystolia, as well as the decrease of the wave amplitudes. BPC 157 treated animals had in the both protocols and in all of the applied doses less prolongation of P wave in particular ($p<0.001$), of QRS complex and PR, QT and RR intervals as well ($p<0.05$). The decrease of the wave amplitudes was also counteracted, with lower mortality in the experimental groups (16.7% vs. 50%). All of the animals who did not survive had T wave elevation.

Discussion: BPC 157 has shown cardioprotective effect in the both protocols and in all of the applied doses. Since prolongation of QT interval was lower in the experimental groups, the predisposition to malignant arrhythmias was also lower, which could explain the lower mortality. The T wave elevation present in all of the non survivors is a sign of impeding cardio toxicity and inevitable death, so we can confirm the conclusion of Mauch et al. and propose to use it in clinical practice as an early sign of a threatening catastrophe.

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KEYWORDS: cardiac arrhythmias, bupivacaine, pentadecapeptide BPC 157, rats.

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Proširenisažetak / Extended abstract

Person-centered integrated approach in an advanced heart failure clinic

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Goal: Cardiovascular disease (CVD) constitutes epidemiological, clinical and social emergency and requires an effective and efficient person and people-centered integrated interventions to empower patients, increase adherence and improve clinical-psycho-social outcome. This interdisciplinary, integrated approach requires holistically attending to the person's needs both through the supportive and the palliative stages of heart failure.

Material and Methods: In 2013, an Advanced Heart Failure Clinic (AHFC) was activated within the Outpatient Cardiovascular Department in Trieste. AHFC is made up of an interdisciplinary team (2 cardiologists, an internist, a psychologist, and 4 dedicated nurses) who collaborate with GPs and healthcare professionals from the four District teams which make up the Province of Trieste. The goal is to provide person-centered, integrated supportive and palliative care to patients with an advanced heart failure (NYHA III-IV) after the discharge from hospital/residential facility, or to those requiring longitudinal monitoring (both as outpatients or at their homes). A Person-Centered Psycho-Social Well-being Questionnaire (PCPSWQ) was developed to investigate personal, social and healthcare well-being as well as the knowledge of the disease and the level of adherence. Clinical and instrumental data were retrieved from the Cardionet® electronic registry of Trieste Cardiovascular Center.

Results: In 2013, AHFC made a total of 479 visits (173 patients; 68% males; mean age 76±9; 68% NYHA 3-4; 92% in polypharmacological therapy; 45% Charlson index >5. 52 questionnaires were administered to 46 patients (38 males, age 74.9±, years of education 8.5; 13 living alone or with a disabled relative). The structured questionnaires were integrated by 44 narrative interviews. 85% of the patients expressed satisfaction for their relationship with their GP/specialist. However, 45% expressed little knowledge or awareness of their disease. 78% stated optimal adherence to the therapy, but only 55% follow an adequate nutrition and lifestyle regimen.

Conclusions: These preliminary results highlight the importance of an integrated, person-centered beehive approach to identify subjective and objective needs and develop multimodal communication instruments to increase patient's knowledge, awareness, self empowerment and self-management capabilities. Person-centered, integrated care needs to be redesigned through a more thorough investigation of patients' clinical, psychological and social dimensions and interdisciplinary teams must develop and implement integrated assessments to prevent fragmentation of the person and care provided to the person.

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muldimensional evaluation, heart failure.

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Prošireni sažetak / Extended abstract

Systolic and diastolic heart failure: similarities and differences

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Heart failure (HF) is defined as an inability of the heart to deliver oxygen at a rate to fulfill the metabolic requirements of the tissues. Over the last decades, the clinical course of different heart disease has been changed. The mortality from acute myocardial infarction has significantly decreased — patients survive, but they often have the residual left ventricular dysfunction and the subsequent development of HF syndrome. Also, the overall life expectancy has become increasingly longer. These changes signed out HF as an epidemic with strong public health implications that are associated with significant mortality, morbidity and healthcare expenditures. HF is nowadays becoming the primary cause of death in the elderly population.

Although the impaired systolic function of the heart with low cardiac output (HF with reduced ejection fraction, HF-REF) is still considered to be the leading form of HF, impaired left ventricular filling in diastole with preserved systolic function can also lead to symptoms of heart failure and is usually defined as HF with preserved ejection fraction (HF-PEF).

According to the available data, almost a half of the patients with symptoms of HF are found to have normal or nearly normal ejection fraction. Despite the high prevalence, HF-PEF pathogenesis and pathophysiology has not been sufficiently elucidated and no effective treatment has been identified.

The scope of the research is to get an overview of the available literature regarding HF with a special emphasis on the similarities and differences between diastolic and systolic forms of the syndrome, early diagnosis and potential new therapeutic targets.

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KEYWORDS: heart failure, preserved ejection fraction, diastole.

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Prošireni sažetak / Extended abstract

We need more regional heart failure clinics in Slovakia in real life

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Purpose: At this time we have only three active heart failure (HF) clinics in the metropolitan areas of Slovakia and no organised HF disease management programme exists in rural, regional settings.

Patients and Methods: We compared clinical characteristics, evidence-based medications and outcomes in 118 patients (pts) from one regional centre with other centres in Slovakia (n = 306) that participated in the Heart Failure Long-Term registry. We statistically analysed the reasons for differences in the benchmark report.

Results: In the regional centre, the patients significantly (p <0.05) older than 65 (74.6% vs 32.7%, odds ratio, OR >5), with non-ischemic etiology (71.2% vs 41.7%, OR 3.46, predominantly valvular etiology), more advanced HF (in NYHA class III-IV: 61% vs 30.1 %, OR 3.63) and fewer males (57.6% vs 70.5%, OR 0.57) were recruited as outpatients. Common comorbidities were significantly (p <0.05) more often present in the regional centre: diabetes (44.1% vs 25%, OR 2.36), chronic renal dysfunction (35.6% vs 10.3%, OR 4.84), current malignant cancer (15.3% vs 1.3%, OR >5), permanent atrial fibrillation (45.8% vs 8.3%, OR >5). At the first glance, it seemed that ACE-inhibitors/sartans (71.2% vs 90.4%, OR 0.26), beta-blockers (78% vs 90.4%, OR 0.38) and mineralocorticoid receptor antagonists (23.7% vs 60.9%, OR 0.20) are significantly (p <0.05) underused in the regional centre. But after considering the objective reasons for non-using these medications in the regional centre, these differences disappeared. In regional centre, more pts have a history of previous hospitalisation (64.4% vs 28.6%, OR 4.52). During a 12 month follow-up more pts in the regional centre died (20.3 % vs 4.4 %, OR >5) and were more often re-hospitalised: 1st (66.1% vs 16.4%, OR >5), respectively the 2nd re-hospitalisation (48.7% vs 11.8%, OR >5). The hazard of death and re-hospitalisation increased with more advanced age and multiple comorbidities.

Conclusion: In Slovakia, HF clinics are urgently needed in the regional settings in order to improve the quality of HF care and optimized outcomes.

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Prošireni sažetak / Extended abstract

Hospital-to-Community Integrated Pathways for Heart Failure: critical aspects and future prospectives

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Chronic care for cardiovascular disease (CVD) poses an ever increasing challenge for the future of economic and social sustainability. Caring for patients with heart failure (HF) requires a shift from fragmentation to harmonization and integration of services along the hospital to territory inpatient-outpatient pathways.

Methods and Results: Since 2009, the Province of Trieste (population app. 250,000) has been developing integrated Hospital-to-Territory pathways. Clinical and instrumental data were retrieved from the Cardionet® electronic registry of Trieste Cardiovascular Center. From November 2009 to October 2013, 2,217 patients with HF were registered in the Cardiovascular Registry of the Province of Trieste (10.4% of total patients; aged 75.5, males 56%, NYHA 3-4 25%, hypertensive heart disease 49%, ischemic 47% and valvular 45%). 93% of the patients were evaluated through echocardiogram upon enrolment. LVEF was 40% (27% of patients), 41-49% (14% of patients), 50% (59% of patients). The age and Charlson index >5 within the three groups was 73, 74 and 76 years respectively (p<0.001) and 38%, 33% and 26% (p<0.001). The 3 groups of patients underwent the treatment with ACE/inhibitors/sartans and betablockers in 78%, 73% and 72%, and in 54%, 62% and 48%, respectively. Nursing interventions for the continuity of healthcare services were activated for 24% and 36% of patients in NYHA 1-2 and 3-4, respectively. Domiciliary or intermediate residential care cardiologic services (as per shared GP-cardiologist healthcare intervention plan) did not show substantial changes throughout the years amounting to 8-10% of the total care interventions. Hospitalizations due to HF within the Province of Trieste continued to decrease from 1225 in 2010 to 1095 in 2013 (-10.6%), as against an overall increase of hospital admissions in the Cardiovascular Department (from 12.9% to 18.8% of the total admissions). All of the patients discharged from the Cardiovascular Department were enrolled within three months by the Community Cardiovascular Center. The implementation of Hospital-to-Community Pathways has resulted in a gradual increase of patient referrals from other departments (from 65 and 17% to 14% and 29% respectively, within 30 or 90 days from the discharge).

Until 2012 all of the patients were enrolled by the Chronic Patient Heart Clinic. Since January 2013, 173 patients (7.8%; 479 visits, 2.8/pt) with advanced HF, frailty and/or multiple comorbidities (68% males; mean age 76±9; 68% NYHA 3-4; 59% LVEF<40%; 53% in atrial fibrillation; 92% undergoing therapy with at least 5 drugs; 45% with Charlson Index >5; 36% with at least one missing BADL, 77% with at least one IADL) were enrolled in the Advanced HF Clinic, an inter-disciplinary, supportive and palliative care team which works in close collaboration with the Social Care / Health Care Districts. 39.3% of the patients were seen at home or within an intermediate residential facility. 69.3% received at least one nursing intervention, 27% at least a psycho-social assessment carried out by a psychologist.

Conclusions: An integrated Hospital-to-Community network for HF allowing for Integrated Pathways between hospital, Intermediate Facilities, Social/Healthcare Districts, outpatient cardiology clinics for chronic patients and for patients with advanced HF requiring supportive and palliative care, can actually reduce hospital admissions and allow for effectively care for a fairly large amount of elderly/frail patients discharged from the internal medicine/geriatric departments with advanced HF, multiple comorbidities and specific polytherapy needs.

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Proširenи sažetak / Extended abstract

Independent influence of previous myocardial infarction, renal function and ejection fraction on the severity of heart failure in men

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The Goal: Processes of cardiac remodelling, especially collagen deposition and following fibrosis, seen both in infarcted and non-infarcted myocardium are important contributors to the development of the impaired left ventricular (LV) function. The objective of this study was to assess the independent influences of various clinical variables, including previous myocardial infarction (MI), on the severity of heart failure (HF) in men.

Patients and Methods: This prospective study included consecutive male patients with acute HF, hospitalized at the Division of Cardiology, Department of Internal Medicine, University Hospital Centre Split. Statistical analysis was performed by means of T-test and linear regression in univariate, and multiple logistic regression in multivariate analysis. The P value of less than 0.05 was considered to be statistically significant.

Results: 87 male patients (mean age 74.3±8.1) were included in the study. There were 21.8% of those with previous MI, 39.1% diabetics, 70.1% non-smokers, 18.4% former smokers and 11.5% current smokers and 56.3% with arterial hypertension. Patients had median (interquartile range) values of creatine clearance 54.5 mg/dL (41.6 - 66.7), EF 45% (35 - 55), NT-proBNP 482.7 pmol/L (181.4 - 1446). In an univariate analysis previous MI (r=0.265; p=0.039), LV ejection fraction EF (r=-0.372; p=0.003) and creatine clearance (r=-0.608; p<0.001) significantly correlated with serum values of NT-proBNP, while all other clinical variables showed no association. In a multivariate analysis, lower EF (ß=-0.272; p=0.008) and lower creatine clearance (ß=-0.544; p<0.001), with adjustment for age, were independent predictors of higher values of NT-proBNP while previous MI (ß=0.072; p=0.486) did not show a significant correlation.

Conclusion: Processes that globally act on the deterioration of LV function, particularly impaired renal function, more significantly contribute to the severity of HF than previous MI.

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Proširenи sažetak / Extended abstract

Clinical profile of hospitalized patients with acutely decompensated heart failure: single centre results

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Goal: Heart failure(HF) is the leading cause of hospitalization in seniors and it often occurs in >70-year-old subjects. The population of Western countries is getting older, due to better treatment and salvage of patients with cardiovascular diseases. To analyze the clinical profile, management and outcome in patients hospitalized for acutely decompensated heart failure (ADHF).

Patients and Methods: The analysis included 1820 patients with ADHF enrolled in Department of Cardiovascular Diseases, Clinical Hospital Center Rijeka, from June 2006 to June 2012.

Results: The mean patient age was 75.1±10.1, 51% were women. 52% of patients had coronary heart disease, treated hypertension 68%, diabetes mellitus 38%, chronic obstructive pulomary disease 16%, chronic kidney disease (defined as eGFR <50 mL/min/1.73 m^2) 56%, anaemia 40%, cerebrovascular disease 8%. At admission 51% of patients had atrial fibrillation, 15% left bundle branch block, 9% right bundle branch block and 7% had permanent pacemaker. Urea value at admission was 11.6±7.5 mmol/L, and serum creatinine 130.5±61.1 μmol/L. NT-proBNP was performed in 36% of patients, with an average value of 1323.4±1673.7 pmol/L. Echocardiography was performed in 73% of patients, with average ejection fraction (EF) of 39.3±14.6% and preserved left ventricular EF (defined as EF 45%) in 39% of patients. The mean NYHA class value was 3.7 (3.5 in alive, and 3.9 in deceased patients). Medical therapy included diuretics (98%), beta blockers (82%), angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers (77%), digoxin (27%), mineralocorticoid receptor antagonists (25%), statins (37%), antiarrhythmics in the narrow sense (20%), oral anticoagulants (36%), and dihydropiridines (17%). In-hospital mortality was 15.7% and 1/3 of all deaths was sudden cardiac death. The average length of hospital stay accounted for to 9.9±17.9 days (10.48±5.73 days in patients released alive and 7.0±12 days in deceased patients).

Conclusion: Although the results of our survey differ in some variables, generally they are comparable with the results of other national surveys. Further, it can be considered useful as it utilizes an observational methodology to answer relevant clinical questions and identify some unsolved issues, in other words, in our Centre we can implement future strategic programmes in accordance with the recommendations of the Heart Failure Association of the European Society of Cardiology.

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Proširenи sažetak / Extended abstract

Cardiovascular disease in women

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Cardiovascular disease (CVD) is the most common cause of death and disability in female patients with a steady increase in incidence. Available data suggest that there are significant differences between men and women in CVD epidemiology, diagnostic procedures, prognosis and effects of the treatment. A series of open questions reflect differences in CVD risk that are defined by different hormonal status throughout the life in men and women. Different sensitivity and specificity for a number of diagnostic cardiovascular tests is described for female patients, as well as the uneven response to the therapy in the practically same clinical circumstances. Also, the mortality from CVD is higher in women than in men. It might be explained by a higher median age and a higher degree of comorbidity. It is still not possible to give precise answers to a number of open questions in this field which is mostly due to the fact that women are generally underrepresented in randomized controlled trials. A similar relationship can be found in the studies that examine the diagnostic and/or therapeutic cardiovascular procedures. Nevertheless, we should be aware that women are more often prescribed nitrates, calcium channel blockers, diuretics and sedatives, but in a minor percentage they receive beta-blockers, statins and aspirin than men. In this review, we have analyzed the available scientific sources on cardiovascular morbidity in women with a special emphasis on open issues and priorities for the future studies.

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Prošireni sažetak / Extended abstract

Functional and circulatory renal changes in advanced heart failure

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Objectives: The aim of the study was to describe the relations between heart and renal functions and to investigate whether reduced glomerular filtration rate is influenced rather by reduced perfusion or venous congestion.

Patients and Methods: A prospective cohort study of 101 patients (69 men, 32 women) with chronic heart failure aged 52 (median age). Patients included in the study consist of two distinct groups. The group of patients with advanced chronic heart failure on the waiting list for orthotopic heart transplantation (N = 78) and the group of patients with pulmonary arterial hypertension (N = 23). The etiology of chronic heart failure in the first group was in 57% ischemic and in 43% non-ischemic. In the whole cohort, 23.7% of patients had diabetes mellitus, 30% were obese and 42.6% had arterial hypertension. We analyzed the blood samples, parameters of echocardiography and right heart catheterization.

Results: Left ventricular ejection fraction correlated with the estimated glomerular filtration rate eGFR (r = 0.214, p = 0.036) in the complete set of patients, but not in the two divided groups. There was no correlation between cardiac output and eGFR in either group. We found a correlation between cardiac output and renal perfusion pressure in a complete set (r = 0.232, p = 0.0225) and in patients with chronic heart failure (r = 0.254, p = 0.0278), but no significant correlation in patients with pulmonary hypertension. There were no significant correlations between central venous pressure and eGFR in any of the studied groups. Echocardiographic monitoring of the right heart sections showed a correlation between TAPSE as a marker of right ventricular function and eGFR in the complete set (r = 0.351, p = 0.0033) and in patients with chronic heart failure (r = 0.417, p = 0.0039), but not in patients with pulmonary hypertension. In the complete set, the mean pulmonary artery pressure (PAP) correlated with the variables determining the renal function: PAP and renal perfusion pressure (r = -0.345, p = 0.002). PAP and eGFR (r = -0.299, p = 0.009). In the other two studied groups, these correlations were not significant.

Conclusion: In the selected group of heart failure patients, we found left and right ventricular functions to be the main determinants for renal function. Current cardiac output or right atrial pressure as the markers of renal perfusion was not associated with renal functions in advanced, but stable heart failure patients with low burden of extracardiac comorbidities.

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KEYWORDS: renal venous congestion, cardiac output, renal perfusion, cardiorenal syndrome, advanced heart failure.

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Effect of right bundle branch block on in-hospital mortality in patients with heart failure

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Goal: The prognostic significance of right bundle branch block (RBBB) in hospitalized heart failure (HF) patients is unclear. Hence, we sought to determine its prognostic value during hospital stay in patients admitted for HF.

Patients and Methods: The study population consisted of the patients treated for HF in Department of Cardiovascular Diseases, University Hospital Centre Rijeka, from 2006 to 2012. Many variables were compared between group without BBB (G1), with left BBB (G2) and with RBBB (G3). Also, the same variables were compared in G3 between patients who were discharged alive and those deceased.

Results: There were totally 1820 patients (aged 75.1±10.1; men 48.8%; mean NYHA class 3.6; NT-proBNP 1,323.4± 1,673.7 pmol/L; echocardiography in 73.4%). G1 consisted of 1380 (75.8%), G2 of 275 (15.1%) and G3 of 165 (9.1%) patients. G3 patients were older than G2 and G1 patients, with fewer women and slower heart rate (HR). Mean NYHA class was 3.7 in G3 and G2 and 3.6 in G1, with NT-proBNP value higher in G3 and G2 than in G1. The lowest left ventricular ejection fraction (EF) was found in G2, with no difference between G3 and G1. Serum urea and creatinine were higher in G3 and G2 than in G1, and chronic obstructive lung disease was more frequent in G1. Mortality in G1, G2 and G3 was 14.3%, 19.6% and 20.6%, respectively. Deceased patients in G3 were older, with lower blood pressure, glomerular filtration rate and EF, and with higher HR, troponin, NYHA class, NT-proBNP, urea and creatinine values than in survivors.

Conclusion: The in-hospital mortality in HF patients with RBBB was as high as in those with LBBB and significantly higher than in patients without bundle branch block. In these patients, older age, lower blood pressure and EF, poorer renal function and higher HR, NYHA class, troponin and NT-proBNP may additionally cause adverse hospital outcome.

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Prošireni sažetak / Extended abstract

Gender and age related differences in patients hospitalized for acutely decompensated heart failure: single centre results

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Goal: To provide a real-life single centre overview of hospitalized patients with acutely decompensated heart failure (ADHF), evaluating differences and similarities according to age and gender, analyzing the clinical profile, management and outcome.

Patients and Methods: The study population consisted of the patients (1,820), enrolled in Department of Cardiovascular Diseases, Clinical Hospital Center Rijeka, from June 2006 to June 2012. Differences were assessed in men and women according to four age groups (I. <64, II. 65-74, III. 75-84, IV. 85 years).

Results: In all patient groups there were 51% women. The mean age of all groups was 75.1±10.1 years. The age of patients that were released alive was 74.7±10.1. 44% of the patients were 75-84 years old, 14 % <64 years old, while 16% were 85 years old. In all patient groups there were 71% of women in the group 85 years old, while 75% of men in the group <64 years old. 80% of men (I.) and 70% of women (IV.) had coronary heart disease. 72% of men (I.) and 76% of women (IV.) had treated hypertension. 71% of men (I.) and 67% of women (IV.) had diabetes mellitus. 79% of men (I.) and 74% of women (IV.) had chronic obstructive pulmonary disease, 86% of men (I.) and 69% of women (IV.) had atrial fibrillation. 74% of men (I.) and 80% of women (IV.) were treated with angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers. 74% of men (I.) and 74% of women (IV.) were treated with beta-blockers. 77% of men (I.) and 76% of women (IV.) were treated with aldosterone antagonists. Median length of hospital stay was 9.9±17.9 days. Mean age of deceased ones was 77.3 ±9.9 years; 80,3±7,4 in women and 73,7±11,4 in men. In-hospital mortality was 8.6% among women and 7.1% among men.

Conclusion: The clinical characteristics of ADHF differ considerably with age and gender. In our centre, during the above mentioned period there were more women with ADHF and they were older, with higher rate of coronary heart disease, treated hypertension, diabetes mellitus, chronic obstructive pulmonary disease and atrial fibrilation in „older elderly“ group 85 years old, compared to men. Angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers, beta-blockers and aldosterone antagonists were mostly prescribed in men 64 years old, also in women 85 years old. Deceased women were older than men.

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Prognostic importance of body mass index in heart failure with preserved ejection fraction at mid-term follow-up

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Aim: To assess the prognostic importance of the body mass index (BMI) in heart failure with preserved ejection fraction (HFPEF) in a prospective study compared to heart failure with reduced ejection fraction (HFREF).

Patients and Methods: The study included a total of 109 patients (69 male, mean age 71±11 years) admitted to Medical wards for heart failure within one year's period (2010-2011). The follow-up was 24 months. The patients were divided into two groups based on left ventricular ejection fraction (LVEF); HFPEF with LVEF more than 40% (n=64) and HFREF with LVEF less than 40% (n=45). We analyzed cut-off points 18.5, 25, 30, 35 for BMI according to BMI classification (underweight, normal, overweight, moderately obese, severely obese). Cumulative endpoint was all-cause mortality or acute myocardial infarction or stroke. Data were analyzed using the JMP9 statistical program. Unless otherwise specified, the data are presented as means.

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Results: BMI was significantly higher in HFPEF vs. HFREF (30.2 vs. 27.7, p<0.05). Severely obese patients were significantly more prevalent in HFPEF vs. HFREF (21% vs. 2%, p<0.01). The patients with HFPEF and BMI 35 had significantly higher cardiovascular (CV) mortality (39% vs. 12%, p<0.05), hospital mortality (31% vs. 8%, p<0.05) and higher prevalence of cumulative endpoint (54% vs. 24%, p<0.05) compared to patients with HFPEF and BMI <35. There was no significant difference in all-cause mortality. A multivariate logistic regression identified BMI as the only independent predictor of hospital mortality (OR 1.16 per unit, CI 1.03-1.35, p<0.05) in HFPEF but not in HFREF.

Conclusions: Patients with HFPEF have significantly higher BMI and higher prevalence of severe obesity (BMI >35). The patients with HFPEF and BMI 35 had significantly higher CV mortality, hospital mortality and higher prevalence of cumulative endpoint compared to patients with BMI <35. BMI was the only independent predictor of hospital mortality, but not of two-year CV and all-cause mortality, in HFPEF.

KEYWORDS: heart failure with preserved ejection fraction, body mass index, prognosis.

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Prošireni sažetak / Extended abstract

Prognostic value of atrial fibrillation in heart failure with preserved ejection fraction at mid-term follow-up

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Aim: To assess the influence of atrial fibrillation on mortality in heart failure with preserved ejection fraction (HFPEF) in a prospective study compared to heart failure with reduced ejection fraction (HFREF). We have hypothesized that atrial fibrillation decreases survival in HFPEF.

Patients and Methods: The study included a total of 109 patients admitted to Medical wards for heart failure within one year's period (2010-2011). The follow-up was 24 months. Patients were divided into two groups based on left ventricular ejection fraction (LVEF); HFPEF with LVEF more than 40% (n=64) and HFREF with LVEF less than 40% (n=45). For each patient we evaluated the presence of atrial fibrillation (AF) on ECG in the history and on admission. Data were analyzed using JMP9 statistical program. Unless otherwise specified, the data are presented as means.

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Results: The prevalence of history of AF was significantly higher in HFPEF vs. HFREF (67% vs. 44%, p<0.05). We observed a trend of higher prevalence of AF on admission in HFPEF vs. HFREF (50% vs. 29%, p=0.058) and significantly higher prevalence of non-sinus rhythm on admission in HFPEF vs. HFREF (56% vs. 34%, p<0.05). There was no significant difference in hospital mortality, cardiovascular mortality and all-cause mortality among patients with and without the history of AF neither in HFPEF nor in HFREF. The same results were found when comparing patients with and without the presence of AF on admission. AF was not an independent predictor of mortality.

Conclusion: We observed significantly higher prevalence of history of AF and significantly higher prevalence of non-sinus rhythm on admission in HFPEF vs. HFREF. We found a trend of higher prevalence of AF on admission in HFPEF vs. HFREF. We did not find AF to be a predictor of two-year mortality neither in patients with HFPEF nor in patients with HFREF.

KEYWORDS: heart failure with preserved ejection fraction, atrial fibrillation, prognosis.

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Prošireni sažetak / Extended abstract

Routinely available biomarkers as long-term predictors of heart failure in patients with single-vessel disease, completely revascularized acute ST-segment elevation myocardial infarction: a follow-up study

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Aim: To assess the efficacy of high sensitive C-reactive protein (hsCRP), cardiac troponin T (cTnT) and creatin kinase (CK) as long-term predictors of heart failure in patients with acute ST-segment elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention (pPCI) with successful and complete revascularization and to compare their predictive value with B-type natriuretic peptide predictive value.

Patients and Methods: This prospective study evaluated 47 patients with acute STEMI who had normal left ventricular ejection fraction (LVEF) (50%) at admittance and underwent complete revascularization. Blood samples were collected from admission to the day 7. The primary endpoint was the reduction of LVEF <50% after 12 months.

Results: Patients who reached primary endpoint had significantly higher mean values of cTnT after 24h (5.11 vs 2.82 µg/L; p=0.0101) and peak values of CK (3375.5 vs 1865 U/L, p=0.0084). Equally, the patients with cTnT after 24h Q4 when compared to the ones with Q1Q3 were 6 times more likely to develop LVEF <50% (OR 6.27, 95% CI 1.35-29.06, p=0.0200). Regarding hsCRP, there was no significant relation between hsCRP and development of primary end-point, neither when the values are dichotomized at a cut-off limit of ≥11 mg/l (p=0.5410) nor when they are split into quartiles (p=0.8482).

Conclusion: cTnT and CK could serve as predictors of reduced LVEF in patients with acute STEMI who had normal systolic function at admission, single-vessel disease, and were successfully revascularized during the primary PCI. However, BNP showed to be a more powerful predictor in this low-risk population, even more powerful than the multimarker score we designed.

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Prošireni sažetak / Extended abstract

The change in pulmonary vascular resistance after left ventricular assist device implantation - the predictive role of platelets revisited

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Purpose: While analyzing the group of patients implanted with a left ventricular assist device (LVAD) at our institution to verify which of the pre- and postoperative factors constitute the optimal survival outcome predictors, we determined a significant increase in postoperative pulmonary vascular resistance (PVR) values in the expired patients1. The aim of this study was to further analyze the data in order to determine which of the preoperative factors were related to the aforementioned increase in postoperative PVR values.

Methods: For the 20 patients (18 M, 2 F; mean age 58.7±8.3 years) that have been implanted with an LVAD in our institution during the past 2 years, preimplantation echocardiography, right heart catheterization (RHC) and laboratory data were collected and compared according to the values of the postimplantation PVR. The groups were compared by using the adequate statistical test (t-test, Mann Whitney U test, statistical significance set at 0.05). Correlation analysis and linear regression were performed.

Results: Among the 20 patients, 14 had postoperative RHC data and 4 of them were proven to have elevated PVR values (>2.4 WU). When comparing the pts. with elevated to those with normal PVR values, no significant difference was found neither in the RV function (FAC 33±7% vs 22±12%, TAPSE 1,0±0,7 cm vs 1.6±0.5 cm, NS), nor in the RV and LV dimensions (RVIDd 34±9 mm vs 35±12 mm, LVIDd 65±10 mm vs 73±9 mm). The borderline significance was found in the left ventricular EF (28±3% vs 19±8%, p=0.06) and the degree of the MR (median values 1 vs 2, p=0.05). The preoperative RHC parameters were not found to be predictive of changes in postoperative PVR (preoperative PVR 4,2±3,4 vs 3,4±1,5 WU, C.I. 1,8±0,7 vs 1,9±0,4 L/min/m^2, TPG 14±11 vs 13±4 mmHg and RVSWI 11,4±2,2 vs 8,9±2,1, NS). As for the laboratory values, only the platelet count significantly differed between the groups (128 ±73 vs 246±65 E3/mm^3, p<0.05). The correlation analysis showed a strong negative correlation between the platelet count and postoperative PVR values (r=-0,761, p<0.01). The linear regression verified the following relationship between the variables PVR=6,247-0,017xPLT, p<0.01).

Conclusion: These preliminary data show that the platelet count is a significant predictor of the postoperative PVR values in patients with an LVAD (a previously shown survival predictor1). Further investigation will be conducted to explain the role of platelets in the etiology of PVR in our group of pts.

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Graft vasculopathy, rejection and mortality predictors in heart transplant patients

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Purpose: We investigated pretransplant and posttransplant factors that could influence survival and development of cardiac allograft vasculopathy (CAV) and graft cellular rejection (CR) in heart transplant patients (Pts).

Methods: 120 study Pts in the follow-up 10 years, mean age 48,8±13,5. The patient characteristics (age, gender, blood type, diagnosis, pulmonary vascular resistance — PVR), transpulmonary gradient, graft ischemic time and duration of extracorporeal circulation, ECC) and pretransplant comorbidities (diabetes mellitus, chronic renal failure, hypertension, hyperlipidaemia) were analysed. Postransplant complications (postHTx hypertension, chronic renal failure — postHTx-RF, steroid diabetes mellitus — SDM) were also correlated with CAV and mortality, as well as biomarkers such as NT-proBNP and troponin T. Immunosuppressive regimens and cellular rejection were also analyzed. For statistical analysis chi-square test, student t-test and ANOVA were used (SPSS vers.21).

Results: Higher transpulmonary gradient (but not PVR) correlated significantly with higher mortality (p=0,003), as well as longer ischemic time (p=0.004) and ECC duration (p=0.043). PostHTx-RF (p=0.023) and SDM (p=0.042) also significantly contributed to mortality. Female gender had an insignificant trend toward longer survival (p=0.079). Higher NT-proBNP values (5,833 vs 2,721 pg/ml, p=0.025) significantly predicted all-cause mortality. There was a trend with higher standardized corticosteroid doses to correlate with lower CAV incidence (p=0.129). NT-proBNP cut-off value of >750 pg/ml has a trend to predict CR (p=0.084). Standardized cyclosporine A concentration (CyA) less than 10 0ng/ml (p=0.023) significantly correlated with CR and CyA between 100-150 ng/ml had the same trend (p=0.067). Other variables had no statistical significance.

Conclusions: Patient pretransplant comorbidities did not have crucial impact on posttransplant survival, expected transpulmonary gradient which proved to be a very powerful parameter influencing survival (while PVR did not). Steroid diabetes and chronic renal failure (excluding early acutisation of preexisting RF) are important postransplant comorbidities contributing to higher mortality. Immunosupression plays an important role for the CAV prevention and in our study more potent corticosteroid therapy proved to lower CAV incidence. CR rejection was not associated with higher CAV incidence, it could be predicted by higher NT-proBNP levels and prevented by higher CyA concentration.

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The influence of gender disparities on the development of heart failure and the relation to fetal programming

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Purpose: Low birth weight is an important predictor of infant health and survival, and is associated with significant mortality and development of multiple diseases in adulthood including an increased cardiovascular risk. Incidence of LBW in the general population is around 5-10%, with several studies showing that female neonates have better outcomes in the perinatal period. Considering this data, if perinatal cardiovascular remodeling is a risk factor for the development of the adult cardiovascular disease, there should be more female patients with both a cardiovascular disorder and a personal history of LBW in our studied group of heart failure patients.

Patients and Methods: 628 adult patients with different types of cardiomyopathies were admitted to our Department during 2012-2013. From that number, we studied 132 patients with known birth weight (88 male and 44 female). 49 had idiopathic DCM (iDCM), 37 had ischemic cardiomyopathy (ICM), 20 patients had secondary cardiomyopathy (valvular, toxic or hypertensive), 14 patients had postmyocarditic cardiomyopathy, 5 patients had hypertrophic cardiomyopathy, 5 patients had arrhythmogenic right ventricular dysplasia, and 2 patients had restrictive cardiomyopathy. The cut-off value for LBW was set at 2,500 g. Gender differences between the normal birth weight and low birth weight groups are shown in **Table 1**.

Table 1. *The distribution of gender among cardiomyopathy subgroups in relation to normal and low birth weight.*

	Normal birth weight		Low birth weight	
	male	female	male	female
iDCM	33	10	2	4
	76.7%	23.3%	33.3%	66.7%
Postmyocarditic CMP	7	4	1	2
	63.6%	36.4%	33.3%	66.7%
ICM	22	10	5	0
	68.8%	31.3%	100%	0%
sDCM	13	7	0	0
	65%	35%		
HCM	2	3	0	0
	40%	60%		
ARVD	3	2	0	0
	60%	40%		
RCM	0	2	0	0
	0%	100%		

iDCM=idiopathic dilated cardiomyopathy, CMP=cardiomyopathy, ICM=ischemic cardiomyopathy, sDCM=secondary cardiomyopathy, HCM=hypetrophic cardiomyopathy, ARVD=arrhythmogenic right ventricular dysplasia, RCM=restrictive cardiomyopathy.

Results: In the both idiopathic dilated cardiomyopathy and postmyocarditic cardiomyopathy subgroups, the ratio of LBW to normal birth weight (NBW) patients was observed to be higher among the females than the males (28.6% of all female iDCM pts were of LBW while only 5.7% were male pts; 33.3% of all female postmyocarditic cardiomyopathies were of LBW, compared to 12.5% male pts). On the other hand, all LBW patients in ischemic cardiomyopathy group were the males.

Conclusion: We observed a larger share of female LBW patients than male LBW patients in the iDCM and postmyocarditic groups, suggesting a relation with fetal programming and later development of iDCM and myocarditis. Conversely, females may be protected from ischaemic cardiomyopathy, independent of fetal conditions.

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Prošireni sažetak / Extended abstract

Community Nurse-led clinic: competence and accountability in the management of complex chronic cardiac care within the integrated Hospital-Territory network

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With the progressive aging of the population, the widespread increase in chronic and degenerative diseases and the need for constant improvement in the quality of services, outpatient nursing represents a new model of community organization and management of nursing care which can respond with competence to the diverse needs of the community.

Nurse-led Clinic takes care of patients with chronic heart disease (486 pts), heart failure (260 pts) and advanced heart failure (173 pts), outpatient and home management of patients with end-stage heart failure (continuous infusion of positive inotropic with portable insulin pumps, 14 pts), management of patients on oral anticoagulant therapy and new oral anticoagulants (398 pts). Across the clinics, the triage nurse takes care of patients who access the clinic through direct access or dedicated phone line for urgent assessment/monitoring of health needs. Out of 46.1% of patients who had a cardiovascular event and/or an active problem, only 1.3% was kept under observation in the ER or hospitalized. These patients had a greater hemodynamic instability that met criteria for activation of hospitalization (severe hypotension, desaturation, brady/ tachyarrhythmias, symptoms and signs of acute heart failure). The rest of the patients, with a minor instability were referred to the clinic nursing program with telephone and/or clinical follow-ups. This allows the activation of specific interventions needed to prevent hospitalization. Where necessary, local services (either district/home and/or social) are activated in order to respond to the needs expressed by the patient and his/her family.

Role of Nurses: Nursing interventions are initially done in conjunction with physician's visits to provide education and counseling for patients and caregivers to improve outcomes (mortality, readmissions to hospital, hospital length of stay). Patients and/or caregivers deemed requiring specific assessment and/or support are referred to a psychologist who also provides specific training and counseling supervision allowing for a steady update and strengthening of nurses' communication and educational skills. Follow-ups vary in frequency (e.g. monthly or bi-monthly) while medical follow-ups still tend to be scheduled quarterly to yearly according to the clinical severity of the patient. The patient's letter contains both medical and nurses' information integrating the both assessments.

Conclusions: The Nurse-led Clinic may allow the improvement of health services and is a key tool for integrating hospital and community care within a health/social care framework of services which accompany the complexity of chronic care from the onset of the disease through supportive and palliative care assistance.

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Prošireni sažetak / Extended abstract

Incidental extraction of a temporary epicardial pacemaker wire with right ventricular perforation during endomyocardial biopsy

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Introduction: Endomyocardial biopsy (EMB) is a relatively safe procedure. Nevertheless, cardiac perforation may occur and can be lethal. It is a real challenge how to manage this clinical urgency. We present a case of a heart transplant patient who suffered right ventricular (RV) perforation as a consequence of an incidental extraction of a temporary epicardial pacemaker wire.

Case report: A 51-year-old patient was admitted for a routine control EMB three months after the heart transplantation. Using Seldinger technique, we introduced a long sheath (7-French) into the RV. Cordis bioptome (2.2 mm jaw) was introduced through the sheath. The jaws of the bioptome were opened and gentle forward pressure was maintained while the jaws were closed. The bioptome was then removed by traction. The initial resistance suddenly vanished and the bioptome leapt into the sheath. To our surprise, the jaws of retracted bioptome held a piece of temporary epicardial pacing wire retained from the previous cardiac surgery. The patient was asymptomatic, but nonetheless we assumed that there was a perforation of the RV free wall with the long sheath sealing the perforation at the same time. We gave iodine contrast through the sheath and the extravasation of the contrast into the pericardial space was seen. With cardiac surgery back-up and under both fluoroscopic and ultrasound surveillance we pulled out the sheath without any symptoms, hemodynamic changes or development of pericardial effusion.

Discussion: The rate of RV perforation caused by a bioptome catheter during EMB is 0.05-5% and leads to tamponade in less than a half of the cases. The mortality is low and the majority of perforations can be managed without pericardiocentesis and/or a surgery accompanied by careful patient monitoring. The withdrawal of the perforating catheters seems to be dangerous if the perforation occurs with a delay or when the symptoms of the cardiac tamponade appear before the withdrawal. Despite the fact that the sheath was 7 Fr large, its withdrawal went without tamponade, probably due to the normal RV muscle wall, pericardial adhesions to the myocardium after cardiac surgery and a very short time the sheath was left at the perforation site. The risk is lower three months after the cardiac surgery by which time the pericardial adhesions to the myocardium should be formed.

To our knowledge, this is the first case of myocardial perforation caused by incidental extraction of a temporary epicardial pacemaker wire as a complication of EMB.

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Prošireni sažetak / Extended abstract

Our experience in the treatment of patients with severe dilatative cardiomyopathy and amiodarone — induced thyrotoxicosis

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Amiodarone-induced thyrotoxicosis (AIT) is a serious medical problem especially in patients with dilatative cardiomyopathy because of a substantial rate of morbidity and mortality. Patients usually present as worsening of arrhythmias and congestive heart failure. Two forms of AIT have been described. Type I occurs in patients with a preexisting adenomatous goiter and results from the excessive hormone production secondary to iodine excess. Type II is found in patients without a preexisting thyroid disease and results from the chemical-induced thyroiditis which causes the follicular damage and release of preformed hormone. AIT develops in 2-3% of patients in iodine sufficient areas such as Croatia. AIT can be managed medically or surgically. Available medical treatment regimens are complex, not uniform and do not consistently provide success. Thyroidectomy was previously considered to be the last treatment option, when medical therapy failed. However, in new reports, thyroidectomy is considered to be an initial treatment option despite the operative risk.

We represent two cases of AIT in patients with previously diagnosed dilatative cardiomyopathy with severe systolic dysfunction of the left ventricle who were taking amiodarone because of the documented non-sustained ventricular tachycardia. Dominant symptoms include refractory congestive heart failure with symptoms of hypo-perfusion and recurrence of arrhythmias (non-sustained ventricular tachycardia in both patients and atrial fibrillation with rapid ventricular response despite the medical treatment in one patient). Both patients did not have the preexisting thyroid disease and AIT type II (or “mixed”) was presumed. Echocardiography showed the impairment of the left and right ventricular ejection fraction and atrioventricular regurgitations. Prolonged treatment with high doses of dobutamin was needed to establish hemodynamic stabilization. AIT was treated by discontinuation of the drug, moderate doses of metyl-prednisolon (40 mg/day) and propiltiouracil (300 mg/day). After 4-6 weeks of the treatment, an improvement was achieved and the patients could wean off dobutamin. Free T4 and T3 started to decline in controls. The patients were discharged from the hospital after 2 and 3 months after the treatment in stable condition, in functional class NYHA II/III, as before AIT developed.

Conclusion: AIT in patients with congestive heart failure is a challenging problem, but with aggressive and intensive medical treatment surgery it can be avoided.

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Proširenи sažetak / Extended abstract

The case of 28-year-old female after Senning procedure with persistent atrial flutter and severe triscuspid regurgitation

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Transposition of the great vessels (TGA) is a rare condition with incidence of 1:5,000. The most common variant is d-transposition or complete transposition. Pivotal surgical procedure (Senning, 1957) has dramatically improved survival. However, typical long term complications include pressure overload of the systemic right ventricle with tricuspid regurgitation and atrial arrhythmias. Most of the patients are in NYHA I-II functional status 30 years after the operation but only 40-50% of them remain in sinus rhythm, while 30% of patients had minimally one episode of atrial flutter. A 28 year-old female was admitted to our Department in November 2011. When she was 9 months old, she underwent Senning procedure because of d-TGA. She was asymptomatic on beta-blocker until the age of 26 when she experienced palpitations and reduced effort tolerance. In addition, she was planning a pregnancy. Echocardiography showed the dilated and hypertrophic systemic right ventricle with reduced systolic function, and moderate to severe tricuspid regurgitation. Atrial conduits have a normal function. Cardiovascular magnetic resonance imaging showed a right ventricular hypertrophy without signs of fibrosis, and preserved systolic function (EF 48%). ECG revealed atrial flutter with 4 episodes of wide QRS tachycardia on 24-hours Holter ECG. Amiodarone and ACE inhibitor were introduced with clinical and Holter ECG improvement. Cardiac surgeons were consulted and the conclusion was that pregnancy with current medical therapy and atrial flutter would be too risky. Surgical therapeutic option would be tricuspid valve replacement with biological prosthesis and concomitant surgical AV node ablation with the implantation of epicardial electrodes of permanent pacemaker. The patient was sent to Charite Hospital in Berlin where successful ablation of atrial flutter was performed. However, at three months follow-up, recurrent atrial flutter was revealed both on ECG and Holter ECG. In April 2013, the patient underwent successful tricuspid valve replacement with biological prosthesis implantation followed by surgical AV node ablation and implantation of 3 epicardial electrodes on the right ventricle under TEE guidance in order to avoid cardiac dyssynchrony. Postoperative course was uneventful and the patient was discharged at day 5. The follow-up after 5 months showed an excellent function of the biological prosthesis in tricuspid position, the patient was asymptomatic and we gave her permission for pregnancy.

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Prošireni sažetak / Extended abstract

Cor triatriatum sinister — a rare cause of right heart failure

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A 40-year-old male was admitted to our Clinic for evaluation of pulmonary arterial hypertension. Transthoracic (TTE) and transesophageal (TEE) two and three-dimensional echocardiography revealed obstructive membrane in the left atrium with small fenestration of only few millimeters, pulmonary artery pressure (PAP) of 60 mmHg and moderately dilated and hypertrophied right ventricle (RV). Late presentation led us to look for concomitant anomalies, so a partial anomalous left pulmonary venous connection was found. The diagnosis was confirmed by computed tomography (MSCT) — upper left pulmonary vein (LUPV) was drained into left brachiocephalic vein via vertical vein, and no lung anomalies were found. On coronary angiography, separate origins of the left anterior descending and circumflex artery were shown. The patient was referred to a cardiac surgeon, but he refused an operative correction at the time. Three years later, he was admitted because of dyspnea on exertion and clinical signs of right sided heart failure. On TTE, impairment of RV function was found, with severe RV dilatation and PAP of 90 mmHg. Cardiac magnetic resonance revealed no significant amount of RV fibrosis, and by right heart catheterization, pulmonary vascular resistance index (PVRI) of 1.45 Wood was calculated. Left-to-right shunt was estimated by radionuclide angiocardiography to 26-30%. After medical stabilization, surgical resection of intraatrial membrane and LUPV reconnection into the left atrium appendage was performed. One month after the operation, the patient was asymptomatic and positive remodeling of RV, normal flow in the left atrium and PAP of 23 mmHg were found.

Cor triatriatum sinister is a very rare condition, especially in combination with anomalous pulmonary venous connection, so it is essential to search for concomitant anomalies. In the patient with signs of RV failure, multimodality approach was used to estimate the RV function. The calculation of PVRI was very important in making a decision whether this patient was operable. Some congenital causes of RV heart failure, such as cor triatriatum with anomalous pulmonary venous connection are important to be recognized in adults since they are surgically correctable due to low PVR. Apart from the diagnosis, multidisciplinary approach is also necessary in the assessment of RV function and PVR, key determinants in successful operation.

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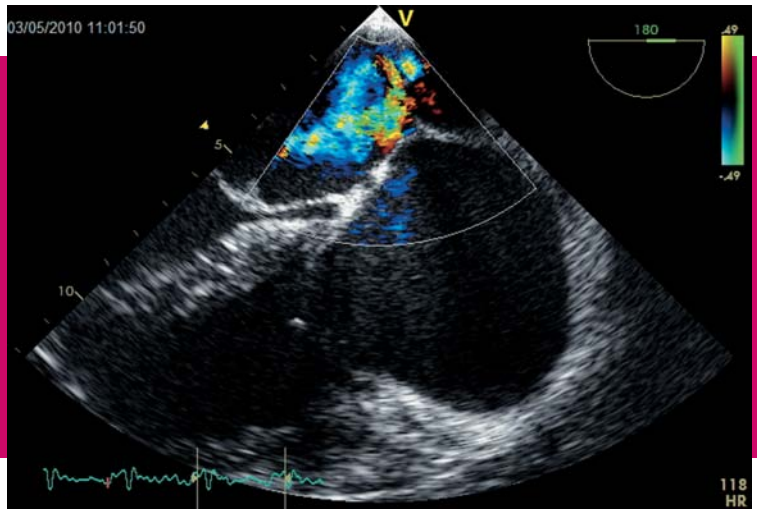

Figure 1. *The transesophageal echocardiogram: obstructive membrane in left atrium. Small fenestration with turbulent flow is seen on the top of the picture.*

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Prošireni sažetak / Extended abstract

Echocardiography and cardiac biomarkers in patients with lung cancer treated with platinum-based chemotherapy

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Objective: Platinum-based chemotherapy is a standard regiment for advanced lung cancer and adjuvant therapy in an early stage. It is ototoxic, nephrotoxic and induces oxidative stress whilst the data regarding cardiotoxicity remain scarce. Our aim was to assess cardiotoxicity of the platinum-based chemotherapy in patients with lung cancer.

Patients and Methods: Patients with lung cancer referred for the first-line platinum-based chemotherapy were included in the study. Ultra-sensitive troponin T (usTnT), N-terminal pro-BNP (NT-proBNP) and echocardiography were performed at baseline, at the end of chemotherapy (visit two) and at the follow-up (visit three). We report mean ± standard deviation and the number (percentage) for numeric and categorical variables, respectively. Elevated usTnT and NT-proBNP was defined as ≥30% increase from the baseline. Significant left ventricular ejection fraction (LVEF) was defined as a decrease of LVEF ≥10% to value ≤55% whereas diastolic dysfunction was defined using the European Society of Cardiology guidelines.

Results: Overall, 41 patients (61±9 years, 54% men) were included. Patients received 5±1 cycles of chemotherapy while 13 (32%) had early stage lung cancer and received adjuvant chemotherapy. During the follow-up, 1 patient died before visit two, whereas 8 patients were not assessed at visit three (2 died, 6 were lost to follow-up). At baseline none of patients had overt heart failure, 4 had ischemic heart disease and one had peripheral obstructive arterial disease present. Values at baseline, visit two and visit three for usTnT, NT-proBNP and LVEF were 0.011±0.005 pg/ml, 0.011±0.005 pg/ml, 0.008±0.003 pg/ml, 266.4±250.1 pg/ml, 257.7±378.1 pg/ml, 225.9±430.0 pg/ml and 68%±8%, 67%±8%, 68%±9%, respectively. Diastolic dysfunction was found in 9 (27%), 6 (27%) and 4 (24%) patients at baseline, visit two and visit three, respectively. From the baseline, significant elevation of usTnT and NT-proBNP to visit two and three was found in 3 (16%), 2 (25%) and 6 (35%), 2 (25%) patients, respectively, but none of the patients developed overt heart failure. A significant reduction of LVEF from baseline was observed in one patient at visit three.

Conclusions: In patients with lung cancer, platinum-based chemotherapy did not induce clinically relevant cardiovascular disease. In some patients, usTnT and NT-proBNP changes suggest subclinical cardiac injury, thus further research is warranted.

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Proširenі sažetak / Extended abstract

Unusual case of chronic heart failure acutisation

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Introduction: Chronic heart failure (CHF) is a result of many different causes, but rarely occurs due to intraatrial masses. Most commonly seen are thrombi related to atrial fibrillation (AF), valvular vegetations and cardiac tumors (mixomas), but the dignosis of extensive mass reaching from the inferior vena cava (IVC) to the right atrium of the heart is an extreme rare finding. The literature reported tumor spread in 1-4% cases of hepatocellular carcinoma (HCC). We report a similar case causing the acutisation of CHF.

Case report: A 83-year-old man reported to the emergency department (ER) for several times in four months due to progressive dyspnea and leg swelling. His medical history included alcoholic liver cirrhosis with hepatocellular carcinoma (HCC) treated by chemoembolisation four years ago, CHF, valvular heart disease, chronic renal disease 3b, AF. He was treated with warfarin therapy for a few months due to the patient noncompliance and also with beta-blocker, digitalis and loop diuretic, whose dose was repeatedly increased after each subsequent visit to the ER. MSCT pulmonary angiography excluded pulmonary embolism. Abdominal ultrasound showed compensated liver chirrosis with solitary HCC. At the time of our examination he had signs of heart failure along with liver decompansation. The abdominal ultrasound noted a mass extending from inferior hepatic vein through IVC all the way to the right atrium which was sized 2.7 cm. Given the extent of malignant disease and the complications, the patient was treated with low molecular weight heparin with gradual impairment of heart and kidney parameters. He died shortly after the admission of bleeding from the upper gastrointestinal tract.

Discussion: The literature suggests that right atrial thrombus may not cause any symptoms, but can sometimes lead to shock from ball valve obstruction of the tricuspid valve, right heart failure, pulmonary emboli and sudden death. This patient had many comorbidities that contribute to the thrombus development and also to heart failure, but HCC is known for its ability to progress through veins. Very high mortality rates are observed for advanced HCC with IVC and intraatrial tumor thrombus extension. Mean survival time is around three months. Pharmacotherapeutic and surgical treatments is equally poor.

Conclusion: The patients with progressive heart failure and liver cirrhosis with HCC should be suspected of having masses of IVC or right atrium that is easily detected by echocardiography or abdominal ultrasound. In our case it was probably spreading of tumor itself.

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KEYWORDS: heart failure, hepatocellular carcinoma, intraatrial mass.

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Proširenи sažetak / Extended abstract

Novel HCN4 gene 'splice-site' mutation causing familial bradycardia

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The hyperpolarization-activated, cyclic nucleotide-gated (HCN) ion channel is the main pacemaker channel of the heart, which modulates the If mixed cationic current responsible for sinus node pacemaker potential. The major HCN channel of the heart is encoded by the *HCN4* gene, mutations which were reported causing inherited sick sinus syndrome.

We performed genetic analysis of a proband with familial bradycardia. The female proband was diagnosed having sick sinus syndrome since the age of 28. She had episodes of dizziness, symptoms of exercise intolerance, but no definite syncope occurred. On resting ECG 40-46/min sinus bradycardia was registered, Holter monitoring showed sinus rhythm with an average frequency of 58/min. Even during active hours 38-48/min sinus bradycardia was noted with the lowest heart rate of 30-33/min during sleep. During stress tests, preserved chronotrop competence was detected with heart rate rising up to 123-150/min. Echocardiography showed normal cardiac structure and function with telesystolic mitral valve prolapse. Many of the family members of the patient have a similar disease.

Genetic analysis was performed on DNA extracted from peripheral blood. The whole coding sequence and the exon-intron boundaries of *HCN4* gene were amplified by polymerase chain reaction, and were direct sequenced.

In the patient's sample, a G-T transition was detected at the first nucleotide of the 'splice site' boundary of exon 5 and intron 5 (c.IVS5+1 G>T). We assume that the consequence of the mutation is that intron 5 is not cleaved during the RNA maturation. As it contains no cryptic stop codon, it is transcribed and translated full length. As a result of the mutation, the mutant protein is 34 amino acids longer than the wild type protein.

To summerize, we identified a new mutation (c.IVS5+1 G>T) in the *HCN4* gene causing familial bradycardia. The mutation has never been reported before, therefore it represents a 'novel' mutation for sick sinus syndrome.

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Prošireni sažetak / Extended abstract

Signaling mechanisms mediating the positive inotropic response to apelin in the intact rat heart

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Background: Apelin is emerging as an important regulator of the cardiovascular system. We previously demonstrated that apelin is one of the most potent endogenous stimulators of myocardial contractility; however, the signal transduction pathways mediating this effect are still obscure. Here we studied the role of protein kinase C (PKC) and extracellular signal-regulated kinase 1/2 (ERK1/2) in the positive inotropic effect of apelin.

Methods and Results: In isolated perfused rat hearts, infusion of apelin (2 nmol/L for 20 min) induced a slowly developing and sustained increase in cardiac contractility. The improvement of cardiac function was accompanied by the activation of PKC and ERK1/2. Apelin induced a transient increase in the translocation of PKC[epsilon], but not PKC[alpha], from the cytosol to the particulate fraction, and a sustained increase in the phosphorylation of ERK1/2 in the left ventricle. Pharmacological inhibition of ERK1/2 activation significantly attenuated the inotropic response to apelin. Although inhibition of PKC reduced the inotropic effect of apelin, it did not prevent the activation of ERK1/2.

Conclusions: Stimulation of apelin receptors enhances myocardial contractility via parallel and independent activation of PKC[epsilon] and ERK1/2 in the intact adult rat heart. Selective activation of PKC[epsilon] and ERK1/2 signaling may represent a novel means to support cardiac function in diseased conditions.

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Prošireni sažetak / Extended abstract

Pharmacological activation of the souble guanylate cyclase inhibits pressure overload-induced cardiac hypertrophy

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Background and Aim: Pathological cardiac hypertrophy is observed in pressure overload of the left ventricle. Elevated intracellular cGMP-levels have been reported to prevent the development of pathological myocardial hypertrophy. We investigated the effects of the chronic activation of the cGMP producing enzyme, soluble guanylate cyclase (sGC) by cinaciguat in a rat model of pressure overload-induced cardiac hypertrophy.

Methods: We performed aortic banding (AB) to evoke pressure overload-induced cardiac hypertrophy in our rats. Sham operated on animals served as controls. Experimental and control groups were treated with 10 mg/kg/day cinaciguat (Cin) or placebo (Co) p.o., respectively. The development of cardiac hypertrophy was investigated by echocardiography. We performed the left ventricular (LV) pressure-volume analysis with a pressure-conductance microcatheter to assess the cardiac function. In addition to our functional experiments, histological and molecular biological measurements were carried out.

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Results: Echocardiography showed marked myocardial hypertrophy in the AB-Co group (left ventricular mass index (LVMi): 3.15±0.09 AB-Co vs. 2.13±0.04 g/kgBW Sham-Co) which was verified by post mortem investigation of the hearts (heart weight/tibial length ratio (HW/TL): 0.384±0.015 AB-Co vs. 0.293±0.008 g/cm Sham-Co) and by histology (cardiomyocyte diameter (CD): 17.37±0.04 AB-Co vs. 14.55±0.12 µm Sham-Co). Increased left ventricular dimensions (left ventricular end-diastolic volume: 414±19 AB-Co vs. 341±19 µl Sham-Co) were observed while the ejection fraction and fractional shortening remained unchanged. Cinaciguat did not alter blood pressure (182.27±7.86 AB-Co vs. 174.63±4.53 mmHg AB-Cin, p=n.s.), but effectively attenuated the left ventricular hypertrophy (LVMi: 2.64±0.06 g/kgBW, HW/TL: 0.339±0.009 g/cm, CD: 15.08±0.10 µm, p <0.05 vs. AB-Co).

Conclusion: Our results demonstrate that chronic stimulation of the NO-cGMP signaling pathway by pharmacological activation of the soluble guanylate cyclase might be a novel therapeutic approach in the prevention of pathological myocardial hypertrophy.

KEYWORDS: aortic banding, pressure overload, cinaciguat, myocardial hypertrophy.

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Prošireni sažetak / Extended abstract

BPC 157 prevents development of MCT-induced pulmonary hypertension and cor pulmonale in rats

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Pentadecapeptide BPC 157 antagonises the incidence of a series of gastrointestinal lesions, it has a positive impact on the healing processes of various wounds, a proven angiogenic effect, protective effect on endothelium and it modulates synthesis of NO. BPC 157 furthermore reduces the duration of arrhythmias induced by ischemic-reperfusional injury in the isolated pig heart, and it also has an antihypertensive effect in the model of L-NAME-induced hypertension.

Monocrotaline (MCT) is a pyrrolizidine alkaloid, which given subcutaneously in the rat model of pulmonary hypertension on the day 1 (80 mg/kg body weight), selectively injures the vascular endothelium of the lung and induces pulmonary vasculitis, induces muscularization and hypertrophy of the media in pulmonary arteries, that lead to an increased vascular resistance and increased pulmonary arterial pressure. MCT-induced pulmonary hypertension is associated with the development of the compensated RV hypertrophy, which progresses to the failure within weeks.

In this study, when administered intraperitoneally from Days 1-29, BPC 157 inhibited the development of muscularization and hypertrophy of the media in pulmonary arteries, it prevented pulmonary hypertension and the right heart hypertrophy and failure. A corresponding efficacy profile was also noted for long-term peroral administration of BPC 157 in drinking water from Days 1-29. Moreover, the death rate significantly decreased in those animals treated with BPC 157.

We conclude that BPC 157 prevents development of MCT-induced pulmonary hypertension and cor pulmonale in rats.

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KEYWORDS: pentadecapeptide BPC 157, monocrotaline, cor pulmonale, pulmonary hypertension, rats.

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Prošireni sažetak / Extended abstract

LDL cholesterol levels in patients with coronary artery disease in real word: data from Cardiovascular Registry of Trieste

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Background: From the literature we know that less than 50% of patients with coronary artery disease (CAD) reaches the target LDL cholesterol <100 mg/dl in clinical practice. The 2012 European Guidelines on Prevention lowers the target to <70 mg/dl in very high risk patients.

Methods: We analyzed the clinical data, levels of LDL cholesterol, the statins prescription and the medium term outcome in patients with chronic coronary artery disease in 5,106 patients with CAD enrolled from November 2009 to December 2012 in Cardiovascolar Registry of Trieste (CVRT). Clinical data were derived from the E-data chart for outpatient clinic (Cardionet®) of Cardiovascular Center of Trieste, Italy.

Results: At the first clinical evaluation only 59.7% of patients with CAD had the level of LDL cholesterol available; they were younger (age >75 yo 42% vs 46%, p=0,002), had more cardiovascular (CV) risk factors, comorbidities (Charlson index >5) and statins prescription (70% vs 61%), but less frequent stroke or TIA. In the group with LDL available, 17% had LDL cholesterol <70% and 53% LDL ct <100 mg/dl. The patients at target level of LDL cholesterol were more frequently males, with more frequent CV risk factors and history of CV events, more frequent comorbidities and ≥5 drugs prescribed. The level of LDL cholesterol influenced the prescription of statins: in the group with LDL cholesterol ≥100 mg/dl, the cardiologists started, increased the dosage or changed the statin therapy in more than twofold of cases, even if only in about 30% of cases. The group of patients at target LDL cholesterol on statin therapy had the best prognosis (survival free from death and/or hospitalization 75% at 3 years). On the other hand, the group of patients with low LDL cholesterol level not on statin therapy (older with more advanced CV and not CV disease) had the worst prognosis (survival free from death and/or hospitalization 45% at 3 years, p< 0.001).

Conclusions: In our population of outpatients with CAD enrolled in CVRT, the target LDL cholesterol <70 mg/dl and <100 mg/dl was reached by 17% and 53% of cases. The availability and target level of LDL cholesterol influenced the statins prescription, but there is still a large room to improve proactive cardiology intervention in very high risk patiens. The medium term outcome is strongly related to the target

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KEYWORDS: coronary heart disease, hyperlipemia, cholesterol, statin, secondary prevention.

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Prošireni sažetak / Extended abstract

Angiology in Croatia

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The author will present the guidelines for peripheral arterial diseases adopted and translated according to the same ones published by the European Society of Cardiology in 2012. The second topic will focus on the importance of patient education as a part of the very important therapeutic aspect in the arterial and venous disease treatment. The author will present two pocket books designed specifically for the vascular patient. The main importance of these texts, guidelines for the patient, is to give answers to many questions posed by patients as a help in improving the quality of their daily life. It is believed that through patient education many of them will become our partners in reducing vascular morbidity and, cardiovascular mortality that would probably reduce health care costs. The author will present some proposals and strategic activities in improving vascular health care in Croatia.

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KEYWORDS: angiology, patient education.

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Prošireni sažetak / Extended abstract

Cardiopulmonary exercise testing in cardiology: more than simple exercise testing

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Exercise tests are frequently used in clinical cardiology practice, as diagnostic and functional evaluation tools. Many exercise tests are designed to produce a single measurement which is relevant to a specific clinical setting (presence of ECG changes consistent with myocardial ischemia in a patient with chest pain and dyspnea; duration of the test to estimate the functional capacity of patients in cardiac rehabilitation programme). Cardiopulmonary exercise testing provides an insight into the numerous variables related to cardiorespiratory function including expiratory ventilation, pulmonary gas exchange (oxygen uptake and carbon dioxide output), along with a continuous ECG monitoring and blood pressure measurement quantifies and links metabolic, cardiovascular and pulmonary responses to exercise. Unlike standard exercise tests, data obtained from cardiopulmonary exercise testing are individualized, which allows us an accurate insight of the patient cardiorespiratory function. Today, with an increased availability of instruments for the facile measurement of exercise gas exchange, cardiopulmonary exercise testing has expanded from clinical research application to a method frequently used in diagnostic estimation of cardiac patients and in therapeutic purpose, for individualised cardiac rehabilitation programme planning.

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KEYWORDS: cardiopulmonary exercise testing, exercise tests, diagnosis, cardiac rehabilitation planning.

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Prošireni sažetak / Extended abstract

Effects of trimetazidine therapy in patients with stable ischaemic heart disease

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Background: Current antianginal medications include beta-blockers and calcium antagonists, which decrease ischaemic severity by reducing cardiac workload, and nitrates, which increase coronary blood flow. Additional therapy with metabolic agents, such as trimetazidine, which shifts cardiac energy metabolism by inhibiting beta-oxidaton of fatty acids by blocking long-chain 3-ketoacyl-CoA thiolase, and which enhances glucose oxidation, may improve cardiac function during ischaemia.

Patients and Methods: We studied 82 patients (53 men and 29 women, mean age 61.6 years, SD 9.11) with ischaemic heart disease and left ventricular dysfunction who were followed-up at our outpatient department. All patients had either acute myocardial infarction and percutaneous transluminal coronary angioplasty, or aorto-coronary bypass. On study entry, all patients underwent echocardiography (EF 41.7%, SD 11.55), cardiopulmonary exercise testing, and had 24 hour Holter monitoring. All of them received trimetazidine dihydrocloridum 35 mg twice a day. After 6-12 months of follow-up, they repeated exercise testing, and had 24 hour Holter monitoring. The results were compared according to diabetes, sex, age and ejection fraction.

Statistics: Wilcoxson rank test.

Results: All patients showed statistically significant ($p< 0.001$) improvement in exercise testing (less pronounced ST depression) and lower number of ventricular premature beats (VPB) in Holter ECG. The results were the same for diabetics and nondiabetics, women and men equally, subgroups according to EF (<40%, 40-50%, >50%) also showed improved results in exercise testing and less VPBs. There were also no differences among the subgroups according to age (<65, and >65 years), sex and diabetes, and age and diabetes.

Conclusion: The addition of trimetazidine 35 mg twice a day to the patients with ischaemic heart disease resulted in greater improvements in functional capacity, better results in exercise testing, less ventricular premature beats regardless of age, sex, diabetes and ejection fraction. The effect of trimetazidine on glucose oxidation optimizes cellular energy processes, thereby maintaining proper energy metabolism during ischaemia. By preserving energy metabolism in cells exposed to hypoxia or ischaemia, trimetazidine prevents a decrease in intracellular ATP levels, thereby ensuring the proper functioning of ionic pumps and transmembrane sodium-potassium flow whilst maintaining cellular homeostasis, which is also indirectly confirmed by our results.

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KEYWORDS: Ishaemic heart disease, trimetazidine, antianginal agents, exercise testing, Holter monitoring.

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Proširenи sažetak / Extended abstract

Assessment of erectile function in cardiovascular patients: the graphic questionnaire as a novel diagnostic test

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The goal: The aim of the study was to investigate the applicability of a new, visual scale — based Graphic Questionnaire (GQ) we proposed for the assessment of erectile dysfunction (ED).

Patients and Methods: Erectile function was assessed in 185 patients under the age of 70, hospitalized at the Department of Cardiovascular Diseases, Clinic for Internal Medicine, University Hospital Centre Rijeka for various cardiovascular disease manifestations by using several self-administered questionnaires: International Index of Erectile Function-5 (IIEF-5); questionnaires used at the baseline and follow-up phase of the Massachusetts Male Aging Study (MMAS single question — MMAS-SQ and a baseline 9-question questionnaire — MMAS-9); the Erection Hardness Score (EHS), Brief Male Sexual Function Inventory (BMSFI), and finally, the newly created GQ. All of the questionnaires referred to one's erectile function during the period of 6 months prior to hospitalization.

Results: The mean age of the patients was 55.65±9.97 years. The most common indications for hospitalization were coronary artery disease (CAD) (n=82, 48%), and decompensated chronic heart failure (n=30, 18%): 37% of patients hospitalized for CAD had ST segment elevation myocardial infarction, 30% had unstable angina pectoris, and 29% presented with non-ST segment elevation myocardial infarction. The prevalence of ED as determined by IIEF-5 was 58% (n= 99) and 70% (n=119), as classified by MMAS-SQ. Patients with ED, defined as any IIEF-5 score less than 22, were on average 5.7 years older (P<0.0001), had higher frequency of diabetes (by 19%, P<0.01), and somewhat higher level of uric acid (by 72 μmol/l, P<0,01). Patients with CAD were 5.06 years older and had lower values of EHS by 0.6 (P<0.05) than non-ischemic patients, independent of age. Correlations of GQ total score with total scores of IIEF-5 (r=0.75, P<0.0001) and BMSFI (r=0.81, P<0.0001), and MMAS-SQ categories (rho=-0,68, P<0.0001) were significant. The patients' age negatively correlated with the total GQ score (r=-0,492, P<0.0001). All three machine learning algorithms (Naive Bayes, k-nearest neighbours and support vector machines with radial-basis kernel) demonstrated a greater accuracy of GQ than IIEF-5, BMSFI and MMAS-9 in predicting ED severity.

Conclusion: Erectile dysfunction is highly prevalent among cardiovascular patients, associated with age, ischemic heart disease and diabetes mellitus. Graphic Questionnaire has demonstrated valuable properties in providing the diagnosis of ED and could be used for its screening in general population.

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KEYWORDS: erectile dysfunction, questionnaire, coronary artery disease.

CITATION: Cardiol Croat. 2014;9(5-6):251.

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Prošireni sažetak / Extended abstract

Illness representation, beliefs about medicines and knowledge of disease risk factors in cardiac patients

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Objective: Illness perception is an important determinant of psychological well-being and functional outcomes in patients with chronic diseases. When patients face the disease, they actively create an organized pattern of beliefs about their condition in order to give the meaning to the experience of illness. Individual model of illness is not always medically accurate, but it is logical and rational from patient's personal point of view. It affects the emotional response to the disease as well as behaviors associated with disease. According to Leventhal's theory of self-regulation, adherence to medical recommendations necessary for adequate (secondary) disease prevention, is determined by an individual model of the disease. A number of studies has showed the correlation between generally negative illness perception and increased future disability as well as slower functional recovery, regardless of the initial medical severity of the condition. This study sought to examine illness representations in cardiac patients, as well as their attitudes about the prescribed medicines and knowledge of disease risk factors.

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Method: The sample consisted of 70 cardiac patients involved in the program of cardiac rehabilitation after myocardial infarction or coronary artery bypass surgery. The brief illness perception questionnaire, Beliefs about medicines questionnaire and Cardiovascular disease risk factors knowledge level scale were administered.

Results: Most of the patients perceive their illness to be chronic but susceptible to a relatively good personal control and especially the treatment control. They don't associate many symptoms with their illness and have lower levels of concern and emotional response, as well as a good sense of comprehension of illness. Most of them also do not perceive their condition as the one with major consequences. According to patients, the most important causes of illness are stress, heritage and lifestyle. Benefits of the prescribed medicines are generally perceived to overweigh potential adverse effects, although 10% of respondents show a negative attitude toward the prescribed medicines.

Global illness perception, knowledge of the disease risk factors and diagnosis are shown to be significant predictors of attitudes toward medicines.

KEYWORDS: illness perception, beliefs about medicines, knowledge of risk factors.

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Prošireni sažetak / Extended abstract

Effect of tomatoes on the prevention of cardiovascular diseases

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Tomato (*Solanum lycopersicum L.*) is an important ingredient in the Mediterranean diet. Studies have shown that this particular type of diet has a very positive effect on human health, including cardiovascular health.[1] Tomatoes are a significant source of nutrients such as lycopene, beta-carotene, folate, potassium, vitamin C, flavonoids and vitamin E. Carotenoid lycopene is highly represented, which is a very powerful antioxidant due to its chemical structure. The nutrients in tomatoes may have a favorable effect on lipid profile, homocysteine, platelet aggregation and blood pressure.[2]

The Women' Health Study (WHS) conducted in the United States over seven years period showed the potential effect of tomatoes on women's health. The study involved nearly 40,000 middle-aged women who were not initially diagnosed with cancer or cardiovascular disease. The results suggest that consumption of ≥7 servings of tomato products per week reduce the risk of cardiovascular disease by nearly 30% compared to consuming <1.5 servings/wk. Particularly significant impact on the vascular events, myocardial infarction and stroke was noticed in people who consumed ≥10 servings of tomato products per week.[3] Research of raw tomato consumption have shown beneficial effect on HDL cholesterol in over-weight women.[4] Processed tomato compared to raw tomato shows better antiplatelet activity, most likely due to a higher content of components which have a positive impact on human health and can be used as an ingredient in functional food.[5] Since tomato is known for its high amount of potassium, the consumption of this vegetable should be limited to people with renal failure or hyperkalemia.

Due to the valuable components, tomatoes and tomato products should be included in the daily diet of cardiac patients. Clinical studies focusing on determining the effect of tomatoes on the prevention of cardiovascular disease will continue.

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KEYWORDS: tomato, lycopene, antioxidant, cardiovascular disease.

CITATION: Cardiol Croat. 2014;9(5-6):253.

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Prošireni sažetak / Extended abstract

Screening for prevention of cardiovascular complications in sports: the challenge going forward

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The three main features requested for the "ideal" pre-participation screening (PPS) in sports are cost-effectiveness, high diagnostic accuracy and feasibility in large populations. Controversy exists concerning increasing an efficacy of the PPS by using echocardiography (ECHO).

500 healthy athletes (aged: 16-32, median age 21 ± 5, 446 males and 54 females [8:1], participating in sports like football, athletics, handball, cycling, basketball, gymnastics) were examined during the period from 2011-2013 in a pilot study focusing on the prevention of cardiovascular complications in sports. All of the athletes were screened according to European PPS protocol with history taking, physical examination and 12-lead ECG registration. Cardiovascular abnormalities were not detected in any case. After that conventional ECHO (M-mode and 2D modalities) the exam was performed in all of the athletes and a broad spectrum of cardiovascular abnormalities was found in 14 cases (2.8%). In 7 (1.4%) athletes it was mitral valve prolapse (hemodynamically significant in 1 case), in 3 (0.6%) — bicuspid aortic valve (significant aortic stenosis in 1 case) and in other 4 cases (0.8%) it was myocarditis, myocardial bridging, noncompaction of the left ventricle and coronary artery fistula. In 4 athletes abnormalities that were found required a temporary or permanent sports activities cessation.

The postulate suggesting that inclusion of ECHO into the PPS protocol may not be cost-effective should be revised today. Currently conventional techniques like M-mode and 2D are inexpensive enough (about 6.00 Euros in Slovakia), technically simple to be performed in the field in large athletic population by pocket-size ultrasound systems, powerful enough for the efficient screening and thus hold the potential to enter a screening protocol.

Well-constructed, sufficiently powered, randomized and long-term controlled studies will allow an objective evaluation of ECHO contribution to the diagnostic evaluation of life-threatening cardiovascular abnormalities in athletes. Considering such evidence, a modified PPS protocol should probably be applied to the sports cardiology practice.

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KEYWORDS: sudden cardiac death, athletes, prevention.

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Proširenisažetak / Extended abstract

Role of nitric oxide and NADPH oxidase-derived superoxide in regulating coronary blood flow and metabolism in cardio-metabolic diseases

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In cardio-metabolic diseases both the coronary circulation and cardiac metabolism are altered. We have studied a condition called hyperhomocysteinemia (HHcy), which can develop as a result of genetic or environmental causes. This metabolic disease is underappreciated, yet even mild or moderate elevation of plasma concentrations of homocystein (Hcy, a sulfur-containing amino acid produced via methionine metabolism) leads to coronary and peripheral arterial and vascular diseases, increased thrombosis and consequently increased mortality. The underlying mechanisms have not been revealed yet.

Our recent studies indicate that there are common pathomechanisms, which may affect all of the cellular functions involved. We have shown that a dysfunction of nitric oxide (NO) mediation of dilator responses in isolated rat arterioles with methionine diet-induced hyperhomocysteinemia develops (*Arterioscler Thromb Vasc Biol. 1999;19(8)*:1899-904) with simultaneously increased TXA2 the activity in arterioles and platelets (*Arterioscler Thromb Vasc Biol. 2000;20(5): 1203-8*). This was due to an oxidative stress-induced dysregulation of arteriolar wall shear stress and blood pressure (*Am J Physiol Heart Circ Physiol. 2003;285(6):H2277-83*). Moreover, HHcy elicited flow-induced constrictions of venules due to increased cyclooxygenase-2 derived thromboxane A2 and reactive oxygen species (*Atherosclerosis. 2010;208(1):43-9*). The alteration in the endothelial function affected the ability of NO to regulate cardiac metabolism as we have found that elevated levels of p22phox, p67phox, and rac-1 indicate an increased NADPH oxidase assembly resulting in an increased superoxide production and in a reduced ability of NO to regulate the mitochondrial function in the myocardium (*Circulation. 2005;111(16):2112-8.*). The interaction of these pathomechanisms explain why HHcy increases the uptake of glucose and lactate and decreases the uptake of free fatty acid by the heart (*Circulation. 2007;115(2):255-62*). Similar alterations could play a role in the development of cardio-metabolic and coronary dysfunction in other metabolic diseases, such as diabetes mellitus, hyperlipidemia and metabolic syndrome.

KEYWORDS: nitric oxide, homocystein, metabolic disease.
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Prošireni sažetak / Extended abstract

Investigation of asymmetric dimetylarginine in patients with coronary artery disease

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Introduction: The concentrations of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase are increased in patients with coronary artery disease (CAD). An elevated concentration of ADMA in the plasma and pericardial fluid (PF) is an independent predictor of worse cardiovascular events in patients undergoing coronary revascularization. We aimed to investigate the changes of pericardial and plasma ADMA levels in patients with CAD, who underwent percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery.

Patients and Methods: 64 patients who underwent PCI or CABG surgery were enrolled in this study (65.5 ± 8.2 years). 52 patients who underwent the valve replacement (VR) served as control subjects (59 ± 6.9 years). Exercise stress test was performed on a treadmill according to the Bruce protocol. ADMA levels were determined by using liquid chromatography — tandem mass spectrometry. Furthermore L-arginine and ADMA concentrations were determined in plasma and PF of patients undergoing coronary artery bypass graft (CABG, n=28) or valve replacement (VR, n=25).

Results: Patients in the CAD group had significantly elevated plasma concentrations of ADMA at rest, compared to the control group (0.59 ± 0.02 μM/l vs. 0.46 ± 0.03 μM/l; p<0.01). ADMA decreased immediately after stent implantation in the PCI group. There was no discernible increase in ADMA in the off-pump CABG group. In contrast, the levels of ADMA were significantly elevated in the group of patients who underwent cardiopulmonary bypass (CPB) (F=0.416, p<0.685 and F=14.751, p<0.001 for the off-pump and CPB groups, respectively). Similarly, a significant increase in ADMA was observed in the peripheral blood (F=30.738, p<0.001) during CPB, while during the off-pump CABG surgery, ADMA remained largely unchanged. The L-arginine/ADMA ratio of both plasma (125.4±10.7 vs.76.7±8.7) and PF (110.4±7.2 vs. 80.8±6.04) were significantly higher in the CABG group compared to the VR group. Furthermore, there was a significant positive correlation between plasma and pericardial L-arginine levels in the CABG group. The PF ADMA was higher in the VR than CABG group.

Conclusion: This clinical study highlights the importance of the investigation of both plasma and pericardial ADMA levels in patients with CAD. Changes of ADMA, and L-arginine/ADMA ratio are reliable, as well as the feasible markers of ischemia-reperfusion injury occurring in patients who underwent coronary revascularization.

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Prošireni sažetak / Extended abstract

Pentadecapeptide BPC157 reduces bleeding and thrombocytopenia after amputation in rats treated with heparin, warfarin, L-NAME and L-arginine

Predrag Sikirić*, Mirjana Stupnišek, Antonio Kokot, Domagoj Drmić, Maša Hrelec Patrlj, Anita Zenko Sever, Božo Radić, Davor Bojić, Aleksandar Včev, Sven Seiwerth

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Rationale: BPC 157 is a stable gastric pentadecapeptide recently implicated with a role in hemostasis. While NO is largely implicated in hemostatic mechanisms, in tail-amputation-models under heparin- and warfarin-administration, both the NO-synthase (NOS)-blocker, L-NAME (prothrombotic) and the NOS-substrate L-arginine (antithrombotic) have been little investigated.

Objective: To investigate the effects of BPC 157 after L-NAME and/or L-arginine administration. Namely, bleeding/-thrombocytopenia (even with anticoagulant administration) after tail-amputation and thrombosis of the abdominal aorta anastomotic site, were both counteracted. BPC 157 also particularly modulates the NO-system and wound-healing, including that of blood vessels.

Methods and Results: Tail amputation, and/or i.v.-heparin (10 mg/kg), i.g.-warfarin (1.5 mg/kg/day for 3 days) were used in rats. Medication includes BPC 157, L-NAME, L-arginine, alone and/or together applied accordingly. After (tail) amputation, with or without i.v.-heparin or i.g.-warfarin, BPC 157 (10 µg/kg, 10 ng/kg, i.p., i.v. (heparin), i.g. (warfarin)) always reduced bleeding time and/or haemorrhage and counteracted thrombocytopenia. As for L-NAME and/or L-arginine, we noted: L-arginine (100 mg/kg i.p.)-rats: more bleeding, less/no thrombocytopenia; L-NAME (5 mg/kg i.p.)-rats: less bleeding (amputation only), but present thrombocytopenia; L-NAME+L-arginine-rats also exhibited thrombocytopenia: L-NAME counteracted L-arginine-increased bleeding, L-arginine did not counteract L-NAME-thrombocytopenia. All of the animals receiving BPC 157 in addition (BPC 157µg+L-NAME; BPC 157µg+L-arginine, BPC 157µg+L-NAME+L-arginine), exhibited decreased haemorrhage and markedly counteracted thrombocytopenia.

Conclusions: L-NAME (thrombocytopenia), L-arginine (increased haemorrhage) counteraction and BPC 157 (decreased haemorrhage, counteracted thrombocytopenia) with rescue against two different anticoagulants, implicate a BPC 157 modulatory and balancing role with rescued NO-hemostatic mechanisms.

KEYWORDS: BPC 157, thrombocytopenia, bleeding, NO system, rats.

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Prošireni sažetak / Extended abstract

Pentadecapeptide BPC 157 counteracts thrombosis and all manifestations of 48h-inferior cava vein ligation (syndrome) in rats

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Background: We implicated stable gastric pentadecapeptide BPC 157 particular beneficial combining (bleeding/thrombocytopenia after amputation and/or anticoagulants and aspirin and abdominal aorta anastomosis-thrombosis both counteracted; wound healing capacity; endothelium protection; interactions with NO-system in different models and various species; particular effect on blood pressure; anti-arrhythmic effect) to counteract deep vein thrombosis (DVT) and inferior caval vein (ICV)-syndrome.

Methods: *Surgery.* In deeply anaesthetized female Wistar rats the ICV was exposed via a midline laparotomy, dissected at the level of the right ovarian vein, and then ligated up to right ovarian vein, and rats were randomly divided into different groups for further experiments and assessments (ICV and aorta blood pressure recordings, ECG recordings, heart rate, blood vessel collateralization, bleeding, vein wall analysis, thermography, indirect ophtalmoscopy of retina). BPC 157 was given as 1ml bath (thrombosis; blood pressure; heart rate; collaterization); or intraperitoneally (bleeding). *Delayed therapy.* BPC 157 (10 µg/kg, 10 ng/kg) was given intraperitoneally, at advanced ligation-time points: 1 h; 2 h; 6 h, 24 h, 48 h. Controls simultaneously received an equivolume of saline (5 ml/kg). Assessments were carried out at 10 min, 30 min, 1 h, 6 h, 24 h and 48 h thereafter.

Results: In rats with 48 h-ICV ligation, BPC 157 salutary effect was elicited at any point of 48h-ligation-time. BPC 157 (10 µg,10 ng/kg, both early (i.e., 1 ml bath at 5 min ligation-time) and delayed therapy (intraperitoneally)) counteracts thrombosis and all manifestations of 48 h-ICV ligation (syndrome), i.e., instead progressive DVT, the length and weight of the formed clot considerably less; instead thickened, intima as thick as the nuclei of normal spindle-shaped endothelial cells; instead substantially increased bleeding with an injury and thrombocytopenia, BPC 157-rats bleed less, and have no thrombocytopenia; blood pressure brought to normal values in both ICV and abdominal aorta, vein hypertension and systemic hypotension counteracted, almost normal eye fundus, tachycardia normalized, attenuated ischemia, gross organ congestion greatly prevented or reduced, collaterals and redistribution of otherwise trapped blood volume rapidly presented, and thereby attenuated drinking, leg edema and cyanosis.

Conclusions: Pentadecapeptide BPC 157 counteracts DVT and all manifestations of 48h-ICV ligation in rats.

KEYWORDS: BPC 157, deep vein thrombosis, inferior cava vein ligation, rats.

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Pregledni članak / Review article

Vitamin D i srčanožilne bolesti
Vitamin D and cardiovascular diseases

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SAŽETAK: Vitamin D je važan hormon u regulaciji mineralnog metabolizma i u procesu mineralizacije kostiju. Kako je receptor za vitamin D prisutan u mnogobrojnim tkivima, postoji veliko zanimanje za istraživanje drugih potencijalnih uloga vitamina D, pogotovo u srčanožilnim bolestima (SŽB). Mnoge studije su pokazale da je manjak vitamina D povezan s povećanim rizikom od razvoja SŽB, uključujući arterijsku hipertenziju, zatajivanje srca i ishemijsku bolest srca. Prospektivne studije su pokazale da manjak vitamina D povećava rizik za razvoj arterijske hipertenzije i iznenadne srčane smrti u bolesnika s postojećim SŽB.

KLJUČNE RIJEČI: vitamin D, srčanožilne bolesti, kardiovaskularni rizik.

SUMMARY: Vitamin D is an important hormone in the regulation of mineral metabolism and bone mineralization process. Since the receptor for vitamin D is present in many tissues, there is a great interest in exploring other potential roles of vitamin D, particularly in cardiovascular diseases (CVDs). Many studies have shown that vitamin D deficiency is associated with an increased risk of developing CVDs, including hypertension, heart failure and ischemic heart disease. Prospective studies have shown that vitamin D deficiency increases the risk of developing hypertension and sudden cardiac death in patients with existing CVD.

KEYWORDS: Vitamin D, cardiovascular diseases, cardiovascular risk.

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Uvod

Klasična uloga vitamina D je povećanje apsorpcije kalcija u crijevima[1]. Aktivni oblik vitamina D, 1,25-dihidroksikolekalciferol (1,25(OH)$_2$D) ponaša se kao steroidni hormon vežući se na vitamin D receptor (VDR) koji je prisutan u mnogim stanicama, uključujući kardiomiocite[2], glatke mišićne stanice krvnih žila[3] i stanice endotela[4]. Istraživanja su pokazala da manjak vitamina D uzrokuje povećanje rizika od razvoja srčanožilnih bolesti (SŽB). Način na koji vitamin D štiti pojedinca od SŽB nije do kraja istražen. Postoje mnoge teorije, uključujući negativnu regulaciju renina i time snižavanje arterijskog tlaka (AT), snižavanje razine paratiroidnog hormona (PTH) i poboljšanje kontrole glikemije (**Tablica 1**).

Fiziologija vitamina D

Vitamin D se pojavljuje u dva oblika: vitamin D$_2$ (ergokalciferol) i vitamin D$_3$ (kolekalciferol). Vitamin D$_2$ koji se nalazi u biljkama i kvascu, proizvod je djelovanja ultraljubičastih zraka na ergosterol dok se vitamin D$_3$ nalazi u masnoj ribi i ulju dobivenom iz bakalarove jetre te maslacu. Vrlo su male količine u mesu, kravljem i ljudskom mlijeku. Vitamin D iz hrane apsorbira se u tankom crijevu ovisno o apsorpciji lipida i hilomikronima prelazi u limfu i u krv te u jetru. Općenito se apsorbira 50% vitamina D unešenog hranom (**Slika 1**).

Introduction

The traditional role of vitamin D is to increase the absorption of calcium in intestines[1]. The active form of vitamin D, 1,25-dihydroxycholecalciferol (1,25(OH)$_2$D) acts as a steroid hormone binding to the vitamin D receptor (VDR), which is present in many cells, including cardiomyocytes[2], smooth muscle cells of blood vessels[3] and endothelial cells[4]. The trials have shown that vitamin D deficiency causes an increase in the risk of developing cardiovascular disease (CVD). The way in which vitamin D protects an individual against CVD has not been fully explored. There are many theories, including the negative regulation of renin and thus lowering blood pressure (BP), lowering the level of parathyroid hormone (PTH) and improved glycemic control (**Table 1**).

Vitamin D physiology

Vitamin D comes in two forms: vitamin D$_2$ (ergocalciferol) and vitamin D$_3$ (cholecalciferol). Vitamin D$_2$ which is found in plants and yeast is the product of action of ultraviolet rays while the ergosterol vitamin D$_3$ is found in fatty fish and oil obtained from cod liver and butter. There are very small amounts of it in meat, cow and human milk. Vitamin D from food is absorbed in the small intestine depending on the absorption of lipids and chylomicrons and enters the lymph, blood and liver. Generally it absorbs 50% of vitamin D which is entered by food (**Figure 1**).

Table 1. *Distribution of VDR in normal tissues/cells.*

Organ/tissue	Expression level	Cell types
Digestive system		
Small intestine	++++++++++	Epithelium
Large intestine	+++++++	Epithelium
Liver	—	
Pancreas	+++	Epithelium
Kidney		
Distal tubule	++++++++	Epithelium
Proximal tubule	++	Epithelium
Glomerular podocytes	+	Podocytes
Respiratory system		
Lung alveolar cells	—	
Bronchus	+++++	Epithelium
Bone		
Osteoblasts	+++++	Osteoblasts
Chondrocytes	+	Chondrocytes
Muscle system	—	
Immune system		
Thymus	+++++	Epithelium
Spleen/lymph node	++	Monocyte/macrophage/T-cell
Endocrine system		
Thyroid	—	
Parathyroid	++++++++	Epithelium
Pituitary gland	+++	Epithelium
Adrenal gland	—	
Brain		
Cerebrum	— ?	
Cerebellum	— ?	
Spinal cord	— ?	
Reproductive system		
Testis	++	Germ cells
Prostate gland	++++	Epithelium
Mammary gland	++++	Epithelium

? — Not completely defined

Izvor: Wang Y, Zhu J, DeLuca HF. Where is the vitamin D receptor?. Arch Biochem Biophys. 2012 Jul 1;523(1):123-33. doi:10.1016/j.abb.2012.04.001.

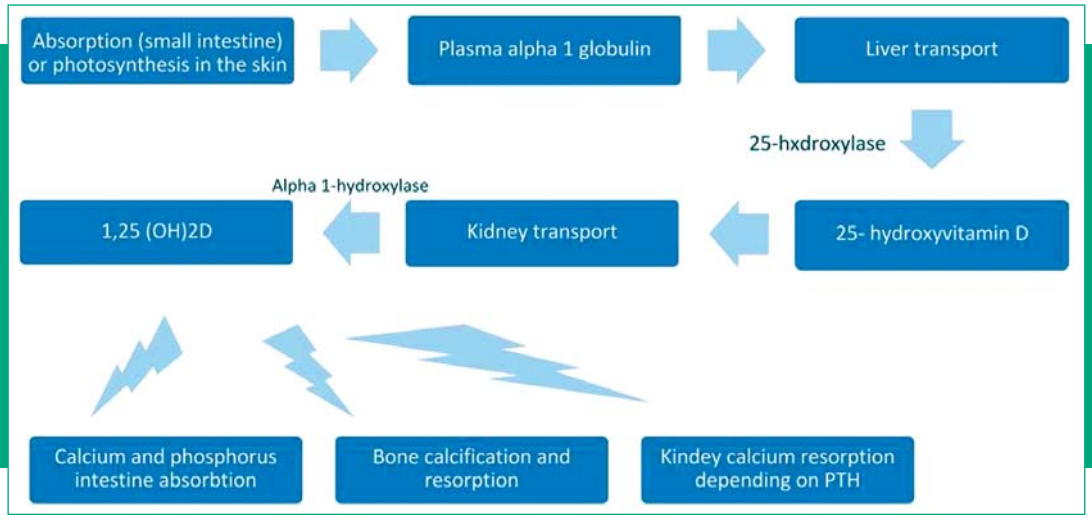

Figure 1. *Vitamin D metabolism.*

U čovjeka se u koži iz 7-dehidrokolesterola djelovanjem ultraljubičastih B zraka iz sunčeva svijetla stvara previtamin D_3, a nakon toga vitamin D_3. U tkiva dospijeva uz pomoć prijenosničke bjelančevine na koju je vezan u krvi. Pretjerano izlaganje sunčevoj svjetlosti ne može dovesti do hipervitaminoze D i toksičnosti jer ultraljubičaste zrake pretvaraju višak vitamina D_3 u biološki inertan izomer[5]. Metabolizam vitamina D_2 ili D_3 u organizmu je jednak. U jetri se D vitamin djelovanjem enzima 25-hidroksilaze citokroma P 450 pretvara u 25-hidroksivitamin D (25(OH)D, kalcidiol) koji nije biološki aktivan[6]. U bubregu se događa najvažniji korak gdje iz 25(OH)D djelovanjem PTH na 1-alfa-hidroksilazu nastaje 1,25 — dihidroksivitamin D ($1,25(OH)_2D$, kalcitriol), čiji učinak u jezgri i građa odgovaraju onima steroidnih hormona[5]. Receptor za vitamin D je prisutan u većini tkiva, uključujući stanice endotela, glatke mišićne stanice krvnih žila i stanice miokarda[7]. I glatke mišićne stanice krvnih žila i stanice endotela imaju sposobnost pretvaranja kalcidiola u kalcitriol[8]. Učinci vitamina D se postižu interakcijom kalcitriola i VDR[5,9,10]. Cirkulirajući kalcitriol prolazi kroz staničnu membranu, ulazi u citoplazmu te se u jezgri veže za VDR. Kompleks VDR-$1,25(OH)_2D$ stvara heterodimer s X-receptorom retinoične kiseline, spaja se s akceptorskim mjestom DNA te potiče transkripciju gena i sintezu nove mRNA. Direktno i indirektno kalcitriol regulira preko 200 gena, uključujući gene važne za proizvodnju renina u bubregu, proizvodnju inzulina u gušterači, oslobađanje citokina iz limfocita, rast i proliferaciju glatkih mišićnih stanica vaskulature i stanica miokarda[5]. S relativnom niskom biološkom aktivnošću, kalcidiol je oblik koji ima najveću koncenraciju u cirkulaciji i uzima ze za određivanje ukupnih zaliha vitamina D_5. Dok endokrino djelovanje aktivnog metabolita, kalcitriola, karakterizira održavanje homeostaze kalcija i fosfata[11], novija istraživanja su usmjerena na autokrine i parakrine aktivnosti vitamin D. Autokrino/parakrino djelovanje vitamina D je najbolje naznačeno u koži i imunološkom sustavu gdje regulira staničnu diferencijaciju i sazrijevanje. Nedavna istraživanja ukazuju da autokrino/parakrino djelovanje u glavnim stanicama kosti također regulira proliferaciju i diferencijaciju. Istraživanja na štakorima su pokazala da je odgovarajuća serumska koncentracija kalcidiola kritična za optimalno zdravlje kosti i za zaštitu od osteoporoze što se podudara s rezultatima kliničkih istraživanja na ljudima[12].

Definicija i prevalencija manjka vitamina D

Iako je kalcitriol aktivan oblika vitamina D, njegova serumska koncentracija ne odražava ukupni status vitamina D te klinički nije od značaja. Serumska koncentracija kalcidiola koja odražava koncentraciju vitamina D i endogenog i egzogenog podrijetla se uzima kao mjera za kliničko određivanje vitamin D statusa[5]. Nekoliko je razloga za to: **1.** vrijeme poluživota kalcidiola je duže od vremena poluživota kalcitriola (-3 tjedna u odnosu na -8 sati), **2.** koncentracija kalcidiola u cirkulaciji je 1.000x veća od koncentracije kalcitriola (ng/ml u odnosu na pg/ml), **3.** stvaranje kalcitriola je uglavnom pod utjecajem PTH koji regulira i koncentraciju kalcija. Zbog toga je moguće da koncentracija kalcitriola bude povišena u bolesnika s teškim manjkom vitamina D, kako bi se održala normalna koncentracija kalcija. Većina stručnjaka se slaže da cirkulirajuća koncentracija kalcidiola predstavlja ukupni vitamin D status pojedinca, ali koja je optimalna koncentracija vitamina D ostaje upitno. Trenutno

Previtamin D_3 is produced in the skin from 7-dihydroxycholesterol by action of ultraviolet B rays from the sunlight, which thereafter turns into vitamin D_3. It enters the tissues with a help of transmission protein to which it is bound in blood. Overexposure to sunlight cannot lead to hypervitaminosis D and toxicity, because ultraviolet rays convert excess vitamin D_3 into biologically inert isomer[5]. Metabolism of vitamins D_2 or D_3 in the organism is the same. In the liver, by activity of the enzyme 25-hydroxylase of cytochrome P 450 vitamin D converts into 25-hydroxyvitamin D (25(OH)D, calcidiol) which is biologically less active[6]. The most important step occurs in the kidney where 1.25-dihydroxyvitamin D ($1.25(OH)_2D$, calcidiol) is produced from 25(OH)D by the activity of PTH on 1-alpha-hydroxylase, the effect of which in the nucleus and composition equals those of steroid hormones[5]. Vitamin D receptor is present in most of the tissues, including endothelial cells, smooth muscle cells of blood vessels and myocardial cells[7]. Both smooth muscle cells of blood vessels and endothelial cells are capable of converting calcidiol to calcitriol[8]. The effects of vitamin D are achieved by the interaction calcitriol and VDR[5,9,10]. Circulating calcitriol passes through the cell membrane, enters the cytoplasm and binds to VDR in the nucleus. VDR complex-$1,25(OH)_2D$ forms heterodimer with X-retinoic acid receptor, binds to the DNA acceptor site and stimulates transcription of genes and the synthesis of new mRNA. Directly and indirectly, calcitriol regulates over 200 genes, including the genes important for the production of renin in the kidney, production of insulin in the pancreas, release of cytokines from lymphocytes, growth and proliferation of vascular smooth muscle cells and myocardial cells[5]. With relatively low biological activity, calcidiol is the form that has the largest concentration in the circulation and is taken for determining the total stock of vitamin D_5. While endocrine activity of the active metabolite, calcitriol, is characterized by maintaining homeostasis of calcium and phosphate[11], recent studies have focused on the autocrine and paracrine actions of vitamin D. Autocrine/paracrine action of vitamin D is best indicated in the skin and the immune system, where it regulates cellular differentiation and maturation. Recent studies indicate that the autocrine/paracrine action in the main bone cells also regulates the proliferation and differentiation. Studies in rats have shown that adequate serum concentration of calcidiol is critical for optimal bone health and for the prevention of osteoporosis which coincides with the results of clinical studies in humans[12].

Definition and prevalence of vitamin D deficiency

Although calcitriol is the active form of vitamin D, its serum concentration does not reflect the overall status of vitamin D and is of no clinical significance. Serum calcidiol concentration that reflects the concentration of vitamin D and of endogenous and exogenous origin is taken as a measure for the clinical determination of vitamin D status[5]. There are several reasons for this: **1.** half-life of calcidiol is longer than the half-life of calcitriol (-3 weeks compared to -8 hours), **2.** concentration of calcidiol in the circulation is 1,000x greater than the concentration of calcitriol (ng/ml compared to the pg/ml) **3.** formation of calcitriol is mainly influenced by regulating PTH which regulates the calcium concentration. For that reason the calcitriol concentration may be elevated in patients with severe vitamin D deficiency, in order to maintain normal calcium concentration. Most experts agree that the circulating concentration of calcidiol represents total vitamin D status of

se manjak vitamina D definira kao koncentracija kalcidiola manja od 20 ng/ml[5,13,14]. Postoji i definicija da koncentracija kalcidiola između 20 i 30 ng/ml označava relativnu insuficijenciju vitamina D, dok koncentracija iznad 30 ng/ml predstavlja zadovoljavajuću koncentraciju vitamina D[5,15,16]. Intoksikacijske koncentracije vitamina D smatraju se one iznad 150 ng/ml i uzrokuju tešku hiperkalcemiju, hiperfosfatemiju i bubrežno oštećenje (**Tablica 2**)[5,13,14]. Čimbenici rizika za manjak vitamina D su sljedeći: nedovoljno izlaganje sunčevoj svjetlosti, tamnija put, uznapredovale godine, hospitalizacija, manjak unosa vitamina D hranom, život u sjevernoj Zemljinoj polutki, sindrom malapsorpcije, lijekovi koji ubrzavaju metabolizam kalcitriola (fenitoin, fenobarbital, kortikosteroidi), kronična bubrežna bolest, disfunckija jetre, pretilost.

an individual, but what is the optimal concentration of vitamin D remains questionable. Currently, vitamin D deficiency is defined as a concentration of calcidiol less than 20 ng/ml[5,13,14]. There is a definition that calcidiol concentration between 20 and 30 ng/ml indicates the relative insufficiency of vitamin D, while the concentration above 30 ng/ml is a sufficient concentration of vitamin D[5,15,16]. Intoxication concentrations of vitamin D are considered to be those above 150 ng/ml and cause severe hypercalcemia, hyperphosphatemia and renal damage (**Table 2**)[5,13,14]. The risk factors of vitamin D insufficiency are the following: insufficient exposure to sunlight, brown tan, advanced age, hospitalization, insufficient intake of vitamin D with food, life in the northern hemisphere, malabsorption syndrome, drugs that speed up the metabolism of calcitriol (phenytoin, phenobarbital, corticosteroids), chronic kidney disease, liver dysfunction, obesity.

Table 2. *Relationship between serum 25-hydroxyvitamin — concentration and health.*

25-Hydroxyvitamin D Concentration (ng/ml)	Status	Health Consequence
< 15	Severe deficiency	Can lead to rickets and severe bone disease
< 20	Deficient	Inadequate bone health and osteoporosis
20-30	Relative insufficiency	Recently considered inadequate for optimal health status
>30	Adequate stores	Optimal health status
>150	Toxicity	Hypercalcemia, hyperphosphatemia, and renal impairment

Patofiziologija vitamina D u srčanožilnim bolestima

Dosadašnja mnogobrojna istraživanja upućuju na inverznu povezanost serumske koncentracije vitamina D i disfunkcije srčanožilnog sustava[17-19]. Prva istraživanja koja su pokušala dokazati povezanost vitamina D i SŽB su rađena na modelima štakora s manjkom vitamina D prije više od 20 godina[20-22]. Ta istraživanja na životinjama su pokazala vezu između manjka vitamina D i hipertrofije srčanih klijetki, fibroze, arterijske hipertenzije. Podupirala su ulogu vitamina D u održavanju srčanožilnog sustava putem neposrednog utjecaja kalcitriola na kardiomiocite i posredno putem djelovanja na cirkulirajuće hormone i kalcij.

Prvi klinički dokazi da bi manjak vitamina D mogao imati utjecaj na razvoj SŽB viđeni su u bolesnika s terminalnim stadijem kronične bubrežne insuficijencije (ESRD)[23]. Zbog smanjene bubrežne funkcije, pretvorba kalcidiola u kalcitriol je smanjena što dovodi do manjka aktivnog oblika vitamina D[24]. Zbog manjka kalcitriola razvija se sekundarni hiperparatireoidizam što dovodi do porasta koncentracije PTH[11,25]. Povišena koncentracija PTH se povezuje s porastom AT i povećanom kontrakcijom miokarda što dovodi do hipertrofije i fibroze miokarda te zatajivanja srca[26]. Smanjenje hiper-

Pathophysiology of vitamin D in cardiovascular diseases

Numerous studies conducted so far suggest an inverse association of serum concentrations of vitamin D and cardiovascular system dysfunction[17-19]. The first studies that were to prove the connection between vitamin D and CVDs were conducted on models of rats with vitamin D deficiency more than 20 years ago[20-22]. These trials on animals showed a link between vitamin D deficiency and cardiac ventricular hypertrophy, fibrosis and arterial hypertension. They supported the role of vitamin D in maintaining the cardiovascular system through the direct impact of calcitriol on cardiomyocytes and indirectly through the effect on circulating hormones and calcium.

The first clinical evidence that vitamin D vitamin deficiency could have an impact on the development of CVDs was seen in patients with end-stage chronic renal disease (ESRD)[23]. Because of the impaired renal function, the conversion of calcidiol to calcitriol is reduced causing thus deficiency of the active form of vitamin D[24]. Calcitriol deficiency causes a development of secondary hyperparathyroidism leading to an elevated concentration of PTH[11,25]. The high PTH concentration is associated with a BP elevation and elevated myocardial contraction which leads to myocardial hypertrophy

trofije lijeve klijetke (HLK)[27] uz smanjenje kardiovaskularne smrtnosti[28, 29] primjećeno je u bolesnika s ESRD i sekundarnim hiperparatireoidizmom koji su dobivali aktivni oblik vitamina D (kalcitriol ili analog). U toj grupi bolesnika povišena koncentracija PTH se smatra primarnim uzrokom srčane disfunkcije te je terapija usmjerena na smanjenje koncentracije PTH. Nekoliko istraživanja je pokazalo da nakon paratireoidektomije u bolesnika s ESRD dolazi do smanjenja AT i HLK, ali neka istraživanja nisu uočila takve rezultate[27,30,31]. Iz tog je proizašlo pitanje da li je povišena razina PTH jedini uzrok srčane disfunkcije u bolesnika s ESRD. Tako je nastala hipoteza o direktnom učinku vitamin D na srčanu funkciju. Receptor za vitamin D je prisutan u mnogim tkivima koja nemaju ulogu u regulaciji metabolizma kalcija kao što su limfociti, stanice kolona, hepatociti i srčani miociti[32]. Izražena ekpresija VDR na drugim tkivima jača teoriju da vitamin D ima i drugu endokrinu ulogu, a ne samo reguliranje homeostaze kalcija9. Vitamin D djelovanjem na VDR u srčanim stanica regulira ulazak kalcija u stanice, kontrolira količinu slobodnog kalcija u citosolu te time regulira kontraktilnost miokarda i kontrolira rast i proliferaciju stanica[20-22,33,34]. Izravne fiziološke posljedice nepostojanja VDR na srčanu funkciju su proučavane u nekoliko studija na životinjama[35-37]. U tim studijama, vitamin D receptor knockout miševi su uspoređeni s miševima divljeg tipa koji imaju prisutan VDR[35,36]. Histološko bojenje miokarda pokazalo je vrlo značajnu staničnu hipertrofiju u vitamin D receptor knockout miševa u usporedbi s miševima divljeg tipa. Hipertrofija miokarda i fibroza miokarda zabilježena je isključivo u vitamin D receptor knockout miševa[35,36]. Istraživanje na vitamin D receptor knockout miševima također dokazuje da vitamin D posredno utječe na rad srca zbog svoje uloge kao negativni regulator renin-angiotenzin-aldosteron sustava (RAAS)[37,38]. Ustanovilo se da je u vitamin D receptor knockout miševa bila prisutna trostruko izraženija ekspresije renin glasničke RNA (mRNA) i više od 2,5x povećanje koncentracije angiotenzin II u plazmi u usporedbi s divljim tipom miševa[38]. Kako kalcitriol regulira PTH i održava koncentraciju kalcija, sekundarni hiperparatiroidizam i hipokalcemija su se neminovno razvili u vitamin D receptor knockout miševa. Vitamin D receptor knockout miševi su prije razvoja sekundarnog hiperparatiroidizma dobivali kalcija za održavanje odgovarajuće razine u serumu. Usprkos normalnoj koncentraciji serumskog kalcija i PTH, u vitamin D receptor knockout miševa i dalje je zabilježena povišena proizvodnja renin mRNA i angiotenzina II što ukazuje da kalcitriol ima izravan utjecaj na RAAS koji je neovisan o kalciju ili PTH.

Osim RAAS aktivacije, pojačana aktivacija imunosnog sustava često se povezuje s SŽB, točnije s aterosklerozom i kalcifikacijom valvula i nestabilnim plakom i njegovim pucanjem[39]. Prekomjerno stvaranje upalnih citokina doprinosi razvoju i progresiji zatajenja srca[40]. Eksperimentalne studije su pokazale da vitamin D igra važnu ulogu u regulaciji nekoliko važnih upalnih i protuupalnih citokina[41-43]. U jednoj studiji je opažena smanjena proizvodnja upalnih citokina (interleukin [IL]-6 i čimbenika tumorske nekroze [TNF] kada su aktivirani monociti bili izloženi kalcitriolu[42]. Slično, u drugoj studiji, produkcija protuupalnog citokina IL-10 se značajno povećala kada su dendritičke stanice bile izložene kalcitriolu u usporedbi s kontrolnim stanicama koje nisu[41]. Ove studije su pokazale da hormonsko djelovanje vitamina D ima aktivnu i izravnu ulogu u regulaciji nekoliko imunomodulatorskih citokina što dovodi do smanjenja upale.

Iz rezultata eksperimentalnih laboratorijskih studija proizašla su mnoga klinička ispitivanja o poveznosti manjka vitamina D i arterijske hipertenzije, a neka od njih su dobila poz-

and fibrosis as well as the heart failure.[26] Reduction of the left ventricular hypertrophy (HLK)[27] along with a reduction of cardiovascular mortality[28, 29] was observed in patients with ESRD and secondary hyperparathyroidism who received the active form of vitamin D (calcitriol or its analog). In this group of patients, the high PTH level is considered to be the primary cause of cardiac dysfunction and the therapy is aimed at reducing the PTH levels. Several trials have shown that parathyroidectomy in patients with ESRD is followed by a decrease in BP and LVH, but some trials have not observed such results[27,30,31]. This brings up a question of whether the high PTH level is the only cause of cardiac dysfunction in patients with ESRD. This is the way how the hypothesis on a direct effect of vitamin D on cardiac function was set up. Receptor for vitamin D is present in many tissues, which do not have a role in the regulation of calcium metabolism such as lymphocytes, colon cells, hepatocytes and cardiac myocytes[32]. The pronounced expression of VDR in other tissues supports the theory that vitamin D also has another endocrine role, not only the regulation of calcium homeostasis9. By activity on VDR, vitamin D in cardiac cells regulates the flux of calcium into the cells, controls the amount of free calcium in the cytosol and thereby regulates myocardial contractility and controls the growth and proliferation of cells[20-22,33,34]. Direct physiological consequences of non-existence of VDR on the cardiac function were studied in several trials on animals[35-37]. In these studies, the vitamin D receptor knockout mice were compared to wild type mice, which have present VDR[35,36]. Histological staining showed a significant cell hypertrophy in the vitamin D receptor knockout mice compared to the wild type mice. Myocardial hypertrophy and myocardial fibrosis was observed only in the vitamin D receptor knockout mice[35,36]. The trial on vitamin D receptor knockout mice also proves that vitamin D directly affects the heart function due to its role as a negative regulator of renin — angiotensin-aldosterone system (RAAS)[37,38]. It was found that the vitamin D receptor knockout mice had three times more pronounced expression of renin messenger RNA (mRNA) and more than 2.5x increase in concentration of angiotensin II in plasma compared to the wild type mice[38]. Since calcitriol regulates PTH and maintains calcium concentration, secondary hyperparathyroidism and hypocalcemia inevitably developed in the vitamin D receptor knockout mice. Vitamin D receptor knockout mice received calcium for maintenance of appropriate serum levels before the development of secondary hyperparathyroidism. Despite normal serum calcium and PTH level, an increased production of renin mRN and angiotensin II is still recorded in vitamin D receptor knockout mice, indicating that calcitriol has a direct impact on RAAS which is independent of calcium or PTH.

In addition to RAAS activation, an increased activation of the immune system is often associated with CVDs, to be more specific, atherosclerosis and calcification of heart valves and unstable plaque and its rupture[39]. Excessive production of inflammatory cytokines contributes to the development and progression of the heart failure[40]. Experimental studies have shown that vitamin D plays an important role in the regulation of several important inflammatory and anti-inflammatory cytokines[41-43]. One trial showed a decreased production of inflammatory cytokines (interleukin [IL]-6 and tumor necrosis factors [TNF] when the activated monocytes were exposed to calcitriol[42]. Similarly, another trial showed that the production of anti-inflammatory cytokine IL-10 significantly increased when dendritic cells were exposed to calcitriol in comparison to control cells that were not exposed to it[41]. These trials showed that hormonal effect of vitamin D has a direct and active role in the regulation of several immunomodulatory cytokines leading to a reduction of inflammation.

itivnu povezanost između deficita vitamina D i arterijske hipertenzije, dok neke studije nisu uspjele dobiti takve rezultate[44].

Dong i sur. su dokazali da kalcitriol djeluje vazoprotektivno na krvne žile u bolesnika s arterijskom hipertenzijom. Djelovanjem na VDR, kalcitriol djeluje povoljno na renovaskularnu disfunkciju u hipertenziji putem učinka na ekpresiju i aktivnost pojedinih ključnih proteina koji sudjeluju u stvaranju slobodnih radikala. Kalcitriol uravnotežuje stvaranje slobodnih radikala, hiperpordukciju angiotenzin 1 receptora te podjedinica NADPH oksidaze te tako sudjeluje u očuvanju funkcije endotela u hipertenziji[45].

Bolesti kardiovaskularnog sustava i vitamin D

Budući da se aktivacija RAAS i imunološkog sustava povezuje s vaskularnim bolestima, istraživanja odnosa nedostatka vitamina D u ljudi i vaskularnih bolesti je logičan korak. Nedostatak vitamina D se povezivao s mnogim bolestima vaskularnog sustava, uključujući bolesti perifernih arterija, aterosklerozu, infarkt miokarda i ishemijski moždani udar. Pojedina istraživanja su pokazala da postoji povezanost između nižih koncentracija kalcidiola i veće učestalosti periferne arterijske bolesti sugerirajući da male razlike u koncentraciji kalcidiola u serumu mogu uvelike utjecati na rizik od razvoja bolesti perifernih arterija[46]. U istraživanju provedenom na bolesnicima sa šećernom bolešću uočeno je da je teška ateroskleroza koja je mjerena debljinom intime medije karotidnih arterija povezana s nižim koncentracijama vitamina D[47]. Bolesnici s manjkom vitamina D imali su značajno veću debljinu intime medije karotidne arterije od bolesnika sa zadovoljavajućom koncentracijom vitamina D .

Jasna povezanost između koncentracije vitamina D i pojave akutnog infarkta miokarda (AIM) nije utvrđena. Jedno istraživanje je čak pokazalo da su bolesnici koji su doživjeli AIM imali povećan unos vitamin D u usporedbi s kontrolnom skupinom, ali nedostatak tog istraživanja je bio što nije navedena serumska koncentracija kalcidiola[48]. Nakon ovog istraživanja proizašle su mnoge studije koje su proučavale koncentraciju kalcidiola bolesnika s AIM i kontrolne zdrave skupine te su došle do rezultata da se razina vitamina D nije bitno razlikovala između skupina[49-51]. Novija istraživanja su ipak uočila povezanost niže koncentracije kalcidiola i povećanog rizika za nastanak AIM, u kojima se manjak vitamina D pokazao kao nezavisni čimbenik rizika za razvoj nefatalnog AIM ili fatalne koronarne bolesti srca s tim da su ispitanici s koncentracijom vitamin D 30 ng/ml i više imali upola manji rizik[52].

Povezanost manjka vitamina D i SŽB koje su definirane kao koronarnih bolest srca, bolest perifernih arterija i cerebrovaskularna bolest također je proučavana u nekoliko studija[53,54]. U istraživanju na preko 400 bolesnika sa šećernom bolešću uočeno je da bolesnici s manjkom vitamina D (definirano kao <20 ng/ml) imaju veću prevalenciju SŽB koja je ostala statistički značajna i nakon prilagodbe za bubrežnu funkciju, lijekove, vrijednost LDL, prisutnost metaboličkog sindroma i vrijednost hemoglobina A1c .

Jedna studija je proučavala može li manjak vitamina D biti prediktor za razvoj SŽB[54]. Proučavano je 1.739 bolesnika bez poznatih SŽB ili bubrežne bolesti te su im izmjerene koncentracije kalcidiola. Bolesnici su praćeni prosječno 5,4 godine te se pratila učestalost AIM, moždanog udara, an-

The results of experimental lab trials resulted in many clinical studies on association between vitamin D deficiency and hypertension, and some of them showed a positive association between vitamin D deficiency and hypertension, while some studies failed to obtain such results[44].

Dong et al. have proved that calcitriol acts in a vasoprotecive way on the blood vessels in patients with arterial hypertension. By action of the VDR, calcitriol has a beneficial effect on renovascular hypertension through the effect on the expression and activity of specific key proteins that are involved in the creation of free radicals. Calcitriol balances the formation of free radicals, hyperproduction of angiotensin receptor 1 and subunits of NADPH oxidase and thus participates in the preservation of endothelial function in hypertension[45].

Cardiovascular diseases and vitamin D

Since the activation of RAAS and the immune system is associated with vascular diseases, the research of the relationship of vitamin D deficiency and vascular diseases is a logical step. Vitamin D deficiency was associated with many vascular diseases, including peripheral artery diseases, atherosclerosis, myocardial infarction and ischemic stroke. Some trials have shown that there is a correlation between lower calcidiol concentrations and higher incidence of peripheral arterial disease, suggesting that small differences in the concentration of calcidiol in serum can greatly affect the risk of developing peripheral artery diseases[46]. The trial conducted on patients with diabetes showed that severe atherosclerosis as measured by intima media thickness of the carotid arteries is associated with lower concentrations of vitamin D[47]. The patients with vitamin D deficiency had significantly greater intima media thickness of the carotid artery than the patients with sufficient concentration of vitamin D.

A clear correlation between the concentration of vitamin D and the occurrence of acute myocardial infarction (AMI) has not been established. One trial even showed that the patients who had a history of AMI showed an increased intake of vitamin D compared with the control group, but the disadvantage of this trial was that the serum concentration of calcidiol was not indicated[48]. This trial was followed by many studies that studied the concentration of calcidiol in patients with AMI and healthy control group and reached a conclusion that the level of vitamin D did not significantly differ among the groups[49-51]. Recent studies have, however showed the connection between a lower concentration of calcidiol and an increased risk of AMI, where vitamin D deficiency proved to be an independent risk factor for the development of non-fatal AMI or fatal coronary heart disease, provided that the subjects with vitamin D concentration of 30 ng/ml and more had twice lower risk[52].

The connection between vitamin D deficiency and CVD defined as coronary heart disease, peripheral artery disease, and cerebrovascular disease has also been studied in several trials[53,54]. The trial conducted on over 400 patients with diabetes showed that patients with vitamin D deficiency (defined as <20 ng/ml) had higher prevalence of CVD which remained statistically significant even after the adjustment for renal function, medications, LDL, presence of metabolic syndrome and value of hemoglobin A1c.

One trial studied whether vitamin D deficiency can be a predictor for the development CVD[54]. 1,739 patients without known CVD or kidney disease were studied and their concentrations of calcidiol were measured. Patients were followed up over a median period of 5.4 years and incidence of

gine pektoris, tranzitorne ishemijske atake, klaudikacija ili zatajivanja srca. Pokazalo se da je nedostatak vitamina D (<5 ng/ml) povezan s povećanim rizikom za razvoj SŽB.

Mnoga opservacijska istraživanja upućuju na povezanost manjka vitamina D i SŽB, uključujući perifernu vaskularnu bolest[46], povećano zadebljanje intime medije karotidnih arterija[47] i AIM[52]. Nadalje, nedostatak vitamina D je povezan sa smrtnošću od SŽB, ali i ukupnom smrtnosti[52,55-57]. Iako su ta istraživanja opservacijska, njihovi podaci podupiru hipotezu predloženu od strane ranih eksperimentalnih studija. Iz meta-analize Autiera i Gandinija koja je uključivala 18 randomiziranih kontroliranih studija je proizašlo da terapija vitaminom D dovodi do smanjenja ukupne smrtnosti za 7%. Bitna je činjenica da su studije koje su bile uključene u analizu koristile međusobno jako različite doze vitamina D[58,59].

Wang i sur. su proučili 8 randomiziranih kontroliranih studija i zaključili da je smanjenje rizika od oboljenja od SŽB pri korištenju srednjih do visokih doza vitamina D neznačajno[58,60].

Vitamin D i zatajivanje srca

Aktivacija RAAS i imunološkog sustava povezana s nedostatkom vitamina D ima potencijal da uzrokuje štetne učinke u bolesnika sa zatajivanjem srca. Odnos između razine vitamina D te učestalost i stupanj zatajivanja srca je istražena u nekoliko studija[60-66]. Istraživanje na Afroamerikancima koji su bili podijeljeni u tri skupine srčanog zatajivanja nije dokazalo povezanost između koncentracije kalcidiola i stupnja srčanog zatajivanja. Jedno drugo istraživanje je proučavalo bolesnike sa zatajivanjem srca koji su prolazili testiranja za listu čekanja za transplantaciju srca[64]. Bolesnici koji su imali teži stupanj zatajivanja srca imali su značajno niže koncentracije kalcidiola od onih s blažim stupnjem.

Podaci iz studije LURIC koja je proučavala povezanost koncentracije kalcidiola i renin-angiotenzin sustava u bolesnika koji su bili podvrgnuti koronarografiji[55] služili su za pročavanje odnosa između manjka vitamina D i smrtnog događaja uzrokovanog srčanim zatajivanjem ili iznenadnom srčanom smrću[67]. Pokazalo se da su bolesnici s teškim nedostatkom vitamina D (kalcidiol <10 ng/ml) imali značajno veći rizik za smrt zbog zatajivanja srca i iznenadne srčane smrti u usporedbi s bolesnicima s optimalnom koncentracijom vitamina D (kalcidiol ≥30 ng/ml). Također se pokazalo da je serumska koncentracija kalcidiola obrnuto proporcionalna koncentraciji NT-proBNP i stupnju NYHA klasifikacije.

Vitamin D i koronarna bolest srca

Koronarna bolest srca (KBS) je i dalje jedan od vodećih uzroka smrti u razvijenim zemljama unatoč napretku medicine. Stariji bolesnici koji su preboljeli akutni koronarni sindrom imaju teže kliničke posljedice što je vezano uz brojne komorbiditete, ali i uz malnutriciju, a snižene koncentracije vitamina D se također spominju kao jedan od bitnih čimbenika. Niske vrijednosti vitamina D se povezuju s pojačanim odlaganjem kacija u koronarnim arterijama, oštećenom funkcijom endotela i povećanim vaskularnim otporom[46,47,68]. *Chen i sur.* su proučavali povezanost vitamina D i težine KBS. Težina KBS je mjerena SYNTAX ljestvicom. Bolesnici koji su imali koncentraciju vitamina D <20 ng/mL, imali su veći rezultat prema ljestvici SYNTAX[69]. *Bajaj i sur.* su pratili 3.019 bolesnika od 65 godina i starije kroz šest godina. Proučavali su dvije grupe bolesnika, jedna s koncentracijom

AMI, stroke, angina pectoris, transient ischemic attack, claudication or heart failure was monitored. It has been shown that vitamin D deficiency (<5 ng/ml) was associated with an increased risk for the development of CVD.

Many observational studies suggest a connection between vitamin D deficiency and CVD, including peripheral vascular disease[46], increased thickening of intima media of the carotid arteries[47] and AMI[52]. Furthermore, vitamin D deficiency is associated with mortality from CVDs, but also with the total mortality[52,55-57] Although these studies are observational ones, their data support the hypothesis suggested by the early experimental studies. Meta-analysis of Autiero and Gandini which included 18 randomized controlled trials showed that the therapy with vitamin D leads to a reduction in total mortality by 7%. The important fact is that the studies that were included in the analysis used doses of vitamins D that differed from each other to a great extent[58,59].

Wang et al. studied eight randomized controlled trials and concluded that the reduction of the risk of CVD while using medium to high doses of vitamin D was insignificant[58,60].

Vitamin D and heart failure

Activation of RAAS and immune system associated with a vitamin D deficiency may cause adverse effects in patients with heart failure. The relation between vitamin D level and incidence and degree of heart failure has been explored in several studies[60-66]. The trial on African-Americans who were divided into three groups of heart failure has not proven the correlation between the concentration of calcidiol and a degree of heart failure. Another trial studied the patients with heart failure who were undergoing the tests for the list for the heart transplant[64]. Patients who had a more severe degree of heart failure had significantly lower concentrations of calcidiol than those with a milder degree.

Data from the LURIC trial which studied the correlation between calcidiol and the renin-angiotensin system in patients who underwent coronarography[55] were used for studying the relationship between vitamin D deficiency and fatal event caused by heart failure or sudden cardiac death[67]. It was shown that patients with severe vitamin D deficiency (calcidiol <10 ng/ml) had a significantly higher risk of death due to heart failure and sudden cardiac death compared to patients with optimal concentration of vitamin D (calcidiol ≥30 ng/ml). It was also shown that the serum concentration of calcidiol is inversely proportional to the concentration of NT-proBNP and degree of NYHA classification.

Vitamin D and coronary heart disease

Coronary artery disease (CAD) remains the leading cause of death in developed countries despite the advance in medicine. Elderly patients who have a history of acute coronary syndrome suffer from severe clinical consequences, which is related to a number of comorbidities, but also to malnutrition, whereas reduced concentrations of vitamin D are also mentioned as one of the important factors. Low levels of vitamin D are associated with an increased depositing of calcium in the coronary arteries, impaired endothelial function and increased vascular resistance[46,47,68]. *Chen and et.* studied the association of vitamin D and severity of CAD. The severity of CAD was measured by SYNTAX scale. Patients who had vitamin D concentration <20 ng/mL, had a higher score on the SYNTAX scale[69]. *Bajaj and et.* have followed up 3,019 patients aged 65 and older for six years.

vitamina D manjom od 20 ng/mL, a druga s koncentracijom ≥20 ng/mL. Konačni ishod koji su pratili je bila KBS i cerebrovaskularni događaj. Nisu uočili značajnu razliku između grupa za rizik od KBS, ali su uočili veći rizik za oboljenje od cerebrovaskularnih događaja u grupi s nižom koncentracijom vitamina D[70].

Unatoč dosadašnjim istraživanjima, samo nekoliko randomiziranih kontroliranih studija je proučavalo učinke dodatka vitamina D na prevenciju SŽB. Većina istraživanja je proučavala učinke niskih doza vitamina D na populaciji relativno niskog rizika[68]. Potrebna su daljnja istraživanja na starijoj populaciji visokog rizika s akutnim koronarnim sindromom kako bi se potvrdila učinkovitost vitamina D u prevenciji.

Nedostatak vitamina D i životna dob

U dječjoj dobi nedostatak vitamina D uzrokuje rahitične promjene na kostima. U odrasloj dobi nedostatka vitamina D se manifestira osteomalacijom (bolovi u kostima, deformacija skeleta) i najčešće se javlja u starijoj dobi. Kod takvih osoba serumska koncentracija kalcidiola je ispod 20 nmol/L, uz povišenu vrijednost PTH.

U zadnjih nekoliko godina postalo je očito da nedostatak vitamina D manjeg stupnja može dovesti do sekundarnog hiperparatireoidizma koji dovodi do razvoja osteoporoze s mogućim teškim komplikacijama i javnozdravstvenim posljedicama[71-73]. Pokazalo se da bolesnici koji su imali spontani prijelom kostiju imaju niže koncentracije vitamina D nego kontrolna skupina.

Dodatak vitamina D i kalcija se pokazao učinkovit u liječenju insuficijencije vitamina D, sekundarnog hiperparatireoidizma i smanjenja rizika od prijeloma kuka i drugih nevertebralnih fraktura u pojedinaca smještenih u domovima za starije osobe[74]. Novija istraživanja nisu uspjela dokazati taj povoljni učinak u osoba koje su smještene u vlastitim domovima[75,76]. Prije mnogo godina manjak vitamina D je bio problem dijagnosticiranja i liječenja dječije dobi pretežno u velikim gradovima. Danas je manjak vitamina D veliki javnozdravstveni problem koji zahvaća populaciju starije dobi koja boravi u domovima za starije osobe. Unatoč brojnim istraživanjima, terapija preparatima kalcija i vitaminom D ne dovodi uvijek do željenog učinka.

Zaključak

Eksperimentalna istraživanja na životinjama pokazala su da nedostatak vitamina D dovodi do povećanog izlučivanja paratiroidnog hormona i aktivacije RAAS i imunološkog sustava. Brojne opservacijske studije na ljudima su također povezala manjak vitamina D i SŽB. Unatoč velikom broju istraživanja, mali broj randomiziranih, kontroliranih studija je proučavao korist dodatka vitamina D za snižavanje kardiovaskularnog rizika. Manji broj istraživanja sugerira da povećanje koncentracije kalcidiola može biti od koristi u bolesnika sa zatajivanjem srca ili povišenim AT.

Iako procjena vitamin D statusa i liječenje dodatkom vitamina D nije rutinski dio liječenja, možda bi se trebao uzeti u obzir u bolesnika kod kojih se ne postižu optimalni rezultati liječenja unatoč provedenoj zadovoljavajućoj terapiji. Potrebna su velika randomizirana kontrolirana istraživanja kako bi se ispitalo ima li liječenje vitaminom D učinka na prevenciju ili liječenje SŽB.

They studied two groups of patients, one with a concentration of vitamin D less than 20 ng/mL, and the other with a concentration ≥20 ng/mL. The final outcome they obtained was CAD and cerebrovascular event. They did not notice a significant difference between the groups regarding the risk of CAD, but noticed a greater risk of cerebrovascular events in the group with a lower concentration of vitamin D[70].

Despite previous trials, only a few randomized controlled trials studied the effects of the addition of vitamin D to prevent CVDs. Most trials studied the effects of low doses of vitamin D on the population of a relatively low risk[68].Further trials are needed on elderly populations with a high risk of acute coronary syndrome in order to verify the effectiveness of vitamin D in prevention.

Vitamin D deficiency and age

In childhood, vitamin D deficiency causes rachitic changes in the bones. In adulthood, vitamin D deficiency was reflected in osteomalacia (bone pain, skeletal deformities) and most often it occurs in older age. In such persons, serum concentration of calcidiol is below 20 nmol/L , with elevated PTH level.

In the last few years it has become apparent that the lack of vitamin D of a minor degree can cause secondary hyperparathyroidism, which leads to the development of osteoporosis with possible severe complications and public health consequences[71-73]. It was shown that the patients who had spontaneous bone fracture have lower concentration of vitamin D than the control group.

The addition of vitamin D and calcium proved to be effective in the treatment of vitamin D insufficiency, secondary hyperparathyroidism and reduction of the risk of hip fracture and other non-vertebral fractures in individuals accommodated in the nursing homes for the elderly[74]. Recent studies failed to demonstrate the beneficial effect in persons who are accommodated in their own homes[75,76]. Many years ago, vitamin D deficiency was the problem regarding diagnosis and treatment at children age mainly in large cities. Today, vitamin D deficiency is a public health problem that affects the elderly population residing in the nursing homes for the elderly. Despite numerous trials, the therapy by using preparations of calcium and vitamin D do not always lead to the desired effect.

Conclusion

Experimental trials on animals have shown that vitamin D deficiency leads to increased secretion of parathyroid hormone and activation of the RAAS and the immune system. Numerous observational studies on humans were also associated with vitamin D deficiency and CVDs. Despite a great number of trials, a small number of randomized, controlled trials have studied the benefit of addition of vitamin D for lowering cardiovascular risk. A small number of trials suggest that increasing concentrations of calcidiol may be beneficial in patients with heart failure or elevated BP.

Although the evaluation of vitamin D status and the treatment by adding vitamin D is not a routine part of the treatment, maybe it should be considered in patients in whom optimal treatment results are not achieved in spite of a satisfactory therapy conducted. Large randomized controlled trials are required to examine whether the treatment with

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vitamin D has an effect on the prevention or treatment of CVD.

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Stručni rad / Professional article

Kombinacijska terapija perindoprilom/amlodipinom — optimalna sinergija u liječenju arterijske hipertenzije i smanjenju kardiovaskularnog rizika

Combination therapy with perindopril / amlodipine — optimal synergy in the treatment of arterial hypertension and cardiovascular risk reduction

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SAŽETAK: Arterijska hipertenzija je vodeći promjenjivi kardiovaskularni čimbenik rizika. U čak 75% bolesnika je potrebna kombinirana antihipertenzivna terapija za postizanje ciljnih vrijednosti arterijskog tlaka (AT). Kombiniranom terapijom postiže se veće snižavanje AT i brže postizanje ciljnih vrijednosti, a primjenom fiksne kombinacije pojednostavljuje se liječenje i poboljšava suradljivost bolesnika. Kombinacija ACE inhibitora i blokatora kalcijskih kanala, osim aditivnog učinka na sniženje vrijednosti AT, donosi dodatnu dobrobit na smanjenje ukupnog kardiovaskularnog rizika.

KLJUČNE RIJEČI: ACE inhibitori, blokatori kalcijskih kanala, arterijska hipertenzija, perindopril, amlodipin.

ABSTRACT: Arterial hypertension is the leading modifiable cardiovascular risk factor. In 75% of patients, the combination antihypertensive therapy is required to achieve target values of blood pressure (BP). The combination therapy leads to greater lowering of BP and faster achievement of target values, whereas the fixed combination simplifies the treatment and improves the patient compliance. The combination of ACE inhibitors and calcium channel blockers, in addition to an additive effect on lowering the value of BP, provides an additional benefit in reducing the overall cardiovascular risk.

KEYWORDS: ACE inhibitors, calcium channel blockers, hypertension, perindopril, amlodipine.

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Srčanožilne bolesti (SŽB) predstavljaju jedan od glavnih javnozdravstvenih problema u svijetu i vodeći su uzrok pobola i smrtnosti.[1] Arterijska hipertenzija (AH) je vodeći promjenjivi čimbenik kardiovaskularnog (KV) rizika s prevalencijom od 25%-35% odrasle populacije, do čak 60%-70% u dobi iznad 70 godina.[2] Rizik od kardiovaskularnog mortaliteta se udvostručuje sa svakim povišenjem arterijskog tlaka (AT) za 20/10 mmHg.[3] Povišeni AT glavni je čimbenik rizika od koronarne bolesti srca (KBS), zatajivanja srca, cerebrovaskularne bolesti, periferne arterijske bolesti, zatajenja bubrega i fibrilacije atrija.[4] Liječenje AH se preporuča odmah u bolesnika s hipertenzijom 3. stupnja, kao i u bolesnika s hipertenzijom 1. i 2. stupnja koji imaju visok ili vrlo visok ukupni rizik od SŽB.

Etiologija hipertenzije je u većini slučajeva multifaktorijalna što otežava, a često čini gotovo nemogućim postizanje kontrole AT djelujući na samo jedan presorni mehanizam. Djelovanje na jednu komponentu u pravilu nakon određenog vremena uzrokuje kompenzatorni odgovor koji smanjuje učinak terapije. Zbog toga je veličina sniženja AT ograničena

Cardiovascular diseases (CVD) are a major public health problem worldwide and the leading cause of morbidity and mortality.[1] Arterial hypertension (AH) is a leading modifiable factor of cardiovascular (CV) risk with a prevalence of 25%-35% of the adult population, up to 60%-70% at the age over 70.[2] The risk of cardiovascular mortality doubles with each elevation of blood pressure (BP) by 20/10 mmHg.[3] Elevated BP is a major risk factor for coronary artery disease (CAD), heart failure, cerebrovascular diseases, peripheral arterial diseases, kidney failure and atrial fibrillation.[4] AH treatment is recommended to be undertaken immediately in patients with grade 3 hypertension, as well as in hypertensive patients of grade 1 and 2 who have a high or very high overall CVD risk.

The etiology of hypertension is multifactorial in most cases, making it difficult and often almost impossible to achieve BP control by acting on only one pressor mechanism. The effect on one component principally causes a compensatory response after a certain time, that reduces the effect of the therapy. Therefore, the size of BP reduction is limited to all indi-

sa svim pojedinačnim skupinama antihipertenzivnih lijekova i prema rezultatima meta analize Law i sur iznosi oko 9,1/5,5 mmHg s minimalnim razlikama obzirom na pojedini razred antihipertenziva.[5]

Više kliničkih istraživanja (ALLHAT, HOT, LIFE) he pokazalo da većina bolesnika treba dva ili više antihipertenziva za postizanje ciljnih vrijednosti AT.[6-9]

Primjenu kombinirane antihipertenzivne terapije podržavaju i aktualne europske smjernice za liječenje AH prema kojima se liječenje može započeti kombinacijom lijekova kod bolesnika s visokim i vrlo visokim KV rizikom. Kombiniranom terapijom postiže se veće snižavanje AT i brže postizanje ciljnih vrijednosti, a primjenom fiksne kombinacije pojednostavljuje se liječenje i poboljšava suradljivost bolesnika.[10] Kombinacijska terapija povezana je s boljom podnošljivosti lijekova naročito kada se nuspojave vezane uz primjenu jednog lijeka neutraliziraju farmakološkim osobinama drugog lijeka. Naime, visoke doze monoterapije nose veći rizik nuspojava.

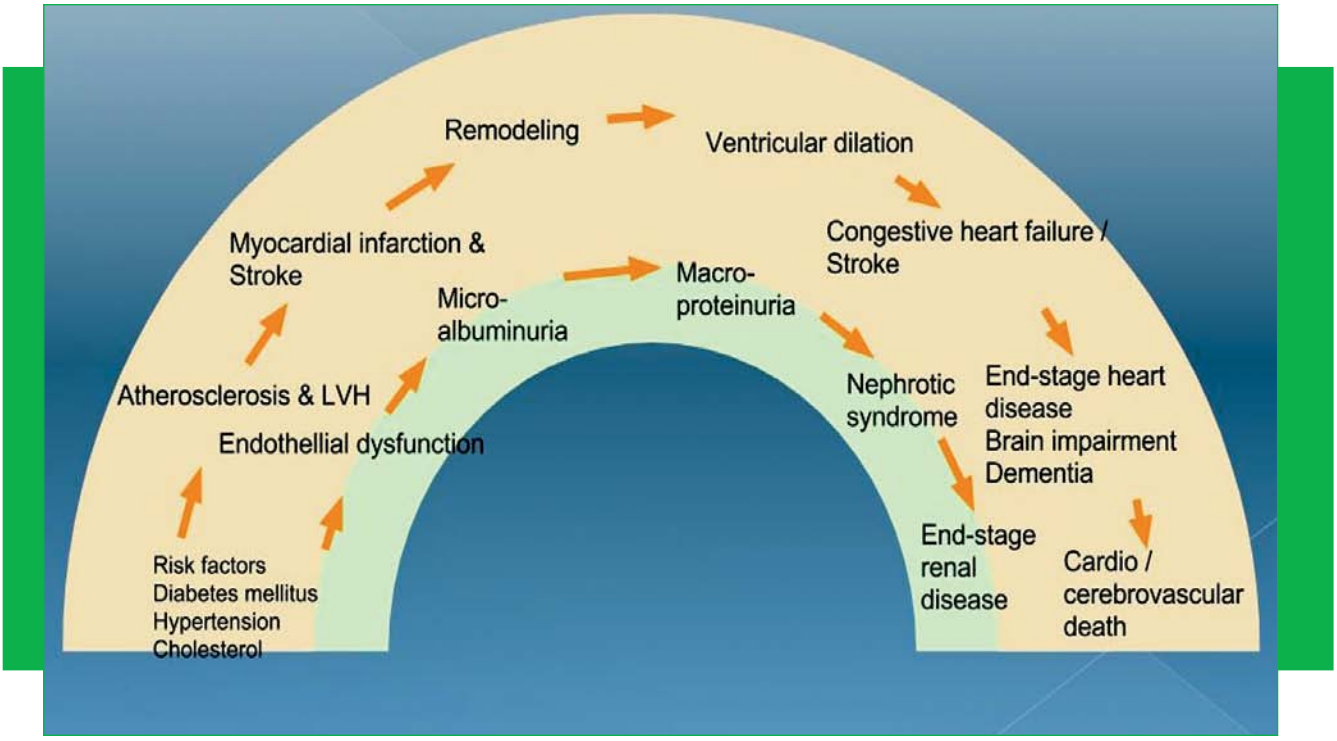
Sedam je glavnih razreda antihipertenzivnih lijekova i broj mogućih kombinacija je velik. Međutim, prema zadnjim smjernicama ESH/ESC iz 2013. i JNC 8 nekim kombinacijama se daje prednost zbog dokazanog sinergističkog učinka na smanjenje ukupnog KV rizika koji nadmašuje dobrobit samog sniženja AT.[10]

vidual classes of antihypertensive drugs and according to the results of the meta-analysis of Law et al it amounts to about 9.1/5.5 mm Hg with minimal differences considering an individual class of antihypertensive drugs.[5]

Large clinical trials (ALLHAT, HOT, LIFE) have shown that the most of the patients need two or more antihypertensive drugs to achieve target BP.[6-9]

The application of the combined antihypertensive therapy is also supported by current European guidelines for the treatment of AH according to which the treatment can begin with a combination of drugs in patients with a high and very high CV risk. The combination therapy leads to greater lowering of BP and faster achievement of target values, while the fixed combination simplifies the treatment and improves the patient compliance.[10] The combination therapy is associated with better tolerability of drugs, especially when the side-effects associated with the use of one drug are neutralized by pharmacological properties of the other drug. The high-doses of monotherapy carry a higher risk of side-effects.

There are seven major classes of antihypertensive drugs and there is a large number of possible combinations. However, according to the latest guidelines of ESH/ESC in year 2013 and JNC 8, some combinations are preferred for the proven synergistic effect on the reduction of the total CV risk outweighing the benefit of BP reduction.[10]



Adapted from: Am Heart J. 1991;121:1244-63.

Figure 1. *Renin-angiotensin-aldosterone system blockers and cardiovascular continuum.*

Mnoge kliničke studije (ADVANCE, ASCOT, EUROPA, PREAMI, PEP CHF, PROGRESS) su pokazale kardiovaskularni i renalni protektivni učinak ACE inhibitora. To se objašnjava protektivnim djelovanjem ACE inhibitora na funkciju endotela i proces ateroskleroze za koje se smatra da su osnovni patofiziološki mehanizmi u procesu tzv. kardiovaskularnog/kardiorenalnog kontinuuma. Koncept tzv. kardiovaskularnog ili kardiorenalnog kontinuuma temelji se na

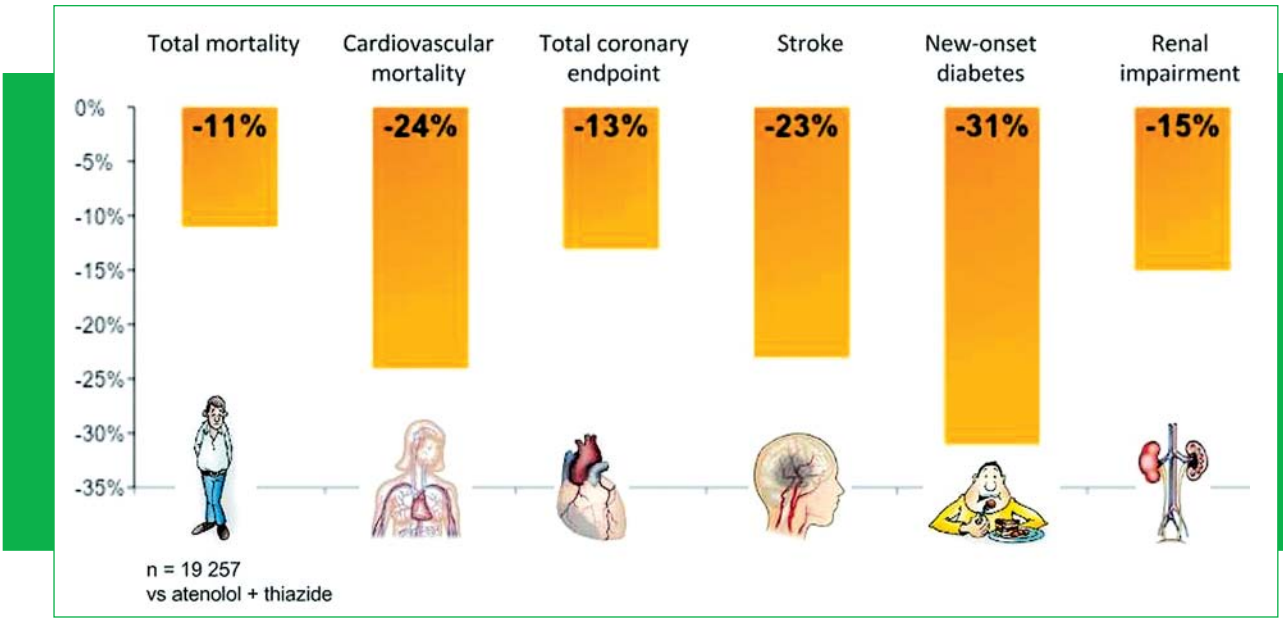
Many clinical trials (ADVANCE, ASCOT, EUROPA, PREAMI, PEP CHF, PROGRESS) showed cardiovascular and renal protective effect of ACE inhibitors. This explains the protective effect of ACE inhibitors on the endothelial function and atherosclerotic process that are considered to be the basic pathophysiologic mechanisms in the process so-called cardiovascular/cardiorenal continuum. The concept of the so-called cardiovascular or cardiorenal continuum is

spoznaji da progresija SŽB počinje već s postojanjem rizičnih čimbenika kao što su AH i dijabetes i vodi kroz KBS do ishemije miokarda (koja se može manifestirati kao angina pektoris, infarkt miokarda ili iznenadna srčana smrt), srčanog zatajivanja i terminalne faze srčane bolesti. Slični princip vrijedi i za nastanak kronične bubrežne bolesti, počevši od mikroalbuminurije kao jednog od najranijih znakova bubrežnog oštećenja, preko jasne proteinurije, sniženja filtracijske funkcije pa sve do terminalnog zatajenja bubrežne funkcije. Čini se da ateroskleroza i endotelna disfunkcija vode glavnu ulogu u ovom procesu. Kronična prekomjerna ekspresija tkivnog ACE dovodi do disbalansa u lokalnoj ekspresiji angiotenzina II/bradikinina što rezultira endotelnom disfunkcijom. ACE inhibitori reduciraju produkciju AT II koji ima glavnu ulogu u oštećenju ciljnih organa te tako smanjuju vazokonstrikciju, adhezivnost molekula, ekspresiju faktora rasta, smanjuju oksidativni stres i apoptozu stanica. Istovremena degradacija bradikinina u sklopu ACE inhibicije podiže razinu kinina što poboljšava vazodilataciju i antiapoptotičko djelovanje. To se najviše pokazalo u EUROPA studiji u kojoj su se određivali markeri endotelijalne funkcije uključujući eNOS, stopa apoptoze i razina vWF u bolesnika s KBS. Kod bolesnika s KBS su izmjerene značajno niže razine eNOS ekspresije i aktivnosti u odnosu na zdrave ispitanike, što se objašnjava prvenstveno prekomjernom tkivnom ekspresijom ACE. Nakon jednogodišnje terapije perindoprilom došlo je do porasta ekspresije eNOS kao i sniženja vWF koji je bazično bio viši kod bolesnika s KBS. Bitno je istaći da ovaj učinak perindoprila na normalizaciju omjera angiotenzina II/bradikinina, smanjenje upalnog procesa i time aptoptoze endotelnih stanica nije tzv. učinak klase ACE inhibitora i prvenstveno ovisi o tkivnom afinitetu lijeka, penetraciji lijeka u aterosklerotski plak i afinitetu za ciljni enzim.[11] Naime, perindopril spada u skupinu ACE inhibitora sa najvećom lipofilnošću i visokim afinitetom za tkivni ACE koji čini gotovo 90% od ukupne distribucije u tijelu i koji je bitan za dugotrajne učinke lijeka.[12] Pored toga, perindopril omogućava gotovo konstatnu 24-satnu kontrolu AT budući da ima T/P (engl. *trough-to-peak*) omjer 75-100% (to znači da će i nakon 24 sata osigurati sniženje 75-100% od maksimalne vrijednosti sniženja tlaka) te dugi poluživot (gotovo 30 sati).[13] Amlodipin je lijek treće generacije blokatora kalcijskih kanala (BKK). Osnovni mehanizam djelovanja jest smanjenje utoka kalcija na razini receptora za kalcij kao i voltažnih kalcijevih kanala u glatkomišićnoj stanici te posljedična vazodilatacija perifernih i koronarnih arterija i arteriola.[14] Tako djeluje i na stanice miokarda i time smanjuje kontrakciju miokarda, pa kod bolesnika sa anginom pektoris smanjuje ishemijsko oštećenje.[15] Prednosti amlodipina u odnosu na ranije generacije BKK su spori i postupni početak djelovanja što za posljedicu ima manje promjene vrijednosti AT, veću vaskularnu selektivnost (više antihipertenzivno, djelovanje, a manje na miokard) i dugotrajno djelovanje (24-satna kontrola AT). Nuspojave amlodipina su uglavnom blage i prolazne. Najčešće nuspojave su posljedica vazodilatacijskog učinka i ovisne su o dozi lijeka, u prvom redu periferni edemi, glavobolja, crvenilo i osjećaj vrućine.

Dodatak ACE inhibitora ili blokatora angiotenzinskih receptora skupini BKK značajno poboljšava toleranciju BKK zbog simpatikolitičkog učinka na renin-angiotenzin-aldosteron sustav (RAAS), kao i djelomičnog neutraliziranja perifernih edema. Naime, uzrok edema je arteriolarna dilatacija uzrokovana BKK s posljedičnim porastom kapilarnog tlaka, a blokatori RAAS svojom prvenstveno venodilatacijom neutraliziraju taj učinak. Pored toga, kombinacija ACE/BKK ima

based on the information that CVD progression begins with the presence of risk factors such as AH and diabetes and leads through CAD to myocardial ischemia (which can be reflected as angina pectoris, myocardial infarction or sudden cardiac death), heart failure and end-stage of the heart disease. A similar principle applies to the development of chronic kidney disease, starting with the microalbuminuria as one of the earliest signs of kidney damage, through clear proteinuria, reduction of the filtration function to the end-stage renal failure. Atherosclerosis and endothelial dysfunction play a main role in this process. Chronic overexpression of tissue ACE leads to imbalance in the local expression of angiotensin II/ bradikinin resulting in an endothelial dysfunction. ACE inhibitors reduce the production of AT II, which plays a major role in damaging target organs and thus reduce vasoconstriction, adhesion of molecules, expression of growth factors, reduce oxidative stress and cell apoptosis. The simultaneous degradation of bradikinin within the ACE inhibition raises the level of quinine which improves vasodilatation and antiapoptotic action. It was best presented in the EUROPA study in which the markers of endothelial function, including eNOS, the rate of apoptosis and vWF levels in patients with CHD were determined. In patients with CAD, significant lower levels of eNOS expression and activity were measured compared to healthy subjects, which is primarily explained by excessive tissue expression of ACE. After one year of the therapy with perindopril, we recorded an increase in eNOS expression and decrease in vWF which was basically higher in patients with CAD. It is important to emphasize that the effect of perindopril on the normalization of the ratio of angiotensin II/bradikinin, reduction of inflammatory process and thus endothelial cell apoptosis is not the so-called effect of the ACE inhibitor class and is primarily dependent on the drug tissue affinity, drug penetration into atherosclerotic plaque and affinity for the target enzyme.[11] Perindopril, namely, belongs to a group of ACE inhibitors with the highest lipophilicity and high affinity for the tissue ACE, which accounts for nearly 90% of the total distribution in the body and which is essential for the long-term effects of the drug.[12] In addition, perindopril allows almost constant 24-hour BP control since it has a through-to-peak ratio of 75-100% (this means that even after 24 hours it will provide a reduction of 75-100% of the maximum value of lowering the pressure) and long half-life (almost 30 hours).[13] Amlodipine is the drug of the third generation of calcium channel blockers (CCB). The main mechanism of action is the reduction of calcium influx at the calcium-sensing receptor level as well as voltage-dependent calcium channels in the smooth muscle cell and consequential vasodilatation of peripheral and coronary arteries and arterioles.[14] This is the way how it acts on the cells of the myocardium thereby reducing the myocardial contraction, and so in patients with angina pectoris it reduces ischemic impairment.[15] The benefits of amlodipine compared to earlier generations of CCB are a slow and gradual onset of action which results in minor changes to BP value, greater vascular selectivity (it has rather antihypertensive action, and less myocardial action) and long-term action (24-hour BP control). The side-effects of amlodipine are mainly mild and transitory. The most common side effects are the consequence of vasodilatation effect and are dependent on the dose of the drug, primarily peripheral edema, headache, flushing and feeling the heat.

The addition of ACE inhibitors or angiotensin receptor blockers to the CCB group significantly improves the tolerance of CBB due to sympatholytic effect on the renin-angiotensin-aldosterone system (RAAS) as well as the partial neutraliza-

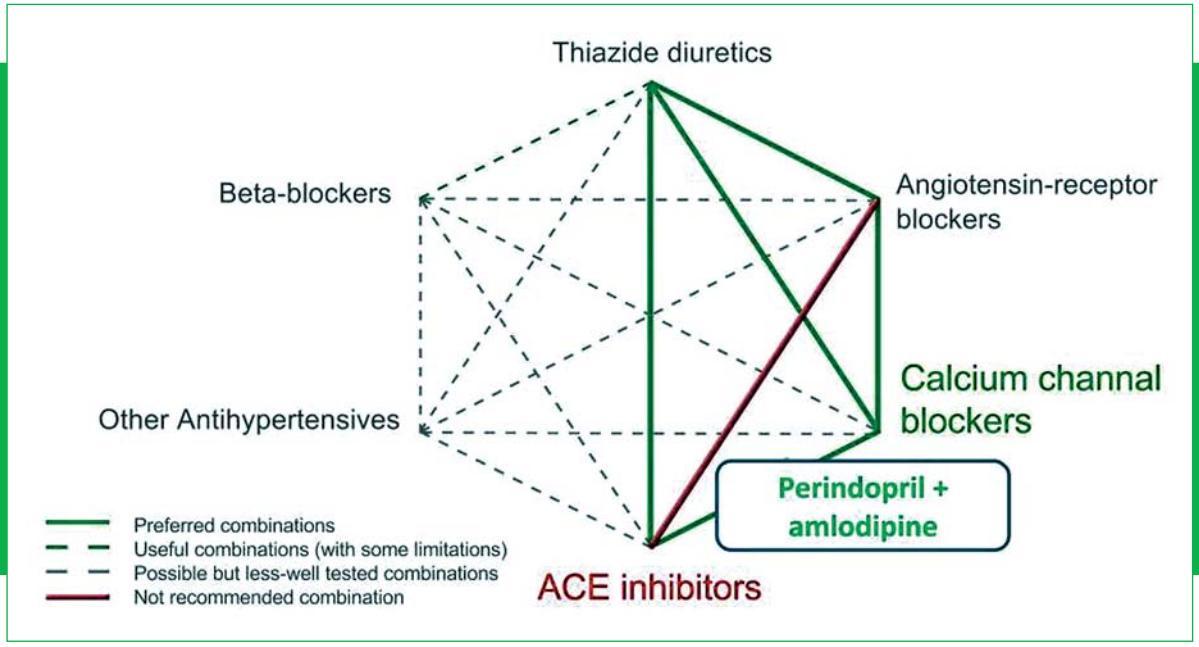


Adapted from Lancet. 2005;366:895-906.

Figure 2. *Combination of perindopril and amlodipine reduces all important CV events and total mortality in hypertensive high risk patients.*

i aditivno djelovanje na sniženje AT. ACE inhibitori induciraju dilataciju dvama različitim mehanizmima: povišenje bradikinina potiče up-regulaciju i ekspresiju aktivnosti eNOS s povećanom proizvodnjom i otpuštanjem NO iz endotela što promovira relaksaciju glatke muskulature putem GMP (gvanozin-monofosfat) — ovisnih kalcijevih kanala. Iz toga slijedi da BKK preveniraju kontrakciju dok ACE inhibitori promoviraju relaksaciju. Nadalje, inhibicijom ACE smanjuje se proizvodnja ATII koji također promovira utok kalcija.[16] Kombinacija perindoprila i amlodipina značajno snižava AT (srednja vrijednost sniženja tlaka čak za 42/23 mmHg) u svih bolesnika s AH neovisno o početnim vrijednostima tla-

tion of the peripheral edema. The cause of the edema is namely arteriolar dilation caused by CCB with a consequential increase in capillary pressure, whereas RAAS blockers neutralize this effect mainly by their venodilatation. In addition, the combination of ACE/CCB has additive effect on lowering BP. ACE inhibitors induce dilation by means of two different mechanisms: the elevation of bradikinin stimulates up-regulation and expression of eNOS activity with an increased production and release of NO from the endothelium which promotes the smooth muscle relaxation via GMP (guanosine monophosphate) — dependent calcium channels. Consequently CCB prevent the contraction, while ACE



Adapted from Eur Heart J. 2013:34;2159-219.

Figure 3. *2013 ESC Guidelines recommend the combination of ACE inhibitor and calcium channel blocker.*

ka, odnosno novodijagnosticiranih, nereguliranih hipertoničara na monoterapiji, nereguliranih hipertoničara na nekoj drugoj kombiniranoj terapiji.[17] U bolesnika s hipertenzijom trećeg stupnja postiže se dodatno sniženje AT (čak za 63/29 mmHg). Primjenom fiksne kombinacije perindoprila i amlodipina postiže se sniženje AT u 74% bolesnika već nakon tri mjeseca terapije. Pored samog sniženja AT, kombinacija perindoprila i amlodipina snižava i sve važne kardiovaskularne incidente i ukupnu smrtnost u hipertenzivnih visoko rizičnih bolesnika (ukupni mortalitet za 11%, kardiovaskularni za 24%, koronarna zbivanja za 13%, moždani udar za 23%, novonastali dijabetes za 31% i bubrežnu insuficijenciju za 15%).[18] Kombinacija perindoprila i amlodipina značajno smanjuje kardiovaskularnu smrtnost u bolesnika sa stabilnom KBS (ukupnu smrtnost za 46%, hospitalizaciju zbog kongestivnog zatajivanja srca za 54%, kardiovaskularni mortalitet za 41%, infarkt miokrda za 28% i zajednički primarni ishod u vidu KV mortaliteta, nefatalnog IM i uspješne resuscitacije srčanog aresta za 34%).18 Osim kod hipertoničara, kombinacija ova dva lijeka smanjuje sve važne kardiovaskularne incidente u bolesnika sa AH i pridruženim drugim dodatnim čimbenicima rizika (za 23% u pušača; za 20% u bolesnika s prethodnom vaskularnom bolesti, za 17% u bolesnika starijih od 60 godina i s oštećenom bubrežnom funkcijom; za 16% u bolesnika s metaboličkim sindromom; za 15% u pretilih i za 13% u bolesnika s tipom 2 šećerne bolesti).[19] Davanje ova dva lijeka u fiksnoj kombinaciji tzv. one-pill povezano je s boljom suradljivošću. ASCOT studija je dokazala da je kombinacija perindopril/amlodipin logična, dobro podnošljiva, isplativa i donosi prognostičku korist, odnosno značajno poboljšava kliničke ishode (kardiovaskularne smrti, infarkta miokarda i moždanog udara za 20%) u visokorizičnih pacijenata (prije svega dijabetičara i bolesnika s već razvijenom ishemijskom bolesti srca) u usporedbi s fiksnom kombinacijom ACE/diuretik.

Na kraju, važno je napomenuti da pojednostavljenje terapije u vidu fiksne kombinirane doze antihipertenziva je samo jedna od strategija za dugoročno održavanje postignutog sniženja AT. Naime, troškovi liječenja također utječu na suradljivost i ustrajnost bolesnika. Stoga, postojanje generičkih lijekova svakako omogućava dostupnost terapije većem broju bolesnika i doprinosi boljoj suradljivosti bolesnika.[20]

Na hrvatskom tržištu u portfelju Krke postoji kombinacija perindoprila i amlodipina pod nazivom Dalneva® u četiri različite doze (4/5 mg, 4/10 mg, 8/5 mg, 8/10 mg) koja je svakako jedna optimalna sinergistička kombinacija za liječenje hipertenzije i ukupnu kardiovaskularnu protekciju.

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inhibitors promote relaxation. In addition, due to ACE inhibition, the production of ATII is reduced, which also promotes calcium influx.[16] The combination of perindopril and amlodipine significantly reduces BP (median value of lowering the pressure even by 42/23 mmHg) in all patients with AH regardless of baseline pressure, or newly diagnosed, unregulated hypertensive patients on monotherapy, unregulated hypertensive patients receiving some other combination therapy.[17] Additional lowering of BP is achieved in the hypertensive patients with grade 3 (even by 63/29 mmHg). Lowering of BP is achieved by using the fixed combination of perindopril and amlodipine in 74% of patients already after three months of the therapy. In addition to lowering of BP, the combination of perindopril and amlodipine also lowers all important cardiovascular events and total mortality in high risk hypertensive patients (total mortality by 11%, cardiovascular mortality by 24%, coronary events by 13%, stroke by 23%, new-onset diabetes by 31% and renal failure by 15%).[18] The combination of perindopril and amlodipine significantly reduces cardiovascular mortality in patients with stable CAD (total mortality by 46%, hospitalization for congestive heart failure by 54%, cardiovascular mortality by 41%, myocardial infarction by 28% and the combined primary endpoint such as CV mortality, nonfatal MI and successful resuscitation of cardiac arrest by 34%).[19] The combination of the two drugs reduces all important cardiovascular events not only in hypertensive patients, but also patients with AH and other associated additional risk factors (by 23% in smokers; by 20% in patients with a history of vascular disease, by 17% in patients over 60 years of age and with impaired renal function; by 16% in patients with metabolic syndrome; by 15% in obese people and by 13% in patients with type 2 diabetes).[17] Administering the two drugs in a fixed combination, one-pill, is associated with better compliance. ASCOT study has demonstrated that the combination of perindopril/amlodipine is a logical, well-tolerated, cost-effective combination and provides the prognostic benefit, or significantly improves clinical outcomes (of cardiovascular death, myocardial infarction and stroke by 20%) in high-risk patients (especially in diabetics and patients with pre-developed ischemic heart disease), compared with a fixed combination of an ACE/diuretic.

Finally, it is important to note that the simplification of the therapy in the form of a fixed-dose combination of antihypertensive drugs is just one of the strategies for long-term maintenance of lowered BP. The costs of treatment are also the factor that can affect patient compliance and persistence. Therefore, the availability of generic drugs definitively makes the therapy affordable to a greater number of patients and contributes to better patient compliance.[20]

On the Croatian market, Krka holds in its portfolio a combination of perindopril and amlodipine entitled Dalneva® in four different doses (4/5 mg, 4/10 mg, 8/5 mg, 8/10 mg), which is certainly an optimal synergistic combination for the treatment of hypertension and overall cardiovascular protection.

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