

THE CROATIAN ACADEMY OF SCIENCES AND ARTS
The Department of Biomedical Sciences in Rijeka
CROATIAN SOCIETY OF HYPERTENSION
WORKING GROUP FOR HYPERTENSION,
CROATIAN CARDIAC SOCIETY
UNIVERSITY OF RIJKA – MEDICAL FACULTY
SOCIETY FOR NEPHROLOGY DEVELOPMENT
„Professor Milovan Radonić“
THE CROATIAN MEDICAL ASSOCIATION - Branch office Rijeka

29th symposium

HYPERTENSION HIGHLIGHTS IN 2019



7th March 2019.

9,00 am

**University Campus Rijeka, University Departments, Lecture hall O-030,
Radmile Matejčić 2, Rijeka**

Organizers

THE CROATIAN ACADEMY OF SCIENCES AND ARTS
The Department of Biomedical Sciences in Rijeka

CROATIAN SOCIETY OF HYPERTENSION

WORKING GROUP FOR HYPERTENSION, CROATIAN CARDIAC SOCIETY

UNIVERSITY OF RIJEKA – MEDICAL FACULTY

SOCIETY FOR NEPHROLOGY DEVELOPMENT

„Professor Milovan Radonić“

THE CROATIAN MEDICAL ASSOCIATION - Branch office Rijeka

Scientific Committee

Daniel Rukavina, president

Ines Drenjančević, Bojan Jelaković, Davor Miličić, Željko Reiner,
Alen Ružić, Luka Zaputović

Organizing Committee

Bojan Jelaković, president

Lovorka Bilajac, Vanja Ivković, Ana Jelaković, Tamara Knežević,
Marko Krmek, Mihaela Marinović Glavić, Tomislav Rukavina, Vanja Vasiljev

Registration: 8.00 – 9.00 am

Free admission. Participants who want a certificate from the Croatian Medical Chamber when register should provide organizers with own favorite cooking recipe with low amount of salt.

Refreshments during breaks and lunch are with no charge.

Parking is free and provided in the building of Student Center Rijeka
(Radmile Matejčić 5)

Official languages are Croatian and English. All slides will be on English

Information

Željana Mikovčić, Department of Biomedical Sciences in Rijeka
Radmile Matejčić 2, Rijeka

Phone: 051 584 826, e-mail: rimed@hazu.hr

**PROGRAM
OPENING
(09.00 – 09.30)**

Introduction

Daniel Rukavina, M.D., PhD, Professor Emeritus, Head of the Department of Biomedical Sciences in Rijeka, Croatian Academy of Sciences and Arts

Bojan Jelaković, M.D., PhD, Professor, University Hospital Center Zagreb, School of Medicine University of Zagreb, President of the Organizing Committee

Welcome addresses

Tomislav Rukavina, M.D., PhD, Professor, Dean, Medical Faculty, University of Rijeka

Davor Miličić, M.D., PhD., Professor, Vice-President, Croatian Academy of Sciences and Arts

Snježana Prijić Samaržija, PhD, Professor, Rector, University of Rijeka, Rijeka, Croatia

9,30 – 11,15 h

I. EPIDEMIOLOGY AND BASIC RESEARCH

Chairmen: Ines Drenjančević and Lovorka Bilajac

Lovorka Bilajac, PhD, Faculty of Medicine, University of Rijeka, Rijeka, Croatia
Epidemiology of hypertension worldwide and Croatia

Ranko Stevanović, M.D., Croatian Institute of Public Health, Zagreb, Croatia
Blood pressure and mortality - data from the Epidemiology of hypertension in Croatia survey (EHUH1) – 17 years of follow-up

Vanja Ivković, M.D., PhD, University Hospital Center Zagreb and Faculty of Health Studies, University of Rijeka, Rijeka, Croatia
Genography in hypertension – Adiponectin as an example

Ines Drenjančević, M.D., PhD, Professor, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia
Salt and renin-angiotensin system

Jerko Barbić, M.D., PhD, Professor, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia
Role of immunity and salt intake on hypertension onset

Ana Stupin, M.D., PhD, Assistant Professor, Faculty of Medicine and Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia
Endothelial dysfunction and salt intake in early stages of hypertension

Akos Koller, M.D, PhD, Professor, Faculty of Medicine, University of Pécs, Pécs, Hungary

Reversing the hypertension-induced microvascular effects by exercise

Coffee break: 11,15 – 11,30

11,30 – 13,00 h

II. SOME OF OVERLOOKED CLINICAL ASPECTS OF HYPERTENSION

Chairmen: Mario Laganović and Sanjin Rački

Mario Laganović, M.D., PhD, Professor, University Hospital Center Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia

Low birth weight and gestation age – determinants of cardiorenal risk in young men

Paolo Palatini, M.D., Professor, University of Padova, Padova, Italy

Isolated systolic hypertension in youth

Ana Jelaković, M.D., University Hospital Center Zagreb, Zagreb, Croatia

Glomerular hyperfiltration - an early alert

Sanjin Rački, M.D., PhD, Professor, Faculty of Medicine, University of Rijeka and Clinical Hospital Center Rijeka, Rijeka, Croatia

Cardiorenal syndromes

Jana Brguljan, M.D., Clinical Hospital Center Ljubljana, Ljubljana, Slovenia

Hypertension in women – before and after menopause

Lunch with a panel of speakers: 13,00 – 14, 00

14,00 – 15,45 h

III. BREAKTHROUGH IN DIAGNOSIS AND TREATMENT OF HYPERTENSION IN 2018

Chairmen: Bojan Jelaković and Vanja Vasiljev Marchesi

Bojan Jelaković, M.D., PhD, University Hospital Center Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia

Highlights of ESC/ESH 2018 guidelines on the management of hypertension

Ante Ivančić M.D, Health Care Center of Istrian County, Pula, Croatia

How to organize management of hypertension in primary care – experience from Istria

Branimir Krtalić, M.D., University Hospital Centre Zagreb, Zagreb, Croatia
How to measure blood pressure in 2019

Vanja Vasiljev Marchesi, PhD, Assistant Professor, Faculty of Medicine, University of Rijeka, Rijeka, Croatia
Physical activity as a cornerstone of blood pressure control and health improvement

Tamara Knežević, M.D., University Hospital Center Zagreb, Zagreb, Croatia
Antihypertensive drugs and albuminuria

Sandra Karanović, M.D, PhD, University Hospital Center Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia
Primary aldosteronism – diagnostic and treatment challenge in 2019

Živka Dika, University Hospital Center Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia
Fibromucular dysplasia – common task

Coffee break: 15, 45 – 16, 00

16,00 – 17,45 h

IV. TREATMENT OF HIGH RISK HYPERTENSIVE PATIENTS

Chairmen: Davor Miličić and Luka Zaputović

Luka Zaputović, M.D., PhD, Professor, Faculty of Medicine, University of Rijeka and Clinical Hospital Center Rijeka, Rijeka, Croatia
Treatment of atrial fibrillation in 2019

Davor Miličić, M.D., PhD, Professor, University Hospital Center Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia
Treatment of heart failure in 2019

Željko Reiner, M.D., PhD, Professor, University Hospital Center Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia
Treatment of dyslipidemia in 2019

Dario Rahelić, M.D., PhD, Assistant professor, Clinical Hospital Dubrava, Zagreb, Croatia
Rational choice of antidiabetic drugs in 2019

Davor Štimac, M.D., PhD., Professor, Faculty of Medicine, University of Rijeka and Clinical Hospital Center Rijeka, Rijeka, Croatia
Effect of bariatric surgery on blood pressure

Viktor Peršić, M.D., PhD, Professor, Thalassotherapia Opatija and Faculty of Medicine, University of Rijeka, Rijeka, Croatia
Rehabilitation and blood pressure control after myocardial infarction

Branko Malojčić, M.D., PhD, Professor, University Hospital Center Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia
Treatment of hypertensive patients after stroke

17,45 – 18,15 h

V. POSTER SESSION AND CLOSING REMARKS

Chairman: Bojan Jelaković

ABSTRACTS

Epidemiology of hypertension worldwide and Croatia

Lovorka Bilajac

Faculty of Medicine, University of Rijeka, Rijeka, Croatia

High blood pressure or hypertension affects more than one billion people around the world. According to epidemiological, clinical and experimental data, hypertension is the leading public health problem and is a major risk factor for the development of coronary heart disease, as well as other diseases including stroke, kidney failure, and congestive heart failure.

Recent researches reveal changes in the prevalence of high blood pressure in the world. Present trends and geographical variations indicate the continuous reduction of hypertension in countries with a high GDP, while hypertension is becoming a leading global challenge in the countries of middle and low-income. According to statistics, the lowest proportion of hypertension in Europe is found in UK (18 percent for men and 12 percent for women), while the lowest in the world share South Korea, the USA, Canada, Peru and Singapore.

According to the recent statistic, the country with the highest age-corrected proportion of men with high blood pressure in 2015 was Croatia (38 per cent of the population), followed by Latvia, Lithuania, Hungary and Slovenia (nearly two in five men in these countries had high blood pressure). Countries with the highest proportion of women with high blood pressure were all in Africa: Niger (36 percent), Chad, Mali; Burkina Faso and Somalia (around one in three women had high blood pressure). The hypertension rate increases with age, and is more common in men than in women and in persons with lower socioeconomic status. On the other hand, 80 % of people are aware about severity of the disease, the 70% is taking therapy, but a proper control of the treatment had only 50% of patients.

The existing data indicate the need for continuous monitoring and challenge to reduce the influence of risk factors on the incidence of hypertension, which is one of the goals of the WHO.

Epidemiology of hypertension in Croatia (EHUH study) - mortality data after 17 years of follow-up

Stevanović R¹, Knežević T², Kriškić V³, Krtalić B², Željковиć Vrkić T², Kos J², Pećin I⁴, Đapić K², Gellineo L, Domislović V⁵, Čatić Ćuti E⁶, Jelaković A², Dika Ž^{2,7}, Capak K¹, Jelaković B^{2,7}

¹ Croatian Public Health Institute, Zagreb, Croatia

² Department of Nephrology, Hypertension, Dialysis and Transplantation, University Hospital Center Zagreb, Zagreb, Croatia

³ Institute for Home Health Care Dominus, Zagreb, Croatia

⁴ Department of Metabolic Diseases, UHC Zagreb, Zagreb, Croatia

⁵ Department of Gastroenterology and Hepatology, UHC Zagreb, Zagreb, Croatia

⁶ General Hospital Zabok and GH of Croatian Veterans, Zabok, Croatia

⁷ School of Medicine University of Zagreb, Zagreb, Croatia

Our aim was to analyze mortality data in random sample of Croatian population, an original cohort from the EHUH study. EHUH study is nation-wide survey on prevalence, treatment and control of hypertension in Croatia. In 2001-2003 a random sample of 1267 subjects were enrolled. Mortality data were analyzed after average period of 17 years. Office blood pressure (BP) was measured in sitting position using mercury sphygmomanometer three times at two visits and once at home visit: total 9 measurements -average BP values were calculated. Mortality data were collected from National Public Health Institute records.

In total there were 228 deaths (17.9%). The main causes of death were cardiovascular diseases (CVD) (43.4%), cancer (28.5%), stroke (10.5%), dementia and degenerative diseases (5.2%), COPD (3.1%). More men than women died from any cause ($X^2=17.17$; $p=0.00003$). More women than men died from CVD compared to cancer and all other causes ($X^2=2.749$; $p=0.009$; $X^2=7.87$; $p=0.005$). Significantly more CV deaths were observed in untreated and uncontrolled hypertensives vs normotensives ($X^2=3.776$; $p=0.051$; $X^2=7.735$; $p=0.005$, respectively). There were no differences between controlled and uncontrolled hypertensives. There were significantly more deaths in obese and overweight than in subjects with normal BMI ($X^2=9.478$; $p=0.002$; $X^2=9.959$; $p=0.001$) with no differences between overweight and obese subjects. Significantly more deaths were noticed in those with lower income (<400Eu/months) ($X^2=17.07$; $p=0.00003$), and with less education (< 8years vs > 12years) ($X^2=25.61$; $p=0.0000$). Those who died consumed more frequently alcohol and smoked ($X^2=10.028$; $p=0.0015$; $X^2=20.408$; $p=0.00006$). Positive medical history for stroke, myocardial infarction, diabetes and dyslipidemia were observed in those who died ($X^2=16.35$; $p=0.0005$; $X^2=33.27$; $p=0.0000$; $X^2=36.05$; $p=0.0000$; $X^2=7.272$; $p=0.006$, respectively).

CVD are the most frequent causes of death being more prevalent in women and were associated with known medical (uncontrolled and untreated HT, past stroke and MI history, diabetes, dyslipidemia), poor life-style (smoking, drinking, physical inactivity) and socioeconomic factors (education, income). Higher CV mortality in women than men was associated with obesity, physical inactivity and socio-economic factors. Masked uncontrolled hypertension (MUCH) was found in 22.2% of patients and at the end of follow-up period it was associated with higher mortality ($X^2=2.722$; $p=0.0009$). We failed to find positive predictive value of BP variability for mortality probably the visit-to-visit period (2 months) was too short.

Genography in hypertension – Adiponectin as an example

Vanja Ivković^{1,2}

¹University Hospital Center Zagreb, Zagreb, Croatia

²Faculty of Health Studies, University of Rijeka, Rijeka, Croatia

Objective: Geographic distributions of various gene polymorphism involved in cardiorenal and cardiometabolic syndrome were published. However, there is scarce data on the genography of adiponectin alleles and genotypes in the apparently healthy population. Our aim was to conduct a meta-analysis of allele and genotype frequencies of two most frequently researched ADIPOQ SNPs (-11377C>G and -11391G>A) in different populations across several countries and continents.

Methods: We conducted a literature search of Medline (76 papers for SNP -11377C>G and 42 papers for -11391G>A). As our aim was to examine only the apparently healthy population only subjects from control groups were included in this analysis. Variations between different populations (genetic distance matrix) were calculated in Arlequin using Fst and exact-tests as metric. Geographical distances were calculated using Geographic Distance Matrix Generator. Correlations between genetic and geographic distances were calculated using Mantel test with 4 models (lin-lin, log-lin, lin-log and log-log) in Isolation By Distance v.3.23.

Results: Polymorphism -11377 C>G (20 populations, N=25 583 subjects) had minor allele frequency (MAF) of 26.25%. Total frequency of genotype C/C was 55.08%, C/G 38.04% and G/G 6.88%. MAF was lowest in Jordanian population (19.06%) and highest in Finnish population (33.14%). There was no evidence of a geographical gradient (p values ranged from 0.457 to 0.571, depending on model). Polymorphism -11391 G>A (16 populations, N=18 543 subjects) had MAF of 10.11%. MAF ranged from 2.66% in Sub-Saharan African population (South African Republic) to 37.20% in the population of India. We did not find any evidence of correlation between geographic and genetic distance (p values ranged from 0.136 to 0.286). Fst values showing genetic variation between different populations were in the range of expected.

Conclusion: Data on global prevalence of 11377C>G and -11391G>A ADIPOQ SNPs alleles and genotypes in 20 and 16 different populations, respectively are presented. Risk from cardiovascular, neoplastic and other diseases is not only a function of lifestyle and environment but also of genetic variation between populations. Analyses of this kind are warranted, can be used as a reference for future research and could help explain varying associations between genetic constellation and risk factors in the development of diseases.

Salt (NaCl) and renin-angiotensin system

Ines Drenjančević

Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

Numerous observational and experimental studies have confirmed the association of sodium intake with blood pressure levels. A high-salt diet is one of the major risk factors in the development and maintenance of hypertension. The renin-angiotensin system (RAS) is a key factor in many cases of essential hypertension, as indicated by the successful treatment of high blood pressure with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers. Indeed, mutations in the renin gene (or

other genes that encode components of the RAS) have been described in the development of hypertension and salt sensitivity.

The RAS is a crucial homeostatic system that controls body fluid volume, electrolyte balance, blood pressure, and neuronal and endocrine functions related to cardiovascular control. The RAS exhibits its effects through the effector molecule angiotensin II, which binds to specific membrane-bound angiotensin receptors located in multiple tissues, including the vasculature.

Endothelial dysfunction underlies hypertension and other cardiometabolic diseases. Endothelial function is impaired with high salt dietary intake prior to increases in blood pressure. Novel studies suggest that this impairment is related to suppressed levels of angiotensin II and that angiotensin II has permissive, modulatory effect on the mechanisms of endothelial function, including changes in oxidative-antioxidative balance, low-grade of inflammation and various vasodilatory and vasoconstrictory pathways.

Besides the mentioned effects of high sodium intake on the RAS, endothelial dysfunction and sympathetic nervous system activity, some other factors should also be considered as important contributors to the blood pressure increase linked to salt intake, including volume expansion (and elevated peripheral resistance in the later phase), functional changes of ion exchangers (such as the Na-Li countertransport) and possibly a reduced activity of the kallikrein-kinin system in the kidney.

Role of immunity and salt intake in hypertension onset

Jerko Barbić^{1,2}

¹Faculty of medicine Osijek, Osijek, Croatia

²University Hospital Osijek, Osijek, Croatia

The significance of the immunity and inflammation in hypertension has been observed for the past four decades. Activation of the immune system is inducing functional and structural changes in organs like blood vessels, kidney, skin and nervous system and recently in skin which have important role in regulation of blood pressure. Data from experimental and clinical studies have implicated that innate and adaptive immunity are involved in development of hypertension. In most cases, hypertension results from a multifaceted interaction of genetic and environmental factors. High salt diet is one of well recognized environmental factor implicated in the development of hypertension. Recently it has been shown that high salt diet may drive the progression and severity of autoimmune diseases through the interaction of salt with various cells of the immune system. This knowledge implies that activation of immune cells by high salt diet may lead to the changes in blood vessels, kidney and nervous system and result of these changes is development of sustainable hypertension. Here we will describe the influence of high salt diet on immune system. Osmotic stress increases in vitro IL-8 gene expression in human mononuclear cells similarly as LPS, and result of this is production of proinflammatory cytokines. Interestingly, macrophages infiltrate the skin of rodents following high salt-diet, suggesting that they may control the electrolyte homeostasis in the skin. It has been demonstrated that Na⁺ can be stored in the skin in abundance over water, creating a local electrolyte environment that does not readily equilibrate with plasma and hence escapes control of renal blood purification. The serum/glucocorticoid regulated kinase 1 (SGK1) have central role in the detection of osmotic stress. Latest data are showing that sodium have role in activation of the T cells

especially in the activation of Th17 cells. Th17 cells are highly pathogenic helper T cells. Salt and Angiotensin II (Ang II) can stimulate Th17 cells to generate IL17. Serum IL 17 level in hypertension patients is much higher than that in normal individuals, and IL 17 concentration is positively correlated with blood pressure values. Dietary salt maybe novel “danger signal” which may be important in the activation of the immune cells, and especially in skin where it has proinflammatory and protective role against microbes. Even more, in the human kidney, the high interstitial sodium concentration in the medulla generates a defense zone with enhanced antibacterial immunity in the area first encountered by bacteria ascending from the bladder. The human body has great ability to conserve sodium by reducing sodium losses in the urine and sweat. Here we show link between salt intake, immune response and hypertension. Wenzel and colleagues made explanation why significant antimicrobial effectors could have direct hypertensive effects by promoting vasoconstriction or sodium retention. Infection per se may cause hypotension through the fluid loss during fever, tachypnea, diarrhea and endothelial dysfunction. Therefore, the risk of hypotension related to inflammation might have favored selection of mechanisms that link salt and immunity to the enhancement of blood pressure.

Endothelial dysfunction and salt intake in early stages of hypertension

Ana Stupin^{1,2}

¹ Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

² Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

Long-term increased dietary salt intake commonly leads to an increase in arterial blood pressure (BP), that results in development of hypertension. This makes high salt (HS) intake, which is present in almost all parts of the world, an emerging risk factor for increased cardiovascular, cerebrovascular and renal morbidity and mortality. However, in a last few decades, it became evident that HS intake can induce significant organ damage and increase the risk for early morbidity and mortality even in the absence of arterial BP changes. A number of studies have demonstrated that such early manifested and BP-independent effect of HS loading presents development of endothelial dysfunction (ED), which has been denoted as a precursor and the earliest detectable outcome of various cardiovascular diseases (CVDs).

In order to elucidate the effects of dietary HS intake on vascular and endothelial function, studies traditionally investigated rodents (primary rats). Results of these studies demonstrated that changes in HS intake significantly alter vascular reactivity in different vascular beds and in response to various stimuli (even in normotensive animals), probably due to ED which was shown to be associated with low levels of angiotensin II (ANG II) and increased oxidative stress. The earliest clinical (human) studies that investigated the effects of HS loading on vascular/endothelial function were predominantly performed in hypertensive patients, and therefore were not been able to separate the effects of HS diet on endothelium from the effect of elevated BP. Thus, it was necessary to start investigating the vascular responses to salt loading in healthy, normotensive individuals as well. The earliest studies in healthy individuals brought conflicting results; while some authors reported that short-term HS loading impairs endothelial function in both macro- and microcirculation (venous occlusion plethysmography, pe-

ripheral arterial tonometry, flow mediated dilation), others failed to demonstrate such effect. However, several later studies have more clearly demonstrated the deleterious effect of HS loading on endothelium that is independent of the changes in arterial BP in healthy individuals. Moreover, some of these studies took step forward in order to investigate at least part of mechanisms mediating HS-induced changes of endothelial function, including its effect of renin-angiotensin system (RAS), oxidative stress, fluid retention, sex-related differences etc. One study demonstrated that HS intake-induced impairments in cutaneous vasodilatation were improved by the local infusion of ascorbic acid, suggesting a role for oxidative stress in contributing to vascular impairment. Moreover, it was reported that 7-days HS loading did not induce significant changes in body composition and fluid status in healthy individuals, indicating that endothelial changes are independent of fluid retention, just as they are BP independent. Regarding possible gender differences in endothelial response to HS loading, it was suggested that men have a greater sensitivity of large conduit arteries to salt loading compared to age-matched women.

Taken together, studies in healthy individuals have largely confirmed what has been learned from animal studies – short-term HS diet impairs endothelial function and vascular reactivity in both macro- and microcirculation independently of BP changes. Moreover, according to the latest results, studies in humans are beginning to give an insight into possible mechanisms (including suppression of RAS, oxidative stress, inflammation and endothelial-leukocyte interaction, adrenergic system activity, fluid retention, endothelial glycocalyx alterations, osmotically inactive sodium storage etc.), as well as gender-based differences in the effect of HS intake on endothelial function.

Low birth weight and gestational age – determinants of cardiorenal risk in young men

Mario Laganović^{1,2}

¹University Hospital Center Zagreb, Zagreb, Croatia

²School of Medicine, University of Zagreb, Zagreb, Croatia

A broad range of epidemiological data supports the hypothesis that risk of hypertension and impaired renal function is, in part, determined before birth. Negative correlation between size at birth and blood pressure and renal function in later life was observed. This phenomenon, termed “programming” has been the subject of intensive investigation, however the mechanisms underlying these associations are not completely elucidated. Impaired renal development, metabolic disturbances, hemodynamic changes are intensively investigated. Growing evidence also suggests increased susceptibility to chronic kidney disease and hypertension in premature born adults. Data on clinical course and factors influencing blood pressure and renal function over time in this particular group of patients are scarce. So, our aim was to determine cardiovascular risk factors and subclinical organ damage in young men born after intrauterine growth restriction (IUGR) and to analyse the relation and effects of premature birth on cardiovascular risk profile and target organ damage and explore possible underlying mechanisms. In follow-up study we investigate influence of birth parameters, kidney size and metabolic factors on blood pressure and renal function after 8 years of follow-up . Results of initial study showed increased cardiovascular risk in young adult men born after IUGR due to increased prevalence of cardiovascular risk factors (smoking, physi-

cal inactivity, higher blood pressure, dyslipidemia), subclinical organ damage (decreased renal function and increased left ventricular mass index) and early signs of atherosclerosis (increased cIMT and pulse pressure). Premature birth and obesity have additional unfavourable effect on blood pressure, metabolic profile and kidney function especially in participants born very premature. Possible underlying mechanisms connecting IUGR and cardiovascular and renal damage in later life could be altered kidney structure (i.e lower nephron number - determined through lower kidney volume) and increased arterial stiffness.

In follow-up study higher systolic and diastolic blood pressure, higher BMI, decrease in kidney volume and increase in eGFR were observed. Overweight and prematurely born participants show further increase in blood pressure as well as metabolic disturbances predominantly in overweight subjects. Multiple regression analysis showed BMI as key determinant of systolic blood pressure and BMI and kidney volume as key determinants of eGFR in IUGR subjects at the end of follow-up.

Observed data shows that increase in BMI is key unfavourable event leading to worsening of blood pressure and metabolic disturbances in this particular group of patients highlighting the importance of implementation of general measures of healthy living.

Isolated systolic hypertension in youth

Paolo Palatini

University of Padova, Padova, Italy

There is still debate in the literature about management of young subjects with isolated systolic hypertension (ISH) because whether ISH in the young (ISHY) implies a worse outcome and needs antihypertensive treatment is increasingly under challenge.

ISH is the most common form of hypertension in the elderly. However, ISH can be present also in young and very young individuals, more commonly in males. Results from the HARVEST study obtained in a population of 18 to 45-year-old grade 1 hypertensive subjects have shown that ISH prevalence was higher in men until 37 years of age and was similar between the two genders at 38-41 years.

Landmark studies by Lund-Johansen and Julius demonstrated that young patients in the earliest stages of hypertension were characterised by a hyperkinetic circulation, involving elevations of cardiac output and heart rate. Also in the Enigma Study, increased cardiac output and stroke volume were the predominant haemodynamic disturbances in ISHY. However, it was also clear that ISHY is a heterogeneous condition, since ~20% of subjects had normal stroke volume, but increased aortic pulse wave velocity. Therefore, at least in some individuals, ISHY might be associated with premature aortic stiffening and a trajectory towards sustained ISH in later life.

From the analysis of the literature two main lines of research and conceptualization have emerged for ISHY. Simultaneous assessment of peripheral and central BP led to the identification of a condition called pseudo or spurious ISH, first described by O'Rourke, which was considered an innocent condition. However, an increase in vascular stiffness has been documented by some authors and according to them ISHY should be considered a condition of true hypertension associated with increased future cardiovascular risk.

Data from the Chicago Heart Association Study study have shown that among men with ISHY the risk of unfavourable outcome was similar to that observed in patients with high-

normal blood pressure (BP). In contrast, in the female gender ISHY was associated with a greater increase in risk of cardiovascular mortality. In the HARVEST study participants in the highest pulse pressure (PP) tertile had a reduced risk of incident hypertension needing treatment and of cardiovascular events compared to those in the bottom tertile. In contrast, participants in the top mean BP tertile had an increase in risk for both outcomes. In summary, the data from the literature indicate that PP has a different prognostic significance in young and elderly individuals. In the elderly, PP is a well-established predictor of risk whereas in young men high PP may even have a protective role.

The first aspect to consider when evaluating a person with ISHY is the possible presence of white coat hypertension because one of the strongest determinants of high PP in these individuals is a pronounced white-coat effect. If ISHY is confirmed by out-of-office measurement, assessment of central hemodynamics and arterial distensibility may provide additional useful information.

According to most recent guidelines, young individuals with ISH should receive recommendations on lifestyle modification (particularly cessation of smoking), and require long-term follow up because some will develop sustained hypertension. In subjects who present with other risk factors and/or have high central BP pharmacological treatment may be considered.

Glomerular hyperfiltration - an early alert

Ana Jelaković

University hospital center Zagreb, Zagreb, Croatia

Glomerular hyperfiltration (GHF), a filtration rate above the normal range can be defined either as an abnormally high whole-kidney glomerular filtration rate (GFR), increased filtration fraction, or as increased filtration per nephron. An increased GFR occurs physiologically after consuming a high-protein meal and during pregnancy, which is the only state of GHF within physiological range.

Main problem with GHF is lack of definition and cut off values. Also, creatinine based eGFR requires uniform method for creatinine assessment. Besides, there is a normal annual (aging) decline in GFR, hence it seems that one cut off cannot be enough when trying to define GHF. Usual cut off for GHF in scientific literature is 95th percentile of eGFR in observed sample or mean + 2 SD, stratified by age and sex, or not. This inconsistency interferes with objective comparison of various surveys and final agreement on definition of GHF.

Increased GFR is proposed mechanism for renal injury in several clinical conditions. According to Brenner theory low number of nephrons at birth leads to glomerular hypertension in remaining nephrons and hyperfiltration on single nephron level. Eventually this led to albuminuria, compensatory glomerulomegaly and early onset of CKD and glomerulosclerosis. GHF at single nephron level is preceding state in unilateral renal agenesis and in acquired reduction of renal mass (kidney donors).

Beside glomerulocentric point of view, the pathophysiological mechanism of GHF can be in nephron tubules and arteries, so called tubulocentric point of view. This is the proposed mechanism of GHF in diabetes and obesity, both ever growing diseases of western civilization.

Glomerular hyperfiltration is a characteristic first sign of impaired renal function in insulin-dependent diabetes mellitus and occurs in the large majority of young Type 1

diabetic patients. GHF is hypothesized to be a precursor of intraglomerular hypertension leading to albuminuria. Further decline of GFR is progressive and parallel with rise in albuminuria which may lead, in the long run, to end-stage renal failure. Experimental and clinical studies found GHF in early stages of hypertension, prehypertension and prediabetes. For GHF to develop a variety of pathogenetic factors should overlap: g increased body mass index, hyperinsulinemia, activation of the sympathetic nervous system, hyperleptinaemia, increased oxidative stress, inflammatory cytokines, etc. There are growing evidence that pathogenesis of GHF in diabetes/prediabetes, obesity and prehypertension/hypertension shear the same mechanism of uneven vasoconstriction of afferent and efferent arterioly, inappropriate sodium and glucose reabsorption in proximal tubuls and positive renotubular feedback to junkstaglomerular cells provoking extra renin release. In mention diseases renin-angiotensin system and sodium load play central role in developing GHF. This is direct affirmation for pharmacological agents with action on the renin angiotensin system and their ability to reduce glomerular hypertension and efficacy in preventing progression of microalbuminuria in diabetes and hypertension. According to current guidelines, only low GFR and microalbuminuria or proteinuria are considered as markers of renal dysfunction. There is strong association between GHF and risk of microalbuminuria found in diabetes and hypertension, GHF should be regarded as a precursor of nephropathy and higher CV risk in these clinical conditions. More extensive use of markers of early organ damage may help clinicians to reach a timelier decision about the initiation of treatment and thus delay cardiovascular complications.

Cardiorenal Syndrome

Sanjin Rački^{1,2}

¹University Hospital Center Rijeka, Rijeka, Croatia

²Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Cardiorenal syndrome (CRS) is the umbrella term used to describe clinical conditions in which cardiac and renal dysfunctions coexist. Pathophysiological mechanisms continue to be unraveled and implications for management continue to be debated. A classification system—incorporating five subtypes—has recently been proposed by Ronco et al. CRS has garnered much attention from both the cardiological and nephrological communities since the condition is associated with significant morbidity and mortality. Renal dysfunction is highly prevalent amongst patients with congestive cardiac failure (CCF) and has been shown to be as powerful and independent a marker of adverse prognosis as ejection fraction. Similarly, patients with renal failure are considerably more likely to suffer cardiovascular disease than matched subjects from the general population.

Epidemiology: renal dysfunction is unfortunately extremely prevalent in patients with CCF. Data from several registries revealed that almost one third of patients have a history of renal dysfunction. Similarly, renal failure is clearly linked with increased adverse cardiovascular outcomes. Almost 50% of deaths in patients with end-stage renal failure (ESRF) are due to cardiovascular diseases, and patients with ESRF are more likely to die from cardiovascular causes than from renal failure itself. Half of patients commencing hemodialysis will suffer a myocardial infarction within the following two years, and mortality in this patient population is high.

Cardiorenal anemia syndrome (CRAS) is a condition per se, was first described almost a decade ago by Silverberg et al. as “a vicious cycle of deterioration that leads to poor outcomes, including faster progression to ESRF and further progression of congestive heart failure”. Their simple model suggested anemia as a condition induced by dysfunction of either organ but also exacerbating dysfunction of either organ.

Management strategies of patients with concomitant cardiac and renal dysfunction remains tremendously challenging due to heterogeneous nature of patients with CRS. There is limited trial data proving mortality benefit for diuretics in CRS, but they have long been deemed an essential management strategy in these patients. In the absence of definitive data proving harm in heart failure population, diuretics should not be withheld from volume-overloaded patients. ACE inhibitors are known to reduce mortality in patients with heart failure, though the majority of these studies excluded patients with significant renal impairment. ACE inhibitors should be used with caution in patients with CRS and renal function monitored closely during initiation and uptitration. This caution should not, however, be used to avoid ACE inhibitor therapy. A concomitant reduction in diuretic dosage may be required (especially once the patient is euvolemic) to facilitate safe uptitration of the ACE inhibitor. The chances of deterioration of renal function after starting ACE inhibitor therapy can also be minimized by avoiding simultaneous use of NSAIDs and ensuring the patient is not hypovolemic at onset of treatment. Use of inotropic support is controversial and should be administered according to individual prescription. Certain pharmacological agents such as nesiritide, which held much promise during development, have failed to make the expected impact. Patients resistant to diuretic therapy may benefit from ultrafiltration (UF) and use of continuous renal replacement therapy (CVVHD or CVVHDF or SLEED).

Future directions: the ability to make a diagnosis of CRS early in a patient’s assessment may allow early introduction of management strategies which would hopefully prevent further clinical and biochemical deterioration. Therefore, the development of novel biomarkers of acute kidney injury is a promising step. Neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury molecule-1, and interleukin-18 have all been shown to act as markers of renal injury in a variety of different clinical scenarios, and further work is ongoing to help define their role in diagnosis and management.

Hypertension in women – before and after menopause

Jana Brguljan^{1,2}

¹University Medical Centre Ljubljana, Slovenia

²Peter Držaj Hospital, Ljubljana, Slovenia

Final result of continuous decline in ovarian reserve, marking the end of woman’s reproductive lifespan is called menopause. Going through the menopause is often an emotional roller coaster ride with mood swings and plenty of ups and downs. During the menopause, there are many changes going on physically and all of these changes are being controlled by the body’s change chemicals: hormones. According to research, about 20% of women do not experience any negative side effects from their menopause, while about 80% of women do.

It is very well known that hypertension is still the most important and modifiable risk factor leading to cardiovascular complications. Hypertension-mediated organ damage means progression of hypertension. The closest connection with blood pressure goes

with stroke. The lower the blood pressure the lower is stroke incidence. The incidence of stroke is lower in the ages from 60-80y, but in all the other life periods there are more stroke registered in women than in men. There is a difference in coronary artery diseases where the incidence is higher in all time periods than in men. Prevalence of hypertension is higher in women after 64years. (Emelia J. Benjamin et al. *Circulation*. 2017;135:e146-e603)

Definitely in the women's life change in hormone production is noticed and there must be a role of estrogen on vascular function and homeostasis which is complex and not entirely understood. Estrogen plays a role in endothelial homeostasis through its action on vascular, cardiomyocyte and brain receptors, causes endothelial vasodilation via upregulation of the nitric oxide pathway and inhibition or down-regulation of sympathetic and renin-angiotensin system (RAS) activity, as well as endothelin production. Therefore, lower estrogen levels after menopause may partially explain lower arterial compliance and increased risk of hypertension in older women. Despite estrogen's potential benefit on vascular function, the addition of exogenous estrogen therapy after menopause has neutral effects on blood pressure (BP). Similarly, there is no impact of exogenous estrogen on CV outcomes. In contrast, exogenous estrogen use with an oral contraceptive pill in premenopausal women increases blood pressure.

Furthermore, women after menopause often gain weight and are not so much physically active as before. Hypertensive men have more traditional CV risk factors compared to women, primarily due to increased rates of smoking and dyslipidemia. In contrast, hypertensive women are older, with more non-traditional risk factors such as abdominal obesity and kidney disease. (Tziomalos K, Giampatzis V, Baltatzis M, et al. Sex-specific differences in cardiovascular risk factors and blood pressure control in hypertensive patients. *J Clin Hypertens* 2014;16:309-12.)

Even though in SPRINT trial there was noticed that lower blood pressure was more beneficial in men than in women, blood pressure level for hypertension diagnosis and target blood pressure level do not differ among men and women. In most of the women population we follow 140/90mmHg as limit for hypertension diagnosis and 130/80mmHg for treatment target in the whole life period.

ABPM and HBPM devices are recommended for use to confirm or diagnose hypertension and especially in pregnancy are more accurate than those used for office measurement. ABPM helps avoid unnecessary treatment of white-coat hypertension, and is useful in the management of high-risk pregnant women with hypertension and those with diabetic or hypertensive nephropathy.

Concerning hypertension treatment salt restriction has theoretical benefits in women given the possible up regulation of RAS after menopause. Weight loss strategies and combined aerobic and resistance exercises have beneficial effect on BP lowering. (<https://www.acc.org/latest-in-cardiology/articles/2018/07/27/09/02/women-and-hypertension>) Based on current ESC/ESH hypertensive guidelines also in all time periods of women's life we recommend fixed dose combination treatment for start and follow up and always individual approach is the most important. (Williams B, Mancia G, Spiering W et al: 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens*. 2018 Oct;36(10):1953-2041) In fertile period, if woman

wants to get pregnant, than avoid RAS blockers and consider beta blockers. From the practical experience, we could say that use of small dose of beta blockers might be effective in some of young women more, than other antihypertensive drugs. In pregnancy metildopa is still preferred drug. Diuretic therapy, via reduced urinary calcium excretion, may have a positive effect on the prevention of bone loss and osteoporosis in postmenopausal women. Calcium channel blockers may be more beneficial in women than ACE inhibitors for stroke prevention.

Finally, we should not forget to ask women about possible preeclampsia in their pregnancy to observe them more carefully for possible cardiovascular or renal events later in their life. (Long-term maternal atherosclerotic morbidity in women with preeclampsia Roy Kessous et al. Heart 2015; 101:442-446)

Individual approach for detection and treatment of hypertension in women should be encouraged to prevent final consequences of undertreated or overlooked hypertension.

2018 ESC-ESH Guidelines for the management of arterial hypertension

Bojan Jelaković

School of Medicine University of Zagreb

In this brief summary, it will be shown what has changed in new European guidelines

Diagnosis It is recommended to base the diagnosis of hypertension on repeated office BP measurements; or Out-of-office BP measurement with ABPM and/or HBPM if logistically and economically feasible. Wider use of out-of-office BP measurement with ABPM and/or HBPM, especially HBPM, as an option to confirm the diagnosis of hypertension, detect white coat and masked hypertension and monitor BP control is recommended. **Treatment threshold** has changes in some groups of patients: A) High-normal BP (130–139/85–89 mmHg): Drug treatment may be considered when CV risk is very high due to established CVD, especially CAD. B) Treatment of low-risk grade 1 hypertension: In patients with grade 1 hypertension at low–moderate risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive, after a period of lifestyle intervention. C) BP-lowering drug treatment and lifestyle intervention is recommended in fit older patients (> 65 years but not > 80 years) when SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated. **BP treatment targets:** It is recommended that the first objective of treatment should be to lower BP to < 140/90 mmHg in all patients and provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower, in most patients. In patients < 65 years it is recommended that, SBP should be lowered to a BP range of 120 to < 130 mmHg in most patients. **BP treatment targets in older patients (65-80 years):** In older patients (≥ 65 years), it is recommended that SBP should be targeted to a BP range of 130 to < 140 mmHg. **BP treatment targets in patients over 80 years:** A SBP target range of 130 to < 140 mmHg is recommended for people older than 80 years, if tolerated. **DBP targets:** A DBP target of < 80 mmHg should be considered for all hypertensive patients, independent of the level of risk and comorbidities. Emphasis is put on considerations of biological rather than chronological age (i.e. the importance of frailty, independence, and the tolerability of treatment). Recommendation that **treatment should never be denied or withdrawn based on age**, provided that treatment is tolerated. **Initiation of drug treatment:** It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in a sin-

gle-pill combinations (SPC). The exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is < 150 mmHg). **Simplified drug-treatment algorithms** with the preferred use of an ACE inhibitor or ARB combined with a CCB or/and a thiazide/thiazide-like diuretic as the core treatment strategy for most patients, with beta-blockers used for specific indications. **Resistant hypertension:** Recommended treatment of resistant hypertension is the addition of low-dose spironolactone to existing treatment, or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone, amiloride, higher-dose thiazide/thiazide-like diuretic or a loop diuretic, or the addition of bisoprolol or doxazosin. A strong emphasis on the **importance of evaluating treatment adherence** as a major cause of poor BP control was introduced. **The important role of nurses and pharmacists** in the education, support, and follow-up of treated hypertensive patients is emphasized as part of the overall strategy to improve BP control. It is our hope that the new Guidelines will improve regular clinic work.

How to organize management of hypertension in primary care – experience from Istria

Ante Ivančić

Health Care Center of Istrian County, Pula, Croatia

Primary Health Care Center (Dom zdravlja) is the only institution in Croatian health care system that can organize and implement a coordinated and integrated secondary prevention of chronic non-communicable diseases.

In the Health Care Center of Istrian County Cardiovascular (CV) prevention projects have been implemented since 2007. In 2017 a new project: “Prevention and rehabilitation of CV diseases in the Istrian County” has been launched with the aim of creating new, innovative models of secondary and tertiary prevention and some of which have already been accepted as part of the regular health care system.

In 7 cities Cardiovascular Counseling Centers (CCC) are established, guided by district nurses, which are the place for individual counseling but also for recruitment of patients for all activities that are being organized and offered.

Focus in the project is on risk factors and non-pharmacological treatment which is often and unjustifiably neglected.

Particular attention is devoted to arterial hypertension (AH) as a leading risk factor. A workshop was designed, run by family doctors or district nurses, with an ambitious idea that every patient with AH once pass the workshop and learn “everything he always wanted to know about his illness, but did not dare to ask”.

An important segment of the project is the promotion of 24-hour ambulatory blood pressure monitoring (ABPM) as a standard search in primary health care and increase of its availability with the aim of enabling “ABPM to everyone”.

The patient is being referred to ABPM by his family physician, the device is being set up and removed by district nurses in the CV counseling centers and the findings are read and commented by his family doctor.

There are 24 ABPM devices in our Institution and wait for the search lasts no longer than 2 weeks. We provided 1166 ABPM ‘s search in 2016, 1727 in 2017, and 2158 in 2018. Since some of the CCC have only started we expect further increase of this numbers in 2019.

ABPM has also an important synergy role as the increasing acceptance of ABPM by family physicians increases the number of patients in the counseling center and the number of participants of workshops and all other services of the project.

Key words: prevention of cardiovascular diseases, arterial hypertension, cardiovascular counseling centers, ambulatory blood pressure monitoring

How to measure blood pressure in 2019

Branimir Krtalić

University Hospital Centre Zagreb, Zagreb, Croatia

The growing impact of hypertension on global health outcomes brings significant attention to the importance of early and accurate diagnosis of hypertensive individuals. A dependable method of measuring arterial blood pressure is needed to achieve such goals and assign each patient to the correct category of hypertension, e.g., optimal, normal, high normal etc. Late 19th and early 20th century marked the beginning of the auscultatory technique era which remains the golden standard. Accuracy is very important, considering that even small errors can cause many individuals not to get proper treatment, or perhaps get unnecessary medications. There are multiple recommendations set forth by ESH/AHA to ensure that measurements are standardized and as close as possible to the actual blood pressure. Some of these include 5-minute resting period for patients prior to taking measurement, using an appropriate-sized cuff, taking three measurements, ensuring proper body position etc. Even after following all the guidelines, there may be a difference between the values measured by auscultation and those measured invasively. Automatic ambulatory blood pressure monitors provide important data on the effect of various external and internal stimuli on blood pressure values during the day. However, if they are based on the classic Riva-Rocci method, they have serious limitations such as the effect of cuff inflating on sleep, lack of data between measurements, effect of body position on blood pressure values, and the unreliability of the examined individual's notes on daily activities. A relatively new monitor, Somnotouch NIBP promises to overcome these limitations by using a different technique known as the Pulse Transit Time. It is based on indirect measuring of arterial blood pressure using a patented algorithm and pulse wave velocity. Each PTT interval begins when the R-wave is detected on ECG and lasts until the plethysmograph on a digit detects the arrival of the pulse wave. Therefore, each PTT interval produces a BP value that is recorded on the device. The device is calibrated by the input of patient's height and a BP value obtained by a classic sphygmomanometer. The technique has been validated through comparison to the Riva-Rocci technique in various scenarios as well as comparing it with invasive direct BP measuring. Other than those already mentioned, possible benefits of the new monitor may be recording of sleep/wake patterns, physical activity, blood oxygen saturation, and a 6-channel ECG. It remains to be seen whether this device is the future of automatic ambulatory blood pressure monitoring. While it does seem to provide comfort to patients due to its lack of an inflating cuff, further testing and research is needed before completely switching from the golden standard – sphygmomanometer technique.

Physical activity as a cornerstone of blood pressure control and health improvement

Vanja Vasiljev Marchesi^{1,2}

¹ Faculty of Medicine, University of Rijeka, Rijeka, Croatia

², Faculty of Health Studies, University of Rijeka, Rijeka, Croatia

Sedentary lifestyle is recognized as an important health risk. The link between physical inactivity and hypertension is well known. The estimation is that 50% of patients with hypertension have sedentary lifestyle. Regular physical activity following the recommended guidelines can lower blood pressure up to 7 mmHg. Besides physical activity other modifiable risk factors connected with hypertension are smoking tobacco, drinking too much alcohol, being obese and nutrition with high salt intake. Therefore, adaptation of healthy lifestyles in patients with hypertension is required.

The aim of this presentation is to present the link between physical (in) activity and hypertension. In the presentation good practices of implementing physical activity in patients' routines will be shown.

Antihypertensive drugs and albuminuria

Tamara Knežević^{1,2}, Lana Gellineo^{1,2}, Ana Jelaković^{1,2}, Vedran Premužić^{1,2}

Živka Dika^{1,2}, Mario Laganović^{1,2}, Bojan Jelaković^{1,2}

¹University Hospital Center Zagreb, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

The effect of various antihypertensive drugs on the onset and reduction of albuminuria is mainly BP driven. Regardless of having a similar antihypertensive effect, different antihypertensive drug classes have a different effect on albuminuria. Patients with albuminuria will usually need more than one drug to achieve blood pressure control, particularly if the aim is also to reduce albuminuria. Albuminuria is independently associated with cardiovascular and renal risk. Microalbuminuria is listed in the recent ESC/ESH guidelines among the hypertension-mediated organ damages. Albumin-to-creatinine ratio was suggested to be included in routine workup for the evaluation of every hypertensive patient and changes in albuminuria were considered to have moderate prognostic value. Because of its specific effects on renal hemodynamic and glomerular structure, the ACEIs and ARBs should be prescribed in maximum tolerated doses. The MRAs can be considered in uncontrolled hypertensive patients. The CCBs can be used in addition to the RAAS blockade. Data on antialbuminuric effect of the new CCBs generation (T-type and N-type calcium channel blockers) is promising and they might be preferential CCBs when available. In case of resistant hypertension, thiazide or thiazide-like diuretic has to be added into the combination with RAAS blockers and other antihypertensive drugs. Low-salt intake has to be recommended for all hypertensive patients, particularly those with albuminuria. A multifactorial and early antialbuminuric approach should be started even when albuminuria values are below the cut-off value for microalbuminuria. Finally, determination of albuminuria is low-cost, easy-to-use test which is proven predictor of CV disease and the recent data support the use of albuminuria as an intermediate endpoint of antihypertensive treatment.

Primary aldosteronism – diagnostic and treatment challenge in 2019

Sandra Karanović^{1,2}

¹School of medicine University of Zagreb, Zagreb, Croatia

²University Hospital Center Zagreb, Zagreb, Croatia

Primary aldosteronism (PA) is a common secondary form of arterial hypertension caused by excess aldosterone secretion: it involves over 11% of the patients referred to specialized hypertension centers, about one fifth of those with resistant hypertension and 6% of the hypertensive patients seen in general practice. Subtypes of PA include aldosterone producing adenomas, unilateral and bilateral adrenal hyperplasia or a rare form of inherited condition of glucocorticoid-remediable aldosteronism known as familial hyperaldosteronism. Patients with PA have higher cardiovascular morbidity and mortality than age-, sex- and blood pressure-matched patients with essential hypertension. Once the diagnosis of PA established, the decision to proceed further with surgical or medical treatment depends on identification of PA subtype - individuals with unilateral disease are candidates for surgical treatment. Half of the patients treated with laparoscopic adrenalectomy become totally cured after the procedure, while remainder need lower levels of medication for blood pressure control. Imaging techniques such as CT or MRI are not accurate enough in localizing the source of aldosterone excess since aldosterone producing microadenomas and most bilateral lesions cannot be detected by these techniques. The gold standard for PA subtyping remains adrenal vein sampling (AVS). It is a technically challenging procedure, mostly because of the unhandy anatomy of the right adrenal vein and for successful AVS a dedicated and experienced interventionist is needed. Hormonal data are normally not available until well after AVS is completed and therefore allow judgement of the achieved selectivity only retrospectively. Apart from these challenges there are also differences in methodology, cutoffs, indices, assay methods, comparators and interpretation between different centers performing AVS. More studies are needed. An ongoing multicenter IPADUA study which is testing rapid intraprocedural cortisol measurement for improving success rate in achieving selectivity of AVS might bring benefit refining diagnosis and reducing the necessity for second-round AVS.

Fibromuscular dysplasia – common task

Živka Dika^{1,2}

¹School of Medicine, University of Zagreb, Zagreb, Croatia

²University Hospital Centre Zagreb, Zagreb, Croatia

Fibromuscular dysplasia (FMD) is a rare, chronic, nonatherosclerotic, noninflammatory arterial disease that is characterized by abnormal cellular proliferation and distorted architecture of the arterial wall, leading to stenosis, aneurysm, dissection or tortuosity of small and medium-sized arteries. The cause of FMD and its prevalence in the general population are unknown. FMD is most commonly seen in young women, although it may occur at any age. Although less common in men, men seem to have a more aggressive course with a higher frequency of aneurysms and dissections. FMD has been reported in virtually every arterial bed but most commonly affects renal and extracranial arteries. Multivessel involvement in patient with FMD is common.

FMD diagnosis and classification are primarily based on imaging. Computed tomographic angiography (CTA), and to a lesser extent magnetic resonance angiography (MRA), are recommended as screening and confirmatory tests for FMD, but catheter-based angiography remains the golden standard to determine the type and severity of the vascular lesions, and as a confirmatory test for unclear cases. Based on angiographic FMD classification, there are two types of arterial lesions: multifocal, alternating areas of stenosis and dilation (the so-called “string of beads”), and focal. Focal FMD may occur in any part of the artery, while multifocal usually occurs in the mid and distal portions of the artery.

Clinical manifestations of FMD are variable and depend on the distribution of vascular bed involvement and the type and severity of the vascular lesions (i.e. stenosis of varying degrees, arterial dissection, arterial aneurysm). FMD lesions can be either symptomatic or clinically silent and can be either hemodynamically significant or not. During its clinical course FMD can progress so that it entails new blood vessels. New stenosis or aneurysms or even arteriovenous fistulas may develop at the site of the existing lesion. Therefore, patients with FMD regardless of initial site of vascular bed involvement should undergo CTA or MRA imaging of all vessels from brain to pelvis at least once to identify other areas of FMD, and to screen for occult aneurysms and/or dissections that can be potentially fatal if not treated on time.

Therapy for patients with FMD may include medical therapy and surveillance, endovascular therapy for stenosis (angioplasty with or without stenting), dissection (stents), or aneurysms (coils, stents); or surgery. Therapeutic decisions depend on the nature and location of vascular lesions (stenosis versus dissection versus aneurysm), presence and severity of symptoms, prior vascular events related to FMD, presence and size of aneurysms, and comorbidities. In the case of hemodynamically significant renovascular FMD, the method of choice is revascularization by percutaneous transluminal renovascular balloon angioplasty (PTRA). After PTRA it is necessary to regularly monitor patients because of the increased risk of restenosis.

Regardless of initial site(s) of artery(ies) involvement, patients with FMD should be followed up closely, at least annually and if needed more frequently.

Treatment of atrial fibrillation in 2019

Luka Zaputović^{1,2}

¹Clinical Hospital Centre Rijeka, Rijeka, Croatia

²Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Atrial fibrillation (AF) is one of the most common heart arrhythmia with estimated prevalence of approximately 3% in adults aged 20 years or older, with a predicted rise in the future, as population is aging. It is one of the major causes of stroke, heart failure, sudden death and other cardiovascular morbidity. Patients with AF have poorer quality of life with symptoms like palpitations, breathlessness, chest pain, sleeping disorders and psychosocial distress. ECG screening for AF is recommended in populations at risk of AF, including older persons, patients with hypertension, diabetes, obesity or chronic kidney disease. The diagnosis of AF is confirmed when ECG is showing irregular RR intervals and no evident P waves for at least 30 seconds. Optimal treatment of underlying cardiovascular conditions, such as hypertension, ischaemic heart disease, valvular heart disease and heart failure, can adequately prevent occurrence of AF. In general

management of AF, it is important to evaluate each patient for AF-related symptoms, using the modified European Heart Rhythm Association (EHRA) score. Patients need appropriate information, education and motivation to support the management of their condition, with proposed life style changes to all suitable cases for more effective treatment. Oral anticoagulation is indicated in most AF patients, unless they are at low risk for cardioembolic stroke based on the CHA₂DS₂-VASc score, or have absolute contraindication for anticoagulation. A non-vitamin K antagonist oral anticoagulant (NOAC) is preferred over warfarin in all patients with non-valvular AF. In patients with valvular AF (i.e., moderate-to-severe mitral stenosis, mechanical heart valves) or severe kidney disease, vitamin K antagonist is indicated. Elevated bleeding risk based on the HAS-BLED score is not a contraindication for anticoagulation, but it should be reduced by treating hypertension, minimising the use of antiplatelets and NSAIDs, eliminating causes of blood loss, achieving stable INR values on vitamin K antagonists and avoiding alcohol intake. Echocardiographic assessment of cardiac function can guide the choice of appropriate rate control therapy. Rate control medications are used in all AF patients to achieve ventricular rate control <110 beats per minute at rest. Increased dosage or additional rate control therapy is used in patients with persistent symptoms of AF. In selected suitable patients rhythm control is the treatment strategy of choice (i.e., restoring and maintaining sinus rhythm) for the quality of life improvement and lower morbidity. Rhythm control therapy should not be used in asymptomatic patients and those with permanent AF. Acute rhythm control can be achieved by electrical and pharmacological cardioversion, used to restore sinus rhythm in selected patients, after managing the risk of stroke. Anti-arrhythmic drugs are selected and used based on the underlying heart disease and their safety profile. Catheter ablation of AF (pulmonary vein isolation) should be considered when antiarrhythmic drugs fail or in suitable patients as first-line treatment for symptomatic paroxysmal AF. Surgical AF ablation can be performed in symptomatic patients during cardiac surgery for other reasons. Oral anticoagulation for stroke prevention should be continued even after apparently successful AF ablation. An integrated approach to AF management is recommended, including a cardiologist, interventional electrophysiologist and experienced cardiac surgeon (AF Heart Team), for guidelines-adherent treatment, aimed to improve outcomes in all patients.

Treatment of dyslipidemia in 2019

Željko Reiner^{1,2}

¹University Hospital Center Zagreb, Zagreb, Croatia

²School of Medicine, University of Zagreb, Zagreb, Croatia

Despite significant progress that has been made in both primary and secondary prevention of coronary heart disease (CHD) over the past decades, the incidence of CHD events remains one of the biggest health problems for many individuals and for society. Dyslipidemia is the most important risk factor for CHD, although arterial hypertension, smoking and obesity are important risk factors as well. The treatment of dyslipidemia has always to start with lifestyle modifications. In order to reduce elevated total and LDL-cholesterol (LDL-C) levels which are the most important type of dyslipidemia, subjects at risk have to avoid dietary trans fats, to reduce dietary saturated fats, to increase dietary fibres, to use functional foods enriched with phytosterols and/or red yeast rice

nutraceuticals as well as to reduce excessive body weight. The reduction of elevated triglycerides (TGs) can be achieved by reducing excessive body weight, reducing alcohol intake, increasing physical activity, reducing total amount of dietary carbohydrates, using supplements of n-3 polyunsaturated fats and reducing the intake of mono- and disaccharides. Most patients will besides lifestyles modification need to take a medicine in order to achieve lipid target values. The medicines which are still the golden standard for lowering elevated LDL-C are statins. High intensity and more potent statins (atorvastatin or rosuvastatin) treatment up to the highest tolerated dose are needed in order to reach the target values set for the specific level of risk. If the target values are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended. It has to be mentioned that some patients are statin intolerant so that they cannot tolerate statin treatment at all or are unable to tolerate a full therapeutic dose because of adverse effects. For primary prevention, and particularly for secondary prevention in patients at very high risk, or with familial hypercholesterolemia (FH) or statin intolerance, if the LDL-C target value is not achieved on a maximum tolerated dose of statin and ezetimibe, a combination with one of the new LDL-C lowering drugs – a PCSK9 inhibitor (alirocumab, evolocumab) is recommended. This is particularly the case in patients with FH. FH is the most common autosomal dominant disorder with a prevalence of heterozygous FH in the developed countries of approximately 1:250. If not treated, FH will result in an increased risk of premature CHD (first event between the age of 30 and 35) due to lifelong elevated LDL-C. Heterozygous FH can increase the cumulative risk for CHD by up to 20-fold. The relative risk to develop premature CHD is about 40-100-fold. Despite all these, FH remains to be under-diagnosed and widely undertreated. However, other high and very high-risk patients can benefit from PCSK9 inhibitors treatment as well. Last year the results of the second large clinical outcome trial with a PCSK9 inhibitor - alirocumab, the ODYSSEY Outcomes study, have been presented. It was performed on 18,924 patients who had an acute coronary syndrome within the previous 12 months and who had residual LDL-C levels ≥ 1.8 mmol/L, after two to 16 weeks of intensive or maximally tolerated statin therapy (atorvastatin or rosuvastatin). After a median follow-up of 2.8 years a significant reduction of major adverse cardiovascular events - CHD death, nonfatal myocardial infarction, unstable angina requiring hospitalization or ischemic stroke occurred in patients treated with alirocumab versus placebo (9.5 vs. 11.1 percent). Therefore, it seems that the year 2019 will be the year of much widely and often use of PCSK9 inhibitors.

Rational choice of antidiabetic drugs in 2019

Dario Rahelić^{1,2}

¹Dubrava University Hospital, Zagreb, Croatia

²School of Medicine, University of Zagreb

Genetics, sedentary lifestyle and high energy intake are major risk factors for obesity and type 2 diabetes. According to International Diabetes Federation, approximately 425 million people worldwide have diabetes and by 2040 this will rise to 642 million. Mentioned figures confirm that diabetes has pandemic proportions. All these highlight importance of high-quality diabetes care. Effective care of people with diabetes beside comprehensive medical care and diabetes education should include self-care of person with diabetes. Proper diet, weight reduction and physical activity are the most

important part of type 2 diabetes treatment. Raising awareness of diabetes, promoting healthy eating and physical activity can result in a slowdown in the number of patients with diabetes. Furthermore, early diagnosis of diabetes and early treatment can significantly reduce the risk of chronic complications. Effective management of diabetes requires individual approach and tight and sustained glycaemic control to lower the risk of macro- and microvascular complications in people with diabetes. The UK Prospective Diabetes Study (UKPDS) found that every 1% reduction in glycated hemoglobin (HbA1c) was associated with a 37% decrease in microvascular disease and a 14% reduction in myocardial infarction. Results of a 10-year follow-up study found that people with type 2 diabetes who maintain good glycemic control experience benefits many years later, including lower rates of myocardial infarction and diabetes-related death. Current diabetes guidelines also emphasize that cardiovascular disease risk reduction should be a focus of therapy, because several landmark studies showed that tight glycemic control improves microvascular outcomes, but has no effect in macrovascular complications. All CVOTs so far were designed to test non-inferiority, with possibility to test for superiority if primary outcome of the trial was confirmed. Trials EMPA-REG, CANVAS, LEADER and SUSTAIN-6 showed superiority in primary outcome therefore significant risk reduction in CV events. As those results were confirmed on top of standard therapy, it puts a new light on therapy management and approach in residual risk reduction in those patients. In 2019 metformin is still first line drug for type 2 diabetes. In the second line, according to results of published cardiovascular outcome trials, SGLT-2 or GLP-1 agonist should be prescribed for patients with type 2 diabetes and established cardiovascular disease. However, all international and national guidelines emphasize importance of individual approach. Individualized treatment should be based on patients' disease progression (stage of disease), current HbA1c level, presence of micro- or macrovascular complications, medication efficacy, possible pleiotropic effects of medication in the light of reducing risk factors for morbidity and mortality, risk of hypoglycemia and weight gain. Effectiveness of therapy must be evaluated as frequent as possible using diagnostic blood tests (HbA1c) but also checking for diabetic complications (e.g., retinopathy, nephropathy, neuropathy). Despite many therapeutic options, patient's attitude and education play major role in the treatment of type 2 diabetes and treatment decisions should be timely and based on evidence-based guidelines that are tailored to individual patient preferences, prognoses, and co-morbidities.

Effect of bariatric surgery on blood pressure

Davor Štimac^{1,2}

¹Clinical Hospital Centre Rijeka, Rijeka, Croatia

²Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Obesity is nowadays most important preventable cause of many diseases. Almost 20% of the Croatian population is obese and bariatric surgery is probably the most successful treatment method.

High blood pressure is commonly seen in obese and overweight, but the direct correlation between them has to be determined.

Randomised controlled trials (RCT) mostly focused on type II *Diabetes Mellitus* showed reduction or discontinuation of antihypertensive drugs and reduction in cardiovascular events after bariatric surgery RCT's in a broad population of hypertensive

obese patients had not been made until recently. GATEWAY RCT published in 2018. compared gastric bypass surgery plus medical therapy with medical therapy alone. Study has shown that bariatric surgery represents an effective strategy in the treatment of obese patients with hypertension. Together with improved metabolic profile such effects have the potential to reduce major cardiovascular events.

It has been proposed that white adipose tissue (WAT) may play a role in explanation of the improvements in blood pressure. WAT in obese people is characterised by chronic low grade inflammation, oxidative stress and imbalance between vasoconstrictors and vasodilators that may impact on vascular phenotype and increased blood pressure. Elevated circulating free fatty acids, greater overall blood volume and activation of renin angiotensin aldosterone system are all connected with obesity.

Blood pressure reduction is present also in patients underwent less radical procedures such are endoscopic methods for treatment of obesity. Results of our own group of patients treated with intragastric balloon will be presented.

Rehabilitation and blood pressure control after myocardial infarction

Viktor Peršić^{1,2}

¹Thalassotherapia Opatija, Opatija, Croatia

²Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Adoption of total preventative and comprehensive rehabilitation measures in patients with advanced cardiovascular disease (CVD aiming to achieve maximum health, personal, family and social sufficiency, as well as preventing a new cardiovascular event, are the main tasks of organized secondary health prevention activities. If successfully implemented, they lead to a significant increase in survival of patients, improvement in their quality of life, reduction of interventional, surgical or percutaneous interventions, with a significant reduction in overall social and economic burden. So far, cardiac rehabilitation has been the best-designed model of care for the secondary prevention of CVD, including blood pressure assessment and hypertension management.

Considering all the positive effects of cardiac rehabilitation which include exercise therapy, The International Council of Cardiovascular prevention and rehabilitation promotes greater involvement of patients after cardiovascular events in the cardiac rehabilitation programs with a view to better control cardiovascular risk factors including blood pressure control and therapy.

Keywords: Cardiac rehabilitation, myocardial infarction, blood pressure control

Treatment of hypertensive patients after stroke

Branko Malojčić^{1,2}

¹University Hospital Center Zagreb, Zagreb, Croatia

²School of Medicine, University of Zagreb, Zagreb, Croatia

Stroke is one of the leading causes of death worldwide and the leading cause of handicap in adult population. Despite of constant improvement of prevention strategies, it is expected that the total number of stroke patients in Croatia will increase by 23% in the next 20 years, mostly because of aging population.

There aren't sufficient quality data on optimal blood pressure values in the acute phase of stroke, nor on the most effective antihypertensive medication. However, the guide-

lines issued by professional societies should represent a strict framework for clinical decisions, aimed at achieving a population-wide effect of adequate control of arterial blood pressure.

Treatment of arterial hypertension is of crucial importance in the prevention of stroke and other neurological diseases associated with cardiovascular risk, such as vascular dementia or movement disorders. Current guidelines suggest that the blood pressure should be kept below < 140 mm Hg after stroke or transient ischemic attack. However, in specific ischemic stroke variants such as lacunar stroke or diabetic brain microangiopathy, the target could be below 130/80 mmHg.

Another specific entity is the intracerebral haemorrhage (ICH) where the role of hypertension as contributing factor is even more pronounced. As we now have enough evidence that the risk of recurrent ICH increases linearly after mean systolic blood pressure of 100-119 mmHg, the target blood pressure after ICH should be as low as possible. Such patients usually require several antihypertensive medications or fixed antihypertensive combinations in order to ensure patients' compliance.

Reversing the hypertension-induced microvascular dysfunction by exercise

Akos Koller^{1,2,3}

¹Faculty of Health Sciences, Semmelweis University, Budapest, Hungary

²University of Physical Education, Budapest, Hungary

³ Medical College, Valhalla, New York , USA

Hypertension elicits changes in the function and structure of large and small vessels, but their effects on the development of increased systemic blood pressure and contributions to the worsening of hypertension are different. In microvessels, such as arterioles, first functional, then morphological remodelling of microvessels occurs. These include reduced release and action of dilator factors (nitric oxide, prostaglandins) and increased production of constrictor molecules (endothelin, thromboxane A_2 , reactive oxygen species, vascular angiotensin II). These changes functionally increase the basal vascular tone of microvessels and constrictor responses to a variety of stimuli. If high blood pressure persists for a long time it results in morphological remodelling of vascular wall, such as thickening of wall, due to increased smooth muscle amount, deposition of collagen, elastin and fibrotic tissues, making the lumen smaller and less elastic. Most of these changes are assumed to be due to the increased intraluminal pressure and most likely to disturbed wall shear stress, thus it was logical to hypothesize that exercise will alleviate these remodelling, because during exercise hemodynamic forces changes and vasodilator factors are released. All of these are leading to the so called post-exercise hypotension. Indeed it has been shown that daily aerobic exercise upregulates the release of nitric oxide and prostaglandins, reduces the release of endothelins and increases the expression of the antioxidant enzymes, such as superoxide dismutase and catalase. As a result, the balance between the dilator and constrictor factors and the basal microvascular tone are restored contributing to the reduction of total peripheral resistance, hence normalizing systemic blood pressure. Importantly hypertension guidelines are emphasizing that treatment of hypertension should be started by regular exercise and changes in life style. Indeed, in the 2018 ESC/ESH Guidelines for the management of arterial hypertension under 7.4.6, regular physical activity is recommended. Specifically "evidence suggests that hypertensive patients should be advised

to participate in at least 30 min of moderate-intensity dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5-7 days per week. Performance of resistance exercises on 2-3 days per week can also be advised. For additional benefit in healthy adults, a gradual increase in aerobic physical activity to 300 min a week of moderate intensity or 150 min a week of vigorous-intensity aerobic physical activity, or an equivalent combination thereof, is recommended". Do it!