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INTRODUCTION

World Heart Federation is an international NGO based in Switzerland. It is dedicated to leading the global fight against heart disease and stroke, focusing on developing countries.

World Heart Federation established the Word Heart Day in 2000 as an annual global observance, to educate people about cardiovascular disease and main methods of its prevention and changes in lifestyle to avoid any cardiovascular diseases, such as heart attack, stroke, heart failure and any other condition related to the same.

World Heart Day aims at raising awareness of cardiovascular disease (CVD).

According to statistics, about 80% of premature deaths caused by cardiovascular disease occur in the developing world. Most of them could be avoided by controlling the main risk factors, such as smoking, alcohol consumption, unhealthy diet, and physical inactivity.

World Heart Day is celebrated on 29th September of every year. It is aimed at drawing people's attention to heart illness and the range of associated health issues.

On average, more than 17 million people die from heart-related illnesses every year.

This is more than the number of people who die from HIV, malaria, and cancer.

Word Heart Day activities and events are organized by the World Heart Federation in collaboration with international and local non-profit governmental and non-governmental organisations.

They include: screenings, lectures, public talks, sporting events, concerts, marathons, walks, fitness sessions, exhibitions and science fairs.

Some landmarks, monuments, and famous buildings choose to go red on this day as a show of cardiovascular disease awareness.

Each year, a new theme for the day is selected, and participants are encouraged to link their events to the current year's theme.

Board for Cardiovascular Pathology of the Department for Medical Sciences of ANUBiH

In the past years the Board for Cardiovascular Pathology has organized the following Symposiums, which resulted in publications published by the ANUBiH:

- Symposium: "I Work with Heart", ANUBiH, 2010.
- International Symposium: "Pulmonary Arterial Hypertension", ANUBIH, Book 39, 2011.
- Symposium: "Risk Factors for the Emergence of Cardiovascular Diseases", ANUBiH, Book 40, 2011.
- Symposium: "Innate Heart Anomalies", ANUBiH, Book 42, 2012.
- International Symposium: "Perspectives in Paediatric Cardiology", ANUBiH, Book 43, 2012, English edition.
- Symposium: "Heart Rhythm Disorders in Children and Adults", ANUBIH, 2013.
- International Symposium: "Acquired and Genetically Predisposed Disease of the Heart in Children", ANUBiH, Book 45, 2014.
- International Scientific Symposium: "Foetal Medicine: From Leonardo da Vinci to Date", ANUBIH, Book 46, 2015.
- International Scientific Symposium: "Mitral Valve Diseases in Children and Adults", ANUBiH, Book 49, 2017, English edition.
- Symposium: "Health Management with Special Attention to Cardiovascular Diseases", ANUBiH, Book 52, 2018, English edition.

Amid the marking of the World Heart Day, the Board for Cardiovascular Pathology of the Department for Medical Sciences of ANUBiH traditionally organizes:

"XI International Scientific Symposium: Heart and …"

Organisation of health protection represents a reflection of a country's stage of development.

The goal of the International Scientific Symposium is to consider:

- Advancements in cardiovascular medicine,
- Risk factors for development of cardiovascular diseases,
- Diagnostic-therapeutic algorithms of cardiovascular diseases in paediatric and adult population,
- Observance and prevention of cardiovascular diseases,

- Professional promotion of systemic interventions,
- Advancement of healthcare in accordance with the EU guidelines.

The Scientific Symposium is intended for:

- Physicians, doctors of family medicine, cardiologists,
- Paediatricians, internists, cardio surgeons, intervention cardiologists, pharmacists, public health specialists, students, postgraduates, students in master and doctoral studies at medical, health and pharmaceutical faculties,
- And all others interested in this field.

Participants of the Symposium:

- Prof. dr. Serša Gregor KCU Ljubljana, Faculty of Health Sciences Ljubljana, Slovenia
- Prof. dr. Vjekoslav Krželj, KCU Split, Faculty of Medical Sciences Split
- Prof. dr. Zumreta Kušljugic, KCU Tuzla, Faculty of Medical Sciences Tuzla
- Prof. dr. Aida Pilav, Faculty of Health Studies Sarajevo
- Prof. dr. Senka Mesihović-Dinarević, Faculty of Medical Sciences Mostar

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CLINICAL APPLICATIONS OF ELECTROCHEMOTHERAPY

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Abstract

Electroporation has several biomedical and industrial applications. The biomedical applications are in the field of drug or gene delivery. Electrochemotherapy utilizes electroporation for the increased delivery of cytotoxic drugs like bleomycin or cisplatin into tumors. The use of electrochemotherapy has spread throughout Europe for the treatment of cutaneous tumors or metastases. It is in the NICE guidelines and is becoming standard ablative technique in treatment of cancer. The technological advancements have also enabled the use of electrochemotherapy for the treatment of deep seated tumors, such as soft tissue or liver tumors. Clinical studies demonstrate good effectiveness on fibrosarcomas, colorectal liver metastases and hepatocellular carcinoma. However, electrochemotherapy is a local treatment that also induces moderate local immune response. This so called "*in situ* vaccination" induced by electrochemotherapy can be exploited in combined treatment with immune checkpoint inhibitors or electrogene therapy with immunostimulating effect. Therefore, gene electrotransfer of plasmid coding for interleukin 12 (IL-12), in combination with electrochemotherapy could result in transformation of electrochemotherapy from local into systemic treatment. This is also of our current interest, and we are undertaking steps to bring this idea from preclinical into clinical testing.

Key words: electroporation, gene electrotransfer, interleukin 12

Clinical importance of ablative techniques

Local ablative techniques are important for treatment of cancer. Some of the most recognized ones are radiofrequency and microwave ablation, cryotherapy and transarterial chemoembolization (TACE). Most of these approaches are thermal ablation techniques that are frequently used for palliation of symptoms in advanced cancers or as ablative techniques for treatment of liver and kidney tumors (Bailey et al.; Meloni et al. 2017; Ismail et al. 2018; Vogl and Gruber-Rouh 2019). Radiotherapy can also be considered as local ablative technique, since it has local effectiveness, but uses ionizing radiation for the cell kill in tumors (Wang and Haffty 2018).

The importance of these ablative techniques has recently been re-evaluated in the light of the new era of immunotherapy of cancer (Takaki et al. 2017; Mazmishvili et al. 2018; Wang and Haffty 2018). Emerging new drugs target the immune system blockade that is developed within the tumors. Tumor cells develop mechanisms to evade immune system control, by exposing ligands that block recognition from the immune system of the organism. These drugs, such as immune checkpoint inhibitors for CTLA-4 and PD-1 receptor or PDL-1 ligand (Ishida et al. 1992; Leach et al. 1996; Freeman et al. 2000), have brought vast improvements in treatment of cancer. About 40% of patients can nowadays be cured with these drugs (Wei et al. 2018; Darvin et al. 2018).

However, their effectiveness can be increased in combination with local ablative techniques (Calvet and Mir 2016; Yan et al. 2018). The reason is that local ablative techniques induce immunogenic cell death (Galluzzi et al. 2016), which stimulates the immune system even more, and synergize with immune checkpoint inhibitors (Dörrie 2017). Several studies nowadays explore these interactions and search for optimal treatment combinations that will push the boundaries in the curative treatment of cancer (McKenzie et al. 2016).

Another ablative technique is electrochemotherapy (Yarmush et al. 2014). It is a bimodal treatment using cytotoxic drugs bleomycin or cisplatin and electroporation as drug delivery system. This local treatment is gaining in importance and has been proven to have comparable antitumor effectiveness to other ablative techniques (Spratt et al. 2014). Its effectiveness is proven on a variety of skin, mucosal and deep seated tumors with complete response rate from 60-90%, depending on the tumor type (Sersa et al. 2008b). The technology is developing fast, and is nowadays practiced in 140 cancer centers

throughout the Europe (Miklavčič et al. 2014; Calvet and Mir 2016). Its use is also well recognized because of its known mechanisms of action, including the induction of the immunogenic cell death (Calvet et al. 2014; Ursic et al. 2018).

What is electrochemotherapy and its mechanisms of action?

Electrochemotherapy combines use of known chemotherapeutic drugs such as bleomycin or cisplatin with tissue electroporation. Electroporation is performed by application of electric pulses to the tumors, with high amplitude, which destabilize the cell membranes of tumor cells in the tissue, and increases the membrane for increased diffusion of drugs, which are otherwise not permeable or have hampered transport through the membrane (Sersa et al. 2008b; Yarmush et al. 2014). Therefore, electroporation is used as drug delivery system for bleomycin or cisplatin. Bleomycin cytotoxicity is increased for several 100 times and cisplatin for 50-70 times. The drugs can be injected intratumorally or intravenously. In both cases because of high cytotoxicity in tumors, facilitated by electroporation, low drug concentrations are needed, and therefore there are no systemic side effects related to drug administration (Gehl et al. 2018).

Besides the drug delivery to cells, other mechanisms of action are also involved in electrochemotherapy. The first are vascular effects of electroporation and electrochemotherapy. Electroporation induces vasoconstriction, which contributes to longer drug retention in the tumors. In addition, it enables drug diffusion into the endothelial cells, which consequently die as well. This leads to vascular disrupting effect of electrochemotherapy (Sersa et al. 2002; Sersa et al. 2008a). This phenomenon is important, because it prevents bleeding of the tumors due to the treatment with needle electrodes. More importantly, electrochemotherapy can be applied for the treatment of bleeding tumors, and can be applied in tissues with high vascularization, such as liver (Jarm et al. 2010; Zmuc et al. 2019).

The second is induction of the immune response. Nowadays it is known that after electrochemotherapy with cisplatin or bleomycin cells die with immunogenic cell death (Calvet et al. 2014; Ursic et al. 2018). This is a signal for the immune system to be activated, and therefore immune cells contribute to eradication of the remaining viable cells and induce complete responses of the treated tumors (Sersa et al. 1996; Sersa et al. 1997). This phenomenon is called *in situ* vaccination, and can be exploited by combination with drugs

that affect immune system of the organism (Sersa et al. 2015; Calvet and Mir 2016).

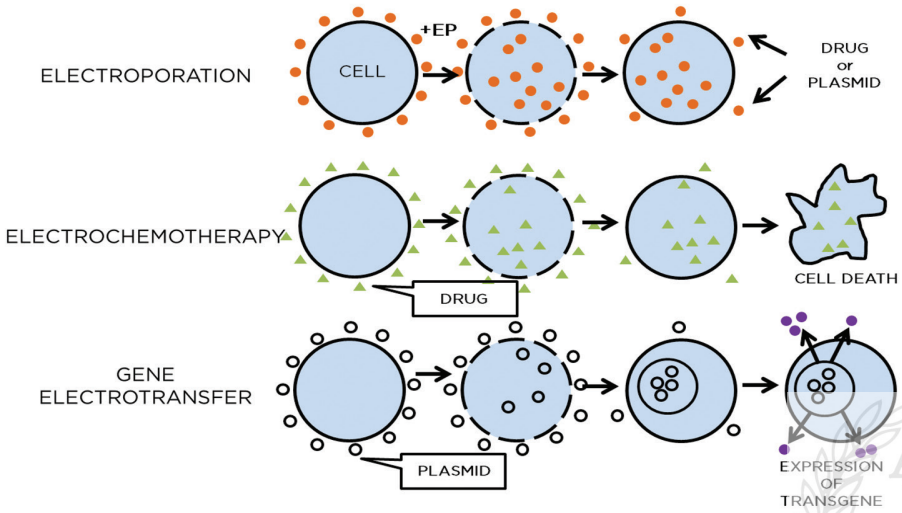

Figure 1. Biomedical application of electroporation. Electroporation: a platform technology for drug and gene delivery. Electrochemotherapy: delivery of chemotherapeutic drugs. Gene electrotransfer: delivery of a plasmid DNA.

What are the clinical applications in treatment of cutaneous tumors?

Currently electrochemotherapy is being used for the treatment of predominantly cutaneous tumors, either primary, recurrent or metastatic. The technology, *i.e.* electric pulse generator approved for clinical use, and pertinent electrodes, is spread throughout Europe in more than 140 cancer centers (Miklavčič et al. 2014; Calvet and Mir 2016). Initially, electrochemotherapy was used primarily with palliative intent, predominantly for melanoma cutaneous metastasis. Later on with publication of Standard Operating Procedures for electrochemotherapy, electrochemotherapy was used for treatment of cutaneous tumors of other histology, such as recurrent breast tumors, Kaposi sarcoma, and lately tumors in head and neck region, either basal cell carcinomas or squamous cell carcinomas (Mir et al. 2006; Gehl et al. 2018). In

the latter case, up to 100% response rate of the treated tumors was reported, whereas for the other tumor types the response rate varies from 50 – 80% (Bertino et al. 2016).

Electrochemotherapy is now in guidelines in many European countries. Most importantly it is in NICE guidelines, where it is also indicated for treatment of primary basal cell carcinomas, when the patients express the preference to be treated by electrochemotherapy (https://www.nice.org.uk). The most important organization that binds the biggest centers using electrochemotherapy is InspECT. The centers involved gather the data of their patients for the mutual, multicenter publications that strongly support the importance of the electrochemotherapy (Campana et al. 2016; Kunte et al. 2017; Rotunno et al. 2018; Matthiessen et al. 2018; Campana et al. 2019).

Lately, the Standard Operating Procedures have also been updated (Gehl et al. 2018). The purpose was to make them simpler and more user friendly. They advise the users and guide the physicians for the selection, and treatment of patients, as well as indicate the possible side effects and how to manage or evade them. This edited version is supposed to further contribute to the spread of the technology same as the first Standard Operating Procedures did (Mir et al. 2006).

Standard question that arises is: What is the efficacy of electrochemotherapy compared to other ablative techniques? This was nicely addressed in the meta-analysis published in 2013 where electrochemotherapy was evaluated to have comparable effectiveness to other ablative techniques (Spratt et al. 2014).

The technology development enabled treatment of deep seated tumors

The technological advancement of electrochemotherapy was in development of more powerful electric pulse generators, and designing of the electrodes for specific tissues and locations. This enabled the advancement of electrochemotherapy into the treatment of deep seated tumors. The first deep seated tumor treated by electrochemotherapy was deep seated metastasis of melanoma, where the treatment plan was also used (Miklavcic et al. 2010). Thereafter, colorectal liver metastases were treated with long needle electrodes that are inserted individually, also upon the prepared treatment plan (Edhemovic et al. 2011). The results of this phase I/II study were encouraging, with 80% response rate of the tumors. What is important is that the

tumors were predominantly located in locations that are difficult to treat, such as those in the vicinity of the major hepatic vessels. This brings the advantage of electrochemotherapy over radiofrequency ablation, because RFA is not effective in such locations due to heat sink effect (Djokic et al. 2018). The encouraging results of this first study have continued into extended phase II study, that is as effective as the first one, but the results have not been published yet.

Also treated were primary hepatocellular carcinomas in patients with impaired liver function, where surgery was not indicated (Djokic et al. 2018). These results are even better than in the study of colorectal metastases (Edhemovic et al. 2014). Complete response rate of even above 90% was observed (Djokic et al. 2018). The study is continuing in the phase II study.

Electrochemotherapy was also used in treatment of deep seated sarcoma tumors, bone metastases, and pancreatic tumors (Campana et al. 2019). These locations are still in the developmental phase, but are promising as well. The step forward would be to access these tumors percutaneously. Therefore, already first attempts were made on lyse hepatic trombi with electroporation (Probst et al. 2018), and also our radiologists have performed the first electrochemotherapy of hepatocellular carcinoma percutaneously (data unpublished).

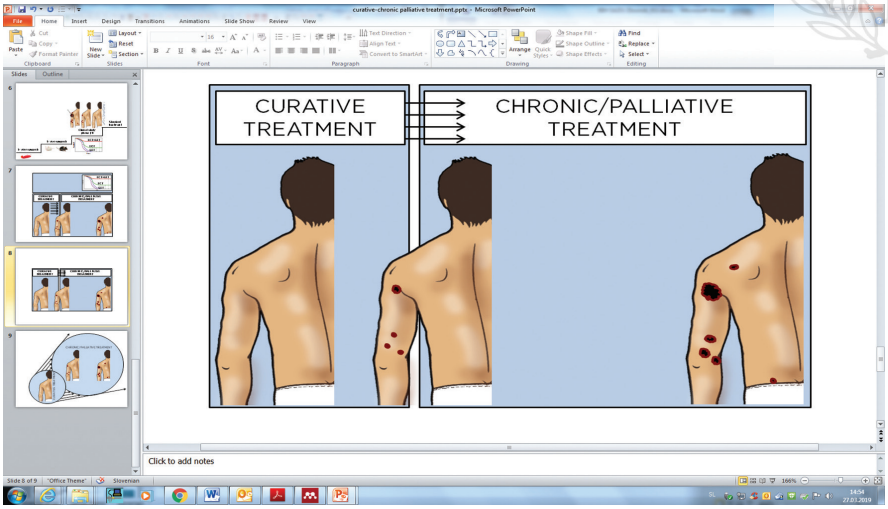

Figure 2. Pushing the boundaries of curative treatment. More patients with oligometastatic disease could benefit from local therapies.

What is the potential of combined electrochemotherapy with immunotherapy?

We are witnessing the revival of immunotherapy, with advent of new generation of drugs, the immune checkpoint inhibitors. These drugs deblock the immune response in the tumors. Namely tumors with time induce blockade of the immune system or resistance of cells to immune cells. Therefore, so called immune checkpoints can be targeted with monoclonal antibodies – immune checkpoint inhibitors (Iwai et al. 2017; Wei et al. 2018). The receptors and ligands are CTLA-4, PD-1 and PDL-1 (Ishida et al. 1992; Leach et al. 1996; Freeman et al. 2000). The drugs are currently used in treatment of melanoma and also some other tumors, with incredible efficacy, but only on 40% of the treated patients. Those 40% of patients can be cured (Darvin et al. 2018). However, there are indications that combining the immune checkpoint inhibitors with electrochemotherapy could increase the response rate over those 40% (Queirolo et al. 2014; Brizio et al. 2015; Calvet and Mir 2016; Heppt et al. 2016). As mentioned before, electrochemotherapy is seen as *in situ* vaccination (Sersa et al. 2015), due to the induction of immunogenic cell death in tumors (Calvet et al. 2014; Ursic et al. 2018), and this could contribute to the increased response rate of the patients (Wang et al. 2018).

The other option is to use immune stimulating approach. In this case in situ vaccination with electrochemotherapy is boosted by immunostimulation with cytokines, such as interleukin – 12. This approach can be also effective in making electrochemotherapy from local to systemic treatment. The model of such treatment combination and the underlying mechanism has been published already (Sersa et al. 2015; Calvet and Mir 2016).

Perspectives

Perspectives of electroporation based treatments is also gene electrotransfer (Cemazar et al. 2010; Yarmush et al. 2014). Plasmid DNA can be inserted into the cells by electroporation, therefore used for gene therapy. Gene therapy is becoming more and more interesting, especially with non-viral drug delivery systems, as gene electrotransfer is. There are already some clinical studies demonstrating feasibility and effectiveness of gene therapy using electroporation (Daud et al. 2008; Spanggaard et al. 2013). In line with this, gene therapy of plasmid coding for IL-12 would be effective in patients, as demonstrated in the study of Daud *et al* (Daud et al. 2008; Daud et al. 2014). Currently we are investigating and preparing a clinical trial where we would

combine electrochemotherapy with gene electrotransfer of plasmid coding for IL-12 into tumors in patients with cutaneous head and neck tumors. This would be a nice translational project into human oncology, which was already demonstrated feasible, safe and effective in veterinary oncology (Cemazar et al. 2017). In summary, biomedical applications of electroporation based technologies are promising and are currently under intensive investigation.

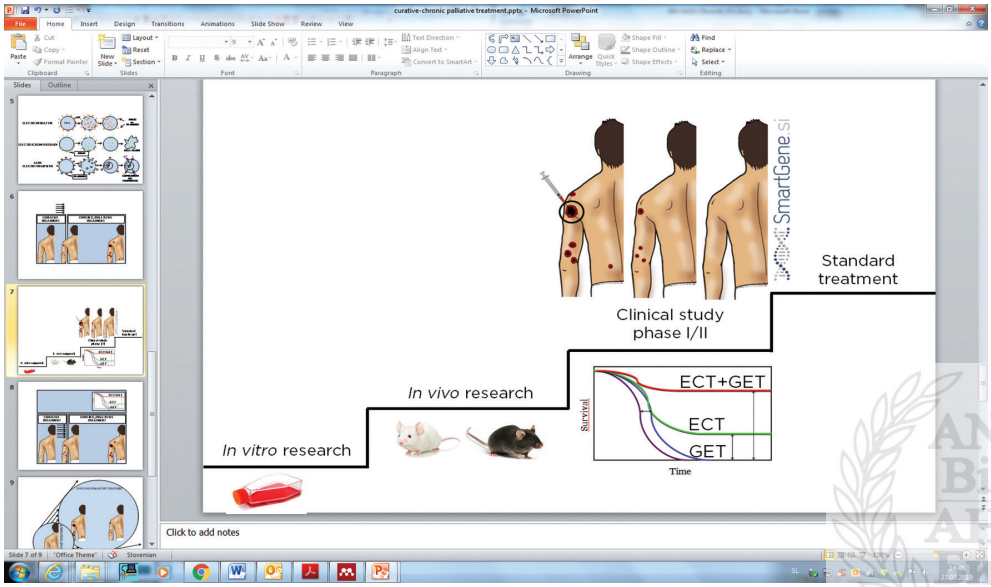

Figure 3. Translational research. The Department of experimental oncology advocate a translational approach, which encompasses both, preclinical and clinical research.

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KLINIČKE APLIKACIJE ELEKTROHEMOTERAPIJE

Sažetak

Elektroporacija ima nekoliko biomedicinskih i industrijskih primjena. Biomedicinske primjene mogu se naći u polju isporuke lijekova ili gena. U elektrohemoterapiji elektroporacija se koristi za povećanu isporuku citotoksičnih lijekova poput bleomicina ili cisplatina u tumore. Primjena elektrohemoterapije proširila se širom Evrope u liječenju kožnih tumora ili metastaza. Uvrštena je u NICE smjernice i postaje standardna ablativna tehnika u liječenju kancera. Tehnološki napredak također je omogućio upotrebu elektrohemoterapije za liječenje duboko usađenih tumora, poput tumora mekog tkiva ili jetre. Klinička ispitivanja pokazuju dobru efikasnost u liječenju fibrosarkoma, kolorektalnih metastaza na jetri i hepatocelularnog karcinoma. Međutim, elektrohemoterapija je lokalni tretman koji također potiče umjerene lokalizirane reakcije imunog sistema. Ova takozvana "*in situ* vakcinacija" izazvana elektrohemoterapijom može se koristiti u kombinovanom tretmanu s inhibitorima kontrolnih tačaka ili elektrogenskom terapijom uz imunostimulirajući efekt. Tako bi genski elektrotransfer plazmidnog koda za interleukin 12 (IL-12) u kombinaciji s elektrohemoterapijom, mogao rezultirati transformacijom elektrohemoterapije iz lokalnog u sistemsko liječenje. To je također naše sadašnje polje interesa i poduzimamo korake kako bismo ovu ideju iz pretkliničkih ispitivanja prenijeli na klinička ispitivanja.

Ključne riječi: elektroporacija, genski elektrotransfer, interleukin 12

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INHERITED METABOLIC DISORDERS AND HEART DISEASES

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Abstract

Inherited metabolic disorders can cause heart diseases, cardiomyopathy in particular, as well as cardiac arrhythmias, valvular and coronary diseases. More than 40 different inherited metabolic disorders can provoke cardiomyopathy, including lysosomal storage disorders, fatty acid oxidation defects, organic acidemias, amino acidopathies, glycogen storage diseases, congenital disorders of glycosylation as well as peroxisomal and mitochondrial disorders. If identified and diagnosed on time, some of congenital metabolic diseases could be successfully treated. It is important to assume them in cases when heart diseases are etiologically undefined. Rapid technological development has made it easier to establish the diagnosis of these diseases. This article will focus on common inherited metabolic disorders that cause heart diseases, as well as on diseases that might be possible to treat.

Key words: inherited metabolic disorders, heart diseases, diagnosis, treatment

Introduction

Metabolism (from Greek: μεταβολή *metabolē* – change, substance modification) is a set of chemical processes occurring in a living organism in order to maintain life. These processes allow the organism to grow and reproduce, to maintain its structure as well as to react to its surroundings. Metabolism is classified in two categories, catabolism and anabolism, depending on metabolic reactions. Catabolism breaks down the organic compounds. During

these processes, energy is either being stored in complex molecules or is being released in response to their degradation, ultimately allowing life. Main mode of actions of metabolism are formation of adenosine triphosphate (ATP), reduced nicotinamide adenine dinucleotide (NADH), as well as synthesis of macromolecules of the organism itself. Anabolism, however, uses the energy for cell compartments build-up and for synthesis of organic compounds, i.e. proteins or nucleic acids (1).

Metabolic chemical reactions are divided into metabolic pathways in which a certain chemical compound transfers into another compound using enzymes. Enzymes are key compounds in metabolism due to their catalytic properties that allow the organism to quickly and effectively perform biologically needed chemical reactions. Moreover, enzymes allow the control of metabolic pathways in response to either changes in the cell environment or some other stimulations (1, 2).

Structure of enzymes is encoded in the genes, and their mutations lead to congenital metabolism deficiencies. Clinical manifestation of hereditary metabolic disorders usually occurs during childhood, although some symptoms can be noticed in adulthood.

Many childhood conditions are caused by single-gene mutations that encode specific proteins. These mutations can result in the alteration of primary protein structure or in the amount of protein synthesized. The function of a protein, whether it is an enzyme, receptor, transport vehicle, membrane component, or structural element, may be compromised or abolished. These hereditary biochemical disorders are termed inherited metabolic disorders (3).

Some inherited metabolic disorders are rare; however, it is estimated that all metabolic diseases affect at least 1% newborns overall. As a result of weak knowledge on these diseases it is difficult to recognise them in patients or are established too late. Increasing number of inherited metabolic diseases are rapidly progressive, thus if not recognised they lead to death or other consequences. On the other hand, if identified and diagnosed timely, some of them are successfully treated (4).

Inherited metabolic disorders can cause hearth diseases, cardiomyopathy in particular, as well as cardiac arrhythmias, valvular and coronary diseases.

Exact prevalence of cardiomyopathy in children is still unknown, and neither is the amount of inherited metabolic diseases. Estimates vary mainly because of different age groups in which children are diagnosed and due to the fact that many cardiomyopathies are slowly developed and become recognised in adulthood.

Rapid technological development has made it easier to establish the causes of the disease among the growing number of children suffering from cardiomyopathy. However, it has remained difficult to estimate the number of patients with unrecognisable asymptomatic cardiomyopathies. Data obtained from various researches state that 26% of children with hypertrophic and 16% of children with dilative cardiomyopathies have metabolic disorders (5, 6).

Inherited metabolic diseases can cause dilative cardiomyopathy, hypertrophic cardiomyopathy, as well as rare restrictive cardiomyopathy (7). Epidemiological study of Paediatric Department of University Hospital of Zagreb observed that in a period of 28 years, 315 children diagnosed with cardiomyopathy were treated, out of which 42.5% were suffering from dilative cardiomyopathy, 37.1% were suffering from hypertrophic and 6.7% from restrictive cardiomyopathy. The rest were suffering from different and rare entity forms of cardiomyopathy (8). More than 40 different inherited metabolic disorders can cause cardiomyopathy, including lysosomal storage disorders, fatty acid oxidation defects, organic acidemias, amino acidopathies, glycogen storage diseases, and congenital disorders of glycosylation as well as peroxisomal and mitochondrial disorders (9).
This article will focus on common inherited metabolic disorders that cause hearth diseases, as well as on diseases that might be possible to treat (Table1.).

Table 1. Common inherited metabolic disorders that cause hearth diseases

1. LYSOSOMAL STORAGE DISEASES
• Pompe disease • Fabry disease • Mucopolysaccharidosis • Mucolipidosis • Oligosaccharidosis
2. FATTY ACID AND CARNITINE METABOLISM DISORDERS
3. MITOCHONDRIAL DISEASES
4. OTHER INHERITED METABOLIC DISEORDERS
• Glycogenosis • Inherited haemochromatosis • Congenital glycosylation disorders • Disorders of amino acid and organic acid metabolism • Disorders of lipoprotein metabolism • Hyperhomocysteinemia

Lysosomal storage diseases

Lysosomes are cell organelles in which degradation of complex molecules occurs and which take part in metabolic processes or are being removed from the cell. Lysosomes can be referred to as cellular 'digestive system'. Lysosomal storage diseases (thesaurismosis) are defined as a set of inherited metabolic diseases that are characterised with storing of macromolecules that have not previously been degraded in lysosomes due to insufficient activity of the enzymes which are crucial for their breakdown. This storing of non-degraded macromolecule can also be due to disabled secretion of lysosomes into cytosol.

Lysosomal storage leads to cell damaging, as well as to damaging of tissues and organs (10).

Lysosomes are present in almost each and every cell in the human's body, therefore lysosomal storage diseases are multisystemic and progressive inherited diseases that affect different organic systems. Moreover, they tend to widely range and variate among the patients.

Cardiomyopathy is a part of the clinical manifestations of lysosomal storage disease. It is often the first or the main symptom for diseases such as Pompe disease and Fabry disease, but is relatively more frequent in mucopolysaccharidosis, mucolipidosis and in some oligosaccharidosis (11).

Pompe disease, or glycogen storage disease type II, is classified as a neuromuscular disease, primary muscular disease, according to the clinical manifestation. Glycogen is stored in lysosomes of all cells, mainly in cardiac, skeletal and smooth muscle cells due to insufficient activation of 1,4-glucosidase. Gene labelled as 17q25.2, q25.3 is responsible for enzyme synthesis. Depending on the occurrence and clinical expression, Pompe disease is usually classified as either infantile-onset or late-onset, whereas the late-onset is further divided into juvenile and adult Pompe disease (12).

Infantile onset is noticeable in first months of life and is characterised with progressive inactivity of muscles and hypertrophic cardiomyopathy as main symptoms of this disease. Untreated patients are prone to dying within the first year of life, either because of cardiac or respiratory system failure (13). Timely application of enzyme replacement therapy tends to drastically change the disease progression and has shown satisfying results in decreasing cardiomyopathy, and thus allows survival of these patients (14). Thus, when hypertrophic cardiomyopathy occurs, it is necessary to check whether it is, in fact, the Pompe disease, which can be performed by measuring enzyme

activity from dried blood spot (15). Less successful results have been obtained among CRIM-negative patients (CRIM – Cross reactive immunological material) (16).

Late-onset Pompe disease type develops less rapidly and it manifests as decreased activity of skeletal and respiratory muscles. Nowadays, different heart diseases are considered to be involved in this onset type as one of the main characteristics of the disease. One of the conditions might include left ventricular hypertrophy, decreased ejection fraction, decreased PR-interval, paroxysmal supraventricular tachycardia, Wolff-Parkinson-White syndrome, as well as dilated ascending aorta (17).

Fabry disease, or Anderson-Fabry disease as first described by authors who discovered it, is the most common lysosomal storage disease after Gaucher disease. This disease is X-linked recessive inherited, although women can also be prone to develop this disease as a result of inactivation of X-chromosomes. This disease is characterised with decreased activity of enzyme α-galactosidase (GLA), leading to glycosphingolipids over-storing in different cell types, particularly in endothelial and vascular muscle cells (18). GLA gene is located on Xq22 chromosome. This disease is usually assumed once the side effects start to manifest, such as kidney failure, heart problems or stroke. However, it is possible to diagnose this disorder in young age. There is a noticeable difference between the classic and the late-onset type of disease. Affected males with the classic phenotype present in childhood with angiokeratomas (telangiectatic skin lesions), hypohidrosis, corneal and lenticular opacities, acroparesthesias, with advancing age develop vascular disease of the kidney, heart, and/or brain. The later-onset phenotype occurs in affected males in the 4th to 8th decade with cardiac disease and/or renal failure. This phenotype is more prevalent than the classic phenotype (19). Heart disease that occurs in Fabry disease is primarily characterised with hypertrophic cardiomyopathy, as well as rhythm disturbances and valvular heart disease (11).

Hypertrophic cardiomyopathy may be the only manifestation of this disease. Therefore, it is vital to check activity of the enzymes responsible for Fabry disease from dried blood spot due to possible treatment using enzyme replacement therapy (20, 21).

Mucopolysaccharidosis are set of rare, but progressive inherited metabolic diseases that are characterised with glycosaminoglycan collection in lysosomes as a result from lack of enzymes that participate in their degradation which ultimately leads to disturbed functioning of the cells, tissues and

organs. Seven different types of mucopolysaccharidosis were described and some of them are divided into their subtypes (22). Clinical manifestations include coarse facial features, recurrent upper respiratory tract and ear infections, noisy breathing, and persistent copious nasal discharge. Obstructive airway disease, notably during sleep, may necessitate tracheotomy. Clinical manifestations also include combined conductive and neurosensory hearing loss and an enlarged tongue, characteristic skeletal dysplasia known as dysostosis multiplex, hydrocephalus, delayed growth and development, as well as mental retardation (11). Heart diseases have been described in all mucopolysaccharidosis types. These include heart valve disease, hypertrophic cardiomyopathy, difficulties in digestion, coronary artery disease, as well as sudden heart death (23). Obstructive airway disease, respiratory infection, and cardiac complications are the common causes of death. Nowadays there are replacement enzymes therapy available for treating mucopolysaccharidosis types I, II, IVA and VI, and some studies have been researching therapies for types IIIA and VII. Patients suffering from type I mucopolysaccharidosis, if diagnosed on time, can effectively be treated by transplantation of haematopoietic stem cells (11). Transplantation of these cells and enzyme replacement therapy decrease hypertrophy of the heart and improve lung function, however no known improvements in treating heart valve disease were noticed (24).

Fatty acid and carnitine metabolism disorders

Mitochondrial β-oxidation of fatty acids is an essential energy producing pathway. It is a particularly important pathway during prolonged periods of starvation, and during periods of reduced caloric intake because of gastrointestinal illness or increased energy expenditure during febrile illness. Under these conditions, the body switches from using predominantly carbohydrate to predominantly fat as its major fuel. Fatty acids are also important fuels for exercising skeletal muscle and are the preferred substrate for the heart. In these tissues, fatty acids are completely oxidized to carbon dioxide and water. The end products of hepatic fatty acid oxidation are the ketone bodies, β-hydroxybutyrate and acetoacetate. These cannot be oxidized by the liver, but are exported to and serve as important fuels in peripheral tissues, particularly the brain, which can partially substitute ketone bodies for glucose during periods of fasting (25). In order to reach a complete use of fatty acids till acetyl coenzyme A and ketone bodies, it is necessary for carnitine cycle

and -oxidation of fatty acids to function properly. Carnitine, whose availability is dependent on a carrier that transports it to the cells, is a crucial factor responsible for successful carnitine cycle functioning. Lack of this carrier, of enzyme of carnitine cycle or lack of enzyme that participates in -oxidation of long chained fatty acids can cause cardiomyopathy with possible heart muscle failure and/or potentially deadly disturbance of heart rhythm (11). Clinical manifestations characteristically involve tissues with a high β-oxidation flux, including liver, skeletal, and cardiac muscle. The most common presentation is an acute episode of life-threatening coma and hypoglycaemia induced by a period of fasting because of defective hepatic ketogenesis. Other manifestations may include chronic cardiomyopathy and muscle weakness or exercise-induced acute rhabdomyolysis (25). Some chronic types can endanger a newborn with cardiac and muscle weakness, hypotonia, as well as with liver failure, disturbances of consciousness, hypoglycaemia and with hyperammonemia. Clinical symptoms and disorder signs are noticed only during metabolic crisis provoked by starving, infections and other stressful situations.

However, if metabolic crisis does not occur, the signs can hardly be detected or can appear as a slight muscle weakness, hypotonia, as signs of cardiomyopathy or liver dysfunction, as well as in a form of frequent disturbance of consciousness in different combinations (4, 25).

Due to impossibility of adequate forming of ketones, nonketotic hypoglycaemia is characteristic of this set of diseases. Analysis of organic acids in urine taken during the crisis periods can provide findings of dicarboxylic acid, the end product of incomplete degradation of fatty acids. During the crisis, it is common to notice increased amount of free fatty acids as well. Concentration of total and free carnitine is decreased, while the analysis of specific acylcarnitines can provide information regarding various diseases of this type (4, 25).

Treatment consists of sufficient calories intake with increased amounts of carbohydrates and decreased amounts of fats that are mainly composed of medium-chained fatty acids. In cases where carnitine carrier is lowered, carnitine is being given (4, 26).

Mitochondrial diseases

Mitochondria are responsible for creating more than 90% of total energy in the body necessary for living and maintaining organ functions. Mitochondrial diseases are primarily characterised with insufficient forming of adenosine

triphosphate (ATP) – energy rich compound that is used in the body for different functions. Cardiac muscle is the main user of this compound in the body. Mitochondriopathies are quite common diseases of inherited metabolism failure and it is estimated that it prevails in 1 out of 5000 (27).

Disturbances and failures of complex processes in mitochondrion can occur due to different mutations in nuclear and mitochondrial DNA responsible for synthesis of approximately 1500 proteins used for maintaining mitochondrion structure and its function.

Organs that require extra energy for their work, such as heart, brain, muscles, liver and kidneys, tend to manifest the symptomatology the most.

However, this can affect many organs and organic systems. Failing to form energy in mitochondrion leads to cardiomyopathy development in majority of patients due to the nuclear DNA gene mutation, whereas the rest of cardiomyopathies occur as a result of mitochondrion DNA mutations (28). Combination of cardiomyopathy and other disorders affecting different organs can often be assumed as mitochondriopathies. It is estimated that cardiomyopathy is found in 20-40% patients with inherited mitochondrial disturbances of forming energy.

Apart from cardiomyopathy, some patients suffering from mitochondrial disturbances of forming energy in heart can suffer from another disorder, such as heart rhythm disturbances, pulmonary hypertension, coronary disease, pericardial effusion and other heart symptoms (11). Mitochondrial diseases clinically manifest between newborn to adult ages and are result of many rare described syndromes. These are hard to diagnose due to various metabolic changes in mitochondria and due to the wide range of variability of clinical manifestations with unpredictable, progressive disorder. As glucose cannot be used to the maximum levels, lactate concentrations are increased which is considered to be one of the causes of congenital lactic acidosis. Disturbances in function of respiratory chain cause increased ratio between lactate and pyruvate, while this ratio is considered to be normal during lack of pyruvate dehydrogenase, meaning the concentration of pyruvate is correspondingly increased. Due to secondary changes in enzyme deficiencies in the respiratory chain the ratio between 3-hydroxibutyric acid and acetoacetic acid is increased. Alanine concentration can be found to be increased in the plasma, while urine can show higher secretion of all amino acids. Organic acid analysis in urine indicate presence of 3-methylglutaconic acid or citrate cycle metabolites. Using histological muscle analysis, it is possible to find ragged red fibres, mitochondrial myopathy specific.

Diseases of this type can be established with specific analysis such as histochemical analysis, use of oxygen measurements and activities of some components of respiratory chain, measuring activities of some enzymes, nuclear and mitochondrial DNA analysis, etc. (4).

Treatment options are limited. It is rarely that results can be positive and if so, it is achieved with ubiquinone and idebenone. Other patients are usually, but not effectively, treated with vitamins, antioxidants and medications that influence resistance development and development of some mitochondrial functions (29).

Other inherited metabolic disorders and heart diseases

Glycogenosis

Apart from Pompe diseases (generalised glycogenosis type II) that have previously been discussed, there are other glycogenosis types that can cause heart disorders. Even though they are classified as primary liver glycogenosis, type 0, III, IV, VI and IX, can provoke muscle weakness in some patients as well as hypertrophic cardiomyopathy (26, 30, 31). Basic treatment of these glycogenosis is a special diet and using glucose polymer aiming to prevent hypoglycaemia and lactacidemia. Nowadays, research studies show that ketogenic diet combined with increased amount of proteins can result in opposite of progressive cardiomyopathy in patients with glycogenosis type III (32).

Inherited haemochromatosis

Inherited haemochromatosis is a result of uncontrolled iron absorption and its over-collection in the body, as well as cell and tissue damaging. Symptoms are expected to appear in childhood among patients suffering from juvenile haemochromatosis, while first signs of patients that developed haemochromatosis due to HFE gene mutation are more noticeable in adulthood (33). Symptoms include cardiomyopathy, arrhythmia, liver disease, endocrinopathy, arthritis and increased skin pigmentation. Apart from the above stated symptoms, diagnosis is also characterised with increased ferritin concentration, high saturation of transferrin with iron, as well as increased iron collection in the tissues. Treatment includes frequent phlebotomy and using iron chelator (34). Cardiomyopathy in haemochromatosis is dilative and is also preceded by diastolic dysfunction and digestion difficulties (35).

Congenital glycosylation disorders

Inherited glycosylation disorders can cause pericarditis and cardiomyopathy that can either be dilative or hypertrophic. This set of diseases usually affects more organic systems so this disorder should be taken as it is, especially if neurological system has been affected too. Standard analysis that prove this set of diseases is isoelectrophoresis of sialotransferrin (11, 36).

Disorders of amino acid and organic acid metabolism

Inherited metabolic disorders of amino acids and organic acids are not common causes of cardiomyopathy, although there are some exceptions. In the long run, cardiomyopathy presents a frequent complication in propionic and methyl-malonic acidemia, therefore such patients should be often controlled. Heart disorders are even more rare in malonic acidemia, β-ketothiolase deficiency, mevalonic acidemia, tyrosinemia and oxalosis (9, 11).

Disorders of Lipoprotein Metabolism

Clinical manifestations of atherosclerosis occur in adulthood when most of the changes in blood vessels are irreversible. Atherosclerosis is a process that starts in young age and is, therefore, possible to act on early in order to prevent its development and the side effects.

Early discovery of dyslipoproteinemia is one of the most important achievements for successful and effective prevention of atherosclerosis development. Inherited genetic diseases are the main causers of primary disorder of lipoprotein metabolism. They can be divided into hypercholesterolemia, hypertriglyceridemia and combination of hyperlipidemia with some other genetically caused dyslipidemia. Out of disorders of lipoprotein metabolism it is hypercholesterolemia that affects the development of atherosclerosis in particular, as well as family lack of apolipoprotein B, polygenic hypercholesterolemia, family dysbetalipoproteinemia, family combined hyperlipidemia and hypoalphalipoproteinemia (37). One third of patients with early myocardial infarction (50 years ago in men and 60 years ago in women) also suffer from hyperlipoprotenimia, while half of the patients have some kind of inherent dyslipoprotenimia (38). Performing cholesterol screening allows establishment of atherogenic lipoprotein levels in serum (total cholesterol, LDL cholesterol, HDL cholesterol). Dyslipoproteinemia is diagnosed regardless of whether it is caused because of excessive and inadequate die, or is caused by primary or secondary disorders of lipid metabolism (39). Cholesterol screening reliability is noticeably increased when universal screening of lipid

profile is being carried out among population (40). This screening can be performed any time after the 2nd year of life, but is mostly preferable to be done in pre-school period, then at the age of 10, and in adolescent age, and should be carried out every 5 years if the results are positive. Universal cholesterol screening carried out among children provides information of which family members are prone to develop coronary disease, and this eventually requires treatment of older family members for coronary disease. Researches show that grandparents death in families where kids have increased cholesterol is up to 2.5 times higher than in families in which kids do not have increased cholesterol (40). Hypercholesterolemia treatment is performed using titrated diet nutrition in children older than two years. It is vital to strictly pay attention to child's body weight and to insist on increased body activity, to control blood pressure regularly and to avoid other potential causers of atherosclerosis development. Therapy also includes medications depending on hypocholesteraemia and depending on results obtained from diet measurements and life habits. Moreover, some ionic exchangers and statins are also used, however their showed variable effects, usually among children above the age of 10 (37).

Hyperhomocysteinemia

Homocysteine is an amino acid that contains sulphur and it occurs due to methionine metabolism. Moderate hyperhomocysteinemia is clinically significant as it provokes dysfunction of endothelium arteries and provokes development of atherosclerosis with side effects such as early infarction, osteoporosis, thromboembolism and is also related to development of schizophrenia, as well as Parkinson's disease. Hyperhomocysteinemia is also provoked by decreased levels of folate in serum, and decreased levels of vitamin B_{12} due to insufficient input resorption of the same compounds, for instance, in chronic inflammatory bowel disease, short bowel syndrome and due to inadequate diet. Polymorphic genes for some enzymes that participate in methionine metabolism can also cause increased levels of homocysteine in serum. The most common are mutations C677T and A1298C on gene for 5,10-methylenetetrahydrofolate reductase (MTHFR). Incidence for the named polymorphs varies in different populations, i.e. for C677T from 9% in North India up to 59% in Mexico. For A1298C, for example, it starts from 17% in China up to 36% in Europe and Canada. Screening and systematic prevention are not carried out. Given the importance and prevalence of hyperhomocysteinemia, as well

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as the possibility of successful treatment, universal screening is advised to be carried out already in childhood (4, 37, 41, 42).

Diagnosis

Inherited metabolic disorders that can cause heart diseases are noticeably different. It is important to assume them in cases where heart diseases are etiologically undefined mainly because some of them can possibly be treated. Tandem mass spectrometry used for newborn screening can provide findings regarding inherited metabolic diseases that provoke heart diseases. However, this is dependent on the number of screening tests performed on the newborn.

Diagnosis of inherited metabolic disorders in a child with cardiomyopathy requires thoughtful investigation with respect to evaluation of the diagnostic metabolites, demonstration of deficient enzyme activity in the appropriate cell type or body fluid, and DNA mutation analysis. For the inherited metabolic disorders associated with excessive acid production, the best time for testing is when the child's metabolism is stressed and the underlying metabolic defects are drawn out. Such times include congestive heart failure, infection, illness, post-surgery, fasting, and during a metabolic decompensation (hypoglycemia, metabolic acidosis, acute encephalopathy). At these times, it is good clinical practice to obtain extra serum and urine samples to hold for future metabolic testing rather than waiting until the child is stabilized, as some of the diagnostic metabolites may be transient or present in only small quantities (9). Laboratory examinations include testing of blood, glucose, acid-base status, lactate, aminotransferase, creatine kinase, ammonium, iron, saturation of transferrin and ferritin, cholesterol, triglycerides, HDL and LDL cholesterol, organic acids in urine, amino acids in plasma, total and free carnitine, acyl carnitine profile, free fatty acids, ketones in urine and/or serum, etc. Some of the mentioned tests are not crucial to perform if the clinical picture suggests a set of metabolic diseases that are not of huge importance.

Many disorders can be confirmed by testing the level of enzymatic activity in white blood cells, serum, or plasma, while others are more easily done in cultured fibroblasts from a skin biopsy. However, the latter requires several weeks for diagnosis, which has led to a push towards developing new assays in white blood cells. The enzyme assay for Pompe disease, Fabry disease and mucopolysaccharidosis type I, II and VI can now be reliably performed using a dried blood spot on a newborn screening card, which shortens the turnaround time for diagnosis to just a couple of days. Dried blood spots have the

added convenience of requiring only a small volume of blood, enzyme stability at room temperature, and easy mailing to the laboratory in an envelope (9). Next generation sequencing methods have had an impact on diagnosis, making it easier to establish the diagnosis. This allows quicker etiological diagnosis to be released for many patients, which previously took months or years (43). Modern methods of gene analysis have drastically decreased the need for 'aggressive methods' in diagnostics such as skeletal and cardiac muscle biopsy. Next generation sequencing methods allow massive parallel sequencing of targeted genetic panels for cardiomyopathy. This includes full coding of genome sequences or sequencing of the entire genome (44).

Next generation sequencing has found changes of one nucleotide and small insertions and deletions. In order to discover more complex genetic changes, it is necessary to perform this method coupled with MLPA (multiplex ligation – dependant probe amplification) or qPCR (quantitative real-time polymerase chain reaction) methods (45).

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NASLJEDNE METABOLIČKE BOLESTI I BOLESTI SRCA

Sažetak

Nasljedne metaboličke bolesti mogu izazivati srčana oboljenja, i to prvenstveno kardiomiopatije, ali i poremećaje srčanog ritma i bolesti zalistaka. Više od 40 različitih nasljednih metaboličkih bolesti može izazvati kardiomiopatiju, uključivši lizosomalne bolesti nakupljanja, poremećaje oksidacije masnih kiselina, organske acidemije, aminoacidopatije, bolesti taloženja glikogena, nasljedna oboljenja glikolizacije te peroksizmalne i mitohondrijske skupine oboljenja. Ako se dijagnosticiraju na vrijeme, neke se nasljedne metaboličke bolesti mogu uspješno liječiti. Zato je važno posumnjati na njih kod etiološki nerazjašnjenih srčanih oboljenja. Razvoj tehnologije omogućuje brže i uspješnije postavljanje dijagnoza nasljednih metaboličkih bolesti. U radu će se prvenstveno obratiti pažnja na one nasljedne metaboličke bolesti koje izazivaju srčana oboljenja i koje je moguće liječiti.

Ključne riječi: nasljedne metaboličke bolesti, bolesti srca, dijagnoza, liječenje

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WHAT IS NEW IN CARDIOVASCULAR MEDICINE?

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Abstract

The rapid pace of change continues to be a hallmark in cardiovascular medicine and many see that pace accelerating in adult cardiovascular medicine as well as in paediatric cardiology medicine. Cardiovascular medicine is an area of clinical practice with a continually rapid expansion of knowledge, guidelines, best practices and new technology. Cardiovascular diseases are the leading cause of mortality in the world and cause major costs for the health sector and economy. Primary care clinicians are challenged to optimally manage a multitude of diseases including congestive heart failure, coronary artery disease, valvular diseases, arrhythmias, lipid disorders, and hypertension. Multimodality imaging techniques are being used more frequently as their utility is better appreciated. Echocardiography has been the mainstay approach, cardiac computerized tomography and magnetic resonance imaging provide a good imaging alternative for patients with multiple complex surgeries. 3D printing has seen a rapid growth in use for planning treatments for patients with congenital heart disease. Simulation using 3D models is emerging as a fundamental resource for teaching procedural techniques and a new standard of care. Artificial intelligence holds the greatest potential for revolutionizing medicine. Innovative technologies in the world of cardiovascular health are expanding every day: wearable computing technologies, bioresorbable stents, leadless pacemaker, valve-in-valve procedure, protein patch for heart muscle growth and others. As a part of lifelong learning process for all professionals in cardiovascular medicine, the imperative is to have continuity of reviewing novelties, with results data from numerous researches in order to treat patient according to best practices and evidence-based medicine.

Key words: cardiovascular, medicine, up-to-date

Introduction

Cardiovascular diseases /CVD/ as a part of cardiovascular medicine, remain the biggest cause of deaths worldwide and cause major costs for health sector and economy (1). Although during the last two decades, rates of cardiovascular mortality declined in many developed countries, they have grown in low and middle income countries. The percentage of premature deaths caused by cardiovascular diseases is in the range of 4% in developed countries and 42% in undeveloping countries. Around 17.9 million people died from CVD in 2016, representing 31% of total deaths. Of these deaths, 85% were due to heart attack and stroke. Of the 17 million premature deaths (under 70 years of age) due to non-communicable diseases in 2015, 82% were in low- and middle-income countries, and 37% are caused by CVD's (2). The majority of cardiovascular diseases can be prevented by addressing behavioural risk factors such as tobacco use, unhealthy diets and obesity, physical inactivity and harmful use of alcohol, through strategic approach in the whole population. Therefore, cardiovascular medicine is a vast area of clinical practice with a continually rapid expansion of knowledge, guidelines, best practices and new technology. Primary care clinicians are challenged to optimally manage a multitude of diseases involving the cardiovascular system, including heart failure, arrhythmias and the circulation affected by abnormal cholesterol metabolism and hypertension. The rapid pace of change continues to be a hallmark in cardiovascular *adult and paediatric cardiology medicine* and many see that pace accelerating.

In the section of *Adult Cardiology* we are going *to review* a few novelties which would be of interest *for primary care practitioners*.

Atrial Fibrillation represents an irregular and often rapid heartrate that can increase risk of strokes, heart failure and other heart-related complications. In Alamneh EA et al from 2016, authors discussed a greater use of direct oral anticoagulants /DOACs/ over warfarin (3). Increased use of DOACs, particularly rivaroxaban, among patients with atherosclerotic disease as a result of the COMPASS study, showed fewer cardiovascular events in patients with peripheral artery disease (PAD) who received low-dose rivaroxaban plus daily aspirin twice daily, compared with aspirin alone (4). Similar results are anticipated from a second trial, VOYAGER PAD (5). These studies are helping to understand the role of very low-dose DOACs in the prevention of thrombotic adverse events in patients with coronary artery disease and PAD.

Artificial intelligence (AI) is defined as the ability of computer systems to perform tasks humans usually perform. Machine learning, while often used interchangeably with AI, is actually a subset of AI in which algorithms, mathematical models and/or computer systems are used to optimize the performance of a given task (6). The *Six broad* areas in which AI will advance the cardiovascular field are: *1. Novel drug discovery/development*. AI is increasingly being used to refine the selection of potential therapies by searching for patterns in molecular biology, structure-function, and clinical trial databases. *2. Precision medicine.* With AI, genetic, environmental and lifestyle data can be quickly assessed to determine who is most likely to benefit from certain interventions. *3. Integration of data from varied sources*. AI enables data from varied sources, such as wearables, social media, the electronic health record, to be integrated into models that can predict the trajectory of both health and disease. *4. Improved efficiency.* AI can help reduce provider dissatisfaction and burnout by minimizing repetitive tasks, prioritizing HER (Health Electronic Record) - based alerts or messages, improving and automating image interpretation in the catheterization or echocardiography laboratory, and presenting a "preferred" treatment plan based on integration of varied data sources. *5. Remote monitoring.* AI can strain out clinically actionable data from the trillions of data bytes collected by wearable devices. *6. Increasing the value of delivered care*. Artificial intelligence is an ideal population tool, given its ability to better predict individuals at greater or lesser risk of developing chronic diseases or related complications, tailoring preventive therapies and allocating limited resources to those most likely to benefit from them. No emerging technology has more promise than AI. There are dozens of articles about the potential for AI in health care and an increasing number of scientific publications. But, overall, almost nothing has yet made its way into clinical practice. One likely reason is that many startup and established tech companies underestimated the complexity of healthcare data and the need to provide strong evidence that the use of AI would improve efficiency and outcomes. It's therefore important that clinicians insist on strong data before relying on AI.

Another aspect of novelty discussed in cardiovascular medicine is the *Patient-Generated Data:* The first "wearable" in cardiovascular medicine dates back to the 1800s, when a watch with a second hand was used to measure heart rate (6). Today, however, wearables are more likely to be patient initiated, measuring everything from heart rate and rhythm to blood pressure, sleep quality and duration, and physical activity (7, 8). There is particular interest in the ability of wearables to affect clinical outcomes in cardiovascular

disease. A major trial evaluating the potential of specialized software for the Apple Watch to detect abnormal heart rhythms is underway. The Apple Heart Study, a virtual, prospective, single-arm pragmatic study has enrolled more than 400,000 participants. The primary outcome is the proportion of participants with an irregular pulse detected by the watch who are diagnosed with AF on subsequent ambulatory ECG patch monitoring. A secondary outcome is to estimate the rate of initial contact with a healthcare provider within three months after the patient is notified of a pulse irregularity (8). To date, data on clinical outcomes from mHealth devices are primarily based on case studies. For instance, Martin and his colleagues recently reported on the case of a woman with paroxysmal AFib whose Apple Watch/Kardia Band detected tachycardiomyopathy, enabling early detection and treatment and likely preventing significant morbidity (9-11). This represents the beginnings of mHealth being integrated into clinical care.

Valvular Heart Disease is characterized by damage to or a defect in one of the four heart valves: the mitral, aortic, tricuspid or pulmonary. The results of the COAPT trial reported in 2018 should have significant implications for the field of valvular heart disease in 2019 (12, 14). The study, which showed that treatment with the *MitraClip combined with guideline-directed medical therapy (GDMT)*, effectively reduced MR and was associated with marked clinical benefits, answered one of the lingering, unanswered question in the field. Is secondary mitral regurgitation simply a marker of a patient with a poor prognosis or a target for intervention/therapy? The results will encourage efforts to "fix MR" in patients with heart failure and secondary MR. The key will be how to do this in a safe, effective and durable manner (13). Other study results expected in 2019 include those from *two trials* comparing *transcatheter aortic valve replacement (TAVR) with surgical aortic valve replacement (SAVR)* in low-risk patients (12, 13, 15). Most people anticipate that TAVR will be noninferior to SAVR, thus opening the door for FDA approval of TAVR to extend to low-risk patients, although several lingering questions remain, including its use in patients with bicuspid valve disease and valve durability. Authors anticipate that if TAVR is noninferior to SAVR, the field of transcatheter approaches for aortic valve will widen and many patients will be eligible for this ground-breaking therapy, which is less invasive and kinder for patient's recovery. Another question in 2019 is whether the FDA will approve *Boston Scientific's Lotus valve* for high-risk and prohibitive risk patients, and how the availability of a third TAVR valve on the market will affect practice patterns (16). Authors predict a greater attention on *tricuspid*

valve disease. Given the lack of medical therapies for advanced tricuspid valve regurgitation, transcatheter tricuspid therapies offer the possibility of a therapy option where no good therapy currently exists (17).

In the update in cardiovascular medicine *for primary care physicians* the topic on *Aortic Disease* evaluates *Fluoroquinolone* use and the potential risk for aortic aneurysm or dissection (18). Based on observational studies suggesting an association between fluoroquinolone use and aortic aneurysm or dissection, the US Food and Drug Administration issued a warning in December 2018 highlighting the association and recommended avoiding fluoroquinolones in patients with known aortic aneurysms or those with risk factors for aneurysm such as Marfan's syndrome, Ehlers-Danlos syndrome, peripheral atherosclerotic vascular diseases, hypertension, and/or advanced age. When considering fluoroquinolone use, we take this uncertainty into account and weigh the overall risks and benefits in each patient.

Arrhythmias: heart arrhythmia, also known as dysrhythmia or irregular heartbeat, is a group of conditions in which the heartbeat is irregular, too fast or too slow. About 80% of sudden cardiac death is the result of ventricular arrhythmias. Arrhythmias may occur at any age but are more common among older population. Most arrhythmias can be effectively treated. The method of cardiac rhythm management depends firstly on whether the patient is stable or unstable. Treatments may include physical manoeuvres, medications, medical procedures such as pacemaker, electricity conversion, or electro- or cryo-cautery. Radiofrequency catheter ablation (RFA) of recurrent sustained monomorphic ventricular tachycardia (SMVT) results in fewer *implantable cardioverter-defibrillator (ICD*) shocks and reduced need for antiarrhythmic drug therapy, but the optimal technique is unknown. The result was similar all cause mortality as in ICD implanted group (19). In a 2019 systematic review of 17 nonrandomized studies, patients who underwent *combined epicardial / endocardial versus endocardial RFA* had lower rates of recurrent VT (20). Subset analysis suggested the benefit was confined to those with ischemic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy. Additional data are required, ideally from randomized trials comparing the two techniques, prior to recommending combined epicardial /endocardial over endocardial RFA for all patients with recurrent SMVT. For patients in atrial fibrillation undergoing *transvenous cardiac implantable electronic device (CIED)* insertion, continued warfarin therapy has been shown to be safer than interrupted warfarin with heparin bridging among patients with the highest thromboembolic risk (>5 percent per year). Safety data, however, are

limited for patients treated with direct oral anticoagulants (DOACs) rather than warfarin (21). In BRUISE CONTROL-2, which included patients undergoing transvenous CIED insertion with CHA2DS2-VASc scores ≥2 who were taking a DOAC for chronic anticoagulation, the incidence of the primary outcome (clinically significant pocket hematoma requiring prolonged hospital stay, interruption of anticoagulation therapy, or surgery for hematoma removal) was the same (2.1 percent) for patients randomized to device insertion while on continued DOAC therapy and for those in whom the DOAC was stopped (22). While these data are promising, additional studies are needed prior to routinely recommending uninterrupted DOAC use during transvenous CIED implantation.

Despite effective interventional and medical therapies for *myocardial infarction (MI),* the risk of early post-MI sudden cardiac death (SCD) remains, especially in patients with severely reduced left ventricular ejection fraction (LVEF). Data conflict on the utility of an implantable cardioverter-defibrillator (ICD) early post-MI. *A wearable cardioverter-defibrillator (WCD)* has been suggested as temporary therapy for patients at high risk for SCD. The randomized VEST trial in patients with an acute MI and LVEF ≤35 percent compared use of a WCD (begun within seven days of hospital discharge) plus usual medical treatment to standard medical treatment alone (23). Over an average follow-up of 84 days, the primary outcome of arrhythmic death was not different for the two groups. Compliance with medical therapy was excellent in both groups, likely contributing to fewer than expected events, while compliance with WCD usage was markedly lower than expected. Among patients with LVEF ≤35 percent who are less than 40 days post-MI, authors discuss the benefits and risks of WCD use and offer it to highly motivated patients who would be candidates for ICD implantation after 40 days.

Another myocardial disease, *acute myocarditis* has been evaluated in the section of *cardiovascular imaging techniques*, discussing several points: the challenge to diagnose acute myocarditis given its varied clinical manifestations. *Cardiovascular magnetic resonance (CMR)* is a key noninvasive test for acute myocarditis as it enables identification of the location and extent of myocardial involvement, but the optimum CMR protocol for identification of acute myocarditis has not been established. A systematic review and meta-analysis included 22 studies comparing the diagnostic accuracy of CMR techniques for acute myocarditis (24). These findings will help refine CMR protocols for the diagnosis of acute myocarditis. Limited data are available on the agreement between left ventricular ejection fraction (LVEF) measurements

by various cardiac imaging modalities. The largest available study of *inter-modality variability of LVEF* analysed core lab data from an international trial enrolling patients with coronary artery disease and reduced LVEF including *echocardiograms, single-photon emission computed tomography, and cardiac magnetic resonance (CMR) imaging* (25). Correlation between LVEF determined by quantitative versus visual echocardiographic methods was greater than the correlation between LVEF assessed by different modalities (such as biplane echocardiography versus CMR). In paired comparisons of LVEF by differing imaging modalities, approximately half fell within range of five absolute percentage points. These observations demonstrate a significant limitation of using LVEF thresholds to guide clinical management and suggest that serial follow-up of a given patient may be best accomplished using a consistent imaging modality. Most published studies suggest that *coronary computed tomography angiography (CCTA) and stress testing (with stress imaging)* are associated with comparable long-term clinical outcomes in stable patients with suspected coronary artery disease (CAD) and in patients with acute chest pain. In the SCOT-HEART trial, which compared standard care (contemporary medical therapy and diagnostic testing at the discretion of the treating physician) with standard care plus CCTA in over 4100 patients with stable chest pain, patients randomized to CCTA with standard care had a reduction in the primary endpoint of CAD death or non-fatal myocardial infarction (2.3 versus 3.9 percent) over an average follow-up of 4.8 years (26). However, in contrast to prior studies comparing CCTA with stress testing, 85% of patients underwent stress electrocardiography (ECG) alone, with only 9 percent subsequently undergoing a stress test with imaging. Ongoing studies of CCTA should provide additional guidance regarding its optimal role in the diagnosis of patients with chest pain and suspected CAD.

Pulmonary hypertension is elevated blood pressure in the pulmonary artery (PA) averaging 25 mm Hg or above at rest. Elevated PA pressure (PAP) can be caused by abnormalities in the precapillary pulmonary arterioles, called pulmonary arterial hypertension (PAH), or by abnormalities that increase left atrial pressure resulting in back pressure on the pulmonary circulation, called pulmonary venous hypertension (PVH). Although the etiology and pathophysiology of PAH and PVH are distinct, they are similar in that both cause elevated PA pressure that inevitably leads to right ventricular (RV) dilation and remodeling, followed by RV failure and death if RV compensation can no longer sustain normal cardiac function. PAH is often characterized by a progressive and sustained increase in pulmonary vascular resistance

that eventually may lead to RV failure. It can be a life-threatening condition if untreated. Therapy for pulmonary hypertension is targeted at the underlying cause and its effects on the cardiovascular system, with success rates varying according to the aetiology. Pulmonary Arterial Hypertension or PAH is a subgroup of PH caused by narrowing of the blood vessels in the lungs. In contrast, PAH occurs in isolation and is very rare. There is a difference between pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH). Pulmonary arterial hypertension (PAH) is a specific subgroup of pulmonary hypertension (PH). The definition of PH is more inclusive than the definition of PAH, meaning that the specific hemodynamic measurements used to define PAH do not apply to PH. For select patients with *pulmonary arterial hypertension (PAH),* advanced therapy including endothelin receptor antagonists (bosentan or macitentan) is widely accepted, but consensus is lacking for those with PAH and congenital heart disease, including Eisenmenger syndrome. In the MAESTRO trial, including over 200 patients with Eisenmenger syndrome with World Health Organization (WHO) functional class II to IV, macitentan versus placebo resulted in a similar mean change in six-minute walk distance (6MWD), but reduced pulmonary vascular resistance (27). In the smaller prior BREATHE-5 trial, bosentan improved both of these measures relative to placebo. Authors continue to use endothelin receptor antagonists for patients with PAH and congenital heart disease given improvement in hemodynamic parameters, although an effect on clinical outcomes has not been established.

Heart Failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. We evaluate novel different methods of treatment. Sacubitril-valsartan (an angiotensin receptor-neprilysin inhibitor) is indicated *in ambulatory patients* with *heart failure* with reduced ejection fraction, but its safety and efficacy in patients with acute heart failure have not been determined (28). *Left ventricular assist devices* are increasingly used to manage *end-stage heart failure*, but device-related complications include stroke. In the MOMENTUM 3 trial, over 300 patients were randomly assigned to implantation with a fully magnetically centrifugal flow pump or an axial flow pump (29). While stroke rates were similar in the two groups during the first six months, strokes were less frequent from six months to two years in the centrifugal flow pump group. A stroke event was associated with reduced two-year survival regardless of the subtype or the initial severity of neurological impairment. This

finding illustrates the impact of device selection and complications on long-term outcomes.

Another topic is *Hypertension,* one of the risk factors for development of cardiovascular diseases. Numerous epidemiological studies have found an association between incrementally higher blood pressure in middle-aged and older adults and the risk of cardiovascular disease in middle-aged and older adults; fewer data are available for the outcomes of *high blood pressure among young adults.* Two large prospective cohort studies of adults younger than 40 years at baseline found that increments in blood pressures >120/>80 mmHg, compared with a blood pressure <120/<80 mmHg, were associated with increasing risk for coronary heart disease and stroke later in life (30, 31). These studies support that hypertension, defined by the 2017 ACC/AHA guidelines as blood pressure ≥130/≥80 mmHg, is an important risk factor for cardiovascular disease, including in young adults. The American Heart Association updated their statement on detection, evaluation, and management of *resistant hypertension* (uncontrolled hypertension despite prescription of three or more antihypertensive medications) (31). The most notable change from prior guidelines relates to the diagnosis of true resistant hypertension. True resistance must be distinguished from pseudo resistance by confirming that blood pressure is above goal when measured in the office using proper technique, by then confirming uncontrolled hypertension with out-of-office measurements (ie, ambulatory blood pressure monitoring or home blood pressure monitoring), and by considering and excluding nonadherence to antihypertensive therapy.

Innovative technologies in the world of cardiovascular health are expanding daily, such as: wearable computing technologies, bioresorbable stents, leadless pacemaker, valve-in-valve procedure, protein patch for heart muscle growth and others (34).

In the current era, *multimodality imaging techniques* are being used more frequently as their utility is better appreciated (32). Echocardiography has been the mainstay approach, and cardiac computerized tomography and magnetic resonance imaging provide a good imaging alternative for patients with multiple complex surgeries. 3D printing has seen a rapid growth in use for planning treatments for patients with congenital heart disease. Simulation using 3D models is emerging as a fundamental resource for teaching procedural techniques and a new standard of care.

In the section of Paediatric cardiology we evaluate treatment of congenital heart defects which are the most common type of birth defects, occurring

in about 1 percent of all live births. A large number of these defects require surgery, especially those in the category of complex congenital heart disease, requiring multiple operations (33). While there have been great advances in surgical technique and outcome, there still remains significant morbidity and mortality, especially in the setting of those requiring multiple operations. A major reason for this is the significant variation in anatomic abnormalities in patients with congenital heart disease, especially in those individuals requiring repeated procedures. As we stated earlier, 3D printing has seen a rapid growth in use for planning treatments for patients with congenital heart disease and carries hope for improving quality, efficiency and outcomes of these procedures. The current paradigm of the practice is to identify pts with complex anatomy who may require repeated procedures that carry significant risk. Life-size models by 3D printing using different materials can be used by the surgeon who can then immediately contemplate the approach and the technical feasibility of the anticipated procedure. The use of 3D-printed models can be used to tailor education to different learners, to effectively teach complex cardiac anatomy to radiology, cardiology and cardiovascular surgery fellows. Training in procedural techniques has been traditionally time-consuming and has the potential to be implicated in procedural complications. Simulation using 3D models is emerging as a fundamental resource for teaching procedural techniques for trainees acquiring advanced skill sets in the field and is similarly being used within practice as a new standard of care. 3D-printed models are also effective *tools for communication* within health care teams and with patients. Within the practice, specific 3D models used to explain disease processes and planned procedures enhance patient understanding and facilitate shared decision-making and informed consent, which ultimately improves patient satisfaction (37). In the paediatric cardiovascular medicine there were three major revolutionary innovations and paradigm shifts in congenital heart disease (CHD) interventions over the last half-century (35, 37). These innovations were: 1. the heart-lung (cardiopulmonary bypass) machine, 2. neonatal cardiac surgery, and 3. transcatheter therapy**.** There are multiple evolving areas of expertise that will potentially shape congenital cardiovascular specialty over the following decades. *The first* is the creation of the *Adult Congenital Heart Disease subspecialty* (36). With up to 90 percent of CHD patients surviving to adulthood in the current era, the coming years will likely see a significant increase in the prevalence of acquired heart disease in this population. Well-coordinated specialized multidisciplinary care from providers with skills in both paediatric and adult medicine will become critical for

the prevention and management of acquired heart disease as well as the long-term sequelae of CHD in this population. *Second,* one of the downstream problems of an aging CHD population is an *increase in the average number of surgical reinterventions in a lifetime, and the need for multiple reoperations in patients with complex anatomy* will invariably result in increase in surgical morbidity and or mortality. Transcatheter valve therapy is now increasingly being used to mitigate or delay the need for multiple high-risk surgical reoperations. The application of this therapy is significantly limited by the anatomic variability of the CHD population making most patients ineligible candidates. The ongoing improvement in the design of valve prostheses and delivery systems specifically engineered to accommodate the anatomic variability of this population will potentially increase the number of patients eligible for this therapy in the years to come. *Third,* the *advances in imaging techniques* (CT, MRI, echocardiography) that include 3-dimensional imaging and the ability to print models and evaluate anatomy in a virtual environment allows a more thorough preparation for a complex intervention. In addition, the ability to practice the actual procedure in advance of the operation provides an effective model for education and may help reduce morbidity and mortality for complex or infrequently performed percutaneous or open surgical procedures. *Fourth,* the *demand for cardiac replacement therapy* will continue to rise as the CHD population ages and the prevalence of end-stage heart failure increases. Unfortunately, the limited availability of *donor heart organs* and pre-sensitization from prior operations have resulted in a huge mismatch between the supply of cardiac allografts and the rising demand due to end-stage heart failure. With the ongoing improvements in the newer generation of *ventricular assist devices* authors anticipate that the use of ventricular assist device as destination therapy for CHD patients with end-stage heart failure may become the standard of care in the near future. Lastly, *stem cell therapy* is an emerging field with many exciting ongoing research studies. For heart failure patients, the urgent need for heart transplantation exceeds the availability of donor hearts. Therefore, cell transplantation has emerged as an interesting and potential solution. The clinical application of stem cell therapy, though still at the preliminary stage, is very promising for slowing down the progression to end-stage heart disease or even potentially reversing myocyte damage from previous insult (38).

Conclusion

During past decades, we have witnessed the birth and exponential growth of cardiovascular interventions in adults and children. More importantly, the coming decades will likely result in more revolutionary innovations in this field. As a part of lifelong learning process for all professionals in cardiovascular medicine, the imperative is to have continuity of reviewing novelties, with research results in order to treat patients according to best practices and evidence-based medicine.

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NOVINE U KARDIOVASKULARNOJ MEDICINI

Sažetak

Brzi tempo promjena i dalje je jedno od obilježja u kardiovaskularnoj medicini, a mnogi primjećuju da se taj tempo ubrzava i u kardiovaskularnoj medicini za odrasle kao i u dječijoj kardiološkoj medicini. Kardiovaskularna medicina je područje kliničke prakse s kontinuirano brzim širenjem znanja, smjernica, najboljih praksi i novih tehnologija. Kardiovaskularne bolesti su vodeći uzrok smrtnosti u svijetu i uzrokuju velike troškove za zdravstveni sektor i ekonomiju. Kliničari primarne njege suočavaju se s izazovom da optimalno upravljaju brojnim bolestima, uključujući kongestivno zatajenje srca, koronarnu bolest arterija, valvularne bolesti, aritmije, poremećaje lipida i hipertenziju. Multimodalne tehnike snimanja koriste se sve češće jer se njihova korisnost sve više cijeni. Ehokardiografija predstavlja osnovni pristup, a srčana kompjuterizovana tomografija i snimanje magnetnom rezonancom pružaju dobru alternativu za snimanje pacijenata s višestrukim složenim operacijama. 3D štampa bilježi brzi rast upotrebe u planiranju tretmana za pacijente s urođenom srčanom bolešću. Simulacija korištenjem 3D modela razvija se kao temeljni resurs u podučavanju proceduralnih tehnika i novih standarda njege. Umjetna inteligencija ima najveći potencijal za revoluciju u medicini. Inovativne tehnologije u svijetu kardiovaskularnog zdravlja šire se svakim danom: nosive računalne tehnologije, bioresorbilni stentovi, bezopasni pejsmejkeri, valve-in-valve procedure, proteinski flasteri za rast srčanog mišića i druge. U sklopu procesa cjeloživotnog učenja za sve stručnjake kardiovaskularne medicine, imperativ je dosljedno praćenje noviteta, uz rezultate brojnih istraživanja, kako bi se pacijenti mogli liječiti u skladu s najboljim praksama i medicinom zasnovanom na dokazima.

Ključne riječi: kardiovaskularno, medicina, ažurnost

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HYPERTENSION – A PUBLIC HEALTH PROBLEM

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Abstract

Aim. The aim of this paper is to present public health importance of hypertension in population as one of the major CVD risk factor as well as a model of integrated approach to hypertension control at community level. **Background.** In spite of wide knowledge of pathophysiology and epidemiology in development of hypertension, ability to easily diagnose it, availability of efficient medications, hypertension continues to have high prevalence and setting up hypertension controls poses significant public health challenge. High prevalence of hypertension exists in all countries of the world, regardless of socioeconomic status of the country. It is estimated that the number of people with hypertension by 2025 will rise by 15-20%, and the number of sick people will increase up to 1.5 billion people worldwide. **Methods.** A review of the relevant literature which discusses the importance of defining clear strategies and interventions in the control of hypertension in countries, with particular emphasis on integrated hypertension management that has the greatest impact. **Discussion.** Effective and efficient hypertension control requires two approaches: population approach and individual approach to high-risk individuals. The balanced combination of population approach and an approach to access high-risk individuals is vital for the effective control of hypertension and cardiovascular diseases. **Conclusions.** Health systems in every country must be flexible and ready to provide adequate model of integrated approach to hypertension control at community level understanding their own local needs.

Key words: hypertension, cardiovascular diseases, control of hypertension

Introduction

In the last few decades there has been a significant increase of noncommunicable diseases (NCD) in the world, such as cardiovascular diseases (CVD), carcinoma, chronical obstructive pulmonary diseases (COPD) and diabetes. Noncommunicable diseases have become one of the main global public health challenges (1, 2) as they are responsible for almost 90% of deaths and for 84% of disease burden in European Region. This burden is increasing disproportionately in countries with low and middle-low income (3, 4).

Common CV diseases risk factors are: tobacco use, inadequate diet, physical inactivity and alcohol abuse. Working actively on these risk factors could prevent onset of disease and premature death from CVD. In connection to this, in 2013, the World Health Assembly adopted the Global Action Plan for the Prevention and Control of Noncommunicable Diseases, providing guidance and policy options. If these options are implemented in the period 2013-2020, they will contribute to the 9 global targets set for noncommunicable diseases, which should be achieved by 2025 compared to the base year 2010 (4).

Numerous population studies have also confirmed that high blood pressure (BP) and/or hypertension is an independent and significant CV and coronary heart disease risk factor. Hypertension has been identified by World Health Organization (WHO) as one of the most significant risk factors for morbidity and mortality worldwide and despite strong evidence for treatment, studies suggest that many people remain sub-optimally controlled (5, 6).

CVD, in general, have the biggest impact on years of healthy life lost, on quality of life lost, as well as on life expectancy differences between populations. Global statistics show that CVD are responsible for every third death, with coronary heart disease being the primary cause of death in the world. It is estimated that 17 million people die of CVD, of heart attacks and strokes especially. (3, 4)

Since NCDs, especially CVDs, are the leading cause of disease and dying in the world, defining the integrated management of CVD, including risk management, is a major challenge for health systems in the countries (7, 8). Good practice in countries states that significant advances in health can be achieved through a well-organized and focused approach to prevention, treatment and disease control, which should be an integral part of the health system. This is possible in health systems that support community intervention programs. To achieve this, major health policy changes, health care organizations, staff training and equipment need to be introduced. Finally, such approaches do

not require significant resources compared to high-sophisticated clinical interventions (1, 2, 4, 7).

The aim of this paper is to present public health importance of hypertension in population as one of the major CVD risk factor as well as a model of integrated approach to hypertension control at community level.

An Integrated Approach to Hypertension Control

In recent decades, significant progress has been made in understanding epidemiology, pathophysiology and risk associated with hypertension as well as in obtaining evidence demonstrating that BP reduction can greatly reduce premature morbidity and mortality (9-12).

For the first time, in 2003, as the number of population and clinical studies in Europe increased and their results provided new evidence, the European Association for Hypertension and the European Association for Cardiology developed their own guidelines for management of hypertension. These guidelines were made in response to the WHO/ISH suggestion to regional experts to prepare recommendations for disease management based on regional conditions (13). Since 2003, regular management reviews have been conducted for hypertension management and the latest issue is from 2018 (14). According to the adopted definitions, hypertension is a condition when the systolic blood pressure (SBP) value is at least 140 mmHg and/or the diastolic blood pressure (DBP) value is at least 90 mmHg (Table 1).

The overall prevalence of hypertension among the adult population is between 30-45% (14). High prevalence of hypertension exists in all countries of the world, regardless of socioeconomic status of the country. Therefore, hypertension becomes a progressive disease or a risk factor for the emergence of CVD. Since there is a rise of other risk factors that lead to hypertension, such as unhealthy eating habits, physical inactivity and obesity, the prevalence of hypertension will increase. It is estimated that the number of people with hypertension by 2025 will rise by 15-20%, and the number of sick people will increase up to 1.5 billion people worldwide.

Table 1. Definitions and Classification of Blood Pressure Levels (mmHg)

Category*	Systolic blood pressure	Diastolic blood pressure
Optimal BP	<120	<80
Normal BP	120-129	80-84
High normal BP	130-139	85-89

Category*	Systolic blood pressure	Diastolic blood pressure
Grade 1 hypertension – mild	140-159	90-99
Grade 2 hypertension - moderate	160-179	100-109
Grade 3 hypertension - severe	≥180	≥110
Isolated systolic hypertension	≥140	<90

If the SBP and DBP values correspond to different categories, a higher BP category will be used. Isolated systolic hypertension may also be graded (step 1, 2, 3) according to the already indicated values of SBP, in the case of DBP being less than 90mmHg.

Source: 2018 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension – Guidelines Committee

The health systems of countries worldwide are still facing inadequate hypertension management. It is necessary to improve management by healthcare workers continually in order to have at least two-thirds of hypertensive patients who would achieve adequate BP control (15-17). All of this opens up the possibility of setting up socio-medical approaches to hypertension control, which basically prevent a continuous, expensive cycle of clinical management of hypertension and its complications (18, 19).

Effective and efficient BP control in population requires two approaches: population approach and individual approach to high-risk individuals. Both approaches are necessary and complementary for effective control and management of elevated BP and hypertension in the community. Particularly, it should be emphasized that a balanced combination of population prevention strategies and a preventive approach to access high-risk individuals as an integrated approach is vital for effective epidemic control and the control of the NCD burden growth in the community in general, particularly hypertension and CVD (4, 8).

Situational Analysis in the Federation of Bosnia and Herzegovina and Canton Sarajevo

CVDs have been the leading cause of death in the Federation of Bosnia and Herzegovina (FB&H) for several decades, with a share of 17.6% in the 2018 morbidity pattern. The most common in this group are hypertensive diseases with an incidence rate of 1639.6/10,000, which is a significant increase over the previous years, in 2016, the incidence rate was 1219.1/10,000 (20). The morbidity rate of hypertension diseases in Canton Sarajevo in 2018 was 1186.9/10,000 population, which is less than the average in the FB&H (1639.6/10,000 population) (20, 21).

The source of consistent data of these diseases is health survey. In the FB&H, in the past 17 years, two representative population surveys have been conducted on assessing the health status of adults – in 2002 and 2012. The results of the survey conducted in 2012 showed that 42% of adults had hypertension (systolic pressure> 140, diastolic> 90mmHg) and/or were taking anti-hypertensive therapy. Compared to that there was no statistically significant difference to the overall prevalence of hypertension in 2002 (40.9%). However, there was a statistically significant difference in the prevalence of hypertension in men, which increased by 8% in 2012 (from 36% to 44%). Over the 10-year period, there was a fall in the prevalence of hypertension in women, also by 8 % (from 45% to 38%) (22-25).

Literature Overview

The CVD problem in the world, in general, was highly ranked in the 70s of the last century. At that time, many health intervention programs were planned at the community level in order to promote health and lifestyle changes.

The first implemented program based on these ideas was the North Karelia Project implemented in Finland in 1972. Significant results were achieved in this project, primarily through hypertension control programs. It started as a pilot project and after significant net reductions, both in risk factors and mortality rates of CVD, state-level activities began. In the 25-year period during these activities in Finland, smoking prevalence among men was significantly reduced. There was also a significant reduction in serum cholesterol and blood pressure levels. In the same period, the mortality rate of CVD for male aged 35-64 was reduced by 68%, coronary heart disease by 73%, cancer by 44%, and for all causes overall mortality was reduced by 49% (26-28).

Since then many projects have been implemented as demonstration projects of WHO programs: CINDI (WHO / EURO), CARMEN (WHO / AMRO), INTERHEALTH (WHO / HQ). The main role of the projects set up in the community is to demonstrate and stimulate the state policy for the prevention of noncommunicable diseases (29).

In developed countries, the main problem in managing hypertension has shifted from screening to effective management, but there is still a relatively low rate of hypertension control in the population. This further promotes population approaches, as well as the implementation of hypertension treatment guides, especially at the PHC level (30, 31).

Model of Integrated Hypertension Management at the Community Level

At the current moment it is necessary to set up an integrated hypertension management model in the FB&H due to the relatively high prevalence of hypertension and major CV risk factors (25).

Population preventive strategies are the most cost-effective (4). These strategies aim to change health behaviour in terms of reducing exposure to risk factors and reducing risk across the population. Big potential is gained, but there are great challenges too.

Preventive measures bring great benefits to the community, yet they seem to bring little benefit to the individual, which can cause negative motivation in the population. This is described as a "preventive paradox." It is therefore necessary to accept the approaches accordingly. The key challenge is to find the right balance between the population approach and the high-risk individual approach (32).

In the community management (population management) approach, active involvement of a large number of actors at all three levels of management (strategic, tactical and operational) in the health sector is essential. (Table 2) (33, 34).

The health sector as a basic public sector is the first place to start the initiative.

Table 2. Cost-Effective Interventions in Reduction of Hypertension Prevalence

Management Levels	Possible Interventions	Actors	Theoretical population coverage
Strategic Management	1. Legislation on salt reduction in industrialized food produced in the domestic industry and the proper labelling of the food contents (for example)	Government of the Country	100%
Tactical Management	1. Health education through mass/social media 2. Campaigns 3. Establishing risk screening 4. Development of diagnostic-therapeutic protocols 5. Education of professionals 6. Development of referral programs e.g. "School for Hypertension at Community Level"	Public Health Institutes Chambers Professional associations Non-governmental organizations	60-80%

Management Levels	Possible Interventions	Actors	Theoretical population coverage
Operational Management	1. Pharmacological treatment and education on healthy lifestyles including dietary advice for persons with SBP over 160mmHg or 140mmHg 2. Pharmacological treatment and education on healthy lifestyles including dietary advice for people with serum cholesterol concentrations over 5.7mmol/l 3. Nicotine replacement therapy with medical advice by a doctor 4. Development of hypertension counselling centres	Primary health care Hospitals	25-45%

The role of strategic management level in the health sector (Government of the country) is significant in reducing the risk. The adoption of legal provisions is one of the possible instruments. This is more cost-effective because of the assumption that laws will lead to changes in agreements rather than just professional recommendations.

Both approaches require consultations with a large number of active actors and a multi-sectoral approach

Unfortunately, countries in transition have a weak regulatory structure and have the greatest dependence on a market that is out of control. In those cases, it is necessary to choose sustainable and implementable activities. Such activities include the implementation of increased cigarette taxes, legal regulations on reducing salt content in industrialized food with appropriate labelling of the contents, supporting healthy food production, or food price subsidies for domestic producers. These approaches should be developed in small countries, with limited financial resources, such as Bosnia and Herzegovina.

The role of tactical management level in health sector, such as Public Health Institutes, Health Professionals' Chambers, Professional Associations of Health Professionals, is in designing, setting up and implementing community intervention programs, through the preparation of promotional-preventive educational messages that are culturally sensitive, providing support for healthy lifestyle changes, establishing risk screening, developing diagnostic-therapeutic protocols, educating professionals, and developing referral programs. Raising the knowledge of social marketing is necessity at this level.

The role of operational healthcare management in the health sector is in active implementation of recommendations, production and distribution of

written materials and active participation in health education. This doesn't just include different levels of healthcare, such as Primary Health Care, secondary and tertiary health care (hospitals, clinics), but also the non-governmental sector. Also, role of local community is important.

Adopting a healthy lifestyle for all individuals is a critical point in the prevention of high BP and an essential part of hypertension management. The sociological framework of lifestyle modification implies setting up behaviour modification models that suggest increasing motivation of patients. Patients' attitudes are largely under the influence of cultural differences, beliefs and previous experiences with health care systems. These attitudes will be understood if health teams build and improve communication with patient and family.

The tables 3 and 4 show the Model of Integrated Hypertension Management - populational and individual approach, as proposed activities in the management process of community intervention programs (33, 34).

Table 3. Proposal of activities in the management process of community intervention programs - populational approach

GOAL – WHAT?	PROCESS-HOW?	PLACE- WHERE?	TIME- WHEN?
1. Reduction of hypertension prevalence by 10% among the adult population	- Legislation on salt reduction in the industrial production of food in the domestic industry and the proper labelling of the food contents	COMMUNITY Coverage 100% of the population	CONTINUOUSLY
2. Reduction of mean BP value in the population in order to promote and improve the cardiovascular health of the population	-Referral program development "School for Hypertension at Community Level"	COMMUNITY Coverage 100% of the population 1. Health workers - Family medicine teams (PHC) 2. Support groups - Healthy population 3. Population at risk 4. Representatives of mass media	MULTI-ANNUAL CONTROLLED PROGRAM IN CANTONS
3. Reduction of smoking, by 10%, especially among younger men	- Campaigns for possibility of using nicotine replacement therapy with medical advice by doctors - Health education through social media	Social Networks - Facebook, Twitter, WhatsApp Places the most frequently visited by this group - Coverage 55% of male population	MULTI-ANNUAL CONTROLLED PROGRAM IN CANTONS

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GOAL – WHAT?	PROCESS-HOW?	PLACE- WHERE?	TIME- WHEN?
4. Obesity reduction especially in middle-aged women population by 10%	- Health education through mass media, social networks - Education at workplaces - Promotion of preparation recipes for low-calorie meals	Social Networks - Facebook, Twitter, WhatsApp - Large shopping centres, non-governmental women's organizations Coverage 40% of female population	MULTI-ANNUAL CONTROLLED PROGRAM IN CANTONS

Table 4. Proposal of activities in the management process of community intervention programs - individual approach

GOAL – WHAT?	PROCESS-HOW?	PLACE- WHERE?	TIME- WHEN?
1. Reduction of undetected hypertension - increase of hypertension detection by 5%	- Blood pressure measurement at each visit to a health institution, when visiting a doctor for any reason. - After three re-measurements at certain time intervals, upon nurse's request, hypertension is diagnosed and a medical record is made with the risk factor measurements - medical history.	Health institutions Coverage 70% of the population	FIVE-YEAR PROGRAM
2. Establishing hypertension diagnosis and evaluating the patient	- Implementation 1. Diagnostic procedures 2. Repeated BP measurements 3. Holter BP 3. Medical history 4. Physical examinations 5. Laboratory and instrumental reviews. - Identification of other possible causes of hypertension - genetics, socio-economic environment - Assessment of presence or absence of organ damage, and cardiovascular diseases	Health institutions Coverage 100% of hypertensive patients	MULTI-ANNUAL CONTROLLED PROGRAM IN CANTONS
3. Estimation of CV risk factors in hypertensive patients	- Applying algorithms for evaluation of the CV - SCORE table	Health institutions Coverage 100% of hypertensive patients	MULTI-ANNUAL CONTROLLED PROGRAM IN CANTONS

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GOAL – WHAT?	PROCESS-HOW?	PLACE- WHERE?	TIME- WHEN?
4. Establishment of non-pharmacological hypertension treatment	- Lifestyle modification - Protocols on healthy lifestyle counselling - Health education and distribution of health promotion materials that contain culturally sensitive messages	Health institutions Coverage 15% of hypertensive patients (between the two hypertension thresholds)	MULTI-ANNUAL CONTROLLED PROGRAM IN CANTONS
5. Establishment of pharmacological hypertension treatment	- Pharmacological treatment protocols, - Support Plan in decisions, - Tracking and feedback information	Health institutions Coverage 40% of hypertensive patients (second degree hypertension) All team members must be involved in reaching the goal (nurses and pharmacists)	MULTI-ANNUAL CONTROLLED PROGRAM IN CANTONS

Discussion

Despite many efforts to diagnose and treat hypertension, this condition continues to be the leading cause of CV morbidity and mortality. It is therefore extremely important to improve the unsatisfactory treatment and hypertension control.

It is well known that, because of the asymptomatic nature, hypertension may remain undetected for a long time. Therefore, in addition to assessing the prevalence of hypertension in the population, it is necessary to evaluate the level of knowledge of hypertensive individuals about their own hypertension, the degree of treatment and control of hypertension, which is only possible through population survey. Early identification of the scale of the problem, early warning and early response enables timely avoidance of the future outbreaks and "explosion" of the risk factors (35, 36).

There are two preventive strategies for hypertension control described in the literature: population and individual strategies. Population strategy for reducing BP in all countries of the world is cost-effective and is especially recommended to countries with limited financial resources such as Bosnia and Herzegovina. Population strategy allows potential control of diseases incidence in the population. Population approach strongly supports the promotion and improvement of cardiovascular health of the population. Multiple interventions on the risk factors are possible by setting up healthy policies

in the country through multi-sectoral approaches in the community. In the population/community management approach, active involvement of a large number of actors at all three levels of management (strategic, tactical and operational) in the health sector is essential. The health sector as a basic public sector is the first place to start the initiative.

On the other hand, the individual approach to disease prevention does not allow to look at the cause of the disease in the environment and anticipate the course of the disease but requires continuous and significant screening of new high-risk individuals. When it comes to hypertension, the individual approach to risky individuals implies detection, treatment, and effective control of high BP. This approach requires effective treatment, both lifestyle modification and pharmacological treatment.

Since the FB&H is in the transition period of its socio-political development, the health systems must be flexible and ready to provide adequate and timely responses to demographic and social changes, changes in epidemiological patterns of diseases, expectations of health care users for quality and their participation in decision-making, inequalities in health among population groups, as well as on the advancement of science and technology (34, 37). Results from two population surveys conducted in the FB&H in 2002 and 2012 showed that there was no statistically significant difference to the overall prevalence of hypertension, which is still is quite high (40.9% vs. 42%) compared to some neighboring countries (Slovenia, Croatia, and Albania) (22).

Hypertension control in the FB&H is not yet well-organized considering absence of common strategic integrated approach. The current PHC reform, which is being done in family medicine teams and by continuous team training, opens up a lot of possibilities for studying approach to high-risk individuals. This primarily includes detection, early diagnosis, and initiation of hypertension treatment. Changing the attitudes of healthcare workers regarding integrated hypertension management is possible at the actual education organization of health workers.

In the light of previous recommendations, activities should be aimed directly towards a clear identification of health needs. Carefully planned, well-designed and implemented diseases control programs, either as a population or as an individual program, are the only powerful tools to address morbidity problems, using preventive measures (22, 38).

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HIPERTENZIJA – PROBLEM JAVNOG ZDRAVSTVA

Sažetak

Cilj. Cilj ovog rada je predstaviti važnost hipertenzije među stanovništvom za javno zdravstvo, kao jedan od glavnih faktora rizika od KVB, kao i model integrisanog pristupa kontroli hipertenzije na nivou zajednice. **Pozadina**. Uprkos raširenoj svijesti o patofiziologiji i epidemiologiji u razvoju hipertenzije, sposobnosti lakog dijagnosticiranja i dostupnosti efikasnih lijekova, hipertenzija i dalje ima veliku prevalenciju, a uspostavljanje kontrole hipertenzije predstavlja značajan izazov za javno zdravstvo. Visoka prevalencija hipertenzije prisutna je u svim zemljama svijeta, bez obzira na socioekonomski status zemlje. Procjenjuje se da će broj oboljelih od hipertenzije do 2025. godine porasti za 15–20%, a broj oboljelih povećat će se do 1,5 milijarde ljudi u cijelom svijetu. **Metode**. Pregled relevantne literature koja govori o važnosti definiranja jasnih strategija i intervencija u kontroli hipertenzije, s posebnim naglaskom na integrisano upravljanje hipertenzijom koje ima najveći **učinak na ovaj problem**. **Diskusija**. Učinkovita i efikasna kontrola hipertenzije zahtijeva dva pristupa: populacijski pristup i individualni pristup pojedincima visokog rizika. Uravnotežena kombinacija populacijskog pristupa i individualnog pristupa visokorizičnim pojedincima od vitalnog je značaja za efikasnu kontrolu hipertenzije i kardiovaskularnih bolesti. **Zaključci**. Zdravstveni sistemi u svim zemljama moraju biti fleksibilni i spremni pružiti adekvatan model integrisanog pristupa kontroli hipertenzije na nivou zajednice, uzimajući u obzir svoje lokalne potrebe.

Ključne riječi: hipertenzija, kardiovaskularne bolesti, kontrola hipertenzije

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CONCLUSIONS

Healthcare systems develop gradually, under the influence of multitude of factors, the most important of which are:

-
- National history and culture
- Dominant political ideology
- Local geographic and climate conditions
- Socio-economic development.

The risks for cardiovascular diseases are associated with:

- Education indicators
- Investments in infrastructure and urbanisation
- Relationship between different variables of risk from cardiovascular diseases and GDP
- Healthcare investments.

Given the current state of health in Bosnia and Herzegovina, and the potentials of cardiovascular medicine, the Board for Cardiovascular Diseases of the Department of Medical Sciences of the Academy of Sciences and Arts considers the following to be true:

- A systemic approach to controlling cardiovascular diseases is necessary, with the aim of integration into modern trends in medicine, which would result in lower morbidity and mortality from cardiovascular diseases, through monitoring risk factors from foetal period to old age;
- Presented advancements in cardiovascular medicine need to be incorporated into medical practice in healthcare in the Southeast Europe;
- Novelties in paediatric cardiology should be applied with the aim of lowering morbidity and mortality, with focus on neonatal cardiology;
- Monitoring of risk factors for development of cardiovascular diseases should be conducted;
- Diagnostic-therapeutic algorithms of cardiovascular diseases in paediatric and adult population should be applied.

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- Professional promotion of systemic interventions should be conducted, thus advancing healthcare in accordance with the EU guidelines.

We are convinced that the conclusions and data provided by this Symposium shall serve as a good foundation and guidelines for future research, which should include pane analyses with participation of a larger number of all relevant stakeholders in our country, as well as in countries of the Southeast Europe.

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