



## REVIEW

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Appointed as member of the Scientific Jury by Order RD-232/09.04.2019 of the Director of the National Centre of Public Health and Analyses (NCPHA), on the grounds of Art. 30, para. 3 of the Regulations on the Implementation of the Law on the Development of Academic Staff in the Republic of Bulgaria and in connection with Art. 30, para. 2 of Regulations on the Implementation of the Law on the Development of Academic Staff in the Republic of Bulgaria, Art. 4, para. 3, item 6 and Art. 19, para. 1 of the Regulations for the Structure and Activities of the NCPHA, Art. 69 of the Regulations for the conditions and the procedure for acquiring academic degrees and occupying academic positions in the NCPHA and a decision of the Scientific Council of NCPHA, with protocol № 27/08.04.2019.

**REGARDING:** dissertation under the theme of: "Medical and social significance of familial hypercholesterolemia in Bulgaria", with scientific officer Prof. Plamen Dimitrov, MD and Assoc. Prof. Mag. Pharm. Evgeni Grigorov MD, for awarding of scientific degree "Doctor" in professional field 7.1. "Medicine" in specialty "Social Medicine and Health Management", to Dr. Svetoslav Valentinov Tsenov, doctoral candidate with individual preparation at the NCPHA, right of defence awarded by order No RD-234/09.04.2019.

### I. Presentation of the doctoral candidate.

**Dr. Svetoslav Tsenov** was born on 29.12.1981. In 2000, he completed his secondary education in the city of Veliko Tarnovo - High School of Mathematics and Natural Sciences. In 2006, he graduated from the Faculty of Medicine at the Medical University of Sofia, and in 2009 he graduated from the Academy of Economics in Svishtov with specialty "Economics". In 2007, Dr. Tsenov immersed himself in the field of clinical trials and the pharmaceutical industry, initially beginning work at the INC Research Clinical Trial Company and later as a sales representative in Sanofi-Aventis Bulgaria. From 2010 until the end of 2017, Dr. Tsenov worked for the pharmaceutical company Amgen Bulgaria growing in his career from senior manager of the department for treatment of "Bones, Nephrology, Dialysis, and Cardiology" to Marketing Director for Central and Eastern Europe, Manager of Pricing, Access and Policy to Medical Director of the company. In 2018, he became the Executive Director of the Pharmaceutical Company Astellas - Bulgaria and its subdivisions in Romania and Hungary.

Dr. Tsenov is a goal-oriented, has a lot of experience in the pharmaceutical industry, with broad horizons, interests and way of thinking. He has a sound working style and communication, is a convincing team player, possesses a dynamic spirit and leadership skills. He has proficiency of the English language in writing and speaking.

## **II. In regard to the dissertation.**

Cardiovascular diseases (CVD) are a serious health problem in Bulgaria and in other European countries. Each year, they account for over 1,8 million deaths (20% of all deaths) in Europe. In Bulgaria, diseases of the circulatory system (including ischemic heart disease and cerebrovascular disease) cause more than 71,000 deaths per year (66% of all deaths). For 2014 alone, 197 deaths per day due to CVD were reported for Bulgaria.

Large-scale epidemiological studies indicate that the major cause of cardiovascular risk is elevated cholesterol in low-density lipoproteins (LDL-C). Mutations in the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene that increase or inhibit LDLR activity have been shown to affect the overall cardiovascular (CV) risk of the individual.

Familial hypercholesterolemia (FH) is a serious, hereditary disease characterized by consistently elevated LDL-C levels since birth. Affected individuals have a significantly increased risk of major CV events such as myocardial infarction (MI) or stroke, as they are frequently diagnosed with a clinically proven cardiovascular disease from an early age. The lack of effective or clinically appropriate treatment options in FH patients poses the highest risk of a serious CV event due to their exposure to chronically high levels of LDL-C throughout their lives.

This major health problem that is turning out to be an issue for Europe and worldwide is at the core of the dissertation of Dr. Tsenov, specifying it as “medical and social significance of familial hypercholesterolemia in Bulgaria”.

In the period 2017-2018, together with the Society of Cardiologists in Bulgaria, a register of patients with familial hypercholesterolemia was introduced in Bulgaria - the first of its kind for the country. Taking into account the current trends related to cardiovascular risk assessment, data were collected with respect to the risk of a cardiovascular event. The main objective of the database is the determination of the structure of the population with the disease with respect to individual diagnostic indicators, risk factors, accompanying diseases, therapeutic behaviour. The monitoring of disease dynamics and the determination of the risk of cardiovascular diseases are also important. A key moment here is defining the link between the main risk factors, the severity of the disease and the outcome for the patient.

The volume of the dissertation is 155 pages, it contains 29 tables and 52 figures. It includes a short presentation of the dissertation - 2 pages, literature review - 72 pages, which comprises of: introduction - 52 pages, modern treatment of patients with hypercholesterolemia - 10 pages, unmet needs of high-risk patients - 6 pages, and future guidelines - 2 pages. The objective, the hypothesis and the tasks are covered in 1 page, materials and methods - in 1 page, and analysis of the results - in 44 pages. The

discussion and the drawn conclusions and recommendations are covered in 6 pages. The contributions of the dissertation are presented in 2 pages, and the references contains 191 sources, only one of them being by Bulgarian authors. These authors, for the past 5 years alone, are 38.2%, which is an evidence of the relevance of the issue and of the competence of the doctoral candidate in regard to the latest achievements and discussions on familial hypercholesterolemia.

The dissertation is laid out in accordance with the requirements and it presents all the results and conclusions of the conducted research.

It is appropriately structured and is written in correct Bulgarian.

### **1. Relevance of the issue and appropriateness of objectives and tasks.**

*The literature review* on the subject is presented on 72 pages and contains a significant number of subtitles. It begins with the discovery of cholesterol and quoting of the first researcher - Nikolay Anichkov who established the relation between hypercholesterolemia and vascular atherosclerotic plaques and ends with the significance of dyslipidemia and familial hypercholesterolemia in regard to CVD mortality rates in Bulgaria, summarising two very important factors of relevance to the success of ongoing therapy and the prevention of high-risk groups of patients. In his review, Dr. Tsenov demonstrates thorough knowledge of the issue and presents the role of cholesterol on the bio-physical properties of the membrane, the membrane fluidity and its permeability. Appropriately and in the most understandable way, he presents cholesterol metabolism, its role as a precursor in the synthesis of various steroid hormones, hepatic efflux of cholesterol and the role of protein convertase subtilisin/kexin type 9 (PCSK9) as a component for regulating LDL-C cholesterol levels. In the literature review, the doctoral candidate focuses on hypercholesterolemia as a major risk factor for CVD and presents the causes of mortality in Europe for 2012 for both men and women. Worrying is the fact that the proportion of CVD in total mortality rates in women is higher than that of men - 52%, with coronary heart disease accounting for 22% of the mortality rate. These facts alone demonstrate the relevance of the subject and the significance of the issue. Successively, Dr. Tsenov presents the patients with the highest risk for a CVD event, as well as an assessment of coronary risk under the SCORE system and draws up the conclusion that high-risk patients should be identified and treated but also those with moderate risk should receive professional guidance on lifestyle changes and undergo drug therapy in some cases. Special attention is given to the patients with hypercholesterolemia, their prevalence in certain areas of Europe, the diagnosis of FH, and a model for nation-wide screening published in 2015 is presented. Dr. Tsenov identifies the different groups at risk for CVD, the burden of CVD and the economic burden associated with health care costs in different countries – United States, Canada, Asia, Europe. Modern treatment of patients with hyperlipidemia is reviewed as well, where the benefits of lowering LDL-C levels are supported by results from many different clinical studies and meta-analyses. Dr. Tsenov specifies current therapeutic alternatives with statins including some of the recent studies on the issue and presents the clinical guidelines with recommendations for treatment of hypercholesterolemia of the European Society of Cardiology and the European Atherosclerosis Society. The risk categories of the two institutions are appropriately presented, as well as information from the European Association for Cardiovascular Prevention and Rehabilitation on

what the target LDL-C values should be depending on the level of CVD risk. In the final pages of the review, the doctoral candidate presents the latest treatment options with medicinal products intended to cover the unmet medical needs of FH patients or patients with very high risk of a CVD event, treatment with monoclonal antibodies of IgG class (evolocumab and alirocumab, inhibitors of protein convertase subtilisin/kexin type 9 PCSK9). The positive data for the success of evolocumab treatment are part of the referenced 7 clinical trials, three of them being randomised controlled phase 2 trials and one ongoing phase 3 trial. The analyses of safety and tolerance data of evolocumab demonstrate the positive safety and tolerance profile of the drug. The conclusion is that evolocumab has a continuous efficiency, regardless of the demographic characteristics of the patient, the comorbidities, the main therapies and baseline levels of LDL-C and that it has a significantly reduced number of side effects in comparison to alirocumab.

**The subject** of the dissertation is relevant and significant both in scientific and social terms and the doctoral candidate unquestionably demonstrates his professional awareness of the issue and the depth of his knowledge that have allowed him to carry out and analyse the results of the tasks in order to achieve the objective of the dissertation.

**The objective** of this dissertation - "to study and analyse the decisive role of the severe forms of dyslipidemia on cardiovascular diseases and to reveal and systematise the main issues and trends associated with familial hypercholesterolemia, as well as to define the scientific and practical approaches, with the aim of improving the diagnosis, prevention, treatment and monitoring of high-risk patients" - is clear and specific and its implementation assumes clinical, economical and social significance for Bulgaria. In order to achieve the objective, the doctoral candidate has set out 5 specific **tasks** to find solution for, including analysis of the available scientific information, analysis of the economic aspects in Bulgaria and finding the appropriate indicator for the outcome of the treatment. The elaboration of a concept for the establishment of a register of FH patients would lead to the introduction of a practical approach for treatment of severe cases and the possibility of adapting the globally recognised recommendations for algorithm of diagnosis and treatment of FH patients.

In order to find a solution for these tasks, Dr. Tsenov has used a database of patients diagnosed with FH on the basis of the Dutch Lipid Clinical Network Criteria in four regional cities of the Republic of Bulgaria. For the observed period, the database includes 143 patients diagnosed with FH from 4 regional cities and the patients from Sofia are from 3 clinical trial centres. The assessment methods used are general and specific, containing various analyses with graphical and tabular presentation of the results. The pharmaco-economical assessment of the cost-effectiveness is performed by using ETPY (Effectively Treated Patient Years), which in essence means patient-years of effective treatment. The presented methods of analysis are modern and are related to the recommendations for best practices of European (ESC/EAS) and American (ACC/AHA) guidelines for dyslipidemia for CVD.

**The statistical analysis** is performed with the help of the STATISTICA statistical package, using different types of analyses: descriptive, variation, Student's T-test, Framingham risk equation, etc.

**The results** from the study are presented in 42 pages and establish the foundation for the elaboration of performance criteria applicable to Bulgaria, as well as an understanding of the clinical and economic value of LDL-C lowering and CVD prevalence. The presented graphics are visual and comparable in relation to the baseline characteristics of the patients from the register, the distribution by gender, the distribution by lipid status indicators, comparable with or without MI, peripheral arterial disease, smoking and AH, CVD, etc. The graphics are illustrative in regard to the different therapeutic and dose regimes that are comparable to the level of LDL-C cholesterol and the presence of a significant CVD event.

The presentation in the “**Discussion**” section of Dr. Tsenov contains an important economical assessment in the Bulgarian context demonstrating that in HeFH patients the use of evolocumab with standard therapy compared to standard therapy alone results in an increase in costs by almost BGN 13,000 per ETPY (Effectively Treated Patient Year). In analysing this fact, Dr. Tsenov suggests that the people who have the power to award extra budget funds necessary for new technologies are usually facing the constant of a fixed budget and the turning of these “additional budgetary resources” into alternative investments in health care becomes a fact. This is the reason more than 2/3 of the Bulgarian population considering the overall quality of healthcare in their country as bad.

In **conclusion**, Dr. Tsenov points out that CVD are the most common cause of mortality in Bulgaria and the most important modifiable risk factor for CVD is LDL-C. Patients with elevated LDL-C have a 20 times higher risk of developing CVD. Early diagnosis and follow-up of FH patients is an important fact reducing the number of patients with CVD. The serious medical, economic and social aspects in patients with familial hypercholesterolemia are reported at global and European level – the World Health Organization and the European Parliament regard the disease as a major priority in healthcare policies of the countries.

*The drawn logical conclusions* are five, correspond to the tasks, and are clear and specific. An important fact is the elaboration of a comprehensive concept for the establishment of a register in Bulgaria as well as the development of criteria for monitoring the disease. The evaluation of familial hypercholesterolemia in the medical, social and economic context proves the significance of the disease in regard to the cardiovascular risk and the mortality rate. The use of the Dutch Lipid Clinical Network Criteria is particularly beneficial in diagnostic terms, in the cascade screening for early identification in the pre-clinical stage and in the use of registers for determining the basic risk factors. A practical approach to control severe and inherited forms of dyslipidemia is proposed.

**The contributions** of the dissertation of Dr. Tsenov have their own original, medical and social aspect, they are of scientific-theoretical and scientific-applied nature. The subject is the country's first for FH, prevention and treatment of the disease. For the first time, the available therapeutic alternatives for dyslipidemia therapy have been evaluated in terms of unmet medical needs. A thorough analysis of the risk categories of patients is presented, the necessity of greater attention towards FH by society, health authorities and medical specialists has been statistically proven because of its crucial role in the development of CVD and mortality.

Dr. Tsenov has 4 publications related to the dissertation, one of them in a foreign magazine. Three of them cite him as the first author. Dr. Tsenov has also participated in 3 scientific forums with scientific reports.

**In conclusion, I may state that the presented dissertation covers completely, in terms of quality and quantity, the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria and of Art. 69 of the Regulations for the conditions and the procedure for acquiring academic degrees and occupying academic positions in the NCPHA, for awarding of a doctoral degree in higher education area 7. "Health and Sport", professional field 7.1. "Medicine" and scientific specialty "Social Medicine and Health Management", and I recommend to the Honourable Scientific Jury to award to Dr. Svetoslav Tsenov the "Doctor" degree.**

PREPARED BY:

  
(Prof. Dr. B. Bogov, MD)

7 May 2019