

REVIEW

of a dissertation under the subject of “*Medical and social significance of familial hypercholesterolemia in Bulgaria*”, presented for public defence before a scientific jury for awarding “Doctor” degree by **Dr. Svetoslav Valentinov Tsenov**, doctoral candidate with individual preparation in specialty :Social Medicine and Health Management” at the National Centre for Public Health and Analyses.

REVIEWER: Prof. Dr. Petko Nenkov Salchev, MD, Director of “Classification Systems, Standards and Innovations” Directorate, National Centre for Public Health and Analyses.

Elected as a reviewer of the presented dissertation on 16 April 2019 at a meeting of the Scientific Jury appointed 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

SCIENTIFIC OFFICERS:

Prof. Dr. Plamen Dimitrov, MD, Director of “Promotion of Health and Prevention of Diseases” Directorate, Deputy Director of the National Centre for Public Health and Analyses

Assoc. Prof. Mag. Pharm. Evgeni Grigorov, MD, head of “Evaluation of Health Technologies” Department at the “Classification Systems, Standards and Innovations” Directorate of the National Centre for Public Health and Analyses

DATA FROM THE PROFESSIONAL BIOGRAPHY OF THE DOCTORAL CANDIDATE

University education:

In 2006, he completed his higher education - master’s degree, Human Medicine, Medical University -Sofia

In 2009, he was awarded a second master's degree in International Finances by the Academy of Economics, Svishtov.

Professional experience:

From 2007 to 2012, he works as a product manager at Sanofi-Aventis Bulgaria, and then in Amgen Bulgaria. From 2013 to 2014, he is the franchise manager of Amgen for Central and

Eastern Europe, and from 2014 to 2016 he is a senior corporate relations manager at Amgen. In 2017, he became the Medical Director of Amgen Bulgaria. From the beginning of 2018 until this moment, he is the Executive Director of Astellas Bulgaria.

Since 2018, he has been a member of the Ethics Committee of the Association of Research-based Pharmaceutical Manufacturers in Bulgaria.

Since 2019, he has been a Deputy Chairman of the Management Board of the Association of Research-based Pharmaceutical Manufacturers in Bulgaria.

Postgraduate courses:

Dr. Tsenov participates in numerous postgraduate courses in the country and abroad, related to the assessment of health technologies, health management, health insurance models etc.

He has proficiency of the English language in writing and speaking. He has excellent computer skills.

He is a member of the Bulgarian Medical Association, Bulgarian Business Leaders Forum.

Dr. Svetoslav Tsenov has excellent theoretical preparation, vast knowledge and broad general culture. His scientific interests are in the field of epidemiology and pharmaco-economics.

EVALUATION OF PRESENTED DISSERTATION

1. Relevance of the issue

The dissertation of Dr. Svetoslav Tsenov covers one relevant issue for our modern healthcare system, including evaluation of the significance of hereditary forms of severe dyslipidemia on cardiovascular morbidity and mortality. Modern healthcare system models are facing a number of challenges related to the demographic trends of ageing population, increase of chronic diseases and the necessity to ensure better quality of life and reduce the risk for these patients. The rate of increase of healthcare costs is significantly higher than GDP growth in most countries and economies. This is a problem even for the developed economies, which also have difficulties in funding their healthcare systems. That is why the need for assessment, prevention, early diagnosis and prophylaxis of cardiovascular diseases, for reduction and control of the risk factors for their development, such as severe dyslipidemia, are extremely important issues for both the healthcare systems and the society.

The chosen subject of the dissertation is relevant - from scientific and from a practical point of view. Medical and social significance of familial hypercholesterolemia, and the elaboration of practical approaches for its diagnosis, monitoring and treatment, could serve as the basis for making informed decisions in the elaboration and validation of a strategy to reduce cardiovascular morbidity and mortality in our country.

The lack of registers of patients with familial hypercholesterolemia in Bulgaria, as well as the importance to define a clear algorithm for diagnosis and monitoring of these patients gives reasonable grounds for the elaboration of this dissertation. The objective is evident from the title of the topic.

2. Structure and layout of the dissertation

The presented dissertation is structured in accordance with the relevant instructions. The dissertation contains 155 pages with 52 figures and 29 tables. The bibliography consists of 191 literature sources, in Cyrillic and Latin.

The dissertation comprises an introduction, a literature review, an objective, tasks and methodology, results and discussion, conclusions, recommendations and contributions, used literature.

The literature review has a volume of 73 pages. The most important issues related to the problem are accurately and systematically presented. The visualisation of the literature review makes a good impression, with the use of numerous figures and tables, giving the opportunity to follow the development of the concept for cardiovascular diseases, as well as to compare the diagnostic and therapeutic alternatives in accordance with the level of the cardiovascular risk.

Information is presented in regard to global, European and national recommendations for diagnosis and treatment of dyslipidemia, familial hypercholesterolemia, impact on modifiable risk factors for cardiovascular diseases, the importance of the problem and the development of the concept of prevention and screening.

The analysis demonstrates the excellent knowledge on the issue of the doctoral candidate. Many paragraphs contain a critical analysis accompanied by a presentation of the personal views of the author.

The literature review is based on 191 sources by Bulgarian and foreign authors. The bibliographic reference contains publications from the last 5 years. The used materials are an evidence of the good knowledge on the subject by the doctoral candidate. Quotations are correct and accurate. As a whole, the literature review confirms Dr. Tsenov's extensive preparation on the subject. The language is clear and accurate.

The creative assessment of the literary materials in the end of the review presents the future guidelines for finding solutions to the problem. Dr. Tsenov summarises the relevance and importance of dyslipidemia and familial hypercholesterolemia in terms of cardiovascular morbidity and mortality, including in Bulgaria. He puts forward two main factors - timely diagnosis and prevention and modern treatment, with clearly defined possibilities for their implementation in our country, in accordance with specific algorithms.

Analysing the data from the literature review, the doctoral candidate logically concludes on the objective of his research and clearly and precisely formulates the tasks for its implementation.

The dissertation is presented in clear and accurate language and is a complete reflection of the problems and conclusions developed.

3. Objective, tasks and methodology of the research

The objective and the tasks of the dissertation are precisely formulated and correspond to the title. There are 5 specific tasks and their implementation is in line with the set main objective and the verification of the hypotheses. The tasks have required the author's own contribution. The object and the subject of the research are clearly and precisely defined.

The author examines data from the available scientific information worldwide in regard to the development of familial hypercholesterolemia and its importance for cardiovascular diseases. The next step is the collection and analysis of data in regard to the economic aspects in the treatment of familial hypercholesterolemia in Bulgaria and establishment of an appropriate indicator measuring the outcome of treatment in real-life conditions. The proposed indicator is a new one and is used in evaluating the cost-effectiveness in rheumatoid arthritis at the time of preparation of the dissertation. A key moment is the development of a comprehensive concept for the introduction of a register of patients with familial hypercholesterolemia in Bulgaria as well as criteria for monitoring the disease. The final step is related to the establishment of a practical approach to control severe and inherited forms of dyslipidemia and monitor patients.

4. Results and discussion

The results are well presented and visualised on 47 pages and fully cover all the tasks set out by the doctoral candidate. In this section, the results are well illustrated in tables and figures. Obtained results are correctly interpreted, namely:

1. Early diagnosis and monitoring of patients with familial hypercholesterolemia, as well as the prevention of cardiovascular diseases in them, is an increasingly relevant issue. The application of the Dutch Lipid Clinical Network Criteria and the conduct of cascade screenings will help improve the outcomes in this high-risk population.

2. The onset of a register for patients with familial hypercholesterolemia monitors disease dynamics and determines the risk of cardiovascular diseases. It is important to note the need to control the modifiable risk factors and determine how their dynamics change the cardiovascular risk for the patient. This, however, requires long-term follow-up of patients, an increase in the number of patients in the database, as well as expanding the range of monitored risk factors. The results of the register confirm for Bulgaria the established dependencies worldwide between familial hypercholesterolemia and the risk of cardiovascular morbidity and mortality, namely - high percentage of patients with FH and myocardial infarction, history of premature cardiovascular events, heredity. Also, a very small percentage of treated patients achieve the target values of LDL-C, as evidenced by randomised clinical trials in Europe and the United States. On the other hand, the pathognomonic findings -

corneal arcus and tendon xanthomas, are observed in an extremely small portion of diagnosed patients, despite the definitive nature of the diagnosis.

3. One of the major problems in patients with familial hypercholesterolemia is the inability to achieve target levels of LDL-C with the conventional anti-lipid therapy - therapy with statins. PCSK9 inhibitors offer effective treatment for these patients, providing a rapid and intense reduction in LDL-C levels only one week after the beginning of the treatment. It is important to determine the economic feasibility of the administration of PCSK9 inhibitors. The continued reduction in LDL-C of at least 50% is an important therapeutic target for patients with a very high risk of cardiovascular events, and the ones that achieve this target may be regarded as effectively treated. The economic analyses show that evolocumab is a high-value effective therapy in this aspect. Moreover, it has been estimated that avoiding a single cardiovascular event is achieved in the treatment of only 7 patients with evolocumab. This also confirms the data from randomised clinical trials demonstrating the cost-effectiveness of evolocumab in FH patients.

5. Conclusions, recommendations and contributions

The five main conclusions presented by Dr. Tsenov characterise the obtained results in detail. They are clearly and precisely formulated and are a result of the precise implementation of the objective and the tasks of the dissertation.

The dissertation has significant contributions of theoretical-cognitive and applied nature. The main contributions are as follows:

1. The objective, the contents and the importance of the first register of patients with familial hypercholesterolemia in Bulgaria have been presented.
2. A practical algorithm for early diagnosis has been proposed using the Dutch Lipid Clinical Network Criteria and the cascade screening for patients with familial hypercholesterolemia.
3. 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 formation of cardiovascular morbidity and mortality.
4. The potential patient populations with maximum effects from the use of PCSK9 inhibitors and the clinical and economic benefits of the new therapeutic options have been studied and evaluated.

I have no remarks and recommendations on the results and conclusions. Dr. Tsenov uses the obtained data appropriately and the analysis is objective.

The dissertation is the basis of 5 publications, one of them international.

Assessment of the professional and personal qualities of the doctoral candidate

I highly appreciate his theoretical knowledge and practical skills. In the course of the dissertation, he demonstrates skills for using literature sources, methodical and computer literacy and teamwork necessary for the successful elaboration of the dissertation. He demonstrates his analytical abilities in designing scientific publications and reports and in their attractive presentation.

Dr. Tsenov knows how to apply the scientific methods of analysis and synthesis, showing skills for an in-depth examination of the available literature, fluent in the application of scientific methods and approaches in the elaboration of the dissertation and in the correct interpretation of the available data and facts.

6. Conclusion

With the development of the dissertation topic, Dr. Svetoslav Tsenov has set an ambitious task, which he has completed perfectly. The dissertation **contains scientific and applied research results that represent an original contribution and cover all** the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria and the Regulations on the implementation of the Law on the Development of Academic Staff in the Republic of Bulgaria. The presented materials and dissertation results cover **completely** the specific requirements for the application of the Law on the Development of Academic Staff in the Republic of Bulgaria. The dissertation is complete, written in professional, appropriate and precise manner. The doctoral candidate meets the necessary criteria for awarding of the scientific degree “Doctor” under the Law on the Development of Academic Staff in the Republic of Bulgaria.

The dissertation shows that the doctoral candidate Dr. Svetoslav Valentinov Tsenov **possesses** in-depth theoretical knowledge and professional skills in the scientific specialty and **demonstrates** qualities and skills for the conduct of an independent research.

My assessment of the dissertation of Dr. Svetoslav Tzenov is positive. In view of the above, I give my **positive opinion** on the above dissertation, the achieved results and contributions and I **propose** to the Scientific Jury to give a positive assessment of the dissertation “Medical and social significance of familial hypercholesterolemia in Bulgaria” for awarding of scientific degree “DOCTOR” to the doctoral candidate Dr. Svetoslav Valentinov Tsenov, for which I will personally give a positive vote.

May 2019

Reviewer:



Prof. Dr. Petko Salchev, MD