

STATEMENT

**By Assoc. Prof. Desislava Ivanova Vankova, MD, MPH, PhD
about the PhD thesis of Dr. Svetoslav Valentinov Tzenov
with a title "Medico-social significance
of familial hypercholesterolemia in Bulgaria"**

By Order № ПД-232 / 09.04.2019 of the NCPHA Director I have been appointed as a member of the Scientific jury for the PhD-procedure with a statement regarding the PhD thesis of Dr. Svetoslav Valentinov Tzenov, independent-training PhD-student at NCPHA, Sofia, in the professional field: 7.1. Medicine, scientific specialty "Social medicine and health care management".

The statement was prepared after an analysis of the presented documentation by the applicant in accordance with the requirements and criteria of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations for the conditions and the order for acquiring academic degrees at NCPHA.

PhD-candidate data

Dr. Svetoslav Valentinov Tsenov graduated from the Mathematics and Natural Sciences School, profile: Biology, Chemistry, English in his hometown of Veliko Tarnovo in 2000. He graduated in Medicine at Sofia Medical University in 2006 and then graduated in Economics at the Svishtov Academy of Economics in 2008-2009. Dr. Tsenov has extensive professional experience in multinational pharmaceutical companies. Immediately after completing his medical education, Dr. Tsenov started working consecutively as a specialist in clinical research, level II (INC Research); as Medical representative, Product & Sales Manager „Oncology and rheumatology“ (Sanofi-Aventis Bulgaria- 2007-2009); as Senior Manager of the Department „Bones, nephrology, dialysis and cardiology“- 2010-2014, Marketing Director of Bone franchise for Central and Eastern Europe - 2013-2014, Market Access Manager- 2014-2017, Medical Director - May, 2017 – Dec., 2017 (Amgen Bulgaria). Since Jan, 2018 Dr Tcenov has been an Executive Director of Astellas Bulgaria. He climbed the classical career ladder, starting at the bottom and getting to the top, to positions with the highest responsibilities in a company, which is a convincing proof of personal characteristics such as purposefulness, consistency, responsibility and commitment to work. These qualities are also important for the PhD and research processes. Dr. Tsenov has applied a structured and in-depth approach to his research work, which is a reflection and a natural continuation of his overall professional and personal development.

Relevance of the PhD-dissertation

Overall, the subject of the dissertation is modern, interesting, and up-to-date. This fact demonstrates the PhD-candidate's excellent knowledge of the national and worldwide medico-social significance of the familial hypercholesterolemia (FH). Representative epidemiological studies have proven that high cholesterol in low-density lipoprotein (LDL-C) is a major cause of the cardiovascular risks. According to the 2018 European Commission report, cardiovascular diseases are the leading cause of mortality in Bulgaria, which is three times higher than the average for Europe. However, mortality data only provides information on the tip of the iceberg because it only shows the worst cardiovascular incidents that have led to death. The World Health Organization (WHO) points out that the only valid source of information related to a particular health problem are the registries. In Bulgaria there are no hospital or population registries of diseases leading to increased cardiovascular risk incl. FH - a serious, inherited disease characterized by steadily elevated LDL-C levels since birth.

Affected individuals are among the people who are at the highest risk of cardiovascular events, and the lack of effective or clinically appropriate treatment options places patients with FH at the highest risk of a severe cardiovascular event due to their chronic lifetime exposure to high levels of LDL-C. On the other hand, relatives with such genes may not have a manifested disease. Therefore, the possibility of early prophylaxis is a key issue in FH. Due to the hereditary nature of the disease, the primary goal should be to reduce both the modifiable risk factors and early diagnosis. The lack of a scientific research in this direction in our country strengthens the relevance of this PhD-dissertation.

Characteristics of the PhD-dissertation

The PhD-dissertation contains 155 pages, including 29 tables and 52 figures. The bibliography consists of 191 scientific sources, both in Cyrillic and in English. Regarding the PhD-research, 4 articles were published. The PhD candidate is a leading author in the three of them.

The dissertation is structured in fourteen chapters. In the first five chapters a literature review is made covering the history of the disease and related pharmacological and medico-social aspects. Overall, a comprehensive overview and analysis of the available scientific information worldwide has been carried out on the global burden of cardiovascular diseases, which is a major public health challenge. The weight of risk factors such as overweight, immobilization, unhealthy eating, smoking, dyslipidemias, etc. are emphasized. Information on contemporary treatments of patients with hyperlipidemias is summarised and the unsatisfied medical needs in patients at high risk patients are presented. Further, data was collected and analysed on the economic aspects of FH treatment in Bulgaria in the direction of finding an appropriate indicator measuring the outcome of a treatment in real-life conditions.

The **aim** and five study objects are clearly formulated. The aim of this PhD-dissertation is to investigate and analyze the determining role of the severe forms of dyslipidemia on the cardiovascular diseases and to reveal and systematize the main problems and trends related to familial hypercholesterolemia, as well as to define scientific and practical approaches in order to improving the diagnosis, prevention, treatment and follow-up of high-risk patients. The scientific hypotheses are formulated in two directions: 1) The severe forms of dyslipidemia and hypercholesterolemia, in particular FH, are a determining factor in the development of cardiovascular diseases in Europe and in Bulgaria. 2) The early diagnosis, prophylaxis, treatment, and follow-up of these conditions would be essential to improve the clinical, economic and social prognosis for the high-risk population.

The **methodology** of the study is well grounded. The location of the survey related to the establishment of the register are hospitals in four cities in Bulgaria (Varna, Plovdiv, Pleven and Sofia). The study period is from January 2017 to June 2018. The Databases with patients diagnosed with FH were made according to the Dutch Lipid Clinical Network Criteria. The applied methodology combines the advantages of classical quantitative methods with the capabilities of pharmacoeconomics analysis - an evaluation of value-effectiveness through the use of the innovative efficacy criterion based on the quality of care: Efficient Patient-Efficient Patient Years (ETPY). Statistical methods are correctly selected and applied. A wide range of statistical methods and indicators are used.

The **results** are presented and discussed in depth in 10th and 11th chapters. The analysis is clearly structured for each of the two parts of the study: 1) results from the FH patients register in Bulgaria and 2) results from the study of the clinical and economic value of the decrease of LDC-C.

1) In the period 2017-2018 along with the Society of Cardiologists in Bulgaria, the first hospital registry of patients with familial hypercholesterolaemia in Bulgaria was established. The size of the patient population is a total of 143 patients from the four cities. Patients were evaluated using the Dutch Lipid Clinical Network Criteria. Data was also collected on the risk of a cardiovascular event. The main observed parameters are: age, sex, height, weight, BMI, history of hypercholesterolemia, clinical criteria of the Dutch Lipid Network. Data on risk factors for development of cardiovascular disease - diabetes, myocardial infarction, peripheral vascular disease, and smoking - are also collected. The registry also includes the individual lab indicators - total cholesterol, LDL, HDL, triglycerides. Concomitant anti-lipid treatment (type and duration), as well as target LDL and time-achievement were followed. The main objective of the database of patients with FH in Bulgaria is to determine the structure of the population with the disease in terms of the individual diagnostic indicators, risk factors, concomitant diseases, therapeutic behavior. A key point is defining the relationship between the main risk factors, the severity of the disease and the outcome for the patient, which is done by appropriate statistical methods.

2) Results of the study on the clinical and economic value of LDL-C decrease: The purpose of the study was to evaluate the effectiveness of specific therapeutic approaches through an adapted already published cohort model of Markov's conditional transitions, the relevance of which has been demonstrated in the health technologies assessment processes. The perspective of consumers in Bulgaria and the duration of lifelong treatment has been taken into account. Such analysis is an important part of the overall assessment process of any health technology.

The conclusions and recommendations are outlined in chapter 12 and the results are summarized in clinical, medico-social and health-economic contexts.

Contributions of the PhD-dissertation

Scientific and theoretical contributions: The study has a pronounced innovative character regarding scope and methodology. The problem of dyslipidemia with regard to the risk of developing cardiovascular disease is defined extensively and in depth. A comprehensive analysis of the risk categories of patients was carried out in accordance with the European and American guidelines. The available alternatives for the treatment of dyslipidemias have been evaluated for the first time in terms of unmet medical needs.

Applied scientific contributions: The study shows how a hospital registry can be created in real-life practice. The purpose, content and meaning of the first national register of patients with FH is presented.

A comprehensive concept was developed for creating a register of patients with familial hypercholesterolemia in Bulgaria as well as criteria for disease monitoring. It is clear that FH is an easy and accessible clinical diagnosis through the criteria of the Dutch Lipid Clinic Network. Adaptation and exploration of the possibilities for introducing globally recognized recommendations for a diagnosis and treatment algorithm in FH has been made. A practical approach has been put in place to overcome severe and inherited forms of dyslipidemia and to monitor patients. Statistically proven was the necessity to attract more attention from society, health authorities and medical specialists regarding the FH problem in Bulgaria. Moreover, the FH problem in Bulgaria plays a crucial role in the cardiovascular disease prevalence and mortality. The potential patient populations with maximum therapeutic effect of PCSK9 inhibitors use have been studied and evaluated and new therapeutic options are outlined regarding clinical and economic benefits.

Conclusion

The presented PhD-dissertation is relevant, original and methodologically innovative. The recommendations to the PhD-candidate are mainly in the direction of sustainability of the FH hospital registry in Bulgaria. The dissertation takes into account the fact that it is necessary to control the modifiable risk factors and to determine how their dynamics change the cardiovascular risk for the patient. There is a need for continued patient follow-up, an increase in the number of patients in the database. Possible next step is the creation of a population registry associated with hyperlipidemias and in particular with FH.

The dissertation with a title "Medico-social significance of familial hypercholesterolemia in Bulgaria" fully meets all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for the implementation of this Law and the Regulations for the conditions and procedure for acquiring academic degrees and occupation of academic positions in NCPHA, Sofia, Bulgaria. The work also covers the uniform minimum requirements for obtaining the educational and scientific degree "Doctor", which is why I give my **positive opinion** and I offer to the honorable members of the Scientific Jury to vote positively for awarding the educational and scientific degree "Doctor" or PHD to Dr. SVETOSLAV VALENTINOV TCENOV in the professional field: 7.1. Medicine, scientific specialty "Social medicine and healthcare management".

Varna
16 of May 2019

Statement author:



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