

OPINION

on a doctoral dissertation under the topic: **Medical and social significance**

**of familial hypercholesterolemia
in Bulgaria**



Author of the dissertation:

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Member of the Scientific Jury preparing the opinion - Prof. Dr. Arman Shnork Postadzhyan, MD, UMPHAT “Sv. Anna”, Medical University, Sofia

The opinion has been drafted in accordance with the Law on the Development of Academic Staff, the Regulations on the implementation of the Law on the Development of Academic Staff and the Regulations for the conditions and the procedure for acquiring academic degrees and occupying academic positions at the Medical University - Sofia.

The dissertation has been discussed, adopted and referred for consideration by the extended Collegium of the “Promotion of Health and Disease Prevention” Directorate at the National Centre of Public Health and Analyses conducted on 29 March 2019 on the basis of Order No ПД-137/06.03.2019 of the Director of NCPHA.

The set of materials and documents provided by Dr. Svetoslav Tsenov on paper and in electronic form complies with the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria and the Regulations on its implementation under the procedure for awarding of a doctoral degree.

Dr. Svetoslav Valentinov Tsenov was born on 29 December 1981. He completed his higher medical education at the Medical University of Sofia in 2006, and in 2009 he graduated from the Academy of Economics in Svishtov with specialty “Economics”. In 2006, he started work as Clinical Studies Specialist, Level II at INC Research, successively going through the following positions: Sales Representative, Product and Sales Manager for Oncology and Rheumatology

(Sanofi-Aventis Bulgaria EOOD), and during the period 2010 - March 2014, he is the Senior Manager of the Treatment Department - bones, nephrology, dialysis and cardiology. In parallel with this, in 2013 - 2014 he is the Marketing Director of the Bone Franchise for Central and Eastern Europe. As such, he is responsible for the development and implementation of the Bone Franchise Strategy in Central and Eastern Europe. From 2014 to 2017, Dr. Tsenov is the Manager of Pricing, Access and Policy at Amgen, Bulgaria, where he is involved in defining the strategic direction for the future development of the portfolio of Amgen - stream products and downstream products in Bulgaria. He is a team leader for market access, government relations, and corporate affairs. He is responsible for the relations with the government - the Treatment Fund, the Ministry of Health, the Healthcare Committee, the Bulgarian Medical Association, NGOs. From May 2017 to December 2017, Dr. Svetoslav Tsenov is the Medical Director of Amgen, Bulgaria. He is the chair of ARPharm's workgroups on biotechnology, osteoporosis and health technology assessment. He is a member of the Board of ARPharm and Amgen's European top managers program - "Horizon". From January 2018 until this moment, he is the Executive Director of Astellas, Bulgaria.

Dr. Tsenov has completed in due time all the tasks and activities specified in the individual curriculum. He has successfully passed a doctoral minimum exam in the specialty and on methodology of scientific research.

In 2017, the European Atherosclerosis Society in collaboration with the European Society of Cardiology published a consensus document bringing together our present knowledge of epidemiological, clinical and genetic research and clearly showing the pathogenetic relationship between elevated LDL-cholesterol levels and subsequent atherosclerotic cardiovascular diseases – myocardial infarction, stroke and peripheral-artery disease. The significance of this document for the clinical practice in our country is underlined by several facts:

- ✓ Cardiovascular diseases account for 62-66% of deaths in the country, according to data of the NCPHA at the MH of the Republic of Bulgaria
- ✓ Outside of other present risk factors, conducted epidemiological studies find out that more than 50% of individuals over 18 years of age have elevated levels of total cholesterol - above 5 mmol/l, and 16-18% - above 6,2 mmol/l
- ✓ There is no register in the country of persons with the most pronounced unmet needs – those with familial hypercholesterolemia and those with high or very high risk of future vascular incidents

- ✓ The assessment of conducted therapeutic interventions for lifestyle changes and the pharmacological interventions are efficient in up to 25-30% of the cases and determine the need of additional efforts for identification of the risk of an individual patient and of expansion of the opportunities for screening and access to efficient therapeutic solutions aimed at reduction of global cardiovascular risk

In countries with established traditions in the development of prophylactic programs, such a strategy has led to significant success in the early identification of patients at risk. A typical example in this regard is the conduct of cascade screening for familial hyperlipidemia and the establishment of programs for secondary prophylaxis after an atherothrombotic incident.

This data justifies the selection of a topic by Dr. Tsenov - Medical and social significance of familial hypercholesterolemia in Bulgaria. The literature review as a systematic and analytical approach to investigating available information is an evidence of the doctoral candidate being a leading expert on the subject.

The objective of this dissertation is clear and concise - 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. In order to be achieved, a database has been used of 143 patients diagnosed with familial hypercholesterolemia in accordance with the assessment criteria under the Dutch Lipid Clinical Network Criteria from four district hospitals in Bulgaria for a period of 18 months. The main observed parameters are as follows: age, gender, height, weight, BMI; history of hypercholesterolemia; risk factors for developing cardiovascular diseases – diabetes, myocardial infarction, stroke, peripheral vascular disease, smoking; laboratory indicators – total cholesterol, LDL, HDL, triglycerides; concomitant anti-lipid treatment – type and duration; target value of LDL and its reaching over time; presence of hypertension and possible treatment; contraindications for anti-lipid treatment.

In the period 2017-2018, a register of patients with familial hypercholesterolemia was introduced in Bulgaria - the first of its kind in the country. The main objective of this register is to dynamically monitor patients - assessment of risk factors, laboratory parameters, lipid profile and treatment.

The clinical criteria of the Dutch Lipid Network have been used as a defining criterion for diagnosis of familial hypercholesterolemia because they are easy and fast to implement, and

on the other hand, they include various aspects of the diagnosis – history, incl. family, symptoms, laboratory indicators, possible genetic diagnosis.

The main results of Dr. Tsenov's work may be summarised as follows:

- ✓ In patients diagnosed with familial hypercholesterolemia, gender distribution is evenly balanced, i.e., there is no dependency between the prevalence of familial hypercholesterolemia and the gender of affected individuals.
- ✓ Patients with LDL-C values between 5 and 10 mmol/l prevail, which, according to the Dutch Lipid Clinical Network Criteria, adds between 3 and 8 points in the final assessment for a diagnosis of familial hypercholesterolemia and confirms the fact that the defining indicator for the diagnosis is the value of LDL-C in combination with at least one more factor.
- ✓ In terms of family history – 63.6% of patients with familial hypercholesterolemia have a first-degree relative with premature cardiovascular disease, 42.7% have a relative with hypercholesterolemia, and only 2.1% have a child with elevated LDL levels. Given the family nature of the disease, the high percentage of patients with established family history confirms the probability of familial hypercholesterolemia.
- ✓ 51% first-degree relatives have premature coronary disease, and 19.6% have premature cerebrovascular disease. These results confirm the significance of cardiovascular pathology for diagnosis in comparison to cerebrovascular pathology.
- ✓ 135 out of 143 patients with diagnosed familial hypercholesterolemia receive lipid-lowering therapy. However, none of the patients at the time of inclusion in the database has achieved target LDL-C values.
- ✓ On the basis of evidence-based guidelines for prevention, a disease-specific efficiency criterion has been established - Effectively Treated Patient Years (ETPY) - and subsequently used in an economic model that compares the addition of evolocumab to SoC (Standard of Care) against only SoC in patients with HeFH. This analysis demonstrates the clinical and economic value of lowering LDL-C with evolocumab from the point of view of the Bulgarian public health system.

The comprehensive review and analysis of the information on familial hypercholesterolemia shows a direct correlation between the existence, the risk of development and the severity of cardiovascular diseases.

Patients with heterozygous familial hypercholesterolemia are particularly vulnerable to CVD events; in the absence of treatment, the likelihood of premature coronary heart disease (CHD) is increased about 20 times. Most of these patients do not achieve adequate reduction of LDL-C despite the lipid-lowering therapy at the current Standard of Care (SoC) putting them at risk for CVD that is 10 times higher than the risk for patients without FH when receiving similar drugs to lower LDL-C. The inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged as an innovative therapy for lowering LDL-C. Evolocumab is the first PCSK9 inhibitor that demonstrates significant reduction in the prevalence of serious CVD events and regression or stabilisation of the atherosclerotic plaque. The results of a study in HeFH patients indicate that the addition of evolucumab to SoC (i.e., high-intensity statin therapy) leads to a decrease in LDL-C levels by about 60%.

The candidate has published four articles related to the topic of the dissertation. The dissertation comprises of 155 pages, including 29 tables and 52 figures. The bibliography includes 191 literary sources, in Cyrillic and Latin.

Based on these facts, the scientific activity during the drafting period has been evaluated as optimal.

Conclusion:

In conclusion, the dissertation presented by **Dr. Svetoslav Valentinov Tsenov** contains scientific, applied scientific and applied results which provide for an original contribution to science and exceed the requirements for awarding of a doctoral degree. The dissertation proves that the doctoral candidate possesses in-depth theoretical knowledge and professional skills in the scientific specialty and demonstrates qualities and skills for the conduct of an independent research.

On these grounds, I propose to the Honourable Members of the Scientific Jury to cast a positive vote and to award a doctoral degree in specialty "Social Medicine and Health Management" at the "Promotion of Health and Prevention of Diseases" Directorate of the National Centre for Public Health and Analyses at the Ministry of Health to Dr. Svetoslav Valentinov Tsenov.

10 May 2019

Prof. Dr. Arman Postadzhiyan, MD

A handwritten signature in blue ink, appearing to read 'Arman Postadzhiyan', with a large, stylized initial 'A' on the left.

Medical University , Sofia

Member of the Scientific Jury