**OPINION**

On the dissertation for awarding the educational and scientific degree "PhD" on the topic:

"MULTIFOCAL ATHEROSCLEROSIS - DIAGNOSTIC AND PROGNOSTIC MARKERS IN DIFFERENT VESSEL SWIMMING POOLS"

Author of the dissertation: Dr. Elitsa Rashkova Gerova - Micic - PhD student regular training in the Angiology clinic, Acibadem City Clinic Tokuda Hospital EAD

Scientific adviser: Prof. Dr. M. Staneva , PhD

Author of the opinion: Prof. Dr. K. Karamfilov, PhD, Head of the Cardiology Clinic at the University Hospital "Alexandrovska", Department of Internal Medicine, Medical Faculty, Medical University of Sofia.

Member of the jury for awarding the scientific and educational degree "PhD", determined by order of the Executive Director and Procurator of Acibadem City Clinic UMHAT Tokuda EAD № 15-05-71 / 04.04.2022

Professional biography: Dr. Gerova was born in 1988, graduated from the Secondary School "Ivan Vazov" in Plovdiv. Since 2014 he has been a doctor in the Department of Vascular Surgery at Sofiamed University Hospital, Sofia. Dr. Gerova majored in Angiology in 2020.

He is a member of the European Society of Vascular Surgery and the Bulgarian Society of Vascular and Endovascular Surgery and Angiology, as well as the MMA.

Assessment of the topicality of the topic: The topic developed by Dr. Gerova is well chosen in terms of relevance and practical benefit. Atherosclerosis is a chronically progressive inflammatory and degenerative disease of the arterial system. One of the main characteristics of the process is its multifocality, there is no vascular pool that is spared from the development of atherosclerosis. The more vascular areas are affected, the higher risk for the patient and the worse his prognosis. In most cases, the clinical manifestation of atherosclerosis occurs with the development of acute and ischemic and thrombotic complications. Therefore, significant efforts are focused on the early diagnosis of patients with atherosclerosis

The rapid development of imaging methods has led to a better understanding of atherosclerotic changes in blood vessels, which in turn has significantly improved the diagnosis. However, there is still no complete model integrating clinical, imaging and laboratory data that can be used as screening in real clinical practice, to predict the development of atherosclerosis and to have prognostic value. Therefore, the in-depth study of the multifocality of atherosclerosis and the role of diagnostic ultrasound is relevant and has significant practical application.

Structure of the dissertation: The dissertation of Dr. Gerova is written on 170 pages and is illustrated with 90 tables and 19 figures. It is structured as follows: Contents - 3 pages, Abbreviations and symbols used - 2 pages Introduction and Literary review - 21 pages, Purpose, Tasks - 1 page, Materials and methods - 17 pages, Own results and discussion - 98 pages , Conclusions and Recommendations - 3 pages, Bibliography - 19 pagesр Appendix - 4 pages. From these data it can be seen that the dissertation is optimally structured, with a good balance between its parts.

A total of 208 literary sources were used, of which 15 Bulgarian and 193 foreign. They are arranged alphabetically.

Literature review: Within 21 pages of literature review, the pathogenesis and various forms of atherosclerosis with involvement of various vascular basins are thoroughly examined. The author demonstrates a very good knowledge of the literature on the subject. Based on the literature review, the dissertation student draws many important conclusions as a transition to the methodology of the study and summarizes the resolved and controversial issues in the field.

Methodology of the research - Purpose, tasks, materials and methods: Based on the in-depth and generalized literature review, the conclusions from it and the solved and unresolved issues, the prerequisites for the research are derived. Dr. Gerova formulates precisely and clearly the purpose of the study - Study of the multifocality of atherosclerosis as a pathological process in order to identify and offer prognostic and diagnostic ultrasound markers.

To achieve this goal, 6 tasks have been set, implemented in full:

1. To study the incidence of multifocal atherosclerosis in patients with peripheral atherosclerosis.

2. To determine the clinical characteristics and risk profile of patients with peripheral and multifocal atherosclerosis.

3. To study with ultrasound methods the morphological (DIMC, plaques, stenoses) changes of the carotid and peripheral arteries (femoral, foot arteries and abdominal aorta) in patients with peripheral atherosclerosis.

4. To determine the relationship between atherosclerotic risk factors and data from ultrasound morphological changes of the carotid and peripheral arteries in patients with multifocal atherosclerosis.

5. To analyze the morphological changes of the carotid, femoral, coronary arteries and abdominal aorta and to evaluate as markers and predictors of atherosclerosis.

6. To develop and propose a set of diagnostic and prognostic markers to optimize the screening and diagnosis of multifocal atherosclerosis

A sufficient number of patients were used to solve the set tasks - 240 divided into five groups. 1st group control, 2nd group only with HANK, 3rd group with involvement of two basins simultaneously (respectively A - HANK and carotids and B - HANK and coronary), 4th group - three pools, conditionally called 5th group - HANK with revascularization from the total group of 200 patients), which was followed for 2 years.

The extremely in-depth and complete imaging diagnostics in the studied population is impressive.

Results and discussion: The presented results are convincing. They are presented clearly and precisely - both for the whole contingent studied and for the individual groups. To obtain them, fully appropriate statistical methods were used, using the specialized statistical package SPSS (Statistical Package for the Social Sciences) version 23.

The results confirm data from previous studies in patients with atherosclerosis regarding the dependence of the risk of adverse events with an increase in the number of affected vascular basins. The risk factors leading to the development of the atherosclerotic process are clearly identified. In patients with advanced atherosclerosis, specific ultrasound and laboratory parameters are indicated to indicate an increased risk. A clear association between ABI values ​​and the likelihood of surviving IMI has been identified. The results for the frequency of distribution of thrombosis of the peripheral arterial system are also important. The results of drug treatment in these high-risk patients clearly highlight the importance of aggressive lipid lowering and antiplatelet therapy.

One of the significant achievements of this dissertation is the Complex of diagnostic and prognostic markers for optimizing screening and diagnostics for multifocal atherosclerosis and Algorithm for optimizing the diagnosis and therapeutic behavior in patients with multifocal atherosclerosis.

Conclusions and Recommendations - on the basis of the dissertation the following 17 conclusions are formulated corresponding to the obtained results.

1. In patients with HANK a high frequency (55%) of multifocal atherosclerosis. Impact in two areas (HANK and IBS / HANK and SME) is diagnosed in 40.4%, and in three (HANK and IBS andSMEs) - at 14.6%.

2. The risk profile of patients for prediction and development of atherosclerotic process is determined by the following factors: male gender, age over 65 years, presence of AH, DM, family burden, exercise, dyslipidemia. The at-risk patient is a man of average age 68 years with HANK, AH, family burden. If available on these factors the risk of developing multifocal is established atherosclerotic process.

3. The first five risk factors in all patients are family history, hypertension, male gender, smoking and alcohol. For survivors of IMI and AMI, the most important quantitative factors are LDL and HDL, and for patients with high CA and FCA AMD, age and cholesterol levels.

4. Diabetes mellitus is a risk factor for HANK and its severity and duration are associated with a more advanced stage of vascular involvement.

5. Patients with HANK have pathological structural and functional changes in the following ultrasound parameters: DIM ICAb, DIM ICA, DIM FCA, plaque, stenosis, thrombosis of carotid and femoral arteries, ABI <0.9, as a sign and markers of multifocal atherosclerotic process.

6. There is an inverse relationship between ABI levels and the likelihood of experiencing IMI - the lower the ABI levels, the higher the likelihood of developing IMI. When the ABI reaches levels of 0.2 then the probability of developing IMI becomes over 50%.

7. In patients with HANK, stenosis of the aoiliac segment is found in almost 1/3 of the patients. Aortic segment thrombosis is diagnosed in just over 1/10. In patients with MSD, thrombosis of the aorto-iliac segment is diagnosed more often (20%) than those without MSB (9.2-9.7%). Aorto-iliac segment thrombosis can be used as a predictor of SMEs.

8. Femoropopliteal segment thrombosis was found in almost half of the studied patients. Stenosis of the femoropopliteal segment bilaterally is found much less frequently. There is a tendency for a higher incidence of femoropopliteal segment thrombosis in patients with coronary heart disease (58.5%) compared to those without (45.2%), as well as in patients with SME (57.0%) compared to those with without (44.0%).

The significant association between femoropopliteal thrombosis and coronary heart disease and / or MSD may be a predictor of multifocal atherosclerosis (MSB and / or coronary heart disease).

9. An important factor in determining the possibility of atherosclerotic process in the cerebrovascular basin in patients with HANK is the statistically significant inversely proportional relationship between CA DIM and ABI - the lower the ABI, the higher the DIM of CA, most often on CCAbif. and ICA.

10. Patients with high levels of DIM are most often men between the ages of 69 and 70, who use alcohol and cigarettes, with an obesity index of 26-27, with a family history and hypertension, as well as the presence of stage III HANK. With cholesterol levels of 5.60-5.70, triglycerides 1.9-2.0, HDL 1.3-1.4 and LDL 2.9.

11. The established right proportional relationship between the AGL of CA and FCA with

components of the lipid profile and mainly with triglycerides - the higher the values ​​of triglycerides, the higher the smoke increases the CCA, CCA bif. , ICA, FCA can be successfully used in patient follow-up and for proper assessment of therapy.

12. The analysis confirms that for CA DIM, a statistically significant pathological difference in DIM levels was found between patients with and without SMEs.

13. The established statistically significant relationship between the increase of CA DIM and the presence of clinical / asymptomatic coronary atherosclerosis is defined as an important factor in the prediction of coronary atherosclerosis.

14. The presence of plaque or stenosis of CA increases the relative risk of occurrence of HANK, IMI or IBS.

15. Higher levels of fibrinogen and pathological lipid profile have been found in more severe atherosclerosis (lower ABI or multifocal involvement). These indicators can be used as markers for the atherosclerotic process.

16. With statin or fibrate treatment, the rate of adverse vascular events in the SME group is manageable, reducing the residual risk in patients with atherogenic dyslipidemia and hypertriglyceridaemia.

17. In more aggressive secondary prophylaxis with a statin, antiplatelet agent and ACE inhibitor, such as group IV therapy, a reduction in the progression of the atherosclerotic process is found.

Contributions ¬– are reflected in the Abstract of the dissertation, and are divided into two groups - with original and confirmatory nature:

With original character:

1. Based on an in-depth analysis of the results of clinical, laboratory and instrumental methods of patients with HANK, their risk has been identified profile and prerequisites for screening and prevention.

2. Patients with HANK have pathological changes in the following ultrasonic parameters: DIM ICAb, DIM ICA, DIM FCA, availabilityof plaques, stenoses, carotid and femoral artery thrombosis, ABI <0.9, as a marker and marker of multifocal atherosclerotic process.

3. Structural changes in all arteries (carotid, iliac, femoral, foot) in patients with HANK have been identified as appropriate markers for detection of multifocal atherosclerosis.

4. The effectiveness of the combined application of ultrasound has been established

markers to optimize the screening and diagnosis of multifocal atherosclerosis.

5. A set of diagnostic and prognostic markers for optimizing the screening and diagnosis of multifocal atherosclerosis - thickening of DIM over 1 mm, carotid and / or femoral plaques

arteries, stenoses and / or thrombosis of carotid and / or femoral arteries, ABI below 0.9, dilatation and aneurysm of the abdominal aorta.

6. It is based on the established results and statistical dependencies developed an algorithm for optimizing the diagnosis and therapeutic behavior in patients with multifocal atherosclerosis

7. The proposed prognostic markers used in the subclinical stage of atherosclerotic process, contribute to the identification of high-risk patients and to optimize prevention and early treatment.

Confirmatory:

1. It is confirmed that the classic risk factors for HANK are fundamental importance for the development of multifocal atherosclerosis - male, over 68 age, hypertension, diabetes, smoking, familial burden, dyslipidemia.

2. The first morphological changes in the arterial wall may be visualized by B-mode ultrasonography. It is confirmed that this non-invasive method is one of the best for early detection

stages of atherosclerosis, as it is easily applicable, the equipment is available in many places, and its resolution is better than that of nuclear magnetic resonance and CT.

3. The presence of plaque or stenosis of CA has been shown to contribute to increase the risk of HANK, IMI or IBS in the range of 4-8%.

4. It has been found that when taking a statin or fibrate unwanted vascular incidents are manageable, reducing residual risk in patients with atherogenic dyslipidemia and hypertriglyceridemia.

5. More aggressive secondary prophylaxis with statin, antiplatelet and ACE inhibitor in high-risk patients contributes to lower progression of the atherosclerotic process.

Abstract - contains 70 pages and reflects exactly everything written in the dissertation.

Publications: In connection with the dissertation the author presents 5 publications and scientific reports in national journals and prestigious international scientific forums - meeting the minimum national criteria.

Remarks: The following remarks can be made without compromising the value of the research:

- Some of the abbreviations are in Cyrillic and others in Latin.

- Foreigners are used in the text.

- The publications are only in Bulgarian editions

Conclusion: I highly appreciate the work of Dr. Gerova due to the relevance and timeliness of the study and mainly in terms of attempts to solve a very important problem - identification of diagnostic and prognostic markers in patients with multifocal atherosclerosis. The presented results of the research and the developed dissertation are a contribution to the Bulgarian scientific literature.

The dissertation presented by Dr. Elitsa Rashkova Gerova - Micic fully meets the requirements of the Law for Development of Academic Staff in the Republic of Bulgaria and the Regulations for the Development of Academic Staff of Acibadem City Clinic Tokuda UHospital EAD for awarding educational and scientific degrees- PhD.

I recommend the members of the esteemed Scientific Jury to vote positively and award the scientific and educational degree "PhD" to Dr. Elitsa Rashkova Gerova - Micic.

06/17/2022 ……………………………

Sofia Prof. K. Karamfilov, MD, PhD