

## Opinion

In a completion of Order 15-05-71/04.04.2022 year,  
Based on art. 4 of the Law for academic development of the academic staff of Republic of Bulgaria, art. 31 from the Regulations the Law for academic development of the academic staff of Republic of Bulgaria, and art. 29 of the Regulation of the Development of the academic staff of Acibadem City Clinic UMHAT Tokuda EAD and Decision of the Scientific Council with protocol 40/10.02.2022 г.

From prof. d-r Ivo Spasov Petrov, MD, PhD, Dsc.  
UMHAT Acibadem City Clinic Cardio-vascular Center

For a thesis in defense of educational and scientific degree “Doctor of Philosophy”

Field in the higher education system 7. “Health and sport”

Professional field 7.1 „Medicine “, specialty 03.01.48 “Angiology”

Author: D-r Elitsa Rashkova Gerova-Micic, MD enrolled by order 260/08.06.2016 г.

Form of doctoral studies: full- time at the Clinic of Vascular Surgery with activity in the medical specialty "Angiology", Doctoral program: "Angiology"

Topic: Multifocality of atherosclerosis – prognostic and diagnostic markers in different vascular pools.

Scientific Leader: prof. d-r Milena Staneva Staneva, MD, PhD

### **Presentation of the procedure and the PhD student**

The presented set of documents (paper and electronic media) is in accordance with the above-mentioned Regulations and Laws. D-r Gerova has provided the necessary documents, needed by the Scientific Jury for completion of the procedure.

### ***Brief remarks on the procedure***

D-r Gerova was enrolled as a full-time doctoral student by order 260/08.06.2017 of the Executive Director of Acibadem City Clinic Tokuda. Deducted with the right to defense the thesis in accordance with art. 74, al. 1, p. 1 from the Law for the Higher Education, art. 2, al. 2, al. 3 and al. 6 from the Regulations of the Law for academic development of the academic staff of Republic of Bulgaria, art. 23, al.6 from the Regulation of the Development of the academic staff of Acibadem City Clinic UMHAT Tokuda EAD and Decision of the Scientific Council from 28/-7/2020, Protocol 32, Order 483/31.07.2020 year.

Covered doctorate minimum in Angiology on 19.06.2019 year.

### ***Biographic reference***

D-r Gerova was born in 1988 year. She had gone through the whole path from caregiver and nurse during her medical education. She graduated from Medical University Sofia in 2014 year; was regular doctor in UMHAT Sofamed, Sofia from 2014 to 2020 year. From 2015 to 2020-

year specialized Angiology in Acibadem City Clinic MBAL Tokuda. From 2017 to 2022 year was a full-time PhD student Acibadem City Clinic MBAL Tokuda.

### ***Postgraduate education***

Specialty in Angiology awarded 2020 year.

### ***Professional experience***

UMHAT Sofiamed and Acibadem City Clinic UMHAT Tokuda, Sofia

***Scientific projects and competitions – none declared.***

## **The Thesis**

### ***Structure***

The thesis is written on 170 pages. It is properly structured in the following heads: Introduction – 2 pages; Review of the literature – 18 pages; Methods – 17 pages; Results and discussion – 98 pages; Conclusion 3 pages; Outcomes and recommendations 3 pages. The reference list consists of 208 scientific works: 15 from Bulgarian authors. The papers in the reference list include different number of authors, which doesn't reduce the significance of the outcomes. There are 90 tables and 19 figures included.

### ***Relevance of the topic***

The aim of the Thesis is contemporary and important from practical point of view. The detection of diagnostic and prognostic noninvasive markers for multifocality of the atherosclerotic process is the corner of populational screening in a region with very high cardio-vascular risk.

### ***Knowledge of the problem***

The PhD student shows deep understating of the problem for the multifocality of atherosclerosis. The Review starts with the pathogenesis of atherosclerosis as a prerequisite for the multifocality; goes through discussion of the process in the various affected regions. Comments on specific biochemical and ultrasound markers. On the basis of the Review the PhD student defines 4 basic proven and solved problems and poses 4 more unsolved/open problems.

### ***Aim and tasks***

The aim of the study was to assess the multifocality of atherosclerosis as a pathological process to define and suggest diagnostic and prognostic ultrasound markers.

To achieve the given aim, d-r Gerova pointed 6 tasks, which comprise the whole process from diagnosis, description of the risk profile, ultrasound predictors for multifocality of atherosclerosis. She suggested, as well, optimization of the screening and diagnostic process.

### ***Methods***

This prospective scientific study included 240 patients – 40-91 years of age, admitted in clinic of Vascular surgery UMHAT "Sofiamed" from July 2017 to July 2020. All patients have undergone CT angiography from renal to tibial arteries, ultrasonographic evaluation of carotid, peripheral arteries and the abdominal aorta, ABI measurement. They were divided into 5 groups:

- Control group – with risk factors without manifested coronary atherosclerosis, (n=40, 17%)



- One affected region– Peripheral artery disease (n=68, 28%)
- Manifestation in two circulation regions – PAD and CAD or PAD and carotid stenosis (n=97, 40%)
- Involvement of three regions (n=35, 16%)
- A group of 120 patients with PAD, comprising patients from all other groups, who were revascularized on top of optimal medical therapy and were followed for 2 years for the dynamics (progress or regress) of the atherosclerotic process.

Many methods were used, all readily accessible in the everyday practice:

- Clinical-angiologic study
- Evaluation of cardio-vascular risk
- Instrumental noninvasive and invasive methods: ECG, CT angiography, ultrasonographic study of the carotids, abdominal aorta and femoral arteries, IBI

The statistical methods are diverse and carefully chosen with respect to the precise data type and questions

### **Results and discussion**

The results are backed with discussion of the potential mechanisms. D-r Gerova has define 17 outcomes for the multifocality of the atherosclerotic process, for the significance of the ultrasonographic evaluation. The role of the statins was confirmed once more.

### **Characteristics of the Thesis and the contributions**

The main contributions of the author (both original and confirmative for the Bulgarian population) are with practical significance. They arise from the everyday practice in a very-high cardio-vascular risk region (Eastern Europe) and mirror the phenotypic characteristics of this group. The author confirmed the effectiveness of combined ultrasound markers from various vascular regions and ABI to optimize screening and diagnosis of multifocal atherosclerosis. The major outcomes of the study were those, associated with the definition of predictors for multifocality:

- There was a significant negative correlation between thickness of intima-media of the carotid artery and ABI. Thus, low ABI in PAD patients might be a marker for carotid artery disease.
- Thrombosis of the aorto-iliac segment may be used as a predictor for cerebro-vascular disease.
- Thrombosis of the femoro-popliteal segment may be used as a predictor for multifocal atherosclerosis (cerebro-vascular or cardio-vascular disease)
- There was a high percent (55%) of multifocal atherosclerosis in patients with PAD.
- ABI and stroke risk were negatively correlated.
- It seems that in all studied groups there was a positive proportional correlation between the IMT of the carotid and femoral arteries, and this correlation was most significant for the control group (table. 52).
- Carotid plaque/stenosis elevates the risk for PAD, stroke or coronary artery disease 4-8%
- The more aggressive secondary prophylaxis with statin, antiaggregant and ACE inhibitor (a therapy used in the 4<sup>th</sup> group) was correlated with the slowest progression of the atherosclerotic process, even though this was the highest risk group.

Based on the results, the author made an algorithm for diagnosis in patients with multifocal atherosclerosis. D-r Gerova suggested prognostic markers for high risk for multifocality, which if used in the early subclinical stage of atherosclerosis, may optimize the screening process

### **Thesis abstract**

It is relevant to the recommendations and includes the main chapters from the main text in proportional parts.

### **Publications**

D-r Gerova provides reference for 5 papers in Bulgarian journals. Three of them are original research papers, out of which 1 is based on the thesis results; 2 clinical cases and 1 abstract from a national congress. She is the first author in 3 of the publications and last author in the other two.

### **Remarks:**

1. We can have atherosclerosis of the coronary arteries without hemodynamically significant coronary stenosis, which is included in the evaluation for the number of diseased vessels (tabl. 48). Nonobstructive coronary artery disease was correlated with significant risk of myocardial infarction (from the literature).  
It is interesting what a result would come out if the presence of nonobstructive coronary artery disease was correlated with the ultrasound markers. Another potential path for further exploration might be the study of a possible correlation between Syntax score and the various ultrasound predictors for multifocality. D-r Gerova confirms the correlation coronary artery disease and diameter IM or ABI. The precise strength of the correlation could be seen with evaluation of Syntax with diameter IM or ABI.
2. An important and generally understudied field was touched in the thesis – namely – the correlation estrogens multifocal atherosclerosis. The continuation of the work in this field by the PhD student may have high practical impact.  
I should remark that all 10 females in the control group (mean age 71 years) were put in the column “estrogens”, the percentage was 100 and different from the other groups. The reason for that would be interesting. It is not clear why such a high percent of advanced age women were on estrogen therapy, what type of estrogens, was the difference in the percentages significant or not and how this affected the results (page 51).
3. It will be interesting to find the PhD Student’s personal opinion on the results from table 52 - namely, the correlation between IMT of the carotid and femoral arteries was most significant in the control group.
4. Interesting from practical point of view is the result stress-multifocal atherosclerosis. It will be important to acquire further results for the Bulgarian population. I recommend the use of standardized tests for stress assessment in other to make the results comparable to other populations’.
5. Conduction of a prospective study with the given number of patients, which was necessary for adequate representation of a common disease (multifocal atherosclerosis), should be appreciated positively regarding the complexity of the task.

The remarks should not be taken as critical, rather as constructive for the further development of the topic and d-r Gerova.

## **Conclusion**

With reference to the provided from the PhD student documents, I evaluate the Thesis “Multifocality of atherosclerosis – prognostic and diagnostic markers in different vascular pools.” **positively**. The qualitative and quantitative criteria, recommended in the National and Local for Acibadem City Clinic UMHAT Tokuda, are met. I suggest the Respected Jury to assess positively as well, the Thesis of d-r Elitsa Gerova-Micic in the filed Medicine, specialty Angiology.

17.06.2022 year

Sofia

/prof. d-r Ivo Spasov Petrov, MD, PhD, DSc/

