OPINION

by Assoc. Prof. Atanas Angelov Atanasov, MD, PhD
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on the dissertation for the acquisition of
educational and scientific degree " **DOCTOR OF SCIENCE** "
in the field of higher education 7. Health and sports,
Professional field 7.1. Medicine,
Scientific specialty: CARDIOLOGY

with the title:

Early abnormalities in the coagulation and fibrinolytic system in paroxismal atrial fibrillation

written by **Assoc. Prof. Mariya Negrinova Negreva, MD, PhD**
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By decree N: P -109-216/20.05.2022 of the Rector of Medical University of Varna I was elected as member of the Scientific Jury and respectively I have been appointed to prepare an opinion on the procedure for obtaining the educational and scientific degree "Doctor of Science" with the candidate Assoc. Prof. Mariya Negrinova Negreva, MD, PhD.

Biographical data and professional development

Assoc. Prof. Mariya Negreva, MD, PhD is a graduate Medical University of Varna in 2006, after which she started work as an intern at the First Clinic of Cardiology with ICU at the University Hospital St. Marina, Varna. In 2008 she became an assistant professor at the Department of Internal Medicine at the Medical University of Varna. In 2013, Assoc. Prof. Negreva acquired the specialty Cardiology, and in 2015, she was awarded the degree "Doctor" with dissertation title: Dynamics of oxidative stress in patients with paroxysmal atrial fibrillation. Since 2016 she has worked as an associate professor in cardiology. Assoc. Prof. M. Negreva had several specializations, mainly in the field of echocardiography, in Germany and Italy. Her scientific works include: one monograph; participation in five textbooks; over 60 full-text articles and 35 participations in national and international forums. He has been a scientific

supervisor of two doctoral students and scientific consultant of one graduate. She conducts practical exercises and gives lectures on internal medicine to Bulgarian and English speaking medical students. She is Head of the educational sector of Cardiology at the First Department of Internal Medicine at the Medical University of Varna.

Topic significance: Atrial fibrillation is the most common arrhythmia, its incidence increasing rapidly over the past two decades. Manifestation of the arrhythmia worsens the quality of life of patients and increases the likelihood of heart failure. Thromboembolic complications are the main problem in this disease. People with atrial fibrillation have a five times higher risk of thromboembolic stroke than the rest of the population. Every fourth ischemic stroke is associated with atrial fibrillation. Extracranial embolic events are significantly rarer but have a high mortality rate.

Paroxysmal atrial fibrillation is one of the clinical forms of the disease. It is often asymptomatic and remains undiagnosed. However, even brief episodes of atrial fibrillation significantly increase the risk of thromboembolic ischemic stroke. On the one hand, this requires targeted search and screening for presence of this arrhythmia and, on the other hand, correct assessment of thromboembolic risk and subsequent anticoagulant prophylaxis.

Scales routinely used over the past decade to assess thromboembolic risk have significantly improved risk stratification. However, the discussion about their precision continues. According to most experts, duration of the arrhythmia is a key factor in thromboembolic risk. At this stage, there is no consensus on the amount of atrial fibrillation burden and its contribution to thromboembolic risk.

In recent years, there has been a trend to reduce the time frame of low thromboembolic risk. Even those at the lowest risk have a periprocedural risk of thromboembolic events after successful cardioversion. This necessitates a discussion of the extent to which the use of only the approved CHA_2DS_2-VASc score is sufficient to accurately assess the thromboembolic risk after cardioversion in episodes of atrial fibrillation lasting up to 48 hours.

Structure of the dissertation: The dissertation is formatted according to the requirements. It consists of 213 pages and is illustrated with 69 figures and 24 tables. The dissertation is well balanced and includes an introduction and literature review (77 pages), aim and tasks (2 pages), materials and methods (17 pages), results and discussion (80 pages), conclusions and contributions (5 pages). The bibliography is very rich and includes a total of 577 sources (5 in Cyrillic). The thesis summary includes 69 figures and 24 tables.

Literature review: The literature review is comprehensive and thoroughly examines the problem, starting with historical data on atrial fibrillation as a disease, going through epidemiological data and assessment of thromboembolic risk and leading to prothrombotic changes in brief episodes of atrial fibrillation. Data from clinical and experimental studies on the coagulation and fibrinolytic system are presented in great detail. The author gives a detailed description of the functioning of the coagulation and fibrinolytic system. Plasma markers for coagulation and fibrinolysis are discussed.
Based on the literature review, Assoc. Prof. Negreva defines several unresolved issues:

- There is no clinical study to analyze in detail the systems of coagulation and fibrinolysis in the course of short <24 hours episodes of atrial fibrillation.
- The periprocedural thromboembolic risk of short <24-hour episodes of atrial fibrillation in very low-risk individuals remains unclear, according to conventional assessment with CHA_2DS_2-VASc score
- The predictive value of coagulation and fibrinolytic plasma markers for risk assessment of thromboembolic events is unclear.

Aim and tasks: The dissertation formulates the main aim of the research as a logical continuation of the literature review: To study the coagulation status of patients with paroxysmal atrial fibrillation and episode duration up to 24 hours, by examining the systems of coagulation and fibrinolysis. 9 specific tasks have been set to achieve this aim.

Materials and methods: To accomplish the set tasks the author analyzed prospectively 51 patients with first episode of paroxysmal atrial fibrillation, who were selected from a total of 338 screened patients. 52 healthy individuals were included as a control group. Twenty indicators of the coagulation and fibrinolysis systems were studied. The used laboratory methods are presented in detail. The most modern statistical methods have been used to interpret the data.

Results and discussion: The results obtained are of an original nature, on a fundamental and clinical level.

The following are the most significant results found:

- Early hypercoagulability has been established in paroxysmal atrial fibrillation with an episode duration of up to 24 hours, even in low-risk thromboembolic features.
- Even at the lowest risk of arrhythmia, periprocedural anticoagulation is required.
- Coagulation and fibrinolytic biomarkers have been identified that clearly indicate the onset of a prothrombotic state.

- The temporal characteristics of the episode are a significant predictor and limiting factor for the established procoagulant deviations. Early cardioversion may reduce periprocedural thromboembolic risk. The time interval of up to 6 hours from the onset of the disease can be considered as the lowest risk for thromboembolic events.
- Biomarkers have been identified that predict an increased risk of atrial fibrillation. It is discussed whether the established procoagulant deviations are a consequence of atrial fibrillation or they precede its clinical manifestation, as part of a still unclear pathophysiological mechanism.

Conclusions: The conclusions correspond to the set goal and tasks. They are well formulated and logically derived from the results obtained.

The candidate is critical of the study and cites as a limitation the one-time study of the coagulation and fibrinolysis systems and lack of follow-up after restoration of sinus rhythm. However, this limitation is a prerequisite for new studies, which could examine the coagulation and fibrinolytic system in dynamics.

Contributions: The dissertation presents results only of original character and is the first of its kind clinical study on coagulation balance in short episodes of atrial fibrillation lasting up to 24 hours. It examines hemostatic indicators, not studied so far.

Evidence of early hypercoagulability in paroxysmal atrial fibrillation with an episode duration of up to 24 hours has been presented, even in low-risk thromboembolic features. The time frame of up to 6 hours for the presence of lower procoagulant activity is outlined. This outlines the need to shorten the time to cardioversion.

The work proposes to redefine the definition of "ideal candidates for acute cardioversion" and narrow down the interval to the first 6 hours of the disease.

Some of the studied biomarkers are potential candidates for predictors of atrial fibrillation, as well as additional prediction of thromboembolic risk beyond the conventional assessment with CHA_2DS_2-VASc score.

Publications and scientific communications in connection with the dissertation: In connection with the dissertation Assoc. Prof. M. Negreva, MD, PhD presents a significant number of publications. All 10 full-text publications are in international journals, and 5 of them are in journals that are referenced and indexed in global databases of scientific information. Four abstracts from

participation in congresses have been published in international journals. So far, there are 8 citations of the publications.

Conclusion: The dissertation treats a very topical issue in the field of cardiology. The presented scientific work reports results only of original character and is the first clinical study of its kind in an area of interest for both clinical and fundamental cardiology. I am convinced that the dissertation of Assoc. Prof. Dr. Mariya Negreva, MD, PhD fully meets the requirements for awarding the educational and scientific degree "Doctor of Science". This gives me reason to confidently suggest to the esteemed Scientific Jury to vote positively for the award of the scientific degree "Doctor of Science" to Assoc. Prof. Mariya Negreva, MD, PhD.

Varna, 26.05.2022

Assoc. Prof. Dr. Atanas Angelov, MD, Ph.D.