REVIEW

by Prof. Mariana Ivanova, MD, PhD

Department of Internal Medicine

Faculty of Medicine, Medical University – Sofia

Clinic of Rheumatology, University Hospital "St. Ivan Rilski" EAD

Regarding: Dissertation for the award of the educational and scientific degree "Doctor" in Internal Medicine entitled "Vascular Effects of Biologic and Targeted Synthetic Therapy in Patients with Rheumatoid Arthritis", authored by Dr. Georgi Aleksandrov Gerganov, full-time doctoral student at the Department of Propedeutics of Internal Diseases, Faculty of Medicine, Medical University – Varna.

Supervisors: Assoc. Prof. Maria Dimova–Mileva, MD, PhD, and Assoc. Prof. Tsvetoslav Georgiev, MD, PhD

Scientific Jury – Rector's Order No. R109–499 / 02.12.2025, Medical University – Varna

The submitted documentation meets the requirements for conducting a PhD defense procedure. Dr. Georgi Aleksandrov Gerganov graduated in Medicine from MU–Sofia in 2011. His professional career began at the Emergency Department of University Hospital "St. Anna" Varna (01.2012–08.2012), followed by work in the Emergency Admission Department of University Hospital "St. Marina" Varna (08.2012–05.2014). Since June 2014 he has worked in the Clinic of Rheumatology of the same hospital, initially as a trainee and later as a rheumatology specialist. Since September 2016 he has been an Assistant Professor at the Department of Propedeutics of Internal Diseases, MU–Varna. He has excellent command of English and intermediate-level musculoskeletal ultrasonography expertise.

The dissertation comprises 178 pages and includes the standard structural sections, illustrated with 28 figures and 63 tables.

The topic of this scientific work is of substantial importance, as contemporary studies indicate that rheumatic diseases, including rheumatoid arthritis (RA), are strongly associated with cardiovascular diseases, which has driven an increase in research in this field. Cardiovascular involvement is a leading cause of mortality in RA due to accelerated atherosclerosis and the increased risk of myocardial infarction and stroke. However, the underlying pathogenic

mechanisms of vascular damage induced by chronic inflammation in RA—particularly the earliest manifestations of vascular endothelial activation and dysfunction—remain incompletely elucidated. Changes in the incidence of cardiovascular events following the introduction of new therapeutic agents and intensified treatment strategies have also been the subject of numerous investigations in recent years, aiming to clarify the role of these therapies in such socially significant comorbidities. In this context, studying the vascular effects of modern therapies and understanding them correctly would lead to safer and more effective management of RA and its associated conditions, ultimately improving the quality and longevity of life in affected patients.

The literature review spans 50 pages and demonstrates that the doctoral candidate possesses a strong awareness of the dissertation topic—covering the etiology of RA, its pathophysiology, including innovative immunological markers that are currently under investigation, as well as existing therapeutic approaches to the disease. Current knowledge regarding the pathogenesis and pathophysiology of vascular damage in RA is extensively presented, along with modern methods for evaluating endothelial dysfunction and arterial stiffness, including both instrumental techniques and serological markers. The doctoral candidate has conducted a thorough review of the available literature in accessible scientific databases concerning the effects of biological and targeted synthetic disease-modifying antirheumatic drugs on vascular injury. The review concludes with an analytical summary in which the author justifies the need to investigate this issue in order to achieve a deeper understanding of the intricate mechanisms underlying the two parallel pathological processes. As a remark, it may be noted that the information in the review is concise, clearly presented, analytically structured, and conceptually organized. The literature review confirms that Dr. Georgi Gerganov has analyzed and synthesized a large body of information and possesses profound knowledge of the topic, enabling meaningful interpretation of the data and comparison of the results obtained in the Bulgarian population with those reported by international research groups.

The Aim is clearly stated and consistent with the research tasks.

The "Patients and Methods" section is presented over 19 pages, provides a clear characterization of the study groups, and describes the investigated parameters in detail. A total of 79 patients with RA were examined, divided into two groups: 41 receiving treatment with the TNF inhibitor adalimumab, 38 treated with the JAK inhibitor upadacitinib, and 30 healthy

controls. The applied research methodology enables the achievement of the stated objective and the provision of an adequate response to the tasks set forth in the dissertation.

The results are presented in tables, illustrated with graphical analyses, and interpreted accurately. Correlation analyses, comparative analyses, and multivariate analyses were performed, including multiple linear regression to evaluate the relationship between the type of treatment and the parameters of arterial stiffness, as well as the endothelial dysfunction marker ADMA. These analyses assess the independent effect of treatment with the JAK inhibitor upadacitinib or the TNF inhibitor adalimumab on indices of arterial stiffness and endothelial dysfunction compared with healthy controls, as well as whether these vascular parameters are influenced by specific disease characteristics of RA. In this way, an accurate assessment was achieved of the relative importance of the factors associated with vascular damage, as well as of the effect exerted by treatment with adalimumab and upadacitinib on these parameters.
In the discussion, each of the obtained results is analyzed with well-grounded reasoning and arguments, and is compared with data from the international literature. A comprehensive review of relevant clinical studies and their outcomes in the field of interest has been carried out. The analysis of the results is thorough and demonstrates the doctoral candidate's ability to collect, evaluate, and interpret information. The conclusions emphasize the key aspects of the research, and both the strengths and limitations of the study are clearly identified.

The contributions of the dissertation are both original and confirmatory, objectively reflecting the scientific significance of the obtained results and their applicability in real clinical practice. They substantiate the importance of controlling rheumatoid arthritis disease activity in order to limit arterial stiffness and cardiovascular risk, and emphasize the need for individualized assessment and monitoring of cardiovascular risk in RA patients to ensure more effective management.
The literature review is extensive and includes 521 bibliographic sources.

Conclusion

I consider that the presented dissertation "Vascular Effects of Biologic and Targeted Synthetic Therapy in Patients with Rheumatoid Arthritis" meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (ZRASRB), its Regulations for Implementation, as well as the Regulations for the Development of the Academic Staff of the

Medical University – Varna, for the acquisition of the educational and scientific degree "Doctor."

The dissertation demonstrates that Dr. Georgi Gerganov possesses the necessary qualities to conduct scientific research, the ability to analyze data, discuss results, and formulate conclusions of both scientific and practical value.

For the above reasons, I give a **positive evaluation** of the dissertation and recommend to the esteemed members of the Scientific Jury to award the educational and scientific degree "Doctor" in Internal Medicine to Dr. Georgi Alexandrov Gerganov, Department of "Propaedeutics of Internal Diseases," Medical University "Prof. Dr. Paraskev Stoyanov" – Varna.

Заличено на основание чл. 5, §1, б. „В“ от Регламент (ЕС) 2016/679

05.01.2026 Signed:

Sofia (Prof. Mariana Ivanova, MD, PhD)