

## REVIEW

in accordance with Order No. R-109-499 / 02.12.2025  
of the Rector of the Medical University “Prof. Dr. Paraskev Stoyanov” – Varna

by Assoc. Prof. Svetlana Hristova Hristova, MD, PhD  
Department of General Medicine, Medical University – Varna

of a dissertation submitted for awarding the educational and scientific degree “**Doctor**”

**Professional field:** Medicine

**Doctoral programme:** Internal Medicine

**Author:** Dr. Georgi Aleksandrov Gerganov

**Department:** Propedeutics of Internal Diseases,  
Medical University “Prof. Dr. Paraskev Stoyanov” – Varna

**Dissertation title:** “*Vascular Effects of Biological and Targeted Synthetic Therapy in Patients with Rheumatoid Arthritis*”

**Form of doctoral training:** Independent doctoral studies

**Supervisors:** Assoc. Prof. Maria Dimova-Mileva, MD, PhD  
Assoc. Prof. Tsvetoslav Georgiev, MD, PhD

### General Presentation of the Procedure and the Doctoral Candidate

The submitted set of documents fully complies with the Law on the Development of Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for its implementation, and the internal regulations of the Medical University “Prof. Dr. Paraskev Stoyanov” – Varna. It includes the complete set of required materials related to the doctoral procedure.

### Brief Biographical Data of the Doctoral Candidate

Dr. Georgi Aleksandrov Gerganov was born on 15 April 1986 in Varna. He graduated from the Medical University of Sofia in 2011. Immediately after graduation, he began his professional career as a resident physician at the Emergency Center of St. Anna University Hospital, Varna, and later at the Emergency Department of St. Marina University Hospital, Varna.

He started his specialization in Rheumatology at the Clinic of Rheumatology at St. Marina University Hospital, where he has been working as a specialist since 2019. His academic career began in 2016 as an Assistant Professor at the Department of Propedeutics of Internal Diseases.

Over the past five years, the doctoral candidate has completed numerous specialized training courses in his field of scientific interest. He has a good command of written and spoken English and is a member of the Bulgarian Society of Rheumatology.

### Relevance of the Topic and Appropriateness of the Objectives

The dissertation submitted for review is highly relevant and of significant practical importance, addressing an essential and socially important issue in modern rheumatology and cardiovascular medicine—namely, the relationship between chronic inflammation, arterial stiffness, markers of vascular damage, and the use of biological and targeted synthetic therapies in patients with rheumatoid arthritis.

The study evaluates the impact of anti-inflammatory treatment on vascular function markers and the risk of atherosclerotic changes. The topic is particularly timely given the well-established increased cardiovascular risk in patients with inflammatory joint diseases, which cannot be explained solely by traditional risk factors.

Currently, there is insufficient real-world clinical data regarding the effects of biological and targeted synthetic therapies on arterial stiffness and endothelial function, which adds both theoretical and practical value to this research and confirms the relevance of the chosen topic.

### Knowledge of the Research Problem

The doctoral candidate demonstrates excellent knowledge of the research topic, as evidenced by a well-

structured literature review. A total of 521 scientific sources were analyzed, with accurate and correct citations. Most references are from the last decade and are directly related to the research topic.

The literature is critically evaluated and creatively interpreted, demonstrating the candidate's ability to perform an in-depth theoretical analysis.

### **Characteristics and Evaluation of the Dissertation**

The dissertation is written in clear and precise academic Bulgarian, meeting all formal requirements. It comprises 179 standard pages and includes the following sections: introduction, literature review, aim and objectives, materials and methods, results and discussion, conclusions, and scientific contributions.

The work is illustrated with 63 tables and 28 figures. The structure is logical and fully aligned with the research objectives. The literature review is analytical and comprehensive, consisting of eight sections covering modern data on rheumatoid arthritis pathogenesis, mechanisms of vascular damage, and the effects of biological and JAK-inhibitor therapies on cardiovascular risk.

### **Aim, Objectives, Subject and Object of the Study**

The aim of the dissertation is clearly and precisely formulated. The object and subject of the study are well defined and fully correspond to the research topic. The five main objectives are specific, well-formulated, and sufficient for achieving the stated aim.

### **Methodology and Scientific Results**

The applied research methods are appropriate and commonly used in similar studies. Inclusion criteria and diagnostic criteria are clearly defined, ensuring correct interpretation of the results. The study design and stages are described in detail. Modern and reliable clinical, laboratory, and instrumental methods were applied. Notably, the study includes ultrasound assessment of arterial stiffness with automated calculation of hemodynamic parameters (PWV,  $\beta$ -stiffness, AI, AC, EP), as well as measurement of the biochemical marker ADMA. Statistical analysis was performed accurately using appropriate parametric and non-parametric tests, correlation and regression analyses, and effect size assessment, allowing for reliable clinical interpretation of the results. The study included 109 participants: 79 patients with rheumatoid arthritis -41 treated with TNF inhibitors, 38 treated with upadacitinib, 30 healthy controls. Standard clinical, laboratory, and instrumental methods were used. Disease activity indices (DAS28-ESR, DAS28-CRP, CDAI), Framingham Risk Score, carotid ultrasound, and arterial stiffness parameters were assessed. ADMA levels were measured, and disease activity was evaluated using PGA, PhGA, and VAS. The results show that patients treated with upadacitinib had significantly higher total cholesterol, LDL, and HDL levels compared to TNF inhibitor-treated patients and controls, consistent with the "lipid paradox" in RA. The Framingham Risk Score was similar across groups but correlated with disease activity, disease duration, and arterial stiffness parameters. ADMA levels did not differ significantly between groups and were influenced only by smoking status. A key practical finding is that ultrasound markers of arterial stiffness are reliable indicators of early vascular damage in RA patients. A significant association was found between arterial stiffness and disease activity (especially CDAI), while ADMA did not correlate with disease activity.

### **Scientific Contributions and Practical Significance**

The dissertation presents original scientific contributions with clear practical value. This is the first comprehensive clinical study in Bulgaria directly comparing TNF inhibitors and the JAK inhibitor upadacitinib with regard to early vascular damage in rheumatoid arthritis. The study demonstrates the value of ultrasound-based arterial stiffness assessment as an accessible tool for early cardiovascular risk evaluation. It also establishes CDAI as a more reliable indicator of vascular involvement compared to DAS28.

### **Personal Contribution of the Doctoral Candidate**

The dissertation demonstrates the candidate's excellent theoretical knowledge and ability to independently conduct scientific research. The work reflects a high level of professional competence and scientific maturity.

## Abstract

The abstract complies with regulatory requirements and accurately reflects the aim, methods, results, conclusions, and scientific contributions of the dissertation.

## Critical Remarks and Recommendations

No critical remarks are noted regarding the content or quality of the dissertation.

## Recommendations for Future Use of the Results

For further academic development, it is recommended that the doctoral candidate increase publication activity to disseminate the research findings to a broader scientific audience.

## CONCLUSION

In conclusion, the presented dissertation represents an independent and scientifically significant study with original contributions of both theoretical and practical importance. The dissertation fully complies with the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria, its implementing regulations, and the regulations of the Medical University “Prof. Dr. Paraskev Stoyanov” – Varna.

Based on the above, I give my positive evaluation of the dissertation and propose that the esteemed Scientific Jury award **the educational and scientific degree “Doctor”** to **Dr. Georgi Aleksandrov Gerganov** in the doctoral programme *Internal Medicine* at the Department of Propedeutics of Internal Diseases, Medical University “Prof. Dr. Paraskev Stoyanov” – Varna.

**19 January 2026**

### Reviewer:

Assoc. Prof. Svetlana Hristova, MD, PhD

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