STANDPOINT

by Prof. Liliya Davidkova Demirevska-Mihaylova, MD
Professor at the Cardiology Clinic, Department „Cardiology, Intensive Care and Internal Medicine “, Military Medical Academy, Sofia

Subject: Dissertation of **Dr. GEORGI ALEXANDROV GERGANOV** - PhD candidate in full-time study for the acquisition of the educational and scientific degree "Doctor" in the doctoral program " Internal Medicine" in the professional field 7.1. Medicine.

Topic of the scientific paper: "VASCULAR EFFECTS OF BIOLOGICAL AND TARGETED-SYNTHETIC THERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS"

Scientific supervisors:
Assoc. Prof. Dr. Maria Dimova-Mileva, PhD,
Assoc. Prof. Dr. Tsvetoslav Georgiev, PhD.

The standpoint was prepared in accordance with Order No. P-109-499/02.12.2025 of the Rector of the Medical University of Varna, concerning the dismissal with the right to defense of Dr. Georgi Alexandrov Gerganov and the appointment of a scientific jury. In accordance with Protocol No. 1/04.12.2025 of the scientific jury, I was appointed to prepare this standpoint.

Dr. Georgi Gerganov has submitted all required materials in compliance with the Law on the Development of Academic Staff in the Republic of Bulgaria and the Regulations for the Development of Academic Staff at the Medical University of Varna. All required procedures and legal deadlines have been followed. I have no remarks regarding the documentation submitted for the preparation of this review. I have not identified any instances of plagiarism or attempts at plagiarism in the materials provided. I declare that I have no conflict of interest with the author.

General presentation of the procedure; appropriateness of the stated aim and objectives

The dissertation and the abstract are well structured and fully meet the established requirements. The dissertation is 177 pages long and includes 63 tables and 28 figures that clearly display the study's results. The bibliography includes 521 references. The structure of the dissertation complies with contemporary academic standards and includes all required sections. The individual sections are well balanced. The language is scientifically precise, and medical terminology is used appropriately. The dissertation was reviewed and approved for public defense at a meeting of the Department Council of the Department of Propaedeutics of Internal Medicine at the Medical University “Prof. Dr. Paraskev Stoyanov” of Varna.

The abstract is 99 pages in length and summarizes the main data and findings presented in the dissertation.

Literature review

The literature review is current, analytical, and well structured, and it contains sufficient and relevant information. It provides a detailed and comprehensive overview of existing

knowledge on the incidence, risk factors, pathophysiology, clinical presentation, diagnosis, and treatment strategies for rheumatoid arthritis. The focus is on how inflammation drives disease and is managed by modern synthetic and biological antirheumatic drugs. The mechanisms responsible for the increased cardiovascular risk and vascular damage associated with rheumatoid arthritis are discussed. The review presents an in-depth analysis of contemporary methods for assessing endothelial dysfunction and arterial stiffness. It also focuses on the effects of biological and targeted synthetic disease-modifying antirheumatic drugs on vascular damage in patients with rheumatoid arthritis.

The conclusions drawn at the end of the literature review provide a clear and well-founded basis for accurately formulating the aim of the study, the specific objectives, and the rationale for conducting the dissertation research.

Purpose, objectives, and methods of the study

The purpose of the study is clearly and precisely defined: to compare ultrasound-derived indicators of arterial stiffness, levels of asymmetric dimethylarginine (ADMA), and lipid parameters among three groups- patients with rheumatoid arthritis treated with the TNF inhibitor adalimumab, patients treated with the JAK inhibitor upadacitinib, and a control group of healthy individuals.

Five objectives are defined, all of which are directly aligned with the stated aim: identification of markers of early vascular damage in patients with rheumatoid arthritis using ultrasound indicators of arterial stiffness and biomarkers (ADMA); analysis of the influence of lipid profile parameters on vascular indices and their changes during treatment; evaluation of the role of disease activity and composite indices (DAS28-ESR, DAS28-CRP, CDAI) in relation to the studied markers; assessment of cardiovascular risk using the Framingham Risk Score; and identification of independent predictors of early vascular damage.

The section "Material and Methods" provides sufficient and detailed information on the studied population, the applied diagnostic and therapeutic approaches, and the statistical methods employed. The dissertation is based on a cross-sectional observational study including 79 patients with rheumatoid arthritis—41 treated with TNF inhibitors and 38 treated with upadacitinib—and 30 healthy volunteers aged over 18 years. Recruitment of the therapeutic groups was conducted among patients treated at the Rheumatology Clinic of University Hospital “St. Marina”, while the control group consisted of healthy volunteers recruited from the staff of the same hospital, all selected according to clearly defined inclusion and exclusion criteria. Following a clinical examination and disease activity assessment using established scales and indices, cardiovascular risk was evaluated with the Framingham Risk Score. Serological methods for assessing disease activity and their clinical significance are described. Arterial stiffness was assessed with an Aloka ProSound Alpha 7 Doppler ultrasound system, equipped with a high-frequency linear transducer (12 MHz) and software that automatically calculated vascular hemodynamic parameters. The evaluated parameters included pulse wave velocity, beta stiffness index, augmentation index, arterial compliance, and elastic modulus. The statistical methods applied are appropriate for the analysis of the study data.

Results and discussion

Since increased cardiovascular risk is a leading contributor to morbidity and mortality in patients with rheumatoid arthritis, its control represents an important goal in the comprehensive management of these patients, and modulation of immune mechanisms may reduce

cardiovascular risk. In this study, Dr. Gerganov evaluates whether significant differences exist in indicators of vascular damage between patients receiving biological therapy with TNF inhibitors, patients treated with the selective JAK1/2 inhibitor upadacitinib, and a control group of healthy volunteers. In this context, the dissertation constitutes a well-designed and successfully implemented comprehensive scientific investigation that presents analyses of demographic characteristics, laboratory parameters, cardiovascular risk, indicators related to disease activity and treatment in patients with rheumatoid arthritis, and ultrasound-derived measures of arterial stiffness. The study groups are appropriately selected, with no statistically significant differences in demographic characteristics, disease activity, or disease duration, except for differences in drug exposure time and use of immunosuppressive therapy.

The discussion is analytical and closely aligned with the study's main aim and objectives. The author provides a critical analysis of the results derived from the comprehensive assessment of the effects of biological therapy with TNF inhibitors and the JAK1/2 inhibitor upadacitinib, compared with healthy controls, on markers of vascular damage, and places these findings in the context of current international literature. The study primarily evaluates arterial stiffness using non-invasive ultrasonographic methods, examines serum levels of ADMA as a biomarker of endothelial dysfunction, and compares these parameters with established disease activity indices. A comprehensive discussion is provided on how biological therapy affects lipid profiles, endothelial dysfunction markers, arterial stiffness, and their connections to disease activity and cardiovascular risk.

The results demonstrate higher levels of total cholesterol, LDL cholesterol, and HDL cholesterol in the upadacitinib-treated group compared with both the control group and the TNF inhibitor–treated group. This result aligns with what is already known about JAK inhibitors as a class, and it suggests that the effect is due to the reduction of inflammation brought about by this treatment.

Ultrasound measurements of arterial stiffness have proven to be dependable markers of early vascular injury in individuals with rheumatoid arthritis. Age is linked to signs of vascular damage in all three groups and has been found to be a key factor predicting changes in arterial stiffness. According to the dissertation findings, high disease activity and the cumulative effects of disease duration and treatment duration are the principal factors contributing to progressive impairment of arterial elasticity and the development of structural vascular damage. Regression analysis shows that upadacitinib-treated patients with longer treatment and higher CDAI scores have greater arterial stiffness, indicating compromised vascular function. In contrast, markers of aortic stiffness in the TNF inhibitor–treated group are comparable to those observed in healthy controls, indicating a potentially protective effect of these agents on vascular function. There are no statistically significant correlations between markers of early vascular damage and the three disease activity indices (DAS28-ESR, DAS28-CRP, CDAI). However, arterial compliance shows a negative correlation with the CDAI. The Framingham cardiovascular risk score is associated with increased arterial stiffness and reflects the presence of early vascular damage.

In multiple linear regression analyses with ADMA as the dependent variable, current smoking emerges as the only statistically significant predictor, being associated with higher ADMA levels, a marker of endothelial dysfunction. This finding is consistent with the well-established relationship between smoking and vascular endothelial injury.

The author appropriately highlights both the strengths of the study, including its innovative approach, inclusion of a control group, and focus on arterial stiffness, and its limitations, namely

the constraints of the ultrasound methodology, the cross-sectional study design precluding causal inference, and the relatively small sample size.

Dr. Gerganov presents his five conclusions in a manner that is concise, clear, and precise. They are consistent with the stated aim and objectives and accurately reflect the specific results obtained.

Contributions and significance for science and practice

A total of twelve contributions are acknowledged, including two that are methodological and ten that are scientific or practical.

Publications related to the dissertation

Dr. Gerganov has published three scientific articles related to the dissertation topic, in two of which he is the first author. In terms of both quantity and quality, these publications meet the national minimum requirements for the award of the educational and scientific degree “Doctor”.

Abstract

The abstract fully satisfies the formal requirements by presenting the content of the dissertation in a concise and structured manner and highlighting the principal research findings. It also includes a list of publications and the main scientific contributions.

Critical remarks.

There are no critical comments to report. The dissertation uses formal academic language but is still straightforward and easy to understand. The use of tables and figures effectively supports the content, and the results are clearly and logically summarized.

CONCLUSION

The dissertation of Dr. Georgi Alexandrov Gerganov presents scientific-methodological, scientific-theoretical, and scientific-applied results that constitute an original contribution to science and fully comply with the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria, its implementing regulations, and the Regulations for the Development of Academic Staff at the Medical University of Varna. Based on these findings, I recommend awarding the educational and scientific degree “Doctor” to Dr. Georgi Alexandrov Gerganov in the scientific specialty “Internal Medicine”.

14.01. 2026.

Sofia **Prof. Dr. Lilia Demirevska-Mihaylova, PhD**