STANDPOINT

on behalf of Prof. Nikolay Margaritov Runev, MD, PhD,
Clinic of Propaedeutics of Internal Medicine "Prof. Dr. St. Kirkovich" -
University Hospital "Aleksandrovska", Medical University - Sofia

Subject: dissertation on the topic:

"Vascular effects of biological and targeted-synthetic therapy in patients with rheumatoid arthritis"

in a doctoral program **"Internal Diseases"** at the professional direction **7.1 Medicine**

for the award of **the educational and scientific degree "Doctor" to** Dr. Georgi Alexandrov Gerganov, a full-time doctoral student at the Department of Propaedeutics of Internal Diseases, Faculty of Medicine, Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

Order No. R-109-499/02.12.2025 of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna for the appointment of a scientific jury.

Structure of the dissertation work

The dissertation is written on 179 pages, of which 49 pages - literature review; 20 pages - purpose, tasks, material and methods; 50 pages - results; 17 pages - discussion; 2 pages - conclusions and contributions; 30 pages - bibliography (total number of cited sources - 521, of which 4 - by Bulgarian authors).

The dissertation is structured in the classical way with relative compliance of the proportions between its separate parts according to the generally accepted requirements in our country.

Relevance of the topic

The topic of the dissertation is relevant both in theoretical and scientific-practical aspects. I have the following reasons for this statement:

1. The patients with rheumatoid arthritis (RA) have an increased cardiovascular risk, which is determined not only by the higher frequency of the traditional risk factors in them, but also by the role of the chronic inflammatory process in RA for the progression of atherosclerosis.

2. Of particular interest are studies on: (1) RA-specific mechanisms of endothelial dysfunction and arterial stiffness, and (2) the influence of the anti-inflammatory therapy on the arterial elasticity in patients with RA.

3. In clinical terms, attention is focused on the effect of biological medications on the dynamics of surrogate markers for early vascular impairment in RA.

Knowledge on the topic

The review shows that Dr. Gerganov **has thoroughly acquainted with the available literature on the subject**. He summarizes that:

1. Various studies have established cardiovascular benefits from biological and targeted synthetic therapies in patients with RA, but the underlying mechanisms are not yet well understood.

2. The literature data show that TNFi treatment is associated with improved endothelial function, reduced intima-media thickness, and a favorable impact on the arterial stiffness indices.

3. However, for JAK inhibitors, the data are relatively contradictory, with no definitive results on their cardiovascular safety. In addition, there are not enough comparative studies on the effects of the different targeted therapies in RA.

Thus, the author fully justifies the idea of his study.

The aim is clearly stated:

To compare the indicators of arterial stiffness assessed by EchoCG, the levels of ADMA and lipid parameters in patients with RA treated with the TNF inhibitor adalimumab compared to those treated with the JAK inhibitor upadacitinib and a control group of healthy individuals.

To achieve this goal, **5 specific tasks** have been set.

The material and methods provide full grounds to believe in the obtained results.

The study included 79 patients with a diagnosis of RA according to the ACR/EULAR criteria for early RA or the New York modified criteria for established RA. They were divided into two groups: (1) 41 - on treatment $\geq$ 6 months with a TNF inhibitor and (2) 38 - on therapy $\geq$ 6 months with the JAK inhibitor upadacitinib. All RA patients were from the Dispensary for patients with inflammatory joint diseases, treated with biological targeted-synthetic disease-modifying antirheumatic drugs of the Rheumatology Clinic at the University Hospital "St. Marina".

The control group included 30 healthy volunteers from the staff of the University Hospital "St. Marina" and the Medical University of Varna, as well as patients at the Rheumatology Clinic, hospitalized due to degenerative joint diseases, i.e. without inflammatory joint diseases or systemic connective tissue disorders.

Clear exclusion criteria were pointed out:

- ✓ coronary atherosclerotic disease, CHF, significant valvular heart disease, permanent atrial fibrillation,
- ✓ previous ischemic stroke, peripheral arterial disease,
- ✓ type 1 or 2 diabetes mellitus, CKD ≥ IIIa stage,
- ✓ therapy with systemic glucocorticoids in a dose of >10 mg prednisolone equivalent,
- ✓ systemic connective tissue disease overlapping with RA (SLE, Sjogren's disease, etc.),
- ✓ oncological disease that is active or has been diagnosed within the last 5 years.

The following **methods** were used:

1. Clinical – medical history, physical status, clinical assessment of joint involvement according to the 28-joint protocol, calculation of the relevant formulae of disease activity indices (DAS28-ESR, DAS28-CRP and CDAI); assessment of 10-year individual cardiovascular risk using the Framingham Risk Score (FRS);

2. Laboratory – ESR, CRP, complete lipid profile, concentration of the endogenous asymmetric dimethylarginine (ADMA) in serum using the quantitative immunoenzymatic method (ELISA);

3. Instrumental – echocardiographic assessment of indicators for arterial stiffness on the right common carotid artery using the Aloka ProSound Alpha 7 device (pulse wave velocity, stiffness beta-index, augmentation index, arterial compliance, elastic deformation constant).

Modern statistical processing of the results was performed using specialized software Jamovi - version 2.6.23, with the null hypothesis defined at a significance level of $\alpha = 0.05$.

The following were used:

- ✓ descriptive statistics: for quantitative variables, mean and standard deviation were calculated, and for categorical variables - absolute frequency (n) and relative frequency (%),
- ✓ one-way analysis of variance (ANOVA) - to assess the differences between the indicators in the three studied groups; before performing ANOVA, the homogeneity of dispersions was checked using the Levene test,
- ✓ Shapiro–Wilk test to assess the normality of the distribution,
- ✓ t-test for comparison of quantitative variables in normal distribution and Mann-Whitney test – when the distribution was different from normal or in the absence of homogeneity of dispersions,
- ✓ chi-square test (χ^2) - for an analysis of categorical variables, and with

small expected frequencies (n<5) Fisher's exact test was used,

✓ correlation analysis: with Pearson coefficient (to assess linear correlation between continuous variables with a normal distribution) or Spearman coefficient (non-parametric method, in the absence of a normal distribution),

✓ multivariate linear regression analysis with a construction of two regression models: (1) comparison of the both treatment groups with the control group with respect to the common indicators for the three groups: age, gender, body mass index, smoking, lipid profile and (2) comparison between the two therapeutic groups in terms of disease-related factors: duration of the disease and the treatment, previous biological medication use, prior corticosteroid therapy, ESR, CRP, disease activity indices.

Characteristics of the results and the discussion:

The author finds the following:

1. In the study population of patients with RA, there are higher values of arterial stiffness indicators, assessed by EchoCG, in case of treatment with the JAK inhibitor upadacitinib compared to controls and insignificantly increased values with TNFi. No statistically significant differences in these indicators are found between the two therapeutic groups (TNFi vs. upadacitinib).

2. The ADMA levels do not differ significantly between the controls and the two treatment groups, as well as between TNFi and upadacitinib. The ADMA levels show a correlation with smoking only.

3. The treatment with upadacitinib is associated with an increase in total cholesterol and LDL-C levels compared to TNFi and controls.

4. A relationship has been found between the arterial stiffness indicators and the disease activity (especially CDAI), while the ADMA levels do not correlate with the disease activity.

5. The data from multivariate regression analysis show that: disease activity, duration of the disease and therapeutic regimen are independent factors associated with the presence of vascular damage.

The results are presented in 63 tables and are well visualized with 28 color figures and diagrams.

An analytical discussion of the obtained clinical and echocardiographic results for the changes in the indicators of arterial stiffness has been made in patients with RA under different therapeutic regimens, as well as a comparison with the literature data. **The limitations** of the study are correctly indicated.

I agree with the reference about the contributions of the dissertation work.

Conclusion:

For the first time in our country, a **single-center study** has been conducted, in which the effects of treatment with TNF-inhibitors and JAK-inhibitor upadacitinib on arterial stiffness indicators are directly compared in patients with RA. The relevance of the chosen topic should be highlighted, as well as the **deep knowledge of the author** of the literature published to date on the discussed questions.

Based on the obtained results, important **conclusions** have been drawn:

✓ on the benefits of the echocardiographic assessment of markers for early vascular impairment in RA and

✓ on the established relationship between the arterial stiffness and the disease activity, presented by CDAI (clinical disease activity index). This index is based entirely on clinical parameters (without the need for laboratory tests), which makes it particularly suitable for application in clinical practice, incl. in ambulatory conditions.

This work can serve as a basis for conducting additional studies aimed to more precise assessment of the cardiovascular risk and to optimize **the complex approach to patients with RA in our country.**

This gives me grounds **to vote in favor** of the award **of the educational and scientific degree "Doctor"** in a doctoral program "Internal Diseases" at the professional direction "Medicine" to Dr. Georgi Alexandrov Gerganov, a full-time doctoral student at the Department of Propaedeutics in Internal Diseases, Faculty of Medicine, Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

12.01.2026

Prof. Dr. Nikolay Runev, MD