OPINION

From

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Regarding: Dissertation for the award of the academic degree of "Doctor" in the field of higher education 7. Health Care and Sports, professional field 7.1 "Medicine," scientific specialty "Cardiology"

To Dr. Dimitar Tihomirov Hristov, Department of Cardiology and Rheumatology, Division of Cardiology, Faculty of Medicine, "Prof. Dr. Paraskev Stoyanov" Medical University, Varna

Thesis Topic: "Clinical Significance of Pentaxin 3 in Patients with Ischemic Heart Disease Who Are Not Candidates for Revascularization"

Scientific Supervisor: Prof. Svetoslav Georgiev, MD, PhD

By Order No. P-109-299/August 20, 2026, of the Rector of Medical University – Varna, I was appointed as a member of the academic jury, and following its first meeting, I was designated to prepare an opinion on the aforementioned dissertation. The submitted documents comply with the requirements of the Law on Academic Degrees and Academic Titles in the Republic of Bulgaria and the regulations of the Ministry of Education and Science and the Medical University of Varna regarding its implementation.

1. Biographical Information and Professional Development

Dr. Dimitar Tihomirov Hristov graduated from the Medical University of Varna in 2020. In January 2021, he began working as a resident at the Second Clinic of Cardiology (Invasive) at St. Marina University Hospital in Varna. He has been a specialist in Cardiology since June 2025. In September 2025, he obtained a certificate in echocardiography, fundamental level, and in June 2025—in ultrasound diagnostics.

Dr. Hristov's primary research interests lie in the field of diagnostic imaging in cardiology, ischemic heart disease, and heart failure. He has two publications in national journals and one publication in a journal indexed in world-renowned scientific databases. He has presented a paper at national conferences.

He is fluent in English (C1 level).

He is a member of the Bulgarian Medical Association and the Bulgarian Society of Cardiologists.

2. Relevance of the Issue

Coronary heart disease (CHD) is a leading cause of death and disability. It affects more than 244 million people worldwide. The issue is particularly relevant for Bulgaria, a country

that ranks among the highest in terms of morbidity and mortality from cardiovascular diseases, including CHD. Coronary atherosclerosis is a major underlying factor in the development of acute and chronic coronary syndrome. Inflammation plays a leading role in the onset and maintenance of the atherosclerotic process and in the occurrence of related adverse events.

Obstructive coronary atherosclerosis is associated with the maintenance of persistent low-grade vascular inflammation. Studies conducted to date demonstrate that the degree of vascular inflammation induced during PCI likely potentiates subsequent neointimal hyperplasia.

Inflammatory biomarkers appear to be a suitable method for predicting the clinical course of coronary artery disease. Numerous biomarkers have been studied, but none have yet been definitively integrated into daily clinical practice. Pentraxins are a family of proteins that are divided into short and long forms. The most extensively studied member of the first group is C-reactive protein. Pentraxin 3 (PTX3) is the prototype of the long pentraxins. It is produced by cells involved in the progression of atherosclerosis and reflects local vascular inflammation. Its role involves modulating endothelial function, inhibiting neoangiogenesis, and increasing oxidative stress. PTX3 has been studied in a number of inflammatory processes—chronic kidney disease, vasculitides, inflammatory bowel diseases, and carcinomas. Its significance in coronary artery disease has not been studied in detail. Most studies have been conducted in acute coronary syndrome. There are no clearly defined reference values. Of interest is the possibility of using it to stratify the risk of instant restenosis and future adverse cardiovascular events in chronic coronary syndrome in patients with angina symptoms who are not candidates for coronary revascularization. This would contribute to intensifying antianginal and lipid-lowering therapy and ensuring strict medical monitoring in high-risk patients, with the aim of delaying the progression to obstructive coronary atherosclerosis and its complications.

These questions guide Dr. Hristov's research toward clarifying them. Given the clinical significance of ischemic heart disease, there is undoubtedly a need to identify readily available markers for assessing risk and determining the therapeutic approach for these patients.

3. Structure of the Dissertation

Dr. Hristov's dissertation is formatted in accordance with the requirements. It consists of 126 pages and includes 27 figures, 23 tables, and 1 appendix. It is well structured and contains the following main sections: introduction, literature review, objectives and tasks, participants and methods, results and discussion, pharmacoeconomic analysis, findings, scientific contributions, conclusion, limitations, future prospects, publications related to the thesis topic, acknowledgments, and bibliography.

The **literature review** spans 39 pages. It is comprehensive and thoroughly examines the role of inflammation in the pathogenesis of atherosclerosis and the methods for clinically assessing the severity of anginal symptoms. Biomarkers of vascular inflammation are discussed in detail. The data available to date on the association between pentraxin 3 and ischemic heart disease (IHD) are described in the context of ST-elevation acute coronary syndrome, non-ST-elevation acute coronary syndrome, and chronic coronary syndrome. The

correlation between this biomarker and established risk factors is demonstrated. Special attention is given to the relationship between PTX3 and statin use. The limitations of PTX3 as a marker of vascular inflammation and the shortcomings of previous scientific studies are highlighted.

Based on the literature review, Dr. Hristov defines what is known about the dissertation topic and what remains unknown and requires further clarification.

The main **objective** of the research is clearly stated: To define the risk of rehospitalization in patients with ischemic heart disease for whom revascularization procedures are not an option by examining pentraxin 3 levels.

Five specific **tasks** have been set, directly related to achieving the stated goal.

The "**Participants and Methods**" section spans 5 pages. A total of 80 individuals were prospectively studied. The inclusion criteria are specified. The steps of the scientific study are described. All participants completed the Seattle Angina Questionnaire. All participants underwent an ECG, had blood drawn for laboratory tests, and underwent echocardiography and selective coronary angiography. The methods used and the procedures for analyzing the results are presented.

Six groups of **results** are defined—related to the demographic characteristics of the study participants, the risk profile of the study cohort, PTX3, the association between PTX3 and the Seattle Angina Questionnaire, the significance of PTX3 for the extent of atherosclerosis, and its role in clinical follow-up.

Some of the most significant preliminary results are as follows:

1. Most patients are treated at home with one or two antianginal medications, the most commonly used of which are beta-blockers and dihydropyridine calcium channel blockers.

2. The most common risk factors in the study population were smoking (42.5%), hypertension (91.35%), type 2 diabetes (26.3%), and dyslipidemia.

3. The mean PTX3 level was 1.88 ± 2.96 (95% CI 1.22–2.54) ng/mL. Levels were higher in women. No correlation was observed between the biomarker levels and traditional risk factors. There was also no association between PTX3 levels and hsCRP. A trend toward lower PTX3 levels was observed in patients treated with high-intensity statins, though this did not reach statistical significance.

4. Analysis of the results based on data from the Seattle Angina Questionnaire revealed that patients with elevated baseline PTX3 levels experienced more frequent episodes of angina, greater physical limitation, and a poorer quality of life.

5. No statistically significant association was observed between PTX3 levels and the number of arteries affected by moderate stenoses.

6. A PTX3 level of ≥ 0.9205 ng/mL was determined to be the optimal cutoff value for predicting the risk of rehospitalization in the study population. Levels above the cutoff were associated with a significantly higher risk, regardless of renal function.

A **pharmacoeconomic analysis** indicated that, in the routine testing of pentraxin 3 in clinical practice, preventing just one rehospitalization in these patients would be sufficient to ensure a favorable cost-effectiveness ratio.

Seven **conclusions** were formulated to summarize the presented results.

The **scientific contributions** are original and confirmatory in nature. This study is one of the first in Bulgaria to investigate the pentraxin 3 biomarker in patients with ischemic heart disease. For the first time in the available literature, a biomarker has been described that may have clinical significance in patients with stable angina pectoris, aiding in the clinical assessment of angina symptoms. Pentraxin 3 may contribute to the stratification of high- and low-risk patient groups for subsequent rehospitalizations due to worsening angina symptoms. A threshold value has been proposed that can be integrated into clinical practice.

The **bibliography** includes 211 references in Latin script.

In connection with the dissertation, two full-text **publications** are presented, one of which appears in a peer-reviewed and indexed journal.

4. Conclusion

Dr. Hristov's dissertation addresses a current diagnostic and therapeutic issue in the field of cardiology. A sufficient number of patients were studied. The evidence presented above demonstrate that the work is original and corresponds to the stated objectives and tasks.

The dissertation meets the requirements for the award of the academic degree of "Doctor," as set forth in the Law on Scientific Research and Academic Staff in the Republic of Bulgaria (ZRASRB) and the Regulations on the Development of Academic Staff at Medical University—Varna.

I confidently give my **positive evaluation** and recommend to the esteemed members of the academic jury that Dr. Dimitar Tihomirov Hristov be awarded the academic degree of "Doctor" in the scientific specialty of "Cardiology."

October 20, 2026

Varna

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

/Assoc. Prof. Dr. Antonia Kisheva, MD, PhD./