OPINION

by

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Pursuant to Order № P-109-299/20.08.2026, issued by the Rector of the Medical University – Varna, concerning a dissertation for the awarding of the educational and scientific degree of "Doctor"

Field of higher education: 7. Healthcare and Sports

Professional field 7.1. Medicine

Scientific specialty: 03.01.47 Cardiology

Department: Cardiology and Rheumatology, Medical University – Varna

Author: Dimitar Tihomirov Hristov, MD

Topic: „Clinical significance of pentraxin 3 in patients with ischemic heart disease who are not eligible for a revascularization procedure“

Research supervisor: Prof. Svetoslav Georgiev, MD, PhD

The set of materials and documents submitted by Dr. Dimitar Tihomirov Hristov in both hard-copy and electronic format complies with the requirements of the Academic Staff Development Act in the Republic of Bulgaria and the Regulations for its implementation, as well as with the regulations of the Medical University – Varna for the acquisition of the educational and scientific degree of "Doctor". This opinion has been prepared in accordance with the Academic Staff Development Act in the Republic of Bulgaria and the Regulations for its implementation at the Medical University – Varna.

1. Biographical information and professional development

Dr Dimitar Tihomirov Hristov graduated from the Medical University - Varna, Bulgaria, in 2020. In January 2021, he commenced his professional career as an Assistant Professor at the Clinic of Interventional Cardiology, St. Marina University Hospital, Varna. Since June 2025, he has been a certified specialist in cardiology. He has obtained professional qualification certificates in Echocardiography (Basic Level) and Vascular Ultrasound Diagnostics.

His research interests focus on cardiovascular imaging, ischaemic heart disease, cardiovascular biomarkers, and heart failure.

2. Significance of the research problem

Ischaemic heart disease (IHD) is a leading cause of mortality and disability worldwide. In this context, the topic of the doctoral dissertation „Clinical significance of pentraxin 3 in patients with ischemic heart disease who are not eligible for a revascularization procedure“ is both relevant and significant. Coronary atherosclerosis is the underlying pathological substrate for the development of both acute and chronic coronary syndromes. Atherosclerosis is associated with persistent low-grade vascular inflammation, making inflammatory biomarkers potential candidates for predicting the clinical course of ischaemic heart disease. To date, no biomarker has been successfully and widely integrated into routine clinical practice for this purpose. Pentraxin 3 (PTX3), a member of the pentraxin family, is considered a vascular-specific biomarker, as it is produced by cells directly involved in the progression of atherosclerosis, including endothelial cells, vascular smooth muscle cells, and macrophages. The biomarker under investigation appears to have the potential to support the initial assessment of the severity and frequency of anginal symptoms, as well as the subsequent risk stratification. This approach could be used to individualize the therapeutic strategy for each patient, optimize antianginal and lipid-lowering therapy when necessary, and potentially reduce the financial burden on the healthcare system. The introduction of an additional biomarker, such as pentraxin 3, into clinical practice could potentially help optimize healthcare expenditure by refining risk stratification and the indications for performing selective coronary angiography (SCA).

3. Structure

The dissertation has a total length of 126 standard pages, comprising 110 pages of main text and 16 pages of references and appendices. The text is illustrated with 30 figures and 23 tables.

The dissertation is structured as follows: Introduction – 2 pages; Literature Review – 38 pages; Aim and Tasks – 1 page; Participants and Methods – 6 pages; Results and Discussion – 48 pages; Pharmacoeconomic Analysis – 2 pages; Implications – 1 page; Contributions – 1 page; Conclusion – 1 page; Limitations and Future Perspectives – 2 pages; List of Publications – 1 page; Appendices – 2 pages; and References – 14 pages.

Dr Hristov's dissertation follows the classical structure, in accordance with the generally accepted requirements and academic standards in Bulgaria.

The reference list is comprehensive and up to date and includes 211 sources, of which 206 are publications in latin-script languages and 5 are references to web pages. A substantial proportion of the cited publications have been published in recent years.

The literature review is comprehensive and provides a detailed review of the role of inflammation in the progression of atherosclerosis, the methods used for the clinical assessment of anginal symptoms, and the biomarkers investigated to date in patients with ischaemic heart disease, including pentraxin 3. Pentraxin 3 is a specific marker of vascular inflammation, in contrast to C-reactive protein (CRP), which, although extensively studied, is a non-specific inflammatory biomarker. Pentraxin 3 is more sensitive, with its plasma levels increasing more rapidly. The review discusses the involvement of PTX3 in cardiovascular pathology and its biological effects, as well as other potential causes of elevated PTX3 levels, which may practically limit its specificity in patients with multiple comorbidities. Particular attention is paid to pentraxin 3 and ischemic heart disease, including acute and chronic coronary syndromes, with its predictive value in STEMI, unstable angina/NSTEMI, and chronic coronary syndrome being examined separately. A literature review has also been conducted regarding the effects of statins on the levels of the biomarker under investigation. The literature review concludes with an overview of the advantages and limitations of pentraxin 3 as a marker of vascular inflammation, as well as the gaps and limitations in current knowledge.

Aim and tasks. The aim of the study is clearly and precisely formulated: To determine the risk of rehospitalizations in patients with ischemic heart disease who are not eligible for a revascularization procedure, by measuring pentraxin 3 values. The author has formulated 5 specific objectives in accordance with the stated aim of the dissertation.

Methods. The study was conducted at the Clinic of Interventional Cardiology – St. Marina University Hospital, Varna, following approval by the Ethics Committee of the Medical University – Varna. The dissertation is based on a prospective follow-up study involving a total of 80 patients aged up to 70 years, in whom coronary atherosclerosis was confirmed by selective coronary angiography. Revascularisation was not indicated in these patients, either because stenosis of less than 70% of the luminal diameter was documented in at least one coronary

artery or because of diffuse coronary atherosclerosis. A total of 80 participants who were treated at the clinic during the period December 2022 – January 2025 were included, with the follow-up period ending in September 2025. The patients were followed up for rehospitalizations due to worsening of angina symptoms, including unstable angina pectoris and fatal or non-fatal myocardial infarction, with subsequent selective coronary angiography ± percutaneous coronary intervention (PCI) being performed. Patients with severe comorbidities, including those with inflammatory diseases, were excluded. The materials and methods are described in detail and in an informative manner. A broad range of methods was employed, including structured interview, clinical examination, laboratory investigations, and instrumental examinations (echocardiography and selective coronary angiography).

The results are well structured and clearly presented using figures and tables. The included patients are homogeneously distributed by sex, most are overweight or obese and have normal left ventricular systolic function. Antianginal therapy was also evaluated, with most patients receiving one or two medications: mainly beta-blockers and dihydropyridine calcium channel blockers. The patients' risk profiles included smoking, hypertension, type 2 diabetes mellitus, and dyslipidemia. No differences were found in pentraxin 3 levels in relation to the presence of traditional risk factors for atherosclerosis, potentially suggesting that pentraxin 3 could be used as an independent additional risk factor. Interestingly, no correlation was observed between pentraxin 3 and CRP levels. Furthermore, a downward trend in biomarker levels was observed in the study population in association with both the presence and intensity of statin therapy, although this trend did not reach statistical significance. The pleiotropic effects of statins are well established, and a reduction in PTX3 levels may potentially serve as an indicator of their anti-inflammatory effects. The relationship between pentraxin 3 levels and selected domains of the Seattle Angina Questionnaire was also examined. PTX3 levels are higher in patients presenting with more pronounced clinical manifestations of the disease. The patients were followed up for a mean period of 16 months, and those with higher baseline biomarker levels were at increased risk of rehospitalization due to worsening of angina symptoms. Furthermore, a threshold value was identified that successfully stratified the patients into low- and high-risk groups.

The discussion provides a logical and in-depth analysis of the results obtained, including appropriate comparisons with data published in the literature.

A total of seven **implications** are presented, summarising the findings of the study.

A **pharmacoeconomic analysis** was conducted, indicating that the strategy involving routine PTX3 testing results in only one fewer rehospitalisation being required to achieve a favourable cost-effectiveness ratio.

The contributions are divided into fundamental contributions and contributions of a confirmatory nature, which have both scientific and practical value. I fully endorse the scientific contributions.

Publications. With regard to the dissertation, two full-text scientific articles have been presented with Dr Hristov as the sole author. One of the articles has been published in a peer-reviewed and indexed journal. Both publications are directly relevant to the subject matter of the dissertation.

In conclusion, the dissertation of Dr. Dimitar Tihomirov Hristov, entitled „Clinical significance of pentraxin 3 in patients with ischemic heart disease who are not eligible for a revascularization procedure“ submitted for the award of the educational and scientific degree of “Doctor,” meets, in terms of its relevance, aims, objectives, methodology, conclusions, and contributions, all the requirements of the Academic Staff Development Act in the Republic of Bulgaria and the Regulations for its implementation at the Medical University – Varna. The dissertation contains scientific and applied results that constitute an original contribution to science. Furthermore, the dissertation has significant scientific and practical value for routine clinical practice and demonstrates favourable economic outcomes associated with the incorporation of PTX3 testing into the follow-up algorithm for patients with an appropriate clinical profile of ischaemic heart disease.

In view of the above, I hereby give my positive assessment and recommend that the members of the Scientific Jury at the Medical University – Varna award

Dr. Dimitar Tihomirov Hristov the educational and scientific degree of "Doctor" in the scientific specialty of Cardiology.

21.10.2026 г. **Associate prof. Vasil Velchev, MD, PhD**

