REVIEW

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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 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 review 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.

Significance and relevance of the topic. The topic of the 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. 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. Specifically in Bulgaria, it is a well-established fact that the country ranks among those with the highest rates of cardiovascular morbidity and mortality, while at the same time having a high number of cardiac catheterization laboratories and a large volume of diagnostic and interventional procedures performed. These statistics demonstrate that a substantial proportion of the financial resources of the Bulgarian healthcare system is allocated to highly specialized investigations and procedures, without this having a significant impact on overall premature mortality due to cardiovascular disease compared with countries where fewer financial resources are invested in this sector. 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.

Structure. The dissertation has a total length of 126 standard pages, comprising 110 pages of main text and 16 pages of references and appendices. It is appropriately structured, with a well-balanced proportion between the literature review (38 pages) and the remaining sections, namely: aim and objectives, participants and methods, results and discussion, conclusions, contributions, and final remarks. The text is illustrated with 30 figures and 23 tables. 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 thesis summary is 72 pages in length and complies with the requirements of the Academic Staff Development Act. It presents the main results and findings of the dissertation and includes the most illustrative figures and tables.

The literature review is comprehensive and well structured. The role of inflammation in atherogenesis is examined in detail, and various biomarkers, including pentraxin 3, are discussed. Pentraxin 3 is a specific marker of vascular inflammation and is locally produced by cells involved in the progression of atherosclerosis, unlike CRP, for example, which is a nonspecific inflammatory biomarker. Pentraxin 3 is more sensitive, with its plasma levels increasing more rapidly. Its involvement in cardiovascular pathology and its biological effects are discussed, as are other potential causes of elevated pentraxin 3 levels, which may substantially reduce 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. The author has defined five specific tasks related to the stated aim.

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. A total of 80 participants who were treated at the clinic during the period 2022–2025 were included. All participants had invasively established coronary atherosclerosis that did not require or was not amenable to revascularization. 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 (SCA) ± 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 study design is presented in a clear and illustrative manner. The statistical methods used are standard for this type of study and were appropriately applied to substantiate the results obtained and the conclusions drawn.

The results are presented over 48 pages and are well structured and illustrated with 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. The patients' risk profiles included smoking, hypertension, type 2 diabetes mellitus, dyslipidemia, and family history. Hypertension was the most common risk factor, with no differences observed between the sexes. 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, which has a biological explanation. Furthermore, no statistically significant effect of statin therapy on pentraxin 3 levels was observed, raising the question of whether these levels may be genetically determined. The relationship between pentraxin 3 levels and selected domains of the Seattle Angina Questionnaire was also examined, with statistically significant correlations being identified for some of the domains. Ultimately, the results of the study support the hypothesis that patients with elevated baseline pentraxin 3 levels experience more frequent episodes of angina, greater physical limitation in daily activities, and poorer quality of life. In both sexes, pentraxin 3 could potentially be used in clinical practice as an adjunct to clinical assessment of the severity and frequency of anginal symptoms. The biomarker may be useful in refining the need for subsequent selective coronary angiography in patients with chronic coronary syndrome. 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, independently of traditional risk factors.

Based on the analysis performed, Dr. Hristov draws the following **conclusions:**

1. Mean pentraxin 3 levels are higher in women compared to men.

2. There is no correlation between pentraxin 3 and C-reactive protein values in patients without clinical and laboratory evidence of inflammatory disease.

3. Pentraxin 3 has the potential to be used in clinical practice as a functional biomarker for angina symptom severity, helping clinical assessment and patient selection for SCA.

4. In the conducted study, patients with pentraxin 3 values < 0,9205 ng/mL have a 5% probability of rehospitalizations due to worsening of angina symptoms during clinical follow-up: median 16 months (IQR 9–23).

5. In the conducted study, pentraxin 3 values ≥ 0,9205 ng/mL demonstrate a sensitivity of 81,8% and a specificity of 55,1% for predicting rehospitalizations due to worsening of angina symptoms during clinical follow-up: median 16 months (IQR 9–23).

6. Measuring pentraxin 3 after SCA in patients who are not eligible for a revascularization procedure may contribute to differentiating a high-risk group according to the risk of subsequent rehospitalizations due to worsening of angina symptoms.

7. The high-risk group requires intensification of statin and antianginal therapy, as well asclose medical follow-up.

The discussion provides a logical and in-depth analysis of the results obtained, including appropriate comparisons with data published in the literature. Although the results and discussion are conventionally presented as separate sections, the structure chosen by the doctoral candidate is more comprehensible in this particular case.

Study limitations. The limitations of the study are presented honestly and objectively. Prospects for future research and further development are also outlined.

Conclusions and contributions. The conclusions drawn are a logical consequence of the results presented. The contributions of the present dissertation are divided into fundamental contributions and contributions of a confirmatory nature. Particular attention

should be paid to the pharmacoeconomic analysis performed, which constitutes an additional fundamental contribution of the doctoral candidate.

Publications. Two scientific articles related to the dissertation have been published, with Dr. Hristov as the sole author. The publications address topics directly related to the subject matter of the dissertation.

In conclusion, the dissertation of Dr. Dimitar 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 demonstrates that the doctoral candidate possesses in-depth theoretical knowledge and professional skills in the relevant scientific specialty, as well as the ability and competence to conduct independent scientific research.

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

14.09.2026 г.

Associate prof. Elena Dimitrova, MD, PhD

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