

To the Chairman of the Scientific Jury,
determined by order №308/22.07.2021
of the Executive Director of
the National Heart Hospital – Sofia

REVIEW

By Prof. Dr. Tchavdar Nikolov Shalганov, MD, PhD

Professor of Cardiology at the National Heart Hospital – Sofia

Member of the Scientific Jury for the competition for the academic position "Associate Professor" in the scientific specialty 03.01.47. Cardiology, determined by order №308/22.07.2021 of the Executive Director of the National Heart Hospital – Sofia by decision of the Scientific Council with protocol №19/29.06.2021.

Subject: Competition for the academic position "Associate Professor" in the field of higher education 7. "Health and Sports", scientific field "Medical Sciences", professional field 7.1 "Medicine", scientific specialty 03.01.47. Cardiology, in the Clinic of Cardiology at the National Heart Hospital, announced in SG, issue 45/28.05.2021.

The only candidate is Dr. Iliana Hristova Petrova-Stoyanova, MD, PhD, full-time assistant in the Clinic of Cardiology at the National Heart Hospital.

The candidate has submitted in time the documentation necessary for the preparation of this review, in accordance with the requirements of the Academic Staff Development Act, the Regulations for the implementation of the Act, and the Regulations for the development of the academic staff in the National Heart Hospital.

I have not had any common publications or scientific projects with the candidate, nor any other conflict of interest to declare.

I. Brief biographical data

Dr. Iliana Petrova-Stoyanova graduated in medicine with honors from the Medical University – Sofia in 2005. She began working as an assistant at the Cardiology Clinic of SBALSSZ – Sofia in 2006. She specialized in cardiology and in 2013 acquired a degree in cardiology at the Medical University – Sofia. As of the date of announcement of this competition, she has a total work experience of 15 years as a medical doctor.

She has national certificate for invasive cardiology since 2013. In July 2020 she obtained a scientific and educational degree "Doctor" after defending a doctoral thesis on " Examination of renal function in patients undergoing invasive angiography by a new biomarker – Neutrophil Gelatinase-Associated Lipocaline (NGAL)".

Dr. Petrova-Stoyanova is a member of the Bulgarian Society of Cardiologists, the Bulgarian Society of Invasive Cardiology, the European Society of Cardiology, European Association of Percutaneous Cardiovascular Interventions, and the Association for Acute Cardiovascular Care. Former secretary of the Working group on acute coronary syndrome at the BSC (term 2010-2012). Reviewer for Renal Failure journal (IF 2.606).

She speaks English and French.

II. Research activity

Research projects

Dr. Iliana Petrova-Stoyanova participated in the research team on a research project on "Changes in the human plasma/serum proteome in patients with heart failure" under a 2008 contract with the Research Fund, in which performers of the project were the Institute of Molecular Biology at the Bulgarian Academy of Sciences, the Central Laboratory of Therapeutic Drug Monitoring and Clinical Pharmacology at the University Hospital "Alexandrovska" and the National Heart Hospital. The project was implemented in March 2012.

Publications

Dr. Petrova-Stoyanova presented for this competition a list of a total of 65 publications, of which:

- 1 doctoral thesis for the educational and scientific degree "Doctor"
- 4 full-text publications related to the doctoral thesis – 2 of them in journals indexed in world databases (first author in all four)
- 11 full-text publications in editions included in the National Reference List of NACID – she is first author in four, and second author in three papers
- 17 scientific abstracts from Bulgarian scientific forums, published in journals from the National Reference List of NACID – in 3 of them she is the first author
- 25 scientific abstracts from international scientific forums, published in collections and journals, indexed in world databases (Web of Science) – she is the first author in 6 of them and second author in another four
- 6 chapters in textbooks and monographic collections in Bulgarian, in which she is the sole author
- 1 monograph entitled "Modern aspects of contrast-induced nephropathy in cardiology", published in 2021

I do not find any data of plagiarism in the publications presented.

Citations

The candidate has submitted a citation reference from the Central Medical Library of the Medical University – Sofia (№305/21.06.2021).

According to the reference, the citations in Bulgarian sources are a total of 10. There is one citation in foreign sources in the Web of Science database and two more in the Google Scholar database.

The **H-index** of Dr. Iliana Petrova in Web of Science is **1**.

The candidate's work, as expected, shows research interests focused mainly on various aspects of invasive cardiology, but also extending to other areas of cardiology. The publications on the presented list include a variety of original studies, chapters in collections and textbooks, case reports and reviews, and can be summarized into several groups: contrast-induced nephropathy; coronary interventions; catheter interventions in acute pulmonary thromboembolism; acute coronary syndromes; hypertension; heart failure.

Contrast-induced nephropathy

In numerous publications, Dr. Petrova-Stoyanova discusses in depth the issue of contrast-induced nephropathy (CIN) in the general and cardiological medical practice.

The works on this topic pay serious attention to all aspects of the problem. The epidemiological data, the frequency of CIN and the risk factors related to its development are considered in detail. The conditions for the occurrence of CIN after angiography and the clinical significance of the problem are indicated. The main mechanisms associated with changes in renal hemodynamics, vasoconstriction, direct cytotoxicity, physicochemical characteristics of contrast agents and oxidative stress, which lead to impaired renal function, are discussed in detail.

The clinical consequences associated with the development of CIN are presented both in the short term (in-hospital mortality, hospital stay, health care costs) and in the long term in terms of progression to chronic kidney disease and overall mortality. The lack of etiological treatment and the multiple pathophysiological mechanisms that act synergistically in the development of CIN determine the emphasis on preventive approaches. Based on the pathophysiological mechanisms, the main directions related to the prevention of CIN are noted. The different hydration regimes, the tools aimed at influencing the oxidative stress, the introduction of formulas for calculating the required amount of contrast agent and the influence of different types of contrasts according to their osmolarity are presented. Attention is also paid to new methods, such as the individualized approach through hemodynamic monitoring during the invasive study in order to improve the effectiveness of prevention.

A significant part of the candidate's publications, still in relation to CIN, are devoted to the new renal biomarker neutrophil gelatinase-associated lipocalin (NGAL) in clinical practice. For the first time in Bulgaria Dr. Petrova-Stoyanova performed reliable laboratory calibration and turbodimetric measurement of NGAL in plasma samples of patients with stable forms of chronic coronary syndrome, indicated for scheduled angiography. In this way she introduced into clinical practice the use of a new biomarker. The biomarker showed a good correlation with serum creatinine and assisted in the early diagnosis of renal abnormalities after contrast angiography. In fact, plasma NGAL increased as early as 4 hours after the end of the procedure in patients developing CIN, and thus a very good diagnostic value is achieved based on the calculated sensitivity and specificity. The candidate has identified a specific group of patients in whom NGAL increases significantly, but without concomitant changes in serum creatinine. This group of patients is thought to have a subclinical form of acute renal injury after angiography. There is also a subset of patients with baseline renal dysfunction in whom NGAL may be a marker of progressive renal impairment. In patients with advanced CKD, NGAL levels were significantly higher than in groups without CKD. At the

same time, the dynamics of NGAL may be slowed down, but its good correlation with serum creatinine is maintained. For the first time, the use of NGAL in a risk scale and determination of the prognosis was demonstrated even before the invasive study was performed. The use of NGAL in the diagnostic algorithm outlines groups with a higher risk of renal dysfunction compared to the assessment based on serum creatinine.

A comprehensive summary of all aspects of the problem of CIN and the use of various biomarkers (including NGAL) for diagnosing subclinical forms of CIN and for predicting the evolution of renal function after contrast studies is made in the monograph of Dr. Petrova-Stoyanova. This work provides an interdisciplinary approach to the problems of CIN, based on nephrological knowledge, established cardiac practices and candidate's own data.

Interventional cardiology

Dr. Petrova-Stoyanova participated in a research team that studied and introduced a completely new method for assessing myocardial ischemia during percutaneous coronary interventions (PCI) by recording an intracoronary electrocardiogram (ECG). The method uses the coronary guide inserted into the main/side branch in bifurcation lesions to record a unipolar ECG signal. An ECG recorded at baseline, during and after PCI from each distal vessel over 1.5 mm caliber, in the area of the stent and proximal to it, marks the areas of ischemia. The results were compared with conventional biomarkers for myocardial necrosis, and patients were followed clinically for up to 12 months after the procedure. Multifactorial regression analysis showed that final ST-elevation in the main and side branches was the only independent predictor of major adverse events as well as the development of in-stent restenosis.

The candidate also participates in the NHH's own register for PCI, with a focus on the treatment of bifurcation lesions by implanting a special BIFurcation Optimization Stent System in two variants – coated with biodegradable polymer impregnated with paclitaxel (BIOSS Expert) or sirolimus (BIOSS Lim). The design of the stent provides much better adaptation to the coronary anatomy and diameter of the main vessel. The effectiveness of the two models in patients with severe angina pectoris was compared, taking into account the immediate results and the remote events within one year. The incidence of in-stent/in-segment restenosis and major adverse cardiac events was significantly lower in the BIOSS Lim variant.

A series of publications review the staged performance of PCI in stable patients with angiographically proven two- and three-vessel coronary artery disease. The NHH's own results show that two-stage PCI does not carry an increased risk, and in many cases patients have significant clinical improvement and even disappearance of symptoms after the first PCI.

A series of scientific abstracts reports NHH's own experience in the treatment of patients with STEMI with a detailed analysis of the risk profile, clinical presentation and therapeutic approach taken. The comparison of the data from different years proved that with the entry of the interventional treatment the in-hospital complications were reduced. Older patients were more likely to present with more severe heart failure (HF), and those over 80 years of age and STEMI treated conservatively had higher in-hospital mortality than patients treated interventionally. Briefly, the interventional approach in adult patients improved short-term outcomes and survival without significantly increasing hemorrhagic complications.

Another series of scientific abstracts examined the risk profile of a specific population with STEMI – women under and over 65 years of age. The analysis of the data from the NHH's own registries showed that older women had a significantly higher incidence of HF during hospitalization and intraaortic counterpulsation was more often required. In-hospital mortality in women over 65 was higher, with age being an independent predictor in univariate analysis.

Some of the abstracts analyzed patients with STEMI and anemia on admission. At baseline, these patients were elderly, with a lower body mass index and impaired renal function. The presence of anemia during treatment lead to a significantly more frequent manifestation of HF, despite similar LV function with other patients, and to less frequent use of PCI. Complications and the need for mechanical ventilation or intra-aortic balloon counterpulsation were significantly more common in this group of patients. Overall, the in-hospital mortality was significantly higher in both the general group of anemic patients and the subgroup of PCI-treated patients compared to patients without anemia. The results show that anemia in the course of STEMI should be considered as an additional risk factor, significantly worsening the short-term prognosis. Targeted analysis on a group of patients with NSTEMI confirmed the described trends. Anemic patients had longer hospital stay, were more likely to develop HF and needed more frequently hemodialysis treatment. Blood transfusions were much more common, despite the similar incidence of in-hospital bleeding. Despite similar treatment regimens, patients with NSTEMI and anemic syndrome had poorer survival.

The candidate also performed a comparative analysis between the main clinical features and risk factors in patients with STEMI versus NSTEMI, which showed that those with NSTEMI were older, with a predominance of already known ischemic disease and previous percutaneous interventions, significantly more frequently accompanied by peripheral -vascular disease and anemic syndrome. Patients with NSTEMI had better control of glycemia and lipid status due to good secondary prophylaxis. Dr. Petrova-Stoyanova also summarized her own data from the NHH during treatment of patients with acute coronary syndrome, with a focus on the association between blood sugar levels at hospitalization and subsequent complications. Regardless of diabetic status, patients with high blood sugar values were significantly more likely to develop heart failure, arrhythmias, and mechanical complications. In patients with known diabetes mellitus, poor glycemetic control was an independent predictor of poor long-term prognosis.

Another aspect of cardiac catheter interventions, well covered in the work of Dr. Petrova-Stoyanova, is the treatment of acute pulmonary thromboembolism by local fibrinolysis, rotational thrombus fragmentation and catheter thrombus aspiration as an alternative to systemic fibrinolysis. The method showed good results with a significant increase in oxygen saturation, oxygen partial pressure, reduction of right ventricular dilatation and improvement of right ventricular dysfunction, a significant decrease in systolic and mean pulmonary artery pressure. The six-month follow-up showed 100% survival with improvement in functional class. The method is an alternative to systemic fibrinolysis in patients at high risk, practically applicable, safe and effective, incl. remotely.

Older publications have focused on *hypertension*. Its relationship to cognitive impairment is discussed, as well as the importance of adequate control of blood pressure to improve cognitive function, the interaction between psychosocial stress and blood pressure, and approaches to reducing stress for better pressure control. The candidate also considered the role of home blood pressure measurement for diagnosing office hypertension and for improved blood pressure control.

Hypertension was also considered as a major risk factor for ischemic heart disease in a national and an international epidemiological study in which Dr. Petrova-Stoyanova participated.

In another group of publications, the candidate examined in detail all aspects of *heart failure* related to the etiology, classification, clinical presentation, and underlying pathophysiological mechanisms. The main therapeutic approaches, approved by clinical guidelines, are comprehensively discussed. Special attention is paid to the hemodynamic changes that occur in the development of chronic HF, and the scientific evidence related to the inclusion of all compensatory mechanisms and their harmful effects in their long-term persistence is presented in detail. The hemodynamic profile of diastolic dysfunction, which underlies heart failure with preserved ejection fraction, is also presented.

III. Teaching activity

A certificate of teaching workload was provided by National Heart Hospital (№2100-644/27.07.2021). It is evident from it that for the last 5 years the teaching load of Dr. Petrova-Stoyanova amounted to an annual average of 250 hours with graduates, interns and students.

In addition, the candidate presented a list of 31 oral presentations without published abstract at national scientific and educational forums, other than the published scientific abstracts described in section II.

IV. Diagnostic and therapeutic activity

Dr. Iliana Petrova-Stoyanova is a specialist with extensive experience in the diagnosis and treatment of cardiovascular disease. Its activities are focused mainly on clinical and invasive cardiology. She is responsible in her work, has organizational skills, and is able to make responsible decisions.

V. Compliance with the minimum national requirements

Dr. Iliana Petrova-Stoyanova presented a completed table of compliance in accordance with Regulations for the implementation of the Academic Staff Development Act.

The fulfillment of the minimum requirements by groups of indicators is as follows:

- Group A – completed (50 points)
- Group B – not required for academic position "Associate Professor"
- Group C – completed. A habilitation thesis is included – a monograph, which fulfills the required minimum of 100 points.
- Group D – completed. The candidate calculated her score at 389.35 points with a required minimum of 200 points. I calculated the actual total to 389.35 points.
- Group E – completed (75 points with a required minimum of 50 points).
- Group F – not required for academic position "Associate Professor"

Total points: 614.35. The calculations in the self-assessment are correct. The required minimum for AD "Associate Professor" is 400 points, therefore the candidate not only fulfills it, but also exceeds it by more than 50%.

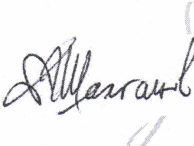
VI. Critical remarks

- The candidate has failed to present complete information on membership in scientific and professional organizations and on participation in various scientific forums in the form of lectures, trainings, etc. without published abstract. This does not affect the scientometric indicators, but may leave the jury with the wrong impression of lesser activity.

In conclusion, Dr. Iliana Hristova Petrova-Stoyanova has a serious teaching load, she has acquired a specialty, she is board-certified in invasive cardiology, has a long medical experience, significant practical skills, and serious experience in research. She has also a large number of publications and a good number of citations. She fulfills and exceeds the minimum national scientometric indicators required by Regulations for the implementation of the Academic Staff Development Act. Therefore, my vote on the candidacy of Dr. Petrova-Stoyanova is "positive" and I allow myself to recommend to the esteemed Scientific Council at the National Heart Hospital to vote also positively for its approval on the academic position "Associate Professor".

Sofia, 31.08.2021

Prof. Dr. T. Shalганov, MD, Ph.D.

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The first part of the document discusses the importance of maintaining accurate records of all transactions. It emphasizes that proper record-keeping is essential for the company's financial health and for providing reliable information to stakeholders. The document outlines the various methods used to collect and analyze data, including interviews, surveys, and focus groups. It also describes the process of identifying key trends and patterns in the data, which are then used to inform strategic decisions. The second part of the document provides a detailed overview of the company's current operations, including its products, services, and market position. It highlights the company's strengths and areas for improvement, and discusses the challenges it faces in a competitive market. The document concludes with a series of recommendations for future actions, which are designed to help the company achieve its long-term goals and maintain its leadership in the industry.

Appendix A
Appendix B
Appendix C
Appendix D
Appendix E