



**To the President of the
Scientific jury appointed by
order of the Executive Director
of the National Heart Hospital
No 309/22.07.2021**

OPINION

From Prof. Borislav Georgiev Georgiev, MD,
Head of Cardiology Clinic at National Heart Hospital

Member of the scientific jury for the competition for the acquisition of the academic position "Associate Professor" in the field of higher education 7. "Health and Sport", professional field 7.1. "Medicine" and scientific specialty "Cardiology" for the needs of the Clinic of Cardiology at the National Heart Hospital EAD announced in SG issue 45/28.05.2021 and according to order No 309/22.07.2021

For the above competition, documents were submitted by one candidate – Dr. Elena Svetlozarova Dimitrova, PhD, Assistant professor at the Clinic of Cardiology of the National Heart Hospital. The opinion was prepared according to the requirements of the Law and the Rules of Development of Academic Staff, as well as the Rules of Procedure for acquiring scientific degrees and holding academic positions in the Republic of Bulgaria and the Rules of Procedure for acquiring scientific degrees and holding academic positions at the National Heart Hospital EAD. The procedure for announcing the competition complies with the requirements of the Law on Scientific Degrees and Scientific Titles. The documents submitted by the applicant are in accordance with the requirements of the regulation for the academic position "Associate Professor" and the rules of the National Heart Hospital EAD. I do not find any gaps in the submitted documentation and declare that I do not have general scientific papers with the candidate.

1. Research

Dr. Elena Dimitrova has presented for the competition:

1.1 Dissertation on "*Prospective follow-up of patients with pulmonary arterial hypertension and evaluation of the effect of specific therapy on the functional class and clinical course of the disease in compliance with a certain protocol for follow-up and escalation of therapy*" and the abstract.

1.2 Publications after acquisition of "Assistant professor" academic position
6 chapters in books,

13 articles in scientific journals, 3 of which are with impact factor
25 published abstracts from national and international conferences.
In 14 of the scientific papers Dr. Elena Dimitrova is the first author.

1.3. Authorship and citations

The official citation from the Central Medical Library mentions 15 citations in Bulgarian scientific journals.

43 citations are found in the Scopus database, and 43 citations are found in the Web of Science. The report states that citations in both databases partially overlap.

2. Profile of research, practical and applied activities

In accordance with the profile of scientific work, Dr. Dimitrova works in 5 main directions:

❖ Direction ***Pulmonary Hypertension and Pulmonary Thromboembolism***: Dr. Dimitrova has presented 2 publications in Bulgarian journals, 3 chapters of books and 2 abstracts from international forums.

❖ Direction ***Coronary artery disease and acute coronary syndrome***: 3 original articles are presented with an analysis of the impact of the first wave of COVID-19 pandemic and the restrictive measures imposed on the number of hospitalized patients with myocardial infarction; with retrospective analysis by one Bulgarian center of incidence and prognostic significance of anemia in patients presenting with acute myocardial infarction with persistent ST-segment elevation and for acute heart failure, complicating the in-hospital phase of acute myocardial infarction with persistent ST-elevation. Dr. Dimitrova has also presented 17 abstracts from scientific conferences, of which 10 – international with publication of the abstracts in journals with impact factor.

❖ Direction ***atrial fibrillation, DC-shock therapy and cardiostimulation***: Here are presented 2 full-text publications describing the results of a registry of patients with atrial fibrillation from the Balkan region BALKAN-AF and analysis of data on the real-world use of anticoagulant therapy in this population, 1 publication comparing the efficacy and safety of a protocol with non-escalating energies compared with standard protocols for DC shock in atrial fibrillation and flutter with an increase in shock energy on each subsequent step and 1 publication examining a series of patients with recurrence of intraventricular obstruction after an alcoholic septal ablation in hypertrophic obstructive cardiomyopathy, which have been successfully treated by permanent cardiostimulation. The applicant also presents 6 abstracts of scientific forums, of which 5 – international with publication of the abstracts in referred journals.

❖ Direction ***pharmacotherapy***: Dr. Dimitrova presents 1 overview of the literature concerning clopidogrel use for various clinical indications, including as part of triple antithrombotic therapy, as well as its comparison with the new more potent antiplatelets prasugrel and ticagrelor, 1 article with several clinical cases from practice and comment on the main considerations in the selection of triple antiplatelets-anticoagulant therapy in accordance with the current recommendations and a chapter of a book with a detailed overview of the place of colchicine as a powerful antiinflammatory agent in the therapy of coronary artery disease, and in particular acute coronary syndrome, as well as a discussion on the results of recent clinical studies in the field.

❖ In the field of ***rare clinical cases and other*** Dr. Dimitrova has presented 3 publications with rare cases of clinical practice, and a chapter of a book provides a detailed overview of the literature, including the efficacy, etiology, pathogenesis, clinical development, diagnostic and therapeutic algorithms in orthostatic hypotension

3. Most significant scientific contributions

Research and clinical activity are in areas which can be grouped into several fields: pulmonary hypertension and pulmonary thromboembolism, coronary artery disease and acute

coronary syndrome, atrial fibrillation and DC-shock therapy, electric cardiac stimulation, pharmacotherapy, rare clinical cases and others.

1. Scientific contributions in the field of pulmonary hypertension and pulmonary thromboembolism

The author has a clear scientific interest in the field of pulmonary hypertension and has been actively involved in the diagnostic and therapeutic process in patients with pulmonary arterial hypertension, as well as in the creation, application and validation of a specific algorithm for follow-up. Of particular importance is the publication in Bulgaria for the first time of aggregated data on the topic of long-term follow-up, the analysis of mortality and direct comparisons with the results of the major international registries. The contributions in the field are also related to the PhD thesis (*dissertation work, publications 7, 8 and 21, abstracts 1-4 and 7*).

A comprehensive overview of the literature on the therapeutic strategy for chronic thromboembolic pulmonary hypertension has been carried out. A particular contribution in the field is the presentation of two own clinical cases with pulmonary thrombendarterectomy (*publications 1 and 2*).

Of special interest is the published rare clinical case of a patient with compression of the left main coronary artery in the setting of high-grade pulmonary arterial hypertension (*publication 3, abstract 5*) – this is the first such published case for Bulgaria.

The candidate presents two real clinical cases of pulmonary arterial hypertension in congenital heart diseases (*publication 23*).

A contribution in the field of pulmonary hypertension is also the detailed and modern overview of the characteristics and the application of the various biomarkers in patients with pulmonary thromboembolism and pulmonary hypertension (*publication 9*). Another contribution in this area is the overview of the novelties and evolution of some of the concepts in the field of pulmonary hypertension concerning pathophysiology of the right ventricle and pulmonary circulation, genetics, hemodynamic definition, classification, diagnosis, risk stratification and therapeutic algorithm presented to the Sixth World Symposium of Pulmonary Hypertension, Nice'2018 (*publications 11 and 12*). A contribution to the field is also the overview of the literature concerning a very common group of patients with pulmonary hypertension with underlying chronic lung disease (*publication 17*). Especially valuable and useful for the practice is the overview on pulmonary hypertension in anticancer therapy – a topic that is extremely relevant in light of the great development in the field of anticancer therapy (*publication 20*).

Based on own data from consecutive hospitalized patients with moderate and high risk pulmonary thromboembolism, the applicant was involved in the creation of a new non-invasive indicator that can be used to predict the risk of in-hospital mortality (*abstract 35*). Risk stratification in patients with pulmonary thromboembolism is essential for the choice of appropriate therapy and prognosis.

2. Scientific contributions in the field of coronary artery disease and acute coronary syndrome

A significant contribution to the field was participation in a study conducted among 200 patients with invasively proven coronary artery disease in which it was studied whether polymorphisms in several candidate-genes were associated with the presence of multifocal

atherosclerosis (carotid or peripheral atherosclerosis) - Endothelin-1 138A I/D and matrix metalloproteinase-3 5A/6A.

A contribution to the field is the analysis of ongoing cardiovascular risk after acute coronary syndrome with a focus on the role of long-term antiplatelet therapy after the 12th month of percutaneous coronary intervention (*publication 10*).

Based on own data from National Heart Hospital, an analysis of the impact of the first wave of the COVID-19 pandemic and the restrictive measures on the number of hospitalized patients with myocardial infarction, their characteristics and the course of the disease was carried out, the results being compared with a similar period in the previous year and commented in the light of published data from Europe and the USA (*publication 13*). These are the only data published so far about Bulgaria on the topic.

In a series of publications and abstracts, based on data from National Heart Hospital, the prognostic role of pre-existing anemia in patients with acute myocardial infarction with and without persistent ST-elevation was analyzed. Anemia was found to be an independent predictor of a complicated course of the myocardial infarction and increased in-hospital mortality (*publication 26, abstracts 13, 16 and 23*). The prognostic role of blood glucose at hospital admission of patients with troponin-positive acute coronary syndrome was also investigated, finding that high blood glucose was an independent predictor of poor prognosis in both patients with concomitant diabetes mellitus and those with no history of diabetes (*abstracts 17 and 31*).

The development on acute heart failure as a complication of the in-hospital phase of acute myocardial infarction was also analysed as frequency. It was found that even with reperfusion treatment as recommended, infarction size and left ventricular dysfunction remained independent predictors for the development of acute heart failure in patients with myocardial infarction with ST-elevation.

Another contribution in the field is the submitted own results of treatment of ST-elevation infarction in adult patients – their poorer prognosis compared to younger patients and the advantages of interventional treatment to reduce complications of heart attack and mortality even in older patients (*abstract 24*) as well as the experience of National Heart hospital in the treatment of adult women with acute myocardial infarction with persistent ST-elevation - their poor short-term prognosis is demonstrated compared to younger women despite the same reperfusion and medication treatment (*abstract 12 and 22*).

A direct comparison of the risk profile of patients with myocardial infarction with and without ST-elevation was also a significant contribution in the Bulgarian population. Patients with non-ST-elevated myocardial infarction had comparable frequencies of most coronary heart disease risk factors compared to ST-elevated myocardial infarction patients and appeared to have better control of risk factors and prognostic biomarkers. As a possible explanation of the observed results, secondary prophylaxis after an event (*abstracts 15 and 30*) is commented. Additionally, the incidence and prognostic value of chronic total occlusion (CTO) was analysed in patients with acute myocardial infarction with and without ST-elevation. It was found that in patients with STEMI the presence of a CTO was a significant predictor of worse long-term prognosis, independent of the presence of concomitant left main or triple vessel disease. In patients with NSTEMI it was found, however, that the presence of a CTO did not affect the prognosis (*abstracts 18, 33 and 34*).

Scientific contribution in the field of acute coronary syndrome is research on the prognostic value of inflammation status at admission of patients with acute myocardial infarction with ST-elevation treated with percutaneous coronary intervention – it was found to be an independent predictor for in-hospital mortality, with patients with the most pronounced inflammation, assessed by leukocyte count and hs-CRP level, having a 5 times higher risk of death (*abstracts 26*).

3. Scientific contributions in the field of atrial fibrillation, DC shock therapy and electrocardiostimulation

The candidate participated in the unique registry of patients with atrial fibrillation from the Balkan region BALKAN-AF. As is known, most data from the practice come from Western Europe, and the data from sub-analyses of large studies with direct oral anticoagulants (DOAC) do not reflect real clinical practice. Therefore, a significant scientific contribution in the field are the results of real life concerning the therapeutic strategy and in particular the use of anticoagulant therapy in patients with atrial fibrillation from the Balkan region (*publications 28 and 29*).

Another contribution in the field is the participation of the author in a registry of patients with atrial fibrillation/flutter undergoing elective synchronised DC cardioversion. In a series of publications real-life data on the efficacy and safety of a protocol with non-escalating energies compared to standard protocols with escalating energies of the shock of each subsequent step are presented (*abstract 20*), as well as an individualized protocol for DC cardioversion relative to the patient's body surface area. It is demonstrated that in patients with a body surface area of less than 2.0 m² first shock with 150 J is as effective as first shock of 200 J in patients with a body surface area of more than 2.0 m². The individualized body surface area protocol for elective cardioversion of patients with persistent atrial fibrillation makes it possible to identify patients in whom low-energy initial shock will be as effective as a shock with maximum energy, which provides a faster procedure with fewer consecutive shocks and better safety (*abstracts 10 and 21*). In recent years, the "gold standard" in DC shock therapy of ventricular and supraventricular arrhythmias has been the application of various types of biphasic impulse, which have higher efficiency and safety than monophasic ones. A contribution is an overview of the application of biphasic truncated exponential (BTE) impulses for DC cardioversion of atrial fibrillation/flutter, and a direct comparison between the efficacy of different pulse energies based on data from the National Heart Hospital.

Another scientific contribution in the field is the presented analysis of the risk profile and prevalence of different risk factors among a real population of patients undergoing elective synchronised cardioversion, comparing two time periods. There is a change in the prevalence of risk factors for atrial fibrillation in male patients and a significant increase in the proportion of patients with high cardiovascular risk in the second period in both sexes (*abstract 25*).

A contribution in the field of cardiostimulation is the presented series of patients with an implanted permanent pacemaker due to relapse of intra ventricular obstruction after an alcoholic septal ablation for the treatment of hypertrophic obstructive cardiomyopathy (*publication 22*). Hypertrophic obstructive cardiomyopathy is a rare pathology that is why it is appropriate that patients with this condition are concentrated at specialized centers due to the specific treatment and follow-up.

4. Scientific contributions in the field of pharmacotherapy

A detailed and practical literature overview concerning the administration of clopidogrel in various clinical indications, including as part of triple antithrombotic therapy, as well as its comparison with the new more potent antiplatelet agents prasugrel and ticagrelor, has been made. The problem of clopidogrel resistance and the relatively new concept of de-escalation of antiplatelet therapy (*publication 15*) have been commented on. By presenting several clinical cases, the main considerations for the selection of triple antiplatelet-anticoagulant therapy in accordance with the current recommendations have been commented on (*publication 18*).

A scientific contribution concerning pharmacotherapy in pulmonary arterial hypertension is the overview of the administration of endothelin receptor antagonist ambrisentan, with particular attention to the evidence from clinical studies (*publication 24*).

Another contribution in the field of pharmacotherapy is the overview concerning the administration of colchicine as a powerful antiinflammatory agent in the therapy of coronary artery disease and in particular acute coronary syndrome, with special comments on the results of recent clinical studies in the field (*publication 16*).

5. Scientific contributions in the field of rare clinical cases and other

A rare clinical case of severe metformin-associated lactic acidosis, complicated by shock, acute renal failure, loss of vision and a subsequent episode of pulmonary embolism (*publication 6*) is a contribution to the field. In addition, a comprehensive overview of the literature was carried out, including the etiology, diagnosis, treatment and prognosis of the rare but extremely serious condition metformin-associated lactic acidosis (*publication 5*).

Other contributions in the field are the presented rare clinical cases of myxedema coma, complicated by cardiac arrest and epileptic status (*publication 14*), chronic aortic dissection type B with the formation of a giant aneurysm and rupture of the false lumen (*publication 4*) and heparin-induced thrombocytopenia in a patient with acute myocardial infarction and oncological disease (*publication 25*). In all publications, in addition to presenting the specific cases, a comprehensive overview of the literature is included.

A scientific contribution is also the detailed overview of the literature, including definition, etiology, pathogenesis, clinical presentation, diagnostic and therapeutic algorithm of orthostatic hypotension, a common condition with increasing importance due to ageing population and increasing comorbidity (*publication 19*).

4. Training and teaching activities

Dr. Elena Dimitrova participates actively in the training in cardiology (students and graduates of cardiology), and for the last 5 years she has had an average of over 250 hours/year. The teaching workload of Dr. Dimitrova corresponds to the requirements for teaching workload for the academic position "Associate Professor".

5. Membership of scientific organisations

Dr. Elena Dimitrova is a member of the following national and international scientific organizations:

- Bulgarian Society of Cardiology
- European Society of Cardiology

According to the requirements of the National Centre for Information and Documentation for the academic position "Associate Professor" Dr. Elena Dimitrova meets more than the minimum requirements. The scientific production of Dr. Dimitrova covers the Minimum National Requirements in accordance with Annex No 1 of the Rules of Application of the National Heart Hospital EAD – total sum 767.2 points. All data are presented understandably and accurately in the submitted for review materials.

In conclusion, I believe that the overall scientific, practical, organizational and teaching activities of Dr. Elena Svetlozarova Dimitrova, PhD., fully meet the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria for acquiring the Academic positions and the Rules for the Development of the Academic Staff in for the academic position "Associate Professor" at the National Heart hospital EAD.

I propose that the esteemed scientific jury award to Dr. Elena Svetlozarova Dimitrova the academic position "Associate Professor" in the field of higher education 7. "Health and Sport", professional department 7.1. " Medicine" and scientific specialty "Cardiology".

26.08.2021

A handwritten signature in black ink, appearing to read 'Borislav Georgiev', with a stylized flourish at the end.

(Prof. Borislav Georgiev, MD, PhD)