

**REVIEW**

From Assoc. Prof. Vasil Dimitrov Velchev, MD, PhD

Clinic of Cardiology at University Hospital Saint Anna, Sofia

Concerning: Competition for the acquisition of the academic position "Associate Professor" in the field of higher education 7. "Healthcare and sports", professional field 7.1. "Medicine", scientific specialty "Cardiology", announced for the needs of the Clinic of Cardiology at National Heart Hospital in SG issue 45/28.05.2021 r. and according to Order № 309/22.07.2021

The review was prepared according to the requirements of the Law for Development of Academic Staff, the Regulations for application of the Law for Development of Academic Staff, the Regulations for the conditions and the procedure for acquiring scientific degrees and holding academic positions in the Republic of Bulgaria and the Regulations for the conditions and the procedure for acquiring scientific degrees and holding academic positions at National Heart Hospital. 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 National Heart Hospital. For the above competition Dr. Elena Svetlozarova Dimitrova, PhD, Assistant Professor at the Clinic of cardiology at National Heart Hospital is the only candidate.

Dr. Elena Svetlozarova Dimitrova was born on February 14, 1984 in Sofia. In 2002 she graduated from First English Language School in Sofia. In 2008 she graduated medicine at Medical University – Sofia. In the period 2009-2013 she was a cardiology resident at the Clinic of cardiology at University Hospital Saint Anna – Sofia. In 2013 after passing successfully a state exam she acquired a degree in cardiology. Since 2014 she has been working at the Intensive Cardiac Care Unit at National Heart Hospital. In 2017 she defended a dissertation "Prospective follow-up of patients with pulmonary arterial hypertension and assessment of the effect of specific therapy on the functional class and clinical course of the disease following a specific protocol for follow-up and escalation of therapy". In 2019 after a contest she became Assistant Professor at the Clinic of cardiology at National Heart Hospital.

She is certified in echocardiography – fundamental level. She is a member of the Bulgarian Society of Cardiology and the European Society of Cardiology.

## **1. Evaluation of research activity**

### **1.1. Publications:**

For the competition Dr. Elena Dimitrova has submitted:

- Dissertation on the topic “Prospective follow-up of patients with pulmonary arterial hypertension and assessment of the effect of specific therapy on the functional class and clinical course of the disease following a specific protocol for follow-up and escalation of therapy” with an abstract;

- 19 publications, 3 of which in international journals with impact factor, in 13 of them Dr. Dimitrova is the first author;

- 25 abstracts from congresses.

### **1.2. Authorship and citations**

According to the submitted citation from CML at Medical University – Sofia there are 15 citations in Bulgarian sources. 43 citations are found in Scopus database and 43 citations are found in Web of Science database – these databases partially overlap.

### **1.3. Scientific forums**

Dr. Dimitrova has participated with oral presentations and posters in a number of scientific forums in Bulgaria and abroad with published abstracts in scientific journals.

### **1.4. Other research activities**

Dr. Dimitrova has been a subinvestigator in a number of international clinical trials phase 2b и 3 in the field of pulmonary hypertension and acute coronary syndrome.

## **2. Profile of research, practical and applied activities**

In accordance with the work profile at the Clinic of cardiology and her scientific specialty Dr. Dimitrova works in 5 main directions:

- Pulmonary hypertension and pulmonary thromboembolism
- Coronary artery disease and acute coronary syndrome
- Atrial fibrillation, DC-shock therapy and cardiac pacing
- Pharmacotherapy
- Rare clinical cases and others

### **3. Scientific contributions**

The candidate's scientific contributions can be grouped in the following 5 main directions: pulmonary hypertension and pulmonary thromboembolism, coronary artery disease and acute coronary syndrome, atrial fibrillation, DC-shock therapy and cardiac pacing, pharmacotherapy, rare clinical cases and others.

#### **3.1. Scientific contributions in the field of pulmonary hypertension and pulmonary thromboembolism**

The candidate has a marked 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 in one of the well known expert centers in Bulgaria (University Hospital Saint Anna, Sofia). 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 associated to the PhD thesis (*dissertation work, publications 7, 8 and 21, abstracts 1-4 and 7*) are:

1.1. The prognostic role of the main clinical, laboratory and instrumental variables used routinely in the assessment of patients with pulmonary arterial hypertension is reviewed;

1.2. A complete algorithm for diagnosis and long-term follow-up of patients with pulmonary arterial hypertension is assessed;

1.3. A first of its kind analysis of the effect of specific therapy during long-term follow-up of patients with pulmonary arterial hypertension is made and the results are compared with data from the major international registries;

1.4. The effect of combination therapy has been evaluated separately in a contemporary cohort of patients with pulmonary arterial hypertension;

1.5. For the first time in Bulgaria a long-term follow-up of patients with pulmonary arterial hypertension treated with specific therapy with an analysis of mortality is made.

A comprehensive review of the literature on the therapeutic strategy in chronic thromboembolic pulmonary hypertension has been made. A particular contribution in the field is the presentation of two own clinical cases with pulmonary thrombendarterectomy

with different disease course treated at one of the most experienced European centres AKH Vienna (*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*) – these cases are rare in clinical practice and this is the first such published case for Bulgaria.

Patients with pulmonary arterial hypertension associated with congenital heart disease are an important subgroup with some peculiarities of diagnosis and treatment. The presented two clinical cases of such patients are also a contribution (*publication 23*).

Another contribution in the field of pulmonary hypertension is the detailed and modern overview of the characteristics and the application of various biomarkers in patients with pulmonary thromboembolism and pulmonary hypertension (*publication 9*). Another contribution in this area is the review 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 on Pulmonary Hypertension held in Nice in 2018 (*publications 11 and 12*). A contribution in the field is also the review of the literature concerning a very common group of patients with pulmonary hypertension – patients with underlying chronic lung disease (*publication 17*). Especially valuable and useful for the practice is the review 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*).

Another contribution is that based on own data from consecutive hospitalized patients with moderate and high-risk pulmonary thromboembolism, the candidate 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*). A well-known fact is that risk stratification in patients with pulmonary thromboembolism is essential for the choice of appropriate therapy and prognosis.

### **3.2. Scientific contributions in the field of coronary artery disease and acute coronary syndrome**

A significant contribution 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 PCR-based genotyping of angiotensin-converting enzyme (ACE I/D), eNOS G894T, endothelin-1 138A I/D and matrix metalloproteinase-3 5A/6A was performed. A high prevalence (29,5%) of multifocal atherosclerosis in patients with coronary artery disease was found and its association with DD genotype of ACE and II genotype of ET-1 (*abstract 19*).

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

Of particular significance is the 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, the results being compared with a similar period in the previous year and commented on in the light of published data from Europe and the USA (*publication 13*). These are the only data published about Bulgaria on the topic so far.

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 in 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*).

Another contribution are the works on acute heart failure as a complication of the in-hospital phase of acute myocardial infarction – its frequency, risk factors for development and prognosis were analyzed. 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. Besides, acute heart failure is associated with a significantly higher in-hospital mortality (*publication 27, abstracts 14 and 27*).

Another contribution in the field are the presented own results of treatment of ST-elevation myocardial infarction in adult patients – their poorer prognosis compared to younger patients and the advantages of interventional treatment to reduce the complications of the myocardial infarction and mortality even in older patients is established (*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 significant contribution is the direct comparison of the risk profile of patients with myocardial infarction with and without ST-elevation for the first time in the Bulgarian population. Patients with non-ST-elevation myocardial infarction had comparable frequencies of most coronary heart disease risk factors compared to patients with ST-elevation myocardial infarction 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 is commented (*abstracts 15 and 30*). 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 prognosis (*abstracts 18, 33 and 34*).

A scientific contribution in the field of acute coronary syndrome is the research on the prognostic value of inflammation status at admission in 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 levels, having a 5 times higher risk of death (*abstracts 26*).

### **3.3. Scientific contributions in the field of atrial fibrillation, DC-shock therapy and cardiac pacing**

The candidate was involved in the unique registry of patients with atrial fibrillation from the Balkan region BALKAN-AF. It is a well-known fact that 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 real-life results 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 candidate 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 m<sup>2</sup> 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 m<sup>2</sup>. 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 the 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 the review 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 National Heart Hospital. A high rate of procedural success and an excellent safety profile were reported for the biphasic impulses under investigation without significant differences between subgroups (*публикация 30, абстракту 28 и 29*).

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 cardiac pacing is the presented case 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 and it is appropriate that patients with this condition are concentrated at specialized centers due to the specific treatment and follow-up.

#### **3.4. Scientific contributions in the field of pharmacotherapy**

A contribution in the field of pharmacotherapy is the detailed and practical literature review concerning the administration of clopidogrel in various clinical settings, including as a part of triple antithrombotic therapy, as well as its comparison with the new more potent antiplatelet agents prasugrel and ticagrelor. The issue of clopidogrel resistance and the relatively new concept of de-escalation of antiplatelet therapy have been commented on (*publication 15*). By presenting several clinical cases, the main considerations when selecting 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 review of the administration of endothelin receptor antagonist ambrisentan, with particular attention to the evidence from clinical trials (*publication 24*).

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

#### **3.5. Scientific contributions in the field of rare clinical cases and others**

The presentation of 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 review 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 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 cancer (*publication 25*). In all publications, in addition to a case presentation, a comprehensive review of the literature is included.

Another scientific contribution is the detailed review 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. Evaluation of teaching activity**

Dr. Elena Dimitrova is an Assistant Professor at the Clinic of cardiology at National Heart Hospital. She participates actively in the training in cardiology of students and residents. Her tuition hours meet the requirements for the academic position "Associate Professor".

#### **5. Evaluation of diagnostic and treatment activity**

The candidate has acquired a scientific degree in cardiology and continues her medical education by participation in different scientific forums and workshops, and as a result she is well acquainted with the novelties in the field. She has excellent abilities in the ultrasound diagnostics of heart diseases, which helps her a lot in her practice.

Dr. Dimitrova is a well trained cardiologist, known and respected by her colleagues, with successful professional realization and active research activity.

In conclusion, I believe that the candidate Dr. Elena Svetlozarova Dimitrova fully meets the requirements of the Law for Development of Academic Staff and the Regulations for the conditions and the procedure for acquiring scientific degrees and holding academic positions at National Heart Hospital. I propose to the members of the esteemed scientific jury to vote positively and to award to the candidate the academic position "Associate Professor" in the field of higher education 7. "Healthcare and sports", professional field 7.1. "Medicine", scientific specialty "Cardiology".

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(Assoc. Prof. Vasil Velchev, MD, PhD)