

To The Chairman of the Scientific Jury
designated by Order No. R-109-239 / July 26, 2019
by the Rector of the Medical University-Varna

Statement

by Prof. Borislav Georgiev Georgiev, PhD
Head of the Cardiology Clinics, MHAT “National Heart Hospital” Sofia,
Member of the Scientific Jury for the competition for the occupation of the academic
position “Associate Professor” in the field of higher education Health and Sports, in the
professional field Medicine and scientific specialty "Cardiology", announced in the State Gazette
no. 43/31.05.2019

There is only one candidate for the above mentioned competition - Dr. Maria Stoyanova Dimova-Mileva, PhD, Clinic of Internal Medicine at the University Hospital "St. Marina"- Varna, Department of Propaedeutics of Internal Medicine, Faculty of Medicine at the Medical University of Varna. The presented documents by the applicant are in accordance with the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria for acquiring the Academic position “Associate professor” and with the Rules for the Development of the Academic Staff in the Medical University-Varna. I don`t find any gaps in the presented documents and I declare that I don`t have joint scientific work with the applicant.

Short CV data of the applicant:

Dr. Maria Stoyanova Dimova-Mileva completed her higher education in medicine in 2001. She has acquired specialties in Internal Medicine - 2014 and Cardiology – 2018. Dr. Dimova received her PhD degree in 2017 after successfully finishing her work on the topic: "*Prospective Follow-up of Patients with Beta-Thalassemia Major for Cardio-vascular Status and Cardio-vascular Pathology*".

1. Scientific and research work

1.1 Publications:

Dr. Maria Dimova-Mileva has presented for the competition the following:

- Monograph: “Anemia and cardiovascular changes” – 2019, edited by the University press of the Medical University- Varna
- 1 Chapter in monograph with other contributors
- 22 real full text publications, of which 1 in English (in journals with impact-factor)
- Number of citations: 10 in Bulgarian literature in non-refereed scientific peer-reviewed journals.

1.2. Scientific forums

Dr. Mari Dimova-Mileva has presented 11 published abstracts of scientific researches in participations of scientific forums in Bulgaria or abroad and 10 participations in students’ sessions.

From the publications presented and cited, Dr. Maria Dimova-Mileva covers the minimum state requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria from 2018 for acquiring the Academic position “Associate professor” and with the Rules for the Development of the Academic Staff in the Medical University-Varna, 2018.

2. Profile of research, practical and applied activity

In Accordance with the profile of scientific and clinical work in the Clinic of Internal Medicine and her specialty in cardiology, the main fields of interest of the publications are cardiovascular aspects of some diseases of the common intern. The cardio-vascular impairment in patients with Thalassemia are of particular scientific interest of the applicant.

3. The most significant scientific contributions

Theoretical-methodological and practical-applied contributions

I. Scientific contributions related to anemia and cardiovascular changes

The author's monograph (B-3-1) reviews and summarizes what is known so far in the scientific literature on the etiology, pathogenesis and prognostic value of anemia on cardiovascular structure and function. The most common iron-deficiency anemia and its unfavorable effect on cardiac function, as well as the effect of iron deficiency without anemia, are discussed in details.

The most up-to-date diagnostic methods and values in practice are presented as well as the modern treatment options. The effect of anemic syndrome on ischemic heart disease, arterial hypertension, and rhythm disorders is discussed.

An analysis of other types of anemia, especially congenital hemoglobinopathies on the cardiovascular system, is presented. For the first time in the cardiology literature in Bulgaria, changes that occur in patients with sickle cell anemia are described. Another important part of the work is the relationship between thalassemia and cardiovascular involvement. The main pathophysiological mechanisms of iron deposition in the parenchymal organs and in particular in the heart and vessels are explored, but it is stressed also that this cannot explain all pathological changes occurring in the cardio-vascular system. All state-of-the-art diagnostic methods for early detection of cardiac impairment, treatment and follow-up approaches are presented.

II. Scientific contributions to cardiovascular impairment and cardiac function assessment in patients with Thalassemia major

The articles (A-1-1, D-8-4, D-8-10, D-8-12, D-8-13) discuss the prevalence of patients with this most common monogenic disease in Bulgaria and in the world, the complications of the diseases and the consequences of the treatment. Cardiovascular damage is a leading cause of morbidity and mortality in patients with thalassemia, with iron deposition in the myocardium being considered to be a major pathophysiological cause. A comparison has been made between patients with thalassemia major who are regularly chemotransfused and age-adjusted healthy controls for the first time in Bulgaria.

A comparison was made between the anthropometric parameters of patients with thalassemia over the age of 18 and the corresponding controls, finding that patients with thalassemia had reduced body area compared to controls. Hemodynamic parameters were compared and the results indicate higher heart rate, higher cardiac output and higher cardiac index while differences in blood pressure and peripheral vascular resistance are not found.

A comparison was also made for some echocardiographic indices. Biochemical parameters were also investigated - the value of NT-proBNP, which is higher in patients with thalassemia compared to controls. Patients with increased NT-proBNP value were found to have a greater left atrial index volume compared to patients with normal value. Such a comparison has not been made so far not only in Bulgaria but also in the study of thalassemic populations in other countries.

The quantitative measurement of iron deposition in tissues is made by T2 * nuclear magnetic resonance imaging, the time value being investigated and measured in milliseconds. All patients who undergo regular chemotransfusions after the age of 10-12 years are pointed to MRI

investigation, and this conducts the dosage of chelation therapy. It is held either annually or every two years, depending on the result previously found. In patients in the cohort studied, it was found that the value of T2 * (normally should be over 20msec) does not correlate with the ejection fraction - such is the data from international literature; does not correlate with the value of NT-proBNP, does not correlate with the indicators of strain and strain rate.

III. Scientific contributions related to rhythmic disorders in patients with thalassemia.

Rhythmic disorders in patients with thalassemia have a different pathogenetic mechanism than that in other patients. This aspect of cardiovascular involvement is presented in a review article. The epidemiology of these disorders is examined - from the most harmless to the life-threatening, the pathophysiological pathways of rhythmic changes at the cellular and molecular level are explained. The methods of diagnostics, monitoring, treatment and prevention are discussed, as well as data from the most recent researches in the field, as well as directions from the latest recommendations for the treatment of transfusion-dependent thalassemia.

IV. Scientific contributions related to heart failure in patients with thalassemia

Treatment of heart failure in patients with thalassemia is performed by a specialised team in dedicated centers for rare anemias. Therapeutic approach has several important differences from that in other patients with heart failure with reduced ejection fraction.

The article for the treatment of heart failure in patients with thalassemia provides guidance on how to use chelation agents in which patients, intensive care regimens for acute heart failure, conventional therapy for heart failure, using the guidelines for patients with thalassemia of the American Heart Association and the International Thalassemia Federation.

V. Scientific contributions related to renal impairment in patients with Thalassemia major and Diabetes Mellitus

Renal impairment in patients with Thalassemia major, resistive Doppler renal artery index in patients with diabetes mellitus, modern biomarkers for renal dysfunction are discussed in few articles (G-7-2, G-7-4, G-8-17). Renal involvement in thalassemia is not one of the leading complications of this disease, it has been less studied and is not well known. An article dealing with renal changes in patients with thalassemia has been published for the first time in Bulgaria presenting the imaging and biochemical methods for early diagnosis.

Kidney changes in diabetes mellitus are well known, articles review the application of state-of-the-art biochemical markers and Doppler features of renal arteries for early diagnosis of renal involvement, presenting the authors' own experience.

VI. Scientific contributions to the field of cardiovascular involvement in thyroid pathology

A series of articles cover the issue (G-7-5; G-8-2, G-8-16) of cardiovascular involvement in hyperthyroidism, presented with recent scientific findings at the level of cardiomyocytes and molecular mechanisms of cardiac involvement in hyperthyroidism in a review. Pulmonary hypertension may occur with increased and decreased thyroid function. This relationship has been poorly studied in world literature, and for the first time in Bulgaria an article reviewing the issue is presented. Another article focuses on the interaction between thyroid dysfunction, diabetes mellitus, and the development of a cardiovascular involvement through a clinical case.

VII. Scientific contributions related to heart failure and accompanying conditions, biomarkers, treatment

In a series of publications (G-8-3, G-8-5, G-8-11, G-9-1) the options for treating heart failure with concomitant diabetes mellitus, the most up-to-date SGLT2 inhibitor medication, and a

small clinical experience in patients with heart failure with preserved ejection fraction is presented. The information known so far for treatment with erythropoietin-stimulating agents and cardiovascular damage, as well as recommendations from the American Kidney Federation, the American Heart Association and the European Heart Association for the treatment of heart failure, are reviewed. A complicated case of a patient with a mechanical valve prosthesis at the aortic place, severe systolic dysfunction, high-grade heart failure, diabetes mellitus, and necrotizing vasculitis is presented, discussing the difficulties and opportunities experienced by the treatment team in the combination of such complex diseases in the same complex patient.

Biomarkers are a powerful emerging field in medicine. In the collective monograph "Biomarkers in cardiovascular disease "From pathogenesis to prognosis", Arbilis 2016, chapter "Progress in the application of biomarkers in diagnosis, risk stratification, treatment and prognosis of heart failure", a review in the biomarkers known to date for the diagnosis, prognostic evaluation and follow-up of treatment outcome in patients with heart failure is fully presented. Not only NT-proBNP is the gold standard but also other biomarkers with less clinical relevance are discussed

VIII. Scientific contributions to the field of congenital heart disease.

The articles (G-8-6, G-8-8) present the current treatment of some of the most common congenital heart malformations such as aortic coarctation, an ASD. The difficulties and challenges of early and correct diagnosis are discussed, as well as the choice of correcting the defect identified through an intervention method, avoiding the severity of open heart surgery.

IX. Scientific contributions to other areas of internal diseases (G-7-3, G-8-15)

For the first time in Bulgaria a project has been developed that studies the attitudes and interests towards Bulgarian folklore among students from universities in Northeastern Bulgaria. The article presents this one-of-a-kind project and the opportunities it offers to young people: through regular practice of folk dances during the compulsory physical and sports activities, to get acquainted with the culture and traditions in Bulgarian folklore, to make new friendships.

For the first time, an overview on the topic of ferroptosis is presented in our literature. Ferroptosis is a new-found form of cell death. It differs from apoptosis and necrosis and results from the accumulation in the cell of iron-dependent lipid peroxidase. During oxidative phosphorylation in the mitochondria, which is a process requiring the presence of iron, reactive oxygen radicals are also synthesized, which, if exceeded by the possibility of neutralization by the reductase systems, and this can lead to damage to various molecules, including nucleic acids, and eventually to death.

Theoretical and methodological contributions

I. Scientific contributions to the field of cardiovascular involvement in cancer

The topic of cardiotoxicity is extremely relevant today because of the increasing incidence of cancer, the development of newer and more powerful chemotherapies whose effects have not been evaluated prospectively (G-8-8, G-8-14). The cardiotoxicity article discusses mechanisms of cardiomyocyte damage, molecular interactions, and biochemical pathways of involvement. The opportunities of imaging methods for detecting metastases in the heart, a localization that is often not actively sought, are discussed.

II. Scientific contributions to pulmonary hypertension in patients with beta-thalassemia

In thalassemia intermedia (TI), also referred to as nontransfusion-dependent thalassemia, as it is in the guidelines and which is about 20–25% of cases of thalassemia, pulmonary hypertension is considered to be the most severe manifestation of cardiovascular involvement and the main cause for heart failure. There is not much data in our cardiology literature on this issue. The article

examines in detail the epidemiology, risk factors, etiology and pathophysiology of pulmonary hypertension in patients with beta-thalassemia, as well as recent data on the use of specific treatment.

III. Scientific contributions to iron deficiency as diagnostic indicators and prognostic value for heart failure

The article reviews the etiology of iron deficiency in patients with heart failure, current diagnostic methods of diagnosis, the prognostic value of iron deficiency, the available therapeutic options for correcting the condition, and the benefits of using them. Iron deficiency in patients with heart failure is a problem that we will increasingly consider as a cause of not coping with complaints. The incidence is high among this group of patients, about 50%, which means that every second with ongoing symptoms and optimal therapy may have an iron deficiency. This is a very topical issue at the moment.

Practical and applied contributions

I. Scientific contributions in the field of Thalassemia intermedia - epidemiology, genetic disorders, diagnosis, clinical features and treatment

The article (G-7-1) presents the latest insights and discoveries in the field of non-transfusion-dependent thalassemia - diagnostic methods, the course of the disease, possible complications and recommended treatment approach. Patients with thalassemia intermedia are less well covered and monitored than those with thalassemia major, the disease itself is not well known. The article provides clear practical guidelines for management of patients with anemic syndrome and directs clinical thinking to this possible etiology.

4. Educational, scientific and organizational activity

Dr. Maria Dimova-Mileva has been an assistant in internal medicine and in cardiology since 2011, with a teaching load of between 156 and 180 academic hours per year (information by MU-Varna).

The academic teaching hours of Dr. Maria Dimova-Mileva corresponds to the requirements occupying the academic position of "Associate Professor".

5. Membership in scientific organizations.

Dr. Maria Dimova-Mileva is a member of the following national and international scientific organizations:

- Bulgarian Society of Cardiology
- European Society of Cardiology
- Bulgarian Heart and Vessel Association

According to the minimum requirements of Medical University of Varna and National Center for Information and Documentation for occupation of the academic position of Associate Professor, Dr. Maria Dimova-Mileva meets more than the minimum requirements.

Based on the above clinical and scientific data of Dr. Maria Dimova-Mileva, she can be characterized as:

- Researcher capable of independent creative scientific work in the field of internal diseases, and in particular in cardiology,
- An erudite doctor with a wide medical perimeter.

In conclusion, I believe that Dr. Maria Dimova-Mileva meets the requirements of the Academic Staff Development Act in the Republic of Bulgaria and the Regulations for the Academic Staff of Development in the Medical University of Varna for the occupation of Academic position “**Associate professor**”. This makes me confident to recommend to the members of the distinguished scientific jury to vote positively for the academic position “**Associate Professor**” in the field of higher education 7. "Health and Sports", professional direction 7.1 "Medicine" and scientific specialty "Cardiology".

10.09.2019

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

(prof. Borislav Georgiev, MD PhD)