

# REVIEW

**By Prof. Dr. Ivo Spasov Petrov**

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Member of the Jury for awarding the scientific and educational degree "PhD", designated by order №355/21.07 2021 by the Executive Director of Acibadem City Clinic Tokuda Hospital EAD

Regarding: PhD thesis of **Dr. Ivayla Zhivkova Zheleva-Kyuchukova**

On the thesis:

**"INTERVENTIONAL TREATMENT IN PATIENTS WITH LEFT MAIN STENOSIS AND CONCOMITANT COMPLEX CORONARY PATHOLOGY"**

for awarding a PhD degree

in the field of higher education- 7. Health and sports, professional field - 7.1. Medicine, doctoral program "Cardiology"

Scientific organization: Acibadem City Clinic UMBAL Tokuda Hospital EAD

Professional field: 7.1. Medicine

## **Qualifications and professional development**

- Graduated in medicine in 1999 at the Medical University - Sofia
- In 2009 - acquired a specialty in "Internal Medicine"
- In 2010 - obtained a certificate of professional qualification in "Invasive Cardiology"
- In 2013 - acquired a specialty in "Cardiology"
- In 2016 - obtained a master's degree in "Health Management".

I have known Dr. Zheleva-Kyuchukova since 2001, from our joint work at St. Ekatherina hospital. Since then, as a young resident in Internal Medicine, she showed great interest in the latest and advanced methods of treatment in the field of cardiology and invasive cardiology. Even in these early stages of her ascending professional development, she showed a taste for scientific developments, maintained an extremely high level of awareness and actively participated in the preparation of scientific reports, both for conference presentations and in the scientific literature,

including international publications. Over the years she has actively participated in numerous medical congresses and symposia, both in Bulgaria and abroad and provides invaluable assistance in organizing and optimizing the scientific program of congresses in Cardiology and Interventional Cardiology, which is another confirmation of her strong interest in developing current and avant-garde methods of treatment in the field of cardiology. Dr. Ivayla Zheleva-Kyuchukova has acquired many additional qualifications and has proven her position as a leading expert in the field of cardiology and invasive cardiology. She is an established expert in the field of cardiovascular diseases and it is no coincidence that she enjoys great respect from patients and great respect and prestige among colleagues. The writing of this dissertation is a logical continuation of her dedicated work in the field of development and validation of advanced methods of treatment in the field of interventional cardiology. Under the guidance of her professional and scientific supervisor, Dr. Valeri Gelev, she achieved the kind of expertise that few interventional specialists in the world have. It is no coincidence that a significant part of the patients described in her scientific work have been treated by her as a first operator and in practically all the others she has played a significant role as an immediate first assistant.

#### **Structure of the dissertation paper**

The dissertation contains 158 printed typewritten pages, of which 124 pages of text and 34 pages of bibliography. It is illustrated with 62 figures and 19 tables. The bibliography includes 276 literary sources, of which 6 are Bulgarian and 270 by foreign authors. The chapters covering the literature review, research methodology, research results, discussion of the results and conclusions and recommendations are clearly and in detail presented and the structure of the development meets the generally accepted requirements.

It is structured as follows:

- Introduction - 3 pages
- Literature review - 40 pages
- Materials and methods - 12 pages
- Results - 38 pages
- Discussion - 25 pages
- Conclusions - 6 pages
- References - 276 titles, 34 pages

#### **Relevance of the topic**

Atherosclerosis and coronary heart disease are socially significant diseases associated with the number one cause of death worldwide in men and women. With increasing life expectancy, unhealthy lifestyles, progressively decreasing physical activity in everyday life and psycho-emotional stress, coronary heart disease is becoming a pandemic.

Left main stenosis is a condition in which the blood supply to a large part of the left ventricular myocardium (often over 90%, in the left type of coronary circulation) is threatened and leads to high mortality as a natural evolution. Due to the lack of definite data from multicenter randomized trials conducted with last generations of drug-emitting coronary stents comparing the results of stenting and aorto-coronary bypass in left main stenosis, the topic of this dissertation is extremely relevant. The problem considered in the study for inversion treatment of left main stenosis in complex coronary pathology makes the present work even more valuable due to its extreme proximity to clinical practice and the potential for application of the conclusions in real practice, not only in Bulgaria.

### **Literature review**

In the present literature review, the author describes in detail the left main stenosis both as part of the whole spectrum of coronary pathology and as a separate nosological unit, requiring special attention and approach. The different approaches in the treatment of left main stenosis are systematically presented, both according to the type of intervention technique chosen and according to the data from the most key clinical studies examining the issue. Particular attention is paid to the information to be systematized in chronological order in view of the progress made in the treatment of left main trunk stenosis, the accumulation of additional data and the improvement of the stents used.

The literature review section describes many different methods for assessing the degree of stenosis, the pros and cons of each of the techniques, as well as recommendations for their use. The author has also included the most important systems for assessing the degree of stenosis, classifications for the types of bifurcation lesions, as well as for the overall coronary pathology, with special attention paid to their application in clinical practice.

I completely agree with the conclusions of the literature review and especially with the thesis that the results of the intervention arms of the randomized trials are no longer relevant due to the upward development of technologies after their publication. The currently valid "classic indications" do not take into account both the optimization of techniques and the results of small series, which speak in favor of expanding the indications to patients with high anatomical complexity, which are a priori excluded from studies at the expense of the gold standard for radical treatment (CABG). These conclusions categorically substantiate the relevance of the topic and the formed comparative groups, namely a group with Syntax score below 32 and Syntax above 32 (with high anatomical complexity).

### **Goal and tasks**

The purpose of this dissertation is clearly and precisely defined, namely: to analyze the clinical, anatomical and procedural characteristics in patients with unprotected left main stenosis and concomitant complex coronary pathology who underwent percutaneous coronary intervention with second generation DES implantation, in order to determine the effectiveness and safety of the procedure in terms of early and remote (2-year) prognosis, as well as the establishment of predictors for major adverse events.

In order to fulfill the goal the author sets herself the following tasks:

- Defining groups after determining the complexity of coronary lesions according to Syntax Score-I in the research contingent of a series of patients with PCI of unprotected LM stenosis with second generation DES.
- Analysis of the demographic, clinical, anatomical and procedural characteristics of patients in the groups.
- Analysis of the results in two-year follow-up of patients with regard to the combined indicators of major cardiovascular events (MACE) – all-cause mortality, cardiac mortality, stroke, repeat revascularization of the target lesion in both groups.
- Determine and compare the time until the first MACE occurs (time-to-first MACE or event-free survival time) in both groups.
- Determination of MACE predictors after PCI of unprotected left main stenosis.
- Introduction of an algorithm for interventional treatment of patients with unprotected left main stenosis with/without accompanying complex coronary anatomy.

### **Material and methods**

The study was conducted prospectively for a period of 5 years, and according to the defined inclusion and exclusion criteria, a total of 136 patients were included, who were initially followed up by examinations after 12 months by telephone. All patients were divided, according to initially defined criteria, into two groups according to the complexity of the coronary pathology, calculated by Syntax Score, below and above 32, respectively. The study was conducted according to a protocol as a set of laboratory parameters, echocardiographic examination and ECG working sample (when the clinical situation allows) for objectification of ischemia. Coronary intervention was performed using standard techniques for stenting, peri-procedural anticoagulation, and post-procedural antiaggregation. The stents used are second-generation drug-eluting, the result of high-tech development in the entire cohort of patients.

The obtained data were processed statistically with appropriately selected and illustrated methods. The specialized statistical package SPSS (Statistical Package for the Social Sciences) version 16.0 was used to process the survey data.

### **Results and discussion**

The author examines in detail the obtained results, divided into groups, as well as a total for the entire cohort of patients. The two groups of patients were compared in their demographic and clinical indicators, with no statistically significant difference in most indicators. In a comparative analysis of patients by groups, compared to the anatomical and procedural characteristics, as expected, a significant difference in the indicators complexity of coronary pathology, complexity of the procedure, procedural time, amount of contrast used, higher frequency of femoral access, higher catheter size and more implanted stents in the group with Syntax Score over 32. In the group with Syntax Score  $\geq 32$  are also registered higher rate of 2-

stent techniques, greater total stent length, higher rate of POT technique, use of high pressure balloons in LAD, reinterventions, etc.

If we can summarize in the group with Syntax Score  $\geq 32$  we have more complex coronary pathology, more complex interventional procedures, in otherwise equivalent patients by demographics. The author lists several concomitant diseases in which a statistically significant association was found with lower survival, namely atrial fibrillation, COPD, chronic kidney disease IIIb according to KDIGO or higher, as well as chronic arterial insufficiency of the limbs.

### **Conclusions from the scientific dissertation**

The presented scientific work is unique for Bulgaria, as in our country only 2 studies have been published, related to left main stenosis, respectively with 12 and 47 patients, with bare metal and drug-eluting first generation stents with follow-up up to 1 year. As the author notes, there are not enough publications on the subject in the international literature to be able to draw reliable conclusions. The dissertation paper is the result of many years of work of the same team on optimization and routine interventional treatment of patients with complex coronary pathology, a significant part of which are patients with left main stenosis and multivessel coronary heart disease responding to patients in group 2. Due to the application of the most advanced methods of treatment in this group following the high criteria and consensus documents of the European Bifurcation Club (EBC), the results of the scientific research and conclusions can be generalized and exposed internationally without worrying about their topicality and high standard. The author draws 17 separate conclusions, and it should be noted that some of them are developed in multiple subsections, visually following the pre-set goal and objectives. The most important conclusions from the study are several, namely:

- The relative proportion of study patients with  $SS \geq 32$  and percutaneous coronary intervention (PCI) of left main stenosis is high (38%) and comparable to international studies (35 - 43%)
- The complexity of the pathology in  $SS \geq 32$  patients is determined by the establishment of the higher rate of the following anatomical features of the left main lesion and the accompanying coronary disease... / see item 4 of Conclusions /
- The complexity of the subsequent PCI in the group with complex anatomy ( $SS \geq 32$ ) is confirmed by a number of significantly higher procedural indicators... / see item 5 of Conclusions /
- After PCI of the left coronary artery trunk, freedom from events in the two-year follow-up was achieved in a high percentage of patients from the two groups (83,8%) without a statistically significant difference between them (81,9% for  $SS < 32$  and 86, 8 % for  $SS \geq 32$ , Log Rank determined  $p = 0.518$ ).
- Previous MI, advanced renal failure ( $\geq 3b$  stage) and double-stent technique have been identified as predictors of major complications after left main PCI, with different representations of the two groups. For  $SS < 32$ , previous MI was most significant ( $p = 0.018$ ), and for  $SS \geq 32$ , advanced renal failure ( $p = 0.032$ ).

- PCI of left main stenosis with second generation DES in patients with concomitant complex distal coronary pathology and the achievement of maximum revascularization is a procedure with minimal risks and favorable follow-up results, of particular importance are the experience of the operator and the capabilities of this type of complex interventions.

I agree with the cited contributions and believe that the research will serve not only to establish in national practice high international standards for the treatment of patients with left main stenosis and multivessel coronary heart disease, but will be a motive for an even more urgent request for reimbursement of methods for assessment and optimization of treatment of coronary lesions, which are currently not reimbursed in the Republic of Bulgaria, although they are a high-grade indication in international clinical guidelines.

#### **Remarks and recommendations**

Some of the acronyms in Cyrillic, for example ЛАД, ЛМ is better to be written in Latin, as they are abbreviations of English terms.

Although not a comparative study, it would be interesting to provide data from the results of surgical treatment over the same period of time in patients with similar clinical indications.

#### **Conclusion**

The dissertation of **Dr. Ivayla Zhivkova Zheleva - Kyuchukova "Interventional treatment in patients with left main stenosis and concomitant complex coronary pathology "** is relevant and meets the scientometric criteria, as well as the rules for the development of the academic staff of Acibadem City Clinic Tokuda University Hospital EAD for awarding educational and scientific degree "Doctor".

Following the critical remarks with deep respect, I recommend the honorable members of the Scientific Jury to vote positively for the award of ESD "Doctor" in the field of higher education - 7. Health and Sports, professional field 7.1 Medicine, doctoral program "Cardiology" of Dr. Ivayla Zhivkova Zheleva - Kyuchukova.

Sofia

10 Aug 2021

  
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