(Translation from Bulgarian)

EXPERT OPINION
by Assoc. Prof. Dr. Petar Yordanov Atanasov, MD
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Re: Procedure for awarding a **doctoral** degree
to **Dr. Ivan Petrov Martinov** for his dissertation paper on topic
PERIOPERATIVE MYOCARDIAL INFARCTION - CLINICAL, DIAGNOSTIC, AND THERAPEUTIC FEATURES
in the scientific specialty of Cardiology (code 03.01.47)
Professional field 7.1. Medicine
Higher education field 7

Brief biographical data about the doctoral candidate

Dr. Ivan Petrov Martinov graduated from the Medical University of Sofia in 1995 with a degree in Medicine. At first, he worked as a resident doctor at the Clinic of Emergency Internal Medicine of N. I. Pirogov University Multi-Profile Hospital for Active Treatment and Emergency Medicine EAD, Sofia where he acquired his Internal Medicine specialty (2003). In the period 2003 – 2005, he participated in courses in Invasive Cardiology at the Invasive Cardiology Departments of the Specialized Hospital for Active Treatment of Cardiovascular Diseases and Lozenets Hospital, and in the establishment of a pacing centre at N. I. Pirogov University Multi-Profile Hospital for Active Treatment and Emergency Medicine. This was followed by a 2-year specialization in Clinical and Interventional Cardiology at the Specialized Hospital for Active Treatment of Cardiovascular Diseases - National Cardiology Hospital, where he was a research associate and acquired a specialty in Cardiology (2007). He is holder of a certificate in Invasive Cardiology (2010) and a certificate in Echocardiography - Fundamental Level (2014). In 2016, he acquired a master's degree in Health Management at the Medical University of Sofia.

Since 2008, Dr. Martinov has been a member of the European Society of Cardiology. In the period 2005 – 2017, he took part in international courses, congresses, and seminars in Invasive Cardiology.

He has participated in 5 clinical trials in heart failure and acute coronary syndrome.

He has got an extensive professional experience of 24 years. In the field of invasive cardiology, he has performed over 5,000 cardiac catheterizations, over 3,000 coronary interventions, over 1,000 primary angioplasties for AMI, over 1,500 peripheral interventions, placed over 50 temporary pacemakers, and implanted over 30 permanent pacemakers.

The dissertation paper of Dr. Ivan Martinov, Perioperative Myocardial Infarction - Clinical, Diagnostic, and Therapeutic Features, is relevant in both scientific and scientific-practical aspects. The reasons for this are as follows:
1) The world's adult population is progressively increasing due to extended life expectancy, especially in developed countries;
2) The adult population has a growing number of concomitant chronic diseases: atherosclerosis, hypertension, diabetes mellitus, anaemia, cancer, chronic lung and kidney diseases, etc.
Cardiovascular diseases remain the leading cause of morbidity and mortality in the world.
3) The frequency of surgical interventions in adults is also increasing, and, due to the concomitant chronic diseases, they are of high or medium severity;
4) Of particular importance is the knowledge of the risk factors, the specific manifestations, diagnosis, course, and therapy of perioperative myocardial infarction (PMI);
5) The assessment of the perioperative risk and the complex behaviour of interdisciplinary teams are leading approaches for achieving better results in interventional and medical treatment and prognosis of PMI.

The dissertation paper consists of 202 pages in accordance with the generally accepted requirements in the Republic of Bulgaria, and is illustrated with 45 tables and 45 figures. Its structure meets the generally accepted requirements in our country.

The literature review presents detailed current literature data on acute coronary syndrome (ACS), in particular on acute myocardial infarction with ST-elevation suffered in an outpatient setting. The results are compared with studies on perioperative acute myocardial infarction (PAMI) in terms of frequency, diagnosis, pathophysiology, risk factors, risk assessment, interventional and medication therapy, prognosis, and mortality.

The literature review ends with conclusions that summarize the solved and unsolved problems and provide guidelines for justifying the goals and objectives of the dissertation paper:
1) Spontaneous acute myocardial infarction with ST-elevation is one of the best-studied nosological units, and there has been a lasting trend in the world to reduce the overall mortality from it.
2) Perioperative myocardial infarction and perioperative STEMI remain serious medical problems. Population, retrospective, and prospective studies have shown significantly higher morbidity and mortality rates than spontaneous MI.

3) The interdisciplinary nature of PMI leads to difficult recognition, late diagnosis, and suboptimal treatment. The developed scales for preoperative risk assessment still do not provide a good enough orientation for clinical behaviour, especially in emergency surgery.
4) Regarding the pathogenesis of perioperative STEMI, there is evidence of a combination of type 1 and type 2 MI, i.e. coronary thrombosis on the background of anaemia, surgical trauma, general anaesthesia, etc.
5) There is a small number of randomized trials and they are mainly related to medication therapy. There are no randomized trials in interventional treatment of patients with perioperative myocardial infarction.
6) The available international guidelines and recommendations are often based on studies in AMI NSTEMI / STEMI and cannot be directly applied to perioperative myocardial infarction.
7) It is necessary and appropriate to develop modern guidelines based on randomized trials and their application as protocols in hospital practice.

The bibliography includes 323 titles, 6 of which are by Bulgarian authors and 317 by foreign authors. Over 50% of the titles are from the last 10 years and over 50% are from the last 5 years, which testifies to the excellent knowledge of the doctoral candidate on perioperative acute myocardial infarction.

The goal of the dissertation paper is clearly formulated: to study the clinical, diagnostic, and therapeutic features of perioperative myocardial infarction (PMI) in patients with non-cardiac surgery compared to those of spontaneous myocardial infarction (SMI), which occurs without surgery.

The tasks for achieving the goal are 7, they are precisely and logically defined and related to the main goal. The goal and tasks are formulated and justified in accordance with the conclusions of the literature review.

Material (subjects)
For a 5-year period, at the Invasive Department of the Cardiology Clinic of N. I. Pirogov University Multi-Profile Hospital for Active Treatment and Emergency Medicine EAD, a total of 1,595 primary coronary interventions (PPCI) were performed in patients with STEMI.

During the same period, 361 patients with cardiac perioperative complications were transferred to the clinic, of which 157 had acute coronary syndromes. In 142 of them, selective coronary angiography (SCAG) was performed as well as 71 primary coronary interventions (PPCI), and it was found that 35 of them or 52% had STEMI.

A total of 112 patients diagnosed with acute myocardial infarction with persistent ST-elevation were included in the study.

Based on the inclusion and exclusion criteria, **35 patients with perioperative STEMI were identified as the main group**, and the remaining **77 patients as a control group with spontaneous STEMI, without cardiac surgery** (using the web-based Research Randomizer platform).

Research methods

The diagnostic methods for diagnosing the patients with myocardial infarction at hospitalization included: clinical examination by a cardiologist (medical history, status); clinical and laboratory tests: CBC, markers for myocardial damage, lipid profile, liver enzymes, blood glucose, residual nitrogen bodies, electrolytes, coagulation status; 12-channel ECG with standard recording parameters; echocardiography; specific diagnostic criteria for risk factors: diabetes mellitus, arterial hypertension, dyslipidaemia, chronic kidney disease, anaemia; use of the RCRI - Revised Cardiac Risk Index – Lee for the main group.

The definition of acute myocardial infarction was made on the basis of the latest Expert Consensus Document of the European Society of Cardiology Fourth Universal Definition of Myocardial Infarction (2017).

For the purposes of the study, perioperative acute myocardial infarction was defined as STEMI occurring from the time of hospitalization in the surgical ward until the 7^{th} postoperative day inclusive (2016).

Therapeutic methods: medication and interventional (selective coronary angiography - SCAG) and percutaneous transluminal angioplasty - PTA).

Statistical methods (analyses): descriptive, variational, graphical, alternative, correlation, Fisher's exact test and $\chi 2$ test, nonparametric Kolmogorov-Smirnov and Shapiro-Wilk tests, Student's T-test, nonparametric Mann-Whitney test, binary logistic regression, ROC curve, criteria for validation of screening tests.
The data were entered and processed using the IBM SPSS Statistics 25.0 statistical package.

Results and discussion

Results are presented and comparative analyses are performed on numerous parameters between the main and control group of patients with STEMI, as well as analyses of parameters specific to the respective group, either main or control.

Comparative analysis of indicators of the two groups of patients with AMI with ST-elevation

The following results are significant:

1. A significantly **lower incidence of the patients with perioperative STEMI** after emergency surgery with high complexity was found compared to the literature data. This is probably due to gaps in the diagnosis of this type of infarction.

2. **The anaemic syndrome** of the patients with STEMI had a significant impact on the results of the surgical intervention and the treatment of perioperative MI. The comparative data show a significantly higher percentage of the patients with **anaemia in the main group (80%)** compared to the control group (16.9%). 66% of the operated patients had **moderate and severe anaemia**, while in the control group 16% had severe and moderate anaemia.

In addition, the relative proportion of **deaths in the patients with anaemia** was statistically significantly higher. Of the 16 patients with anaemia, 68.8% died, while 31.3% of patients without anaemia died ($p = 0.010$).

The anaemic syndrome affected some **parameters of the interventional procedures** that were monitored and analysed in the study.

Reperfusion therapy - Stenting / *POBA*. The increased incidence of postoperative anaemia is associated with an increased risk of haemorrhagic or active bleeding, leading to deviations from the standard protocol for therapeutic behaviour in STEMI. The decision for stenting is difficult and only plain old balloon angioplasty (POBA) is performed. The comparative analysis shows that a similar trend was observed in the study, with the non-stented patients in the main group with perioperative anaemia reaching 39.2%, and despite the small number of patients with anaemia in the control group, all were stent.

On the other hand, anaemia leads to ***changes in the post-procedure antiplatelet therapy*** upon discharge: reduction or discontinuation of anticoagulant and / or antiplatelet therapy in patients with perioperative STEMI. In the main group, 22.9% of the patients deviated from the standard dual antiplatelet therapy (DAPT), with the predominance of Clopidogrel monotherapy and even without therapy, and in the control group 100% of the patients were on DAPT.

3. Differences in interventional procedures in the two groups with myocardial infarction with STEMI

The time from the onset of symptoms to the intervention in the main group of patients was ≥ 12 hours, although the patients were transferred from the surgical ward of the hospital, and in the control group it was less than 12 hours.

Access for interventional procedures: in the study, radial access had a significantly higher share in the control group - in 94.8%, and femoral access was more often used in the main group - in 20%. The increased incidence of femoral access in the main group was due more to the critical condition in which patients entered the catheterization room, often with severely compromised haemodynamic parameters.

Peri- and post-procedural complications. There was a statistically significant difference in post-procedural complications between the two study groups: acute left ventricular failure (ALVF), blood transfusion, and death in patients with PMI. Predictors of ALVF are EchoCG-EF <39%, anterior infarction, and excessive infusion therapy.

4. Revised Risk Score Index in perioperative STEMI. Revised cardiac risk index (RCRI) was first calculated and applied to the non-cardiac surgery group, and, although no significant association was found with some clinical and angiographic criteria, such as ALVF and No-reflow, it shows a significant correlation with increased lethality.

5. Mortality

5.1. Hospital mortality. In the main group of patients with perioperative STEMI, the nosocomial mortality was 25.7% and was significantly higher than the mortality in the control group - 9.1%, which is 2.8 times higher. This is the main starting point for analysing the data in order to identify the causes and predictors of the increase in mortality in perioperative STEMI.

5.2. Factors influencing the risk of death, determined by the ROC curve

The comparison of the results of the binary logistic regression analysis of the **two studied groups** shows that

• In the main group, EchoCG EF, with values ≤ 39%, is associated with about 13 times higher risk of death;

• The ALVF complication, which in both cases is risky, is significantly higher in the control group.

The summary of the results of the study outlines 3 problems related to gaps in the perioperative assessment of the patients in terms of cardiovascular risk, severity of surgery, and type of anaesthesia and monitoring, with changed medication therapy in the patients with perioperative STEMI and changed protocol for interventional treatment of perioperative STEMI.

In order to overcome these problems and rethink the strategy for preoperative assessment, diagnosis, and therapy of patients with perioperative STEMI, for closer interdisciplinary collaboration between surgeons, anaesthesiologists, resuscitators, and cardiology consultants, Dr. Martinov offers a written and schematic **Hospital Algorithm for Behaviour in Perioperative Myocardial Infarction (STEMI).**

There are 7 **conclusions** from the dissertation paper, presenting a logical summary of the own results of the author in the sequence of the tasks planned.

The **contributions** of the dissertation paper are original: 3 of them are of scientific and theoretical nature and 3 of scientific and applied nature. Of significant scientific and scientific-practical value is the algorithm created for the first time in the country for assessment of the perioperative risk of AMI, implementation of hospital logistics by an interdisciplinary team, and interventional treatment of patients with acute myocardial infarction after emergency non-cardiac surgery.

There are 5 **scientific publications** related to the dissertation paper: two publications in *Speshna Meditsina* (Emergency Medicine) journal and 3 are participations with reports in the National Congress of Cardiology, the National Congress of Emergency Medicine, and the Bulgarian course in Coronary Physiology and Non-Coronary Vascular Physiology.

In conclusion, the dissertation paper of Dr. Ivan Martinov, **Perioperative Myocardial Infarction - Clinical, Diagnostic, and Therapeutic Features,** is an in-depth, multifaceted study of an interdisciplinary nature, with a pronounced relevance not only for the cardiac, but for the surgical science and practice, too. The long experience of Dr. Martinov as an excellent clinical and invasive cardiologist who has mastered and applied various diagnostic and therapeutic non-invasive and invasive methods for the treatment of patients at different wards and clinics of N. I. Pirogov University Multi-Profile Hospital for Active Treatment and Emergency Medicine EAD allows him to make multifaceted studies and analyses, summaries, and conclusions about the clinical, diagnostic, and therapeutic features of perioperative myocardial infarction in comparison with spontaneous myocardial infarction. Of special scientific and practical value is the **Hospital Algorithm for Behaviour in Perioperative Myocardial Infarction (STEMI)** created and presented by Dr. Martinov.

The dissertation paper presented fully meets the requirements of the Development of Academic Staff in the Republic of Bulgaria Act and the Regulations for the development of the academic staff at N. I. Pirogov University Multi-Profile Hospital for Active Treatment and Emergency Medicine EAD, Sofia and I strongly recommend to the members of the respected scientific committee to award Dr. Ivan Petrov Martinov, Head of the Invasive Department at the Cardiology Clinic of N. I. Pirogov University Multi-Profile Hospital for Active Treatment and Emergency Medicine EAD, a doctoral degree in Cardiology.

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