Translation from Bulgarian

EXPERT OPINION

on a dissertation paper for awarding a doctoral degree

Topic: **Perioperative Myocardial Infarction - Clinical, Diagnostic, and Therapeutic Features**

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Professional biography:
Dr. Ivan Martinov was born in 1971 in Sofia. He graduated from the Medical University of Sofia in 1995 with a degree in Medicine, and began his professional career at the Clinic of Emergency Internal Medicine of N. I. Pirogov University Multi-Profile Hospital for Active Treatment and Emergency Medicine EAD, Sofia in 1997 as a resident doctor. In 2005, he became a research associate at the National Cardiology Hospital; from 2007 to 2011, he worked as a cardiologist at the Cardiology Department of Tokuda Hospital Sofia, and from 2011 to 2013, as an invasive cardiologist at Hr. Botev MHAT, Vratsa.

Since 2013, Dr. Martinov has been Head of the Invasive Department at the Cardiology Clinic of N. I. Pirogov University Multi-Profile Hospital for Active Treatment and Emergency Medicine EAD.

Dr. Martinov acquired specialties in Internal Medicine in 2003 and Cardiology in 2007, and 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.
He took part in many training courses at home and abroad and has been awarded the title of Fellow of the European Society of Cardiology.

Assessment of the relevance of the topic: The topic developed by Dr. Martinov was well chosen in terms of relevance and practical benefit. The progressive aging of the population and the increasing life expectancy, as well as the progress in surgical treatment techniques lead to a progressive increase in surgical interventions. Proper assessment of the benefit-risk balance of such treatment in old polymorbid patients is often difficult, interdisciplinary (which in turn is associated with major logistical difficulties), and complex due to the integration of many important data included in the consideration.

One of the most serious perioperative complications is myocardial infarction due to the widespread risk factors for ischemic heart disease and their long-term impact that deepens with age. The developed algorithms and scales for the assessment of perioperative cardiac risk give some perspective, but there is no specific, important, practical information regarding therapeutic behaviour, especially in emergencies.

Therefore, the identification of the factors determining perioperative acute coronary syndrome (PACS), its diagnosis, clinical course, and treatment is of great value for the clinical practice.

Structure of the dissertation paper: The dissertation paper of Dr. Martinov consists of 202 pages and is illustrated with 41 tables and 43 figures. For better clarity, the dissertation paper was divided into 12 chapters. It was structured as follows: **Introduction** - 2 pages, **Literary Review** - 90 pages, **Goal, Tasks** - 1 page, **Materials and Methods** - 16 pages, **Results** - 39 pages, **Discussion** - 18 pages, **Conclusions** - 1 page. From these data, it can be seen that the dissertation paper is optimally structured, with a good balance between its parts.

A total of 323 literary sources were used, of which 6 by Bulgarian authors and 317 by foreign authors. They are arranged alphabetically.

Literature review: On 90 pages, the fundamentals of Acute Coronary Syndrome (ACS) - definition, classification, pathology, clinical picture, and treatment - are thoroughly examined. Very well described and in great detail is perioperative AMI, with all known data on its specifics in terms of

diagnosis, pathophysiology, and behaviour. The important aspects related to risk stratification and the unknown in practical terms are also clearly outlined. This emphasizes the importance of the problem. The author demonstrates a very good knowledge of the literature on the subject. Based on the literature review, the dissertation author drew very important conclusions as a transition to the research methodology:

1. Acute myocardial infarction with persistent ST-elevation is one of the best studied nosological units. After a decade of evolution in diagnosis, risk stratification, outpatient and inpatient logistics, reperfusion therapy, and medication therapy, in-hospital mortality has been reduced from 30% in the mid-20th century to 3-5% today. Globally, there has been a steady trend of declining overall mortality from STEMI.

2. Perioperative myocardial infarction and perioperative STEMI remain a serious medical problem. There is a large number of population, retrospective, and prospective studies that show a significantly higher morbidity and mortality rate than in spontaneous one. The interdisciplinary nature of the problem leads to difficult recognition, late diagnosis, and suboptimal treatment. The scales developed for preoperative risk assessment still do not provide a good enough orientation for clinical behaviour, especially in emergency surgery.

3. 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.

4. There is a small number of randomized trials and they are mainly related to medication therapy. There are no randomized trials regarding the interventional treatment of patients with perioperative myocardial infarction.

5. The available guides, i.e. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA) and 2017 Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery, do not provide sufficient clarity in the part of interventional treatment in perioperative acute coronary syndrome. Recommendations are often based on NSTEMI/STEMI studies and cannot be directly interpolated on perioperative myocardial infarction.

6. In connection with the aging population and the increase in concomitant heart diseases, as well as against the background of the increasing number of surgeries, the incidence of perioperative cardiovascular complications, including perioperative myocardial infarction, is expected to increase. It is especially necessary and appropriate to develop modern guidelines based on randomized trials and implement them as protocols in hospital practice.

Research methodology - Goal, tasks, materials, and methods: Based on the in-depth and generalized literature review and the conclusions therefrom, the prerequisites for the research were derived. Dr. Martinov formulated, accurately and clearly, the **goal** of the study: "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.".

To achieve this goal, 7 tasks were set and fully implemented:

1. To determine the frequency of perioperative myocardial infarction with ST-elevation in patients with emergency non-cardiac surgery treated at N. I. Pirogov University Multi-Profile Hospital for Active Treatment and Emergency Medicine EAD.

2. To determine the influence of the proven risk factors in spontaneous STEMI on the course and prognosis of perioperative myocardial infarction with ST-elevation and to test scales for the assessment of cardiovascular risk in emergency surgery.

3. To analyse the role of postoperative anaemia in the treatment of patients with perioperative myocardial infarction with ST-elevation and its outcome.

4. To establish the differences in the manifestation, course, and outcome of perioperative AMI in comparison with those of spontaneous acute myocardial infarction with ST-elevation.

5. To determine the specifics of medication and interventional treatment of perioperative myocardial infarction with ST-elevation.

6. To analyse the results of interventional treatment of patients with PMI-STEMI in comparison with the results in spontaneous STEMI for the respective period of time: procedural success, complications, in-hospital mortality.

7. To create an algorithm for the implementation of hospital logistics and interventional treatment of patients with perioperative STEMI in emergency non-cardiac surgery.

For the tasks set, a sufficient number of patients diagnosed with acute myocardial infarction with persistent ST-elevation were included: 112, divided into two groups. One of the groups – Group 1 or the main group – consisted of 35 patients with perioperative STEMI undergoing non-cardiac surgery, and Group 2 – the control group – included 77 patients with primary coronary intervention in spontaneous STEMI. The including and excluding factors were clearly defined. It is noteworthy that patients representing all age groups and undergoing surgical interventions with varying degrees of complexity were included. This is a clear signal for the wide applicability of the conclusions made on the basis of the results of the research, as there is no unrepresented group. The methods used are suitable for the implementation of the goal and tasks. The diagnostic and therapeutic process is fully in line with the current guidelines for behaviour in patients with STEMI.

Results, analysis, and discussion: The presented results are convincing. They are presented clearly and precisely, both for the whole contingent studied and for the individual groups. To obtain them, a number of (12) perfectly suitable statistical methods were used, using the SPSS specialized statistical package (Statistical Package for the Social Sciences), version 25.0.

The results confirm data from previous studies in patients with perioperative STEMI in terms of risk factors, gender, age, and previous interventions. In the analysis of the two studied groups, the higher frequency of the studied post-procedural complications of Group 1 (the main group) is impressive, and the possible causes are analysed in detail. The factors influencing the risk of death are divided into **quantitative** (age, systolic blood pressure, baseline haemoglobin, procedural time, contrast, hospital stay and echoCG EF for the main group and age, and systolic blood pressure, heartrate, baseline Hb, baseline troponin, echoCG EF respectively for the control group), and **category** (the complications of no-reflow, acute left ventricular failure (ALVF), Revised Cardiac Risk Index (= 1) and those of a protective nature: radial access, stenting, restored final TIMI flow, postprocedural therapy - NTG – for the main group, and shock and ALVF and those of a protective nature: radial access and stenting – for the control group respectively).

The summary of the results and discussion identifies important practical behavioural problems in patients with perioperative AMI: gaps in the perioperative assessment of patients (adequate preoperative assessment of cardiovascular risk, early detection of STEMI, and rapid contact with an invasive

cardiologist), a problem with medication therapy (especially antithrombotic treatment) leading to deviations from the STEMI interventional treatment protocol and inevitably worse clinical outcomes.

One of the significant achievements of the dissertation paper is the developed **Algorithm for Behaviour** in Perioperative Myocardial Infarction (STEMI).

Conclusions: based on the dissertation paper, the following 7 conclusions were formulated, which correspond to the results obtained:

1. It was found that in emergency surgical interventions of great complexity, the frequency of patients with perioperative STEMI treated at N. I. Pirogov University Multi-Profile Hospital for Active Treatment and Emergency Medicine was significantly lower than the literature data.

2. The risk factors for perioperative STEMI (male patients, diabetes mellitus, hypertension, suffered myocardial infarction, suffered cerebral infarction, previous percutaneous transluminal coronary angioplasty (PTCA), previous aortocoronary bypass (ACB), dyslipidaemia, renal failure), when considered separately, did not show statistically significant differences in the patients with STEMI. In the main group, the relative share of patients with peripheral vascular disease (PVD) was significantly higher, in contrast to the control group.

3. The comparative data showed a statistically significant increased haemorrhagic risk in the majority of the patients with perioperative STEMI compared to the control group. This risk was associated with the surgery performed and the presence of severe and moderate anaemia in a significant proportion of the patients with perioperative STEMI.

4. There was a significant difference in the manifestation and course of PMI: scarce initial symptoms, severe general condition, acute heart failure (shock), difficult diagnosis, late response of the treating team (the patients with PMI were in hospital, but they were late presented in the invasive ward compared to the outpatient patients with SMI), more frequent anterior localization of the infarction, low ejection fraction, prolonged hospital stay, and significantly higher mortality.

5. It was found that the interventions in PMI and SMI, performed according to a common protocol, were without distinction in terms of procedural, scopic time, and contrast used. There was a significant difference in PMI with more frequent use of femoral access, lower stenting rate, and,

often, completion of the procedures with plain old balloon angioplasty (POBA). There was also a significant difference in the antiplatelet therapy used: fewer patients on double antiplatelet therapy, with a predominance of Clopidogrel monotherapy and even without therapy.

6. The results of the interventional treatment of the patients with PMI, compared to the patients with SMI, were significantly worse in terms of the restoration of blood flow in the infarcted artery and the final angiographic result, leading to complications such as ALVF and increased hospital mortality.

7. Based on the data from the study, an algorithm for in-hospital logistics was developed, aimed at preoperative stratification of cardiac risk, adequate monitoring in the perioperative period, timely response in diagnosing coronary events in close collaboration between cardiac, surgical, and anaesthesiology / resuscitation teams, and timely interventional treatment.

Contributions: they are reflected in the Abstract of the dissertation paper, and are divided into two groups: of scientific-theoretical and confirmatory nature and scientific-applied nature:

Scientific-theoretical contributions

1. For the first time in the literature, a comparative study was performed as well as an analysis of the specifics of the manifestation, course, therapy, and outcome in patients with perioperative STEMI compared to spontaneous STEMI.

2. For the first time in our country, increased haemorrhagic risk was studied in patients with perioperative STEMI, related to the performed surgical intervention and the presence of severe anaemic syndrome, which determines the problems in the implementation of medication and interventional treatment of such patients.

3. For the first time in our country, the specifics of the interventional and medication treatment of patients with perioperative STEMI were determined, and the results of the interventional treatment of patients with PMI were analysed in comparison with the results of patients with SMI.

Scientific-applied contributions

4. For the first time in our country, the Revised Cardiac Risk Index - Lee (RCRI) was validated for use in emergency surgery.

5. For the first time in our country, the constellation of quantitative factors of risk and protective nature, influencing the risk of lethal outcome of patients with perioperative and spontaneous STEMI, was determined.

6. For the first time in our country, an algorithm was created for the assessment of perioperative risk of AMI, for the implementation of hospital logistics by an interdisciplinary team and interventional treatment of patients with acute myocardial infarction after emergency non-cardiac surgery.

Abstract: contains 87 pages and reflects exactly the content of the dissertation paper.

Publications: In connection with the dissertation paper, the author presented 2 publications in national journals and 3 participations in national scientific forums, which meet the minimum national criteria.

Remarks: Without reducing the value of the research, the following remarks can be made:

- Some of the abbreviations are in Cyrillic and others are in Latin;
- Foreign words were used in the text;
- The publications are in Bulgarian editions only.

Conclusion: I highly appreciate the work of Dr. Martinov due to the relevance of the study and, mainly, the attempts to solve a very important problem, i.e. improving behavior in patients with perioperative AMI.

The dissertation paper presented by Dr. Ivan Petrov Martinov 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 for awarding a doctoral degree in Cardiology.

I recommend to the members of the esteemed scientific committee to vote in favour and award a doctoral degree to Dr. Ivan Martinov.

29.04.2021 ……
Sofia Prof. Dr. D. Vasilev, MD