

Translation from Bulgarian

EXPERT OPINION

By Prof. Dr. Plamen Gatsov, MD, MedScD

ON THE DISSERTATION PAPER

of

Dr. Ivan Petrov Martinov

PERIOPERATIVE MYOCARDIAL INFARCTION - CLINICAL, DIAGNOSTIC, AND
THERAPEUTIC FEATURES

For acquiring a doctoral degree in Cardiology

1. Paper Relevance

The first coronary intervention to treat acute myocardial infarction (AMI) was performed by Dr. J. Hartzler in 1979, just two years after the onset of catheter coronary interventions by A. Gruentzig (1977). After many years of debate and gradual gaining of experience, in the mid-1990s, the first randomized trials showed the superiority of percutaneous coronary intervention in AMI over conservative therapy and drug thrombolysis (Brody, 1994). In the following years, there was huge evidence of the benefit of primary coronary catheter intervention in acute ST-elevation myocardial infarction and its advantages over any other treatment. This interventional treatment, together with the constantly evolving drug therapy accompanying the treatment of such patients, has led to a significant reduction in hospital mortality from acute myocardial infarction over the last 40 years from about 20% to currently below 5%. There are sufficiently clear guidelines for treatment in spontaneous myocardial infarction with ST-elevation. The situation is quite different with acute myocardial infarction, which occurs in the course of treatment of other diseases, such as non-cardiac surgery. These "perioperative" myocardial infarctions (PMI) have a number of features that distinguish them in clinical, diagnostic, and therapeutic terms from "spontaneous" ones. First, they occur in surgical wards, unequipped and without the necessary competence to diagnose and treat such conditions. Second, these are patients with symptoms of the underlying disease, which can blur the picture of AMI. Third, the presence of an operative wound and the risk of bleeding make the use of standard treatment, including anticoagulants and antiplatelets, potentially dangerous for increased bleeding and developing a severe anaemic syndrome. Last but not least, these patients are very often elderly, with many concomitant diseases. Along with these negative factors, there are also positive ones, such as the presence of medical staff at the time of the infarction, as well as often the possibility of interventional treatment within the same hospital. Clarifying the specifics of perioperative MI and creating clear rules of diagnosis and treatment in

such cases is an extremely important task. This was the task set by Dr. I. Martinov in his dissertation paper.

2. Structure of the dissertation paper

The dissertation consists of 202 pages, 45 figures, and 45 tables. The bibliographic reference contains 323 titles, of which 6 by Bulgarian authors.

a) Literature review

The literature review is presented on 69 pages. It is well structured, clear enough, and extensive. The definitions of the main used concepts are presented. The modern classification of AMI is also presented, as well as the basic criteria for diagnosis. The evolution over the years in the diagnosis and treatment as well as the features of logistics and post-procedure treatment of AMI are considered. The main modern guidelines AMI diagnosis and treatment are discussed in detail, with special attention paid to the risk groups and the factors influencing the prognosis in AMI with ST-elevation (STEMI). The literature data on the relationship between anaemic syndrome, therapeutic strategies, and outcome in patients with AMI are reviewed. Special attention is paid to studies concerning the features of perioperative myocardial infarction in non-cardiac surgery, including the most commonly used scales for assessing the risk of cardiovascular complications, as well as the therapeutic behaviour in such patients. The questions that have not been clarified so far are also clearly stated.

b) Goal and tasks

The goal is clearly stated: "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 are defined in 7 points selected to clarify the most important stages in achieving the goal set.

c) Methods

Of all intervened 1,595 primary myocardial infarctions with ST-elevation at the Cardiology Clinic of N. I. Pirogov University Multi-Profile Hospital for Active Treatment and Emergency Medicine for a period of 6 years (from early 2010 to late 2015), the dissertation author selected as the main group 35 patients in whom the infarction occurred in the hospital in the period after the non-cardiac surgery. For the same period of time, after application of the relevant inclusion and exclusion criteria as well as equalization by "blurring" factors such as gender and age, Dr. I. Martinov included 77 patients admitted to the clinic with spontaneous MI with ST-elevation. The term *Perioperative Myocardial Infarction (PMI)* is clearly defined. The RCRI (Revised Cardiac Risk Index - Lee) used later in the dissertation paper to assess the risk of cardiovascular complications in patients with surgery is described. The definitions of the studied risk factors, i.e. diabetes mellitus,

arterial hypertension, dyslipidaemia, chronic kidney disease, anaemia, are presented. The used laboratory and instrumental tests are listed, as well as the used therapeutic methods, both medication and interventional. Twelve statistical methods were used, which are sufficient for complete statistical processing and presentation of the results.

3. Results and discussion

The results of the study are presented clearly and are well illustrated with figures and tables. The dissertation author did not find a significant difference between the main and control groups in terms of risk factors such as diabetes mellitus, arterial hypertension, chronic kidney disease (CKD), suffered myocardial infarction, cerebral infarction, previous coronary intervention or coronary artery bypass grafting. The only statistically significant difference was the presence of peripheral vascular disease (PVD), which was much more common in the patients with perioperative STEMI. Angina pectoris was less common in the main group. Acute left ventricular failure (ALVF) was significantly more common in the main group compared to the control group. While in the group with spontaneous MI the lower localization predominated, in the group with perioperative MI the anterior localization of the infarction predominated. The femoral access for catheterization was significantly more common in the main group, which was due to the more severe condition of the patients upon admission to the cath lab, while in the control group the radial access prevailed. There was no statistically significant difference between the groups in terms of procedural time, X-ray load, and amount of contrast. There was no such difference in the degree of stenosis either. In the studied group, there were statistically more cases of using only balloon dilatation, without stenting. The two groups did not differ in the frequency of stent thrombosis, as well as in the no-reflow in the "guilty" artery. The main group more often had a low TIMI-degree of restored blood flow than the control group. Regarding the periprocedural therapy, the patients from the main group were significantly more often left without any antiplatelet therapy, or only on Clopidogrel, while in the control group the double antiplatelet therapy with Brilique + Aspirin prevailed. In the main group, the complications of ALVF, blood transfusion, and death were significantly more common. The patients in this group also had a longer hospital stay. There was a tendency for perioperative MI to appear most often in the period from 48 to 72 hours after the surgery. It was found that the low values of the Revised Cardiac Risk Index were associated with a higher chance of survival for the patients than for those with an intermediate risk score. Anaemia was more common in the main group of patients. The probability of death was much higher in the patients with anaemia for both groups. The presence of anaemia was associated with a lower likelihood of stenting. A single antiplatelet therapy with Clopidogrel was more common in the patients with PMI. The analysis of quantitative indicators showed that the risk of death decreased with increasing systolic blood pressure and left ventricular ejection fraction (LVEF). The examination of the categorical signs showed that the risk of death was reduced by the use of stenting and the better TIMI blood flow at the end of the procedure, while the presence of no-reflow, ALVF, and high Revised Cardiac Risk Index increased the risk of death. The regression analysis showed that the factors with the greatest weight in terms of the risk of death in the patients were ALVF and low LVEF. The ROC curve analysis found that a heart rate <80 / min, baseline Hb <138 g / l, creatinine and troponin above the upper limits, as well as LVEF below or equal to 39% were predictors of death. Not surprisingly, the presence of shock was associated with a 45-fold increased risk of death.

At the end of his dissertation paper, Dr. I. Martinov summarized the problem, pointing out serious shortcomings in the perioperative assessment of patients and a problem with the medications used in patients with PMI, leading to deviations from the protocol for treatment of patients with STEMI. As a result of the experience gained, the dissertation author developed a practical algorithm for screening, diagnosis, and treatment of PMI. The conclusions from the dissertation paper were logically defined in 7 points.

The contributions were grouped, with 3 of them being of scientific and theoretical nature and 3 of scientific and applied nature. Dr. Martinov has 5 scientific publications related to his dissertation paper, of which 2 in *Speshna Meditsina* (Emergency Medicine) journal and 3 reports at Bulgarian scientific forums with international participation.

4. Some critical remarks

1. In analysing the quantitative indicators, the conclusion that a prolonged hospital stay reduces the risk of death is logically incorrect.
2. The protective effect on mortality of post-procedural application of NTG remains unclear. As long as patients are not randomized to this indicator, it is not possible to assess whether this is the case. The significance of this finding remains unclear to me.
3. As the dissertation author noted, the choice of intervention access (either transradial or transfemoral) is taken by the operating surgeon depending on the severity of the patient's condition (transfemoral in more severe patients), so it is not a cause of adverse outcome in patients, but a part of the approach in such high-risk patients.

5. Conclusion

In his dissertation paper, Dr. Ivan Martinov made the very first in Bulgaria analysis of the features that distinguish PMI from spontaneous MI. Based on his own experience in the treatment of this type of patients at N. I. Pirogov University Multi-Profile Hospital for Active Treatment and Emergency Medicine, he drew interesting and important-for-the-practice conclusions. The analysis of the results helped him to develop a practical algorithm for diagnosis and treatment in patients with perioperative STEMI, which obviously have a number of features in clinical, diagnostic, and therapeutic terms that distinguish them from patients with spontaneous MI. These results will be useful for all physicians involved in the treatment of such patients. Despite the critical remarks above, I believe that the dissertation paper is valuable and fully meets the criteria for acquiring a doctoral degree in Cardiology. I call on the esteemed scientific committee to vote in favour.

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Author: *[ill. sign.]*

(Prof. Pl. Gatsov)