

REVIEW

In connection with a dissertation for the award of the educational and scientific degree "DOCTOR" on the topic: "Clinical results in interventional revascularized patients with myocardial infarction"

Author of the dissertation:

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Prepared the review -

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A review has been prepared in accordance with the Academic Staff Development Act (ACAS), the Regulations for the Application of the Academic Staff (PRAS) and the Regulations on the Terms and Conditions for Acquisition of Scientific Degrees and Occupation of Academic Positions (PURPNSZAD) in MHAT "NKB" EAD.

The presented set of materials on paper / electronic media is in accordance with the procedure for acquiring the scientific and educational degree "Doctor" and the regulations of MHAT "NHH" EAD. I do not find plagiarism in the review of the dissertation, abstract and publications submitted to me for review, related to the dissertation development.

I declare the lack of common scientific developments with the doctoral student and a potential conflict of interest.

Acute coronary syndrome and acute myocardial infarction in particular represent the final stage in the evolution of atherosclerotic coronary involvement, a disease still leading in the structure of cardiovascular morbidity and mortality.

According to the National Center for Public Health and Analysis for Bulgaria, mortality from coronary heart disease and its acute manifestations is declining - a favorable trend that is hardly the same in diverse groups of patients. Modern aspects emphasize the importance of the biology of the atherosclerotic process, as well as local morphological characteristics of atherosclerotic plaques, leading to a high risk of future vascular accidents.

Outside of any dispute, the patient's risk characteristics such as diabetes, kidney disease, dyslipoproteinemia and others determine the long-term prognosis mainly due to their association with advanced changes in the coronary vessels. Multiclonal coronary involvement - alone and in combination with other risk characteristics determines a group of patients at high absolute risk of future coronary interventions. In this aspect, the behavior of these patients, the type of revascularization and the time for its implementation after an already experienced acute coronary syndrome are an open question.

These data motivate the choice of topic by Dr. Iskra Bayraktarova - "Clinical results in interventional revascularized patients with myocardial infarction." The dissertation is essential also due to the lack of systematic data for our country and the provision of such by a leading high-volume center, such as the NCB.

Structure of the dissertation:

Dr. Bayraktarova's dissertation is written on 162 standard pages, of which:

1. Title page - 1

2. Acronyms - 1

3. Literary review - 28
4. Purpose, tasks - 2
5. Materials and methods - 12
6. Own results - 53
7. Discussion - 28
8. Conclusions and contributions - 4
9. Literature – 17

The ratio overview: methodical: result-disassembly part is optimal, respectively 25: 10: 65%. The dissertation contains a total of 5 figures, 33 tables. The bibliography includes 203 sources, of which 4 are in Cyrillic and 199 in Latin. Most of the cited titles are directly related to the studied problem.

Characteristic features of work:

The topic of the dissertation "Clinical results in interventionally revascularized patients with myocardial infarction" is aptly selected in terms of the importance of the problem, current relevance and projection into the future. In essence, a large-scale follow-up of the clinical course of interventional patients with acute myocardial infarction with and without ST-segment elevation, hospitalized and treated in the acute stage of the disease at the Clinic of Cardiology of the NCC.

Characterization was performed according to the type of myocardial infarction, the type of coronary involvement and the type and time of revascularization, and patients with surgical revascularization were excluded from the analysis. In addition, a wide range of clinical, laboratory and instrumental studies were analyzed. Patient data were collected from the clinic's database for the period 2014 (for patients with STEMI) and 2013-2015 (for those with NSTEMI).

The three main periods of follow-up of patients are defined - 1) in-hospital period; 2) period of delayed planned revascularization - until the 90th day after the primary revascularization; 3)

period of outpatient follow-up - from the last planned revascularization for the patient to the end of follow-up. For patients who are not referred for phased planned revascularization, the outpatient follow-up period begins immediately after discharge for the index event.

This is the first in-depth study in Bulgaria, which compares the baseline characteristics, inpatient treatment in the acute period and long-term results in patients with ACS and monoclonal and multiclonal coronary heart disease, taking into account the effect of the achieved degree of interventional revascularization. on survival and cardiovascular events.

The literature review as a systematics and analyticalness in considering the available information presents the doctoral student as a leading expert on the issue. The epidemiology and pathogenesis of ACS, the open artery theory, the importance of multiclonal coronary involvement for long-term prognosis are covered in turn, with special emphasis on the timing of subsequent coronary revascularization. At the end of the literature review, the data are systematized, which makes a good impression. The factual preconditions for the study are derived from the review in the form of a conclusion.

The aim of the dissertation is formulated clearly and precisely - to follow patients with myocardial infarction (with and without elevation of the CT segment) with optimal drug and interventional treatment according to international guidelines and internal protocols of behavior in a single highly specialized center with respect to their long-term prognosis by assessing the effect of the additional interventional revascularization undertaken on survival, mortality, frequency and time to onset of new ischemic events.

The following tasks are formed:

1. Based on a set of clinical and instrumental inclusion and exclusion criteria to select a group of patients treated for myocardial infarction with and without CT-elevation in the Cardiology Clinic and the Department of Emergency Cardiology of the National Cardiology Hospital - Sofia for the period 2014 (for patients with STEMI) and 2013-2015 (for those with NSTEMI).

2. To analyze the treatment carried out in the acute period in the context of the demographic characteristics of the patients, the established coronary anatomy, the complications that occurred during the hospital phase and thereafter, the additional therapeutic interventions and the achieved early (during the hospital stay) therapeutic effect and survival.
3. To establish the additional therapeutic procedures undertaken in the short term (up to 3 months from the primary event), regarding interventional revascularization of the available stenoses of coronary arteries, not related to the infarction.
4. To conduct a prospective follow-up of the collected patient group in terms of adverse events (death by any cause, new heart attack, new SCAG, new revascularization, new ischemic stroke) in patients after the end of the active therapeutic period.
5. To evaluate the survival in the separate subgroups (STEMI / NSTEMI, one-, two- and three-clone patients) according to the achieved revascularization and to make an analysis of the predictors for the remote prognosis.
6. To assess the mortality rates, the frequency of adverse events and the time to their occurrence in the formed subgroups.
7. To assess mortality rates, the frequency of adverse events in the three time periods - in-hospital, short-term (up to 3 months after the primary event) and remote (from 3 months to the end of follow-up).

The research methodology regarding the studied non-invasive and invasive indicators and accepted definitions is appropriate for the reliability and reliability of the reported results and includes clinical (history and physical examination), instrumental non-invasive and invasive, laboratory and statistical research methods. Leading in the evaluation is the evaluation of selective coronary angiography, as mainly indicators related to the localization of the atherosclerotic process are analyzed.

On the basis of the collected completed questionnaires and subsequent documents from hospitalizations and examinations, the follow-up of the patients was carried out and it is divided into two periods: near and far follow-up period. The near period is the period of delayed planned staged revascularization - 90 days from the date of the primary event, when at the discretion of the treatment team and at the request of the patient an attempt was made to achieve complete revascularization.

Patients noted during the initial stay as planned for follow-up were explicitly monitored to see if and when it occurred, whether it met the criteria for complete revascularization, how it was achieved (interventionally or surgically), and if not, what the cause was. The remote period is the period of outpatient follow-up and lasts until the beginning of March 2018. or until a fatal event has occurred in the meantime.

The following new ischemic events, as well as the period until their occurrence, were monitored together and separately, in days:

- new hospitalization for acute coronary syndrome (the diagnosis at discharge was accepted as valid;
- new invasive emergency assessment;
- new revascularization and total number of revascularisations performed by the end of follow-up;
- New ischemic stroke
- Death for any reason

Due to the impossibility to estimate the exact cause of death in a large number of cases, the endpoint was analyzed mortality for any reason

The obtained results are convincing and presented clearly, accurately - in general for the studied contingent, as well as by subgroups, giving the opportunity to track and compare the data. Completely appropriate statistical methods have been used to obtain them.

The main results of the work of Dr. Bayraktarova can be summarized in the following directions:

1. In the studied high-risk Bulgarian population with STEMI and NSTEMI, a significantly higher frequency of registered new ischemic events and death was found for the follow-

up period compared to that established in randomized clinical trials. To a large extent these data are due to the high-risk characteristics of the included patients, as the individual differences STEMI / NSTEMI confirm the latter condition as a significant carrier of adverse course in the long run and the need for specially designed treatment strategies.

2. A high degree of adherence to ESC is established. Recommendations for treatment of ACS during the in-hospital stay of the examined patients corresponding to a high-volume academic center
3. A small proportion of patients with IBD are referred for planned staged complete revascularization despite the lack of systemic limitations. The decision for a long-term therapeutic approach is made during the primary coronary procedure by the interventional cardiologist and is not discussed subsequently. This result is significant and shows undiscovered potential for changing the unfavorable prognosis in these patients.
4. Patients with the highest SS risk are relatively less likely to receive full step-by-step interventional revascularization, although they would benefit most from it.
5. The strategy for full phased revascularization within 3 months after the index event is effective and safe.
6. . Patients with ICD and complete revascularization have:
 - a long-term prognosis comparable to that of monoclonal patients in terms of the incidence of new ischemic events and death from any cause;
 - Significantly better prognosis than patients with ICD and incomplete revascularization.
7. A regression model with a high predictive value for increased risk of death in follow-up of patients with ACS has been developed, including the following indicators: age, presence of SMEs, AF during the current stay, stem stenosis or STO, deterioration of the Killip class, conducting dialysis and the presence of incomplete revascularization until the 90th day.

The conclusion corresponds to the obtained results, the same applies to the conclusions made.

The contributions of the dissertation are of emphasized scientific and applied nature, well formulated and are the result of the research.

I believe that the topic discussed by the doctoral student is among the important issues of modern cardiology and deserves to be enriched and expanded in the future. By its nature, this is one of the first for our country more systematic reporting of results from the follow-up of patients with revascularized ACS, multiclinal involvement and performed or not subsequent revascularization.

The prognosis data for the evolution of the disease and the ongoing therapy clearly demonstrate the significant unmet needs even in a leading university center, and I expect similar data if the study is conducted at the national level.

I am convinced that the topic of doctoral studies and the volume of work done significantly exceeds the legal requirements for successful defense of a doctoral thesis. I particularly welcome the successful attempt to systematize and present the data with the most appropriate statistical processing methods, as well as the summary of the data at the end of each chapter.

In connection with the doctoral thesis, Dr. Bayraktarova is the author of two publications - one in a journal indexed and referenced in a global database and one in a referenced national journal. Excerpts from the dissertation are presented as posters and oral presentations at national and international forums such as the National Congress of Interventional Cardiology and the National Congress of Cardiology and two editions of the Acute Cardiac Care working group of the European Society of Cardiology.

In conclusion, the dissertation presented by Dr. Iskra Hristova Bayraktarova contains scientific, scientific-applied and applied results, which represent an original contribution to science and meet the requirements for awarding educational and scientific degree "DOCTOR". The dissertation shows that the doctoral student has in-depth theoretical

knowledge and professional skills in the scientific specialty, demonstrating qualities and skills for independent conduct and discussion of research.

On these grounds I vote positively and I propose to the esteemed members of the Scientific Jury to vote positively and propose to the Executive Director of the NHH the award of the scientific and educational degree "Doctor" in the doctoral program of cardiology to Dr. Iskra Hristova Bayraktarova

A handwritten signature in blue ink, appearing to read 'Arman Postadjian'.

30.05.2021

Prof. Dr. Arman Postadjian, MD

Medical University of Sofia

Member of the Scientific Jury