

To the Chairman of the Scientific Jury
appointed by

The Rector of MU - Varna

REVIEW

By **Prof. Dr. Kiril Karamfiloff Karamfiloff**, Ph.D,
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on dissertation for the award of PhD in the field of higher education 7. Health and Sport, professional field 7.1. "Medicine", for scientific specialty "Cardiology" and doctoral program "Cardiology", approved for review as a member of the Scientific Jury (Protocol № 1/1/11.08.2023) in accordance with the procedure according to Order N: P-109-367/08.08.2023 of the Rector of the Medical University - Varna.

"APPLICATION OF ECHOCARDIOGRAPHIC METHODS FOR FUZZY STRATIFICATION
DETERMINING THE VOLUME OF SURGERY IN PATIENTS WITH ISCHEMIC MITRAL
REGURGITATION"

by Dr. Daniela Stoyanova Panayotova

full-time PhD student at the First Department of Internal Medicine,
Faculty of Medicine at Medical University - Varna

Scientific supervisor.

Scientific consultant: Prof. Natalia Nikolova, MD

Career profile of the PhD student

Dr. Daniela Stoyanova Panayotova graduated from the Medical University (Medical Academy) Sofia in 1986. She started working in the Department of Internal Medicine in Sofia, Bulgaria. In the period 1993 - 94 she moved to the Cardiology Department at the IVth City Hospital in Pernik. In 1993 she worked in the Cardiology Department of the University Hospital in Sofia. From 1995 to 2001 he worked at the Clinic of Cardiology of the Military Medical Academy in Sofia. From 2001 to 2002 she was a cardiologist at the Cardiology Clinic of the II City Hospital in Sofia, then from 2002 she moved to Kuwait, where she worked from 2004 to 2005 as a cardiologist in the Department of Cardiology, Adan Hospital. From 2005 to the present moment she is a cardiologist at the Clinic of Cardiac Surgery, University Hospital "St. Marina" Varna. University of Varna. Since 2016 he is an assistant professor of cardiology English-speaking training at the Department of Cardiovascular Surgery and Angiology, Faculty of Medicine, Medical University - Varna.

She acquired her specialty in Internal Medicine in 1993 and her specialty in Cardiology in 1998. Since 2013 she has been certified as an "Expert level in Echocardiography". She has a Master's degree in "Health Management" from Medical University - Varna acquired in the period 2012-2014.

General description of the presented materials

I have been provided with the dissertation and abstract in electronic and printed versions, which fully comply with the requirements of the Law on Cardiovascular Risk Assessment and the Regulations for its implementation at the Medical University "Prof. Dr. P. Stoyanov" - Varna. I have also been provided with copies of 4 publications related to the dissertation in electronic and printed form, one of the publications is in a journal with IF.

Significance of the topic:

The dissertation topic is actual and dissertationable. Independent of the application of the most up-to-date treatment of ischemic heart disease (IHD) with the methods of invasive cardiology, a significant proportion of patients with acute myocardial infarction (AMI) develop secondary, ischemic mitral regurgitation (IMR). In the guidelines published in recent years on the management of ischemic heart disease and on the treatment of valvular heart disease, there are no fully categorical data and recommendations on the need for operational correction of the significant IMR. Randomised trials on this topic have included relatively small patient groups,

and in the majority of them "mitral valve repair" (MVRP) is understood to mean only restrictive annuloplasty. There are recommendations for valvular prosthesis in significant and high-grade MI, despite the available evidence that when PIMK is successfully performed during cardiac revascularization surgery and there is no recurrence postoperatively, mid- and long-term outcomes are superior to those after MC prosthesis.

Dissertation Structure:

The dissertation is presented in 170 standard typewritten pages and is structured in 6 main sections with supplementary paragraphs in most of them and 2 applications. It is illustrated with 15 colour and black and white figures, 32 tables and 42 mathematical formulae. The list of cited literature includes 324 titles, 5 in Bulgarian and 319 in Latin (English). The main sections are.

In the introduction, the dissertation justifies the significant medico-social aspect of the problem - CHD and the associated significant IMR.

The literature review includes 12 sections, most of which have subsections. The current status of the problem of CHD complicated with secondary MR is described in detail. The definition of MI, mechanisms of occurrence and evolution of this condition are discussed in detail. The main attention is paid to echocardiographic diagnostics with all possibilities of modern echocardiographic devices. Diagnostic emphasis is on the preoperative assessment of mitral valve morphology and function, intraoperative pre- and postoperative assessment of MI in the light of surgical correction options and outcomes when undertaken. Other imaging modalities for refining the diagnosis, such as CTA and MRI, are also included. The section on the surgical management of CHD complicated by significant MI describes the various surgical techniques, their positive effects and drawbacks. The authors also discuss the possibility of interventional, percutaneous correction of mitral regurgitation.

The last sections of the literature review summarize the current level of knowledge of the topic and debatable aspects of the problem in Bulgarian and foreign literature. Special attention is paid to the modern methods of mathematical data processing and the advantages obtained in their application.

On the basis of the literature review, Dr. Panayotova draws conclusions about the increasing role of CHD and its complications in the modern world of increased life expectancy, respectively affecting more elderly people. The tendency of secondary MR to catch up and overtake

degenerative valvular heart disease should be considered in the long term in view of the social significance of this disease. Every patient with CHD, especially those surviving AMI, should be followed up clinically and by echocardiography for the likelihood of developing MI, which without appropriate treatment worsens life expectancy and quality of life. There is still a lack of definitive data on the optimal treatment of CHD complicated by MR- a more precise and detailed assessment is needed in which cases and to what extent MV repair can contribute to better postoperative outcomes.

The main goal formulated by the dissertation is: Using appropriate echocardiographic and clinical indicators to improve the quality and to digitalize the certainty in the individual choice of surgical treatment (combined CABG + MV repair or isolated CABG surgery), as well as the diagnosis of the medical status (relatively preserved or relatively impaired) of patients with CHD complicated by chronic MR, through the application of fuzzy sets. The aim is clearly defined and focuses on the possibilities for successful selection of an appropriate surgical treatment volume.

The 5 tasks set by the dissertator are specific and directly related to the stated aim. I would emphasize the ambition to apply modern mathematical methods to refine the allocation of patients to the appropriate treatment group, while updating the database existing at the Cardiac Surgery Clinic where she works, and to demonstrate the positive impact of MC plasty in the patients included in the study.

The clinical aspect of the thesis includes 169 patients with CHD complicated with chronic significant MI, operated in the Cardiac Surgery Clinic of the University Hospital "St. Marina" - Varna in the period 2007 - 2022. 6 inclusion criteria and 7 exclusion criteria were used. All patients underwent surgical revascularization (CABG), and in 85 of them, revascularization was combined with MV repair (MV repair + CABG). Having that basis, the patients were divided into two main groups - group A with combined surgery and group B with isolated CABG. The allocation was based on demographic, clinical and echocardiographic criteria. Echocardiographic parameters were described in detail and measured at three time periods: preoperatively, in the early postoperative period (5 to 30 days), and at a time point remote from surgery (follow-up 6 to 54 months). These studies are illustrated with echocardiographic images, coming from Dr Panayotova's own practise. Dividing the patients of the two main groups A and B into subgroups with similar general condition (A1 and B1, A2 and B2) allows comparison between patients with relatively preserved (A1 - B1), or relatively impaired (A2 - B2) general condition. This allows to

have more accurate assessment of postoperative outcomes. Analysing the 75-dimensional records for each patient using the sophisticated mathematical models of 'fuzzy sets', Dr Panayotova, with the help of her research consultant Prof. Natalia Nikolova, offers the possibility of a more precise assessment of the "degree of belonging" of each patient to the group in which he is included. The maximum degree of belonging is 1 - for patients who are most suitable for the respective group, and the minimum is 0 - for patients who are not suitable. With an affiliation rate below 0.5, the patient is considered borderline suitable/unsuitable and further criteria should be sought for the optimal treatment method. Examples with real or fictitious patients are given in appendix 1 of the thesis so that anyone interested can see how the 6-step basic allocation algorithm is applied in practice in the city. A and gr. B, the 6-step auxiliary allocation algorithm in subg. A1 and subg. A2 and the 7-step auxiliary allocation algorithm in subg. B1 and subg. B2.

In this section of the dissertation, a comparison, illustrated by tables, is made on the quality and reliability of the results achieved with the fuzzy stratification algorithms and Bayesian classifiers proposed in this dissertation, in which analogous data (15 discrete and 12 continuous discretized features) are introduced.

Results and discussion: Dr Daniela Panayotova fully illustrated and analyzed the results of her study. The section is structured in three chapters, each with additional subsections. The first part focuses on the creation of a complete system of examples for the application of the main and the two auxiliary fuzzy algorithms for the allocation of patients to the respective groups and subgroups, which also determines the volume of surgical intervention - combined (MV repair + CABG) or isolated (CABG) revascularization. The second part on way in which "fuzzy samples" are formed of patients characterized by degrees of belonging above 0.5 and below 0.5 in each group and subgroup. Patients with a degree of belonging below 0.5 have less similarity to the main characteristics of the groups and subgroups, respectively less weight in determining the main characteristics of the groups. In these patients, it is important to find the optimal type and extent of treatment, and this may include additional, more complex surgical methods. The third part is dedicated to the application of deductive statistical methods and the comparison of results using them.

The method of "pseudo-control groups" is introduced - when a real control group cannot be established for ethical and professional reasons. This method allows groups with relatively similar characteristics to be compared, which in this thesis are subgroups A1 and B1, or A2 and B2. In

this part of the dissertation, the effect of the combined operation (MV repair + CABG) is evaluated by applying the "fuzzy pseudo-control groups" method given in detail in Appendix 2. Using the integral parameters "regurgitation fraction" in % and "degree of mitral regurgitation" in an 8-point scale, the effect of the combined operation was evaluated in patients from each of the subgroups A1 (relatively preserved general condition) and A2 (relatively impaired condition).

Conclusions of the study:

The final section draws 4 conclusions that follow logically from the overall material and its exposition, the statistical analyses performed and the interpretation of the data.

- The algorithms applied in the thesis calculate only the maximum of four possible coefficients that predetermines the classification of a patient to a given subgroup;
- If the maximum of the degree of belonging μ is less than 0.5, the patient is considered an outlier and does not participate in the following calculations. Thus, subgroup characteristics can be more adequately estimated;
- Based on the different degrees of belonging, a different stratification of patients into groups and subgroups can be created, and hence a different treatment recommendation;
- For the purposes of the study, it was decided that four subgroups were an appropriate balance between the homogeneity achieved within the subgroups and the size of the resulting subgroup samples.

The findings confirm the scientific and practical value of the stated aim and objectives is achieved. They provide a guideline for improving the performance in determining the volume of surgical intervention in patients with CHD complicated by chronic significant ischemic mitral regurgitation.

Contributions:

1. A 6-step fuzzy algorithm (MA) was created for patients with CHD complicated with MR, which for an individual patient identifies the degrees of belonging to two inhomogeneous groups: A (MV repair + CABG) or B (isolated CABG).
2. Two conditional fuzzy algorithms were created to homogenize the stratification of each of groups A and B. If MA classified a patient into group A with complete certainty, the 6-step conditional fuzzy algorithm AAA computed the conditional degrees of membership of the patient into two homogeneous subgroups by medical status: A1 (relatively preserved) or A2 (relatively impaired). If the MA has classified a patient into group B with complete

certainty, then the 7-step conditional fuzzy algorithm AAA calculates the conditional degrees of membership of the patient to two homogeneous subgroups by medical status: B1 (relatively preserved) or B2 (relatively impaired).

3. The MA, AAA and AAB algorithms are organized in a diagnostic-stratification system that, for an individual patient with CHD complicated by MI, determines the patient's subgroup (A1, A2, B1 or B2) and his absolute degree of membership in that subgroup.
4. A complete system of 49 examples for all possible combinations of MA, AAA, and AAB algorithm outputs was created to illustrate in a medically understandable way the application of the fuzzy algorithms created. In practical terms, such a system facilitates and personalizes decision making about the approach to a complicated medical situation such as CHD complicated with chronic significant MI.
5. Using the fuzzy pseudo-control group method, the positive influence of anuloplasty on the integral parameters regurgitation fraction and mitral regurgitation rate was statistically demonstrated.

Contribution to the work in the institution where Dr. Panayotova works is the completion and expansion of the existing database of patients with CHD complicated with chronic significant MR in the Cardiosurgery clinic.

The abstract is structured according to the requirements. Its content corresponds to the thesis.

Conclusion - The dissertation work of Dr Daniela Panayotova is a comprehensive study on significant clinical material, which concerns important, relevant and not fully understood important questions about the volume of surgical treatment in patients with CHD complicated with chronic secondary mitral regurgitation. The proposed algorithms for stratification of patients into groups and subgroups according to their general and cardiac condition can formalize and facilitate decision making about the need for complex surgical intervention, and Appendix 1 can help in this process for a wider range of physicians. Indicators giving the extent to which a particular patient belongs to the relevant group and subgroup can serve as a starting point for future studies.

On the basis of everything stated so far, the relevance and importance of the problems studied, I believe that the dissertation of Dr. Panayotova fully meets the requirements for the award

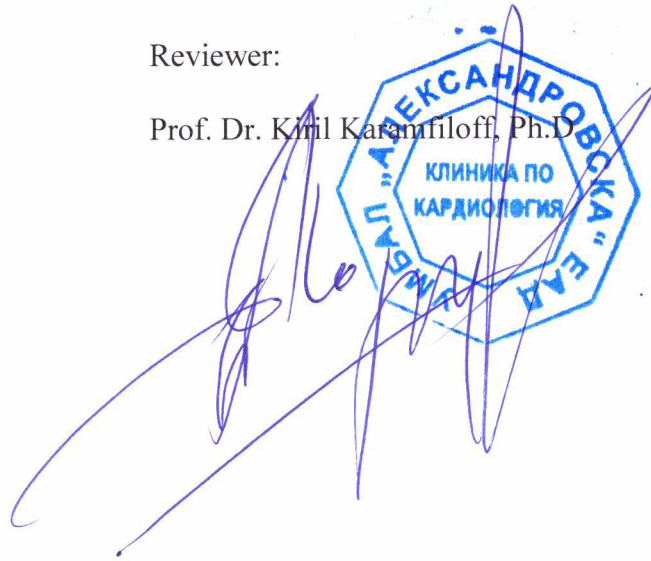
of the degree of Doctor of Education and Science. I give my **POSITIVE** evaluation and propose the Honourable Scientific Jury to vote positively for the award of the degree of Doctor of Education and Science to Dr. Daniela Stoyanova Panayotova in the scientific specialty "Cardiology".

23 September 2023.

Varna

Reviewer:

Prof. Dr. Kiril Karamfiloff, Ph.D



The image shows a handwritten signature in blue ink over a blue octagonal stamp. The stamp contains the text: "КЛИНИКА ПО КАРДИОЛОГИЯ" (Clinic for Cardiology) and "АЛЕКСАНДРОВСКА" (Alexandrovska). The signature is written in a cursive style and overlaps the stamp.