

**To the Chairman of the
Scientific Jury, appointed by
order of the Executive Director
of Acibadem City Clinic
UMHAT Tokuda EAD №640 /
26.11.2021**

R E V I E W

Prof. Dr. Dimitar Georgiev Petkov MD, DSc

**Head of the Clinic of Cardiac Surgery at the University Hospital "St. Ekaterina ",
member of the Scientific Jury for awarding the scientific and educational degree PhD-
" Doctor ", determined by an order of the Executive Director of Acibadem City Clinic
UMHAT Tokuda EAD №640 / 26.11.2021.**

Subject: PhD thesis of Dr. Ivilin Plamenov Todorov,

PhD student in free form of education at the Clinic of Cardiac Surgery, Acibadem City
Clinic UMHAT Tokuda EAD,

on the topic

"SURGICAL TREATMENT IN PATIENTS WITH PROSTHETIC VALVE ENDOCARDITIS"

Scientific adviser: Assoc. Prof. Dr. Dimitar Nikolov, Ph.D.

By order of the Scientific Council of Acibadem City Clinic UMHAT Tokuda Sofia I have been appointed external member of the scientific jury and reviewer of the dissertation of Dr. Ivilin Plamenov Todorov, presented under the procedure for obtaining the educational and scientific degree "Doctor" in the scientific specialty " Cardiovascular surgery.

I declare that I have no conflict of interest with the candidate.

Brief biographical data

Dr. Ivilin Plamenov Todorov graduated from high school in 2001 at the National High School of Natural Sciences and Mathematics "Acad. Lyubomir Chakalov "Sofia - specialty: Biology and Biotechnology. In the same year he was admitted to the Medical University - Sofia and graduated from medical school in 2007. As a student in 2002. starts working at the hospital "St. Ekaterina as a nurse in the Department of Anesthesiology, Intensive Care and Intensive Care, and later as a volunteer at the Clinic of Cardiac Surgery at the same hospital. In 2007 he started working as an intern at the newly opened cardiac surgery department at Tokuda Hospital in Sofia. In 2009 she won a competition and was enrolled in a specialization in cardiac surgery at the Medical University of Sofia. Acquired a degree in cardiac surgery in 2014. In 2019 he completed a master's degree in public health and health management.

From 2019 is an assistant professor of cardiac surgery at the Medical Faculty of Sofia University "St. Kliment Ohridski". Married, has three children. He has attended a number of courses and trainings abroad (Austria, Germany, Switzerland and Croatia).

Significance of the topic

The topic of the dissertation is contemporary and significant, affecting one of the most serious complications of valvular reparative and valvular replacement surgery - prosthetic valve endocarditis.

Controlling and dealing with infections of cardiac structures, and in particular heart valves, remains a major clinical challenge. The difficulties in management and treatment are even greater when the infection involves an artificial prosthetic valve, as in this case the risks of reoperative cardiac surgery are superimposed, which at times can be significant. Although many of the indications for surgical treatment are similar to those associated with native valve infections in reoperative surgery, it is often difficult to completely clear the infection due to the presence of contaminated prosthetic material. Antibiotic treatment alone is rarely effective, and communication between cardiac surgeons, cardiologists, and infectious disease physicians is often critical to a favorable treatment outcome.

Structure of the dissertation:

The dissertation of Dr. Todorov is designed on 132 pages according to the requirements and contains an introduction, literature review, research methodology with goals and objectives, materials and methods, analysis of results, discussion, conclusions and recommendations, bibliography. The dissertation material is illustrated with 9 photos, 15 figures, 5 diagrams and 38 tables. Contributions are presented only in the Abstract, where a list of publications and scientific communications on the topic is attached.

The introduction is on 1 page and clearly outlines the reasons for the research undertaken by the dissertation. The literature review of 38 pages presents in detail and comprehensively the main contemporary research in the field, which is the subject of the dissertation. Efforts to elucidate the main risk factors for prosthetic endocarditis have been followed. The achievements on which the diagnosis and modern treatment of this disease are based are clearly outlined. The advantages and disadvantages of the used surgical and therapeutic methods are shown, as well as the problems that still need to be solved. The analysis of the literature impresses with its depth, shows excellent awareness and competence in the interpretation of data by various authors. Based on the literature review, the dissertation defines the prerequisites for conducting the study.

The "**research methodology**" section covers 24 pages. It presents the purpose and objectives of the study, characterizes the clinical material and describes in detail the methods used.

The aim is to analyze the clinical characteristics and results of surgical treatment of patients with early and late prosthetic endocarditis with emphasis on nosocomial PVE, in order to determine the factors leading to a high risk of complications and nosocomial mortality. Dr. Ivilin Todorov sets himself the following tasks:

1: To analyze pre-, intra- and postoperative outcomes in patients operated on for early and late prosthetic endocarditis.

2: To prepare a profile of the profile of deceased patients operated on PVE and to determine the factors predicting a high risk of nosocomial complications and mortality.

3: To specify the degree of correlation between preoperative ultrasound and intraoperatively established data in the diagnosis of PVE and its complications.

4: To compare the data of patients with angiographic balloon LIMA-occlusion and those without occlusion in operations on PVE, and previous coronary surgery with passable LIMA-LAD graft, determining the degree of safety and benefits of the method.

5: To examine the data of patients with PVE with negative blood cultures and unidentified causative agent to determine whether this affects the outcome of treatment.

Methodological approach: The study included 79 consecutive patients (45 men and 34 women) hospitalized with a diagnosis of "Prosthetic valve endocarditis according to the criteria of the Duke Institute", who underwent reoperative intervention with valve reprosthesis of one or more valves. at the Clinic of Cardiac Surgery of Acibadem City Clinic UMHAT Tokuda Sofia. Patients are divided into two groups (with early and late prosthetic endocarditis) depending on the time elapsed since the previous operation and the onset of infection. Two subgroups of patients with and without the use of the LIMA angiographic balloon occlusion method, in patients with previous coronary surgery and a working LIMA-LAD graft, were created to investigate the benefits and safety of the method.

The clinical material is described in detail, with good illustration. The inclusion and exclusion criteria are clearly presented. The surgical methods are described in detail and give a clear idea of the work performed.

In the data processing a wide range of different modern and relevant to the specific study statistical methods was used. Carefully conducted statistical analysis allows to make the most accurate and clear conclusions. A large number of clinical indicators and parameters were monitored, which correspond to the design of the study and provide comprehensive information in the implementation of the tasks.

Results: The obtained results are presented on 28 pages of the dissertation, and are well illustrated and meet the objectives of the study.

Discussion of the results is presented systematically and analyzes the data obtained by comparing, where possible, with other publications on the topic.

Based on the obtained results and their analyzes, the proposed method for myocardial protection in patients with PVE and working LIMA-LAD graft is of interest as relatively easy to implement and with very good postoperative results.

The model predicting increased in-hospital mortality is also of clinical importance, based on intraoperative data and patient characteristics.

Conclusions: Dr. Ivilin Todorov offers 10 conclusions. They derive directly from the tasks set and the research conducted.

1. The main indications for urgent surgical treatment of PVE are evidence of rapidly progressive HF / cardiogenic shock and / or drug-induced sepsis. In patients with controlled infection are:

- Progressive HF, the result of hemodynamically significant prosthetic valve dysfunction;
- presence of vegetations > 10 mm;
- spread of infection with the formation of para-valvular abscess

2. Microbiological agent was isolated on average in 41.8% of cases, and the percentage of isolated microorganisms from blood cultures was without statistically significant difference between the two groups. The most common pathogen is *Enterococcus faecalis*, followed by the *Staphylococcus* group, accounting for 73.3% of all cases with a proven cause.

3. Demonstration of a microbiological agent and antibiotic treatment does not improve survival and shorten the period of hospitalization.

4. There is a high correlation between the preoperative TEE data and the findings established during the operative intervention, despite the presence of valve prostheses, which complicate the study. This makes TEE, the tool of choice in the diagnosis of PVE.

5. Biological and mechanical valve prostheses are equally affected, regardless of whether the prosthetic valve endocarditis is early or late.

6. With adequate diagnosis and timely surgical treatment - early prosthetic endocarditis is not a predictor of increased in-hospital mortality.

7. The main factors that predict increased in-hospital mortality are:

- surgery on 2 or 3 heart valves;
- postoperative development of refractory heart failure requiring implantation of an intra-aortic balloon pump;
- transient impairment of cerebral blood supply;
- renal replacement therapy in the early postoperative period;
- preoperative IV NYHA functional class;
- state of shock upon admission to the operating room;
- emergency surgical treatment;

8. The duration of ECC and the time of aortic clamping are important prognostic perioperative factors for increased in-hospital mortality.

9. The use of angiographic balloon LIMA occlusion is a reliable, easily applicable and relatively safe technique that improves surgical outcomes and prognosis in patients in need of reoperative cardiac surgery for PVE.

10. Prosthetic endocarditis is a challenge for the treatment team. A multidisciplinary team is needed, including cardiologists, cardiac surgeons, microbiologists, infectious disease specialists and anesthesiologists and resuscitators, to determine the most appropriate approach for patients with PVE to reduce perioperative and postoperative mortality.

The bibliography is arranged alphabetically and contains 208 cited titles, of which 11 are in Cyrillic and 197 in Latin.

The abstract is presented in Bulgarian and contains 80 pages and reflects what was written in the dissertation. It is durable as required.

Contributions: The contributions are reflected in the Abstract and are 12, divided into two groups - scientifically applied and original (7) and confirmatory (5) and are important for cardiac surgery in our country.

Contributions with scientifically applied and original character

1. A complete summary analysis of clinical, instrumental and morphological data in patients operated on early and late prosthetic endocarditis was performed.

2. Patients without an isolated causative agent were found to have similar treatment duration and survival in the study.

3. For the first time in a study conducted in Bulgaria in patients with PVE, factors for increased risk of complications and mortality during surgical treatment were specified.

4. The developed prognostic model determines preoperative risk factors with high predictive value for death in valve reoperation on the occasion of PVE:

- uncontrolled sepsis,
- state of shock,
- IV NYHA - functional class heart failure,
- need for two or three-valve prosthetics.

5. The established perioperative factors for increased risk, related to the surgical intervention itself - duration of ECC and aortic clamping are of original nature.

6. For the first time in Bulgaria in the surgical treatment of PVE and previous coronary surgery with a working LIMA-LAD graft, a method for angiographic balloon LIMA occlusion is proposed for optimal myocardial protection, as well as improving surgical results and patient survival.

7. For the first time in our country the causes are specified and the results of the surgical treatment of patients with early and late prosthetic valve endocarditis are analyzed.

Contributions of a confirmatory nature

1. The diagnostic possibilities of the most accessible instrumental methods - EchoCG (TTE and TEE) in the assessment of patients with PVE are specified.

2. The high diagnostic value of trans-oesophageal echocardiography for the detection and evaluation of vegetations, abscesses, and valvular dehiscences is confirmed.

3. The literature data on the demographic, clinical and laboratory characteristics of patients operated on PVE, as well as on the main indications for surgical treatment are confirmed:

- evidence of progressive HF, despite ongoing drug treatment, most often as a result of progression of valve dysfunction (or paraprosthetic regurgitation)
- the presence of large vegetations (> 10 mm)
- paravalvular spread of the infection

4. The literature confirms that the most common pathogens in patients with PVE are enterococci, staphylococci and streptococci, as well as a significant percentage of PVE with negative blood cultures.

5. The importance of the interdisciplinary approach, involving specialists from different fields - cardiologists, cardiac surgeons, microbiologists, infectious disease specialists and anesthesiologists, and resuscitators in making the most optimal therapeutic decision, and reducing the risk of peri- intra- and postoperative complications is confirmed. and death in patients with prosthetic valve endocarditis.

Publications: In connection with the dissertation Dr. Ivilin Todorov presents 2 publications in journals and participation in a scientific forum.

I believe that the present text is important for clinical practice in our country.

Conclusion: The presented dissertation is distinguished by its relevance and practical focus. The goal is clearly stated and reflects the good awareness of the author about the current knowledge and achievements in the field of the discussed problem. The tasks that the dissertation sets for its implementation are well thought out and suggest a thorough and critical approach in the development of each component of the study. It deserves high praise and their good illustration in relevant figures and tables. The discussion reflects a very good literary awareness and extensive clinical experience. Among the abundance of data, the dissertation manages to highlight the most important and based on them, after a thorough and critical analysis to be able to draw important conclusions for clinical practice. The conclusions and contributions highlighted at the end of the dissertation have a high theoretical and practical value. The dissertation meets the requirements and scientific criteria, which gives me reason to propose to

the esteemed Scientific Jury to vote positively for the award of the scientific degree PhD "Doctor" to Dr. Ivilin Plamenov Todorov.

04.01.2022

Prepared by:

Sofia

Prof. Dr. Dimitar Georgiev Petkov, MD, DSc