

**To the Chairman of the
Scientific Jury appointed by
order of the Executive Director
of NHH No 111/01.03.2023**

REVIEW

By prof. Vasil Jordanov Chervenkov, MD, PhD,
Head of Vascular surgery Department MHAT Acibadem City Clinic Tokuda, Sofia
Member of the scientific jury for awarding the scientific and educational degree "Philosophy
Doctor", determined by an order of the Executive Director of National Heart Hospital
№-111/01.03.2023

Regarding: dissertation work on the topic "Comparative analysis of treatment methods in chronic total occlusions of the superficial femoral artery" for awarding the educational and scientific degree "Doctor" to Dr. Boyka Ilieva Stoyanova, vascular surgeon at the Clinic for Vascular Surgery of the MHAT NHH , PhD student of independent training in the scientific specialty "Vascular Surgery", professional direction 7.1 Medicine, field of higher education 7 Health care and sports.

Scientific tutor - Prof. Mario Stankev, MD, PhD

The review was prepared according to the Law on the Development of the Academic Staff, the Regulations for the Application of the LAD and the Regulations for the Terms and Conditions for Acquiring Scientific Degrees and Holding Academic Positions at MHAT NHH EAD.

For the competition, Dr. Boyka Ilieva Stoyanova has presented all the necessary documents in accordance with the requirements of the regulation for acquisition educational and scientific degree "PhD" and rules of National Heart Hospital for its implementation. I find no gaps in the documentation presented. There is no evidence of plagiarism.
I declare that I have no conflict of interest with the candidate.

Importance of the topic

Peripheral arterial disease (PAD) is a socially significant disease that requires highly qualified medical assistance to perform procedures with great complexity and frequent use of expensive consumables and equipment. This results in high medico-economic costs in developed countries. The disease itself causes severe socio-psychological damage to the individual and is often associated with a high percentage of disability and mortality.

While questions about the etiopathogenesis of the disease are clearly defined, there is still no consensus on the type of treatment. Conservative therapy is of proven benefit to the patient, with a number of medications and programs being developed and routinely included in the treatment of patients with peripheral arterial disease. However, when the need for invasive treatment is reached, the choice is not so easy. For several decades in vascular-surgical practice, there has been a wide discussion about which method of treatment should be the first choice - operative or endovascular?

There are meta-analyses supporting both types of treatment, but the vascular community remains divided due to the lack of a large single-center study on the issue. Given all this, I define the topic of the dissertation work as very relevant not only for our country, but also in a global aspect. Although the ideal method of treatment does not yet exist, in her scientific work Dr. Stoyanova reflects in detail the three available methods (operative, endovascular, and now hybrid), compares them with each other and draws conclusions with great practical application.

Structure of the PhD thesis:

The dissertation work is structured in accordance with the standards for the preparation of scientific work for the acquisition of a scientific and educational degree "Doctor". It includes 233 pages, 111 tables and 55 figures. The bibliography consists of 276 sources - 5 in Cyrillic and 271 in Latin, and most of them are from the last 10 years. The scientific work has the following structure: title page (1 page), abbreviations used (2 pages), table of contents (1 page), introduction (1 page), literature review (46 pages), purpose and tasks (1 page), materials and methods (2 pages), results (57 pages), discussion (81 pages), conclusions and contributions (3 pages), conclusion (1 page) and bibliography (24 pages). The proportion between the individual parts of the dissertation are respected.

The abstract consists of 166 pages, prepared according to the requirements.

The literature review includes 46 pages with good structure, consistency of exposition and good knowledge of the topic. In addition to data on the etiopathogenesis of the disease and the global burden of atherosclerosis, the author also describes many facts about the available endovascular consumables, as well as studies related to it. Emphasis is also placed on the globally debated issue of the use of drug-coated devices. Accurately and objectively formulate the two opposing opinions on the treatment of patients with chronic total occlusions (CTO) of a. femoralis superficialis, AFS (operative vs. endovascular). Here, however, the dissertation adds a focus on hybrid surgery, which is increasingly entering practice. The complications of the three methods are described in detail. Unsolved questions are also raised - the focus of future studies.

The aim of the dissertation work is clearly and precisely formulated: "To carry out a comparative analysis of treatment methods for chronic total occlusions of a. femoralis superficialis".

In accordance with the formulated goal dr. Stoyanova identifies 6 specific **tasks**:

1. To determine the primary, primary assisted and secondary patency in each of the treatment methods, both in the whole group and in the subgroups of patients with diabetes and chronic limb threatening ischemia (CLTI)
2. To determine the influence of risk factors on patency in the three treatment methods
3. To determine the influence of previously performed reconstructions (upcoming, same and following segment) on the patency of the current reconstruction
4. To determine the influence of previous antiplatelet/anticoagulant therapy on the patency of the reconstruction
5. To determine the group of patients with multifocal atherosclerosis (MFA) among those with PAD
6. To build a treatment algorithm for patients with CTO of AFS

Research methodology

The dissertation presents the only single-center retrospective clinical study of its kind in Bulgaria at the moment, comparing the three types of treatment among the impressive number of 449 patients with chronic occlusions of a. femoralis superficialis, underwent treatment. A valuable aspect of the scientific work is the long follow-up period - 5 years. For clarity, patients were divided into three groups according to the type of treatment: operative treatment (151 patients), endovascular treatment (198 patients) and hybrid surgery (100 patients).

The statistical analysis was performed with the statistical package SPSS 20.0, using current statistical methods.

The treatment methods are meticulously described, step by step, with the author emphasizing the potentially possible details that could "defect" and lead to undesirable results in individual types of invasive treatment. I find this particularly useful in order to build a successful treatment technique for vascular specialists.

The results of the analysis are presented on 57 pages, divided into three subgroups according to the type of treatment performed - operative, endovascular and hybrid. The rich visualization of the results (a large number of figures and tables) and their detailed description is impressive.

The discussion covers 81 pages. The author compares the indications for the treatment of patients according to the time of the study (2012-2017) and those up to now, outlining the constant changes and the clearly imposed trend for "first endovascular treatment". At the same time, the indications for performing hybrid surgery (multisegmented involvement, comorbidity) are clearly and accurately stated. The dissertation develops in detail the topic of risk factors and their positive influence from drug treatment. The reconstructions of each of the treatment methods are discussed in detail and compared with each other, and the results are compared with a large database of worldwide and extremely recent meta-analyses and studies. Dr. Stoyanova makes a detailed comparative analysis of the three treatment methods in terms of the success rate of the reconstructions and the need for reinterventions. The complications that occurred and their possible causes are described objectively, and they are compared with the world results. A special emphasis is the discussion of the post-procedural drug therapy – various variants of the therapy prescribed at that time are described. Medications "required" for each treatment according to currently available guidelines are discussed. The types of patency of the reconstructions are precisely presented, and also among two particularly critical groups of patients – those with diabetes and CLTI, which I consider useful in a practical aspect. For the first time in Bulgaria, the question of the impact of the previous reconstructions on the patency is being addressed.

The conclusions are presented on the specific tasks:

Task 1: To determine the primary, primary assisted and secondary patency in each of the treatment methods, both in the whole group and in the subgroups of patients with diabetes and CLTI.

1. Endovascular and hybrid treatment are associated with better patency (primary, primary assisted and secondary) both in the overall group and in the subgroups of patients with diabetes and CLTI;

2. The greatest benefit from surgical treatment would be given to patients with a life expectancy of more than two years.

Task 2: To establish the influence of risk factors on patency in the three treatment methods

3. Among the known risk factors with the greatest severity were male sex and advanced age, female sex and young age, smoking, arterial hypertension, dyslipidemia. Diabetes mellitus and concomitant involvement of the other two vascular beds are reported as independent risk factors.

4. The administration of adequate antithrombosis and lipid-lowering therapy (statin) pre- and post-procedural leads to a significant reduction in cardiovascular risk and limb-related events (increase in claudication distance, reduction of patients reaching to CLTI as well as those requiring intervention, reduction of retrobolosis and frequency of reinterventions, reduction of amputations and mortality);

Task 3: To establish the influence of the previously performed reconstructions (overstanding, same and substanced segment) on the patency of the present reconstruction

5. In surgical treatment for AFS CTOs, only the previously performed reconstructions in the femoral segment are important, and in the hybrid – those in the superior aorto-iliac segment, and in both cases the patency is significantly better in the initial treatment.

6. In endovascular treatment for AFS CTO, the previously performed reconstructions in the aorto-iliac and femoral segments had no effect on patency.

Task 4: To establish the influence of prior antiplatelet/anticoagulant therapy on the patency of reconstruction

7. Prior antithrombotic therapy had no effect on patency in AFS surgical and endovascular treatment for CTO. In hybrid treatment, less patency was found with prior antiplatelet therapy.

Task 5: To determine the MFA patient group among those with PAD

8. In patients with AFS CTO, the concomitant MSD amounts to 45.2%, and it is most prevalent among those with hybrid treatment and mainly at the expense of asymptomatic carotid stenosis. Concomitant CHD is estimated at 20%, without significant difference in the different treatment groups. Simultaneous involvement of the three vascular pools was found in 11.14%.

9. Among patients receiving treatment for AFS CTO there was a lower incidence of CHD and simultaneous involvement of the three vascular pools compared to that of patients with carotid stenosis.

Last but not least, I consider the proposed algorithm for the treatment of patients with chronic total occlusions of a. femoralis superficialis, as well as that for endovascular treatment in a femoral segment for particularly useful in a practical aspect, as they shed new light on the subject, namely the division of patients according to the presence of previous reconstructions. Therefore, I consider the proposed algorithms to be new not only among the Bulgarian vascular-surgical society, but also in a global aspect.

The contributions are 9 in total, presented as follows:

Scientific-practical contributions:

1. This is the first time in Bulgaria that such a large one-center clinical study comparing endovascular, operative and hibirid treatment in patients with AFS CTO is conducted;
2. For the first time, an AFS treatment algorithm for patients with CTOs is proposed that emphasizes treatment options after previously conducted reconstructions in the same femoral segment;
3. The endo first strategy with the administration of drug-coated devices is recommended, and open surgery should be maintained as a treatment option after a single-vascular, hybrid and surgical one;
4. It is always recommended to administer autovenous (usually ipsilateral GSV) before synthetic graft in bypass surgery. In the absence of a sufficient one, other alternatives should be considered venous grafts (contralateral GSV, SSV, veins by hand). If possible, anastomoses are constructed T-L;
5. If it is not possible to perform autovenous bypass, semi-closed endarterectomy and synthetic bypass are an acceptable alternative;

Confirmatory contributions:

6. It was confirmed that the construction of T-L anastomoses in bypass surgery in the femoro-popliteal segment leads to better patency and preservation of the limb;
7. The superiority of drug coated balloons against ordinary ones in terms of patency in endovascular treatment of AFS CTOs was confirmed;
8. It was found that the presence and number of implants did not affect patency in hiberide treatment of AFS CTO;
9. It was confirmed that endovascular treatment of AFS CTOs was associated with the highest percentage of limb storage, but at the expense of an increased frequency of reinterventions.

Dr. Stoyanova is a vascular surgeon known to the community for his many participations in scientific forums. For the needs of the procedure, she presented 3 of her available **publications** and 5 **participations in scientific forums** on the subject.

General remarks and recommendations

To publish proposed treatment algorithms in international journals. To pay attention to the precision in writing the bibliography.

In conclusion, the dissertation work developed by Dr. Boyka Ilieva Stoyanova on the topic "Comparative analysis of treatment methods in chronic total occlusions of the superficial femoral artery" presents interesting and detailed scientific results and offers practically valuable innovations in the treatment of patients. I believe that the dissertation meets the requirements for awarding the educational and scientific degree "Doctor".

Based on the above mentioned merits of the PhD thesis of Dr. Boyka Stoyanova, I recommend to the members of the esteemed scientific jury to vote positively and to award to Dr. Boyka Ilieva Stoyanova the educational and scientific degree "Philosophy Doctor" in the scientific specialty "Vascular Surgery", professional field 7.1 Medicine, field of higher education 7 Health and sports.

10.05.2023

Prepared by:

(Prof. Vasil Chervenkov, MD, PhD)


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