To Chairman of Scientific Jury,
appointed by order of
Executive Director of the NCH
No. 70/19.02.2024.

REVIEW

By associate professor Nadelin Krasimirov Nikolov MD, PHD, Chief of vascular surgery theater - Department of Vascular Surgery, National Cardiology Hospital, Sofia

Regarding the dissertation thesis titled:

"Surgical Treatment Methods for Iliac Occlusive Disease - A Comparative Analysis"

Of Bistra Petrova Boneva

Due to conferment of the educational and scientific degree "Doctor", PhD Program in Vascular Surgery Department, National Cardiology Hospital , Sofia

Scientific Supervisor: Profesor Mario Stankev, MD, PHD

In accordance with the decision of the Scientific Jury, approved pursuant to Order No. 70 dated February 19, 2024, issued by the Executive Director of the Multi-profile Hospital for Active Treatment "National Cardiology Hospital" (NCH), Sofia, this document constitutes a review addressed to the members of the same jury.

Brief Biographical and Professional Achievements of the Doctoral Candidate:

Dr. Bistra Boneva completed her medical education in 2013, earning a Master's degree in Medicine with a professional qualification as a physician. In 2019, she successfully acquired a specialty in vascular surgery, followed by obtaining a Master's degree in Public Health and Health Management in 2020. During the same period, Dr. Boneva successfully completed a course in highly specialized activity, verified with a certificate of proficiency in the field of endovascular surgery. Since 2023, she has been enrolled in the doctoral program at the Department of Vascular Surgery at the National Cardiology Hospital (NCH).

Structure of the dissertation thesis

The dissertation is composed of 236 standard pages, enriched with visual elements, including 48 tables and 58 illustrative figures. The bibliographic section of the work presents an extensive review of the scientific literature, comprising 286 literary sources. Among these, 8 are publications in Cyrillic, while the remaining 278 are in Latin script, reflecting the international character and significance of the research topic.

Literature review

The literature review presents a comprehensive analysis characterized by careful structuring of the discussed topics and a highlighted relevance of the subject matter. It systematically presents current knowledge and identifies problems related to the epidemiology, clinical manifestations, diagnosis, and treatment of peripheral arterial disease (PAD). The review thoroughly examines various classifications and introduces both classic and newly accepted terms related to the clinical manifestations and diagnosis of the disease. Special attention is given to data on the natural course of PAD, as well as its association with other clinical manifestations of multifocal atherosclerosis (MFA). An important aspect of the review is the examination of contemporary approaches to the treatment of PAD and the management of risk factors in MFA. A significant portion of the material is dedicated to the analysis of revascularization decisions, treatment methods depending on the anatomical localization and clinical presentation of PAD, as well as comparative evaluations between different therapeutic strategies.

Objective and Tasks of the Dissertation Thesis

The objective of the scientific study is precisely defined - to develop a treatment algorithm for patients affected by iliofemoral occlusive disease. In determining the therapeutic approach, key aspects are considered: risk factors, the patient's accompanying comorbidity, the multifocal involvement of various vascular basins, and the history of previous reconstructive interventions in the affected iliac segment.

To successfully achieve the set goal, the following specific tasks have been established:

1. Analysis of the interaction between risk factors, the degree of progression, and the stage of the disease, and their impact on the involvement of adjacent vascular beds, as well as on the possibilities for surgical intervention and the long-term effectiveness of reconstructive procedures.

2. Evaluation of the technical success, efficiency, primary patency, and complications arising in patients following the three main types of vascular reconstructions.

3. Optimization of the preoperative analysis for patients with peripheral arterial disease to define the most suitable surgical revascularization strategy.

4. Identification of the alternative application of the three treatment methodologies and evaluation of their effectiveness in different clinical scenarios.

5. Comparison of the advantages of the hybrid approach versus traditional open surgical treatment in patients with complex vascular lesions, with a particular focus on short-term and long-term treatment outcomes.

Clinical Material and Methods

By elaborating on the clinical material and methods, this section establishes the scientific basis of the research, ensuring that the study is conducted with rigor and integrity, and that the findings are reliable and applicable to the broader context of vascular surgery.

The study was conducted within the Department of Vascular Surgery at the National Cardiology Hospital (NCH) over a ten-year period from January 2009 to December 2018. It represents a single-center, retrospective analysis of patients admitted and treated for iliac occlusive disease. The clinical material encompasses a total of 521 patients who underwent 580 interventions. Based on the treatment method in the aortoiliac segment, patients were categorized as follows: endovascular treatment (EVT) was applied in 182 cases (31.38%), hybrid surgical treatment (HST) in 183 cases (31.55%), and traditional open surgical treatment (OST) was performed in 215 cases (37.07%).

In the selection of patients for inclusion in the study, the Fontaine classification and the TASC II anatomical classification were applied. The assessment of the appropriateness of surgical intervention was based on a comprehensive vascular surgical analysis, which included reviewing the medical history and current clinical status of the patient, with emphasis on both the vascular issue and the overall health condition, as well as the presence of comorbid diseases. In her scientific work, Dr. Boneva thoroughly and extensively presents the methodology for performing the three types of surgical interventions that are the subject of this study. Patient monitoring post-procedure was conducted in accordance with a pre-established protocol, with registered complications being evaluated according to strict, unified criteria recognized in the field of vascular surgery. For the analysis of the collected clinical data, evaluation of the results, and conducting a comparative analysis, the doctoral candidate applied appropriate statistical methods.

For the processing of clinical data and the performance of comparative analysis, the doctoral candidate utilized the specialized statistical software package SPSS version 20.0 (Statistical Package for Social Sciences). Methods of descriptive statistics were included to present the main characteristics of the study group. The CHI-square test was used to analyze the relationships between categorical variables, as well as the Cramer's V coefficient to assess the strength of the association between them. Analysis of variance (ANOVA) was applied to compare the mean values of continuous variables across multiple groups. The Kaplan-Meier survival analysis was used to evaluate the patency of reconstructions over time, and the Log Rank test and Wilcoxon Signed Ranks Test were applied to compare the survival curves among the three revascularization methods. These statistical methods and analyses provide a scientifically grounded and accurate investigation of the obtained clinical results.

It is essential to emphasize that the clinical material included in Dr. Boneva's dissertation provides a current statistical base that describes the profile of the Bulgarian patient suffering from atherosclerosis in the first quarter of the 21st century. This represents a valuable contribution to the understanding of the distribution, characteristics, and therapeutic challenges in treating atherosclerosis in Bulgaria, reflecting the specifics of the national patient population in the context of contemporary medical and social conditions.

Results

The results obtained during the scientific study are presented with a high degree of accuracy and correctness in the dissertation thesis, and their structured organization significantly facilitates the process of comparative analysis. In the detailed statistical processing of the collected data, several correlations were identified that provoke interest in the scientific and medical communities and provide potential for optimizing therapeutic approaches in treating the pathology under consideration. Among the significant relationships discovered are those between the gender of the patients, the degree of arterial hypertension, smoking habits, preceding transient ischemic attacks (TIA), etc., and the choice of revascularization method for chronic total occlusions in the iliac arterial segment. The analysis reveals that patients in the second stage of chronic arterial insufficiency-PAD and those with chronic kidney disease (CKD) often undergo less invasive interventions, such as endovascular treatment (EVT), which underscores the need for an individualized approach to each clinical situation to optimize the treatment process.

The average statistical data regarding the duration of patency maintenance of vascular reconstructions across different types of interventions hold particular practical value. This information serves as a reliable guide for vascular surgeons regarding the expected outcomes of treatment procedures in the specific anatomical segment. Equally crucial are the conclusions drawn from the analysis of the collected data, indicating that undertaking any revascularization

procedures in the iliac segment carries a risk of losing patency in 50% of cases after a five-year period. These findings not only highlight the importance of careful selection of treatment approaches but also emphasize the need for ongoing monitoring and evaluation of the long-term efficacy of vascular interventions. This is essential for optimizing the treatment strategy and enhancing the quality of life of patients.

The recorded complications, including thrombosis and mortality, clearly favor the hybrid and endovascular treatment methods, an advantage that warrants particular attention. The analysis of the patency of reconstructions between patients with claudication symptoms and those with critical limb ischemia reveals better initial results in the first group, an advantage that, however, diminishes proportionally with the lengthening of the observation period. The comparative analysis among the three revascularization strategies in cases with clinical manifestation of intermittent claudication also highlights the superiority of hybrid surgical treatment (HST) and endovascular treatment (EVT) over open treatment in managing such lesions.

Statistical analyses of the impact of multifocal atherosclerosis, diabetes, and previous vascular reconstructions on the choice of treatment strategy and subsequent patency of interventions provide important scientific and practical insights.

In conclusion, the analyses of the collected data were conducted with meticulousness and rigor, providing comprehensive information regarding both the complexity of the clinical course of multifocal atherosclerosis and the myriad of factors that must be considered when formulating treatment approaches. These conclusions highlight the importance of the chosen therapeutic strategies and suggest the necessity of a personalized approach towards each individual patient, with the aim of optimizing treatment outcomes and improving quality of life.

Conclusions

These conclusions not only underscore the critical importance of tailoring treatment strategies to individual patient profiles but also highlight the ongoing need for research and development in the field of vascular surgery to address the challenges posed by iliofemoral occlusive disease. Within her doctoral dissertation, Dr. Boneva formulates a number of key conclusions based on the comprehensive clinical and scientific research she conducted. She identifies that:

1. Among the analyzed risk factors, the most significant impact on the choice of surgical strategy is exerted by male gender, active smoking, the presence of arterial hypertension, chronic kidney disease, and the involvement of the carotid artery basin by multifocal atherosclerosis (MFA). Additionally, higher values in the ASA classification, patient age, the presence of diabetes, and dyslipidemia, along with the involvement of other vascular basins (coronary and visceral), are

determined as independent risk factors influencing clinical decisions. An interesting aspect of the study is the absence of a statistically significant difference in the patency of vascular reconstructions among the three groups of patients based on these risk factors. This emphasizes the complexity of the interactions between various risk factors and their cumulative effect on the long-term outcomes of treating vascular diseases, indicating the need for a deeper understanding and an individualized approach when making therapeutic decisions.

2. The severity of peripheral arterial disease (PAD) and the characteristics of clinical presentation demonstrate a statistically significant, albeit weak, correlation with the choice of revascularization methods. Endovascular treatment (EVT) predominates in cases of intermittent claudication (IC), while patients with critical limb threatening ischemia (CLTI) often undergo more aggressive revascularization approaches. This observation underscores the importance of careful patient stratification based on their clinical condition and the degree of disease when making decisions for revascularization treatment.

The analysis shows that the stage of PAD and specifics of clinical presentation significantly impact the patency of vascular reconstructions. In cases of critical limb ischemia, patency is lost significantly faster, necessitating particular attention in treatment planning and the potential application of aggressive therapeutic strategies. These conclusions highlight the importance of early identification and adequate assessment of the stage of PAD and clinical presentation as critical factors in determining the most suitable revascularization approach and in increasing the chances of maintaining long-term patency of reconstructions.

3. Dr. Boneva's study reveals that the three treatment methods used - endovascular treatment (EVT), hybrid surgical treatment (HST), and open surgical treatment (OST) - show comparable results in terms of technical success, primary patency, and the frequency of limb salvage. This demonstrates their interchangeability as potential therapeutic alternatives within the context of these critical endpoints of the treatment process.

Furthermore, the data from the dissertation emphasize that the highest number of general and specific complications were recorded in cases treated with the open surgery method (OST), followed by those who underwent hybrid surgical treatment (HST). This finding is significant for clinical practice and should be considered when choosing an appropriate revascularization method, especially when evaluating the risk-benefit balance for the patient.

The equivalence in technical success and primary patency between different treatment methods underscores the importance of an individualized approach to each clinical situation, taking into account both the potential benefits and the risks associated with each therapeutic strategy. It is crucial to provide a comprehensive assessment of patients, including both the anatomical and physiological characteristics of the disease, as well as the overall health condition and comorbidity, to increase the chances of successful treatment and minimize complications.

4. The preoperative assessment requires a careful, personalized approach that takes into account the unique characteristics of each patient and the specific details of the clinical case. This approach is particularly important for high-risk patients, where endovascular treatment (EVT) and hybrid surgical treatment (HST) often represent safer and preferred alternatives due to their lower invasiveness and associated risk of complications.
The need to improve postoperative monitoring and evaluation systems for long-term treatment outcomes is emphasized. This includes regular monitoring for potential complications, assessment of functional recovery, and measurement of patient quality of life. Such practices are crucial for optimizing the treatment process and can significantly contribute to improving the health status and overall well-being of patients following revascularization interventions.
These guidelines highlight the importance of an integrated and comprehensive approach to the treatment of patients with vascular diseases, aiming to achieve optimal results through careful planning and execution of a treatment strategy tailored to the individual needs and risk profiles of patients.

5. Hybrid surgical treatment (HST) is distinguished by higher primary patency and a lower frequency of complications compared to open surgical treatment (OST), representing a significant advantage. However, a notable drawback is the higher likelihood of needing subsequent reinterventions to maintain the patency of the vascular reconstructions. This fact underscores the need for careful selection of patients for whom this method is applied, especially considering the long-term results and the quality of life of the recipients of this treatment.
In the context of treating high-risk patients, HST is positioned as the preferred revascularization strategy. This is due to its ability to effectively combine endovascular and surgical techniques within the same operative access, allowing simultaneous intervention on multiple arterial segments responsible for limb blood supply. This revascularization strategy offers significant advantages in managing complex vascular lesions, optimizing therapeutic effectiveness, and potentially reducing recovery time and long-term complications.
Thus, HST represents an innovative and flexible approach in vascular surgery that can offer substantial benefits for certain patient groups, especially those at increased risk of operative complications. Its application requires an in-depth assessment of the patient profile and adequate planning to maximize benefits and reduce potential risks.

Contributions

The doctoral dissertation offers significant contributions to the field of vascular medicine in Bulgaria, based on the extensive clinical material and detailed analyses conducted within the study. The distinguished contributions include:
- Conducting the first of its kind in Bulgaria, an extensive single-center clinical study that compares the efficacy and safety of endovascular treatment (EVT), hybrid surgical treatment (HST), and traditional open surgery in treating occlusive disease in the iliac segment. This study

represents an important step towards expanding knowledge and improving therapeutic practices in the country.

- The study provides a basis for a reasoned and scientifically supported recommendation for the application of EVT as a primary strategy for lesions that do not affect the common femoral artery (CFA), or the choice of HST in cases of extensive disease involving the infrainguinal arterial segment - CFA. In this context, traditional open surgery is recommended as an alternative after attempts at endovascular or hybrid revascularization, offering strategic guidance for optimizing therapeutic approaches in vascular surgery.

These findings not only contribute to the scientific community and clinical practice in Bulgaria but also serve as a foundation for developing more effective and personalized treatment strategies for patients with occlusive diseases in the iliac segment. The presented results and recommendations can significantly influence future clinical decisions and improve the quality of life for patients suffering from this complex pathology.

Dr. Boneva's research provides a solid foundation for formulating strategic recommendations in the field of vascular surgery, based on compelling scientific and statistical evidence. The key contributions and recommendations derived from the study include:

1. Recommendation for the primary application of EVT: The study recommends endovascular treatment (EVT) as the primary approach for lesions not affecting the common femoral artery (CFA), and hybrid surgical treatment (HST) for cases with extensive disease involvement including the CFA. Open surgery is identified as a suitable alternative following attempts at endovascular or hybrid revascularization.
2. Application of OST in certain patient groups: The systematic scientific analysis emphasizes that open surgery (OST) is appropriate for patients with an expected long life span and minimal burden of comorbid diseases and risk factors, thereby optimizing long-term patency and quality of life.
3. HST as a strategy for high-risk patients: The study establishes hybrid surgical treatment (HST) as the most suitable revascularization strategy for high-risk patients with extensive disease spread, thanks to its ability to minimize complications and improve clinical outcomes.
4. Development of a treatment algorithm: For the first time, a treatment algorithm for patients with occlusions in the iliac segment is presented, focusing specifically on optimizing the therapeutic approach following previous reconstructions in the same arterial segment, thereby providing a leading guide for clinical practice.

These contributions significantly enrich the scientific literature and practical application in the field of vascular surgery, providing valuable guidelines for the treatment of patients with occlusive disease in the iliac segment and contributing to the improvement of treatment outcomes and the quality of life of affected patients.

Publications Related to the Dissertation Work

In accordance with the academic standards and criteria for successful completion of the doctoral degree, the doctoral candidate has demonstrated a significant contribution to the scientific community through the presentation of four full-text publications, one of which is in English and the remaining three are in Bulgarian. This multilingual approach ensures broad access and dissemination of the research results both nationally and internationally.

Additionally, the doctoral candidate presented a scientific statement at an international forum, highlighting the significance and relevance of the conducted research, as well as the researcher's commitment to discussion and knowledge exchange within the global scientific community. This statement serves as a platform for presenting the main conclusions and recommendations emanating from the doctoral work and provides an opportunity for receiving feedback and suggestions for future research directions.

The publications and scientific statement represent an important aspect of the doctoral dissertation, emphasizing the candidate's contribution to scientific knowledge in the field of vascular surgery and providing a foundation for further research and practical application of the obtained results.

Conclusion:

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From the analysis of the doctoral work presented by Dr. Bistra Petrova Boneva, it is clear that she has demonstrated sufficient scientific knowledge, professional skills, and significant experience in the field of vascular surgery. Particularly noteworthy are her skills in statistical processing and analysis of clinical data, as well as her ability to interpret the results in the context of vascular diseases. Such skills are crucial for progress in medical sciences and form the basis for the development of effective therapeutic strategies.

Based on the presented facts and evidence of the scientific and professional contribution of the dissertation, it is entirely appropriate to give a positive assessment of Dr. Boneva's work. She not only meets the high standards and requirements for the awarding of the doctoral degree but also offers a significant contribution to the field of vascular surgery.

Therefore, I propose to the esteemed members of the Scientific Jury to support the candidacy of Dr. Bistra Petrova Boneva for the awarding of the doctoral degree in the specialty "Vascular Surgery," in recognition of her high scientific contribution and professional achievements in medicine.

Review Prepared by:

March 20, 2024

(Assoc. Prof. Dr. Nadelin Nikolov, MD)