

Review

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Concerning a dissertation - work for the educational and scientific degree of 'Doctor'

Doctoral Program in Angiology within the field of higher education 7, Healthcare and Sports, professional specialization 7.1, Medicine.

Author: Polya Todorova Antova, m.d.

Doctoral program format: Independent study

Scientific unit: Angiology dpt.

Theme: Peripheral Arterial Disease of the lower extremities in women – risk factors, clinical presentation and disease outcome "

Academic supervisor: Prof. Milena Staneva, MD, PHD

1. General presentation of the procedure and the doctoral candidate

The review is prepared in accordance with the Law on the Development of Academic Staff (LDAS), the Regulations for the Implementation of LDAS (RILDAS), and the Regulations on the Conditions and Procedure for Obtaining Academic Degrees and Holding Academic Positions (RCPADHAP) at "Acibadem City Clinic Tokuda University Hospital" JSC. The submitted set of materials and documents by Dr. Polya Todorova Antova is in compliance with the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria and its implementing regulations, as well as with the rules of "Acibadem City Clinic Tokuda University Hospital" JSC regarding the procedure for obtaining the academic degree of "Doctor."

The dissertation has been discussed and proposed for defense by the extended Scientific Board of the Angiology Clinic at Acibadem City Clinic Tokuda University Hospital. During a meeting of the Scientific Council of "Acibadem City Clinic Tokuda" JSC, with the Executive Director and the Attorney of the hospital, I have been appointed as an external member of the Scientific Committee in connection with the dissertation of Dr. Polya Antova. I have been tasked with presenting the review.

No plagiarism has been identified in the provided report

Polya Antova MD, was born in 1986. In 2011, she completed her medical degree at the Medical University of Sofia. In 2012, she began her professional career as a resident in angiology at the Cardiology and Angiology Clinic, followed by the Vascular Surgery and Angiology Clinic at Tokuda Hospital Sofia. Since 2017,

she has been working as an angiology specialist at the Angiology Clinic at "Acibadem City Clinic Tokuda" JSC. In June 2016, after successfully passing the state exam, she was appointed the title "specialist" in "Angiology" from the Medical University of Sofia, and she also holds a certificate in Vascular Ultrasound Diagnostics (VSD) from the Medical University of Sofia.

She participates annually in national and international scientific forums with presentations.

She is a member of the Bulgarian Society of Angiology, the Bulgarian Association of Medical Ultrasound, the Bulgarian Association of Neurosonology and Cerebral Hemodynamics.

She has been a member of the Scientific Council of "Acibadem City Clinic Tokuda" JSC from September 2021 to June 2023.

2. The Relevance of the Topic

The doctoral dissertation is based on her own practical experience and addresses an exceptionally relevant clinical issue - Peripheral Arterial Disease of the lower extremities in women, which is the third most common cardiovascular disease (CVD) after Ischemic heart disease (IHD) and Cerebrovascular Disease (CVD). This condition results in severe disabling consequences that deteriorates the quality of life for the patients.

Despite the prevalence of Peripheral Arterial Disease (PAD) in the population, its clinical manifestation in women is often asymptomatic and atypical, which delays its diagnosis. According to numerous clinical studies and scientific medical publications, there is a growing trend towards gender-specific risk factors and exposures which necessitates their targeted investigation, interpretation, and the potential for active prevention and monitoring. The doctoral candidate is well aware of the problem and creatively assesses the literature. The provided data motivates Antova's MD choice of topic.

3. Characterization and Assessment of the Doctoral Dissertation and Contributions

Dr. Antova's doctoral dissertation is a 146-page document, complemented by 22 figures and 48 tables. It is well-structured and comprises the following sections: Abbreviations and Symbols Used - 2 pages; Introduction - 2 pages; Literature Review - 26 pages; Aim and Objectives - 1 page; Materials and Methods - 7 pages; Original Findings - 62 pages; Discussion and Conclusion - 23 pages; Conclusions and Recommendations - 3 pages; Bibliography - 18 pages. The bibliography includes references to 218 sources, with 5 in Cyrillic and 213 in Latin script

The introduction effectively formulates the problem and provides a well-founded rationale for the purpose of the doctoral dissertation.

The literature review is exceptionally well-structured, following a logical progression that aligns with the diagnostic and therapeutic algorithm. It comprehensively explores the pivotal role of risk factors accompanying the manifestations of Peripheral Arterial Disease (PAD) in the studied population. These factors are of paramount importance in the differential diagnostic approach and play a key role in determining the subsequent therapeutic strategy and for preventing the necessity for re-interventions.

The review culminates with a conclusive summary, which serves as the foundation for the study.

The objective of the doctoral dissertation is clearly and precisely formulated in alignment with the dissertation's theme: to define the risk profile, characteristics in the course, and the outcome of Peripheral Arterial Disease (PAD) in the lower extremities in patients, with a specific focus on the influence of gender and the development of a personalized diagnostic, treatment and monitoring algorithm for female patients.

To fulfill the objective, the following tasks have been formulated:

1. To determine and compare the demographic and social characteristics of Peripheral Arterial Disease (PAD) in both genders to identify the risk group based on gender.
2. To ascertain and compare the gender-related dependencies regarding the frequency of risk factors and co-existing conditions in PAD patients.
3. To define and compare the gender-related dependencies on the clinical stage of the disease at its initial diagnosis and the extent of involvement in the arterial system of the lower extremities.
4. To track patients of both genders over the course of one year and assess their condition following treatment.
5. To monitor disease outcomes and determine the frequency of subsequent vascular interventions in both genders.
6. Based on the obtained results, to determine the significance of gender as a risk factor for PAD.
7. To develop and validate an algorithm for the prevention, diagnosis, and monitoring of PAD in female patients, with a focus on recommendations for secondary prevention.

The studied **material** is sufficient in volume to address the specified objectives and tasks. The study includes 200 PAD patients, all above 18 years of age: 100 women and 100 men, with ages ranging from 38 to 92 years and an average age of 68 years ± 10 . These patients were sequentially examined by an angiology specialist.

The research for the period 2018-2020 is based on an electronic database and is retrospective, while data collection for patient follow-up during the period 2020-2022 is conducted prospectively. The methodology provides detailed descriptions of risk factors, examination methods, administered treatments, and patient follow-up in the context of PAD. The study compares the course and characteristics of the disease between men and women.

The use of the statistical methods in the study is a guarantee of the credibility and applicability of the cited results. The utilization of a rich array of specialized statistical methods for data analysis demonstrates a high level of professionalism.

The results and discussion: The doctoral dissertation excels in clarity, precision, and specificity. The results are analyzed in detail and align with the research objectives and tasks.

Conclusions and Contributions: Dr. Antova logically draws eight conclusions, regarding the profile of women with Peripheral Arterial Disease (PAD), which correspond to the research objectives.

1. Regarding the demographic and social characteristics of women with PAD, with statistical significance, we found that:

- Women with PAD are older than men with PAD, with a $p=0.05$, where over half of the women (52%) are above the age of 70, while only 38% of men fall into this category. In both genders, the highest relative proportion of patients is in the age group >70 years.
- Women with PAD are more often widowed - 32%, compared to only 4% of men, with a $p= 0.001$.
- Women with PAD less frequently reside in rural areas - 12%, in contrast to 21% of men, with a $p=0.03$.

2. Regarding the frequency of risk factors and accompanying conditions in women with PAD, statistically significant differences between the two genders are identified in relation to:

- Women with PAD less frequently have a medical history of the disease, as observed in 52% of women compared to 72% of men, with a $p= 0.009$.
- Women with PAD are less likely to be smokers, with 33% of women being smokers compared to 66% of men, with a $p= 0.001$.
- Women with PAD more frequently have accompanying arthropathy, with 19% of women having this condition compared to 7% of men, with a $p= 0.019$.

- Women with PAD more frequently have accompanying neuropathy, with 55% of women having this condition compared to 40% of men, with a $p= 0.047$.

- Women with PAD more frequently to have some extent of carotid atherosclerosis, with 63% of women having this condition compared to 40% of men, with a p -value of 0.001.

3. Regarding the medications taken:

- Women with PAD less frequently take anticoagulant therapy, with 37%, compared to 52% of men, with a $p= 0.046$.

- Women with PAD more frequently take analgesics, with 33%, compared to 5% of men, with a $p= 0.001$.

4. Regarding the clinical stage of the disease at its initial diagnosis, the following data with statistical significance are observed:

- Women with PAD are more frequently in the advanced stages of the disease at the time of its initial diagnosis, with 48% of women being in stages III and IV of PAD, compared to 27% of men, with a $p= 0.002$.

- Women with PAD are more frequently found to have an Ankle-Brachial Index (ABI) of less than 0.3, with 23% of women compared to 12% of men, with a $p= 0.024$.

- Women with PAD are more frequently without prior vascular interventions, with 53% compared to 34% of men, with a $p= 0.016$.

5. In terms of the extent of involvement in the arterial system of the lower extremities, the following gender-related significant differences have been identified:

- Women with PAD more frequently have multiple arterial lesions, with 73% of women compared to 58% of men with hemodynamically significant involvement in more than one artery, with a $p= 0.037$.

- Women with PAD more frequently have vascular thrombosis, with 78% of women compared to 50% of men, with a $p= 0.001$.

6. In women with PAD, the involvement of the popliteal artery and distal arteries is more frequent:

- In women with PAD, stenosis of the popliteal artery $>70\%$ is more frequently found, with 15% of women compared to 3% of men, with a $p= 0.007$.

- Thrombosis of the posterior tibial artery is more common in women with PAD - 34% of women compared to 14% of men, with a $p= 0.006$.

- Women with PAD are more frequently found to have thrombosis of the peroneal artery - 18% of women compared to 7% of men, with a $p= 0.018$.

7. Regarding subsequent treatment, it is observed that:

- Women with PAD less frequently undergo surgical treatment, with 26% of women, compared to 42% of men, with a $p= 0.025$.

- Women with PAD less frequently undergo hybrid treatment, with 8% of women compared to 22% of men, with a $p= 0.009$.

8. In the data related to the follow-up of patients after treatment has been initiated or conducted, the following statistically significant differences

between the two genders have been identified:

- Women with PAD are less frequently followed up at the 6th-month after therapy, with 40% of women compared to 57% of men that had an examination within that time frame.
- Women with PAD are less frequently followed up at the 12-month after the diagnosis of the disease and the initiation of therapy, with 36% of women compared to 69% of men, with $p= 0.023$ and 0.001 .
- Women with PAD more frequently do not return for follow-up examinations, with 47% of women compared to 30% of men, with a $p= 0.020$.

Based on the findings, recommendations for the prevention, diagnosis, and treatment of women with PAD have been developed. The contributions of the dissertation include 6 original contributions, 01 of which is theoretical, and the remaining 5 have a distinctly scientific and applied character. I highly appreciate Dr. Antova's development in several areas:

Contributions with a scientific-theoretical character:

1. The scientific research deeply evaluates the impact of risk factors in the studied patients with PAD. With these qualities, the work is the first of its kind in terms of its nature and volume in Bulgaria.

Contributions with a scientific-applied character:

1. The developed algorithm for managing women with PAD, based on the material and findings from the study, is characterized by high practical value.
2. Particularly noteworthy are the unresolved issues, which serve as the main motivation for continuing clinical research and developing ways to improve post-discharge patient care.
3. Due to the significant number of patients who do not attend follow-up appointments, it is advisable to consider an innovative strategy for actively surveying women who have undergone endovascular/surgical therapy and encouraging them through telephone reminders to actively participate in regular follow-up examinations, to ensure post-procedural prevention and monitoring.
4. Based on the accumulated data and experience, an algorithm has been developed and tested, which could serve as a basis for building a national program for the active rehabilitation of patients with PAD following treatment. It also includes proposals for maintaining strict control over risk factors to improve the quality of life.
5. The study group is substantial in size and could serve for clinical observation and publication in an international journal.

4. The abstract complies with legal requirements. It is written in 69 pages and adequately reflects the results presented in the dissertation. In a concise and clear manner, it provides an overview of the overall structure of the work, the methods used, the results, and the main conclusions.

5. Assessment of Publications and the Personal Contribution of the Candidate

Dr. Antova has published 2 articles in national journals and presenting 2 scientific reports at national scientific forums. One of these publications has been published in a journal with an IF. In 1 publication, she is the first author, and she has authored 1 publication as the sole author and 2 scientific reports. This level of scientific activity demonstrates that the doctoral candidate is consistent in her scientific work and exceeds the national minimum requirements for the educational and scientific degree of "Doctor."

I believe that the research topic explored by the doctoral candidate is among the important questions in modern vascular medicine. It represents a profound and systematic evaluation of risk factors and the diagnosis, treatment, and monitoring of the studied patients. Peripheral arterial disease (PAD) remains a significant issue in healthcare worldwide and in Bulgaria. It continues to be underestimated and even more so among women. The primary challenge in treating peripheral arterial disease (PAD) in women is their delayed seeking of medical attention, as well as the higher prevalence of asymptomatic disease. In most cases, this leads to more advanced disease at the time of the initial examination and an increased risk of adverse events and mortality.

The recommendations provided, based on the research findings and conclusions, hold high practical value. They could serve as a foundation for the development of a national program for the prevention of PAD in women, as well as the creation of a rehabilitation program after treatment, with a focus on maintaining strict control of risk factors. Such initiatives have the potential to enhance the quality of life for these patients.

CONCLUSION

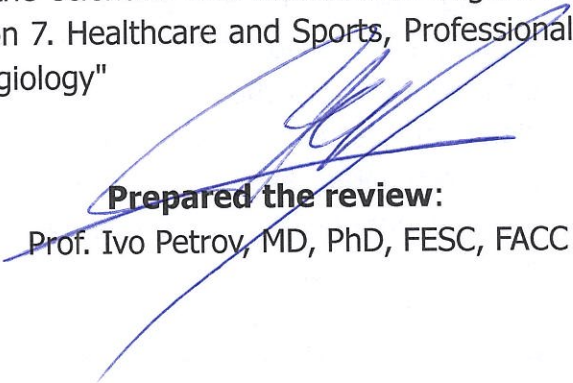
The doctoral thesis encompasses both scientific-theoretical and scientific-applied findings, which constitute an original contribution to the field, significantly expanding our knowledge in the domain of multifocal atherosclerosis and angiology. The document is composed in a rigorous scientific style. It complies with all the requirements outlined in the Law for the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for the Implementation of LDASRB, and the Regulations of Acibadem City Clinic Tokuda University Hospital EAD. Dr. Antova has successfully completed all the tasks and

activities outlined in her individual study plan. She has also passed the comprehensive examination for doctoral candidates in her field of specialization and in research methodology. The materials presented and the results of the dissertation fully comply with the specific requirements established in accordance with the regulations of "Acibadem City Clinic Tokuda University Hospital" EAD for the implementation of the Law on the Development of the Academic Staff in the Republic of Bulgaria.

Dr. Polya Todorova Antova is a specialist in angiology with 11 years of work experience. The doctoral candidate demonstrates qualities and skills for independent scientific research.

Based on the information provided, I give my positive assessment and confidently recommend to the members of the Scientific Jury to evaluate positively the dissertation work "Peripheral Arterial Disease of the Lower Extremities in Women - Risk Profile, Clinical Presentation, Disease Outcome" and to award to Dr. Polya Todorova Antova the scientific and educational degree of "DOCTOR" in the field of Higher Education 7. Healthcare and Sports, Professional Field 7.1. Medicine, Doctoral Program "Angiology"

31.10.2023 г.
Sofia


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