



**ULBS**

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DOCTORAL SCHOOL: MEDICINE

DOCTORAL THESIS - SUMMARY

***PERIPHERAL ARTERIAL PATHOLOGY OF THE  
LOWER LIMBS - DYNAMIC CHANGE OF THE  
COMPLEX MANAGEMENT STRATEGY***

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**Phd thesis contains 149 pages, has an iconography made up of 33 figures and 52 tables.**

**The thesis is divided into 3 parts – current state of knowledge, special contributions and bibliography (includes a total of 222 references).**

**KEYWORDS – peripheral arterial disease, coronary heart disease, risk factors, interventional and medical treatment, cilostazol.**

## **CURRENT STATE OF KNOWLEDGE**

### **INTRODUCTION**

Peripheral arterial disease of the lower limbs is a pathology that refers to acute or chronic obstruction of the arteries in the lower limbs. There are several causes of this obstruction, for example, embolism, thrombosis, vasculitis, diseases that generally affect the arteries, although the most common is atherosclerotic.<sup>1</sup>

Atherosclerotic damage to the arteries of the lower limbs is correlated with an increased risk of developing major cardiovascular events, by the deposition of atheroma plaques in the coronary and cerebral arteries.<sup>2</sup> These patients may present for various pathologies, so the damage to the arteries by atherosclerosis should be sought in more detail, even if there are no obvious symptoms.

### **EPIDEMIOLOGY**

At the time of the current study, it is not possible to discuss an incidence or a prevalence of the pathology at a global level, everything depending on the population studied or the study method used.

It is estimated that the prevalence of chronic obliterative arteriopathy is directly related to age. This can also be seen due to most studies, which use the ankle-brachial index measurement as a method. The prevalence of the pathology in people under 40 years of age is 6% and 15-20% in the population over 65 years old.<sup>3,4</sup> In most studies, the condition generally occurs more frequently in males. Approximately 50% of affected individuals are at the time of asymptomatic examination.<sup>5</sup>

### **PHSIOPATHOLOGY**

Atherosclerosis is a pathology characterized by damage to the walls of blood vessels and is the formation of atheromas in the intima of the medium and large arteries. It is the leading cause of morbidity and mortality in most Western European countries and the United States. An increase in prevalence has been observed in developing countries. In terms of incidence, it is directly proportional to the lifespan of people in developed countries.<sup>6,7</sup>

The process of atherogenesis is initiated by the retention and deposition of lipoproteins mainly in the extracellular space of the intima. These lipoproteins are subject to oxidative changes and give rise to products of aldehyde degradation of fatty acids and phospholipids, but also hydroperoxides. These changes cause chronic inflammation, so a complex, set of

inflammatory cytokines and various cellular components are involved in the onset and progression of atherosclerosis.<sup>6-11</sup>

In the evolution of atheroma plaques there is also a vascular remodeling by reactive changes in the vascular wall. Initially, the plate tends to grow outwards, so that the diameter of the lumen becomes larger, being an expansive remodeling. A decrease in lumen can only be observed when the atherosclerotic plaque exceeds about 40% of the delimited area. In contrast, atheroma plaque may also be responsible for lumen blockage, but this phenomenon occurs in the late evolution of plaque.<sup>6-11</sup>

## **RISK FACTORS**

The etiology of chronic arteriopathy is atherosclerotic in general, therefore the risk factors are directly related to it: smoking, hypertension, hypercholesterolemia, diabetes. We also mention the biological markers of inflammation, which appeared more recently in the investigation of peripheral vascular pathology: C-reactive protein, fibrinogen and hyperhomocysteinemia.

### **1. Smoking**

An article on the association of cigarette smoke with peripheral arterial disease has been published since 1995, which does not seem to be influenced by other mechanisms.<sup>12</sup> Becker and colleagues published an article demonstrating the association of smoking in the occurrence of cardiovascular disease.<sup>13</sup>

### **2. Dyslipidemia**

Dyslipidemia, as a risk factor, has been studied in several articles. It is estimated that high levels of LDL (low density cholesterol) cholesterol and low values of HDL (high density cholesterol) cholesterol, but also hypercholesterolemia associate the patient with a high risk of developing peripheral arterial disease.<sup>14</sup>

### **3. Diabetes mellitus**

Diabetes is one of the factors that causes an increased risk of peripheral arterial disease. In the same article published by Joosten et al., diabetes is closely associated with chronic peripheral artery artery disease, closely related to the duration of the onset of diabetes.<sup>15</sup>

In 2001, Jude concluded that patients with peripheral arterial disease, associated with diabetes, benefit from amputation of a limb due to complications 5 times more common and with a much higher mortality. <sup>16</sup>

#### 4. High blood pressure

We define hypertension in the doctor's office as values higher than 140 mmHg in the value of systolic blood pressure and values higher than 90 mmHg for the diastolic one. <sup>17</sup> In several studies, high blood pressure is the second risk factor for peripheral arterial disease, along with smoking.

#### 5. Other risk factors

It is known that in the pathophysiology of atherosclerosis there is also inflammation, so there may be correlations between inflammatory markers and peripheral arterial disease.

a. fibrinogen and C-reactive protein (CRP)

b. homocysteine

c. Chronic kidney disease

Several studies have shown the association of creatinine values, and implicitly chronic kidney disease, with peripheral arterial disease, especially in patients with stage V CKD. <sup>18,19</sup>

d. Genetic factors

The exact role of genetic inheritance in peripheral arterial disease has not yet been elucidated. Camelli and colleagues conducted a study on identical twins and showed that 48% of the variability of the ankle-brachial index could be explained by genetic effects.<sup>20</sup> Similarly, in the Framingham study, the relationship between family history of arterial disease was demonstrated. peripheral, with prediction especially on the occurrence of intermittent claudication. <sup>21</sup>

## **HISTORY**

A correct and detailed anamnesis is very important in diagnosing peripheral arterial pathology. Along with the personal pathological history, the evaluation of risk factors (hypertension, diabetes, dyslipidemia, active or passive smoking status, etc.), comorbidities, and the symptoms for which it occurs. Physical activity, lifestyle, certain eating habits must also be evaluated. <sup>22</sup>

Among the reasons for hospitalization, the most important become the pain in the lower limbs and the walking distance at which they occur. Intermittent claudication is a term used for pain, paresthesia, fatigue or discomfort in the lower limbs, which occur when walking, at different distances, or at rest, single or bilateral. The term "claudication" derives from the latin "claudicare", which means "to limp". Leg pain is usually due to femoral or popliteal artery stenosis, as the gastrocnemius muscle is the largest consumer of oxygen while walking, and thus the most common symptoms of peripheral arterial disease appear. Claudication is usually located in the immediate vicinity of the stenosis. Also, as claudication in the ankle or foot, occurs in the occlusion of the tibial or peroneal artery.

A subjective staging, depending on the walking distance until the appearance of claudication, are those of Leriche Fontaine or Rutherford.

### **OBJECTIVE CLINICAL EXAMINATION**

A complex cardiovascular examination includes an inspection of the lower limbs, whether there are trophic disorders, with continuity or not, skin color; if there is hair. Signs of atherosclerosis, such as muscle atrophy, may also be seen on inspection.

Clinical examination also includes palpation of the pulses in the lower and upper limbs, along with palpation of the abdomen, femoral artery, popliteal, pedicular, tibial. If the patient is diabetic, the absence of sensitivity is observed, the thermal and painful ability is decreasing, along with the decrease of osteotendion reflexes.

Blood pressure is measured in both arms, and an asymmetry greater than 15 mmHg is associated with an increased risk of vascular disease and also death.<sup>23</sup>

### **LABORATORY TESTS**

The most common laboratory tests are used to identify certain risk factors for peripheral arterial disease and, in particular, for atherosclerosis:

- CBC;
- lipid profile (total cholesterol, HDL and LDL cholesterol, triglycerides);
- glycemia and glycated hemoglobin;
- tests to investigate kidney function (urea, creatinine, ionogram, uric acid);
- examination of urine (summary of urine for proteinuria and microalbuminuria).

As additional tests:

- lipoprotein (a) if there is a family risk of developing premature heart disease;

- glucose tolerance test.

## **DIAGNOSTIC METHODS**

### **1. Ankle-brachial index**

Ankle-brachial index (ABI) is a non-invasive, inexpensive and fast way to diagnose and follow up on patients with peripheral arterial disease. It can be used in certain ethnic groups of patients who do not have risk factors for an assessment of the risk of developing cardiovascular pathology.<sup>24</sup> ABI has a normal value between 0.9-1.4. A value below 0.9 indicates peripheral arterial disease.

Oscillometry is an investigation that has been used less and less lately.

### **2. Ultrasound examination by Duplex ultrasonography**

Ultrasound examination of patients with suspected peripheral arterial disease can be done in different forms (mode B, pulsed Doppler mode or continuous Doppler, color and power Doppler), using different ultrasound probes. In this way it is possible to visualize with a much greater accuracy, the existing lesion at the level of the blood vessel, the collateral circulation can be evaluated, as well as the presence of stenoses and their impact in distality; has a good reproducibility on stenoses greater than 50% detected in the lower limbs.<sup>25-26</sup> Ultrasound examination is done both for diagnosis and follow-up of patients and for screening. Patients are followed pre and postoperatively (after an interventional revascularization therapy or even bypass).<sup>27</sup>

### **3. Angiography using computer tomography**

Angiography of the lower limbs, which is performed using the contrast agent, injected into a peripheral vein and then visualizing the entire arterial pathway assessed using multidetector computed tomography, involves certain disadvantages due to the still high costs and low availability of computed tomographs.

Among the advantages of using this investigation we mention the non-invasive and fast acquisition of images, the possibility of reconstructing the arterial tree in 3D model.

Among the disadvantages of using this investigation, we mention the use of iodinated contrast agent (important for those with contraindications to its use) and radiation exposure.

### **4. Exercise test**

The exercise test can usually be performed on the treadmill. To highlight the occurrence of pain in the lower limbs or walking distance, there are several protocols, but Strandness is preferred, with an inclined plane of 10%. This is a fast, cheap and effective method to assess the etiology of lower limb pain, due to the occurrence of both peripheral arterial disease and degenerative bone lesions in the elderly.

#### 5. Angiography using magnetic resonance imaging

It is another imaging investigation, less used in the examination of the patient with peripheral arterial pathology; it is performed both natively and with contrast medium.

#### 6. Digital subtraction angiography

Contrast-enhanced angiography is one of the imaging standards for peripheral arterial disease assessment. It is an invasive method, with a risk of complications. It is performed by injecting iodinated contrast agent into the artery punctured by the Seldinger method. This investigation is usually performed to better highlight the arterial shaft on the affected limbs, although it is usually performed on patients who will receive interventional or surgical treatment.

### **TREATMENT**

The treatment approach of patients with peripheral arterial disease includes the specific location of symptoms and the risk of major cardiovascular events.

The drug classes that are part of the specific therapy for arterial disease are diverse, such as lipid-lowering, antihypertensive, antiplatelet. In fact, the treatment of peripheral arterial disease includes reducing cardiovascular mortality and morbidity, but also improving patients' quality of life by reducing symptoms, ie improving pain in the leg while walking, eliminating back pain and reducing the risk of acute ischemia.

In addition to the drug treatment, we must mention the non-pharmacological one, with general measures such as daily physical activity, smoking cessation, but also hyposodium diet and healthy eating. All these have the role of reducing the risk of cardiovascular events, such as stroke, acute myocardial infarction, the need for amputation of the lower limbs, but also the exitus.

For a better example of treatment, we try to divide it into several categories, methods to reduce the prevalence of peripheral arterial pathology.



1. Non-pharmacological methods
  - Physical activity
  - Quitting smoking
  - Hygienic-dietary measures
  
2. Pharmacological therapy
  - Lipid-lowering drugs
  - Antithrombotic therapy: single or dual, associated or not with oral anticoagulants, both
  - Therapy of risk factors: hypertension, diabetes, obesity
  - vasodilators
  - New therapies / other medications administered - Stem cell therapy
  
3. Surgical / interventional treatment

Along with the medicinal and non-pharmacological treatment, the surgical or interventional treatment must also be mentioned. The choice of these types of treatment depends on the location of the lesions and the degree of damage, as well as the length of the stenoses. Newer solutions, such as pharmacologically active balloons or stents designed for different locations, should also be considered for this therapy.

## **CONCLUSIONS**

Peripheral arterial disease of the lower limbs is a pathology caused mainly by atherosclerosis and causes with various presentations in the medical service. The appearance of symptoms, such as pain in the lower limbs and their different intensity from one patient to another, as well as the degree of damage highlights our therapeutic behavior.

The identification of risk factors, such as smoking, hypertension, obesity by promoting sedentary lifestyle, dyslipidemia and performing appropriate investigations, determines drug and / or surgical therapy. Patients may also present for other conditions, so it is necessary to perform a minimal test, ankle-arm index or palpation of the pulse in the arteries of the lower limbs. In a study published in 2001, which included approximately 500 patients with lower limb arterial disease (PAD), a third of them could not walk more than 480 m in plan, as they were classified as "hidden " PAD.<sup>28</sup>

Over the past decade, two editions of the European Society of Cardiology's guide to the diagnosis and treatment of peripheral arterial disease have been developed.<sup>29</sup> Significant

changes came in the therapy of this pathology, preferring venous bypass for lesions under the popliteal artery, to the detriment of endovascular treatment, while for higher lesions from the iliac artery and abdominal aorta, endovascular treatment remained the first intention only. In experienced centers and surgical treatment is preferred, as indicated in guide IIa. Also in the current guide, clopidogrel is preferred for drug therapy compared to aspirin.<sup>30</sup>

## **PERSONAL CONTRIBUTION**

### **INTRODUCTION**

Atherosclerotic disease remains one of the most common causes of peripheral arterial disease (PAD) and therefore the primary therapeutic target.<sup>31</sup> Identification of PAD can be made clinically, by history or physical examination, or based on subclinical identification of peripheral atherosclerotic disease by modalities. noninvasive. PAD is defined by the partial or complete obstruction of one or more peripheral arteries. In asymptomatic individuals, for example, the presence of arterial murmurs has been linked to coronary heart disease.<sup>32</sup> In patients with any manifestation of peripheral arterial disease, clinical and paraclinical evaluation is also required to detect possible sites of atherosclerosis, especially for atherosclerosis. ischemic heart disease. There are situations in which the detection of lesions at other sites of arterial disease can also change subsequent therapy.

Coronary heart disease (CHD) remains the leading cause of morbidity and mortality in the US, 42% of patients with CHD also have peripheral arterial disease.<sup>33,34</sup>

Patients with peripheral arterial disease are at risk of developing cardiovascular events, as well as critical lower limb ischemia and also influencing quality of life.<sup>4,35</sup> These patients have frequently associated ischemic heart disease and cerebrovascular disease.<sup>36</sup>

The evaluation of patients with the ankle-arm index will show that those with values below the allowed limit had a history of acute myocardial infarction, stroke or congestive heart failure.<sup>37</sup>

### **FIRST STUDY– substudyA**

Risk factors in peripheral arterial disease, influencing hospitalization and treatment adherence.

## **WORKING HYPOTHESIS**

This paper aims to achieve the following objectives:

1. Highlighting the associated risk factors and their relationship with peripheral arterial disease
2. The impact of risk factors on the length of hospitalization
3. Adherence of patients to drug treatment in relation to the stage of arterial disease, by the classification Leriche – Fontaine

## **MATERIAL AND METHOD**

For the current research, 126 hospitalized patients were studied between 01.01.2016 - 31.12.2018, in the Cardiology Clinic of the Sibiu County Emergency Clinical Hospital for pain in the lower limbs, interpreted as manifestations of peripheral arterial disease (without the need for emergency surgical or interventional treatment), and not associated with other pathologies that required therapy that interferes with current arterial pathology, and then investigated in the Center for Invasive and Noninvasive Research in Cardiac and Vascular Pathology in Adults.

All of these patients selected for inclusion in the current study were:

- Agreement for the inclusion in the database of the hospital, without the appearance of personal data;
- Ankle-brachial index;
- Doppler cardiac ultrasound;
- Detailed anamnesis on risk factors and treatment;
- Coronarography according to the guidelines of the European Society of Cardiology (the 60 patients);

Patients were excluded from the study:

- Those who had the ankle-arm index with normal values;
- Patients suffering from other diseases, which required other types of emergency surgery, those with heart decompensation;
- Patients allergic to contrast agent or iodinated preparations;
- Those in whom the differential diagnosis for leg pain, highlighted other pathologies.

Data collection - prospective analysis of all patients, clinical observation sheets from the documentation of the following characteristics was used:

- documentation of risk factors for the mentioned pathology: smoker, diabetes, chronic ischemic heart disease or hypertension;
- laboratory tests, those relevant for the identification of risk factors, high levels of total cholesterol and LDL-cholesterol, or low HDL-cholesterol, values of C-reactive protein or fibrinogen;
- evaluation of drug treatment administered at home, during hospitalization and discharge from our clinic;
- detailed documentation of coronary angiography and significant lesions.

## **STUDY METHODOLOGY**

The blood pressure in the upper and lower limbs was determined using a sphygmomanometer, with the patient lying on his back. After obtaining the maximum values of the two blood pressure, the calculation method was used:

$$\text{ABI} = \text{maximum lower limb tension} / \text{maximum upper limb tension}$$

Also, the ultrasound examination of the arteries of the lower limbs, laboratory tests to detect the values of total cholesterol, HDL-cholesterol and LDL cholesterol were performed.

For the statistical analysis of the data from the current study, the Microsoft Excel programs from Microsoft Office Professional Account 2016 and SPSS 22 were used.

## **DISCUSSIONS**

Identification of symptomatic PAD was associated with a 70% increased risk of cardiovascular events and an 80% increased risk of death compared with patients without PAD.<sup>38</sup> In patients with, compared to those without acute coronary syndromes, a history of stroke or ischemic attack. Transient PAD is associated with worse outcomes and more extensive CHD.<sup>39</sup> Hospitalizations with PAD, as a potential marker of severity, have been linked to poorer outcomes.<sup>38</sup>

The basis of the relationship of PAD with CHD and cardiovascular events can be defined by clinical overlap, with established atherosclerotic risk factors that predict the development of both PAD and CHD. These include male gender, age, diabetes, smoking, hypertension, hyperlipidemia and chronic kidney disease, among others.<sup>40</sup>

Moreover, patients with PAD are known to have abnormal peripheral vasodilation and paradoxical vasoconstriction in response to increased metabolic needs during stress. This

failure of arterial vasodilation can lead to increased systemic overload, which in turn affects cardiac output and oxygen release.<sup>41</sup>

Until then, the latest PAD guidelines focus on changing the aggressive risk factor, including initiating antiplatelet therapy, lipid lowering treatment, and optimizing glycemic control and blood pressure in patients with PAD, with the highest level of recommendation for symptomatic patients.<sup>42-44</sup>

ABI, Doppler sonography and other non-invasive techniques are recommended for the diagnosis of PAD in patients with a history of atherosclerosis. In addition, lifestyle changes in patients with PAD and pharmacotherapy should be considered.<sup>45</sup>

## **CONCLUSIONS**

1. The predominance of the male gender, in proportion of 74.6%.
2. The origin from the urban environment in proportion of 56.35%, without significant differences with the rural environment.
3. The age evaluated in our group was 71.42% between 60 and 80 years, which positions this pathology in the pathologies of the elderly.
4. Smokers are represented by only 26.20% of patients, those with hypertension of 68%, those with ischemic heart disease 79%, while those with diabetes only 32%, which does not include these pathologies as favoring peripheral arterial disease, highlighted in our group.
5. The average length of hospitalization was 9 days.
6. Smoking patients have fewer days of hospitalization, but no statistical significance, with  $p = 0.221$ .
7. Neither dyslipidemic or hypertensive patients are those who influence the length of hospitalization, without statistical significance, with  $p = 0.724$ , respectively  $0.769$ .
8. Diabetes was associated with a shorter hospital stay, and was at the limit of statistical significance, with  $p = 0.078$ .
9. Chronic kidney disease was associated with a longer hospital stay and statistical significance, with  $p = 0.006$ .
10. Patients with more advanced stages of peripheral arterial disease have greater adherence to drug treatment with statins and beta-blockers, which cannot be said about cilostazol.

## **FIRST STUDY – substudy B**

Risk factors in peripheral arterial disease associated with ischemic heart disease (coronary heart disease)

### **WORKING HYPOTHESIS**

This paper aims to achieve the following objectives:

1. Relationship between peripheral arterial disease and coronary lesions (diagnosed exclusively by angiocoronarography)
2. The impact of risk factors on coronary lesions highlighted in patients with peripheral arterial disease.

### **MATERIAL AND METHOD**

For the current research, 60 of the 126 patients hospitalized between 01.01.2016-31.12.2018, in the Cardiology Clinic of the Sibiu County Emergency Clinical Hospital, were studied. Of these 126, only 60 were eligible for coronary angiography, according to the guidelines of the European Society of Cardiology.

The mode of inclusion and exclusion from the study coincides with subplot A.

For the data collection, the prospective analysis of all patients, of the clinical observation sheets from the documentation of certain characteristics, mentioned above was used.

### **STUDY METHODOLOGY**

As previously mentioned, for the current study, patients benefited from several investigations: measuring blood pressure in both upper and lower limbs, determination of the ankle-brachial index, ultrasound examination and coronary examination.

The present paper aims to observe the predominance of risk factors for peripheral and coronary artery disease. For this research, the 60 patients who were selected for coronary angiography were studied, out of the 126, who presented for pain in the lower limbs and in whom the ankle-brachial index had values below the allowed limits (ABI <0.9), as well as those who did not require emergency surgical treatment (eg acute ischemia). It should be noted

that heart decompensated patients, those without indication for coronary angiography, but also those who refused this investigation were eliminated from the study.

Patients were investigated angiocoronarographically and statistical correlations were made to see if there was any link between the stage of peripheral arterial disease and coronary artery lesions. For a significant correlation, the patients were divided into two groups, those with claudication at > 200 m or <200 m, and the coronary lesions in the lesion of the left coronary artery trunk, anterior descending artery, right coronary artery or circumflex artery.

Microsoft Excel programs from Microsoft Office Professional Account 2016 and SPSS 22 were used for statistical processing of the data from the current study.

## **DISCUSSIONS**

In the data available at the time of the study, it is estimated that approximately 30% of patients with PAD also have a history of ischemic heart disease (IHD) and approximately 70% have univascular coronary heart disease on angiocoronarography.<sup>46-47</sup>

In the CONFRIM registry, the prevalence of obstructive IHD in patients with PAD was 25%, with an annual mortality of 1.6% compared to 0.7% in patients who did not have severe IHD.<sup>48</sup> In the REACH registry, patients who had both PAD and IHD were 57%.<sup>49</sup>

The risk of cardiovascular death increases from 2.5 to 6 in patients with peripheral arterial disease, and the mortality rate increases from 4.3 to 4.9%.<sup>50</sup>

However, it was noted that patients with PAD and IHD concomitantly are more likely to be prescribed antiplatelet therapy, beta-blockers, ACE inhibitors and statins compared to patients with IHD alone. However, medical therapy alone does not alleviate the excess risk associated with PAD.<sup>38</sup>

Peripheral arterial disease in association with coronary heart disease may be asymptomatic, as walking distance is limited by the occurrence of angina pectoris or even dyspnea (phenomena of left ventricular failure).

Reviewing the data from the medical literature, in correlation with the current study, we must keep in mind that arterial disease can have multiple locations, which has been highlighted. If the arterial disease has multiple locations, it is also associated with a more reserved prognosis, and studies done for the need for screening in several vascular territories, for these has not shown any benefit.<sup>29</sup>

## CONCLUSIONS

1. The average age of patients is 68.98 years, a fairly advanced age.
2. Predominance of males, in proportion of 78.3%.
3. Among the risk factors evaluated, smoking is associated with 46.7% of patients, diabetes in 36.7%, dyslipidemia in 38.2%, and hypertension in 73.3% of them.
4. The stage of peripheral arterial disease, by the classification Leriche - Fontaine has no statistical correlation with coronary lesions.
5. Patients with a single coronary lesion, compared to those with more than one, in stage IIb Leriche - Fontaine presented multicoronary lesions. At this evaluation, the correlation was found at the limit of statistical significance, with  $p = 0.056$ .
6. The evaluation of the walking distance and the impact on the coronary lesions at the level of the anterior descending artery showed that 90% of the lesions are found in those who cover a distance of less than 200m without claudication.
7. Smokers have multicoronary lesions and advanced stages of peripheral disease, but no impact on statistical significance.
8. The correlation between the presence of diabetes and PAD stage showed several coronary lesions, with statistical significance,  $p = 0.008$ .
9. The patient with smoking and hypertension has an important correlation for the lesions highlighted in the anterior descending artery, as aggravating factors, with  $p = 0.048$ .
10. Antiplatelet or anticoagulant therapy could not be properly evaluated due to the small number of patients included in the study.
11. Advanced stages of peripheral arterial disease have a 1.85 times higher risk of having tricoronary lesions.

## SECOND STUDY

Comparative study between invasive and noninvasive investigations performed in patients with peripheral arterial pathology of the lower limbs

### INTRODUCTION

Peripheral arterial disease is a partial or complete occlusion of one or more arteries leading to a suppression of blood flow and ischemia. Numerous processes are described in the stenosis process, among which the most common is atherosclerosis. Peripheral arterial disease



is a major economic health problem and it is estimated that over 200 million people worldwide are affected by this disease, of which at least 20% have some degree of claudication.<sup>51</sup>

Patients with peripheral arterial disease have a high risk of adverse cardiovascular events, including cardiovascular death, stroke, and myocardial infarction, as well as significant limb adverse events, including severe limb ischemia and amputation.<sup>30</sup>

## **WORKING HYPOTHESIS**

Patients with peripheral arterial disease usually consult specialized medical services late, so they require thorough investigations. In addition to noninvasive investigations, such as the ankle-brachial index, peripheral arterial ultrasound and contrast-enhanced angiography, they also require invasive investigations such as peripheral arteriography with digital subtraction.

This paper aims to achieve the following objectives:

1. The association of known risk factors for atherosclerosis and, in particular, for peripheral arterial disease of the lower limbs.
2. Correlations between classical drug therapy and interventional therapy for different risk factors.
3. Interventional therapy versus drug therapy on the studied group.
4. Associations between invasive and noninvasive investigations at different levels of examination: aorta and iliac arteries, femoral arteries, popliteal arteries and the region below the knee.

## **MATERIAL AND METHOD**

For the current research, 51 patients evaluated for the diagnosis of peripheral arterial disease of the lower limbs, evaluated by invasive methods during 2017-2018, were studied.

All of these patients selected for inclusion in the current study were:

- Agreement for the inclusion in the database of the hospital, without the appearance of personal data;
- Ankle - brachial index - which had values lower than 0.9 (the patient presents asymptomatic or symptomatic pathology with trophic lesions);<sup>2,29</sup>

- Arterial ultrasound of the lower limbs, which shows atherosclerotic lesions, with different degrees of damage. Ultrasound was performed by experienced cardiologists, although there were interobserver differences.

The following were excluded from the study:

- patients with painful complaints in the lower limbs, but in whom the arm ankle index had values higher than 0.9;
- patients who have received surgical treatment by amputation of the affected lower limb;
- patients who were in stage IV Leriche-Fontaine.

For the data collection, the prospective analysis of all patients, of the clinical observation sheets was used.

## **STUDY METHODOLOGY**

Blood pressure in the upper and lower limbs was determined using a sphygmomanometer, with the patient lying on his back. The maximum value of systolic blood pressure at the level of the brachial artery and at the level of the posterior tibial artery was noted, using a portable miniDoppler.

$ABI = \text{maximum tension in the lower limb} / \text{maximum tension in the upper limb}$

Arterial ultrasound examination of the lower limbs to detect atherosclerotic damage of varying degrees, from minimal atheroma deposits to severe stenosis in the arteries. All patients who were included in the current study also benefited from performing angio CT on the lower limbs, arteriographic examination and laboratory tests.

For the statistical processing of the data from the current study, the Microsoft Excel programs from Microsoft Office Professional Account 2016 and SPSS 20 were used.

## **DISCUSSIONS**

Peripheral arterial disease of the lower limbs is a pathology with slow progression, which is mainly addressed to patients towards the end of the second and third age. Therefore, they address both emergency medical services and family doctors.

The current study included stable patients, known to have intermittent claudication that occurred both while walking and at rest, who presented to the cardiology department on a scheduled basis for detailed investigations of peripheral arterial pathology.

The current research aimed at evaluating the risk factors, modifiable or not, as well as the association with ischemic heart disease, the therapeutic attitude for them, being necessary only drug or interventional treatment.

The need for drug or interventional therapy in these patients was assessed by two known parameters, age and BMI, which were shown to increase predictability by more than 50% (58.8%), age being a positive indicator for interventional treatment, while an increased BMI opts for drug treatment (without statistical significance due to the small number of cases). The existing data in the literature do not document the choice of type of treatment depending on the patient's age.

Due to the need for invasive investigations for these patients, they were evaluated with CT angiography or digital subtraction angiography, at different levels of examination, observing a positive correlation with different degrees of intensity, depending on the location of the stenosis, being also statistically significant. , with  $p = 0.0001$  and  $\rho = 0.514$ . According to these data, patients with PAD can benefit from either investigation.

## CONCLUSIONS

1. Peripheral arterial disease is more common in elderly patients, with a mean age of 65.09 years.
2. It is more common in males, with an incidence of 76.47%.
3. The best known risk factors for peripheral arterial disease of the lower limbs are: hypertension in the proportion of 76%, hypercholesterolemia 41%, smokers 37.25% and diabetes 22%.
4. Cilostazol reduced the need for intervention therapy, with statistical significance, by  $p = 0.029$ .
5. Statin administration did not influence the need for interventional therapy.
6. No statistical correlation was observed between the origin of the patient, the risk factors or the sex of the patient and the therapeutic behavior (medicinal or interventional).
7. Any invasive investigation for the diagnosis of PAD may be chosen if it is performed for the terminal abdominal aorta or the ili-femoral arteries, with a statistically important correlation, with  $p = 0.0001$ , while on the tibio-peroneal arteries subtraction angiography is preferred. digital, being more faithful and therapy can be performed in the same session.

8. It has been observed that patients with a higher PAD receive drug treatment (without statistical significance).

## **DISCUSSIONS / LIMITATIONS OF THE STUDY**

Atherosclerotic pathology is a complex one, with multiple locations and with an important impact on the body, but also on the health system with multiple hospitalizations, and possible acute complications.

Peripheral arterial disease affects the patient's quality of life, remaining a problem of investigation, because only 10-15% of them consult a doctor for symptoms, and only 25% receive appropriate treatment.<sup>29</sup>

The investigation of the patient is a detailed one, with his history, screening for comorbidities, risk factors and even the presence of disabilities. The anamnesis also includes the associated symptoms, such as dyspnea and NYHA class, the classification of angina pectoris according to the Canadian classification, the appearance of intermittent claudication for patients with peripheral arterial disease. Along with the consumption of toxins, the patient's adherence to the current medication must be evaluated.<sup>52</sup>

Objective examination of the patient with atherosclerotic disease, especially that of peripheral arterial disease should include general status, signs of heart failure, rhythmic / arrhythmic heart sounds, the presence of cardiac or carotid murmurs, pulse at the peripheral arteries, neurological signs present, but also blood pressure monitoring.

The current study was performed in the Cardiology Clinic of the Sibiu County Emergency Clinical Hospital and it is observed that a relatively small number of patients were included in the study, because it is not a regional hospital and not specifically for investigating arteriopathic patients. The study could have been performed as a screening of patients with peripheral arterial pathology, although previous studies have shown no benefit, but only consumed financial resources.

It also required a complex team to investigate these patients, starting with the clinical cardiologist, then the interventionist, radiologist and laboratory physician (to perform biochemical analyzes), which demonstrates that the cardiovascular pathology is a complex one, in which requires a holistic approach.

Therefore, an attempt is made to outline what is necessary to perform in front of a patient with this pathology:

1. The anamnesis corresponding to the highlighting of the risk factors, the walking distance at which the intermittent claudication of the lower limbs occurs,
  - the appearance of dyspnea and angina;
  - adherence to treatment;
  - healthy lifestyle;
  - monitoring body weight, blood pressure or pulse.
2. Objective clinical examination on devices and systems - attention should be paid to the blowing of the large arteries (aorta, carotid arteries, femoral arteries, renal arteries, etc.), along with the presence of bilateral symmetrical pulse in the posterior tibial arteries and pedical ;
  - general status;
  - signs and symptoms of heart failure;
  - blood pressure;
  - sequelae of neurological suffering.
3. Paraclinical investigations
  - Laboratory tests - evaluate renal function, liver function, glycemia with glycosylated hemoglobin, lipidogram (cholesterol, HDL - cholesterol, LDL-cholesterol, triglycerides), BNP;
  - electrocardiogram in 12 leads and if necessary, and extended with straight or posterior leads, to highlight the rhythm and repolarization changes;
  - transthoracic echocardiography in M, 2D mode but also Doppler - to evaluate the systolic and diastolic function of the left ventricle, but also of valvulopathies;
  - arterial ultrasound of the lower limbs;
  - evaluation of physical activity;
  - assessment of fragility (in the elderly);
  - angioCT of lower limbs;
  - contrast angiography.
4. Treatment
5. Patient education - doctor-patient communication has a very strong impact at this stage. He must understand as well as possible this pathology, its implications and possible

complications. Therefore, lifestyle changes, increased walking distance, and adherence to treatment play the most important role.

Peripheral arterial disease has been studied in recent years, with the development of two guidelines of the European Society of Cardiology, one in 2011 and the next in 2017. Changes between the two guidelines on the disease side of the lower limbs is that bypass is preferred with a large saphenous vein for lesions in the infra-popliteal region (recommendation class I), and for aorto-iliac lesions, surgical treatment for aorto-iliac or aorto-bi-femoral occlusions (recommendation class IIa) is preferred compared to 2011 in which primary endovascular treatment is preferred.<sup>29</sup>

As newly introduced recommendations, we mention statins administered to increase walking distance, and the administration of anticoagulants if the patient has atrial fibrillation and CHADS-VASC score greater than 2 (recommendation class I), and screening for lower limb arterial disease at patients diagnosed with coronary heart disease (recommendation class IIb). Data from the COMPASS study recommend the use of clopidogrel compared to aspirin (recommendation class IIb).<sup>29</sup>

It should be noted that the modern management of peripheral arterial pathology, especially intermittent claudication, includes the administration of statins and daily exercise, and in patients who have received revascularization treatment.

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