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SUMMARY

NEW PERSPECTIVES IN THE INVASIVE TREATMENT OF LOWER EXTREMITY ARTERY DISEASE

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SUMARY

PhD thesis contains 113 pages, has an iconography made up of 32 figures and 38 tables.

The thesis is divided into three main parts: the general part includes the current state of knowledge, the special part includes personal contributions and references.

The bibliography includes a total of 206 references.

Keywords: lower extremity artery disease, interventional treatment, baloon percutaneous angioplasty, stent percutaneous angioplasty, flexion lesions

CHAPTER 1

CURRENT STATE OF KNOWLEDGE

1.1 Definition

Peripheral arterial disease of the lower limbs sums up all the lesions located in the arterial bed of the lower limbs, both atherosclerotic and non-atherosclerotic [(1)].

1.2 Epidemiology

Globally, approximately 202 million people are affected by peripheral arterial disease, of which 40 million are European [(2,3)]. The pathology usually begins after the age of 50, with an exponential increase after the age of 65. The total number of patients with peripheral artery disease has increased impressively in recent years, with a 23% increase in the last decade, due to total population increase, aging population, increased incidence of diabetes and smoking, but also due to coexistence of different cardiovascular risk factors[(2, 3)].

Mortality associated with lower limbs arterial disease (LEAD) increased significantly from 1990 to 2010 in Western Europe, when it reached 3.5 per 100,000 inhabitants [(2)].

1.3 Risk factors

Although different lesions locations in the arterial bed have major common risk factors for atherosclerosis, risk factors impact and available evidence show a difference depending on the arterial location [(1)].

Smoking is a major risk factor for peripheral arterial disease [(2.4)], with a fraction attributable to the diagnosed population of 44% [(2.5)]. The smoking impact on different segments of the arterial bed in the lower limbs seems to be differentiated, the most significant association being with lesions in the femoral segment, followed by the iliac and infra-popliteal segment [(6)].

High blood pressure is associated with an increased prevalence of LEAD with a risk rate ranging from 1.32 to 2.20 in large epidemiological studies [(2,4,7)]. Although the relative risk associated with high blood pressure is modest in some studies, the increased prevalence of hypertension, especially in elderly patients, places hypertension among the important risk factors [(2)].

Hypercholesterolemia, especially elevated LDL-cholesterol, is a significant contributor to LEAD [(2,4)]. Hypercholesterolemia has proven to have a gradual and progressive impact on the atherosclerotic pathology development. HDL-cholesterol has been shown to be protective against atherosclerotic disease in the vast majority of studies [(2,5)].

Elevated triglycerides values appear to be associated with LEAD in univariate analyzes, but in multivariate analyzes have not been shown to be an independent risk factor [(2,4,8)].

Diabetes mellitus is a strong risk factor for LEAD with an odds ratio ranging from 1.9 to 4 in populational studies [(2,4)], the risk increasing with longer diabetes evolution The prognosis of patients with peripheral arterial disease and diabetes is weaker compared to patients without diabetes, with a 5-fold increase of amputation risk and a pattern of lesion development mainly in the distal arteries [(2,9)].

Inflammation is an element involved in the atherosclerotic process. Various inflammatory markers, for example C-reactive protein, fibrinogen or interleukin-6, are associated with an increased risk of development and progression of LEAD [(2,10,11,12)].

1.4 Prognosis

Atherosclerosis is often generalized, but even patients with a single location are at risk of cardiovascular events fatal and non-fatal [(1)].

Many studies have shown an increased risk of total mortality, cardiovascular mortality and morbidity (myocardial infarction, stroke) in symptomatic or asymptomatic patients with peripheral arterial disease of the lower limbs, even after adjusting of conventional risk factors[(1,13)].

The prevalence of coronary artery disease in patients with LEAD is high, ranging from 46 to 71% [(14,15,16,17)]. Not only the presence but also the severity of LEAD is correlated with coronary heart disease: up to 90% of patients who presented with critical lower limb ischemia also had coronary heart disease [(1)].

The predictive value of the lesions location in the lower limb arteries for the presence of coronary artery disease has been evaluated in several studies. The lesions coexistence in the supra and infra-popliteal segments, was associated with multivascular coronary artery disease [(14,17).] Significant infra-popliteal lesions are an important predictor of coronary heart disease, being associated with multivascular coronary heart disease and the presence of lesions in the common trunk of the left coronary artery [(14)].

1.5 Diagnostic approach

1.5.1 Anamnesis

Medical and family history are essential in being assessed [(1)]. Family history includes ischemic heart disease, history of stroke, aortic aneurysm and last but not least peripheral arterial disease [(1,18,19,20)].

The anamnesis includes the assessment of cardiovascular risk factors and comorbidities[(1)] and also of premature cardiovascular events (cardiovascular arrest with death or resuscitated cardiovascular arrest in first-degree relatives up to 55 years, in men, or 65 years in women)[(2)].

The main signs and symptoms to be evaluated are [(2)]:

- ✓ Walking impairement / intermittent claudication:
  1. Type: fatigue, cramps, pain, discomfort, burning
  2. Location: buttocks, thigh, calf or leg
  3. Timing: triggered by exercise, more often climbing than descending, frequently disappears at rest, chronically.
  4. Distance
- ✓ Low amplitude pulse in lower extermities arteries
- ✓ Murmur on lower arteries auscultation
- ✓ Evaluation of skin temperature and / or associated trophic disorders

1.5.2 Laboratory tests

Routine biological evaluation includes [(2)]: glycemia, serum creatinine and creatinine clearance, lipid profile, urine summary: microalbuminuria, proteinuria, haemoleukogram, uric acid.

1.5.3 Diagnostic methods

1.5.3.1 Ankle –brachial index (ABI)

ABI is a useful noninvasive investigation for LEAD diagnosis and monitoring. It is also a strong marker of generalized atherosclerosis and cardiovascular risk [(1)].

Interpretation [1]:

- For the diagnosis of LEAD, the value of each separate leg is interpreted.
- For the stratification of cardiovascular risk: it is considered the lowest value measured at both legs

An ABI less than or equal to 0.90 is correlated with an 2 to 3 times fold increased risk of cardiovascular and total death [1,21,22]. An ABI greater than 1.4 represents arterial stiffness and is also correlated with a higher risk of cardiovascular events and mortality [1,21,22].

1.5.3.2 Duplex ultrasonography

Duplex ultrasonography (DUS) is often the first step in vascular paraclinical evaluation for both screening and diagnosis. DUS can detect subclinical arterial disease, which is important for cardiovascular risk assessment [1,23].

1.5.3.3 Digital subtraction angiography

Digital subtraction angiography (DSA) has been considered a reference standard for vascular imaging [1].

As advantages, angiography brings a high quality resolution providing imaging accuracy, the disadvantages of the procedure being the risk of complications at the puncture site, the adverse effects related to contrast agent and the fact that the procedure is irradiating.

1.5.3.4 Computed tomography angiography (CTA)

Multidetector CTA is a noninvasive investigation that has several advantages in patients with peripheral arterial disease: short examination time, high resolution, 3D reconstruction and wide availability. CTA allows the determination of interventional strategies related to the location and severity of identified atherosclerotic lesions and the status of the arterial bed upstream / downstream of obstruction. The major disadvantage of CTA is the lack of accuracy in assessing the severity of arterial lesions located below the knee; at this level invasive angiography is still the gold standard method of diagnosis[1].

1.5.3.5 Magnetic resonance angiography

Magnetic resonance angiography (MRA) provides both functional and morphological information, useful to distinguish anterograde and retrograde perfusion and to estimate the stenosis severity[1].

The benefits of the examination come from its non - invasiveness and lack of radiation, but the high cost, the use of the contrast agent and the time spent for the whole procedure are elements which make this examination less used [24].

1.6 Lower extremity artery disease therapy

1.6.1 Non-pharmacological and pharmacological treatment in LEAD

Patients with peripheral arterial disease have multiple associated pathologies, so their treatment is complex, requiring non-pharmacological, pharmacological, interventional and also surgical methods.

1.6.1.1 Non-pharmacological therapy

Non-pharmacological therapy includes regular exercise, mainly after a well-defined schedule, adherence to treatment, smoking cessation, avoidance of exposure to cold, healthy eating, but also proper hygiene of the lower limbs [(1)] .

1.6.1.2 Pharmacological treatment

Pharmacological therapy includes several classes of drugs, acting on the pathology and also on modifiable risk factors or not. The classes required for the therapy of these patients are lipid-lowering drugs, antiplatelet agents, vasodilators and medication for comorbidities.

Antiplatelet therapy used in patients with lower limb arterial disease has been studied in several trials, but their specific indications remain unclear [(25)]. The CAPRIE study showed that the use of clopidogrel reduced the risk of ischemic events in patients with LEAD by 23.8% compared to the use of aspirin. Acetylsalicylic acid has also been studied over the years. Thus, a meta-analysis with 18 randomized trials, which included 5,000 patients with symptomatic peripheral disease or not, did not show a correlation between aspirin administration and a reduced risk of cardiovascular mortality compared to placebo [(26,27).]

Another antiplatelet agent, such as ticagrelor, a reversible P2Y12 inhibitor studied in EUCLID trial, showed no benefit compared to clopidogrel in arteriopathic patients [(28)].

The WAVE study published in 2007 showed no benefit in the primary endpoint for cardiovascular death in administration of warfarin in combination with antiplatelet agents in patients with arteriopathy, only increasing the risk of massive bleeding events [(29)].

Among the vasodilators used in the drug treatment of peripheral arterial disease we mention pentoxifylline, which has brought its benefit through its anti-inflammatory properties. Although its properties are known, in most studies it has not been shown to be effective for claudication, and thus in the European Cardiology Society's Guide for peripheral artery disease pentixifyline has a class II, level of evidence B indication[(1)].

By the year 2000, cilostazol was approved for the treatment of intermittent claudication. Cilostazol produces an inhomogeneous dilation of the vascular beds, with a predilection for the femoral bed [(30)].

Essential drug therapy for peripheral arterial disease also includes hypolipeminates, to reduce cholesterol, stabilize atheroma plaques and thus reduce the events due to atherosclerosis. Pharmacologically, a short-acting statin, such as atorvastatin, has been shown to be safe and effective in reducing blood levels of triglycerides and LDL-C [(30)].

Vorapaxar , a drug with anti-inflammatory and antiplatelet properties, studied in the TRA 2P-TIMI 50 trial, significantly reduced the risk of ischemia in patients with a history of peripheral disease. In patients with bleeding risk (older than 75 years, body weight less than 60 kg) it is not recommended unless the benefit outweighs the risk (IIb indication in AHA ACC guideliness) [(30)].

1.6.2 Interventional treatment of lower extermity artery disease

The interventional treatment addressed to the peripheral arterial disease of the lower limbs is performed in special conditions, in the Cardiac Catheterization Laboratory by the interventional cardiologist or the interventional radiologist.

Depending on the anatomical diagnosis and the extent of the disease in the arterial axis detected by invasive imaging (direct arteriography) or non-invasive imaging (computed tomography or magnetic resonance angiography, arterial ultrasonography), the interventional doctor decides on the invasive treatment technique. Percutaneous angioplasty can be performed by simple balloon, drug-active balloon, self-expanding stent or expandable

balloon-stent device implant. The whole procedure is performed under double antiplatelet therapy (aspirin and clopidogrel) and effective anticoagulation with sodium heparin.

1.6.2.1 Interventional treatment in the aorto-iliac segment

Endovascular therapy of aorto-iliac disease represents the first choice, according with operator's experience, lesions anatomy (short iliac lesions <5cm - IC, long and / or bilateral iliac lesions in patients with multiple comorbidities - IIaB, occlusive aorto-iliac lesions may be endovascularly treated by an experienced team without affecting the possibility of further surgical treatment - IIbB) and logistical support, this intention deriving from the low morbidity and mortality rate and periprocedural success in proportion of more than 90% at 5 years after the procedure [(1)] – the 5 years patency is comparable with that of surgical treatment [(32)] . In the case of ilio-femoral occlusive lesions, hybrid revascularization techniques that include endovascular stent therapy in the iliac segment and surgical treatment (endarterectomy or bypass) in the femoral segment should be considered.

Regarding the devices used, self-expanding or expandable balloon stents are the most used, the choice of stent type depending mainly on the experience and preference of the operator.

1.6.2.2 Interventional treatment in the femoro-popliteal segment

The main problem for endovascular treatment at this level is the arterial disease extension over long segments. In addition, the superficial femoral artery is subjected to significant mechanical forces with the leg movement. Depending on the extent of the disease and together with the vascular surgeon, the revascularization technique is decided: surgical or endovascular [(1)]. The first-intention endovascular strategy (stent - indication IIa, drug-active balloon - indication IIb) is recommended for short lesions (<25 cm) (IC indication) [(1)].

Current studies and trials have focused on the effectiveness of various interventional methods of revascularization in the femoro-popliteal segment (simple-balloon PTA, drug-active balloon PTA, PTA with different types of stents) regarding medium and long-term patency that represents the main limitation of invasive versus surgical therapy.

The efficacy and safety profile of the different interventional procedures were compared in several trials. Thus, in most patients, the use of drug-active stents and coated stents was superior, regarding the long-term patency (1-5 years), to the use of simple metal stents, versus simple balloon angioplasty [(33, 34)]. Drug-active balloon angioplasty was associated with a lower rate of restenosis compared to simple balloon angioplasty [(35,36)]. Comparing nitinol stent percutaneous angioplasty with simple balloons percutaneous angioplasty, the former proved to have superior patency at both 1 and 3 years [(37)]. The stents intrinsic characteristics are decisive for their resistance to extrinsic mechanical forces. Nitinol stents, the most widely used self-expanding stents, have several advantages: biocompatibility, increased elasticity, with reduced stiffness, thus limiting the fracture risk.

1.6.2.3 Interventional treatment of lesions in the flexion regions

The treatment of stenoses or occlusions in these regions was, until recently, dedicated to surgical treatment. Regarding the interventional treatment, it was performed by balloon angioplasty [(1)], directional arterectomy and laser therapy [(38,39)], with unsatisfactory results, and stent angioplasty. Mechanical stress secondary to flexion-extension in the femuropopliteal space can cause stent fracture and thrombosis [(40,41)].

Endovascular treatment with self-expanding stents versus balloon angioplasty has been evaluated in several trials. At 1 year evaluation after the revascularization procedure, patients treated with self-expanding stents had a 50% reduction in restenosis compared to patients treated with balloon angioplasty [(41,42,43)]. The design of the self-expanding stents, made of a nitinol braid, mimics the reticular structure of the native vessel, giving them radial strength,

flexibility and kinking resistance. Such stents are: Zilver PTX, Life stent, S.M.A.R.T, Eluvia, SuperaTM Stent, Innova s.a. The patency of these stents at 1 year varies from 67% to 91%, and at 3 years from 70% to 94% [49].

1.6.2.4 Interventional treatment in the infra-popliteal segment

Infra-popliteal arterial disease is most commonly seen in diabetic patients, often associated with superficial femoral artery lesions. Lesions at this level are often associated with critical limb ischemia. Angiography with digital subtraction extended to the plantar arch is mandatory for the evaluation of revascularization options [1].

Endovascular therapy may be the first choice for stenotic lesions and short occlusions. In the case of long occlusions, the autologous vein by-pass offers superiority for long-term patency and for lower limb saving compared to interventional therapy. However, in patients with high surgical risk and / or in the absence of the autologous vein, endovascular therapy may be attempted [1].

Interventional treatment is performed using balloons dedicated for below the knee (BTK) lesions, without significant differences between simple balloons and drug-active balloons, regarding the long-term patency (12 months) [1,44].

The angiographic results can be suboptimal, situations in which balloon angioplasty can be followed by the implantation of stent devices dedicated to below the knee lesions, the drug-active ones being clearly superior to the non-pharmacological ones [45].

1.7 Surgical treatment of lower extremity artery disease

Surgical treatment of peripheral artery disease of the lower limbs includes several techniques adapted to lesions location and disease severity: endarterectomy, bypass: "anatomical" or "extraanatomical", amputation.

CHAPTER 2

PERSONAL CONTRIBUTIONS

2.1 Introduction

Peripheral artery disease of the lower limbs is a major public health problem, both by frequency and by the negative impact on the patient but also on the family and society.The clinical suspicion of peripheral artery disease must be further confirmed by a clear diagnostic algorithm, which sums up several invasive or non-invasive imaging investigations.

The therapeutic strategy for patients with peripheral artery disease of the lower limbs includes two components [(1)]: addressing specific symptoms and signs and the risk of a specific injury; management of cardiovascular risk factors directly correlated with the increased risk of cardiovascular events.

The guidelines support the best medical therapy (BMT) strategy, which includes non-pharmacological measures (smoking cessation, healthy diet, weight loss, exercise therapy, preferably supervised [(1, 46,47)]) associated with the pharmacological component, which includes lipid-lowering, antithrombotic, vasodilating, antihypertensive medication [(1,48)].

If, despite the above-mentioned therapeutic measures, the patient remains symptomatic (intermittent claudication) and daily activities are compromised, revascularization therapy should be considered [(1)]; revascularization therapy requires primarily an accurate diagnosis of the lesion to be treated, that can be performed by CTA and / or digital subtraction angiography. After defining the lesion to be treated, the therapeutic conduct is established.

Revascularization therapy can be performed by two techniques, interventional or surgical, depending on the lesions location, extent and complexity and the patient's comorbidities, but also by hybrid techniques that combine the interventional strategy with the surgical one.

Endovascular therapy has shown rapid progress in recent times, and thus the extension of its use to complex lesions [(2)].

The main technique used is balloon angioplasty; however, restenosis occurs quite frequently, with restenosis rates increasing from proximal (iliac) segment to distal (infrapopliteal) segment.Stent therapy is frequently performed to improve a primary suboptimal outcome secondary to balloon angioplasty (residual stenosis, extensive recoil, flow-limiting dissection) and long-term patency. Currently, different types of stents with variable mechanical properties are available. As in balloon angioplasty, in stent angioplsty, the main problem is intrastent restenosis, which is more difficult to treat than restenosis after balloon angioplasty.

The flexion areas (distal iliac artery, common femoral artery, proximal and distal superficial femoral artery and popliteal artery) are an interventional challenge due to the increased risk of stent fracture and secondary complications (intrastent thrombosis) in context of particular mechanical forces found in these anatomical areas. For these arterial segments, self-expanding nitinol stents have been developed with particular mechanical properties (elasticity, increased resistance to torsional forces). The 1 year patency of these stents varies from 67% to 91%, and at 3 years from 70% to 94% [(49)].

Drug-active balloons and stents decrease the development of neointimal hyperplasia being more and more frequently used, studies showing that they have better results on long-term patency (two years follow-up up) compared to conventional balloons and simple metal stents [(2)].

2.2 Study of LEAD patients evolution according to the chosen therapeutic strategy: medical therapy versus interventional therapy - percutaneous balloon angioplasty versus percutaneous stent angioplasty

2.2.1 Study objectives

The objectives of the study were divided into primary and secondary objectives:

Primary objectives	1. Minor (below the tibio-tarsal joint) / major (above the tibio-tarsal joint) amputation rate at 1 year after initiation of therapy in the three groups of subjects 2. Need for reintervention (restenosis> 75% assessed by symptomatic ultrasound - intermittent claudication, resting pain, trophic disorders) in patients treated by percutaneous balloon / stent dilation
Secondary objective	1. Comparative analysis of the evolution of the claudication index, Leriche-Fontaine classification, ankle-brachial index in the three groups of subjects 2. Comparative analysis of the factors that determined the unfavorable evolution of the patients (amputation, need for revascularization) in the three groups of subjects

2.2.2 Material and method

The present study followed prospectively, over a period of 12 months, 91 patients with peripheral artery disease of the lower limbs enrolled between January 2017 and December 2019 and evaluated at the Sibiu County Emergency Clinical Hospital, at the Invasive and Non-Invasive Research Center in the field of Cardiac and Vascular Pathology in Adults (CVASIC). Patients were divided into 3 groups:

- Group I: patients with drug therapy (28 patients) (stage IIa Leriche-Fontaine patients with optimal medical therapy and physical therapy, stage IIb, III, IV Leriche-Fontaine patients patients without interventional or surgical revascularization option (4 PTA failed) because of vascular anatomy, increased surgical and anesthetic risk.
- Group II: percutaneously revascularized patients with simple balloon devices (33 patients)
- Group III: percutaneously revascularized patients with stent devices (30 patients) - 30 simple metal stents were implanted, of which 5 self-expanding and 25 balloon-expandable stents.

Peripheral artery disease of the lower limbs has been defined in accordance with the definition proposed by current guidelines, 2017 European Society of Cardiology (ESC) Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). The lower limbs arterial tree was divided into 3 segments:

- Iliac segment: common iliac artery, external iliac artery, internal iliac artery
- Femoral segment: common femoral artery, superficial femoral artery, deep femoral artery
- Infra-popliteal segment: popliteal artery, anterior tibial artery, tibio-peronium trunk, posterior tibial artery, fibular artery.

Inclusion criteria:

1. Male / female patients over 18 years of age
2. Patients initially diagnosed with lower limb arterial disease stages II-IV Leriche-Fontaine
3. Patients explored by digital subtraction angiography to assess lesions severity in the lower limbs arterial axis.

Exclusion criteria:

1. Age under 18 years
2. Allergy to iodinated contrast agent
3. Chronic stage IV kidney disease, according to the KDOQI classification (cretinine clearance between 15 - 30 ml / kg / 1.73 m2, clearance calculated by Cockroft-Gault formula). Patients with chronic stage V kidney disease underwent hemodialysis after administration of the contrast agent.
4. Patients with minor / major lower limb amputation prior to study enrollement
5. Patients with severe comorbidities that may have interfered with the patient's ability to move: decompensated heart failure, respiratory failure, stroke with secondary motor deficit, neurological diseases with limited mobility, neoplasms regardless of location, advanced liver disease (Child-Pugh C liver cirrhosis), stage IV chronic kidney disease.

The patients were followed for a period of 1 year from the beginning of the therapy, with the following sequence of visits:

- Visit 1: evaluation of the patient, performing peripheral angiography and establishing the therapeutic conduct (drug therapy, interventional therapy - percutaneous balloon / stent angioplasty). The initial assessment of patients was performed clinically and paraclinically according to the following protocol:

General data	Age, sex, background, height, weight
Clinical data	Symptoms / signs at onset, Leriche - Fontaine classification, claudication index, walking maximum distance, angina pectoris, treatment (statin, antiplatelet agent, vasodilator, additional treatment), blood pressure, ankle-brachial index
Cardiovascular risk factors	Smoking, diabetes mellitus, arterial hypertension, chronic kidney disease, dyslipidemia, obesity
Laboratory parameters	Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, urea, creatinine, creatinine clearance (calculated by Cockroft-Gault formula), uric acid, C-reactive protein (normal values 0-5 mg / dl)
Lower limbs digital subtraction angiography	Identification of lesions in the lower limbs arterial axis and severity assesment: angiographically insignificant (no lesion or stenosis <50%) or angiographically significant (stenosis ranging from 50% to 75%, stenosis > 75%, occlusion)
Angiocoronarography	Performed concomitantly with lower limb angiography, with the definition of coronary artery disease as angiographically non-significant (without stenosis or coronary stenosis <50%) or angiographically significant (coronary stenosis ≥ 50%)

- Visit 2: evaluation of patients immediately after revascularization by the ankle-brachial index; in the case of patients in group I for the ankle-brachial index,

the value from visit 1 was repeated.

- Visit 3: Evaluation of patients at 1 month: claudication index, ankle-brachial index, post-revascularization restenosis (clinical, ultrasound / angiography)
- Visit 4: Evaluation of patients at 1 year: claudication index, ankle-brachial index, Leriche-Fontaine classification, post-revascularization restenosis (clinical, ultrasound), amputation

All data were collected in the form of a database with qualitative and quantitative variables, being interpreted statistically using the IBM SPSS Statistics program. The normality of the distribution of quantitative variables was analyzed with the Shapiro-Willk test. Normally distributed quantitative variables were expressed as mean ± standard deviation (SD), and variables with non-normal distribution were expressed as median. The Pearson Chi-Square test for qualitative variables and the Kruskal-Wallis test for quantitative variables were used to assess risk factors and medication in the three patient groups. Statistical significance was considered at a P value <0.05 (two-tailed).

2.2.3 Results and discussions

Peripheral artery disease of the lower limbs, a disease predominantly of atherosclerotic nature, remains an important public health problem, often underdiagnosed or late diagnosed in advanced stages, when therapeutic resources are limited.

Depending on the imaging aspects and the disease extent, the specific revascularization treatment is chosen: surgical (less and less used), interventional or hybrid [(1,50)]. Optimal medical therapy remains addressed, but adapted, to all patients diagnosed with peripheral artery disease of the lower limbs, regardless of the non-pharmacological treatment applied.

The division and follow-up of patients into 3 comparable groups (group 1 - drug-treated patients, group 2 and group 3 -interventional-treated patients) derives from direct contact between the cardiologist and the patient with interventional revascularisation or with optomal medical therapy, while surgically revascularized patients remain most of the times under the suervision of the vascular or cardiovascular surgeon.

Regarding the demographic differences (sex, age), biological parameters and cardiovascular risk factors, no notable differences were highlighted between the groups followed. In contrast, from the statistically point of view, hypertension was more common in the interventional balloon revascularized group (angioplasties performed predominantly in the femural arteries and in older patients, where hypertension is more common) compared to the revascularized stent group (predominantly performed angioplasties in the iliac arteries, most patients being younger, with a lower incidence of hypertension) [(1)].

The group of drug-treated patients mostly included patients with a high claudication rate, which is why they remained on maximum drug treatment, but with slight benefits, or in extreme cases, patients in advanced stages (III - IV Leriche-Fontaine), outside of revascularization resources, patients who frequently have been amputated.

There were no significant differences between groups in terms of treatment compliance (approximately 70% of patients in each follow-up group were compliant with the indicated treatment).

The diagnostic approach in the case of direct arteriography was performed mainly by radial approach. The therapeutic approach was different depending on the anatomy and location of the lesions to be treated. The anterograde therapeutic approach was performed at the common femoral artery level. The retrograde approach at the popliteal and tibial arteries was performed under real-time ultrasound guidance or by anterior marking of the puncture site.

Regarding the option of balloon or stent angioplasty, this may be influenced by the lesion location [(1)]: the iliac axis was treated exclusively by stent implant; the femoral axis, due to the specific anatomy, but also to the involvement of torsional forces, can favor the fracture

of stent devices. Consequently, for femoral segment, the revascularisation technique used was balloon angioplasty per primam, especially in the case of long lesions.

At the same time, an explanation for stent angioplasty predominantly at the iliac level was that, at this level, severe stenoses and not occlusions were dilated (to avoid the complications of tempting angioplasty in chronic occlusions at this level). In contrast, at the femoral level, mainly balloon angioplasties were performed, because long lesions were treated, including occlusions, and elective stent implantation addressed short and nonocclusive lesions. The approach of such a strategy derives from the attempt to avoid as much as possible the restenosis of the arterial axis, more frequent at the femoral level in long lesions, long occlusions, implantation of long stents, with overlapping and smaller diameters (5-6 mm), these elements favoring intrastent restenosis and implicitly the need for reintervention. Sakamoto et al. showed that the risk of restenosis after nitinol-type stent angioplasty in femoral and popliteal occlusive lesions is higher in females and for small-diameter stents [(51)]. On the other hand, at the iliac level, shorter, non-occlusive lesions were treated with stents with larger diameters (7-8 mm).

Consequently, stent angioplasty was required in two situations [(1)]:

- complications and suboptimal result of balloon angioplasty, when due to vascular recoil, intense calcific lesions and local dissection, the stent implant was imposed
- when the stenotic lesions were short and far from the flexion areas.

The main problem of stent angioplasty was restenosis and / or stent fracture, more common in the case of long stents, multiple stenting with overlapping or implant near the flexion areas [(52,53,54,55)].

12 months patency in balloon or stent revascularized groups was paradoxically higher in the balloon-treated group, this situation being explained by the fact that only balloon expandable stents, rigid and with lengths over 60 mm, were used. In contrast, the mean patency duration of the revascularized vessel was longer in stent treated group.

The treatment of post angioplasty restenosis, with stent or balloon was individualized: it was successfully interventional intervened again in post baloon-angioplasty restenosis, while intra-stent stenosis was referred for surgical treatment, as a consequence of the failure of percutaneous reintervention. Radical treatment (amputations) was more common in the drug-treated group. This situation derives from the fact that patients with mild symptoms (Leriche Fontaine IIa classification) had a slight improvement in symptoms, while patients with advanced symptoms (Leriche Fontaine III-IV classification) outside the revascularization resources ended up in this situation.

The final results showed clear differences in terms of the indicators followed: arm-brachial index, claudication index, amputation between the interventional-treated (baloon and stent angioplasty) groups and the drug-treated group. At the same time, significant differences were found between the interventionally treated groups: balloon PTA versus stent PTA. The stent-treated group achieved a significant and persistent increase in the ankle-brachial index, claudication index, a decrease in the amputation rate, even if the restenosis rate was slightly higher than in the case of the PTA balloon group.

These can be explained by the fact that, often, after simple balloon angioplasty, although angiographically final result seems good (no noticeable dissection, no residual stenosis), invasive blood pressure measurements have shown however a suboptimal increase in blood pressure, and thus of the ankle-brachial index, a situation remedied by completing angioplasty with stent implant, which subsequently determined a significant increase in these parameters. For these reasons, I emphasize the importance of the retrograde approach, even if it is sometimes more difficult and has some deficiences (the arterial axis proximal to the lesion is not visualized, sometimes requiring another arterial approach for this purpose); invasive pressure control can bring objective data flow from arterial bed distal to the lesion.

The ankle-brachial index and the claudication index were not influenced at 1 year in patients with intra stent occlusive restenosis, because they were addressed to the vascular surgery service.

Post balloon PTA restenosis was often non-occlusive, facilitating percutaneous reintervention.

Consequently, the interventional treatment had a visible impact on the treated patients evolution;although interventionally treated groups included a significant number of patients in stage III, IV Leriche Fontaine (threatening chronic ischemia of the lower limb), they did not reach amputation, compared to the drug-treated group, where, although patients in the advanced stages with optimal medical therapy were few, the rate of amputations was significantly higher.

2.2.4 Conclusions

1. No significant differences in demographics, biological parameters and risk factors were found, with the exception of arterial hypertension, which was more common in patients with percutaneous balloon revascularization.
2. The diagnostic approach in the case of direct arteriography was mainly performed by radial approach. The anterograde or retrograde therapeutic approach was individualized and performed at the level of several arteries (brachial artery, common femoral artery, popliteal artery, anterior and poaterior tibial arteries).
3. Angioplasty of the iliac arteries was performed almost exclusively with stent.
4. At the femoral level, on the other hand, the interventional treatment was individualized and performed with either a stent or a balloon.
5. The advantage of stent angioplasty was especially the better short and medium term patency, in terms of time to restenosis, compared to balloon angioplasty.
6. Regarding the primary objectives:
    - the 12 months restenosis rate was, paradoxically, higher in the group of revascularized patients with stent, compared to the group of patients revascularized with balloon
    - the amputation rate was significantly lower in the groups of patients treated interventionally compared to the group of patients treated with drugs.
7. In the groups of patients treated interventionally, patients who, at presentation, had chronic threatening lower limb ischemia (stages III and IV Leriche Fontaine) were followed. At the end of the study, in the drug-treated group, there is an increase in the percentage of cases in stage III or IV Leriche Fontaine versus balloon and stent groups, where stage IIa or stage IIb predominated.
8. Regarding the secondary objectives, the evolution over time of the claudication index, Leriche Fontaine classification, ankle-brachial index, was significantly better in the group of patients revascularized with stent, compared to the group of patients revascularized with balloon, respectively to the group of drug-treated patients.

2.3 Particular cases of flexion lesions treatment - case series

2.3.1 Study objectives

The objectives of the present analysis are:

- evaluation of self-expanding nitinol stents patency, stents implanted in the flexion areas (common femoral artery, superficial femoral artery proximal and distal segment, popliteal artery) at 1 month, 6 months and 12 months post-revascularization; stent patency was defined as the absence of restenosis (arterial stenosis > 50% assessed by duplex ultrasonography using the ratio of maximum systolic velocities > 2 as a parameter) and the absence of the need for reintervention for intrastent stenosis
- absence of the need for reintervention for intrastent stenosis at 1 month, 6 months and 12 months post-revascularization

- absence of the need for amputation at any level in the lower limb revascularized at 1 month, 6 months and 12 months post-revascularization
- evaluation of stent fracture during the follow-up period

2.3.2 Material and method

The present analysis is a case series that included 10 patients with LEAD with intermittent disabling claudication (stage IIb Leriche Fontaine) or critical lower limb ischemia (stages III or IV Leriche-Fontaine) caused by severe atherosclerotic lesions in the flexion areas of the lower limbs (common femoral artery, superficial femoral artery proximal and distal segment, popliteal artery) in whom percutaneous anigoplasty was performed with new generation self-expanding stents made of a fine nitinol braid (wire-interwoven self expanding nitinol stent). Patients were followed prospectively for a period of 12 months

All patients were evaluated according to the following protocol:

A. Visit 1
   1. anamnesis, clinical examination, cardiovascular risk factors evaluation: sex, age, height, weight, claudication index, presence / absence of trophic disorders, Leriche-Fontaine classification, arm-brachial index, smoking, dyslipidemia, arterial hypertension, diabetes mellitus, chronic kidney disease
   2. evaluation of multiple locations of atherosclerotic disease: carotid arteries - carotid ultrasonography±carotid angiography, coronary arteries - coronary angiography
   3. lower extremity peripheral angiography with digital subtraction: lesion location, lesion severity (stenosis> 75%, occlusion), lesion length, calcification severity (moderate – segmental scopic visible calcium, severe -integral scopic visualization of the artery due to calcification), implanted stent dimensions (length, diameter), preprocedurally and postprocedurally ankle-brachial index invasively determined.

B. Visits 2 (1 month post-revascularisation), 3 (6 months post-revasvascularissation), 4 (12 months post-revascularisation): claudication index, Leriche-Fontaine category, ankle-brachial index, Duplex ultrasonography, radiographic examination

2.3.3 Results and discussions

This case series, with prospective follow-up, of 10 patients with symptomatic LEAD (disabling intermittent claudication or critical lower limb ischemia) treated with wire-interwoven self-expanding nitinol stents dedicated to the flexion areas shows a good clinical performance with improved symptomatology, improved Leriche-Fontaine class, arm brachial index and life quality.

Flexion lesions interventional treatment with devices developed specifically for the implant in these anatomical regions involves two important aspects:

1. Short-term and long-term patency of the treated vessel
2. Evaluation of associated co-morbidities that may represent relative or absolute contraindication to surgical treatment, especially due to the increased anesthetic risk

The group included 10 patients, one fifth of whom had severe lesions in the common femoral artery, the rest had lesions in the popliteal artery, isolated or extending to the distal segment of the superficial femoral artery. Patency at 1, 6, 12 months was 90%, and occlusive restenosis was 10% produced 1 month after stent implantation in context of treatment non-compliance to dual antiplatlet therapy and continued smoking. The results confirm the data in

the literature regarding short- and medium-term patency of the revascularized vessel [40].

About one-third of revascularized patients with flexion stents had a history of interventional balloon treatment on the same lesion, showing the inferiority of balloon angioplasty in terms of short- and medium-term patency. Studies on popliteal artery lesions have shown that the average 2 years patency after balloon angioplasty was approximately 47% [56,57,58].

An important benefit of the patients treated with wire-interwoven self-expanding nitinol stents in the study group was symptoms marked improvement immediately after the procedure: 80% of them had disabling claudication, and 20% had threatening lower extremity chronic ischemia. At the same time, patients with threatening chronic lower extremity ischemia did not reach amputation despite an increased WIfI score. Also, the popliteal or femoral treated lesions were not singular: during the same procedure 60% of the patients underwent percutaneous revascularization of other severe lesions (5 patients underwent stent implantation and 1 patient underwent balloon dilation).

Patients were imagistically explored: carotid duplex ultrasound±carotid arteriography and coronary angipgraphy. In this context it was found an important association with carotid artery disease (80%) and angiocoronarographic, significant coronary disease (> 50% left main stenosis;> 75% anterior descendig artery, circumflex artery, right coronary artery stenosis). This situation causes a significant perioperative risk of coronary events in case of surgery, thus requiring appropriate screening, including performing angiocoronarography in certain specific situations [1].

Taking into account the aspects presented above, in patients with severe injuries in the flexion areas, interventional treatment with wire-interwoven self-expanding nitinol stents is the first choice due to the reduced periprocedural complications and the good short and medium term patency.

2.3.4 Conclusions

1. Self-expanding nitinol stents have a good short and medium term primary patency in the target group, being consistent with the literature data.
2. No stent fractures of any kind were found in the devices used for treating patients.
3. Nearly one-third of revascularized patients were previously treated with balloon angioplasty on the same lesion.
4. The vast majority of patients in the study had disabling intermitent caudication, and a smaller percentage had lower extremity chronic threatening ischemia.
5. Despite the pronounced symptoms, no amputations were found in the target group.
6. Arterial disease in the lower exxtremity was not only localized in the treated areas.
7. More than half of the revascularized patients with flexion stents were revascularized in other lesions of the arterial axis during the same procedure, highlighting the complexity of the treated cases.
8. In the follow-up group, an important association was found between LEAD and carotid artery disease.
9. Almost half of the patients followed showed severe coronary artery lesions, involving an increased risk of cardiovascular events.
10. Flexion lesions interventional treatment with a dedicated stent implant represent currently a feasible treatment option.

2.4 Lower extremity artery disease as a predictor of coronary artery disease

2.4.1 Objectives of the study

1. Assessment of the presence of a significant association between LEAD and significant coronary heart disease
2. Assessment of the association between different locations of arterial lesions in the lower extremity arterial axis (iliac segment, femoral segment, infrapopliteal segment) and significant / non-significant coronary artery disease, monovascular / multivascular coronary artery disease and left main lesions.

2.4.2 Material and method

The present study is a retrospective study that evaluated 203 patients with symptomatic LEAD (intermittent claudication or critical limb ischemia), who underwent in the same procedure lower extremity digital subtraction angiography and coronary angiography; the patients were evaluated in Sibiu County Emergency Clinical Hospital, Invasive and Non-Invasive Research Centre in Cardiac and Vascular Pathology in Adults - CVASIC between January 2017 and December 2019. Patients with peripheral arterial lesions of non-atherosclerotic or embolic etiology were excluded, including only LEAD patients of atherosclerotic cause.

Inclusion criteria:

1. Male / female patients over 18 years of age
2. Patients initially diagnosed with lower extremity arteriy disease stages II-IV Leriche-Fontaine
3. Patients explored in the same operating time by digital subtraction peripheral angiography for loewr extremity artery lesions and coronary angiography.

Exclusion criteria:

1. Age under 18 years
2. Allergy to iodinated contrast agent
3. Chronic stage IV kidney disease, according to the KDOQI classification (cretinine clearance between 15 - 30 ml / kg / 1.73 m2, clearance calculated by Cockroft-Gault formula). Patients with chronic stage V kidney disease underwent hemodialysis after contrast agent administration.
4. LEAD of non-atherosclerotic or embolic etiology
5. Patients with minor / major lower extremity amputation prior to study enrollement
6. Patients with severe comorbidities that may have interfered with the patient's ability to move: decompensated heart failure, respiratory failure, stroke with secondary motor deficit, neurological diseases with limited mobility, neoplasms regardless of location, advanced liver disease (Child- Pugh C liver cirrhosis), chronic kidney disease (stage IV).

LEAD and coronary artery disease have been defined as angiographically significant in the context of the presence of at least one arterial / coronary lesion causing arterial lumen stenosis ≥50%.

Lower extremity arterial axis was divided into 3 segments:

- Iliac segment: common iliac artery, external iliac artery, internal iliac artery
- Femoral segment: common femoral artery, superficial femoral artery, deep femoral artery
- Infra-popliteal segment: popliteal artery, anterior tibial artery, tibio-perionium trunk, posterior tibial artery, fibular artery.

Coronary artery disease has been defined as significant or non-significant, monovascular or multivascular coronary artery disease.

Cardiovascular risk factors – arterial hypertension, dyslipidemia and diabetes mellitus - have been defined according to current guidelines of the European Society of Cardiology. Patients were considered smokers if they were active smokers or former smokers, but less than 1 year of abstinence. Normal values of C-reactive protein in the hospital laboratory ranged from 0 to 5 mg / dl. Chronic kidney disease was classified in stages I - V, according to the KDOQI classification, and creatinine clearance was calculated with the Cockroft-Gault formula.

Statistical analysis was performed using the IBM SPSS Statistic Software. Qualitative variables were expressed as numbers (percentages) and quantitative variables were initially analyzed for normality of distribution. Normally distributed quantitative variables were expressed as mean ± standard deviation (SD), and variables without normal distribution were expressed as median. The Pearson Chi-square test was used to assess the association of LEAD with coronary artery disease. As a measure of association we used the coefficient gamma - γ (Kendall's tau-c). Data were considered statistically significant at a P value <0.05 (two-tailed).

2.4.3 Results and discussions

LEAD and coronary artery disease affect men more frequently than women. Age older than 45 years for men, and older than 55 years for women, is associated with increased risk for both conditions [3, 59]. In the studied group, the male gender was predominant, and the average age corresponds to literature data.

The increased incidence of smoking, arterial hypertension and hypercholesterolemia in the studied patients also coincides with the literature data. [16,17].

Multiple localization of arterial disease is common in patients with atherosclerotic lesions, 60-70% for LEAD [1] and 46-71% for coronary artery disease [15,16,17]. Significant coronary artery disease was found in more than two-thirds of the patients evaluated in this study, half of whom had multivascular coronary artery disease and a quarter had monovascular coronary artery disease. The interest in the association of lower extremity artery disease with coronary artery disease is explained by the fact that the main cause of death of patients with peripheral arterial disease is ischemic heart disease (up to 50% of deaths of patients diagnosed with LEAD) [60].

Proximal lesions defined as iliac, femoral, or popliteal stenoses are more often associated with monovascular or absent coronary artery disease. When proximal and distal lower extremity arteries are involved, there is a higher likelihood of association with multivascular coronary artery disease [17]. The results of our study were consistent with the above data: infrapopliteal lesions were associated with both the presence and severity of coronary artery disease, femoral lesions were associated with multivascular coronary artery disease, while iliac lesions were not significantly associated with coronary artery disease.

The prognosis of LEAD is different depending on the lesions location [17]. The presence of distal arterial disease is associated with a more reserved prognosis compared to patients who do not have distal arterial disease. On the other hand, there were no prognostic differences for patients with proximal arterial disease [61]. LEAD with multiple localization at the level of the arterial axis determined a more reserved prognosis for these patients [62]. These prognostic differences can be explained by the more important association of distal or

multiple localized arterial disease with multivascular coronary artery disease compared to proximal LEAD.

2.4.4 Conclusions

1. Significant coronary artery disease has an increased prevalence in patients with symptomatic LEAD.
2. Significant lesions in different segments of lower extremity arterial axis are differently associated with coronary artery disease.
3. Significant infra-popliteal lesions appear to be the best predictor of coronary artery disease, being associated with significant coronary artery disease, multivascular coronary artery disease and the presence of left main lesions. Therefore, significant infra-popliteal lesions correlate with the presence of significant coronary lesions and also with their severity quantified by the number of vessels affected and by the presence of left main lesions.
4. Significant lesions in the femoral segment are strongly associated with multivascular coronary artery disease, but there has been no direct association with significant coronary artery disease and left main lesions.
5. No significant associations between iliac segment lesions and significant multivascular coronary artery disease or left main lesions were found.
6. The results of the study suggest that coronary angiography should be performed in patients with symptomatic LEAD, paying particular attention to patients with significant lesions with femoral and infra-popliteal localization. In addition, low levels of physical activity in patients with LEAD may reduce the symptoms of angina pectoris, so coronary angiography screening for patients diagnosed with LEAD may be an option for these patients.

2.5 Study of cardiovascular risk factors association with lower extremity artery disease versus coronary artery disease

2.5.1 Study objectives

I. Assessment of the association of cardiovascular risk factors - smoking, diabetes mellitus, arterial hypertension, chronic kidney disease, hypercholesterolemia, hypertriglyceridemia, C-reactive protein - with LEAD
II. Assessment of the association of cardiovascular risk factors - smoking, diabetes, hypertension, chronic kidney disease, hypercholesterolemia, hypertriglyceridemia, C-reactive protein - with coronary artery disease

2.5.2 Material and method

The present study is a retrospective study that evaluated 203 patients with symptomatic LEAD (intermittent claudication or critical limb ischemia), who performed in the same operator time lower extremity digital subtraction angiography and coronary angiography in the Sibiu County Emergency Clinical Hospital, Invasive and Non-Invasive Research Centre in Cardiac and Vascular Pathology in Adults - CVASIC between January 2017 and December 2019. Patients with peripheral arterial lesions of non-atherosclerotic or embolic etiology were excluded, including only patients with LEAD of atherosclerotic cause.

Inclusion criteria:

1. Male / female patients over 18 years of age
2. Patients initially diagnosed with lower extremity artery disease stages II-IV Leriche-Fontaine

3. Patients examined in the same operating time with digital subtraction angiography for the evaluation of lesions in the lower extremity arterial axis and coronary angiography.

Exclusion criteria:

1. Age under 18 years
2. Allergy to iodinated contrast agent
3. Chronic stage IV kidney disease, according to the KDOQI classification (cretinine clearance between 15 - 30 ml / kg / 1.73 m2, clearance calculated by Cockroft-Gault formula). Patients with chronic stage V kidney disease underwent hemodialysis after contrast agent administration.
4. LEAD of non-atherosclerotic or embolic etiology
5. Patients with minor / major lower limb amputation prior to study enrollement
6. Patients with severe comorbidities that may have interfered with the patient's ability to move: decompensated heart failure, respiratory failure, stroke with secondary motor deficit, neurological diseases with limited mobility, neoplasms regardless of location, advanced liver disease (Child-Pugh C liver cirrhosis), chronic kidney disease (stage IV).

LEAD and coronary artery disease have been defined as angiographically significant in the presence of at least one arterial / coronary lesion causing arterial lumen stenosis ≥50%.

Lower extremity arterial axis was divided into three segments:

- Iliac segment: common iliac artery, external iliac artery, internal iliac artery
- Femoral segment: common femoral artery, superficial femoral artery, deep femoral artery
- Infra-popliteal segment: popliteal artery, anterior tibial artery, tibio-perionium trunk, posterior tibial artery, fibular artery

Coronary artery disease has been defined as significant or non-significant, monovascular or multivascular coronary artery disease.

Arterial hypertension, dyslipidemia and diabetes melitus have been defined according to current guidelines of the European Society of Cardiology. Patients were considered smokers if they were active smokers or former smokers, but less than 1 year of abstinence. Normal C-reactive protein values ranged from 0 to 5 mg / dl. Chronic kidney disease was classified into stages I-V according to the KDOQI classification, and creatinine clerence was calculated by the Cockroft-Gault formula.

Statistical analysis was performed using the IBM SPSS Statistics program. The Shapiro-Wilk test was used to assess the normality of quantitative data. Normally distributed quantitative variables were expressed as mean ± SD, and variables without normal distribution were expressed as median. The Pearson Chi-square test, for qualitative variables, and the Kruskal Wallis test, for quantitative variables, were used to assess the association of cardiovascular risk factors with LEAD and coronary artery disease. The results were considered statistically significant at a P value (two-tailed) of less than 0.05.

2.5.3 Results and discussions

The predominance of males in the studied group is consistent with the data described in the literature, both LEAD and coronary artery disease affecting men more frequently than women. The average age of the studied group corresponds to the information in the literature;

It is well known that the risk of developing coronary artery disease and LEAD increases with age and includes men older than 45 years and women older than 55 years [3, 59].

The increased incidence of smoking, arterial hypertension and hypercholesterolemia in the study group coincides with literature data [2, 59]. In the study group, the association of smoking with significant lesions in the iliac and femoral segments was increased, but this association was not statistically significant for the infra-popliteal segments.

Regarding smoking and coronary artery disease, there is a close association with ischemic heart disease [59]. Heavy smokers - more than 20 cigarettes per day - have a 2-3 times higher risk of developing coronary srtery disease. [59, 63]. In our study, the smoking population had no significant association with coronary artery disease.

In the study group, arterial hypertension had a significant association with coronary artery disease, but no significant association with LEAD.

Hypercholesterolemia has a significant contribution in the development of peripheral arterial disease, being independently associated with incident LEAD [5]. In addition, in large epidemiological studies, elevated HDL-Cholesterol levels have been shown to be protective for coronary artery disease and LEAD [2,64]. Hypertriglyceridemia was associated with LEAD in univariate analyzes, but in multivariate analyzes it no longer proves to be an independent risk factor [2,4,8]. In the study group, hypercholesterolemia and hypertriglyceridemia were not associated with significant arterial stenoses of the iliac, femoral, infra-popliteal and coronary arteries.

The association between diabetes mellitus and LEAD has been proven in populational studies, with odds ratios ranging from 1.9-4 [2,4]. For the study group, diabetes was strongly associated with significant coronary and multivascular disease. Moreover, the percentage of diabetic patients with multivascular coronary artery disease was significantly higher than those with monovascular or insignificant disease. On the other hand, diabetes was not associated with LEAD in the study group, probably due to the low number of enrolled patients and the small percentage of diabetic patients studied.

Classic cardiovascular risk factors are often found in patients with chronic kidney disease, but chronic kidney disease also brings other specific risk factors that promote the atherosclerotic process (chronic inflammation, hypoalbuminemia, increased risk of calcification) [65]. Chronic kidney disease is also an independent risk factor for coronary artery disease, being associated with both its development and its severity [66]. In the present study, chronic kidney disease was significantly associated with multivascular and significant coronary artery disease, but there was no association with LEAD.

A large number of studies have shown that inflammation plays an important role in the atherosclerosis pathophysiology [2]. Highly sensitive protein C is a marker of inflammation and is associated with an increased risk of LEAD developing and progressing and also with an increased risk of developing LEADcomplications [67]. In the present study, C-reactive protein was determined and not the highly sensitive fraction, without significant associations with LEAD.

2.5.4 Conclusions:

1. LEAD and coronary artery disease share the same cardiovascular risk factors. The association intensity between each conventional and unconventional cardiovascular risk factor with LEAD and coronary hartery disease is an important topic in large epidemiological studies. Among the risk factors evaluated in this study, smoking and hypertension had the highest prevalence followed by chronic kidney disease and hypercholesterolemia.
2. In the study group, only smoking was strongly associated with LEAD. The other risk factors - diabetes mellitus, arterial hypertension, dyslipidemia, chronic kidney disease and C-reactive protein - did not show a statistically significant association with LEAD.

3. In the case of coronary artery disease, diabetes mellitus, arterial hypertension, dyslipidemia and chronic kidney disease have been associated with the presence and severity of coronary lesions; on the other hand, smoking did not show a significant association with coronary stenoses greater than 50%.

2.6 General conclusions

1. Significant coronary artery disease has an increased prevalence in patients with symptomatic peripheral arterial disease.
2. Significant lesions in different segments of the lower extremity arterial axis are differently associated with coronary artery disease.
3. Significant infra-popliteal lesions appear to be the best predictor of coronary heart disease, being associated with significant coronary artery disease, multivascular coronary artery disease and the presence of left main lesions. Therefore, significant infra-popliteal lesions correlate with the presence of significant coronary lesions and also with their severity quantified by the number of vessels affected and by the presence of left main lesions.
4. Significant lesions in the femoral segment are strongly associated with multivascular coronary artery disease, but no direct association with significant coronary artery disease and left main lesions has been found.
5. No significant associations were found between iliac segment lesions and significant multivascular, coronary or left main coronary artery disease.
6. LEAD and coronary artery disease share the same cardiovascular risk factors. The association intensity between each conventional and unconventional cardiovascular risk factor with LEAD and coronary artery disease is an important topic in large epidemiological studies. Among the risk factors evaluated in this study, smoking and hypertension had the highest prevalence followed by chronic kidney disease and hypercholesterolemia.
7. In the study group, only smoking was strongly associated with LEAD. The other risk factors - diabetes mellitus, arterial hypertension, dyslipidemia, chronic kidney disease and C-reactive protein - did not show a statistically significant association with LEAD.
8. The diagnostic approach in the case of direct arteriography was mainly performed by radial approach. The anterograde or retrograde therapeutic approach was individualized and performed at the level of several arteries (brachial artery, common femoral artery, popliteal artery, anterior and posterior tibial arteries).
9. Iliac arteries angioplasty was performed almost exclusively with stent devices.
10. At the femoral level instead, the treatment was individualized, performed either with a stent or with a balloon.
11. The advantage of stent angioplasty was in particular better short and medium term patency, in terms of time to restenosis, compared to balloon angioplasty.
12. Regarding the primary objectives:
    - the restenosis rate at 12 months was, paradoxically, higher in the group of revascularized patients with stent, compared to the group of patients revascularized with balloon.
    - the amputation rate was significantly lower in the groups of patients treated interventionally compared to the group of patients treated with drugs.
13. In the groups of patients treated interventional, patients who, at presentation, had chronic threatening ischemia of the lower extremities (stages III and IV Leriche Fontaine) were followed. At the end of the study, in the medication group, there is an increase in the percentage of cases in stage III or IV versus balloon / stent groups, where stage IIa or stage IIb predominated.

14. Regarding the secondary objectives, the evolution over time of the claudication index, Leriche-Fontaine classification, ankle-brachial index, was significantly better in the stent revascularized patients group, compared to balloon revascularized patients group, respectively the drug-treated patients group.
15. The wire-interwoven self-expanding nitinol stents have a good short and medium term primary patency in the target group, being consistent with the literature.
16. No stent fractures of any kind were found in the devices used for treating patients.
17. More than half of the revascularized patients with flexion stents were revascularized also in other lesions of the arterial axis during the same procedure, highlighting the complexity of the treated cases.
18. Flexion lesions interventional treatment with a dedicated stent implant represent currently a feasible treatment option.

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