VILNIUS UNIVERSITY

Aušrinė Navickienė

THE EVALUATION OF REVASCULARIZATION METHODS FOR TIBIAL ARTERIES IN PATIENTS WITH DIABETES

Summary of doctoral dissertation

Biomedical sciences, medicine (06 B)

Vilnius, 2015

The Dissertation has been prepared at the Vilnius University during the period 2011–2015.

Scientific Supervisor – dr. Gintaras Kalinauskas (Vilnius University, biomedical sciences, medicine – 06B)

Dissertation is defended at the Medical Research Council of Vilnius University.

Chairperson – prof. dr. Janina Tutkuvienė (Vilnius University, biomedical sciences, medicine – 06B).

Members:

prof. habil. dr. Vytautas Jonas Sirvydis (Vilnius University, biomedical sciences, medicine – 06B),

prof. dr. Jolanta Dadonienė (Vilnius University, biomedical sciences, medicine – 06B),

prof. dr. Tomas Poskus (Vilnius University, biomedical sciences, medicine – 06B),

dr. Evaldas Girdauskas (Central Hospital Bad Berka, Germany, biomedical sciences, medicine – 06B).

Dissertation will be defended at the open session of the Medical Research Council at 11.30 on the 11th of December 2015, in the Vilnius University, Faculty of Medicine, Grand Auditorium. Adress: M. K. Ciurlionio 21, Vilnius, Lithuania.

Summary of doctoral dissertation was sent on the 11th of November 2015.

The dissertation can be viewed in the Vilnius University Library and on the website address *www.vu.lt/lt/naujienos/ivykiu-kalendorius.*

VILNIAUS UNIVERSITETAS

Aušrinė Navickienė

CUKRINIU DIABETU SERGANČIŲ LIGONIŲ BLAUZDOS ARTERIJŲ KRAUJOTAKĄ ATKURIANČIŲ METODŲ ĮVERTINIMAS

Daktaro disertacijos santrauka

Biomedicinos mokslai, medicina (06 B)

Vilnius, 2015

Disertacija rengta 2011–2015 metais Vilniaus universitete.

Mokslinis vadovas – dr. Gintaras Kalinauskas (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B)

Disertacija ginama Vilniaus Universiteto Medicinos mokslo krypties taryboje:

Pirmininkė – prof. dr. Janina Tutkuvienė (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B).

Nariai:

prof. habil. dr. Vytautas Jonas Sirvydis (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B).

prof. dr. Jolanta Dadonienė (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B).

prof. dr. Tomas Poškus (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B).

dr. Evaldas Girdauskas (Centrinė ligoninė Bad Berka, Vokietija, biomedicinos mokslai, medicina – 06B).

Disertacija bus ginama viešame Medicinos mokslo krypties tarybos posėdyje 2015 m. gruodžio mėn. 11 d. 11.30 val. Vilniaus universiteto Medicinos fakulteto Didžiojoje auditorijoje. Adresas: M.K. Čiurlionio gatvė 21, Vilnius, Lietuva.

Disertacijos santrauka išsiuntinėta 2015 m. lapkričio 11 d.

Disertaciją galima peržiūrėti Vilniaus universiteto bibliotekoje ir VU interneto svetainėje adresu: *www.vu.lt/lt/naujienos/ivykiu-kalendorius*

CONTENTS

ABBREVIATIONS

ABI	–	Ankle Brachial Index
ACOC / AHA	–	American Heart Association (American College of Cardiology / American Heart Association)
AH	–	Arterial Hypertension
ASP	–	Ankle Systolic Pressure
CAD	–	Coronary Artery Disease
CLI	–	Critical Limb Ischemia
DM	–	Diabetes Mellitus
DSA	–	Digital Subtraction Angiography
ECG	–	Electrocardiogram
FTS	–	Femoral–Tibial Bypass
HDL	–	High–Density Lipoproteins
IBD	–	Ischemic Brain Disease
LDL	–	Low–Density Lipoproteins
LMWH	–	Low Molecular Weight Heparin
M	–	Median
MI	–	Myocardial Infarction
PAD	–	Peripheral Arterial Disease
PTA	–	Percutaneous Transluminal Angioplasty
PTS	–	Popliteal – Tibial Bypass
RF	–	Renal Failure
SD	–	Standard Deviation
TAG	–	Triglycerides
TASC	–	TransAtlantic Inter-Society Consensus
$TcPO^2$	–	Oxygen Partial Pressure
TP	–	Thumb Pressure
VMKL	–	Vilnius City Clinical Hospital
VULSK	–	Vilnius University Hospital Santariskiu Klinikos

1. INTRODUCTION

Diabetes Mellitus (DM) is one of the most pressing and threatening health problems of the twenty-first century. In 2013 the world had a population of 382 million adults affected by the disease. It is forecasted that by the year 2035, this figure will rise to 592 million (1). In Lithuania DM currently affects 5% of the population. Approximately 3500 people die annually from DM in Lithuania. The main causes of death, facilitated by DM are CHD and MI. They are persistent chronic complications of DM, which facilitates early aging, reduces working capacity, causes disability and accelerates mortality. The huge increase in the incidence of the disease is inevitably linked to the growth of frequency of DM complications. Individuals suffering from DM possess 1.5-2.5 times higher risk for symptomatic or asymptomatic PAD, compared to DM-free patients (2). DM is the main non-traumatic cause of lower limb amputations in the world - every 30 seconds a person suffering from diabetes undergoes lower-leg amputation of varying level (2). The main causes of amputation are extremity ulcers and gangrene, which are determined by a number of mechanisms: peripheral neuropathy and autonomic dysfunction, microangiopathy and macroangiopathy in addition to numerous others. It is hoped that the number of DM complications can be prevented by timely diagnosis of the disease, proper glycemic control, early detection of complications and the appropriate treatment. However, epidemiological data shows that globally there currently are 175 million people with diabetes, to whom the proper diagnosis has not been established (3). Critical limb ischemia is usually mistakenly confused with a complication of DM - peripheral nerve damage - neuropathy, especially for patients in the early stages of the disease. For these patients conservative treatment measures of CLI can be applied (2) as opposed to later stages of CLI when often medical treatment is not sufficient surgical interventions are needed, leading to the loss of limb and increased patient's disability.

CLI is the most difficult clinical presentation of peripheral arterial occlusive disease, which can be defined as pain at rest, ulcers or gangrene

due to peripheral arterial occlusive disease. It develops when peripheral arterial occlusive disease affects two or more limb arterial segments and the total efficiency of collateral blood circulation is substantially reduced. CLI treatment in patients with DM, especially with trophic ulcers and infections, is a significant challenge for vascular surgeons. Multidisciplinary treatment, including aggressive revascularisation, can help to prevent major amputations.

For the patients affected by DM typical lesions of crural and popliteal arteries develops. Open surgery, suturing autologous venous graft in the crural or pedal arteries, has been considered the golden standard for revascularization. However, this approach may be limited by the patient's risk of comorbidities, predicted short length of life of the patient or absence of autologous venous graft.

Angioplasty of arteries located below the knee, can lead to good results at a low-grade narrowing of the arteries, especially when there are no major disruptions of foot blood circulation, despite that it often leads to a large number of restenosis. Endovascular technology is more often preferred as opposed to open surgical intervention. Schanzer and Conte recommends endovascular procedure for patients, whose chances of survival are less than two years, it is not possible to use the bypass autologous vein graft, perioperative risk is significantly increased or when the occluded arterial segment is not long (4).

Prior to publication of American Heart Association (American College of Cardiology / American Heart Association) guidelines in 2011 there was no formal consensus and guidelines for treatment of critical limb ischemia. These guidelines, based on BASIL study, summarised that both circulatory recovery techniques are very similar in outcome for patients who were suitable for both endovascular and open surgical technique (5). Meta-analysis of the literature, conducted in 2014, showed that there was no significant difference in clinical outcomes, using endovascular treatment or an open operating revascularisation in patients with CLI. Unfortunately, due to the lack of high quality data, the studies were inconclusive in

recommending to chose open surgery or endovascular treatment, especially for certain specific groups of patients or patients with anatomical variances. Therefore, it remains a major dilemma which method of revascularization is the most suitable for diabetic patients.

In Lithuania, only the open surgery treatment options were researched for patients with DM. The results of this research were published (6). However, no studies have been performed, where a comparison between endovascular and open surgical approaches were analysed for patients with both CLI and DM.

Treatment of patients comorbid with DM and PAD is a significant challenge. Timely and well-chosen treatment can save the limb and reduce disability. Therefore it is necessary to conduct further randomised studies, which would allow designing the treatment algorithm for patients comorbid with DM and PAD.

1.1. Aim and objectives of research

The aim of research:

To evaluate early and late outcomes and affecting factors of tibial angioplasty as opposed to arterial bypass to tibial arteries for diabetic patients.

Objectives:

1. Investigate and evaluate diabetes and critical leg ischemia in patients who underwent tibial angioplasty or bypass surgery, the demographic characteristics of the formation of atherosclerosis enhancing factors and clinical characteristics.
2. Investigate and evaluate peripheral arterial disease diagnostics for diabetic patients.
3. Evaluate early and late outcomes of tibial angioplasty and open surgery in diabetic patients.
4. Assess the factors affecting tibial artery angioplasty and open operations for this population.

5. Determine limb loss risk for diabetic and the disease-free patients in the early and late postoperative periods.
6. Assess patient survival after reconstructive surgery of tibial arteries.

1.2. Novelty and clinical relevance of the research

Up to date, there has been no research in Lithuania, which would analyse diabetic patients with tibial artery reconstructive procedures i.e. bypass surgery and angioplasty, following outcomes of these procedures and comparison of the results with disease-free control group.

Globally this problem has already been analysed, though unfortunately the published results are quite contradictory and there is no agreement, which arterial reconstructive procedures are preferable for this group of patients. In this paper, we analysed and compared treatment outcomes of CLI for patient population with DM and disease-free one.

Performed data analysis proved that in treatment of CLI, diabetes negatively affects bypass functioning and the long-term results of blood-circulation restoration after PTA.

Additionally, analysis of data demonstrated that treating CLI patients with DM, tibial bypass surgery improves blood circulation for a longer period of time rather than PTA.

It was found that DM does not affect patient survival after tibial artery reconstructive surgery.

2. RESEARCH METHODOLOGY

2.1. Location and chronology of research

The research study was carried out in Vilnius University Faculty of Medicine, Vascular Surgery Centre in Cardiovascular Clinical centre located in Vilnius Clinical Hospital (VMKL). In this hospital the first specialised vascular surgery department in Lithuania was created in 1967, it was lead by prof. V. Triponis.

In this department, prior to 1970, first operations of aortic arch branches, visceral arterial reconstruction, autologous venous grafts in the lower leg and foot arteries were performed. In 1983 two sections of Vascular Surgery department and Interventional Radiology Department were created. In Interventional Radiology Department first successful endovascular aortic branches treatment was performed. Endovascular procedures of tibial arteries were performed since 1992. Vascular surgery centre in the period of 1991 to 2015 was led by prof. V. Triponis and Dr. R.Vaitkevičius. Currently the centre is associated with centre of general surgery.

The data was collected in first and second vascular surgery departments of Vilnius City Clinical Hospital since 2010 on January. Clinical data of patients with second type DM for whom reconstructive surgery was conducted - bypasses in the lower leg and foot arteries or tibial arteries endovascular TPA procedures due to CLI.

Research data was collected since 2011. Cutoff point for the study was 1 October 2014. Data concerning patients deaths was revised using Population Register Service of Lithuania.

Permission for biomedical research was issued by Vilnius Regional Biomedical Research Ethics Committee. Permit number - 158200-13-572-167.

2.2. Sample group of patients

In chronological order 234 cases of atherosclerotic CLI of primary tibial open bypass surgery and primary endovascular tibial TPA procedures were registered in the period of 1st of January 2010 to 1st of October 2013.

Sample was divided into two groups:

1) Patients without DM (hereinafter - Group I) – researched controlled group, 124 patients (53.0 % of subjects);
2) Patients with DM (hereinafter - Group II) – researched group of patients, 110 patients (47.0 % of subjects).

Patients' demographic and clinical data – atherosclerosis risk factors, harmful habits, DM control data, indications to perform operations or

endovascular procedures, angiographic data, inlet and outlet connections and PTA methods, ABI, TS and the NFA was recorded.

In the absence of contraindications, all patients following surgery in the early postoperative period were prescribed low-molecular-weight heparin, for outpatient treatment – antiagregants (100 mg of aspirin per day). After endovascular procedures aspirin (100 mg daily) and clopidogrel (75 mg, ie four tablets on the first day and then – 1 tablet per day) was prescribed.

Early and late outcomes of treatment were analysed. The early post-operative period of time - up to 7 days following surgery or endovascular procedures or hospitalization period. Following examination of was conducted patients after 3, 6, 12, 24, 36 months postoperatively. According to the available patient contact information, invitation letters were sent. Patients unable or unwilling to attend were contacted by phone. The data was obtained on all patients.

Beginning of monitoring data – date of surgery or angioplasty.

Monitoring terminated – if:

- the limb was amputated,
- patient died,
- patient refused to be tested,
- the study was cut off

2.3. Methodology of tibial or feet artery bypass and angioplasty

All analysed bypasses and angioplasty procedures for critical leg ischemia were performed below the knee - in the tibial arteries. All bypasses were primary, i.e. patients have not previously undergone any surgical intervention of this nature. Before surgery or endovascular procedure in all cases lower extremity angiography was carried out. Indications to perform arterial reconstructive procedures were based on recommendations of TASC 2007. Type A, B, C cases - endovascular treatment, if possible. Type C or D - bypass surgery. The overall condition of the patients was also assessed, in addition to wound infections, their size and distribution.

Decision which procedure to choose was taken by the treating physician and interventional radiologist. Bypass surgery was performed using autologous vein grafts (inverted or not, after removing venous valves with an instrument) of the femoral or popliteal arteries to form a upper connection of the bypass (bypass end sutured to the artery side) to the tibioperoneal trunk (Truncus tibioperonealis), the anterior tibial artery (a. Tibialis anterior), dorsal foot artery (a. dorsalis pedis), rear foot artery (a. tibialis posterior) or peroneal artery (a. peronea), so as to form the lower bypass connection (bypass sutured end to the side or end of the arteries). Endovascular procedures were performed using local anaesthetic (1% lidocaine solution). The tibial artery stenoses or occlusions were entered with 0.018 to 0.035 inch wire. 2.5-3 mm diameter angioplastic balloons were used for PTA procedure.

PTA procedure was carried out as indicated in at least one, or where possible, two or more tibial arteries - the tibioperoneal trunk, anterior tibial artery, posterior foot artery or peroneal arteries. Intraoperative success is considered to be - if the arterial lumen was expanded up to 80 % of normal artery diameter without arterial dissection or distal embolisation.

2.4. Data assessment methodology before operation and clinical examination oder of the study period

Early postoperative period - 1st day and hospital in-patient stay period after reconstructive procedures. Late postoperative period - within 30 days after the reconstructive procedure. Primary bypass operation or the primary blood circulation restoration (primary patency) after PTA procedure - when examined bypass function, arterial blood circulation after PTA good. There is no additional arterial reconstructive procedures. Large amputation - extremity amputation of tibial or thigh level. Small amputation - amputation of fingers and at the level of transmetatarsal joint

DM has been established, if the plasma glucose level of> 126 mg / dl or after a two-hour blood glucose level> 200 mg / dL after 75 g glucose tolerance test. Or if the DM was established by physician endocrinologist (based on

medical history). Fasting glucose levels may not be sufficiently sensitive to first optional test. Some patients whose fasting glucose levels less than 7.0 mmol / l and, as mentioned, within 2 hours. after the glucose load equal to or greater than 11.1 mmol / l, determined mellitus. Glucose in the test for 2 hours. after exertion is more sensitive and reliable test for diabetes complications and higher risk of cardiovascular disease risk. Glucose level after 2 hours glucose load situated between diabetes (≥ 11.1 mmol / l) and normal level of blood glucose (<7.8 mmol / l) is called impaired glucose tolerance.

For patients with CLI both in the experimental group (diabetes patients) and the comparator group (those without DM), overall condition as assessed by evaluating anamnesis, laboratory test results and objective examination results. Comorbidities and harmful habits were also assessed. Only patients with Type II diabetes were included to the sample group as patients with Type I of DM were excluded due to low sample number.

For the purposes of research two groups of patients were separated:Type II DM, treated with diet and oral medications, and Type II DM, treated with insulin.

Well controlled DM was determined on the basis of glycosylated haemoglobin parameter:

- Well compensated DM - glycosylated haemoglobin (Hb A1) <7 % of total Hb or 29-42 mmol / mol;
- Uncompensated DM - glycosylated haemoglobin (Hb A1)> 7 % of total Hb, or> 42 mmol / mol.

Deep and superficial sensation sensory was tested during standard clinical examination. Surface senses were tested by using a pile and needle, deep senses - tuning-fork. Heart condition was evaluated by a cardiologist consultation, electrocardiograms and cardiac ultrasound (if it was carried out) data. It was rated if a patient had current stable or unstable angina, symptomatic arrhythmias, atrial fibrillation, myocardial infarction and coronary cardiovascular stent implantation or bypass procedure. According to the World Health Organisation criteria, hypertensive disease was diagnosed when systolic blood pressure was more than 140 mmHg

and diastolic was more than 90 mm Hg. It was also evaluated how many medicaments were used to control disease (one, two or more than two).

Cerebrovascular pathology was assessed on the basis of medical history and neck vascular ultrasound data (asymptomatic, but visible using double-scan ultrasound, previous TIA or RIND, previous stroke).

Renal function was evaluated according to laboratory data measuring potassium, urea and creatinine concentration levels in blood and urine. Renal insufficiency was diagnosed and documented by physician nephrologist, if renal function was observed for more than 3 months with abnormal renal function or structure or if the glomerular filtration rate was less than 60 ml / min / 1.73 m2 in renal impairment, or if it was absence.

Laboratory biochemical tests were used to evaluate cholesterol levels in blood and its' distribution of fractions.

Degree of obesity was evaluated and determined. Blood-circulation of the limb was assessed during visual inspection before operating procedure. The patient's limb arterial blood circulation was assessed by clinical examination:

Palpation of communal femoral artery, popliteal artery and feet arteries pulse was conducted;

- Auscultation of lower limb arteries was performed; artery systolic murmur is associated with narrowing of the arteries;
- Duplex ultrasound of lower limb arteries was performed together with ankle pressure measurement; if it was more than 50 mmHg, it was rated as critical leg ischemia;
- The ankle-brachial index measurement was performed;
- Thumb systolic pressure measurement was conducted; if it was less than 30 mmHg, it was rated as the CLI;
- Thumb and brachial indices were calculated

Through examination of ulcers and gangrenous lesions leg tissue trophic was evaluated. Ischemia was rated according to Fontaine classification (stage III - constant pain, Stage IV - gangrene involving a single finger, stage IV B - gangrene that has spread to the foot).

2.5. Research methodology in the postoperative period

Bypasses function and blood circulation recovery after endovascular procedures was registered, evaluated and analysed assessing the early and late outcomes of treatment and patient survival rates after these operations.

Circulatory restoration or improvement was assessed on the basis of pulse palpation, ABI measurement TP measurement, on some occasions arterial ultrasound data. Angiography was performed only in case of a suspicion of bypass thrombosis or restenosis after endovascular procedures. The success of the late postoperative period has been assessed on the basis of:

- Subjective parameters (cessation of persistent pain, no further need to use pain-relieving medicines);
- Objective parameters (limb wound healing after undergone arterial revascularisation).

Patients were treated conservatively after angiographic approval of bypass thrombosis (if there was no possibility of making a second reconstructive surgery due to complex anatomical features or absence of satisfactory autologous vein graft) in addition to the absence of trophic disorders.

Patients were treated conservatively or endovascular procedure was repeated after angiographic approval of restenosis. In case of inability to perform reconstructive procedures and in cases of the spread of gangrene or infection, patients undergone a major limb amputation in the level of the thigh or calf.

3. STATISTICAL DATA ANALYSIS

Statistical analysis was performed using 'Microsoft Excel 2003', and IBM SPSS 'Statistics 23 for Windows' programs. Arithmetic means, standard deviations (SD), minimum and maximum values of quantitative parameter were analysed.

Proportions and confidence intervals of qualitative parameters were calculated. Comparing the differences between the experimental groups

Student's t test for quantitative parameters and $\chi 2$ test for comparison of proportions were applied. In some cases, differences between the proportions were assessed by Fisher's exact test. To determine the statistical reliability $p < 0.05$ significance level was chosen. To evaluate survival, limb preservation, bypass functioning time the standard of Kaplan-Meier method was applied.

4. RESULTS

The study included 234 patients. All of them were treated for critical leg ischemia by open surgical method i.e. bypass to tibial arteries, or endovascular procedure - tibial arterial PTA. Patients were divided into two groups: 1) control group - those patients without DM (hereinafter - Group I), 124 cases (53.0 % of subjects); 2) study group - patients with DM (hereinafter - Group II), 110 cases (47.0 % of subjects). Most of the patients in both groups were men: Group I - 87 (70.2 %), Group II - 67 (60.9 %). DM patients group (Gr. II) had slightly higher proportion of women, but the difference was not statically significant, according to the criterion $\chi 2$, $p = 0.14$.

Table 1. Distribution of test subjects by sex

	I gr.		**II gr.**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Male	87	70,2	67	60,9	154	65,8
Female	37	29,8	43	39,1	80	34,2
Total	124	100,0	110	100,0	234	100,0

The average age in both groups did not differ (by t test, $p = 0.83$). The largest proportional group of subjects in both groups was 71-80 years olds. There was observed a noticeable difference between average age of men and women. Men's avergae age (in both groups combined) was 70.9 years, women's average age (in both groups combined) was 77.8 years.

Table 2. Distribution of test subjects by age

	I gr.	II gr.	Total
N	124	110	234
Average	73,4	73,2	73,3
SD	10,9	9,6	10,3
Min	37	48	37
Max	93	91	93

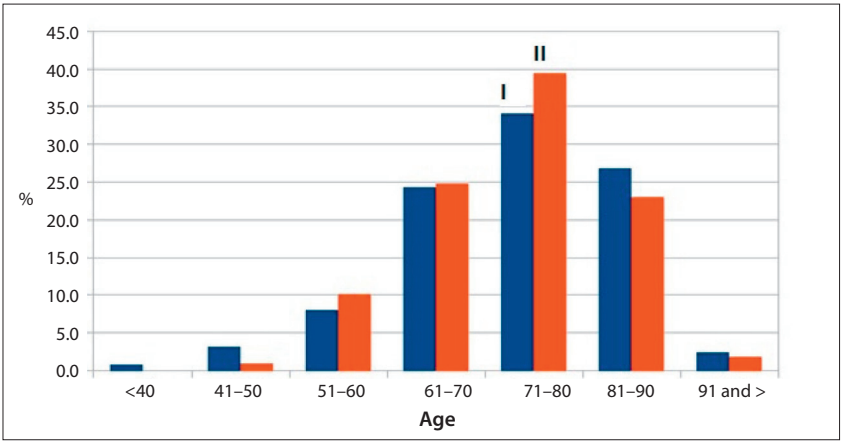

Fig. 1. Comparison of test subject groups by age

121 (51.7 %) of procedures were performed for patients, who smoke. Smokers proportion does not differ between groups (by t test, p = 0.62). Men's group of smokers is significantly larger - 108 of 154 (70.1 %). Group of women smokers is low - only 13 of 80 (16.3 %).

Table 3. The prevalence of smoking among subjects

	I gr.		II gr.		Total	
	N	%	N	%	N	%
Non-smoking	58	46,8	55	50,0	113	48,3
Smoking	66	53,2	55	50,0	121	51,7
Total	124	100,0	110	100,0	234	100,0

4.1. Data on comorbidities

Diabetes patients

110 patients had DM. The study included patients with only type II diabetes. The duration of diabetes was known for 103 patients, for 7 patients the duration of the disease remained unknown. There were 42 patients (40.8%) diagnosed with DM for less than 10 years 42 patients More than 10 years - 61 patients (59.2 %).

Treatment of diabetes mellitus: data was obtained for 105 test subjects, for 5 cases, treatment was not known. Oral anti-diabetic drugs was used to treat 61 patients (58.1 %.) Of 105 patients, insulin was used to treat 44 (41.9 %). Diabetes control was measured according to glycosylated haemoglobin level: the data was known about 107 patients, data was unavailable for 3 patients. Compensated f diabetes was found for 37 subjects (34.6 %), Uncompensated - for 70 subjects (65.4 %), $p < 0.005$.

Patients with cardiac pathology:

Within the study group (DM group) heart disease was found for 96 patients (96 %). Because this group lacked data of 10 cases, calculations were performed on the remaining 100 patients. Within the control study group (Group I) cardiac pathology was found for 117 patients (94.4%). The distribution of the studied groups was evaluated by chi-test, $p = 0.57$.

The higher incidence of cardiac disease was observed in groups of older patients:

- Average age of patients with no-cardiac pathology - 69.6 years;
- Cardiac ischemia observed in ECG - 72.2 years;
- Stable angina pectoris - 73.6 years;
- Unstable angina pectoris - 75.3 years.

Table 4. The comparison of the incidence of cardiac disease

	I gr		II gr		Total	
	n	**%**	**n**	**%**	**n**	**%**
None	7	5,6	4	4,0	11	4,9
Ischaemia in ECG	40	32,3	25	25,0	65	26,0
Stable angina	50	40,3	45	45,0	95	42,4
Unstable angina	27	21,8	26	26,0	53	23,7
Atrial fibrilation	19	15,3	11	10,0	30	13,4
Total	**124**	**100,0**	**100**	**100,0**	**224**	**100,0**

Hypertensive disease :

Hypertensive disease was found for 213 patients (91.4%) of 233 (one case known):

- Group I - 107 out of 124 subjects had it (86.3%);
- Group II - 106 of the 109 subjects had it (97.2%).

Despite the high general morbidity, on this instance there is a significant difference between groups (Fisher's exact test, p = 0.004).

The incidence of cerebrovascular diseases:

Cerebrovascular pathology within the study group (DM group) was found for 69 patients (62, 8%) in the control study group - for 65 patients (52.4%). The distribution within the two groups was evaluated by $\chi 2$ test, p = 0.16 was obtained.

Table 5. The comparison of the incidence of cerebrovascular disease

	1 gr		2 gr		Total	
	n	**%**	**n**	**%**	**n**	**%**
None	59	47,6	41	37,3	**100**	**42,7**
Asymptomatic	13	10,5	22	20,0	**35**	**15,0**
TIA or RIND	33	26,6	28	25,5	**61**	**26,1**
Previous stroke	19	15,3	19	17,3	**38**	**16,2**
Total	**124**	**100,0**	**100**	**100,0**	**224**	**100,0**

Digestive system diseases (gastric or duodenal ulcers, erosions, inflammation, gall bladder stones, pancreatitis). A total of 85 (37.3%) of 228 patients (some cases unknown) suffered from digestive system diseases: Group I - 39 of the 121 subjects (32.2%); Group II - 46 of the 107 subjects (43.0%). A higher percentage of patients with digestive diseases was observed in the DM group, but the difference is not statistically significant ($\chi 2$ criterion under $p = 0.09$).

Respiratory diseases (bronchitis, pneumonia, chronic obstructive pulmonary disease) A total of 61 (26.6%) of 229 patients (some cases are unknown) were diagnosed with respiratory diseases: Group I - 31 of 123 (25.2%); Group II - 30 of the 106 subjects (28.3%). The difference between the groups is not statistically significant $p > 0.05$.

Urinary disorders (cystitis, urethritis, kidney stones) A total of 76 (33.0%) of 230 patients (some cases unknown) had urinary system diseases: Group I - 42 of the 122 subjects (34.4%); Group II - 34 of the 108 subjects (31.4%). The difference between the groups is not statistically significant $p > 0.05$. Only 7 patients with a history of renal insufficiency were on dialysis. All of them there in DM group.

The data on obesity was lacking on about 40 cases. Group I - 33 of the 106 subjects (31.1%, which is slightly less than one-third); Group II - 51 of the 88 research (58.0%, well over half). There was a significant difference between the two groups ($\chi 2$ criterion under $p = 0.0002$). Obesity is strongly associated with female gender: 42 (33.1%) of 127 men are obese; 42 (62.7%) out of 67 women are obese. This is a general epidemiological problem.

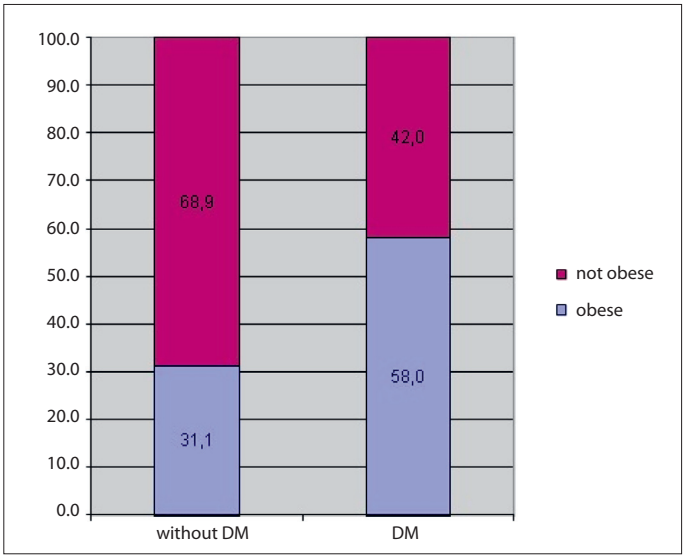

Fig. 2. The comparison of incidence of obesity

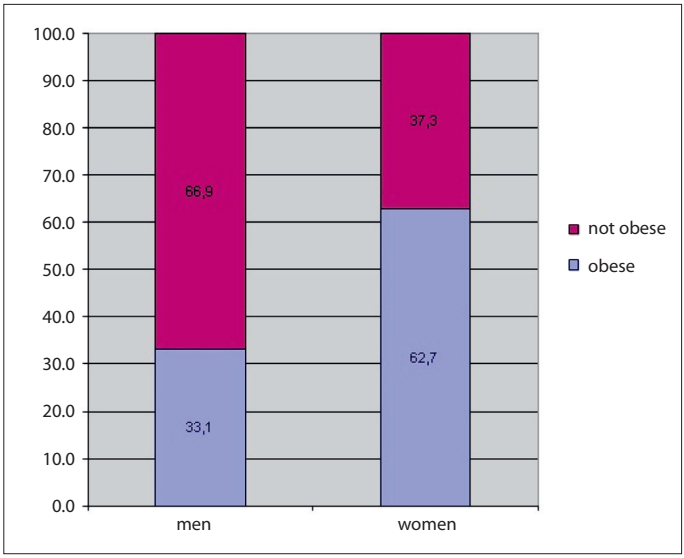

Fig. 3. Distribution of obesity according to sex

Table 6. The comparison of cholesterol rates

	I gr.	**II gr.**	**Total**
N	84	86	170
Average	6,13	6,36	6,25
SD	1,25	1,33	1,29
Min	3,65	3,90	3,65
Max	8,60	8,90	8,90

The difference between the groups is not significant (by t test), p = 0.25.

Table 7. The comparison of the cholesterol fractions indicators (LDL cholesterol)

	I gr.	**II gr.**	**Total**
N	84	87	171
Average	3,36	3,52	3,45
SD	1,02	0,99	1,00
Min	0,80	1,60	0,80
Max	6,10	5,30	6,10

The difference between the groups is not significant (by t test), p = 0.30.

Table 8. The comparison of the cholesterol fractions indicators (HDL cholesterol)

	I gr.	**II gr.**	**Total**
N	82	82	164
Average	0,99	0,99	0,99
SD	0,38	0,37	0,37
Min	0,49	0,60	0,49
Max	3,40	2,40	3,40

The difference between the groups is not significant (by t test), p = 0.96.

Table 9. The comparison of the cholesterol fractions indicators (TAG)

	I gr.	II gr.	Total
N	82	82	164
Average	2,09	2,15	2,12
SD	0,66	0,71	0,69
Min	0,74	0,80	0,74
Max	3,80	3,40	3,80

The difference between the groups is not significant (by t test), p = 0,55.

4.2. Limb ischemia staging

The greater part of both the test and the comparison group of patients were treated with surgery or endovascular procedures at stage IV ischemia - in total 140 cases (61, 7%) (according to $\chi 2$ test, $p < 0.05$).

Within Group I there was no data about one patient's ischemia stage, within Group II for 6 patients. Within DM group (Gr. II) there were significantly more procedures performed at stage IV ischemia (by $\chi 2$ test, $p < 0.05$).

Table 10. Comparison of experimental groups according to Fontaine classification of limb ischemia stage

	III stage of ischaemia		IV stage of ischaemia	
	n	**%**	**n**	**%**
I gr	51	41,5	72	58,5
II gr	36	34,6	68	65,4
Total	**87**	**38,3**	**140**	61,7

4.3. Wound infection

There were 81 (57.9%) total bacterial culture-confirmed cases of wound infection of 140 (with ulcers). Significant difference between the groups was observed, as the DM group (Gr. II) was significantly more affected by cases of infection, $p < 0.01$ (by $\chi 2$ test).

Table 11. The comparison of wound infection cases, $p < 0,01$ (by $\chi 2$ testą).

	Confirmed infection		**No infection**	
	n	**%**	**n**	**%**
I gr	34	47,2	38	52,8
II gr	47	69,1	21	30,9
Total	**81**	**57,9**	**59**	42,1

The level of limb blood circulation reduction was measured using the ankle-brachial index, excluding those patients for whom ABI was not informative or not measured. Averages among groups are very similar, according to t-test, $p = 0.72$. But it was noted that ABI was more uninformative within the study group (Group II).

Table 12. The comparison of ABI measurement

	I gr	**II gr**	**Total**
N	99	59	158
Average	**0,36**	**0,35**	**0,36**
SD	0,18	0,20	0,19
min	0,00	0,00	0,00
max	0,79	0,77	0,79

For patients for whom ABI was non-informative, thumb pressure was measured:

Within Group I for 50 (87.7%) of the 57 patients TP was less than 30;

Within Group II for 65 (86.7%) of the 75 patients TP was less than 30

Averages were assessed by t-test, there was no significant difference, $p = 0.30$.

Table 13. The comparison of TP measurement

	I gr	**II gr**	**Total**
N	57	75	132
Average	**0,13**	**0,16**	**0,15**
SD	0,13	0,13	0,13
min	0,00	0,00	0,00
max	0,34	0,42	0,72

4.4. Sensation (superficial and deep)

186 cases of data were collected (93 - Group I, 93 - Group II).

DM group of patients was significantly affected by loss of surface ($p < 0.005$) and deep sensations ($p < 0.005$).

Table 14. The comparison of superficial and deep sensory indicators

	Superficial sensation is satisfactory		Superficial sensation is distorted		Deep sensation is satisfactory		Deep sensation is distorted	
	n	%	n	%	n	%	n	%
I gr	83	89,2	10	10,8	86	92,5	7	7,5
II gr	33	35,5	60	64,5	59	63,4	34	36,6
Total	116	62,4	70	37,4	145	78	41	22,0

4.5. Angiographic data

Complete arterial occlusion located below the knee artery was identified for 199 of the 234 subjects (85.0%). The number of the occluded arteries varied from 1 to 5 per patient.

Within groups, distribution of occlusion is similar (difference was insignificant, $p = 0.34$)

Group I - 108 out of 124 subjects (87.1%);

Group II - 91 out of 110 subjects (82.7%).

Popliteal artery below the knee (AP) - 84 cases (48 and 36 cases);

Anterior tibial artery (ATA) - 123 cases (63 and 60);

Posterior tibial artery (ATP) - 136 cases (67 and 69);

Peroneal artery (A per.) - 76 cases (37 and 39);

Tibioperoneal trunk (tr.tibioperonealis) - 17 cases (12 and 5).

Table 15. Distribution of occluded tibial arteries

	n	**%**
1 artery	49	24,6
2 arteries	51	25,6
3 arteries	51	25,6
4 arteries	40	20,1
5 arteries	8	4,0
Total	**199**	**100,0**

Arterial narrowing (stenosis) in total was identified for 167 cases out of 234 (71.4%). Within groups, the situation is similar (difference was insignificant, p = 088):

Group I - 89 cases out of 124 (71.8%);

Group II - 78 cases out of 110 (70.9%).

AP - 43 cases (24 and 19);

ATA - 76 cases (43 and 33);

ATP - 45 cases (25, 20);

APE - 51 case (29 and 22);

TTP (Tr. Tibioperonealis) - 22 cases (8 and 14).

Table 16. Distribution of stenosed tibial arteries

	n	**%**
1 artery	68	40,7
2 arteries	51	30,5
3 arteries	40	24,0
4 arteries	6	3,6
5 arteries	2	1,2
Total	**167**	**100,0**

4.6. Methodology of operations

In total 111 bypass operations of the arteries below the knee and 123 tibial artery PTA procedures (47.4% and 52.6%) were performed.

Distribution within groups of types of operations was very similar:

Group I - respectively 60 and 64 cases (48.4 and 51.6%);

Group II - respectively 51 and 59 cases (46.4 and 53.6%).

In 9 cases even after bypass surgery a second operation was performed of which:

- 5 endarterectomies (4 in the first group, 1 in the second group);
- 4 PTA procedures all from the second group.

4.7. The following data is given on the first operation

A small trend is noticeable - the type of operation is associated with the patient's sex. Within both groups it was noted that for men (154 cases) 80 bypass operations and 74 PTA (51.9% and 48.1%) were performed, in contrast to women when PTA surgery was more frequent- bypass 31 and 49 of the PTA (respectively 38.7% and 61, 3%).

The significance was assessed by $\chi 2$ test, P = 0.055, which is already close to the statistical significance threshold.

Type of operation is not associated with the patients' age. The average patient age when undertaking bypass operation was 72.8 years, and for the PTA average age was 73.7 years. The difference according to t test was insignificant, p = 048.

The type of surgical procedures by type of ischemic phase was compared. According to $\chi 2$ test, p = 0.35 there was no difference (i.e. there was no link between the presence of ulcers and operation type).

Table 17. Group I subjects distribution by type of surgical procedure performed

	Ulcers are present		**No ulceration**	
	n	**%**	**n**	**%**
Bypass	27	52,9	32	44,4
PTA	24	47,1	40	55,6
Total	**51**	**100,0**	**72**	**100,0**

Table 18. Distribution of subjects according to the type of surgical procedure performed within Group II (DM)

	No ulcers		Ulceration	
	n	**%**	**n**	**%**
Bypass	16	44,4	32	47,1
PTA	20	55,6	36	52,9
Total	**36**	**100,0**	**68**	**100,0**

According to $\chi 2$ test, $p = 0.80$ there was no difference.

Group I (those patients without DM)

For almost all of the cases autologous vein graft was sutured- 57 out of 60 cases (in one case it was not indicated, in one case PTFE prosthesis was used, in one case - composite shunt).

Variances of autologous vein grafts:

- 31 reversed,
- 18 unreversed,
- 1 stated in situ
- 7 nothing was stated.

Group II (DM) In 51 cases, autologous vein graft was sutured in 49 cases (in one case indicated type of suturing was not indicated, in one case - composite shunt).

Variances of autologous vein grafts:

- 28 reversed,
- 10 reversed only with degraded valves
- 7 referred to in situ
- 4 no additional information given

Localisation of proximal and distal junctures.

It was noted that in Group II (DM) proximal anastomosis was located more often in the popliteal artery (Group I 18.6%, Group II - 33.3% of cases), though this trend is statistically unreliable according to $\chi 2$ test, $P = 0.08$.

Table 19. Comparison of experimental groups by bypass proximal anastomosis localisation

Artery	I gr		II gr	
	n	%	n	%
AFC	7	12,3	5	9,8
AFS	33	57,9	21	41,2
APF	8	14,0	8	15,7
AP	12	21,1	17	33,3
Total	57		51	

Table 20. Comparison of experimental groups by bypass distal anastomosis localisation

Artery	I gr		II gr	
	n	%	n	%
ATP	15	25,4	12	23,5
ATA	18	30,5	14	27,5
A. peronea	11	18,6	14	27,5
TTP	10	16,9	4	7,8
ADP	5	8,5	7	13,7
Total	59		51	

4.8. Technique of percutaneous transluminal angioplasty

PTCA procedures were carried out for 123 patients: 64 procedures were in Group I, in Group II there were 59 procedures. It is not possible to aggregate and calculate the percentage because of the different figure of arteries treated using endovascular method. The distribution of the arteries, where PTA was conducted within Group I:

- 19 cases: 1 artery (29.2%),
- 36 cases: 2 arteries (55.4%),
- 8 caes: 3 arteries (12.3%),
- 2 cases: 4 arteries (3.1%).

The distribution of the arteries, where PTA was conducted within Group II:

- 21 cases: 1 artery (33.9%, calculated from 62 cases)
- 28 cases: 2 arteries (45.2%),
- 10 cases: 3 arteries (16.1%),
- 2 cases: 4 arteries (3.2%),
- 1 case: 5 arteries (1.6%),
- 1 case: number of arteries was not indicated

Table 21. Comparison of experimental groups localisation of PTA in tibial arteries

Artery	I gr	II gr
AP	17	17
TTP	13	12
ATP	24	24
ATA	28	33
A. peronea	24	13

4.9. Early postoperative results

There was no statistically significant difference in early postoperative results after bypass surgery and after endovascular procedures within both groups of tested patients. In early postoperative period the primary patency rate in open surgery and PTA groups was in the DM group 99.0 ± 0.1% of the patients, for the disease free group it was 99.1 ± 0.9%, p> 0.05. Limbs were salvaged in DM group for 98.1 ± 0.1% of the patients, for the disease free group it was - 97.4 ± 0.1%, p> 0.05. In the early postoperative period, significantly more limbs were saved for patients with diabetes, whose diabetes was compensated as opposed to patients, who had uncompensated diabetes. Blood circulation restoration and preservation of the limb for DM patients was evaluated comparing patients with and without neuropathy.

Statistical differences were observed.

Primary patency was 96.8 ± 0.2% of the patients with neuropathy, and to 100 ± 0.0% of the patients, whose senses were not distorted, p> 0.05.

Limbs were saved for 98.4 ± 0.1% of the patients with neuropathy, and 96.4 ± 0.1% of the patients, whose senses are not distorted, p> 0.05.

Primary patency for compensated DM patients in 97.1 ± 2.8% of cases, for uncompensated DM it was 99.9 ± 0.01% of patients, p <0.05.

DM compensated limb salvage group of 100 ± 0.0%, uncompensated - 97.0 ± 0.2% of patients, p < 0.05.

Blood circulation restoration and preservation of the limb was evaluated according to gender. In the early postoperative period, there were performed significantly more amputations for women rather than men.

For men primary patency was 99.2 ± 0.08% of cases, for women - 98.7 ± 0.1%, p> 0.05. Men limbs were saved 98.6 ± 0.1 of cases, for women - 96.2 ± 0.2%, p <0.05.

Blood circulation restoration and preservation of the limb, was compared for smokers and non-smokers. Statistical differences were found. Primary patency 99.8 ± 0.01% of smokers and 99.9 ± 0.01 for non-smokers, p> 0.05, respectively limbs were saved 99.1 ± 0.01% and 99.5 ± 0.04 of cases, p> 0.05.

4.10.Late postoperative results

Within the test group 51 tibial artery bypasses and 59 PTA tibial procedures were performed. In the control group 60 bypass graft operations in tibial artery and 61 PTA tibial procedures were performed. All procedures were performed in order to improve limb arterial blood circulatio . The total of the two procedures cumulative primary patency rate (bypass surgery and PTA) within the test group (DM group) after 1 and 2 years was (mean ± standard deviation) M ± SD: 77.9 ± 4.4% and 27.5 ± 5.4%. In the control study group after 1 and 2 years it was M ± SD: 84.6 ± 3.7% and 34.7 ± 5.2%. There was no statistically significant difference, log rank test p > 0.05 (Fig. 4).

Cumulative restoration of blood circulation was compared among the two subject groups taking in notice one of the main factor contributing to the progression of atherosclerosis - smoking.

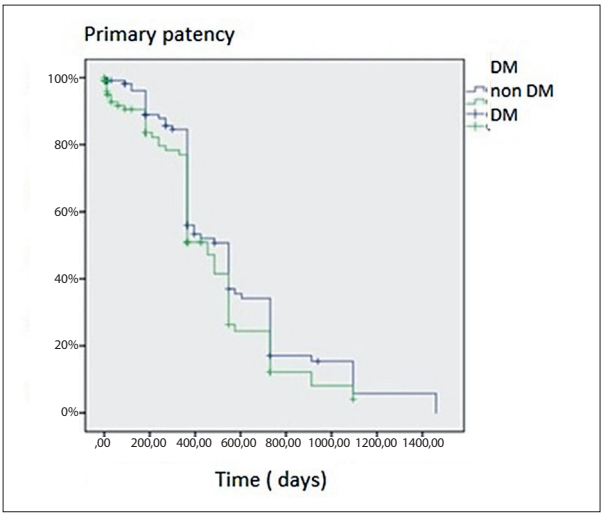

Fig. 4. Kaplan-Meier- table analysis of cumulative primary patency after tibial artery reconstructive surgery for DM and non-DM patient groups

Within the DM group there were 51 smokers, after 1 and 2 years cumulative primary patency was M ± SD: 78.1 ± 4.2%, 35.2 ± 5.4%, log rank test $p > 0.05$. Within the control group there were 62 smokers. Primary patency after 1 and 2 years was M ± SD: 74.8 ± 3.7% 27.3 ± 5.2%, log rank test $p = 0.07$.

Influence of smoking within control group was close to being statistically reliable. In DM test group, it had no statistically significant influence.

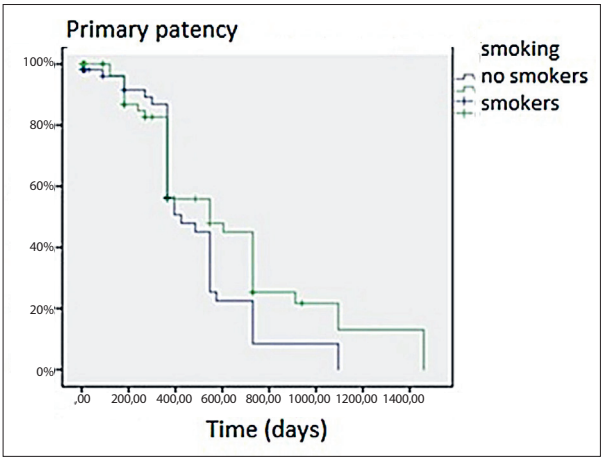

Fig. 5. Kaplan-Meier- table analysis of cumulative primary patency after tibial artery reconstructive surgery within DM group as affected by smoking of patients

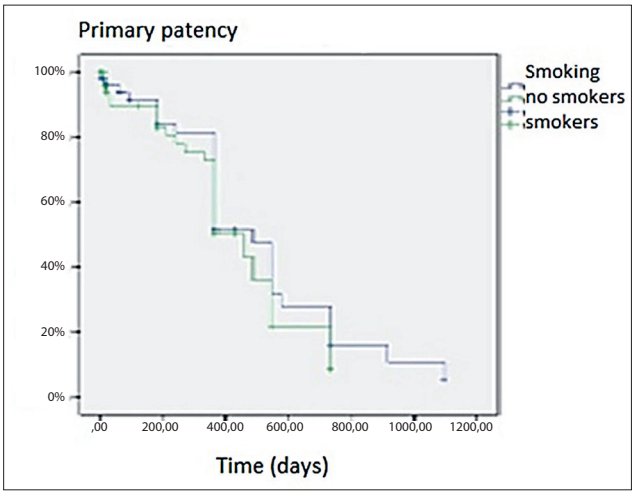

Fig. 6. Kaplan-Meier- table analysis of cumulative primary patency after tibial artery reconstructive surgery within control group as affected by smoking of patients

Within the test DM group after 2 years limbs were saved for 76.5 ± 4.7% of smokers, within control group, it was 81.0 ± 3.4% of smokers. In terms of the impact of smoking, there was no statistically reliable significance, log rank test $p > 0.05$ (Fig. 7 and Fig. 8).

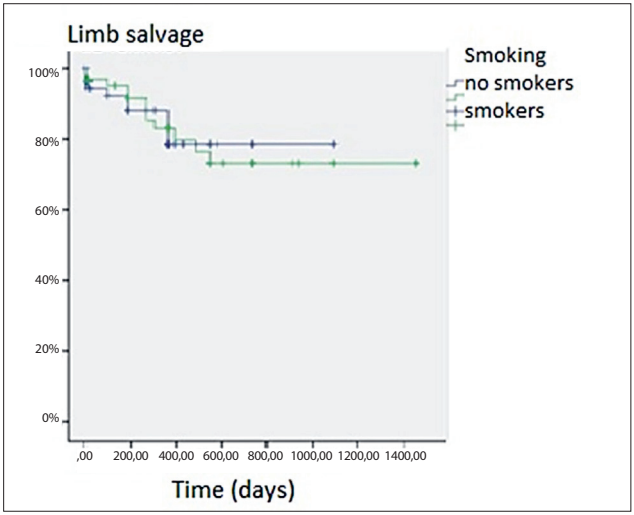

Fig. 7. Kaplan-Meier- table analysis of cumulative limb salvage after tibial artery reconstructive surgery within test DM group as affected by smoking of patients

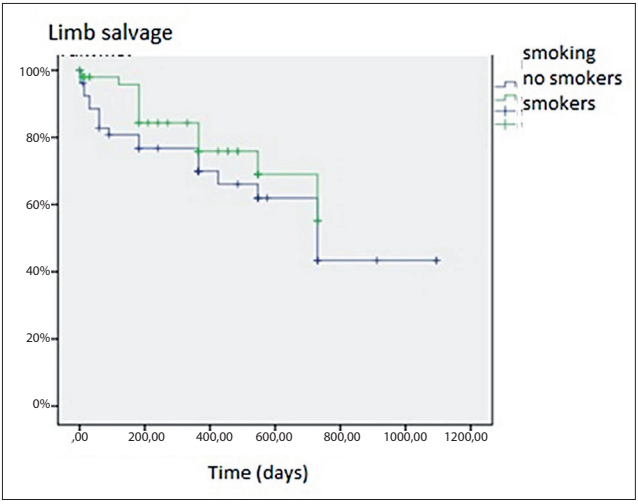

Fig. 8. Kaplan-Meier-table analysis of cumulative limb salvage after tibial artery reconstructive surgery within control group as affected by smoking of patients

Total cumulative primary bypass patency within test DM group after 1 and 2 years M ± SD: 62.7 ± 6.7%, 45.8 ± 4.4%, within control group after 1 and 2 years M ± SD: 66.4 ± 4 , 9%, 58.5 ± 6.4%, log rank test $p > 0.05$ (Fig. 9).

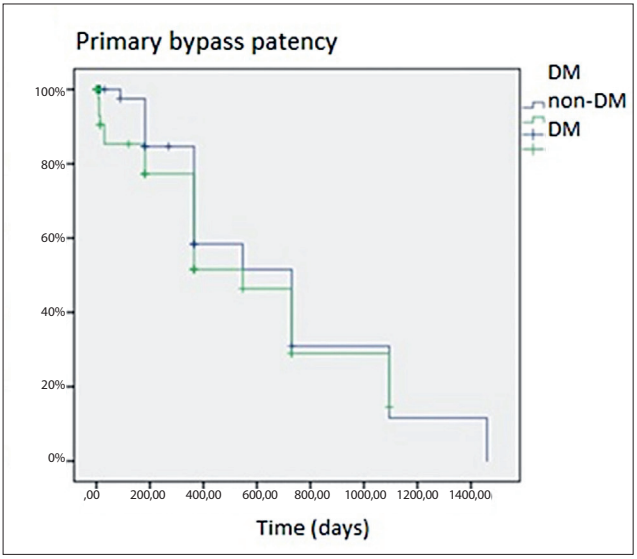

Fig. 9. Kaplan-Meier-table analysis of total cumulative primary bypass patency within both test and control groups

Total cumulative primary PTA patency within test DM group after 1 and 2 years M ± SD: 51.1 ± 4.7% and 20.9 ± 4.3%, within control group - by 59.9 ± 5.2%, 31 9 ± 5.4%, log rank test p > 0.05 (Fig. 10).

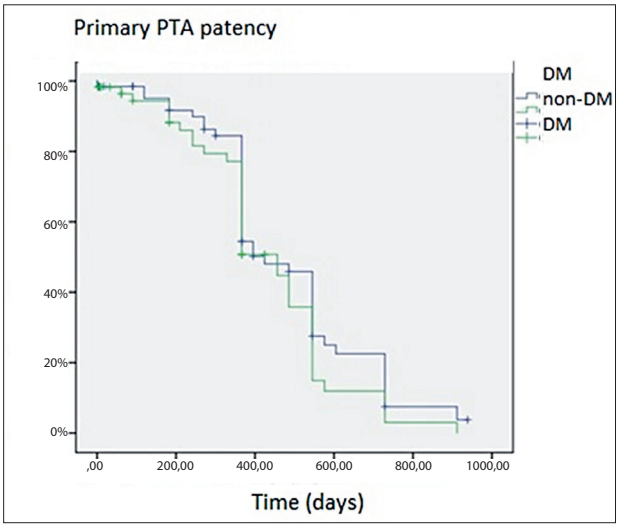

Fig. 10. Kaplan-Meier-table analysis of total cumulative primary PTA patency within both test and control groups

Cumulative limb salvage after bypass operations within the DM group after 1 and 2 years was M ± SD: 79.8 ± 4.1% and 63.5 ± 5.9%, within control group - by 86.5 ± 3.4% and 74, 5 ± 4.9%, log rank test, p <0.05.

Within test DM group there were performed statistically significantly more and earlier amputations than in the control study group (Fig. 11).

Cumulative limb salvage after PTA procedure within test DM group after 1 and 2 years was M ± SD: 84 ± 6.4%, 75.0 ± 4.9%, within control group it was 87.7 ± 7.4% and 81, 3 ± 4.7%, log rank test p > 0.05. The statistical reliability of the results was not found (Fig. 12).

Cumulative primary bypass patency was evaluated according to the duration of DM morbidity. DM patients were divided into two groups: First group was when patients had DM for more than 10 years and second one was, when patients had DM for less than 10 years.

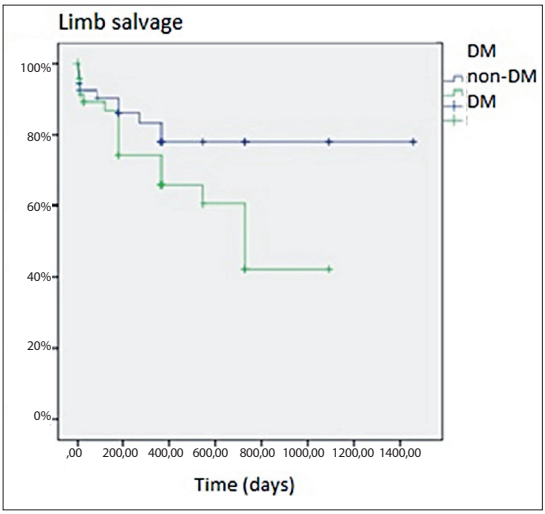

Fig. 11. Kaplan-Meier- table analysis of cumulative limb salvage after bypass operations within both test DM and control groups

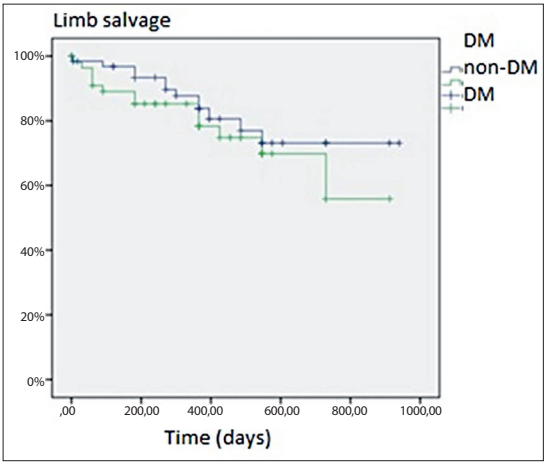

Fig 12. Kaplan-Meier-table analysis of cumulative limb salvage after PTA procedure within test DM and control groups

DM for <10 years of cumulative primary bypass patency after 1 and 2 years M ± SD: 67 ± 13% and 27 ± 15%. In group of DM> 10 years it was 29% ± 13 and 29 ± 13%, log rank test $p > 0.05$ (Fig. 13).

Patients with DM for <10 years cumulative primary PTA patency after 1 and 2 years was M ± SD: 14 ± 9.0% and ± 0.0 0,0%, within uncompensated DM group - respectively 19 ± 8.0% and 0.0 ± 0.0%, log rank test, p > 0.05 (Fig. 14).

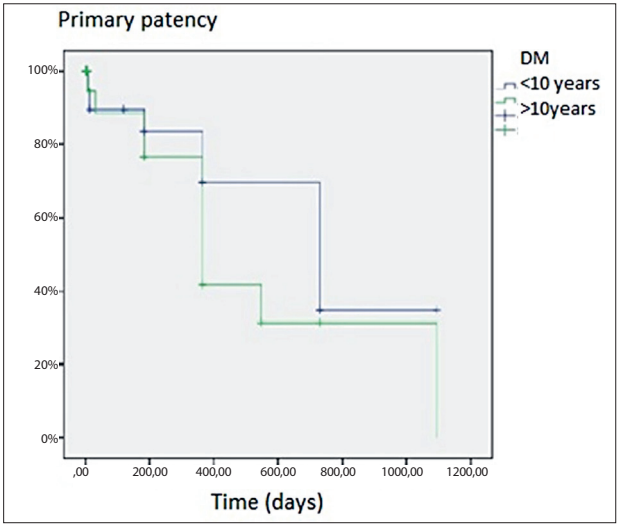

Fig. 13. Kaplan-Meier- table analysis of total cumulative primary bypass patency depending on duration of DM morbidity

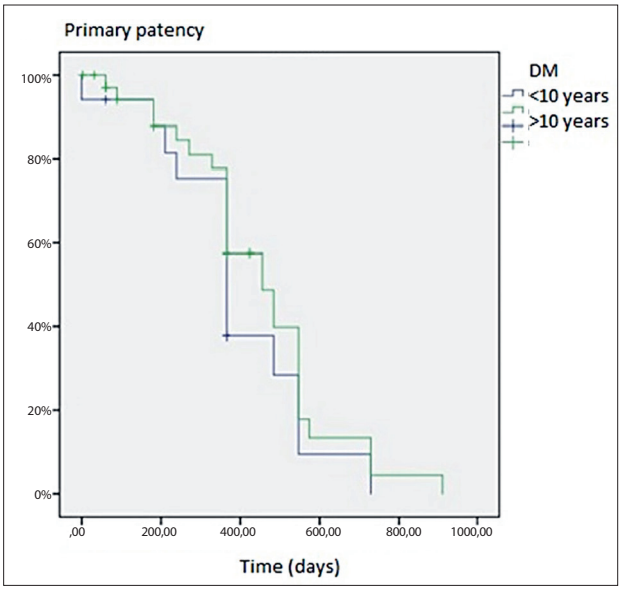

Fig. 14. Kaplan-Meier- table analysis of total cumulative primary PTA patency after PTA depending on duration of DM morbidity

Cumulative limb salvage after bypass operations within DM <10 group after 1 and 2 years M ± SD: 62 ± 12% and 49 ± 15%, within DM> 10 years group - respectively 57 ± 16% and 19 ± 16%, log rank test p > 0.05. There is no statistical difference between groups (Fig. 15).

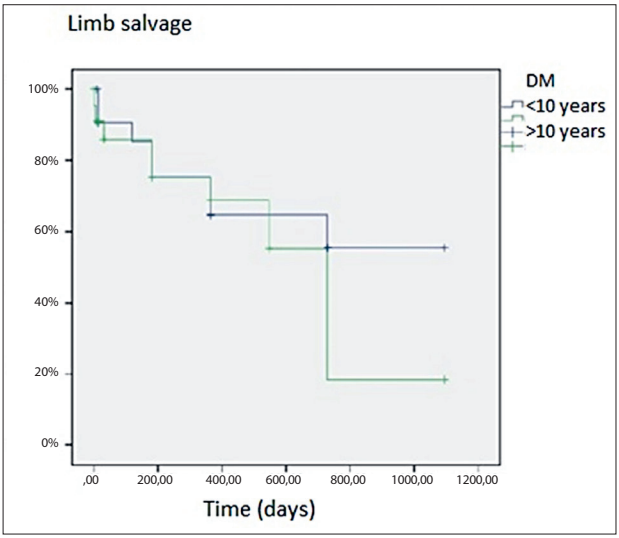

Fig. 15. Kaplan-Meier- table analysis of cumulative limb salvage after bypass operations depending on the duration of DM morbidity

Cumulative limb salvage after PTA procedure within DM <10 age group after 1 and 2 years M ± SD: 82 ± 12% and 27 ± 32%, within DM> 10 years group - by 61 ± 10% and 61 ± 10%, log rank test p> 0.05. Statistically reliability was not found (Fig. 16).

Cumulative bypass functioning was compared for patients diagnosed with compensated and uncompensated DM.

In case of compensated DM cumulative primary bypass patency after 1 and 2 years was M ± SD: 72.7 ± 7.8% and 33.7 ± 5.8%, in case of uncompensated DM group it was 82.3 ± 5.1% and 23.1 ± 6.7%, log rank test p > 0.05 (Fig. 17).

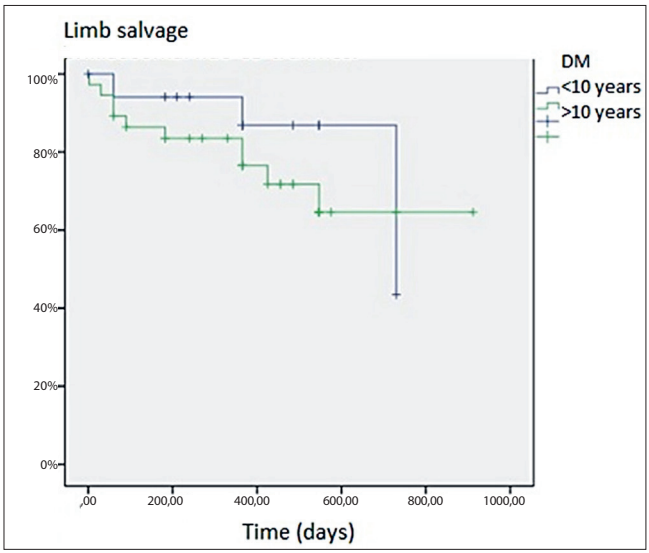

Fig. 16. Kaplan-Meier- table analysis of cumulative limb salvage after PTA procedure depending on the duration of DM morbidity

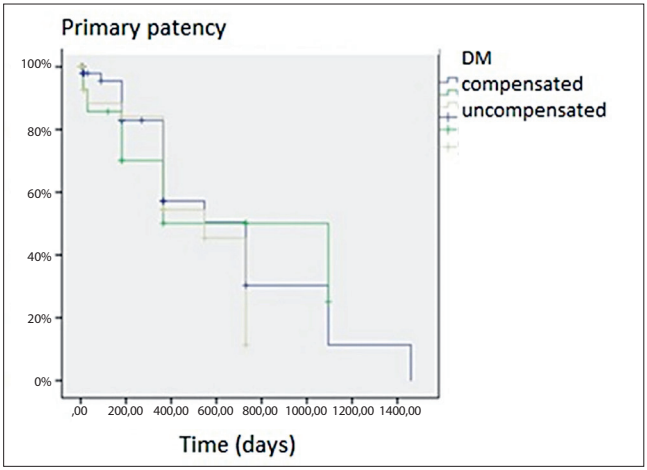

Fig. 17. Kaplan-Meier-table analysis of total cumulative primary bypass patency depending on the control of DM

In case of compensated DM, the cumulative primary PTA patency after 1 and 2 years was M ± SD: 85.7 ± 6.7% and 44.3 ± 5.7%, in case of uncompensated DM group it was 79.4 ± 4.7% 39 1 ± 4.7%, log rank test $p > 0.05$ (Fig. 18).

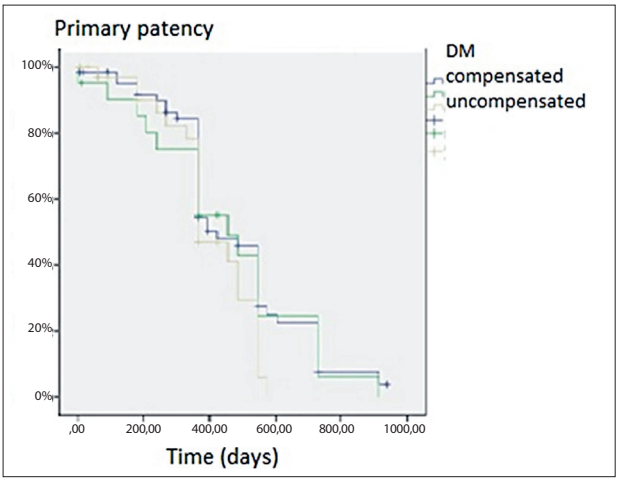

Fig. 18. Kaplan-Meier- table analysis of total cumulative primary PTA patency depending on the DM control

Cumulative limb salvage after bypass operations for compensated DM group after 1 and 2 years was M ± SD: 74.4 ± 3.4% and 68.8 ± 5.4%, for uncompensated DM group it was 69.1 ± 4.2% 59.4 ± 4.9%, log rank test $p > 0.05$. There was no statistical difference between groups (Fig. 19).

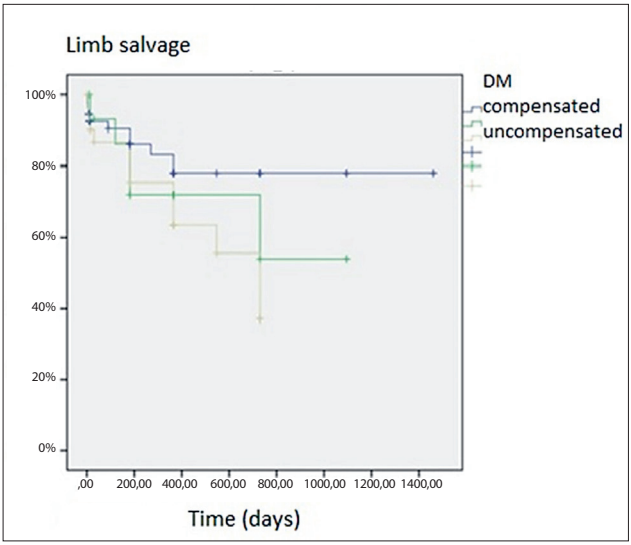

Fig. 19. Kaplan-Meier- table analysis of total cumulative limb salvage after bypass surgery, depending on the control of DM

Cumulative limb salvage after PTA procedure for compensated DM group after 1 and 2 years was M ± SD: 99.8 ± 0.2% and 96.0 ± 4.7%, for uncompensated DM group it was 77.2 ± 5.2% and 61.1 ± 5.4%, log rank test, p <0.05. It was observed that more limbs were saved in compensated DM group (Fig. 20).

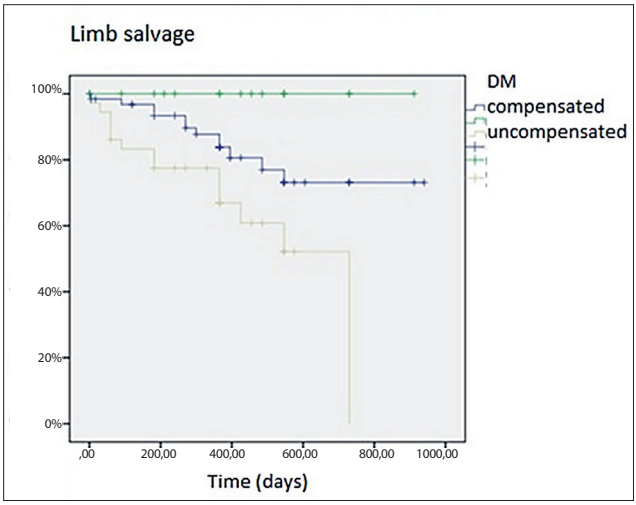

Fig. 20. Kaplan-Meier- table analysis of total cumulative limb salvage after PTA, depending on the DM control

Restoration of cumulative blood flow was assessed breaking down DM patients into two groups - with and without neuropathy.

The group of DM patients with neuropathy cumulative primary bypass patency after 1 and 2 years was M ± SD: 78.9 ± 5.4% and 43.7 ± 6.7%, for patients with no neuropathy it was respectively 83.6 ± 3.8% and 33, 1 ± 5.1%, log rank test p > 0.05. The statistical reliability of the difference of results was not found (Fig. 21).

In case of neuropathy, cumulative primary PTA patency after 1 and 2 years was M ± SD: 72.7 ± 6.4% and 64.7 ± 5.4%, without neuropathy it was respectively, 84.7 ± 4.5% and 74.3 ± 3.4%, log rank test p < 0.05. It was observed that statistically significantly blood flow restoration results after PTA were better in the absence of neuropathy (Fig.22).

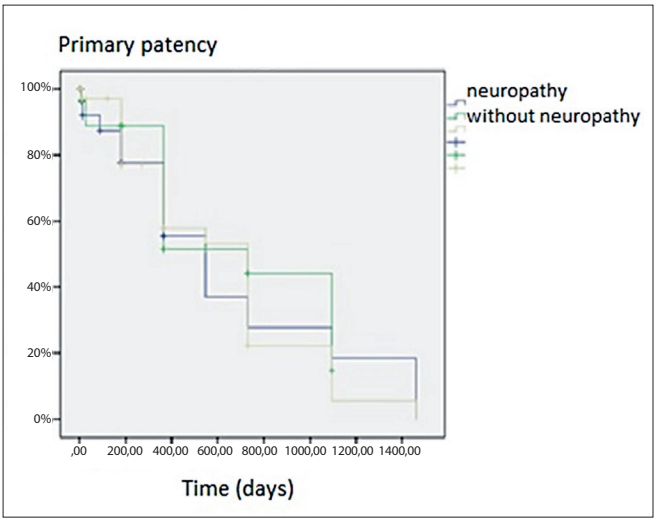

Fig. 21. Kaplan-Meier-table analysis of total cumulative primary bypass patency depending on the presence of neuropathy

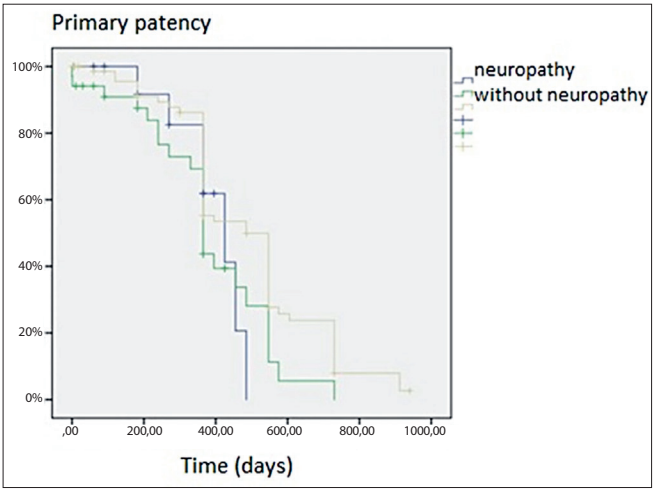

Fig. 22. Kaplan-Meier-table analysis of total cumulative primary PTA patency depending on the presence of neuropathy

Cumulative limb salvage after bypass operations for patients with neuropathy after 1 and 2 years was M ± SD: 81.2 ± 2.6% and 72.7 ± 4.7%, for patients with no neuropathy it was respectively 84.6 ± 4.2% and 71.8 ± 6.1%, log rank test $p > 0.05$. There was no statistically reliable difference between groups (Fig. 23).

Cumulative limb salvage after PTA procedure for patients with neuropathy after 1 and 2 years M ± SD: 84, 4 ± 4.6% and 73.5 ± 3.7%, for patients with no neuropathy it was respectively 89.8 ± 5.1% and 84.7 ± 6.2%, log rank test, p <0.05. Significantly more limbs were saved and amputation was performed later for the group of patients without neuropathy (Fig. 24).

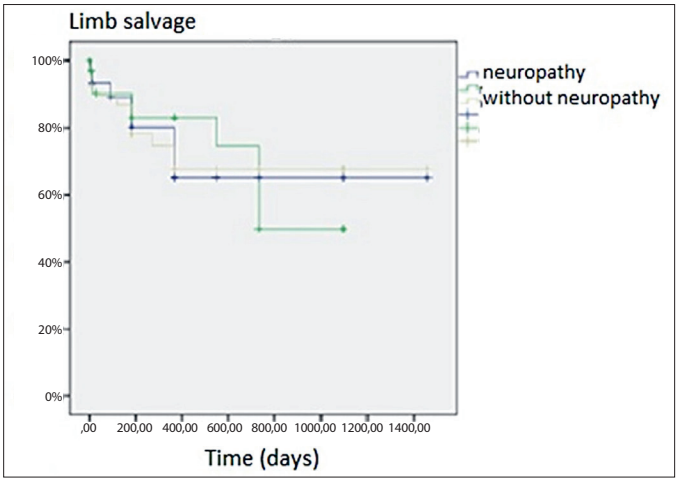

Fig. 23. Kaplan-Meier-table analysis of total cumulative limb salvage after bypass surgery depending on neuropathy

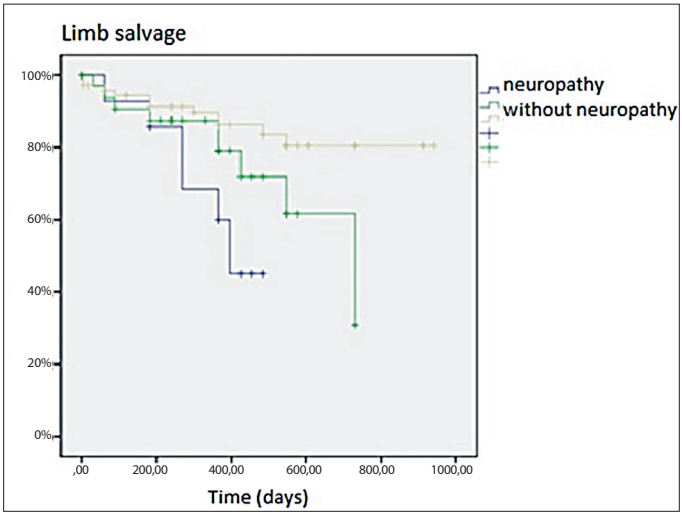

Fig. 24. Kaplan-Meier-table analysis of total cumulative limb salvage after PTA depending on neuropathy

Influence of patients' sex was evaluated on the restoration of blood flow according to the type of operation. It was found that women primary bypasses patency after 1 and 2 years was M ± SD: 48.2 ± 5.2% and 38.7 ± 6.2%, for men it was 67.4 ± 5.8%, 58.6 ± 5 ,1%, log rank test, p> 0.05. Male sex was associated with longer and better functioning bypasses, though it was not statistically reliable (Fig. 25).

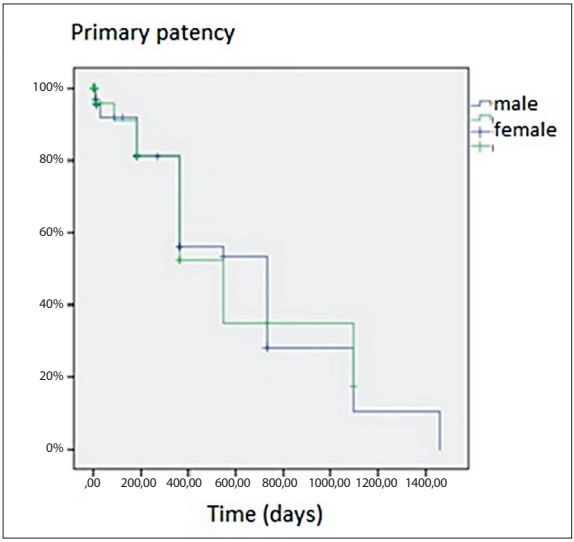

Fig. 25. Kaplan-Meier- table analysis of total cumulative primary bypass patency depending on sex

Initial primary PTA patency for women after 1 and 2 years was M ± SD: 65.7 ± 5.2% and 57.1 ± 4.6%. For men it was respectively, 84.5 ± 4.7%,80 ± 3, 0%, log rank test, p> 0.05 (Fig. 26).

Separately 7 patients with renal insufficiency on dialysis were analysed. Of these, 1 year after the initial blood flow restoration, it succeeded in 4 (57.1%) and amputation was performed in 3 patients (42.9%). Fisher test, p> 0.05. Perhaps the statistical difference was not found due to a very small number of patients.

Influence of atrial fibrillation for blood flow restoration results was analysed.

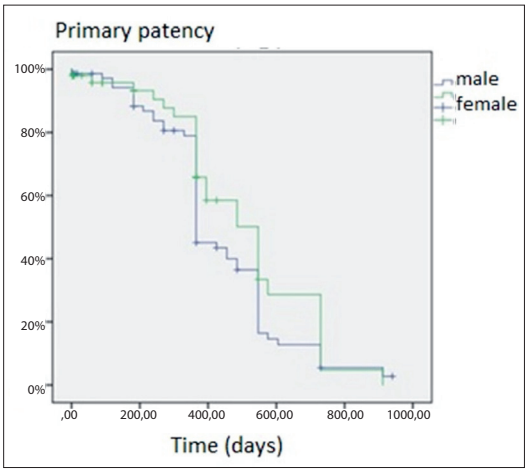

Fig. 26. Kaplan-Meier-table analysis of total cumulative primary PTA patency by sex

Within PTA group of patients, 30 patients were diagnosed with chronic atrial fibrillation. For 16 of them (53.3%) blood flow was not restored. For patients with no know atrial fibrillation, blood flow was not restored for 17 (31.2%) patients. Within the group of PTA patients, it was statistically confirmed that patients with atrial fibrillation had worse late outcomes, log rank test, $p < 0.05$.

4.11. Survival Rates

Patient survival rates were analysed using the Kaplan-Meier statistical method. Survival time was evaluated from the date of completion of the procedure before the end of the study or the patients' date of death. Data on fatalities was obtained from the population registry services.

Mean survival rates were estimated and compared according to demographic, social and clinical indicators. The survival rates of study cohort until the end of the study was 72%. The average survival time was 44,19 months.

If all patients would have survived, the survival rate would be aligned with the duration of the investigation. It was found that no tested factors: type of procedure performed -PTA or open surgery, gender, smoking, the

incidence of diabetes or coronary artery disease had statistically significant impact on survival rates.

No difference between test and control groups was observed, p> 0.05 (Fig. 27).

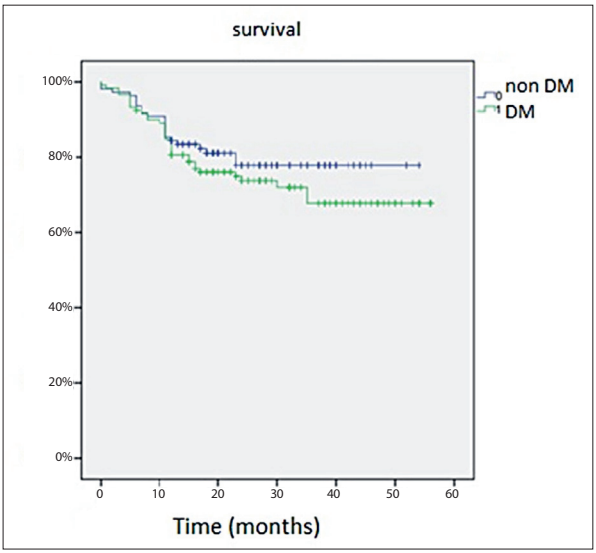

Fig. 27. The survival curve depending on the incidence of DM

The difference between men's and women's survival rate is not statistically significant p > 0.05 (Fig. 28).

The difference between smokers and non-smokers patients survival rates is not statistically significant either, p > 0.05 (Fig. 28).

There was no difference in survival rates depending on PAD stage (Fontaine III or Fontaine IV), p > 0.05 (Fig. 30).

There was no statistically significant difference comparing the survival rates of patients who undergone open bypass surgery or PTA, p> 0.05 (Fig. 31).

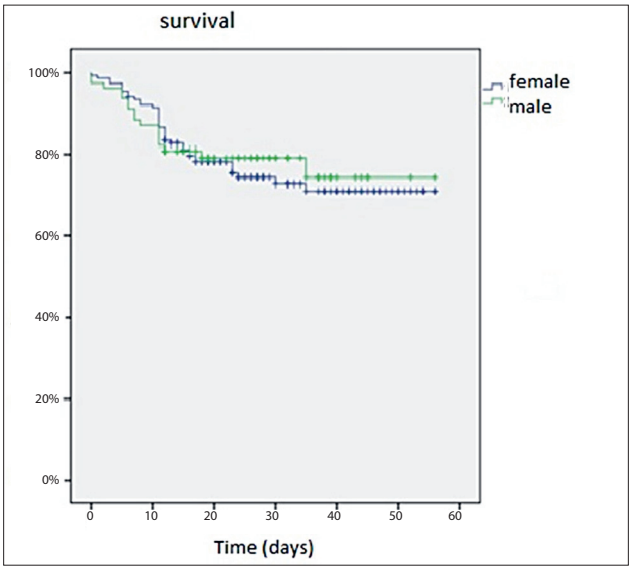

Fig. 28. The survival curve depending on sex

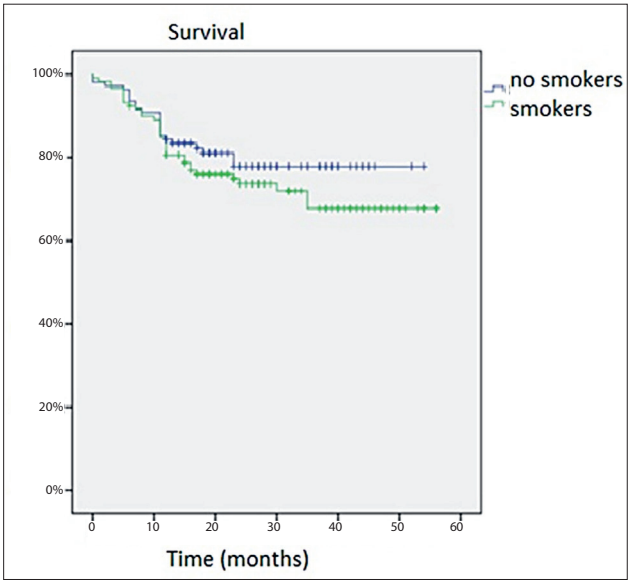

Fig. 29. The survival curve depending on smoking

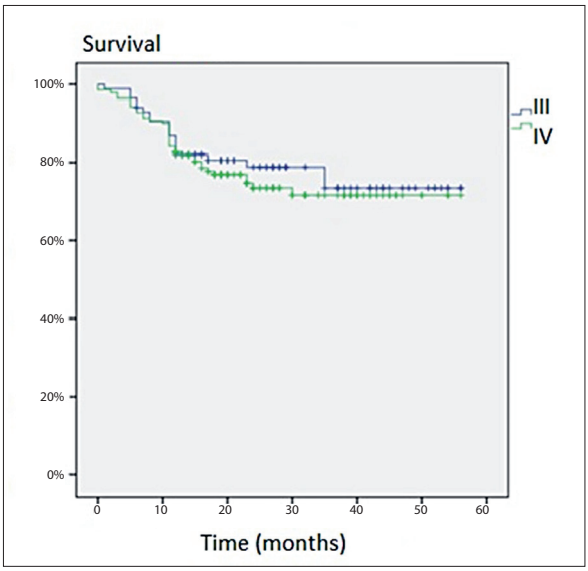

Fig. 30. The survival curve depending on the stage of PAD

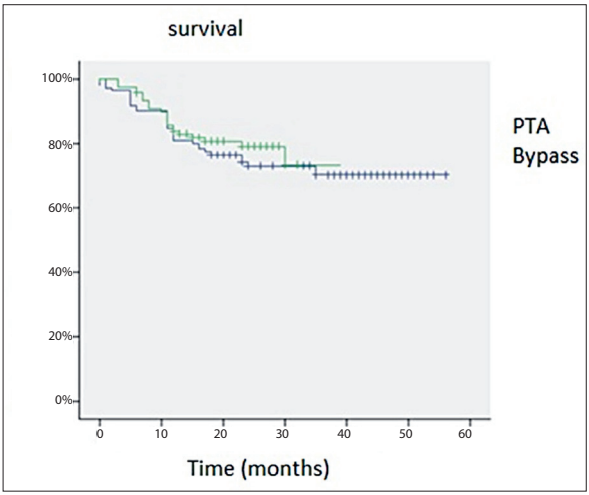

Fig. 31. The survival curve depending on the type of reconstructive surgery, $p > 0.05$

5. CONCLUSIONS

1. Demographic factors - female gender, older age, atherosclerosis inducing factors - smoking, obesity and clinical factors - arterial hypertension, coronary heart disease, cerebrovascular disorders, long duration of diabetes, poorly compensated diabetes and the presence of peripheral neuropathy are the most important risk factors for critical limb ischemia, when treatment of tibial artery reconstruction is indicated for patients with diabetes.
2. It is obligatory to measure the pressure of the thumb, determine the thumb index for diabetic patients with peripheral occlusive disease and critical limb ischemia. In order to establish operative technique, angiographic assessment is necessary.
3. Diabetes does not affect restoration of blood circulation to the lower leg arteries after reconstructive operations in the early postoperative period for patients with critical limb ischemia. Diabetes does have a tendency to worsen bypass function and long-term restoration of blood circulation after endovascular procedures. For diabetic patients, the cumulative total efficiency of bypass functioning after two years is better than the cumulative blood circulation restoration after endovascular procedures.
4. Female gender, neuroischaemia together with neuropathy and atrial fibrillation are negative prognostic factors affecting functioning of bypasses and blood circulation restoration after endovascular procedures for patients with diabetes.
5. In the early postoperative period, more limbs are saved for men and patients with compensated diabetes. Risk of limb loss increases when bypass is occluded after open repair as opposed to deterioration of arterial blood circulation after endovascular procedures. For patients with uncompensated diabetes, limb amputations are performed earlier and more often.
6. Survival after reconstructive surgery of tibial arteries is 44 months on average. The type of operation - open bypass or endovascular procedure does not affect overall survival rates.

6. PRACTICAL RECOMMENDATIONS

1. In order to establish the severity of the disease before surgery and blood circulation improvement after surgery, measuring TP and calculating TI for is beneficial for all DM patients with CLI. In order to establish which procedure is suitable, angiography is recommended.
2. It is recommended to choose an open bypass surgery for younger patients, whose survival period is predicted to be longer, comorbidites are less advanced, DM is controlled better, in cases when longer occlusion segments of tibial arteries are radiologically diagnosed and there is a sufficient autologous vein graft.
3. PTA is a first method of treatment for older patients or patients with more complicated comorbidities, who would benefit only from reduced symptoms and temporarily saved limb. If PTA is technically unsuccessful, then it is recommended to perform an open bypass surgery.

CUKRINIU DIABETU SERGANČIŲ LIGONIŲ BLAUZDOS ARTERIJŲ KRAUJOTAKĄ ATKURIANČIŲ METODŲ ĮVERTINIMAS

Santrauka

1. ĮVADAS

Aterosklerozė ir cukrinio diabeto komplikacijos – aktualios senstančios visuomenės problemos. Vienas iš svarbiausių aterosklerozės vystymosi rizikos veiksnių yra cukrinis diabetas. Aterosklerozės klinikinės išraiškos yra išeminė širdies liga, galvos smegenų išemija ir periferinių arterijų okliuzinė liga .

Asmenys, sergantys cukriniu diabetu, turi 1,5–2,5 kartus didesnę riziką sirgti simptomine ar besimptome periferine arterijų okliuzine liga, palyginti su cukriniu diabetu nesergančiais asmenimis. Cukrinis diabetas yra pagrindinė netrauminių apatinių galūnių amputacijų priežastis pasaulyje – kas 30 sekundžių diabetu sergančiam žmogui atliekama didžioji ar mažoji kojos amputacija. Pagrindinė amputacijos priežastis – galūnės opos ir gangrena, kurių išsivystymui daro įtaką daugelis mechanizmų: periferinė neuropatija ir autonominė disfunkcija, mikroangiopatija ir makroangiopatija bei daugelis kitų. Vilties suteikia tai, jog daugelio cukrinio diabeto komplikacijų galima išvengti laiku diagnozavus ligą, tinkamai kontroliuojant glikemiją, anksti nustačius komplikacijas bei ėmusis tinkamos gydymo taktikos. Cukriniu diabetu sergantiems pacientams esant kritinei kojos išemijai būdingi blauzdos ir pakinklio arterijų, esančių žemiau kelio sąnario, pakenkimai. Atvira chirurgija, siuvant autoveną į blauzdos ar pėdos arterijas, buvo laikoma „auksiniu“ revaskuliarizacijos standartu. Tačiau šį būdą gali riboti paciento rizika dėl gretutinės patologijos, prognozuojamo trumpo išgyvenimo periodo ar autovenos nebuvimas. Žemiau kelio sąnario esančių arterijų angioplastika gali duoti gerų rezultatų esant nedidelio laipsnio arterijų susiaurėjimams, ypač kai nėra didelių pėdos trofikos pažeidimų, nepaisant didelio restenozių skaičiaus. Tobulėjant endovaskulinėms technologijoms,

vis dažniau vietoj atviros chirurginės intervencijos renkamasi endovaskulinė procedūra.

Cukriniu diabetu ir kritine kojos išemija sergančių ligonių gydymas yra labai aktuali problema. Laiku ir gerai parinktas gydymas gali išsaugoti galūnę ir sumažinti neįgalumą. Todėl būtini tolesni atsitiktinių imčių tyrimai, kurie leistų sudaryti gydymo algoritmą.

2. DARBO TIKSLAS IR UŽDAVINIAI

Darbo tikslas:

Įvertinti cukriniu diabetu sergančių pacientų blauzdos arterijų angioplastikos ir atviros chirurgijos, t. y. šuntavimo į blauzdos arterijas, ankstyvuosius ir vėlyvuosius rezultatus bei šiems rezultatams poveikį darančius veiksnius.

Darbo uždaviniai:

1. Ištirti ir įvertinti cukriniu diabetu bei kritine kojų išemija sergančių pacientų, kuriems atlikta blauzdos arterijų angioplastika ar šuntavimo operacija, demografinius ypatumus, aterosklerozės susiformavimą didinančius veiksnius bei klinikines charakteristikas.
2. Ištirti ir įvertinti periferinės okliuzinės ligos diagnostikos ypatumus sergantiems cukriniu diabetu.
3. Ištirti ir įvertinti cukriniu diabetu sergančių pacientų blauzdos arterijų angioplastikos ir atviros operacijos ankstyvuosius ir vėlyvuosius rezultatus.
4. Įvertinti veiksnius, turinčius poveikį šių pacientų blauzdos arterijų angioplastikai ir atviroms operacijoms.
5. Nustatyti cukriniu diabetu sergančių ir šia liga nesergančių pacientų galūnės netekimo riziką ankstyvuoju ir vėlyvuoju pooperaciniu laikotarpiu.
6. Įvertinti pacientų išgyvenamumo trukmę po atliktų blauzdos arterijų rekonstrukcinių operacijų.

3. DARBO NAUJUMAS IR KLINIKINIS AKTUALUMAS

Iki šiol Lietuvoje nebuvo mokslinių darbų, kuriuose būtų analizuoti cukriniu diabetu sergančių ligonių blauzdos arterijų rekonstrukcinių procedūrų, tai yra šuntavimo operacijų, ir angioplastikos, rezultatai ir jie nebuvo palyginti su rezultatais tų ligonių, kurie neserga CD. Pasaulio literatūroje šie klausimai nagrinėjami, tačiau aprašyti rezultatai gana skirtingi ir neprieinama prie vienos nuomonės, kurią iš arterijų rekonstrukcinių procedūrų vertėtų pasirinkti šios grupės pacientams gydyti. Šiame darbe nagrinėjami ir palyginami CD sergančių ir nesergančių pacientų KKI gydymo rezultatai.

Atlikta duomenų analizė įrodė, kad gydant KKI cukrinis diabetas turi įtakos blogesniam šuntų funkcionavimui bei ilgalaikiam kraujotakos atkūrimui po atliktų PTA procedūrų.

Gautų duomenų analizė įtikino, kad gydant KKI pacientams, sergantiems CD, kraujotaka ilgesniam laikui pagerinama atliekant šuntavimo į blauzdos arterijas operacijas nei PTA.

Nustatyta, kad CD neturi įtakos pacientų išgyvenamumui po blauzdos arterijų rekonstrukcinių operacijų.

4. METODIKA

Tyrimas buvo atliktas Vilniaus universiteto Medicinos fakulteto Širdies ir kraujagyslių klinikos Kraujagyslių chirurgijos centre, veikiančiame Vilniaus miesto klinikinėje ligoninėje (VMKL).

Tiriamieji suskirstyti į dvi grupes:

1) kontrolinė tiriamoji grupė – nesergančių CD ligonių grupė (toliau – I grupė), 124 atvejai (53,0 proc. tiriamųjų);
2) tiriamoji grupė – sergančių CD ligonių grupė (toliau – II grupė), 110 atvejų (47,0 proc. tiriamųjų).

Registruoti ligonių demografiniai, klinikiniai duomenys – aterosklerozės rizikos veiksniai, žalingi įpročiai, CD kontrolės duomenys, indikacijos atlikti operacijas ar endovaskulines procedūras, angiografiniai duomenys, įtekėjimo ir ištekėjimo jungčių bei PTA metodai, KŽI bei NS ir NŽI.

Statistinė duomenų analizė atlikta naudojant „Microsoft Exel 2003“ ir IBM „Statistics SPSS 23 for Windows“ programas.

Buvo analizuojami kiekybinių parametrų aritmetiniai vidurkiai, standartiniai nuokrypiai (SD), minimalios bei maksimalios reikšmės. Apskaičiuotos kokybinių parametrų proporcijos ir pasikliautiniai intervalai.

Lyginant skirtumus tarp tiriamų grupių, buvo taikytas Stjudento t testas (kiekybiniams parametrams) ir $\chi 2$ testas (lyginant proporcijas). Kai kuriais atvejais skirtumai tarp proporcijų vertinti pagal Fišerio tikslųjį testą.

Statistiniam patikimumui nustatyti pasirinktas $p < 0,05$ reikšmingumo lygmuo.

Išgyvenamumui, galūnės išsaugojimo, šunto funkcionavimo laikui analizuoti taikytas standartinis Kaplano–Mejerio metodas.

5. REZULTATAI

Bendras abiejų procedūrų (šuntavimo operacijos ir PTA) kumuliacinis kraujotakos atkūrimas CD grupėje po 1 ir 2 metų buvo (vidurkis ± standartinė paklaida) V ± SP: 77,9 ± 4,4 proc. ir 27,5 ± 5,4 proc. Kontrolinėje tiriamojoje grupėje po 1 ir 2 metų V ± SP: 84,6 ± 3,7 proc. ir 34,7 ± 5,2 proc. Statistiškai patikimo skirtumo nėra, Log Rank testas $p > 0,05$.

Bendras šuntų kumuliacinis funkcionavimas CD grupėje po 1 ir 2 metų V ± SP: 62,7 ± 6,7 proc., 45,8 ± 4,4 proc., ne CD grupėje po 1 ir 2 metų V ± SP: 66,4 ± 4,9 proc., 58,5 ± 6,4 proc., Log Rank testas $p > 0,05$

Bendras kumuliacinis kraujotakos atkūrimas po PTA CD grupėje po 1 ir 2 metų V ± SP: 51,1 ± 4,7 proc., 20,9 ± 4,3 proc., ne CD grupėje – atitinkamai 59,9 ± 5,2 proc., 31,9 ± 5,4 proc., Log Rank testas $p > 0,05$.

Kumuliacinis galūnės išsaugojimas po šuntavimo operacijų CD grupėje po 1 ir 2 metų V ± SP: 79,8 ± 4,1 proc. 63,5 ± 5,9 proc., ne CD grupėje – atitinkamai 86,5 ± 3,4 proc. ir 74,5 ± 4,9 proc., Log Rank testas $p < 0,05$. CD grupėje amputacijų atlikta statistiškai patikimai daugiau ir anksčiau nei kontrolinėje tiriamojoje grupėje

Kumuliacinis galūnės išsaugojimas po PTA procedūros CD grupėje po 1 ir 2 metų V ± SP: 84, ± 6,4 proc., 75,0 ± 4,9 proc., ne CD grupėje – atitinkamai 87,7 ± 7,4 proc. ir 81,3 ± 4,7 proc., Log Rank testas $p > 0,05$. Statistinio patikimumo nerasta.

6. IŠVADOS

1. Demografiniai veiksniai – moteriškoji lytis, vyresnis amžius, aterosklerozės išsivystymą didinantys veiksniai – rūkymas, nutukimas, bei klinikiniai veiksniai –hipertenzinė liga, širdies vainikinių kraujagyslių liga, galvos smegenų kraujotakos sutrikimai, ilga cukrinio diabeto trukmė, blogai kompensuotas cukrinis diabetas bei periferinės neuropatijos buvimas, yra svarbiausi kojų kritinės išemijos, kuriai gydyti reikalinga blauzdos arterijų rekonstrukcija, rizikos veiksniai ligoniams, sergantiems cukriniu diabetu.
2. Periferinei okliuzinei ligai ir kritinei kojos išemijai diagnozuoti ligoniams, sergantiems cukriniu diabetu, būtina išmatuoti nykščio spaudimą, nustatyti nykščio indeksą. Operacijos technikai parinkti būtina atlikti angiografinį ištyrimą.
3. Cukrinis diabetas neturi įtakos kritine kojos išemija sergančių ligonių kraujotakos atkūrimui rekonstrukcinėmis blauzdos arterijų operacijomis ankstyvuoju pooperaciniu laikotarpiu.
   Cukrinis diabetas turi įtakos blogesniam šuntų funkcionavimui ir ilgalaikiam kraujotakos atkūrimui po atliktos endovaskulinės procedūros.
   Cukriniu diabetu sergantiems ligoniams pirminis **šuntų** kumuliacinis funkcionavimas po dvejų metų yra geresnis nei pirminis kumuliacinis kraujotakos atkūrimas po atliktos endovaskulinės procedūros.
4. Neigiami veiksniai, darantys poveikį šuntų funkcionavimui bei kraujotakos atkūrimui po atliktos endovaskulinės procedūros pacientams, sergantiems cukriniu diabetu, yra moteriškoji lytis, neuroišemija kartu su neuropatija bei prieširdžių virpėjimas.
5. Ankstyvuoju pooperaciniu laikotarpiu galūnių daugiau išsaugoma vyrams ir kompensuoto cukrinio diabeto ligoniams.
   Galūnės netekimo rizika didesnė šunto užakimo atveju nei esant pablogėjusiai arterinei kraujotakai po atliktos endovaskulinės procedūros. Sergantiems nekompensuotu cukriniu diabetu ligoniams galūnės amputacijos yra atliekamos anksčiau ir dažniau.
6. Išgyvenamumo trukmė po atliktų rekonstrukcinių blauzdos arterijų operacijų yra 44 mėnesiai. Išgyvenamumo trukmei gretutiniai rizikos veiksniai bei operacijos pobūdis – atvira operacija ar endovaskulinė procedūra – įtakos neturi.

DOKTORANTO GYVENIMO APRAŠYMAS

Vardas pavardė: Aušrinė Navickienė

Darbovietė: Vilniaus miesto klinikinė ligoninė,
Chirurgijos ir kraujagyslių chirurgijos klinika,
Gydytoja kraujagyslių chirurgė

Adresas: Antakalnio g. 57, LT-10207 Vilnius, Lietuva

Telefonas: (8 5) 239 14 68

Išsilavinimas:

1998 m.	Vidurinis išsilavinimas, Vilniaus 12-oji vidurinė mokykla
1998–2004 m.	Gydomosios medicinos specialybės diplomas, Vilniaus universiteto Medicinos fakultetas
2004–2005 m.	Medicinos gydytojos diplomas, Vilniaus universitetas
2005–2011 m.	Gydytojos kraujagyslių chirurgės diplomas, Vilniaus universitetas
2011–2015 m.	VUMF Širdies ir kraujagyslių ligų klinikos doktorantė
2010 m.	A. Marcinkevičiaus vardinės stipendijos laureatė

Publikacijos:

1. Navickienė A., Triponis V. Cukrinio diabeto įtaka pėdos infekcijos gydymo rezultatams. Smulkiųjų kojos arterijų chirurgijos vaidmuo. Medicinos teorija ir praktika 2011-T. 17(Nr. 4), 525-529.
2. Navickienė A., Builytė U. Cukriniu diabetu sergančių ligonių rizikos faktorių įtaka periferinės arterijų okliuzinės ligos išsivystymo ir gydymo rezultatams. Medicinos teorija ir praktika.“ 2014-T.20(Nr. 4), 401-409.
3. Navickienė A., Builytė U., Kalinauskas G. Comparison of outcome after infrapopliteal angioplasty and pedal bypass surgery. Lietuvos chirurgija 2015, 14(3): 149-158.

Tyrimų rezultatų sklaida:

Trijuose pranešimuose vietiniuose moksliniuose renginiuose:

1) Navickienė A. Neuroišeminės pėdos infekcijos chirurginis ir antimikrobinis gydymas. Vilniaus miesto universitetinės ligoninės konferencija „Antimikrobinė terapija klinikinėje praktikoje“, 2014 m.
2) Navickienė A. Pėdos arterijų šuntavimo operacijų rezultatai. 4-asis Lietuvos kraujagyslių chirurgų ir angiologų suvažiavimas, 2012 m.
3) Navickienė A. Cukrinio diabeto įtaka pėdos infekcijos gydymo rezultatams. Smulkiųjų kojos arterijų chirurgijos vaidmuo. 4-asis Lietuvos kraujagyslių chirurgų ir angiologų suvažiavimas, 2012 m.

Dviejuose pranešimuose tarptautiniuose moksliniuose renginiuose:

1) Navickienė A. Triponienė D. Triponis V. Efficacy of dorsal pedal bypass for limb salvage in diabetic patients. ESVS, 2013 September, Budapest, Hungary.
2) Navickienė A. Outcome analysis of infrapopliteal percutaneous transluminal angioplasty and pedal bypass graft surgery for individuals with critical limb ischemia. Controversies and updates in vascular surgery, 2014 January, Paris, France.