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Results of surgical treatment of ruptured abdominal aortic aneurysms (rAAA) in our own material

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Abstract

Introduction: *Aortic aneurysm rupture is defined as bleeding beyond tunica adventitia of a dilated aortic wall. The incidence of ruptured abdominal aortic aneurysm (rAAA) varies between 5.6 and 17.5 per 100,000 inhabitants per year and seems to have decreased over the past two decades.*
The aim of the work was to assess the results of treatment of patients with ruptured abdominal aortic aneurysm.
Material and methods: *Analysis encompassed patients who had undergone surgery for ruptured abdominal aortic aneurysm between 2011 and 2017. A total of 140 patients were operated on due to ruptured abdominal aortic aneurysm. Evaluation of treatment outcomes was based on a retrospective analysis of patients' medical records, assessing the results of treatment based on the following parameters: peri- and postoperative mortality, serious peri- and postoperative complications (acute coronary syndrome, gut ischemia, renal failure, respiratory failure, lower limb ischemia).*
Results: *Results confirm that peri-and postoperative mortality due to ruptured abdominal aortic aneurysm remain high despite continuous progress. Further development of intravascular repair techniques (EVAR) and anesthesiologic management may facilitate better treatment outcomes. However, this requires a great deal of organizational effort to ensure 24/7 availability of multi-specialist teams (vascular surgeon, anesthesiologist, radiology technician, nursing staff) capable of performing intravascular procedures.*
Conclusions: *Surgical management of patients with ruptured abdominal aortic aneurysm continues to be associated with high mortality rates and a significant number of postoperative complications.*

Key words: ruptured abdominal aortic aneurysm, surgical treatment of abdominal aortic aneurysms, endovascular repair (EVAR)

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Introduction

According to the guidelines of the European Society of Vascular Surgery, the incidence of ruptured abdominal aortic aneurysm (PTAB) in Western countries varies between 5.6 and 17.5 per 100,000 inhabitants per year and appears to have decreased over the past two decades [1]. In the United States, it decreased from 18.7/100,000 in 1994 to 13.6/100,000 in 2003 and according to data from the Swedish Vascular Registry over the years 2008-2012 it amounted to 6.07–8.15/100,000 inhabitants [2, 3]. According to data from 1990s, the overall mortality rate in case of a rupture of aortic aneurysm is very high and reaches 80–90%. Subsequent reports demonstrated that it remains high and ranges from 32% to 80%, although according to data from

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specialized centers from the years 2002–2015, in the United States it varied from 20% to 46%, and between 21.6% and 29.6% in Sweden [1, 3–5].

A ruptured aortic aneurysm is defined as bleeding beyond the tunica adventitia of a dilated aortic wall. It can be classified as a rupture into the free peritoneal cavity or as retroperitoneal rupture, where peritoneal tissues cause temporary tamponade and limit blood loss. An aneurysm is considered symptomatic when it is painful, but no breaking of the aortic wall is noted. Inclusion of "symptomatic" aneurysms in the "ruptured" group by some researchers might have improved the outcomes of studies [1]. The incidence of urgent surgeries has decreased with an increase in the number of routine screenings. A patient with a previously diagnosed abdominal aortic aneurysm, who is admitted to hospital with hemorrhagic shock and other symptoms of an aneurysm rupture, does not require further diagnostics and should be taken to the operating theater as soon as possible. Depending on availability, only an urgent ultrasound examination for confirmation of the diagnosis is sufficient. However, Lloyd et al. [6] conducted a study in patients with PTAB who have not undergone surgery for various reasons; they noted that 87.5% of patients survived more than 2 hours, concluding that the majority of patients who arrived at hospital remained hemodynamically stable enough to perform a CT scan to decide on further treatment.

"Permissive hypotension" is recommended in perioperative management, as aggressive fluid therapy intensifies bleeding. In 1991, Crawford [7] published a trial including 180 patients noting significant improvement in survival with systolic blood pressure being maintained at 50–70 mm Hg with fluid restriction. Van der Vliet et al. [8] were the first to publish the results of application of a protocol for maintaining systolic blood pressure between 50 and 100 mm Hg, with potential use of nitrates and limiting fluid supply to 500 ml during the preoperative period. In addition to obvious "surgical" factors, such as: duration of surgery, blood loss, aortic cross-clamping time, the presence of "abdominal compartment syndrome" is also important. It is observed in 10–55% of patients operated on due to rAAA, contributing to multiorgan failure and postoperative mortality [9]. This parameter should be monitored in the postoperative period; finding of intraabdominal pressure over 20 mm Hg is an indication for decompression of the abdominal cavity using temporary closure techniques [10].

Development of endovascular techniques has contributed to improved treatment outcomes, but endovascular procedures, such as implantation of stentgraft in place of abdominal aortic aneurysm (EVAR) in the treatment of rAAA, are still not widely available [1]. The widespread use of intravascular techniques in the treatment of rAAA still faces many barriers related to both patient's condition (hemodynamic instability) and aneurysm morphology, as well as logistic challenges: 24/7 availability of personnel qualified in performing intravascular techniques (vascular surgeon, radiology technician, anesthetics team, nursing staff), "hybrid" operating theater, a wide choice of stentgrafts. Reports confirming the undoubted benefits of endovascular rAAA treatment relate to a selected patient group [11]. It is estimated that around 60% of cases of rAAA are suitable for EVAR due to aneurysm anatomy (between 18% and 83% according to various authors) [12]. The randomized Amsterdam Acute Aneurysm Trial included 83 patients, 46% of whom were eligible for EVAR, and eventually 35% of patients were treated with this method [13]. Discrepancies in reports on the utility of EVAR are caused by application of various systems as well as different anatomical criteria. Most authors apply the same anatomical criteria for rAAA as in elective treatments. However, assuming that in cases of emergency when saving patient's life is a priority, increasingly more liberal anatomical criteria are acceptable, especially when it comes to the length of the neck of the aneurysm. It is accepted that use of EVAR in the first stage of treatment with a possibility of converting to open surgery results in better mortality rates than primary open treatment. Further progress associated with introducing new stentgraft systems will make the use of EVAR in rAAA more accessible.

According to the guidelines of the European Society for Vascular Surgery, endovascular treatment (EVAR) of rAAA should be considered if the anatomy of the aneurysm allows and if the center has the staff and access to equipment required to perform intravascular procedures.

The aim of the work is to present the results of treatment of patients with ruptured abdominal aortic aneurysm in our own material in the context of the current European guidelines, as well as under the conditions of the Polish health service.

Material and methods

We performed a retrospective analysis of the medical records of patients treated between 2011 and 2017 due to a ruptured abdominal aortic aneurysm at the vascular surgery department, which provides services to patients from the entire province. A significant group consisted of patients referred from other hospitals, sometimes more than 100 km away. One hundred and forty patients, 18 women and 122 men, were treated over that period. Average age of patients was 74.2 years (39 to 94 years), the average age of women was 79.8 years,

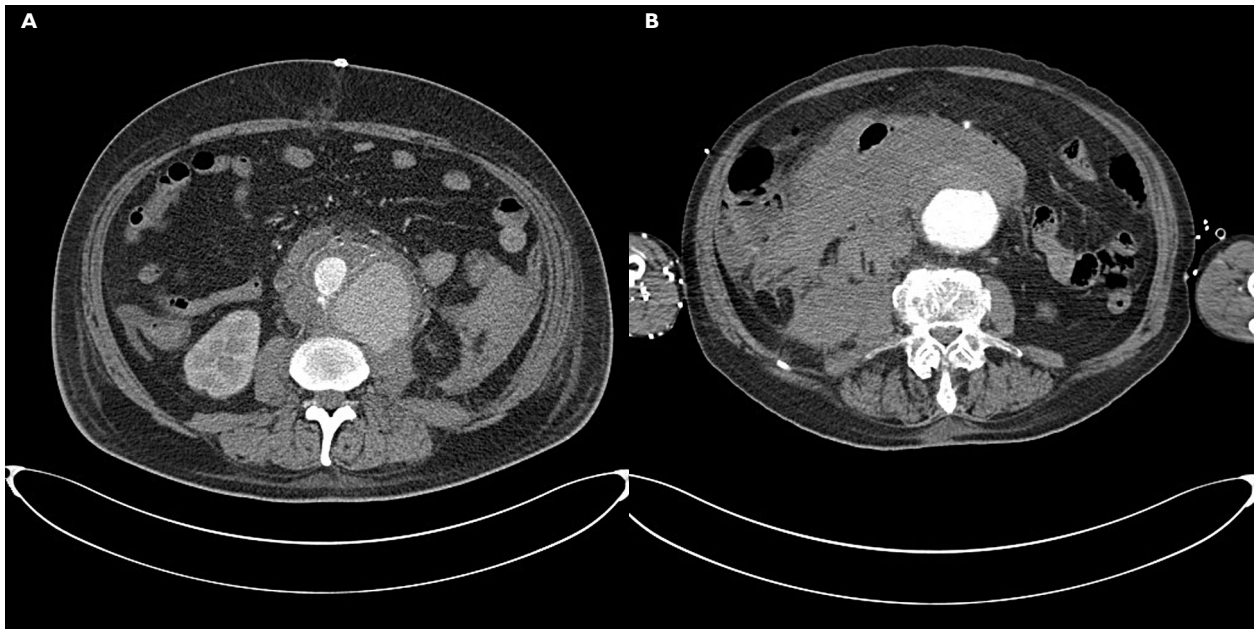

Figure 1A, B. Angio-CT of ruptured abdominal aortic aneurysm (horizontal plane)

the average age of men — 73.8 years. Among men, 27 (19.3%) did not exceed the age of 65, there were no cases of rAAA among women below 65 years of age.

Patients' condition was assessed on admission according to the ASA scale as well as based on complete blood counts and creatinine levels.

We analyzed the time it took for a patient diagnosed with rAAA to reach the operating theater, under the operative conditions of the Hospital Emergency Department and Clinical Department of Vascular Surgery of the 4WSKzP, measured as the time from patient registration at the Emergency Department (ED) to the beginning of the operation according to the surgical protocol. Despite the progress in diagnostics, patients without prior imaging (CT and/or ultrasound), who required ultrasound or angio-CT to confirm the diagnosis of rAAA at the ED were still referred to our center, which increased the time of transition to the operating theater (Figs 1, 2). This only concerned patients, who were hemodynamically stable, as patients diagnosed with AAA and symptoms of hemorrhagic shock were sent directly from the ED to the operating theater without further diagnostics, unnecessary in such cases. CT scan was performed on admission in 72 patients (51%), 43 patients had CT imaging performed at the referring center, 25 patients went directly to the operating theater without further diagnostics.

Evaluation of treatment outcomes took into account such parameters as: peri- and postoperative mortality, duration of stay in the ITU, duration of hospital stay, and complications such as: bowel ischemia, lower limb ischemia, respiratory failure, kidney failure.

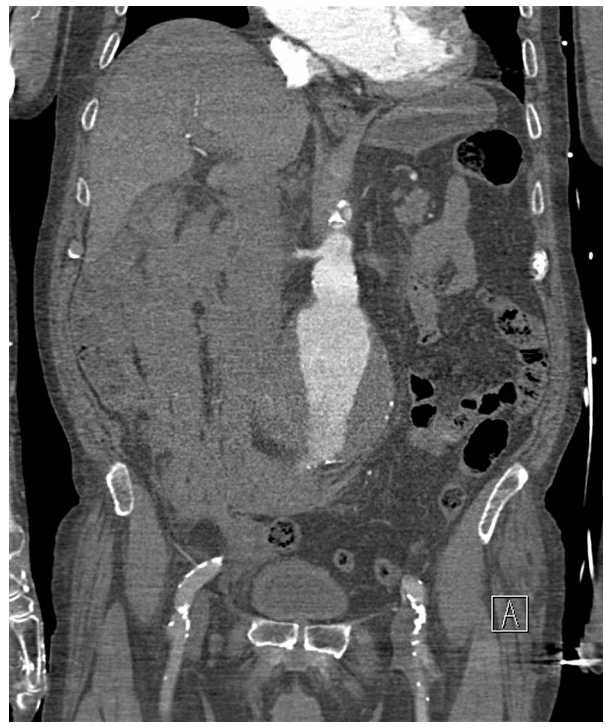

Figure 2. Angio-CT of ruptured abdominal aortic aneurysm (frontal plane)

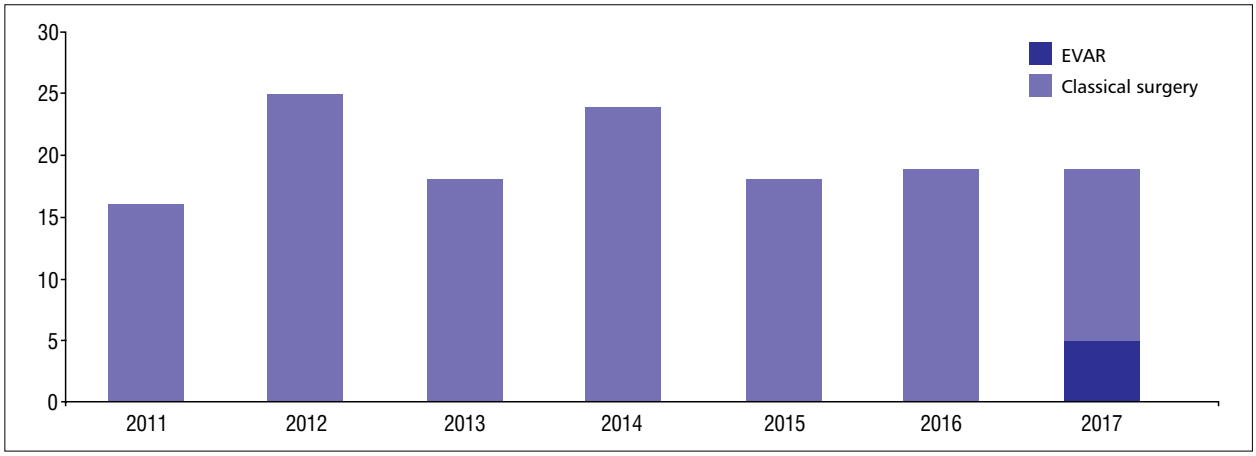

Figure 3. Numbers of surgical procedures due to ruptured abdominal aortic aneurysm in subsequent years

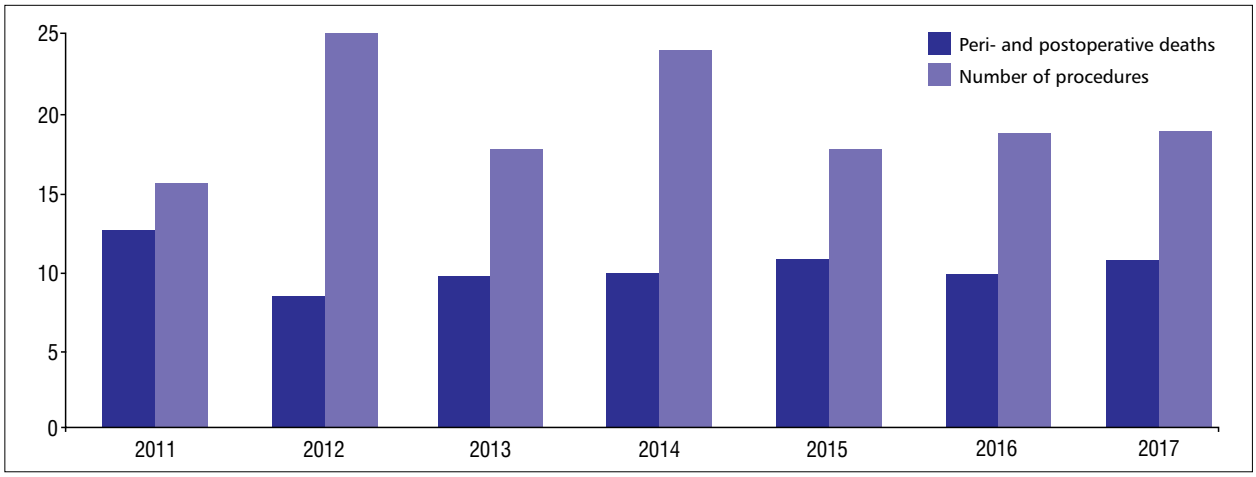

Figure 4. 30-day mortality after surgical treatment of rAAA

Statistical analysis

Analysis of the collected data was performed using Statistica v. 13.3 for Windows. Quantitative data was presented as means and standard deviations or medians and compared using Student's t-test and Mann-Whitney U test. Test results with $P < 0.05$ were considered statistically significant.

Results

One hundred and forty patients were treated for ruptured abdominal aortic aneurysm between 2011 and 2017. The only criterion disqualifying from treatment of ruptured aneurysm was lack of patient's consent and one such a case was reported. The number of surgeries in the subsequent years was similar and ranged between 16 and 25 per year. Classic surgery was performed in 135 cases. Procedures were performed by vascular surgery specialists, all via midline laparotomy, obtaining intraoperative confirmation of rupture of aortic aneurysm and/or iliac arteries. A total of 39 patients were diagnosed with aneurysms involving iliac arteries, and in 7 patients aneurysm involved the ostia of renal arteries, which required clamping the aorta above the renal arteries. A straight dacron prosthesis was implanted in 100 patients, an aortobiiliac prosthesis in 7 patients, aortobifemoral in 32 cases, and one patient died after general anesthetic introduction before the beginning of surgery. Five patients were treated endovascularly, EVAR was performed in 4 cases and extension of stent-graft aortic extension was done in one patient (Fig. 3).

Of the 140 operated patients, 67 died during the peri- or postoperative period (the overall 30-day mortality rate was 47.8%) (Fig. 4), including 17 patients

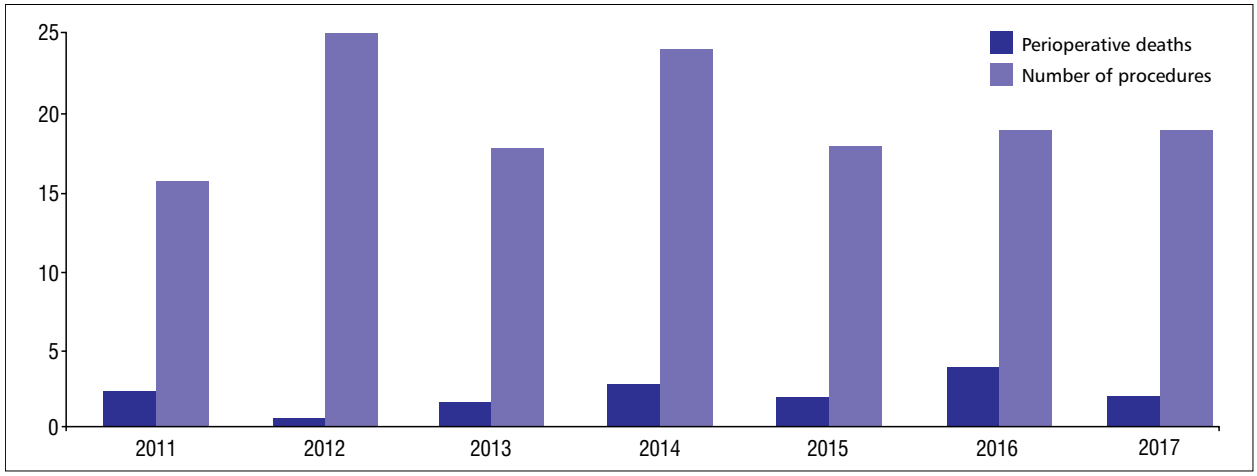

Figure 5. Number of perioperative deaths

who died during or on the day of surgery (mortality rate 12.1%) (Fig. 5). The average age of patients who died was 73.9 years and did not significantly differ from the average age of patients who survived the procedure — 74.57 years (P = 0.7008). The average time to the operating table, measured from the time of patient registration in the ED until the beginning of the procedure was 139.6 minutes, ranging from 30 to 335 minutes and was significantly shorter for patients who died: 100.3 min compared to 186.2 minutes in patients who survived the procedure. The differences can be explained by the fact patients from the second group were in better general condition, which more often allowed performing an angio-CT study. Among 72 patients who had CT examination performed at the ED 44 patients survived (61%). Patients' condition assessed according to the ASA scale was 3.7 on average; 4.1 for group one (patients who died) and 3.4 for group two — this difference was statistically significant (P = 0.0022). In patients from group 1, mean blood hemoglobin concentration was significantly lower at 10.1% compared to group two — 11.5% (P = 0.0134). With respect to renal function, serum creatinine concentrations averaged 1.70 mg%; 1.83 mg% (range 0.56—5.72 mg%) in group one and 1.58 mg% (range 0.62—5.30 mg%) in group two, without statistically significant differences between groups (P = 0.2542). Patients operated on due to ruptured abdominal aortic aneurysm required an average of 3.7 units of red blood cells; significantly more blood was transfused intraoperatively in patients from the first group — 4.6 units of RBC per patient on average, compared to the second group — 2.9 units of RBC per patient on average (P = 0.0123).

Mean duration of hospitalization in patients who were discharged from hospital was 14.2 days and ranged from 6 to 65 days. The mean duration of stay in intensive care was 6.1 days and ranged between 1 and 64 days. Typical complications described in the literature, such as: intestinal ischemia, lower limb ischemia, respiratory failure, renal failure, acute coronary syndrome, and psychosis (Table 1) were observed postoperatively. Complications were observed in 35 of the 73 patients (48%) who survived the procedure and were discharged from hospital. Among this group, 41 patients required intensive care; mean time of stay at the ITU was 11.9 days (the longest stay of 64 days), the most common cause of prolonged stay at the ITU was respiratory failure requiring mechanical ventilation. Of the 67 patients who died, only 36 (53.7%) were admitted to the ITU. In our opinion, more patients should have been admitted to the ICU, at least on the first day after surgery, but this was not always possible due to the lack of ITU beds. Furthermore, the main criterion qualifying for ITU admission was the need

Table 1. Complications of surgical treatment of rAAA

Type of complication	Number
Renal	8
Intestinal necrosis	8
Acute lower limb ischemia	2
Endoleaks after EVAR	1
Acute coronary syndrome	5
Psychosis	5
Respiratory failure	12
Number of patients in total	**73**

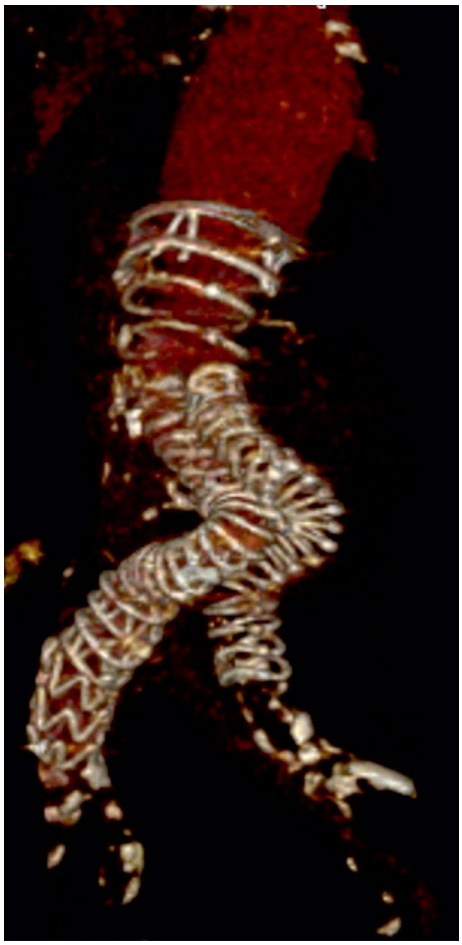

Figure 6. Ruptured abdominal aortic aneurysm after EVAR

for mechanical ventilation due to respiratory failure; patients who did not require mechanical ventilation were sometimes not admitted to the ITU despite their poor general condition, i.e. requiring catecholamine infusions or multiple transfusions of blood products.

Twenty-three patients required repeated surgery, 14 patients (60.9%) died in the postoperative period. In 8 patients, resection of the sigmoid or small intestine was performed due to ischemia (6 of them died during the postoperative course), 7 patients were reoperated due to acute lower limb ischemia (5 died during the postoperative course), 7 patients were reopened due to symptomatic hematoma/bleeding of the operated area (3 died), one patient had a second-look surgery with the removal of the previously applied packing.

With development of endovascular surgery, a new group of patients with ruptured abdominal aortic aneurysms after previous stentgraft implantation arose. There were 4 such patients in our material. Three of them underwent classic surgery, two of them had a vascular prosthesis implanted (Figs 6, 7) after removal

Figure 7. Stentgraft removed during surgical repair of ruptured abdominal aortic aneurysm after EVAR

of a stentgraft, in one patient aneurysm wall was sutured and sealed around the graft with a piece of the prosthesis ("banding"). In one patient, aneurysm rupture was observed in the course of type I leak after EVAR. In the first stage, an attempt was made at endovascular treatment – a stentgraft extension, but an angio-CT performed to symptoms of renal failure showed obstruction of the left renal artery (despite the fact that it was patent in DSA performed during the endovascular procedure) with a persistent leak. Ultimately the patient also required classic surgery — removal of the stentgraft with implantation of a vascular prosthesis.

In one case of a morbidly obese patient with aneurysm rupture into the peritoneal cavity, only aneurysm closure (aneurysmorrhaphy) was performed in the first stage of treatment due to severe general condition and difficult anatomical conditions. Ultimately, deferred endovascular procedure (EVAR) was used to treat the aneurysm after patient's general condition had stabilized.

Discussion

Demographic data confirm that the problem of abdominal aortic aneurysm rupture mainly affects men (they represented 87.1% of patients) and elderly people (mean age 74.2 years) [14–16]. It is worth noting that 27 patients were under 65 years of age (19.3%) and they were all men, i.e. 22.1% of men were below the age generally accepted as an indication for screening [17]. In the analysis conducted by Laine et al. [18] on a group of 585 patients with rAAA , 486 of subjects were men (83.1%) and 18.3% of patients were below 65 years of age (21.4% of men and 3.0% of women). The above data may suggest that the age of men included in AAA screening programs should be lowered.

Results obtained in our material confirm that management of patients with ruptured abdominal aortic

aneurysm continues to be associated with high mortality rates and a significant number of postoperative complications.

Poor general status according to ASA scale, low blood count as well as high serum creatinine levels can be considered risk factors for postoperative mortality. Undoubtedly, the need to repeatedly transfuse blood products (RBC) is also an important risk factor for death.

The number and nature of reported complications corresponds to those reported in the literature on rAAA. In a publication by Gawenda et al. [19], the occurrence of intra- and postoperative bleeding was observed in 12–14% of patients, intestinal ischemia in 3-13%, respiratory failure in 26–47%, and renal failure in 26–42%. A particularly dangerous complication is intestinal ischemia requiring gut resection. In our material, out of 123 patients who survived the procedure, it occurred in 8 patients, representing 6.5% of the study population. Six of them died in further postoperative course, representing an 80% mortality rate, which is comparable to the literature data, e.g. 73–100% according to Gawenda [19].

Effectiveness of treatment depends on many factors. Increased health awareness among the public and greater availability of basic diagnostic tests, including abdominal ultrasound, may be a significant factor limiting the incidence of abdominal aortic aneurysm rupture. Early diagnosis and elective treatment, especially in the age of development of endovascular surgery, can protect the patient from the disaster of the "aortic rupture". Management at the primary care level seems important, so that a patient with a "pulsating tumor in the abdomen" would not wait too long for necessary treatment [14].

At the level of emergency medical services, it is important that patients with suspected or diagnosed ruptured abdominal aortic aneurysm should be sent to centers specialized in the operative management of rAAA as soon as possible. At the level of preoperative management, it is important to remember the principle of "permissible hypotonia" to limit blood loss until surgery.

Peri- and postoperative anesthetic management is an extremely important aspect of treatment, from the moment of admission to hospital, through management in the operating theater, to the treatment of early and late complications of rAAA in the Intensive Therapy Unit. Further developments in this area may contribute to improving treatment outcomes [15].

Further improvement of treatment outcomes is possible due to the application of endovascular techniques in the treatment of patients with rAAA. The available literature data concerning the results of endovascular treatment of rAAA indicate lower mortality rates compared to classic surgery, ranging between 18% and 53%, and according to some researchers even less than 20%. It should be mentioned, however, that a selected group of patients is referred for intravascular treatment and a group of patients undergoing classic surgery includes cases that are much more difficult, such as those with pararenal aneurysms that have been disqualified from EVAR, or patients in poor general condition. The possibility of intravascular treatment of ruptured aneurysms requires a significant organizational and financial effort, which is not easy under today's conditions of the Polish health service. Qualification for EVAR in urgent cases requires access to rapid imaging diagnostics (computer angiotomography). Surgical treatment in such cases is possible in a fully-equipped hybrid operating room, dedicated to intravascular procedures, offering the possibility of immediate conversion to open surgery and accessibility to the equipment needed in EVAR. Endovascular treatment of rAAA also requires 24-hour availability of staff specialized in performing such procedures (vascular surgeon specialized in EVAR, radiology technicians, nursing staff) [16].

Summarizing, it is worth presenting the work of Swedish authors, where Gunnarson et al. analyzed the results of treatment of ruptured abdominal aortic aneurysms included in the Swedish Vascular Register between 2008 and 2012 [3]. They compared centers where endovascular treatment is the primary practice strategy (EVAR in more than 50% of patients with rAAA) with centers preferring classic surgery. A total of 1,304 patients were enrolled. Two hundred and thirty-six patients were treated in three "endovascular" centers (EVAR in 74.6% of cases), while 1068 patients were operated on in 26 "classic" centers (EVAR in 15.6% of cases). There was no significant difference in the 30-day mortality rates, which amounted to 28.0% in the "endovascular" group and 27.4% in the "classic" group. Overall, patients undergoing endovascular surgery (regardless of the center) were older (76.4 vs 74 years) and were characterized by lower mortality rates (21.6% vs. 29.6%). It can be, therefore, concluded that in order to achieve such good results of treatment among patients with rAAA, it is necessary to improve the entire health care system, from the level of primary care, through the emergency response system, to specialized vascular surgery centers with access to modern endovascular techniques [16].

Conclusions

1. Surgical treatment of patients with ruptured abdominal aortic aneurysm continues to be associated with high mortality rates and a significant number of postoperative complications.

2. The following can be considered as unfavorable prognostic factors in rAAA: poor general condition according to the ASA scale, low baseline complete blood count values, high baseline serum creatinine levels, the need for multiple transfusions of blood products (RBC).
3. Effective surgical treatment of patients with ruptured abdominal aortic aneurysm is possible if patients are efficiently referred to centers specialized in the treatment of rAAA with access to intravascular treatment and possibility of providing comprehensive perioperative care in intensive therapy units.
4. Further improvement of treatment outcomes is possible thanks to the use of intravascular techniques in a fully equipped hybrid operating room dedicated to intravascular procedures with the option of immediate conversion to open surgery and accessibility to the entire equipment needed for EVAR.

Conflict of interest:

None.

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Infection-related complications in patients with end-stage renal failure dialyzed through a permanent catheter

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Abstract

Introduction: *Progression of renal failure leads to an increase in the number of patients who require forming dialysis access. Old age and rising morbidity make it impossible to form a native arteriovenous fistula and a permanent catheter becomes the first choice. The presence of a catheter frequently generates complications, including infections, which may result in a higher mortality rate.*

Material and methods: *A retrospective analysis data has been conducted, involving 398 patients who had permanent catheters implanted from 2010 to 2016. Out of this group, 65 patients who suffered infection-related complications have been identified. Risk factors for infection and a survival rate of the population have been estimated.*

Results: *Between 2010 and 2016, 495 catheters were implanted for 398 patients aged 68.73 (13.26) years on average. 92 catheter-related infections (23.1%) were recorded in 65 patients. Multivariate logistic regression showed, that the risk factors of infectious complications were: younger age (P = 0.000), coronary artery disease (P = 0.006) and heart failure (P = 0.000). Mortality in the mean 1.38 ± 1.17 years follow-up period was comparable in infectious and non-infectious subgroups (53.85% vs 49.25%; P = 0.588). A higher risk of death in the infectious population was associated with the presence of additional intravascular and intracardiac implanted materials (P = 0.027) and a severe course of infection with hypotension (P = 0.027), thrombocytopenia (P = 0.029) and a high leucocytes/platelets ratio (0.017).*

Conclusion: *Infectious complications in patients dialyzed with permanent catheters are dangerous especially in patients with severe clinical course. The mortality rate is high, although similar to all dialyzed by permanent catheters.*

Key words: end-stage renal disease, permanent dialysis catheter, infectious complications, death risk

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Introduction

The end-stage renal disease leads to an increasing number of patients who require dialysis therapy and kidney transplant. In Poland, approximately 4.5 million people suffer from chronic kidney disease and 21,043 patients receive renal replacement therapy [1, 2]. Aging of the population and high morbidity of this group of patients

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makes it difficult to create a native arteriovenous fistula, still called the gold standard of vascular access. Dialysis often starts with a permanent catheter inserted into the venous system and its long-term use is limited by a high risk of infection and death [2, 3]. Dialysis patients are a group particularly vulnerable to infections, mostly those spreading through the bloodstream. This exposure is largely associated with the presence of infection entry via vascular access to dialysis. In addition, the development of end-stage renal disease (ESRD) is more common in patients with comorbidities: diabetes, hypertension, atherosclerosis. The course of uremia leads to further dysfunction of many organs and systems. Dialysis treatment makes it possible to remove uremic toxins and to balance water and electrolytes, but not completely. This results in permanent suppression of the immune system with greater exposure to infectious complications.

Infectious complications are one of the most common reasons for the loss of catheter function. Infections related to vascular access account for 50–80% of all infections that occur in this patient group, and they lead to the death of 10% of dialyzed patients [1, 4].

The aim of this study was to identify risk factors of infection-related complications and death risk in a group of patients who were dialyzed through permanent catheters over a period of seven years' observation.

Material and methods

The information obtained from the National Health Fund (NFZ) provided clinical data for a retrospective analysis of 398 patients from the Świętokrzyskie Province who had their first permanent catheter inserted from 1 January 2010 to 31 December 2016. Out of this group, 65 patients who suffered 92 infection-related complications were identified, and risk factors for infection and death of these patients were estimated. The study considered impact of the following clinical factors on infection-related complications: arterial hypertension, coronary disease, atrial fibrillation, heart failure, generalized atherosclerosis, diabetes, history of stroke, neoplastic disease, chronic obstructive pulmonary disease, presence of cardiac implants (cardiac implantable electronic device-CIED, artificial valves, biomaterials for vascular prosthetic devices implanted in aorta and peripheral vessels), and venous thrombosis.

Catheter-related infections were diagnosed according to the criteria worked out by American and European Centres of Prevention and Disease Control (HAI: Healthcare Associated Infection, CDC: Centers for Disease Control and Prevention; ECDC: European Centers for Disease Control and Prevention) [5, 6, 7]. Infectious complications were divided into infections of a catheter insertion site, infection of a catheter tunnel, bacteraemia accompanied by high temperature, shaking chills, hypotension and rising inflammatory parameters. Catheter Related Bloodstream Infection (CRBSI) was defined as an infection of the vascular bed occurred within 48 hours from inserting or removing a catheter with positive blood culture and isolating the same microorganism from peripheral blood and from pus from the catheter insertion site. Growth in quantitative culture from a catheter tip must be $> 10^3$CFU/ml and the number of CFU microorganisms should be five times as high as peripheral blood. Detection time of samples taken in an automatic system exceeds 2 hours and a sample taken from a catheter is marked positive earlier than is the case for a sample of peripheral blood.

Central Line-Associated Bloodstream Infection (CLABSI) was defined as an infection in a patient with a central catheter when blood culture is positive while catheter site culture is negative [5, 7–9].

Based on the analysis of available medical records of 47 patients out of 65 subjects with infectious complications, a precise assessment of the influence of procedural factors on the development of infection was performed. For this group of 47 patients the following data were also analysed: reasons for catheter insertion and removal, reasons for subsequent hospitalizations after its insertion, a number of catheters implanted for one person, total and average functioning time of one catheter and the functioning times of the catheter inserted after a dialysis fistula, time from catheter insertion to the onset infection, location of venous access and location of a catheter tip. A detailed analysis of the following data was also carried out: a course of infection-related complications, including the time of hospitalization, the occurrence of septicaemia, infective endocarditis, pneumonia, abscesses distant from vascular access site, kind of infection-inducing bacteria based on blood and catheter tip cultures as well as recurrence of infection. The analysis also involved values of biochemical tests and the impact of individual factors on a survival rate among patients affected by infection-related complications.

The study was approved by the Bioethics Committee of Świętokrzyska Medical Council: Resolution No 21/2017.

Statistical methods

Distribution of all continuous variables was evaluated by the Shapiro-Wilk test. The continuous data were presented as mean with the standard deviation. Categorical data are presented as absolute numbers and percentage. Continuous variables were compared by Student's t-test and Mann-Whitney U test, while chi-square test with Yates correction was used to compare dichotomous variables.

Uni- and multivariable linear regression was used to determine risk factors of catheter infection

Only variables with a value of $P \leq 0.05$ at univariate analysis were included in the multivariate analysis.

Cumulative survival curves for all-cause death were constructed by the Kaplan-Meier methods. Survival curves were compared among groups with the log-rank test.

The differences were found as statistically significant when $p < 0.05$.

Results

In the period from January 2010 to December 2016, 495 permanent catheters were implanted in 398 people (194 men,48.7%) with a mean age of 68.73 (13.26) years. In the whole study group (n = 398) there were 92 (23.1%) catheter-related infectious complications in 65 (16.3%) patients. In 28 (6.1%) patients repeated infections were observed.

More frequent infectious complications have been observed in patients with a longer dwell time of catheter(s) who needed catheter replacement, patients with thrombotic complications including stroke, generalized atherosclerosis, diabetes, arterial hypertension, chronic atrial fibrillation, coronary artery disease, heart failure, history of neoplastic disease and other comorbidities. During the mean 1.38 (1.17) years (min 0.0 max 6.70 years) follow-up 199 deaths occurred (50.0%). There was no significant difference in survival between patients with infectious complications (35, 53.85%) and those without infectious complications (164, 49.25%) (Table 1).

The univariable analysis demonstrated that generalized atherosclerosis, diabetes, thrombotic catheter complications, neoplastic disease, atrial fibrillation, arterial hypertension, coronary artery disease, previous stroke, heart failure and co-existing diseases were risk factors of a catheter-related infection (CRI) (Table 2).

In the studied group of 398 people, there were 92 catheter related infectious complications in 65 patients. The mean infection rate was 0.46 per 1,000 catheter days.

A detailed analysis of medical records of the separate subgroup of 47 patients with catheter related infectious complications identified 68 infections (13 patients suffered from repeated infections). The total functioning time of all catheters from insertion of the catheter to infection was 13,074 days, the time of the longest functioning catheter in this group was 1,108 days. The total time of hospitalization due to infectious complications for the group (n = 47) was 798 days, the average time of hospitalization was 11.73 days. 61 hospitalized patients were treated successfully and discharged from the hospital while 7 patients died.

In the analyzed subgroup of 47 patients with infectious complications, 8 patients (11.76%) developed pneumonia and 3 (4.41%) had endocarditis. In 13 (19.11%) cases, the infection required the removal of a permanent catheter.

A comparison of the location of the catheter tip in the superior vena cava and the inferior vena cava did not show an effect of the catheter placement on the incidence of infection ($p = 0.68$). Similarly, the duration of catheter functioning had no effect on the risk of infection in this group ($P = 0.621$). A comparison of the position of the catheter tip in the superior vena cava and the inferior vena cava did not show an effect of the position of the catheter on the occurrence of infection ($P = 0.68$).

A detailed analysis of blood culture and catheter tip culture identified 42 (61.77%) cases of CRBSI, 22 (32.35%) cases of bacteraemia with a negative blood culture and catheter culture qualified as CLABSI, and 4 cases (5.88%) of local infection that required hospitalization, with a negative blood and catheter cultures, and those were mainly abscesses. Infection symptoms in a catheter insertion site were found in 25 (37.64%) cases, in 16 (23.53%) cases infection occurred together with implications of distant organs, including 8 (11.76%) cases of pneumonia, 3 (4.41%) cases of infective endocarditis and 5 (7.35%) cases of distant skin infections. In 13 (19.11%) cases, the infection required the removal of a permanent catheter.

Infection lesions in catheter insertion site (25 cases) co-existed in 18 cases with CRBSI, in 6 cases with CLABSI (with negative catheter cultures), and in 1 case, a positive catheter culture was not accompanied by general symptoms: it was an infection of the skin and a catheter tunnel only.

The study identified 68 infections in 47 dialysed patients; 39 (57.35%) cases were caused by Gram-positive bacteria, and 29 (42.64%) by Gram-negative bacteria. Gram-positive infections were caused in 20 (29.41%) by *Staphylococcus aureus*, and in 19 (27.94%) cases by other staphylococci, mainly by *Staphylococcus epidermidis*. The most common Gram-negative pathogens were *Klebsiella pneumoniae* revealed in 8 (11.76%) cases and *Escherichia coli* in 8 (11.76%) cases. Summary of pathogens and their effect on the course of infection associated with the catheter in 68 infectious complications are shown in the (Table 4).

A detailed analysis of survival among 47 patients with infection-related complications showed a higher death risk among patients with cardiac implantable electronic devices (CIED) and biomaterials implanted in peripheral vessels. A worse prognosis was identified among patients with infection accompanied by

Table 1. Clinical data of patients dialyzed by permanent catheter and comparison of subgroups with and without catheter-related infections

	Patients with permanent catheters	Patients with catheter-related infection	Patients without infective complications	P Mann-Withney "U"/χ^2 test
Number (n, %)	398 (100.0%)	65 (100.0%)	333 (100.0%)	
Age [years] mean ± SD	68.73 (13.26)	66.04 (13.20)	69.26 (13.23)	P = 0.073
Male (n, %)	194 (48.74%)	36 (55.38%)	158 (47.45%)	P = 0.301
No of catheters inserted after failure of previously created dialysis fistula (n, %)	129 (32.41%)	26 (40.00%)	103 (30.93%)	P = 0.199
Dwell times of dialysis catheter(s) [days] mean ± SD	505.2 (428.3)	548.3 (449.0)	496.7 (424.3)	P = 0.347
Average time of catheter usability (days; SD)	435.7 (398.2)	419.4 (392.1)	438.9 (399.9)	P = 0.718
No of patients with single catheter (n, %)	322 (80.90%)	41 (63.08%)	281 (84.38%)	P = 0.0001
No of patients with one catheter replacement (n, %)	58 (14.57%)	15 (23.08%)	43 (12.91%)	P = 0.053
No of patients with two catheter replacements (n, %)	16 (4.02%)	8 (12.31%)	8 (2.40%)	P = 0.0007
Venous thrombotic complications (n, %)[a]	66 (16.58%)	18 (27.69%)	48 (14.41%)	P = 0.014
Generalized atherosclerosis (n, %)[b]	108 (27.14%)	33 (50.77%)	75 (22.52%)	P = 0.000
Diabetes (n, %)	73 (18.34%)	21 (32.31%)	52 (15.62%)	P = 0.003
Arterial hypertension (n, %)	109 (27.39%)	35 (53.85%)	74 (22.22%)	P = 0.000
Coronary disease (n, %)	44 (11.06%)	22 (33.85%)	22 (6.61%)	P = 0.000
Atrial fibrillation (n, %)	12 (3.02%)	7 (10.77%)	5 (1.50%)	P = 0.000
Heart failure (n, %)	78 (19.60%)	37 (56.92%)	41 (12.31%)	P = 0.000
Past history of stroke (n, %)	4 (1.01%)	3 (4.62%)	1 (0.30%)	P = 0.012
History of neoplastic disease (n, %)	78 (19.60%)	21 (32.31%)	57 (17.12%)	P < 0.008
Co-existing diseases (n, %)[c]	87 (21.86%)	22 (33.85%)	65 (19.52%)	P < 0.017
Death during follow-up (n, %)	199 (50%)	35 (53,85)	164 (49,25%)	P = 0.588

No: number; SD: standard deviation; av: average; NS: no statistically significant difference.
[a]history of venous thromboembolism
[b]atherosclerosis diagnosed at least in two locations
[c]co-existing diseases affecting the patients studied, not analysed individually, marked with the following codes the International Statistical Classification of Diseases and Related Health Problems — ICD-10: D 50; D53; D64; E03; E04 E27; G65 J20; J42; J44; J45; J 81; J 96; K26; K50; K65; K76; L08; L97; M06; M 32; M 34; S68

hypotension, high leucocytosis, a lower level of blood platelets and a high leucocytes/blood platelets (WBC/PLT) ratio. Present study showed that a type of bacteria Gram (+) or Gram (–) had no effect of the higher death risk (Table 5).

Univariable regression analysis shown that the following factors contributed to higher risk of death: presence of cardiac implants and a severe course of infection with hypotension, high leucocytosis, thrombocytopenia and a high WBC/PLT ratio (Table 6).

Discussion

Permanent catheters are an option for patients requiring hemodialysis for whom the formation of a fistula from own vessels is impossible or contraindicated. Dialysis through a tunnelled catheter may lead to numerous dangerous consequences. Catheter-related infection occur 41% more frequently than is the case among patients with native A-V fistula [10–12]. According to National Kidney Foundation patients with

Table 2. Risk factors of CRI — results of univariable linear regression analysis

Infection-related complications	OR	95%C	P-value
Patient's age	0.983	0.964–1.002	0.076
Generalized atherosclerosis	3.548	2.043–6.159	0.000
Diabetes	2.579	1.415–4.699	0.002
Venous thrombotic complications	2.274	1.217–4.250	0.010
Neoplastic disease	2.311	1.275–4.189	0.006
Atrial fibrillation	7.917	2.421–25.888	0.001
Arterial hypertension	4.083	2.348–7.103	0.000
Coronary artery disease	7.233	3.688–14.185	0.000
Heart failure	9.411	5.208–17.005	0.000
Co-existing diseases	2.109	1.178–3.777	0.012

The multivariable linear regression analysis has shown that independent risk factors of CRI were: younger age of patients, the presence of coronary artery disease and heart failure (Table 3); OR: odds ratio, CI: confidence inteval

Table 3. The risk factors of CRI — results of multivariable linear regression analysis

Infection-related complications	OR	95%CI	P-value
Patient's age	0.955	0.931–0.979	0.000
Generalized atherosclerosis	1.859	0.751–4.598	0.178
Diabetes	0.783	0.352–1.745	0.549
Thrombotic complications	1.429	0.661–3.092	0.363
Neoplastic disease	1.556	0.751–3.225	0.233
Co-existing diseases	1.320	0.643–2.710	0.448
Atrial fibrillation	1.923	0.414–8.920	0.402
Arterial hypertension	1.840	0.909–3.725	0.089
Coronary artery disease	3.412	1.423–8.179	0.006
Heart failure	4.532	2.013–10.202	0.000

OR: odds ratio; CI: confidence inteval

a catheter run the twice as high risk as those using A-V fistula [5, 8], and the BSI (bloodstream infection) rate is 4.85 times as high when tunnelled catheters are used [11]. The present study identified 92 (23.1%) catheter-related infection of an average infection rate of 0.46 per 1,000 catheter days. In case of tunnelled catheters, according to various sources, the frequency of infectious complications ranges from 0.5 to 5.5 per 1,000 catheter days [11–15]. The large discrepancy of results is probably related to the diversity of the studied populations and the research methodology. Long-term observation of a large group of patients in whom 2,230 permanent catheters were implanted during 23 years showed 226 infectious complications, with an infection rate of 0.514 per 1000 catheter days [16]. In another study, which analysed various types of vascular access over 6 years, the infection rate for permanent catheters was 1.03 per 1,000 patient days [11]. The next investigation, assessed the impact of the availability of specialist nephrological care on the risk of infection demonstrated 0.19 infections per 1000 catheter days [15]. According to a systematic overview of 200 prospective studies, an average BSI rate for tunnelled catheters amounted to 1.6 per 1,000 catheter days [17], while in the latest reports of 2019, this rate was estimated at 2.26 per 1,000 catheter days [13].

The present study showed that catheter-related infection occurred more often in a younger age and in patients with coronary artery disease and heart failure. One study comparing the risk of infection in younger patients (18–74 years old) dialyzed by a permanent catheter with a group of elderly patients (over 75 years) also demonstrated a higher infection risk among the younger patients (1.95 per 1,000 catheter days) than the older ones (0.55 per 1,000 catheter days) [18]. Other data regarding the impact of various factors on the occurrence of catheter-related infections are not uniform due to the variety of parameters assessed. Most often the effect of diabetes is emphasized, which in the current study

Table 4. Summary of pathogens and their impact on the course of 68 catheter-related infections

	Catheter related bloodstream infection (42)	Central line- associated bloodstream infection (22)	Infections requiring hospitalization; negative blood and catheter cultures (4)	Symptoms of catheter site infection in the whole group (25)	Infection affecting organs distant from infection source (abscesses, infective endocarditis, pneumonia) (14)
Gram-positive bacteria	26	11	2	17	9
Staphylococcus aureus	11	8	1	10	3
Staphylococcus epidermidis	11	1	0	4	3
Staphylococcus hemolyticus	1	1	0	1	1
Methicillin-susceptible, coagulase-negative *Staphylococcus species*	0	1	0	0	0
Serratia marcescens	1	0	0	0	1
Coagulase-negative *Staphylococcus*	2	0	1	2	1
Gram-negative bacteria	16	11	2	8	5
Klebsiella pneumoniae	4	4	0	2	1
Klebsiella oxytoca	1	2	0	2	0
Escherichia coli	5	3	0	0	3
Morganella morganii	3	0	0	1	0
Enterobacter cloacae	2	0	0	2	0
Pseudomonas aeruginosa	0	0	1	1	0
Enterococcus faecalis	1	1	1	0	1
Citrobacter freundii	0	1	0	0	0
Candida glabrata (co-existing infection)	1	0	0	0	0

During follow-up 199 deaths occurred (50,0%). There were no significant differences between infectious (35; 53.85%) and non-infectious (164; 49,25%) group. Table 1, Figure 1.

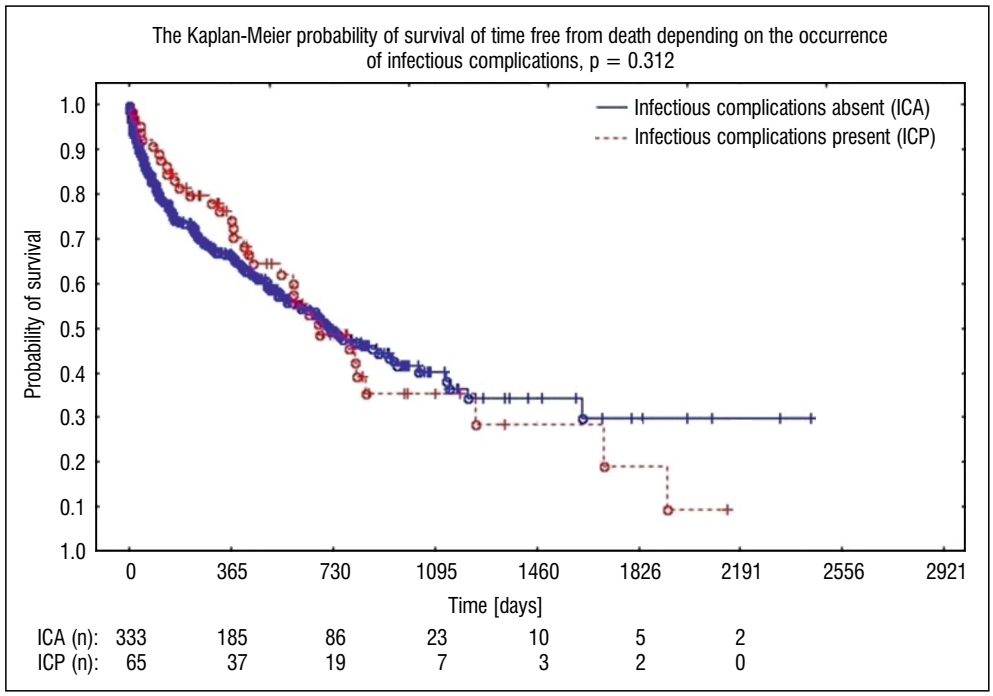

Figure 1. Kaplan Meier time free of death in groups of patients divided depending on dialysis catheter infection presence

was an important risk factor in univariable analysis. A large group of patients dialyzed with permanent catheters showed that the risk factors for infectious complications were: prior bacteraemia, diabetes mellitus, time from catheter implantation > 90 days, and hypertension [16]. Risk factors identified by another report included diabetes, generalized atherosclerosis, history of bacteraemia and carrying Staphylococcus *aureus* in the nasal cavity if coupled with long-term use of a catheter [13]. Other observation which involved 102 patients with 42 catheter-related infections also identified diabetes, a low level of albumins and haemoglobin as factors contributing to infection-related complications [11]. In turn, a recent analysis of early catheter infection found an essential role of carrying MRSA (methicillin resistant) *Staphylococcus aureus*, previous catheter-related infection and bacteraemia or bacteriuria occurring up to 3 months before catheter insertion [1, 6, 13].

In most cases, Gram-positive bacteria are responsible for infection among dialyzed patients: it is reported that they caused up to 75% catheter-related infections [6, 7, 13, 19, 20], with two pathogens being the most frequent: *Staphylococcus epidermidis* (35%) and *Staphylococcus aureus* (35%). Gram-negative pathogens were found in up to 40% of cases [5, 6, 9, 17, 21, 22]. Our results showed similar proportions: 57.35% of infections were caused by Gram-positive bacteria, including *Staphylococcus aureus* (29.41%) and other Staphylococci (27.94%), mainly by *Staphylococcus epidermidis*. Infections caused by Gram-negative bacteria accounted for 42.64 %.

Blood infection due to vascular access is a serious challenge both in terms of diagnosis and therapy, which is especially noticeable in intensive care units, where it accounts for about 20–40% of all hospital infections [22–24]. The current study confirmed a low probability of survival of patients with infectious complications (53,85%) during the follow-up period, however, it was comparable to the high mortality rate of dialyzed patients without infection (49.25%; P = 0,588). The apparent lack of significant influence of infection on the survival of this group of patients is probably associated with the strong impact of other known risk factors for death in patients with renal failure: premature atherosclerosis and associated metabolic disorders.

The mortality rate among dialysis patients depends on the type of vascular access and is higher in patients with catheters and fistulas made of artificial materials [1, 4, 17, 22, 24–27]. Paradoxically, progress in medicine has led to an increase in infection rate by introducing artificial materials to build new vascular access. One study which analysed a large population of 2,666 patients dialyzed by catheters showed 32% mortality rate over the period of observation. The study showed that patients with tunnelled catheters had 6.9-fold higher mortality from sepsis compared to patients dialyzed with A-V fistula [28]. The results of our study showed that the following factors contributed to the higher risk of death: the presence of heart and vessels implants and

Table 5. Factors affecting survival among patients dialyzed through permanent catheters and suffering infection-related complications

Infection-related complications	Death	Survivors	P Mann-Withney "U"/χ^2 test
No of patients (n, %)	7 (14.9%)	40 (85.1%)	–
Average age (years, SD)	73.579 (6.80)	66.55 (14.41)	0.174
Female patients (n, %)	4 (57.14%)	23 (57.50%)	0.692
Hospitalization time (days, SD)	12.57 (6.63)	13.40 (9.94)	0.756
Time from catheter insertion to infection occurrence (months, SD)	8.62 (8.80)	3.97 (4.21)	0.124
Generalized atherosclerosis (n, %)	7 (100%)	25 (62.50%)	0.128
Diabetes (n, %)	2 (28.57%)	17 (42.50%)	0.783
Thrombotic complications (n, %)	0 (0.00%)	5 (12.50%)	0.745
Infection-related complications over the last 6 months (n, %)	5 (71.43%)	23 (57.50%)	0.783
Neoplastic disease (n, %)	3 (42.86%)	13 (32.50%)	0.919
COPD (n, %)	1 (14.29%)	3 (7.50%)	0.888
Atrial fibrillation (n, %)	3 (42.86%)	5 (12.50%)	0.154
Arterial hypertension (n, %)	6 (85.71%)	29 (72.50%)	0.787
Coronary artery disease (n, %)	5 (71.43%)	18 (37.50%)	0.379
NYHA class I–II (n, %)	2 (28,57%)	22 (55,00%)	0.379
NYHA class III–IV (n, %)	5 (71.43%)	17 (42.50%)	0.315
Stroke (n, %)	0 (0.00%)	4 (10.00%)	0.888
Cardiac implants (n, %)	5 (71.43%)	10 (25.00%)	0.046
Positive catheter culture (n, %)	6 (85.71%)	28 (70.00%)	0.690
Local symptoms of infection (n, %)	1 (14.29%)	15 (37.50%)	0.445
Positive blood culture (n, %)	7 (100%)	38 (95.00%)	0.682
Positive blood culture, Gram-positive bacteria (n, %)	4 (57.14%)	19 (47.50%)	0.951
Positive blood culture, Gram-negative bacteria (n, %)	3 (42.86%)	21 (52.50%)	0.951
Systemic symptoms of infection (n, %)	7 (100%)	36 (90.00%)	0.888
Pneumonia (n, %)	2 (28.57%)	4 (10.00%)	0.457
Infective endocarditis (n, %)	0 (0.00%)	2 (5.00%)	0.682
Hypotension (n, %)	5 (71.43%)	10 (25.00%)	0.046
Patients with recurring infection-related complications (n, %)	1 (14.29%)	12 (30.00%)	0.690
Venous access: right angle (n, %)	2 (28.57%)	25 (62.50%)	0.208
Venous access: left angle (n, %)	2 (28.57%)	7 (17.50%)	0.868
Venous access: left subclavian vein (n, %)	2 (28.57%)	1 (2.50%)	0.078
Venous access: right subclavian vein (n, %)	0 (0.00%)	2 (5.00%)	0.682
Venous access: left femoral vein (n, %)	0 (0.00%)	0 (0.00%)	–
Venous access: right femoral vein (n, %)	1 (14.29%)	3 (7.50%)	0.888
Catheter tip location: superior vena cava (n, %)	6 (85.71%)	35 (87.50%)	0.629
Catheter tip location: inferior vena cava (n, %)	1 (14.29%)	4 (10.00%)	0.745
Catheter removal due to infection (n, %)	3 (42.86%)	8 (20.00%)	0.404
Patients with catheter no > 1	0 (0.00%)	4 (10.00%)	0.888
Procalcitonin (ng/mL; av., SD)	29.91 (15.39)	32.00 (70.89)	0.108
CRP (C-reactive protein) (mg/L; av., SD)	2.6 (1.72)	1.38 (1.11)	0.141
Leucocytes (U/L; av., SD)	14.20 (5.23)	10.63 (5.89)	0.056
Haemoglobin (mg/dl; av., SD)	9.31 (1.98)	10.09 (1.44)	0.316
Platelets (K/L; av., SD.)	104 (56)	171 (78)	0.015
Leucocytes/platelets ratio (av., SD)	0.16 (0.09)	0.08 (0.06)	0.002

COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; CIED: cardiac implantable electronic devices

Table 6. Risk factors of death of patients with catheter related infections

Infection-related complications	OR	95%CI	P
Cardiac implants [a]	7.500	1.193–47.159	0.027
hypotension	7.500	1.193–47.159	0.027
Leucocytosis	1.089	0.962–1.233	0.167
Platelets (PLT)	0.153	0.027–0.869	0.029
Leucocytes/platelets ratio	1.165	1.024–1.326	0.017

[a]presence of CIED or biomaterial implanted to peripheral vessels; OR: odds ratio; CI: confidence inteval

severe infection with hypotension, high leukocytosis, thrombocytopenia and a high ratio of leukocytes to platelets. Previous reports confirmed an unfavourable prognosis for cases of similar constellation of inflammatory parameters in dialyzed patients [11, 13, 29–32].

The present study also demonstrated that the presence of artificial devices and biomaterials increase mortality risk in the course of infection in patients dialyzed with permanent catheters (OR = 7.5; 95%CI: 1.193–47.159; P = 0,027). Likewise, previous reports showed a negative effect of the presence of the cardiac implantable electronic devices on the development of infectious complications. Endocarditis, bacteremia and sepsis were often complications observed in this population, especially in patients dialyzed with permanent catheters [17, 23, 25, 26, 33]. Infectious complications caused by a dialysis catheter are a serious problem. Although the study was conducted on a small group and was retrospective, it showed certain risk factors for death and poor prognosis in this burdened group, similar to those of other researchers. The situation requires further observation and conducting a prospective study, preferably on a larger group of patients, in order to obtain better results.

Study limitations

This study is a retrospective analysis and it was conducted on the basis of selected data made available by the National Health Fund. Detailed clinical data concerning infection-related complications were available for 47 patients only.

Conclusions

Infections in patients dialyzed with permanent catheters are a common, serious complication. The specific risk factors of catheter-related infections include younger age, coronary artery disease and heart failure. Mortality of patients with infectious complications is very high, but comparable to the survival of all dialyzed by the permanent catheter. A higher mortality rate among patients with catheter-related infection increase with the presence of additional intravascular and intracardiac implanted materials and a severe course of infection with hypotension, thrombocytopenia and a high leucocytes/platelets ratio.

Conflict of interest

None.

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The role of physical activity in prevention and treatment of peripheral vascular disorders

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Abstract

Peripheral vascular diseases constitute one of the most significant medical and social problems. Physiotherapy plays an important role among and in addition to various treatment modalities. Physiotherapy for vascular disorders applied in vessel disease treatment primarily consists of reasonable and regular exercises and activities, and selected physical procedures. The review paper presents current data concerning the most commonly applied exercises and physical procedures in selected peripheral vascular diseases.

Key words: vessel diseases, physiotherapy, treatment

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Introduction

Vascular diseases impair the quality and comfort of life of patients. Epidemiologic data indicate that 20–50% of adult population suffer from venous and arterial vascular diseases of various etiology [1]. The higher morbidity rate is characteristic for women rather than men. Peripheral vascular diseases are divided into organic (e.g. peripheral artery occlusive disease, Buerger's disease, lower limb varicosis) and angioneurotic disorders (e.g. Raynaud's syndrome) [2].

Each year the number of publications in the international medical journals concerning vascular disease treatment increases. The level of current researches is very high. They enable a better understanding of the etiopathophysiology of vessel system disorders, and they also present the new ways of treatment of these patients [3, 4].

The principles of primary prophylaxis in patients for arterial diseases

The major purpose of primary prophylaxis of vascular disorders is the education of the society about the causes and consequence of the disease, about risk factors (arterial hypertension, obesity, diabetes etc.) and their treatment. This includes education about proper diet and nutrition including a high amount of proteins, vegetables and fruits. The positive attitude towards a healthy lifestyle (more walks, bicycle riding, swimming) by an adequate understanding of physical activity is the integral element. Common ailments should be avoided [5, 6].

For secondary prophylaxis, one has to combat risk factors and introduce modification into a present lifestyle. All patients with BMI index > 25, patients not following their diets, patients with diagnosed arterial hypertension, patients with increased blood glucose or total cholesterol level and smokers are recommended to initiate measures of secondary prophylaxis [7, 8].

In the case of patients suffering from peripheral artery disease (PAD) with symptoms of intermittent claudication, one aim of physical therapy is to create collateral circulation providing ischemic areas with the adequate blood supply. One of the methods to achieve this is to increase arterial tension increase in blood vessels proximal to the place of obstruction, and simultaneously reduce vascular resistance in segments

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distally from the place of obstruction. In the case of people with a sedentary lifestyle, the increase of physical activity in basic activities of daily living (ADL) will provide a major benefit. This should be initiated after the baseline determination of individual risk and patient's competence and condition. This concept is defined as a functional physical activity. It includes walking, short distance bicycle riding, stairs climbing instead of taking an elevator, or ordinary garden activities [9, 10].

It is essential to mention that patients with critical limb ischemia (CLI) do not qualify for exercise training. CLI in patients with lower limb PAD is defined, as chronic ischemic pain occurring during rest, lasting for more than two weeks, or as ischemic lesions in the form of foot ulceration or necrosis. CLI is associated with a high risk of limb loss and occurrence of vascular episodes in the form of myocardial infarction and cerebrovascular accident [11, 12].

An excellent exercise unit in case of Fontaine's stage I or II chronic lower limb ischemia is walking training aimed at increasing blood flow to the leg and thereby recruiting collaterals. Additionally, regular exercises extend the period of intermittent claudication. Treatment of patients with claudication includes not only extension of claudication distance, but also the countermeasures against multiple ischemia incidents and blood resupply to limbs. In addition, it stimulates the gastrocnemius muscle pump thereby increasing venous blood outflow [13, 14].

The principles of primary prophylaxis in patients for venous diseases

Besides aforesaid physical activity, the following factors play a significant role in the prophylaxis of chronic venous disorders and lymphatic oedema: keeping proper body mass and following a diet, avoiding obstructions, tight clothes, high heels, hot baths, sauna and sunbathing. It is crucial to drink at least 2,5 litres of neutral fluids and rest with lower limbs placed 15cm higher than the heart level [15]. Patients with lymphatic oedema have to avoid therapeutic procedures, blood pressure measurements and blood collection from the limb affected with lymphoedema [6, 16].

Working patients need to take care of the adequate, ergonomic place of work (using proper bolsters, avoiding prolonged standstill, and if possible, doing exercises aiming at sural region mobility (bending of dorsum/sole of feet, standing on tiptoes/heels in sedentary position, mark time while in sedentary position) [17, 18].

In primary prophylaxis of chronic venous disorders, it is also recommended to wear compression stockings, especially in case of those patients, who work mostly in sedentary/standing positions, and those, whose family history revealed similar venous disorders [19, 20].

In primary prophylaxis or venous disease, it is also recommended to place limbs higher (bolster during sleep, sitting etc. for passive congestions reducing oedema and pain), and to avoid excessive, standing or sedentary position [5, 6].

Currently, the term *travel syndrome* has been coined — it is one of the most significant risk factors of venous thromboembolic disease. With long-term plane travels, however, it can occur during long car, train or bus travels. One should bear it in mind while planning long travels. Travellers need to wear loose clothes not compressing lower limbs and waist, drink appropriate amount of fluids and often tighten their leg muscle as well. Whereas in case of people with at least one venous thromboembolism risk factor, who are to travel longer than 8 hours, it is recommended to wear low-level compression stockings or/and take a single prophylactic dose of low molecular weight heparin around 2 hours before travel [21]. Moreover, bed rest constitutes one of the major causes of the high risk of venous thromboembolism development; thus, the bed rest period should be minimised taking into consideration the patients' clinic condition. Besides minimising immobility, other physical methods play a significant role in primary thromboprophylaxis: graded compression stocking and intermittent pneumatic compression [22, 23]. Anticoagulant primary prophylaxis has to be used not only at surgical wards but also at non-surgical ones and in ambulatory treatment. It was proven that the venous thromboembolism risk profile is as high in hospitalised patients as in patients treated at their homes [24].

Diagnostics evaluation before initiation of physiotherapy needs in lower limb PAD

1. Exclusion of critical limb ischemia.
2. Diagnosis of comorbidities not allowing to perform exercise training.
3. Standardized evaluation of patient's performance as a baseline exam.

March test — consists in marking the distance a patient is able to cover without typical ischemic pains. A patient under physiotherapist's assistance should move in a pace 120 steps per 1 minute (3 steps per second). During tests, the attention is paid to the fact when and where limb pain occurs, and if a patient weighs down both legs equally [25, 26].

The results should be classified into three groups according to Waibel:

1. Minor disorders of muscular blood flow in limbs, pain does not occur after three-minute exercise.
2. Medium disorders of muscular blood flow in limbs, pain occurs after one up to three minutes of exercise.
3. Severe peripheral disorder, pain occurs in the first minute of exercise.

Older people should do 60–90 steps per minute, because other post-exertional symptoms may occur, such as dyspnoea or stenocardial pain. The trail should not be performed in IV class of PAD. Other functional assessment methods of patients with PAD includes ankle-brachial index (ABI) and Ratschow test [25]. During ABI, the measurement is carried out in supine position; by means of Doppler probe (so-called "Doppler blind probe") blood flow is located in the dorsal artery of foot and posterior tibial artery. Having pumped up sphygmomanometer bladder placed above lateral malleolus and impeded blood flow in the artery, the pressure is released in the cuff. The moment the blood flow starts again in the artery is noted as the systolic blood pressure. The procedure is repeated for both limbs, and then ABI is calculated by dividing higher malleolar pressure value by higher brachial systolic blood pressure (the pressure should be measured on both limbs, and the higher one should be applied in calculations). The normal ABI index range is 0,9–1,15. ABI below 0,9 is the symptom of stenoses. In patients with diabetes or renal failure, ABI may be falsely higher (over 1,3) as a result of blood vessel calcification — these cases require toe-brachial index [27, 28].

Ratschow test allows determining if the lower limb arterial lumen or iliac girdle is occluded. Patient in supine position bends and straightens feet with lower limbs raised up vertically — around 40 moves per minute. If one foot or both turns pale, or sural pain occurs, it proves ischemia. In verticalisation (or sedentary position) reactive hyperaemia (> 15s) and delayed superficial vein ingurgitation on feet (> 20s) are observed [29].

Physiotherapy in selected vascular diseases

Kinesiotherapy

Exercise training basic form of *best medical therapy* (BMT) for vascular disorders [30]. It may be treated as a basic therapeutic method replacing other, more costly treatment methods [31].

Lower limb peripheral artery disease (PAD)

Lower limb PAD requires exercise training. Patients up to 60 do 120 steps per minute, 60 ± 60 steps per minute, first 20 minutes, then 45 minutes 2–3 times/ /day. The distance should be 2/3 of claudication distance, thus one avoids the distance preceding pain. Recommended period of exercises — at least 20 weeks. Standing on tiptoes up to 30 repetitions 2–3 times/day and tiptoe push-ups are also beneficial. Their aim is the additional thigh and buttock muscle overloading [2, 14]. What is more, stair climbing, cycloergometer riding and swimming are recommended [32]. Despite the proven increase of endurance and march capacities and patients' general condition improvement, march training influences also biochemical and physiological organism mechanisms. Its positive impact on the fibrinolytic activity of patients with chronic limb ischemia has been proved [33]. Moreover, kinesiotherapy leads to better oxidative saturation of arterial blood, reduced concentration of LDL- cholesterol fraction in blood, and improvement of carbohydrate metabolism in patients with coexistent diabetes. March training results also in muscle morphology changes, walking economisation, changed pain perception, and, which is the most important for patients, it actually prolongs the claudication distance and improves general fitness [34, 35].

By peripheral occlusions, circulation disorders concern in major cases the most peripheral limb parts (hands and feet). Blood flow in cutaneous vessels can be improved by lower placement of limbs. Sleeping with one limb lower, stretched beyond a bed at an angle of 30° supported by something soft brings relief. Raising the head of a bed or performing Ratschow and Buerger's exercises are also beneficial [36]. The exercises consist of alternate limb raising and lowering, causing active congestion and ischemia of muscles by changing the position. Another Ratschow exercise requires a patient in the supine position to lift lower limb at an angle of 90° and grab thighs simultaneously with both hands in posterior region of the knee; then a patient performs rotation in crurotalar joints till first exhaustion symptoms (2–5 minutes). Next steps are limb lowering beyond a bed (2–5 minutes), resting in supine position and repetition of rotation in joints. The exercises should be performed in the morning and in the evening [37, 38]. In case of peripheral vessel diseases with intermittent claudication as the only symptom, a patient should not be recommended to refrain from walking. A patient has to perform moderate and thoroughly planned general and limb exercises, spend 1 hour walking to prevent amyotrophy. Limiting physical exercises, walking in particular, is a big mistake [15, 16].

Bürger's exercises are variation of above exercises. A patient in supine position lifts one's lower limbs at an angle of 45° and bends feet and toes rhythmically up to 3–4 minutes (up to endurance limit); then, a patient sits with lowered limbs for 3–4 minutes (reactive congestion). Next, a patient rests in supine position up to 3–4 minutes and repeats the exercise. Rhythmical changes of positions enhance blood outflow and inflow to limbs, having a positive effect on pain symptom intensity by vessel peristalsis. The exercise cycle should last 0,5–1 hour, 2–3 times/day. Additionally, one can perform bicycle crunch in ambulatory conditions. Cycloergometer training, outdoor walking, aerobics and benign jogging may also be a part of active rehabilitation. Besides those

aforementioned physical activities, it is also recommended to stand on tiptoes/heels, climb stairs (patients with competent cardiovascular system) [2, 36].

Chronic venous disorders and lower limb deep venous thrombosis

In venous diseases, kinesiotherapy should include active lower limb exercises, enhance blood outflow as a result of muscle pump operation, isometric exercises and pelvic girdle exercises. Apart from that, everyday walks, bicycle or cycloergometer riding or swimming play significant roles as well [25].

The easiest form of exercises is alternating dorsal bending and plantar extension of feet performed twice a day, especially in case of sedentary lifestyle [1, 39].

In venous diseases, one should refrain from long sedentary positions with lowered lower limbs, and folding legs; while resting limbs should be placed higher than the rest of the body [40]. Patients are also recommended to avoid exertional exercises requiring abdominal press such as mountain biking, weightlifting, tennis on a hard surface, squash and other physical activity forms significantly overloading sural muscles and requiring sudden accelerations [25].

Early patients' mobilisation is also very important in patients with lower limb deep venous thrombosis. It has been proven that early mobilisation of patients with simultaneous compression therapy appliance does not increase the risk of pulmonary thromboembolism, but reduces pain and limb oedema, and improves the quality of patient' life and venous vessel fibrinolysis. If ballooning clot/thrombus is not diagnosed, a patient should be mobilised within 24 hours, and compression therapy should be applied during mobilisation [20, 41]. High levels of physical activity at one month were shown to be associated with reduced severity of post-thrombotic symptoms during the subsequent 3 months [42].

Lymphoedema

Lymphoedema is characterised by accumulation of interstitial fluid in skin and subcutaneous tissue as a result of lymphoid system dysfunction, containing e.g. water, proteins, erythrocytes, lymphocytes, islet cells, cytokines and keratinocytes, fibroblasts and endothelial cells. It leads to chronic inflammation process and results in fibrosis of the skin and subcutaneous tissue [16, 43]. Brunner distinguishes fives stages of lower limb lymphatic oedema [25].

1. Benign oedema of feet and lower leg occurring at the end of a day, resolving spontaneously after lifting a limb.
2. Whole-day oedema resolving spontaneously after night with positive Stemmer sign (skin fold thickening above the second toe, skin hard to lift).
3. Permanent oedema, not resolving after limb evelating.
4. Permanent foot-deforming oedema, often complications of skin inflammation, (erysipelas, eczema, lymphatic fistulas).
5. Elephantiasis — large foot-deforming oedema with skin thickening, muscle lesions (dystrophy), compromising functioning of a limb.

Lymphatic oedema is prone to accretion without adequate treatment. In lymphatic oedema treatment, complex decongestive therapy (CDT) plays a major role. It was proven that CDT appliance is much more efficient than monotherapy appliance. The proper appliance of CDT therapeutic element combination leads to oedema reduction, enables sustaining the therapy effects and limits the occurrence of complication. The essential parts of complex decongestive therapy constitute kinesiotherapy, compression therapy and manual lymphatic drainage (MLD) [6, 44].

Physical activity constitutes a significant addition to CDT. It is aimed at mobilisation of myoarticular pump and better reabsorption of fluids at vessel capillary level. Recommended kinesiotherapy forms, similar as in patients with chronic venous disorders, are: walks, endurance march, jogging, nordic walking, bicycle riding on flat terrains, hiking, dancing, swimming and cross-country skiing. Patients with lymphatic oedema should do exercises and breathing exercises, especially diaphragmatic breathing. One should bear in mind that exercises facilitating lymph outflow have to be performed in the lymph drainage direction. Both, in chronic venous disorders and lymphatic oedema the following kinesiotherapy forms are contradicted: exertional forms requiring abdominal press forms overloading sural muscles and requiring sudden accelerations [12, 13].

It should be highlighted that physical activity gives better results with simultaneous compression therapy by bandages or other compression materials. Otherwise, movement and exercises may intensify lymphostasis and increase oedema. Swimming or water gym are exceptions — water environment takes the role of compressor [11,13].

Compression therapy

Compression therapy is found to be golden standard in chronic venous disorder and lymphatic oedema treatment. The mechanism of beneficial compression therapy influence is connected with lowering of venous blood pressure by reduction or elimination of reflex, facilitation of muscle pump functioning (lowering of march pressure), decrease of venous diameter and restoration of venous valves by drawing cusps nearer, reduction of congestion, improvement of lymphatic

drainage by compression of subcutaneous tissues (increase of intratissued pressure, increased oedemic fluid absorption, reduction of protein amount in tissues, which may can to regression of lipodermatosclerosis lesions) [45].

Because of the fact that compression therapy has direct influence only on hydrostatic intratissued pressure, but it does not influence oncotic pressure (i.e. osmotic pressure of protein colloid), it is highly possible that discontinuation or end of compression will cause fast oedema recurrence [13].

Compression therapy indications include chronic venous incompetence (in venous ulceration), thrombosis of superficial and deep veins, lymphatic oedema, post-traumatic oedema, erysipelas, vessel inflammation oedema, after venous sclerotherapy or surgical treatment of varices; whereas, the compression therapy contra-indications are the following severe advanced peripheral vessel sclerosis (III or IV stage according to Fontain class) ABI < 0,8 by high compression, absolute p/w-ABI < 0,6, decompensated circulation incompetence, skin lesions with characteristic intense exudate, sensation disorder (advanced peripheral neuropathy), hypersensitivity to compression stocking material [20, 25]. It can take the form of bandages, compression textiles or intermittent pneumatic compression [46, 47].

Compression products (knee-length socks, stockings and pantyhose) are manufactured in four compression categories [47]:

- I compression level (20–30 mm Hg): anti-thrombotic prophylaxis at-risk groups, venous disorder prophylaxis, venous disorder treatment in C1-C2 stage, I stage of lymphatic oedema;
- II compression level (30–40 mm Hg): thrombotic inflamation of veins, after invasive procedures (sclerotherapy or surgical treatment of varices), ulceration recurrence prophylaxis, C3-C4 stage (oedema, trophic lesions), II and III stage of lymphatic oedema;
- III compression level (40–50 mm Hg): advanced trophic lesions in chronic venous incompetence, chronic venous ulceration, varices of large venous trunks with severe oedema, III and IV stage of lymphatic oedema;
- IV compression level (50–60 mm Hg): irreversible venous oedema, venous ulceration in post-thrombotic syndrome, severe post-thrombotic syndrome, IV and V stage of lymphatic oedema.

Two types of compression are distinguished i.e.: flexible and inflexible compression. Flexible compression is generated by bandage with a medium or high level of tensility and compression products, and it is independent with regards to muscle activity but it creates high static pressure. Thus, they should not be worn overnight [48]. On the other hand, inflexible compression is created by non-tensile or little tensile bandages or layered compression products. Inflexible compression is not recommended in case of inactive patients [49].

Pneumatic massage is a type of therapy using special, sequentially inflated compression cuffs i.e. pressotherapy. Pressotherapy consists of simultaneous or alternate tissue massage by means of compression cuffs with overlapping chambers. The method facilitates the treatment of patients with lymphatic and venous incompetence. It is also applied in upper limb oedema in female patients after mastectomy and anti-thrombotic prophylaxis. The single procedure should last around 60 minutes (dependent on the stage of disease), be sequential (filling of next chambers from circle to nearer limb parts) and performed once a day for 5-6 days/ /week. After pneumatic drainage (active compression) passive compression (bandaging, compression products) should be applied [25, 50].

Manual lymphatic drainage (MLD)

Major MLD's purposes are the following: increasing lymph outflow, especially from stasis areas, mobilisation of lymphatic vessels and flow intensification through lymph nodes, stimulating new lymph connection development between outflow areas i.e. anastomoses, and analgesic and regeneration activity [51].

MLD consists of stimulation of lymphatic system by special movements causing forced, but benign, lymphatic outflow. MLD requires three techniques: stroking, rubbing and pressing.

Lymphatic massage is based on four basic Vodder's strokes: "stationary circle", "rotary", "pump" and "scoop". Massage strength depends on the area of the body. It is carried out by outstretched hand placed flat parallel to a patient's skin without creams or oils. The procedure always begins with neck where two lymphatic trunks converge with venous system, then trunk quarters free from oedema adjacent to oedematous limb, and oedematous area at the end. The general MLD principle is drainage of the most proximal segment in order to lead there oedema from the lower segment. And, for instance, drainage in women after right-side mastectomy with axillary lymphadenectomy is conducted in the following sequence: neck, upper trunk quarter at non-operated left side, upper trunk quarter at operated right side, upper limb at operated right side starting from shoulder to arm, forearm, and, eventually, hand [25, 52].

MLD's indications include lymphatic oedema (primary and secondary), venous oedema, post-traumatic oedema, lipid oedema, oedema as a result of lack of physical activity, oedema in arterial circulation disorders, chronic abacterial inflammatory oedema,

idiopathic oedema. MLD's contra-indications are the following active inflammations (risk of septicaemia), active neoplasm processes, lymph node metastases, NYHA III–IV class of circulation incompetence; whereas local contra-indications of MLD include: in neck region — hyperthyreosis, in abdominal region — pregnancy, menstruation, non-specific enteritis, in limb region — thrombophlebitis. MLD procedure should be always performed with compression therapy [52, 53].

Physical procedures in selected peripheral blood vessel diseases

Physical procedures are a significant part of complex blood vessel treatment. Hydrotherapeutic procedures in the form of bath or aqua massage should be mentioned here. Baths should be taken in cool or lukewarm water (25–33°C). Cold constricts venous vessels massaging them gently. In some cases of lymphatic oedema (contraindications: active skin and subcutaneous tissue inflammation) rotary massage of lower/upper limbs is beneficial. Whereas, aqua massage is the special type of massage carried out during bath by applying high-pressure underwater spray of various temperatures [54].

Movement in water has a positive effect not only on the heart, but also on blood vessels. Impact of pressure and water stream leads to blood vessel massage, cardiac blood circulation and lymph circulation improvement. Faster blood circulation leads to better oxygen and nutrition supply of tissues and organs, and fitness/ /endurance improvement [32, 55]. Water compression in particular body regions, so-called "water compression therapy", reduces venous vessel diameter and capillary permeability, improves blood outflow from limbs, and strengthens vascular walls (prevents oedema and lymph stasis) [32].

The most common procedures in a spa treatment of this group of patients are carbonic acid baths: dry or gas with natural or synthetic CO_2. Carbon dioxide permeating through the skin has a direct impact on capillaries and axon reflex of skin arterioles causing capillary and bigger blood vessel vasodilation. It enhances the cardiac activity and reduces arterial blood pressure. Bath is applied in patients with functional arterial circulation disorders, capillary circulation disorders, arteriosclerosis peripheral blood vessel diseases, and I and II class arterial hypertension [54, 56].

Other forms of complex baths are radium water baths. Their appliance causes peripheral arterial vasodilation, reduction of arterial pressure, toning of the autonomic nervous system, a decrease of blood viscosity. Main indications include:peripheral vessel diseases and I and II class arterial hypertension [54, 56].

Peloid baths are another optional procedure for patients with peripheral vessel diseases. This therapy uses the natural properties of organic-mineral substances created in geological processes, so-called peloids. Peloids mixed with water create paste with therapeutic properties. Peloid procedures consist of simultaneous, gradual and steady tissue overheating and therapeutic influence of organic elements in peloid — mainly humin acids.

Both mechanisms lead to small vessel vasodilation and tissue hyperaemia. The procedures are applied in arteriosclerosis peripheral blood vessel diseases, Buerger's disease and venous ulceration of legs [42, 54].

One of the most commonly applied termotherapeutic procedures in vessel diseases are paraffin procedures in the form of compresses and wraps. Beneficial effects of the procedures are connected with the increase of blood flow. Paraffin procedures are applied usually in functional peripheral vessel diseases. The characteristic symptoms of the procedures are vessel reactions (local and general) and blood vessel performance according to *Dastre-Morat law*. However, one should bear in mind that termotherapeutic procedures are forbidden in patients with cardiac incompetence and arterial hypotension, which sometimes occur together with peripheral vessel diseases [54, 56].

Electrotherapeutic procedures are conducted mostly by means of direct current (galvanism), which reduces smooth muscle tension and widens their lumen as a result of current flow between two electrodes placed along peripheral arteries (applied in limb circulation disorders), and iontophoresis consisting in delivery of ionised medicine molecule through skin to tissues as a result of direct current flow (Bűrger's disease and Raynaud's syndrome). Procedures using alternating current with low and medium frequency (50–5000 Hz) e.g. diadynamic therapy — Barnard current, electrostimulation — TENS, high voltage electrostimulation, Träbert current – Ultra Reiz, Nemec interference current, stimulating neuromuscular system with heat properties. They are applied mainly in the treatment of peripheral blood flow in Bűrger's disease and Raynaud's syndrome, lower leg venous ulceration and vascular pain. High-frequency currents (e.g. low- and microwave diathermy) are also applied in Bűrger's disease and venous and lymphatic peripheral circulation disorders [54, 56].

Ultrasounds constitute another physical treatment method. The essence of their therapeutic impact is connected with heat and mechanic effect (micromassage). It causes vessel vasodilation (by direct heat activity and release of histaminelike substances), activity reduction of sympathetic nervous system and stimulation of tissue regeneration process. Ultrasounds are widely applied in treatment of Raynaud's syndrome, Bűrger's disease and lower leg venous ulceration [54, 56].

Light therapy procedures are applied in peripheral vessel diseases, particularly in order to achieve local hyperaemia (tissue overheating — heat erythema), and blood microcirculation as a result. Additional procedures lead to microcirculation biostimulation, which enhances regeneration of damaged blood vessels, improves local circulation and rheological properties of blood. This therapeutic effect is observed mainly during low-energy light therapy by LED diodes, and polarised light therapy. In angiology, light therapy is used mainly in treatment in lower leg venous ulceration and arteriosclerosis lower limb blood vessel diseases [57, 58].

In the description of physiotherapeutic procedures in blood vessel diseases, one should not omit the developing area of physical medicine applying an alternate magnetic field. Clinical experience of authors in the appliance of magnetotherapy, magnetostimulation and magnetotherapy in treatment of skin diseases, vessel diseases and their complications, proves the therapeutic effects of the treatment e.g. in diabetic foot, lower limb venous and arterial ulceration, and Bürger disease. The basis of biological effects of these therapies is the influence of electrodynamic and magnetomechanic phenomena, and ion cyclotron resonance, on widely perceived cell metabolism. It results in acceleration of electrolyte exchange between a cell and its environment, increase in mitotic activity, antimutagenic effect, growth in enzyme activity and increase in ATP and DNA synthesis. At tissue level, one observes improvement of peripheral blood microcirculation and increase in activity and excitability of nerve fibres with angiogenesis stimulation. Nevertheless, it should be bear in mind that the severe patient's condition and limb circulation disorders require careful physical treatment appliance taking into consideration the patient's current condition and contraindications [59–61].

Conclusion

Blood vessel diseases result in lower quality life of patients, disability, and even life-threatening complications. Although diagnostic methods have been improved, factors of their occurrence examined, surgical methods developed and new medicines introduced, vessel diseases constitute a severe medical problem, and physiotherapy still plays an essential role in prophylaxis and peripheral vessel disease treatment. Physiotherapy is particularly important in rehabilitation in the last stage of treatment leading to optimal patient's condition.

Conflict of interest

None.

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Selected biomarkers of atherosclerosis: clinical aspects

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Abstract

Atherosclerosis is a inflammatory-immunological-degenerative process. Cardiovascular diseases account for 42% of premature deaths among men and 52% of premature deaths among woman. Identification of classical biomarkers of atherosclerosis, such as LDL, HDL and triglycerides may not be helpful in patients with moderate or unusual cardiovascular risk. Non-classical indicators of atherosclerosis include markers of the inflammatory process, markers of atherosclerotic plaque injury, acute phase proteins, ischemic markers, markers of tissue necrosis, markers of myocardial dysfunction. The identification of CVD biomarkers enables the classification of patients to appropriate cardiovascular risk groups. Knowledge about the CVD risk group makes it possible to take rapid therapeutic intervention aimed at limiting this risk. Pharmacotherapy for cardiovascular diseases is primarily based on lowering cholesterol's level in the blood. Additional properties of statins (the most important lipid-lowering drugs) enable their pleiotropic effect by limiting the progression of atherosclerotic lesions by reducing the volume of atherosclerotic plaque. Further research on the pathogenesis of atherosclerosis will allow learning new risk factors and new biomarkers of this disease.

Key words: biomarkers, atherosclerosis, cardiovascular risk, cardiovascular diseases, statins

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Introduction

Atherosclerosis is a inflammatory-immunological-degenerative process involving small and medium-caliber arteries, which is responsible for the majority of CVD (cardiovascular diseases) [1]. Atherosclerotic lesions arise in childhood and even in fetal life [2]. Cardiovascular diseases account for 42% of premature deaths among men and 52% of premature deaths among woman [3]. Cardiovascular diseases are the most common cause of death in Poland. According to GUS (Central Statistical Office) data, in 2014 these diseases accounted for > 48% of premature deaths of Poles. Atherosclerosis is also responsible for peripheral arterial diseases (PAD), and what is more, it is the most important cause of amputation of legs [4]. Risk factors of progression of atherosclerotic lesions are divided into modifiable and unmodifiable, as well as, classical and non-classical [5] (Fig. 1). According to the National Health Service (NHS), the biggest life threats in developed countries are hypertension, smoking, hypercholesterolemia, obesity, dietary mistakes, lack of physical activity, excessive alcohol consumption, infections, non-traffic accidents, traffic accidents, illegal drug use, murders, medical complications, war, pregnancy and childbirth. The prevalence of the most important risk factors for cardiovascular disease in Poland was examined in the NATPOL 2011 Study (Fig. 2.). The most important cause of premature deaths in the world is hypertension [6]. The Cardiovascular Disease Prevention and Treatment Program (POLKARD 2017–2020), which aims to combat the classic risk factors for atherosclerosis, introduce modern effective diagnostic and therapeutic methods and act to level out disproportions arising in the country

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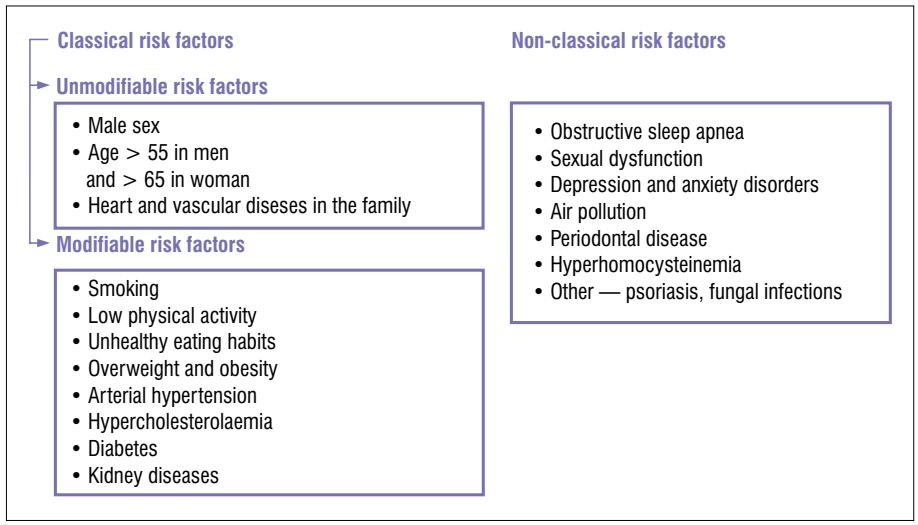

Figure 1. Risk factors for cardiovascular diseases [based on 5]

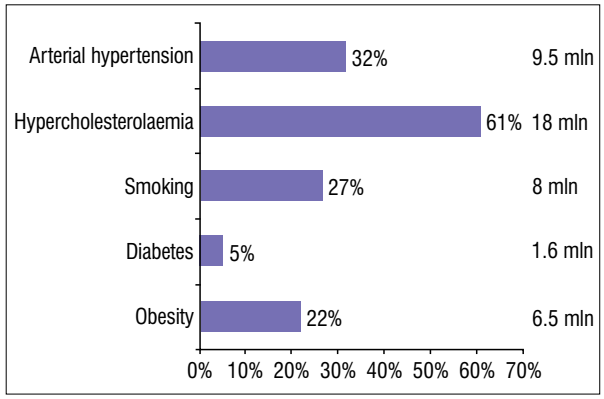

Figure 2. Prevalence of risk factors for cardiovascular diseases in Poland among patients aged 18–79 according to the results of the NATPOL 2011 Study

in accessing highly specialized health services in the field of cardiology, pediatric cardiology, cardiac surgery and neurology. Early detection of atherosclerotic lesions enables the introduction of appropriate prophylaxis aimed at reducing cardiovascular risk. Biomarkers can be used in the early detection of atherosclerosis. The main risk factors (classical risk factors) for CVD affecting cardiovascular risk are SBP (systolic blood pressure), total cholesterol, age, sex and smoking [5]. Cardiovascular risk can be presented as a risk of death (European systems: Euro-SCORE, Pol-SCORE) or as a risk of a cardiovascular event (American systems, for example, *Framingham Risk Score*). The influence of classical CVD risk factors on the incidence of CVD is shown in fig. 3. It is also worth remembering about other risk factors for CVD. An important risk factor of CVD is also diet. It has been reported that oxysterols increase inflammation, lipid markers levels and reflect accelerated endothelial dysfunction [7]. The number of CVD risk factors does not always correlate with the actual cardiovascular risk. In 1/5 of patients with diagnosed coronary artery disease, no classic risk factors are found, while 40% have only one risk factor [8, 9].

Pathogenesis of atherosclerosis

Atherosclerosis is a chronic disease with a multifactorial pathogenesis. It mainly concerns the aorta, coronary vessels, and in particular the branching of these vessels. Atherosclerotic lesions localize in the *tunica intima* and *tunica media* of vascular wall. The location of atherosclerotic lesions varies between men and women. Among women, atherosclerotic lesions are located in the carotid arteries — 24.1%; coronary arteries — 4.5%; abdominal aorta — 22.8% and ilio-lumbar arteries — 30.1%. Among men, the incidence of atherosclerosis in the above locations is as follows: 36.9%; 26.1%; 27.2% and 54.1% [10]. Atherosclerosis can be generalized — including > 3 vascular bearings; indirect — including 2-3 vascular bearings and local — including 1 vascular bearing [10]. Atherosclerosis gradually narrows the lumen of the vessel, which reduces the flow of blood to the tissues, leading to their ischemia. The scientific beginnings of research on atherosclerosis date back to the second half of the 19th century. In 1856 Rudolf Virchow showed that atherosclerotic lesions are composed of large amounts of lipid components (cholesterol and triglycerides). Another researcher dealing with ather-

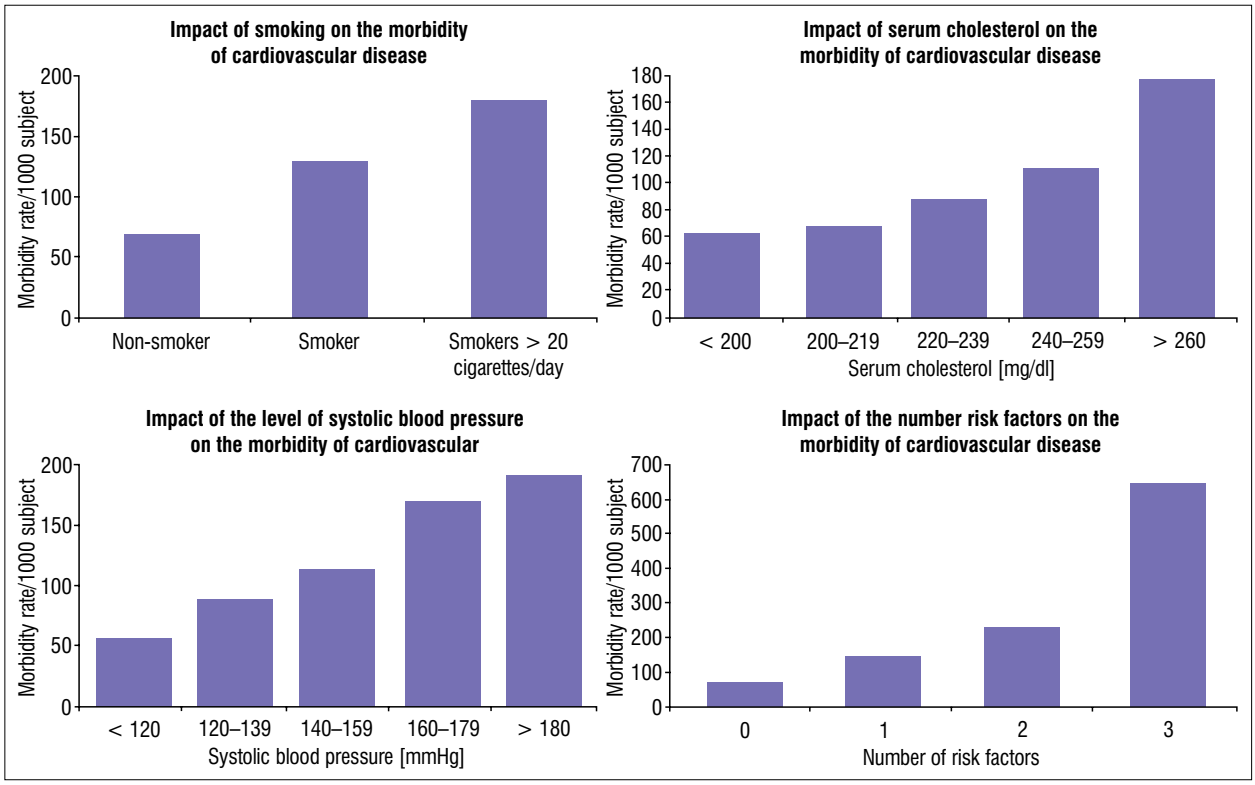

Figure 3. Morbidity of ischemic heart disease depending on the number of cigarettes smoked, serum cholesterol, level of systolic blood pressure and the number of risk factors — *Framingham Heart Study*

osclerosis was Nikolai Aniczkov. In 1913, he showed that the use of a cholesterol-rich diet in a rabbit for a dozen or so weeks leads to atherosclerotic lesions. In 1874, Joseph Goldstein and Michael Brown described the mechanism of cholesterol uptake by the cells at the participation by the $apoB_{100}$/apoE receptor. Another important event in the history of atherosclerosis research was Russell Ross's demonstration that the key to atherosclerosis is the interaction of monocytes/macrophages with vascular endothelium (modified theory of uniform response to injury). Macrophages under the vascular endothelium remove cholesterol, transforming into foam cells. Foam cells produce, among others, extracellular matrix metalloproteinases (MMPs) that damage the vascular endothelium [11]. Atherosclerotic lesions are classified according to AHA (American Heart Association) recommendations [12]. There are three types of atherosclerotic lesions that constitute the early phase of the atherosclerotic process. Type I is characterized by the presence of cholesterol-containing foam cells. The II type is characterized by an increase in the number of foam cells and the appearance of pathologically altered smooth muscle cells. Type III is characterized by extracellular lipid accumulation and the onset of fibrosis. Atherosclerotic changes begin in early childhood and even fetal life. It should be mentioned that the stages I–III are reversible [13]. Further accumulation of lipids in the vascular wall leads to the formation of atherosclerotic plaques. Lipids constitute 10–70% of the volume of atherosclerotic plaque. The construction of atherosclerotic plaque can be varied. In type IV, the surrounding enamel-sheath core consists only of the inner membrane. In type V, the atherosclerotic plaque is surrounded by collagen and smooth muscle cells. In addition, type V is divided into subtypes. The Va subtype is characterized by a pronounced lipid core, the Vb subtype is characterized by calcifications, while the Vc subtype is characterized by a lack of the core and a large amount of connective tissue. Atherosclerotic plaques type IV and V were found in 20% of men aged 30–34 [14]. Type VI is an unstable atherosclerotic plaque (damage of inner membrane) or atherosclerotic plaque that has burst. Types V and VI atherosclerotic plaque are irreversible [15]. Gradually enlarging atherosclerotic plaque does not cause clinical symptoms until the narrowing of light does not exceed 70–80% of the diameter of the vessel, which significantly reduces blood flow, eg to the myocardium — a stable example of angina pectoris. In contrast, atherosclerotic plaque rupture, most often at less than 50% of the vessel lumen, is responsible for rapidly occurring symptoms such as acute coronary syndrome or stroke [16]. In 79.5% of

patients with coronary artery disease, PAD is diagnosed. Among patients with PAD, atherosclerosis occurred in 52.2%, while atherosclerosis of the lower limbs in 68.5% of them [17]. The severity of the progression of atherosclerotic lesions depends on the number of risk factors. With age, thickening of the inner membrane occurs, which is caused by forces acting on the vessel (mainly shear stress). The dishes become thicker and have a higher average. Thickening of the inner membrane promotes the loss of vascular endothelial cell integrity which leads to increased migration of LDL and monocyte lipoproteins into the inner wall layer of the vessel. The accumulation of lipids and cells of the immune system in the vascular wall promotes the development of atherosclerosis [18, 19].

Biomarkers of atherosclerosis

Identification of classical biomarkers of atherosclerosis, such as LDL (low-density lipoprotein), HDL (high-density lipoproteins), and triglycerides may not be helpful in patients with moderate or unusual cardiovascular risk. For more accurate management, non-classical atherosclerosis biomarkers may be helpful in these patient groups. Biomarker (indicator) of high clinical value should be characterized by high sensitivity, high repeatability of results and the possibility of application in clinical practice (low cost of laboratory mark) [7]. Biomarkers of atherosclerosis are characteristic of its particular stages. These include markers of the inflammatory process, markers of atherosclerotic plaque injury, acute phase proteins, ischemic markers, markers of tissue necrosis and markers of myocardial dysfunction.

Biomarkers of the inflammatory proces

Interleukin 6 (IL-6)

One of the most important and most multi-functional interleukins. Together with TNF-α (tumour necrosis factor α), it belongs to pro-inflammatory cytokines. IL-6 is mainly produced by monocytes and macrophages. IL-6 levels increase with age and are associated with increased mortality in nondisabled persons over age 65 from both cardiovascular and non-cardiovascular events [20]. IL-6 is elevated in coronary heart disease patients and may be a biomarker of inflammation related to cardiovascular risk. IL-6 is involved in the formation of atherosclerotic plaques [21–23].

Myeloperoxidase (MPO)

Myeloperoxidase is a biomarker of both the inflammatory process and the destabilization of atherosclerotic plaque. MPO is produced by neutrophils and macrophages. Participates in the antimicrobial and antiviral reactions through the production of hypochlorous acid (HOCl). Myeloperoxidase also participates in the oxidation of LDL lipoproteins (oxLDL). Oxidized LDL are highly atherogenic. Higher MPO activity in the blood of patients with ischemic heart disease was demonstrated in comparison to healthy people. In addition, plasma MPO levels have been shown to be higher in patients with acute coronary syndrome [24].

Tumour necrosis factor α (TNF-α)

Tumour necrosis factor α is the most important cytokine that mediates effector pathways in both inflammatory disease target tissues and in atherosclerotic vessels. In addition, TNF-α is involved in the formation and enlargement of atherosclerotic plaques. TNF is an inhibitor of eNOS (endothelial nitric oxide synthase), increases the production of reactive oxygen species and reduces the effect of EDHF (endothelium-derived hyperpolarizing factor). These mechanisms lead to impairment of vasodilatation and damage to the vascular endothelium due to the severity of inflammation [25]. Is a biomarker of increased cardiovascular risk [26]. It has been shown that the concentration of TNF-α in the blood increases with age. Elderly people who had higher levels of TNF-α in the blood more often had clinically diagnosed atherosclerosis [27].

Matrix metalloproteinase 9 (MMP-9)

Metalloproteinases are a very large family of calcium-dependent, zinc-containing endopeptidases. MMP-9 is associated with inflammation and destabilization of atherosclerotic plaque. MMP-9 increases the infiltration of monocytes under the vascular endothelium. In addition, there is a positive correlation between the concentration of MMP-9 in the blood and the size of the lipid core and the risk of atherosclerotic plaque rupture [28]. Patients with unstable angina and NSTEMI (non-ST-elevation myocardial infarction) have increased levels of MMP-9 in the blood [29]. A positive correlation was found between the increased concentration of MMP-9 in the blood and the occurrence of myocardial infarction or stroke. However, it was not found that the elevated concentration of this metalloproteinase was a strong and independent cardiovascular risk factor [30].

Intercellular adhesion molecule 1 (ICAM-1; CD54) and vascular cell adhesion protein 1 (VCAM-1; CD106)

The most important for the development of atherosclerosis are ICAM-1 and VCAM-1. The presence of these adhesive molecules has been demonstrated in vessels predisposed to the development of atherosclerosis and within existing atherosclerotic lesions [31]. The ligand for ICAM-1 is LFA-1 (lymphocyte function-associated

antigen 1), which occurs on all types of leukocytes. The ligand for VCAM-1 is VLA-4 (very late antigen-4), found on monocytes and lymphocytes. Adhesion molecules are involved in the first stage of leukocyte penetration into the vascular endothelium - rolling. The interaction between ICAM-1 and LFA-1 and VCAM-1 and VLA-4 is supported by PECAM-1 (platelet endothelial cell adhesion molecule 1). PECAM-1 is located on the surface of vascular endothelial cells at sites affected by the inflammatory process, therefore the migration of leukocytes under the vascular endothelium is intensified in the vascular regions where the process of inflammation occurs [32]. Increased expression of ICAM-1 and VCAM-1 has been shown to be an indicator of subclinical atherosclerosis [33].

C-reactive protein (CRP)

C-reactive protein is an acute phase marker. CRP is a biomarker of inflammation and destabilization of atherosclerotic plaque. CRP is produced mainly in hepatocytes as a result of IL-6 stimulation. It belongs to the pentraxin family. It can be used for the early identification of high cardiovascular risk patients. The FDA (Food and Drug Administration) recommends the determination of CRP concentration in the blood using the high sensitivity method (hsCRP, high-sensivity CRP). An increase in CRP concentration in blood above 10 mg/l indicates an inflammatory proces [34]. The increase in CRP in the blood leads to: activation of the complement system, LDL oxidation, increased LDL to macrophages, reduction of NO (nitric oxide) production, stimulation of TF (tissue factor) secretion by macrophages, increase in the concentration of adhesion molecules, increase of blood clotting due to the increase of PAI gene expression -1 (plasminogen activator inhibitor-1). CRP also stimulates the production of IL-12 and INFγ (interferon γ) [34]. CRP is an important indicator of the risk of acute coronary syndrome without ST segment elevation [35].

Growth/differentiation factor 15 (GDF15)

Growth factor produced by macrophages, cardiomyocytes and endothelial cells in response to the inflammatory process. It can be a potential biomarker in the stratification of cardiovascular risk. The GDF-15 concentration below 1200 ng/l corresponds to the low cardiovascular risk (upper limit of reference values for healthy people), 1200-1800 ng/l — moderate (average) CVD risk, and exceeding 1800 ng/l — high CVD risk [36]. The increase in GDF-15 levels is accompanied by atherosclerosis, atrial fibrillation, heart failure, pulmonary embolism, acute inflammation, renal failure and also some cancers [37]. The increased concentration of GDF-15 in response to inflammation aims to reduce the inflammation in the myocardium, its pathological remodelling and apoptosis of cardiomyocytes [38].

Fibrinogen

Fibrinogen is an acute-phase protein produced by the liver. It can be used to assess cardiovascular risk in patients with atypical cardiovascular profile [39]. It has been shown that fibrinogen concentration is higher in people with cardiovascular system diseases compared to healthy people. In addition, it has been found that determining fibrinogen levels in the blood may be useful in assessing the risk of thrombosis. Fibrinogen increases plasma viscosity, increases blood coagulation (through increased fibrin and increased aggregation of platelets), increases inflammation [40].

Uric acid

Uric acid is the final metabolite of purine bases. Numerous epidemiological studies have shown that increased uric acid levels in the blood are an independent risk factor for cardiovascular disease [41]. Other studies suggest that hyperuricemia is not a risk factor of CVD but is a complication of CVD (obesity, the use of diuretics, hypertension, insulin resistance) [42]. Further clinical trials are needed to assess the clinical usefulness of the determination of uric acid levels in the blood.

Lipoprotein (a) — Lp (a)

Lipoprotein (a) is a modified LDL lipoprotein by attaching a specific apolipoprotein (a) to apoB100 [43]. Increased plasma Lp (a) is a genetically determined, independent, causative risk factor for cardiovascular disease. The physiological functions of Lp (a) include wound healing, promoting tissue repair and vascular remodelling. Like other lipoproteins, Lp (a) is also susceptible to oxidative changes, leading to extensive formation of proinflammatory and proatherogenic oxidized phospholipids, oxysterols, oxidized lipid-protein adducts in Lp (a) molecules that consolidate the progression of atherosclerotic lesions and intimal thickening by induction of M1 macrophages, inflammation, autoimmunity and apoptosis [44]. In a prospective cohort study by Zhang et al. showed that elevated plasma Lp (a) concentration was a factor increasing the risk of stroke in adult Chinese [45]. Sadkowska et al. [46] on a group of 142 men conducted a study to determine the usefulness of measuring Lp (a) and homocysteine in plasma. The subjects were divided into 4 groups depending on the number of pathological changes in the coronary vessels. Both Lp (a) and homocysteine have been shown to be elevated in patients with coronary artery disease. In their conclusions, the authors state that routine determination of homocysteine in patients with signs of coronary heart disease and determination of lipoprotein (a) in people

with a positive family history of cardiac disease may be diagnostically and clinically useful.

Biomarkers of destabilization of atherosclerotic plaque

Oxidized low-density lipoprotein — (oxLDL) and anti oxidized low-density lipoprotein antibody — anti oxLDL antibody

Oxidized low-density lipoprotein (oxLDL) is of key importance in the pathogenesis of atherosclerosis and the pathophysiology of major cardiovascular and brain events [47]. The oxLDL molecule acts as an antigen leading to the production of anti oxLDL antibodies [48]. Autopsy studies have shown that increased levels of oxLDL increase the risk of atherosclerotic plaque rupture [49]. In addition, many studies have shown that an increase in blood oxLDL levels positively correlates with the risk of developing coronary artery disease and worsens the prognosis in such patients [50]. LDL oxidation can affect different components of its molecule, which is why different anti-oxLDL antibodies can be formed. IgM anti-oxLDL antibodies have been shown to reduce the risk of severe coronary artery disease. In the case of IgG anti-oxLDL class, this compound is more complex and requires further research [50].

Soluble CD40 ligand (sCD40L)

Protein — CD40 receptor-ligand. It is mainly produced by cells of the immune system, vascular endothelial cells, vascular walls and epithelium. The CD40 receptor is found on B lymphocytes, macrophages, vascular endothelial cells and myocytes. Separation of sCD40L leads to the production of MMPs and destabilization of the atherosclerotic plaque. Increased sCD40L concentration was demonstrated in patients with myocardial infarction and unstable ischemic heart disease [51]. OPUS-TIM116 Study showed higher blood sCD40L concentration compared to the control group (0.78 μg/l *versus* 0.52 μg/l) [52]. In addition, it has been shown that increased sCD40L concentration in the blood occurs in patients with psoriasis [53]. The role of a CVD biomarker is unclear [7].

Placental growth factor (PlGF)

PlGF is a growth factor that belongs to the family of EGF (endothelial growth factor). It plays an important role in the pathogenesis of atherosclerosis by stimulating angiogenesis and increasing the migration of monocytes and macrophages into the vascular endothelium. As a biomarker, it can be important in assessing cardiovascular risk among overweight children, obesity or metabolic syndrome. It has been shown that children with excessively increased body weight and with the metabolic syndrome have higher PlGF levels in the blood compared to healthy children. In addition, a positive correlation was found between PlGF concentration in the blood and troponin concentration in the blood [54].

Pregnancy-associated plasma protein A; pappalysin 1 (PAPP-A)

The protein produced by the placenta. It is a metalloproteinase. Probably PAPP-A is involved in the destruction of the fibrous cap of the plaque leading to its destabilization. Increased levels of PAPP-A have been demonstrated in patients with myocardial infarction, unstable ischemic heart disease and in patients who died suddenly due to CVD [55]. The CAPTURE Study showed that the increase in blood levels of PAPP-A in patients with acute coronary syndromes is of unfavourable prognostic importance. As of today, there are technical problems in the performance of PAPP-A assays, because it occurs in the heterotetrameric form (in pregnant women) and homodimeric (in patients with acute coronary syndromes). PAPP-A may be used as a marker of death risk in acute coronary syndromes and identification of atherosclerotic plaques susceptible to rupture [56].

MicroRNA (miRNA)

MicroRNAs are short segments of RNA containing 18–25 nucleotides. They arise in the process of transcription of intron (non-coding) sequences and exon (encoding) sequences. Probably the expression of 1/3 of human genes is regulated by miRNA. miRNAs are involved in the pathogenesis of many diseases [57]. Selected miRNAs involved in the development of the atherosclerotic process are presented in the Table 1.

The biomarkers of athersclerotic plaque destabilization also include the previously described MPO, MMP-9 and CRP

Interestingly, an increase in atherosclerotic destabilization has been observed in patients with active ankylosing spondylitis. Increased blood levels of sCD40L and PlGF were observed in these patients. Importantly, these patients were not burdened with classic cardiovascular risk factors [59]. Whole-body cryotherapy decreases the levels of Inflammatory, oxidative stress, and atherosclerosis plaque markers in male patients with active phase ankylosing spondylitis in the absence of classical cardiovascular risk factors [60]. Chronic inflammatory state in these patients cause increased cardiovascular and cerebrovascular mortality [61].

Table 1. Characteristics of selected microRNA involved in the development of atherosclerotic process [based on 58]

MicroRNA (miRNA)	Role in the atherosclerotic process
miRNA-126	Inhibition of VCAM-1
miRNA-155, -222, -424, -503, -9, -17, -20a, -106a	Regulation of monocyte differentiation into macrophages in atherosclerotic plaque
miRNA-147, -155, -342-5p	Activation of M1 macrophages, increase secretion of TNF-α and IL-6
miRNA-125a, -146a, -33, -155	Inhibition of lipid accumulation in atherosclerotic plaque
miRNA-15a, -16	Modulation of macrophage apoptosis
miRNA-21, miRNA-34a	Production of MMP-9, VSMC proliferation
miRNA-210	Tubulogenesis and stimulation of macrophage migration
miRNA-146a	The formation of the Th1 mononuclear phenotype
miRNA-29	Inhibition of elastin expression
miRNA-221/222	Stimulation of cell proliferation or apoptosis
miRNA-365	Stimulation of endothelial cells apoptosis
miRNA-100, -127, -145, -133a, -133b	High expression in symptomatic atherosclerotic plaques in carotid arteries

Biomarkers of thrombocyte activation

Lipoprotein-associated phospholipase A2 (Lp-PLA2) and secretory phospholipase A2 (sPLA2)

Lp-PLA2 is a protein also known as platelet-activating factor acetylhydrolase (PAF-AH). It is mainly produced by monocytes and macrophages. Lp-PLA2 has pro-inflammatory and atherogenic effects. Takes part in the oxidation of LDL lipoproteins. Increased Lp-PLA2 has been shown to increase cardiovascular risk. Inhibition of Lp-PLA2 (by the Darapladib) has a positive effect on the risk of CVD, therefore Lp-PLA2 may become a future target for pharmacotherapy [62]. sPLA2 is the phospholipase A2 isozyme. It is produced by inflammation cells in the atherosclerotic plaque and by ischemic cardiomyocytes. The relationship between sPLA2 concentration and CVD risk was demonstrated [63].

The biomarkers of thrombocyte activation are also described sCD40L.

Biomarkers of neurohormonal activation

Copeptin

Copeptin is the C-terminal peptide of pre-provasopressin. It is produced by brain cells. After transport from the hypothalamus to the pituitary gland and pre-provasopressin cleavage, the copeptin is released into the circulation in stoichiometric amounts along with vasopressin. Both neuropeptides are mainly secreted in response to hemodynamic or osmotic changes. Copeptin is more stable in blood than vasopressin, which is why it has been used in laboratory diagnostics. It has been shown that the increased concentration of copeptin in blood positively correlates with the risk of developing coronary heart disease and the risk of death due to CVD [64].

Midregional proadrenomedullin (MR-proADM)

It is produced by the adrenal medulla, the heart and vascular endothelial cells. It is a promising biomarker of the risk of developing coronary heart disease and heart failure. In addition, MR-proADM may be a prognostic biomarker after STEMI (ST-Elevation Myocardial Infarction) [65].

Biomarkers of shear stress in the vascular endothelium

Shear stress biomarkers include various miRNAs. miRNA-143 and miRNA-145 change the phenotype of vascular smooth muscle cells to contractile. miRNA-126-5p limits the proliferation of vascular endothelial cells, whereas miRNA-92a enhances the development of inflammatory processes in the vascular wall [58].

Biomarkers of blood vessel microcalcification

Microcalcification of the atherosclerotic plaque increases the risk of its rupture. miRNA-125b is involved in the differentiation of vascular smooth muscle cells into osteoblasts that build up calcium in the atherosclerotic plaque [58].

Changes in the structure and function of blood vessels with age

The structure and function of blood vessels change with age. These changes include a reduction in the number of elastic elements, such as collagen and elastin [66]. The blood vessels are becoming more rigid, which results in an increase in the speed of the pulse wave and its amplitude. The reflected pulse wave from the arterioles increases the afterload of the left ventricle, which leads to increased systolic blood pressure. The increase in afterload results in the enlargement of the left ventricle and decrease in coronary flow leading to heart failure. The lack of return of the pulse wave during diastole leads to a decrease DBP (diastolic blood pressure). An increase in SBP and a decrease in DBP leads to an increase in pulse pressure. The pulse pressure (SBP – DBP) increases after 50–60 years due to the structural changes described above. A positive correlation was found between pulse pressure and cardiovascular risk. An increase pulse pressure > 63 mm Hg dramatically increases the risk of CVD. It is worth noting that the increase in heart rate with age can be prevented through regular physical activity [67, 68]. With age, there is a reduction in nitric oxide production while increasing the production of endothelin-1. Endothelin-1 has a strong vasoconstrictive, proinflammatory and prooxidative activity. In addition, during the aging of the body, the production of proteins and pro-inflammatory cytokines, such as CRP, IL-6, IL-8, TNF-α, increases. All these changes lead to an increase in the progression of atherosclerotic lesions (Fig. 4.) [69, 70].

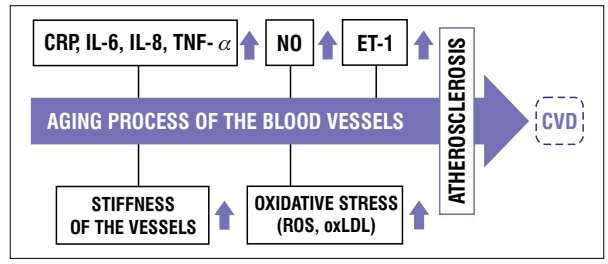

Figure 4. Structural and functional changes of blood vessels with age [on based 19, 66–70]. CRP: C-reactive protein; IL-6: interleukin 6; IL-8: interleukin 8; TNF-α: tumor necrosis factor α; NO: nitric oxide; ET-1: endothelin 1; ROS: reactive oxygen species; oxLDL: oxidazed low-density lipoprotein; CVD: cardiovascular diseases

The influence of statins and PCSK-9 inhibitors on atherosclerotic plaque

Statins reduce cardiovascular risk by reducing LDL cholesterol and pleiotropic effects. The most effective are the so-called strong statins (rosuvastatin, atorvastatin) [71]. Pleiotropic properties of statins include anti-inflammatory activity (decreased production of CRP, serum amyloid A, IL-6, IL-8, ICAM-1), lipid-lowering effect (reduction of endogenous cholesterol biosynthesis, increase in LDL receptors — $apoB_{100}$/apoE), anticoagulant (increase in NO production, increase in fibrinolytic activity, decrease in ET-1 production) and antioxidant activity (reduction of reactive oxygen species production, reduction of glutathione reduction, reduction of lipoprotein oxidation, reduction of NADPH oxidase activation, increased eNOS activity) [72]. Numerous studies have demonstrated the beneficial effect of statin therapy on reducing the progression of atherosclerosis. In the Kumbhani et al. study, it was concluded that statin therapy reduced the exacerbation of ischemia, the need for revascularization, the need for amputation. Statins restricted progression of PAD [73]. In addition, intensive statin therapy has been shown to reduce the volume of atherosclerotic plaque (by 7.69 mm^3) and increase the lumen of the vessel by 0.81 mm^3. Rosuvastatin more effectively reduces the volume of atherosclerotic plaque compared to atorvastatin [74]. Auscher et al. [75] showed that the use of statins leads to stabilization of the atherosclerotic plaque, and thus reduce the risk of its rupture.

Proprotein convertase of subtilisin/kexin type 9 (PCSK-9) was discovered in 2003. PCSK-9 is an inhibitor of the LDL lipoprotein receptor (LDL-R). PCSK 9 binds with LDL-R on the surface of liver cells and promotes degradation of LDL(R) in the liver cells by the lysozyme pathway and prevents its recycling back to the liver cell surface [76]. PCSK-9 inhibitors are human monoclonal antibodies (evolocumab, alirocumab). Phase I and II studies have shown that evolocumab reduces LDL levels by 40 to 80%, apolipoprotein B100 levels by 30–59% and apolipoprotein A by 18–36% [77–79]. In the GAUSS2 study, evolocumab showed a greater reduction in LDL compared to ezetimibe (56.1% versus 36.9%) [79]. The study of Stein et al. showed that the use of alicocumab in patients (n = 62) with hypercholesterolemia who had an initial LDL concentration of 140–170 mg/dl led to a reduction in LDL concentration by 29–68% [80]. PCSK 9 inhibitors have excellent lipid-lowering properties and beneficial effect on CV outcome [76]. According to the FDA (Food and Drug Administration), the indications for the use of PCSK-9 inhibitors are 1) patients suffering from homozygous familial hypercholesterolemia (HOFH) and heterozygous familial hypercholesterolemia (HeFH); 2) non-familial hypercholesterolemia patients who are severely statin intolerant (secondary prevention) and 3) as a research tool [76].

Table 2. Biomarkers of atherosclerosis — *resume*

Biomarkers of atherosclerosis			
Biomarkers of the inflammatory process	**Biomarkers of destabilization of atherosclerotic plaque**	**Biomarkers of thrombocyte activation**	**Biomarkers of neurohormonal activation**
IL-6	oxLDL	Lp-PLA2	Copeptin
MPO	antibody anti oxLDL	sPLA2	MR-proADM
TNF-α	sCD40L	sCD40L	
MMP-9	PIGF		
ICAM-1	PAPP-A		
VCAM-1	miRNA		
CRP	CRP		
GDF-15	MMP-9		
Fibrinogen	MPO		
Uric acid			
Lipoprotein (a)			
Biomarkers of shear stress in the vascular endothelium	**Biomarkers of blood vessel microcalcification**		
miRNA	miRNA		

Summary

The pathogenesis of atherosclerosis is very complex. Biomarkers of atherosclerotic lesions are often risk factors for its occurrence. These are proteins, enzymes, microRNAs and others (Fig. 5). There are many modern biomarkers that can become routine in the laboratory diagnosis of CVD in the future. Modern pharmacotherapy allows limiting the progression of the atherosclerotic process by affecting all its stages — from increasing the LDL cholesterol to the atherosclerotic plaque rupture. Further research will provide further information on the pathogenesis of atherosclerosis, and as a result, new risk factors and biomarkers will be recognized.

Conflict of interest:

None.

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Stent fracture after endovascular treatment patient with subclavian vein thrombosis: difficult diagnosis and complication of venous thoracic outlet syndrome

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Abstract

Subclavian vein thrombosis is relatively rare. It constitutes 4 to 10% of all cases of venous thrombosis and is often associated with compression or cannulation of the subclavian vein. We present the case of a patient with Paget-Schroetter syndrome treated in our center for right subclavian vein thrombosis as a result of the venous thoracic outlet syndrome (VTOS). In the case described below, VTOS was unrecognized and the stent fracture following endovascular treatment led to a relapse of venous thrombosis. Secondary angioplasty and stenting with subclavian vein decompression was successfully made. The patient was regularly monitored throughout the following year and there was no relapse of clinical symptoms. Conclusions: in case of subclavian vein thrombosis, decompression is a very important step in the management of VTOS. It prevents recurrence of thrombosis and potential complications.

Key words: stent fracture, subclavian vein thrombosis, venous thoracic outlet syndrome, Paget Schroetter syndrome

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Introduction

Subclavian vein thrombosis is relatively rare. It constitutes 4 to 10% of all cases of venous thrombosis [1, 2]. Most often, it is secondarily associated with central vein cannulation, hypercoagulation and cancers. In 20% of cases, is idiopathic and it is impossible to clearly indicate its cause. In these cases, thrombosis is often associated with compression of the subclavian vein and is a clinical manifestation of the venous thoracic outlet syndrome (VTOS).

In patients with VTOS, the subclavian vein (SCV) is compressed between the clavicle, the first rib, anterior scalene muscle, costoclavicular ligament, and subclavicular muscle. Chronic compression leads to fibrosis of the wall and narrowing of the vessel lumen. Slowed and turbulent flow results in thrombus formation which then leads to the clinical manifestation of venous thrombosis.

Medical imaging of thrombosis located in this region includes ultrasound, computed tomography angiography (aCT), and magnetic resonance angiography (aMRI). Modern endovascular techniques allow restoring blood flow as soon as a few weeks from the onset of symptoms. Treatment of venous thrombosis inflicted by compression syndrome should include decompression surgery.

We present the case of a patient with Paget-Schroetter syndrome treated in our center for right subclavian vein thrombosis as a result of the venous thoracic outlet syndrome (VTOS). In the case described below, VTOS was unrecognized and the stent fracture following endovascular treatment led to a relapse of venous thrombosis.

This 42-year-old female patient, an architect by occupation, was referred to our facility in May and June 2015 due to pain and oedema of the right upper

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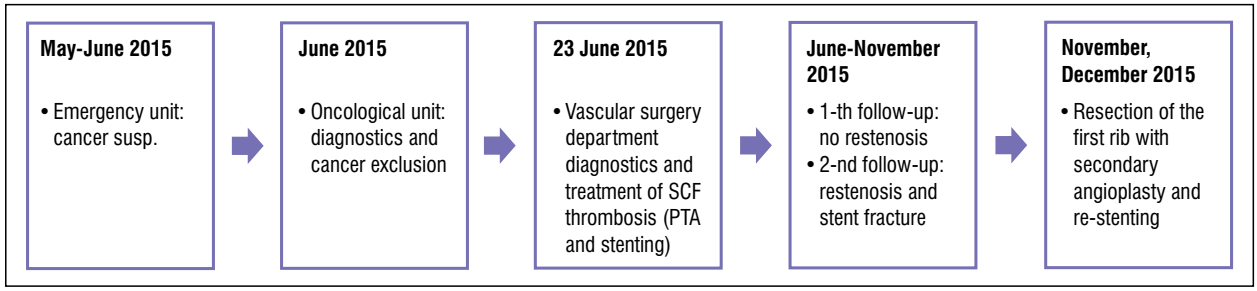

Figure 1. Diagnostics and treatment of patients with subclavian vein thrombosis

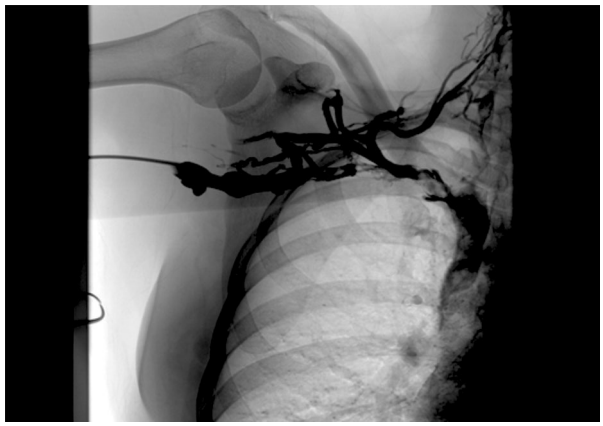

Figure 2. Preliminary phlebography

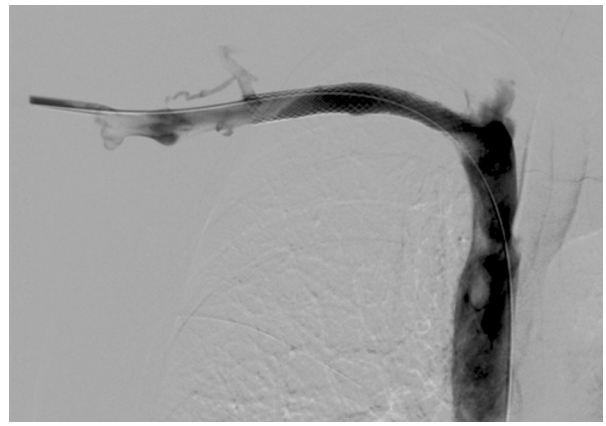

Figure 3. Final phlebography of the subclavian vein after angioplasty and stent placement

limb. Figure 1 presents the patient's history of visits and hospitalizations. Comorbidities included Hashimoto's thyroiditis and degenerative lesions in the cervical spine. The patient had a family history of breast cancer (both mother and sister). The first symptoms started at the beginning of May 2015. Between May and June 2015, the patient was seen several times in the Hospital Emergency Unit and underwent diagnostics in the Oncology Center. The family history of cancer and the cervical spondylotic radiculopathy suspicion skewed the diagnosis. Two ultrasound examinations during Emergency Unit visits did not reveal SCV (subclavian vein) thrombosis, which was finally established during the follow-up consultation on June 23, 2015. Subclavian vein thrombosis was diagnosed approximately two months after the onset of first symptoms. The computed tomography confirmed diagnosis of proximal subclavian vein thrombosis but no signs of compression and anatomical malformations such as additional cervical rib were detected.

The patient was qualified for phlebography. Occlusion of SCV was confirmed (Fig. 2) and angioplasty of the subclavian vein was performed with stenting (Wallstent Uni 10 × 68 mm, Boston Scientific) (Fig. 3). Control phlebography showed correct flow in the stent and absence of collaterals. No compression and narrowing of the stent were detected between the first rib and clavicle during dynamic phlebography with adducted and elevated limb. Therefore, no further surgery was required at this stage.

After the procedure, limb edema and pain decreased and the patient was discharged the next day. Between July and November 2015, the patient was seen in the outpatient clinic. The first follow-up visit did not reveal any signs of SVC thrombosis recurrence. Approximately three months after discharge, a follow-up CT scan was performed which revealed signs of narrowing and stent fracture (Fig. 4). Recurrence of clinical symptoms was also observed at that time. The VTOS with recurrent stent thrombosis was diagnosed and the patient was qualified for open surgery. The first rib (Fig. 5) was resected through supraclavicular and infraclavicular access sites.

In the second stage, re-angioplasty with second stent implantation was performed (Wallstent Uni 10 × 42 mm, Boston Scientific) (Fig. 6). The patient was regularly monitored throughout the following year and there was no relapse of clinical symptoms. A follow-up

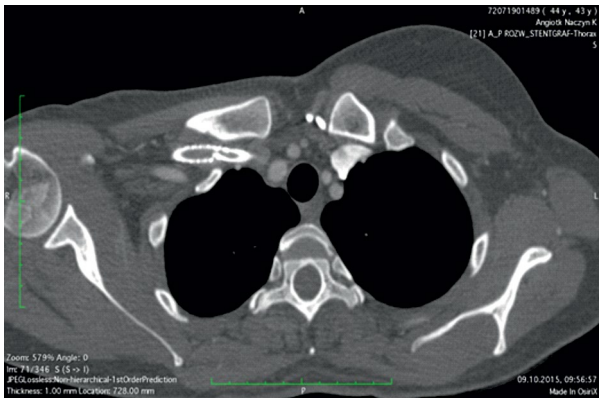

Figure 4. Stent fracture in SCV

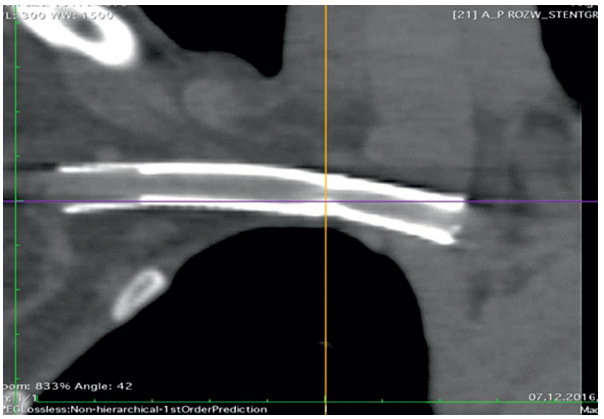

Figure 7. CT follow-up after 12 months

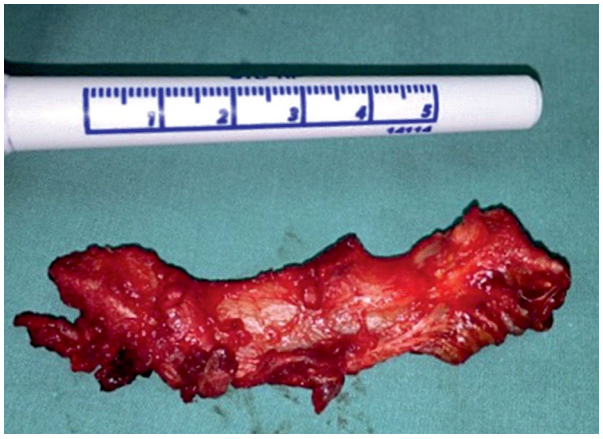

Figure 5. The first rib was removed

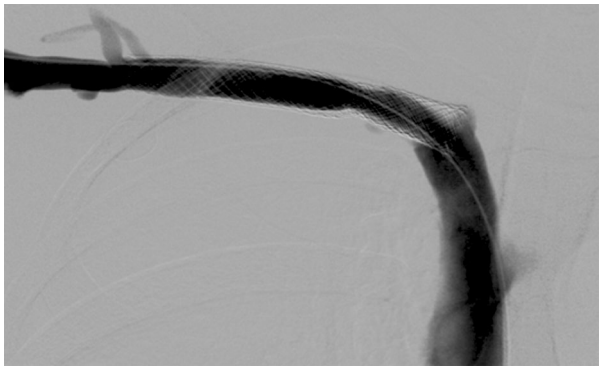

Figure 6. Re-stenting of SCV

CT scan revealed a stenosis of approximately 40% in the stent fracture site.

Discussion

Subclavian vein thrombosis due to thoracic outlet syndrome, also known as the Paget-Schroetter syndrome, mostly affects young, healthy, active people. The case of the 42-year-old female patient presented in this paper reveals not only diagnostic difficulties and complications such as stent fracture but also the risk of recurrence of subclavian vein thrombosis. The time between the onset and diagnosis was long and reached nearly two months.

The ultrasound performed at that time did not reveal any signs of SVC thrombosis. Although the ultrasound is specifically tailored to detect vein thrombosis, the acoustic echo-shadow of the clavicle makes the assessment difficult. It is easier to diagnose SCV thrombosis when the thrombus extends through the subclavian and axillary veins [3]. In the described case, the distal parts of the subclavian vein and axillary and brachial veins were not affected (Fig. 2).

The CT scan and MR imaging are more precise methods that allow detection of VTOS as well as thrombosis. These types of examinations should be conducted with the limb abducted and elevated above the head [3, 4].

According to some authors, phlebography is the most effective diagnostic method, particularly useful in patients with recurrent symptoms within six weeks after the previous episode [4]. In this case, after one-month follow-up, Adson's maneuver was negative and no other signs of stent compression were detected. No further treatment or additional invasive diagnostic methods were required.

Causal treatment is a very important step in the management of VTOS. It prevents recurrence of thrombosis and potential complications. Decompression of the neurovascular bundle improves the function of the limb, as does thrombolysis. There are different opinions regarding the sequence of procedures [5]. In most cases of SCV thrombosis in the course of VTOS, it is recommended to start with catheter-directed thrombolysis

(CDT) and vessel decompression as a second stage. This recommendation concerns mostly patients with primary thrombosis when the onset occurred up to two weeks before treatment [6]. In these cases, a CDT with r-tPA and pharmacomechanical thrombectomy are usually very effective. Such treatment may be completed with balloon angioplasty. Stenting, however, is not recommended in cases when decompression surgery was not performed due to the high risk of stent damage and early recurrence of thrombosis [7].

Urschel et al. compared the results of treatment in 22 patients with primary SCV and primary stenting with 384 patients treated surgically after initial thrombolytic therapy. All patients with stents required re-intervention due to recurrent thrombosis within six weeks after implantation. By contrast, no cases of thrombosis have been reported in patients treated with thrombolysis and VTOS decompression [8].

The decompression surgery was not performed initially in the case described here due to no apparent anatomical malformations, such as a cervical rib. Since there was a long delay between the first symptoms and treatment (> 6 weeks), thrombolysis was not indicated as well. Therefore, primary angioplasty was performed and, due to residual stenosis, the self-expandable stent was implanted. The vascular and clinical results following endovascular treatment were very good. Intraoperative radiological images did not reveal stent compression. Clinical symptoms relieved within a few days. Despite the initial good outcomes, stent fracture and re-thrombosis that required surgical treatment occurred within the first few months.

In the case of VTOS, decompression surgery is recommended directly after revascularization or no later than one month after thrombolytic treatment. Patients with a higher risk of thrombosis recurrence, such as in residual stenosis, require more urgent surgery [9].

There are three operational access sites: axillar, supraclavicular, and infraclavicular. The axillary access site allows good visualization of the costo-clavicular region and resection of the first rib [10]; however, in the case of thrombosis resulting from VTOS, simultaneous phlebography and angioplasty should be performed. The paraclavicular access site additionally allows reconstruction of the subclavian vein with a venous patch or venous graft [11, 12]. Some authors recommend only the subclavian access site, possibly followed by balloon angioplasty. This procedure provides sufficiently good intraoperative insight into the costo-clavicular space while minimizing the risk of damaging the phrenic nerve [13, 14]. In the patient discussed in this article, paraclavicular access was used in order to obtain a good long-term result.

Anticoagulant therapy is another important aspect of treating patients with subclavian vein thrombosis. This type of therapy should be applied for several months after initial treatment with low molecular weight heparin. The question of if and when such treatment should be terminated remains open. Following the elimination of the initial factor of thrombosis, anticoagulants can be discontinued after three months. Patients with recurrent thrombosis require chronic administration of anticoagulants [15], which is the treatment that was implemented in this case.

Conclusions

In our opinion decompression is a very important stage of VTOS treatment and should be done before or immediately after endovascular treatment. Diagnostics of subclavian vein thrombosis requires aCT scans, aMRI, and dynamic phlebography, especially in unclear and recurrent cases. Removal of the first rib seems to be the most effective decompression procedure in VTOS.

Conflict of interest

None.

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LETTER TO THE EDITOR

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Komentarz ekspertów w dziedzinie angiologii do „Rekomendacji dotyczących postępowania w chorobie tętnic kończyn dolnych (LEAD) na podstawie wytycznych ESVS/ESC 2017 — stanowiska ekspertów Polskiego Towarzystwa Chirurgii Naczyniowej, Polskiego Towarzystwa Nadciśnienia Tętniczego, Polskiego Towarzystwa Leczenia Ran oraz Sekcji Farmakoterapii Sercowo-Naczyniowej Polskiego Towarzystwa Kardiologicznego" (Acta Angiol 2019; 25, 4, doi: 10.5603/AA.2019.0015)

prof. dr hab. n. med. Aleksander Sieroń[1], prof. dr hab. n. med. Andrzej Szuba[2], prof. dr hab. n. med. Agata Stanek[3], prof. dr hab. n. med. Rafał Niżankowski[4], dr n. med. Marek Krzanowski[5], dr hab. n. med. Paweł Maga[6], dr n. med. Karol Suppan[7]

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Na XI Konferencji Naukowo-Szkoleniowej Polskiego Towarzystwa Chirurgii Naczyniowej w Bydgoszczy organizowanej w dniach 3–5.10.2019 roku zostały przedstawione „Polskie wytycznyczne postępowania w chorobie tętnic kończyn dolnych (LEAD) na podstawie Wytycznych ESVS/ESC 2017 — Stanowisko Ekspertów Polskiego Towarzystwa Chirurgii Naczyniowej, Polskiego Towarzystwa Nadciśnienia Tętniczego, Polskiego Towarzystwa Leczenia Ran oraz Sekcji Farmakoterapii Sercowo-Naczyniowej Polskiego Towarzy-

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stwa Kardiologicznego", które także pod takim samym tytułem były dostępne w wersji on-line na stronie czasopisma „Acta Angiologica".

„Wytyczne" prof. Jawienia i współautorów, już na „pierwszy rzut oka" sprawiały wrażenie dokumentu przygotowanego z niewystarczającą dokładnością, biorąc pod uwagę jego ważność w dziedzinie angiologii/ /chirurgii naczyniowej. Trudno było nie dopatrzeć się w omawianych wytycznych celowego pomijania kompetencji specjalisty angiologa w opiece nad pacjentem z LEAD (*lower extremity arterial disease* — choroba tętnic kończyn dolnych). Dlatego Konsultant Krajowy oraz konsultanci wojewódzcy w dziedzinie angiologii, a także osoby zainteresowane „dobrem" angiologii w Polsce, po licznych odebranych telefonach od angiologów niebędących chirurgami, po zapoznaniu się z ww. „wytycznymi" napisali bezzwłocznie w październiku komentarz do nich, wskazując na zawarte w nich „uchybienia" o znaczeniu merytorycznym, a także celowym pomijaniu roli angiologa w opiece nad pacjentem z LEAD. Komentarz powinien ukazać się razem z „wytycznymi", aby zwrócić uwagę Czytelnika na przedstawiane problemy.

Nasz Komentarz nie ukazał się. Wytyczne ze strony on-line zostały zastąpione „Rekomendacjami" i następnie ukazały się w wersji papierowej w „Bibliotece Acta Angiologica". Cieszymy się, że nasz przesłany komentarz przyczynił się do poprawy merytorycznej „Rekomendacji". Tak jak zaznaczył redaktor prowadzący, „błędy naprawiono w końcowej korekcie".

W „pierwotnej" wersji dokumentu jako członkowie zespołu leczącego pacjenta z LEAD wymienieni zostali wszyscy specjaliści (łącznie z „ekspertem w zakresie rzucania palenia"), pielęgniarka, podolog, ale angiolog został pominięty. W tym miejscu po korekcie dokumentu wpisano angiologa.

Natomiast nie poprawiono rycin 20 i 22. W algorytmie kierowania pacjentów z LEAD do opieki (ryc. 22, s. 76 Biblioteki AA) lekarz POZ kieruje pacjenta z podejrzeniem choroby do chirurga naczyniowego (a nie do angiologa) i dopiero chirurg naczyniowy po zakwalifikowaniu pacjenta do leczenia zachowawczego kieruje pacjenta do angiologa/chirurga naczyniowego. Ponadto, angiolog/chirurg naczyniowy kierują pacjenta do neurologa w celu wykonania USG tętnic szyjnych (!), a do arteriografii pacjent kierowany jest przez: nefrologa, diabetologa, kardiologa, internistę i neurologa, ale nie przez angiologa. Na rycinie 20 na s. 68 „na szczycie" zespołu biorącego udział w opiece nad pacjentem z LEAD umieszczono chirurga naczyniowego, natomiast angiolog został ujęty na równi z kardiologiem i diabetologiem.

Podpisani Autorzy deklarowali chęć współpracy z Zespołem tworzącym „Wytyczne" wraz Zespołem desygnowanym przez Konsultanta Krajowego w dziedzinie chirurgii naczyniowej. Takie opracowanie, bardzo w naszej ocenie potrzebne, przyniosłoby pożytek nie tylko chirurgom naczyniowym i angiologom, ale także lekarzom, którzy podczas swojej pracy spotykają się z problemami naczyniowymi kończyn dolnych.

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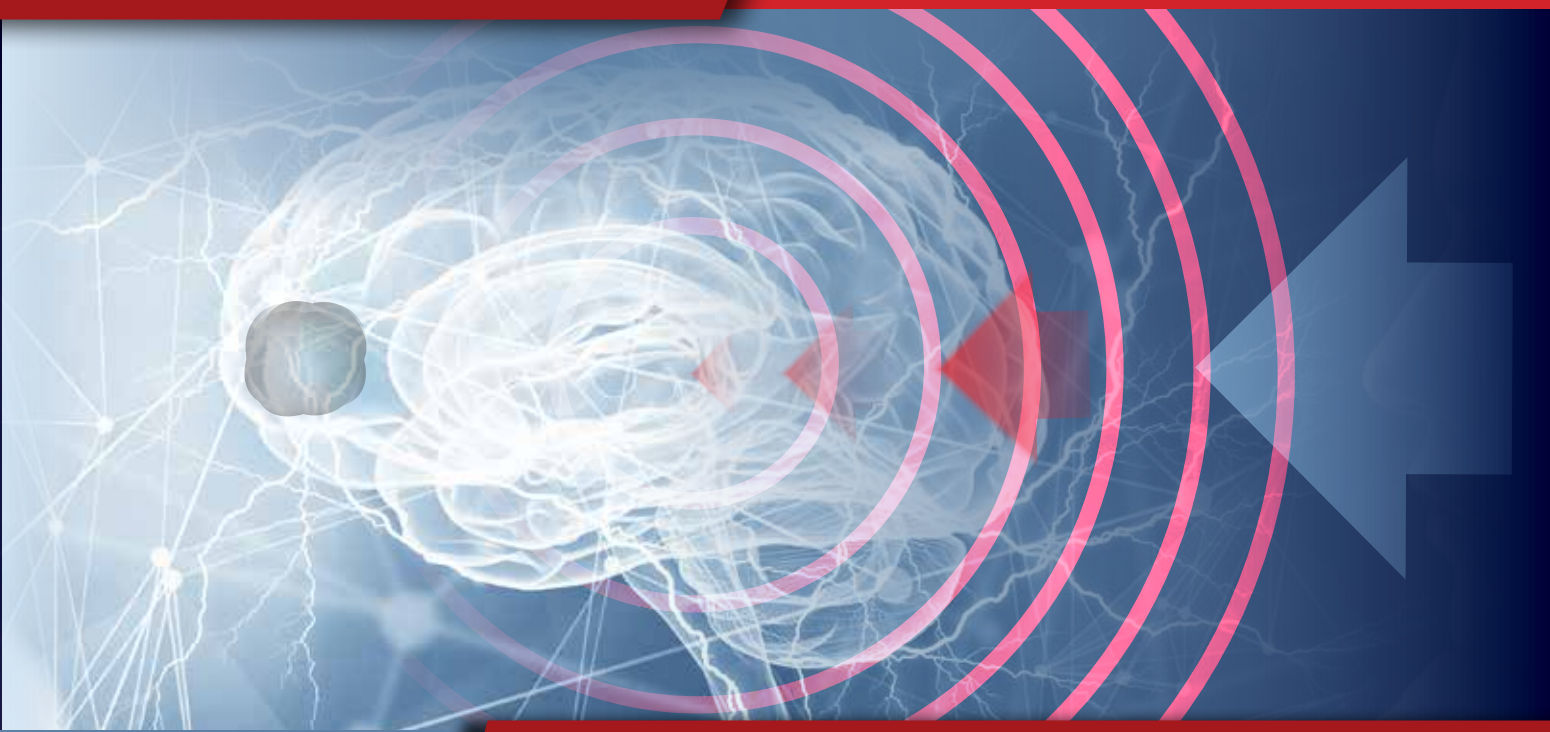

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