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EVALUATION OF SURGICAL EMBOLECTOMY FOR ACUTE LIMB ISCHEMIA AND ENDOVASCULAR THERAPIES FOR CHRONIC ISOLATED INFRARENAL AORTIC STENOSIS

Ph.D. Thesis

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List of abbreviations

ABI: ankle-brachial index
AF: atrial fibrillation
ALI: acute limb ischemia
BMT: best medical therapy
CABG: coronary artery bypass grafting
COPD: chronic obstructive pulmonary disease
CTA: computed tomography angiography
DM: diabetes mellitus
DSA: digital subtraction angiography
DVT: deep vein thrombosis
IAS: infrarenal aortic stenosis
IQR: interquartile range
MI: myocardial infarction
MRA: magnetic resonance angiography
OR: odds ratio
PAD: peripheral artery disease
PE: pulmonary embolism
PTA: percutaneous transluminal angioplasty
SE: standard error
TIA: transient ischemic attack

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1. Introduction

1.1. Arterial steno-occlusive disease

There are acute (onset of symptoms within 2 weeks), subacute (onset of symptoms beyond 2 weeks but within 3 months), and chronic (onset of symptoms beyond 3 months) types of arterial stenoses and occlusions. (1–3) The stenoses/occlusions can affect any arterial segment; however, one of the most common locations is the lower extremity. (2, 4–6) The term peripheral artery disease (PAD) is used in both narrow and broad senses. (4, 6–9) In my dissertation, PAD includes only steno-occlusive lesions causing limb ischemia; acute PAD is discussed in relation to the upper and lower extremities, while chronic PAD is discussed in relation to the infrarenal aorta.

1.1.1. Acute limb ischemia

Acute limb ischemia (ALI), which often leads to major amputation, is diagnosed in 3–45.7 out of 100 000 people each year. (2) It is considered a vascular surgical emergency with significant morbidity and mortality. (2, 4, 10–12) Acute limb ischemia develops as a result of either embolization or *in situ* thrombosis. (4, 7, 9, 13–15)

1.1.1.1. Etiology

Embolization

The embolus is usually formed by aggregated platelets, but air, fat, tumor tissue, and foreign body may also be embolic components. (16–20) The origin of the embolus can be the heart due to arrhythmia (e.g., atrial flutter or fibrillation), heart failure, myocardial infarction (MI), valvular disease, or other pathology (e.g., myxoma). (17–19, 21–27) Of course, aortic atherosclerotic plaques with a thrombogenic surface and aortic and peripheral aneurysms with mural thrombus should not be left out of the list of embolic sources. (28, 29) The most extensive form of atherosclerotic degeneration of the aorta is known as shaggy aorta syndrome. (28) In the case of aneurysms, destabilization of the mural thrombus and consequent distal embolization may occur spontaneously or as a complication of manipulation during endovascular procedures. (29) It is also worth mentioning paradoxical embolization, when a venous thrombus

becomes a non-pulmonary arterial embolus in patients with atrial or ventricular septal defects. (19, 21, 22)

In situ thrombosis

Arterial thrombosis is a complex pathological process that may be attributed to (1) atherosclerosis, (2) degenerative vessel wall changes, (3) hypercoagulable state, (4) vasculitis, (5) infectious disease, (6) traumatic injury, and (7) certain types of drug use, but it may also be idiopathic. (10, 21, 24–26, 30, 31) Hypercoagulable states can be inherited (e.g., factor V Leiden mutation and antithrombin III or protein C or S deficiency) or acquired (e.g., associated with prolonged bed rest, pregnancy, or malignancy). (21, 24, 32–34) In the context of arterial thrombosis, Takayasu's and giant cell arteritis and Buerger's disease (thromboangiitis obliterans) should be highlighted among the vasculitis, while syphilis and tuberculosis should be highlighted among the infectious diseases. (20, 21, 23, 24, 26, 30, 32) And it is not news that patients receiving angiogenesis inhibitors and immunomodulatory or chemotherapeutic agents are at high risk of thromboembolic events. (24)

Many of these conditions are interrelated and can occur simultaneously in the same patient. They may also have the same risk factors. For example, smoking and diabetes mellitus (DM) can predispose to both atherosclerosis and hypercoagulable state. (20, 21) Therefore, to identify the underlying cause of *in situ* thrombosis, a comprehensive evaluation of the patient's past medical history and physical examination and laboratory findings is necessary.

1.1.1.2. Symptoms

Compared to patients with *in situ* thrombosis, patients with embolism usually present with complaints/symptoms sooner (within hours) as collaterals are often absent. (21, 22, 26, 30) Symptoms of ALI may include pain, pallor, coldness, pulselessness, paresthesia, and paralysis. (9) Pain, pallor, coldness, pulselessness, and numbness of the affected extremity are common ischemic symptoms; they are found in almost all patients with ALI. However, not all ALI patients develop paralysis, and if they do, it is a poor prognostic sign. (9)

Rutherford's is one of the most widely accepted classifications for judging the severity of ALI. (Table 1) (35) Rutherford stage I refers to viable, not immediately threatened limbs. Patients with Rutherford stage IIa and IIb ALI require invasive intervention as soon as possible, and the limb can be saved if revascularized promptly. Rutherford stage III, on the other hand, is a condition in which major tissue loss or permanent nerve damage is inevitable. (35)

Table 1. Rutherford classification for acute limb ischemia (35)

Category	Description/Prognosis	Findings		Doppler signal	
		Sensory loss	Muscle weakness	Arterial	Venous
I Viable	Not immediately threatened	None	None	Audible	Audible
IIa Marginally threatened	Salvageable if promptly treated	None or minimal (toes)	None	Inaudible	Audible
IIb Immediately threatened	Salvageable with immediate revascularization	More than toes, rest pain	Mild, moderate	Inaudible	Audible
III Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis	Inaudible	Inaudible

1.1.1.3. Diagnosis

The first step in making a diagnosis is to assess the patient's complaints and symptoms, the second is to review the past medical history, and the third is a physical examination. Palpation of the peripheral pulses is an essential part of the physical examination. Electrocardiogram and blood tests (determination of complete blood count, chemistry panel, electrolytes, creatinine phosphokinase, and prothrombin and activated partial thromboplastin time) should also be performed. (3, 36, 37) Handheld Doppler and radiological imaging (ultrasound, computed tomography angiography [CTA], and/or digital subtraction angiography [DSA]) are of great importance in localizing

emboli/thrombi. On ultrasound, the fresh embolus/thrombus is hypoechoic and no color or Doppler signal can be obtained from the occluded arterial segment. (36, 37) Ultrasound and CTA can both be used to detect arterial calcification, atherosclerotic plaques, and other abnormalities besides thromboembolism. However, the main advantage of CTA is that it provides rapid visualization of several arterial segments at the same time. In acute thromboembolism, DSA images show a sharp-edged occlusion with collaterals either present or absent. Magnetic resonance angiography (MRA) is not routinely carried out in such cases because of its time-consuming nature.

1.1.1.4. Treatment

Initial treatment should consist of immediate administration of intravenous heparin bolus (80 units/kg) and continuous infusion (18 units/kg/hr). (9) Invasive therapy for ALI can be endovascular, open surgery, or a combination of both. The type of intervention depends on the etiology of the ALI, the location of the embolus/thrombus, the existing contraindications to endovascular or open surgery, and local experience. (10, 38–41) The results of randomized clinical trials have not demonstrated the superiority of endovascular techniques over open surgery in terms of limb salvage or 30-day mortality. (10, 42) Based on data from national registries in Europe and the United States, open surgery is still three to five times more frequent than endovascular methods. (30, 43, 44)

Endovascular therapy

In patients in whom the severity of ALI allows this (Rutherford stage I and IIa), catheter-directed thrombolysis may be considered as a first-line treatment. (2, 9) Absolute contraindications to thrombolytic therapy include active hemorrhagic diathesis, gastrointestinal bleeding within 10 days, established cerebrovascular event, neurosurgical intervention and intracranial trauma within 3 months, and the presence of compartment syndrome. (2, 9) Today, other endovascular approaches also play an important role. For example, percutaneous mechanical thrombectomy is mainly applied for infrainguinal ALI. One form of percutaneous mechanical thrombectomy is manual embolus/thrombus aspiration, which basically requires only a large lumen catheter and a syringe. (31) When coupled with catheter-directed thrombolysis, a higher primary

success rate of 90% and a limb salvage rate of 86% can be achieved. (31, 39, 45) However, dedicated devices, such as the Indigo Aspiration System (Penumbra Inc., Alameda, CA, USA), are now available for the majority of percutaneous mechanical thrombectomies. (46, 47) Stenting is rarely indicated, only if severe residual stenosis is detected. (30, 40)

Open surgery

Open surgical embolus/thrombus removal, with or without adjunctive therapy, is an accepted and widely used method for the treatment of ALI. Since Dr. Thomas J. Fogarty developed the arterial embolectomy catheter named after him in 1961, (Figure 1) embolectomy has become simple and safe. (26, 41) During embolectomy, the Fogarty catheter is inserted through a surgical incision into the segment proximal or distal to the occlusion, the balloon is inflated, and the catheter is pulled out. The procedure is continued until adequate inflow or back bleeding is observed. (26) The outcome of embolectomy depends on the integrity of the intima, the degree of embolus/thrombus adhesion, and the patency of the run-off arteries. (25, 44, 48–50) In case of residual embolus/thrombus and/or distal embolization, further treatment (e.g., stent implantation or intraoperative thrombolysis) may be needed. (26, 27, 40, 41, 44)

If embolization or *in situ* thrombosis affects an atherosclerotic limb or a dilated arterial segment, endarterectomy or interposition or bypass grafting is the standard choice in addition to or instead of surgical embolectomy. (2, 9, 51)

Delayed or unsuccessful invasive intervention or failed management of acute compartment syndrome often leads to major amputation; (27, 44, 52) and unfortunately, the prognosis for ALI from thromboembolism is poor even with early intervention; the in-hospital and/or 30-day mortality rate is 0–66%. (21, 25, 27, 40, 49, 50, 53) In the last 30 years, few published studies, most of which evaluated the lower limbs, have addressed the determinants of postoperative morbidity and mortality. (21, 25, 27, 40, 49, 50, 53)

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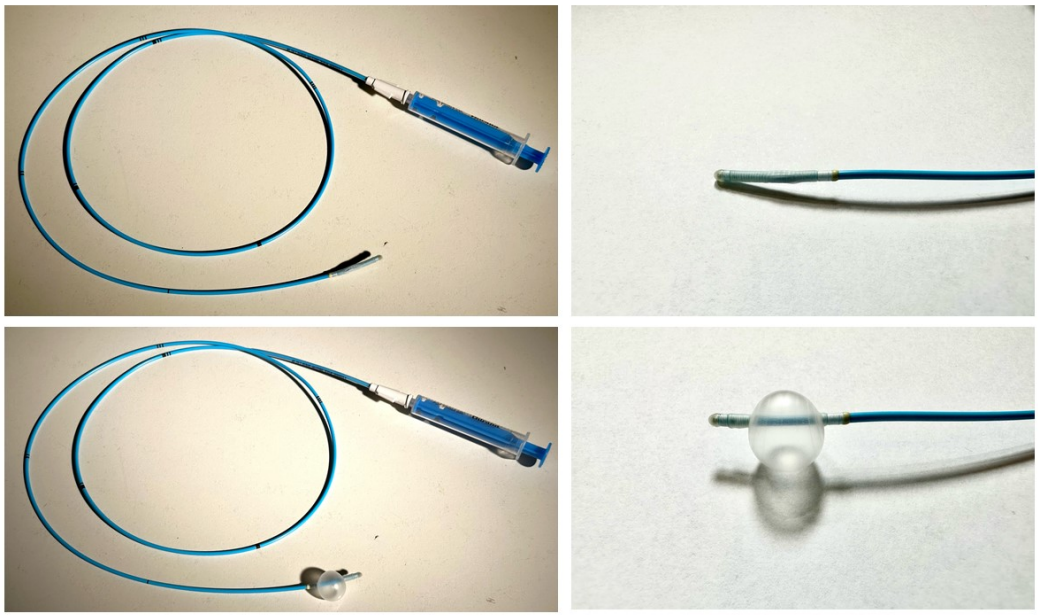

Figure 1. Fogarty catheter (The image was made by Ákos Bérczi.)

1.1.2. Chronic infrarenal aortic stenosis

Infrarenal aortic stenosis (IAS) can be isolated or combined with involvement of the bifurcation and common iliac arteries. In this dissertation, only the isolated IAS is discussed.

Stenosis is relatively rare in the infrarenal aorta. (54–57) Isolated IAS is most common in women in their 30s, 40s, and 50s. (55–58) Besides female sex, the main risk factors for IAS are heavy smoking, elevated blood lipid levels, and hypoplastic aortic syndrome. (54–60)

1.1.2.1. Etiology

The pathogenesis of isolated IAS in adults is almost always due to atherosclerosis. Atherosclerosis is a multifactorial fibroproliferative inflammatory process based on the interaction of genetic and environmental variables. (61–63) Atherosclerotic disease starts with injury to the vascular endothelium. (61, 63–65) Endothelial damage causes the infiltration of low-density lipoprotein particles into the intima of the arterial wall, where they are then oxidized and stimulate an inflammatory response. The recruitment of leukocytes and the release of proinflammatory cytokines and chemokines further exacerbate the inflammatory response, thus contributing to the formation of

atherosclerotic plaques. (61, 65) Atherosclerotic plaques are composed of a lipid-rich core, necrotic debris, and a fibrous cap of smooth muscle cells and extracellular matrix proteins. (61, 65) Over time, atherosclerotic plaques can result in luminal narrowing and reduced blood supply to vital organs.

1.1.2.2. Symptoms

The lower limb symptoms of IAS can be categorized according to the Rutherford and Fontaine classification. (Table 2) (35, 66) The most common symptom of significant IAS is intermittent claudication accompanied by fatigue, cramps, discomfort, or pain, especially in the buttock and thigh muscles. Symptoms are triggered by exercise and are consistently relieved by short periods of rest. Critical limb ischemia usually only develops if there is also stenosis or occlusion in the lower limb. Critical limb ischemia is defined by the presence of chronic ischemic rest pain and/or ulceration/gangrene, and is associated with a high risk of amputation, cardiovascular events, and mortality. (1, 9, 67)

Table 2. Rutherford and Fontaine classification of chronic peripheral artery disease (35, 66)

Rutherford			**Fontaine**	
Grade	**Category**	**Clinical presentation**	**Stage**	**Clinical presentation**
0	**0**	Asymptomatic	**I**	Asymptomatic
I	**1**	Mild claudication	**IIa**	Mild claudication
	2	Moderate claudication	**IIb**	Moderate-to-severe claudication
	3	Severe claudication		
II	**4**	Ischemic rest pain	**III**	Ischemic rest pain
III	**5**	Minor tissue loss	**IV**	Ulceration or gangrene
	6	Major tissue loss		

1.1.2.3. Diagnosis

The first diagnostic test for PAD is palpation of the peripheral pulses (in the case of IAS, the femoral pulses are weakly palpable or not palpable at all), the second is

measurement of the ankle-brachial index (ABI; an ABI of 0.9 or less indicates PAD with 75% sensitivity and 86% specificity), (8, 9, 68, 69) and the third is a Handheld Doppler examination. Diabetes mellitus, chronic kidney failure, or other diseases can lead to an inability to compress the tibial arteries. These patients may have an ABI >1.4 and require further non-invasive diagnostic testing. (8, 68, 69) Among the imaging modalities, ultrasound can provide information on the extent of the area reduction caused by IAS, its morphology, and the length of the affected aortic segment. However, other imaging techniques may also be needed to select the type of invasive therapy and to accurately map the status of the lower limb arteries. The most widely accepted diagnostic tool is the CTA, which has a sensitivity and specificity of 90–100% for the detection of PAD. (3, 6, 9, 51) Magnetic resonance angiography without contrast is reserved almost exclusively for patients with proven iodine allergy or chronic kidney disease. Limitations of MRA include the lack of visualization of arterial calcification and overestimation of the grade of stenosis. (3, 9, 36) Digital subtraction angiography is no longer practically used to confirm IAS.

1.1.2.4. Treatment

Treatment of IAS can be divided into best medical therapy (BMT) and invasive therapy. Invasive therapy should be considered when the patient's activities of daily living are compromised. (9, 51)

Best medical therapy

The BMT is based on non-pharmacological and pharmacological modification and management of cardiovascular risk factors. Non-pharmacological methods aim to promote lifestyle changes, while pharmacological treatment involves the use of antiplatelet, lipid-lowering, antihypertensive, etc. drugs. Antiplatelet medications are indicated in symptomatic cases or after revascularization. (6, 9, 51) Statins have been shown to reduce both cardiovascular events and mortality. (70, 71) According to the guidelines of the European Society of Cardiology and the European Society of Hypertension, the recommended value of blood pressure should not exceed 140/90 mmHg. (72) Diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers can all be given as monotherapy or

in various combinations to optimize blood pressure in patients with PAD. (72) Due to the word count limit of the dissertation, I will not describe BMT for other cardiovascular risk factors (e.g., DM).

Invasive therapy

Until the early 2000s, open surgery (endarterectomy or interposition grafting) was the primary invasive treatment for isolated IAS (and aortoiliac lesions), with an early mortality rate of 1–3% and a 5-year patency rate of 76–91%. (51, 73) Over the last 20 years, however, endovascular therapy, especially stenting, has gradually become the first-line method, mainly due to the significantly lower mortality rate, the absence of erectile dysfunction in men, and the minimally invasive nature of the technique. (56, 58, 59, 74, 75) Percutaneous transluminal angioplasty (PTA) alone is rarely performed. Stenting can be done with balloon- or self-expanding stents. Both can be bare metal stents and covered stents. Stents are made of metal or metal alloys (e.g., stainless steel, cobalt–chromium alloys, and titanium and its alloys). (76) For covered stents, the frame of the stent is covered with a material, usually polytetrafluoroethylene. (76) The most important differences between balloon- and self-expanding stents are listed in Table 3. (76) Covered stents have two main advantages: (1) they reduce the likelihood of distal embolization, and (2) they can prevent extravasation if aortic rupture occurs as a complication.

There are only a limited number of major publications on the results of endovascular treatment in patients with IAS (more than 20 patients plus long-term follow-up, N=3); (55, 77, 78) and, for example, the long-term patency of covered stents implanted for IAS is not yet known.

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Table 3. Comparison of balloon- and self-expanding stents (76)

Parameter	Balloon-expanding stent	Self-expanding stent
Radial strength	Can collapse if a critical external pressure is exceeded	Have no strength limitation and elastically recover even after complete flattening or radial crushing
Radial stiffness	A balloon-expanding stent is stiffer than a self-expanding stent of identical design	
Acute recoil	Balloon-expanding stents recoil less than self-expanding stents when placed in calcified lesions	
Chronic recoil	Become smaller in diameter over time	Become larger in diameter over time
Delivery profile	Dictated by the profile of the balloon upon which it is mounted	Dictated by the strut dimensions (specifically the width)
Placement accuracy	Foreshortening: rare → placement accuracy: easy to implement	Foreshortening: frequent → placement accuracy: not easy to implement

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2. Objectives

2.1. Study I (Amputation and mortality rates of patients undergoing upper or lower limb surgical embolectomy and their predictors – Institutional Review Board Approval No. 113/2021)

In the last 30 years, few published studies, most of which evaluated the lower limbs, have addressed the determinants of postoperative morbidity and mortality. Therefore, our study aimed to provide detailed information on the success of not only lower limb but also upper limb surgical embolectomies, as well as factors influencing amputation and mortality.

2.2. Study II (Early and long-term results of the endovascular treatment of patients with isolated infrarenal aortic stenosis – Institutional Review Board Approval No. 128/2016)

The purpose of our study was to report on the complications and long-term outcome of endovascular interventions for rare, isolated infrarenal aortic manifestations performed in our center, as there are only a limited number of major publications on this topic (more than 20 patients plus long-term follow-up, N=3).

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3. Methods

3.1. Study I (Amputation and mortality rates of patients undergoing upper or lower limb surgical embolectomy and their predictors)

3.1.1. Patient selection

A retrospective, single-center (Heart and Vascular Center, Semmelweis University) analysis of 347 patients with acute upper or lower limb ischemia who underwent surgery between May 1, 2005 and December 31, 2019 was carried out. A total of 407 open and 105 purely endovascular procedures for acute upper or lower limb thromboembolic events were performed during this period. Patients with ALI due to traumatic or iatrogenic injury, patients with a history of aortic or upper or lower limb arterial dissection or endovascular and/or open surgical repair at the site of occlusion, patients in whom the embolus/thrombus was eliminated through purely endovascularly means, and patients who could only undergo amputation were not included in this study.

3.1.2. Diagnosis of acute limb ischemia

The diagnosis of ALI was made by angiologists and/or vascular surgeons based on patient complaints/symptoms (sudden onset of limb pain) and physical (pallor, paresthesia, and/or paresis of the affected limb, and absent pulses distal to the site of occlusion), handheld Doppler, and/or imaging (ultrasound, CTA, and/or DSA) findings. (2, 9, 35)

3.1.3. Medication and surgery

At the time of diagnosis of ALI, patients received 5 000 units of intravenous heparin; this dose was administered every 6 hours until the patient underwent surgery. An additional 10 000 units of heparin was given in the operating room. Postoperative medication was determined by the etiology of ALI and the patient's comorbidities. If a distinction could be made between the two etiologies (embolism versus thrombosis), long-term anticoagulation therapy with coumarin derivates was recommended for revascularization due to embolism, whereas antiplatelet and statin therapy was recommended for revascularization due to native arterial thrombosis.

For revascularization, embolectomy with a Fogarty catheter was first attempted in all patients. The operations were performed under general or local anaesthesia. The size of the Fogarty catheter (2–5F) varied depending on the diameter of the arteries involved. (In patients with ALI caused by an aneurysm with mural [or intraluminal] thrombus, not only embolectomy but also aorto-aortic interposition grafting or popliteal bypass grafting was carried out.) In the upper limb, the site of surgical exploration was at the level of the origin of the deep brachial artery or, more commonly, in the cubital fossa, where the brachial artery divides into the radial and ulnar arteries. In the lower limb, the incisions were made either at the bifurcation of the common femoral artery and/or at the popliteal artery below the knee, where the crural vessels were separately accessible for catheter passage. Embolectomy was considered technically successful if good inflow and backflow was obtained from the affected arterial segment(s). Except for the last 5 years of the study period, intraoperative or postprocedural DSA was not routinely used and occurred only if deemed necessary by the operating surgeon. If DSA was performed and small residual emboli/thrombi were revealed in the runoff arteries, recombinant tissue plasminogen activator (5–10 mg; Actilyse, Boehringer Ingelheim RCV GmbH & Co KG, Wien, Austria) was administered. The recombinant tissue plasminogen activator was injected directly into the emboli/thrombi or as close to them as possible. However, if DSA demonstrated large residual emboli/thrombi or chronic stenosis in the iliofemoral or popliteal segment, further embolectomy or bypass grafting or bare metal or covered stent implantation was carried out. Stenting was also required if a flow-limiting dissection developed as a complication of the embolectomy. These adjunctive endovascular or more extensive surgical procedures (with or without fasciotomy) and amputations were done in the same or another session as the embolectomy. The indication for fasciotomy was pain, postoperative calf swelling, and the presence of paresthesia and/or paresis. During the fasciotomy, two long incisions were made on the medial and lateral sides of the calf, reaching all four muscle compartments. Patients were regularly assessed for muscle viability and necrectomies were performed if necessary. Open wounds from fasciotomy incisions were treated with smart dressings, negative pressure therapy, and gradual approximation techniques. If primary closure was not achieved within two weeks, skin grafting followed.

3.1.4. Data collection

Patient demographics, risk factors for arterial disease, medical history, the severity of ALI, preoperative medication regimen, embolus/thrombus localization, procedural information, in-hospital complications/adverse events and their related interventions, and 30-day mortality were reviewed in electronic medical records. Demographic variables and risk factors for arterial disease included sex, age, smoking, hypertension, hyperlipidemia, and DM. Patient's history of cardiac and ischemic cerebral diseases, aneurysm, endovascular or open surgical repair, amputation, deep vein thrombosis (DVT), pulmonary embolism (PE), hypercoagulable state, chronic obstructive pulmonary disease (COPD), and malignancy was also collected. The severity of ALI was determined according to the Rutherford classification. (35) For medication, the focus of the study was on anticoagulants, steroids, and chemotherapy. Evaluation of the localization of the embolus/thrombus was based on physical examination, handheld Doppler and imaging findings, and/or intraoperative results. Procedural information included the time between the onset of symptoms and embolectomy, the location of arterial exposure, and the type of procedure(s) executed in case of embolectomy failure. Reocclusion, distal embolization, reperfusion injury, compartment syndrome, incision site complications, acute kidney injury, MI, stroke, minor or major amputation, and death were examined as in-hospital complications/adverse events. Incision site complications were taken into account if they necessitated additional interventions, prolonged hospital stay, or both. The 30-day mortality was equivalent to death within 30 days of discharge from the hospital. Minor amputation was defined as removal of a hand or foot, or a part thereof, while amputations above the wrist and ankle joints were considered major amputations.

3.1.5. Statistical analysis

Statistical analysis was performed with SPSS Statistics for Windows (Version 27.0.; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as medians (interquartile ranges [IQRs]) and compared using the Mann–Whitney *U* test. Categorical data were expressed as counts (percentages) and compared using the Fisher's exact test. Univariate logistic regression was applied to calculate odds ratios (ORs). Variables that were statistically significant in the univariate model were

additionally used in a multivariate logistic regression analysis adjusted for sex and age. All statistical tests were two-tailed. The threshold of statistical significance was $P<0.05$.

3.2. Study II (Early and long-term results of the endovascular treatment of patients with isolated infrarenal aortic stenosis)

3.2.1. Patient selection

A retrospective analysis was performed on 40 consecutive patients with isolated IAS from a single institution (Heart and Vascular Center, Semmelweis University) who underwent radiological intervention between 1 January 2001 and 31 December 2017.

3.2.2. Diagnosis of infrarenal aortic stenosis

Imaging modalities (color Doppler ultrasound, CTA, MRA, and/or DSA) were used to confirm the possibility of IAS based on the patient's complaints (e.g., intermittent claudication), physical examination findings (weakly palpable or non-palpable femoral pulses), and ABI values.

3.2.3. Endovascular therapy

All radiological interventions were carried out under local anesthesia. Patients were monitored by electrocardiography, blood pressure measurement, and pulse oximetry. All procedures were performed by a radiologist with at least 5 years of experience. Access was obtained by puncture of the common femoral artery or brachial artery. After sheath insertion, 5 000 units of heparin were administered intra-arterially. Diagnostic DSA images were taken first. Significant stenosis was defined as luminal narrowing >70%. After crossing the lesion with a 0.035-inch guidewire, patients had PTA or stenting (selective, primary, or direct). Selective stenting was defined as the placement of a stent after PTA with suboptimal results (residual stenosis >30% or extensive intimal dissection). Primary stenting was defined as the placement of a stent after predilation of the lesion, irrespective of the PTA outcome. Direct stenting was defined as the placement of a stent without predilation of the lesion. (79) The decision whether to use a self-expanding or balloon-expanding stent was made by the interventional radiologist performing the procedure. Self-expanding stents were oversized by 10%; balloon-expanding stents were not oversized. Stent length was chosen to be the shortest that

covered the lesion. The final result was shown on completion angiography and the images were evaluated for distal embolization. Technical success was defined as <30% residual stenosis of the target lesion without dissection or extravasation.

Patients who had not received any antiplatelet therapy prior to the procedure were initiated on aspirin or clopidogrel. Aspirin treatment was started with an oral loading dose of 300 mg, whereas clopidogrel treatment was started with an oral loading dose of 300–600 mg. The lifetime maintenance dose was 100 mg/day for aspirin and 75 mg/day for clopidogrel.

Clinical success was defined as a one-stage improvement in Fontaine stage or a change from stage IIb to stage IIa. Primary patency at follow-up was defined as open stents without reintervention. Assisted primary patency was defined as open stents after intervention for restenosis.

3.2.4. Data collection

The electronic medical records were reviewed for patient demographics, risk factors for chronic arterial steno-occlusive disease, medical history, antiplatelet and statin therapy, pre- and postinterventional images, procedural information, and pre- and postprocedural clinical status. Demographic variables and risk factors for chronic arterial steno-occlusive disease included sex, age, smoking, hypertension, hyperlipidemia, DM, and obesity. Obesity was defined as a body mass index ≥30 kg/m^2. Patient's history of chronic kidney disease, endovascular or open surgical repair of coronary arteries, aortic arch branches, and lower extremity arteries, and diseases relevant to the development of IAS (e.g., antiphospholipid syndrome) was also collected. Digital subtraction angiography images were used to determine the diameter of the infrarenal aorta and the grade and length of the IAS before the intervention, and the grade of residualis stenosis and the presence of complications after the intervention. The diameter of the infrarenal aorta (measured above the IAS), the grade and length of the IAS, and the grade of residual stenosis were quantified using software integrated into our workstation (Leonardo Workstation, Siemens AG, Erlangen, Germany). The presence and extent of calcification was judged on fluoroscopic images taken before the procedure as described by Doris et al., (80) and mildly, moderately, and heavily calcified groups were distinguished. (Mild calcification: one punctate [<5 mm] calcification or multiple

punctate calcifications. Moderate calcification: one linear [>5 mm] calcification or one linear calcification and one punctate calcification or one linear calcification and multiple punctate calcifications or two linear calcifications. Heavy calcification: two linear calcifications and one punctate calcification or two linear calcifications and multiple punctate calcifications or three linear calcifications or continuous calcification with no visible breaks.) (80) Procedural information included access site, type of invasive treatment (PTA versus stenting [selective, primary, or direct]), and balloon and stent characteristics (manufacturer, diameter, length, and type [self-expanding versus balloon-expanding]). Clinical status before and after the intervention was assessed using the Fontaine classification and the ABI. (66) Technical and 4-week clinical success, early (≤30 days) complications, mortality, and further endovascular or open surgical reconstruction were also analyzed. Late follow-up period (>30 days) was characterized by restenosis, reintervention, and primary and assisted primary patency rates.

3.2.5. Statistical analysis

Statistics were calculated using StatSoft Statistica 13.4 (Moonsoft Oy, Espoo, Finland) and GraphPad Prism 7.01 (GraphPad Software Inc., La Jolla, CA, USA) software. Continuous data were presented as medians and IQRs; categorical data were given as counts (percentages). Differences in aortic diameter between women and men were assessed using the Mann–Whitney *U* test. A Kaplan-Meier analysis was performed to determine primary and assisted primary patency rates. A P-value <0.05 was considered statistically significant.

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4. Results

4.1. Study I (Amputation and mortality rates of patients undergoing upper or lower limb surgical embolectomy and their predictors)

4.1.1. Patient characteristics

Of the 347 patients, 207 (59.7%) were female, 140 (40.3%) were male, and the median age was 76 years (IQR, 63.2–82.6 years). One hundred and forty-one patients (40.6%) were active smokers and 253 patients (72.9%), 86 patients (24.8%), and 92 patients (26.5%) had known hypertension, hyperlipidemia, and DM, respectively. (Table 4) The medical history of the patients can be seen in Table 5. Acute limb ischemia was categorized as stage I in four patients (1.2%), stage IIa in 92 patients (26.5%), and stage IIb in 251 patients (72.3%). (Table 4) At the time of embolization/thrombosis, 78 patients (22.5%) received anticoagulant therapy, seven patients (2%) received steroid therapy, and 52 patients (15%) received chemotherapy. (Table 4) The cause of anticoagulation was atrial fibrillation (AF) in 52 cases, other cardiac diseases in 15 cases, ischemic stroke in six cases, DVT and/or PE in three cases, and hypercoagulable state in two cases. (Table 5) Despite the medical recommendation, 15 patients did not take the oral anticoagulant.

Table 4. Patient demographics, risk factors for arterial disease, the severity of acute limb ischemia, and preoperative medication regimen

Patient demographics, risk factors, severity of ALI, and preoperative medication regimen	All patients (N=347)	Patients with upper limb embolectomy (N=134)	Patients with lower limb embolectomy (N=213)	P-value
Patient demographics				
Female, N (%)	207 (59.7)	88 (65.7)	119 (55.9)	0.070
Age (years), median (IQR)	76 (63.2–82.6)	76 (64–83.5)	76.2 (61.6–82.2)	0.509
Risk factors				
Smoking, N (%)	141 (40.6)	50 (37.3)	91 (42.7)	0.318
Hypertension, N (%)	253 (72.9)	100 (74.6)	153 (71.8)	0.568
Hyperlipidemia, N (%)	86 (24.8)	31 (23.1)	55 (25.8)	0.572
DM, N (%)	92 (26.5)	38 (28.4)	54 (25.4)	0.537
Severity of ALI				
Stage I, N (%)	4 (1.2)	0 (0)	4 (1.9)	0.162
Stage IIa, N (%)	92 (26.5)	46 (34.3)	46 (21.6)	**0.009**
Stage IIb, N (%)	251 (72.3)	88 (65.7)	163 (76.5)	**0.036**
Preoperative medication regimen				
Anticoagulant therapy, N (%)	78 (22.5)	30 (22.4)	48 (22.5)	0.974
Steroid therapy, N (%)	7 (2)	3 (2.2)	4 (1.9)	0.817
Chemotherapy, N (%)	52 (15)	24 (17.9)	28 (13.1)	0.226

ALI, Acute limb ischemia; *DM*, diabetes mellitus; *IQR*, interquartile range.

Table 5. Patient medical history

Pre-existing diseases/abnormalities and previous invasive vascular procedures, N (%)	All patients (N=347)	Patients with upper limb embolectomy (N=134)	Patients with lower limb embolectomy (N=213)	P-value
Cardiac disease				
Arrhythmia	90 (25.9)	30 (22.4)	60 (28.2)	0.232
AF	67 (19.3)	25 (18.7)	42 (19.7)	0.807
Coronary artery disease	59 (17)	19 (14.2)	40 (18.8)	0.267
Valvular disease	8 (2.3)	3 (2.2)	5 (2.3)	1.000
Heart failure	3 (0.9)	1 (0.7)	2 (0.9)	1.000
Ischemic cerebral disease				
Amaurosis fugax, TIA	19 (5.5)	7 (5.2)	12 (5.6)	0.870
Stroke	14 (4)	7 (5.2)	7 (3.3)	0.372
Aneurysm				
Aortic aneurysm	1 (0.3)	0 (0)	1 (0.5)	1.000
Peripheral aneurysm	2 (0.6)	1 (0.7)	1 (0.5)	1.000
Peripheral endovascular therapy*	83 (23.9)	35 (26.1)	48 (22.5)	0.167
Peripheral open surgical repair*	62 (17.9)	22 (16.4)	40 (18.8)	0.106
Amputation				
Minor amputation	5 (1.4)	0 (0)	5 (2.3)	0.161
Major amputation	3 (0.9)	0 (0)	3 (1.4)	0.287
DVT and/or PE	3 (0.9)	1 (0.7)	2 (0.9)	1.000
Hypercoagulable state	2 (0.6)	1 (0.7)	1 (0.5)	1.000
COPD	7 (2)	2 (1.5)	5 (2.3)	0.711
Malignancy	72 (20.7)	30 (22.4)	42 (19.7)	0.588

AF, Atrial fibrillation; *COPD*, chronic obstructive pulmonary disease; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism; *TIA*, transient ischemic attack.

*Unrelated to the site of acute arterial occlusion.

4.1.2. Embolus/thrombus localization

The embolus/thrombus was localized to the upper limb in 134 patients (38.6%) and the lower limb in 213 patients (61.4%). Simultaneous upper and lower limb involvement did not occur in any of the patients. No patient had bilateral embolization/thrombosis on the upper limb, while 18 patients (5.2%) had bilateral embolization/thrombosis on the lower limb.

In the upper limb, the following arteries were affected: the subclavian artery in 11 cases, the axillary artery in 11 cases, the brachial artery in 118 cases, the radial artery in 47 cases, the ulnar artery in 57 cases, and the interosseous artery in 12 cases. The involvement of more than one artery was seen in 69 patients.

In the lower limb, the following arteries were affected unilaterally or bilaterally: the common iliac artery in four cases, the external iliac artery in 31 cases, the common femoral artery in 81 cases, the deep femoral artery in 83 cases, the superficial femoral artery in 89 cases, the popliteal artery in 112 cases, the anterior tibial artery in 37 cases, the tibioperoneal trunk in 26 cases, the posterior tibial artery in 11 cases, and the peroneal artery in seven cases. The involvement of more than one artery was observed in 140 patients.

4.1.3. Procedural information

In the upper limb, the time between the onset of symptoms and embolectomy was less than 24 hours in 98 patients (73.1%), 1 to 7 days in 28 patients (20.9%), and more than 1 week in eight patients (6%). The site of surgical exploration was the transition between the axillary and brachial artery in 20 cases (14.9%), the brachial artery in 104 cases (77.6%), and both locations in 10 cases (7.5%). Embolectomy was technically successful in 118 patients (88.1%). Fifteen patients received additional invasive treatment (intra-arterial thrombolytic therapy with or without further embolectomy, N=5; innominate artery stenting, N=2; and subclavian artery stenting, N=8). Each patient had adjunctive therapy only once. The median time between embolectomy and adjunctive therapy was 4 hours (IQR, 0.5–12.5 hours). Concomitant amputation with embolectomy was unavoidable in one case (major amputation, N=1). Neither stage IIb ALI (25/36 versus 63/98, P=0.683) nor failed embolus/thrombus removal (5/36 versus

10/98, P=0.546) was significantly more common in patients who underwent embolectomy after 24 hours.

In the lower limb, the time between the onset of symptoms and embolectomy was less than 24 hours in 138 patients (64.8%), 1 to 7 days in 51 patients (23.9%), and more than 1 week in 24 patients (11.3%). The site of surgical exploration was one of the common femoral arteries in 84 cases (39.4%), one of the popliteal arteries in 80 cases (37.6%), the equilateral common femoral and popliteal arteries in 15 cases (7%), the common femoral artery on one side and the popliteal artery on the opposite side in seven cases (3.3%), the common femoral artery on both sides in 17 cases (8%), and the popliteal artery on both sides in 10 cases (4.7%). Embolectomy was technically successful in 176 patients (82.6%). Twenty-seven patients received additional invasive treatment (intra-arterial thrombolytic therapy [Figure 2] with or without further embolectomy, N=15; common iliac or external iliac artery stenting, N=5; superficial femoral artery stenting, N=5; femoral patch plasty, N=4; aorto-aortic interposition grafting, N=2; and/or femoropopliteal bypass grafting, N=4). Eight patients had adjunctive therapy twice. For those who received adjunctive therapy only once, the median time between embolectomy and adjunctive therapy was 7 hours (IQR, 2.8–10 hours), while for those who received adjunctive therapy twice, the median time between embolectomy and second adjunctive therapy was 12.5 hours (IQR, 9.5–18.8 hours). Fasciotomy was required in 12 cases. Concomitant amputation with embolectomy was unavoidable in 10 cases (major amputation, N=10). Neither stage IIb ALI (58/75 versus 105/138, P=0.867) nor failed embolus/thrombus removal (14/75 versus 13/138, P=0.083) was significantly more common in patients who underwent embolectomy after 24 hours.

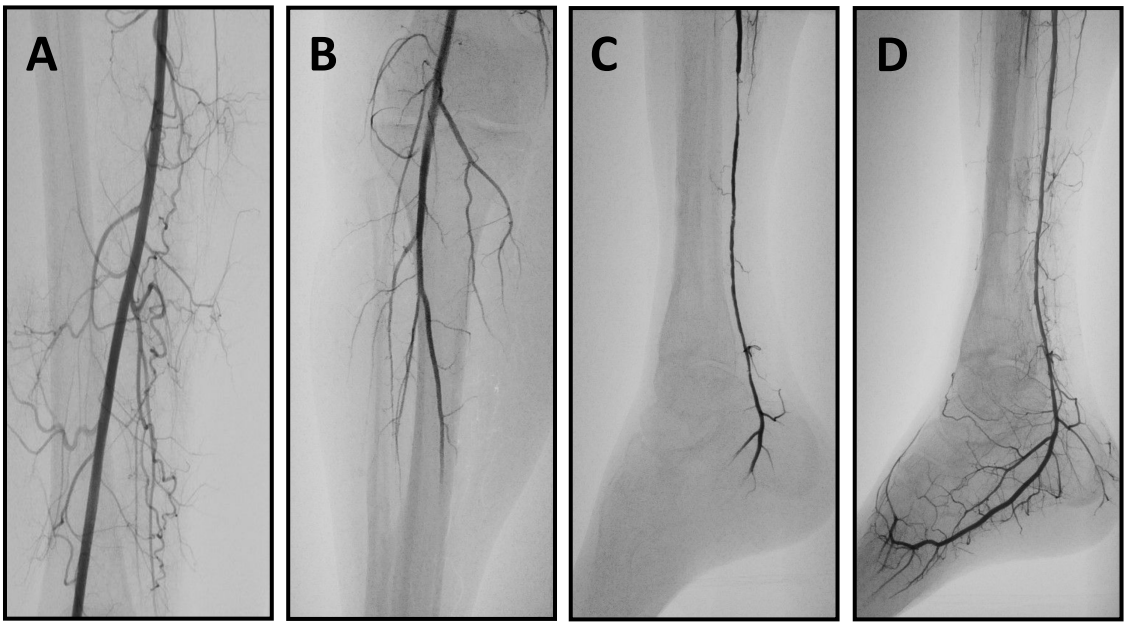

Figure 2. Right posterior tibial artery embolectomy combined with intra-arterial thrombolytic therapy ([A] No evidence of atherosclerosis or embolism in the superficial femoral artery. [B] No evidence of atherosclerosis or embolism in the popliteal artery. Chronic occlusion of the distal two-thirds of the anterior tibial artery and peroneal artery as a result of a vascular injury sustained during excision of a sarcoma 5 years ago. Acute occlusion of the distal two-thirds of the posterior tibial artery by embolism. [C] Contrast material filling in the posterior tibial artery after removal of the embolus with a Fogarty catheter. No contrast material filling in the plantar arch. [D] Perfect morphology of the posterior tibial artery and plantar arch on angiography 24 hours after intra-arterial administration of 10 mg recombinant tissue plasminogen activator directly into the posterior tibial artery.)
(The digital subtraction angiography images were made by Edit Dósa.)

4.1.4. In-hospital complications/adverse events and 30-day mortality

The median length of hospital stay was 3.8 days (IQR, 2.1–6.6 days). The presumed cause of embolization/thrombosis was a pre-existing disease in 204 patients (58.8%) and a newly discovered disease/condition in 39 patients (11.2%; AF, N=20; other cardiac diseases, N=15; aortic aneurysm, N=1; and popliteal aneurysm, N=3). In 104 cases (30%), the cause was not found.

In-hospital complications/adverse events are summarized in Table 6. The in-hospital reocclusion rate was 5.2%, the acute kidney injury rate was 1.2%, the MI rate was 1.2%, the stroke rate was 1.2%, the major amputation rate was 9.5%, and the mortality rate was 2.6%. Two out of three patients who had upper limb major amputation and two out of 30 patients who had lower limb major amputation died during their hospital stay. Reperfusion injury occurred in 25 patients (7.2%) and compartment syndrome in 20 patients (5.8%). Compartment syndrome was not significantly more common in those who underwent surgery after 24 hours (8/111 versus 12/236, P=0.473) and in those who received adjunctive therapy (5/42 versus 15/305, P=0.079). Reperfusion injury led to severe metabolic abnormalities (hyperkalemia, metabolic acidosis, and rhabdomyolysis/myoglobinuria) in three patients and loss of limb in two patients. The 30-day mortality rate was 4.9% (upper limb, N=3 [2.2%] and lower limb, N=14 [6.6%]). The cause of in-hospital death was cardiorespiratory insufficiency in four cases, cardiogenic shock in one case, end-stage heart failure in one case, MI in one case, stroke in one case, and sepsis in one case. The cause of 30-day death was MI in three cases, stroke in three cases, gastrointestinal bleeding in two cases, and unknown in nine cases.

Table 6. In-hospital complications/adverse events

Complications/adverse events, N (%)	All patients (N=347)	Patients with upper limb embolectomy (N=134)	Patients with lower limb embolectomy (N=213)	P-value
Reocclusion	18 (5.2)	9 (6.7)	9 (4.2)	0.197
Distal embolization	12 (3.5)	3 (2.2)	9 (4.2)	0.383
Reperfusion injury	25 (7.2)	5 (3.7)	20 (9.4)	0.055
Compartment syndrome	20 (5.8)	0 (0)	20 (9.4)	**<0.001**
Incision site complications	23 (6.6)	9 (6.7)	14 (6.6)	0.958
Acute kidney injury	4 (1.2)	0 (0)	4 (1.9)	0.162
MI	4 (1.2)	1 (0.7)	3 (1.4)	1.000
Stroke	4 (1.2)	2 (1.5)	2 (0.9)	0.562
Amputation	34 (9.8)	3 (2.2)	31 (14.6)	**<0.001**
Minor amputation	1 (0.3)	0 (0)	1 (0.5)	1.000
Major amputation	33 (9.5)	3 (2.2)	30 (14.1)	**<0.001**
Death	9 (2.6)	3 (2.2)	6 (2.8)	1.000

MI, Myocardial infarction.

4.1.5. Predictors of in-hospital major amputation and in-hospital plus 30-day mortality

Due to the statistically low number of cases, predictive factors could only be examined in relation to lower limb embolectomies and embolectomies in the entire patient population; of the predictors, only those for in-hospital major amputation and in-hospital plus 30-day mortality were determined. The predictive role of all the parameters described in the 3.1.4. Data collection subsection has been evaluated. The parameters found to be significant in univariate and multivariate analyses are presented in Tables 7 and 8. In patients with lower limb embolectomy, the time between the onset of symptoms and embolectomy was a predictor of in-hospital major amputation (OR, 1.78), while previous stroke was a predictor of mortality (OR, 7.16). (Table 8) In patients with upper or lower limb embolectomy, two predictive factors were identified

for in-hospital major amputation: 1) the time between the onset of symptoms and embolectomy (OR, 1.92) and 2) compartment syndrome (OR, 3.51). (Table 8)

Table 7. Significant predictors of in-hospital major amputation and in-hospital plus 30-day mortality – univariate analysis

Parameters	Odds ratio	Confidence interval	P-value
Major amputation in patients with lower limb embolectomy			
Time between the onset of symptoms and embolectomy	1.67	1.01–2.78	**0.047**
Compartment syndrome	3.98	1.44–11	**0.008**
Major amputation in patients with upper or lower limb embolectomy			
DM	2.23	1.07–4.66	**0.033**
Previous minor amputation	6.69	1.08–41.56	**0.041**
Lower limb involvement	7.16	2.14–23.95	**0.001**
Time between the onset of symptoms and embolectomy	1.67	1.01–2.78	**0.047**
Compartment syndrome	6.23	2.29–16.99	**<0.001**
Mortality in patients with lower limb embolectomy			
Previous stroke	8.34	1.72–40.36	**0.008**
Mortality in patients with upper or lower limb embolectomy			
Malignancy	2.61	1.13–6.03	**0.025**
Chemotherapy	2.80	1.15–6.82	**0.024**

DM, Diabetes mellitus.

Table 8. Significant predictors of in-hospital major amputation and in-hospital plus 30-day mortality – multivariate analysis

Parameters	Odds ratio	Confidence interval	P-value
Major amputation in patients with lower limb embolectomy			
Time between the onset of symptoms and embolectomy	1.78	1.05–3.01	**0.033**
Major amputation in patients with upper or lower limb embolectomy			
Time between the onset of symptoms and embolectomy	1.92	1.10–3.34	**0.022**
Compartment syndrome	3.51	1.17–10.52	**0.025**
Mortality in patients with lower limb embolectomy			
Previous stroke	7.16	1.43–36.01	**0.017**

4.2. Study II (Early and long-term results of the endovascular treatment of patients with isolated infrarenal aortic stenosis)

4.2.1. Patient characteristics

The median age of the 40 patients (28 women, 12 men) was 60 years (IQR, 54.8–68 years). All patients were symptomatic; 85% had intermittent claudication, 5% had rest pain, and 10% had ulcers or gangrene. Atherosclerotic risk factors included smoking in 30 patients (75%), hypertension in 34 patients (85%), hyperlipidemia in 15 patients (37.5%), DM in nine patients (22.5%), obesity in six patients (15%), and chronic kidney disease in three patients (7.5%). Four patients (10%) had a history of percutaneous coronary artery intervention or coronary artery bypass grafting, five patients (12.5%) had a history of supra-aortic endovascular or open surgical reconstruction, and 13 patients (32.5%) had a history of lower extremity percutaneous or open surgical revascularization. After the procedure, all patients received antiplatelet therapy and 57.5% were also taking a statin. (Table 9)

Table 9. Patient demographics, atherosclerotic risk factors, previous invasive vascular procedures, and medication regimen

Patient demographics, atherosclerotic risk factors, previous invasive vascular procedures, and medication regimen	Patients (N=40)
Patient demographics	
Female, N (%)	28 (70)
Age (years), median (IQR)	60.8 (54.8–68)
Atherosclerotic risk factors and pre-existing diseases	
Smoking, N (%)	30 (75)
Hypertension, N (%)	34 (85)
Hyperlipidemia, N (%)	15 (37.5)
DM, N (%)	9 (22.5)
Obesity, N (%)	6 (15)
Chronic kidney disease, N (%)	3 (7.5)
Previous invasive vascular procedures	
Percutaneous coronary artery intervention or CABG, N (%)	4 (10)
Supra-aortic endovascular or open surgical reconstruction, N (%)	5 (12.5)
Lower extremity percutaneous or open surgical revascularization, N (%)	13 (32.5)
Preprocedural medication regimen	
100 mg aspirin monotherapy or 75 mg clopidogrel monotherapy, N (%)	30 (75)
Dual antiplatelet therapy, N (%)	7 (17.5)
Statin therapy, N (%)	13 (32.5)
Periprocedural medication regimen	
Aspirin loading (300 mg) or clopidogrel loading (300–600 mg), N (%)	3 (7.5)
Postprocedural medication regimen	
100 mg aspirin monotherapy or 75 mg clopidogrel monotherapy, N (%)	33 (82.5)
Dual antiplatelet therapy, N (%)	7 (17.5)
Statin therapy, N (%)	23 (57.5)

CABG, Coronary artery bypass grafting; *DM*, diabetes mellitus; *IQR*, interquartile range.

4.2.2. Lesion, procedure, balloon, and stent characteristics

None of the lesions involved the origin of the common iliac arteries. The presumed underlying disease in all patients was atherosclerosis; two patients also had primary antiphospholipid syndrome. The median aortic diameter above the lesion was 12.1 mm (IQR, 10.7–14.7 mm); the diameter was significantly (P<0.035) smaller in women (11.6 mm [IQR, 10.5–13.9 mm]) than in men (13.5 mm [IQR, 12.1–16.2 mm]). The median grade of IAS was 80% (IQR, 70–80%); its median length was 19.9 mm (IQR, 13–29.4 mm). Mild calcification was observed in 18 cases (45%), moderate in 11 cases (27.5%), and heavy in three cases (7.5%).

Access was obtained by puncture of the common femoral artery (N=39) or brachial artery (N=1). Four patients (10%) were treated with PTA alone; the balloon diameter was 8 mm in one case, 10 mm in two cases, and 14 mm in one case; the balloon length was 40 mm in three cases and 60 mm in one case. Thirty-six lesions (90%) were stented. (Figures 3 to 5) Stent types and stent characteristics are listed in Tables 10 and 11.

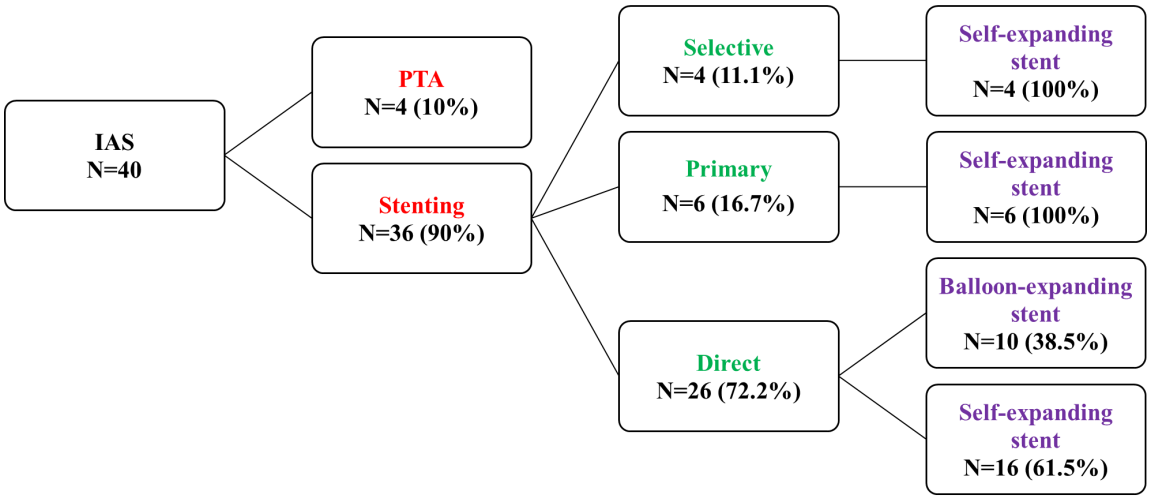

Figure 3. Endovascular treatment types

IAS, Infrarenal aortic stenosis; *PTA*, percutaneous transluminal angioplasty.

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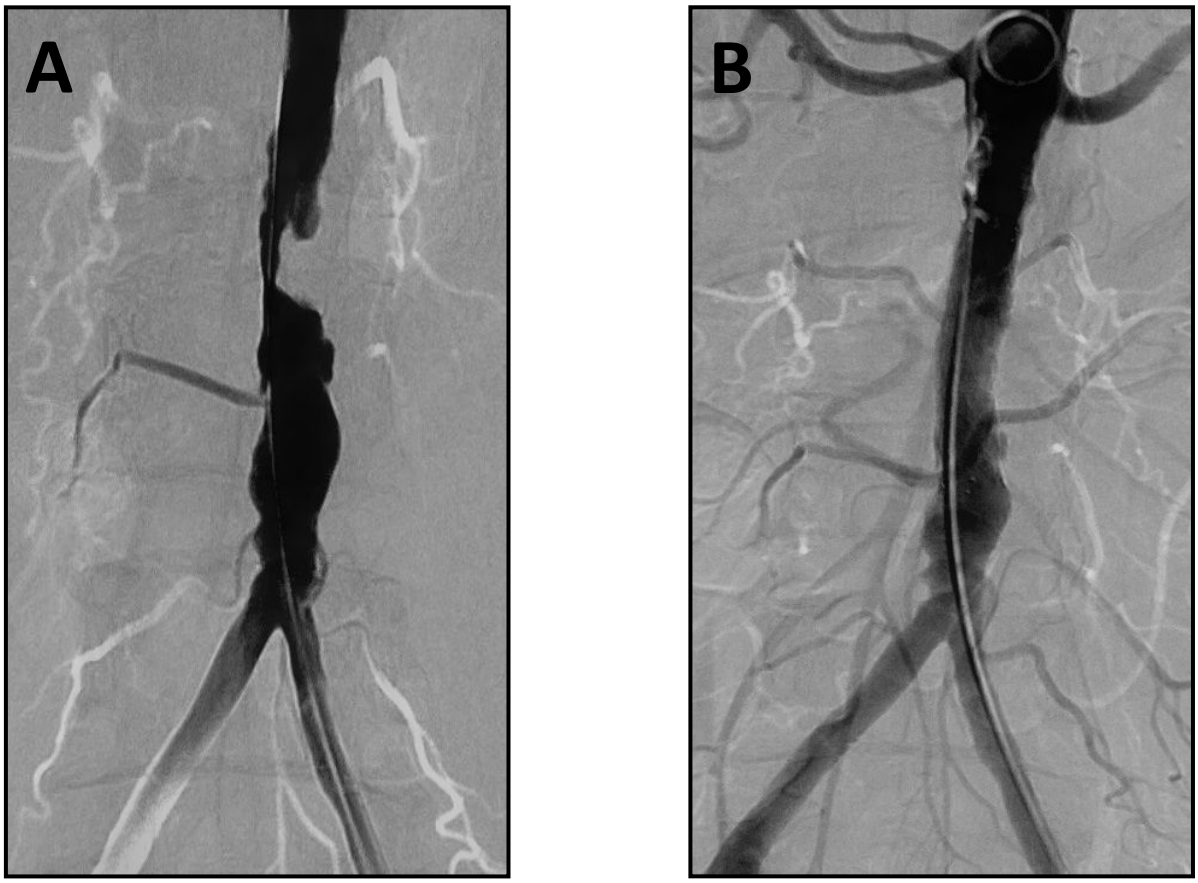

Figure 4. Primary stenting ([A] The digital subtraction angiography image shows a high-grade isolated infrarenal aortic stenosis. [B] The completion angiography shows a good morphological result [Epic stent {Boston Scientific Corp., Marlborough, MA, USA}, 14 mm x 40 mm; balloon used for postdilation: Advance 35LP {Cook Medical Inc., Bloomington, IN, USA}, 12 mm x 40 mm])

(The digital subtraction angiography images were made by Edit Dósa.)

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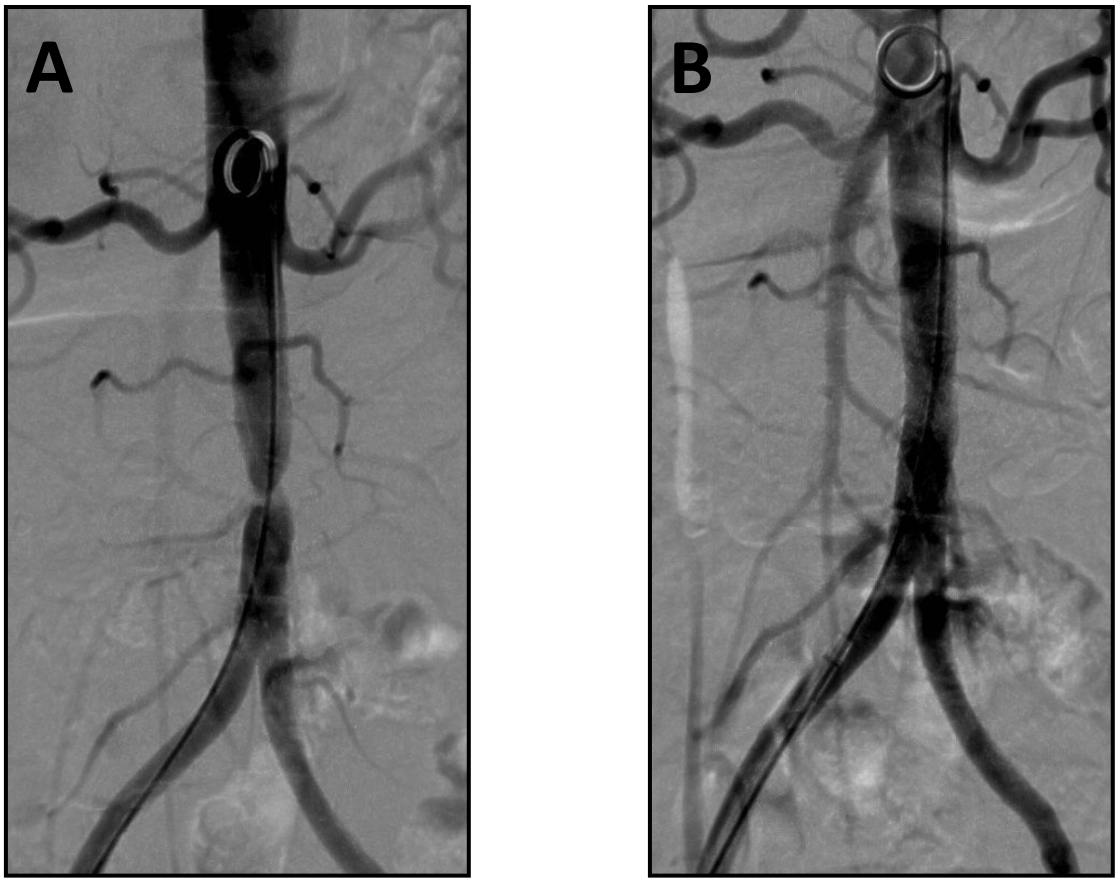

Figure 5. Direct stenting ([A] The digital subtraction angiography image shows a short, high-grade isolated infrarenal aortic stenosis. [B] The completion angiography shows a good morphological result [Dynamic stent {Biotronik AG, Bülach, Switzerland}, 10 mm x 38 mm])

(The digital subtraction angiography images were made by Edit Dósa.)

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Table 10. Stent types

Stents (N=36)	Manufacturer	Size (diameter × length; mm)
Self-expanding (N=26)		
Epic (N=10)	Boston Scientific Corp., Marlborough, MA, USA	12–14 × 40–60
Sinus XL (N=8)	Optimed, Ettlingen, Germany	16–22 × 40–80
Memotherm-FLEXX (N=3)	C. R. Bard Inc., New Providence, NJ, USA	12 × 60
Wallstent (N=2)	Boston Scientific Corp., Marlborough, MA, USA	16 × 40
JoStent SelfX (N=1)	Abbott Vascular Inc., Santa Clara, CA, USA	10 × 90
S.M.A.R.T. Control (N=1)	Cordis Corp., Johnson & Johnson Co., Miami, FL, USA	14 × 30
Zilver Vena (N=1)	Cook Medical Inc., Bloomington, IN, USA	16 × 60
Balloon-expanding (N=10)		
Dynamic (N=8)	Biotronik AG, Bülach, Switzerland	10 × 38–56
WaveMax (N=1)	Abbott Vascular Inc., Santa Clara, CA, USA	10 × 28
Palmaz Genesis (N=1)	Cordis Corp., Johnson & Johnson Co., Miami, FL, USA	8 × 38

Table 11. Stent characteristics

Characteristics	Stents (N=36)
Diameter	
Self-expanding (mm), median (IQR)	14 (14–16)
Balloon-expanding (mm), median (IQR)	10 (10–10)
Length	
Self-expanding (mm), median (IQR)	50 (40–60)
Balloon-expanding (mm), median (IQR)	38 (38–38)

IQR, Interquartile range.

4.2.3. Early postprocedural period (≤30 days)

The technical success rate was 97.5%. In one case, aortic rupture occurred; contrast extravasation was detected immediately after balloon inflation following implantation of a self-expanding stent (stent diameter, 14 mm; stent length, 30 mm; balloon diameter, 12 mm; balloon length, 40 mm). Surgical exploration was performed, during which the stent was removed and a prosthetic tube was placed into the injured aortic segment. The patient's postoperative period was uneventful. This patient was excluded from the follow-up analyses. No complications occurred in the other 39 patients. The 30-day all-cause mortality rate was 0%.

Additional reconstruction of a non-aortic segment to achieve complete clinical success (symptom relief) was needed in eight patients (20.5%; distal common iliac artery stenting, N=3; femorofemoral crossover bypass grafting, N=2; distal common iliac artery stenting plus femorofemoral crossover bypass grafting, N=1; profundoplasty plus femorofemoral crossover bypass grafting, N=1; common femoral artery reconstruction, N=1).

Fontaine classification showed an improvement of at least one stage in 30 patients (76.9%); Fontaine stage changed from IIb to IIa in seven cases (17.9%); the number or size of ulcers did not change in two patients (5.1%). The median value of resting ABI increased from 0.52 (0.40–0.62) before intervention to 0.95 (0.89–1.02) at 4-week follow-up.

4.2.4. Late follow-up period (>30 days)

The median follow-up of the 39 patients was 61 months (17–101 months). Significant (≥70%) restenosis was found in three patients (7.7%), one in the PTA subgroup and two in the stenting subgroup. The primary patency rate was 100% at 6 months, 97.1% at 12 and 24 months, and 88.1% at 60 and 96 months. (Figure 6)

One case of restenosis was not treated because the symptoms did not seriously affect the patient's quality of life and the grade of restenosis had not increased over the previous 6 years. Two symptomatic patients (5.1%) underwent reintervention (PTA with plain balloon, N=1; stenting, N=1); these patients were also diagnosed with a second restenosis at 25 months (first restenosis at 9 months) and 68 months (first restenosis at 53 months). Second restenoses were treated with PTA with a plain balloon. Both patients had multilevel steno-occlusive arterial disease with foot ulcers (Fontaine stage IV); one of them also had an antiphospholipid syndrome. The former patient underwent above-knee amputation 1 month after the second intervention. The assisted primary patency rates were 100% at 6, 12, and 24 months, 96% at 60 months, and 89.6% at 96 months. (Figure 6)

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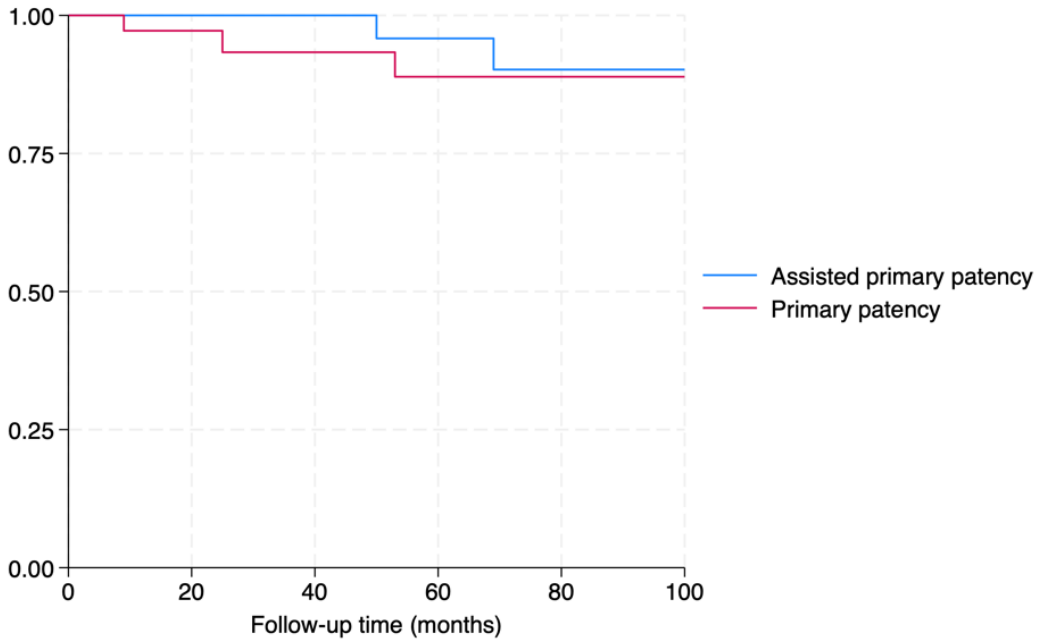

Figure 6. Primary and assisted primary patency rates

SE, Standard error.

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5. Discussion

5.1. Study I (Amputation and mortality rates of patients undergoing upper or lower limb surgical embolectomy and their predictors)

In our single-center study, the results of upper and lower limb surgical embolectomies were analyzed in a large cohort. There are few complex (comprehensive) studies in the literature on surgical embolectomy in patients with ALI. Only two relevant publications were found for upper limb embolectomies. One is a retrospective evaluation of 405 patients in the Danish national registry, (25) while the other is a meta-analysis. (21) The purpose of the latter was to investigate the relationship between AF and peripheral thromboembolism in terms of incidence, risk factors, risk-modifying drugs, and prognosis. (21) In the context of lower limb embolectomies, three recent retrospective studies should be highlighted. Kempe et al. (40) conducted a single-center study in 170 patients, while the other two studies were multicenter and involved 136 and 1749 patients, respectively. (50, 53) Apart from our study, there is only one study in total that includes both upper and lower limb embolectomies: a single-center retrospective Turkish study in 822 patients. (27)

The short-term outcomes of surgical limb embolectomies can be characterized by amputation and mortality rates. The prevalence and predictive parameters of amputation and mortality are discussed below. However, comparison of the rates is hampered by the fact that amputation and mortality time intervals often differ from study to study, and neither the type of amputation nor the time intervals are (accurately) defined. In our study, in-hospital amputation rates for the upper limb, lower limb, and the entire patient population were 2.2%, 14.6%, and 9.8%, respectively. The incidence of upper limb amputations in Andersen's (21) meta-analysis ranged from 0% to 8% (based on 22 studies conducted between 1932–1962 and 1993–2017), while Dag et al. (27) demonstrated an incidence of 2.8%, which is very similar to our result. The lower limb amputation rates in the two relevant publications were 16% (major, 15% and minor, 1%) (40) and 10.8%, (50) while our in-hospital rate was between the two. Data on amputation of the lower limbs were not provided by the other two major studies. (27, 53) The combined amputation rate of upper and lower limb embolectomies is available in only one study; Dag et al. (27) mentioned an amputation incidence of 13.6%, which

is slightly higher than the incidence we obtained. Kempe et al. (40) was the only study to state that the amputation rate was given for a period of 90 days. None of the other publications specified the time interval to which the amputation rate applied.

In our study, the in-hospital mortality rates for the upper limb, lower limb, and the entire patient population were 2.2%, 2.8%, and 2.6%, respectively, while the 30-day mortality rates for the upper limb, lower limb, and the entire patient population were 2.2%, 6.6%, and 4.9%, respectively. Andersen's (21) meta-analysis revealed a mortality rate of 0–66% (based on 15 studies) for upper limb embolectomies. Previous publications indicate that the mortality rate for lower limb embolectomies is 6.9–18%. (40, 50, 53) These mortality rates refer to in-hospital and/or 30-day mortality. (40, 50, 53) The combined mortality rate of upper and lower limb embolectomies is available in only one study in which the authors mention a 2% “early” postoperative mortality. (27) However, the authors did not define what was meant by “early”. The mortality rates reported in our study are among the lowest of those published.

In our study, predictive factors could only be examined in relation to lower limb embolectomies and embolectomies in the entire patient population; of the predictors, only those for in-hospital major amputation and in-hospital plus 30-day mortality were determined. We have shown that the time between the onset of symptoms and embolectomy is a predictor of lower limb major amputation, while the time between the onset of symptoms and embolectomy and compartment syndrome are predictors of all (upper plus lower limb) major amputations. Others have identified previous vascular surgical procedure, (40) presence of gangrene, (40) need for fasciotomy, (40) and re-embolectomy (27) as predictors of amputation. Dag et al., (27) like us, emphasize the importance of admission time, as a duration longer than 6 hours – presumably through a complex cascade induced by ischemia and hypoxia in the affected limb – significantly increases the risk of amputation (OR, 40.3).

In our study, history of stroke proved to be a predictor of in-hospital plus 30-day mortality in patients with lower limb embolectomy. Information on predictors of mortality in the literature is limited to lower limb embolectomies. Two studies report predictive factors for mortality. One considers previous vascular surgical procedure and concurrent stroke, (50) while the other considers male sex, functional dependence, chronic heart failure, recent angina/MI, chronic renal insufficiency, and steroid use as

predictors of mortality (50) in addition to age. (40, 50) Based on these findings, patients with comorbidities that potentiate the process of atherosclerosis or patients who already have manifest vascular disease appear to be a special risk group in terms of mortality.

The limitations of our study may have influenced the results. First, patients were retrospectively enrolled. Second, it is not always possible to clearly distinguish an acute embolic case from an acute thrombotic case, so these cases were analyzed as a group rather than separately. Third, unlike mortality, for amputations, only in-hospital data could be retrieved from our database.

5.2. Study II (Early and long-term results of the endovascular treatment of patients with isolated infrarenal aortic stenosis)

Isolated obstructive atherosclerosis of the infrarenal aorta is a relatively rare disease. Aortic endarterectomy and aortobi-iliac or aortobifemoral bypass surgery are the traditional treatments for significant infrarenal aortic steno-occlusive disease. These operations have good long-term results; the 10-year cumulative patency rate is 86% for both localized endarterectomy (9, 81) and aortobifemoral bypass. (82) One of the main advantages of endovascular therapy over surgery is that it has a mortality rate of less than 1%, (57, 58) while surgical treatment has a mortality rate of up to 4% and morbidity of up to 21%. (59, 83, 84) In addition, aortobifemoral surgical reconstructions can lead to erectile dysfunction in up to one third of men. (78, 83) Percutaneous transluminal angioplasty was introduced in the early 1980s to treat aortic stenosis. (78) The technical success rate of aortic PTA is between 95% and 100%; (82) however, restenosis compromises mid- and long-term outcomes. (85) Theoretically, better results can be achieved with stent implantation than with PTA alone, but this comparison has not been tested in prospective randomized trials. More recent publications show that stenting is more often performed than PTA alone, (58) similar to our study, in which 90% of lesions were stented and only 10% were treated with PTA alone.

There are only three comprehensive studies available on isolated IAS: a single-center study with a relatively high number of patients (N=34) and a long follow-up (81 months), (57) a multicenter study with a high number of patients (N=86) but a shorter follow-up (31 months), (58) and a single-center study with a low number of patients (N=9) but a long follow-up (110 months). (86) In our single-center study, 40 patients

were included. As in previous publications, (56, 59, 87) our patient population consisted mainly of middle-aged women smokers, many of whom also had hypertension and whose IAS developed due to atherosclerosis. All patients presented with symptoms; 85% had intermittent claudication, 5% had rest pain, and 10% had ulcers or gangrene.

The complication rates of interventional procedures range widely. In a 2003 study (N=86; summarizing the results of 18 European vascular surgery centers), eight complications (9%) occurred within 30 days, including peripheral embolism, femoral thrombophlebitis, sepsis, and retroperitoneal hematoma. (58) Lastovickova and Peregrin (88) observed no complications in 18 isolated IAS patients treated primarily with self-expanding nitinol stents. In a study of 34 patients, in which self-expanding stents were used in most cases, a total of three complications were mentioned: an infarct within the medulla oblongata (occurring 2 days after the intervention), an access site bleeding, and a femoral pseudoaneurysm. (57) In 2006, Poncyljusz et al. (77) reported two cases of groin hematoma in 26 patients with isolated IAS who underwent direct stenting. The hematomas did not require surgical treatment or blood transfusion. We had one major complication (2.5%), an aortic rupture, which was diagnosed after the stent was implanted. At the time (2003), a covered stent of the right size was not readily available in our department. Covered stents are becoming more widely used in most countries. However, covered stents also have disadvantages (e.g., a larger introducer sheath is required and the cost of a covered stent is much higher than a bare metal stent). As in other studies, there was no evidence of mesenteric ischemia following any of our procedures. (59, 86, 88) Theoretically, stents covering the inferior mesenteric artery can cause mesenteric ischemia; however, clinical practice shows that this only occurs in patients diagnosed with occlusive disease of the superior mesenteric artery or celiac artery, enlarged and tortuous inferior mesenteric artery, or bilateral hypogastric artery occlusion. (78)

There is debate about the type of stent used (self-expanding stent or balloon-expanding stent). Self-expanding stents have a smaller profile and the delivery system reduces the risk of stent loss. In many cases, however, the radial force of a self-expanding stent is not sufficient to achieve the desired diameter, but postdilation usually solves this problem perfectly. Self-expanding stents have smaller cells; thus, in theory, the possibility of distal embolization is reduced. However, clinical experience has not

proved this theory. (78) In our study, self-expanding stents were used in 72.2% of cases and balloon-expanding stents in 27.8%.

Six of the eight most comprehensive studies on the topic did not mention restenosis and reintervention. (57, 59, 77, 86–88) In one of the two studies that reported restenosis, seven (9.2%) of 76 patients had recurrent luminal narrowing, two of whom were treated with PTA, while four patients underwent aortobifemoral bypass surgery, and one patient was followed-up. (58) Another study published in 2018 demonstrated a restenosis rate of 18% and successful reinterventions in all cases: two with PTA and one with PTA plus stent placement. (56) In our study, three restenoses (7.7%) were detected and two reinterventions (5.1%) were carried out.

The earliest study in 2003 (with a mean follow-up of 31 months) revealed a cumulative primary patency rate of 77% in 86 patients at 60 months using a variable combination of PTA (12%) and stenting (88%). (58) A 2006 study (with a mean follow-up of 18 months) showed a 24-month assisted primary patency rate of 100% in 26 patients using only balloon-expanding stents. (77) The most recent study (with a mean follow-up of 50.4 months) demonstrated 100% primary patency at 5 years and 91% primary patency at 10 years in 34 patients with both balloon-expanding and self-expanding stents. (57) In our study, the assisted primary patency rates were 100% at 6, 12, and 24 months; 96% at 60 months; and 89.6% at 96 months.

The limitations of our study were the retrospective nature, the type of endovascular treatment used (PTA versus stenting), the type of stent used (balloon-expanding versus self-expanding), and the heterogeneity due to the long time (17 years).

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6. Conclusions

6.1. Study I (Amputation and mortality rates of patients undergoing upper or lower limb surgical embolectomy and their predictors)

Amputation and mortality rates after surgical embolectomies in patients with ALI are high. Patients with prolonged admission time, compartment syndrome, and history of stroke are at increased risk of limb loss or death. To avoid amputation and death, patients with ALI should undergo surgical intervention as soon as possible and receive close monitoring in the peri- and postprocedural periods.

6.2. Study II (Early and long-term results of the endovascular treatment of patients with isolated infrarenal aortic stenosis)

Endovascular therapy for isolated IAS provides a safe and effective long-term treatment strategy.

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7. Summary

Peripheral artery disease has acute (symptoms occur within 2 weeks), subacute, and chronic forms (symptoms occur after 3 months). In my dissertation, acute PAD was discussed in relation to the upper and lower limbs, and chronic PAD was discussed in relation to the infrarenal aorta.

With respect to surgical embolectomies for acute upper (N=134) or lower limb thromboembolism (N=213), we found that (1) in-hospital major amputation rates for the upper limb, lower limb, and total patient population were 2.2%, 14.1%, and 9.5%, respectively, and in-hospital plus 30-day mortality rates were 4.5%, 9.4%, and 7.5%, respectively; (2) in patients with lower limb embolectomy, the predictor of in-hospital major amputation was the time between the onset of symptoms and embolectomy (OR, 1.78), whereas the predictor of in-hospital plus 30-day mortality was prior stroke (OR, 7.16); and (3) in the overall patient cohort, there were two predictors of in-hospital major amputation: the time between the onset of symptoms and embolectomy (OR, 1.92) and compartment syndrome (OR, 3.51). Thus, patients with ALI have high rates of amputation and mortality following surgical embolectomy. In order to avoid amputation and death, patients with ALI should undergo surgical intervention as soon as possible and should be closely monitored in the peri- and postprocedural periods.

In regard to isolated IAS (N=40; median stenosis grade, 80% [IQR, 70–80%]; median lesion length, 19.9 mm [IQR, 13–29.4 mm]; and the presence of heavy calcification, 7.5%) treated with PTA (10%) or stenting (90%), we reported a complication rate of 2.5%, a 30-day all-cause mortality rate of 0%, and the following primary patency rates: 100% at 6 months, 97.1% at 12 and 24 months, and 88.1% at 60 and 96 months. The assisted primary patency rates were 100% at 6, 12, and 24 months, 96% at 60 months, and 89.6% at 96 months. We have shown that endovascular intervention of isolated IAS can be performed with excellent long-term patency rates.

My future research plans include evaluating the short- and long-term efficacy of invasive radiological (pharmacomechanical) elimination of acute emboli/thrombi and the treatment of IAS with covered stents.

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9. Bibliography of the candidate's publications

9.1. Peer-reviewed articles with relevance to the current work

1. **Bérczi Á**, Nguyen DT, Sarkadi H, Nyárádi BB, Beneda P, Szőnyi Á, Philippovich M, Szeberin Z, Dósa E. (2022) Amputation and mortality rates of patients undergoing upper or lower limb surgical embolectomy and their predictors. PLoS One, 17: e0279095. **IF: 3.7**

2. **Bérczi Á**, Vértes M, Dat NT, Bérczi V, Nemes B, Hüttl K, Dósa E. (2021) Early- and long-term results of the endovascular treatment of patients with isolated infrarenal aortic stenosis. J Vasc Surg, 73: 510–515.e2. **IF: 4.860**

9.2. Other peer-reviewed articles

1. Juhász G, Csőre J, Suhai FI, Gyánó M, Pataki Á, Vecsey-Nagy M, Pál D, Fontanini DM, **Bérczi Á**, Csobay-Novák C. (2022) [Diagnostic performance of non-contrast magnetic resonance angiography in patients with lower extremity arterial disease]. Orv Hetil, 163: 1782–1788. **IF: 0.6**

2. Nguyen DT, **Bérczi Á**, Nyárády BB, Szőnyi Á, Philippovich M, Dósa E. (2022) Short- and Mid-Term Outcomes of Stenting in Patients with Isolated Distal Internal Carotid Artery Stenosis or Post-Surgical Restenosis. J Clin Med, 11: 5640. **IF: 3.9**

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9.3. Published abstracts

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2. Nguyen TD, Vértes M, Bayerle P, **Bérczi Á**, Dósa E. (2019) Az arteria poplitea stenosisok/occlusiók endovascularis terápiájának eredményessége. Érbetegségek, Suppl. 2, page: 73.

3. **Bérczi Á**, Vértes M, Nguyen TD, Nemes B, Csobay-Novák Cs, Hüttl K, Dósa E. (2019) Az infrarenalis aorta stenosis miatt végzett interventiók hosszútávú kimenetele. Érbetegségek, Suppl. 2, page: 83.

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