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

Ph.D. thesis (short version)

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1. Introduction

There are acute, subacute, and chronic types of arterial stenoses and occlusions. The stenoses/occlusions can affect any arterial segment; however, one of the most common locations is the lower extremity. The term peripheral artery disease (PAD) is used in both narrow and broad senses. 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.

Acute limb ischemia (ALI) is considered a vascular surgical emergency. It develops as a result of either embolization or *in situ* thrombosis. Open surgical embolus/thrombus removal, with or without adjunctive therapy, is an accepted and widely used method for the treatment of ALI. Delayed or unsuccessful invasive intervention or failed management of acute compartment syndrome often leads to major amputation; 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%. In the last 30 years, few published studies, most of which evaluated the lower limbs, have addressed the determinants of postoperative morbidity and mortality.

Stenosis is relatively rare in the infrarenal aorta. The pathogenesis of isolated infrarenal aortic stenosis (IAS) in adults is almost always due to atherosclerosis. Until the early 2000s, open surgery 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%. 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. 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).

2. Objectives

2.1. Amputation and mortality rates of patients undergoing upper or lower limb surgical embolectomy and their predictors

Our aim was 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. Early and long-term results of the endovascular treatment of patients with isolated IAS

Our aim was to report on the complications and long-term outcome of endovascular interventions for rare, isolated IAS.

3. Methods

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

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. 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 the study.

The diagnosis of ALI was made by angiologists and/or vascular surgeons based on patient complaints/symptoms and physical, handheld Doppler, and/or imaging findings.

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. For revascularization, embolectomy with a Fogarty catheter was first attempted in all patients. 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.) 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 digital subtraction angiography (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.

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.

For statistical analysis, SPSS Statistics for Windows (Version 27.0.; IBM Corp., Armonk, NY, USA) was used.

3.2. Early and long-term results of the endovascular treatment of patients with isolated IAS

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.

Imaging modalities were used to confirm the possibility of IAS based on the patient's complaints, physical examination findings, and ankle-brachial index (ABI) values.

All radiological interventions were performed by a radiologist with at least 5 years of experience. Access was obtained by puncture of the common femoral artery (CFA) 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 percutaneous transluminal angioplasty (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. The decision whether to use a self-expanding or balloon-expanding stent was made by the interventional radiologist performing the procedure. 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. 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.

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.

Statistical analysis was performed with StatSoft Statistica 13.4 (Moonsoft Oy, Espoo, Finland) and GraphPad Prism 7.01 (GraphPad Software Inc., La Jolla, CA, USA) software.

4. Results

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

Patient characteristics

Of the 347 patients, 207 (59.7%) were female and the median age was 76 (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 diabetes mellitus (DM), respectively. Acute limb ischemia was categorized as Rutherford stage I in four patients (1.2%), Rutherford stage IIa in 92 patients (26.5%), and Rutherford stage IIb in 251 patients (72.3%). 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. The cause of anticoagulation was atrial fibrillation in 52 cases, other cardiac diseases in 15 cases, ischemic stroke in six cases, deep vein thrombosis and/or pulmonary embolism in three cases, and hypercoagulable state in two cases. Despite the medical recommendation, 15 patients did not take the oral anticoagulant.

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.

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 axillary artery in 20 cases (14.9%), the brachial artery in 104 cases (77.6%), and both arteries in 10 cases (7.5%). Embolectomy was technically successful in 118 patients (88.1%). Fifteen patients received additional invasive treatment. Each patient had adjunctive therapy only once. The median time between embolectomy and adjunctive therapy was 4 (IQR, 0.5–12.5) hours. Concomitant amputation with

embolectomy was unavoidable in one case (major amputation, N=1).

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 CFAs 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 CFA on one side and the popliteal artery on the opposite side in seven cases (3.3%), the CFA 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. Eight patients had adjunctive therapy twice. For those who received adjunctive therapy only once, the median time between embolectomy and adjunctive therapy was 7 (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 (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).

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

The median length of hospital stay was 3.8 (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. In 104 cases (30%), the cause was not found.

The in-hospital reocclusion rate was 5.2%, the acute kidney injury rate was 1.2%, the myocardial infarction (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%. Reperfusion injury occurred in 25 patients (7.2%) and compartment syndrome in 20 patients (5.8%). Reperfusion injury led to severe metabolic abnormalities 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.

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. In patients with lower limb embolectomy, the time between the onset of symptoms and embolectomy was a predictor of in-hospital major amputation (*multivariate logistic regression analysis adjusted for sex and age:* OR, 1.78; CI, 1.05–3.01; P=0.033), while previous stroke was a predictor of

mortality (OR, 7.16; CI, 1.43–36.01; P=0.017). 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; CI, 1.10–3.34; P=0.022) and 2) compartment syndrome (OR, 3.51; 1.17–10.52; P=0.025).

4.2. Early and long-term results of the endovascular treatment of patients with isolated IAS

Patient characteristics

The median age of the 40 patients (28 women) was 60 (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 *(body mass index ≥30 kg/m^2)* 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.

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 (IQR, 10.7–14.7) mm; the diameter was significantly (*Mann–Whitney U test:* P<0.035) smaller in women (11.6 [IQR, 10.5–13.9] mm) than in men (13.5 [IQR, 12.1–16.2] mm). The median grade of IAS was 80 (IQR, 70–80) %; its median length was 19.9 (IQR, 13–29.4) mm. 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 on fluoroscopic images taken before the procedure)* was observed in three cases (7.5%).

Access was obtained by puncture of the CFA (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 (selective, N=4; primary, N=6; and direct, N=26). Stent characteristics are listed in Table 1.

Table 1. 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)

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. 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%).

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.

Late follow-up period (>30 days)

The median follow-up of the 39 patients was 61 (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.

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. The assisted primary patency rates were 100% at 6, 12, and 24 months, 96% at 60 months, and 89.6% at 96 months.

5. Conclusions

5.1. 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.

5.2. Early and long-term results of the endovascular treatment of patients with isolated IAS

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

6. Bibliography of the candidate's publications

6.1. 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**

6.2. 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**

3. Bérczi Á, Simon AN, Szabó G, Csobay-Novák C. (2022) [Percutaneous transaxillary endovascular repair of

a degenerated aortic homograft]. Orv Hetil, 163: 1606–1609. **IF: 0.6**

4. Csőre J, Suhai FI, Gyánó M, Pataki ÁA, Juhász G, Vecsey-Nagy M, Pál D, Fontanini DM, **Bérczi Á**, Csobay-Novák C. (2022) Quiescent-Interval Single-Shot Magnetic Resonance Angiography May Outperform Carbon-Dioxide Digital Subtraction Angiography in Chronic Lower Extremity Peripheral Arterial Disease. J Clin Med, 11: 4485. **IF: 3.9**

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6. Bérczi Á, Kaposi NP, Sarkadi H, Péter Cs, Bérczi V, Dósa E. (2021) Vascular procedures during the COVID-19 pandemic in a high volume Eastern European interventional radiology department. IMAGING, 13: 138–141. **IF: -**

7. Nguyen TD, Bayerle P, Vértes M, **Bérczi Á**, Dósa E. (2021) Mid-term results and predictors of restenosis in patients undergoing endovascular therapy for isolated popliteal artery steno-occlusive disease. IMAGING, 13: 69–75. **IF: -**

8. Vértes M, Nguyen DT, Székely G, **Bérczi Á**, Dósa E. (2020) Middle and Distal Common Carotid Artery Stenting: Long-Term Patency Rates and Risk Factors for

In-Stent Restenosis. Cardiovasc Intervent Radiol, 43: 1134–1142. **IF: 2.740**

9. Vértes M, Nguyen DT, Székely G, **Bérczi Á**, Dósa E. (2020) The incidence and risk factors of stent fracture in patients treated for proximal common carotid artery stenosis. J Vasc Surg, 71: 824–831.e1. **IF: 4.268**

10. Hüttl AB, Hüttl A, Vértes M, Nguyen DT, **Bérczi Á**, Hüttl K, Dósa E. (2019) The presence of long and heavily calcified lesions predisposes for fracture in patients undergoing stenting of the first part of the subclavian artery. J Vasc Surg, 70: 1146–1154.e1. **IF: 3.405**

6.3. Published abstracts

1. Bérczi Á, Nyárádi BB, Szeberin Z, Dósa E. (2022) A felső vagy alsó végtagi sebészi embolectomián átesett betegek amputációs és mortalitási rátái, valamint azok prediktív faktorai. Érbetegségek, Suppl. 2, page: 79.

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.