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Safety and Efficacy of Rotational Thrombectomy for Treatment of Peripheral Artery Diseases

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Für meine Familie

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List of Abbreviations

ABI:	Ankle-brachial index
AIE:	External iliac artery
ASA:	Acetylsalicylic acid
ATA:	Anterior tibial artery
BMI:	Body-mass index
CIRSE:	Cardiovascular and Interventional Radiological Society of Europe
CLI:	Critical limb ischemia
CTA:	Computed tomography angiography
DCB:	Drug-coated balloon
DSA:	Digital subtraction angiography
DUS:	Duplex ultrasound
F:	French
MRA:	Magnetic resonance angiography
PA:	Popliteal artery
PAD:	Peripheral artery disease
POBA:	Plain-old balloon angioplasty
POTA:	Posterior tibial artery
PTA:	Percutaneous transluminal angioplasty
QoL:	Quality of Life
RT:	Rotational thrombectomy
SFA:	Superficial femoral artery
TASC:	Transatlantic Intersociety Consensus

1 Introduction

1.1 Definition, Burden, and Epidemiology of Peripheral Artery Disease

Peripheral artery disease (PAD) describes a condition of compromised blood flow to the peripheral arteries caused by gradual stenosis or complete occlusion (Lawall *et al.*, 2015). In 95% of cases, chronic PAD is caused by arteriosclerosis and atherothrombosis (Lawall *et al.*, 2015). This study engages with PAD of the lower extremity.

The reduction of blood flow is due to progressive plaque formation in the arteries promoted by cardiovascular risk factors, such as diabetes mellitus, elevated systolic blood pressure, serum cholesterol level, and nicotine abuse (Fowkes *et al.*, 1992). Eraso et al. (2014) also retained chronic kidney disease as a risk factor. Other cardiovascular risk factors are a family history of early-onset cardiovascular events caused by atherosclerosis, age, and male gender. Furthermore, patients exposed to three and more risk factors have increased odds of PAD to more than tenfold (Eraso *et al.*, 2014). Poredos et al. (2017) described hemodynamic forces, e.g., shear stress as another factor to formation of atherosclerosis.

In the beginning, vascular lesions can be asymptomatic. Subsequently, degrading blood supply leads to symptomatic disease: Leng and Fowkes (1992) described two major symptoms caused by PAD. First, intermittent claudication, declared as a less severe muscle pain, present during exertion. Second, rest pain, sensed as a continuous, intense pain.

If blood supply is critically reduced, rest pain and tissue loss indicate critical limb ischemia (CLI) (Malyar *et al.*, 2013). Acute limb ischemia (ALI) can be caused by fast loss of perfusion, mainly because of embolization or thrombosis due to rupture of a plaque. Finally, amputation of part of the limb may be required, especially in acute events or if necrosis infection is endangering patient’s life by impending sepsis. Amputation leads to pain, permanent disability and impairs patient’s independency and quality of life (QoL). However, even if therapy is

successful and reperfusion of endangered tissue is achieved, an ischemic reperfusion edema can lead to a compartment syndrome and cell death. Cell death can cause rhabdomyolysis and thereby acute renal failure. In summary, clinical presentation of PAD is ranging from asymptomatic to CLI with consequences and complications, even threatening patient's limb and life.

Undertreatment is a major issue, too: PAD patients are not receiving intensive treatment for dyslipidemia and hypertension. Antiplatelet therapy is less frequently prescribed than for patients with cardiovascular disease, as shown by Hirsch et al. (2001). In addition, Reinecke et al. (2015) showed that the frequencies of treatment with percutaneous arterial intervention and revascularization or bypass surgery decreases with higher Rutherford categories, leaving chronic limb ischemia (CLI) patients undertreated.

PAD is a widely spread disease in Germany. Its age-adjusted prevalence in Germany is reaching 19.8% of all patients in a primary care setting (Diehm *et al.*, 2004). Moreover, slightly more than a quarter (27.6%) of those patients shows signs of a severe disease stage (Diehm *et al.*, 2004). A study by Fowkes et al. (2013) described a rise in worldwide prevalence between the years 2000 and 2010 by 23.51%. PAD of the lower limb itself is the third leading cause of atherosclerotic vascular morbidity after coronary heart disease and stroke (Fowkes *et al.*, 2013). Patients with severe disease frequently also suffer from heart failure, which is of prognostic value (Aboyans and Ricco, 2018). Another frequent comorbidity is atrial fibrillation (Aboyans and Ricco, 2018).

Gender differences in PAD have been observed as well. While the absolute number suffering from PAD is higher in women than in men (Hirsch et al., 2012, cited in Malyar et al., 2013), less hospital care is given to women with PAD than to men (Malyar *et al.*, 2013). Egorova et al. (2010) showed that women have a significantly higher procedural mortality than men. Fortunately, time trends indicate a reduction in mortality for both men and women.

Regarding the humanistic burden of PAD, Marrett et al. (2013) found that patients with PAD have decreased QoL and suffer from more work impairment. Bauersachs et al. (2019) also emphasize the economic burden of

atherothrombotic disease with the tendency to increase with higher survival rates and aging of the population. Malyar et al. (2013) saw an increased prevalence of atherosclerotic risk factors in Western countries as an additional factor for the rise in PAD and its economic challenges. Malyar et al. (2013) observed an increase of 21% between 2007 and 2009 in total reimbursement costs, a total of €2.6 billion, for the in-hospital treatment of PAD. The authors quantify 4.84% PAD-related costs of costs due to all hospitalizations in the year 2009. CLI patients, representing 43.5% of hospitalized PAD patients, are responsible for approximately 52% of all PAD reimbursement costs. Tobacco smokers cause significantly higher costs due to higher hospitalization rates and higher number of hospital episodes for peripheral or visceral atherosclerosis and coronary heart disease. Duval et al. (2015) concluded that tobacco cessation programs may be cost effective.

The severity of this disease, the increasing prevalence, as well as humanistic and socio-economic burden associated with PAD warrant continuous investigations into the best possible treatment.

1.2 Diagnostic Algorithm for Peripheral Artery Disease

The following information is intended to highlight the most important aspects of the diagnosis of PAD, in order to better understand the methods and results of the analysis performed.

Medical history (cardiovascular risk factors, atherosclerotic comorbidities), clinical presentation and physical examination are the first aspects in assessing PAD (Lawall *et al.*, 2017). To objectify walking impairment, walking distance can be measured using a treadmill test (Aboyans *et al.*, 2018).

The first line, non-invasive test for screening and diagnosis of PAD is the assessment of Ankle-brachial index (ABI) (Aboyans *et al.*, 2018). The ABI represents the ratio of the systolic pressure of the brachial artery to the systolic pressure of the posterior tibial or the dorsalis pedis artery of each leg. The ABI is assessed by using a blood pressure cuff and a Doppler probe (Diehm *et al.*,

2004). Pulse abolition and ABI ≤ 0.9 indicate PAD and, therefore, further investigation with imaging, while ABI ≥ 1.4 can be a sign of calcified arteries (Lawall *et al.*, 2017). The calcification leads to arterial stiffening and thereby higher pressure is needed to occlude the vessel when measuring the systolic blood pressure, leading to false-high measurements.

If the patient is symptomatic and ABI is abnormal, imaging should be followed as per guideline (Lawall *et al.*, 2017): The primary imaging method is duplex ultrasound (DUS) to confirm vascular lesions. Further diagnostic methods are contrast-enhanced magnetic resonance angiography (MRA) or computed tomography angiography (CTA) (Lawall *et al.*, 2017). Both methods are on the one hand low invasive and give a three-dimensional impression but have no possibility of intervention on the other hand.

Once a therapeutic target suitable for endovascular therapy has been identified, digital subtraction angiography (DSA) is the next step. DSA is an invasive imaging method of blood vessels using conventional X-ray. Other unessential structures for diagnosing blood vessels, e.g., soft tissue and bones, are digitally subtracted. Thereby, the investigator can assess the structures of interest with less overlay and artefacts. Catheter-directed, selective application of contrast agent and the possibility of therapeutic intervention are the main advantages. Nephrotoxicity of contrast agents, radiation and the invasive approach are drawbacks. Purely diagnostic DSA without intervention may also be useful before surgical approach to identify patent arteries for distal bypass (Aboyans *et al.*, 2018). Otherwise, conservative therapy does not need confirmation by DSA.

The non-invasive imaging methods (DUS, CTA, MRA) are suitable for characterization and evaluation of the revascularization strategy in synopsis with clinical presentation and hemodynamic tests (Aboyans *et al.*, 2018). The decision of imaging beyond DUS should be made by a team of vascular specialists (Lawall *et al.*, 2017).

1.3 Classifications

1.3.1 Classification of Peripheral Artery Disease: Fontaine's Stages and Rutherford's Categories

To stratify PAD by the clinical presentation, two classifications are common: The Fontaine stages and the Rutherford categories are based on the presentation of symptoms.

Fontaine divides peripheral artery disease into four stages (Fontaine, Kim and Kieny, 1954) (Table 1):

Table 1: **Fontaine's Stages of Peripheral Artery Disease.**
Adapted from Fontaine et al. (1954) with permission from the Swiss Society for Surgery.

Stage		Clinical presentation
I		No symptoms
II	II a	Intermittent claudication after > 200 m
	II b	Intermittent claudication after < 200 m
III		Ischemic rest pain
IV		Ulceration or gangrene

Rutherford et al. (1997) grade chronic limb ischemia into six categories, specifying categories 4 to 6 as chronic critical limb ischemia (Table 2).

Table 2: **Rutherford's Categories of Chronic Limb Ischemia.**
Reprinted from Journal of Vascular Surgery, Vol. 26 (3), Rutherford *et al.*, "Recommended standards for reports dealing with lower extremity ischemia: Revised version", pp. 517–538 Copyright 1997 with permission from Elsevier.
Abbreviations: AP, Ankle pressure; PVR, pulse volume recording; TP, toe pressure; TM, transmetatarsal.
* Grades II and III, categories 4, 5, and 6, are embraced by the term chronic critical ischemia.
** Five minutes at 2 mph on a 12% incline.

Grade	Category	Clinical presentation	Objective criteria
0	0	Asymptomatic – no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise; AP after exercise > 50 mmHg but at least 20 mmHg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise** and AP after exercise < 50 mmHg
II*	4	Ischemic rest pain	Resting AP < 40 mmHg, flat or barely pulsatile ankle or metatarsal PVR; TP < 30 mmHg
III*	5	Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP < 60 mmHg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mmHg
	6	Major tissue loss – extending above TM level, functional foot no longer salvageable	Same as category 5

1.3.2 Classification of Arterial Lesion: TASC Classification

The Transatlantic Intersociety Consensus (TASC) classification divides aorto-iliac and femoral-popliteal lesions into four categories (A-D) based on location and morphology (Norgren *et al.*, 2007) (Figures 1 and 2). The recommendations for treatment derived from the TASC classification, advocating the endovascular procedure primarly for TASC categories A and B, have been weakend by the increasing success of percutaneous interventions (Lawall *et al.*, 2017).

Thus, in this analysis, the TASC classification was used only to represent lesion characteristics as location and morphology, but not to reason endovascular vs surgical treatment approach.

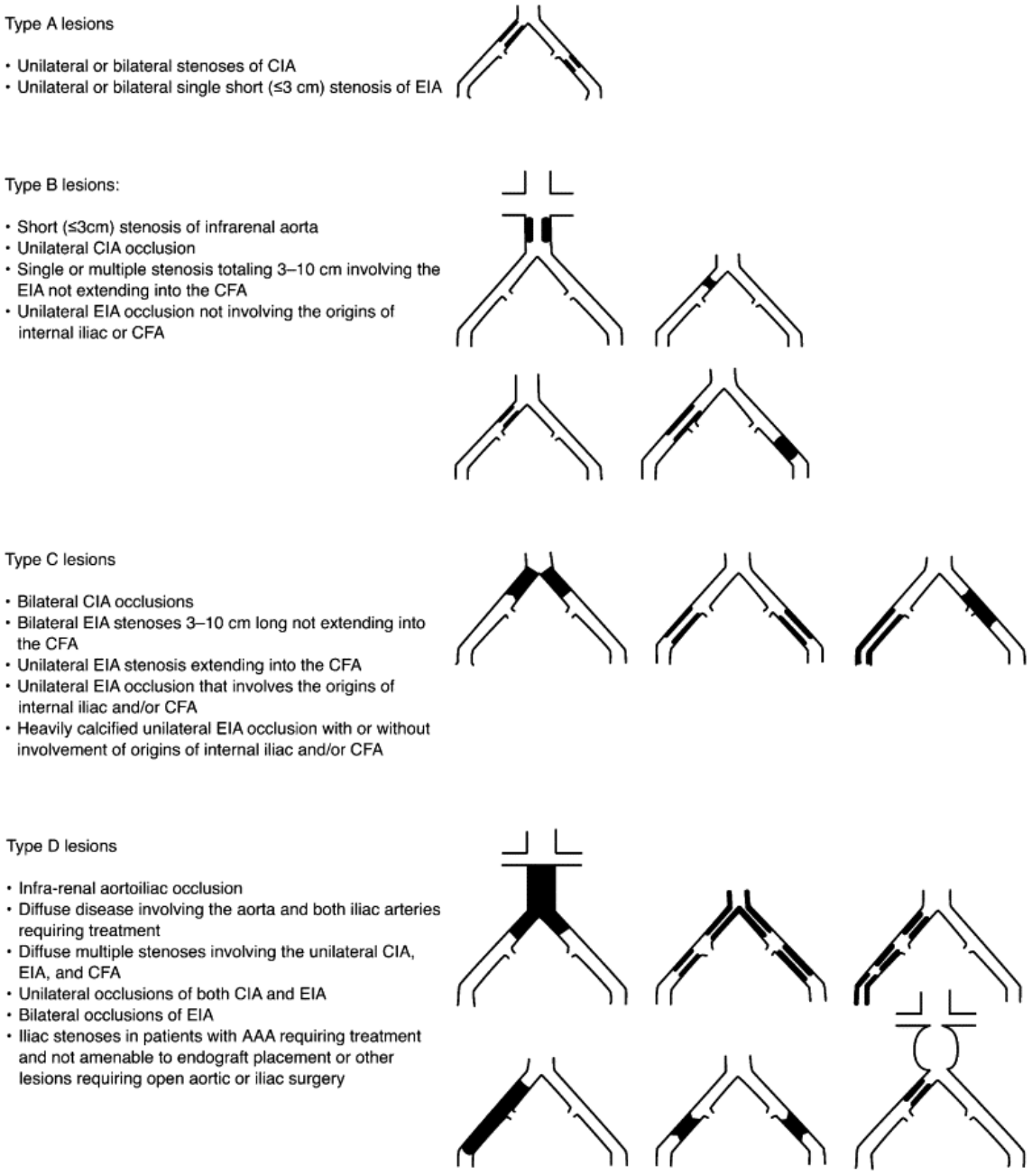
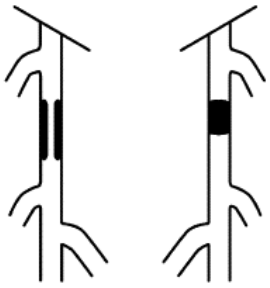


Figure 1: **TASC Classification of Aorto-Iliac Lesions.**
Abbreviations: CIA, common iliac artery; EIA, external iliac artery; CFA, common femoral artery; AAA, abdominal aortic aneurysm.
Reprinted from Journal of Vascular Surgery, Vol. 45, Norgren *et al.*, "Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)", pp. S5–S67, Copyright 2007, with permission from Elsevier.

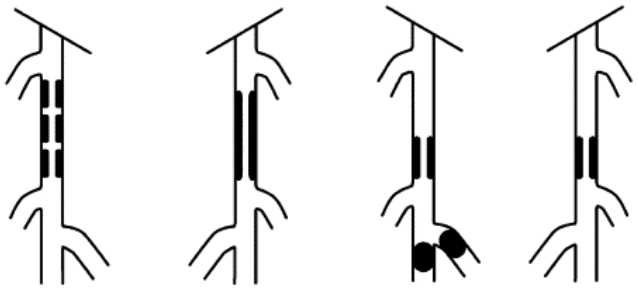
Type A lesions

- Single stenosis ≤10 cm in length
- Single occlusion ≤5 cm in length



Type B lesions:

- Multiple lesions (stenoses or occlusions), each ≤5 cm
- Single stenosis or occlusion ≤15 cm not involving the infrageniculate popliteal artery
- Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass
- Heavily calcified occlusion ≤5 cm in length
- Single popliteal stenosis



Type C lesions

- Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification
- Recurrent stenoses or occlusions that need treatment after two endovascular interventions

Type D lesions

- Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery)
- Chronic total occlusion of popliteal artery and proximal trifurcation vessels

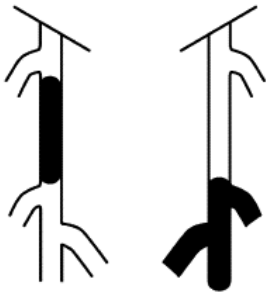


Figure 2: **TASC Classification of Femoral-Popliteal Lesions.**
Abbreviations: CFA, common femoral artery; SFA, superficial femoral artery.
Reprinted from Journal of Vascular Surgery, Vol. 45, Norgren *et al.*, "Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)", pp. S5–S67, Copyright 2007, with permission from Elsevier.

1.3.3 Classification of Complications: CIRSE Classification

The Cardiovascular and Interventional Radiological Society of Europe (CIRSE) classification provides a uniform reporting system for complications (Table 3). Both outcome and severity of sequelae determine the CIRSE class (Filippiadis *et al.*, 2017).

Table 3: **CIRSE Classification.**
Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer US, CardioVascular and Interventional Radiology, "Cirse Quality Assurance Document and Standards for Classification of Complications: The Cirse Classification System", Filippiadis, D. K. *et al.*, Copyright 2017.

CIRSE Class	Description
1	Complication during the procedure which could be solved within the same session; no additional therapy, no post-procedure sequelae, no deviation from the normal post-therapeutic course
2	Prolonged observation including overnight stay (as a deviation from the normal post-therapeutic course < 48 h); no additional post-procedure therapy, no post-procedure sequelae
3	Additional post-procedure therapy or prolonged hospital stay (> 48 h) required; no post-procedure sequelae
4	Complication causing a permanent mild sequelae (resuming work and independent living)
5	Complication causing a permanent severe sequelae (requiring ongoing assistance in daily life)
6	Death

1.4 Therapy of Peripheral Artery Disease

1.4.1 Conservative Therapeutic Options

Treatment of PAD is based on several approaches. To limit progress of arteriosclerosis promoting PAD, control or termination of risk factors is crucial. To reduce risk factors, a healthy diet and physical activity are recommended in recent guidelines (Aboyans *et al.*, 2018). Reduction of risk factors also includes cessation of smoking, assessment and treatment of diabetes mellitus with strict

glycemic control, controlled blood pressure < 140/90 mmHg and pharmacotherapy of dyslipidemia. Aboyans et al. (2018) recommended that all patients with PAD should receive statins to reduce LDL cholesterol < 70mg/dl or decrease it by 50%. Also, statins are administered for patients presenting with intermittent claudication to improve walking distance.

Secondary prevention of cardiovascular events in patients with PAD is additionally warranted by antiplatelet therapy. This means that symptomatic PAD and status after revascularization indicate long-term single antiplatelet therapy. After endovascular revascularization, pharmacological therapy with anticoagulant and antiplatelet drugs should be debated, taking risk of hemorrhage on the one hand and thrombotic risk on the other hand into account, keeping the combined therapy as short as possible (Aboyans and Ricco, 2018). But patients with asymptomatic, isolated PAD of the lower limbs should not routinely receive antiplatelet therapy due to lack of proven benefit (Aboyans *et al.*, 2018).

Structured walking exercise is very important, since long term outcomes of sole invasive treatment has not been proven better than exercise for patients with limited walking distance (Gardner et al., 2001 and Steinacker et al., 2002 cited in Lawall et al., 2015). Vasoactive drugs should be given to patients who cannot execute adequate walking exercise and suffer from impaired quality of life (Lawall *et al.*, 2015).

CLI indicated by rest pain and tissue damage, may need pain control, if pain control cannot be achieved by revascularization. Nonsteroidal anti-inflammatory medication and opioids are options (Norgren *et al.*, 2007). Treatment of ulcers and infection need to be part of conservative therapy.

1.4.2 Arterial Revascularization

Arterial revascularization is a symptomatic treatment if patients' QoL is impaired by pain and decreased mobility (Lawall *et al.*, 2015). It is indicated for patients with CLI and can improve symptoms for patients with intermittent claudication.

However, arterial revascularization does not solve the underlying progress of arteriosclerosis (Lawall *et al.*, 2015).

Two main approaches are available: Vascular surgery and percutaneous endovascular intervention. Surgical methods are thromboendarterectomy, thromboembolectomy with Fogarty catheter and bypass surgery with autologous vein transfer or alloplastic bypass-material. One drawback of the surgical approach is the perioperative and anesthetic risk, especially for elderly patients. Malyar et al. (2013) analyzed data of all hospitalizations in Germany in 2005, 2007 and 2009 and found that patients with CLI were older, about half of them being > 75 years old. So, elderly and sometimes frail patients are the main target group.

The established alternative strategy to surgery for acute limb ischemia is an endovascular approach. Recently, endovascular procedures became more preferable to open surgery if indication is given (Lawall *et al.*, 2016), offering low-impact treatment especially for elderly and multimorbid patients. The BASIL trial (Bradbury *et al.*, 2005) compared the outcome of bypass surgery and endovascular intervention with plain-old balloon angioplasty (POBA) in patients with severe limb ischemia. The authors concluded that patients with less than one to two years of life expectation are probably better served with an angioplasty first strategy. Clinical state, lesion classification, comorbidities and patients' wish need to be taken into account (Lawall *et al.*, 2015). The procedural risk and possible benefit must be weighed up (Norgren *et al.*, 2007). An interdisciplinary, vascular team should balance the decision for the management of PAD (Aboyans *et al.*, 2018).

The basic principle of the endovascular approach is to gain access to the artery system by percutaneous puncture. The endovascular intervention is then guided by intravascular contrast medium and DSA. Endovascular intervention offers the possibilities of thromboaspiration, angioplasty and local catheter-directed thrombolysis. In addition, there are different types of mechanical thrombectomy. Combinations of several strategies can be applied. These endovascular methods are characterized below.

Thromboaspiration is an endovascular technique where a suction catheter is advanced to remove occlusive material. This is especially helpful with recent onset of occlusion and therefore fresh occlusive material. It is not meant to remove organized, firm atherosclerotic plaques.

For percutaneous transluminal angioplasty (PTA), the target lesion is crossed with a guidewire and dilated with a balloon (POBA). Additionally, a stent can be implanted to prevent reocclusion by recoil. These target lesions are mainly atherosclerotic plaques.

With catheter-directed thrombolysis, the lytic agent can be administered through a catheter directly into the target vessel. It is a well-established method for acute (< 14 days) ischemia (Lawall *et al.*, 2015) and therefore unorganized thrombus. A systemic effect of the agent cannot be eliminated, so the main drawback is the risk of hemorrhage, e.g., intracerebral, especially for elderly patients.

An interesting approach to endovascular procedures are different techniques of mechanical thrombectomy. Hydrodynamic catheters like the Hydrolyzer (Cordis, Miami, Fl, USA) or AngioJet (Possis Medical, Minneapolis, MN, USA) use a fluid jet to disperse the thrombus and then remove the thrombotic material by the venturi effect (Höpfner *et al.*, 1996).
Pharmacomechanical thrombectomy catheters like the Trellis (Medtronic, Minneapolis, MN, USA) offer a combined treatment: The clotted area gets isolated by a balloon distal and proximal of the lesion. Then, the thrombolytic drug selectively targets the treatment area. The agent is spread by oscillation of the catheter. Finally, the catheter can aspirate the drug and the dissolved material (Karnabatidis *et al.*, 2011).
The OmniSonics Resolution Wire (OmniSonics Medical Technologies, Inc, Wilmington, MA, USA) uses low power acoustic energy around its wire and thereby disperses the thrombus (Karnabatidis *et al.*, 2011).

Mechanical thrombectomy techniques also include rotational thrombectomy (RT). The technique and the Rotarex®S catheter will be further described in the following.

1.5 Rotational Thrombectomy with the Rotarex®S Catheter

1.5.1 System Design

The Rotarex®S (Becton, Dickinson and Company, New Jersey, USA) catheter is a thrombectomy device that carries a hydrophobic coated stainless-steal spiral inside and glides over a guidewire (Figures 3 and 4). The tip of the catheter carries two cylinders (Figure 5). The rounded end of the outer cylinder carries an opening for the guidewire. The outer cylinder is connected to the spiral and rotating. At the tip, the outer cylinder has facets. The rotations of the facets and the thereby induced vortex in the vessel abrade the occluding material. The inner cylinder is fixed to the catheter shaft. Both cylinders have two fenestrations each. The rotations of the spiral inside the catheter induce a negative pressure. The catheter aspirates without additional suction. Inside, the material is fragmentized and drained off into a collecting bag by the helix. The catheter is linked to an electric motor drive and is operated by an electronic control unit. The motor accelerates the spiral to 40.000-60.000 rotations per minute, depending on the size of the catheter, which equals a minimum of 80.000 cuts per minute. Therefore, the device detaches occluded material up to 1 cm per second. The motor drive and the cable to the electronic control unit are reusable after sterilization.

There are different catheter sizes for different vessel diameters and lengths. There is a 6 French (F), 8F, and 10F catheter. The 6F catheter offers either 110 cm or 135 cm length. The corresponding minimum vessel diameter is 3 mm. The 8F catheter comes with 85 cm or 110 cm length, the associated minimum vessel diameter is 5 mm. The 10 F system is only available in 85 cm for a vessel diameter of minimum 7 mm. Blood loss is limited by the respective aspiration rate of 45 ml/min for the 6F system, 75 ml/min for the 8F system, and 130 ml/min for the 10 F system. Therefore, blood loss usually does not reach clinical relevance.

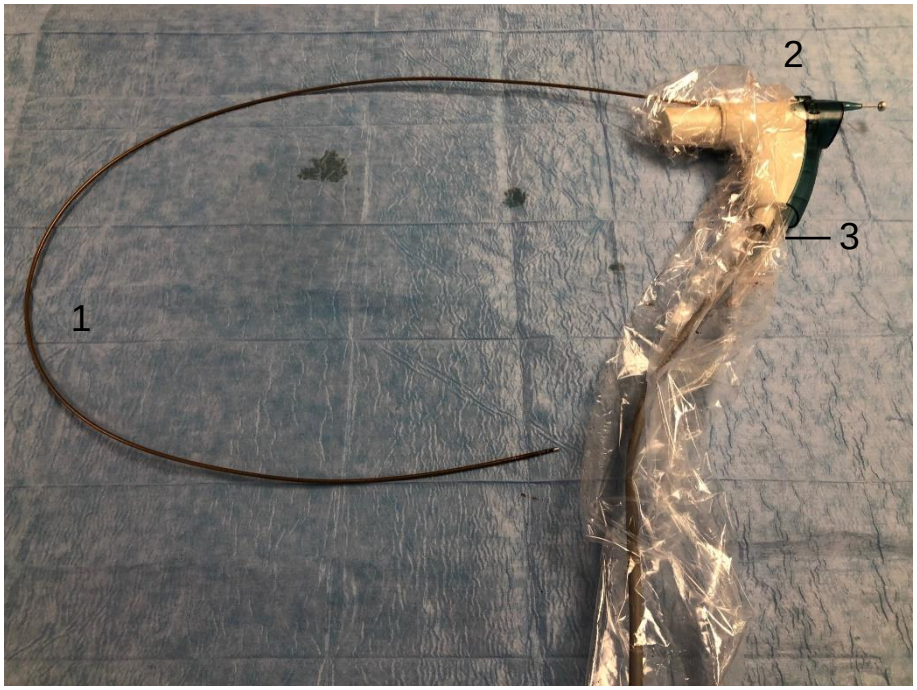


Figure 3: **Overview of the Rotarex®S Catheter System.**
(1) Catheter, (2) handle with reusable motor unit in sterile draping, (3) outlet tube that leads detached material into the collecting bag (not shown).
Own illustration.

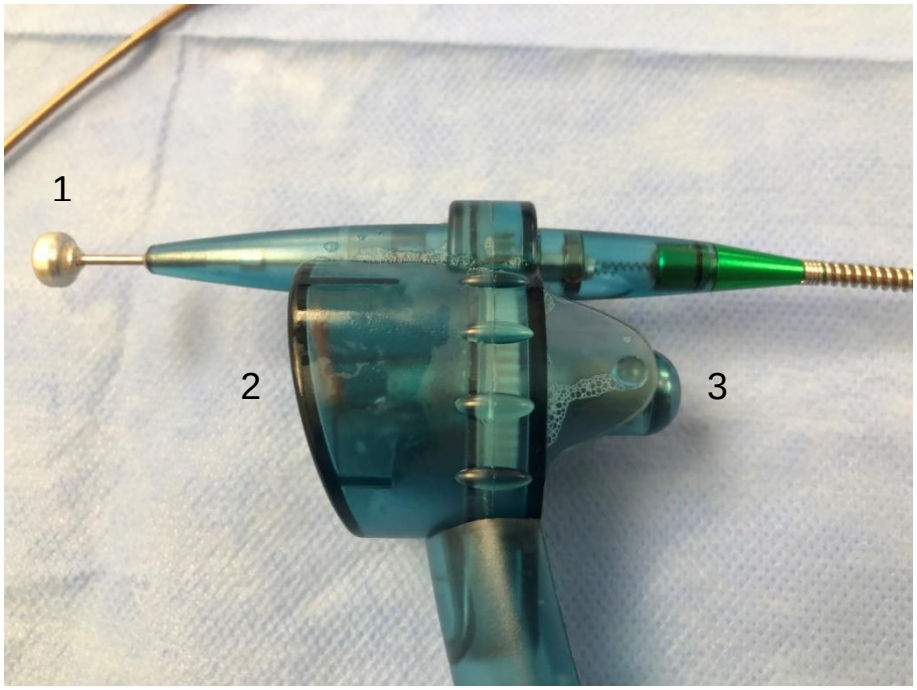


Figure 4: **Rotarex®S Catheter Handle.**
(1) Guidewire adapter, (2) gearbox, (3) magnetic clutch to attach motor inside. The reusable motor and switch are not in the picture.
Own illustration.

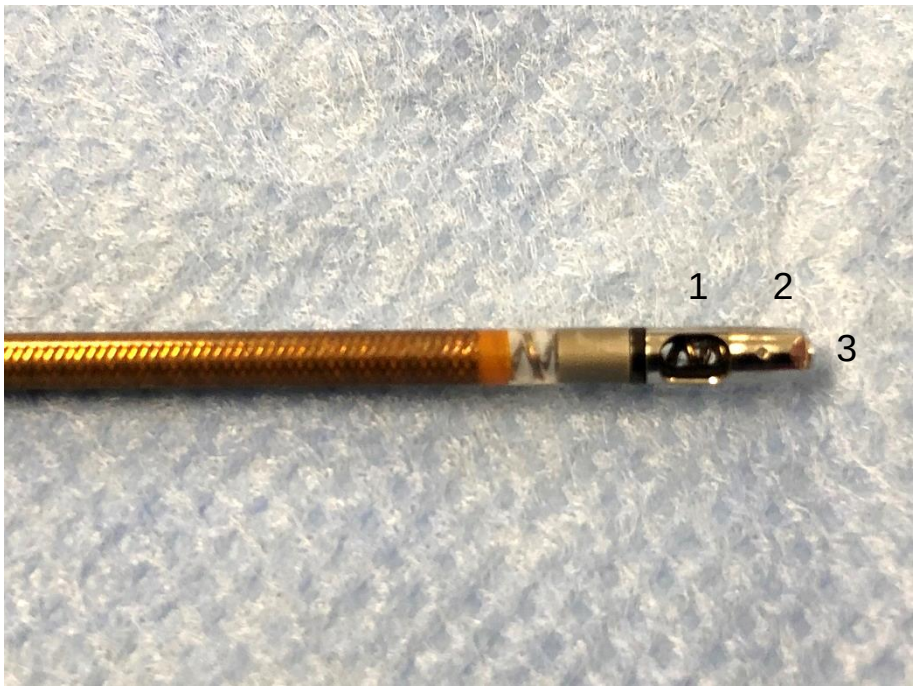


Figure 5: **Rotarex®S Catheter Head and Helix.**
(1) Aspiration window with rotating helix and (2) rotating outer cylinder. The fixed inner cylinder is not distinguishable. (3) The beveled tip is blunt and detaches occlusive material atraumatically by rotating.
Own illustration.

1.5.2 Intentional Use

The Rotarex®S catheter can be used for treatment of acute, subacute, and chronic arterial occlusions of native vessels, in-stent occlusions, bypass-grafts, and dialysis accesses. It performs atherectomy and thrombectomy.

Contraindications are given by the manufacturer in the Instructions for Use. It is contraindicated to use the Rotarex®S catheter in the venous vasculature, in undersized vessels and in the cardiopulmonary, coronary, carotid, cerebral, and renal vasculature. Also, the Rotarex®S catheter cannot be used if the patient is not suited for atherectomy/thrombectomy. This may include patients with imbalanced coagulation system or contraindication for anticoagulation.

The manufacturer particularly warns to use the Rotarex®S catheter in areas of persistent vasospasm, tortuous vessels, or locations with preexisting damage or broken stents and stent grafts. In case the guidewire is positioned subintimal, the

manufacturer advises to reposition and ensure intraluminal location before rotational thrombectomy.

The Instructions for Use also highly recommend advancing the catheter slowly through the occlusion, since the risk of distal embolization is increased by faster approaches.

1.5.3 Example of Rotarex®S Thrombectomy

To illustrate the use of the Rotarex®S catheter, the following Figures 6 and 7 show a typical treatment scenario. The patient is 55 years of age with cardiovascular risk factors (arterial hypertension, nicotine abuse, dyslipidemia, and adiposity) and PAD, Fontaine stage 2b. A drug-eluting stent was implanted on August 25, 2011. The patient returned on June 21, 2012 with chronical in-stent restenosis of the superficial femoral artery (SFA) and popliteal artery (PA), segment 1, TASC B (Figure 6, A). Figure 6, B and C show the patent crural (B) and pedal (C) outflow.

Revascularization was achieved through antegrade approach after four passages of a 6F Rotarex®S catheter. The eccentric presentation of the lumen indicates neointimal hyperplasia (Figure 6, D). Thus, a covered stent (Viabahn®) was implanted, slightly extending distal (Figure 7, E, F). Post-dilatation was performed with a 5 mm balloon (Figure 7, G). The final angiography showed sufficient flow without remaining stenosis (Figure 7, H).

The ABI increased from 0.62 before to 1.2 after the treatment.

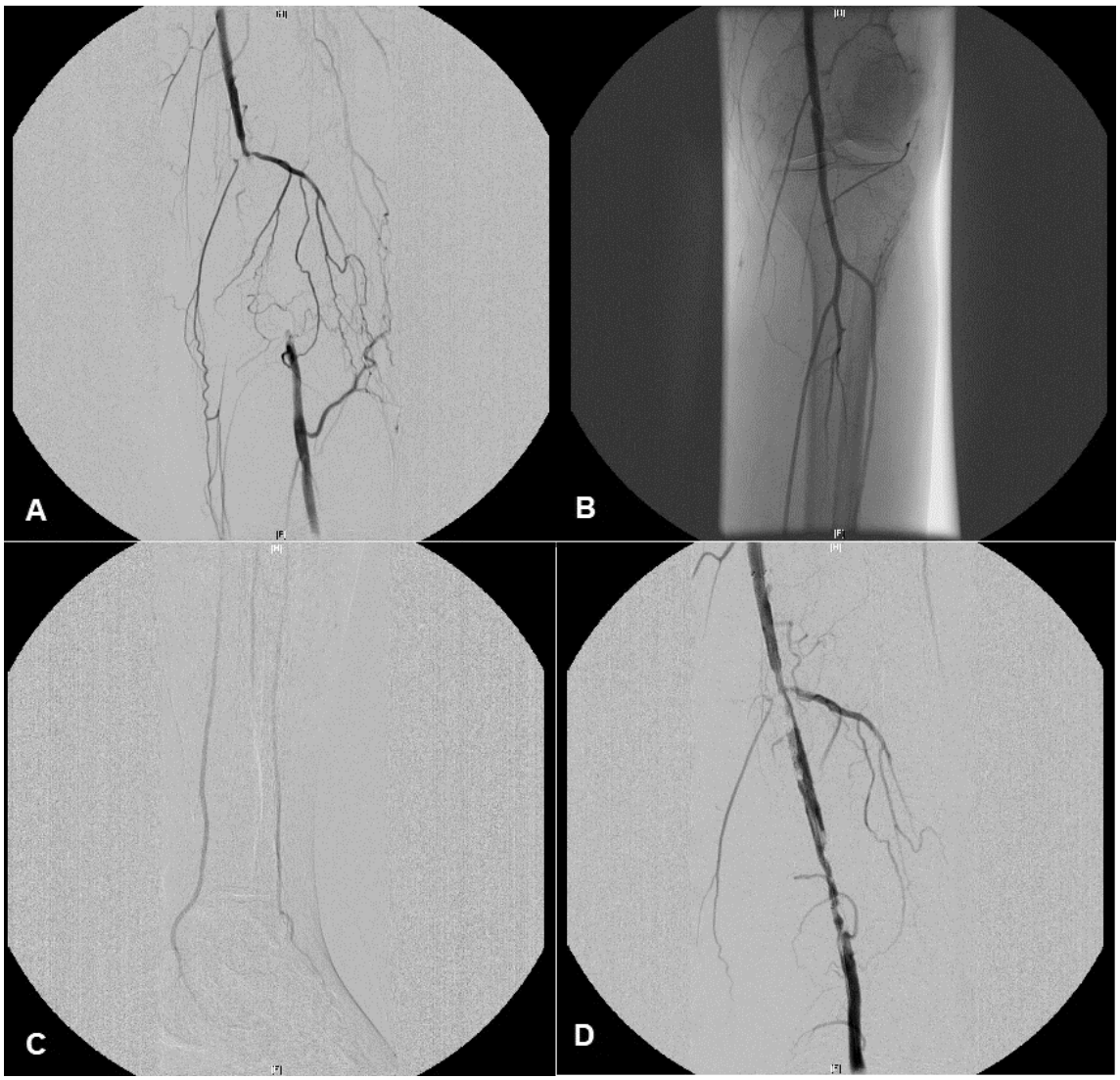


Figure 6: **DSA Imaging 1 of Treatment of In-Stent Restenosis with the Rotarex®S Catheter at the Tübingen University Hospital, June 21, 2012.**
A: In-stent restenosis of the superficial femoral artery and first popliteal segment. Collateral vessel proliferation indicates chronical occlusion. B: Patent crural outflow. C: Patent pedal outflow. D: After 4 passages of a 6F Rotarex®S catheter eccentric lumen visible, indicating neointimal hyperplasia.
Abbreviation: DSA, digital subtraction angiography.
Own illustration.

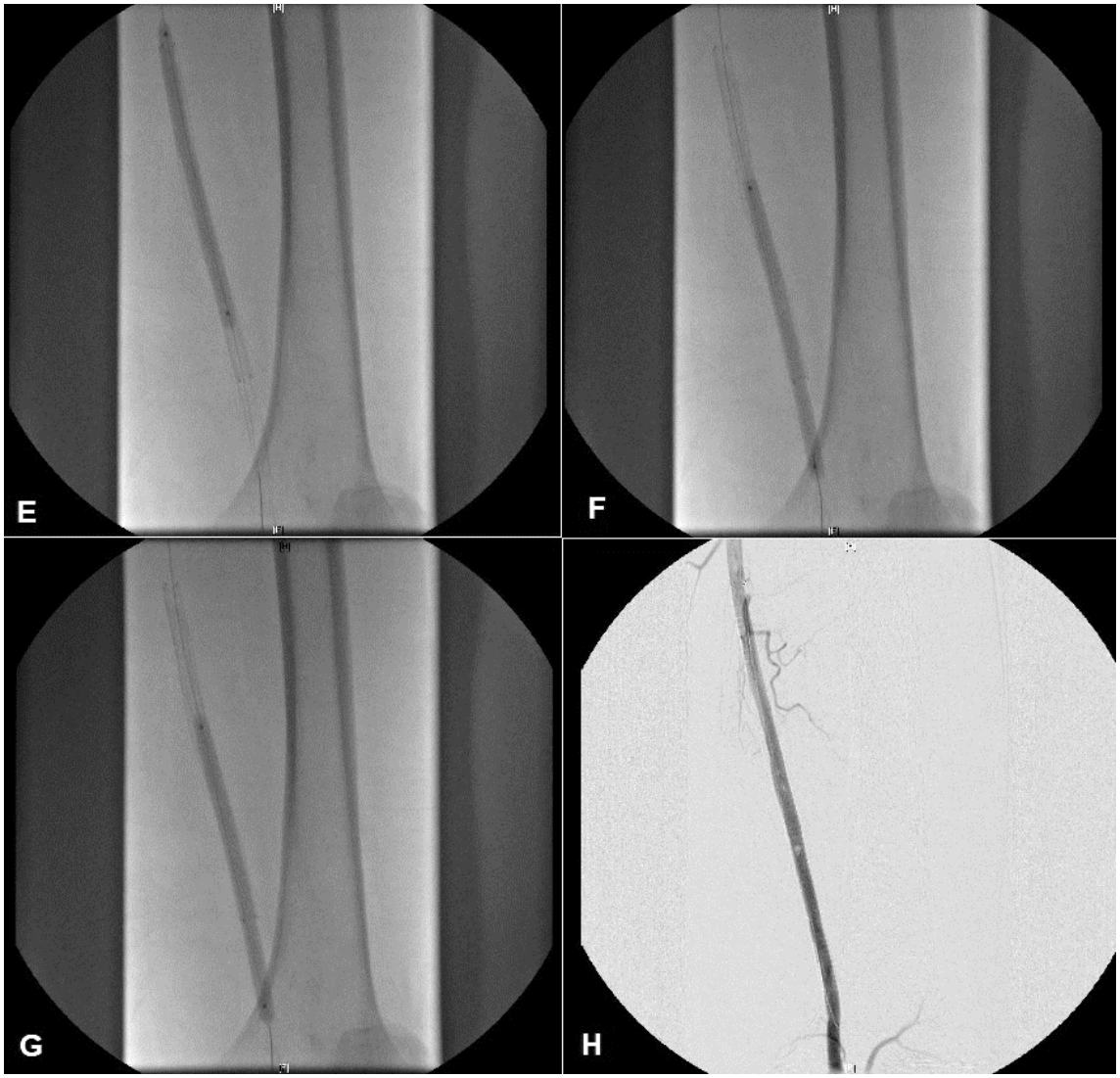


Figure 7: **DSA Imaging 2 of Treatment of In-Stent Restenosis with the Rotarex®S Catheter, Adjunctive Therapy, at the Tübingen University Hospital, June 21, 2012.**
E: Implantation of a covered stent (Viabahn®), proximal. F: Implantation of a covered stent (Viabahn®), distal extension. G: Post-dilatation with 5 mm balloon. H: Result: Patent outflow, no residual stenosis.
Abbreviation: DSA, digital subtraction angiography.
Own illustration.

1.5.4 State of Research

Percutaneous mechanical removal of thrombotic material with RT seems to be a useful option for the therapy, but so far, research is limited.

Besides the general benefits of an endovascular approach, there are additional benefits of mechanical thrombectomy: There is rapid re-opening of the vessel

and thereby reperfusion of the limb and unmasking stenosis (Fluck *et al.*, 2020). Here, the quick setup of the Rotarex®S catheter system is in favor (Lichtenberg, Stahlhoff and Boese, 2013b). By debulking of the occlusion, subsequent angioplasty can be performed with lower pressure, which decreases the risk of plaque recoil and dissection (Katsanos *et al.*, 2017). Dissection again may need treatment with a stent implantation. Nevertheless, dissection can also be caused by RT. Additionally, thrombectomy improves drug uptake into the arterial wall after drug-coated balloon and the number of stent-implantation can be reduced (Bulvas, 2019).

The major drawbacks are: the premise of a fresh, unorganized thrombus, deficient debulking, complications like dissection, perforation and embolization and the design complexity (Schmitt *et al.*, 1999). Additionally, the Rotarex®S catheter is only approved for lesions proximal to segment III of the popliteal artery (Fluck *et al.*, 2020).

Lichtenberg, Stahlhoff and Boese (2013b) summarized the preexisting research for the treatment with RT for acute and subacute occlusions of the lower limb in a review. In the analyzed studies, technical success rates had been above 90%. A high count of post-thrombectomy angioplasty including balloon dilatation and stent implantation had been registered. Perforation rates had been reported between 1 and 10%. Calcified vessels had seemed to be particularly prone to perforations. Other reported complications were distal embolization, bleeding complications, and unsuccessful recanalization. Compared to the “Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity: The STILE trial,” (1994), amputation-free survival at 12 months after rotational thrombectomy was higher than after catheter directed thrombolysis or vascular surgery. The authors evaluated the treatment with RT as safe and efficient for acute occlusion of lower extremity arteries. Yet, specific indications need further investigation.

Among those specific indications is treatment of bypass occlusion. So far, insights into treatment of bypass occlusions are particularly limited. Lichtenberg et al. (2013a) provide data on an effective treatment of bypass occlusions with the

Rotarex®S catheter in only a small single-center cohort. They achieved promising patency rates over a follow-up period of 12 months.

In summary, the available data provides good evidence for acute and subacute occlusions of femoropopliteal lesions (Katsanos *et al.*, 2017). The available research for the application of the Rotarex®S catheter for specific indications, as chronic occlusions for both native, in-stent and bypass occlusions, is rather limited. Also, chronic occlusions mostly are linked to arteriosclerosis, so the prevalence of (heavy) calcified lesions, being a special challenge for safe application of Rotarex®S catheter, is higher than the aforementioned. Norgren et al. (2007) stated that the patency after PTA is more impaired the further distal the treated lesion is located. Additionally, data is scarce for rotational thrombectomy in the iliac arteries (Fluck *et al.*, 2020).

On the other hand, Lichtenberg (2010) highlights the importance of the availability of any revascularization method and the importance of the expertise of the interventionist. Therefore, the presented analysis of the interventions at the Tübingen University Hospital seems additionally reasonable as a quality assurance. Also, Freitas et al. (2017) emphasized that "*data regarding […] effectiveness and safety in a real-world scenario are scarce*". While randomized controlled trials achieve high quality data, they can never reflect the normal day-to-day circumstances under which most patients receive treatment. Thus, the question arises: How do safety and efficacy perform without pre-study filtering of the patients?

1.6 Aim of the Study

1.6.1 Objectives

Aim of the presented study is to evaluate safety and efficacy of RT with the Rotarex®S catheter for the treatment of acute, subacute, and chronic infrarenal arterial occlusions of native vessels, in-stent occlusions, and bypass-grafts. The presented analysis assesses RT retrospectively, so data represents a real-life

application. The Rotarex®S device was used either as a single or as an adjunctive method of revascularization.

This analysis sets out to determine:

- patients' characteristics
  - age and sex
  - stage of PAD and occlusion age
  - cardiovascular risk factors
- procedural and adjunctive therapy parameters
- target lesion parameters
- outcome: technical success
  - passage with the guidewire
  - revascularization
  - material failure
- outcome: clinical success
  - clinical success defined as sufficient blood supply at end of procedure
  - hemodynamical success: improvement of ABI
  - improvement of walking distance
  - reintervention rates
  - freedom of target vessel revascularization in the first 30 days after RT procedure
  - amputation
- outcome: complications
  - frequency of distal embolization, dissection, and perforation in total for interventions and due to Rotarex®S catheter
  - CIRSE grade
  - treatment of complications

The following subcohorts are of particular interest, since so far, literature only provides limited insights:

- treatment of iliac arteries
- treatment of bypass grafts
- treatment of calcified vessels
- comparison of the 6F and the 8F Rotarex®S catheter
- comparison of the different locations of treatment
- comparison of the occlusion ages

These subcohorts are compared to the parameters of technical and clinical success and parameters of complications. Additionally, we analyzed if distal embolization and used adjunctive therapy (drug-coated balloon [DCB], POBA, stent) showed significant relationship.
We also set out to see if occlusion age, size of the Rotarex®S catheter, and application of DCB can influence patency.

1.6.2 Study Design

A retrospective, observational, single-center analysis of data generated between 2010 and 2020 at the Tübingen University Hospital with a non-randomized cohort which underwent (adjunctive) treatment with RT.

1.6.3 Licenses

Permission for the reproduction of tables und figures of other origin has been obtained. Acknowledgements to each source are given in the caption.

2 Material and Methods

2.1 Choice of Data

For this retrospective study, the register for endovascular interventions at the Department of Interventional Radiology at the Tübingen University Hospital had been searched for patients who received treatment with the Rotarex®S device between April 2010 and November 2019.

Each patient has been screened for reintervention. Since the data was collected partially in January 2020 and in June 2020, two reinterventions, one from January 2020 and one from April 2020, are added to the data set. It should be noted that it is possible that reinterventions in 2020 are missing, since the patients included in January 2020 have not been revisited in June 2020 for reintervention in 2020. A total of 300 unique patients with 405 consecutive interventions received intervention with the Rotarex®S catheter (Artzner *et al.*, 2022).

Overall, eight interventions of seven patients were excluded: Six interventions were excluded, since RT was used in abdominal arterial vessels or in a transjugular intrahepatic portosystemic shunt. Two additional interventions were excluded because clinical data was missing. In the final study cohort, we included data of 397 consecutive interventions of 293 unique patients (Figure 8). Patients presented with acute, subacute or chronic arterial (sub-)occlusion of the lower limb and were included into analysis regardless of the Rutherford category and origin of occlusion (atherosclerotic, atherothrombotic or embolic origin) (Artzner *et al.*, 2022).

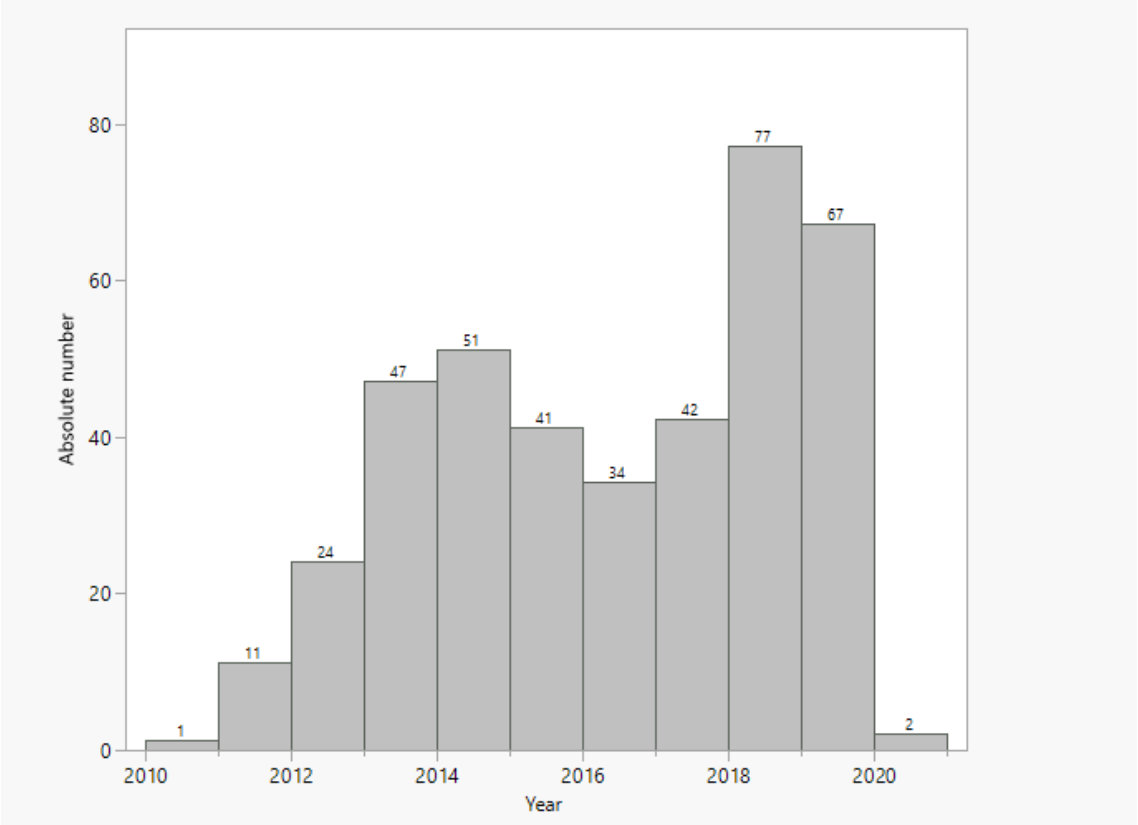


Figure 8: **Number of Interventions with the Rotarex®S Catheter at the Tübingen University Hospital by Year after Exclusion of Inadequate Data.**
Own illustration.

2.2 Parameter for Analysis

2.2.1 Patients

Patients' clinical data was retrieved from a computer-based medical information system in a Microsoft Excel worksheet.

We assessed patient demographics (sex, date of birth), underlying medical conditions at time of hospital admission and cardiovascular risk profile by the computer-based discharge letters. Cardiovascular risk profile contained arterial hypertension, diabetes mellitus, chronic renal failure, history of smoking, coronary artery disease, dyslipidemia, and adiposity (Artzner *et al.*, 2022).

Patients' PAD was categorized according to the Rutherford categories and the Fontaine stages (Artzner *et al.*, 2022).

We took the following parameters from the computer-based discharge letters (Table 4):

Table 4: **Patient Variables from Discharge Letters.**
Abbreviation: PAD, peripheral artery disease.

Variable	Label	Level of measurement
Age	-	Continuous
Sex	1, male 2, female	Dichotomous
Acute health condition	-	Free text
Occlusion age	1, acute 2, subacute 3, chronic	Nominal
Rutherford's category	0, asymptomatic 1, mild claudication 2, moderate claudication 3, severe claudication 4, ischemic rest pain 5, minor tissue loss 6, major tissue loss	Ordinal
Fontaine's stage	1, asymptomatic 2a, claudication at a distance > 200 m 2b, claudication at a distance < 200 m 3, rest pain 4, necrosis and/or gangrene of the limb	Ordinal
Diabetes mellitus	1, yes; 0, no	Dichotomous
Arterial hypertension	1, yes; 0, no	Dichotomous
Chronic renal insufficiency	1, yes; 0, no	Dichotomous
Coronary heart disease	1, yes; 0, no	Dichotomous
Nicotine abuse	1, yes; 0, no	Dichotomous
Dyslipidemia	1, yes; 0, no	Dichotomous
Adiposity	1, yes; 0, no	Dichotomous

The acute health condition was first gathered in form of free text. Afterwards, it has been transferred to a nominal variable (Table 5). Labels 10 and 11 were prepared for acute limb ischemia and CLI. These labels were not used because the other labels of Table 5 were more fitted to describe the acute health condition. However, acute limb ischemia is represented in the occlusion age parameter and CLI can be deducted from the PAD classification.

Table 5: Code List for Acute Health Condition.

Label	Acute health condition
1	Trauma
2	Contraindication for thrombolysis
3	Tumor disease
4	Discontinued anticoagulation
5	Endangitis obliterans
6	Contraindication for surgery
7	Heparin-induced thrombocytopenia
8	Embolism
9	Peri-operative/Peri-interventional
12	Several health conditions

The occlusion age represents acute, subacute (< 14 days and acute on chronic events) and chronic events. We combined subacute and acute on chronic occlusions in one category because both lesion types carry a thrombus with older and fresher parts.

Patients were counted as diabetic if they had been diagnosed with diabetes mellitus in a discharge letter or if they had received oral antidiabetic drugs and/or insulin. Same rule applies to patients with hypertension or dyslipidemia: Either the diagnosis had been given in a discharge letter and/or the patient had received the corresponding medication for these conditions. Any type of former or ongoing nicotine abuse was recorded. Cut-off for adiposity was a body-mass index (BMI)

of 30.0 and higher. If no BMI was given in the discharge letter, it was retrospectively calculated if body height and weight were available from the discharge letter.

2.2.2 Procedure and Adjunctive Therapy

The first step of the standard procedure is disinfection and sterile draping of the leg. It is followed by puncture of the femoral artery to gain antegrade or cross-over access to the arterial system. Contrast medium is injected, and DSA performed to detect occlusion. Next, a 0.0182” guidewire is placed through the target lesion. Then, a Rotarex®S catheter with 6F or 8F is run through the lesion, several passages are possible (Artzner *et al.*, 2022).
If feasible at the operator’s discretion, RT is used in below-the-knee lesions.
To visualize results, a control angiography is taken. Additional treatment, such as POBA, DCB angioplasty or stenting of the vessel is warranted, if single treatment by mechanical thrombectomy with Rotarex®S was completely or partly insufficient. If indicated, intra-arterial thrombolysis is performed before, during or after the interventional procedure (Artzner *et al.*, 2022).
In some cases, these revascularization methods were applied before the use of RT. The access side is closed with a hemostasis device.
Periprocedural 5 000 international units of low-molecular-weight heparin are administered. Patients receive a bolus of 500 mg acetylsalicylic acid (ASA) and 300 mg clopidogrel. Patients must maintain bed rest in supine position for 12 h post procedure. Dual antiplatelet therapy with ASA (100 mg/d) and clopidogrel (75 mg/d) is recommended to pursue after discharge for 12 weeks if a DCB was used, otherwise 4 weeks (Artzner *et al.*, 2022).
Afterwards, a monotherapy with ASA (100 mg/d) or clopidogrel (75 mg) is standard practice if no contraindications occur.

To assess the procedure, reports on diagnostic findings and DSA images were viewed. Procedural detail and used medical devices were taken from the computer-based radiology information system and documented in a Microsoft Excel worksheet (Artzner *et al.*, 2022).

The following parameters (Table 6) were gathered from the reports of diagnostic findings and the DSA images:

Table 6: **Procedure Variables from Reports of Diagnostic Findings and Digital Subtraction Angiography Images.**
Abbreviations: POBA, plain-old balloon angioplasty; DCB, drug-coated balloon; F, French.

Variable	Label	Level of measurement
Date of intervention	-	Continuous
Duration of procedure	-	Continuous
Access	1, cross-over 2, antegrade 3, both	Nominal
Size in F of sheath catheter	-	Nominal
Pre-dilatation before Rotarex®S	1, yes; 0, no	Dichotomous
Size in F of Rotarex®S	6, 6F Rotarex®S 8, 8F Rotarex®S	Nominal
Number of used Rotarex®S	-	Continuous
Passages of Rotarex®S	-	Continuous
Result after Rotarex®S	-	Free text
Stenosis after Rotarex®S	1, yes; 0, no	Dichotomous
Adjunctive treatment of stenosis	1, yes; 0, no	Dichotomous
POBA	1, yes; 0, no	Dichotomous
DCB	1, yes; 0, no	Dichotomous
POBA and DCB	1, yes; 0, no	Dichotomous
Stenting	1, yes; 0, no	Dichotomous
Not fully treatable	1, yes; 0, no	Dichotomous
Thrombolysis medication		Free text
Thrombolysis duration		Continuous
Point in time of thrombolysis	1, before 2, after 3, both 4, periinterventional	Nominal

The duration of intervention was measured by the time stamp of the first angiography image documentation to the last.

‘Not fully treatable’ represents cases where residual thrombus stayed in the vessel lumen or re-occurred during the procedure and no sufficient flow was established. Also, complete reocclusion during intervention is counted here.

Some patients had complex treatment course over several days and repeated treatments with RT and thrombolysis. In that case, one individual patient corresponds to several interventions. Each intervention was counted as accompanied with thrombolysis, the point in time of thrombolysis was also recorded for each intervention. The overall time of thrombolysis was only counted once for the whole series of interventions.
Any periinterventional thrombolysis was counted with 1 minute.

2.2.3 Target Lesion

Reports of diagnostic findings (DSA and CT angiography) and DSA images from the computer-based radiology information system were viewed to record characteristics of the target lesion (Table 7) (Artzner *et al.*, 2022). Details were documented in a Microsoft Excel worksheet.

Table 7: Part 1: Target Lesion Variables from Reports of Diagnostic Findings (DSA and CT Angiography), and Digital Subtraction Angiography Images.

Variable	Label	Level of measurement
Treated side	1, left; 2, right	Dichotomous
Diameter target lesion	-	Continuous
Lesion length	1, shorter than 20 cm 2, longer than 20 cm	Nominal
In-Stent lesion	1, yes; 0, no	Dichotomous
Bypass lesion	1, yes; 0, no	Dichotomous
TASC classification	-	Ordinal
Calcification of target lesion	0, none 1, minor 2, medium 3, severe	Ordinal
Calcification of target lesion (dichotomous)	1, yes; 0, no	Dichotomous
Occluded vessel	-	Free text

Table 7: **Part 2: Target Lesion Location Variables from Reports of Diagnostic Findings (DSA and CT Angiography), and Digital Subtraction Angiography Images.**

Variable	Label	Level of measurement
Location of target lesion	0, iliac arteries 1, thigh 2, lower leg 3, whole leg 4, iliac and leg	Nominal
Iliac arteries	1, yes; 0, no	Dichotomous
Arteries of the whole leg	1, yes; 0, no	Dichotomous
Arteries of the thigh	1, yes; 0, no	Dichotomous
Arteries of the lower leg	1, yes; 0, no	Dichotomous
Superficial femoral artery	1, yes; 0, no	Dichotomous
Popliteal artery	1, yes; 0, no	Dichotomous
Tibial-fibular trunk	1, yes; 0, no	Dichotomous
Anterior tibial artery	1, yes; 0, no	Dichotomous
Posterior tibial artery	1, yes; 0, no	Dichotomous
Fibular artery	1, yes; 0, no	Dichotomous
Other arteries	-	Free text
Number of treated segments	-	Continuous
Most distal segment	1, iliac arteries 2, superficial femoral artery 3, popliteal artery segment 1/2 4, popliteal artery segment 3 5, tibial-fibular trunk 6, anterior tibial artery 7, posterior tibial artery 8, fibular artery 9, bypass graft	Nominal

Due to the retrospective approach, diameter and length of treated vessels were estimated in comparison to the size of the used balloon or stent since no length measurements are documented in the DSA images. Lesion types included native arteries and in-stent lesions and bypass grafts. It was not registered if the target lesions were of atherosclerotic, atherothrombotic or embolic origin. In addition, lesions were classified based on the TASC classification (Norgren *et al.*, 2007).

Calcification of the vessel was visually estimated by the CTA run to diagnose occlusion of arteries (Artzner *et al.*, 2022). The level of calcification was then specified in an ordinal variable. A dichotomous variable shows any amount of calcification vs none.

The occluded vessel was first registered in free text and then translated into dichotomous variables. Location of target lesions included the region of abdominal aorta, iliac, superficial and profound femoral arteries, and popliteal arteries. We defined segments to distinguish the location of the target lesion as follows: The iliac arteries originate from the aortic bifurcation, including external and internal iliac arteries and reach until the inguinal ligament. They are followed by the common femoral artery which leads to the superficial femoral artery. The popliteal artery comes next and is divided into three segments: In the DSA image, segment one starts at the edge of femur, followed by segment two, starting at the upper edge of the patella. Segment three is defined by the beginning of the tibia until the separation of the anterior tibial artery and the tibial-fibular trunk (Figure 9). The tibial-fibular trunk then divides into the posterior tibial artery (POTA) and the fibular artery. The segment most distal of the treated vessel was also recorded.

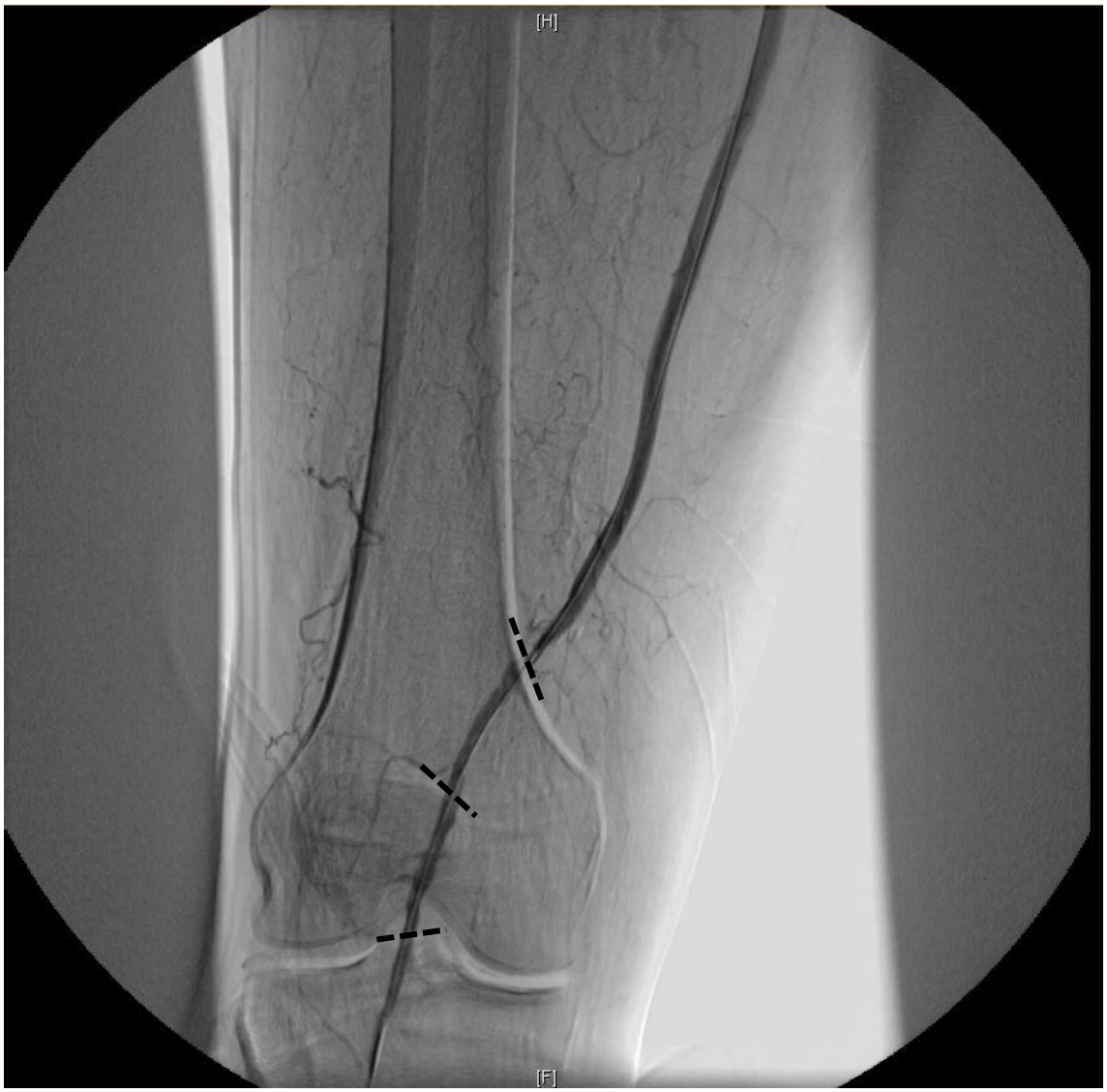


Figure 9: **DSA Image of the Segments of Popliteal Artery Indicated by Dashed Lines.** Segment 1 is defined by the edge of femur, segment 2 is defined by the upper edge of the patella, segment 3 is defined by the beginning of the tibia until the separation of the anterior tibial artery and the tibial-fibular trunk (not displayed). **Abbreviation:** DSA, digital subtraction angiography.
Own illustration.

2.2.4 Technical Success

Technical success was determined due to the reports of diagnostic findings and DSA images from the computer-based radiology information system (Table 8). Details were documented in a Microsoft Excel worksheet.

Table 8: Technical Success Variables from Reports of Diagnostic Findings and DSA Images.

Variable	Label	Level of measurement
Technical success: passage	1, yes; 0, no	Dichotomous
Technical success: revascularization	1, yes; 0, no	Dichotomous
Reason for failure	-	Free text
Material failure	1, yes; 0, no	Dichotomous

The variable *technical success: passage* stands for the possible passage of the target lesion with the guidewire. The variable *technical success: revascularization* represents if the Rotarex®S catheter was able to establish any kind of blood flow through the target lesion, regardless if clinically sufficient or not.

If technical success was not achieved, explanation was given as *reason for failure.*

Material failure including breakage of the catheter was recorded.

2.2.5 Clinical Success

The clinical records were searched for re-admission to the Tübingen University Hospital and information of later visits was included in the survey to follow up clinical success (Table 9). This information was taken from discharge letters, outpatient letters, reports of diagnostic findings and reports of surgery.

Table 9: Clinical Success Variables from Clinical Records (Discharge Letters, Outpatient Letters, Reports of Diagnostic Findings, Reports of Surgery).

Variable	Label	Level of measurement
Clinical success	1, yes; 0, no	Dichotomous
Ankle-brachial index pre treatment	-	Continuous
Ankle-brachial index post treatment	-	Continuous
Walking distance pre treatment	-	Continuous
Walking distance post treatment	-	Continuous
Reintervention type	-	Free text
Reintervention date	-	Continuous
Freedom of target lesion revascularization within 30 days	1, yes; 0, no	Dichotomous
Amputation	1, yes; 0, no	Dichotomous
Amputation after Rotarex®S	1, yes; 0, no	Dichotomous

Clinical success of intervention is defined as a sufficient blood flow to the limb by the interventionist's discretion at the end of the procedure or the end of additional catheter-directed thrombolysis (Artzner *et al.*, 2022). Clinical success is also achieved if the patient received surgery in addition to the index procedure. In case patients eventually underwent amputation, clinical success was still achieved if the index procedure ensured blood flow to the amputation stump. If no functional recanalization was accomplished and/or patients died during their hospital stay connected to the study-procedure, no clinical success was achieved.

Clinical outcome as walking distance and ABI were documented. Due to the retrospective design of the study, walking distances were not always taken from objective testing, but from subjective estimation by the patient reflected in the discharge or outpatient letter. When patients' anamnesis gave a range of walking distance, the shorter distance was counted. Also, there was no time span limit

before and after the index procedure for the collection of ABI and walking distance.

Patency was recorded as total time to reintervention and in reintervention within the first 30 days after revascularization (Artzner *et al.*, 2022). We compared the patency regarding occlusion age, size of the Rotarex®S catheter and application of DCB with Kaplan-Meier survival analysis.

Amputations after the index procedure were recorded (Artzner *et al.*, 2022). Amputations due to other reasons, e.g., trauma, were not included.

2.2.6 Complications

Information about complications was gathered from reports of diagnostic findings, DSA images from the radiology information system, and from the clinical records, reports of surgery, and discharge and outpatient letters (Table 10) (Artzner *et al.*, 2022).

Table 10: Complication Variables from Reports of Diagnostic Findings, DSA Images, Reports of Surgery, Discharge and Outpatient Letters.

Variable	Label	Level of measurement
Complication	1, yes; 0, no	Dichotomous
Complication in detail	1, dissection 2, perforation 3, pain 4, AV-Fistula 5, wire fracture 6, compartment syndrome 7, other 8, secondary hemorrhage 9, death	Nominal
Complication after this device	1, Rotarex®S 2, adjuvant therapy 3, underlying disease 4, indistinct	Nominal
Interventional treatment of complication	-	Free text
Distal embolization	1, yes; 0, no	Dichotomous
Relevance of distal embolization	0, irrelevant 1, minimal: treated with 48 h heparinization 2, relevant: treated with thrombolysis or aspiration	Nominal
CIRSE class	-	Ordinal

Complications were recorded in free text variable and then translated into groups of frequent events. The prior used therapy was recorded as the causing therapy. Complications not clearly assigned to a certain cause, for example appearance

of compartment syndrome, were categorized as complications of underlying disease. Minor bleedings solved during intervention and spastics are not counted as complications, since they are inherent events of angiographic interventions.

Distal embolization was of special interest to analyze safety of RT; therefore, it was counted apart from complications. The severity of embolization was graded by the consequences it provoked. Irrelevant embolization had no need for further treatment, minimal embolization was treated with 48 h of heparinization. Larger embolization was either treated with thromboaspiration or thrombolysis as to the interventionist's discretion.

The CIRSE classification (Filippiadis *et al.*, 2017) was used to standardize grading of complications and therefore make data more comparable with other studies (see 1.3.3 Classification of Complications: CIRSE Classification) (Artzner *et al.*, 2022). Complications solved during the procedure, respectively CIRSE class 1 and 2, meant, e.g., treatment with prolonged POBA, stent deployment and thromboaspiration.

2.3 Ethics and Informed Consent

Patient's informed consent to treatment was obtained at the time of treatment. Since this study has a retrospective design, it was not possible to obtain written informed consent of the patient to take part in this study.

An application for ethical review (No.: 749/2019BO2) was submitted on October 16, 2019 to the Ethical board of the University of Tübingen. A positive review was secured for data collection for this study on October 31, 2019.

2.4 Statistical Analysis

Data was first gathered in table form in a Microsoft Excel sheet.

JMP® 15 was used for descriptive analyzation of the gathered data. Descriptive analyzation includes frequencies, minimum, maximum, arithmetic mean, median, interquartile range, and standard deviation (Artzner *et al.*, 2022).

Testing was performed using the IBM SPSS® Statistics 26 software. Significance was set at $p < 0.05$. To compare metric variables, we used the t-test for independent samples (Artzner *et al.*, 2022). It should be noted that due to the retrospective design of the study, for a part of the individuals the data was only available pre or post intervention and partially, it was possible to record both values. Therefore, the presented data represents a mix of paired and unpaired samples. Nevertheless, the results are of relevance, since the t-test for independent samples is robust, the sample size is large, and the effect is very plausible. To compare ordinal variables, we used the non-parametric Mann-Whitney U test (Artzner *et al.*, 2022), which is a robust test for the presented mix of dependent and independent samples.

To compare groups, Chi-square test by Pearson was run to test significance in the relationship between nominal and ordinal scaled variables (Artzner *et al.*, 2022). We compared the aforementioned subcohorts regarding the technical and clinical success and occurrence of complications. For significance tests of non-binary variables, subanalysis was conducted to examine which parameter was responsible for significance. If expected cell frequencies were below five and the basis of the calculation was not a 2x2 crosstabulation, a two-sided Monte-Carlo-Significance with 10 000 random sample tables was tested (Artzner *et al.*, 2022). Fisher's exact test was used for 2x2 crosstabulation and expected cell frequencies below five. The effect size is either given as the phi coefficient for 2x2 crosstabulations or the Cramér's V for all other crosstabulation sizes (Artzner *et al.*, 2022).

Kaplan-Meier survival analysis was used to test patency regarding occlusion age, size of the Rotarex®S catheter and application of DCB (Artzner *et al.*, 2022). We

analyzed the time until reintervention or inclusion, which was set as June 17, 2020.

Since there has been parallel testing without adjustment of the alpha error, results have exploratory character.

Figures 8 and 11 were drawn with JMP® 15. Figures 10, 12, 13, 15, 16, 17 and 18 were created with the IBM SPSS® Statistics 26. Figures 6, 7, 9 and 14 were assembled with Microsoft Paint. We used Microsoft Word to produce tables.

3 Results

3.1 Patients

To characterize the patient cohort, discharge letters were evaluated. The final study cohort had 397 interventions of 293 individuals (Artzner *et al.*, 2022). We registered a share of 64.7% male patients (n = 189), one value was missing. At time of intervention, patients had a mean age of 69.8 ± 12.0 years (Artzner *et al.*, 2022).

The medical condition at hospital admission was collected and is visualized in Figure 10. There is a high count of missing values, so it is of exploratory value. The combination of multiple factors forms the largest group *several*. For example, one patient had a contraindication for surgery due to myocardial infarction and contraindication for thrombolysis due to tumor disease. Therefore, this was categorized as *several*.

Contraindication for thrombolysis and tumor disease are the second largest groups of medical conditions (Figure 10). Common contraindications for thrombolysis were history of intracranial hemorrhage, large hematoma, and perioperative status. Furthermore, the constellation of discontinued anticoagulation due to an intervention/surgery (e.g., coloscopy) plus subsequent thrombolysis contraindication (polypectomy/surgery) was observed.
A tumor disease can contraindicate thrombolysis, e.g., if a cerebral tumor bears the potential of intracerebral bleeding. On the other hand, tumor disease might cause an arterial occlusion through increased thrombophilia as a paraneoplastic syndrome. In conclusion, a tumor might act as either the cause of an occlusion or the reason why therapeutic options were limited. To sum up, the individual medical conditions can make interventional treatment the only therapeutic option for a patient.

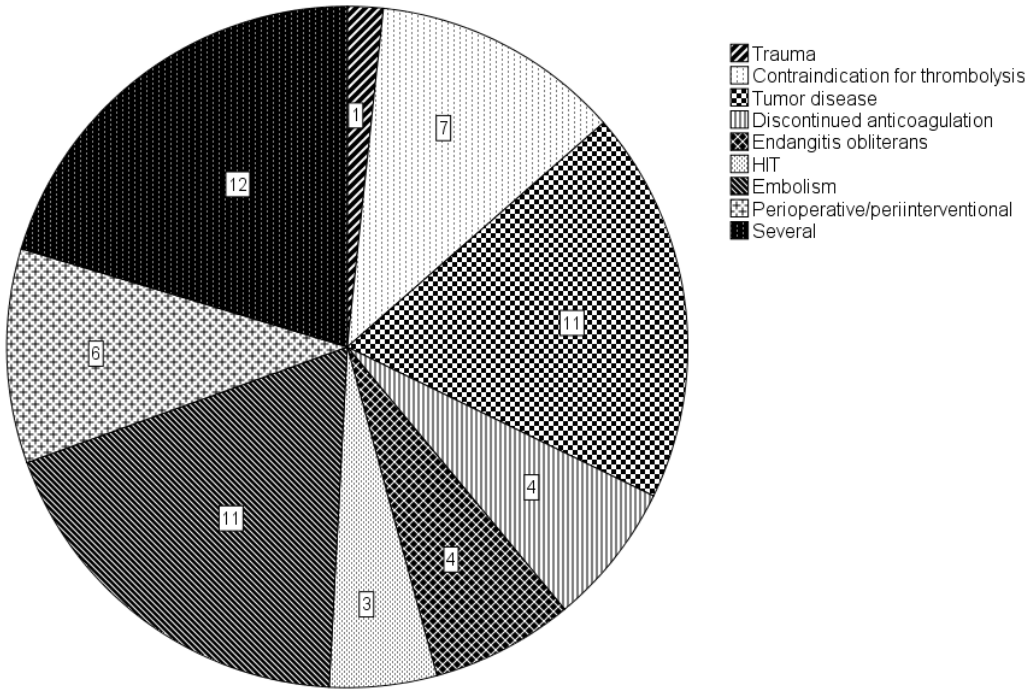


Figure 10: **Pie Chart of Medical Condition at Hospital Admission with Absolute Number of Appearance.**
Abbreviation: HIT: Heparin-induced thrombocytopenia.
Own illustration.

We also registered the occlusion age (Figure 11): Most interventions were done for an acute event (n = 182; 47.5%), while subacute and acute on chronic events were counted 85 times (22.2%) (Artzner *et al.*, 2022). A number of 116 (30.3%) interventions were done for chronic disease (Artzner *et al.*, 2022). 14 values of occlusion age were missing.

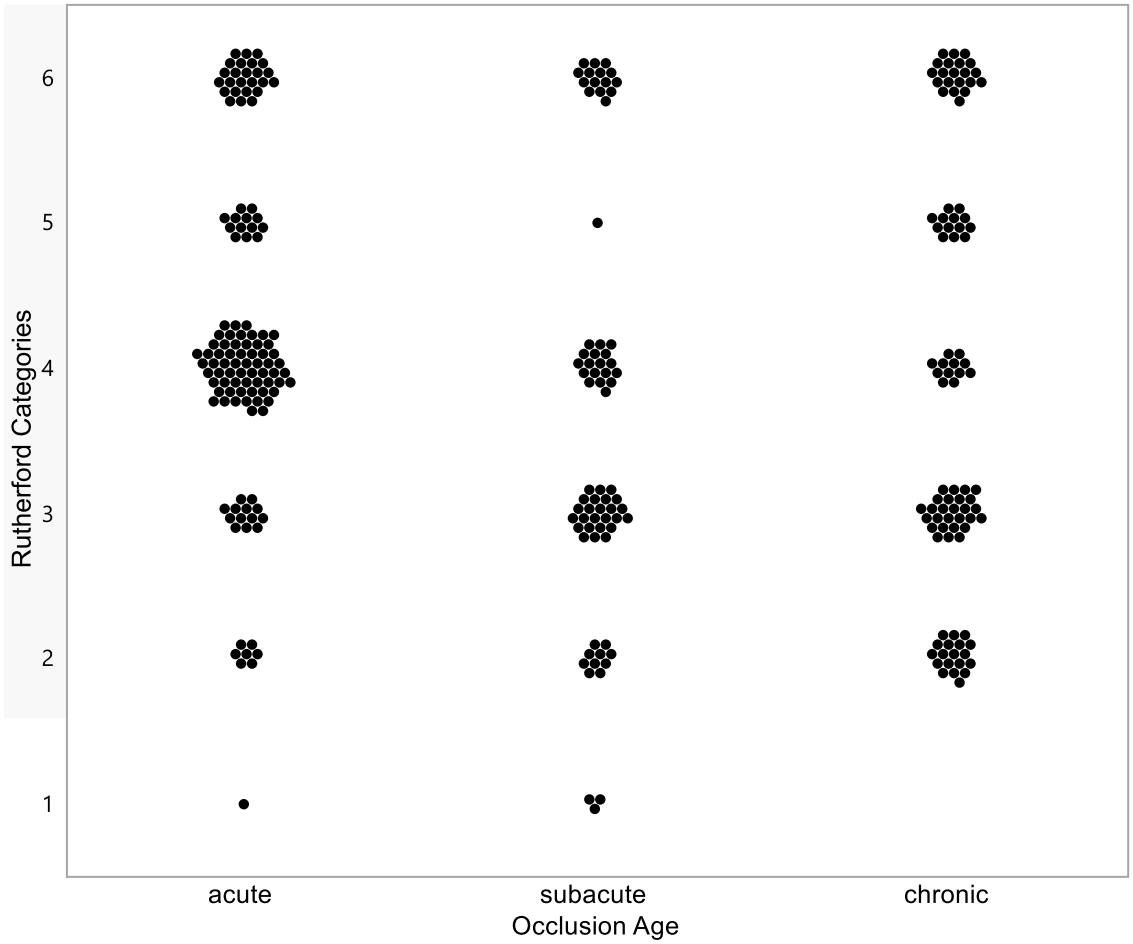


Figure 11: **Number of Interventions Sorted by Occlusion Age and Rutherford's Categories.**
One dot equals one intervention.
Own illustration.

Predominant were the Rutherford categories 3 (n = 69; 23.5%) and 4 (n = 94; 32.1%) (Artzner *et al.*, 2022) and the Fontaine stages 2b (n = 165; 45.2%), 3 (n = 94; 25.8%) and 4 (n = 102; 27.9%). There are more counts in total for the Fontaine stages (n = 365) than for the Rutherford categories (n = 293) because the scale is simpler and demands less detailed information about the symptoms and presentation of the patient. Therefore, it was better applicable for this retrospective study. As presented in Table 11, the share of CLI, respectively the Fontaine stages III and IV, was 53.7%.

Table 11: Results of Classification of Clinical Status of Peripheral Artery Disease.
Adapted from Artzner et al. (2022), © Thieme.

Fontaine's stage	n (%) / 365 patients	Rutherford's category	n (%) / 293 patients
I	0 (0)	0	0 (0)
II a	4 (1.1)	1	4 (1.3)
II b	165 (45.2)	2	37 (12.6)
		3	69 (23.5)
III	94 (25.8)	4	94 (32.1)
IV	102 (27.9)	5	27 (9.2)
		6	62 (21.2)

"Cardiovascular risk factors were frequently present" (Artzner *et al.*, 2022) (Table 12). Predominantly, arterial hypertension (n = 241; 82.3%) followed by former or ongoing nicotine abuse (n = 151; 51.5%), dyslipidemia (n = 144; 49.1%), and adiposity (n = 65; 22.2%) (Artzner *et al.*, 2022). A count of 100 (34.1%) patients were diagnosed with coronary artery disease, 95 (32.4%) with diabetes mellitus, and 66 (22.5%) with chronic renal insufficiency (Artzner *et al.*, 2022).

Table 12: Prevalence of Cardiovascular Risk Factors of Patients Treated with Rotarex®S Catheter.
Adapted from Artzner et al. (2022), © Thieme.

Cardiovascular risk factor	n (%) / 293 individual patients
Arterial hypertension	241 (82.3)
History of nicotine abuse	151 (51.5)
Dyslipidemia	144 (49.1)
Adiposity	65 (22.2)
Coronary artery disease	100 (34.1)
Diabetes mellitus	95 (32.4)
Chronic renal insufficiency	66 (22.5)

3.2 Procedure and Adjunctive Therapy

Next, the parameters of the index procedure are reported (Table 13): The duration of the procedures is described by a median of 78 min (Artzner *et al.*, 2022) (interquartile range 50 min), ranging from 4 min to 288 min. One very short ‘4 min intervention’ was the second intervention for one patient on the same day with reoccurred thrombotic load.

The cross-over approach was performed in 219 (55.3%), the antegrade approach in 166 (41.9%) interventions (Artzner *et al.*, 2022). Additionally, 11 approaches were performed from retrograde, brachial or both cross over and retrograde (Artzner *et al.*, 2022). For one intervention the value was missing. According to the site of approach, sheath devices with diameters ranging from 6 to 8F were used, mostly 6F (n = 356/396; 89.9%).

In most interventions, no pre-dilatation before Rotarex®S Catheter application was performed (n = 362/396; 91.4%). Mostly, a 6F Rotarex®S Catheter was used (n = 365; 92.2%), otherwise, an 8F Rotarex®S Catheter was used, one value was missing (Artzner *et al.*, 2022). Only in six cases (1.5%) a second catheter was needed.

Table 13: Results of the Procedure with the Rotarex®S Catheter.

Procedural detail	**n (%)**
Vascular access site:	
○ Antegrade	166 / 396 (41.9)
○ Cross-over	219 / 396 (55.3)
○ Retrograde	8 / 396 (2.0)
○ Both antegrade and cross-over	1 / 396 (0.3)
○ Several access sites	2 / 396 (0.5)
Sheath diameter device:	
○ 6F	356 / 396 (89.9)
○ 7F	10 / 396 (2.5)
○ 8F	30 / 396 (7.6)
Size of Rotarex®S	
○ 6F	365 / 396 (92.2)
○ 8F	31 / 396 (7.8)
Predilatation	34 / 396 (8.6)

Immediately after Rotarex®S Catheter application, residual stenosis of the target lesion was highly prevalent (n = 349/390; 89.5%) (Artzner *et al.*, 2022). Therefore, treatment was followed with POBA (n = 270; 68%), DCB (n = 149; 37,5%), POBA and DCB (n = 87; 21,9%) and/or stenting (n = 163; 41.1%) (Artzner *et al.*, 2022).

If no or no adequate result was achieved with or without adjunctive therapy, patients were categorized as *not fully treatable* (n = 146; 36.8%). This was mainly the case when a significant amount of residual thrombus stayed in the vessel lumen and no sufficient flow was established. If an advantage for the patient's outcome was assumed by the interventionist's discretion, patients received thrombolysis in addition.

A total of 127 interventions (32%) were accompanied by catheter-directed thrombolysis (Artzner *et al.*, 2022). The point in time of thrombolysis was available

for 123 interventions: Thrombolysis was administered before (n = 11; 8.9%), after (n = 72; 58.5%) or both before and after (n = 24; 19.5%) the intervention, when thrombectomy with Rotarex®S Catheter was performed (Artzner *et al.*, 2022). Periinterventional thrombolysis was administered at 16 interventions (13%) (Artzner *et al.*, 2022). We registered 5 individual patients who underwent a prolonged combined treatment of Rotarex®S catheter and thrombolysis over two (n = 4) to three (n = 1) days. Predominantly, native vessels received additional thrombolysis (70.1% of thrombolysis). Additional thrombolysis was done for bypass occlusion in 29.9%.

The thrombolytic agent was available in 120 cases: Mainly urokinase (n = 78; 65%), followed by Actilyse® (Alteplase) (n = 39; 32.5%) was used (Artzner *et al.*, 2022). Furthermore, in three cases, Reopro® (Apixaban) or Argatra® (Argatroban) were administered (Artzner *et al.*, 2022). For seven cases, the administered drug was not registered. In median, patients received thrombolysis for 27h:09min (Interquartile Range 30h:24min), ranging between 1 hour and 158h:58min in a more complex course.

3.3 Target Lesion

We observed the following target lesion characteristics (Table 14): The left leg was marginally more often treated (n = 219; 55.2%) than the right leg (n = 178; 44.8%). The median diameter of the target lesions (n = 373) was 6 mm, ranging from 2.5 mm to 12 mm (Artzner *et al.*, 2022). The target lesions were mostly longer than 20 cm (n = 244, 61.5%) (Artzner *et al.*, 2022). The majority were native vessels with or without preexisting stent (Artzner *et al.*, 2022). These lesions divided mainly into TASC C (n = 144; 42.6%) and TASC D lesions (n = 97; 28.7%) (Artzner *et al.*, 2022). Occlusion of bypass grafts was treated 59 times (14.9%) (Artzner *et al.*, 2022). Since estimation of the degree of calcification of the target vessel depended on the existence of a CTA scan, this data was missing for 203 cases. Calcification of the target vessel was prevalent in 150 from 194 cases (77.3%) with CTA scan, mostly of minimal (n = 57; 29.4%) and medium (n = 76; 39.2%) quantity (Artzner *et al.*, 2022).

The location of target lesion was in iliac arteries (n = 28; 7.1%), iliac arteries and arteries of the whole leg (n = 20; 5.0%), solely femoropopliteal above the knee (n = 236; 59.4%), femoropopliteal and below the knee (n = 107; 27.0%), and solely below the knee (n = 6; 1.5%) (Artzner *et al.*, 2022). Other target vessels were the deep femoral artery, the internal iliac artery, and the abdominal aorta.

Table 14: **Results of the Target Lesion Treated with the Rotarex®S Catheter.**
Reprinted from Artzner et al. (2022), © Thieme.

Angiographic details of target lesions	**n / total (%)**
Lesion length:	
○ < 20 cm	153 / 397 (38.5)
○ > 20 cm	244 / 397 (61.5)
Vessel type:	
○ **Native**	**338 / 397 (85.1)**
• without stent	148 / 397 (37.3)
• with preexisting stent	190 / 397 (47.9)
○ **Bypass**	**59 / 397 (14.9)**
• without stent	45 / 397 (11.3)
• with preexisting stent	14 / 397 (3.5)
TASC:	
○ A	10 / 338 (3.0)
○ B	87 / 338 (25.7)
○ C	144 / 338 (42.6)
○ D	97 / 338 (28.7)
Calcification:	
○ None	44 / 194 (22.7)
○ Minimal	57 / 194 (29.4)
○ Medium	76 / 194 (39.2)
○ Severe	17 / 194 (8.8)
Location of target lesion:	
○ Iliac arteries	28 / 397 (7.1)
○ Iliac and leg arteries	20 / 397 (5.0)
○ Arteries of the whole leg	107 / 397 (27.0)
○ Solely arteries of the thigh	236 / 397 (59.4)
○ Solely arteries of the lower leg	6 / 397 (1.5)

Target vessels of the leg in detail are shown in Table 15:

Table 15: Target Vessels of the Leg Treated with Rotarex®S Catheter.

Target Vessel	n (%)
Superficial femoral artery	272 / 397 (68.5)
Popliteal artery	208 / 397 (52.4)
Tibial-fibular trunk	30 / 397 (7.6)
Anterior tibial artery	6 / 397 (1.5)
Posterior tibial artery	3 / 397 (0.8)
Fibular artery	3 / 397 (0.8)

A maximum of four segments of the arteries in total has been treated in one intervention, in median two segments.

The following Figure 12 shows the distribution of vessels' sizes by the absolute count of interventions (total n = 373): This again reflects that the most common target lesions were in the SFA and PA, which typically have a 5 mm to 6 mm diameter.

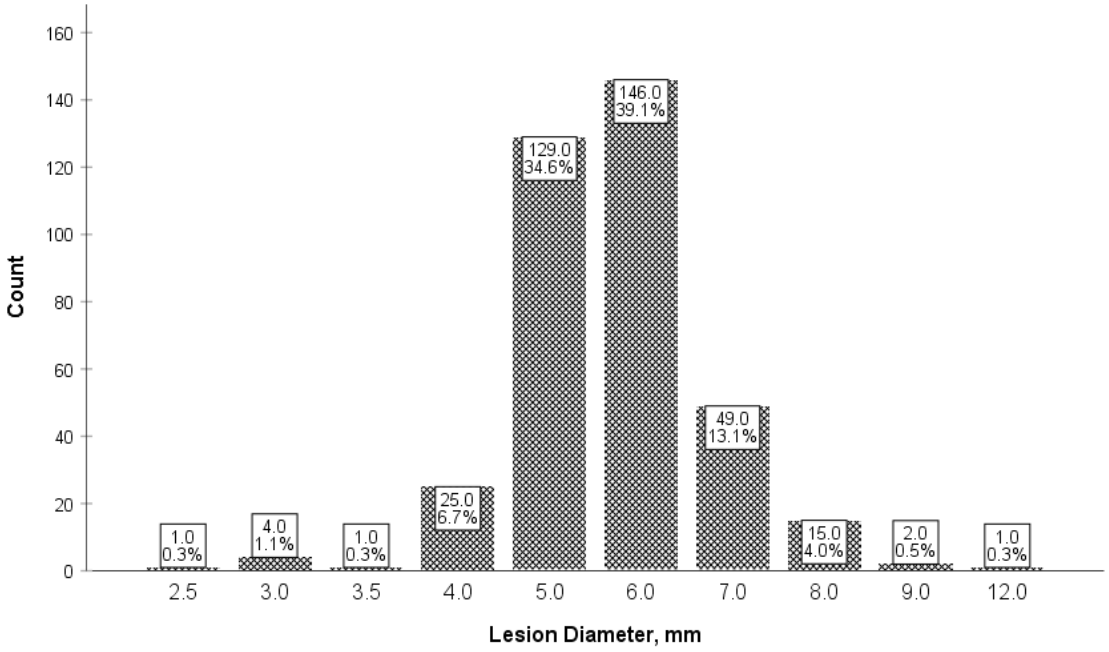


Figure 12: Bar Graph of the Absolute Count of Interventions by the Lesion Diameter in Millimeter (mm).
Available data for n = 373 interventions.
Own illustration.

The following Figure 13 gives an overview over the most distal segment treated. According to the license of the Rotarex®S catheter, it is contradicted to use the Rotarex®S catheter in vessels smaller than 3 mm diameter. This is well represented in the following chart, showing that predominantly, the most distal use was in the arteries of the thigh.

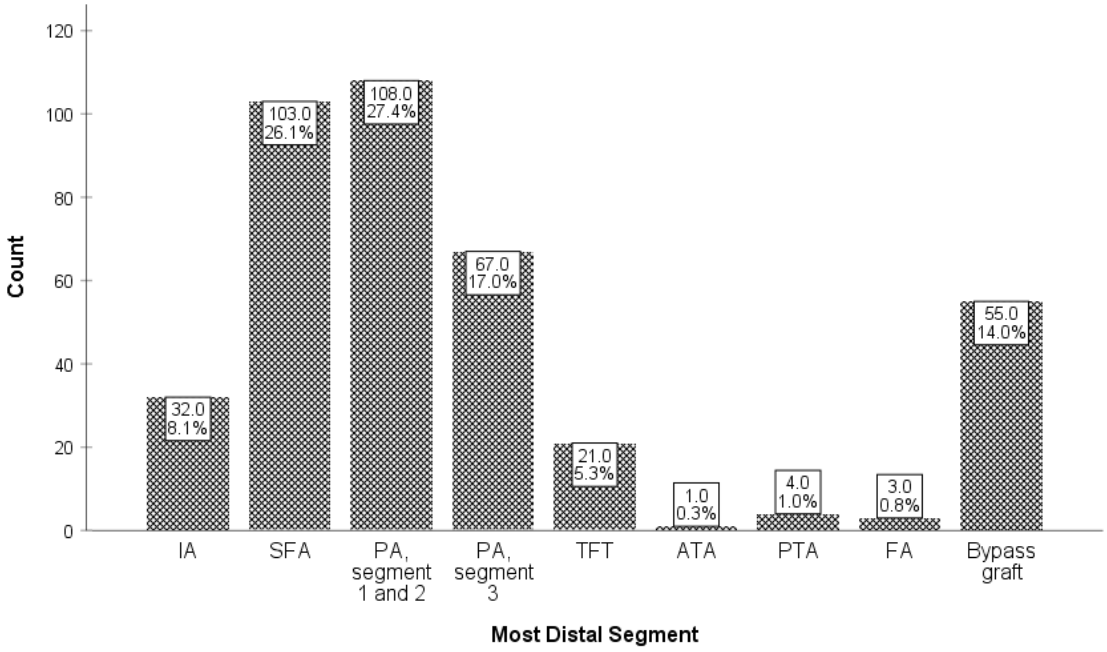


Figure 13: **Bar Graph of the Absolute Count of Interventions by the Most Distal Arterial Segment Treated.**
Available data for n = 394 interventions
Abbreviations: IA, iliac arteries; SFA, superficial femoral artery; PA, popliteal artery. TFT, tibial-fibular trunk; ATA, anterior tibial artery; POTA, posterior tibial artery; FA, fibular artery.
Own illustration.

3.4 Technical Success

To evaluate safety and efficacy of RT with the Rotarex®S catheter, we need to look at the technical success.

Technical success in terms of passing the occlusion with the guidewire was 100% (Artzner *et al.*, 2022). Technical success in terms of revascularization was achieved in 361 (90.9%) cases. In 36 (9.1%) cases, no or no sufficient flow was accomplished after use of RT (Artzner *et al.*, 2022). It should be noted: Even if no revascularization was achieved, it often was possible to still reduce the thrombotic load.

Material failure was documented in seven cases (n = 7/396; 1.8%) (Artzner *et al.*, 2022). Four cases of material failure were described in the report of diagnostical findings only as “material defects” without further explanation in the report of diagnostical findings, but the thrombus material was described as “older”.

Remarkably, two times of material failure happened to the same patient in two different procedures: In one case, the helix broke during the treatment of a chronic occlusion. In the other case, the Rotarex®S catheter was run while the sheath catheter was pulled back. The Rotarex®S catheter cut off the guidewire. It was possible to retrieve the part of the guidewire remaining in the vessel by performance of a snare maneuver (Figure 14). In another case, the system stalled several times without creating distal flow, so the interventionist switched to POBA.

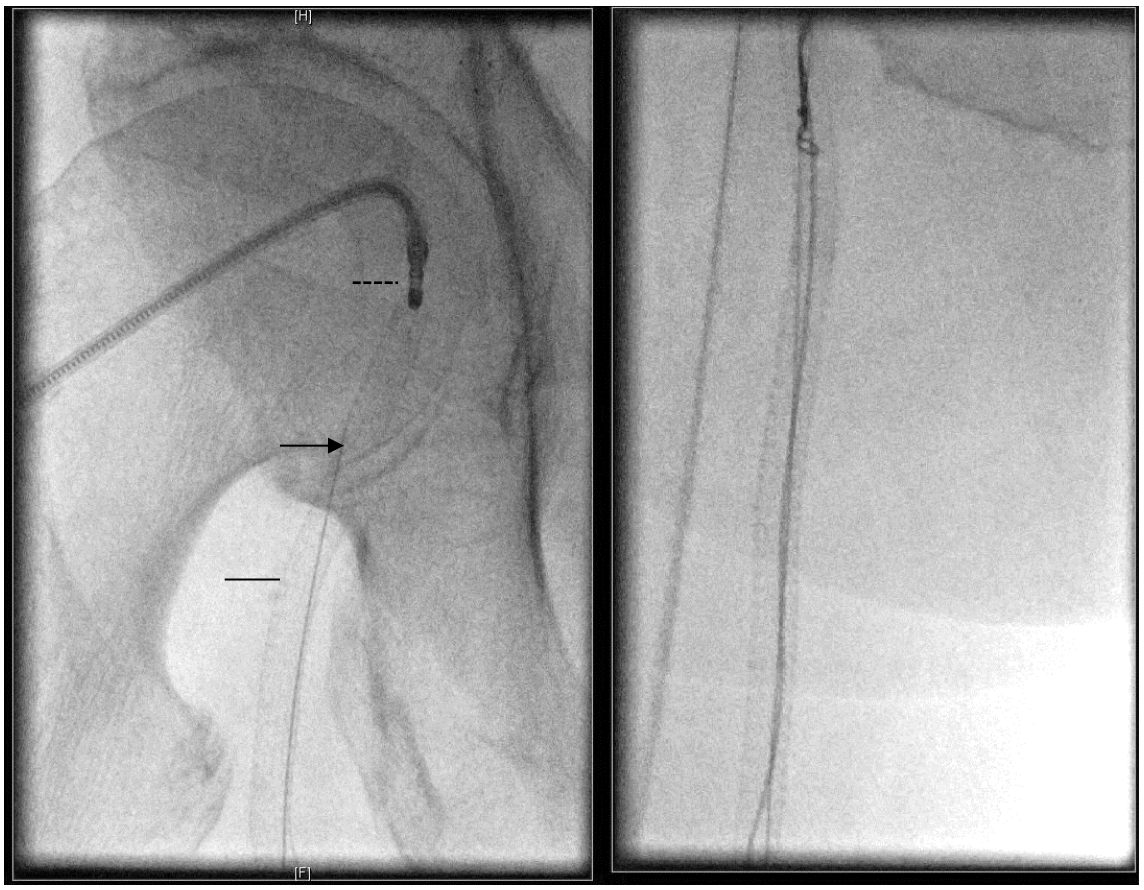


Figure 14: **DSA Images of Cut Guidewire Retrieved with Snare Maneuver.**
Left picture: Rotarex®S (dashed line) cuts guidewire (arrow), guidewire remains in stented artery (solid line).
Right picture: Retrieving of guidewire with snare maneuver.
Abbreviation: DSA, digital subtraction angiography.
Own illustration.

3.5 Clinical Success

In total, 359 (90.4%) procedures were considered clinically successful (Artzner *et al.*, 2022). This includes cases with additional, successful thrombolysis and patients eventually treated surgically. A count of 10 interventions ended eventually with amputation but were nevertheless considered clinically successful because they substantially contributed to the vascularization to the amputation stump (Artzner *et al.*, 2022). Clinical success was missed for patients with no functional recanalization and/or patients who died during their hospital stay connected to the study-procedure. In total, 26 interventions (6.5%) were followed by amputation during the period of record (Artzner *et al.*, 2022).

To evaluate perfusion status of the affected limb, the ABI was collected before and after intervention (Figure 15). ABI more than 1.3 was excluded from the analysis due to the possibility of underlying media sclerosis to confound the ABI. The arithmetic mean of ABI before the intervention was 0.33 ± 0.29 (Artzner *et al.*, 2022) ranging from 0 to 1.09. This represents severe PAD. ABI after intervention was higher with mean 0.81 ± 0.25 (Artzner *et al.*, 2022) ranging from 0 to 1.3. Using the t-test for independent samples, we found a significant difference for ABI before and after the treatment, the difference being +0.48 (SD ± 0.03), 95% CI = {0.43 - 0.54}, $p < 0.0001$ (Artzner *et al.*, 2022). In conclusion, the ABI reaches values representing healthy perfusion status and mild PAD values after the intervention.

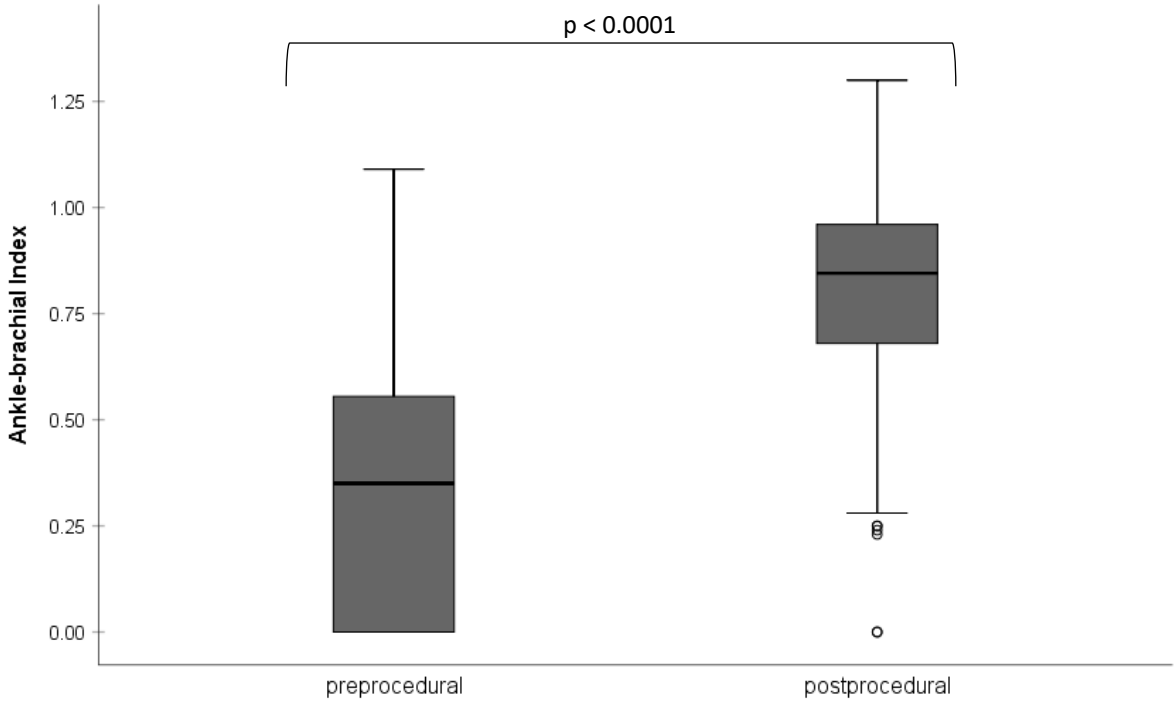


Figure 15: **Box Plot of Ankle-Brachial Index Preprocedural and Postprocedural.** Own illustration.

Walking distance was separated in three groups: Shorter or longer than 200 m and unlimited walking distance. There is a high count of missing values: Walking distances before the intervention were available in 147 cases (Artzner *et al.*, 2022). After the intervention, there were only 48 available values. Mainly, patients before intervention were able to walk less than 200 m (n = 138; 93.9%) (Artzner *et al.*, 2022). After treatment, 52.1% (n = 25) were not limited in their walking distance, another 25.0% (n = 12) reported a walking distance between 200 m and 4000 m and only 22.9% (n = 11) were only able to walk less than 200 m (Artzner *et al.*, 2022). Mann-Whitney U test showed significance for the difference, $p < 0.0001$ (Artzner *et al.*, 2022).

Reintervention was needed for 141 patients (35.5%) (Artzner *et al.*, 2022). Among these, another revascularization within 30 days after the index procedure, either interventional or surgical, was done for 33 (8.5%) patients (Artzner *et al.*, 2022). For 10 patients, no 30-day freedom of revascularization was evaluable, either due to death or due to missing data.

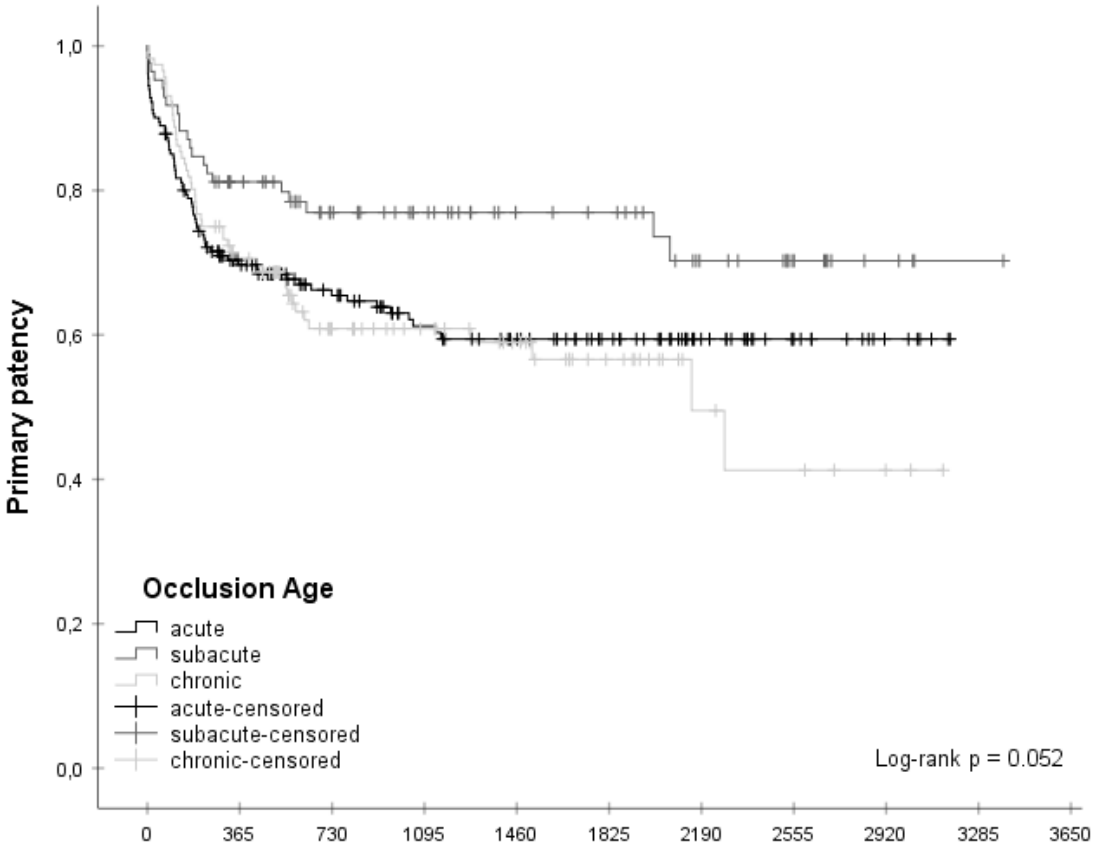
Using Kaplan-Meier survival analysis, the patency defined as the freedom from reintervention regarding the occlusion age (n = 382) has been further analyzed (Table 16, Figure 16). Time is represented either in days until reintervention or days until the inclusion date, which was set as the June 17, 2020.

It becomes apparent that the best long-term outcome without reintervention is for the subacute and acute occlusion age groups, while chronic occlusions have the lowest overall freedom of reintervention (Artzner *et al.*, 2022). Log-rank test almost reaches significancy for the difference between the groups (p = 0.052) (Artzner *et al.*, 2022).

Another interesting aspect is: Although chronic occlusion age has the worst overall long-term outcome, it shows the best patency rates in the first three months after intervention, while acute occlusion age has the worst 3 months patency (Table 16).

Table 16: Short-Term Patency for the Occlusion Age Groups the First Year After Intervention with the Rotarex®S Catheter.
Adapted from Artzner et al. (2022), © Thieme.

Time	Acute	Subacute	Chronic
1 Month	0.901	0.953	0.974
3 Months	0.850	0.918	0.931
6 Months	0.772	0.847	0.802
1 Year	0.697	0.812	0.705



Acute	111	86	68	59	47	28	14	6	0	0
Subacute	63	48	39	29	27	17	10	4	1	0
Chronic	77	46	36	28	17	7	5	2	0	0

Numbers at Risk

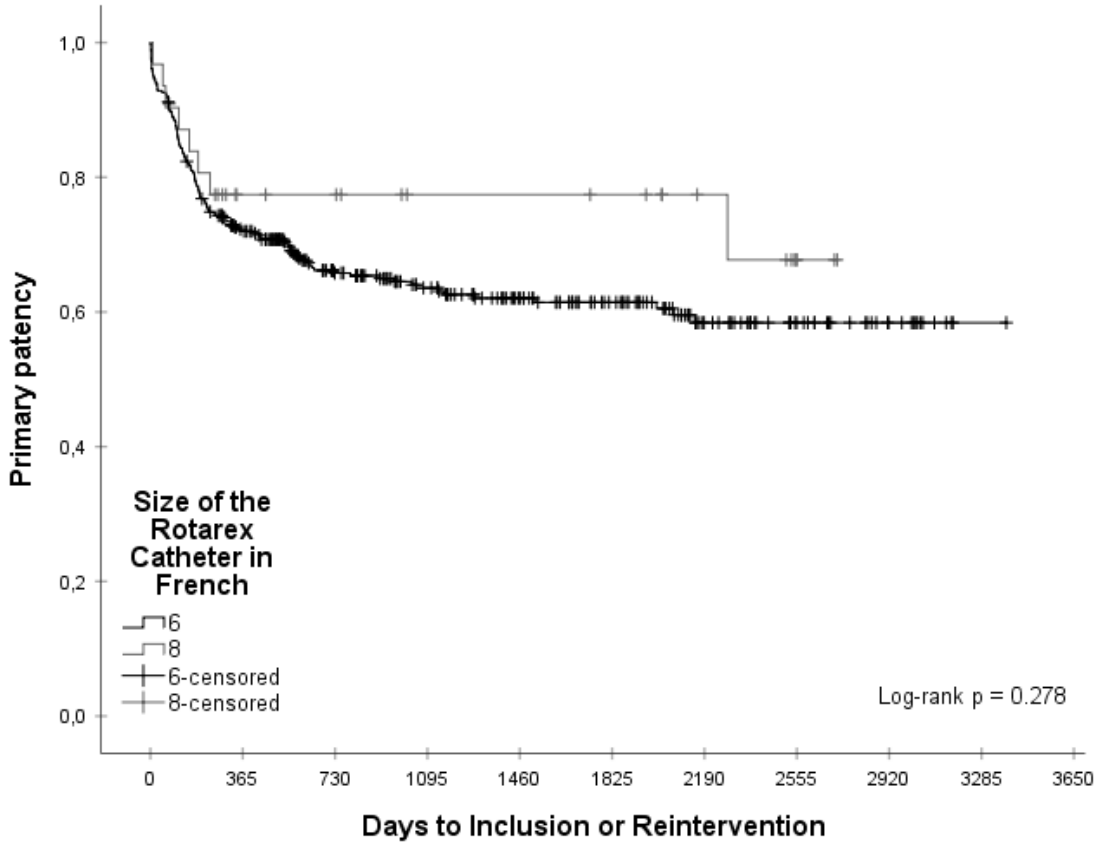
Figure 16: **Kaplan-Meier Survival Curve for Primary Patency of the Different Occlusion Age Groups and Numbers at Risk.**
Primary patency is the time from intervention to first reintervention to maintain or reestablish patency or to inclusion.
Reprinted from Artzner et al. (2022), © Thieme.

The patency according to the size of the catheter has been analyzed with Kaplan-Meier survival analysis to evidence efficacy of the different sizes of Rotarex®S catheters (n = 395) (Table 17, Figure 17). Same obligations apply as for the Kaplan-Meier analysis according to the occlusion ages. The power is limited because the data set for the 8F catheter is small (n = 31).

Log-rank test clearly reaches no significancy (p = 0.278). The limited informative value seems to point at marginally better long-term patency after treatment with an 8F Rotarex®S catheter. Overall, 36% of patients treated with 6F Rotarex®S catheter (n = 364) receive reintervention, while 25.8% of the patients treated with the 8F Rotarex®S catheter receive reintervention.

Table 17: Short-Term Patency for the Rotarex®S Catheter Size Groups the First Year After Intervention.

Time	6 French	8 French
1 Month	0.929	0.968
3 Months	0.887	0.903
6 Months	0.790	0.806
1 Year	0.720	0.774



6 French	240	167	133	105	81	45	26	12	1	0
8 French	18	17	13	13	12	8	3	0	0	0

Numbers at Risk

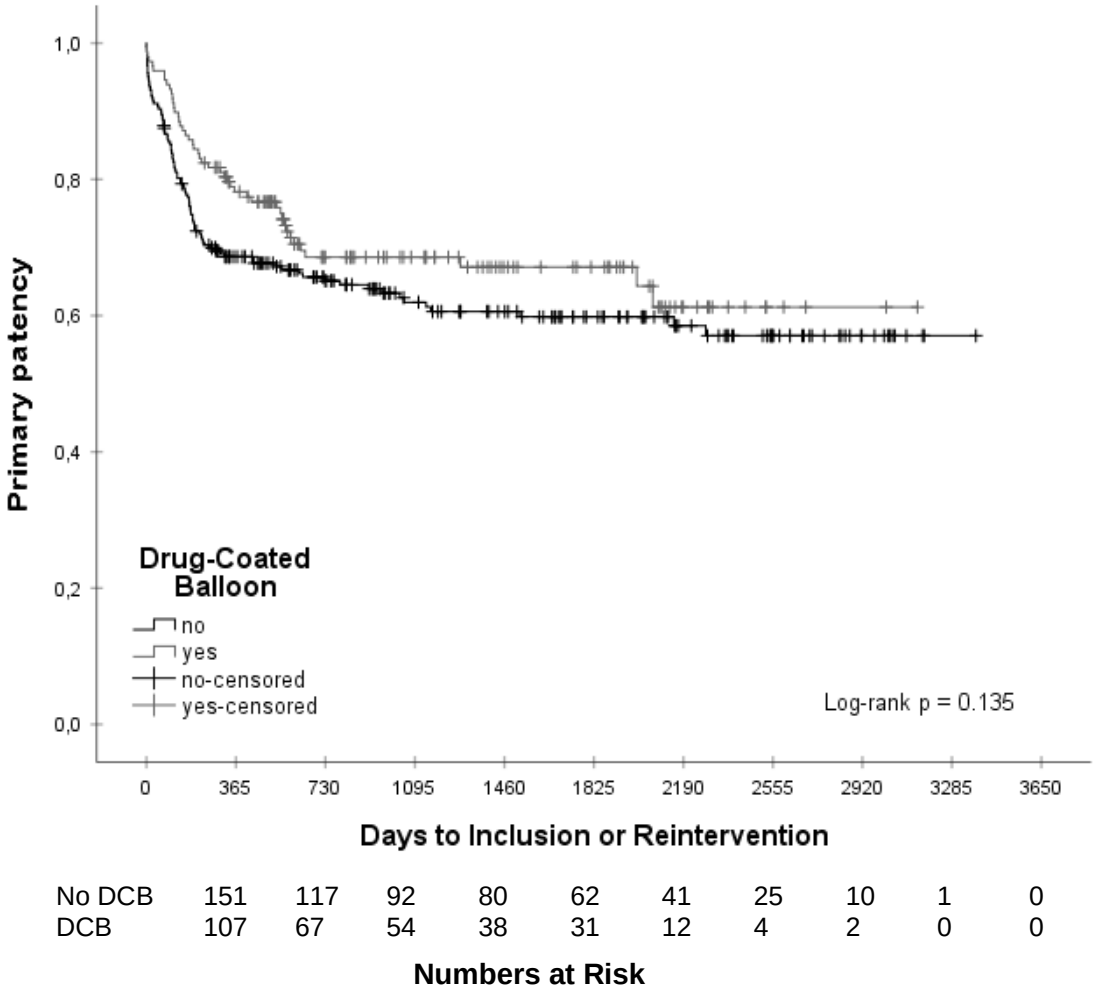
Figure 17: **Kaplan-Meier Survival Curve for Primary Patency of the Rotarex®S Catheter Size Groups and Numbers at Risk.**
Primary patency is the time from intervention to first reintervention to maintain or reestablish patency.
Own illustration.

Using Kaplan-Meier survival analysis, we analyzed the influence of the application of DCB to the patency (n = 396) (Table 18, Figure 18). Same obligations apply as for the Kaplan-Meier analysis according to the occlusion ages.

Visually, it seems like the application of a DCB leads to a better patency, but Log-rank test reaches no significancy (p = 0.135) (Artzner *et al.*, 2022). In total, patients treated with DCB received reintervention in 31.1%, while patients treated without DCB received reintervention in 37.9%.

Table 18: Short-Term Patency for the Adjunctive Treatment with Drug-Coated Balloon the First Year After Intervention.
Adapted from Artzner et al. (2022), © Thieme.

Time	DCB	No DCB
1 Month	0.959	0.911
3 Months	0.939	0.855
6 Months	0.858	0.753
1 Year	0.782	0.686



No DCB	151	117	92	80	62	41	25	10	1	0
DCB	107	67	54	38	31	12	4	2	0	0

Numbers at Risk

Figure 18: Kaplan-Meier Survival Curve for Primary Patency of Adjunctive Treatment with Drug-Coated Balloon Groups and Numbers at Risk.
Primary patency is the time from intervention to first reintervention to maintain or reestablish patency.
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3.6 Complications

In total, we registered 183 adverse events in the final study cohort (46.1%) (Artzner *et al.*, 2022). These divide into distal embolization and other complications.

Distal embolization, as an important safety aspect of RT, is analyzed separately from the other complications. We monitored distal embolization in 89 / 397 (22.4%) interventions (Artzner *et al.*, 2022). The severity was registered for 86 cases of distal embolization: In 58 / 86 events (67.4%), periinterventional aspiration thrombectomy or subsequent thrombolysis was needed. In 24 / 86

(27.9%) interventions, distal embolization was counteracted with heparin in therapeutic dose over 48 hours. Four events (4.7%) of distal embolization had no therapeutic consequence.

We monitored 94 other complications in 87 / 397 (21.9%) interventions. Most frequently, dissections appeared (n = 41 / 397; 10.3%), followed by perforations (n = 17 / 397; 4.3%). Other complications were arteriovenous fistula (n = 7 / 397; 1.8%), compartment syndrome associated with the intervention (n = 7 / 397; 1.8%), secondary hemorrhage at the puncture site (n = 5 / 397; 1.3%), fracture of the guidewire (n = 2 / 397; 0.5%), and strong pain (n = 1 / 397; 0.3%).

In total, there were 11 / 397 (2.8%) events in the miscellaneous group: Stent compression attributed to the Rotarex®S catheter (n = 1), proximal dislocation of thrombotic material to the deep femoral artery attributed to RT (n = 1), increasing thrombus load after intervention (n = 1), cardiovascular instability (n = 2), wide complex tachycardia (n = 1), reperfusion edema without compartment syndrome and need for transfusion of erythrocytes after thrombolysis (n = 1), failure of percutaneous closure device Angio-Seal® with occlusion of common femoral artery (n = 1), and intracranial hemorrhage during thrombolysis (n = 3). Most of these complications are not directly attributed to RT (Table 19).

We monitored 3 deaths during the hospital stay. Two patients died due to intracranial hemorrhage during thrombolysis and one patient died due to acute limb ischemia with no achieved revascularization after thoracic trauma (n = 3 / 397; 0.8%).

We identified three causes for complications. The study device, other used devices, and the underlying disease. Complications were seen after Rotarex®S Catheter in 28 cases (n = 28 / 397; 7.1%) (Artzner *et al.*, 2022), and after adjuvant therapy like POBA, DCB, stenting or thrombolysis in 44 cases (n = 44 / 397; 11.1%). Complications like compartment syndrome and secondary hemorrhage were classified as due to the underlying disease (n = 18 / 397; 4.5%). Table 19 gives a detailed overview of the connection between complication category and cause.

Table 19: Complication by Causing Treatment in Absolute Number n and Percentage (%) of Final Study Cohort (n = 397).
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Complication category	Rotarex®S catheter n (%)	Adjuvant therapy n (%)	Underlying disease n (%)	Unknown n (%)	Total
Dissection	8 (2.0)	30 (7.6)	0 (0)	3 (0.8)	41 (10.3)
Perforation	11 (2.8)	6 (1.5)	0 (0)	0 (0)	17 (4.3)
Pain	0 (0)	1 (0.3)	0 (0)	0 (0)	1 (0.3)
Arteriovenous Fistula	5 (1.3)	1 (0.3)	0 (0)	1 (0.3)	7 (1.8)
Guidewire Fracture	2 (0.5)	0 (0)	0 (0)	0 (0)	2 (0.5)
Compartment Syndrome	0 (0)	0 (0)	7 (1.8)	0 (0)	7 (1.8)
Miscellaneous	2 (0.5)	4 (1.0)	5 (1.3)	0 (0)	11 (2.8)
Secondary Hemorrhage	0 (0)	0 (0)	5 (1.3)	0 (0)	5 (1.3)
Death during hospital stay	0 (0)	2 (0.5)	1 (0.3)	0 (0)	3 (0.8)
Total	28 (7.1)	44 (11.1)	18 (4.5)	4 (1.0)	94 (23.7)

To classify the severity of complications, the CIRSE classification system was used (Table 3 and Table 21). Most complications were fully treatable during the intervention, so CIRSE grade 1 was most common (n = 71 / 94; 75.5%). Severe complications of CIRSE grade 5 (complication causing permanent severe sequelae) and CIRSE grade 6 (death), only appeared for seven patients (Artzner *et al.*, 2022). These severe cases are described in the following.

1. CIRSE 5: One patient (ID 42) with suspected dilated cardiomyopathy presented with multiple embolies causing CLI of the right leg. The patient received treatment with RT and catheter-directed thrombolysis (23.5h) on two consecutive days, but large amount of thrombus reoccurred on the

second day. During the hospital stay, reocclusion occurred and the patient developed compartment syndrome. Amputation was performed 16 days after the last treatment with RT. This course of events is considered due to the underlying critical disease of the patient.

2. CIRSE 5: One patient (ID 137) received additional thrombolysis after Rotarex®S catheter treatment. The patient developed intercranial hemorrhage during thrombolysis (Artzner *et al.*, 2022). The patient received lower leg amputation 14 days later.
3. CIRSE 5: One patient (ID 147) with status post abdominal surgery two days prior to the intervention presented with CLI due to occlusion of PA 3, TTF and POTA. After application of Rotarex®S catheter, the angiogram showed an AV-fistula and a significant amount of residual thrombus. Due to the status post-surgery, thrombolysis was contraindicated. The patient underwent amputation of the thigh 14 days later.
4. CIRSE 5: One patient (ID 251) with thromboangitis obliterans presented with acute long occlusion of SFA and PA. Debulking with RT was incomplete, so the patient received additional thrombolysis. During this, the patient developed compartment syndrome requiring surgery and rhabdomyolysis causing acute renal damage.
5. CIRSE 6: One patient (ID 87) received treatment for an acute SFA occlusion after a road accident, causing thorax trauma with covered rupture of the thoracic aorta. In addition, status post-hemihepatectomy contraindicated for thrombolysis. It was not possible to achieve revascularization during the intervention, so the patient received argatroban via syringe pump. The treatment was not successful, and the patient died three days later.
6. CIRSE 5 and 6: One patient (ID 211) received treatment with the Rotarex®S catheter for acute, complex TASC D occlusion of the AIE, SFA and PA including segment 3. Revascularization was not achieved with the Rotarex®S catheter and POBA, so treatment was followed up with thrombolysis. During thrombolysis, the patient developed intracranial

hemorrhage with intracranial pressure symptoms and died two days later (Artzner *et al.*, 2022). Two complications were registered.

7. CIRSE 5 and 6: One patient (ID 227) received treatment of chronic bypass occlusion. The 6F Rotarex®S catheter left significant amount of thrombus, so thrombolysis was followed. The patient developed intracranial hemorrhage and died (Artzner *et al.*, 2022).

Table 20: CIRSE Classification Distribution in Absolute Number n and Percentage (%).
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CIRSE	n / 94 (%)
1	71 (75.5)
2	1 (1.1)
3	12 (12.8)
4	1 (1.1)
5	6 (6.4)
6	3 (3.2)

The treatment of complications was available for 87 cases and is shown in Table 20. More than half of these treatments were interventional methods. Other methods were administration of circulation-affecting medication, transfusion of erythrocyte concentrate, conservative hemostasis methods, hemostasis pad and snare maneuver to retrieve cut guidewire (n = 2). No treatment was either due to no need or no option.

Table 21: **Treatment of Complications in Absolute Number n and Percentage (%) of Complication Treatments.**
Abbreviation: POBA, plain-old balloon angioplasty.

Treatment	n / 87 (%)
GORE® VIABAHN® Endoprosthesis / covered stent-graft	17 (19.5)
Rotarex®S Catheter	2 (2.3)
POBA	9 (10.3)
Stent (drug-eluting or bare-metal)	17 (19.5)
Thrombolysis	1 (1.1)
Surgery	7 (8.0)
Several	10 (11.5)
Other	9 (10.3)
No Treatment	15 (17.5)

3.7 Subcohort Comparison to Outcome Parameters with Chi-Square Tests

3.7.1 Iliac Arteries vs Lower Limb Arteries

Chi-square tests were conducted to compare interventions of solely iliac arteries to solely lower limb arteries regarding different outcome variables. Therefore, cases with interventions of combined lesions including iliac and lower limb arteries (n = 20) had to be excluded beforehand. The significant chi-square tests are shown in Table 22. The other tests conducted which did not reach significance are to be found in the appendix.

Among others, the chi-square test was used to compare iliac arteries and lower limb arteries regarding the aspect *Complication attributed to Rotarex®S (vs other device vs no complication)*. Two expected cell frequencies were below five. Results show significance between iliac arteries and *Complication attributed to Rotarex®S (vs other vs no)*, $\chi^2(2) = 7.365$, $p = 0.025$, Cramér's V = 0.140, Monte-Carlo-Significance $p = 0.022$ (Artzner *et al.*, 2022). There were more

complications attributed to Rotarex®S catheter when treatment was necessary in iliac arteries than in lower limb arteries (Artzner *et al.*, 2022).

Also, a chi-square test was conducted to compare iliac arteries and lower limb arteries regarding the aspect *Perforation attributed to Rotarex®S*. One expected cell frequency was below five. Results show significance between iliac arteries and *Perforation attributed to Rotarex®S*, $\chi^2(1) = 7.613$, Fisher (2-sided): $p = 0.031$, $\varphi = -0.142$. This shows that significantly more perforations attributed to RT happened in iliac arteries.

Table 22: **Chi-Square Tests of Iliac Arteries vs Lower Limb Arteries.**
Iliac arteries (n = 28; Group 1), lower limb arteries (n = 349; Group 2).
Abbreviation: MC, Monte-Carlo-Significance.

Aspect	**n Group 1**	**% Group 1**	**n Group 2**	**% Group 2**	**Chi-square test**	**Expected cell frequencies below five**
Complication attributed to Rotarex®S (vs other vs no)	4	14.3	21	6.0	$\chi^2(2) = 7.365$ $p = 0.025$ Cramér's V = 0.140 MC $p = 0.022$	2
Perforation attributed to Rotarex®S	3	10.7	7	2.0	$\chi^2(1) = 7.613$ $p = 0.006$ $\varphi = -0.142$ Fisher (2-sided): $p = 0.031$	1

3.7.2 Bypass Grafts vs Native Vessels

Chi-square tests were used to compare treatment of bypass grafts and native vessels (with or without preexisting stent) regarding different outcome variables.

The first aspect was *technical success (revascularization)*. No expected cell frequency was below five. The chi-square test shows a significant difference between the bypass graft group (78% technical success) and the native vessel group (93.2% technical success), $\chi^2(1) = 14.129$, $p < 0.001$, $\varphi = -0.189$.

A chi-square test was used to compare treatment of bypass grafts and native vessels regarding *not fully treatable* lesions. No expected cell frequency was below five. Results showed a significant difference between treatment of bypass grafts and native vessels regarding *not fully treatable* lesions, $\chi^2(1) = 31.900$, $p < 0.001$, $\varphi = 0.283$. Bypass grafts were less often fully treatable.

Consequently, the chi-square test comparing treatment of bypass grafts and native vessels regarding *additional catheter-directed thrombolysis after Rotarex®S Catheter* showed significance, $\chi^2(1) = 38.105$, $p < 0.001$, $\varphi = 0.310$ (Artzner *et al.*, 2022). No expected cell frequency was below five.

Also, a chi-square test was used to compare treatment of bypass grafts and native vessels regarding *freedom of target vessel revascularization 30 days after the index procedure*. One expected cell frequency was below five. Results showed a significant difference, $\chi^2(1) = 7.307$, Fisher (2-sided): $p = 0.016$, $\varphi = -0.137$. Native vessels showed the better patency in the first 30 days after intervention.

There was no significant difference calculated regarding the appearance of *perforation attributed to RT* between the bypass graft and the native vessel group, $\chi^2(1) = 1.975$, Fisher (2-sided): $p = 0.381$, $\varphi = -0.071$. One expected cell frequency was below five. But it should be noted: All 11 perforations after Rotarex®S catheter happened in native vessels.

These chi-square tests are shown in Table 23. The other tests conducted which did not reach significance are to be found in the appendix.

Table 23: **Chi-Square Tests of Bypass Graft vs Native Vessel.**
Bypass graft (n = 59, Group 1), native vessel (n = 338, Group 2).
Abbreviation: TL, target lesion.

Aspect	n Group 1	% Group 1	n Group 2	% Group 2	Chi-square test	Expected cell frequencies below five
Technical success (revasculari-zation)	46	78.0	315	93.2	$\chi^2(1) = 14.129$ $p < 0.001$ $\varphi = - 0.189$	0
Not fully treatable	41	69.5	105	31.1	$\chi^2(1) = 31.900$ $p < 0.001$ $\varphi = 0.283$	0
Additional catheter-directed thrombolysis after Rotarex®S	33	55.9	63	18.6	$\chi^2(1) = 38.105$ $p < 0.001$ $\varphi = 0.310$	0
Freedom of TL revasculari-zation 30 days after index procedure	46	82.1	308	93.1	$\chi^2(1) = 7.307$ $p = 0.007$ $\varphi = - 0.137$ Fisher (2-sided): $p = 0.016$	1
Perforation attributed to Rotarex®S	0	0.0	11	3.3	$\chi^2(1) = 1.975$ $p = 0.160$ $\varphi = - 0.071$ Fisher (2-sided): $p = 0.381$	1

3.7.3 Calcified Vessels vs Non-Calcified Vessels

We calculated chi-square tests to compare interventions of calcified and non-calcified vessels regarding different outcome variables.

Among others, we compared calcified and non-calcified vessels regarding the aspect *not fully treatable*. No expected cell frequency was below five. Results showed a significant difference, $\chi^2(1) = 4.775$, $p = 0.029$, $\varphi = -0.157$. Non-calcified vessels were more often not fully treatable.

The chi-square test also showed significant difference between calcified and non-calcified vessels regarding *additional catheter-directed thrombolysis after Rotarex®S catheter*, $\chi^2(1) = 5.182$, $p = 0.023$, $\varphi = -0.163$. No expected cell frequency was below five. In consequence, non-calcified vessels needed thrombolysis more often.

Also using the chi-square test, we found significantly more *distal embolization* after application of Rotarex®S catheter in non-calcified vessels than in calcified vessels (36.4% vs 18.7%), $\chi^2(1) = 6.076$, $p = 0.014$, $\varphi = -0.177$.

There is no chi-square test regarding the *perforation attributed to Rotarex®S catheter* because the available data only includes cases with calcification (n = 7) and data for the calcification status of the other cases of perforation after Rotarex®S catheter (n = 4) was missing.

These chi-square tests are shown in Table 24. The other tests conducted which did not reach significance are to be found in the appendix.

Table 24: **Chi-Square Tests of Calcified Vessel vs Non-Calcified Vessel.**
Calcified vessel (n = 150, group 1), non-calcified vessel (n = 44, group 2).

Aspect	n Group 1	% Group 1	n Group 2	% Group 2	Chi-square test	Expected cell frequencies below five
Not fully treatable	64	42.7	27	61.4	$\chi^2(1) = 4.775$ $p = 0.029$ $\varphi = - 0.157$	0
Additional catheter-directed thrombolysis after Rotarex®S	41	27.3	20	45.5	$\chi^2(1) = 5.182$ $p = 0.023$ $\varphi = - 0.163$	0
Distal embolization	28	18.7	16	36.4	$\chi^2(1) = 6.076$ $p = 0.014$ $\varphi = - 0.177$	0

3.7.4 Size 6 French vs Size 8 French Rotarex®S Catheter

Chi-square tests were conducted to compare interventions using the 6F Rotarex®S catheter and the 8F Rotarex®S catheter regarding different outcome variables.

Using the chi-square test, we compared the sizes of the Rotarex®S catheter regarding the administration of *additional thrombolysis after Rotarex®S catheter* treatment. No expected cell frequency was below five. Results showed a significant difference between the sizes of the Rotarex®S catheter and the administration of additional thrombolysis, $\chi^2(1) = 5.796$, $p = 0.016$, $\varphi = - 0.121$. Thrombolysis was more often administered after treatment with the 6F Rotarex®S catheter.

A chi-square test was used to compare the sizes of the Rotarex®S catheter and the occurrence of *complication attributed to RT.* Two expected cell frequencies were below five. Results showed a significance for the size of Rotarex®S catheter and the occurrence of complication attributed to the treatment with Rotarex®S

catheter, $\chi^2(1) = 12.788$, $p = 0.002$, Cramér's $V = 0.180$. The 8F Rotarex®S catheter was related to more complications (Artzner *et al.*, 2022).

The chi-square test also showed a significant relationship between the size of Rotarex®S catheter and the occurrence of *perforation* attributed to the treatment with Rotarex®S catheter, $\chi^2(1) = 12.768$, $p < 0.001$, $\varphi = 0.180$. The 8F Rotarex®S catheter was connected to more perforations. One expected cell frequency was below five.

These chi-square tests are shown in Table 25. The other tests conducted which did not reach significance are to be found in the appendix.

Table 25: **Chi-Square Tests of Size 6 French vs Size 8 French Rotarex®S Catheter.** Size 6 French (n = 365, Group 1), size 8 French (n = 31, Group 2) Rotarex®S. **Abbreviation:** MC, Monte-Carlo-Significance.

Aspect	n Group 1	% Group 1	n Group 2	% Group 2	Chi-square test	Expected cell frequencies below five
Additional catheter-directed thrombolysis after Rotarex®S	94	25.8	2	6.5	$\chi^2(1) = 5.796$ p = 0.016 φ = - 0.121	0
Complication attributed to Rotarex®S (vs other vs no)	21	5.8	6	19.4	$\chi^2(2) = 12.788$ p = 0.002 Cramér's V = 0.180 MC p = 0.004	2
Complication attributed to Rotarex®S (vs other/no)	21	5.8	6	19.4	$\chi^2(1) = 8.320$ p = 0.004 φ = 0.145 Fisher (2-sided): p = 0.013	1
Perforation attributed to Rotarex®S	7	1.9	4	12.9	$\chi^2(1) = 12.768$ p < 0.001 φ = 0,180 Fisher (2-sided): p = 0.007	1

3.7.5 Comparison of the Different Locations of Target Lesions

Chi-square tests were used to compare treatment of different locations of the target lesion in the arterial system regarding different outcome variables.

A chi-square test was used to compare the location of target lesion and *clinical success*. Results showed significance, $\chi^2(4) = 16.518$, p = 0.002, Cramér's V = 0.204. The Bonferroni post hoc test showed significantly less *clinical success* occurrences if the target lesion incorporates both iliac arteries

and arteries of the leg (13 vs 18 expected). This comparison was responsible for the significance.

There was a significant relationship between the location of the target lesion and a *not fully treatable* lesion, $\chi^2(4) = 29.514$, $p < 0.001$, Cramér's V = 0.273. The Bonferroni post hoc test showed significantly less not fully treatable lesions in the upper leg (thigh) (62 vs 87 expected) and significant more not fully treatable lesions in combined lesions of thigh and lower leg (57 vs 39 expected).

The chi-square test was used to compare the location of target lesion and the occurrence of *complications attributed to Rotarex®S catheter vs complications attributed to other adjunctive treatment vs no complication*. Results showed significance, $\chi^2(4) = 19.106$, $p = 0.014$, Cramér's V = 0.155. The Bonferroni post hoc test showed that significantly less complications occurred attributed to the Rotarex®S catheter if treatment was located in the thigh (8 vs 16 expected). This comparison is responsible for the significance. The comparison for *complications attributed to Rotarex®S catheter vs other and no complication* showed the same result.

The chi-square test comparing location of target lesion and CIRSE class also showed significance, but 22 cells have an expected count below five. Thus, a Monte-Carlo-Test was followed, missing significance ($p = 0.052$).

These chi-square tests are shown in Table 26. The other tests conducted which did not reach significance are to be found in the appendix.

Table 26: Comparison of Location of Target Lesion Regarding Outcome Variables with Chi-Square Tests.
Location of target lesion (n = 397).

Aspect	Chi-square test	Expected cell frequencies below five	Monte-Carlo-Significance (2-sided)
Clinical success	$\chi^2(4) = 16.518$ $p = 0.002$ Cramér's V = 0.204	3	$p = 0.004$
Not fully treatable	$\chi^2(4) = 29.514$ $p < 0.001$ Cramér's V = 0.273	2	$p < 0.001$
Complication attributed to Rotarex®S (vs other vs no)	$\chi^2(4) = 19.106$ $p = 0.014$ Cramér's V = 0.155	7	$p = 0.021$
Complication attributed to Rotarex®S (vs other/no)	$\chi^2(4) = 11.340$ $p = 0.023$ Cramér's V = 0.169	3	$p = 0.028$
CIRSE	$\chi^2(16) = 36.852$ $p = 0.002$ Cramér's V = 0.325	22	$p = 0.052$

3.7.6 Comparison of the Occlusion Ages

We conducted chi-square tests to compare treatment of different occlusion ages (acute, subacute, chronic) regarding different outcome variables.

A chi-square test showed significant difference between the occlusion age and *clinical success*, $\chi^2(2) = 22.838$, $p < 0.001$, Cramér's V = 0.244. No expected cell frequency was below five. The Bonferroni post hoc test showed: Significantly less acute occlusions achieved clinical success (152 vs 165 expected) and significantly more subacute occlusions showed clinical success (84 vs 77 expected). These sub-comparisons were responsible for the significance of the chi-square test.

The chi-square test showed significant difference between the occlusion age and the aspect *not fully treatable*, $\chi^2(4) = 20.782$, $p < 0.001$, Cramér's V = 0.233. No expected cell frequency was below five. The Bonferroni post hoc test showed that

significantly more acute occlusions were not fully treatable (85 vs 66 expected) and significantly less chronic occlusions were not fully treatable (24 vs 42 expected). These sub-comparisons were responsible for the significance of the chi-square test.

Chi-square test also showed significant relationship of the occlusion age and *additional catheter-directed thrombolysis after Rotarex®S catheter*, $\chi^2(2) = 34.118$, $p < 0.001$, Cramér's V = 0.298. No expected cell frequency was below five. The Bonferroni post hoc test showed that significantly more acute occlusions were accompanied with catheter-directed thrombolysis (69 vs 45 expected) and significantly less chronic occlusions were treated with additional catheter-directed thrombolysis (12 vs 28 expected). These sub-comparisons were responsible for the significance of the chi-square test.

A chi-square test showed significant difference between the occlusion age and *freedom of target vessel revascularization in the first 30 days after the index procedure*, $\chi^2(2) = 11.357$, $p = 0.003$, Cramér's V = 0.174. No expected cell frequency was below five. The Bonferroni post hoc test showed that significantly less acute occlusions are free of target lesion revascularization in the first 30 days after the index procedure (155 vs 163 expected). This comparison was responsible for the significance of the chi-square test.

These chi-square tests are shown in Table 27. The other tests conducted which did not reach significance are to be found in the appendix.

Table 27: Comparison of Occlusion Ages Regarding Outcome Variables with Chi-Square Tests.
Occlusion ages (n = 383)
Abbreviation: TL, target lesion.

Aspect	Chi-square test	Expected cell frequencies below five
Clinical success	$\chi^2(2) = 22.838$ $p < 0.001$ Cramér's V = 0.244	0
Not fully treatable	$\chi^2(4) = 20.782$ $p < 0.001$ Cramér's V = 0.233	0
Additional catheter-directed thrombolysis after Rotarex®S	$\chi^2(2) = 34.118$ $p < 0.001$ Cramér's V = 0.298	0
Freedom of TL Revascularization 30 days after index procedure	$\chi^2(2) = 11.357$ $p = 0.003$ Cramér's V = 0.174	0

3.7.7 Comparison of Distal Embolization Regarding Adjunctive Therapy

To get insights on which adjunctive treatment after application of Rotarex®S catheter bears an increased risk of distal embolization, chi-square tests were conducted. There is no significant relationship between the adjunctive treatment after the Rotarex®S catheter and occurrence of distal embolization, as shown in Table 28.

Table 28: **Chi-Square Tests of No Distal Embolization vs Distal Embolization.**
No distal embolization (n = 308, Group 1), distal embolization (n = 89, Group 2).
Abbreviations: DCB, drug-coated balloon; POBA, plain-old balloon angioplasty.

Aspect	n Group 1	% Group 1	n Group 2	% Group 2	Chi-square test	Expected cell frequencies below five
POBA	203	65.9	67	75.3	$\chi^2(1) = 2.787$ $p = 0.095$ $\varphi = 0.084$	0
DCB	117	38.0	32	36.0	$\chi^2(1) = 0.122$ $p = 0.727$ $\varphi = - 0.018$	0
POBA + DCB	67	21.8	20	22.5	$\chi^2(1) = 0.021$ $p = 0.885$ $\varphi = 0.007$	0
Stenting	128	41.6	35	39.3	$\chi^2(1) = 0.142$ $p = 0.706$ $\varphi = - 0.019$	0

4 Discussion

4.1 Summary of the Results

In summary, the presented study cohort of 397 interventions of 293 individuals is composed of patients with almost half acute and almost one third with chronic occlusion (Artzner *et al.*, 2022). Respectively, the Rutherford categories reflected CLI for over 60% of patients (Artzner *et al.*, 2022). Patients expressed a high prevalence of cardiovascular risk factors, especially arterial hypertension and nicotine abuse.

The procedure was usually performed with a 6F Rotarex®S catheter in cross-over or antegrade technique. Residual stenosis after Rotarex®S catheter was highly prevalent and was treated with either POBA and/or DCB and/or stenting. One third of patients was not fully treatable, and one third of patients received additional thrombolysis. Treated lesions were mainly complex TASC C and D lesions with more than 20 cm length (Artzner *et al.*, 2022) and mainly diameter of 5 mm or 6 mm. Also, 14.9% in this study collective were bypass occlusions. Predominantly, the femoral region was targeted, but iliac and crural arteries were also treated if needed and feasible. Three quarters of lesions showed calcification. This represents the clinical routine at the Tübingen University Hospital.

The technical success rate was high with 100% success of passing the occlusion with a guidewire and an achieved revascularization in 91%. Material failure was documented in seven (1.8%) applications of the Rotarex®S catheter, but information is too incomplete to deduce causality.

We monitored 183 adverse events (Artzner *et al.*, 2022). There were 89 cases (22.4%) of distal embolization, which in two thirds needed intense treatment (Artzner *et al.*, 2022). Other complications were observed in 87 interventions (22%). Among those were 41 dissections and 17 perforations, including 11 perforations after Rotarex®S catheter. The complications were only CIRSE grade 1 in 75%, so fully treatable during the intervention and with no sequelae.

Unfortunately, seven patients suffered from severe complications with CIRSE classes 5 and 6. None of these events were directly device-related, but either associated with thrombolysis or a severe preexisting medical condition.

Clinical success was accomplished for 90% of procedure. The ABI, as a representative of the perfusion status, was significantly higher after treatment (Artzner *et al.*, 2022). Anamnestic walking distance less than 200 m significantly decreased from 94% before to 23% of patients after treatment (Artzner *et al.*, 2022). More than one third of patients underwent reintervention in the study period, 8.5% within the first 30 days after the Rotarex®S procedure (Artzner *et al.*, 2022). Subacute and acute occlusion ages seem to have better long-term results than treatment of chronic occlusion age without reaching significance. Procedures with the 8F Rotarex®S catheter and procedures with DCB seem to have better patency, but data did not reach significance.

Furthermore, our data lead to the following insights: Native vessels had better results for freedom of target lesion revascularization the first 30 days after the procedure than bypass grafts. The treatment of the thigh with RT is often successful and shows little complication. Complex lesions incorporating iliac and leg arteries were more often not fully treatable and therefore achieved significantly less clinical success.

Significantly often, not fully treatable lesions were non-calcified vessels and bypass grafts. Bypass grafts achieved less often revascularization (technical success). So, additional catheter-directed thrombolysis was more frequently done for bypass grafts and for non-calcified vessels (Artzner *et al.*, 2022). Also, additional thrombolysis was more often done for lesions treated with the 6F Rotarex®S catheter.

The treatment of subacute occlusion age achieved good results regarding clinical success. Chronic occlusions were less often not fully treatable, so they needed less subsequent catheter-directed thrombolysis.
However, acute occlusion age was associated with more not fully treatable lesions, and so they showed less clinical success and needed subsequent catheter-directed thrombolysis more often. Acute occlusion age achieved less

freedom of target lesion revascularization in the first 30 days after the RT procedure.

Complications, especially perforation, were seen more often in iliac arteries and if an 8F Rotarex®S catheter was used. Non calcified lesions were associated with significantly more distal embolization.

4.2 Study Design

This study has a retrospective observational approach and analyses data generated at the Tübingen University Hospital as a single center non-randomized cohort. All individuals received treatment either solely or additionally with RT. The time span included reflects almost the whole period since RT was first established at the Tübingen University Hospital. Patients were only excluded if RT was not applied in the infrarenal arteries or if adequate clinical information was missing.

The parameters used for assessing the clinical status prior to intervention and the outcome parameters (ABI, walking distance, Rutherford classification) are the established scales to evaluate peripheral artery disease (Sacks *et al.*, 1997) and are used in comparable studies (Freitas *et al.*, 2017);(Kronlage *et al.*, 2017); (Liao *et al.*, 2019).

4.3 Patients

The presented study is characterized by a minimally filtered patient collective that represents the contemporary treatment at the Tübingen University Hospital. The data regarding age, sex, frequency of cardiovascular risk factors and share in CLI (53.7%) is comparable to other studies: Loffroy et al. (2020a) analyzed the application of the Rotarex®S catheter in in-stent restenosis or occlusion. Their study cohort had a share of CLI of 51.5%.

However, our study possibly underestimates the share of critical low perfusion status. In our study, most patients had peripheral vascular disease, but some patients presented with acute limb ischemia due to non-atherosclerotic reasons. The share of CLI in our study is deducted from the Fontaine stage, so patients

without PAD, who therefore did not count into the Fontaine stage parameter, also might have had a tissue-threatening low perfusion status in the limb.

Research in RT for treatment of PAD is limited, because so far, RT had only been examined for specific subcohorts of patients (Artzner *et al.*, 2022). Either studies were focused on a vessel type, e.g., de-novo or in-stent lesions or bypass grafts, or focused on a location, e.g., iliac or femoropopliteal lesions, or a particular occlusion age. For example, Freitas et al. (2017) conducted a single-center, retrospective analysis of the Rotarex®S catheter in a comparable large sample size, but excluded in-stent lesions, chronic occlusion age and bypass occlusion. Recent studies by Bulvas et al. (2019) and Stanek et al. (2016) excluded the chronic occlusion age. Therefore, it is difficult to compare our collective, even though it represents the clinical routine. There is only one study which analyzed a comparable mixed cohort of infrarenal, bypass, native, and in-stent and of every occlusion age by Laganà et al. (2011), but the sample size of 22 patients was small (cf. p. 84) (Artzner *et al.*, 2022).

What makes our study stand out is a large patient collective with every kind of vessel type. Moreover, we included every occlusion age with about 30% of patients with chronic occlusion age. The broad clinical data makes this study rare and needs to be considered when comparing it to other studies. However, the presented study underachieved in determining the results for certain subcohorts. The below-the-knee treatments or the 8F Rotarex®S catheter results are only of exploratory value due to small sample sizes.

4.4 Procedure and Adjunctive Therapy

The intervention examined is the (sole or additional) use of RT in the standard procedure performed in the clinical routine of treatment of peripheral artery disease at the Interventional Radiology Department of the Tübingen University Hospital. The standard procedure follows the common practice of interventions under x-ray control, gaining access to the vessel, placing a guidewire, and then advancing different devices to achieve vascular reperfusion. During the

procedure, low-molecular-weight heparin is administered and after the procedure, patients without contraindication receive ASA and clopidogrel.

More than half of the documented procedures were performed with the cross-over approach. Earlier, the cross-over access was limited by the only available catheter length being too short for complete debulking (Lichtenberg, 2010). In our study, the longer 110 cm Rotarex®S catheter system was available. In consequence, it was possible to include the treatment of the iliac arteries and therefore get insights into the prospects and limitations of such treatment.

Remarkably, six out of seven cases of material failure happened during a cross-over approach. The target lesions of these treatments were in-stent femoropopliteal lesions (n = 6) and one femoropopliteal bypass. Lichtenberg et al. (2013b) have recommended wire-reinforced cross-over sheaths for the cross-over approach to prevent breakage of the catheter. These reinforced sheaths are typically used for the cross-over approach in our study. However, breakage of the helix was only reported in one case. The other times, the device did not create any flow, cut the guidewire or the defect was not further explained. There is a comparable case of a cut guidewire reported by Han et al. (2021), where the Rotarex®S guidewire tip coiled and could not have been removed. Eventually, they were able to retrieve the wire using the snare maneuver. Unfortunately, there is no reporting about how other interventionists avoid material failure, e.g., using a reinforced sheath. Still, regarding the safety of RT it is necessary to emphasize that the events in our study were solved periinterventional and none of these events endangered the patient.

The preferred size of the Rotarex®S catheter was the 6F system in over 90% in our study. The median vessel diameter was 6 mm. The instructions for use suggest the 8F system for vessel diameters between 5 mm and 8 mm. In conclusion, it may be possible to lower the count of *not fully treatable* lesions (36.8% in this study), hence the amount of additional catheter-directed thrombolysis in our analysis by using the larger catheter (Artzner *et al.*, 2022). Especially patients with lysis contraindication or high risk for hemorrhage might benefit from a generous use of the 8F catheter if a higher local risk of perforation

is acceptable. The Kaplan-Meier analysis indicated that a more frequent use of the 8F Rotarex®S catheter could be beneficial for the long-term patency, too.

Residual stenosis persisted in 89.5% of our interventions (Artzner *et al.*, 2022). A study of Scheer et al. (2015) investigated the treatment with the Rotarex®S catheter of acute, subacute and chronic occlusions of SFA and/or popliteal arteries. The authors had comparable results (89.7%) after application of Rotarex®S catheter plus PTA. Stahlberg et al. (2021) explained their residual stenosis rate of 82% for the treatment of acute and subacute occlusions due to the high percentage (in total 77%) of moderate and severe calcifications in their study cohort. In comparison, the share of moderate and severe calcification is 48% in our study, so our data does not support the theory of Stahlberg et al. (2021).

In consequence, adjuvant therapy completed the RT procedure regularly. Predominantly, the interventionists used POBA (68%), followed by DCB (37.5%), a combination of POBA and DCB (21.9%) and/or stenting (41.1%) (Artzner *et al.*, 2022). Adjuvant therapy with PTA, DCB and stenting is also reported very frequently throughout literature, as Lichtenberg (2010) observed in an overview article.

A study of Laganà et al. (2011) is the most comparable to our study regarding a broad spectrum of target lesion types but limited due to a small number of patients. The authors registered no additional need for adjunctive therapy for the acute occlusions of native iliac arteries. But for the subacute and chronic lesions of bypass grafts, stents, and stents grafts, POBA was needed in 36.4%, cutting balloon in 27.3% and stenting in 22.8% of procedures.

A recent study by Loffroy et al. (2020a) examined the Rotarex®S catheter in in-stent restenosis or occlusion, iliac and infrainguinal arteries and with any occlusion age. They observed additional POBA in 74.2%, drug-coated balloon in 12.5%, both 10.2% and stent-in-stent implantation in 66.4% of a total of 128 patients. The high amount of stent implantation and lower amount of drug-coated balloon may be because the authors examined exclusively patients with in-stent restenosis.

Overall, our numbers of adjunctive therapy seem reasonable, even though the

comparability is limited. The high amount of adjunctive therapy shows that RT can rarely serve as a single method of revascularization. Nevertheless, RT can serve as an important element of the revascularization strategy.

To get insights on which combination with adjunctive therapy bears the least risk of distal embolization, we compared the adjunctive methods to the distal embolization status using the chi-square test. This is only of exploratory value because it purely reflects correlations instead of causality. There was no significant relationship detectable. Therefore, our results do not contradict the results of Latacz et al. (2019), Liao et al. (2019) and Wang et al. (2020), who showed that DCB is a safe and feasible combination with mechanical thrombectomy.

Additional catheter-directed thrombolysis was conducted in one third of patients, which appears higher than in previous studies (Artzner *et al.*, 2022). A share of 58% followed RT, 20% took place both before and after the index procedure, 9% solely before, and 13% of periinterventional administration. Freitas et al. (2017) analyzed 525 patients with acute and subacute de novo, post-angioplasty and/or post-atherectomy femoropopliteal lesions. Their patients received additional thrombolysis in 13.9%, but it seems like they only registered additional thrombolysis that was administered after the index procedure. We counted also pre- and periinterventional application.

Furthermore, 29.9% of our patients with additional thrombolysis were treated for bypass occlusion. Our analysis shows that bypass occlusion is significantly often connected to thrombolysis compared to native vessels (Artzner *et al.*, 2022). This type of target lesion was not included in the study by Freitas et al. (2017).

Furthermore, Freitas et al. (2017) treated the SFA, AP or a combination of these vessels in 94.9%. Worthy of mentioning is that share of treatment of iliac arteries in our study was twice as high as in the analysis by Freitas et al. (2017). They used an 8F Rotarex®S catheter in 40.8%. Our share of the infrainguinal vessels was 86.4%, but we mainly used a 6F Rotarex®S catheter (92.2%). As stated before, the more generous use of the 8F Rotarex®S catheter might lead to a reduction of additional catheter-directed thrombolysis.

In conclusion, counting all administration of thrombolytics regardless of the point

in time, the composition of our study cohort and the preferred size of a 6F Rotarex®S catheter might explain the higher share in additional thrombolysis in our analysis.

4.5 Target Lesion

The parameter lesion length was estimated in comparison to applied devices with a particular length like a balloon, because no measurement was given in the angiography.

Stahlberg et al. (2021) recently investigated the influence of the lesion length on technical success rates. The authors achieved a technical success rate of 92% with a mean lesion length of 21.7 cm. In our broad study cohort, we considered the lesion length longer than 20 cm in 61,5% of cases. We registered an overall technical success of 90.9% and a clinical success rate of 90.4%. Therefore, our data supports that the lesion length is not a strong predictor for technical and clinical success rates (Artzner *et al.*, 2022).

Unfortunately, there is no information of the TASC classification of the study cohort of Stahlberg et al. (2021). But we can see that our rather complex cohort with 71.3% TASC C and D lesions also broke the 90% mark of technical and clinical success (Artzner *et al.*, 2022). This also weakens the paradigm of leaving TASC D lesions preferably to the surgical approach (Norgren *et al.*, 2007).

4.6 Technical and Clinical Success

The technical success of revascularization rate found in our investigation (90.9%) correlates well with the literature: Generally acknowledged is a high technical success rate of primary revascularization of more than 90% (Lichtenberg, 2010), which we were able to achieve (Artzner *et al.*, 2022). But the direct comparison with previous studies is challenging: First, target lesions with varying features have been analyzed. Second, the technical success is based on different definitions in the literature. Often, technical success is defined as remaining stenosis smaller than 30%, sometimes 50% after application of Rotarex®S catheter. In our study, the measurement of distances in the DSA imaging was not

possible due to the retrospective design of the study. That is why we divided technical success into passage with the guidewire, which was achieved in 100%, and the technical success of revascularization. Consequently, the remaining stenosis might well be larger than 30% or even 50% after a technical successful revascularization by our definition. In synopsis with the achieved clinical success of 90.4%, which represented the sufficient blood flow to the limb by the interventionist's discretion at the end of the procedure or the end of additional catheter-directed thrombolysis, the results of the analysis presented are consistent with the literature.

Likewise, there are different definitions of clinical success throughout previous investigations: The reporting standards for clinical evaluation of new peripheral arterial revascularization devices by Sacks et al. (1997) define clinical success as the improvement by at least one clinical category. Other authors add the increase in ABI > 0.1 (Stanek, Ouhrabkova and Prochazka, 2016).

The retrospective study presented here does not have a structured follow-up, so there is no evaluation of the Rutherford classes after treatment. To evaluate hemodynamic success, ABI before and after Rotarex®S catheter treatment is evaluated. We excluded values > 1.3 because of confounding by media sclerosis. The ABI post intervention increased by 0.48 to a 0.81 in mean, which was statistically significant. Stanek et al. (2016) had comparable results with examining acute and subacute occlusions of peripheral arteries and bypasses with a significant increase of 0.45 in mean ABI. The authors did not exclude ABI > 1.3.

Kronlage et al. (2017) analyzed the treatment with Rotarex®S catheter and/or thrombolysis for (sub)acute CLI and found a mean ABI post Rotarex®S catheter intervention of 0.87 (Rotarex®S only) respectively 0.88 (Rotarex®S plus thrombolysis), also in agreement with our study.

Bulvas et al. (2019) investigated the Rotarex®S catheter with or without adjuvant therapy in a cohort of 316 patients with acute and subacute lower limb ischemia with a significant increase in mean ABI to 0.78 after intervention.

In total, our study agrees to former studies, indicating the efficient contribution of RT to clinical successful revascularization in terms of ABI improvement.

Another scale to measure clinical success is the walking distance pre and post treatment. It is reasonable to assume that the walking distance influences the QoL of patients. However, due to the retrospective design of this study, our results are based on the statement of the patients and had not been objectively measured by a treadmill test or the Walking Impairment Questionnaire (Nicolaï *et al.*, 2009). This parameter is also limited by a high number of missing values. Most patients were able to walk less than 200 m (93.9%) when admitted to the hospital. After treatment, this fraction is reduced to 22.9%. Furthermore, 52.1% were not limited in their walking distance after the intervention. In comparison, the walking distance is reported by a study of Lichtenberg et al. (2013a), who analyzed the outcome after Rotarex®S catheter for acute femoropopliteal bypass occlusion. They reported a mean walking distance of 312 m after 12 months. Further studies with focus on QoL, participation, and function of patients with PAD would be eligible.

One central challenge regarding the treatment of arterial occlusion is a high restenosis rate (Scheer *et al.*, 2015). Data from several reports indicate 18% to 54% restenosis rate after Rotarex®S treatment for acute and subacute occlusions of femoropopliteal arteries (Wissgott et al., 2008, Schmitt et al., 1999, Wissgott et al., 2011a cited by Scheer et al., 2015). Restenosis is also limiting the success of interventional treatment (PTA and stent implantation) of chronic occlusions (Wissgott *et al.*, 2011b).
Since there is no structured follow-up in our study, we assess reintervention rates as an indirect indicator of restenosis (Artzner *et al.*, 2022). In our sample, 35.5% of interventions were followed with reinterventions. Therefore, our reintervention rates match the established restenosis rates by Scheer et al. (2015).

Patients with chronic occlusion age had the highest rates of reintervention in our sample. Wissgott et al. (2011b) evaluated the treatment of 40 chronic occlusions of iliac and femoropopliteal arteries with the Rotarex®S device in a prospective study. During follow-up of 12 months, they observed a low restenosis rate of 22.5%. However, the share in target lesion location is not completely comparable to our study. The study cohort of Wissgott et al. (2011b) consisted of 5% (n = 2) iliac arteries, our total study cohort included 12.1% iliac arteries (n = 48).

A previous study by Kang (2015) showed that aortoiliac lesions show a restenosis rate of 10% per year. Also, the patient collective of Wissgott et al. (2011b) showed fewer complex lesions, 60% being TASC A and B lesions, while our chronic subcohort had 60% TASC C and D pathology. The TASC classification reflects the degree of pathology and therefore has predictive power regarding the outcome (Norgren *et al.*, 2007). Additionally, we found significantly less clinical success in combined lesions of iliac and leg arteries, so typically TASC C and D lesions. These factors may have served as co-founders to the restenosis/reintervention rate. Additionally, our sample includes reinterventions that took place more than 12 months later. The possible follow-up time span is up to 10 years. The comparability is also limited because restenosis does not directly indicate for reintervention. In summary, this may explain the difference in the restenosis/reintervention rates.

Scheer et al. (2015) also investigated the combination of Rotarex®S catheter with DCB (paclitaxel-coated) for treatment of 20 patients with acute, subacute, and chronic femoropopliteal occlusion. The authors observed a low restenosis rate of 6.9% after six months. Also, DCB reduced restenosis to 12.5% compared to a restenosis rate of 45.5% in a study by Latacz et al. (2019). In our Kaplan-Meier survival analysis we found a decrease in reintervention rates for the patients treated with a DCB, but results missed significance (Artzner *et al.*, 2022). Our data supports the postulated decrease in restenosis rates if the Rotarex®S treatment is augmented with DCB but is limited by the absence of significance and the indirect measurement by reintervention rate. Also, the unstructured and longer follow-up time in our study needs to be considered when comparing the higher percentages in the study presented with the results by Scheer et al. (2015).

The monitored interventions were accompanied by a 6.5% amputation rate after the intervention (Artzner *et al.*, 2022). All available documents of a patient's file have been viewed for an amputation procedure, so follow-up times differed. Amputation-free survival after 12 months had been numbered between 89% and 100% in previous studies (Zeller et al., 2002, Berczi et al., 2002, Duc et al., 2005, Stanek et al., 2016 cited by Lichtenberg and Stahlhoff, 2016). In conclusion, the amputation rate observed matches well with the literature (Artzner *et al.*, 2022).

4.7 Complications

Distal embolization is particularly interesting to examine in order to understand safety of RT. One, because it often requires further and intense treatment. In our study, two thirds had to be treated with either aspiration or thrombolysis. Two, it is often the source of later restenosis and occlusion (Latacz *et al.*, 2019). The distal embolization rate in our analysis was 22.4%, which is high compared to other studies (Artzner *et al.*, 2022). Previous studies found an incidence of distal embolization of 0 to 24% (Stanek et al., 2010, Stanek et al., 2013, Zeller et al., 2002, Schmitt et al., 1999, Duc et al., 2005, Wissgott et al., 2008, and Berczi et al., 2002 cited by Stanek et al., 2016). More recent studies seem to present lower rates (Vorwerk et al., 2019, Freitas et al., 2017, Bulvas et al., 2019).

We did not document at which point of the intervention the distal embolization appeared. That means, our high distal embolization rate is partially due to other devices and represents the distal embolization rate of the overall intervention more than of the Rotarex®S catheter (Artzner *et al.*, 2022). In comparison, Bulvas et al. (2019) reported a distal embolization rate of 12.7%, half of them noted after admission of the Rotarex®S catheter. We did not find a relationship between a particular additional therapy method and distal embolization.
Furthermore, we recorded any kind of distal embolization. One third of the embolizations were of no consequences or simply treated with 48 h heparinization. It is unclear if other studies had recorded distal embolization without consequences or considered them inherent to arterial interventions and therefore not an adverse event to report.

Stanek et al. (2016) found a significant relationship between distal emobolization and the occlusion age. They stated that acute, non-organized lesions are related to distal embolization. Wissgott et al. (2011b) investigated 40 chronic occlusions and observed no distal embolization. This could strengthen the theory of acute occlusions being more likely to embolize. A recent study by Stahlberg et al. (2021) identified a thrombus density < 45 Hounsfield units as a risk factor for periprocedural distal embolization. This could be in line with our results, showing

that non-calcified vessels, so potentially containing acute, unorganized thrombus is related to more distal embolization.

To avoid distal embolization and the consequences thereof, previous studies recommended peripheral filter protection (Karnabatidis et al., 2006 cited by Katsanos et al., 2017). A peripheral filter was not used in our study. Other authors (Duc *et al.*, 2005) achieved reduction of distal embolization rate by ensuring that as much occlusive material as possible was removed by the catheter before eventually recreating peripheral flow.

Other complications appeared in 21.9% of interventions. Most frequent were dissections. As presented in Table 19, only 8 dissections (2%) were observed after RT (Artzner *et al.*, 2022). The larger part (7.6%) was related to adjuvant therapy.

A recent study by Rusch et al. (2020) analyzed safety and efficacy of the Rotarex®S catheter compared to the AngioJet™ (Boston Scientific) in an in vitro pulsatile flow model. On the one hand, the Rotarex®S catheter showed better results regarding thrombus removal. On the other hand, the authors found significantly more macro-emboli, dissections, and microscopic vascular injuries in the Rotarex®S group. Vessel injuries like dissection are a serious throwback of the Rotarex®S catheter because it can require additional stenting. However, the Rotarex®S catheter did cause less dissections than the established adjuvant treatment devices like DCB and POBA in our study (cf. Table 19). Moreover, the dissections rates are comparable to other studies (Artzner *et al.*, 2022): Freitas et al. (2017) investigated the Rotarex®S catheter for treatment of acute and subacute arterial lesions. The authors reported dissection in 23 cases (4.4%) as procedure related, 8 of them device related. Wissgott et al. (2011b) analyzed chronic occlusions of the iliac and femoropopliteal arteries and had a 5% dissection rate.

In our study, the most frequent complication associated to RT was perforation (2.8%) (Artzner *et al.*, 2022). In a literature review, Lichtenberg (2010) described perforation rates between 1% and 10%, especially highly calcified arteries being prone to perforation. Lichtenberg et al. (2013b) suspected that calcified plaques

get trapped in the helix. This creates a pull on the vessel wall which potentially perforates under this stress. Our population including the chronic occlusion age had calcified lesions to a large extent (77.4%). Therefore, we assume that the lesions treated in our study were prone to perforation.

Stanek et al. (2016) investigated in the RT treatment of acute and subacute occlusions of peripheral arteries and bypasses. They observed a comparable low perforation rate of 2.3% (n = 3) minor perforations managed conservatively. They did not record the amount of calcification of the target vessel. The authors speculated that other studies with higher perforation rates mainly used an 8F Rotarex®S catheter, while they mainly used a 6F Rotarex®S catheter (87.5%). Our data supports the assumption made by Stanek et al. (2016): Significantly more perforations occurred with the 8F than with the 6F device in our analysis. In addition, our study population included the iliac arteries, which seem to be especially delicate to treat. We found significantly more perforations after application of Rotarex®S catheter in iliac arteries than in infrainguinal vessels. This comparison might be biased, since the iliac arteries are treated by default more often with the 8F Rotarex®S catheter.

In this large patient sample, there were seven patients with CIRSE 5 and 6 complications. In three cases RT and catheter-directed thrombolysis were insufficient or additional catheter-directed thrombolysis contraindicated. Four cases were direct adverse events of thrombolysis, but thrombolysis was used because debulking with RT was insufficient. This underlines again the severe complications of thrombolysis and how important efficient mechanical debulking and therefore reduction of thrombolysis is.

4.8 Subcohorts

This analysis set out to gain insights on specific subcohorts. We conducted chi-square tests to compare different treatment locations and outcome variables. We saw that significantly less clinical success occurred in combined target lesions of both iliac arteries and arteries of the leg. Combined lesions of the upper and lower leg were also less often fully treatable with RT. Assuming that combined lesions

of pelvic and leg arteries are complex TASC C and D lesions, it fits the observations of Norgren et al. (2007), who introduced the TASC classification in the article “Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)”. They reported that the TASC classification has predictive power to the outcome.
We observed significantly more perforations in the iliac arteries, but significantly less complications in the thigh. This is potentially cofounded by the catheter size, because usually the thigh was treated with the 6F Rotarex®S catheter system, which had lower complication rates than the 8F Rotarex®S catheter system, which predominantly was used in the iliac arteries.

Our analysis shows that technical success rates were significantly lower in the bypass group (78% vs 93.2%), therefore interventions of bypass grafts were labeled more often as *not fully treatable* and received more often catheter-directed thrombolysis (Artzner *et al.*, 2022). Bypass grafts seem to be particularly prone to rethrombosis and therefore poorer success rates, which was also observed by Stanek et al. (2016). In addition, the freedom of target lesion revascularization in the first 30 days after the procedure was significantly lower.
However, there were no perforations monitored in the bypass group and there was no significant cumulation of complications in general. Wissgott et al. (2013) engaged with the treatment of acute and subacute femoropopliteal bypass occlusions. They used an 8F Rotarex®S catheter in 60%. A high technical success rate (97.6%) and a complication rate of 4.8% indicated a safe and effective treatment with the Rotarex®S catheter for treatment of bypass grafts. In conclusion, the endovascular mechanical thrombectomy approach first seems to be legitimate for bypass occlusions, even though the success rates in our analysis are not as high as for native arteries.

Calcification of the lesion is an important factor for safety and efficacy of the treatment with RT. Previous studies have shown that treatment with PTA often underperforms in calcified vessels and there is a high risk of dissection (Shammas et al., 2012 cited by Roberts et al., 2014), perforation (Duc et al., 2005; Loffroy et al., 2020b; Laganà et al., 2011), and distal embolization (Davies et al., 2010 cited by Roberts et al., 2014). We found moderate and severe calcification

in 48% of the interventions. Our data does not show a significant difference between calcified and not calcified vessels concerning perforation.
In addition, our data disagrees with the observations of Davies et al. (2010, cited by Roberts et al., 2014): We monitored significantly less distal embolization in the calcified vessel group. Furthermore, calcified lesions were significantly less often not fully treatable, and therefore received less additional catheter-directed thrombolysis. Assessment of calcification status depended on the availability of a CTA scan of the treatment area. Potentially, there is a selection bias in our study due to which patients received a CTA.

In the study presented, RT was conducted with a 6F and an 8F Rotarex®S catheter. Wissgott et al. (2011b) suggested in their study on the Rotarex®S catheter for treatment of chronic occlusions of the iliac or femoropopliteal arteries to reduce residual stenosis after RT using the 8F catheter. In our study, the 8F group received significantly less additional catheter-directed thrombolysis, so potentially, the complete debulking of thrombus is more feasible with the larger system. On the other hand, the 8F system showed about four times more often complications, especially perforations. Maybe patients with higher thrombolysis risk, e.g., if acute occlusion happens in a perioperative period, would profit from a more liberal use of the 8F system to ensure complete debulking and therefore avoid thrombolysis, even at the price of higher perforation risk. A review by Loffroy et al. (2020b) came to the same conclusion. Also, perforation mainly resulted in lower CIRSE grades, while often thrombolysis complications were ranked in higher CIRSE grades.

Another objective of our study was to gather information on different occlusion ages. In our study, acute occlusions were significantly more often not fully treatable, needed more often catheter-directed thrombolysis and achieved significantly less clinical success. Acute occlusions also showed the lowest 30 days patency but achieved better patency results in the long run than chronic occlusions. In a large study by Freitas et al. (2017) on treatment of acute and subacute arterial lesions with the Rotarex®S catheter, the authors were able to reduce thrombolysis rate to approximately 14% of interventions. Our overall rate of subsequent catheter-directed thrombolysis after RT was 24.2%. This

difference might be based on our inclusion of treatment of bypass grafts, which significantly more often needed subsequent catheter-directed thrombolysis (Artzner *et al.*, 2022).

Wissgott et al. (2011b) assessed the treatment of chronic occlusions of the iliac or femoropopliteal arteries with the Rotarex®S device. They monitored a high technical success rate of 100%. During follow-up of 12 months, a large count of 22.5% restenosis was monitored, which is an often-observed issue in the treatment of chronic occlusion age. In our study, chronic occlusion age, too, showed the most reinterventions. On the other hand, chronic occlusions were less often not fully treatable, so these occlusions needed less additional thrombolysis.
Wissgott et al. (2008) supposed that the 10F Rotarex®S catheter system could solve the issue of incomplete debulking and remaining thrombus as a source of restenosis in large vessel sizes like iliac arteries and bypass grafts. However, the perforation rate in our study was significantly higher with the 8F Rotarex®S catheter. Therefore, our data hypothesizes that the use of a 10F catheter could potentially cause even higher perforation rates.

In our study, most interventions were complemented by additional treatment methods, such as POBA, DCB, and stenting. We asked if there was a favorable additional treatment regarding the distal embolization rate. There was no significant relationship detected by the conducted chi-square tests. Recent studies investigation of the combination of Rotarex®S catheter plus DCB by Scheer et al. (2015) and Latacz et al. (2019b) support low complication rates. Both author groups found low restenosis rates after application of Rotarex®S catheter plus DCB. Our study found decreased reintervention rates for patients treated with DCB without statistical significance. In conclusion, DCB is a sensible adjunctive therapy to accompany RT with low complication rates and increased patency.

4.9 Limitations

General limitation of this study is a retrospective approach (Artzner *et al.*, 2022) as a single-center analysis with no randomization and no control group. Even though the study presented has a large patient collective, the subcohorts of interest, e.g., the below-the-knee interventions, are partially too small to deduct insights. Generally, the study cohort is very heterogenous with different target vessel characterization and different technical approaches by several interventionalists. There is no confirmation of our findings in a prospective randomized controlled trial with structured follow-up (Artzner *et al.*, 2022). Also, this patient collective was admitted to the interventional radiology, so the generalizability for the population is limited.

The data is based on the reports of diagnostic findings, discharge letters, and outpatient letters. These were written to document the treatment methods and results for clinical routine. The demanded details of this analysis could not have been foreseen and therefore are not documented. During retrospective data collection it was not possible to measure distances in the imaging software, and no ruler was routinely used during procedures. This affected protocolling the length and diameter of vessels, but also limited the reporting of residual stenosis, and thereby defining clinical and technical success by percentage of residual stenosis. There was no structural scoring of the amount of calcification of the vessel, only a visual estimation depending on CTA. Therefore, the reporting standards for clinical evaluation of new peripheral arterial revascularization devices by Sacks et al. (1997), that ensure comparability with other studies, were not applied.

In some cases, it remained unclear which complication was caused by which device, if it was not possible to deduct the order of the happenings with the reports of diagnostic findings. If catheter-directed thrombolysis was applied, it was sometimes not possible to differentiate between adjunctive treatment for clinical success (improve runoff) or as a salvage method for embolization or as a secondary intervention when RT could not provide revascularization. Clearly, this calls for a more detailed look on the causing device or treatment.

The information given in the letters of discharge was often incomplete. This refers to the occlusion age treated or which Rutherford category the patient initially presented with. The Rutherford category was also used to classify acute occlusions, if given in the letter of discharge. A classification for acute occlusion would have been more appropriate. The existence of cardiovascular risk factors was deducted from the letters of discharge and has not been further verified.

The parameter *medical condition at hospital admission* was first documented as a free text variable and then transferred into nominal categories. By the time of the transfer into nominal categories, the original source has not been revisited, so there can be systematic error and loss of information. E.g., the medical condition at hospital admission was documented as “critical ischemia”. Since this could be both acute or chronic limb ischemia, it was not integrated into the analysis.

The follow-up is based on the documentation of reassessment during later visits of the patient at the Tübingen University Hospital. There was no information if a better Rutherford category was achieved after the RT procedure. The walking distance was recorded by the patient’s own estimation and not determined in a clinical test. Also, the reassessment of parameters like patency, ABI, and walking distances was collected without standardized interval to the index procedure. For patients who had intervention in a more recent time, the post-intervention investigation span is respectively shorter.
There have been two inclusion periods, one in January 2020 and one in June 2020, and patients who were included in January 2020 have not been reviewed in June 2020. Therefore, the follow-up period differs slightly between patients.
The inclusion date for the Kaplan-Meier analysis has been chosen but does not reflect the exact date of inclusion for every individual patient.

Potentially, patients who needed reintervention or had complication might have gone to a different clinic for treatment. It is unclear, how much this confounded the follow-up. Some patients might have been too sick for another reintervention or they did not consent, which would lead to overestimation of patency. Surgical reinterventions might be underestimated.

4.10 Conclusion

Despite these limitations, this study provides insights on patients treated in the daily clinical routine at the Tübingen University Hospital. It shows that the interventions at the Tübingen University Hospital achieve a comparably good quality as patients managed in a study setting (Wissgott *et al.*, 2011a). We found significant results in a large sample size that are in line with previous studies.

In summary, our data lead to the following insights: Our patients had a large share of complex TASC C and D lesions (Artzner *et al.*, 2022). Nevertheless, we achieved a high technical and clinical success rate, which reflects in significant increase in ABI and walking distance. Therefore, the paradigm of surgically treating TASC C and D lesions seems outdated.

The interventions in this study were accompanied by a high amount of adjunctive therapy. RT was rarely sufficient as the sole method of revascularization. Positive results were achieved for the treatment of the thigh and subacute and chronic occlusion ages. Challenging was the treatment of complex lesions, acute occlusion, non-calcified vessels, and bypass grafts. These occlusions often needed subsequent catheter-directed thrombolysis. However, RT, especially the 8F Rotarex®S catheter, can contribute to debulking and therefore reduce additional catheter-directed thrombolysis (Artzner *et al.*, 2022). Thereby, RT is a reasonable addition to the revascularization strategy.

The application in the iliac arteries and the 8F Rotarex®S catheter were more prone to complications. Overall, we observed 11 perforations after RT. There were 89 cases (22.4%) of distal embolization. Non-calcified lesions were associated with significantly more distal embolization. Severe complications with CIRSE classes 5 and 6 were observed for seven interventions but were not directly device-related.

Patients with higher thrombolysis risk or lysis contradiction, e.g., elderly, might benefit from a more generous use of a larger catheter size to avoid subsequent catheter-directed thrombolysis (Artzner *et al.*, 2022). Our study indicates that this might lead to more local adverse events like perforation, but we did not see

perforation in bypass occlusions. Furthermore, all perforations we have seen were treatable during intervention.

We saw better long-term patency for subacute and acute occlusions than for chronic occlusions. The 8F Rotarex®S catheter might provide better patency than the 6F catheter. The combination of RT with DCB is safe and seems to lead to better patency, but data did not reach significance.

Regarding further studies, we recommend prospective, controlled trials with a standard follow-up protocol. They should include parameters of QoL and walking function. The role of the occlusion age in embolization and the treatment of chronic, iliac, and calcified lesions, and bypass grafts is yet to be fully understood. The 10F system might bring advantages in iliac and bypass occlusions, but data of high quality is yet missing.

Treatment of acute, subacute, and chronic infrarenal arterial occlusions of native vessels, in-stent occlusions, and bypass-grafts with RT is generally a safe and efficient method (Artzner *et al.*, 2022). The individual presentation of the patients and their lesion characteristic influence the result of the treatment. The decision of the treatment approach should be made individually for each patient and preferably by a team of vascular experts.

5 Abstract

5.1 English Abstract

This study sets out to evaluate safety and efficacy of mechanical rotational thrombectomy (RT) with the Rotarex®S catheter system in patients with acute, sub-acute or chronic arterial occlusion of the lower limb. Previous studies show good evidence for the safe and efficient treatment of acute and subacute femoropopliteal occlusion. Research on clinical routine treatment of occlusions in the iliac arteries and the arteries below the knee, chronic and highly calcified occlusions and bypass grafts is limited.

The presented study is a retrospective, observational, single-center, non-randomized analysis of 397 interventions in 293 patients treated with (adjunctive) treatment with RT at the Tübingen University Hospital. The study cohort consisted of 64.7% male patients and patients who had a mean age of 69.8 years. Patients expressed a high prevalence of cardiovascular risk factors, especially arterial hypertension (82.3%) and nicotine abuse (51.5%). Rutherford's categories reflected critical limb ischemia for 62.5% of patients.

Target lesions were arterial (sub-)occlusions of native vessels (n = 338, 85.1%) with (47.9%) or without (37.3%) preexisting stents and bypass-grafts (n = 59, 14.9%). Occlusion ages were acute (47.5%), subacute (22.2%) and chronic (30.3%). Lesions were mainly complex TASC C (42.6%) and D (28.7%) lesions with more than 20 cm length (61.5%) and mainly diameters of 5 mm (34,6%) or 6 mm (39,1%). Lesions showed calcification in 77.4%. A 6 French Rotarex®S Catheter was used in 365 patients (92.2%). Residual stenosis was highly prevalent (89.5%) after Rotarex®S Catheter application and treated with adjunctive therapy (Balloon, 68%; Stent, 41.1% or DCB, 37.5%). A total of 127 interventions (32%) were accompanied by catheter directed thrombolysis.

Successful revascularization was achieved in 361 (90.9%) cases. In total, 359 (90.4%) procedures were clinically successful. The ABI increased significantly after treatment to a mean 0.81. Walking distance less than 200 m significantly

decreased from 94% of patients before to 23% after treatment. A share of 35.5% of patients underwent reintervention, 8.5% within the first 30 days after the Rotarex®S procedure. In a Kaplan-Meier survival analysis we found better patency for subacute and acute occlusion ages than chronic occlusion age. Also, the 8F Rotarex®S catheter treatment showed better patency than the 6F Rotarex®S catheter treatment. Furthermore, procedures with inclusion of DCB seem to have better patency, but all three analyzations did not reach significance.

We monitored 183 adverse events. There were 89 cases (22.4%) of distal embolization. Chi-square test showed significant relationship between non-calcified lesions and distal embolization. Other complications were observed in 21.9% of interventions. Most of them were dissections (10.3%), 17 perforations (4.3%), including 11 perforations after Rotarex®S catheter. Complications were only CIRSE grade 1 in 75.5%. Complications with CIRSE classes 5 and 6 were observed in seven interventions. These events were not directly related to the Rotarex®S catheter. The iliac arteries and the 8F Rotarex®S catheter showed significant cumulation of complications, especially perforation.

Analysis of subcohorts lead to the following significant insights: The treatment of arteries of the thigh with RT is often successful and shows little complication. Treatment of acute occlusion, non-calcified vessels and bypass grafts seems to be challenging and often indicates for subsequent catheter-directed thrombolysis. Catheter-directed thrombolysis was more frequent after 6F Rotarex®S catheter. The application in the iliac arteries and the 8F Rotarex®S catheter were more prone to complications. Therefore, patients with higher thrombolysis risk or lysis contradiction, e.g., elderly, might benefit from a more generous use of a larger catheter size to avoid subsequent catheter-directed thrombolysis, if a higher perforation risk is acceptable.

Mechanical thrombectomy using the Rotarex®S device is a useful option to treat acute, sub-acute or chronic infrarenal arterial occlusions and bypass grafts. The individual presentation of the patients and their lesion characteristic influence the result of the treatment. Prospective studies in this issue are recommended.

5.2 Deutsche Zusammenfassung

Ziel dieser Studie ist es, die Sicherheit und Wirksamkeit der mechanischen Rotationsthrombektomie (RT) mit dem Rotarex®S-Kathetersystem bei Patienten mit akutem, subakutem oder chronischem Arterienverschluss der unteren Extremität zu untersuchen. Frühere Studien zeigten die sichere und effiziente Behandlung von akuten und subakuten femoropoplitealen Verschlüssen. Die Forschung zur klinischen Routinebehandlung von Verschlüssen in den Beckenarterien und den Arterien unterhalb des Knies sowie von chronischen und stark verkalkten Verschlüssen und von Bypässen ist begrenzt.

Dies ist eine retrospektive, beobachtende, nicht-randomisierte Analyse von 397 Eingriffen bei 293 Patienten, die am Universitätsklinikum Tübingen mit (zusätzlicher) RT behandelt wurden. Die Studienkohorte bestand zu 64,7% aus Männern mit einem Durchschnittsalter von 69,8 Jahren. Kardiovaskulären Risikofaktoren waren häufig, insbesondere arterielle Hypertonie (82,3%) und Nikotinabusus (51,5%). Die Rutherford-Kategorien zeigten bei 62,5 % der Patienten eine kritische Extremitätenischämie.

Behandelt wurden arterielle (Sub-)Verschlüsse nativer Gefäße (n = 338, 85,1%) mit (47,9%) oder ohne (37,3%) Stents und Bypässe (n = 59, 14,9%). Die Okklusionen waren akut (47,5%), subakut (22,2%) oder chronisch (30,3%). Es handelte sich primär um komplexe TASC C- (42,6%) und D-Läsionen (28,7%) mit einer Länge von mehr als 20 cm (61,5%) und Durchmessern von 5 mm (34,6%) oder 6 mm (39,1%). Die Zielgefäße wiesen in 77,4 % eine Verkalkung auf. Bei 365 Patienten (92,2%) wurde ein 6-French-Rotarex®S-Katheter verwendet. Nach der Anwendung des Rotarex®S-Katheters waren residuale Stenosen sehr häufig (89,5 %) und wurden mit einer Zusatztherapie behandelt (Ballon, 68 %; Stent, 41,1 % oder Drug-Coated Balloon 37,5 %). Insgesamt 127 Eingriffe (32%) wurden von einer kathetergestützten Thrombolyse begleitet.

Die Revaskularisierung war in 361 (90,9%) Fällen erfolgreich. Insgesamt waren 359 (90,4%) Eingriffe klinisch erfolgreich. Nach der Behandlung stieg der ABI signifikant auf durchschnittlich 0,81 an. Die Gehstrecke < 200 m sank signifikant von 94% auf 23%. Eine Reintervention erhielten 35.5% der Patienten, 8,5%

innerhalb der ersten 30 Tage nach der Rotarex®S-Behandlung. Die Kaplan-Meier-Überlebensanalyse zeigte eine bessere Durchgängigkeit für subakute und akute Verschlüsse als für chronische Verschlüsse. Der 8F Rotarex®S-Katheter erzielte eine bessere Durchgängigkeit als der 6F Rotarex®S-Katheter. Die Behandlung mit Drug-Coated Balloon scheint eine verbesserte Durchgängigkeit zu haben, aber alle drei Analysen erreichten keine Signifikanz.

Wir beobachteten 183 unerwünschte Ereignisse. In 89 Fällen (22,4%) kam es zu einer distalen Embolie. Der Zusammenhang zwischen nicht verkalkten Läsionen und distaler Embolie war signifikant. Andere Komplikationen wurden bei 21,9 % der Eingriffe beobachtet. Die meisten waren Dissektionen (10,3%), gefolgt von 17 Perforationen (4,3%), darunter 11 Perforationen nach Rotarex®S-Katheter. Komplikationen waren nur CIRSE-Grad 1 in 75,5% der Fälle. Komplikationen mit CIRSE-Grad 5 und 6 wurden bei sieben Eingriffen beobachtet. Diese standen nicht in direktem Zusammenhang mit dem Rotarex®S-Katheter. Die Beckenarterien und der 8F-Rotarex®S-Katheter zeigten eine signifikante Kumulation von Komplikationen, insbesondere Perforation.

Die Behandlung der Oberschenkelarterien mit RT ist häufig erfolgreich und komplikationsarm. Akute Verschlüsse, nicht verkalkte Gefäße und Bypässe scheinen schwieriger zu behandeln zu sein und brauchen häufig kathetergestützte Thrombolyse. Diese wurde auch häufiger nach 6F Rotarex®S-Katheter angewendet. Die Behandlung von Beckenarterien und der 8F Rotarex®S-Katheter waren anfälliger für Komplikationen. Patienten mit erhöhtem Thrombolyserisiko könnten von der Verwendung eines größeren Katheters profitieren, um eine anschließende kathetergestützte Thrombolyse zu vermeiden, wenn ein höheres lokales Perforationsrisiko akzeptabel ist.

Die mechanische Thrombektomie mit dem Rotarex®S-Gerät ist eine nützliche Option zur Behandlung akuter, subakuter oder chronischer infrarenaler Arterienverschlüsse und Bypässen. Die individuelle Präsentation der Patienten und ihre Läsionscharakteristik beeinflussen das Ergebnis der Behandlung. Es werden prospektive Studien zu diesem Thema empfohlen.

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7 Appendix

All conducted chi-square tests (Appendix Table I – VI):

Appendix Table I: **Part 1: Chi-Square Tests of Iliac Arteries vs Lower Limb Arteries.** Iliac arteries (n = 28; group 1), lower limb arteries (n = 349; group 2). **Abbreviations:** TL, target lesion; MC, Monte-Carlo-Significance.

Aspect	n Group 1	% Group 1	n Group 2	% Group 2	Chi-square test	Expected cell frequencies below five
Technical success (Revascularization)	27	96.4	317	90.8	$\chi^2(1) = 1.017$ p = 0.313 φ = - 0.052 Fisher (2-sided): p = 0.493	1
Clinical success	26	92.9	320	91.7	$\chi^2(1) = 0.047$ p = 0.829 φ = - 0.011 Fisher (2-sided): p = 1.000	1
Not fully treatable	13	46.4	121	34.7	$\chi^2(1) = 1.564$ p = 0.211 φ = 0.064	0
Additional catheter-directed thrombolysis after Rotarex®S	4	14.3	84	24.1	$\chi^2(1) = 1.386$ p = 0.239 φ = 0.061	0
Freedom of TL Revascularization 30 days after Index procedure	27	96.4	311	90.9	$\chi^2(1) = 0.988$ p = 0.320 φ = 0.052 Fisher (2-sided): p = 0.493	1
Complication attributed to Rotarex®S (vs other vs no)	4	14.3	21	6.0	$\chi^2(2) = 7.365$ p = 0.025 Cramér's V = 0.140 MC p = 0.022	2
Complications attributed to Rotarex®S (vs none/other)	4	14.3	21	6.0	$\chi^2(1) = 2.862$ p = 0.091 φ = 0.087 Fisher (2-sided): p = 0.103	1
CIRSE	-	-	-	-	$\chi^2(4) = 0.918$ p = 0.922 Cramér's V = 0.106 MC p = 1.000	8
Perforation attributed to Rotarex®S	3	10.7	7	2.0	$\chi^2(1) = 7.613$ p = 0.006 φ = - 0.142 Fisher (2-sided): p = 0.031	1
Distal embolization	4	14.3	83	23.8	$\chi^2(1) = 1.317$ p = 0.251 φ = 0.059	0
Amputation after Rotarex®S	1	3.6	22	6.3	$\chi^2(1) = 0.338$ p = 0.561 φ = 0.030 Fisher (2-sided): p = 1.000	1

Appendix Table II: **Chi-Square Tests of Bypass Graft vs Native Vessel.**
Bypass graft (n = 59, group 1), native vessel (n = 338, group 2).
Abbreviations: TL, target lesion; MC, Monte-Carlo-Significance.

Aspect	n Group 1	% Group 1	n Group 2	% Group 2	Chi-square test	Expected cell frequencies below five
Technical success (Revasculari-zation)	46	78.0	315	93.2	$\chi^2(1) = 14.129$ $p < 0.001$ $\varphi = - 0.189$	0
Clinical success	52	88.1	307	90.8	$\chi^2(1) = 0.421$ $p = 0.517$ $\varphi = - 0.033$	0
Not fully treatable	41	69.5	105	31.1	$\chi^2(1) = 31.900$ $p < 0.001$ $\varphi = 0.283$	0
Additional catheter-directed thrombolysis after Rotarex®S	33	55.9	63	18.6	$\chi^2(1) =$ 38.105 $p < 0.001$ $\varphi = 0.310$	0
Freedom of TL Revasculari-zation 30 days after Index procedure	46	82.1	308	93.1	$\chi^2(1) = 7.307$ $p = 0.007$ $\varphi = - 0.137$ Fisher (2-sided): $p = 0.016$	1
Complication attributed to Rotarex®S (vs other vs no)	2	3.4	25	7.4	$\chi^2(2) = 1.968$ $p = 0.374$ Cramér's V = 0.070 MC p = 0.370	1
Complication attributed to Rotarex®S (vs other/no)	2	3.4	25	7.4	$\chi^2(1) = 1.272$ $p = 0.259$ $\varphi = - 0.057$ Fisher (2-sided): $p = 0.400$	1
CIRSE	-	-	-	-	$\chi^2(4) = 5.665$ $p = 0.226$ Cramér's V = 0.255 MC p = 0.213	7
Perforation attributed to Rotarex®S	0	0.0	11	3.3	$\chi^2(1) = 1.975$ $p = 0.160$ $\varphi = - 0.071$ Fisher (2-sided): $p = 0.381$	1
Distal embolization	16	27.1	73	21.6	$\chi^2(1) = 0.880$ $p = 0.348$ $\varphi = 0.047$	0
Amputation after Rotarex®S	3	5.1	23	6.8	$\chi^2(1) = 0.243$ $p = 0.622$ $\varphi = - 0.025$ Fisher (2-sided): $p = 0.781$	1

Appendix Table III: **Chi-Square Tests of Calcified Vessel vs Non-Calcified Vessel.** Calcified vessel (n = 150, group 1), non-calcified vessel (n = 44, group 2). **Abbreviations:** TL, target lesion; MC, Monte-Carlo-Significance.

Aspect	n Group 1	% Group 1	n Group 2	% Group 2	Chi-square test	Expected cell frequencies below five
Technical success Revascularization	139	92.7	37	84.1	$\chi^2(1) = 2.972$ p = 0.085 φ = 0.124 Fisher (2-sided): p = 0.134	1
Clinical success	131	87.3	37	84.1	$\chi^2(1) = 0.308$ p = 0.579 φ = 0.040	0
Not fully treatable	64	42.7	27	61.4	$\chi^2(1) = 4.775$ p = 0.029 φ = - 0.157	0
Additional catheter-directed thrombolysis after Rotarex®S	41	27.3	20	45.5	$\chi^2(1) = 5.182$ p = 0.023 φ = - 0.163	0
Freedom of TL Revascularization 30 days after Index procedure	129	89.0	36	87.8	$\chi^2(1) = 0.043$ p = 0.836 φ = 0.015 Fisher (2-sided): p = 0.785	1
Complication attributed to Rotarex®S (vs other vs no)	12	8.0	2	4.5	$\chi^2(2) = 2.154$ p = 0.341 Cramér's V = 0.105 MC p = 0.368	1
Complication attributed to Rotarex®S (vs other/no)	12	8.0	2	4.5	$\chi^2(1) = 0.606$ p = 0.436 φ = 0.056 Fisher (2-sided): p = 0.740	1
CIRSE	-	-	-	-	$\chi^2(4) = 3.200$ p = 0.525 Cramér's V = 0.273 MC p = 0.552	8
Distal embolization	28	18.7	16	36.4	$\chi^2(1) = 6.076$ p = 0.014 φ = - 0.177	0
Amputation after Rotarex®S	9	6.0	2	4.5	$\chi^2(1) = 0.135$ p = 0.714 φ = 0.026 Fisher (2-sided): p = 1.000	1

Appendix Table IV: **Chi-Square Tests of Size 6 French vs Size 8 French Rotarex®S**. Size 6 French (n = 365, group 1), Size 8 French (n = 31, group 2). **Abbreviations:** TL, target lesion; MC, Monte-Carlo-Significance.

Aspect	n Group 1	% Group 1	n Group 2	% Group 2	Chi-square test	Expected cell frequencies below five
Technical success Revascularization	334	91.5	26	83.9	$\chi^2(1) = 2.016$ p = 0.156 φ = - 0.071 Fisher (2-sided): p = 0.184	1
Clinical success	329	90.1	29	93.5	$\chi^2(1) = 0.383$ p = 0.536 φ = 0.031 Fisher (2-sided): p = 0.755	1
Not fully treatable	135	37.0	11	35.5	$\chi^2(1) = 0.028$ p = 0.868 φ = - 0.008	0
Additional catheter-directed thrombolysis after Rotarex®S	94	25.8	2	6.5	$\chi^2(1) = 5.796$ p = 0.016 φ = - 0.121	0
Freedom of TL Revascularization 30 days after Index procedure	326	91.3	28	96.6	$\chi^2(1) = 0.967$ p = 0.325 φ = 0.050 Fisher (2-sided): p = 0.493	1
Complication attributed to Rotarex®S (vs other vs no)	21	5.8	6	19.4	$\chi^2(2) = 12.788$ p = 0.002 Cramér's V = 0.180 MC p = 0.004	2
Complication attributed to Rotarex®S (vs other/no)	21	5.8	6	19.4	$\chi^2(1) = 8.320$ p = 0.004 φ = 0.145 Fisher (2-sided): p = 0.013	1
CIRSE	-	-	-	-	$\chi^2(4) = 1.924$ p = 0.750 Cramér's V = 0.149 MC p = 0.760	8
Perforation attributed to Rotarex®S	7	1.9	4	12.9	$\chi^2(1) = 12.768$ p < 0.001 φ = 0,180 Fisher (2-sided): p = 0.007	1
Distal embolization	82	22.5	6	19.4	$\chi^2(1) = 0.160$ p = 0.689 φ = - 0.020	0
Amputation after Rotarex®S	24	6.6	2	6.5	$\chi^2(1) = 0.001$ p = 0.979 φ = - 0.001 Fisher (2-sided): p = 1.000	1

Appendix Table V: **Comparison of Location of Target Lesion Regarding Outcome Variables with Chi-Square Tests.**
Target lesion locations (n = 397).
Abbreviations: TL, target lesion; MC, Monte-Carlo-Significance.

Aspect	Chi-square test	Expected cell frequencies below five	Monte-Carlo-Significance (2-sided)
Technical success Revascularization	$\chi^2(4) = 6.653$ $p = 0.155$ Cramér's V = 0.129	3	
Clinical success	$\chi^2(4) = 16.518$ $p = 0.002$ Cramér's V = 0.204	3	p = 0.004
Not fully treatable	$\chi^2(4) = 29.514$ $p < 0.001$ Cramér's V = 0.273	2	p = 0.000
Additional catheter-directed thrombolysis after Rotarex®S	$\chi^2(4) = 8.153$ $p = 0.086$ Cramér's V = 0.143	2	
Freedom of TL Revascularization 30 days after Index procedure	$\chi^2(4) = 2.928$ $p = 0.570$ Cramér's V = 0.087	3	
Complication attributed to Rotarex®S (vs other vs no)	$\chi^2(4) = 19.106$ $p = 0.014$ Cramér's V = 0.155	7	p = 0.021
Complication attributed to Rotarex®S (vs other/no)	$\chi^2(4) = 11.340$ $p = 0.023$ Cramér's V = 0.169	3	p = 0.028
CIRSE	$\chi^2(16) = 36.852$ $p = 0.002$ Cramér's V = 0.325	22	p = 0.052
Perforation attributed to Rotarex®S	$\chi^2(4) = 8.112$ $p = 0.088$ Cramér's V = 0.143	4	
Distal embolization	$\chi^2(4) = 5.850$ $p = 0.211$ Cramér's V = 0.121	3	
Amputation after Rotarex®S	$\chi^2(4) = 8.238$ $p = 0.083$ Cramér's V = 0.144	3	

Appendix Table VI: **Comparison of Occlusion Ages Regarding Outcome Variables with Chi-Square Tests.**
Occlusion ages (n = 383).
Abbreviations: TL, target lesion; MC, Monte-Carlo-Significance.

Aspect	Chi-square test	Expected cell frequencies below five	Monte-Carlo-Significance (2-sided)
Technical success Revascularization	$\chi^2(2) = 4.713$ $p = 0.095$ Cramér's V = 0.111	0	
Clinical success	$\chi^2(2) = 22.838$ $p < 0.001$ Cramér's V = 0.244	0	
Not fully treatable	$\chi^2(4) = 20.782$ $p < 0.001$ Cramér's V = 0.233	0	
Additional catheter-directed thrombolysis after Rotarex®S	$\chi^2(2) = 34.118$ $p < 0.001$ Cramér's V = 0.298	0	
Freedom of TL Revascularization 30 days after Index procedure	$\chi^2(2) = 11.357$ $p = 0.003$ Cramér's V = 0.174	0	
Complication attributed to Rotarex®S (vs other vs no)	$\chi^2(4) = 0.320$ $p = 0.989$ Cramér's V = 0.020	0	
Complication attributed to Rotarex®S (vs other/no)	$\chi^2(2) = 0.244$ $p = 0.885$ Cramér's V = 0.025	0	
CIRSE	$\chi^2(8) = 13.292$ $p = 0.102$ Cramér's V = 0.281	12	$p = 0.065$
Perforation attributed to Rotarex®S	$\chi^2(2) = 2.140$ $p = 0.343$ Cramér's V = 0.075	2	
Distal embolization	$\chi^2(2) = 2.648$ $p = 0.266$ Cramér's V = 0.083	0	
Amputation after Rotarex®S	$\chi^2(2) = 5.395$ $p = 0.067$ Cramér's V = 0.119	0	

8 Erklärung zum Eigenanteil an der Dissertationsschrift

Die Arbeit wurde in der Klinik für Diagnostische und Interventionelle Radiologie unter der Betreuung von Prof. Dr. med. Gerd Grözinger, stellvertretender Ärztlicher Direktor der Klinik für Diagnostische und Interventionelle Radiologie des Universitätsklinikum Tübingen, durchgeführt.

Die Konzeption der Studie erfolgte in Zusammenarbeit mit Prof. Dr. med. Gerd Grözinger, PD Dr. med. Christoph P. Artzner, Oberarzt der Klinik für Diagnostische und Interventionelle Radiologie des Universitätsklinikum Tübingen, und Dr. med. Rick de Graaf, Chefarzt der Abteilung für Diagnostische und Interventionelle Radiologie/Nuklearmedizin am Klinikum Friedrichshafen.

Die Daten wurden nach Einarbeitung durch Prof. Dr. med. Gerd Grözinger und PD Dr. med. Christoph P. Artzner von mir eigenständig erhoben.

Die Konzeption der statistischen Auswertung erfolgte in Zusammenarbeit mit Prof. Dr. med. Gerd Grözinger und PD Dr. med. Christoph P. Artzner. Die Durchführung der statistischen Auswertung und die Darstellung der Ergebnisse einschließlich der Erstellung der Tabellen 4 - 28 und Grafiken 3 – 18 erfolgte eigenständig durch mich. Ebenso erfolgte die Einordnung der Ergebnisse im Rahmen der Diskussion eigenständig durch mich.

Ich versichere, das Manuskript selbstständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Tübingen, den 30.05.2022

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Isabelle Martin

9 Erklärung zum Eigenanteil an der erfolgten Publikation

Mein Eigenanteil an der Publikation

Artzner C, Martin I, Hefferman G, Artzner K, Lescan M, de Graaf R, Grözinger G. Safety and Efficacy of Rotational Thrombectomy for Treatment of Arterial Occlusions of the Lower Extremities: A Large Single-Center Retrospective Study. RöFo: Fortschritte auf dem Gebiet der Röntgenstrahlen und der Bildgebenden Verfahren, 2022.

umfasste die Planung der Studie in Zusammenarbeit mit Prof. Dr. med. Gerd Grözinger, PD Dr. med. Christoph P. Artzner und Dr. med. Rick de Graaf.

Nach Einarbeitung durch Prof. Dr. med. Gerd Grözinger und PD Dr. med. Christoph P. Artzner führte ich die Datenerhebung vollständig durch.

Die Konzeption der statistischen Auswertung erfolgte in Zusammenarbeit mit Prof. Dr. med. Gerd Grözinger und PD Dr. med. Christoph P. Artzner. Die statistische Auswertung wurde überwiegend durch mich durchgeführt.

Die Ergebnisse wurden überwiegend durch mich dargestellt. Die Anfertigung der Tabellen 1, 2, 4 und 5 und Grafiken 2 und 3 erfolgte vollständig durch mich. In Teilen wurden Ergebnisse und Tabelle 3 durch PD Dr. med. Christoph P. Artzner ergänzt und dargestellt. Grafiken 1 und 4 wurden vollständig von PD Dr. med. Christoph P. Artzner erarbeitet. Die Interpretation und Diskussion der Ergebnisse erfolgten durch mich und PD Dr. med. Christoph P. Artzner.

Die Zusammenstellung der Inhalte der Studie für die o.g. Publikation führte mehrheitlich PD Dr. med. Christoph P. Artzner durch, teilweise in Zusammenarbeit mit PD Dr. med. Mario Lescan. Gerald Hefferman, M.D., und Dr. med. Kerstin Artzner lasen das Manuskript im Hinblick auf formale Aspekte Korrektur und waren an der Überarbeitung beteiligt. Das Manuskript wurde auch durch PD Dr. med. Mario Lescan hinsichtlich formaler Aspekte Korrektur gelesen.

Die Organisation der Einreichung für die o.g. Publikation erfolgte mehrheitlich durch PD Dr. med. Christoph P. Artzner.

Erklärung zum Eigenanteil an der erfolgten Publikation

Die vorliegende Einschätzung über die erbrachte Eigenleistung wurde mit den am Artikel beteiligten Ko-Autoren/Ko-Autorinnen einvernehmlich abgestimmt.

Tübingen, den 19.03.2023

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Isabelle Martin

10 Liste der Veröffentlichungen

Teile der vorliegenden Dissertationsschrift wurden auf dem Interventionell Radiologischen Olbert Symposium (IROS) 2022 in Salzburg als Poster vorgestellt:

- Isabelle Martin, Christoph Artzner, Rick De Graaf, Gerd Grözinger „Sicherheit und Wirksamkeit des Rotarex®S Kathetersystems – Ergebnisse aus einer großen Single-Center-Kohorte“

Außerdem wurden Teile der vorliegenden Dissertationsschrift bereits in der folgenden Publikation veröffentlicht:

- Artzner C, Martin I, Hefferman G, Artzner K, Lescan M, de Graaf R, Grözinger G. Safety and Efficacy of Rotational Thrombectomy for Treatment of Arterial Occlusions of the Lower Extremities: A Large Single-Center Retrospective Study. RöFo: Fortschritte auf dem Gebiet der Röntgenstrahlen und der Bildgebenden Verfahren, 2022.

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Lebenslauf

Der Lebenslauf wurde aus Gründen des Datenschutzes entfernt.