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The Clinical Impact of Access Site Selection for Successful Lower Limb Interventions

PhD Thesis

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LIST OF PUBLICATIONS

Publications directly related to the subject of the dissertation

I. **Csavajda, A.,** Toth, K., Kovacs, N., Rona, S., Vamosi, Z., Berta, B., Kulcsar, F. Z., Bertrand, O. F., Hizoh, I., & Ruzsa, Z. (2024). The Clinical Impact of Access Site Selection for Successful Thrombolysis and Intervention in Acute Critical Lower Limb Ischaemia (RAD-ALI Registry). *Life (Basel, Switzerland)*, *14*(6), 666. **IF: 3.2**

II. Ruzsa, Z**., Csavajda, Á.,** Hizoh, I., Deák, M., Sótonyi, P., Bertrand, O. F., Kwan, T., Merkely, B., & Nemes, B. (2022). TRIACCESS Study: Randomized Comparison Between Radial, Femoral, and Pedal Access for Percutaneous Femoro-popliteal Artery Angioplasty. *Journal of endovascular therapy: an official journal of the International Society of Endovascular Specialists*, *29*(2), 215–225. **IF: 2.6**

III. Ruzsa, Z., **Csavajda, Á.,** Nemes, B., Deák, M., Sótonyi, P., Bertrand, O. F., & Merkely, B. (2021). Distal Radial Artery Access for Superficial Femoral Artery Interventions. *Journal of endovascular therapy: an official journal of the International Society of Endovascular Specialists*, *28*(2), 255–261. **IF: 3.089**

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I. **Csavajda, Á.,** Nardai, S., Bertrand, O. F., & Ruzsa, Z. (2023). Superficial temporal artery access for carotid artery stenting: A case report. *Clinical case reports*, *11*(2), e6947. **IF: 0.7**

II. Achim, A., Lackó, D., Hüttl, A., Csobay-Novák, C., **Csavajda, Á.,** Sótonyi, P., Merkely, B., Nemes, B., & Ruzsa, Z. (2022). Impact of Diabetes Mellitus on Early Clinical Outcome and Stent Restenosis after Carotid Artery Stenting. *Journal of diabetes research*, *2022*, 4196195. **IF: 4.3**

III. **Csavajda, Á.,** Bertrand, O. F., Merkely, B., & Ruzsa, Z. (2020). Superficial temporal artery access for percutaneous coronary artery stenting during the COVID-19 pandemic: a case report. *European heart journal. Case reports*, *5*(2), ytaa520. **IF: -**

IV. Kwan, T. W., Htun, W. W., Lee, S., **Csavajda, Á.,** Patel, A., Shah, S., Huang, Y., Liou, M., Merkely, B., & Ruzsa, Z. (2020). Approach to Tibiopedal Retrograde Revascularization of Below-The-Knee Peripheral Arterial Diseases With or Without Transradial Guidance Peripheral Angiography. *The Journal of invasive cardiology*, *32*(1), 6–11. **IF: 2.022**

V. Ruzsa, Z., **Csavajda, Á.,** Deák, M., Viktor, Ó., Hizoh, I., Nemes, B., Bertrand, O. F., Merkely, B., & Kwan, T. W. (2020). Direct transpedal pressure measurement during transpedal below-the-knee interventions in critical limb ischemia. *Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions*, *96*(4), 904–912. **IF: 2.692**

VI. **Csavajda, Á.,** Deák, M., Domsik, P., & Ruzsa, Z. (2019). Distal radial and Transpedal access for iliac artery chronic total occlusion recanalisation using the rendezvous technique. *Archives of Clinical and Medical Case Reports*, *03*(06). **IF: -**

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LIST OF ABBREVIATIONS

ACT: activated clotting time

ALI: acute limb ischemia

ATA: anterior tibial artery

BA: brachial artery

BTK: below-the-knee

CDT: catheter-directed thrombolysis

CFA: common femoral artery

CI: confidence interval

CLI: critical limb ischemia

CTO: chronic total occlusion

DP: dorsal pedal

DR: distal radial

FA: femoral artery

GW: guidewire

HR: hazard ratio

MACE: major adverse cardiac event

MAE: major adverse event

MALE: major adverse limb event

MT: mechanical thrombectomy

PA: peroneal artery

PAD: peripheral arterial disease

PFA: profunda femoris artery

PR: proximal radial

PT: posterior tibial

PTA: percutaneous transluminal angioplasty

RA: radial artery

RAO: radial artery occlusion

SFA: superficial femoral artery

TP: transpedal

1. INTRODUCTION

1.1 Overview

Peripheral arterial disease (PAD) is an extremely common and complex condition, affecting nearly 200 million people worldwide [1]. Its clinical manifestations are critical limb ischemia (CLI) and acute limb ischemia (ALI). These conditions are of great clinical importance due to the severe complications they can cause, as well as there high rates of comorbidity and mortality. Symptoms may present as pain at rest or, in more severe cases, as tissue damage in the form of ulcers and/or gangrene. The prevalence of PAD in patients with serious comorbidities (such as advanced age, hypertension, and diabetes mellitus) and complex anatomy is steadily increasing, which has led to the rapid development and broader application of endovascular interventions.

Recent advances in endovascular therapy have enabled prompt treatment of PAD; however, most procedures are still performed via traditional femoral access sites. The femoral artery (FA) puncture remains a universally accepted entry point for lower extremity interventions, and it has stood the test of time. It is still widely used for several reasons: it is easy to access, it allows for the use of larger devices due to the vessel's larger caliber, and the complications associated with the puncture, along with their treatment options, are well understood. Despite these advantages, the femoral access site has several disadvantages that are not encountered with other access points, such as prolonged bed rest and a higher incidence of vascular complications [2]. However, it is important to note that the safety of the femoral approach has significantly improved with the widespread adoption of ultrasound-guided puncture and vascular closure devices.

Alternative access sites in PAD treatment include the upper limb arteries - the radial (RA) and brachial arteries (BA) [3,4] – as well as pedal access [5-7]. However, these sites have several limitations in everyday clinical practice. Despite these technical limitations, they have gained significant popularity in the field of peripheral interventions because they offer greater patient comfort and are associated with fewer vascular access site complications. This trend aligns with the current direction in healthcare to provide safe, effective care while reducing costs and minimizing risks.

The first randomized clinical trial in the literature comparing RA, BA and FA access was the ACCESS study, published in 1997 [8]. In this study 900 patients undergoing elective percutaneous coronary angioplasty were randomly assigned to radial, brachial, or femoral percutaneous transluminal coronary angioplasty performed with a 6F catheter. Failed

interventions were more frequent with radial catheterization, while the other two access types were associated with a higher incidence of serious complications related to the access site (0% vs. 2.3% vs. 2%; $p<0.05$). There was no significant difference in the number of devices used, fluoroscopy time, or the duration of the intervention.

Since the ACCESS trial, the success rate of interventions has improved with the development of more advanced tools. Agostoni et al. analyzed the results of randomized trials published up to 2003 comparing transradial and transfemoral access [9]. The meta-analysis reviewed data from 12 randomized studies involving 3.224 patients, including both diagnostic and therapeutic interventions. No significant difference in the frequency of adverse cardiac events was found between the two access methods. Radial interventions significantly reduced the number of complications related to the access site, but due to failed procedures, it was more often necessary to switch to a secondary entry site.

The aim of this doctoral thesis is to analyze the access sites used during peripheral interventions in terms of the anatomical approach, indications, advantages, disadvantages, and potential complications. Additionally, it presents the current state of peripheral interventional vascular approaches through three different clinical trials and interprets the scientific contribution of these results in the field of peripheral interventions.

1.2 Access Site Selection for Lower Limb Interventions

The choice of access site for lower limb interventions primarily depends on the technical possibilities and the accessibility of the lesions from an anatomical perspective. The traditional gold standard for lower limb interventions is FA access. Due to its location, FA access is generally easy for puncture and hemostasis, and it provides access to almost all arterial territories in most cases [10,11]. However, femoral puncture may inaccessible or only partially accessible in certain situations. In such cases, BA access can be a good alternative, particularly for aortoiliac, femoral, or popliteal interventions. BA access allows for the use of larger devices, up to 8 French sheaths, compared to RA or pedal access.

A common anatomical limitation of RA access is the distance between the puncture site and the target lesion. However, with the advent of dedicated peripheral intervention devices, radial and pedal access have recently gained great popularity, primarily due to their low rate of vascular complications and improved patient comfort [6,7,12,13].

Access site selection is particularly important in elderly patients, where the risk of intervention increases significantly compared to younger patients. This is due to the more frequent occurrence and more severe course of vascular complications. Transradial

catheterization often presents significant technical difficulties in this population because of the stiff, calcified, and tortuous vessels in the upper limbs. However, in the field of coronary angiography and percutaneous coronary interventions, the multicenter prospective OCTOPLUS study previously demonstrated that, in patients over 80 years of age, transradial access significantly reduces the occurrence of vascular complications without the need for switching to FA access in significant numbers due to technical obstacles [14]. Therefore, in elderly patients, despite the expected technical challenges, the use of transradial access is more justified than in younger populations.

1.3 Transbrachial Access for Lower Limb Interventions

1.3.1 Anatomy and Types of Access

The BA begins as a continuation of the axillary artery at the lower border of the teres major tendon and runs along the medial bicipital sulcus toward the elbow groove [15]. In the elbow groove, next to the tendon of the biceps brachii, it passes medially under the lacertus fibrosus [16]. The BA lies adjacent to the brachial veins, the median nerve, and the radial nerve. Within the cubital fossa, approximately 1 cm below the elbow, it divides into the radial and ulnar arteries. Its major branch is the profunda brachii artery, which originates under the teres major and latissimus dorsi muscles at the axillo-brachial transition and runs toward the dorsal side of the upper arm, accompanied by the radial nerve [15,16]. In case of BA occlusion, its extensive collateral network ensures blood supply to the arm.

Based on the anatomy of the BA, brachial puncture can be classified as follows (Figure 1):

1. **Low brachial puncture:** This access site is in the region of the antecubital fossa, where the biceps muscle extends into tendons. The vascular complication rate with this technique is relatively low [17].
2. **High brachial puncture:** The advantage of this puncture technique is that BA access and compression after the intervention are easier, potential hematomas can be recognized earlier, and there is less risk of nerve compression [18].

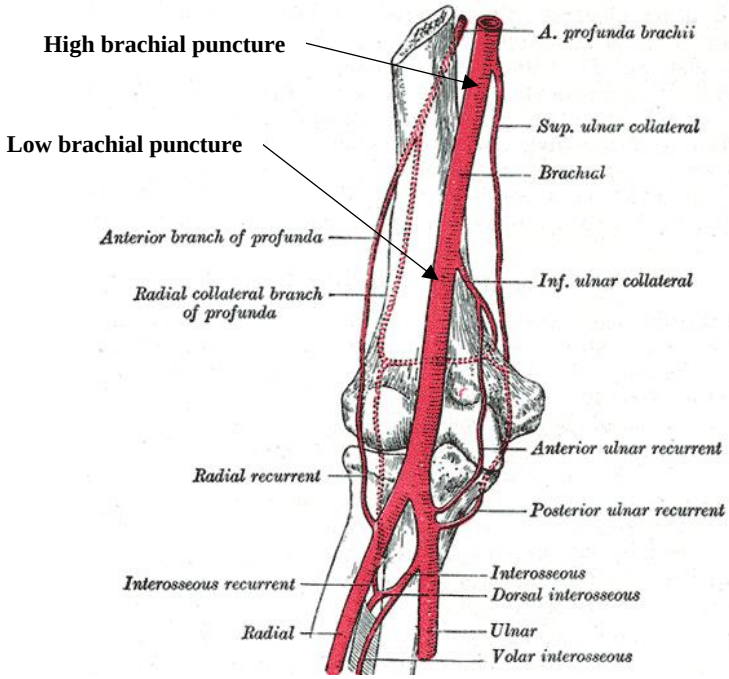

Figure 1. Anatomy of the brachial artery and brachial access types.

1.3.2 Possible Indications

- Severely diseased or occluded femoral or iliac arteries
- Failed femoral puncture
- Pathological abnormalities detected at the femoral puncture site or on the femoral artery (e.g., skin infections, inguinal lymphadenopathy, hematoma, aneurysm, pseudoaneurysm)
- Morbidly obesity

1.3.3 Relative Contraindications

- Tortuosity or stenosis of the subclavian artery
- Flexion contracture of the upper limb

1.3.4 Absolute Contraindications

- Amputation of the upper limb
- Occlusion of the subclavian artery

1.3.5 Limitations and Advantages

The main technical limitation is the challenge of intervening on vessels below the knee (BTK) due to the lack of adequately long devices. These vessels are difficult to reach from a BA puncture, and the number of potential complications is higher due to the long, tortuous vascular path [19,20]. Another disadvantage is the difficulty in ensuring sterility at the

penetration site and providing radiation protection for the operator's hands in the arm is positioned parallel to the body.

The major advantage of BA access compared to FA access is the significantly shorter recovery time after the intervention [21]. In the absence of complications, patients can often be managed within a day. Additionally, due to the anatomical location of the vessel, observation of the puncture site and recognition of complications are easier. Compared to RA access, the spasm rate of the BA is much lower, and it provides access to more distal lower extremity vascular territories [21].

1.3.6 Possible Complications

1.3.6.1 Vascular Complications

1. **Local hematoma:** Livid discoloration and swelling around the injection site. It mainly occurs when there is a high degree of anticoagulation or thrombolysis, or when compression is inadequate. Delayed treatment of a hematoma can lead to compression of surrounding tissues, potentially resulting in nerve palsy, limb ischemia, or even venous thrombosis [22].
2. **Pseudoaneurysms:** Usually a late complication occurring in 0.3-0.5% of cases. It develops when the injection site is not properly closed, allowing blood to enter the perivascular space and form a sac-like structure [23]. The sac's wall is formed by the hematoma and perivascular structures. Factors contributing to pseudoaneurysm development include long sheaths, uncontrolled hypertension, anticoagulation, improper puncture technique, calcified vessels, female gender, and inadequate post-procedure compression. Common symptoms include arm pain and local swelling, with a pulsating mass and systolic murmur detectable on physical examination [22]. Pseudoaneurysms may sometimes be asymptomatic, so if a patient experiences severe pain post-procedure, duplex ultrasound should be used to confirm or rule out the diagnosis. One of the most serious complications of a pseudoaneurysm is rupture, particularly if the sac exceeds 3 cm in size.
3. **Embolization:** A rare complication. Right-sided BA puncture increases the risk, as catheter manipulation through the aortic arch can lead to plaque rupture and embolization into the carotid and vertebral arteries, potentially causing ischemic stroke. The risk of embolization is higher with BA puncture than with RA access.
4. **Thrombosis:** One of the most significant complications, with an incidence of 1-6%. Thrombosis is typically caused by endothelial damage from the catheter or guidewire

(GW). Women are at higher risk due to smaller vessel diameters [20]. The risk of thrombosis increases with larger catheter sizes and may be exacerbated by reduced cardiac output, inadequate anticoagulation, or insufficient antiplatelet therapy [20].

5. **Infections:** Infections can occur due to the entry of various microorganisms through the skin or catheters, or through hematogenous spread from distant sites. Aseptic precautions and antibiotic use are recommended in the presence of a hematoma.

1.3.6.2 Neurological Complications

Paralysis of the median, ulnar, or radial nerves can occur during BA catheterization, caused by direct nerve compression, compression by a hematoma or pseudoaneurysm, secondary ischemic damage, or direct nerve injury during arterial puncture [24]. Consequently, thorough and close monitoring of the penetration site and the affected limb is necessary after the intervention.

1.4 Transfemoral Access for Lower Limb Interventions

1.4.1 Anatomy and Types of Access

Below the inguinal ligament, the FA continues as an extension of the external iliac artery (Figure 2) [15]. Initially, it descends through the iliopectineal fossa and then into the anterior muscular compartment of the thigh. This compartment is bordered by the adductor longus and vastus medialis muscles. The lower part of the compartment is covered by a strong, deep fascia known as the lamina vastoadductoria, which forms the adductor canal [15]. The FA lies lateral to the femoral vein in the upper third of the thigh. From the adductor canal, the vascular sheath containing the artery and vein enters the popliteal groove through the adductor hiatus, where they continue as the popliteal artery and vein. One of the FA's most significant branches is the profunda femoris artery (PFA), which branches off approximately 4 centimeters below the inguinal ligament, slightly laterally and posteriorly. The PFA is crucial in cases of FA occlusion, as it supports a rich collateral network to maintain distal blood supply [15].

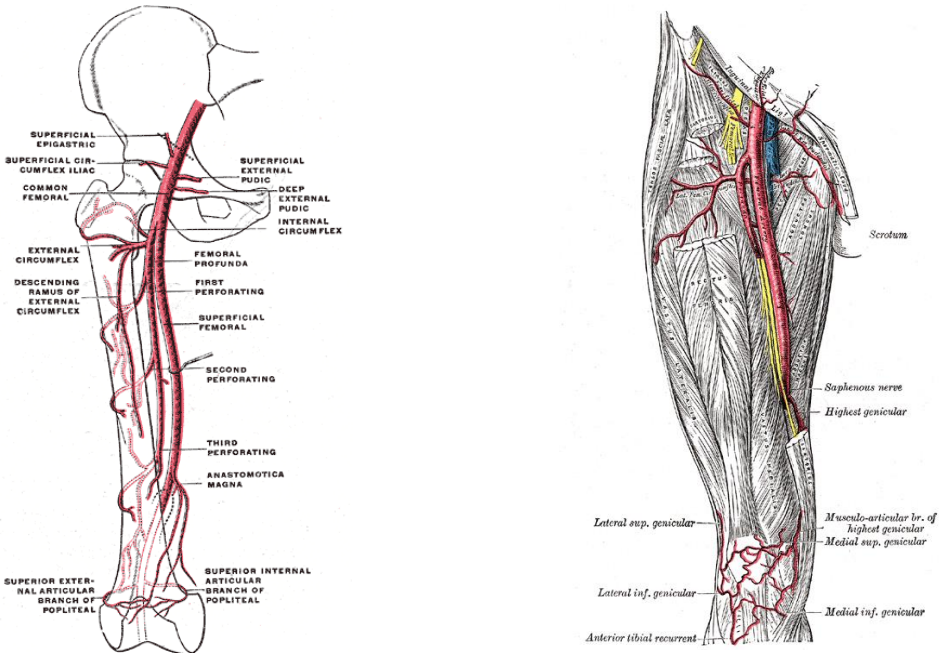

Figure 2. Anatomy of the femoral artery and its course in relation to different tissue structures.

The selection of the appropriate access site is facilitated by anatomical reference points, which are determined based on both bony and soft tissue landmarks (Figure 3).

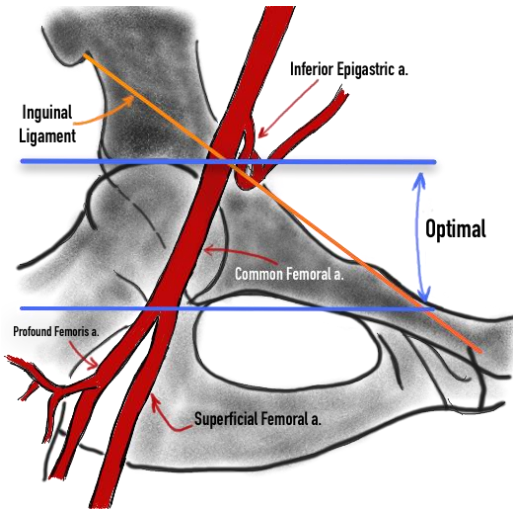

Figure 3. Ideal puncture site of the common femoral artery according to anatomical landmarks.

A high FA puncture increases the risk of retroperitoneal hemorrhage, while a low puncture increases the risk of pseudoaneurysm or arteriovenous fistula. A high puncture can damage the inferior epigastric artery, leading to retroperitoneal bleeding, whereas a low puncture makes adequate hemostasis difficult due to the absence of a bony surface. In addition to orientation based on the physical examination, the puncture should be guided by fluoroscopy, as in the vast majority of patients, the common femoral artery (CFA) runs along

the medial third of the femoral head [25,26]. In recent years, ultrasound-guided FA puncture has gained increasing popularity, which may be attributed to the "loss of femoral puncture skill" due to the more frequent use of RA puncture. The FAUST study prospectively analyzed the importance of ultrasound-guided punctures during interventions [27]. Compared to fluoroscopically guided vascular access, ultrasound guided access improved the rate of adequate cannulation in patients with high CFA bifurcations (82.6% vs. 69.8%; $p<0.01$), improved success rates (83% vs. 46%; $p<0.0001$), reduced the number of attempts (1.3 vs. 3; $p<0.0001$), and decreased the risk of vein puncture (2.4% vs. 15.8%; $p<0.0001$). The use of ultrasound is particularly important in elderly, obese patients or in those for whom thrombolysis is planned, to reduce the risk of bleeding. It also allows for the avoidance of puncturing significantly calcified sections of blood vessels, which often leads to inadequate hemostasis.

Three different types of femoral puncture can be distinguished depending on the section of the vessel being treated and the technical limitations:

1. **Antegrade puncture:** Primarily used for direct access to the femoropopliteal segment and BTK lesions. This approach enables the use of less contrast medium and provides stronger support in cases of chronic occlusions. It is also preferred for complex interventions, as it allows for better catheter and wire manipulation. Fluoroscopy or ultrasound guidance is recommended to prevent the GW from slipping into the PFA.
2. **Retrograde puncture:** Conventionally used during ipsilateral iliac interventions or when using a crossover approach for contralateral iliac or femoropopliteal interventions.
3. **Contralateral access:** The most common approach for treating infrainguinal lesions is contralateral femoral puncture. Several diagnostic catheters (e.g., Simmons1, IMA, Cobra) are suitable for performing the crossover, and in most cases, it is necessary to advance a hydrophilic GW to the opposite side first, which is then replaced by an extra-support GW through the diagnostic catheter. Contralateral access should be avoided in cases of extremely angulated aortic bifurcations or stenosis at the origin of the CFA.

1.4.2 Relative Contraindications

- Obesity
- Extensive postoperative scarring
- Aorto-bifemoral bypass
- Lower limb amputation
- Aortic aneurysm

1.4.3 Absolute Contraindications

- Aortic occlusion
- Leriche-syndrome
- Aortic aneurysm with thrombus

1.4.4 Possible Complications

The main disadvantage of femoral access is the high incidence of vascular complications, which can be reduced primarily through the use of fluoroscopy or ultrasound guidance, appropriate compression, or femoral closure devices. However, despite our best efforts, the incidence of complications remains relatively high, which in certain cases increase mortality, prolong hospital stays, and raise medical costs [2,28]. The most frequently occurring complications and their treatment options are listed in Table 1.

Table 1. Complications related to femoral access and their treatment options.

COMPLICATIONS	FURTHER COMPLICATIONS	TREATMENT OPTIONS
Hematoma	Anemia, Neuropathy	Conservative treatment strategy, Hematoma evacuation
Retroperitoneal hemorrhage	Anemia, Neuropathy, Hemorrhagic shock	Surgical treatment
Thrombosis / Embolism	Potential loss of limb	Catheter directed thrombolysis, Aspiration thrombectomy, Surgical thrombectomy or embolectomy
Infection	Septic shock	Conservative treatment strategy, Surgical treatment (hematoma evacuation)
AV-fistula	Claudication, Steal syndrome, High-output cardiac failure	Local compression, Surgical treatment, Transcatheter embolization
Pseudoaneurysm	Anemia, Neuropathy, Rupture, Embolization	Local compression, Ultrasound guided thrombin injection, Surgical treatment

1.5 Transpedal Access for Lower Limb Interventions

1.5.1 Basic Anatomy and The Use of Transpedal Access

In coronary revascularization, transradial arterial access has been shown over the years to be safer than the traditional transfemoral approach. This has led to a steady increase in the number of transradial coronary interventions [29]. Similarly, efforts to reduce the vascular complications associated with endovascular peripheral procedures have spurred the search for alternative arterial access sites, such as the transpedal (TP) approach [30]. The safety and

effectiveness of this approach have been demonstrated in numerous studies [6,7,31-33]. Potential benefits include early patient ambulation, early discharge, and improved patient satisfaction [34,35]. The only complicating factor is the learning curve associated with this alternative access point.

Pedal entry options include the dorsal pedal (DP) artery / anterior tibial artery (ATA), posterior tibial (PT) artery, and peroneal artery (PA) (Figure 4).

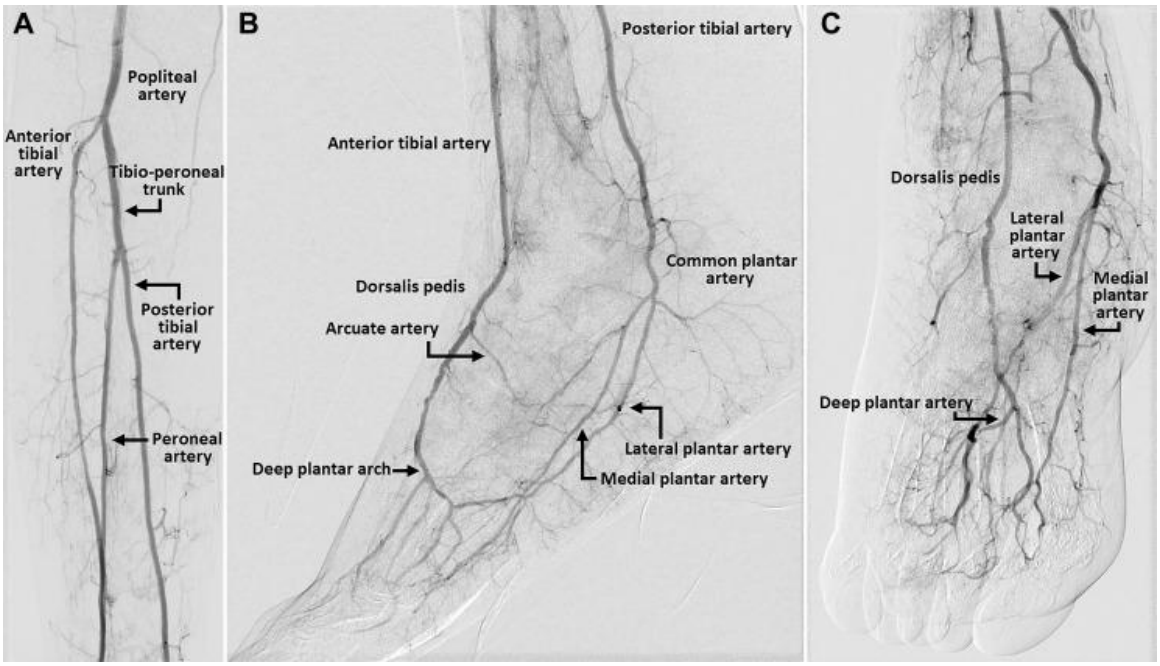

Figure 4. Normal angiographic anatomy of the below-the-knee arteries.

The BTK arteries are supplied by branches of the popliteal artery at the upper edge of the interosseous gap between the tibia and fibula [15]. The ATA runs within the extensor compartment of the leg, then passes to the dorsum of the foot under the retinaculum musculorum extensorum, which compresses the tendons of the extensor muscles. From there, it continues as the DP artery, running beneath the tendons of the extensor muscles toward the 1st interosseous space [15]. The DP artery penetrates deep into the sole and gives branches to the medial and lateral ankle. The PT artery runs between the superficial and deep layers of the leg's flexor muscles and later between the tendons of the flexor digitorum longus and flexor hallucis longus muscles. Its branches include the PA and the medial and lateral plantar arteries, the latter of which forms the arterial arch of the sole in conjunction with the DP artery [15].

Puncture is almost always performed under the guidance of color Doppler ultrasound. This allows for the selection of the appropriate vessel, determination of the vessel size, and avoidance of vein puncture, especially when manipulating the PT artery. The color flow also

shows the anterograde or retrograde flow, which helps identify CTOs and estimate lesion lengths. Vessel wall calcification and plaque locations can also be identified, facilitating the selection of the ideal puncture point [6].

Puncture by palpation is an option, but in the vast majority of patients, pulsation is not palpable due to diffuse peripheral vascular disease. Fluoroscopy can be used during the puncture procedure if the vessel walls are heavily calcified. Angiographic road-mapping, in which anterograde angiography is performed from an FA or RA access site to identify the pedal vessels, is also useful in access point selection [6].

1.5.2 Possible Complications

1.5.2.1 Major Complications

The incidence of major complications with TP access is very low, as supported by several studies. Most major complications are iatrogenic, resulting from the intervention itself, and include vessel occlusion or acute thrombosis, potentially leading to amputation or, very rarely, death. These complications are mainly due to damage caused by interventional devices within the vessel or inadequate anticoagulation during the procedure. However, in the vast majority of studies investigating retrograde access, no major adverse events were reported [6,34,36,37].

1.5.2.2 Minor Complications

The incidence of minor complications is also low, and they are relatively easy to manage. These are mostly vascular complications related to the entry site, including hematoma formation, vessel occlusion, vasospasm, or pseudoaneurysm formation. Vascular occlusion can be easily treated with anterograde balloon dilatation, and vasospasm can be managed with intra-arterial nitroglycerin administration [7]. Pseudoaneurysms can be successfully treated with ultrasound-guided thrombin injection, with an almost complete success rate and no occurrence of ischemia, rupture, or thromboembolization [38].

Several strategic considerations are necessary to reduce the number of vascular complications. Ultrasound guidance is required to choose the optimal puncture point, which should be on an intact vessel section. After access is gained, careful guidewire manipulation and the use of a hydrophilic glide sheath are recommended to avoid iatrogenic vessel wall trauma. Additionally, the use of an intra-arterial antispasmodic cocktail and appropriate anticoagulation is essential. After the procedure, the sheath should be removed immediately, followed by appropriate hemostasis.

1.6 Transradial Access for Lower Limb Interventions

1.6.1 Development and Types of Transradial Access

Interventional cardiology has seen revolutionary changes in coronary revascularization since the 1980s. Lucien Campeau performed the first radial angiogram at the Montreal Heart Institute in 1989 [39]. Campeau's study recommended using 5F diagnostic catheters to access the radial arteries, aiming to reduce the rate of bleeding complications. Ferdinand Kiemeneij performed the first transradial PCI on August 14, 1992 [40]. Despite the slower development that followed, the trend toward transradial puncture has grown, making it almost the primary access point. While FA puncture used to be the traditional access point for most diagnostic and therapeutic interventions, transradial access has gained increasing importance due to its lower vascular complication rate, faster mobilization, and better patient comfort [41,42]. Numerous randomized clinical trials have confirmed the superiority of transradial access in reducing bleeding risk and mortality. Based on this evidence, the European Society of Cardiology designated transradial access as the site of choice for coronary interventions in 2013 and again in 2015 as Class I Level B recommendation [43]. In 2021, both the American and European guidelines confirmed this for both stable and acute patients [44,45].

Transradial access for peripheral procedures has since been proven safe and feasible by several studies and reports [46,47]. Initial cases involved treating subclavian and aortoiliac lesions, as well as renal and mesenteric arteries. Since then, it has also been used for complex peripheral and BTK interventions.

Recently, there has been growing interest in DR artery access. Since 2017, several studies have been published, with Kiemeneij et al. first reporting the high success rate of DR artery access [48]. The first randomized trial, the DAPRAO trial, opened new horizons [49]. Since then, DR access has become increasingly widespread in endovascular interventions, recognized for its high success rate, low complication rate, and many advantages over PR artery access [48,50-53].

1.6.2 Proximal Radial Artery Access

The artery is punctured 2 cm proximal to the styloid process at an angle of 30-45 degrees [54]. Due to its superficial location, the artery is easy to locate, puncture, and compress. One of its most important features is the bony base, which makes the artery relatively easy to puncture despite its small size, as the radius prevents its displacement. However, especially in elderly patients, the RA, with its stiff walls and elongated, winding course within loose subcutaneous tissue, can easily escape the needle. Due to the lack of a soft tissue compartment,

significant blood loss is unlikely, and bleeding is quickly recognized, in contrast to bleeding from the FA. Furthermore, in the majority of patients, satisfactory collateral circulation from the ulnar artery helps prevent ischemic damage to the hand, even in case of complications [8].

1.6.3 Distal Radial Artery Access

Distal to the styloid process of the radius, the radial artery forms the superficial palmar arch with its branches, then crosses the anatomical snuffbox under the tendons of the abductor pollicis longus and extensor pollicis brevis muscles, directly above the scaphoid and trapezium bones. The RA continues on the dorsum of the hand and finally curves medially into the palm, connecting with the ulnar artery branch to form the deep palmar arch [55]. Figure 5 shows the anatomy of the DR artery and possible alternative puncture points. These puncture points are located further from the carpal anastomotic networks and the superficial palmar arch but offer the same advantages as conventional RA access. Additionally, they allow for the maintenance of antegrade flow in the PR artery during hemostatic compression of the DR artery, reducing the risk of radial artery occlusion (RAO) [56]. Another advantage of the DR technique compared to traditional PR artery puncture is faster hemostasis, greater comfort for both the patient and the operating physician, and preservation of the PR artery segment for future interventions or arterial graft harvesting [57,58].

However, the smaller size of the DR artery may require special devices. Additionally, due to pronounced tortuosity and angulation, the course of the vessel is less predictable, which may result in more puncture attempts [56].

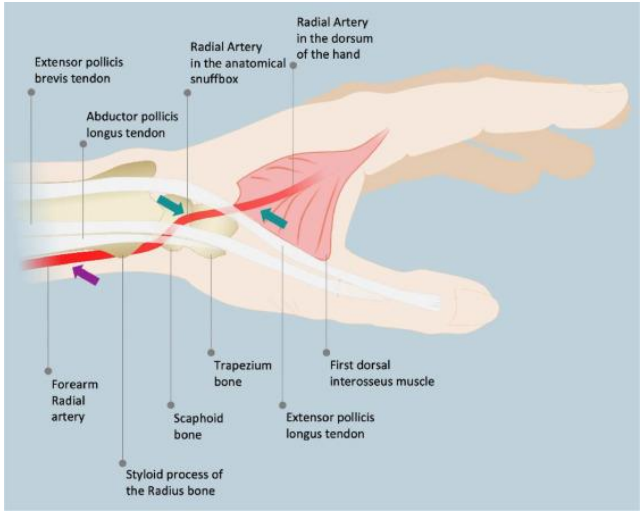

Figure 5. Anatomically determined location of DR artery puncture. The purple arrow shows the location of the traditional PR artery puncture, while the blue arrows indicate the corresponding puncture points of the DR artery.

1.6.4 Possible Complications of Transradial Access

One of the most common complications of transradial access is spasm of the RA. The mechanical stimulus caused by the puncture and the GW can directly provoke vasospasm, while the pain caused by manipulation can indirectly trigger it. Vasospasm can reduce patient comfort, hinder catheter movement, and often lead to the failure of the intervention. To reduce the likelihood of vasospasm, spasmolytic treatment can be used, along with appropriate local anesthesia, atraumatic puncture techniques, and the use of hydrophilic-coated devices [54].

Although vascular complications are rare, early detection is crucial. Small hematomas often form following transradial puncture and typically respond well to conservative therapy. However, patients who complain of pain or paresthesia require a thorough investigation. The progression of hematomas can be prevented with gentle compression.

Dissection or perforation of the RA can occur due to wires or catheters. In such cases, the initial reaction may be to terminate the procedure, but if it can be safely continued, this is often the best course of action. The catheter can tamponade the vessel, and the dissection or perforation usually resolves by the end of the procedure. This can be confirmed with arteriography performed at the conclusion of the intervention.

According to literature, the incidence of RAO after intervention ranges from 1% to 10% [59]. These occlusions are typically asymptomatic but can cause arm pain and discomfort. Vascular ultrasound can be used to verify RAO and assess the patency of the ulnar artery. Preventive measures, including the administration of heparin, the use of smaller sheaths, and adequate hemostasis, can help minimize the rate of RAO.

2. OBJECTIVES

The common goal of the research that forms the basis of the thesis was to compare and analyze the success and complication rates of different access sites in patients undergoing percutaneous intervention due to acute or chronic limb ischemia.

2.1 The Clinical Impact of Access Site Selection for Successful Thrombolysis and Intervention in Acute Critical Lower Limb Ischaemia (RAD-ALI Registry)

ALI is of great clinical importance due to its consequent serious complications and high comorbidity and mortality rates. Current advances in endovascular therapy enable prompt treatment of ALI; however, most treatment is performed via traditional FA access sites. Alternatives to FA access in ALI are the upper limb access sites of the RA and BA or pedal access, but these access sites have many limitations in everyday clinical practice. Our primary aim was to investigate the rate of complications related to the access site in patients with acute limb vascular occlusion. In addition to the objective that forms the basis of this thesis, our additional goal was to investigate the 1-year outcomes of CDT and mechanical thrombectomy (MT) for ALI and to evaluate predictors of long-term outcomes of CDT and MT in lower limb arteries.

2.2 TRIACCESS Study: Randomized Comparison Between Radial, Femoral, and Pedal Access for Percutaneous Femoro-popliteal Artery Angioplasty

The main anatomical limitation of percutaneous SFA interventions is the narrow access lumen in the case of upper extremity and BTK arteries, while in the case of RA the limitation is the distance between the puncture point and the target lesion. The aim of this randomized study was to compare the success and complication rates of different access sites during the percutaneous endovascular treatment of SFA stenoses, as well as the crossover to another puncture site.

2.3 Distal Radial Artery Access for Superficial Femoral Artery Interventions

The standard access site used during coronary interventions is the PR artery, which has recently gained more popularity in peripheral interventions as well, due to better patient comfort and the low rate of major access site complications. During percutaneous SFA interventions, the PR access has a high technical success rate and a low rate of major access site complications, but RAO occurs in up to 5%. DR artery access, initially only used during Cimino fistula percutaneous transluminal angioplasties (PTAs), is now used during both coronary and peripheral interventions. The main advantages of this type of access are easy

compressibility and a low incidence of RAO. The aim of this study was to evaluate the acute success and complication rates of DR approach and to compare it with the results of conventional PR approach during SFA interventions.

3. METHODS

3.1 The Clinical Impact of Access Site Selection for Successful Thrombolysis and Intervention in Acute Critical Lower Limb Ischaemia (RAD-ALI Registry)

3.1.1 Study Design and Patient Population

Between 2008 and 2019, consecutive patients with ALI were treated with CDT in a large community hospital (data collection and systematization, data analysis, performing statistical tests and drawing conclusions). We collected the data of these patients and performed a retrospective analysis. We enrolled only patients who, based on the decision of the vascular team, underwent CDT. Patients were randomized to the RA (n=17), BA (n=9) and FA (n=58) groups. Access site selection was operator decision and all procedures were performed by five skilled operators. The National Ethical Review Committee (reference number BMEÜ/1639-1/2022/EKU) approved the study. All study activities were in accordance with the ethical standards of the Hungarian Medical Research Council and with the 1964 Helsinki Declaration. Written informed consent was obtained from all patients prior to their inclusion in the study.

We performed a retrospective, single center trial (Bacs-Kiskun County Teaching Hospital, Kecskemet, Hungary).

3.1.2 Inclusion and Exclusion Criteria

Inclusion criteria: Patients with ALI classified as Rutherford stage I, IIA, or IIB; acute lower extremity vascular occlusion confirmed based on emergency diagnostic angiography; clinic attendance starting within 14 days; age > 18 years; and had signed the patient information sheet and consent form were included.

Exclusion criteria: Patients were excluded if they had a non-viable lower limb (Rutherford stage III); did not sign the patient information sheet or the consent form; had hemodynamic instability; did not have significant vascular occlusion on diagnostic angiography; were not admitted to the clinic within 14 days; age<18 years; or had inflammatory skin lesions at the planned penetration sites; presence of contraindications for acute lower extremity thrombolytic therapy:

ABSOLUTE MAJOR	RELATIVE MAJOR	MINOR
- continuous or active bleeding - intracranial hemorrhage - compartment syndrome - severe limb ischemia that warrants immediate surgery	- major surgery or trauma in the last 10 days - uncontrolled hypertension: 180 mmHg systolic or 110 mmHg diastolic blood pressure - non-compressible vascular puncture - intracranial tumor - recent eye surgery - neurosurgery within 3 months - sensitivity or allergy to contrast material or the thrombolytic - intracranial trauma within 3 months - gastrointestinal bleeding within 10 days - confirmed cerebrovascular event (including TIA within two months) - recent internal or non-compressible bleeding	- liver failure, including coagulopathy - bacterial endocarditis - pregnancy or postpartum - diabetic hemorrhagic retinopathy - life expectancy<1 year

3.1.3 Procedural Endpoints

Primary endpoints ("safety endpoints"): major adverse events (MAEs), major adverse limb events (MALEs), and occurrences of complications related to the access site.

Secondary endpoints ("efficacy endpoints"): technical and clinical success, efficacy of the treatment, fluoroscopy time, radiation dose, procedure time, and the crossover rate to an alternative puncture site.

3.1.4 Antithrombotic and Thrombolytic Regimen

CDT involved the use of a recombinant tissue plasminogen activator administered directly into the artery. It consisted of an initial dose of 10 mg followed by a maintenance dose of 1 mg/h. Intravenous sodium heparin was administered to prevent catheter thrombosis. The heparin was administered as an initial bolus of 60 IU/kg and a maintenance dose of 1000 IU/h, adjusted based on the activated partial thromboplastin time. After a loading dose of 300 mg

aspirin and 300 mg clopidogrel, patients who underwent stenting procedures, were received a dual antiplatelet therapy regimen consisting of 100 mg aspirin and 75 mg clopidogrel daily for 2 months. Conversely, patients who solely underwent only balloon angioplasty were prescribed received lifelong aspirin therapy.

3.1.5 Catheter Directed Thrombolysis

Arteriography and thrombolysis should be considered in patients in whom the etiology is in favor of ALI or where arterial thrombosis is strongly suspected based on the physical examination. The implementation of local thrombolysis basically follows standard endovascular principles and norms. As a first step, the carefully selected arterial penetration point is punctured (if available, under ultrasonography guidance). CDT was performed after selective angiography over a 5F pigtail catheter. The CDT was always initiated after a guidewire transversal test was conducted (the lesion was passed with a 0.18-inch guidewire) over a multiport thrombolytic catheter. Thrombolysis was continued for at least 12, optimally 24 h and reimaging was performed to determine success of thrombus dissolution (thrombolysis beyond 48 h entails an extremely high risk of bleeding with a substantially unchanged success rate). If the thrombus continued to impede or completely block the flow despite the use of thrombolysis, additional thrombus aspiration was conducted. Similarly, if the lesion was significantly stenosed or dissected, additional balloon angioplasty or stent implantation was performed (Figure 6). The choice of treatment varied based on the location of the occlusion, the extent of clot formation, and the etiology.

In cases of thromboembolism, vascular surgery was the preferred treatment and the decision was reached after consultation among the members of the vascular team. In cases of atherothrombosis, CDT was the preferred treatment, and the vascular team also made this decision. Based on the above, only patients who underwent thrombolysis were included in our present study.

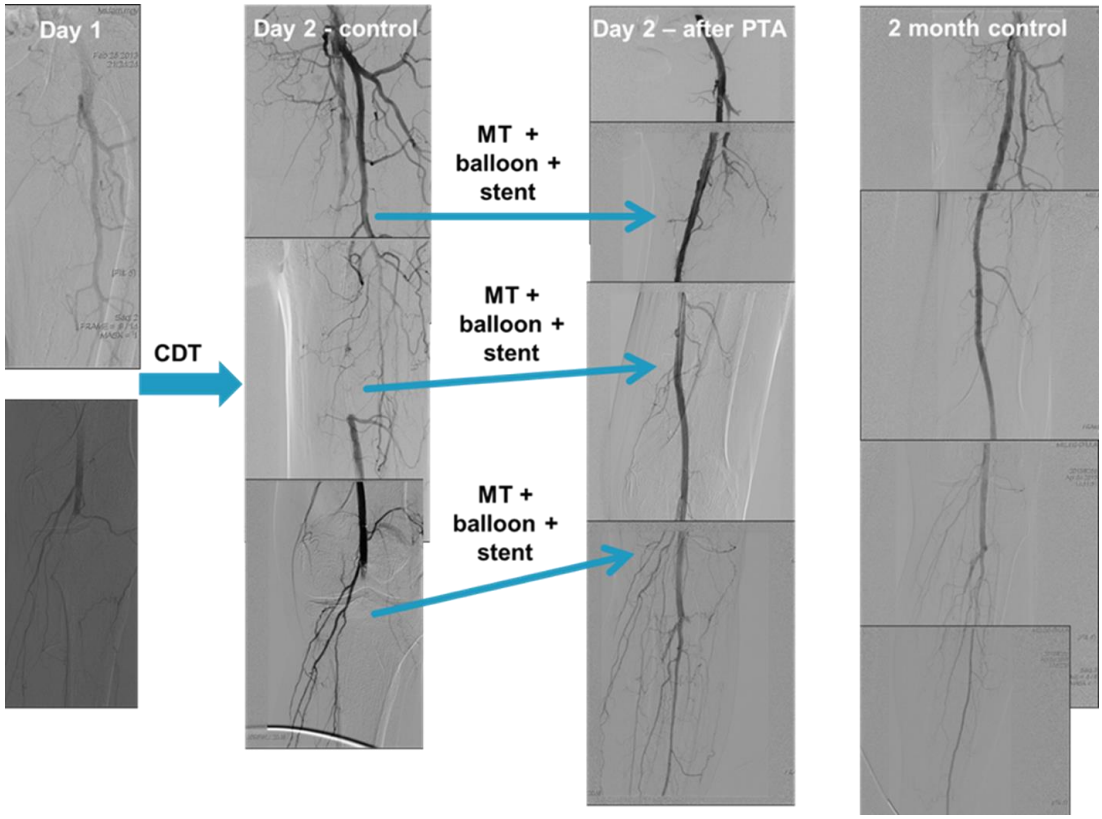

Figure 6. Catheter-directed thrombolysis (CDT) performed via access from a radial artery. Selective angiography performed using a radial approach (over a 5F pigtail catheter) shows a left common femoral artery occlusion without distal run-off. (Day 1) A guidewire transversal test, in which the lesion was passed with an 0.18-inch guidewire, was conducted over a multiport thrombolytic catheter. CDT was then initiated. On the first postoperative day, control angiography shows incomplete thrombus resolution and distal embolization. (Day 2—control) Mechanical thrombectomy, additional balloon angioplasty, and stent implantation was performed in the left superficial femoral artery and in the left popliteal artery. Control angiography shows successful recanalization with acceptable flow in the BTK arteries. (Day 2—after PTA). Abbreviations: CDT—catheter-directed thrombolytic therapy; MT—mechanical thrombectomy; PTA—percutaneous transluminal angioplasty.

3.1.6 Definitions

3.1.6.1 Major Adverse Event

A MAE was evaluated by considering a combination of outcomes, including death, myocardial infarction, stroke, major amputation of the lower limb, and the need for repeat revascularization procedures of the target vessel by percutaneous transluminal angioplasty or by arterial bypass graft surgery during the follow-up period.

3.1.6.2 Major Adverse Limb Event

A MALE was defined as either untreated loss of patency of the revascularization, reintervention on the revascularized segment, or major amputation (above or BTK) of the revascularized limb.

3.1.6.3 Vascular Complication

Major vascular complications referred to a reduction in, or total loss of, the arterial pulse or the emergence of a pseudoaneurysm or arteriovenous fistula as identified during the patient's follow-up examination. Minor vascular complications were characterised as hematomas that did not necessitate any specific intervention. These hematomas were limited to a size of 2 cm in diameter in the puncture areas of the RA or ulnar artery, or 5 cm in diameter in the puncture areas of the FAs or BAs. A drop in the hemoglobin level of more than 3 g/dL was considered major bleeding, as was bleeding that required transfusion.

3.1.6.4 Technical Success

The successful outcome of a technical procedure occurred when a PTA led to a residual stenosis of less than 30% while ensuring satisfactory anterograde blood flow. A suboptimal result was identified by a slow flow and/or a residual stenosis of between 30% and 50% after PTA.

3.1.6.5 Clinical Success

The primary measure of clinical success involved observing an enhancement of at least one clinical category within the Rutherford classification. Primary patency referred to the condition where a treated lesion remained open and unobstructed over time, without requiring any additional medical procedures such as angioplasty, surgery, or amputation. Limb salvage was the successful prevention of major amputation, preserving the affected limb. We also evaluated the treatment as a success if the functionality of the limb was maintained in the first 7 days and no major amputation occurred.

3.1.6.6 Access-Site Crossover

If technical difficulties arose in connection with the intervention performed through the primary penetration site, or if performing the intervention from this puncture point was not possible, the use of a 'crossover' site was deemed necessary. That is, the puncture area was switched to another puncture area.

3.1.7 Follow-up

All patients underwent a physical examination immediately after the procedure and every day during hospitalization. In the third, sixth, and twelfth months after the intervention, a detailed clinical follow-up examination was performed on all patients.

3.1.8 Statistical Analysis

The unordered chi-squared test with a simulated p-value (10^7 replicates) was employed to evaluate categorical data. Pairwise comparisons were made using Fisher's exact test adjusted according to the Benjamini–Hochberg method to account for multiple comparisons [60]. For ordered larger contingency tables, the ordered approximative general independence test (10^7 resamples) was employed. All continuous parameters showed non-normal distribution; therefore, they were described using the median and interquartile range. The three treatment groups were evaluated using the approximative Kruskal–Wallis's test (10^7 resamples), using the Dunn's test and the Holm adjustment as a post hoc test in cases of statistical significance. The null hypothesis was rejected if p was ≤0.025. All analyses were carried out with R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) using the additional packages coin 1.4-2, R companion 2.4.30, and Dunn test 1.3.5. All analyses were conducted on an intention-to-treat basis. Cox regression was performed using MedCalc version 22.016 (MedCalc Software Ltd., Ostend, Belgium) statistical software. $p<0.05$ was considered statistically significant.

3.2 TRIACCESS Study: Randomized Comparison Between Radial, Femoral, and Pedal Access for Percutaneous Femoro-popliteal Artery Angioplasty

3.2.1 Study Design and Patient Population

In the prospective, multicenter study conducted between 2018 and 2019, 180 symptomatic patients with SFA stenosis were randomized between RA (n=60), FA (n=60) and TP (n=60) access site groups. Randomization was performed blindly using sealed envelopes. All cases were performed by 3 operators trained in both transradial and transpedal access sites. The National Ethical Review Committee (OGYÉI/2499/2018) approved the study, and all patients signed a patient informed consent form before enrollment.

3.2.2 Inclusion and Exclusion Criteria

Inclusion criteria: Patients with significant SFA stenosis, claudication (Fontaine IIa, IIb, III, IV), or CLI (ischemic rest pain, crural or pedal ulcer and gangrene).

Exclusion criteria: Patients were excluded who did not have access to all the penetration gates (RA, FA, TP) recorded in the study, occlusion of more than 2 BTKs, isolated popliteal artery disease, non-viable lower limb, strict contraindication to double antiplatelet therapy planned for at least 1 month, heart failure (ejection fraction<35%), significant valvular disease, age over 85 years, severe renal failure (glomerular filtration rate<30 mL/kg), sepsis, a co-morbidity with a life expectancy of less than 3 years.

3.2.3 Procedural Endpoints

Primary endpoints: major adverse limb and cardiac events at one- and six-month follow-up periods, procedural success.

Secondary endpoints: clinical success, occurrence of complications related to the access site, procedural or renal complications, hospitalization time, fluoroscopy time, radiation dose, procedure time, contrast consumption and the crossover rate to an alternative puncture site.

3.2.4 Antithrombotic Regimen

After administration of a loading dose of 325 mg aspirin and 300 mg clopidogrel, patients who underwent stent implantation received dual antiplatelet therapy for 2 months (100 mg aspirin and 75 mg clopidogrel per day). Patients who underwent balloon angioplasty received lifelong aspirin therapy. Initially, for the intervention, 5000 IU of heparin sodium and 250 ug of nitroglycerin were injected into the radial or pedal artery through the sheath. In addition, the patient received additional heparin sodium to reach a dose of 100 IU/kg. Routine ACT measurement was not performed during the interventions.

3.2.5 Description of SFA Intervention

In all cases, the punctures were performed under the guidance of vascular ultrasound. On the first postoperative day, the patency of the radial, femoral and pedal arteries was also checked by ultrasound.

3.2.5.1 SFA Intervention from RA

After local anesthesia, the puncture of the RA and the insertion of the sheath (Terumo Co., Japan, 5F) were performed. A GW was inserted into the descending aorta using a pigtail catheter. In the case of complex aortic anatomy, we reached the descending aorta with the help of a loop technique with a pigtail catheter or with the use of a Simmons catheter. Afterwards, aortography was performed from an anteroposterior projection with a 5F 125 cm pigtail catheter. After that, the introducer sheath and the diagnostic catheter were replaced with a

dedicated RA sheathless guiding catheter (Asahi Co., Japan, 6.5F 90 cm or 6F 120 cm) through a 260 cm long, 0.035 GW (Starter or Jindo, Amplatz). After angiography, the CFA was cannulated using a telescopic method with a 125 cm multipurpose diagnostic catheter, and then the lesion was passed with the GW. For balloon dilations, we used balloons with a shaft length of 180 cm (Pacific Extreme). Stent implantation was performed only in case of significant recoil or flow-limiting dissection. Self-expanding stents with a shaft length of 180 cm (Sinus Superflex; Optimed) were used from the RA approach. In the case of complex, highly calcified lesions, the TP route with Supera (Abbot Co.) or Zilver PTX (Cook) stents was chosen as the second access port. All stents were post-expanded. After the intervention, the sheath was immediately removed, and a dedicated radial compression device (Terumo Band; Terumo Co.) was used for 4 hours to ensure adequate hemostasis [61]. SFA intervention performed from transradial penetration is shown in Figure 7.

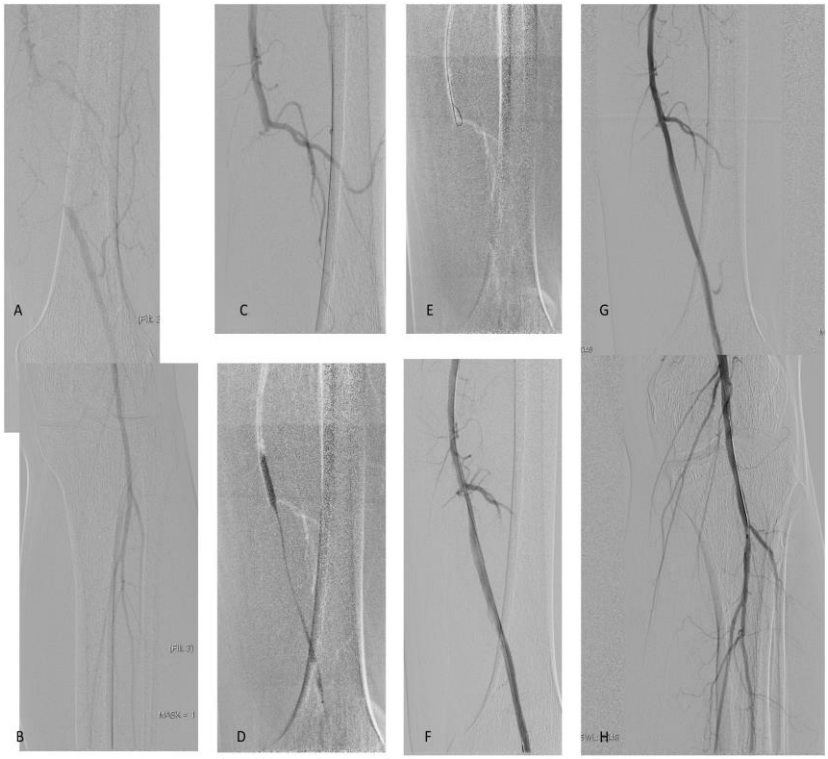

Figure 7. SFA intervention from transradial access. (A-C) Angiography shows right SFA CTO. (D) Selective angiography. (E) Subintimal angioplasty with balloon support. (F) After successful reentry and balloon angioplasty. (G-H) Final angiography shows good flow without dissection.

3.2.5.2 SFA Intervention from FA

Because of the better catheter and GW manipulation, we primarily preferred anterograde puncture in the case of complex interventions. After a successful puncture, a 6F sheath (Cordis) was introduced into the SFA. Contralateral femoral penetration was used in case of obesity or severe CFA calcification. A 4F sheath (Cordis) was used and the contralateral iliac artery was reached with a 150 cm 0.035 guide wire using a 4F USL catheter (Cordis). After that, the 4F sheath was replaced with a 45 or 65 cm 6F guiding sheath (Terumo Co.).

The contralateral access site was closed with Angio-Seal vascular closer device (Terumo Co.), while a compression bandage was applied to the anterograde puncture site after manual compression for 6 hours.

3.2.5.3 SFA Intervention from TP

After ultrasound-guided puncture, the TP artery was cannulated using a 4F Terumo TR sheath. The lesion was passed with a 0.14-inch Progress 40 GW using a 0.35-inch CX support catheter (Cook). After balloon angioplasty, stenting was performed only in case of flow-limiting dissection. In the case of 6F compatible stents, the initial sheath was replaced with a 6F slender sheath (Terumo). After the intervention, the sheath was immediately removed and a non-occlusive dressing was applied for 4 hours [6]. All patients were mobilized immediately after the intervention. SFA intervention performed from TP approach is shown in Figure 8.

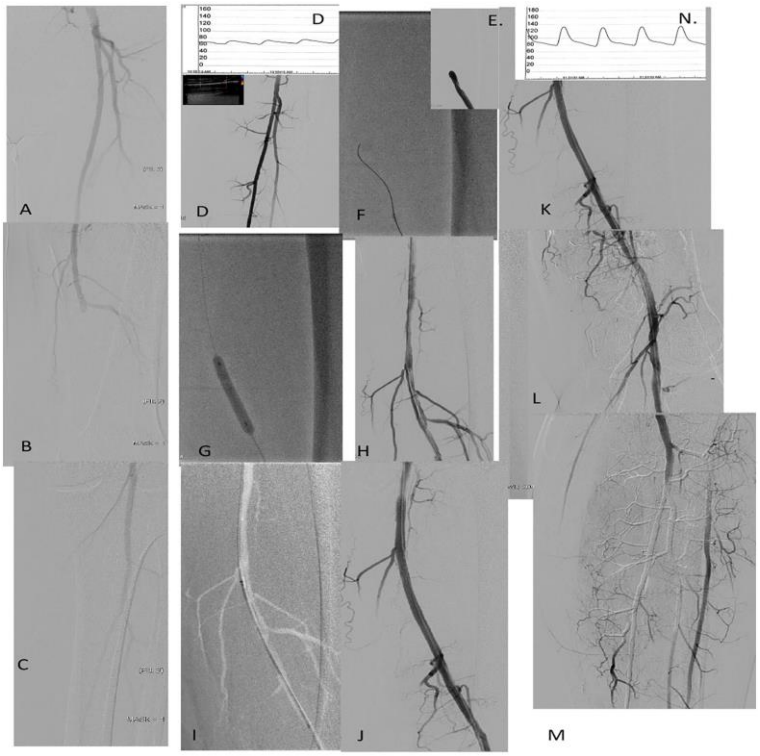

Figure 8. Femoro-popliteal artery intervention from TP access. (A-C) CTO of the right femoro-popliteal artery. (D-E) Ultrasound-guided TP artery access, selective angiography and pedal pressure measurement. (F) Subintimal GW advancement. (G) Retrograde balloon dilatation after successful reentry. (H) Dissection requiring treatment. (I-J) Stent positioning and implantation. (K-M) Final angiography shows no residual stenosis or dissection. (N) TP pressure measurement after the intervention shows significant improvement.

3.2.6 Follow-up

After the intervention, a physical examination was performed on all patients. All patients were called back for a clinical follow-up examination after 3 and 6 months. Furthermore, all patients with CLI and non-healing wounds returned for treatment of outflow tract disease.

3.2.7 Definitions

3.2.7.1 Major Adverse Cardiac Event

A major adverse cardiac event (MACE) was defined as cerebrovascular event, myocardial infarction or death.

3.2.7.2 Major Adverse Limb Event

A MALE was defined as either untreated loss of patency of the revascularization, reintervention on the revascularized segment, or major amputation (above or BTK) of the revascularized limb [62].

3.2.7.3 Vascular Complication

Major vascular complications referred to the reduction or complete loss of arterial pulse, or the appearance of pseudoaneurysm or arteriovenous fistula, identified during the patient's follow-up examination. Minor vascular complications included hematomas that did not require any specific intervention. These hematomas were defined as 2 cm in diameter at the RA or ulnar artery puncture sites, or 5 cm in diameter at the FA or BA artery puncture sites. A drop in hemoglobin level of more than 3 g/dL was considered major bleeding, as was bleeding requiring transfusion [62].

3.2.7.4 Technical Success

The successful outcome of a technical procedure occurred when a PTA led to a residual stenosis of less than 50% while ensuring satisfactory anterograde blood flow. An optimal result was considered if the residual stenosis was <30% with fast flow. A suboptimal result was identified by a slow flow and/or a residual stenosis of between 30% and 50% after PTA.

3.2.7.5 Clinical Success

The primary measure of clinical success involved observing an enhancement of at least one clinical category within the Rutherford classification [63].

3.2.7.6 Limb Salvage

Limb salvage was defined as the successful prevention of major amputations, as well as the preservation of the affected limb.

3.2.8 Statistical Analysis

Categorical data in $2\times k$ tables were analyzed using the unordered chi-squared test with a simulated p-value of 1×10^7 replicates. For statistical significance, pairwise testing was performed using the Fisher's exact test. To account for multiple comparisons, p-values were adjusted according to Benjamini and Hochberg testing with the Hommel's adjustment for pairwise comparisons [60]. Continuous parameters were examined for normality using the D'Agostino–Pearson and Shapiro–Wilk tests. As all continuous parameters except 1 (patients' height) showed a nonnormal distribution, we used the median with interquartile range for their description. The approximate Kruskal–Wallis test with 1×10^7 resamples was applied for comparisons of the 3 treatment groups, whereas the Dunn test with Holm's adjustment was performed as a post hoc test. The null hypothesis was rejected if $p\leq\alpha/2$, and alpha was set at 0.05. All statistical analyses and graphical interpretation of the results were conducted using R (version 4.1.0) (R Foundation for Statistical Computing) using the coin 1.4–1, f Basics 3042.89.1, R companion 2.4.1, and Dunn test 1.3.5 packages. All analyses were done on an intention-to-treat basis.

3.3 Distal Radial Artery Access for Superficial Femoral Artery Interventions

3.3.1 Study Design and Patient Population

Between 2016 and 2019, 195 patients with symptomatic SFA stenosis (>70% diameter stenosis) underwent PTA through RA penetration using sheathless guiding. We intervened on 38 patients with DR access (mean age 68.5 ± 8.5 years; 26 men), and 157 patients (mean age 67.3 ± 9.8 years; 101 men) with PR access. Patients in whom we could not reach the CFA with the 125 cm diagnostic catheter due to right transradial penetration were excluded. Patients with bilateral RAO and ulnar artery accesses were also excluded. The effect of the learning curve was analyzed each year by comparing the procedural data obtained in the first 20 cases with the other patients. The indication for the interventions was intermittent claudication in 85

patients, and CLI in 110 patients. The Institutional Review Committee accepted the study (SE TUKEB 212/2016) and all patients signed the consent form before the treatment.

3.3.2 Procedure

The preferred approach for interventions was the right RA; contralateral penetration was used in case of occlusion of the right RA. Ultrasound guidance was used for all DR punctures, and was optional when PR access was used. TP puncture used as part of dual access cases was also performed under ultrasound guidance.

Patients received a loading dose of 325 mg of aspirin and 300 mg of clopidogrel on the day of the intervention. After the puncture, a dedicated 5F radial sheath (Terumo, Tokyo, Japan) was introduced, and then a ,,radial cocktail" (5000 units of Na-heparin, 2.5 mg of verapamil, 250 ug of nitroglycerine) was administered. Additional Na-heparin was used until reaching 100 U/kg, but ACT was not routinely measured. A 5F, 125 cm pigtail catheter was led into the descending aorta via a J tip GW, and then an aortography was performed. The latter helped, among other things, to assess the distance between the penetration point and the lesion.

After that, in case of PR penetration, the diagnostic catheter and introducer sheath were replaced with a dedicated 6F 120 cm long transradial sheathless guiding system (SheathlessPV; Asahi Intecc, Aichi, Japan) through a 260 cm long, 0.035-inch GW (Starter or Jindo, Amplatz). In case of DR penetration, 6F, 100 cm coronary transradial sheathless guide (Eaucath; Asahi Intecc.) was used. The CFA was cannulated with a 125 cm multipurpose diagnostic catheter (telescopic method) and the lesion was passed with the GW. For the intervention, we used roadmap superselective imaging through the diagnostic catheter to minimize the amount of contrast. Balloons with a shaft length of 180 cm (Pacific Extreme; Medtronic, Minneapolis, MN, USA) were used and stent implantation was performed only in case of significant recoil and flow limiting dissection. Self-expanding stents with a shaft length of 180 cm (Sinus Superflex, OptiMed, Ettlingen, Germany) from PR penetration, while in complex cases Supera (Abbott Vascular, Santa Clara, CA, USA) or Zilver PTX stents (Cook Medical, Bloomington, IN, USA) were used for TP stenting. All stents were post-expanded. Before removing the transpedal slender sheath, transradial angiography was performed to assess the patency of the pedal vessels. After removal of the radial sheath, adequate hemostasis was ensured with the help of a Terumo Band applied for 4 hours in PR cases and a Seal-One device (Perouse Medical, a Vygon company, Ivry le Temple, France) applied for 4 hours in DR cases. The patency of the RAs was checked using ultrasound. After the intervention, the patients were mobilized immediately.

3.3.3 Antithrombotic Regimen and Follow-Up

Patients who underwent balloon angioplasty received lifelong aspirin therapy. Patients who underwent stent implantation received dual antiplatelet therapy (100 mg of aspirin and 75 mg of clopidogrel daily) for 2 months. All patients were called back for a clinical follow-up examination after 3 and 12 months.

3.3.4 Statistical Analysis

Continuous variables are expressed as the mean ± standard deviation or the median with interquartile range (Q1, Q3). Categorical variables are presented as the count (percentage). The patient groups were compared using either the Mann-Whitney U test or the Kruskal-Wallis's test. The treshold of statistical significance was $p<0.05$. Statistical analysis was performed using Graph Pad Prism software (version 8.0; GraphPad Software, San Diego, CA, USA).

4. RESULTS

4.1 The Clinical Impact of Access Site Selection for Successful Thrombolysis and Intervention in Acute Critical Lower Limb Ischaemia (RAD-ALI Registry)

Between 2008 and 2019, 84 consecutive patients fulfilling the inclusion criteria underwent CDT for ALI, and their data were analysed retrospectively. CDT was initiated using RA (n=17), BA (n=9), and FA (n=58) approaches. The demographic and clinical data are summarised in Table 2.

Table 2. Demographic and clinical data.

Variable	RA Group (n = 17)	BA Group (n = 9)	FA Group (n = 58)	p Value Overall	p Value RA vs. BA Groups	p Value RA vs. FA Groups	p Value BA vs. FA Groups
Age, median (IQR), years	67.0 (59.0–69.0)	60.0 (57.0–63.0)	64 (55.3–71.0)	0.4558	NA	NA	NA
Female	5 (29.4%)	2 (22.2%)	12 (20.7%)	0.8428	NA	NA	NA
BMI, median (IQR), kg/m^2	29.8 (23.3–30.9)	23.1 (21.5–25.3)	25.3 (22.5–29.4)	0.1653	NA	NA	NA
Hypertension	16 (94.1%)	8 (88.9%)	48 (82.8%)	0.6326	NA	NA	NA
Current smoker	12 (70.6%)	7 (77.8%)	43 (74.1%)	1.0	NA	NA	NA
Diabetes mellitus	4 (23.5%)	3 (33.3%)	14 (24.1%)	0.8529	NA	NA	NA
CAD	2 (11.8%)	2 (22.2%)	9 (15.5%)	0.7936	NA	NA	NA
Previous PTA	4 (23.5%)	3 (33.3%)	18 (31.0%)	0.8683	NA	NA	NA
Chronic renal failure	1 (5.9%)	2 (22.2%)	7 (12.1%)	0.5044	NA	NA	NA
COPD	2 (11.8%)	5 (55.6%)	9 (15.5%)	0.0172 *	0.0424 *	1.0	0.0424 *
Clinical presentation				0.5966	NA	NA	NA
Rutherford stage I	0 (0.0%)	0 (0.0%)	0 (0.0%				
Rutherford stage IIA	13 (76.5%)	6 (66.7%)	47 (81.0%)				
Rutherford stage IIB	4 (23.5%)	3 (33.3%)	11 (19.0%)				
Rutherford stage III	0 (0.0%)	0 (0.0%)	0 (0.0%)				

Abbreviations: BA—brachial artery; BMI—body mass index; CAD—coronary artery disease; COPD—chronic obstructive pulmonary disease; FA—femoral artery; IQR—interquartile range; NA—not assessed; RA—radial artery; PTA—percutaneous transluminal angioplasty. Categorical outcomes: chi-squared test with simulated p-value (10^7 replicates); post hoc test: Fisher's exact test adjustment according to Benjamini–Hochberg method. For ordered larger contingency tables, the ordered approximative general independence test (10^7 resamples) was used. Continuous outcomes: approximative Kruskal–Wallis's test with 10^7 resamples; post hoc test: Dunn's test and the Holm adjustment; alpha = 0.05; reject H0 if $p \leq alpha/2$. * Statistically significant.

4.1.1 Angiographic and Procedural Data

The angiographic and procedural data are summarized in Tables 3 and 4. CDT was technically successful in 74/84 patients (88%), but additional MT and angioplasty and/or stent implantation was necessary in 17 (20.2%) and 45 (53.6%) cases, respectively, to obtain good angiographic results. Clinical success was achieved in 74/84 cases (88%). Procedurally related factors were not statistically different in the subgroups (see Table 4) and hospitalization time (15.9 ± 14.5 days vs. 7.7 ± 2.8 days vs. 11.5 ± 6 days) was also not statistically different among the three groups (p=ns).

Table 3. Angiographic data.

Variable	RA Group (*n* = 17)	BA Group (*n* = 9)	FA Group (*n* = 58)	*p* Value Overall	*p* Value RA vs. BA Groups	*p* Value RA vs. FA Groups	*p* Value BA vs. FA Groups
Superficial femoral artery							
Diameter stenosis, %	ND	ND	ND				
Lesion length, mm	ND	ND	ND				
Reference diameter, mm	ND	ND	ND				
Popliteal artery							
Diameter stenosis, %	ND	ND	ND				
Lesion length, mm	ND	ND	ND				
Reference diameter, mm	ND	ND	ND				
Lesion type				0.6932	NA	NA	NA
TASC A	0 (0.0%)	0 (0.0%)	0 (0.0%				
TASC B	3 (17.6%)	1 (11.1%)	4 (6.9%)				
TASC C	0 (0.0%)	1 (11.1%)	5 (8.6%)				
TASC D	14 (82.4%)	7 (77.8%)	49 (84.5%)				
CTO	1 (5.9%)	0 (%)	1 (1.7%)	0.5256	NA	NA	NA

Abbreviations: BA—brachial artery; CTO—chronic total occlusion; FA—femoral artery; NA—not assessed; ND—not determined; RA—radial artery; TASC—Trans-Atlantic Inter-Society Consensus. Categorical outcomes: chi-squared test with simulated p-value (10^7 replicates); post hoc test: Fisher's exact test adjustment according to Benjamini–Hochberg method. For ordered larger contingency tables, the ordered approximative general independence test (10^7 resamples) was used. Continuous outcomes: approximative Kruskal–Wallis's test with 10^7 resamples; post hoc test: Dunn's test and the Holm adjustment; alpha = 0.05; reject H0 if $p \leq alpha/2$.

Table 4. Results.

Outcomes	RA Group (*n* = 17)	BA Group (*n* = 9)	FA Group (*n* = 58)	*p* Value Overall	*p* Value RA vs. BA Groups	*p* Value RA vs. FA Groups	*p* Value BA vs. FA Groups
Procedural success	ND	ND	ND	NA	NA	NA	NA
Clinical success	14 (82.4%)	8 (88.9%)	52 (89.7%)	0.8666	NA	NA	NA
Access site complications	0 (0.0%)	3 (33.3%)	18 (31.0%)	0.0254 *	0.0485 *	0.0235 *	1.0
Major adverse events at 12 months	7 (41.2%)	6 (66.7%)	29 (50.0%)	0.4879	NA	NA	NA
Crossover	8 (47.1%)	5 (55.6%)	50 (86.2%)	0.0021 *	1.0	0.0054 *	0.0708
Additional thrombectomy	3 (17.6%)	2 (22.2%)	12 (20.7%)	1.0	NA	NA	NA
Additional angioplasty/stent	8 (47.1%)	5 (55.6%)	32 (55.2%)	0.8883	NA	NA	NA
Median procedural time (IQR), minutes	40 (25.0–57.5)	82.5 (76.3–91.3)	45.0 (35.0–58.8)	0.0218 *	0.0135 *	0.3229	0.0076 *
Median fluoroscopy time (IQR), minutes	10.0 (6.4–19.5)	23.8 (19.7–28.0)	12.8 (8.4–18.4)	0.1111	NA	NA	NA
Median radiation dose (IQR), dyne	19.9 (9.9–31.8)	27.8 (19.7–37.3)	12.6 (7.9–21.5)	0.1246	NA	NA	NA
Median contrast volume (IQR), mL	120.0 (90.0–163.0)	117.5 (95.0–165.0)	120.0 (79.5–160.0)	0.7656	NA	NA	NA

Abbreviations: BA—brachial artery; FA—femoral artery; IQR—interquartile range; NA—not assessed; ND—not determined; RA—radial artery. Categorical outcomes: chi-squared test with simulated p-value (10^7 replicates); post hoc test: Fisher's exact test adjustment according to Benjamini–Hochberg method. For ordered larger contingency tables, the ordered approximative general independence test (10^7 resamples) was used. Continuous outcomes: approximative Kruskal–Wallis's test with 10^7 resamples; post hoc test: Dunn's test and the Holm adjustment; alpha = 0.05; reject H_0 if $p \leq alpha/2$. * Statistically significant.

4.1.2 Procedural Complications and 1-Year Follow-Up

The procedural complications and long-term follow-up data are summarized in Tables 4 and 5. The cumulative incidence of MAEs at 12 months was 50%. The major amputation rate was 22.6% and the mortality rate 21.5% (regarding patients who have undergone major amputation). Among the major amputations performed, a significant proportion (73.7%) were femoral amputations. Four patients were identified as having stage IIA according to the Rutherford classification, while 10 had stage IIB. Crural amputations represented 26.3% of the overall number of amputations. Within this subset, four patients were classified as having stage IIA according to the Rutherford classification and one as having stage IIB. The overall rate of stroke was 9.5%: five (5.9%) cases of ischemic stroke and three (3.5%) of hemorrhagic stroke, with a 50% mortality rate. The overall rate of major vascular complication was 9.5% (0%, 11.1%, and 12.1% in the RA, BA, and FA groups, respectively), with a 25% mortality rate.

Table 5. Perioperative and long-term complications.

Perioperative Complications	**RA Group (*n* = 17)**	**BA Group (*n* = 9)**	**FA Group (*n* = 58)**	**All Patients (*n*= 84)**
Access site complications	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Major	0 (0)	1 (11.1)	7 (12.1)	8 (9.5)
Occlusion	0 (0)	0 (0)	0 (0)	0 (0)
Haematoma	0 (0)	0 (0)	4 (6.9)	4 (4.8)
Bleeding	0 (0)	1 (11.1)	1 (1.7)	2 (2.4)
Pseudoaneurysm	0 (0)	0 (0)	2 (3.4)	2 (2.4)
Minor	0 (0)	2 (22.2)	11 (18.9)	13 (15.5)
Occlusion	0 (0)	0 (0)	0 (0)	0 (0)
Haematoma	0 (0)	2 (22.2)	11 (18.9)	13 (15.5)
Bleeding	0 (0)	0 (0)	0 (0)	0 (0)
Summary	0 (0)	3 (33.3)	18 (31.0)	21 (25)
MAE at 12 months	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Death	3 (17.6)	4 (44.4)	5 (8.6)	12 (14.3)
Major amputation	4 (23.5)	2 (22.2)	13 (22.4)	19 (22.6)
Re-PTA or bypass (TLR or TVR)	2 (11.8)	1 (11.1)	12 (20.7)	15 (17.8)
Myocardial infarction	0 (0)	0 (0)	2 (3.4)	2 (2.4)
Stroke	2 (11.8)	1 (11.1)	5 (3.5)	8 (9.5)
Summary (all events)	11 (64.7)	8 (88.9)	37 (63.8)	56 (66.7)
Summary (patients with events)	7 (41.2)	6 (66.7)	29 (50)	42 (50)
MALE at 12 months	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Major amputation	4 (23.5)	2 (22.2)	13 (22.4)	19 (22.6)
Re-PTA or bypass (TLR or TVR)	2 (11.8)	1 (11.1)	12 (20.7)	15 (17.8)
Repeated ALI	2 (11.8)	2 (22.2)	7 (12.1)	11 (13.1)
Summary (all events)	8 (47.1)	5 (55.6)	32 (55.2)	45 (53.6)
Summary (patients with events)	6 (35.3)	3 (33.3)	25 (43.1)	34 (40.5)

Abbreviations: ALI—acute lower limb ischaemia; BA—brachial artery; FA—femoral artery; MAE—major adverse event; MALE—major adverse limb event; PTA—percutaneous transluminal angioplasty; RA—radial artery; TVR—target vessel revascularisation; TLR—target lesion revascularisation.

4.1.3 MAE and MALE Predictors

The adjusted variables used in the Cox regression model used to investigate MAEs and MALEs, which were considered together as the reference model, were entry site, Rutherford stage, target vessel, clinical success, additional procedure, and diabetes mellitus. In all cases, data from the 12-month follow-up period were taken into account during the analysis, and $p<0.05$ was considered statistically significant.

Among the adjusted variables examined for MAEs, statistically significant differences were observed for cases of RA penetration (HR, 0.27; 95% CI, 0.07–0.96; p=0.0429; Table 6).

Table 6. Cox proportional hazards regression, major adverse events.

Covariate	b	SE	Wald	P	HR	95% CI of HR
Access site = 'Brachial'	0.019559	0.55671	0.0012343	0.9720	1.01975	0.34246–3.03650
Access site = 'Radial'	−1.31657	0.65040	4.09757	*0.0429	0.26805	0.07492–0.95908
Rutherford stage = 'IIB'	1.29269	0.42676	9.17549	*0.0025	3.64257	1.57814–8.40757
Target vessel = 'AA'	0.61379	1.10952	0.30603	0.5801	1.84742	0.20995–16.25564
Target vessel = 'BTK'	−0.32042	1.06561	0.090418	0.7636	0.72584	0.08990–5.86011
Target vessel = 'CFA'	0.25333	0.75989	0.11114	0.7388	1.28831	0.29053–5.71286
Target vessel = 'CIA'	0.60224	0.68160	0.78068	0.3769	1.82620	0.48013–6.94610
Target vessel = 'EIA'	3.31489	1.15999	8.16636	*0.0043	27.51928	2.83291–267.32563
Target vessel = 'Graft'	0.18943	0.48137	0.15486	0.6939	1.20856	0.47045–3.10472
Target vessel = 'PA'	0.32409	0.52773	0.37715	0.5391	1.38277	0.49152–3.89013
Additional procedure = 'No'	0.38637	0.33879	1.30061	0.2541	1.47162	0.75756–2.85876
Clinical success = 'No'	2.04401	0.57854	12.48263	*0.0004	7.72154	2.48453–23.99742
Diabetes mellitus = 'Yes'	0.78023	0.39279	3.94574	*0.0470	2.18197	1.01042–4.71190

Abbreviations: AA—abdominal aorta; BTK—below the knee; CFA—common femoral artery; CI—confidence interval; CIA—common iliac artery; EIA—external iliac artery; HR—hazard ratio; PA—popliteal artery; SE—standard error. * Statistically significant.

4.2 TRIACCESS Study: Randomized Comparison Between Radial, Femoral, and Pedal Access for Percutaneous Femoro-popliteal Artery Angioplasty

We performed PTA from RA, FA or TP penetration in 180 patients with significant SFA stenosis. A second entry gate was used in 30%, 3.3% and 30% of patients in the RA, FA and TP groups ($p<0.01$). Claudication complaints were the indication in 53.3% of patients, CLI in 46.7% of patients. Demographic and clinical data are shown in Table 7.

Table 7. Demographic and clinical data.

Variable	Radial group (n=60)	Femoral group (n=60)	Pedal group (n=60)
Demographic data			
Age (years)	68.5 (62.0–75.0)	70.0 (63.5–77.0)	67.0 (62.0–71.3)
Female	19 (31.7%)	27 (45.0%)	30 (50.0%)
Hypertension	54 (90.0%)	56 (93.3%)	60 (100.0%)
Current smokers	13 (21.7%)	25 (41.7%)	24 (40.0%)
Diabetes mellitus	30 (50.0%)	36 (60.0%)	27 (45.0%)
IDDM	9 (15.0%)	11 (18.3%)	12 (20.0%)
NIDDM	21 (35.0%)	25 (41.7%)	15 (25.0%)
Weight (kg)	74.5 (68.0–90.0)	74.0 (67.0–85.0)	78.0 (70.0–87.8)
Height (cm)	166.6 (8.1)	169.6 (7.5) SD	165.6 (9.7)
	167.0 (162.8–172.2)	170.0 (164.0–175.0)	165.0 (157.8–172.0)
COPD	7 (11.7%)	3 (5.0%)	4 (6.7%)
Renal insufficiency	22 (36.7%)	38 (63.3%)	34 (56.7)
Cardiac and vascular history			
CAD	26 (43.3%)	25 (41.7%)	28 (46.7%)
Previous PTA	28 (46.7%)	25 (41.7%)	24 (40.0%)
Previous CABG	8 (13.3%)	4 (6.7%)	4 (6.7%)

Abbreviations: PTA – percutaneous transluminal angioplasty.

4.2.1 Angiographic and Procedural Data

The angiographic and procedural data are contained in Tables 8 and 9. Technical and clinical success was achieved in 96.6%, 100%, and 100% of the patients in the RA, FA and TP groups, respectively (p=ns). Regarding the procedurally related factors, there was no significant difference between the subgroups, but the X-Ray dose was significantly lower in the TP group (160.1 vs. 153.1 vs. 63.1 Dyn ($p<0.01$)). The crossover rate was 30% (2/60 case to femoral, 18/60 case to pedal), 3.3% (2/60 case to pedal), and 30% (16/60 to radial and 2/60 to pedal) in the RA, FA, and TP groups, respectively ($p<0.01$). The hospitalization time was significantly lower in the radial group (2.9 vs. 3.45 vs. 3.1 days; $p<0.01$).

Table 8. Angiographic data.

Angiographic and procedural data of the target lesions	Radial group (n=60)	Femoral group (n=60)	Pedal group (n=60)
Superficial femoral artery			
Diameter stenosis (%)	93 (90–96)	84.1 (76.8–91.3)	94.9 (76.8–91.3)
Lesion length (mm)	101 (83–118.9)	100.9 (75.6–126.2)	143.8 (92.7–12.7)
Reference diameter (mm)	5.2 (5–5.3)	5 (4.9–5.2)	5.2 (5.1–5.4)
Popliteal artery			
Diameter stenosis (%)	93.4 (84.6–102.3)	80.9 (70.2–91.7)	85.4 (7.2–94.6)
Lesion length (mm)	95.2 (35–155.4)	78.1 (47.6–108.5)	100 (55.7–114.2)
Reference diameter (mm)	4.3 (3.8–4.7)	4.4 (4.2–4.7)	4.1 (3.5–4.7)
Lesion type			
TASC A	11 (18.3%)	20 (33.3%)	8 (13.3%)
TASC B	17 (28.3%)	24 (40%)	14 (23.3%)
TASC C	7 (11.6%)	4 (6.7%)	4 (4.7%)
TASC D	25 (41.6%)	12 (20%)	34 (56.7%)
Chronic total occlusion (%)	36 (47.9%)	30 (50%)	45 (75%)

Table 9. Results.

Outcomes	Radial group (n=60)	Femoral group (n=60)	Pedal group (n=60)	p-Value overall	p-Value radial versus femoral	p-Value radial versus pedal	p-Value femoral versus pedal
Procedural success	58 (96.7%)	60 (100.0%)	60 (100.0%)	0.3297	NA	NA	NA
Access site complications	2 (3.3%)	10 (16.7%)	2 (3.3%)	0.0085	0.0442	1.0000	0.0442
Major adverse cardiac events at 30 days	1 (1.7%)	1 (1.7%)	1 (1.7%)	1.0000	NA	NA	NA
Major adverse cardiac events at 6 months	3 (5.0%)	4 (6.7%)	1 (1.7%)	0.5371	NA	NA	NA
Major adverse limb events at 30 days	2 (3.3%)	2 (3.3%)	0 (0.0%)	0.5479	NA	NA	NA
Major adverse limb events at 6 months	12 (20.0%)	10 (16.7%)	5 (9.2%)	0.2179	NA	NA	NA
Major amputation at 6 months	2 (3.3%)	2 (3.3%)	0 (0.0%)	0.5479	NA	NA	NA
Limb salvage at 6 months	58 (96.7%)	58 (96.7%)	60 (100.0%)	0.5479	NA	NA	NA
Survival at 6 months	58 (96.7%)	57 (95.0%)	1 (98.3%)	0.8722	NA	NA	NA
Crossover/dual access	18 (30.0%)	2 (3.3%)	18 (30.0%)	0.0002	0.0002	1.0	0.0002
Stent implantation	23 (38.3%)	38 (63.3%)	45 (75.0%)	0.0002	0.0154	0.0003	0.2360
CTO success rate	34/36 (94.4%)	30/30 (100.0%)	46/46 (100.0%)	0.1713	NA	NA	NA
Median procedural time (IQR), min	30.0 (20.0–41.3)	30.0 (22.8–51.3)	35.0 (28.8–51.3)	0.1510	NA	NA	NA
Median contrast volume (IQR), mL	92.5 (63.8–130.0)	66.0 (47.0–90.0)	67.5 (33.8–92.5)	0.0003	0.0018	0.0003	0.2382
Median fluoroscopy time (IQR), s	537.0 (353.5–850.0)	516.0 (252.0–836.8)	414.0 (224.5–848.5)	0.2025	NA	NA	NA
Median radiation dose (IQR), dyne	14.4 (6.9–28.0)	32.3 (9.2–73.0)	7.6 (4.0–18.7)	0.0004	0.0841	0.0092	0.0002

Abbreviations: CTO-chronic total occlusion; IQR-interquartile range. Categorical outcomes: Chi-squared test with stimulated p-value (10^7 replicates), post hoc test: Fisher's exact test adjustment according to Benjamini and Hochberg. Continuous outcomes: approximative Kruskal-Wallis test with 10^7 resamples, post-hoc test: Dunn test with Holm's adjustment; alpha = 0.05; reject H0 if $p \leq alpha/2$.

4.2.2 Perioperative Complications and Long-Term Follow-Up

Perioperative complications and long-term follow-up are summarized in Table 9 and Figure 9.

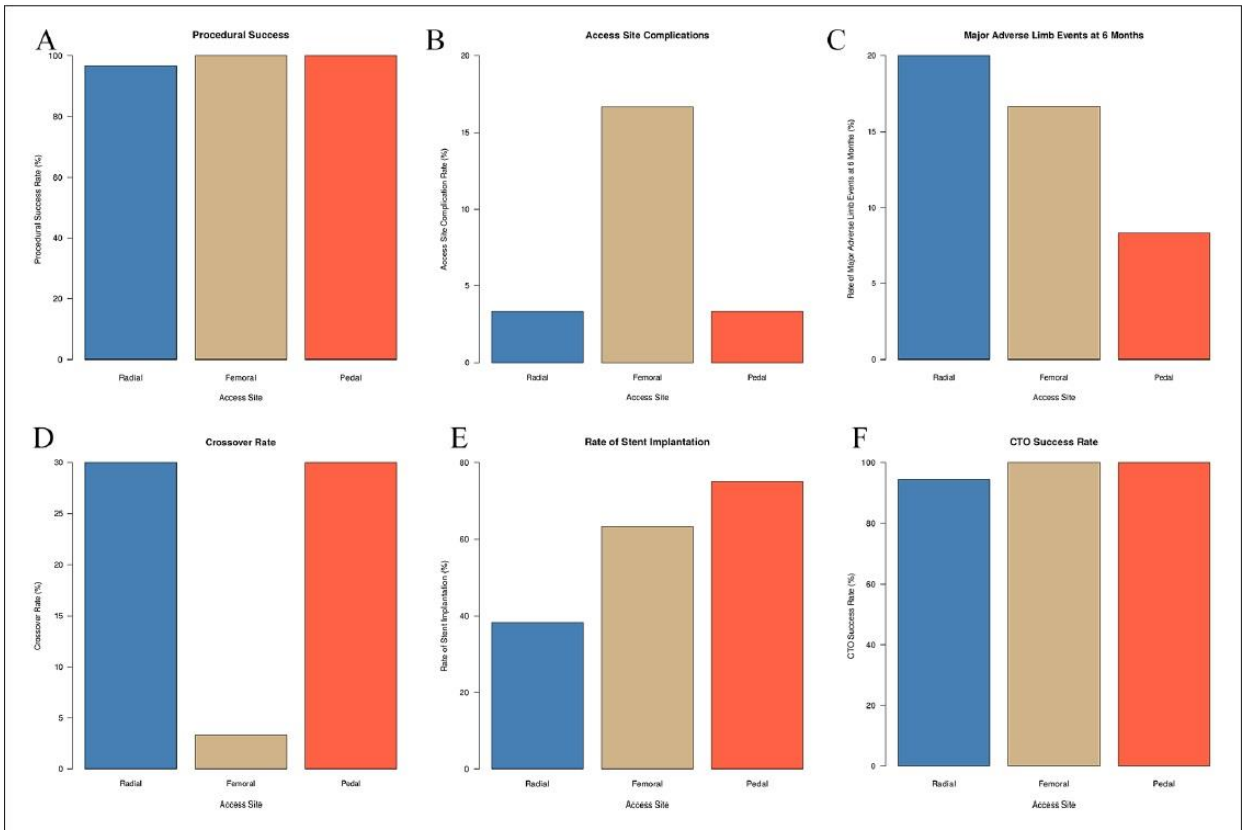

Figure 8. (A) Procedural success. (B) Access site complications. (C) MAEs at 6 months. (D) Crossover rate. (E) Rate of stent implantation. (F) CTO success rate.

The cumulative 6-months MACEs incidence in the RA, FA and TP groups was 5%, 6.7% and 1.7% (p=0.10). The cumulative 6-months MALEs incidence in the RA, FA and TP groups was 20%, 16.7% and 10% (p=0.54). The major amputation rate was 3.3%, 3.3% and 0.0% in the RA, FA and TP groups (p=0.55). The cumulative access site complication rate int the RA, FA and TP groups was 3.3% (0% major and 3.3% minor), 16.7% (3.3% major and 13.3% minor), and 3.3% (3.3% major and 0% minor), respectively (p=0.01). The sheath size has not significantly affected the rate of vascular access site complications. Anterograde and cross over approach has been used in 54 (90%) and in 6 (10%) patients. The rate of vascular complications in the anterograde and crossover cases was 10% (2 major (20%) and 8 minor (80%)) and 0% (p=0.57).

4.3 Distal Radial Artery Access for Superficial Femoral Artery Interventions

4.3.1 Angiographic and Procedural Data

The angiographic and procedural data are summarized in Table 10. Technical success was achieved in 188 patients (96.4%), of which the rate was 97.3% (37 of 38 patients) in the DR group and 96.2% (151 of 157 patients) in the PR group (p=0.9). Femoral crossover was not necessary in the DR group, while in the PR group it was necessary to switch to FA penetration in 5 cases (3.2%) (p=0.59). Dual penetration (transradial and transpedal) was required in 14 cases in the DR group (36.8%) and in 28 cases in the PR group (18.9%; p<0.01). There was no significant difference between the two groups regarding radiation dose, fluoroscopy time, procedure time and contrast use.

Table 10. Procedural data.[a]

	Proximal Radial Access (n=157)	Distal Radial Access (n=38)
Balloon angioplasty in the SFA	157 (100)	38 (100)
Stenting in the SFA	39 (24.8)	15 (39,4)
Stent length, mm	122.2±85	164±77.5[b]
Dual access (pedal and radial)	28 (16.5)	14 (36.8)[b]
Crossover to femoral access	5 (3.2)	0 (0)
Success	151 (96.2)	37 (97.3)
Radiation dose, Gy/cm^2	33.5 [7.45, 59.5]	24.1 [16.5, 31.7]
Fluoroscopy time, s	762.5 [659.6, 865.4]	663 [540, 787]
Procedure time, min	36.4 [32.6, 40.2]	37.1 [31.1, 43.1]
Contrast volume, mL	119.5 [107.7, 131.3]	93.3 [80.4, 106.2]

Abbreviations: SFA-superficial femoral artery. [c]Continuous data are presented as the mean ± standard deviation or median [interquartile range Q1, Q3]; categorical data are given as the count (percentage). [b]p<0.05.

4.3.2 Complications and Outcomes in Follow-Up

Complications and outcomes are listed in Table 11. The complication rate related to the access site was 2.6% and 7% in the DR and PR groups (p=0.46). The only access site

complication in the DR group was a minor hematoma, while a >2cm hematoma in the forearm was observed in one patient in the PR group. 6 DR patients (15.7%) and 23 PR patients (14.6%) had MAEs at 6 months. 3 patients (7.8%) in the DR group and 8 patients in the PR group (5.1%) died (p=0.38).

Table 11. Complications and outcomes in follow-up.[a]

Variables	Proximal Radial Access (n=157)	Distal Radial Access (n=38)
Procedural complications	1 (0.6)	0
Distal embolization	1 (0.6)	0
Perforation	0	0
Acute vessel closure	0	0
Access site complications	11 (7.0)	1 (2.6)
Major	1 (0.6)	0
RAO (symptomatic)	0	0
Forearm hematoma (>2 cm)	1	0
Minor	10 (6.3)	1 (2.6)
RAO (asymptomatic)	7 (4.4)	0
Forearm hematoma (<2 cm)	3 (1.9)	1 (2.6)
Major adverse events at 6 months		
Death	8 (5.1)	3 (7.8)
Major amputation	11 (6.5)	1 (0.6)
Redo PTA	9 (5.7)	1 (0.6)
Myocardial infarction	0	0
Stroke	1 (0.6)	1 (0.6)
Total of all events	29 (18.4)	6 (15.7)
Patients with events	23 (14.6)	6 (15.7)

Abbreviations: PTA-percutaneous transluminal angioplasty; RAO-radial artery occlusion. [a]Data are given as the number (percentage).

4.3.3 Impact of The Learning Curve

The impact of the learning curve is contained in Table 12. As time progressed, there was no significant difference in either group between procedure times, fluoroscopy times, radiation doses or the amount of contrast after the first 20 cases, despite the high number of complex cases. A significant decrease in fluoroscopy time and contrast amount can be observed over the years, but there was no statistical difference in procedure times and radiation dose. After the first year, the crossover rate was significantly lower for the last 158 patients (p=0.01).

Table 12. Impact of the learning curve.[a]

	2015 (n=47)	2016 (n=75)	2017 (n=35)	2018 (n=38)	2019 (n=10)
Procedure time, min	28.8 [24, 33]	37.3 [30, 43]	44.6 [37, 51]	37.1 [31, 43]	36.5 [26, 46]
Fluoroscopy time, s	784 [671, 897]	689.1 [501, 876][b]	490.5 [708, 1072][c]	663.6 [540, 787][b]	570.9 [368, 773][c]
Radiation dose, Gy/cm^2	29.6 [7, 65]	18.3 [12, 24]	18.2 [14, 22]	13.2 [9.9, 16.5]	14.2 [5, 24]
Contrast volume, mL	100.3 [82, 118]	115.1 [99, 130]	93.3 [80, 106][b]	92.3 [80, 106][b]	84.5 [51, 117][c]
Crossover	3 (6.3)[c]	0	0	0	0
TASC A,B	45 (95.7)[b]	56 (74.6)[b]	18 (51.4)[b]	31 (81.6)[b]	3 (30)
TASC C,D	2 (4.2)	19 (25.3)[b]	17 (48.6)[b]	7 (18.4)[b]	7 (70)[b]

Abbreviations: TASC-TransAtlantic Inter-Society Consensus. [a]Continuous data are presented as the median [interquartile range Q1, Q3]; categorical data are given as the count (percentage). [b]p<0.05. [c]p<0.01.

5. DISCUSSION

For the first time in our studies, different approaches (RA [DR and PR], FA, BA, TP) were compared for acute and chronic peripheral lower extremity interventions, focusing on success rates, safety, complication rates related to access sites, outcomes during the follow-up period, and the significance of the combined use of individual entry sites.

We demonstrated several important findings:

(1) Access site complications were very rare in the RA and TP groups when adequate hemostasis was used, and these were associated with shorter hospitalization period.

(2) DR access was associated with a very low access site complication rate.

(3) FA access is well-suited for patients with poor distal runoff and those requiring dedicated stents, but the access site complication rate is very high.

(4) The crossover rate in the RA and TP groups was significantly higher than in the FA group.

(5) The X-ray dose in the TP group was significantly lower than in the RA and FA groups.

(6) Significant independent predictors of long-term MAEs were determined, with RA access independently associated with a reduced risk of MAEs.

(7) Hybrid approaches can be utilized to reduce the rate of access site complications.

With the development of dedicated interventional tools, the use of alternative access sites has gained increasing importance of endovascular interventions. One such alternative is RA access. The main advantages of RA access include a low complication rate and better patient comfort due to faster mobilization and shorter hospitalization periods [12,13,64-66]. Our study confirmed these findings: the overall rate of major vascular complications was significantly lower compared to FA access. However, the main disadvantages are the high crossover rate and the difficulty in delivering devices to the target lesion [13]. Due to the decreasing anatomical and technical limitations with the development of the device system, it is now widely used for SFA interventions [13,65-67]. Despite advances in device technology, RAO occurred in our study, but it was 0% in cases of ultrasound-guided DR access using a slender sheath. This outcome is likely due to the advantages of DR puncture, which allows for easier compression and ensures adequate hemostasis, resulting in a low incidence of RAO [68,69]. Additionally, due to the anatomical location of the DR artery (in subcutaneous tissue), compartment syndrome does not occur. The most common complications with DR access are arteriovenous fistula and pseudoaneurysm [70]. Arteriovenous fistula is often asymptomatic

and usually requires only local compression without further intervention [71]. Pseudoaneurysm can be treated successfully with ultrasound-guided compression. The biggest technical disadvantage of DR access is the difficulty in delivering GWs toward the PR artery due to the smaller vessel caliber and acute angulation of the artery. Another limitation of distal puncture is the need for longer instruments; however, in our study, we found no difference in the success of interventions between the PR and DR groups. Ultrasound-guided puncture is recommended to overcome these limitations, as it allows for the determination of vessel size, course, and the severity of atherosclerosis before puncture [72]. Ultrasound guidance was used in all DR puncture cases, facilitating easy anterior single-wall puncture, avoidance of multiple punctures and selection of a disease-free, angulation-free segment. Intraprocedural complications (hematoma formation, dissection, spasm) can also be easily detected. Two previous meta-analyses also confirmed that ultrasound use for conventional RA puncture, compared palpation, resulted in faster puncture and less hematoma formation [73,74].

Antegrade FA puncture is traditionally used during SFA PTAs because it offers a straightforward puncture path and strong backup support when using large femoral devices. If anterograde puncture is difficult or impossible, crossover contralateral access can be considered, though this approach is sometimes limited by severe calcification, vessel tortuosity, or iliac artery angulation. The main disadvantages of FA puncture, confirmed in our study, are the high complication rate and longer hospitalization time [2]. However, significant improvements in complication rates can be achieved with ultrasound guidance.

The number of TP access procedures has increased in recent years, primarily to treat complex peripheral lesions from a retrograde direction that could not be successfully treated with anterograde access. Thus, TP access is a good alternative for lower extremity percutaneous interventions, as described by Kwan et al. The access site complication rate was 0%, with an 8% femoral crossover rate [6]. A recent meta-analysis by Welling et al. examined 1.168 TP punctures, with a puncture success rate of 94%, a technical success rate of 84%, and distal complications (perforation, vasospasm, distal occlusion) in 4.1% of cases [75]. Another meta-analysis of 881 patients reported on overall success rate of 92.6%, with dissection (7.49%), perforation (1.36%), and embolization (1.25%) as complications [76]. In our study, we did not observe complications related to TP access, though one patient experienced proximal dissection after stent implantation, which was treated with a drug-eluting stent. The main advantages of TP puncture are the low risk of vascular complications and easy, quick hemostasis.

Another key finding of our study was that the X-ray dose in the TP group was significantly lower than in the RA and FA groups. Previously, Shah et al. compared TP with FA approaches in a cohort of non-randomized PAD patients, finding fewer access site complications, less contrast use, and shorter fluoroscopy and procedure times in the TP group [77].

In addition to alternative access sites, hybrid approaches can reduce the complication rates while maintaining high technical success rate. During SFA interventions, a combination of RA and TP access was effective [67], though the combined use of BA and FA access was associated with a high vascular complication rate despite ultrasound guidance for FA puncture [10,78]. Patel et al. reported that primary transradial or transpedal access was successful in 74% and 54% of cases, respectively, with a 99% success rate in failed cases when a hybrid strategy was used [67].

Our study has several limitations worth mentioning. The low number of patients and their uneven distribution across subgroups made it challenging to analyze the entire population. Future studies should account for this and, as the patient population grows, continually reevaluate research findings. Given the beneficial effect of ultrasound in reducing vascular complications, further comparison of different access sites during peripheral interventions based on standardized ultrasound-guided puncture protocols may be warranted in the future.

6. CONCLUSIONS

Thanks to rapid technical developments in recent years, peripheral PTAs have expanded alongside coronary interventions. Our study, which forms the basis of this thesis, concludes that both acute and chronic lower limb peripheral vascular diseases can be safely and effectively treated with RA, FA, BA, and TP access, but RA and TP access are associated with a lower complication rate and shorter hospitalization period. This rate can be further reduced by using hybrid access techniques. Despite the higher complication rate, FA puncture remains a viable option, especially in patients with severely diseased outflow tracts who require dedicated stents and other large-caliber devices. The potential advantages of alternative access sites can be most effective when chosen and applied with appropriate indications and careful consideration of potential complications and their solutions.

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