Retrospective analysis of the Spur™-stent and drug-coated balloon intervention for infrapopliteal lesions: long-term patency, mortality and amputation-free survival

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RETROSPECTIVE ANALYSIS OF THE SPUR™-STENT AND DRUG-COATED BALLOON INTERVENTION FOR INFRAPOPLITEAL LESIONS: LONG-TERM PATENCY, MORTALITY AND AMPUTATION-FREE SURVIVAL

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LIST OF ABBREVIATIONS

ABI – Ankle- brachial index

ACE-inhibitors – Angiotensin-converting enzyme inhibitors

CAD – Coronary artery disease

CLTI – Chronic limb-threatening ischemia

CTA – Computed tomography angiography

DCB – Drug-coated balloon

DES – Drug-eluting stent

DUS – Duplex ultrasound

eGFR – Estimated glomerular filtration rate

FDA – Food and drug administration

LDL – Low-density lipoprotein

MACE – Major adverse cardiovascular events

MALE – Major adverse limb events

MRA – Magnetic resonance angiography

PAD – Peripheral artery disease

SD – Standard deviation

TAI – Thrombocyte aggregation inhibitors

TBI – Toe-brachial index

VKA – Vitamin K antagonists

1. INTRODUCTION

1.1. Peripheral artery disease (PAD) - A Comprehensive Overview

According to the most recent definition, peripheral artery disease (PAD) is defined as a condition affecting the arteries supplying the lower limb, manifesting in either chronic or acute form (1,2). Acute PAD presents with a sudden limb-threatening reduction of arterial perfusion (3). In contrast, chronic PAD is a progressive disease that often remains asymptomatic but can also present with intermittent claudication, rest pain or nonhealing lesions of the leg (3–5). Chronic PAD is more prevalent than the acute form and will be the primary focus of this thesis. Approximately 95% of chronic PAD are attributed to underlying atherosclerotic processes, with the remaining cases being based on inflammatory, genetic, or traumatic causes (1). Any level of the lower limb can be affected by PAD and combined multistage presentations covering several regions are also commonly observed (6).

PAD is a very prevalent disease with high incidences reported both on a national and global level (3,7,8). Approximately 200 million people are estimated to be affected worldwide. While PAD currently has a higher prevalence in high-income countries, its incidence is also rapidly increasing in middle- and low-income countries(7). Globally, especially North America and Europe are affected by this disease with the very lowest prevalences being reported in Asian or African countries. This can partly be attributed to especially high incidences of chronic PAD in the elderly and diabetic population as the risk of developing the disease is progressing with age and diabetic status. However, with estimations suggesting that only around 50 % of individuals affected by the disease develop symptoms, a high number of undetected cases is assumed, which complicates reports on prevalence and emphasizes the importance of screening for asymptomatic disease in risk groups (3–5,9).

Immense economic strain is imposed on national healthcare systems by PAD, especially considering the rising age and spread of diabetes worldwide. Patients affected by PAD often have frequent hospital visits with a high rate of readmission and require costly interventions and care. In addition to that, opportunity cost of absence from workplaces and disability claims in late stages of the disease impact the public (10,11). Moreover, the patient him/herself can be severely limited in the overall quality of life due to physical limitations and complications of the disease like the reduction of possible walking distance, withdrawal from social participation, increased dependence on others and generally reduced ability to cope with the demands of everyday life.

95% of chronic PAD can be at linked to atherosclerosis, referring to a generalised and progressive fatty plaque buildup in large- to midsize arteries that limits vessel diameter, reduces

arterial elasticity and impedes blood flow and exchange of oxygen and nutrients(1). Atherosclerotic changes are initially based on endothelial dysfunction alongside high levels of low-density lipoprotein (LDL) which facilitates the deposition of oxidised lipoprotein in the subendothelial layers of an artery (12). These deposits trigger an inflammatory response, causing monocytes to adhere to the endothelial layers, migrate to the intimal layer and differentiate into macrophages that engulf the oxidised LDL and thus become so-called foam cells that coalesce into a buildup of fatty streaks (13,14). Fatty streaks are the earliest visible sign of atherosclerotic processes in a vessel and they can be already observed in a significant amount of young people (15). The underlying inflammation due to the presence of LDL is a systemic condition and in PAD, the changes following from it are localised at the peripheral vascular bed, even though similar processes can often be observed at multiple vascular sites at the same time. Following the development of fatty streaks, smooth muscle cells are induced to proliferate and migrate to the vessel's intimal layer as well, where they cover the streaks with a fibrous cap alongside inclusion of necrotic tissue. Those atheromatous plaques can further calcify, progressively limiting the vessels diameter and changing local blood flow dynamics (13–15). The composition of plaques can change over time and depending on their stability, they might rupture, causing acute occlusion of the vessel as it happens in acute limb ischemia. Even if acute occlusive events do not take place, the progressively shrinking vessel radius impedes the local circulation and severely diminishes oxygen and nutrient delivery according to Laplace's law. In chronic PAD, this initially translates into symptoms of intermittent claudication, where the partial stenosis of a vessel induces muscular pain that can be precipitated by exercising and be relieved by rest. If the occlusion of a vessel is complete, ulcerations, gangrene or necrosis can develop (4,5). Compensatory formation of collateral conduits is often observed, but can be insufficient.

Both nonmodifiable and modifiable risk factors for PAD have been established. Nonmodifiable risk factors include age, male gender, individual family history and ethnic background (2,16,17). Established modifiable risk factors are smoking habits, a sedentary lifestyle, high levels of inflammatory cytokines and a diagnosis of arterial hypertension, hyperlipidaemia, or diabetes mellitus (12,16,18–20). Of note, active smoking enhances the progression of the disease once established and a history of smoking alone constitutes a risk factor to develop PAD and, thus emphasizing a huge potential for prevention.

Lifestyle modifications and optimal medical treatment can significantly prevent the occurrence and slow down disease progression of PAD. The most important lifestyle modification is smoking cessation, flanked by a healthy diet and regular exercise (16,21–25).

Optimal medical management of concomitant diseases that present risk factors such as hyperlipidaemia, arterial hypertension and diabetes mellitus is also mandatory. This includes antiplatelet and lipid-lowering drug therapy, strict regulation of blood sugar levels and monitoring of blood pressure (3,26,27). Due to the prevalence of PAD among the diabetic population and the high number of undetected cases in asymptomatic early stages of the disease, regular screening for PAD is recommended for diabetics (28). The earlier treatment is initiated, the higher impact it has and progression into late and severe stages can be prevented. Once PAD has been established, medical checkups and patient education, including teaching of proper and regular self-examination of the feet, can further aid in prevention of progression into the severe final stages of PAD.

The associated complications of PAD are severe. First of all, the overall mortality is increased, which is even more accentuated in the later most severe stages of chronic limb-threatening ischemia (CLTI) (1,5,29). This might be attributed to the underlying atherosclerotic pathophysiology of the disease, which is not limited to the peripheral vasculature alone, but extends to coronary, cerebral or renal vascular territories as well, explaining increased rates of cardiovascular deaths and cardiovascular events, such as ischemic strokes and myocardial ischemia (1,26,27,30). Moreover, chronic renal disease is also closely associated with PAD (31). Furthermore, PAD is the leading cause for amputations, especially in severe CLTI (4). Additionally, the combination of concomitant diabetes-induced insulin resistance can lead to blindness, which severely impacts mobility and everyday life competence. Due to the numerous and grave complications of untreated disease progression, early diagnosis and compliance with treatment and the suggested lifestyle modifications is advisable.

The diagnosis of PAD is mostly clinical (5). Thorough anamnesis, physical exam findings such as diminished or absent pulses, skin defects, dry and thin skin peripheral skin and a prolonged capillary refill time can be found. High diagnostic emphasis is also placed on the ankle-brachial index (ABI)-calculation with pathological values below 0.9, as it will be discussed in the next subchapter. In addition to this, imaging methods such as Doppler Ultrasound imaging, magnetic resonance angiography (MRA) or computed tomography angiography (CTA), can aid in diagnosis. Above all, initial awareness of medical providers is crucial due the potential of asymptomatic presentation, as the disease is still underrecognized.

To sum up, PAD is a highly prevalent and common disease worldwide, especially in countries with aging population and considering the rising incidence of diabetes mellitus globally. Initial endothelial dysfunction triggers further development of chronic atherosclerosis, an inflammatory condition inducing changes in arteries, leading to partly or completely reduced

blood flow and resulting in characteristic symptoms, most notably intermittent claudication. PAD offers a huge potential for prevention, and once the disease is established, strict therapy adherence can prevent severe complications.

1.2. Disease Classification Systems and Functional Assessment of Clinical Performance

Several methods exist to establish the diagnosis of chronic PAD and classify its severity, the most relevant of which will be presented below:

Calculation of the ABI presents an established, fast, and reliable method to noninvasively diagnose the presence and severity of PAD (32,33). Only a blood pressure cuff, a doppler ultrasound device and ultrasound gel are required and the test is relatively cost-effective, which probably contributed to its widespread adoption (34–38). It is calculated by dividing the highest systolic pressure measured at the patient's ankle by the highest systolic pressure measured at the patient's arm. Either the dorsal artery of the foot or the posterior tibial artery can be evaluated for the ankle pressure and the brachial artery is used to determine the blood pressure at the arm (37,39). If the calculated index value is below 0.9, the diagnosis of PAD can be made (35,37,38,40,41). Values below 0.9 can be further stratified into mild forms of PAD when the index is between 0.71 – 0,9, moderately severe PAD if the index value ranges from 0.41 – 0.7 and high-grade severe forms of PAD from 0 – 0.4. This severity stratification aids as an additional treatment guide and allows for long-term monitoring of the disease. Normal ABI-values are expected to be 1 or >1. However, values above 1.3 indicate non-compressibility of the arterial vessel walls due to calcification. This is associated with diabetes mellitus, chronic kidney disease and increased age (39,42–46). ABI-values above 1.3 are not suitable for interpretation and these cases, the toe brachial index (TBI) is used instead and will be explained below. Pathologic ABI-values as defined to be 0.9 or > 0.9 are not only a diagnostic criterion for PAD, but also an independent risk factor for overall cardiovascular morbidity and mortality (36,41,47,48). Diagnostic accuracy of the ABI-method is very specific with 99% specificity and 95% sensitivity of pathologic values when matched with angiographically confirmed PAD (32,34,36,49). To sum up, the ABI-value can be easily, quickly, and noninvasively be measured and aids in diagnosis of PAD and follow-up of treatment. If its values are not open to interpretation due to vessel calcification that impedes external compression, the TBI-values are used instead.

TBI-values are measured similarly to the ABI, but instead of measuring ankle blood pressure, toe pressure is measured at the digital arteries of the toes (2). In addition to that, a

smaller than usual blood pressure cuff that can be wrapped around the toes is required. Calculation of the TBI-index is done by dividing the highest systolic blood pressure measured at the toes by the highest systolic blood pressure measured at the arms. Calculated values are deemed to be normal if they are larger than 0.7 (2,37,50,51). Values below 0.7 are diagnostic of PAD and are stratified into mild PAD if the index ranges from 0.5 – 0.7, moderate PAD if the index ranges from 0.35 to 0.5 and severe PAD if the index falls short of 0.35. Values exceeding a certain value are not excluded since the small distal arteries of the toes are less affected by vessel calcification (51). In conclusion, the TBI is calculated from the pressure measured at the toes, is less affected by vessel calcification and allows for stratification into different degrees of severity of PAD.

The Rutherford classification is the international standard classification used to precisely diagnose the severity of PAD since 1986 (52). Both classifications for acute and chronic PAD exist. Since only the chronic form of PAD is of concern for this thesis, it is shortly described: The Rutherford classification divides patients into seven possible categories ranging from asymptomatic to highly symptomatic with major tissue loss in the most severe stages of PAD (34,53). Stage 0 encompasses completely asymptomatic individuals without hemodynamically relevant occlusive disease that show no pathologic findings when exercising on a treadmill. Category 1 is used to describe individuals with symptoms of mild claudication that becomes evident after walking 200 meters and a post-exercise ankle pressure above 50 mmHg, that is at least 20mmHg lower than the value at rest. The standardized treadmill protocol of exercise involves a 12% incline and a speed of 3km/h. Category 2 includes patients with moderate claudication that occurs below walking a distance of 200 meters and with post-exercise ankle pressures that are between categories 1 and 3. Category 3 describes severe claudication that prevents a patient from completing standard treadmill exercise with post-exercise ankle pressures of below 50 mmHg. If patients experience ischemic pain already at rest, the Rutherford-category 5 is reached and the patient experiences resting ankle pressures to be below 40mmHg with toe pressures of below 30 mmHg. Categories 5 and 6 describe patients with minor and major tissues loss and resting ankle pressures to be smaller than 60mmHg and toe pressures below 40mmHg. Minor tissue loss as in category 5 is defined as a nonhealing ulcer or focal gangrene with diffuse ischemia of the foot. Major tissue loss if category 6 is defined to extend above the metatarsal level where the functional foot is no longer salvageable. In a nutshell, the international and widely adopted Rutherford classification allows for precise stratification of the various heterogenous presentations of PAD taking into account objective and subjective criteria as well as the severity of symptoms.

Corresponding to the more international standard Rutherford-classification, the European Fontaine classification system for PAD was presented first in 1954 and is less detailed but roughly corresponds to the distinctions made in the Rutherford classification system(35,53). It groups patients into a total of four stages with stage 1 including asymptomatic patients, stage 2 referring to any level of intermittent claudication, stage 3 describing rest pain and stage 4 featuring any level of ulceration or necrosis of the foot.

Assessment of hemodynamic pressures and waveform patterns of arterial flow with a doppler ultrasound probe also presents an additional non-invasive tool for evaluation of the peripheral vascular situation and the severity of PAD (36,38,54–56). Flow and patency can be assessed of any artery that can be localised with the doppler probe depending on the examiner's skills. Both the baseline pressures and waveform patterns and dynamic examination findings before and after interventions or before and after exercise are of diagnostic value. In addition to this, sudden and marked pressure differences over the course of a vessel can indicate possible locations of arterial stenosis or occlusions, as this causes a larger pressure gradient between neighbouring points along the vessel (36). In general, lower pressures correspond to more compromised blood flow and a more severe progression of PAD, corresponding to the description within the Rutherford classification. In addition to that, conclusions about the general patency of specific vessels can be made using this method. Maximum systolic pressure is expressed in absolute numbers of mmHg and hemodynamic flow patterns are grouped into monophasic, biphasic and triphasic waveforms (37,54,57–59). Triphasic signals can be observed in healthy arteries and its three phases consist of a sharp systolic peak, an audible flow reversal at the beginning of diastole due to the elastic recoil (the Windkessel effect) of the aorta and a smaller forward flow in the later parts of diastole. Triphasic flow can be found exclusively in the vasculature of extremities and muscles and net blood flow occurs in systole. Biphasic flow patterns consist of only two phases of flow and omit the small forward flow in the later parts of diastole. A biphasic waveform can indicate mild to moderate disease of the respective artery. Monophasic signals on the other hand, indicated compromised arterial flow and significant arterial pathology as only the broad systolic peak can be observed. Notably, the systolic peak is more broad and less sharp as in both other waveform patterns. No reversal of flow occurs. The only healthy arteries constantly displaying this signal type are those supplying blood flow to the brain. If the vasculature of extremities suddenly changes into a monophasic signal, this reflects vasodilation distal to a stenotic area. To conclude, assessment of specific arterial flow with a doppler ultrasound probe allows to inexpensively and quickly track disease progression of PAD and evaluate long-term success of treatment as well as a comparison of

local flow conditions before and after certain events. This can be further enhanced by a detailed description of the disease stage using the Rutherford classification or calculating the ABI- or TBI-indexes.

1.3. Therapy Principles for Infrapopliteal Lesions

1.3.1. Interventional Endovascular and Surgical Therapy Options

Endovascular-based methods of therapy have increasingly emerged as the current mainstay of therapy for infrapopliteal PAD over the last years (60–67). In contrast to more open surgical approaches, their minimally-invasive nature allows for treatment of vessels from within the vessel lumen with the aid of catheter-based systems that are maneuvered and positioned using Seldinger-Technique (68). Access to the vasculature and target vessel is initially gained by puncturing the femoral or radial artery, from where on the catheter will be positioned to the target vessel lesion. There, expandable balloons or stents are commonly used to dilate the local stenosis and improve blood flow. Recent innovations have incorporated drug-coating to balloons and stents to locally and precisely deliver antiproliferative substances that are thought to enhance effectivity of dilation and maintain long-term patency success through inhibition of restenosis, which will be discussed in more detail in the next subchapter.

Another option is the mechanical removal of atherosclerotic plaques during atherectomy. Here, the catheter is guided to the target vessel site as before and a rotating cutting blade is used to locally remove plaque buildup that is then carried away by the blood stream of collected with designated embolus-protection systems (69,70).

Moreover, even acute thrombi of the infrapopliteal vasculature are amenable to minimally invasive treatment either through aspiration thrombectomy that mechanically removes the thrombus with special catheters or by means of locally applied endovascular thrombolysis (71).

Furthermore, newer emerging options in the realm of endovascular therapy include endovascular deep venous arterialization and percutaneous bypass creation. Deep venous arterialisation is carried out via gaining catheter-access to both the arterial and venous system and creating an artificial arteriovenous fistula between a proximal artery and distally located suitable vein just proximal to the target vessel stenosis and fissuring the venous valves (72–74). Percutaneous bypass creation however, involves a diversion of the impaired blood flow through an autologous or synthetic stent graft. If endogenous stents are aimed for, the ipsilateral parallel femoral artery is commonly used. The graft is the re-anastomosed with the proximal end of the

nonpatent lesion (75,76).

Overall, the endovascular approach has multiple advantages (62,77–81): Vascular access during catheter-based interventions are less physically demanding since no large incisions are required and thus the risk of complications such as wound healing impairment, infections and overall mortality are lessened (62,82,83). Local anaesthesia or light sedation suffices for the intervention, which additionally minimizes risks (68). Due to the minimally invasive strategy, shorter hospital stays are required as opposed to endovascular therapy plans, adding economic incentives in favour of endovascular therapy (11,84–86). In addition to this, the oftentimes comorbid conditions of the patient population of PAD, can limit the individual patient's eligibility for surgical procedures. Current European and American guidelines thus recommend endovascular approaches as the first line of treatment for PAD of the lower limb (1,87–89).

Of note, local requirements for certification of the medical personnel are in place, but in Germany there currently is no standardized minimum institutional case volume of endovascular interventions for PAD as it exists for cardiac catheter labs, which might sometimes result in more heterogenous therapy outcomes that do not necessarily reflect those of high-volume centres and more experienced practitioners (90).

In contrast to this, the historically older open surgical bypass creation encompasses primary harvesting of suitable autologous ipsilateral veins, followed by insertion and attachment of this graft to bypass the area of limited flow. Various methods of harvesting this autologous vein are known, but all require suitable graft veins which limits the amount of patients eligible for this procedure because a proportion of patients does not have sufficient veins to be used as grafts, especially in infrapopliteal lesions with concurrent comorbidities (91). Moreover, the more costly surgical procedure requires general anaesthesia that can be unfavourable for many elderly patients, is technically more complex and generally leaves more room for complications (62,81,83). Furthermore, the duration of hospitalisation is longer than in endovascular therapy and places a relatively higher demand on the healthcare system (11,84–86). Overall, the relatively increased workload for healthcare providers, higher invasiveness, prolonged recovery time for patients, higher costs and limited applicability of the open surgical bypass approach have contributed to the recent development of favouring a primarily endovascular first approach to patients with lower extremity PAD alongside a relative decline in the proportion of bypass procedures for the lower limb (60–65).

Of note, the special anatomy of the infrapopliteal opposed to the suprapopliteal circulation of the lower extremity must be considered. It must be emphasized that more clinical

expertise and clear-cut well-established recommendations exist for the vasculature proximal to the popliteal artery that cannot be simply generalized to the vasculature below the knee. Notably, the circulation below the knee encompasses more parallel and longer vessels of smaller diameter (6,92). Though infrapopliteal PAD is a very prevalent subgroup of PAD, the functional outcomes tend to be worse than in other anatomical segments (93–95). In addition to this, endovascular therapy has initially borrowed approaches applied to the anatomically similarly delicate coronary circulation and utilized devices designed for the coronary vasculature since no designated devices were specifically approved for the infrapopliteal region (96–101). In fact, the first device approved for medical use below the knee in Europe received approval only in 2018 (102–105). The concept of drug-coated balloons (DCBs) and stents was also first developed in the realm of percutaneous coronary interventions and has now become a common standard procedure in cardiac catheter labs for the treatment of myocardial ischemia (106–109). However, in contrast to the well-padded coronary vasculature, the lower limb and especially popliteal area is exposed to more mechanical stressors that challenge long-term stent stability through complications such as stent deformation or fractures (101,110,111).

1.3.2. Current Therapy Recommendations for Infrapopliteal PAD

Therapy for below-the-knee PAD includes a combined strategy to maintain patients' quality of life and minimize symptoms of the disease in everyday life. For all subdomains of therapy, it is important to consider the various stages of the disease and tailor the multi-disciplinary approach to the many comorbidities of this complex group of patients (112).

Firstly, the reduction of known risk factors for severe progression of the disease is recommended. This includes the treatment of concomitant diseases like hypertension, coronary artery disease (CAD), diabetes mellitus, obesity or cerebral vessel-processes according to the most recent treatment protocols for the respective disease. Moreover, in patients with Rutherford stages 5 and 6 that have developed ulcerations or necrosis of the lower limb, the multidisciplinary approach also has to include the organisation of long-term and often outpatient wound care, which can be challenging to implement for patients (113).

Secondly, another major aspect of therapy is establishing a change in lifestyle of the patients: Smoking cessation is of note here since it is both a risk factor to develop PAD as well as significantly worsens the progression to further severe complications of the disease once diagnosed (3,23–25). Establishing a weight loss and a pattern of regular physical activity helps to improve overall cardiovascular function, attenuate symptoms of the disease and promote the

growth of collateral vessels to bypass existing vascular lesions and improve endothelial function, thus significantly extending patient's walking distance and maximising their resources for everyday life (3,23,25,114–117). A combination of strength and endurance training is recommended and long-term motivation of patients can be achieved by organised training plans or training alongside a partner. Moreover, a specialised diet plan for PAD has not been developed, but a generally balanced and healthy diet including plentiful fruits and vegetables as well as whole-grain products help to halt progression of the disease, support general health and also maintain a tight glucose-control for the diabetic subset of patients (3,6,21–23). However, the well-known shortcomings of sustainable human behaviour change are notoriously challenging and can be frustrating (113,118).

Thirdly, pharmacologic approaches are an important pillar of treatment for PAD (3,6,23–25). Prevention of thromboembolisms is achieved via thrombocyte-aggregation inhibitors (TAI) and anticoagulation. Statins are used to lower lipid levels with particular emphasis on LDL-levels and slowing the buildup of atherosclerotic plaques. The combination of both groups reduces the overall risk for adverse cardiovascular events. Moreover, antihypertensive medication plans to target arterial hypertension and antidiabetic treatment for diabetes mellitus help to slow the disease progression of PAD by attenuating these common comorbidities. In select cases, exercise training can be further supported by the use of the specialised TAI, vasodilators, angiotensin-converting enzyme inhibitors (ACE)-inhibitors and statins (25,119–123).

In more advanced and symptomatic stages of the disease and if conservative treatment has failed to improve symptoms more invasive procedures like the endovascular or open surgical procedures described in previous passages can be employed. Endovascular treatment can include the usage of minimally-invasive stents or balloons and vascular surgery commonly involves bypass creation for the more complex lesions. Here, it is important to consider that the disease is often not limited to the infrapopliteal segment alone, but often spans the vasculature of several regions, thus highlighting the need for an all-encompassing non-generalized approach to the individual circumstances. In acute presentations of lower limb ischemia due to thrombosis or embolic processes, fast interventional therapy and heparin anticoagulation is mandatory (3,24).

Novel approaches like the usage of stem-cells, growth factors and gene therapy and could potentially improve the burden of symptoms and enhance recovery in the future, but are not part of standard therapy recommendations yet (124–132).

Above all, therapy outcomes can be greatly maximised by paying attention to the

patient's will, individual circumstances that might limit therapy adherence and in particular by effectively coordinating a multidisciplinary approach given the complexity of the disease and the presence of numerous comorbidities (133–136).

1.3.3. Antiproliferative Drug-Coating

DCBs are equipped with antiproliferative coatings to limit the formation of a neointima after the endovascular intervention. The coating contains antiproliferative drugs that are applied to the vessel wall to minimize local cell growth, targeting mainly the smooth muscle cells that can proliferate and cause restenosis of the affected lesion. The main aim of DCB-coating is long-term patency of the treated vessel to prevent downstream ischemia and reduce the need for a repeated intervention.

For the coating, drugs like paclitaxel, sirolimus or everolimus with known antiproliferative effect are well established. In experimental models, coatings containing arsenic trioxide, zotarolimus or a combination of tamoxifen and tacrolimus have been used (137). Since paclitaxel-coated technology is the main thematic focus of this thesis, the following paragraphs will deal with paclitaxel as a prominent and representative example of the antiproliferative category:

Paclitaxel is a lipophilic, hydrophobic substance that is smaller than 1kD (138–141). It quickly binds to intracellular components, thus preventing systemic distribution, excretion or local breakdown (139,142). Its real-life solubility also differs when attached to the coating of a DCB in a crystalline versus amorphous physical state. Its half-life when dissolved in the bloodstream can be approximated to be one day (139).

Due to chemical and binding properties, paclitaxel resides in tissues for a prolonged time and is even described to locally exceed the concentration that was applied overall (139,141). Thus it is not surprising, that after a single application of paclitaxel-coated devices, a remaining drug concentration from the initially applied amount of approximately 9% after 28 days, 3% after 3 months and 1% after 6 months have been described (139,143). However, it has also been claimed, that up to 90% of the drug applied will immediately be washed off to the general circulation (144).

Considering the larger picture, paclitaxel in endovascular therapy is not used as a solvent but embedded in the coating of a device. The lipophilicity of the used drug and the hydrophilicity of its excipient, will determine how crystalline the coating will be. If a drug is present in its crystalline form (instead of the amorphous form), this will lead to a change in

solubility. Moreover, paclitaxel crystal particles can have a half-life of weeks to months and have been found to be present in tissue sites distal to the target lesion 90 days after the target lesion intervention when no paclitaxel was detectable at the target lesion site anymore (142). Paclitaxel is absorbed into the subintimal space by protein binding. It binds non-specifically to serum proteins with high-affinity binding sites and can be found at maximum concentration in the intracellular space of the vessel's media. In addition to this, transmembrane transport via histone protein mediates intracellular binding. Paclitaxel distributes both in the vessel's media and adventitia (137,140,142,143,145,146).

Pharmacologic action of paclitaxel is mediated by the formation of abnormal multipolar spindles that stabilize the cell's microtubules in a way that prevents their depolymerization. Thus, the cytoskeleton is reorganized and cell division is halted at the G2-/M-phase of the cell cycle (140,147). Thus, cell proliferation and differentiation are stopped and eventually apoptosis can be induced (147). In addition to that, it is reported that in very low doses, paclitaxel will not completely block mitosis, but instead cause aneuploidy, meaning an aberrant number of chromosomes, which will also inhibit cell division (148).

Antiproliferative drug coating of DCBs mainly aims to target the vessel's smooth muscle cells in the fashion described above. Smooth muscle cells trigger intimal hyperplasia when localized barotrauma due to vessel manipulation is recognized (149). Smooth muscle proliferation is triggered by platelet-derived growth factor B starting on the second day after vessel manipulation. It reaches its maximum growth dynamic on the seventh day and intimal cell number starts to decrease from the 14th day on(139,150). It is assumed that the antirestenotic effect of paclitaxel can be attributed to the long-term presence of the drug in the vessel's vicinity, but an alternative hypothesis is that its presence during the first week might already be sufficient via very early inhibition of the critical starting triggers of the proliferation cascade that occur in the first week post-intervention (139,150). Regardless, conventional DCBs have been shown to create a high enough concentration of paclitaxel to effectively inhibit smooth muscular cell activity up to three months after their use (139).

Paclitaxel undoubtedly affects overall vessel health and exerts its main effect on smooth muscle, but several other cell types have been noted by be affected by the drug as well: Macrophages, that are triggered by initial inflammatory stimuli due to mechanical barotrauma, are effectively halted in their motion by paclitaxel (146). Furthermore, endothelial cells have been demonstrated to already be affected by picomolar concentrations of the drug, thus explaining its antiangiogenic properties (151,152). Moreover, it is cytotoxic to human stem cells even at lower doses than would be required for smooth muscle cells (152).

The current market dose for paclitaxel-coated endovascular balloons is in the range from 2 to 3,5µg/mm2, which is also consistent with the dose used for the Luminor™-DCB (iVascular) described in this thesis (137,153). However, a recent trial with an even lower dose of paclitaxel suggested a similar effect and improved healing (154). The optimal drug dose is still not known.

The final bioavailability and pharmacokinetics of paclitaxel embedded in endovascular devices is indeed also influenced by a huge variety of factors regardless of its dose. First of all, at the local vessel site, diffusive and convective forces and local flux conditions, play an important role (137,138,155). Secondly, binding sites and the interaction with native proteins can influence drug distribution kinetics and bioavailability at the cellular level (138,155). Moreover, temperature can change solubility and impact the drug's release and its transfer into deeper tissue layers (137). Furthermore, for optimal homogenous distribution of the drug, it is mandatory that the device evenly applies its drug coating to the vessel, thus minimizing areas of high concentration and possible toxicity but also preventing areas where only subtherapeutic doses of paclitaxel are applied (156).

In addition to that, the vessel structure itself determines part of the final pharmacologic effect, especially regarding its surface, lipid content, protein composition and the presence of calcifications.

Despite its lipophilic properties, the lipid content of a vessel is shown to be inversely proportional to paclitaxel uptake, pointing to the degree of protein binding to be a more meaningful predictor of drug distribution instead. Additionally, tubulin, the protein targeted most directly by the drug, is upregulated and increasingly expressed in the subintimal space in animals fed a cholesterol-rich diet and minimized drug transfer in the presence of atherosclerosis has been shown. However, normal rates of drug transfer could be established in the atherosclerotic arteries by the use of higher inflation pressures, but not in non-atherosclerotic arteries (146,157).

Elastin is one of the proteins, that promote the absorption and deposition of lipophilic drugs such as paclitaxel. It structure is negatively affected by the presence of calcifications in the vessel, thus explaining decreased a decreased effect of paclitaxel if vessel calcifications exist (137,145).

In addition to that, ballon pressure and inflation time also matter (158,159).

However, most attention has been given to the coating the drug is embedded in. The best possible coating would be designed to provide uniform and homogenous drug distribution of a drug what is locally retained for a maximum amount of time, while minimizing local toxicities

and downstream release of excipient particles off the device (137,143,145,153,154). To achieve this, the ratio of drug to its excipient must be carefully considered (154). A more crystalline coating (as opposed to amorphous coating) allows for a higher drug concentration and prolongs tissue retention while lessening local drug toxicity (143,145,160). Despite this, there is growing suspicion that crystalline coatings might produce downstream embolization of large particles that can occlude vessels or increase amputation risk (153,154,159–161). Furthermore, cases of acute hypersensitivity reactions localized on the lower leg weeks after treatment with paclitaxel-eluting devices have been described (153,162–164). However, the significance of this observation is unknown. Nevertheless, the Food and Drug administration (FDA) has encouraged healthcare providers, to closely discuss possible risks and benefits devices coated in paclitaxel and consider alternative modes of treatment (165). Technical methods to improve drug coating and minimize embolization of its constituents, have been explored and might be of greater significance in the development of future endovascular device technologies (137).

To sum up, paclitaxel is a small lipophilic compound with unique binding properties, explaining its long residence in the vessel wall after a single application. Its main effect is to halt the growth of smooth muscle cells of the vascular wall in the initial stages after an intervention, but other cell types are affected as well. There are many more factors influencing local pharmacokinetics and biological effect and the optimal drug dose is still debatable. Crystalline coating techniques improve drug delivery, and concerns of possible downstream embolus creation from parts of crystalline drug coating have been raised, but significance of this is still unclear.

1.3.4. Spur-stent

The Spur-stent-System™ (Reflow Medical) is a novel stent system developed for use in the infrapopliteal vasculature for the treatment of CLTI, which marks the more severe final stages of PAD. It can be used both for de novo or restenotic lesions and is compatible with a guidewire size of 0.14 inches. In contrast to conventional stents, it is intended for temporary use only and will be completely retrieved after the intervention with none of its parts remaining in the vessel. It dilates the vessel's lumen upon expansion by the medical practitioner and is additionally equipped with radial spikes (so-called spurs) that directly penetrate the vessel wall in a radial fashion to create channels for enhanced drug absorption of the respective drug coating of subsequently used commercially DCBs. The device is shown in Figure 1 below. Vessel preparation with the Spur-stent system is immediately followed by use of a DCB such as the

Luminor-DCB within the same intervention. The Spur-stent system is made of nitinol and a hydrophilic coating, but itself does not carry pharmaceutic effects (70,166,167).

Figure 1. Mechanism of Action of the Spur-stent system
Source: Spur EU [Internet]. Reflow Medical [cited 2024 Jul 28]. Available from: https://www.reflowmedical.com/spur-eu/

The way of action of the Spur-stent is the combination of mechanical preparation of the vessel by this stent and thus enhanced pharmacologic effects of subsequently used DCBs. Its radially-aligned spikes pierce the vessel wall, which allows antiproliferative drugs to be delivered and absorbed directly at their target site, namely media and adventitia of the vessel to reduce later vessel restenosis and recoil immediately after treatment. Their perforating action is assumed to be of particular use for heavily calcified or complex lesions, where plaques impede drug absorption. This could be one further step towards a more individualized therapy. They are also thought to change the vessel's compliance and might reduce possible vessel dissection. Since nothing will be permanently left at the lesion site, they do not impede the vessel's physiologic function while still providing mechanic support during the intervention. The more delayed risks of in-stent restenosis or stent thrombosis are also thought to be minimized due to the postinterventional absence of the stent, but data to support this is not available yet. In addition to this, the irritation of long-term local implants can be avoided.

In total, the spike mechanism is intended to penetrate the vessel wall to create temporary channels for improved target-site antiproliferative drug delivery by subsequent DCBs to

minimize recoil directly after the intervention as well as long-term prevention of vessel restenosis.

Several studies have examined the effect and safety of the Spur-stent (167). After successful initial preclinical evaluation in pigs, the first-in-human trial was a prospective, single-center and single-arm study encompassing 23 patients treated in the Dominical Republic (168). It combined the Spur-stent together with a paclitaxel-coated DCB and demonstrated a vessel patency of 88.9% at 6 months after the intervention. There were no perioperative deaths and freedom from target lesion revascularization of limb amputation was 94.1% (167).
In another study, 26 patients in Austria were included in a prospective single-center, single-arm pilot study where the Spur-stent was combined with a sirolimus-coated DCB. Again, good patency rates of 89,5% 12 months post intervention. 95% freedom from major adverse limb (MALE)-events, 95,2% freedom from revascularization, wound size reduction by 54.0% and Rutherford-score improvement by 68,2% was noted (169,170).

The following trial combined the Spur-stent again with a paclitaxel-coated balloon and involved 107 patients with infrapopliteal PAD in ten medical centers in the EU and New Zealand. It was prospective, multi-centric, randomized and single-arm. Here, a patency of 74.4% of lesions, 98,9% freedom from MALE-events, 89,5% freedom from revascularization at 12 months after the intervention, wound size reduction by 63,1% and Rutherford score improvement by 58,4% compared to baseline was demonstrated so far, but the study is still ongoing (171,172).

Very recently, a smaller pilot study including 10 patients in New Zealand has also begun to evaluate the transfer of the Spur-stent principle to coronary lesions, but results are not evident yet (173–175).

Despite the good results in studies of its manufacturer, there are still gaps in the literature regarding clinical perspective and real-life effects of usage of this Stent. Especially long-term results and a direct comparison to treatment results of similar endovascular treatment options would be desirable. Further large-scale real-life randomized studies are currently still lacking. Moreover, an economic cost-benefit consideration has not been conducted yet. In addition to this, examination under real-life clinical conditions and careful analysis of its effect for different patient groups could be of use. This might also offer possibilities to fuel further development of its technology, such as the application of drugs directly to the tip of the Stent's spurs.

1.3.5. Luminor Drug-Coated Balloon (DCB)

The Luminor™-DCB (iVascular) is a DCB catheter that follows the widespread principle of vessel dilation in combination with locally applying its antiproliferative drug coating to the dilated target lesion affected by PAD (176). It is homogenously coated in paclitaxel and a lipophilic organic ester excipient to halt cell proliferation and reduce long-term restenosis of target lesions. Guidewire of 0.014, 0.018 and 0.035 inches are available and the balloon itself is available in mini size till max size, allowing for flexibility to fit different types of lesions in everyday interventional practice. In this study, the Luminor-DCB was expanded and left in place at the target site for 120 seconds.

Its nanotechnology coating has been designed to allow an even absorption of paclitaxel but minimize systemic drug use while navigating to the target site. Upon DCB dilation, the drug is pressed against the vessel wall, where its antiproliferative effects prevent restenosis to maintain long-term patency of the targeted vessel (176).

There have been several large clinical trials concerning the clinical use of the Luminor-DCB in the femoropopliteal region with convincing primary patency rates, freedom from amputation and rates of freedom from revascularizations up to five years after the intervention ranging from 74.8% to 82.1% (177,178). Another large trial focusing on femoropopliteal lesions is still ongoing, but its preliminary data suggests a confirmation of those results with freedom from revascularizations being 95,4% one year after the intervention with the Luminor-DCB (179,180).

There also have been two clinical trials targeting the use of the Luminor-DCB for below-the knee and tibial vascular lesions. Both have demonstrated freedom from revascularization at 12 months postoperatively to be 86,6% and 81.6% respectively as well as good rates of primary patency and amputation-free survival (179,181,182). The publication of more long-term data is eagerly awaited. Overall, these trials demonstrate clinical effectiveness of the already more widely used Luminor-DCB in clinical practice.

Despite large-scale studies in realistic settings of clinical practice, further data supporting the DCB's long-term effects in comparison with similar endovascular treatment options are still welcome and would help to further consolidate knowledge about its advantages and drawbacks.

2. OBJECTIVES

2.1. Aims of the study

The aim of this thesis is to investigate the therapeutic usefulness and risk profile of the use of Spur-stents as additional vessel modification before standard DCB use in infrapopliteal vessels.

Patients with chronic PAD receiving target lesion preparation with the Spur-stent before commercially-available standard DCBs are compared to propensity-score matched patients with similar-sized infrapopliteal lesions that received only Luminor-DCBs without additional previous vessel preparation by the Spur-stent. The group receiving target vessel modification prior to standard DCB-use is from here on referred as Spur-group and the group of matches receiving only the Luminor-DCB without additional vessel preparation is hereinafter referred to as the Luminor-group.

To assess clinical performance and risks, reintervention-free survival, overall mortality, major adverse cardiovascular event (MACE)-free survival, MALE-free survival, and the occurrence of ipsilateral postprocedural minor and major amputations were compared in both groups. Moreover, long-term patency and periinterventional target vessel assessment as a marker of success of therapy were examined along with an exploration of the characteristics of both patient groups to discover possible confounders given the retrospective nature of this study.

2.2. Hypothesis

It is hypothesized that vessel preparation by the expansion of radially aligned spikes of the Spur-stent facilitates drug uptake of the succeeding DCBs and thus increases the antiproliferative effect, minimizing the need for reintervention and minimizing the restenosis rate.

3. SUBJECTS AND METHODS

3.1. Study design

This study was designed to include a total of 24 patients with chronic PAD treated over the course of 55 months from August 2017 to March 2022 at MEDINOS Vascular-Centre Sonneberg, Germany. 12 consecutive patients treated with the Spur-stent to enhance drug uptake prior to standard DCB-use were propensity-score matched to 12 patients with similar lesion characteristics having received only the paclitaxel-coated Luminor™-DCB (iVascular). In total 28 endovascular devices were used on 24 legs with up to two Spur-stents™ (Reflow Medical) being used during the same intervention. Repeated expansions of the same intravascular device were included as well. Prior to the use of Luminor-DCB, the vessel preparation with plain old balloon angioplasty for 60 seconds was followed by 120 seconds of treatment with the Luminor-DCB. Concomitant use of other DCB-systems on different sites of the same leg during the examined intervention was possible. Exclusively infrapopliteal target lesions were included as defined by the P3-segment of the popliteal artery and all vessels distal to it. Data was gathered to assess perioperative improvement and long-term outcomes at three, six, 12, 28, 36 and 60 months after the procedure as well as preoperatively and immediately postoperatively. Preoperative time was defined as up to 45 days before the intervention. The postoperative time was defined as up to three days after the procedure. The three and six-month-follow-ups were given an allowed variance of ±30 days and the 12-60 months follow-up-time points were given an allowed variance of ±60 days to group and meaningfully analyze data while reducing data loss given the retrospective nature of the study and considering the natural variations in real-world patient schedules.

3.2. Data collection

Data for this single-center study was collected from the clinic's data bank system Orbis (Orbis®, Dedalus Healthcare, Bonn, Germany) in combination with initial patient identification via the clinic's handwritten surgical implant and procedure handbook. Patients were randomly given numbers for anonymization and data was collected in Microsoft Excel 2016 (Excel 2016®, Microsoft Office Home and Student, Microsoft Corporation, Redmond, WA, USA) and Microsoft Word 2016 (Word 2016®, Microsoft Office Home and Student, Microsoft Corporation, Redmond, WA, USA).

Collected data included date of birth, date and time of intervention, number and type of intravascular devices used during the procedure and amount of expansions per device, target vessel and leg side of the procedure, length and diameter of the intravascular device, sex, acute

or chronic indication for therapy, perivascular lysis therapy, date and cause of death or date of last confirmed alive contact to a medical institution, last confirmed date without major amputations, last confirmed date of patent target vessel, diagnosis of arterial hypertension, diagnosis of CAD, diagnosis of diabetes mellitus type 2, all known ABI- and TBI-values, all known Rutherford-scores, amputation status prior to intervention, date and side of minor and major amputations, date of MACE- and MALE-events, date of ipsilateral reinterventions and prescription of direct oral anticoagulants (DOACs), vitamin-K-antagonists (VKAs), statins and TAI as written in the medical reports.

In this context, MACE-events were defined to include strokes, myocardial ischemic attacks, and deaths due to cardiovascular causes and MALE-events were defined either ipsilateral major amputations or any therapeutic endovascular procedure targeting the target vessel on the ipsilateral leg. Both MACE- and MALE-events were recorded exclusively after the index procedure.

3.3. Ethical approval

This study has been approved by the IRB (institution review board) of the Medical School REGIOMED-Kliniken Coburg GmbH on the 19th of February 2024. In addition to complete anonymization of patients and its retrospective nature, it complies with the declaration of Helsinki of the WMA (world medical association) in its latest version of 2013.

3.4. Citation software

The reference management-software Zotero (Zotero®, Digital Scholar, Vienna, VA, USA) was used to organise and cite bibliographic references as well as to generate appropriate bibliography and take notes.

3.5. Statistical analysis

Data was handled using the programs Microsoft Excel 2016 (Excel 2016®, Microsoft Office Home and Student, Microsoft Corporation, Redmond, WA, USA) for import and visual output generation and IBM SPSS Statistics (SPSS Statistics®, IBM Corporation, Armon, NY, USA) for statistical analysis.

Propensity-score matching was performed using an optimal matching strategy without replacement. The aim was to ensure the smallest possible differences in propensity scores across

all pairs and matches were based on lesion length, age and gender. Each group member was matched to one unique member of the other group and no member was matched to multiple members of the other group.

For analysis and comparison of significances of associations between two categorial variables the Chi-square test and Fisher's exact test were used. A 2x2 contingency table was used to calculate the expected frequencies for each variable. If the expected frequencies included numbers < 5, Fisher's exact test was used. Otherwise, the Chi-square test was implemented.

Comparison and evaluation of continuous numeric data was conducted with the Mann-Whitney-U test and the independent Two-sample T-test. Prior to this, normality of the data was examined using the Shapiro-Wilk test and equal variances of the data were checked using Levene's test for equal variances. When the data was normally distributed with equal variances, the independent Two-sample T-test was employed and if there was a violation of normality within the data, the Mann-Whitney-U test was applied.

Kaplan-Meier survival analysis was applied to evaluate event-free survival within both patient groups. Cases were censored at the day of death and if their follow-up intersected with the present date on the 1st of March 2024 and was thus still in the future. The Mantle-Cox test (also known as log-rank test) was used to determine the significance of differences of event-free survival for both groups and the Greenwood-Formula was used to determine standard error of survival.

All cases of calculation of confidence intervals referred to the 95% confidence interval and all calculated p-values were considered to be statistically significant if $P < 0.05$ as it is common standard.

4. RESULTS

4.1. Patient characteristics

24 Patients were treated from August 2017 to March 2022 at MEDINOS Vascular-Centre Sonneberg, Germany. There were 12 patients each in the Spur-group and the propensity-matched comparative Luminor-Group. 28 examined endovascular devices were used in total, encompassing 16 Spur-stents (57.1%) in the Spur-group and 12 DCBs (42.9%) in the Luminor-group. In four (33.3%) of the 12 interventions in the Spur-group, two Spur-stents were used within the same leg, while the remaining 66.7% (n=8) of patients having received only one Spur-stent. Two (16.7%) of the 16 Spur-stents used were expanded twice within the same vessel, while the remaining 14 stents (87.5%) being expanded only once during the intervention in which they were utilized. None of the patients were treated twice and each intervention encompassed only one leg.

The patients were predominantly male (91.7%) with only one female member in both groups (8.3%). Average age on the day of the intervention for all patients was 73.5±8.8 years. The average age in the Spur-group was 71.1±8.1 years and 76±8.5 years in the Luminor-group, indicating the age of the Spur-group patients being relatively skewed towards younger individuals. This difference was not significant with $P = 0.164$.

There was a slight predominance of interventions being conducted on the left (58.3%, n=14) versus right lower limb (41.7%, n=10).

79.2% of all 24 patients were diagnosed with diabetes mellitus type 2 at the time of intervention (n=19), 25.0% were diagnosed with CAD (n=6) and 79.2% of them were diagnosed with arterial hypertension (n=19). The prevalence of neither of those three diseases did significantly differ between both examined patient groups with $P = 0.640$ for CAD, $P = 0.317$ for Diabetes Mellitus and $P = 1.000$ for arterial hypertension.

According to the medical record upon discharge after the examined procedure, 20.8% of all Patients (n=5) were prescribed DOACs, 58.3% were prescribed Statins (n=14), 16.7% were prescribed VKA (n=4) and 95.8% were prescribed TAI (n=23). Continued prescription of TAI 6 months after the intervention was observed in 62.5% (n=15) of patients. There was no significant difference in the distribution of any of the prescribed drug classes among the Spur- and Luminor-group.

Periinterventional kidney function assessment was based on the estimated glomerular filtration rate (eGFR)-value taken on the day of intervention according to the recorded lab results. In both groups stages 1 and 2 of the eGFR-categorization of chronic renal insufficiency (corresponding to an eGFR higher than 60 ml/min) were predominant with 38.9% of patients

(n=7) in each category. Patients grouped to an eGFR-value corresponding to stage 3 of chronic renal insufficiency were present in 17.7% (n=3) and just one patient was assigned an eGFR-value corresponding to stage 4 (5.6%) with 33.3% (n=6) patients where the periinterventional eGFR could not reliably be determined in retrospect.

In one case (4.2% of all patients) within the Luminor-group there was endovascular lysis therapy on the day prior to the intervention involving the DCB. For the remainder of patients, no periprocedural endovascular lysis therapy was noted.

A more complete overview and comparative presentation of the mentioned characteristics of patients can be found in Table 1.

Table 1. Baseline characteristics of population, Comparison of demographic data and characteristics of the Spur-group and Luminor-group

Parameter		Spur-group (n=12)	Luminor-group (n=12)	Total (n=24)	*P*
Age	Average (SD)	71.1±8.1	76±8.5	73.5±8.5	0.164§
Number of intravascular devices				28 (100%)	
	Spur-stent	16 (57.1%)	0 (0%)		-
	Luminor-DCB	0 (0%)	12 (42.9%)		-
Sex	Male	11 (91.7%)	11 (91.7%)	22 (91.7%)	1.000*
	Female	1 (8.3%)	1 (8.3%)	2 (8.3%)	
Laterality	Left Leg	8 (66.7%)	4 (33.3%)	14 (58.3%)	0.220†
Device size	Average diameter (SD)	3.1±0.3	3.4±0.5	3.2±0.4	0.110‡
	Median diameter (Q1-Q3)	3 (3-3)	3 (3-4)	3 (3-3)	0.110‡
	Length average (SD)	60±0	68±10.3	63.6±7.8	0.660‡
	Length Median (Q1-Q3)	60 (60-60)	60 (60-80)	60 (60-60)	0.660‡
Endovascular lysis therapy	On the day of procedure	0 (0%)	0 (0%)	0 (0%)	-
	One day prior to procedure	0 (0%)	1 (8.3%)	1 (4.2%)	1.000*
Disease Prevalence	Diabetes mellitus	11 (91.7%)	8 (66.7%)	19 (79.2%)	0.317*
	Arterial hypertension	10 (83.3%)	9 (75%)	19 (79.2%)	1.000*
	CAD[a]	2 (16.7%)	4 (33.3%)	6 (25%)	0.640*
Prescribed drugs	TAI[b]	12 (100%)	11 (91.7%)	23 (95.8%)	1.000*
	Statins	5 (41.7%)	9 (75%)	14 (58.3%)	0.214†
	DOACs[c]	2 (16.7%)	3 (25%)	5 (20.8%)	1.000*
	VKA[d]	2 (16.7)	2 (16.7%)	4 (16.7%)	1.000*

Data is reported as either number (%), as mean ± standard deviation or as median (Q1 - Q3).

Age is given in years and intravascular device size is expressed in mm.
* Fisher's exact test
† Chi-Square test
‡ Mann-Whitney-U test
§ Independent Two-sample T-test
[a] Coronary artery disease
[b] Thrombocyte aggregation inhibitors
[c] Direct oral anticoagulants
[d] Vitamin K antagonists

4.2. Interventions and intravascular devices

Within the Spur-stent group average Spur-stent diameter was 3.1±0.3mm and length was 60±0mm for all cases. Average DCB-diameter within the Luminor-group was 3.4±0mm and length was 68.3±10.3mm.

The anterior tibial artery was targeted most often within the Spur-group (56.3%, n=9), followed by the fibular artery (25.0%, n=4), the posterior tibial artery (12.5%, n=2) and lastly the transition between fibular artery and popliteal artery (6.3%, n=1). In the Luminor-group the distribution of targeted vessels was more homogenous with 33.3% (n=4) DCBs targeting the popliteal artery and 16.7% (n=2) targeting the fibular artery, anterior tibial artery, posterior tibial artery and the transition between fibular artery and popliteal artery each.

4.3. Death and Follow-up

All patients were followed-up for an average of 762.3± 407.9 days from the intervention till either death or the last confirmed date alive as proven by contact to a medical institution. Average overall duration from intervention till death was 436.8±398.1 days in the Luminor-group. No deaths were noted in the Spur-group. The average duration of the interval from intervention to the last date where the patency of target lesion vessel could be verifiably confirmed was 451.7±352.5 days. Average age on the day of death was 79.6±5.7 years

4.4. Periprocedural score changes

4.4.1. Perioperative ABI and TBI-scores

Figure 2 illustrates a comparative overview of the perioperative development of ABI- and TBI-values of both groups and demonstrates an initial increase in average ABI from pre- to postoperative periods in both groups. ABI-values exceeding 1.3 were omitted from this graph since they indicate non-compressible arteries, which is a noninformative fact for this analysis. However, by 6 months after the procedure, the Luminor-group maintains higher ABI-Values compared to the Spur-group. TBI-values at the sixth postoperative month were only collected in the Spur-group, but not in it control Luminor-group. This explains the absence of TBI-values for the Luminor-group at 6 months.

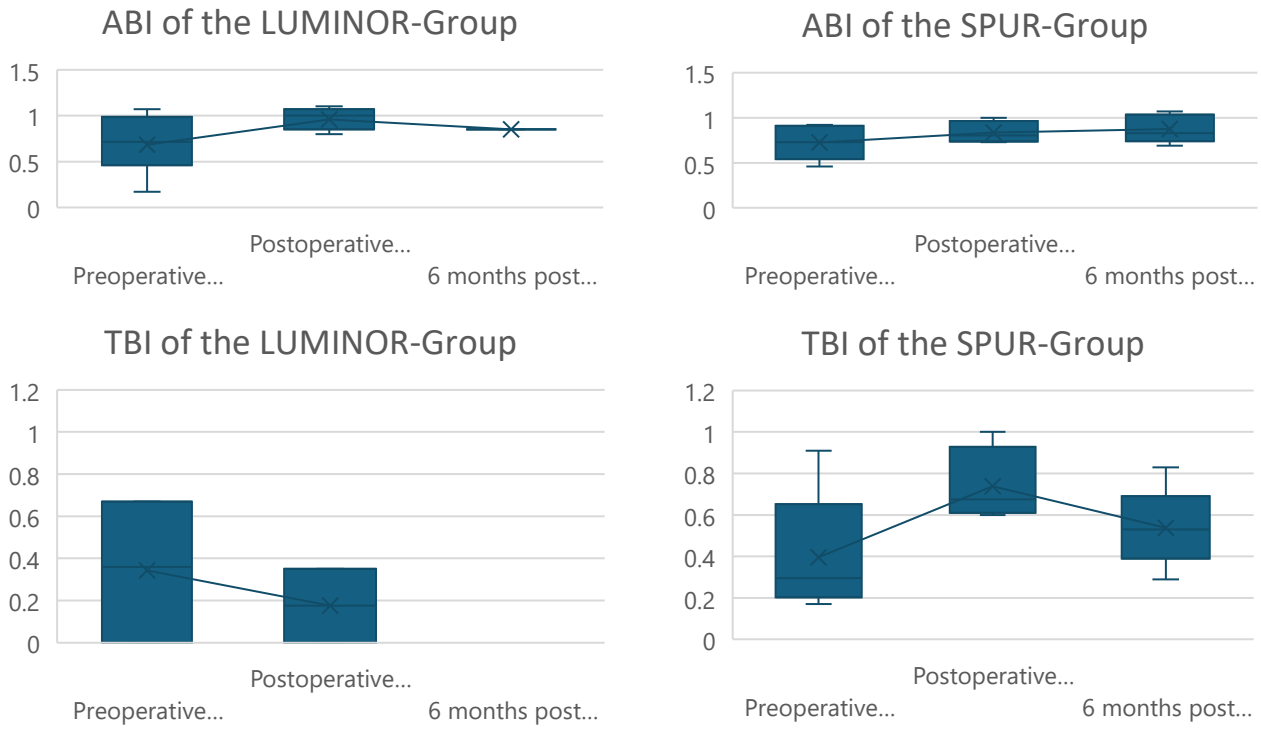

Figure 2. Box plots. ABI-values and TBI-values are presented in the preoperative period, postoperative period, and 6 months after the procedure day. Left-sided: results of the Luminor-group; Right-sided: results of the Spur-group.

4.4.2. Perioperative Rutherford-Scores

As shown in Table 2, most patients were classified as Rutherford stage 5 from the preoperative period till the postoperative period and/ or day of discharge in both the Spur- and Luminor-group. The median Rutherford-Stage in the Spur-group sixth till 12th month of follow-up was lower (Median Stage 3 at 6 months post-procedure, Median Stage 1 at 12 months post-procedure, Median stage 1 at 24 months post-procedure) than in the Luminor-group (Median Stage 4 at 6 months post-procedure, Median Stage 5 at 12 months post-procedure and Median stage 5 at 24 months post-procedure). This was reversed at the follow-up of 36 months post-procedure with Median Stage 5 for the Spur-group and Stage 3 for the Luminor-group. It may however be noted that this finding is based on a limited sample size in the months of postprocedural follow-up. Follow-up of Rutherford-Stages was cut off after 36 months due to insufficient data.

Table 2. Median and Prevalence of Rutherford-Stages in the Spur-group compared to the Luminor-group.

Time Point	Group	Median stage	Stage 5 count (%)	Stage 4 count (%)	Stage 3 count (%)	Stage 2 count (%)	Stage 1 count (%)	Stage 0 count (%)
Preoperative period (up to 45 days prior to intervention)	Spur-group	Stage 5	11 (91.7)	1 (8.3)	0 (0)	0 (0)	0 (0)	0 (0)
	Luminor-group	Stage 5	9 (81.8)	1 (9.1)	0 (0)	1 (9.1)	0 (0)	0 (0)
Procedure day	Spur-group	Stage 5	11 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Luminor-group	Stage 5	10 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Day of Discharge	Spur-group	Stage 5	5 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Luminor-group	Stage 5	4 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
6 months post-procedure ±30 days	Spur-group	Stage 3	6(50)	0 (0)	0 (0)	0 (0)	2 (16.7)	4 (33.3)
	Luminor-group	Stage 4	1 (33.3)	2 (66.7)	0 (0)	1 (33.3)	0 (0)	0 (0)
12 months post-procedure ±60 days	Spur-group	Stage 1	4 (33.3)	0 (0)	0 (0)	0 (0)	2 (16.7)	6 (50)
	Luminor-group	Stage 5	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
24 months post-procedure ±60 days	Spur-group	Stage 1	1 (33.3)	0 (0)	0 (0)	0 (0)	2 (66.7)	0 (0)
	Luminor-group	Stage 5	2 (66.7)	0 (0)	0 (0)	1 (33.3)	0 (0)	0 (0)
36 months post-procedure ±60 days	Spur-group	Stage 5	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Luminor-group	Stage 3	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)

Data are presented as absolute number of cases (%).

4.4.3. Perioperative Duplex ultrasound-examination findings

As concerning the arterial flow pressures of both groups measured by duplex ultrasound (DUS)-examination for each vessel targeted by an intervention, there was a marked total increase from an average of 131.7±69.2 mmHg preoperatively to 160.6±63.1 mmHg directly postoperatively. Three months after the procedure the average was 190±53.5 mmHg. From then on, the average of 189.6±64.6 mmHg at 6 months postoperatively and 180±59.9 mmHg at one year after the procedure was almost stable. The analysis was cut off beyond one year of analysis due to insufficient data.

A more detailed comparison of the distribution of directly pre- and postoperative measurements among both groups is displayed in Figure 3. Here the average of 135.4±73.7 mmHg preoperatively and of 156.4±64.8 mmHg postoperatively in the Spur-group was demonstrated. In the Luminor-group the average was 113.2±59.5 mmHg perioperatively and 156.9±64.3 mmHg postoperatively. This corresponds to an 15.5% increase of pre- to postoperative findings in the Spur-group and a 38.6% increase in the Luminor-group.

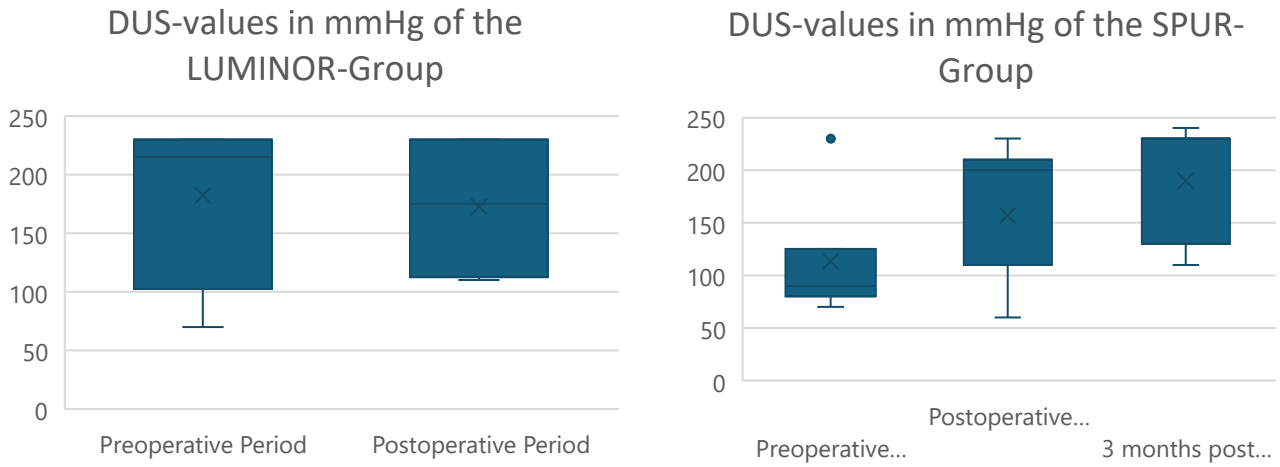

Figure 3. Box plots. Measured DUS-values in mmHg are presented in the preoperative period, postoperative period, and 3 months after the procedure day. Left-sided: results of the Luminor-group; Right-sided: results of the Spur-group.

Patency determined using DUS-examination was assessed for each vessel by signal flow curve characteristics. A difference of 0% (n=0) postoperative nonpatent vessels in the Spur-group opposed to 16.7% (n=1) in the Luminor-group was demonstrated. However, the small sample size should be noted. A direct perioperative comparison of the DUS-Signals in the Spur- and Luminor-group during the preoperative and postoperative period is presented in Figure 4. Standard error is drawn as error bars to compare means across the entirety of patients and

demonstrates relatively short error bars, indicating moderate variability and robust generalizability of the results. Both groups show a slight overall improvement of signal patency after the procedure as it is evident by fewer non-patent postoperative signals. Moreover, the Spur-group displays a more homogenous preoperative signal distribution.

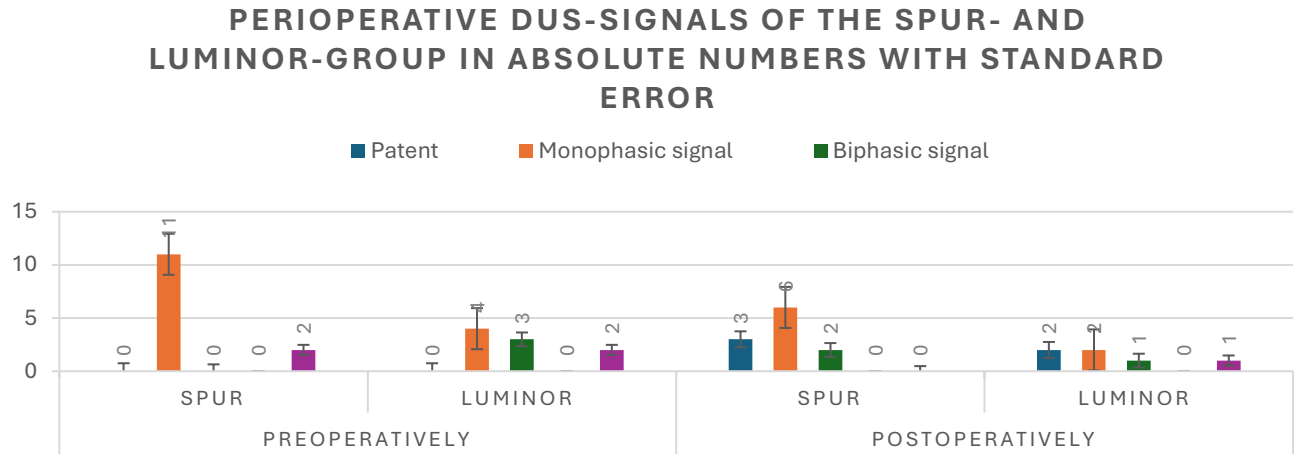

Figure 4. Stacked bar chart. Perioperative comparison of preoperative to postoperative DUS-Signals in the Spur-group and Luminor-group in absolute numbers with drawn standard error bars.
Data are presented as absolute number of cases. The very left bar in each section indicates a patent signal, the second from the left indicates a monophasic signal, the middle bar a biphasic signal, the second from the right a triphasic signal and the very right bar a nonpatent signal.

4.5. Postprocedural events

Postprocedural reinterventions, minor and major amputations, MALE-events, MACE-events and deaths are explored in detail for both the Spur- and Luminor-group in Table 3.

Table 3. Comparison of postinterventional events of the Spur-group and the Luminor-group.

Parameter		**Spur-group (n=12)**	**Luminor-group (n=12)**	**Total (n=24)**	***P****
Reinterventions	Days till reintervention	511±0	512.5±528.2	512±373.5	1.000
	Total reinterventions	1 (8.3%)	2(16.7%)	3(12.5%)	0.755
Minor amputation	Days till minor amputation	29.2±58.1	14.6±15.8	21.9±40.9	0.841
	Total minor amputations	5 (41.7%)	5 (41.7%)	10 (41.7%)	1.000
Major amputation	Days till major amputation	-	186±241.8	186±241.8	-
	Total major amputations	0 (0%)	2 (16.7%)	2 (8.3%)	0.478†
MALE-events	Days till MALE-event	511±0	349.3±384.7	381.±341	0.800
	Total MALE-events	1 (8.3%)	4(33.3%)	5(20.8%)	0.291
MACE-events	Days till MACE-event	471±227.7	541.3±361.1	513±282.2	0.827‡
	Total MACE-events	2(16.7%)	3(25%)	5(20.8%)	0.713
Death	Postoperative time till death	-	436.8±398.1	436.8±398.1	-
	Age at death	-	79.6±5.7	79.6±5.7	-
	Total deaths	0 (0%)	8 (66.7%)	8 (33.3%)	0.001†

Data is reported as either absolute and relative (%) frequency or as mean+- standard deviation.
Age is presented in years.
* Mann-Whitney-U test
† Fisher's exact test
‡ Independent Two-sample T-test

4.5.1. Reinterventions

Reinterventions were present in 4.2% (n=1) of the SPUR-Group and in 8.3% (n=2) of patients from the Luminor-group. The duration from intervention till the date of the first reintervention was 511 for the Spur-group and an average of 512.5±528days for the Luminor-group respectively. Multiple reinterventions were not observed. A more detailed comparative overview of the occurrence of reinterventions in both groups can be seen in Table 3.

According to Kaplan-Meier analysis, the overall reintervention-free survival was 4.4±0.3 years and the 95% CI from 3.8 to 5.0. In the Spur-group the average reintervention-free survival was 2.9±0.1 years with a 95% CI from 2.7 to 3.2. In comparison, the average reintervention-free survival of the Luminor-group was 4.1±0.6 years with a 95% CI of 3.0 to 5.2. According to the Mantle-Cox-test (also known as log-rank test), (P = 0.325), no significant difference between the reintervention-free survival among both groups was indicated. Postoperative reintervention-free survival both groups is displayed in Figure 5 and Table 4. The x-axis of Figure 5 is cut at three years postoperative follow up due to insufficient data caused by censoring beyond this time point. The upper curve represents the Spur-group, showing the relative number of patients remaining over time, while the lower curve corresponds to the Luminor-group. Vertical ticks indicate censoring, either due to pending follow-up or deaths, as further specified in the table. Of note, the standard error in the third postoperative year of the Luminor-group exceeds 10% and thus suggests caution when interpreting data beyond this time point. The aforementioned lack of significant differences according to the Mantle-cox test (P = 0.325), becomes evident in this graph since the curves of both groups show a rather similar development over time.

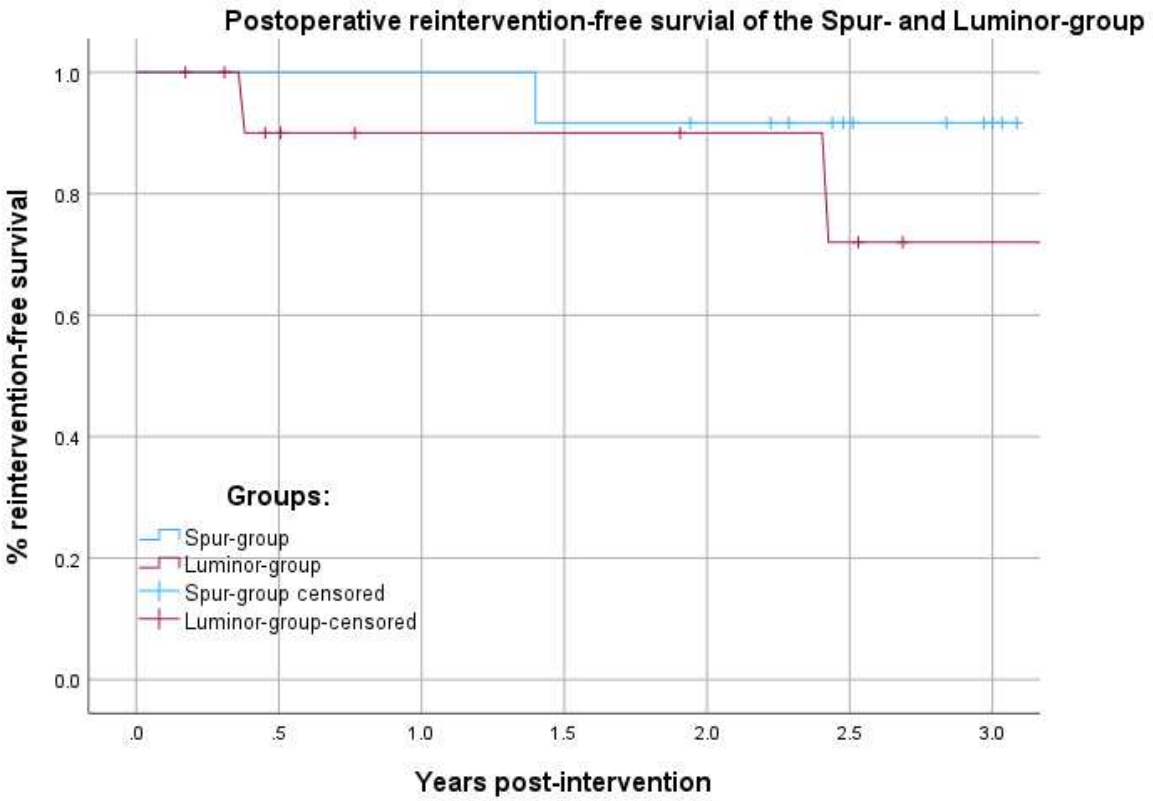

Figure 5. Kaplan-Meier survival chart. Display of reintervention-free postoperative survival for the Spur-group and Luminor-group. The upper curve represents the Spur-group, showing the relative number of patients remaining over time and the lower curve corresponds to the Luminor-group. Vertical ticks indicate censoring either due to pending follow-up or deaths, as further specified in the table 4.

Table 4. Survival table of reintervention-free postoperative survival for the Spur-group and Luminor-group. Corresponding to Figure 5, the number of patients at risk, number of events, amount and cause of censoring as well as standard error of survival are displayed up to the third postoperative year. Data in the table are presented in absolute numbers, % of Standard error and % of the group.

Table 4. Survival table of reintervention-free postoperative survival for the Spur-group and Luminor-group. Corresponding to Figure 5, the number of patients at risk, number of events, amount and cause of censoring as well as standard error of survival are displayed up to the third postoperative year. Data in the table are presented in absolute numbers, % of Standard error and % of the group.

		Start	One-year post-op	Two years post-op	Three years post-op
SPUR-Group	Number at risk (% of total patients)	12 (100.0%)	12 (100.0%)	10 (83.3%)	3 (25.0%)
	Number of reintervention-events	0	0	1	1
	Total censored cases	0	0	1	8
	Pending follow-up censoring	0	0	1	8
	Non-Event death censoring	0	0	0	0
	Standard error	0.0%	0.0%	8.0%	8.0%
LUMINOR-Group	Number at risk (% of total patients)	12 (100.0%)	6 (50.0%)	5 (41.7%)	2 (16.7%)
	Number of reintervention-events	0	1	1	2
	Total censored cases	0	5	6	8
	Pending follow-up censoring	0	5	6	7
	Non-Event death censoring	0	0	0	1
	Standard error	0.0%	9.5%	9.5%	17.8%

4.5.2. Minor amputations

16.7% (n=4) of patients in both groups had received one minor amputation pre-intervention. Furthermore, one patient (4.2%) had received two minor amputations and none had received major amputations prior to the intervention and 79.2% (n=19) had received neither. A more detailed overview of minor amputations within both groups is presented in Table 3.

In comparison, postprocedural ipsilateral minor amputations occurred in 41.7% (n=5) of patients in the Spur-group as well as 41.7% (n=5) of patients in the Luminor-group. They occurred with an average of 14.6±15.8 days from intervention to minor amputation in the Spur-group and 29.2±58.1 days in the Luminor-group. In a total 20.8% (n=5) of patients from both groups, there were two interventional minor amputations noted.

When analyzed with Kaplan-Meier analysis, the overall minor amputation-free survival was 3.1±0.5 years (95% CI from 2.2 – 4.1). Minor amputation-free survival of the Spur-group was 1.8±0.4 years (95% CI from 1.0 – 2.7) and in the Luminor-group 3.3±0.7 years (95% CI 2.0 – 4.7). According to the Mantle-Cox-test, with $P = 0.768$ there was no significant difference among both groups. Postoperative minor amputation-free survival both groups is displayed in Figure 6 and its explanatory Figure 5. The x-axis of Figure 6 is truncated at three years postoperative follow up due to insufficient data caused by censoring beyond this time point. The lower curve represents the Spur-group, showing the relative number of patients remaining over time, while the upper curve corresponds to the Luminor-group. Vertical ticks indicate censoring, either due to pending follow-up or deaths, as further specified in the table. Of note, the standard error throughout the entire time of analysis in both groups exceeds 10% and thus suggests caution when interpreting the data. The mentioned lack of significant differences according to the Mantle-cox test ($P = 0.768$), is underlined in this graph since the curves of both groups mirror each other with all minor amputations occurring shortly after the interventions and no further minor amputations but only sporadic censoring beyond this time point.

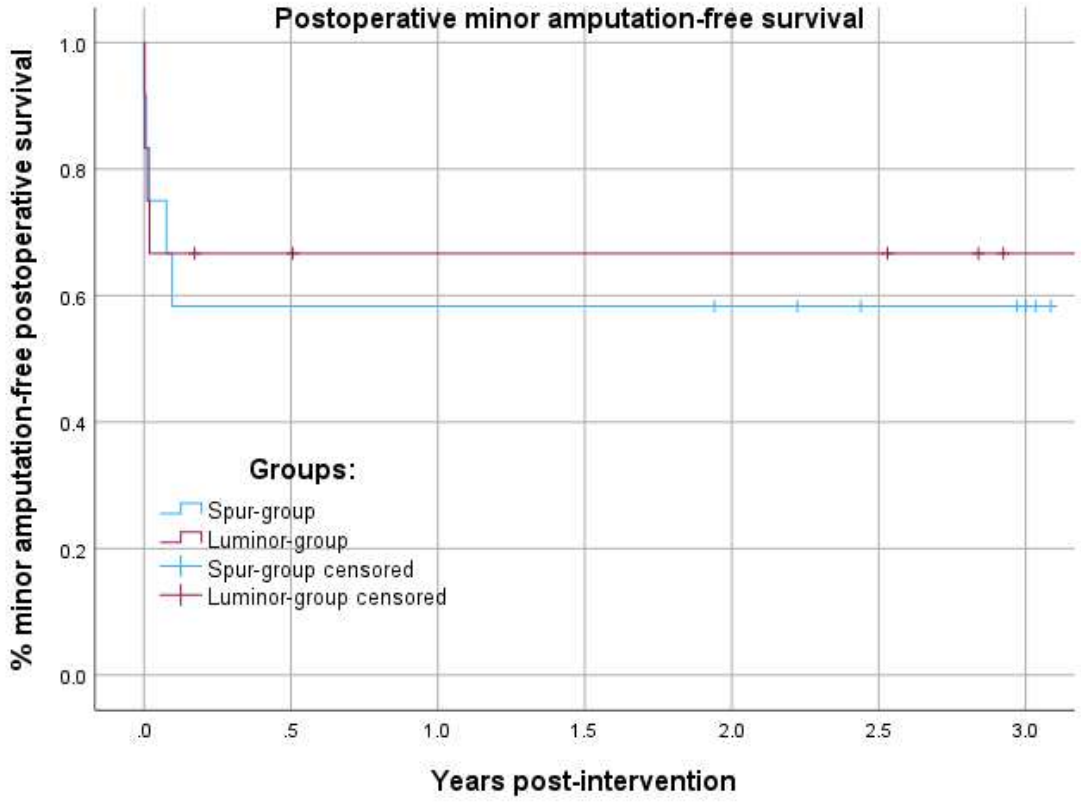

Figure 6. Kaplan-Meier survival chart. Display of minor amputation-free postoperative survival for the Spur-group and Luminor-group. The lower curve represents the Spur-group, showing the relative number of patients remaining over time and the upper curve corresponds to the Luminor-group. Vertical ticks indicate censoring either due to pending follow-up or deaths, as further specified in the table 5.

Table 5. Survival table of minor amputation-free postoperative survival for the Spur-group and Luminor-group. Corresponding to Figure 6, the number of patients at risk, number of events, amount and cause of censoring as well as standard error of survival are displayed up to the third postoperative year. Data in the table are presented in absolute numbers, % of Standard error and % of the group.

		Start	One-year post-op	Two years post-op	Three years post-op
SPUR-Group	Number at risk (% of total patients)	12 (100.0%)	7 (58.3%)	6 (50.0%)	3 (25.0%)
	Number of minor amputation-events	0	5	5	5
	Total censored cases	0	0	1	4
	Pending follow-up censoring	0	0	1	4
	Non-Event death censoring	0	0	0	0
	Standard error	0.0%	14.2%	14.2%	14.2%
LUMINOR-Group	Number at risk (% of total patients)	12 (100.0%)	6 (50.0%)	6 (50.0%)	3 (25.0%)
	Number of minor amputation-events	0	4	4	4
	Total censored cases	0	2	2	5
	Pending follow-up censoring	0	0	0	1
	Non-Event death censoring	0	2	2	4
	Standard error	0.0%	13.6%	13.6%	13.6%

4.5.3. Major amputations

Postprocedural ipsilateral major amputations were observed in two cases (8.3%) within the Luminor-group. Both occurred 15 and 357 days after target vessel intervention respectively. The major amputation on the 15th postinterventional day was indicated due to diabetic foot syndrome with fibrinous, necrotic, and wet deposits on the toes alongside extensive dry gangrene of the heel and arch of the foot without signs of infection on an edematous, reddened, and overheated foot. Ulcerations of the heel had already been documented to be present 6.5 years ago and the patient had been diagnosed with diabetes 24 years ago.

The major amputation of a lower leg on the 357th day after intervention in the second patient was indicated due to persistent rest pain in foot and calf for five days. An attempt of endovascular lysis therapy was undertaken, but did not yield the desired effect. This major amputation was later additionally revised and augmented into an amputation of the upper leg 85 days after the primary lower leg amputation due to large necrotic areas within the stump and a progressive stump infection that had reached the bone.

On the other hand, no amputations were observed in the Spur-group. A comparison of the distribution of major amputations can be found in Table 3.

Since there were no major amputations in the Spur-group, no major amputation-free survival of this group or could be calculated. Major amputation-free survival of the Luminor-group was 4.0±0.7 years with a 95% CI from 2.7 – 5.3. Postoperative major amputation-free survival both groups is displayed in Figure 7 and its explanatory Table 6. The x-axis of Figure 7 is truncated at three years postoperative follow-up due to insufficient data caused by censoring beyond this time point. The upper curve represents the Spur-group, showing the relative number of patients remaining over time, while the lower curve corresponds to the Luminor-group. Vertical ticks indicate censoring, either due to pending follow-up or deaths, as further specified in the table. It should be noted that the standard error of the Luminor-group throughout the displayed exceeds 10% and thus suggests caution when interpreting data of this group. The stark difference in amputation rates between both groups becomes evident in this graph since no major amputations are observed in the Spur-group but two major amputations occur within the first year of follow-up of the Luminor-group. However, the large standard error in the Luminor-group counsels caution of interpretation.

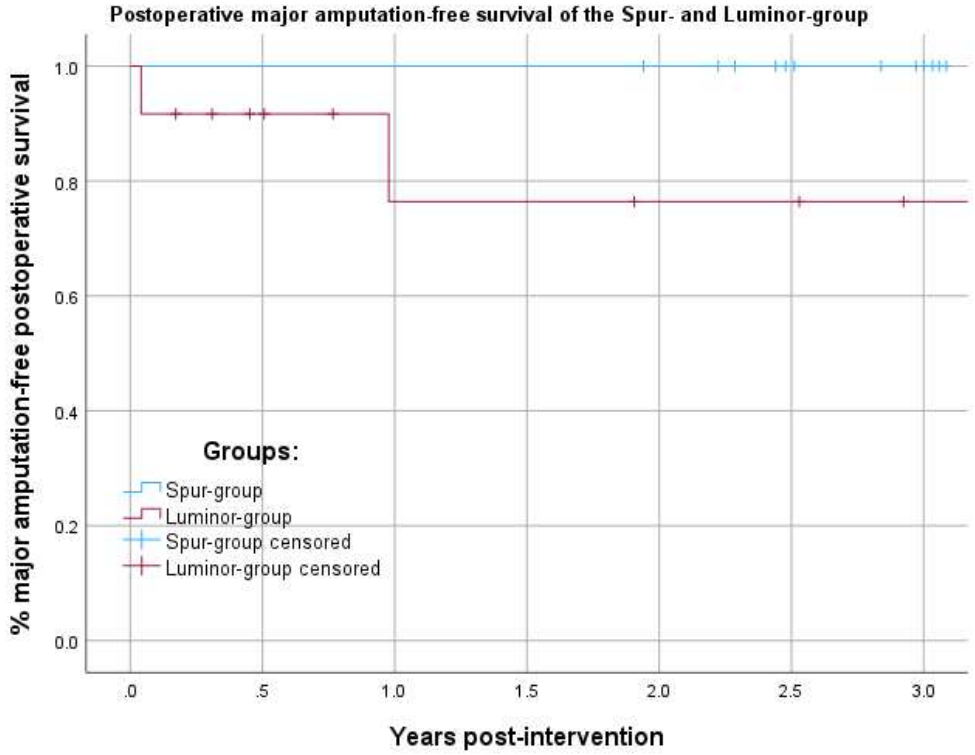

Figure 7. Kaplan-Meier survival chart. Display of major amputation-free postoperative survival for the Spur-group and Luminor-group. The upper curve represents the Spur-group, showing the relative number of patients remaining over time and the lower curve corresponds to the Luminor-group. Vertical ticks indicate censoring either due to pending follow-up or deaths, as further specified in the table 6.

Table 6. Survival table of major amputation-free postoperative survival for the Spur-group and Luminor-group. Corresponding to Figure 7, the number of patients at risk, number of events, amount and cause of censoring as well as standard error of survival are displayed up to the third postoperative year. Data in the table are presented in absolute numbers, % of Standard error and % of the group.

		Start	One-year post-op	Two years post-op	Three years post-op
SPUR-Group	Number at risk (% of total patients)	12 (100.0%)	12 (100.0%)	11 (91.7%)	4 (33.3%)
	Number of major amputation-events	0	0	0	0
	Total censored cases	0	0	1	8
	Pending follow-up censoring	0	0	1	8
	Non-Event death censoring	0	0	0	0
	Standard error	0.0%	0.0%	0.0%	0.0%
LUMINOR-Group	Number at risk (% of total patients)	12 (100.0%)	5 (41.7%)	4 (33.3%)	2 (16.7%)
	Number of major-events	0	2	2	2
	Total censored cases	0	7	8	10
	Pending follow-up censoring	0	2	2	2
	Non-Event death censoring	0	5	6	8
	Standard error	0.0%	15.5%	15.5%	15.5%

4.5.4. Major adverse limb (MALE)-events

MALE-events were observed in 4.2% (n=1) of the Spur-group 511 days after the intervention. Following the intervention in the Luminor-group, MALE-events were noted in 16.7% (n=4) on average 349.3±384.7 days after the intervention. In 1 patient of the Luminor-group, more than one MALE-event was recorded. A tabular overview of MALE-events in both groups can be seen in Table 3.

Kaplan-Meier analysis demonstrated an overall MALE-free survival of 4.0±0.4 years with a 95% of 3.2-4.8. For the Spur-group MALE-free survival was 2.9±0.1 years (95% CI from 2.7 – 3.2) as opposed to 2.9±0,8 years MALE-free survival (95% CI 1.4 – 4.4) for the Luminor-group. $P = 0.031$ of the Mantle-Cox-test showed a significant difference of MALE-free survival among both groups.

The positive statistical significance of difference according to the Mantle-cox test ($P =$

0.031) in postoperative MALE-free survival of the SPUR-Group and Luminor-group in years after the intervention is depicted in the Kaplan-Meier-curve of Figure 8 and its explanatory Figure 7. Markedly fewer reinterventions are evident in the Spur-group as opposed to four in the Luminor-group.

In Figure 8 the upper curve depicts the Spur-group and the lower curve the Luminor-group. The x-axis cut truncated at three years postoperative follow up due to insufficient data caused by censoring beyond this time point. Vertical ticks indicate censoring, either due to pending follow-up or deaths, as further specified in the table. Postoperative follow-up was cut off after three years due to insufficient data caused by censoring from there on. Of note, the Standard error of the worse-surviving Luminor-group is large with 17.4% in the first and second year and 21.2% in the third year as opposed to 0% in the first and 8.0% in the second and third year of the Spur-group. In addition to this, it may be noted that all seven censored cases of the Luminor-group were due to premature death, whereas censoring of eight cases in the Spur-group was exclusively due to their follow-up time coinciding with the present and their follow-up time thus not having been completed yet.

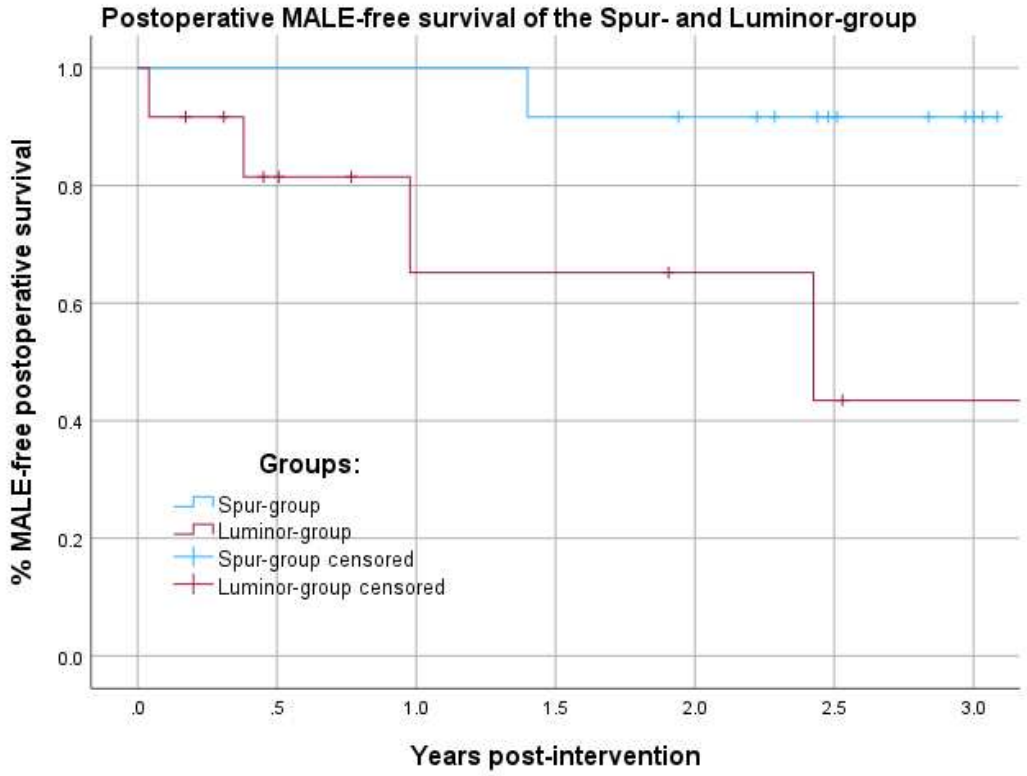

Figure 8. Kaplan-Meier survival chart. Display of major amputation-free postoperative survival for the Spur-group and Luminor-group. The upper curve represents the Spur-group, showing the relative number of patients remaining over time and the lower curve corresponds to the Luminor-group. Vertical ticks indicate censoring either due to pending follow-up or deaths, as further specified in the table 7.

Table 7. Survival table of major amputation-free postoperative survival for the Spur-group and Luminor-group. Corresponding to Figure 8, the number of patients at risk, number of events, amount and cause of censoring as well as standard error of survival are displayed up to the third postoperative year. Data in the table are presented in absolute numbers, % of Standard error and % of the group.

		Start	One-year post-op	Two years post-op	Three years post-op
SPUR-Group	Number at risk (% of total patients)	12 (100.0%)	12 (100.0%)	10 (83.3%)	3 (25.5%)
	Number of MACE-events	0	0	1	1
	Total censored cases	0	0	1	8
	Pending follow-up censoring	0	0	1	8
	Non-Event death censoring	0	0	0	0
	Standard error	0.0%	0.0%	8.0%	8.0%
LUMINOR-Group	Number at risk (% of total patients)	12 (100.0%)	4 (33.3%)	3 (25.0%)	1 (8.3%)
	Number of MACE-events	0	3	3	4
	Total censored cases	0	5	6	7
	Pending follow-up censoring	0	0	0	0
	Non-Event death censoring	0	5	6	7
	Standard error	0.0%	17.4%	17.4%	21.2%

4.5.5. Major adverse cardiovascular (MACE)-events

MACE-events were observed in 16.7%(n=2) of the Spur-group patients on average 471±227.7 days after the intervention and in 12.5%(n=3) in the Luminor-group on average 541.3±361.1 days after the intervention.

Of those, in one patient (4.2%) of the Luminor-group there was more than one MACE-event in the same patient during the follow-up-period. Average MACE-free survival as determined by Kaplan-Meier analysis was 2.8±0.2 years (95% CI 2.4 at the lower bound to 3.2 at the upper bound) and 3.3± 0.5 years (95% CI at the lower bound 2.3 to 4.2 at the upper bound) in the Spur- and Luminor-group respectively. *P* was 0.334 and can thus not be considered significant. More detailed information about the occurrence of MACE-events in both groups can be found in Table 3.

Postoperative MACE-free survival both groups is displayed in Figure 9 and its explanatory Table 8. The x-axis of Figure 9 is truncated at three years postoperative follow up due to insufficient data caused by censoring beyond this time point. The upper curve represents the Spur-group, showing the relative number of patients remaining over time, while the lower curve corresponds to the Luminor-group. Vertical ticks indicate censoring, either due to

pending follow-up or deaths, as further specified in the table. Of note, the standard error in the second and third postoperative year of the Luminor-group exceeds 10% and thus suggests caution of interpretation beyond this time point. The progression of both curves roughly corresponds with a slight superiority of the Spur-curve, mirroring the mentioned lack of significant differences according to the Mantle-cox test ($P = 0.334$).

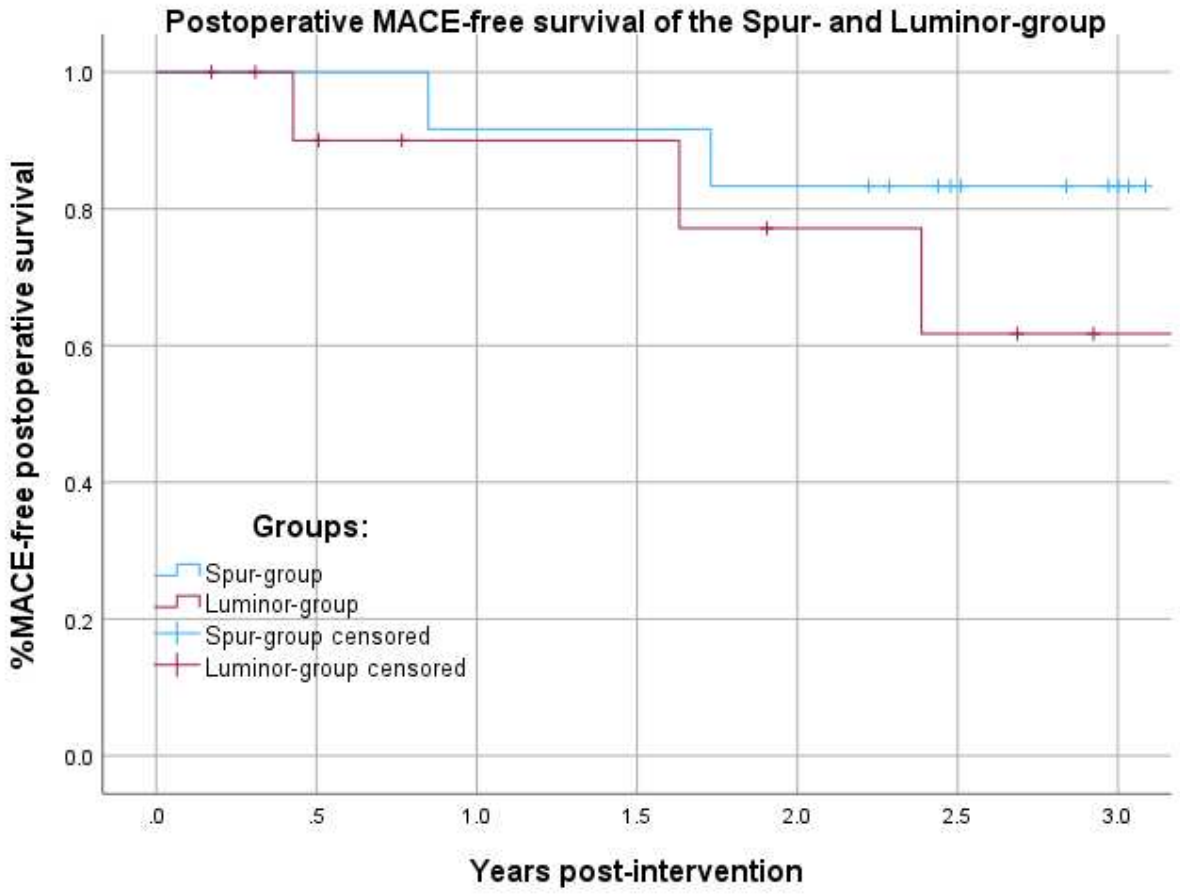

Figure 9. Kaplan-Meier survival chart. Display of MACE-free postoperative survival for the Spur-group and Luminor-group. The upper curve represents the Spur-group, showing the relative number of patients remaining over time and the lower curve corresponds to the Luminor-group. Vertical ticks indicate censoring either due to pending follow-up or deaths, as further specified in the table 8.

Table 8. Survival table of MACE-free postoperative survival for the Spur-group and Luminor-group. Corresponding to Figure 9, the number of patients at risk, number of events, amount and cause of censoring as well as standard error of survival are displayed up to the third postoperative year. Data in the table are presented in absolute numbers, % of Standard error and % of the group.

		Start	**One-year post-op**	**Two years post-op**	**Three years post-op**
Spur-Group	Number at risk (% of total patients)	12 (100.0%)	11 (91.7%)	10 (83.3%)	3 (25.0%)
	Number of MACE-events	0	1	2	2
	Total censored cases	0	0	0	7
	Pending follow-up censoring	0	0	0	7
	Non-Event death censoring	0	0	0	0
	Standard error	0.00%	8.00%	10.80%	10.80%
Luminor-Group	Number at risk (% of total patients)	12 (100.0%)	7 (58.3%)	5 (41.7%)	2 (16.7 %)
	Number of MACE-events	0	1	2	3
	Total censored cases	0	4	5	7
	Pending follow-up censoring	0	0	0	1
	Non-Event death censoring	0	4	5	6
	Standard error	0.00%	9.50%	14.40%	18.00%

4.5.6. Death

Postinterventional deaths occurred exclusively in the Luminor-group and no postoperative deaths were noted in the SPUR-Group. In the Luminor-group, a total of 8 patients died (33.3% of this group) on average 436.8±398.1 days after the intervention. If specified, the leading cause of death was evenly distributed with 25% (n=2) each among death of infectious, cardiovascular, miscellaneous nature and causes where the exact cause of death could not be specified. On average, patients died at 79.6±5.7 years of age. With $P = 0.001$, this distribution of deaths among both groups is highly statistically significant.

Postoperative occurrence of deaths within both groups is displayed in Figure 10 and its explanatory Table 9 as absolute postoperative survival. The x-axis of Figure 10 is cut at three years postoperative follow up due to insufficient data caused by censoring beyond this time point. The upper curve represents the Spur-group, showing the relative number of patients remaining over time, while the lower curve corresponds to the Luminor-group. Vertical ticks indicate censoring, due to pending follow-up where the respective time point still lies in the future. Of note, the standard error in the first, second and third postoperative year of the Luminor-group exceeds 10% and thus suggests caution when interpreting the results. The

marked absence of deaths in the Spur-group becomes evident in this graph, but the high number of censored cases in this group can also be noted, whereas only one case in the Luminor-group was censored.

To sum up, the only two significant findings in the analysis of periprocedural events and procedure circumstances were a significantly ($P = 0.001$) higher rate of death in the Luminor-group and better postoperative MALE-free survival in the Spur-group ($P = 0.031$).

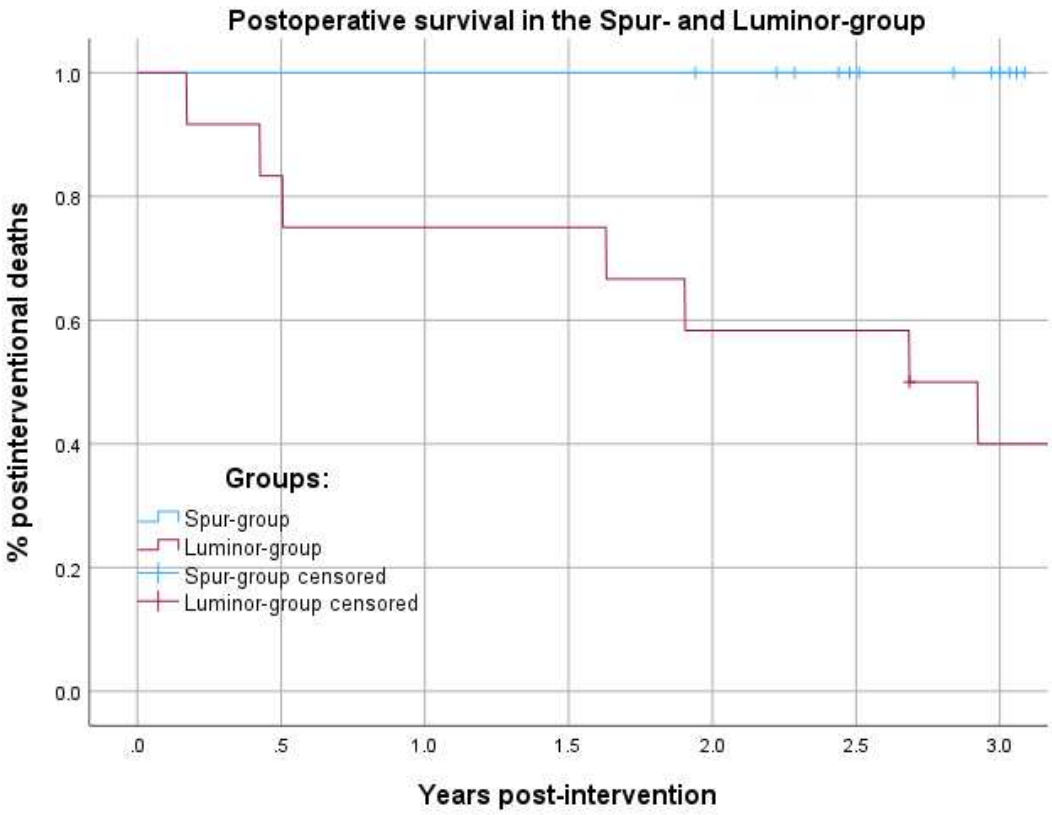

Figure 10. Kaplan-Meier survival chart. Display of postoperative survival for the Spur-group and Luminor-group. The upper curve represents the Spur-group, showing the relative number of patients remaining over time and the lower curve corresponds to the Luminor-group. Vertical ticks indicate censoring either due to pending follow-up or deaths, as further specified in the table 9.

Table 9. Survival table of postoperative survival for the Spur-group and Luminor-group. Corresponding to Figure 10, the number of patients at risk, number of events, number of censored cases as well as standard error of survival are displayed up to the third postoperative year. Data in the table are presented in absolute numbers, % of Standard error and % of the group.

		Start	**One-year post-op**	**Two years post-op**	**Three years post-op**
Spur-group	Number at risk (% of total patients)	12 (100.0%)	12 (100.0%)	11 (91.7%)	4 (33.3%)
	Number of deaths	0	0	0	0
	Total censored cases due to pending follow-up	0	0	1	8
	Standard error	0.0%	0.0%	0.0%	0.0%
Luminor-group	Number at risk (% of total patients)	12 (100.0%)	9 (75.0%)	7 (58.3%)	4 (33.3%)
	Number of deaths	0	3	5	7
	Total censored cases due to pending follow-up	0	0	0	1
	Standard error	0.0%	12.5%	14.2%	14.6%

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5. DISCUSSION

The objective of this thesis was to assess usefulness and possible risks of the Spur-stent as an additional modification before DCB placement in chronic infrapopliteal PAD and to explore possible confounders by careful analysis of patient characteristics. 12 consecutive patients that received the Spur-stent at our vascular center were propensity-matched in retrospect to similarly-sized lesions. The hypothesis was that vessel preparation with the Spur-Stent facilitated drug uptake and minimized postoperative need for reinterventions due to restenosis.

Key findings of this study were significant absence of death and major amputations alongside markedly improved MALE-free survival in the Spur-group as opposed to the Luminor-group. This partly confirmed the hypothesized minimization of postoperative need for care, since MALE-events were defined to encompass both reinterventions and major amputations. However, the direct comparison of reintervention-free survival showed no significant difference. This might be either due to the structural limitations in study design with very small groups and its retrospective nature preventing the desired effect from being shown significantly or the effect size not having been large enough to detect a significant difference. On the opposite, it can also be possible that the stark difference in incidence of major amputations between both groups skewed the significance of MALE-free survival since major amputations and reinterventions were grouped together. Larger prospective studies could aid in determining whether this lack of significance in reintervention-free survival was due to the structural limitations of the study design or the pronounced difference in major amputations distorting the significance of MALE-free survival.

The pronounced difference of death- and major amputation rates between both groups, however were an unexpected finding but have nevertheless been clearly established.
Improvement of periprocedural ABI and TBI-scores was slightly more accentuated in the Spur-groups whereas absolute arterial pressures as determined by DUS-examination demonstrated markedly higher periprocedural increases in the Luminor-group. This warrants further investigation in larger patient groups, but underlines the mildly positive tendencies for adding the Spur-stent to vascular procedures of infrapopliteal lesions. The rest of the data was inconspicuous.

In the context of existing research, the well-established reliable use of the Luminor-DCB is once again confirmed as it mirrors perioperative improvement in clinical parameters in large trials on the femoropopliteal circulation (177,178,180). However, a direct comparison with the results on infrapopliteal use of the Luminor-DCB are not yet feasible, since long-term effects of ongoing trials are not yet finally published (181,182).

The performance of the Spur-stent in our study aligns well with the promising preliminary findings of the largest clinical trial on its use in the infrapopliteal vascular bed so far, since a similarly high freedom from MALE-events at one year was observed in this trial with 98.9% of patients remaining MALE-free after the first year. However, its final long-term results with full completion of follow up are eagerly awaited (171).

Moreover, unlike previous studies on the Spur-stent, the specially matched comparison group in this thesis underlines the advantages of our observational study design (170). Thus, unlike previous studies, which were single-group and lacked any form of comparison, our study provides a more robust analysis.

Several methodological implications might be worthy of discussion here: First of all, the severely limited number of a total of 24 patients, allows for clear determination of only very marked effects and is prone to massive influence of individual outliers. Secondly, its retrospective design might have induced preselection bias of the novel Spur-stent for a clinically more favorable set of patients. Moreover, this might have limited completeness and accuracy of data during the follow-up time. It has been tried to make up for this by allowing a certain range of days as possible dates for follow-up values. However, this approach could have also diminished precision of the data. Thirdly, the lack of randomization in the consecutively composed Spur-group, might have led to inclusion of unexplored confounders. In addition to that, the regional homogeneity of patients, might limit generalizability of the findings to the general population. On the other hand, a huge structural strength of this study lies in the single-center design with the same investigators conducting the assessments. This uniformity in personnel and consistency of standards within the same hospital, has ensued a more standardized methodology and possibly minimized deviations. Furthermore, the regional homogeneity of patients might have lessened unwanted inter-regional confounders.

Should the tendencies softly proposed by this thesis be confirmed in larger and more significant studies, the Spur-stent methodology could improve the outcomes of treatment of chronic PAD, reduce overall long-term treatment costs and slow-down the progression of the disease for the individual patient. In addition to that, it could further help to clearly define therapy choice recommendations for below-the-knee lesions.

This study implies several promising suggestions for further research: Large-scale, randomized and prospective studies could help to clarify to the aforementioned ambiguities of interpretation. Special regard should be given to an optimal statistical power and effect sizes to gain more insight into the real-world significance of research findings. Moreover, partially blinded studies with blinding of patients and researchers could increase objectivity. Blinding of

the interventionalist will probably be impractical. Additionally, multicentered studies with uniform follow-up protocols and standardized examination criteria would be desirable. An additional clinical question for further research could be evaluation of the Spur-stent methodology versus other permanent drug-eluting-stents (DES).

The presented patient samples are representative for the local population of the German Thuringia as far as the semi-consecutive patient collection allows for. In comparison with similar trials on patients with chronic PAD, they are indeed comparable to the standard population of PAD-patients since similar age ranges and rate of diabetics have been reported in large recent meta-analysis studies (149,183).On the contrary, the percentage of male participants is unusually high in this study when compared to the average gender distribution in those trials, limiting representativeness of our study population in this regard.

However, generalizability to the general public might be limited due to regional variations in lifestyle, nutrition or ethnicity, which have been shown to markedly influence disease prevalence and progression (2,3,23).

To sum up, this thesis assessed usefulness and risks of Spur-stent use as an additional modification before placement of conventionally used DCB in the endovascular treatment of chronic PAD in below-the-knee lesions. An absence of death and major amputations in the Spur-group were a significant finding when compared to the Luminor-group. Furthermore, there was markedly improved MALE-free survival in the Spur-group. The hypothesized difference in reintervention-free survival between both groups could not be confirmed, but this might be due to the structural design of the study. Methodological strengths of this thesis are its single-center design with uniform investigator assessment, regional homogeneity of its patients and a non-single-group approach. It is limited by small sample size, retrospective design, lack of randomization and potential preselection bias. Larger, prospective and randomized studies with optimal statistical power are needed to confirm the findings and resolve ambiguities to refine clear therapy recommendations for below-the-knee lesions. Further research could compare the Spur-stent methodology with other permanent DES. This study suggests that the Spur-stent approach could improve treatment outcomes for chronic infrapopliteal PAD treatment and thus slow disease progression, minimizing individual and societal burden of this prevalent disease. Its promising results underline the need for continued investigation to discover the optimal endovascular therapy strategy in below-the-knee lesions and advancing healing in vascular medicine.

6. CONCLUSION

Based on the results of this study, the following conclusions can be drawn:

1. The rate of death during the follow-up period was significantly (P = 0.001) higher in the Luminor-group than in the Spur-group.
2. Postoperative MALE-free survival was significantly better in the Spur-group (P = 0.031) than in the Luminor-group.
3. There was no difference in MACE-free survival between both groups. (P= 0.334)
4. There was no difference in reintervention-free survival between both groups (P = 0.325).
5. There was no difference in minor amputation-free survival between both groups (P = 0.768).
6. No major amputations were observed in the Spur-group and the major-amputation free survival of the Luminor-group was 4.0±0.7 years (95% confidence interval: 2.7 - 5.3).
7. Periprocedural ABI-improvement occurred in both groups, but the effect was more stable at 6 months post-intervention in the Spur-group than in the Luminor-group.
8. Periprocedural TBI was initially increased in the Spur-group and reduced in the Luminor-Group.
9. Periprocedural improvement of absolute arterial pressures as determined by DUS was 2.49 times higher in the Luminor-group than in the Spur-group.
10. Both groups demonstrated a slight periprocedural improvement of arterial signal patency as determined by DUS.
11. Baseline patient, device and intervention-related characteristics were not significantly different among both groups.

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8. SUMMARY

Objectives: This study aims to determine the therapeutic efficacy and potential risks of the Spur-stent as an additional vessel preparation technique before standard DCB-use in endovascular therapy for infrapopliteal chronic PAD. The primary outcomes of minor and major amputation-free survival, reintervention-free survival, MALE-free survival, MACE-free survival, overall mortality, and assessments of postinterventional vessel patency were collected for a maximum follow-up-period of 5 years. Patient characteristics were analyzed to detect possible confounders.

Material and methods: This retrospective thesis included 24 patients with chronic PAD treated between August 2017 and March 2022 at Medinos Vascular Centre in Sonneberg, Germany. Interventions of the P3-segment of the popliteal artery and further distal arteries were included. Follow-up data was collected prior to and after the procedure and at 3, 6, 12, 24, 36, 48 and 60 months after the procedure. Data was sourced from the clinic's Orbis database system and surgical implant records. Propensity-score matching of consecutive patients treated with the Spur-stent followed by conventional DCB was conducted and matched to patients of similar lesion length and gender that received Luminor-DCB alone. Event-free survival was analyzed using Kaplan-Meier methodology.

Results: The rate of death during the follow-up period was significantly ($P = 0.001$) higher in the Luminor-group than in the Spur-group. Postoperative MALE-free survival was significantly better in the Spur-group ($P = 0.031$) than in the Luminor-group with an average of 511±0 days from intervention to MALE-events in the Spur-group and an average of 349.3±384.7 days from intervention to MALE-events in the Luminor-group. There were no significant differences in MACE-free survival ($P = 0.334$), reintervention-free survival ($P = 0.325$) and minor amputation-free survival ($P = 0.768$) between both groups. No major amputations were observed in the Spur-group, but 2 major amputations on average 186±241.8 days after the intervention were observed in the Luminor-group. Major amputation-free survival of the Luminor-group was 4.0±0.7 years.

Conclusion: Differences in reintervention-free survival could not be proven clearly, which might have been due to limitations in study design. However, major amputation-free survival and mortality was significantly better for patients treated with the adjunctive Spur-stent. There was an overall tendency of improved vessel patency parameters in the Spur-group, suggesting the effectiveness of this device. Further large, prospective, randomized, and multi-group studies comparing the Spur-stent to other endovascular treatment options are required.

9. CROATIAN SUMMARY

Naslov: Retrospektivna analiza Spur™-Stenta i balonske intervencije obložene lijekom za infrapoplitealne lezije: dugoročna prohodnost, smrtnost i preživljenje bez amputacije

Ciljevi: Ova studija ima za cilj utvrditi terapijsku učinkovitost i potencijalne rizike Spur-stenta kao dodatne tehnike pripreme žila prije standardne uporabe balona obloženog lijekom u endovaskularnoj terapiji infrapoplitealne kronične periferne arterijske bolesti. Primarni ishodi preživljenja bez manje i veće amputacije, preživljenja bez ponovne intervencije, preživljenja bez većih nepovoljnih događaja na udovima, preživljenja bez većih nepovoljnih kardiovaskularnih događaja, ukupnog mortaliteta i procjene postintervencijske prohodnosti krvnih žila prikupljeni su za maksimalno praćenje -up-period 5 godina. Analizirane su karakteristike pacijenata kako bi se otkrili mogući zbunjujući.

Materijal i metode: Ovaj retrospektivni rad uključio je 24 bolesnika s kroničnom perifernom arterijskom bolešću liječenih između kolovoza 2017. i ožujka 2022. u Medinos Vascular Ventre u Sonnebergu, Njemačka. Uključene su intervencije P3-segmenta poplitealne arterije i daljnjih distalnih arterija. Podaci o praćenju prikupljeni su prije i nakon zahvata te 3, 6, 12, 24, 36, 48 i 60 mjeseci nakon zahvata. Podaci su dobiveni iz kliničkog sustava baze podataka Orbis i zapisa o kirurškim implantatima. Provedeno je usklađivanje rezultata sklonosti uzastopnih pacijenata liječenih Spur stentom nakon čega je slijedio konvencionalni balon obložen lijekom i uparen s pacijentima slične duljine lezije i spola koji su primili samo balon obložen lijekom Luminor. Preživljenje bez događaja analizirano je pomoću Kaplan-Meierove metodologije.

Rezultati: Stopa smrtnosti tijekom razdoblja praćenja bila je značajno (P = 0,001) viša u Luminor grupi nego u Spur grupi. Postoperativno preživljenje bez većih štetnih događaja na udovima bilo je značajno bolje u Spur skupini (P = 0,031) nego u Luminor skupini s prosjekom od 511±0 dana od intervencije do velikih štetnih događaja na udovima u Spur skupini i prosječno 349,3±384,7 dana od intervencije do velikih neželjenih događaja udova u Luminor grupi. Nije bilo značajnih razlika u preživljenju bez većih nepovoljnih kardiovaskularnih događaja (P= 0,334), preživljenju bez ponovne intervencije (P = 0,325) i preživljenju bez manje amputacije (P = 0,768) između obje skupine. Nisu uočene veće amputacije u Spur-skupini, ali 2 velike amputacije u prosjeku 186±241,8 dana nakon intervencije uočene su u Luminor-skupini. Glavno preživljenje bez amputacije Luminor grupe bilo je 4,0±0,7 godina.

Zaključak: Razlike u preživljenju bez reintervencije nisu se mogle jasno dokazati, što je moglo biti posljedica ograničenja u dizajnu studije. Međutim, veće preživljenje i smrtnost bez amputacije bili su značajno bolji za pacijente liječene dodatnim Spur-stentom. Postojala je opća tendencija poboljšanja parametara prohodnosti krvnih žila u Spur grupi, što ukazuje na učinkovitost ovog uređaja. Potrebne su daljnje velike, prospektivne, randomizirane studije s

više skupina koje uspoređuju Spur-stent s drugim opcijama endovaskularnog liječenja.