Introduction

Critical limb ischemia (CLI) represents a medically frail subgroup of patients presenting with peripheral arterial disease (PAD). Arterial revascularization was shown to be among the cornerstone treatment strategies aimed at reducing rates of amputation and improving quality of life. Based on comparable clinical outcomes, endovascular revascularization was established as first line revascularization strategy and is currently favoured over surgical revascularization in most CLI patients. These comparable clinical outcomes, however, were observed despite significantly higher patency rates for bypass surgery. Based on these findings, the tide-over concept was established, hypothesizing that infrapopliteal patency was deemed necessary only for the duration of ulcer healing but not thereafter for the maintenance of skin integrity. Recent investigations, however, refute the tide-over concept: First, the clinical need for repeated target lesion revascularization (TLR) after tibial arterial angioplasty was observed to be as high as 48% within 12 months. Second, recent series showed that several clinically relevant outcome parameters such as time of wound healing, amputation, need for target lesion revascularization and death are directly associated with tibial arterial patency. Therefore, efforts to improve infrapopliteal patency have recently been intensified.

Incidence of Restenosis after Endovascular Therapy of Tibial Arteries

CLI patients frequently present with multilevel PAD including the infrapopliteal arterial segment. The infrapopliteal arterial segment has challenged clinical and interventional vascular physicians with...
Pathophysiology of Restenosis after Endovascular Therapy of Tibial Arteries

To date, the pathophysiology of infrapopliteal restenosis is not fully understood. Based on morphological similarities to coronary arteries, however, two pathophysiological mechanisms are mainly considered to be responsible for the excessive burden of tibial restenosis subsequent to angioplasty: early elastic recoil and neointimal proliferation.\(^{13}\)

While the occurrence of elastic recoil appears in an early phase, neointimal proliferation appears in the later course after balloon angioplasty. Due to mechanical irritation of the arterial wall, a process with proliferation and migration of smooth muscle cells to the intima is launched and maintained leading to neointimal proliferation.

In contrast, elastic recoil leads to lumen compromise within minutes after balloon angioplasty due to a dynamic but passive reaction of the arterial wall mediated by its elastic components. According to observations from coronary arteries, a luminal compromise \(>10\%\) due to elastic recoil is associated with an increased risk of restenosis in the latter course.\(^{14}\)

Baumann and colleagues recently investigated elastic recoil in tibial arteries.\(^{15}\) A total of 30 consecutive CLI patients undergoing tibial plain-old balloon angioplasty (POBA) were evaluated on the incidence and the severity of elastic recoil based on minimal lumen diameter (MLD) measurements as provided by quantitative angiography. Elastic recoil defined as a lumen compromise \(>10\%\) and was observed in 29/30 (97\%) patients with a mean lumen compromise of 29\%. These observations underline that elastic recoil subsequent to balloon angioplasty is frequently present in tibial arteries and may contribute to the burden of high tibial restenosis.

Clinical Impact of Restenosis after Endovascular Therapy of Tibial Arteries

Moreover, tibial patency was shown to directly impact on clinical outcomes within one observational multicenter-center\(^7\) and two randomized studies.\(^8,9\) Iida, et al. performed a multicenter trial intending to analyze the correlation of restenosis and clinical outcomes.\(^7\) The authors analyzed a consecutive series of \(n = 63\) CLI patients\(^9\) undergoing POBA of tibial stenosis/occlusions with a lumen compromise \(\geq 75\%\).\(^7\) Repeat angiography was routinely performed after 3 and 12 months to evaluate tibial restenosis which was defined as a lumen compromise of \(>50\%\). Binary restenosis was observed in 73\% and 82\% after 3 and 12 months, respectively. Based on restenosis, Iida and coworkers evaluated the duration of wound healing and found that the time required for wound healing was longer in patients with tibial restenosis: 127 days versus 66 days (\(p = 0.02\)).

In addition to the observations from Iida, et al. clinical outcomes were analyzed by Rastan, et al. and Liistro, et al. within randomized settings.\(^8,9\) Rastan and colleagues compared the clinical efficacy of DES with those of bare metal stents (BMS) for tibial PAD.\(^9,16\) Within that series, a total of \(n = 161\) patients was randomly assigned to DES (\(n = 82\)) or BMS (\(n = 79\)). After one year, restenosis (\(\geq 50\%\) by angiography) was observed in 44.4\% in the BMS and in 19.4\% in the DES group (\(p = 0.02\)).\(^9\) Amputation rates were 2.6\% versus 12.2\% (\(p = 0.03\)) and need for target vessel revascularization was 9.2\% versus 20.0\% (\(p = 0.06\)). Thus, improved clinical outcomes observed in the DES group were attributed to higher patency rates.

Liistro et al. evaluated DEB for tibial revascularization in comparison with POBA within the DEBATE-BTK trial.\(^8\) For that purpose, a total of \(n = 132\) CLI
patients were randomly assigned to receive either POBA (n = 65) or DEB (n = 67) and analyzed for binary restenosis, TLR and major amputation. Binary restenosis was defined as lumen compromise >50% by angiography and/or DUS applying a peak systolic velocity ratio (PSVR) of ≥2.5 for restenosis definition. Thereby, mean lesion length was 129 mm in patients treated with DEB versus 131 mm for POBA (p = 0.7). After 12 months of follow-up, binary restenosis was observed in 27% versus 74% (p < 0.001) comparing DES with POBA. The need for TLR was 18% versus 43% (p = 0.002), whereas amputation rates were 0% versus 2% (p = 0.9), respectively. Based on these favourable clinical outcomes in line with a reduction of tibial restenosis, intentions to improve tibial patency have been intensified.

Concepts of Improvement of Restenosis Rates after Endovascular Therapy of Tibial Arteries

Based on the pathophysiological mechanism of elastic recoil, the concept of mechanical scaffolding as provided by stents was evaluated for tibial restenosis. However, the application of BMS for tibial revascularization showed no benefit when compared with balloon angioplasty within several studies. Based on the first prospective and randomized comparison of self-expandable Nitinol stent placement versus POBA were published. No difference were observed with respect to upward shift on Rutherford scale, mortality, amputation and technical success after 12 months comparing BMS (n = 45 patients) versus POBA (n = 47 patients) for tibial angioplasty. Thereby, the EXPAND study underlined the hypothesis that neointimal proliferation outweighs the potential benefit of mechanical scaffolding of BMS in tibial arteries.

To address and minimize neointimal proliferation while providing mechanical scaffolding in tibial arteries, the concept of DES was established. To date, a total of 5 randomized trials have been performed, comparing either DES with BMS or DES with POBA (Table 1). Throughout all trials, DES was superior when compared to its counterparts with respect to arterial patency. Of note, the use of DES was shown to be associated with improved clinical outcomes when compared to the use of BMS in one randomized study.

Of note, however, mean lesion length within all of the DES randomized trials was ≤31 mm, which is substantially shorter than most tibial lesions encountered in daily routine. Within a consecutive series of 105 CLI patients, mean tibial lesion length in everyday clinical practice was shown to be 87 mm in stenotic and 124 mm in occlusive tibial lesions. Accordingly, only a minor proportion (11%) of that study population was represented by the above-mentioned randomized DES trials with regards to lesion morphology. Thus, patients included in these randomized trials represent only a neglectable fraction of the spectrum of CLI patients treated in daily routine.

In contrast to stent technology, DEB were introduced promoting the concept to leave nothing behind and to better address tibial lesion morphology. To date, however, data on DEB for tibial revascularization are sparse. Current information on DEB technology for tibial revascularization are based on one series by Schmidt et al. comparing DEB with an historical comparison of POBA from a comparable study setting and one single-center randomization (DEB versus POBA) performed by Liistro and colleagues. Schmidt, et al. were the first to publish first-experience data using DEB for tibial revascularization within a non-randomized single center trial. A total of n = 104 patients (n = 109 limbs) with a mean tibial lesion length of 176 mm were analyzed undergoing tibial revascularization using DEB. After 3 months, restenosis defined as lumen compromise >50% on repeat angiography was 27.4%. In comparison to the results from an earlier study at the same center using POBA for tibial revascularization, DEB was shown to reduce tibial restenosis in >60% (27.4% versus 68.8%) .

The first prospective and randomized comparison of DEB versus POBA for tibial revascularization was performed by Liistro, et al. within the aforementioned DEBATE-BTK trial. Thereby, a significant reduction in binary restenosis was observed after 12 months 27% versus 74% when comparing DES (n = 67) and POBA (n = 65). Serial angiography was applied in >90% of patients and defined as a lumen compromise >50% for the evaluation of restenosis. Of note, however, repeat angiographies were not evaluated by an independent core-lab but by blinded investigators. The remaining patients were evaluated for tibial restenosis using duplex sonography. In addition, a reduction of tibial TLR rates for DEB when
Table 1  Randomized trials on DES vs. BMS and DES vs. POBA for infrapopliteal revascularization

<table>
<thead>
<tr>
<th>Name of Study</th>
<th>Number of Patients</th>
<th>Indication for PTA</th>
<th>DES</th>
<th>BMS</th>
<th>Mean LL</th>
<th>Evaluation of Patency</th>
<th>Follow-up</th>
<th>Patients at follow-up</th>
<th>Patency</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falkowski 23)</td>
<td>50</td>
<td>RC 3: n = 34</td>
<td>Sirolimus (Cypher) stent: n = 25</td>
<td>Sonic stent: n = 25</td>
<td>17.8 mm angiography</td>
<td>6 months</td>
<td>n = 50</td>
<td>DES: 84.0%</td>
<td>BMS: 24.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Below 24)</td>
<td>30</td>
<td>RC 5: n.i.</td>
<td>Sirolimus (Cypher) stent: n = 14</td>
<td>BX-velocity stent: n = 16</td>
<td>31.3 mm angiography</td>
<td>2/6 months</td>
<td>n = 22 (2 months)</td>
<td>DES: 91.0%/91.0%</td>
<td>BMS: 54.5%/33.0%</td>
<td>n.i.</td>
</tr>
<tr>
<td>Yukon 16)</td>
<td>161</td>
<td>RC 2: n = 10</td>
<td>Sirolimus (Yukon): n = 82</td>
<td>Placebo-coated: n = 79</td>
<td>31 mm</td>
<td>primarily by duplexsonography if not appropriate with angiography</td>
<td>12 months</td>
<td>n = 125</td>
<td>DES: 80.6%</td>
<td>BMS: 55.6%</td>
</tr>
<tr>
<td>Destiny 22)</td>
<td>140</td>
<td>RC 4: n = 63</td>
<td>Everolimus stent: n = 74</td>
<td>Multi-link Vision stent: n = 66</td>
<td>17.4 mm angiography</td>
<td>12 months</td>
<td>n.i.</td>
<td>DES: 85.0%</td>
<td>BMS: 54.0%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Achilles 21)</td>
<td>200</td>
<td>RC 3–5 (mean 4.1)</td>
<td>Sirolimus (Cypher): n = 99</td>
<td>POBA: n = 101</td>
<td>27 mm angiography</td>
<td>12 months</td>
<td>n = 154</td>
<td>DES: 77.6%</td>
<td>POBA: 58.1%</td>
<td>0.019</td>
</tr>
</tbody>
</table>

RC: Rutherford category; n: number; DES: drug-eluting stent; BMS: bare metal stent; PTA: percutaneous angioplasty; POBA: plain-old balloon angioplasty; n.i.: no information

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The Value of Tibial Patency in CLI

Complex tibial arterial obstructions are warranted. Anti-restenosis technologies for CLI patients with tibial artery intervention have shown promising results. DEB with POBA in patients undergoing tibial arterial revascularization has shown improved clinical outcomes when compared with POBA. This observation is most probably based on the high incidence of neointimal proliferation mediated by persisting mechanical irritation of the arterial vessel wall provided by the stent. In contrast, DES technology was shown to reduce tibial restenosis when compared to BMS and POBA. Accordingly, the application of DES for infrapopliteal angioplasty was observed to improve clinical outcomes, which itself was shown to be associated with higher patency rates. However, a widespread application of currently available DES is currently limited by arterial lesion morphology.

Recently, the first randomized study comparing DEB with POBA in patients undergoing tibial arterial revascularization has shown promising results. Further studies aimed at determining appropriate anti-restenosis technologies for CLI patients with complex tibial arterial obstructions are warranted.

Conclusions

Tibial restenosis remains the major problem after endovascular revascularization despite the introduction of dedicated technical developments. In contrast to earlier observations, tibial patency does impact on mid- and long-term clinical outcomes in CLI patients. Accordingly, intentions to reduce tibial restenosis have been intensified and warrant further scrutiny.

The introduction of BMS for tibial revascularization showed no benefit with respect to patency and clinical outcomes when compared with POBA. This observation is most probably based on the high incidence of neointimal proliferation mediated by persisting mechanical irritation of the arterial vessel wall provided by the stent. In contrast, DES technology was shown to reduce tibial restenosis when compared to BMS and POBA. Accordingly, the application of DES for infrapopliteal angioplasty was observed to improve clinical outcomes, which itself was shown to be associated with higher patency rates. However, a widespread application of currently available DES is currently limited by arterial lesion morphology.

Recently, the first randomized study comparing DEB with POBA in patients undergoing tibial arterial revascularization has shown promising results. Further studies aimed at determining appropriate anti-restenosis technologies for CLI patients with complex tibial arterial obstructions are warranted.

Disclosure Statement

There is no conflict of interest.

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