PACLITAXEL-ELUTING DEVICES IN PERIPHERAL VASCULAR INTERVENTIONS
To Julia, Elmer, and Linus. With gratitude and love.
PACLITAXEL-ELUTING DEVICES IN PERIPHERAL VASCULAR INTERVENTIONS

PATRICK BJÖRKMAN

ACADEMIC DISSERTATION

To be presented, with permission from the Faculty of Medicine at the University of Helsinki, for public examination in the Auditorium at Folkhälsan, Topeliusgatan 12, on November 2nd 2018 at 12 noon.

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<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABI</td>
<td>Ankle-brachial index</td>
</tr>
<tr>
<td>ACT</td>
<td>Activated clotting time</td>
</tr>
<tr>
<td>AVF</td>
<td>Arteriovenous fistula</td>
</tr>
<tr>
<td>AVG</td>
<td>Arteriovenous graft</td>
</tr>
<tr>
<td>BA</td>
<td>Balloon angioplasty</td>
</tr>
<tr>
<td>BMS</td>
<td>Bare metal stent</td>
</tr>
<tr>
<td>BSX</td>
<td>Bypass surgery</td>
</tr>
<tr>
<td>cGMP</td>
<td>Cyclic guanosine monophosphate</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CLI</td>
<td>Critical limb ischemia</td>
</tr>
<tr>
<td>CLTI</td>
<td>Chronic limb threatening ischemia</td>
</tr>
<tr>
<td>CTA</td>
<td>Computed tomography angiography</td>
</tr>
<tr>
<td>DA</td>
<td>Directional atherectomy</td>
</tr>
<tr>
<td>DAPT</td>
<td>Dual antiplatelet therapy</td>
</tr>
<tr>
<td>DCB</td>
<td>Drug-coated balloon</td>
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<tr>
<td>DES</td>
<td>Drug-eluting stent</td>
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<tr>
<td>ESRD</td>
<td>End-stage renal disease</td>
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<tr>
<td>FDA</td>
<td>Food and drug administration</td>
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<tr>
<td>GSV</td>
<td>Great saphenous vein</td>
</tr>
<tr>
<td>HUH</td>
<td>Helsinki University Hospital</td>
</tr>
<tr>
<td>IC</td>
<td>Intermittent claudication</td>
</tr>
<tr>
<td>IH</td>
<td>Intimal hyperplasia</td>
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<tr>
<td>ISR</td>
<td>In-stent restenosis</td>
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<tr>
<td>LEAD</td>
<td>Lower extremity artery disease</td>
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<tr>
<td>MRA</td>
<td>Magnetic resonance arteriography</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Services</td>
</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>PAD</td>
<td>Peripheral artery disease</td>
</tr>
<tr>
<td>POBA</td>
<td>Plain old balloon angioplasty</td>
</tr>
<tr>
<td>PTA</td>
<td>Percutaneous transluminal angioplasty</td>
</tr>
<tr>
<td>PTFE</td>
<td>Polytetrafluoroethylene</td>
</tr>
<tr>
<td>PSVR</td>
<td>Peak Systolic Velocity Ratio</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
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<tr>
<td>SFA</td>
<td>Superficial femoral artery</td>
</tr>
<tr>
<td>SSGSV</td>
<td>Single-segment great saphenous vein</td>
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<tr>
<td>TASC</td>
<td>Transatlantic intersociety consensus</td>
</tr>
<tr>
<td>TLR</td>
<td>Target lesion revascularization</td>
</tr>
<tr>
<td>vEGF</td>
<td>Vascular endothelial growth factor</td>
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<tr>
<td>VGD</td>
<td>Vein graft disease</td>
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4. ABSTRACT

**Background:** Paclitaxel is a cytostatic and cytotoxic agent that is widely used for oncologic treatment of various tumors. Its cytostatic effects through tubulin binding have also showed promising results in combating vascular stenosis. It is delivered to the site via drug-coated balloons (DCB) or drug-eluting stents (DES).

Peripheral artery occlusive disease (PAD) affects approximately 200,000,000 people worldwide. Therapeutic options for occluded or stenosed arteries include open surgical bypass and endovascular treatment and balloon angioplasty with or without stents. Both therapies induce intimal hyperplasia as a biological response: as part of the arterialization of the graft in the first, and as an intimal injury healing process in the latter. Restenosis due to intimal hyperplasia is a common problem in both groups.

Dialysis through an arteriovenous fistula (AVF) is the standard of care in patients with chronic kidney disease (CKD). The fistula is created by anastomosing a vein to an artery, typically in the forearm, thus exposing the vein to arterial pressure and flow. The biological response in the venous wall is complex, and is further aggravated by the commonly numerous comorbidities of dialysis patients. Intimal hyperplasia in the venous segment of the fistula is a frequent cause for stenosis and AVF failure.

**Aims of the thesis:** The aim of this thesis was to investigate the potential benefit of paclitaxel for prevention of restenosis and maintaining conduit patency in bypass vein grafts and arteriovenous fistulae, and furthermore to compare patency of leg revascularization with paclitaxel eluting stents and open bypass surgery.

**Materials and methods:** The thesis consists of four parts. First, 93 consecutive cases of DCB treated restenoses in native arteries, vein grafts, and AVFs were retrospectively analyzed for potential improvement in the TLR-time after DCB compared with the time from the previous angioplasty to the DCB. Second, the effect of DCB for vein graft stenosis was analyzed in a prospective single-center randomized controlled trial (RCT). 60 patients were randomized. Follow-up was 1 year. Primary and secondary endpoints were TLR-free survival and graft patency. Third, the effect of DCB on AVF stenosis was investigated in a prospective single-center RCT. 39 patients were randomized, and follow-up was 1 year. Primary endpoint was freedom from TLR. Fourth, DES
and open prosthetic femoropopliteal above-knee bypass surgery were compared in a prospective, multi-center RCT. 46 patients were randomized and followed for 2 years. Primary endpoint was stent/conduit patency and secondary endpoint was clinical status (Rutherford classification, ankle-brachial index)

**Results:** In the first study, the overall time from DCB to endpoint was 572 days, compared to 240 days from previous BA to DCB (p<0.01). The difference was clear in all three clinical groups although the benefit disappeared over time in the AVF group.

In the second study, 57 patients were ultimately analyzed. In this prospective trial, no statistically significant benefit could be demonstrated from DCB during 1-year follow-up although there was a non-significant trend toward better secondary patency in the DCB group (p=0.08). In a subgroup analysis, *de novo* lesions seemed to benefit from DCB (p=0.03).

In the third trial, 36 patients were eventually analyzed. TLR-free survival was clearly worse in the DCB group. In the BA group 22.2% reached an endpoint during 1 year, compared to 88.9% in the DCB group (RR 7.09 for DCB, p<0.01).

In the fourth trial, drug-eluting stents and prosthetic above-knee bypass grafts showed remarkably similar patency rates up to two years of follow-up. 12-month secondary patency in the DES and BSX groups was 74 % compared to 80 % (P= .750). There were no statistically significant differences in primary patency, assisted primary patency, secondary patency, or clinical findings at any point of follow-up.

**Conclusions:** DCBs show safety and potential benefit in the treatment of vein graft stenosis, although the study was underpowered to demonstrate this. Especially for young (recently created) AVFs there might be potential harm from use of DCB; the mechanism of this remains unclear but paclitaxel might damage the thin venous wall more profoundly than other sites. When compared to prosthetic above-knee surgery, endovascular recanalization and DES show similar outcomes in both graft patency and clinical measures.
5. INTRODUCTION

It has been estimated that PAD affects roughly 200 million people worldwide (Fowkes, 2013). Due to ageing populations, the prevalence of PAD is increasing, with a majority of the patients living in low-income regions of the world. Restoring blood flow and perfusion to body parts distal from an arterial occlusion is known as revascularization. The open surgical bypass has for decades been the gold standard of arterial revascularization. In this operation, the occlusion is bypassed with a prosthetic or venous conduit. Ideally, a single-segment great saphenous vein is used. In complex cases, the conduits can be created from arm veins or spliced from multiple shorter segments. However, in the past 20 years, minimally invasive endovascular revascularizations have revolutionized the field of vascular surgery. With this technique, the occlusions are crossed with guide wires and treated with balloons and stents inside the artery from a percutaneous puncture typically to the groin. The field of endovascular surgery is highly technical, with a myriad of different devices that have been developed and experimented with. These include balloons, pressure balloons, balloons with different coatings, metal stents, drug-eluting stents, resorbable stents (scaffolds), atherectomy catheters, laser catheters, etc. In spite of this, there is no clear scientific consensus on whether endovascular surgery really is better for the patient in terms of long-term outcomes and procedure patency (Bradbury et al, 2010). Large randomized trials are only now being run to determine this (Menard et al, 2016; Popplewell, et al, 2016). The problematic establishment of clinical equipoise between the options complicates these trials.

Chronic kidney disease (CKD) is a major burden on health care systems worldwide. The global prevalence of CKD stage III or above has been estimated at 11-13 % (Hill et al, 2016). CKD is an independent risk factor for other cardiovascular disease as well as overall quality of life. End-stage CKD is managed by dialysis. In hemodialysis, the patient’s blood is circulated externally through mechanical and chemical filtering to compensate for the renal dysfunction. Hemodialysis requires access to the vascular system through regular punctures. To facilitate this, arteriovenous fistulae (AVF) are constructed. In a native AVF, a vein is anastomosed with a nearby artery. Typically these are the cephalic vein and radial artery in the forearm, but many variations of this occur. After such a reconstruction, the vein is exposed to near-arterial blood pressure and blood flow. As a biological response, the vein thickens and enlarges, thus generating high flow for dialysis as well as an increased tolerance to the frequent punctures. The same end-result can also be achieved by
means of an arteriovenous graft (AVG), in which a prosthetic graft is sewn between an artery and a vein. In this method, the graft itself is often the site of puncture.

The innermost layer of blood vessels is known as the intimal endothelium. Common to venous bypasses and AVFs is that this endothelium is injured, often as an inevitable consequence of the surgery, but also as the pressure and flow environments change from venous to arterial. As response-to-injury, the intimal layer thickens and remolds. This remodeling can in turn cause a new narrowing, or stenosis. This is known as intimal hyperplasia. The same phenomenon is seen in arterial stenoses or occlusions after endovascular treatment: the intimal endothelium is injured and hyperplasia can occur. The hyperplasia can grow inside deployed stents from its edges, this is known as in-stent restenosis.

To combat intimal hyperplasia, drug-covered balloons and drug-eluting stents have been developed. The general theory is that a cytostatic drug that is delivered locally to the site of injury might prevent subsequent hyperplasia and restenosis. Drug-eluting treatment has been well studied and proved effective in coronary artery disease (Picard et al, 2017) and to some extent in femoropopliteal disease (Micari et al, 2017), but conclusive evidence of its worth in peripheral disease is still lacking. This is especially true for bypass vein grafts and AVFs.

The purpose of this thesis was to investigate drug-eluting devices in peripheral vascular surgery with emphasis on vein grafts and arteriovenous fistulae. In addition, open femoropopliteal revascularization with synthetic conduits is compared to endovascular treatment with a drug-eluting stent.
6. REVIEW OF THE LITERATURE

6.1. Peripheral Artery Disease

6.1.1. Definition

άθήρα (athera): greek ‘gruel’

σκλήρωσις (sklerosis): greek ‘hardening’

The definition of peripheral artery disease (PAD) is stated as atherosclerotic disease in vessels other than those supplying blood flow to the brain or heart. Peripheral arterial diseases include lower extremity arterial disease (LEAD), upper extremity arterial disease, carotid artery disease as well as mesenteric and renal artery disease. LEAD is the most common manifestation of PAD. PAD is underdiagnosed and affects at least 200,000,000 people globally (Fowkes et al, 2016).

Atherosclerosis and signs of peripheral artery disease are seen already in ancient Egyptian mummies (Thompson et al, 2014; Clarke et al, 2014) and the Greek emperor Claudius (10 B.C. – 54 A.D.) was affected with “a limp” and has given rise to the term “claudication” (from the Latin claudicare, to limp).

PAD is often not necessarily symptomatic. Clinically manifest PAD is by far most common in the infraaortic arteries. The biological and molecular processes of PAD and underlying atherosclerotic disease are complex and not yet fully understood. Intimal calcification is thought to be secondary to the formation of atherosclerotic plaques in the vessel wall. Monocytes penetrate into the degenerated intimal endothelium and then accumulate fats as macrophages to form the plaque. Intimal calcification is also associated with the proliferation of vascular smooth muscle cells. Medial calcification (arteriosclerosis) occurs independently of atherosclerosis and is associated with aging, diabetes mellitus and chronic kidney disease (Ho and Shanahan, 2016).

PAD often co-exists with other manifestations of atherosclerotic disease. It has been estimated that 60-70% of patients with LEAD also have cerebrovascular and/or coronary artery disease (Norgren et al, 2007). Implicitly this means that the population suffering from PAD is relatively old and multimorbid, which in itself is a risk factor. Table 1 shows the Trans-Atlantic Intersociety Consensus (TASC) II classification of infrainguinal PAD.
### TASC II Category and Imaging Findings

<table>
<thead>
<tr>
<th>TASC II Category</th>
<th>Imaging Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Single stenosis &lt;10 cm</td>
</tr>
<tr>
<td></td>
<td>Single occlusion &lt; 5 cm</td>
</tr>
<tr>
<td>B</td>
<td>Single occlusion &lt;5 cm or heavy calcification with multiple &lt;5 cm occlusions or single &lt;15 cm occlusion</td>
</tr>
<tr>
<td></td>
<td>Multiple lesions (stenoses or occlusions) each &lt; 5 cm</td>
</tr>
<tr>
<td></td>
<td>Single lesion &lt;10 cm, excluding infrageniculate popliteal artery</td>
</tr>
<tr>
<td></td>
<td>Single or multiple lesions in the absence of continuous crural outflow</td>
</tr>
<tr>
<td></td>
<td>Single popliteal lesion</td>
</tr>
<tr>
<td>C</td>
<td>Multiple or single lesion &gt;15 cm</td>
</tr>
<tr>
<td></td>
<td>Recurrent lesions (after 2 endovascular treatments)</td>
</tr>
<tr>
<td>D</td>
<td>Chronic total occlusion of CFA or SFA &gt;20 cm</td>
</tr>
<tr>
<td></td>
<td>Chronic total occlusion of the trifurcation</td>
</tr>
</tbody>
</table>

**Table 1. TASC II classification of femoropopliteal PAD**

#### 6.1.2. Clinical manifestations of LEAD

The clinical manifestations of LEAD and subsequent reduction in oxygen supply to the lower limb classically range from intermittent claudication (IC) to ischemic rest pain and ischemic wounds and/or tissue loss. Ischemic rest pain and tissue lesions are classified as chronic limb threatening ischemia (CLTI). The progression of symptoms is not linear by definition, and CLTI may be the first sign of LEAD (Mätzke and Lepäntalo, 2001). The severity of LEAD is graded using the Fontaine and Rutherford classifications (table 2.) (Fontaine, 1954; Rutherford et al, 1986 (revision 1997)). The prognosis of CLTI is significantly worse than for IC or asymptomatic LEAD, although disease progression can be unpredictable. In a Finnish prospective study, 100 patients with CLTI were treated with angioplasty and compared with an age and sex matched control group. There was a significantly better 1-year survival in the control group (Jämsen et al, 2002). 10-year mortality for patients with gangrene approaches 95% (Dormandy et al, 1999).
<table>
<thead>
<tr>
<th>Fontaine</th>
<th>Rutherford</th>
</tr>
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<tbody>
<tr>
<td>Stage</td>
<td>Category</td>
</tr>
<tr>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td>IIa</td>
<td>1</td>
</tr>
<tr>
<td>IIb</td>
<td>2 &amp; 3</td>
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<tr>
<td>III</td>
<td>4</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
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<td>6</td>
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</table>

Table 2. Fontaine and Rutherford classifications of peripheral artery disease. Critical ischemia is indicated with *italics*.

6.1.3. Revascularizations

Surgical bypass has for many years been considered the gold standard of lower-limb revascularization, and single-segment vein graft bypass remains the standard-of-care. The range of endovascular techniques and approaches has increased exponentially in the last 10-15 years, resulting in a subsequent decrease in the number of performed open bypasses. Both approaches are plagued by distinct and well-established mid- and long-term complications such as restenosis and graft occlusion.

Bypass Surgery

Mathieu Jaboulay described the first vascular anastomosis in 1896; it was made between two canine arteries by circular eversion suture (Bouchet, 2010). Nobel Prize winner Alexis Carrel together with Charles Guthrie further developed vascular anastomosis techniques in the early 20th century. This work included the first venous segments placed as interposition grafts in arterial circulation. Jean Kunlin in Strasbourg performed the first bypass operation for obstructive disease in 1948 (Testart, 1995). This was a femoropopliteal bypass to treat an occlusion of the superficial femoral artery (SFA). Today, the gold standard for bypass surgery is considered to be autologous vein grafting preferably with a single-segment great saphenous vein. This has demonstrated very
high patency rates in many trials (Arvela et al, 2012; Saarinen et al, 2016). Alternatively, bypasses are performed with autologous graft material from the short saphenous vein, arm veins, or prosthetic conduits. A fresh Cochrane review of nineteen randomized controlled trials for graft material in femoropopliteal bypass surgery shows moderate-quality evidence for autologous vein conduits in terms of long-term patency (Ambler and Twine, 2018). For CLTI, revascularization with autologous vein is superior to any other approach with regard to wound healing and limb salvage; this is true especially for crural and pedal bypasses, where the patency of prosthetic bypass is extremely poor (Arvela et al, 2010).

Currently, open femoropopliteal bypass surgery remains a first-hand option in many centers worldwide. The of prosthetic conduits for above-knee bypasses remains popular due to many surgeons’ preference to save the saphenous vein for possible future below-knee or distal bypasses, and due to much shorter operations.

**Endovascular Revascularization**

“The angiographic catheter can be more than a tool for passive means for diagnostic observation; used with imagination, it can become an important surgical instrument” – Charles T. Dotter, 1963

Angiography was first described by the Portuguese neurologist and Nobel Prize winner Egas Monis in 1927. The first angiograms were used for cerebral diagnostics, and early procedures required the needle to stay inside the vessel lumen until completion. The procedure was improved by the introduction of the Seldinger technique in 1953. This made access safer by allowing the needle to be exchanged for a blunt sheath over a dedicated guide wire (Seldinger, 1953). The field of peripheral endovascular procedures was pioneered by American radiologist and inventor Charles Dotter, who first described the transluminal angioplasty (Dotter et al, 1964). Dotter had also previously in 1950 invented and developed an automatic x-ray magazine. This new magazine made acquiring images every 2 seconds possible (0.5 frames per second in today’s terms) (Payne, 2001). Together with William Cook, Dotter developed a number of catheters, including the first dilatation catheters, and other equipment to further develop endovascular possibilities. Prototype metal stents were developed in the 1960’s. The balloon expandable stent technology was introduced in 1985 (Palmaz et al, 1985). The endovascular approach leaped forward in the 1980’s and 1990’s alongside the development of non-invasive vessels imaging, such as ultrasound, magnetic
resonance imaging and computer-assisted tomography. These allowed for better planning of procedures, and really began to make this approach a rival to traditional open surgery.

Direct prospective comparisons between open and endovascular surgery are scarce. At 4 years, McQuade saw similar outcomes between polytetrafluoroethylene (PTFE) bypass grafts and nitinol stents in occlusive SFA disease (McQuade et al, 2010). Linnakoski demonstrated similar results in a retrospective analysis of 131 patients who had undergone synthetic bypass or endovascular revascularization and stenting (Linnakoski et al, 2013). For femoropopliteal lesions, covered stent grafts have been studied, and considered to be safe and even superior options to bare nitinol stents (Zeller et al, 2014; Bosiers et al, 2015). The CRITISCH-registry demonstrated non-inferiority of the so-called “endovascular first”-approach, given that the treating physician is free to customize the treatment using current endovascular technology (Bisdas et al, 2016). The Scandinavian THRUPASS –study reported clearly worse outcomes for TASC B/C lesions of the SFA after Viabahn stent graft compared to PTFE bypass, and recommended bypass surgery over stent grafts (Lepäntalo et al, 2009).

6.1.4. The arteriovenous fistula

The worldwide prevalence of chronic kidney disease is estimated at 11-13%, and increasing (Hill et al, 2016). This is largely due to the increase in the prevalence of diabetes mellitus and subsequent diabetic kidney disease (Glassrock et al, 2017). Diabetic kidney disease accounts for roughly half of end-stage renal disease prevalence. ESRD requires artificial removal of waste products and water from the blood. The means of accomplishing this include hemodialysis, peritoneal dialysis, and renal transplantation. Hemodialysis, where the patient’s blood is circulated through a semi-permeable membrane for filtration, is the most common method. According to the Finnish Kidney Registry, the prevalence of dialysis in Finland in 2016 was 886 per million, with an incidence of new dialysis patients of 102 per million in the same year. This is relatively low by European and Scandinavian standards; in Sweden the corresponding numbers are 25% higher.

Hemodialysis requires continuously repeated access to the vascular circuit, usually with two dialysis needles. For more than half a century, in end-stage renal disease, the arteriovenous fistula (AVF) has been the preferred choice of vascular access for dialysis. This is due to lower infection
rates and better patency compared to percutaneous and tunneled access devices (Woo et al, 2009). Typically, the AVF is constructed by anastomosing the cephalic vein and radial artery in the forearm (Cimino-fistula) but other fistulae are also used depending on the anatomy and possible earlier AVFs of the patient. The aim of an AVF is to increase the blood flow in a superficial vein in order to make the vein grow in size while simultaneously making the flow rates sufficiently high for successful dialysis. AVFs are not maintenance-free, and most problems with AVFs are associated with slow maturation rates of the fistulas. In one study up to 50% of predialysis patients with AVFs still have to initiate dialysis through a central catheter (Lee et al, 2015). Primary failure of an AVF is defined as failure to mature to support 2 dialysis catheters within 3 months after the first cannulation. Intimal hyperplasia has in the literature been regarded as the primary cause of primary failure. Other causes of primary failure include technical error and arterial inflow stenosis. Percutaneous angioplasty has been regarded as the gold standard for endovascular salvage of AVFs (Nassar et al, 2006). The arteriovenous graft (AVG) is a popular option to AVF. In this method a synthetic graft is anastomosed between an artery and a vein, typically in the forearm. The great advantage of the AVG is that it is almost instantly available for dialysis access, and does not need a period of maturation. AVGs exhibit a higher stenosis rate than AVFs (May et al, 1997). This is partly caused by the absence of endothelium in the graft (Gibson et al, 2001; Young et al, 2002).
6.2. Vascular Biology: the Endothelium

6.2.1. Normal endothelium

The arterial wall can be divided into three anatomically distinct layers (tunicae), namely the tunica intima, the tunica media and the tunica adventitia. The intima is the thinnest and innermost of the anatomical layers. It is composed of a single layer of endothelial cells, namely the endothelium, and their supportive subendothelial lamina. The endothelium serves as an inner lining of the vessel to facilitate laminar blood flow, and acts as a barrier to control molecular movement through the vessel wall. The endothelium has a wide range of physiological functions. These are facilitated by the endothelium’s ability to respond to various chemical and physical stimuli by producing factors that in turn control vascular tone, inflammation, smooth muscle cell proliferation, and various other phenomena in the vessel wall. One of the key mediating factors in the endothelium is nitric oxide (NO). In 1980 Furchgott and Zawadzki recognized an endothelium-derived relaxing factor, and subsequent studies showed that this was indeed NO (Furchgott and Zawadski, 1980). NO is a potent vasodilator though cyclic guanosine monophosphate (cGMP)-mediation in the vascular smooth muscle cells. NO is activated by the shear stress of the blood flow, as well as many circulating agents such as adenosine, and vascular endothelial growth factor (vEGF) (Corson et al, 1996; Govers and Rabelink, 2001). In the normal, healthy and intact endothelium, NO is the dominating agent in maintaining vascular homeostasis through suppression of inflammation, cell growth, and thrombosis.

In endothelial activation (endothelial dysfunction) this balanced situation is disturbed and the NO-dominance diminished, and shifted toward reactive oxygen species (ROS). ROS activate many of the same mediators as NO, but with radically different chemical results (Förstermann and Münzel, 2006). As a consequence, the anti-inflammatory and anti-thrombotic homeostasis is imbalanced. Atherosclerosis is thought to, at least in part, be caused by the activated endothelium. Furthermore, overall systemic inflammation activity is higher in patients with PAD as compared to stable coronary disease (Rein et al, 2015).
6.2.2. Restenosis and intimal hyperplasia

6.2.2.1. Pathogenesis

Restenosis means the narrowing or occlusion of an artery previously treated by endovascular angioplasty. Since the first coronary balloon angioplasties, restenosis has been identified as one of the main limitations for long-term success of these procedures. The same phenomenon is seen in peripheral arteries, bypass grafts (both coronary and peripheral) and AV-fistulas (Clowes and Reidy, 1991). Intimal hyperplasia also accounts for the in-stent restenosis observed inside stented segments of arteries.

The intimal endothelium is crucial in the pathogenesis and development of vascular restenosis, as it is in much other vascular pathology. When an artery is dilated with an endovascular balloon, the intima is mechanically injured. The repair response triggers intimal hyperplasia and vessel remodeling at the site of injury (response-to-injury). This can lead to recurrent stenosis or even occlusion of the artery at the same site, prompting reinterventions due to deteriorating clinical symptoms and manifestations. Restenosis can be alleviated by use of bare metal stents to counter the intimal hyperplasia. Stents, however, are limited by in-stent restenosis when smooth muscle cells migrate inside the stent from the stent-native artery border.

After the index intervention, development of intimal hyperplasia starts early and peaks between 6 and twelve months (Kastrati et al, 1997). After placement of BMS in coronary arteries, long-term follow-up has demonstrated a triphasic intimal response with early restenosis, intermediate regression, and a late restenotic phase (Kimura et al, 2002). After placement of DES the first phase was weakened but there seems to be catch-up over time; this is probably due to a chronic state of inflammation (Virmani et al, 2002)

6.2.2.2. Vein graft disease, intimal hyperplasia, and restenosis in vein grafts

30-40 % of coronary and peripheral vein grafts occlude or develop stenosis in the first twelve months after bypass reconstruction (Alexander et al, 2005; Conte et al, 2006). Vein graft disease
(VGD) is a chronic, multi-phased, inflammatory process that can lead to graft failure or loss (de Vries and Quax, 2018). Pioneers Carrel and Guthrie already identified intimal hyperplasia as an important cause for graft failure (Carrell, 1906). Initially, the remodeling process begins with the harvesting and surgical preparation of the conduit when the vessel wall is iatrogenically exposed to mechanical as well as pressure trauma (Hocking et al, 2011; Angelini et al, 1987). Additive damage can result from warm ischemia in storage solution and the practice of marking the vein with skin markers for orientation (Davies et al, 1994; Eagle et al, 2011). The de facto impact of the aforementioned damage on graft physiology and cellular function is not well studied or understood. One study did demonstrate SMC and endothelial dysfunction in harvested GSV grafts, as well as clear signs of elevated oxidative stress markers (Osgood et al, 2014). The authors argued for less damaging means of graft harvesting to preserve cellular function and consequently graft patency. Some data has been published in favor of so-called “no touch”-harvesting, in which the vein is harvested together with the perivenous fat; this technique has shown comparable patency rates with internal mammary artery grafts for coronary bypass surgery (Samano et al, 2015). As the vein graft is eventually exposed to arterial pressure the graft thickens, and some degree of intimal hyperplasia is probably a “normal” response and part of the arterialization process. It should also be noted that, especially in a population aged from 60 to 80, a vast majority (<90%) of macroscopically normal saphenous veins are not microscopically free from phlebsclerostosis and intimal thickening already before grafting (Stanley et al, 1973; Milroy et al, 1989; Thiene et al, 1980). Furthermore, the arterilization of a vein still renders the graft non-elastic due to changes in the fibers of the muscle-layer.

Restoration of the endothelial layer occurs after 10-14 days depending on animal model studied (Brody et al, 1972). In a long human bypass, it likely takes much longer (Ehsan et al, 2002).

The pathology of graft failure can be divided into three stages: early graft failure (0-1 months), intermediate graft failure (1-12 months), and late graft failure (1-10 years). The pathology behind the failure varies dramatically between these stages. Early failure is typically caused by surgical error and technical issues as well as thrombosis. Intermediate failure is a consequence of intimal hyperplasia, inflammation, and vessel remodeling. Late failure on the other hand involves atherosclerotic plaque development and further thickening and stiffening of the graft (Ward et al, 2017).
6.2.2.3. Intimal hyperplasia and restenosis in AVFs

A common problem in AVFs is primary and recurrent stenosis. In AVFs approximately 0.1 – 0.5 thromboses occur per graft year, the corresponding rate in AVGs is 0.5 – 2 (Quencer and Oklu, 2017). Intimal hyperplasia and restenosis in AVFs is pathologically even more complex than in the arterial setting, mainly due to patient-related factors. CKD and ESRD lead to molecular changes in the function of the venous endothelium. This occurs especially in the venous segment of the fistula, and leads to prolonged maturation, failed dialysis and potential occlusion and loss of the access. The process of intimal hyperplasia and subsequent stenosis in AVFs seems to be biologically more complex than that in PAD, and has been linked to a number of variables. These include age, surgical technique and trauma, shear stress, uremia, hypoxia, smoking, cytomegalovirus infection, diabetes, body-mass index, plasma cholesterol, other vascular disease, among others (Wong et al, 1996; Feldman H et al, 2003; Aitken E et al, 2014; Smith G et al, 2012). The molecular pathways of these factors are suspected to be similar (Brahmbhatt et al, 2016). There is further recurrent endothelial injury from repeated punctures with a dialysis needle. In

60% of stenoses in radiocephalic fistulas, the hyperplasia and consequent stenosis occurs at the
anastomosis. In brachiocephalic fistulas the stenosis is typically in the cephalic arch (Sivanesan et
al, 1999; Hammes et al, 2008). An anatomical classification of causes has been proposed (Roy-
Chaudhury et al, 2006): ‘Upstream’ causes include surgical trauma, comorbidities, non-
physiological flow conditions at the anastomosis, endothelial dysfunction and inflammation.
‘Downstream’ causes are secondary to upstream causes and include the biological responses of
the vein to the arterialization after placement of fistula.

6.2.2.4. In-stent Restenosis in arterial stents

Considered the archenemy or Nemesis of interventional cardiologists, in-stent restenosis (ISR) has
been a key factor that has fuelled the development of bare-metal stents as well as drug-eluting
stents and drug-coated balloons over the last 20 years. Vascular smooth muscle cell formation and
migration is induced by mechanical stretching of the artery, medial dissection, and by intimal
damage from percutaneous transluminal angioplasty (PTA) and stent struts (Buccheri et al, 2016).
ISR is considered to be a chronic inflammatory response to the persistent trauma to the arterial
wall caused by the stent (chronic wall stress) and its struts (damage to the endothelium and
protrusion into deeper layers). This hypothesis is supported by evidence of systemic levels of
inflammatory markers that are elevated after stent deployment (Farb et al, 2002).

6.3. Drugs against vascular smooth muscle cell proliferation

6.3.1. Paclitaxel

The history of paclitaxel (Taxol) is interesting. It was first discovered in the bark of the Pacific yew
tree (Taxus brevifolia) after 650 random plant samples were screened for anti-tumor qualities in a
program commissioned by the National Cancer Institutes in 1962. The process of bark harvesting
left the tree dead, and early on production and interest were limited by uncertainty regarding the
spread and size of the natural population of T.brevifolia. The early production method was
laborious, and yielded only 0.5 g of paclitaxel per 12 kg of dried bark. This lead to intensive
research on paclitaxel synthesis amid concerns and conflicts of interest between environmental preservation and cancer treatment (Danishevsky et al, 1991; Walsh and Goodman, 1999).

The structure of paclitaxel was described in 1971 in a paper from RTI laboratories (Wani et al, 1971). Its mechanism of action was described in several studies during the late 70’s (Fuchs et al, 1978; Schiff et al, 1979; Horwitz et al 1982). Paclitaxel is an anti-mitotic agent by way of tubulin binding. It binds to tubulin, thus stabilizing its microtubule structure. This hinders disassembly of tubulin, which is required for chromosomes to reach metaphase configuration, and effectively blocks the progression of cell mitosis. Clinical phase I and II trials were conducted in the late 80’s. Many of the phase I trials had to be aborted due to hypersensitivity reactions, and the phase II trials were eventually performed with strict protocols for premedication (Kris et al, 1986; Wiernik et al, 1987; Einzig et al, 1991). Exceptional efficacy was seen against ovarian cancer in particular (McGuire et al, 1989; Niloff, 1991). It also showed potential in breast cancer, squamous cell carcinoma of the head and neck, and melanoma (Ettinger, 1993; Foa et al, 1994). Food and Drug Agency (FDA) approval for marketing was issued in December 1992.

The first reports of in vivo and in vitro paclitaxel and vascular smooth muscle cell inhibition are from the mid-90s (Sollott et al, 1995; Axel et al, 1997).

Paclitaxel is today by far the most common drug used on drug-coated balloons and drug-eluting stents for peripheral use.

6.3.2. Sirolimus

Sirolimus (or rapamycin) is a macrolide antibiotic produced by the Streptomyces hygroscopicus. It was first extracted in the beginning of the 70s from soil samples from Easter Island (Rapa Nui) in a joint U.S. and Canadian probing mission for new anti-fungal agents (Vezina et al, 1975). It was quickly found to be a potent immunosuppressant, but it was not until 1995 that FDA approval was acquired for use in kidney transplant patients to prevent organ rejection (Napoli and Taylor, 2001; Miller, 1999). Sirolimus was observed to inhibit smooth muscle cell growth and migration, and when administered orally, improve patency after endovascular angioplasty (Gregory et al, 1993; Poon et al, 1996). The first pilot studies on sirolimus-eluting coronary stents were impressive, as restenosis was virtually eradicated (Rensing et al, 2001).
Sirolimus is thought to effect neointimal hyperplasia by inhibition of smooth muscle cell proliferation and migration, and inhibition of differentiation of smooth muscle progenitor cells. Early sirolimus-eluting stents were associated with a higher rate of thrombotic complications, which may be due to impaired endothelialization (Oyabu et al, 2006; Higo et al, 2009)

6.3.3. Everolimus

Everolimus is a more selective derivative of sirolimus. Its mechanism of action is similar to sirolimus. The more selective inhibition may lead to retaining many of the benefits of sirolimus while eliminating side effects such as glucose intolerance and immunosuppression.

6.3.4. Adverse effects

The paclitaxel molecule is lipophilic, which allows for it to be passively absorbed through the intimal wall (Creel et al, 2000; Levin et al, 2004). Animal studies have yielded a maximal inhibition of neointimal formation with a balloon-coating concentration of 3 µg/mm² (Creel et al, 2000). However, the optimal concentration in vivo has not been determined, and is limited by the commercially available balloons. One study compared three different balloons, two coated with 2 µg/mm² paclitaxel and one with 3 µg/mm² (Gongora et al, 2015). The results showed that all coatings reached therapeutic levels at all time points during the study, but the lower doses showed a histologically more mature neointima with less fibrin deposits. Loss of drug has also raised concern especially in peripheral usage: Kelsch showed that from the balloon roughly 30% is delivered to the vessel wall, while 60% is lost into the blood flow and 10% remains on the balloon (Kelsch et al, 2011). Treatment with paclitaxel eluting balloons and stents has also demonstrated persistently reduced wound healing at treated sites. One case report showed short-term restenosis in both bare metal and drug eluting stents in the coronaries after treatment (Nasuno et al, 2016). After atherectomy the lesions were retreated with DES and BMS. Five years later, the lesions were free from restenosis but optical coherence tomography showed atheroma-like neointima at the DES sites, while the neointima looked regular at the BMS sites. The potential toxic and inflammatory effect of paclitaxel on arterial walls has been studied in porcine models, with inconclusive results and unpredictable uptake patterns (Radeleff et al, 2010).
Cases of aneurysm formation at peripheral sites of DCB angioplasty have been described in the literature (Diamantopoulos et al, 2015). One of the described aneurysms formed at the distal anastomosis of a bypass vein graft.

Discussion about distal embolization, deteriorating Rutherford classification, and toxicity of paclitaxel-coated balloon angioplasty is ripe in the vascular community. However, scientific data to support these claims is scarce. A PubMed search [paclitaxel AND toxicity AND vessel NOT (cancer OR carcinoma)] in April 2018 did not yield any human studies in support of this theory. It seems clear, though, on the basis of the previously cited literature, that the wound healing and neointimal formation is impaired on a cellular level.

6.4. Drug-eluting and Drug-coated Technology

6.4.1. Balloons and Stents in peripheral Arteries

In the 1970s, systemically administered antiproliferative agents were investigated in order to combat restenosis. While these were well tolerated, the effect on prevention of restenosis was minimal as the local concentration of the agent in the arterial wall was too low (Hamon et al, 1998). DCBs were developed with the idea of covering the entire treated arterial wall locally with an antiproliferative agent while leaving no potentially thrombogenic stent or scaffolding behind. This way, 400 -1000 times higher concentrations could be achieved in the arterial wall (Muller et al, 1992; Fram et al, 1997). These studies were done on methotrexate and heparin, respectively, which failed to prevent restenosis. However, the balloon catheter as a means of drug delivery was considered promising. At the same time, the risk for future in-stent restenosis is obviously avoided.

**Drug-eluting stents**

DES were first approved by FDA for use in coronary arteries in 2003. They have since claimed their place in routine treatment of coronaries. In 2007 a meta-analysis showed remarkable benefit from DES compared to BMS with regard to TLR-free survival (Stettler et al, 2007). Both sirolimus and paclitaxel showed good efficacy against restenosis. This success in coronary artery disease did not
initially translate into comparable results in the treatment of peripheral lesions. The SIROCCO-study was the first randomized trial using DESs in femoropopliteal stenoses and/or occlusions (Duda et al, 2005; Duda et al, 2006). A sirolimus-coated self-expanding nitinol stent was randomized against bare-metal nitinol stents, and the trial failed to show benefit from the DES. Similar results were seen in the STRIDES-trial, in which an everolimus-eluting stent with a long elution profile was compared to BMS (Lammer et al, 2011). Cook Medical (Cook Medical Inc., Bloomington, IN, USA) introduced the Zilver PTX, a drug-eluting version of their Zilver-stent for SFA-lesions and reported very good results initially (Dake et al, 2011; Dake et al, 2011). These results were corroborated by later follow-up papers on the same population (Dake et al, 2013; Dake et al, 2016). This trial has been criticized for comparing DES to outdated technology, i.e. the Zilver BMS, but it still remains the largest prospective study on the subject at hand. The Zilver PTX also showed early promise for TASC C/D lesions (Bosiers et al, 2013). The paclitaxel-eluting Eluvia stent has also shown safety and long-term durability in a randomized trial (Müller-Huisbeck et al, 2016 and 2017). Furthermore, DESs have been studied for infra-popliteal lesions, mainly the Xience Prime –stent by Abbott (Abbott Inc., Abbott Park, IL, USA), which is an everolimus-eluting stent originally engineered for use in the coronaries, but later modifications (Xience Prime BTK) are intended for deployment in the tibial vessels. The DESTINY-trial compared the Xience-stent to BMS in patients with CLI (Bosiers et al, 2012). Patency at 1 year was remarkably high in the DES treatment group, 85.2%, compared to 54.4% in the BMS control group. The YUKON-trial showed benefit in event-free survival and amputation rates after focal sirolimus-eluting stenting (Rastan A et al, 2012 and 2015). The trial was prospective and included 131 patients. The ACHILLES-trial (Scheinert et al, 2012) reported significantly lower binary restenosis rates for sirolimus-eluting stents compared to PTA alone. This study failed to show benefit in individual clinical endpoints (amputation-free survival, Rutherford class, bypass, death), but when these were compounded there was a clear benefit from DES. This difference was exceptionally clear in diabetic patients, although the study was not powered for subanalysis. In the industry-independent PADI-trial a paclitaxel-eluting stainless steel coronary stent was compared to PTA with bailout bare-metal stenting (Maartens et al, 2009; Spreen et al, 2015; Spreen et al, 2017). Both interim and long-term follow-up (1, 3, and 4 years) showed statistically significant benefit from DES with regard to both TLR and clinical hard endpoints such as freedom from major amputation. Overall survival was comparable between the treatment groups.
Drug-coated balloons

The first trials and reports about drug-coated balloons for peripheral lesions were reported in the late 90’s. The early trials failed to show benefit for use of bare metal stents, while drug-coated balloons, especially those with paclitaxel, fairly quickly showed promising potential against arterial restenosis. The THUNDER-trial (Tepe et al, 2008) included 154 patients with femoropopliteal stenoses or occlusions in three study arms: BA, DCB, and paclitaxel in the contrast medium. DCB showed significantly lower TLR-rates and late lumen loss at 6, 12 and 24 months of follow-up. A follow-up paper reported lasting benefit over five years (Tepe et al, 2015). The multi-center, prospective FEMPAC-trial also reported better TLR-free survival at 6 months for DCB in femoropopliteal disease (Werk et al, 2008). In this trial use of DCBs also correlated with clinical improvement, as there was a significant improvement of Rutherford classification in the DCB group compared to the controls. The LEVANT I –trial was an industry-sponsored (C.R.Bard Inc, New Providence, NJ, USA), three-armed, prospective trial. Patients with femoropopliteal lesions were randomized to BA, DCB, or stenting and within the stent-group to DCB or BA before stent deployment (Scheinert et al, 2014). 101 patients were enrolled and analyzed. Use of DCB showed reduced late lumen loss with a safety comparable with the BA controls. The follow-up LEVANT II trial showed better patency rates and non-inferiority in terms of safety (Rosenfield et al, 2015). This trial was a large multi-center effort with 476 patients. The PACIFIER trial investigated prevention of restenosis in femoropopliteal arteries, and did show durable benefit over plain balloon angioplasty up to three years after intervention (Werk et al, 2011; Werk et al, 2013; Werk et al, 2014). The IN.PACT series of trials by Medtronic (Medtronic plc, Dublin, Ireland) aimed to establish the efficacy of DCB in a variety of clinical settings. In the IN.PACT SFA–trials 331 patients were randomized (2:1) for DCB vs. BA in symptomatic femoropopliteal disease (Tepe et al, 2015; Laird et al, 2015). There were almost 9 times more target lesion revascularizations in the BA group. There was not, however, any difference in the quality of life or improvement in walking distance at 1 year between the treatment groups. The IN.PACT DEEP trial investigated the efficacy of DCB in infrapopliteal lesions in patients with CLI (Zeller et al, 2014). It saw 358 patients randomized 2:1. While patency and primary safety was comparable to BA, there was a trend toward increased rates of major amputations in the DCB-group. This eventually led to the DCB for infrapopliteal vessels by Medtronic being withdrawn from the market. Medtronic has launched the IN.PACT BTK
study to re-evaluate these results. The DEBATE-SFA trial included 104 patients with symptomatic femoropopliteal lesions. The study groups were DCB+BMS or BA+BMS. Patency rates were improved after predilatation with a DCB (Liistro et al, 2013). The DEBATE-BTK trial is an industry-independent trial, which randomized 132 diabetic patients with infrapopliteal lesions for treatment with DCB or BA (Liistro et al, 2011; Liistro et al, 2013). At one year there was a striking reduction of 1-year restenosis, target lesion revascularization, and target vessel occlusion in favor of the DCB-group. The rate of limb salvage was extremely high in this cohort, with only one major amputation during 12 months of follow-up. In this study, patients were included only after successful recanalization of a tibial vessel, which may contribute to this strikingly low number of amputations. The DEBATE-ISR trial included 44 diabetic patients with femoropopliteal in-stent restenosis (Liistro et al, 2014). Their 12-month TLR-free survival was compared with a historical control group. There was a significantly better outcome in the DCB-group. The prospective DEBELLUM-trial included 50 patients with claudication or CLI for treatment with BA or DCB (Fanelli et al, 2012; Fanelli et al, 2014). The patients presented with de novo lesions or stenoses in femoropopliteal and infrapopliteal vessels. At both 6 and 12 months, there was a significant benefit from DCBs with regard to TLR-rate, thrombosis, increase in ABI, and decrease in Fontaine classification. The rate of major adverse effects was also lower in the DCB-group. Fresh interim results from the ongoing Lutonix 014 Global Below the Knee Study with 314 patients also demonstrate both efficacy and safety at six months after use of DCB in crural arteries (Thieme et al, 2018). The IDEAS trial randomized infrapopliteal long occlusions to DCB or DES. Follow-up was only six months, but showed improved patency after DES (Siablis et al, 2014).

A systematic review on DCBs in SFA-lesions was published in 2016 (Katsanos et al, 2016). This review included 11 randomized trials and 1609 patients. The primary cause for treatment was intermittent claudication (1403 patients). This review concluded that the use of DCBs more than halved the rate of restenosis and TLR. The difference was as significant in the presence of stents. There was no demonstrable difference in the rate of hard endpoints such as major amputations and death. These were rare in both groups, probably due to the relatively benign baseline characteristics. 2016 also saw the publication of a Cochrane review of DCB vs. plain balloon angioplasty (Kayssi et al, 2016). This review also included 11 trials with a total of 1838 patients. 9 trials were industry sponsored, and all but one reported outcomes at 12 months. One trial reported on outcomes at five years. DCB showed better patency rates, longer freedom-from-TRL,
and less binary restenosis. Importantly, however, there was no statistical significance in outcomes such as death, freedom-from-amputation, change in Rutherford classification, or change in ABI. Furthermore, there was no benefit from DCB in a subgroup analysis of patients with CLI, and another subgroup of tibial vessel lesions. According to the Cochrane review, many of the studies are hampered by major bias because of inadequate reporting on stenting. The use of bailout stenting in most trials was left to the discretion and judgment of the interventionist without clear criteria. Furthermore, the results are not separately reported for the stented lesions. In two trials (FemPac and PACIFIER) the rate of bailout stenting was higher in the control group. There is potential bias from variation in DAPT-regime between the studies, as the length of this was not standardized and depended for example on bailout stenting. While paclitaxel-coated balloons were used in all studies, the dose varied between the different balloons. A systematic review and meta-analysis of the published data on DCB/DES in infrapopliteal arteries did see potential benefit from DES compared to PTA/BMS (Zhang et al, 2017), while no obvious advantage could be seen from use of DCBs. The rates of clinically driven TLR, rate of amputation, and restenosis were lower in the DES-group although without any effect on overall mortality. This analysis is also limited by many of the same factors as the Cochrane review: there is heterogeneity in both the anatomical and clinical features of the included subjects as both claudicants and CLTI-patients were enrolled. Furthermore, the median lesion length in the treatment of infrapopliteal lesions is only <3 cm, which according to the authors is not in line with daily practice. This review included nine studies with 707 patients in the DCB/DES group and 606 in the PTA/BMS group. It did not report on whether the included studies were industry sponsored.

6.4.2. Vein grafts

To date, the literature on use of DCBs in vein graft stenoses is quite limited. Histologically, one could argue that the process of IH in autologous grafts is comparable to in-stent restenosis, where smooth-muscle cells migrate inside the graft. One small, randomized trial did not demonstrate benefit from use of DCB over BA in bypass vein grafts (Kitrou et al, 2014). This study included synthetic grafts and perianastomotic stenosis, which probably increases the histological heterogeneity of the included lesions. Similar results were observed in a Danish registry review comparing bare metal stents to drug-eluting stents in vein grafts in coronary bypass surgery, and
another retrospective study comparing BA to DCB in peripheral grafts (Hougaard et al, 2014; Linni et al, 2016). The latter included 83 patients and has a follow-up of >2 years. In a recent small retrospective analysis, 39 patients with failing autologous grafts were analyzed for primary, assisted primary, and secondary patency after DCB or BA (Jongsma et al, 2017). There was no difference between the groups, and use of DCB was discouraged on financial grounds. Surgical repair has been claimed to provide a more durable solution for persistent graft stenosis (McCallum et al, 2015).

![Image of stenosis of a femopopliteal vein graft](image)

**Figure 2. Stenosis of a femopopliteal vein graft**

6.4.3. Hemodialysis access

There are only few published studies comparing DCB and BA in stenotic lesions in dysfunctional arteriovenous fistulae. One prospective randomized trial showed significant benefit from the use
of DCBs over plain BA at six and twelve months (Katsanos et al, 2012; Kitrou et al, 2015). This showed one-year primary patency of 5% (BA) vs. 35% (DCB). The mean time from fistula creation to PTA was 2.5 years. This trial included 65% prosthetic AV-grafts. The same group published a cost-effectiveness analysis on the same material, which concluded that DCB might be a cost-effective option, but that larger studies are warranted (Kitrou et al, 2015). Another study with 39 patients (21 AV-grafts) also showed significant benefit from DCBs in terms of TLR (Kitrou et al, 2017). In this group the mean access age was also quite high, approximately 2.5 years in both groups. A meta-analysis of the small randomized and non-randomized studies published before 2016 showed increased patency at 6 months after DCB, but this difference vanished at 12 months (Khawaja et al, 2016). The meta-analysis included 254 interventions in 162 patients, and as the material was considered clinically heterogeneous, clinically applicable conclusions could not be drawn. Another review concluded that, in the light of data published so far, DCBs may have role in the treatment of dysfunctional AVFs but larger studies are needed to confirm this (Karnabatidis and Kitrou, 2017). Lai published a small pilot study on juxta-anastomotic inflow lesions for radiocephalic AVFs (Lai et al, 2014). TLR-rates were improved in the DCB group, but this study only recruited 10 patients (20 lesions).

There is a large ongoing prospective trial for DCB in AVFs. The study is sponsored by C.R.Bard Inc and has a goal of 285 patients. Expected study completion is in October 2018. Interim results have favored DCB.

Stent grafts have also been studied for AVF revascularization, and have demonstrated a clinical benefit in a recent prospective trial with 2-year follow-up (Haskal et al, 2016). They have been proposed as an option especially for perianastomotic stenoses.
6.4.4. Drug-coated devices in in-stent restenosis

Quite a few trials have been run on DCB for ISR lesions. A retrospective study showed that restenosis does occur after DCB-treatment, although later (Habara et al, 2015). The DEBATE-series
included a trial with diabetic patients with symptomatic femoropopliteal ISR who underwent DCB-angioplasty. Event-free survival was compared with historical controls. At three years, DCB failed to show benefit in terms of TLR (Grotti et al, 2015). The FAIR RCT showed better patency and improved clinical outcomes after DCB-angioplasty for femoropopliteal ISR. The trial included 119 patients in 5 centers, with a follow-up of twelve months (Krankenberg et al, 2015). In a subgroup from the Zilver PTX Global Registry, patients who developed ISR were treated with DES for ISR. DES showed promising early, midterm, and long-term results (Zeller et al, 2013).

6.5. Cost-effectiveness

Studying and determining cost-effectiveness across different healthcare systems for drug-coated therapies has proven difficult. Usually, plain stents and balloons are priced and reimbursed favorably to their drug-coated counterparts, but based on the literature their clinical benefit might offset these costs. The cost of the device plays only a minor part in the overall treatment cost, which further complicates calculations. Based on British reimbursement details from the National Health Services (NHS), 28 studies comparing DCB, DES, and BMS for femoropopliteal were systematically analyzed and pooled. Over 5000 lesions were included. DCB showed the highest clinical and economic value with 24-month TLR as endpoint. Katsanos et al, 2016). NNT for DCB, DES, and BMS were 5.4, 6, and 10.8, respectively. This lead to an estimated cost for avoided TLR at roughly £200 for DCB and DES, and £1200 for BMS. Another systematic review assessed cost-effectiveness in the American Medicare-setting (Sridharan et al, 2018). In line with the British study, DCB was considered the by far most cost-effective device, although it was noted that the use of more than one device per patient significantly reduces their economic value. In this analysis, DESs showed the highest 1-year primary patency rates at 79 %, compared with DCBs at 74 %. The overall baseline costs for POBA and DCB were roughly the same, and the cost for one patent limb at 1 year was identical. Reintervention rates were modeled based on a meta-analysis of published data. The number needed to treat (NNT) to avoid one TLR was 10 for DCB over POBA, while the NNT for DES over DCB was 20.
7. AIMS OF THE CURRENT STUDY

I. To investigate if any benefit can be seen using DCB compared to POBA in a retrospective series restenosis in native arteries, vein grafts, and AV-fistulas

II. To compare the outcome of the endovascular treatment of vein graft stenosis with DCB vs. BA

III. To compare the outcome of the endovascular treatment of AV-fistula stenosis with DCB vs. BA

IV. To compare the outcomes of drug-eluting stents with prosthetic bypass for occlusive femoropopliteal disease
8. MATERIALS AND METHODS

8.1. Study I

In this retrospective study, data from 93 consecutive DCB-angioplasties between January 2012 and December 2013 was analyzed. The study included restenotic lesions in native arteries, bypass vein grafts, and AV-fistulas. All patients in the cohort had undergone at least 1 earlier BA for the index lesion. The time from previous BA was compared to the time from DCB to TLR or loss of graft/AVF. The follow-up protocols varied between the indications for treatment, but the primary endpoints were identical. Endpoints for primary patency were any revascularization of the same lesion or graft occlusion. Endpoint for secondary patency was loss of artery/graft/AVF. Follow-up ended at a date where there was a record of an open vessel in the case history. If no endpoint was reached at the date of review (end of February 2014), the lesion was presumed to be open and asymptomatic. This was crosschecked with hospital and population records for interventions (including kidney transplant and central access) and death. Cases were excluded due to primary use of DEB (n=3), use of DEB in a prosthetic bypass graft (n=1), use of DEB in complex brachiojugular AVF (n=1) and insufficient or unavailable patient data (n=7).

The DCBs in this trial was the In.Pact Admiral, Pacific and Amphirion paclitaxel coated balloons (Medtronic, Minneapolis, MN, USA). The Amphirion balloons were withdrawn from use in BTK lesions during the studied period of time. All the lesions were predilated with a conventional balloon prior to drug eluting BA.

Follow-up depended on the indication for the procedure, and was performed according to the standard protocols at our institution: native artery lesions causing claudication without CLTI were not routinely followed up, but the patient was advised to contact the hospital if the claudication did reoccur. CLTI cases were followed at the outpatient clinic until the ischemic wound was healed. Vein grafts were followed up with duplex ultrasound by a vascular nurse, which also led to the treatment of significant asymptomatic graft stenoses found by duplex ultrasound. Vascular access patients were not under routine surgical surveillance. AVF patients were referred back to the vascular clinic by nephrologists as needed, usually due to problems in dialysis through the treated access. If dialysis was successful, the AVF was assumed to be without significant stenosis.
8.2. Study II

Patients with significant stenosis or restenosis in femoropopliteal or femorodistal vein grafts requiring PTA were randomized between March 2013 and December 2015. All bypasses had been performed using translocated, non-reversed and valvulectomized vein. The autogenous grafts included both single-segment and spliced great saphenous and arm veins. The stenoses were detected by routine graft surveillance, or in symptomatic patients who presented at the emergency department. Grafts were measured with duplex-ultrasound for diameter, cross-section area and peak systolic velocity ratio (PSVR). A PSVR of 2.5 was defined as threshold for intervention. Lesions <15 mm from an anastomosis were excluded. Angiography was performed in the angio suite through ipsilateral or crossover access from common femoral artery or direct graft puncture. The lesion was crossed with a guide wire and thereafter predilated with a conventional angioplasty balloon for a minimum 90 seconds before randomization. It was then redilated with DCB or BA according to allocation (90 sec.). Sizing was performed intraoperatively from the angiography images by the treating interventionist. At the start of intervention, all patients were administered 5000 IU heparin regardless of weight and activated clotting time. This trial used a balloon with a paclitaxel coating of 3.5 μg/mm² with urea as excipient (Medtronic IN.PACT, Medtronic, Minneapolis, MN, USA). Technical success was defined as residual stenosis <30% in the completion angio and no graft rupture. All patients, except those on warfarin, received dual antiplatelet therapy postoperatively (ASA 100 mg + Clopidogrel 75 mg). This was continued for 3 months. Patients on warfarin received concurrent ASA 50 mg for three months. A vascular nurse performed follow-up at 1, 6, and 12 months. The follow-up examination included clinical evaluation for symptoms and ABI, as well as duplex ultrasound assessment of the graft and the index lesion. As the studied intervention aims only at graft patency, the threshold for reintervention was set as a PSVR of >2.5 regardless of clinical findings.

Primary endpoint was TLR-free survival. Secondary outcome measures were graft occlusion, assisted primary patency and secondary patency. Based on the published literature at trial design, a 12-month TLR-rate for the BA and DCB groups of 30% and 10%, respectively, was assumed. The required sample size was defined as 140 (70+70).
8.3. Study III

Randomization was done between August 2013 and February 2016. Patients were referred from the dialysis unit due to difficult or failed dialysis or occluded AVF. All lesions were in the extra-anastomotic venous segment (>15 mm from AV-anastomosis). Central vein stenoses and lesions <15 mm from the anastomosis were excluded. After ultrasonographic confirmation of significant venous stenosis the AVF was accessed through arterial or venous puncture. The patients were routinely administered 5000 IU heparin. The lesion was crossed with a guide wire and dilated for 90 seconds with a 1 mm undersized plain balloon. Randomization was performed after predilatation. The stenosis was redilated with DCB or BA according to randomization (90 sec.). This trial was done on a DCB-balloon with a paclitaxel coating of 3.5 μg/mm² and used urea as excipient (Medtronic IN.PACT, Medtronic, Minneapolis, MN, USA). Technical success was defined as residual stenosis <30%. High-pressure balloons were not allowed. All patients received DAPT for 1 month postoperatively: ASA 100 mg + clopidogrel 75 mg, or warfarin + ASA 50 mg if the patient was already on warfarin. Research nurses performed duplex ultrasound follow-up immediately after the procedure and at 1, 6 and 12 months. Re-interventions were prompted by recurrent problems with dialysis only. Primary endpoint was TLR-free survival and any loss of the AV-fistula.

With a two-sided 5% significance level and a statistical power of 80% the necessary sample size was determined at 140 (70+70) patients based on literature available at the time of trial design.

8.4. Study IV

Patients were included between 2011 and 2014, follow-up ended in 2016 at 6 hospitals in Finland (Helsinki, Oulu, Turku and Kuopio university hospitals and the central hospitals in Lahti and Joensuu). 5-25 cm SFA-occlusions were eligible for inclusion. The lesions were diagnosed and measured from magnetic resonance angiography (MRA) or computed tomography angiography (CTA). Clinical manifestations included rest pain or severe claudication (Rutherford class II-IV). Patients with severe CLTI (wounds or tissue loss) were excluded due to use of synthetic grafts, as were patients with previous endovascular interventions to the femoropopliteal segment. Concomitant inflow or outflow procedures were not allowed. Patients were randomized to
endovascular recanalization and DES or prosthetic above-knee femoropopliteal bypass 2:1 (DES:BSX).

**Bypass surgery**

Bypass surgery was performed with a 6 mm heparin-bonded polytetrafluoroethylene (PTFE) graft. Inflow was taken from the common femoral artery and the distal anastomosis was to the supragenicular popliteal artery (P1). The graft was tunneled anatomically or subcutaneously depending on surgeon’s preference. Patients were heparinized with an activated clotting time (ACT) between 200 and 300 seconds for the duration of arterial clamping. Completion control was performed with flow measurement.

**Balloon Angioplasty and Drug-Eluting Stent**

Patients received 5000 IU systemic heparin at procedure start. Access was obtained from the ipsilateral or contralateral common femoral artery. The occlusion was recanalized and crossed intraluminally or subintimally prior to PTA and stent deployment. The Zilver PTX drug-eluting stent was then delivered and post-dilated according to instructions-for-use. Completion control was performed by angiography.

**Follow-up and outcome measures**

Primary outcome measure was overall stent or graft patency. Secondary outcome measures were primary and assisted patency, change in ABI, as well as amputation-free survival. Follow-up was performed by clinical evaluation for duplex ultrasound at 1, 6, 12, and 24 months postoperatively.

All patients except those on warfarin were started on life-long ASA treatment in both treatment groups. Patients in the DES group received DAPT for three months postoperatively. DES-patients on warfarin were started on concurrent low-dose ASA for the same period. Dual antiplatelet therapy was not prescribed after bypass surgery.
8.5. Statistical analysis

For the randomized trials, statistical analysis was performed with SPSS version 22 and 24 (IBM, Armonk, NY, USA). Continuous variables are expressed as means and range or medians and interquartile range (IQR) and dichotomous variables as percentages. Continuous variables were compared using Mann-Whitney test and dichotomous variables using Chi-square. Patency rates were analyzed with Log-rank (Mantel-Cox) testing. Relative risk was calculated by $RR = (a/(a+b))/(c/(c+d))$. There were no missing TLR data in any of the trials. Missing data for baseline analysis was managed by pairwise deletion. In the AVF study (III) TLR-free survival was further compared with nonparametric Mann-Whitney analysis due to the small sample size.
9. RESULTS

9.1. Study I

Eventually, 81 cases were included. Statistical analyses were performed for the whole group, and separately for three groups based on anatomical site of the intervention: native arteries (N=31), bypass vein grafts (N=27) and AVF (N=23). Patients in the native artery group were on average 7 years older than patients in the other groups. Males were clearly overrepresented in the AVF group, as is, unsurprisingly, kidney disease and diabetes. In the overall series, the median time from the BA to DEB was 240 days compared to 572 days from DEB to an endpoint (p<0.01). The time from DEB to endpoint was significantly longer in all three groups compared to the time from previous BA to DEB (Table 3). Figures 4. a-c show the Kaplan-Meier plots for the different groups. There is a clear difference in endpoint-free survival in the lower limb groups. In the AVF group the difference vanishes over time, and at 1 year the plots are similar. The 1-year freedom from primary endpoint with BA vs. DEB in the entire cohort was 19.5 % vs. 53.7 %, respectively. The corresponding figures at 2 years were 4.9 % and 12.2 %.

A.
Figure 4. The Kaplan-Meier plots for BA and DCB in native arteries (A), bypass vein grafts (B), and AVF (C). The outcome measures were TLR and loss of graft or AVF.
Table 3. Mean TLR-free survival in days

9.2. Study II

Two hundred and fifty-four patients were evaluated for eligible stenosis. One hundred and ninety-four patients were excluded, with the vast majority due to perianastomotic (<15 mm from anastomosis) stenosis. Other reasons included unavailable research personnel. The trial was discontinued due to slow recruitment at 60 patients.

Figure 5. CONSORT flow chart for study II
Eventually, 57 cases were ultimately included in the statistical analysis. Three randomized cases were excluded due to primary technical failure (graft rupture and bail-out stenting (N=2), aborted procedure (N=1)). Baseline homogeneity characteristics were comparable in both study groups. Technical details of the interventions, such as dilatation time and balloon size, were similar in both groups. Six patients died during follow-up, of which four were in the DCB group. There was one major amputation in the BA group. The overall TLR-rate at one year was 34.5 % and 46.4 % in the DCB and BA groups, respectively (P=.33). Relative risk for DCB was 0.81 (95% CI 0.40-1.63, P=.596). Five (8.8 %) grafts occluded during the follow-up, 1/29 (3.4 %) and 4/28 (14.3 %) in the DCB and BA groups respectively (P=0.36). There was a trend towards benefit from DCB: assisted primary patency was 93.1% (DCB) vs. 85.7% (BA) (P=.362) while secondary patency was 100 % in the DCB group compared to 89.3% in the BA group (P=.076). Figure 6 shows the Kaplan-Meier plot for secondary patency.

![Secondary patency after balloon dilatation of vein graft stenosis with DCB (solid line) or BA (dashed line)](image)

**Figure 6.** Secondary patency after balloon dilatation of vein graft stenosis with DCB (solid line) or BA (dashed line)

An *ad hoc* subanalysis was performed on previously untreated stenoses. The TLR-rate was significantly lower in these *de novo* lesions after DCB (15.0 % compared to 18.9 %, P=.03).
9.3. Study III

Thirty-nine patients were randomized. Baseline patient characteristics were comparable between the study groups. The CONSORT flow chart can be seen in figure 7.

![CONSORT diagram template](image)

**Figure 7. CONSORT flow chart for study III.**

The study was discontinued due to slow recruitment. In cases with duplicate lesions, only a single lesion (the most proximal with regard to endovascular approach) was included in the analysis. 3 patients were excluded after randomization due to technical failure, as the predilated lesion could not be crossed with the stiffer DCB-catheter. Thirty-six patients were eventually analyzed. Mean time of balloon inflation was 278 seconds in the DCB group and 274 seconds in the BA group (P=0.84). The mean balloon sizes were 4.9 mm (DCB) and 5.7 mm (BA) (P=0.07). 4/18 (22.2%) of the stenoses in the BA group reached an endpoint within one year, compared to 16/18 (88.9%) in
the DCB group (RR for DCB 7.09, 95% CI 0.10-6.73, P=0.001). Mean time-to-endpoint was 110 (95% CI 71-150) and 193 (95% CI 74-311) days in the DCB and BA groups, respectively (P=0.06). TLR-free survival and patient numbers can be seen in figure 8.

![Graph showing primary patency](image)

**Figure 8.** Primary patency after balloon dilatation of AVF stenosis with DCB (solid line) and BA (dashed line)

In a sensitivity analysis including the 3 patients excluded due to aborted intervention, the difference remained clearly significant regardless of the allocation of the excluded patients (P<0.001 for both scenarios). 18 of the primary endpoints were re-PTAs (3 BA, 15 DCB), 2 surgical repairs (1 BA, 1 DCB) and 1 AVF-occlusion (DCB).

Five patients died during follow-up, of which four were in the BA group. These four in the BA group died with an open AVF on average at 145 (100-180) days after the intervention, whereas the one in the DCB group died after re-revascularization at 240 days after the index intervention. Two patients from the BA group were lost to follow-up: One due to withdrawal of consent after
randomization, and the other for unknown reasons after re-revascularization. TLR-data from these cases could still be included in the analysis, although they did not attend follow-up appointments. Two patients (1 BA, 1 DCB) received a functioning kidney transplant within 1 year of inclusion. The AVFs of these patients were still included in the study, even if dialysis was ceased. In an ad hoc subanalysis, there was no difference between outcomes with regard to previous PTA (P=0.681).

9.4. Study IV

Eventually, 46 patients were randomized in the different centers. Baseline characteristics were well balanced between the study groups. Five patients were excluded due to immediate technical failure, i.e. unsuccessful recanalization. These were salvaged by distal and/or venous bypass, and were thus not eligible for intention-to-treat analysis. No deaths or major amputations were seen in either group during 12-month follow-up. One patient in the DES group died at 24 months from procedure due to unrelated disease. The number of patients lost to follow-up at 6, 12, and 24 months was 0 (0.0 %), 6 (14.2 %) and 11 (26.2 %), respectively.

Forty-one patients were analyzed. Six month primary patency was 82.6 % (DES) vs. 72.2 % (BSX) (P=.447) and secondary 91 % vs. 83 % (P=.450). 12-month secondary patency in the DES and BSX groups was 74 % compared to 80 % (P=.750). There were no statistically significant differences in primary, assisted primary, or secondary patency at 1, 6, 12, or 24 months (table 4, figure 9). ABI (median) increased from .54 to .93 in the DES-group and from .65 to 1.02 in the BSX-group immediately after the procedure, and there was no significant difference between the groups at the baseline or during the follow-up (table 5). Relative risk for stenting at 1 year was .96 (P=.893, any endpoint). In the DES-group, the median number of stents was 2 (range 1-4) with a median diameter of 6 mm.

In one case the attempted recanalization resulted in severe distal dissection and acute ischemia, which eventually could be salvaged with a distal bypass. We did not report the results for patients with technical failures, but no statistically significant difference was seen in a sensitivity analysis including these patients. Furthermore, one case in the DES group received a covered stent as a
bailout treatment after perforation and hemorrhage. This did not compromise patency, as the DES in question was patent at two years. 18.5% in the DES group were excluded due to failed recanalization. Technical success in the BSX group was 100%.

**Figure 9.** Secondary patency in percentages after drug-eluting stent (dashed line) or bypass revascularization (solid line)
<table>
<thead>
<tr>
<th></th>
<th>DES</th>
<th>BSX</th>
<th>P-value (log-rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 m</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary patency (%)</td>
<td>87.0</td>
<td>88.9</td>
<td>.872</td>
</tr>
<tr>
<td>Assisted primary patency (%)</td>
<td>87.0</td>
<td>88.9</td>
<td>.872</td>
</tr>
<tr>
<td>Secondary patency (%)</td>
<td>87.0</td>
<td>94.4</td>
<td>.454</td>
</tr>
<tr>
<td><strong>6 m</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary patency (%)</td>
<td>87.0</td>
<td>72.2</td>
<td>.447</td>
</tr>
<tr>
<td>Assisted primary patency (%)</td>
<td>91.3</td>
<td>77.8</td>
<td>.247</td>
</tr>
<tr>
<td>Secondary patency (%)</td>
<td>91.3</td>
<td>83.3</td>
<td>.450</td>
</tr>
<tr>
<td><strong>12 m</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary patency (%)</td>
<td>63.2</td>
<td>66.7</td>
<td>.931</td>
</tr>
<tr>
<td>Assisted primary patency (%)</td>
<td>68.4</td>
<td>73.3</td>
<td>.840</td>
</tr>
<tr>
<td>Secondary patency (%)</td>
<td>73.7</td>
<td>80.0</td>
<td>.750</td>
</tr>
<tr>
<td><strong>24 m</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary patency (%)</td>
<td>56.3</td>
<td>71.4</td>
<td>.830</td>
</tr>
</tbody>
</table>

**Table 4. Patency rates during follow-up**

<table>
<thead>
<tr>
<th>ABI</th>
<th>DES</th>
<th>BSX</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>range</td>
<td>mean</td>
</tr>
<tr>
<td>0 m</td>
<td>.93</td>
<td>.63-1.38</td>
<td>1.02</td>
</tr>
<tr>
<td>1 m</td>
<td>.99</td>
<td>.39-1.85</td>
<td>.94</td>
</tr>
<tr>
<td>6 m</td>
<td>.93</td>
<td>.59-2.00</td>
<td>.80</td>
</tr>
<tr>
<td>12 m</td>
<td>.86</td>
<td>.73-.98</td>
<td>.85</td>
</tr>
</tbody>
</table>

**Table 5. Postoperative ankle-brachial index during follow-up**
10. DISCUSSION

10.1. Limitations

The main limitation of the studies included in this thesis is the small sample sizes, which significantly hampers the statistical power as well as the clinical conclusions that can be drawn. For the randomized trials, power calculations were performed based on the literature available at trial design. This yielded sample sizes of N=140 (70+70) for studies II and III, and 490 for study IV. All trials had to be stopped significantly short of their respective goals. For trials II and III the main reason was slow recruitment due to very strict inclusion criteria; had perianastomotic lesions been included, the goals would probably have been reached in a reasonable time period. With study III, we also experienced logistical problems with the trial design, as patients from the dialysis unit were referred directly to the interventional radiologists, and inclusion to the study (which required involvement of the vascular clinic’s research staff) was too often omitted. For study IV, recruitment across the different centers was also extremely slow. The reason for this, however, was primarily a lack of clinical equipoise: few surgeons would want to randomize their patients with short SFA lesions to DES vs. prosthetic bypass in the first place, as other treatment options seemed more suitable and less risky in the clinical setting with mainly claudicants (venous bypass, plain BA, DCB). Usage of synthetic bypass material meant that patients with tissue loss had to be excluded automatically.

For study I, the main limitation is its unconventional design. We artificially created a control group of the same patients and the same lesions, which of course automatically meant that patients in the DCB group had n+1 interventions to the same lesion. This inevitably also led to the fact that some patients were on more potent antithrombotic medication at the time of the second intervention. The TLR-rate was also compared across the three groups, which has little clinical relevance, as the lesions in arteries, grafts, and AVFs are quite different both biologically and clinically. Subanalyses within the groups were naturally also performed.
10.2. Study I

Study I was a hypothesis generating pilot study. The somewhat unorthodox study design showed patency rates that are in line with the available literature: there seems to be sustained TLR-benefit from DCB in SFA-lesions (only 13% in this study were crural lesions), a less remarkable but still clear benefit in bypass vein grafts, and transient, if any, benefit in AVFs. This study should be seen as a pilot for the subsequent studies (II and III), and as a quality control of nearly 100 consecutive DCB treatments at our institution.

A systematic review of the small randomized and non-randomized studies published so far showed increased patency at 6 months after DCB, but this difference vanished at 12 months (Khawaja et al, 2016). The results in the AVF group of study I are quite well in line with these findings.

10.3. Study II

Biomechanical and anatomical properties of vein grafts differ greatly from native arteries, and less is known about the potential of drug-coated devices in this field. The results of this RCT are quite nicely in line with the mainly retrospective data that has been published earlier (Linni et al, 2016;): There is no statistically significant benefit from DCB in terms of patency or TLR, but there is a slight but consistent trend toward better patency rates and TLR-free survival in DCB group throughout follow-up. In previously untreated lesions there seems to be TLR benefit from DCB, although this is based on a subanalysis from an underpowered trial.

The indications for use of DCBs in peripheral graft restenosis are, as of yet, not firmly established even as maintenance interventions for bypass graft stenosis are relatively common. Most times the stenosis is asymptomatic, and caught by the graft surveillance protocol. The indication for PTA is graft maintenance, as occlusion often leads to loss of the vein graft, and the availability of good vein material for bypass is limited. Study I showed that there might be some benefit from DCB compared to BA in the treatment of graft stenosis. Study II does not provide conclusive evidence in favor of DCBs as a routine solution for vein graft stenoses. However, it suggests that when a lesion is treated for the first time, there may be benefit from using a DCB. The difference in
outcome rates between de novo stenosis and restenosis is interesting. Several factors may contribute to this result. By definition, stenoses treated with primary PTA include lesions caused by all underlying etiologies. On the contrary, recurrent stenosis may hypothetically more often be due to other reasons than IH. These can include technical errors in anastomoses, inadequate valvulectomy, an erroneously placed clip or ligature in a graft branch et cetera. These stenoses of course do not benefit from the use of drug-coated devices, which could explain the difference in outcome.

At our institution, the practice so far has been to use DCBs in grafts with a history of one or more balloon angioplasties. However, our results indicate that this practice may need to be revised: there seems to be no benefit from use of DCB in the recurrent lesions, but rather when the vein graft stenosis is treated for the first time.

One small, randomized trial did not demonstrate benefit from use of DCB over BA in bypass vein grafts (Kitrou et al, 2014). This study included synthetic grafts and anastomotic stenosis, and is thus not directly comparable to our design. Similar results were observed in a large Danish registry review comparing bare metal stents to drug-eluting stents in vein grafts in coronary bypass surgery (Hougaard et al, 2014). In a recent small retrospective analysis, 39 patients with failing autologous grafts were analyzed for primary, assisted primary, and secondary patency after DCB or BA (Jongsma et al, 2017). There was no difference between the groups, which is consistent with our results.

The primary reason for exclusion after assessment for eligibility was perianastomotic stenosis; inclusion of these would have yielded a much bigger sample size. However, this way the histology and pathogenesis of the included lesions are more homogenous, and confounding from surgical trauma to the graft at the anastomoses is minimized. As a consequence of the limited number of patients, there is a high probability of type II error in the results, ie. that there is a significant result even though the analysis does not show it (false negative). The main strength of the study is that it is to date the largest prospective RCT, with comprehensive follow-up with no cases lost to follow-up.
10.3. Study III

Compared to arterial stenoses, stenotic AVF-lesions are rarely calcified, and could more often be secondary to neointimal hyperplasia. We hypothesized that this study design would demonstrate clinical benefit from hyperplasia suppression by paclitaxel. On the contrary, our trial demonstrated harm from DCBs.

The retrospective studies on the use of DCBs in AVFs have generally showed promising results in favor of DCB, although the sample sizes have been limited (Patanè et al, 2014; Massmann et al, 2015; Cildag et al, 2016). The recent review by Khawaja showed short-lived patency benefit from DCB; the benefit had disappeared at one year (Khawaja et al, 2016). This review included 254 interventions in 162 patients. The material was considered clinically heterogeneous and clinically applicable conclusions could not be drawn.

One prospective randomized trial did show significant benefit from the use of DCBs over plain BA at six and twelve months (Katsanos et al, 2012; Kitrou et al, 2015). The trial by Kitrou showed one-year primary lesion patency of 5% (BA) vs. 35% (DCB). In our study the corresponding numbers were dramatically different: 75% and 10.5%, respectively. The mean baseline age of the fistulas in our trial was much shorter (6 months vs. 2.5 years). This is probably significant and may explain the differences in outcome. Furthermore, the Kitrou trial included 65% prosthetic AV-grafts, and is as such not directly comparable to our design.

The peripheral arterial trials usually show benefit from the DCB beginning at around 6-12 months after intervention, which is consistent with the biology behind intimal hyperplasia. In this trial, however, the negative slope of the survival plot for DCBs is quite steep from the very early stages of follow-up. The difference may thus not be caused by intimal hyperplasia, but rather that something damages the AVF immediately after the intervention in the DCB treatment group.

The potential toxic and inflammatory effect of paclitaxel on arterial walls has been studied in animal models, with inconclusive results and unpredictable outcomes (Radeleff et al, 2010; Kelsch et al, 2011). The results in our study strongly suggest that using drug-coated balloons in AVFs can even be harmful, at least in “young”, more immature AVFs created less than one year before the intervention. The exact reason for this remains unknown, but complex biological and hemodynamic circumstances probably play a role. The obvious hypothesis is that treating a
stenosis in a fairly young and immature AVF effectively means exposing a thin venous wall to paclitaxel. The thinner venous wall could be more susceptible to the local overdosage and potential toxic effects of paclitaxel. There is no published literature on potential paclitaxel toxicity in the peripheral venous wall. One small retrospective series suggested safety and efficacy in the treatment of central vein stenosis in dialysis patients (Hongsakul et al, 2018). No data has been published on the use of DAPT after endovascular treatment of AVF lesions, and hypothetically the intimal recovery can be slower after DCB, thus advocating a more aggressive postoperative antithrombotic regime. CKD affects the pharmacodynamics of ASA and clopidogrel, which further complicates interpretation and analysis. One randomized trial showed potential benefit from use of prolonged DAPT after coronary stenting (both drug-eluting and bare metal stents) in patients with CKD (Siddiqi et al, 2015).

This study is hampered by its small sample size and the slow rate of randomization. We aimed at a significantly higher number of patients. In retrospect, perianastomotic lesions should probably have been included, as the role of IH in these is at least as high as in more distal stenosis. However, even with this small number of patients the results are seemingly unambiguous, as the difference in outcome between the groups is so dramatic. Despite this, we cannot exclude the inherent risk for type I error (false positive). The power calculation was performed with the assumption that DCBs would lead to clinical benefit, and is rendered pointless by the diametrically opposite results. Indeed, using the relative risk from this trial for a power calculation, a trial would only need 8 events during follow-up to demonstrate the superiority of BA over DCB.

10.4. Study IV

This RCT did not demonstrate significant differences between femoropopliteal AK bypass with PTFE-prosthesis and endovascular recanalization and stenting with Zilver-PTX stenting. At 6 months, the primary and secondary patencies were slightly, but not significantly, higher in the stent group compared to bypass, but this difference disappeared over the next six months. At 12 months the respective rates were surprisingly similar: 63.2 % vs. 66.7 % and 74 % vs. 80 %. Indeed, at two years, the patency rate was better in the BSX group (56 % vs. 71 %, P=.397) but at this stage the number-at-risk is substantially lower than at the earlier follow-ups.
For the time being, open femoropopliteal BSX remains a first-hand option in many centers worldwide. Due to many surgeons’ preference so save the saphenous vein for possible future use for distal bypass, use of prosthetic grafts for AK bypasses remains popular. Use of a prosthetic conduit is also much faster than harvesting the GSV. The Zilver PTX DES is designed specifically for femoropopliteal locations. A prospective, randomized trial reported significantly better 24-month event-free survival among patient receiving a DES than among those treated with PTA alone (86.6% vs. 77.6%, P< .01). Primary patency at 24 months of the DES group was 74.8% vs. 32.4% for the PTA group. Patency rates at 5 years further favored the Zilver PTX (Dake et al, 2011, 2013, 2016). 14 The Zilver PTX trials have shown patency rates in the 80 %-range at 12 months, which are comparable to our results.

In 2009, the Scandinavian Thrupass study demonstrated a clear benefit in favor of bypass surgery vs. the Gore Thrupass endoluminal PTFE (Viabahn). This trial demonstrated an astonishing 95% 1-year patency in the bypass treatment group, whereas the corresponding number was only 48% for the thrupass group (Lepäntalo et al, 2009) . In 2007, Kedora demonstrated comparable 1-year outcomes between the Viabahn covered stent (CS) and prosthetic suprageniceral femoropopliteal bypass (Kedora et al, 2007). This study included 100 limbs in a prospective setting. In this study, 6 and 12-month patency rates were 82 % (BSX) vs. 81.8 % (CS) and 73.5 % vs. 74.2 %, respectively. It should be mentioned that this study also included TASC A lesions. In our study the patency rates were somewhat higher at 6 months and lower at 12 months, but still in comparable figures.

Quite a large group, 5 cases (5/27, 18.5 %), was excluded from the DES group due to failed recanalization, whereas the primary technical success rate in the BSX group was 100 %. Dake reported a 95% technical success rate in the Zilver PTX trial, in which patients were randomized before recanalization (Dake et al, 2011). The trial included 479 patients compared to 27 in the DES group in study IV so there is a high probability of a type I error in this comparison. This issue is significant, as patency results after primary bypass are remarkably better compared to secondary bypass after failed endovascular treatment (Meecham et al, 2018).

In this trial there was a significant difference between the groups in time from diagnosis to treatment. The time from CT or MR angiography to treatment was 60 days in the DES group and 125 days in the BSX group (P<.01). This is likely due to hospital logistics and the more rigorous medical work-up prior to bypass surgery. There was no evidence that this delay would have
resulted in clinical deterioration in the BSX patients prior to surgery, as the vast majority of patients presented with claudication and not CLTI, where time is of essence (Noronen et al, 2017).

Despite limitations, this work gives valuable information on the outcome after these two procedures and it seems that the DES is not inferior to prosthetic AK bypass in patients with SFA occlusion 25 cm or less. In the era of the ongoing BASIL 2 and BEST-CLI trials, this is to date the only prospective trial to date comparing DES with bypass surgery, and the results do indicate that drug-eluting stents are comparable to prosthetic grafts with regard to patency (Menard et al, 2016; Popplewell, et al, 2016). Another strength of the trial is comprehensive follow-up at 6 months, and acceptable follow-up rates up to 24 months. In anticipation of larger trials, the results from this trial loosely favor endovascular revascularization and use of DES for SFA lesions instead of an open synthetic bypass.

10.5. Future Horizons

The past decade has seen drug-coated and drug-eluting devices claiming their place in the treatment of peripheral arterial disease. Clinical practice is increasingly shifting towards balloon angioplasty combined with DCB or stent rather than BA alone. Many studies show clinical benefit particularly in femoropopliteal native artery lesions, with recent trials suggesting benefit several years postoperatively. Long-term results from the BASIL 2 and BEST-CLI trials will probably be available within the next five or so years, and hopefully there will be evidence to assist in customizing and optimizing treatment for patient groups as well as individual patients.

To target the inflammatory pathways of IH, balloon-delivered dexamethasone has been studied and found to be promising in the prevention of restenosis (Razavi et al, 2018). Prospective trials are needed to further explore this possibility.

Atherectomy devices for endovascular endarterectomy and debulking of the plaque have been available on the market since the mid 2000’s. Directional atherectomy (DA) seems to be a safe and effective treatment modality (McKinsey et al, 2014). A recent trial comparing DA vs. DA + DCB has been published, but no demonstrable gain from BA has been proven although initial technical success and bailout stenting rates were better in the BA + DCB group (Zeller et al, 2017). Vessel
preparation with DA or other means prior to DCB angioplasty is a field of intensive academic debate, even if no large prospective data is available to date.

The ongoing Lutonix AVF study will be interesting. In light of the previously published data, the results will probably suggest better TLR-free survival in favor of DCB even if no long-term benefit might be seen. The AVFs included in this study are likely to be mature and older compared to our group. Based on the results from Study IV in this thesis, it would be of extreme importance to further study the biological responses to paclitaxel in the venous wall and the young, immature AVF.
11. CONCLUSIONS

I. In our retrospective material, use of drug-coated balloons was clearly beneficial in native artery occlusions and stenoses as compared to plain balloon angioplasty. The gain was less clear in vein grafts, and vanishing in arteriovenous fistulas.

II. Angioplasty with DCB for bypass vein graft stenosis does not show statistically significant benefit in terms of patency or target lesion revascularization, although a trend is seen in favor of DCB. In de novo stenosis, the benefit was clearer.

III. Use of DCB may be harmful in the treatment of stenosis of the recently constructed AVF. More studies are needed on potential cytotoxic and thrombogenic aftermaths of paclitaxel in the venous endothelium.

IV. Endovascular recanalization and drug-eluting stents show similar patency rates compared to prosthetic bypass surgery in femoropopliteal occlusion with two-year follow-up.
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13. REFERENCES


(17) Carrel A, Guthrie CC. Uniterminal and Biterminal Venous Transplantations.; 1906.


(52) Gibson KD, Gillen DL, Caps MT, Kohler TR, Sherrard DJ, Stehman-Breen CO. Vascular access survival and incidence of revisions: a comparison of prosthetic grafts, simple autogenous fistulas,


