Published in final edited form as:

Tech Vasc Interv Radiol. 2016 June ; 19(2): 145–152. doi:10.1053/j.tvir.2016.04.007.

Techniques in Vascular and Interventional Radiology Drug Delivery Technologies in the Superficial Femoral Artery

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Abstract

Peripheral Arterial Disease (PAD) affects over 8 million people in the United States alone. While great strides have been made in reducing the burden of cardiovascular disease the prevalence of PAD is expected to rise as the global population ages. PAD characterized by narrowing of arterial blood can be asymptomatic or cause acute limb threatening claudication. It has been classically treated with bypass, but these techniques have been supplanted by endovascular therapy. Plain old Balloon Angioplasty (POBA) has been successful in helping revascularize lesions, but its effect has not been durable due to restenosis. This prompted the creation of several technologies aimed at reducing restenosis. These advances slowly improved outcomes and the durability of endovascular management. Amongst the main tools used in current endovascular practice are drug delivery devices aimed at inhibiting the inflammatory and proliferative pathways that lead to restenosis. This review will examine the current drug delivery technologies used in the SFA.

Keywords

SFA; PAD; Drug Coated Balloon; Drug Eluting Stent

Introduction

Atherosclerotic peripheral artery disease (PAD) affecting the lower extremities is a common condition associated with a great deal of morbidity and mortality. The prevalence of PAD rises rapidly after age 50 and is greater than 10 percent for patients in their 8th and 9th decades of life. [1] PAD is associated with many risk factors including the male gender, obesity, smoking, diabetes, hypertension, and increasing age. [2] Historically the treatment

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of PAD has been surgical bypass; however, this has been largely replaced by endovascular therapy due to its reduced morbidity and mortality. [3–5]

Since the first angioplasty by Dotter in 1964 and the first stent placement by Puel and Sigwart in 1986, there has been marked progress in the world of endovascular intervention aimed to treat symptomatic PAD. [6, 7] Plain old balloon angioplasty (POBA) has an initial benefit, but it does not account for vessel recoil, remodeling, and eventual restenosis. As a result, the stent was developed to prevent negative recoil and stabilize the vessel. However, it too did not prove to be a durable intervention. One of the major problems with stent placement was in stent restenosis (ISR), characterized by increased neointima leading to occlusion. This has led to the development of many devices aimed at reducing restenosis. As a whole, the technologies introduced to reduce restenosis have been generally successful. Compared to POBA with or without bare metal stents (BMS), drug coated balloons (DCB) with or without BMS placement has proven to reduce rates of restenosis and amputation across several trials. [8] Additionally, drug-eluting stents (DES) have shown to significantly reduce stenosis. [9]

Peripheral endovascular intervention and treatment of restenosis is especially complicated in the superficial femoral artery (SFA). [10] There are many factors to consider in the approach to SFA treatment including clinical severity, lesion composition, morphology, and patient co-morbidities among many others. Additionally, one must consider the biomechanical forces affecting the SFA as these have important implications on the therapeutic approach. Endoprosthesis in the SFA need to be able to accommodate these forces. Restenosis is of critical importance in the setting of SFA disease due to the nature of the disease. [11] Clinically patients are often largely asymptomatic or have limited symptoms until a critical level of stenosis occurs often threatening the limb. [12] Rundback and colleagues have devised an excellent framework for the therapeutic approach to femoro-popliteal disease. [13]

There have been many technologies introduced to combat restenosis in SFA intervention. In recent years, drug delivery technologies either via stent or via balloon have become the preferred method owing to better clinical outcomes. This review will focus on the mechanisms of restenosis and drug delivery technologies used to treat restenosis in the SFA.

Mechanisms of restenosis

Restenosis in the setting of SFA disease shares similar pathologies to those seen in other vascular beds including coronary artery disease and hemodialysis vascular access failure. It is characterized by elastic recoil, inflammation, hyperactive proliferation of smooth muscle cells, and negative remodeling. [14, 15] Recoil occurs due to stretching of the elastic laminae in the surrounding vascular tissue after dilation. This recoil occurs secondary to the overstretch injury over the course of a few minutes. Stenting has shown to reduce this recoil, but it does not counteract the other changes that take place during angioplasty and stent placement. [6] Several injuries occur during vascular intervention. First, there is endothelial denudation and stretch injury during angioplasty. Next, inflammation occurs with an increase in exposure of lipids and subintimal markers, such as fibronectin, Von Willebrand

Factors, among others, that aggregate platelets. [16, 17] If a stent is used, platelet aggregation and thrombus formation/remodeling are also seen acutely.

Smooth muscle cells, which are primarily resident in the media become activated due to cytokine release which can activate inflammatory and proliferative cytokines in the medial layer.[15, 18–20] This activation leads to collagen remodeling, cellular mitosis and migration. This also causes an increase in proliferation of vascular smooth muscle cells towards the neointima and activates fibroblasts in the adventitia. This process also attracts inflammatory cells and induces fibrosis with collagen matrix deposition. Along with these pathways, changes in shear stress and patient factors are likely to greatly impact restenosis. [14, 21–23] The inflammatory and proliferative states induced by vascular intervention are the target of many technologies aimed to reduce restenosis. [24][19]

Technologies used in devices to prevent restenosis

There have been several technologies used clinically to reduce in stent restenosis including brachytherapy, rotational atherectomy, covered stents, drug eluting stents (DES) and drug-coated balloons. Brachytherapy aimed at reducing cellular proliferation was shown to be less efficacious than paclitaxel and sirolimus eluting stents. [25, 26] However, in one-study differences between brachytherapy and sirolimus eluting stent were found to be non-significant 5 years out. [27] Rotational atherectomy (RA), a debulking technique, was also found be less efficacious than plain old balloon angioplasty (POBA) alone and in fact RA prior to DES placement had worse outcomes at 9 months compared to DES alone. [28, 29] Directional atherectomy devices have shown some promise, but are still subject to a higher risk of embolic effects and perforation. [30] Covered stents have shown some promise but can limit collateral vessels, have lower rates of primary patency, and are prone to edge stenosis. Newer devices coated with heparin and contoured edges have improved these outcomes, but more work is needed comparing these to current drug eluting technologies. [11, 31–33]

As a result of these trials, drug coated balloons and stents remain the preferred method of preventing restenosis. There are countless molecules and therapies aimed at reducing stenosis, which have been explored in pre-clinical work. However, this review will focus on the mainly used therapies and those in the pipeline in or close to human trials. The main drugs used in these technologies are paclitaxel and “-limus” type drugs.

Paclitaxel

Paclitaxel originally derived from the Pacific Yew, shifts the cell towards microtubule assembly.[34] This leads to aberrant tubule formation which prevent cell mitosis. [34, 35] Additionally, this prevents the activation of several protein kinases that are linked to depolymerization and reduce transcription factors such as $\text{Nf-}\kappa\text{B}$. These combined effects lead to reduced proliferation and migration. Paclitaxel was found to be a good therapeutic agent owing due to its lipophilic nature, which allowed easy passage into the cell. This property is enhanced when it is mixed it with contrast and creation of liposomes in cancer models. [36, 37] Additionally in early studies, it reduced smooth muscle cell proliferation

compared to other classic anti-proliferative drugs such as methotrexate and colchicine. [34, 38] Due to its size and hydrophobicity, paclitaxel distributes evenly but mostly remains in the subintimal layer as it binds microtubules. [39]

Of note, there are two forms of paclitaxel; crystalline and amorphous. Early devices used crystalline coating. In animal models comparing these two methods, both were found to deliver equal amounts during angioplasty, however the crystalline coating was found to have higher retained levels of paclitaxel with reduced neointimal formation, fibrin levels, and delayed healing. It is the most commonly used form. [40]

“-limus” type drugs

“-limus” type drugs are compounds closely related to sirolimus (rapamycin), a naturally occurring macrolide antibiotic with immune modulating properties [41–43]. It acts via several mechanisms in immune modulation and vascular smooth muscle cell (VSMC) proliferation. Sirolimus complexes with FKBP12, an FK506 binding protein and inhibits mTOR (mammalian target of rapamycin). mTOR is a kinase in the PI3K/AKT pathway and is also downstream in the proliferative TGF-Beta pathway. mTOR exists in two complexes mTORC1 and mTORC2, inhibition of mTORC1 is thought to limit the protein synthesis and cell cycle progression. mTORC2 is sirolimus insensitive and is thought to play a role in apoptosis and cytoskeleton modulation. In addition to its mTOR modulation, sirolimus induces P27 Kip1, a cyclin dependent kinase inhibitor that halts the cell cycle. A third way sirolimus is thought to inhibit VSMC proliferation is by inhibiting NF- κ B by binding to FKBP51, preventing anti-apoptotic genes, making it more sensitive to Tumor Necrosis Factor - α (TNF- α) induced apoptosis. It is important to note that TNF- α is highly expressed during both natural and iatrogenic vascular injury. [41–43] Additionally, unlike paclitaxel which binds tubules in all cells, sirolimus preferentially targets VSMCs due to its cellular receptor FKBP12 which is highly expressed in VSMCs. These properties also allow for more heterogeneous distribution throughout vessel wall, as sirolimus is not trapped in the endovascular surface.[39]

Concerning immune modulation rapamycin blocks IL-2 activation and the resulting T cell proliferation. It is important to note that there are differences between the “-limus” drugs for example, tacrolimus also binds to FKBP12, but then interacts with calcineurin which blocks the activation of nuclear factors of activated T lymphocytes (NFATs) and also blocks IL-2 but at the transcriptional level. These may have an impact given that inflammation can play a role in vascular injury response; also owing to tacrolimus' differing binding properties, it can actually stimulate smooth muscle cell production. Additionally, Tacrolimus does not bind as strongly to FKBP51 resulting in less TNF- α dependent apoptosis. It is these later two effects that likely explain the lack of efficacy in tacrolimus eluting stents in comparison to BMS. [41–43]

Other important “-limus” drugs include everolimus, which also inhibits mTOR, but has higher lipophilicity and thus requires a lower dose for therapeutic action. However, everolimus failed to show higher inhibition of VSMCs in diabetics compared to paclitaxel, despite being more efficacious pre clinically. This difference may have been due to the

apoptotic effect of paclitaxel. Zotarlimus another analogue also has increased lipophilicity, leading to a reduction in loading doses.

Interestingly both paclitaxel and “-limus” type drugs have been shown to cause changes in the vascular endothelium. These changes are thought to lead to lack of endothelialization and may affect late outcomes. [22] These effects may explain the pathological differences seen in ISR between different stents, drug eluting stents tend to have late ISR composed of mainly cellular matrix compared to classic ISR characterized by a high density of SMCs. [44] These differences may also explain the rare complications of very late stent thrombosis characterized by vasculitis and high fractions of eosinophilic cells. [45] There are still a great many unknowns regarding the healing response to drug eluting molecules that need to be addressed by future studies.

Dosing and Excipients

Dosing is dependent on both the drug used and the modality of delivery. The rationale of current dosing came from early coronary studies using DCB paclitaxel iopromide crimped on balloons which showed a good response with 3-ug/mm². [46] This dose was also used in THUNDER trial and Femoral Paclitaxel trial. Both studies proved the safety of iopromide-paclitaxel-coated balloon angioplasty in the femoropopliteal region and had fewer target lesion revascularization events than POBA up to five years out. [47–49]. Several animal studies have looked at ranges between 1-ug/mm² up to 9-ug/mm² utilizing different excipients and found good results with all doses, however the highest doses were associated with more thrombotic events. All of these doses transmit more than the inhibitory dose needed, to limit endothelial and smooth muscle cell proliferation and migration, into the vessel wall.[35] Additionally there is the impact of excipients, which will be discussed later. Similar studies were carried out for sirolimus, which found that stents coated with 185-μg were effective in reducing in stent stenosis, by 50%. [16, 50] These trials served as the basis for dosing; while devices differ, most devices are close to these concentrations and have shown great efficacy with few complications.

Beyond the dose and coating, the method in which drugs are delivered greatly affects their efficacy. This can be broken down into two parts; device (balloons or stents) and excipients. Drug excipients have a large impact on the amount of drug delivery through the arterial wall, embolization, and washout during insertion. This is in addition to the inherent differences present in the inhibitors themselves. [51–53] The major excipients used in the SFA are urea (IN.PACT Admiral DCB, Medtronic Inc., Santa Rosa, CA, USA) and polysorbate/sorbitol (LUTONIX® DCB, Bard Peripheral Vascular, Inc.) There are several other promising polymers, which modulate elution mainly in coronary applications, but there are no devices to date for use in the SFA.

Urea is a naturally occurring compound in the blood that allow for efficient transfer of drug into the vessel. Studies have shown a better response with urea vs early iopromide coating techniques, this is hypothesized to result from urea enhancing drug transfer. [54] However, the urea matrix is more prone to drug loss in the vasculature than other excipients. Studies have shown that 20–40% of the loaded paclitaxel loaded in urea and iopromide based

excipients is lost when balloons are shaken in an empty vial. 30% loss was also seen in animal models using urea-matrix coating. This is in contrast to the less than 0.1% loss when paclitaxel is loaded on polysorbate and sorbitol. This later compound was chosen after review over 200 possible excipients for its ability to allow for homogenous coating with limited loss, but still allowed for efficient transfer.[51] Animal studies have shown that paclitaxel doses of $2\mu\text{g}/\text{mm}^2$ - $4\mu\text{g}/\text{mm}^2$ are effective in reducing restenosis. However, the higher doses demonstrated longer durability and with few non-significant embolic muscle changes noted distally with polysorbate and sorbitol excipients. This suggests that higher doses may provide better therapeutic outcomes as long as embolic complications are limited with the use of coatings and excipients. Work directly comparing doses and formulations is lacking at this time. [51]

For drug eluting stents, the polymers used have implications in drug delivery but also in long-term effects. For example, the early stents using zotarlimus were hindered by late stenosis. [50] This led to the creation of a slower release excipient composed of three different polymers; a hydrophobic C10 polymer, a hydrophilic C19 polymer, and polyvinyl pyrrolidinone. These three combined polymers allow for elution of 85% of the drug within 60 days and the rest over a 6-month period. [55, 56]

The major polymers used in drug eluting stents can be broken down into two types; durable and bioabsorbable. [57] The durable polymers are thought to cause chronic inflammation, hypersensitivity, and lead to increased risk of late stenosis. This resulted in the development of bioabsorbable polymers that leave behind only a BMS after the drug is eluted. Studies have found that bioabsorbable polymers lead to better outcomes than durable polymers. However, two devices using durable polymers had lower rates of stent thrombosis at all-time points. These are the fluorinated polymer based cobalt-chromium everolimus-eluting stent (Xience V and Promus, Boston Scientific Marlborough, MA) and the platinum chromium everolimus-eluting stents (Promus Element, Boston Scientific Marlborough, MA) [57, 58] These exclusions are likely due to the lack of thrombogenicity in these polymers despite their lack of degradation. However, more work needs to be done in developing effective long term, non-reactive drug polymers and excipients for stents.

The major drug coated balloons in the SFA are the IN.PACT Admiral DCB (Medtronic Inc., Santa Rosa, CA, USA) and the LUTONIX® DCB (Bard Peripheral Vascular, Inc. Tempe, AZ, USA) The IN.PACT Admiral has $3.5\mu\text{g}/\text{mm}^2$ paclitaxel with a urea excipient. This device limits washout prior to inflation by keeping active drug within folds during the uninflated state. The LUTONIX® DCB has paclitaxel $2\mu\text{g}/\text{mm}^2$ paclitaxel and a polysorbate/sorbitol excipient. [59]

The drug eluting stents include the Zilver PTX, Dynalink, Sirolimus coated SMART, and the upcoming Eluvia DES. The Zilver PTX (Cook Medical, Bloomington, Indiana, USA) uses no coating, but encloses the stent in the sheath as to prevent pre delivery washout. This setup causes rapid paclitaxel delivery followed by rapid washout from the artery with 20% at 14 days and then rapidly falling off. Plasma levels of paclitaxel are $6.0\text{ng}/\text{ml} \pm 1.9$ at 20 minutes and are completely undetectable at 10 hours. [60] The Eluvia DES (Boston Scientific, Marlborough, MA, USA) is in clinical trials and is a nitinol stent that uses a very

slow release polymer to deliver paclitaxel. Dynalink E- Stent, is a dynalink nitinol self-expanding stent (Abbott Laboratories, Abbott Park, IL, USA) coated with everolimus at 225 $\mu\text{g}/\text{cm}^2$ with a ethylene vinyl alcohol copolymer (EVAL, Kuraray Co, Ltd, Tokyo, Japan). The polymer has been used in many medical applications and allows for 80% elution over 90 days. The sirolimus coated SMART (Shape Memory Alloy Recoverable Technology) stent, (Cordis, a Johnson and Johnson Company, Miami Lakes, FL, USA) is also a nitinol stent. It is loaded with 90- μg sirolimus/ cm^2 with a 5- to 10- μm copolymer matrix. This combination elutes the drug over seven days.

Adventitial targeting

The major tools used to prevent stenosis today rely on endothelial drug delivery; however, there is also the possibility of adventitial delivery. This would target the fibroblast migration towards the intima as well as diffuse into the more interior layers. The benefits of perivascular drug delivery are the less invasive nature of the procedure leading to less endothelial denudation, stretch trauma and likely less systemic drug effects. Additionally this approach would lack complications such as migration, fracture, embolic effects, etc. Several animal studies have looked at perivascular delivery of a variety of compounds, cells, particles in many methods, nanospheres, gels, scaffolds, sponges, viral particles etc. [61, 62] There are few in human trials looking a stem cells, gene therapy. Percutaneous delivery of allogeneic endothelial cells has shown promise in a small safety study of 21 patients applied at the SFA after angioplasty and stenting. [63, 64] In another safety study, twenty patients received adventitial delivery of dexamethasone endovascularly through a microcatheter and microneedle system. Both of these studies showed promising results during short-term follow up periods. [65] These studies demonstrate technical feasibility and suggest that adventitial delivery is a promising therapeutic modality.

Emerging technologies: Stent materials

One of the other areas of advancement is in stent material. [66] Stent material has evolved over time from stainless steel to better alloys using cobalt, platinum, nickel, and titanium among others. While nitinol and other modern stent materials are useful in treating occlusions due to their structural properties, [67, 68] any durable stent is prone to several possible complications, since it is a permanent foreign body. One of the newer materials being explored are polymers such as poly-L-lactic acid (PLLA), polyglycolic acid, polycaprolactone and copolymers. [69] There have also been many animal studies looking at bland and drug eluting biodegradable stents with good results. [70] There have been a handful of small human trials using good safety results and promising patency. [71]

One important note of consideration is that histological samples showed an inflammatory response to the scaffold itself in some cases. [72] However, the drug-loaded scaffolds appear to overcome this response. [71]

In addition to polymers, iron and magnesium alloys have been considered as alternative dissolvable stent materials. These elements are naturally occurring in the body. Additionally varying concentrations of Mg^{2+} ions have been shown to alter the expression of several

genes implicated in the pathogenesis of ISR with in VSMCs. These modulatory effects could be used to develop a dissolvable stents that limit proliferation as they are resorbed. [73] Many alloys using both iron and magnesium have been used in animal studies. However, more work is needed in the development and analysis of alloys. [66, 74] As a whole, these new technologies have yet to be used in large-scale clinical trials. However, given unique challenges of the SFA, biodegradable stents seem to be a promising solution to ISR.

Conclusion

Stenosis in the SFA is a challenging area for interventionalists. While there are many options available, the unique nature of the SFA complicates the durability of these interventions. However, there has been much progress in the treatment of PAD in the SFA. Devices have evolved in many ways prolonging primary patency and improving clinical outcomes. The drugs used have been optimized with the use of excipients and polymers to enhance their efficacy while reducing complications. Stent materials have improved and in the future will likely serve to provide temporary structural support and drug elution. Even more promising than these advancements are the technologies still in the pipeline both in animal and early human trials.

Although, novel materials and new drug delivery platforms are constantly being developed. There are still a great number of unknown factors that play into restenosis both in the SFA and in other areas of intervention. Basic science has enabled many of the advancements seen today and will continue to do so. Future studies should also focus on the differences in efficacy and usability of the devices in the SFA to help guide patient management.

Acknowledgments

Disclosures: AB has received a Medical Student grant from Radiological Society of North America Research and Education Foundation Research Medical Student Grant #RMS1510 Dr. Misra work been funded by the National Heart, Lung, And Blood Institute (HL098967).

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Figure 1.
At time of drug delivery via DCB, drug diffuses into the “endoluminal surface reservoir”
From here the drug diffuses into deeper vascular tissues overtime inhibiting restenosis.
Courtesy of Dr. Michael Dake

Figure 2.
Molecular mechanisms of drug actions.

Table 1

Summarizes major characteristics between drugs, excipients, and polymers used in SFA devices.

Drug	Characteristics	SFA Devices
Paclitaxel	<ul style="list-style-type: none"> • Inhibits Microtubule disassembly preventing cytoskeletal restructuring and spindle formation. • Prevents Cell Cycle advancement • Prevents Migration • Targets all Cells • Lipophilic 	<ul style="list-style-type: none"> • IN.PACT Admiral • LUTONIX DCB • Zilver PTX DES • Eluvia DES
-limus type drugs	<ul style="list-style-type: none"> • Acts via binding of FKP51 and FKBP12. This along with other actions act on NF-κB, Mtor and the P27/KIP1 pathways to inhibit cell cycle advancement and protein production. • Targets VSCMs • Inhibits proliferation • Promotes Apoptosis • Reduces Inflammation • Varying Lipophilicity 	<ul style="list-style-type: none"> • Dynalink E-Stent • SMART Stent

Excipient	Characteristics	SFA Devices
Urea	<ul style="list-style-type: none"> • High wash out prior to delivery • Rapid Delivery effective Transfer • No Inflammatory response. 	<ul style="list-style-type: none"> • IN.PACT Admiral
Polysorbitol/ Sorbate	<ul style="list-style-type: none"> • Limited washout prior to delivery • Rapid Delivery Effective transfer • No Inflammatory response. 	<ul style="list-style-type: none"> • LUTONIX DCB

Polymer	Characteristics	SFA Devices
No Polymer	<ul style="list-style-type: none"> • Risk for washout • Rapid Delivery 	<ul style="list-style-type: none"> • Zilver PTX DES
Ethylene vinyl alcohol copolymer	<ul style="list-style-type: none"> • Dissolving Polymer allows for long-term elution 90 days. 	<ul style="list-style-type: none"> • Dynalink E-Stent
Co-Polymer Matrix	<ul style="list-style-type: none"> • Polymer allows for extended elution 7 days. 	<ul style="list-style-type: none"> • SMART Stent

* Information on Eluvia was not included.