



EXCIMER LASER IN PERIPHERAL ARTERY DISEASE

Evidence Review

Excimer Laser Atherectomy in Peripheral Artery Disease

A Comprehensive Review of Evidence

Introduction

Although balloon and stent technologies have rapidly evolved over the last 10 years, some lesions remain difficult to treat with traditional PTA techniques. The advent of the Excimer laser has allowed patients to be treated in a minimally invasive way whilst ablating atherosclerotic tissue that obstructs the blood flow to the lower limbs.

LASER is an acronym for Light Amplification by Stimulated Emission of Radiation. The concept of the Excimer laser is to generate light energy of 308nm in wavelength. This wavelength has particular characteristics whereby it ablates only the tissue it touches, altering or dissolving the plaque without damaging the surrounding tissues.

Medical devices concerned

The CVX-300[®] excimer laser platform coupled with excimer laser catheters is indicated for use in several applications within the minimally invasive interventional cardiovascular market.



The Turbo Elite[™] catheter is designed for peripheral atherectomy. The Turbo-Elite[™] laser atherectomy catheter is indicated for the treatment of peripheral arterial disease (PAD) located in the legs.

By working at the molecular level, Turbo-Elite is capable of powering through challenging infrainguinal stenoses and occlusions, providing the precision and control required to preserve vessels and save limbs.



The Turbo-Tandem[™] laser guide catheter with incorporated laser atherectomy catheter was designed to create larger lumen. It is indicated for atherectomy of native infrainguinal arteries and for the treatment of fempop artery in-stent restenosis in bare metal stents with adjunctive percutaneous transluminal angioplasty (PTA).

The objective of this document is to provide a summary of the current evidence on the Excimer laser for:

1. **Critical Limb Ischemia (CLI)**
2. **In-Stent-Restenosis (ISR)**
3. **Non-crossable Chronic Total Occlusions (CTO)**

Critical Limb Ischemia (CLI)

Critical Limb Ischemia (CLI) is associated with multilevel atherosclerotic disease dominated by long, total occlusions and a large thrombus burden.¹ Because of the severity of their disease, a large percentage of patients may be poor surgical candidates.² Additionally, only 20% to 30% of patients with tibial disease have an anatomy favorable to traditional PTA, requiring alternative tools for revascularization.³ In the UK, approximately 5-6,000 major limb amputations are carried out every year. The most common reason for amputation is a loss of blood supply to the affected limb (CLI), which accounts for 70% of lower limb amputations.⁴ In a study published by Jordan et al. the average length of acute inpatient stay was 63 days with a 30-day mortality rate of 15.3% and inpatient mortality of 29.3%.⁵

The following three studies have investigated the use of the Excimer Laser in the treatment of Critical Limb Ischemia.

Laird et al. evaluated the effectiveness of Excimer laser-assisted angioplasty for CLI patients who were poor candidates for surgical revascularization.⁶ They conducted a prospective multicenter registry with 6 months follow up in 14 sites across the US and Germany. 145 patients were enrolled with 155 critically ischemic limbs of Rutherford Class 4, 5 and 6. 71% of patients had some type of lower extremity tissue loss. The treatment included laser atherectomy followed by PTA and optional stenting (45%).

The results of this study showed a 93% limb salvage rate at 6 months with a 86% procedural success, which was measured as <50% residual stenosis in all treated limbs.

Bosiers et al. conducted a similar study.⁷ Their aim was to provide safety and efficacy evidence of the LACI (Laser-Assisted Atherectomy for the Treatment of Critical Limb Ischemia) treatment strategy and methodology as specifically practiced in Belgium. They prospectively enrolled 48 consecutive patients in 5 centers in Belgium. Patients were diagnosed with CLI of Rutherford 4, 5 and 6 and were poor surgical candidates. They achieved 85% procedural success measured as <50% residual stenosis and a 90.5% limb salvage rate at 6 months.

Allie et al. conducted a retrospective study to confirm safety and efficacy of Excimer Laser atherectomy therapy in the treatment of severe infrapopliteal disease and CLI.⁸ They analyzed 62 patients with CLI of Rutherford class 5 and 6. Similarly to the previous 2 studies, they achieved 91.8% limb salvage rate at 6 months and 83.3% at 12 months with a procedural success over 95%.

All three studies conclude that Excimer laser-assisted angioplasty for CLI offers high technical success (>85%) and high limb salvage rates (>90%) in patients who are poor candidates for traditional surgical revascularization.

In-Stent Restenosis (ISR)

"The more liberal use of endovascular treatment for peripheral artery occlusive disease is aligned with an over-whelming and still unresolved problem of restenosis. It is a matter of debate whether stent-supported angioplasty has any positive impact on technical and clinical outcomes. Particularly in longer femoropopliteal artery lesions, restenosis is high and exceeds 50% after plain balloon angioplasty alone. Improved outcomes were reported after stent-supported angioplasty with newer-generation nitinol stents".⁹ However, due to its difficult to treat morphology, In-stent Restenosis (neointimal hyperplasia) remains an unresolved major challenge of endovascular therapy.

Neointimal hyperplasia has the characteristics to rehydrate and recoil very quickly. The three mechanisms of action of the laser make it uniquely suitable for the treatment of neointimal hyperplasia. Due to the fact it is not mechanically macerating morphology, but vaporizing only the tissue in contact, the laser is capable of removing the plaque in a safe manner and minimizing thromboembolic effects. These thromboembolic effects are one of the risks when treating an ISR lesion due to the soft fragile structure of the plaque. Removing the major portion of the plaque with the laser and modifying the remaining small portion, allows for balloon deployment with lower pressure. This may cause less arterial wall damage, and thus delays rehydration and recoiling of the initial disease. The laser is safe to use in ISR because it does not disturb the underlying stent¹⁰ and can be safely used even without a guidewire due to the fact it cannot exit the stent struts.

Recent studies confirmed that the use of Excimer laser atherectomy with adjunctive balloon angioplasty results in significantly better acute and midterm efficacy and safety outcomes for treatment of peripheral femoropopliteal Intra Stent Restenosis compared to conventional PTA alone.

Schmidt et al. evaluated the safety and performance of the Spectranetics Excimer laser atherectomy for the treatment of femoropopliteal

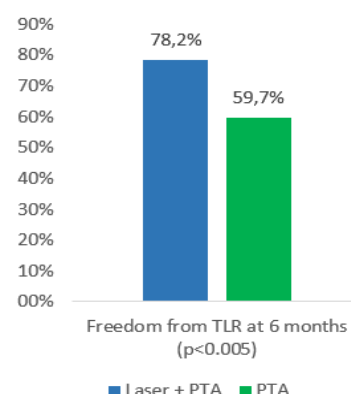
artery in-stent restenosis. They conducted a prospective multi-center registry with 6 months and 12 months follow up in 5 sites across Germany. In the 90 patients enrolled, 84 lesions were isolated SFA, isolated popliteal and 2 SFA-popliteal. These lesions were Rutherford class 2-5. 34.1% of treated lesions were totally occluded.¹¹

The study shows that per cent diameter stenosis was reduced from 87.1% to 7.4% after laser atherectomy and balloon angioplasty, as measured by the angiographic core lab. The cumulative major event rate was 2.2% through 30 day post-procedure. Procedural success rate was 96.7%. And a freedom from TLR rate at 6 and 12 months of 87.8% and 64.4%, by Kaplan Meier analysis. The primary Patency at 6 and 12 months is 64.4% and 37.8% (DUS $\geq$ 2.5 PSV). At 12 months patients saw significant and sustained improvement in ankle-brachial index and walking ability. Laser atherectomy in ISR lesions also preserved excellent stent integrity throughout the duration of the study.

In the EXCITE ISR trial, Dippel et al. evaluated the safety and efficacy of excimer laser atherectomy (ELA) with adjunctive percutaneous transluminal angioplasty (PTA) versus PTA alone for treating patients with chronic peripheral artery disease with femoropopliteal bare nitinol in-stent restenosis (ISR).¹²

This prospective multicenter randomized controlled study was conducted across 40 centers and enrolled 250 patients, randomly divided into ELA + PTA and PTA groups by a 2:1 ratio. The mean lesion length was 19.6 cm versus 19.3 cm, and 30.5% versus 36.8% of patients exhibited total occlusion.

With a Freedom of TLR rate at 6 months of 78.2%, the ELA + PTA group demonstrated superiority versus PTA alone group (59.7%).

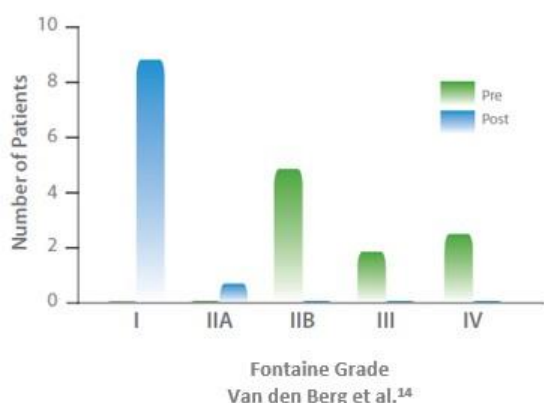


Also, ELA + PTA subjects demonstrated superior procedural success with significantly fewer procedural complications.¹³ The results of the EXCITE randomized controlled ISR trial warranted laser atherectomy to be the only FDA approved technology (Laser technology includes Turbo Power™ & Turbo Tandem™) for ISR.

Current evidence shows promising results for laser atherectomy combined with Drug coated balloon as a treatment of In-Stent Restenosis.

Van den Berg et al. evaluated the use of Excimer laser angioplasty and drug eluting balloon in a single centre cohort registry.¹⁴ In total they enrolled 10 patients and all patients had previously undergone balloon angioplasty and stent placement. All procedures were technically successful. No residual stenosis was seen angiographically and patients were followed up in a range of 2-20 months.

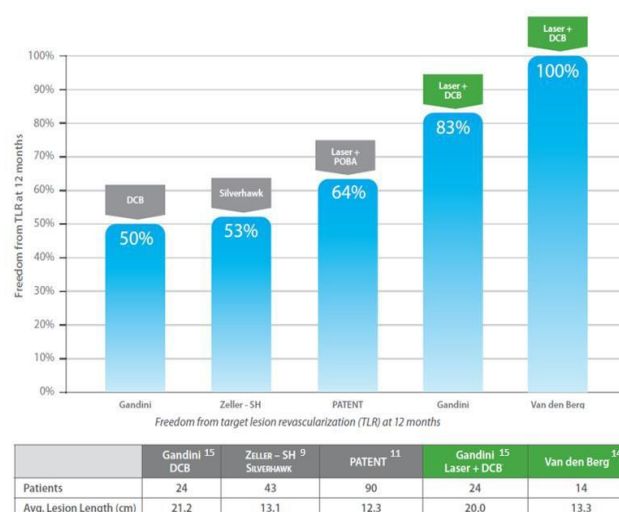
The clinical stage improved in all patients. The patients that were followed up by angiography and/or Duplex did not demonstrate any signs of neo-intimal hyperplasia.



Gandini et al. conducted a prospective randomized study to compare the efficacy and safety of laser debulking and drug coated balloon (DCB) angioplasty to treatment with DCB angioplasty alone. The examined patient population were all affected by Critical Limb Ischemia and superficial femoral artery (SFA) stent occlusion.¹⁵ They enrolled 48 patients in total, randomized 1:1. Their results show patency rates at 6 months and 12 months of 91.7% and 66.7% for the laser + DCB group versus 58.3% and 37.5% for the DCB alone group.

The TLR at 12 months is for the combination of laser with DCB 17% versus 50% for the DCB alone group. Major amputation rate in the group treated with laser and DCB is also lower than in the group DCB alone with 8% versus 48%. They conclude that the combination of laser and DCB has favorable outcomes when compared to DCB alone.

All these studies show initial promising results for the combination use of Excimer laser and DCB. The freedom from TLR at 12 months of >83% in the Laser+DCB treatments compared to 50% for DCB alone suggest significant improvement.



Non-crossable Chronic Total Occlusions (CTO)

To treat a lesion with a balloon or stent, a wire needs to be crossed through the lesion. CTO's often have a so-called "proximal cap" which due to its tough structure can prevent a guidewire or any device from crossing the lesion. This makes a CTO a challenging lesion to treat. If a lesion cannot be crossed with a guidewire, there are not so many options left to treat. One option is to pass the lesion via the subintimal space and to re-enter the true lumen after the occlusion. However, this treatment option is often a complicated procedure and results shows higher In-stent Restenosis rates compared to staying in the true lumen.¹⁶

This could be due to a dissection in the wall to allow subintimal passage. Arterial wall damage initiates elastic recoil for which the patient has to be treated again after a period. Another difficulty in subintimal treatment could be re-entering the true lumen, especially in diffuse disease, when the “distal landing zone” (re-entry point to the true lumen) is very difficult to define due to the severe diffuse disease or calcium.

Also distal embolization is one of the risk factors which occurs in 5-8% of the cases during subintimal angioplasty.¹⁷

The laser has the unique capability of passing a total occlusion by means of the unique “step-by-step” method. The guidewire is brought into the origin of the lesion until no further progress can be made. The laser catheter is then advanced until the origin of the lesion and laser ablation is delivered. Due to its mechanisms of action, the laser is able to advance without wire guidance by ablating and modifying the plaque burden. Because of the photo ablative process the laser does not only debulk but also modifies the molecular structure of the lesion, allowing the wire to cross the lesion after this modification. For further recanalization, the laser catheter and the wire are sequentially advanced “step-by-step” until the end of the lesion is reached. The laser is capable of treating even very long totally occluded lesions without disturbing the surrounding tissues. Also it minimizes the distal embolization due to its vaporizing aspects. *“This technique helps to maintain an intraluminal guidewire position, thereby reducing the potential for clinically relevant dissections and the number of stents required to repair them.”*¹⁸ By modifying the molecular structure of moderately calcified lesions and debulking the major portion, the laser allows the guidewire and or balloon to pass lesions which were not crossable before. Following this, the stent and or balloon can be deployed with a low pressure causing less arterial wall damage and reducing the risk of balloon failures and under deployed stents.

The following studies investigated the use of the laser in chronic total occlusions:

H.J. Steinkamp, M. Werk, M. Haufe and R. Felix conducted a prospective single center trial.¹⁹ This trial was done to demonstrate the effectiveness of the laser angioplasty after unsuccessful recanalization of the superficial femoral artery (SFA) with conventional interventional techniques. It is a prospective single center trial with 94 patients. All these patients presented with an occlusion of the SFA and underwent unsuccessful recanalization with conventional PTA prior to this study. The average occlusion length of the SFA was 17.5 cm. The primary attempt was performed with Terumo wires (different kinds) as well as different catheters. After failing to cross with wires or catheters, the laser was used (performing step-by-step technique). The application of laser angioplasty demonstrated a successful recanalization of the SFA in 80.9% (76/94 patients). Primary-assisted and secondary patency rates were 50.0%, 65.8% and 73.7%, respectively at 12 months follow up. In 4 cases complications occurred, however, in only 1 case this was related to the laser.

C. Wissgott, P. Kamusella, C. Lüttke and R. Andresen conducted a similar study.²⁰ They examined the application of Excimer laser atherectomy (ELA) in 40 patients with refractory occlusions in femoro-popliteal arteries, where the initial conventional PTA recanalization attempts, were unsuccessful. The mean lesion length was 17.5 cm and the initial recanalization was performed with stiff Terumo guidewires supported by various catheters. After an unsuccessful attempt to cross the lesion with a wire, an Excimer laser catheter was used to perform the step-by-step technique. After successfully crossing the lesion with a wire, balloon dilatation was performed in all cases; in 10% (4/40) of cases additional stenting was required.

This study showed an initial technical success rate of 90% (36/40) which resulted in a primary, primary-assisted and secondary patency rate at 12 months follow up of 58.9%, 67.8% and 83.2%. The complication rate of 5% proves to be low relative to the difficulty of the intervention in otherwise refractory occlusions.

The primary and secondary patency rate of ELA compared to the results of PTFE-grafts shows that ELA is a very good alternative for patients with severe comorbidities and poor surgical candidacy, particularly CLI patients. According to these results, ELA recanalization provides a low stent rate alternative to surgical procedures for refractory occlusions.

This can offer patients with increased operative risks, a promising and low-risk therapeutic procedure.

Scheinert et al. reported the results of 318 patients treated with Excimer laser assisted recanalization.^{21,22} In total they treated 411 chronic SFA occlusions with a mean lesion length of 19.4±6 cm. The success rate was 90.5% and it showed a low stenting rate of 7.3%.

The LACI-Refractory Total Occlusion (RTO) analysis, evaluated a subset of patients from the LACI 2 trial, the LACI CIS series and the LACI Belgium trial. They selected the patients with chronic refractory total occlusions to guidewire recanalization. In total 46 patients (47 limbs) underwent laser treatment with the step-by-step technique to cross the occlusion prior to the guidewire. With an average of 4.4 lesions treated per limb, the total of treated lesions with the step-by-step method was 205. The average lesion length was 73.4±7.3mm. Location of the lesions varied from SFA to infrapopliteal (67% SFA, 11% popliteal, 20% infrapopliteal). Procedural success was achieved in 72%, straight-line flow to the foot was established in 79% of the limbs. In 95% of the surviving patients they achieved limb salvage.

One should be aware that this limb salvage rate was achieved in a population that would likely

have underwent amputation as they were poor surgical candidates and could not have undergone balloon angioplasty.

All the above studies conclude that severe occlusions of the femoropopliteal arteries, that are refractory to conventional PTA crossing techniques, can successfully be recanalized in 80-90% of the cases with Excimer laser.

Conclusions

The evidence above shows that the use of laser has beneficial results in the treatment of CLI, ISR and CTO.

For those patients who suffer from CLI who would likely have been abandoned for amputation due to their poor candidacy for surgery, treatment with the laser is a good method to avoid amputation. With the technical success rate of >85% and a limb salvage rate of >90% the laser proves to be effective in even the most severe cases.

Stenting and balloon angioplasty is aligned with restenosis (for POBA it exceeds 50%) and is still an unresolved problem. Laser atherectomy is the only FDA approved technology (Laser technology includes Turbo Power™ & Turbo Tandem™) for ISR. Moreover, the study results propose that the use of laser in combination with DCB has significant better results than DCB alone. The unique capabilities of the Excimer laser to cross lesions without a wire, allow for successful recanalization in >80% of otherwise refractory to conventional PTA lesions. Moreover, with the step-by-step technique it is possible to stay intraluminal when passing a CTO. Intraluminal recanalization has proven lower restenosis rates in comparison to subintimal recanalization.

Not all lasers are the same. Only the photoablative process associated with the Excimer laser produces a safe and effective endovascular vaporization of complex morphologies including obstructive atherosclerotic and/or thrombotic material.

Cost Benefits

Sherif Sultan et al. conducted a single center trial to compare the outcome of CELA (Cool Excimer Laser Angioplasty) versus tibial balloon angioplasty (TBA) in occlusive tibial lesions in patients with CLI, TASC II D lesions²³. They conclude that CELA has enhanced immediate clinical improvement, sustained clinical improvement, amputation-free survival and freedom from target extremity revascularization and that it provides an improved Q-TWiST in a COST-EFFECTIVE manner.

They evaluated the costs involved and showed that the mean total cost and cost per QALY were reduced with CELA compared to TBA, with ICER of €2073.19 per QALY gained in favor of CELA.

Improved Quality time for the Patient

Sultan et al. also evaluated in the same trial²² the Q-TWiST (Quality Time Spent Without Symptoms of Disease or Toxicity of Treatment). They conclude that the patients treated with CELA had a significant improved Q-TWiST at 3 years (10.5 months versus 7.17 months in TBA group, P=.048).

	TBA	CELA	P Value
Tox	0.17 months	0.16 months	.327
TWiST	5.36 months	9.5 months	.062
Prog	2.91 months	1.8 months	.071

Tox = Time spent with toxicity of treatment

TWiST = Time Spent Without Symptoms of Disease or Toxicity of Treatment
Prog = Time spent with secondary intervention

Q-TWiST = Quality Time Spent Without Symptoms of Disease or Toxicity of Treatment

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Important Safety Information

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