Turbo Power Laser Atherectomy Combined with Drug Coated Balloon Angioplasty for the Treatment of Femoropopliteal De Novo/ Restenotic and In-Stent Restenosis Lesions

Study Protocol
V2.0

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FUNDING: Investigator-Initiated Study Grant from Spectranetics

Protocol Summary:

Title:	Turbo Power Laser Atherectomy Combined with Drug Coated Balloon Angioplasty for the Treatment of Femoropopliteal De Novo/ Restenotic and In-Stent Restenosis Lesions
Study Objectives:	To determine outcomes of combined Turbo Power laser atherectomy + drug coated balloon (DCB) angioplasty for the treatment of femoropopliteal de novo/restenotic lesions and in-stent restenosis (ISR). Better understanding of these outcomes will help guide optimal treatment algorithms for this difficult to treat cohort of patients.
Primary Endpoint:	Rate of freedom from target lesion revascularization (TLR) at one year
Secondary Endpoints:	• Procedural success (≤30% residual stenosis) • Procedural safety (freedom from significant embolization (sequelae), or dissection) • Freedom from major amputation at 30d, 6mo & 12mo • Freedom from death at 30d, 6mo & 12mo • Freedom from TLR 6 months • Patency at 12 months (up to 20 patients)
Study Population:	The intended population will consist of all patients undergoing endovascular treatment of femoropopliteal de novo/restenotic lesions and in-stent restenosis with Turbo Power + DCB treatment.
Design:	This is a retrospective, single-site, non-randomized study.
Sample Size:	Up to 120 patients will be enrolled at Cardiovascular Institute of the South
Treatment	De novo, restenotic or in-stent restenosis lesions treated with Turbo Power Laser atherectomy + Drug-coated balloon angioplasty
Inclusion criteria:	All patients from Cardiovascular Institute of the South who were treated for femoropopliteal de novo/restenotic lesions or in-stent restenosis using Turbo Power laser atherectomy plus drug coated balloon angioplasty between 2016-2017.
Exclusion criteria:	Any incomplete data on procedural approach and treatment.
Duration:	Review of patient data and inclusion into the study is expected to take up to 6 months. Patient data will be included through 12 months post-procedure.
Study start:	Upon receipt of all appropriate approvals and a fully executed contract with the site prior to that site enrolling.

1. BACKGROUND INFORMATION

Peripheral artery disease (PAD) is a condition where arteries become narrowed due to plaque and thrombus buildup and this reduces blood flow to the limbs. Millions of Americans are affected by PAD and many more may be asymptomatic. Individuals with PAD have an increased risk for heart disease, aortic aneurysms, stroke and an increased mortality. Due to the prevalence of PAD in society, research is ongoing to help treat this disease. [1, 2]

Percutaneous transluminal angioplasty (PTA) has been one of the most widely used methods of treating PAD; however, it is well know that complications and patency rates are disappointing. Many studies have suggested combining PTA with a debulking therapy could provide better results so there is less tissue compressed. There are many atherectomy devices on the market, but to our knowledge, there is a need to determine the optimal algorithm to best treat PAD.[3]

Excimer laser ablation (ELA) has been performed since 1994 when the first devices received CE mark. There are many devices that modify or remove obstructions in the arteries, but the Excimer laser is unique as it ablates or vaporizes tissue at the catheter tip. The catheter contains optical fibers that transmit pulses of ultraviolet light at 308nm that break down blockages at the molecular level. The laser catheters ablate lesions consisting of plaque, thrombus, neointimal hyperplasia, and calcium.

The Laser Angioplasty for Critical Ischemia (LACI) Registry used excimer laser catheters ranging from 0.9 to 2.5 mm to debulk infrainguinal arteries followed by balloon angioplasty and optional stenting. From visual assessment, baseline lesion stenosis was 92% ± 12% and after laser use, this decreased to 55% ±24% ($p<0.001$). 88% of lesions were located in the femoropopliteal arteries[4].

The CELLO Registry used excimer laser catheters to enlarge the lumen of the superficial femoral artery or proximal popliteal. A 2.0mm Turbo-Elite laser catheter was used to create a pilot channel and the Turbo Booster laser catheter was utilized to increase the lumen diameter. The primary effectiveness endpoint for this study was a decrease of 20% or greater after all laser by core lab assessment. During the study the diameter stenosis was reduced from 77% ± 15% at baseline to 34.7% ± 17.8% post all laser[5].

The EXCITE Study used Turbo-Elite catheters to create a 2.0 mm pilot channel for Turbo Tandem in femoropopliteal in-stent restenosis (ISR) lesions. Operators could use the Turbo-Elite for multiple passes and enlarging the lumen, but Turbo Tandem was the device used to conduct maximal debulking. This study was randomized to compare ELA + PTA to PTA only with the final mean diameter stenosis by visual assessment at 11.5% vs 18.1% respectively ($p=0.004$)[6]. The protocol was amended during the study to collect visual assessment data post Turbo-Elite. In 94 patients, Turbo-Elite effectively reduced baseline stenosis from 88.3% ± 12.2% to 49.2% ± 24.8% with an average mean reduction of 39.1% ± 24.1%. In a post hoc core lab analysis, the baseline stenosis of 84.8% ± 14.7% was reduced to 58.1% ± 13.5% with an average mean reduction of 26.8% ± 14.3%.

While studies have shown the decrease in stenosis with excimer laser atherectomy in a variety of lesion morphologies and arteries, there are no studies specific to Turbo Power laser atherectomy plus drug coated balloon in a variety of lesion morphologies.

2. OBJECTIVE(S)

The objective of this study is to determine outcomes of combined Turbo Power laser atherectomy plus drug coated balloon angioplasty for the treatment of femoropopliteal de novo/restenotic lesions and in-stent restenosis (ISR). Better understanding of these outcomes will help guide optimal treatment algorithms for this difficult to treat cohort of patients.

3. DESIGN

This is a retrospective, single-site, non-randomized study. Up to 120 subjects will be included in this study at Cardiovascular Institute of the South. Patient data will be reviewed through 12 months post-procedure. Out of the 120 patients, up to 20 patients will be included for a sub-analysis of patency. These 20 patients must be compliant with physician discharge instructions to be included in this cohort.

Primary Endpoint:
Rate of freedom from target lesion revascularization (TLR) at one year

Secondary Endpoints:
The secondary endpoints consist of:

- Procedural success (≤30% residual stenosis)
- Procedural safety (freedom from significant embolization (sequelae), or dissection)
- Freedom from major amputation at 30d, 6mo & 12mo
- Freedom from death at 30d, 6mo & 12mo
- Freedom from TLR 6 months
- Patency at 12 months (up to 20 patients)

The device involved in this study is the Spectranetics' Turbo Power laser catheter followed by drug coated balloon angioplasty. These devices are currently available in the United States. The Turbo Power laser catheter is currently indicated for the treatment of peripheral arterial disease including treatment of in-stent restenosis (ISR). Additionally, the two drug-coated balloons on the market in the United States during this retrospective timeframe were IN.PACT Admiral (Medtronic) and Lutonix 035 (CR Bard). They are both indicated for treatment of peripheral arterial disease and specifically, IN.PACT Admiral is indicated for ISR treatment. The present protocol does not involve invasive investigational interventions.

4. SELECTION OF SUBJECTS

4.1 Study Population

Patients will be recruited from the investigator's general patient population, and they must meet all of the inclusion/exclusion criteria listed below.

4.2 Inclusion criteria

All patients from Cardiovascular Institute of the South who were treated for femoropopliteal de novo/restenotic lesions or in-stent restenosis using Turbo Power laser atherectomy plus drug coated balloon angioplasty during 2016-2017.

4.3 Exclusion criteria

Patients will be excluded if there is any incomplete data on procedural approach and treatment.

Discontinuation of Subject Enrollment

Whenever possible, every subject should remain in the study until the completion of all data collection is complete. However, a subject's participation may be discontinued at any time during the study. The rationale for discontinuation must be documented in the source documentation and in the data collection form.

Factors leading to discontinuation may include:

- Subject Withdrawal- A subject that has been consented prior to this amendment, may withdraw consent at any time for any reason or no reason at all. Withdrawal should not affect the subject's relationship with the physician, and no penalty or loss of benefits (if any) should occur. Every effort should be made by the research study staff to obtain the reason for the withdrawal of consent.
- Investigator Termination- An investigator may discontinue a subject in a study due to a significant adverse event or due to failure to cooperate with study requirements.
- Lost-To-Follow-Up- Lost to follow-up is defined as the inability to obtain a response from the subject on three separate days. These contacts may be telephone calls or emails to subject (or subject representative and/or primary care provider if subject unable to be contacted); however at least one effort should be a certified letter to the subject's last known address.

4.4 Treatment Group

Treatment was performed at the physician's discretion. The subjects included in this retrospective study were treated with Turbo Power laser atherectomy as well as drug-coated balloon angioplasty.

5. SAMPLE SIZE AND STATISTICAL CONSIDERATIONS

5.1 The study is designed to include up to 120 patients. Descriptive statistics (arithmetic mean, median as indicated, minimum and maximum and standard deviation) will be calculated for continuous variables. Absolute frequencies and percentages will be obtained for qualitative variables. 95% Confidence intervals will be provided. In

calculation of percentages, patients with missing data will not be considered, unless otherwise specified. All baseline characteristics will be summarized. Descriptive statistics will be used to summarize the values and changes from baseline across time.

6. PROCEDURES

6.1 Data Review

All patients from Cardiovascular Institute of the South who were treated for femoropopliteal de novo/restenotic lesions or in-stent restenosis using Turbo Power laser atherectomy plus drug coated balloon angioplasty between 2016-2017 will be considered for study enrollment.

A review of the study candidate's medical history, procedure and data 12-months post-procedure will be performed and documented on the study CRFs.

Up to 20 patients that have been compliant with the physician's discharge instructions will be included in a subgroup. This subgroup will be specifically reviewed for long-term patency by the duplex ultrasound core lab. These patients will have a duplex ultrasound conducted within 305-425 days post-procedure (±60 days of 12-months post-procedure).

6.2 Angiographic Core Lab

An angiographic core lab will be employed to review procedural angiography on the 120 patients. They will assess baseline lesion characteristics and post-procedural diameter stenosis.

6.3 Duplex Ultrasound Core Lab

In the 20 patient subgroup, restenosis of the target lesion will be assessed by the duplex ultrasound core lab. These patients will have a duplex ultrasound conducted within 305-425 days post-procedure (±60 days of 12-months post-procedure). This will provide long-term patency data in these 20 patients.

7. ETHICAL PROCEDURES

7.1 Declaration of Helsinki

This study will be conducted according to the US FDA standards of Good Clinical Practice (FDA Title 21 Code of Federal Regulations part 11, 50, 54, 56 and 812), the Declaration of Helsinki, and the ICH Guidelines.

7.2 Patient informed consent

We are requesting a waiver of consent from IRB as this is a retrospective review and the data already exists. The patient's personal identifying information will not be compromised or disclosed.

Data from patients that have previously declined consent will not be included in the study.

7.3 Institutional Review Board (IRB)

The study may not be started at the proposed medical institution until all required approvals for the study have been obtained.

7.4 Deviations from the Investigational Plan

An Investigator is required to conduct this study in accordance with this investigational protocol, applicable laws and regulations, and any conditions of approval imposed by the Ethics Committees.

- An Investigator shall notify the reviewing Ethics Committee of any deviation from the investigational plan to protect the life or physical well being of a patient in an emergency. Such notices shall be given as soon as possible, but no later than 3 working days after the emergency has occurred.
- Except in such an emergency, prior approval by the Ethics Committee is required for a change in or deviation from the plan that could affect the scientific soundness of the plan, or the rights, safety or welfare of the patients.

8. DATA COLLECTION *AND MANAGEMENT*

8.1 *Required Data*

For the duration of the study, the Investigator and their delegates will maintain complete and accurate documentation, including but not limited to, medical records, study progress notes, signed subject informed consent forms (if applicable), correspondence with the reviewing IRB, correspondence with the Sponsor's designee and Study Monitor, adverse event reports, and information regarding subject discontinuation or completion of the study.

8.2 *Missing Values and Sensitivity Analysis*

Every attempt will be made to obtain missing values. Missing values will be queried and reconciled where possible. In the event missing values are unable to be resolved, sensitivity analyses will be conducted and compared using various scenarios.

8.3 *Confidentiality*

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of

subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

All data and information collected during this study will be considered confidential by the. All data used in the analysis and summary of this study will be anonymous, and without reference to specific subject names. Access to subject files will be limited to authorized personnel of the Investigator, Clinical Site research staff and authorized Regulatory Authorities. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study

8.4 *Source Documents*

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents, and data records include but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at core laboratories involved in the clinical trial.

Regulations require that the Investigator maintain information in the subject's medical records that corroborate data collected for the study.

8.5 *Case Report Forms*

This study will use a paper case report form (CRF) as the primary data collection instrument and data will be entered into an electronic database at the sponsor site. All data requested on the CRF should be entered or if missing, explained. If any entry error has been made, correct and enter the correct data in the CRF.

8.6 *Record Retention*

The Investigator will retain study essential documents for at least two years after completion of the trial.

9. Abbreviations/Definitions

Acute Procedural Success: Defined as a ≤30% residual stenosis in the target lesion immediately post assigned treatment. This assessment will be correlated with the ACL finding.

Claudication: Poor circulation and blockage of blood in the leg arteries produces an aching, tired, cramping and sometimes burning pain in the hips, thighs, or calves when the leg muscles do not receive the oxygen rich blood required during exercise or at rest.

Dissection: A separation of the vessel structures or formation of a false lumen. Flow-limiting dissection is considered Grade D or greater.

GRADE	DISSECTION DESCRIPTION
A	Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.
B	Filling defect parallel to the lumen of the vessel disappearing with the passage of contrast material.
C	Dissection protruding outside the lumen of the vessel persisting after passage of contrast material.
D	Spiral shaped filling defect with delayed runoff of the contrast material in the distal vessel.
E	Persistent luminal filling defect with delayed anterograde flow
F	Filling defect accompanied by total occlusion

Distal Embolization: Free-flowing blood clot or lesion material located distal from the treated lesion. Significant distal embolization: In event of clinical sequelae, treatment was needed to remove emboli.

Major Amputation: Unplanned amputation of the target limb where prosthesis is required for standing or walking.

Occlusion: No flow identified within the arterial segment by ultrasound and/or angiogram.

Patency: Loss of patency will be determined by duplex ultrasound (DUS). DUS analysis will be performed per core lab protocol

Percent Stenosis: Native vessel diameter as measured at the most narrow point of the lesion divided by the estimated native vessel diameter at that location using angiographic images with visual estimate.

P1 Segment of the Popliteal Artery: the first portion of the popliteal artery between the Hunter canal and the popliteal fossa.

P2 Segment of the Popliteal Artery: from the popliteal fossa to the knee joint

P3 Segment of the Popliteal Artery: from the knee joint to the take-off of the anterior tibial artery

Provisional Procedures: Additional devices used at time of procedure that exclude Turbo Power laser atherectomy and drug-coated balloon.

Rutherford Categories:

Category	Clinical Criteria
0	Asymptomatic – No hemodynamically significant occlusive disease; Mild claudication
1	Mild Claudication
2	Moderate Claudication
3	Severe Claudication
4	Ischemic Rest Pain
5	Minor tissue loss – Non-healing ulcer; Focal gangrene with diffuse pedal ischemia
6	Major tissue loss – Extending transmetatarsally; functional appendage/limb no longer salvageable

Target Lesion Revascularization (TLR): A Target Lesion Revascularization is defined as any percutaneous or surgical intervention to treat a restenosis or reocclusion, in the target lesion.

Target Vessel Revascularization (TVR): Any percutaneous or surgical intervention to treat a restenosis or reocclusion within the target vessel.

9. REFERENCES

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