Directional versus Orbital Atherectomy plaque modification and luminal area assessment of the femoro-popliteal artery Via Intravascular Ultrasound

(DIRECT TRIAL)

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NYUSOM Study Number:	S18-00005
Funding Sponsor:	Medtronic Vascular, INC 3576 Unocal Place, Santa Rosa, CA 95403 (707) 566-1238
Regulatory sponsor:	NYU
Study Product:	CSI's DIAMONDBACK 360® Peripheral Orbital Atherectomy System (St.Paul, MN); Medtronic's Hawkone Directional Atherectomy system (DAS) (Minneapolis, MN).
Study Product Provider: *[If applicable]*	N/A
ClinicalTrials.gov Number	TBD NCT03495453

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

ABI: Ankle Brachial Index
ACC/AHA: American College of Cardiology/American Heart Association
AE: Adverse Event
AEAC: Adverse Event Adjudication Committee
BA: Baloon angioplasty
CFR: Code of Federal Regulations
CLI: Critical Limb Ischemia
CRF: Case Report Form
CSI: Cardiovascular Systems, Inc.
DAS: Directional Atherectomy System
DCB: Drug coated balloon
DICOM: Digital Imaging and Communications in Medicine
DSMB: Data Safety Monitoring Board
FDA: Food and Drug Administration
HIPAA: Health Insurance Portability and Accountability Act
ICF: Informed Consent Form
ICMJE: International Committee of Medical Journal Editors
IDE: Investigational Device Exemption
IRB: Institutional Review Board
IVUS: Intravascular Ultrasound
NYU: New York University
OAD: Orbital Atherectomy Device
OAS: Orbital Atherectomy System
PAD: Peripheral Artery Disease
PI: Principal Investigator
QCA: Qualitative Comparative Analysis
QoL: Quality of Life
RGA: Returned Goods Authorization
SAE: Serious Adverse Event
SFA: Superficial Femoral Artery
US: United States
VIAS: Video Image Analysis Software

Protocol Summary

Title	Directional versus Orbital Atherectomy plaque modification and luminal area assessment of the femoro-popliteal artery Via Intravascular Ultrasound
Short Title	DIRECT TRIAL
Brief Summary	A single center prospective, randomized study will be conducted to investigate plaque removal and luminal gain using CSI's DIAMONDBACK 360® Peripheral Orbital Atherectomy System (OAS) (St.Paul, MN) versus Medtronic's Hawkone Directional Atherectomy system (DAS) (Minneapolis, MN) assessed by angiography and Intravascular Ultrasound (IVUS) in patients diagnosed with symptomatic obstructive femoro-popliteal disease will be analyzed. Subjects will be randomized in a 1:1 fashion to receive treatment with either OAS (using CSI device) followed by Inpact Admiral drug coated balloon (DCB) or DAS (using the Hawkone device) followed by DCB. Subjects in both arms will undergo IVUS before and after atherectomy, as well as at the conclusion of the procedure. Clinical data will be collected at baseline, immediately prior to the procedure, during and immediately after the procedures, and within 30 days, 6 and 12 months office visits after the procedure. Data may also be collected at office or hospital visits that are not scheduled but occur up to 12 months after the procedure, if they pertain to treatment related to the obstructive femoro-popliteal disease. Data to be collected for this study includes demographics, medical history, procedural parameters and follow-up. The study will be conducted at one study center, 60 subjects will be accrued in the trial with 30 patients enrolled in the OAS arm and 30 patients enrolled in the DAS arm.

Objectives	To investigate the hard and soft plaque removal with directional and orbital atherectomy by analyzing changes in plaque volume and composition and vessel size using intravascular ultrasound (IVUS). Freedom from complications, target vessel patency and target lesion revascularization (TLR) at 6 months and one year will also be evaluated.
Endpoint	Primary Endpoint: Acute luminal gain (increase in minimal luminal area via IVUS measurement immediately following atherectomy) Secondary Endpoints: -Plaque burden reduction. The plaque composition and amount of removed plaque will be analyzed via IVUS. -Device success (≤ 30% residual stenosis following atherectomy, as measured by angiography, without adjunctive endovascular interventions) -Rate of procedural angiographic complications such as dissection, perforation, emboli, abrupt closure, need for bail out stenting. -Major Adverse Event Rate at 30 days post procedure defined as clinical TLR, major unplanned amputation of the treated limb, or all-cause mortality -Rate of clinical TLR, unplanned amputation of the treated limb, or all-cause mortality at 6 and 12months post index treatment. -Primary patency at 1 year defined as freedom from target lesion restenosis detected with duplex ultrasound Peak Systolic Velocity Ratio (PSVR) is ≤ 2.4 -Rate of Hemodynamic Improvement as assessed by changes in ABI at 6 and 12 months as compared to post-procedural baseline (i.e., within 30 days). -Improvement in Rutherford Clinical Category within 30 days, at 6 months and at 12 months, defined as an improvement in clinical status indicated by a decrease of one or more in Rutherford Clinical Category compared to baseline, that is attributable to the treated limb (in cases of bilateral disease).

Study Duration	The duration of the study is expected to be approximately 2 years from the date of first enrollment (1 year for enrollment of approximately 100 subjects and a year for follow-up of 60 accrued subjects).
Participant Duration	It will take 12 month for each individual participant to complete all participant visits.
Population	• The patients with obstructive superficial femoral or popliteal arteries disease as the main reason for their symptoms will be enrolled in this study.
Study Sites	NYU Langone Health
Number of participants	Number of participants projected for the entire study 100
Description of Study Procedure	All subjects will undergo percutaneous revascularization of the femoro-popliteal arteries using a DAS or OAS device and balloon angioplasty as per the randomization arm. All patients will undergo at least 3 runs of IVUS: • a pre-treatment run to assess the severity and morphology of the plaque composition • a post-atherectomy run to assess changes post atherectomy treatment • a post drug coated balloon angioplasty (followed atherectomy) to assess changes in overall volumes.
Statistical Analysis	The sample size for the study is not based on any statistical hypothesis. The mean differences between pre-procedure and post-procedure measures will be analyzed using paired t-tests. A p-value of ≤ 0.05 will be considered to indicate statistical significance. Descriptive statistics will be generated to describe study findings (i.e. subject demographics, plaque volume, lumen volume, vessel size, etc.).

1. Key Roles

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2. Introduction

2.1 Regulatory Classification

The sponsor has determined that this study is a medical device study which involves products currently on the market in the USA and these products have received clearance for use by the Food and Drug Administration (FDA). The clinical study requires the medical devices to be used in accordance with its FDA-cleared labeling. Therefore, it is a study which is exempt from the investigational device exemption (IDE) regulations of the FDA. There are no investigational products or procedures used in this study.

2.2 Study Description

A single center prospective, randomized study will be conducted to investigate plaque removal and luminal gain using CSI's DIAMONDBACK 360® Peripheral Orbital Atherectomy System (OAS) (St.Paul, MN) versus Medtronic's Hawkone Directional Atherectomy system (DAS) (Minneapolis, MN) assessed by angiography and Intravascular Ultrasound (IVUS) in patients diagnosed with symptomatic obstructive femoro-popliteal disease will be analyzed.

Subjects will be randomized in a 1:1 fashion to receive treatment with either OAS (using CSI device) followed by Inpact Admiral drug coated balloon (DCB) or DAS (using the Hawkone device) followed by DCB. Subjects in both arms will undergo IVUS before and after atherectomy, as well as at the conclusion of the procedure.

Clinical data will be collected at baseline, immediately prior to the procedure, during and immediately after the procedures, and within 30 days, 6 and 12 months office visits after the procedure. Data may also be collected at office or hospital visits which are not scheduled but may occur up to 12 months after the procedure, if they pertain to treatment related to the obstructive femoro-popliteal disease. Data to be collected for this study includes demographics, medical history, procedural parameters and follow-up.

The study will be conducted at one study center, 100 subjects will be enrolled, with 60 subject accrued in the trial: 30 patients randomized to the OAS arm and 30 patients randomized to the

DAS arm. The duration of the study is expected to be approximately 2 years from the date of first enrollment (1 year for enrollment of 60 subjects and a year for follow-up).

2.3 Study Background and Justification

Peripheral arterial disease (PAD) of the lower extremities has an incidence and prevalence equal to that of coronary artery disease and is a major cause of morbidity and mortality. Endovascular treatment of femoral-popliteal lesion in patients with symptomatic PAD has been shown to improve exercise capacity and quality of life[1]. Heavy plaque burden calcification is one of the most important predictors of unsuccessful angioplasty and poor short and long term procedural outcomes. Fitzgerald et al.[2] demonstrated that 74% of dissections after balloon angioplasty occurred in lesions with significant calcification.

Percutaneous removal of atherosclerotic material using atherectomy devices reduces the complications of traditional angioplasty such as dissection, elastic recoil and disruption of the internal elastic lamina of the artery. Directional and orbital atherectomy are two of the most common atherectomy approaches used to treat lower extremity PAD.

Directional atherectomy devices such as the Hawkone, Turbohawk and Silverhawk use a side cutting steerable blade that also has a distal nosecone to capture debris. The directional cutting design allows for extensive removal of calcific debris from the entire lumen while minimizing the direct trauma to the true intima. The Definitive LE study was an 800 patient prospective registry that demonstrated the safety and effectiveness of DAS in infrainguinal PAD. Primary patency rates were >90% after 6 months in both the claudicant and critical limb ischemia(CLI) groups.[3] Smaller randomized trials of directional atherectomy vs traditional balloon angioplasty have demonstrated superior outcomes with directional atherectomy especially when treating long calcified lesions[4].

Orbital atherectomy devices such as the Diamondback 360 use a diamond coated eccentrically mounted burr that spins in an orbit and increases in size at higher revolutions. This technique causes preferential sanding of the calcified plaque and a fixed luminal gain and can be used in vessel ranging from 2mm-7mm in diameter. IVUS analysis of lesions treated with orbital atherectomy significant lesion modification by modifying the calcified component of the plaque burden.[5] The Compliance 360 trial randomized 65 patients to either balloon angioplasty (BA) or OAS and BA. This trial showed that compared to BA alone, OAS+ BA yields better luminal gain and decreases incidence of adjunctive stenting.[6] Similarly, the Calcium 360 randomized trial of orbital atherectomy + BA vs. BA alone showed superiority with use of the orbital atherectomy device.[7]

Most trials comparing atherectomy + BA to BA alone were done without the use drug coated balloons. DCB's have shown superiority when compared to plain old balloon angioplasty alone. A recently published meta-analysis of 11 trials with 1838 patients confirmed that DCB's are superior with regards to endpoints such as primary vessel patency, restenosis rates and target lesion revascularization.[8] The combination of both atherectomy with DCB may further improve the results of lower extremity PAD percutaneous intervention. Several trials are currently in progress that are evaluating this hypothesis. The Definitive AR trial is a randomized control trial comparing DAS+ DCB vs DCB alone. Long term data has yet to be published but preliminary results show that DAS+DCB may be superior especially in long as well as calcified lesions when appropriate de-bulking was attained (<30% residual post DAS stenosis).

While both directional and orbital atherectomy systems have demonstrated improved outcomes versus balloon angioplasty alone, no studies have been performed to directly compare whether one form of atherectomy is superior to the other. With the increased incidence of significant PAD and the increased need for atherectomy in order to achieve successful percutaneous intervention, it would be extremely beneficial to know whether one type of atherectomy system is preferred over another. There are several theoretical advantages of DAS over OAS: DAS allows for possibly larger amount of plaque removal (de-bulking) which leads to a larger luminal gain and vessel diameter that in turn may lead to a better long term vessel patency rates and lower rates of target vessel revascularization. The purpose of this study will be to evaluate whether directional atherectomy is superior to orbital atherectomy in treating long femoro-popliteal lesions.

2.4 Study Objectives and Endpoints

2.4.a. Primary Objective

- To investigate the hard and soft plaque removal with directional and orbital atherectomy by analyzing changes in plaque volume and composition and vessel size using IVUS). Freedom from complications, target vessel patency and target lesion revascularization (TLR) at 6 months and one year will also be evaluated.

2.4.b. Primary Endpoint

Acute luminal gain (increase in minimal luminal area via IVUS measurement immediately following atherectomy)

2.4.c. Secondary Endpoints

- Plaque burden reduction. The plaque composition and amount of removed plaque will be analyzed via IVUS.
- Device success (≤ 30% residual stenosis following atherectomy, as measured by angiography, without adjunctive endovascular interventions)
- Rate of procedural angiographic complications such as dissection, perforation, emboli, abrupt closure, need for bail out stenting.
- Major Adverse Event Rate at 30 days post procedure defined as clinical TLR, major unplanned amputation of the treated limb, or all-cause mortality
- Rate of clinical TLR, unplanned amputation of the treated limb, or all-cause mortality at 6 and 12months post index treatment.
- Primary patency at 1 year defined as freedom from target lesion restenosis detected with duplex ultrasound Peak Systolic Velocity Ratio (PSVR) is ≤ 2.4
- Rate of Hemodynamic Improvement as assessed by changes in ABI at 6 and 12 months as compared to post-procedural baseline (i.e., within 30 days).
- Improvement in Rutherford Clinical Category within 30 days, at 6 months and at 12 months, defined as an improvement in clinical status indicated by a decrease of one or more in Rutherford Clinical Category compared to baseline, that is attributable to the treated limb (in cases of bilateral disease).

3. Investigator Selection and Responsibilities

3.1 Investigator Selection

In order for investigators to participate in the study, they must meet the following criteria:

- A qualified physician, such as an interventional radiologist, vascular surgeon or cardiologist
- Qualified to practice medicine at NYU
- Able to provide adequate time and staff support for the study
- Able to comply with the protocol and legal contract for the study
- At an institution that has access to a registered IRB.

3.2 Investigator Responsibilities

The investigator is responsible for protecting the rights, safety, and welfare of subjects. An investigator must conduct the investigation in accordance with the study contract with the sponsor of the study, the protocol, the FDA regulations that apply to this study including 21 CFR 50 [Protection of Human Subjects] and 21 CFR 56 [Institutional Review Boards (IRB)], and any conditions of approval imposed by an IRB.

The Principal Investigator (PI) and other staff conducting the study will be trained prior to performing any activities for the study. Should the PI choose to delegate study related tasks to qualified personnel under their supervision, they must be trained on the study relative to the tasks that have been assigned to them.

4. Methodologies

4.1 Study Design

The study design is a single-center, prospective, randomized control trial to assess the performance of OAS and DAS for removal of plaque including calcium in patients who have femoro-popliteal disease. Subjects will have a baseline visit to determine eligibility for the study, will receive treatment according to this study protocol, and will be followed with office visits at within 30 days, 6 and 12 months after the procedure to collect data. Study participation will be complete when the last study subject enrolled has been followed for 12 months after the procedure.

4.2 Subject Selection

The research coordinator (RC) and IRB-approved study team doctor will have primary responsibility for screening and enrolling eligible candidates. The RC will review NYULMC's Epic system to identify patients with peripheral artery disease from the NYU cardiology practices and patients scheduled for a revascularization procedure in the Cardiac Catheterization Laboratory. The research coordinator will review the medical records to identify the patient and confirm with the principal investigator or Sub Investigator if the patient meets the clinical inclusion and exclusion criteria. If the physician is amenable, the coordinator will approach the patient for a possible consent and enrollment.

It is expected that approximately 100 participants will sign IRB approved consent in order to accrue 60 subjects to the trial: 30 patients randomized to the OAS arm and 30 patients randomized to the DAS arm.
Once the subject has signed the approved study informed consent form (ICF), and has met all inclusion and no exclusion criteria, the subject will be considered eligible to be enrolled to the trial. Subjects may be either male or female, and must meet all of the inclusion criteria and none of the exclusion criteria in order to be randomized to the either arm of the trial treatment.

4.3 Inclusion Criteria

- Subject's age ≥ 18 years;
- Subject (or Legal Guardian if applicable) is willing and able to provide consent before any study-specific test or procedure is performed, signs the consent form, and agrees to attend all required follow-up visits.
- Chronic, symptomatic lower limb ischemia defined as Rutherford categories 1-4
- Target lesion(s) located in a superficial femoral or popliteal arteries
- Degree of stenosis ≥70% via Qualitative Comparative Analysis (QCA)
- Total Lesion Length ≥ 80 mm and ≤ 250 mm
- Reference Vessel ≥ 3.0 mm and <6.5mm
- Patent infrapopliteal artery, i.e., single vessel runoff or better with at least one of three vessels patent (<50% stenosis) to the ankle or foot with no planned intervention.
- Subject is an acceptable candidate for percutaneous intervention using the OAS or DAS in accordance with their labeled indications and instructions for use

4.4 Exclusion Criteria

Subjects who have an:

- Previously stented target lesion/vessel.
- Subjects who have undergone prior surgery of the SFA/PA in the target limb to treat atherosclerotic disease.
- Presence of aneurysm in the target vessel.
- Interventional treatment is intended for in-stent restenosis at the peripheral vascular site.
- Target vessel with moderate or severe angulation (*e.g.,* > 30°) or tortuosity at the treatment segment that precludes safe advancement of the atherectomy device.
- Pre-planned interventional treatment includes planned laser, brachytherapy or atherectomy procedure other than OAS or DAS.
- Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated.
- Known hypersensitivity/allergy to antiplatelet, anticoagulant, thrombolytic medications
- Platelet count <80,000 mm^3 or >600,000 mm^3 or history of bleeding diathesis.
- Patient has any known coagulation disorder, including hypercoagulability
- Receiving dialysis or immunosuppressant therapy.
- Patient has evidence of intracranial or gastrointestinal bleeding within last 3 months.
- Patient has history of severe trauma, fracture, major surgery or biopsy of a parenchymal organ within past 14 days,

- Female patient who is pregnant or nursing a child,
- Current participation in another investigational drug or device clinical study that has not completed the primary endpoint at the time of randomization/enrollment or that clinically interferes with the current study endpoints.

4.5 Data Storage

All subjects who sign the ICF will receive a study ID number. The Subject's source documents and data, under this ID number, will be placed in a subject research binder and inputted into the REDCap database, which is stored on NYULMC's password protected, strongly firewalled server that has been certified by NYULMC's HIPAA Compliance Officer in adherence to DHHS data collection policies. This electronic data storage complies with the FDA Title 21 CFR Part 11 standards for Electronic Records and Electronic Signatures. The subject's research binders will be kept in the secure place in the research office.

5. Study Procedures

5.1 Overview of Data Collection Requirements

Clinical data will be collected upon enrollment at the Baseline Visit, at the time of the procedure, and at within 30 days, and 6 and 12 months after the procedure. Data will also be collected during unscheduled office visits should adverse events connected to the procedure or device occur or should a subject death occur during the 12 months of study follow up after the subject's procedure. Data to be collected includes demographics, medical history, etc. The data requirements are summarized in Table 1.

Data Criteria	Baseline visit	Procedure	Visit 1	Visit 2 (6 mon)	Visit 3 (12 mon)
Compliance Window	**30 days prior to procedure**	**n/a**	**Within 30 days after procedure**	**+/- 30 days**	**+/- 30 days**
Subject Informed Consent	✓				
Inclusion/Exclusion Criteria	✓				
Subject Medical History	✓				
IVUS/DICOM images*		✓			
ABI	✓		✓	✓	✓
Arterial Duplex Ultrasound			✓		✓
Rutherford	✓		✓	✓	✓

Follow-up Visit Form			✓	✓	✓
Adverse Event Form	**As they occur**				
Deviation Form					
***IVUS/DICOM images to be collected immediately prior to and immediately following use of the OAS/Hawkone and again following Drug Coated Balloon Angioplasty procedures.**					

Table 1 Study Data Collection

5.2 Informed Consent

Prior to initiation of any study specific procedures, an IRB approved Informed Consent Form must be signed and dated by the subject. Subjects must be given ample time to review the ICF and have questions answered before signing. The signed Informed Consent Form must be filed in the hospital/clinic medical chart or with the study subject documentation and be available for review by the IRB. A copy of the signed ICF must also be given to the subject for their records. A subject number will be assigned to the subject after the consent has been signed.

5.3 Baseline Visit (Pre-procedure assessments - up to 30 days)

The following data must be collected within 30 days prior to the index procedure for all subjects:

- Demographics and medical history obtained
- Physical assessment including:
- Weight and height
- Rutherford Clinical Category Assessment
- Ankle-Brachial Indices (ABI) measurements
- Antiplatelet medication usage (if applicable)

5.4 Procedure Visit

Prior to Index procedure the confirmation of clinical assessments of the inclusion and exclusion criteria must have been met. On the day of the procedure, the patient will be prepped for percutaneous intervention per institutional standards.
Patients may be admitted on the day of the procedure for hydration, if deemed medically necessary. Antiplatelet medication should be initiated prior to procedure at a dose deemed appropriate by the Investigator. Investigator will manage the cardiovascular risk factors and comorbidities for all patients according to standard care. Investigator should ensure close monitoring of the amount of contrast for subjects with elevated serum creatinine levels.

Diagnostic angiography of the lower extremities must be performed using standard techniques to confirm angiographic eligibility of the target lesion. Femoro-popliteal arterial lesions intended for treatment at the time of the index procedure that met the inclusion and didn't meet exclusion criteria will be considered target lesions.

Randomization Protocol
A statistician generated list of random treatment allocations (i.e., a randomization schedule) will be used to assign subjects to treatments in a 1:1 ratio of directional atherectomy to orbital atherectomy treatment groups after successfully crossing the target lesion. The randomization assignment sheet will be blinded to the PI.

Index Procedure
After randomization, all subjects will undergo percutaneous revascularization of the femoro-popliteal arteries using a DAS or OAS device and drug coated balloon angioplasty as per the randomization arm.
Adjunctive procedures will be performed at the treating physician's discretion. Use of the same balloon for all dilations is strongly recommended, 1:1 balloon to healthy segment ratio to nominal pressure for at least 3 minutes of duration of balloon inflation.

During the index procedure, the angiographic complications such as emboli, dissections, perforations or abrupt closures will be assessed, treated and recorded as needed.

Intravascular Ultrasound (IVUS)
All patients will undergo at least 3 runs of IVUS:

- a pre-treatment run to assess the severity and morphology of the plaque composition
- a post-atherectomy run to assess changes post atherectomy treatment
- a post drug coated balloon angioplasty (followed atherectomy) to assess changes in overall volumes.

The ruler must be utilized for each procedure for precise measurement of the diseased, treated, and IVUS evaluated segment(s).

The Opticross™ 18 peripheral imaging catheter (Boston Scientific Corp) is a 6-French (Fr) compatible catheter that performs intravascular analysis of the culprit lesion, measuring grey-scale images over a 0.014˝ guidewire. This device is used routinely at the study center.

1. Automated pullback (1.0 mm/sec) must be implemented by using the disposable pullback device.
2. All pullbacks must be performed at a sufficiently distal point using an external ruler to mark the precise start point.
3. Images should be recorded on DICOM format and archived on DVD for off-line analysis. Anonymized IVUS images and selected angiograms (pre-treatment view of stenosis, IVUS location and final post-treatment angiogram) will be sent to the Core Laboratory for evaluation.

Adverse Event Collection
Complete SAE collection and assessment

5.5 Follow up.

All randomized/enrolled subjects will be evaluated prior to discharge from the index procedure and continue follow up evaluation at 30 days, 6 months, and 12 months after the index procedure. Requirements of each follow-up evaluation are described below.

Visit 1. 30 days Follow up (within 30 days)

All enrolled subjects must be evaluated within 30 days after the index procedure. The following assessments must be performed during this visit.

- Rutherford Clinical Category Assessment
- ABI Measurements
- Serious Adverse Events collection and assessment
- Arterial Duplex Ultrasound
- Antiplatelet medications assessment

Visit 2. 6 month Follow up (182 days +/-30 days)

All enrolled subjects must be evaluated 6 months after the index procedure. The following assessments must be performed during 6 month office visit.

- Rutherford Clinical Category Assessment
- ABI Measurements
- Serious Adverse Events collection and assessment
- Antiplatelet medications assessment

Visit 3. 12 month Follow up (365 days +/-30 days)

All enrolled subjects must be evaluated 12 months after the index procedure. The following assessments must be performed during 12 month office visit.

- Rutherford Clinical Category Assessment
- ABI Measurements
- Serious Adverse Events collection and assessment
- Arterial Duplex Ultrasound
- Antiplatelet medications assessment

5.6 Unscheduled Visits

An unscheduled follow-up is defined as an office or hospital visit or phone call to the clinic by the subject that is not required by the study protocol but is usually related to an event and occurs between the study baseline visit and 12 months after the procedure. If the subject has an unscheduled follow-up and:

- No serious adverse events noted during unscheduled visit – no forms need to be completed
- Serious adverse event noted – The Adverse Event CRF needs to be completed for each event.

The subject will still be required to return for the next scheduled follow-up visit if the unscheduled visit is out of the compliance follow-up window.

5.7 Trial Completion

The trial will be considered complete:

- after all subjects have completed the 12-month follow-up visit;
- withdrew from the study prior to the 12-month follow-up visit;
- have died;
- or presented at time when the follow-up visit window is closed.

5.8 Study Exit

5.8.a. Lost to Follow-up

Every effort must be made to retain study subjects for the duration of the study. If the subject fails to comply with the protocol requirements to attend the follow up visits, the study center should make at least two attempts to contact the subject. Each of the attempts to contact the subject must be documented in the subject's medical record.

5.8.b. Subject Withdrawal

If the subject chooses to withdraw from the study, the Investigator should attempt to obtain the reasons for the subject's request to withdraw from the study. Once a subject has voluntarily withdrawn, all of the subject's data will be used in the study up to and including the date of withdrawal.

6. Adverse Events, Deviations & Complaints

6.1 Adverse Events

The only Adverse Events (AE) that will be collected in the study are those events that meet the definition of serious injury, also called a serious adverse event (SAE) , which is required for post market surveillance of medical devices by the FDA

6.2. Serious Adverse Event Definitions

Serious Adverse Event (SAE) that:

1. Led to a death;
2. Led to a serious deterioration in the health of the subject that:
- resulted in a life-threatening illness or injury;
- resulted in permanent impairment of a body structure or a body function;
- or a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- resulted in in-patient hospitalization or prolongation of existing hospitalization;
- resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function;
3. Led to fetal distress, fetal death or a congenital abnormality or defect.

6.3. Serious Adverse Event Classification

The relationship of the SAE to the atherectomy device will be classified by the investigator.

The investigator will use the following definitions in classifying the relationship of SAE to the study procedures or the medical device:

Device Related: A SAE that is directly related to the atherectomy device.

Procedure Related: A SAE that is directly attributable to the procedure using the atherectomy device. Usually, these events occur within 2 weeks of the procedure.

6.4. Serious Adverse Event Reporting

All serious adverse events must be collected, assessed and recorded on the appropriate eCRF.
All relevant source documentation for event will be stored in the subject binder.
Adverse event information will be collected up until each subject's study completion of the trial.
All adverse events will be reported as per IRB requirements.

6.5. Study Deviations

A study deviation is defined as an event where the study is not conducted according to the protocol, the study contract, FDA regulations or requirements imposed by the reviewing IRB.

6.6. Product Return, Device Malfunction, and Complaints

In the case of device malfunction, device-related adverse events, compromised product, or complaints, the device is to be returned to the manufacturer. Contact CSI Customer Service at

1-877-274-0901; or Medtronic Customer Service at 1 800-633-8766 to obtain a Returned Goods Authorization (RGA) number. Every effort should be made to return the device to the Sponsor in a timely manner.

7. Risk Analysis

7.1 Potential Risks and Mitigations

The medical devices used in this study have received clearance by the FDA to be on the market in the US. Therefore, the risk profile is established and there should be no additional risk to the subject due to the use of the OAS/DAS during the procedure as a result of this study.

The risks associated with the endovascular procedure may include, but are not limited to the following:

- Amputation
- Aneurysm
- Arterial dissection
- Arterial perforation
- Arterial rupture
- Arterial spasm
- Arteriovenous fistula
- Bleeding complications
- Death
- Embolism or arterial thrombosis
- Emergency or non-emergency arterial bypass surgery
- Hematoma
- Hypotension
- Infection
- Ischemia
- Restenosis of the treated segment
- Total occlusion of the peripheral artery
- Vascular complications that could require surgical repair

7.2 Potential Benefits

Participation in this study is voluntary. There will be no direct benefits of participating in this study. Information gathered from this study may help with further DAS/OAS development that may benefit future patients who suffers from peripheral artery disease.

8. Statistical Methods and Data Analysis

8.1 Data Management

Electronic case report forms (CRF) will be used to collect the data from the study. Data will be stored in a secure, password-protected database which will be backed up at periodic intervals to archive data. At the end of the study, data will be archived and retained by NYU.

8.2 Statistical and Data Analysis Methods

The Biostatistician from NYULMC will perform the analysis in collaboration with the Principal Investigator. No interim analyses are planned.

Descriptive statistics will be generated to describe study findings (i.e. subject demographics, plaque volume, lumen volume, vessel size, etc.).The mean differences between pre-procedure and post-procedure measures will be analyzed using paired t-tests. The pre- and post-procedure changes in the primary and secondary outcomes will be compared between the two treatment arms by the Intention to treat (ITT) principle. Multivariable linear regressions will be used to compare the change between treatments adjusting for subject demographics and other covariates. A p-value of ≤ 0.05 will be considered to indicate statistical significance.

Group sample sizes of 30 and 30 achieve 80% power to detect a difference of 0.7 standard deviation difference in the mean of the primary outcome between the two groups with a significance level 0.05.

<u>IVUS DICOM Image Analysis</u>

Anonymized IVUS Images and selected angiograms should be recorded on DICOM format and archived on DVD for off-line analysis.

Quantitative assessment of the treated segments will be performed using planimetry echoPlaque software (Inedc, Mountain View, CA).

9. Data Safety Monitoring

Due to the fact that this is an investigator initiated trial there will be no external monitoring or auditing for this study. In this study, a Clinical Event Committee (CEC) or a Data Safety Monitoring Board (DSMB) will not be used. The Principal Investigator will conduct interim monitoring of any serious adverse event at the time of occurrence and annually to assure the continuing safety of participants, relevance of the study question, appropriateness of the study protocol compliance and integrity of the accumulating data. The PI in conjunction with NYU IRB will be responsible for monitoring the data and conducting safety reviews every12 months when annual re-approval is sought. During the review process, the PI and NYU IRB will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. This study will not have predefined stopping rules due to the fact that both devices are proven to be safe in multiple clinical trials and approved by FDA for routine clinical practice.

10. Investigator Records and Reports

10.1 Investigator Records

The investigator is responsible for the preparation (review and signature) and/or retention of the records cited below.

- Subject's case history records, including: signed/dated subject consent form, observations of serious adverse events, relevant medical history and results of tests or exams performed in this study, and dates of follow-up office visits.
- Protocol and amendments
- IRB approval documents and correspondence

10.2 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission of all case report forms (CRFs), serious adverse events (SAEs), and deviations from the protocol.

The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in Table 2.

Table 2: Investigator Reports for Study

Report:	To:	Description/Constraints:
Serious Adverse Events (SAEs)	IRB per policy	Immediate notification, but no later than 5 business days after discovery of event.
Death	IRB per policy	Immediate notification, but no later than 5 business days after discovery of death.
Deviations to the Protocol		As soon as possible after occurrence of deviation.

11. Publication

11.1 Clinical Trial Registration

This study will be submitted for inclusion in the clinical trial registry at: *http://www.ClinicalTrials.gov* for publication purposes.

The following statement will be included in the informed consent form for the study to notify the prospective subjects for the study: "A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This website will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

11.2 Publication Review

Any previously unpublished information provided to the Investigators by the Sponsor, such as patent applications, manufacturing processes and basic scientific data, is considered confidential and will remain the sole property of the Sponsor. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the Sponsor's written consent.

An Investigator may publish the study experience from his/her own site. The Sponsor reserves the right to review the manuscript prior to submission in order to verify accuracy of the data. The Investigator may proceed with the publication when notified by the Sponsor.

12. Bibliography

1) Fakhry F et al. Endovascular Revascularization and Supervised Exercise for Peripheral Artery Diseasand Intermittent Claudication: A Randomized Clinical Trial. *JAMA*, 2015 Nov;314(18):1936-44.

2) Fitzgerald PJ, Ports TA, Yock PG. Contribution of localized calcium deposits to dissection after angioplasty. An observational study using ultrasound. *Circulation* 1992; *86:64-70.*

3) Mckinsey JF et al. Lower Extremity Revascularization Using Directional Atherectomy. 12 Month Prospective results of the DEFNITIVE LE Study. *J AM Coll Cardiol Intv* 2014;7:923-33

4) Shammas NW et al. Percutaneous Lower-extremity Arterial Interventions with Primary Balloon Angioplasty Versus SilverHawk Atherectomy and Adjunctive Balloon Angioplasty: Randomized Trial *J Vasc Interv Radiol* 2011; 22:1223:1228

5) Babaev A et al. Orbital Atherectomy Plaque Modification of the Femoropopliteal Artery Via Intravascular Ultrasound (TRUTH Study) *Vascular and Endovascular Surgery* 2015; 49: 188-194

6) Datillo R et al. The COMPLIANCE 360° Trial: a randomized, prospective, multicenter, pilot study comparing acute and long-term results of orbital atherectomy to balloon angioplasty for calcified femoropopliteal disease. *J Invasive Cardiol* 2014; 26:8 355-60

7) Shammas NW et al. Comparison of Orbital Atherectomy Plus Balloon Angioplasty vs Balloon Angioplasty Alone in Patients with Critical Limb Ischemia. Results of the CALCIUM 360 Randomized Pilot Trial. *J Endovasc Ther* 2015;19:480-488

8) Kayssi a et al. Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for peripheral arterial disease of the lower limbs. *Cochrane database syst rev ;* 2016 4;(8):CD011319.