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ASPiRE

Antiplatelet Strategy for Peripheral Arterial Interventions for Revascularization of Lower Extremities

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Investigator's signature page

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Antiplatelet Strategy for Peripheral Arterial Interventions for Revascularization of Lower Extremities

TRIALCENTER: _____

Print Name of Trial Center)

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the trial as described in the protocol and according to GCP and other applicable regulatory requirements. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the trial as described in the protocol.

_____	_____	_____
Principal Investigator Print name:	Signature	Date

Protocol Synopsis

ASPiRE
Antiplatelet Strategy for Peripheral Arterial Interventions for Revascularization of Lower Extremities

PI	Name: Subhash Banerjee, MD Phone number: 214-857-1608 Email: Subhash.banerjee@utsouthwestern.edu
TRIAL OBJECTIVE	
Primary Objective	To evaluate whether clopidogrel 75 mg daily on a background of aspirin 81 mg/d for U.S. sites (75-100 mg/d for international sites) for clinically indicated duration or an additional 12 months will lead to an increased rate of primary patency, limb salvage, non-fatal myocardial infarction (MI), ischemic stroke, and survival, in patients receiving endovascular treatment of PAD at end of study treatment
Control Arm	clopidogrel 75 mg daily on a background of aspirin 81 mg/d for U.S. sites (75-100 mg/d for international sites) for clinically indicated duration with a minimum of 30 days.
Test Arm (as applicable)	clopidogrel 75 mg daily on a background of aspirin 81 mg/d for U.S. sites (75-100 mg/d for international sites) for clinically indicated duration + 12 months
Endovascular interventions included	Iliac Femoropoliteal Below-the knee
TRIAL DESIGN	
Trial Design	Prospective, two-arm, multicenter randomized clinical trial.
Planned Number of Subjects	202 subjects will be enrolled in each arm (total subjects = 404)
Clinically indicated dual antiplatelet therapy (DAPT) duration	Clinically indicated DAPT duration will be based on the longest pre-discharge following an index peripheral intervention procedure, DAPT duration. This will be determined based on: peripheral intervention device IFUs, preceding coronary intervention, acute coronary syndrome or other guideline-based clinical or device

	specific DAPT durations.
Planned Number of Sites / Countries	Approximately 18 investigational centers in the U.S.. are expected to participate. No center will be allowed to enroll more than 40% of planned total enrollment.
Primary Endpoint	Primary Endpoint (subject-based): The first occurrence of index limb arterial occlusion, surgical intervention, endovascular intervention, amputation of the affected limb (vessel occlusion or failure), MI, ischemic stroke or death at 12 months from index procedure or end of study treatment, whichever is longer
Secondary Endpoints	Secondary Endpoints through end of study treatment: • The first occurrence of any individual component of the primary endpoint • First occurrence of the following during follow-up: cardiovascular death, or MI, or ischemic stroke, or any amputation above the ankle. • Severe bleeding defined according to the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO) classification
Tertiary Endpoints	• Moderate bleeding defined according to the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO) classification
Randomization	• Patients scheduled for a planned discharge will be randomized on a 1: 1 basis using a computerized central randomization portal available through RedCap® to either of the following treatment groups: ◦ ASA (81 mg U.S. sites; 75-100 mg international sites) + clopidogrel: for clinically indicated duration (control arm) ◦ ASA (81 mg U.S. sites; 75-100 mg international sites) + Clopidogrel 75mg: for clinically indicated duration +12m (treatment arm) Randomization will be performed at the within 2 weeks of an eligible procedure
Follow-up schedule	All potential subjects will be evaluated for enrollment after the index procedure pre-discharge or within 14 days of the procedure. Follow-up schedule will include patient visits at 30 days and q6 months till the end of study treatment The trial will be considered complete with regard to the primary endpoint after all enrolled subjects have

	completed a 12-month or end of study treatment follow-up evaluation, have died, have a documented premature discontinuation, or whose follow-up window has closed. Follow-up window is +7 days for the 30-day visit and +15 days for all other visits.
Key Inclusion Criteria	General: • Signed informed consent • At least 18 years old • Documented symptomatic iliac, femoropopliteal (FP) or below-the knee artery (BTK) atherosclerotic disease (Rutherford/Becker category 2, 3 or ≥4) • Undergone clinically indicated uncomplicated endovascular intervention to one or more locations of the iliac, femoropopliteal below-the knee arteries • Estimated survival ≥1 year in the judgment of the primary operator • Pre-index procedure use of ASA, clopidogrel or both at any dose Angiographic: • De novo or restenotic lesions in the common and/or external iliac artery, superficial femoral artery (SFA), popliteal artery, tibio-peroneal (TP) trunk, anterior tibial (AT) artery, peroneal artery (PA) or posterior tibial (PT) artery (applies to all target lesions if multiple) • Subjects with multiple planned procedures can be enrolled after the completion of the last planned procedure.
Key Exclusion Criteria	General: • Complicated qualifying procedure (perforation, flow limiting dissection, distal embolization requiring re-intervention, need for repeat endovascular, surgical revascularization, amputation or blood transfusion prior to hospital discharge following index procedure • Extended hospital stay >7 days following the index procedure • Allergy to aspirin or clopidogrel • Life expectancy less than 12 months due to other medical co-morbid condition(s) that could limit the subject's ability to participate in the trial, limit the subject's compliance with the follow-up requirements, or impact the scientific integrity of the trial • Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated. • Intolerance to antiplatelet, anticoagulant, or thrombolytic medications • Platelet count <90,000 mm^3 or >600,000 mm^3

	• Serum creatinine >2.5 mg/dL • Dialysis-dependent end stage renal disease • Pregnancy • Current participation in another drug or device trial that requires interruption of dual-antiplatelet therapy with aspirin or clopidogrel for the duration of this study • Planned surgeries, endovascular or other non-vascular or cardiac procedures • Warfarin or other chronic oral anticoagulant use • Contraindication(s) to the use of antithrombin or antiplatelet agents (history of intra-cerebral bleed, presence of intracerebral mass, recent or <6 weeks gastrointestinal bleed, blood transfusion within the last 6 weeks, any trauma requiring surgery or blood transfusion within the last 4 weeks or any surgical procedure within the last 4 weeks. <u>Angiographic:</u> • Endovascular intervention to iliac, FB or BTK artery bypass graft • Persistent, intraluminal thrombus of the proposed target lesion at the completion of the index procedure • Perforated vessel as evidenced by extravasation of contrast media • Vascular graft, aneurysm or postsurgical stenosis of the target vessel
Multiple Interventions During Index Procedure	Multiple interventions during an index procedure will be allowed as long as the procedure is deemed successful and uncomplicated by the primary operator and no additional procedures are planned
Statistical Methods	
Sample size parameters	• The occurrence of the primary endpoint is expected to be approximately 49% at 12 months in the control group[17] • A 30% relative risk reduction in the incidence of primary endpoint would be clinically important • To detect a 30% relative reduction in the 1-year primary event rate from 49% to 34.0%[17] with 80% power at the two-sided, .05 significance level, assuming a 12-month recruitment period and a 1 0 % dropout rate at 1 year, a total of 404 (368+36) patients will be randomized (202 in each group) and followed-up for endpoints for 12 months or until end of study treatment, whichever is longer
Statistical analysis	• Continuous variables will be summarized as mean±standard deviation and compared using the t-test or the Wilcoxon rank-sum test, as appropriate • Discrete variables will be presented as frequencies and group percentages and compared using the chi-square

	test
	• For all comparisons a two-sided probability of <0.05 will be considered statistically significant
	• All analyses were performed using the SAS 9.1 or recent version (SAS Institute Inc., Cary, North Carolina)
	• Primary endpoint will be assessed as per an intention-to treat principle
	• Subsequent analysis will also be performed based on as treated groups
	• Pre-specified subgroup analyses will include:
	  • Stent vs. non-stent groups
	  • DES vs. BMS
	  • Above and below-the knee treatment
	  • Claudication vs. CLI groups

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1. Introduction and Rationale

Peripheral arterial disease (PAD) is extremely prevalent worldwide and affects over 206 million people.[1] Over 36 million patients with PAD are estimated to be present in the United States. Percutaneous revascularization therapies have evolved dramatically, yet the long-term success of these therapies remains modest and the morbidity and mortality associated with PAD remains high, with up to 30% mortality risk at 5 years [2]. Nearly, 3.2 million endovascular procedures are performed annually.[3, 4] Though, this exceeds interventional procedures performed for coronary artery disease (CAD), the current PAD guidelines are silent regarding the need and optimal duration of antiplatelet therapy (APT) for patients following an endovascular procedure for claudication or critical limb ischemia (CLI). [5] The lack of data and clinical studies is by far the greatest impediment to the formulation of such guideline recommendations critically needed by providers and patients alike, especially given the current limited durability of lower extremity endovascular procedures.[6]

2. Clinical outcomes following lower extremity endovascular interventions

Endovascular or surgical revascularization procedures are performed on individuals with lifestyle-limiting claudication or CLI.[7] Percutaneous transluminal angioplasty (PTA) is a well-established endovascular technique for revascularizing obstructed lower limb arteries. This technique is associated with good patency in iliac artery interventions; however with dismal patency rates for infra-inguinal interventions.8 Stents have improved patency of lower extremity arterial interventions, mainly applied at the aortic bifurcation or in iliac segments.[9] Until recently stents in the femoropopliteal district were associated with a higher risk of re-occlusion because of the smaller diameter of these vessels.[6] However, the new generation of self-expanding nitinol stents or paclitaxel-coated balloons have yielded better results than those obtained with standard balloons at the femoropopliteal level.[10] Compared to surgical procedures, endovascular techniques are less invasive and are associated with lower morbidity and mortality and shorter recovery time.[11] The main disadvantage of endovascular intervention is the low rates of long-term success, with relatively frequent clinical deterioration and restenosis during follow-up. Thus, reintervention is often necessary in patients treated with endovascular intervention for symptomatic with PAD.[12] In addition to the type of intervention, early studies have demonstrated the impact of clopidogrel discontinuation on acute thrombotic occlusion of the limb post- endovascular intervention.[13] In addition clopidogrel use in patients with PAD has been associated with improved mortality and non-fatal myocardial infarction (MI) events.[14]

3. Antiplatelet agents following lower extremity endovascular intervention

It has been shown that dual antiplatelet therapy is a very important factor for short- and long-term success in coronary interventions. Thus, based on the results of randomized clinical trials,

current guidelines recommend dual antiplatelet therapy consisting of clopidogrel and aspirin for 12 months after percutaneous coronary intervention (PCI) for acute coronary syndromes and/or use of drug-eluting stents.[15]

After peripheral artery interventions, there is still some uncertainty regarding the optimal peri- and post-interventional antiplatelet treatment of clopidogrel and/or aspirin .[6] The results of the Management of peripheral arterial interventions with mono or dual antiplatelet therapy (MIRROR) study showed that patients treated with clopidogrel+aspirin compared to aspirin alone had significantly lower target lesion revascularization (TLR) rates at 6 months.[17] Nevertheless, the duration of dual antiplatelet therapy remains unknown and not been addressed by well-powered randomized clinical trials. The investigators of the MIRROR study therefore conducted an additional clinical follow-up of MIRROR patients at 12 months to evaluate the persistence or extinction of the clinical advantage of dual antiplatelet therapy.[18] At 6 months, clopidogrel patients had significantly lower rates of TLR compared to placebo patients [2 (5%) vs. 8 (20%), p=0.04]. None of the TLR was due to thrombotic occlusion of previously recanalized arteries. There were no significant differences in the rate of binary restenosis at 6 months. After stopping clopidogrel/placebo, the significant difference in TLR disappeared [9 (25%) clopidogrel vs. 12 (32.4%) placebo (p=0.35)]. Thus in contrast to the first report of a reduction in the TLR at 6 months in the MIRROR study, this advantage of dual antiplatelet therapy does not persist after stopping clopidogrel. The investigators concluded that prolonged dual therapy (>6 months) should be considered in patients who are at high risk for restenosis.

Peripheral catheter interventions are performed under local anesthesia allowing early and full mobilization. However, as a result of this intervention, atherosclerotic plaques are ruptured and platelets aggregate at the site of injury.[19] Extensive vessel wall damage coupled with low shear stress and poor infrapopliteal outflow are mostly responsible for the occurrence of reocclusion.[20]

Additionally, in the initial phase after catheter intervention, a hypercoagulable state prevails, as parameters of activated coagulation, including thrombin-antithrombin complexes (TAT), D-Dimer and Fibrinopeptide A (Fa) become elevated in the plasma.[21] This activated coagulation system produces conditions favorable for early thrombotic occlusion, where 'early' is usually defined as a period covering the first four weeks after the intervention. Subsequently, intimal hyperplasia may follow which is responsible for intermediate and late-term restenosis and reocclusion. Intimal hyperplasia occurs as a result of denudation (tearing off of the inner lining) of the endothelium caused by manipulation of the vessel wall with the catheter. Reported rates of arterial reocclusion or symptomatic restenosis following femoropopliteal PTA are between five and twenty-five per cent for early events and about 40% one year.[6] The five year patency rate was reported to be 83% for iliac and 58% for femoropopliteal PTA, whilst patients with stenoses or occlusions of less than 3 cm had a favorable long-term patency rate of 74%.[22]

Patients with CLI or those subjected to local thrombolysis show higher incidences of reocclusion.[23] The implantation of drug-eluting or nitinol stents, or treatment by intravascular brachytherapy following PTA are considered as interventions with the capacity of reducing the occurrence of intimal hyperplasia, however may be associated with delayed endothelialization

and increased risk of thrombosis.

Drug interventions with antiplatelet agents to prevent thrombosis and/or reocclusion of the treated segments would make an important contribution to the sustained success of endovascular treatment, along with its contribution towards reducing overall mortality in patients with PAD. Current peri-interventional treatment strategies mostly include aspirin intake before and after PTA, initial administration of either unfractionated heparin (Ellis 1989) followed mostly by antiplatelet drugs or anticoagulants on a long-term basis (Do 1994; Hess 1985; Shammas 2003b; Watson 2000). However, these practices have never been tested in the setting of an adequately powered randomize controlled trial.

The Swedish trial on aspirin (50 mg daily) use after PTA was a negative study, whereas the study by Heiss et al showed greater patency and a dose effect favoring a higher dose of aspirin (100- 300 mg daily).24 At time points three and 12 months there were 798 and 575 patients included with OR 1.38 (95% CI 0.85 to 2.23) and 0.98 (95% CI 0.64 to 1.48), respectively, for primary occlusion. In fact, one clinical trial called CAMPER (Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization) (CAMPER) was started in the USA evaluating clopidogrel combined with ASA versus ASA after femoropopliteal angioplasty. Unfortunately, this study had to be stopped due to insufficient randomization numbers after one year.

4. Trial Objectives

To evaluate whether clopidogrel 75 mg QD on a background of ASA 81 mg/d for U.S. sites (75-100 mg/d for international sites) for clinically indicated duration with a minimum of 30 days or an additional 12 months will lead to an increased rate of primary patency, limb salvage, freedom form ischemic stroke and survival, in patients receiving endovascular treatment of PAD.

5. Trial hypothesis

We hypothesize that DAPT with ASA and clopidogrel administered for an additional 12 months after a clinically indicated duration following iliac, FP or BTK endovascular intervention will improve primary patency, limb salvage, freedom form ischemic stroke and survival, in patients with symptomatic PAD.

6. Trial endpoints

Clinical endpoints will be analyzed in all subjects who are enrolled, regardless of whether the trial treatment administered successfully completed for the desired duration. A subject will be considered enrolled in the trial when he/she is randomized to one of the treatment arms of the study. All endpoints are subject-based unless otherwise specified.

The primary endpoint is subject-based of the longer of a 12-month or end of study treatment endpoint of the first occurrence of index limb arterial occlusion, surgical intervention,

endovascular intervention, amputation of the affected limb (primary patency and limb salvage), MI, ischemic stroke or death (survival)

The secondary endpoints are subject-based on the longer of a 12-month or end of study treatment endpoints that include: (a) the first occurrence of any individual component of the primary endpoint, (b) the first occurrence of the following during follow-up: cardiovascular death, or MI, or ischemic stroke, or any amputation above the ankle and (c) severe bleeding defined according to the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO) classification

The tertiary endpoint is based on the longer of a12-month or end of study treatment moderate bleeding according to the GUSTO classification

Clinically indicated DAPT duration will be based on the longest pre-discharge following index peripheral intervention procedure DAPT duration. This will be determined based on: peripheral intervention device IFUs, preceding coronary intervention, acute coronary syndrome or other guideline-based clinical or device specific DAPT duration.

Study treatment will be discontinued at the first occurrence of a primary endpoint as defined in the table below. Patients, however, can resume taking aspirin, Clopidogrel, or both based on their provider's clinical decision.

Primary endpoint definition(s)	**Secondary/Tertiary endpoint definition(s)**
Occlusion of the target limb documented by any imaging procedure performed clinically Any surgical or endovascular revascularization procedure on the index limb Amputation above the ankle of the index limb Death from any cause Ischemic stroke: An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction confirmed by a neurologist MI: Detection of a rise in cardiac troponin (cTn) with at least one value 3x above the 99th percentile upper reference limit (URL) and with at least 1 of the following: • Symptoms of ischemia • New or presumed new significant (≥1 mm) ST- segment–T wave (ST–T) changes or new left bundle branch block (LBBB)	As described in section 6, except for: GUSTO bleeding criteria: 1. Severe or Life-threatening: Intracerebral hemorrhage resulting in substantial hemodynamic compromise requiring treatment 2. Moderate: Requiring blood transfusion but not resulting in hemodynamic compromise 3. Mild: Bleeding that does not meet above criteria

• Development of pathological Q waves in the ECG	

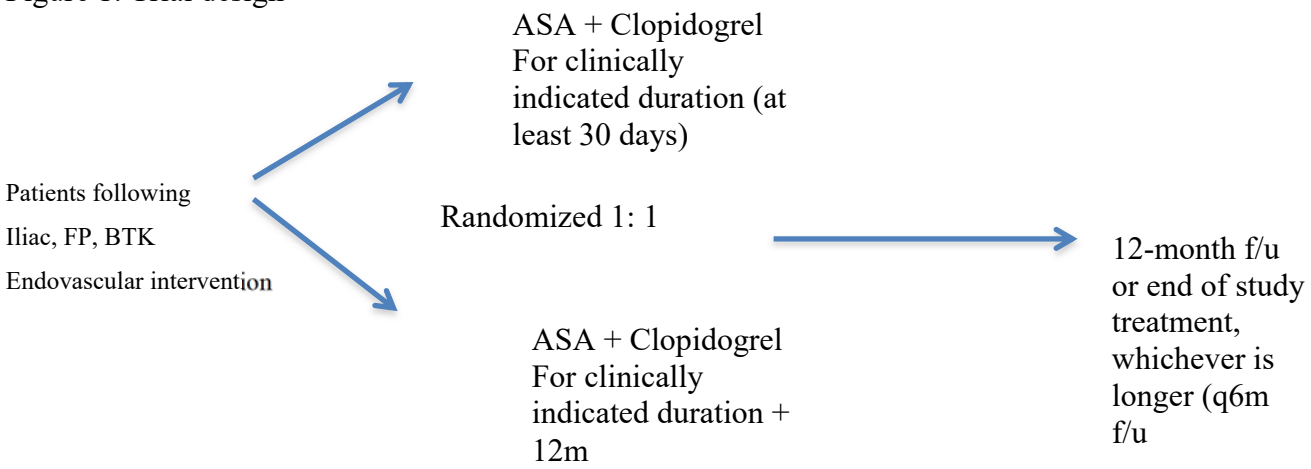
7. Trial design

This is a prospective, multi-center, two-arm randomized clinical trial to evaluate whether clopidogrel 75 mg QD on a background of ASA 81 mg for U.S. sites (75-100 mg/d for international sites) for clinically indicated duration with a minimum of 30 days or an additional 12 months will lead to an increased rate of primary patency, limb salvage and survival, in patients receiving endovascular treatment of PAD.

Up to 404 subjects at approximately 18 centers in the United States are planned. Assuming 10% attrition at 12 months, enrollment of a minimum of 404 would yield at least 368 evaluable subjects for the longer of a12-month or end of study treatment endpoint. No center will be allowed to enroll more than 40% of the subjects.

A schematic of the trial design is provided in Figure 1.

Figure 1: Trial design



8. Justification of trial design

A multitude of clinical studies and analyses have attempted to address the question of optimal DAPT duration following endovascular peripheral arterial intervention for symptomatic PAD and have either not been adequately powered or have been abandoned. This study needs to be undertaken as a randomized controlled trial to try and conclusively answer the question in an unbiased fashion. This modification will facilitate recruitment and make the study consistent with current clinical practice. The relevance of the study results will is significantly elevated.

9. Method of assigning subjects to treatment

Patients scheduled for a planned discharge will be randomized on a 1: 1 basis using a central computerized randomization portal available through RedCap® to either of the following treatment groups:

ASA (81 mg/d for U.S. sites; 75-100 mg for international sites) + clopidogrel:for clinically indicated duration with a minimum of 30 days (control arm)

ASA (81 mg/d for U.S. sites; 75-100 mg for international sites) + clopidogrel 75 mg: for clinically indicated duration + 12m (treatment arm)

An inclusion and exclusion checklist needs to be completed via computerized randomization portal available through RedCap® prior to randomization of the subject.

10. Trial population

Table 1 on the following pages outlines the specific inclusion and exclusion criteria for the trial, according to general and angiographic categories. Before enrollment in the trial, a subject must meet all of the inclusion and none of the exclusion criteria.

Key Inclusion Criteria	General: • Signed informed consent • At least 18 years old • Documented symptomatic iliac, femoropopliteal (FP) or below-the knee artery (BTK) atherosclerotic disease (Rutherford/Becker category 2, 3 or ≥4) • Undergone clinically indicated uncomplicated endovascular intervention to one or more locations of the iliac, femoropopliteal below-the knee arteries • Estimated survival ≥1 year in the judgment of the primary operator • Pre-index procedure use of ASA, clopidogrel or both at any dose Angiographic: • De novo or restenotic lesions in the

	common and/or external iliac artery, superficial femoral artery (SFA), popliteal artery, tibio-peroneal (TP) trunk, anterior tibial (AT) artery, peroneal artery (PA) or posterior tibial (PT) artery (applies to all target lesions if multiple) • Subjects with multiple planned procedures can be enrolled after the completion of the last planned procedure.
Key Exclusion Criteria	General: • Complicated qualifying procedure (perforation, flow limiting dissection, distal embolization requiring re-intervention, need for repeat endovascular, surgical revascularization, amputation or blood transfusion prior to hospital discharge following an index procedure • Extended hospital stay >7 days following the index procedure • Allergy to aspirin or clopidogrel • Life expectancy less than 12 months due to other medical co-morbid condition(s) that could limit the subject's ability to participate in the trial, limit the subject's compliance with the follow-up requirements, or impact the scientific integrity of the trial • Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated. • Intolerance to antiplatelet, anticoagulant, or thrombolytic medications • Platelet count <90,000 mm^3 or >600,000 mm^3 • Serum creatinine >2.5 mg/dL • Dialysis-dependent end stage renal disease

	• Pregnancy • Current participation in another drug or device trial that requires interruption of dual-antiplatelet therapy with aspirin or clopidogrel for the duration of the study • Planned surgeries, endovascular or other non-vascular or cardiac procedures • Concurrent warfarin or other chronic oral anticoagulant therapy • Contraindication(s) to the use of AT (history of intra-cerebral bleed, presence of intracerebral mass, recent or <6 weeks gastrointestinal bleed, blood transfusion within the last 6 weeks, any trauma requiring surgery or blood transfusion within the last 4 weeks or any surgical procedure within the last 4 weeks. Angiographic: • Endovascular intervention to iliac, FB or BTK artery bypass graft • Persistent, intraluminal thrombus of the proposed target lesion at the completion of the index procedure • Perforated vessel as evidenced by extravasation of contrast media • Vascular graft, aneurysm or postsurgical stenosis of the target vessel

11. Withdrawal and replacement of subjects

While trial withdrawal is discouraged, subjects may withdraw from the trial at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects will not undergo any additional follow-up, nor will they be replaced (the justified sample size considers an estimated allowance for attrition).
Potential reasons for subject discontinuation are as follows:

I. Withdrawal of consent
II. Secondary to an Adverse Event
III. A Principal Investigator, IRB or a regulatory body deemed safety concern
IV. Lost to follow-up

12. Trial procedures

The schedule of observations and assessments to take place during the trial are listed in **Table 2.**

Table 2: Trial Event Schedule

	enrollment	30day (±7days)	6m[4,5] (± 15 days)	12m and q6m till end of study treatment [3, 4,5] (±15 days)
Informed consent	+			
Inclusion/Exclusion	+			
Physical Examination [1]	+	+	+	+
Rutherford Classification	+	+	+	+
ABI	+	+	+	+
TASC classification	+			
Serum creatinine	+	+	+	+
Hemoglobin	+	+	+	+
Platelet count	+	+	+	+
Recommended Anti-Coagulant Therapy Assessment	+	+	+	+
WIQ (section 1)	+	+	+	+
AE assessment [2]		+	+	+
Concomitant medications	+	+	+	+

1. Physical examination includes gross assessment of standard organ systems (e.g., cardiac, pulmonary, etc).
2. AE assessments and reporting include AE, SAE and MAE.
3. End of study treatment visit will be performed when patient completes duration of assigned study treatment. This visit may fall between q6m visit schedule for some patients.
4. Phone visits can be done if patients refuse in-clinic visit during the follow up period, or who are do not show up to their follow up visits. Labs and ABIs will be collected and

documented, if available in their medical records during the follow up period. Study team should document 2 attempts to schedule in-clnic visits before phone visits are completed during follow-up

5. Patients who do not complete their follow up visits in -clinic will not be provided a refill of aspirin and Plavix (if randomized to the long arm) They will remain on the study as ITT and phone follow-up may be completed to collect data. Prescriptions may be renewed when patients complete an in-clinic visit.

13. Informed consent

All subjects who are potential trial candidates must provide written informed consent before enrollment.

Subjects must sign the trial-specific, most recent version of the Institutional Review Board (IRB) approved Informed Consent form before any trial-specific interventions. Trial personnel should explain to the subject that even if a he or she agrees to participate in the trial and signs an Informed Consent form, careful assessment of inclusion/exclusion criteria may demonstrate that the subject is not a suitable candidate for the trial, and, therefore, the subject will not be allowed to participate.

Trial Center personnel will maintain a Screening/Enrollment Log to document enrolled subjects and select information about candidates who fail to meet the general or angiographic entry criteria.

14. Sample size estimate

The occurrence of the primary endpoint is expected to be approximately 49% in the control group, derived on the basis of current literature review and preliminary data form XLPAD registry.[18]

A 30% relative risk reduction in the incidence of primary endpoint would be clinically important. To detect a 30% relative reduction in the primary event rate from 49% to34% [17] with 80% power at the two-sided, 0.05 significance level, assuming a 12-month recruitment period and a 10% dropout rate at 1 year, a total of 404 patients will be randomized (202in each group) and followed-up for endpoints for longer of a 12-month or end of study treatment period.

15. Control of systematic bias/errors

In determining subject eligibility for the trial, the Investigator or his/her designee's assessment of inclusion/exclusion parameters will be used.

An independent Clinical Events Committee (CEC) will review clinical events that occur during the trial. The CEC will be blinded to the trial center and subject identification to the extent possible. An independent Data Safety Monitoring Board (DSMB) will review adverse events that occur during the trial.

16. Eligibility of subjects, exclusions and missing data

All subjects who are enrolled will be eligible for evaluation, regardless if they receive the control or active arm drug treatments for the assigned durations or not. Sensitivity analyses to account for missing data will be performed and may include imputation of missing data if deemed appropriate. The distribution of prognostic factors between subjects with and without data will be examined. Statistical models that account for censored data will be employed in appropriate circumstances, e.g., for time-to-event outcomes. Outlier values will be evaluated for their validity. All data will be included unless judged to be invalid. The robustness of the primary endpoint conclusion will be assessed based on these analyses.

17. Analysis set

The primary endpoint will be analyzed on an intent-to-treat basis and on a per-protocol basis analysis will also be performed. For intent-to-treat analysis, all subjects who sign the IRB/EC-approved written Informed Consent form and are enrolled into the trial will be included in the analysis, regardless of whether they receive the control or active arm drug treatments for the assigned durations or not. For per-protocol analysis, only subjects who receive the control or active arm drug treatments for the assigned durations will be included in the analysis.

The primary analysis set for testing of the primary endpoint is the intent-to-treat analysis set. No formal interim analyses are planned for the purpose of stopping this trial early for efficacy.

18. Availability of aspirin and clopidogrel

As both these drugs are approved worldwide and used routinely in post endovascular interventions, they would be used on the basis of use as per routine clinical practice and as per local/regional drug procurement and dispensing practices.

19. Statistical analysis

Continuous variables will be summarized as mean±standard deviation and compared using the t-test or the Wilcoxon rank-sum test, as appropriate. Discrete variables will be presented as frequencies and group percentages and compared using the chi-square test. For all comparisons a two-sided probability of <0.05 will be considered statistically significant. All analyses were performed using the SAS 9.4 or recent version (SAS Institute Inc., Cary, North Carolina). Primary endpoint will be assessed as per an intention-to treat principle.
Subsequent analysis will also be performed based on per-protocol basis. Pre-specified

subgroup analyses will include:

1. Stent vs. non-stent groups
2. DES vs. BMS
3. Above and below-the knee intervention

4. Claudication vs. CLI groups

20. Post-procedure endpoints

Post-procedure information will be collected at regularly scheduled follow-up examinations, as detailed in the clinical trial schedule, and will be summarized using the descriptive statistics described above.

Primary Endpoint

For the primary endpoint of 12-month composite of primary patency, limb salvage, MI, ischemic stroke and survival, with 95% confidence bounds will be calculated in the active arm and compared to control treatment duration. If this bound is less than that of control, then the primary endpoint will be considered met. All enrolled subjects are to be assessed for adverse events at follow-up visits. Assuming a maximum of 10% attrition due to non-compliance, loss to follow-up or death or non-compliance with follow-up, a minimum of 184 subjects in each arm are expected to be evaluable for the primary endpoint.

Secondary Endpoints

Secondary endpoints will be summarized at the specified time points using the descriptive statistics described above, individually or in comparison between the treatment groups. Statistical analyses of the following secondary endpoints will be summarized for descriptive purposes and without adjustments for multiplicity:

- Changes in ABI from baseline to hospital discharge, 30 days, 6 months and 12 months post-procedure will be analyzed using paired two-sided Student *t*-tests.
- Changes in Walking Impairment Questionnaire scores from baseline to 30 days, 6 month, and 12 months post-procedure will be analyzed using paired two-sided Student *t*-tests.
- Freedom from Target Lesion Revascularization Kaplan-Meier estimates and plots will be presented to 12 months post-procedure

Pooling Across Institutions

Analyses will be performed using data pooled across institutions. Analyses to justify pooling will include the following:

- The primary endpoint presented by institution.
- An assessment of the 'poolability' of the institutions using a 2-by-(number of institutions) contingency table of outcome versus institution. Fisher's Exact Test will be used to assess homogeneity. Institutions with fewer than five subjects will be combined based on geographic region if possible.
- If the institutions are found to be significantly heterogeneous with respect to the

primary endpoint, additional analyses will be conducted to assess differences between institutions in baseline and procedural variables that might explain differences in primary outcome.

Other Analysis Methods

Kaplan-Meier plots of time-to-event variables will be constructed for clinical outcomes.

21.Data management

Data collection and processing

Subject data will be collected in a secure electronic data capture (EDC) system via the Internet. The Principal Investigator or Sub-investigator must ensure the accuracy and completeness of the recorded data entered into the EDC and also by providing his/her electronic signature on the appropriate paper Case Report Forms (CRF). The Investigator's signature for specific CRF will be documented in compliance with local regulations.
Changes to data previously submitted to the sponsor will require a new signature by the Investigator to acknowledge and approve the changes. The coordinating or primary study site team will compare the data entered into EDC and paper CRF for discrepancy and require a response from the site PI/Sub-I.

Audits may be performed for quality assurance of data handling against source documents

Visual and/or computer data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. The trial center will be responsible for resolving all queries in the database in a timely manner.

22.Monitoring

Monitoring of trial centers will be made periodically during the trial, as outlined in the trial monitoring plan, to ensure that all aspects of the current, approved protocol/amendment(s) are followed.

Original source documents will be reviewed for verification of data in the electronic database. The Investigator/institution guarantees direct access to original source documents, including electronic medical records, if applicable, by monitoring personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a subject that is seen by a non-trial physician at a non-trial institution, photocopies of the original source documents must be made available for review. In the event such records cannot be released, the study site will allow verification of the source data by passive viewing of the source electronic

medical record screen handled exclusively by the site coordinator/investigator(s).

The trial also may be audited for quality assurance by monitors or its designees, as well as inspected by appropriate regulatory authorities.

It is important that the Investigator and relevant trial personnel are available during monitoring visits, audits and inspections, and that sufficient time is devoted to the process.

Monitoring plan

Designated monitor(s) funded and supported by the PI will undertake site monitoring. Such monitoring visits will be conducted for. sites on a six monthly basis

23.Adverse Events

All Adverse Events (AE) and Serious Adverse Events (SAE) will be reported through EDC and analyzed through study follow-up period.

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a subject. This definition does not imply that there is a relationship between the adverse event and the treatment under investigation. *Note 1:* In addition, the definition of AE applies to any event with an onset post-randomization procedure or to any underlying diseases, present at baseline, that exacerbate in severity post-randomization procedure. Therefore, any underlying disease that was present at the time of enrollment is not to be reported as an AE, but any increase in the severity in the underlying disease is to be reported as an AE. This definition includes events occurring in the follow-up period.

Serious Adverse Event (SAE)	An adverse event that:
	• led to death;
	• led to a serious deterioration in the health of the subject that:
	  • resulted in a life-threatening illness or injury,
	  • resulted in a permanent impairment of a body structure or a body function,

	• required in-hospitalization or prolongation of existing hospitalization, • resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function

Clinical events to be considered and reported as expected SAE include, but are not limited to:

- MAE (see definitions)
- Stent Thrombosis
- Bleeding complication as per GUSTO definition
- Vascular event requiring target limb surgical or endovascular intervention or amputation
- Any hospitalization

Relationship

The Investigator must assess the relationship of the adverse event to the participation in the study and use of antiplatelet drugs using the following criteria categories and definitions:

- Unrelated: The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the study related drugs
- Possible: The adverse event is determined to be potentially related to the study related drugs, and an alternative etiology is equally or less likely compared to the potential relationship to the study related drug
- Probable: There is a strong relationship to study related drug or recurs on re-challenge, and another etiology is unlikely
- Highly Probable: There is no other reasonable medical explanation for the event

The Investigator must assess the relationship of the adverse event to the study related drug using the following categories and definitions:

- Unrelated – The adverse event is determined to be due to a concurrent illness or effect of a device/drug and is not related to the study related drug use
- Possible – The adverse event is determined to be potentially related to the index procedure, and an alternative etiology is equally or less likely compared to the potential relationship to study related drug use
- Probably – There is a strong relationship to index procedure, or recurs on re-challenge, and another etiology is unlikely
- Highly Probable – There is no other reasonable medical explanation for the event

Outcome

The Investigator must document the outcome of the AE using the following categories:

- Resolved without residual effects
- Resolved with residual effects
- Recovering/Resolving
- Not Recovered/Not Resolved
- Death
- Unknown

Reporting Requirements

Trial personnel must report to the study PI's office any SAE or MAE by fax within 24 hours of learning of the event. When faxing in notification of an event, a fax confirmation report must be retained at the site as adequate documentation of timely event reporting. Source documentation should record when the site became aware of the event. Trial personnel must forward follow-up information and the completed adverse event CRF to the as the event continues and/or resolves.

All adverse events will be recorded in the electronic database managed by the primary study team at the primary institution and report them at each DSMB meeting. A description of the event, including the start date, resolution date, action taken, assessment, and outcome should be provided, along with the Investigator's assessment of the relationship between the AE and the trial treatment. All adverse events also need to be reported to the local IRB within 24 hours of knowledge of the study team.

24. Risk-benefit analysis

Based on review of the scientific literature, outcomes of design verification, the results of preclinical studies, and known adverse drug effects, the benefit of treatment with the aspirin and clopidogrel post-iliac, FP and BTK endovascular intervention outweighs the risks. However, the effect of unknown factors accounting for unanticipated side effects cannot be completely excluded, therefore observation and follow-up of subjects is required as outlined in the protocol.

Risks associated with aspirin and clopidogrel drug therapy may include:

a. Allergic reaction

b. Amputation

c. Aneurysm

d. Angina/coronary ischemia

e. Arrhythmia

f. Arteriovenous fistula

g. Death

h. Drug-drug interactions
i. GI bleeding
j. Hemorrhage/hematoma
k. Hypotension / Hypertension
l. Myocardial infarction (MI)
m. Need for urgent intervention or surgery
n. Pseudoaneurysm
o. Renal insufficiency or failure
p. Restenosis of stented artery
q. Rupture of the retroperitoneum or other organ
r. Stroke
s. Thrombosis / Thrombus
t. Tissue ischemia/necrosis
u. Vasospasm
v. Vessel injury, examples include perforation, dissection, intimal tear, rupture
w. Vessel occlusion

Risk minimization

The risks associated with the aspirin and clopidogrel use are relatively well established, and the preceding risks represent the most up-to-date understanding of risks associated. The study team will employ measures throughout the course of this investigation, to minimize these risks to subjects choosing to participate. In general, efforts will be made to minimize these risks by:

i. Selecting Investigators who are experienced and skilled clinicians and expert in endovascular procedures
ii. Clearly defining inclusion/exclusion criteria to ensure only appropriate subjects are enrolled
iii. Ensuring that the treatment and follow-up of the subjects are consistent with current medical practices

Specifically, every subject participating in this trial will undergo the following:

a. Medical history, physical examination, and laboratory assessment prior to the procedure to identify factors which may increase risk
b. Required review of anti-coagulant and anti-platelet medication before and after enrolment into the trial

Data safety monitoring board (DSMB)

A DSMB will meet every 6 months as scheduled or sooner based on reported AE and review all adverse events at these meetings and make recommendations to the study executive committee regarding the conduct and continuation of the trial, with/without recommendations for the study team(s) and or the executive committee/PI. The DSMB will include 5 members with a chair and all decisions will be adopted by a clear majority and all proceeding minutes recorded and stored with the primary study team/PI's office. A minimum of 3 members will be required to conduct the proceedings of the DSMB.

Clinical events committee (CEC)

A Clinical Events Committee with pertinent expertise that reviews and adjudicates important endpoints and relevant adverse events reported by trial Investigators.

Committee membership will include practitioners of peripheral endovascular procedures, as well as other experts with the necessary therapeutic and subject matter expertise, to adjudicate the event categories outlined above. CEC responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter.

The CEC will adjudicate the following events:

- All Deaths
- Myocardial infarction (MI) that occurs during index hospitalization
- Target lesion revascularization (TLR), surgical or endovascular
- Target vessel revascularization (TVR), surgical or endovascular
- Target limb/extremity revascularization (TER), surgical or endovascular
- Amputation of index limb or any amputation
- Stent Thrombosis or target iliac, FP or BTK vessel occlusion
- Any urgent limb/extremity revascularization surgical or endovascular procedure
- Bleeding events
- Any stroke

25. Ethical considerations

Declaration of Helsinki

The Investigator will ensure that this trial is conducted in full conformity with the recognized version of the Declaration of Helsinki per country regulation, and with the regulations and guidelines of the Food and Drug Administration (FDA) and all country/state/local regulations; whichever affords the greater protection to the subject.

Institutional Review Board

A copy of the protocol, proposed Informed Consent form, other written subject information, and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written IRB approval of the protocol and Informed Consent form and a copy of the Investigator Signature Page must be received by primary study site/team before recruitment of subjects into the trial.

The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the Informed Consent form. The Investigator must notify the IRB of deviations from the protocol or MAE (i.e. death, MI, TLR, or amputation) and stent thrombosis occurring at their site, and other AE/SAE reports.

The Investigator is responsible for obtaining annual IRB approval and renewal throughout the duration of the trial. Copies of the Investigator's reports and the IRB continuance of approval must be sent to primary study coordinating site/team.

Amending the Protocol and/or Informed Consent

This protocol is to be followed exactly, and can be altered only by written amendments. Administrative changes that do not affect the subject benefit/risk ratio (e.g., editorial changes for clarity) may be made without any further approvals. Any change that would require alteration of the Informed Consent form must receive approval from appropriate coordinating site/PI's office personnel and from the IRB prior to implementation. Following approval, protocol amendment(s) will be distributed to all protocol recipients with instructions to append them to the protocol.

Emergency Actions

Study coordinating site/PI accepts the right of the Investigator to deviate from the protocol in an emergency when necessary to safeguard the life or physical well-being of a trial subject. The Investigator must give notice of any emergency deviation, and justification for the deviation, to the study coordinating site/PI and the IRB as quickly as possible, no later than 24 hours after the emergency.

Protocol Adherence

Prior to beginning the trial, the Investigator must sign the Investigator Agreement and Signature page documenting his/her agreement to conduct the trial in accordance with the protocol. An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Each deviation from the protocol must be documented with the date and reason for the deviation and reported to the study coordinating site/PI and to the IRB, per local guidelines and government regulations.

Trial Administration

Investigators are required to conduct the trial in accordance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

Record Retention

The Investigator/study coordinating site/PI's office will maintain all essential trial documents and source documentation, in original format, that support the data collected on the trial subjects in compliance with the GCP guidelines. Documents must be retained for at least 2 years after completion of the study, unless extended by the coordinating site IRB.

Criteria for Terminating Trial

Study coordinating site/PI reserves the right to terminate the trial, but intends only to exercise this right for valid scientific or administrative reasons and reasons related to the protection of subjects. Investigators and associated IRB will be notified in writing in the event of termination.

Criteria for Suspending/Terminating a Trial Center

Study coordinating site/PI reserves the right to stop the enrollment of subjects at a trial center at any time after the trial initiation visit if no subjects have been enrolled or if the center has systemic or major protocol non-compliance without justification or fails to follow remedial actions.

1. Appendix:

Walking impairment score

Patients will be asked to complete a walking impairment questionnaire (score range: 0 to 14,080) at baseline, and then every 6 months for 12 months or until the end of study treatment visit depending on the randomization arm. A patient with a total score of 0 on question 2 would not be able to walk indoors around his/her home without claudication, while a maximum score of 14,080 would be achieved by a patient who can walk 5 blocks (1,500 feet) without claudication. The questionnaire will exclude patients with bilateral superficial femoral artery interventions, to minimize patient bias resulting from partial symptomatic improvements following successful intervention of one extremity, later followed by treatment of the contra- lateral superficial femoral artery.

All , clinical adjudication and adverse events monitoring will be performed by an independent data oversight and safety monitoring board.

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