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INTRODUCTION

Background and Significance

Peripheral arterial disease (PAD) affects millions of people worldwide[1,2]. Management of PAD has evolved from open surgery to an endovascular first approach leading to increased volume of endovascular interventions[3]. Endovascular femoropopliteal intervention has emerged as a standard treatment for symptomatic PAD with acceptable patency rates[4-6].

Histologic observation of bare metal stents with early failure shows association with platelet rich thrombus, and high counts of platelets and neutrophils associated with stent struts[7,8]. Additionally, high inflation pressures associated with balloon angioplasty often causes local tissue damage leading to platelet activation. Identifying role of platelet activation in endovascular treatment failures contributes to current practice standards of prescribing antiplatelet medication following endovascular intervention.

Current standard of care is prescription of dual antiplatelet therapy (DAPT) for femoropopliteal angioplasty or stenting. DAPT is active use of any two anti-platelet agents, often low dose aspirin plus P2Y12 inhibitor (clopidogrel, ticagrelor, prasugrel)[9]. There is improved stent patency and reduced adverse cardiovascular events in patients taking DAPT versus aspirin monotherapy[10-13].

Clopidogrel is the most common additional antiplatelet agent prescribed, but 4-30% of patients taking clopidogrel fail to achieve clinically expected platelet inhibition. This persistent platelet reactivity is commonly referred to as high on-treatment platelet reactivity (HPR) despite compliant antiplatelet use and increases risk of endovascular intervention failure and associated adverse clinical events in these patients[15-17]. Clopidogrel is a pro-drug metabolized by CYP2C19 enzyme into its active form. Failure to respond appropriately to clopidogrel is largely due to genetic polymorphisms within CYP2C19 enzyme resulting in variable metabolization of clopidogrel into the active metabolite[14].

Alternative antiplatelet medications can overcome HPR through different metabolic pathways. Of these, ticagrelor is often used to overcome HPR for patients taking clopidogrel with favorable outcomes[18]. Overall, there is paucity of evidence looking at HPR and lower extremity arterial endovascular interventions without consensus or guidelines on how to address this problem. Thus, we propose an unblinded, randomized control trial comparing testing and treating for HPR versus not testing for HPR with guideline based therapy in patients having femoropopliteal angioplasty or stenting.

Preliminary Studies

The MIRROR trial first demonstrated the benefit of DAPT in patients with lower extremity interventions. Subgroup analysis of the DAPT treatment arm showed that of the failures, XX% were resistant to clopidogrel based on XX testing. Spiliopoulos et al, reported 64% target lesion re-intervention (TLR) in patients with HPR on clopidogrel versus 8% TLR in non-HPR for superficial femoral artery interventions[17]. VerifyNow system was used for HPR testing and defined as >234 platelet reactivity units (PRU). Guo et al reported 34.6% primary patency for superficial femoral artery interventions in patients with reduced CYP2C19 activity compared with 73.1% in those with non-HPR[19]. Bernlochner et al reported similar patency rates in patients with HPR versus non-HPR who had lower extremity arterial interventions[21]. However, they only required one month of DAPT. Furthermore, the Journal for Vascular Surgery recently published a summary on antiplatelet resistance and concluded that there was not enough evidence to recommend any clinical recommendations[22].

Public Health Relevance Statement

Lower extremity arterial endovascular intervention is first line treatment for symptomatic peripheral arterial disease. Current evidence suggests that antiplatelet medication prolongs patency of these interventions. Standard of care is prescribing clopidogrel and low dose aspirin for patients having femoropopliteal interventions. Patients with HPR following standard of care are at risk of early stent failure resulting in re-interventions, potential limb loss, and increased cost. Our research will add the first randomized data about how to address HPR in lower extremity arterial endovascular interventions.

Environment: Facilities and Other Resources Statement

University of Pittsburgh is a large volume, multicenter, tertiary care center with over 175 specialties. Our research effort will be limited to our flagship hospital and primary referral center, UPMC Presbyterian hospital which has 795 beds; UPMC Shadyside with close to 520 beds; UPMC Passavant with over 399 beds; and UPMC St. Margaret with close to 249 beds. These locations perform over 700 lower extremity angiograms and perform over 300 femoropopliteal angioplasty or stent

procedures annually. Each site is equipped with biplaner fluoroscopy, radiology and nursing staff, VerifyNow testing system, and available research personell.

Outpatient hospital clinics are located at UPMC Shadyside, UPMC Passavant, and UPMC St. Margaret. All of our clinics are staffed with board certified vascular surgeons, physician extenders, nurses, and medical assistants. Additionally, each of our clincis has their own non-invasive vascular lab capable of performing both physiologic arterial testing and duplex ultrasound evaluation to help diagnose patency.

Our dedicated research team includes 2 research coordinators and a biostatistician with extensive experience in trial design and execution. Our resarch coordinators are trained in phlebotomy with primary offices at UPMC Shadyside. However, our staff routinely travels to all sites and has ability to transport specimens to desired locations. All research sites are staffed with board certified vascular surgeons, integrated vascular surgery residents, and vascular surgery fellows who will perform the procedures.

High on-treatment reactivity will be tested for using both VerifyNow testing system and pharmacogenetic testing. All research sites are equipped with VerifyNow testing systems. Pharmacogenetic testing is performed at UPMC presbyterian campus through the pharmacogenetics department. Our pharmacogentic department is a leader in studying high on-treatment reactivity and has a validated testing strategy. All specimens will be stored in generator backed up freeze with phone allerting system for any malfunction.

RESEARCH PLAN
SPECIFIC AIMS

Primary Outcome:

Primary Research Question: In patients having femoropopliteal arterial endovascular interventions, should routine HPR testing and treatment be performed?

Hypothesis: Routine testing for HPR will identify patients at risk for early stent failure. Switching patients with HPR to ticagrelor will improve patency of intervention compared to non-HPR patients.

Primary response variable: one-year primary patency

- Definitions:
  - One year- 365 days from date of intervention
  - Primary patency is a binary variable defined as the following at the site of original intervention:
    - Freedom from reintervention
    - Less than 80% stenosis on duplex ultrasound
    - Less than 70% stenosis on computed tomography angiography
    - Freedom from complete vessel thrombosis
- Justification: primary patency is one of the most reported outcomes when assessing lower extremity arterial interventions. Clear definition of primary patency is the most reproducible outcome data with regards to interventional success.
- Ascertainment: standard surveillance of patients receiving lower extremity endovascular interventions occur at a minimum of 1,6,12 months.

Secondary Outcomes:

1. Research Question: What is the one-year primary assisted patency of femoropopliteal balloon angioplasty or stenting compared to non-HPR patients?

   Hypothesis: Patients with HPR will have reduced one-year primary assisted patency compared to patients with non-HPR

   - Response variable: One-year primary assisted patency
   - Description: One-year assisted primary patency is a binary variable measuring stent patency after reintervention following loss of primary patency (excluding stent thrombosis-see outcome number 2). This outcome will be monitored for 365 days following initial stent placement/enrollment.

- Ascertainment: standard surveillance of patients receiving lower extremity endovascular interventions occur at a minimum of 1,6,12 months.

2. Research Question: What is the one-year secondary patency of femoropopliteal balloon angioplasty or stenting compared to non-HPR patients?

   Hypothesis: Patients with HPR will have reduced one-year secondary patency compared to patients with non-HPR

   - Response variable: One-year secondary patency
   - Description: One-year secondary patency is a binary variable measuring patency after reintervention specifically for complete thrombosis and thus loss of primary patency. Stent is defined as patent if it is open to any degree. This outcome will be monitored for 365 days following initial stent placement/enrollment.
   - Ascertainment: standard surveillance of patients receiving lower extremity endovascular interventions occur at a minimum of 1,6,12 months.

3. Research Question: What is the one-year amputation free survival of patients with HPR versus non-HPR following femoropopliteal balloon angioplasty or stenting?

   Hypothesis: Patients with HPR will have decreased one-year amputation free survival compared to patients with non-HPR

   - Response variables: amputation and mortality
   - Description: Amputation is defined as surgical removal of tissue and bone from ipsilateral lower extremity. This will be tracked for 365 days following initial stent placement. This will be further subdivided into major and minor amputation. Major amputation defined as amputation proximal to the ankle joint and minor amputation defined as amputation distal to the ankle joint. Death is defined by sustained loss of pulse and ability to breathe.
   - Ascertainment: standard surveillance of patients receiving lower extremity endovascular interventions occur at a minimum of 1,6,12 months at which time patient interview, questionnaire, and chart review will be performed.

4. Research Question: What is the prevalence of HPR in our patient population following femoropopliteal balloon angioplasty or stenting?

   Hypothesis: Local HPR prevalence will range between 25-30%

   - Response variable: HPR
   - Description: Positive HPR test will be defined as follows:
     - VerifyNow testing system- results greater than 234 platelet reactivity units (PRU)
     - CYP2C19 pharmacogenetic testing- poor metabolizers (PM) and intermediate metabolizers (IM)
   - Ascertainment: VerifyNow testing will be performed day of procedure and pharmacogenetic testing will be performed at end of study.

5. Research Question: What is the difference in major adverse cardiovascular events (MACE) in HPR versus non-HPR patients following femoropopliteal artery balloon angioplasty or stenting?

   Hypothesis: Patients with HPR will have increased MACE compared to patients with non-HPR

   - Response variable: composite of myocardial infarction, stroke, and death
   - Description: Myocardial infarction is defined by EKG changes, elevated troponin, and chest pain confirmed by cardiologist. Stroke is defined by any neurological change associated with brain imaging showing new infarct confirmed by neurologist. Death is defined by sustained loss of pulse and ability to breathe.
   - Ascertainment: standard surveillance will occur at 1,6,12 months at which time patient interview and questionnaire will be performed. Additional chart review will be performed as needed.

6. Research Question: How do results of VerifyNow testing system correlate with pharmacogenetic testing of CYP2C19 polymorphisms in patients having femoropoplital arterial endovascular interventions?

   Hypothesis: Pharmacogenetic testing and VerifyNow testing system results will not be statistically different.

   - Response variable: PRU>234 for VerifyNow testing system ; poor metabolizers and intermediate metabolizers with genetic testing.
   - Description: We will test for a difference in HPR detection between the two testing methods.
   - Ascertainment: VerifyNow testing will only be administered to half the patients and those who have loss of patency. Every study subject will have pharmacogenetic testing performed at end of study.

DESIGN

Design: Open label phase III randomized clinical trial (RCT) comparing routine testing and treating for HPR versus no testing with guideline based care for HPR in patients with lower extremity arterial disease undergoing balloon angioplasty or stenting of superficial femoral artery or popliteal artery.

- Treatment arm: Routine HPR testing using VerifyNow testing system on all patients the day of intervention. Patients with HPR will be prescribed ticagrelor instead of clopidogrel. All patients will have pharmacogenetic testing for CYP2C19 polymorphisms after trial completion.
- Control arm: no initial HPR testing. All patients prescribed clopidogrel. All patients will have pharmacogenetic testing for CYP2C19 polymorphisms after trial completion.

Allocation Ratio: 1:1 between treatment arm and control arm

Randomization Plan: Fixed block randomization with random block size. We will stratify based on patients who received a stent. Randomization will be generated by STATA and uploaded in REDcap. Randomization allocation will be computer generated and obtained by member of research team prior to date of procedure.

Blinding: This will be an unblinded study

- Justification: Test results will need to be available to clinical team to switch HPR patients to ticagrelor. Ticagrelor is twice a day dosing compared to clopidogrel which is daily. This difference can be realized by both patients and surgeons. So, these factors prevent blinding. The cost of medication blinding is too expensive and is not feasible for this study.

PARTICIPANTS AND RECRUITMENT

The study population will be comprised of patients with peripheral arterial disease undergoing lower extremity endovascular balloon angioplasty or stenting of superficial femoral artery or popliteal artery.

Inclusion criteria:

- Inpatients or outpatients
  Justification: population of interest.
- 18-90 years of age
  Justification: population of interest
- Patients with peripheral arterial disease and preoperative imaging suggestive of superficial femoral artery or popliteal artery disease amenable to angioplasty or stenting.
  Justification: population of interest. Will allow for patients to randomized and consented prior to date of procedure

Exclusion criteria:

- Patients treated on an emergency basis
  Justification: pathology of patients treated urgently often includes higher thrombus burden which introduces treatment bias.
- Planned intervention on prior site of open surgical intervention (autogenous or autologous bypass, endarterectomy, or patch angioplasty)
  Justification: Sites of prior surgical repair undergo variable levels of postoperative inflammation, fibrosis, and vessel geometry which can greatly effect outcome, and are difficult to adjust for.

- Planned intervention at site exclusive of superficial femoral artery or popliteal artery
  Justification: site of treatment outside the scope of this study
- Planned re-stenting at site of prior stent placement
  Justification: Prior stent placement potentially restricts the effectiveness of additional stent and introduces selection bias
- Patients less than 18 years old or greater than 90 years old
  Justification: Not our population of interest
- Planned re-angioplasty at site of prior angioplasty
  Justification: Intervening on the same site introduces selection bias
- Known inability to tolerate antiplatelet regimen before enrollment
  Justification: Overall effect size is determined by effectiveness of antiplatelet medication. If patients are known to be intolerant to antiplatelet medications they will introduce error to study.
- Patients who plan on receiving follow up care outside the UPMC system
  Justification: Portion of patients treated at our institution know a-priori that they will follow up at outside institutions. We want to reduce loss to follow up.
- Current use of prasugrel
  Justification: this is a similar antiplatelet medication to ticagrelor that may confound results
- Current use of oral anticoagulation medication
  Justification: concomitant use of oral anticoagulation will likely confound results

SCREENING AND ENROLLMENT:

Screening and Enrollment Protocol: Outpatients scheduled for lower extremity angiography procedures will be flagged and disclosed to research team while in clinic or by secure email. Diagnostic imaging will be reviewed by medical staff. Research team will contact patients to discuss study, answer inclusion/exclusion criteria, and review study protocol. Patients meeting eligibility criteria and willing to participate in study will be randomized

HPR Testing Protocol: We will use both VerifyNow and CYP2C19 genetic testing to identify HPR in study subjects.

Treatment Arm: VerifyNow testing will be performed the day of procedure. Blood sample for genetic testing will be collected on day of procedure or at follow up visit for genetic testing to be performed at conclusion of study.

Control Arm: No initial testing. Blood sample for genetic testing will be collected on day of procedure or at follow up visit for genetic testing to be performed at conclusion of study.

- VerifyNow testing will be ordered through UPMC laboratory, collected by UPMC nurses, and billed to research account. Testing results will be available in electronic medical record.
- Pharmacogenetic testing will be obtained by research team in purple top tube. This sample must be refrigerated and transported to pharmacogenetics laboratory in cooler within 5 days of sample collection. The research team will take this sample to pharmacogenetics lab where it will be frozen for later analysis.

Antiplatelet Prescribing Protocol: VerifyNow testing system requires therapeutic drug levels at time of testing for accurate results. So, all patients need to be on clopidogrel prior to testing:

1. Patients already taking aspirin and 75mg clopidogrel daily will be continued on these medications without modification
2. Patients who are not taking aspirin will be prescribed 81mg aspirin daily to begin immediately.
3. Patients who are not on clopidogrel will be prescribed clopidogrel as follows:
   a. If angiography is scheduled more than 7 days out from initial encounter:
      i. Prescribe clopidogrel at 75mg daily to begin at the time of scheduling angiography.
   b. If angiography is scheduled less than 7 days from first patient encounter:
      i. Prescribe a one-time, single loading dose of 300mg clopidogrel
      AND
      ii. Prescribe clopidogrel 75mg daily to begin the day after the loading dose
   c. Research team will call patient within a week of scheduled procedure to verify adherence to this protocol. If patient fails to follow prescription instructions:
      i. Instruct patient to take a one-time, single loading dose of 300mg clopidogrel (4 tablets)

AND

ii. Instruct patient to take clopidogrel 75mg daily to begin the day after the loading dose

4. Antiplatelet therapy will be prescribed for at least one year following intervention.
5. After one year, continuation of antiplatelet medication is solely at discretion of patient and physician

Angiography Protocol: All angiograms will be performed by board certified vascular surgeons. Angiograms will be performed using standard fluoroscopy at one of several approved locations: UPMC Presbyterian, UPMC, Shadyside, UPMC Passavant, or UPMC St. Margaret. Procedural technique will remain completely at the discretion of the surgeon.

Follow up protocol:

1 month follow up:
- Case report form
- Peripheral vascular laboratory testing

6 month follow up:
- Case report form
- Peripheral vascular laboratory testing

12 month follow up:
- Case report form
- Peripheral vascular laboratory testing

Justification: This is standard follow up schedule

Peripheral vascular testing protocol:

- Duplex testing
  - Angioplasty protocol
    - Color Doppler Imaging
      - At location of intervention
    - Spectral Doppler
      - Common femoral artery (CFA)
      - Superficial femoral artery (SFA)
      - Popliteal artery (POP)
      - Any areas concerning for stenosis should have velocities taken just proximal to narrowing and at the area narrowing to allow for velocity ratio calculation.

  - Stent protocol
    - Color Doppler Imaging
      - Single image of the proximal stent and the native inflow artery
      - Image(s) of the mid portion(s) of the stent
      - Single image of the distal stent including the native outflow artery
    - Spectral Doppler
      - Common femoral artery (CFA)
      - Superficial femoral artery (SFA)
      - Inflow artery just proximal to the stent (PROX A)
      - Proximal stent (STENT P)
      - Mid stent segment(s) (STENT M)
      - Distal stent (STENT D)
      - Outflow artery just distal to stent (DIST A)
      - Any other areas concerning for stent associated stenosis
- Spectral Doppler analysis
  - Systolic velocity ratio (Vr) = (maximum systolic velocity)/ (systolic velocity in the least proximal normal vessel)
  - Vr should be calculated for all areas where there is concern for stenosis

- Interpretation of NIV
  - Restenosis is defined as velocity >300cm/s OR Vr>3.0
  - Stent thrombosis (ST) defined as complete loss of any obtainable Doppler shift at area of concern

Case Report Form Protocol: Patients will answer questions at each follow up visit elucidating adherence, as well as, addressing potential care received outside our hospital system. This form will be built into electronic medical record (EMR) as a hard stop. Clinical staff will interview patient and fill in the answers appropriately. The research team will then gather information from EMR and input to REDcap:

1. Was antiplatelet medication stopped for any reason?
2. How many antiplatelet medication doses were missed since last visit with us?
3. Have you had any reintervention procedures on ipsilateral lower extremity?
4. Have you had any amputation procedure on study lower extremity?
5. Have you had any unexpected or prolonged bleeding events?
6. Have you been hospitalized for unexpected or prolonged bleeding?
7. Have you been diagnosed with stroke since last visit?
8. Have you been diagnosed with heart attack since last visit?
9. Have you been hospitalized for any reason?

Data Collection and Storage

We will be using a secure web based data entry system, REDcap. Research team will input all screening and baseline characteristics into this system. Procedural and platelet reactivity information will be entered by research team once available. Follow up information and case report form information will be entered once available. Limited access will be provided to this system. All data external to REDcap will be kept in the password-protected v-drive. The v-drive is already in use by the investigators and the division and has adequate space for the data. The investigators and clinical team currently have access electronic medical records. There will be no monetary funds or resources necessary to conduct the database maintenance.

g. STATISTICAL EVALUATION

Sample Size Calculation

Patency for patients with HPR are derived from the two prospective studies, which use both primary patency and target limb revascularization as outcome. Since these are different, we have inflated the one-year primary patency rate to 40% for patients with HPR. Average one-year primary patency of femoropopliteal endovascular interventions is about 76%. Prevalence of HPR is about 25% based on local testing. Setting alpha at 0.05, beta at 0.2, and power at 0.8; we will need 29 HPR patients to detect a difference in primary patency between HPR and non-HPR patients. Assuming 20% loss to follow up and 15% treatment failure (inability to perform angioplasty or stenting), we will have to test 179 patients. Therefore, we need a total of 358 patients.

Statistical Analysis

We will use intention to treat analysis. Our primary outcome is primary patency which is a dichotomous variable. We believe that Rutherford scale and smoking status may affect the outcome and a priori we plan to adjust for these variables. We will compare primary patency between our groups using proportional comparisons with chi squared or Fischer's exact testing followed by adjusted logistic regression. Secondary analysis will be performed looking at time to event data Kaplan Meier Estimator with Cox proportional hazard ratios. Significance will be determined based on alpha less than 0.05.

Secondary outcomes of one-year secondary patency and one-year amputation free survival are also categorical variables that will be analyzed in similar fashion. Secondary outcome of major adverse cardiovascular is a categorical variable and will be analyzed using simple descriptive statistics, univariate and multivariate logistic regression. Prevalence of HPR will be reported as a proportion and compared using chi squared testing. We will perform subgroup analysis on the stent group. Again, significant results will be reported based on alpha less than 0.05.

h. SIGNIFICANCE AND CONCLUSON

Preliminary studies of HPR in lower extremity arterial endovascular interventions report decreased patency in those who have HPR. Our study will be the first randomized study comparing treatment and testing for HPR in patients with lower

extremity arterial endovascular interventions. Results from this study can help reshape practice guidelines leading to improved management of lower extremity arterial disease.

h. LITERATURE CITED

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Figure 1. Baseline characteristics

Baseline Characteristics		
	Treatment Arm n=	**Control Arm n=**
Age (mean, sd)		
Gender (% male)		
BMI (mean, sd)		
Race		
Caucasian (%)		
Black (%)		
Asian (%)		
Smoking		
current (%)		
prior (%)		
Hypertension (%)		
Hyperlipidemia (%)		
Diabetes (%)		
Dialysis (5)		
CAD (%)		
history of PCI (%)		
CHF (%)		
Rutherford Scale		
3 (%)		
4 (%)		
5 (%)		
Baseline Antiplatelet Use		
Clopidogrel (%)		
Ticagrelor (%)		
Aspirin (%)		
Baseline Statin Use (%)		
Proton Pump Inhibitor (%)		
Antidepressants (%)		

BMI=body mass index, CAD=coronary artery disease, PCI=percutaneous coronary intervention, CHF=congestive heart failure

Figure 2. Outcomes

Outcomes					
	Treatment Arm n=	**Control Arm n=**	**OR**	**Adjusted OR**	**p value**
Primary patency (%)					
Primary Assisted Patency (%)					
Secondary patency (%)					
Amputation (%)					
major					
minor					
Major Adverse Cardiovascular Events (%)					
VerifyNow PRU					
Pharmacogenetic Testing (%)					

UM					
EM					
IM					
PM					