Clopidogrel Monotherapy in High Bleeding Risk Patients Undergoing Percutaneous Coronary Interventions:

A Safety Assessment, Pilot Study to Reduce Post-Discharge Bleeding

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CHAMP Study: Clopidogrel with High bleeding risk and Adverse events with Monotherapy in patients undergoing Percutaneous coronary interventions

Short Title: Clopidogrel monotherapy in patients with high bleeding risk

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Proposal Summary

Clopidogrel Monotherapy in High Bleeding Risk Patients Undergoing Percutaneous Coronary Interventions: A Safety Assessment, Pilot Study to Reduce Post-Discharge Bleeding

CHAMP Study: Clopidogrel with High bleeding risk and Adverse events with Monotherapy in patients undergoing Percutaneous coronary interventions

What We Know

- High bleeding risk is common (30%) among patients undergoing PCI at Mayo Clinic, Rochester.
- Most bleeds occur within 30 days of PCI.
- Current studies analyzing shortened DAPT regimens exclude the crucial first 30 days.

What This Study Adds

- Genotype-based stratification of patients receiving antiplatelet therapy after PCI.
- Evaluation of the safety and efficacy of clopidogrel monotherapy with deescalation from DAPT within the first week.
- Clopidogrel monotherapy provides an inexpensive regimen with lower bleeding risk compared to alternative agents and regimens.
- *First study to evaluate antiplatelet monotherapy within 7 days of PCI.*

Post-discharge bleeding (PDB) with dual antiplatelet therapy (DAPT) in patients undergoing percutaneous coronary interventions (PCI) is associated with increased morbidity and mortality.[1-5] Approximately 1 in 20 post-PCI patients following DAPT are readmitted for bleeding, with the highest incidence occurring within 30 days of discharge. Patients with PDB are also at increased risk for subsequent death or myocardial infarction (MI), with the highest risk occurring within the first 60 days after a bleeding-related hospitalization.[6, 7] The bleeding hazard further increases with newer P2Y12 inhibitors and oral anticoagulants. The risk of bleeding is modifiable and attempts at reduction in PDB provides an opportunity to improve safety of PCI. In that regard, reduction in PDB has been demonstrated following early aspirin discontinuation and shortened DAPT duration. The Ticagrelor with or without Aspirin in High-Risk Patients after PCI (TWILIGHT) trial demonstrated a doubling of major bleeding risk in patients randomized to ticagrelor with aspirin as compared to ticagrelor alone without an increase in ischemic endpoints with ticagrelor monotherapy.[8] More recently, two randomized trials demonstrated the safety of P2Y12 monotherapy (mainly clopidogrel) following one and three months of DAPT in low-risk patients receiving drug-eluting stents (DES).[9, 10] Similarly, Acetyl Salicylic Elimination Trial (ASET) confirmed the safety of prasugrel monotherapy following DES in stable coronary artery disease.[11] These studies excluded patients with high bleeding risk (HBR), however, the results were consistent in demonstrating reduction in PDB without any increase in the ischemic events. The MASTER DAPT trial demonstrated noninferiority of 1 month of DAPT in HBR patients compared to standard DAPT for 2 or more months in terms of net adverse events and major cardiac/cerebral ischemic events. There was also a lower rate of major or clinically significant minor bleeds in the group receiving only a month of DAPT.[12]

Approximately 15% patients undergoing PCI have HBR and are generally excluded or underrepresented in the DES trials.[13, 14] These patients will benefit from shorter duration of DAPT. However, contemporary clinical trials are done with newer stent designs (polymer-free)[13] include older adults with no inclusion criteria that denote HBR[15] or have prespecified subgroup with HBR[16] significantly limiting the generalizability. The decline in the rates of stent thrombosis with newer generation stents coupled with paucity of data to guide clinical decision-making in this high-risk group highlights the importance to develop simple treatment protocols to lower their bleeding risk. Early bleeding hazard with aspirin coupled with time-dependent increase in major bleeding events underscores the need to aggressively deescalate DAPT, albeit not at the expense of heightened ischemic risk. Such reduction in concomitant ischemic events can be achieved with genotype guidance. A post-hoc analyses of TAILOR PCI demonstrated an almost 80% risk reduction for ischemic events with genotype guidance in the first 3 months after PCI, the highest risk period following PCI. Potential advantages of genotype-guided $P2Y_{12}$ inhibitor therapy in which a large number of patients receive clopidogrel (given an approximate 50% to 70% prevalence of *CYP2C19* noncarriers) and the remainder receive more potent alternative $P2Y_{12}$ inhibitors is lower cost and lower risk for bleeding for this group as compared with patients receiving either ticagrelor or prasugrel. Furthermore, reduction in ischemic events with newer P2Y12 inhibitors could only be demonstrated among CYP2C19 loss-of-function (LOF) carriers, underscoring the utility of upfront genetic testing prior to routine DAPT prescription in patients with HBR undergoing PCI. Our specific aims of the present pilot and safety study are:

Specific Aim 1: Test the hypothesis that clopidogrel monotherapy is safe following successful PCI among 100 consecutive patients with HBR and meeting the inclusion criteria (100 *active* patients, excluding patients who have been enrolled then withdrawn for various reasons such as starting an additional blood thinner, patient preference, etc.). To ensure that we have data on 100 active patients that complete their 1 month visit, we will plan to accrue up to 150 patients. The primary safety end point will be showing noninferiority of clopidogrel monotherapy in reducing ischemic events stratified by presence or absence of CYP2C19 LOF allele (QuantStudio with Chemagic DNA extraction). All patients will receive clopidogrel (600 mg load & 75 mg maintenance) and aspirin (324 mg load & 81 mg maintenance) for the first week. Those with *CYP2C19 2**or *3** LOF allele (*CYP2C19* LOF carriers)] will be prescribed prasugrel or ticagrelor [prasugrel 60 mg load, maintenance 10 mg or 5 mg (for patients ≥ 75 years or < 60 kg) daily or ticagrelor 180 mg load, maintenance 90 mg twice daily (dose escalation with bolus will occur regardless of the timing of the last clopidogrel dose)]. Non-carriers (or those with inconclusive results) will continue with clopidogrel 75 mg daily maintenance dose. Aspirin will be stopped in all patients once *CYP2C19* results are available.

Specific Aim 2: Among participants enrolled in aim 1, aim 2 will determine the incidence of BARC 3 or 5 bleeding events. Other secondary endpoints are post-dismissal all-cause death, any MI up to 180 days, repeat revascularization, or any other BARC bleeding episodes.

SIGNIFICANCE

Reduction in PDB following PCI is a Major Unmet Need: PDB is common and is seen in approximately 5%; and 20% of those bleeds manifest in the first month following PCI. The increase in complexity of patients undergoing PCI and the concerns for late stent thrombosis led to prolongation of duration of DAPT following PCI. Coincidentally, patients with HBR were excluded, underrepresented, or were given bare metal stents. Recent trials have demonstrated superiority of DES over bare metal stents in patients with HBR and showed safety and efficacy of one-month DAPT. The duration of DAPT for at least 30 days, even among HBR patients, is still the standard of care even as most bleeding risk following PCI resides within the first month. Further reduction in duration of DAPT needs to be carefully weighed against heightened ischemic risk, especially among patients presenting with acute

coronary syndrome. The challenges in defining the optimal management of HBR patients undergoing PCI include heterogeneity in its definition and paucity of relevant clinical data.

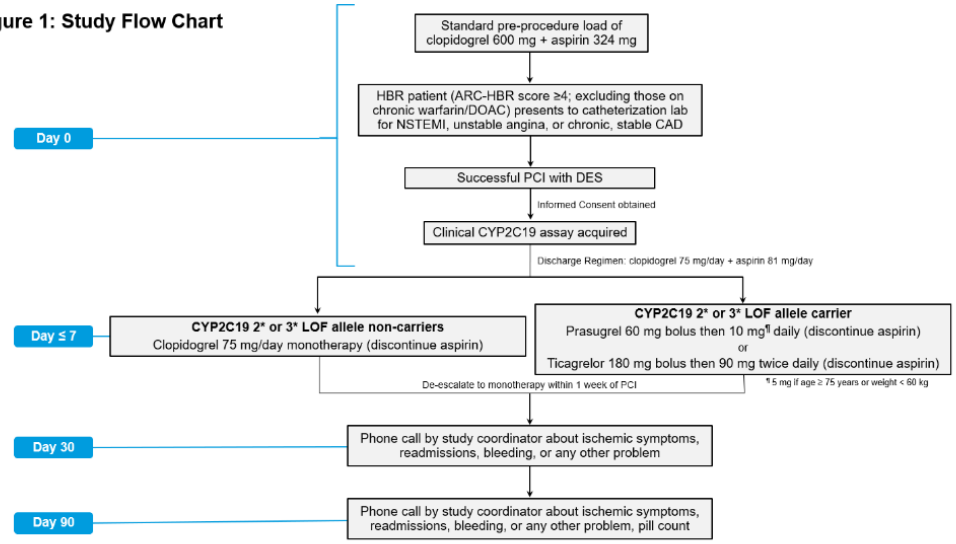
Proposed Strategy to Reduce PDB through Genotype-Guided Clopidogrel Monotherapy: Reduction in the ischemic risk with current generation of DES, modulation of atherothrombotic risk with guideline-directed therapy and shift in patient case-mix towards greater noncardiac morbidity and mortality have identified strategies to lower bleeding without compromising anti-ischemic efficacy. In that regard, trials have shown superiority and safety of DES over bare metal stents with 1 month of DAPT. Most PDB occurs early and underscores the need to abbreviate further the duration of DAPT. More recently, aspirin-free prasugrel therapy following successful stenting in patients with stable coronary artery disease has demonstrated safety. The limitations of that pilot study were use of prasugrel that is associated with higher bleeding (1 patient died with massive intracranial bleed), inclusion of only stable CAD, and no genotype guidance. Our study is a natural, provocative iteration of aspirin-free, clopidogrel monotherapy guided by genotype stratification and will include participants with ACS.

Proposed Strategy to Reduce Ischemic Hazard: Cardiac mortality due to MI dominates in the first week after PCI, and the mortality risk is relatively high for 2 weeks after PCI.[17] The risk of acute or subacute stent thrombosis with current generation stents is low. Utilization of *CYP2C19* genotype–guided prescription of oral P2Y12 inhibitor therapy after PCI may improve that ischemic risk by individualizing antiplatelet therapy according to the CYP2C19 LOF allele status.[18, 19] The potential benefit of this precision medicine approach by individualizing antiplatelet therapy may be more relevant early after PCI. In a post hoc analysis from the TAILOR-PCI, 80% risk reduction in ischemic events with genotype-guided oral P2Y12 inhibitor therapy was seen in the first 3 months after PCI.[20] High prevalence (50%-70%) of non-carriers of CYP2C19 allows very early deescalation into clopidogrel monotherapy in most patients with HBR and tailors newer P2Y12 inhibitors with higher bleeding risk only to patients with CYP2C19 LOF allele. PDB and ischemic PCI data will be actively monitored and entered from same number of controls deemed to have HBR. The central goal of our proposal is to address the unmet need of an effective P2Y12 inhibitor protocol among patients with HBR who undergo PCI to lower their incidence of PDB by leveraging the information from their CYP2C19 genotype. This will allow individualizing antiplatelet treatment while potentially lowering their bleeding and ischemic hazards.

APPROACH: Methodology – ***General Methods***

1. Design Overview. For *Aim 1*, up to 150 participants with HBR on DAPT with clopidogrel and aspirin, who have undergone successful PCI will be stratified by the CYP2C19 LOF allele within one week of DAPT initiation. If present, participants will be given prasugrel or ticagrelor monotherapy, and non-carriers will continue with clopidogrel monotherapy. The primary safety endpoint will be a composite of post-dismissal cardiac death/spontaneous MI <30 days or stent thrombosis <90 days of discharge. For *Aim 2*, the same subjects will undergo post-dismissal assessment for BARC 3 or 5 bleeding, all-cause death, any MI, and/or repeat revascularization up to 180 days. Informed consent followed by genotype assessment will be obtained prior to discharge. Loading dose of clopidogrel (600 mg) will be given to all patients and maintenance dose of 75 mg daily will be given, as indicated. We will allow patients to be given loading dose (324 mg) of aspirin either before or at the time of PCI. The choice of stents, access site and treatment site will be at the discretion of the treating physician (**Figure 1**).
2. Clopidogrel and prasugrel/ticagrelor administration. This study will be single-center, single-arm, open label, first-in-human, and a proof-of-concept, pilot and safety study. All participants in the first week will receive clopidogrel bolus (600 mg) and maintenance (75 mg) and aspirin bolus (324 mg, if not on aspirin) and 81mg maintenance. Participants with HBR who meet the inclusion criteria will be stratified by CYP2C19 LOF allele. Non-carriers (or those with inconclusive results) will continue with maintenance dose of clopidogrel monotherapy at 75 mg daily. If LOF allele is present, they will be prescribed either prasugrel or ticagrelor monotherapy [prasugrel 60 mg load, maintenance 10 mg daily; ticagrelor 180 mg load, maintenance 90 mg twice daily; dose escalation with bolus regardless of timing of the last clopidogrel dose]. Prasugrel will be the preferred agent except when absolutely contraindicated (history of stroke/transient ischemic attack or active bleeding). Patients ≥ 75 years or < 60 kg will receive prasugrel at a reduced dose of 5 mg daily. If there is

Figure 1: Study Flow Chart



a relative contraindication to prasugrel (as determined by the treating physician), the participant will be given ticagrelor. Maintenance aspirin will be discontinued in both arms once genotype testing has been confirmed. (**Figure 1**).

3. Medication adherence, provision of prasugrel/ticagrelor and follow-up: Each enrolled participant will be carefully followed, pre-dismissal education about medication compliance and potential switch to prasugrel or ticagrelor will be given to each participant. A phone call by the study coordinator informing the participant about the results of genotype will be made within the first week of PCI. Study coordinator will mail 3-month supply of prasugrel or ticagrelor to patients with CYP2C19 LOF allele and contact them for the receipt of the medication and will instruct initiation of the loading and maintenance dose. The number of remaining tablets (pill count) at 3-month follow-up will be counted and recorded to assess adherence using a drug accountability report at 3 months. Non-carriers will continue clopidogrel monotherapy. Our main aim is to ensure safety of the participants. Close monitoring and follow-up of each patient will be done. Study-related events will be assessed by the study coordinator at hospital discharge and at 1 and 3 months after PCI by telephone. If patients could not be reached by telephone after multiple attempts, the site coordinator will conduct a medical record review to assess follow-up. All cardiovascular-related end points and hospitalizations will be reviewed and adjudicated by an independent committee blinded to study groups and P2Y12 inhibitor received by the patient. Only study-related events confirmed by the adjudication committee will be included in the analysis.
4. Trial Duration: 90 days. This is based on the observations that the highest bleeding and ischemic risk following PCI is within first 90 days. Importantly, a post-hoc analysis demonstrated an almost 80% risk reduction for ischemic events with genotype guidance in the first 3 months after PCI.
5. Definitions and Role of Data and Safety Monitoring Board (DSMB): All deaths will be considered cardiac unless a clear noncardiac cause can be ascertained. Spontaneous MI will be defined according to the fourth universal definition.[21] Periprocedural MI (< 48 hours post-PCI) will be defined according to the 2013 definition of the Society for Cardiovascular Angiography and Interventions.[22] Stent thrombosis will be defined and classified according to the Academic Research Consortium–2 definition.[23] BARC bleeding will be defined as previously reported.[24] All endpoints will be independently adjudicated by the clinical event committee. An independent DSMB will oversee the individual and collective safety of the patients in the study during enrollment and follow-up. To provide the steering committee with timely feedback on potential safety issues, the DSMB will review the data 3 times during the trial: (1) When the 25th patient is enrolled, (2) when the 50th patient is enrolled, (3) when the 100th patient is enrolled, and (4) when the 100th actively enrolled patient completes 1-month follow-up.
6. Subjects
   a) *Inclusion Criteria*: Informed consent after successful PCI [no non-fatal MI/stroke/repeat target revascularization/bleeding/acute kidney injury] and academic research consortium-high bleeding risk (ARC-HBR) score ≥4.
   b) *Exclusion Criteria*: Chronic use of warfarin or direct oral anticoagulant (DOAC), unsuccessful PCI (see above), lesions with angiographic thrombus, prior PCI within 6 months (except for staged PCIs within the same hospitalization or within 7 days of initial PCI, in which case enrollment will occur following the final planned/staged PCI), planned PCI greater than 7 days but less than 6 months following index PCI, planned surgical intervention to treat any cardiac or noncardiac condition within 6 months (excluding transcutaneous valve interventions and pacemakers), high risk lesion/stent characteristics (>50% unprotected left main disease, bifurcation disease requiring 2 stents technique, rotational atherectomy, vein graft, unprotected left main intervention, or history of definite stent thrombosis), women of child-bearing age unless negative pregnancy test is done, life expectancy <1 year, known drug/alcohol dependence, and assessment that the patient will not be compliant with the study protocol.
   c) *Subject Accrual Plan:* The recruitment will be drawn from the Earl Wood Cardiac Catheterization Laboratory (>1,500 PCIs/year) and Cardiology inpatient services at St. Mary's Hospital. Day 1 will include screening following successful PCI, bleeding risk calculation (ARC-HBR), enrollment, informed consent, and clinical CYP2C19 assay collection. On day 30, a study coordinator phone call will occur to assess ischemic symptoms, readmission, and bleeding. On day 90, a study coordinator phone call will again assess ischemic symptoms, readmissions, and bleeding. All encounters will include drug education and assurance of compliance.
   d) *Reassessment:* The study coordinator will make phone calls at one and three months to inquire about ischemic symptoms, readmissions at other hospitals with MI, or any bleeding.

7. **Control Cohort:** A cohort of similar patients will be identified from the Mayo Clinic catheterization laboratory PCI registry to determine rates of ischemic and bleeding events in a cohort of HBR post-PCI patients reveiving standard of care DAPT after PCI. These patients will be identified by registry review, and we will utilize ICD diagnosis codes to identify bleeding and ischemic events. Retrospective chart review will verify the clinical situation to ensure the validity of the coded diagnoses (to minimize errors inherent to diagnosis coding). There will be no direct patient contact, and patients who refused registry research participation will be excluded from this study. We aim to obtain the following

data:

A. Events
- Event type (category below); diagnosis codes selected from Mayo Clinic database of ICD codes (https://intranet.mayo.edu/charlie/quantitative-health-sciences-groups/rochester-epidemiology-project/index-of-possible-codes-for-specific-conditions-diseases/)
- Date of ischemic/bleeding event
- Bleeding Categories
  - *Hemorrhage, gastrointestinal*
  - *Stroke (hemorrhagic)*
  - *Disease, cerebrovascular (hemorrhagic)*
  - *Hematuria*
- Ischemic Categories
  - *Infarction, myocardial*
  - *Disease, cerebrovascular (TIA, ischemic stroke)*

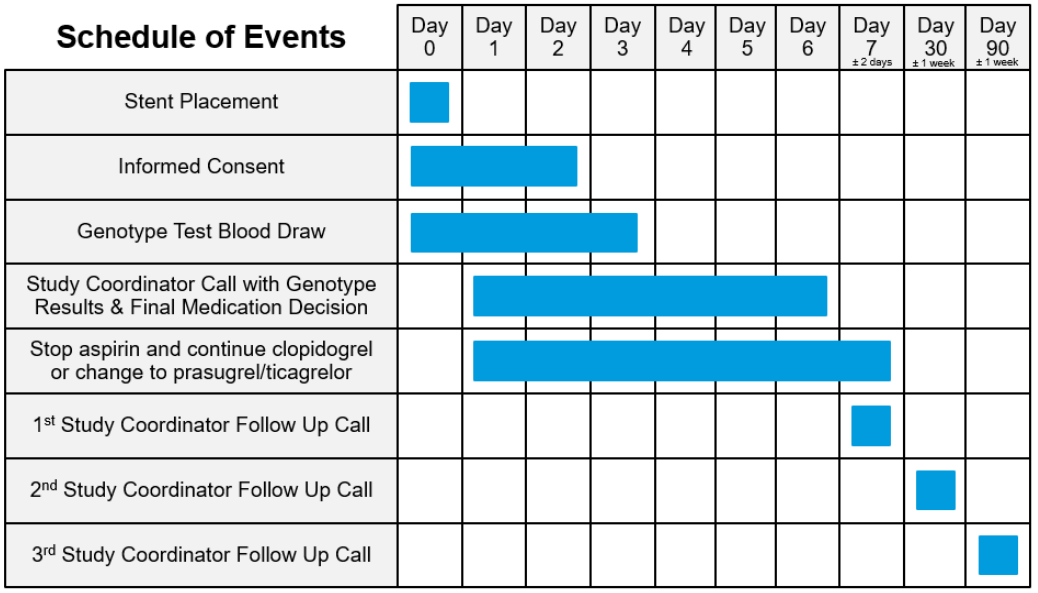
B. Inclusion
- Successful PCI
- Approx. 1 year date range TBD (n = 1500 patients; targeting contemporary PCI patients within the last 2 years).

C. Exclusion
- Enrolled in CHAMP Trial

D. Demographic/Procedure Info to Capture from PCI Registry
- Age/DOB
- Sex
- Race
- Event type (STEMI, NSTEMI/unstable angina, chronic CAD)
- PCI date
- Hemoglobin at time of PCI
- Hemoglobin at time of bleeding event (obtain from chart review; not available in registry)
- Creatinine and eGFR at time of PCI
- Use of clopidogrel, prasugrel, ticagrelor
- Use of oral anticoagulant (warfarin, apixaban, rivaroxaban)

Aim 1: Detailed Approach

The objective of aim 1 is to determine if clopidogrel monotherapy following successful PCI is safe among non-carriers of CYP2C19 LOF allele. The *hypothesis* is that carriers of CYP2C19 LOF genotype are unable to metabolize clopidogrel effectively to an active drug that blocks P2Y12 receptors and inhibit platelet aggregation and are therefore at heightened ischemic risk following PCI. We will reduce bleeding risk by giving clopidogrel monotherapy only to non-carriers. Our *approach* to test this hypothesis is stratifying HBR patients after successful PCI into those with CYP2C19 LOF allele and those with inconclusive results or who are



non-carriers. Within first week of DAPT initiation, non-carriers will receive clopidogrel monotherapy, and prasugrel/ticagrelor will be given to patients with CYP2C19 LOF allele. The *rationale* for this aim is to individualize antiplatelet therapy and to reduce bleeding risk by stratifying P2Y12 pharmacotherapy by the CYP2C19 LOF genotype. Large number (50%-70%) of patients are non-carriers and in them clopidogrel monotherapy would suffice and the remainder will receive prasugrel or ticagrelor thereby lowering bleeding risk, cost, and unique adverse effects related to ticagrelor (e.g., bradycardia, dyspnea) or excess bleeding related to prasugrel. Recruitment should not be a challenge at Mayo Clinic, Rochester where 30% of PCI patients are HBR.

Background. The highest risk for readmissions for bleeding is within 30 days of discharge, and those with PDB are also at heightened ischemic risk for death/MI within the first 60 days of bleeding-related hospitalization. These findings suggest a critical period after bleeding events when patients are most vulnerable for further adverse events. Contemporary studies have abbreviated the DAPT duration (1-3 months) or have deescalated the intensity of P2Y12 inhibitors only after this critical period is over. There is an urgent need to test early antiplatelet deescalation leveraging CYP2C19-LOF allele-based stratification.

Preliminary Studies. HBR patients represent 30% of all patients who underwent PCI in the Mayo Clinic, Rochester catheterization laboratory between January 2010 and July 2021. Role of genotyping in reducing the incidence of major bleeding following PCI: TAILOR PCI demonstrated a 34% risk reduction of ischemic events (HR 0.66, 95% CI 0.43-1.02, p=0.06) at 12 months with genotype guided P2Y12 inhibitor therapy.[20] Importantly in that trial, a post-hoc analysis demonstrated an almost 80% risk reduction (p=0.001) for ischemic events with genotype guidance in the first 3 months after PCI, the highest risk period following PCI. A recent meta-analysis using data from 7 randomized control trials with 15,949 patients demonstrates a 30% risk reduction in ischemic events (95% CI 0.59-0.83) in CYP2C19LOF allele patients with the use of ticagrelor/prasugrel vs clopidogrel and a RR of 1.0 (95% CI 0.80-1.25) in wild-type or no LOF patients indicating that CYP2C19 genotype played a significant role in driving the benefit of ticagrelor/prasugrel.[25]

Table 1: Criteria for High Bleeding Risk at the Time of Percutaneous Coronary Intervention

Major	Minor
	Age ≥75 years
Anticipated use of long-term oral anticoagulation	
Severe or end-stage chronic kidney disease (eGFR <30 mL/min)	Moderate chronic kidney disease (eGFR 30 to 59 mL/min)
Hemoglobin <11 g/dL	Hemoglobin 11.0 to 12.9 g/dL for men and 11.0 to 11.9 g/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion
Moderate or severe thrombocytopenia (platelet count <100×10^9/L) present prior to PCI	
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
Recent major surgery or major trauma within 30 days before PCI	Long-term use of oral nonsteroidal antiinflammatory drugs (NSAIDs) or steroids
Active malignancy (excluding nonmelanoma skin cancer) within the past 12 months	
Previous spontaneous intracranial hemorrhage (at any time) Previous traumatic intracranial hemorrhage within the past 12 months Presence of a bleeding arteriovenous malformation Moderate or severe ischemic stroke within the past 6 months	Any ischemic stroke at any time not meeting the major criterion
Nondeferrable major surgery on DAPT	

Research Design

1. *Assessment of high bleeding risk:* Academic Research Consortium (ARC) defined 1-year high bleeding risk as a BARC 3 or 5 risk of ≥4% or a risk of intracranial hemorrhage of ≥1%.[26] The variables included in this risk model are listed in **Table 1**. Twenty clinical criteria were chosen as major or minor, and patients are at high risk for bleeding if at least 1 major or 2 minor risk criteria are met. This model successfully identified high bleeding risk patients following PCI.[27]
2. *Assessment of CYP2C19LOF Allele:* Clinical CYP2C19 assay will be run on QuantStudio with Chemagic DNA extraction that assesses CYP2C19 (*2, *10, *17, *35) The results will be expected within 72 hours of receipt of the samples. Once received, the results will be communicated to the participants and clopidogrel monotherapy will be initiated or samples of prasugrel or ticagrelor will be mailed.

Expected Outcomes. From these data, we will determine whether there is increased ischemic risk in HBR non-carriers of CYP2C19 LOF genotype receiving clopidogrel monotherapy post-PCI. Close monitoring of participants receiving clopidogrel monotherapy or prasugrel/ticagrelor monotherapy for any cardiac deaths, spontaneous MI and stent thrombosis will be done.

Potential Problems and Alternative Strategies. The results of genotype-based assay will be available at or following the participant's discharge. To ensure compliance with clopidogrel monotherapy or switch among participants with CYP2C19 LOF allele, the study coordinator will call them with the results, mail the 90-day prescription for prasugrel or ticagrelor and ensure its receipt and initiation. Based on the expert consensus, pharmacodynamic data, escalation in patients with *CYP2C19 2** or *3** LOF allele will require stopping clopidogrel and switching to 60 mg loading dose of prasugrel or 180 mg loading dose of ticagrelor regardless of the timing of the last dose of clopidogrel followed by standard maintenance dose of prasugrel 10 mg daily (5 mg if age ≥ 75 years or weight < 60 kg) or ticagrelor 90 mg twice daily. We have elected to exclude patients on chronic warfarin or DOAC. While this is an ARC major criterion for HBR, aspirin is already being discontinued frequently post-PCI in many patients to avoid triple therapy, and we want to ensure that this study is truly evaluating antiplatelet monotherapy and is not confounded by use of chronic anticoagulants. Patient enrollment is another potential problem, but our group has a strong track record of successfully enrolling participants into

Table 2: Percent of Patients with Death or Myocardial Infarction After PCI

Year	30 days	60 days	90 days
2010	14%	16%	17%
2011	17%	20%	22%
2012	10%	11%	13%
2013	9%	11%	13%
2014	6%	8%	8%
2015	6%	8%	9%
2016	5%	6%	7%
2017	5%	6%	6%
Total*	9%	11%	12%

*MI data unavailable after 2017; Data from Mayo Clinic, Rochester; MI, myocardial infarction

clinical trials, including genotype-directed randomization for the TAILOR PCI trial. We will approach potential participants for informed consent before dismissal following the PCI procedure. For participant with same-day dismissal, we will approach them either before coronary angiography or pre-dismissal once the sedation from the procedure wears off.

Aim 2: Detailed Approach

Aim 2 includes participants enrolled in Aim 1, and this data will determine the incidence of post-discharge BARC 3 or 5 bleeding events. Other secondary endpoints are post-dismissal all-cause death, any MI up to 180 days, repeat revascularization, or any other BARC bleeding episodes. The rate of death or MI post-PCI at Mayo Clinic, Rochester is presented in **Table 2**.

Introduction. PDB is common and is seen in approximately 5% and 20% of those bleeds manifest in the first month following PCI. Longer observation is needed to accurately define its incidence, source, severity, and time dependency. The ischemic hazard usually follows admission due to PDB and is likely due to interruption or discontinuation of DAPT. Insights into its time course, relationship with antecedent bleeding, type of MI (STEMI vs. NSTEMI) and prognosis are equally relevant. Prolongation of observation is critical to delineate time course of both bleeding and ischemic hazards. The *objectives of Aim 2* are to determine the frequency, time course, type, severity, and prognosis of both ischemic and bleeding events till the end of 6 months. The *working hypothesis* is that most PDB and ischemic events occur early after PCI, however, increase in both ischemia and bleeding may continue, especially among participants with ACS. We further hypothesize that participants receiving clopidogrel monotherapy will continue to demonstrate lower incidence of bleeding as compared to the standard of care with DAPT. Our *approach* to test this hypothesis will be to do extended period of observation till 6 months and record both bleeding and ischemic events. The *rationale* for this aim is that the main driver for increase in PDB and consequent ischemia is the intensity and duration of DAPT, however most bleeds and ischemia occur early, questioning the need to extend the duration of DAPT. After successful completion of the proposed studies for Aim 2, it is our *expectation* that using a prospective design, we will have identified predictors of PDB and ischemia.

Background. Recent randomized trials have investigated different antithrombotic strategies, including monotherapy with a $P2Y_{12}$ inhibitor, aiming to assess the best balance between ischemic and bleeding risks after PCI. Shortening of DAPT duration is safe and has not demonstrated an increase in the incidence of ischemic risk. The limitations of the existing trials are, 1) that DAPT is given for 1-3 months, and there is an urgent need aspirin-free P2Y12 inhibition in the first month following PCI that overlaps with high risk period for PDB, 2) TWILIGHT trial randomized higher-risk patients only after demonstrating no ischemia or bleeding for the initial 3 months following PCI thereby selecting lower-risk patients for PDB, 3) ASET pilot study included only low-risk, stable patients who were given prasugrel. Older age is one of the main drivers of bleeding and along with prior TIA/stroke, or low body weight will significantly limit the applicability of monotherapy with prasugrel. In that regard, individualizing P2Y12 therapy guided by genotyping at the time of PCI allows us to use clopidogrel with lower attendant bleeding risk among non-carriers (prevalence of 60%-70%) and limiting the use of newer P2Y12 inhibitors to the rest. Accurate assessment and prolongation of period of observation is relevant especially among participants presenting with ACS. The central goal of Aim 2 is to study the incidence of PDB and ischemia during the first 6 months following PCI with DES. This aim leverages the support from existing Mayo Clinic PCI database in whom all the information is routinely collected following a coronary intervention.

Preliminary Studies. *Research Design:* Same 150 participants from Aim 1 will be enrolled, however, data for Aim 2 will be collected at six months. Our main strategy for this aim is to demonstrate whether clopidogrel monotherapy, guided by genotype, is associated with lower bleeding and ischemic events during extended period of observation, especially relevant in participants presenting with ACS. *Expected Outcomes:* Upon completion, we will have comprehensive data on incidence, severity, predictors, type, and time trends for both PDB and ischemia. In recent years, several trials have analyzed PCI in HBR patients examining DAPT regimens and outcomes to balance the risk of ischemia and bleeding. **Table 3** (see supplemental material) summarizes these key trials. Extending the period of observation allows us to monitor the participants longer and demonstrate the safety of clopidogrel monotherapy. From this aim we will determine whether clopidogrel monotherapy is safe in all-comers following successful PCI, especially among participants presenting with ACS, as the current guidelines recommend at least 6 months of DAPT. Importantly, with this aim, we will focus on the period between 3 and 6 months for both ischemic and bleeding events. The idea is that by providing early deescalation with a P2Y12 inhibitor, clopidogrel will lead to lowering in the incidence of PDB. The observation period will continue even beyond 6 months as all participants will be entered into the Mayo Clinic database. We expect that subjects receiving clopidogrel monotherapy will have reduced PDB during 6 months of observation. If the data confirm our hypotheses, we will expect our hypothesis and will have shown after completion of Aim 2 that clopidogrel monotherapy is safe and effective during 6 months of observation.

Potential Problems & Alternative Strategies. Participants may not report minor bleeds. Minor bleeds are generally nonactionable and don't carry the same prognostic connotation as more severe BARC 3 bleeds. We will, however, attempt to capture all bleeds, including BARC 2. Participants may be admitted to out-of-network facilities with PDB and/or any ischemic event that may not be captured routinely. We have a strong post-PCI surveillance program to contact the participants and retrieve such records. Specific adverse events monitored will include death, type I NSTEMI, STEMI, stent thrombosis, upper gastrointestinal (GI) bleed, lower GI bleed, GI bleed of unclear source, intracranial bleed (hemorrhagic stroke, subdural

hemorrhage, etc.), ischemic stroke, radial artery access site complication, femoral artery access site complication, and/or other clinically significant bleeding event. Drug compliance may be an issue. To ensure higher rates of compliance, study coordinators will underscore the importance of medication compliance before discharge.

Statistical Considerations: Sample size estimation: Due to the exploratory nature of the study, no formal sample size calculations will be performed. Continuous variables will be expressed as mean ± SD or as median with interquartile range. Categorical variables will be expressed as frequencies and percentages. Stoppage Rule: On the basis of prior pilot studies with similar designs and more recently the ASET study, a sample size of 100 active patients is planned with a similar safety stopping rule based on the presence of definite stent thrombosis.[11, 28-30] In the present study, if we observe more than 2 cases of definite stent thrombosis, the study will be halted and further recruitment will be terminated. The cutoff rates for definite stent thrombosis is determined based on the incidence of stent thrombosis (1.2% at 30 days and 1.7% at 1 year, in the Bern-Rotterdam registry).[29]

Project Timeline & Budget: Year 1 will include IRB submission/approval. Patient recruitment and conducting the study will occur in year 1 and year 2 if necessary. Statistical analysis and manuscript preparation/submission will occur in year 2. The budget for this project is $100,000 ($99,987 – see attached budget).

Future Directions: The incidence of PDB following PCI is associated with significant morbidity and mortality, and the incidence will continue to grow with the aging population. Safe, early deescalation of inhibitors P2Y12 remains the cornerstone of management.[31] Stratification based on the CYP2C19 LOF allele allows us to use clopidogrel monotherapy with less bleeding compared to newer (ticagrelor or prasugrel). Upon completion of this project, we will have identified whether clopidogrel monotherapy among non-carriers of this allele can lower the incidence of PDB without compromising safety. This holds great potential to allow for a much larger population of patients at HBR to benefit from this protocol. If this study confirms our hypothesis, the next steps will be to test clopidogrel monotherapy in a large multicenter trial to determine whether its administration is safe and lowers the incidence of PDB. Further study would also be warranted to evaluate the underlying mechanisms of improvement and to demonstrate whether longer-term treatment (beyond 3 months) is safe. Finally, other doses and combinations can be tested along with further research to define the optimal dosing duration and schedule. Prior to proceeding to these future studies, our study will test the *concept hypothesis* that clopidogrel monotherapy is safe and effective to reduce PDB among participants undergoing PCI with DES. If our hypotheses are not confirmed, future directions will include testing of alternative ways to reduce PDB. In addition, routine use of PPI can be considered to optimize their safety and effectiveness. Our goal is to better understand the PDB bleeding among patients undergoing PCI with DES. If correct, our hypothesis will impact future trial designs and future practice.

Supplemental Material

	STOP-DAPT-2	XIENCE 28	XIENCE 90	ONYX ONE	EVOLVE SHORT DAPT	MASTER DAPT
	2019	2020	2020	2020	2021	2021
	3,045	1,605	2,047	1,996	2,009	4,579
	Open-label RCT	Open-label, non-randomized	Open-label, non-randomized	Single-blind RCT	Non-randomized	Open-label RCT
	XIENCE DES	XIENCE DES	XIENCE DES	Resolute Onyx or BioFreedom	SYNERGY DES	DES
	1 mo. DAPT, then clopidogrel monotherapy v. 12 mo. DAPT.	1 mo. DAPT then aspirin monotherapy (if no ischemic event by 1 mo.) v. control from XIENCE V (DAPT for 6-12 months; 2012).	3 mo. DAPT then aspirin monotherapy (if no ischemic event by 3 mo.) v. control from XIENCE V (DAPT for 6-12 months; 2012).	1 mo. DAPT, then aspirin or P2Y12 inhibitor with either stent (randomized 1:1).	3 mo. DAPT, then aspirin monotherapy v. 12 mo. DAPT controls	1 mo. DAPT, then single antiplatelet v. ≥2 mo. DAPT (6 mo. if no indication for oral anticoagulant; 2 mo. if indication), then single antiplatelet agent.
	12 months	6 months	12 months	12 months	≥12 months	12 months
	1° endpoint was composite of CV death, MI, stroke, definite ST, or major or minor bleeding at 12 months. with a relative noninferiority margin of 50%.	1° objective: Evaluate safety (all death or MI) of 1 mo. DAPT v. 12 mo. 2° objective: Impact of 1 mo. DAPT v. 12 mo. BARC 2-5 bleeding	1° objective: Evaluate safety (all death or MI) of 3 mo. DAPT v. 12 mo. 2° objective: Impact of 3 mo. DAPT v. 12 mo. BARC 2-5 bleeding + rate of stent thrombosis.	1° outcome: Safety composite of CV death/MI/ST at 12 mo. 2° outcome: Target-lesion failure, effectiveness composite of CV death, or target vessel MI/lesion revascularization	Co-1° endpoints: (a) death/MI compared with a historical control and (b) study stent-related definite/probable ST compared to a performance goal.	(1) Net adverse events (composite: all death/MI/stroke, major bleed); (2) major adverse cardiac or cerebral events (composite: all death/MI/stroke); (3) major or clinically relevant nonmajor bleed.
	1 mo. DAPT was *both* noninferior and superior to 12 mo. DAPT for the 1° endpoint occurring in 2.4% with 1 mo. DAPT and 3.7% with 12 mo. DAPT (AD, −1.34%[95%CI, −2.57% to −0.11%]; HR, 0.64 [95% CI, 0.42-0.98]); p < .001 for noninferiority and p=0.04 for superiority.	Composite of all death or MI 3.5% v. 4.3% (control), *p* for noninferiority = 0.0005. BARC type 2 to 5 bleeding rate 4.9% v. 5.9% (control); p=0.19 for superiority. Major bleed (BARC type 3 to 5) 2.2% v. 4.5% (control) p =0.0156 for superiority. Definite/probable ST 0.3% between 3 and 12 months (but *not* a powered 2° endpoint in this study).	Composite of all death or MI 5.4% v. 5.4% (control), *p* for noninferiority = 0.0063. BARC type 2 to 5 bleeding rate 5.1% v. 7.0% (control); *p* =0.0687 for superiority. Major bleed (BARC type 3 to 5) 2.2% v. 6.3% (control) p < 0.0001 for superiority. Definite/probable ST 0.2% between 3 and 12 months.	1° outcome 17.1% Resolute Onyx and 16.9% BioFreedom (RD, 0.2 %points; upper boundary of the 1-sided 97.5% CI, 3.5; noninferiority margin, 4.1; p=0.01 for noninferiority). 2° outcome 17.6% Onyx Resolut and 17.4% BioFreedom (RD, 0.2 %points; upper boundary of the one-sided 97.5% CI, 3.5; noninferiority margin, 4.4; p=0.007 for noninferiority).	Adjusted rate of death/MI between 3 mo. and 15 mo. was 5.6% among pts receiving 3 mo. DAPT v. 5.7% in the 12 mo. DAPT control (propensity adjusted difference −−0.12%; 97.5% upper bound =1.63%, < the prespecified margin of 2.52, *p*= 0.0016 for noninferiority). Rate of stent-related ST between 3 and 15 mo. was 0.2% in the 3 mo. DAPT group (97.5% upper bound =0.63%; *p*=0.0005 compared to 1% performance goal).	Net adverse clinical events 7.5% 1 mo. DAPT v. 7.7% standard DAPT (difference, −0.23 %points; 95% CI, −1.80 to 1.33; p<0.001 for noninferiority). Major adverse cardiac/cerebral event 6.1% 1 mo. DAPT v. 5.9% standard DAPT (difference, 0.11 %points; 95% CI, −1.29 to 1.51; p=0.001 for noninferiority). Major or clinically relevant nonmajor bleed 6.5% 1 mo. DAPT v. 9.4% standard DAPT (difference, −2.82 %points; 95% CI, −4.40 to −1.24; p<0.001 for superiority).
	1 mo. DAPT followed by clopidogrel alone compared to 12 mo. DAPT resulted in a significantly lower rate of a composite of CV and bleeding events meeting criteria for both noninferiority and superiority.	1 mo. DAPT regimen (then aspirin alone) in HBR pts is noninferior for ischemic and BARC 2-5 bleeding and reduce BARC 3-5 bleeding complications at 12 months compared to longer, traditional DAPT regimens up to 12 months.	3 mo. DAPT regimen (then aspirin alone) in HBR pts is noninferior for ischemic and BARC 2-5 bleeding and reduce BARC 3-5 bleeding complications at 12 months compared to longer, traditional DAPT regimens up to 12 months.	In HBR pts who receive 1 mo. DAPT after PCI, Onyx Resolute stents were noninferior to BioFreedom stents with regard to safety and efficacy composite outcomes.	Favorable ischemic outcomes in HBR pts undergoing PCI with Synergy stenting and 3 mo. of P2Y12 inhibitor therapy.	1 mo. of DAPT noninferior to ≥ 2 mo. DAPT with regard to net adverse clinical events & major adverse cardiac/cerebral events. 1 mo. DAPT also resulted in lower incidence of major or clinically relevant nonmajor bleeds.

Key
1° = primary
2° = secondary
AD = absolute difference
BARC = Bleeding Academic Research Consortium
BioFreedom (BioSensors Interventional Technologies) = polymer-free umirolimus/biolimus A9 drug-coated stent
BMS = bare metal stent
CAD = coronary artery disease
CI = confidence interval
CV = cardiovascular
DAPT = dual antiplatelet therapy
DCS = drug coated stent
DES = drug eluting stent
HBR = high bleed risk
HR = hazard ratio
MACE = major adverse cardiac event
MI = myocardial infarction
mo. = months
n = number of participants in study
pts = patients
RCT = randomized controlled trial
RD = risk difference
Resolute Onyx (Medtronic) = durable-polymer, slow-release zotarolimus-eluting stent
RR = relative risk
ST = stent thrombosis
TVR/TLR = target vessel/lesion revascularization
E-ZES = Zotarolimus-Eluting Endeavor Sprint Stent

References

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ZEUS-HBR[32]
SENIOR[15]
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TWILIGIGHT[8]
STOP-DAPT-2[10]
XIENCE 28 (Presented by Valgimigli TCT Connect 2020)
XIENCE 90 (Presented by Mehran TCT Connect 2020)
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