Tailored Antiplatelet Initiation to Lesson Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention (TAILOR-PCI)

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PROTOCOL

Tailored **A**ntiplatelet **I**nitiation to **L**essen **O**utcomes Due to Decreased Clopidogrel **R**esponse after **P**ercutaneous **C**oronary **I**ntervention: TAILOR-PCI

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1. GLOSSARY OF TERMS

ACC	American College of Cardiology
AHA	American Heart Association
ACS	acute coronary syndrome
AHRC	Applied Health Research Center
BAP	Biospecimens Accessioning and Processing Lab
bid	twice daily
CABG	Coronary Artery Bypass Graft
CAD	coronary artery disease
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CRF	case report form
CV	cardiovascular
DCIS	DreamCIS, Inc.
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
HHS	Health & Human Services
FDA	Food and Drug Administration
HR	Hazard Ratio
MACE	major adverse cardiovascular event
MI	myocardial infarction
NSTEMI	non-ST elevation myocardial infarction
PCI	percutaneous coronary intervention
PHS	Public Health Service
PI	Principal Investigator
qd	every day
SCAI	Society for Cardiovascular Angiography and Interventions
STEMI	ST-elevation myocardial infarction
WT	wild type

2. SPECIFIC AIMS AND OBJECTIVES / HYPOTHESES

TAILOR-PCI is a prospective, randomized trial testing the hypothesis that after percutaneous coronary intervention (PCI), ticagrelor 90 mg bid is superior to clopidogrel 75 mg qd in reducing a composite endpoint of major adverse cardiovascular events (MACE), i.e. non-fatal myocardial infarction, non-fatal stroke and cardiovascular (CV) death, severe recurrent ischemia, and stent thrombosis (primary endpoints) in *CYP2C19* reduced function allele patients. Patients who undergo PCI will be randomized to a conventional therapy arm (i.e. to receive clopidogrel 75 mg once daily without prospective genotyping guidance) versus a prospective *CYP2C19* genotype-based anti-platelet therapy approach (ticagrelor 90 mg bid in *CYP2C19**2 or *3 reduced function allele patients, clopidogrel 75 mg once daily in non-*2 or -*3 *CYP2C19* patients). Buccal swabs will be obtained for those subjects randomized to the prospective genotyping arm. All subjects will have a blood sample drawn for DNA analysis but genotyping using these DNA samples will be performed only after completion of the duration of anti-platelet therapy (i.e. after one year). In cases where the initial sample collected to analyze the DNA at the one year time point is found to be an unviable sample, the subject will be contacted and asked to provide another DNA sample via a blood sample or saliva sample. The primary endpoints will be assessed prospectively in the retrospectively identified reduced function *CYP2C19* allele patients receiving clopidogrel 75 mg once daily and compared with the prospectively identified reduced function *CYP2C19* allele group receiving ticagrelor 90 mg bid. A total of 5,270 patients will be enrolled.

2.1 Primary Hypotheses

Hypothesis 1A: As compared with clopidogrel, treatment with ticagrelor will result in significantly reduced risk of MACE, i.e. non-fatal myocardial infarction, non-fatal stroke, CV death, severe recurrent ischemia, and stent thrombosis if not captured in other events, in patients with reduced function *CYP2C19* allele(s) (as identified retrospectively by the ABI TaqMan platform) who undergo PCI. This hypothesis will be tested with a two-sided test at a Type I error rate of 0.05.
Hypothesis 1B: In patients undergoing PCI who are wild type with respect to CYP2C19 (by TaqMan), and who receive clopidogrel, prospective knowledge of their genotype (according to the Spartan® platform results) does not alter the risk of MACE. This hypothesis will be tested formally only if the null hypothesis for Hypothesis 1A is rejected.

2.2 Secondary Aims and Objectives

To assess the incidence of major or minor bleeding in patients with reduced function *CYP2C19* allele(s) receiving ticagrelor versus clopidogrel

2.3 Exploratory Pre-specified Outcomes

1. The individual components of the primary outcome.
2. To assess the effect of *CYP2C19*17* on bleeding risk and MACE.
3. The effect of *CYP2C19**2 or *3 genotype on multiple recurrent MACE events in the individual subject.
4. To compare the occurrence of MACE in patients with reduced function *CYP2C19* allele(s) receiving clopidogrel to those with wild type (WT) genotype receiving clopidogrel.
5. To compare the occurrence of MACE in patients with reduced function *CYP2C19* allele(s) receiving ticagrelor to those with WT genotype receiving clopidogrel.
6. To assess the effect of coronary artery disease (CAD) presentation: a) Stable coronary artery disease b) Unstable angina or non-ST elevation myocardial infarction (NSTEMI), and c) ST-elevation myocardial infarction (STEMI) on the effectiveness of ticagrelor in patients with reduced function *CYP2C19* allele(s) and on the association of *CYP2C19* genotype and occurrence of MACE.

7. To assess the mechanism of coronary stent thrombosis in patients with reduced function *CYP2C19* allele(s) receiving ticagrelor versus clopidogrel.
8. To compare MACE and bleeding outcomes in all patients randomized to the conventional therapy arm versus the prospective genotyping arm.
9. To assess implementation of a CLIA-approved *CYP2C19* pharmacogenetic testing on the Spartan® platform (accuracy of genetic testing by sequence analysis and genotype failure rates).
10. To assess compliance with dual anti-platelet therapy by phone survey.
11. Performing a pharmacoeconomic analysis of the conventional therapy approach as compared with the genotype based approach in subjects who undergo PCI.
12. To assess patients' attitudes towards genotyping and the results of genotyping by survey.

3. BACKGROUND AND SIGNIFICANCE

Several studies have suggested that *CYP2C19*2* (rs4244285) and *3 (rs4986893) allele carriers may have a reduced ability to metabolize clopidogrel and hence have an impaired response to clopidogrel as measured by platelet function ([1,2,3,4]). The Food and Drug Administration (FDA) has advised practitioners to "consider alternative treatment or treatment strategies in patients identified as *CYP2C19* poor metabolizers" and who are to receive clopidogrel. The FDA based this boxed warning on a small, crossover trial that evaluated pharmacokinetics and antiplatelet responses to clopidogrel in 40 healthy subjects[(5)]. The use of platelet function studies as an endpoint in this and other larger clinical studies limits the clinical relevance of genotyping since the relationship between cardiovascular endpoints and platelet function studies is unclear and confounding.

There are several studies that suggest that *CYP2C19**2 and *3 allele carriers may have increased major adverse cardiovascular events with the use of clopidogrel after coronary stent implantation and in acute coronary syndromes[(1,2,6)]. However, in none of these trials was genotyping performed comprehensively and prospectively and were hence prone to bias. Furthermore, pharmacogenetic analysis was performed in a sub-group of patients who had DNA collected and not in the entire cohort of patients.

Both clopidogrel and ticagrelor are FDA approved for use in patients who undergo PCI and coronary stent implantation. Ticagrelor has been shown to be superior to clopidogrel in a large trial involving 18,624 patients with acute coronary syndrome in reducing cardiovascular deaths, stroke and myocardial infarction (hazard ratio 0.84, 95% CI, 0.77-0.92)[(7)]. Ticagrelor has also been shown to be safer in patients undergoing coronary artery bypass graft (CABG) and has the additional benefit of reversible inhibition. However, ticagrelor caused an increased risk of non-CABG-related bleeding. In addition, prasugrel (another anti-platelet drug that irreversibly inhibits the $P2Y_{12}$ receptor) has been shown to be superior to clopidogrel in reducing the risk of cardiovascular death, myocardial infarction (MI), and stroke in a large trial involving 13,608 patients with moderate-to-high-risk acute coronary syndromes with scheduled PCI (HR 0.81, 95% CI, 0.73-0.90)[(8)]. However, prasugrel also led to significantly higher rates of bleeding, including life-threatening and fatal bleeding. The findings from these 2 trials have been inconsistently adopted into routine use post-PCI, and the recent availability of generic clopidogrel has also contributed to the delayed uptake of prasugrel and ticagrelor into routine clinical practice of acute coronary syndrome (ACS) and post-PCI in the United States and Canada.

Routine clinical use of genotyping for *CYP2C19* in patients who undergo coronary stent implantation is not recommended due to lack of evidence as per recent guidelines published by the American College of Cardiology (ACC), American Heart Association (AHA), and Society for Cardiovascular Angiography and Interventions (SCAI)[(9)]. Hence, the standard of care at present is to treat all patients who undergo PCI with standard dose of clopidogrel without preemptive genotyping. If genotyping is performed and patients are preemptively identified as being predisposed to potentially inadequate platelet inhibition based on their genotype, treating these patients with a $P2Y_{12}$ inhibitor (prasugrel or ticagrelor) would be a

Class IIb (level of evidence C) indication[9] and treating these patients (who presumed to be poorer metabolizers) with an alternative anti-platelet agent to clopidogrel is implied in the FDA boxed warning. However, there appears to be adequate equipoise in the cardiovascular community as to the best approach in treating these patients. Hence, the purpose of this study is to determine the optimal anti-platelet therapy for patients with *CYP2C19* reduced function alleles who undergo PCI.

4. PRELIMINARY STUDIES

Mega[1] explored the effect of *CYP2C19* reduced function allele in a separate cohort of 1,477 subjects with acute coronary syndromes who were treated with clopidogrel in the TRITON-TIMI 38. The pharmacogenetic cohort receiving clopidogrel represented approximately 10% of the total original study population. Among the clopidogrel-treated subjects there was a 12.1% composite event rate of death from cardiovascular causes, myocardial infarction, and stroke as compared with 8% of patients with WT *CYP2C19* genotype (i.e. relative 53% increased risk). The risk of stent thrombosis in the carriers was 2.6% as compared with 0.8% in the WT group.

Simon[3] observed similar results in their analysis of 2,208 patients in the FAST-MI cohort. They observed a higher event rate in carriers of two *CYP2C19* reduced function alleles (21.5% vs. 13.3%, adjusted hazard ratio (HR), 1.98; 95% CI, 1.10-3.58). In patients undergoing PCI (n=1535), the adjusted risk of death, MI, or stroke was 3.58 times higher in patients with 2 *CYP2C19* reduced function alleles (95% CI, 1.76-7.51, p=0.005).

In a collaborative meta-analysis, with data extracted from 9 previous studies[10] involving 9,685 study participants receiving clopidogrel (91.3% with PCI, 54.5% with ACS), carriers of 1 (HR, 1.55; 95% CI, 1.11-2.17) or 2 (HR, 1.76; 95% CI, 1.24 – 2.50, p=0.002) reduced function *CYP2C19* alleles had a significantly increased risk of composite end point (CV death, MI, or stroke). Furthermore, a significantly increased risk in stent thrombosis was observed with carriers of 1 (HR, 2.67; 95% CI, 1.69-4.22, p<.0001) or 2 (HR, 3.97; 95% CI, 1.75-9.02, p=.001) reduced function *CYP2C19* alleles. Similarly, a study by Hulot[11] of 4,905 patients with PCI showed an odds ratio of 3.45 for stent thrombosis for individuals carrying a *CYP2C19**2 allele.

Shuldiner[2] reported a genome-wide association study that identified *CYP2C19* to be significantly associated with platelet aggregation response to clopidogrel. The *CYP2C19**2 variant was shown to account for 12% of the variation in platelet aggregation to ADP. The relationship of *CYP2C19**2 genotype to cardiovascular outcomes was analyzed in 227 patients undergoing PCI; carriers of the reduced function allele were found to have a composite event rate (myocardial infarction, ischemic stroke, stent thrombosis, unplanned target vessel revascularization, unplanned non-target vessel revascularization, hospitalization for coronary ischemia, and death secondary to any cardiovascular cause) of 20.9% as compared with 10% event rate in non-carriers.

In contrast, a pharmacogenetic analysis of two large trials by Pare[12] comparing the effects of clopidogrel versus placebo, the CURE study in acute coronary syndromes and the ACTIVE A study in atrial fibrillation of 6,215 patients combined, showed similar benefit of clopidogrel as compared with placebo in both carriers and non-carriers of the reduced function allele. Hence, the beneficial effect of clopidogrel as compared with placebo was maintained irrespective of reduced function *CYP2C19* carrier status. However, only 14.5% of the participants in this study underwent PCI with stent as compared with >70% in other studies that have demonstrated a positive correlation between *CYP2C19* carrier status and response to clopidogrel. The genetic sub study of CHARISMA also did not find any interaction between clopidogrel and *CYP2C19* status[13]. Similar to CURE and ACTIVE A, this study did not include a post-PCI population.

The PLATO study evaluated patients with acute coronary syndrome who were treated with ticagrelor or clopidogrel[7]. Amongst the 18,624 patients enrolled in PLATO, 10,285 patients had provided samples for genetic analysis[14]. The primary event rate of the composite of cardiovascular death, myocardial infarction, or stroke after 12 months of treatment was 8.6% in patients treated with ticagrelor versus 11.2% in the patients treated with clopidogrel when analyzed for all patients with any loss of function allele, including *CYP2C19* genotype. However, *CYP2C19* genotype did not play a role in influencing response to ticagrelor. In patients who were treated with clopidogrel, although a significant difference in event rate was observed in the first 30 days of treatment for those with any loss of function allele as compared with WT, this difference in outcome was not observed when the full follow-up period of 12 months was analyzed. This reduced interaction of *CYP2C19* polymorphisms was explained in part by just 64% of the genetic cohort having had percutaneous coronary intervention stent procedure. The event rate in patients receiving clopidogrel who had reduced function *CYP2C19* genotype was 11.2% while those receiving clopidogrel with no loss of function *CYP2C19* allele was 10%.

In a more recent meta-analysis by Holmes[15], evaluating 32 studies of 42,016 patients, a treatment-only analysis revealed that carriers of one or two reduced function *CYP2C19* alleles were at a higher risk for cardiovascular events (relative risk 1.18, absolute risk increase of 8-12 events per 1000 individuals). However, there was a significant small study bias. When this analysis was restricted to studies with 200 or more events, the relative risk of increased events was not significant, and when confined to genetic studies nested within randomized trials, the *CYP2C19* genotype was not significantly associated with cardiovascular events. A limitation of this meta-analysis was the lack of specific analysis for patients undergoing stenting compared with other medical treatments, including the inclusion of a large number of patients whom were being treated for reasons other than stenting (e.g. atrial fibrillation, STEMI).

Overall, preliminary studies have demonstrated an association between *CYP2C19* reduced function alleles, clopidogrel response, and outcomes in patients undergoing PCI. These studies have all been retrospective in nature and a recent large meta-analysis suggests no significant association between *CYP2C19* genotype and cardiovascular events with clopidogrel use. Whether such patients with 1 or 2 *CYP2C19* reduced function alleles might benefit from alternative anti-platelet therapy is controversial and has not yet been studied in a prospective, randomized fashion.

The RAPID GENE study randomized 187 patients undergoing PCI for ACS or stable coronary disease to a strategy of rapid point-of-care genotyping or to standard treatment. For patients assigned to the rapid genotyping strategy, those that were identified as carriers of the *CYP2C19*2* allele were switched to prasugrel, while non-carriers and those in the standard treatment group received clopidogrel 75mg daily. The strategy of rapid genotyping in conjunction with personalized antiplatelet therapy, led to a reduction in HPR in *CYP2C19*2* carriers compared to those in the standard group (0% vs. 30.4%). In the study, the point-of-care genetic test demonstrated a sensitivity of 100% and a specificity of 99.3%. These results provided the proof-of-concept that bedside genotyping was feasible and accurate[16].

5. BASIC STUDY DESIGN

This will be a multi-site, open label, prospective randomized trial involving ACS and stable CAD patients who come to the cardiac catheterization laboratory at Mayo Clinic, Mayo Clinic Health System (MCHS), and other U.S.A., and international sites.

Only ACS patients who come to the cardiac catheterization laboratory at the international sites, and both ACS and Non-ACS patients who come to the cardiac catheterization laboratory at Mayo Clinic, MCHS, and other U.S.A. sites will be considered for recruitment. The anticipated number of patients amongst the U.S.A. sites will be over 4,000 patients who undergo PCI per year and amongst the international sites, over 6,000 ACS patients who undergo PCI per year. Eligible, consented patients will undergo

randomization after PCI to either a conventional therapy arm or prospective genotyping arm. The conventional therapy arm patients will receive clopidogrel once daily after the index PCI and will be retrospectively genotyped for *CYP2C19**2, *3 and *17 alleles after completion of one year of treatment with clopidogrel. The prospective genotyping arm patients will be genotyped prospectively for *CYP2C19**2, *3 and *17 alleles and will receive treatment based on their genotype. In this group, patients who have the *CYP2C19* reduced function allele [i.e. *2 allele (heterozygous or homozygous) or *3 allele (heterozygous or homozygous)] patients will receive ticagrelor 90 mg bid. The WT *CYP2C19* patients will receive clopidogrel 75 mg once daily. If ticagrelor is discontinued prematurely in the reduced function *CYP2C19* allele patient due to intolerance and there is no contraindication for continued dual anti-platelet therapy, the patients and their physicians will be advised to substitute ticagrelor with prasugrel at 10 mg daily (5 mg in patients weighing less than 60 kg or age >75 years)[17] or clopidogrel 150 mg daily.

In Caucasians, the *2 allele frequency is 15-20% and *3 allele frequency is less than 1%, but up to 29% and 9%, respectively, in Asians. Although we are genotyping for *3, because of its low frequency in our predominant Caucasian population, we expect to detect very few such patients in Rochester (more may be expected from the Canadian, Arizona, and Florida sites). We expect (assuming Hardy-Weinberg equilibrium) approximately 4% of patients to be homozygous for the *2 allele (*2/*2), 32% to be heterozygous for the *2 allele, and 64% to be WT. Thus, we will expect around 36% of patients that go on to PCI will be carriers of one or two *2 alleles. However, to be conservative we will estimate 30% of the 4,255 enrolled Caucasian patients and 50% of the 1,015 Asian patients, or ~ 1,784 patients to be carriers of the *CYP2C19* reduced function allele. After randomization, we anticipate there will be approximately 892 patients in each group, i.e. the conventional therapy group receiving clopidogrel who are retrospectively identified to have *CYP2C19* reduced function allele and the prospectively genotyped group whose therapy was guided by the Spartan device results and are retrospectively identified to have CYP2C19 reduced function.

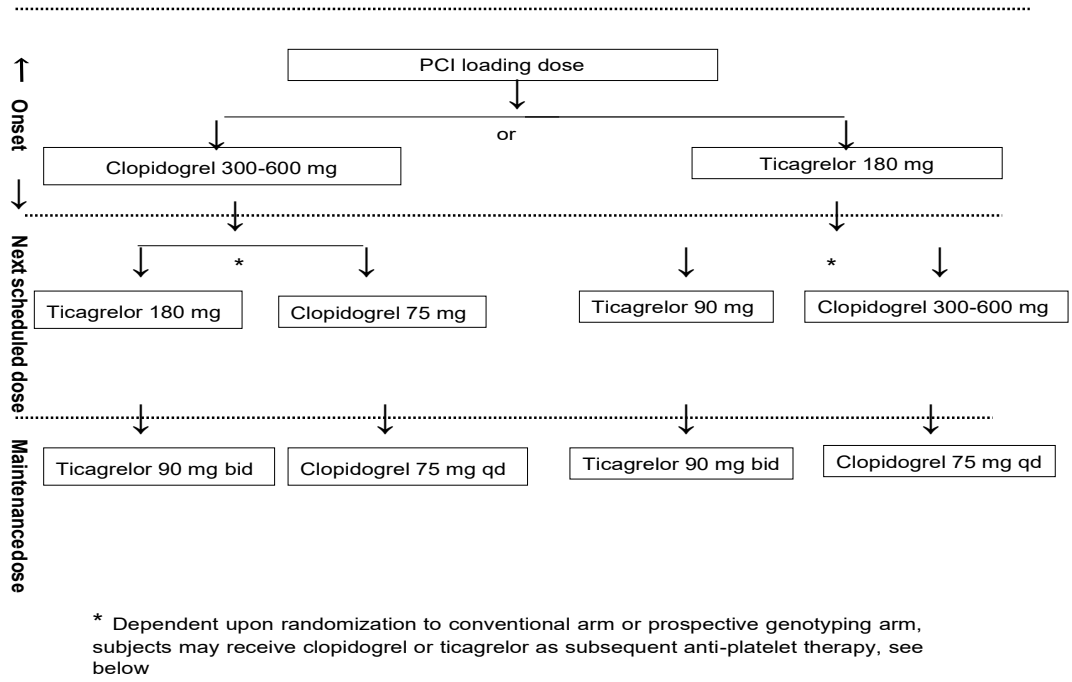
The *CYP2C19**17 allele frequency in Caucasians is approximately 21-23% and 3% in Asians, and it occurs at a frequency of ~26% of Caucasian patients with the *2 allele. The *17 allele is considered a gain-of-function allele and has been shown in some studies to lead to enhanced response to clopidogrel (via platelet function testing) and a higher rate of bleeding events[7,18,19,20]. However, other studies have not demonstrated increased platelet inhibition or altered clinical outcomes with the *17 allele [2,3,21,22]. Taken together, it is unclear how patients with the *17 allele would respond to clopidogrel, and the combined effect of *2 and *17 on *CYP2C19* function and response to clopidogrel is additionally uncertain. Therefore, for the purposes of this study, *17 will not be taken into consideration for prospective treatment decisions. However, we will utilize the *17 information to perform retrospective secondary analyses to determine its effect (alone and in the presence of *2 or *3) on bleeding risk and MACE.

DNA will be collected and stored for retrospective analysis for both the prospective genotyping group and the conventional treatment group. DNA will be analyzed by the ABI TaqMan platform sometime after the one year time point from the PCI and completion of duration of anti-platelet therapy to identify those patients with one or two copies of *CYP2C19* reduced function allele. In cases where the initial sample collected to analyze the DNA at the one year time point is found to be an unviable sample, the subject will be contacted and asked to provide another DNA sample via a blood sample or saliva sample. In the prospective genotyping group, DNA will be analyzed prospectively using the Spartan Bioscience platform after PCI. Patients with *CYP2C19**2 or *3 reduced function allele will be assigned to receive ticagrelor 90 mg. twice daily. Subjects without the reduced function allele will be assigned to receive clopidogrel 75 mg once daily. The goal of the study is to determine the difference in MACE in the *CYP2C19* reduced function allele prospectively genotyped group receiving ticagrelor compared with the retrospectively genotyped and identified group receiving clopidogrel. It is hypothesized that there will be

lower events in the ticagrelor arm compared with clopidogrel. The design of the study is outlined in the figures below.

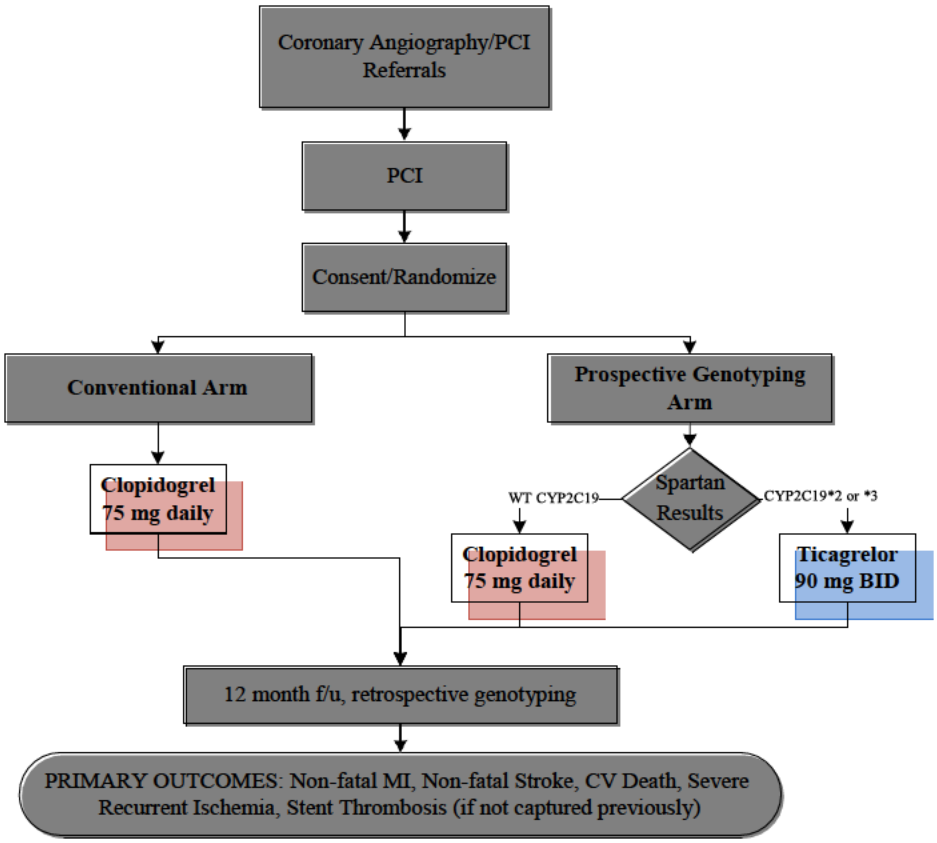
Loading dose pre-PCI:
All patients will receive a standard loading dose of antiplatelet therapy per the individual institution's routine clinical guidelines (prior to PCI, during PCI, or first dose after PCI), i.e. clopidogrel 300-600 mg or ticagrelor 180 mg. If patients receive ticagrelor 180 mg as a loading dose, and are then assigned to receiving clopidogrel as maintenance therapy, a loading dose of clopidogrel 300-600 mg as per institutional preference will be recommended post-randomization as the next scheduled dose and 75 mg once daily as subsequent maintenance dosing. Similarly, when a transition is made from clopidogrel to ticagrelor, those loaded with 300-600 mg clopidogrel and assigned to receiving ticagrelor will get as a next scheduled dose, ticagrelor 180 mg as a loading dose post-randomization and will then receive 90 mg twice daily as maintenance therapy[23].

Figure 1



* Dependent upon randomization to conventional arm or prospective genotyping arm, subjects may receive clopidogrel or ticagrelor as subsequent anti-platelet therapy, see below

Figure 2



ABBREVIATIONS:
PCI: Percutaneous coronary intervention
WT: Wild type

6. STUDY POPULATION AND ELIGIBILITY CRITERIA

6.1 Study Population and Source of Participants

The study population will be all patients who present with ACS, or stable CAD at the selected U.S.A. sites, and those who present with ACS at the selected international sites, and undergo PCI, require anti-platelet therapy for at least 12 months, and have consented to the study. The source of participants will be patients who are referred to the cardiac catheterization laboratory and may be eligible for PCI. Patients are referred to the cardiac catheterization laboratory from the outpatient clinic, emergency room, or the hospital setting.

6.2 Inclusion/Exclusion Criterion

6.2.1 Inclusion

- Patient ≥18 years of age
- Patient presents with ACS or stable CAD
- Patient is eligible for PCI
- Patient is willing and able to provide informed written consent
- Patient is willing to provide a DNA sample (via blood draw or saliva) for genotyping

6.2.2 Exclusion

- Patient not able to receive 12 months of dual anti-platelet therapy
- Failure of index PCI
- Patient or physician refusal to enroll in the study
- Patient with known *CYP2C19* genotype prior to randomization
- Planned revascularization of any vessel within 30 days post-index procedure and/or of the target vessel(s) within 12 months post-procedure
- Anticipated discontinuation of clopidogrel or ticagrelor within the 12 months follow up period (e.g. for elective surgery)
- Serum creatinine >2.5 mg/dL within 30 days of index procedure
- Platelet count <80,000 or >700,000 cells/mm^3, or white blood cell count <3,000 cells/mm^3 if persistent (at least 2 abnormal values) within 30 days prior to index procedure.
- History of intracranial hemorrhage
- Known hypersensitivity to clopidogrel or ticagrelor or any of its components
- Inability to take aspirin at a dosage of 100 mg or less
- Patient is participating in an investigational drug or device clinical trial that has not reached its primary endpoint
- Patient previously enrolled in this study
- Patient is pregnant, lactating, or planning to become pregnant within 12 months
- Patient has received an organ transplant or is on a waiting list for an organ transplant
- Patient is receiving or scheduled to receive chemotherapy within 30 days before or after the procedure

- Patient is receiving immunosuppressive therapy or has known immunosuppressive or autoimmune disease (e.g. human immunodeficiency virus, systemic lupus erythematous, etc.)
- Patient is receiving chronic anticoagulation therapy (i.e. vitamin K antagonist, direct thrombin inhibitor, Factor Xa inhibitor)
- Concomitant use of simvastatin/lovastatin >40 mg qd
- Concomitant use of potent CYP3A4 inhibitors (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) or inducers (carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, and rifapentine)
- Non-cardiac condition limiting life expectancy to less than one year, per physician judgment (e.g. cancer)
- Known history of severe hepatic impairment
- Patient has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions
- Patient has an active pathological bleeding, such as active gastrointestinal (GI) bleeding
- Current (within 6 months) substance abuse (e.g. alcohol, cocaine, heroin, etc.)

7. STUDY INTERVENTIONS

7.1 Intervention

The study interventions include a blood draw, three buccal swabs (in the prospective genotype arm), a genotyping survey (first 1,000 subjects), randomization, and genotype analysis. Genotyping for *CYP2C19* will be retrospective in the conventional therapy arm and both prospective and retrospective in the *CYP2C19* prospective genotyping arm. A survey regarding patients' perceptions of genotyping and the results of genotyping will also be performed on the first 1,000 subjects.

7.2 Randomization

Patients will be randomized to one of two groups. The two arms are: the conventional therapy arm in which the patients will receive clopidogrel with retrospective genotype analysis performed at the end of one year of treatment, and the prospective genotyping arm, in which patients will have prospective genotyping performed to guide anti-platelet therapy. Patients in this group who are identified to have reduced function *CYP2C19* allele will receive ticagrelor and patients with WT *CYP2C19* allele will receive clopidogrel. Drug therapy with ticagrelor and clopidogrel will be given as per clinical guidelines. Both of these drugs are FDA approved and will be given for FDA approved indications for at least 12 months after index PCI. Ticagrelor will be administered at 90 mg twice daily, and clopidogrel will be administered at 75 mg daily. All patients will receive a standard loading dose of antiplatelet therapy per the individual institution's routine clinical guidelines (prior to PCI, during PCI, or first dose after PCI), i.e. clopidogrel 300-600 mg or ticagrelor 180 mg. If patients receive ticagrelor 180 mg as a loading dose, and are then assigned to receiving clopidogrel as maintenance therapy, a loading dose of clopidogrel 300-600 mg as per institutional preference will be recommended as the next scheduled dose and 75 mg once daily as subsequent maintenance dosing. Similarly, when a transition is made from clopidogrel to ticagrelor, those loaded with 300-600 mg clopidogrel and assigned to receiving ticagrelor will get as a next scheduled dose, ticagrelor 180 mg as a loading dose and will then receive 90 mg twice daily as maintenance therapy[23]. Specific randomization-guided treatment (i.e. clopidogrel or genotype-guided ticagrelor) will commence within 72 hours after index PCI as soon as clinically possible. If ticagrelor is discontinued

prematurely in the reduced function *CYP2C19* allele patient due to intolerance and there is no contraindication for continued dual anti-platelet therapy, the patients and their physicians will be advised to substitute ticagrelor with prasugrel at 10 mg daily (5 mg in patients weighing less than 60 kg *and age ≥75 years*)[17] or clopidogrel 150 mg daily.

7.3 Concomitant Therapies

Current ACC/AHA guidelines for the management of acute coronary syndromes including unstable angina, NSTEMI, and STEMI will be followed uniformly for all patients[24,25]. The drug prescribing information for ticagrelor recommends the use of aspirin at a maintenance dose of 75-100 mg daily. Concomitant administration of lovastatin or simvastatin and ticagrelor will increase lovastatin or simvastatin plasma concentrations. Hence, lovastatin or simvastatin doses greater than 40 mg when administered concomitantly with ticagrelor will be avoided as per prescribing information. Concomitant use of potent CYP3A4 inhibitors (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) or inducers (carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, and rifapentine) cannot be used as well. Cardiovascular medications taken during the study will be recorded in the source documentation and in the electronic case report form (eCRF).

Avoid concomitant use of clopidogrel with omeprazole or esomeprazole. Consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite. Dexlansoprazole, lansoprazole, and pantoprazole had less effect on the antiplatelet activity of clopidogrel than did omeprazole or esomeprazole.

7.4 Dose Justification

The dose of clopidogrel and ticagrelor will be prescribed as per clinical guidelines as described in the published prescribing information for both these drugs. This information is outlined in Appendix A.

7.5 Side Effects

The side effects of these FDA-approved drugs have been fully outlined in the Appendix as per the published prescribing information.

7.6 Summary of the Risks and Benefits

7.6.1 Potential Benefits:

This study involves administration of ticagrelor with potential beneficial effects in patients with reduced function *CYP2C19* allele. Thus, if subjects receive ticagrelor rather than clopidogrel, they could potentially experience greater clinical benefit.

7.6.2 Potential Risks

Buccal Swab
There are no known risks associated with obtaining a buccal swab.

Blood draw
Blood draw will occur after venous and or arterial access has been obtained for the cardiac catheterization procedure and a determination has been made that PCI will be performed. A total of 10 mL of blood will be collected after venous and or arterial access for clinical reasons or a separate venipuncture for a research blood draw. Potential risks

of blood drawing include bleeding at the puncture site, bruising, pain, and rarely, infection at the site of the needle stick. These risks occur in a very small portion of the population. If a subject's initial blood sample is not available or processed appropriately, we may obtain a replacement10 mL blood sample either by a separate research blood draw or by addition to a clinical blood draw.

Genotyping
The risks of learning genetic test results may include emotional upset, insurance or job discrimination, and/or family conflicts from learning unknown information about family members. Patients in the conventional therapy arm may request that their genotyping results be sent to their physicians at the end of the study. Patients in both groups may discuss with their physicians the potential risks, benefits, and costs of choosing to have the results verified by clinical genetic testing in a CLIA certified lab and to learn the test results.

Anti-platelet Therapy
Patients in this study will be undergoing PCI as part of their clinical care. Oral anti-platelet therapy after PCI is clinically indicated and is considered standard of care. Therefore, patients in the study will have the potential risks associated with their anti-platelet therapy. These potential risks, however, are not considered potential risks of the study because anti-platelet therapy is indicated for their clinical care. Clopidogrel and ticagrelor are both FDA approved to prevent thrombosis in the ACS population, and will be administered at recommended doses for maintenance therapy as per standard guidelines.

Ticagrelor
Common adverse events include major and minor bleeding (8.7%), headache (6.5%), raised serum creatinine (7.4%), cough (4.9%), dyspnea (13.8%), atrial fibrillation (4.2%), and syncope (1.7%).

Ticagrelor may cause significant, sometimes fatal, bleeding. Hence patients with active pathological bleeding or history of intracranial hemorrhage, bleeding diathesis, and on chronic anticoagulation such as warfarin will be excluded.

Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor; thus patients unable to take aspirin at 100 mg or less will be excluded.

In a randomized, double-blind study of patients with acute coronary syndrome, major bleeding events (not related to CABG) were reported in 4.5% of patients who received ticagrelor (n=9235) compared with 3.8% of patients who received clopidogrel (n=9186). Both were co-administered with aspirin and other standard therapy for 6 to 12 months. The bleeding episodes were fatal or life-threatening in 2.1% of ticagrelor-treated patients compared with 1.9% of clopidogrel-treated patients. Fatal events were reported in 0.2% of patients in each group. Fatal or life-threatening intracranial bleeding was reported in 0.3% and 0.2% of ticagrelor- and clopidogrel-treated patients, respectively[7]. In a randomized, double-blind study of patients with acute coronary syndrome who underwent CABG surgery, major bleeding events were reported in 85.8% of patients who received ticagrelor (n=770) compared with 86.9% of patients who received clopidogrel (n=814). Both were co-administered with aspirin and other standard therapy for 6 to 12 months. The bleeding episodes were fatal/life-threatening in 48.1% of ticagrelor-treated

patients compared with 47.9% of clopidogrel-treated patients. Fatal bleeding events were reported in 0.9% and 1.1%, respectively, of patients[7].

If possible, minor bleeding should be managed without discontinuing ticagrelor therapy since therapy discontinuation increases the risk of myocardial infarction, stent thrombosis, and death. Although discontinuation increases the risk of subsequent adverse cardiovascular events, ticagrelor should be stopped 5 days prior to surgery, when possible. Hence if a surgical procedure is planned including CABG, surgery patients will be excluded since they will be unable to complete the 12-month duration of anti-platelet therapy.

In a randomized, double-blind study of patients with acute coronary syndrome, headache was reported in 6.5% of patients who received ticagrelor (n=9235) compared with 5.8% of patients who received clopidogrel (n=9186). In a randomized, double-blind study of patients with acute coronary syndrome, a greater than 50% increase in serum creatinine levels were reported in 7.4% of patients who received ticagrelor (n=9235) compared with 5.9% of patients who received clopidogrel (n=9186). Both were co-administered with aspirin and other standard therapy for 6 to 12 months. Creatinine levels generally did not progress, and often decreased with continued treatment[26]. Dyspnea associated with ticagrelor therapy was usually mild to moderate and often resolved during continued treatment. Underlying disease should be ruled out in patients who develop new, prolonged, or worsening dyspnea during ticagrelor treatment. There is no specific treatment required if dyspnea is confirmed to be caused by ticagrelor. Ticagrelor should be continued without interruption [product information: Brilinta® oral tablets, ticagrelor oral tablets. AstraZeneca LP (per manufacturer), Wilmington, DE, 2011]. In a randomized, double-blind study of patients with acute coronary syndrome, dyspnea (exertional, nocturnal, paroxysmal nocturnal, and at rest) was reported in 13.8% of patients who received ticagrelor (n=9235) compared with 7.8% of patients who received clopidogrel (n=9186). The concomitant use of potent cytochrome P450 3A4 inhibitors (e.g. clarithromycin, ketoconazole, itraconazole, voriconazole) is associated with increased plasma levels of ticagrelor, hence patients would be at an increased risk for bleeding. Patients taking these drugs are excluded from this protocol and patients enrolled in the study will be cautioned not to commence therapy with these agents.

If ticagrelor is discontinued prematurely in the reduced function CYP2C19 allele patient due to intolerance and there is no contraindication for continued dual anti-platelet therapy, the patient and their physician will be advised to substitute ticagrelor with prasugrel at 10 mg daily (5 mg in patients weighing less than 60 kg or age≥75 years)[17] or clopidogrel 150 mg daily.

Clopidogrel

Triple therapy with aspirin, clopidogrel, and warfarin led to a greater risk of bleeding than dual therapy with aspirin and clopidogrel following coronary stent placement. A retrospective study to evaluate bleeding risk in 107 consecutive patients on chronic warfarin therapy who received triple therapy was compared with a cohort of 107 randomly selected patients receiving dual therapy following coronary stent placement. Following a loading dose of clopidogrel 300 milligrams (mg) at the time of stent placement, all patients received clopidogrel 75 mg daily, as well as aspirin (81 mg or 325 mg). Patients on triple therapy were started on a maintenance dose of warfarin the day following stent placement. Patients were followed for a mean duration of 211 +/- 114 days and 250 +/- 137 days in the triple and dual therapy groups, respectively. Patients on

triple therapy were younger than the patients on dual therapy (mean age, 69 +/- 11 years vs 74 +/- 6 years, respectively; p=0.03). Eighty-two percent (82%) of patients in the triple therapy group had hypertension compared with 68% in the dual therapy group (p=0.01). Following stent placement, major bleeding was 6.6% in the triple therapy group and 0% in the dual therapy group (p=0.014), and minor bleeding was 14.9% and 3.8% (p=0.01) in the triple and dual therapy groups, respectively. One death occurred due to intracranial hemorrhage in a patient on triple therapy with a history of major bleeding[27]. Therefore, patients on chronic vitamin K antagonist therapy will be excluded from this study.

In the Platelet inhibition and patient Outcomes (PLATO) trial, patients randomized to ticagrelor prior to surgical intervention for acute coronary syndrome had significantly fewer cardiovascular deaths, MI, or stroke compared with patients on clopidogrel[7]. This analysis of PLATO, a multicenter, randomized, double-blind, double-dummy controlled trial of ticagrelor or clopidogrel in patients aged 53 to 69 years old presenting with acute coronary syndrome, compares the composite event rates in patients undergoing invasive management (coronary angiography, percutaneous coronary intervention (PCI), coronary artery bypass graft). Ticagrelor patients (n=6,732) received a 180 milligram (mg) loading dose then 90 mg twice daily (plus placebo clopidogrel); clopidogrel patients (n=6,676) received a 300 mg loading dose then 75 mg once daily (plus placebo ticagrelor) for 6 to 12 months. PCI patients were eligible for an additional 300 mg clopidogrel loading dose (or placebo) at investigators' discretion (event rates did not vary significantly when stratified by clopidogrel loading dose). All patients received aspirin 75 to 100 mg per day. At 12 months post-intervention, cardiovascular death, MI or stroke (primary composite endpoint) occurred in 569 (9%) ticagrelor patients compared with 665 (10.7%) clopidogrel patients [hazard ratio, 0.84; 95% confidence interval (CI), 0.75-0.94; p=0.0025]. Incidences of cardiovascular death (5.3% vs 6.6%; p=0.0023) and MI (3.4% vs 4.3%; p=0.025) were significantly lower in the ticagrelor group compared with the clopidogrel group, although the incidences of stroke were not significantly different between the 2 groups. Total major bleeding [per Thrombolysis in Myocardial Infarction (TIMI) definition] occurred in 689 ticagrelor patients (11.5%) and 691 clopidogrel patients (11.6%) (95% CI 0.89 to 1.10; p=0.8803), and severe bleeding (per Global Use of Strategies to Open Occluded Coronary Arteries definition) occurred in 185 (2.9%) of ticagrelor patients compared with 198 (3.2%) of clopidogrel patients (95% CI 0.74 to 1.12; p=0.3785). Dyspnea occurred more frequently in ticagrelor patients compared with clopidogrel patients (13.9% versus 8%, p less than 0.0001) and was cause for discontinuing therapy in 0.8% of the ticagrelor group[28].

8. RECRUITMENT PROCEDURES

8.1 Common Recruitment Procedures

All patients undergoing PCI are treated by a cardiologist in the cardiac catheterization laboratory and hence recruitment efforts will be primarily based on targeting patients that are referred for coronary angiography to be performed in the cardiac catheterization laboratory. Some important recruitment strategies to be considered include:

- Presentations or meetings with cardiologist practices within each center to educate care providers regarding the genotyping assay, possible results of the assay, the lack of proven therapies in *CYP2C19* reduced function allele patients and the TAILOR-PCI trial. Each site should have some method of identifying patients referred to the cardiac catheterization laboratory. Referrals to the cardiac catheterization laboratory for most hospitals are present in databases or scheduling

calendars that can be accessed. Study coordinators can use this list to screen for eligible patients. Screening of outpatient or hospitalization records will be undertaken for patient eligibility.

- Patients who are being seen for clinic visits, determined by their physician to have a need to be scheduled for a cardiac catheterization procedure, and are eligible for a PCI. The physician will discuss with the patient the need for the procedure and inform them that there is a research study available. The physician will then contact a member of the clinical research team to speak with the patient. A list of study contact names and numbers will be placed in the clinic for the physicians to easily access study staff.
- Patients who present to the hospital may need coronary angiography. The physician determines eligibility for a PCI. The study coordinator and/or physician may discuss with the patient the research study.

8.2 Informed Consent

As a general guidance, patients will typically be approached when referred for coronary angiography in the outpatient or the inpatient setting or within 48 hours after index PCI. When a potential subject is identified, the study coordinator and/or site principal investigator (PI) will review the inclusion and exclusion criteria. If the patient is eligible, the study coordinator and/or PI will explain the study, review the consent form, answer questions, and if the patient is willing to participate, the consent form will be signed.

If the subject is consented prior to coronary angiography, the subject will then undergo coronary angiography as scheduled and only if PCI is performed and the patient requires at least one year of dual anti-platelet therapy, will the subject then be enrolled in the study, randomized, and begin anti-platelet drug therapy based on randomization to the conventional therapy arm or the prospective genotyping arm.

8.3 Confidentiality and HIPAA/Privacy Requirements

Subjects enrolled in the study will be identified with a study number. Within each participating site, subjects will also be identified by their site-specific registration number and their name but these subject identifiers will not be released outside of the respective participating sites and any publications will exclude any kind of subject identifiers that could be correlated with the specific subject. Genotype data will be collected specifically for the research protocol and clinical and demographic data will also be collected from the subject's medical records for the purposes of the research protocol, but all data will be de-identified before being released to any of the participating sites.

9. SCREENING PROCEDURES

Subjects will be referred to the study or will be identified using the recruitment strategies outlined in section 8. The subject's clinical records will be reviewed to determine if the subject meets the entry criteria. Additional information may be collected from face to face or phone interviews with the subject and/or the subject's physician. If the subject meets entry criteria and is willing to participate, informed consent will be obtained.

The subject will have blood drawn for genotyping at the time of coronary angiography only if they are to undergo a PCI with required dual anti-platelet therapy for at least 12 months. For those subjects who are consented following PCI, blood sampling will be conducted by the phlebotomy team. Subjects will then be randomized to the conventional therapy or prospective genotyping arm. The blood samples of all subjects will be stored for genotyping to be performed at the end of 12 months after index PCI. The

subjects who are randomized to prospective genotyping will have 3 buccal swabs taken and processed for rapid genotyping and, based on the genotype, will be assigned to clopidogrel or ticagrelor.

10. BASELINE EVALUATIONS AND RANDOMIZATION

10.1 Evaluations Performed During the Baseline Period

Results from any standard of care tests and procedures related to angiography and PCI, which are performed by participants' physicians, will be collected and used for this study.

Routine standard of care tests & procedures related to coronary angiography and PCI procedures typically include:

- Phlebotomy for routine blood work including complete blood count and creatinine
- Electrocardiogram
- Clinical history
- Physical examination
- Pregnancy test (for women of child-bearing potential if not done clinically within 7 days prior to PCI)

Research tests & procedures:

- Obtain permission to obtain protected health information from outside facilities for any events or hospitalizations related to study endpoints for up to 12 months after enrollment.
- Obtain 10 mL of blood.
- Obtain 3 buccal swabs for rapid genotyping assay.
- A survey will be conducted on the first 1,000 subjects regarding subjects' perception towards and experience with genotyping. This survey will be collected during the baseline visit and repeated at 6 months following PCI.

Conventional therapy arm

Participants randomized to this group will be retrospectively genotyped 1 year after index PCI. After randomization, the Biospecimens Accessioning and Processing (BAP) Laboratory will be notified to process the blood samples for genomic DNA extraction and storage for future analysis. After one year, Mayo Laboratories will utilize the ABI TaqMan assay for analysis of three variants in the *CYP2C19* gene: *2, *3, and *17.

Briefly, the TaqMan assay uses PCR primers to amplify the gene segment in which the *CYP2C19**2, *3, and *17 alleles are located, as well as three sets of 2 separate detection probes, each of which is specific for WT and variant alleles. Each probe is labeled with a different detection fluorescent dye, along with a quencher dye. During amplification, the detection probe anneals to its target sequence. If there is complete complementarity between the probe and the target sequence, then the probe is cleaved by the 5' nuclease activity of Taq DNA polymerase when the enzyme extends from the upstream primer into the region of the probe. When this cleavage occurs, the detection dye is released from the quencher dye and a fluorescent signal is detected. The dependence on polymerization ensures that cleavage of the probe occurs only if the target sequence is being amplified. The ABI PRISM 7500 Sequence Detection System is a flexible system designed to take full advantage of the benefits of fluorogenic probe detection. The 7500 system has a built-in thermal cycler and a laser directed via fiber optic cables to each of the 96 sample wells. The system is capable of distinguishing and quantitating multiple fluorophores in each sample well. The software analyzes the data by first calculating the contribution of each component dye to the experimental spectrum. Each reporter signal is then

divided by the fluorescence of an internal reference dye (ROX) in order to normalize for non-PCR related fluorescence fluctuations occurring well to well or over time

Prospective genotyping arm

Participants randomized to this group will be prospectively genotyped for *CYP2C19* variants. Study coordinators at each site will utilize the rapid turnaround Spartan Bioscience *in vitro* diagnostic assay for analysis of three variants in the *CYP2C19* gene: *2, *3, and *17. Briefly, a sample collection kit containing three Spartan swabs will be utilized to obtain three buccal swabs from each study participant and inserted into their respective reaction tubes. The tube will be tapped to mix the sample and reagents and then the swab will be inserted into the Spartan Analyzer. The Analyzer is a thermal cycler with optical detection capability. It is designed to determine an individual's *CYP2C19**2, *3, and *17 genotype. The unit utilizes optical detection channels to detect WT and variant alleles via a proprietary oligonucleotide capture and fluorescent detection method. After one year of index PCI, like the non-prospective genotyping arm, all subjects in the prospective genotyping arm will also have the ABI TaqMan assay for analysis of three variants in the *CYP2C19* gene: *2, *3, and *17 and results will be correlated to have a uniform platform for comparison and this will also result in validation of the Spartan diagnostic assay platform.

10.2 Randomization Procedures

After a subject has been consented, completed coronary angiography, and has met eligibility requirements, the subject will be randomized. Randomization will be performed using Medidata Balance. Subjects will be randomized at a 1:1 ratio to either 1) conventional therapy or 2) prospective genotyping with genotype-guided antiplatelet therapy (either clopidogrel or ticagrelor). Randomization will be stratified by age, sex, site, and CAD presentation (stable CAD, unstable angina/NSTEMI or STEMI).

10.3 Genomic Research

A 10 mL blood sample will be collected from subjects for plasma samples, DNA extraction, ABI TaqMan assay for *CYP2C19**2, *3, and *17 genotype, and future genomic research. In cases where the initial sample collected to analyze the DNA at the one year time point is found to be an unviable sample, the subject will be contacted and asked to provide another DNA sample via a blood sample or saliva sample. For subjects who provide consent to allow their DNA to be stored for future genomic analysis other than the *CYP2C19* genotyping being performed for the purposes of this study, their DNA will be stored in the BAP laboratory for future studies. Subjects will be given the option to opt in or out of the genomic component of the study.

11. FOLLOW-UP EVALUATIONS

11.1 Evaluations Performed During the Follow-up Period

Subjects will be contacted by site coordinators via telephone at 30 days (-2/+7 days), 6 months (+/- 28 days) and 12 months (+/- 28 days) after the date of their index PCI to assess alive/dead status, determine if the subject has been hospitalized since their PCI or a last follow-up phone call, and to assess drug compliance and current drug regimen. Education levels and computer literacy data also will be collected during one of these calls which may help to interpret the outcomes of the study. At least 3 attempts (on different days) will be made to contact subjects. Antiplatelet therapy drug compliance will be assessed during the phone call. If subjects were hospitalized, copies of the discharge summaries of those hospitalizations will be obtained. If 3 unsuccessful attempts are made to contact subjects by telephone, a medical record review can be conducted to obtain follow-up

information.

11.2 Evaluations for Study Completion, Study Withdrawals, and Treatment Discontinuation

Study Completion
A subject will be considered to have completed the study if he or she completed all assessments and procedures during the index PCI and follow-up period of 1 year for primary endpoint events. All randomized patients will have a follow-up assessment (telephone contact at 1, 6, and 12 months) to determine survival status and hospitalization data. If the subject dies during this period, the study coordinator and/or PI should make every effort to obtain details of the subject's death from the relevant hospital or subject's physicians and/or relatives. If confirmation of death is not available through these mechanisms, the study coordinator and/or PI will attempt to confirm the subject's death through a death index search.

Study Withdrawal
If the subject is lost to follow up, every effort will be made to contact the subject and determine the reason that will then be documented, including the measures taken to follow-up. If subject withdraws or drops out of the study, the reason for withdrawal from the study is to be documented on the case report form (CRF) and in the source document. The study coordinator or investigator must attempt to document re-hospitalization data unless the subject expressly refuses to provide this information. If subjects withdraw from the main part of the study, they will be given the following options regarding future genomic research: either the DNA extracted will be retained and used as specified in the original consent form; or the subject may withdraw consent for *CYP2C19* genotyping and/or future unspecified genomic research, in which case the DNA sample will be destroyed. If the subject withdraws consent for future genomic research alone and would want to continue the main part of the study, the DNA sample will be destroyed after *CYP2C19* genotyping is performed.

Treatment discontinuation
A subject may be discontinued from dual anti-platelet therapy if:
- The investigator or treating physician believes that for safety reasons (e.g. bleeding complications) it is the in the best interest of the subject to stop treatment.
- The subject becomes pregnant and treating physician feels the risks of treatment outweigh the benefits.
- The subject dies.

Subjects who terminate dual anti-platelet therapy due to an adverse event should be followed to determine the outcome of the adverse event, in addition to the pre-specified follow-up assessments as above. Interruption of treatment will not be considered treatment discontinuation. If ticagrelor is discontinued prematurely in the reduced function *CYP2C19* allele patient due to intolerance and there is no contraindication for continued dual anti-platelet therapy, the patients and their physicians will be advised to substitute ticagrelor with prasugrel at 10 mg daily (5 mg in patients weighing less than 60 kg or age ≥ 75 years)[17] or clopidogrel 150 mg daily.

11.3 Study Schedule of Assessments

Enrolled subjects will be required to complete up to 5 study visits/contacts (screening, randomization, and telephone follow-up on months 1, 6, and 12).

Table 1. Schedule of Assessments to be performed during the study

	Screening/Randomization V1 & 2			Treatment (Phone Interview)			EOT/Safety Endpoint
				V3	V4	V5	
	Pre-Procedure **	Index Procedure	Post-Procedure	30 Days (-2/+7 days)	6 months (+/-28 days)	12 months (+/- 28 days)	
Assessment of Eligibility	x						
Informed Consent	x						
Genotyping Survey[6]	x				x		
Hospitalization Intake[1]	x						
Medications	x		x	x	x	x	x
Vitals	x						
β-HCG Pregnancy test[2*]	x						
Creatinine*	x		x				
CK/CK-MB*	x		x				
Troponin T/I*	x		x				
Angiogram/PCI procedure*		x					
Genotyping			x[3]			x	x[4]
Randomization			x				
Hospitalization Dismissal			x				
Electrocardiogram*	x		x				
Follow-up outcomes	x			x	x	x	x
Study Endpoint Events			x	x	x	x	x[4]
Death Event Form[4]							
End of Treatment						x	x[4 5]
Education Level & Computer Literacy ***				x			

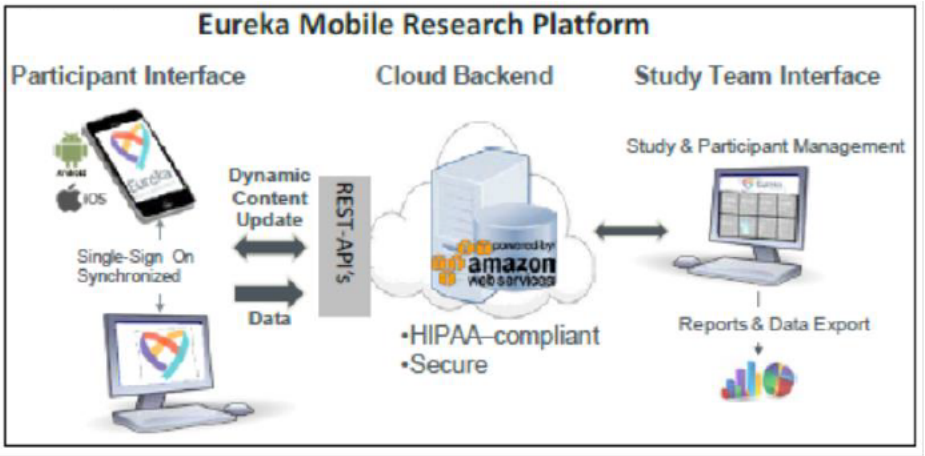
[1] Hospitalization forms to be completed for each hospitalization during study participation
[2] Only in women of childbearing potential (local urine or serum pregnancy test)
[3] Complete only if randomized to prospective genotyping
[4] Complete only if subject dies after randomization and before 12 month treatment phase
[5] Complete only if subject terminates participation prior to 12 months
[6] Completed for first 1,000 subjects only
*Data only will be collected from these clinically indicated tests/procedures
**If subject is screened/randomized post-procedure, these items will be collected post-procedure
***This information will be collected once at any of these phone interviews, unless the patient has already completed these visits. Because these questions were not part of the original consent, the patient will be given the chance to opt out of these questions.

11.4 Digital & Extended Follow-Up Sub-Study

The research objective of the digital registry sub-study is similar to the research objective of the parent NIH funded TAILOR-PCI trial, which is to assess major adverse cardiovascular events in patients who have undergone percutaneous coronary intervention (PCI) based on their CYP2C19 genotyping status, beyond the 1 year follow up of the parent study. Our sub-study to create a registry is important for multiple reasons. The extended follow up allows for collection of a greater number of events and hence more power to test the primary hypothesis of TAILOR-PCI. The registry will inform the CV community of the real world practice of continuing dual anti-platelet therapy (DAPT) beyond 1 year post PCI. We will also be able to define the role of the CYP2C19 genotype on the clinical efficacy of clopidogrel beyond 1 year post-PCI, a variable that has not yet

been assessed in prior extended DAPT studies primarily due to the lack of CYP2C19 genotyping in those studies.

Figure 3



The primary purpose of this sub-study is to establish, by leveraging the resources and unique strengths of 2 NIH funded proposals, the TAILOR-PCI trial (UO1HL 128606) and the Eureka Mobile Research Platform (EMRP) (5U2CEB021881), the TAILOR-PCI trial registry to follow subjects beyond 1 year post-PCI. The overall EMRP plan is depicted in Figure 3. We will be asking interested US and Canadian sites to refer their patients for the extended TAILOR-PCI digital follow-up study, and interested patients will be directed to enroll by digital means (Figures 4 & 5). Patients will be contacted via phone, text, email, or a letter. Within this communication, there will be a subject specific unique participant code tied to the TAILOR-PCI Subject ID and a URL link provided to type into a browser, allowing the participant to sign up for the study online. Once virtual registration is complete and subjects have provided their name, birthdate, email address, and established a Eureka password, the participants are directed to an electronic consent form. After reading the consent form, participants can choose to participate by clicking the button "I Agree to Participate" or opt out by choosing "Not Now". Next, they will see the Authorization to Release Protected Health Information – Research Form, which can be signed in a HIPAA-compliant DocuSign document that will be sent to the digital registry study team at Mayo Clinic (Figure 5). Because the subject is registered by study ID, their consent form will only be made accessible on the cloud (described in Figure 3) and to qualified and designated TAILOR-PCI digital registry personnel at Mayo Clinic. Once patients have provided electronic consent, they will be able to verify their phone number, enter a Eureka verification code, receive a text message with the Eureka App download link, and download the Eureka App to their phone (iOS and Android). Patients have the right to decline from participating in this digital registry program and then will no longer be recruited for the digital follow-up.

If patients are more than 24 months past their PCI, they will not be eligible for the digital registry. However, these patients will be contacted by phone, and with their verbal consent, they will be asked a similar set of questions asked at 1/6/12 months for one extended follow-up call. If education level and computer literacy questions were not asked previously, they will be included in this call, however the patient may choose to opt out of these questions.

Similarly, if patients are at 13-24 months past the index PCI and were not consented for the 18/24 month extended follow-up calls, these patients will be contacted by phone. With their verbal consent, they will be asked a similar set of questions asked at 1/6/12 months for extended follow-up at 18 and 24 months (± 28 days for both calls). If education level and computer literacy questions were not asked previously, they will be included in one of these calls, however the patient may choose to opt out of these questions. If subjects were enrolled at US or Canadian sites, they may also be approached about participating in the digital registry. Subjects enrolled in Mexico or Korea will not be eligible for the digital registry, but may still participate in extended follow-up telephone calls.

If 3 unsuccessful attempts are made to contact subjects by telephone, a medical record review can be conducted to obtain follow-up information. Medical records may be reviewed beyond the initial length of study identified in the signed consent form, as a retrospective chart review. If the subject has died, the study coordinator and/or PI should make every effort to obtain details of the subject's death from the relevant hospital or subject's physicians and/or relatives. If confirmation of death is not available through these mechanisms, the study coordinator and/or PI will attempt to confirm the subject's death through a death index search.

Table 2. Digital Registry Schedule of Events

Visit Windows	Baseline Visit	Weekly Activities	Monthly Activities from digital consent date up to 24 mos. post index PCI	Activities every 6 months from digital consent date
Informed Consent	x			
Eureka Registration	x			
Heart Rate	x (before and after the 6 minute walk test)	x (30 sec HR)	x (before and after the 6 minute walk test)	
Duke Activity Score	x		x	
Dyspnea Scale	x		x	
Angina Diary	x	x		
Seattle Angina Score	x		x	
6 minute walk test	x		x	
Geofencing (optional)**	x			
BORG Scale	x (after the 6 minute walk test)		x (after the 6 minute walk test)	
Medication Review **	x		x	
Hospitalization Review **	x		x	
Anxiety Survey	x			x

**If additional information is required for patient entry visits, a member of the study team may reach out to the patient by phone to inquire about any ER visits, hospitalizations, or cardiac events.

Specifically, the digital registry activities are based on patient provided questionnaires such as: Seattle Angina Questionnaire, Duke Activity Status Index, Modified Medical Research Council Dyspnea Scale, and Anxiety survey: GAD-7. Other patient reported data collected may include the angina diary, hospital-geofencing, heart rate and activity measurements, and a self-performed 6-minute walk test. Hospital-geofencing refers to the ability of the Eureka application to identify if the subject has been within 200 meters of a hospital for 4 hours or longer. If so, a notification will be sent to patients inquiring about their symptoms, reason for hospitalization, and what specific tests were done (Figure 6). The 6 minute walk test is a self-performed test used in conjunction with the Eureka application. As part of the test, the application will measure the patient's heart rate at rest, after test completion, and during recovery. The accelerometer function of the application measures the total distance walked in the allotted time, and also determines whether the patient has a change in cadence (pace), or takes time to rest. After the test, the subject will complete a Borg Rating of Perceived Exertion Scale survey which will include rating breathing difficulty at the worst part of the test and what if anything kept the subject from walking farther and faster.

The following disclaimer for participants will be included on the TAILOR-PCI digital follow-up website and informed consent form: The information obtained will be used solely for the purpose of research and will not be used to provide you with clinical care. If you experience any new or worsening symptoms, please contact your health care provider, or seek medical attention. If you think you are having a medical emergency, call 911.

To compare the accuracy of hospital-geofencing in discerning MACE, these subjects may also be contacted for follow-up by a study team member using a telephone script to determine whether MACEs have occurred. In the case that a hospitalization was not registered, the patient will be able to self-report any events as part of the follow-up phone notifications. If MACEs have occurred in subjects participating in the digital follow-up, Mayo Clinic Data Coordinating Center (MCDCC) will receive this indication in the file received from UCSF Eureka Data Coordinating Center (EDCC). If needed, a Mayo Clinic Digital Follow-Up study team member may obtain the subject's identifying information and Authorization to Release Protected Health Information from UCSF EDCC in order to request medical records from the patient's health care facility to ascertain clinical events. If MACEs are noted for subjects participating in the extended follow-up phone calls done by site study coordinators, medical records devoid of all patient identifiers will be sent to a designated study team member at the MCDCC to ascertain clinical events, as is being done in the parent TAILOR-PCI trial.

The consented subject in the digital follow-up may provide access to phone accelerometer-based step-counts and any self-report or connected device measures (such as weight or blood pressure) through HealthKit in iOS and GoogleFit in Android; may allow geolocation for determination when they are hospitalized; and may turn on notifications to allow the University of California San Francisco Eureka Data Coordinating Center to send push notifications for activities and surveys for hospitalization detection. Specifically, in addition to the consent, the participant will have to actively allow each of these as separate items (eg. share each HealthKit or GoogleFit item, turn on "share my location", and turn on "allow notifications"). In other words, they could opt out of any or all of these activities if they choose to do so.

Patient Confidentiality:

Patient-provided digital data will reside encrypted on the subject's phone until an internet connection is established, at which time the data is transmitted encrypted to the UCSF-Eureka data servers automatically. Once transfer is automatically confirmed via the endpoint (this happens as part of the built in API transferring data privately between the app and server), the data is deleted from the phone. The data servers are on a HIPAA-compliant stack in Amazon Web Services (BAA in place) and data is stored encrypted. The data being obtained is primarily patient-reported data. The transmitted data will be hosted on a HIPAA compliant cloud based platform provided by Amazon Web Services that is accessible to and managed by the University of California San Francisco Eureka Data Coordinating Center. This platform will generate a unique participant code tied to the TAILOR-PCI Subject ID that will also tie to the unique Eureka User ID created during registration. A Mayo Clinic Digital Follow-Up study team member may also access the subject's identifying information to request medical records from the patient's health care facility to ascertain clinical events. Follow-up study data from phone calls collected on TAILOR-PCI subjects is stored in the Medidata Rave system which is compliant with Code of Federal Regulations Title 21 (21 CFR) Part 11 and the Federal Information Security Management Act (FISMA). Both the physical and network security of the Medidata system is ensured through multiple measures. Physical security of the Medidata centers is managed through building guards, smart-ID badges with electronic access, video surveillance, and biometric scanners. Network security starts with border protection that includes routers and load balancers to provide high availability even during Distributed Denial of Service (DDOS) attacks. Data is protected from workstation to destination through the use of Secure Socket Layer (SSL) encryption with a minimum key length of 256 bits. The hosting site has dedicated disaster recovery facilities and automatically creates back-up files of the database on a regular basis according to standard research procedures. Each study site has access to only the data of subjects enrolled at their site. The site study coordinators will have edit access to the data and are responsible for entry and editing of all information obtained through follow-up phone calls. A Mayo Clinic Digital Follow-Up study team member will be responsible for entering digital enrollment in Medidata Rave, in addition to hospitalization and study endpoints obtained from medical records, if not already recorded by the site study coordinator. The Medidata web

interface will log users out of the application after extended periods of inactivity. Medidata Rave creates copies of the data formatted as SAS data sets on a server maintained by the Division of Biomedical Statistics and Informatics at Mayo Rochester on a nightly basis. These secondary files are only accessible by the Mayo statisticians and are controlled by UNIX group-access control. Login access to Division of BSI Unix workstations is secured by user-password controls. All study files stored on BSI servers are backed up nightly. All database and Web servers are secured by a firewall and through controlled physical access. All disk drives that provide network services, and all user computers, are protected using virus-scanning software.

Figure 4

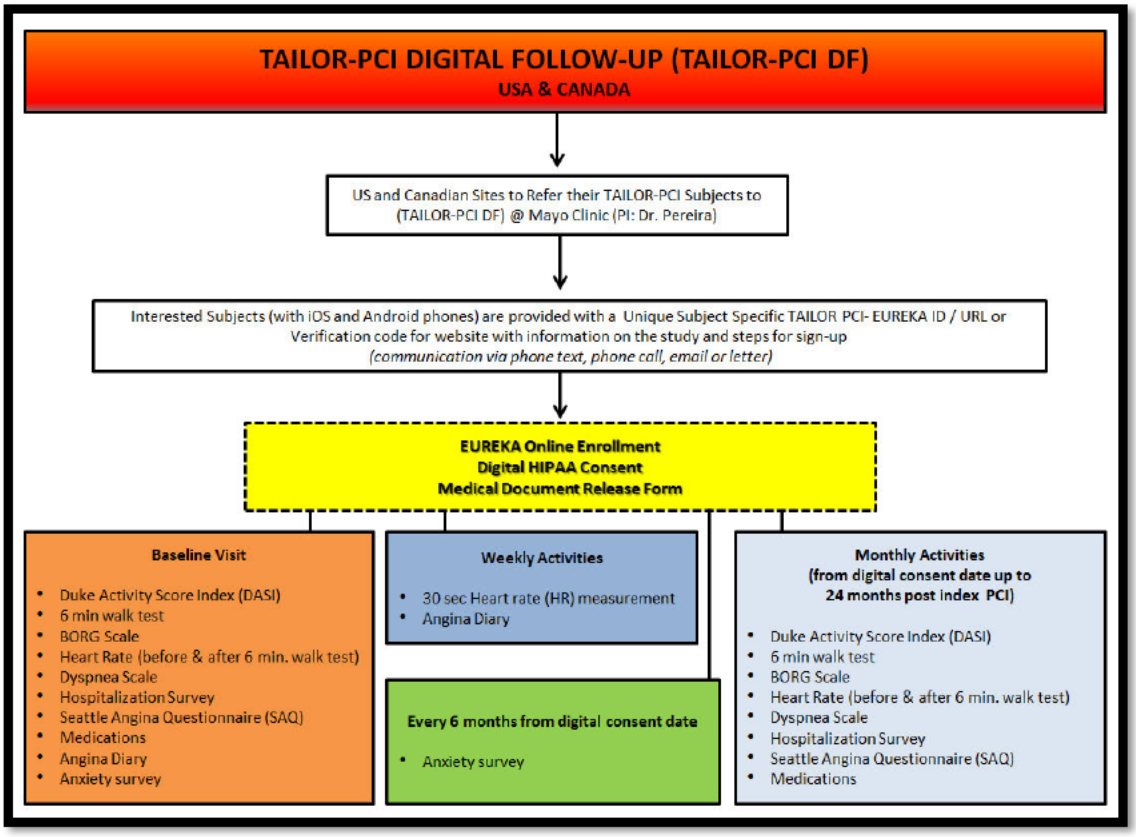
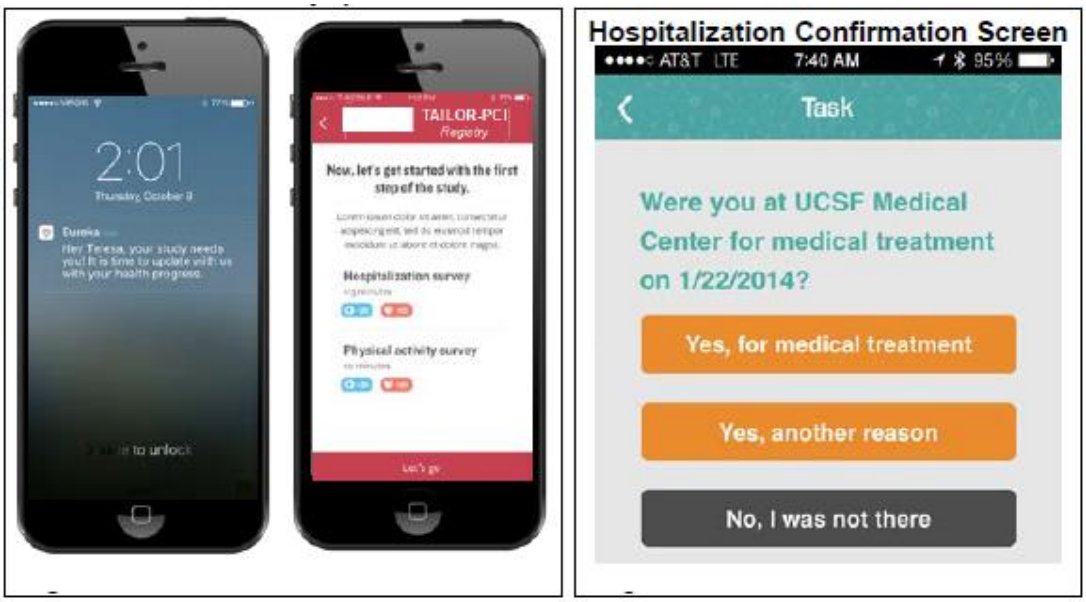


Figure 5

Figure 6



12. OUTCOME DETERMINATIONS

12.1 Primary Outcome

The primary outcome will be the time to occurrence of the composite endpoint of a major adverse cardiac event (MACE), i.e. non-fatal myocardial infarction, non-fatal stroke, CV mortality, severe recurrent ischemia, and stent thrombosis if not captured in other events, from the time of randomization through one-year of follow-up.

12.2 Secondary and Exploratory Pre-specified Outcomes

Secondary outcomes will include: The incidence of major or minor bleeding in subjects with reduced function *CYP2C19* allele(s) receiving ticagrelor versus clopidogrel.

Exploratory pre-specified outcomes include:

- The effect of *CYP2C19**17 genotype on bleeding risk, MACE, stroke, and CV survival.
- The effect of *CYP2C19**2 or *3 genotype on multiple recurrent events (MACE, stroke, and CV survival) in the individual subject.
- Performing a pharmacoeconomic analysis of the conventional therapy approach as compared with the genotype-based approach in subjects who undergo PCI.
- Comparing the occurrence of MACE in subjects with reduced function *CYP2C19* allele(s) to those with WT genotype receiving clopidogrel.
- Comparing the occurrence of MACE in subjects with reduced function *CYP2C19* allele(s) receiving ticagrelor to those with WT genotype receiving clopidogrel.
- Assessing the effect of CAD presentation: a) Stable coronary artery disease; b) Unstable angina or NSTEMI; and c) STEMI on the effect of ticagrelor in subjects with reduced function *CYP2C19* allele(s) and on the association of *CYP2C19* genotype and occurrence of MACE.
- To assess the mechanism of coronary stent thrombosis in subjects with reduced function *CYP2C19* allele(s) receiving ticagrelor versus clopidogrel.
- To assess implementation of a CLIA-approved *CYP2C19* pharmacogenetic testing on the

Spartan platform (accuracy of genetic testing by sequence analysis, and genotype failure rates).

- Exploratory outcomes will also include the individual components of the primary outcome.
- To assess compliance with dual anti-platelet therapy by phone survey.
- To assess patients' attitudes towards genotyping and the results of genotyping.

12.3 Clinical Event Definition and Adjudication

All clinical endpoints will be adjudicated by an independent Adjudication Committee that will be blinded to study treatment. The following clinical event definitions will be used by the Adjudication Committee:

Cardiovascular death
Death from cardiovascular causes or cerebrovascular causes and any death without another known cause.

Myocardial infarction
The diagnosis of myocardial infarction is dependent on whether it is *spontaneous*- or *procedure*- related:

- *Spontaneous*: Cardiac biomarkers (creatinine kinase-myocardial band, Troponin T or I) exceed the upper limit of normal according to the individual hospital's laboratory parameters or clinical presentation which is consistent or suggestive of ischemia.
- *Procedure-related excluding index PCI*:
    - In subjects with normal pre-procedural cardiac biomarkers, myocardial infarction within 24 hours post-PCI is indicated by cardiac biomarkers elevated above 3 times the upper limit of normal.
    - In subjects with elevated pre-procedural biomarkers, myocardial infarction within 24 hours post-PCI is indicated by cardiac biomarkers elevated above 3 times the upper limit of normal after biomarkers have exhibited a rise and fall indicative of completion of the presenting infarct.
    - MI greater than 24 hours post-PCI but prior to discharge is evidenced by any of the following:
        a. A rise and fall in cardiac biomarkers (preferably troponin) with at least one of the values in the abnormal range for that laboratory, together with at least one of the developments listed below, is a manifestation of myocardial infarction. The

           abnormal range for your laboratory means levels above the 99th percentile of the upper reference limit (URL) for normal subjects.
            i. Ischemic symptoms;
            ii. ECG changes indicative of new ischemia (new ST-T changes, new left bundle branch block, or loss of R wave voltage);
            iii. Development of pathological Q waves in 2 or more contiguous leads in the ECG (or equivalent findings for true posterior MI);
            iv. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
            v. Documentation in the medical record of the diagnosis of acute myocardial infarction based on the cardiac biomarker pattern in the absence of any items enumerated in 1-4 due to conditions that may mask their appearance (e.g. peri-operative infarct when the subject cannot report ischemic symptoms, baseline left bundle branch block, or ventricular pacing).
        b. Imaging evidence of a region with new loss of viable myocardium at rest in

the absence of a non-ischemic cause. This can be manifested as:

i. Echocardiographic, CT, MR, ventriculographic or nuclear imaging evidence of left ventricular thinning, or scarring and failure to contract appropriately (i.e. hypokinesis, akinesis, or dyskinesis);
ii. Fixed (non-reversible) perfusion defects on nuclear radioisotope imaging (e.g. MIBI, thallium).

- Peri-CABG (within the first 72 hours following CABG) is defined as an increase of biomarkers greater than 5 times the upper limit of normal for your laboratory (i.e. above 5 times the 99th percentile upper reference limit for a 'normal' population) compared with the pre-CABG biomarker value closest to the time of surgery plus one of the following:
  - New pathological Q waves or new LBBB;
  - Angiographically documented new occlusion or thrombosis of a graft or native coronary artery since the preoperative angiogram;
  - Imaging evidence of new loss of viable myocardium at rest in the absence of a non-ischemic cause.

Severe recurrent cardiac ischemia
Recurrent cardiac ischemia and at least one of the following, but not fulfilling the criteria for MI:

- New or presumed new ischemic ECG changes (ST elevation ≥1 mm (0.1 mV) or ST depression ≥0.5 mm (0.05 mV), or T wave inversion ≥1 mm (0.1 mV) in at least 2 adjacent leads)
- Leading to urgent revascularization (PCI or CABG) unless not advised on reasoned grounds. Urgent revascularization (PCI or CABG) must occur during the same hospitalization as an in- patient episode of recurrent ischemia or be performed during the re-hospitalization resulting from an out-patient episode of recurrent myocardial ischemia. In countries where waiting lists for revascularization procedures exist, revascularization within 30 days of an episode of recurrent ischemia will qualify as urgent. For patients with a previous PCI, it will be recorded if revascularization is necessary for previously treated vessels (i.e. urgent target vessel revascularization) and any occurrences of stent thrombosis will be documented. PCI is defined as any attempt at revascularization even if not successful (e.g. angioplasty, atherectomy, or stenting).
- Other definitions:
  - Recurrent cardiac ischemia: Cardiac ischemic symptoms >10 minutes at rest (started with exercise or spontaneously and did not resolve with rest), resulting in hospitalization if an outpatient, or prolongation of hospitalization if an inpatient but not fulfilling criteria for MI.
  - Cardiac ischemic symptoms: chest pain or discomfort or equivalent (e.g. neck or jaw symptoms, dyspnea believed to represent an angina pectoris equivalent) believed due to impaired coronary flow secondary to atherosclerotic disease.

Stent thrombosis
Definite (presence of acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion) or probable (unexplained deaths within 30 days after the procedure or acute myocardial infarction involving the target-vessel territory without angiographic confirmation)[29].

Cerebrovascular accident (CVA)
Loss of neurological function caused by an ischemic or hemorrhagic event with residual symptoms lasting at least 24 hours after onset or leading to death.

Transient ischemic attack (TIA)

Loss of neurological function that was abrupt in onset but with complete return of function within 24 hours, presumed to be due to vascular etiology.

Bleeding
All bleed events that require some form of intervention (e.g. doctor's visit, ER visit, hospitalization) will be captured, recorded, and classified as major, minor, or minimal.

- **Major bleeding**
  Symptomatic intracranial hemorrhage or clinically overt bleeding (including imaging) with a hemoglobin drop of ≥5 g/dL (adjusted for transfusion by 1 g/dL per unit of transfused blood).

- **Minor bleeding**
  Clinically overt bleeding (including imaging) with a hemoglobin drop of 3 to <5 g/dL (adjusted for transfusion by 1 g/dL per unit of transfused blood).

- **Minimal bleeding**
  Clinically overt bleeding (including imaging) with a hemoglobin drop of <3 g/dL (adjusted for transfusion by 1 g/dL per unit of transfused blood)[30].

Coronary Artery Bypass Grafting (CABG)
A type of surgery that improves blood flow to the heart. During CABG, a healthy artery or vein from the body is connected, or grafted, to the blocked coronary artery. The grafted artery or vein bypasses (that is, goes around) the blocked portion of the coronary artery. This creates a new path for oxygen- rich blood to flow to the heart muscle. Surgeons can bypass multiple coronary arteries during one surgery.

Percutaneous Coronary Intervention (PCI)
Also called coronary angioplasty, this is a procedure used to open clogged heart arteries. Angioplasty involves temporarily inserting and inflating a tiny balloon where the artery is clogged to help widen the artery.

Ventricular Fibrillation
A condition in which there is uncoordinated contraction of the cardiac muscle of the ventricles in the heart, making them quiver rather than contract properly.

Ventricular Tachycardia

A type of tachycardia, or a rapid heartbeat, that starts in the bottom chambers of the heart, called the ventricles.

Other cardiac surgeries
Any other surgery on the heart (excluding CABG). Examples include ventricular assist device, pacemaker, valve repair, and heart transplant.

13. QUALITY CONTROL ACTIVITIES

13.1 Training Sessions and Certification Procedures

An Operations Manual details overall study processes and procedures. It will contain instructions describing how the study is conducted, what procedures are performed, in what order, by whom, and under what circumstances. Investigator and study coordinator training sessions will be held to provide appropriate instruction regarding the study.

13.1.1 Genotyping via SPARTAN® Bioscience

Spartan Bioscience will provide installation and training of personnel to use the equipment and run the buccal swabs. Each study site will receive a Spartan Analyzer. Spartan will perform instrument installation. Following equipment installation, Spartan will provide training to study personnel at each site. Each trainee will have the opportunity to run a minimum of two independent runs with the Spartan *CYP2C19* assay, and Spartan will additionally guide the trainees through more runs as needed to ensure independent trainee competency in performing the assay from start to finish.

Each site will perform analytical validation of the Spartan platform's performance characteristics prior to analyzing study samples. Buccal swabs obtained from volunteers will be analyzed on the Spartan instruments and compared to oral fluid DNA results obtained from a currently existing validated *CYP2C19* automated fluorescent Sanger sequencing assay. All non-Rochester sites will obtain buccal swabs for analysis on their own Spartan instruments and ship one oral fluid sample to Mayo Rochester for *CYP2C19* sequence analysis.

13.1.2 Genotyping via ABI TaqMan

The laboratory performing this assay has extensive experience with this platform. Probes and primers will be designed utilizing ABI's design services. Development and analytical validation will occur as per the laboratory's established guidelines. The laboratory will utilize a currently existing validated *CYP2C19* automated fluorescent Sanger sequencing assay to verify accuracy of the TaqMan assay as well as troubleshoot any potential samples with unclear genotypes via the TaqMan assay. Each operator of the assay will be trained as per the laboratory guidelines.

13.1.3 Database Training

AHRC, DCIS, and the Project Coordinator will arrange for each individual site coordinator to be trained with the variable definitions and data sources to ensure uniform data collection across study sites.

14. PARTICIPANT SAFETY, ADVERSE EVENTS, CLINICAL ENDPOINTS, AND OTHER REPORTING

14.1 Institutional Review Boards

Before initiating this study, the protocol, informed consent forms, recruitment materials, and other relevant information will be reviewed and approved by Mayo Clinic and respective institutional review boards (IRB) or research ethics boards (REB). Any amendments to the protocol must be approved by each institution's IRB or REB before they are implemented. Any amendments to the protocol and consent form(s) will be communicated to the sites upon Mayo IRB approval.

14.2 Adverse Events

All subjects randomized to conventional therapy will receive clopidogrel; subjects randomized to the prospective genotyping group will receive clopidogrel or ticagrelor based on their genotype. Known adverse events associated with both medications will not be considered study related and will not be recorded as such in the trial because they have already been identified with the specific antithrombotic therapy, which is clinically indicated for the subjects' clinical

care. However, participating sites must follow the policy of the IRB/REB they are utilizing, which may include reporting of these events to their respective ethics board.

Adverse event reporting and monitoring is applicable to the study-specific procedures of this study, including a blood draw, three buccal swabs (in the prospective genotype arm), a genotyping survey (first 1,000 subjects) randomization, and genotype analysis (which will be used in the prospective genotype arm to determine which of two FDA-approved antithrombotic treatments will be used as prophylactic therapy for PCI). Any adverse event related to study-specific procedures must be reported to the Project Coordinator.

In addition, any problem or event which, in the opinion of the local investigator, was unanticipated, places subjects or others at a greater risk of harm than was previously known or recognized, and was possibly related to the research procedures will be reported to the Project Coordinator within 48 hours of notification. The site coordinator will record the information in the source documentation and will forward all relevant medical information to the Project Coordinator who will prepare the documents for Adjudication Committee review.

14.3 Clinical Endpoints

Information on all clinical endpoints will be recorded in the source documentation and in the eCRF. This information will be adjudicated by an independent Adjudication Committee that will be blinded to study treatment.

When a MACE is suspected, the site coordinator and/or PI will notify the Project Coordinator. The site coordinator will record the information in the source documentation and in the eCRF and will forward all relevant medical information to the Project Coordinator who will prepare the documents for Adjudication Committee review.

When any bleed requiring diagnostic study or intervention (e.g. doctor's visit, change in medication, ER visit, hospitalization) is suspected, the site coordinator will record the information in the source documentation and in the eCRF and will forward all relevant medical information to the Project Coordinator who will prepare the documents for Adjudication Committee review.

14.4 Other

Known adverse events associated with both medications will not be considered study related and will not be recorded as such in the trial because they have already been identified with the specific antithrombotic therapy, which is clinically indicated for the subjects' clinical care. However, when any death occurs, the site coordinator will record the information in the source documentation and in the eCRF and will forward all relevant medical information to the Project Coordinator who will prepare the documents for Adjudication Committee review.

15. STATISTICAL CONSIDERATIONS

15.1 Study Design

This is a multicenter, prospective, two-arm, unblinded trial with 1:1 randomization between the conventional therapy arm treated with clopidogrel at standard dose and a prospective genotype tailored approach using clopidogrel in WT and ticagrelor in reduced function *CYP2C19* genotype subjects. Subjects in the conventional therapy group will undergo retrospective genotyping one year after PCI to identify those with reduced function *CYP2C19* alleles. The study goal is to assess the effectiveness of ticagrelor in reducing the risk of 1-year MACE in

subjects who carry the reduced function *CYP2C19* allele. Subjects will be followed by telephone contact for 1 year after index PCI. Endpoint analysis will occur after all subjects have reached the study endpoint. Predefined major protocol violations/deviations are missing data for the primary efficacy end point, violation of inclusion criteria, and additional protocol violations that will be possibly defined during the blind data review. Missing patients will be censored at the last follow-up visit. Alive or dead status will be specifically searched for all missing patients.

15.2 Sample Size and Power Considerations

15.2.1 Primary Endpoint

Sample size and power calculations for the study are based on the following assumptions:

- 2-sided log-rank test
- $\alpha = .05$
- Randomization ratio of 1:1

Data from the Mayo Rochester PCI registry demonstrate a 1 year rate of death, MI, or stroke of about 7.5% in PCIs from 2008-2009. Furthermore, the PLATO trial suggests we can expect stent thrombosis or severe, recurrent ischemia in about an additional 3%, resulting in a baseline rate of 10.5%. The rate is expected to be higher in *2 or *3 allele carriers who are discharged on clopidogrel, thus we assume a baseline rate of 12% for primary endpoint in the control arm.

Two studies suggest that the expected rate of 12% in Korean patients treated with clopidogrel after PCI for ACS. Kim et al.[31] observed a 10.1% event rate for death, myocardial infarction ,or stroke at 12 months in 306 patients with at least one CYP2C19*2 or *3 allele treated with PCI for acute myocardial infarction. As noted above, the PLATO trial suggests that stent thrombosis and severe recurrent ischemia may add 3% to this rate, which would result in a baseline rate over 12%. Oh et al.[39] observed a 10.7% event rate for cardiac death, myocardial infarction and repeat revascularization at 12 months in 1011 patients treated with a drug-eluting stent (22% AMI, 78% stable) and carrying at least one CYP2C19*2 allele. Assuming the event rate is higher in the

AMI subgroup and that the addition of stent thrombosis to the endpoint would increase the event rate, this study also suggests that a 12% event rate in the control group of Koreans may be expected.

Given that the vast majority of patients at the Mayo sites are of European heritage, we expect a reduced function allele prevalence of about 30% in those patients. The Canadian hospitals have a more diverse ethnic mix of patients, and we expect their prevalence to be anywhere from 30-50%. Thus, our sample size calculations assume an overall prevalence of reduced function allele carriers of 30% among patients recruited at those sites. We also assume the prevalence to be 50% in patients enrolled from South Korea and expect to enroll 1,015 subjects from there. Furthermore, we assume no more than 5% of patients will be lost to follow-up or drop out.

Based on data from Mega[1] and Schuldiner[2], a hazard ratio as low as 0.60 for ticagrelor versus clopidogrel in reduced function allele carriers may be expected. We intend to power the study to detect a hazard ratio of 0.65 or smaller. This will

require a total of 1,694 patients with reduction function alleles to be randomized, and thus 5,270 patients will be enrolled.

Table 3. Required sample size for 80% power

	Minimum detectable effect, hazard ratio		
	0.60	0.65	0.70
Number with reduction function allele required	1,241	1,694	2,401
Number with reduced function to enroll assuming 5% drop out	1,307	1,784	2,528
Number with reduced function allele enrolled at South Korean sites	508	508	508
Number with reduced function allele to enroll at non-Korean sites	799	**1,276**	2,020
Total number enrolled at Korean sites, assuming 50% prevalence	1,015	**1,015**	1,015
Total number to enroll at non-Korean sites, assuming 30% prevalence	2,665	**4,255**	6,734
Total number enrolled	3,680	**5,270**	7,749

15.2.2 Revised Sample Size Calculations

At the time of this protocol revision (Version 8), the estimated event rate for the primary endpoint across all LOF subjects is 4.8%, substantially lower than the assumptions made in Section 15.2.1. We propose performing updated power calculations using a revised minimum detectable effect of a hazard ratio of 0.50. This effect size is justified by several arguments. First, ticagrelor has already been shown to reduce MACE events by about 16% in all ACS patients, regardless of genotype, in the PLATO trial. However, because our study treatment represents a precision medicine, pharmacogenomic approach, we expect a much greater treatment effect in the targeted LOF population. Second, such effect sizes have been seen in other studies involving CYP2C19 *2 and *3 alleles(2,40). Third, a meta-regression analysis of studies comparing event rates in (primarily) clopidogrel-treated patients who were LOF vs. WT suggested an inverse relationship between the overall event rate and the WT vs. LOF advantage, such that the predicted HR

in very low event rates was consistent with 0.50. Finally, at low event rates, a large effect must exist within the LOF population in order to achieve reasonable number-needed-to- treat (NNT) values, since the genotype-guided dual antiplatelet treatment is expected to have no effect in the WT population. For example, if the event rate is 4% in LOF subjects on clopidogrel, and 2% in LOF subjects on ticagrelor, that 50% reduction would equate to a NNT of 50 subjects within the LOF sub-population. If the prevalence of LOF alleles is 30% in the overall population, that would equate to an NNT of 167. Under initial assumptions, the NNT in the LOF sub-population would have been 25 subjects, equating to an overall NNT of 75. Thus, from the perspective of NNT, we are powered to detect a smaller effect than under initial assumptions.

Additional assumptions play a role in the power calculations. First, we assume that around the total enrollment mark of 3900 subjects, 20% of subjects enrolled from

that point forward will be from Korea. This is lower than observed so far (30%), due to the impending activation of additional sites in North America. Increasing this percentage would result in a smaller required sample size, as it would increase the prevalence of LOF subjects in the study. We also assume that the current prevalence of LOF carriers will continue in Korean (59%) and North American (28%) subjects. Increasing either of these prevalences would reduce the number of subjects required. The power calculations are based on a two-sided log-rank test at a Type I error rate of 0.05 with an expected randomization ratio of 1:1. Table 3 demonstrates the calculations for total subjects enrolled assuming an event rate of 4.5%. Table 4 gives required sample sizes for varying event rates and power levels. These tables show that the previous planned sample size of 5270 subjects provides at least 80% power if the event rate is at least 4.0%.

Table 4. Revised Sample Sizes for a Minimum Detectable Hazard Ratio of 0.50 with an overall event rate of 4.5%

	80% Power	*85% Power*	*90% Power*
N of LOF subjects required	1560	1784	2086
N of LOF subjects accounting for 5% dropout	1643	1878	2196
N of LOF patients expected from Korea	747	828	937
N of LOF patients expected from North America	896	1050	1259
Total patients expected from Korea	1275	1413	1599
Total patients expected from North America	3192	3742	4486
Total number of patients to enroll	4467	5155	6085

Table 5. Required Sample Sizes for a Minimum Detectable Hazard Ratio of 0.50 at varying event rates and power assumptions

Baseline event rate	**Power at n=5270**	**Sample size needed for given power**		
		80%	*85%*	*90%*
5.0%	**89.3%**	3955	4570	5409
4.5%	**85.8%**	**4467**	**5155**	**6085**
4.0%	**81.6%**	5052	5827	6875

15.2.3 Secondary Endpoint

To assess the incidence of major or minor bleeding not related to CABG. The PLATO trial observed a 1-year rate of major or minor bleeding of 14.6% in subjects receiving clopidogrel, and the genetic sub-study observed no significant decrease in major bleeding in those with loss-of-function alleles. Thus, assuming a 14.6% rate of major or minor bleeding at 12 months in reduced function subjects receiving clopidogrel, 1,694 subjects will provide 80% power if the bleeding rate in the ticagrelor group is at least 19.7%.

15.3 Randomization

Subjects will be randomized on a 1:1 ratio stratified by age, sex, site, and CAD presentation, i.e. unstable angina/NSTEMI, STEMI, or stable CAD.

15.4 Statistical Comparisons of Baseline Factors

For continuous variables such as age, means, and standard deviations overall and within treatment group will be calculated. If the variable is moderately to severely skewed, medians and 25th and 75th percentiles will be computed. For discrete variables, frequencies and percentages will be calculated both overall and within treatment group. Standardized differences will be used as a measure of imbalance between the groups.

15.5 Specification of the Primary Analyses

Hypothesis 1A. The effect of genotype-guided antiplatelet therapy versus conventional care in patients with a reduced function *CYP2C19* allele will be estimated using a Cox proportional hazards regression model, with covariates including variables used for stratified randomization and other subject factors associated with MACE. The analysis will be conducted under the intention-to-treat principle, with follow-up beginning at randomization, but with genotype defined by the Taqman genotyping assay. Those whose prospectively defined genotype disagrees with their TaqMan-based genotype will nevertheless be analyzed based on the TaqMan result, which is the only result that is available in both arms. A sensitivity analysis will be done, taking into account the Spartan result. In the retrospective genotyping group, reduced function status will be determined by the TaqMan assay results at least one year after PCI. Subjects who withdraw or are lost during follow-up will be treated as censored at the date of last contact. Patients who complete follow-up at 12 months will be considered censored from that point onward. The proportional hazards assumption will be assessed visually using plots of scaled Schoenfeld residuals. A two-sided likelihood ratio test will be used to assess the significance of the partial effect of treatment; a p-value less than 0.05 will be considered statistically significant. Kaplan- Meier curves will be used to display survival free of MACE estimates over the first year of follow-up.

Hypothesis 1B. It is also important to determine the effect of genotype-guided antiplatelet therapy versus conventional care in patients with the wild type CYP2C19 allele. In this case, both groups will be given clopidogrel, but the genotype-guided group patients and their physicians will know prospectively that they have the wild-type allele, at least based on the Spartan platform. The analysis will be done as outlined above in the LOF group, again defined by the TaqMan-based assessment of wild-type status. It is expected that the null hypothesis will prevail, but it is important to confirm that knowledge of genotype in and of itself does not have an effect on the rate of MACE events.

Finally, note that the entire allocation of type 1 error is placed on Hypothesis 1A, and the analysis of Hypothesis 1B is seen as confirmatory of the null hypothesis. If the null hypothesis in 1A is rejected, i.e. a treatment benefit is seen with ticagrelor versus clopidogrel in LOF patients (or the converse), then (and only then) a formal test of Hypothesis 1B will be conducted at the 0.05 level. The purpose of this second test is to inform the overall assessment of treatment effect in the entire randomized study population. In any case, an assessment of treatment effect in the overall randomized study population will be done for estimation and descriptive purposes only, since it will have insufficient power to detect a treatment effect. If the null hypothesis in 1B is rejected, then that result will be factored into any overall assessment of benefit of the prospective genotyping treatment strategy.

15.6 Specification of the Secondary Analyses

For secondary analyses involving 1-year endpoints (e.g. MACE, bleeding), Cox proportional hazards models with appropriate covariates will be used to compare the 1-year rate of secondary endpoints according to intention-to-treat classification. A p-value less than 0.05 will be considered statistically significant. Additionally, unadjusted treatment effects will also be estimated and tested as a secondary analysis. Confidence intervals for binomial measures will be computed using the Wilson CI method for 95% coverage probability. Mechanisms of stent failure for subjects with coronary stent thrombosis and with reduced function *CYP2C19* allele will be compared between ticagrelor and clopidogrel using Pearson's chi-squared test.

15.7 Subgroup Analyses

15.7.1 Interaction Between CAD Presentation and Genotype-guided Therapy

We will analyze the primary endpoint of MACE between reduced function allele carriers on clopidogrel versus those on ticagrelor within ACS presentation class, stable CAD, unstable angina/NSTEMI, and STEMI. We will test for the significance of the interaction between CAD presentation and genotype-guided antiplatelet therapy with a Cox proportional hazards model.

15.7.2 Interaction Between *17 Carriers and *2/*3 and Antiplatelet Therapy

We will analyze MACE and bleeding endpoints with Cox proportional hazards models with main effects for *17 allele carrier, *2/*3 carrier and clopidogrel vs. ticagrelor therapy. We will test for interactions between antiplatelet therapy and *17 allele, plus interaction between *17 and *2/*3 alleles.

15.7.3 Additional Subgroup Analyses

We will analyze the effect of genotype-guided therapy on the primary endpoint of MACE in reduced function carriers within the subgroups of current smokers, elderly patients (age ≥75 years), women, diabetics, white/Caucasians, Asians, patients with creatinine clearance <30 mL/min, and on proton pump inhibitors. Interaction tests will be used to test whether the effect of genotype-guided antiplatelet therapy is different between these subgroups and the remaining reduced function allele carriers.

It should be noted that these subgroup analyses will have less power than the primary analysis, while being subject to greater type 1 error because of multiple comparisons. While not proposing formal multiple comparisons procedures, we propose to invoke usual calculations for controlling the risk of type I errors, and to regard these subgroup analyses as exploratory.

15.8 Monitoring for Futility and Efficacy

Both efficacy and futility monitoring require three estimates: 1) a best current estimate of the treatment effect, as well as 2) uncertainty of the estimate (standard error and/or confidence interval), and 3) an estimate of what proportion of the study's final information is currently in hand, that is, the current value of "information time". Information time is critical both in assessing conditional power (futility) as well as in doing interim testing using group sequential approaches. Appendix C details how to

construct a combined likelihood combining the information from the complete and the incomplete subject data, which produces the first two required estimates, using likelihood calculations, and specifically, using the profile likelihood method to get down to the one-dimensional likelihood for the treatment effect parameter.
Appendix C also details how to estimate information time (the third required measure). Once we have a current z-score (effect divided by standard error) for the treatment effect, as well as our current estimate of information time, we can then do standard calculations for conditional power (futility) and efficacy

Futility Monitoring: We propose that this assessment be based on our calculation of conditional power, as described in Appendix C. In addition to the conditional power calculation, we will provide the modified unconditional power calculation based on current estimates of event rates and the estimate and 95% CI of the average event rate in LOF subjects. We specifically propose that at the time of DSMB reviews, that consideration be given to stopping the trial if the ratio of conditional power to initial power falls below the proportion of remaining information time. For example, if the initial power is 85%, and the proportion of remaining information time is 40%, then the conditional power should exceed 34% (0.85*0.4). The basis for the moving target of conditional power is the "sunk cost" argument. The initial study design is assumed to equate the expected utility of a positive result with the cost of the entire study. By equating the ratio between conditional power and initial power, the cost-benefit ratio is maintained. This means that the bar for conditional power for continuing gets progressively lower, as more of the total study costs become a "sunk cost."

Efficacy Monitoring: Although we neither recommend, nor anticipate,stopping early for efficacy, we recognize the need to provide for an exit strategy that permits a statistically valid conclusion to be drawn when it is desired to stop the trial and claim efficacy. We therefore propose using the efficacy stopping boundary proposed by Peto and Haybittle[41,42], namely we use a 2-sided nominal p-value of 0.001 for all interim looks (critical value 3.291), where the looks are at 40%, 60%, and 80% of information time, and we are thereby entitled to conduct the final test at the 0.0495 level (critical value = 1.965 rather than 1.960). This procedure accommodates the fact that our knowledge of information time is limited by the vagaries of incomplete (and changing) endpoint ascertainment and incomplete genetic ascertainment. The use of a fixed critical value independent of information time is very helpful in this unique context of uncertainty around the precise value of information time. This means a critical value of 3.291 would obtain at any interim look, independent of at what interim time the look occurred. At the final look, the critical value of 1.965 rather than 1.96 will be applied, which has an infinitesimal impact on power. We propose up to 3 interim looks, and that these occur at information times of approximately 40%, 60%, and 80%.

15.9 Assumptions Monitoring

15.9.1 Event Rate in the Stable CAD Patients

To increase generalizability of the study, we have included PCI for stable CAD as part of the inclusion criteria. Recognizing, however, that the event rate in this

population may be substantially lower than in the ACS population, we intend to plan for the possibility that the inclusion of the stable CAD patients might jeopardize the power of the trial. Thus, once the first batch of TaqMan results is available for the conventional arm subjects, we will monitor event rates monthly within the reduced function subjects of this arm and quit enrollment of stable CAD patients if the event rate for the primary endpoint is *significantly lower* than that for ACS subjects and we are *nearly certain* that continued enrollment will reduce the study power below 75%. *Significance* of the difference between stable CAD and ACS subjects in the conventional treatment arm will be assessed by a one-sided log rank test conducted at a 0.005 Type I error rate. The assessment of study power will be conducted using Bayesian estimation methods. The 1- year event rate will be estimated from the reduced function subjects in the conventional treatment arm. Using Bayes Theorem we will calculate the posterior distribution of study power, given the current event rate and a prior distribution for the event rate (beta distribution with a mean of 0.12 and 99% of the probability density between 0.04 and 0.20), while maintaining the initial study design assumptions of hazard ratio and sample size. In particular, we will calculate the probability that the power of the study will exceed 75%. We will be *nearly certain* that continued enrollment will reduce the study power below 75% if the aforementioned probability is less than 1%. Additionally, we will assess whether the generalizability of findings is jeopardized. While generalizability does not mean that we must have adequate power for the stable CAD subgroup (since the entire study would then be overpowered), it is reasonable to expect that the hazard ratio for prospective genotyping ought to at least trend in the correct direction (<1.0) within the subgroup. Thus, we will calculate the probability that the stable CAD subgroup hazard ratio could be ≥1.0 under the assumption of a true hazard ratio of 0.50 and expected enrollment of 1,694 reduced function subjects. The probability calculation will depend on the expected final number of stable CAD reduced function subjects and the event rate within that group. To be conservative, we will use the upper limit of a 99% confidence limit for the event rate when calculating the probability of discordant hazard ratio.

15.9.2 Event Rate in Subjects Enrolled at Korean Sites

Similarly, there is some concern that the event rate for the primary endpoint may be substantially lower in patients enrolled at Korean sites. We will follow a similar procedure as above to safeguard the power of the trial. Once the first batch of TaqMan results is available for the conventional arm subjects, we will monitor event rates monthly within the reduced function subjects of this arm and quit enrollment of subjects at Korean sites if the event rate for primary endpoint is *significantly lower* than that of subjects enrolled at non-Korean sites and we are *nearly certain* that continued enrollment in Korea will reduce the study power below 75%. *Significance* of the difference between Korean-enrolled and non-Korean enrolled subjects in the conventional treatment arm will be assessed by a one-sided log rank test conducted at a 0.005 Type I error rate. The assessment of study power will be conducted using Bayesian estimation methods. The 1- year event rate will be estimated from the reduced function subjects in the conventional treatment arm. Using Bayes Theorem we will calculate the posterior distribution of study power, given the current event rate and a prior distribution for the event rate (beta distribution with a mean of 0.12 and 99% of the probability density between 0.04 and 0.20), while maintaining the initial study design assumptions of hazard ratio and sample size. In particular, we will calculate the probability that the power of the study will exceed 75%. We will be *nearly certain* that continued

enrollment will reduce the study power below 75% if the aforementioned probability is less than 1%.

15.9.3 Cross-over Monitoring

Cross-over may potentially affect the power of the study. Patients in the conventional therapy arm who switch to ticagrelor prior to experiencing the primary endpoint may lower the event rate of the conventional therapy arm, resulting in a smaller treatment effect and lower power. Similarly, patients in the prospective genotyping arm who are assigned ticagrelor and who switch to clopidogrel may increase the event rate of the prospective genotyping arm, also resulting in a loss of statistical power. Here we define the cross-over rate as the proportion of enrolled subjects who switch from their protocol- assigned dual antiplatelet therapy to the other treatment. This does not include patients who switched to another treatment (such as prasugrel) or who stop treatment altogether, as we expect these occurrences to be rare and their effects on power difficult to predict. Each month, the cross-over rate in each arm will be calculated and the effect on statistical power according to a priori study assumptions calculated. If the revised power is less than 60%, the DSMB will be notified and asked to approve continuation of the trial. Study enrollment and activities will continue while the DSMB deliberates. The study statistician will provide power calculations for the trial based on the current cross-over rate in each arm using both a priori study assumptions as well as observed enrollment and event rates at that time. Based on the current study assumptions, a cross-over rate of 10% will, on average, result in a reduction in statistical power to around 60%.

15.9.4 Spartan Performance Monitoring

Disagreement between the Spartan and TaqMan results may also affect the power of the trial. For example, if the Spartan device incorrectly identifies a reduced function carrier as a wild-type carrier, that subject would be prescribed clopidogrel, potentially increasing the event rate in the prospective genotyping arm. As TaqMan genotyping results become available, we will monitor the agreement between Spartan and TaqMan results among subjects with conclusive test results, both overall and at each study site. If the disagreement exceeds 5% at any site with 20 or more subjects analyzed, or exceeds 10% at any site with less than 20 subjects analyzed, enrollment at that site will be suspended until the Spartan device is re-validated as per the pre-enrollment validation process.

16. TRIAL MANAGEMENT

16.1 Data Management Oversight

Data management oversight will be the responsibility of contracted data coordinating centers**,** AHRC (North American sites) and DCIS (Korean sites), and Mayo Clinic Rochester. The responsibilities of AHRC, DCIS, and Mayo Clinic are outlined below:

Table 6.	AHRC	DCIS	Mayo
TRIAL MANAGEMENT			
Protocol Development			x
Protocol implementation	x	x	
Site selection			x
Site management	x (CAN)	x (KOR)	x (U.S.A.)
Onsite Monitoring (Reg. Binders, source data verification)	x	x	
Document collection/Trial Master File	x (CAN)	x (KOR)	x (U.S.A.)
Global communication			x
Archiving			x
Committee selection			x
Committee coordination			x
MEETINGS			
Internal team meetings during start-up/biweekly during recruitment	x	x	x
BUSINESS OPERATIONS			
Financial management			x
Contracts			x
SUPPLIES AND SERVICES			
Translations if needed	x	x	
Central lab/vendor			x
SAFETY			
Study Endpoint and SAE review • Generate reports for review by appropriate committees			x*
DATA/REPORTING			
Database development	x (consult)		x
Source documents development			x
Data review and validation/query management	x		
Data freeze/lock and database lock	x		
Data reports • DSMB/IRB/REB • Accrual reports • Check assumptions used to design the trial (MACE rates, *CYP2C19* frequency) • Regular data summaries			x
Interim analysis			x
Data analysis			x
Adjudication			x

*Adjudication & DSMB Committees

16.2 Quality Assurance

Quality control will be ensured through oversight by AHRC at the U.S.A. and non-Korean international sites and DCIS at the Korean sites, who will review the medical records and electronic data for all participants on a regular basis for completeness and consistency. Quality and completeness of data entry will be reviewed as soon as possible after data entry, within 5 business days of data entry for the first 5 participants randomized at each site, and within 15 days of data entry thereafter. AHRC will generate data quality reports monthly for review by the study team. Data

queries generated by identification of incomplete or inconsistent data will be raised directly within the electronic eCRF and should be resolved by the study coordinator or PI in a timely manner. Corrections or changes in the data management system are tracked with the retention of the original data and the corrected data with the date of data entry and submitting personnel. Sites with persistent delays or difficulties in data capture will be provided additional study-based training.

16.3 Quality Control Procedures

Two levels of database quality control will be performed. The first level consists of programmatic consistency checks and/or range checks. The second level of database quality is a record or panel level of control. Programs will be written to identify suspected duplicate and blank or missing records and records not double-entered within and across database tables. AHRC at the U.S.A. and non-Korean international sites and DCIS at the Korean sites will be responsible for communication and action on reports generated directly from Medidata Rave®. The Mayo statistician will be responsible for all other reports. These internal data quality and process compliance audits are routinely conducted on internal ongoing studies to document the frequency of random errors and identify systematic deviations so that they can be corrected. Other periodic quality control checks will document the frequency of random entry errors and identify systematic and process errors.

In general, the following issues will be addressed:

- Data completeness: Completion by the clinical centers of all evaluations mandated by the protocol is checked.
- Procedural errors: Errors in performing study procedures, e.g. taking the blood samples.

Remedial action will be taken as appropriate; otherwise, the protocol and Operations Manual may be revised as appropriate. Training and recertification will be made available to redress deficiencies and misunderstandings.

16.4 Site Monitoring

See Appendix D.

16.5 Study Completion and Closeout Procedures

AHRC and DCIS will conduct closeout procedures for each site in accordance with the trial Monitoring Plan. Study closeout activities are performed to confirm that the site investigator's study obligations have been met and post-study obligations are understood. Verification that study procedures have been completed, data have been collected, and study intervention(s) and supplies are returned to the responsible party or prepared for destruction will be conducted at the end of the trial. The following (minimally) will be verified:

- Comparison of the investigator's correspondence and study files against the Coordinating Center's records for completeness;
- Assurance that all data queries have been completed;
- Assurance that correspondence and study files are accessible for external audits;
- Assurance that the investigator will notify the IRB/REB of the study's completion and store a copy of the notification;
- Participant notification of the study completion.

16.6 Hardware and Software Configuration

16.6.1 Hardware and Database Software

Study data will be captured and stored using Medidata Rave (Medidata Solutions) with servers physically located in Houston, Texas. Study personnel will interact with the database via web browser.

16.6.2 Statistical Software

SAS version 9.3 or higher (Cary, NC) will be used as the principal application for the management of analysis data files and statistical computations. R will be used to provide supplementary functions as needed.

16.6.3 Access Control and Confidentiality Procedures

Access permissions to the Medidata Rave system will be set at the time of the database build and will be updated as necessitated by personnel changes. Each study site will only have access to subjects enrolled at their site. Only the site study coordinators will have edit access to the data and will be responsible for entry and editing. Other study personnel will be granted read-only access, as appropriate. Medidata Rave will create copies of the data as SAS data sets on a server maintained by the Division of Biomedical Statistics and Informatics at Mayo Rochester on a nightly basis. These secondary files will be accessible by the Mayo statistician.

16.6.4 Security

Database and Web servers will be secured by a firewall and through controlled physical access. The Medidata Rave system has security features to ensure that study personnel accessing the database have the proper authority to perform the functions he or she requests of the system. Unix group-access control will provide access security for the secondary SAS data sets used by the Mayo statistician. Workstation login is secured by extensive user-password facilities under Unix and Windows.

16.6.5 Back-up Procedures

Medidata Rave automatically creates back-up files of the database on a regular basis according to standard research procedures. Additionally, the hosting site has dedicated disaster recovery facilities.

16.6.6 Virus Protection

All disk drives that provide network services and all user computers will be protected using virus-scanning software. Standard research policies will be applied to update these protection systems periodically throughout the study.

16.6.7 Data Management Activities

In general, the following data management procedures will be applied:

- Paper CRFs will be designed specifically for the needs of this study and will serve as a tool to assist the study coordinator with data entry into an electronic database. Subject identification information to be captured will include the participant's study-specific ID number, initials, and date of birth as allowed by local IRB/REB. The

subject's name, address, medical record number and social security number will not be captured in the electronic database.

- Information will be abstracted from the participant's medical charts and other source documents. All CRFs will be completed according to the current Good Clinical Practice (GCP) guidelines. Training on completing the CRFs will be included in the training session described in the Manual of Procedures.
- For every record type, the data dictionary will identify key fields (e.g. the participant's ID number and the type and date of evaluation); the field type (e.g. numeric, character, checklist, or date), and ranges for impossible and improbable values.
- There will not be double data entry for this study

16.6.8 Reports and Summaries

A variety of standard progress reports will be prepared either automatically by Medidata Rave or as directed by the Mayo statistician during the course of the trial and includes:

- Data Status/Exception Reports: lag in entering CRFs into the database, missing visits, missing pages, listing of outstanding queries, and summary of totals of outstanding queries;
- Quality Control Reports: duplicates, missing from table, blanks;
- Data Surveillance Reports: query frequencies, perfect data;
- Protocol Deviation Reports: numbers of ineligible participants enrolled in the study;
- Weekly accrual reports (overall and by trial arm and genotype); and
- Data and Safety Monitoring Board (DSMB) reports: Accrual reports, eligibility violations, demographics, *CYP2C19* genotype results, endpoints rates, and other key information needed for assessing the quality and safety of the trial. These will be provided to the DSMB at least 1 week prior to their next scheduled meeting.

Reports will be prepared for the periodic meetings of the Adjudication Committee containing information required for clinical event assessment. Some reports, such as the data exception report, may be generated more frequently as required.

16.7 Biological Sample Management

For the prospective genotype-guided arm, three buccal swabs will be obtained to be immediately processed and analyzed by the Spartan RX. All subjects will have one 10 mL tube of EDTA anticoagulated blood collected and will be sent to the Mayo Clinic Rochester BAP laboratory for DNA extraction for 12 month *CYP2C19* genotyping, as outlined. FedEx will be used for shipping so that shipments may be tracked. For subjects who provide consent to allow their DNA to be stored for future genetic analysis other than the *CYP2C19* genotyping being performed for the purposes of this study, their DNA will be stored in the BAP laboratory for future studies. Subjects who enroll at Mayo Clinic Rochester or the University of Ottawa Heart Institute and who provide consent to allow their sample to be stored for future research will have plasma extracted from their whole blood sample to be stored in the BAP laboratory for future use. Sample kits, shipping containers, and FedEx air bills will be provided to the other sites by Mayo Rochester.

17. STUDY ADMINISTRATION

17.1 Cooperative Agreement Mechanism

The funding mechanism used to undertake this project is a "Subcontract Agreement" between Mayo Clinic Rochester and participating study sites. Under the subcontract agreement, the Steering Committee, supports, and/or stimulates the study and is substantially involved with investigators in conducting the study by facilitating performance of the effort in a "partner" role. The site PI serves on the Steering Committee, and he/she or another scientist at that site may serve on other project committees, when appropriate. At the same time, however, the Steering Committee does not assume a dominant role, direction, or prime responsibility for this research project.

Site PIs have lead responsibilities in all aspects of the project at their site, including implementing any modifications to the trial design, conduct of the trial, quality control, and collaboration with other investigators, unless otherwise provided for by the Steering Committee.

Mayo Clinic retains custody of and has primary rights to the center-specific and collaborative data, subject to government rights-of-access consistent with current Health & Human Services (HHS), Public Health Service (PHS), and National Institutes of Health (NIH) policies. The protocol and governance policies call for the continual submission of data centrally to the MCR Biostatistics Core for the collaborative database. At a minimum, the database will contain the key variables selected by the Steering Committee for: standardization across all clinical centers; the submittal of copies of the collaborative datasets to each site PI upon completion of the project; procedures for data analysis; reporting and publication; and procedures to protect and ensure the privacy of medical and genetic data and records of individuals.

During or within 3 years beyond the end date of the project period, unpublished data, unpublished results, data sets not previously released, or other study materials or products are to be made available to any third party only with the approval of the Steering Committee.

Upon completion of the project, the overall PI is expected to put the intervention materials and procedure manuals into the public domain and/or make them available to other investigators according to the approved plan for making data and materials available to the scientific community for the conduct of research at no charge other than the costs of reproduction and distribution.

The Steering Committee reserves the right to terminate or curtail the project (or an individual award) in the event of: a) failure to develop or implement mutually agreeable collaborative measurement, participant eligibility, and data management sections of the protocols; b) substantial shortfall in subject recruitment, follow-up, data reporting, quality control, or other major breech of protocol; c) substantive changes in the agreed-upon protocols with which the Steering Committee cannot concur; d) reaching a major project outcome substantially before schedule with persuasive statistical significance; or e) human subject ethical issues that may dictate a premature termination.

Any disagreement that may arise in scientific/programmatic matters (within the scope of the award) between award recipients and the Steering Committee may be brought to arbitration. An arbitration panel will be composed of 3 members: one selected by the Steering Committee or by the individual site PI in the event of an individual disagreement; a second member selected by the Principal Investigator, and the third member selected by the other 2 members. This special arbitration procedure in no way affects the site PI's right to appeal an adverse action that is otherwise appealable in accordance with the PHS regulations at 42 CFR part 50, Subpart D, and HHS regulation at 45 CFR part 16 under applicable statutes, regulations, and terms of the award.

17.2 Steering Committee

The Steering Committee is the main governing body of the project. The composition of the Steering Committee may be found in appendix E. Each member of the Steering Committee will have an individual vote. All decisions are determined by majority vote. The Chair of the Steering committee will be the deciding vote in case of a tie.

All major scientific decisions are determined by the Steering Committee. It assumes overall responsibility for the design and conduct of the trial. It appoints (and disbands) committees and subcommittees as the need arises; designs, approves, and implements the study protocols; oversees the development of the Operations Manual; monitors subject recruitment and treatment delivery; evaluates data collection and management; oversees quality assurance procedures; and implements changes and enhancements to the study as required. It also has primary responsibility for facilitating the conduct of the trial and reporting the project's results. The Steering Committee will meet at least twice annually, preferably at one of the national or international cardiology meetings or via teleconference if necessary.

17.3 Executive Committee

The Steering Committee will set the overall guidance of the conduct of the TAILOR-PCI trial. There will be the need, however, for ongoing management decisions and input from trial leadership outside of the regularly scheduled Steering Committee meetings. The Executive Committee will serve to provide day-to-day guidance of the trial, will serve to provider overall coordination of issues outside of the Steering Committee, and will serve to enhance communications among all of the sites and sub-committees of TAILOR-PCI. It will be comprised of a small number of the Steering Committee membership including the PI, the Steering Committee Chair, the Co-PI, and other members who are recognized as senior clinicians or trialists. The Executive Committee will liaison with the Steering Committee when appropriate and will serve as the major communications channel for all of the site coordination.

17.4 Publications Committee

See Appendix F.

17.5 Data and Safety Monitoring Board

See Appendix G.

17.6 Adjudication Committee

All reported adverse events and clinical endpoints, including any bleeds requiring intervention, will be adjudicated by an independent Adjudication Committee that will be blinded to study treatment.

17.6.1 Adverse Event and Clinical Endpoint Reporting

When any problem or event which, in the opinion of the local investigator, was unanticipated, places subjects or others at a greater risk of harm than was previously known or recognized, and was possibly related to the research procedures occurs, the site coordinator and/or PI will notify the Project Coordinator within 48 hours of becoming aware of the event. The site coordinator will record the information in the source documentation and will forward all relevant medical information to the Project Coordinator who will prepare the documents for Adjudication Committee review.

When a MACE is suspected, the site coordinator and/or PI will notify the Project Coordinator within 48 hours of becoming aware of the event. The site coordinator will record the information in the source documentation and in the eCRF and will forward all relevant medical information to the Project Coordinator who will prepare the documents for Adjudication Committee review.

When any bleed requiring diagnostic study or intervention (e.g. doctor's visit, change in medication, ER visit, hospitalization) is suspected, the site coordinator will record the information in the source documentation and in the eCRF and will forward all relevant medical information to the Project Coordinator who will prepare the documents for Adjudication Committee review.

When any death occurs, the site coordinator will record the information in the source documentation and in the eCRF and will forward all relevant medical information to the Project Coordinator who will prepare the documents for Adjudication Committee review.

17.7 Monitoring

See Appendix H.

17.8 Informed Consent Procedures

All eligible patients will provide written informed consent using procedures reviewed and approved by the Mayo Clinic IRB and respective institutional IRBs/REBs at other U.S.A. and international sites. Informed consent will be undertaken by study personnel in person with the patient. The patient has the option of declining participation. No study procedures will be conducted until the signed documents have been provided. Any modifications to the protocol that warrants revision to the informed consent document will be reviewed and approved by each site's respective IRB/REB. The revised consent form will be shared with previously enrolled subjects and a new signature obtained as directed by each site's respective IRB/REB.

17.9 Confidentiality

Subjects enrolled in the study will be identified with a study number. Within each participating site, subjects will also be identified by their site-specific registration number and their name but these subject identifiers will not be released outside of the participating site. Genotype data will be collected specifically for the research protocol. Clinical and demographic data will also be collected from the subject's medical records for the purposes of the research protocol but all data will be de-identified before being released outside of that participating site. Any publications will exclude any kind of subject identifiers that could be correlated with the specific subject.

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APPENDICES

A. Ticagrelor and Clopidogrel Dose Justification and Side-effects

Ticagrelor Dose Justification (normal dosage, oral route)

Acute coronary syndrome - Thrombosis; Prophylaxis
For patients with ACS, unstable angina, NSTEMI, or STEMI, the recommended ticagrelor loading dose is 180 mg orally once plus aspirin (usually 325 mg), followed by a maintenance dose of ticagrelor 90 mg twice daily with aspirin 75 to 100 mg once daily. Maintenance doses of aspirin greater than 100 mg daily are not recommended[28].

Percutaneous coronary intervention - Thrombosis; Prophylaxis

a. For patients with ACS, unstable angina, NSTEMI, or STEMI undergoing PCI, the recommended maintenance dose of ticagrelor is 90 mg twice daily with aspirin 75 to 100 mg once daily. Maintenance doses of aspirin greater than 100 mg daily is not recommended[28].
b. Subjects who have received a loading dose of clopidogrel may be started on ticagrelor maintenance dosing[28]. Ticagrelor should be discontinued at least 5 days prior to surgery, when possible[28]. Ticagrelor is contraindicated in patients with severe hepatic impairment.

Clopidogrel Hydrogen Sulfate Dose Justification (normal adult dosage, oral route)

Clopidogrel should be discontinued 5 days prior to elective surgery, if an antiplatelet effect is not desired[21].

1. Acute ST segment elevation myocardial infarction - Percutaneous coronary intervention - Thrombosis; Prophylaxis
    a. Initial loading dose, 300 mg or 600 mg ORALLY plus aspirin once prior to or at the time of PCI[34]
    b. Maintenance, 75 mg ORALLY plus aspirin once daily[34]
    c. Bare metal stents: duration of therapy for at least 12 months[34]
    d. Drug-eluting stents: duration of therapy for at least 12 months; continuation of therapy beyond 15 months may be considered[34]
2. Acute ST segment elevation myocardial infarction - Thrombosis; Prophylaxis
    a. Optional loading dose of 300 mg ORALLY, followed by 75 mg ORALLY once daily in combination with aspirin 75 to 325 mg, with or without thrombolytics[28]
3. Cerebrovascular accident, Recent - Thrombosis; Prophylaxis
    a. 75 mg ORALLY once daily[28]
4. Myocardial infarction, Recent - Thrombosis; Prophylaxis
    a. 75 mg ORALLY once daily[28]
5. Non-ST segment elevation myocardial infarction, acute - Percutaneous coronary intervention - Thrombosis; Prophylaxis
    a. Initial loading dose, 300 mg to 600 mg with aspirin 75 to 325 mg as soon as possible; maintenance, 75 mg ORALLY plus aspirin 75 to 325 mg once

daily[35,36]
   b. Alternate loading dose, 600 mg ORALLY, followed by 150 mg maintenance dose daily for 6 days, then 75 mg daily in low bleeding risk patients[36,37]
   c. Bare metal stents: duration of therapy for at least 1 month and ideally up to 12 months[36]
   d. Drug-eluting stents: duration of therapy for at least 12 months[1]
6. Non-ST segment elevation myocardial infarction, acute - Thrombosis; Prophylaxis
   a. Loading dose, 300 mg ORALLY once; maintenance, 75 mg ORALLY once daily with aspirin 75 mg to 325 mg ORALLY once daily[35,36]
7. Percutaneous coronary intervention - Thrombosis; Prophylaxis - Unstable angina
   a. Initial loading dose, 300 mg to 600 mg with aspirin 75 to 325 mg as soon as possible; maintenance, 75 mg ORALLY plus aspirin 75 to 325 mg once daily[26,35]
   b. Alternate loading dose, 600 mg ORALLY, followed by 150 mg maintenance dose daily for 6 days, then 75 mg daily in patients with low bleeding risk[35,36]
   c. Bare metal stents: duration of therapy for at least 1 month and ideally up to 12 months[36]
   d. Drug-eluting stents: duration of therapy for at least 12 months[36]
8. Peripheral arterial occlusive disease - Thrombosis; Prophylaxis
   a. 75 mg ORALLY once daily[35]

Dosage in Hepatic Insufficiency

1. Dosage adjustments for clopidogrel are not necessary in patients with hepatic impairment[35].
2. No dosage adjustment is necessary for mild to moderate cirrhosis (Child-Pugh class A or B) based on a 10-day multiple-dose study in subjects with cirrhosis and matched controls. The mean peak concentration, time to peak concentration, and area under the concentration-time curve (AUC) for clopidogrel's major metabolite (SR 26334) did not differ statistically between groups. The geometric mean for AUC in patients with cirrhosis failed to reach the predetermined threshold of clinical significance (1.5 times above the geometric mean in controls). The mean percentage inhibition of platelet aggregation and mean bleeding time prolongation factor were statistically similar between cirrhotics and controls[38].

Dosage in Geriatric Patients

1. No dosage adjustments are necessary[35,39].
2. Clopidogrel 75 milligrams/day for 10 days was associated with statistically similar reductions of 55% to 57% in adenosine diphosphate (ADP)-induced platelet aggregation among healthy young, healthy elderly, and elderly patients with intermittent claudication. All three groups also experienced statistically equivalent prolongation of bleeding time (by a factor of 1.47 to 1.59). For clopidogrel's metabolite, SR 26334, the average peak concentration and the extent of absorption were significantly higher in the two elderly groups compared with the young volunteers, which did not translate into an age-related pharmacodynamic difference[39].
3. Loading Dose: In the FAST-MI Registry analysis of patients 75 years of age and older with acute myocardial infarction (n=791; mean age 81 +/- 4 years old), a clopidogrel loading dose (greater than or equal to 300 mg) was not associated with an increased risk of major bleeding or transfusion but did not significantly decrease 12 month mortality when compared with standard clopidogrel therapy (less than 300

mg). There were 466 patients who received a clopidogrel loading dose of at least 300 mg (300 mg in 384 patients, 375 mg in 5 patients, 450 mg in 16 patients, 600 mg in 60 patients, ad 900 mg in 1 patient) and 325 patients who received standard

clopidogrel therapy (75 mg in 287 patients, 150 mg in 27 patients, and 225 in 11 patients). One year survival (80.7% compared with 73.5%; p=0.02) and one year event free survival (77.3% compared with 68.6%; p=0.009) were higher in patients treated with a clopidogrel loading dose [(40)]

18.1.1 Ticagrelor Side Effects

- Cardiovascular effects may include atrial fibrillation (4.2%), bradyarrhythmia (Holter-detected), chest pain (3.1%), hypertension (3.8%), hypotension (3.2%), loss of consciousness, and syncope.
- Endocrine/Metabolic effects may include gynecomastia (0.23%).
- Gastrointestinal effects may include diarrhea (3.7%), and nausea (4.3%).
- Hematologic effects may include bleeding, major (4.5%), and bleeding major and minor (8.7%).
- Musculoskeletal effects may include backache (3.6%), and chest pain, non-cardiac (3.7%).
- Neurologic effects may include dizziness (4.5%) and headache (6.5%).
- Renal effects may include increased uric acid level and raised serum creatinine level (7.4%).
- Respiratory effects may include cough (4.9%) and dyspnea (13.8%).
- Other side effects may include fatigue (3.2%).

18.1.2 Clopidogrel Side Effects (<2% unless otherwise stated)

- Cardiovascular effects may include coronary artery stent thrombosis, hypotension, and vasculitis.
- Dermatologic effects may include acute generalized exanthematous pustulosis, bullous dermatosis, contusion, erythema multiforme, erythematous rash, fixed drug eruption, lichen planus, pruritus, Stevens-Johnson syndrome, and urticaria.
- Gastrointestinal effects may include colitis, gastrointestinal hemorrhage (2%-2.7% with aspirin), and pancreatitis.
- Hematologic effects may include agranulocytosis, aplastic anemia, major bleeding (0.8% to 3.7%), non-major bleeding (3.6% to 5.1%), granulocytopenic disorder, hemolytic uremic syndrome, leukemia, leucopenia, neutropenia, pancytopenia (severe), postoperative hemorrhage, thrombocytopenia, and thrombotic thrombocytopenic purpura.
- Hepatic effects may include hepatitis, hepatotoxicity, liver failure, and liver function tests abnormal (up to 3% of patients).
- Immunologic effects may include anaphylactoid reaction, immune hypersensitivity reaction, and serum sickness due to drug.
- Musculoskeletal effects may include arthralgia, acute arthritis, myalgia, and tendinitis.
- Neurologic effects may include disorder of taste, epidural hematoma, intracranial hemorrhage, and loss of taste.
- Ophthalmic effects may include intraocular hemorrhage (0.05%).
- Psychiatric effects may include confusion.
- Renal effects may include abnormal renal function, hematuria, kidney disease, and serum creatinine raised.
- Respiratory effects may include bronchospasm, interstitial pneumonia, non-cardiogenic pulmonary edema, and respiratory tract hemorrhage.

- Other effects may include angioedema, drug withdrawal, rebound effect, and postoperative infection.

B. Clinical Trial Management Systems (CTMS)

CTMS is the Mayo Clinic Research Committee-endorsed institutional resource for clinical data management. CTMS is a robust institutional effort initiated in 2009 to address emerging changes within the data and statistical coordinating centers affiliated with National Cancer Institute (NCI)-funded cooperative groups. In 2009, NCI selected Medidata Rave (http://www.mdsol.com/) as the required data collection tool for all cooperative studies. To capitalize on Mayo Clinic and the NCI's investment in Medidata Rave, Mayo Clinic formalized a three-tier data management infrastructure with the Medidata Rave product as the premier system.

Medidata Rave is a product for multi-center clinical trials conducted under 21 CFR Part 11 requirements. This web-based system provides ease of use coupled with an integrated randomization module (Medidata Balance), custom reporting, robust data validation routines, and straightforward integration with SAS.

Electronic Data Capture

Medidata Rave allows for data collection in multisite studies. During the course of the data entry into Medidata Rave, the system provides real-time within-CRF and inter-CRF data consistency verification. Medidata Rave is flexible in nature so that all data can be entered even if "required" fields and or other consistency checks requirements are not satisfied. The system uses an internal "flagging" or "query" system to distinguish the valid from the invalid data thereby ensuring compliance with the FDA guidance document "Computerized Systems Used in Clinical Trials." All data discrepancy issues are tracked and audited by the system to ensure the highest quality data is available for analysis and study reporting.

Contained within the CTMS initiative at Mayo Clinic is a diverse set of administrative and technical personnel to support the development and implementation of clinical trials in Medidata Rave. While the time necessary to program Medidata Rave's eCRFs has been directly budgeted, the CTMS initiative supports protocol independent activities such as software/server maintenance, data standards, institutional system integrations, SAS data, and training of study personnel through institutional resources.

The dedicated virtual private network (VPN) connection between Mayo Clinic and Medidata Rave provides the conduit for data connectivity. Clinical trial data hosted in Medidata Rave is accessible when needed for SAS using the SAS OnDemand Connection, in combination with Mayo Clinic's SAS Pipeline program, which creates a common and direct combination of the metadata (labels, formats, etc.) and data (raw values) into SAS datasets on a scheduled (nightly) basis. This process removes the need to separately label and format the entire clinical trial database separately in SAS.

Medidata Balance

Randomization encounters challenges in complex multisite clinical studies in which random assignment to study drug must be completed prior to the baseline visit and a subject can fail to attend the baseline visit or be deemed ineligible for the study based on the final inclusion/exclusion criteria assessed at the baseline visit. It is possible that some individuals will not receive active treatment after treatment assignment has been established. Medidata Balance uses a novel multidimensional dynamic allocation algorithm minimizing imbalances

across multiple dimensions including overall study, sites, factors, and cross-factor strata. It is also highly flexible with extensive weighting and can be applied to most randomization scenarios including unbalanced designs. The algorithm in Medidata Balance represents a novel multidimensional dynamic allocation algorithm for treatment assignments.

C. Statistical Calculations

Likelihood Method for Real Time Estimation of Treatment Effect and Event Rates: At any point in time during the TAILOR-PCI trial, there are two sources of data on the treatment effect: 1) data from subjects with 1 complete year of follow-up and TaqMan processing completed ("complete" data), and 2) the data on those with less than 1 year of follow-up or without TaqMan processing, half of whom have been genotyped using SPARTAN ("incomplete"). The *complete* subjects have complete endpoint and genotype data, while the *incomplete* subjects have incomplete endpoint and incomplete genotype data. Nevertheless, both sets of data have information on the treatment effect, and this information can be quantified. The analysis of the subjects who have undergone TaqMan is straightforward; a good approximation is a binomial comparison between the two LOF groups, in terms of their one year event rate. To recover the information in the prospectively randomized subjects who have not had TaqMan analysis complete, we propose the following simplified yet highly accurate approach.

There are 3 groups: 1) prospectively genotyped, loss of function carriers (PG-LOF) who are given ticagrelor, 2) prospectively genotyped, wild type subjects (PG-WT) who are given clopidogrel and 3) conventional therapy (CT) who are given clopidogrel. Let us simplify the primary endpoint to a binary outcome X (yes or no) with a probability that depends on: genotype(G), treatment(Rx), and follow-up time. Specifically, we assume that, for a subject with genotype G, treatment Rx, and observed for *t* years, the probability of an event is:

$$\mathbf{Pr}\{\boldsymbol{X = 1 | G, Rx, t}\} = \boldsymbol{\lambda}_{\boldsymbol{G,Rx}} * \frac{\mathbf{[1 - S(t)]}}{\mathbf{[1 - S(1)]}}$$

$$= \boldsymbol{w(t) * \lambda_{G,Rx}}$$

where S(.) is the overall underlying survival curve for freedom from events, *t* is time in years. Note that if the subject experiences the primary endpoint, the value of *t* is not tied to the event time itself, but rather reflects the visit date (roughly 1 month, 6 months, or one year) representing the effective amount of follow-up for that patient (time from randomization to last follow-up date). To calculate S(.), we simply use the Kaplan-Meier curve for the entire study population. This fraction therefore represents the fraction of a "risk year" to which that subject was exposed, i.e. it is an estimate of the proportion of events occurring within a year that have occurred at the follow-up time for the specific individual. Note that we consider *w(t)* to be a fixed quantity, rather than a parameter, though technically it is estimated from the entire data set.

We further assume that the event rates (1-year probabilities) are:

$$\boldsymbol{\lambda_{WT,CL} = \lambda_1}$$

$$\boldsymbol{\lambda_{LOF,TIC} = \lambda_2}$$

$$\boldsymbol{\lambda_{LOF,CL} = \lambda_3}$$

We also assume that the rate of wild type subjects exposed to clopidogrel (λ_1) is the same whether they are in the conventional therapy or the prospective genotyping group. This is a fundamental assumption, but one which will also be ultimately tested.

The treatment effect of interest can be expressed as $\boldsymbol{\lambda_2/\lambda_3}$, that is, the relative risk associated with ticagrelor in LOF subjects. The trial's primary hypothesis is that this number is substantially less than 1.0. (Relative risk reduction is 1 minus this quantity). Finally, let α be the population prevalence of the LOF genotype in the population being randomized. We can now define the likelihood contributions of members of each of the three groups of "incomplete" subjects.

For those in the PG-WT and PG-LOF groups, the likelihood contributions, respectively, are:

$$\boldsymbol{L(\lambda_1|X,t) = [\lambda_1 * w(t)]^X * [1 - \lambda_1 * w(t)]^{(1-X)}}$$

$$\boldsymbol{L(\lambda_2|X,t) = [\lambda_2 * w(t)]^X * [1 - \lambda_2 * w(t)]^{(1-X)}}$$

For those in the CT group, the likelihood contribution is a weighted average of the likelihood contributions that would be obtained under (WT, CLOP) and (LOF, CLOP) conditions, weighted by the probability of each genotype, namely:

$$\boldsymbol{L(\lambda_1, \lambda_3, \alpha|X,t) = (1-\alpha) * L_1(X,t) + \alpha * L_3(X,t)}$$

where L_1 and L_3 have the obvious definitions parallel to the 'known-genotype' likelihoods spelled out above. If this were the only data available, then the 4 parameters (λ_1, λ_2, λ_3, α) would not be identifiable, i.e. α and λ_3 would be completely confounded. However, we have one further piece of data: the numbers of LOF and WT subjects in the PG group. These numbers can be put into a binomial likelihood with α as the only parameter. The random variable corresponding to this proportion is statistically independent (at least uncorrelated), with all the other likelihood pieces. Therefore, the overall likelihood is the product of all the conditional likelihood pieces for the members of the 3 groups, along with this binomial likelihood for the prevalence of LOF. This serves to identify both α and therefore λ_3 as parameters. Thus in this complete likelihood, all 4 parameters are identified. Thus, the *incomplete* data provides a likelihood that *is* informative about the treatment effect (subject to the null hypothesis assumption regarding the effect of knowledge of genotype on the WT/CLOP response). The likelihood from these data can be combined with the simple TaqMan binomial data to derive a combined likelihood which incorporates both pieces of information.

Estimation of Information Time: We can also estimate the proportion of total study information contained in the current data. First, we estimate the expected information at the end of the trial as the

inverse of the expected square of the standard error of the hazard ratio of interest. Our expected power of 85.8% implies that our expected z-score at the end of the trial is 3.031. Given a minimum detectable effect size of 0.50, the expected standard error at study end is 0.2287 (log(0.5)/3.031). Thus the expected final information is 19.1. Second, the available information in the current data is calculated using a profile likelihood approach to estimate the standard error of the current estimate of the treatment effect. The ratio of the current information to the expected final information is the estimated information time.

Calculation of conditional power: Conditional power is a function of the current effect estimate z-score and information time. Its formula is:

$$CP(t, Z_t) = 1 - \Phi[\left(\frac{\boldsymbol{\Phi^{-1}(0.975)} - Z_t * \sqrt{t}}{\sqrt{(1-t)}}\right) - (\boldsymbol{\Phi^{-1}(0.975) + \Phi^{-1}(P_0)}) * \sqrt{(1-t)}]$$

where t is information time, Z_t is the current z-score, Φ is the cumulative Gaussian distribution function, Φ^{-1} is its inverse and P_0 is the unconditional study power under initial study assumptions. Z_t will be calculated from the log of the estimated effect and its estimated standard error.

D. Site Monitoring

AHRC (U.S.A. and Canadian sites) and DCIS (Korean sites) will conduct periodic on-site monitoring visits during the course of the study. At a minimum, AHRC and DCIS will ensure that the monitor reviews eligibility, safety, and outcome data for the first 3-5 subjects. Additional monitoring visits will be scheduled in accordance with the Trial Monitoring Plan. Over the entire study, it is anticipated that 10% of all randomized subjects will be monitored.

The purposes of monitoring visits are to:

- Ensure the rights and safety of participants;
- Confirm that the study is conducted in accordance with Good Clinical Practice (GCP) guidelines;
- Ensure maintenance of required documents;
- Verify adherence to the protocol;
- Monitor the quality of data collected;
- Ensure accurate reporting and documentation of study endpoints and unanticipated, serious, and related problems; and
- Ensure that IRB/REB submissions/approvals are up-to-date.

During monitoring visits, the data recorded on CRFs are reviewed and verified against source documents to ensure:

- Informed consent has been obtained and documented in accordance with IRB/REB/FDA regulations;
- The information recorded on the forms is complete and accurate;
- There are no omissions in the reports of specific data elements;
- Missing examinations are indicated on the forms; and
- Participant disposition when exiting the study is accurately recorded.

E. Steering Committee membership

Dr. Chet Rihal *Chair*	**Dr. Ahmed Hasan**	**Dr. Derek So**
Dr. Dawn Abbott	**Dr. David Holmes**	**Dr. Liewei Wang**
Dr. Jang-Ho Bae	**Dr. Myung Ho Jeong**	**Dr. Richard Weinshilboum**
Dr. Linnea Baudhuin	**Dr. Amir Lerman**	
Dr. Michael Farkouh	**Dr. Verghese Mathew**	
Dr. Bernard Gersh	**Dr. Naveen Pereira**	
Dr. Shaun Goodman	**Dr. Yves Rosenberg**	
Dr. Paul Gordon	**Dr. Jorge Saucedo**	

F. Publications Committee

The Executive Committee will serve as an ad hoc Publications Committee and will take ultimate responsibility for final data analysis and submission of the TAILOR-PCI trial for publication and presentation. It will also review all requests for publication and sub-studies and adjudicate any controversies regarding publications. It will make decisions by a majority vote but will strive for consensus if at all possible in its work to prioritize publication requests. It is the intent of the Steering Committee to include all site PI's as authors for the first publication. Order of authorship (outside of the PI and Steering Committee Chair) will be based upon enrollment success, adherence, data completion and other trial effort at the individual sites. The processes and tasks of the Publications Committee for establishing authorship has been described in detail by Whellan et al.[25]

G. Data and Safety Monitoring Board

A data and safety monitoring board (DSMB) will be assembled twice per year to ensure data quality and participant safety and to provide independent advice to the Steering Committee regarding progress and the appropriateness of study continuation. Minutes will be taken during each meeting and shared with each site. The Mayo statistician will generate statistical reports for the DSMB. If the assumptions upon which the power and sample size calculations were based appear not to hold in the enrolled patients (e.g. the primary endpoint rate is lower than expected), the DSMB may advise the Steering Committee to modify the protocol to allow a larger sample size. At least one additional member will be added to the DSMB to review the digital follow-up sub-study with relevant technology experience.

H. Monitoring

On-site monitoring activities will be performed at all sites by AHRC at the U.S.A. and non-Korean international sites and DCIS at the Korean sites. The monitor will review the Regulatory Binder, the first 3-5 subjects, and then some percentage thereafter at each site in accordance with standard operating procedures set forth in the Trial Monitoring Plan. Information regarding the types of visits is outlined in the Operations Manual.