Cover Page

Study Title: *Chewed versus integral pill of ticagrelor in in selected patients undergoing coronary angiography --a platelet reactivity study and patient outcomes study.*

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Project title: Chewed versus integral pill of ticagrelor in in selected patients undergoing coronary angiography --a platelet reactivity study and patient outcomes study.

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BACKGROUND

Patients with acute coronary syndrome (ACS) and stable coronary artery disease usually require percutaneous coronary intervention (PCI) with stent deployment to open stenosed or occluded coronary arteries. Ticagrelor (Brilinta) is an orally administered third generation thienopyridine and reversible P2Y12 receptor antagonist and has been shown to improve patient outcomes as compared to other antiplatelet medications. In the PLATO trial published in 2009, for example, patients with ACS treated with ticagrelor experienced a significantly lower rate of death, repeat myocardial infarction, and stroke.

Despite advancements in medical therapy, studies have demonstrated delayed antiplatelet effects of oral P2Y12 inhibitors and higher than expected platelet reactivity hours after drug administration. Due to elevated risk of peri-procedural thrombotic events in patients undergoing PCI, the goal of achieving platelet inhibition more rapidly should be addressed.

The delayed antiplatelet effects of medications like ticagrelor are likely related to impaired drug absorption. Many patients presenting with acute coronary syndromes have decreased gastrointestinal motility. Additionally, if morphine is administered by medical providers for chest pain absorption of antiplatelet medications such as ticagrelor may be delayed. Research performed to date has demonstrated more rapid absorption and platelet inhibition when ticagrelor is administered in crushed or chewed form to patients with ST segment elevation MI (STEMI)

In December 2017, a trial compared a chewed sublingual form of ticagrelor to standard pill form in patients with STEMI. It also showed more rapid absorption and platelet inhibition within hours of drug administration. To our knowledge, our study will be the first to compare platelet reactivity in non ST segment elevation acute coronary syndrome (NSTE-ACS) and patients with stable CAD undergoing PCI who received chewed ticagrelor.

Specific Aims:

To compare the effect of ticagrelor chewed pills with the effect of equal dose of integral pills in decreasing platelet reactivity and adverse event rates in all patients being treated for NSTE-ACS and stable coronary artery disease, undergoing percutaneous coronary intervention.

Primary objective:

Determine platelet inhibition at baseline, and early at 1 hour and 4 hours after loading dose.

Secondary objective:

Assess major adverse cardiac and cerebrovascular event (MACCE) rate at 30 days and 1 year.

1. Death;
2. Repeat myocardial infarction;
3. Need for urgent revascularization;
4. Cerebrovascular accident;
5. Rate of stent thrombosis and in-stent stenosis at 30 days and 1 year;
6. Bleeding: Defined as major, minor, or minimal bleeding based on TIMI criteria.

Hypothesis:

Chewed ticagrelor pill is superior to integral pill in decreasing platelet reactivity.

Primary Outcome Measures:

Residual platelet reactivity by Platelet Reactivity Units (PRU) VerifyNow 1 hour and 4 hours after ticagrelor loading dose (LD) and percent of patients with a high residual platelet reactivity (PRU > 208) 1 hour and 4 hours after ticagrelor LD.

Secondary Outcome Measures:

1. Bleeding events: Major, minor, minimal bleeding (TIMI criteria) events.
2. Occurrence of dyspnea and/or symptomatic bradycardia.
3. Major adverse cardiac and cerebrovascular event (MACCE) rate: Death, Myocardial infarction, Stent Thrombosis, Urgent revascularization, Cerebrovascular accident at 30 days and 1 year.

STUDY DESIGN

This will be an interventional study to evaluate the superiority of chewed ticagrelor in comparison to integral pill form. Superiority will be defined as a reduction of platelet reactivity in both groups undergoing PCI.

Study population will include 132 patients. They will be stratified into 2 groups: Patients with NSTE-ACS and patients with stable coronary artery disease (CAD) undergoing coronary angiography for non-urgent reasons.

Inclusion criteria:

1. Patients presenting with NSTEMI-ACS or stable CAD undergoing coronary angiography for urgent or non-urgent reasons.

Exclusion criteria:

1. Age <18 years or Age >90 years;
2. Known coagulopathy, bleeding diathesis, or active bleeding;
3. Known chronic therapy with clopidogrel, prasugrel, or ticagrelor;
4. Known history of intracranial bleed or intracranial neoplasm;
5. Suspected aortic dissection;
6. Severe hemodynamic instability, cardiogenic shock;
7. Life expectancy <1 year;
8. Known severe liver or renal disease (CrCl < 30, or dialysis dependent);
9. Taking drugs known to interfere with CYP3A4 metabolism (Azoles, Clarithromycin, Ritonavir, Saquinavir, Nelfinavir, Indinavir, Atazanavir);
10. Any use of GP llb-llla inhibitors 48-hours before the procedure or any use during the procedure;
11. Any use of Cangrelor during or after the procedure;
12. Hemoglobin <10 g/dL, PLT <80x10"9/L;
13. Pregnant or lactating females;

14. Known allergy to study medication;
15. Fibrinolytic use within past 48 hours;
16. Inability to give consent;
17. Known sick sinus syndrome (SSS) or high degree AV block without pacemaker protection.

Written informed consent:

Patients presenting for both urgent and elective left heart catheterization will be consented by the personnel delegated by the investigator before any study-related activity.

Randomization:

Patients will be randomized prior to PCI. Patients from each strata (NSTE—ACS, and patients with stable CAD) will be randomized in a 1:1 fashion to receive a loading dose of 180mg ticagrelor in integral pill form (swallowed) or chewed form.

Study procedures:

Patients admitted to the inpatient cardiology service with NSTE-ACS meeting eligibility criteria are often treated medically before reaching the catheterization suite for coronary angiography and possible percutaneous coronary intervention. These patients often receive the loading dose of 180mg ticagrelor on the medical floor. In order to enroll these patients, the baseline PRU level blood draw, can be obtained on the floor before that loading dose is administered. The subsequent 1-hour and 4-hour blood draws can be obtained on the medical floor or in catheterization suite.

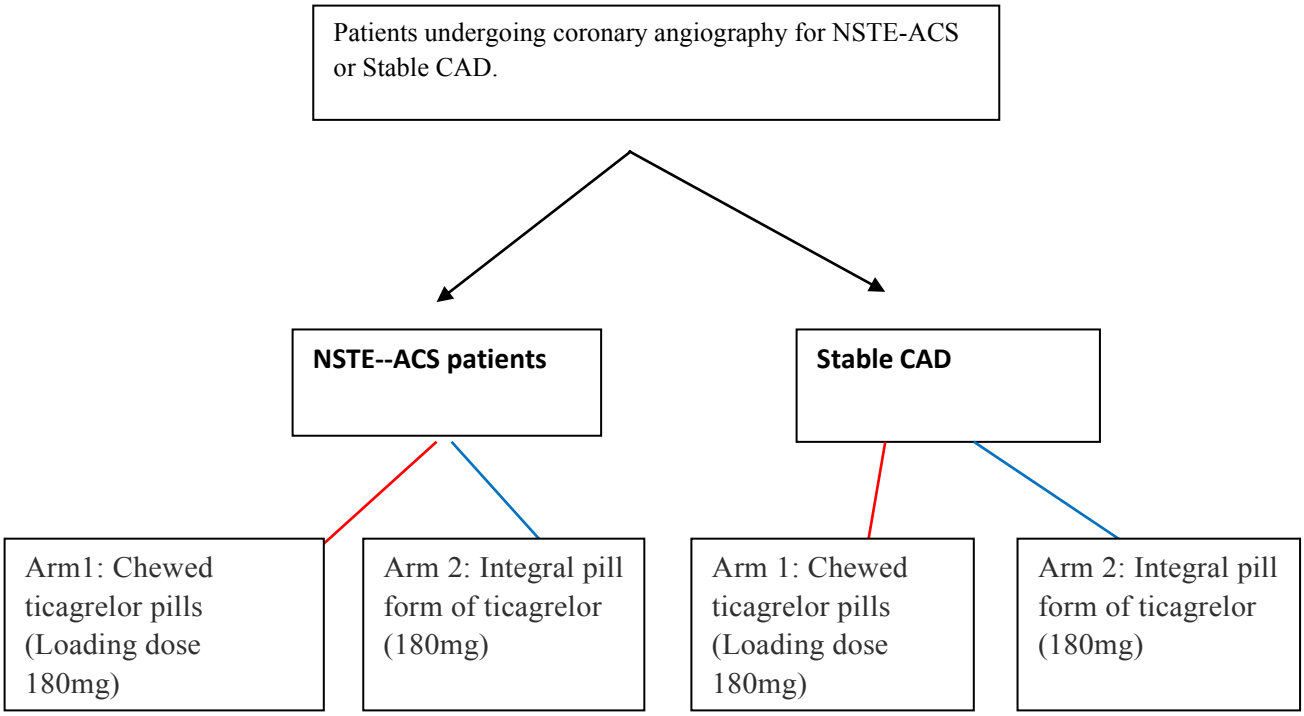
Patients scheduled to undergo and elective (non-urgent) coronary angiography for stable CAD who meet eligibility criteria will have blood drawn for a baseline PRU level prior to administration of the study drug. After the procedure, two subsequent blood draws will be taken at precise times: 1 hour +/-60 minutes, and 4 hours +/- 90 minutes after loading dose administration. All other procedures are considered standard of care.

Arm	**Intervention/Treatment**
Arm One: Chewed ticagrelor pills (Loading dose 180mg)	Drug: Ticagrelor chewed pills. The loading dose will be administered as soon as possible by hospital floor nurse or Catheterization Lab staff after a baseline PRU level is drawn.Patients will be asked to

	chew and swallow followed by 25-50mL of water.
Arm Two: Integral pill form of ticagrelor (Loading dose 180mg)	Drug: Ticagrelor integral pills. The loading dose will be administered as soon as possible by hospital floor nurse or Catheterization Lab staff after a baseline PRU level is drawn. ~~and before the end of the PCI.~~ Patients will swallow the loading dose followed by 25-50mL of water.

Subject will have orders to continuing ticagrelor during admission status. After the 4th hour blood draw the primary outcome will be complete. Patients will be encouraged to remain on ticagrelor with an outpatient prescription to measure secondary outcomes.

Flow Chart



Patient's EMR will be reviewed at 30 days and at 1 year to document any primary or secondary outcome measures. Duration of the study is one year.

Data collection

Baseline Characteristics	**Procedure Related information**	**Post-procedure Related Information**
Gender Body mass index, kg/m2 Current smoker Hypertension Diabetes mellitus Dyslipidemia Prior coronary artery disease Prior aspirin Prior beta-blockers Prior statins LVEF (%) Creatinine clearance, mL/min Hemoglobin (gr/dl) Platelet count, 1,000/mm3 Low-density lipoprotein (mg/dl) High-density lipoprotein (mg/dl)	Consenting Randomization Baseline PRU test Loading dose administration Access (femoral, Radial) Start catheterization Culprit vessel Type of stent Number of stents Fluoro time/dose Contrast volume Narcotic use	PRU 1 hour PRU 4 hours Length of stay Date of death Repeat MI Stent thrombosis 30 days CVA Urgent Revascularization TIMI Minimal bleeding TIMI Minor bleeding TIMI Major bleeding Access site complication (hematoma, pseudoaneurysm, need for surgical or percutaneous repair)

Data will be collected by the personnel delegated by the PI. Preliminary data will be analyzed after enrollment of 65 patients.

Timeline /Schedule of events

	Visit 1 Baseline	**Visit 2** Procedure	**Visit 3** Post Procedure	**Visit 4** Discharge	**Visit 5** 30 day follow up- (+/- 14 d) EMR-Chart review	**Visit 6** 1 yr follow up- (+/- 14 d) EMR-Chart review
Inclusion/ Exclusion	X					
Informed Consent Obtained	X					
Demographics, Medical History, Con Meds	X					
Angiography /PCI Procedure		X				
Blood draw for PRU	X baseline, 1-hour and 4-hour levels can be collected before coronary angiography for patients admitted to hospital floor	X	1 h after PCI 4h after PCI			

	before procedure					
MAACE Event documentation				X	X	X

Statistical Analysis

Patient characteristics will be presented as proportions for categorical variables and mean ± standard deviation (SD) and or Median [lower quartile (01) - upper quartile (03)] for continuous variables. Comparison of categorical variables for patients who will receive integral pill form of ticagrelor and the other the chewed form will be performed using the chi-square and Fisher's exact test while the two sample t test will be done to assess differences in continuous patient characteristics. Visual displays of event free Survival and cumulative incidence curves will be generated by the Kaplan-Meier approach and event free survival among groups compared using the log rank test. In addition to time point analysis, an alternating logistic regression (ALR) will be fitted to evaluate P2Y12 reaction units (PRU) levels at baseline (before LD), 1 hour, and 4 hours. Further analysis will entail fitting both univariate and multivariate Cox proportional-hazards models to examine the association between baseline characteristics and each of outcomes: In-stent thrombosis and restenosis, MACCE, and the need for repeat revascularization within 1-year separately. All analyses will be done using SAS Version 9.4 (SAS Institute, Cary, NC) and tests performed at a 5% level of significance.

Monitoring Plan

The goal of monitoring in this study is primarily to make sure that the primary data are collected and recorded properly and consenting process was done.

The Principal Investigator will be responsible for monitoring the safety environment of the participants, and will ensure that

a) Only subjects who meet the study eligibility criteria will be enrolled. All subject inclusion/exclusion criteria were reviewed and verified with source documents, when applicable.

b) The informed consent process will be obtained prior to proceeding with any study procedures. Any problems with informed consent will also be documented, and reported to the IRB, if required.

c) Data is collected and analyzed as specified in the protocol.

d) Adverse events are reviewed promptly and reported as required.

e) Privacy and confidentiality of subjects is maintained. Consent forms will be stored in a room accessible only to research personnel.

f) Subject withdrawals will be documented for the reason of withdrawal.

g) Subjects will be informed during the informed consent process that study results may be disseminated in the form of presentations at conferences and publications in journals. The data/results that will be presented will only include anonymous/aggregate data,nothing that will identify subjects.

h) A regulatory binder will be kept to document: IRB approvals, protocol versions, informed consents (all versions), all formal communications with the IRB (approval letters,

acknowledgements), Delegation of Authority Log.

This study will be listed on ClinicalTrials.gov prior to enrollment of subjects.
https://clinicaltrials.gov/ct2/manage-recs/fdaaa

Human Protections

This prospective randomized trial may require patients to undergo additional lab draws at intervals described above if samples cannot be taken from peripheral intravenous (IV) lines already in place. Risks associated with lab draws include, but are not limited to, bleeding, infection, and patient discomfort. Highly trained technicians will be drawing blood, if required, to mitigate the risks described above. Breaching patient confidentiality will be minimized by storing subject information in password-protected devices and by limiting access to data to those named on the IRB form. Additionally, data will be reported in aggregate form only.

Dissemination and Future Funding Plan

Results of the study will be submitted to multiple peer-reviewed journals for review. No study of this kind known at the time of submission has compared to platelet reactivity and patient outcomes in NSTE-ACS and patients with stable CAD undergoing percutaneous coronary intervention (PCI). Potential targets for publication include, but are not limited to, *the journal of the American College of Cardiology, European Heart Journal, Circulation,* and the *Journal of interventional Cardiology*.

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