Statistical Analysis Plan

Title: Fentanyl and Crushed Ticagrelor (FACT) PCI: A Randomized Control Trial of Patients Undergoing Percutaneous Coronary Intervention with Fentanyl and Crushed or Integral Ticagrelor and Comparison of Platelet Reactivity

Version 2.1

December 10, 2025

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Version History

Version	Date	Author	Changes
1.0	October 15, 2025	Adishwar Rao	Initial version
2.0	October 31, 2025	Adishwar Rao	Updated to reflect early stopping decision.
2.1	December 10, 2025	Jeremy Albright	Clarified language in data analysis section, updated software.

Introduction

a. Background and Rationale

Ticagrelor is an orally administered P2Y12 receptor antagonist in patients undergoing percutaneous coronary intervention (PCI)[1]. Ticagrelor inhibits platelet activation and aggregation. Fentanyl is routinely administered as conscious sedation during the PCI procedures. Recent studies have shown that Opioid analgesics delay P2Y12 receptor antagonist mediated platelet aggregation[2]. Delay in platelet aggregation could lead to increased adverse events including stent thrombosis, myocardial infarction and death. In a recent trial, the impact of Fentanyl on Ticagrelor mediated platelet aggregation was evaluated[3]. There was delayed platelet aggregation with increased adverse clinical events in patients receiving Fentanyl and Ticagrelor. This was thought to be related to decreased absorption of Ticagrelor leading to delayed platelet aggregation. However, a recent study showed that crushed Ticagrelor has more bioavailability and reaches peak earlier than oral Ticagrelor[4,5]. Based on these results, it could be hypothesized that crushed Ticagrelor might mitigate some of the ill effects of Fentanyl. Hence, we propose this trial to assess the impact of Fentanyl on platelet aggregation in patients receiving crushed Ticagrelor during PCI.

b. Study Objectives

The primary objective is to test the influence of Fentanyl on pharmacodynamics of crushed vs non-crushed (integral) ticagrelor in patients who are undergoing PCI.

Study Design

a. Study Overview

Research location

The study is conducted at The Guthrie Clinic, Robert Packer Hospital, Sayre, PA, 18840.

Design and Hypotheses

The study is a single center, randomized clinical trial designed to assess the influence of Fentanyl on pharmacodynamics of crushed vs non- crushed ticagrelor in patients undergoing PCI at Robert Packer Hospital.

Hypothesis: In patients undergoing PCI who receive fentanyl for conscious sedation, *crushed* ticagrelor produces faster and greater inhibition of platelet function over the first 6 hours after a loading dose than *non-crushed* ticagrelor, as measured by a smaller $AUC_{0–6}$ of the platelet-function test.

- **H_0 (null):** There is no difference in the $AUC_{0–6}$ of platelet function between fentanyl-sedated PCI patients receiving crushed ticagrelor and those receiving non-crushed ticagrelor.

- **H_1 (alternative):** The $AUC_{0–6}$ of platelet function is lower (indicating greater platelet inhibition) in fentanyl-sedated PCI patients receiving crushed ticagrelor compared with non-crushed ticagrelor.

Summary of Endpoints:

- The primary endpoint is the area under the Platelet Function Testing (PFT)-time curve ($AUC_{0–6}$) for the first 6 hours after the loading dose of Ticagrelor.
- The secondary end points at discharge and 30 days:
    - Stent thrombosis
    - Recurrent myocardial infarction
    - All-cause mortality
    - Stroke
    - TIMI minor and major

b. Study Groups

Recruitment and Consent

Recruitment: Participants will be recruited from Robert Packer Hospital patients who are undergoing elective or non-elective PCI. Participants will be screened for eligibility and those who meet the inclusion/exclusion criteria will be invited to take part.

Consent: Written consent will be required for all study participants prior to participation and will be obtained by the principal investigator (PI) or a sub-investigator. After fulfilling the inclusion and exclusion criteria, consent will be obtained.

Randomization and Allocation Concealment

Randomization: Subjects are randomized by simple randomization which remained concealed from the researchers until the end of enrollment. Randomization was done by a random number

generated computer program using Research Randomizer (Version 4.0) by someone not involved in the research. The randomization schedule was placed in sealed envelopes to be concealed from the researcher until time of consent.

> Urbaniak, G. C., & Plous, S. (2013). Research Randomizer (Version 4.0) [Computer program]. http://www.randomizer.org/

Blinding

The study is not blinded.

Inclusion criteria

- Patients ≥ 18 years of age
- Undergoing clinically indicated elective or non-elective PCI
- Able to swallow oral medications

Exclusion criteria:

- Contraindications to ticagrelor or fentanyl (or other opiates)
- Pregnancy
- Any use of $P2Y_{12}$ inhibitors within 14 days
- Known coagulation disorders
- Pre-procedural treatment with an anticoagulant (oral anticoagulant or low molecular weight heparin)
- Platelet count < 100,000/mm^3
- Impaired renal function (Estimated glomerular filtration < 45 ml/min/1.73 m^2)
- Impaired hepatic function (Based on medical history)
- Prior or planned transcatheter aortic valve replacement

c. Intervention

Treatment protocol

- All patients will be medicated with at least Fentanyl 25 mcg intravenously prior to start of the procedure. Additional sedation will be at the discretion of the treating physician.
- In the crushed Ticagrelor arm, subjects will receive 180 mg of crushed Ticagrelor, which will be crushed using EZY CRUSH pill crusher and mixed with 30 cc of drinking water, whereas patients in the other arm will receive an integral tablet of Ticagrelor loading dose (180 mg).
- Platelet function testing (PFT) in each patient will be performed (platelet vasodilator-stimulated phosphoprotein assay, multiple electrode aggregometry, Verify Now assay).
- The PFT will be performed at randomization, 30 mins, 2, 4, and 6-hour intervals from the time of Ticagrelor administration. Blood (2cc filled completely) will be collected in blue top tubes (coag sodium citrate 3.29). The platelets must not be disturbed by jarring after collection. The blood must not be shaken after collection, and it must be hand carried to the lab. At each sampling time point, a second blue top tube will be collected for sampling

assurance. The first sample at each time point will be processed. If a testing error occurs, the second sample will be processed for data purposes.

- Patients will be treated according to current American Heart Association / American College of Cardiology guidelines.
- The choice of the access of the procedure (radial or femoral) and the type of implanted stent will be at the discretion of the operator.
- All patients will receive maintenance doses of ticagrelor (90 mg) twice daily post PCI.

d. Sample Size

This is an exploratory study; therefore, no formal sample size calculation was conducted. The planned sample size is based on feasibility considerations and is considered sufficient to generate preliminary estimates and assess study procedures.

The study plans to enroll 80 participants, 40 participants who had elective PCI and 40 participants who had non-elective (emergent) PCI.

Update to Sample Size 10/31/2025: The study was terminated prematurely on January 27, 2025 due to a poor accrual rate. Challenges were encountered in recruitment in the post-COVID-19 era in the rural community hospital along with increased use of Cangrelor in subjects with ACS. The increased utilization of other therapeutic agents, such as generic prasugrel further reduced the recruitment and relevance of this study.

There were a total of 45 participants randomized at the time the study closed to accrual. Of the 45, seven participants withdrew, leaving a total of 38 participants for analysis. Due to the small sample size, the data from elective (scheduled) and non-elective (emergent) PCI will be combined for analysis to compare crushed versus non-crushed Ticagrelor.

Outcomes

a. Primary Outcomes

The primary outcome is the area under the PFT-time curve ($AUC_{0–6}$) for the first 6 hours after the loading dose of Ticagrelor.

Platelet Function Testing will be collected at 5 time-points after Ticagrelor administration.

- Baseline (time 0) – immediately prior to ticagrelor loading dose
- 0.5 hours after dose
- 2 hours after dose
- 4 hours after dose
- 6 hours after dose

The actual clock time for each draw will be collected.

The Platelet Function Testing assay will be *VerifyNow Platelet Reactivity Assay* which is used institutionally. Results are reported in platelet reactive units (PRUs). Based on previous studies,

208 will be used as an estimated cutoff to distinguish therapeutic and subtherapeutic platelet inhibition, with PRUs equal to or less than 208 being considered therapeutic [6].

b. Secondary Outcomes

The secondary outcomes are:

- Stent thrombosis at discharge
- Stent thrombosis at 30 days
- Recurrent myocardial infarction at discharge
- Recurrent myocardial infarction at 30 days
- All-cause mortality at discharge
- All-cause mortality at 30 days
- Stroke at discharge
- Stroke at 30 days
- TIMI bleeding (minor and major, per TIMI criteria) at discharge
- TIMI bleeding (minor and major, per TIMI criteria) at 30 days

Time-window rules (apply to all endpoints):

"At discharge" = events occurring during the index hospitalization from time of ticagrelor loading dose until the formal hospital discharge time (documented in chart).

"At 30 days" = events occurring from time of ticagrelor loading dose up to 30 days (day 30 inclusive). Events that already occurred during index hospitalization are counted in the "at discharge" endpoint and also contribute to cumulative 30-day counts. The exact event date/time must be recorded.

Events will be identified through review of the electronic medical record, discharge summaries, procedure reports, and 30-day follow-up documentation or contact.

For each outcome, the presence or absence of the event will be recorded for each participant at both time points.

c. Other Prespecified Outcomes

Other prespecified outcomes include:

- Hospital Length of Stay (Hours)
- Hospital Readmission within 30 days

Statistical Analysis

a. General Considerations

Due to the premature termination and small sample size, the data from elective (scheduled) and non-elective (emergent) PCI will be combined for analysis to compare crushed versus non-

crushed Ticagrelor. The analysis of the primary outcome will be per protocol, as it is a sum across five timepoints and any patient with incomplete data would necessarily have a lower score. The remaining tests will be performed on the intention-to-treat sample.

We will report absolute counts and their respective percentages for categorical variables, means and standard deviations for non-skewed numeric variables, or medians and interquartile ranges for numeric variables exhibiting notable skew (assessed graphically). Differences between treatments will be assessed using the Fisher exact test for categorical variables, t-tests for numeric variables exhibiting normality, and Mann-Whitney tests for skewed numeric variables.

The statistical significance of the results will be determined using at a two-sided p-value of less than 0.05. Missing data will be handled with listwise deletion on a test-by-test basis.

b. Baseline Data

Descriptive statistics of the study population will include:

- Demographics (age, gender, race)
- Prior or current imaging studies (to evaluate underlying propensity to ischemic pathophysiology)
- Presence of MI on admission (based on clinical presentation, electrocardiogram (EKG) changes, and/or elevated troponins)
- Cardiovascular risk factors and comorbidities
    - Smoking
    - Type 2 diabetes mellitus
    - Hypertension
    - Hyperlipidemia
    - Prior Coronary Artery Disease
    - Renal Insufficiency
    - Gastroesophageal Reflux Disease
    - Obstructive Sleep Apnea, and
    - Body Mass Index (BMI).

      Standard definitions were used to classify patients as having or not having these comorbidities.

c. Primary Outcomes

PFT will be used to quantify the antiplatelet effect of a ticagrelor loading dose over the first 6 hours after administration. The primary outcome is the area under the platelet-function vs. time curve from 0 to 6 hours after the loading dose (AUC_{0-6}). AUC_{0-6} captures both the magnitude and the time course of platelet inhibition produced by ticagrelor.

AUC_{0-6} will be calculated using the linear trapezoidal rule with measured platelet function values at the actual elapsed times. If actual draw times deviate slightly from planned times, we use the actual elapsed hours.

The trapezoidal rule formula between two consecutive timepoints (t_i, t_{i+1}) with values y_i and y_{i+1} is:

$$Area_i = ((y_i + y_{i+1}) / 2) \times (t_{i+1} - t_i)$$

Total AUC = Σ $Area_i$ across intervals from 0 to 6 hours.

d. Secondary Outcomes

For each categorical secondary outcome, the count and percentage of patients experiencing the event in each group will be calculated at both discharge and 30 days. Between-group comparisons of event rates will be performed using Fisher's exact test (if expected cell counts <5). Length of stay will be summarized with medians and IQRs, and the p-value from a Mann-Whitney test will be reported.

e. Software

Data will be analyzed with R version 4.4.1, R Core Team, Vienna, Austria

References:

1. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Nat Rev Cardiol. 2015;12:30-47.

2. Rollini F, Franchi F. The Conundrum of Platelet P2Y12 Inhibition in ST-Segment Elevation Myocardial Infarction. Circ J. 2016;80:2429-2431.

3. McEvoy et al. Effect of Intravenous Fentanyl on Ticagrelor Absorption and Platelet Inhibition Among Patients Undergoing Percutaneous Coronary Intervention: The PACIFY Randomized Clinical Trial. Circulation. 2017;CIRCULATIONAHA.117.031678

4. Zafar M.U., Farkouh M.E., Fuster V., et al. (2009) Crushed clopidogrel administered via nasogastric tube has faster and greater absorption than oral whole tablets. J Interv Cardiol 22:385–389.

5. Teng R., Carlson G., Hsia J. (2014) Crushing ticagrelor tablets accelerates exposure compared with intact tablets (abstr). J Am Coll Cardiol 63(Suppl 12):A229.

6. Ibrahim K, Goli R, Shah R, Resar J, Schulman S, McEvoy J (2018) Effect of intravenous fentanyl on ticagrelor absorption and platelet inhibition among patients undergoing percutaneous coronary intervention: Design, rationale, and sample characteristics of the PACIFY randomized trial. Contemporary Clinical Trials 64: 8-12.