A Randomized Controlled Trial of patients undergoing Percutaneous Coronary Intervention who receive Ticagrelor and Fentanyl

FACTPCI (Fentanyl and Crushed Ticagrelor PCI) trial

Protocol dated October 28, 2019

Principal Investigator: Sudhakar Sattur MD

Sub-Investigators:
Safi Khan MD, Abdel Rahman Omer MD, Daniel Sporn MD and Edo Kaluski MD.

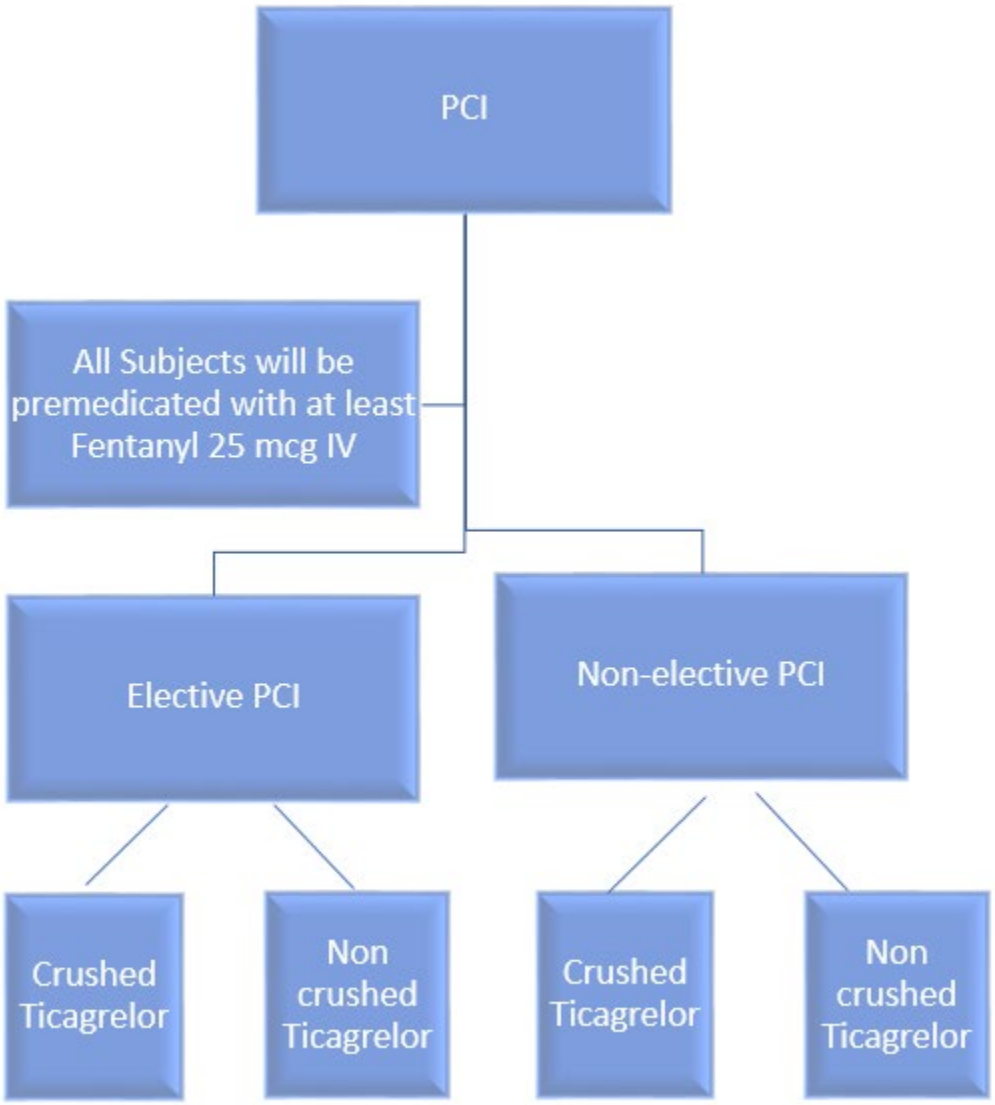
The Guthrie Clinic
One Guthrie Square
Sayre, PA 18840

Background:
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, 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 felt 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.

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

Methods & design:

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. The plan is to enroll 80 patients in this study. Forty patients each in the elective and non-elective PCI groups. Further In each group, patients will be randomized in a 1:1 ratio to either crushed or non-crushed Ticagrelor arms.



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 us 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

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.

Risks:

It is expected that the risk of taking Ticagrelor crushed is the same as taking Ticagrelor not-crushed. The crushed tablet may enter the blood stream faster. There may be risks that are not known. The risks of Ticagrelor are provided in the package insert

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022433s020lbl.pdf

Benefits:

The potential benefit to patients is that crushed Ticagrelor may have more bioavailability and reach peak earlier than non-crushed Ticagrelor. Crushed Ticagrelor may be useful to use following conscious sedation with Fentanyl, and may counter the delay in P2Y12 receptor antagonist mediated platelet aggregation that is associated with Fentanyl. Improved inhibition of platelet aggregation may lead to reduced adverse events including stent thrombosis, myocardial infarction and death.

For patients who are randomized to receive the non-crushed Ticagrelor, there is no anticipated benefit as this would be what is routinely done.

Study endpoints:

- The primary endpoint is the area under the 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 are as follows -
    - Stent thrombosis
    - Recurrent myocardial infarction
    - All-cause mortality
    - Stroke
    - TIMI minor and major

Data Collection:
Information regarding patient characteristics will be obtained from the electronic medical record. Data will include: medical record number; age; sex; race; BMI; and medical history; date of PCI; radial or femoral access of the procedure; type of implanted stent; crushed or non-crushed ticagrelor; platelet function testing at baseline, 30 min, 2, 4,and 6, hours. Data will be collected at discharge and 30 days to include events of: stent thrombosis, recurrent myocardial infarction, all-cause mortality, stroke, or TIMI.

Statistics

- All continuous data will be expressed as mean ± standard deviation and compared

using a two-tailed Student's t-test when appropriate or the Mann–Whitney U test.
- Categorical variables will be expressed as a percentage and compared using chi-square or Fisher's exact test when appropriate.

Discussion:

This study is expected to provide crucial data on the influence of Fentanyl on crushed vs non-crushed Ticagrelor associated platelet function in patients undergoing PCI. The findings of this study would have a major impact on clinical practice as Fentanyl is currently used as sedation in more than 95% of patients undergoing PCI.

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.