STUDY PROTOCOL

Chewing versus Traditional Oral Administration of Ticagrelor in ST-elevation Myocardial Infarction - A Platelet Reactivity Study

PRINCIPAL INVESTIGATOR:

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Background
The P2Y12-receptor amplifies platelet activation in response to ADP (1). Dual anti-platelet therapy (DAPT) with a P2Y12-receptor antagonist and aspirin is the standard of care for the treatment of ischemic patients (2-5). The co-administration of a P2Y12-receptor inhibitor and aspirin reduces platelet reactivity to a greater extent than each drug can achieve separately (6-7). Clopidogrel is a second-generation thienopyridine. It is orally administered, and requires two metabolic transformations to effect platelets (8). The third-generation thienopyridine prasugrel is also a prodrug, but requires only a single-step oxidation in the liver by CYP to become active (9). The metabolic conversion of prasugrel is more efficient, and results in higher in vivo availability (10). Ticagrelor is also administrated orally but in contrast to clopidogrel and prasugrel is not a prodrug and hence does not require activation (9). Ticagrelor directly inhibits the platelet P2Y12-receptor through allosteric modulation (9).

In the PLATO trial, ticagrelor therapy was also superior to clopidogrel treatment in patients with recurrent cardiovascular events, STEMI, diabetes mellitus, chronic kidney disease, with or without loss-of-function polymorphisms in CYP2C19, aged >75 years, with a body mass <60 kg, and with a history of stroke or transient ischemic attack (11-14). In order to further achieve platelets inhibition a recent trial has evaluate the superiority of ticagrelor 180 mg LD crushed pills versus integral tables of equal dose in decreasing residual platelet reactivity 1 hour after the administration in ST elevation myocardial infarction patients (15). However, no trial has evaluated the efficacy of ticagrelor administrated sub lingual in ACS patients.

Objective
To examine chewing versus traditional oral administration of ticagrelor in ST-elevation Myocardial Infarction (STEMI) patients on platelet reactivity.

Design
The proposed study is a randomized-controlled, conducted among STEMI patients treated with ticagrelor. All patients will be treated with ticagrelor
loading dose (180 mg/day) and aspirin (100mg/day) according to the contemporary guidelines for treating STEMI. Eligible patients will be recruited during hospitalization due to STEMI.

Inclusion Criteria:
1. Patients presenting with STEMI
2. Informed, written consent

Exclusion Criteria:
1. Age < 18 years or Age > 90 years
2. Active bleeding; bleeding diathesis; coagulopathy
3. Increased risk of bradycardic events
4. History of gastrointestinal or genitourinary bleeding <2 months
5. Major surgery in the last 6 weeks
6. History of intracranial bleeding or structural abnormalities
7. Suspected aortic dissection
8. Any other condition that may put the patient at risk or influence study results or investigator's opinion (severe hemodynamic instability, unconsciousness, known malignancies or other comorbid conditions with life expectancy <1 year)
9. Administration in the week before the index event of clopidogrel, ticlopidine, prasugrel, ticagrelor, thrombolytics, bivalirudin, low-molecular weight heparin or fondaparinux.
10. Concomitant oral or IV therapy with strong CYP3A inhibitors or strong CYP3A inducers, CYP3A with narrow therapeutic windows
11. Known relevant hematological deviations: Hb <10 g/dl, PLT<100x10^9/l
12. Use of coumadin derivatives within the last 7 days
13. Chronic therapy with ticagrelor, prasugrel, clopidogrel or ticlopidine
14. Known severe liver disease, severe renal failure
15. Known allergy to the study medications
16. Pregnancy
17. Human immunodeficiency virus treatment
18. The use of IIbIIIA receptor antagonists in the 48 hours before enrollment (if abciximab use then in the last 14 days).
19. If the patients cannot sign percutaneous coronary intervention (PCI) informed consent for any reason.

Baseline characteristics and in-hospital therapy will be recorded, including, comorbidities, medications, clinical presentation, ECG data, blood test results including troponin and CPK levels, hemoglobin and renal function test, angiographic characteristics and therapy and in-hospital events such as arrhythmias, heart failure, recurrent ischemia and bleeding.

Randomization will be performed on admission. Patients will be randomized to receive loading dose of either 180mg chewing ticagrelor or 180mg orally ticagrelor. Platelet reactivity will be assessed during hospitalization [during enrollment at 30 min, 1 hour (or before administration of IIBIIIA inhibitors during percutaneous coronary intervention-PCI), 4-6 hours following initiation of ticagrelor therapy (or after 48 hours if IIBIIIA inhibitors were administrated during percutaneous coronary intervention)]. Patients will then receive oral ticagrelor (90mg bid) without any interruption for the entire study period.

Patients will be followed up by telephone/clinic at 30 days
* Or before administration of IIBIIIA inhibitors during percutaneous coronary intervention.

** Or after 48 hours if IIBIIIA inhibitors were administrated during percutaneous coronary intervention.

**Platelet function tests will include:**

Platelet reactivity with the VerifyNow® PRUTest™ Accumetrics

**End-points**

**Primary Outcome Measures:**

Residual platelet reactivity by Platelet Reactivity Units (PRU) VerifyNow 1 hour after ticagrelor loading dose (LD).
Secondary Outcome Measures:
1. The percent of patients with a high residual platelet reactivity (PRU > 208) 30 min, 1 hour and 4-6 hours after ticagrelor LD.
2. Bleeding events: Major, minor, minimal bleeding (TIMI criteria) events.
3. Occurrence of dyspnea and/or symptomatic bradycardia.
4. Major adverse cardiac and cerebrovascular event (MACCE) rate at 30 days (Death, Myocardial infarction, Urgent revascularization, Cerebrovascular accident).
5. Stent Thrombosis rate at 30-day.

Estimated Enrollment: 100 patients.

Statistical Analysis
The primary and secondary endpoints of the study will be assessed by treatment allocation on an intention-to-treat basis.
The required sample size is based on the primary end point of the study, with the use of a meaningful difference between sublingual and oral loading dose groups of one standard deviation from mean baseline values. Using a 1:1 randomization design, a total of 100 patients will be required to obtain at least 80% power and a 5% one-sided type I error, assuming ≤15% withdrawal rate following enrollment.
Student’s t-test will be used to test for a difference in prespecified endpoints between the 2 randomized groups in an intention-to-treat basis.
In the analysis, if the assumption of normality is violated, a nonparametric test (Mann–Whitney test or Wilcoxon signed-rank test) will be performed.
The effect of treatment allocation on the clinical secondary end points will be assessed using Cox proportional hazards regression analysis.
References


