Ticagrelor versus Clopidogrel and Eptifibatide Bolus in Patients with Stable or Unstable Angina Undergoing Coronary Intervention: A Randomized Pharmacodynamic Study

Study Protocol & Statistical Analysis Plan

NCT02925923

December 17, 2019

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In the Ad Hoc percutaneous coronary intervention (PCI) study (Presented at the SCAI meeting, 2015), 100 patients with troponin-negative acute coronary syndrome were randomized to receive ticagrelor (180mg loading dose [LD] and 90mg after 12hr) or clopidogrel (600mg LD and 75 mg after 12 h) with aspirin 75–100mg daily. P2Y12 reactivity unit [PRU] using VerifyNow^{TM} assay was measured pre-LD, and at 0.5, 2 and 8 h post LD. At 2 h, PRU was lower with ticagrelor vs. clopidogrel (98.4 ± 95.4 vs. 257.5 ± 74.5, respectively; $p<0.001$). PRU diverged as early as 0.5 h post ticagrelor LD and there was a significant reduction in the PRU level with ticagrelor. The rate of high on-treatment PRU level was significantly reduced with ticagrelor compared with clopidogrel at 2 h (13.3% vs. 78.3%, respectively ;$p<0.001$). However, ticagrelor still did not cover the first 30 min of the procedure.

The Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAR-REACT) study reported that pretreatment with 600 mg clopidogrel provides outcomes similar to those achieved with a strategy of pretreatment with the addition of abciximab [1] However, an important consideration in the decision for pretreatment is the associated risk of bleeding in those patients requiring coronary bypass surgery. The Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS study) [2] showed that the administration of eptifibatide with either a 300 mg or 600 mg of clopidogrel provides the most sustained platelet inhibition and was associated with the lowest incidence of myonecrosis compared with those who received clopidogrel alone. The incremental increase in myonecrosis observed in patients with higher levels of post-treatment platelet reactivity lend strong support to the concept that activated platelets during PCI play a central role in the mediation of post-stent myonecrosis. However, the findings of ISAR-REACT trial is not relevant when physicians decide not to pretreat patients whose coronary anatomy is unknown before the stenting.

Since stenting and the use of thienopyridines have become routine, there has been a decrease in the incidence of acute closure, but because of concern with respect to bleeding complications after PCI, adopting a bolus injection or brief infusion of glycoprotein inhibitors (GPI) has reduced such complications. In this respect, Kini et al [3] demonstrated that among patients undergoing PCI, GPI bolus only reduced vascular/bleeding complications with similar MACE and reduced cost when compared with GPI bolus plus continuous infusion. In addition, GPI bolus only improved ambulatory PCI and reduced length of stay. Marmur et al. [4] compared long-term mortality after bolus only administration of abciximab, eptifibatide, and tirofiban during PCI and demonstrated that eptifibatide, when given as bolus-only during PCI, improved the long-term survival compared to abciximab. Furthermore, Fung et al. [5] demonstrated that in patients undergoing non-emergent PCI, the post-procedural infusion of eptifibatide can be abbreviated to <2 h and that was not inferior to 18-h infusion in preventing ischemic events. Furthermore, they concluded that the abbreviated infusion of eptifibatide reduced both cost and post-procedural major bleeding.

We recently randomized 70 patients with Non-ST-Segment Myocardial Infarction (NSTEMI) to ticagrelor 190 mg loading and eptifibatide bolus-only (TEP) vs. ticagrelor loading and eptifibatide bolus plus 2 h infusion (TEPI) administrated before stenting [Fig. 1]. Light transmission aggregometry was performed and percent inhibition of platelet aggregation (%IPA) was calculated at baseline, and at 2 , 6 , and 24 h using ADP,TRAP, collagen, and arachidonic acid (AA). Cardiac enzymes, hemoglobin and hematocrit were measured at baseline and at 24 h. The event rates were determined at 30-day follow-up. We demonstrated that in patients randomized to TEP vs. TEPI, there were no significant difference in the %IPA values at 2 h and 6 h with ADP 5 μM (100% ± 0.01 vs. 99% ± 0.25 and 99% ± 2.4 vs. 99% ± 1.2, respectively) and with ADP 20 μM as well as with collagen. However, %IPA was lower at 24 h (still >60% platelet inhibition) compared with that at 2 h and 6 h. Percent IPA with TRAP 10 or 20 μM was higher at 6 h in patients randomized to

TEPI vs. TEP (87% ± 13 vs. 74% ± 17; P<0.01, respectively), but this had no bearing on outcomes since ADP was highly inhibited by ticagrelor at 6 h. There were no significant differences in troponin or hemoglobin levels among the groups. During follow- up, and there was no stent thrombosis or myocardial infarction.

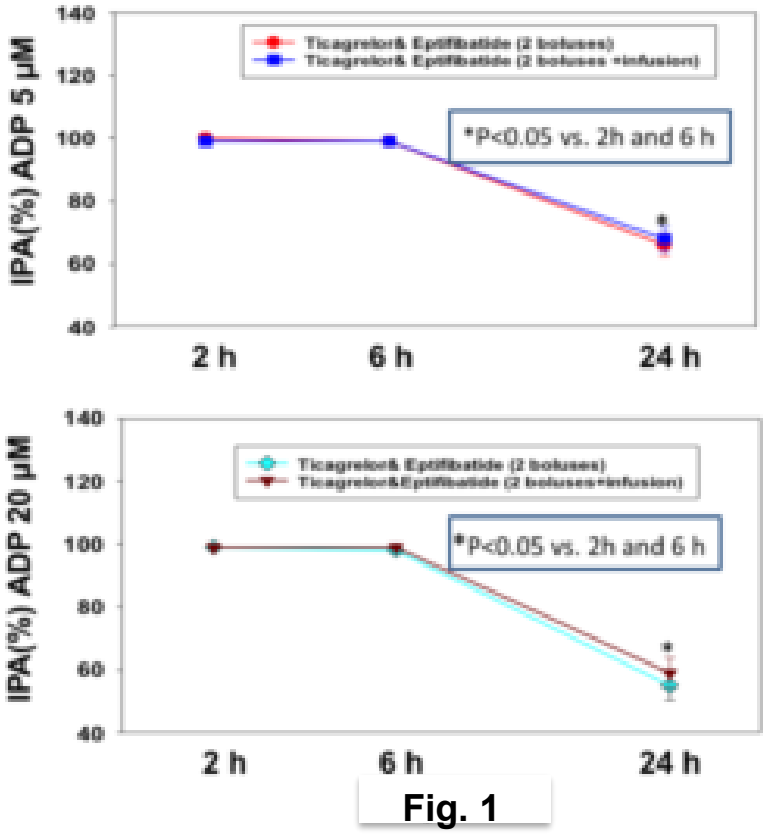


Fig. 1

We concluded that %IPA values with ADP and collagen were not significantly different comparing ticagrelor with eptifibatide bolus only vs. ticagrelor and eptifibatide bolus plus 2 h infusion. Eptifibatide bolus only highly inhibited platelets aggregation while allowing bridging to the antiplatelet effect of ticagrelor and circumventing the need for continuous eptifibatide infusion. There was no significant difference in bleeding or MI between the 2 groups.

RATIONALE

The antiplatelet effect of clopidogrel is slow in onset, variable, and irreversible; approximately 15 to 30% of patients are non-responsive [6]. Furthermore, a 75-mg/d clopidogrel maintenance dose requires at least 5 days, and a 600-mg loading dose of clopidogrel requires up to 8 hours to achieve a 50% steady state of inhibition of ADP-induced platelet aggregation [7-9]. The difference in the clinical effects of ticagrelor compared with clopidogrel lies in the fact that ticagrelor exerts more rapid, more potent, and more consistent inhibition of platelets [10,11]. In the CLEAR

PLATELETS study [2], administration of eptifibatide with either a 300 mg or 600 mg of clopidogrel provided the most sustained platelet inhibition and was associated with the lowest incidence of myonecrosis compared with 600 mg loading dose of clopidogrel administered in the cath lab . The Platelet Inhibition and Patient Outcomes (PLATO) trial [12] demonstrated that dual antiplatelet therapy with aspirin and ticagrelor was superior to aspirin and clopidogrel in reducing thrombotic complications in patients with acute coronary syndrome undergoing PCI. Glycoprotein IIb/IIIa inhibitors (GPI) bolus and infusion was used with ticagrelor in 40% of patients in the PLATO trial. However, GPI use was not randomized and the benefit of which cannot be substantiated. On the other hand, the CLEAR PLATELET study showed clopidogrel and eptifibatide bolus and infusion was associated with reduced myonecrosis. In addition, they showed that platelet inhibition was significantly higher with 600 mg vs. 300 mg of clopidogrel. In the Ad Hoc PCI study, ticagrelor or clopidogrel was administered before PCI in patients with unstable angina and there was a significant reduction in the PRU level with ticagrelor as compared with clopidogrel. We demonstrated that %IPA with ticagrelor and eptifibatide bolus was not significantly different than ticagrelor and eptifibatide bolus and short infusion.

The inhibition of platelets is significantly faster and stronger with Ticagrelor than clopidogrel. We hypothesized that inhibition of platelet aggregation with ticagrelor alone will be non-inferior to that of clopidogrel and eptifibatide bolus. The present study will be the first to investigate the pharmacodynamic effects of ticagrelor vs. clopidogrel plus eptifibatide bolus in patients undergoing elective PCI in patients with troponin negative unstable angina or stable angina. If ticagrelor alone is indeed non-inferior to clopidogrel and eptifibatide bolus, this will pave the way for a large randomized study to demonstrate the safety and efficacy of ticagrelor alone as compared with concomitant administration of clopidogrel and eptifibatide.

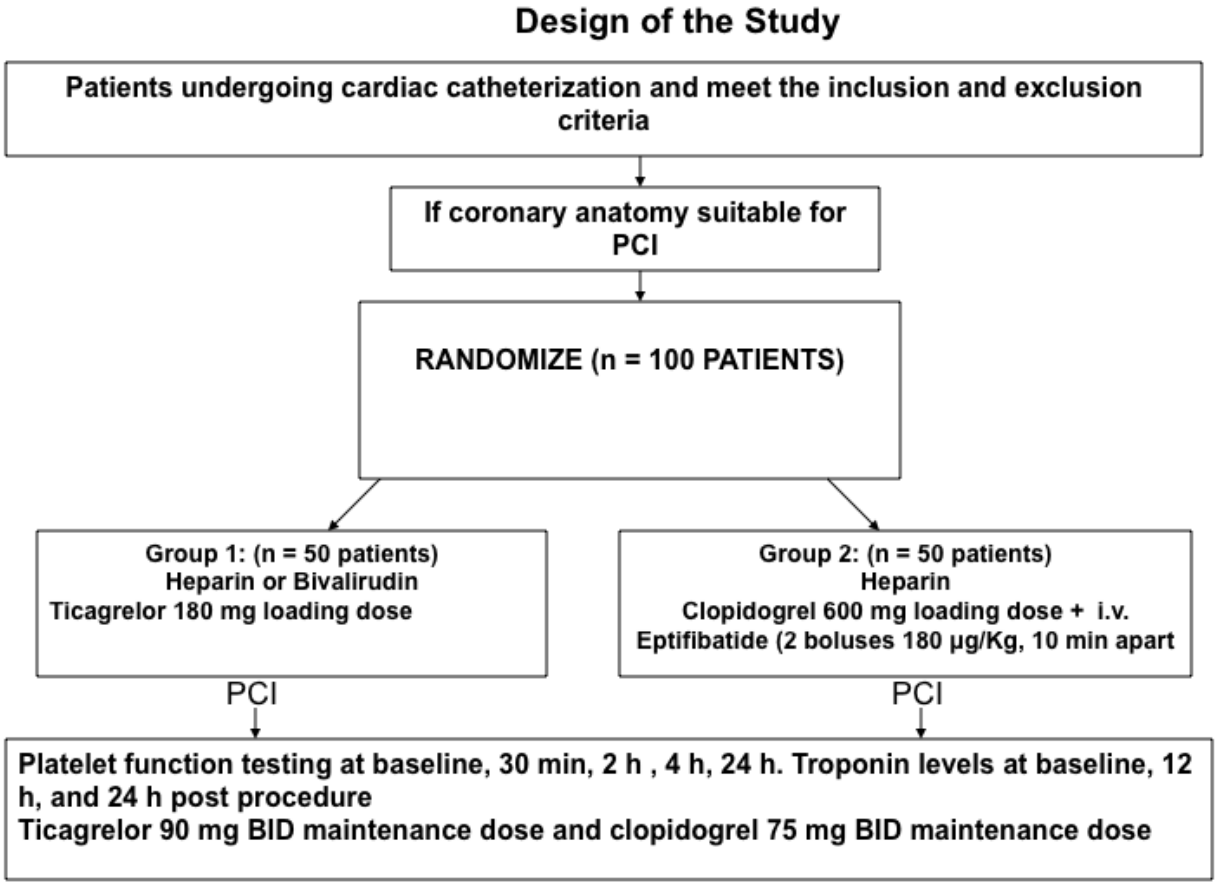
Study Hypothesis: To compare the percent inhibition of platelet aggregation with ticagrelor compared with clopidogrel and eptifibatide bolus in patients with stable angina or in patients with troponin-negative unstable angina.

Inclusion Criteria:
Patients with stable angina with evidence for at least >10% perfusion defect (moderate to large ischemia) or patients with troponin-negative unstable angina.

Exclusion Criteria: A need for oral anticoagulation therapy; an increased risk of bradycardia, and concomitant therapy with a strong cytochrome P-450 inhibitors; surgery<4 weeks; The use of any thienopyridines prior to randomization; upstream use of GP IIb/IIIa inhibitors;
bleeding diathesis or major bleeding episode within 2 weeks; thrombocytopenia; incessant chest pain; hemodynamic instability; NSTEMI as evidenced by elevation of troponin levels; renal failure with a serum creatinine >2.0 mg/dL; and anemia with HCT<30%.

Methods
In this study, 100 patients with stable angina or troponin negative unstable angina, will be randomized to ticagrelor loading dose versus clopidogrel loading dose and eptifibatide bolus only administrated before PCI. Platelet function testing will be performed at baseline, at 30 min post-loading dose, 2 h, and 4 h, and 24 h. All patients will be started on aspirin 81 mg prior to procedure . Heparin 60 units/kg will be administered intravenously before PCI. PCI will be performed in accordance with standard clinical practice. Please see Fig. 2, Design of the study below and Table 1.

Fig. 2



Blood Sampling for Platelet Function Testing

Blood will be collected from an antecubital vein into vacutainer tubes (Becton-Dickinson, Franklin Lakes, NJ) that contain 3.2% trisodium citrate for light-transmittance aggregometry. All measurements will be performed at the UAB thrombosis research laboratory.

Light-Transmittance Aggregometry

Platelet aggregation induced by ADP (5 and 20 μm), TRAP (10 and 20 μm) platelet-rich plasma will be measured with a Chronolog Optical Aggregometer (model 490-4D; Chronolog Corporation, Havertown, Pa). The final extent of aggregation, measured at 6 minutes after agonist addition, and the maximal extent of aggregation will be expressed as the percent change in light transmittance from baseline with platelet-poor plasma as a reference. Inhibition of platelet aggregation (IPA) will be calculated as follows:

$$IPA(\%) = 100\% \times \frac{PAt - PAb}{PAb}$$

Where PA is platelet aggregation, b is predosing, and t is postdosing.

Statistical Analysis

The present study is an exploratory trial to investigate the percent inhibition of platelet activity (%IPA) (measured by light-transmittance aggregometry) comparing the loading dose of ticagrelor

with loading dose of clopidogrel and 2 boluses of eptifibatide measured at all time-points. Since there are no preliminary data available, no power calculation was performed. Statistical analysis will be performed using the Statistical Package for Social Sciences, version 22.0, software package for Windows (SPSS, Inc., Chicago, Illinois). Data will be presented as mean ± 1 SD or frequencies; a value of $P< 0.05$ will be considered statistically significant. %IPA of ticagrelor and 2 boluses of eptifibatide vs. loading dose of clopidogrel and 2 boluses of eptifibatide will be compared at all time-points using repeated measures ANOVA. Continuous variables will be compared between the 2 treatment groups with Student t test. For comparisons of categorical data, the Chi-Square test will be performed.

End-Points

The primary end point of the study is to compare %IPA induced by ADP at 2 h, in patients randomized to the loading dose of ticagrelor with loading dose of clopidogrel and 2 boluses of eptifibatide measured at 2 h post loading dose. Secondary endpoints of the study are to compare %IPA induced by ADP and TRAP in patients randomized to the loading dose of ticagrelor with loading dose of clopidogrel and 2 boluses of eptifibatide at all time-points. Other secondary outcomes include: 1) the occurrence of post-procedural myonecrosis comparing the 2 groups. Ischemic myonecrosis will be defined as elevated post-procedure troponin-1 level >0.26 µg/l; and 2) the rate minor (a fall in hemoglobin of 3 to <5 g/dL) and major bleeding (a fall in the hemoglobin >5 g/dL) between the groups.

Anticipated Findings

Since platelet inhibition with ticagrelor starts rapidly, we expect that %IPA at 2 h will be no significantly different than clopidogrel and eptifibatide bolus. In addition, since eptifibatide half-life is short, we expect that %IPA at 24 h will be higher with ticagrelor than clopidogrel and eptifibatide bolus.

We anticipate the results of the present study will set the stage for a large randomized trial comparing myonecrosis, stent thrombosis, death, myocardial infarction, bleeding, and costs in patients randomized to ticagrelor only vs. loading dose of clopidogrel and 2 boluses of eptifibatide.

Table 1: Schedule of treatment

	Index Hospitalization

Time-range	Baseline	Procedure	Discharge	4 weeks
Time range for completion	Same day prior		During	± 1 week
Point of Interest	Hospital			Physician office
Informed consent	X			
History	X			
Physical exam	X			X
ECG	X		X	X
Hgb/Hct	X		X	X
Troponin	X	Q 8 h	X	
Platelet function testing	X	X		
Adverse Event assessment including chest pain score and number of antianginal medications		X	X	X

REFRENCES

1. Kastrati H, Dirschinger J, Berger PB, Schömig A**.** Abciximab in patients with acute coronary syndromes A, Mehilli J, Neumann F-J, Dotzer F, ten Berg J, Bollwein H, Graf I, Ibrahim M, Pache J, Seyfarth M, Schühlen undergoing percutaneous coronary intervention after clopidogrel pretreatment. The ISAR-REACT 2 randomized trial. JAMA 2006; 295:1531–8

2. Gurbel PA, Bliden KP, Zaman KA, et al. Clopidogrel loading with eptifabitide to arrest the reactivity of platelets: Results of the clopidogrel loading with eptifabitide to arrest the reactivity of platelets (CLEAR PLATELETS) Study. Circulation 2005;111:1153-59

3. Kini AS, Chen VH, Krishnan P, Lee P, Kim MC, Mares A, Suleman J, Moreno PR, Sharma SK. Bolus-only versus bolus + infusion of glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention. 2008 156:513-9.

4. Marmur JD, Poludasu s, Lazar J. Long-term mortality after bolus-only administration of abciximab, eptifibatide, or tirofiban during Percutaneous Coronary Intervention. Cath Cardiovasc Interv 2009; 73:214–221.

5. Fung AY, Saw J, Starovoytov A, Densem C, Jokhi P, Walsh SJ, Fox RS, Humphries KH, Aymong E, Ricci DR, Webb JG, Hamburger JN, Carere RG, Buller CE. Abbreviated infusion of eptifibatide after successful coronary intervention. The BRIEF-PCI (Brief Infusion of Eptifibatide Following Percutaneous Coronary Intervention) randomized trial. J Am Coll Cardiol 2009;53:837–45

6. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003; 107**:** 2908–13.

7. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. Circulation 2007; 2923–32.

8. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; 357: 2001–15

9. Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol* 2007; 50**:** 1852–56.

10. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J* 2006; **27:** 1038–47.

11. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009; 120: 2577–85.

12. Cannon CP, Harrington RA, James S, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 2010; 375**:** 283–93