Platelet Inhibition with CANgrelor and Crushed TICagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention: The CANTIC Study

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Background and Significance:

Dual antiplatelet therapy consisting of aspirin and an ADP $P2Y_{12}$ receptor antagonist is the cornerstone of treatment for the prevention of thrombotic events in patients with acute coronary syndrome (ACS), including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI) [1-3]. The new-generation $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor are associated with more prompt and potent platelet inhibition, and better clinical outcomes than clopidogrel in ACS patients [4]. Therefore, prasugrel and ticagrelor are considered the first choice in this setting [1-4]. However, in STEMI patients undergoing PPCI there is a delayed onset of action of oral $P2Y_{12}$ receptor inhibitors, including prasugrel and ticagrelor, which require more than 2 hours to exert their full antiplatelet effects, and thus exposing these high-risk patients to an increased risk of early thrombotic complications [5-8]. The mechanism of this delayed onset of antiplatelet effect is likely multifactorial due to the presence in the setting of STEMI of specific conditions that translate into delayed drug absorption which in turn affect the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of oral $P2Y_{12}$ receptor inhibitors [5-8]. Crushing prasugrel and ticagrelor improves their PK and PD profiles as it favors drug absorption and onset of antiplatelet effects and because of this, it is commonly used in STEMI patients undergoing PPCI [9,10]. However, despite the use of crushed tablets, up to one-third of patients may still have high on-treatment platelet reactivity (HPR) within the first 2 hours after loading dose (LD) administration of these oral agents [9,10]. These findings support the need for intravenous agents with more rapid platelet inhibiting effects.

Cangrelor is a potent intravenous $P2Y_{12}$ receptor inhibitor with rapid onset and offset of action associated with a greater reduction in ischemic events, including stent thrombosis,

compared with clopidogrel in $P2Y_{12}$ receptor naïve patients undergoing PCI (including stable coronary artery disease, non-STE-ACS and STEMI) [4,11,12]. To date most studies have explored cangrelor in the setting of PCI subjects treated with clopidogrel and the clinical profile of cangrelor among patients treated with prasugrel or ticagrelor is currently unknown. This is noteworthy because ACS patients, in particular STEMI undergoing PPCI, are commonly treated with either prasugrel or ticagrelor. Moreover, cangrelor is also more likely to be used in these higher risk settings. PD investigations conducted *in vitro* or *ex vivo* in stable patients have shown cangrelor to be associated with enhanced platelet inhibition compared with that induced by prasugrel and ticagrelor [13-15]. However, the PD effects of cangrelor in STEMI patients undergoing PPCI treated with a newer generation $P2Y_{12}$ receptor inhibitor and how this compares with a crushed formulation of the oral drug is unexplored. Because of a potential for drug-drug interactions with thienopyridines, drug regulating authorities only recommend that ticagrelor, and not prasugrel, be administered concomitantly with cangrelor [16-18]. Accordingly, ticagrelor is being chosen to test our study hypothesis in this investigation and will be administered as a crushed formulation as this has shown to be associated with fastest onset of effects of an oral formulation agent.

Study Aim

The aim of this prospective randomized study is to investigate the PD effects of cangrelor in STEMI patients undergoing PPCI treated with crushed ticagrelor.

Research plan

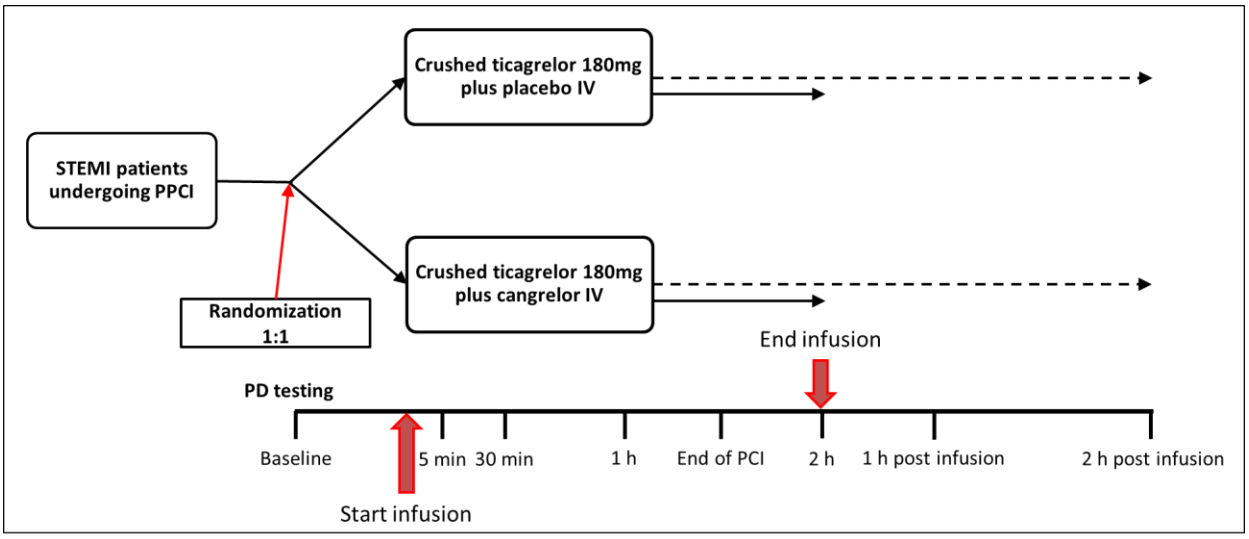
Research Design

The proposed investigation is a prospective, randomized, double-blind, parallel design PD study. This study will be performed at the University of Florida Health Jacksonville - Division of Cardiology. Patients will be recruited and consented at the Emergency Department or Catheterization Laboratory of our Institution. Patients will be screened by cardiology research staff, who will verify that all candidates meet inclusion criteria. After providing written informed consent, STEMI patients undergoing PPCI will be eligible for randomization. After diagnostic angiography and prior to commencement of the PCI procedure, patients will be randomly assigned 1:1 to receive either cangrelor (30 μg/kg bolus followed by 4 μg/kg/min infusion) or matching placebo (normal saline bolus and infusion). The bolus will be administered at the same time of a 180mg crushed ticagrelor LD and infusion will be continued for 2 h. The 180-mg LD of ticagrelor will consist in 2 ticagrelor 90-mg tablets that will be crushed using a commercially available syringe crusher. After, 5 rotations of the crushing mechanism, 25mL water will be aspirated into the syringe and mixed by shaking for 30 seconds. This suspension will be dispensed into a 165mL dosing cup. The syringe crusher will be rinsed using additional 25 mL water, which will be added to the dosing cup for a total of 50mL suspension administered orally to patient. Patients will be administered the ticagrelor LD in the cardiac catheterization laboratory after diagnostic angiography and before starting PPCI (before passing the wire through the target lesion).

All patients will be treated as per local standard of care, which includes 325 mg aspirin LD and 4000 IU of unfractioned heparin at time of presentation. The choice of intravenous anticoagulant during PPCI (heparin or bivalirudin) will be at discretion of the physician

performing PPCI. After PCI, all patients will receive aspirin 81 mg/d indefinitely and ticagrelor 90 mg bid for at least 12 months. The PCI procedure will be performed as per local practice standards, including the route of access (femoral vs. radial), use of aspirations device, and stent type. Patients receiving glycoprotein IIb/IIIa inhibitors before the primary end point time point will be excluded due to their interference with the VerifyNow assay.

PD assessment will be performed at the following 8 time points: baseline (before LD administration), 5 minutes, 30 minutes, 1 hour, and 2 hours after bolus, at the end of PCI (when the guide catheter was removed at procedure completion), and 1 hour and 2 hours after stopping the infusion. A flow diagram of the study is presented below.



Study Population

Inclusion criteria:

- Patients with STEMI undergoing primary PPCI
- Age > 18 years old

Exclusion criteria:

- Inability to provide written informed consent
- Known history of prior intracranial bleeding

- On treatment with a $P2Y_{12}$ receptor antagonist (ticlopidine, clopidogrel, prasugrel, ticagrelor) in the prior 10 days
- Known allergies to aspirin, ticagrelor or cangrelor
- On treatment with oral anticoagulant
- Treatment with glycoprotein IIb/IIIa inhibitors before the primary end point time point
- Fibrinolytics within 24 hours
- Active bleeding
- High risk of bleeding
- Known platelet count $<80x10^6$/mL
- Known hemoglobin <10 g/dL
- Intubated patients (prior to randomization)
- Known creatinine clearance <30 mL/minute or on hemodialysis.
- Known severe hepatic dysfunction
- Patients with sick sinus syndrome (SSS) or high degree AV block without pacemaker protection
- Current treatment with drugs interfering with CYP3A4 metabolism (to avoid interaction with ticagrelor): Ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, and telithromizycin.
- Pregnant or lactating females.

Blood sampling and Laboratory assessments

Blood samples (10 mL) will be drawn through the arterial access sheet used for the PCI procedure for time points (until the end of PCI) while patient are in the cath lab; post-cath lab samples will be drawn through venous sampling. Samples will be collected in anticoagulated and serum tubes at each study time point for all PD assessments. The first 2-4 mL of blood will be discarded to avoid spontaneous platelet activation.

Laboratory assessments will include 2 PD assays:

1. VerifyNow PRU assay
2. VASP-PRI assay

Description of laboratory assays

1) VerifyNow PRU: The VerifyNow System is a turbidimetric based optical detection system which measures platelet induced aggregation as an increase in light transmittance (Accumetrics, San Diego, CA) and will be utilized according to manufacturer's instructions, as previously described [5]. The assay is based on microbead agglutination and uses specific reagents for the pathways of interest. The VerifyNow PRU assay, by combining ADP+PGE1, measures changes in platelet function specific to $P2Y_{12}$ receptor inhibitors. The assay is based upon the ability of activated platelets to bind fibrinogen. Fibrinogen-coated microparticles aggregate in proportion to the number of GP IIb/IIIa receptors expressed. Microbead aggregation is more rapid and reproducible if platelets are activated; therefore the reagents are incorporated into the assay channel to induce platelet activation without fibrin formation. Light transmittance increases as activated platelets bind and aggregate fibrinogen-coated beads. The instrument measures this change in optical signal and reports results in $P2Y_{12}$ Reaction Units (PRU).

2) Whole blood vasodilator-stimulated phosphoprotein (VASP): VASP phosphorylation (VASP-PRI) is a marker of $P2Y_{12}$ receptor reactivity, which is the target for ticagrelor. VASP will be assessed according to standard protocol using labeled monoclonal antibodies by flow cytometry with the Platelet VASP-FCM kit (Biocytex Inc., Marseille, France) as previously described [5]. PGE1 increases VASP-P levels by stimulation of adenylate cyclase. Binding of ADP to $P2Y_{12}$ leads to Gi-coupled inhibition of adenylate cyclase. Therefore, the addition of ADP to PGE1-

stimulated platelets reduces PGE1-induced VASP-P levels. If $P2Y_{12}$ receptors are successfully inhibited by ticagrelor or cangrelor, addition of ADP will not reduce the PGE1-stimulated VASP-P levels. The platelet reactivity ratio (PRI) will be calculated after measuring VASP-P levels after stimulation with PGE1 (MFI PGE1) and also PGE1 + ADP (MFI PGE1 + ADP). The $P2Y_{12}$ reactivity ratio = ([MFI PGE1] – [MFI PGE1 + ADP]/[MFI PGE1]) x 100%.

Primary and secondary objectives

The primary end point of our study is the comparison in platelet reactivity measured by VerifyNow PRU between crushed ticagrelor LD plus cangrelor infusion and crushed ticagrelor LD (plus placebo infusion) at 30 min after the LD and cangrelor (or placebo) bolus. We hypothesize that adding cangrelor will significantly reduce PRU in patients with STEMI undergoing PPCI. Secondary objectives will include: 1) the comparison in PRU between cangrelor and placebo at the other time points; 2) the comparison in PRI at all time points; 3) the comparison in rates of HPR between cangrelor and placebo at all time points. According to consensus definition, HPR will be defined as PRU>208 or PRI >50% [19].

Sample Size Computation, Power Analysis and Statistical Analysis

Assuming a common standard deviation of 70 PRU, a sample size of 20 patients per group will allow to detect a 70 PRU difference between groups (~160 PRU with ticagrelor vs ~90 PRU with ticagrelor plus cangrelor) with 85% power and a two-sided $\alpha = 0.05$. Considering the 2 arms and a possible ~25% rate of invalid results due to hemolysis, technical problems, or drop-out, we plan to randomize up to 50 patients, in order to have complete data for the primary

end point analysis. Our sample size is based on data derived from previously published studies [10,20,21].

The PD population will include all patients with PD data and without a major protocol deviation thought to affect significantly the PD of ticagrelor or cangrelor. The PD population will be used for analysis of all primary and secondary PD variables. Erroneously treated patients (e.g., those randomized to one treatment but actually given the other) will be accounted for based on the actual treatment received.

Categorical variables will be expressed as frequencies and percentages. Continuous variables will be presented as mean ± SD or median [IQR]. Continuous variables will be analyzed for normal distribution with the Kolmogorov-Smirnov test. Comparisons between categorical variables will be performed using two-tailed Fisher's exact test or the Pearson's chi-square test. Student´s t test, Mann-Whitney U-test and Wilcoxon test will be used to compare continuous variables when appropriate. An analysis of covariance will be used to evaluate the primary end point and all between-group comparisons in platelet reactivity. A mixed linear model will be used to evaluate the overall difference between groups over time and within-group comparisons. A p value <0.05 will be considered statistically significant for superiority analyses. Statistical analysis will be performed using a SPSSv22.0 software (SPSS Inc. Chicago, IL).

Publication Strategy/Additional Information

Subjects will be identified with a number and data collection sheets will all be stored in a locked area. Data will be kept for 6 years after enrollment ends to comply with HIPAA regulations. Patients will receive a handout with the names and telephone numbers of the doctors involved in the study. Study subjects will be identified first (months 1-12): we expect to

randomize 4-5 subjects monthly and complete enrollment in 12 months (total: 50 subjects randomized). Months 13-14 will be implied for statistical analysis and manuscript preparation. Results will be presented at the first available major cardiovascular meeting (e.g. AHA, ACC, ESC), and final manuscript will be submitted to publication to one of major cardiovascular journals (e.g. JACC, Circulation, European Heart Journal).

Possible Discomforts and Risk

In clinical trials, the most common clinical side effect of cangrelor was bleeding. Severe/moderate bleeding occurred in 0.8% of patients receiving cangrelor, as compared to 0.6% of those receiving placebo. Other side effects include dyspnea (1.3%), worsening renal function (3.2% of patients with severe renal impairment), and hypersensitivity (0.05%) [11,12].

All clinical events described above, if they were to occur, as well as death, myocardial infarction, stroke, and urgent revascularization procedure with PCI or coronary artery bypass grafting will be recorded. Bleeding data will be collected using BARC definitions [22]. Clinical events will be evaluated by a local committee, comprised of 2 faculty members (2 cardiologists), not directly involved in the research. In the event of a report of a serious adverse event the local committee will meet and antiplatelet treatment management will be managed according to physician recommendation.

Definition of Adverse Events

An adverse event is any unintended or undesirable experience that occurs during the course of the clinical investigation whether or not it is considered to be therapy related. This includes any newly occurring event or previous condition that has increased in severity or

frequency since the initiation of study treatment. Adverse events will be followed until resolution while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study therapy will be followed until resolution or until the patient starts a new treatment regimen.

Serious Adverse Events (SAE): An adverse event occurring while on study and considered related (reasonable possibility that the study treatment caused the adverse experience) to the study treatment that results in any of the following outcomes:

- Death
- A life-threatening adverse experience.
- A persistent or significant disability, incapacity, or is a congenital anomaly, or birth defect.
- Requires inpatient hospitalization, or prolongation of existing hospitalization.

The definition of serious adverse event also includes 'important medical event'. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and/or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Conflict of Interest

Dr. Angiolillo is a consultant for Chiesi, the maker of cangrelor, and Astra Zeneca, the maker of ticagrelor.

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