STUDY REPORT SYNOPSIS

Utilization of Ticagrelor in the Upstream Setting for Non-ST-Segment Elevation Acute Coronary Syndrome (UPSTREAM): An ED-Based Clinical Registry

A Phase IV, post-approval, multicenter, prospective, observational registry of consecutive patients with a working diagnosis of NSTEMI and treatment with an OAP agent (ticagrelor, clopidogrel, or prasugrel) 4-72 hours upstream of diagnostic angiography

Milestones:	Completion
Phase of development:	Phase IV
Sponsor:	AstraZeneca
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This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale: Medical care of patients with non-ST-segment elevation myocardial infarction (NSTEMI) who are invasively managed can be divided into two phases: “upstream” and “downstream.” The upstream interval encompasses all care provided prior to diagnostic angiography and therefore includes the risk stratification, empiric decision making, and diagnostic and therapeutic actions of emergency medical service (EMS) personnel, emergency physicians, hospitalists and other internists, and non-interventional cardiologists.

Ticagrelor (BRILINTA™, AstraZeneca) is indicated for the reduction of thrombotic events (cardiovascular death, myocardial infarction [MI], and stroke) in patients with acute coronary syndromes (ACS; unstable angina [UA], NSTEMI, or ST elevation myocardial infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass graft (CABG) surgery.

Antiplatelet therapy is part of the foundational approach to ACS management across the continuum of care, and the increasing numbers of antiplatelet options could make treatment decisions more individualized, more challenging, and more important for providers than ever before. This is particularly true in the emergency department (ED) setting, where there is an opportunity to initiate definitive, rapid-onset antiplatelet therapy for ACS upstream of diagnostic angiography using ticagrelor.

Ticagrelor has a unique mechanism of action, binds reversibly to platelets, and is dosed twice daily— all in contradistinction to the alternative oral antiplatelet (OAP) agents (ticlopidine, clopidogrel, and prasugrel). There is therefore a need to educate healthcare providers on ticagrelor’s optimal use and its potential role in contemporary ACS therapy. This UPSTREAM registry seeks to generate data regarding contemporary management of NSTEMI patients “upstream” and the use of OAPs in that setting in particular.

Objectives: The primary objective of the UPSTREAM registry is to address the data gap regarding the course of NSTEMI between ED arrival and diagnostic angiography in detail, by characterizing and following the ED and peri-ED use of OAP agents. In addition to exploring ED treatment patterns and, retrospectively, evaluating success of both ischemic and bleeding risk stratification prior to definition of the coronary anatomy, data captured via the UPSTREAM registry will allow attribution of ischemic and bleeding outcomes to pre-catheterization antiplatelet therapy in the management of NSTEMI. This registry further seeks to demonstrate that contemporary use of upstream ticagrelor is associated with a smooth transition of care into the outpatient, secondary prevention setting, for the first 30 days after hospitalization. Finally, it will allow characterization of patient selection factors and processes for ticagrelor vs alternative OAP agents at hospital discharge.

Study design: Phase IV, post-approval, multicenter, prospective, observational registry of consecutive patients with a working diagnosis of NSTEMI and treatment with an OAP agent (ticagrelor, clopidogrel, or prasugrel) 4-72 hours upstream of diagnostic angiography.

Data source: Contemporaneous patient health records, telephonic contact with some subjects

Study population: Adults with biomarker-confirmed non-ST-segment elevation myocardial infarction (NSTEMI) and treated with an oral platelet $P2Y_{12}$ inhibitor at least 4 hours prior to diagnostic coronary angiography, no more than 72 hours after initial presentation (n = 3355). Subjects eligible for 30-day follow-up were those who specifically received ticagrelor as their only oral $P2Y_{12}$ agent treatment at presentation, throughout hospitalization, and by prescription at index hospital discharge (n = 1087, a subset of the).

Inclusion criteria: Patients (≥18 years of age) with a working diagnosis of NSTEMI and treatment with an oral $P2Y_{12}$ inhibitor (ticagrelor, clopidogrel, or prasugrel) either in the emergency department (ED), or in any case within the timeframe that emergency physicians consider to be "upstream"–within the first 48 hours of care and at least 4 hours before diagnostic angiography. In addition, only those patients who undergo a diagnostic coronary angiography within 72 hours of ED arrival will be eligible for UPSTREAM.

Exclusion criteria: As this was an observational study, the only exclusion criterion was failure to meet inclusion criteria.

Statistical methods: UPSTREAM was a prospective and retrospective, observational registry study. Descriptive statistics were used to summarize the primary and the secondary endpoints as well as other data collected in the study. Continuous variables were summarized using the number of patients reflected in the calculation (n), mean, median, interquartile range, minimum, and maximum. The time interval between upstream antiplatelet treatment and diagnostic catheterization was be treated as a continuous variable for study. Categorical data was summarized using frequencies and percentages.

Results: A total of 3,355 patients were enrolled, of whom 1,087 were "ticagrelor-consistent" and had 30-day follow-up.

- The mean (+/-SD) age was 63.3+/-12.5 y and 62.6% were male. The typical UPSTREAM patient was a moderately obese male in his early sixties, who often had had prior revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting surgery [CABG]). About one-quarter had pathologic ST-segment depression at presentation, and nearly one in five was already taking a $P2Y_{12}$ inhibitor; this was not a low-risk population.
- Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) ischemic risk scores placed these patients in the intermediate risk range and Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology (ACC) and American Heart Association (AHA) Guidelines? (CRUSADE) bleeding risk scores were in the moderate risk range.

- The loading dose in UPSTREAM was clopidogrel in 45.6%, ticagrelor in 53.6%, and prasugrel in 0.8%. When used as the upstream loading $P2Y_{12}$ inhibitor, the dose of clopidogrel was 150mg in 1.4%, 225mg in 0.53%, 300mg in 57.5%, 475mg in 0.07%, 600mg in 37.7% and 900mg in 0.07%. The loading dose of ticagrelor in upstream load was 180mg in 98.2% and 270mg in 1.8%, and for prasugrel was 60mg in 81.3% and 30mg in 18.7%.
- The median upstream interval (loading dose to angiography) was 17:27 hours and did not change appreciably over the course of the data collection period (2/15 – 10/19).
- Access was radial in 48.6% and femoral in 51.4%. Over the course of data collection for the registry, the proportion of patients in whom radial access was used increased steadily, from 16.7% to 77.1%. Although the number of bleeding complications overall was low, there appeared to be no difference between the two access routes.
- Post-angiography management was medical only in 32.3%, PCI in 59.4%, and CABG in 8.3%. Intervention types were similar across treatment groups. The percentages of PCI-treated subjects undergoing one, two, or three stent implantations was 66.5%, 24.6%, and 8.6%, respectively.
- Median length of stay was 2.7 days, and median time from angiography to CABG was 3.6 days.
- In-hospital mortality was 0.51% and major bleeding (TIMI) was 0.24%; the in-hospital major adverse cardiac event (MACE) rate was 0.7% and stent thrombosis occurred in 0.18%. All of these rates are quite low compared to randomized clinical trial data on NSTEMI management.
- No significant differences were seen between the ticagrelor and clopidogrel cohorts in hospital, but 16% received more than one $P2Y_{12}$ inhibitor in-hospital, which confounds any potential differentiation.
- On follow-up of the ticagrelor-consistent cohort (93.2% response), 86.7% of patients reported taking ticagrelor as directed. Of the 12.6% of follow-up patients who reported discontinuing the prescribed dose of ticagrelor, 3.8% had done so for bleeding, 32.9% for dyspnea (and therefore 4.2% of the ticagrelor-consistent cohort), 27.8% for cost, 13.9% because of preference for a once-daily option, and 21.5% for other reasons. (This rate of patient-reported dyspnea is higher than that seen in the Platelet Inhibition and Patient Outcomes (PLATO) trial overall (0.9%) and may be a better representation of actual patient experience.) During the follow-up interval, 7.4% (n=80 patients, 0.08% overall) reported rehospitalization, 17.5% (n=14, 1.3% overall) of which were related to confirmed ACS, though only nine of these 14 (representing 0.009% of the ticagrelor-consistent cohort) were taking ticagrelor as prescribed. During follow-up, 1.0% reported bleeding complications that caused them to seek medical attention; none were found to be major in severity.

Conclusion: In an observational study of clinician-directed therapy, we found that the use of a loading dose of either ticagrelor or a thienopyridine at least four hours before diagnostic angiography was associated with very low rates of ischemic and bleeding complications, as well as in-hospital plus (in the ticagrelor-consistent cohort) 30-day mortality, among patients with confirmed NSTEMI and managed invasively. An upstream loading dose of the more potent platelet inhibitor ticagrelor was not associated with a higher bleeding risk than clopidogrel (99% of thienopyridine loads), which is less a less potent agent. In general, upstream loading of $P2Y_{12}$ inhibitors was associated with very low rates of bleeding and short length of stay in a large cohort of NSTEMI patients managed invasively.

Publications:

- Pollack CV, Bhandary DD, Frost A, Peacock WF, Diercks DB, Silber SH, Rao SV, Bangalore S, Reicher B, Burke L, DeRita R, Khan ND. Initial report from an Emergency Department-based registry of NSTEMI patients given upstream advanced oral antiplatelet therapy. *Circulation* 2016;134: A12079. Also presented at Scientific Sessions, American Heart Association, New Orleans, Nov 2016.
- Pollack CV, Bhandary DD, Frost A, Peacock WF, Rao SV, Silber SH, Diercks DB, DeRita R, Bhalla N, Bangalore S, Khan ND. *Circulation* 2018;138:A12797. Also presented at Scientific Sessions, American Heart Association, Chicago, Nov 2018.
- Pollack CV, Peacock WF, Bhandary DD, Silber SH, Bhalla N, Rao SV, Diercks DB, Frost A, Bangalore S, Heitner J, Johnson C, DeRita R, Khan ND. Oral antiplatelet therapy administered upstream to patients with NSTEMI: Primary Report of the Utilization of Ticagrelor in the Upstream Setting for Non-ST-Segment Elevation Acute Coronary Syndrome (UPSTREAM) Registry. *Crit Pathw Card.* E-publish ahead of print DOI: 10.1097/HPC.0000000000000243