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Oral Antiplatelet Therapy Administered Upstream to Patients With NSTEMI

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Objective: To describe from a noninterventional registry (Utilization of Ticagrelor in the Upstream Setting for Non-ST-Segment Elevation Acute Coronary Syndrome), the short-term ischemic and hemorrhagic outcomes in patients with non-ST elevation myocardial infarction (MI) are managed with a loading dose (LD) of a $P2Y_{12}$ inhibitor ($P2Y_{12}$i) given at least 4 hours before diagnostic angiography and delineation of coronary anatomy. Prior data on the effects of such "upstream loading" have been inconsistent.

Methods: In 53 US hospitals, we evaluated the in-hospital care and outcomes of patients with confirmed non-ST elevation MI managed with an interventional strategy and loaded upstream (at least 4 h before diagnostic angiography) with oral $P2Y_{12}$i therapy. Patients entered into the database were grouped into 1 of 4 cohorts for analysis: (1) overall cohort, (2) thienopyridine (clopidogrel or prasugrel) load, (3) ticagrelor load, and (4) ticagrelor-consistent. The fourth cohort is a subset of cohort 3 that received ticagrelor throughout the index hospital stay and at discharge. We evaluated in-hospital clinical course and ischemic and bleeding outcomes in all patients and also 30-day outcomes in the ticagrelor-consistent cohort.

Results: A total of 3355 patients were enrolled, of whom 1087 had 30-day follow-up. The mean (±SD) age was 63.3 ± 12.5 years, and 62.6% were male. Thrombolysis in MI and Global Registry of Acute Coronary Events scores placed these patients in the intermediate risk range, and CRUSADE scores were in the moderate risk range. The LD in Utilization of Ticagrelor in the Upstream Setting for Non-ST-Segment Elevation Acute Coronary Syndrome was clopidogrel in 45.6%, ticagrelor in 53.6%, and prasugrel in 0.8%. The median upstream interval (LD 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%. Postangiography management was medical only in 32.3%, percutaneous coronary intervention in 59.4%, and coronary artery bypass grafting in 8.3%. Median length of stay was 2.7 days, and median time from angiography to coronary artery bypass grafting was 3.6 days. In-hospital mortality was 0.51%, and major bleeding (thrombolysis in MI) was 0.24%; the in-hospital major adverse cardiovascular events rate was 0.7%, and stent thrombosis occurred in 0.18%. No significant differences were seen between the ticagrelor and clopidogrel cohorts in hospital, but 16% received more than 1 $P2Y_{12}$i in-hospital. On follow-up (93.2% response), 86.7% of patients reported taking ticagrelor as directed.

Conclusions: Upstream loading of $P2Y_{12}$i was associated with very low rates of bleeding and short length of stay in a large cohort of non-ST elevation MI (NSTEMI) patients managed invasively.

Key Words: antiplatelet therapy, NSTEMI, P2Y12 inhibition, upstream treatment

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In non-ST-segment elevation (NSTE) myocardial infarction (MI), activated platelets aggregate and adhere to injured vessel walls, and secrete procoagulants, promoting clot formation and obstruction or downstream clot embolization, resulting in myocardial damage.[1] In recognition of this key role of platelets in coronary thrombosis, dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor ($P2Y_{12}$i) has become a standard of care and has been shown to improve ischemic outcomes after acute coronary syndrome (ACS) but with an increase in bleeding events.[1]

Among the pivotal studies for antagonism of the $P2Y_{12}$ receptor by an oral agent in the past 10 years, only 1 provided data on the consistent "upstream" administration of dual antiplatelet therapy (DAPT), that is, on DAPT given before definition of the coronary anatomy by diagnostic angiography (DA). The study of Platelet Inhibition and Patient Outcome (PLATO) trial randomized patients to receive clopidogrel plus ASA or ticagrelor plus ASA upon presentation so that DAPT was ostensibly therapeutic at the time of initial angiography.[2] The length of the upstream interval—the time between administration of DAPT and DA, which then yielded fully informed risk stratification to help direct subsequent therapy for NSTEMI—varied substantially in PLATO, from <3 to 72 hours.[2]

The potential benefits of upstream loading are medical stabilization before DA and to blunt the impact of percutaneous coronary intervention (PCI)-induced disruption of the vascular endothelium, which in the absence of $P2Y_{12}$i further activates platelets. Time from presentation to DA, even in clinical trials of invasive management for NSTEMI, varies widely; in 1 recent study, the delay was <12 hours in 40.5% of patients, ≥12–<24 hours for 34.9%, and ≥24 hours in 24.6%.[3] An overriding concern over routine use of upstream DAPT for NSTEMI is that a proportion of patients may require coronary artery bypass grafting (CABG). The duration of DAPT effect requires a waiting period of 5–7 days before cardiac surgery to reduce perioperative bleeding,[4,5] with attendant risks of recurrent ischemia during the waiting period.[4–6] Given that 12% or less of NSTEMI patients are likely to require near-term CABG,[7] concern for surgical bleeding or delayed surgery must be balanced against the potential benefit of earlier potent ADP inhibition for the remaining 88%, who unfortunately cannot always be prospectively identified.

In PLATO, the benefit of ticagrelor preloading in NSTEMI was affirmed, albeit the study was designed as a preloading study.[2] The ACTION PCI metaanalysis of randomized controlled trials showed that clopidogrel pretreatment significantly reduced major coronary events by 23%, primarily driven by the reduction

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in peri-PCI MI. While there was an increased rate of major bleeding, there was no difference in all-cause mortality.[8] The Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty (ARMYDA)-5 PRELOAD study showed 600-mg in-lab clopidogrel load pre-PCI had similar 30-day outcomes to a routine 4- to 8-hour preload and concluded that in-lab clopidogrel administration is a safe alternative to routine pretreatment before knowing patients' coronary anatomy.[9]

Given that evidence for upstream $P2Y_{12}$i is conflicting and guidelines offer limited support, we conducted a multicenter, prospective, observational registry, to describe the incidence of in-hospital major cardiac events and bleeding in patients given oral antiplatelet therapy with different $P2Y_{12}$i given at least 4 hours before DA. The secondary aims were to evaluate 30-day outcomes in a cohort of patients who were treated consistently with ticagrelor from upstream load to index hospital discharge prescription and to evaluate the risk:benefit balance of upstream loading of $P2Y_{12}$i in the invasively managed NSTEMI population.

METHODS

Registry Design and Setting

The Utilization of Ticagrelor in the Upstream Setting for Non-ST-Segment Elevation Acute Coronary Syndrome (UPSTREAM) registry was an emergency department (ED)-based observational, noninterventional registry evaluating the clinical outcomes of patients with NSTEMI (defined by local troponin assays plus clinical confirmation) who were scheduled to undergo DA *and* received a loading dose (LD) of ASA plus clopidogrel, ticagrelor, or prasugrel at least 4 hours before the procedure and within 72 hours of initial ED presentation. This definition of "upstream" treatment was based on American College of Cardiology Foundation/American Heart Association guidelines, which state that troponin-positive NSTE-ACS patients should undergo DA within 72 hours,[10] and on the expected onset of action of 180 mg ticagrelor or 600-mg clopidogrel (although, in fact, some subjects received a 300-mg LD of clopidogrel).[11]

Fifty-three US hospitals contributed data to UPSTREAM, with their participation approved by their respective ethics committees. Sites agreed to submit data on consecutive patients who met eligibility criteria, and management (including selection and dosing of $P2Y_{12}$i) was neither directed nor impacted in any way as a result of patient inclusion in the registry. Sites were not selected nor stratified based on anticipated use of a specific $P2Y_{12}$i. In accordance with IRB guidance, patients or their legally authorized representatives signed a written informed consent document allowing submission of their in-hospital data and, only in ticagrelor-consistent cases, of their posthospitalization data, to the registry files. Patient information was entered locally without personal health information into a secure, Health Insurance Portability and Accountability Act compliant, CFR-part 11-compliant, web-based electronic data collection system.

Selection of Participants

Patients at least 18 years of age with a working diagnosis of NSTEMI and treatment per local practice with a LD of an $P2Y_{12}$i agent (ticagrelor, clopidogrel, or prasugrel) within the first 72 hours of care but at least 4 hours before DA were considered eligible and could be approached for consent. Because informed consent was not necessary for treatment, many sites obtained consent for data collection after management of NSTEMI was already underway. Patients were excluded if the upstream $P2Y_{12}$i LD was given outside these time parameters (either >72 h after presentation or <4 h before DA) or if the patient did not undergo angiography. Patients who were transferred into an enrolling facility were eligible as long as complete data were available and inclusion criteria were met.

In all subjects, in-hospital data were collected through index hospital disposition and included discharge ASA and $P2Y_{12}$i regimens. We identified 4 cohorts for analysis: (1) the overall population of upstream-treated patients, (2) those whose upstream $P2Y_{12}$i LD was a thienopyridine (clopidogrel or prasugrel), and (3) those whose upstream $P2Y_{12}$i LD was ticagrelor. A fourth "ticagrelor-consistent" cohort, whose only $P2Y_{12}$i upstream, throughout the hospitalization, and by prescription at index hospital discharge, was ticagrelor, had additional data collected in person, telephonically, or by direct record review at 30 (+10 d) after discharge. This allowed evaluation of 30-day readmission among other posthospitalization outcomes, in this subcohort.

Measurements

The population of treated subjects is described by demographics, with baseline risk calculated by use the Global Registry of Acute Coronary Events (GRACE)[12] and Thrombolysis In Myocardial Infarction (TIMI) NSTE-ACS[13] risk scores, and Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) score.[14] Prehospital and in-hospital data included serial vital signs, electrocardiogram (ECG) findings, and pertinent laboratory values including serial troponin assays. Type and timing of upstream $P2Y_{12}$i LD was recorded and used to confirm eligibility with respect to time of presentation and initiation of angiography. Access route and findings of coronary angiography were recorded, as were use of intravenous antiplatelet therapy (platelet glycoprotein IIb/IIIa inhibitors or cangrelor, if any), and periprocedural anticoagulant. Postangiography management strategy (medical management only vs. PCI vs. CABG) and any procedure-related complications were collected. Postcatheterization lab course, including use of $P2Y_{12}$i and any in-hospital bleeding or ischemic complications, was documented. Discharge prescriptions for $P2Y_{12}$i and ASA, if any, were recorded. Postdischarge follow-up in the ticagrelor-consistent cohort included data collection on compliance with $P2Y_{12}$i and scheduled follow-up, reports of unscheduled care potentially related to ACS, adverse effects potentially referable to ticagrelor, and reports of bleeding.

Outcomes

In-hospital outcomes for all patients were collected, including the composite and individual components of cardiovascular death, MI, or stroke (collectively, major adverse cardiovascular events [MACE]), and major bleeding. Bleeding was classified according to the TIMI,[15] PLATO,[2] and Bleeding Academic Research Consortium (without adjudication) scales[16]; bleeding reported by the patient at 30-day follow-up is presented descriptively.

Additional outcomes of interest included the relationship of the duration of the upstream interval to ischemic and bleeding outcomes, the distribution of postangiography management, and $P2Y_{12}$i practice including switching from 1 agent to another. The ticagrelor-consistent cohort was also evaluated for 30-day outcomes of rehospitalization, MACE, bleeding, and discontinuation of ticagrelor.

Analysis

Descriptive statistics are used to summarize the primary findings of this observational registry, by cohort and by post-DA management. Continuous variables are summarized using the number of patients reflected in the calculation (n), mean, SD (SD), median, and interquartile range (25, 75 IQR) when appropriate. Categorical data are summarized using frequencies and percentages.

RESULTS

Overall Study

Between February 2015 and September 2019, 3355 patients with NSTEMI who received upstream $P2Y_{12}$i were entered into the

TABLE 1. Characterization of the Overall UPSTREAM (n = 3355), Thienopyridine Upstream Load (n = 1555), and Ticagrelor Upstream Load (n = 1800) Cohorts

	Overall Cohort	Thienopyridine-load Cohort	Ticagrelor-load Cohort
Mean (SD) age, y	63.3 (12.5)	64.7 (12.6)	62.1 (12.2)
% male	62.6	62.2	63.0
% nonwhite race	30.2	25.8	31.8
Mean (SD) BMI, kg/m^2	30.9 (11.1)	31.1 (11.6)	30.1 (8.7)
% with DM	36.7	36.5	36.9
% with DM treated with insulin	16.2	17.2	15.2
% current smoker	23.9	23.2	24.4
% previous PCI	26.1	28.9	23.1
% previous CABG	14.3	17.8	11.0
% with pathologic ST-segment depression	18.9	18.6	19.2
% with transient ST-segment elevation	0.61	0.81	0.45
% with first/second/third first troponin positive	44.0/23.1/8.7	41.6/24.6/8.8	45.9/22.2/8.6
Median (IQR) duration upstream interval	17:27 (10:41, 27:42)	18:17 (11:27, 29:27)	16:52 (10:05, 26:09)
% with multivessel disease at DA	15.5	18.1	13.3
% medically managed after DA	32.3	35.4	29.6
% PCI after DA	59.4	55.9	62.2
% CABG after DA	8.3	8.6	8.1
% upstream LD with clopidogrel	45.6	98.3	0
% upstream LD with ticagrelor	53.6	0	100
% upstream LD with prasugrel	0.77	1.6	0
% treated in-hospital with >1 OAP	15.9	14.7	17.0
Median (IQR) LOS, non-CABG	2.9 (2.1, 4.1)	2.9 (2.1, 4.1)	2.7 (2.0, 3.8)

BMI, body mass index; CABG, coronary artery bypass grafting; DA, diagnostic angiography; DM, diabetes mellitus; IQR, interquartile range; LD, loading dose; LOS, length of stay; OAP, oral antiplatelet; PCI, percutaneous coronary intervention.

UPSTREAM database. The mean (±SD) age was 63.3 ± 12.5 years and 62.6% were male. Baseline information on these patients is found in Table 1. Within the overall registry population, there were no substantive differences apparent between the thienopyridine-load and ticagrelor-load cohorts, but no formal statistical analysis was performed because the choice of agent was not randomized and completely at the discretion of the treating physician. The ticagrelor-consistent cohort is a subset of the ticagrelor-load cohort and will be discussed only for its 30-day outcomes.

A total of 53 US hospitals enrolled subjects in the registry, with the first site enrolling its first subject in February 2015 and the last included site enrolling its first patient in December 2018. The most common "first positive" troponin in these NSTEMI patients was the first assay (44.0%); the second assay was first positive in 23.1%, and the third was first in 8.7%. On initial ECG, 19.2% of patients had ST-segment depression in the ED or ambulance and 0.68% had transient ST-segment elevation but were diagnosed as NSTEMI. Initial ECGs were read as normal in 19.8%, abnormal but not diagnostic of ischemia in 28.9%, and with nonspecific ST-T-wave changes in 27.6%. Old Q-waves were identified in 4% of the cohort. On initial presentation, 17.8% of subjects were already taking a $P2Y_{12}$i as an outpatient (70.0% clopidogrel, 27.3% ticagrelor, 2.7% prasugrel). Other risk factors were evident, with 36.7% having diabetes and 23.9% being current tobacco smokers.

The ASA LD (prehospital and emergency department) was 81 mg in 2.1%, 162 mg in 10.2%, 243 mg in 3.9%, 324/325 mg in 83.5%, and >324/325 mg in 0.3%. The qualifying $P2Y_{12}$i LD was clopidogrel in 1529 (45.6%), ticagrelor in 1800 (53.6%), and prasugrel in 26 (0.8%). As per protocol, all subjects in this analysis underwent DA. The median (IQR) time between $P2Y_{12}$i LD and DA (the "upstream interval") was 17:27 (10:41, 27:42) hours, was similar in the 2 load cohorts (thienopyridine or ticagrelor), and did not change appreciably over the course of data collection. Postangiography in-hospital management was medical only in 32.3%, PCI in 59.4%, and CABG in 8.3%. The median (IQR) hospital length of stay in non-CABG patients was 2.9 (2.1, 4.1) days. In-hospital mortality was 0.51% (0.15% cardiovascular), and major bleeding (per TIMI scale) occurred during the index hospitalization in 0.24%; all were similar between load cohorts (Table 1).

Thienopyridine- and Ticagrelor-Load Cohorts

As shown in Table 1, the 2 cohorts were generally similar, but the ticagrelor-load group had quantitatively lower rates of prior PCI and CABG. The thienopyridine-load group had somewhat higher rates of multivessel disease at DA but rates of CABG between the 2 groups on the index hospitalization were similar. Ticagrelor-loaded patients were more likely to go on to PCI and less likely to have post-DA medical management. The upstream interval was shorter among ticagrelor-loaded patients than thienopyridine-loaded patients.

Ischemic Complications

TIMI and GRACE risk scores calculated at presentation generally placed the UPSTREAM cohort in the intermediate risk range. These risk scores and the individual incidence of the components of MACE) are listed in Table 2. During the index hospitalization, 0.7% of upstream-treated patients sustained a MACE complication, including nonfatal re-MI, nonfatal stroke, or cardiovascular death. The rate of in-hospital definite or probable acute stent thrombosis during the index hospitalization was 0.18%.

Hemorrhagic Complications

During the index hospitalization, 0.24% of upstream-treated patients suffered a bleeding complication not related to CABG that

TABLE 2. Ischemic/Thrombotic Outcomes of the Overall UPSTREAM (n = 3355), Thienopyridine Upstream Load (n = 1555), and Ticagrelor Upstream Load (n = 1800) Cohorts

	Overall Cohort	Thienopyridine-load Cohort	Ticagrelor-load Cohort
Mean (SD) TIMI (NSTE) risk score	2.8 (1.3)	3.00 (1.3)	2.7 (1.2)
Mean (SD) GRACE risk score	91.1 (29.2)	94.1 (30.1)	88.5 (28.3)
% in-hospital cardiovascular mortality	0.15	0.13	0.16
% in-hospital all-cause mortality	0.51	0.38	0.55
% in-hospital nonfatal re-MI	0.06	0.06	0.06
% in-hospital nonfatal ischemic stroke	0.33	0.45	0.22
% in-hospital definite/probable stent thrombosis	0.18	0.12	0.22

GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; NSTE, non-ST-segment elevation; TIMI, thrombolysis in myocardial infarction.

qualified as "major" on the TIMI scale. Transfusions were rare across UPSTREAM (see Table 3). The CRUSADE bleeding risk score placed the overall UPSTREAM cohort in the moderate risk range. Table 3 also shows blood product usage and other parameters pertinent to the assessment of bleeding complications in upstream-treated non-CABG patients.

Angiography and PCI

Vascular 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%. The respective rates of in-hospital transfusion of packed red blood cells in these 2 groups were 0.31% and 0.35%. Closure devices were employed in 56.8% of the femoral access cases. Although the number of bleeding complications overall was low, there appeared to be no difference between the 2 access routes.

The percentages of PCI-treated subjects undergoing 1, 2, or 3 stent implantations was 66.5%, 24.6%, and 8.6%, respectively. Of the total stents placed, 7.9% of stents were bare-metal and 92.1% were drug-eluting.

TABLE 4. CABG Cohorts Within Overall UPSTREAM (n = 3355), Thienopyridine Upstream Load (n = 1555), and Ticagrelor Upstream Load (n = 1800) Cohorts

	Overall Cohort	Thienopyridine-load Cohort	Ticagrelor-load Cohort
% with DM	43.6	41.2	45.1
% with DM treated with insulin	17.1	16.0	18.1
% with prior PCI	22.2	19.1	25.0
% emergency CABG, e.g., coronary artery dissection	1.1	0.76	1.4
Median (IQR) time DA to surgery, d	3.6 (2.3, 5.6)	3.5 (1.5, 5.6)	4.1 (2.6, 5.6)
% On-pump CABG	73.1	70.2	75.7
% 3 vessels by-passed	36.4	29.8	42.4
% >3 vessels by-passed	26.2	29.0	23.6
% arterial grafts	48.4	47.9	51.2
% <2 u PRBC transfused	10.9	9.2	12.5
% ≥2 u PRBC transfused	5.1	5.3	4.9
% platelets transfused	1.1	1.5	0.69
Median (IQR) hospital LOS, d	11.1 (8.3, 14.1)	11.1 (8.3, 14.1)	11.08 (8.3, 14.0)

CABG, coronary artery bypass grafting; DA, diagnostic angiography; DM, diabetes mellitus; IQR, interquartile range; LOS, length of stay; PCI, percutaneous coronary intervention; PRBC, packed red blood cells.

Complications in the Catheterization Lab

Among the 3355 patients who underwent DA after upstream $P2Y_{12}$i loading, 3.5% experienced a complication in the catheterization lab during angiography or PCI. These included 0.80% with thrombus, 0.63% with coronary artery dissection, 0.48% with slow or no flow, 0.39% with dysrhythmia, and 0.42% with transient hypotension. One patient died in the laboratory. During or within the first 24 hours after the catheterization laboratory procedure, 0.36% of subjects received transfusions of blood products.

CABG Cohort

Among the 275 patients who underwent CABG on the index hospitalization, 43.6% had diabetes. The overall median (IQR) time

TABLE 3. Hemorrhagic Outcomes of the Overall UPSTREAM (n = 3355), Thienopyridine Upstream Load (n = 1555), and Ticagrelor Upstream Load (n = 1800) Cohorts

	Overall Cohort	Thienopyridine-load Cohort	Ticagrelor-load Cohort
Mean (SD) CRUSADE bleeding risk score	39.3 (14.0)	41.0(14.2)	37.9 (13.6)
% in-hospital non-CABG TIMI major bleeding, radial access for DA	0.21	0.12	0.22
% in-hospital non-CABG TIMI major bleeding, femoral access for DA	0.03	0	0.05
% in-hospital non-CABG PLATO major bleeding	0.98	0.96	1.0
% in-hospital BARC 3 or 5 bleeding	1.6	1.8	1.3
% femoral artery closure devices used	55.0	64.9	46.5
% in-hospital non-CABG ≤ 2 u PRBC transfused	0.21	0.32	0.11
% in-hospital non-CABG > 2 u PRBC transfused	0.12	0.13	0.11
% in-hospital non-CABG platelets transfused	0.47	0.58	0.39

BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass grafting; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; DA, diagnostic angiography; PLATO, PLAtelet inhibition and patienT Outcome; PRBC, packed red blood cells; TIMI, Thrombolysis In Myocardial Infarction.

from DA to surgery was 3.6 (2.3, 5.6) days with little difference between the 2 $P2Y_{12}$i load options. Surgery was performed on-pump in 73.1% and off-pump in 26.9%. Arterial grafts were used in 48.4% and venous grafts in 51.2%. Blood product usage related to CABG was quite conservative and is shown in Table 4.

Hospital Course After Diagnostic Angiography

The median (IQR) length of stay (LOS) after DA and PCI was 1.2 (1.0, 2.2) days; patients treated medically after DA had LOS of 1.3 (0.97, 2.9) days. Patients who underwent CABG had a median (IQR) index hospital LOS of 11.1 (8.3, 14.1) days. Postangiography in-hospital events included 58 patients reported as having some degree of heart failure (HF). In addition, 11 patients experienced cardiac arrest, but none were fatal. There were 12 patients with nonfatal stroke (11 ischemic [one of these also had HF], 1 hemorrhagic), 2 patients with confirmed in-hospital reinfarctions, and 28 same-stay unplanned returns to angiography (1e of whom also had HF and 1 had nonfatal arrest).

$P2Y_{12}$i Doses and Switches

When used as the upstream loading $P2Y_{12}$i, the dose of clopidogrel was 150 mg in 1.4%, 225 mg in 0.53%, 300 mg in 57.5%, 475 mg in 0.07%, 600 mg in 37.7%, and 900 mg in 0.07%. The LD of ticagrelor in upstream load was 180 mg in 98.2% and 270 mg in 1.8%, and for prasugrel was 60 mg in 81.3% and 30 mg in 18.7%.

Within the entire UPSTREAM cohort, 16.0% of subjects received more than one $P2Y_{12}$i medication during the index hospitalization. In addition, 4.2% received a consistent agent during hospitalization but were switched to a different agent at discharge; the most common such switch was from ticagrelor to clopidogrel. At discharge, the recommended daily dose of ASA was 81 mg in 94.6%, 162 mg in 1.9%, and 325 mg in 3.5%.

Follow-up

The ticagrelor-consistent cohort comprised 1087 subjects, indicating that 713 patients who received an upstream LD of ticagrelor were not maintained on ticagrelor through discharge prescription. Thirty-day (+10) posthospitalization follow-up was completed on 93.2% of these 1087 patients. None of the 6.8% lost to follow-up appeared in the Social Security Death Index at the time of follow-up at 6+ months after discharge. During the follow-up period, 86.7% of those responding reported compliance with twice-daily ticagrelor, 12.6% reported discontinuing the prescribed dose of ticagrelor or never filled the original prescription, and the remainder were taking ticagrelor, but only once daily. Compliance with the directed dose of ASA was reported by 97.4%, and 88.2% had completed their first scheduled follow-up visit. No additional cases of stent thrombosis were reported at 30-day follow-up in the ticagrelor-consistent cohort.

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), overall 27.8% for cost, 13.9% because of preference for a once-daily option, and 21.5% for other reasons. During this 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, although only 9 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.

DISCUSSION

In an observational study of clinician-directed therapy, we found that the use of a LD of either ticagrelor or a thienopyridine at least 4 hours before DA 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 LD 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. Overall, only around 8% went on to CABG post-DA, thus presenting potential concerns for surgical delays. Our findings support that the use of an upstream $P2Y_{12}$i does not infer an excessive bleeding risk, and therefore are consistent with the Guidelines' I-A recommendation of administering to patients with definite UA/NSTEMI at medium or high risk, and in whom an initial invasive strategy is selected, dual antiplatelet therapy *on presentation*.[17] While our results are limited to that of an observational cohort, they are supported by other randomized data as well.

Adenosine diphosphate (ADP) is a potent activator of platelets and is present at high levels locally when a coronary atherosclerotic plaque ruptures or fissures spontaneously, and at the time of PCI.[18] Among patients with NSTE-ACS, the PCI-CURE subgroup analysis (n = 2658) showed that pretreatment with clopidogrel before PCI decreased the 30-day risk of cardiovascular death, nonfatal MI, or urgent target-vessel revascularization by 30%, although the "upstream interval" (a term not applied at that time) in these patients was about 6 days.[19] A metaanalysis of 7 studies evaluating 32,383 patients who were preloaded with a thienopyridine showed a 16% reduction in MACE but no impact on the single endpoint of mortality, whether DA was followed by medical management or PCI, but overall there was an excess of major bleeding among pretreated patients.[20]

The first randomized comparison of upstream $P2Y_{12}$i to no pretreatment in NSTEMI patients was A Comparison of Prasugrel at PCI or Time of Diagnosis of Non-ST Elevation Myocardial Infarction.[21] In the upstream treatment arm, prasugrel 30 mg was administered at the time of diagnosis and an additional 30 mg was given in the laboratory if DA confirmed the need for PCI; in the no pretreatment arm, 60 mg prasugrel was given after DA only if PCI was elected. Upstream dosing did not improve 7-day MACE but did significantly increase 7-day TIMI major bleeding, whether or not patients had PCI.[21] These findings, along with the design of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI 38), resulted in current guidelines recommendations to initiate prasugrel only when PCI is imminent; these same guidelines recommend that ticagrelor (based on the PLATO design) or clopidogrel (CURE) be given at the time of diagnosis of NSTE-ACS.[10]

In PLATO, the benefit of ticagrelor (180 mg LD/90 mg bid), which like prasugrel is associated with a rapid onset of action and a greater level of platelet inhibition, but also with a more rapid offset of pharmacodynamic action than clopidogrel,[22] was compared with clopidogrel (300–600 mg LD/75 mg qd) for the prevention of vascular events and death in patients with ACS. Ticagrelor therapy was associated with a significant reduction in the primary efficacy endpoint (MACE) compared with clopidogrel at 30 days and through 12 months. Ticagrelor significantly reduced the incidence of CV death and nonfatal re-MI and nominally reduced all-cause mortality but did not significantly reduce stroke.[2] There were no differences in the primary safety endpoint of PLATO-defined or TIMI major bleeding, and despite the fact that patients in the ticagrelor group were allowed to undergo CABG within 24–72 hours following discontinuation of study medication (compared with 5 d in the clopidogrel cohort), CABG-related bleeding event rates were similar between the 2 groups. Non-CABG-related major bleeding event rates were higher following ticagrelor treatment, but occurred early, reinforcing this registry's collection on 30-day outcomes for ticagrelor-treated patients. The efficacy advantages of ticagrelor, administered

in PLATO to all subjects upstream of DA, were consistent versus clopidogrel regardless of whether the management strategy selected upfront was invasive or conservative,[23] whether or not post-DA management was PCI, medical, or CABG[24] There was also no impact of age, risk factors, body weight, prior medical history (including transient ischemic attack or stroke), type of ACS, or clopidogrel metabolism genotype on this benefit.[2] These data from PLATO supported the development of the current observational registry to examine the benefit:risk assessment of upstream loading of $P2Y_{12}$i and particularly ticagrelor in NSTEMI as currently practiced by physicians who utilize that strategy.

In UPSTREAM, a wholly observational and noninterventional registry in which eligibility for inclusion was based entirely on the treating clinician's decision to administer upstream $P2Y_{12}$i in NSTEMI patients intended for DA, the 3355 patients presented at moderate ischemic risk (TIMI mean score 2.8 and GRACE mean 91) and moderate-to-high bleeding risk (CRUSADE, mean 39) according to validated scales. The typical UPSTREAM patient was a moderately obese male in his early 60s, who often had had prior revascularization (PCI or CABG). About one-quarter had pathologic ST-segment depression at presentation, and nearly 1 in 5 was already taking a $P2Y_{12}$i. Most patients received a full LD (324/325 mg) of ASA, and just under half were given upstream clopidogrel, while just over half received upstream ticagrelor loads. The nearly 1% who received upstream prasugrel were treated off-label.

The median duration of the "upstream interval" after loading was 17–18 hours, which qualifies as "early invasive" and is sufficiently long for any of the $P2Y_{12}$is to be active at the time of angiography. The very low incidence of both ischemic and hemorrhagic complications across UPSTREAM does not allow for assessment of a potential correlation between length of upstream interval and complications, but the generally good outcomes among these patients—in-hospital mortality 0.51%, major bleeding 0.24%, non-CABG LOS of only 3 days—offer little opposition to the concept of upstream loading.

The UPSTREAM cohort experienced quite low in-hospital mortality; assuming most patients would have type 1 NSTEMI because they presented to an ED with ischemic symptoms,[25] in-hospital mortality would be expected to exceed 4%,[26] although historically this number also includes patients who were not managed invasively. The absolute contribution of upstream $P2Y_{12}$i loading to the difference in mortality cannot be elucidated, but it is quite provocative that upstream loading in this registry was indeed associated with a very low incidence of bleeding complications as well.

There is no reason to suspect that the interventional cardiologists who treated the patients enrolled in UPSTREAM had unusual insight into those patients' risk profile, including likelihood of CABG. These patients qualified for inclusion because those physicians chose to give them upstream $P2Y_{12}$i, not because the patients were randomized to receive it, yet ischemic complications (measured by incidence of MACE) and hemorrhagic complications (TIMI major bleeding) during hospitalization were both well under 1%, again raising no undue concern about upstream loading in these patients. It is of note that the distribution of radial versus femoral angiography access in UPSTREAM was virtually equal across the entire cohort, but that reflects an evolution in current expert guidance.[27] This—as well as the use of closure/hemostatic devices in more than half of cases—may have contributed to the low incidence of in-hospital major bleeding in UPSTREAM. Unlike several prior studies,[28] there was no apparent advantage in safety to the radial approach in UPSTREAM, although the choice also was not randomized and may reflect operator experience and competence. The higher bleeding risk with ticagrelor in patients with an upstream interval of longer than 3 hours seen in a PLATO secondary analysis,[29] while not directly assessed in UPSTREAM, is not evident in the current data.

In UPSTREAM, CABG was not common despite the prevalence of diabetes and multivessel disease. Blood loss as measured by transfusion in the CABG cohort was quite limited despite earlier $P2Y_{12}$i loading and, in fact, was lower than historical controls.[30] In upstream-loaded patients, the interval from DA to surgery was only 3–4 days. Contemporary data from the National Cardiovascular Data Registry indicate that the median time from DA to CABG among patients with NSTEMI who are *not* treated with upstream $P2Y_{12}$i is 43.5 hours,[31] and so the incremental difference may not be as striking as it first appears, particularly since in PLATO, guidance for CABG in ticagrelor-loaded patients was to wait only 24–72 hours.[2]

The overall in-hospital MACE rate in UPSTREAM was 0.7%, which is quite low compared with other studies. Indeed, the occurrence of thrombotic—and bleeding—events in UPSTREAM was very low across both the ticagrelor and thienopyridine-load cohorts. It is noteworthy then that the use of more potent antiplatelet therapy upstream yielded similar safety and efficacy results to that seen with clopidogrel. Longer follow-up intervals for both cohorts may have revealed a more significant difference.

$P2Y_{12}$i LDs were inconsistent, and 15.9% of patients received more than 1 $P2Y_{12}$i during hospitalization. Switching $P2Y_{12}$i during therapy in patients who are tolerating their drug is generally not recommended unless there is a clinical reason to do so.[32,33] Multiple factors could impact the decision to switch therapy: severity of coronary artery disease, likelihood of compliance, out-of-pocket cost that could influence adherence, adverse effects, and cotherapy for the presence of atrial fibrillation. There have been no prospective studies evaluating the impact of $P2Y_{12}$i switch during acute or secondary preventive care for NSTEMI.

Of patients discharged on ticagrelor, 4.2% reported discontinuation of treatment due to dyspnea. This rate is higher than that seen in PLATO overall (0.9%)[34] and may be a better representation of actual patient experience. It has been previously noted ticagrelor-related dyspnea is usually mild or moderate in intensity and in PLATO did not appear to be associated with differences concerning any efficacy or safety outcomes with ticagrelor compared with clopidogrel therapy in ACS patients.[34]

LIMITATIONS

This is an observational registry and is subject to all the limitations ordinarily ascribed to that design; these data are not intended to support cause-and-effect conclusions. There is likely selection bias in enrollment into UPSTREAM; although we enrolled consecutive patients with NSTEMI given an upstream LD of a $P2Y_{12}$i, that cohort of patients may not be fully representative of NSTEMI patients in general. Some may not undergo DA, some may receive a $P2Y_{12}$i only in the catheterization laboratory, and different physicians even at the same site might use varying criteria for administering upstream $P2Y_{12}$i. These criteria may include perceived ischemic risk, perceived bleeding risk, concern for near-term CABG, or anticipated time to DA, all of which are variable. Patients were enrolled in UPSTREAM over a 5-year period and evolution of management approaches may have occurred at some institutions during that time. Finally, we collected 30-day outcomes only on the ticagrelor-consistent patients and so the follow-up results may not be generalizable to all $P2Y_{12}$is.

CONCLUSIONS

The UPSTREAM data represent contemporary outcomes when patients with NSTEMI receive a LD of either ticagrelor or clopidogrel at least 4 hours in advance of DA. These patients, while not randomly selected in UPSTREAM, nonetheless had very

low rates of ischemic complications, bleeding complications, and in-hospital plus (in the ticagrelor-consistent cohort) 30-day mortality with this strategy. Only about 8% of patients with NSTEMI went on to CABG after angiography, and while their lengths of stay were prolonged when compared with PCI- or medically treated patients, they were managed with very low transfusion rates. These data suggest that upstream $P2Y_{12}$i can be of benefit to many patients with NSTEMI who are being managed with an early invasive strategy.

DISCLOSURES

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