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Timing of Oral $P2Y_{12}$ Inhibitor Administration in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome

Giuseppe Tarantini, MD, PhD,[a,*] Marco Mojoli, MD,[b,*] Ferdinando Varbella, MD,[c] Roberto Caporale, MD,[d] Stefano Rigattieri, MD,[e] Giuseppe Andò, MD, PhD,[f] Plinio Cirillo, MD, PhD,[g] Simona Pierini, MD,[h] Andrea Santarelli, MD,[i] Paolo Sganzerla, MD,[j] Luisa Cacciavillani, MD, PhD,[a] Luciano Babuin, MD, PhD,[a] Nicoletta De Cesare, MD,[k] Ugo Limbruno, MD,[l] Alberto Massoni, MD,[m] Andrea Rognoni, MD,[n] Daniela Pavan, MD,[b] Flavia Belloni, MD,[n] Carlo Cernetti, MD,[o] Luca Favero, MD,[o] Francesco Saia, MD,[p] Luca Nai Fovino, MD, PhD,[a] Giulia Masiero, MD,[a] Loris Roncon, MD,[q] Valeria Gasparetto, MD,[r] Marco Ferlini, MD,[s] Federico Ronco, MD,[t] Roberta Rossini, MD, PhD,[u] Paolo Canova, MD,[v] Daniela Trabattoni, MD,[w] Alessandra Russo, MD,[x] Vincenzo Guiducci, MD,[y] Carlo Penzo, MD,[z] Fabio Tarantino, MD,[aa] Ciro Mauro, MD,[bb] Elena Corrada, MD,[cc] Giovanni Esposito, MD, PhD,[g] Alfredo Marchese, MD,[dd] Sergio Berti, MD, PhD,[ee] Matteo Martinato, RN, PhD,[a] Danila Azzolina, MS,[a] Dario Gregori, PhD,[a] Dominick J. Angiolillo, MD, PhD,[ff] Giuseppe Musumeci, MD,[gg] for the DUBIUS Investigators, on behalf of the Italian Society of Interventional Cardiology

ABSTRACT

BACKGROUND Although oral $P2Y_{12}$ inhibitors are key in the management of patients with non-ST-segment elevation acute coronary syndrome, the optimal timing of their administration is not well defined.

OBJECTIVES The purpose of this study was to compare downstream and upstream oral $P2Y_{12}$ inhibitors administration strategies in patients with non-ST-segment elevation acute coronary syndrome undergoing invasive treatment.

METHODS We performed a randomized, adaptive, open-label, multicenter clinical trial. Patients were randomly assigned to receive pre-treatment with ticagrelor before angiography (upstream group) or no pre-treatment (downstream group). Patients in the downstream group undergoing percutaneous coronary intervention were further randomized to receive ticagrelor or prasugrel. The primary hypothesis was the superiority of the downstream versus the upstream strategy on the combination of efficacy and safety events (net clinical benefit).

RESULTS We randomized 1,449 patients to downstream or upstream oral $P2Y_{12}$ inhibitor administration. A pre-specified stopping rule for futility at interim analysis led the trial to be stopped. The rate of the primary endpoint, a composite of death due to vascular causes; nonfatal myocardial infarction or nonfatal stroke; and Bleeding Academic Research Consortium type 3, 4, and 5 bleeding through day 30, did not differ significantly between the downstream and upstream groups (percent absolute risk reduction: -0.46; 95% repeated confidence interval: -2.90 to 1.90). These results were confirmed among patients undergoing percutaneous coronary intervention (72% of population) and regardless of the timing of coronary angiography (within or after 24 h from enrollment).

CONCLUSIONS Downstream and upstream oral $P2Y_{12}$ inhibitor administration strategies were associated with low incidence of ischemic and bleeding events and minimal numeric difference of event rates between treatment groups. These findings led to premature interruption of the trial and suggest the unlikelihood of enhanced efficacy of 1 strategy over the other. (Downstream Versus Upstream Strategy for the Administration of $P2Y_{12}$ Receptor Blockers In Non-ST Elevated Acute Coronary Syndromes With Initial Invasive Indication [DUBIUS]; NCT02618837)
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From the [a]Department of Cardiac, Thoracic, and Vascular Sciences and Public Health, University of Padova, Padova, Italy; [b]Azienda Sanitaria Friuli Occidentale, Ospedale Santa Maria degli Angeli, Pordenone, Italy; [c]Ospedali Riuniti, Rivoli, Italy; [d]Ospedale Civile dell'Annunziata, Cosenza, Italy; [e]Sandro Pertini Hospital, Rome, Italy; [f]Azienda Ospedaliera Universitaria Policlinico

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Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor inhibitor is the standard of care in patients with acute coronary syndromes (ACS) (1). Ticagrelor and prasugrel are oral $P2Y_{12}$ inhibitors associated with more effective platelet inhibition and better clinical outcomes compared with clopidogrel in patients with ACS (2–4). Hence, prasugrel and ticagrelor are preferred over clopidogrel for the treatment of patients with ACS (1). The optimal timing of the administration of oral $P2Y_{12}$ inhibitors has been largely debated, particularly among patients with non–ST-segment elevation (NSTE) ACS (5). In fact, although administration of an oral $P2Y_{12}$ inhibitor before defining coronary anatomy, known as a pre-treatment strategy, has the theoretical advantage of providing more ischemic protection while patients wait to undergo coronary angiography and reduces the risk of periprocedural thrombotic complications among those undergoing percutaneous coronary interventions (PCIs), it may also increase the risk of periprocedural bleeding in patients treated by PCI or coronary artery bypass grafting (CABG), thus increasing the length of stay and hospital costs (6–8).

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In NSTE-ACS, pre-treatment with prasugrel has shown to increase the risk of bleeding, without providing any benefit regarding ischemic events (8). Accordingly, guidelines recommend against the upstream use of prasugrel in patients with NSTE-ACS (9–12). Although pre-treatment with ticagrelor is widely adopted, there are limited data on the safety and efficacy of this strategy compared with that of waiting to define coronary anatomy before administration of an oral $P2Y_{12}$ inhibitor (6). Guidelines have provided conflicting recommendations on pre-treatment, leading to variances in practice patterns (9–12). The DUBIUS (Downstream Versus Upstream Strategy for the Administration of $P2Y_{12}$ Receptor Blockers In Non-ST Elevated Acute Coronary Syndromes With Initial Invasive Indication) trial assessed the efficacy and safety of a strategy of pre-treatment with ticagrelor compared with no pre-treatment and administration of ticagrelor or prasugrel after defining coronary anatomy in patients with NSTE-ACS with planned invasive management.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ARR = absolute risk reduction

BARC = Bleeding Academic Research Consortium

CABG = coronary artery bypass grafting

MI = myocardial infarction

NSTE = non-ST-segment elevation

PCI = percutaneous coronary interventions

RCI = repeated confidence interval

UFH = unfractionated heparin

METHODS

TRIAL DESIGN AND OVERSIGHT. The DUBIUS trial was an investigator-initiated, phase 4, double randomized, adaptive, open label, multicenter clinical trial. Details of the study design and protocol of the trial are provided in the Supplemental Appendix. The Service for Clinical Trials and Biometrics, University of Padova, Italy, was the data coordinating center. The protocol was approved by the National Italian Drug Agency (Agenzia Italiana del Farmaco) and by local ethics committees at each site. All patients provided written informed consent. The study complies with the Declaration of Helsinki. The study was performed under the auspices of the Italian Society of Interventional Cardiology, which was also the funding institution. The Azienda Ospedaliera di Padova, a public health care institution, was the study sponsor. The funding institution and the sponsor were not involved in writing the manuscript or interpreting the results. Participating centers and investigators are reported in the Supplemental Appendix.

"Gaetano Martino," Messina, Italy; [g]Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy; [h]Ospedale Bassini, Cinisello Balsamo, Italy; [i]Cardiovascular Department, Infermi Hospital, Rimini, Italy; [j]ASST Bergamo Ovest, Ospedale di Treviglio, Italy; [k]Policlinico San Marco, Zingonia, Italy; [l]Azienda Ospedaliera Grosseto, Grosseto, Italy; [m]Ospedale Universitario "Maggiore della Carità," Novara, Italy; [n]Ospedale S. Spirito, Rome, Italy; [o]Ospedale di Treviso ULSS 2, Treviso, Italy; [p]University Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy; [q]Hospital Santa Maria della Misericordia, Rovigo, Italy; [r]Ca Ospedale P.Pederzoli, Peschiera del Garda, Italy; [s]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [t]Ospedale dell'Angelo, Mestre, Italy; [u]SS. Croce e Carle Hospital, Cuneo, Italy; [v]Dipartimento Cardiovascolare, ASST Papa Giovanni XXIII, Bergamo, Italy; [w]Centro Cardiologico Monzino, IRCCS, Milano, Italy; [x]ASST Valle Olona, Presidio Ospedaliero San Antonio Abate, Gallarate, Italy; [y]Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy; [z]Azienda Ospedaliero Universitaria di Ferrara Arcispedale Sant'Anna, Ferrara, Italy; [aa]Morgagni-Pierantoni Hospital, Forlì, Italy; [bb]Antonio Cardarelli Hospital, Naples, Italy; [cc]Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy; [dd]Anthea Hospital, GVM Care & Research, Bari, Italy; [ee]Fondazione Toscana G. Monasterio, Ospedale del Cuore G. Pasquinucci, Massa, Italy; [ff]Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida; and the [gg]Division of Cardiology, Azienda Sanitaria Ospedaliera Ordine Mauriziano, Torino, Italy. *Drs. Tarantini and Mojoli contributed equally to this work. A full list of DUBIUS Investigators, collaborators, and their affiliations is provided in the Supplemental Appendix.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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STUDY POPULATION. Key eligibility criteria were as follows: 1) age ≥18 and <85 years; 2) hospital admission for NSTE-ACS, including unstable angina and non-ST-segment elevation myocardial infarction (MI), defined according to guidelines (11); and 3) a planned invasive management strategy, defined as a scheduled coronary angiography within 72 h from hospital admission. Key exclusion criteria included use of chronic oral anticoagulation, any contraindication to ticagrelor or prasugrel, and treatment with a loading dose of any $P2Y_{12}$ inhibitor within the prior 7 days. (Patients on chronic therapy with clopidogrel or ticlopidine were eligible for study entry.) A detailed list of exclusion criteria is reported in Supplemental Table 1.

RANDOMIZATION. The study design is illustrated in Supplemental Figure 1. All participants enrolled were randomly assigned in a parallel 1:1 fashion, to receive pre-treatment with ticagrelor (upstream strategy) or no pre-treatment (downstream strategy). In the downstream group, all patients undergoing PCI were further randomized in a 1:1 fashion to the administration of ticagrelor or prasugrel. The second randomization was performed as soon as possible after angiography to allow for administration of the loading dose of the assigned agent before proceeding with PCI, if feasible. Patients and investigators were not blinded to study treatments. Randomizations were blocked by age (>75 or ≤75 years). The randomization was centrally managed through an online randomization module by the Service for Clinical Trials and Biometrics. The random allocation sequence was concealed from investigators. During study monitoring, the actual allocation was checked with respect to the randomization generated by the central system. The randomization procedure was performed by the principal investigator or a delegated subinvestigator using the web interface.

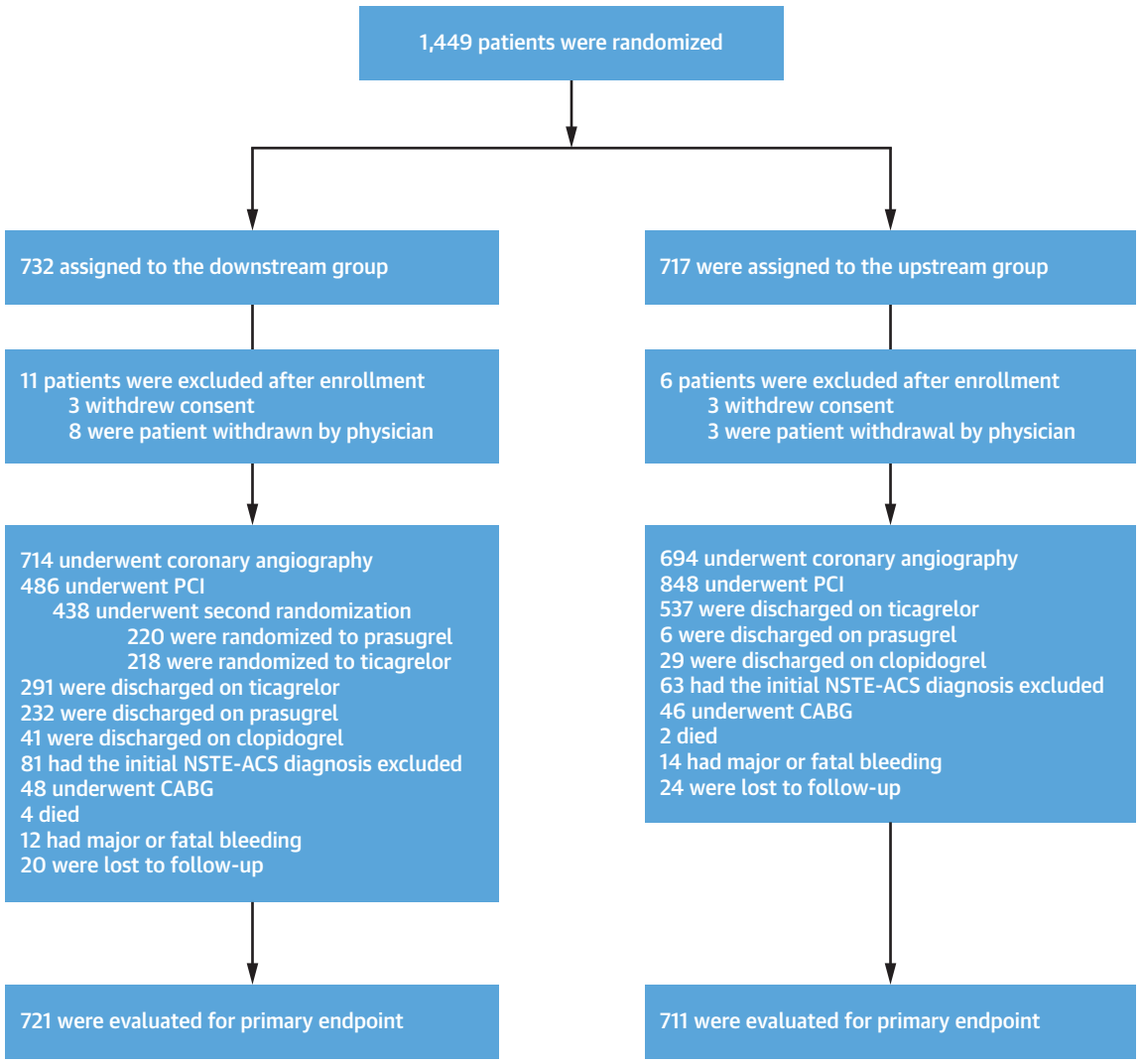
TRIAL PROTOCOL. Participants were enrolled and randomized as soon as possible after admission. Patients randomized to the upstream group were treated with ticagrelor. Patients randomized to the downstream group and undergoing PCI were further randomized to treatment with ticagrelor or prasugrel (Supplemental Figure 1). Patients were treated with a loading dose (ticagrelor, 180 mg, or prasugrel, 60 mg) followed by maintenance dosing (ticagrelor, 90 mg twice daily, or prasugrel, 10 mg daily). In patients >75 years of age or with a body weight of <60 kg, the daily maintenance dose of prasugrel was 5 mg daily. In the downstream group, it was recommended that the assigned treatment be administered at the start of the PCI procedure; if this was not feasible, the drug was required to be administered as soon as possible after PCI. In patients with an indication to undergo CABG, antiplatelet therapy was managed according to guidelines (12). In general, resumption of a $P2Y_{12}$ inhibitor was recommended as soon as considered safe after CABG. If the initial diagnosis of NSTE-ACS was not confirmed, the antiplatelet treatment regimen was defined at the discretion of the treating physician. Standard of care anticoagulation regimens were used. If the patient was expected to undergo angiography within 24 h, it was recommended that a target activated clotting time of 200 to 250 s be maintained with unfractionated heparin (UFH) until the procedure. Otherwise, the anticoagulation regimen was based on the clinician's judgement regarding the use of UFH, enoxaparin, or fondaparinux. In patients undergoing PCI, both UFH and bivalirudin were allowed in the periprocedural period.

TRIAL ENDPOINTS AND DEFINITIONS. The primary endpoint was a composite of death from vascular causes (death from cardiovascular causes or cerebrovascular causes and any death without another known cause), nonfatal MI, or nonfatal stroke and major or fatal bleeding (types 3, 4, and 5 on the Bleeding Academic Research Consortium [BARC] scale, with type 3 indicating major bleeding; type 4, CABG-related bleeding; and type 5, fatal bleeding) at 30 days after randomization (13,14). Secondary endpoints included the individual components of the primary endpoint, death from any cause, stent thrombosis, target vessel repeated revascularization, and target lesion revascularization. A detailed description of the endpoints is included in Supplemental Table 2. The primary and secondary endpoints were adjudicated according to source data by at least 2 members of the event adjudication committee who were unaware of the trial group assignments.

FOLLOW-UP AND MONITORING. Clinical follow-up was scheduled at 30 ± 7 days by outpatient office visits. Source data were monitored for potential endpoint-related events. According to the prespecified monitoring plan, the frequencies of remote and onsite monitoring were determined based on regular risk assessment of the trial.

STATISTICAL METHOD. Statistical analysis and data reporting followed the Adaptive Designs CONSORT Extension Statement (15). The primary hypothesis was superiority of a downstream versus an upstream administration strategy (Protocol, Supplemental Appendix). The sample size was calculated based on the initial assumption that the event rate of the

FIGURE 1 Randomization, Treatment, and Follow-Up



The primary endpoint was assessed in all patients eligible for the analysis and according to the randomly assigned trial group, irrespective of the actual treatment received (the intention-to-treat population). Patients were evaluated from randomization (time 0) until death, withdrawal of consent, or the last contact date. ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; NSTE = non-ST-segment elevation; PCI = percutaneous coronary interventions.

combined primary endpoint would be 11% of patients in the upstream arm and 8% of patients in downstream arm (8,16). Assuming a dropout rate of approximately 10%, we calculated that 1,260 patients in each group would be needed for the trial to have 80% power to detect a risk difference of 3% in the rate of the primary endpoint between groups with the use of a 2-sided alpha level of 0.05.

ADAPTIVE DESIGN. To compensate for discrepancies between the expected and the observed incidence of the primary endpoint, the sample size was computed using an adaptive approach in 3 study stages, meaning that 3 interim analyses followed by sample size recalculation were planned. After having reached the sample size foreseen for each of the 3 stages, an evaluation using a 95% repeated confidence interval (RCI) was scheduled. If the value 0 was contained in the interval, a sample size reassessment was required based on the actual incidence rates of the primary endpoint. Otherwise, data would be passed to the steering committee for a decision on the continuation or anticipated end of enrollment. The primary analysis considers the intention-to-treat population

TABLE 1 Baseline Characteristics*

	Downstream Group (n = 721)	Upstream Group (n = 711)
Age, yrs	65 (56–73)	64 (72–57)
Age >75 yrs	145/721 (20.1)	136/711 (19.1)
Female	164/694 (23.6)	171/675 (25.3)
Cardiovascular risk factors		
Diabetes	170/705 (24.1)	163/693 (23.5)
Current smoker	384/706 (54.4)	385/694 (55.5)
Arterial hypertension	473/708 (66.8)	469/694 (67.6)
Hyperlipidemia	344/705 (48.8)	331/697 (47.5)
Medical history		
Myocardial infarction	110/708 (15.5)	135/692 (19.5)
PCI	118/710 (16.6)	141/693 (20.3)
Aortocoronary bypass surgery	24/706 (3.3)	31/663 (4.7)
Weight <60 kg	45/688 (7)	51/675 (8)
Chronic kidney disease	32/709 (6.5)	32/693 (4.6)
Dialysis	2/32 (6.2)	1/31 (3.2)
Diagnosis at admission		
Unstable angina	141/681 (20.7)	145/678 (21.4)
NSTEMI	540/681 (79.3)	533/678 (78.6)
GRACE score	122 (103–143)	122 (101–142)
CRUSADE score	22 (16–30)	21 (16–31)
Coronary angiography	714/714 (100)	694/702 (98.9)
Revascularization strategy		
PCI	486/712 (68.3)	484/690 (70.1)
CABG	48/712 (6.7)	46/690 (6.6)
Medical management	178/712 (25)	160/690 (23.2)

Values are median (interquartile range) or n/N (%). *There were no significant between-group differences at baseline.

CABG = coronary-artery bypass grafting; CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines; GRACE = Global Registry of Acute Coronary Events; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.

consisting of all participants randomized in each of the 2 randomization groups, regardless of the treatment actually received. As a secondary hypothesis, we considered the noninferiority of prasugrel versus ticagrelor in the PCI group of the downstream strategy in terms of the primary endpoint. This analysis was planned only in the case of trial completion without early stops. A more detailed description of the analysis is reported in the Protocol (Supplemental Appendix). Power calculations were made using the R system (17) and gsDesign libraries (18).

ANALYSIS. The primary endpoint was analyzed using a 95% RCI for the absolute risk reduction (ARR) expressed as a percentage. The RCI was computed using the $(1 - \alpha)$ confidence level reached by study design at the interim assessment. The alpha level was divided up for interim looks according to the O'Brien and Fleming alpha spending function allocation (19). A robust Huber-White standard error estimate has been also considered, accounting for correlation within the center (20). The Kaplan-Meier cumulative incidence of the primary endpoint has been reported, together with the log-rank test for the comparison of downstream versus upstream event-free survival curves. The ARR (RCI) was also reported for the secondary 30-day endpoints, and the confidence level has been allocated across interim locks to account for multiple comparisons by using the O'Brien and Fleming spending rule. Data were summarized as the median and interquartile range. Categorical variables were reported as frequencies and percentages. The analysis was performed using the R system (17) and the RMS libraries (21).

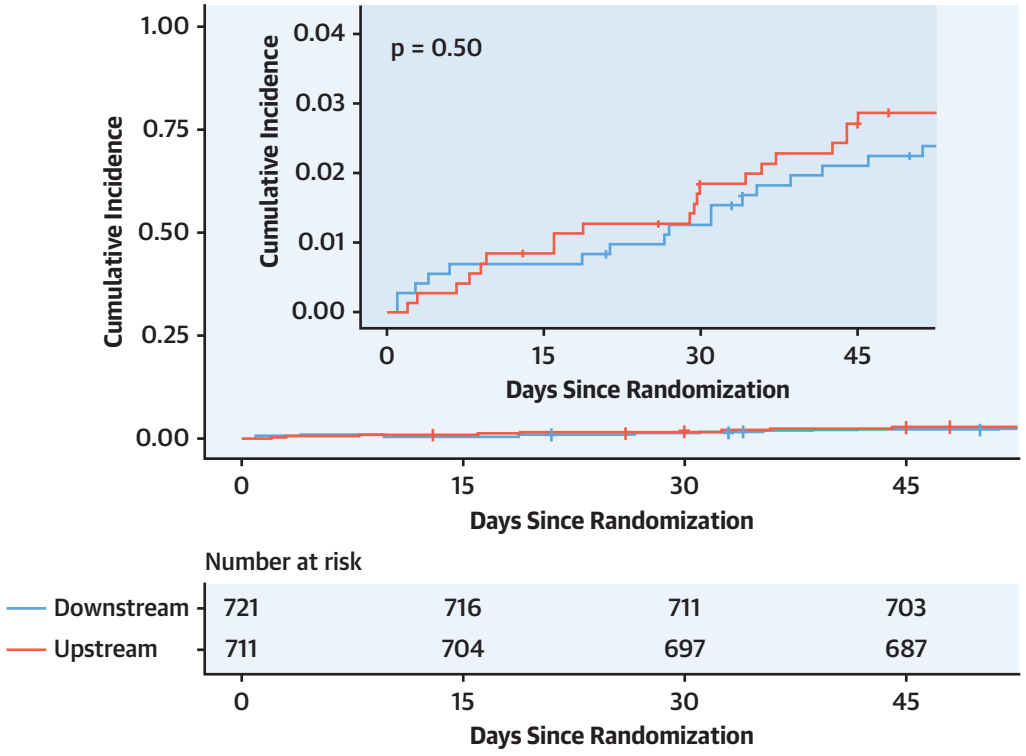
RESULTS

STUDY POPULATION. From December 2015 through May 2020, a total of 1,449 patients with NSTE-ACS were enrolled at 30 centers in Italy who were randomly assigned to an upstream (n = 717) or downstream (n = 732) strategy of oral $P2Y_{12}$ inhibitor administration. Of the total enrolled population, 1,432 patients were available for the second interim analysis, 711 in the upstream group and 721 in the downstream group. The remaining 17 patients were excluded from the interim analysis because of patient withdrawal of consent (n = 6) or patient withdrawal by physician (n = 11) (**Figure 1**). Baseline characteristics of the patient population are listed in **Table 1** and Supplemental Table 3.

At the interim analysis, the value of the conditional power was found to be critically low (0.13), far below the conventional threshold of 0.30 defining the so-called unfavorable zone (22). Because the value 0 was contained in the primary endpoint estimate confidence interval, based on a pre-specified stopping rule for futility of finding 1 strategy to be superior or inferior to the other, the results were provided to the study steering committee. Based on the projection that approximately 50,000 patients would be needed for the trial to assess superiority of the downstream strategy over the upstream strategy with the observed event rates, the steering committee decided to stop enrollment for a futility scenario.

INTERVENTION AND FOLLOW-UP. Coronary angiography was performed in 99.2% of patients, at a median time of 23.3 h (interquartile range: 4.0 to 30.0 h) after randomization. A radial approach was used in 94.5% of patients. PCI was performed in 72% of the patients, CABG in 6%, and no revascularization in 22% (nonobstructive coronary artery disease in 8% of patients, no coronary artery disease in 9%, and

CENTRAL ILLUSTRATION **Cumulative Incidence of the Primary Endpoint Up to 30 Days**



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The Kaplan-Meier curves show the cumulative incidence of the primary endpoint, which was a composite of death from vascular causes (death from cardiovascular causes or cerebrovascular causes and any death without another known cause), nonfatal myocardial infarction, or nonfatal stroke and major or fatal bleeding (types 3, 4, and 5 on the Bleeding Academic Research Consortium scale). The **inset** shows the same data on an expanded *y*-axis.

revascularization not feasible or indicated in 5%). Detailed data regarding medications are reported in Supplemental Tables 4 and 5. Angiographic and procedural characteristics are reported in Supplemental Table 6. CABG was performed at a median time of 7.5 days after randomization. At discharge, the initial diagnosis of NSTE-ACS was excluded in 11% of patients. Among patients treated by PCI in the upstream group, 95% were discharged on ticagrelor, 2% on prasugrel, and 3% on clopidogrel. In the PCI-treated population of the downstream group, 50% of patients were on ticagrelor, 47% on prasugrel, and 2% on clopidogrel. Between admission and angiography, 57% of patients received UFH, and 43% received low-molecular-weight heparin or fondaparinux. In the PCI cohort, peri-procedural UFH, enoxaparin, and bivalirudin were used in 97%, 3%, and 0.1% of patients, respectively. The rate of peri-procedural use of glycoprotein IIb/IIIa was 7% in the downstream group and 5% in the upstream group. Detailed data regarding medications are reported in Supplemental Tables 4 and 5.

The 30-day follow-up was complete in all but 44 patients (24 in the upstream group and 20 in the downstream group). The majority of patients (84%) were evaluated by office visit as per protocol, and the remaining were evaluated by telephone contact or structured follow-up letter. At follow-up, the randomized therapy was discontinued in 6% of patients in the upstream group and 5% of patients in the downstream group ($p = 0.40$). Adherence to the study drug, defined as compliance with ≥80% of the study drug as assessed by pill count or estimated by patient interview, was 87% in the upstream group and 84% in the downstream group ($p = 0.15$)

ENDPOINTS. The rate of the primary endpoint—death due to vascular causes; nonfatal MI; nonfatal stroke; and BARC type 3, 4, 5 bleeding at 30 days after

TABLE 2 Clinical Endpoints at 30 Days of Follow-Up

	Downstream Group (n = 721)	Upstream Group (n = 711)	Absolute Risk Reduction, % (95% RCI)
Primary endpoint: death due to vascular causes, myocardial infarction, stroke, and BARC type 3, 4, or 5 bleeding	21 (2.9)	24 (3.3)	-0.46 (-2.87 to 1.89)
Death due to vascular causes	3 (0.4)	2 (0.2)	0.13 (-0.96 to 1.28)
Myocardial infarction	7 (0.9)	7 (0.9)	-0.01 (-1.53 to 1.49)
Stroke	2 (0.2)	1 (0.1)	0.14 (-0.84 to 1.19)
BARC type 3, 4, or 5 bleeding	12 (1.6)	14 (1.9)	-0.30 (-2.24 to 1.57)
Death from any cause	4 (0.5)	2 (0.2)	0.27 (-0.83 to 1.50)
Definite or probable stent thrombosis	1 (0.1)	3 (0.4)	–
Transient ischemic attack	0 (0.0)	1 (0.1)	–
Target vessel revascularization	0 (0.0)	3 (0.4)	–
Target lesion revascularization	1 (0.1)	2 (0.2)	–

Values are n (%) unless otherwise indicated.
BARC = Bleeding Academic Research Consortium scale; RCI = repeated confidence interval.

randomization—did not differ significantly between the downstream and upstream groups (respectively, 2.9% and 3.3%; ARR: -0.46; 95% CI: -2.87 to 1.89) (**Central Illustration, Table 2**). These results were confirmed among patients undergoing coronary angiography within or after 24 h from enrollment and those undergoing PCI (Supplemental Figure 2). Additional analyses are reported in Supplemental Tables 7 to 12. Similar findings were also observed by adjusting the final estimate for history of MI or myocardial revascularization (Supplemental Table 13). Major or fatal bleeding were the most common adverse events contributing to the composite primary endpoint, without differences between groups. As an exploratory analysis, within the PCI subgroup of the downstream arm, the rate of the primary endpoint did not significantly differ between patients treated with prasugrel and those treated with ticagrelor (4.1% and 3.1%, respectively; ARR: 0.9; 95% CI: -3 to 5).

DISCUSSION

In this multicenter, randomized, adaptive trial conducted in invasively treated patients with NSTE-ACS, low and similar rates of the primary endpoint between groups were observed. Accordingly, the study was stopped after the second interim analysis to prevent a futile randomization of patients to treatments very unlikely to be associated with different clinical outcomes. Adverse events contributing to the combined primary endpoint were less frequent than anticipated. Early patient stratification and treatment, high rates of a radial approach, and broad implementation of secondary prevention measures may have contributed to our study findings. Even if this trial had been conceived with an adaptive design, it should be noted that the discrepancy between the initially predicted and the observed event rates was remarkable. Sample size calculations were based on the ACCOAST (A Comparison of Prasugrel at PCI or Time of Diagnosis of Non-ST Elevation Myocardial Infarction) study (8) and on the NSTE-ACS subanalysis of the PLATO (Platelet Inhibition and Patient Outcomes) study (16). Those studies, however, differed from this trial in many respects. First, the bleeding risk in DUBIUS was considerably lower than in ACCOAST (median Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines [CRUSADE] scores of 22 and 34, respectively), and the ischemic risk was lower than in PLATO (median Global Registry of Acute Coronary Events score of 122 in DUBIUS vs. 130 in PLATO). Second, the definitions of bleeding types used in the 2 previous studies were earlier definitions than BARC (Thrombolysis In Myocardial Infarction, STEEPLE [Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation], and GUSTO [Global Use of Strategies to Open Occluded Arteries] in ACCOAST; PLATO, Thrombolysis In Myocardial Infarction, and GUSTO in PLATO). Third, no previous data were available related to the downstream administration of ticagrelor. Fourth, the interval between enrollment and angiography was shorter in ACCOAST than in DUBIUS (4 vs. 23.3 h), whereas angiography was performed up to 10 days after randomization in the PLATO substudy.

The concept of pre-treatment as a potentially beneficial strategy in patients with NSTE-ACS originally emerged on the basis of the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial), PCI-CURE, and CREDO (Clopidogrel for the Reduction of Events During Observation) trials

(23–25). Based on the potential benefits of early administration of clopidogrel observed in these studies, guidelines recommend the use of upstream treatment with clopidogrel. Subsequently, in PLATO, ticagrelor was associated with an early benefit over clopidogrel in invasively treated patients with NSTE-ACS, irrespective of the timing of angiography (3,26). However, to date, no randomized trials have specifically assessed the relative benefits of pre-treatment compared to no pre-treatment with ticagrelor in patients with NSTE-ACS. A strategy of pre-treatment with ticagrelor versus treatment with prasugrel after defining coronary anatomy was evaluated in the subgroup of patients with NSTE-ACS randomized in the ISAR-REACT 5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) trial, in which prasugrel was associated with a greater reduction in ischemic events compared with ticagrelor at 1 year (27). However, 41% of patients enrolled in ISAR-REACT 5 had ST-segment elevation MI (STEMI), all of whom were pre-treated with oral $P2Y_{12}$ inhibitors. Other key differences between trials included the oral $P2Y_{12}$ inhibitors used in the downstream arm (prasugrel in ISAR-REACT 5 and ticagrelor or prasugrel in DUBIUS) and the median time interval between loading dose administration and coronary angiography in non-pre-treated patients (61 min in the NSTE-ACS cohort of ISAR-REACT 5 and 24 h in DUBIUS). Despite these differences, in ISAR-REACT 5 clinical outcomes were similar between the groups during the first 30 days, much in line with the DUBIUS findings, and the differences in the treatment arms emerged with prolongation of treatment up to 1 year.

In this trial, we hypothesized that a no-pre-treatment strategy would be superior to pre-treatment in terms of net outcomes. We based this superiority assumption on an anticipated predominant impact of bleeding events in the pre-treatment group as compared with ischemic events in the no-pre-treatment group. Such an assumption was mainly based on the ACCOAST trial, which directly compared pre-treatment with no pre-treatment with the same potent $P2Y_{12}$ inhibitor (i.e., prasugrel) among patients with non-ST-segment elevation MI with planned invasive management (2 to 48 h before coronary angiography) and showed a detrimental effect at 30 days in terms of safety (i.e., increase major bleeding and life-threating bleeding) without any signals of efficacy (8).

The relatively limited time delay between clinical presentation and invasive management that characterizes present clinical practice has led to questioning of the benefits associated with a pre-treatment strategy versus waiting to define coronary anatomy first (5–7,26). The median interval of 23.3 h between randomization and coronary angiography observed in DUBIUS reflects the common practice of early invasive strategy in patients with NSTE-ACS and may have contributed to the observed low adverse event rates. To this extent, a subanalysis of the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) study found that a substantial proportion of adverse events occurred within 72 h from randomization, with urgent target vessel revascularization being the most common (28). Similarly, the TIMACS (Timing of Intervention in Acute Coronary Syndromes) trial demonstrated that delayed revascularization was associated with an increased incidence of urgent target vessel revascularization, thus supporting routine early invasive assessment and revascularization in NSTE-ACS (29).

Current guidelines recommend the use of ticagrelor or prasugrel over clopidogrel in patients with NSTE-ACS in the absence of contraindications. By design, DUBIUS focused on patients eligible for treatment with these more potent $P2Y_{12}$ inhibitors. Because of the slower onset of its antiplatelet effect and less intense platelet inhibition, it is plausible that routine pre-treatment with clopidogrel may be differentiated from pre-treatment with the more potent agents both in terms of risk of bleeding and ischemic events and in terms of the interaction with the timing of invasive assessment and revascularization (5,6).

STUDY LIMITATIONS. The results of DUBIUS need to be considered in the context of a trial interrupted prematurely for futility and thus are exploratory per the pre-defined analytical plan of the trial. Nevertheless, to our knowledge, this is the first study to test pre-treatment with ticagrelor in a randomized fashion selectively in patients with NSTE-ACS. In line with other available evidence, our findings suggest that a pre-treatment strategy does not offer any benefit and raises the potential for harm.

DUBIUS assessed the impact of upstream and downstream strategies when using the potent oral $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, as currently recommended by the guidelines. Accordingly, our findings cannot be extended to treatment strategies involving other oral $P2Y_{12}$ inhibitors (i.e., clopidogrel). Moreover, an indication to early

invasive assessment (i.e., within 72 h) was one of the eligibility criteria, with a median observed interval of 23.3 h. Therefore, these results cannot be extended to strategies that do not include an early invasive evaluation (e.g. within 72 h from clinical presentation).

A close monitoring was performed during the entire follow-up to minimize the loss of patients; even so, a total of 44 patients (3.0%) were lost to follow-up. Patients lost to follow-up are a common issue in clinical trials in the cardiovascular field (30). Although we cannot exclude that some of the patients lost to follow-up may have experienced an adverse event, the observed dropout rate was similar between study groups and was lower than the assumed rate used for the sample size calculations.

A numeric imbalance was observed between the 2 groups. All participants were randomly assigned to the upstream or the downstream strategy. A permuted block randomization of size 4 was performed stratifying by age (>75 or ≤75 years) and center with a 1:1 allocation ratio. Among the centers reporting a lower enrollment rate, some did not close the blocks; the strata with incomplete randomized blocks can lead to a residual imbalance between treatment groups (31). However, randomly allocated groups do not need to be the same size for true baseline comparability. If the characteristics of participants are comparable, any differences in group sizes do not bias the results or reduce the statistical power of the study (32).

Our findings do not necessarily extend to higher-risk populations because we cannot exclude significant variations of the ARR of the primary endpoint under this condition. An additional analysis of the generalizability of trial results is reported in the Supplemental Appendix.

The results should be interpreted with caution, because finding no significant difference in this case is not sufficient to confidently conclude that there is no difference between treatments.

CONCLUSIONS

In this multicenter, randomized trial, conducted in patients with NSTE-ACS with planned invasive treatment, both a downstream treatment strategy with an oral $P2Y_{12}$ inhibitor (prasugrel or ticagrelor) and a ticagrelor-based pre-treatment strategy showed low and similar rates of the composite 30-day major ischemic and bleeding events. Our findings suggest the unlikelihood of enhanced efficacy of 1 strategy over the other.

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ADDRESS FOR CORRESPONDENCE: Dr. Giuseppe Tarantini, Cardiology Clinic, Department of Cardiac, Thoracic and Vascular Sciences, Policlinico Universitario, Via Giustiniani 2, 35128 Padova, Italy. E-mail: giuseppe.tarantini.1@gmail.com. Twitter: @G_Tarantini01.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with NSTE-ACS, treatment with ticagrelor before coronary angiographic intervention offers no advantage over later post-procedural initiation of prasugrel or ticagrelor when both efficacy and safety outcomes are considered.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether ticagrelor pre-treatment might be advantageous for selected patient subgroups.

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KEY WORDS bleeding, ischemia, non-ST-segment elevation acute coronary syndrome, oral $P2Y_{12}$ inhibitors

APPENDIX For a list of the participating centers and investigators and a simulation study, as well as supplemental tables and figures, please see the online version of this paper.