Original Investigation

Anticoagulation With Otamixaban and Ischemic Events in Non–ST-Segment Elevation Acute Coronary Syndromes
The TAO Randomized Clinical Trial

Philippe Gabriel Steg, MD; Shamir R. Mehta, MD, MSc; Charles V. Pollack Jr, MD, MA; Christoph Bode, MD; Marc Cohen, MD; William J. French, MD; James Hoekstra, MD; Sunil V. Rao, MD; Witold Ruzyllo, MD; Juan M. Ruiz-Nodar, MD, PhD; Manel Sabaté, MD; Petr Widimsky, MD; Robert Gabor Kiss, MD; Jose Luis Navarro Estrada, MD; Hanoch Hod, MD; Prafulla Kerkar, MD; Sema Guneri, MD; Murat Sezer, MD; Mikhail Ruda, MD; José Carlos Nicolau, MD; Claudio Cavallini, MD; Iftikhar Ebrahim, MD; Ivo Petrov, MD; Jae-Hyung Kim, MD; Myung-Ho Jeong, MD; Gabriel Arturo Ramos Lopez, MD; Peep Laanmets, MD; Frantisek Kovar, MD; Christophe Gaudin, MD; Karen C. Fanouillere, MSc; Pascal Minini, PhD; Elaine B. Hoffman, PhD; Angele Moryusef, MD; Stephen D. Wiviott, MD; Marc S. Sabatine, MD, MPH; for the TAO Investigators

IMPORTANCE The optimal anticoagulant for patients with non–ST-segment elevation acute coronary syndromes (NSTE-ACS) managed with an invasive strategy remains controversial.

OBJECTIVE To compare the clinical efficacy and safety of otamixaban, a novel intravenous direct factor Xa inhibitor, with that of unfractionated heparin plus downstream eptifibatide in patients with NSTE-ACS undergoing a planned early invasive strategy.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, active-controlled superiority trial that enrolled 13 229 patients with NSTE-ACS and a planned early invasive strategy, at 568 active sites in 55 countries and conducted between April 2010 and February 2013. A planned interim analysis was conducted for otamixaban dose selection.

INTERVENTIONS Eligible participants were randomized to otamixaban (bolus and infusion, at 1 of 2 doses) or unfractionated heparin plus, at the time of percutaneous coronary intervention, eptifibatide. The otamixaban dose selected at interim analysis was an intravenous bolus of 0.080 mg/kg followed by an infusion of 0.140 mg/kg per hour.

MAIN OUTCOMES AND MEASURES The primary efficacy outcome was the composite of all-cause death or new myocardial infarction through day 7.

RESULTS Rates of the primary efficacy outcome were 5.5% (279 of 5105 patients) randomized to receive otamixaban and 5.7% (310 of 5466 patients) randomized to receive unfractionated heparin plus eptifibatide (adjusted relative risk, 0.99 [95% CI, 0.85-1.16]; $P = .93$). There were no differences for the secondary end points, including procedural thrombotic complications. The primary safety outcome of Thrombosis in Myocardial Infarction major or minor bleeding through day 7 was increased by otamixaban (3.1% vs 1.5%; relative risk, 2.13 [95% CI, 1.63-2.78]; $P < .001$). Results were consistent across prespecified subgroups.

CONCLUSIONS AND RELEVANCE Otamixaban did not reduce the rate of ischemic events relative to unfractionated heparin plus eptifibatide but did increase bleeding. These findings do not support the use of otamixaban for patients with NSTE-ACS undergoing planned early percutaneous coronary intervention.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Philippe Gabriel Steg, MD, Université Paris-Diderot, Département Hospitalo-Universitaire FIRE, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, 46 rue Henri Huchard, 75018 Paris, France (gabriel.steg@bch.aphp.fr).

Major progress has been made in the management of non–ST-segment elevation acute coronary syndromes (NSTE-ACS) because of the availability of potent combinations of oral antiplatelet agents and injectable anticoagulants and the increasing use of an invasive strategy.[1-5] Nevertheless, the risk of adverse outcomes remains substantial,[6] and there is no consensus on a single optimal injectable anticoagulant that can be used across the continuum of care from the emergency setting through revascularization (when applicable). Unfractionated heparin (UFH), particularly when combined with a glycoprotein IIb/IIIa receptor inhibitor at the time of percutaneous coronary intervention (PCI),[7] remains an effective and widely used therapy, and its use is supported by US and European guidelines.[1,2] Unfractionated heparin, however, has limitations, including a narrow therapeutic window, a somewhat unpredictable anticoagulant response, and activation of the platelet factor 4 receptor.[8] The addition of glycoprotein IIb/IIIa receptor inhibitor to UFH at the time of PCI enhances the efficacy of UFH for the treatment of ACS,[1,2] although it increases bleeding risk.

The synthetic intravenous direct factor Xa inhibitor, otamixaban, inhibits thrombin generation in a dose-dependent manner, with a rapid onset and offset of action, linear kinetics, and limited renal elimination.[9-11] The phase 2, dose-ranging Study Program to Evaluate the Prevention of Ischemia With Direct Anti-Xa Inhibition in Acute Coronary Syndromes 1–Thrombosis in Myocardial Infarction 42 (SEPIA-ACS1 TIMI 42) trial involving patients with NSTE-ACS and a planned invasive strategy, even though not powered for efficacy, showed a reduction in the combined outcome of death or myocardial infarction in patients treated with otamixaban compared with UFH plus eptifibatide and showed similar bleeding rates with otamixaban at midrange doses.[12] Previous studies with factor Xa antagonists in ACS have identified a risk of procedural thrombotic complications that mandate careful titration of these drugs or additional antithrombotic agents at the time of PCI,[13] but this was not seen at midrange doses of otamixaban. Thus, given its rapid onset and offset, intravenous administration, and predictable anticoagulant response that does not require monitoring, otamixaban was attractive as a single anticoagulant to be used across the continuum of care for NSTE-ACS, from emergency care through intervention.

CABG *coronary artery bypass graft*

NSTE-ACS *non–ST-segment elevation acute coronary syndromes*

PCI *percutaneous coronary intervention*

UFH *unfractionated heparin*

The Treatment of Acute Coronary Syndromes with Otamixaban (TAO) trial was designed as a superiority trial to compare the clinical efficacy and safety of otamixaban with that of UFH plus downstream eptifibatide in patients with NSTE-ACS with a planned invasive strategy.

Methods

Study Patients

The design of the TAO trial has been published.[14] In brief, eligible patients were those with NSTE-ACS scheduled to undergo an early invasive strategy (angiography and PCI, if indicated, to be performed within 36 hours of randomization and at the latest on day 3; eTable 1 in the Supplement). All patients provided written informed consent. In every participating country, the study was approved by ethics committees in accordance with local guidelines. The main exclusion criteria were revascularization procedure already performed for the qualifying event; acute ST-segment elevation myocardial infarction; receipt of a therapeutic dose of injectable anticoagulant for more than 24 hours before randomization; or treatment with abciximab. If received in the 24 hours before randomization, treatment with UFH or bivalirudin must have been discontinued at least 90 minutes but no longer than 150 minutes before starting otamixaban and the last dose of low-molecular-weight heparin or fondaparinux must have been received at least 8 hours before starting otamixaban.

Study Treatments

The study used a double-blind design, with 2 stages.[14] During the first stage, until a planned interim analysis, patients were randomized using a centralized interactive voice-web response system, stratified by center, to the UFH-plus-eptifibatide group or to 1 of 2 otamixaban dosing groups (intravenous bolus of 0.080 mg/kg followed by an infusion of either 0.100 mg/kg per hour or 0.140 mg/kg per hour) in a 1:1:1 ratio (eFigure 1 in the Supplement). The infusions of otamixaban or placebo and UFH or placebo were initiated and discontinued simultaneously. The planned interim analysis, to be performed after at least 1969 patients had been randomized in each group and had completed a 7-day follow-up (approximately 35% fractional information), allowed the data monitoring committee to choose (using a predefined algorithm and while maintaining the blind for patients, investigators, and sponsor) the optimal otamixaban-dose group (in this case the higher-dose group) to continue until study end. Thus, in the second stage, patients were randomized in a 1:1 ratio either to the UFH-plus-eptifibatide group or to the otamixaban group (intravenous bolus of 0.080 mg/kg followed by a 0.140-mg/kg per hour infusion). Investigators and patients were blinded for the drug and the dose.

In the UFH-plus-eptifibatide group, throughout both study stages, patients received UFH (60-IU/kg intravenous bolus [maximum, 4000 IU] followed by an infusion of 12 IU/kg per hour [maximum, 1000 IU/h] to maintain an activated partial thromboplastin time at 1.5-2.0 times the control group) as soon as possible after randomization and continued until the end of PCI. At the time of PCI, additional UFH boluses could be administered if the activated clotting time was not in the 200- to 250-seconds range. For the investigators to remain blinded, all activated partial thromboplastin time–activated clotting times completed to adjust UFH or placebo were performed using an encrypted device (Hemochron Signature Elite machine, International Technidyne Corp).

Blinded treatment with eptifibatide was initiated at the start of PCI, with a 180-μg/kg bolus immediately before PCI, followed by a continuous infusion of 2.0 μg/kg per minute, and

a second 180-µg/kg bolus 10 minutes later. For patients with a creatinine clearance lower than 50 mL/min, the infusion rate was reduced to 1 µg/kg per minute. The infusion was to be given for 18 to 24 hours after PCI or until hospital discharge, whichever came first, with an option for blinded bailout eptifibatide (for those randomized to otamixaban) or placebo (for those originally randomized to UFH plus eptifibatide) to be given only when deemed necessary by the investigator (who remained blinded to all study drugs). If angiography did not lead to PCI, eptifibatide or placebo was not administered and the duration of anticoagulation with UFH and placebo and otamixaban and placebo was left to the investigator's discretion, but could not exceed 4 days or to hospital discharge, whichever came first.

In addition to the blinded study medication, all randomized patients were to receive both aspirin and an oral adenosine diphosphate receptor antagonist (eg, clopidogrel, prasugrel, ticagrelor) in accordance with local label or guidelines.

Outcomes

The primary efficacy outcome was the composite of all-cause death or new myocardial infarction from randomization to day 7. Secondary efficacy outcome measures included the primary outcome up to day 30, the composite of all-cause death, new myocardial infarction, or any stroke from randomization to day 7; rehospitalization or prolongation of hospitalization due to a new episode of myocardial ischemia or myocardial infarction from randomization to day 30; all-cause death from randomization to day 30; and periprocedural and postprocedural thrombotic complications during the index PCI (including postprocedural stent thromboses, categorized according to the Academic Research Consortium classification[15]). Myocardial infarctions were categorized according to the 2007 universal definition.[16] Key efficacy and safety outcomes, including all procedural complications, were adjudicated by a clinical events committee (TIMI Study Group, eAppendix in the Supplement), unaware of treatment assignments, and, in the case of procedural complications, with review of the angiograms.

The primary safety outcome was the composite of Thrombosis in Myocardial Infarction (TIMI) major or minor bleeding (coronary artery bypass graft [CABG]-related and non-CABG-related surgery), measured from randomization through day 7. Other safety outcome measures included CABG-related and non-CABG-related bleedings according to the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO), Bleeding Academic Research Consortium (BARC),[17] and Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Symptoms (CURRENT-OASIS 7)[18] classifications.

Statistical Analysis

Assuming an event rate of the composite of all-cause death or new myocardial infarction through day 7 in the UFH-plus-eptifibatide group of 5.0%, a relative risk (RR) reduction of 25%, a binomial 1-sided (α = .025) superiority test for the comparison of 2 proportions, and a 2-stage adaptive design with 1 interim analysis at 35% fractional information, simulations showed that 13 220 patients (5625 per group for the 2-stage, 2-group study) would yield 88% power for demonstrating the superiority of otamixaban.

At the interim analysis planned after at least 1969 patients had been randomized and reached day 7 follow-up in each group,[14] the otamixaban dose for stage 2 of the trial was selected as described in eFigure 1 in the Supplement. At that time, the rates of the primary efficacy outcome in the higher-dose otamixaban group was 4.7% (the one selected to go forward) and was 5.6% in the UFH-plus-eptifibatide group (adjusted RR, 0.848; 95% CI, 0.662-1.087) but the lower-dose group fulfilled the prespecified criteria for futility with a RR of more than 1 (primary efficacy outcome, 6.3%; RR, 1.130; 95% CI, 0.906-1.408) and was discontinued.

All efficacy analyses and bleeding analyses were performed on the intention-to-treat population, except for thrombotic procedural complications, which were analyzed on the randomized PCI population (ie, all randomized patients who underwent an index PCI). The primary efficacy outcome comparison used the Fisher exact test and a closed testing procedure for ensuring a global 2-sided α level of .05.[14] Secondary outcomes were to be examined in a hierarchical testing procedure if the primary outcome reached statistical significance. Events occurring among patients who received the discontinued otamixaban dose were not considered in primary outcome analyses, which pertained only to participants randomized to the higher dose of otamixaban vs UFH plus eptifibatide, not to the low-dose otamixaban group. There was no prespecified testing for safety variables. For efficacy and safety outcomes, the 6 patients without an event and who were not followed up to day 7 were considered event free at day 7 (for both efficacy and safety events), unless otherwise specified. Continuous variables are reported as medians (interquartile ranges [IQRs]). Categorical variables are reported as frequencies and percentages. Analyses were performed using SAS version 9.2 (SAS Institute Inc).

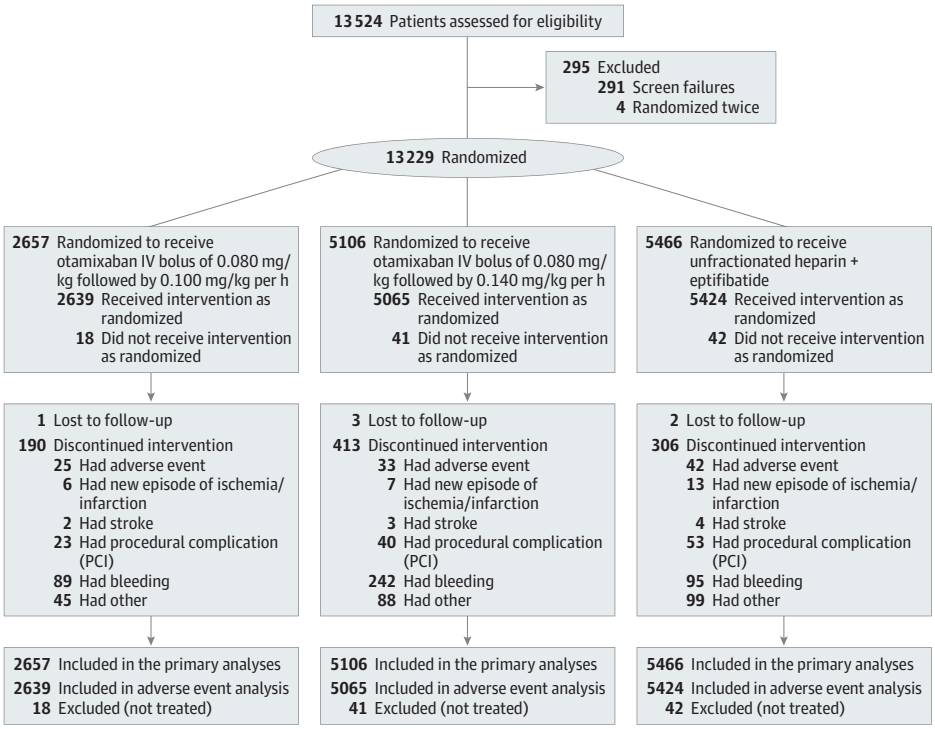
Results

Patient Characteristics and Treatments

Overall, 13 229 patients were randomized into the trial from 568 active sites in 55 countries between April 2010 and February 2013 (**Figure 1**). At the prespecified interim analysis, the data monitoring committee terminated enrollment of patients to the 0.100-mg/kg per hour otamixaban group because of futility (efficacy hazard ratio [HR] >1.0 vs UFH plus eptifibatide) and thus selected the 0.140-mg/kg per hour otamixaban group to continue enrollment until the end of the trial.

The baseline characteristics of the 13 229 randomized patients were well matched between groups and typical of an ACS trial population. Overall, 11 646 patients (88.0%) of the population had elevated biomarkers and 5404 (40.8%)

Figure 1. Patient Flow Chart



The top reasons for screening failure include 75 patients living in countries in which labeling for eptifibatide is not approved for this use, 50 patients who received anticoagulatant treatment or abciximab, 12 patients who would not likely be available for follow-up at 180 days, 10 patients who were unable to discontinue their current anticoagulation in order to transition to investigational products, and 10 patients who could not be treated by aspirin and clopidogrel or another antiplatelet agent according to their country's local labeling. PCI indicates percutaneous coronary intervention.

had electrocardiographic changes; 4994 patients (37.9%) had ST-segment depression of at least 1 mm, 769 (5.8%) had transient ST elevation, and 281 (2.1%) had left bundle-branch block. Approximately 40% of the patients had a GRACE (Global Registry of Acute Coronary Events) risk score higher than 133 points.

Treatments given during the index hospitalization are summarized in **Table 1**, which compares those included in the primary efficacy analysis. Almost all patients received aspirin and an oral adenosine diphosphate receptor antagonist, with a majority taking clopidogrel, with a 600-mg or higher loading dose in 28.2% (n = 3736). The adenosine diphosphate antagonist was almost always (97.3%) administered prior to PCI, at a median interval of 16:00 hours (IQR, 6:37-23:15 hours) before PCI. A total of 8320 patients (62.9%) had received an injectable nonstudy drug anticoagulant in the 24 hours before randomization, mostly low-molecular-weight heparin or UFH. Angiography was performed in 13 125 patients (99.2%) and led to PCI in 8656 patients (65.4%) and to CABG surgery in 682 patients (5.2%). Radial access was used in more than half of the patients in both groups. The median duration of study anticoagulant administration was 4:06 hours (IQR, 3:12-9:44 hours) in the otamixaban group and 4:12 hours (IQR, 3:14-11:50 hours) in the UFH-plus-eptifibatide group. Study anticoagulant was prematurely discontinued in 413 patients (8.1%) in the otamixaban group and in 306 (5.6%) of the UFH plus eptifibatide group ($P < .001$).

Efficacy

Follow-up to day 7 was available for 13 223 (99.95%) of the patients. The primary outcome of death or myocardial infarction through day 7 occurred in 5.5% of the patients treated with otamixaban 0.140 mg/kg per hour vs 5.7% of the patients treated with UFH plus eptifibatide (RR, 0.99 [95% CI, 0.85-1.16]; $P = .93$; **Table 2** and **Figure 2**). Otamixaban did not significantly reduce the risk of any of the components of the primary outcomes, either death or myocardial infarction (of which the vast majority were periprocedural), or of any of the secondary efficacy outcomes (Table 2). The rate of thrombotic procedural complications was 4.0% in patients treated with otamixaban vs 4.6% in patients treated with UFH plus eptifibatide (RR, 0.88 [95% CI, 0.70-1.10]; Table 2; and eTable 2 in the Supplement); in particular, the rates of stent thrombosis were 1.3% vs 1.6% (RR, 0.81; 95% CI, 0.55-1.20) and the rates of catheter or guidewire thrombus were less than 0.1% vs 0.3% (RR, 0.12; 95% CI, 0.02-0.94). Analysis of the primary outcome by 30 days confirmed the absence of a reduction with otamixaban (RR, 1.02 [95% CI, 0.89-1.17]; $P > .99$).

In the lower-dose otamixaban group, discontinued by the data monitoring committee for futility based on the interim analysis, the rate of the primary outcome at day 7 was 6.3% (adjusted RR, 1.11; 95% CI, 0.92-1.33; eFigure 2 in the Supplement). The efficacy and safety outcomes with otamixaban 0.100 mg/kg per hour vs UFH plus eptifibatide are shown in eTable 3 in the Supplement.

Table 1. Baseline Characteristics of the Patients, Procedure Characteristics, and Treatments in the Intention-to-Treat Population According to Treatment Group

Factor	No. (%) of Patients[a]	
	Otamixaban (0.080-mg/kg Bolus and 0.140-mg/kg per Hour Infusion) (n = 5106)	Unfractionated Heparin + Eptifibatide (n = 5466)
Age, median (range), y	62 (25-94)	62 (20-92)
Women	1545 (30.3)	1641 (30.0)
White[b]	4454 (87.2)	4739 (86.7)
Body weight, median (IQR), kg	80 (37-168)	79 (37-198)
BMI, median (range)	27.7 (15.2-65.8)	27.6 (15.1-69.3)
Region		
North America (US and Canada)	663 (13.0)	717 (13.1)
Western Europe	1014 (19.9)	1042 (19.1)
Eastern Europe	1713 (33.5)	1828 (33.4)
Asia	428 (8.4)	490 (9.0)
Other[c]	1288 (25.2)	1389 (25.4)
Baseline creatinine clearance, median (IQR), mL/min[d]	90 (68-115)	89 (68-114)
Medical history		
Diabetes mellitus	1427 (27.9)	1581 (28.9)
Hypertension	3624 (71.0)	3907 (71.5)
Current smoker	1719 (33.7)	1817 (33.3)
Stroke or TIA	267 (5.2)	282 (5.2)
Myocardial infarction	965 (18.9)	1055 (19.3)
Inclusion criteria		
Biomarker elevation[e]	4523 (90.2)	4834 (88.4)
ECG changes[f]	2042 (40.0)	2232 (40.8)
Time since onset of last episode and randomization, median (IQR), h	15 (9-20)	15 (8-20)
TIMI risk score category at baseline[g]		
0-2	1596 (31.3)	1686 (30.8)
3-4	2502 (49.0)	2629 (48.1)
5-7	1008 (19.7)	1151 (21.1)
GRACE risk score category at baseline[h]		
<96	690 (14.5)	714 (14.0)
96-112	872 (18.4)	942 (18.5)
113-133	1353 (28.5)	1426 (27.9)
>133	1831 (38.6)	2023 (39.6)
Anticoagulant use in the 24 h before randomization		
Unfractionated heparin	1538 (30.1)	1668 (30.5)
LMWH	1682 (32.9)	1786 (32.7)
Fondaparinux	185 (3.6)	193 (3.5)
Bivalirudin	2 (<0.1)	1 (<0.1)
Antiplatelet therapy taken within 24 h before randomization (and/or long-term)		
Aspirin	4932 (96.6)	5282 (96.6)
Oral ADP receptor antagonist	4430 (86.8)	4700 (86.0)
Clopidogrel	4186 (82.0)	4467 (81.7)
Prasugrel	126 (2.5)	115 (2.1)
Ticagrelor	151 (3.0)	168 (3.1)
Antiplatelet therapy received between randomization and discharge		
Aspirin	4949 (96.9)	5307 (97.1)
Oral ADP receptor antagonist	4646 (91.0)	4971 (90.9)
Clopidogrel	4294 (84.1)	4602 (84.2)
Prasugrel	251 (4.9)	274 (5.0)
Ticagrelor	205 (4.0)	218 (4.0)

(continued)

Table 1. Baseline Characteristics of the Patients, Procedure Characteristics, and Treatments in the Intention-to-Treat Population According to Treatment Group (continued)

Factor	No. (%) of Patients[a]	
	Otamixaban (0.080-mg/kg Bolus and 0.140-mg/kg per Hour Infusion) (n = 5106)	Unfractionated Heparin + Eptifibatide (n = 5466)
Treatment received between randomization and discharge		
Statin	4692 (91.9)	5050 (92.4)
ACE inhibitor or angiotensin receptor blocker	3915 (76.7)	4240 (77.6)
β-Blocker	4214 (82.5)	4488 (82.1)
Management during the index admission		
Coronary angiography	5054 (99.0)	5432 (99.4)
PCI	3328 (65.2)	3554 (65.0)
CABG surgery	251 (4.9)	295 (5.4)
Neither PCI nor CABG	1475 (28.9)	1583 (29.0)
Access route for angiography		
Femoral	2305 (45.6)	2592 (47.7)
Radial or other	2749 (54.4)	2838 (52.3)
Time between randomization and angiography, median (IQR), min	239 (185-370)	241 (185-396)
Duration of study anticoagulant, median (IQR), min	246 (192-584)	252 (194-710)

Abbreviations: ACE, angiotensin-converting enzyme; ADP, adenosine diphosphate; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CABG, coronary artery bypass graft; ECG, electrocardiogram; GRACE, Global Registry of Acute Coronary Events; IQR, interquartile range; LMWH, low-molecular-weight heparin; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction.

[a] Population sizes vary according to characteristics studied.

[b] Self-reported from a category list.

[c] Argentina, Australia, Brazil, Chile, Colombia, Egypt, Israel, Jordan, Lebanon, Mexico, New Zealand, Panama, Peru, South Africa, Tunisia, Turkey.

[d] Computed using the Cockroft and Gault formula.

[e] Elevation of cardiac biomarkers within 24 hours of randomization, defined as elevated troponin T, troponin I, or creatine kinase MB higher than the upper limit of normal.

[f] New ST-segment depression 0.1 mV or higher (≥1 mm), or transient (<30 min) ST-segment elevation 0.1 mV or higher (≥1 mm) in at least 2 contiguous leads on the ECG.

[g] TIMI score of 0 to 2 indicates low risk of death or ischemic events; 3 to 4, intermediate risk; and 5 or higher, high risk.

[h] GRACE score less than 113 indicates low risk for hospital death; 113 to 139, intermediate risk; and 140 or higher, high risk.

Subgroups

The effect of otamixaban on the primary efficacy outcome was examined across prespecified subgroups and did not differ as a function of baseline characteristics, medical history, prior treatment with antithrombotic agents, disease characteristics, or patient management (**Figure 3**). The outcome also did not differ as a function of baseline risk assessed by the TIMI or GRACE risk scores (nonprespecified subgroups) or as a function of duration of infusion of study drug anticoagulant (subgroup defined after randomization; Figure 3 and eFigure 3A in the Supplement). There was a nonsignificant sex-by-treatment interaction (P = .053).

Safety

Patients in the otamixaban group had an increased rate of the primary safety outcome of TIMI major or minor bleeding at day 7 compared with patients in the combination of UFH-plus-eptifibatide group (3.1% vs 1.5%; RR, 2.13 [95% CI, 1.63-2.78]; P < .001; Table 2). Otamixaban consistently increased all types of bleeding events, regardless of the severity or bleeding classification scheme used (Table 2; and eTable 4 in the Supplement), and without interaction across patient subsets, including demographics, previous treatment, risk scores, biomarkers or management (eFigure 3B and eFigure 4 in the Supplement). Study anticoagulant was discontinued because of bleeding in 242 patients (4.7%) in the otamixaban group and in 95 patients (1.7%) in the UFH-plus-eptifibatide group (P < .001). Except for bleeding, there were no differences in the rate of adverse events or serious adverse events or liver-function abnormalities (eTable 5 in the Supplement). The lower dose of otamixaban (before this dose group was discontinued at the interim analysis) increased the rate of the primary safety outcome (TIMI major or minor bleeding up to day 7) compared with UFH plus eptifibatide (RR, 1.57; 95% CI, 1.13-2.18).

Discussion

Compared with UFH and eptifibatide, otamixaban was not superior in reducing the risk of ischemic outcomes in patients with NSTE-ACS whose conditions were managed with an invasive strategy. Meanwhile, the risk of major or minor bleeding was approximately doubled with otamixaban. These results were consistent across patient subgroups. A lower dose of otamixaban did not achieve better results.

The SEPIA-ACS1 TIMI 42 dose-ranging trial had suggested a clinical benefit of otamixaban in NSTE-ACS, in a population similar to that enrolled in TAO.[12] In a post hoc

Table 2. Efficacy and Safety Outcomes at 7 Days and at 30 Days After Randomization

Outcome	No. (%) of Patients		Relative Risk (95% CI)[a]
	Otamixaban (0.080-mg/kg Bolus and 0.140-mg/kg per Hour Infusion) (n = 5106)	Unfractionated Heparin + Eptifibatide (n = 5466)	
Efficacy outcomes (intent-to-treat population)			
Primary efficacy outcomes: all-cause death or MI at day 7	279 (5.5)	310 (5.7)	0.99 (0.85-1.16)
Components of primary efficacy outcomes			
All-cause death	53 (1.0)	47 (0.9)	1.21 (0.82-1.78)
MI	239 (4.7)	276 (5.0)	0.93 (0.78-1.10)
Type of MI (universal definition[16])[b]			
Type 1	20 (0.4)	31 (0.6)	0.69 (0.39-1.21)
Type 2	0	2 (<0.1)	Not estimable
Type 3	0	0	Not estimable
Type 4a	180 (3.5)	206 (3.8)	0.94 (0.77-1.14)
Type 4b	8 (0.2)	12 (0.2)	0.71 (0.29-1.74)
Type 5	35 (0.7)	28 (0.5)	1.34 (0.82-2.20)
Secondary outcomes			
All-cause death, MI, or stroke at day 7	298 (5.8)	324 (5.9)	0.98 (0.85-1.15)
Procedural thrombotic complications during index PCI	(n = 3328)	(n = 3554)	
Any	134 (4.0)	163 (4.6)	0.88 (0.70-1.10)
Stent thrombosis (ARC[15])	44 (1.3)	58 (1.6)	0.81 (0.55-1.20)
Stroke at day 7	20 (0.4)	16 (0.3)	1.34 (0.69-2.58)
Efficacy outcomes (intent-to-treat population) at day 30			
All-cause death or MI	354 (6.9)	383 (7.0)	1.02 (0.89-1.17)
Rehospitalization or prolonged hospitalization due to new ischemia/MI	81 (1.6)	96 (1.8)	0.90 (0.67-1.21)
All-cause death	90 (1.8)	85 (1.6)	1.17 (0.87-1.58)
MI	288 (5.6)	325 (5.9)	0.95 (0.81-1.11)
Safety outcomes[b]			
Primary safety outcome (TIMI major or minor bleeding at day 7)	159 (3.1)	80 (1.5)	2.13 (1.63-2.78)
TIMI major	89 (1.7)	41 (0.8)	2.32 (1.61-3.36)
Non-CABG-related major	46 (0.9)	21 (0.4)	2.35 (1.40-3.92)
CABG-related major	43 (0.8)	20 (0.4)	2.30 (1.36-3.91)
TIMI minor	71 (1.4)	40 (0.7)	1.90 (1.29-2.79)
Any clinically overt bleed	607 (11.9)	306 (5.6)	2.12 (1.86-2.42)
TIMI requiring medical attention	359 (7.0)	169 (3.1)	2.27 (1.90-2.72)
TIMI minimal	136 (2.7)	55 (1.0)	2.65 (1.94-3.61)
Intracranial bleeding	5 (<0.1)	1 (<0.1)	5.35 (0.63-45.80)

Abbreviations: ARC, Academic Research Consortium; CABG, coronary artery bypass graft; CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; UFH, unfractionated heparin.

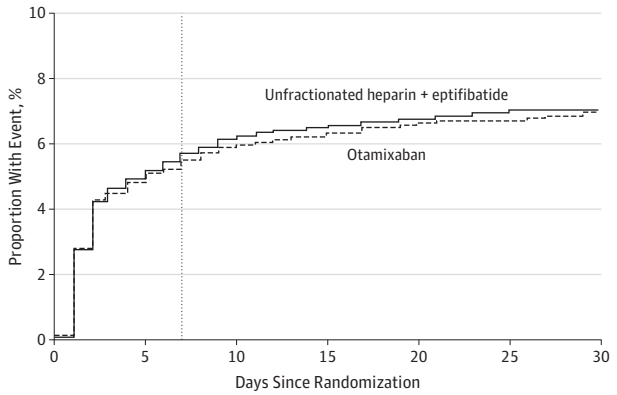
[a] vs Unfractionated heparin and eptifibatide.

[b] A patient can be counted in several categories: type 1, spontaneous MI; type 2, MI secondary to ischemia; type 3, sudden unexpected cardiac death; type 4a, MI associated with PCI; type 4b, MI associated with stent thrombosis; type 5, MI associated with CABG surgery.

analysis, a 44% to 48% RR reduction in death or myocardial infarction was seen in the midrange doses compared with UFH plus eptifibatide, similar to those tested in the TAO trial. However, even though SEPIA-ACS1 was a large, dose-ranging trial, with 3241 patients, there were only 17 to 22 deaths or myocardial infarctions in each group; consequently, there were wide confidence intervals around the point estimates for effect size, which overlap the effect seen in TAO (eFigure 5 in the Supplement). Moreover, in a dose-ranging trial, a relatively high event rate in the UFH-plus-eptifibatide group can falsely inflate the estimated treatment effect across multiple experimental groups, hence the need for a definitive phase 3 trial such as TAO, with 15-fold more outcomes per group.

Another difference between the 2 trials is the dosing of eptifibatide: in SEPIA-ACS1[12] a single bolus was administered at randomization, whereas in TAO eptifibatide was given as a double bolus but only in patients undergoing PCI, as recommended in guidelines.[1,2] This difference may have affected efficacy and safety, explaining in particular why the excess risk of bleeding with otamixaban appeared greater in TAO than in SEPIA-ACS1. The rates of death or myocardial infarction were slightly

Figure 2. Kaplan-Meier Analyses of the Primary Efficacy Outcome for Otamixaban, 0.140 mg/kg per Hour vs Control



No. at risk				
Otamixaban	5106	4801	4766	4747
Unfractionated heparin + eptifibatide	5466	5132	5097	5080

Dotted line indicates day 7. Primary efficacy outcomes include all-cause death or myocardial infarction at day 7.

higher in TAO than in SEPIA-ACS1, possibly reflecting the increased sensitivity of troponins. In SEPIA-ACS1, myocardial infarctions were evenly distributed between spontaneous and periprocedural, whereas in TAO approximately three-quarters of the myocardial infarctions were periprocedural. The ability of any anticoagulant (as opposed to antiplatelet therapy) to affect the proportion of patients exhibiting peri-PCI elevation in the era of more sensitive cardiac biomarkers of necrosis may be more limited.

Procedural thrombotic complications were increased at lower doses of otamixaban in SEPIA-ACS1[12] and thus played an important role in selecting the dose for phase 3. The TAO study confirmed that with sufficiently high doses of intravenous Xa inhibition, procedural thrombotic complications do not appear to be an issue. In TAO, the rate of guidewire or catheter thrombosis was lower with otamixaban. This contrasts with previous experiences with low doses of an Xa inhibitor with fondaparinux in the OASIS-7 trial[19] and may be related to the relatively high dose of otamixaban used in this trial, which was associated with increased bleeding compared with UFH plus eptifibatide.

Despite the limitations of UFH as an anticoagulant,[8] no single agent has emerged as an unambiguous standard of care for anticoagulation in NSTE-ACS, and guidelines offer several options, with UFH, bivalirudin, low-molecular-weight heparin, or fondaparinux.[1,2] Consequently, there is marked variation in the use of anticoagulants for ACS, with frequent overlap between multiple anticoagulants, particularly when ACS patients proceed to PCI.[20-25] Otamixaban is theoretically attractive as anticoagulant for NSTE-ACS: it is an injectable agent with rapid onset and offset, modest renal elimination, and predictable anticoagulant effect that obviates the need for monitoring. The TAO results, however, demonstrate lack of efficacy benefit but marked increases in bleeding when compared with UFH plus a glycoprotein IIb/IIIa receptor inhibitor, even with the majority of patients undergoing transradial PCI.

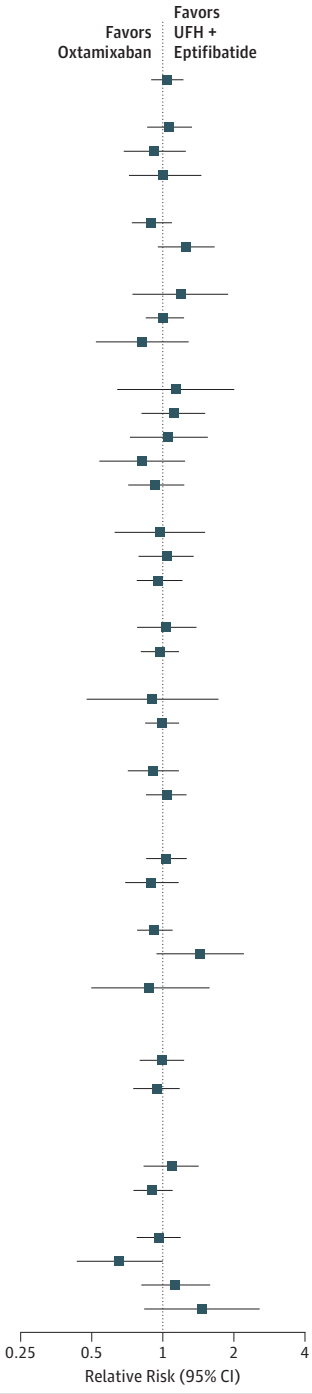
The lack of difference between otamixaban and UFH plus eptifibatide was not related to lack of power. In fact, the global study power based on the observed event rate in the UFH-plus-eptifibatide group was 90.3%, higher than the planned 88% power.[14] TAO was a superiority trial, and although there is the possibility that otamixaban might have achieved noninferiority to UFH plus eptifibatide, the consistent increase in bleeding makes use of otamixaban a nonviable clinical option, and it is unlikely that a higher otamixaban dose would have achieved superior efficacy results without intolerable bleeding. Conversely, a reduced dose also had increased bleeding compared with UFH plus eptifibatide, with numerically higher rates of ischemic outcomes than UFH plus glycoprotein IIb/IIIa receptor inhibitor. These results suggest a narrow therapeutic window for acute Xa inhibition and that increasing the intensity of anticoagulation via this mechanism will not achieve superior efficacy-safety balance in ACS in the modern era of intervention, when patients are receiving combined injectable anticoagulation, dual antiplatelet therapy, and routine early intervention.

Study Limitations

Most patients (62.9%) had received injectable anticoagulation before randomization, and the duration between onset of the ischemic episode and randomization was more than 12 hours in a majority of patients. Conversely, the duration of study drug infusion was relatively brief, reflecting the short interval between presentation and angiography in contemporary practice and therefore the limited time for novel agents to bring differential benefit. Both these factors would tend to attenuate the effect of study treatment on outcomes. However, exclusion of patients who had received a prior anticoagulant would have made enrollment extremely challenging, and delaying angiography to maximize study drug duration would be impractical and possibly unethical. Furthermore, these limitations were also present in SEPIA-ACS1, and, within TAO, the treatment effects did not appear affected by pretreatment with anticoagulation or

Figure 3. Selected Subgroup Analysis of the Primary Efficacy Outcome at Day 7 in the Otamixaban, 0.140 mg/kg per Hour Group vs Control

Subgroup	No. With Primary Outcome/ Total No. of Patients: Otamixaban 0.140 mg/kg/h	No. With Primary Outcome/ Total No. of Patients: UFH/ Eptifibatide	Relative Risk (95% CI)	*P* Value for Intervention
Overall	279/5106	310/5466	0.99 (0.85-1.16)	
Age, y				
<65	148/3019	155/3205	1.01 (0.81-1.26)	
65-<75	75/1325	92/1428	0.88 (0.65-1.18)	.75
≥75	56/762	63/833	0.97 (0.69-1.37)	
Sex				
Men	175/3561	218/3825	0.86 (0.71-1.05)	.05
Women	104/1545	92/1641	1.20 (0.91-1.58)	
Weight, kg				
<60	35/416	33/448	1.14 (0.72-1.80)	
60-<100	210/3997	234/4342	0.97 (0.81-1.17)	.51
≥100	33/687	41/670	0.78 (0.50-1.23)	
Geographic region				
Asia	22/428	23/490	1.10 (0.62-1.94)	
Eastern Europe	79/1713	79/1828	1.07 (0.79-1.45)	
Western Europe	52/1014	52/1042	1.03 (0.71-1.49)	.78
North America	36/663	49/717	0.79 (0.52-1.21)	
Other	90/1288	107/1389	0.91 (0.69-1.19)	
Creatine clearance, mL/min				
<50	34/439	39/475	0.94 (0.61-1.47)	
50-80	94/1510	101/1628	1.00 (0.76-1.32)	.93
>80	147/3115	167/3321	0.94 (0.76-1.16)	
Diabetes mellitus history				
Yes	82/1427	90/1581	1.01 (0.75-1.35)	.71
No	197/3679	220/3885	0.95 (0.78-1.14)	
TIA/stroke history				
Yes	16/267	19/282	0.89 (0.47-1.69)	.80
No	263/4837	291/5181	0.97 (0.82-1.14)	
Prior aspirin				
Yes	106/2059	131/2259	0.89 (0.69-1.14)	.41
No	173/3047	179/3207	1.02 (0.83-1.25)	
Anticoagulant ≤24 h before randomization				
Yes	177/3201	186/3420	1.02 (0.83-1.24)	.39
No	102/1905	124/2046	0.88 (0.68-1.14)	
Patient management[a]				
With PCI index	210/3328	246/3554	0.91 (0.76-1.09)	
CABG surgery index	41/251	34/295	1.42 (0.93-2.16)	.16
PCI or index CABG without index[a]	21/1475	26/1583	0.87 (0.49-1.53)	
Access site or index PCI[a]				
Femoral	137/2381	156/2654	0.98 (0.78-1.22)	.78
Nonfemoral	135/2673	150/2776	0.93 (0.75-1.17)	
Time from ischemic episode to randomization, h				
<12	99/1856	101/2053	1.08 (0.83-1.42)	.28
≥12	180/3246	209/3409	0.90 (0.75-1.10)	
Duration of study drug, h[a]				
<5	153/3149	169/3321	0.95 (0.77-1.18)	
5-<12	35/734	55/752	0.65 (0.43-0.98)	.09
12-<24	66/807	63/869	1.13 (0.81-1.57)	
≥24	25/373	22/481	1.47 (0.84-2.56)	



The x-axis is on a logarithmic scale. Primary efficacy outcomes include all-cause death or myocardial infarction at day 7. CABG indicates coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; and UFH, unfractionated heparin.
[a]Defined after randomization.

according to duration elapsed between the last ischemic episode and randomization. In routine clinical practice, many patients with ACS do not receive glycoprotein IIb/IIIa receptor inhibitors.[20-22] Therefore, otamixaban, compared with UFH alone, might have achieved superior efficacy; however, this benefit would likely have been achieved at the expense of a higher increase in bleeding risk. Almost all patients in this trial and in SEPIA-ACS 1 were treated with clopidogrel; the efficacy and safety of potentially lower doses of otamixaban on a background of stronger adenosine diphosphate receptor blockade remain unknown. Unfractionated heparin plus eptifibatide was selected as the control treatment. Other regimens might have offered a different benefit-risk profile,[13,19,26,27] but because otamixaban did not display superior efficacy and did show worse safety, this point is moot.

Conclusion

Otamixaban did not reduce ischemic events compared with UFH plus eptifibatide but increased bleeding among patients with NSTE-ACS and a planned invasive strategy. These findings do not support the use of otamixaban for patients with NSTE-ACS undergoing planned early percutaneous coronary intervention.

ARTICLE INFORMATION

Group Information: The TAO investigators members are listed in the eAppendix in the Supplement.

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Author Affiliations: Université Paris-Diderot, Sorbonne-Paris Cité, Paris, France, INSERM U-698, Paris, France, Département Hospitalo-Universitaire FIRE, Hôpital Bichat, Assistance Publique–Hôpitaux de Paris, Paris, France (Steg); McMaster University and the Population Health Research Institute, Hamilton Health Sciences, Hamilton, Ontario, Canada (Mehta); Department of Emergency Medicine, Pennsylvania Hospital, University of Pennsylvania, Philadelphia (Pollack); Medizinische Universitatsklinik, Freiburg, Germany (Bode); Division of Cardiology, Newark Beth Israel Medical Center, Mount Sinai School of Medicine, Newark, New Jersey (Cohen); David Geffen School of Medicine at UCLA, Torrance, California (French); Wake Forest Baptist Health, Winston-Salem, North Carolina (Hoekstra); The Duke Clinical Research Institute, Durham, North Carolina (Rao); Institute of Cardiology, Warsaw, Poland (Ruzyllo); Servicio de Cardiología, Hospital General Universitario de Alicante, Alicante, Spain (Ruiz-Nodar); Servicio de Cardiologia, Hospital Clinic, IDIBAPS; Barcelona, Spain (Sabaté); Cardiocenter, Third Faculty of Medicine, Charles University, Prague, Czech Republic (Widimsky); Department of Cardiology, Military Hospital, Budapest, Hungary (Kiss); Hospital Italiano de Buenos Aires, Buenos Aires, Argentina (Estrada); Leviev Heart Center, Chaim Sheba Medical Center, Tel Hashomer, Israel (Hod); Seth GS Medical College & KEM Hospital Parel, Mumbai, India (Kerkar); Department of Cardiology, Faculty of Medicine, Dokuz Eylül University, Izmir, Turkey (Guneri); Department of Cardiology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey (Sezer); Cardiovascular Division, Cardiology Research Center, Moscow, Russian Federation (Ruda); Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil (Nicolau); Ospedale Santa Maria della Misericordia, Perugia, Italy (Cavallini); Netcare Unitas HospitalNetcare Unitas Hospital, Centurion, Gauteng, South Africa (Ebrahim); Clinic of Cardiology and Angiology, Tokuda Hospital, Sofia, Bulgaria (Petrov); Department of Cardiology, The Catholic University of Korea College of Medicine, Seoul (Kim); Chonnam National University Hospital, Gwangju, Republic of Korea (Jeong); Hospital Civil Dr Juan I Menchaca, Guadalajara, Mexico (Lopez); North-Estonia Medical Center Foundation, Tallinn (Laanmets); Internal Clinic, University Hospital, Martin, Slovak republic (Kovar); sanofi R&D, Paris, France (Gaudin, Fanouillere, Minini); sanofi, Bridgewater, New Jersey (Moryusef); TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Hoffman, Wiviott, Sabatine).

Author Contributions: Dr Steg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Steg, Mehta, Pollack, Bode, Cohen, Hod, Gaudin, Fanouillere, Wiviott, Sabatine.
Acquisition of data: Steg, Mehta, Pollack, Bode, Cohen, Hoekstra, Rao, Ruzyllo, Ruiz-Nodar, Sabaté, Widimsky, Navarro Estrada, Kerkar, Guneri, Sezer, Cavallini, Ebrahim, Petrov, Kim, Jeong, Ramos Lopez, Laanmets, Kovar, Moryusef.
Analysis and interpretation of data: Steg, Mehta, French, Kiss, Ruda, Nicolau, Cavallini, Gaudin, Fanouillere, Minini, Hoffman, Wiviott, Sabatine.
Drafting of the manuscript: Steg, Jeong, Fanouillere, Minini, Moryusef.
Critical revision of the manuscript for important intellectual content: Steg, Mehta, Pollack, Bode, Cohen, French, Hoekstra, Rao, Ruzyllo, Ruiz-Nodar, Sabaté, Widimsky, Kiss, Navarro Estrada, Hod, Kerkar, Guneri, Sezer, Ruda, Nicolau, Cavallini, Ebrahim, Petrov, Kim, Ramos Lopez, Laanmets, Kovar, Gaudin, Fanouillere, Minini, Hoffman, Wiviott, Sabatine.
Statistical analysis: Jeong, Fanouillere, Minini, Hoffman, Wiviott, Sabatine.
Obtained funding: Steg, Gaudin, Moryusef, Sabatine.
Administrative, technical, or material support: Steg, Cohen, Hoekstra, Rao, Navarro Estrada, Ebrahim, Gaudin, Moryusef.
Study supervision: Steg, Hoekstra, Ruiz-Nodar, Kiss, Navarro Estrada, Sabaté, Kim, Kovar, Gaudin, Wiviott.

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Drs Ruzyllo, Sezer, Ruda, Ebrahim, Petrov, Jeong, Ramos Lopez, Kovar, and Minini reported no conflicts.

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Role of Sponsor: The trial was designed and conducted as a collaboration between the sponsor and the academic executive committee. The sponsor was responsible for data collection and management. The data were analyzed in parallel by the sponsor and the TIMI Study Group, which had an independent copy of the trial database and verified all analyses;data interpretation was performed in parallel by the sponsor and the executive committee. The sponsor provided editorial assistance for manuscript preparation and reviewed the manuscript and offered nonbinding comments. Approval of the manuscript and the decision to submit the manuscript for publication was made by the executive committee.

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