TAO : Treatment of Acute Coronary Syndromes with Otamixaban

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clinicaltrials.gov : NCT01076764

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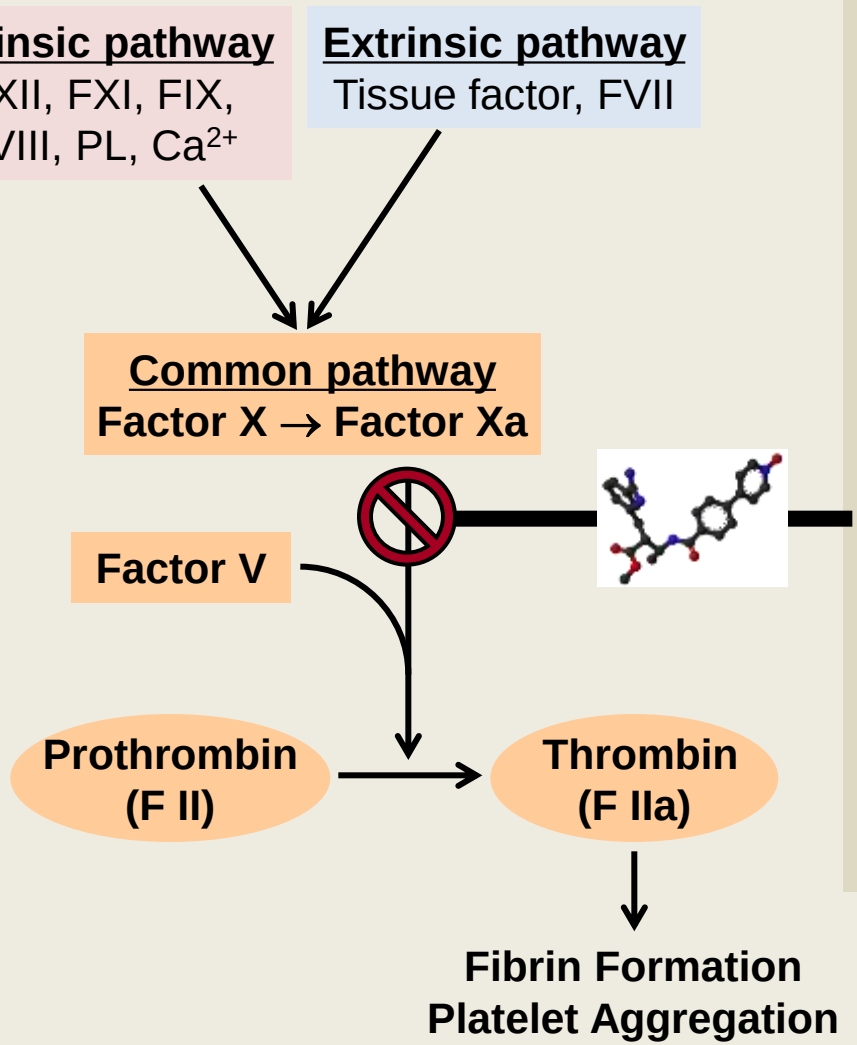
Background

- Anticoagulation is an important therapy for NSTE-ACS, but there is no accepted gold standard, and all existing options (UFH, bivalirudin, enoxaparin, fondaparinux) have limitations

- Otamixaban, a novel injectable factor Xa antagonist, has shown promise in a phase II dose-ranging trial – SEPIA-ACS1 TIMI 42[1] – when compared with UFH plus eptifibatide

[1]Sabatine MS, *et al. Lancet* 2009;374:787-795



OTAMIXABAN

- **Specific, direct, IV, Factor Xa inhib**
  - **Proximal inhib of coag cascade**
- **Small molecule**
  - **Inhibits clot-bound factor Xa, which is inaccessible to large molecules & indirect inhibitors**
- **Favourable PK/PD profile**
  - **Short-acting (half-life 30 min)**
  - **Weight-based bolus & infusion**
  - **No need for monitoring**
  - **No significant renal elimination**

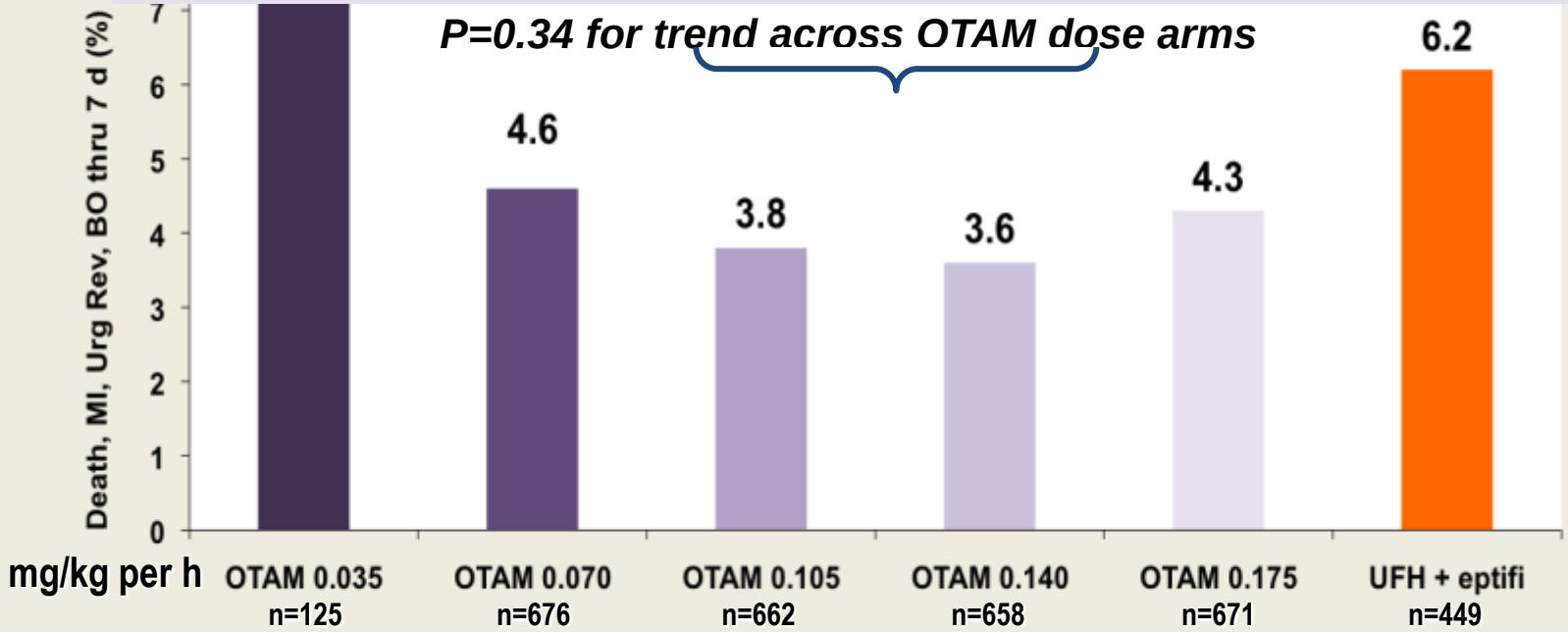
Background

Primary efficacy endpoint of SEPIA ACS

Death, MI, urgent revascularization, or bailout GP IIb/IIIa

RR vs UFH (95% CI)	1.16 (0.56-2.38)	0.74 (0.45-1.21)	0.61 (0.36-1.02)	0.58 (0.34-0.996)	0.69 (0.42-1.15)

At mid range doses, Death or MI reduction: RR 0.54 (95% CI 0.32-0.91)
***P*=0.02**



Sabatine MS, *et al. Lancet* 2009;374:787-795

Study design

Moderate- to high-risk NSTE-ACS with planned early invasive strategy (n=13,220)

Aspirin + ADP receptor antagonist at or before randomization

R

Otamixaban 0.08+0.10 (n=1969)

Otamixaban 0.08+0.140 (n=1969)

UFH + eptifibatide (n=1969)

Interim analysis
One dose goes forward*

*Selected by DSMB while maintaining the blind

(n=5625)

(n=5625)

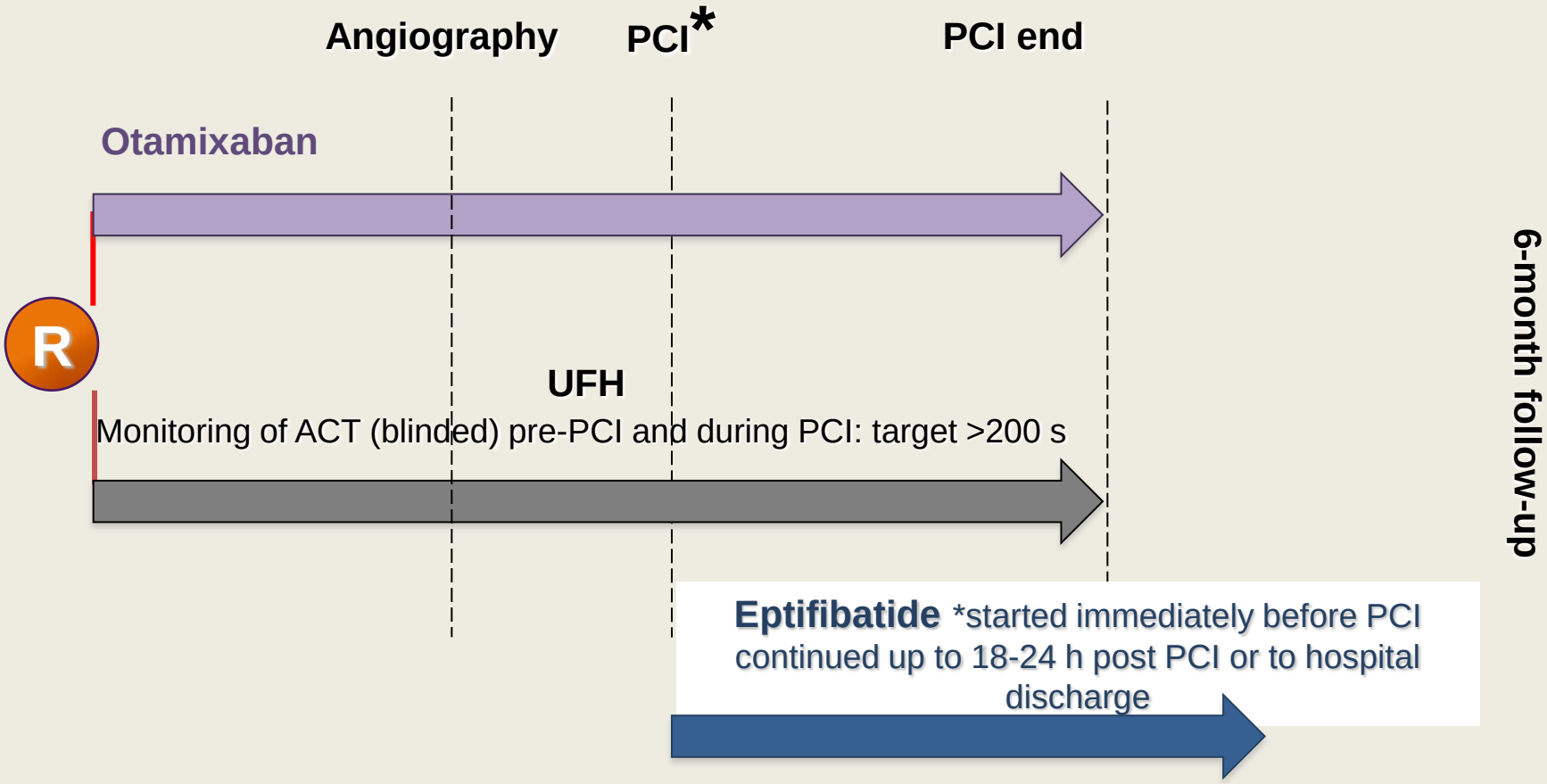
Double-blind, triple-dummy study

Primary efficacy endpoint: death/MI at day 7
Primary safety endpoint: TIMI major +minor bleeds at day 7

ClinicalTrial.gov ID: NCT01076764.

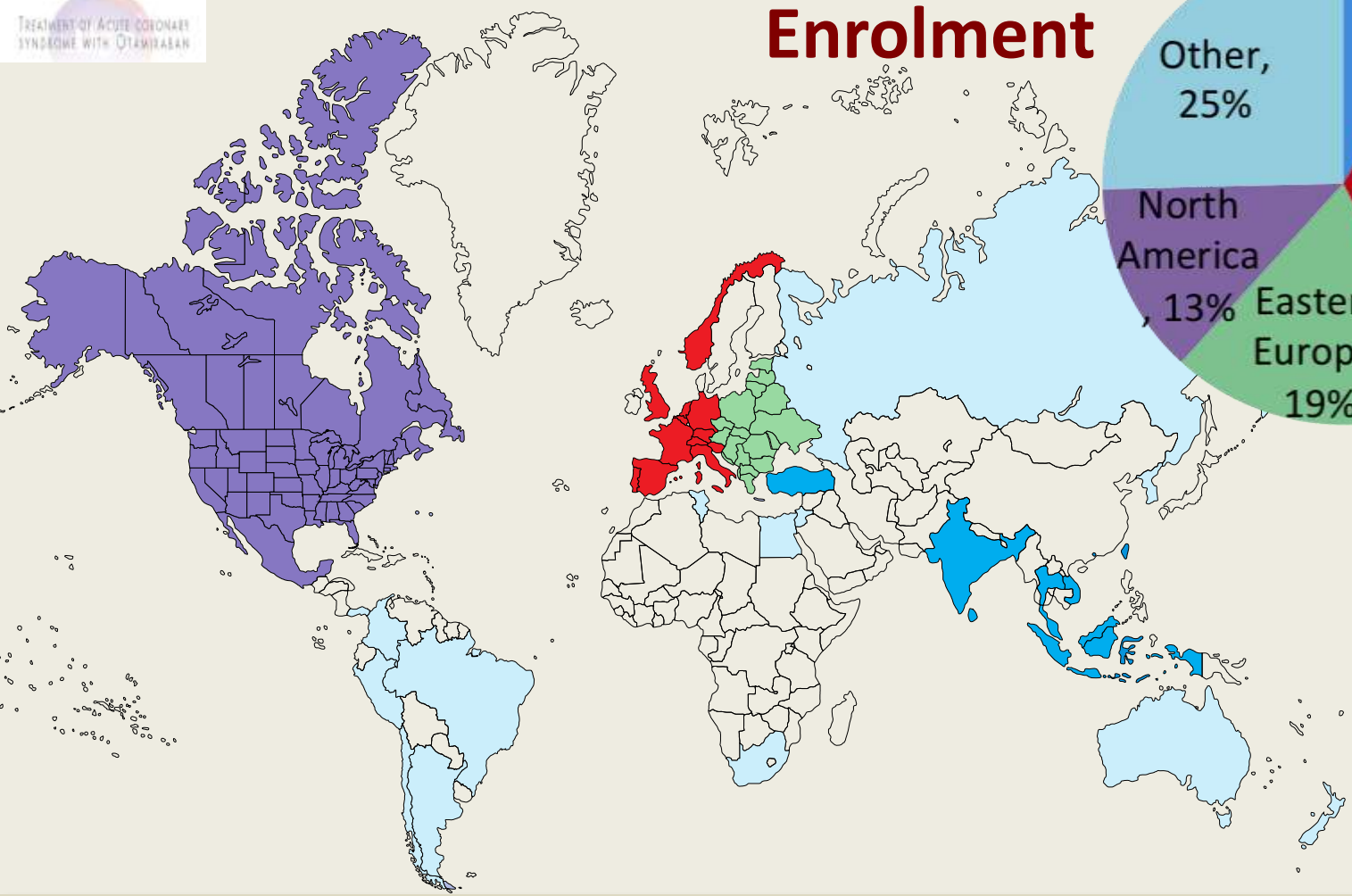
Steg PG, *et al.* ***Am Heart J*** 2012;164:817-24

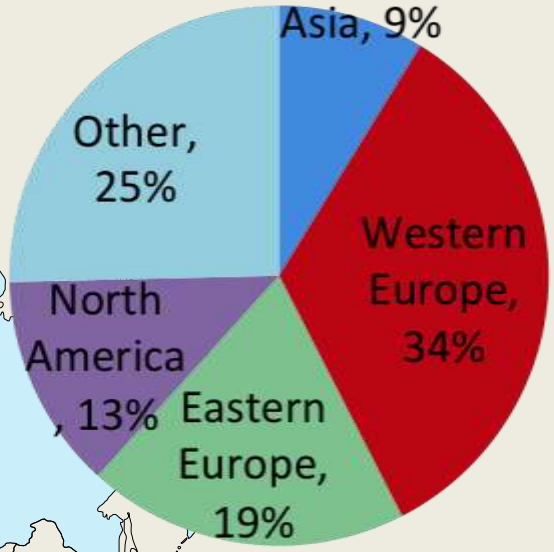
Treatments



*If no PCI is performed, otamixaban and UFH can be continued as per investigator's judgment and up to day 4 maximum. Eptifibatide is withheld.

Enrolment





13,229 patients randomized into the trial from 568 active sites in 55 countries between April 2010 and February 2013

Follow-up available in 13,223 (99.9%)

Patient baseline characteristics

Factor	Otamixaban 0.080 mg/kg bolus and 0.140 mg/kg/hour infusion (n=5106)	UFH plus eptifibatide (n=5466)
Age, y, median (min, max)	62 (25, 94)	62 (20, 92)
Women, %	30.3	30.0
Caucasian/white, %	87.2	86.7
Body weight, kg, median (IQR)	80 (37-168)	79 (37-198)
Creatinine Cl mL/min	90 (68-115)	89 (68-114)
Medical history, %		
Diabetes mellitus	27.9	28.9
Hypertension	71.0	71.5
Current smoker	33.7	33.3
Stroke or TIA	5.2	5.2
Myocardial infarction	18.9	19.3

Population sizes vary according to characteristics studied

Patients and procedure characteristics, and treatments

Factor, % or median (IQR)[1]	Otamixaban 0.080 mg/kg bolus and 0.140 mg/kg/h infusion (n=5106)	UFH plus eptifibatide (n=5466)
Inclusion criteria		
Biomarker elevation	90.2	88.4
ECG changes	40.0	40.8
Time since onset of last episode and randomization, h	15 (9, 20)	15 (8, 20)
Anticoagulant use in the 24 h before randomization		
Unfractionated heparin	30.1	30.5
LMWH	32.9	32.7
Fondaparinux	3.6	3.5
Bivalirudin	<0.1	<0.1
Antiplatelet therapy[2]		
Aspirin	96.6	96.6
Oral ADP receptor antagonist	86.8	86.0
Clopidogrel	82.0	81.7
Prasugrel	2.5	2.1
Ticagrelor	3.0	3.1

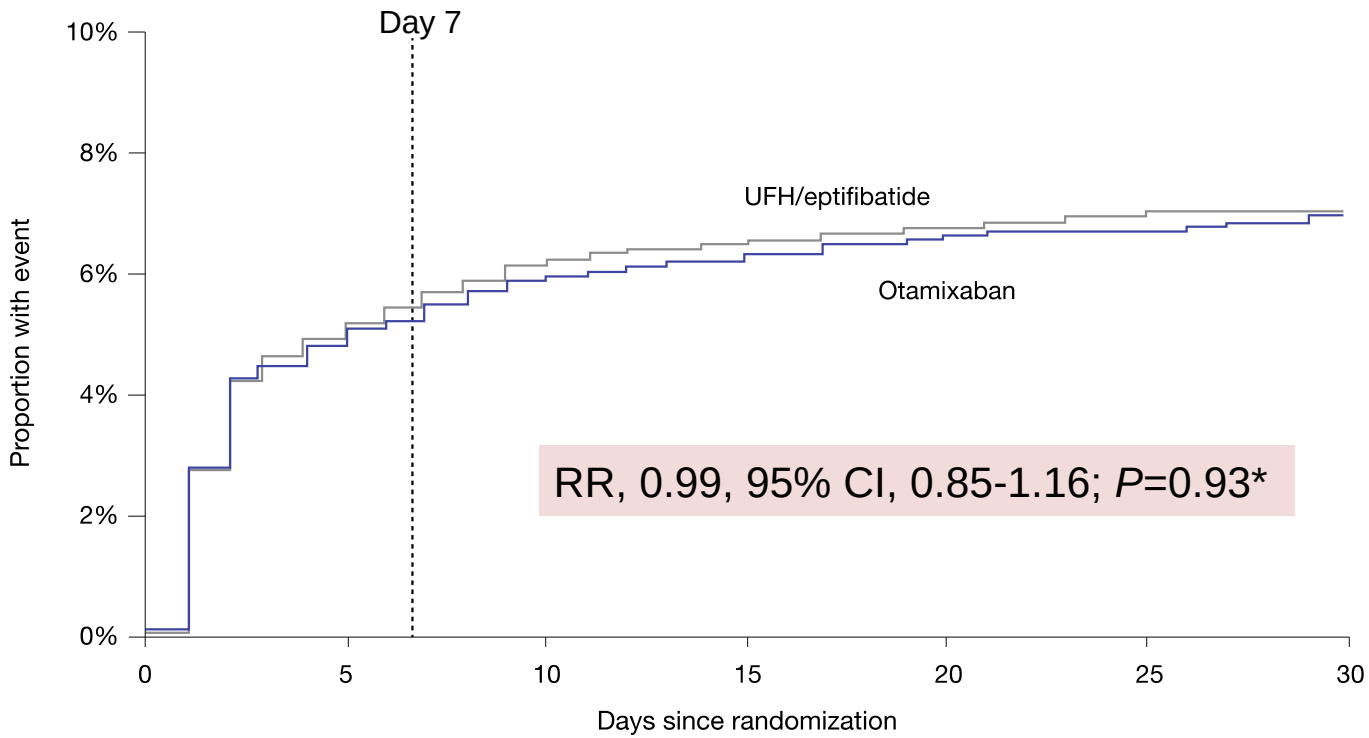
[1]Population sizes vary according to characteristics studied . [2]Taken within 24 h before randomization (and/or chronically)

Patients and procedure characteristics, and treatments

Factor, % or median (IQR)	Otamixaban 0.080 mg/kg bolus and 0.140 mg/kg/h infusion (n=5106)	UFH plus eptifibatide (n=5466)
Management during the index admission		
Coronary angiography	99.0	99.4
Percutaneous coronary intervention	65.2	65.0
CABG	4.9	5.4
Neither	28.9	29.0
Access route for angiography		
Femoral	45.6	47.7
Radial or other	54.4	52.3
Time between randomization and angiography, min	239 (185-370)	241 (185-396)
Duration of study anticoagulant, min	246 (192-584)	252 (194-710)

Population sizes vary according to characteristics studied

Primary efficacy outcome for otamixaban 0.140 mg/kg per hour vs control



No. at Risk	Day 0	Day 10	Day 20	Day 30
Otamixaban	5106	4801	4766	4747
UFH + eptifibatide	5466	5132	5097	5080

*Fisher's exact test

Efficacy outcomes at 7 days after randomization

Outcome, No. (%)	Otamixaban 0.080 mg/kg bolus and 0.140 mg/kg/h infusion (n=5106)	UFH plus eptifibatide (n=5466)	Relative risk (95% CI)
Primary outcome **All-cause death or MI at day 7**	279 (5.5)	310 (5.7)	0.99 (0.85-1.16)
Components of primary outcome			
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)
Secondary outcomes			
All-cause death, MI, or stroke at day 7	298 (5.8)	324 (5.9)	0.98 (0.85-1.15)
Stroke at day 7	20 (0.4)	16 (0.3)	1.34 (0.69-2.58)
Type of MI (universal definition)[1]			
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)

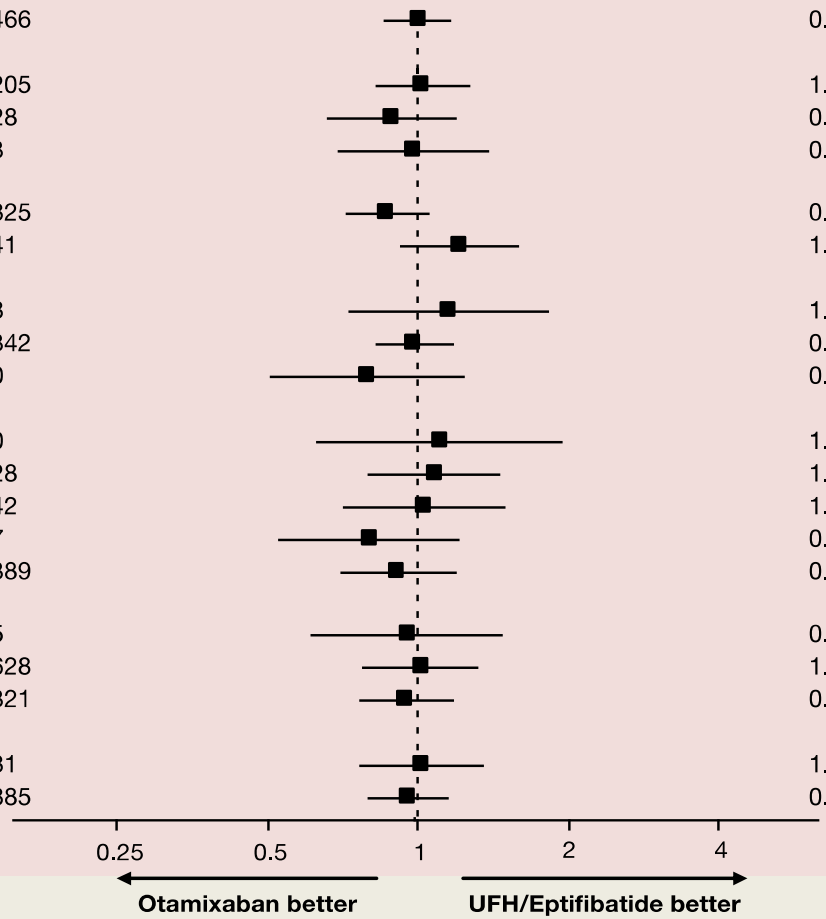
[1]A patient can be counted in several categories.

Thrombotic procedural complications during PCI

Outcome, No. (%)	Otamixaban 0.080 mg/kg bolus and 0.140 mg/kg/h infusion (n=3328)	UFH plus eptifibatide (n=3554)	Relative risk (95% CI)
Any, including stent thrombosis	134 (4.0)	163 (4.5)	0.88 (0.70-1.10)
Abrupt or threatened closure	11 (0.3)	15 (0.4)	0.78 (0.36-1.70)
Side branch closure	13 (0.4)	17 (0.5)	0.82 (0.40-1.68)
Distal embolization	29 (0.9)	33 (0.9)	0.94 (0.57-1.54)
No or slow reflow	57 (1.7)	54 (1.5)	1.13 (0.78-1.63)
New intracoronary thrombus	16 (0.5)	27 (0.8)	0.63 (0.34-1.17)
Catheter or guidewire thrombus	1 (<0.1)	9 (0.3)	0.12 (0.02-0.94)
Stent thrombosis (ARC definition)	44 (1.3)	58 (1.6)	0.81 (0.55-1.20)
Definite	21 (0.6)	32 (0.9)	0.70 (0.40-1.21)
Probable	15 (0.5)	17 (0.5)	0.94 (0.47-1.88)
Possible	8 (0.2)	9 (0.3)	0.95 (0.37-2.46)

Prespecified subgroup analyses of primary efficacy outcome at day 7 in otamixaban† vs control (1)

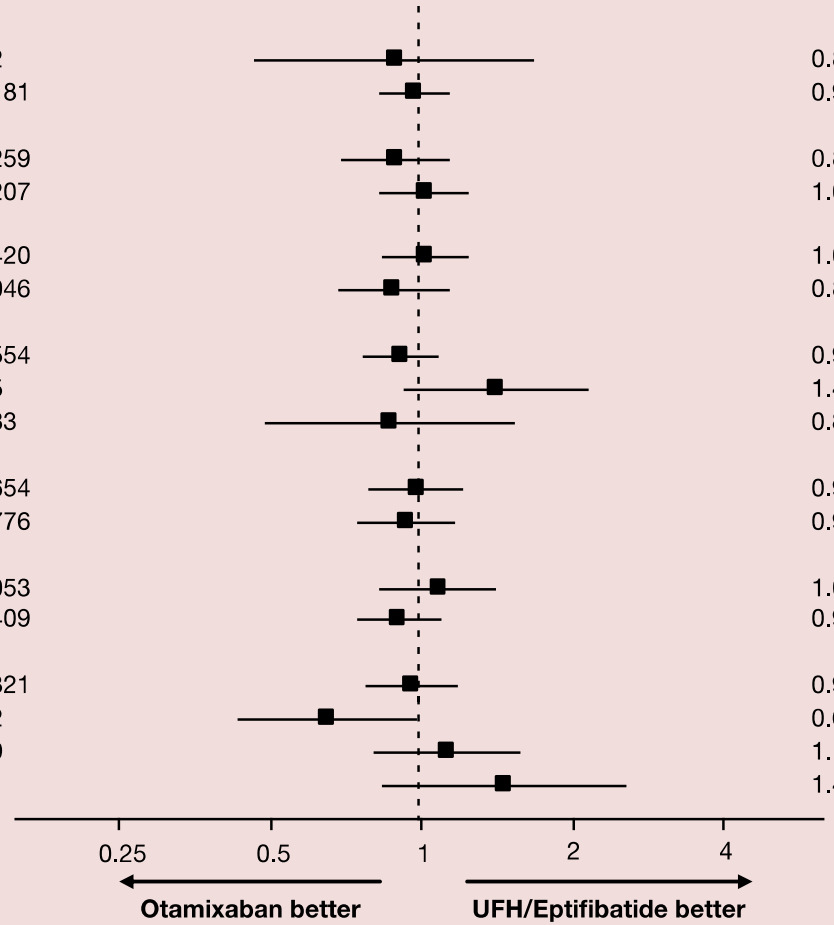
Subgroup	Otamixaban 0.140 mg/kg/h	UFH/Eptifibatide	Relative risk (95% CI)	P Value for Interaction
Overall	279/5106	310/5466	0.99 (0.85-1.16)	
Age (years)				0.75
<65	148/3019	155/3205	1.01 (0.81-1.26)	
65-75	75/1325	92/1428	0.88 (0.65-1.18)	
≥75	56/762	63/833	0.97 (0.69-1.37)	
Sex				0.05
Male	175/3561	218/3825	0.86 (0.71-1.05)	
Female	104/1545	92/1641	1.20 (0.91-1.58)	
Weight (kg)				0.51
<60	35/416	33/448	1.14 (0.72-1.80)	
60-100	210/3997	234/4342	0.97 (0.81-1.17)	
≥100	33/687	41/670	0.78 (0.50-1.23)	
Geographic region				0.78
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)	
North America	36/663	49/717	0.79 (0.52-1.21)	
Other	90/1288	107/1389	0.91 (0.69-1.19)	
Creatinine clearance (ml/min)				0.93
<50	34/439	39/475	0.94 (0.61-1.47)	
50-80	94/1510	101/1628	1.00 (0.76-1.32)	
>80	147/3115	167/3321	0.94 (0.76-1.16)	
Diabetes mellitus history				0.71
Yes	82/1427	90/1581	1.01 (0.75-1.35)	
No	197/3679	220/3885	0.95 (0.78-1.14)	



Logarithmic scale †0.140 mg/kg per h

Prespecified subgroup analyses of primary efficacy outcome at day 7 in otamixaban† vs control (2)

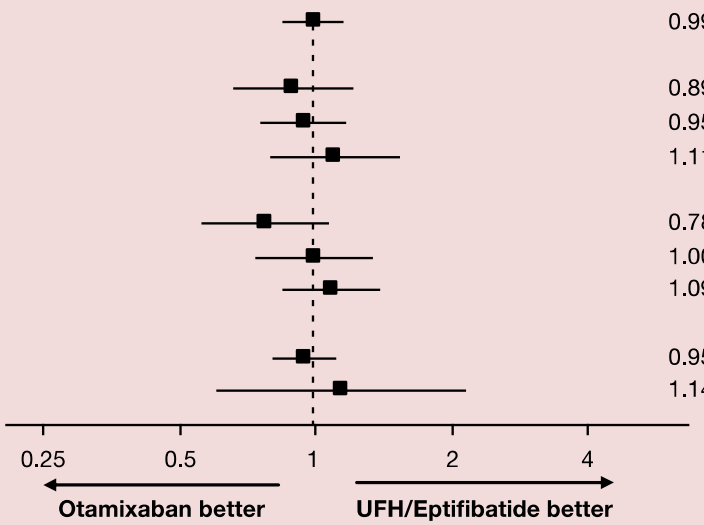
Subgroup	Otamixaban 0.140 mg/kg/h	UFH/Eptifibatide	Relative risk (95% CI)	P Value for Interaction
TIA/stroke history				0.80
Yes	16/267	19/282	0.89 (0.47-1.69)	
No	263/4837	291/5181	0.97 (0.82-1.14)	
Prior aspirin				0.41
Yes	106/2059	131/2259	0.89 (0.69-1.14)	
No	173/3047	179/3207	1.02 (0.83-1.25)	
Anticoagulant ≤24h before randomization				0.39
Yes	177/3201	186/3420	1.02 (0.83-1.24)	
No	102/1905	124/2046	0.88 (0.68-1.14)	
Patient management*				0.16
With index PCI	210/3328	246/3554	0.91 (0.76-1.09)	
With index CABG	41/251	34/295	1.42 (0.93-2.16)	
Without index PCI or index CABG	21/1475	26/1583	0.87 (0.49-1.53)	
Access site of index PCI*				0.78
Femoral	137/2381	156/2654	0.98 (0.78-1.22)	
Non-femoral	135/2673	150/2776	0.93 (0.75-1.17)	
Time from ischemic episode to randomization				0.28
<12h	99/1856	101/2053	1.08 (0.83-1.42)	
≥12h	180/3246	209/3409	0.90 (0.75-1.10)	
Duration of study drug*				0.09
<5h	153/3149	169/3321	0.95 (0.77-1.18)	
5-12h	35/734	55/752	0.65 (0.43-0.98)	
12-24h	66/807	63/869	1.13 (0.81-1.57)	
≥ 24h	25/373	22/481	1.47 (0.84-2.56)	



*Defined post randomization. †0.140 mg/kg per h

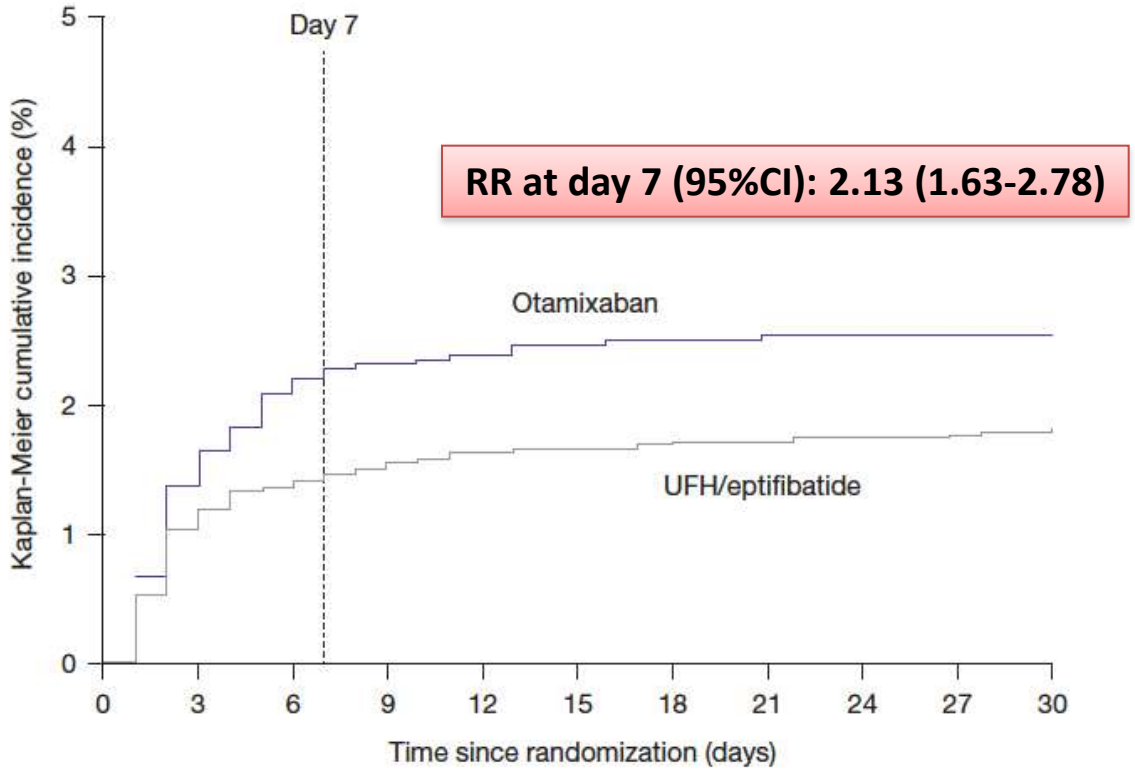
Post-hoc subgroup analyses of primary efficacy outcome at day 7

Subgroup	Otamixaban 0.140 mg/kg/h	UFH/Eptifibatide	Relative risk (95% CI)	P Value for Interaction
Overall	279/5106	310/5466	0.99 (0.85-1.16)	
TIMI risk score				0.63
0-2	71/1596	84/1686	0.89 (0.66-1.22)	
3-4	144/2502	160/2629	0.95 (0.76-1.18)	
≥5	64/1008	66/1151	1.11 (0.79-1.55)	
GRACE score				0.27
<113	60/1562	82/1656	0.78 (0.56-1.07)	
113-139	81/1631	85/1703	1.00 (0.74-1.34)	
≥140	115/1553	119/1746	1.09 (0.85-1.39)	
Cardiac marker elevation at inclusion				0.58
Yes	260/4523	292/4834	0.95 (0.81-1.12)	
No	19/583	18/632	1.14 (0.61-2.16)	



TIMI 0-2, low risk of death or ischemic events; TIMI 3-4, intermediate risk; TIMI ≥5, high risk
GRACE score <113, low risk for hospital death; GRACE 113-139, intermediate risk; GRACE ≥140, high risk

Primary safety outcome (TIMI major + minor bleed) for otamixaban 0.140 mg/kg/hour vs control



No. at Risk

	Day 0	Day 7	Day 15	Day 30
Otamixaban	5106	4855	4805	4654
UFH + eptifibatide	5466	5293	5257	5086

Safety outcomes

Outcome[1]	Otamixaban 0.080 mg/kg bolus and 0.140 mg/kg per hour infusion (n=5106)	UFH plus eptifibatide (n=5466)	Relative risk (95% CI)
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)

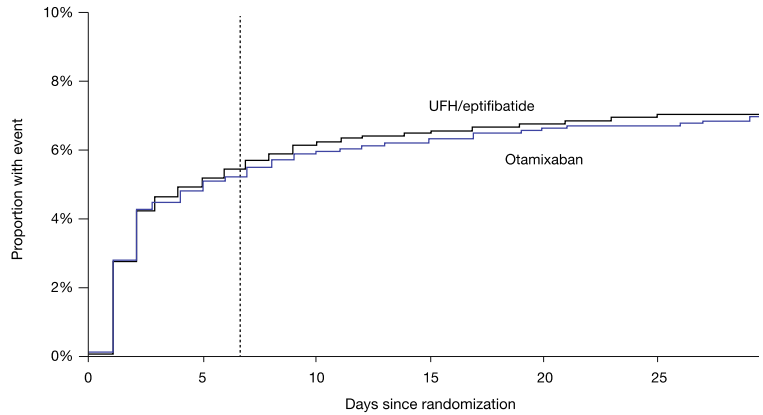
ARC, Academic Research Consortium. [1]A patient can be counted in several categories.

Primary efficacy and safety outcomes for otamixaban 0.140 mg/kg/hr vs control

Efficacy

Death or MI

Day 7

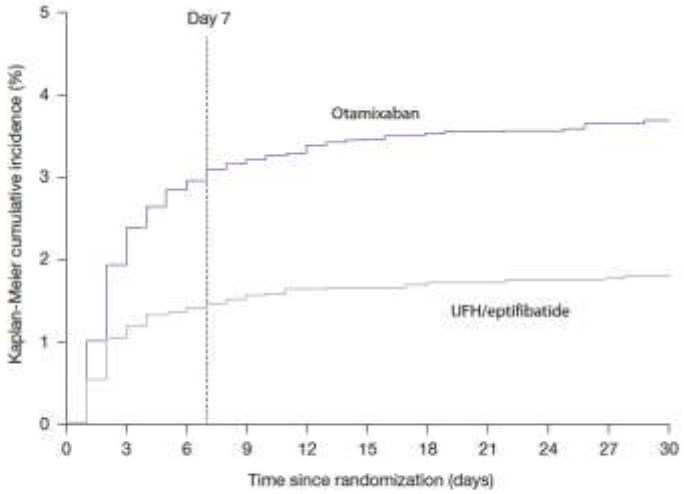


No. at Risk	Day 0	Day 10	Day 20
Otamixaban	5106	4801	4766
UFH + eptifibatide	5466	5132	5097

RR, 0.99, 95% CI, 0.85-1.16; *P*=0.93*

Safety

TIMI major or minor bleed



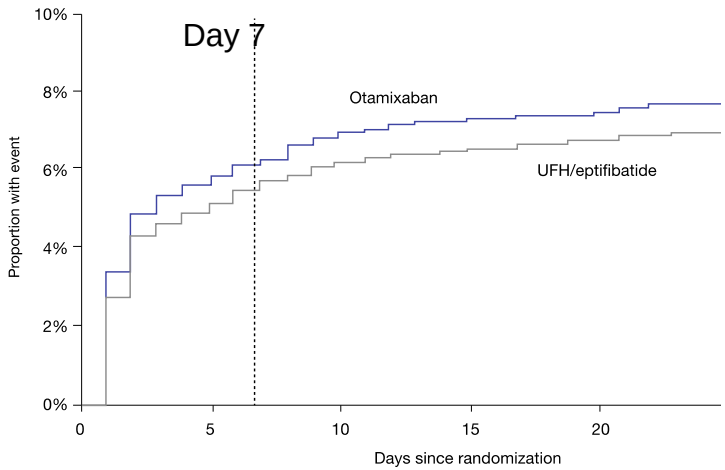
No. at Risk	Day 0	Day 7	Day 15	Day 30
Otamixaban	2657	2552	2533	2431
UFH + eptifibatide	5466	5293	5257	5086

RR, 2.13, 95% CI, 1.63-2.78

Primary efficacy and safety outcomes for otamixaban 0.100 mg/kg/hr vs control

Efficacy

Death or MI

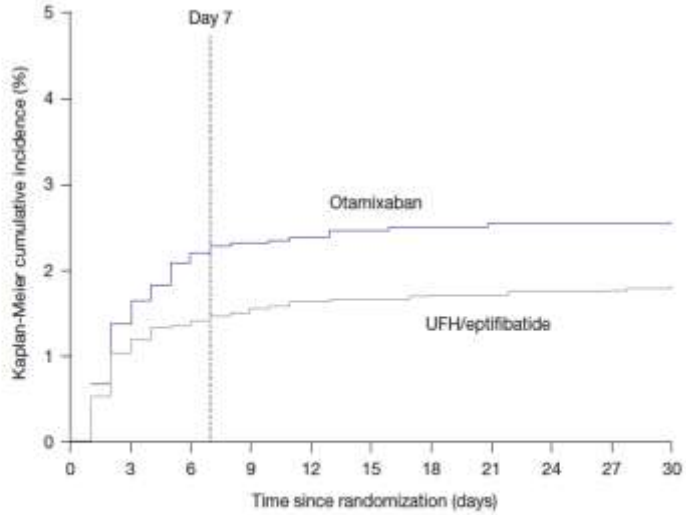


No. at Risk	Day 0	Day 10	Day 20
Otamixaban	2657	2472	2456
UFH + eptifibatide	5466	5132	5097

RR, 1.11, 95% CI, 0.92-1.33

Safety

TIMI major or minor bleed



No. at Risk	Day 0	Day 7	Day 15	Day 30
Otamixaban	5106	4855	4805	4654
UFH + eptifibatide	5466	5293	5257	5086

RR, 1.57, 95% CI, 1.13-2.18

Conclusions

- Compared with unfractionated heparin and eptifibatide, otamixaban was not superior, as it did not reduce the risk of ischaemic outcomes in NSTE-ACS patients 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
- These results suggest an unfavorable efficacy/safety balance for acute Xa inhibition in the modern era of dual antiplatelet therapy and routine early intervention for ACS.

Original Investigation

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

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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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