KEY LEARNINGS from OTAMIXABAN DEVELOPMENT

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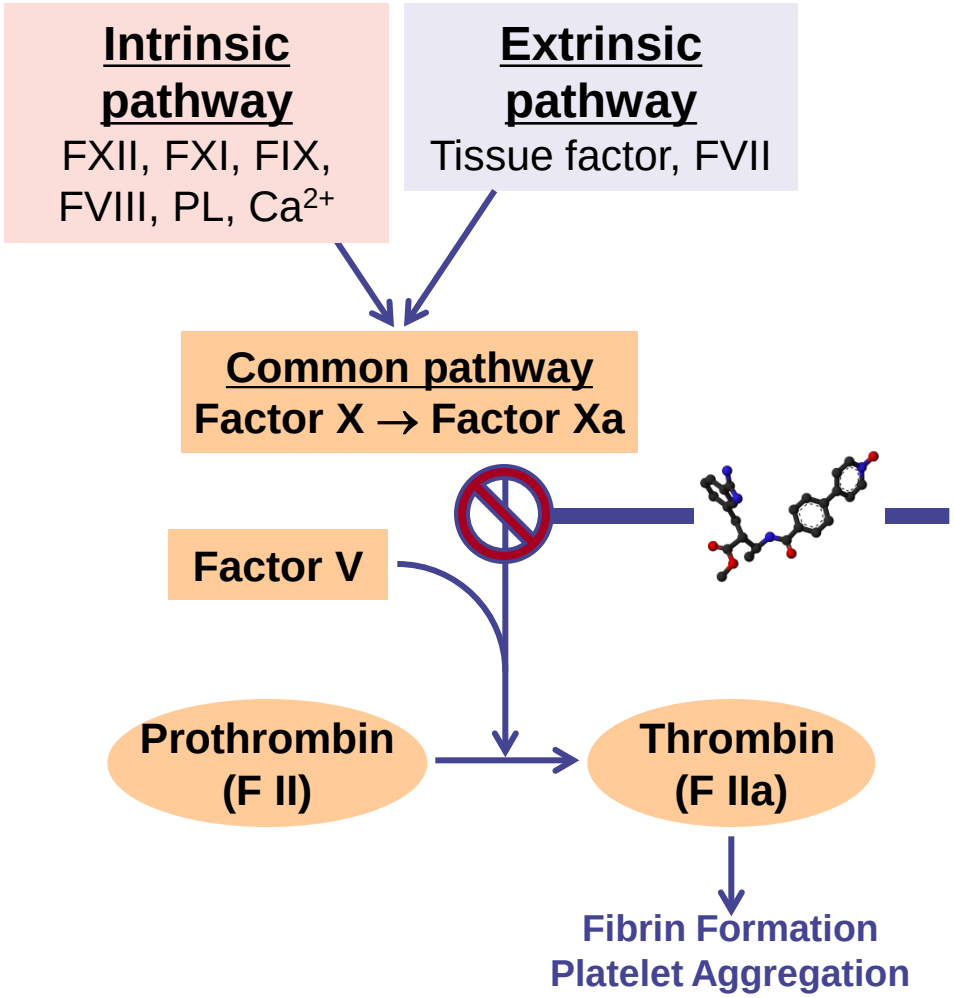
Otamixaban



- **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**
- **Favorable PK/PD profile**
  - **Short-acting (half-life 30 min)**
  - **Weight-based bolus & infusion**
  - **No need for monitoring**
  - **No significant renal elimination**

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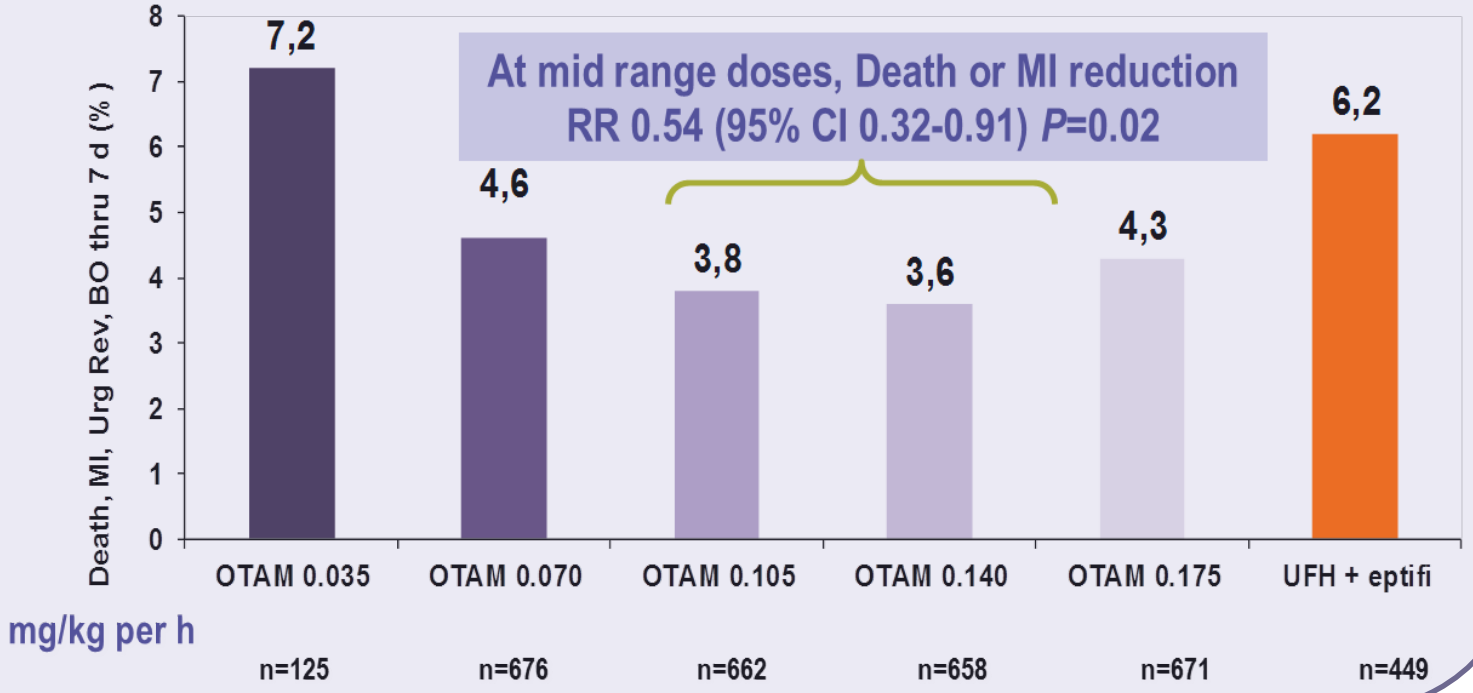
Phase 2 Results in NSTE-ACS Patients

Primary efficacy endpoint at Day 7

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)

P=0.34 for trend across OTAM dose arms



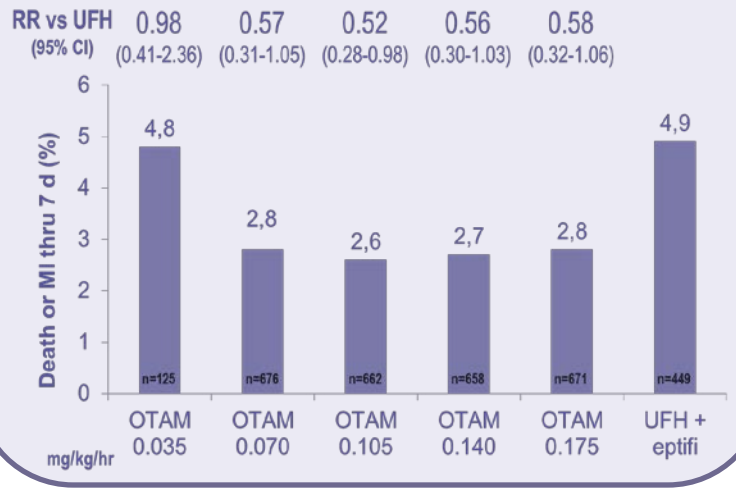
ClinicalTrial.gov ID: NCT00317395.

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

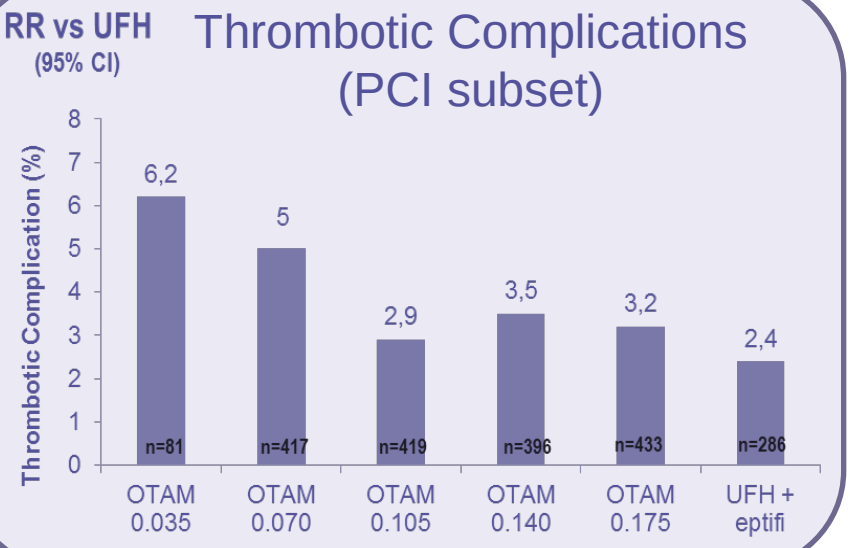
Phase 2 Results in NSTE-ACS Patients

Other endpoints at Day 7

Death or MI



Thrombotic Complications (PCI subset)



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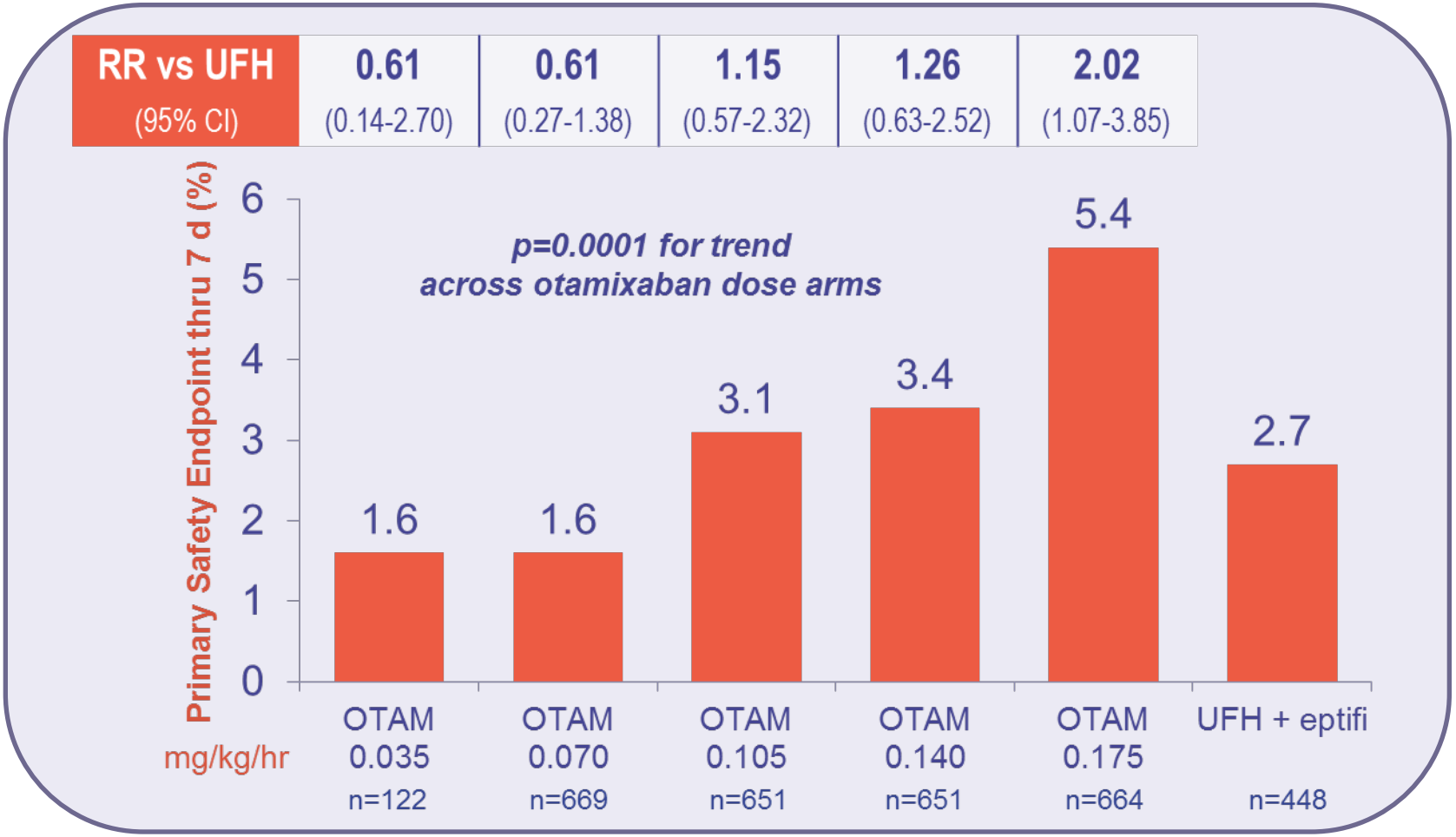
Sabatine MS, *et al. Lancet* 2009;374:787-795

Phase 2 Results in NSTE-ACS Patients

Primary Safety Endpoint at Day 7

TIMI Major or Minor Bleed not related to CABG



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

Interpretation of SEPIA-ACS Results for Designing Phase III Trial

- Significant dose-response for the primary safety endpoint
- The primary efficacy composite showed best results of 42% RRR with the 0.105 and 0.140 mg/kg per hour infusion doses
  - **U-shape curve with less effect at lower (0.070 mg/kg per hour) and higher (0.175 mg/kg per hour) infusion doses, suggesting that the observed RRR at theses doses would be an overestimate**

  ➔ The expected RRR for Phase 3 was set lower, i.e. 25%

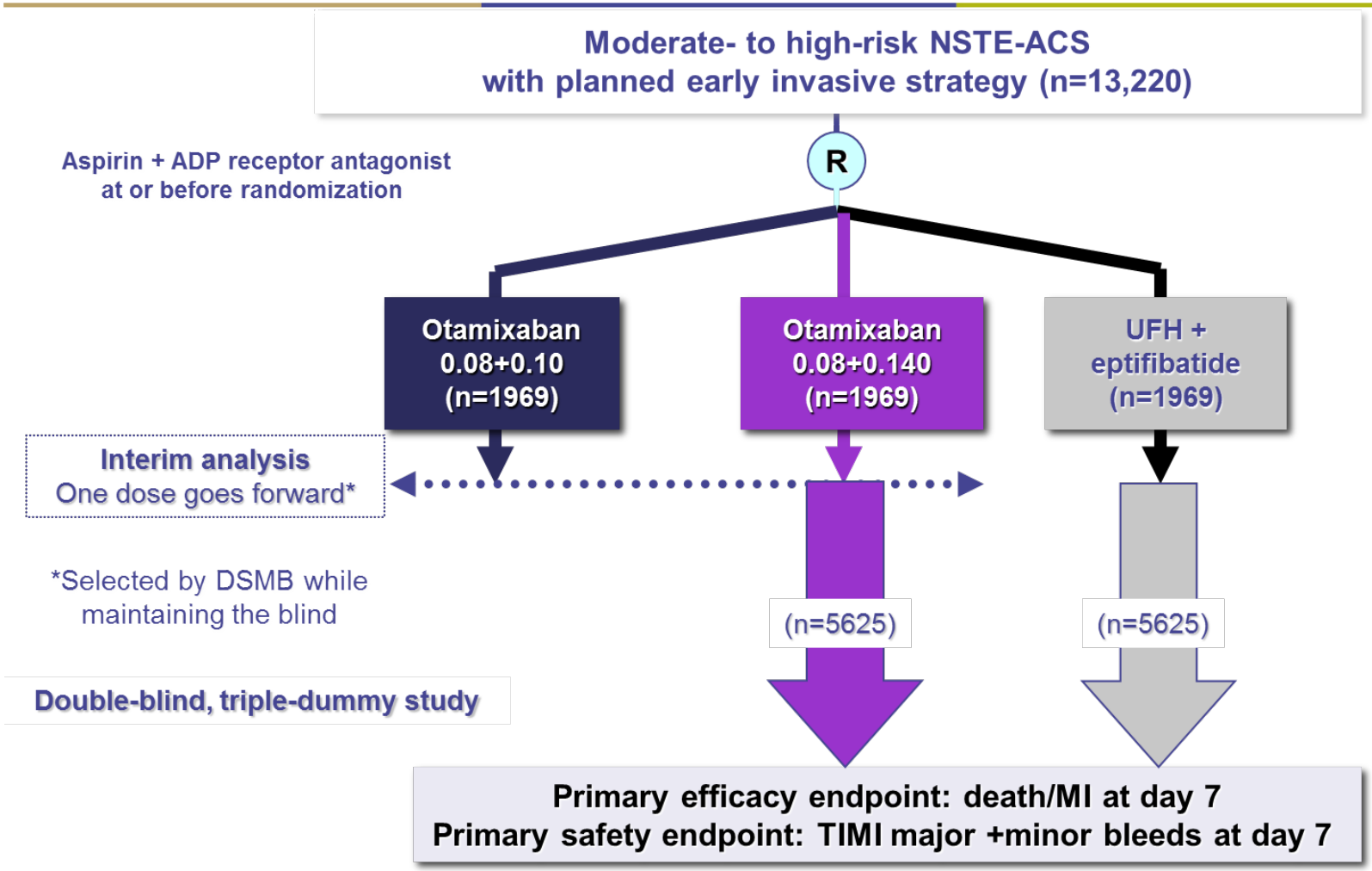
- The composite of death or MI is the strongest endpoint
  - **Other components of the primary endpoint (urgent revascularization or bailout) showed a more neutral effect**

  ➔ Death or MI were selected as the primary endpoint for Phase 3

FDA EOP2 and EMA Scientific Advice for Designing Phase III Trial

- Many discussions on dose for Phase III trial
  - **FDA request that 2 doses be investigated**
    - including a higher than the originally planned 0.100 mg/kg/h to give best chances for otamixaban to lower risk of irreversible events (death or MI)
  - **EMA request that the 'to-be-marketed dose' be substantiated by a significant superiority in clinical efficacy versus comparator**
- Adaptive design with randomisation starting with both 0.100 and 0.140 mg/kg/h doses versus control arm UFH (+eptifibatide if PCI)
  - **To comply with expectations of both Agencies**
  - **While preserving a reasonable sample size**
  - **Planned interim analysis to continue with lower dose unless a higher benefit/risk ratio is observed with the higher dose**
- Agreement reached on the proposed study design

Study Design



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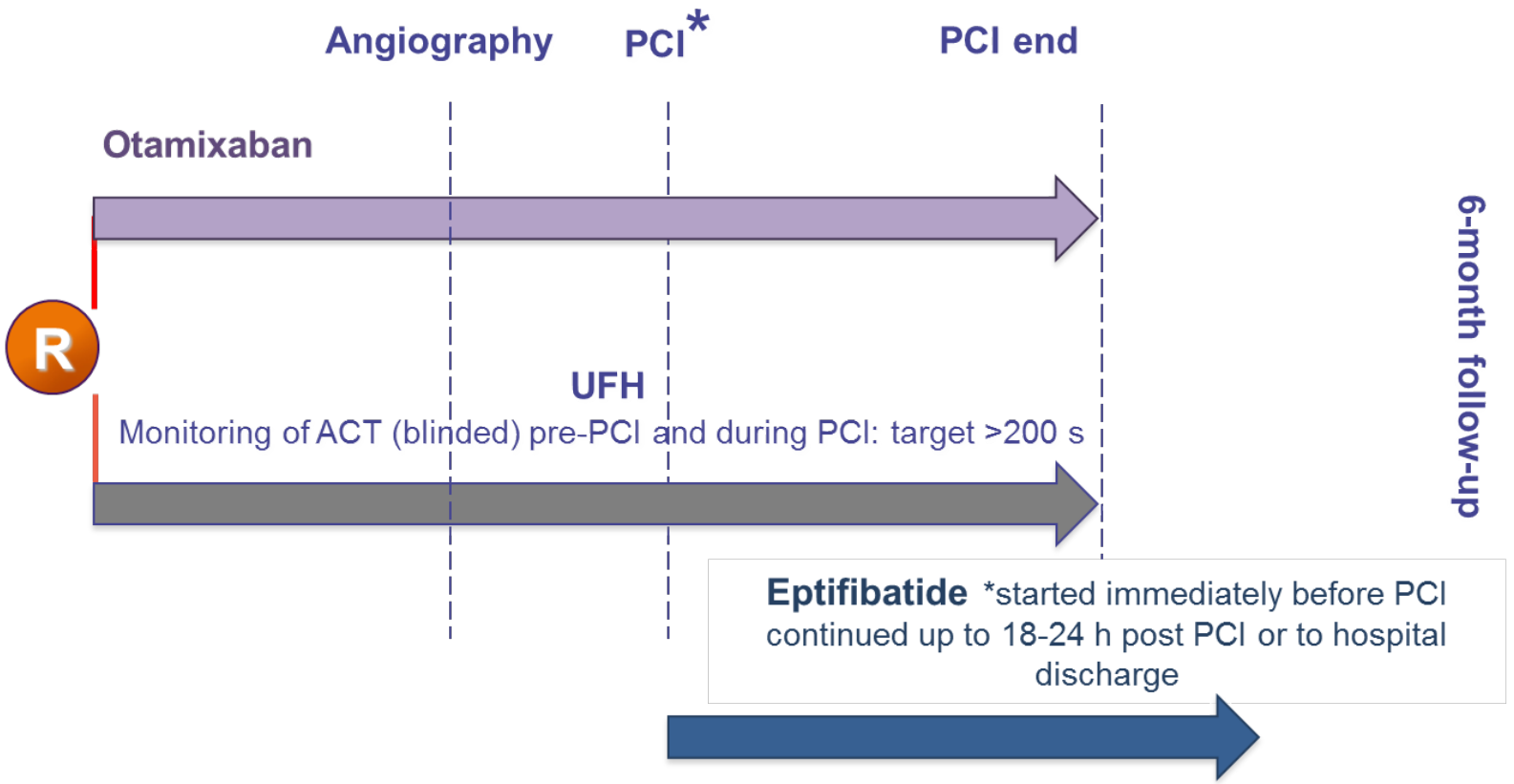
ClinicalTrial.gov ID: NCT01076764.
Steg PG, *et al.* ***Am Heart J*** 2012;164:817-24

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.

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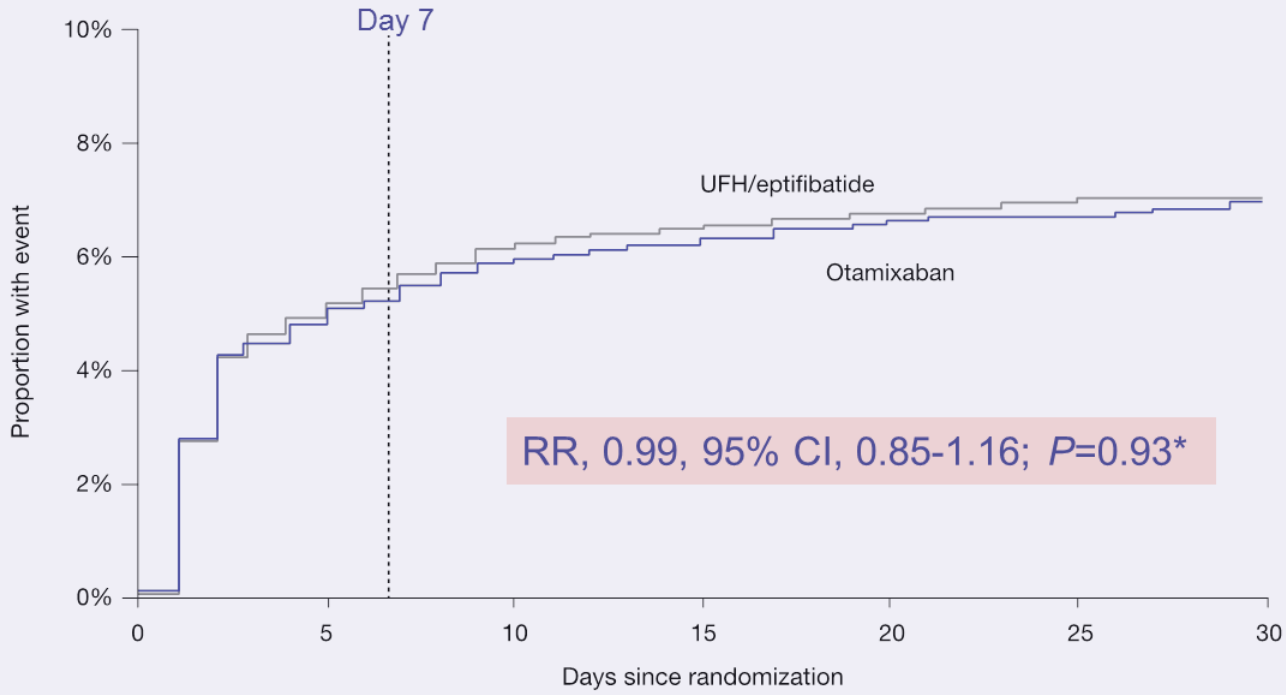
ClinicalTrial.gov ID: NCT01076764.
Steg PG, *et al.* ***Am Heart J*** 2012;164:817-24

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

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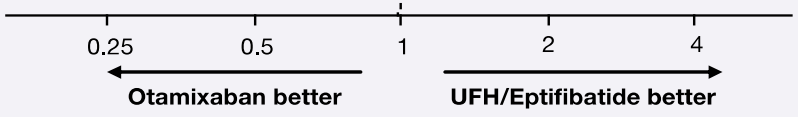
Steg PG, *et al. JAMA* 2013;310:1145-1155

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

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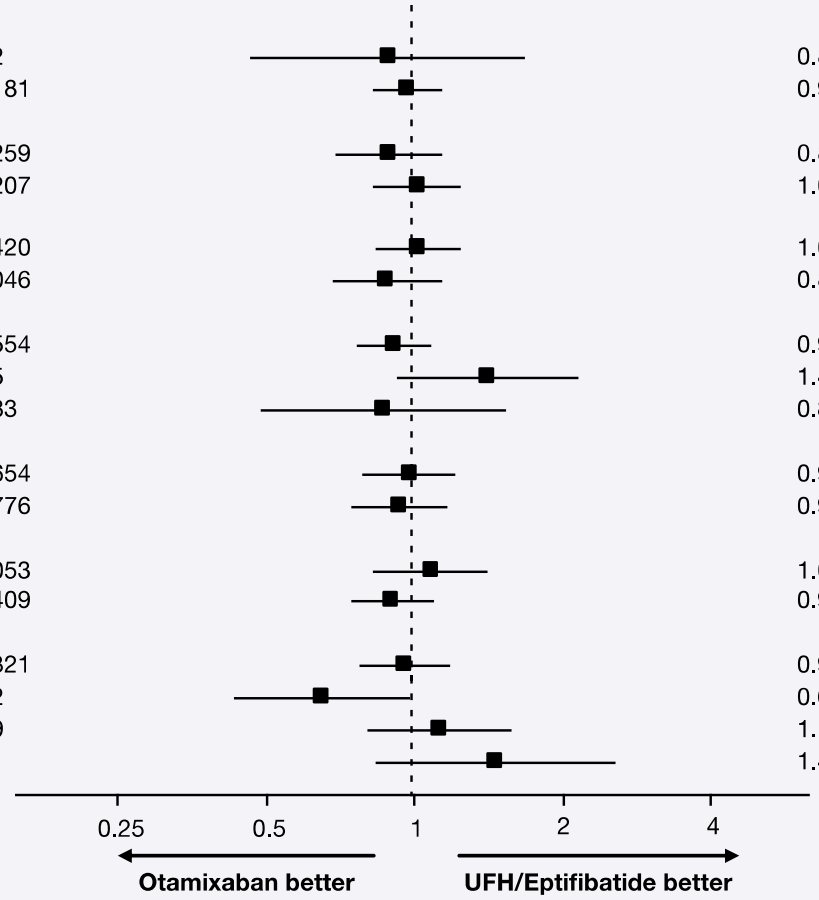
Steg PG, *et al. JAMA* 2013;310:1145-1155

Prespecified Subgroup Analyses of Primary Efficacy Outcome at Day 7 in Otamixaban† vs Control (2)

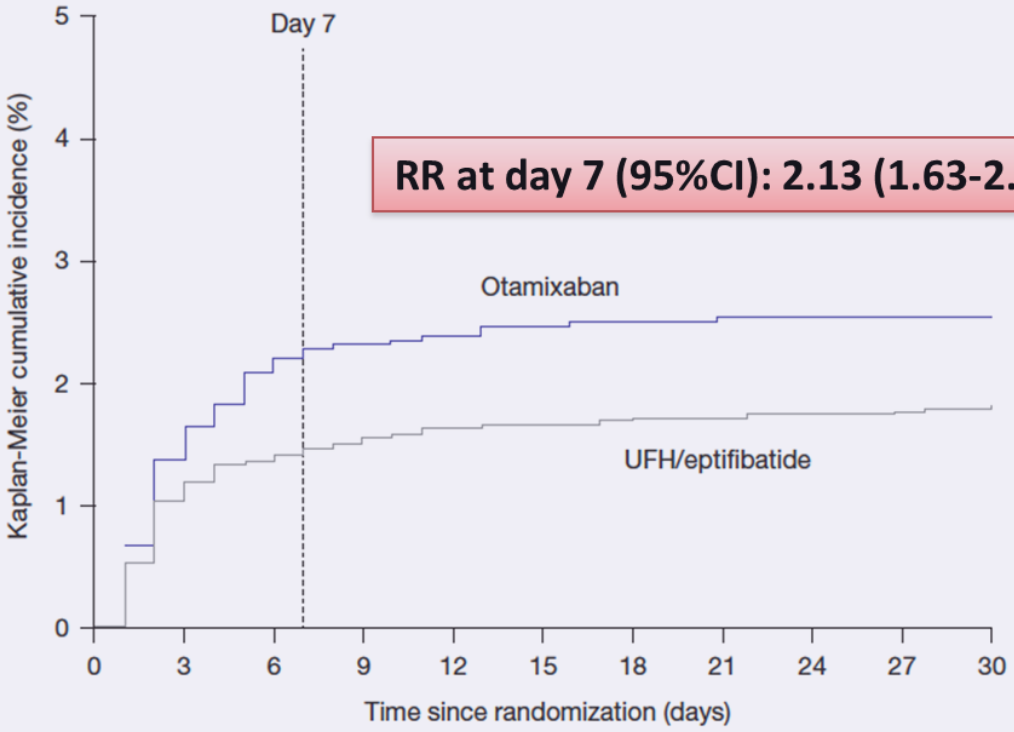
Subgroup	Otamixaban 0.140 mg/kg/h	UFH/Eptifibatide	Relative risk (95% CI)	P Value for Interaction
TIA/stroke history				0.80
Yes	16/267	19/282	0.89 (0.47-1.69)	
No	263/4837	291/5181	0.97 (0.82-1.14)	
Prior aspirin				0.41
Yes	106/2059	131/2259	0.89 (0.69-1.14)	
No	173/3047	179/3207	1.02 (0.83-1.25)	
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

Steg PG, *et al. JAMA* 2013;310:1145-1155

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

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Steg PG, *et al. JAMA* 2013;310:1145-1155

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)

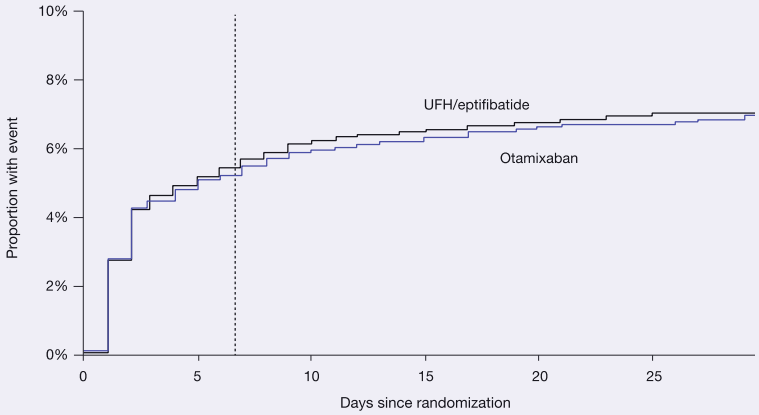
ARC, Academic Research Consortium. 1A patient can be counted in several categories.

Primary Efficacy and Safety Outcomes for Otamixaban 0.140 mg/kg/hr vs Control

Efficacy

Death or MI

Day 7

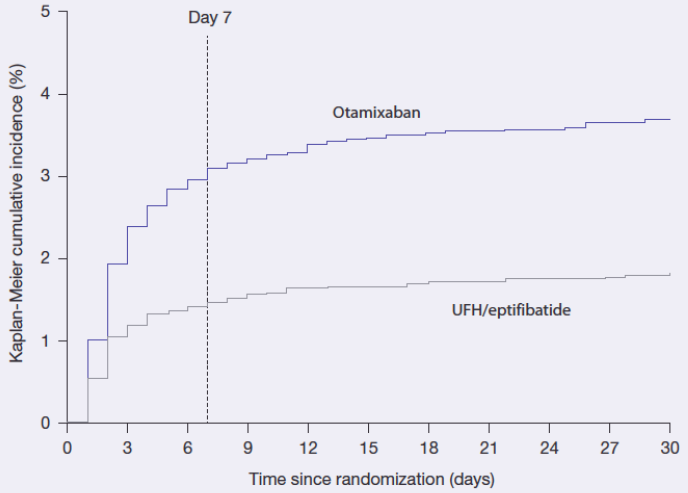


No. at Risk	Day 0	Day 10	Day 20
Otamixaban	5106	4801	4766
UFH + eptifibatide	5466	5132	5097

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

Safety

TIMI major or minor bleed



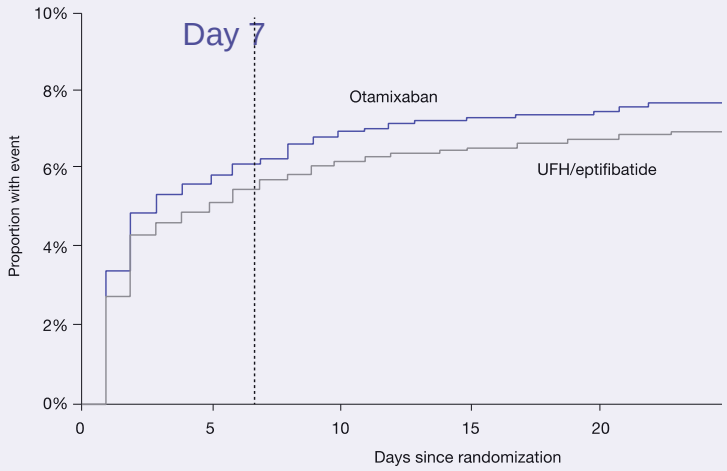
No. at Risk	Day 0	Day 7	Day 15	Day 30
Otamixaban	2657	2552	2533	2431
UFH + eptifibatide	5466	5293	5257	5086

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

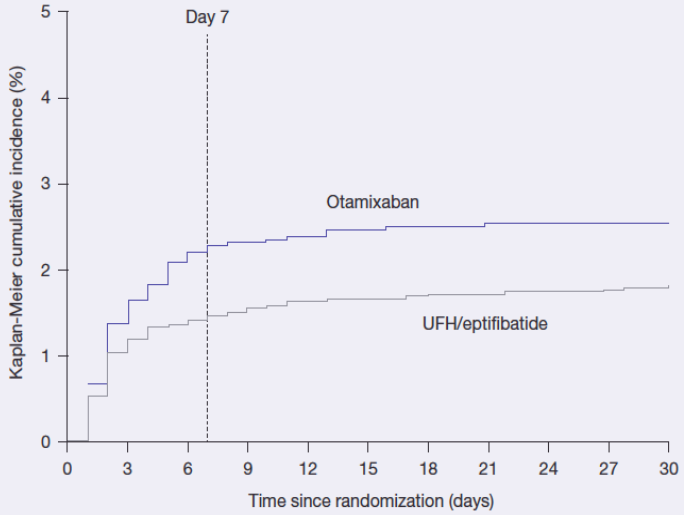


No. at Risk	Day 0	Day 10	Day 20
Otamixaban	2657	2472	2456
UFH + eptifibatide	5466	5132	5097

RR, 1.11, 95% CI, 0.92-1.33

Safety

TIMI major or minor bleed



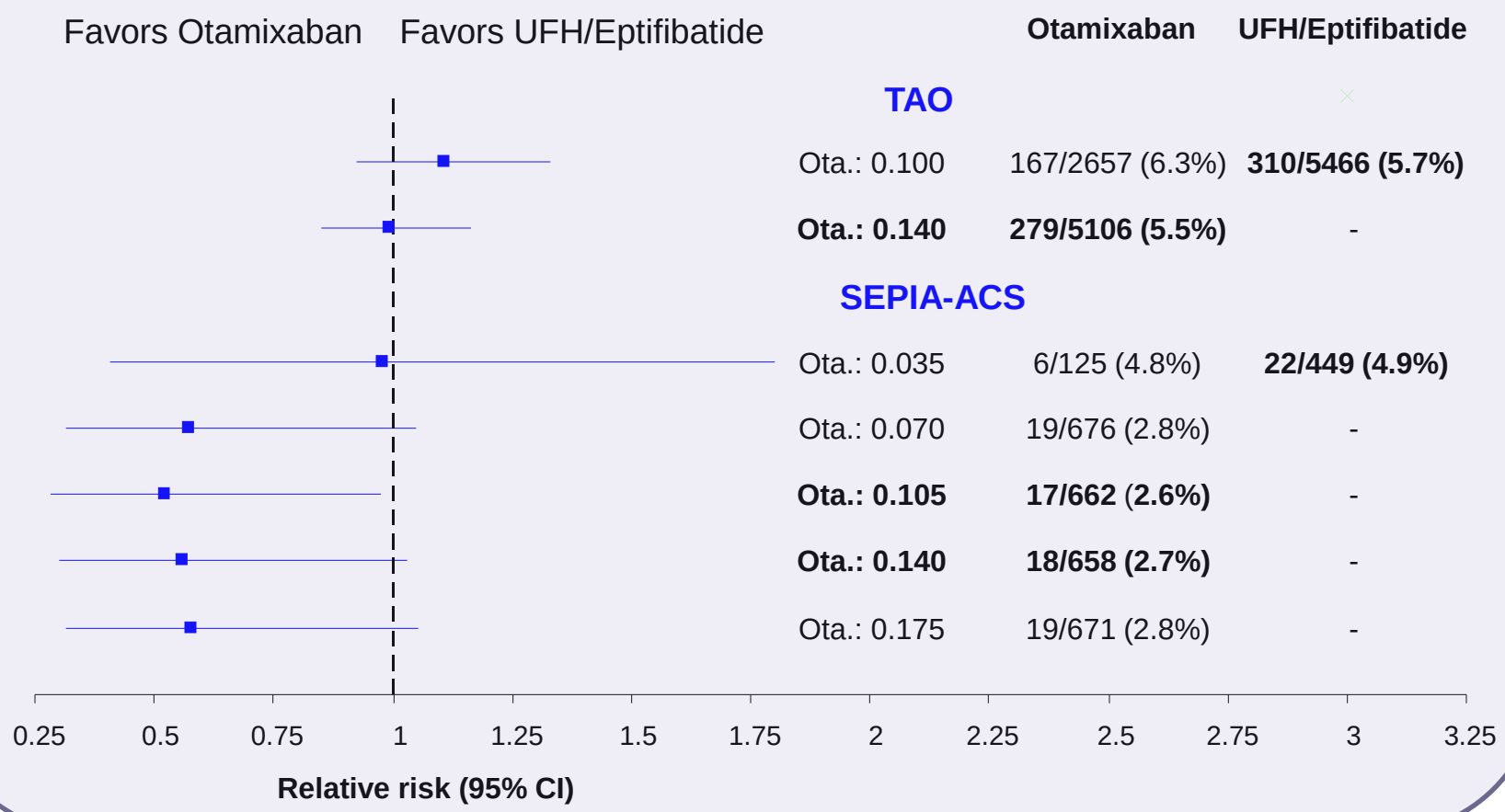
No. at Risk	Day 0	Day 7	Day 15	Day 30
Otamixaban	5106	4855	4805	4654
UFH + eptifibatide	5466	5293	5257	5086

RR, 1.57, 95% CI, 1.13-2.18

Interpretation of Discrepancy between SEPIA-ACS and TAO Results

- The design of TAO was logical, on the basis of SEPIA ACS results
  - **Based on clinical events in SEPIA ACS**
  - **Appropriate choice of the primary efficacy components**
  - **Target RRR of 25%, presumed less than effect size in SEPIA-ACS**
- Although the results were disappointing, the TAO study was conclusive in answering an important clinical question
- Imbalance modifiers do not explain discrepancy
- The following may explain discrepancy
  - **A small number of events of death or MI in the phase 2B study**
    - Only 20 events per arm in phase 2, while the TAO primary analysis was based on about 300 events per arm, i.e. 15 time more
  - **A 'random-high' bias in interpretation of phase 2B results (by selecting doses, primary composite endpoint and D7 time) is possible**
  - **Due to variability, results in Phase 2B and in Phase 3 are not inconsistent**
    - A 10% RRR is not ruled out by the 1% observed in TAO
    - TAO Primary Efficacy results partially overlap SEPIA-ACS results

TAO Primary Efficacy Results Partially Overlap SEPIA-ACS Results



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Conclusion

- 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.

Thank You