Factor Xa inhibitors in ACS – Lessons from recent trials (OASIS-5 and TAO trials): TCT AP 2014

Duke Heart Center

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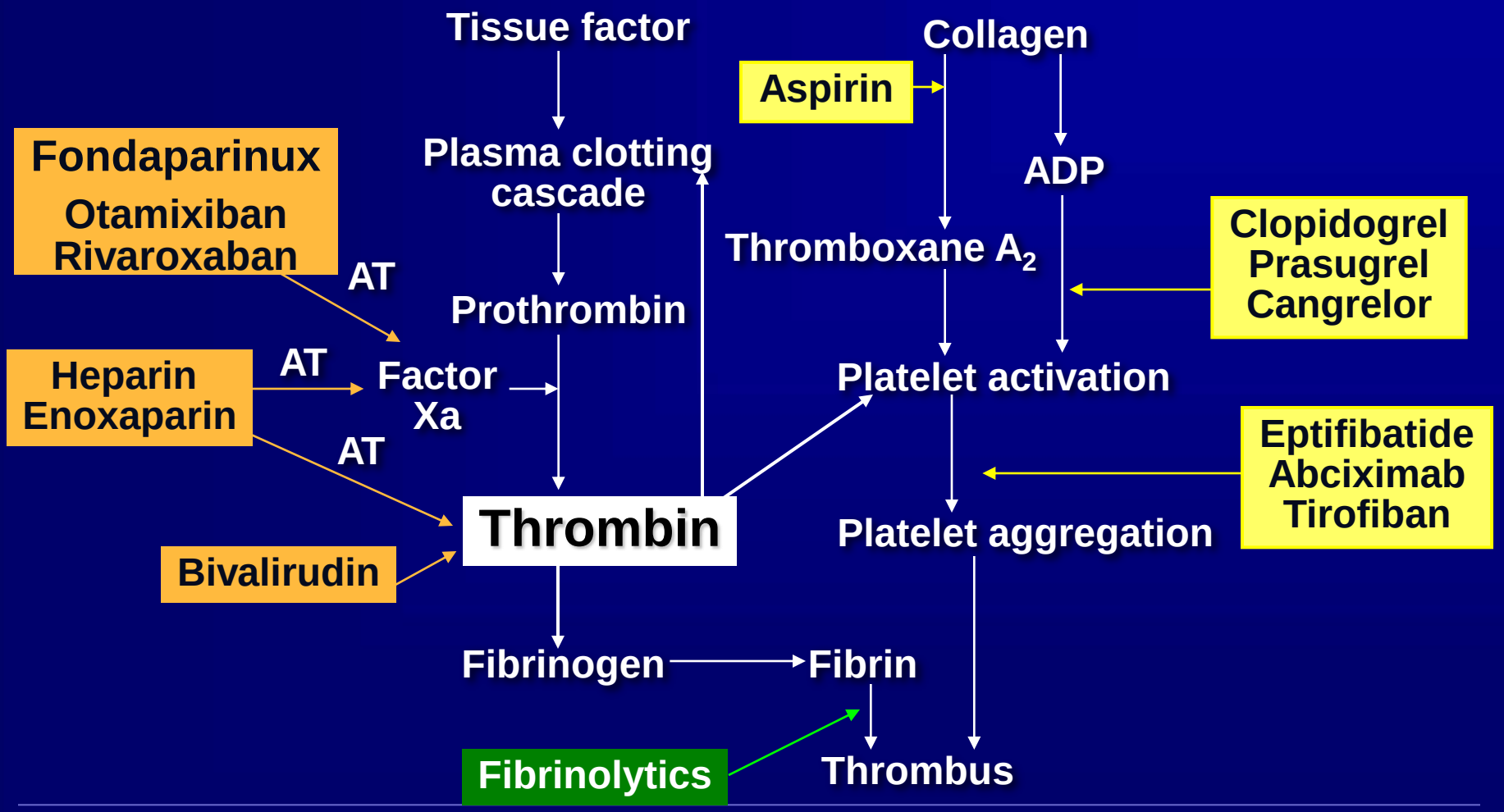
Disclosures

- Interventional cardiologist
- Research Grants:
  - NHLB, AHRQ, AstraZeneca, Pleuristem, Johnson and Johnson, Maquet / Datascope
- Advisory Board/Consulting:
  - Genzyme, Bayer, Baxter Healthcare, Ortho McNeil Jansen, theHeart.org, Medscape, Maquet, CSI technologies
- Professional Society Roles:
  - Member ACC/AHA AUC Task Force
  - Chair of Writing Group for ACC/AHA Coronary Revascularization Appropriateness Criteria
  - Chair of AHA Diagnostic and Interventional Cath Committee

Outline

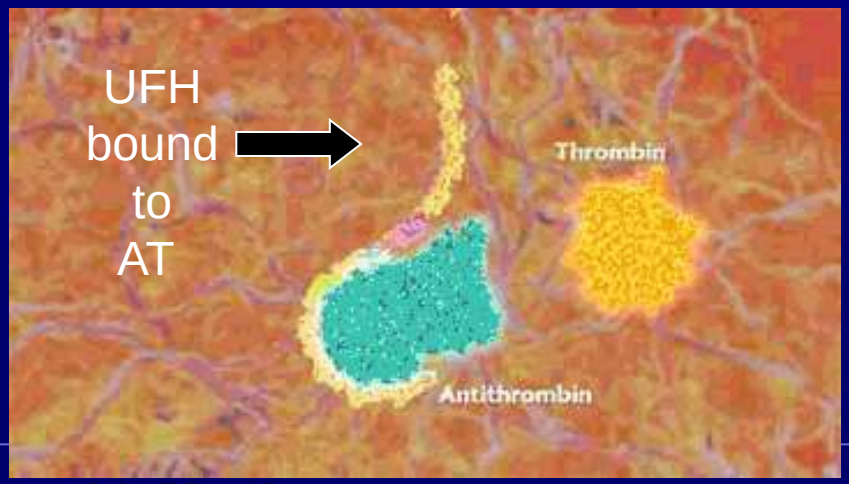
- What is the rationale for more anticoagulation (Factor Xa inhibitors or otherwise)
- Results of Trials
- Conclusions
  - Current Treatment Algorithm

Sites of Anticoagulant Drug Action



Unfractionated Heparin (UFH)

- 5,000-30,000 Daltons
- Heterogeneous mixture of polysaccharide chains with varying effects on anticoagulant activity
- Accelerates the action of circulating antithrombin (AT), a proteolytic enzyme which inactivates factors IIa (thrombin), IXa, Xa
- Prevents thrombus propagation, but does not lyse existing thrombi



Sites of action for anticoagulants

Dual Pathway Hypothesis: Will inhibition of both thrombin and Factor Xa (prothombin-thrombin) improve clinical outcomes

Factor Xa

Factor IIa (thrombin)

Fondaparinux
Otamixaban
Rivaroxaban
Apixaban

Enoxaparin

Unfractionated Heparin

Bivalirudin

Fondaparinux

- **Factor Xa inhibitor**
- **Synthetic pentasaccharide**
- **$t_{1/2}$ = 17-21 hrs**
- **Inactive against thrombin already generated**
- **Advantages over UFH**
  - Decreased plasma protein, endothelial cell binding
  - More predictable, sustained anticoagulation
  - Once-daily dosing
  - No laboratory monitoring

OASIS-5: Study Design

Exclude
Age < 21
Contraindication to enox
Hemorrhagic stroke < 12 mo
Creat > 3 mg/dL (265 umol/L)

Patients w/ NSTE ACS

Chest pain < 24 hours
2/3:
Age > 60
ST-segment Δ
↑ cardiac markers

Randomize

n = 20,000

ASA, clopidogrel, IIb/IIIa, planned cath per local practice

Fondaparinux 2.5 mg sc qd

PCI < 6 h: IV fondaparinux 2.5 mg w/o IIb/IIIa, 0 w/ IIb/IIIa
PCI > 6h: IV fondaparinux 5 mg w/o IIb/IIIa, 2.5 mg w/ IIb/IIIa

Enoxaparin 1 mg/kg sc bid

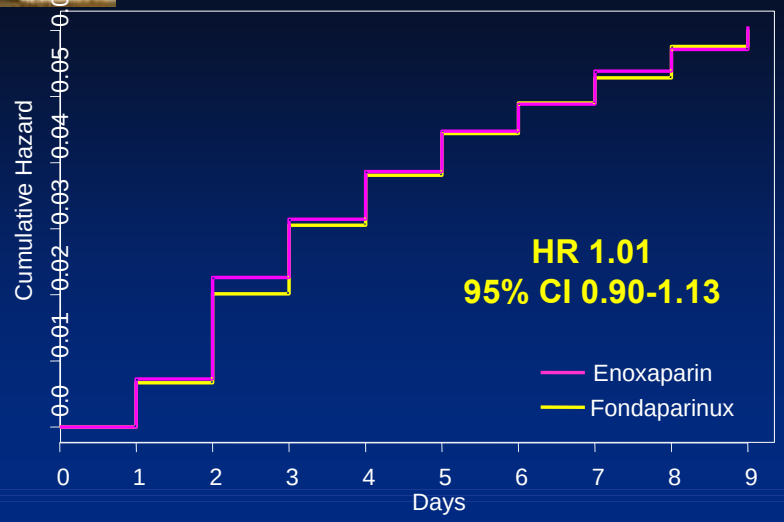
PCI < 6 h: no UFH
PCI > 6h: IV UFH
100 U/kg w/o IIb/IIIa
60 U/kg w/ IIb/IIIa

Outcomes

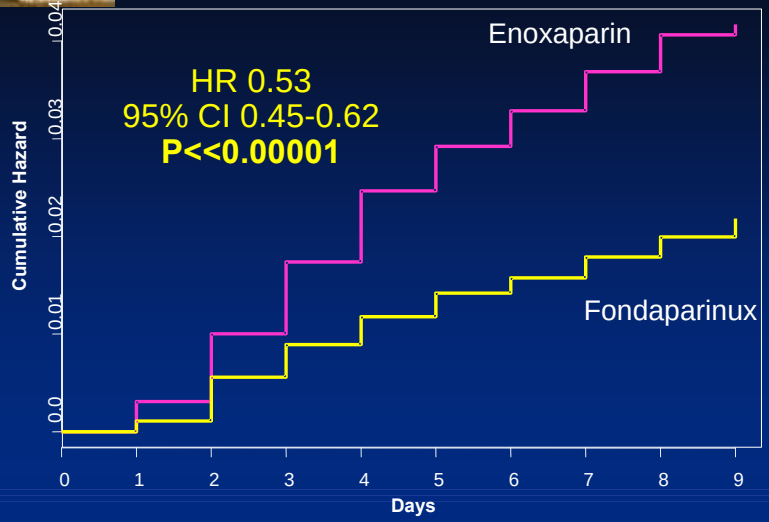
Primary	Efficacy:	Death, MI, refractory ischemia at 9 days
	Safety:	Major bleeding at 9 days
	Risk/Benefit:	Death, MI, refractory ischemia and major bleeding at 9 days
Secondary	Above and each component separately at day 30 and 6 months	

Yusuf S, et al. *N Engl J Med*. 2006;354(14):1464-76.

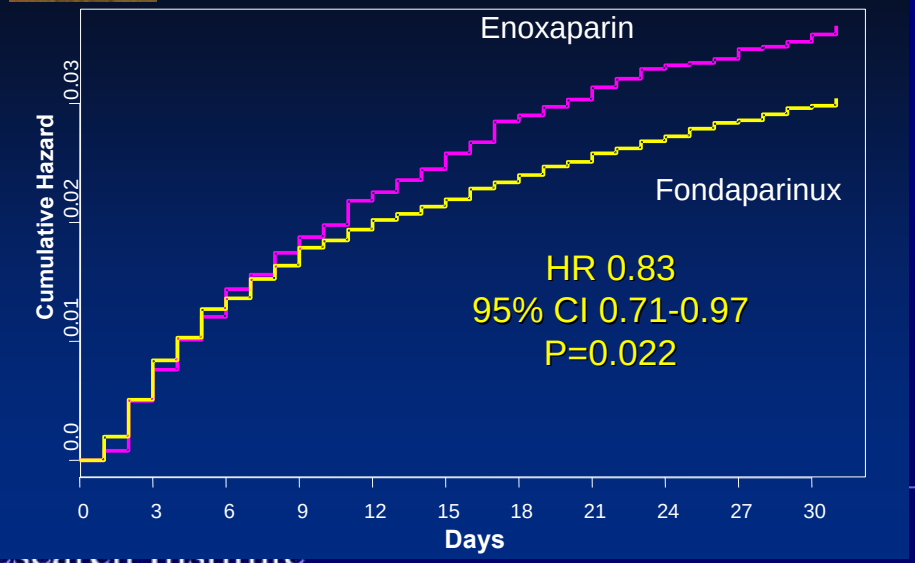
Death/MI/RI: Day 9



Major Bleeding: 9 Days



Mortality: Day 30



OASIS 5:

PCI Procedural Complications

Events (30 Days)	Enoxaparin n=3089	Fondaparinux n=3118	P value
Any UFH during PCI	53.8%	18.8%	
Any procedural complication	8.6%	9.6%	0.18
Abrupt closure	1.1%	1.5%	0.20
★ Catheter thrombus	0.5%	1.3%	0.001
Vascular access	8.1%	3.3%	<0.0001
Pseudo-aneurysm	1.6%	1.0%	0.39
Large hematoma	4.4%	1.6%	<0.0001

Yusuf S, et al. *N Engl J Med*. 2006;354(14):1464-76.

Conclusion Oasis 5

- **Fondaparinux at the dose studied reduces bleeding and mortality in patients with NSTEMI ACS**
- **Patients were treated for average 5 days prior to cath lab, small but increased risk of catheter thrombosis.**

TAO : Treatment of Acute Coronary Syndromes with Otamixaban

Philippe Gabriel Steg* on behalf of the TAO investigators

***DHU-FIRE, Hôpital Bichat, Assistance Publique – Hôpitaux de Paris, Université Paris – Diderot, INSERM U-698, Paris, France**

***Disclosures: Research grants (to INSERM U698):** NYU school of Medicine, Sanofi, Servier. **Speaking or consulting:** Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Daiichi-Sankyo-Lilly, GlaxoSmithKline, Medtronic, Novartis, Otsuka, Pfizer, Sanofi, Servier, The Medicines Company, Vivus. **Stockholding:** Aterovax.

The TAO trial was supported by SANOFI

clinicaltrials.gov : NCT01076764

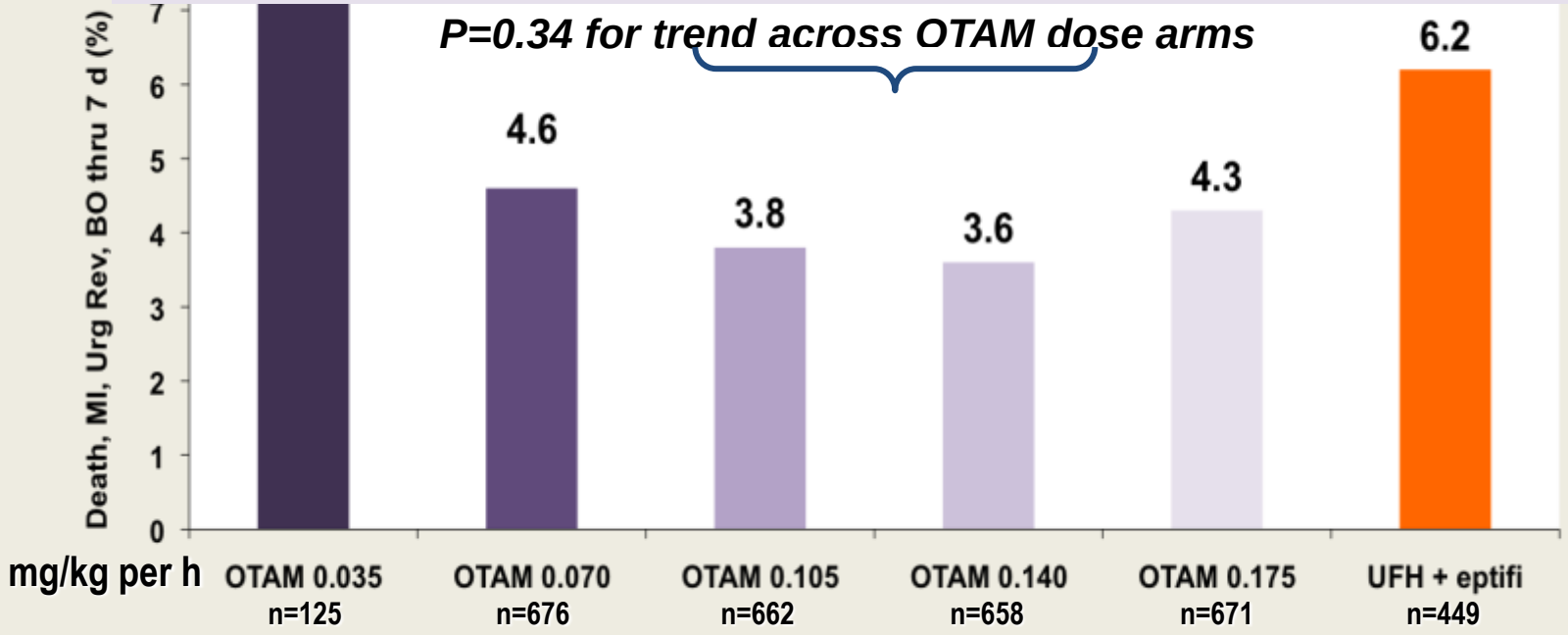
Background

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)

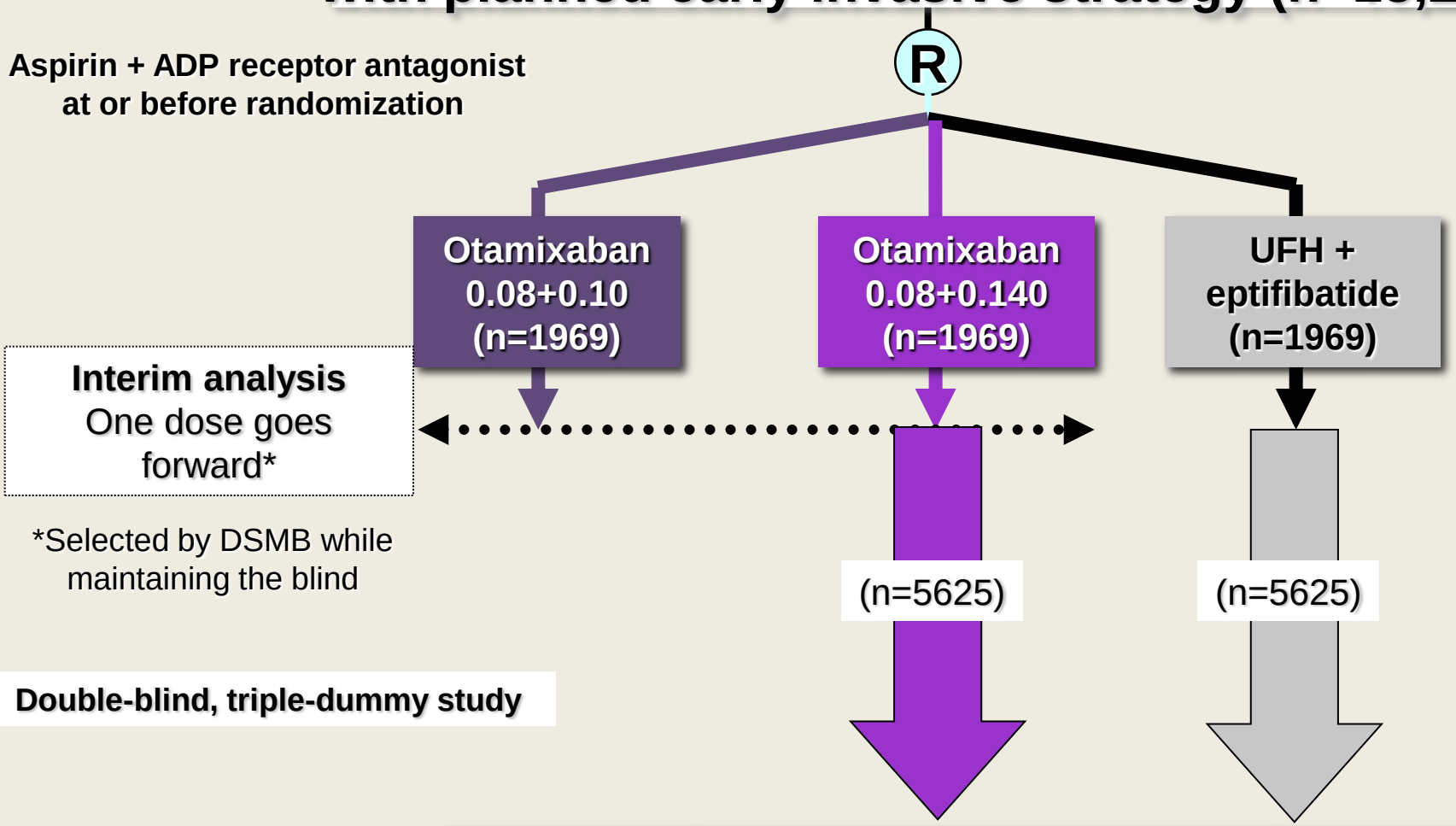
At mid range doses, Death or MI reduction: RR 0.54 (95% CI 0.32-0.91)
***P*=0.02**



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)



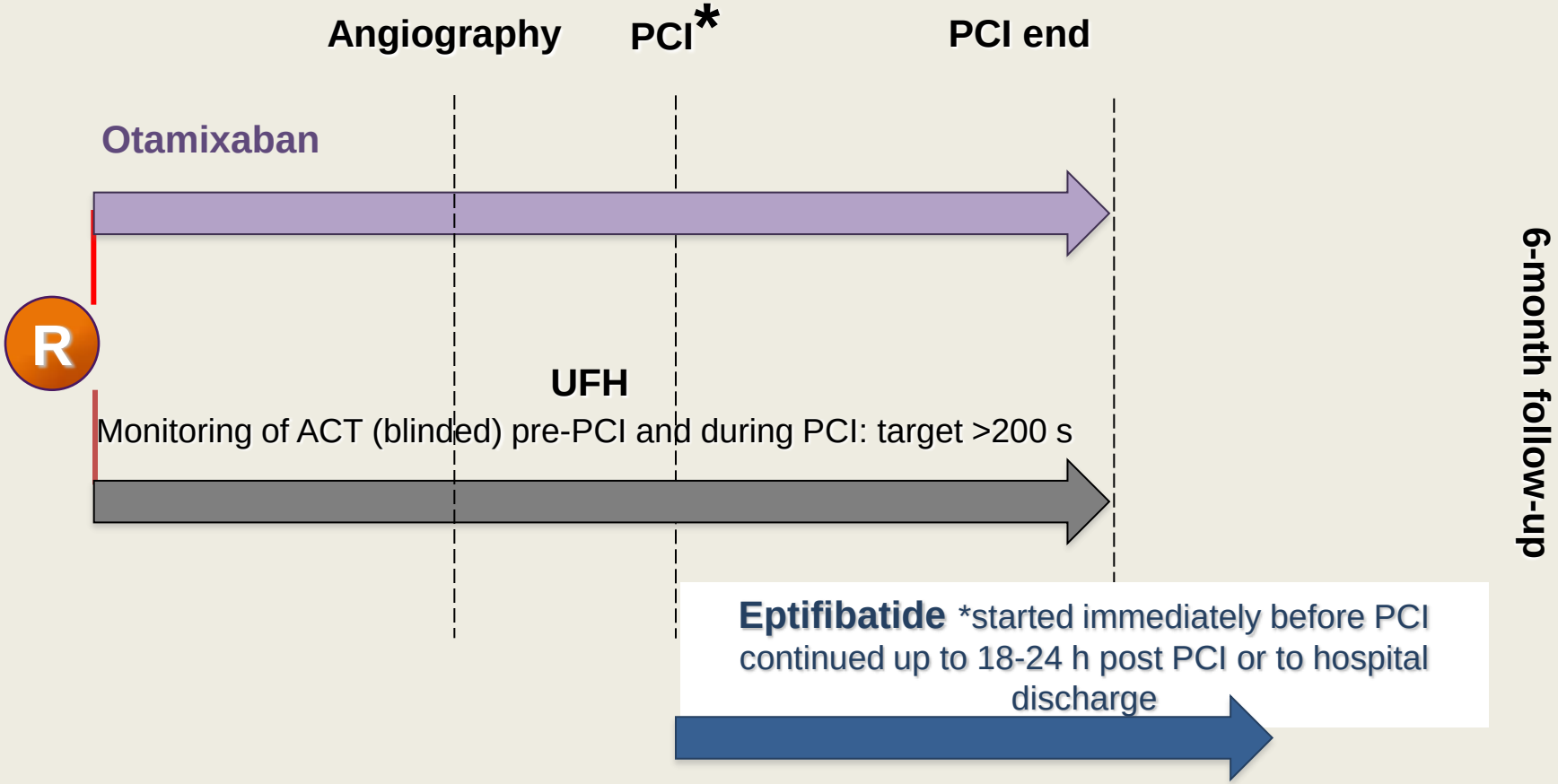
Primary efficacy endpoint: death/MI at day 7

Primary safety endpoint: TIMI major +minor bleeds at

ClinicalTrial.gov ID: NCT01076764.

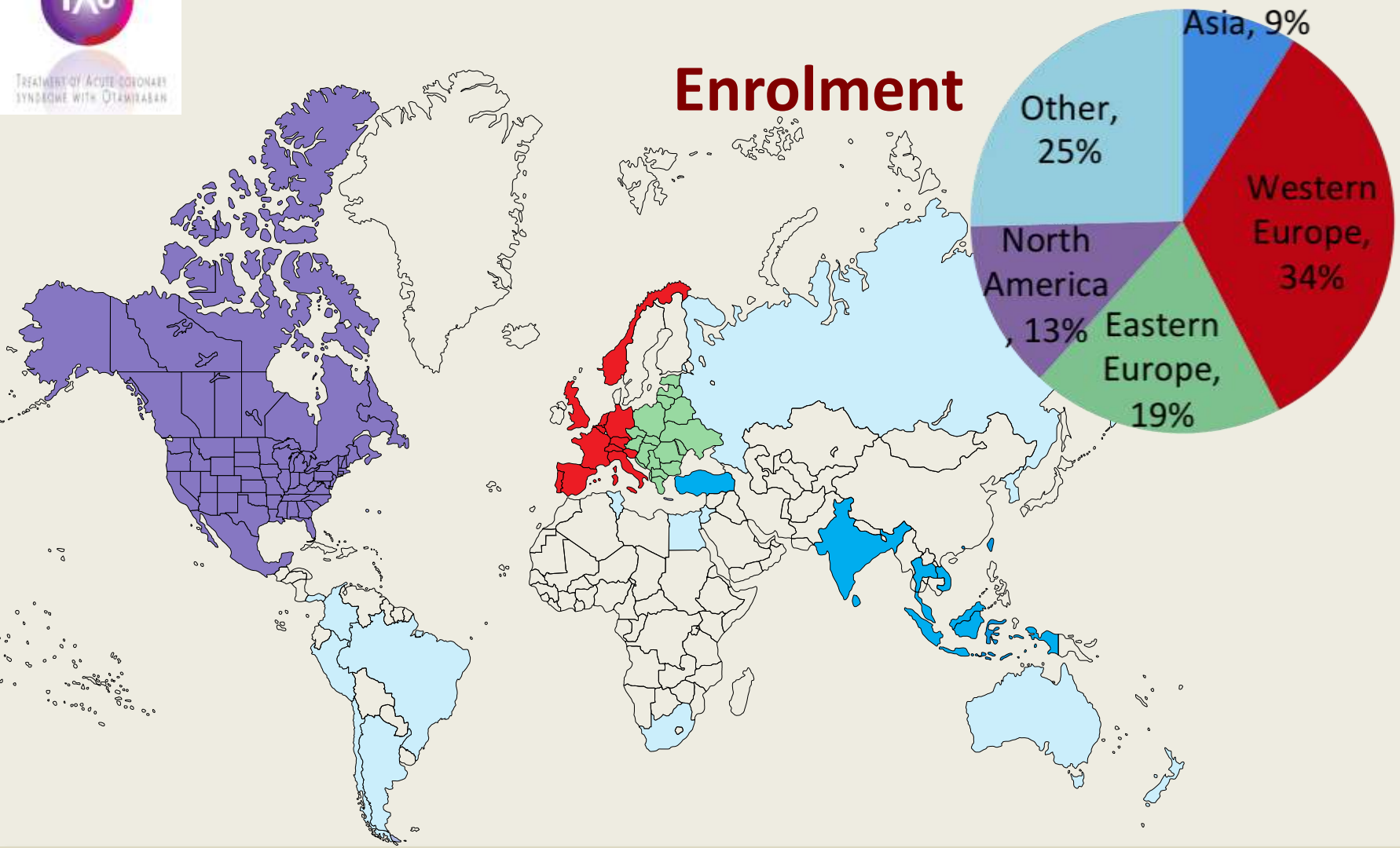
Steg PG, *et al.* ***Am Heart J*** 2012;164:817-24

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%)

Patients and procedure characteristics, and treatments

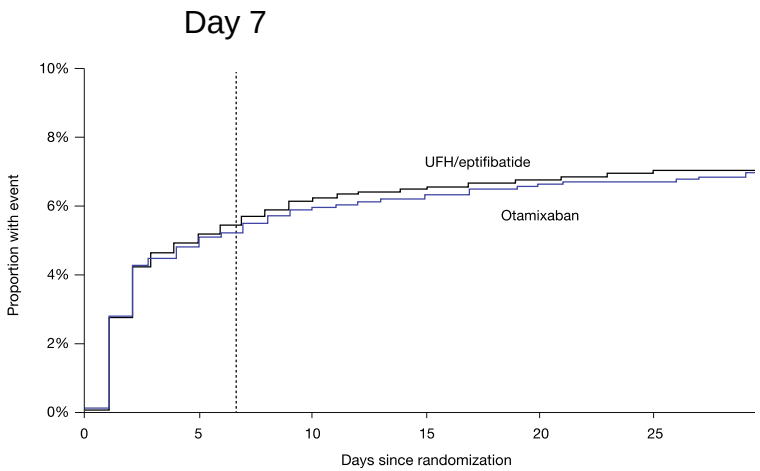
Factor, % or median (IQR)	Otamixaban 0.080 mg/kg bolus and 0.140 mg/kg/h infusion (n=5106)	UFH plus eptifibatide (n=5466)
Management during the index admission		
Coronary angiography	99.0	99.4
Percutaneous coronary intervention	65.2	65.0
CABG	4.9	5.4
Neither	28.9	29.0
Access route for angiography		
Femoral	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 and safety outcomes for otamixaban 0.140 mg/kg/hr vs control

Efficacy

Death or MI

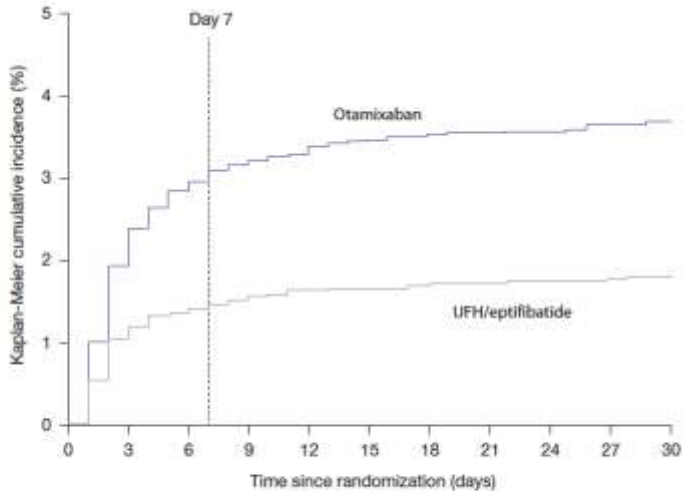


No. at Risk	Day 0	Day 10	Day 20
Otamixaban	5106	4801	4766
UFH + eptifibatide	5466	5132	5097

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

Safety

TIMI major or minor bleed



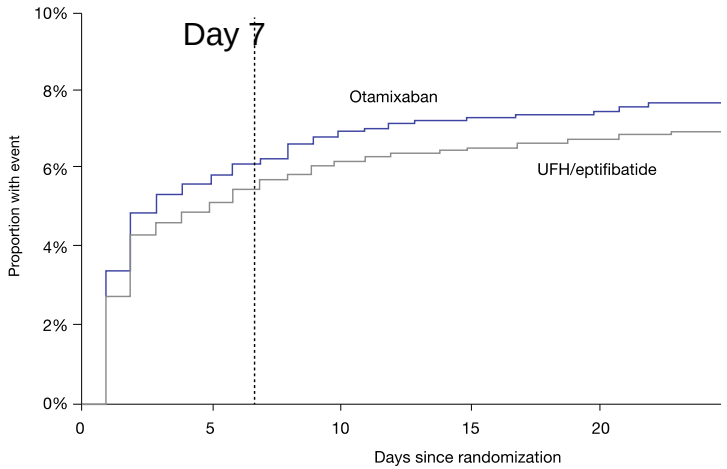
No. at Risk	Day 0	Day 7	Day 15	Day 30
Otamixaban	2657	2552	2533	2431
UFH + eptifibatide	5466	5293	5257	5086

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

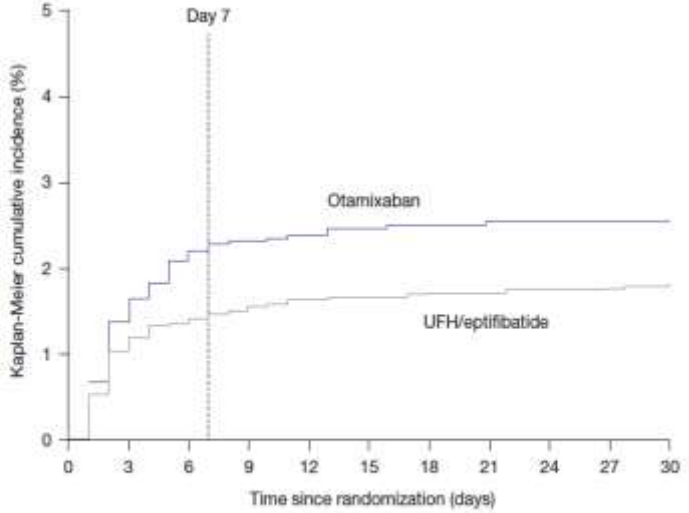


No. at Risk	Day 0	Day 10	Day 20
Otamixaban	2657	2472	2456
UFH + eptifibatide	5466	5132	5097

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.

Conclusion Oasis 5 and TAO Trials

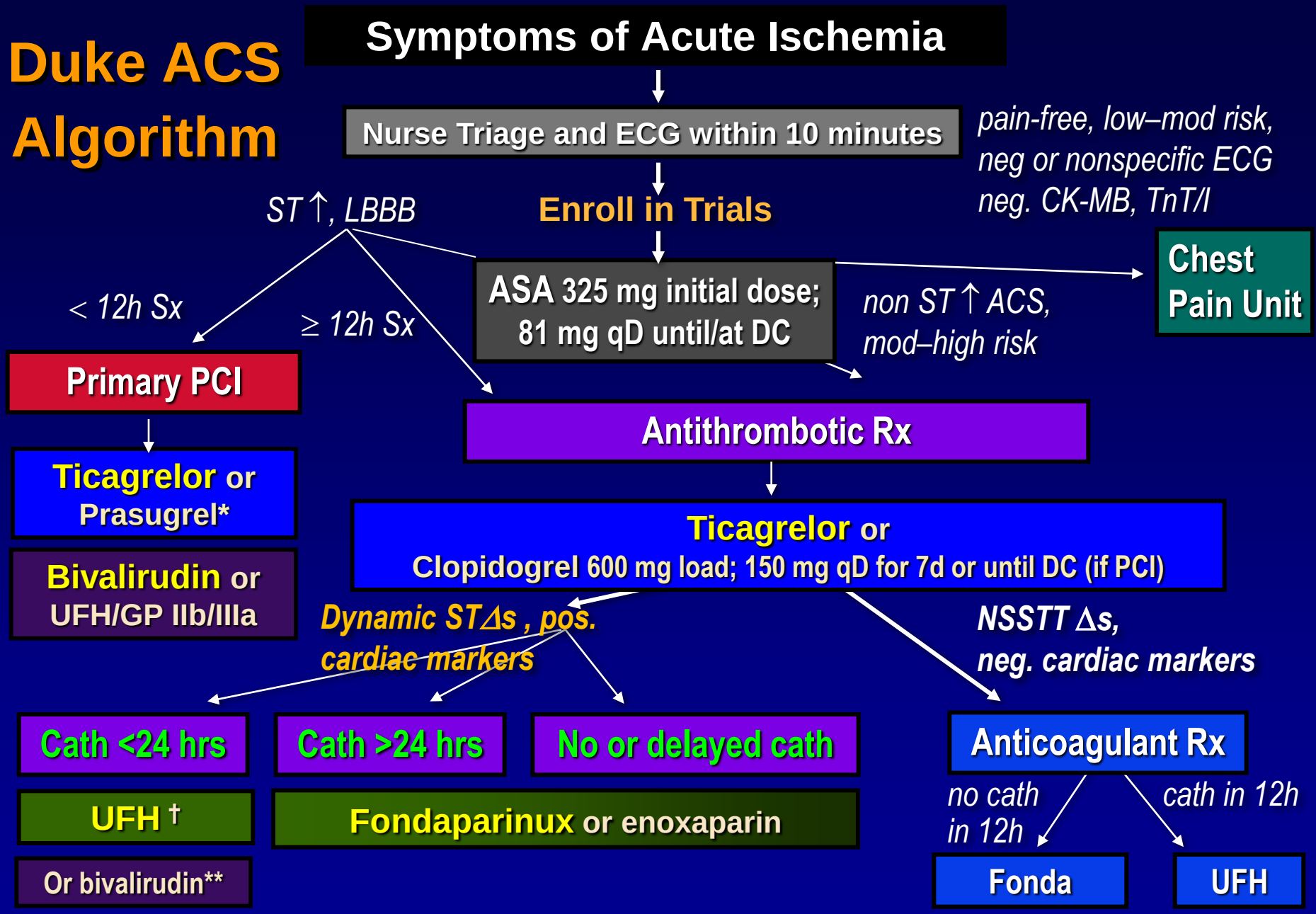
OASIS 5

- Fondaparinux at the dose studied reduces bleeding and mortality in patients with NSTEMI ACS
- Patients were treated for average 5 days prior to cath lab, small but increased risk of catheter thrombosis.

TAO Trials

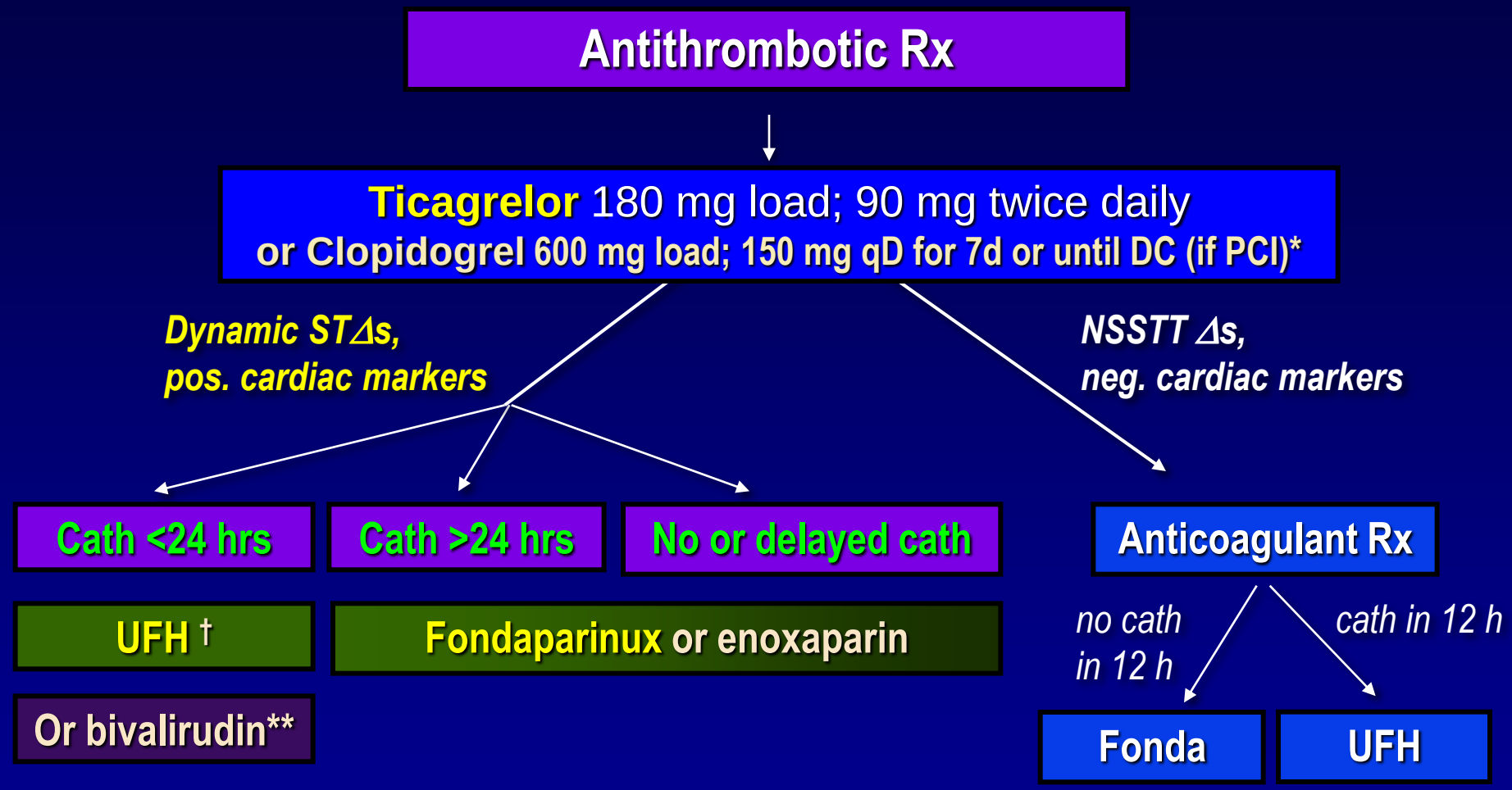
- Otamixiban did not reduce MACE and increased bleeding at both doses

Duke ACS Algorithm



*Prasugrel for primary PCI (if no h/o TIA or stroke); †GP IIb/IIIa at time of PCI or if refractory ischemia; **Consider bivalirudin for cath <12 hours

Duke ACS Algorithm: NSTE ACS



*Unless high bleeding risk; decrease to 75 mg qD at DC; 75 mg qD if no PCI
†GP IIb/IIIa at time of PCI or if refractory ischemia
**Consider bivalirudin for cath <12 hours

Factors in Choosing Which Anticoagulant

Condition	UFH	LMWH	Fonda	Bival
Severe renal insuff.	yes	avoid	avoid	yes-dose adjust
↑ bleeding risk	neutral	avoid	yes	yes
Thrombocytopenia	worst	better	better	best
Early cath strategy	yes	generally avoid	avoid	yes

Continue anticoagulant until (effective) revascularization or day 7/hospital discharge, whichever comes first