



**Sudy program to Evaluate the Prevention
of Ischemia with direct Anti-Xa inhibition:**

SEPIA-ACS1 – TIMI 42

**A randomized, double-blind, triple-dummy, dose-ranging study to
evaluate the clinical efficacy and safety of **OTAMIXABAN** in
patients with NSTEMACS and planned early invasive strategy**

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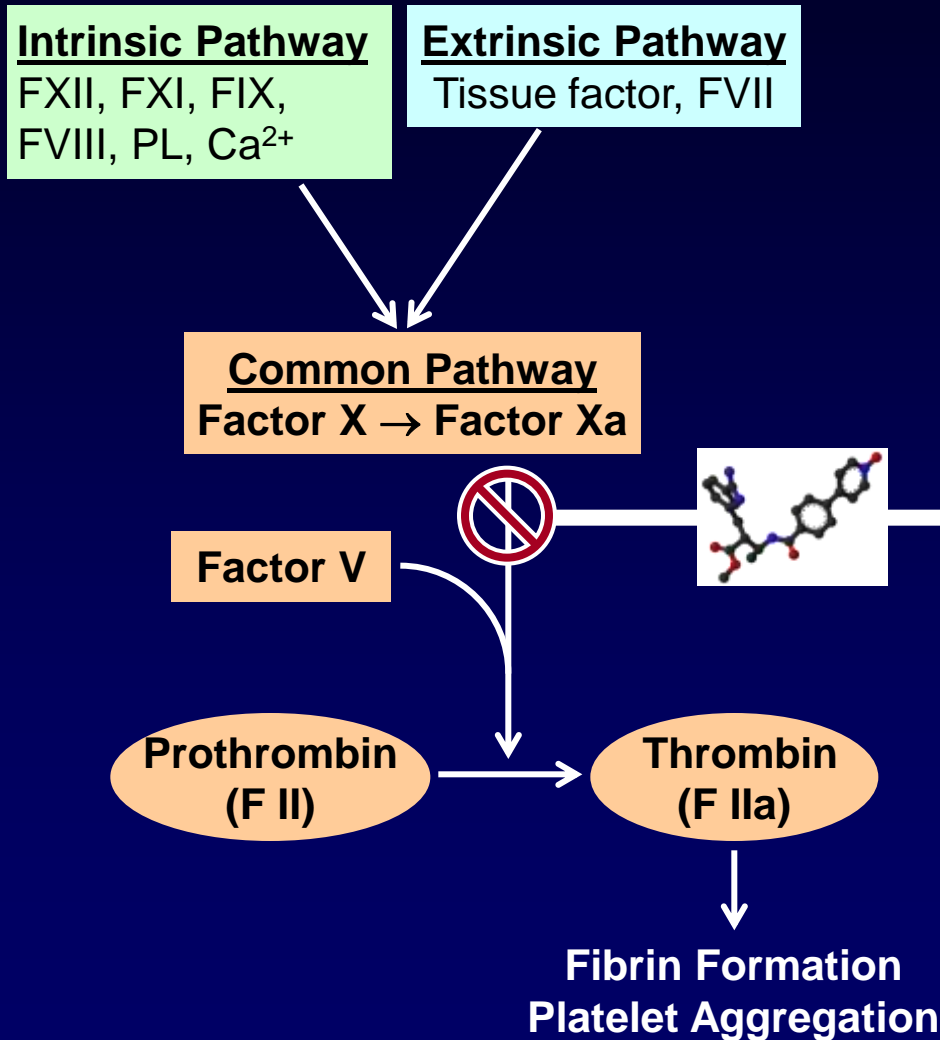
on behalf of the SEPIA-ACS1 TIMI 42 Investigators

Disclosures

SEPIA-ACS1 TIMI 42 was supported by a research grant from sanofi-aventis

M Sabatine has received honoraria and consulting fees from sanofi-aventis and honoraria from Bristol-Myers Squibb.

Coagulation Cascade



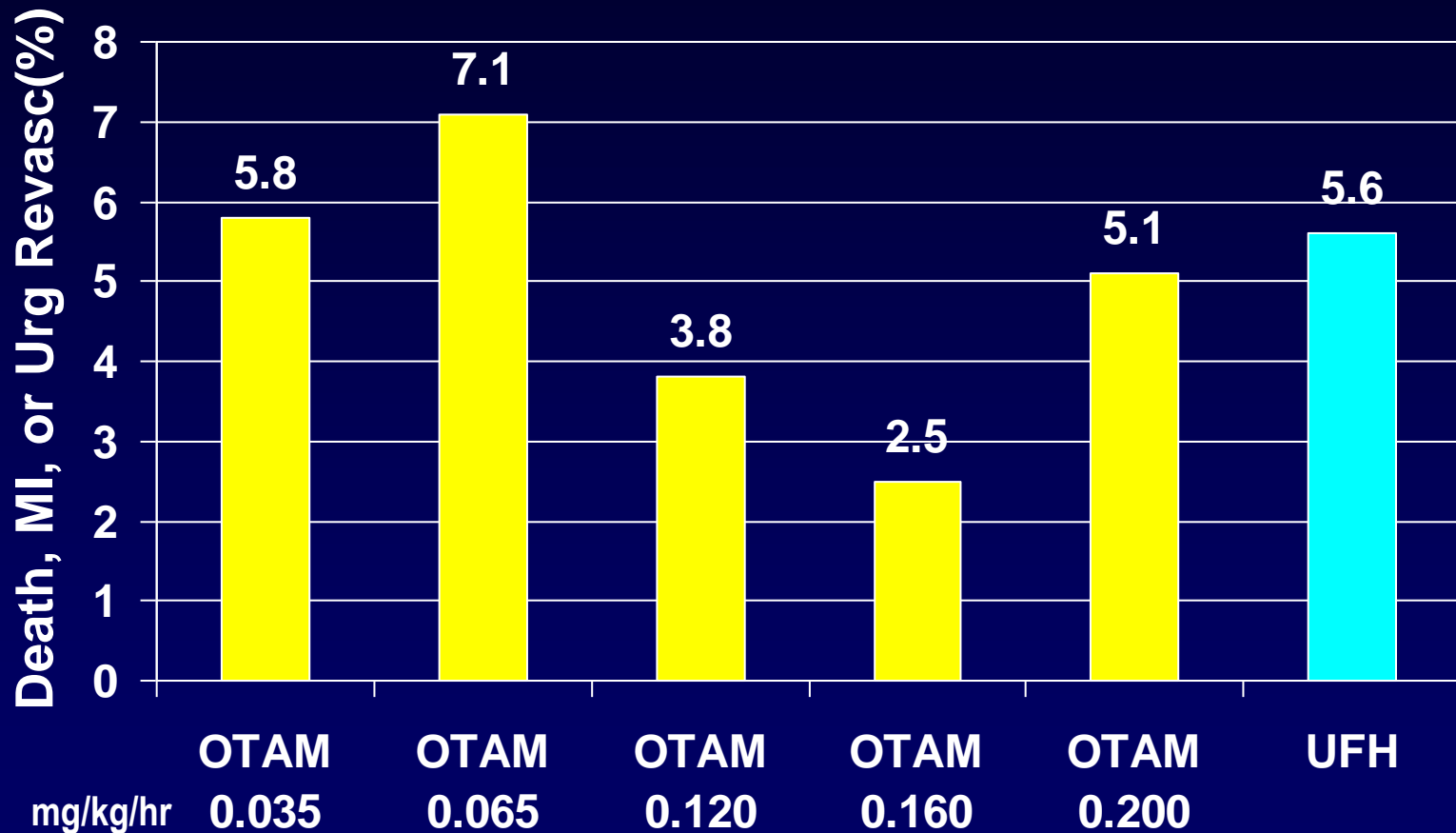
OTAMIXABAN

- **Specific Factor Xa inhibitor**
 - Proximal inhib of coag cascade
- **Small molecule, direct inhibitor**
 - Inhibits clot-bound factor Xa, which is inaccessible to large molecule & indirect inhibitors
- **Reversible, half-life 30 min**
 - Wt-based IV bolus & infusion
 - No significant renal elimination
 - Rapid initiation & d/c of anticoag

Clinical Efficacy Composite

947 patients undergoing non-urgent PCI

Greater reduction in thrombin generation w/ OTAM vs. UFH





Study Design

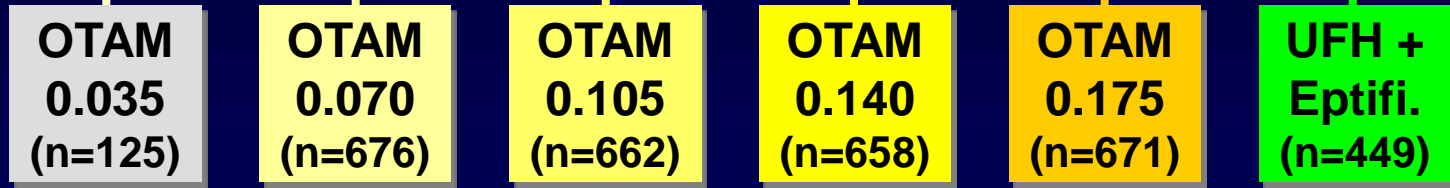


**Mod-to-High Risk NSTEMI ACS (ST deviation or \oplus biomarker)
w/ Planned Early Invasive Strategy**

Aspirin + Clopidogrel (loading dose)

at or before randomization

R



Bail-out eptifibatide in otamixaban groups if rec. ischemia or thrombotic complic. during PCI

Coronary angiography \pm PCI within 3 days

**OTAM / UFH until end of PCI (or longer if indic)
Eptifibatide until 18-24 h after end of PCI**

1° EP: Death, MI, Urgent Revasc, Bail-out IIb/IIIa thru 7 d

Follow-up at Day 30, Day 90, Day 180



Major Exclusion Criteria



- **Treatment with anticoagulant during index presentation for >24 h prior to randomization**
- **Requirement for treatment with an oral anticoagulant**
- **Contraindications to eptifibatide:**
 - **bleeding w/in previous 30 days or known bleeding diathesis**
 - **severe hypertension (SBP >200 mmHg or DBP >110 mmHg)**
 - **major surgery or trauma in the past 6 wks**
 - **history of stroke in the past 30 d or any history of hemorrhagic stroke**
 - **creatinine clearance <30 ml/min or dependence on renal dialysis**
- **Platelet count <100,000/ul; INR \geq 2**
- **Prior PCI within 30 days of randomization**
- **Cardiogenic shock**



Trial Organization



TIMI Study Group Brigham and Women's Hospital Harvard Medical School	E Braunwald, MD (Chair) MS Sabatine, MD, MPH (PI) EM Antman, MD (Co-PI) CH McCabe (Director) S Crugnale (Project Manager) CF Contant (Director of Biostats)
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Data Monitoring Cmte	P Theroux, MD (Chair) JP Bassand S Kelsey
Sponsor Sanofi-Aventis	A Moryusef, M Brynildsen S Hitier, T Colineau, S Ribadeau-Dumas, P Taistra, C Mahdi



Steering Committee



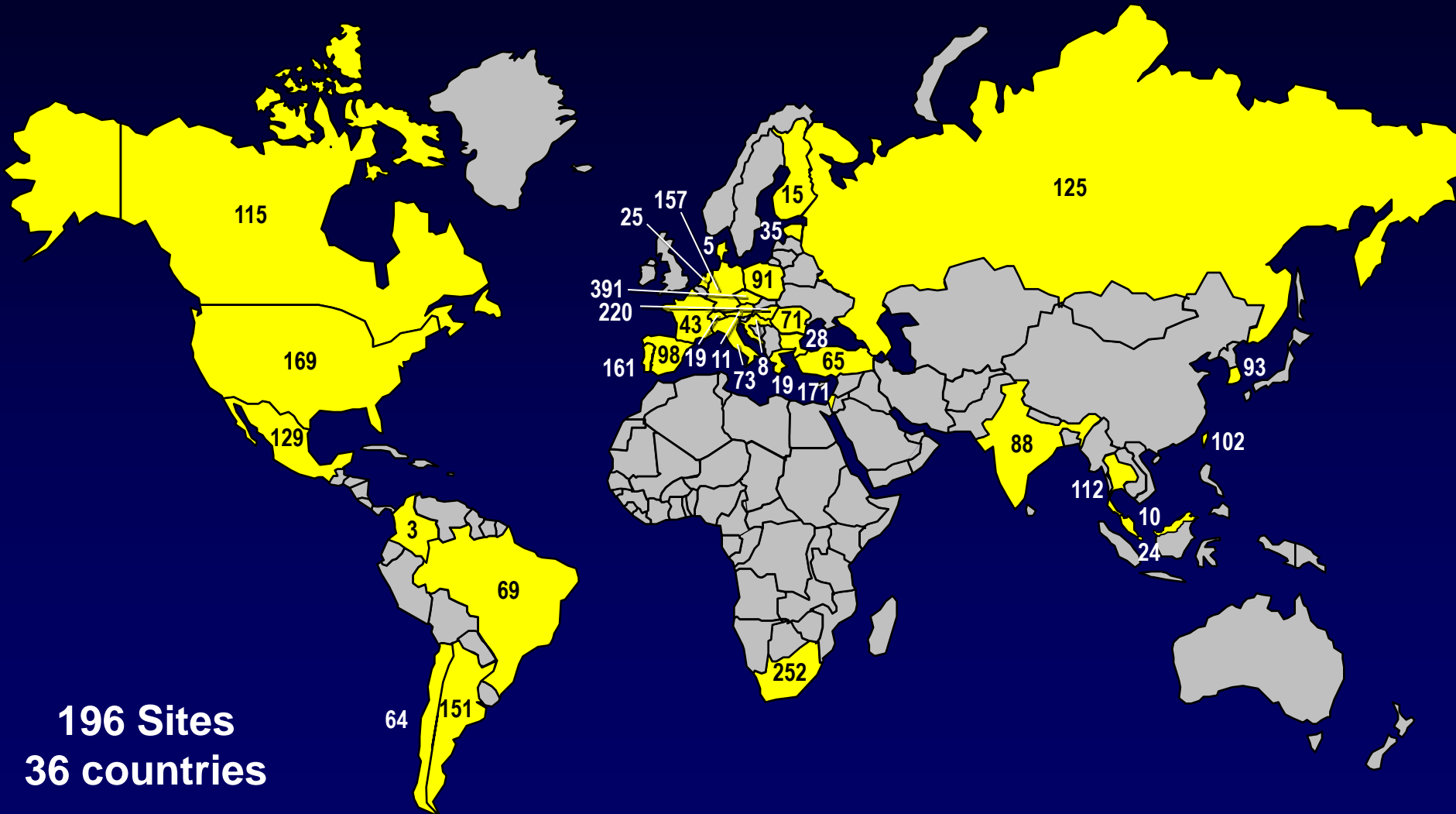
Argentina	JL Navaro Estrada	Israel	H Hod
Brazil	JC Nicolau	Italy	G DeFerrari
Canada	S Goodman	Mexico	F Petersen
Chile	R Corbalan	Netherlands	F Verheugt
Croatia	M Bergovec	Poland	W Ruzyllo
Czech Republic	P Widimsky	Portugal	R Ferreira
Denmark	P Clemmensen	Russia	M Ruda
Estonia	J Voitk	South Africa	IO Ebrahim
Finland	I Tierala	South Korea	M Jeong
France	G Montalescot	Southeast Asia	R Zambahari
Germany	C Bode	Spain	J Ruiz-Nodar
Greece	D Alexopoulos	Turkey	Z Ongen
Hungary	RG Kiss	United States	MS Sabatine
India	BS Raju		



Worldwide Participation



3241 Patients Randomized



196 Sites
36 countries



Baseline Characteristics



Variable	Value
Age, yrs	61 ± 12
Male, %	69
Hypertension, %	70
Dyslipidemia, %	50
Current smoker, %	32
Diabetes mellitus, %	29
Prior MI, %	21
Creatinine clearance, ml/min	95 ± 36
ST segment deviation ≥ 0.1 mV, %	57
Elevated cardiac biomarker of necrosis, %	77

No clinically relevant imbalances between treatment arms



Medications

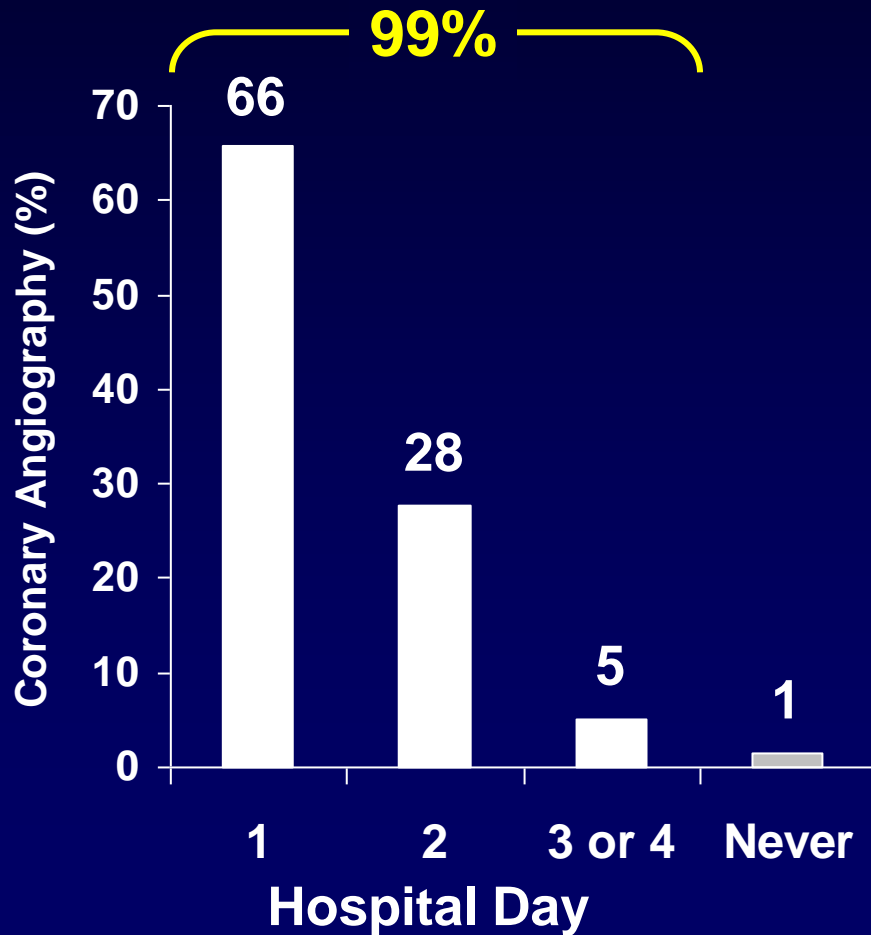


Treatment	Value
Study Med Duration, median hr:min	
Drug A (OTAM or pbo) & Drug B (UFH or pbo)	5 hrs
Drug C (Eptifibatide or pbo)	21 hrs
Aspirin, %	98
Clopidogrel, %	98
Dosed before angiography	95
Open label anticoag before study med*, %	65
UFH	34
LMWH	35
β-blocker, %	83
Statin, %	87

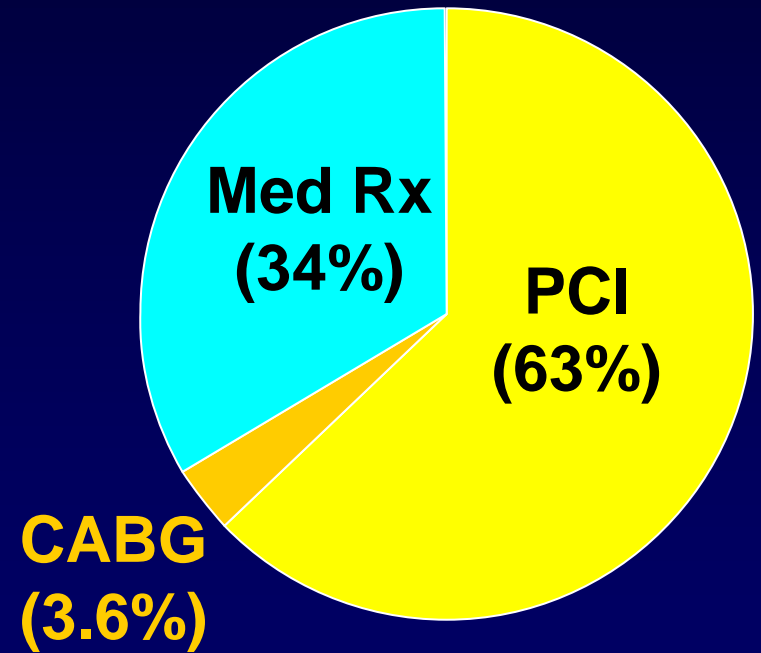
*Patients could have received more than 1 type of anticoagulant prior to study med



Cardiac Procedures



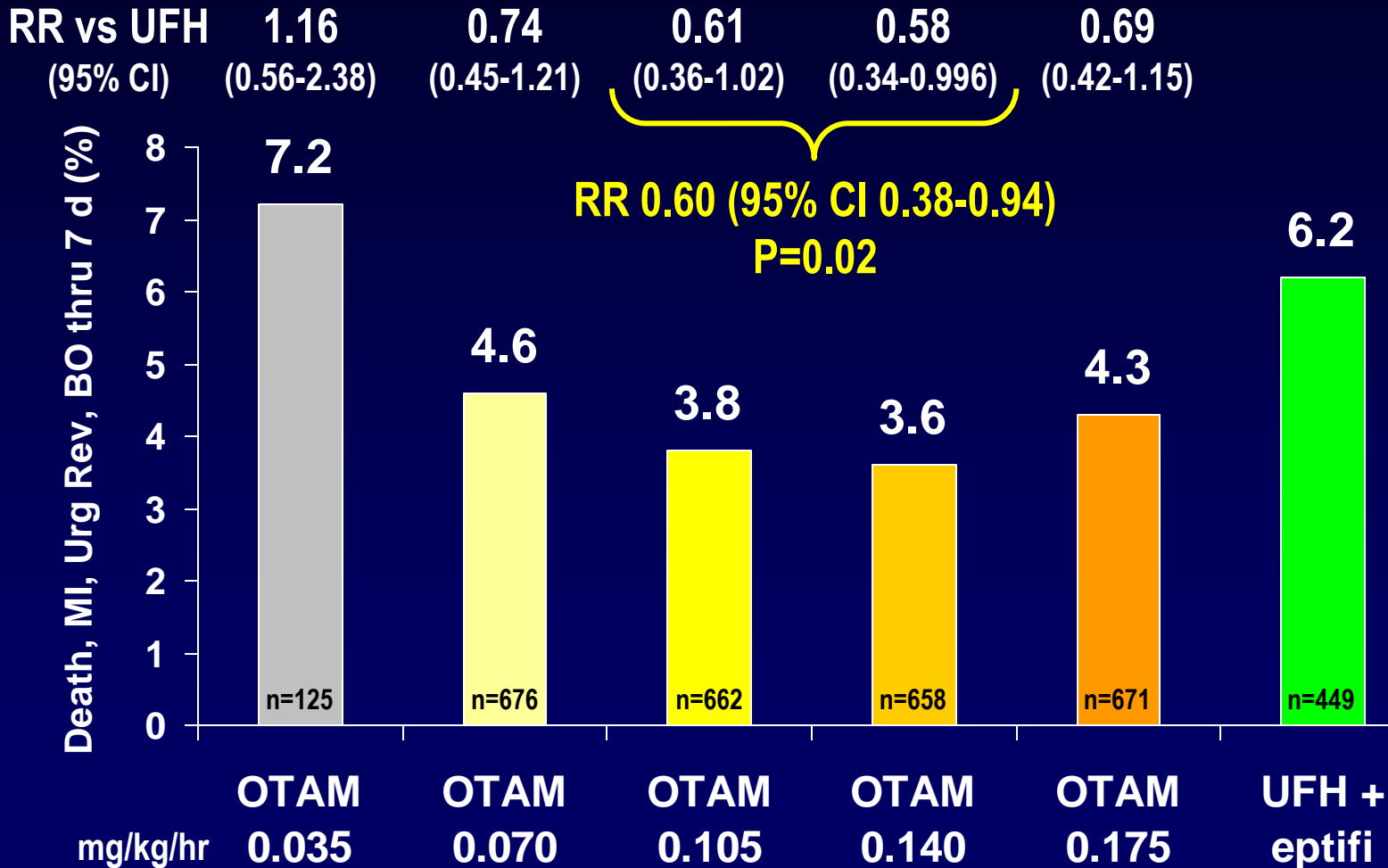
Coronary Treatment





Primary Efficacy Endpoint

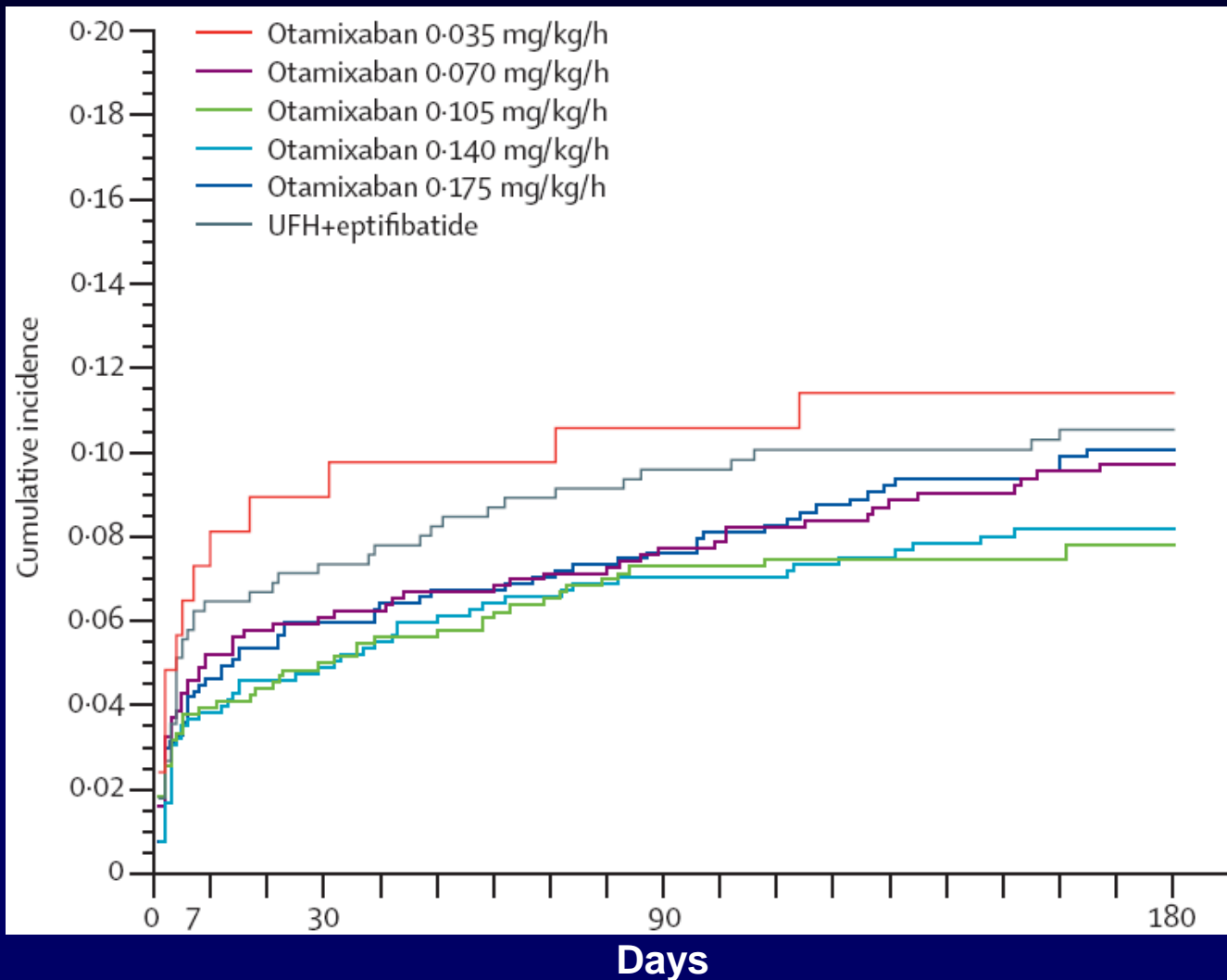
Death, MI, Urg Revasc, or Bailout GP IIb/IIIa



P=0.34 for trend across OTAM Dose Arms



Primary Endpoint over 180 Days

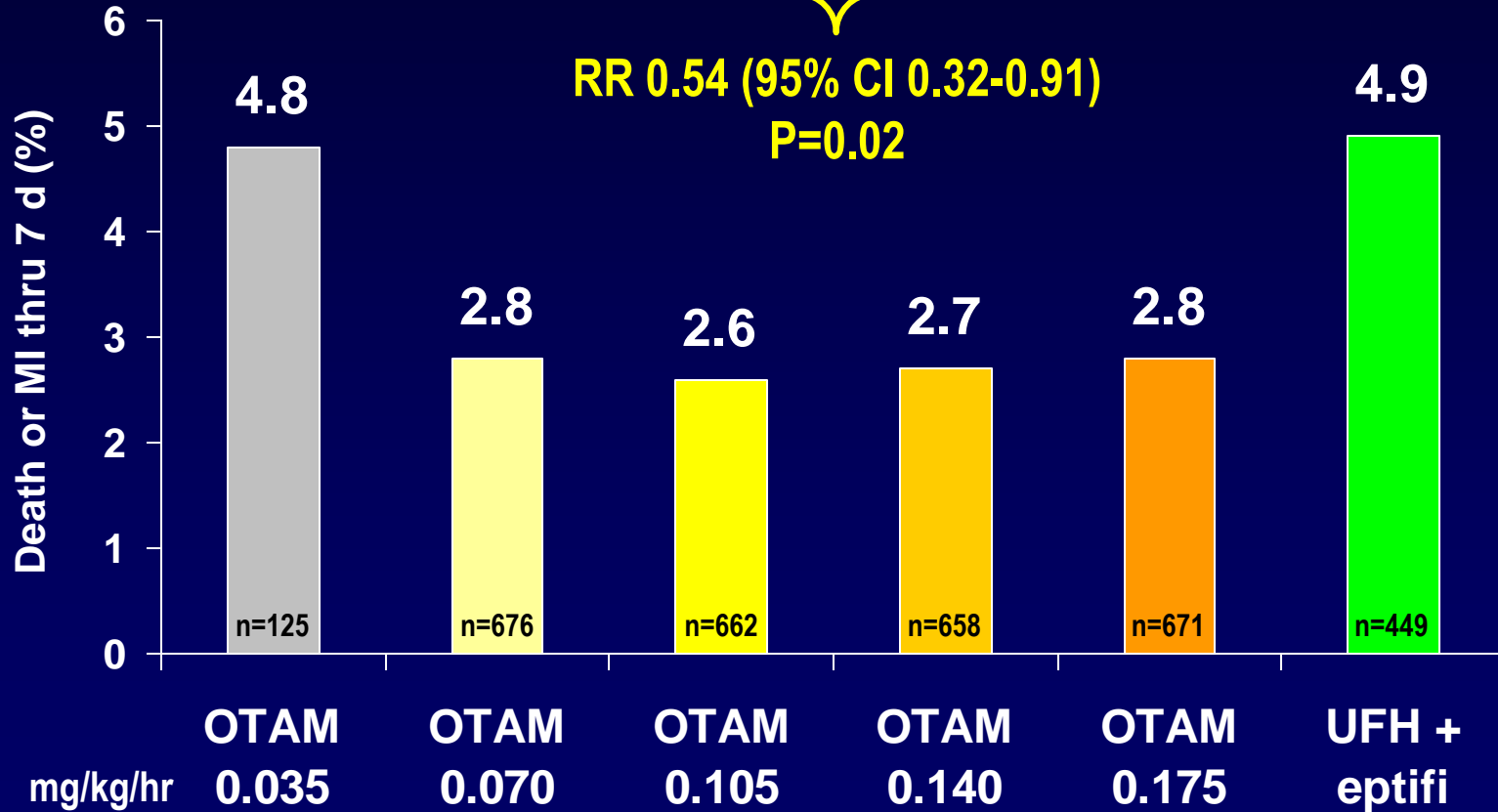




Death or MI

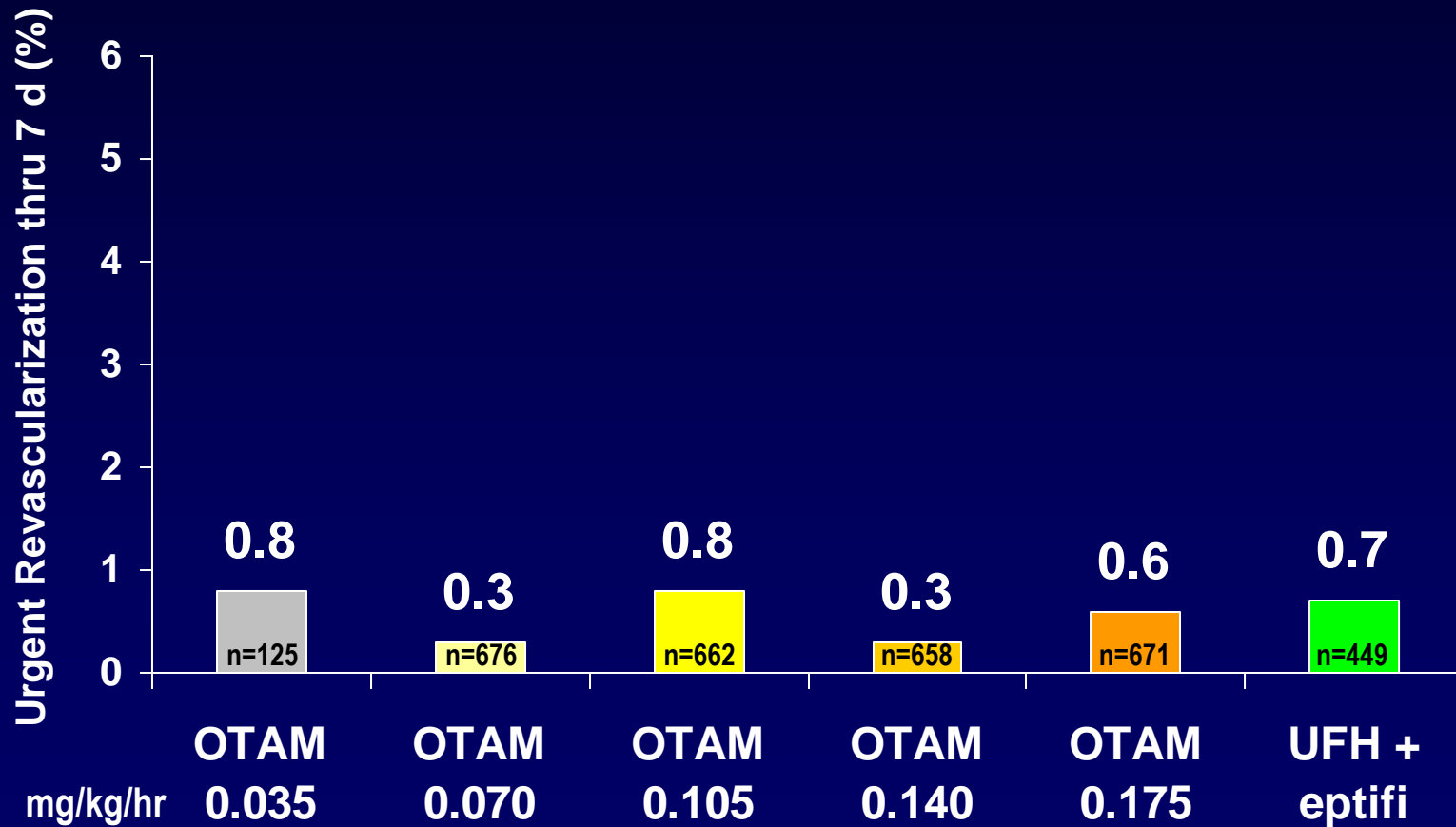


RR vs UFH 0.98 0.57 0.52 0.56 0.58
(95% CI) (0.41-2.36) (0.31-1.05) (0.28-0.98) (0.30-1.03) (0.32-1.06)



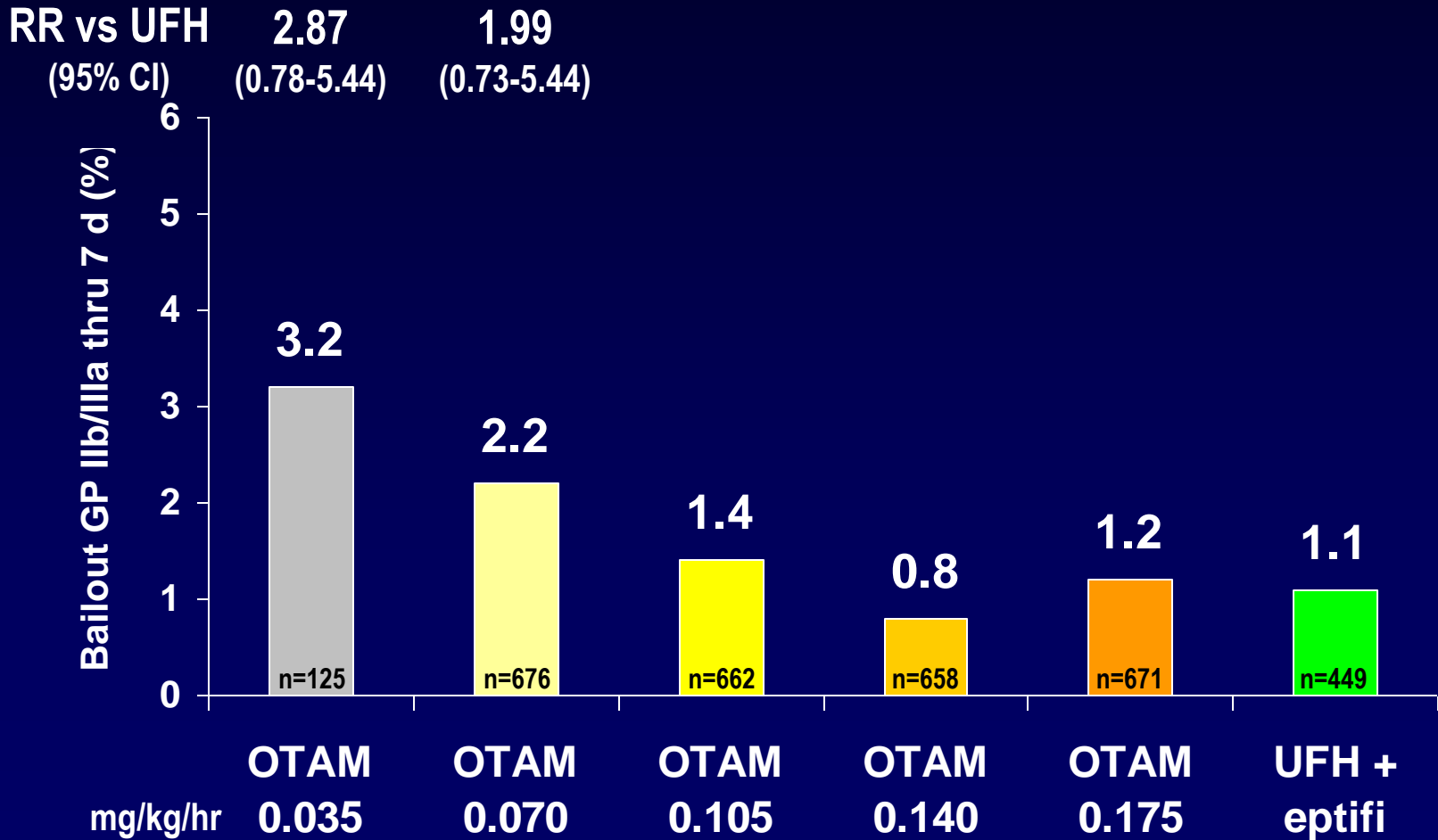


Urgent Revascularization





Bailout GP IIb/IIIa Inhibitor

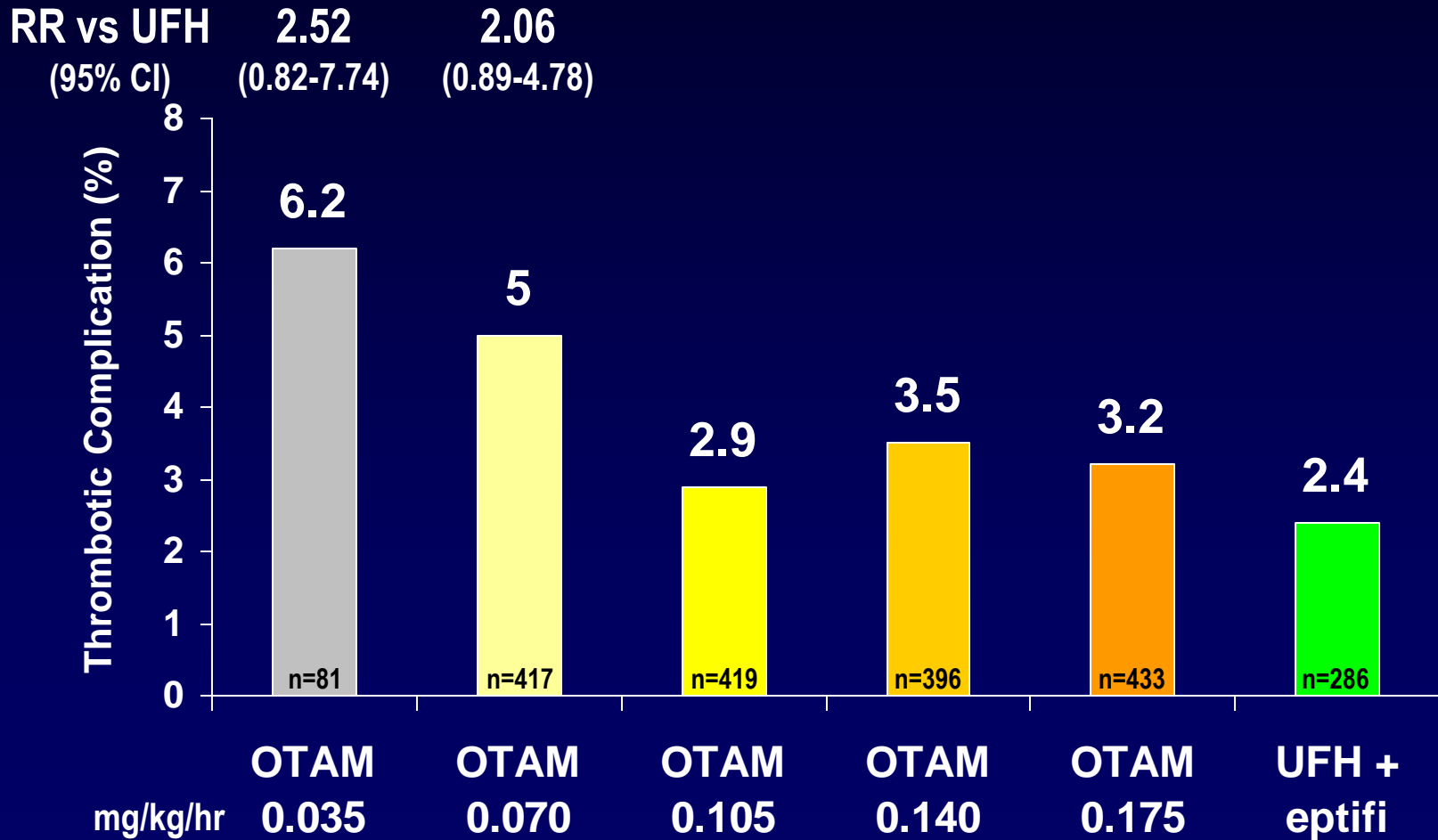




Thrombotic Complications



PCI Subset, $n=2032$ (63%)



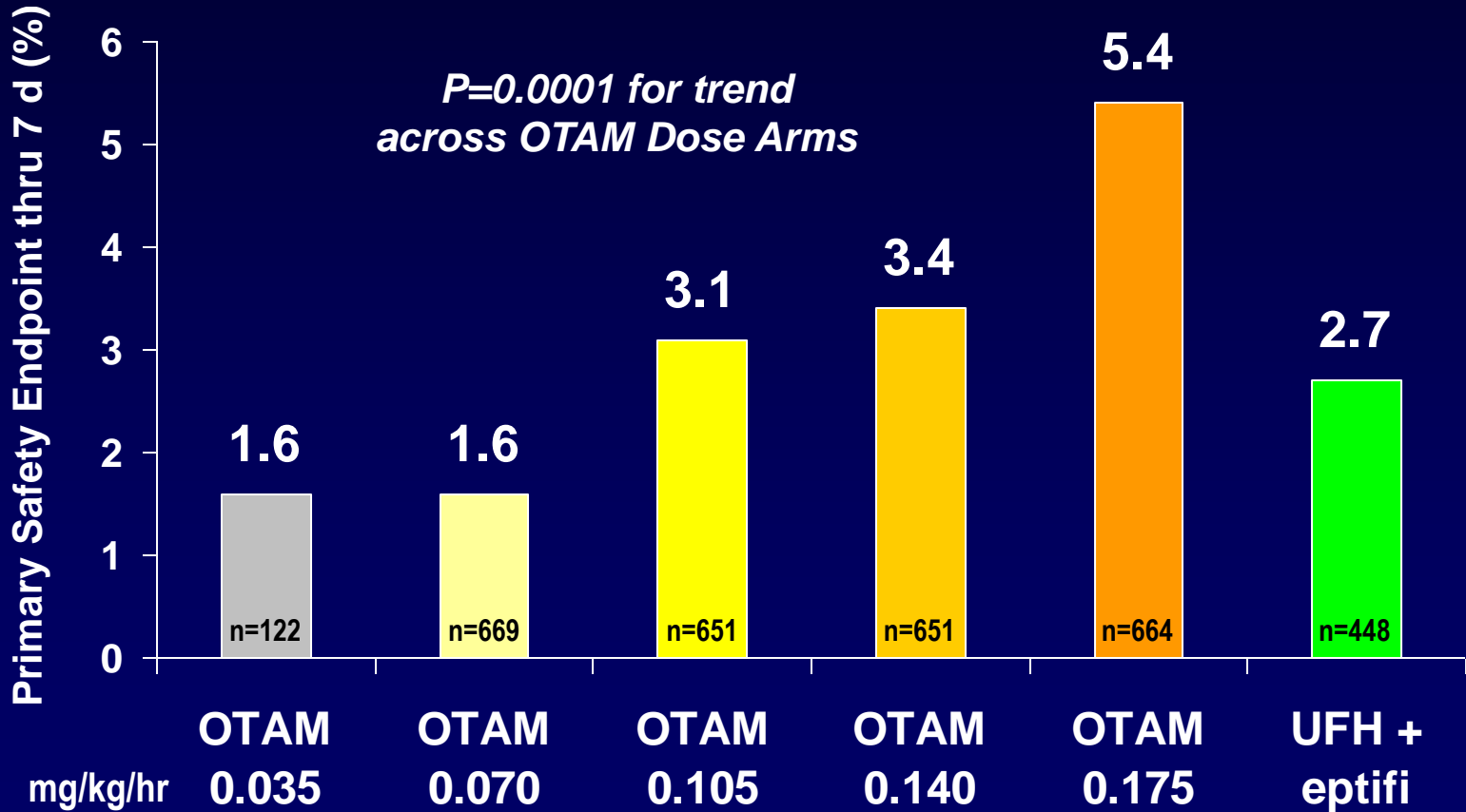


Primary Safety Endpoint

TIMI Major or Minor Bleed unrelated to CABG

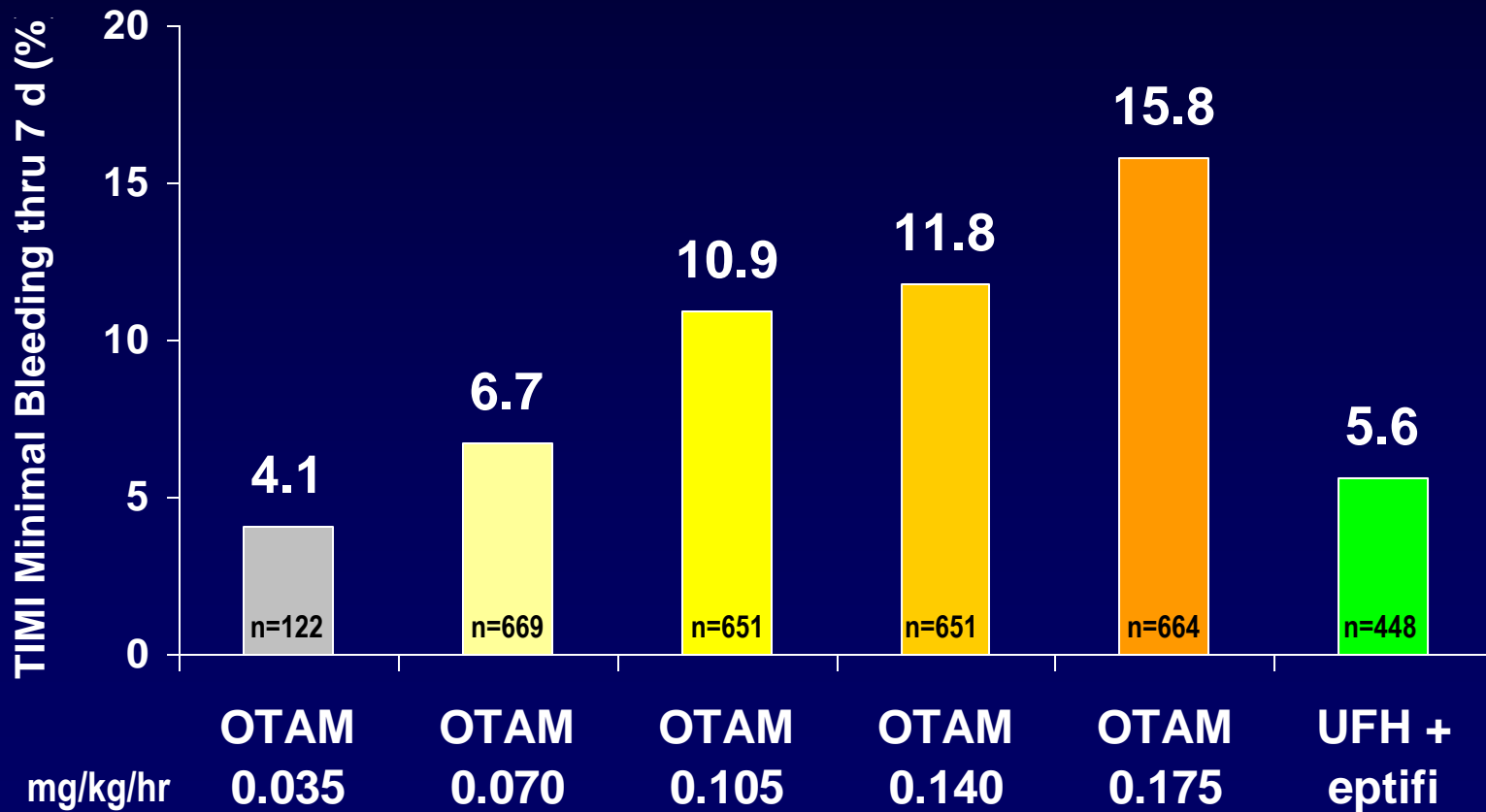


RR vs UFH	0.61	0.61	1.15	1.26	2.02
(95% CI)	(0.14-2.70)	(0.27-1.38)	(0.57-2.32)	(0.63-2.52)	(1.07-3.85)



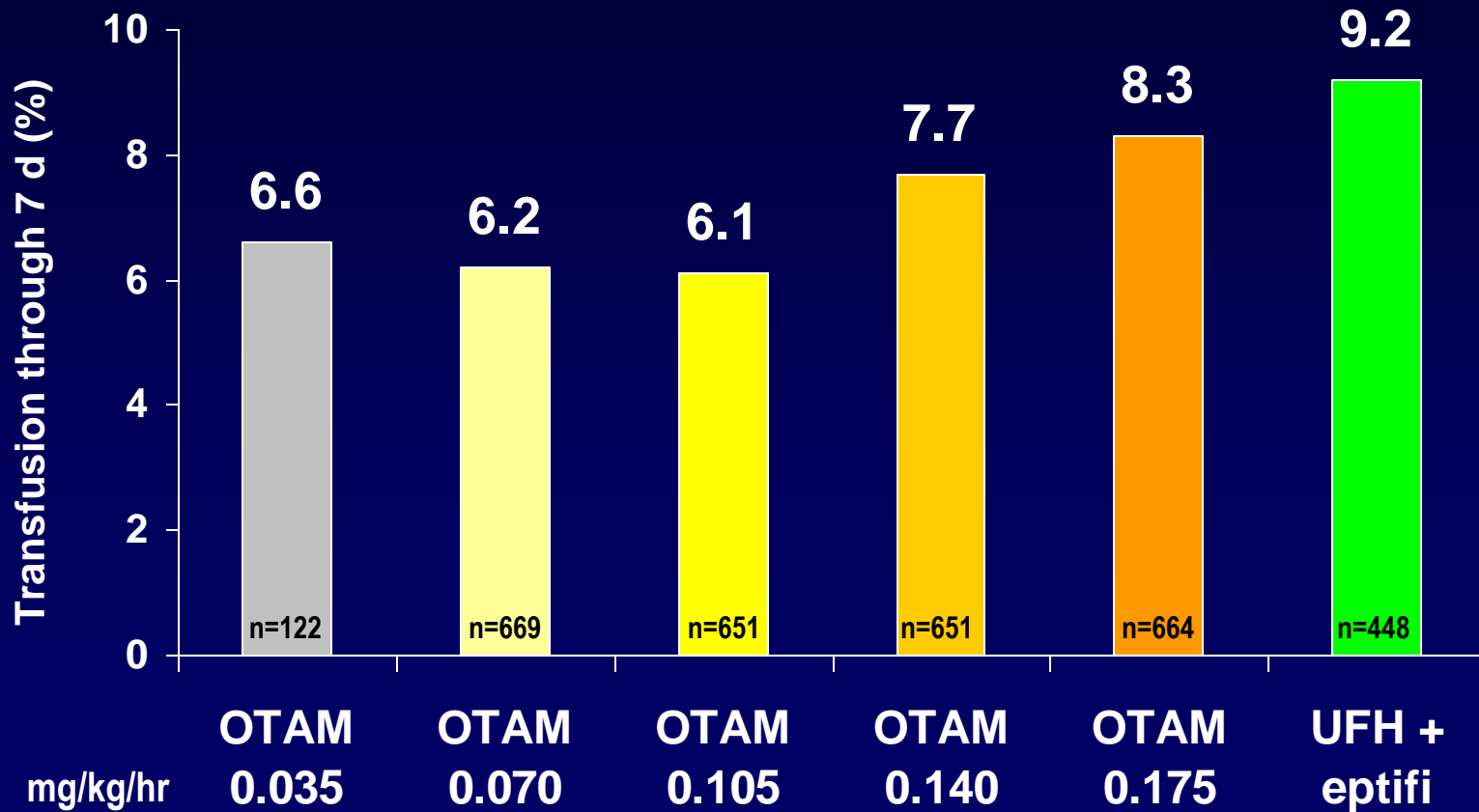


TIMI Minimal Bleeding





RBC Transfusion





Conclusions



- Otamixaban 0.105-0.140 mg/kg/h assoc w/ up to 40% ↓ in death or ischemic events compared w/ UFH + eptifibatide
- Otamixaban \leq 0.070 mg/kg/h assoc with ↑ need for bailout GP IIb/IIIa and thrombotic complications during PCI
- Otamixaban 0.175 mg/kg/h assoc with ↑ major & minor bleeding compared with UFH + eptifibatide; doses of 0.105-0.140 mg/kg/h not assoc w/ signif ↑ in major/minor bleeding
- Otamixaban 0.105-0.140 mg/kg/h appears to be best range for further study as a replacement for UFH + GP IIb/IIIa