Anticoagulant Therapy in Acute Coronary Syndromes

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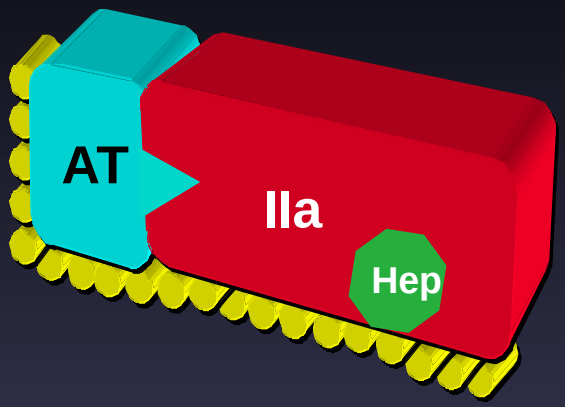
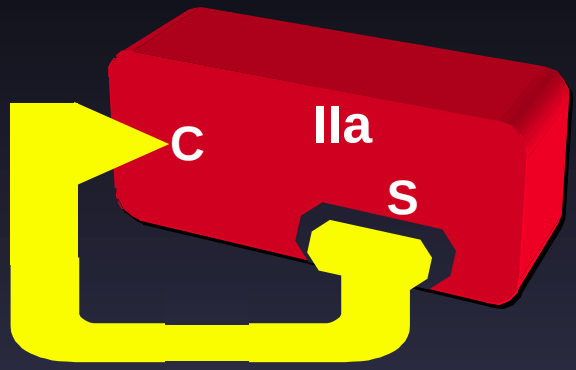
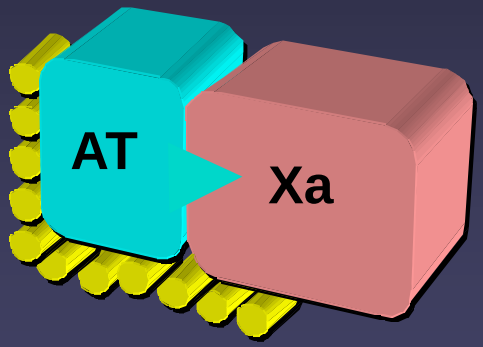
Four Anticoagulant Choices



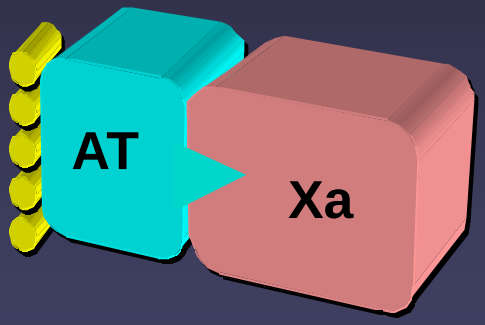
UFH



Direct antithrombin



LMWH

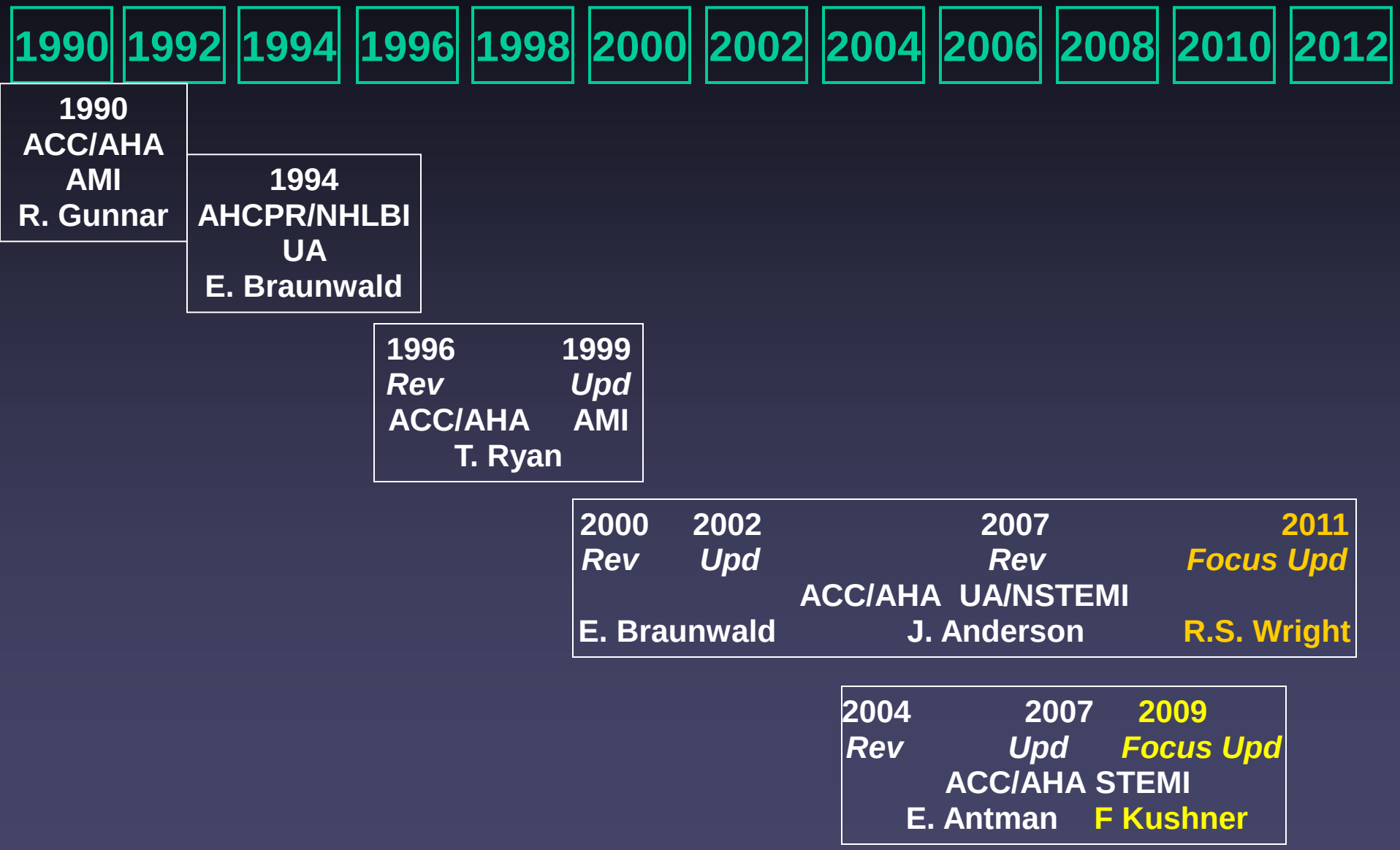


Pentasaccharide

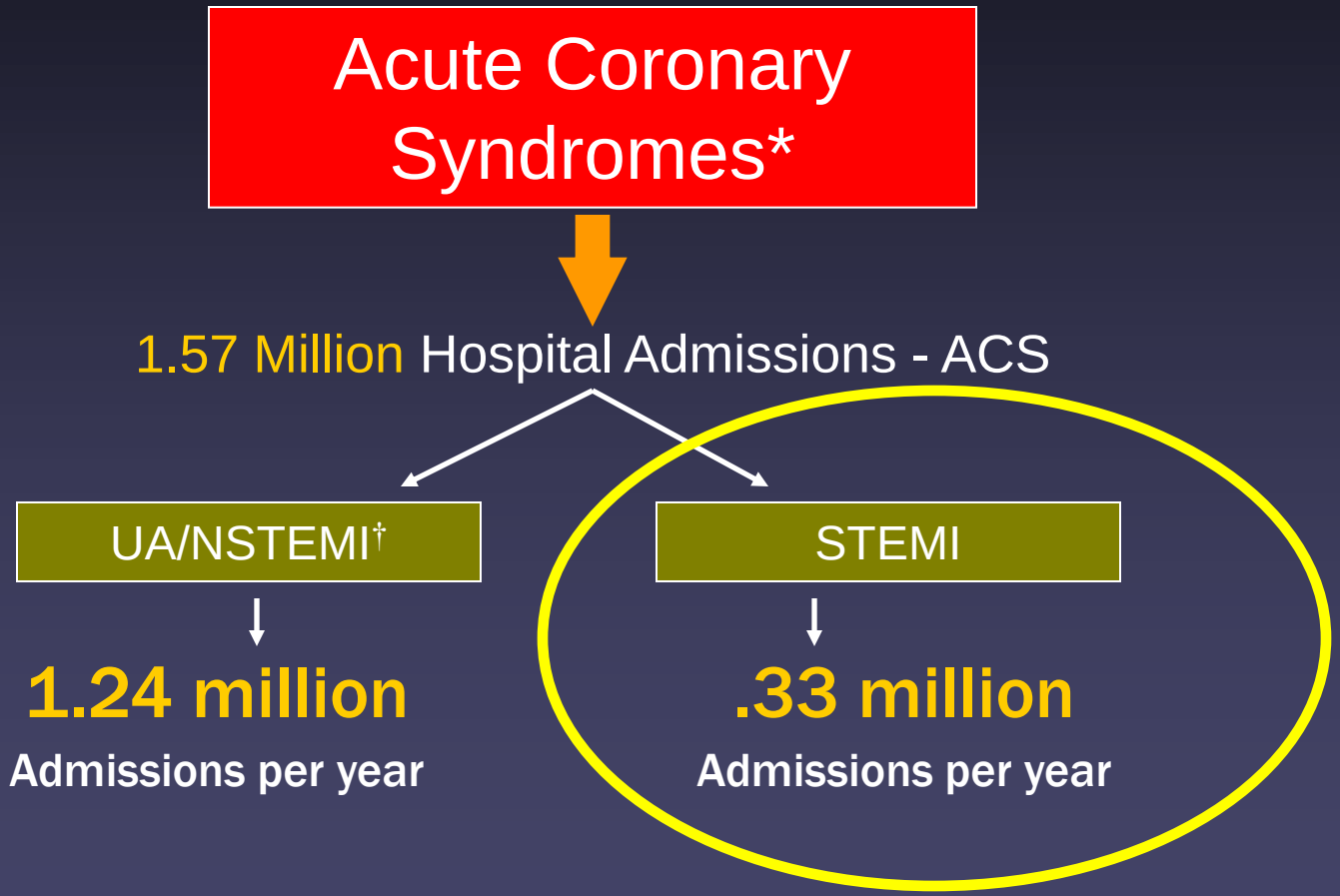
Konkle BA, Schafer AI. In: Zipes DP, Libby P, Bonow RO, Braunwald E, eds. *Braunwald's Heart Disease*. Vol 2. 7th ed. Philadelphia: Elsevier Saunders; 2005:2067-2092.

= saccharide unit.

Evolution of US Guidelines for ACS



Hospitalizations in the U.S. Due to Acute Coronary Syndromes (ACS)



Heart Disease and Stroke Statistics – 2007 Update. Circulation 2007; 115:69-171.
*Primary and secondary diagnoses. †About 0.57 million NSTEMI and 0.67 million UA.

Unfractionated Heparin (UFH)

*AHA/ACC 1999 Guidelines**

UFH: Bolus 60 U/kg (max 4000 U)
Infusion 12 U/kg/h (max 1000 U/h)

Adjust aPTT to 1.5 to 2.0 times control

Treat for 48 hours, longer if high risk for systemic or venous thromboembolism

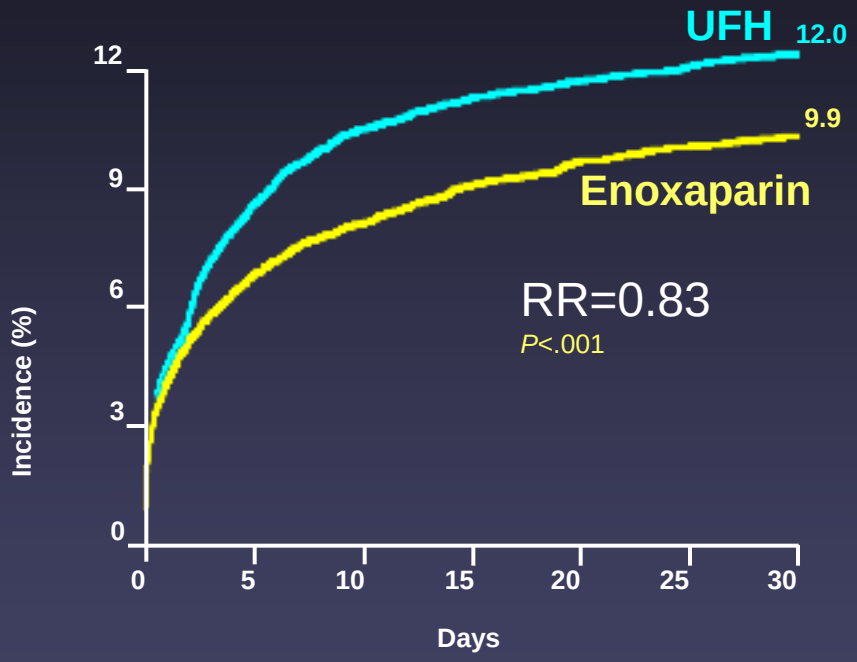
*Circulation 1999;100:1016-30

Current Recommendations in STEMI:
Fibrinolysis – Class I (except Class II with SK per ESC)
Primary PCI – Class I
No Reperfusion – Class II (ACC/AHA), Class I (ESC)

Main Results From ExTRACT–TIMI 25

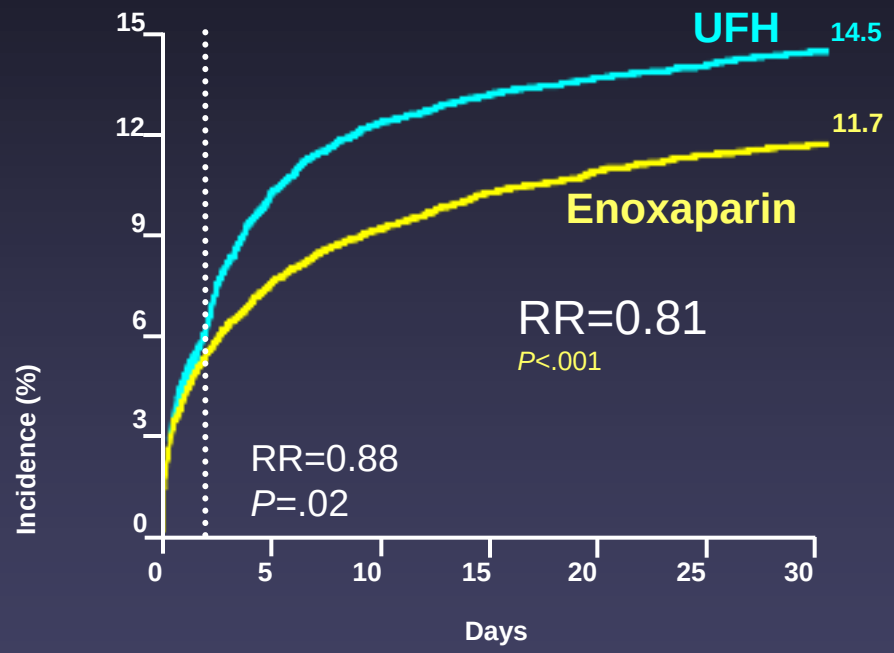
Primary End Point:

Death or nonfatal re-MI by 30 days



Main Secondary End Point:

Death, nonfatal re-MI, or urgent revascularization by 30 days

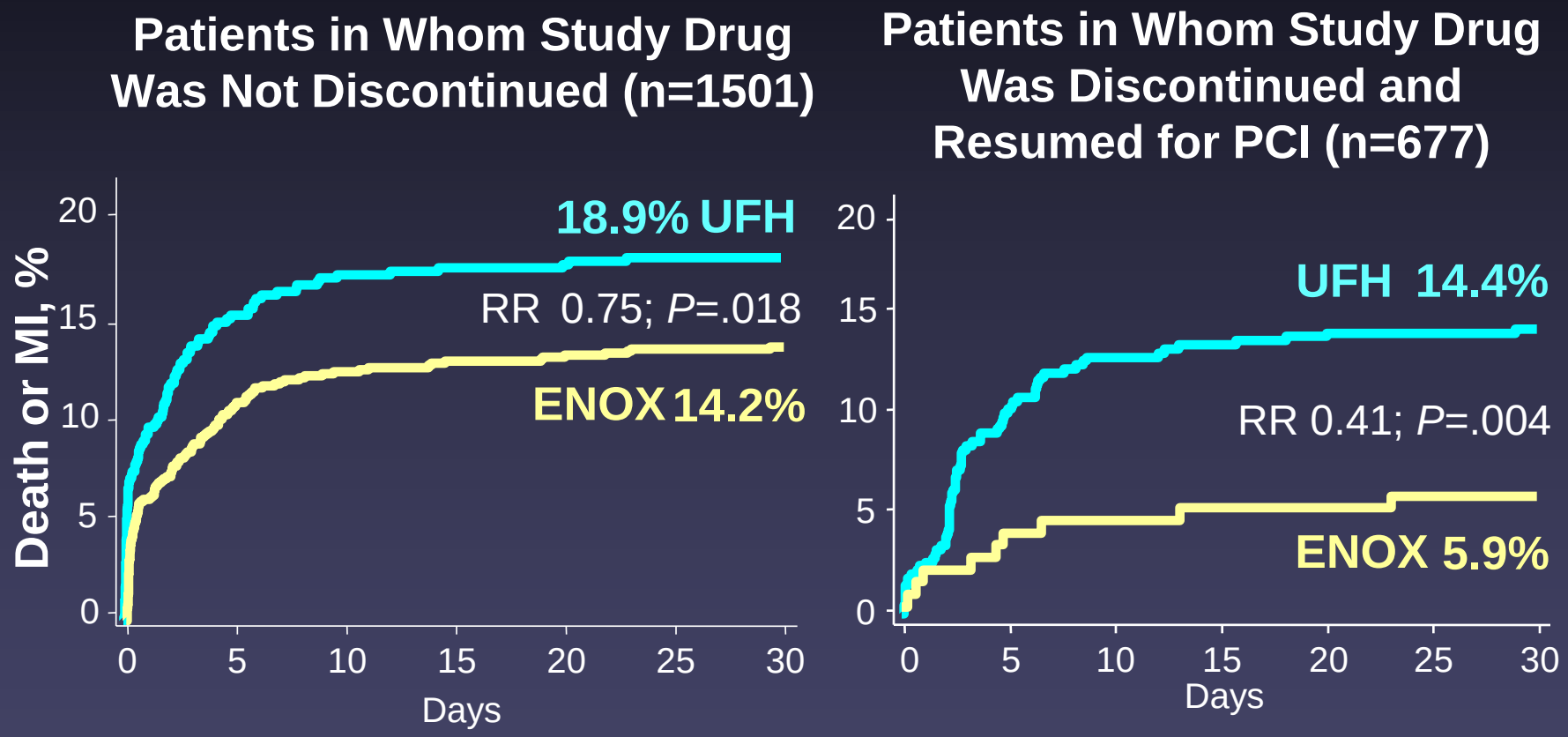


- **Major bleeding at 30 days: 1.4% with UFH vs 2.1% with enoxaparin (*P*<.001)**
- **ICH: 0.7% for UFH vs 0.8% for enoxaparin (*P*=.14)**

Antman EM, et al. *N Engl J Med*. 2006;354:1477-1488.

Current Recommendations: Fibrinolysis – Class I (except Class II with SK per ESC)

PCI-ExTRACT–TIMI 25: Death or Nonfatal MI by 30 Days Among PCI Patients



Gibson CM. JACC 2007;49:2238-46

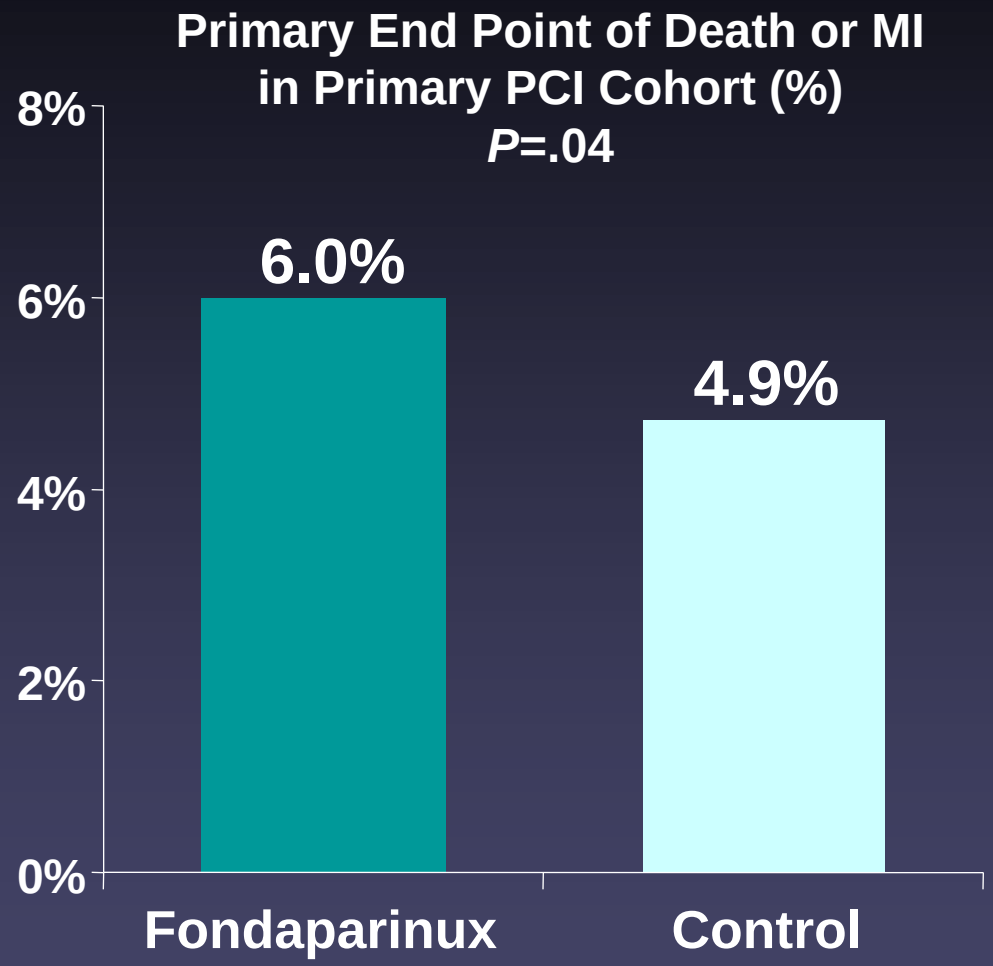
Current Recommendations: PCI – Class I-B (ACC/AHA)

PCI-ExTRACT: Safety in PCI Cohort

Event	ENOX n=2238	UFH n=2377	RR	*P*
TIMI Major Bleed	1.4%	1.6%	0.87 (0.55-1.39)	.56
TIMI Minor Bleed	3.3%	2.4%	1.34 (0.95-1.88)	.09
TIMI Major or Minor Bleed	4.6%	4.0%	1.15 (0.88-1.51)	.31
ICH	0.2%	0.4%	0.42 (0.13-1.35)	.18
Stroke	0.3%	0.9%	0.30 (0.12-0.75)	.006

Gibson CM. JACC 2007;49:2238-46
Adapted with permission from www.clinicaltrialresults.org.

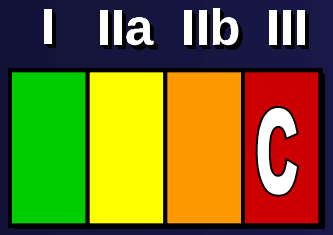
OASIS-6: PCI Substudy at 30 Days



- There was no benefit with fondaparinux for the primary end point in patients undergoing primary PCI (6.0% vs 4.9%, *P*=.04)
- Guiding catheter thrombosis in the primary PCI cohort occurred more often with fondaparinux compared with control (n=22 vs n=0, *P*<.001)

Yusuf S, et al. *JAMA*. 2006;295:1519-1530.
Adapted with permission from www.clinicaltrialresults.org.

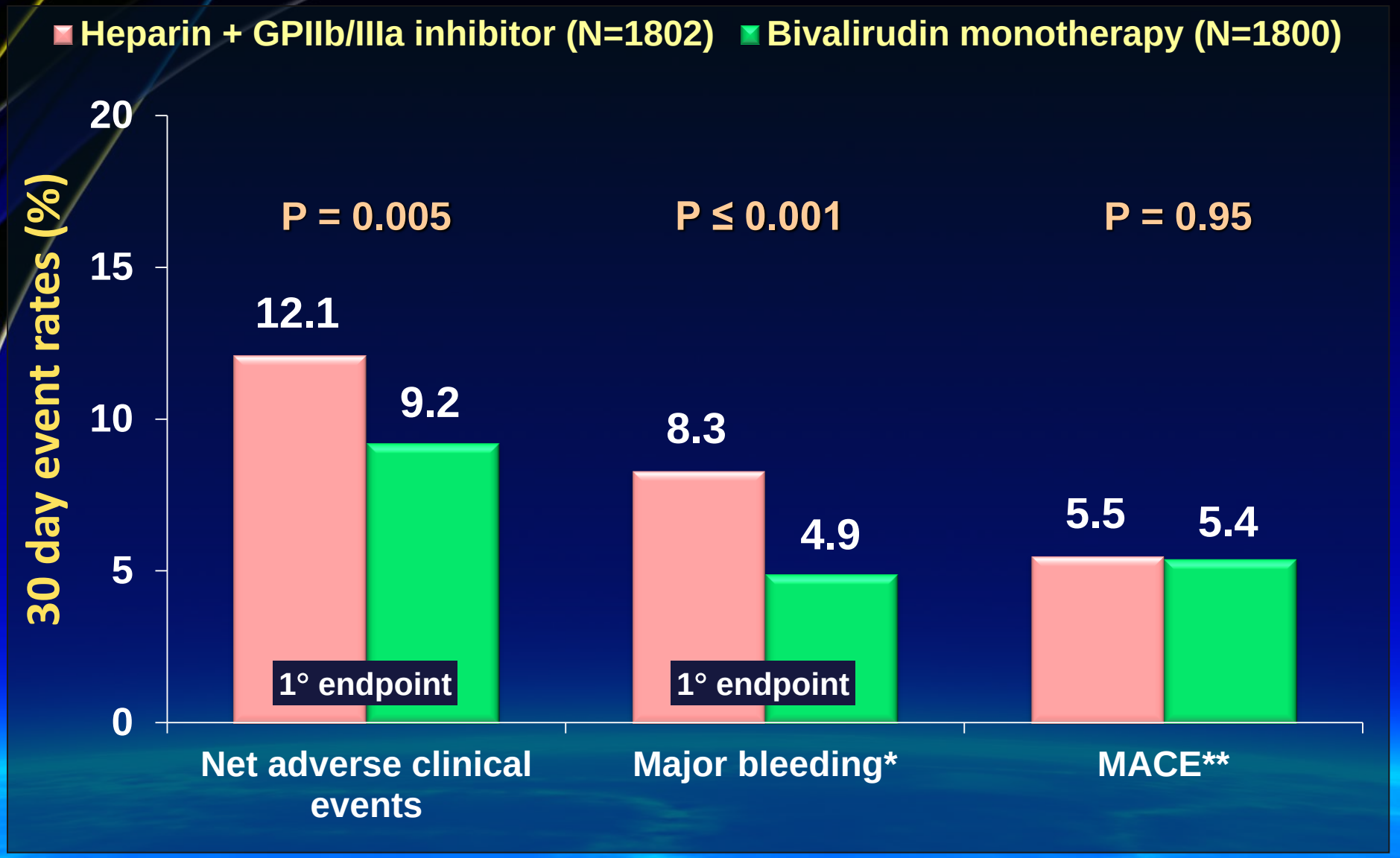
Fondaparinux



Because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant to support PCI. An additional anticoagulant with anti-IIa activity should be administered.

Antman EM. *JACC* 2008;51:210-247.

HORIZONS AMI: Primary Outcomes



*Not related to CABG

**MACE = All cause death, reinfarction, ischemic TVR or stroke

Stone GW NEJM 2008;358:2218-30

HORIZONS AMI

30 Day Stent Thrombosis (N=3,124)

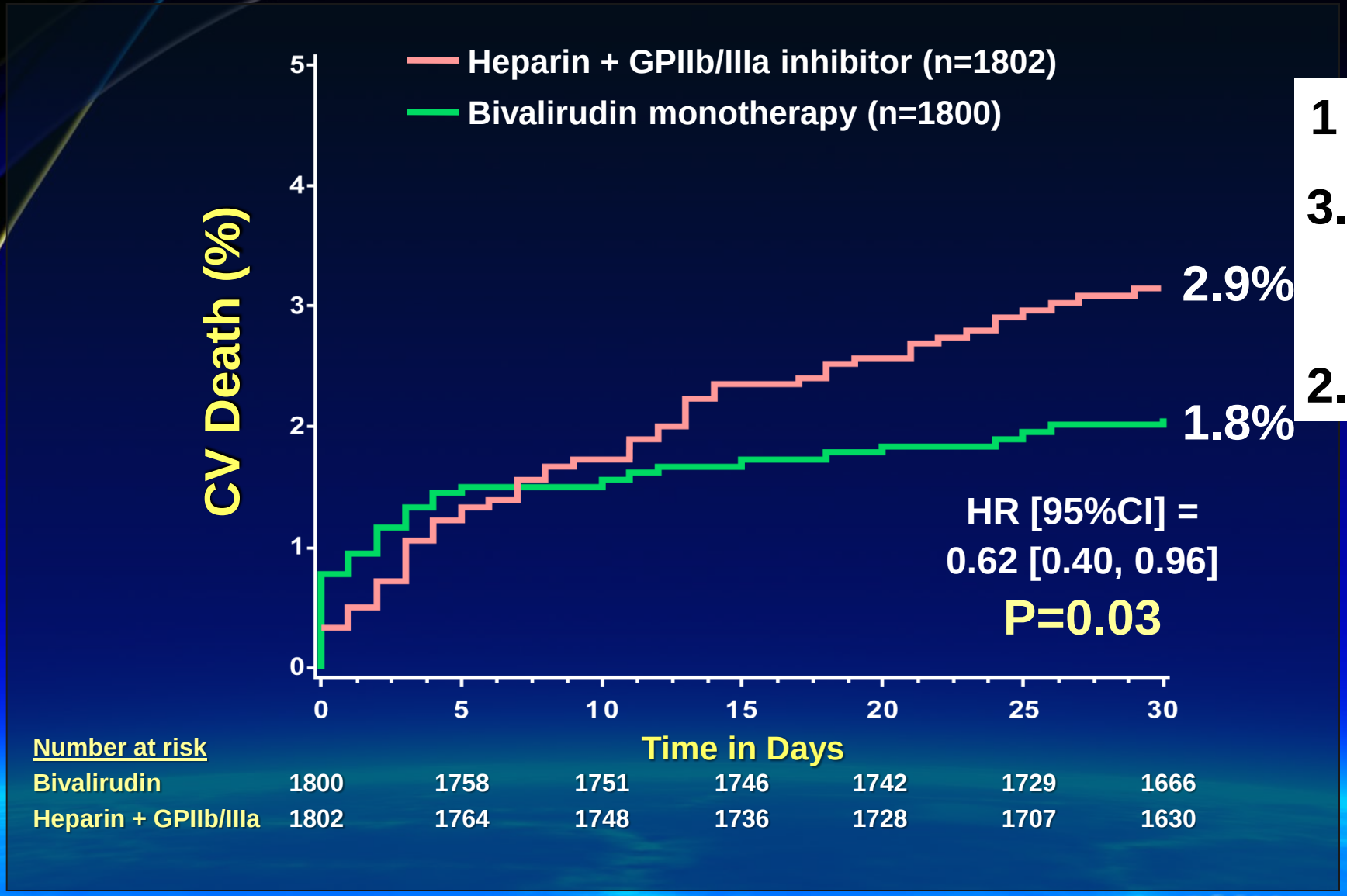
	UFH + GP IIb/IIIa (N=1553)	Bivalirudin (N=1571)	P Value
ARC definite or probable*	1.9%	2.5%	0.33
- definite	1.4%	2.2%	0.11
- probable	0.5%	0.3%	0.26
- acute (≤24 hrs)	0.3%	1.3%	0.0009
- subacute (>24 hrs – 30d)	1.7%	1.2%	0.30

*Protocol definition of stent thrombosis, CEC adjudicated

Stone GW NEJM 2008;358:2218-30

HORIZONS-AMI

30 Day Cardiovascular Mortality



	1 Yr
	3.8%
	2.1%

Stone GW NEJM 2008;358:2218-30

Mehran R. Lancet 2009;374:1149-59

HORIZONS-AMI

Bivalirudin – 2009 New Recommendations

Class I (LOE B):

Bivalirudin is useful as a supportive measure for primary PCI with or without prior UFH

Class IIa (LOE B):

In patients at high risk of bleeding, bivalirudin is reasonable

Kushner FG. Circ 2009;120:2271-306

Secondary Prevention: Warfarin

Modified Class I Recommendation

- Managing warfarin to an INR equal to 2.0-3.0 for paroxysmal or chronic AF or flutter is recommended, and in post-MI patients when clinically indicated (eg, AF, LV thrombus)

New Class I Recommendation

- Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely

New Class I Recommendation

- In patients requiring warfarin, clopidogrel, and aspirin therapy, an INR of 2.0-2.5 is recommended with low-dose aspirin (75-81 mg) and a 75-mg dose of clopidogrel

AF = atrial fibrillation.

Antman EM, et al. *J Am Coll Cardiol.* 2008;51:210-247.

Recent ACS: STEMI, NSTEMI, UA

Stabilized 1-7 Days Post-Index Event

Exclusions: increased bleeding risk, warfarin use, ICH, prior stroke if on ASA + thienopyridine

ASA 75 to 100 mg/day

Stratified by Thienopyridine Use at MD Discretion

Placebo	Rivaroxaban 2.5 mg BID	Rivaroxaban 5.0 mg BID
n=5,176	n=5,174	n=5,176

PRIMARY ENDPOINTS:

EFFICACY: CV Death, MI, Stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

SAFETY: TIMI major bleeding not associated with CABG

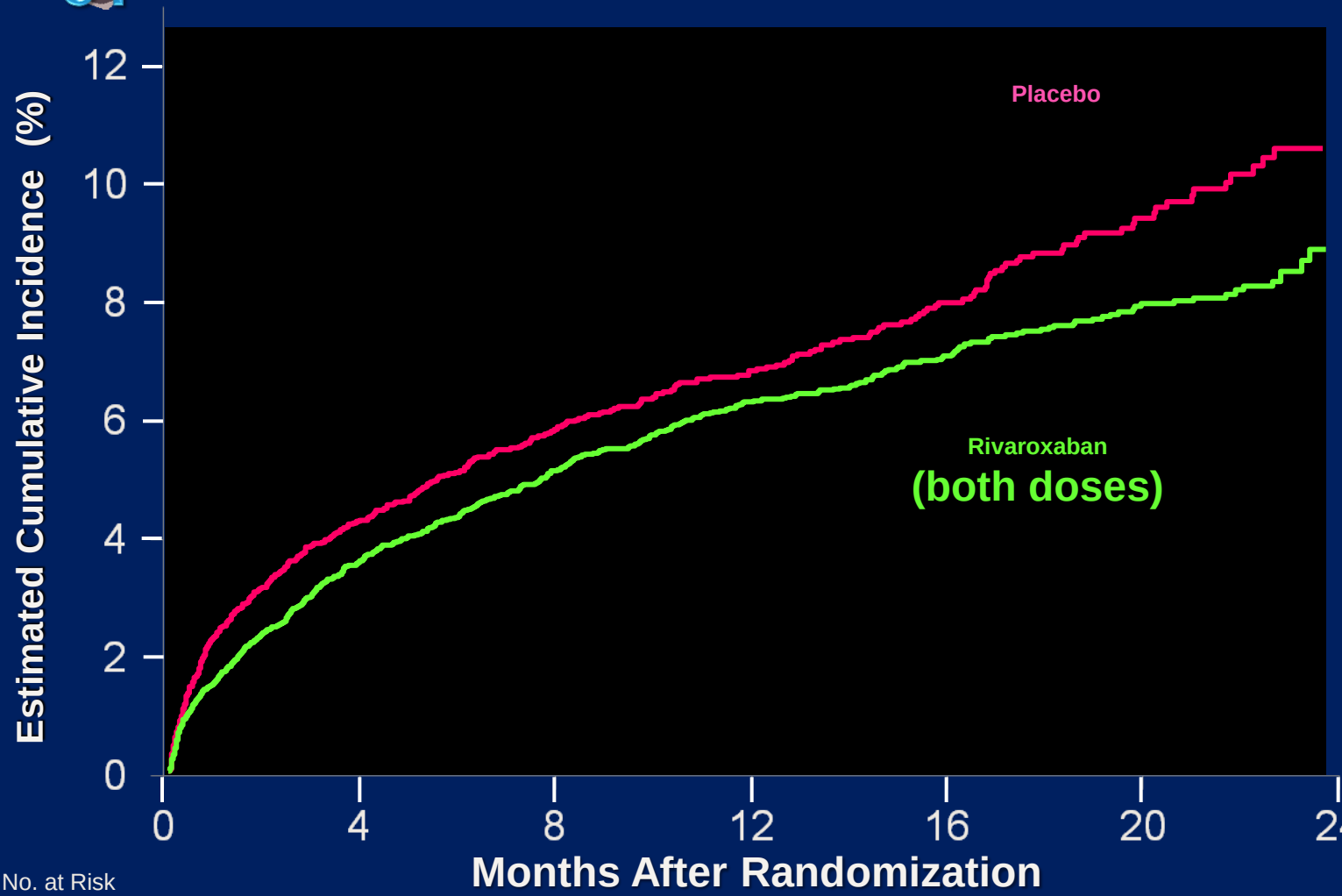
Event driven trial with 1,002 primary efficacy events

Gibson CM, *Am Heart J* 2011

ATLAS ACS 2 TIMI 51

PRIMARY EFFICACY ENDPOINT:

CV Death / MI / Stroke



2 Yr KM Estimate

Placebo 10.7%

Rivaroxaban (both doses) 8.9%

HR 0.84 (0.74-0.96)

mITT p = 0.008
ITT p = 0.002

ARR 1.8%
NNT = 56

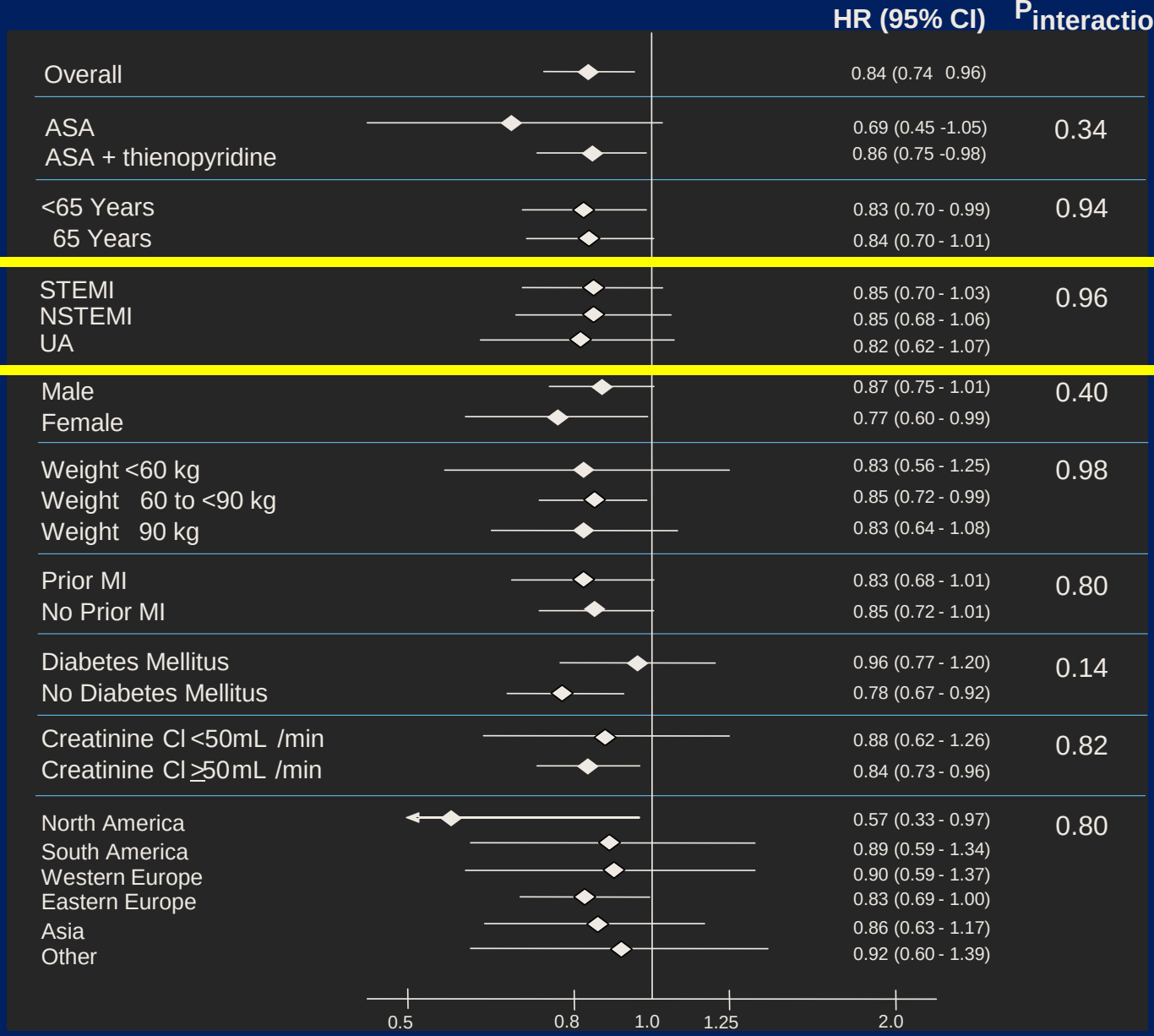
No. at Risk							
Placebo	5113	4307	3470	2664	1831	1079	421
Rivaroxaban	10229	8502	6753	5137	3554	2084	831

HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches.

Mega JL, *NEJM* 2011

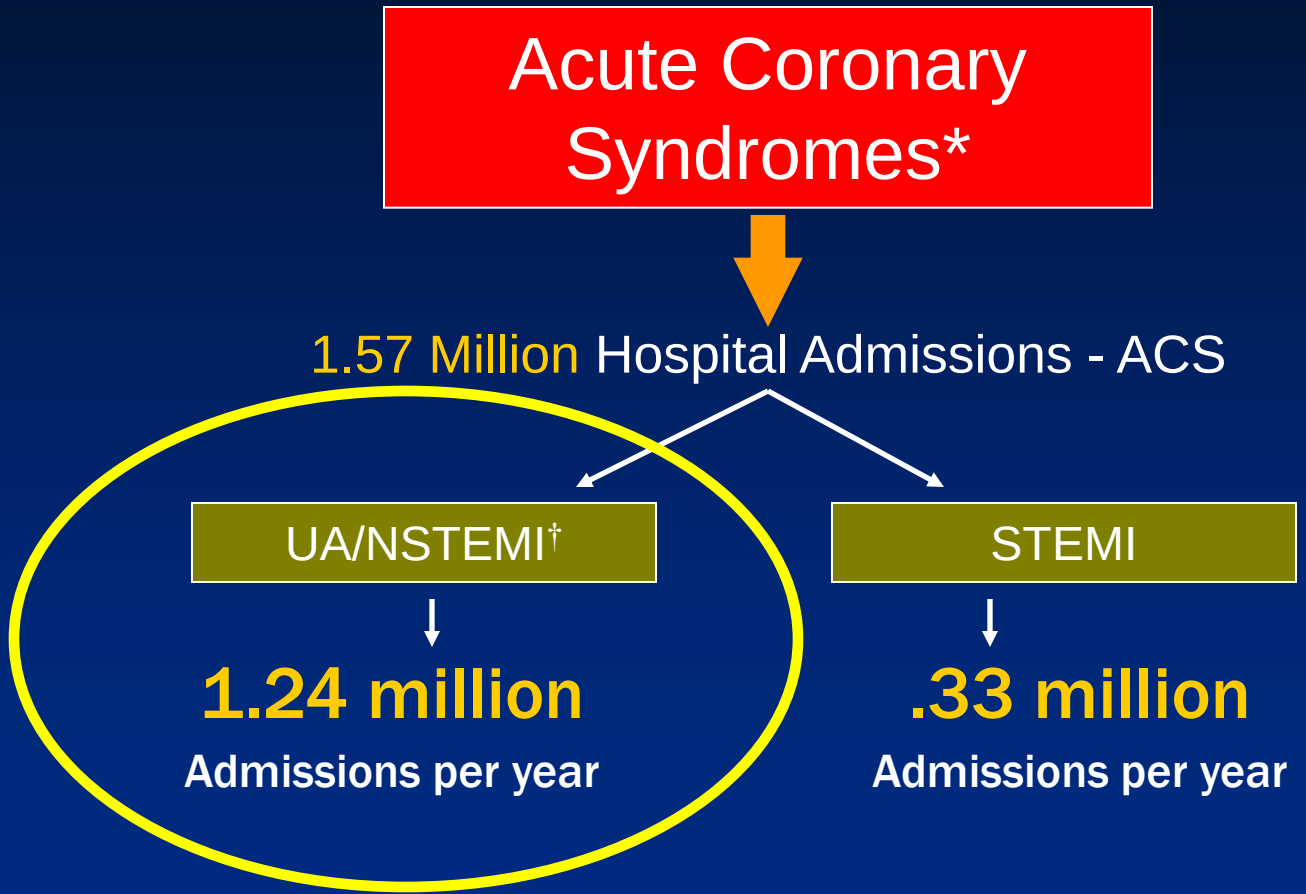
PRIMARY EFFICACY SUBGROUP RESULTS

All Rivaroxaban vs. Placebo



Mega JL, *NEJM* 2011

Hospitalizations in the U.S. Due to Acute Coronary Syndromes (ACS)



Heart Disease and Stroke Statistics – 2007 Update. Circulation 2007; 115:69-171.
*Primary and secondary diagnoses. †About 0.57 million NSTEMI and 0.67 million UA.

Enoxaparin Versus UFH in NSTEMI/UA

- Meta-analysis of 6 randomized trials with 21,946 patients with NSTEMI/UA
- Enoxaparin associated with a lower incidence of death/MI at 30 days with no increase in blood transfusions or major bleeding

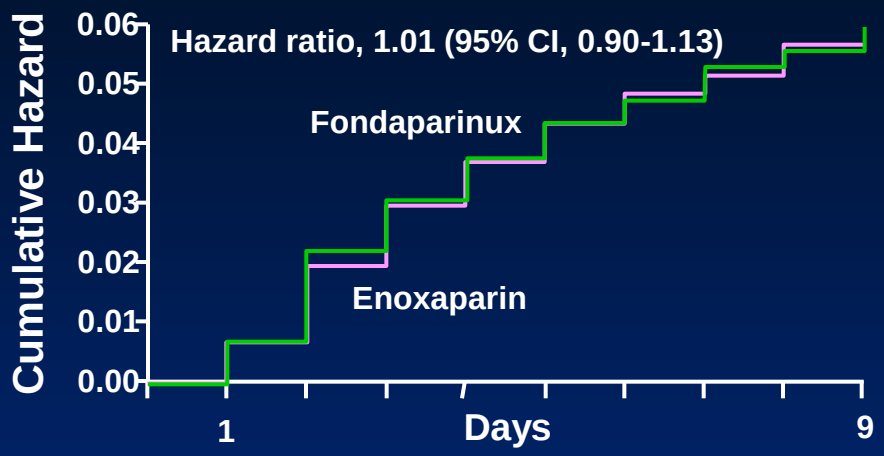
Event	Enoxaparin	UFH	OR (95% Confidence Interval)
30-Day Death	3.0%	3.0%	1.00 (0.85-1.17)
30-Day Death/MI	10.1%	11.0%	0.91 (0.83-0.99)
Transfusion ≤ 7 Days After Randomization	7.2%	7.5%	1.01 (0.89-1.14)
Major Bleeding ≤ 7 Days After Randomization	4.7%	4.5%	1.04 (0.83-1.30)

OR: odds ratio

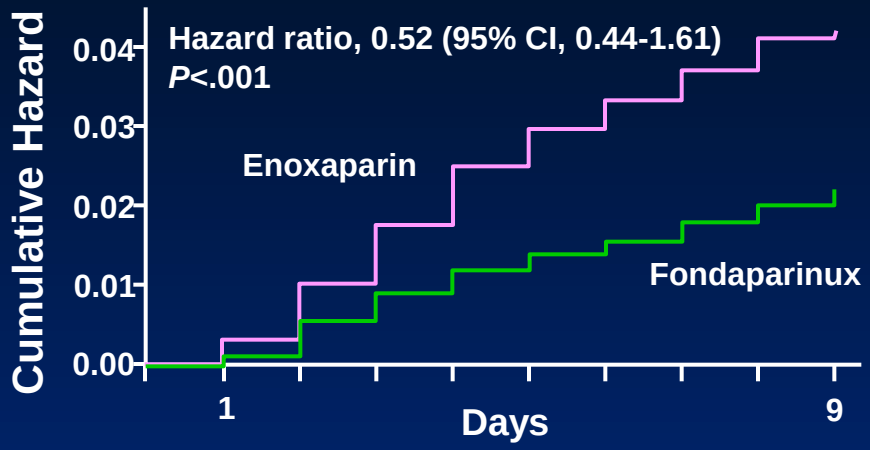
Petersen JL, et al. *JAMA*. 2004;292:89-96.

OASIS-5: Fondaparinux vs Enoxaparin

Death, MI, or Refractory Ischemia Through Day 9



Major Bleeding Through Day 9



30 Day and 6 Month Results

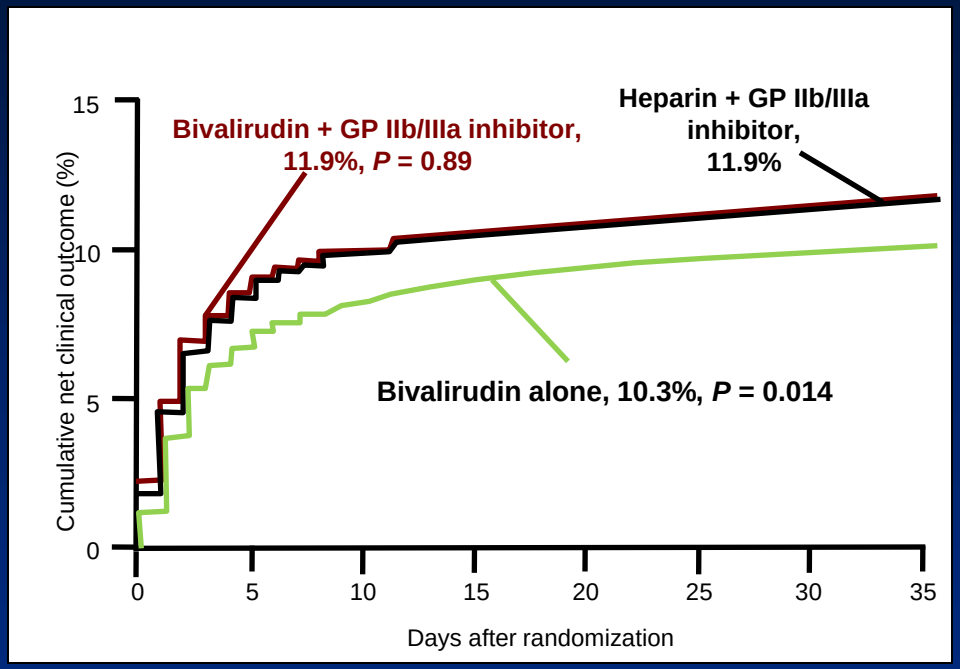
Event	Fondaparinux	Enoxaparin	*P*
Mortality Day 30	2.9%	3.5%	.02
Mortality 6 Mths	5.8%	6.5%	.05

1.5% thrombus on catheter (in fonda group) if no UFH given

Yusuf S, et al. *N Engl J Med*. 2006:354:1464-1476.

Direct Thrombin Inhibitors in NSTEMI/UA

- In ACUITY 13,819 patients with ACS were randomized to:
  - Bivalirudin alone
  - UFH or enoxaparin + a GP IIb/IIIa inhibitor
  - Bivalirudin + GP IIb/IIIa inhibitor
- Major bleeding was significantly lower with bivalirudin alone than with heparin + GP IIb/IIIa inhibitor and bivalirudin + GP IIb/IIIa inhibitor
  - (3.0% vs 5.7% vs 5.3%, respectively; $P < 0.001$)
- Net clinical outcome favored bivalirudin



Net clinical outcome: ischemic endpoints (death, MI, or unplanned revascularization for ischemia) plus bleeding

ACUITY: Acute Catheterization and Urgent Intervention Triage Strategy

Stone GW, *N EJM*. 2006;355:2203-2216.

Latest Guideline Recommendations

- Invasive Strategy
  - Class I-A: Enoxaparin or UFH
  - Class I-B: Bivalirudin or fondaparinux
- Conservative Strategy
  - Class I-A: Enoxaparin or UFH
  - Class I-B: Fondaparinux

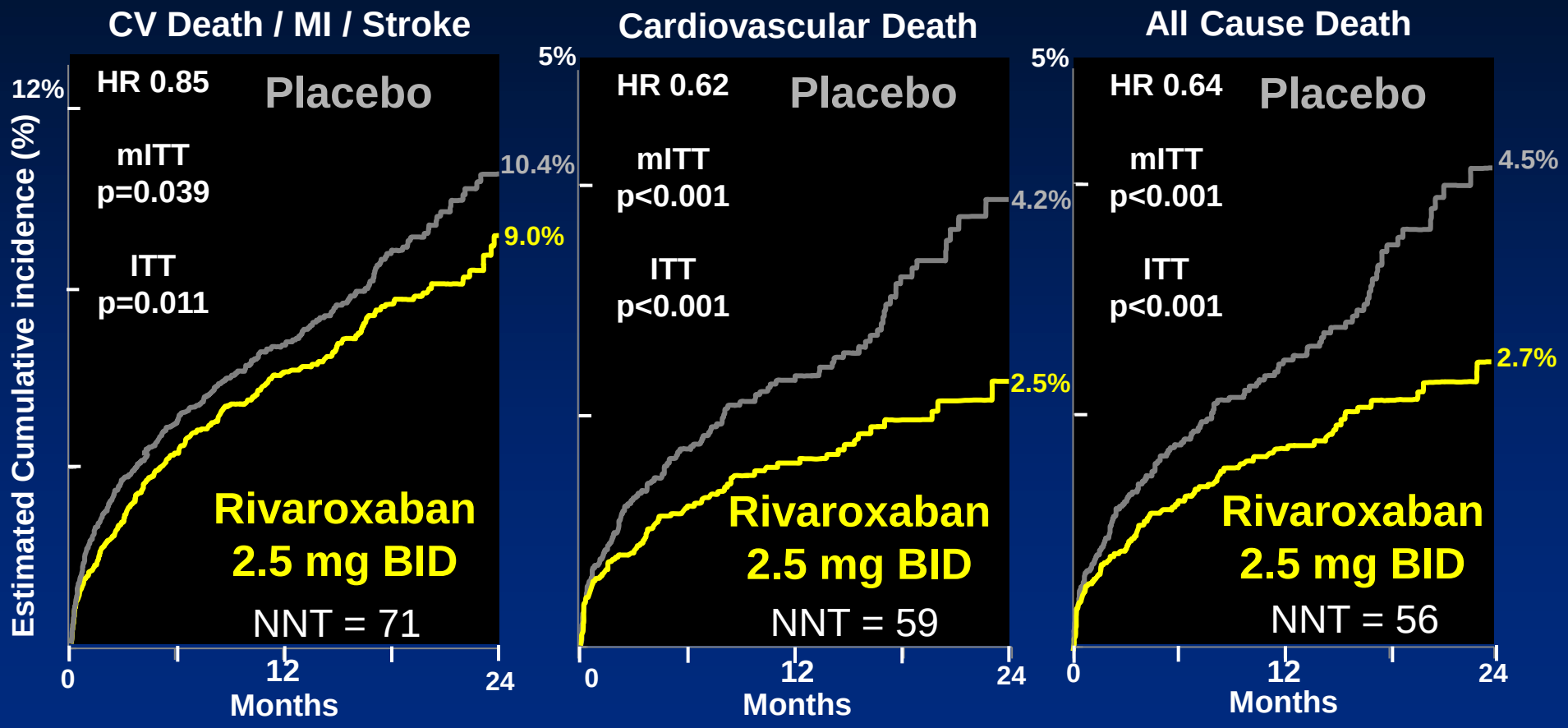
  (NOTE: Enoxaparin or fondaparinux are preferable (Class IIb-B)

Anderson JL et al. 2011 ACCF/AHA Focused Update of the UA/NSTEMI Guidelines. *Circ* 2011

ATLAS ACS 2 TIMI 51

EFFICACY ENDPOINTS: Very Low Dose 2.5 mg BID

Patients Treated with ASA + Thienopyridine



Mega JL, *NEJM* 2011

ATLAS ACS 2 TIMI 51

SAFETY ENDPOINTS

Treatment-Emergent Non CABG TIMI Major Bleeding*

Analysis	Placebo	2.5 mg Rivaroxaban	5.0 mg Rivaroxaban
2 Yr KM Estimate	0.6%	1.8% HR 3.46	2.4% HR 4.47

p<0.001

p<0.001

Liver Function Test (ALT > 3xULN)

ALT > 3X ULN	1.6%	1.3% p=NS	1.4% p=NS

There was no excess of either combined ALT > 3x ULN and Total Bilirubin > 2x ULN cases among patients treated with Rivaroxaban, or SAEs.

Post-Treatment CVD / MI / Stroke##

1-10 Days After Last Dose	1.8%	1.4% p=NS	2.2% p=NS

*: First occurrence of Non-CABG TIMI major bleeding events occurred between first dose to 2 days post last dose as adjudicated by the CEC across thienopyridine use strata; Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine are provided; Stratified log-rank p-values are provided; #: Raw percentage of subjects with abnormal value measured between first dose to 2 days post last dose among subjects with normal baseline measurement; ##: Raw percentage.

Mega JL, *NEJM* 2011

PK/PD of 5 Novel Oral Agents

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)	Betrixaban (PRT054021)
Target	IIa (thrombin)	Xa	Xa	Xa	Xa
Hrs to Cmax	2	2-4	1-3	1-2	NR
CYP metabolism	None	32%	15%	<4%	None
Bioavailability	7%	80%	66%	>45%	34-47%
Transporters	P-gp	P-gp/BCRP	P-gp	P-gp	P-gp
Protein binding	35%	>90%	87%	55%	NR
Half-life	12-14h	9-13h	8-15h	8-10h	19-20h
Renal elimination	80%	66%*	25%	35%	<5%
Linear PK	Yes	No	Yes	Yes	Yes

BCRP = breast cancer resistance protein; CYP = cytochrome P450; NR = not reported; P-gp = P-glycoprotein

* 33% unchanged, 33% inactive metabolite

Ruff CR and Giugliano RP. Hot Topics in Cardiology 2010;4:7-14
Ericksson BI et al. Clin Pharmacokinet 2009; 48: 1-22
Ruff CR et al. Am Heart J 2010; 160:635-41

Summary

- Many choices for adjunctive antithrombotic therapy in STEMI and NSTE-ACS
- Recent Guideline Updates – *Must Read* !
- Pick the anticoagulant that best fits the patient and clinical situation
- Bivalirudin (if PCI) and fondaparinux (NSTE-ACS) are newer options to consider, especially if there is an ↑ risk of bleeding
- Future therapies may include use of novel oral anticoagulants, especially post ACS and when anticoagulation is otherwise indicated