LMWH in PCI

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What are the unsolved issues?

CATH LAB

Unstable Angina
Enox 1mg/kg for how long prior to cath?

Which anticoagulant? Which monitoring?

1- Transition to the cathlab?

2- LMWH in the cath lab?

3- Biological monitoring?

Elective PCI
Primary PCI
0.5 mg/kg IV?

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1- Transition to the cath lab

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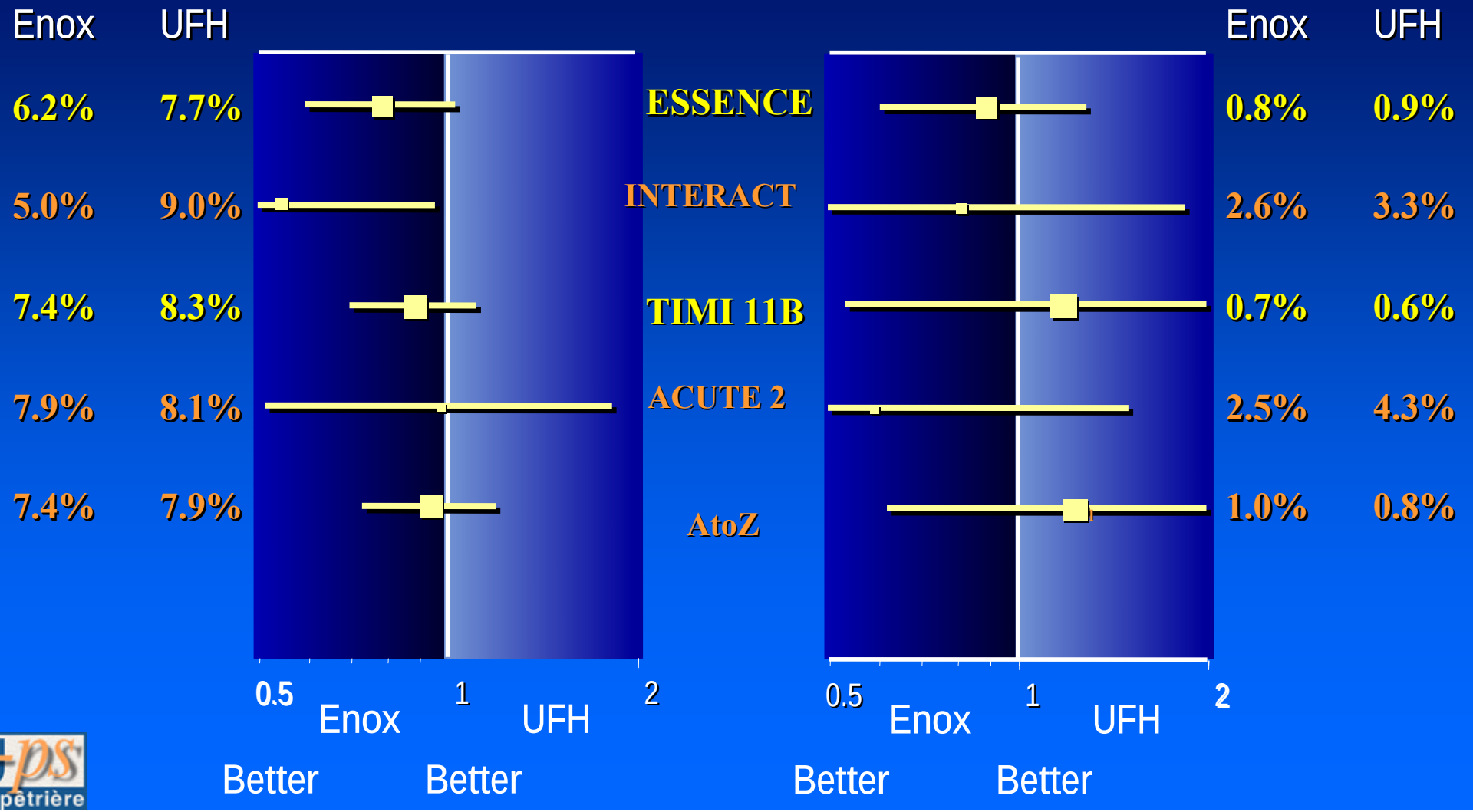
Systematic Overview:
30-Day Death/MI and In-hospital Transfusions



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Key questions?

- Can we safely bring patients on enoxaparin forward to the cath lab?
- What is the role of enoxaparin in high-risk NSTE-ACS patients managed with an early invasive strategy?

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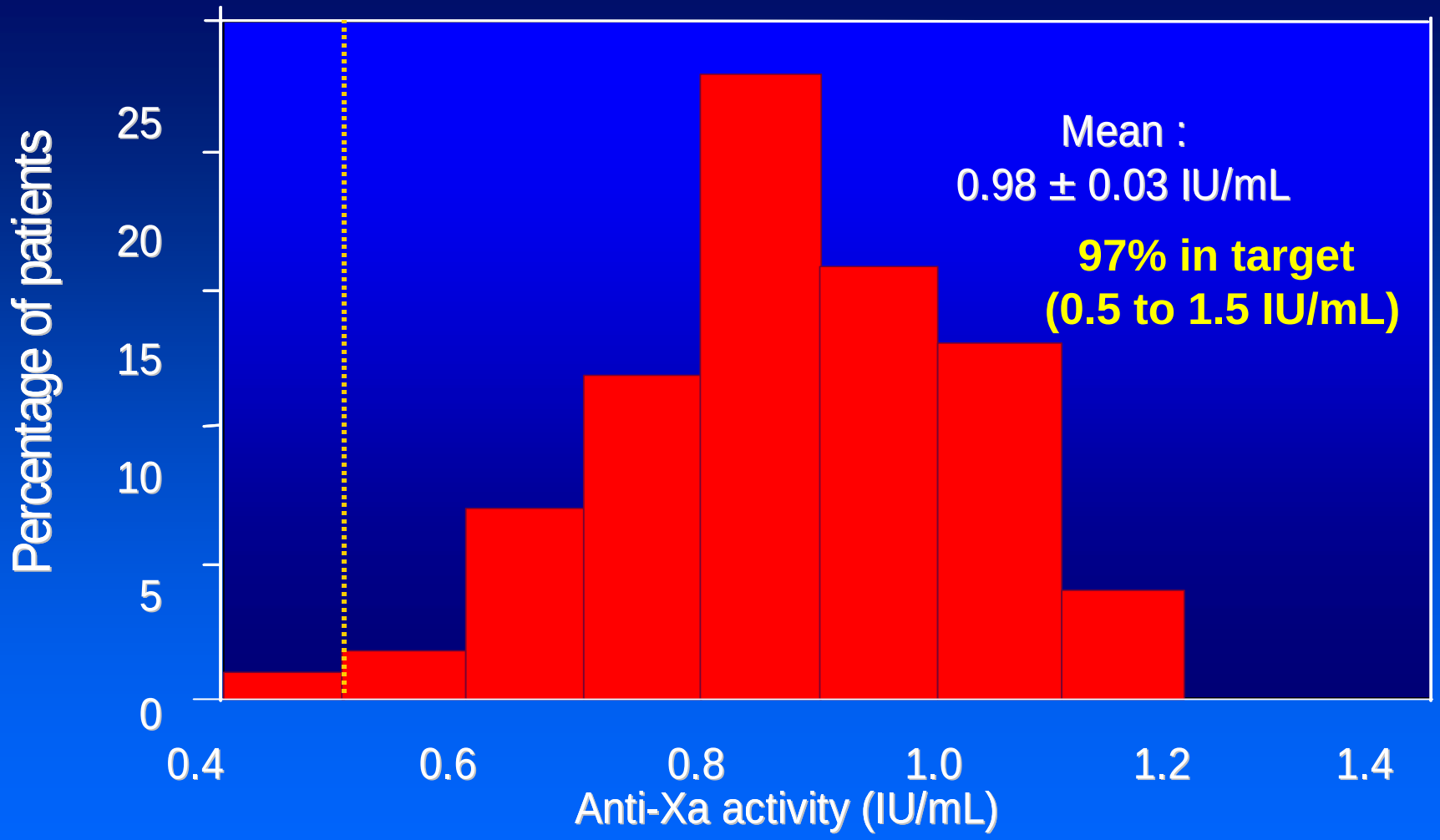
PCI Within 8 hrs of SC Enoxaparin



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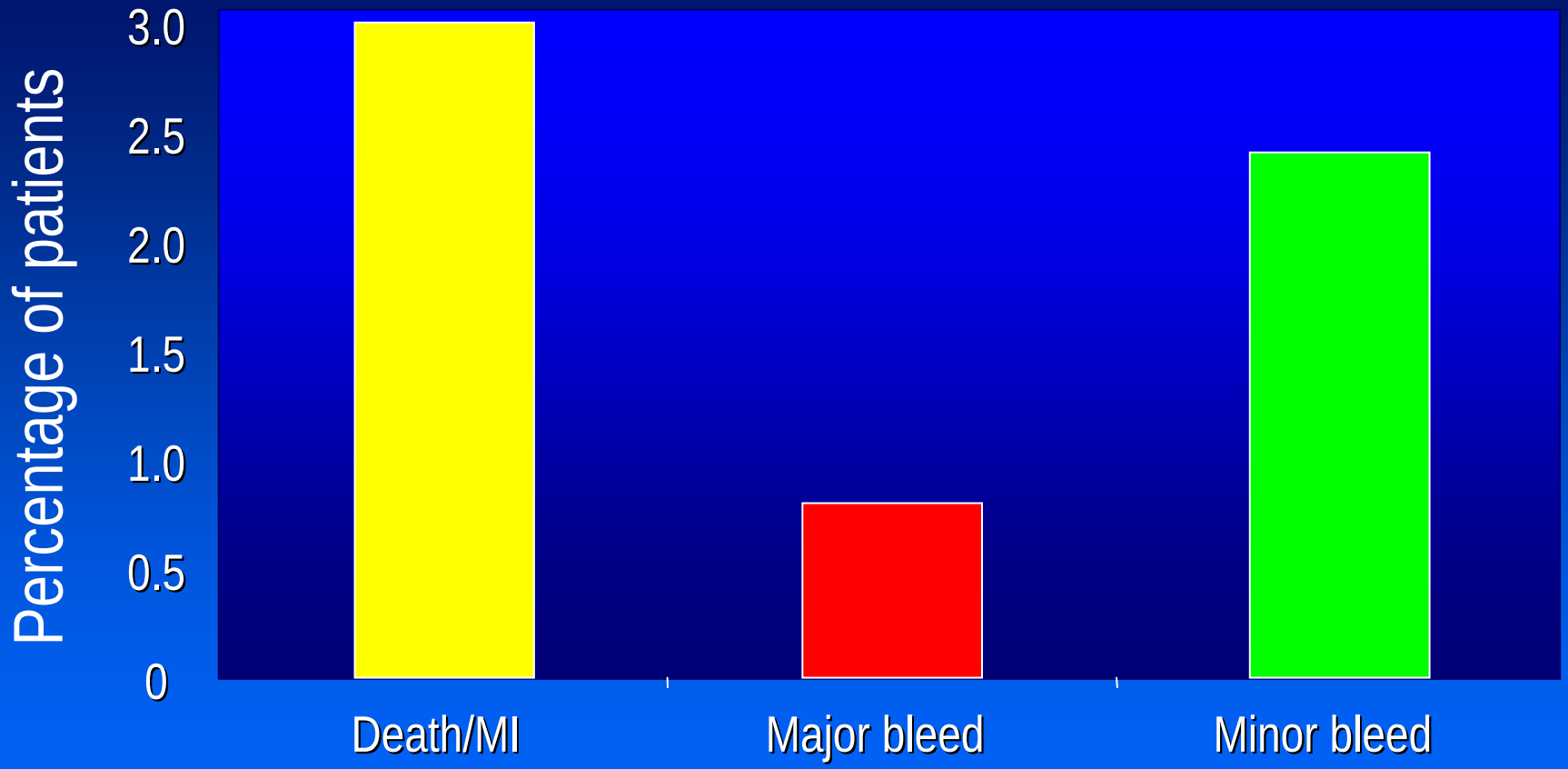
Collet JPh, Montalescot G, Choussat R et al. Circulation 2001;103:658

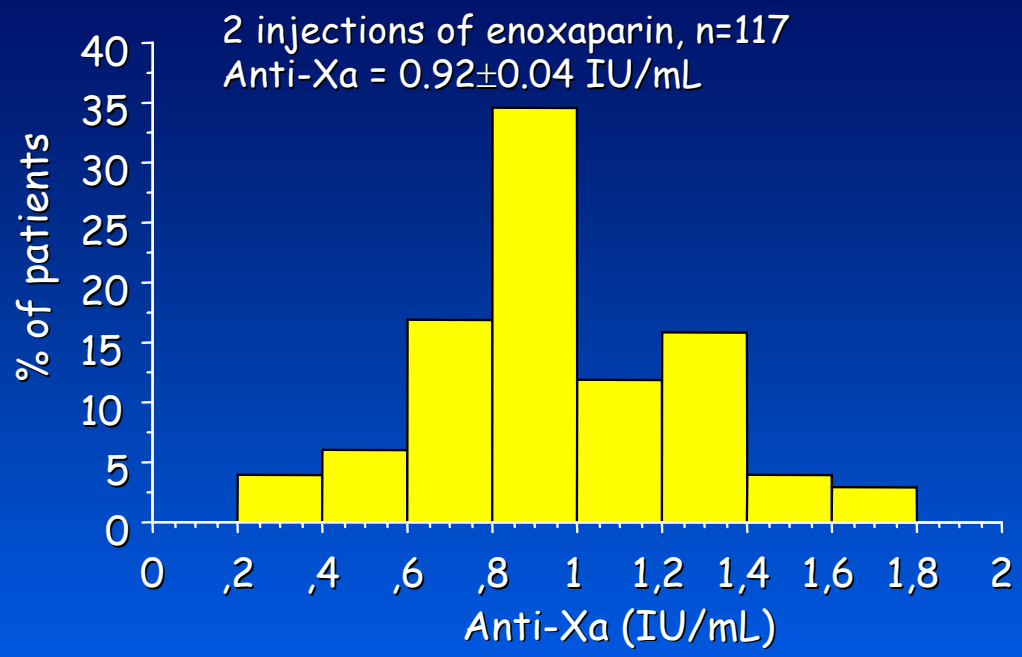
PCI: 30-day clinical outcome

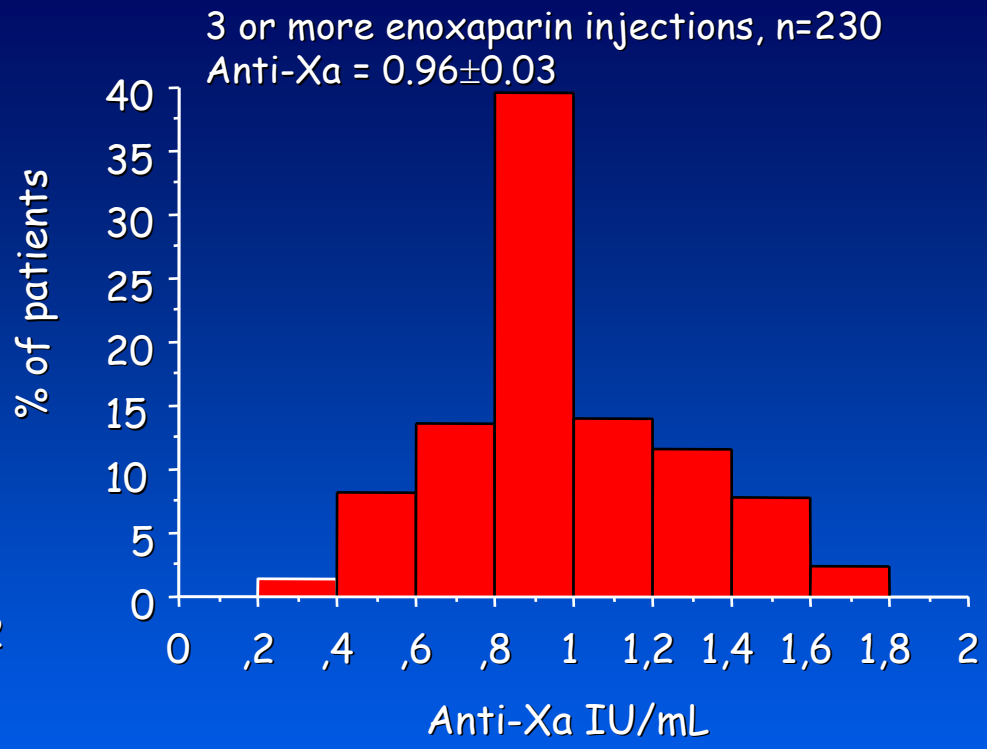


No acute closure and no urgent revascularization

Collet JPh, Montalescot G, Lison L, Choussat R et al. Circulation 2001;103:658

Early vs Late with enoxaparin





Trt duration	16.9±0.5 hrs	vs	69.2±3.0 hrs (p<0.01)
IIb/IIIa-inh.	58.1%	vs	31.7% (p<0.01)

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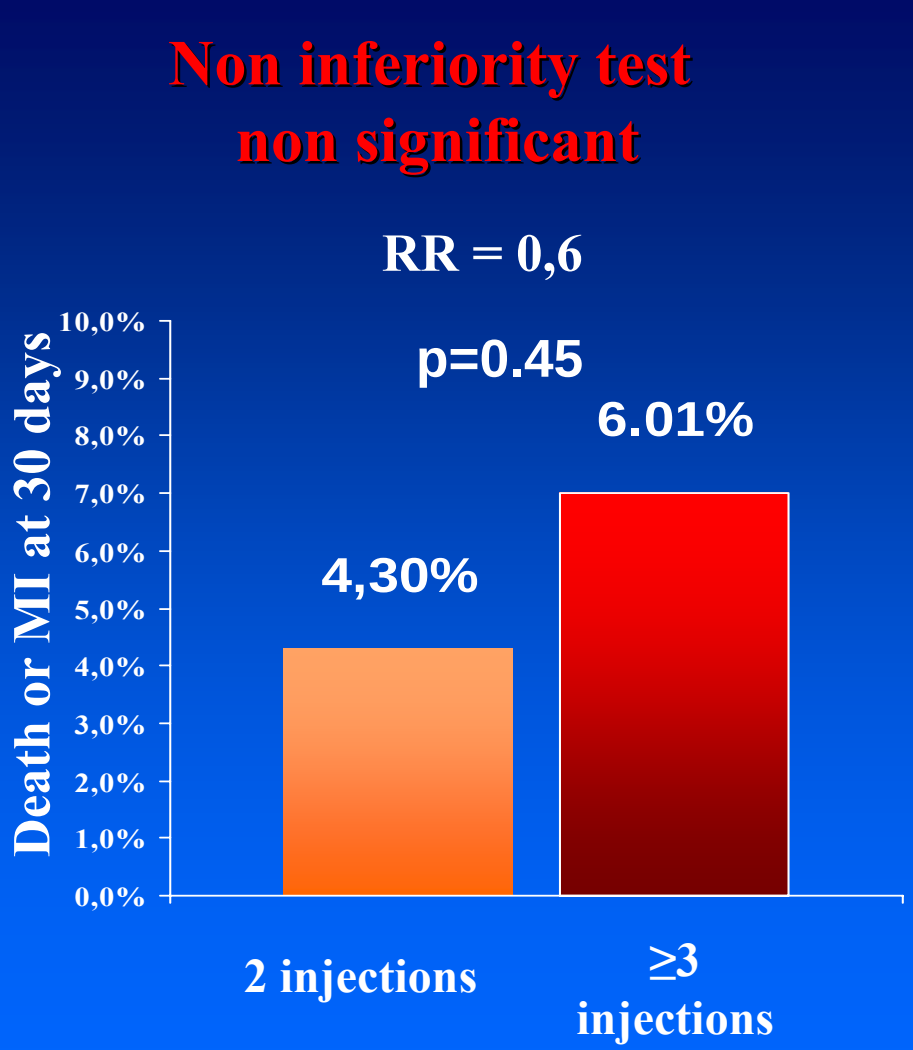
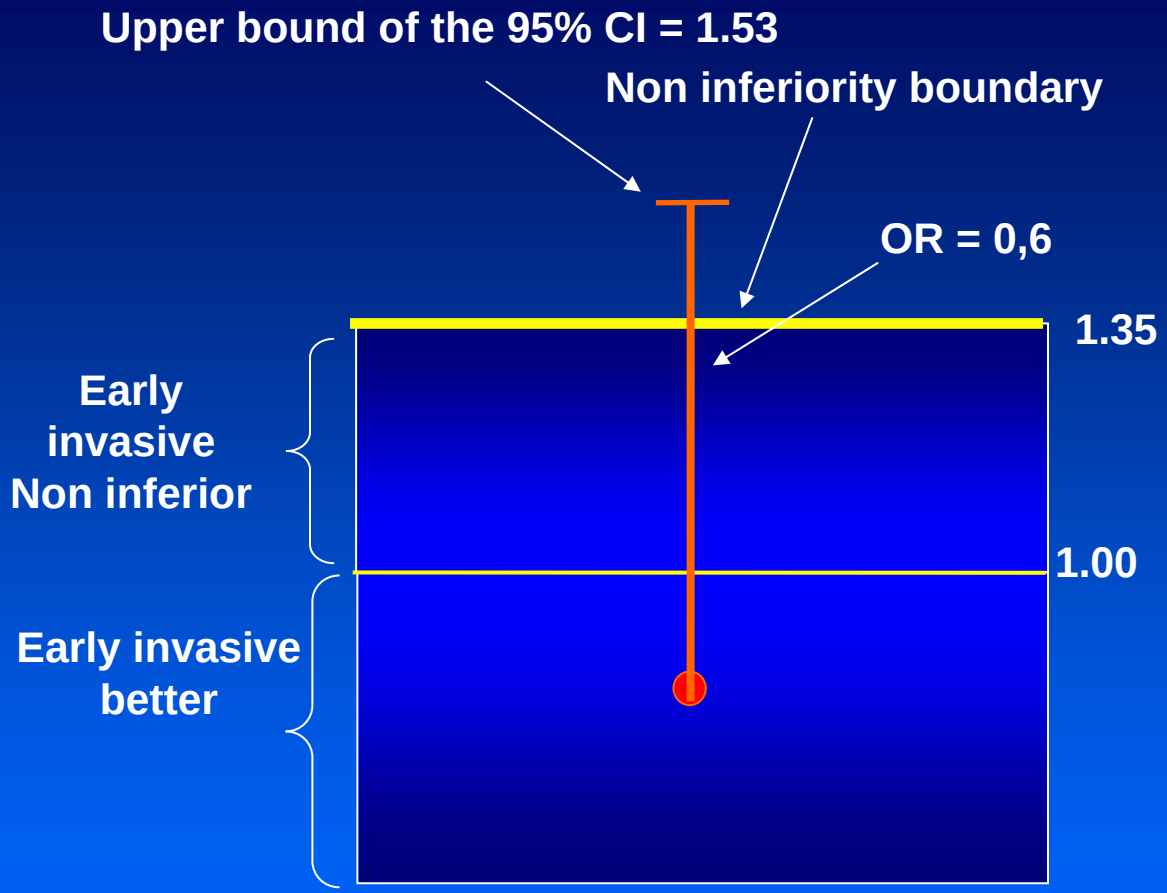
Collet JPh et al. Am Heart J 2004 147: 655-61

Death or MI

Non inferiority test non significant





Hypothesis of non inferiority No demonstrated

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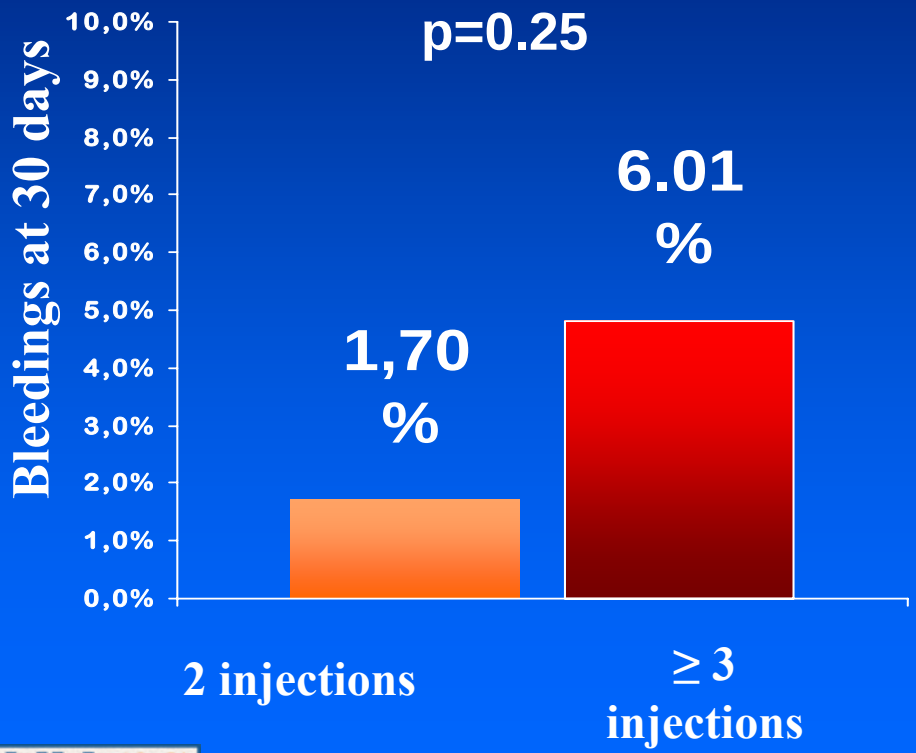
Collet JPh et al. Am Heart J 2004 147: 655-61

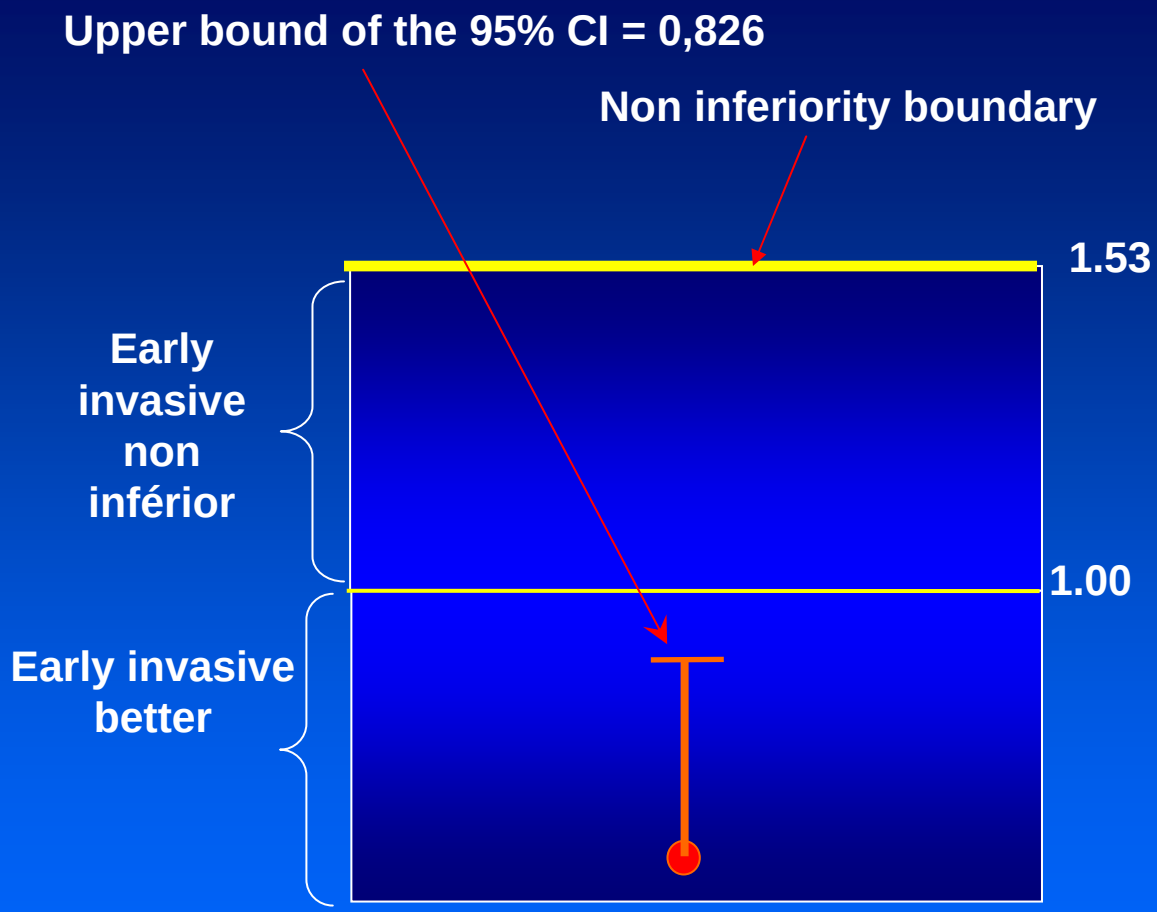
Bleedings (minor and major)

Non inferiority test significant

OR = 0.22

p=0.25





Both strategies are equivalent

Collet JPh et al. Am Heart J 2004 147: 655-61

Conclusions 1

- Transition to the cath lab for PCI within 8 hours is safe; is associated with a stable and effective anticoagulation level; without any additional anticoagulant;

- A rapid invasive strategy with only 2 s/c injections of enoxaparin provides :

  - similar levels of anticoagulation,

  -is associated with a favorable trend for ischemic events

  -is associated with an equivalent safety

as a more prolonged “upstream” treatment with enoxaparin.

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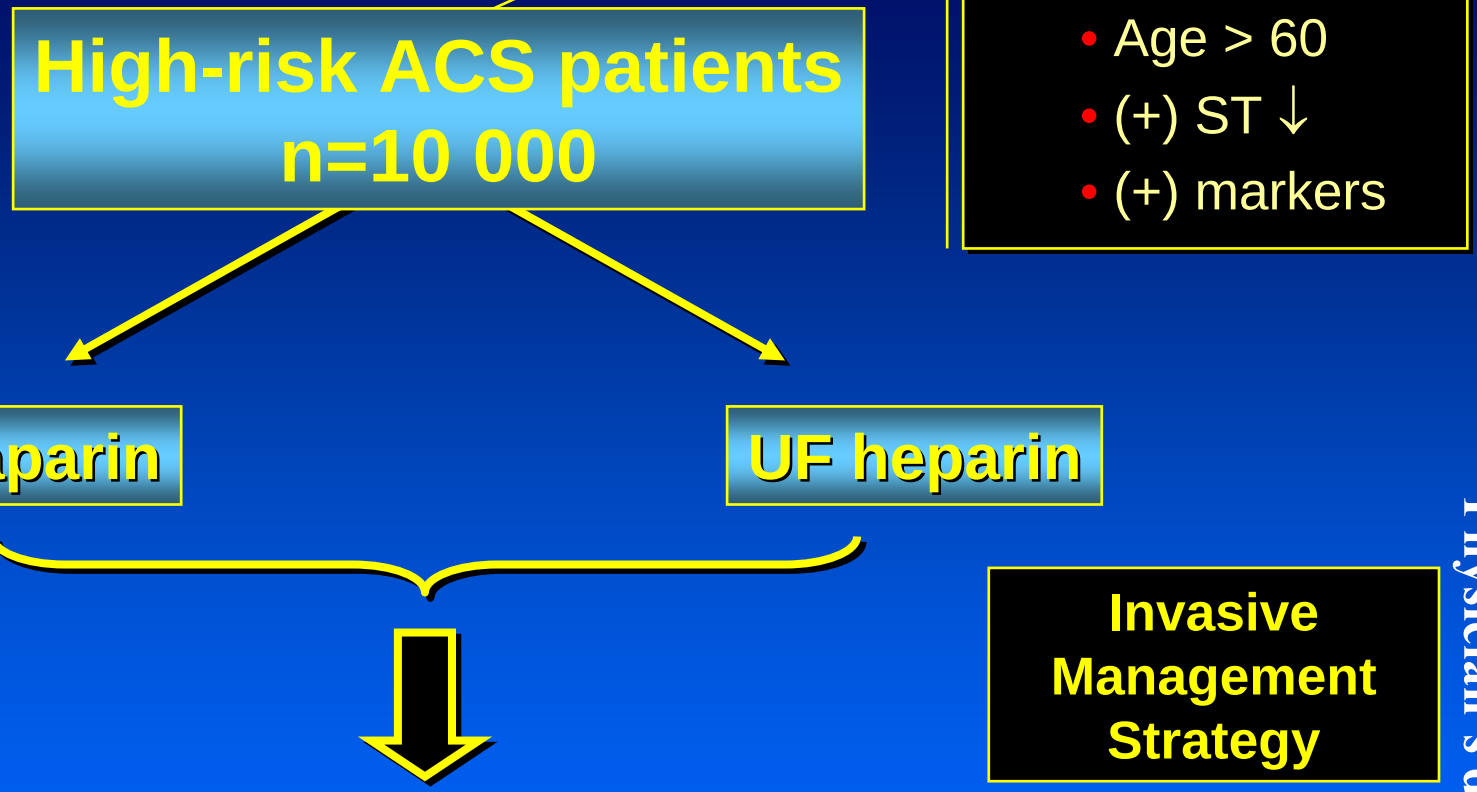
SYNERGY Trial



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Risk profile and management

	Enoxaparin (n = 4993)	UFH (n = 4985)
Aspirin (%)	95	95
Beta blocker (%)	86	86
Ace inhibitor (%)	64	62
Statin (%)	69	70
Clopidogrel (%)	62	63
GP IIb-IIIa inhibitor (%)	56	58

	Enoxaparin (n = 4993)	UFH (n = 4985)
Cath during baseline hosp (%)	92	92
Time to cath* (hours)	22 (6, 44)	21 (6, 43)
Percutaneous intervention	46	47
Time to PCI* (hours)	23 (6, 49)	22 (6, 48)
CABG (%)	19	18
Time to CABG* (hours)	91 (44, 167)	89 (45, 166)
Days hospitalized*	5 (3, 8)	4 (3, 8)

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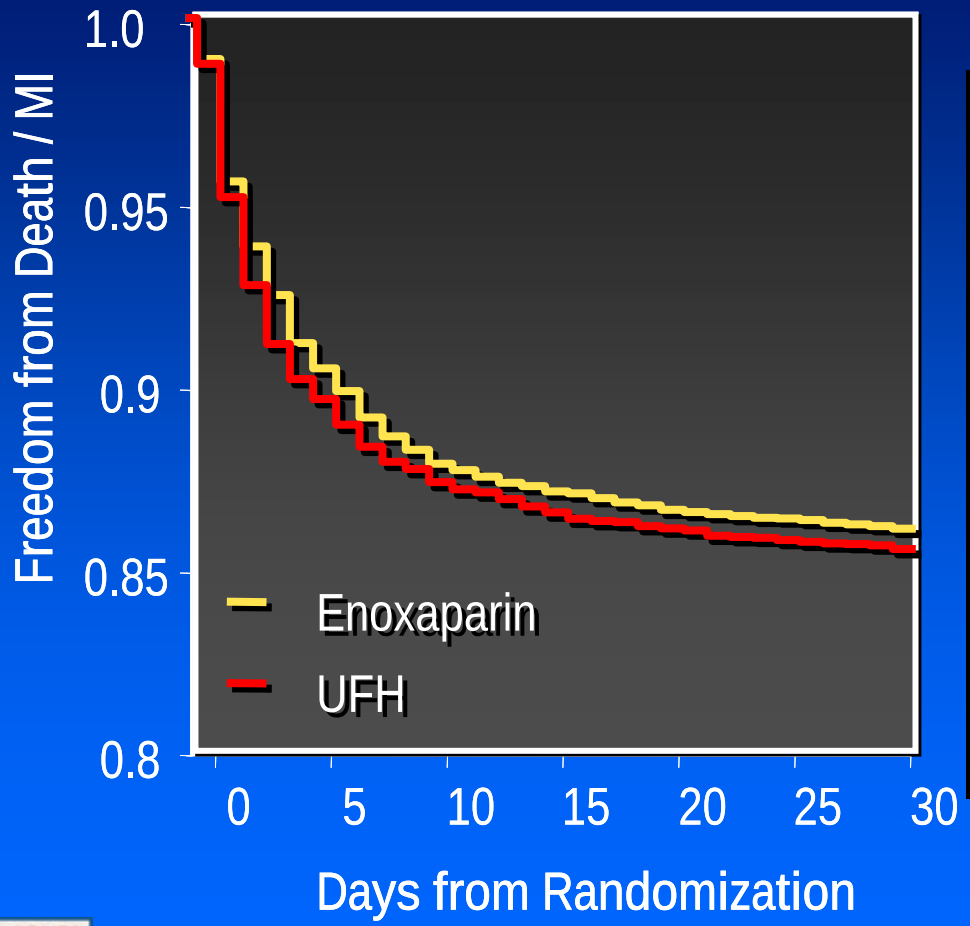
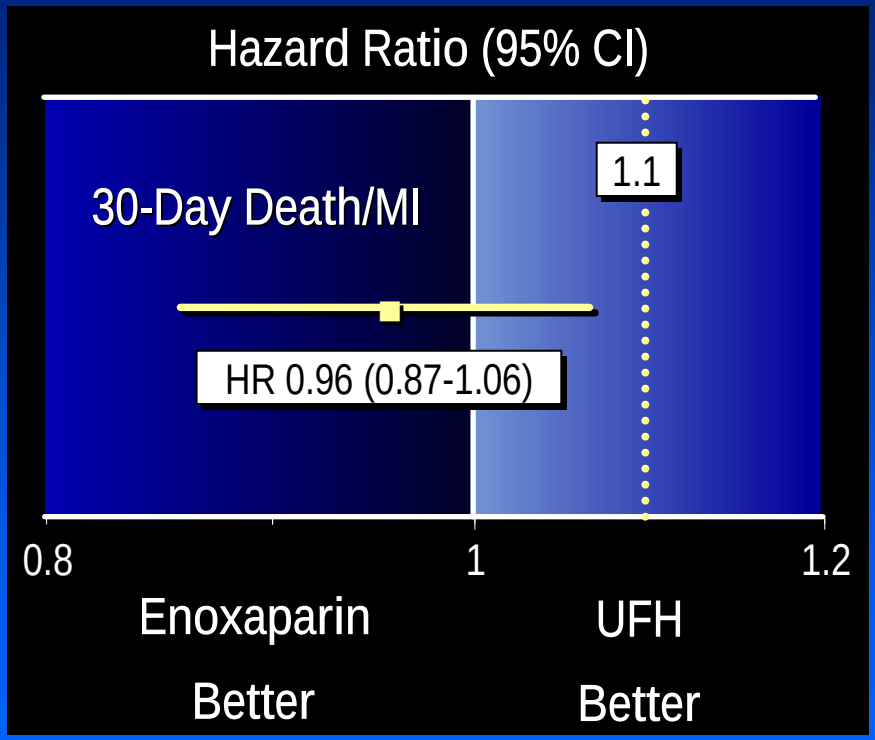
Efficacy





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Safety

	Enoxaparin (n = 4993)	UFH (n = 4985)	P-value
GUSTO severe	2.9	2.4	0.106
TIMI major - clinical:	9.1	7.6	0.008
CABG-related	6.8	5.9	0.081
Non-CABG-related	2.4	1.8	0.025
H/H drop - algorithm	15.2	12.5	0.001
Any RBC transfusion	17.0	16.0	0.155
ICH	< 0.1	< 0.1	NS

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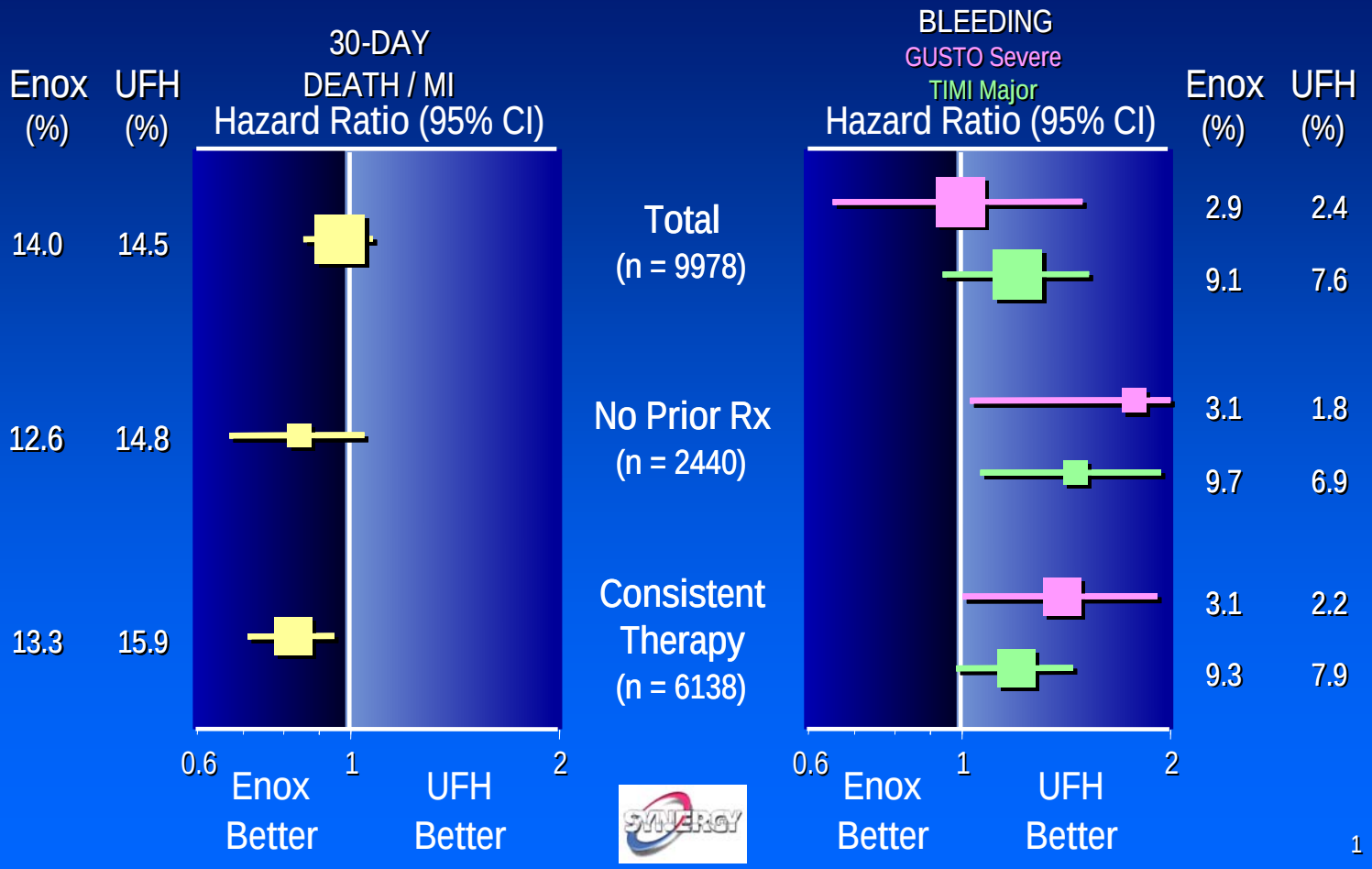
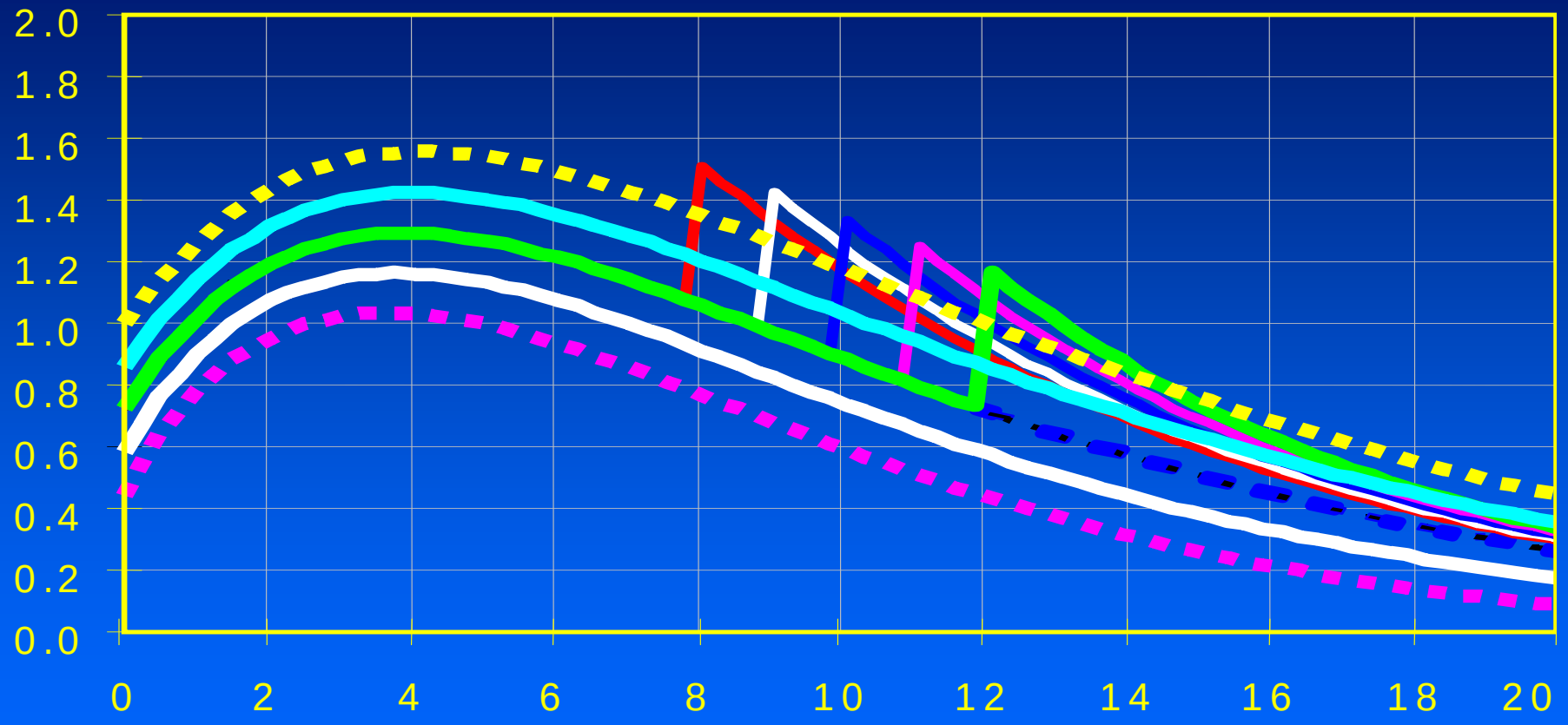
Outcomes according to prior antithrombin therapy



After 8 hours?



(Catheter Cardiovasc Interv. 2004).

Predicted and Actual Anti-Xa Plasma Activity (IU/ml, mean ± SD)

	Maximum value (Post bolus)					Minimum value (2-hour post bolus)				
PCI	N	*Predicted*	Actual	Ratio	% in target	N	Predicted	*Actual*	Ratio	% in target
8-<9h	12	*1.51±0.16*	1.42±0.35	94%	100%	11	*1.16±0.16*	1.10±0.37	95%	92%*
9 -<10h	12	*1.42±0.16*	1.19±0.31	84%	100%	11	*1.08±0.16*	0.95±0.24	88%	100%
10 -<11h	11	*1.33±0.15*	1.23±0.31	92%	100%	10	*0.99±0.16*	0.94±0.27	95%	100%
11 -<12h	9	*1.25±0.15*	1.06±0.30	85%	89%*	12	*0.92±0.15*	0.81±0.21	88%	89%*

Ratio = Actual/Predicted

*100% if exclude one patient with imputed IV dosing error

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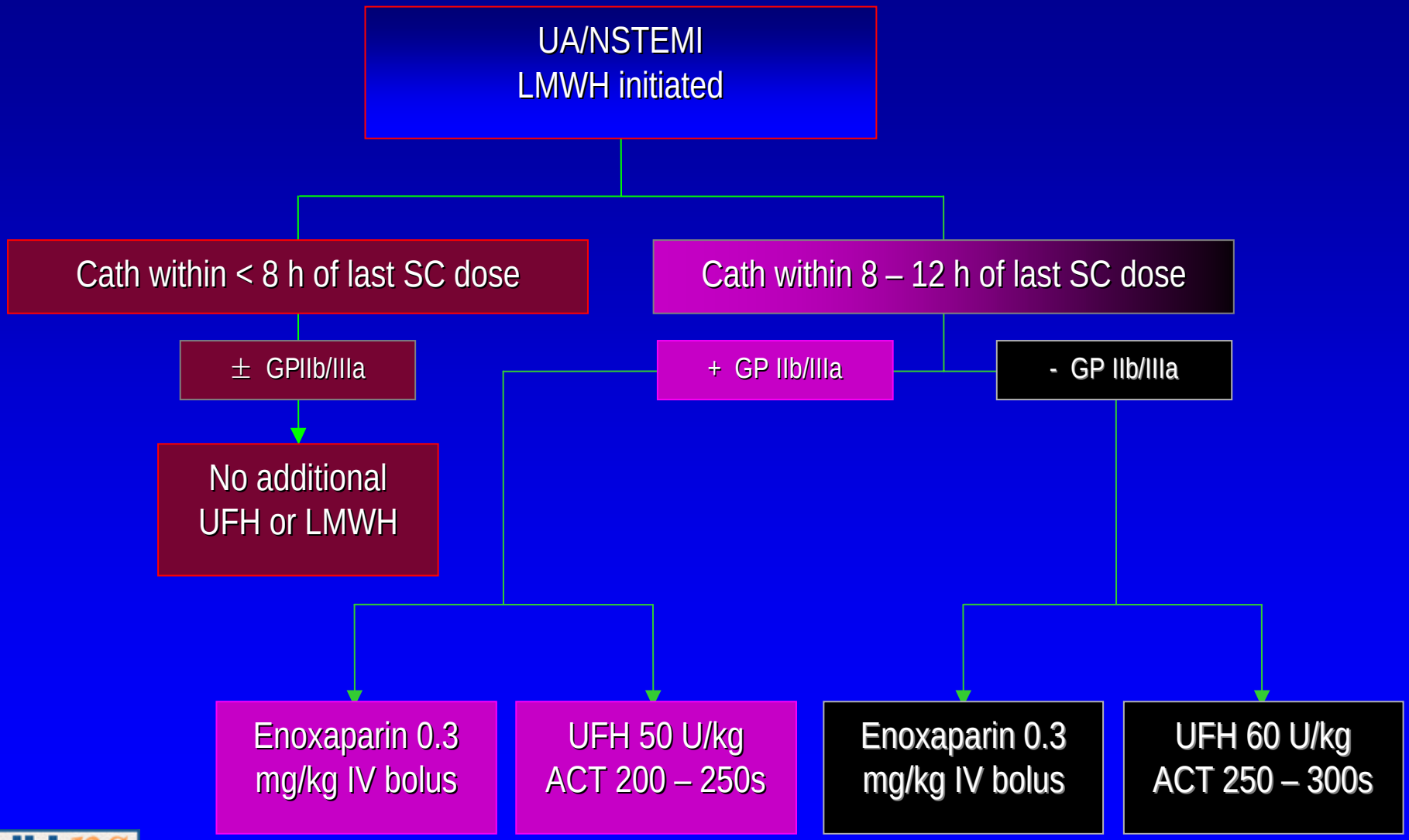
Task force recommendations



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Kereiakes DM, Montalescot G et al. Am Heart J 2002; 144: 615-24

2- LMWH in the cath lab

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LMWH started in the cath lab
(IV injections / Elective)

- **Optimal anticoagulation** with UFH in PCI remains **uncertain** ;

- **Limited experience** is available with iv **LMWH** in PCI ;

- High dosages of LMWH providing elevated levels of anticoagulation and requiring delayed sheath removal have been studied in NICE 1 and 4.

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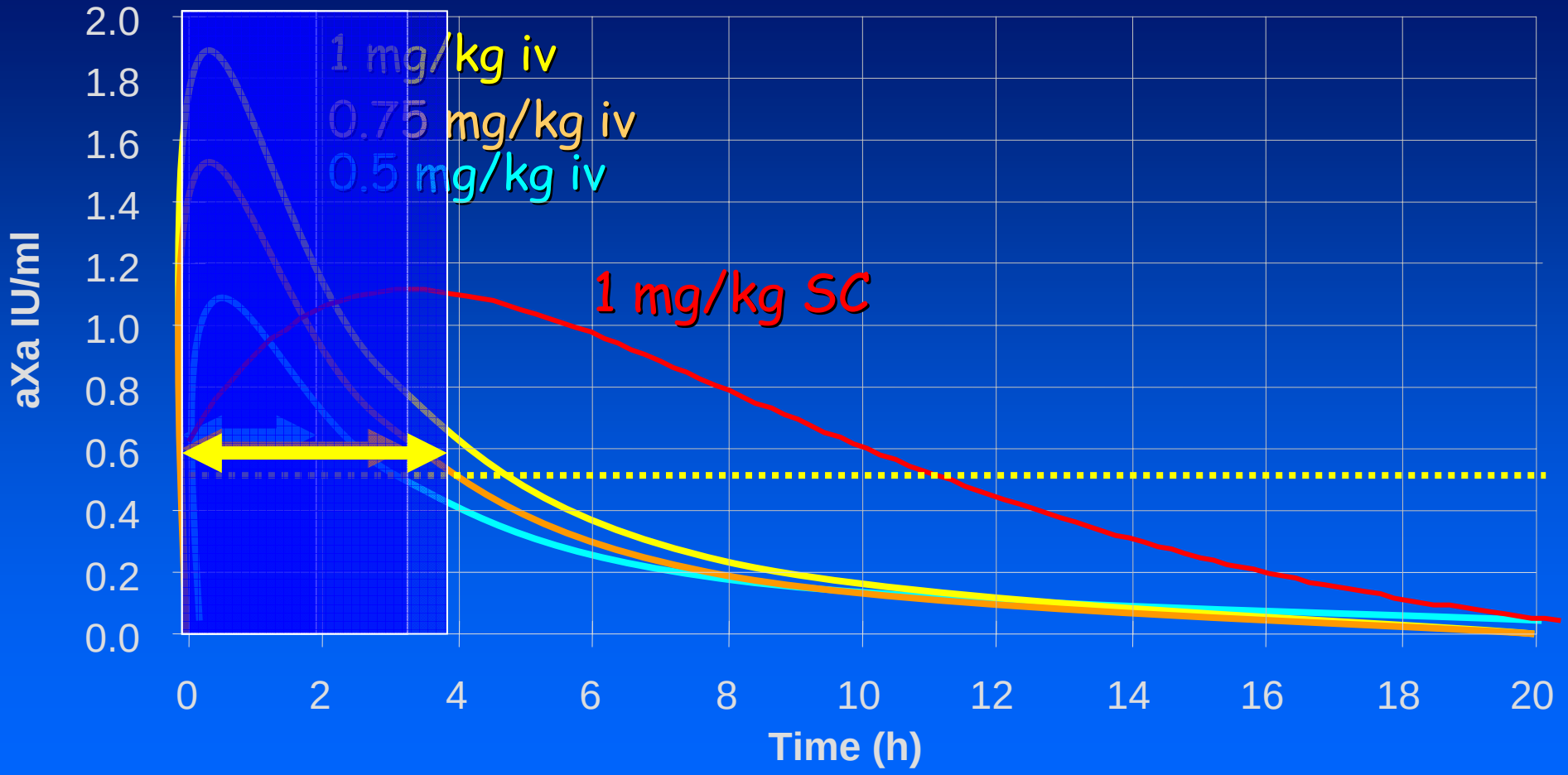
Anticoagulation with iv enoxaparin



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Study population

Population:

- 600 consecutive patients undergoing PCI
- No anticoagulation prior to entry into the Cath Lab
- Eptifibatide (n= 151, 25%)
- Abciximab for ST↑MI (n=31, 5%)

We defined 3 groups at higher risk of bleeding:

- Renal dysfunction: creat cl $\leq$ 40 mL/min
- Elderly: age > 75 years
- Overweight : > 100 kgs

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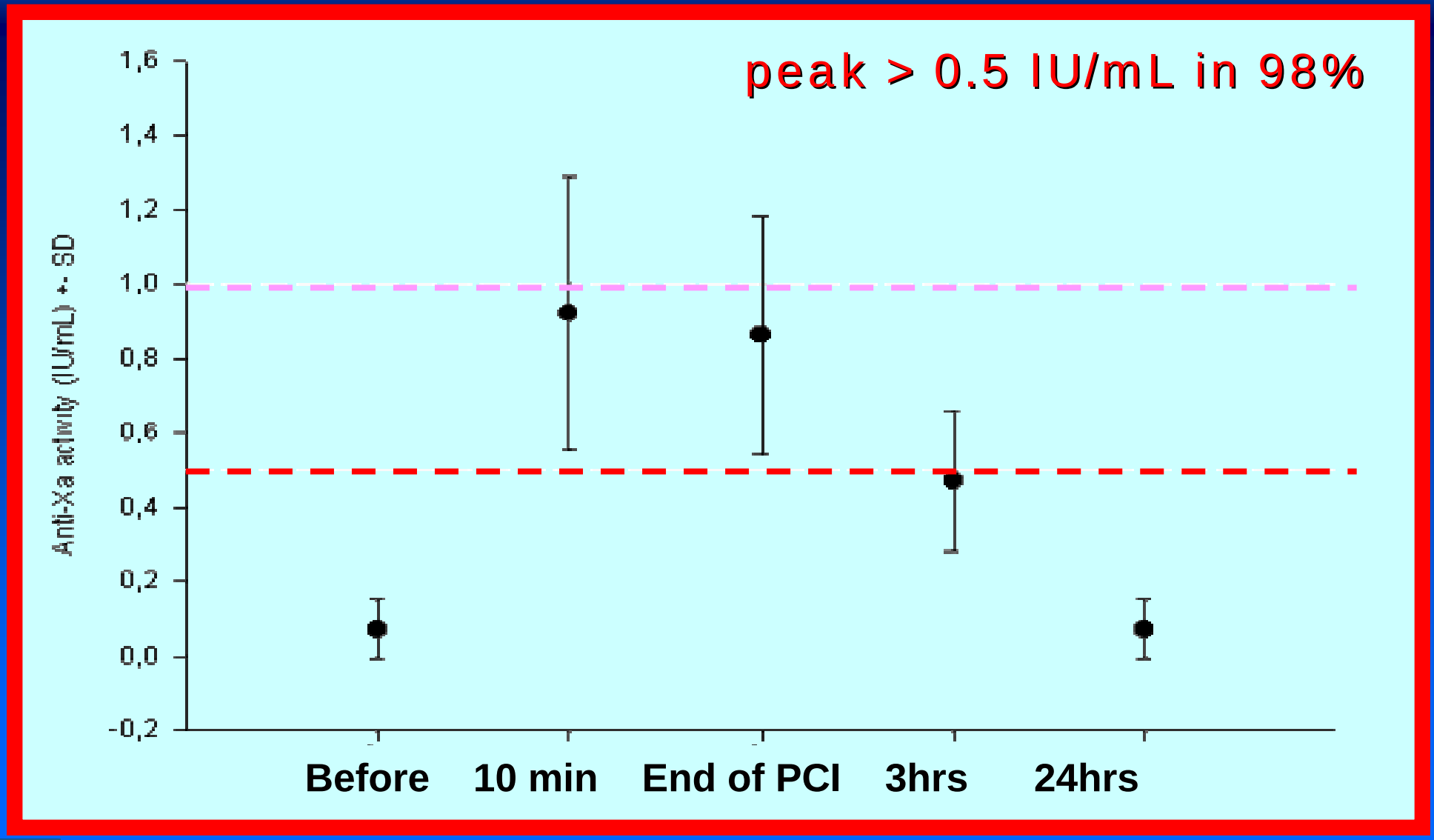
Choussat et al. J Am Coll Cardiol 2002 40:1943-50

Anti-Xa Activity During and After PCI



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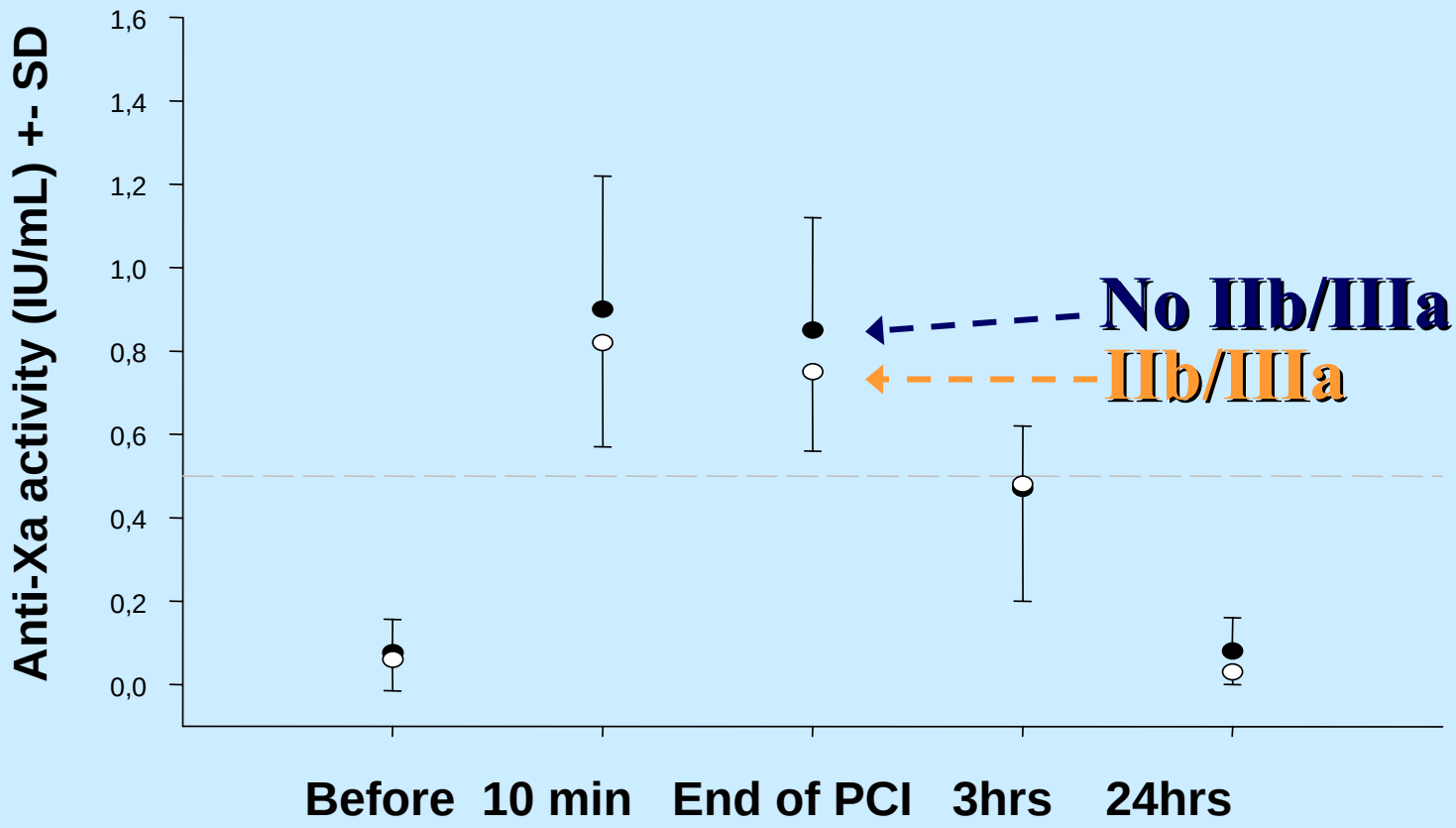
IV Enoxaparin (0.5mg/kg) with or without IIb/IIIa I.



Anti-Xa (IU/mL) According to Renal Function

	Creatinine Cl. (mL/min) > 40	Creatinine Cl. (mL/min) ≤ 40
Start of PCI	0.9 ± 0.3	0.9 ± 0.2
End of PCI	0.8 ± 0.2	0.8 ± 0.2
At 3-hours	0.5 ± 0.2	0.5 ± 0.1

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Anti-Xa (IU/mL) according to weight

	Weight	
	≤ 100 kg	> 100 kg
Start of PCI	0.9 ± 0.3	1.0 ± 0.3
End of PCI	0.8 ± 0.2	0.9 ± 0.3
At 3-hours	0.5 ± 0.1	0.4 ± 0.2

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Anti-Xa Activity According to Age

	Age	
	≤ 75 y	> 75 y
Start of PCI	0.9 ± 0.3	0.9 ± 0.3
End of PCI	0.8 ± 0.2	0.8 ± 0.2
At 3-hours	0.5 ± 0.1	0.4 ± 0.1

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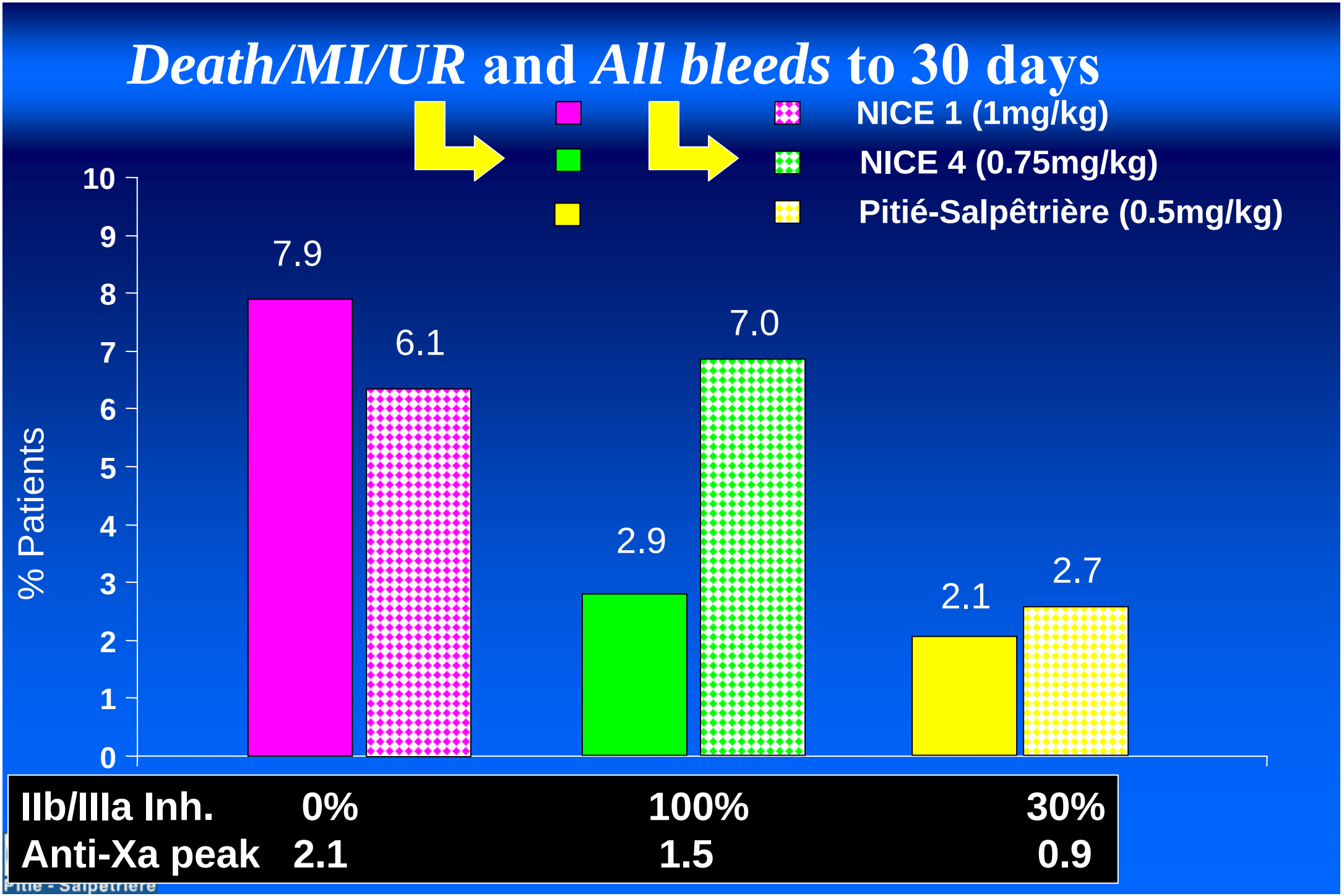
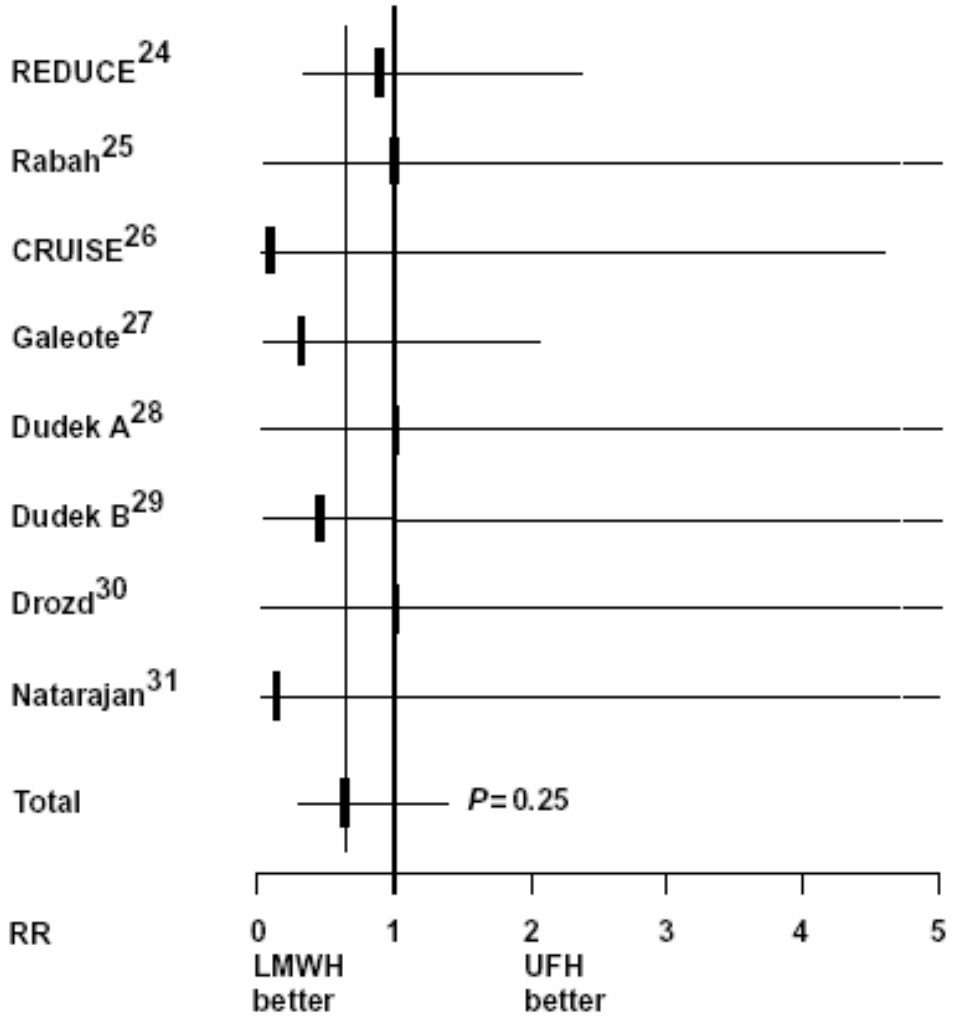
Death/MI/UR and *All bleeds* to 30 days



Major bleeds with IV enoxaparin



	LMWH	UFH	RR	95% CI
REDUCE[24]	7/306	8/306	0.88	[0.33—2.35]
Rabah[25]	1/30	1/30	1.00	[0.09—11.3]
CRUISE[26]	0/129	3/132	0.08	[0.00—4.57]
Galeote[27]	1/50	4/49	0.29	[0.04—2.04]
Dudek A[28]	0/200	0/200	1.00	[0.00—255]
Dudek B[29]	0/112	0/50	0.45	[0.00—113]
Drozd[30]	0/50	0/50	1.00	[0.00—252]
Natarajan[31]	0/160	2/161	0.11	[0.00—6.93]
Total	9/1037	18/978	0.63	[0.29—1.37]

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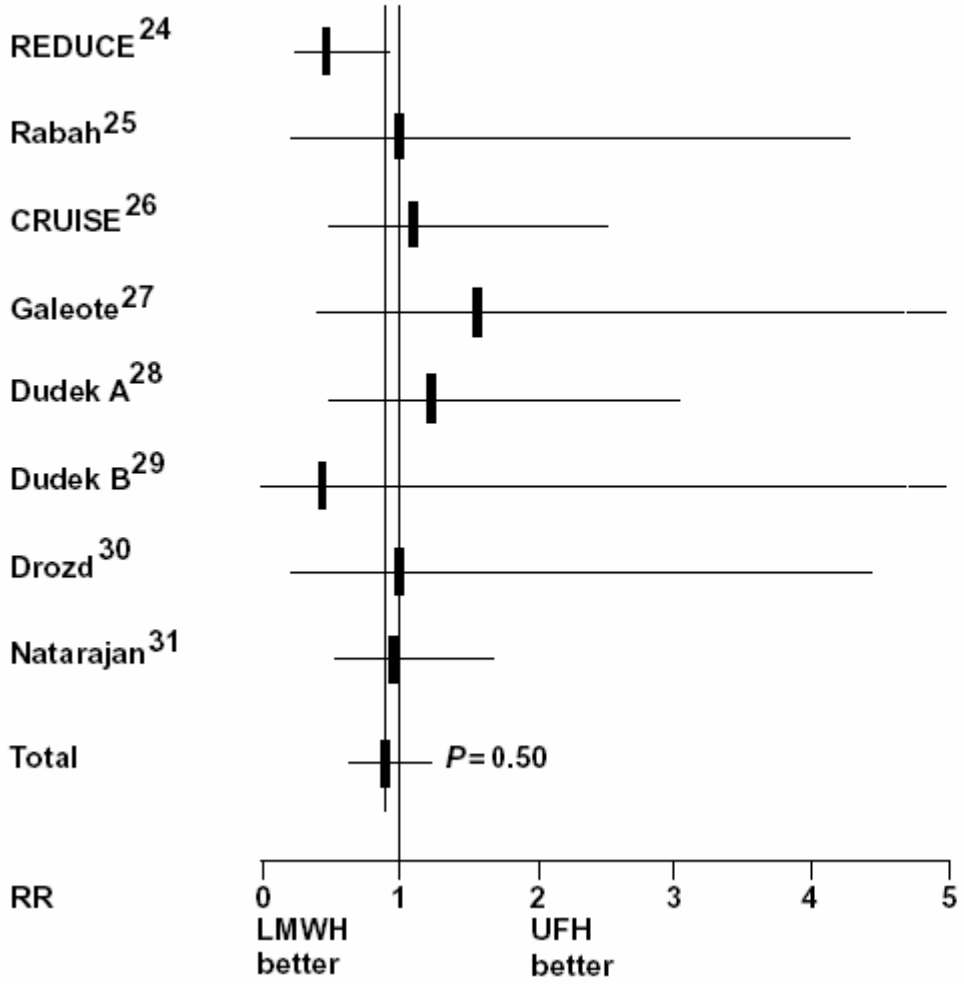
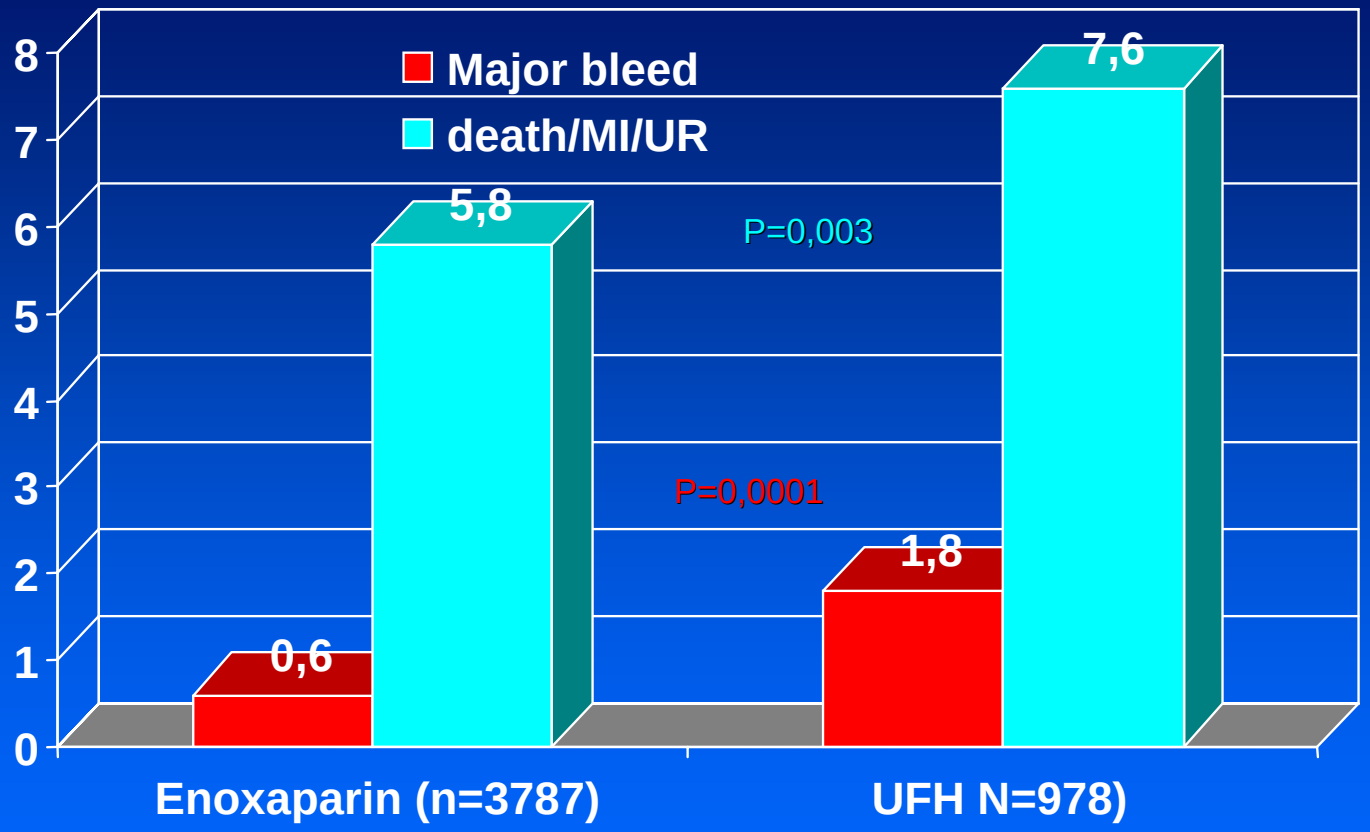
Efficacy of IV enoxaparin



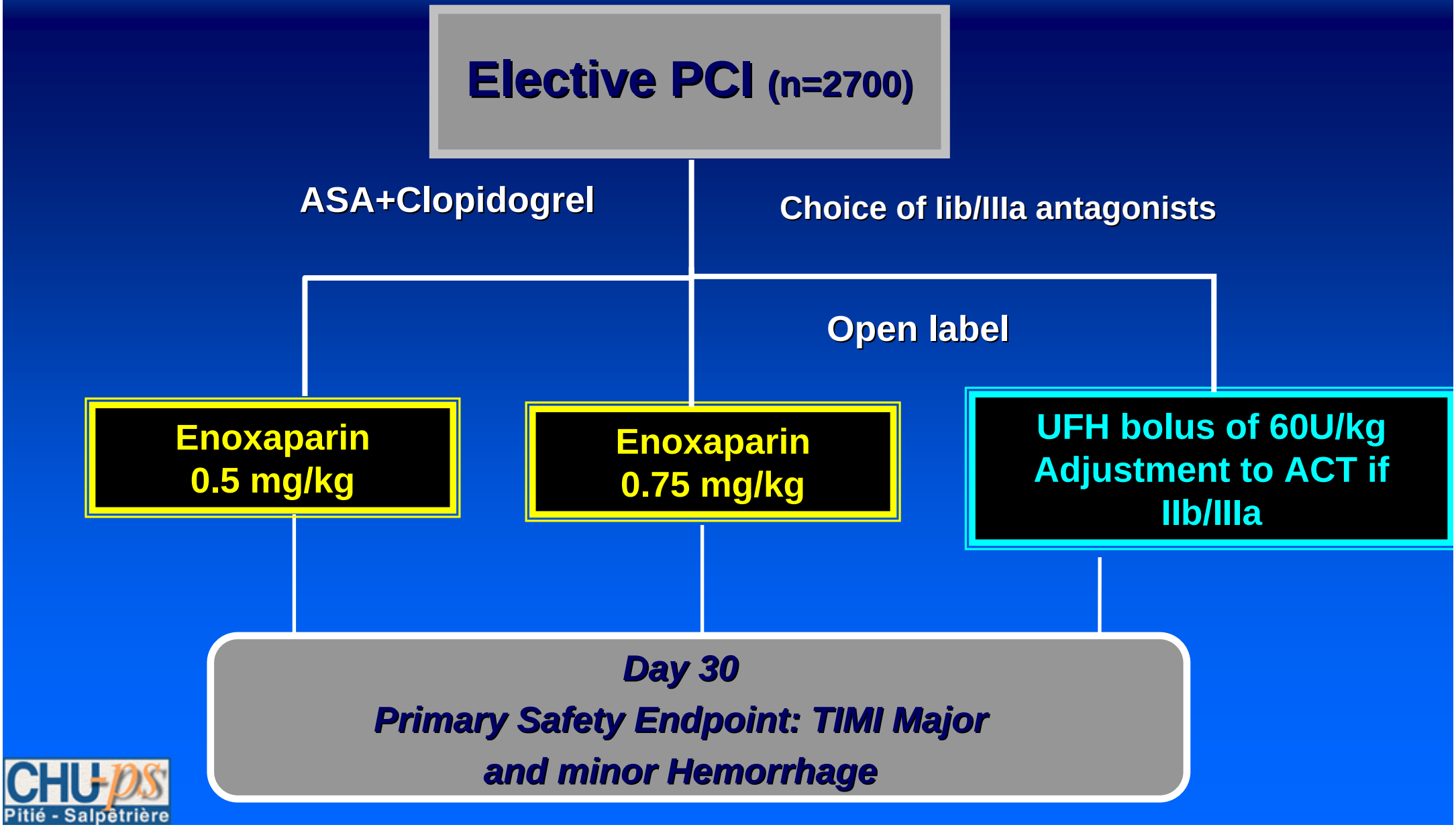
	LMWH	UFH	RR	95% CI
REDUCE[24]	12/306	25/306	0.49	[0.25—0.94]
Rabah[25]	3/30	3/30	1.00	[0.23—4.28]
CRUISE[26]	11/129	10/132	1.12	[0.50—2.53]
Galeote[27]	5/50	3/49	1.58	[0.42—5.97]
Dudek A[28]	10/200	8/200	1.24	[0.51—3.04]
Dudek B[29]	0/112	0/50	0.45	[0.00—113]
Drozd[30]	3/50	3/50	1.00	[0.23—4.43]
Natarajan[31]	21/160	22/161	0.96	[0.55—1.67]
Total	65/1037	74/978	0.90	[0.65—1.23]

death, myocardial infarction, urgent revascularization

Pooled analysis



STEEPLE: Protocol Design



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Conclusions 2

A single iv bolus of 0.5 mg/kg of enoxaparin just before PCI:

- provides an adequate level of anticoagulation all along the procedure
- simplifies the anticoagulation management (no monitoring)
- allows the use (or not) of GPIIb/IIIa inhibitors
- appears to be safe and effective
- allows immediate sheath removal

In the meta-analysis of randomized studies, there were non-significant trends favoring LMWH over UFH for both the efficacy endpoint (6.2% versus 7.5%) and major bleeding (0.9% versus 1.8%).

The analysis of all pooled data, randomized or not, showed improved efficacy (5.8% versus 7.6%) and major bleeding (0.6% versus 1.8%) with LMWH (n=3787) compared with UFH (n=978).

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3- Should we monitor anti-Xa?

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Anti-Xa activity

Background

- ✓Low-molecular-weight heparins are widely used for the treatment of acute coronary syndromes (ACS),
- ✓Enoxaparin is recommended for use at a dose of 1 mg/kg s.c. every 12 h, with no anticoagulation monitoring.
- ✓The relationship of anti-Xa activity to clinical outcome is still unknown.

Objectives

- ✓To assess whether anti-Xa levels were correlated with either ischemic events or bleeding in a real-world population of ACS patients.

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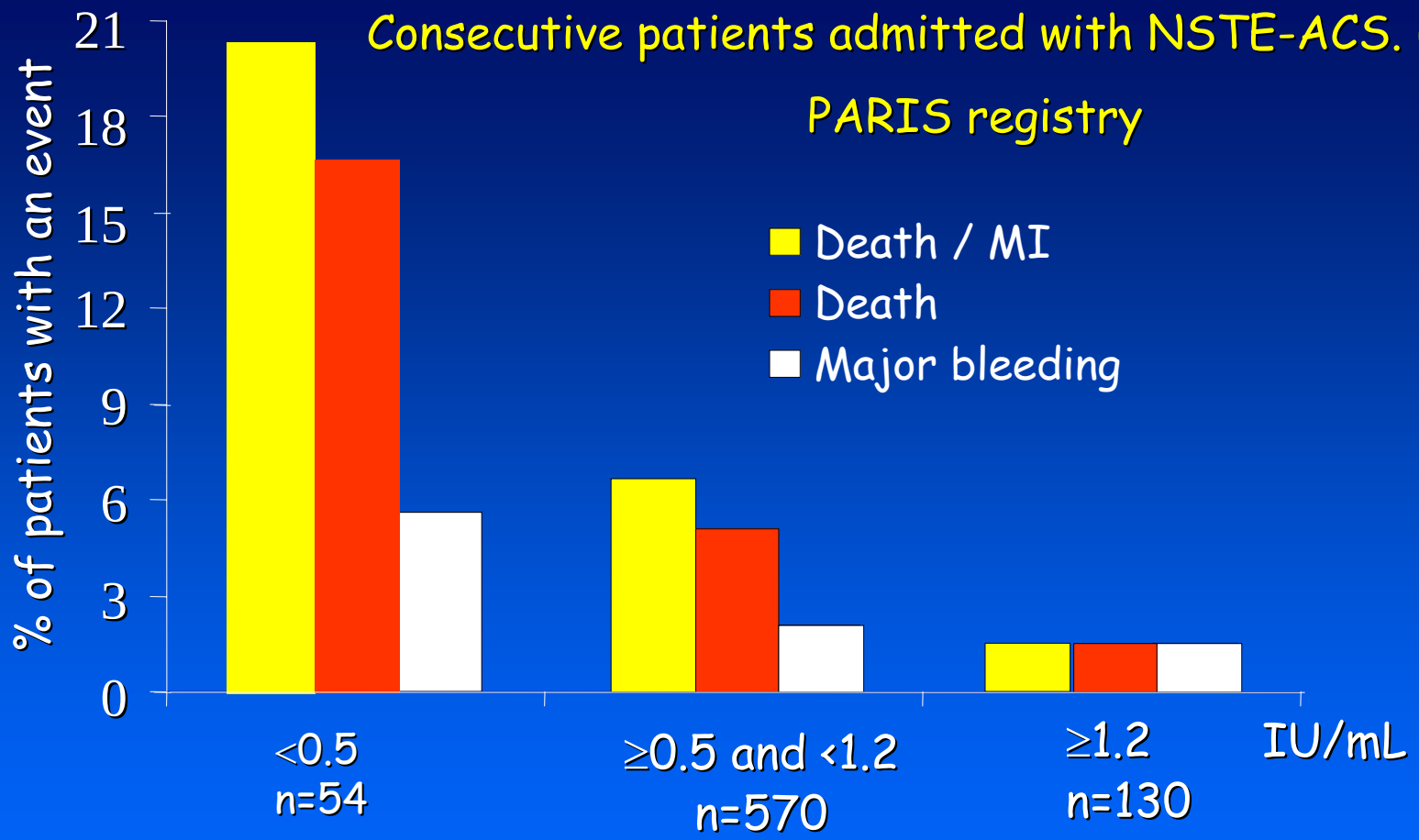
Montalescot G, Collet JP, et al. Circulation. 2004. In Press

Event rates at 30-day according to anti-Xa activity



Higher rates of death (p=0.0007), death or MI (p<0.0001) and major bleedings (p=NS) were associated with low anticoagulation.

Montalescot G, Collet JP, et al. Circulation. 2004. In Press

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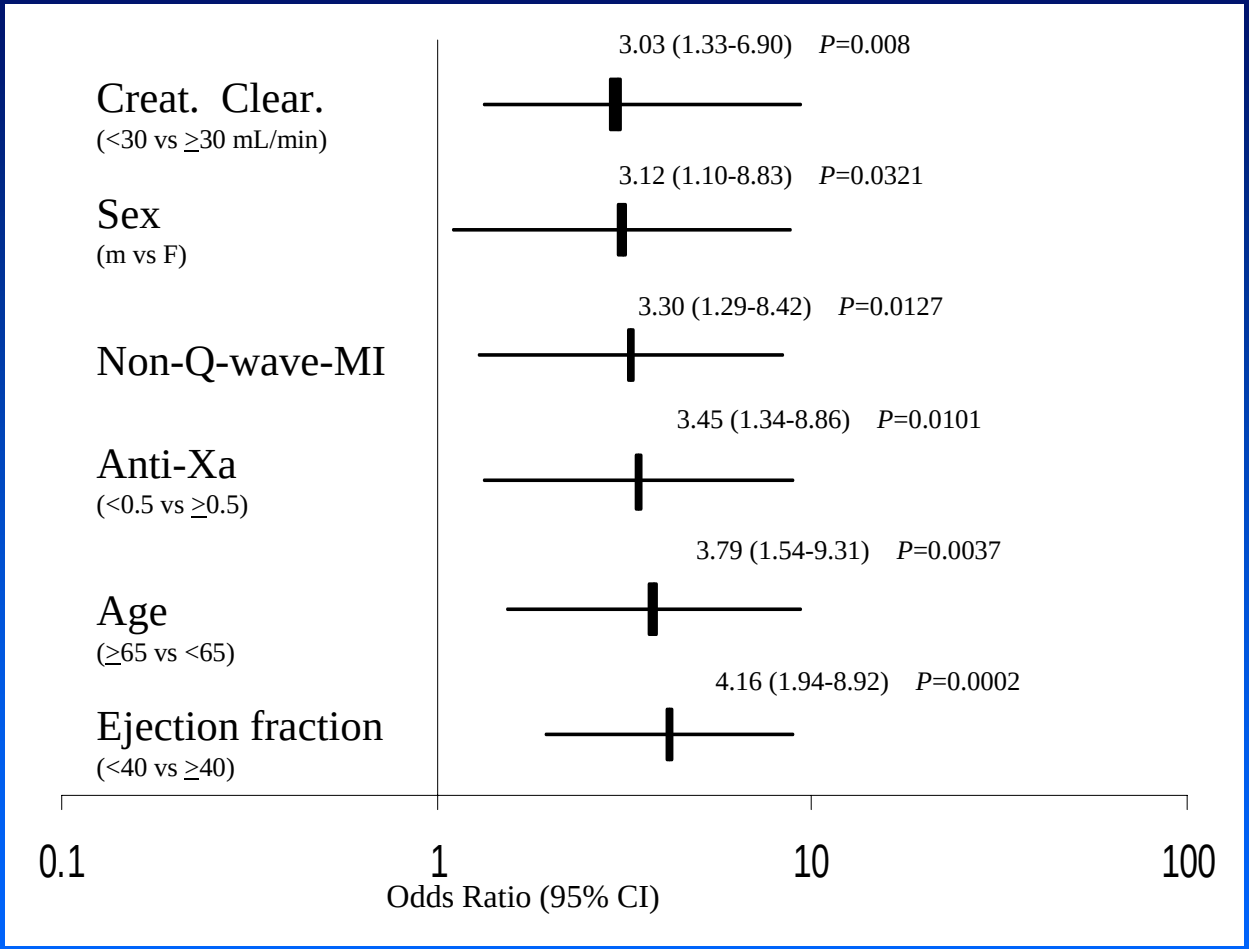
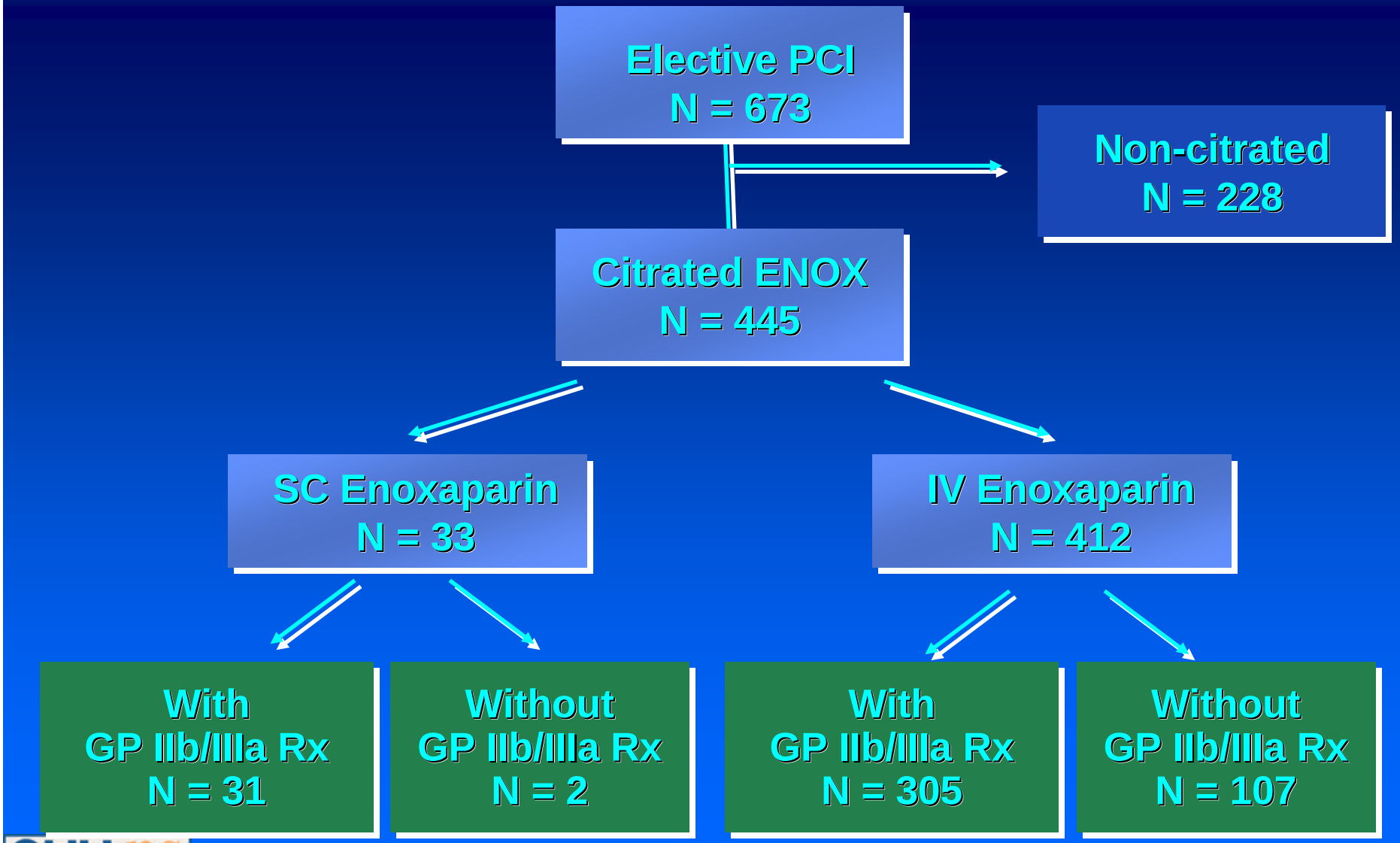
Anti-Xa predicts death



Montalescot G, Collet JP, et al. Circulation. 2004. In Press

Enox Clotting time



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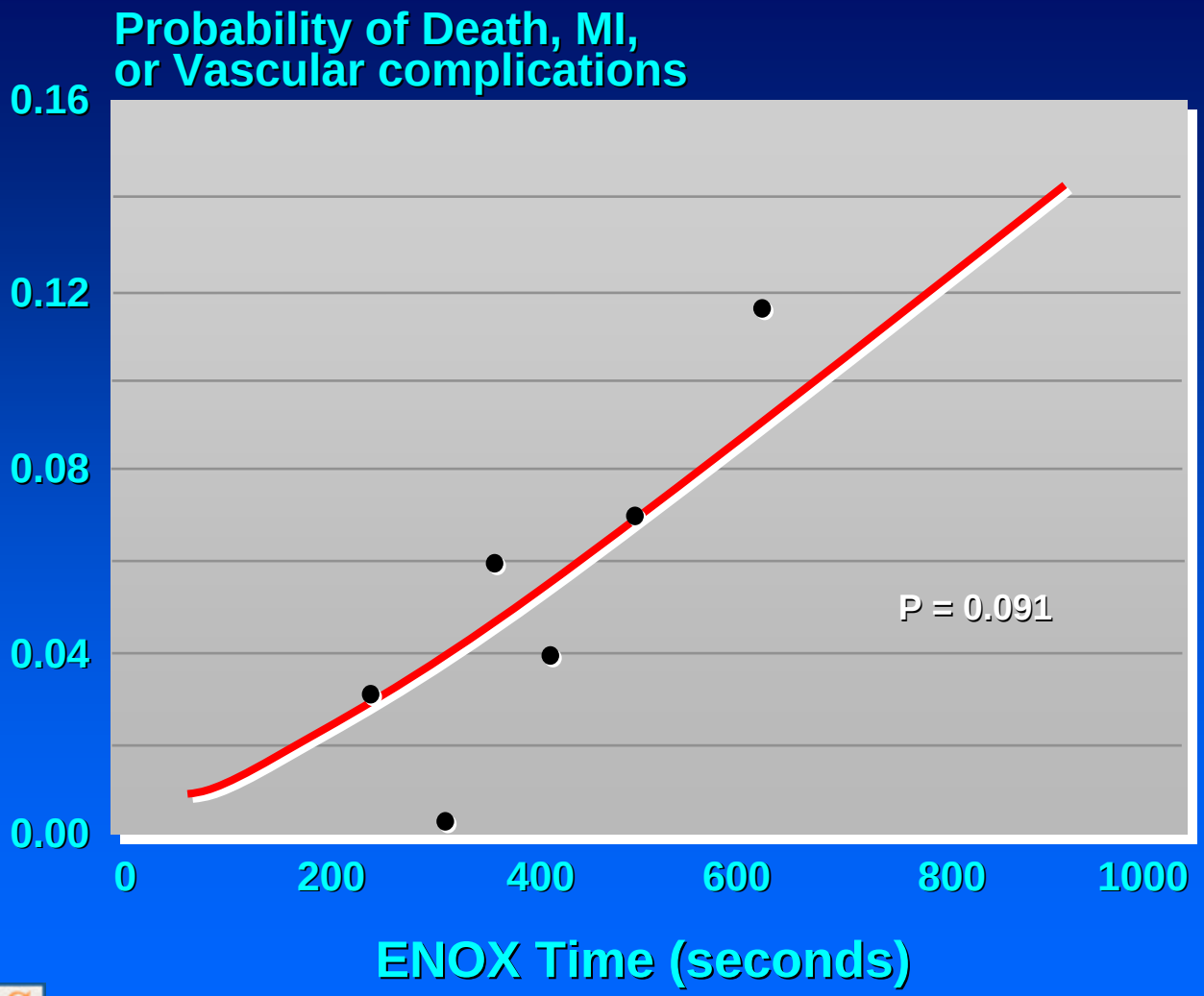
Moliterno et al.J Am Coll Cardiol 2003;42:1132-1139.

Mace and vascular complications



A positive, but not significant trend (p=0.091) was discovered between cardiac outcomes and citrated ENOX clotting times considering samples collected immmediately prior to PCI initiation.

log-logistic dose-response model with a non-zero background

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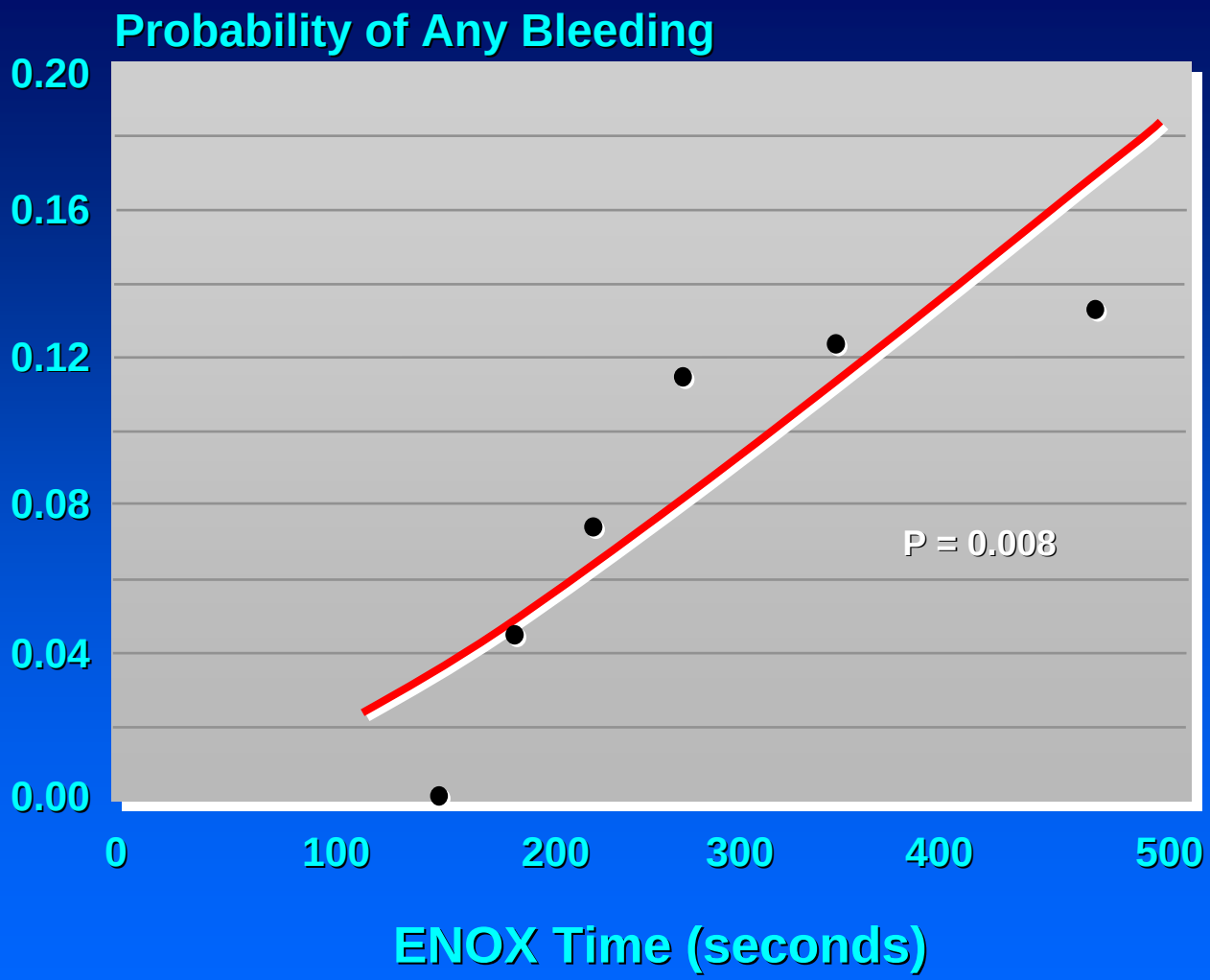
Bleeding complications



Inverse estimation techniques were used to calculate the clotting time to ensure ≤ 5% chance of "any bleed". On average, to have ≤ 5% chance of "any bleed" one would need to have a citrated clotting time ≤ 182 sec. before sheath removal

log-logistic dose-response model with a non-zero background

Summary

- ELECT reconfirms the safety of PCI among patients receiving enoxaparin;
- Death, MI, Urgent TVR = 5.4%
- Rare (<1%) TIMI major or minor bleeding
- Optimal clotting time*
  - Anti-Xa = 0.8-2.0 IU/ml
  - ENOX = 250-450 seconds
  - Safe sheath pull ENOX ⩽ 200-250 seconds
- Further analysis for subgroups receiving IIb/IIIa Rx and closure devices

*Depending on concomitant IIb/IIIa use

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Conclusions 3

- Low anti-Xa activity in enoxaparin-treated ACS patients is strongly and independently associated with early mortality;
- This highlights the need for the complete anticoagulation of ACS patients with enoxaparin when used as an upstream antithrombin therapy.
- Anti-Xa monitoring should be considered in high risk patients for both bleeding or ischemic events.

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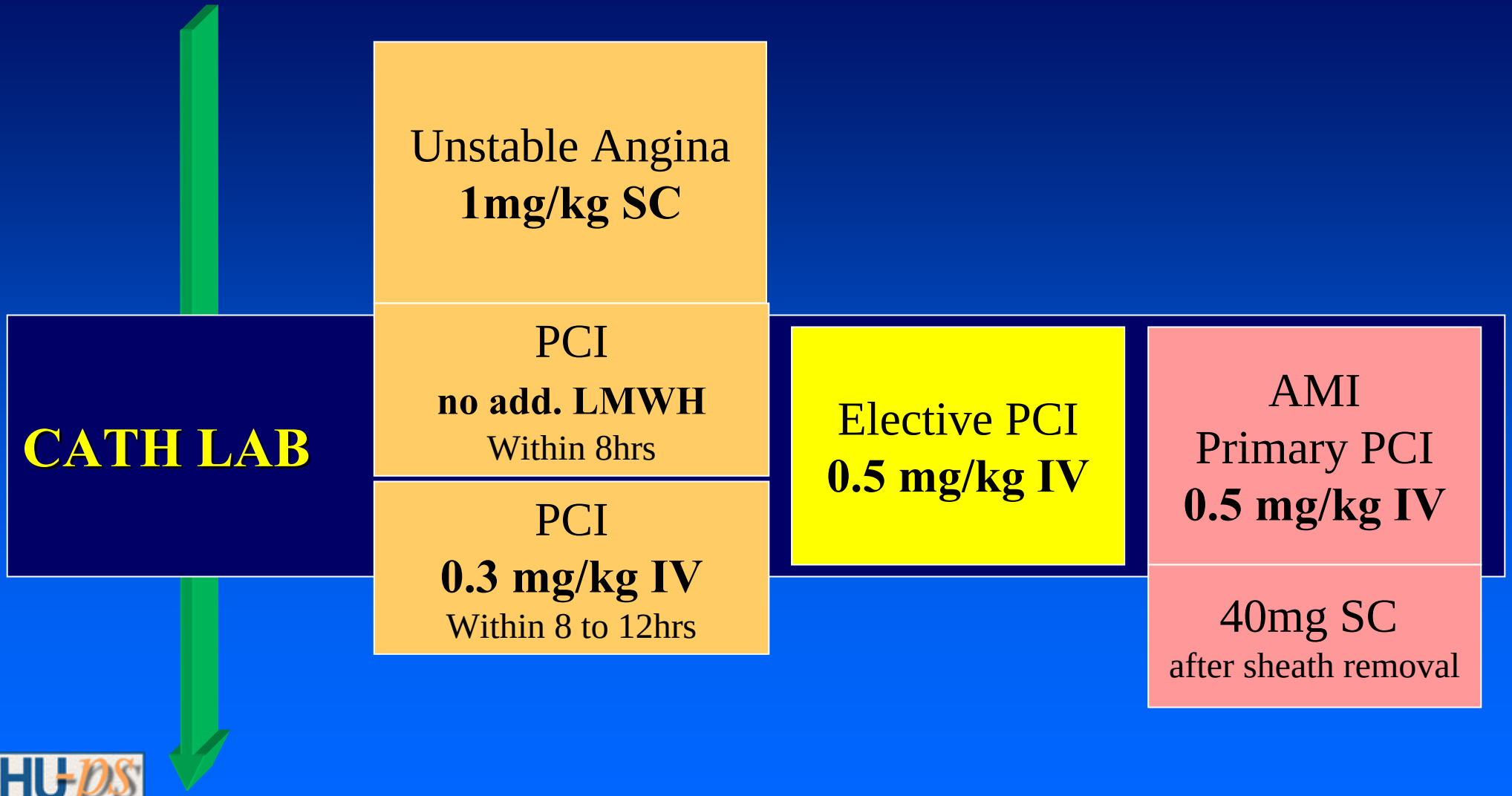
General Conclusions



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