

Advances in Antithrombotic Therapy

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Objectives

- To outline the pharmacology of newer antithrombotic agents
- To review the recent evidence for antithrombotic therapy in the management of ACS
- To describe the current role of these agents

STEMI

- UFH
 - PCI or surgical revascularization (C)
 - Reperfusion therapy with tPA, RPA, TNK (C)
 - Reperfusion therapy with streptokinase if high risk for systemic emboli (B)

www.acc.org/clinical/guidelines/stemi/Guideline1/index.htm

STEMI

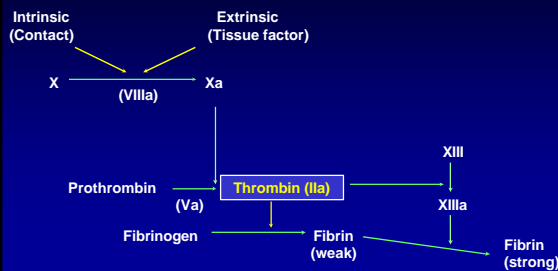
- LMWH
 - Alternative to UFH as ancillary therapy for patients <75 years who are receiving fibrinolytic therapy (B)
 - Normal renal function

www.acc.org/clinical/guidelines/stemi/Guideline1/index.htm

NSTACS

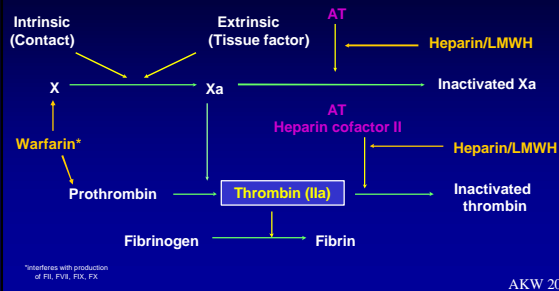
- Anticoagulation with LMWH or UFH should be added to antiplatelet therapy with ASA and/or clopidogrel (A)
- Enoxaparin is preferable to UFH as an anticoagulant in patient with NSTACS, unless CABG is planned within 24 h (A)

SIMPLIFIED CLOTTING CASCADE



AKW 2002

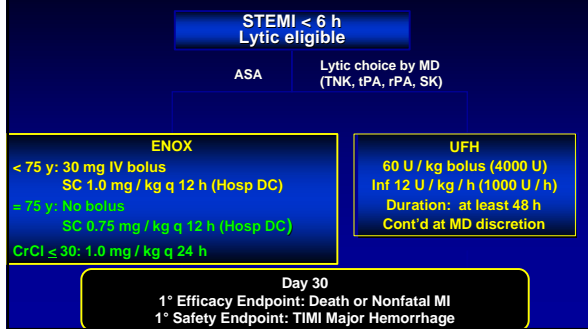
MECHANISM OF ACTION OF ANTICOAGULANTS



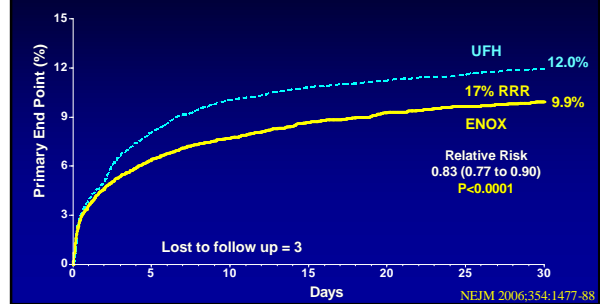
New Clinical Trials

- Enoxaparin
 - STEMI Extract TIMI 25
- Fondaparinux
 - NSTACS OASIS 5
 - STEMI OASIS 6
- Bivalirudin
 - NSTACS ACUTY

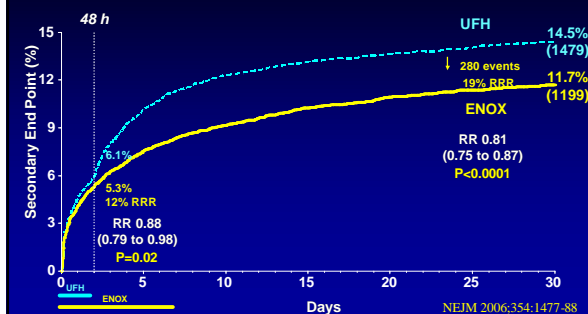
Protocol Design



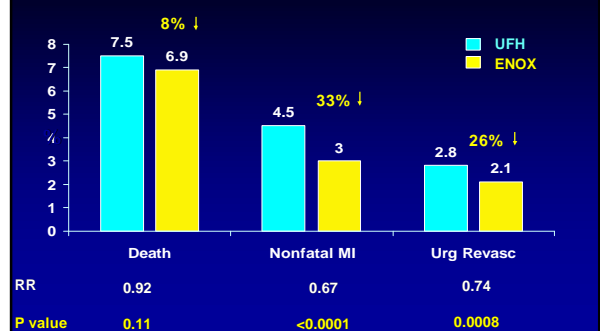
Primary End Point (ITT) Death or Nonfatal MI

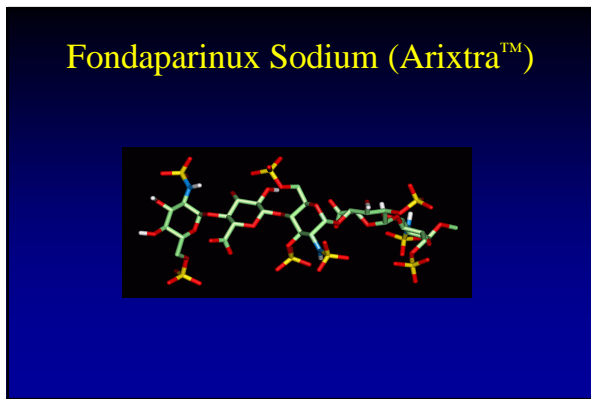
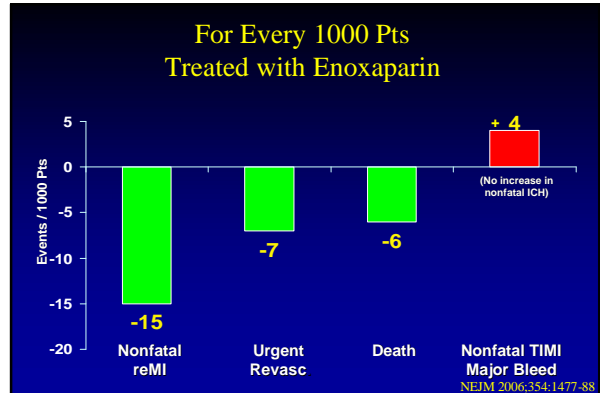
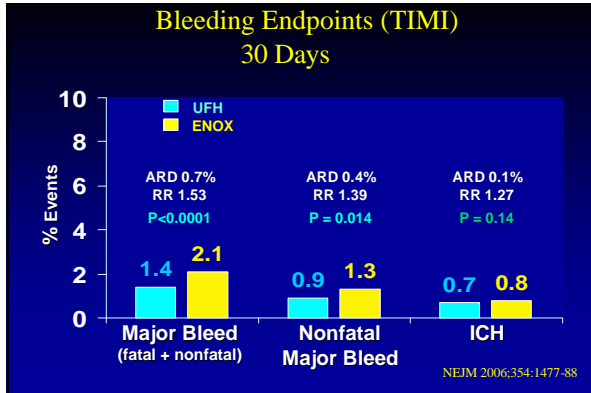


Major Secondary End Point Death or Nonfatal MI or Urgent Revascularization (ITT)

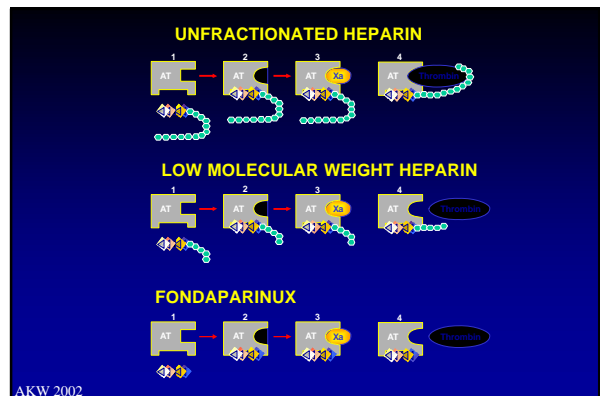
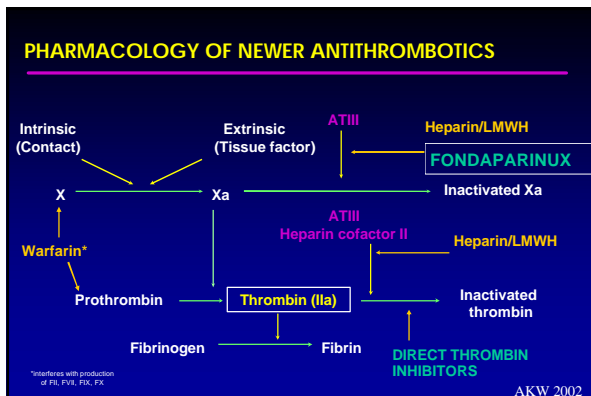


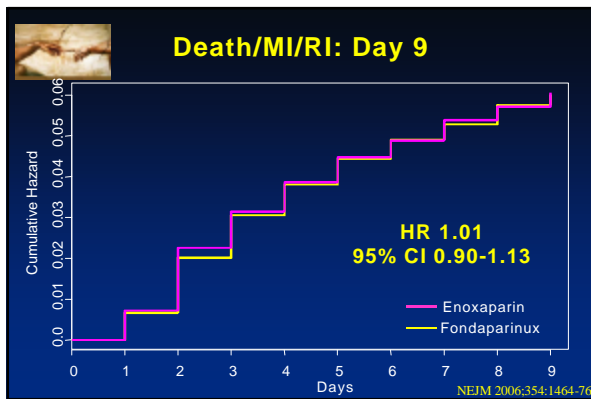
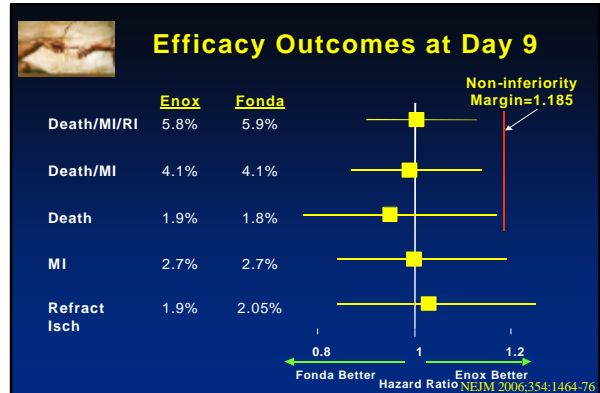
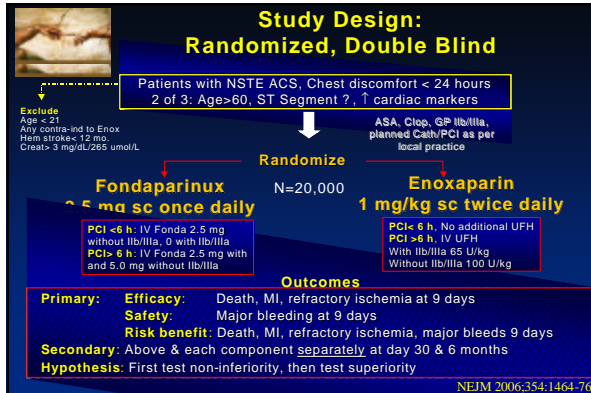
Outcomes at 30 Days (ITT)





- ### Fondaparinux
- Synthetic pentasaccharide affecting thrombin generation
 - High affinity for AT receptor
 - VTE prophylaxis/treatment
 - Subcutaneous once daily dosing
 - No monitoring required

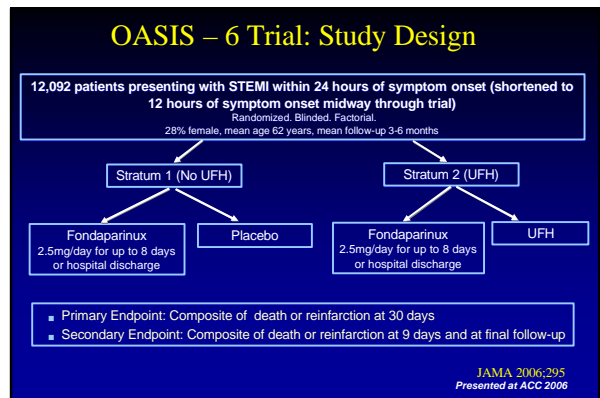
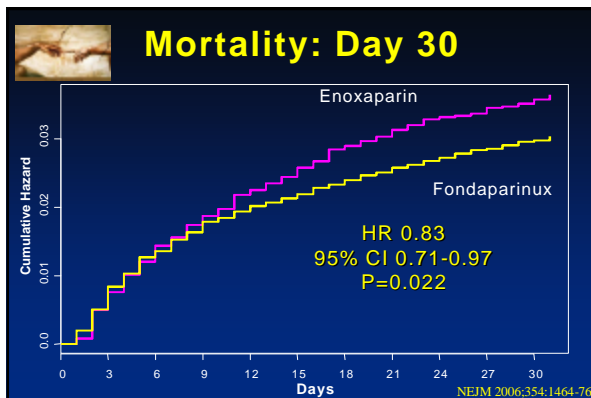




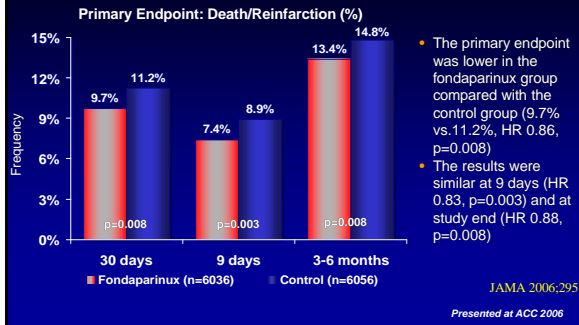
Bleeding Rates: Day 9

Outcome	Enox (%)	Fonda (%)	HR (95% CI)	P value
No. Randomized	10021	10057		
Total Bleed	7.0	3.2	0.44 (0.39-0.51)	<<0.0001
Major Bleed	4.0	2.1	0.53 (0.45-0.62)	<<0.0001
TIMI Major Bleed	1.3	0.7	0.54 (0.41-0.73)	<<0.0001
Minor Bleed	3.1	1.1	0.35 (0.28-0.43)	<<0.0001

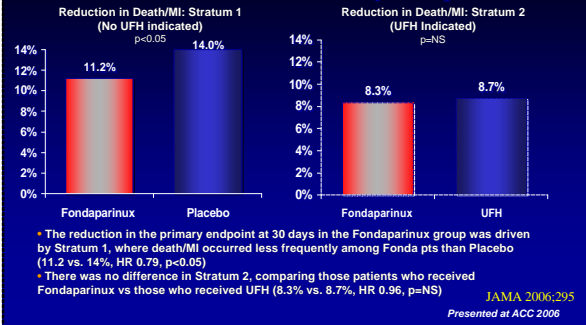
NEJM 2006;354:1464-76



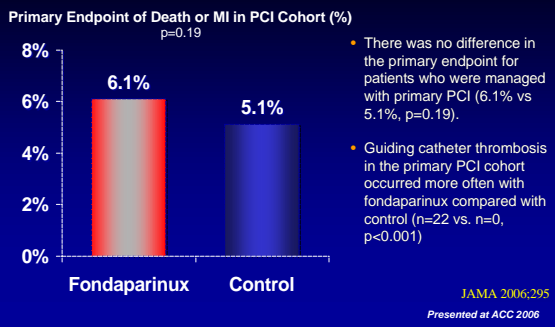
OASIS – 6 Trial: Primary Endpoint



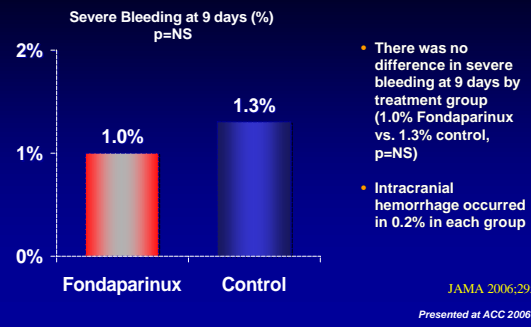
OASIS – 6 Trial: Primary Endpoint



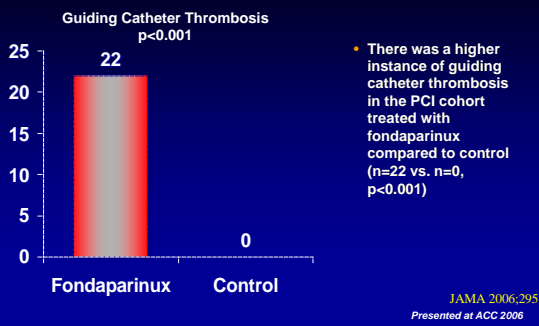
OASIS - 6 Trial: PCI Substudy at 30 Days



OASIS - 6 Trial: PCI Substudy (cont.)



OASIS - 6 Trial: PCI Substudy (cont.)



OASIS-5 and OASIS 6 combined: 30-day main efficacy and bleeding outcomes for UFH/enoxaparin vs fondaparinux

End point	UFH/enoxaparin, n=13 242 (%)	Fondaparinux, n=13 270 (%)	HR (95% CI)	p
Death/MI/stroke	8.0	7.2	0.91 (0.83-0.99)	0.030
Death	4.3	3.8	0.89 (0.79-1.00)	0.052
MI	3.8	3.5	0.92 (0.81-1.04)	0.196
Stroke	1.0	0.8	0.82 (0.64-1.07)	0.143
Major bleeding	4.4	3.0	0.67 (0.59-0.76)	<0.00001

Mehta S. World Congress of Cardiology 2006: September 6, 2006: Barcelona, Spain.

OASIS-5 and OASIS-6 combined: Data from patients undergoing PCI

End point	UFH/ enoxaparin	Fondaparinux	HR	95% CI
Major bleed at day 30 (%)				
All PCI patients	5.4	3.0	0.54	0.42-0.69
UFH prior to PCI	5.2	3.6	0.69	0.32-1.46
Death/MI/stroke at day 30 (%)				
All PCI patients	7.9	7.9	0.99	0.84-1.18
UFH prior to PCI	12.7	11.8	0.92	0.60-1.41
Catheter thrombosis (%)				
All PCI patients	0.2	0.9	3.58	1.64-7.83

Mehta S. World Congress of Cardiology 2006; September 6, 2006; Barcelona, Spain.

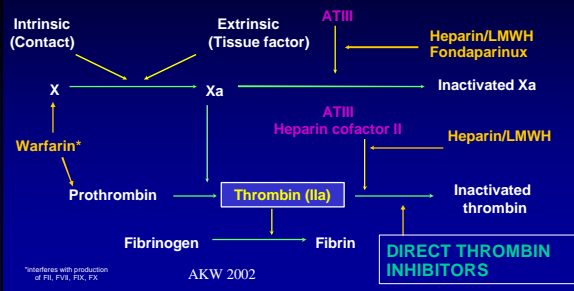
DIRECT THROMBIN INHIBITORS



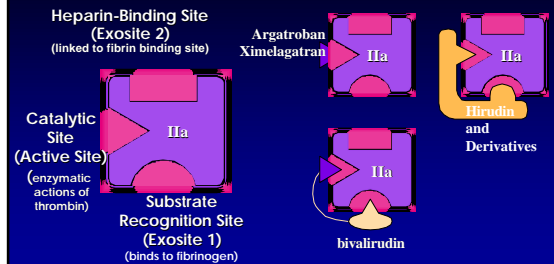
Hirudin: Isolated from the European leech *Hirudo medicinalis*

AKW 2002

MECHANISM OF ACTION OF ANTICOAGULANTS



DIRECT THROMBIN INHIBITORS

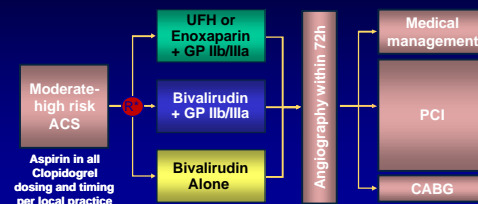


Bivalirudin

- administered IV
- cleared by renal and non-renal mechanisms
- Half-life 20-30 min
- clearance significantly reduced in moderate to severe renal dysfunction and may be associated with an increased risk of bleeding
- aPTT and ACT prolonged in a dose-dependent manner
- Current indication – patients with unstable angina going for PCI

Study Design – First Randomization

Moderate-high risk unstable angina or NSTEMI undergoing an invasive strategy (N = 13,800)



*Stratified by pre-angiography thienopyridine use or administration

ACUITY Design. Stone GW et al. AHJ 2004;148:764-75

3 Primary Endpoints (at 30 Days)

1. Composite net clinical benefit =

2. Ischemic composite
or

3. Major bleeding

- Death from any cause
- Myocardial infarction
 - During medical Rx: Any biomarker elevation >ULN
 - Post PCI: CKMB >ULN with new Q waves or >3x ULN w/o Q waves
 - Post CABG: CKMB >5x ULN with new Q waves, >10x ULN w/o Q waves
- Unplanned revascularization for ischemia

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3 Primary Endpoints (at 30 Days)

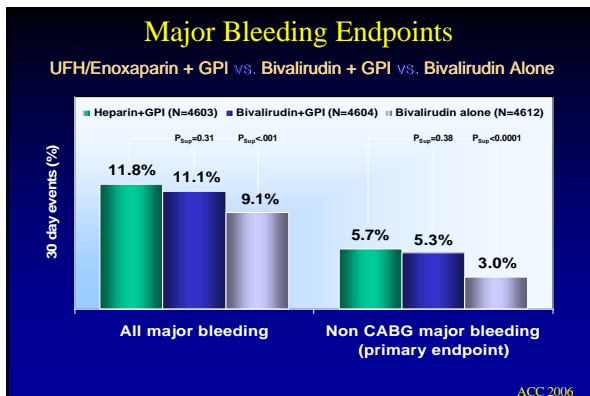
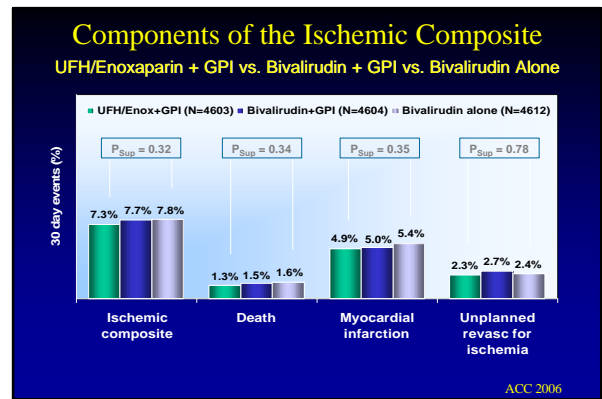
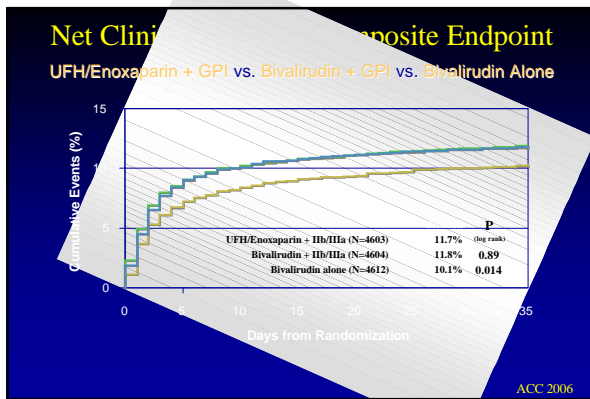
1. Composite net clinical benefit =

2. Ischemic composite
or

3. Major bleeding

- Non CABG related bleeding
 - Intracranial bleeding or intraocular bleeding
 - Retroperitoneal bleeding
 - Access site bleed requiring intervention/surgery
 - Hematoma =5 cm
 - Hgb β =3g/dL with an overt source or β =4g/dL w/o overt source
 - Blood product transfusion
 - Reoperation for bleeding

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Summary Table

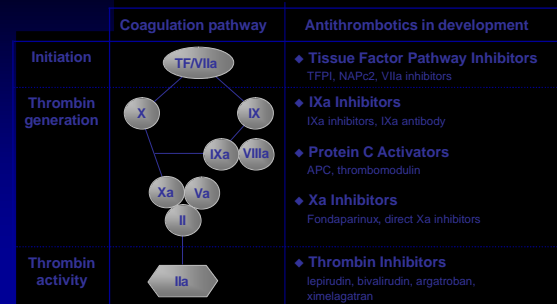
	UFH	Enoxaparin	Fondaparinux	Bivalirudin
STEMI	✓	✓	✓	✗
NSTACS	✓	✓	✓	✓

Question on Clinical Trial Results

- Which agent has demonstrated a greater superiority over UFH in the management of STEMI
 - Fondaparinux OASIS 6
 - Enoxaparin Extract TIMI 25

Clinicaltrialresults.org

NEW ANTITHROMBOTIC AGENTS



Am Heart J 2001;142:S3-8.