HIT Me With Your Best Shot

A Review of Heparin-Induced Thrombocytopenia

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Learning Objectives

1. Review the epidemiology, risk factors, pathophysiology, signs and symptoms and diagnosis of heparin-induced thrombocytopenia (HIT).
2. Review the evidence for the pharmacologic options used in the treatment of HIT.
3. Identify the advantages and disadvantages of each pharmacologic treatment option.
4. Discuss the management of a patient with HIT.

Case Scenario - PB

- 29 y/o female presented to ED after a skiing accident, which resulted in a fractured left knee

Case Scenario (cont) - PB

- Required knee surgery – successful/uneventful
- Discharged from hospital three days later
- DVT prophylaxis
  - Enoxaparin 30mg q12h x 7 days
- Four days after d/c – came back to hospital with swelling and pain in the upper left leg

Case Scenario (cont) - PB

- Presented to hospital @ 2100 on a Friday night… ultrasound gone for the day
- Dose of enoxaparin given
  - 60 mg
- Patient told to return to hospital the next morning for an ultrasound
- Next morning – ultrasound positive for VTE
- Blood-work drawn

Definitions

- Non-Immune Heparin-Associated Thrombocytopenia
  - Previously Type I HIT
- Immune Heparin-Induced Thrombocytopenia
  - Previously Type II HIT

	Non-Immune HIT	Immune HIT
Frequency	10-30%	1-3%
Time from initiation of heparin therapy	<5 days	>5 days
Reduction in plt count	Mild	Moderate-Severe
HIT antibodies	Absent	Present
Risk of thrombosis	Low	High
Management	Observe	D/C heparin Use alternative anticoagulant

Shantsila E et al, Chest 2009.

Epidemiology

- Up to 8% of patients receiving heparin will develop the antibody associated with HIT
- ~ 1-3% of these patients will progress to develop HIT
- 1/3 of patients who develop HIT will suffer from venous and/or arterial thrombosis

Shantsila E et al, Chest 2009.

Risk Factors

- Longer duration of therapy
- UFH vs. LMWH
- Cardiovascular vs. Orthopedic surgery
- Post-surgical vs. Medical patients
- Female vs. Male patients

Coutre S. Up-to-Date 2010.

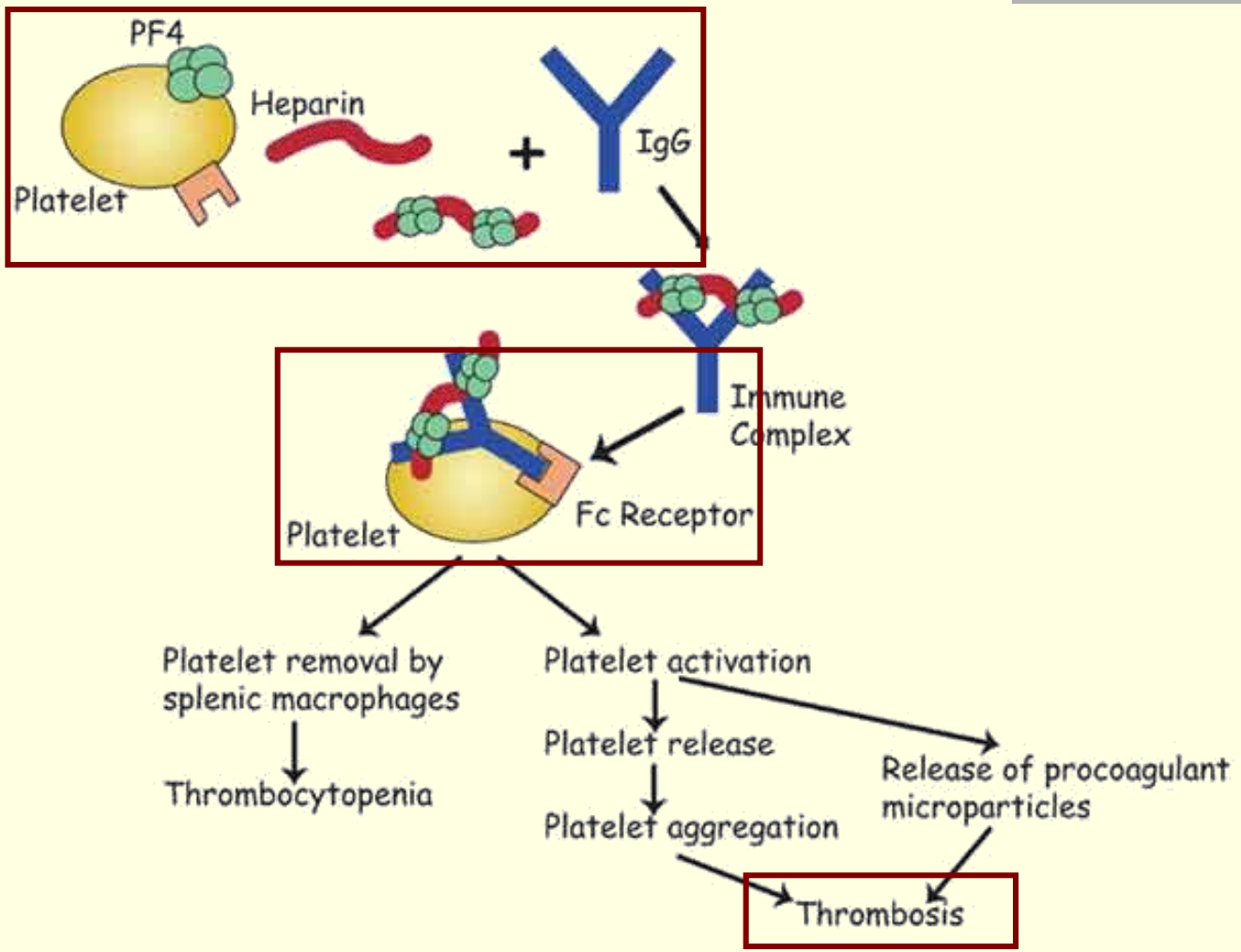
Pathophysiology

The pathogenesis of HIT can be described in 3 stages:

1. Immune reaction with generation of HIT antibodies
2. Platelet activation and ↑ thrombin generation
3. Extension of existing thrombosis or the development of new thrombosis

Franchini M et al. Thrombosis Journal 2005.

Pathophysiology



http://home.ccr.cancer.gov

Clinical Presentation

Thrombocytopenia

- Suspect HIT if:
  - Platelets < $150X10^9$ cells/L
  - Fall in platelets > 50%
  - Typically 5-14 days following heparin administration
- ACCP Guidelines recommend platelet monitoring in patients at high or intermediate risk of HIT

Warkentin TE et al, Chest 2008; Coutre S, Up-To-Date 2010; Shantsila E et al., Chest 2009

Clinical Presentation

Thrombocytopenia (cont'd)

- Platelet Monitoring
  - Received heparin within past 100 days - baseline and at 24 hours
  - High risk – every other day
  - Intermediate risk – q 2-3 days from day 4-14
  - As clinically indicated
- Very severe thrombocytopenia (platelets < 15-20X10^9 cells/L) not usually HIT
- Variations in thrombocytopenia presentation

Warkentin TE et al, Chest 2008; Coutre S, Up-To-Date 2010; Shantsila E et al., Chest 2009

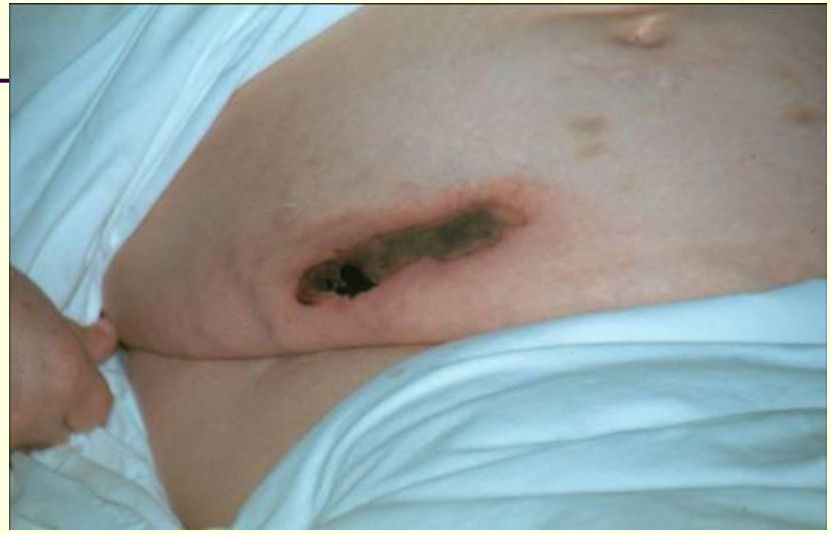
Clinical Presentation

Thrombosis

- Main contributor to the severity of HIT
- Unpredictable
- Can develop at any vascular location
  - Venous more commonly in post-op patients
  - Arterial more commonly in cardiac patients
- Development or extension of a thrombosis in patients receiving prophylactic therapy with UFH or LMWH should always raise a suspicion of HIT

Coutre S, Up-To-Date 2010; Shantsila E et al., Chest 2009

Clinical Presentation



Other manifestations

- Skin lesions
- Acute systemic reactions
- Disseminated intravascular coagulation
- Venous limb gangrene in HIT patients treated with anticoagulants

Coutre S, Up-To-Date 2010; Shantsila E et al., Chest 2009

Case Scenario (cont) - PB

- PB returns to hospital the next morning
- Ultrasound performed
  - Positive for VTE
- Blood work drawn
  - CBC
  - Chem
  - Coagulation Panel

Diagnosis

- Clinical criteria
  - Thrombocytopenia
  - Thrombosis
- Laboratory diagnosis
  - ^{14}C serotonin release assay (SRA)
  - enzyme-linked immunosorbent assay (ELISA)
  - Heparin-induced platelet aggregation (HIPA)
- Pre-Test Probability – the 4 T's

Coutre S, Up-To-Date 2010; Shantsila E et al., Chest 2009

Pre-Test Probability of HIT

Category	2 Points	1 Point	0 Points
Thrombocytopenia	>50% fall OR Nadir of 20-100X10^9 cells/L	30-50% fall OR Nadir of 10-19X10^9 cells/L	<30% fall OR Nadir < 10X10^9 cells/L
Timing of platelet count fall	Onset Day 5-10 OR ≤1 day if heparin exposure within past 30 days	Onset beyond Day 10 (or unclear, but consistent with HIT) OR ≤1 day if heparin exposure within past 30-100 days	Fall at < Day 4 with no recent heparin exposure
Thrombosis or other sequelae	Confirmed thrombosis, skin necrosis, or acute systemic reaction after heparin bolus	Progressive, recurrent, or silent thrombosis; non-necrotizing (erythematous) skin lesions	None
Other cause for thrombocytopenia	None evident	Possible	Definite

High probability = 6-8 points
Intermediate probability = 4-5 points
Low probability = 0-3 points

Coutre S, Up-To-Date 2010;
Shantsila E et al., Chest 2009

Case Scenario (cont) - PB

- CBC:
  - Platelets = $98X10^9$ cells/L
    - Baseline = $294X10^9$ cells/L
  - All other parameters WNL
- Chem:
  - WNL
- Coag
  - PT 13.4s (12.2-14.6)
  - INR 0.97 (0.89-1.11)
  - PTT 26.2s (25.8-34.2)
- What's PB's Pre-Test Probability?

Laboratory Diagnosis

SRA

- "gold standard"
- High specificity – a positive result would support the diagnosis of HIT
- High cost (~$150/test)

ELISA

- High sensitivity – a negative test makes HIT highly unlikely
- Detects both clinically irrelevant (nonpathogenic) and clinically relevant antibodies
- Cost ~$60/test

Coutre S, Up-To-Date 2010; Shantsila E et al., Chest 2009

Laboratory Diagnosis

HIPA

- High specificity (>90%) – a positive result would support the diagnosis of HIT
- Positive test would include low background aggregation with no heparin, aggregation with the addition of a low concentration of heparin, and absent aggregation with high heparin concentrations.
- SRA typically done here
  - Has to be sent away
  - Turn-around is 4-6 weeks
  - Diagnosis is based on clinical presentation and ruling out other causes of thrombocytopenia

Coutre S, Up-To-Date 2010; Shantsila E et al., Chest 2009

Case Scenario (cont) - PB

- PB is diagnosed with HIT
- Blood sample drawn to be sent away for SRA testing…
- Now what?

Management of HIT

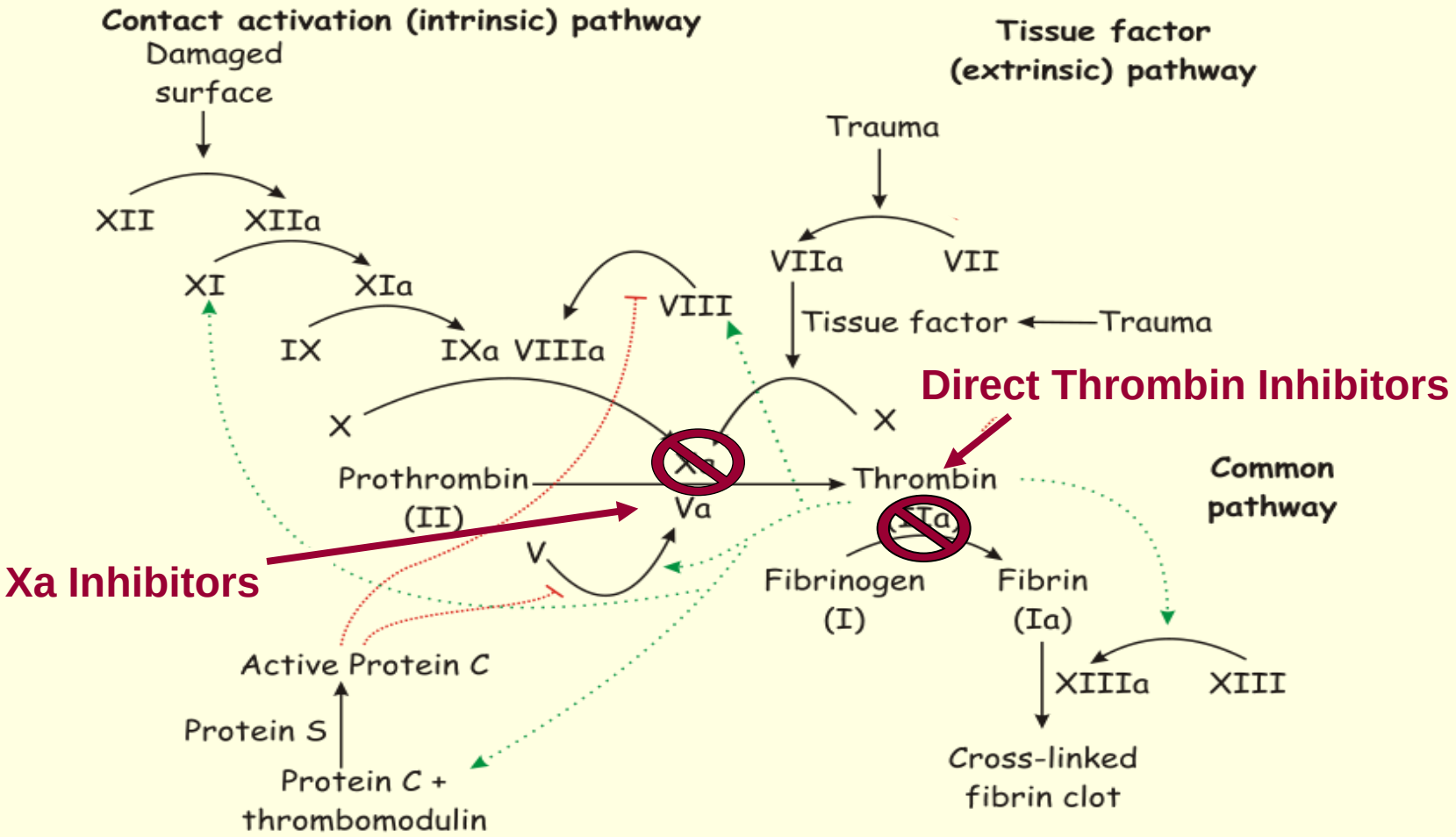
- Heparin from ALL sources should be discontinued
  - Heparin-coated catheters
  - Heparin flushes/locks
- Alternative non-heparin, anticoagulation therapy should be initiated immediately
  - Argatroban
  - Lepirudin
  - Bivalirudin

  } Direct Thrombin Inhibitors
  - Danaparoid
  - Fondaparinux

  } Xa Inhibitors

Warkentin TE et al, Chest 2008; Coutre S, Up-To-Date 2010; Shantsila E et al., Chest 2009

Alternative Anticoagulants



www.wikipedia.org

Which agent is best for PB?

2008 ACCP Guidelines

Treatment of HIT

- Danaparoid → Grade 1B
- Argatroban → Grade 1C
- Lepirudin → Grade 1C
- Bivalirudin → Grade 2C
- Fondaparinux → Grade 2C

Warkentin TE etal., Chest 2008

Danaparoid (Orgaran®)

- Only agent that is currently on formulary
- Only option that has been evaluated in a prospective randomized controlled study
- Has the unique property of specific suppression of HIT antibody-induced platelet activation
- Potential for sc administration
  - IV still currently recommended for HIT
- No effect on INR
- BUT recent backorder issues

Chong BH et al. Thromb Haemost 2001; Warkentin TE et al., Chest 2008; Shantsila E et al., Chest 2009.

Fondaparinux (Arixtra®)

- Limited data on use in HIT
- Dose for HIT not established
- Relatively low-cost compared to other agents
- 2008 Case Report of fondaparinux-induced thrombocytopenia in a patient previously treated with a LMWH
- Grade 2C in 2008 ACCP Guidelines

Shantsila E et al., Chest 2009; Warkentin TE et al, Chest 2008; Rota et al. Thromb Haemost 2008.

Bivalirudin (Angiomax®)

- Indicated in patients undergoing PCI or cardiac surgery who have or are at risk of HIT
- No data in other HIT settings
- Some potential pharmacologic advantages
  - Short t½
  - Enzymatic metabolism
  - Low immunogenicity
  - Minimal effect on INR prolongation
- Grade 2C in 2008 ACCP Guidelines

Shantsila E et al., Chest 2009; Warkentin TE et al, Chest 2008; Rota et al. Thromb Haemost 2008.

Argatroban
Review of Evidence

- 2008 ACCP Guidelines
  - Grade 1C recommendation
  - Recommendation is based on two prospective trials ARG 911 and ARG 915

ARG 911

Prospective multicentre cohort study

- Historical controls
- Hospitalized patients with isolated HIT or HIT associated with thrombosis (2 study arms)
  - Isolated HIT
    - Argatroban n=160
    - Control n=147
  - HIT with thrombosis
    - Argatroban n=144
    - Control n=46

Lewis BE et al. Circulation 2001.

ARG 911

Interventions

- Argatroban 2.0 mcg/kg/min targeting an aPTT 1.5-3.0 X baseline
  - Average of 6 days
- Historical controls treated with local standard of practice – heparin discontinuation and/or oral anticoagulation

Lewis BE et al. Circulation 2001.

ARG 911

Composite Endpoint

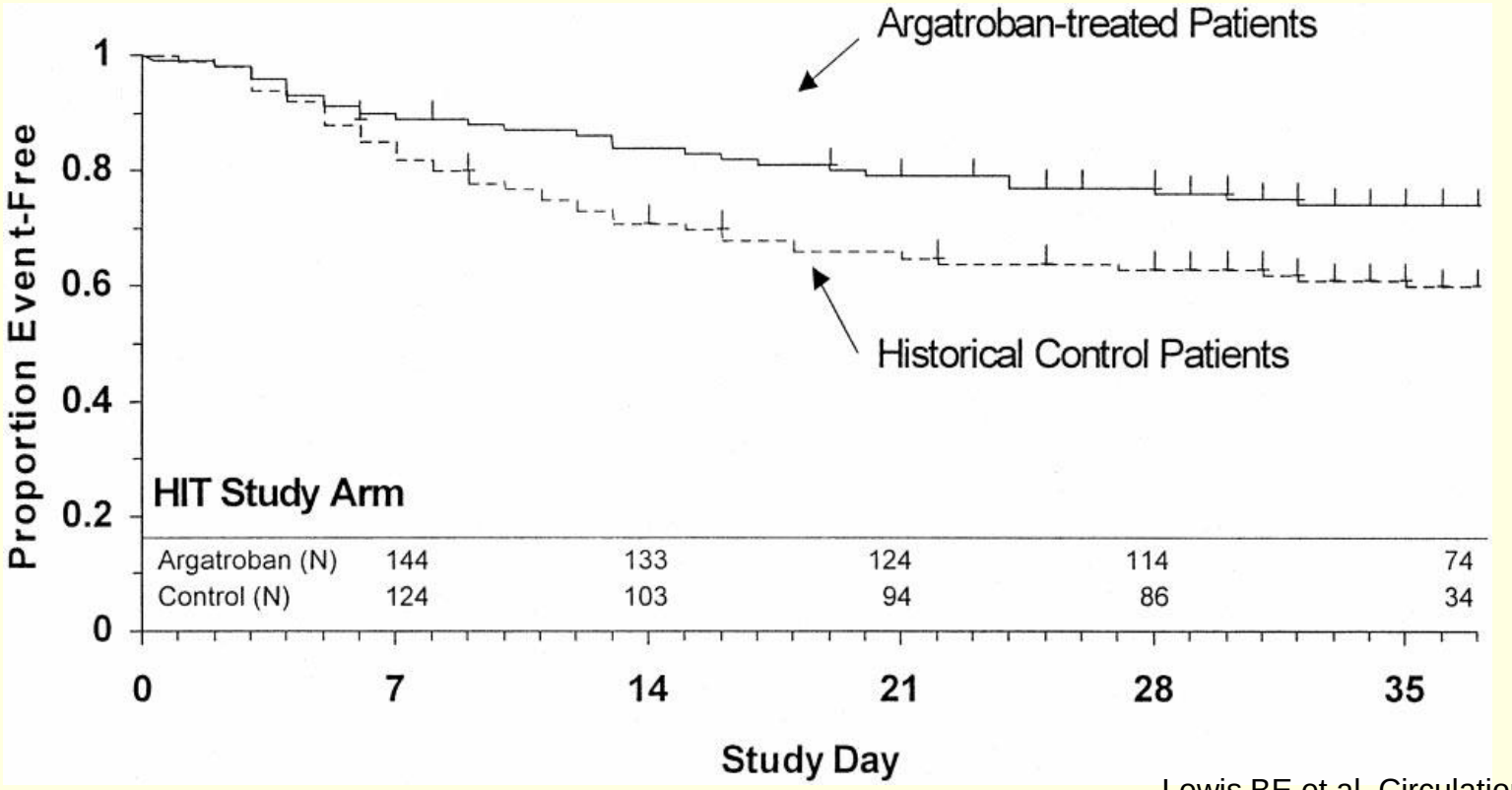
- All cause mortality, all-cause amputation, and new thrombosis
- Isolated HIT: 25.6% vs. 38.8%, p=0.014
  - OR=0.54 (95%CI 0.33-0.88)
- HIT with thrombosis (HITTS): 43.8% vs. 56.5%, p=0.13
  - OR=0.60 (95% CI 0.31-1.17)

Lewis BE et al. Circulation 2001.

ARG 911

Time-to-event analysis – Isolated HIT

- HR 0.60 (95% CI 0.40-0.89)

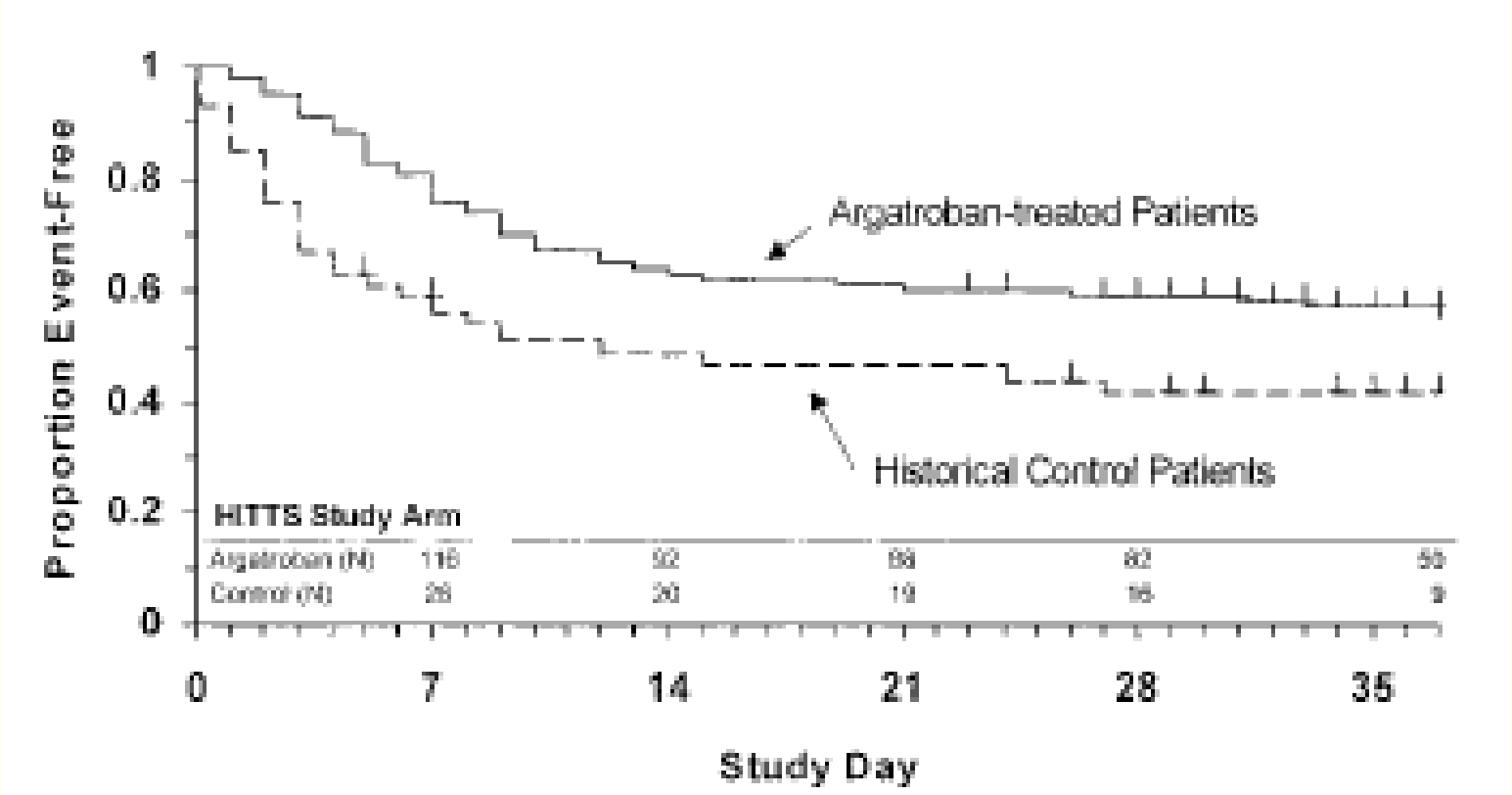


Lewis BE et al. Circulation 2001.

ARG 911

Time-to-event analysis –HIT with thrombosis

- HR 0.57 (95% CI 0.36-0.90)



Lewis BE et al. Circulation 2001.

ARG 911

TABLE 2. Categorical Efficacy Analyses

	HIT Arm			HITTS Arm		
Parameter	Control (n=147)	Argatroban (n=160)	*P*	Control (n=46)	Argatroban (n=144)	*P*
Composite end point*	57 (38.8)	41 (25.6)	0.014	26 (56.5)	63 (43.8)	0.131
	Odds ratio=0.54 (95% CI, 0.33–0.88)			Odds ratio=0.60 (95% CI, 0.31–1.17)		
Components by severity†						
Death (all causes)	32 (21.8)	27 (16.9)	0.311	13 (28.3)	26 (18.1)	0.146
Amputation (all causes)	3 (2.0)	3 (1.9)	1.000	4 (8.7)	16 (11.1)	0.787
New thrombosis	22 (15.0)	11 (6.9)	0.027	9 (19.6)	21 (14.6)	0.486
Death caused by thrombosis	7 (4.8)	0 (0.0)	0.005	7 (15.2)	1 (0.7)	<0.001
Any new thrombosis‡	33 (22.4)	13 (8.1)	<0.001	16 (34.8)	28 (19.4)	0.044

Lewis BE et al. Circulation 2001.

ARG 911

TABLE 5. Bleeding Incidence

	HIT Arm		HITTS Arm	
	Control (n=147)	Argatroban (n=160)	Control (n=46)	Argatroban (n=144)
Major bleeding,* n (%)	12 (8.2)	5 (3.1)	1 (2.2)	16 (11.1)
	P=0.078		*P*=0.077	
	Odds ratio=0.36 (95% CI, 0.12–1.05)		Odds ratio=5.56 (95% CI, 0.72–50.0)	
Minor bleeding,* n (%)	60 (40.8)	64 (40.0)	19 (41.3)	60 (41.7)

*Patients with >1 event are counted only once.

- Most common adverse events:
  - Diarrhea, Pain, Rash, Hemorrhage, Purpura, Thrombophlebitis

Lewis BE et al. Circulation 2001.

ARG 915

Prospective multicentre cohort study

- Historical controls
- Hospitalized patients with isolated HIT or HIT associated with thrombosis (2 study arms)
  - Isolated HIT
    - Argatroban n=189
    - Control n=139
  - HIT with thrombosis
    - Argatroban n=229
    - Control n=46

Lewis BE et al. Arch Intern Med 2003.

ARG 915

Interventions

- Argatroban 2.0 mcg/kg/min targeting an aPTT 1.5-3.0 X baseline
  - Average of 5-7 days
- Historical controls treated with local standard of practice – heparin discontinuation and/or oral anticoagulation

Lewis BE et al. Arch Intern Med 2003.

ARG 915

Composite Endpoint

- All cause mortality, all-cause amputation, and new thrombosis
- Isolated HIT: 28% vs. 38.8%, p=0.04
  - OR=0.61 (95%CI 0.39-0.98)
- HIT with thrombosis (HITTS): 41.5% vs. 56.5%, p=0.07
  - OR=0.55 (95% CI 0.29-1.03)

Lewis BE et al. Arch Intern Med 2003.

ARG 915

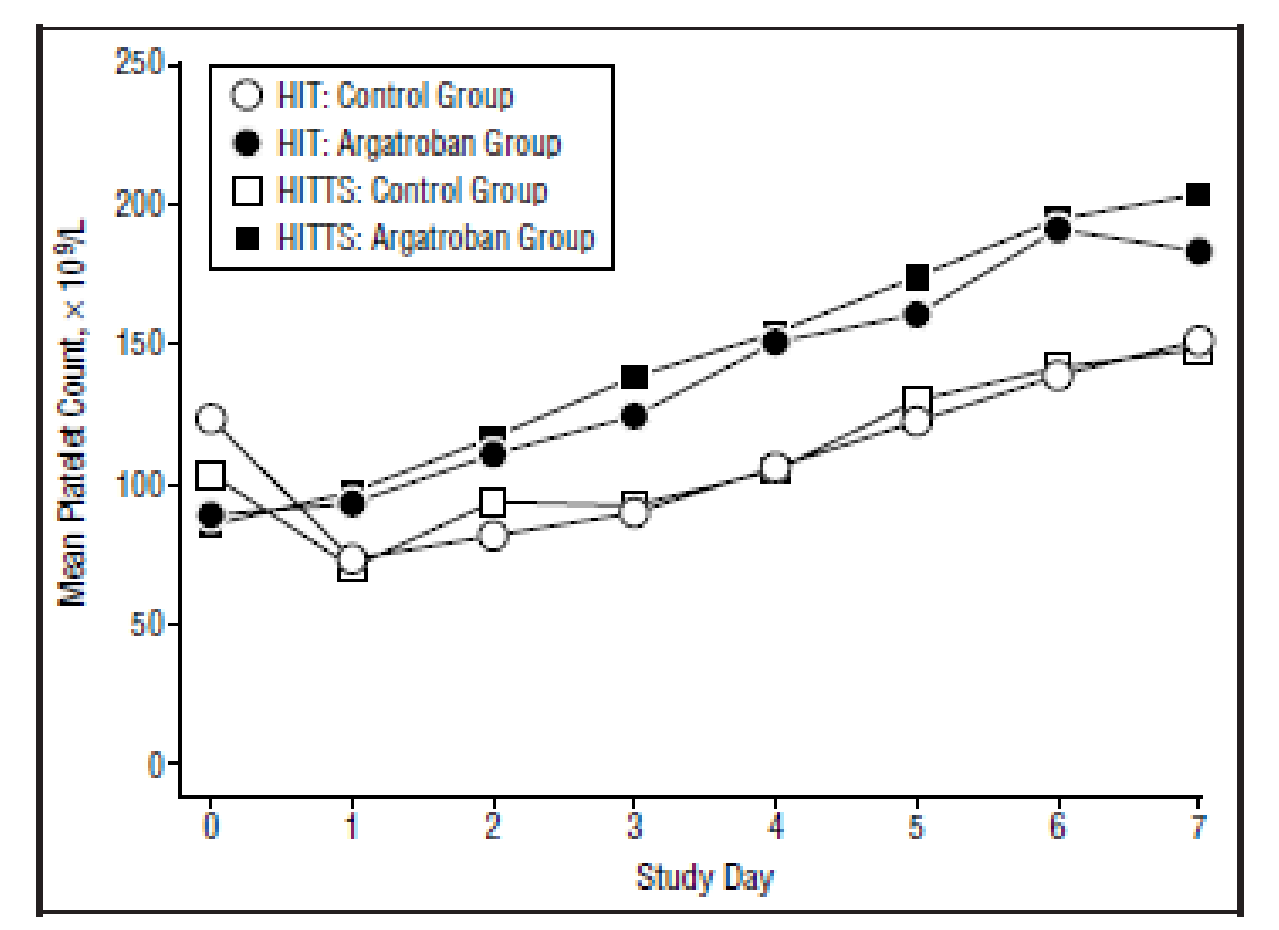
Table 2. Efficacy Outcomes in 418 Argatroban-Treated Patients and 185 Historical Controls by Study Arm*

	Isolated HIT			HIT With Thrombosis		
Outcome	Control Group (n = 139)	Argatroban Group (n = 189)	*P* Value	Control Group (n = 46)	Argatroban Group (n = 229)	*P* Value
Composite end point†	54 (38.8)	53 (28.0)	.04	26 (56.5)	95 (41.5)	.07
Death (all causes)‡	29 (20.9)	36 (19.0)	.78	13 (28.3)	53 (23.1)	.45
Death due to thrombosis	6 (4.3)	1 (0.5)	.04	7 (15.2)	6 (2.6)	.002
Amputation (all causes)‡	4 (2.9)	8 (4.2)	.57	5 (10.9)	34 (14.8)	.64
New thrombosis‡	32 (23.0)	11 (5.8)	<.001	16 (34.8)	30 (13.1)	<.001

Lewis BE et al. Arch Intern Med 2003.

ARG 915

- More rapid recovery of platelet counts (p<0.01)



Lewis BE et al. Arch Intern Med 2003.

ARG 915

Table 3. Major and Minor Bleeding Incidence in 418 Argatroban-Treated Patients and 185 Historical Controls by Study Arm*

	Isolated HIT			HIT With Thrombosis		
Outcome†	Control Group (n = 139)	Argatroban Group (n = 189)	*P* Value	Control Group (n = 46)	Argatroban Group (n = 229)	*P* Value
Major bleeding	12 (8.6)	10 (5.3)	.27‡	1 (2.2)	14 (6.1)	.48§
Minor bleeding	57 (41.0)	59 (31.2)	.08	19 (41.3)	87 (38.0)	.74

Lewis BE et al. Arch Intern Med 2003.

Additional Studies

Retrospective Analyses of ARG 911 & 915

- Argatroban-treated patients were less likely to experience stroke
  - Stroke rate: 2.6% vs. 5.2%
    - OR 0.31 (95% CI 0.10-0.96, p=0.041)
  - Stroke-associated mortality: 1% vs. 3.1%
    - OR 0.18 (95% CI 0.03-0.92, p=0.039)
- Thrombotic composite endpoint: death due to thrombosis, amputation secondary to thrombosis, new thrombosis
  - Isolated HIT: HR 0.27 (95% CI 0.15-0.49, p<0.001)
  - HIT with thrombosis: HR 0.42 (95% CI 0.23-0.77, p=0.005)

LaMonte MP et al. Crit Care Med 2004; Lewis BE et al. Chest 2006.

Argatroban
Advantages

- Positive efficacy trials
- Has been studied in different patient populations
- No dose adjustment required in renal insufficiency
- Short t½ →quick reversal of anticoagulant effect with discontinuation of therapy
- Higher level of evidence compared to fondaparinux and bivalirudin

Argatroban
Disadvantages

- Converting patients to warfarin therapy
  - INR issues
  - ↑risk of venous limb ischemia and gangrene
- Must be dose adjusted in hepatic failure
  - Prolonged t½
- May have to dose adjust in critically ill patients
- No antidote
- Short t½ → risk of rebound hypercoagulability and thrombosis

Lepirudin
Review of Evidence

- 2008 ACCP Guidelines
  - Grade 1C recommendation
  - Recommendation is based on three prospective trials: HAT-1, HAT-2 and HAT-3 and a post-marketing study: DMP

Lepirudin
Review of Evidence

HAT-1, HAT-2 and HAT-3 Studies

- Design: Prospective, multicenter, historically controlled trials

- Treatment regimens

  - A1. Known TEC: 0.4mg/kg bolus, then 0.15mg/kg/h infusion

  - A2. Known TEC undergoing thrombolysis: 0.2mg/kg bolus, then 0.1mg/kg/h infusion

  - B. No known TEC: 0.1mg/kg/h infusion

  - C. For anticoagulation during CPB: 0.2mg/kg primer, 0.25mg/kg bolus, then infusion adjusted by ECT

Lubenow J et al. Thromb Haemost 2005.

Lepirudin
Review of Evidence

- N = 403 patients

  - HAT-1, n=82, HAT-2, n=116, HAT-3, n=205

- Outcomes

  Efficacy

  - aPTT prolongation and platelet count recovery

  - Incidence of new arterial or venous TECs, limb amputations and death

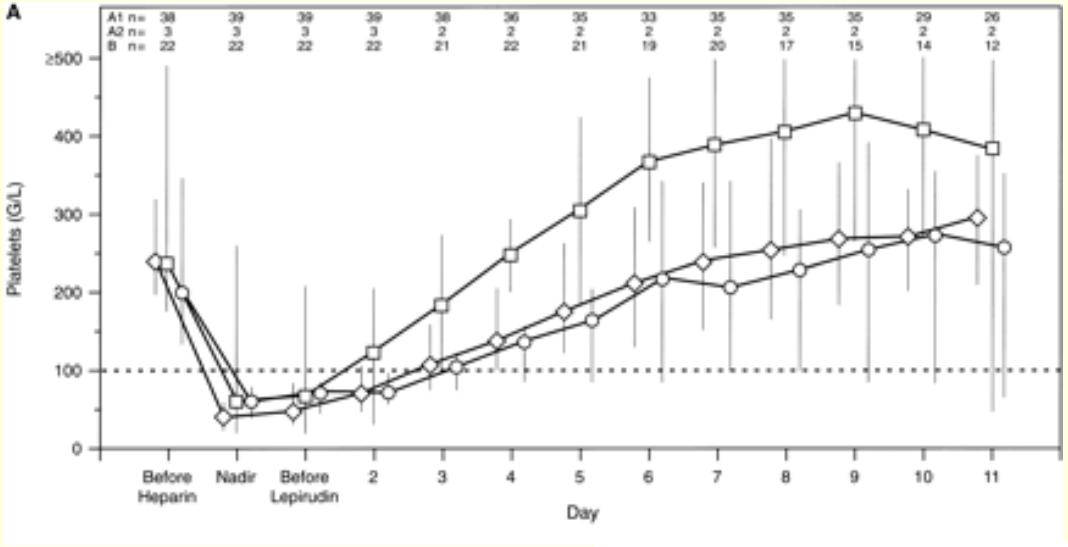
  Safety

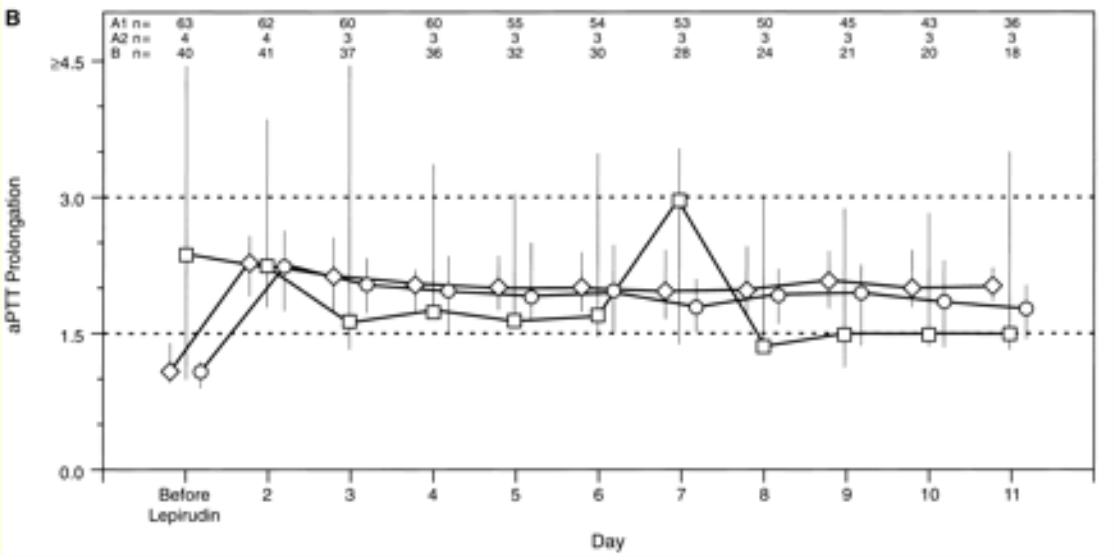
  - Incidence of major bleeding complications

Lubenow J et al. Thromb Haemost 2005.

Lepirudin

Review of Evidence





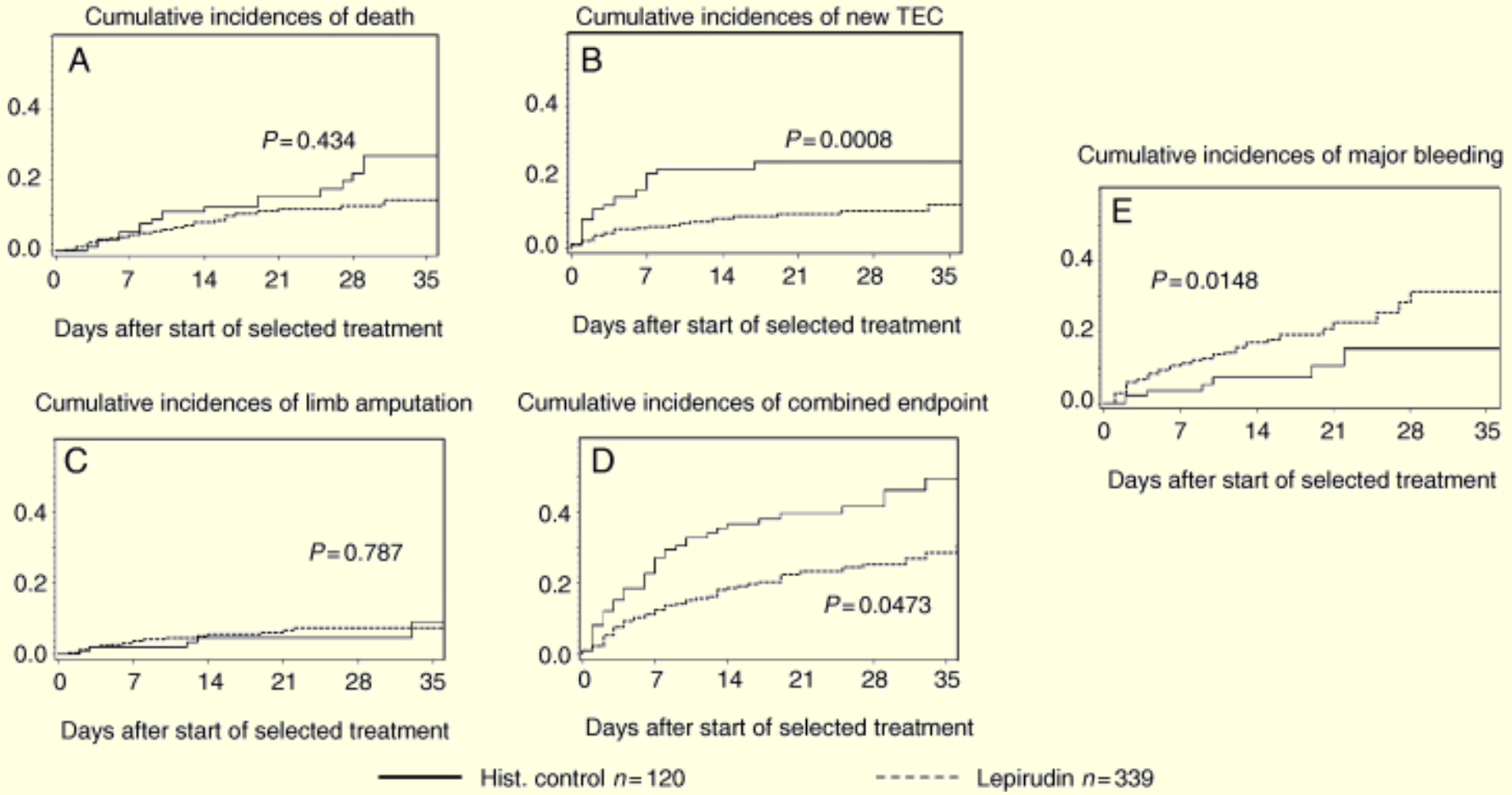
Greinacher A et al. Circulation 1999 (Vol 100).

Lepirudin
Review of Evidence

	Outcomes from diagnosis of HIT			Outcomes from start of treatment		
	Total n=403	**Historical Controls n=120**	**P-value**	**Total n=403**	**Historical control n=120**	**P-value**
Death	47 (11.7)	21 (17.5)	0.095	47 (11.7)	21 (17.5)	0.095
Limb amputation	26 (6.5)	8 (6.7)	0.933	22 (5.5)	8 (6.7)	0.618
New TEC	56 (13.9)	37 (30.8)	<0.0001	30 (7.4)	30 (25.0)	<0.0001
Combined	109 (27.0)	53 (44.2)	0.0001	82 (20.3)	52 (43.3)	<0.0001
Major bleeding	71 (17.6)	7 (5.8)	0.0015	71 (17.6)	7 (5.8)	0.0015

Lubenow J et al. Thromb Haemost 2005.

Lepirudin
Review of Evidence



Lubenow J et al. Thromb Haemost 2005.

Lepirudin
Review of Evidence

Drug Monitoring Program (DMP) Study

- 1325 patients
- 3 groups:
  - Treatment
  - Prophylaxis
  - Miscellaneous Indications
- Evaluated same clinical endpoints as HAT studies

Lubenow N et al. Blood 2002.

Lepirudin
Review of Evidence

Drug Monitoring Program (DMP) Study

- Lepirudin was started immediately following clinical diagnosis of HIT

	Treatment	Prophylaxis
Death	10.9%	12.3%
Limb amputation	5.8%	1.3%
New TECs	5.2%	2.1%
Combined	21.9%	15.7%

Lubenow N et al. Blood 2002.

Lepirudin
Advantages

- Positive efficacy trials
- Has only a minimal effect on INR
- May be used in patients with abnormal hepatic function
- Higher level of evidence compared to fondaparinux and bivalirudin

Lepirudin
Disadvantages

- Strict laboratory monitoring required (aPTT)
- Dosage adjustment in renal impairment
- Fatal anaphylactic reactions have been reported
- Risk of bleeding

Argatroban vs. Lepirudin

- Lepirudin trials required diagnostic confirmation of HIT, whereas argatroban trials did not
- Duration of therapy was longer in lepirudin trials than argatroban trials (12-14 days vs. 6-7 days)
- Baseline platelet counts were lower in argatroban trials

Gajra A et al. Drug Metab. Toxicol. 2008.

Summary

Anticoagulants for treatment of HIT

Variables	Argatroban	Lepirudin	Bivalirudin	Danaparoid	Fondaparinux
Structure	Synthetic, l-arginine derivative	Recombinant form of hirudin	Synthetic peptide	Mixture of glycosaminoglycans	Synthetic pentasaccharide
Activity	Direct thrombin inhibitor	Antithrombin	Antithrombin	Anti-factor Xa	Anti-factor Xa
Elimination	Hepatobiliary	Renal	Enzymatic (80%), renal	Renal	Renal
Half-life	40–50 min	80 min	25 min	18–24 h	17–20 h
Monitoring	aPTT, ACT	aPTT, ACT, ECT	aPTT, ACT, ECT	Anti-Xa level	Anti-Xa level†
Dosing in HIT	Initial infusion rate, 2 μg/kg/min IV (no initial bolus); a reduced initial infusion rate (0.5–1.2 μg/kg/min)	Bolus 0.2–0.4 mg/kg IV (only in case of life- or limb-threatening thrombosis); maximum initial infusion rate, 0.10 mg/kg/h IV (target, 1.5–2.0 × patient's baseline or mean of laboratory normal range)	Initial infusion rate, 0.15–0.20 mg/kg/h IV (target, 1.5–2.5 × patient's baseline or mean of laboratory normal range [no initial bolus])	Bolus: 2,250 units IV; infusion, 400 units/h × 4 h, then 300 units/h × 4 h, then 200 units/h IV, subsequently adjusted by anti-Xa levels (target, 0.5–0.8 anti-Xa units/mL)	Doses for HIT treatment need to be established. Because of limited data available on the drug in HIT, fondaparinux could be tried only when other medicines in this table are not available or contraindicated
Dose adjustment	Hepatic insufficiency	Renal dysfunction	Renal dysfunction	Renal dysfunction, body weight	Renal dysfunction

Shantsila E et al. CHEST 2009.

Summary

Anticoagulants for treatment of HIT

Drug	Approx. Daily Cost
Danaparoid	$200
Lepirudin	$500
Argatroban	$665
Bivalirudin	$600

Case Wrap Up

- PB was hospitalized and immediately initiated on lepirudin
  - 12 mg IV bolus
  - 6mg/hr via continuous IV infusion
  - Target = 1.5-2.0 X baseline aPTT
- Warfarin 5 mg daily was started once PB's platelets were $150X10^9$ cells/L
  - Overlapped with lepirudin for 6 days
  - INR on Days 5 and 6 were 2.0-3.0
- Platelets on Day 5 were $280X10^9$ cells/L

Case Wrap Up

Conclusion

- HIT is a potentially life-threatening condition that requires prompt diagnosis and treatment
- According to the CHEST guidelines, danaparoid has the greatest recommendation grade due to availability of strong evidence
- No head to head trials comparing argatroban and lepirudin

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